National Institute for Health and Care Excellence

Final

Cardiovascular disease: risk assessment and reduction, including lipid modification

[C] Evidence review for statins: efficacy and adverse effects

NICE guideline CG181

Evidence review underpinning recommendations 1.4.11 to 1.4.43 and research recommendations in the NICE guideline

May 2023

Final

Developed by National Institute for Health and Care Excellence

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1.1 Review question

What is the clinical and cost effectiveness of statin therapy for adults without established CVD and with established CVD?

1.1.1 Introduction

Statins are recognised as the first choice lipid modification therapy to reduce CVD events. Statin therapy was first appraised by NICE as part of the technology appraisal TA94 ('Statins for the prevention of cardiovascular events' 2006). This was followed by clinical guidelines which made specific recommendations about use of statins for primary prevention, secondary prevention, type 1 and type 2 diabetes and people with CKD. In 2014, the guideline recommended that when prescribing a statin, a statin of high intensity (see Table 1) and low acquisition cost should be used. Since that date, further RCT evidence and individual patient data meta-analyses have been published as well as changes in NHS costs which may further inform these recommendations. Furthermore, evidence continues to emerge regarding advice that can be given about adverse effects when taking statins. Updated systematic reviews are therefore required to determine whether recommendations in these areas should be amended to reflect the current evidence base.

Table 1: Statin intensity classification based on the percentage reduction in low-density lipoprotein (LDL) cholesterol they can produce

Intensity	Statin and dose	LDL-cholesterol reduction (%)
Low intensity	Fluvastatin 20 or 40 mg Pravastatin 5, 10, 20 or 40 mg Simvastatin 10 mg	20% to 30%
Medium intensity	Atorvastatin 10 mg Fluvastatin 80 mg Rosuvastatin 5 mg Simvastatin 20 or 40 mg	31% to 40%
High intensity	Atorvastatin 20, 40 or 80 mg Rosuvastatin 10, 20 or 40 mg	Greater than 40%

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 2: PICO characteristics of review question

Population	Adults (aged 18 years and older) with or without established CVD, including those with type 1 diabetes, type 2 diabetes or chronic kidney disease.
Interventions	Statins • **Low intensity:** 20-30% reduction in LDL-c ○ fluvastatin 20–40 mg ○ pravastatin 10–40 mg ○ simvastatin 10 mg • **Medium intensity:** 31-40% reduction in LDL-c ○ atorvastatin 10 mg ○ fluvastatin 80 mg

	○ rosuvastatin 5 mg ○ simvastatin 20–40 mg • **High intensity:** >40% reduction in LDL-c ○ atorvastatin 20–80 mg ○ rosuvastatin 10–40 mg Note: Simvastatin 80 mg is no longer used because of risk of myopathy and muscle symptoms and so will not be included in the update. Any existing data on this drug dose will be removed from the analyses.
Comparisons	• Placebo/usual care/no treatment • Different intensities • High intensity vs other high intensity drug/dose
Outcomes	• All-cause mortality • Cardiovascular mortality • Non-fatal myocardial infarction • Non-fatal ischaemic stroke • Combined major adverse cardiovascular events (CVD death, nonfatal MI, nonfatal ischaemic stroke) • Quality of life, any validated measure
Study design	• RCTs • Systematic reviews of RCTs • Published NMAs and IPDs of RCT data will be considered for inclusion.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

This was an update of the review in the 2014 update of CG181, new data have been added into the previous analyses. The following changes were also made to the approach taken in 2014:

- The outcome of non-fatal stroke was changed to non-fatal ischaemic stroke. All previously included studies were reviewed and where ischaemic stroke was reported this was extracted and assessed for risk of bias. These data were also updated in the analysis.
- The composite outcome of combined major adverse cardiovascular events was added. All previously included studies were reviewed and any data on this outcome was extracted, assessed for risk of bias and added to the analysis.
- No stratification by populations was planned. Presence or absence of CKD and primary and secondary prevention populations were prespecified as subgroup analyses to be explored if heterogeneity was observed.

As in the 2014 update of CG181, network meta-analysis was not prioritised for this review. This was because by definition higher intensity statins will be more effective, and the committee did not anticipate a move away from recommending high intensity statins. Therefore, ranking the efficacy of statins by intensity would not add value.

For time-to-event outcomes, hazard ratios and risk ratios were reported, including in forest plots. Given that more data were available for the dichotomous analyses and the overall findings did not differ from the time-to-event effect estimates, in order to maximise the available pooled data risk ratios were considered for decision making and are the only data included in GRADE. This approach was defined in the review protocol and was consistent with the 2014 update of CG181.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A search was conducted for randomised trials assessing the efficacy of UK-licenced statins for cardiovascular risk reduction. Seven randomised trials reported in 9 papers were added to the review; [75, 78, 87, 88, 105, 155, 189, 192, 195] and 43 previously included studies were also retained in the analysis. [9, 12, 20, 24, 27, 33, 34, 39, 47, 52, 54, 73, 90, 94, 99-101, 108, 112-114, 119, 127, 129, 134, 137, 139, 143, 144, 147, 151, 154, 156, 159, 162, 164, 165, 167, 170, 176, 190, 191, 196]

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

Placebo-controlled studies

Of the total number of included studies, 38 were placebo comparisons;[9, 12, 20, 24, 27, 33, 39, 47, 75, 87, 88, 90, 94, 100, 101, 108, 112-114, 119, 137, 139, 143, 144, 147, 151, 154, 155, 162, 164, 165, 167, 170, 176, 189-192] summarised in Table 3 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 7).

Among the placebo-controlled studies, the following populations were represented (studies may be counted in more than one category):

- Primary prevention (16 studies)[12, 20, 27, 39, 47, 87, 88, 108, 113, 114, 119, 147, 155, 162, 165, 192]
- Secondary prevention (20 studies)[9, 24, 33, 75, 94, 101, 112, 137, 139, 143, 144, 151, 154, 164, 167, 170, 176, 189-191]
- Type 2 diabetes (3 studies)[27, 39, 90]
- Chronic kidney disease (1 study)[87]
- Rheumatoid arthritis (1 study)[88]

No studies were identified in people with type 1 diabetes.

Active-control studies

There were 14 were head-to-head statin comparison studies,[34, 52, 54, 73, 78, 99, 105, 127, 129, 134, 156, 159, 195, 196] which are summarised in Table 4 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 9, Table 11, Table 13 and Table 14).

Among the head-to-head statin comparison studies, the following populations were represented (studies may be counted in more than one category):

- Primary prevention (2 studies)[73, 159]
- Secondary prevention (12 studies)[34, 52, 54, 78, 99, 105, 127, 129, 134, 156, 195, 196]
- Type 2 diabetes (1 study)[105]

No studies were identified in people with type 1 diabetes or chronic kidney disease.

The comparisons available were as follows:

- High versus low intensity (3 studies) [34, 52, 78]
- High versus medium intensity (4 studies) [99, 134, 159, 195]
- High versus high intensity (2 studies)[105, 127]
- Medium versus low intensity (1 study)[196]

Studies of medium versus medium and low versus low intensity statins were not included within the 2022 update analysis.

LDL-cholesterol values

Of the 38 studies identified that compared statin versus placebo only 20 reported final LDL-cholesterol values for both the statin and placebo arms (Table 5).[9, 20, 24, 27, 33, 39, 75, 87, 88, 94, 100, 108, 155, 162, 167, 170, 176, 189-191]

Of the 14 studies identified that compared higher dose statin versus lower dose statin, 10 reported final LDL-cholesterol values for both statin arms (**Table 6**).[54, 73, 78, 127, 129, 134, 156, 159, 195, 196]

Other studies reported LDL-cholesterol changes in alternative representations for example, percentage change from baseline levels, p value of change, final value in statin arm only, or graphical representation only.

Outcome definitions

Major adverse cardiovascular events

The combined outcome of major adverse cardiovascular events is defined differently across the literature. For this review, the following approach was taken to ensure only definitions similar enough to that in the protocol, and suitable for pooled analysis, were included.

- Definitions that incorporate any of the following events were excluded from the analysis for being too indirect:
  - all-cause mortality
  - transient ischaemic attack
  - peripheral vascular disorder
  - peripheral artery bypass graft
  - amputation because of atherosclerotic disease
- Definitions that omit fatal or non-fatal stroke were excluded from the analysis for being too indirect.
- Definitions that included the following terms, which fall within the cardiovascular death component, were not excluded nor downgraded for indirectness:
  - Resuscitation after cardiac arrest
  - Sudden cardiac death
- Definitions that included the following terms, which fall within the cardiovascular death component, were not excluded nor downgraded for indirectness:
  - Coronary intervention procedure
  - Recanalisation

Myocardial infarction (MI)

The preferred outcome was non-fatal MI, but if only total events (fatal and non-fatal) were reported, then this was included in the analysis and not downgraded for indirectness because the effect on fatal and non-fatal events is similar.

Stroke

The preferred outcome was non-fatal ischaemic stroke. However, if only ‘stroke’ is reported (including ischaemic and haemorrhagic, and/or fatal and non-fatal), this was included and not downgraded for indirectness because the effect on fatal and non-fatal events is similar and

the inclusion of haemorrhagic stroke data would only create a small dilution of the ischemic stroke effect.

1.1.4.2 Excluded studies

The review undertaken in the previous update of the guideline was used as a basis for this updated review. Of the studies included previously, a total of 4 studies were excluded from the analysis in this update because one of the interventions was simvastatin 80 mg, which is no longer used due to safety concerns.[7] One of these was a placebo controlled study[177] and the remaining 3 were head-to-head statin trials.[18, 50, 66] One study comparing low versus low intensity statins was also removed from the updated analysis as this was not a comparison of interest in the current review protocol.[79]

Regarding study populations, it was noted that trials in exclusively heart failure populations were excluded from the analysis in the previous update, such as the CORONA[89] and GISSI-HF[173] trials. As there is limited uncertainty about how to treat people with heart failure, which will be based on the underlying cause, it was agreed that heart failure populations would also be excluded from analysis in the present update.

Six potentially relevant Cochrane reviews[2-6, 181] were identified but could not be included; 5 because they did not include any outcomes relevant to the protocol[2-6] and 1 because all relevant studies were already included in the 2014 update of this guideline.[181] However, all studies included in the reviews were cross-checked for inclusion in this review.

For reasons for exclusion from the updated search, see the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 3: Summary of studies comparing statins versus placebo for efficacy outcomes

Study name	Population	Intervention 1: class	Intervention 1: details	Number randomised intervention group	Comparison	Number randomised comparison group	Follow up
Adults without established CVD							
Anderssen 2005[12] HYRIM	Adults without established CVD	Low-intensity statin	Fluvastatin 40 mg	283	Placebo	285	4 years
Anon 2002[108] ALLHAT-LLT	Adults without established CVD	Low-intensity statin	Pravastatin 40 mg	5170	Placebo	5185	Mean 4.8 years
Asselbergs 2004[20] PREVEND-IT	Adults without established CVD	Low-intensity statin	Pravastatin 40 mg	433	Placebo	431	Mean 46 months
Mercuri 1996[113] CAIUS	Adults without established CVD	Low-intensity statin	Pravastatin 40 mg	151	Placebo	154	3 years
Nakamura 2006[119] MEGA	Adults without established CVD	Low-intensity statin	Pravastatin 20 mg	3866	Placebo	3966	Mean 5.3 years
Salonen 1995 [155] KAPS	Men without established CVD	Low-intensity statin	Pravastatin 40 mg	224	Placebo	223	3 years (Unclear)
Shepherd 1995[165] WOSCOPS	Adults without established CVD	Low-intensity statin	Pravastatin 40 mg	3302	Placebo	3293	4.9 years
Beishuizen 2005[27]	Adults with type 2 diabetes without established CVD	Medium-intensity statin	Simvastatin 20 mg	125	Placebo	125	2 years
Colhoun 2004[39] CARDS	Adults with type 2 diabetes without established CVD	Medium-intensity statin	Atorvastatin 10 mg	1429	Placebo	1412	Median 3.9 years
Mok 2009[114]	Adults without established CVD	Medium-intensity statin	Simvastatin 20 mg	113	Placebo	114	2 years

Study name	Population	Intervention 1: class	Intervention 1: details	Number randomised intervention group	Comparison	Number randomised comparison group	Follow up
Sever 2003[162] ASCOT-LLA	Adults without established CVD	Medium-intensity statin	Atorvastatin 10 mg	5168	Placebo	5137	Median 3.3 years
Kimura 2017 [87] ASUCA	Adults with CKD and hyperlipidaemia without established CVD	Medium-intensity statin plus diet therapy (treat-to-target) *Target serum LDL-C level was <100 mg/dl*	Atorvastatin 10mg/day initially, then adjusted to 5-20mg/day (average final dose 10.5 mg)	168	Non-statin treatment plus diet therapy	166	2 years
Crouse 2007[47] METEOR	Adults without established CVD	High-intensity statin	Rosuvastatin 40 mg	702	Placebo	282	2 years
Kitas 2019 [88] TRACE-RA	Adults with rheumatoid arthritis without established CVD	High-intensity statin	Atorvastatin 40mg	1504	Placebo	1498	Median 2.51 years
Ridker 2008[147] JUPITER	Adults without established CVD	High-intensity statin	Rosuvastatin 20 mg	8901	Placebo	8901	Median 1.9 years
Yusuf 2016 [106, 192] HOPE-3	Adults with additional clinical cardiovascular risk factor without established CVD	High-intensity statin	Rosuvastatin 10mg	6361	Placebo	6344	Median 5.7 years
Adults with established CVD							
Anon 1998[139] LIPID	Adults with established CVD	Low-intensity statin	Pravastatin 40 mg	4512	Placebo	4502	6.1 years
Anon 2000[144] GISSI	Adults with established CVD	Low-intensity statin	Pravastatin 20 mg	2138	No treatment – open label	2133	Mean 23 months
Byington 1995[33] PLAC II	Adults with established CVD	Low-intensity statin	Pravastatin 40 mg	75	Placebo	76	3 years
Hosomi 2015 [75] J-STARS	Adults with established CVD (history of non-	Low-intensity statin	Pravastatin 10 mg	793	No treatment – open label	785	5 years

Study name	Population	Intervention 1: class	Intervention 1: details	Number randomised intervention group	Comparison	Number randomised comparison group	Follow up
	cardioembolic ischemic stroke)						
Pitt 1995[137] PLAC I	Adults with established CVD	Low-intensity statin	Pravastatin 40 mg	206	Placebo	202	3 years
Riegger 1999[151]	Adults with established CVD	Low-intensity statin	Fluvastatin 40 mg	187	Placebo	178	1 year
Sacks 1996[154] CARE	Adults with established CVD	Low-intensity statin	Pravastatin 40 mg	2081	Placebo	2078	5 years
Shepherd 2002[164] PROSPER	Adults with established CVD	Low-intensity statin	Pravastatin 40 mg	2891	Placebo	2913	Mean 3.2 years
Teo 2000[176] SCAT	Adults with established CVD	Low-intensity statin	Simvastatin 10 mg	230	Placebo	230	3-5 years
Yokoi 2005[191]	Adults with established CVD	Low-intensity statin	Pravastatin 20 mg	186	Usual care – open label	187	3 years
Anon 1994[143] 4S	Adults with established CVD	Medium-intensity statin	Simvastatin 20 mg	2221	Placebo	2223	5.4 years
Lemos 2003[101] LIPS	Adults with established CVD	Medium-intensity statin	Fluvastatin 80 mg	844	Placebo	833	3–4 years
Meade 1999[112] HPS	Adults with established CVD	Medium-intensity statin	Simvastatin 40 mg	10269	Placebo	10267	5 years
Shukla 2005[167]	Adults with established CVD	Medium-intensity statin	Atorvastatin 10 mg	75	Placebo	75	1 year
Yamada 2007[190]	Adults with established CVD	Medium-intensity statin	Atorvastatin 10 mg	19	Usual care – open label	19	3 years
Yakusevich 2012[189]	Adults with first acute ischaemic cerebrovascular	Medium-intensity statin	Simvastatin 40mg	86	Usual care – open label	97	Up to 1 year

Study name	Population	Intervention 1: class	Intervention 1: details	Number randomised intervention group	Comparison	Number randomised comparison group	Follow up
	accident in carotid system						
Amarenco 2006[9] SPARCL	Adults with established CVD	High-intensity statin	Atorvastatin 80 mg	2365	Placebo	2366	Median 4.9 years
Athyros 2002[24] GREACE	Adults with established CVD	High-intensity statin	Atorvastatin 20 mg	800	Usual care – open label	800	Mean 3 years
Sola 2006[170]	Adults with established CVD	High-intensity statin	Atorvastatin 20 mg	54	Placebo	54	1 year
Koren 200[494] ALLIANCE	Adults with established CVD	High-intensity statin (treat-to-target)	Atorvastatin up to 80 mg Median dose: 40.5 mg 45% of patients received 80 mg	1217	Usual care – open label	1225	Mean 51.5 months
Adults with or without established CVD							
Knopp 2006[90] ASPEN	Adults with type 2 diabetes (79% without established CVD)	Medium-intensity statin	Atorvastatin 10 mg	1211	Placebo	1199	Median 4 years
Lemos 2013[100]	Adults with CKD with or without established CVD	High-intensity statin	Rosuvastatin 10 mg	22	Placebo	29	2 years

Table 4: Summary of studies comparing statins head-to-head for efficacy outcomes

Study name	Number patients	Population details	Intervention 1: class	Intervention 1: details	Intervention 2: class	Intervention 2: details	Follow up
Adults without established CVD							
Hong 2009[73]	100	Adults without established CVD	High-intensity statin	Rosuvastatin 10 mg/day	Medium-intensity statin	Simvastatin 20 mg/day	1 year
Schmermund 2006[159]	471	Adults without established CVD with ≥ 2 CV factors and moderate calcified coronary atherosclerosis	High-intensity statin	Atorvastatin 80 mg/day	Medium-intensity statin	Atorvastatin 10 mg/day	1 year
Adults with established CVD							
Cannon 2004[34] PROVE IT TIMI 22	4162	Adults with ACS (18% diabetes)	High-intensity statin	Atorvastatin 80 mg/day	Low-intensity statin	Pravastatin 40 mg/day	2 years
Deedwania 2007[52]	891	Adults with history of CAD (23% diabetes)	High-intensity statin	Atorvastatin 80 mg/day	Low-intensity statin	Pravastatin 40 mg/day	1 year
Im 2018 [78]	2000	Clinically stable adults with established CVD who received drug-eluting stents	High-intensity statin	Atorvastatin 40 mg/day	Low-intensity statin	Pravastatin 20 mg/day	1 year open label
Nissen 2005[128, 129] REVERSAL	654	Adults requiring coronary angiography	High-intensity statin	Atorvastatin 80 mg/day	Low-intensity statin	Pravastatin 40 mg/day	18 months
Egede 2013[54] VIRHISTAMI	87	Patients with STEMI	High-intensity statin	Rosuvastatin 40 mg/day	Medium-intensity statin	Rosuvastatin 5 mg/day	1 year
Larosa 2005[99] TNT	10,001	Adults with stable CHD (15% diabetes)	High-intensity statin	Atorvastatin 80 mg/day	Medium-intensity statin	Atorvastatin 10 mg/day	4.9 years
Pedersen 2005[134] IDEAL	8888	Adults who were post-MI (12% diabetes)	High-intensity statin	Atorvastatin 80 mg/day. The dose of atorvastatin could be decreased to	Medium-intensity statin	Simvastatin 20 mg/day. If, at 24 weeks, total-C >190 mg/dl	4.8 years - open label

Study name	Number patients	Population details	Intervention 1: class	Intervention 1: details	Intervention 2: class	Intervention 2: details	Follow up
				40 mg/day for adverse events. At 24 weeks 250 (6%) people had the dose reduced to 40 mg/day. At the end of the study, 587 (13%) people had the dose reduced to 40 mg/day.		(5.0 mmol/litre), the dose of simvastatin could be increased to 40 mg/day. At the end of the study, 1034 (23%) were prescribed simvastatin 40 mg/day.	
Zhao 2014 [195] CHILLAS	1355	Adults hospitalised for acute myocardial infarction or unstable angina pectoris; clinically stable for 24 hours.	High-intensity statin	Atorvastatin 20-40 mg/day	Medium-intensity statin	Atorvastatin 10 mg/day	Median 2 years - open label (assessor blinded)
Liu 2016[105]	591	Adults with acute coronary syndrome and type 2 diabetes mellitus	High-intensity statin	Atorvastatin 40 mg/day	High-intensity statin	Atorvastatin 20 mg/day	1 year – open label
Nicholls 2011[127] SATURN	1385	Adults with coronary disease (15% diabetes)	High-intensity statin	Atorvastatin 80 mg/day	High-intensity statin	Rosuvastatin 40 mg/day	2 years
Satoh 2009[156]	100	Adults with CAD	Medium-intensity statin	Atorvastatin 10 mg/day	Low-intensity statin	Pravastatin 10 mg/day	1 year
Zou 2003[196]	197	Adults with ACS (14% diabetes)	Medium-intensity statin	Simvastatin 20 mg/day	Low-intensity statin	Simvastatin 10 mg/day	1 year - open label

See Appendix D for full evidence tables.

LDL-cholesterol data

Table 5: Baseline and final LDL-cholesterol levels in statin versus placebo studies

Study name	Statin and dose	Intensity	LDL cholesterol (mmol/litre); Mean (SD)				Follow-up time
			Statin Baseline	Statin Final	Placebo Baseline	Placebo Final	
Anon 2002[108] ALLHAT-LLT	Pravastatin 40 mg	Low	3.77 (0.55)	4.77 (0.91)	3.76 (0.55)	5.32 (0.95)	Mean 4.8 years
Asselbergs 2004[20] PREVEND-IT	Pravastatin 40 mg	Low	4.1 (1.0)	3.1 (0.9)	4.0 (1.0)	3.9 (0.1)	Mean 46 months
Byington 1995[33] PLAC II	Pravastatin 40 mg	Low	4.33 (SE: 0.06)	3.11 (0.59)	4.25 (SE: 0.05)	4.31 (0.56)	3 years
Hosomi 2015 [75] J-STARS	Pravastatin 10mg	Low	NR	NR	NR	NR	5 years
Salonen 1995 [155] KAPS	Pravastatin 40mg	Low	4.9 (0.6)	3.4 (0.65)	4.9 (0.6)	5.0 (0.69)	3 years
Yokoi 2005[191]	Pravastatin 20 mg	Low	2.98 (0.52)	2.98 (0.52)	3.67 (0.53)	3.64 (0.52)	3 years
Beishuizen 2005[27]	Simvastatin 20 mg	Medium	3.41 (0.72)	2.64 (0.96)	3.53 (0.72)	3.76 (0.83)	2 years
Colhoun 2004[39] CARDS	Atorvastatin 10 mg	Medium	5.36 (0.83)	2.11 (0.7)	3.46 (SE: 0.01)	3.12 (0.8)	Median 3.9 years
Kimura 2017 [87] ASUCA	Atorvastatin 10mg/day initially, then adjusted to 5-20mg/day	Medium	NR	NR	NR	NR	2 years
Sever 2003[162] ASCOT-LLA	Atorvastatin 10 mg	Medium	3.4 (0.7)	2.32 (0.72)	3.4 (0.7)	3.27 (0.81)	Median 3.3 years
Shukla 2005[167]	Atorvastatin 10 mg	Medium	2.23 (0.62)	1.91 (0.49)	2.17 (0.49)	2.25 (0.44)	1 year
Yakusevich 2012 [189]	Simvastatin 40mg	Medium	2.2 (0.6)	1.8 (0.3)	2.23 (0.9)	1.8 (0.3)	1 Year
Yamada 2007[190]	Atorvastatin 10 mg	Medium	3.08 (0.70)	1.97 (0.47)	2.97 (0.96)	2.84 (0.91)	3 years
Amarenco 2006[9] SPARCL	Atorvastatin 80 mg	High	3.43 (SE: 0.01) mg/dl	1.89 (0.62)	3.46 (SE: 0.01)	3.32 (0.75)	Median 4.9 years
Athyros 2002[24]	Atorvastatin 20 mg	High	4.65 (0.70)	2.51 (0.10)	4.63 (0.72)	4.37 (0.83)	Mean 3 years

Study name	Statin and dose	Intensity	LDL cholesterol (mmol/litre); Mean (SD)				Follow-up time
			Statin Baseline	Statin Final	Placebo Baseline	Placebo Final	
GREACE							
Kitas 2019 [88] TRACE-RA	Atorvastatin 40mg	High	Median (IQR): 3.2 (2.7 to 3.8)	2.21 (SE: 0.03)	Median (IQR): 3.2 (2.7 to 3.8)	2.98 (SE: 0.03)	Median 2.51 years
Koren 2004[94] ALLIANCE	Atorvastatin 80 mg	High	3.80 (SE: 0.02)	2.46 (0.70)	3.78 (SE: 0.02)	2.84 (0.70)	Mean 51.5 months
Lemos 2013[100]	Rosuvastatin 10 mg	High	3.10 (0.92)	2.03 (1.15)	2.40 (0.52)	2.5 (0.70)	2 years
Sola 2006[170]	Atorvastatin 20 mg	High	3.05 (0.39)	2.28 (0.94)	3.21 (0.52)	2.64 (0.87)	Mean 35 months

Table 6: Baseline and final LDL-cholesterol levels in head-to-head statin studies

Study name	Statin 1: class	Statin 1: details	Statin 1: Baseline LDL cholesterol (mmol/litre) Mean (SD)	Statin 1: Final LDL cholesterol (mmol/litre) Mean (SD)	Statin 2: class	Statin 2: details	Statin 2: Baseline LDL cholesterol (mmol/litre) Mean (SD)	Statin 2: Final LDL cholesterol (mmol/litre) Mean (SD)	Follow-up time
Hong 2009[73]	High	Atorvastatin 40 mg/day	1.92 (0.71)	1.75 (0.59)	Low	Pravastatin 20 mg/day	1.92 (0.68)	2.55 (0.74)	1 year
Zou 2003[196]	High	Atorvastatin 40 mg/day	1.92 (0.71)	1.75 (0.59)	Low	Pravastatin 20 mg/day	1.92 (0.68)	2.55 (0.74)	1 year
Nicholls 2011[127] SATURN	High	Atorvastatin 80 mg/day	3.9 (0.7)	2.04 (0.78)	Low	Pravastatin 40 mg/day	3.9 (0.7)	2.85 (0.67)	2 years
Nissen 2005[128, 129] REVERSAL	High	Atorvastatin 80 mg/day	3.14 (SE: 0.01)	2.09 (0.52)	Medium	Simvastatin 20 mg/day, Simvastatin 40 mg/day (23%)	3.14 (SE: 0.01)	2.58 (0.52)	1.5 years
Satoh 2009[156]	High	Atorvastatin 80 mg/day	Screening: 3.96 (1.06) Baseline: 2.74 (0.57)	2.25 (0.86)	Medium	Atorvastatin 10 mg/day	Screening: 4.03 (1.09) Baseline: 2.79 (0.53)	2.82 (0.72)	1 year

Study name	Statin 1: class	Statin 1: details	Statin 1: Baseline LDL cholesterol (mmol/litre) Mean (SD)	Statin 1: Final LDL cholesterol (mmol/litre) Mean (SD)	Statin 2: class	Statin 2: details	Statin 2: Baseline LDL cholesterol (mmol/litre) Mean (SD)	Statin 2: Final LDL cholesterol (mmol/litre) Mean (SD)	Follow-up time
Schmermund 2006[159]	High	Atorvastatin 20-40 mg/day	2.72 (0.82)	1.99 (0.74)	Medium	Atorvastatin 10 mg/day	2.71 (0.91)	2.17 (0.75)	1 year
Im 2018 [78]	High	Rosuvastatin 40 mg/day	3.10 (0.71)	1.62 (0.59)	High	Atorvastatin 80 mg/day	3.10 (0.75)	1.82 (0.59)	1 year
Pedersen 2005[134] IDEAL	Medium	Atorvastatin 10 mg/day	4.09 (0.72)	2.56 (0.72)	Low	Pravastatin 10 mg/day	3.86 (0.77)	2.90 (0.74)	4.8 years
Zhao 2014 [195] CHILLAS	Medium	Simvastatin 20 mg/day	3.51	2.83 (0.75)	Low	Simvastatin 10 mg/day	5.52	3.03 (0.53)	Median 2 years

1.1.6 Summary of the effectiveness evidence

Placebo comparison

Table 7: Clinical evidence summary: statins versus placebo stratified by statin intensity

Outcomes	№ of participants (studies) *Follow-up (range)**	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo (by intensity)	Risk difference with Statins
All-cause mortality - Low intensity vs placebo	50425 (13 RCTs) *23 months – 6.1 years*	⊕⊕⊕⊕ High[a]	RR 0.89 (0.84 to 0.94)	83 per 1,000	9 fewer per 1,000 (13 fewer to 5 fewer)
All-cause mortality - Medium intensity vs placebo	43021 (9 RCTs) *2 – 5.4 years*	⊕⊕⊕⊕ High[a]	RR 0.85 (0.80 to 0.90)	102 per 1,000	15 fewer per 1,000 (20 fewer to 10 fewer)

All-cause mortality - High intensity vs placebo	43371 (8 RCTs) *1 – 5.7 years*	⊕⊕⊕⊕ High[a]	RR 0.91 (0.83 to 0.99)	47 per 1,000	4 fewer per 1,000 (8 fewer to 0 fewer)
CV mortality - Low intensity vs placebo	50574 (12 RCTs) *1 – 6.1 years*	⊕⊕⊕⊕ High[a]	RR 0.84 (0.78 to 0.91)	52 per 1,000	8 fewer per 1,000 (11 fewer to 5 fewer)
CV mortality - Medium intensity vs placebo	42431 (8 RCTs) *1 – 5.4 years*	⊕⊕⊕⊕ High[a]	RR 0.81 (0.75 to 0.87)	63 per 1,000	12 fewer per 1,000 (16 fewer to 8 fewer)
CV mortality - High intensity vs placebo	42282 (6 RCTs) *1.9 – 5.7 years*	⊕⊕⊕⊕ High[a]	RR 0.80 (0.70 to 0.92)	20 per 1,000	4 fewer per 1,000 (6 fewer to 2 fewer)
Non-fatal MI - Low intensity vs placebo	41036 (14 RCTs) *1 – 6.1 years*	⊕⊕⊕◯ Moderate[b]	RR 0.78 (0.72 to 0.84)	60 per 1,000	13 fewer per 1,000 (17 fewer to 10 fewer)
Non-fatal MI - Medium intensity vs placebo	28585 (6 RCTs) *1 – 5.4 years*	⊕⊕⊕⊕ High	RR 0.62 (0.55 to 0.68)	63 per 1,000	24 fewer per 1,000 (28 fewer to 20 fewer)
Non-fatal MI - High intensity vs placebo	38532 (6 RCTs) *1.9 – 5.7 years*	⊕⊕⊕⊕ High	RR 0.51 (0.42 to 0.62)	16 per 1,000	8 fewer per 1,000 (9 fewer to 6 fewer)
Non-fatal ischaemic stroke - Low intensity vs placebo	44766 (11 RCTs) *23 months – 6.1 years*	⊕⊕⊕◯ Moderate[b]	RR 0.83 (0.74 to 0.93)	26 per 1,000	4 fewer per 1,000 (7 fewer to 2 fewer)
Non-fatal ischaemic stroke - Medium intensity vs placebo	38533 (6 RCTs) *1 – 5.4 years*	⊕⊕⊕◯ Moderate[b]	RR 0.73 (0.66 to 0.81)	44 per 1,000	12 fewer per 1,000 (15 fewer to 8 fewer)
Non-fatal ischaemic stroke - High intensity vs placebo	42268 (6 RCTs) *1.9 – 5.7 years*	⊕⊕⊕◯ Moderate[b]	RR 0.74 (0.65 to 0.84)	23 per 1,000	6 fewer per 1,000 (8 fewer to 4 fewer)
Major adverse cardiovascular events (MACE) - Low intensity vs placebo	10483 (3 RCTs) *23 months – 3.2 years*	⊕⊕⊕◯ Moderate[b]	RR 0.85 (0.76 to 0.94)	127 per 1,000	19 fewer per 1,000 (31 fewer to 8 fewer)

Major adverse cardiovascular events (MACE) - Medium intensity vs placebo	2410 (1 RCT) *4 years*	⊕⊕⊕◯ Moderate[b]	RR 0.91 (0.75 to 1.11)	150 per 1,000	14 fewer per 1,000 (38 fewer to 17 more)
Major adverse cardiovascular events (MACE) - High intensity vs placebo	35238 (3 RCTs) *1.9 – 5.7 years*	⊕◯◯◯ Very low[b,c]	RR 0.71 (0.58 to 0.89)	49 per 1,000	14 fewer per 1,000 (21 fewer to 5 fewer)
Quality of life assessed with: EQ5D Scale from: 0 to 1	2141 (1 RCT) *2.5 years*	⊕⊕◯◯ Low[d,e]	-	0.7 points	Median 0.04 points lower

**Some studies reported follow-up as a mean and others as a median value*
a. For mortality imprecision was assessed on the basis of the whether the confidence intervals crossed the line of no effect
b. 95% confidence interval crosses one MID (0.8)
c. Very serious inconsistency (I^2 = 77%): too few studies to investigate subgroups
d. Baseline differences in EQ-5D score
e. Imprecision could not be assessed

Time to event results

Table 8: Time-to-event results for statins versus placebo (stratified by statin intensity)

Outcome	Intensity of statin	HR (95%C)	Number of studies
All-cause mortality	Low	0.85 (0.78,0.92)	5
	Medium	0.77 (0.68, 0.87)	3
	High	0.89 (0.79, 1.00)	3
CV mortality	Low	0.83 (0.54, 1.28)	3
	Medium	0.90 (0.66, 1.23)	1
	High	0.75 (0.59, 0.94)	3
Non-fatal MI	Low	0.77 (0.68, 0.87)	5
	High	0.47 (0.37, 0.60)	3
Non-fatal stroke	Low	0.89 (0.76, 1.05)	4
	Medium	0.68 (0.54, 0.86)	2
	High	0.75 (0.65, 0.87)	4
MACE	Low	0.85 (0.74, 0.98)	1
	Medium	0.90 (0.73, 1.11)	1

Outcome	Intensity of statin	HR (95%C)	Number of studies
	High	0.70 (0.56, 0.88)	3

High versus low intensity statin

Table 9: Clinical evidence summary: High versus low intensity statin

Outcomes	№ of participants (studies) *Mean follow-up (range)*	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low intensity statin	Risk difference with High intensity
All-cause mortality	7053 (3 RCTs) *1 – 2 years*	⊕⊕⊕⊕ High[a]	RR 0.61 (0.44 to 0.85)	26 per 1,000	10 fewer per 1,000 (15 fewer to 4 fewer)
CV mortality	7052 (3 RCTs) *1 – 2 years*	⊕⊕⊕⊕ High[a]	RR 0.62 (0.39 to 1.00)	12 per 1,000	5 fewer per 1,000 (7 fewer to 0 fewer)
Non-fatal MI	6162 (2 RCTs) *1 – 2 years*	⊕◯◯◯ Very low[b,c]	RR 0.55 (0.15 to 2.02)	53 per 1,000	24 fewer per 1,000 (45 fewer to 54 more)
Stroke	7053 (3 RCTs) *1 – 2 years*	⊕⊕◯◯ Low[c]	RR 0.88 (0.51 to 1.51)	8 per 1,000	1 fewer per 1,000 (4 fewer to 4 more)
Major adverse cardiovascular event (MACE)	891 (1 RCT) *1 year*	⊕⊕◯◯ Low[d,e]	RR 0.68 (0.50 to 0.91)	202 per 1,000	65 fewer per 1,000 (101 fewer to 18 fewer)

a. For mortality imprecision was assessed on the basis of the whether the confidence intervals crossed the line of no effect
b. Serious inconsistency (I2 = 66%): too few studies to investigate subgroups
c. 95% confidence interval crosses both MIDs (0.8, 1.25)
d. High rate of missing data and unclear allocation concealment
e. 95% confidence interval crosses one MID (0.8)

Time to event results

Table 10: Time-to-event results for high versus low intensity statin

Outcome	HR (95%C)	Number of studies
All-cause mortality	0.63 (0.21, 1.89)	1
CV mortality	-	0
Non-fatal MI	0.23 (0.05, 1.06)	1
Non-fatal stroke	0.51 (0.09, 2.89)	1
MACE	0.71 (0.46, 1.10)	1

High versus medium intensity statin

Table 11: Clinical evidence summary: High versus medium intensity statin

Outcomes	№ of participants (studies) *Mean follow-up (range)*	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with medium intensity statin	Risk difference with high intensity
All-cause mortality	18889 (2 RCTs) *4.8 – 4.9 years*	⨁⨁◯◯ Low[a,b]	RR 0.99 (0.89 to 1.10)	69 per 1,000	1 fewer per 1,000 (8 fewer to 7 more)
CV mortality	18889 (2 RCTs) *4.8 – 4.9 years*	⨁◯◯◯ Very low[a,b,c]	RR 0.92 (0.72 to 1.17)	36 per 1,000	3 fewer per 1,000 (10 fewer to 6 more)
Non-fatal MI	19356 (3 RCTs) *1 – 4.9 years*	⨁⨁◯◯ Low[a,d]	RR 0.81 (0.72 to 0.91)	65 per 1,000	12 fewer per 1,000 (18 fewer to 6 fewer)
Stroke	9355 (2 RCTs) *1 – 4.8 years*	⨁⨁◯◯ Low[a,d]	RR 0.87 (0.70 to 1.08)	37 per 1,000	5 fewer per 1,000 (11 fewer to 3 more)

Outcomes	№ of participants (studies) *Mean follow-up (range)*	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with medium intensity statin	Risk difference with high intensity
Major adverse cardiovascular event (MACE)	20244 (3 RCTs) *2 – 4.9 years*	⨁◯◯◯ Very low[d,e,f]	RR 0.86 (0.75 to 1.00)	116 per 1,000	16 fewer per 1,000 (29 fewer to 0 fewer)

a. Majority of the evidence at high risk of performance bias: Additional interventions not balanced between groups: additional statins
b. For mortality imprecision was assessed on the basis of the whether the confidence intervals crossed the line of no effect
c. Serious inconsistency (I^2 = 59%): too few studies to investigate subgroups
d. 95% CI crosses one MID (0.8)
e. Evidence at high risk of bias (unbalanced additional interventions, or unclear allocation concealment)
f. Serious inconsistency (I^2 = 56%): too few studies to investigate subgroups

Time to event results

Table 12: Time-to-event results for medium versus high intensity statin *(note opposite direction of effect due to comparison reported in studies)*

Outcome	HR (95%C)	Number of studies
All-cause mortality	0.94 (0.75, 1.19)	3
CV mortality	1.09 (0.94, 1.28)	2
Non-fatal MI	1.24 (1.11, 1.40)	2
Non-fatal stroke	-	0
MACE	1.17 (1.01, 1.36)	3

High versus high intensity statin

Table 13: Clinical evidence summary: High versus high intensity statin

Outcomes	№ of participants (studies) *Mean follow-up*	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with high intensity	Risk difference with High intensity
All-cause mortality: Atorvastatin 40 mg vs atorvastatin 20 mg	591 (1 RCT) *1 year*	⨁⨁◯◯ Low[a]	RR 0.54 (0.20 to 1.44)	37 per 1,000	17 fewer per 1,000 (30 fewer to 16 more)
CV mortality: Atorvastatin 80 mg vs rosuvastatin 40 mg	1380 (1 RCT) *2 years*	⨁⨁◯◯ Low[a]	RR 1.00 (0.14 to 7.10)	3 per 1,000	0 fewer per 1,000 (2 fewer to 18 more)
Non-fatal MI - Atorvastatin 80 mg vs rosuvastatin 40 mg	1380 (1 RCT) *2 years*	⨁⨁◯◯ Low[a]	RR 1.00 (0.44 to 2.30)	16 per 1,000	0 fewer per 1,000 (9 fewer to 21 more)
Non-fatal MI - Atorvastatin 40 mg vs atorvastatin 20 mg	591 (1 RCT) *1 year*	⨁⨁⨁◯ Moderate[b]	RR 0.44 (0.19 to 1.00)	61 per 1,000	34 fewer per 1,000 (50 fewer to 0 fewer)
Non-fatal stroke - Atorvastatin 80 mg vs rosuvastatin 40 mg	1380 (1 RCT) *2 years*	⨁⨁◯◯ Low[a]	RR 0.67 (0.11 to 3.99)	4 per 1,000	1 fewer per 1,000 (4 fewer to 13 more)
Non-fatal stroke - Atorvastatin 40 mg vs atorvastatin 20 mg	591 (1 RCT) *1 year*	⨁⨁⨁◯ Moderate[b]	RR 0.49 (0.24 to 1.04)	68 per 1,000	35 fewer per 1,000 (52 fewer to 3 more)
Major adverse cardiovascular events (MACE) - Atorvastatin 80mg vs rosuvastatin 40mg	1380 (1 RCT) *2 years*	⨁⨁◯◯ Low[b]	RR 0.95 (0.65 to 1.38)	75 per 1,000	4 fewer per 1,000 (26 fewer to 29 more)

a. 95% confidence interval crosses both MIDs (0.8, 1.25)
b. 95% confidence interval crosses one MID (0.8)

Medium versus low intensity statin

Table 14: Clinical evidence summary: Medium versus low intensity statin

Outcomes	№ of participants (studies) *Mean follow-up*	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low intensity statin	Risk difference with Medium intensity
CV mortality	197 (1 RCT) *1 year*	⨁◯◯◯ Very low[a,b]	RR 0.99 (0.14 to 6.89)	20 per 1,000	0 fewer per 1,000 (18 fewer to 120 more)
Non-fatal MI	197 (1 RCT) *1 year*	⨁◯◯◯ Very low[a,b]	RR 0.58 (0.24 to 1.41)	122 per 1,000	51 fewer per 1,000 (93 fewer to 50 more)

a. High rate of missing data
b. 95% confidence interval crosses both MIDs (0.8, 1.25)

See Appendix F for full GRADE tables.

2 Statins in the prevention of cardiovascular disease – adverse effects

2.1 Review question

What is the risk of adverse effects from statin treatment?

2.1.1 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 15: PICO characteristics of review question

Population	Adults (aged 18 years and older) with or without established CVD, including those with type 1 diabetes, type 2 diabetes or chronic kidney disease.
Interventions	Statins • **Low intensity:** 20-30% reduction in LDL-c ○ fluvastatin 20–40 mg ○ pravastatin 10–40 mg ○ simvastatin 10 mg • **Medium intensity:** 31-40% reduction in LDL-c ○ atorvastatin 10 mg ○ fluvastatin 80 mg ○ rosuvastatin 5 mg ○ simvastatin 20–40 mg • **High intensity:** >40% reduction in LDL-c ○ atorvastatin 20–80 mg ○ rosuvastatin 10–40 mg Note: Simvastatin 80 mg is no longer used because of risk of myopathy and muscle symptoms and so will not be included in the update. Any existing data on this drug dose will be removed from the analyses.
Comparisons	Primary analysis: • All statins versus placebo/usual care/no treatment If harm is found for all statins compared with control, then analyse by • Intensity categories (as defined above) • Individual agents within each intensity class
Outcomes	• Rhabdomyolysis (creatine kinase (CK)>10 times normal) • Myalgia • Liver (transaminases>3 times normal level) • New onset diabetes • Worsening of diabetes: ○ Diabetes adverse event of ketosis or glucose control complications ○ Rise in HbA1c of ≥0.5% from baseline ○ Escalation of diabetes medication • Cognitive decline (by validated questionnaire) or dementia • Haemorrhagic stroke
Study design	• RCTs • Systematic reviews of RCTs • Published NMAs and IPDs of RCT data will be considered for inclusion. If insufficient data are found, further studies will be sought as follows:

- Unblinded RCTs or systematic reviews of these (for objective endpoints only)
- N of 1 randomised trials or systematic reviews of these (for muscle pain endpoints only)

2.1.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy. This was an update of the review in the 2014 update of CG181, and new data have been added into the previous analyses.

The following changes were also made to the approach taken in 2014:

- The outcomes of worsening of diabetes, cognitive decline or dementia and haemorrhagic stroke were added. All previously included studies were reviewed and any data on these outcomes was extracted, assessed for risk of bias and added to the analysis.
- Unblinded RCT data for subjective outcomes was removed from the analyses.
- The primary analysis was all statins compared with placebo, and different statin intensities categories were only analysed if harm was found in the primary analysis.

A call for evidence was also undertaken to identify any additional data that could address this review question. No trials that met the protocol criteria were identified from the submissions (see Appendix K). However, 3 systematic reviews were identified from the reference lists of submitted published articles that were ordered for consideration; one of these was subsequently included in the review.[172]

2.1.3 Adverse effect evidence

2.1.3.1 Included studies

A search was conducted for randomised trials assessing the efficacy of UK-licenced statins for cardiovascular risk reduction. Seven randomised trials reported in 10 papers were added to the review;[29, 75, 78, 83, 88, 105, 116, 192, 194, 195] and 24 previously included studies were also retained in the analysis.[9, 12, 24, 25, 27, 34, 39, 47, 52, 74, 90, 94, 99-101, 108, 112, 114, 119, 127, 129, 134, 139, 141, 143, 144, 147, 151, 156, 159, 162, 164, 165, 167] These are summarised in Table 16.

Two published systematic reviews were included. These were both identifed from sources other than the database search. One[172] was identified through reference list searching of submissions in the call for evidence and the other[53], published after the search cut-off, was identified by a committee member. These are summarised in Table 17.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

Placebo-controlled studies

The 30 placebo controlled studies are summarised in Table 16 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 18).

Among the placebo-controlled studies, the following populations were represented (studies may be counted in more than one category):

- Primary prevention (16 studies)[12, 27, 29, 39, 47, 83, 88, 108, 114, 119, 147, 162, 165, 192, 194]
- Secondary prevention (12 studies)[9, 24, 75, 94, 101, 112, 139, 143, 144, 151, 164, 167]

- Type 2 diabetes (3 studies)[27, 39, 90]
- Chronic kidney disease (2 studies)[25, 116]
- Rheumatoid arthritis (1 study)[88]

No studies were identified in people with type 1 diabetes.

Active-control studies

These were not included in the review because no harm was found in terms of clinically important differences based on the absolute risk difference in the primary analysis of any statin versus placebo.

Systematic reviews

Additional data not published in the primary trial reports was available from 2 published systematic reviews.[53, 172] Data were extracted only for the individual trials that met our review protocol, and risk of bias was assessed by checking the original trial reports because this was not provided in the published systematic reviews.

These data were incorporated into the guideline analyses as follows:

- Muscle adverse event data from an individual patient data meta-analysis[53]
  - The outcome of 'any muscle pain' was used as the closest match to the review protocol 'myalgia'.
  - The outcome of 'myopathy' was used as the closest match to the review protocol 'rhabdomyolysis'. This included any event coded as myopathy or rhabdomyolysis owing to the frequent absence of creatine kinase data.
  - Outcome data from individual patient analyses were not pooled with the composite data from other trials included in our analyses because the data acquisition was significantly different.
- New-onset diabetes data.[172]

Composite data not published in the original trial reports were available for this outcome from 2 placebo controlled trials.[9, 101] These data were pooled with the data available from other primary reports, using the number without diabetes at baseline as the denominator. This was deemed appropriate because event rates for studies included in both the published systematic review and in this guideline analysis were the same.

2.1.3.2 Excluded studies

The review undertaken in the previous update of the guideline was used as a basis for this updated review. Of the studies included previously, a total of 2 head-to-head statin trials were excluded from the 2014 analysis in this updated review because one of the interventions was simvastatin 80 mg, which is no longer used due to safety concerns.[18, 50]

One study comparing low versus low intensity statins was also removed from the updated analysis as this was not a comparison of interest in the current review protocol.[79]

As noted in section 1.1.4.2 Excluded studies, heart failure populations are excluded from the analysis.

Six potentially relevant Cochrane reviews[2-6, 181] were identified but could not be included; 5 because they did not include any outcomes relevant to the protocol[2-6] and 1 because all relevant studies were already included in the 2014 update of this guideline.[181] However, all studies included in the reviews were cross-checked for inclusion in this review.

See the excluded studies list in Appendix J.

2.1.4 Summary of studies included in the adverse effect evidence

Table 16: Summary of studies comparing statins versus placebo for adverse effects

Study name	Population	Intervention 1: class	Intervention 1: details	Number randomised intervention group	Comparison	Number randomised comparison group	Follow up
Adults without established CVD							
Anderssen 2005[12] HYRIM	Adults without established CVD	Low-intensity statin	Fluvastatin 40 mg	283	Placebo	285	4 years
Anon 2002[108] ALLHAT-LLT	Adults without established CVD	Low-intensity statin	Pravastatin 40 mg	5170	Placebo	5185	Mean 4.8 years
Mou 2016[116]	Adults with CKD (Biopsy-proven chronic glomerulonephritis) without established CVD	Low-intensity statin	Pravastatin 20 mg	25	Usual care – open label	23	96 weeks (2 years)
Nakamura 2006[119] MEGA	Adults without established CVD	Low-intensity statin	Pravastatin 20 mg	3866	Placebo	3966	Mean 5.3 years
Shepherd 1995[165] WOSCOPS	Adults without established CVD	Low-intensity statin	Pravastatin 40 mg	3302	Placebo	3293	4.9 years
Baigent 2005[25] UK-HARP-I	Adults with CKD without established CVD (<9% had prior vascular disease)	Medium-intensity statin	Simvastatin 20 mg	224	Placebo	224	1 year
Beishuizen 2005[27]	Adults with type 2 diabetes without established CVD	Medium-intensity statin	Simvastatin 20 mg	125	Placebo	125	2 years
Colhoun 2004[39] CARDS	Adults with type 2 diabetes without established CVD	Medium-intensity statin	Atorvastatin 10 mg	1429	Placebo	1412	Median 3.9 years
Keech 1994[83]		Medium-intensity statin	Simvastatin 20mg	208	Placebo	207	3 years

Study name	Population	Intervention 1: class	Intervention 1: details	Number randomised intervention group	Comparison	Number randomised comparison group	Follow up
	Adults at higher-than-average risk of CHD without established CVD	Medium-intensity statin	Simvastatin 40mg	206			
Mok 2009[114]	Adults without established CVD	Medium-intensity statin	Simvastatin 20 mg	113	Placebo	114	2 years
Sever 2003[162] ASCOT-LLA	Adults without established CVD	Medium-intensity statin	Atorvastatin 10 mg	5168	Placebo	5137	Median 3.3 years
Bosch 2019[29, 106, 192] HOPE-3	Adults with additional clinical cardiovascular risk factor without established CVD	High-intensity statin	Rosuvastatin 10mg ± blood pressure lowering (candesartan-hydrochlorothiazide)	807	Placebo ± blood pressure lowering (candesartan-hydrochlorothiazide)	819	Median 5.7 years
Crouse 2007[47] METEOR	Adults without established CVD	High-intensity statin	Rosuvastatin 40 mg	702	Placebo	282	2 years
Kitas 2019 [88] TRACE-RA	Adults with rheumatoid arthritis without established CVD	High-intensity statin	Atorvastatin 40mg	1504	Placebo	1498	Median 2.51 years
Ridker 2008[147] JUPITER	Adults without established CVD	High-intensity statin	Rosuvastatin 20 mg	8901	Placebo	8901	Median 1.9 years
Yusuf 2016[106, 192] HOPE-3	Adults with additional clinical cardiovascular risk factor without established CVD	High-intensity statin	Rosuvastatin 10mg	3181	Placebo	3168	Median 5.7 years
Zhang 2019[194]	Adults with hypertension without prior stroke	High-intensity statin	Rosuvastatin 10mg	366	Placebo	366	59.8 months
Adults with established CVD							

Study name	Population	Intervention 1: class	Intervention 1: details	Number randomised intervention group	Comparison	Number randomised comparison group	Follow up
Anon 1998[139] LIPID	Adults with established CVD	Low-intensity statin	Pravastatin 40 mg	4512	Placebo	4502	6.1 years
Anon 2000[144] GISSI	Adults with established CVD	Low-intensity statin	Pravastatin 20 mg	2138	No treatment – open label	2133	Mean 23 months
Hosomi 2015[75] J-STARS	Adults with established CVD (history of non-cardioembolic ischemic stroke)	Low-intensity statin	Pravastatin 10 mg	793	No treatment – open label	785	5 years
Riegger 1999[151]	Adults with established CVD	Low-intensity statin	Fluvastatin 40 mg	187	Placebo	178	1 year
Shepherd 2002[164] PROSPER	Adults with established CVD	Low-intensity statin	Pravastatin 40 mg	2891	Placebo	2913	Mean 3.2 years
Anon 1994[143] 4S	Adults with established CVD	Medium-intensity statin	Simvastatin 20 mg	2221	Placebo	2223	5.4 years
Lemos 2003[101] LIPS	Adults with established CVD	Medium-intensity statin	Fluvastatin 80 mg	844	Placebo	833	3–4 years
Meade 1999[112] HPS	Adults with established CVD	Medium-intensity statin	Simvastatin 40 mg	10269	Placebo	10267	5 years
Shukla 2005[167]	Adults with established CVD	Medium-intensity statin	Atorvastatin 10 mg	75	Placebo	75	1 year
Amarenco 2006[9] SPARCL	Adults with established CVD	High-intensity statin	Atorvastatin 80 mg	2365	Placebo	2366	Median 4.9 years
Athyros 2002[24] GREACE	Adults with established CVD	High-intensity statin	Atorvastatin 20 mg	800	Usual care - open label	800	Mean 3 years
Koren 2004[94] ALLIANCE	Adults with established CVD	High-intensity statin	Atorvastatin up to 80 mg Median dose: 40.5 mg	1217	Usual care – open label	1225	Mean 51.5 months

Study name	Population	Intervention 1: class	Intervention 1: details	Number randomised intervention group	Comparison	Number randomised comparison group	Follow up
			45% of patients received 80 mg				
Adults with or without established CVD							
Knopp 2006[90] ASPEN	Adults with type 2 diabetes (79% without established CVD)	Medium-intensity statin	Atorvastatin 10 mg	1211	Placebo	1199	Median 4 years
Lemos 2013[100]	Adults with CKD with or without established CVD	High-intensity statin	Rosuvastatin 10 mg	22	Placebo	29	2 years

Table 17: Summary of systematic reviews comparing statins versus placebo for adverse effects

Systematic review	Review methods	Outcomes reported	Protocol outcome(s)	Comments
CTT group 2022[53]	Individual participant data meta-analysis of statin trials with ≥1000 participants and 2-yr follow-up Unpublished data from trial PI/sponsor Unclear if outcomes were consistently reported or recorded within included trials as often not in primary papers (although CTT sought such info on this)	Any muscle pain (myalgia, limb pain, other musculoskeletal pain, muscle cramp or spasm) Myopathy (any event coded as myopathy or rhabdomyolysis owing to the frequent absence of creatine kinase data)	Myalgia Rhabdomyolysis (CK >10x ULN)	Muscle pain event rates much higher than in trial reports Rhabdomyolysis events more similar to trials (some higher, some lower) Variation in methods used to record muscle symptoms
Swerdlow 2015[172]	Summary-level meta-analysis. Previously unpublished data for 2 placebo-controlled trials (LIPS [supplied by industrial sponsor] and SPARCL [published 2011]).	New-onset diabetes, as defined in trials: adverse event report or physician report; glucose lowering therapy; raised fasting plasma glucose [≥7.0 mmol/L] on at least one occasion; or T2D defined according to WHO 1999 criteria.	New-onset diabetes	

See Appendix D for full evidence tables

2.1.5 Summary of the adverse effect evidence

Placebo comparison

Table 18: Clinical evidence summary: statins versus placebo

Outcomes	№ of participants (studies) *Follow-up (range)**	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo: adverse effects	Risk difference with Statins
Rhabdomyolysis ('myopathy' from IPD analysis)	103020 (13 RCTs) *1 – 6.1 years*	⨁⨁⨁◯ Moderate[a]	OR 2.12 (1.20 to 3.73)[b]	0 per 1,000	0 fewer per 1,000 (0 fewer to 0 more)
Rhabdomyolysis from studies not in IPD analysis	9848 (9 RCTs) *1 – 5 years*	⨁⨁◯◯ Low[c]	Not estimable	1 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)
Myalgia ('Any muscle pain' from IPD analysis)	103020 (13 RCTs) *1 – 6.1 years*	⨁⨁⨁⨁ High	RR 1.02 (1.01 to 1.04)	264 per 1,000	5 more per 1,000 (3 more to 11 more)
Myalgia data from studies not in IPD analysis	1852 (3 RCTs) *2 – 3 years*	⨁◯◯◯ Very low[d,e]	RR 0.95 (0.70 to 1.28)	101 per 1,000	5 fewer per 1,000 (30 fewer to 28 more)
Liver adverse events	102862 (20 RCTs) *1 – 5.7 years*	⨁⨁⨁◯ Moderate[f]	OR 1.70 (1.46 to 1.99)	5 per 1,000	0 fewer per 1,000 (0 more to 0 more)
New onset diabetes	95317 (14 RCTs) *1.9 – 5.7 years*	⨁⨁⨁⨁ High	RR 1.11 (1.04 to 1.17)	43 per 1,000	5 more per 1,000 (2 more to 7 more)
Worsening of diabetes	621 (1 RCT) *3 years*	⨁◯◯◯ Very low[e,g,h]	OR 4.48 (0.07 to 286.49)	0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)
Haemorrhagic stroke	68050 (6 RCTs) *1 – 6.1 years*	⨁⨁⨁◯ Moderate[h]	RR 1.17 (0.92 to 1.49)	3 per 1,000	1 more per 1,000 (0 fewer to 2 more)

New-onset dementia	22162 (2 RCTs) *5 – 5.7 years*	⊕◯◯◯ Very low[e,j]	RR 1.11 (0.72 to 1.70)	4 per 1,000	0 fewer per 1,000 (1 fewer to 2 more)
Cognitive decline or dementia - High intensity vs Placebo - decrease of at least 5 points on DSST, 2 points on mMoCA and 10% on TMT-B	1626 (1 RCT) *5.7 years*	⊕⊕◯◯ Low[k]	RR 1.01 (0.95 to 1.07)	731 per 1,000	7 more per 1,000 (37 fewer to 51 more)
Cognitive decline or dementia - High intensity vs Placebo - based on changes in MMSE or DSE score	732 (1 RCT) *5 – 5.7 years*	⊕⊕⊕◯ Moderate[l]	RR 0.57 (0.40 to 0.83)	186 per 1,000	80 fewer per 1,000 (111 fewer to 32 fewer)
Cognitive decline or dementia - Medium intensity vs Placebo - cognitive impairment	10180 (1 RCT) *3.3 years*	⊕◯◯◯ Very low[e,m,n]	RR 0.96 (0.59 to 1.58)	6 per 1,000	0 fewer per 1,000 (3 fewer to 4 more)
Cognitive decline (change from baseline) - Low intensity vs placebo: Mini mental state examination (scale 0-30 - higher is better)	5804 (1 RCT) *3.2 years*	⊕⊕◯◯ Low[o,p]	-	-	MD 0.06 points

**Some studies reported follow-up as a mean and others as a median value*
a. Outcome indirectness: creatine kinase levels not used in the definition
b. Peto odds ratio used instead of risk difference because summary statistics using risk difference were not informative for committee discussion for this outcome and only 1 study had zero events in both arms.
c. Sample size <80% of optimal information size
d. Majority of evidence at high risk of attrition bias
e. 95% confidence interval crosses both MIDs (0.8 and 1.25)
f. Serious heterogeneity (I^2 = 55%) not explained by statin intensity subgroups
g. High risk of attrition bias (number missing greater than event rate) and high risk of outcome reporting bias (self-reported)
h. Serious outcome indirectness: definition does not match the protocol
i. 95% confidence interval crosses one MID (1.25)
j. Serious risk of outcome reporting bias: unclear how defined or if consistently recorded for all participants, and not prespecified
k. Serious risk of selection bias: prespecified subgroup analysis among those aged >70 years but not stratified at randomisation for this variable, and not all participants agreed to the cognitive assessment. Serious risk of outcome reporting bias: not prespecified. For baseline and change scores on the assessment tools see full evidence table.
l. 95% CI crosses one MID (0.8)
m. Unclear allocation concealment and outcome definition
n. Serious outcome indirectness: unclear if a validated questionnaire was used
o. Final scores not reported, only the difference in change from baseline, with the direction of effect unclear.
p. MID = 0.775 (0.5 x median baseline SD for MMSE score)

See Appendix F for full GRADE tables.

3 Cost-effectiveness of statins

3.1 Economic evidence

New studies evaluating the cost effectiveness of statins were sought since the search cut-off date in the previous update of CG181 (November 2013). Studies that were previously included in CG181 were also considered for inclusion in this update. Studies published before 2007 and with a USA setting were excluded in line with the updated economic review protocol (see Appendix A). New studies and relevant studies from the 2014 update of CG181 are described here.

Economic modelling was undertaken as part of the 2014 CG181 update comparing low, medium and high intensity statins at different cardiovascular risk levels. This is also described in this section.

Note that although the clinical review is not stratified by population on the basis that relative treatment effects are likely to be similar, absolute effects, and so cost-effectiveness, will vary by baseline risk of cardiovascular events and so studies are presented by population.

Note that a call for evidence was made for new evidence addressing research recommendation 3.2: "What is the improvement in the cost-effectiveness metrics for statin therapy in reducing CVD that can be obtained when using a complete individual patient-based outcomes meta-analysis data set compared with using published outcomes data?". This did not identify any additional includable studies (see Appendix K).

3.1.1 Included studies

6 economic evaluations (2 new since the CG181 2014 update) were included that compared statins with either no statin or between statins.

- **People with established CVD (secondary prevention) – 3 studies**
  - Two published analyses included in the CG181 2014 update[15, 121]
  - The original economic modelling analysis undertaken for the CG181 2014 update[120]
  - No additional studies were included published since the CG181 2014 update.
- **People without established CVD (primary prevention) – 3 studies**
  - 1 published analysis included in the CG181 2014 update[111]
  - The original economic modelling analysis undertaken for the CG181 2014 update[120]
  - 1 new study published since the CG181 2014 update – an external update of the CG181 2014 update model[68]
  - Note that the original CG181 2014 update modelling included a separate analysis for people with type 2 diabetes using UKPDS for CV risk. However, as QRISK was recommended for use in people with type 2 diabetes in 2014, the main primary prevention population analyses are considered appropriate for this population (and the UKPDS analysis is not presented below).
- **People with CKD – 1 study**
  - 1 new economic evaluation published since the CG181 2014 update[157]

These are summarised in the economic evidence profiles below (Table 19 to Table 23) and the economic evidence tables in Appendix H.

3.1.2 Excluded studies

40 economic studies relating to this review question were identified but were excluded due to limited applicability and/or methodological limitations or the availability of more applicable evidence. 29 of these were assessed as part of the CG181 2014 update and 11 were new

studies identified and assessed as part of this update. These are listed in Appendix J, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix G.

Note also that two studies that were included in the CG181 2014 update (Choudhry, 2011[37] and Erickson, 2013[55]) were excluded due to having a US perspective, and one (Ward 2005[184]) was excluded as it was published before 2007 in line with the revised economic review protocol for this update. The latter was the model developed for the original NICE technology appraisal of statins, and was updated and superseded by the 2014 CG181 modelling.

3.2 Summary of included economic evidence

3.2.1 People with established CVD (secondary prevention)

Table 19: Economic evidence profile: high, medium and low intensity statin versus no statin, for secondary prevention in adults with CVD

Study	Applicability	Limitations	Other comments	Total cost[d]	Total QALYs	Cost effectiveness	Uncertainty
NICE CG181, 2014 (UK)[120]	Partially applicable[a]	Minor limitations[b]	• Cost–utility analysis • Decision model incorporating CV health states; diabetes AE included • Comparators: 1. no statins 2. low-intensity statins[c] 3. medium-intensity statins[c] 4. high-intensity statins[c] • People with established CVD • Effectiveness: meta-analysis of placebo-controlled trials from 2014 CG181 systematic review and meta-analysis • Annual statin costs: UK 2014 costs (see Table 24) • Time horizon: lifetime • Base case men age 60 years	1. £9,404 2. £11,116 3. £11,057 4. £11,057	1.6.293 2.6.579 3.6.675 4.6.841	• High intensity vs no treatment: £2,959 per QALY gained • Low and medium intensity ruled out by dominance or extended dominance	• High-intensity statin treatment was cost effective 86.6%, medium intensity 11.7%, low intensity 1.7% and no treatment in 0%. • High intensity statin was the most cost-effective option for all age (40, 50, 60, 70) and gender subgroups. • ICER using A80 instead of A20 cost for high intensity: £3,275 per QALY gained. • Threshold analysis within high intensity class: A40/A80 cost effective compared to A20 if 1%/2% more effective.[e] • Conclusions not sensitive to a wide range of sensitivity analyses except when all risk ratios are taken at end of range and if rate of non-CV death not constant between statin categories. • Conclusions not sensitive to removal of all-cause mortality affect (2022).[f]

Abbreviations: CVD = cardiovascular disease; ICER = incremental cost-effectiveness ratio; QALY: quality-adjusted life year

(a) Designed in accordance with NICE reference case. 2014 costs may not reflect current costs; rosuvastatin has since become available generically although is not used in the base case analysis and is not the lowest cost high intensity statin. The instrument and value sets are not reported for utility weights used to estimate QALYs.

(b) Transition probabilities after CVD first event are potentially out of date however conclusions weren't sensitive to this. Inclusion of an effect of statins on non-CV mortality may not be appropriate but conclusions aren't sensitive to exclusion of this. Based on a published update of the 2014 CG181 model for primary prevention, some inputs could be more up to date, however most changes reduced the ICER in the primary prevention model and are considered highly unlikely to change secondary prevention conclusions.

(c) Low intensity = F20-40, P10-40 and S10; medium intensity = A10, F80, R5 and S20-40; high intensity = A20-80, R10-40 and S80.
(d) 2014 UK pounds. Cost components incorporated: statin costs and monitoring, acute and ongoing CVD costs, diabetes adverse effect costs. Lowest cost statin in each intensity category used in base case: S10, S20, A20.
*(e) 1% increase in effectiveness is applied as: revised RR for high vs placebo = 1 - ((1-original RR) * 1.01). For example, RR with 1% increase in effectiveness if original RR 0.8: revised RR = 1 – ((1-0.8)*1.01)) = 0.798.*
(f) The base case analysis included a benefit for non-cardiovascular mortality with statins but this may not be appropriate. Risk ratios for non-cardiovascular mortality were changed to 1 for all statin comparators. Low and medium intensity options remained ruled out by dominance or extended dominance. The ICER for high intensity (A20) compared to no treatment increased to £3,171 from £3,077 (deterministic analysis).

Table 20: Economic evidence profile: high intensity statins versus medium intensity statins for secondary prevention in adults with CVD

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
NICE CG67 (UK)[121]	Partially applicable (a)	Potentially serious limitations (b)	• Cost–utility analysis • Decision model • Comparators: ○ high-intensity statins (atorvastatin 80 mg) ○ lower-intensity statins (simvastatin 20 mg, atorvastatin 10 mg or pravastatin 40 mg) • People with either ACS or CHD (separately) • Effectiveness: meta-analysis of 4 head-to-head trials • Annual statin costs: UK 2008 costs atorvastatin 80 mg: £368 • Time horizon: lifetime • Cost year: 2008 (UK)	ACS: £1,418 CHD: £2,389	ACS: 0.32 QALYs CHD: 0.08 QALYs	ACS: £4,397 per QALY gained CHD: £28,361 per QALY gained	Both conclusions (high-intensity statins are cost effective at a threshold of £20,000 per QALY for ACS but not for CHD) were robust to one-way sensitivity analyses varying effectiveness of treatment, age, cost of CVD event states, utilities, and number of consultations. The results were sensitive to the cost of statins, with high-intensity treatment dominating lower-intensity statins for CHD patients when the cost of simvastatin 80 mg (£65) is used instead of atorvastatin 80 mg, assuming equal effectiveness.
Ara 2009 (UK)[15]	Partially applicable(d)	Potentially serious limitations(e)	• Cost–utility analysis • Decision model • Comparators:	S80−S40: £588 A80−S40: NR(g)(g)	S80−S40: 0.111 QALYs A80−S40: NR(g)	S80−S40: £5,319 per QALY gained	In the base case scenario in the paper(f) the conclusion was found to be robust to all sensitivity analyses apart from when the relative clinical

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			○ simvastatin 80 mg (S80, high intensity)[c] ○ atorvastatin 80 mg (A80, high intensity) ○ rosuvastatin 40 mg (R40, high intensity) ○ simvastatin 40 mg (S40, medium intensity) • People with recent ACS • Effectiveness: taken from a network meta-analysis of 28 trials of statin effectiveness in reducing LDL cholesterol, converted to reductions in CVD events using published analysis of relationship between LDL lowering and CVD events • Annual statin costs: UK 2008 costs (S40: £17, S80: £34, R40: £387), with A80 projected to be £92[f] • Time horizon: lifetime • Cost year: 2007 (UK)	R40−S40: £3,941	R40−S40: 0.316	A80−S40: £3,172 per QALY gained R40−S40: £12,484 per QALY gained A80−S80: A80 dominates S80 (is less costly and more effective) R40−A80: ICER NR, but A80 is stated as the preferred, cost-effective treatment at a threshold of £20,000 per QALY gained	effectiveness of medium and high intensity statins are varied. These sensitivity analyses were not carried out relating to the scenario with lower-cost (£92 per year) A80 shown here. Different assumptions regarding adherence to statins were also studied, but these also had only moderate effect on cost effectiveness, both in the base case and for lower-cost A80 – with the ICER for A80 versus S40 varying between £3,155 and £7,331 dependent on the pattern of adherence. The analysis was also repeated with a third, lower possible A80 cost of £21 per year. The ICER was not stated, but at this cost A80 was the preferred, cost-effective intervention at all cost-effectiveness thresholds

Abbreviations: ACS: acute coronary syndrome; CHD: coronary heart disease; CV: cardiovascular; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

(a) Designed in accordance with NICE reference case.

(b) The costs used, especially for statins, are out of date, making the results unreliable. This is unlikely to affect the conclusion favouring high-intensity statins for higher risk (ACS) secondary prevention patients but is likely to change the conclusion favouring lower-intensity statins for lower risk (CAD) secondary prevention patients.

(c) Note that simvastatin 80mg was removed from the 2022 review protocol as it is no longer used.

(d) Based on UK ACS population, following NICE reference case.

(e) Model does not account for any adverse events. Effectiveness of statins in reducing CVD events is based on a meta-analysis of effectiveness in reducing LDL cholesterol, linked to relationship between cholesterol reduction and CVD event reduction rather than direct evidence of reduction in CVD events. Cost of atorvastatin 80 mg assumed to fall to £92 or £20.78 annually once off patent; actual current cost is lower.

(f) The papers examined a base case using the then current (branded) atorvastatin 80 mg price of £368 per year, but conducted a sensitivity analysis using potential future annual generic costs of £92 – it is this sensitivity analysis which is summarised in this table. Current costs are lower.

(g) Incremental costs and outcomes and ICERs are given for the base case (in which all high-intensity statins are cost effective compared to simvastatin 40 mg at a cost-effectiveness threshold of £20,000 per QALY gained, but with rosuvastatin 40 mg dominating atorvastatin 80 mg and being cost effective compared to simvastatin 80 mg), but not for the sensitivity analyses with lower-priced atorvastatin shown here.

3.1.2 People without established CVD (primary prevention)

Table 21: Economic evidence profile: statin versus no statin, for primary prevention in adults without CVD

Study	Applicability	Limitations	Other comments	Total cost	Total QALYs	Cost effectiveness	Uncertainty
McConnachie 2014[111] (UK)	Partially applicable[(a)]	Minor limitations[(b)]	• Cost–utility analysis • Intervention: pravastatin 40 mg (low intensity statin) for 5 years versus placebo, followed up for a further 10 years (with similar statin usage in both arms after end of trial) • Effectiveness: taken from WOSCOPS trial (UK) with 10 years further follow-up hospital admissions data from linked NHS health records • Annual statin costs: pravastatin 40 mg (£36) • Follow up: 15 years	−£710[(c)]	0.136 QALYs	5-year statin treatment is dominant	95% CI for cost saving per person: −£1,090 to −£320. 95% CI for QALYs gained per person: 0.025 to 0.247. One-way sensitivity analyses showed that the intervention was still cost saving if hospital costs or ongoing costs of CVD events were varied by ±25%. If statin and monitoring costs were increased by 400% then it was no longer cost saving but still highly cost effective.
NICE CG181, 2014 (UK)[120]	Partially applicable[(d)]	Potentially serious limitations[(e)]	• Cost–utility analysis • Decision model incorporating CV health states; diabetes AE included • Comparators:	CV risk 10%[(h)] 1. £3,013 2. £4,353 3. £4,199	CV risk 10% 1.11.414 2.11.619 3.11.698	CV risk 10% • High intensity vs no treatment:	• At 10% CV risk high-intensity statins were cost effective 74.5%, medium 25.5%, low 0% and no treatment 0%.

Study	Applicability	Limitations	Other comments	Total cost	Total QALYs	Cost effectiveness	Uncertainty
			1. no statins 2. low-intensity statins[f] 3. medium-intensity statins[f] 4. high-intensity statins[f] • People without established CVD; analysis by CV risk • Effectiveness: meta-analysis of placebo-controlled trials from 2014 CG181 systematic review and meta-analysis • Annual statin costs: UK 2014 costs (see Table 24) • Time horizon: lifetime • Base case age male 60 years; 10% CV risk costs and QALYs shown here • CV risk: QRISK2[g]	4. £4,285	4.11.723	£4,125 per QALY gained • Low and medium intensity ruled out by dominance or extended dominance 10-year CV risk threshold high intensity remains CE: 6.8%	• High intensity remains cost-effective if A80 cost used (analysis within high intensity class not undertaken). • At 10% CV risk high intensity statins were the most cost-effective option for all age (40, 50, 60, 70) and gender subgroups. • Risk threshold high intensity remain CE is 5.2% for women age 60yrs; it increases with age for both men and women to a max of 6.8% and 7.3% at age 70 years); medium intensity is CE to a lower risk threshold. • Conclusion for base case were not sensitive to a wide range of sensitivity analyses except when all risk ratios are taken to be at the end of their range and if the rate of non-CV death was not constant between statin categories, and when baseline transition probabilities were reduced by 20% in combination with using A80 costs.
Guthrie 2023 (external update of 2014 CG181 model) (UK) [68]	Directly applicable[i]	Minor limitations[j]	• CG181 model above with some model inputs updated; adjustment for competing risk of non-CV death; removal of diabetes AE; removal of effect on non-CV death	CV risk 10%[k] 1.£6,943/ £6,013 2.£7,868/ £6,933 3.£7,336/ £6,463	CV risk 10% 1.13.460/ 12.057 2.13.616/ 12.191 3.13.724/ 12.284	CV risk 10% • High intensity vs no treatment: £1,217/ £1,469 per QALY gained	• At 10% CV risk high-intensity statin treatment was cost effective 100%. • Conclusions for base case not sensitive to wide range of one-way sensitivity analyses except when a risk reduction was applied for non-

Study	Applicability	Limitations	Other comments	Total cost	Total QALYs	Cost effectiveness	Uncertainty
			• Annual statin costs: UK 2021 costs (see Table 24) • Base case men/women age 60 years; 10% CV risk costs and QALYs shown here • CV risk: QRISK3	4.£7,353/ £6,443	4.13.797/ 12.350	• Low and medium intensity ruled out by extended dominance or dominance	CV death for low or medium statin only. • High intensity statins were the most cost-effective option irrespective of CV risk in all age and gender subgroups, except some very low risk scenarios in older people where medium intensity statins were the most cost-effective option (M 2% risk and >74yrs, M2-4% risk and >78yrs, F 2% risk and >76yrs). • Risk threshold: when two-way combinations of age (40-80 years) and 10-year CV risk (2-40%) were analysed, high intensity statins were the most cost-effective option for all plausible risk/age combinations analysed. • Conclusions were not sensitive to lower secondary CVD event rates, the re-inclusion of a diabetes adverse effect as per 2014 CG181 model base case or updating of RRs to match this guideline update and September 2022 statin costs. High intensity statins remained cost-effective in the same age/risk groups or increased to all. • In exploratory analyses including direct treatment disutility (a type of process utility aiming to reflect the inconvenience of taking medication) high intensity statins

Study	Applicability	Limitations	Other comments	Total cost	Total QALYs	Cost effectiveness	Uncertainty
							were no longer cost effective in certain age/risk groups.

Abbreviations: AE = adverse event; CVD = cardiovascular disease; ICER = incremental cost-effectiveness ratio; QALY: quality-adjusted life year

(a) Looks at Scottish men aged 45–54 at start. Follows NICE reference case where possible. Utility values taken from Ward 2005. Doesn't look at different statin intensities. 2012 costs may not reflect current costs.

(b) Baseline event rate based on the WOSCOPS study, not a meta-analysis or whole UK epidemiology – reflects men aged 45–54 in West Scotland, but likely to be relatively similar to men throughout UK. Effectiveness of pravastatin based on WOSCOPS rather than a meta-analysis of multiple trials, but WOSCOPS was carried out in the UK so is highly relevant. Uses real-world NHS resource use over a 15 year follow up, applying 2012 NHS HRG costs and 2012 cost of pravastatin. The current pravastatin costs are lower (£21 a year) while the current HRG costs are likely to be higher.

(c) 2012 UK pounds.

(d) Designed in accordance with NICE reference case. 2012 costs and earlier resource use may not reflect current UK context; more recent CVD event cost data was found to be available in subsequent Guthrie 2023 model update. [68] The instrument and value sets are not reported for utility weights used to estimate QALYs.

(e) Methods to incorporate CV risk and risk reduction in analysis improved in subsequent Guthrie 2023 model update. Inclusion of non-CV mortality reduction with statins applied which may not reflect current evidence interpretation. Transition probabilities after CVD first event are potentially out of date however conclusions weren't sensitive to this. Conclusions about the CVD risk threshold at which high intensity statins are cost-effective for a primary prevention population could be affected by limitations.

(f) Low intensity = F20-40, P10-40 and S10; medium intensity = A10, F80, R5 and S20-40; high intensity = A20-80, R10-40 and S80. In all cases, once a first CVD event occurs (and they enter the secondary prevention part of the model) people receive A80 in line with the 2014 CG181 recommendation for secondary prevention.

(g) A separate analysis was also run for people with type two diabetes with CV risk based on UKPDS however, as QRISK2 was recommended for use in people with type 2 diabetes in the CG181 2014 update only the main analysis using QRISK2 is presented here.

(h) 2014 UK pounds. Cost components incorporated: statin costs, acute and ongoing CVD costs, diabetes adverse effect costs. Lowest cost statin in each intensity category used in base case: S10, S20, A20.

(i) Follows NICE reference case and uses recent UK statin costs and has updated CVD event costs.

(j) Transition probabilities after CVD first event are potentially out of date however conclusions weren't sensitive to this. Does not include diabetes adverse effect included in 2014 CG181 model but effect size may not to be clinically important and additional sensitivity analysis using 2014 CG181 base case assumptions did not affect conclusions. RRs were based on the 2014 CG181 clinical review and meta analyses which have been updated as part of this update however conclusions were largely unaffected in additional sensitivity analysis.

(k) 2021 UK pounds. Cost components incorporated: statin and monitoring costs, acute and ongoing CVD costs. Lowest cost statin in each intensity category used in base case: S10, S20, A20.

Guthrie 2023: risk-threshold where high intensity statins are cost effective

As described in the evidence table above, Guthrie 2023 reported two-way results where age was varied between 40 and 80 years and 10-year risk was varied between 2% and 40%.[68] This found that high intensity statins were cost effective for every age/risk combination except:

- Men aged 74 to 80 years with 2% risk
- Men aged 80 years with 4% risk
- Women aged 76 to 80 years with 2% risk

To help interpretation of these results, the QRISK3 online calculator was used to calculate the minimum possible 10-year CV risk at different ages and the risk for a typical person of white ethnicity without comorbidities. These are shown in Table 22. The input values used are detailed in the table footnotes. The minimum risk is calculated using the most favourable inputs allowed by the calculator rather than the minimum that occurs in reality although it is assumed the allowed ranges were based on what was considered possible, albeit ones that might occur rarely. From this it can be seen that the scenarios that high intensity statins were not the most cost-effective option are not plausible real-world scenarios. Therefore it can be concluded that the analysis found high intensity statins to be cost effective for all people aged 40 to 80 years with a 10-year CV-risk above 2%. It is also noted that minimum possible risk and typical risk for a person of white ethnicity without comorbidities and a non-smoker aged 40 years of age are all below 2% risk.

Table 22: 10-year CV risk by age (QRISK3)

Age	Female		Male	
	Min possible[a]	Typical (no comorbidities/ non-smoker)[b]	Min possible[a]	Typical (no comorbidities/ non-smoker)[b]
40	0.1%	0.7%	0.3%	1.6%
50	0.5%	2%	0.8%	4.4%
60	1.4%	5%	2%	9.3%
70	3.7%	11.7%	4.8%	17.7%
80	9.7%	24.7%	11.1%	31.5%

(a) Most favourable inputs allowed in online QRISK3 calculator selected. Ethnicity Chinese; UK postcode RH4 2BL (most favourable unclear but this is more favourable than default); non-smoker; no diabetes; no additional clinical risk indicators; minimum cholesterol/HDL ratio 1.0; minimum systolic BP 70mmHg; SD of at least two most recent systolic blood pressure readings (mmHg) 0; minimum BMI 20kg/m^2.

(b) Ethnicity 'white or not stated'; non-smoker; no diabetes; no additional clinical risk indicators; postcode, cholesterol/HDL ratio, systolic BP, SD of at least two most recent systolic blood pressure readings (mmHg) and BMI left blank and so QRISK tool has estimated – it doesn't say how but assume it is typical for age/ethnicity.

3.1.3 People with CKD

Table 23: Economic evidence profile: statins versus no statin in people with CKD

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Schlackow 2019 (UK)[157]	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Cost–utility analysis • Decision model incorporating CKD stages (3B, 4, 5, on dialysis, with kidney transplant) and	**CKD stage 3B** 2−1 £900 3-2 £100	**CKD stage 3B** 2−1 0.23 3-2 0.02	**Cost per QALY gained** **By CKD stage 3B**	Uncertainty from probabilistic analysis not available for only comparators relevant to review protocol.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			cardiovascular events (major atherosclerotic events, haemorrhagic stroke, vascular death) • Comparators: 1. No lipid lowering 2. Atorvastatin 20mg daily 3. Atorvastatin 40mg daily • People with CKD stages 3B, 4 and 5 not on dialysis[c] • Effectiveness: • Annual statin costs: UK 2019 • Time horizon: lifetime • Base case age male 60yrs • CV risk:	**4** 2−1 £3,100 3-2 £300 **5B, ND** 2−1 £4,700 3-2 £400 **5-yr CV risk** **Low (<10%)** 2−1 £2,000 3−2 £200 **Medium (10%-20%)** 2−1 £2,500 3−2 £200 **High (≥20%)** 2−1 £3,900 3−2 £300	**4** 2−1 0.30 3-2 0.03 **5B, ND** 2−1 0.27 3-2 0.02 **5-yr CV risk** **Low (<10%)** 2−1 0.27 3-2 0.02 **Medium (10%-20%)** 2−1 0.27 3-2 0.02 **High (≥20%)** 2−1 0.27 3-2 0.02	• 2 vs 1 £3,700 • 3 vs 2 £5,400 **4** • 2 vs 1 £10,400 • 3 vs 2 £11,400 **5 not on dialysis** • 2 vs 1 £18,800 • 3 vs 2 £19,800 **5-yr CV risk** **Low (<10%)** • 2 vs 1 £7,800 • 3 vs 2 £9,500 **Medium (10%-20%)** • 2 vs 1 £9,300 • 3 vs 2 £10,300 **High (≥20%)** • 2 vs 1 £14,100 • 3 vs 2 £14,900	Conclusions were not sensitive to inclusion of potential adverse effects or reduced compliance with treatment. ICERs were substantially reduced when the annual treatment costs for RRT was assumed similar to those for CKD stage 5 not on dialysis.

Abbreviations: 95% CI: 95% confidence interval; CHD: coronary heart disease; CVD: cardiovascular disease; QALY: quality-adjusted life year

(a) 2003-2011 resource use from international trial and 2009/2011 UK unit costs may not reflect current UK context.

(b) Baseline event rate based on the WOSCOPS study, not a meta-analysis or whole UK epidemiology – reflects men aged 45–54 in West Scotland, but likely to be relatively similar to men throughout UK. Effectiveness of pravastatin based on WOSCOPS not meta-analysis of multiple trials, but WOSCOPS was carried out in UK and so is highly relevant. Uses real-life NHS resource use over 15 year follow up, applying current NHS HRG costs and recent cost of pravastatin.

(c) 2012 UK pounds.

3.3 New economic modelling

New modelling was not prioritised for this topic.

3.4 Unit costs

Table 24 and Table 25 show current statin costs (September 2022) and the costs at the time of the 2014 update of CG181 to inform consideration of whether changes may affect interpretation of cost-effectiveness analyses. Usage of different preparations are also shown for information in Table 24. Differences in cost between different high intensity statins now and at the time of the 2014 CG181 modelling are shown in Table 25.

All drugs are lower cost than at the time of the 2014 CG181 update except fluvastatin. Most changes are small except for rosuvastatin which is considerably cheaper due to a generic preparation now being available.

Table 24: Statin costs and usage

Statin	Current costs		2014 CG181 costs	Usage 2021/2022
	28 days	Annual	Annual	
Atorvastatin				
10 mg	£0.66	£9	£13	9%
20 mg	£0.89	£12	£16	34%
30 mg	£24.51	£320		0%
40 mg	£0.97	£13	£20	18%
60 mg	£28.01	£365		0%
80 mg	£1.35	£18	£32	8%
Fluvastatin				
20 mg	£3.01	£39	£30	0%
40 mg	£3.39	£44	£31	0%
80 mg (2x40 mg)	£6.78	£88	£62	0%
80 mg (MR)	£19.20	£250		0%
Pravastatin				
10 mg	£1.30	£17	£15	1%
20 mg	£1.36	£18	£18	1%
40 mg	£1.64	£21	£23	1%
Rosuvastatin				
5 mg	£0.92	£12	£235	2%
10 mg	£1.07	£14	£235	1%
20 mg	£1.27	£17	£339	1%
40 mg	£1.77	£23	£387	0%
Simvastatin				
10 mg	£0.74	£10	£10	1%
20 mg	£0.77	£10	£11	9%
40 mg	£0.89	£12	£14	12%

Source: costs are from NHS Drug Tariff September 2022 online[126]; usage is based on the Prescription Cost Analysis for England 2021/22.[32]
Costs are for capsules or tablets. Chewable tablets were also available for atorvastatin 10 mg and 20 mg. Oral suspensions were also available for atorvastatin and simvastatin. Simvastatin 80 mg was also available but was not included in the updated evidence review protocol as it is no longer used and so is not included here.
Usage includes all preparations including these doses and includes those as part of combined preparations.

As shown in Table 25 the differences in costs between the high intensity statin options have reduced since the 2014 update of CG181.

In the 2014 CG181 modelling for both primary and secondary prevention the base case analyses were based on an assumption of equivalent effectiveness between all high-intensity statins due to a lack of evidence comparing the effectiveness of the different doses in terms of reducing clinical end points. Under this assumption, the cheapest high-intensity statin – atorvastatin 20 mg – would be the most cost effective and so this cost is used in the base case analyses. Atorvastatin 20 mg is still the lowest cost option however cost differences between high intensity options are now smaller. The differences between atorvastatin and rosuvastatin options have reduced substantially.

Table 25: High intensity statins cost differences

High intensity statins		2014 CG181 costs		Current costs	
		Annual	Difference vs A20	Annual	Difference vs A20
Atorvastatin	20 mg	£16	-	£12	-
	40 mg	£20	£3.26	£13	£1.04
	80 mg	£32	£15.91	£18	£6.00
Rosuvastatin	10 mg	£235	£218.75	£14	£2.35
	20 mg	£339	£322.98	£17	£4.95
	40 mg	£387	£370.86	£23	£11.47

Source: costs are from NHS Drug Tariff September 2022 online.[126]

4 The committee's discussion and interpretation of the evidence

This committee discussion combines the reviews on statin efficacy and adverse events.

4.1 The outcomes that matter most

The outcomes agreed by the committee as critical for decision making for the efficacy of statins were:

- All-cause mortality
- Cardiovascular mortality
- Non-fatal myocardial infarction (MI)
- Non-fatal ischaemic stroke
- Combined major adverse cardiovascular events (CVD mortality, nonfatal MI, nonfatal ischaemic stroke)
- Quality of life, any validated measure

For the adverse event review, the critical outcomes were agreed as:

- Rhabdomyolysis (creatine kinase at least 10 times normal)
- Myalgia
- Liver (transaminases >3 times normal level)
- New onset diabetes
- Worsening of diabetes
- Cognitive decline (by validated questionnaire) or dementia
- Haemorrhagic stroke

Evidence was available for all outcomes of interest, although quality of life was only reported by one study.

Cholesterol levels were not included as a surrogate outcome because what is of most importance to patients is whether a cardiovascular event occurs. It had already been established that data on these hard outcomes was available in the literature and therefore should be used for decision making.

However, it was agreed that details of the LDL-cholesterol reduction during treatment would be extracted, although not analysed as an outcome. This was to provide information on the achieved reductions with reference to the definitions of statin intensity based on anticipated LDL-cholesterol lowering. This will contextualise the risk reductions for the listed outcomes in terms of the LDL-cholesterol reduction that led to that effect.

4.2 The quality of the evidence

Efficacy

For the placebo comparison, the majority of the efficacy evidence was of high or moderate quality. Outcomes judged to be of moderate quality were downgraded due to imprecision. This gave the committee confidence that the reported effect estimates were likely to be representative of the true effect. One exception to this was the combined outcome of MACE for high intensity statins compared to placebo, which was graded as very low quality due to imprecision and inconsistency in the evidence. However, the committee noted that the overall direction and size of the relative effect for this outcome was consistent with the conclusions from the review and did not reduce their confidence in the findings. There were

too few studies to formally explore whether the pre-specified subgroups explained the heterogeneity, but the committee noted that differences between the studies in the definition of MACE may have contributed. However, there was insufficient detail in the study definitions to interrogate this possibility, or why less heterogeneity was seen for the low-intensity statin versus placebo analysis. Another exception was quality of life, which was only reported in one study reporting EQ-5D, however there were baseline differences in EQ-5D values and the study did not report full details of the outcome data and so this was graded as low quality.

For the head-to-head comparisons (studies comparing statins of different intensities or comparing different high intensity statin regimens), the majority of the efficacy evidence was of low or very low quality, with the most common reason for downgrading being imprecision. This reflects the smaller number of trials and so smaller pooled sample size available comparing different statin intensities or agents than for the placebo comparison.

Adverse events

The evidence for adverse muscle effects from an individual patient data (IPD) meta-analysis and for new onset diabetes was rated as high quality. Evidence for liver adverse events was of moderate quality, with downgrading due to inconsistency that was not explained by pre-defined subgroups, and haemorrhagic stroke was also of moderate quality with downgrading for imprecision. The IPD data for rhabdomyolysis was downgraded for indirectness because the outcome definition did not use the criteria of creatine kinase at least 10 times the upper limit of normal, resulting in a moderate quality rating. However, the committee agreed that the findings were still useful as they were aware that there was variability in reporting of muscle effects in most trials. The committee discussed the inconsistency in the ways that trials reported muscle pain, but agreed that this did not represent an important risk of bias or indirectness as it is variably defined in clinical practice. The evidence for muscle events from original trial reports of studies not included in the IPD analysis, worsening of diabetes and cognitive decline or dementia was mostly of low or very low quality, with downgrading often due to imprecision and risk of bias, which reduced the committees' confidence in the findings for these outcomes. The reasons for risk of bias included selection bias (subgroup analysis but not stratified at randomisation for this variable), attrition bias (the number of participants with missing data being greater than event rate), outcome reporting bias (self-reported or unclear definition). The addition of studies published since the previous update of this guideline did not alter the assessment of the quality of evidence for most outcomes. However, confidence in the findings for myalgia and the rare outcome of rhabdomyolysis was increased by the inclusion of a recently published IPD meta-analysis for these outcomes.

4.3 Benefits and harms

Efficacy

The effect estimate for most comparisons and outcomes did not change sufficiently to change the conclusions from those outlined in the previous update of the guideline.

For time-to-event outcomes, the summary statistics were very similar between the hazard ratios and relative risk estimates, but as fewer studies reported the hazard ratios, there was greater uncertainty around these estimates. Therefore, the committee have used the dichotomous data to inform their discussions to maximise the power of the analyses. It was noted that in one study the direction of effect favoured placebo for cardiovascular mortality. This was in a secondary prevention population unlike the other 2 studies in the analysis, but the reason for the inconsistency was unclear.

Placebo-controlled trials

All outcomes showed a direction of effect favouring the use of statins to reduce the risk of fatal and non-fatal cardiovascular (CV) events. The benefit was greatest for non-fatal MI for both relative and absolute risk estimates. An increasing benefit in terms of the relative risk of

events with increasing statin intensity was noted for the outcomes of CV mortality and non-fatal MI, which supports the recommendation of high intensity statins as the most effective option. This effect was supported by the newly added composite outcome of MACE, and the committee noted that based on the relative risk this outcome demonstrated a greater benefit of high intensity statins than was seen with low- or medium-intensity statins compared with placebo. However, confidence in this evidence was limited by the inconsistent way in which MACE was defined between the trials.

It was noted that the control group risk was considerably lower in the studies of high intensity statins compared to those for medium or low intensity. The committee queried why this might be and noted that these studies may have included a slightly different population that may be lower baseline risk. However, it was noted that benefit was still greater in the high intensity studies, which supports the conclusion that even lower risk groups can benefit from statin treatment.

The committee commented that even though some of the evidence was rated as low or very low quality, the direction of effect was similar throughout, and consistent with the previous guideline evidence review, increasing confidence in the evidence.

Head-to-head trials

High-intensity statins showed a benefit for reduced rates of CVD events compared to low- or medium-intensity statins.

A newly added study comparing atorvastatin 40mg and 20 mg suggested a consistent benefit of the 40 mg dose for all outcomes. However, the committee noted that this was a single, small, open-label RCT in a secondary prevention population with type 2 diabetes. They noted that the magnitude of the relative effects were greater than might be expected and that there was considerable imprecision around the point estimates, which lowered their confidence in the findings representing the true effect. Although they agreed that it is in line with the view that increased lowering of LDL-cholesterol will provide an increased benefit in CVD event reduction, the limitations in the evidence meant the committee agreed that this was not sufficient to change the recommended starting dose of 20mg atorvastatin.

They also noted that as stated in the 2014 version of the guideline, starting on the lowest effective dose may be more acceptable to some people, and increasing the number of people starting statin treatment when appropriate (as part of a shared decision) would have more impact than increasing the recommended starting dose.

The committee also noted that one study included in the previous update of this guideline compared atorvastatin 80 mg with rosuvastatin 40 mg in a secondary prevention population and found no clinically important difference in their effectiveness but that no new evidence comparing rosuvastatin with atorvastatin within the high intensity were available. It was therefore concluded, in agreement with the 2014 committee conclusion, that it was not possible to judge whether there were differences between the two statins in terms of reducing CVD events. They therefore thought appropriate to retain atorvastatin as the recommended statin to initiate, but noted that if adverse effects were experienced, one option that could be considered would be switching to rosuvastatin. The committee agreed by consensus this was consistent with what happened in clinical practice currently, and agreed to add it to the recommendations of options to consider if adverse events were experienced.

Adverse effects

As for the efficacy review, the committee agreed that the updated evidence review for adverse effects was largely supportive of the recommendations from the previous iteration of the guideline.

Placebo-controlled trials

New evidence from an IPD meta-analysis was available for the outcomes of rhabdomyolysis and myalgia. This increased the power to detect the likely true effect for these outcomes compared to the data available in the previous update of the guideline.

For rhabdomyolysis the inclusion of data from this analysis showed an increased relative risk of this adverse event in people taking statins compared to placebo, which the committee agreed represented a real effect that it was important for people to be aware of. However, they noted that the event rate for rhabdomyolysis was extremely low, which the committee discussed to be reassuring and reflective of what they see in clinical practice.

For myalgia, the committee noted that the broad definition of 'any muscle pain' used in the IPD meta-analysis resulted in much higher event rates compared to those reported in the primary trial publications that met the guideline review protocol. However, this definition had been determined based on knowledge of how data were reported across the literature, and was agreed to be as robust and consistent as possible across trials. The overall finding was for a small relative and absolute increase in cases of any muscle pain for people taking statins compared with placebo. The committee noted that it was likely the effect was largely driven by the increased risk with high-intensity statins, with which approximately 16% of people reported experiencing muscle pain. However, this was not thought to represent a clinically important harm of statins and was outweighed by the benefit seen for CVD event reduction. It was also noted that none of the trials of high-intensity statin compared to placebo used atorvastatin 20mg which is currently recommended as the first line statin for primary prevention (1 used rosuvastatin 10mg, 1 used rosuvastatin 20 mg and 1 used atorvastatin 80 mg). The committee concluded that the proportional risk increase was a reliable estimate and could be applied to specific populations with varying baseline risks.

Based on discussion of both the relative risks, which were agreed to be more generalisable to specific populations, and the absolute risks based on the trial populations, the committee agreed that a recommendation should be added to reassure people who are offered a statin that the increased risk of muscle pain associated with statin use is small and the rate of severe muscle adverse events (rhabdomyolysis) is extremely low. The committee decided this was an important addition due to the common misperception that statin use is highly likely to cause adverse muscle-related symptoms and the negative impact this has on statin uptake among people who are likely to benefit from this intervention. They noted that the evidence for high intensity statins compared with placebo reported a relative risk of 1.09, which indicates that only approximately 1 in 12 cases of muscle pain (8.3%) would actually be attributable to the statin. For the pooled analysis of any statin intensity compared with placebo this figure was even less, with approximately 1 in 51 cases of muscle pain (2%) being caused by the statin. Therefore, they also added a recommendation to reassure people who do experience muscle pain while taking a statin that this symptom is more likely to have an alternative cause unless creatine kinase levels are found to be significantly elevated.

The committee were also aware that the data from the IPD meta-analysis showed most of the increased risk of muscle events to be within the first 12 months of treatment, with no notable excess events reported beyond that time. Based on this and the evidence showing that even within the first 12 months muscle symptoms are more likely to be due to causes other that the statin treatment, the committee agreed to remove the statement in the previous recommendation to consider other causes of muscle adverse events only if statins were previously tolerated for more than 3 months.

For new-onset diabetes, the committee discussed the evidence of an incremental increase in relative risk and absolute risk difference with increasing statin intensity, which they noted as support for the increased risk being a real effect related to statins. However, the overall increase in risk was small and thought not to be clinically important in terms of an individual's personal risk. The committee discussed the heterogeneity in the definition of diabetes used between the trials, partly due to the different dates at which the trials were undertaken.

However, they discussed that relative effects may not be impacted by differing definitions even though absolute rates would be. The committee discussed the implications of the small increase in diabetes seen in the data. They highlighted that it may relate to a shift in biochemical markers that mean people meet the definition for a diagnosis of diabetes but the change is not great enough to expose people to additional risks in terms of macro- and micro-vascular complications. They also discussed that this was also the prevailing view about drug-induced diabetes from other interventions, such as beta-blockers and thiazides. Although, it was agreed that the evidence was not conclusive, the consensus opinion of the committee was that this was the most likely explanation of the data.

Only one small study reported on worsening of diabetes, this evidence was rated as very low quality and was not thought sufficient to base any conclusion on.

Regarding haemorrhagic stroke, there was a suggestion of a possible harm based on an increased relative risk. However, the event rate was very low, and the committee agreed that the absolute risk difference did not represent a clinically important harm.

The committee also noted that there does not appear to be any evidence of an effect on cognitive decline and dementia, and any declines observed likely reflected normal age-related decline.

Since no clinically important harms were observed when comparing all statin intensities with placebo, as stated in the review protocol, no analysis was performed to assess specific statin intensity subgroups for the adverse event outcomes.

Summary

Overall, the committee agreed that the body of evidence for both the efficacy of statins and the risk of adverse events continues to support the use of high intensity statins for both primary and secondary prevention of CVD events. This was based on the benefit of statins for reducing the risk of CVD events, particularly non-fatal MI, outweighing the small increase in risk of adverse events (rhabdomyolysis, muscle pain, raised liver transaminases and new-onset diabetes).

The committee discussed the recommendation for 20mg atorvastatin for primary prevention. It was highlighted that being able to tell people they are starting on a relatively low dose can have a positive effect upon those individuals who may be reluctant to consider statins. This view was endorsed by the lay representatives on the committee. Committee members also highlighted that people should have their dose increased if they are not achieving sufficient lipid lowering and agreed this was addressed in recommendations for following up people on statins.

In the previous update of this guideline, types 1 and 2 diabetes and CKD were explored as subgroup analyses. No evidence of heterogeneity was found between these subgroups and the other populations for most outcomes and so the data were not stratified by these variables in the current update. Although not analysed separately a small amount of evidence was added to the review for people with type 2 diabetes and CKD (1 new study for each population). The committee agreed there was nothing to suggest a change in recommendations was required for these populations. It was agreed that as the recommendation for statins for type 2 diabetes were the same as the general population, a separate recommendation was no longer required.

The committee considered that although the recommendation to offer statins does not specify age limitations, the a separate recommendation to consider statins for those aged 85 or older should be retained, as there was a risk this population may otherwise be overlooked when considering treatment due to not having a formal risk assessment undertaken. The committee agreed that factors which might make treatment not suitable were particularly important here, including comorbidities, polypharmacy and frailty, amongst others.

The committee agreed that the existing recommendations aligned to reported potential adverse effects of statin treatment were still appropriate. However, they agreed that the additional data for the evidence for muscle pain and rhabdomyolysis added certainty in conclusions that the risk of this occurring was low, and so that message should be reinforced in the recommendations. It was also agreed that the evidence for increasing efficacy with increasing statin intensity for CV mortality and non-fatal MI supports the recommendation of a high-intensity statin.

4.4 Cost effectiveness and resource use

People with established CVD (secondary prevention)

No new economic studies relating to statins for secondary prevention in people with established CVD were included in this update review. Two published studies included in the 2014 update and the 2014 CG181 model results were discussed and the committee considered whether any changes in the clinical evidence, clinical context or costs since the 2014 CG181 update were likely to change conclusions. The 2014 model was considered the most applicable evidence so is discussed here.

The 2014 CG181 model compared no statin, low intensity statin, medium intensity statin and high intensity statin in a population with established CVD. It found that high intensity statins were the most cost-effective option for secondary prevention in a population with established CVD. High intensity statins had an ICER of £2,959 per QALY gained compared to no treatment (low and medium intensity statins ruled out by dominance or extended dominance) for men aged 60 years. ICERs were similar and the conclusions consistent for other age cohorts and for women. This was based on using the lowest cost statin in each intensity group which was atorvastatin 20mg costs for high intensity statins. If the cost of atorvastatin 40 mg or 80 mg was used instead the ICER remained well below £20,000 per QALY gained. The base-case analysis was based on the assumption of equivalent effectiveness between all high-intensity statins, due to a lack of evidence comparing the effectiveness of the different doses in terms of reducing clinical end points. On this basis the cheapest high-intensity statin – atorvastatin 20 mg – would be the most cost effective. However, a threshold analysis within the high intensity group found that atorvastatin 40 mg and 80 mg would be cost effective compared to atorvastatin 20 mg if they were 1% and 2% more effective, respectively.

The committee noted that a new primary prevention analysis using the same model had published since the 2014 CG181 modelling and this updated some of the inputs that are also used in this secondary prevention analysis. They considered whether these changes might change the conclusions from the 2014 CG181 secondary prevention model if they were implemented but concluded they would not. Most changes to inputs would improve cost effectiveness and those that would not were found not to change results substantially and so were considered unlikely to change overall conclusions.

The costs of high intensity statins had reduced since the 2014 CG181 update. Atorvastatin 20 mg, 40 mg and 80 mg had reduced by a modest amount and the cost of rosuvastatin had reduced substantially as a non-proprietary version is now available.

The committee agreed the recommendation for atorvastatin 80 mg should be retained for secondary prevention. No new clinical studies comparing atorvastatin 80mg with another high intensity statins were included in the clinical review. It was noted that the 2014 committee considered that the additional benefits required for atorvastatin 80mg to be cost effective compared to atorvastatin 20 mg were likely to be achievable. The current committee agreed with this view, highlighting that published analyses were available looking at the relationship between LDL cholesterol and CV outcomes and that estimated additional benefit using these supports this conclusion.

The committee discussed the fact that the cost of rosuvastatin has reduced since the 2014 CG181 update and is now more similar to atorvastatin costs. One study was included in the 2014 clinical review comparing high intensity atorvastatin and rosuvastatin and did not find a clinically significant difference in CVD outcomes and no new evidence was identified for this update. At the time of the current update development, atorvastatin 80 mg cost £17 per year and rosuvastatin 40 mg cost £22 per year. The committee also noted that there was much more evidence and experience related to atorvastatin. Taking these factors into account they agreed atorvastatin 80 mg should be the recommended high intensity statin for secondary prevention but noted that if people experienced adverse effects thought to be related to atorvastatin one option might be to try rosuvastatin instead.

People without established CVD (primary prevention)

One new published analysis (Guthrie 2023)[68] relating to statins for primary prevention was included in the updated review. Guthrie 2023 was an NIHR-funded update of the 2014 CG181 model. The committee also considered the original 2014 CG181 model and a published study included in the 2014 CG181 update. Guthrie 2023 was considered the most applicable evidence.

Guthrie 2023 used the 2014 CG181 model structure and approach and updated various inputs from the 2014 CG181 model including statin costs, CVD event costs, baseline and CVD event utilities, how changes in risk over time and treatment effects are implemented in the model, mortality data, adjustment for competing risk of non-CV death, removal of statin-induced diabetes adverse effect and removal of the effect on non-CV death.

Guthrie 2023 compared no statin, low intensity statin, medium intensity statin and high intensity statin in a population without established CVD. Statin costs included drug costs and associated annual healthcare visits and monitoring tests. Risk assessment costs were assumed common to everyone and not included. Atorvastatin 20mg costs were used for high intensity statins. In Guthrie 2023 high intensity statins were more cost effective than in the original 2014 CG181 model. For example, the ICER reduced from £4,125 to £1,217 per QALY gained compared to no treatment for a cohort of men aged 60 years with 10% 10-year CV risk (low and medium intensity statins ruled out by dominance or extended dominance). The updated CVD event costs had the greatest effect in reducing the ICER – costs were higher in this update and so cost savings are greater. Changes in how CVD risk increases over time were implemented in the model had the next greatest effect.

Guthrie 2023 presented results for men and women for two-way combinations of age (40-80 years) and 10-year CV risk (2-40%) and found high intensity statins were the most cost-effective option for all plausible risk/age combinations analysed. The committee discussed that the 2014 CG181 committee recommend high intensity statin treatment for primary prevention in people with a 10-year CV risk of at least 10%. It was noted that the choice of this threshold was however largely based on consensus and in the 2014 CG181 model it was also cost effective to treat people with lower 10-year CV risk (although not as low as in Guthrie 2023).

The committee considered the changes to methods and inputs that had been made in Guthrie 2023 and agreed they were generally appropriate. There was some uncertainty about the removal of the diabetes adverse effect given the relative treatment effects in the clinical review for this update were essentially the same in the 2014 CG181 review and so an additional sensitivity analysis was run in the Guthrie 2023 model with this included and this did not change conclusions about cost effectiveness. Guthrie 2023 used relative treatment effects from the 2014 CG181 guideline review and it was noted that there had been some minor additions to the review in this update. Relative treatment effects remained similar and so were not expected to change conclusions. However an additional sensitivity analysis was also run with the updated relative treatment effects. This also did not affect conclusions.

It was noted that while high intensity statins were cost effective across the plausible age/risk combinations analysed, cost effectiveness increased as 10-year CV risk increased. This is because when the same relative risk reduction is applied to a higher baseline risk, absolute differences in CVD events between no statins and high intensity statins are greater, which means QALY gains were greater and cost-offsets from avoiding CVD events were higher. For example, for a 60-year old man with 10% 10-year CVD risk, costs and QALYs were higher with high intensity statins than no statins and the ICER was £1,217 per QALY gained compared to no statin treatment. For a 60-year-old man with 20% 10-year CVD risk, total costs were lower overall with high intensity statin compared to no statins, and QALYs higher, making it the dominant option. Cost-effectiveness also increased as age reduced (for a given 10-year CV risk level). This is because a lifetime model is used in the analysis and even when 10-year risk is the same, younger people will have higher risk over the full lifetime modelled and so differences in CVD events with high intensity statins and no statins are greater. The committee also noted that, while not captured in the model, individuals with the same 10-year CV-risk but higher lipid levels might get higher absolute benefit from statin treatment.

The committee noted that the model assumes constant relative risk reduction over time. This was considered a reasonable assumption for modelling purposes but highlighted that reduced lipid levels in the long term may in fact confer greater benefits than that estimated using shorter term trial data, although this is difficult to quantify.

In the original 2014 CG181 model, the analysis was based on the assumption of equivalent effectiveness between all high-intensity statins, due to a lack of evidence comparing the effectiveness of the different doses in terms of reducing clinical end points. The same approach is taken in Guthrie 2023. On this basis the cheapest high-intensity statin – atorvastatin 20 mg – would be the most cost effective. The committee noted higher doses would be expected to offer greater risk reduction. The cost of atorvastatin 40 mg is very similar to atorvastatin 20 mg (an additional cost of around £1 annually at the time of discussion) and it was noted that only a very small additional benefit in terms of reducing CVD events would be needed for 40 mg to be cost effective compared to 20 mg.

It was noted that Guthrie 2023 also undertook analyses incorporating ‘direct treatment disutility’. This is described as a type of process utility related to the inconvenience of obtaining prescriptions and medicines, needing to modify lifestyles to take medicines and attending healthcare visits for monitoring treatment, distinct from specific harms or other effects of treatment. Guthrie 2023 undertook research to quantify this effect and then incorporated it into QALY estimates under different assumptions about duration of effect. In some scenarios its inclusion meant that high intensity statins were not cost effective in certain groups. However, it was noted that this effect is more about individual decision making. The authors noted some limitations to the analysis, including that respondents to the stated-preference survey may not be representative of the population, and that there is no consensus on which direct treatment disutilities should be used for cost-effectiveness analyses. The committee considered the results and limitations and agreed that while it is important to account for risks and benefits in all decision making, consideration of direct treatment disutility in this way is not standard practice in NICE methods and could equally apply to other treatments for CVD prevention. Therefore, using these results to inform recommendations at the population-level could introduce inconsistencies in decision making. The committee concluded that while these results provided an interesting insight into quality of life from the perspective of the individual, these analyses were consistent with applying the principle of shared-decision making when considering statin treatment, and would not

change the conclusions the committee had agreed on for the population level recommendations.

CKD

One new economic analysis was included in people with CKD stages 3B, 4 and 5 not on dialysis. It was mostly a primary prevention population and people with a history of MI or revascularisation were excluded but 15% had a prior history of non-coronary vascular disease. It used individual patient level data combined with effectiveness estimates based on LDL lowering. It found that atorvastatin 20mg was cost effective compared to no statin treatment and that atorvastatin 40mg was cost effective compared to atorvastatin 20mg based on effectiveness estimated from LDL lowering data. Note that other lipid lowering interventions were also analysed but were not considered as they were not part of the review protocol for this update. The committee concluded that these results were consistent with the wider primary prevention conclusions and supported the existing recommendations for high intensity statins in people with CKD for primary prevention of CVD.

4.5 Other factors the committee took into account

The committee discussed who should be offered or considered for statin treatment. The committee noted that cost-effectiveness modelling found high intensity statins cost effective for all plausible risk/age combinations analysed (40-80 years and 2-40% 10-year CV risk). They discussed that if a lower risk threshold for treatment were selected, this would mitigate more events, but it would move the recommendations on treatment with a statin to a population-based approach. Practical considerations were also agreed to be important in deciding what recommendations are likely to have the greatest positive impact on preventing CVD events. The committee highlighted that people are often reluctant to start statin treatment and many don't adhere to treatment in the long term if they do start. It was also noted that people at higher risk are likely to be more motivated to start treatment and will benefit more. It was noted that achieving better coverage at even the 10% threshold would be significant progress. 2021 national audit data reports only 45% of people with a QRISK score of 10% or more are on lipid-lowering therapy and only 56% of people with a QRISK score of 20% or more, it is unclear whether this is due to people not being offered a statin, or people declining to take them, but thought likely to be a combination of both. The importance of making recommendations that are acceptable to the healthcare community and feasible to implement was therefore considered important to take into account. The majority of the committee agreed that getting more people to start statins at the existing threshold was more important than lowering the threshold. Part of the reason for that decision was concern about otherwise diverting stretched primary care resources away from this goal. It was agreed that it will be important to update the patient decision aid that accompanies this guideline to support implementation.

However, given the clinical and cost-effectiveness evidence the committee agreed that statins should not be restricted strictly for people with 10-year CV risk scores over 10%. In particular they noted that younger people near the 10-year risk treatment threshold or with additional risk factors will have higher lifetime risk and potential to benefit from lipid lowering and should not be excluded from treatment. Therefore, a new recommendation was added to support individualised care, by allowing consideration of atorvastatin 20mg for the primary prevention of CVD for people with a QRISK3 score less than 10% who have non-modifiable CVD risk factors or if there was a strong individual preference.

The 'consider' recommendation for people who are less than 10% risk will enable healthcare professionals to have a discussion about the risks and benefits of statin treatment with people who they think will benefit from statins if, based on their clinical judgement, they believe that is the most appropriate thing to do.

The committee reviewed and discussed the related recommendations included in the 2014 update of the guideline. These included recommendations on ensuring there is an informed discussion between the person and the healthcare professional when deciding whether to take statins, what tests and assessments should be carried out and recommendations for follow-up of people on statins, including annual medication reviews. Also recommendations highlighting the importance of discussing the importance of lifestyle modifications and optimising management of any modifiable risk factors. The committee acknowledged the impact of a potential increase in statin prescribing, but agreed that these remained important principles of CVD risk reduction and they should be retained in the guideline.

The committee also noted that there remained a lack of evidence in older people, and it remained true that few trials assessing cardiovascular outcomes have recruited many people over 80 years. Similarly, there was still no evidence for people with type 1 diabetes despite this population being at increased CVD risk. The committee agreed that both of these research recommendations remained important and had not been addressed and so should be retained in this update.

The committee considered the 2014 research recommendation for comparative effectiveness and risks of alternative doses of atorvastatin. Although the committee retained the recommendation for atorvastatin 20mg as the starting statin dose, this was based partly on limitations in the evidence reviewed, but also considering the pragmatics of starting on a higher dose and the implications this may have on uptake of statins. Although there was no evidence comparing all of the doses of atorvastatin (20, 40 and 80mg) in a primary prevention population the committee agreed that is unlikely this research recommendation would be undertaken as a very large sample size would be required to demonstrate effect, and statins are now widely used in clinical practice so it is not a priority area of uncertainty.

The committee were aware that one research recommendation from the 2014 was in development at the time of undertaking this update; cost effectiveness using individual patient-level data. The committee agreed this research question has been addressed and could now be removed.

4.6 Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.11 to 1.4.28 and 1.4.29 to 1.4.33 and 1.4.34 to 1.4.43.

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Appendices

Appendix A – Review protocols

Review protocol for statin efficacy

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	Statin therapy for the primary and secondary prevention of CVD
2.	Review question	What is the clinical and cost effectiveness of statin therapy for adults without established CVD and with established CVD?
3.	Objective	The aim of this review is to update the evidence on the clinical and cost effectiveness and safety of different statin intensities in people with and without established CVD.
4.	Searches	Key papers: Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, et al. (2016) Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. New England Journal of Medicine 374(21):2021–31 (#95) Feinstein MJ, Jhund P, Kang J, Ning H, Maggioni A, Wikstrand J, et al. Do statins reduce the risk of myocardial infarction in patients with heart failure? A pooled individual-level reanalysis of CORONA and GISSI-HF. European Journal of Heart Failure 17(4):434–41 (#87) The following databases (from November 2013) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • Date limitations – from November 2013 • English language studies

ID	Field	Content
		• Human studies Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Primary and secondary prevention of cardiovascular disease
6.	Population	Inclusion: Adults (aged 18 years and older) with or without established CVD, including those with type 1 diabetes, type 2 diabetes or chronic kidney disease. Exclusion: • Children aged < 18 years of age • People with familial hypercholesterolaemia. • People with familial clotting disorders that increase cardiovascular risk. • People with other monogenic disorders that increase cardiovascular risk. • People at high risk of CVD or abnormalities of lipid metabolism because of endocrine or other secondary disease processes other than diabetes. • People receiving renal replacement therapy.
7.	Intervention	Statins (assume class effect), oral administration: • Atorvastatin • Fluvastatin • Pravastatin • Rosuvastatin • Simvastatin

ID	Field	Content
		These will be analysed in the following groups: • Low intensity: 20-30% reduction in LDL-c • fluvastatin 20–40 mg • pravastatin 10–40 mg • simvastatin 10 mg • Medium intensity: 31-40% reduction in LDL-c • atorvastatin 10 mg • fluvastatin 80 mg • rosuvastatin 5 mg • simvastatin 20–40 mg • High intensity: >40% reduction in LDL-c • atorvastatin 20–80 mg • rosuvastatin 10–40 mg
8.	Comparator	Placebo/usual care/no treatment Different intensities (as defined above) High intensity vs other high intensity drug/dose Different intensities (as defined above) will be compared with each other or with placebo/usual care/no treatment
9.	Types of study to be included	Inclusion: • RCTs • Systematic reviews of RCTs • Published NMAs and IPDs of RCT data will be considered for inclusion. • Exclusion: • Cross over RCTs • Non-randomised studies • Follow-up < 1 year • Conference abstracts

ID	Field	Content
10.	Other exclusion criteria	Trials of statins with aims other than CVD prevention or lipid lowering (e.g. for preventing chemotherapy toxicity) Non-English language studies. Conference abstracts will be excluded as there are already many full text published studies available in the CG181 analysis.
11.	Context	Statins are recognised as the first-choice lipid modification therapy to reduce CVD events. Statin therapy was first appraised by NICE as part of the technology appraisal TA94 ('Statins for the prevention of cardiovascular events' 2006). This was followed by clinical guidelines which made specific recommendations about use of statins in people with and without diabetes. However, many people at significant risk of CVD do not receive cholesterol-lowering therapies or are treated inadequately. Recently, the clinical and epidemiological evidence on the benefits of lipid lowering has increased and there is new evidence that may impact on the current recommendations.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • All-cause mortality (time-to-event) • Cardiovascular mortality (time-to-event) • Non-fatal myocardial infarction (time-to-event) • Non-fatal ischaemic stroke (time-to-event) • Combined major adverse cardiovascular events (CVD death, nonfatal MI, nonfatal ischaemic stroke) • Quality of life, any validated measure (continuous) • Time points • The minimum follow-up is 1 year • The longest available follow-up will be used for each trial, and all these timepoints will be pooled. Cholesterol levels will not be included as a surrogate outcome for CVD risk because it is whether or not a CVD event occurs that is important to patients and data on this will be available.

ID	Field	Content
		However, details of the LDL-cholesterol reduction during treatment (continuous; final score in preference to change score if available) will be extracted, although not analysed as an outcome. This will provide useful information on the observed achieved reductions with reference to the definitions of statin intensity based anticipated on LDL-cholesterol lowering. This will contextualise the risk reductions for the listed outcomes in terms of the LDL-cholesterol reduction that led to that effect. For MI and stroke, non-fatal events will be the preferred outcome measure. However, if only total (fatal and non-fatal) events are reported in a trial this will be included for these outcomes. This will not be downgraded for indirectness as the effect on fatal and non-fatal ischaemic events is similar. For stroke, ischaemic stroke is the preferred outcome measure. However, if only 'stroke' is reported (including ischaemic and haemorrhagic), this will be included but downgraded for indirectness because haemorrhagic stroke appears to be increased with statins, which will diluting the benefit on ischaemic stroke. We will include how the outcome of stroke was defined, including whether CT or MRI was used.
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions

ID	Field	Content
		• correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the following checklists as described in Developing NICE guidelines: the manual. Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) For IPD meta-analyses of RCTs, no validated checklist is available. ROBIS and IPD-specific published checklists will be trialled and used or modified as appropriate.
15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Where available, outcome data from new studies will be meta-analysed with corresponding data included in CG 181. For time-to-event outcomes, if sufficient information is provided, hazard ratios will be reported in addition to risk ratios. Only one measure will be considered for decision making. This will be agreed with the committee taking into account the proportion of studies that report sufficient data to calculate the risk ratio and the hazard ratio, in order to maximise the available pooled data. If there are differences in effect estimates between the two measures, potential reasons for this will be considered in the interpretation of the evidence. For continuous outcomes, if the same outcome is reported on different numerical scales these will be pooled where possible. If the studies use the same outcome measured in different units, this will be converted one to another using a simple multiplier. Otherwise, the standardised mean difference will be calculated if different scales are used for the same outcome across studies.

ID	Field	Content
		Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups, including studies at higher risk of bias, using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ If published individual participant data meta-analyses are included, any additional studies identified for inclusion (that are not included within the published analysis) will be analysed separately, and individual participant data will not be sought. Where meta-analysis is not possible, data will be presented and quality assessed individually per study and outcome. WinBUGS will be used for network meta-analysis, if possible given the data identified. This will be discussed with the committee to determine whether it is appropriate and of added benefit to conduct a network meta-analysis given the available data once the pairwise analysis has been completed.
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Different agents/doses within each intensity class (e.g. atorvastatin 20 mg vs 80 mg) • Primary versus secondary prevention • Presence versus absence of CKD • Age: <75 versus ≥75

ID	Field	Content			
		• Sex • Ethnicity/family origin: black, Asian, white, mixed, other • Presence versus absence of autoimmune disease			
17.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
18.	Language	English			
19.	Country	England			
20.	Anticipated or actual start date	21.03.2022			
21.	Anticipated completion date	19.04.2023			
22.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☑	☑
		Piloting of the study selection process		☑	☑
		Formal screening of search results against eligibility criteria		☑	☑
		Data extraction		☑	☑
		Risk of bias (quality) assessment		☑	☑
		Data analysis		☑	☑

ID	Field	Content
23.	Named contact	5a. Named contact NICE Guideline Development Team NGC 5b Named contact e-mail CVDupdate@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)
24.	Review team members	From the NICE Guideline Development Team NGC: • Serena Carville, Guideline lead • Eleanor Samarasekera, Senior systematic reviewer • Maheen Qureshi, Systematic reviewer • Kate Lovibond, Health economist • Lina Gulhane, Information specialist
25.	Funding sources/sponsor	This systematic review is being completed by NICE Guideline Development Team NGC.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual.

ID	Field	Content	
		Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10178	
28.	Other registration details	NA	
29.	Reference/URL for published protocol		
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	Cardiovascular disease; lipid modification; statin.	
32.	Details of existing review of same topic by same authors	NA	
33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information		
35.	Details of final publication	www.nice.org.uk	

Review protocol for statin adverse effects

ID	Field	Content
0.	PROSPERO registration number	Not registered

ID	Field	Content
1.	Review title	Adverse effects of statins for the primary and secondary prevention of cardiovascular disease (CVD)
2.	Review question	What is the risk of adverse effects from statin treatment?
3.	Objective	To determine latest evidence on adverse effects of statins for lipid modification therapy.
4.	Searches	Key papers: Protocol for analyses of adverse event data from randomized controlled trials of statin therapy. Cholesterol Treatment Trialists' (CTT) Collaboration [36] The following databases (from 2013) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Primary and secondary prevention of cardiovascular disease

ID	Field	Content
6.	Population	Inclusion: Adults (aged 18 years and older) with or without established CVD, including those with type 1 diabetes, type 2 diabetes or chronic kidney disease. Exclusion: • Children aged < 18 years of age • People with familial hypercholesterolaemia. • People with familial clotting disorders that increase cardiovascular risk. • People with other monogenic disorders that increase cardiovascular risk. • People at high risk of CVD or abnormalities of lipid metabolism because of endocrine or other secondary disease processes other than diabetes. • People receiving renal replacement therapy
7.	Intervention	Statins (assume class effect), oral administration: • Atorvastatin • Fluvastatin • Pravastatin • Rosuvastatin • Simvastatin These will be analysed in the following groups: • Low intensity: 20-30% reduction in LDL-c • fluvastatin 20–40 mg • pravastatin 10–40 mg • simvastatin 10 mg • Medium intensity: 31-40% reduction in LDL-c • atorvastatin 10 mg • fluvastatin 80 mg • rosuvastatin 5 mg • simvastatin 20–40 mg • High intensity: >40% reduction in LDL-c

ID	Field	Content
		• atorvastatin 20–80 mg • rosuvastatin 10–40 mg
8.	Comparator	Primary analysis: • All statins versus placebo/usual care/no treatment • If harm is found for all statins compared with control, then analyse by • Intensity categories (as defined above) • Individual agents within each intensity class
9.	Types of study to be included	Inclusion: • RCTs with double blinding • Systematic reviews of RCTs • Published NMAs and IPDs of RCT data. • If insufficient data are found, further studies will be sought as follows: • Unblinded RCTs or systematic reviews of these (for objective endpoints only) • N of 1 randomised trials or systematic reviews of these (for muscle pain endpoints only) Decisions on whether RCT evidence is sufficient will be made by committee discussion, and considered for each outcome separately. Exclusion: • Cross over studies (except for muscle pain outcomes) • Unblinded studies for subjective endpoints • Non randomised studies, including • Cohort studies • Case series • Case studies • Follow-up < 1 year • Conference abstracts

ID	Field	Content
10.	Other exclusion criteria	Trials of statins with aims other than CVD prevention or lipid lowering (e.g. for preventing chemotherapy toxicity) Non-English language studies. Conference abstracts will be excluded as there are already many full text published studies available in the CG181 analysis.
11.	Context	Despite the weight of conclusive research and consistent national and international guidelines, many people at significant risk of CVD do not receive cholesterol-lowering therapies or are treated inadequately. Anxieties about the adverse effects associated with statins may mean healthcare professionals are reticent about offering them, and people are reluctant to start or continue statin treatment. Depending on dosage, 30% to 50% of people stop taking statins within 6 years. Over the past 5 years, the clinical and epidemiological evidence on the benefits of lipid lowering, as well as the risk of adverse effects of statins, has increased.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical. Adverse events (dichotomous): • Rhabdomyolysis (CK>10 times normal) • Myalgia • Liver (transaminases>3 times normal level) • New onset diabetes • Worsening of diabetes: • Diabetes adverse event of ketosis or glucose control complications • Rise in HbA1c of ≥0.5% from baseline • Escalation of diabetes medication • Cognitive decline (by validated questionnaire) or dementia • Haemorrhagic stroke • Time points • The minimum follow-up is 1 year

ID	Field	Content
		The longest available follow-up will be used for each trial, and all these timepoints will be pooled.
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Non randomised, including cohort, studies: Cochrane ROBINS-I Case control study: CASP case control checklist Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool

ID	Field	Content
		For IPD meta-analyses of RCTs, no validated checklist is available. ROBIS and IPD-specific published checklists will be trialled and used or modified as appropriate.
15.	Strategy for data synthesis	Pairwise meta-analyses will be performed, where appropriate, using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Where available, outcome data from new studies will be meta-analysed with corresponding data included in CG 181. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups, including studies at high or very high risk of bias, using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ If published individual participant data meta-analyses are included, any additional studies identified for inclusion (that are not included within the published analysis) will be analysed separately, and individual participant data will not be sought. Where meta-analysis is not possible, data will be presented and quality assessed individually per study and outcome.

ID	Field	Content			
		WinBUGS will be used for network meta-analysis, if possible given the data identified. This will be discussed with the committee to determine whether it is appropriate and of added benefit to conduct a network meta-analysis given the available data once the pairwise analysis has been completed.			
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Different agents/doses within each intensity class (e.g. atorvastatin 20 mg vs 80 mg) • Comparator: placebo versus no treatment/usual care • Presence versus absence of diabetes • Presence versus absence of CKD • BMI <25 versus ≥25 • Age: <75 versus ≥75 • Sex • Ethnicity/family origin: black, Asian, white, mixed, other			
17.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
18.	Language	English			
19.	Country	England			
20.	Anticipated or actual start date	21.03.2022			
21.	Anticipated completion date	19.04.2023			
22.	Stage of review at time of this submission	Review stage		Started	Completed

ID	Field	Content		
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
23.	Named contact	5a. Named contact NICE Guideline Development Team NGC 5b Named contact e-mail CVDupdate@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
24.	Review team members	From the NICE Guideline Development Team NGC: • Serena Carville, Guideline lead • Eleanor Samarasekera, Senior systematic reviewer • Maheen Qureshi, Systematic reviewer • Kate Lovibond, Health economist • Lina Gulhane, Information specialist		
25.	Funding sources/sponsor	This systematic review is being completed by NICE Guideline Development Team NGC.		
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring		

ID	Field	Content	
		and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10178	
28.	Other registration details	NA	
29.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	Cardiovascular disease; lipid modification; statin; tolerability; intolerance; adverse effect.	
32.	Details of existing review of same topic by same authors	NA	
33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued

ID	Field	Content
34.	Additional information	NA
35.	Details of final publication	www.nice.org.uk

Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. Databases searched: • Centre for Reviews and Dissemination NHS Economic Evaluations Database (NHS EED) – all years (closed to new records April 2015) • Centre for Reviews and Dissemination Health Technology Assessment database – all years (closed to new records March 2018) • International HTA database (INAHTA) – all years • Medline and Embase – from 2014 (due to NHS EED closure)
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2007, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies included in the 2014 CG181 update and published between 2007 and the 2014 CG181 cut-off date (November 2013) will be reconsidered for inclusion as per this protocol. Studies published since November 2013 will be considered for inclusions.

Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[124]

Inclusion and exclusion criteria

- If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.
- If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).

	• Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2007 or later but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2007 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

B.1 Clinical search literature search strategies: Cardiovascular disease prevention: statins therapy and adverse events

The literature searches detailed below are for the reviews:

- What is the clinical and cost effectiveness of statin therapy for adults without established CVD and with established CVD?
- What is the risk of adverse effects from statin treatment?

They complied with the methodology outlined in Developing NICE guidelines: the manual.(NICE2014)

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 26: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	2013 – 13 April 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	2013 – 13 April 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews Jan 2013 to Issue 6 of 12, June 2022 Cochrane Central Register of Controlled Trials Jan 2013 to Issue 6 of 12, June 2022	Exclusions (clinical trials, conference abstracts)

Database	Dates searched	Search filter used
Epistemonikos (The Epistemonikos Foundation)	2013 to 13 June 2022	Systematic review Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	*Cardiovascular Diseases/
2.	*Heart diseases/
3.	*Myocardial Ischemia/
4.	exp *Angina Pectoris/
5.	*Coronary Disease/
6.	*Coronary Artery Disease/
7.	exp *Coronary Stenosis/
8.	*Myocardial Infarction/
9.	exp *Heart Failure/
10.	*Arrhythmias, cardiac/ or *Atrial fibrillation/
11.	*Vascular Diseases/
12.	*Hypertension/
13.	*Atherosclerosis/
14.	*Peripheral Arterial Disease/
15.	*Peripheral Vascular Diseases/
16.	*Arteriosclerosis/
17.	*Cerebrovascular Disorders/
18.	exp *Stroke/
19.	exp *brain ischemia/
20.	exp *heart arrest/
21.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
22.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
23.	(MI or myocardial infarct*).ti,ab.
24.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
25.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
26.	(hypertension or hypertensive*).ti,ab.
27.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
28.	(atheroscleros* or arterioscleros*).ti,ab.
29.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
30.	(ACS or angina or acute coronary syndrome*).ti,ab.
31.	(AF or atrial fibrillation).ti,ab.
32.	((chronic or congestive) adj2 heart failure).ti,ab.
33.	or/1-32

34.	letter/
35.	editorial/
36.	news/
37.	exp historical article/
38.	Anecdotes as Topic/
39.	comment/
40.	case report/
41.	(letter or comment*).ti.
42.	or/34-41
43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43
45.	animals/ not humans/
46.	exp Animals, Laboratory/
47.	exp Animal Experimentation/
48.	exp Models, Animal/
49.	exp Rodentia/
50.	(rat or rats or mouse or mice or rodent*).ti.
51.	or/44-50
52.	33 not 51
53.	limit 52 to English language
54.	*Hydroxymethylglutaryl-CoA Reductase Inhibitors/
55.	((Hydroxymethylglutaryl or HMG) adj (Coenzyme A or CoA)).ti,ab,kf.
56.	*Atorvastatin/
57.	*Rosuvastatin Calcium/
58.	exp *Pravastatin/
59.	*Fluvastatin/
60.	exp *Lovastatin/
61.	(statin* or atorvastatin* or rosuvastatin* or pravastatin* or fluvastatin* or lovastatin* or pitavastatin* or simvastatin*).ti,ab,kf.
62.	or/54-61
63.	53 and 62
64.	randomized controlled trial.pt.
65.	controlled clinical trial.pt.
66.	randomi#ed.ab.
67.	placebo.ab.
68.	randomly.ab.
69.	clinical trials as topic.sh.
70.	trial.ti.
71.	or/64-70
72.	Meta-Analysis/
73.	Meta-Analysis as Topic/
74.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
75.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.

76.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
77.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
78.	(search* adj4 literature).ab.
79.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
80.	cochrane.jw.
81.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
82.	or/72-81
83.	63 and (71 or 82)
84.	limit 83 to yr="2013 -Current"

Embase (Ovid) search terms

1.	*cardiovascular disease/
2.	*coronary artery disease/
3.	*vascular disease/
4.	*coronary artery atherosclerosis/
5.	*peripheral vascular disease/
6.	*peripheral occlusive artery disease/
7.	*arteriosclerosis/
8.	*ischemic heart disease/
9.	exp *Stroke/ or *stroke patient/
10.	*coronary artery obstruction/
11.	*hypertension/
12.	*heart disease/
13.	*heart arrhythmia/
14.	*heart fibrillation/ or *heart atrium fibrillation/
15.	*heart failure/ or exp *congestive heart failure/
16.	*acute coronary syndrome/ or exp *angina pectoris/ or *heart infarction/
17.	*cerebrovascular disease/
18.	*cerebrovascular accident/
19.	exp *brain ischemia/
20.	exp *heart arrest/ or *heart death/
21.	*brain infarction/
22.	*atherosclerosis/
23.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
24.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
25.	(MI or myocardial infarct*).ti,ab.
26.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
27.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
28.	(hypertension or hypertensive*).ti,ab.
29.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.

30.	(atheroscleros* or arterioscleros*).ti,ab.
31.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
32.	(ACS or angina or acute coronary syndrome*).ti,ab.
33.	(AF or atrial fibrillation).ti,ab.
34.	((chronic or congestive) adj2 heart failure).ti,ab.
35.	or/1-34
36.	letter.pt. or letter/
37.	note.pt.
38.	editorial.pt.
39.	case report/ or case study/
40.	(letter or comment*).ti.
41.	(conference abstract or conference paper).pt.
42.	or/36-41
43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43
45.	animal/ not human/
46.	nonhuman/
47.	exp Animal Experiment/
48.	exp Experimental Animal/
49.	animal model/
50.	exp Rodent/
51.	(rat or rats or mouse or mice or rodent*).ti.
52.	or/44-51
53.	35 not 52
54.	limit 53 to English language
55.	*Hydroxymethylglutaryl-CoA Reductase Inhibitors/
56.	((Hydroxymethylglutaryl or HMG) adj (Coenzyme A or CoA)).ti,ab,kf.
57.	exp *Simvastatin/
58.	*Atorvastatin/
59.	*Rosuvastatin/
60.	exp *Pravastatin/
61.	*Fluvastatin/
62.	*pitavastatin/
63.	(statin* or atorvastatin* or rosuvastatin* or pravastatin* or fluvastatin* or lovastatin* or pitavastatin* or simvastatin*).ti,ab,kf.
64.	or/55-63
65.	54 and 64
66.	random*.ti,ab.
67.	factorial*.ti,ab.
68.	(crossover* or cross over*).ti,ab.
69.	((doubl* or singl*) adj blind*).ti,ab.
70.	(assign* or allocat* or volunteer* or placebo*).ti,ab.

71.	crossover procedure/
72.	single blind procedure/
73.	randomized controlled trial/
74.	double blind procedure/
75.	or/66-74
76.	systematic review/
77.	Meta-Analysis/
78.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
79.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
80.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
81.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
82.	(search* adj4 literature).ab.
83.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
84.	cochrane.jw.
85.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
86.	or/76-85
87.	65 and (75 or 86)
88.	limit 87 to yr="2013 -Current"

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Cardiovascular Diseases] this term only
#2.	MeSH descriptor: [Heart Diseases] this term only
#3.	MeSH descriptor: [Myocardial Ischemia] this term only
#4.	MeSH descriptor: [Angina Pectoris] explode all trees
#5.	MeSH descriptor: [Coronary Disease] this term only
#6.	MeSH descriptor: [Coronary Artery Disease] this term only
#7.	MeSH descriptor: [Coronary Stenosis] explode all trees
#8.	MeSH descriptor: [Myocardial Infarction] this term only
#9.	MeSH descriptor: [Heart Failure] explode all trees
#10.	MeSH descriptor: [Arrhythmias, Cardiac] this term only
#11.	MeSH descriptor: [Vascular Diseases] this term only
#12.	MeSH descriptor: [Atrial Fibrillation] this term only
#13.	MeSH descriptor: [Hypertension] this term only
#14.	MeSH descriptor: [Atherosclerosis] this term only
#15.	MeSH descriptor: [Peripheral Vascular Diseases] this term only
#16.	MeSH descriptor: [Peripheral Arterial Disease] this term only
#17.	MeSH descriptor: [Arteriosclerosis] this term only
#18.	MeSH descriptor: [Cerebrovascular Disorders] this term only
#19.	MeSH descriptor: [Stroke] explode all trees
#20.	MeSH descriptor: [Brain Ischemia] explode all trees
#21.	MeSH descriptor: [Heart Arrest] explode all trees

#22.	((cardiovascular or cardio vascular) near/3 (event* or disease* or disorder*)):ti,ab,kw
#23.	((coronary or peripheral vascular or heart or peripheral arter*) near/3 (disease* or event* or disorder*)):ti,ab,kw
#24.	(MI or myocardial infarct*):ti,ab,kw
#25.	((heart or cardiopulmonary or cardiac) near/3 (death* or arrest* or attack*)):ti,ab,kw
#26.	(CVD or CHD or CAD or PAD or CVA):ti,ab,kw
#27.	(hypertension or hypertensive*):ti,ab,kw
#28.	((high or raised or elevated) near/2 (blood pressure or bp)):ti,ab,kw
#29.	(atheroscleros* or arterioscleros*):ti,ab,kw
#30.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke):ti,ab,kw
#31.	(ACS or angina or acute coronary syndrome*):ti,ab,kw
#32.	(AF or atrial fibrillation):ti,ab,kw
#33.	((chronic or congestive) near/2 heart failure):ti,ab,kw
#34.	(or #1-#33)
#35.	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] this term only
#36.	((Hydroxymethylglutaryl or HMG) near/1 (Coenzyme A or CoA)):ti,ab,kw
#37.	MeSH descriptor: [Atorvastatin] this term only
#38.	MeSH descriptor: [Rosuvastatin Calcium] this term only
#39.	MeSH descriptor: [Pravastatin] explode all trees
#40.	MeSH descriptor: [Fluvastatin] this term only
#41.	MeSH descriptor: [Lovastatin] explode all trees
#42.	(statin* or atorvastatin* or rosuvastatin* or pravastatin* or fluvastatin* or lovastatin* or pitavastatin* or simvastatin*):ti,ab,kw
#43.	(or #35-#42)
#44.	#34 and #43
#45.	conference:pt or (clinicaltrials or trialsearch):so
#46.	#44 not #45

Epistemonikos search terms

1.	(title:((title:(Cardiovascular Disease* OR "Heart disease*" OR "Myocardial Ischemia" OR "Angina Pectoris" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Stenosis" OR "Myocardial Infarction*" OR "Heart Failure" OR Arrhythmia* OR "Atrial fibrillation" OR "Vascular Disease*" OR Hypertension OR Atherosclerosis OR "Peripheral Arterial Disease*" OR "Peripheral Vascular Disease*" OR Arteriosclerosis OR "Cerebrovascular Disorder*" OR Stroke OR strokes OR "brain ischemia" OR "heart arrest*" OR "heart attack*" OR "cardiac arrest*" OR "cardiac attack*" OR "heart failure*" OR "high blood pressure" OR angina OR "acute coronary syndrome*") OR abstract:(Cardiovascular Disease* OR "Heart disease*" OR "Myocardial Ischemia" OR "Angina Pectoris" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Stenosis" OR "Myocardial Infarction*" OR "Heart Failure" OR Arrhythmia* OR "Atrial fibrillation" OR "Vascular Disease*" OR Hypertension OR Atherosclerosis OR "Peripheral Arterial Disease*" OR "Peripheral Vascular Disease*" OR Arteriosclerosis OR "Cerebrovascular

	Disorder*" OR Stroke OR strokes OR "brain ischemia" OR "heart arrest*" OR "heart attack*" OR "cardiac arrest*" OR "cardiac attack*" OR "heart failure*" OR "high blood pressure" OR angina OR "acute coronary syndrome*")) AND (title:(Hydroxymethylglutaryl-CoA OR "HMG-CoA" OR "Hydroxymethylglutaryl-Coenzyme" OR statin* OR atorvastatin* OR pravastatin* OR rosuvastatin* OR simvastatin* OR fluvastatin* OR lovastatin*) OR abstract:(Hydroxymethylglutaryl-CoA OR "HMG-CoA" OR "Hydroxymethylglutaryl-Coenzyme" OR statin* OR atorvastatin* OR pravastatin* OR rosuvastatin* OR simvastatin* OR fluvastatin* OR lovastatin*))) OR abstract:((title:(Cardiovascular Disease* OR "Heart disease*" OR "Myocardial Ischemia" OR "Angina Pectoris" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Stenosis" OR "Myocardial Infarction*" OR "Heart Failure" OR Arrhythmia* OR "Atrial fibrillation" OR "Vascular Disease*" OR Hypertension OR Atherosclerosis OR "Peripheral Arterial Disease*" OR "Peripheral Vascular Disease*" OR Arteriosclerosis OR "Cerebrovascular Disorder*" OR Stroke OR strokes OR "brain ischemia" OR "heart arrest*" OR "heart attack*" OR "cardiac arrest*" OR "cardiac attack*" OR "heart failure*" OR "high blood pressure" OR angina OR "acute coronary syndrome*") OR abstract:(Cardiovascular Disease* OR "Heart disease*" OR "Myocardial Ischemia" OR "Angina Pectoris" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Stenosis" OR "Myocardial Infarction*" OR "Heart Failure" OR Arrhythmia* OR "Atrial fibrillation" OR "Vascular Disease*" OR Hypertension OR Atherosclerosis OR "Peripheral Arterial Disease*" OR "Peripheral Vascular Disease*" OR Arteriosclerosis OR "Cerebrovascular Disorder*" OR Stroke OR strokes OR "brain ischemia" OR "heart arrest*" OR "heart attack*" OR "cardiac arrest*" OR "cardiac attack*" OR "heart failure*" OR "high blood pressure" OR angina OR "acute coronary syndrome*")) AND (title:(Hydroxymethylglutaryl-CoA OR "HMG-CoA" OR "Hydroxymethylglutaryl-Coenzyme" OR statin* OR atorvastatin* OR pravastatin* OR rosuvastatin* OR simvastatin* OR fluvastatin* OR lovastatin*) OR abstract:(Hydroxymethylglutaryl-CoA OR "HMG-CoA" OR "Hydroxymethylglutaryl-Coenzyme" OR statin* OR atorvastatin* OR pravastatin* OR rosuvastatin* OR simvastatin* OR fluvastatin* OR lovastatin*))))

B.2 Health Economics literature search strategies:

Health economic evidence was identified by conducting literature searches as below. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 18 Jan 2022	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	Health Economics 1 January 2014 – 18 Jan 2022	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception – 18 Jan 2022	English language

Medline (Ovid) search terms

1.	economics/
1.	value of life/
2.	exp "costs and cost analysis"/
3.	exp Economics, Hospital/
4.	exp Economics, medical/
5.	Economics, nursing/
6.	economics, pharmaceutical/
7.	exp "Fees and Charges"/
8.	exp budgets/
9.	budget*.ti,ab.
10.	cost*.ti.
11.	(economic* or pharmaco?economic*).ti.
12.	(price* or pricing*).ti,ab.

13.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
14.	(financ* or fee or fees).ti,ab.
15.	(value adj2 (money or monetary)).ti,ab.
16.	or/1-16
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/18-25
26.	randomized controlled trial/ or random*.ti,ab.
27.	26 not 27
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice or rodent*).ti.
34.	or/28-34
35.	17 not 35
36.	limit 36 to English language
37.	*Hydroxymethylglutaryl-CoA Reductase Inhibitors/
38.	((Hydroxymethylglutaryl or HMG) adj (Coenzyme A or CoA)).ti,ab,kf.
39.	*Atorvastatin
40.	*Rosuvastatin Calcium/
41.	exp *Pravastatin/
42.	*Fluvastatin/
43.	exp *Lovastatin/
44.	(statin* or atorvastatin* or rosuvastatin* or pravastatin* or fluvastatin* or lovastatin* or pitavastatin* or simvastatin*).ti,ab,kf.
45.	or/38-45
46.	37 and 46
47.	limit 47 to yr="2014 -Current"

Embase (Ovid) search terms

1.	health economics/
2.	exp economic evaluation/
3.	exp health care cost/

4.	exp fee/
5.	budget/
6.	funding/
7.	budget*.ti,ab.
8.	cost*.ti.
9.	(economic* or pharmaco?economic*).ti.
10.	(price* or pricing*).ti,ab.
11.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12.	(financ* or fee or fees).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	or/1-13
15.	letter.pt. or letter/
16.	note.pt.
17.	editorial.pt.
18.	case report/ or case study/
19.	(letter or comment*).ti.
20.	(conference abstract or conference paper).pt.
21.	or/15-20
22.	randomized controlled trial/ or random*.ti,ab.
23.	21 not 22
24.	animal/ not human/
25.	nonhuman/
26.	exp Animal Experiment/
27.	exp Experimental Animal/
28.	animal model/
29.	exp Rodent/
30.	(rat or rats or mouse or mice or rodent*).ti.
31.	or/23-30
32.	14 not 31
33.	limit 32 to English language
34.	*Hydroxymethylglutaryl-CoA Reductase Inhibitors/
35.	statin*.ti,ab,kf.
36.	((Hydroxymethylglutaryl or HMG) adj (Coenzyme A or CoA)).ti,ab,kf.
37.	exp *Simvastatin/
38.	*Atorvastatin/
39.	*Rosuvastatin/
40.	exp *Pravastatin/
41.	*Fluvastatin/
42.	*pitavastatin/
43.	(statin* or atorvastatin* or rosuvastatin* or pravastatin* or fluvastatin* or lovastatin* or pitavastatin* or simvastatin*).ti,ab,kf.
44.	or/34-43

45.	33 and 44
46.	limit 45 to yr="2014 -Current"

NHS EED and HTA (CRD) search terms

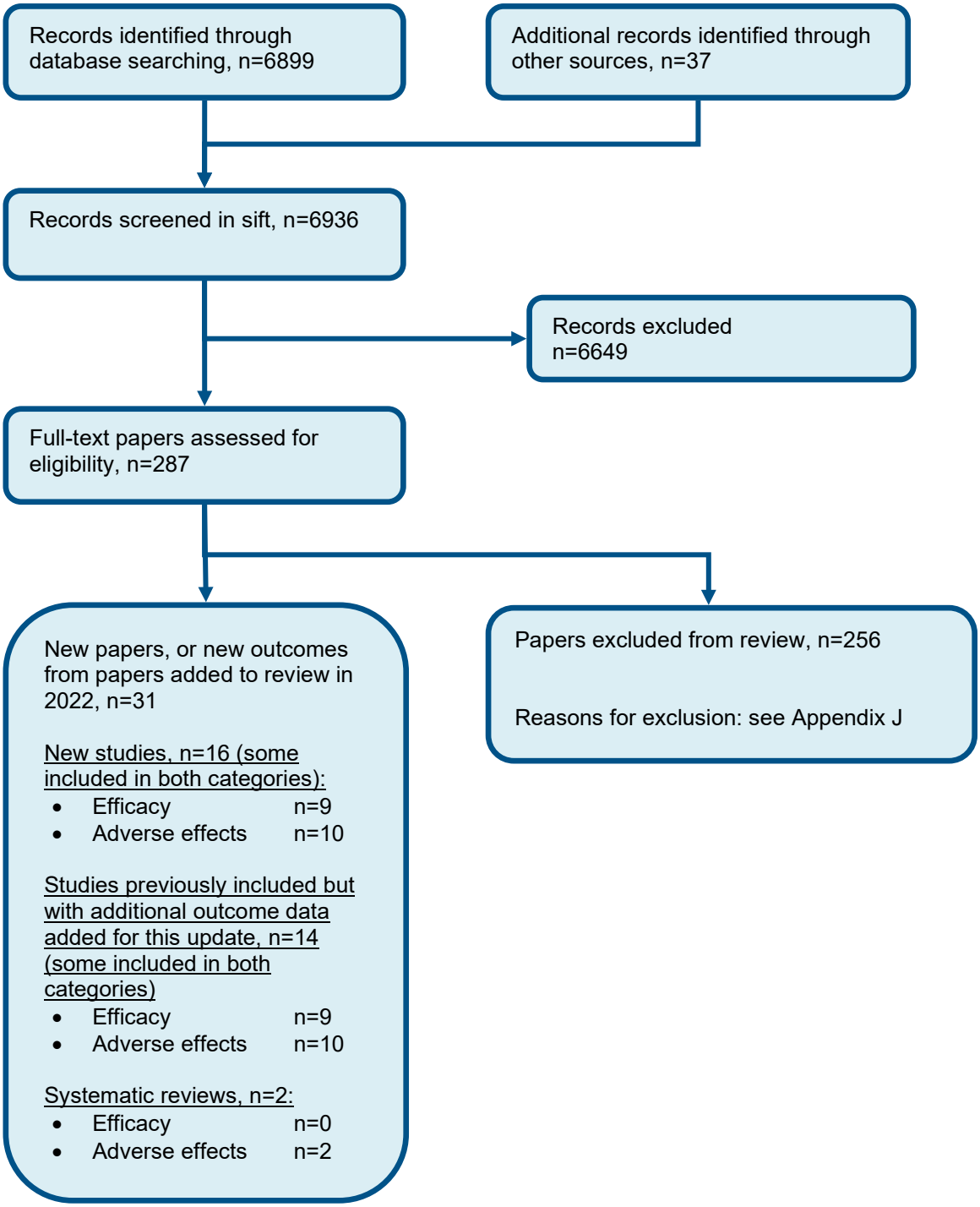
#1.	MeSH DESCRIPTOR Hydroxymethylglutaryl-CoA Reductase Inhibitors EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Atorvastatin EXPLODE ALL TREES
#3.	MeSH DESCRIPTOR Rosuvastatin Calcium EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Pravastatin EXPLODE ALL TREES
#5.	MeSH DESCRIPTOR Fluvastatin EXPLODE ALL TREES
#6.	MeSH DESCRIPTOR Lovastatin EXPLODE ALL TREES
#7.	((((Hydroxymethylglutaryl or HMG) adj (Coenzyme A or CoA))))
#8.	((statin* or atorvastatin* or rosuvastatin* or pravastatin* or fluvastatin* or lovastatin* or pitavastatin* or simvastatin*))
#9.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10.	* IN NHSEED
#11.	#9 AND #10
#12.	* IN HTA
#13.	#9 AND #12

INAHTA search terms

1.	("Lovastatin"[mhe]) OR ("Fluvastatin"[mh]) OR ("Pravastatin"[mhe]) OR ("Rosuvastatin Calcium"[mh]) OR ("Atorvastatin"[mh]) OR (((Hydroxymethylglutaryl or HMG) adj (Coenzyme A or CoA)) OR ((statin* or atorvastatin* or rosuvastatin* or pravastatin* or fluvastatin* or lovastatin* or pitavastatin* or simvastatin*))) OR ("Hydroxymethylglutaryl-CoA Reductase Inhibitors"[mh])

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of statins



Appendix D – Effectiveness evidence

D.1 Previously included studies

D.1.1 CG181 2014 update evidence tables

Study (subsidiary papers)	**Amarenco 2006[9] (Briel 2004 [31], Amarenco 2007 [11], Goldstein 2008 [64], Goldstein 2009 [65], Amarenco 2010 [10])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=4731)
Countries and setting	Conducted in Multiple countries; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Median 4.9 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: TIA diagnosed by a neurologist within 30 days after the event. Stroke was defined by focal clinical signs of central nervous system dysfunction of vascular origin that lasted for at least 24 hours; TIA was defined by the loss of cerebral or ocular function for less than 24 hours, presumably owing to atherosclerotic causes.
Stratum	Adults with established CVD: Men and women with a history of stroke or transient ischaemic attack
Subgroup analysis within study	Post-hoc subgroup analysis: Post-hoc subgroup analysis was conducted in groups of patients who achieved different levels in reduction of LDL-cholesterol from baseline (Amarenco et al. 2007b), by baseline stroke subtypes (Amarenco et al. 2010), and by the severity of the index stroke (Goldstein et al. 2009), and by sex (Goldstein et al. 2008b)
Inclusion criteria	Men and women over 18 years of age who had an ischemic or haemorrhagic stroke or a TIA, 1 to 6 months before randomisation. Patients with haemorrhagic stroke were included if they were deemed by the investigator to be at risk

	ischemic stroke or CHD. Patients had to be ambulatory, with a modified Rankin score of no more than 3, and to have an LDL cholesterol level of at least 100 mg/dL and no more than 190 mg/dL.
Exclusion criteria	Atrial fibrillation, other cardiac sources of embolism, and subarachnoid haemorrhage.
Recruitment/selection of patients	Patients were enrolled between Sept 1998 and March 2001.
Age, gender and ethnicity	Age - Other: Atorvastatin 63 (SE 0.2) years, placebo 62.5 (SE 0.2). Gender (M:F): 60%/40%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women (Men and women).
Extra comments	Patients who were taking lipid-altering drugs had to stop these medications 30 days before the screening phase of the study. Baseline total cholesterol (mg/dL): mean (SE) 211.4 (0.6) in atorvastatin group and 212.3 (0.6) in the placebo group; LDL-cholesterol (mg/dL: mean (SE) 132.7 (0.5) in atorvastatin group and 133.7 (0.5) in the placebo group. After treatment: total cholesterol (mg/dL): mean (SE) 147.2 (0.6) in atorvastatin group and 208.4 (0.6) in the placebo group; LDL-cholesterol (mg/dL): mean (SE) 72.9 (0.5) in atorvastatin group and 128.5 (SE 0.5) in the placebo group. The percentage of people with diabetes at baseline was not reported; 69% had a stroke, and 31% had a TIA.
Indirectness of population	No indirectness
Interventions	(n=2365) Intervention 1: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg/day. Duration Median 4.9 years. Concurrent medication/care: Dietary advice (NCEP Step 1); 2% had received a prior statin therapy. After randomisation, the following % of patients were aspirin or other antiplatelet drug (excluding heparin): 94%; ACE inhibitor: 47%; dihydropyridine derivative: 28%; beta blocker: 32%; ARBs: 14%; vitamin K antagonist (including warfarin): 12% (n=2366) Intervention 2: Placebo. Placebo. Duration Median 4.9 years. Concurrent medication/care: Dietary advice (NCEP Step 1); 3% had received a prior statin therapy. After randomisation, the following % of patients were taking aspirin or other antiplatelet drug (excluding heparin): 94%; ACE inhibitor: 47%; dihydropyridine derivative: 30%; beta blocker: 33%; ARBs: 15%; vitamin K antagonist (including warfarin): 12%, or open-label statins: 25%
Funding	Study funded by industry (Supported by Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 80 MG versus PLACEBO

Protocol outcome 1: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Stroke (fatal and non-fatal) at Median 4.9 years; Group 1: 265/2365, Group 2: 311/2366; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Stroke (fatal and non-fatal) at Median 4.9 years; HR 0.84 (95%CI 0.71 to 0.99) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Rhabdomyolysis at Median 4.9 years; Group 1: 2/2365, Group 2: 3/2366; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at Median 4.9 years; Group 1: 216/2365, Group 2: 211/2366; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : All-cause mortality at Median 4.9 years; HR 1 (95%CI 0.82 to 1.21) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 4: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Death from cardiovascular disease at Median 4.9 years; Group 1: 78/2365, Group 2: 98/2366; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Death from cardiovascular disease at Median 4.9 years; HR 0.78 (95%CI 0.58 to 1.06) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse event: Myalgia at 5 years
- Actual outcome for Adults with established CVD : Myalgia at Median 4.9 years; Group 1: 129/2365, Group 2: 141/2366; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults with established CVD : Alanine or aspartate aminotransferase > 3 times the upper limit of the normal group on 2 occasions at Median 4.9 years; Group 1: 51/2365, Group 2: 11/2366; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 7: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at Median 4.9 years; Group 1: mean 1.89 mmol/l (SD 0.62); n=2365, Group 2: mean 3.32 mmol/l (SD

0.75); n=2366; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Anderssen 2005[12]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=568)
Countries and setting	Conducted in Unknown; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults without established CVD : Hypertensive males
Subgroup analysis within study	Not applicable
Inclusion criteria	Men aged 40-74 years receiving drug treatment for hypertension, total cholesterol 4.5-8.0 mmol/l, triglycerides <4.5 mmol/l, BMI 25-35kg/m², and sedentary lifestyle (<1h per week of regular exercise).
Exclusion criteria	Symptomatic CVD (MI, angina pectoris, stroke), CHF, type 1 diabetes mellitus, history of coronary intervention, need for treatment with lipid-lowering medications other than the study drug, known or suspected hepatic or renal impairment or malignancy, history of alcohol and/or drug abuse, vegetarian diet or diet comprising a high omega-3 fatty acid intake, and inability to perform physical exercise.
Age, gender and ethnicity	Age - Mean (SD): Fluvastatin alone 56.8 (8.6) years, placebo alone 57.7 (8.2) years, fluvastatin and lifestyle 57.9(8.7) years, placebo and lifestyle 56.4 (9.1) years. Gender (M:F): 568/0. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men).

Extra comments	2x2 Factorial study design with patients being randomised twice to fluvastatin versus placebo and then lifestyle interventions versus usual care. Baseline total cholesterol mean (SD); fluvastatin 5.84 (0.75), placebo 5.95 (0.93), fluvastatin and lifestyle 6.02 (0.85), placebo and lifestyle 5.99 (0.90). Three month total cholesterol reduction; fluvastatin 5.93 to 5.01 mmol/l. Baseline LDL-cholesterol mean (SD); fluvastatin 3.78 (0.7), placebo 3.86 (0.86), fluvastatin and lifestyle 3.97 (0.82), placebo and lifestyle 3.91 (0.78). Three month LDL-cholesterol fluvastatin reduction 3.87 to 3.02 mmol/l.
Indirectness of population	No indirectness
Interventions	(n=283) Intervention 1: Low intensity statin - Fluvastatin 40 mg. Fluvastatin 40 mg/day (Lescol, Novartis Pharma). Duration 4 years. Concurrent medication/care: Calcium antagonists 37%, beta blockers 19%, diuretics 28%, ACE inhibitors 31% Comments: Group includes Fluvastatin alone (142) plus Fluvastatin with lifestyle intervention (141) (n=285) Intervention 2: Placebo. Placebo. Duration 4 years. Concurrent medication/care: Calcium antagonists 40%, beta blockers 22%, diuretics 26%, ACE inhibitors 31% Comments: Group includes Placebo alone plus Placebo with lifestyle interventions
Funding	Study funded by industry (Novartis Pharma)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults without established CVD : Rhabdomyolysis (CK>10 times normal) at 4 years; Group 1: 0/283, Group 2: 1/285; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : Mortality at 4 years; Group 1: 4/283, Group 2: 5/285; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	Anon 1994[143] (Pyorala 1997 [140])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=4444)
Countries and setting	Conducted in Denmark, Norway, Sweden; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 5.4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Patients with CHD (angina pectoris or MI)
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women, age 35-70; history of angina pectoris or acute MI; serum total cholesterol >5.5 mmol/l.
Exclusion criteria	Premenopausal women of childbearing potential; secondary hypercholesterolaemia; unstable or Prinzmetal angina; tendon xanthomata; planned coronary artery surgery or angioplasty; MI during the preceding 6 months; anti arrhythmic therapy; CHF requiring treatment with digitalis, diuretics, or vasodilators; persistent atrial fibrillation; cardiomegaly, haemodynamically important valvular heart disease; history of completed stroke; impaired hepatic function; partial ileal bypass; history of drug or alcohol abuse; poor mental function; other serious disease; current treatment with another investigational drug, or hypersensitivity to HMG-CoA reductase inhibitors.
Recruitment/selection of patients	Recruited from 94 Scandinavian clinical centres.
Age, gender and ethnicity	Age - Mean (SD): Placebo men: 58.1 (7.2) years; placebo women: 60.51 (5.7) years; simvastatin men: 58.2 (7.3) years; simvastatin women: 60.5 (6.4) years. Gender (M:F): 3617/827. Ethnicity: Not stated (assumed white)
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of

	CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women (Men and women).
Extra comments	Baseline values, mean (SD) (mmol/l) total cholesterol: placebo: 6.75 (0.66), simvastatin: 6.75 (0.67). LDL-cholesterol: placebo: 4.87 (0.65), simvastatin: 4.87 (0.66).
Indirectness of population	No indirectness
Interventions	(n=2221) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day. Target treatment was total cholesterol 3.0-5.2 mmol/l. 37% of patients had their dose raised to 40 mg/day during the first 6 months after randomisation. 2 patients had their dose reduced to 10 mg/day. Duration 5.4 years. Concurrent medication/care: Aspirin: 37%; beta blockers: 57%; calcium antagonist: 32%; isosorbide mono/dinitrate: 31%; thiazides: 7%; warfarin: 1%; fish oil: 13% (n=2223) Intervention 2: Placebo. Matching placebo. 35 patients were switched to lipid-lowering drugs, either because total cholesterol rose above the protocol-specified limit of 9.0 mmol/l (16 patients) or because such therapy was initiated by non-study physicians (19 patients). Duration 5.4 years. Concurrent medication/care: Aspirin: 37%; beta blockers: 57%; calcium antagonist: 30%; isosorbide mono/dinitrate: 33%; thiazides: 6%; warfarin: 2%; fish oil: 13%
Funding	Study funded by industry (Merck Research Laboratories, Rahway, New Jersey, USA)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Definite acute MI at 5.4 years; Group 1: 164/2221, Group 2: 270/2223; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: Non-fatal definite MI (diabetes subgroup) at 5.4 years; Group 1: 7/105, Group 2: 24/97; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Any cerebrovascular event at 5.4 years; Group 1: 61/2221, Group 2: 95/2223; Risk of bias: Low; Indirectness of outcome: serious indirectness (includes TIA)

Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years - Actual outcome for Adults with established CVD : Rhabdomyolysis at 5.4 years; Group 1: 1/2221, Group 2: 0/2223; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : CK >10 times ULN at 5.4 years; Group 1: 6/2221, Group 2: 1/2223; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: All-cause mortality at 5 years - Actual outcome for Adults with established CVD : All-cause mortality at 5.4 years; Group 1: 182/2221, Group 2: 256/2223; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with type 2 diabetes: All-cause mortality (diabetes subgroup) at 5.4 years; Group 1: 15/105, Group 2: 24/97; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : All-cause mortality at 5.4 years; HR 0.7 (95%CI 0.58 to 0.85) Calculated – from logrank P-value; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: CV mortality at 5 years - Actual outcome for Adults with established CVD : CV mortality at 5.4 years; Group 1: 136/2221, Group 2: 207/2223; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with type 2 diabetes: CV mortality (diabetes subgroup) at 5.4 years; Group 1: 12/105, Group 2: 20/97; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse event: Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with established CVD : AST >3 times ULN at 5.4 years; Group 1: 20/2221, Group 2: 23/2223; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : ALT >3 times ULN at 5.4 years; Group 1: 49/2221, Group 2: 33/2223; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 7: Adverse event:New onset diabetes at 5 years - Actual outcome for Adults with established CVD : New onset diabetes at 5.4 years; Group 1: 198/2116, Group 2: 193/2126; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	Anon 1998[139] (White 2000 [186], Hunt 2001 [77], Marschner 2001 [110], Simes 2002 [168], Hague 2003 [69], Keech 2003 [84])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=9014)
Countries and setting	Conducted in Australia, New Zealand; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 8 years (6 years intervention)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Men and women with CHD and a broad range of cholesterol levels
Subgroup analysis within study	Stratified then randomised: Stratified according to the qualifying event (MI or unstable angina) and clinical centre
Inclusion criteria	Patients after acute MI or a hospital discharge diagnosis of unstable angina between 3 and 36 months before study entry. After patients entered a 8 week single-blind run-phase of dietary advice, their plasma total cholesterol level had to be between 155-271 mg/dL and the fasting triglyceride level less than 445 mg/dL 4 weeks before randomisation to qualify for the trial.
Exclusion criteria	Clinically significant medical or surgical event within 3 months before study entry, cardiac failure, renal or hepatic disease, and the current use of any cholesterol-lowering agents.
Recruitment/selection of patients	Patients were recruited from 87 centres; patients entered an 8-week long single-blind placebo run-in phase during which they received dietary advice aimed at reducing their fat intake to less than 30% of total energy intake; patients were randomised between June 1990 and December 1992.
Age, gender and ethnicity	Age - Median (range): 62 (55-68) years. Gender (M:F): 83%/17%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: People aged 75 years or under 4. People with a family history of CVD:

	Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women (Men and women).
Extra comments	Baseline total cholesterol mg/dL, median (IQR): 218 (196-241) pravastatin, 218 (196-240) placebo; LDL-cholesterol mg/dL, median (IQR): 150 (130-170) pravastatin, 150 (131-170) placebo; at the end of treatment: 179 mg/dL pravastatin (the authors stated that this was 18% points greater than in the placebo group (p<0.001), but did not report the final value in the placebo group); the authors also reported that LDL-cholesterol was reduced by 25% more in the pravastatin group than the placebo group (actual values were not reported). Participants with diabetes mellitus: 9%; participants with MI at baseline: 64%; participants with stroke at baseline: 4%.
Indirectness of population	No indirectness
Interventions	(n=4512) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration 6.1 years. Concurrent medication/care: Dietary advice (no further details reported) (n=4502) Intervention 2: Placebo. Placebo. Duration 6.1 years. Concurrent medication/care: Dietary advice (no further details reported)
Funding	Study funded by industry (Supported by a grant from Bristol-Myers Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Any MI (not clear if all non-fatal) at 6.1 years; Group 1: 366/4512, Group 2: 463/4502; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : MI (not clear if all non-fatal) at 8 years (6 years intervention + 2 years open label pravastatin) ; Group 1: 435/4512, Group 2: 570/4502; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Any stroke at 6.1 years; Group 1: 169/4512, Group 2: 204/4502; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: Stroke at 6.1 years; Group 1: 34/542, Group 2: 53/535; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Total stroke at 8 years (6 years intervention + 2 years open label pravastatin) ; Group 1: 224/4512, Group 2: 272/4502;

Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: All-cause mortality at 5 years - Actual outcome for Adults with established CVD : All-cause mortality at 6.1 years; Group 1: 498/4512, Group 2: 633/4502; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : Death from any cause at 8 years (6 years intervention + 2 years open label pravastatin) ; Group 1: 717/4512, Group 2: 888/4502; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : All-cause mortality at 6.1 years; HR 0.82 (95%CI 0.73 to 0.92) Calculated – from logrank P-value; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 4: CV mortality at 5 years - Actual outcome for Adults with established CVD : Death due to cardiovascular disease at 6.1 years; Group 1: 331/4512, Group 2: 433/4502; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : Death due to cardiovascular disease at 8 years (6 years intervention + 2 years open label pravastatin) ; Group 1: 461/4512, Group 2: 596/4502; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse event:New onset diabetes at 5 years - Actual outcome for Adults with established CVD : New onset diabetes at 6.1 years; Group 1: 126/3496, Group 2: 138/3501; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	Anon 2000[144]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=4271)
Countries and setting	Conducted in Italy; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: mean 23 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Post-MI
Subgroup analysis within study	Not applicable:
Inclusion criteria	6 months post-acute MI; stable post-infarction clinical condition; stable plasma cholesterol levels between 200 and 250 mg/dL or >250mg/dL if this alone not a sufficient reason for treating the patient (absence of other risk factors).
Exclusion criteria	Contraindications to study treatments; comorbid conditions indicating an unfavourable survival prognosis over a short period of time (for example, malignancy); mental of physical disorders substantially affecting patients compliance; known congenital coagulation defects, known hepatic diseases, renal diseases with serum creatinine ≥3.5mg/dL; presence of other conditions requiring cholesterol-lowering treatment (for example, hypertriglyceridemia ≥500mg/dL); diseases requiring cyclosporine treatment.
Recruitment/selection of patients	Population recruited from cohort of patients randomised to different cholesterol-lowering regimens (n-3 polyunsaturated fatty acids versus vitamin E versus combination versus standard treatment).
Age, gender and ethnicity	Age - Mean (SD): Pravastatin 59.7 (10.4) years, control 60.0 (10.4) years. Gender (M:F): 3684/587. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of

	CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol mmol/l; pravastatin 5.94, control 5.92, total cholesterol at 2 years; pravastatin 5.35, control 5.82. Baseline LDL-cholesterol mmol/l; pravastatin 3.93, control 3.92, LDL cholesterol at 2 years; pravastatin 3.34, control 3.8. Diabetes mellitus; pravastatin 12.9%, control 14.4%. Modifications of study protocol in February 1995 (2 years in to study) - patients with total cholesterol >250mg/dL no longer randomised, patients already randomised with total cholesterol >250mg/dL offered cholesterol lowering therapy if not contraindicated, lower cut-off level of 200mg/dL abolished. In December 1996 trial stopped due to ethical and practical reasons following results of CARE trial.
Indirectness of population	No indirectness
Interventions	(n=2138) Intervention 1: Low intensity statin - Pravastatin 20 mg. Pravastatin 20 mg/day. Dose increased to 40 mg for 4.1% of intervention group, dose reduced to 10 mg for 3.1% of intervention group, adjunctive cholesterol-lowering drug prescribed for 2.2% of intervention group. Duration mean 23 months. Concurrent medication/care: Secondary prevention post-MI. Concomitant treatment: n-3 PUFA 50.1%, vitamin E 49.8%, aspirin 79.8%, other antiplatelet therapy 13.5%, beta blockers 42.7%, calcium antagonists 32.2%, ACE inhibitors 40.2%, nitrates 59.0%, diuretics 10.1% (n=2133) Intervention 2: Placebo. No treatment. Duration mean 23 months. Concurrent medication/care: Secondary prevention post-MI. Concomitant treatment: n-3 PUFA 50.3%, vitamin E 49.1%, aspirin 77.8%, other antiplatelet therapy 13.3%, beta blockers 43.2%, calcium antagonists 32.1%, ACE inhibitors 42.8%, nitrates 59.0%, diuretics 10.8%
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI (probable and definite) at 23 months; Group 1: 39/2138, Group 2: 41/2133; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Non-fatal stroke (probable and definite) at 23 months; Group 1: 16/2138, Group 2: 15/2133; Risk of bias: High;

Indirectness of outcome: No indirectness Protocol outcome 3: All-cause mortality at 5 years - Actual outcome for Adults with established CVD : All fatal events at 23 months; Group 1: 72/2138, Group 2: 88/2133; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: CV mortality at 5 years - Actual outcome for Adults with established CVD : CV mortality at 23 months; Group 1: 52/2138, Group 2: 65/2133; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse event: Myalgia at 5 years - Actual outcome for Adults with established CVD : Muscular pain or weakness at 23 months; Group 1: 6/2138, Group 2: 0/2133; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with established CVD : Transaminases >3 times normal level on 2 consecutive occasions at 23 months; Group 1: 15/2138, Group 2: 0/2133; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 7: Adverse event:New onset diabetes at 5 years - Actual outcome for Adults with established CVD : New onset diabetes at 23 months; Group 1: 96/1743, Group 2: 105/1717; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	Anon 2002[108] (Margolis 2009 [109])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=10,355)
Countries and setting	Conducted in Canada, Puerto Rico, USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Mean 4.8 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fasting lipid profiles and ECG
Stratum	Adults without established CVD : Men and women with hypertension and at least 1 other CHD risk factor
Subgroup analysis within study	Stratified then randomised: Stratified by centre and antihypertensive treatment arm
Inclusion criteria	Prior enrolment in ALLHAT RCT (age ≥55 years and stage 1 or 2 hypertension with at least 1 additional CHD risk factor); fasting LDL-cholesterol level of 120 to 189 mg/dL for those with no known CHD, or 100 to 129 mg/dL for those with known CHD; and fasting triglyceride levels lower than 350 mg/dL.
Exclusion criteria	Participants currently receiving lipid-lowering therapy, taking large doses of niacin, or taking probucol in the last year; were known to be intolerant of statins or to have significant liver or kidney disease or contraindications for statin therapy; or had a known secondary cause of hyperlipidaemia.
Recruitment/selection of patients	Participants were drawn exclusively from ALLHAT, a 4-armed antihypertensive trial, recuited from 513 clinical centres, enrolment took place from March 1994 though to May 1998.
Age, gender and ethnicity	Age - Mean (SD): Pravastatin 66.4 (7.6) years, usual care 66.3 (7.5) years. Gender (M:F): 51%/49%. Ethnicity: 41% White; 34% Black; 19% Hispanic; 6% other
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of

	CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women (Men and women).
Extra comments	Baseline total cholesterol (mg/dL): mean (SD) pravastatin; 223.7 (26.9), usual care; 223.7 (26.7). Baseline LDL-cholesterol (mg/mL): mean (SD) pravastatin; 145.6 (21.4), placebo; 145.5 (21.3). At year 4 total cholesterol: mean (SD) pravastatin; 184.3 (35.3), control; 205.9 (36.6). At year 6 total cholesterol: mean (SD) pravastatin; 177.6 (33.8), control; 196.5 (37.3). At year 4 LDL-cholesterol: mean (SD) pravastatin; 104.5 (28.1), control; 128.7 (32.6). At year 6 LDL-cholesterol: mean (SD) pravastatin 104.0 (29.1), control; 121.2 (34.6). People with type 2 diabetes: 35%; people with a history of CHD: 14%.
Indirectness of population	No indirectness
Interventions	(n=5170) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Initially pravastatin participants began with a dosage of 20 mg taken each evening and increased to 10 mg/day as needed to achieve at least a 25% decrease in LDL-cholesterol. After the first 1000 participants had been enrolled, an uniform dosage of 40 mg/day was adopted. Study practitioners retained the option to lower the dose of pravastatin, or discontinue the drug if significant adverse effects occurred. Duration Mean 4.8 years. Concurrent medication/care: Dietary advice (NCEO Step I diet); study practitioners could prescribe other lipid-lowering interventions, including cholesterol-lowering drugs not supplied by the study (n=5185) Intervention 2: Placebo. Usual care; treated for LDL-cholesterol lowering according to the discretion of a participant's primary care physician, although vigorous cholesterol-lowering therapy in the usual care group was discouraged unless warranted by a change in clinical circumstances. Duration Mean 4.8 years. Concurrent medication/care: Dietary advice (NCEP Step I diet)
Funding	Equipment / drugs provided by industry (Supported by contract NO1-HC-35130 with the National Heart, Lung, and Blood Institute. Bristol-Myers Squibb supplied pravastatin, and financial support was also provided by Pfizer)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO Protocol outcome 1: Non-fatal stroke at 5 years - Actual outcome for Adults without established CVD : Non-fatal stroke at 6 years; Group 1: 156/5170, Group 2: 175/5185; Risk of bias: Low; Indirectness of outcome: No indirectness	

Protocol outcome 2: All-cause mortality at 5 years - Actual outcome for Adults without established CVD : All-cause mortality at 6 years; Group 1: 631/5170, Group 2: 641/5185; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: CV mortality at 5 years - Actual outcome for Adults without established CVD : CV mortality at 6 years; Group 1: 295/5170, Group 2: 300/5185; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults without established CVD : Alanine transaminase >3 times the upper limit of normal at 6 years; Group 1: 21/5170, Group 2: 0/5185; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse event:New onset diabetes at 5 years - Actual outcome for Adults without established CVD : New onset diabetes at 6 years; Group 1: 238/3017, Group 2: 212/3070; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: LDL-cholesterol reduction at 1 year - Actual outcome for Adults without established CVD : LDL-cholesterol at 6 years; Group 1: mean 4.77 mmol/l (SD 0.91); n=5170, Group 2: mean 5.32 mmol/l (SD 0.95); n=5185; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; Adverse event: Myalgia at 5 years; Quality of life at 5 years

Study (subsidiary papers)	Armitage 2010[18] (Bowman 2007 [30])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=12064)
Countries and setting	Conducted in United Kingdom; Setting: SEARCH trial. 88 UK hospitals
Line of therapy	1st line
Duration of study	Intervention time: Mean (SD): 6.7 years (1.5)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Post-MI
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18-80 years; history of previous MI; current statin use or clear indication for this treatment (and no clear indication for folic acid); total-C ≥3.5 mmol/l if already on statin or ≥4.5 mmol/l if not; no clear contraindications to the study treatment
Exclusion criteria	Predominant medical problems that could reduce compliance with long-term study treatment.
Recruitment/selection of patients	Pre-randomisation run-in phase: simvastatin 20 mg/day (and placebo vitamins) and instructed to stop taking any non-study statin.
Age, gender and ethnicity	Age - Mean (SD): 64 (9) years. Gender (M:F): 10012/2052. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).

Extra comments	Baseline values (mmol/l): total-C: 4.23 (0.73); LDL-C: 2.50 (0.61). Average mean differences (SE) for simva 80 minus simva 20: total-C: -0.40 (0.01); LDL-C: -0.35 (0.01).
Indirectness of population	No indirectness
Interventions	(n=6033) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day. Duration 6.7 years. Concurrent medication/care: Aspirin (or another antiplatelet) 91%; warfarin: 5%; beta blocker: 48%; nitrate: 44%; calcium channel blocker: 27%; ACE inhibitor: 38%; angiotensin II receptor antagonist: 4%; hypoglycemics (oral or insulin): 8% (n=6031) Intervention 2: High intensity statin - Simvastatin 80 mg. Simvastatin 80 mg/day. Duration 6.7 years. Concurrent medication/care: Aspirin (or another antiplatelet) 91%; warfarin: 5%; beta blocker: 48%; nitrate: 44%; calcium channel blocker: 27%; ACE inhibitor: 38%; angiotensin II receptor antagonist: 4%; hypoglycemics (oral or insulin): 8%
Funding	Study funded by industry (Merck, UK Medical Research Council, British Heart Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus SIMVASTATIN 80 MG

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 6.7 years; Group 1: 463/6033, Group 2: 397/6031; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Non-fatal stroke at 6.7 years; Group 1: 230/6033, Group 2: 209/6031; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Definite rhabdomyolysis at 6.7 years; Group 1: 0/6033, Group 2: 7/6031; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : 10<CK≤40 ULN at 6.7 years; Group 1: 12/6033, Group 2: 45/6031; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: All-cause mortality at 5 years - Actual outcome for Adults with established CVD : All-cause mortality at 6.7 years; Group 1: 970/6033, Group 2: 964/6031; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: CV mortality at 5 years - Actual outcome for Adults with established CVD : Any vascular death at 6.7 years; Group 1: 572/6033, Group 2: 565/6031; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse event:New onset diabetes at 5 years - Actual outcome for Adults with established CVD : New diabetes at 6.7 years; Group 1: 591/6033, Group 2: 633/6031; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	Asselbergs 2004[20] (Asselbergs 2005 [21])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=864)
Countries and setting	Conducted in Netherlands; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: mean 46 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Hospitalisation values for blood pressure and cholesterol were based on guidelines of GPs from the Netherlands in 1998; outcome measures were reported in detail
Stratum	Adults with CKD: Men and women with microalbuminuria (with a low prevalence of diabetes mellitus, and low prevalence of previous CVD event; also normal blood pressure and cholesterol level at baseline)
Subgroup analysis within study	Post-hoc subgroup analysis: High and low albuminuria
Inclusion criteria	Participants in the PREVEND IT had to have persistent microalbuminuria, a blood pressure <160/100 mm Hg and no use of hypertensive medicine, and a total cholesterol level <8.0 mmol/l, or <5.0 nmol/l in case of previous MI, and no use of lipid-lowering medication
Exclusion criteria	Creatinine clearance <60% of the normal age-adjusted value and use of ACE inhibitors or angiotensin II receptor antagonists.
Recruitment/selection of patients	PREVEND IT is a sub study of the PREVEND program (a program to assess the value of microalbinuria as an indicator of increased cardiovascular and renal risk in the general population). In 1997 to 1998, all inhabitants (28 to 75 years) of the city of Groningen were asked to send in a morning urine sample, and to fill out a questionnaire. From April 1998 to June 1999, subjects willing to participate in PREVENT IT
Age, gender and ethnicity	Age - Mean (SD): 51 (12) years. Gender (M:F): 65%/35%. Ethnicity: 95-97% 'White'

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol (mmol/l): mean (SD) 5.8 (1.1) (in both treatment groups); LDL-cholesterol: 4.1 ((1.0) pravastatin and 4.0 (1.0) placebo; At 4 years total cholesterol: 4.8 (1.0) (n=376) pravastatin group and 5.6 (1.1) (n=382) in the placebo group; LDL-cholesterol: 3.1 (0.9) (n=375) in the pravastatin group and 3.9 (0.9) (n=379) in the placebo group; Baseline data: 2.8% in active and 2.3% had diabetes mellitus; 0.2% in active and 0.7% in placebo had MI; 4.4% in active and 2.3% in placebo group had a prior CVD event.
Indirectness of population	No indirectness
Interventions	(n=433) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration Mean 46 months. Concurrent medication/care: Some of the participants also received fosinopril 20 mg (n=431) Intervention 2: Placebo. Placebo. Duration Mean 46 months. Concurrent medication/care: Some of the participants also received fosinopril 20 mg
Funding	Academic or government funding (Funded by a grant from the Dutch Kidney Foundation and the Netherlands Heart Foundation, and an unrestricted grant from Bristol Myers Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with CKD: Hospitalisation for nonfatal myocardial infarction and/or myocardial ischaemia at 46 months; Group 1: 8/433, Group 2: 15/431; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with CKD: Cerebrovascular accident at 46 months; Group 1: 7/433, Group 2: 4/431; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: CV mortality at 5 years - Actual outcome for Adults with CKD: Cardiovascular mortality at 46 months ; Group 1: 4/433, Group 2: 4/431; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with CKD: LDL-cholesterol at 46 months ; Group 1: mean 3.1 mmol/l (SD 0.9); n=433, Group 2: mean 3.9 mmol/l (SD 0.1); n=431; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	Athyros 2002[24] (Athyros 2005 [23], Athyros 2007[22])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1,600)
Countries and setting	Conducted in Greece; Setting: Conducted in out-patient clinics or usual care outside of the hospital.
Line of therapy	1st line
Duration of study	Intervention time: Mean 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CHD defined as a history of prior MI or >70% stenosis of least 1 coronary artery, as documented by a coronary angiogram.
Stratum	Adults with established CVD : Men and women with established coronary heart disease
Subgroup analysis within study	Post-hoc subgroup analysis: Subgroup analysis was conducted in women, patients with diabetes mellitus, arterial hypertension, age 60-75 years, congestive heart failure, recent unstable angina or prior revascularisation. In addition, analyses were conducted in patients with coronary heart disease and metabolic syndrome (Athyros et al. 2007), and combined treatment with a statin plus low dose ASA compared with each drug alone or neither drug (Athyros et al. 2005)
Inclusion criteria	Patients <75 years with established CHD; LDL cholesterol >100 mg/dL and triglycerides <400 mg/dL. There was no other limit in lipid profile values. Patients with recent ACS were not excluded.
Exclusion criteria	Renal or liver dysfunction, prior hypolipidaemic treatment, childbearing potential and any significant disease likely to limit life to less than the duration of the study (for example, malignancies and heart failure NYHA class II or IV). Patients that were scheduled for coronary revascularisation were also excluded. Patients with liver enzyme increase more than 3-fold ULN, creatine kinase 5 to 10 times ULN, or myalgia without serum creatine kinase elevation would be removed from the study.
Recruitment/selection of patients	Consecutive patients were randomised over a 2-year period; all patients with a LDL-cholesterol >100 mg/dL after a 6-week period on hypolidaemic diet (NCEP step 2) were enrolled into the study.

Age, gender and ethnicity	Age - Mean (SD): Atorvastatin 58 (2) years, usual care 59 (14) years. Gender (M:F): 79%/21%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol (mg/dL): mean 257 (SD) (39) in atorvastatin group and 255 (37) in the usual care group; LDL-cholesterol (mg/dL): mean (SD) 180 (27) in atorvastatin group and 179 (28) in usual care group. After treatment: total cholesterol (mg/dL): mean (SD) 165 (10) in atorvastatin group and 245 (41) in the usual care group; LDL-cholesterol (mg/dL): mean (SD) 97 (4) in atorvastatin group and 169 (32) in usual care group. At baseline, 20% of patients had diabetes mellitus, 81% had MI, 7% had CHF, and 8% had recent unstable angina.
Indirectness of population	No indirectness
Interventions	(n=800) Intervention 1: High intensity statin - Atorvastatin 20 mg. Atorvastatin 20 mg/day (for most participants). Starting dose was 10 mg/day. If the goal of LDL cholesterol of <100 mg/day was not reached within 6 weeks, the dose was increased to 20 mg/day. With evaluations every 6 weeks the dose was titrated up to 80 mg/day. The average dose was 24 mg/day (4% of patients had 10 mg/day, 82% 20 mg/day, 11% 40 mg/day, and 3% 80 mg/day). Duration mean 3 years. Concurrent medication/care: 89% patients were taking aspirin or other antiplatelet agents, 86% were taking beta blockers, 55% were taking ACE inhibitors or ATI antagonists, 13% were taking nitrates, 25% were taking calcium channel blockers, 11% were taking diuretics, and 98% were taking hypolipidemic drugs (n=800) Intervention 2: Placebo. Usual care - this included lifestyle changes, such as hypolipidemic diet, weight loss, exercise plus any necessary drug treatment (for example, lipid-lowering agents). Duration mean 3 years. Concurrent medication/care: Simvastatin was used in 5% of usual care patients, atorvastatin in 3%, pravastatin in 3% and fluvastatin in 1%. 86% patients were taking aspirin or other antiplatelet agents, 84% were taking beta-blockers, 53% were taking ACE inhibitors or ATI antagonists, 16% were taking nitrates, 28% were taking calcium channel blockers, 13% were taking diuretics, and 14% were taking hypolipidemic drugs.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 3 years; Group 1: 21/800, Group 2: 51/800; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Stroke at 3 years; Group 1: 9/800, Group 2: 17/800; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : Total mortality at 3 years; Group 1: 23/800, Group 2: 40/800; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Coronary mortality at 3 years; Group 1: 20/800, Group 2: 38/800; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse event: Myalgia at 5 years
- Actual outcome for Adults with established CVD : Myalgia at 3 years; Group 1: 0/800, Group 2: 0/800; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults with established CVD : Liver enzyme increase > 3-fold of the upper limit of normal at 3 years; Group 1: 7/800, Group 2: 3/800; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 7: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at 3 years; Group 1: mean 2.51 mmol/l (SD 0.1); n=800, Group 2: mean 4.37 mmol/l (SD 0.83); n=800; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Baigent 2005[25]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=448)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with CKD: Adults with CKD
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18 or older, predialysis patient with the most recent serum or plasma creatinine level of 1.7 mg/dL or greater (≥150 micromol/litre), a haemodialysis or peritoneal dialysis patient or had a functioning renal transplant (with any creatinine level) and their own nephrologist or primary care physician did not consider there was a definite indication for or contraindication to cholesterol lowering therapy or aspirin.
Exclusion criteria	Physician considered that cholesterol-lowering therapy should be prescribed, recent history of acute uraemia, history of chronic liver disease, inflammatory muscle disease (for example, dermatomyositis or polymyositis) or creatinine kinase level >3 times ULN, previous adverse reaction to statin or history of aspirin hypersensitivity, concurrent treatment with a contraindicated drug (non-study statin, fibrate, niacin, macrolide antibiotic, systemic azole antifungal, nefazodone, oral anticoagulant therapy), high immediate risk for bleeding (active peptic ulceration, recent injury or haemophilia), child bearing potential with absence of a reliable method of contraception, a life-threatening condition other than CKD or vascular disease, frequent non-attendance or known non-compliance or drug/alcohol abuse.
Recruitment/selection of patients	Patients randomised between October 1999 and March 2001, recruitment was discontinued after an interim analysis showed that the annual rate of major bleeding events was less than anticipated.

Age, gender and ethnicity	Age - Mean (SD): Simvastatin only 52 (15) years, simvastatin plus aspirin 54 (14) years, aspirin only 52 (16) years, double Placebo 54 (15) years. Gender (M:F): Male/Female Ratio Simvastatin only 79/33 Simvastatin Aspirin 78/34 Aspirin only 81/32 Double Placebo 76/35. Ethnicity: Simvastatin Aspirin: White 92% Black 3.6% Indian 3.6% Other 0.9%. Simvastatin Only: White 88.4% Black 7.1% Indian 1.8% Other 1.8%. Aspirin Only: White 88.5% Black 7.1%, Indian 3.5%, Other 0.9%. Double Placebo: White 91% Black 5.4% Indian 3.6% Other 0%
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	2x2 factorial design with simvastatin only, simvastatin plus aspirin, aspirin only and double placebo groups. Baseline characteristics: Diabetes; simvastatin plus aspirin 10.7%, simvastatin only 10.7%, aspirin only 11.5%, double placebo 9.9%. Baseline total cholesterol mmol/l: simvastatin 5.22, placebo 5.15, total cholesterol at 1 year mmol/l; simvastatin 4.22, placebo 5.07. Baseline LDL-cholesterol mmol/l; simvastatin 3.21, placebo 3.13, LDL-cholesterol at 1 year mmol/l simvastatin 2.3, placebo 2.95.
Indirectness of population	No indirectness
Interventions	(n=224) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day. Duration 1 year. Concurrent medication/care: Not reported Comments: 42 (19%) stopped Simvastatin active treatment during the trial (n=224) Intervention 2: Placebo. N/A. Duration 1 year. Concurrent medication/care: Not reported Comments: 40 (18%) stopped placebo Simvastatin during the trial
Funding	Study funded by industry (Merck & Co.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus PLACEBO Protocol outcome 1: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years	

- Actual outcome for Adults with CKD: CK >10 times normal at 1 year; Group 1: 1/224, Group 2: 0/224; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with CKD: ALT >3 times normal level at 1 year; Group 1: 2/224, Group 2: 1/224; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	Beishuizen 2004[28] (Beishuizen 2005[27])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=250)
Countries and setting	Conducted in Netherlands; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with type 2 diabetes: Type 2 diabetes without established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosed with type 2 diabetes for at least 1 year, aged 30-80 years, without a history of CVD (defined as CAD, ECG criteria for a past MI, ischaemic stroke, peripheral artery bypass surgery, percutaneous transluminal angioplasty or amputation because of atherosclerotic disease), fasting total cholesterol 4.0-6.9 mmol/L, triglycerides <6.0 mmol/l.
Exclusion criteria	CK more than 3 times ULN, ALT more than 2 times ULN, creatinine clearance <30 ml/min, use of lipid lowering therapy within 8 weeks of start of the trial.
Recruitment/selection of patients	Patients were recruited from the departments of internal medicine at 2 non-academic teaching hospitals in the Netherlands.
Age, gender and ethnicity	Age - Mean (SD): Simvastatin 58.8 (11.3) years, placebo 58.2(11.4). Gender (M:F): Simvastatin 61/64, placebo 57/68. Ethnicity: Simvastatin Caucasian 66% Indo-Asian 22% other 11%. Placebo Caucasian 69% Indo-Asian 16% other 15%
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6.

	People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Initially, patients were randomised to receive either cerivastatin or placebo. In August 2011, when cerivastatin was withdrawn from the market, participants were instructed to discontinue trial medication. The study was not unblinded and 1 month later cerivastatin was replaced by simvastatin. Statin and matching placebo were given according to original allocation. Baseline total cholesterol mean mmol/l; simvastatin 5.49, placebo 5.60, at 2 years simvastatin 4.49, placebo 5.74. Baseline LDL-cholesterol mean mmol/l; simvastatin 3.44, placebo 3.55, at 2 years simvastatin 2.58, placebo 3.78.
Indirectness of population	No indirectness
Interventions	(n=125) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day (Merck Sharp & Dohme). Duration 2 years. Concurrent medication/care: Insulin 50% (n=125) Intervention 2: Placebo. N/A. Duration 2 years. Concurrent medication/care: Insulin 55%
Funding	Equipment / drugs provided by industry (Bayer, Merck Sharp & Dohme)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with type 2 diabetes: Non-fatal coronary events at 2 years; Group 1: 0/125, Group 2: 4/125; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with type 2 diabetes: CK elevated at 2 years; Group 1: 0/125, Group 2: 0/125; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with type 2 diabetes: All-cause mortality at 2 years; Group 1: 3/125, Group 2: 4/125; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse event: Myalgia at 5 years
- Actual outcome for Adults with type 2 diabetes: Myalgia at 2 years; Group 1: 18/125, Group 2: 26/125; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with type 2 diabetes: ALT >3 times normal level at 2 years; Group 1: 1/125, Group 2: 0/125; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with type 2 diabetes: LDL-cholesterol at 2 years; Group 1: mean 2.64 mmol/l (SD 0.96); n=125, Group 2: mean 3.76 mmol/l (SD 0.83); n=125; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal stroke at 5 years; CV mortality at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	Byington 1995[33] (Furberg 1993 [61], Furberg 1994 [60], Crouse 1995 [46])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=151)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Extracranial carotid atherosclerosis quantified by B-mode ultrasonography
Stratum	Adults with established CVD : Men and women with moderately elevated LDL cholesterol levels and CAD
Subgroup analysis within study	Stratified then randomised: Stratified by a patient's LDL-cholesterol concentration
Inclusion criteria	Coronary disease manifested by a history of heart attack (a documented acute MI with typical evolutionary ECG and enzyme changes) or by cardiac catheterisation with evidence of >50% stenosis; LDL-cholesterol levels had to be between the 60th and 90th percentiles for age and gender and diet-resistant. Patients also had to demonstrate at least 1 qualifying extracranial carotid lesion with an IMT≥1.3 mm on B-mode ultrasound examination.
Exclusion criteria	Plasma triglyceride concentration ≥350 mg/dL, secondary hyperlipidemia, recent myocardial infarction (≥6 months), severe or unstable angina pectoris, uncontrolled CHF or hypertension, significant gastrointestinal disease or surgery that might interfere with drug absorption, and treatment with certain drugs including corticosteroids, androgens, other lipid-lowering agents, or antacids containing aluminium salts.
Recruitment/selection of patients	The authors stated that 1700 participants were identified, but most were excluded due to lipid values outside of the eligibility criteria. Trial follow-up ended in January 1993 (no other details reported).
Age, gender and ethnicity	Age - Mean (SD): 63 years (SD not reported). Gender (M:F): 85%/15%. Ethnicity: Not reported

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol (mg/dL): mean (SE) pravastatin; 235.6 (2.86) and 234.1 (2.33) placebo; LDL-cholesterol: mean (SE) pravastatin; 167.5 (2.24) and 164.3 (2.07) placebo; After 3 years: total cholesterol (mg/dl): mean (SE) pravastatin; 185.7 (2.49) and 235.0 (2.47) placebo; LDL-cholesterol: mean (SE) pravastatin; 120.3 (SE 2.20) and 166.6 (2.20) placebo; Baseline data on percentage of people with diabetes, and prior MI or stroke were not reported.
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 10-40 mg/day. Duration 3 years. Concurrent medication/care: Not reported Comments: 4% of patients had pravastatin 10 mg/day and 23.5% had 20 mg/day dosage (n=76) Intervention 2: Placebo. Placebo. Duration 3 years. Concurrent medication/care: Not reported Comments: 4 patients in the placebo group were placed on active medication by their physicians during the 3 years of follow-up
Funding	Study funded by industry (Bristol-Myers Squibb to the Bowman Gray School of Medicine)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal plus fatal MI at 3 years; Group 1: 2/75, Group 2: 10/76; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : Mortality at 3 years; Group 1: 3/75, Group 2: 5/76; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at 3 years; Group 1: mean 3.11 mmol/l (SD 0.59); n=75, Group 2: mean 4.31 mmol/l (SD 0.56); n=76; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Cannon 2004[34]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=4162)
Countries and setting	Conducted in Australia, Canada, United Kingdom, USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Mean 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Hospitalised for an acute coronary syndrome within the preceding 10 days
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women who were at least 18 years old were eligible for inclusion if they had been hospitalised for ACS (acute MI (with or without ECG evidence of ST-segment elevation) or high-risk unstable angina in the preceding 10 days). Patients had to be in stable condition and were to be enrolled after a percutaneous revascularisation procedure if one was planned. Finally, patients had to have a total cholesterol level of 240 mg/dL (6.21 mmol/l) or less, measured at the local hospital within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours. Patients who were receiving long-term lipid-lowering therapy at the time of their index acute coronary syndrome had to have a total cholesterol level of 200 mg/dL (5.18 mmol/l) or less at the time of screening in the local hospital.
Exclusion criteria	Coexisting condition expected to shorten survival to less than 2 years, were receiving therapy with any statin at a dose of 80 mg/day at the time of their index event or lipid-lowering therapy with fibric acid derivatives or niacin that could not be discontinued before randomisation, had received drugs that are strong inhibitors of cytochrome P-450 3A4 within the month before randomisation or were likely to require such treatment during the study period (because atorvastatin is metabolised by this pathway), had undergone PCI within the previous 6 months (other than for the qualifying event) or CABG within the previous 2 months or were scheduled to undergo bypass surgery in response to the index event, had factors that might prolong the QT interval, had obstructive hepatobiliary disease or other serious hepatic disease, had an

	unexplained elevation in the creatine kinase level that was more than 3 times ULN and that was not related to MI, or had a creatinine level of more than 2.0 mg/dL (176.8 micromol/litre).
Recruitment/selection of patients	Between Nov 2000 and Dec 2001.
Age, gender and ethnicity	Age - Mean (SD): 58 years. Gender (M:F): 78%/22%. Ethnicity: White 91%
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Lipid values (mmol/l). Baseline: Total cholesterol: 4.65 (pravastatin 40 mg), 4.68 (atorvastatin 80 mg); LDL-cholesterol: 2.74 (pravastatin 40 mg), 2.74 (atorvastatin 80 mg). End of study: LDL-cholesterol: 2.46 (pravastatin), 1.60 (atorvastatin 80 mg). Prior MI: 18%; CABG: 11%; diabetes mellitus: 18%.
Indirectness of population	No indirectness
Interventions	(n=2063) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration 2 years. Concurrent medication/care: Dietary counselling: 100% of patients, aspirin: 93%, warfarin: 8%, clopidogrel or ticlodipine: 72% percent initially and 20% at 1 year, beta-blockers: 85%, ACE inhibitors: 69%, ARBs: 14% (n=2099) Intervention 2: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg/day. Duration 2 years. Concurrent medication/care: Dietary counselling: 100% of patients, aspirin: 93%, warfarin: 8%, clopidogrel or ticlodipine: 72% percent initially and 20% at 1 year, beta blockers: 85%, ACE inhibitors: 69%, ARBs: 14%
Funding	Study funded by industry (Bristol-Myers Squibb and Sankyo)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus ATORVASTATIN 80 MG Protocol outcome 1: Non-fatal MI at 5 years - Actual outcome for Adults with established CVD : MI at 2 years; Group 1: 153/2063, Group 2: 139/2099; Risk of bias: Low; Indirectness of outcome: No indirectness	

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Stroke at 2 years; Group 1: 21/2063, Group 2: 21/2099; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Rhabdomyolysis at 2 years; Group 1: 0/2063, Group 2: 0/2099; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 2 years; Group 1: 66/2063, Group 2: 46/2099; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Death from CHD at 2 years; Group 1: 29/2063, Group 2: 23/2099; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults with established CVD : Elevation in alanine aminotransferase>3 times upper limit of normal at 2 years; Group 1: 23/2063, Group 2: 69/2099; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	Colhoun 2004[39] (Colhoun 2005 [41], Armani 2006 [17], Hitman 2007 [72], Newman 2008 [125], Charlton-Menys 2009 [35], Colhoun 2009 [40])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=2841)
Countries and setting	Conducted in Irish Republic, United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Median 3.9 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diabetes mellitus defined using the 1985 WHO criteria
Stratum	Adults with type 2 diabetes: Patients with type 2 diabetes without high concentrations of LDL-cholesterol
Subgroup analysis within study	Not stratified but pre-specified: Subgroup analyses were conducted by age, sex, and baseline lipids. In addition, post hoc subgroup analysis was conducted in patients without a prior history of cardiovascular disease (Colhoun 2005), by kidney status (Colhoun 2009), and baseline ratios of ApoB and ApoA-I (Charlton-Menys et al. 2009)
Inclusion criteria	Men and women aged 40-75 years with type 2 diabetes mellitus diagnosed at least 6 months before study entry were included as long as they had at least 1 or more of the following: a history of hypertension; retinopathy; microalbuminuria or macroalbimnuria; or currently smoking. All patients reported current smoking were counselled to quit. Mean serum LDL-cholesterol had to be 4.14 mmol/l or lower and serum triglycerides 6.78 mmol/l or less during baseline visits.
Exclusion criteria	Past history of MI, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease, plasma creatinine concentration >150 micromol/litre, glycated haemoglobin of more than 12%, or if during the baseline phase they had less than 80% compliance with placebo.
Recruitment/selection of patients	Investigators identified potentially eligible individuals by reviewing computerised registers of patients and by opportunistic assessment of people attending diabetes clinics. Patients were randomised between Nov 1997 and June 2001.

Age, gender and ethnicity	Age - --: . Gender (M:F): 68%/32%. Ethnicity: 95% White
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Lipid values mean (SD) (mmol/l) - Baseline total cholesterol; 5.36 (0.83) in atorvastatin group and 5.35 (0.82) in the placebo group, LDL-cholesterol; 3.04 (0.72) in atorvastatin group and 3.02 (0.70) in the placebo group. At 4 years total cholesterol; 4.12 (0.84) in atorvastatin group and 5.28 (0.91) in the placebo group, LDL-cholesterol (mmol/); 2.11 (0.70) in atorvastatin group and 3.12 (0.80) in the placebo group. There was no information on the percentage of people with cerebrovascular disease at baseline (as this was part of the exclusion criteria). All patients had diabetes.
Indirectness of population	No indirectness
Interventions	(n=1429) Intervention 1: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10 mg/day. Duration Median 3.9 years. Concurrent medication/care: If lipid-lowering had to be started for any clinical indication during the study period the investigator could prescribe additional treatment on top of study drug including: atorvastatin 10 mg; simvastatin (up to) 40 mg, pravastatin (up to) 40 mg; fluvastatin (up to) 80 mg, and cerivastatin 0.3 mg (before its withdrawal). (n=1412) Intervention 2: Placebo. Placebo. Duration Median 3.9 years. Concurrent medication/care: If lipid-lowering had to be started for any clinical indication during the study period the investigator could prescribe additional treatment on top of study drug including: atorvastatin 10 mg; simvastatin (up to) 40 mg, pravastatin (up to) 40 mg; fluvastatin (up to) 80 mg, and cerivastatin 0.3 mg (before its withdrawal).
Funding	Study funded by industry (The study was funded by Diabetes UK, the UK Department of Health, Pfizer UK, and Pfizer Inc.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 10 MG versus PLACEBO Protocol outcome 1: Non-fatal MI at 5 years	

- Actual outcome for Adults with type 2 diabetes: Non-fatal MI at Median 3.9 years; Group 1: 25/1428, Group 2: 41/1410; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with type 2 diabetes: Non-fatal stroke at Median 3.9 years; Group 1: 39/1428, Group 2: 21/1410; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: Non-fatal stroke at Median 3.9 years; HR 0.52 (95%CI 0.31 to 0.89) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with type 2 diabetes: Rhabdomyolysis at Median 3.9 years; Group 1: 0/1428, Group 2: 0/1410; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: All-cause mortality at 5 years
- Actual outcome for Adults with type 2 diabetes: All-cause mortality at Median 3.9 years; Group 1: 61/1428, Group 2: 82/1410; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: All-cause mortality at Median 3.9 years; HR 0.73 (95%CI 0.52 to 1.01) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: CV mortality at 5 years
- Actual outcome for Adults with type 2 diabetes: Fatal MI and other acute coronary heart disease death at Median 3.9 years; Group 1: 18/1428, Group 2: 24/1410; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: Adverse event: Myalgia at 5 years
- Actual outcome for Adults with type 2 diabetes: Myalgia (treatment associated) at Median 3.9 years; Group 1: 14/1428, Group 2: 17/1410; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 7: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults with type 2 diabetes: Alanine transaminase and aspartate transaminase >3 times the upper limit of normal at Median 3.9 years; Group 1: 23/1428, Group 2: 18/1410; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 8: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with type 2 diabetes: LDL-cholesterol reduction at Median 3.9 years; Group 1: mean 2.11 mmol/l (SD 0.71); n=1429, Group 2: mean 3.12 mmol/l (SD 0.8); n=1412; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Crouse 2007[47]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=876)
Countries and setting	Conducted in Multiple countries; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults without established CVD : low risk for CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 45 to 70 years (men) or 45 to 70 years (women); screening LDL-cholesterol level of 120 to less than 190mg/dL (3.1 to <4.9mmol/l) for those with only age as CHD risk factor or 120 to less than 160mg/dL (3.1 to <4.1 mmol/l) for individuals with 2 or more CHD risk factors and a 10 year risk of CHD events of less than 10%; HDL-cholesterol level of 60 mg/dL or lower (≤1.6mmol/l); level of triglycerides lower than 500mg/dL (<5.7 mmol/l); and maximum CIMT measurements between 1.2 mm and less than 3.5 mm from 2 separate ultrasound examinations.
Exclusion criteria	Use of lipid lowering therapies in the previous 12 months, clinical evidence of CAD or other peripheral atherosclerotic disease, prior revascularisation procedures, 10 year CHD risk 10% or more, diabetes mellitus, uncontrolled hypertension, or familial hypercholesterolaemia, or serum creatinine concentration higher than 2mg/dL (>177 micromol/litre).
Recruitment/selection of patients	Study conducted at 61 primary care centres in the USA and Europe between Aug 2002 and May 2006.
Age, gender and ethnicity	Age - Mean (SD): Rosuvastatin 57 (6.2) years, placebo 57 (6.0) years. Gender (M:F): Rosuvastatin 421/281; Placebo 167/115. Ethnicity: White race(%) Rosuvastatin 94 Placebo 95

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Total cholesterol baseline mean (mmol/l); rosuvastatin 5.92, placebo 5.95, total cholesterol at 2 years; rosuvastatin 3.93, placebo 5.97. LDL-cholesterol at baseline mean (mmol/l); rosuvastatin 4.01, placebo 3.98, LDL-cholesterol at 2 years; rosuvastatin 2.07, placebo 3.98.
Indirectness of population	No indirectness
Interventions	(n=702) Intervention 1: High intensity statin - Rosuvastatin 40 mg. Rosuvastatin 40 mg. Duration 2 years. Concurrent medication/care: Aspirin 2%, Antihypertensive 14% (n=282) Intervention 2: Placebo. N/A. Duration 2 years. Concurrent medication/care: Aspirin 3%, Antihypertensive 14%
Funding	Study funded by industry (AstraZeneca)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ROSUVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults without established CVD : Adverse event report of myocardial infarction at 2 years; Group 1: 1/700, Group 2: 0/281; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults without established CVD : Rhabdomyolysis at 2 years; Group 1: 1/700, Group 2: 2/281; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : Adverse event report of all deaths at 2 years; Group 1: 1/700, Group 2: 0/281; Risk of bias: High; Indirectness of

outcome: No indirectness Protocol outcome 4: Adverse event: Myalgia at 5 years - Actual outcome for Adults without established CVD : Myalgia at 2 years; Group 1: 89/700, Group 2: 34/281; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults without established CVD : Transaminases >3 times normal level on 2 consecutive occasions at 2 years; Group 1: 4/700, Group 2: 1/281; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal stroke at 5 years; CV mortality at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	De lemos 2004[50]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=4497)
Countries and setting	Conducted in Argentina, Australia, Belgium, Chile, China, Colombia, Croatia, Estonia, Finland, France, Germany, Greece, Hong Kong (China), Hungary, Israel, Italy, Latvia, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, USA, Venezuela; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Up to 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Patients with ACS
Subgroup analysis within study	Not applicable
Inclusion criteria	Phase A. Open-label noninferiority trial comparing enoxaparin with unfractionated heparin in patients with non–ST-elevation ACS who were treated with tirofiban and aspirin. Patients were required to have chest pain at rest lasting 10 minutes or longer within the previous 24 hours, which was associated with either ST elevation or depression of 0.5 mm or higher, or with elevated levels of creatine kinase–MB or troponin. Phase Z. Patients between the ages of 21 and 80 years with either non–ST-elevation ACS or ST-elevation MI; total cholesterol level ≤6.48 mmol/l. Initially, patients were entered into phase Z only if they presented with non–ST-elevation ACS, were stabilised during phase A of the trial for at least 12 consecutive hours within 5 days after symptom onset, and met at least 1 of the following high-risk characteristics: age older than 70 years; diabetes mellitus; prior history of CAD, PAD, or stroke; elevation of serum creatine kinase–MB or troponin levels; recurrent angina with ST-segment changes; ECG evidence of ischemia on a predischarge stress test; or multivessel coronary artery disease determined by coronary angiography. Patients enrolled in phase A who did not meet stability and high-risk criteria were not eligible for continuation to phase Z. The protocol was amended to allow patients with non–ST-elevation ACS who were not enrolled in phase A and patients with ST-elevation MI to enter directly into phase Z. Patients in the latter category were required to receive fibrinolytic therapy or

	PCI if they presented within 12 hours of symptom onset and no reperfusion therapy if symptom onset was longer than 12 hours prior to presentation. Patients were also required to meet criteria for stability and have at least 1 high-risk feature in addition to cardiac biomarker elevation.
Exclusion criteria	Patients receiving statin therapy at the time of randomisation, if CABG was planned, or if PCI was planned within the first 2 weeks after enrolment. Patients with alanine aminotransferase (ALT) level >20% above ULN; increased risk for myopathy due to renal impairment (serum creatinine level >2.0 mg/dl [176.8 micromol/litre]) or concomitant therapy with agents known to enhance myopathy risk, such as fibrates, cyclosporine, macrolide antibiotics, azole antifungals, amiodarone, or verapamil; prior history of non-exercise-related elevations in creatine kinase level or nontraumatic rhabdomyolysis.
Recruitment/selection of patients	Phase Z of the A to Z trial.
Age, gender and ethnicity	Age - Median (range): 61 (52-69). Gender (M:F): 76%/24%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear
Extra comments	. Lipid levels in mmol/l. Baseline (simvastatin 20 mg): Total cholesterol: 4.77 (4.27-5.34); LDL-cholesterol: 2.87 (2.46-3.39). Baseline (simvastatin 80 mg): Total cholesterol: 4.79 (4.22-5.31); LDL-cholesterol: 2.90 (2.43-3.37). 2-years (simvastatin 20): Total-cholesterol: 4.07 (3.57-4.56); LDL-cholesterol: 2.10 (1.71-2.49). 2-years (simvastatin 80 mg): Total cholesterol: 3.57 (3.16-4.09); LDL-cholesterol: 1.71 (1.40-2.12). Values expresses as median (25th-75th percentiles) mmol/l. Diabetes: 24%. Hypertension: 50%. STEMI: 40%. Non-ST-segment elevation ACS: 60%.
Indirectness of population	No indirectness
Interventions	(n=2232) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Placebo for 4 months followed by simvastatin 20 mg/day. Duration 2 years. Concurrent medication/care: Aspirin: 98%; beta blockers: 90%; ACE inhibitors: 72% Comments: Patients who had LDL-cholesterol levels >3.37 mmol/l at month 8 or any subsequent visit were provided additional dietary, lifestyle, and compliance counselling. If after 6 weeks the LDL-cholesterol level remained >3.37 mmol/l, the investigator could either add a bile acid sequestrant or discontinue the study drug and initiate open-label statin therapy. The study drug was discontinued if the LDL-cholesterol level was 1.04 mmol/l or lower.

	(n=2265) Intervention 2: High intensity statin - Simvastatin 80 mg. Simvastatin 40 mg/day for 1 month followed by simvastatin 80 mg/day. Duration 2 years. Concurrent medication/care: Aspirin: 98%; beta blockers: 90%; ACE inhibitors: 70% Comments: Patients who had LDL-cholesterol levels >3.37 mmol/l at month 8 or any subsequent visit were provided additional dietary, lifestyle, and compliance counselling. If after 6 weeks the LDL-cholesterol level remained >3.37 mmol/l, the investigator could either add a bile acid sequestrant or discontinue the study drug and initiate open-label statin therapy. The study drug was discontinued if the LDL-cholesterol level was 1.04 mmol/l or lower.
Funding	Study funded by industry (Merck & company, Whitehouse Station, NJ)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus SIMVASTATIN 80 MG

Protocol outcome 1: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 2 years; HR 0.79 (95%CI 0.61 to 1.02) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: CV mortality at 5 years
- Actual outcome for Adults with established CVD : CV mortality at 2 years; HR 0.75 (95%CI 0.57 to 1) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : MI at 2 years; Group 1: 155/2232, Group 2: 151/2265; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : MI at 2 years; HR 0.96 (95%CI 0.77 to 1.21) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Stroke at 2 years; Group 1: 35/2232, Group 2: 28/2265; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Stroke at 2 years; HR 0.79 (95%CI 0.48 to 1.3) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Levels of CK >10 times the upper limit of normal at 2 years; Group 1: 1/2230, Group 2: 9/2263; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 6: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 2 years; Group 1: 130/2232, Group 2: 104/2265; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 7: CV mortality at 5 years - Actual outcome for Adults with established CVD : CV mortality at 2 years; Group 1: 109/2232, Group 2: 83/2265; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 8: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with established CVD : Levels of AST or ALT >3 times the upper limit of normal at 2 years; Group 1: 8/2068, Group 2: 19/2132; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	Deedwania 2007[52]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=893)
Countries and setting	Conducted in Multiple countries; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : History of CAD
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 65-85 years; documented history of CAD; baseline LDL-cholesterol between 2.6-6.5 mmol/l; ≥1 episode of myocardial ischemia with a total duration of ≥3 minutes during 48-hour ambulatory ECG monitoring at the screening visit.
Exclusion criteria	Not stated
Recruitment/selection of patients	Patients already receiving lipid-lowering therapy entered a washout period of ≥6 weeks; patients on digitalis glycosides underwent a 4-week washout period.
Age, gender and ethnicity	Age - Mean (SD): Atorvastatin: 72.4 (5.1) years, pravastatin: 72.6 (5.2) years. Gender (M:F): 70%/30%. Ethnicity: White (97%)
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6.

	People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Baseline values (mmol/l). Total cholesterol: atorvastatin 5.8, pravastatin 5.7. LDL-cholesterol: atorvastatin 3.8, pravastatin 3.7. Least-squares mean percent changes in lipid parameters at 1 year: Total cholesterol: atorvastatin -39.5, pravastatin -21.3. LDL-cholesterol: atorvastatin -55.4, pravastatin -32.4. MI: atorvastatin 45.5%, pravastatin 46.3%. Cerebrovascular accident: atorvastatin 2.2%, pravastatin 6.1%. CABG: atorvastatin 26.5%, pravastatin 32.4%. Angioplasty: atorvastatin 31.6%, pravastatin 28.5%. Angina: atorvastatin 94.4%, pravastatin 93.0%. Hypertension: atorvastatin 66.4%, pravastatin 62.7%. CHF: atorvastatin 5.4%, pravastatin 5.2%. Diabetes mellitus: atorvastatin 22.4%, pravastatin 24.0%.
Indirectness of population	No indirectness
Interventions	(n=445) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration 1 year. Concurrent medication/care: Not stated (n=446) Intervention 2: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg/day. Duration 1 year. Concurrent medication/care: Not stated
Funding	Study funded by industry (Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus ATORVASTATIN 80 MG

Protocol outcome 1: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Stroke at 1 year; Group 1: 3/445, Group 2: 1/446; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Rhabdomyolysis at 1 year; Group 1: 0/445, Group 2: 0/446; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : CPK >10 times ULN at 1 year; Group 1: 1/445, Group 2: 0/446; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 1 year; Group 1: 18/445, Group 2: 6/446; Risk of bias: Low; Indirectness of outcome: No

indirectness - Actual outcome for Adults with established CVD : All-cause mortality at 1 year; HR 0.31 (95%CI 0.12 to 0.79) Calculated – from Kaplan Meier curve; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: CV mortality at 5 years - Actual outcome for Adults with established CVD : CV mortality at 1 year; Group 1: 10/445, Group 2: 4/445; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse event: Myalgia at 5 years - Actual outcome for Adults with established CVD : Myalgia at 1 year; Group 1: 5/445, Group 2: 8/446; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with established CVD : ALT or AST >3 times ULN at 1 year; Group 1: 1/445, Group 2: 19/446; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	Egede 2013[54]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=87)
Countries and setting	Conducted in Denmark; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Angiographic assessment
Stratum	Adults with established CVD :
Subgroup analysis within study	Not applicable
Inclusion criteria	1) STEMI; 2) No prior treatment with statins or other lipid lowering drugs; and 3) a non-significant lesion in 1 of the 2 non-culprit coronary arteries (angiographic diameter stenosis ≥20% and <50%.
Exclusion criteria	1) age below 18 or above 81 years; 2) unconscious patients; 3) serum creatinine >176 micromol/litre; 4) hypothyroidism (TSH >1.5 times ULN); 5) current liver disease (ALAT >2 times ULN); 6) unexplained creatine kinase; 8) prior myopathy or serious hypersensitivity reaction caused by statins; 9) women with child-bearing potential not using chemical or mechanical contraception; 10) pregnant or breastfeeding women; 11) history of malignancy unless a disease-free period of more than 5 years was present; 12) participation in another RCT; 13) treatment with cyclosporine or fibrates.
Age, gender and ethnicity	Age - Mean (SD): Low dose rosuvastatin 60.0 (10.3) years, high dose rosuvastatin 62.0 (9.9) years. Gender (M:F): 73:14. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6.

	People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: Medium intensity statin - Rosuvastatin 5 mg. Rosuvastatin 5 mg/day. Duration 1 year. Concurrent medication/care: Beta blockers, calcium antagonists, ACE inhibitors, ATII inhibitors, diuretics (n=43) Intervention 2: High intensity statin - Rosuvastatin 40 mg. Rosuvastatin 40 mg/day. Duration 1 year. Concurrent medication/care: Beta blockers, calcium antagonists, ACE inhibitors, ATII inhibitors, diuretics
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ROSUVASTATIN 5 MG versus ROSUVASTATIN 40 MG Protocol outcome 1: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at 1 year; Group 1: mean 1.6 mmol/l (SD 0.7); n=39, Group 2: mean 1.6 mmol/l (SD 0.7); n=38; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Gottlieb 2008[66]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=31)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Angiographic confirmation.
Stratum	Adults with established CVD :
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 18 years, required to have documented atherosclerosis in at least 1 vascular territory defined as: at least moderate (>3.9 mm wall thickness) aortic atherosclerosis seen on transoesophageal echocardiography or moderate coronary heart disease (>50% stenosis) in at least 1 coronary artery seen at cardiac catheterisation or more than 50% carotid lesion or symptomatic peripheral vascular disease as assessed by ultrasound. Not on a dose equivalent to or greater than 80 mg of simvastatin.
Exclusion criteria	Metallic implants and claustrophobia, contraindications for a nasogastric catheterisation, elevated baseline liver transaminases and serum creatinine (>2 times normal) or inability to give informed consent.
Recruitment/selection of patients	Single centre
Age, gender and ethnicity	Age - Mean (SD): Simvastatin 80 mg; 71.3 (8.3) years, simvastatin 20 mg; 65.5 (9.3) years. Gender (M:F): 24:7. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of

	CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day. Duration 1 year. Concurrent medication/care: Not reported (n=19) Intervention 2: High intensity statin - Simvastatin 80 mg. Simvastatin 80 mg/day. Duration 1 year. Concurrent medication/care: Not reported
Funding	Study funded by industry (Merck, National Institute Aging, Donald W Reynolds Johns Hopkins CV Center, NIH/NCRR grant, NHLBI grant, Johns Hopkins Field Center)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus SIMVASTATIN 80 MG Protocol outcome 1: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at 1 year; Group 1: mean 2.63 mmol/l (SD 0.19); n=12, Group 2: mean 1.6 mmol/l (SD 0.7); n=19; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Hong 2008[74]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in South Korea; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Quantitative coronary angiography
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Angina patients who had mild to moderate degree of coronary stenosis with vulnerable plaque. A mild to moderate degree of coronary stenosis was defined as a diameter stenosis of 30% to 60%. Vulnerable plaque was defined as plaque with a large lipid core with a thin fibrous cap.
Exclusion criteria	MI, severe LVDF (ejection fraction <40%), hepatic or renal dysfunction.
Recruitment/selection of patients	Recruited from hospital.
Age, gender and ethnicity	Age - Mean (SD): Rosuvastatin 60 (8) years, atorvastatin 62 (9) years. Gender (M:F): 18/12. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: (Men and women).
Indirectness of population	No indirectness

Interventions	(n=16) Intervention 1: High intensity statin - Rosuvastatin 20 mg. Rosuvastatin. Duration 1 year. Concurrent medication/care: Aspirin, clopidigrel, ACE inhibitor, ARB, beta blocker, calcium channel blocker (n=14) Intervention 2: High intensity statin - Atorvastatin 40 mg. Atorvastatin. Duration 1 year. Concurrent medication/care: Aspirin, clopidigrel, ACE inhibitor, ARB, beta blocker, calcium channel blocker
Funding	Academic or government funding (The Korean Society of Circulation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ROSUVASTATIN 20 MG versus ATORVASTATIN 40 MG

Protocol outcome 1: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Rhabdomyolysis at 12 months; Group 1: 0/16, Group 2: 0/14; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at baseline and follow-up, mean change at 12 months; Group 1: mean 1.68 mmol/l (SD 0.64); n=16, Group 2: mean 1.86 mmol/l (SD 0.67); n=14; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Hong 2009[73]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=100)
Countries and setting	Conducted in South Korea; Setting: Cardiovascular Centre
Line of therapy	1st line
Duration of study	Intervention time: I year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Adults with CV disease
Subgroup analysis within study	Not applicable:
Inclusion criteria	Patients with de novo non-culprit/non-target lesions without significant stenosis by coronary angiogram (diameter stenosis <50%), lesions with a plaque burden <0.75 by gray-scale IVUS, and lesions located in 1 of 3 major epicardial arteries in which stent implantation was not performed.
Exclusion criteria	Patients with severely calcific lesions, haemodynamically unstable patients, cardiogenic shock, recommended CABG, and previous history of administration of lipid-lowering agents including statin.
Recruitment/selection of patients	Not specified.
Age, gender and ethnicity	Age - Mean (SD): 50 years (SD not reported). Gender (M:F): 77%/23%. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).

Extra comments	Baseline total cholesterol mean (SD) (mg/dL): 191 (34) in simvastatin group and 189 (27) in the rosuvastatin group; LDL-cholesterol mean SD) (mg/dL): 119 (30) in simvastatin group and 116 (28) in the rosuvastatin group. There was no information on the percentage of people with cerebrovascular disease at baseline (as this was part of the exclusion criteria), 26% had diabetes in the simvastatin group and 22% had diabetes in the rosuvastatin group.
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20mg/day. Duration 1 year. Concurrent medication/care: At baseline: nitrates: 92%; calcium channel blocker: 82%; beta blocker: 80%; angiotensin II receptor antagonist: 28%; angiotensin-converting enzyme inhibitor: 22% (n=50) Intervention 2: High intensity statin - Rosuvastatin 10 mg. Rosuvastatin 10 mg/day. Duration 1 year. Concurrent medication/care: At baseline: nitrates: 94%; calcium channel blocker: 86%; beta blocker: 76%; angiotensin II receptor antagonist: 24%; angiotensin-converting enzyme inhibitor: 20%
Funding	Academic or government funding (Partly supported by Cardiovascular Research Foundation, Seoul, Korea and a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Korea.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus ROSUVASTATIN 10 MG

Protocol outcome 1: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : Death due to any cause at 1 year; Group 1: 0/50, Group 2: 0/50; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at 1 year; Group 1: mean 2.01 mg/dl (SD 0.52); n=50, Group 2: mean 1.66 mg/dl (SD 0.54); n=50; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse

	event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Ito 2001[79]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=665)
Countries and setting	Conducted in Japan; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 3.9 years (median)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥60 years; serum total cholesterol levels 5.7-7.2 mmol/l.
Exclusion criteria	Familial and secondary hypercholesterolemia.
Recruitment/selection of patients	Recruited from 52 hospitals, universities and clinics across Japan.
Age, gender and ethnicity	Age - Mean (SD): 72.8 (5.7). Gender (M:F): 138/527. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline values mean (mmol/l): Total cholesterol: Pravastatin 5 mg: 6.5; Pravastatin 20 mg: 6.5. LDL-cholesterol: Pravastatin 5 mg: 4.2; Pravastatin 20 mg: 4.3. MI: Pravastatin 5 mg: 3%; Pravastatin 20 mg: 3%. Angina pectoris: Pravastatin 5 mg: 10%; Pravastatin 20 mg: 9%. CVD: Pravastatin 5 mg: 14%; Pravastatin 20 mg: 11%. ASO: MI: Pravastatin

	5 mg: 1%; Pravastatin 20 mg: 1%. Diabetes mellitus: Pravastatin 5 mg: 31%; Pravastatin 20 mg: 29%. Hypertension: Pravastatin 5 mg: 51%; Pravastatin 20 mg: 50%. Decrease in cholesterol levels from baseline between 3 months and 3 years: Total cholesterol: Pravastatin 5 mg: 11-13%; Pravastatin 20 mg: 15-17%; LDL-cholesterol: Pravastatin 5 mg: 17-20%; Pravastatin 20 mg: 23-26%.
Indirectness of population	No indirectness
Interventions	(n=334) Intervention 1: Low intensity statin - Pravastatin 5 mg. Pravastatin 5 mg/day. Duration 3.9 years. Concurrent medication/care: Not reported (n=331) Intervention 2: Low intensity statin - Pravastatin 20 mg. Pravastatin 10-20 mg/day. Duration 3.9 years. Concurrent medication/care: Not reported
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 5 MG versus PRAVASTATIN 20 MG Protocol outcome 1: Non-fatal MI at 5 years - Actual outcome: Non-fatal MI at 3.9 years; Group 1: 4/334, Group 2: 1/331; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: All-cause mortality at 5 years - Actual outcome: All-cause mortality at 3.9 years; Group 1: 20/334, Group 2: 14/331; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: CV mortality at 5 years - Actual outcome: CV mortality at 3.9 years; Group 1: 6/334, Group 2: 8/331; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	Knopp 2006[90]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=2411)
Countries and setting	Conducted in Multiple countries; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Median 4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Type 2 diabetes defined by WHO
Stratum	Adults with type 2 diabetes: Individuals with type 2 diabetes, with and without prior MI or interventional procedure, and LDL-cholesterol levels below guideline targets
Subgroup analysis within study	Not stratified but pre-specified: Subgroup analysis was conducted in primary and secondary prevention diabetic subjects
Inclusion criteria	Males and females, aged 40-75 years, with type 2 diabetes diagnosed ≥3 years before screening, LDL-cholesterol ≥140 mg/dL if subjects had documented MI or an interventional procedure >3 months before screening or LDL cholesterol ≥160 mg/dL if not. Triglyceride levels were required to be ≥600 mg/dL at all visits. The protocol was amended 2 years after start of study to enrol subjects without prior MI or interventional procedure.
Exclusion criteria	Type I diabetes; MI, interventional procedure, or episodes of unstable angina ≥3 months before screening; HbA1c >10%; active liver disease or hepatic dysfunction; severe renal dysfunction or nephrotic syndrome; congestive heart failure treated with digoxin; creatine phosphokinase ≥3 times ULN; blood pressure >160/100 mmHg; BMI >35 kg/m2; abuse of alcohol and/or drugs; hypersensitivity to the study medication; participation in another clinical study within 30 days of screening; placebo run-in compliance rate <80%; current or planned pregnancy; or use of excluded medications (immunosuppressive agents, drugs know to interact with the study medications or affect clinical laboratory parameters, and drugs associated with increased risk of rhabdomyolysis with statins).
Recruitment/selection of patients	Recruited between 1996 and 1999 at 70 centres. Within 4 weeks of screening, subjects entered the 6-week, single-blind, placebo-baseline period, at the end of which baseline values were obtained and subjects were randomly assigned.

Age, gender and ethnicity	Age - Mean (SD): 61.1 (SD 8.1) years (atorvastatin) and 61.0 (SD 8.2) years (placebo). Gender (M:F): 66%/34%. Ethnicity: 84% white, 7% black
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol mean (SD) (mg/dL): 194 (31) in both treatment groups: LDL-cholesterol mean (SD): 113 (25) in atorvastatin group and 114 (26) in placebo group. End of treatment: total cholesterol mean (mg/dL): -19.70 in atorvastatin group and -1.41 in placebo group; LDL-cholesterol: -30.29 in atorvastatin group and -1.09 in placebo group. At baseline, all people had diabetes, 16% people had had a prior MI, 13% had an interventional procedure, 16% had angina, 9% had PAD, 5% had cerebrovascular disease, and 9% had arrythmia.
Indirectness of population	No indirectness
Interventions	(n=1211) Intervention 1: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10 mg/day. Duration Median 4 years. Concurrent medication/care: Concomitant medications: described as metabolic and nutritional: 98.3%, cardiovascular 78.7%, musculoskeletal: 71.9%, anti-infective: 57.1%, antihypertensive: 55.5%, and central nervous system: 53.9% (n=1199) Intervention 2: Placebo. Placebo. Duration Median 4 years. Concurrent medication/care: Concomitant medications: described as metabolic and nutritional: 98.1%, cardiovascular 84.4%, musculoskeletal: 71.8%, anti-infective: 55.8%, antihypertensive: 59.5%, and central nervous system: 52.6%
Funding	Study funded by industry (Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 10 MG versus PLACEBO

Protocol outcome 1: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with type 2 diabetes: Rhabdomyolysis at Median 4 years; Group 1: 1/1211, Group 2: 1/1199; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 5 years
- Actual outcome for Adults with type 2 diabetes: All-cause mortality at Median 4 years; Group 1: 70/1211, Group 2: 68/1199; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: CV mortality at 5 years
- Actual outcome for Adults with type 2 diabetes: CV mortality at Median 4 years; Group 1: 38/1211, Group 2: 37/1199; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse event: Myalgia at 5 years
- Actual outcome for Adults with type 2 diabetes: Myalgia at Median 4 years; Group 1: 36/1211, Group 2: 19/1199; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults with type 2 diabetes: Abnormal liver function tests (no other details) at Median 4 years; Group 1: 17/1211, Group 2: 14/1199; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	Koren 2004[94] (Koren 2005 [92], Koren 2009 [93])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=2442)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Mean 51.5 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CHD defined as a history of acute MI >3 months before screening, PCI > 6 months before screening, CABG >3 months before screening, or unstable angina > 3 months before screening.
Stratum	Adults with established CVD : Men and women with known CHD
Subgroup analysis within study	Unclear: Subgroup analyses (unclear if a priori or post hoc) were conducted by gender, age (Koren 2009), and race
Inclusion criteria	Men or women >18 years of age with known CHD; LDL-cholesterol levels between 110 mg/dL and 200 mg/dL for patients receiving lipid-lowering medication and between 130 mg/dL and 250 mg/dL for patients receiving no lipid-regulating therapy.
Exclusion criteria	None reported.
Recruitment/selection of patients	Patients were randomised between July 1995 and June 1998. The study was conducted in 16 centres (centres could be a staff model health maintenance organisation, a community physician open-provider health maintenance organisation, or a Veterans Affairs system). Letters were sent to patients inviting them to be screened for the study at research centres.
Age, gender and ethnicity	Age - Mean (SD): Atorvastatin 61.1 (9.0) years, placebo 61.3 (8.6) years. Gender (M:F): 82%/18%. Ethnicity: 84% White/Caucasian; 11% Black; 0.8% Asian, 4% Other
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: People aged 75 years or under 4. People with a family history of CVD:

	Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol mean (SE) (mg/dl): mean 226 (1.0) in atorvastatin group and 225 (1.2) in placebo group; LDL-cholesterol mean (SE): mean 147 (0.8) in the atorvastatin group and 146 (0.9) in the placebo group. End of treatment: total cholesterol mean (SE) (mg/dl): mean 170 (1.1) in atorvastatin group and 189 (1.4) in placebo group; LDL-cholesterol mean (SE): mean 95 (0.8) in the atorvastatin group and 110 (0.8) in the placebo group. At baseline, 22% had diabetes, 58% had a prior MI, 39% had a PCI, 50% had CABG 21% had unstable angina, 7% had CHF, 7% had stroke, and 4% had peripheral revascularisation.
Indirectness of population	No indirectness
Interventions	(n=1217) Intervention 1: High intensity statin - Atorvastatin 80 mg. Patients were started on atorvastatin 10 mg/day which was doubled every 4 weeks until LDL-cholesterol level of <80 mg/dL or a max dose of 80 mg/day was achieved. The median dose of atorvastatin received by the patients was 40.5 mg/day (45% received 80 mg/day). Duration mean 51.5 months. Concurrent medication/care: Not reported (n=1225) Intervention 2: Placebo. Usual care: patients in the usual care group were maintained on the lipid-lowering programme already prescribed by their regular physicians (treated at the discretion of their physician). Duration Mean 51.5 months. Concurrent medication/care: Lipid regulating therapy could include atorvastatin after its approval in 1997
Funding	Study funded by industry (Parke-Davis and Pfizer Pharmaceuticals funded the study)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 80 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at Mean 51.5 months; Group 1: 52/1217, Group 2: 94/1225; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Non-fatal MI at Mean 51.5 months; HR 0.52 (95%CI 0.38 to 0.74) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years

- Actual outcome for Adults with established CVD : Stroke at Mean 51.5 months; Group 1: 35/1217, Group 2: 39/1225; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Stroke at Mean 51.5 months; HR 0.87 (95%CI 0.55 to 1.38) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Rhabdomyolysis at Mean 51.5 months; Group 1: 0/1217, Group 2: 0/1225; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 4: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at Mean 51.5 months; Group 1: 121/1217, Group 2: 127/1225; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : All-cause mortality at Mean 51.5 months; HR 0.92 (95%CI 0.72 to 1.18) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 5: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Cardiac death at Mean 51.5 months; Group 1: 43/1217, Group 2: 61/1225; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Cardiac death at Mean 51.5 months; HR 0.69 (95%CI 0.47 to 1.02) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 6: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at Mean 51.5 months; Group 1: mean 2.46 mmol/l (SD 0.7); n=1217, Group 2: mean 2.84 mmol/l (SD 0.7); n=1225; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	Larosa 2005[99] (Waters 2004 [185], Shepherd 2008 [166])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=10001)
Countries and setting	Conducted in Australia, France, Germany, Netherlands, United Kingdom, USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: median of 4.9 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults without established CVD : Patients with stable CHD
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged between 35-75 years; clinical evident CHD defined by 1 or more; previous MI, angina with objective evidence of atherosclerotic CHD and a history of coronary revascularisation.
Exclusion criteria	Hypersensitivity to statin; liver disease or hepatic dysfunction defined as alanine or aspartate aminotransferase >1.5 times ULN; pregnant women or breastfeeding; nephrotic syndrome; uncontrolled diabetes mellitus; uncontrolled Hypothyroidism; uncontrolled hypertension; a MI, coronary revascularisation procedure or severe/unstable angina within 1 month of screening; any planned surgical procedure for the treatment of atherosclerosis; an ejection fraction <30%; haemodynamically important valvular disease; gastrointestinal disease limiting drug absorption or partial ileal bypass; any nonskin malignancy, malignant melanoma or other survival-limiting disease; unexplained creatine phosphokinase levels >6 times ULN; concurrent therapy with long-term immunosuppressant; concurrent therapy with lipids-regulating drugs not specified as study treatment in the protocol; history of alcohol abuse; participation in another clinical trial concurrently or within 30 days before screening.
Recruitment/selection of patients	Any previously prescribed lipid-regulating drugs discontinued at screening, and patients require a wash-out period of ≥6 weeks before visit 2. After discontinuation, all eligible patients commence treatment with atorvastatin 10 mg/day on an open-label basis. Patients with LDL-cholesterol between 3.5-6.5 mmol/l and triglycerides ≤6.8 mmol/l at visit 2 are

	eligible to continue the study during the run-in period. Randomisation from July 1998 to December 1999. History of systemic hypertension: 53.7%; Diabetes mellitus: 15.0%; peripheral vascular disease: 11.0%; CHF: 7.6%.
Age, gender and ethnicity	Age - Mean (SD): Atorvastatin 10 mg; 60.9 (8.8) years, atorvastatin 80 mg; 61.2 (8.8) years. Gender (M:F): 8099/1902. Ethnicity: white 94.1%
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Baseline values mean (SD) (mmol/l): Total cholesterol: 4.5 (0.7); LDL-cholesterol: 2.5± (0.5). 41.8% prior MI; 24.1% angina with evidence of coronary disease; 82.2% prior coronary revascularisation. 3107 patients had CKD at baseline (3070 had stage 3 CKD, eGFR 30-59 ml/min/1.73m2; 29 had stage 4 CKD, eGFR 15-29 ml/min/1.73m2).
Indirectness of population	No indirectness
Interventions	(n=4995) Intervention 1: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg per day. Duration 4.9 years. Concurrent medication/care: Aspirin: 87.6%; beta blockers: 55.1%; calcium antagonist: 25.6%; ACE inhibitor: 27.6%; nitrates: 31.8%; current HRT: 3.05% of women; spironolactone: 22.4%; ARBs: 1.8% (n=5006) Intervention 2: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10mg per day. Duration 4.9 years. Concurrent medication/care: Aspirin: 87.6%; beta blockers: 55.1%; calcium antagonist: 25.6%; ACE inhibitor: 27.6%; nitrates: 31.8%; current HRT: 3.05% of women; spironolactone: 22.4%; ARBs: 1.8
Funding	Study funded by industry (Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 10 MG versus ATROVASTATIN 80MG

Protocol outcome 1: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : death from any cause at 4.9years; HR 1.01 (95%CI 0.85 to 1.19) Reported; Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 2: CV mortality at 5 years
- Actual outcome for Adults with established CVD : death from CHD at 4.9years; HR 0.8 (95%CI 0.61 to 1.03) Reported; Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 3: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal non procedure related MI at 4.9years; Group 1: 308/5006, Group 2: 243/4995; Risk of bias: low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Non-fatal non procedure related MI at 4.9years; HR 0.78 (95%CI 0.66 to 0.93) Reported; Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Rhabdomyolysis at 4.9 years; Group 1: 0/5006, Group 2: 0/4995; Risk of bias: low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: Rhabdomyolysis at 4.9 years; Group 1: 0/1505, Group 2: 0/1602; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 5: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 4.9 years; Group 1: 284/4995, Group 2: 282/5006; Risk of bias: low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: All-cause mortality at 4.9 years; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 6: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Death from CHD at 4.9 years; Group 1: 127/5006, Group 2: 101/4995; Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 7: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults with CKD: Persistent elevation in ALT and/or AST (two measurement >3 ULN 4-10 days apart) at 4.9 years; Group 1: 1/1505, Group 2: 22/1602; Risk of bias: ; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Persistent elevation ALT and/or AST at 4.9 years; Group 1: 8/3324, Group 2: 38/3225; Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Non-fatal stroke at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	Lemos 2003[101]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1677)
Countries and setting	Conducted in Multiple countries; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 3-4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Post-PCI
Subgroup analysis within study	Not applicable:
Inclusion criteria	Undergone first successful PCI (defined as residual stenosis <50% and absence of in-hospital post-procedure MI, repeated revascularisation or death), fulfilment of at least 1 of the following criteria: total cholesterol 135-270 mg/dL (3.5 to 7.0 mmol/l) with fasting triglycerides <540 to <400 mg/dL; total cholesterol <212 mg/dL (5.5 mmol/l) for patients whose lipids levels were measured between 24 hours and 4 weeks after an episode of MI; total cholesterol <232 mg/dL (6.0 mmol/l) for patients with diabetes.
Exclusion criteria	Previous PCI or CABG, high blood pressure (>180/100 mmHg) despite drug treatment, poor left ventricular function (LVEF <30%), severe noncoronary heart disease, severe renal dysfunction (serum creatinine >1.8mg/dL [160 micromol/litre]), obesity (BMI>30kg/m^2), malignant or other disease resulting in decreased life expectancy.
Recruitment/selection of patients	Between April 1996 and October 1998, patients were recruited from 77 referral centres in Europe, Canada and Brazil.
Age, gender and ethnicity	Age - Other: Mean; fluvastatin 60 years, placebo 60 years. Gender (M:F): No overall male/female ratio; fluvastatin 709/135, placebo 691/142. Ethnicity: Not reported

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol mean (mmol/l); fluvastatin 5.2, placebo 5.2. Baseline LDL-cholesterol mean (mmol/l); fluvastatin 3.4, placebo 3.4. LDL-cholesterol at 6 weeks mean (mmol/); fluvastatin 2.5, placebo 3.8. Diabetes (%); fluvastatin 14, placebo 10 (significant p<0.05).
Indirectness of population	No indirectness
Interventions	(n=844) Intervention 1: Medium intensity statin - Fluvastatin 80 mg. Fluvastatin 80 mg/day (Lescol, Novartis Pharma). Duration 3-4 years. Concurrent medication/care: Not reported but stated that groups well matched (n=833) Intervention 2: Placebo. N/A. Duration 3-4 years. Concurrent medication/care: Not reported but stated that groups well matched
Funding	Study funded by industry (Novartis Pharma)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUVASTATIN 80 MG versus PLACEBO

Protocol outcome 1: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Rhabdomyolysis CK>10 times normal at 3-4 years; Group 1: 0/844, Group 2: 3/833; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 3-4 years; Group 1: 35/844, Group 2: 49/833; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Cardiac death at 3-4 years; Group 1: 13/844, Group 2: 24/833; Risk of bias: High; Indirectness of outcome: No

indirectness Protocol outcome 4: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with established CVD : Transaminases >3 times normal level on 2 consecutive occasions at 3-4 years; Group 1: 10/844, Group 2: 3/833; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	Lemos 2013[100]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=79)
Countries and setting	Conducted in Brazil; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Nephrology clinic
Stratum	Adults with CKD: CKD
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged <18 years with CKD and followed for at least 3 months by nephrologist.
Exclusion criteria	Chronic inflammatory diseases, active malignancy, HIV, viral hepatitis, use of steroids.
Recruitment/selection of patients	From nephrology clinic.
Age, gender and ethnicity	Age - Mean (SD): Statin 58.4 (8.7) years, no treatment 57.4 (12.7) years. Gender (M:F): 86/60. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: People without autoimmune disease 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Indirectness of population	No indirectness

Interventions	(n=38) Intervention 1: High intensity statin - Rosuvastatin 10 mg. Rosuvastatin 10 mg/day. Duration 2 years. Concurrent medication/care: Standard care for CKD; ACE inhibitors, diuretics, beta blockers, calcium channel blockers (n=41) Intervention 2: Placebo. No treatment. Duration 2 years. Concurrent medication/care: Standard care for CKD; ACE inhibitors, diuretics, beta blockers, calcium channel blockers
Funding	Study funded by industry (Genzyme Corporation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ROSUVASTATIN 10 MG versus PLACEBO Protocol outcome 1: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with CKD: LDL-cholesterol at 2 years; Group 1: mean 2.03 mmol/l (SD 1.15); n=22, Group 2: mean 2.5 mmol/l (SD 0.7); n=29; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	Meade 1999[112] (Collins 2003 [42], Collins 2004 [43], Armitage 2005 [19], HPS 2002[108, 117])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=20563)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Prior MI: 41%. History of coronary disease: 24%. No history of coronary disease: 35%.
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women aged 40–80 years with non-fasting blood total cholesterol concentrations of at least 3.5 mmol/l were eligible provided they were considered to be at substantial 5-year risk of death from CHD because of a past medical history of: (i) coronary disease (MI, unstable or stable angina, CABG, or angioplasty); or (ii) occlusive disease of non-coronary arteries (non-disabling stroke not thought to be haemorrhagic, transient cerebral ischaemia, leg artery stenosis [for example, intermittent claudication], carotid endarterectomy, other arterial surgery or angioplasty); or (iii) diabetes mellitus (whether type 1 or type 2); or (iv) treated hypertension (if also male and aged at least 65 years, in order to be at similar risk to the other disease categories). No upper limit of blood cholesterol concentration for inclusion was imposed since there were people (such as those who had not previously had a MI, or were female or elderly) in whom many clinicians were substantially uncertain as to the benefits of lowering even an 'elevated' cholesterol. But, anyone in whom statin therapy was considered by their own doctor to be clearly indicated was not to be randomised.
Exclusion criteria	Chronic liver disease or evidence of abnormal liver function; severe renal disease or evidence of impaired renal function; inflammatory muscle disease or evidence of muscle problems; concurrent treatment with cyclosporine, fibrates, of high dose niacin; child bearing potential; severe heart failure; some life-threatening condition other than vascular disease or diabetes; or conditions that might limit long-term compliance.

Recruitment/selection of patients	Recruited from 69 UK hospitals. Randomisation between July 1994 and May 1997. Run-in phase: 4 weeks of placebo (to allow review of liver enzymes, creatinine, and creatine kinase by the central lab before starting any simvastatin) followed by 4-6 weeks of a fixed dose of simvastatin 40 mg/day (to allow a pre-randomisation assessment of the LDL-cholesterol lowering responsiveness of each individual).
Age, gender and ethnicity	Age - Mean (SD): 64.0 (8.4) years. Gender (M:F): 15454/5082. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline concentration, mmol/l (of patients subsequently randomised, prior to any statin treatment); total cholesterol: 5.9, LDL-cholesterol: 3.4. Average concentrations during follow up: total cholesterol: simvastatin: 4.2, placebo: 5.4; LDL-cholesterol: simvastatin: 2.3, placebo: 3.3. Diabetes: 29%. Hypertension: 41%. Prior MI: 41%. History of coronary disease: 24%. No history of coronary disease: 35%.
Indirectness of population	No indirectness
Interventions	(n=10269) Intervention 1: Medium intensity statin - Simvastatin 40 mg. Simvastatin 40 mg/day. Until spring 1998, patients prescribed non-study statins were routinely advised to stop their simvastatin or placebo tablets, but subsequently that policy was changed so that non-study statin regimens of up to the equivalent, in lipid-lowering potency, of about 40 mg/day simvastatin could be added to the study simvastatin or placebo tablets. About 1/3 of patients taking non-study statins continued with their study tablets. Duration 5 years. Concurrent medication/care: Aspirin or another antiplatelet: 63%; oral anticoagulant: 5%; nitrate: 31%; beta blocker: 26%; calcium antagonist: 30%; ACE inhibitor: 20% (n=10267) Intervention 2: Placebo. Matching placebo. Until spring 1998, patients prescribed non-study statins were routinely advised to stop their simvastatin or placebo tablets, but subsequently that policy was changed so that non-study statin regimens of up to the equivalent, in lipid-lowering potency, of about 40 mg/day simvastatin could be added to the study simvastatin or placebo tablets. About 1/3 of patients taking non-study statins continued with their study tablets. Duration 5 years. Concurrent medication/care: Aspirin or another antiplatelet: 63%; oral anticoagulant: 5%;

	nitrate: 31%; beta blocker: 26%; calcium antagonist: 30%; ACE inhibitor: 20%
Funding	Academic or government funding (UK Medical Research Council, the British Heart Foundation, Merck, Roche)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome: Non-fatal MI at 5 years; Group 1: 357/10269, Group 2: 574/10267; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome: Non-fatal stroke at 5 years; Group 1: 348/10269, Group 2: 466/10267; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Any stroke at 5 years; Group 1: 444/10269, Group 2: 585/10267; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: Any stroke (diabetes group) at 5 years; Group 1: 149/2978, Group 2: 193/2985; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome: CK >3 times ULN at 5 years; Group 1: 11/10269, Group 2: 6/10267; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: CK >3 times ULN (diabetes group) at 5 years; Group 1: 4/2978, Group 2: 2/2985; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: All-cause mortality at 5 years
- Actual outcome: All-cause mortality at 5 years; Group 1: 1328/10269, Group 2: 1507/10267; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: CV mortality at 5 years
- Actual outcome: Vascular death (coronary, stroke, other vascular) at 5 years; Group 1: 781/10269, Group 2: 937/10267; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome: ALT >4 times ULN at 5 years; Group 1: 42/10269, Group 2: 32/10267; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: ALT >4 times ULN (diabetes group) at 5 years; Group 1: 14/2978, Group 2: 11/2985; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 7: Adverse event:New onset diabetes at 5 years

- Actual outcome: Development of new diabetes at 5 years; Group 1: 335/7291, Group 2: 293/7282; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	Mercuri 1996[113]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=305)
Countries and setting	Conducted in Italy; Setting: CAIUS study. Primary care (lipid clinics)
Line of therapy	1st line
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Carotid artery lesion detected by quantitative B-mode ultrasound imaging; fasting lipid profiles using standard procedures approved by the European Society of Arthersclerosis.
Stratum	Adults without established CVD : Men and women with isolated, moderate elevation of low-density lipoprotein cholesterol and ultrasinographic evidence of early carotid artery atherosclerosis, and who were asymptomatic for cardiovascular diseases.
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women, 45 to 65 years old with moderately elevated LDL cholesterol (three baseline determinations of LDL cholesterol between 3.88 and 6.47 mmol/L and triglycerides level <2.82 nmol/L), free of symptoms and/or signs of coronary artery disease, and at least 1 carotid artery lesion detected by quantitative B-mode ultrasound imaging.
Exclusion criteria	Persistent liver function abnormalities, other serious medical conditions, and regular use of lipid-lowering agents, anticoagulants, and calcium antagonists.
Recruitment/selection of patients	Patients were screened in 7 lipid clinics. Eligible participants were enrolled in a 6-week single blind run-in period in which they were treated with placebo and advised to follow a low fat diet. After an additional evaluation of lipid values to confirm their eligibility, patients were then randomised.
Age, gender and ethnicity	Age - Mean (SD): 55.0 (5.99) years. Gender (M:F): 53%/47%. Ethnicity: Not reported

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Family history of CVD (Overall 45% of participants had a family history of CVD - but no subgroup analysis was conducted). 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Baseline: Total cholesterol mmol/L: 6.72 (SD 0.57) (Pravastatin); 6.80 (SD 0.63) (Placebo); LDL cholesterol mmol/L: 4.66 (SD 0.49) (Pravastatin); 4.71 (SD 0.53) (Placebo); Follow-up: Total cholesterol mmol/L: mean difference -1.01 (SEM 0.08) (Pravastatin); 0.18 (SEM 0.07) (Placebo); LDL cholesterol mmol/L: -1.03 (SEM 0.07) (Pravastatin); 0.09 (SEM 0.06) (Placebo); No baseline information was presented on the % of people with diabetes, MI, stroke, or any other CVD event
Indirectness of population	No indirectness
Interventions	(n=151) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg once a day. Duration 3 years. Concurrent medication/care: Not reported (n=154) Intervention 2: Placebo. Placebo manufactured to exactly resemble pravastatin. Duration 3 years. Concurrent medication/care: Not reported
Funding	Study funded by industry (Independent research grants provided by Bristol-Myers Squibb, and in part by a grant from the Italian National Research Council)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults without established CVD : Non-fatal MI at 3 years; Group 1: 1/151, Group 2: 2/154; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	Mok 2009[114]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=227)
Countries and setting	Conducted in Hong Kong (China); Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults without established CVD : Mild to moderately elevated LDL-cholesterol
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged between 36 and 75 years, any MCA stenosis as detected by transcranial doppler, free of stroke or TIA and CHD, ≥1 risk factors for atherosclerosis, for example, diabetes mellitus, hypertension or smoking, mild to moderately elevated fasting LDL-cholesterol of 3.0-5.0 mmol/l.
Exclusion criteria	Known history of MI, angina, atrial fibrillation, CHF, serum triglyceride >4.5 mmol/l, ALT >20% ULN, elevated creatinine kinase, creatinine level >180 micromol/litre, women of child bearing age, patients already on lipid lowering drugs, known allergy to statins, presence of neurodegenerative diseases (for example, Alzheimer's disease), limited life expectancy of <2 years, contradictions to MRI, for example, metal implants.
Recruitment/selection of patients	Patients recruited between 1996 and 2000 at 3 regional hospitals in Hong Kong.
Age, gender and ethnicity	Age - Mean (SD): Simvastatin 63.0 (14.0) years, placebo 62.5 (13.0) years. Gender (M:F): No overall male/female; simvastatin 60/40, placebo 60/43. Ethnicity: Chinese
Further population details	1. Black and minority ethnic groups: Chinese 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: People aged 75 years or under 4. People with a family history of CVD: Not applicable / Not

	stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol mean mmol/l; simvastatin 5.85, placebo 5.87. End of study total cholesterol mean mmol/l; simvastatin 4.46, placebo 5.88. Baseline LDL-cholesterol mean mmol/l; simvastatin 3.92, placebo 3.89. End of study total cholesterol mean mmol/; simvastatin 2.49, placebo 3.77. Diabetes (%); simvastatin 92.2, placebo 89.0.
Indirectness of population	No indirectness
Interventions	(n=113) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day. Duration 2 years. Concurrent medication/care: Antihypertensives 77.7%, oral hypoglycaemics 75.7%, antiplatelet agents 15.5% (n=114) Intervention 2: Placebo. N/A. Duration 2 years. Concurrent medication/care: Antihypertensives 75%, oral hypoglycaemics 79%, antiplatelet agents 19%
Funding	Study funded by industry (Merck Sharp and Dohme Ltd)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: Non-fatal stroke at 5 years
- Actual outcome for Adults without established CVD : Non-fatal stroke at 2 years; Group 1: 3/113, Group 2: 4/114; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults without established CVD : Rhabdomyolysis CK>10 times normal at 2 years; Group 1: 0/113, Group 2: 0/114; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : All-cause mortality at 2 years; Group 1: 0/113, Group 2: 7/114; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults without established CVD : Transaminases >3 times normal level at 2 years; Group 1: 0/113, Group 2: 0/114; Risk of bias: Low; Indirectness of

outcome: No indirectness Protocol outcome 5: LDL-cholesterol reduction at 1 year - Actual outcome for Adults without established CVD : LDL-cholesterol at 2 years; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	Nakamura 2006[119] (Nakamura 2007 [118], Kushiro 2009 [95])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=8214)
Countries and setting	Conducted in Japan; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 9 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Total cholesterol concentration 5.69-6.98 mmol/l; serum lipids were measured at a central laboratory
Stratum	Adults without established CVD : Adults with hypercholesterolaemia and no history of CHD or stroke
Subgroup analysis within study	Not applicable: Patients were stratified according to sex, age, and medical institution; post hoc analysis was also conducted in patients with hypertension (n=3277) (Kushiro 2009)
Inclusion criteria	Men and post-menopausal women aged 40-70 years with a bodyweight of 40 kg or more and hypercholesterolaemia.
Exclusion criteria	Familial hypercholesterolaemia and a history of CHD or stroke (the authors stated that other exclusion criteria have been reported in a previous publication).
Recruitment/selection of patients	Participants were enrolled between February 1994 and March 1999.
Age, gender and ethnicity	Age - Mean (SD): 58.2(7.3) and 58.4 (7.2) years. Gender (M:F): 32%/68%. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).

Extra comments	Baseline total cholesterol mean (SD) mmol/l; 6.27 (0.31) in both treatment groups. LDL-cholesterol mean (SD) mmol/l; 4.05 (0.45) pravastatin + diet and 4.05 (0.45) diet only; the authors stated that after 5 years, total cholesterol was reduced by 11.5% in the pravastatin + diet groups versus 2.1% in the diet alone group; LDL-cholesterol was reduced by 18% and 3.2% in the 2 groups, respectively. At baseline 21% of participants had diabetes. No other details on percentage of people with prior MI, or stroke, or any other CVD event were presented. 26% were taking calcium-channel blockers, 12/13% were taking ACE inhibitors/ARB, and 8% were taking beta blockers
Indirectness of population	No indirectness
Interventions	(n=3866) Intervention 1: Low intensity statin - Pravastatin 20 mg. Pravastatin 10-20 mg/day + diet. Duration mean 5.3 years. Concurrent medication/care: Diet (following the National Cholesterol Education Program step 1 diet) (n=3966) Intervention 2: Placebo. Diet only. Duration mean 5.3 years. Concurrent medication/care: Diet (following the National Cholesterol Education Program step 1 diet). Mild hypolipidaemidic drugs (for example, γ-oryzanol, riboflavin butyrate, pantethine) could also be prescribed.
Funding	Study funded by industry (Funds were provided by the Japanese Ministry of Health, Labor and Welfare for the first 2 years of the study, and thereafter the study was funded by Sankyo Co. Ltd.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : Total mortality at 5.3 years; HR 0.72 (95%CI 0.51 to 1.01) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: CV mortality at 5 years
- Actual outcome for Adults without established CVD : Cardiovascular death at 5.3 years; HR 0.63 (95%CI 0.3 to 1.33) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: Non-fatal MI at 5 years
- Actual outcome for Adults without established CVD : Non-fatal MI at 5.3 years; Group 1: 16/3866, Group 2: 30/3966; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults without established CVD : Fatal and non-fatal MI at 5.3 years; HR 0.52 (95%CI 0.29 to 0.94) Reported; Risk of bias: Unclear; Indirectness of

outcome: No indirectness Protocol outcome 4: Non-fatal stroke at 5 years - Actual outcome for Adults without established CVD : Stroke at 5.3 years; Group 1: 50/3866, Group 2: 62/3966; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for Adults without established CVD : Stroke at 5.3 years; HR 0.83 (95%CI 0.57 to 1.21) Reported; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: All-cause mortality at 5 years - Actual outcome for Adults without established CVD : Total mortality at 5.3 months; Group 1: 55/3866, Group 2: 79/3966; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 6: CV mortality at 5 years - Actual outcome for Adults without established CVD : Cardiovascular death at 5.3 years; Group 1: 11/3866, Group 2: 18/3966; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 7: Adverse event:New onset diabetes at 5 years - Actual outcome for Adults without established CVD : New onset diabetes at 5.3 years; Group 1: 172/3013, Group 2: 164/3073; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	Nicholls 2011[127]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1385)
Countries and setting	Conducted in Multiple countries; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Patients with CAD
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Age 18 to 75 years, had at least 1 vessel with 20% stenosis on clinically indicated coronary angiography and a target vessel for imaging with less than 50% obstruction. Patients who had not been treated with a statin in the preceding 4 weeks were required to have an LDL-cholesterol level at entry >2.6 mmol/l; those who had received such treatment were required to have a level >2.1 mmol/l.
Exclusion criteria	Patients who had received intensive lipid-lowering therapy for >3 months in the previous year or had uncontrolled hypertension, CHF, renal dysfunction, or liver disease.
Recruitment/selection of patients	Recruited from 208 centres from Jan 2008 to June 2009. Run-in period: 2-week treatment with half-maximal dose of either atorvastatin or rosuvastatin.
Age, gender and ethnicity	Age - Mean (SD): Atorvastatin: 57.9 (8.5) years, rosuvastatin: 57.4 (8.6) years. Gender (M:F): Atorvastatin; 386/133, rosuvastatin; 379/141. Ethnicity: White 96%
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of

	CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Baseline total cholesterol mean mmol/l; atorvastatin 5.00, rosuvastatin 5.01. During treatment total cholesterol mean mmol/l; atorvastatin 3.73, rosuvastatin 3.60. LDL-cholesterol mean mmol/l; atorvastatin: 1.82, rosuvastatin 1.62. Diabetes; atorvastatin 16.8%, rosuvastatin 13.8%. Hypertension; atorvastatin 70.7%, rosuvastatin 70.0%. Previous MI; atorvastatin 26.4%, rosuvastatin 22.5%. Previous PCI; atorvastatin 21.6%; rosuvastatin, 25.2%. Prior statin use; atorvastatin 61.5%, rosuvastatin 58.3%.
Indirectness of population	No indirectness
Interventions	(n=691) Intervention 1: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg/day. Duration 2 years. Concurrent medication/care: Antiplatelet agent: 97.9%; beta blocker: 61.1%; ACE inhibitor: 44.5%; ARBs: 15.8% (n=694) Intervention 2: High intensity statin - Rosuvastatin 40 mg. Rosuvastatin 40 mg/day. Duration 2 years. Concurrent medication/care: Antiplatelet agent: 97.5%; beta blocker: 60.6%; ACE inhibitor: 43.5%; ARBs: 16.7%
Funding	Study funded by industry (AstraZeneca pharmaceutical)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 80 MG versus ROSUVASTATIN 40 MG

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 2 years; Group 1: 11/689, Group 2: 11/691; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Non-fatal stroke at 2 years; Group 1: 2/689, Group 2: 3/691; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : CK >10 ULN at 2 years; Group 1: 4/668, Group 2: 1/668; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Rhabdomyolysis at 2 years; Group 1: 0/689, Group 2: 0/691; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: CV mortality at 5 years

- Actual outcome for Adults with established CVD : CV mortality at 2 years; Group 1: 2/689, Group 2: 2/691; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with established CVD : AST >3 ULN at 2 years; Group 1: 11/668, Group 2: 3/668; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : ALT >3 ULN at 2 years; Group 1: 14/668, Group 2: 5/668; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at 2 years; Group 1: mean 1.82 mmol/l (SD 0.59); n=689, Group 2: mean 1.62 mmol/l (SD 0.59); n=694; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; All-cause mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	Nissen 2005[130] (Nissen 2005,[129] Nissen 2005[128])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=502)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Angiographically documented CAD
Stratum	Adults with established CVD :
Subgroup analysis within study	Not applicable
Inclusion criteria	Angiographic evidence of CAD (stenosis of at least 20%), LDL-cholesterol level of 125 to 120 mg/dL after statin washout period of 4 to 8 weeks.
Exclusion criteria	None stated.
Recruitment/selection of patients	Recruited from 34 centres; patients with clinical indication for angiography.
Age, gender and ethnicity	Age - Other: Mean; atorvastatin 80 mg; 55.8 years, pravastatin 40 mg; 56.6 years. Gender (M:F): 72%/28%. Ethnicity: White; 89%
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).

Indirectness of population	No indirectness
Interventions	(n=249) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg. Duration 18 months. Concurrent medication/care: Not reported (n=253) Intervention 2: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg. Duration 18 months. Concurrent medication/care: Not reported
Funding	Study funded by industry (Pfizer)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus ATORVASTATIN 80 MG Protocol outcome 1: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at 18 months; Group 1: mean 2.58 mmol/l (SD 0.52); n=249, Group 2: mean 2.09 mmol/l (SD 0.52); n=253; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Pedersen 2005[134]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=8888)
Countries and setting	Conducted in Denmark, Finland, Iceland, Netherlands, Norway, Sweden; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 4.8 years (median)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Post-MI
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≤80 years; history of a definite MI who qualified for statin therapy according to national guidelines at the time of recruitment.
Exclusion criteria	Any known contraindications to statin therapy; previous intolerance to statins in low or high doses; liver enzyme >2 times ULN; pregnancy or breastfeeding; nephrotic syndrome; uncontrolled diabetes mellitus; uncontrolled hypothyroidism; plasma triglyceride levels >6.8 mmol/l; CHF; haemodynamically important valvular heard disease; gastrointestinal conditions affecting absorption of drugs; treatment with other drugs that seriously affect the pharmacokinetics of statins; treatment with other lipid-lowering drugs; previously treated with statins who already had titration to a dose higher than the equivalent of 20 mg/day of simvastatin.
Recruitment/selection of patients	Recruited from 190 ambulatory cardiology and private specialist centres, from March 1999 to March 2001. Records of patients previously treated at the centres were screened for the main eligibility criteria. Potentially eligible patients were invited for a screening visit.
Age, gender and ethnicity	Age - Mean (SD): Simvastatin 61.6 (9.5) years; atorvastatin 61.8 (9.5) years. Gender (M:F): 7187/1701. Ethnicity: Not reported

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Baseline cholesterol, mg/dL (SE): LDL-cholesterol; simvastatin 121.4 (0.5), atorvastatin 121.6 (0.5). Total cholesterol; simvastatin 195.9 (0.6), atorvastatin 196.8 (0.6). HDL-cholesterol; simvastatin 46.1 (0.2), atorvastatin 46.0 (0.2). Cholesterol at 5 years mg/dL (SE): LDL-cholesterol: simvastatin 99.8 (0.9), atorvastatin 80.0 (1.0). Total-cholesterol: simvastatin 176.8 (1.0), atorvastatin 153.4 (1.3). HDL-cholesterol: simvastatin 50.6 (0.5), atorvastatin 50.1 (0.5). Diabetes: simvastatin 12.1%, atorvastatin 12.0%. Aspirin: simvastatin 79.5%, atorvastatin 78.7%. Warfarin or dicoumarol: simvastatin 12.6%, atorvastatin 12.6%. Beta blockers: simvastatin 73.7%, atorvastatin 76.1%. Calcium antagonists: simvastatin 18.9%, atorvastatin 19.9%. ACE inhibitors: simvastatin 30.7%, atorvastatin 29.2%. ARBs: simvastatin 6.1%, atorvastatin 5.9%.
Indirectness of population	No indirectness
Interventions	(n=4449) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day. If, at 24 weeks, total cholesterol >190 mg/dL (5.0 mmol/l), the dose of simvastatin could be increased to 40 mg/day. At the end of the study, 1034 (23%) were prescribed simvastatin 40 mg/day. Duration 4.8 years. Concurrent medication/care: Aspirin: 79.5%. Warfarin or dicoumarol: 12.6%. Beta blockers: 73.7%. Calcium antagonists: 18.9%. ACE inhibitors: 30.7%. ARBs: 6.1%. Pre-randomisation statin. Simvastatin: 50.1%. Atorvastatin: 11.5%. Pravastatin: 9.7%. Other statins: 4.5%. (n=4439) Intervention 2: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg/day. The dose of atorvastatin could be decreased to 40 mg/day for adverse events. At 24 weeks 250 (6%) people had the dose reduced to 40 mg/day. At the end of the study, 587 (13%) people had the dose reduced to 40 mg/day. Duration 4.8 years. Concurrent medication/care: Aspirin: 78.7%. Warfarin or dicoumarol: 12.6%. Beta blockers: 76.1%. Calcium antagonists: 19.9%. ACE inhibitors: 29.2%. ARBs: 5.9%. Pre-randomisation statin. Simvastatin: 50.3%. Atorvastatin: 11.2%. Pravastatin: 9.4%. Other statins: 4.2%.
Funding	Study funded by industry (Study sponsored by Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus ATORVASTATIN 80 MG

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 4.8 years; Group 1: 321/4449, Group 2: 267/4439; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Fatal or non-fatal stroke at 4.8 years; Group 1: 174/4449, Group 2: 151/4439; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Myopathy defined as CPK>10 x ULN at 2 consecutive measurements with muscle symptoms at 4.8 years; Group 1: 0/4449, Group 2: 0/4439; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 4.8 years; Group 1: 374/4449, Group 2: 366/4439; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: CV mortality at 5 years
- Actual outcome for Adults with established CVD : CV mortality at 4.8 years; Group 1: 218/4449, Group 2: 223/4439; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 6: Adverse event: Myalgia at 5 years
- Actual outcome for Adults with established CVD : Myalgia at 4.8 years; Group 1: 51/4449, Group 2: 97/4439; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 7: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults with established CVD : ALT>3 x ULN at 2 consecutive measurements at 4.8 years; Group 1: 5/4449, Group 2: 43/4439; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 8: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at 4.8 years; Group 1: mean 2.58 mmol/l (SD 0.52); n=4449, Group 2: mean 2.09 mmol/l (SD 0.52); n=4439; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Pitt 1995[137]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=408)
Countries and setting	Conducted in Canada, USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The authors stated that the angiographic protocol and quantitative analysis methodology had been previously described. Other methods were also reported.
Stratum	Adults with established CVD : Patients with mild to moderate hypercholesterolemia and coronary artery disease
Subgroup analysis within study	Not applicable
Inclusion criteria	CABG evidenced by 1 or more stenoses ≥50% or recent MI or coronary angioplasty; average LDL-cholesterol concentration ≥130 mg/dL but <190 mg/dL and triglyceride levels ≤350 mg/dL despite adherence to a fat restricted diet for a minimum of 4 weeks.
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Mean 57 years. Gender (M:F): 38%/62%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear (51/206 (25%) patients in the pravastatin group and 56/202 (28%) patients in the placebo group had a family history of atherosclerosis, but no subgroup analysis was conducted). 5. People with

	autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol and LDL-cholesterol were not reported separately for each treatment group. The authors stated that in the pravastatin group, the average percent change from baseline was -19% for total cholesterol and -28% for LDL-cholesterol; in the placebo group the average percent change from baseline was +2% for total cholesterol and +1% for LDL-cholesterol; At baseline 21% of participants had prior MI, 27% had prior angioplasty and 2% had prior CABG. No information was presented on percentage of people with diabetes
Indirectness of population	No indirectness
Interventions	(n=206) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration 3 years. Concurrent medication/care: Not reported (n=202) Intervention 2: Placebo. Placebo. Duration 3 years. Concurrent medication/care: Not reported
Funding	Study funded by industry (Supported by a grant from Bristol-Myers Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 3 years; Group 1: 7/206, Group 2: 16/202; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Stroke at 3 years; Group 1: 0/206, Group 2: 2/202; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : Total deaths at 3 years; Group 1: 4/206, Group 2: 6/202; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 4: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Cardiac death at 3 years; Group 1: 2/206, Group 2: 2/202; Risk of bias: Unclear; Indirectness of outcome: No

indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	Raggi 2005[141]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=615)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Calcium volume score, LDL-cholesterol level
Stratum	Overall: Hyperlipidaemic women
Subgroup analysis within study	Not applicable
Inclusion criteria	Post-menopausal women with calcium volume score ≥30. Lipid criteria; LDL-cholesterol level ≥ 3.4 mmol/l for women with CHD, or ≥2 risk factors and a 10 year risk of CVD of 10% to 20%; LDL-cholesterol ≥4.1 mmol/l for patients with ≥2 CHD risk factors and 10 year CVD risk of <10%; or patients with 0 to 1 risk factors.
Exclusion criteria	Intolerance to statins, for example, hypersensitivity or hepatic dysfunction with aspartate transaminase (AST) or alanine transaminase (ALT) levels ≥1.5 x ULN at any time between screening and randomisation, treatment with lipid-lowering drugs other than HRT within 3 months of screening, evidence of secondary hyperlipidemia (as in nephrotic syndrome), renal dysfunction (creatinine ≥1.5 mg/dl), uncontrolled type 1 or type 2 diabetes mellitus (defined by HbA1c >10%), MI <6 months before screening, uncontrolled hypothyroidism (defined by thyroid stimulating hormone >1.5 times ULN) and plasma triglyceride levels >6.8 mmol/l).
Recruitment/selection of patients	Recruited from 96 sites, subjects underwent initial screening visit.
Age, gender and ethnicity	Age - Mean (SD): Atorvastatin; 64.2 (6.5) years, pravastatin 64.5 (6.0) years. Gender (M:F): 0:475. Ethnicity: 92% Caucasian

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear (92% Caucasian). 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women
Indirectness of population	No indirectness
Interventions	(n=257) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg. Duration 1 year. Concurrent medication/care: Not reported (n=218) Intervention 2: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg. Duration 1 year. Concurrent medication/care: Not reported
Funding	Study funded by industry (Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus ATORVASTATIN 80 MG

Protocol outcome 1: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome: Rhabdomyolysis at 1 year; Group 1: 0/257, Group 2: 1/218; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome: ALT/AST > 3 times upper limit normal at 1 year; Group 1: 0/257, Group 2: 7/218; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: LDL-cholesterol reduction at 1 year
- Actual outcome: LDL-cholesterol at 1 year; Group 1: mean 3.34 mmol/l (SD 0.8); n=257, Group 2: mean 2.38 mmol/l (SD 0.93); n=218; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	**Ridker 2008[147] (Ridker 2007 [148], Ridker 2008 [146], Kones 2009 [91], Ridker 2009 [150], Everett 2010 [56], Mora 2010 [115], Ridker 2010 [149], Albert 2011 [8], Hsia 2011 [76], Ridker 2012[145])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=4631)
Countries and setting	Conducted in Multiple countries; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Median 3.9 years
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Measurement of lipids levels, high-sensitivity C-reactive protein levels, hepatic and renal function, blood glucose levels, and glycated haemoglobin values were performed in a central laboratory
Stratum	Adults without established CVD : Apparently healthy men and women with low-density lipoprotein levels <130 mg/dL and high-sensitivity C-reactive protein levels of 2.0 mg/dL or higher
Subgroup analysis within study	Unclear: Stratified according to centre; pre-specified subgroup analyses were performed according to the presence or absence of major CV risk factors. Subgroup analyses were also conducted for a number of other variables, including sex (Mora 2010), LDL-cholesterol levels (Hsia 2011), ethnicity (Albert 2011), diabetes risk factor (Ridker 2012), and baseline renal function (Ridker 2010).
Inclusion criteria	Men 50 years of age or older and women 60 years of age or older without a history of CVD; with an LDL-cholesterol level <130 mg/dL and a high sensitivity C-reactive protein level of 2.0 mg/dL or more; willingness to participate for the duration of the trial, provision of written informed consent, and a triglyceride level <500 mg/dL.
Exclusion criteria	Previous or current use of lipid-lowering therapy, current use of post-menopausal hormone-replacement therapy, evidence of hepatic dysfunction (an alanine aminotransferase level >2 times ULN), a creatine kinase level >3 times upper limit of the normal range, a creatinine level that was higher than 2.0 mg/dL, diabetes, uncontrolled hypertension, cancer within 5 years before enrolment, uncontrolled hypothyroidism, and a recent history of alcohol or drug abuse or another medical condition that might compromise safety or the successful completion of the study. Patients with inflammatory

	conditions such as severe arthritis, lupus or inflammatory bowel disease were also excluded as well as patients taking immunosuppressant agents such as cyclosporine, tacrolimus, azathioprine, or long-term oral glucocorticoids.
Recruitment/selection of patients	All potentially eligible participants underwent a 4-week placebo run-in phase; only those who successfully completed the run-in phase were enrolled. Between Feb 2003 and Dec 2006, 89,890 people were screened.
Age, gender and ethnicity	Age - Mean (SD): 68 (SD 11) years. Gender (M:F): 62%/38%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear (Subgroup analysis was conducted for White, Non-white, Black and Hispanic participants (Albert 2011) (data not extracted)). 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear (Subgroup analysis conducted for =<65 years/>65 years for the primary outcome only: the combination of nonfatal MI, nonfatal stroke, and arterial revascularisation, hospitalisation for unstable angina, or confirmed death from cardiovascular causes). 4. People with a family history of CVD: Not applicable / Not stated / Unclear (12% of participants had a family history of CHD; subgroup analysis was conducted for the primary outcome only: the combination of nonfatal MI, nonfatal stroke, and arterial revascularisation, hospitalisation for unstable angina, or confirmed death from cardiovascular causes). 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women (Subgroup analysis was conducted separately for women and men (see Mora et al. 2010) (data not extracted)).
Extra comments	. Baseline total cholesterol (mg/dL): median (IQR) 186 (168-200) in rosuvastatin group and 185 (169-199) in placebo group. LDL-cholesterol (mg/dL): median (IQR) 108 (94-119) in both groups (total cholesterol was not reported). At 48 months median (IQR) LDL-cholesterol was 55 (44-70) in rosuvastatin group and 109 (94-124) in the placebo group. At baseline, 12% had a family history of premature CHD, 42% had metabolic syndrome, and 17% were using aspirin. As per inclusion criteria, no patients were to have a history of CVD or diabetes.
Indirectness of population	Serious indirectness
Interventions	(n=8901) Intervention 1: High intensity statin - Rosuvastatin 20 mg. Rosuvastatin 20 mg/day. Duration Median 1.9 years. Concurrent medication/care: Not reported, other than 17% were taking aspirin (n=8901) Intervention 2: Placebo. Placebo. Duration Median 1.9 years. Concurrent medication/care: Not reported, other than 17% were taking aspirin

Funding	Study funded by industry (Societa Prodotti Antibiotici, Pfizer, Signam Tau, and AstraZeneca)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ROSUVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: All-cause mortality at 5 years

- Actual outcome for Adults without established CVD : All-cause mortality at Median 1.9 years; HR 0.8 (95%CI 0.67 to 0.97) Reported; Risk of bias: Low; Indirectness of outcome:

Protocol outcome 2: Non-fatal MI at 5 years

- Actual outcome for Adults without established CVD : Non-fatal MI at Median 1.9 years; Group 1: 22/8901, Group 2: 62/8901; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: MI at Median 1.9 years; Group 1: 8/1638, Group 2: 20/1629; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: MI at Median 1.9 years; HR 0.4 (95%CI 0.17 to 0.9) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults without established CVD : Non-fatal MI at Median 1.9 years; HR 0.35 (95%CI 0.22 to 0.58) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Non-fatal stroke at 5 years

- Actual outcome for Adults without established CVD : Non-fatal stroke at Median 1.9 years; Group 1: 30/8901, Group 2: 58/8901; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: Stroke at Median 1.9 years; Group 1: 10/1638, Group 2: 14/1629; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: Stroke at Median 1.9 years; HR 0.71 (95%CI 0.31 to 1.59) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults without established CVD : Non-fatal stroke at Median 1.9 years; HR 0.52 (95%CI 0.33 to 0.8) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years

- Actual outcome for Adults without established CVD : Rhabdomyolysis at Median 1.9 years; Group 1: 16/8901, Group 2: 10/8901; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: Creatinine >100% increase from baseline at Median 1.9 years; Group 1: 3/1638, Group 2: 0/1629; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: All-cause mortality at 5 years

- Actual outcome for Adults without established CVD : All-cause mortality at Median 1.9 years; Group 1: 198/8901, Group 2: 247/8901; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: All-cause mortality at Median 1.9 years; Group 1: 34/1638, Group 2: 61/1629; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: CV mortality at 5 years

- Actual outcome for Adults without established CVD : CV mortality at Median 1.9 years; Group 1: 45/8901, Group 2: 57/8901; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 7: Adverse event: Myalgia at 5 years

- Actual outcome for Adults with CKD: Muscular weakness, stiffness, or pain at Median 1.9 years; Group 1: 292/1638, Group 2: 303/1629; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 8: Adverse event:Liver (transaminases >3 times normal level) at 5 years

- Actual outcome for Adults without established CVD : ALT >3 times ULN at Median 1.9 years; Group 1: 23/8901, Group 2: 17/8901; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: ALT >3 times ULN on consecutive visits at Median 1.9 years; Group 1: 2/1638, Group 2: 4/1629; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 9: Adverse event:New onset diabetes at 5 years

- Actual outcome for Adults without established CVD : Newly diagnosed diabetes at Median 1.9 years; Group 1: 270/8901, Group 2: 216/8901; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 10: LDL-cholesterol reduction at 1 year

- Actual outcome for Adults with CKD: All-cause mortality at Median 1.9 years; HR 0.56 (95%CI 0.37 to 0.85) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : LDL-cholesterol final values at 2 years; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at 5 years

Study	Riegger 1999[151]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=365)
Countries and setting	Conducted in Czech Republic, Germany; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Symptomatic CHD
Subgroup analysis within study	Not applicable
Inclusion criteria	Stable symptomatic CHD (clinically diagnosed with exercise-ECG finding of >0.1 mV ST-segment depression), total cholesterol ≥250 mg/dL at first screening, LDL-cholesterol >160 mg/dL and triglycerides ≤300 mg/dL completion of 4 week cholesterol-lowering diet.
Exclusion criteria	PCI in 6 months prior to start of study, planned PCI or CABG, CHF NYHA III and IV, hypersensitivity or intolerance to HMG-CoA reductase inhibitors, therapy with non-registered drugs or participation in other experimental studies within 3 months of start of trial, diseased and conditions which could influence the pharmacokinetics or pharmacodynamics of the trial medication, for example, gastrointestinal diseases, liver and kidney diseases, AST and ALT >120% ULN, γ-GT, ALP, bilirubin and creatinine above 150% ULN, pregnant or breastfeeding women, women of child bearing age not using adequate contraception, non-permitted concomitant medication (probucol, digitalis, steroid hormones, antacids containing aluminium, immunosuppressive therapy, erythromycin, ketoconazole, para-aminosalicylic acid), medication abuse, drug abuse and/or alcohol abuse. Patients likely to be non-compliant were also excluded.
Recruitment/selection of patients	Multicentre trial conducted in the Czech Republic and Germany. Planning began in 1993.

Age, gender and ethnicity	Age - Mean (SD): Fluvastatin 59.4 (7.5) years, placebo 60.2 (7.2) years. Gender (M:F): Fluvastatin; 63%/37%, placebo; 60%/40%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol mean mmol/l; fluvastatin 7.47, placebo 7.34. Total cholesterol at 1 year mean mmol/l; fluvastatin 6.17, placebo 6.98. Baseline LD- cholesterol mmol/l; fluvastatin 5.12, placebo 4.99. LDL-cholesterol at 1 year mmol/l; fluvastatin 3.74, placebo 4.6. Proportion with diabetes; fluvastatin 4.3%, placebo 6.7%. Prior to randomisation all patients underwent a 10 week run in period, the first 4 weeks on a lipid-lowering diet and the following 6 weeks receiving treatment with fluvastatin 40mg/day 'to assess the lipid-lowering effect'. Of the 572 patients entered into the lead-in period, 365 were randomised.
Indirectness of population	No indirectness
Interventions	(n=187) Intervention 1: Low intensity statin - Fluvastatin 40 mg. Fluvastatin 40 mg/day; if LDL-cholesterol decreased ≤30% at 6 weeks, dosage increased to 40 mg twice daily. Dose was increased for 85 patients (45.5%) according to the protocol. Duration 1 year. Concurrent medication/care: ACE inhibitors 18.7%, calcium antagonists 31.6%, beta blockers 23.0%, nitrates 52.9%, diuretics 7.5%, acetylsalicylic acid 43.9% (n=178) Intervention 2: Placebo. Placebo once daily; if LDL-cholesterol decreased ≤30% at 6 weeks, dosage increased to placebo twice daily. Duration 1 year. Concurrent medication/care: ACE inhibitors 21.9%, calcium antagonists 33.7%, beta blockers 18.6%, nitrates 59.0%, diuretics 5.6%, acetylsalicylic acid 40.4%
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUVASTATIN 40 MG versus PLACEBO Protocol outcome 1: Non-fatal MI at 5 years	

- Actual outcome for Adults with established CVD : Non-fatal MI at 1 year; Group 1: 0/187, Group 2: 1/178; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years - Actual outcome for Adults with established CVD : Elevation of CK at 1 year; Group 1: 0/187, Group 2: 1/178; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: CV mortality at 5 years - Actual outcome for Adults with established CVD : CV mortality at 1 year; Group 1: 2/187, Group 2: 4/178; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal stroke at 5 years; All-cause mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	Sacks 1996[154] (Goldberg 1998 [63], Lewis 1998 [102], Lewis 1998 [103], Flaker 1999 [57], Plehn 1999 [138], Tonelli 2003 [179])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=4159)
Countries and setting	Conducted in Canada, USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Criteria for a qualifying MI included typical symptoms and an elevated serum level of creatine kinase
Stratum	Adults with established CVD :
Subgroup analysis within study	Not applicable: For the primary outcome (death from coronary disease or non-fatal MI) a number of subgroup analyses were undertaken, including sex, age, hypertension, diabetes, cholesterol level.
Inclusion criteria	Men and postmenopausal women (21 to 75 years of age) who had an acute MI between 3 and 20 months before randomisation, plasma total cholesterol levels less than 240 mg/dL, LDL-cholesterol levels of 115 to 174 mg/dL, fasting triglyceride fasting glucose levels of less than 350 mg/dL, fasting glucose levels of no more than 220 mg/dL, left ventricular ejection fractions of no less than 25%, and no symptomatic CHF.
Exclusion criteria	Participants with 2+ proteinuria or greater on routine dipstick testing or serum creatinine values more than 1.5 times ULN.
Recruitment/selection of patients	Patients were recruited from 80 participating centres between Dec 1989 and Dec 1991.
Age, gender and ethnicity	Age - Mean (SD): 59 (9) years. Gender (M:F): 86%/14%. Ethnicity: White: 92-93%; Other: 7-8% (no other details reported by study authors)

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: People aged 75 years or under (Subgroup analysis was conducted in patients aged 65 to 75 years (Lewis et al. 1998), data not extracted). 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women (Men and women, subgroup analysis was conducted in postmenopausal women only (Lewis et al. 1998a), data not extracted).
Extra comments	Baseline: Total cholesterol mean (SD) mg/dL; 209 (17) pravastatin and placebo group have the same mean. LDL-cholesterol mean (SD) mg/dL; 139 (15) pravastatin and placebo group have the same mean. 5 year follow-up; authors stated that the LDL-cholesterol level was 28% lower in the pravastatin group compared to the placebo group; pravastatin lowered the mean LDL-cholesterol level by 32% (no other details were reported). At baseline 14% in active group and 15% in placebo group has diabetes, all patients had a MI. Other subgroup analysis conducted include revascularised patients (Flaker et al. 1999), persons with mild chronic renal insufficiency (Tonelli et al. 2003), women (Lewis et al. 1998), age (Lewis et al. 1998), and diabetic and glucose-intolerant participants (Goldberg et al. 1998)
Indirectness of population	No indirectness
Interventions	(n=2081) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration 5 years. Concurrent medication/care: Patients continued to take all prescribed medication, for cardiac and other conditions that they had been receiving at baseline including; aspirin - 83%, beta blockers - 41%, nitrate - 32%, calcium-channel blocker - 40%, ACE inhibitor - 15%, diuretic agent - 11%, insulin - 2.4%, oral hypoglycemic agent - 5%, estrogen - 8.4% (n=2078) Intervention 2: Placebo. Placebo. Duration 5 years. Concurrent medication/care: Patients continued to take all prescribed medication, for cardiac and other conditions that they had been receiving at baseline including; aspirin - 83%, beta blockers - 39%, nitrate - 33%, calcium-channel blocker - 38%, ACE inhibitor - 14%, diuretic agent - 11%, insulin - 2.6%, oral hypoglycemic agent - 7%, estrogen - 10.3%)
Funding	Study funded by industry (Supported by a grant from Bristol-Myers Squibb)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO Protocol outcome 1: All-cause mortality at 5 years	

- Actual outcome for Adults with CKD: All-cause mortality at 5 years; HR 0.81 (95%CI 0.61 to 1.08) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Non-fatal MI at 5 years - Actual outcome for Adults with established CVD : Non-fatal MI at 5 years; Group 1: 135/2081, Group 2: 173/2078; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with type 2 diabetes: Non-fatal MI at 5 years; Group 1: 28/282, Group 2: 37/304; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults with CKD: Fatal or non-fatal MI at 5 years; Group 1: 65/844, Group 2: 90/867; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with CKD: Fatal or non-fatal MI at 5 years; HR 0.73 (95%CI 0.52 to 1.01) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Non-fatal stroke at 5 years - Actual outcome for Adults with established CVD : Stroke at 5 years; Group 1: 54/2081, Group 2: 78/2078; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with type 2 diabetes: Stroke at 5 years; Group 1: 19/282, Group 2: 24/304; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults with CKD: Stroke at 5 years; Group 1: 29/844, Group 2: 46/867; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with CKD: Stroke at 5 years; HR 0.62 (95%CI 0.39 to 1) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years - Actual outcome for Adults with CKD: CK >10 ULN at 5 years; Group 1: 6/844, Group 2: 3/867; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: All-cause mortality at 5 years - Actual outcome for Adults with established CVD : All-cause mortality at 5 years; Group 1: 180/2081, Group 2: 196/2078; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with CKD: All-cause mortality at 5 years; Group 1: 86/844, Group 2: 111/867; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: CV mortality at 5 years - Actual outcome for Adults with established CVD : Death from coronary heart disease at 5 years; Group 1: 96/2081, Group 2: 119/2078; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with type 2 diabetes: Death from coronary heart disease at 5 years; Group 1: 27/282, Group 2: 30/304; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 7: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with CKD: Abnormalities on liver function test at 5 years; Group 1: 5/844, Group 2: 5/867; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	Satoh 2009[156]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=100)
Countries and setting	Conducted in Japan; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CAD based on (i) typical chest pain (ii) exercise induced myocardial ischaemia (iii) angiography (iv) absence ACS last 3 months
Stratum	Adults with established CVD :
Subgroup analysis within study	Not applicable
Inclusion criteria	Stable CAD and statin naive.
Exclusion criteria	Clinical signs of acute infection, severe renal failure or rheumatoid disease, malignant disorder or primary wasting disorder.
Recruitment/selection of patients	Consecutive patients.
Age, gender and ethnicity	Age - Mean (SD): 64.9 (10.1) years. Gender (M:F): 60:40. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: People with autoimmune disease 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Indirectness of population	No indirectness

Interventions	(n=50) Intervention 1: Low intensity statin - Pravastatin 10 mg. Pravastatin 10 mg. Duration 1 year. Concurrent medication/care: Aspirin, ACE/ARB inhibitors, beta-blockers, calcium antagonists, nitrates (n=50) Intervention 2: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10 mg. Duration 1 year. Concurrent medication/care: Aspirin, ACE/ARB inhibitors, beta-blockers, calcium antagonists, nitrates
Funding	Academic or government funding (Japanese Ministry of Education, Science, Sports & Culture, Keiryokai Research Foundation, Open Translational Research Centre, Advanced Medical Science Centre, Iwate Medical University.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 10 MG versus ATORVASTATIN 10 MG Protocol outcome 1: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at 1 year; Group 1: mean 2.9 mmol/l (SD 0.74); n=50, Group 2: mean 2.56 mmol/l (SD 0.72); n=50; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Schmermund 2006[159]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=471)
Countries and setting	Conducted in Germany, Russia, United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Angiography
Stratum	Adults without established CVD : Without CVD (≥2 CV risk factors)
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Triglycerides <400 mg/dL, (2) ≥2 CV risk factors (smoking, hypertension, diabetes, family history CVD, HDL-cholesterol <45 mg/dL, LDL-cholesterol ≥160 mg/dL) (3) the absence of high grade coronary stenoses (angiographically defined as ≥50% diameter lumen narrowing) by coronary angiography or a normal result of non-invasive exercise stress testing (4) CAC score according to Agatston method ≥30.
Exclusion criteria	Prior ischaemic heart disease, unstable angina, CHF, atrial fibrillation, type 1 diabetes, uncontrolled type 2 diabetes, treatment with lipid lowering drugs >4 weeks within 6 months study start.
Recruitment/selection of patients	Subjects screened at 55 sites in 3 countries.
Age, gender and ethnicity	Age - Mean (SD): Atorvastatin 80 mg; 61 (8) years, atorvastatin 10 mg; 62 (8) years. Gender (M:F): 217:149. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6.

	People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Indirectness of population	No indirectness
Interventions	(n=236) Intervention 1: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10 mg. Duration 1 year. Concurrent medication/care: Not reported (n=235) Intervention 2: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg. Duration 1 year. Concurrent medication/care: Not reported
Funding	Study funded by industry (Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 10 MG versus ATORVASTATIN 80 MG

Protocol outcome 1: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults without established CVD : Rhabdomyolysis at 1 year; Group 1: 0/233, Group 2: 0/234; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Myalgia at 5 years
- Actual outcome for Adults without established CVD : Myalgia at 1 year; Group 1: 5/233, Group 2: 7/234; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults without established CVD : Transaminases > 3 times upper limit normal at 1 year; Group 1: 2/233, Group 2: 2/234; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults without established CVD : LDL-cholesterol at 1 year; Group 1: mean 2.82 mmol/l (SD 0.72); n=233, Group 2: mean 2.25 mmol/l (SD 0.72); n=234; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	Sever 2003[162] (Sever 2004 [161], Sever 2011 [160])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=10305)
Countries and setting	Conducted in Denmark, Finland, Iceland, Irish Republic, Norway, Sweden, United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Median 3.3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients with untreated hypertension defined as systolic blood pressure of 160 mm Hg or more, diastolic blood pressure of 100 mm Hg or more, or both, or treated hypertension with systolic blood pressure of 140 mm Hg or more, diastolic blood pressure 90 mm Hg or more, or both.
Stratum	Adults without established CVD : Hypertensive patients who had average or lower-than-average cholesterol concentrations, and who had at least 3 other cardiovascular risk factors
Subgroup analysis within study	Stratified then randomised: Randomisation using the minimisation procedure; also pre-specified subgroup analyses by diabetes status, smoking, obesity, LVH, age, sex, vascular disease, renal dysfunction, and metabolic syndrome. Long-term follow-up analysis was also conducted in subjects recruited to the trial in the UK only (Sever et al. 2011) (data not extracted)
Inclusion criteria	Men, aged 55 years or older, with either untreated hypertension or treated hypertension, and not taking a statin or fibrate, patients had to have at least 3 of the following risk factors for CVD; left-ventricular hypertrophy, other specified abnormalities on electrocardiogram, type 2 diabetes, PAD, previous stroke or transient ischaemic attack, microalbuminuria or proteinuria, smoking, ratio of plasma total cholesterol to HDL-cholesterol of 6 or higher, or premature family history of CHD.
Exclusion criteria	Previous MI, currently treated angina, a cerebrovascular event within the previous 3 months, fasting triglycerides higher than 4.5 mmol/l, heart failure, uncontrolled arrhythmias or any clinically important haematological or biochemical abnormality on routine screening.

Recruitment/selection of patients	Most patients were recruited from family practice. Patients were recruited between Feb 1998 and May 2000.
Age, gender and ethnicity	Age - Mean (SD): 63 (8.5) years. Gender (M:F): 81%/19%. Ethnicity: 95% White
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: People aged 75 years or under (Subgroup analysis in patients >60 and =<60 years on the primary end-point (non-fatal plus fatal CHD)). 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men).
Extra comments	Baseline total cholesterol mean (SD) mmol/l; 5.5 (0.8) in both treatment groups. Baseline LDL-cholesterol mean (SD) mmol/l; 3.4 (0.7) in both treatment groups. At end of follow-up: total cholesterol mean (SD) mmol/l; mean 4.21 (0.85) atorvastatin, 5.21 (0.91) placebo; LDL-cholesterol mean (SD) mmol/l: 2.32 (0.72) atorvastatin,3.27 (0.81) placebo. At baseline; 25% of people had diabetes, 10% had a previous stroke or transient ischaemic attack, 14% had left-ventricular hypertrophy, 14% had ECG abnormalities other than LVH, 5% had peripheral vascular disease and 4% had other relevant CVD.
Indirectness of population	No indirectness
Interventions	(n=5168) Intervention 1: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10 mg/day. Duration Median 3.3 years. Concurrent medication/care: Any lipid-lowering treatment other than a fibrate or a statin, in use before randomisation could be continued during the study (n=5137) Intervention 2: Placebo. Placebo. Duration Median 3.3. years. Concurrent medication/care: Any lipid-lowering treatment other than a fibrate or a statin, in use before randomisation could be continued during the study
Funding	Study funded by industry (Principally supported by Pfizer, and also funded by Servier Research Group, and Leo Laboratories)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 10 MG versus PLACEBO

Protocol outcome 1: Non-fatal stroke at 5 years

- Actual outcome for Adults without established CVD : Stroke (fatal and non-fatal) at Median 3.3 years; Group 1: 89/5168, Group 2: 121/5137; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults without established CVD : Stroke (fatal and non-fatal) at Median 3.3 years; HR 0.73 (95%CI 0.56 to 0.96) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults without established CVD : Rhabdomyolyisis at Median 3.3 years; Group 1: 1/5168, Group 2: 0/5137; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : All-cause mortality at Median 3.3 years; Group 1: 185/5168, Group 2: 212/5137; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults without established CVD : All-cause mortality at Median 3.3 years; HR 0.87 (95%CI 0.71 to 1.06) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 4: CV mortality at 5 years
- Actual outcome for Adults without established CVD : CV mortality at Median 3.3 years; Group 1: 74/5168, Group 2: 82/5137; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults without established CVD : CV mortality at Median 3.3 years; HR 0.9 (95%CI 0.66 to 1.23) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse event:New onset diabetes at 5 years
- Actual outcome for Adults without established CVD : Development of diabetes mellitus at Median 3.3 years; Group 1: 154/3910, Group 2: 134/3863; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults without established CVD : Development of diabetes mellitus at Median 3.3 years; HR 1.15 (95%CI 0.91 to 1.44) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 6: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults without established CVD : LDL-cholesterol at Median 3.3 years; Group 1: mean 2.32 mmol/l (SD 0.72); n=5168, Group 2: mean 3.27 mmol/l (SD 0.81); n=5137; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Quality of life at 5 years

Study (subsidiary papers)	Shepherd 1995[165] (Freeman 2001 [59])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=6595)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Mean 4.9 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Detailed methods of assessment were reported in the paper
Stratum	Adults without established CVD : Men with moderate hypercholesterolemia and no history of MI
Subgroup analysis within study	Not stratified but pre-specified: Subgroup analysis by age (<55 or ≥55 years), smoking status, and whether at least 2 of the following risk factors were present: smoking, hypertension, a history of chest pain or intermittent claudication, diabetes, and a minor ECG abnormality associated with CHD
Inclusion criteria	Men 45-64 years of age; fasting LDL-cholesterol level of at least 155 mg/dL (during second and third visits to clinic before randomisation) with at least one value of 174 mg/dL or above and one value of 232 mg/dL or below; no serious ECG abnormalities according to Minnesota code 1, 1-l, 5-l, or 7-1-l or arrhythmia such as atrial fibrillation; and no history of MI or other serious illness, although men with stable angina who had not been hospitalised with the previous 12 months were eligible.
Exclusion criteria	Not reported.
Recruitment/selection of patients	Screening clinics were established in primary medical care facilities throughout the West of Scotland district. Participants were enrolled between September 1991 and May 1995
Age, gender and ethnicity	Age - Mean (SD): 55.2 (5.5) years. Gender (M:F): 100% male. Ethnicity: Not reported

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men).
Extra comments	Baseline total cholesterol mean (SD) mg/dL; 272 (23) pravastatin, 272 (22) placebo. Baseline LDL-cholesterol mean (SD) mg/dL; 192 (17) for both groups. No other data were reported. At baseline 1% of participants has diabetes, 5% had angina, and 3% had intermittent claudication.
Indirectness of population	No indirectness
Interventions	(n=3302) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration 4.9 years. Concurrent medication/care: Dietary advice (n=3293) Intervention 2: Placebo. Placebo. Duration 4.9 years. Concurrent medication/care: Dietary advice
Funding	Study funded by industry (Supported by a grant from Bristol-Myers Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults without established CVD : Non-fatal MI at 4.9 years; Group 1: 143/3302, Group 2: 204/3293; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults without established CVD : Non-fatal MI at 4.9 years; HR 0.7 (95%CI 0.56 to 0.86) Calculated – from logrank P-value; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults without established CVD : Non-fatal stroke at 4.9 years; Group 1: 40/3302, Group 2: 47/3293; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : All-cause mortality at 4.9 years; Group 1: 106/3302, Group 2: 135/3293; Risk of bias: Unclear; Indirectness of

outcome: No indirectness - Actual outcome for Adults without established CVD : All-cause mortality at 4.9 years; HR 0.78 (95%CI 0.6 to 1) Calculated – from logrank P-value; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 4: CV mortality at 5 years - Actual outcome for Adults without established CVD : Death from all cardiovascular causes at 4.9 years; Group 1: 50/3302, Group 2: 73/3293; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for Adults without established CVD : Death from all cardiovascular causes at 4.9 years; HR 0.68 (95%CI 0.47 to 0.97) Calculated – from logrank P-value; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse event: Myalgia at 5 years - Actual outcome for Adults without established CVD : Myalgia at 4.9 years; Group 1: 20/3302, Group 2: 19/3293; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults without established CVD : Aspartate aminotransferase (>3 times the upper reference limits) at 4.9 years; Group 1: 26/3302, Group 2: 20/3293; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for Adults without established CVD : Alanine aminotransferase (>3 times the upper reference limits) at 4.9 years; Group 1: 16/3302, Group 2: 12/3293; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 7: Adverse event:New onset diabetes at 5 years - Actual outcome for Adults without established CVD : New onset diabetes at 4.9 years; Group 1: 75/2999, Group 2: 93/2975; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	Shepherd 2002[164] (Shepherd 2004 [163])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=5804)
Countries and setting	Conducted in Irish Republic, Netherlands, United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Mean 3.2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Lipoprotein profiles were measured at the Centre for Disease Control certified central lipoprotein laboratory in Glasgow. A 12-lead ECG was recorded yearly.
Stratum	Adults with established CVD : Older men and women (70-82) with a history of, or risk factors for, vascular disease
Subgroup analysis within study	Not stratified but pre-specified: Subgroup analysis by smoking status, history of hypertension, sex, diabetes, and LDL- and HDL-cholesterol, and also gender and pre-existing disease
Inclusion criteria	Men and women aged 70-82 years with either pre-existing vascular disease (coronary, cerebral, or peripheral) or raised risk of such disease because of smoking, hypertension, or diabetes; total cholesterol 4.0-9.0 mmol/l and triglycerides less than 6.0 mmol/l.
Exclusion criteria	Participants with poor cognitive function were excluded. Also, those who used less than 75%, or more than 120% of the placebo medication during a single-blind placebo period were excluded.
Recruitment/selection of patients	Participants were enrolled between Dec 1997 and May 1999. After screening, eligible patients entered a 4-week single-blind placebo period.
Age, gender and ethnicity	Age - Mean (SD): 75.4 (3.3) years in pravastatin group, 75.3 (3.4) years in placebo group. Gender (M:F): 48%/52%. Ethnicity: Not reported

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: People aged over 75 years (All people included in this trial were between 70-82 years of age). 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women (Men and women; subgroup analysis was conducted in women).
Extra comments	Baseline total cholesterol mean (SD) mmol/l; 5.7 (0.9) in both treatment groups. Baseline LDL-cholesterol mean (SD) mmol/l; 3.8 (0.8) in both treatment groups. The authors stated that at 3 months' follow-up pravastatin significantly improved LDL-cholesterol by -34% (95 mg/dL - no other details were reported); 11% of patients in both groups had a history of diabetes; 13% in pravastatin group and 14% in placebo group had a history of MI; 11% in both groups had a history of stroke or transient ischaemic attack.
Indirectness of population	No indirectness
Interventions	(n=2891) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration Mean 3.2 years. Concurrent medication/care: Nutrition and health advice (n=2913) Intervention 2: Placebo. Placebo. Duration Mean 3.2 years. Concurrent medication/care: Nutrition and health advice
Funding	Study funded by industry (Supported by an investigator grant from Bristol-Myers Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 3.2 years; Group 1: 222/2891, Group 2: 254/2913; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Non-fatal MI at 3.2 years; HR 0.86 (95%CI 0.72 to 1.03) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Non-fatal stroke at 3.2 years; Group 1: 116/2891, Group 2: 119/2913; Risk of bias: Low; Indirectness of outcome: No

indirectness - Actual outcome for Adults with established CVD : Non-fatal stroke at 3.2 years; HR 0.98 (95%CI 0.76 to 1.26) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years - Actual outcome for Adults with established CVD : Rhabdomyolysis at 3.2 years; Group 1: 0/2891, Group 2: 0/2913; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: All-cause mortality at 5 years - Actual outcome for Adults with established CVD : All-cause mortality at 3.2 years; Group 1: 298/2891, Group 2: 306/2913; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : All-cause mortality at 3.2 years; HR 0.97 (95%CI 0.83 to 1.14) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: CV mortality at 5 years - Actual outcome for Adults with established CVD : Death due to coronary heart disease, stroke and vascular at 3.2 years; Group 1: 251/2891, Group 2: 293/2913; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse event: Myalgia at 5 years - Actual outcome for Adults with established CVD : Myalgia at 3.2 years; Group 1: 36/2891, Group 2: 32/2913; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 7: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with established CVD : Alanine and aspartate transaminases >3 the upper limit of normal at 3.2 years; Group 1: 1/2891, Group 2: 1/2913; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 8: Adverse event:New onset diabetes at 5 years - Actual outcome for Adults with established CVD : New onset diabetes at 3.2 years; Group 1: 165/2510, Group 2: 127/2513; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	Shukla 2005[167]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=150)
Countries and setting	Conducted in India; Setting: Not specified
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Angiographically proven CAD
Stratum	Adults with established CVD : Patients with CAD and average or below average cholesterol levels
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing coronary angioplasty and showing proven CAD were enrolled if LDL-cholesterol was <130 mg/dL and total cholesterol <200 mg/dL.
Exclusion criteria	Patients with a history of recent MI, altered liver function test, altered renal parameters, triglycerides >200 mg/dL, those already receiving lipid lowering drug therapy or alcohol intake >3 peg per day, were excluded. Patients with secondary causes of elevated cholesterol levels were also excluded (steroid therapy, hypo/hyperthyroidism, antacid containing aluminium) and so were patients with any major systemic illness.
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Other: Pravastatin mean 57 years, placebo mean 55 years. Gender (M:F): 118:32. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).

Extra comments	Baseline total cholesterol mean (SD) mg/dL; 144 (26)atorvastatin, 148 (32) placebo group. Baseline LDL-cholesterol mean (SD) mg/dL; 86 (24) atorvastatin group, 84 (19) placebo group. 5% in the atorvastatin group and 4% in the placebo group had PAD. There was no information on the percentage of people with diabetes.
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10 mg. Duration 1 year. Concurrent medication/care: All patients received dietary advice and lifestyle modification (n=75) Intervention 2: Placebo. Placebo. Duration 1 year. Concurrent medication/care: All patients received dietary advice and lifestyle modification
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 10 MG versus PLACEBO

Protocol outcome 1: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL cholesterol at 1 year; Group 1: mean 1.91 mmol/l (SD 0.49); n=73, Group 2: mean 2.25 mmol/l (SD 0.44); n=72; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Sola 2006[170]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=108)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients had New York Heart Association functional class II to IV heart failure; left ventricular ejection fraction was documented by echocardiography or ventriculography during the 1 year before enrolment. Patients were classified as having non-ischaemic cardiomyopathy if they had no prior clinical history of a MI and no coronary artery stenoses >50% on cardiac catheterisation performed during year before enrolment.
Stratum	Adults with established CVD : Patients with non-ischaemic forms of cardiomyopathy
Subgroup analysis within study	Unclear
Inclusion criteria	Men and women aged 18 years or older with an NYHA functional class II to IV heart failure due to a non-ischaemic aetiology; left ventricular ejection fraction =<35%; stable doses of heart failure medications for 3 months before enrolment
Exclusion criteria	Patients were excluded if they had been receiving a statin during the 6 months before enrolment, had had a prior adverse event related to statin use, had diabetes mellitus.
Recruitment/selection of patients	No details reported
Age, gender and ethnicity	Age - Mean (SD): 53.3 (SD 6.2) years atorvastatin, 54.1 (SD 6.9) placebo. Gender (M:F): 62%/38%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of

	CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline LDL-cholesterol mean (SD) mg/dL; 118 (15) atorvastatin,124 (20) placebo. Baseline total cholesterol was not reported. At 12 months LDL-cholesterol mean (SD) mg/dL; 93 (9) atorvastatin 124 (17). Patients with diabetes mellitus were excluded from this trial.
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: High intensity statin - Atorvastatin 20 mg. Atorvastatin 20 mg/day. Duration 12 months. Concurrent medication/care: At baseline: 85% were taking ACE inhibitor or ARB; 67% beta blocker; 9% aldosterone blocker; 65% diuretics (n=54) Intervention 2: Placebo. Placebo. Duration 12 months. Concurrent medication/care: At baseline: 91% were taking ACE inhibitor or ARB; 72% beta blocker; 11% aldosterone blocker; 65% diuretics
Funding	Other author(s) funded by industry (One of the study authors had been an advisory board member for Sanofi-Aventis and Bristol Myers Squibb and on the speakers bureau for Sanofi-Aventis, Bristol Myers Squibb and Takeda Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : Total mortality at 12 months; Group 1: 4/54, Group 2: 4/54; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at 12 months; Group 1: mean 2.28 mmol/l (SD 0.94); n=54, Group 2: mean 2.64 mmol/l (SD 0.87); n=54; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Teo 2000[176]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=460)
Countries and setting	Conducted in Canada; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 3 to 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Patients with angiographic evidence of coronary atherosclerosis
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥21 years with no upper age limit, total serum cholesterol levels 4.1 - 6.2 mmol/l, HDL-cholesterol <2.2 mmol/l, triglycerides <4 mmol/l and lower than total cholesterol, angiographically detectable coronary atherosclerosis in ≥3 major coronary artery segments, left ventricular ejection fraction >35%.
Exclusion criteria	Coronary angioplasty or CABG within 6 months of recruitment, clear indications for or contraindications to study drugs, clinical instability, imminent need for intervention, other significant cardiac or systemic disease, potential non-compliance, inability to give informed consent
Recruitment/selection of patients	Patients recruited and followed up from June 1991 to July 1995 in 4 Canadian centres.
Age, gender and ethnicity	Age - Mean (SD): Simvastatin 61(9) years, placebo 61(10) years. Gender (M:F): No overall male/female ratio, simvastatin 201/29, placebo 209/21. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6.

	People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	2x2 factorial design with patients randomised to simvastatin versus placebo and enalapril versus placebo. There was a 1 month single-blind placebo run-in phase. Protocol was modified to permit identification of those with cholesterol levels persistently >5.5 mmol/l and to reallocate them to active simvastatin, in a double blind fashion.
Indirectness of population	No indirectness
Interventions	(n=230) Intervention 1: Low intensity statin - Simvastatin 10 mg. Simvastatin 10 mg/day commenced then dose automatically titrated until maximum dose of 40 mg/day or, if side effects occurred, maximally tolerated dose. Duration 3-5 years. Concurrent medication/care: Aspirin 90%, beta blockers 48%, nitrates 66%, calcium channel blockers 12% Comments: Outcomes reported as Simvastatin arm (including Simvastatin alone and Simvastatin plus Enalapril) (n=230) Intervention 2: Placebo. Placebo. Duration 3-5 years. Concurrent medication/care: Aspirin 90%, beta blockers 47%, nitrates 63%, calcium channel blockers 17% Comments: Outcomes reported as Simvastatin arm (including Simvastatin alone and Simvastatin plus Enalapril)
Funding	Study funded by industry (Merck Frosst Canada & Co)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 10 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 3-5 years; Group 1: 10/230, Group 2: 9/230; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Non-fatal stroke at 4-5 years; Group 1: 2/230, Group 2: 6/230; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 3-5 years; Group 1: 13/230, Group 2: 6/230; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: CV mortality at 5 years - Actual outcome for Adults with established CVD : Cardiac mortality at 3-5 years; Group 1: 7/230, Group 2: 4/230; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at 3-5 years; Group 1: mean 2.33 mmol/l (SD 0.49); n=230, Group 2: mean 3.43 mmol/l (SD 0.56); n=230; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Terry 2007[177]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=80)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Angiographic evidence of coronary artery calcium ≥ 50 U
Stratum	Adults without established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 21 to 75 years, CAC triglycerides ≥ 50 U by CT, 600 mg/dL, 1 of the following;(1) HDL-cholesterol ≤ 50 mg/dL, LDL-cholesterol 100 to 130 mg/dL, and ≥ 2 other risk factors that modify LDL-cholesterol goal, (2) HDL-cholesterol ≤ 50 mg/dL, LDL-cholesterol 130 to 190 mg/dL, and < 2 other risk factors that modify LDL-cholesterol goal. Positive risk factors affecting goal were; age (1) ≥54 years men, ≥55 years in women, (2) parent or sibling history CAD age <55 years for men or <65 years for women, (3) current smoker, (4) hypertension, (5) HDL-cholesterol < 53 mg/dL.
Exclusion criteria	Valvular disease, diabetes, aminotransferase >20% ULN, creatine kinase >50% ULN, creatinine >1.8 mg/dL, thyroid abnormalities, women of childbearing age not practicing birth control, consumption >10 units alcohol/week, untreated hypertension, known intolerance to simvastatin.
Recruitment/selection of patients	From previous studies and mass mailing.
Age, gender and ethnicity	Age - Mean (SD): Simvastatin 66 (6) years, placebo 66 (5) years. Gender (M:F): 73:7. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear (Aged 21 to 75 years). 4. People

	with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: High intensity statin - Simvastatin 80 mg. Simvastatin 80 mg. Duration 1 year. Concurrent medication/care: Dietary advice and standard care (n=40) Intervention 2: Placebo. Placebo. Duration 1 year. Concurrent medication/care: Dietary advice and standard care
Funding	Other author(s) funded by industry (Merck Pharmaceuticals, Wake Forest University General Clinical Research Center North Carolina)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 80 MG versus PLACEBO Protocol outcome 1: LDL-cholesterol reduction at 1 year - Actual outcome for Adults without established CVD : LDL-cholesterol at 1 year; Group 1: mean 1.91 mmol/l (SD 0.49); n=40, Group 2: mean 3.26 mmol/l (SD 0.49); n=40; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Yamada 2007[190]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=38)
Countries and setting	Conducted in Japan; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: M-mode and 2-dimensional ECG performed
Stratum	Adults with established CVD : Patients with mild to moderate CHF
Subgroup analysis within study	Unclear: No subgroup analysis
Inclusion criteria	Patients with mild to moderate CHF with radionuclide left ventricular ejection fraction <40% and serum cholesterol levels from 150 to 280 mg/dL; patients had to have at least 1 hospital admission for worsening heart failure and were required to be stable on conventional therapy, including beta blockers, for at least 3 months before study entry.
Exclusion criteria	Use of lipid lowering agents during the 6 months before the start of the study, severe renal dysfunction, severe liver disease, ACS, PCI or CABG within the 6 months before study entry, and acute or chronic inflammatory diseases involving organs other than the heart.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 64 (SD 11) years. Gender (M:F): 79%/21%. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6.

	People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol mean (SD) mg/dL; 198 (SD) atorvastatin, 195 (32) placebo. Baseline LDL-cholesterol mean (SD) mg/dL; 119 (27) atorvastatin, 115 (SD 37) placebo. At follow-up total cholesterol mean (SD) mg/dL; 154 (25) atorvastatin group, 192 (33) placebo. At follow-up LDL-cholesterol mean (SD) mg/dL; 76 (18) atorvastatin, 110 (35) placebo. At baseline, 22% of people had diabetes mellitus, and 53% were ischaemic.
Indirectness of population	Serious indirectness: 53% patients had ischaemic CHD
Interventions	(n=19) Intervention 1: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10 mg/day. Duration 3 years. Concurrent medication/care: At baseline, 95% of patients were taking ACEI/ARB, 89% diuretics, 68% digoxin, and 84% beta blocker (n=19) Intervention 2: Placebo. Usual care: conventional therapy (beta blockers, ACE inhibitors, ARBs, and diuretics) were not altered for the first 6 months, thereafter the study was opened. Duration 3 years. Concurrent medication/care: At baseline, 100% of patients were taking ACE inhibitors/ARBs, 83% diuretics, 63% digoxin, and 68% beta blocker
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 10 MG versus PLACEBO

Protocol outcome 1: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Death as a result of cardiac events at 3 years; Group 1: 0/19, Group 2: 2/19; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at 3 years; Group 1: mean 1.97 mmol/l (SD 0.47); n=19, Group 2: mean 2.84 mmol/l (SD 0.91); n=19; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; Adverse event: Myalgia at 5 years;

	Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Yokoi 2005[191]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=373)
Countries and setting	Conducted in Japan; Setting: ARTHEROMA study. Settings were secondary care centres (cardiovascular medical centres)
Line of therapy	1st line
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Determination of MI was made on the basis of typical chest pain and several serum enzyme values. Ischaemic stroke required both typical symptoms and an ischaemic pattern on brain computed tomography or angiogram.
Stratum	Adults with established CVD : Japanese CAD patients with slightly to moderately elevated cholesterol concentrations.
Subgroup analysis within study	Unclear
Inclusion criteria	Patients with CHD, 40-69 years of age, serum total cholesterol concentration 195-265 mg/dL, and 1 stenosis of greater than 25% in major coronary segments on visual assessment (according to the American Heart Association reporting system).
Exclusion criteria	Not reported.
Recruitment/selection of patients	Participating institutions were screened for enrolment between August 1994 and September 1997.
Age, gender and ethnicity	Age - Mean (SD): 59.3 (6.5) years. Gender (M:F): 83%/17%. Ethnicity: Japanese
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).

Extra comments	Baseline total cholesterol mean (SD) mg/dL; 226.2 (17.2) diet + pravastatin, 224.8 (17.5) diet. Baseline LDL-cholesterol mean (SD) mg/dL; 143.3 (20.6) diet + pravastatin, 142.0 (20.6) diet. Follow-up at 3 years total cholesterol mean (SD) mg/dL; 196.8 (23.0) diet + pravastatin, 223.2 (21.4) diet. Follow-up at 3 years LDL-cholesterol mean (SD) mg/dL 115.3 (20.0) diet + pravastatin, 140.7 (20.1) diet. At baseline, 19% of participants had diabetes mellitus, 14% had acute MI, 31% had prior MI, 41% had unstable angina pectoris, 12% had stable angina pectoris, and 2% had silent MI.
Indirectness of population	No indirectness
Interventions	(n=186) Intervention 1: Low intensity statin - Pravastatin 20 mg. Pravastatin 10-20 mg/day. Duration 3 years. Concurrent medication/care: Not reported (n=187) Intervention 2: Placebo. Usual care. Duration 3 years. Concurrent medication/care: Dietary counselling: low-fat and calorie reduced diet, no other drug treatments were reported
Funding	Academic or government funding (Japanese Ministry of Health and Welfare)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Myocardial infarction at 3 years; Group 1: 2/182, Group 2: 4/179; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Stroke at 3 years; Group 1: 5/182, Group 2: 4/179; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 3 years; Group 1: 1/182, Group 2: 2/179; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at 3 years; Group 1: mean 2.98 mmol/l (SD 0.52); n=182, Group 2: mean 3.64 mmol/l (SD 0.52); n=179; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	Zou 2003[196]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=197)
Countries and setting	Conducted in China; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Adults with established CVD : Patients with ACS (within 48 hours of randomisation)
Subgroup analysis within study	Not applicable
Inclusion criteria	≤48 hours of hospitalisation for a diagnosis of unstable angina or acute MI, total cholesterol ≥4.65 mmol/l or LDL-cholesterol ≥2.59 mmol/l.
Exclusion criteria	Not reported.
Age, gender and ethnicity	Age - Mean (range): Simvastatin 10 mg 61.2 (9.9) years, simvastatin 20 mg 61.3 (10.3) years. Gender (M:F): 123/74. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Baseline total cholesterol mean (mmol/l); simvastatin 10 mg 6.09, simvastatin 20 mg 4.98. Baseline LDL-cholesterol (mmol/l); simvastatin 10 mg 5.52, simvastatin 20 mg 3.51 cholesterol; 3.51. Follow-up at 1 year total cholesterol mean (mmol/l) simvastatin 10 mg 5.47, simvastatin 20 mg 4.78. Follow-up at 1 year LDL-cholesterol mmol/l; simvastatin 10 mg

	3.03, simvastatin 20 mg 2.83. Diabetes; simvastatin 10 mg 12%, simvastatin 20 mg 15%. Hypertension; simvastatin 10 mg 64%, simvastatin 20 mg 69%.
Indirectness of population	No indirectness
Interventions	(n=98) Intervention 1: Low intensity statin - Simvastatin 10 mg. Simvastatin 10 mg/day. Duration 1 year. Concurrent medication/care: ACE inhibitors: 26%; aspirin: 95%; beta-blockers: 90%; Calcium antagonist: 19%; nitrates: 31% (n=99) Intervention 2: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day. Duration 1 year. Concurrent medication/care: ACE inhibitors: 28%; aspirin: 97%; beta-blockers: 85%; Calcium antagonist: 23%; nitrates: 26%
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 10 MG versus SIMVASTATIN 20 MG

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : MI at 1 year; Group 1: 12/98, Group 2: 7/99; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Coronary death at 1 year; Group 1: 2/98, Group 2: 2/99; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL cholesterol at 1 year; Group 1: mean 3.03 mmol/l (SD 0.53); n=98, Group 2: mean 2.83 mmol/l (SD 0.75); n=99; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

D.1.2 Additional outcomes extracted 2022

Anon 1994

Bibliographic Reference	Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S); Lancet; 1994; vol. 344 (no. 8934); 1383-1389

Study details

Secondary publication of another included study- see primary study for details	**Please See full details in CG181 2014 update evidence table.**

Study arms

Simvastatin 20 mg (N = 2221)

20 or 40 mg (37% had dose raised to 40 mg)

Placebo (N = 2223)

Outcomes

Study timepoints

- 5.4 year (median)

Raw data

Outcome	Simvastatin 20 mg, 5.4 year, N = 2221	Placebo, 5.4 year, N = 2223
Non-fatal haemorrhagic stroke No of events	n = 0 ; % = 0	n = 2 ; % = 0.1

Non-fatal haemorrhagic stroke - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)

Non-fatal haemorrhagic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Loss to follow-up unclear and very low event rate)
Overall bias and Directness	Overall Directness	Directly applicable

Anon 2000

Bibliographic Reference	Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico); Italian Heart Journal; 2000; vol. 1 (no. 12); 810-820

Study details

Secondary publication of another included study- see primary study for details	**See full details in CG181 2014 update evidence table**
Additional comments	

Study arms
Pravastatin 40 mg (N = 2138)
No treatment (N = 2133)
Outcomes
Study timepoints
- 23 month (mean)

Raw data

Outcome	Pravastatin 40 mg, 23 month, N = 2138	No treatment, 23 month, N = 2133
Major adverse cardiovascular events Cardiovascular mortality, non-fatal MI and non-fatal stroke No of events	n = 101	n = 113

Major adverse cardiovascular events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)

Raw data-Major adverse cardiovascular events – No Of Events-Pravastatin 40 mg-No treatment-t23

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Deviations from intended interventions)
Overall bias and Directness	Overall Directness	Directly applicable

Anon, 2002

Bibliographic Reference	MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial; The Lancet; 2002; vol. 360 (no. 9326); 7-22

Study details

Secondary publication of another included study- see primary study for details	**See full details in CG181 2014 update evidence table**

Study arms

Simvastatin 40 mg (N = 10269)

Placebo (N = 10267)

Outcomes

Study timepoints

- 5 year

Dichotomous data

Outcome	Simvastatin 40 mg, 5 year, N = 10269	Placebo, 5 year, N = 10267
New-onset dementia No of events	n = 31	n = 31
Haemorrhagic stroke No of events	n = 51	n = 53

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)

New-onset dementia

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Outcome not prespecified nor defined)
Overall bias and Directness	Overall Directness	Directly applicable

Haemorrhagic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Amarenco, 2006

Bibliographic Reference Amarenco, P.; Bogousslavsky, J.; Callahan, A., III; Goldstein, L.B.; Hennerici, M.; Rudolph, A.E.; Sillesen, H.; Simunovic, L.; Szarek, M.; Welch, K.M.; Zivin, J.A.; High-dose atorvastatin after stroke or transient ischemic attack; New England journal of medicine; 2006; vol. 355 (no. 6); 549-559

Study details

Secondary publication of another included study- see primary study for details	**Full details available in CG181 evidence table.**
Trial name / registration number	SPARCL

Study arms
Atorvastatin 80 mg (N = 2365)
High intensity statin
Placebo (N = 2366)

Outcomes
Study timepoints
- Baseline
- 6 year (Median follow-up 4.9 years (range in survivors 4-6.6 years))

Dichotomous data extracted 2022

Outcome	Atorvastatin 80mg, Baseline, N = 2365	Atorvastatin 80mg, 6 year, N = 2272	Placebo, Baseline, N = 2366	Placebo, 6 year, N = 2253
Ischaemic stroke	n = 0	n = 334	n = 0	n = 407
MACE Stroke plus any major coronary event (death from cardiac causes, nonfatal myocardial infarction, or resuscitation after cardiac arrest) No of events	n = 0	n = 218	n = 0	n = 274

Time to event data extracted 2022

Outcome	Atorvastatin 80mg vs Placebo, Baseline, N2 = 2365, N1 = 2365	Atorvastatin 80mg vs Placebo, 6 year, N2 = 2366, N1 = 2366
MACE First major cardiovascular event Hazard ratio/95% CI	-	0.8 (0.69 to 0.92)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)

Extracted 2022-Iscaehemic stroke-Atorvastatin 80mg-Placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns (No information about allocation concealment)
Overall bias and Directness	Overall Directness	Directly applicable

Extracted 2022-MACE-Atorvastatin 80mg-Placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns (No information about allocation concealment)
Overall bias and Directness	Overall Directness	Directly applicable

Time-to-event data extracted 2022-MACE-Atorvastatin 80mg-Placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns (No information about allocation concealment)
Overall bias and Directness	Overall Directness	Directly applicable

Outcomes

Study timepoints

- 4.9 year (Median 4.9 years (range in survivors 4-6.6 years))

Dichotomous data extracted 2022

Outcome	Atorvastatin 80 mg, 4.9 year, N = 2365	Placebo, 4.9 year, N = 2366
Haemorrhagic stroke No of events	n = 55	n = 33

Haemorrhagic stroke - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)

Dichotomous data extracted 2022-Haemorrhagic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Deedwania, 2007

Bibliographic Reference	Deedwania, P.; Stone, P.H.; Merz, C.N.B.; Cosin-Aguilar, J.; Koylan, N.; Luo, D.; Ouyang, P.; Piotrowicz, R.; Schenck-Gustafsson, K.; Sellier, P.; Stein, J.H.; Thompson, P.L.; Tzivoni, D.; Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: Results of the Study Assessing Goals in the Elderly (SAGE); Circulation; 2007; vol. 115 (no. 6); 700-707

Study details

Secondary publication of another included study- see primary study for details	**Please See full details in CG181 2014 update evidence table**

Study arms

Atorvastatin 80 mg (N = 446)

Pravastatin 40 mg (N = 445)

Outcomes

Study timepoints

- 1 year

Raw data

Outcome	Atorvastatin 80 mg, 1 year, N = 446	Pravastatin 40 mg, 1 year, N = 445
Major adverse cardiovascular events Cardiovascular deaths, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization procedures, fatal and nonfatal stroke, and hospitalization for unstable angina No of events	n = 61	n = 90

Major adverse cardiovascular events - Polarity - Lower values are better

Time-to-event

Outcome	Atorvastatin 80 mg vs Pravastatin 40 mg, 1 year, N2 = 446, N1 = 445
Major adverse cardiovascular events cardiovascular deaths, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization procedures, fatal and nonfatal stroke, and hospitalization for unstable angina Hazard ratio/95% CI	0.71 (0.46 to 1.1)

Major adverse cardiovascular events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
Raw data Major adverse cardiovascular events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (>10% missing data and unclear allocation concealment)
Overall bias and Directness	Overall Directness	Directly applicable

Time-to-event-Major adverse cardiovascular events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (>10% missing data and unclear allocation concealment)
Overall bias and Directness	Overall Directness	Directly applicable

Gupta, 2017

Bibliographic Reference	Gupta, A.; Thompson, D.; Whitehouse, A.; Collier, T.; Dahlof, B.; Poulter, N.; Collins, R.; Sever, P.; Investigators, Ascot; Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase; Lancet; 2017; vol. 389 (no. 10088); 2473-2481

Study details

Secondary publication of another included study- see primary study for details	**Sever 2003[162]** **ASCOT-LLA**

Study arms

Atorvastatin 10 mg (N = 5186)

Placebo (N = 5137)

Outcomes

Study timepoints

- 3.3 year (median)

Raw data

Outcome	Atorvastatin 10 mg, 3.3 year, N = 5101	Placebo, 3.3 year, N = 5079
Cognitive decline Symptoms or events reported that are concerning for potential cognitive decline No of events	n = 31	n = 32

Cognitive decline - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)
Cognitive decline

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Unclear allocation concealment and outcome definition)
Overall bias and Directness	Overall Directness	Indirectly applicable (unclear if validated questionnaire used)

Hong, 2008

Bibliographic Reference	Hong, Y.J.; Jeong, M.H.; Chung, J.W.; Sim, D.S.; Cho, J.S.; Yoon, N.S.; Yoon, H.J.; Moon, J.Y.; Kim, K.H.; Park, H.W.; Kim, J.H.; Ahn, Y.; Cho, J.G.; Park, J.C.; Kang, J.C.; The effects of rosuvastatin on plaque regression in patients who have a mild to moderate degree of coronary stenosis with vulnerable plaque; Korean Circulation Journal; 2008; vol. 38 (no. 7); 366-373

Study details

Secondary publication of another included study- see primary study for details	**See full details in CG181 2014 update evidence table**

Study arms
Atrovastatin 40 mg (N = 14)

Rosuvastatin 20 mg (N = 16)

Outcomes
Study timepoints
- 1 year

Raw data

Outcome	Atorvastatin 40 mg, 1 year, N = 14	Rosuvastatin 20 mg, 1 year, N = 16
Cognitive loss not defined further No of events	n = 0 ; % = 0	n = 0 ; % = 0

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)
Raw data-Cognitive loss

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Insufficient reporting and outcome not defined)
Overall bias and Directness	Overall Directness	Directly applicable

Knopp, 2006

Bibliographic Reference	Knopp, R.H.; d'Emden, M.; Smilde, J.G.; Pocock, S.J.; Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN); Diabetes Care; 2006; vol. 29 (no. 7); 1478-1485

Study arms
Atorvastatin 10mg (N = 1211)
Medium intensity statin

Placebo (N = 1199)

Outcomes

Study timepoints

- 4.25 year (Median follow-up 4 years)

Dichotomous data extracted 2022

Outcome	Atorvastatin 10mg, 4.25 year, N = 1211	Placebo, 4.25 year, N = 1199
MACE Cardiovascular death (fatal myocardial infarction, fatal stroke, sudden cardiac death, heart failure, or arrhythmic non-sudden cardiovascular death), nonfatal or silent myocardial infarction, nonfatal stroke, recanalization, coronary artery bypass grafting, resuscitated cardiac arrest, or worsening or unstable angina requiring hospitalization. No of events	n = 166	n = 180

MACE - Polarity - Lower values are better

Time to event data extracted 2022

Outcome	Atorvastatin 10mg vs Placebo, 4.25 year, N2 = 1211, N1 = 1199
MACE First MACE Hazard ratio/95% CI	0.9 (0.73 to 1.12)

MACE - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
Dichotomous data extracted 2022 - MACE- No Of Events-Atorvastatin 10mg-Placebo-t4.25

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Time to event data extracted 2022 – MACE – Hazard Ratio Nine Five Percent CI-Atorvastatin 10mg-Placebo-t4.25

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

LaRosa, 2005

Bibliographic Reference	LaRosa, J.C.; Grundy, S.M.; Waters, D.D.; Shear, C.; Barter, P.; Fruchart, J.C.; Gotto, A.M.; Greten, H.; Kastelein, J.J.; Shepherd, J.; Wenger, N.K.; Intensive lipid lowering with atorvastatin in patients with stable coronary disease; New England journal of medicine; 2005; vol. 352 (no. 14); 1425-1435

Study details

Secondary publication of another included study- see primary study for details	**See full details in CG181 2014 update evidence table**
Additional comments	

Study arms

Atorvastatin 80 mg (N = 4995)

Atorvastatin 10 mg (N = 5006)

Outcomes

Study timepoints

- 4.9 year (median)

Raw data

Outcome	Atorvastatin 80 mg, 4.9 year, N = 4995	Atorvastatin 10 mg, 4.9 year, N = 5006
Major adverse cardiovascular events death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke. No of events	n = 434	n = 548

Major adverse cardiovascular events - Polarity - Lower values are better

Time to event

Outcome	Atorvastatin 80 mg vs Atorvastatin 10 mg, 4.9 year, N2 = 4995, N1 = 5006	Atorvastatin 10 mg vs Atorvastatin 80 mg, 4.9 year, N2 = 5006, N1 = 4995
Major adverse cardiovascular events (HR inverted in analysis to match classification of experimental and control intervention in the review) death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke. Hazard ratio/95% CI	1.28 (1.13 to 1.45)	0.78 (0.69 to 0.89)

Major adverse cardiovascular events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
Raw data Major adverse cardiovascular events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns (Unclear allocation concealment)
Overall bias and Directness	Overall Directness	Directly applicable

Time to event-Major adverse cardiovascular events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns (Unclear allocation concealment)
Overall bias and Directness	Overall Directness	Directly applicable

Study arms
Atorvastatin 80 mg (N = 4995)

Atorvastatin 10 mg (N = 5006)

Outcomes
Study timepoints

- 4.9 year (median)

Raw data

Outcome	Atorvastatin 80 mg, 4.9 year, N = 4995	Atorvastatin 10 mg, 4.9 year, N = 5006
Haemorrhagic stroke No of events	n = 16	n = 17

Haemorrhagic stroke - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)
Raw data-Haemorrhagic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns (Unclear allocation concealment)
Overall bias and Directness	Overall Directness	Directly applicable

Nakamura, 2006

Bibliographic Reference	Nakamura, H.; Arakawa, K.; Itakura, H.; Kitabatake, A.; Goto, Y.; Toyota, T.; Nakaya, N.; Nishimoto, S.; Muranaka, M.; Yamamoto, A.; Mizuno, K.; Ohashi, Y.; Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial; Lancet; 2006; vol. 368 (no. 9542); 1155-1163

Study details

Secondary publication of another included study- see primary study for details	**Please See full details in CG181 2014 update evidence table.**

Study arms
Pravastatin (N = 3866)

Pravastatin 10-20mg plus diet

Usual care (N = 3966)
Usual care plus diet

Outcomes
Study timepoints
- 5.3 year (mean)

Raw data

Outcome	Pravastatin, 5.3 year, N = 3866	Usual care, 5.3 year, N = 3966
Ischaemic stroke No of events	n = 34 ; % = 0.9	n = 46 ; % = 1.2
Haemorrhagic stroke No of events	n = 16 ; % = 0.4	n = 14 ; % = 0.4

Haemorrhagic stroke - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
Ischaemic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Unclear allocation concealment and high rate of deviation from protocol in control group)
Overall bias and Directness	Overall Directness	Indirectly applicable (Mean dose of pravastatin <10 mg)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)
Haemorrhagic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Unclear allocation concealment and high rate of deviation from protocol in control group)
Overall bias and Directness	Overall Directness	Indirectly applicable (Mean dose of pravastatin <10 mg)

Pedersen, 2005

Bibliographic Reference	Pedersen, T.R.; Faergeman, O.; Kastelein, J.J.; Olsson, A.G.; Tikkanen, M.J.; Holme, I.; Larsen, M.L.; Bendiksen, F.S.; Lindahl, C.; Szarek, M.; Tsai, J.; High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial; JAMA; 2005; vol. 294 (no. 19); 2437-2445

Study details

Secondary publication of another included study- see primary study for details	**See full details in CG181 2014 update evidence table**

Study arms
Atorvastatin 80 mg (N = 4439)

Simvastatin 20 mg (N = 4449)

Outcomes
Study timepoints
- 4.8 year

Raw data

Outcome	Atorvastatin 80 mg, 4.8 year, N = 4439	Simvastatin 20 mg, 4.8 year, N = 4449
Major adverse cardiovascular events Major coronary events (coronary death, hospitalization for nonfatal acute myocardial infarction, or cardiac arrest with resuscitation.) and stroke No of events	n = 553	n = 608

Major adverse cardiovascular events - Polarity - Lower values are better

Time to event

Outcome	Simvastatin 20 mg vs Atorvastatin 80 mg, 4.8 year, N2 = 4449, N1 = 4439
Major adverse cardiovascular events Hazard ratio/95% CI	0.87 (0.78 to 0.98)

Major adverse cardiovascular events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
Raw data-MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Deviations from protocol: additional statins unbalanced between groups)
Overall bias and Directness	Overall Directness	Directly applicable

Time to event-MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Deviations from protocol: additional statins unbalanced between groups)
Overall bias and Directness	Overall Directness	Directly applicable

Study arms
Atorvastatin 80 mg (N = 4439)
Simvastatin 20 mg (N = 4449)
Outcomes

Study timepoints

- 4.8 year

Raw data

Outcome	Atorvastatin 80 mg, 4.8 year, N = 4439	Simvastatin 20 mg, 4.8 year, N = 4449
Haemorrhagic stroke No of events	n = 6	n = 6

Haemorrhagic stroke - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)

Raw data-Haemorrhagic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Deviations from protocol: additional statins unbalanced between groups)
Overall bias and Directness	Overall Directness	Directly applicable

Pitt, 1995

Bibliographic Reference	Pitt, B.; Mancini, G.B.; Ellis, S.G.; Rosman, H.S.; Park, J.S.; McGovern, M.E.; Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. PLAC I investigation; Journal of the American College of Cardiology; 1995; vol. 26 (no. 5); 1133-1139

Study arms

Pravastatin 40mg (N = 206)

Low intensity statin

Placebo (N = 202)

Outcomes

Study timepoints

- 3 year

Dichotomous data extracted 2022

Outcome	Pravastatin 40mg, 3 year, N = 206	Placebo, 3 year, N = 202
Total Cardiac Events MI (fatal/non-fatal), other cardiac death, stroke, bypass surgery, coronary angioplasty No of events	n = 55	n = 81

Total Cardiac Events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
Dichotomousdataextracted2022-TotalCardiacEvents-NoOfEvents-Pravastatin 40mg-Placebo-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Concerns in double counting within the outcome)
Overall bias and Directness	Overall Directness	Directly applicable

Ridker, 2008

Bibliographic Reference	Ridker, P.M.; Danielson, E.; Fonseca, F.A.; Genest, J.; Gotto, A.M., Jr.; Kastelein, J.J.; Koenig, W.; Libby, P.; Lorenzatti, A.J.; MacFadyen, J.G.; Nordestgaard, B.G.; Shepherd, J.; Willerson, J.T.; Glynn, R.J.; Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein; New England journal of medicine; 2008; vol. 359 (no. 21); 2195-2207

Study details

Secondary publication of another included study- see primary study for details	**See full details in CG181 2014 update evidence table**

Study arms

Rosuvastatin 20mg (N = 8901)

High intensity statin

Placebo (N = 8901)

Outcomes
Study timepoints
- 5 year (Median follow-up 1.9 years)

Dichotomous data extracted 2022

Outcome	Rosuvastatin 20mg, 5 year, N = 8901	Placebo, 5 year, N = 8901
MACE Occurrence of first; Myocardial infarction, stroke, or confirmed death from cardiovascular causes No of events	n = 83	n = 157

MACE - Polarity - Lower values are better

Time to event data extracted 2022

Outcome	Rosuvastatin 20mg vs Placebo, 5 year, N2 = 8901, N1 = 8901
MACE Time to first event Hazard ratio/95% CI	0.53 (0.4 to 0.69)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
Dichotomous data extracted 2022 – MACE - No Of Events-Rosuvastatin 20mg-Placebo-t5

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Outcomes
Study timepoints

- 1.9 year (Median)

Dichotomous data extracted 2022

Outcome	Rosuvastatin 20 mg, 1.9 year, N = 8901	Placebo, 1.9 year, N = 8901
Haemorrhagic stroke No of events	n = 6	n = 9

Haemorrhagic stroke - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)
Dichotomous data extracted 2022-Haemorrhagic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Shepherd, 2002

Bibliographic Reference	Shepherd, J.; Blauw, G.J.; Murphy, M.B.; Bollen, E.L.; Buckley, B.M.; Cobbe, S.M.; Ford, I.; Gaw, A.; Hyland, M.; Jukema, J.W.; Kamper, A.M.; MacFarlane, P.W.; Meinders, A.E.; Norrie, J.; Packard, C.J.; Perry, I.J.; Stott, D.J.; Sweeney, B.J.; Twomey, C.; Westendorp, R.G.; Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial; Lancet; 2002; vol. 360 (no. 9346); 1623-1630

Study details

Secondary publication of another included study- see primary study for details	**For full details see CG181 evidence table.**

Study arms
Pravastatin 40mg (N = 2891)
Low intensity statin

Placebo (N = 2913)

Outcomes
Study timepoints
- 4 year (Mean follow-up 3.2 years, range 2.8-4 years)

Dichotomous data extracted 2022

Outcome	Pravastatin 40mg, 4 year, N = 2891	Placebo, 4 year, N = 2913
MACE Coronary heart disease death, or non-fatal MI, or fatal or non-fatal stroke No of events	n = 408	n = 473

MACE - Polarity - Lower values are better

Time to event data extracted 2022

Outcome	Pravastatin 40mg vs Placebo, 4 year, N2 = 2891, N1 = 2913
MACE Hazard ratio/95% CI	0.85 (0.74 to 0.97)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
Dichotomous data extracted 2022 – MACE – No Of Events - Pravastatin 40mg-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Time to event data extracted 2022 – MACE – Hazard Ratio Nine Five Percent CI - Pravastatin 40mg-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Outcomes

Study timepoints

- Baseline
- 3.2 year (Mean follow-up 3.2 years (range 2.8-4 years))

Continuous data extracted 2022

Outcome	Pravastatin 40 mg vs Placebo, 3.2 year vs Baseline, N2 = 2891, N1 = 2913
Cognitive decline (MMSE scale (0-30)) Mean (SE)	0.06 (0.051)

Cognitive decline - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)

Continuous data extracted 2022 Cognitive decline

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

D.2 Newly included studies 2022

Bosch, 2019

Bibliographic Reference	Bosch, J.; O'Donnell, M.; Swaminathan, B.; Lonn, E. M.; Sharma, M.; Dagenais, G.; Diaz, R.; Khunti, K.; Lewis, B. S.; Avezum, A.; Held, C.; Keltai, M.; Reid, C.; Toff, W. D.; Dans, A.; Leiter, L. A.; Sliwa, K.; Lee, S. F.; Pogue, J. M.; Hart, R.; Yusuf, S.; Investigators, Hope-; Effects of blood pressure and lipid lowering on cognition: Results from the HOPE-3 study; Neurology; 2019; vol. 92 (no. 13); e1435-e1446

Study details

Secondary publication of another included study- see primary study for details	**This study is a sub-study of Yusuf et al. 2016 which also reports results of the HOPE-3 trial.**
Other publications associated with this study included in review	Lonn, E., et al. (2016). "Novel Approaches in Primary Cardiovascular Disease Prevention: The HOPE-3 Trial Rationale, Design, and Participants' Baseline Characteristics." Canadian Journal of Cardiology 32(3): 311-318. Yusuf, S., et al. (2016). "Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease." New England Journal of Medicine 374(21): 2021-2031.
Trial name / registration number	HOPE-3. Clinicaltrial.gov = NCT00468923.
Study type	Randomised controlled trial (RCT)
Study location	Multicenter international trial - including Canada, Ireland, Argentina, United Kingdom, Philippines, Israel, Brazil, Sweden, Hungary, Australia and South Africa.
Study setting	Outpatient follow up.
Study dates	May 2007 (obtained from clinicaltrials.gov) to October 31st 2015.
Sources of funding	This study was funded through grants from the Canadian Institute of Health Research and AstraZeneca.
Inclusion criteria	Men at least 55 years of age and women at least 65 years of age with at least 1 additional clinical cardiovascular risk factor or women at least 60 years of age with 2 additional risk factors.
Exclusion criteria	Established, guideline-based indication for either study drug; the cognition and function substudy restricted eligibility to participants who were at least 70 years old because these participants were at highest risk of cognitive decline.

Recruitment / selection of participants	See Yusuf 2016.
Intervention(s)	Statins - Rosuvastatin (high intensity) N=807 The study pools together two groups: 1) Rosuvastatin 10mg once a day with a candesartan/hydrochlorothiazide placebo 2) Rosuvastatin 10mg once a day with candesartan/hydrochlorothiazide 16/12.5mg once a day. Both over a 4 week run-in period and then continued until the end of the trial (median follow-up was 5.7 years). Concomitant therapy: Other medications were used by some individuals. Aspirin = 113, Beta-blocker = 99, Calcium channel blocker = 146, Oral hypoglycaemic agent = 15.
Population subgroups	Different agents/doses within each intensity class: High intensity Primary versus secondary prevention: Primary prevention Presence versus absence of chronic kidney disease: Not stated/unclear Age (<75 versus ≥75): <75 (mean was 74.2 in active arm, 74.1 in placebo arm) Sex: Mixed - majority female (58.0% in active arm, 60.4% in placebo arm) Ethnicity/family origin (black, Asian, white, mixed, other): Mixed Presence versus absence of autoimmune disease: Minority with rheumatoid arthritis (1.2% in active arm, 1.7% in placebo arm)
Comparator	Placebo N=819 The study pools together two groups: 1) Double placebo (for both rosuvastatin and candesartan/hydrochlorothiazide) 2) Candesartan/hydrochlorothiazide 16/12.5mg once a day with a rosuvastatin placebo. Both over a 4 week run-in period and then continued until the end of the trial (median follow-up was 5.7 years). Concomitant therapy: Other medications were used by some individuals. Aspirin = 133, Beta-blocker = 112, Calcium channel blocker = 148, Oral hypoglycaemic agent = 21.
Number of participants	1181
Duration of follow-up	Median 5.7 years.
Indirectness	Outcome indirectness - Dichotomous reporting of quality of life.
Additional comments	No additional information provided on the method of analysis. Appears to be only completers who were included in the analysis.

Study arms
Statins - Rosuvastatin (high intensity) (N = 807)

The study pools together two groups: 1) Rosuvastatin 10mg once a day with a candesartan/hydrochlorothiazide placebo 2) Rosuvastatin 10mg once a day with candesartan/hydrochlorothiazide 16/12.5mg once a day. Both over a 4 week run-in period and then continued until the end of the trial (median follow-up was 5.7 years). Concomitant therapy: Other medications were used by some individuals. Aspirin = 113, Beta-blocker = 99, Calcium channel blocker = 146, Oral hypoglycaemic agent = 15.

Placebo (N = 819)

The study pools together two groups: 1) Double placebo (for both rosuvastatin and candesartan/hydrochlorothiazide) 2) Candesartan/hydrochlorothiazide 16/12.5mg once a day with a rosuvastatin placebo. Both over a 4 week run-in period and then continued until the end of the trial (median follow-up was 5.7 years). Concomitant therapy: Other medications were used by some individuals. Aspirin = 133, Beta-blocker = 112, Calcium channel blocker = 148, Oral hypoglycaemic agent = 21.

Characteristics

Study-level characteristics

Characteristic	Study (N = 1626)
Ethnicity Sample size	n = NA ; % = NA
South Asian Sample size	n = 74 ; % = 4.6
Chinese Sample size	n = 382 ; % = 23.5
Other Asian Sample size	n = 132 ; % = 8.1
Black Sample size	n = 32 ; % = 2
White Sample size	n = 392 ; % = 24.1

Arm-level characteristics

Characteristic	Statins - Rosuvastatin (high intensity) (N = 807)	Placebo (N = 819)

% Female Sample size	n = 468 ; % = 58	n = 495 ; % = 60.4
Mean age (SD) (years) Mean (SD)	74.2 (3.6)	74.1 (3.3)
Age over 75 years Study reports a subgroup where 551 people were >75 years, but it is unclear whether this is reporting both the people in the statin and placebo arm and so how many people are of this age in both arms. Sample size	NR	NR
Existing CVD diagnoses Sample size	-	-
Hypertension Sample size	n = 352 ; % = 43.6	n = 376 ; % = 45.9
Type 2 diabetes Only states diabetes mellitus - assumed to be type 2 diabetes given demographic features Mean (SD)	45 (5.6)	49 (6)
Chronic kidney disease Sample size	NR	NR
Family history of CVD Sample size	NR	NR
Autoimmune disease Sample size	-	-
Rheumatoid arthritis Sample size	n = 10 ; % = 1.2	n = 14 ; % = 1.7
Serious mental illness Sample size	NR	NR
Socioeconomic group Sample size	NR	NR
LDL cholesterol level at baseline (mg/dL) Mean (SD)	127.5 (34.6)	126.5 (34.4)
LDL cholesterol level at the end of follow-up Mean (SD)	NR (NR)	NR (NR)

Reduction in LDL cholesterol (absolute) Mean reduction of 24.8 mg/dL in the statin arm compared to the placebo arm Mean (SD)	NR (NR)	NR (NR)

Outcomes

Study timepoints

- Baseline
- 5.7 year (Median end follow up time)

Efficacy - dichotomous outcome (1)

Outcome	Statins - Rosuvastatin (high intensity), Baseline, N = 1181	Statins - Rosuvastatin (high intensity), 5.7 year, N = 1181	Placebo, Baseline, N = 1180	Placebo, 5.7 year, N = 1180
All-cause mortality (dichotomous) Reported in CONSORT diagram. Rosuvastatin active/placebo = 57, Rosuvastatin and candasartan/hydrochlorothiazide = 42. Candasartan/hydrochlorothiazide and placebo = 61. Double placebo = 59. No of events	-	n = 99 ; % = 8.4	-	n = 120 ; % = 10.2

All-cause mortality (dichotomous) - Polarity - Lower values are better

Efficacy - dichotomous outcome (2)

Outcome	Statins - Rosuvastatin (high intensity), Baseline, N = 1181	Statins - Rosuvastatin (high intensity), 5.7 year, N = 807	Placebo, Baseline, N = 1180	Placebo, 5.7 year, N = 819
Quality of life (EQ-5D, new impairment in basic activities of daily living) This is a dichotomous reporting of quality of life and should be considered as an indirect outcome if included in the analysis. No of events	-	n = 265 ; % = 21.2	-	n = 275 ; % = 22.5

Quality of life (EQ-5D, new impairment in basic activities of daily living) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
All-cause mortality (dichotomous)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Quality of life (EQ-5D, new impairment in basic activities of daily living)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable (Outcome indirectness due to dichotomous reporting of an outcome stated to be continuous in the protocol)

Outcomes
Study timepoints

- Baseline
- 5.7 year (Median end follow up time)

Adverse effects - dichotomous outcome

Outcome	Statins - Rosuvastatin (high intensity), Baseline, N = 1181	Statins - Rosuvastatin (high intensity), 5.7 year, N = 807	Placebo, Baseline, N = 1180	Placebo, 5.7 year, N = 819
Cognitive decline A decrease of at least 5 points on the DSST, at least 2 points on the mMoCA and at least 10% on the TMT-B. Number who developed dementia was also reported (12 in rosuvastatin arm, 8 in placebo). No of events	-	n = 597 ; % = 74	-	n = 599 ; % = 73.1

Cognitive decline - Polarity - Lower values are better

Adverse effects - Continuous outcomes

Outcome	Statins - Rosuvastatin (high intensity), 5.7 year vs Baseline, N = 1181	Placebo, 5.7 year vs Baseline, N = 1180
Change in DSST score N available at follow-up: 807 vs 819 Mean (SD)	-5.37 (19.3)	-5.47 (17.3)
Change in mMoCA score N available at follow-up: 996 vs 1013 Mean (SD)	-0.46 (0.06)	-0.41 (0.06)
Change in TMT-B score (seconds) N available at follow-up: 252 vs 220 Mean (SD)	4.46 (3.7)	2.71 (4)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)

Cognitive decline - Rosuvastatin (high intensity)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Hosomi, 2015

Bibliographic Reference	Hosomi, N.; Nagai, Y.; Kohriyama, T.; Ohtsuki, T.; Aoki, S.; Nezu, T.; Maruyama, H.; Sunami, N.; Yokota, C.; Kitagawa, K.; Terayama, Y.; Takagi, M.; Ibayashi, S.; Nakamura, M.; Origasa, H.; Fukushima, M.; Mori, E.; Minematsu, K.; Uchiyama, S.; Shinohara, Y.; Yamaguchi, T.; Matsumoto, M.; Collaborators, J. Stars; The Japan Statin Treatment Against Recurrent Stroke (J-STARS): A Multicenter, Randomized, Open-label, Parallel-group Study; EBioMedicine; 2015; vol. 2 (no. 9); 1071-8

Study details

Secondary publication of another included	**No additional information.**

study- see primary study for details	
Other publications associated with this study included in review	Nagai 2014 - protocol paper
Trial name / registration number	NCT00221104
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	123 centers: all regional core hospitals
Study dates	March 2004 - February 2009
Sources of funding	Initially supported by a grant from the Ministry of Health, Labour and Welfare, Japan. After the governmental support expired, it was conducted in collaboration between Hiroshima University and the Foundation for Biomedical Research and Innovation.
Inclusion criteria	45 to 80 years old History of non-cardioembolic ischemic stroke within the preceding one month to three years Total cholesterol level between 4.65 and 6.21 mmol/L (180 to 240 mg/dL) at enrolment, without use of statins
Exclusion criteria	Cerebral infarction of determined rare aetiology Infarction associated with catheterization or surgery Preferred use of statins for the treatment of co-morbid coronary artery disease
Recruitment / selection of participants	Participants were recruited from 123 centres
Intervention(s)	Participants in the intervention group received 10mg/day of pravastatin. Administration was initiated within 1 month after randomization, and the treatment was continued until final observation. Diet and exercise therapies were reinforced when total cholesterol levels consistently exceeded 6.21 mmol/L (240 mg/dL) at routine clinical visits. Increase of pravastatin dose or addition of other non-statin drugs (such as ion exchange resin, eicosapentaenoic acid, and ezetimibe) was allowed only when such reinforcements were insufficient. Even under such conditions, use of other statins (such as simvastatin and atorvastatin) was prohibited.
Population subgroups	No additional information
Comparator	In the control group, administration of any statin was prohibited, although use of other non-statin drugs was allowed when necessary.

Number of participants	1589 randomised 793 allocated to intervention, 626 completed trial per protocol 785 allocated to control, 674 completed trial per protocol
Duration of follow-up	5 years
Indirectness	No additional information
Additional comments	Intention to treat, safety analysis and per protocol for different outcomes

Study arms

Statins - Pravastatin (low intensity) (N = 793)

10mg/day

No treatment (N = 785)

Characteristics

Arm-level characteristics

Characteristic	Statins - Pravastatin (low intensity) (N = 793)	No treatment (N = 785)
% Female Sample size	n = 248 ; % = 31.3	n = 143 ; % = 31
Mean age (SD) (years) Mean (SD)	66.1 (8.4)	66.4 (8.6)
Age over 75 years Sample size	NR	NR
Ethnicity Sample size	NR	NR
Existing CVD diagnoses Sample size	n = NR	NR
Hypertension Sample size	n = 596 ; % = 75.2	n = 604 ; % = 76.9
Coronary artery disease Sample size	n = 37 ; % = 4.7	n = 44 ; % = 5.6

Type 2 diabetes Sample size	n = 185 ; % = 23.3	n = 184 ; % = 23.4
Chronic kidney disease Sample size	n = 195 ; % = 24.6	n = 183 ; % = 23.3
Family history of CVD Sample size	NR	NR
Autoimmune disease Sample size	NR	NR
Serious mental illness Sample size	NR	NR
Socioeconomic group Sample size	NR	NR
LDL cholesterol level at baseline (mmol/L) Mean (SD)	3.35 (0.63)	3.35 (0.64)
LDL cholesterol level at the end of follow-up Sample size	NR	NR
Reduction in LDL cholesterol (absolute) Sample size	NR	NR

Efficacy outcomes

Study timepoints

- Baseline
- 5 year

Efficacy - time to event outcomes

Outcome	Statins - Pravastatin (low intensity) vs No treatment, Baseline, N2 = 793, N1 = 785	Statins - Pravastatin (low intensity) vs No treatment, 5 year, N2 = 793, N1 = 785
Cardiovascular death Hazard ratio	NA	1.23 (0.79-1.93)

Non-fatal myocardial infarction Reports myocardial infarction. Assumed to be non-fatal. Hazard ratio	NA	0.55 (0.16-1.89)
Non-fatal ischaemic stroke (stroke and TIA) Downgrade for indirectness for including TIA. Hazard ratio	NA	0.95 (0.71-1.28)

Cardiovascular death - Polarity - Lower values are better

Non-fatal myocardial infarction - Polarity - Lower values are better

Non-fatal ischaemic stroke (stroke and TIA) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)

Efficacy-time-to-event outcomes-Non-fatal myocardial infarction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- Cardiovascular death

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy-Non-fatal ischaemic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Adverse event outcomes
Study timepoints
- Baseline
- 5 year

Continuous Outcomes

Outcome	Pravastatin, Baseline, N = 793	Pravastatin, 5 year, N = 780	No treatment, Baseline, N = 785	No treatment, 5 year, N = 785
Haemorrhagic stroke (%) event rate per year (not included in meta-analysis) Nominal	NA	2.35	NA	2.47

Haemorrhagic stroke - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Pravastatin, Baseline, N = 793	Pravastatin, 5 year, N = 780	No treatment, Baseline, N = 785	No treatment, 5 year, N = 785
Rhabdomyolysis definition of rhabdomyolysis not specified No of events	-	n = 2 ; % = 0.3	-	n = 1 ; % = 0.1
Liver enzymes (AST >3 x ULN) No of events	-	n = 8 ; % = 1	-	n = 4 ; % = 0.5
Liver enzymes (ALT >3 x ULN) No of events	-	n = 6 ; % = 0.8	-	n = 2 ; % = 0.3

Rhabdomyolysis - Polarity - Lower values are better
Liver enzymes (AST >3 x ULN) - Polarity - Lower values are better
Liver enzymes (ALT >3 x ULN) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)
Rhabdomyolysis

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (unblinded and outcome not defined)
Overall bias and Directness	Overall Directness	Directly applicable

Liver enzymes (AST>3xULN)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Liver enzymes (ALT>3xULN)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Im, 2018

Bibliographic Reference	Im, E.; Cho, Y. H.; Suh, Y.; Cho, D. K.; Her, A. Y.; Kim, Y. H.; Lee, K.; Kang, W. C.; Yun, K. H.; Yoo, S. Y.; Cheong, S. S.; Shin, D. H.; Ahn, C. M.; Kim, J. S.; Kim, B. K.; Ko, Y. G.; Choi, D.; Jang, Y.; Hong, M. K.; High-intensity Statin Treatments in Clinically Stable Patients on Aspirin Monotherapy 12 Months After Drug-eluting Stent Implantation: A Randomized Study; Revista Espanola de Cardiologia; 2018; vol. 71 (no. 6); 423-431

Study details

Secondary publication of another included study- see primary study for details	**No additional information.**
Other publications associated with this study included in review	No additional information.

Trial name / registration number	Clinicaltrials.gov = NCT01557075
Study type	Randomised controlled trial (RCT)
Study location	South Korea
Study setting	Multicenter trial (15 centers). Outpatient follow up.
Study dates	August 2010 to November 2014.
Sources of funding	This study was supported by grants from the Korea Healthcare Technology Research & Development Project, Ministry for Health & Welfare, Republic of Korea (Nos. A085136 and H115C1277), the Mid-career Researcher Program through the National Research Foundation funded by the Ministry of Education, Science & Technology, Republic of Korea (No. 2015R1A2A2A01002731), Yuhan Corporation, Korea, CJ HealthCare, Korea, Daiichi Sankyo Korea Co, Ltd and the Cardiovascular Research Center, Seoul, Korea.
Inclusion criteria	Clinically stable people who underwent drug-eluting stent implantation approximately 12 months previously and subsequently received aspirin monotherapy with discontinuation of clopidogrel.
Exclusion criteria	Experienced adverse clinical events within 12 months after drug eluting stent implantation; currently received single or dual antiplatelet therapy other than aspirin; were allergic to or experienced adverse effects of aspirin or statins; were <20 years old; were pregnant; had a life expectancy less than or equal to 2 years; had an indication for prolonged high-intensity statin treatment.
Recruitment / selection of participants	People who had received stents at the center.
Intervention(s)	Statins - Atorvastatin (high intensity) N=1000 Oral atorvastatin 40mg/day. Concomitant therapy: Everyone received aspirin monotherapy (dose not stated, possibly 75mg/day). The majority of participants received a statin before the study (92%), around 64% received a beta-blocker, 38% received a calcium channel blocker and 60% received ACE inhibitors or angiotensin-2 receptor antagonists.
Population subgroups	Different agents/doses within each intensity class: High intensity vs. low intensity Primary versus secondary prevention: Secondary prevention Presence versus absence of chronic kidney disease: Not stated/unclear (However, measures renal deterioration so potentially no chronic kidney disease) Age (<75 versus ≥75): <75 (mean was 64 years) Sex: Mixed - majority male (71.4% in high intensity arm, 70.1% in low intensity arm) Ethnicity/family origin (black, Asian, white, mixed, other): Not stated/unclear Presence versus absence of autoimmune disease: Not stated/unclear
Comparator	Statins - Pravastatin (low intensity) N=1000

	Oral pravastatin 20mg/day. Concomitant therapy: Everyone received aspirin monotherapy (dose not stated, possibly 75mg/day). The majority of participants received a statin before the study (92%), around 64% received a beta-blocker, 38% received a calcium channel blocker and 60% received ACE inhibitors or angiotensin-2 receptor antagonists.
Number of participants	2000
Duration of follow-up	12 months
Indirectness	No additional information.
Additional comments	Intention to treat analysis (all people included in the final analysis).

Study arms

Statins - Atorvastatin (high intensity) (N = 1000)

Oral atorvastatin 40mg/day. Concomitant therapy: Everyone received aspirin monotherapy (dose not stated, possibly 75mg/day). The majority of participants received a statin before the study (92%), around 64% received a beta-blocker, 38% received a calcium channel blocker and 60% received ACE inhibitors or angiotensin-2 receptor antagonists.

Statins - Pravastatin (low intensity) (N = 1000)

Oral pravastatin 20mg/day. Concomitant therapy: Everyone received aspirin monotherapy (dose not stated, possibly 75mg/day). The majority of participants received a statin before the study (92%), around 64% received a beta-blocker, 38% received a calcium channel blocker and 60% received ACE inhibitors or angiotensin-2 receptor antagonists.

Characteristics

Arm-level characteristics

Characteristic	Statins - Atorvastatin (high intensity) (N = 1000)	Statins - Pravastatin (low intensity) (N = 1000)
% Female Sample size	n = 286 ; % = 28.6	n = 299 ; % = 29.9
Mean age (SD) (years) Mean (SD)	64 (12)	64 (12)
Age over 75 years	NR	NR

Sample size		
Ethnicity Sample size	NR	NR
Existing CVD diagnoses Sample size	-	-
Stable angina Sample size	n = 539 ; % = 53.9	n = 542 ; % = 54.2
Unstable angina Sample size	n = 315 ; % = 31.5	n = 340 ; % = 34
Acute myocardial infarction Sample size	n = 146 ; % = 14.6	n = 118 ; % = 11.8
Hypertension Sample size	n = 600 ; % = 60	n = 613 ; % = 61.3
Type 2 diabetes Sample size	n = 292 ; % = 29.2	n = 279 ; % = 27.9
Chronic kidney disease Sample size	NR	NR
Family history of CVD Sample size	NR	NR
Autoimmune disease Sample size	NR	NR
Serious mental illness Sample size	NR	NR
Socioeconomic group Sample size	NR	NR
LDL cholesterol level at baseline (mg/dL) Mean (SD)	74.1 (27.6)	74.2 (26.4)
LDL cholesterol level at the end of follow-up (mg/dL) Mean (SD)	67.8 (23)	98.8 (28.8)

Reduction in LDL cholesterol (absolute) (mg/dL) People in low intensity arm gained (due to people being on statins before, reducing to low intensity likely lead to an increase). Mean (SD)	-5.3 (24.9)	25.9 (25.7)

Outcomes

Study timepoints

- Baseline
- 1 year

Efficacy - Dichotomous outcomes

Outcome	Statins - Atorvastatin (high intensity), Baseline, N = 1000	Statins - Atorvastatin (high intensity), 1 year, N = 1000	Statins - Pravastatin (low intensity), Baseline, N = 1000	Statins - Pravastatin (low intensity), 1 year, N = 1000
All-cause mortality No of events	-	n = 5 ; % = 0.5	-	n = 8 ; % = 0.8
Cardiovascular mortality No of events	-	n = 0 ; % = 0	-	n = 4 ; % = 0.4
Non-fatal myocardial infarction Assumed that the myocardial infarctions reported were all non-fatal. No of events	-	n = 2 ; % = 0.2	-	n = 9 ; % = 0.9
Non-fatal ischaemic stroke Assumed that reported stroke included only ischaemic strokes and these were non-fatal. No of events	-	n = 2 ; % = 0.2	-	n = 3 ; % = 0.3
Combined major adverse cardiovascular events Assumption that people only had one event of a cardiovascular death, non-fatal myocardial infarction or non-fatal ischaemic stroke due to the rarity of the event No of events	-	n = 4 ; % = 0.4	-	n = 16 ; % = 1.6

All-cause mortality - Polarity - Lower values are better
Cardiovascular mortality - Polarity - Lower values are better
Non-fatal myocardial infarction - Polarity - Lower values are better
Non-fatal ischaemic stroke - Polarity - Lower values are better
Combined major adverse cardiovascular events - Polarity - Lower values are better

Efficacy - Time-to-event outcomes

Outcome	Statins - Atorvastatin (high intensity) vs Statins - Pravastatin (low intensity), Baseline, N2 = 1000, N1 = 1000	Statins - Atorvastatin (high intensity) vs Statins - Pravastatin (low intensity), 1 year, N2 = 1000, N1 = 1000
All-cause mortality Hazard ratio	NA	0.63
All-cause mortality Mean (95% CI)	NA (NA to NA)	NA (0.21 to 1.91)
Non-fatal myocardial infarction Assumed that the myocardial infarctions reported were all non-fatal. Hazard ratio	NA	0.23
Non-fatal myocardial infarction Assumed that the myocardial infarctions reported were all non-fatal. Mean (95% CI)	NA (NA to NA)	NA (0.05 to 1.05)
Non-fatal ischaemic stroke Assumed that reported stroke included only ischaemic strokes and these were non-fatal. Hazard ratio	NA	0.51
Non-fatal ischaemic stroke Assumed that reported stroke included only ischaemic strokes and these were non-fatal. Mean (95% CI)	NA (NA to NA)	NA (0.09 to 2.83)

All-cause mortality - Polarity - Lower values are better

Non-fatal myocardial infarction - Polarity - Lower values are better
Non-fatal ischaemic stroke - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
Efficacy-All-cause mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy-Cardiovascular mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- Non-fatal myocardial infarction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy -Non-fatal ischaemic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- -Combined major adverse cardiovascular events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy-Time-to-event outcomes-All-cause mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy-Time-to-event outcomes-Non-fatal myocardial infarction-

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy-Time-to-event outcomes-Non-fatal ischaemic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Outcomes

Study timepoints

- Baseline
- 1 year

Adverse effects - Dichotomous outcomes

Outcome	Statins - Atorvastatin (high intensity) , Baseline, N = 1000	Statins - Atorvastatin (high intensity) , 1 year, N = 708	Statins - Pravastatin (low intensity), Baseline, N = 1000	Statins - Pravastatin (low intensity), 1 year, N = 721
New onset diabetes No of events	-	n = 10 ; % = 1.4	-	n = 6 ; % = 0.8

New onset diabetes - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)

New-onset diabetes

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Keech, 1994

Bibliographic Reference	Keech, A.; Collins, R.; MacMahon, S.; Armitage, J.; Lawson, A.; Wallendszus, K.; Fatemian, M.; Kearney, E.; Lyon, V.; Mindell, J.; et, al.; Three-year follow-up of the Oxford Cholesterol Study: assessment of the efficacy and safety of simvastatin in preparation for a large mortality study; Eur Heart J; 1994; vol. 15 (no. 2); 255-69

Study details

Trial name / registration number	Oxford Cholesterol Study
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Participants were identified from the Oxfordshire Regional Health Authority central records for discharges, and records from the Oxford Community Stroke Project.
Study dates	Enrolment November 1988 to January 1990.
Sources of funding	Supported by a grant from Merck Sharp & Dohme (MSD), who also supplied calendar-packed trial treatment.
Inclusion criteria	Aged between 40 and 75 years and at higher than average risk of CHD because of a history of myocardial infarction, angina pectoris, stroke, transient ischaemic attack, peripheral vascular disease, treated diabetes mellitus or treated hypertension.
Exclusion criteria	Any clear contraindications to, or indications for, an HMG-CoA reductase inhibitor in the view of that individual's family doctor; total blood cholesterol level below 3-5 mmol/l; age less than 40 years; history of any stroke, myocardial infarction or admission to hospital for unstable angina within the last 6 months; some importantly life-threatening condition other than vascular disease; concurrent treatment with cyclosporin, or a condition which might result in transplantation and the need for cyclosporin; child-bearing potential (i.e. pre-menopausal women not using a reliable method of contraception); a history of alcohol or drug abuse; psychiatric or physical disability that might limit compliance or ability to attend the clinic; an apparently low risk of cardiac events.

Recruitment / selection of participants	Identified individuals were invited to a screening clinic, where patients completed a detailed questionnaire about past medical and treatment history, smoking, alcohol consumption and exercise. Height and weight were measured for calculation of BMI. Seated blood pressure, and a non-fasting blood sample were taken. All screened individuals were given dietary information similar to that contained in the American Heart Association stage 1 diet guidelines, and other personalised information on risk factor modification. At the end of the 8 week run-in period on placebo, individuals were randomized into the study if they had remained compliant with study tablets, appeared willing and able to continue for at least 5 years, did not report adverse events (with placebo) or any intervening acute vascular events, and had acceptable laboratory blood tests (i.e. alanine aminotransferase [ALT] < 70 U/l [1.5 x ULN], creatinine <200 umol/l and total cholesterol >=35 mmol/l).
Intervention(s)	40 mg daily simvastatin (two 20 mg active tablets each evening) 20 mg daily simvastatin (one 20 mg active and one matching placebo tablet each evening)
Population subgroups	Not reported
Comparator	2 placebo tablets
Number of participants	621
Duration of follow-up	3 years
Indirectness	None
Additional comments	Intention-to-treat

Study arms
Simvastatin 40 mg (N = 206)

Simvastatin 20 mg (N = 208)

Placebo (N = 207)

Characteristics
Arm-level characteristics

Characteristic	Simvastatin 40 mg (N = 206)	Simvastatin 20 mg (N = 208)	Placebo (N = 207)
% Female Nominal	15	empty data	16
Mean age (SD)	63.4 (7.6)	63.4 (7.4)	63.7 (7.3)

Mean (SD)			
Age over 75 years Nominal	NR	NR	NR
Ethnicity Nominal	NR	NR	NR
MI No of events	n = 127 ; % = 62	n = 128 ; % = 62	n = 128 ; % = 62
Angina Pectoris No of events	n = 134 ; % = 65	n = 138 ; % = 66	n = 138 ; % = 67
Coronary heart disease No of events	n = 166 ; % = 81	n = 173 ; % = 83	n = 176 ; % = 85
Stroke No of events	n = 19 ; % = 9	n = 18 ; % = 9	n = 20 ; % = 10
Peripheral vascular disease No of events	n = 20 ; % = 10	n = 21 ; % = 10	n = 21 ; % = 10
Treated diabetes No of events	n = 6 ; % = 3	n = 7 ; % = 3	n = 7 ; % = 3
Creatinine (umol/L) Mean (SD)	121 (73)	115 (79)	114 (62)
Family history of CVD Nominal	NR	empty data	NR
Autoimmune disease Nominal	NR	NR	NR
Serious mental illness Nominal	NR	NR	NR
Socioeconomic group Nominal	NR	NR	NR
Screening Mean (SD)	4.84 (1.04)	4.85 (1.13)	4.71 (1.1)
Randomisation Mean (SD)	2.71 (0.93)	2.9 (0.87)	4.57 (1.09)

LDL cholesterol level at end of follow-up (mmol/L) Mean (SD)	2.9 (1.25)	3.15 (1.04)	4.5 (1.33)
Reduction in LDL cholesterol (absolute) Nominal	NR	NR	NR

Outcomes

Study timepoints

- 3 year

Raw data

Outcome	Simvastatin 40 mg, 3 year, N = 206	Simvastatin 20 mg, 3 year, N = 208	Placebo, 3 year, N = 207
Muscle pain No of events	n = 108 ; % = 52.4	n = 117 ; % = 56.3	n = 106 ; % = 51.2
Myalgia unclear if included in 'muscle pain' outcome No of events	n = 2 ; % = 1	n = 4 ; % = 1.9	n = 2 ; % = 1
Transaminases >3 x ULN ALT and/or AST No of events	n = 0 ; % = 0	n = 1 ; % = 0.5	n = 2 ; % = 1
Worsening of diabetes instability of control No of events	n = 0 ; % = 0	n = 1 ; % = 0.5	n = 0 ; % = 0

Muscle pain - Polarity - Lower values are better

Transaminases >3 x ULN - Polarity - Lower values are better

Worsening of diabetes - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)

Muscle pain_3 yr

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Transaminases>3xULN_3 yr

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Worsening of diabetes

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable (Outcome definition does not match the protocol)

Muscle pain-Myalgia

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Kimura, 2017

Bibliographic Reference	Kimura, G.; Kasahara, M.; Ueshima, K.; Tanaka, S.; Yasuno, S.; Fujimoto, A.; Sato, T.; Imamoto, M.; Kosugi, S.; Nakao, K.; Effects of atorvastatin on renal function in patients with dyslipidemia and chronic kidney disease: assessment of clinical usefulness in CKD patients with atorvastatin (ASUCA) trial; Clinical & Experimental Nephrology; 2017; vol. 21 (no. 3); 417-424

Study details

Secondary publication of another included	**No additional information**

study- see primary study for details	
Other publications associated with this study included in review	No additional information
Trial name / registration number	University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) UMIN000001778
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	No additional information
Study dates	April 2009 - March 2011
Sources of funding	The ASUCA trial was funded by Department of EBM Research Institute of Advancement of Clinical and Translational Science Kyoto University Hospital with an unrestricted grant from Pfizer Japan
Inclusion criteria	40-75 years of age Not treated with statins Positive proteinuria and eGFR at least 60 (mL/min/1.73 m2) eGFR <60 ml/min/1.73 m2 at enrolment LDL-C ≥140 mg/dl in subjects not taking any dyslipidaemia treating agents or LDL-C ≥100 mg/dl in those taking dyslipidaemia-treating agents other than statins
Exclusion criteria	eGFR <30mL/min/1.73m2; systolic blood pressure at least 180mmHg or diastolic pressure at least 110mmHg; haemoglobin A1c at least 8.5%; familial hypercholesterolaemia; secondary hypercholesterolaemia including nephrotic syndrome; liver dysfunction including acute hepatitis, chronic acute hepatitis, liver cirrhosis and hepatoma; past history of severe side effects of atorvastatin; pregnancy, possibility of pregnancy or breast-feeding women
Recruitment / selection of participants	No additional information
Intervention(s)	Participants in the intervention group received diet therapy with atorvastatin treatment. All patients received an adequate dietary advice of the non-face-to-face method. The initial dose of atorvastatin was 10 mg/day and then adjusted to 5–20 mg/day. If the LDL-C level did not reduce to the target, additional anti-dyslipidemic drugs except statins and fibrates were allowed to be used. The final average dosage of atorvastatin at the end of follow-up period was 10.5 mg.
Population subgroups	No additional information

Comparator	Participants in the control group received diet therapy with non-statin treatment. All patients received an adequate dietary advice of the non-face-to-face method. If dietary treatment in the failed to reduce LDL-C level to the target level within the first 3 months, additional anti-dyslipidemic drugs except statins were allowed to be administered.
Number of participants	349 randomised 176 allocated to intervention, 150 completed 173 allocated to control, 155 completed
Duration of follow-up	2 years
Indirectness	No additional information
Additional comments	Intention to treat

Study arms

Atorvastatin (N = 168)

10mg/day initially, then adjusted to 5-20mg/day plus diet therapy

Usual care (N = 166)

Non-statin treatment plus diet therapy

Characteristics

Arm-level characteristics

Characteristic	Atorvastatin (N = 168)	Usual care (N = 166)
% Female Sample size	n = 63 ; % = 37.5	n = 58 ; % = 34.9
Mean age (SD) Mean (SD)	63.2 (7.9)	63.1 (8.3)
Age over 75 years Nominal	NR	NR
Ethnicity Nominal	NR	NR
Existing CVD diagnoses Nominal	NR	NR

Type 2 diabetes Type of diabetes not specified Sample size	n = 58 ; % = 34.5	n = 55 ; % = 33.1
Chronic kidney disease Nominal	NR	NR
Family history of CVD Nominal	NR	NR
Autoimmune disease Nominal	NR	NR
Serious mental illness Nominal	NR	NR
Socioeconomic group Nominal	NR	NR
LDL cholesterol level at baseline (mg/dL) Mean (SD)	142.2 (26.7)	145.9 (29.4)
LDL cholesterol level at the end of follow-up Nominal	NR	NR
Reduction in LDL cholesterol (absolute) Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 2 year

Dichotomous Outcomes

Outcome	Atorvastatin, Baseline, N = 168	Atorvastatin, 2 year, N = 168	Usual care, Baseline, N = 166	Usual care, 2 year, N = 166
Combined major adverse cardiovascular events No of events	-	n = 4 ; % = 2.4	-	n = 2 ; % = 1.2

All-cause mortality No of events	-	n = 1 ; % = 0.6	-	n = 1 ; % = 0.6
Cardiovascular mortality (sudden cardiac death) No of events	-	n = 1 ; % = 0.6	-	n = 0 ; % = 0
Non-fatal myocardial infarction Assumed to be non-fatal due to it being present in the arm without sudden death. No of events	-	n = 0 ; % = 0	-	n = 1 ; % = 0.6

Combined major adverse cardiovascular events - Polarity - Lower values are better
All-cause mortality - Polarity - Lower values are better
Cardiovascular mortality (sudden cardiac death) - Polarity - Lower values are better
Non-fatal myocardial infarction - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
Combined major adverse cardiovascular events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes - All-cause mortality- No Of Events - Atorvastatin-Usual care-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes- Cardiovascular mortality (sudden cardiac death) – No Of Events – Atorvastatin - Usual care-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes - Non-fatal myocardial infarction – No Of Events - Atorvastatin-Usual care-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Kitas, 2019

Bibliographic Reference	Kitas, G. D.; Nightingale, P.; Armitage, J.; Sattar, N.; Belch, J. J. F.; Symmons, D. P. M.; Consortium, Trace Ra; A Multicenter, Randomized, Placebo-Controlled Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients With Rheumatoid Arthritis; Arthritis & Rheumatology; 2019; vol. 71 (no. 9); 1437-1449

Study details

Secondary publication of another included study- see primary study for details	**No additional information.**
Other publications associated with this study included in review	No additional information.
Trial name / registration number	ISRCTN: 41829447.
Study type	Randomised controlled trial (RCT)
Study location	Multicenter - United Kingdom.
Study setting	Outpatient follow up.
Study dates	Start of recruitment: August 2007. End of recruitment: March 2014. End of follow-up: March 2016.
Sources of funding	Supported by Arthritis Research UK (grants 16514 and 19704) and the British Heart Foundation (grant SP/06/001). Unrestricted grants for establishing a TRACE RA biobank were provided by Pfizer UK.
Inclusion criteria	Fulfilled the American College of Rheumatology 1987 criteria for rheumatoid arthritis; were >50 years of age or had a rheumatoid arthritis disease duration of >10 years; gave informed consent.
Exclusion criteria	Already taking a statin; known cardiovascular disease deemed to require statin therapy (acute coronary syndrome, unstable angina, myocardial infarction with or without ST elevation; stable CHD/CVD deemed to require statin treatment on clinical grounds); diabetes;

	regular use of contraindicated drugs including statins, cytochrome P450 activators/inhibitors, drugs known to affect lipid levels (colestipol, ezetimibe etc.); primary muscle disease or CK >3 x ULN; known familiar hyperlipidaemia; acute liver disease; severe renal dysfunction (stage 3 or 4) or creatinine >200 micromol/L or receiving renal replacement; uncontrolled hypothyroidism; hypersensitivity or intolerance to statins; pregnant, breast feeding or of child bearing potential not using adequate contraception; alcohol abuse; participating in another clinical trial; drinking more than 240mL of grapefruit juice per day; any other serious illness.
Recruitment / selection of participants	Recruitment from multiple centers. Identified from medical records based on the eligibility criteria using the Trial Screening Form. Information was given to eligible patients.
Intervention(s)	Statins - Atorvastatin (high intensity) N=1504 Oral atorvastatin 40mg once daily. Concomitant therapy: No additional information (some drugs were contraindicated while in the trial, such as other statins and drugs that interfere with cytochrome P450 activity, but otherwise it can be assumed that other medication could be started as required)
Population subgroups	Different agents/doses within each intensity class: High intensity Primary versus secondary prevention: Primary Presence versus absence of chronic kidney disease: People with CKD stage 3-4 or receiving renal replacement were excluded. Age (<75 versus ≥75): <75 (mean age 61.1 for atorvastatin arm, 60.9 for placebo arm) Sex: Majority female (74% for statin arm, 75% for placebo arm) Ethnicity/family origin (black, Asian, white, mixed, other): Majority white (98%) Presence versus absence of autoimmune disease: All had rheumatoid arthritis.
Comparator	Placebo N=1498 Placebo once daily. Concomitant therapy: No additional information (some drugs were contraindicated while in the trial, such as other statins and drugs that interfere with cytochrome P450 activity, but otherwise it can be assumed that other medication could be started as required)
Number of participants	3002
Duration of follow-up	Median 2.51 years. Trial was terminated early due to a lower than expected event rate (0.70% per annum).
Indirectness	No additional information.
Additional comments	Intention to treat analysis with tests to explore whether missing data is missing at random and appropriate procedures to then impute the missing data if required.

Study arms

Statins - Atorvastatin (high intensity) (N = 1504)

Oral atorvastatin 40mg once daily. Concomitant therapy: No additional information (some drugs were contraindicated while in the trial, such as other statins and drugs that interfere with cytochrome P450 activity, but otherwise it can be assumed that other medication could be started as required)

Placebo (N = 1498)

Placebo once daily. Concomitant therapy: No additional information (some drugs were contraindicated while in the trial, such as other statins and drugs that interfere with cytochrome P450 activity, but otherwise it can be assumed that other medication could be started as required)

Characteristics

Arm-level characteristics

Characteristic	Statins - Atorvastatin (high intensity) (N = 1504)	Placebo (N = 1498)
% Female Sample size	n = 1107 ; % = 74	n = 1120 ; % = 75
Mean age (SD) (years) Mean (SD)	61.1 (8.3)	60.9 (8.5)
Age over 75 years Sample size	NR	n = NR
Ethnicity Sample size	-	-
White Sample size	n = 1394 ; % = 98	n = 1407 ; % = 98
Existing CVD diagnoses Sample size	-	-
Hypertension Sample size	n = 322 ; % = 22	n = 335 ; % = 23
Type 2 diabetes Sample size	NR	NR
Chronic kidney disease (mL/minute/1.73 m²) EGFR (median [IQR]) Median (IQR)	79 (59 to 110)	79 (58 to 111)
Family history of CVD	n = 285 ; % = 22	n = 263 ; % = 20

Sample size		
Autoimmune disease All had rheumatoid arthritis Sample size	n = 1504 ; % = 100	n = 1498 ; % = 100
Serious mental illness Sample size	NR	NR
Socioeconomic group Sample size	NR	n = NR
LDL cholesterol level at baseline (mmol/L) Median (IQR)	3.2 (2.7 to 3.8)	3.2 (2.7 to 3.8)
LDL cholesterol level at the end of follow-up (mmol/L) Mean (SE)	2.21 (0.03)	2.98 (0.03)
Reduction in LDL cholesterol (absolute) Sample size	NR	NR

Outcomes

Study timepoints

- Baseline
- 2.51 year (Median 2.51 years. Trial was terminated early due to a lower than expected event rate (0.70% per annum).)

Efficacy - Dichotomous outcomes

Outcome	Statins - Atorvastatin (high intensity), Baseline, N = 1504	Statins - Atorvastatin (high intensity), 2.51 year, N = 1504	Placebo, Baseline, N = 1498	Placebo, 2.51 year, N = 1498
Combined major adverse cardiovascular events Mean 95% CI is actually HR 95% CI - the value provided compares the two arms. (Nonfatal MI, nonfatal presumed ischaemic stroke, transient ischaemic attack, coronary or non-coronary revascularisation, cardiovascular death - excluding cerebral haemorrhage and non-coronary death) No of events	-	n = 24 ; % = 1.6	-	n = 36 ; % = 2.4

Combined major adverse cardiovascular events Mean 95% CI is actually HR 95% CI - the value provided compares the two arms. (Nonfatal MI, nonfatal presumed ischaemic stroke, transient ischaemic attack, coronary or non-coronary revascularisation, cardiovascular death - excluding cerebral haemorrhage and non-coronary death) Hazard ratio	NA	0.60	NA	NA
Combined major adverse cardiovascular events Mean 95% CI is actually HR 95% CI - the value provided compares the two arms. (Nonfatal MI, nonfatal presumed ischaemic stroke, transient ischaemic attack, coronary or non-coronary revascularisation, cardiovascular death - excluding cerebral haemorrhage and non-coronary death) Mean (95% CI)	NA (NA to NA)	NA (0.32 to 1.15)	NA (NA to NA)	NA (NA to NA)
Non-fatal ischaemic stroke Mean 95% CI is actually HR 95% CI - the value provided compares the two arms. No of events	-	n = 2 ; % = 0.1	-	n = 7 ; % = 0.5
Non-fatal ischaemic stroke Mean 95% CI is actually HR 95% CI - the value provided compares the two arms. Hazard ratio	NA	3.52	NA	NA
Non-fatal ischaemic stroke Mean 95% CI is actually HR 95% CI - the value provided compares the two arms. Mean (95% CI)	NA (NA to NA)	NA (0.73 to 16.93)	NA (NA to NA)	NA (NA to NA)
All-cause mortality No of events	-	n = 25 ; % = 1.7	-	n = 27 ; % = 1.8
Non-fatal myocardial infarction Mean 95% CI is actually HR 95% CI - the value provided compares the two arms. No of events	-	n = 11 ; % = 0.7	-	n = 20 ; % = 1.3
Non-fatal myocardial infarction Mean 95% CI is actually HR 95% CI - the value provided compares the two arms.	NA	1.84	NA	NA

Hazard ratio				
Non-fatal myocardial infarction Mean 95% CI is actually HR 95% CI - the value provided compares the two arms. Mean (95% CI)	NA (NA to NA)	NA (0.88 to 3.84)	NA (NA to NA)	NA (NA to NA)
Cardiovascular mortality (coronary death) Mean 95% CI is actually HR 95% CI - the value provided compares the two arms. No of events	-	n = 2 ; % = 0.1	-	n = 2 ; % = 0.1
Cardiovascular mortality (coronary death) Mean 95% CI is actually HR 95% CI - the value provided compares the two arms. Custom value	NA	1.00	NA	NA
Cardiovascular mortality (coronary death) Mean 95% CI is actually HR 95% CI - the value provided compares the two arms. Mean (95% CI)	NA (NA to NA)	NA (0.14 to 7.11)	NA (NA to NA)	NA (NA to NA)

Combined major adverse cardiovascular events - Polarity - Lower values are better

Non-fatal ischaemic stroke - Polarity - Lower values are better

All-cause mortality - Polarity - Lower values are better

Non-fatal myocardial infarction - Polarity - Lower values are better

Cardiovascular mortality (coronary death) - Polarity - Lower values are better

Efficacy - Continuous outcome

Outcome	Statins - Atorvastatin (high intensity), Baseline, N = 1422	Statins - Atorvastatin (high intensity), 2.51 year, N = 1062	Placebo, Baseline, N = 1408	Placebo, 2.51 year, N = 1079
Quality of life (EQ-5D) Median IQR values reported Median (IQR)	0.62 (0.52 to 0.8)	0.66 (0.52 to 0.8)	0.69 (0.52 to 0.8)	0.7 (0.52 to 0.8)

Quality of life (EQ-5D) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
Efficacy- Combined major adverse cardiovascular events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- Non-fatal ischaemic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- All-cause mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- Non-fatal myocardial infarction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- -Cardiovascular mortality (coronary death)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- Quality of life (EQ-5D)-Median IQR

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Outcomes

Study timepoints

- Baseline
- 2.51 year (Median 2.51 years. Trial was terminated early due to a lower than expected event rate (0.70% per annum).)

Adverse effects - Dichotomous outcomes

Outcome	Statins - Atorvastatin (high intensity), Baseline, N = 1504	Statins - Atorvastatin (high intensity), 2.51 year, N = 1504	Placebo, Baseline, N = 1498	Placebo, 2.51 year, N = 1498
Rhabdomyolysis (CK>10 times normal) Zero events No of events	-	n = 0 ; % = 0	NR	n = 0 ; % = 0
Liver (transaminases >3 times normal level) Reports transaminases 2-5x upper limit of normal. Downgrade for indirectness. No of events	-	n = 90 ; % = 6	-	n = 69 ; % = 4.6

Rhabdomyolysis (CK>10 times normal) - Polarity - Lower values are better

Liver (transaminases >3 times normal level) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)

Rhabdomyolysis (CK>10 times normal)-Atorvastatin (high intensity)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Liver (transaminases)- Atorvastatin (high intensity)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable (Due to outcome reporting 2-5 x upper limit of normal rather than >3 times)

Liu, 2016

Bibliographic Reference	Liu, Z.; Xu, Y.; Hao, H.; Yin, C.; Xu, J.; Li, J.; Wang, Y.; Xu, D.; Efficacy of high intensity atorvastatin versus moderate intensity atorvastatin for acute coronary syndrome patients with diabetes mellitus; International Journal of Cardiology; 2016; vol. 222; 22-26

Study details

Secondary publication of another included study- see primary study for details	**No additional information.**
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Outpatient follow up.
Study dates	August 2012 to December 2014
Sources of funding	This work was not supported by any funding.
Inclusion criteria	Acute coronary syndrome patients with type 2 diabetes mellitus (including people treated with anti-diabetic agents who currently had controlled diabetes) who underwent primary or early PCI; age no more than 80 years.
Exclusion criteria	Chronic atorvastatin at least 20mg/day (or equivalent dose with other statins) before PCI; abnormal liver enzymes (ALT and AST more than 40 U/L); blood creatinine >2mg/dL; muscle disease.

Recruitment / selection of participants	People who had a PCI at the center.
Intervention(s)	Statins - Atorvastatin 40mg (high intensity) N=297 Oral atorvastatin 40mg/day. Concomitant therapy: All PCI were performed with standard technique and using drug-eluting stents only. All people were pre-treated with aspirin (loading dose 300mg, 100mg/day) and clopidogrel (loading dose 300mg, 75mg/day) after hospitalisation. Primary PCI patients were pre-treated with aspirin 300mg and clopidogrel 600mg usually 30 minutes before PCI. Following PCI, aspirin and clopidogrel were administered for a minimum of 12 months.
Population subgroups	Different agents/doses within each intensity class: High intensity vs. high intensity Primary versus secondary prevention: Secondary prevention Presence versus absence of chronic kidney disease: Not stated/unclear Age (<75 versus ≥75): <75 (mean was 61.6 in the 40mg group, 62.1 in the 20mg group)) Sex: Mixed (48.2% male in the 40mg group, 50.3% male in the 20mg group) Ethnicity/family origin (black, Asian, white, mixed, other): Not stated/unclear Presence versus absence of autoimmune disease: Not stated/unclear
Comparator	Statins - Atorvastatin 20mg (high intensity) N=294 Oral atorvastatin 20mg/day. Concomitant therapy: All PCI were performed with standard technique and using drug-eluting stents only. All people were pre-treated with aspirin (loading dose 300mg, 100mg/day) and clopidogrel (loading dose 300mg, 75mg/day) after hospitalisation. Primary PCI patients were pre-treated with aspirin 300mg and clopidogrel 600mg usually 30 minutes before PCI. Following PCI, aspirin and clopidogrel were administered for a minimum of 12 months.
Number of participants	591
Duration of follow-up	1 year
Indirectness	No additional information.
Additional comments	Method of analysis unclear.

Study arms
Statins - Atorvastatin 40mg (high intensity) (N = 297)

Oral atorvastatin 40mg/day. Concomitant therapy: All PCI were performed with standard technique and using drug-eluting stents only. All people were pre-treated with aspirin (loading dose 300mg, 100mg/day) and clopidogrel (loading dose 300mg, 75mg/day) after hospitalisation. Primary PCI patients were pre-treated with aspirin 300mg and clopidogrel 600mg usually 30 minutes before PCI. Following PCI, aspirin and clopidogrel were administered for a minimum of 12 months.

Statins - Atorvastatin 20mg (high intensity) (N = 294)

Oral atorvastatin 20mg/day. Concomitant therapy: All PCI were performed with standard technique and using drug-eluting stents only. All people were pre-treated with aspirin (loading dose 300mg, 100mg/day) and clopidogrel (loading dose 300mg, 75mg/day) after hospitalisation. Primary PCI patients were pre-treated with aspirin 300mg and clopidogrel 600mg usually 30 minutes before PCI. Following PCI, aspirin and clopidogrel were administered for a minimum of 12 months.

Characteristics

Arm-level characteristics

Characteristic	Statins - Atorvastatin 40mg (high intensity) (N = 297)	Statins - Atorvastatin 20mg (high intensity) (N = 294)
% Female Sample size	n = 154 ; % = 51.9	n = 146 ; % = 49.7
Mean age (SD) (years) Mean (SD)	61.6 (8.7)	62.1 (10.2)
Age over 75 years Sample size	NR	NR
Ethnicity Sample size	NR	NR
Existing CVD diagnoses Sample size	-	-
previous myocardial infarction Sample size	n = 36 ; % = 12.1	n = 43 ; % = 14.6
Previous percutaneous coronary intervention Sample size	n = 53 ; % = 17.9	n = 57 ; % = 19.4
Previous coronary artery bypass graft Sample size	n = 9 ; % = 3	n = 11 ; % = 3.7
previous stroke Sample size	n = 41 ; % = 13.8	n = 37 ; % = 12.6

Hypertension Sample size	n = 196 ; % = 66	n = 208 ; % = 70.8
STEMI Sample size	n = 146 ; % = 49.2	n = 144 ; % = 49
NSTEMI Sample size	n = 67 ; % = 22.6	n = 72 ; % = 24.5
Type 2 diabetes Sample size	NR	NR
Chronic kidney disease Sample size	NR	NR
Family history of CVD Sample size	NR	NR
Autoimmune disease Sample size	NR	NR
Serious mental illness Sample size	NR	NR
Socioeconomic group Sample size	NR	NR
LDL cholesterol level at baseline (mmol/L) Mean (SD)	3.2 (0.9)	3.1 (0.7)
LDL cholesterol level at the end of follow-up Sample size	NR	NR
Reduction in LDL cholesterol (absolute) Sample size	NR	NR

Outcomes

Study timepoints

- Baseline
- 1 year

Efficacy - Dichotomous outcomes

Outcome	Statins - Atorvastatin 40mg (high intensity), Baseline, N = 297	Statins - Atorvastatin 40mg (high intensity), 1 year, N = 297	Statins - Atorvastatin 20mg (high intensity), Baseline, N = 294	Statins - Atorvastatin 20mg (high intensity), 1 year, N = 294
All-cause mortality No of events	-	n = 6 ; % = 2	-	n = 11 ; % = 3.7
Non-fatal myocardial infarction Assuming that all spontaneous myocardial infarctions were non-fatal. No of events	-	n = 8 ; % = 2.7	-	n = 18 ; % = 6.1
Non-fatal ischaemic stroke Assuming that all strokes were non-fatal and ischaemic in nature. No of events	-	n = 10 ; % = 3.4	-	n = 20 ; % = 6.8
Combined major adverse cardiovascular events (major adverse coronary events) No of events	-	n = 25 ; % = 8.4	-	n = 43 ; % = 14.6

All-cause mortality - Polarity - Lower values are better

Non-fatal myocardial infarction - Polarity - Lower values are better

Non-fatal ischaemic stroke - Polarity - Lower values are better

Combined major adverse cardiovascular events (major adverse coronary events) - Polarity - Lower values are better

Efficacy - Time to event outcome

Outcome	Statins - Atorvastatin 40mg (high intensity) vs Statins - Atorvastatin 20mg (high intensity), Baseline, N2 = 297, N1 = 294	Statins - Atorvastatin 40mg (high intensity) vs Statins - Atorvastatin 20mg (high intensity), 1 year, N2 = 297, N1 = 294
Combined major adverse cardiovascular events (major adverse coronary events) Hazard ratio	NA	0.61
Combined major adverse cardiovascular events (major adverse coronary events)	NA (NA to NA)	NA (0.36 to 0.91)

Mean (95% CI)		

Combined major adverse cardiovascular events (major adverse coronary events) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)

Efficacy -All-cause mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy -Non-fatal myocardial infarction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- Non-fatal ischaemic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- Combined major adverse cardiovascular events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy-Time-to-event outcome- Combined major adverse cardiovascular events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Outcomes

Study timepoints

- Baseline
- 1 year

Adverse effects - Dichotomous outcomes

Outcome	Statins - Atorvastatin 40mg (high intensity) , Baseline, N = 297	Statins - Atorvastatin 40mg (high intensity) , 1 year, N = 297	Statins - Atorvastatin 20mg (high intensity), Baseline, N = 294	Statins - Atorvastatin 20mg (high intensity), 1 year, N = 294
Liver (transaminases>3 times normal level) ALT more than 3-fold but less than 5-fold upper reference limit No of events	-	n = 10 ; % = 7.4	-	n = 7 ; % = 4.8
Myalgia (myalgia/myasthenia) No of events	-	n = 3 ; % = 1	-	n = 2 ; % = 0.7

Liver (transaminases>3 times normal level) - Polarity - Lower values are better

Myalgia (myalgia/myasthenia) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)

Liver (transaminases>3xULN)- Atorvastatin 40mg (high intensity) - Atorvastatin 20mg (high intensity)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Myalgia (myalgia/myasthenia)- Atorvastatin 40mg (high intensity) v Atorvastatin 20mg (high intensity)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Lonn, 2016

Bibliographic Reference	Lonn, E.; Bosch, J.; Pogue, J.; Avezum, A.; Chazova, I.; Dans, A.; Diaz, R.; Fodor, G. J.; Held, C.; Jansky, P.; Keltai, M.; Keltai, K.; Kunti, K.; Kim, J. H.; Leiter, L.; Lewis, B.; Liu, L.; Lopez-Jaramillo, P.; Pais, P.; Parkhomenko, A.; Peters, R. J.; Piegas, L. S.; Reid, C. M.; Sliwa, K.; Toff, W. D.; Varigos, J.; Xavier, D.; Yusoff, K.; Zhu, J.; Dagenais, G.; Yusuf, S.; Investigators, Hope-; Novel Approaches in Primary Cardiovascular Disease Prevention: The HOPE-3 Trial Rationale, Design, and Participants' Baseline Characteristics; Canadian Journal of Cardiology; 2016; vol. 32 (no. 3); 311-8

Study details

Secondary publication of another included study- see primary study for details	**Bosch, J.; O'Donnell, M.; Swaminathan, B.; Lonn, E. M.; Sharma, M.; Dagenais, G.; Diaz, R.; Khunti, K.; Lewis, B. S.; Avezum, A.; Held, C.; Keltai, M.; Reid, C.; Toff, W. D.; Dans, A.; Leiter, L. A.; Sliwa, K.; Lee, S. F.; Pogue, J. M.; Hart, R.; Yusuf, S.; Investigators, Hope-; Effects of blood pressure and lipid lowering on cognition: Results from the HOPE-3 study; Neurology; 2019; vol. 92 (no. 13); e1435-e1446**
Other publications associated with this study included in review	No additional information

Mou, 2016

Bibliographic Reference	Mou, S.; Wang, Q.; Yu, Z.; Shao, X.; Tian, L.; Yuan, Y.; Shi, B.; Ma, L.; Che, X.; Zhang, M.; Fang, W.; Ni, Z.; Pravastatin improves renal progression in patients with chronic glomerulonephritis; International Journal of Clinical and Experimental Medicine; 2016; vol. 9 (no. 2); 1732-1739

Study details

Secondary publication of another included study- see primary study for details	**No additional information**
Other publications associated with this study included in review	No additional information

Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	No additional information
Study dates	April 2009 - March 2012
Sources of funding	Supported in part by the National Basic Research Program of China (973 Program No. 2012CB517602). The study was also sponsored by SRF for ROCS, SEM and project 81102700 and 81070548 supported by NSFC. The work was also sponsored by grant 09dZ1973600 and 10JC1410100 from Science and Technology Commission of Shanghai Municipality China and 2010L063A from Shanghai healthy Bureau
Inclusion criteria	>18 years of age Proteinuria ≥0.5 g/24 h and ≤ 3.5 g/24 h Biopsy-proven chronic glomerulonephritis
Exclusion criteria	Overt infection during the last 3 months prior to the study History of malignancy or other chronic inflammatory disease, such as systemic lupus erythematosus or rheumatoid arthritis
Recruitment / selection of participants	No additional information
Intervention(s)	All participants received basic therapy throughout the study including dietary and life style instruction as well as anti-hypertension. Participants also received oral pravastatin treatment with 20 mg/day for 96 weeks
Population subgroups	Diabetes 4/48 patients had diabetes Chronic Kidney Disease 18/48 patients had stage 3/4 CKD BMI Population mean (SD) = 23.62 (3.30) Age Population mean (SD) = 50.83 (14.25) Sex Not reported Ethnicity Not reported

Comparator	All patients received basic therapy throughout the study including dietary and lifestyle instruction as well as anti-hypertension
Number of participants	48 randomised 25 allocated to intervention 23 allocated to control
Duration of follow-up	96 weeks
Indirectness	No additional information
Additional comments	Intention to treat

Study arms

Pravastatin (N = 25)

20mg/day plus usual care including dietary and lifestyle instruction

Usual care (N = 23)

Including dietary and lifestyle instruction

Characteristics

Arm-level characteristics

Characteristic	Pravastatin (N = 25)	Usual care (N = 23)
% Female Nominal	NR	NR
Mean age (SD) Mean (SD)	53.16 (11.05)	47.61 (17.62)
Age over 75 years Nominal	NR	NR
Ethnicity Nominal	NR	NR
Existing CVD diagnoses Nominal	NR	NR
Type 2 diabetes Sample size	n = 3 ; % = 12	n = 1 ; % = 4.3

Chronic kidney disease Stage 3/4 CKD Sample size	n = 10 ; % = 40	n = 8 ; % = 34.7
Family history of CVD Nominal	NR	NR
Autoimmune disease Nominal	NR	NR
Serious mental illness Nominal	NR	NR
Socioeconomic group Nominal	NR	NR
LDL cholesterol level at baseline (mmol/L) Mean (SD)	3.56 (0.74)	3.48 (0.91)
LDL cholesterol level at end of follow-up (mmol/L) Mean (SD)	2.46 (0.66)	3.39 (0.75)
Reduction in LDL cholesterol (absolute) (mmol/L) Nominal	-1.1	-0.09

Outcomes

Study timepoints

- Baseline
- 96 week

Dichotomous Outcomes

Outcome	Pravastatin , Baseline, N = 25	Pravastatin , 96 week, N = 25	Usual care, Baseline, N = 23	Usual care, 96 week, N = 23
New onset diabetes No of events	-	n = 0 ; % = 0	-	n = 0 ; % = 0

New onset diabetes - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)
New-onset diabetes

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Unblinded and no definition of outcome)
Overall bias and Directness	Overall Directness	Directly applicable

Nagai, 2014

Bibliographic Reference	Nagai, Y.; Kohriyama, T.; Origasa, H.; Minematsu, K.; Yokota, C.; Uchiyama, S.; Ibayashi, S.; Terayama, Y.; Takagi, M.; Kitagawa, K.; Nomura, E.; Hosomi, N.; Ohtsuki, T.; Yamawaki, T.; Matsubara, Y.; Nakamura, M.; Yamasaki, Y.; Mori, E.; Fukushima, M.; Kobayashi, S.; Shinohara, Y.; Yamaguchi, T.; Matsumoto, M.; Investigators, J. Stars; Rationale, design, and baseline features of a randomized controlled trial to assess the effects of statin for the secondary prevention of stroke: the Japan Statin Treatment Against Recurrent Stroke (J-STARS); International Journal of Stroke; 2014; vol. 9 (no. 2); 232-9

Study details

Secondary publication of another included study- see primary study for details	**Protocol paper for Hosomi 2015 - relevant details included there.**

Salonen, 1995

Bibliographic Reference	Salonen, R.; Nyyssönen, K.; Porkkala, E.; Rummukainen, J.; Belder, R.; Park, J. S.; Salonen, J. T.; Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries; Circulation; 1995; vol. 92 (no. 7); 1758-1764

Study details

Secondary publication of another included	**No additional information.**

study- see primary study for details	
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Kupio, Finland.
Study setting	Outpatient follow up.
Study dates	January 1990 to January 1993.
Sources of funding	Supported by grants from the Academy of Finland and the Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ.
Inclusion criteria	All men included in the KIHD study (an observational population study) with serum LDL-C levels of 4.25 mmol/L or more and body mass index of <32kg/m2 and liver enzymes (alanine aminotransferase and aspartate aminotransferase) not exceeding 1.5-fold the laboratory upper normal limit.
Exclusion criteria	No additional information.
Recruitment / selection of participants	People participating in a larger observational population study who fell into the inclusion criteria.
Intervention(s)	Statins - Pravastatin (low intensity) N=224 Oral pravastatin 40mg once a day. Concomitant therapy: No additional information.
Population subgroups	Different agents/doses within each intensity class: Low intensity Primary versus secondary prevention: Majority primary (6-8% had previously had a myocardial infarction) Presence versus absence of chronic kidney disease: Not stated/unclear. Age (<75 versus ≥75): <75 (mean pravastatin = 57.4, range 44-65; mean placebo = 57.5, range: 44-63) Sex: All male Ethnicity/family origin (black, Asian, white, mixed, other): Not stated/unclear Presence versus absence of autoimmune disease: Not stated/unclear
Comparator	Placebo N=223

	Placebo once a day. Concomitant therapy: No additional information.
Number of participants	447
Duration of follow-up	Likely 3 years given recruitment window, unclear.
Indirectness	No additional information.
Additional comments	Unclear method of analysis. Likely completers only.

Study arms

Statins - Pravastatin (low intensity) (N = 224)

Oral pravastatin 40mg once a day. Concomitant therapy: No additional information.

Placebo (N = 223)

Placebo once a day. Concomitant therapy: No additional information.

Characteristics

Arm-level characteristics

Characteristic	Statins - Pravastatin (low intensity) (N = 224)	Placebo (N = 223)
% Female Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Mean age (SD) (years) Mean (SD)	57.3 (4.3)	57.5 (4.4)
Age over 75 years Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Ethnicity Sample size	NR	NR
Existing CVD diagnoses Sample size	-	-
Prior myocardial infarction	n = 20 ; % = 8.9	n = 14 ; % = 6.3

Sample size		
Hypertension Sample size	n = 78 ; % = 34.8	n = 70 ; % = 31.4
Type 2 diabetes Sample size	n = 7 ; % = 3.1	n = 4 ; % = 1.8
Chronic kidney disease Sample size	NR	NR
Family history of CVD Sample size	NR	NR
Autoimmune disease Sample size	NR	NR
Serious mental illness Sample size	NR	NR
Socioeconomic group Sample size	NR	NR
LDL cholesterol level at baseline (mmol/L) Mean (SD)	4.9 (0.6)	4.9 (0.6)
LDL cholesterol level at the end of follow-up (mmol/L) Mean (SD)	3.4 (0.65)	5 (0.69)
Reduction in LDL cholesterol (absolute) Mean (SD)	NR	NR (NR)

Outcomes

Study timepoints

- Baseline
- 3 year (Unclear, appears to be 3 years based on recruitment time)

Efficacy - Dichotomous outcomes

Outcome	Statins - Pravastatin (low intensity), Baseline, N = 224	Statins - Pravastatin (low intensity), 3 year, N = 224	Placebo, Baseline, N = 223	Placebo, 3 year, N = 223
All-cause mortality Combination of noncardiac deaths, fatal myocardial infarction and other cardiac death. No of events	-	n = 4 ; % = 1.8	-	n = 3 ; % = 1.3
Cardiovascular mortality Combination of fatal myocardial infarction and other cardiac death No of events	-	n = 2 ; % = 0.9	-	n = 2 ; % = 0.9
Non-fatal myocardial infarction No of events	-	n = 3 ; % = 1.3	-	n = 6 ; % = 2.7
Non-fatal ischaemic stroke Assumed to be ischaemic stroke. Taken from stroke value (1 noncardiac death was due to a stroke, unclear if this stroke is included in this number) No of events	-	n = 2 ; % = 0.9	-	n = 4 ; % = 1.8

All-cause mortality - Polarity - Lower values are better
Cardiovascular mortality - Polarity - Lower values are better
Non-fatal myocardial infarction - Polarity - Lower values are better
Non-fatal ischaemic stroke - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
Efficacy -All-cause mortality-

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy -Cardiovascular mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- Non-fatal myocardial infarction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- Non-fatal ischaemic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Stoekenbroek, 2015

Bibliographic Reference	**Stoekenbroek, R. M.; Boekholdt, S. M.; Fayyad, R.; Laskey, R.; Tikkanen, M. J.; Pedersen, T. R.; Hovingh, G. K.; Incremental Decrease in End Points Through Aggressive Lipid Lowering Study, Group; High-dose atorvastatin is superior to moderate-dose simvastatin in preventing peripheral arterial disease; Heart; 2015; vol. 101 (no. 5); 356-62**

Study details

Secondary publication of another included study- see primary study for details	**No additional information.**
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT00159835

Study type	Randomised controlled trial (RCT)
Study location	Multicenter - Sweden, Norway, Finland, Denmark, Iceland and the Netherlands.
Study setting	Outpatient follow up.
Study dates	March 1999 to March 2005
Sources of funding	Sponsored by Pfizer.
Inclusion criteria	Men and women aged 80 years or younger with a history of definite myocardial infarction and who qualified for statin therapy according to national guidelines at the time of recruitment.
Exclusion criteria	Contraindications to statin therapy; previous intolerance to statins in low or high doses; liver enzyme levels more than 2 times the upper limit of normal; pregnancy or breastfeeding; nephrotic syndrome; uncontrolled diabetes mellitus; uncontrolled hypothyroidism; plasma triglyceride levels higher than 600mg/dL (6.8mmol/L); congestive heart failure (New York Heart Association classification IIIb or IV); haemodynamically important valvular heart disease; gastrointestinal conditions affecting absorption of drugs; treatment with other drugs that seriously affect the pharmacokinetics of statins; treatment with other lipid-lowering drugs; people previously treated with statins were excluded if they had already had a titration to a dose higher than the equivalent of 20mg/day of simvastatin.
Recruitment / selection of participants	Records of people previously treated at the centers were screened against the eligibility criteria and potentially eligible people were involved for a screening visit.
Intervention(s)	Statin - Atorvastatin (high intensity) N=4439 Oral atorvastatin 80mg/day. Concomitant therapy: No additional information.
Population subgroups	Different agents/doses within each intensity class: High vs. medium Primary versus secondary prevention: Secondary Presence versus absence of chronic kidney disease: Not stated/unclear Age (<75 versus ≥75): <75 (mean age was between 61.4 and 65.8 years) Sex: Predominantly male (around 20% were female) Ethnicity/family origin (black, Asian, white, mixed, other): Not stated/unclear Presence versus absence of autoimmune disease: Not stated/unclear
Comparator	Statin - Simvastatin (medium intensity) N=4449 Oral simvastatin 20-40mg/day. Concomitant therapy: No additional information.

Number of participants	8888
Duration of follow-up	4.8 years (median follow up).
Indirectness	No additional information.
Additional comments	Method of analysis not clearly stated.

Study arms

Statin - Atorvastatin (high intensity) (N = 4439)

Oral atorvastatin 80mg/day. Concomitant therapy: No additional information.

Statin - Simvastatin (medium intensity) (N = 4449)

Oral simvastatin 20-40mg/day. Concomitant therapy: No additional information.

Characteristics

Arm-level characteristics

Characteristic	Statin - Atorvastatin (high intensity) (N = 4439)	Statin - Simvastatin (medium intensity) (N = 4449)
% Female Sample size	n = 849 ; % = 19.1	n = 852 ; % = 19.2
Mean age (SD) (years) Mean (SD)	61.8 (9.5)	61.6 (9.4)
Age over 75 years Sample size	NR	NR
Ethnicity Sample size	NR	NR
Existing CVD diagnoses Sample size	-	-
Peripheral arterial disease Sample size	n = 180 ; % = 4	n = 194 ; % = 4
Systemic hypertension Sample size	n = 1457 ; % = 33	n = 1467 ; % = 33

History of cerebrovascular disease Sample size	n = 317 ; % = 7	n = 338 ; % = 8
History of congestive heart failure Sample size	n = 292 ; % = 7	n = 243 ; % = 6
Type 2 diabetes Sample size	n = 532 ; % = 12	n = 537 ; % = 12
Chronic kidney disease Sample size	NR	NR
Family history of CVD Sample size	NR	NR
Autoimmune disease Sample size	NR	NR
Serious mental illness Sample size	NR	NR
Socioeconomic group Sample size	NR	NR
LDL cholesterol level at baseline (mg/dL) Mean (SD)	121.6 (34.5)	192.7 (41.3)
LDL cholesterol level at the end of follow-up Mean (SD)	NR (NR)	NR (NR)
Reduction in LDL cholesterol (absolute) Mean (95% CI)	-38.3 (-39.2 to -37.5)	-19.7 (-20.5 to -18.8)

Outcomes

Study timepoints

- Baseline
- 4.8 year (Median follow up)

Efficacy - dichotomous outcomes

Outcome	Statin - Atorvastatin (high intensity), Baseline, N = 4439	Statin - Atorvastatin (high intensity), 4.8 year, N = 4439	Statin - Simvastatin (medium intensity), Baseline, N = 4449	Statin - Simvastatin (medium intensity), 4.8 year, N = 4449
All-cause mortality No of events	-	n = 366 ; % = 8.2	-	n = 374 ; % = 8.4
Cardiovascular mortality No of events	-	n = 223 ; % = 5	-	n = 174 ; % = 3.9
Non-fatal myocardial infarction No of events	-	n = 267 ; % = 6	-	n = 321 ; % = 7.2
Non-fatal ischaemic stroke (stroke) Assumed to be ischaemic stroke and non-fatal No of events	-	n = 151 ; % = 3.4	-	n = 174 ; % = 3.9
Combined major adverse cardiovascular events (major cardiovascular events) No of events	-	n = 411 ; % = 9.3	-	n = 608 ; % = 13.7

All-cause mortality - Polarity - Lower values are better

Cardiovascular mortality - Polarity - Lower values are better

Non-fatal myocardial infarction - Polarity - Lower values are better

Non-fatal ischaemic stroke (stroke) - Polarity - Lower values are better

Combined major adverse cardiovascular events (major cardiovascular events) - Polarity - Lower values are better

Efficacy - time to event outcomes

Outcome	Statin - Atorvastatin (high intensity) vs Statin - Simvastatin (medium intensity), Baseline, N2 = 4259, N1 = 4255	Statin - Atorvastatin (high intensity) vs Statin - Simvastatin (medium intensity), 4.8 year, N2 = 4259, N1 = 4255
Non-fatal myocardial infarction Hazard ratios provided for people without a history of peripheral arterial disease only Hazard ratio	NA	0.84

Non-fatal myocardial infarction Hazard ratios provided for people without a history of peripheral arterial disease only Mean (95% CI)	NA (NA to NA)	NA (0.71 to 1)
Combined major adverse cardiovascular events (major cardiovascular events) Hazard ratios provided for people without a history of peripheral arterial disease only Hazard ratio	NA	0.91
Combined major adverse cardiovascular events (major cardiovascular events) Hazard ratios provided for people without a history of peripheral arterial disease only Mean (95% CI)	NA (NA to NA)	NA (0.79 to 1.04)

Non-fatal myocardial infarction - Polarity - Lower values are better

Combined major adverse cardiovascular events (major cardiovascular events) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)

Efficacy -All-cause mortality-

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- Cardiovascular mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- Non-fatal myocardial infarction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns

Overall bias and Directness	Overall Directness	Directly applicable

Efficacy--Non-fatal ischaemic stroke (stroke)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy-MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy-time-to-event outcomes-Non-fatal myocardial infarction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy- time-to-event outcomes -MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Yakusevich, 2012

Bibliographic Reference	Yakusevich, Vv; Malygin, Ay; Lychenko, Sv; Petrochenko, As; Kabanov, Av; The efficacy of high-dose simvastatin in acute period of ischemic stroke; Rational pharmacotherapy in cardiology; 2012; vol. 8 (no. 1); 4-16

Study details

Secondary publication of	**No additional information.**

another included study- see primary study for details	
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Russia
Study setting	Initially inpatient to outpatient follow up
Study dates	2008-2010.
Sources of funding	Not stated/unclear.
Inclusion criteria	People with the first acute ischaemic cerebrovascular accident in carotid system (diagnosis verified by computer or magnetic resonance tomography of the brain in the acute stage of disease - 24-48 hours from first symptoms onset).
Exclusion criteria	People with recurrent stroke; haemorrhagic stroke; consciousness level below 13 points by the Glasgow scale as well as patients with presumably unfavourable concomitant diseases.
Recruitment / selection of participants	Inpatients with acute stroke
Intervention(s)	Statins - Simvastatin (medium intensity) N=86 Oral simvastatin 40mg once a day in addition to standard therapy. Follow up for up to 12 months. Concomitant therapy: Standard therapy included antiplatelet drugs (acetylsalicylic acid), neurotrophic drugs and neuromodulators, correction of hypertension, atrial fibrillation and chronic heart failure.
Population subgroups	Different agents/doses within each intensity class: Medium Primary versus secondary prevention: Secondary Presence versus absence of chronic kidney disease: Not stated/unclear Age (<75 versus ≥75): <75 (mean age statin = 65.5, usual care = 65.8). Sex: Mixed (55% women, 45% men) Ethnicity/family origin (black, Asian, white, mixed, other): Not stated/unclear Presence versus absence of autoimmune disease: Not stated/unclear

Comparator	Usual care N=97 Standard therapy only. Concomitant therapy: Standard therapy included antiplatelet drugs (acetylsalicylic acid), neurotrophic drugs and neuromodulators, correction of hypertension, atrial fibrillation and chronic heart failure.
Number of participants	183
Duration of follow-up	Up to 1 year
Indirectness	No additional information.
Additional comments	Method of analysis unclear. Appears to be ITT no dropouts.

Study arms

Statins - Simvastatin (medium intensity) (N = 86)

Oral simvastatin 40mg once a day in addition to standard therapy. Follow up for up to 12 months. Concomitant therapy: Standard therapy included antiplatelet drugs (acetylsalicylic acid), neurotrophic drugs and neuromodulators, correction of hypertension, atrial fibrillation and chronic heart failure.

Usual care (N = 97)

Standard therapy only. Concomitant therapy: Standard therapy included antiplatelet drugs (acetylsalicylic acid), neurotrophic drugs and neuromodulators, correction of hypertension, atrial fibrillation and chronic heart failure.

Characteristics

Arm-level characteristics

Characteristic	Statins - Simvastatin (medium intensity) (N = 86)	Usual care (N = 97)
% Female Sample size	n = 49 ; % = 56.98	n = 54 ; % = 55.7
Mean age (SD) (years) Mean (SD)	65.5 (7.2)	65.8 (9.3)
Age over 75 years Sample size	NR	NR
Ethnicity Sample size	NR	NR

Existing CVD diagnoses Sample size	-	-
Hypertension Sample size	n = 68	n = 74 ; % = 76.3
previous myocardial infarction Sample size	n = 10 ; % = 8.6	n = 8 ; % = 8.2
Atrial fibrillation Sample size	n = 14 ; % = 16.3	n = 12 ; % = 12.4
Type 2 diabetes Sample size	n = 8 ; % = 9.3	n = 10 ; % = 9.7
Chronic kidney disease Sample size	NR	NR
Family history of CVD Sample size	NR	NR
Autoimmune disease Sample size	NR	NR
Serious mental illness Sample size	NR	n = NR
Socioeconomic group Sample size	NR	NR
LDL cholesterol level at baseline (mmol/L) Mean (SD)	2.2 (0.6)	2.23 (0.9)
LDL cholesterol level at the end of follow-up Mean (SD)	1.8 (0.3)	1.8 (0.3)
Reduction in LDL cholesterol (absolute) Mean (SD)	NR (NR)	NR (NR)

Outcomes

Study timepoints

- Baseline

- 1 year

Efficacy - dichotomous outcomes

Outcome	Statins - Simvastatin (medium intensity), Baseline, N = 86	Statins - Simvastatin (medium intensity), 1 year, N = 86	Usual care, Baseline, N = 97	Usual care, 1 year, N = 97
Cardiovascular mortality States 'total of deceased' but this appears to be the total of people who died from stroke or MI. No of events	-	n = 13 ; % = 15.12	-	n = 16 ; % = 16.5
Non-fatal myocardial infarction No of events	-	n = 4 ; % = 4.65	-	n = 5 ; % = 5.15
Non-fatal ischaemic stroke No of events	-	n = 4 ; % = 4.65	-	n = 7 ; % = 7.2
Combined major adverse cardiovascular events Adding together the cardiovascular deaths with the nonfatal myocardial infarctions and ischaemic strokes (assuming that no one had multiple events due to the rareness of the events) No of events	-	n = 21 ; % = 24.4	-	n = 28 ; % = 28.9

Cardiovascular mortality - Polarity - Lower values are better

Non-fatal myocardial infarction - Polarity - Lower values are better

Non-fatal ischaemic stroke - Polarity - Lower values are better

Combined major adverse cardiovascular events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
Efficacy- Cardiovascular mortality-

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy -Non-fatal myocardial infarction-

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy -Non-fatal ischaemic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy -MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Yusuf, 2016

Bibliographic Reference	Yusuf, S.; Bosch, J.; Dagenais, G.; Zhu, J.; Xavier, D.; Liu, L.; Pais, P.; Lopez-Jaramillo, P.; Leiter, L. A.; Dans, A.; Avezum, A.; Piegas, L. S.; Parkhomenko, A.; Keltai, K.; Keltai, M.; Sliwa, K.; Peters, R. J.; Held, C.; Chazova, I.; Yusoff, K.; Lewis, B. S.; Jansky, P.; Khunti, K.; Toff, W. D.; Reid, C. M.; Varigos, J.; Sanchez-Vallejo, G.; McKelvie, R.; Pogue, J.; Jung, H.; Gao, P.; Diaz, R.; Lonn, E.; Investigators, Hope-; Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease; New England Journal of Medicine; 2016; vol. 374 (no. 21); 2021-31

Study details

Secondary publication of another included study- see primary study for details	**The trial had a 2-by-2 factorial design. The trial evaluated cholesterol lowering with rosuvastatin at a dose of 10 mg per day, blood-pressure lowering with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day, and the combination of both interventions for the prevention of cardiovascular events among persons who did not have cardiovascular disease and were at intermediate risk (defined as an annual risk of major cardiovascular events of approximately 1%).**

	The study pools together two groups: 1) Rosuvastatin 10mg once a day with a candesartan/hydrochlorothiazide placebo 2) Rosuvastatin 10mg once a day with candesartan/hydrochlorothiazide 16/12.5mg once a day. Both over a 4 week run-in period and then continued until the end of the trial. **Data reported in this extraction relate to both the 2x2 analysis and to the arms assessing rosuvastatin vs placebo only clarified in the outcomes table.**
Other publications associated with this study included in review	Lonn, E., et al. (2016). "Novel Approaches in Primary Cardiovascular Disease Prevention: The HOPE-3 Trial Rationale, Design, and Participants' Baseline Characteristics." Canadian Journal of Cardiology 32(3): 311-318. Bosch, J., et al. (2019). "Effects of blood pressure and lipid lowering on cognition: Results from the HOPE-3 study." Neurology 92(13): e1435-e1446.
Trial name / registration number	HOPE-3 ClinicalTrials.gov NCT00468923
Study location	Multicenter international trial in 228 centres in 21 countries - including Canada, Ireland, Argentina, United Kingdom, Philippines, Israel, Brazil, Sweden, Hungary, Australia and South Africa.
Study setting	Outpatient
Study dates	Recruitment started May 2007. Follow-up completed October 31st 2015.
Sources of funding	This study was funded through grants from the Canadian Institute of Health Research and AstraZeneca.
Inclusion criteria	Men older than 55 years and women older than 65 years with at least 1 additional CV risk factor, a moderately elevated waist-to-hip ratio, a history of low high-density lipoprotein cholesterol (HDL-C), recent tobacco use, dysglycemia, a family history of premature coronary heart disease, or early renal dysfunction, or women 60 years of age or older who had at least two such risk factors.
Exclusion criteria	Participants with cardiovascular disease and those with an indication for or contraindication to statins, angiotensin-receptor blockers, angiotensin-converting–enzyme inhibitors, or thiazide diuretics.
Recruitment / selection of participants	15,469 people were screened, 14,665 eligible study participants entered an active single-blind run-in phase of 4 weeks, during which they received both active study drugs. A fasting blood sample and a first-morning urine sample were obtained before administration of any study drugs for central analyses of lipids and other biomarkers and for local review of eligibility. Adherent participants who tolerated the study drugs were randomized using central concealed randomization, stratified by centre (with fixed randomization blocks). A total of 505 (3.4%) participants were not randomized after the run-in phase because of side effects. The majority of failures during the run-in phase resulted from participants' unwillingness to continue (595 [4.0%]) or poor adherence (860 [5.9%]).
Intervention(s)	Rosuvastatin 10 mg/d

Population subgroups	Different agents/doses within each intensity class: High intensity Primary versus secondary prevention: Primary prevention Presence versus absence of chronic kidney disease: Not stated/unclear Age (<75 versus ≥75): <75 (mean was 65.8 in active arm, 65.7 in placebo arm) Sex: Mixed - (Percentage female 46.4% in active arm, 46.1% in placebo arm) Ethnicity/family origin (black, Asian, white, mixed, other): Mixed Presence versus absence of autoimmune disease: Not stated/unclear
Comparator	Placebo
Number of participants	12,705 adhered to the assigned regimen during the run-in period and did not have an unacceptable level of adverse events: Rosuvastatin 6361, Placebo 6344. When considering arms for Rosuvastatin + Placebo, and Placebo + Placebo only, n values are 3181 and 3168 respectively.
Duration of follow-up	5 years Follow-up visits occurred at 6 weeks after randomization and every 6 months thereafter and assessed adherence, side effects, use of concomitant drugs, and outcome events. Data on BP, lipids and other biomarkers, lifestyle, cognitive function, erectile dysfunction, health care use, and quality of life were obtained at baseline and at follow-up.
Indirectness	None
Additional comments	Main analysis is intention to treat, with Kaplan-Meier used for co-primary outcomes (MACE)

Study arms
Rosuvastatin 10 mg (N = 3181)
High intensity statin

Placebo (N = 3168)

Characteristics

Study-level characteristics

Characteristic	Study (N =)
LDL cholesterol level at the end of follow-up Custom value	Only reported in graphical format, for a subset of participants. MD between group also reported.

Reduction in LDL cholesterol (absolute) Custom value	Only reported in graphical format

Arm-level characteristics

Characteristic	Rosuvastatin 10 mg (N = 3181)	Placebo (N = 3168)
% Female Nominal	46.4	46.1
Mean age (SD) Mean (SD)	65.8 (6.4)	65.7 (6.3)
Age over 75 years Custom value	NR	NR
Ethnicity (%) Custom value	Chinese 29.1, Hispanic 27.4, White 20.2, South Asian 14.6, Other Asian 5.4, Black 1.8, Other 1.5	Chinese 29, Hispanic 27.6, White 19.9, South Asian 14.6, Other Asian 5.6, Black 1.8, Other 1.6
Existing CVD diagnoses Custom value	Excluded	Excluded
Type 2 diabetes (n (%)) Custom value	374 (5.9)	357 (5.6)
Chronic kidney disease (n (%)) 'Early renal dysfunction' Custom value	169.9 (2.7)	181 (2.9)
Family history of CVD (n (%)) 'Family history of premature chronic heart disease' Custom value	1675 (26.3)	1660 (26.2)
Autoimmune disease Custom value	NR	NR
Serious mental illness Custom value	NR	NR
Socioeconomic group Custom value	NR	NR
LDL cholesterol level at baseline	127.8 (36.1)	127.9 (36)

Standardised Mean (SD)		

Outcomes

Study timepoints

- 5 year (Median 5.6 years)

Dichotomous data from 2x2 design

Outcome	Rosuvastatin 10 mg, 5 year, N = 6361	Placebo, 5 year, N = 6344
All-cause mortality No of events	n = 334 ; % = 5.3	n = 357 ; % = 5.6
Cardiovascular mortality No of events	n = 154 ; % = 2.4	n = 171 ; % = 2.7
Myocardial infarction (Non-fatal not reported separately) No of events	n = 45 ; % = 0.7	n = 69 ; % = 1.1
Ischemic Stroke No of events	n = 41	n = 77
MACE Death from CV causes, non-fatal MI or non-fatal stroke No of events	n = 235 ; % = 3.7	n = 304 ; % = 4.8

All-cause mortality - Polarity - Lower values are better
Cardiovascular mortality - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischemic Stroke - Polarity - Lower values are better
MACE - Polarity - Lower values are better

Time to event data from 2x2 design

Outcome	Rosuvastatin 10 mg vs Placebo, 5 year, N2 = 6361, N1 = 6344
All-cause mortality Hazard ratio/95% CI	0.93 (0.8 to 1.08)

Cardiovascular mortality Hazard ratio/95% CI	0.89 (0.72 to 1.11)
Myocardial infarction Hazard ratio/95% CI	0.65 (0.44 to 0.94)
Stroke HR not provided for ischemic, or non-fatal separately Hazard ratio/95% CI	0.7 (0.52 to 0.95)
MACE Hazard ratio/95% CI	0.76 (0.64 to 0.91)

Dichotomous data, active vs placebo only

Outcome	Rosuvastatin 10 mg, 5 year, N = 3181	Placebo, 5 year, N = 3168
All-cause mortality No of events	n = 171 ; % = 5.4	n = 178 ; % = 5.6
Cardiovascular mortality No of events	n = 79 ; % = 2.5	n = 91 ; % = 2.9
Myocardial infarction No of events	n = 26 ; % = 0.8	n = 37 ; % = 1.2
Stroke No of events	n = 37 ; % = 1.2	n = 53 ; % = 1.7
MACE No of events	n = 122	n = 157

All-cause mortality - Polarity - Lower values are better
Cardiovascular mortality - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Stroke - Polarity - Lower values are better
MACE - Polarity - Lower values are better
Reporting 2 arms of the 2x2 study: Rosuvastatin + placebo vs double placebo

Time to event data Active vs placebo only

Outcome	Rosuvastatin 10 mg vs Placebo, 5 year, N2 = 3181, N1 = 3168
MACE Hazard ratio/95% CI	0.77 (0.67 to 0.97)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
All-cause mortality-

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Cardiovascular mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Myocardial infarction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Ischemic Stroke-

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Overall bias and Directness	Overall Directness	Directly applicable

Time-to-event data-All-cause mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Time-to-event data-Cardiovascular mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Time-to-event data-Myocardial infarction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Time-to-event data-Stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Time-to-event data-MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Outcomes

Study timepoints

- 5 year (Median follow-up 5.6 years)

Dichotomous data from 2x2 analysis

Outcome	Rosuvastatin 10mg, 5 year, N = 6361	Placebo, 5 year, N = 6344
Rhabdomyolysis (CK >10 times normal) No of events	n = 1 ; % = 0	n = 0 ; % = 0
Liver function abnormality No of events	n = 25	n = 14
New onset diabetes No of events	n = 232 ; % = 3.9	n = 226 ; % = 3.8
Haemorrhagic stroke No of events	n = 11	n = 8

Rhabdomyolysis (CK >10 times normal) - Polarity - Lower values are better
Liver function abnormality - Polarity - Lower values are better
New onset diabetes - Polarity - Lower values are better

Dichotomous data for active vs placebo only

Outcome	Rosuvastatin 10mg, 5 year, N = 3181	Placebo, 5 year, N = 3168
Rhabdomyolysis (CK >10 times normal) No of events	n = 1	n = 0

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)
Rhabdomyolysis (CK>10timesnormal)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Liver function abnormality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Overall bias and Directness	Overall Directness	Directly applicable

New-onset diabetes

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Haemorrhagic stroke

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Rhabdomyolysis (CK>10timesnormal)-(active vs placebo only)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Zhang, 2019

Bibliographic Reference	Zhang, H.; Cui, Y.; Zhao, Y.; Dong, Y.; Duan, D.; Wang, J.; Sheng, L.; Ji, T.; Zhou, T.; Hu, W.; Chen, Y.; Sun, S.; Gong, G.; Chai, Q.; Liu, Z.; Effects of sartans and low-dose statins on cerebral white matter hyperintensities and cognitive function in older patients with hypertension: a randomized, double-blind and placebo-controlled clinical trial; Hypertension Research - Clinical & Experimental; 2019; vol. 42 (no. 5); 717-729

Study details

Secondary publication of another included study- see primary study for details	**No additional information.**
Other publications associated with this	No additional information.

study included in review	
Trial name / registration number	ChiCTR-IOR-17013557
Study type	Randomised controlled trial (RCT)
Study location	China.
Study setting	Community-dwelling
Study dates	April 2008 to November 2010
Sources of funding	Supported by the National Natural Science Foundation of China (81670432, 81470489, 81500232); Natural Science Foundation of Shandong Province, China (ZR2014HM098, ZR2016HM82, ZR2014HL012); the Key Research and Development Project of Shandong Province (2018GSF118044, 2017GSF218060, 2017GSF18169, 2011GSF11822); the Project of Healthy and Family Planning Commission of Shandong Province (2017WS076); the Project of Shandong Academy of Medical Sciences (2017-32); and the Innovation Project of Shandong Academy of Medical Sciences.
Inclusion criteria	Hypertensive elderly patients aged 60 years and older (hypertension defined as systolic blood pressure at least 140mmHg and/or diastolic blood pressure at least 90mmHg, or self-reported use of blood pressure-lowering medications in the last 2 weeks).
Exclusion criteria	Secondary hypertension; definite hypersensitivity or contraindication to the study medications; stroke or transient ischaemic attack; Mini-Mental State Examination score less than or equal to 23; Alzheimer's disease; Parkinson's disease; claustrophobia; bipolar disorder; schizophrenia; seizures; drug or alcohol abuse; malignancy; renal failure and dialysis treatment; liver disease; inability to walk to the clinic; unable to have MRI; unwillingness to provide informed consent.
Recruitment / selection of participants	No additional information.
Intervention(s)	Statins - Rosuvastatin (high intensity) N=366 Combination of two groups: 1) Rosuvastatin 10mg once a day and placebo once a day, 2) Rosuvastatin 10mg once a day and telmisartan 40mg increased to 80mg once a day if needed. Concomitant therapy: Hydrochlorothiazide (12.5mg increased to 25mg daily if needed) was used as a baseline medication in all treatment arms.
Population subgroups	Different agents/doses within each intensity class: High Primary versus secondary prevention: Primary Presence versus absence of chronic kidney disease: Not stated/unclear Age (<75 versus ≥75): <75 (mean age 70.69 years) Sex: Mixed (female = 47.8%)

	Ethnicity/family origin (black, Asian, white, mixed, other): Not stated/unclear Presence versus absence of autoimmune disease: Not stated/unclear
Comparator	Placebo N=366 Combination of two groups: 1) telmisartan 40mg increased to 80mg once a day if needed and placebo once a day, 2) double placebo once a day. Concomitant therapy: Hydrochlorothiazide (12.5mg increased to 25mg daily if needed) was used as a baseline medication in all treatment arms.
Number of participants	732
Duration of follow-up	59.8 months (12-65 months)
Indirectness	No additional information.
Additional comments	No additional information. Method of analysis unclear.

Study arms

Statins - Rosuvastatin (high intensity) (N = 366)

Combination of two groups: 1) Rosuvastatin 10mg once a day and placebo once a day, 2) Rosuvastatin 10mg once a day and temisartan 40mg increased to 80mg once a day if needed. Concomitant therapy: Hydrochlorothiazide (12.5mg increased to 25mg daily if needed) was used as a baseline medication in all treatment arms.

Placebo (N = 366)

Combination of two groups: 1) temisartan 40mg increased to 80mg once a day if needed and placebo once a day, 2) double placebo once a day. Concomitant therapy: Hydrochlorothiazide (12.5mg increased to 25mg daily if needed) was used as a baseline medication in all treatment arms.

Characteristics

Arm-level characteristics

Characteristic	Statins - Rosuvastatin (high intensity) (N = 366)	Placebo (N = 366)
% Female Sample size	n = 180 ; % = 49.2	n = 170 ; % = 46.4
Mean age (SD) (years) Mean (SD)	70.9 (6.28)	70.47 (6.14)

Age over 75 years Sample size	NR	NR
Ethnicity Sample size	NR	NR
Existing CVD diagnoses Sample size	NR	NR
Type 2 diabetes Sample size	NR	NR
Chronic kidney disease Sample size	NR	NR
Family history of CVD Sample size	NR	NR
Autoimmune disease Sample size	NR	NR
Serious mental illness Sample size	NR	NR
Socioeconomic group Sample size	NR	NR
LDL cholesterol level at baseline (mmol/L) Mean (SD)	3.28 (0.67)	3.21 (0.68)
LDL cholesterol level at end of follow-up Mean (SD)	2.85 (NR)	3.36 (NR)
Reduction in LDL cholesterol (absolute) Mean (SD)	NR (NR)	NR (NR)

Outcomes

Study timepoints

- Baseline
- 59.8 month (Mean follow up)

Adverse effects - dichotomous outcome

Outcome	Statins - Rosuvastatin (high intensity), Baseline, N = 366	Statins - Rosuvastatin (high intensity), 59.8 month, N = 366	Placebo, Baseline, N = 366	Placebo, 59.8 month, N = 366
Cognitive decline Defined as changes in the MMSE score and/or DRS score. Mean 95% CI is actually the CI for the hazard ratio comparing between the arms. No of events	-	n = 39 ; % = 10.7	-	n = 68 ; % = 18.8
Cognitive decline Defined as changes in the MMSE score and/or DRS score. Mean 95% CI is actually the CI for the hazard ratio comparing between the arms. Hazard ratio	NA	0.54	NA	NA
Cognitive decline Defined as changes in the MMSE score and/or DRS score. Mean 95% CI is actually the CI for the hazard ratio comparing between the arms. Mean (95% CI)	NA (NA to NA)	NA (0.36 to 0.8)	NA (NA to NA)	NA (NA to NA)

Cognitive decline - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)
Cognitive decline-Rosuvastatin (high intensity)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Cognitive decline-custom-Rosuvastatin (high intensity)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Zhao, 2014

Bibliographic Reference	Zhao, S. P.; Yu, B. L.; Peng, D. Q.; Huo, Y.; The effect of moderate-dose versus double-dose statins on patients with acute coronary syndrome in China: Results of the CHILLAS trial; Atherosclerosis; 2014; vol. 233 (no. 2); 707-712

Study details

Secondary publication of another included study- see primary study for details	**No additional information.**
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Outpatient follow up
Study dates	November 2007 to November 2010
Sources of funding	This study was sponsored by "The 11th Five-Year Plan" of PR China.
Inclusion criteria	18-80 years of age; hospitalised for acute myocardial infarction or unstable angina pectoris; clinically stable for 24 hours.
Exclusion criteria	Hypersensitive to statin; receiving therapy with atorvastatin at a dose greater than 20mg/day (or equivalent dose of other statins) before enrolment or treatment with other lipid-lowering drugs such as fibric acid derivatives or niacin that could not be discontinued; life expectancy <2 years due to a coexisting condition; in the final stage of chronic congestive heart failure; have obstructive hepatobilliary disease or other serious hepatic or kidney diseases; have an unexplained elevation in creatine kinase level more than 3 times the upper limit of normal and not related to myocardial infarction; have undergone surgery or serious trauma within the preceding 2 month; have a baseline level of LDL cholesterol less than 1.29 mmol/L (50mg/dL).
Recruitment / selection of participants	No additional information.
Intervention(s)	Statins - Atorvastatin (high intensity) N=680

	Oral atorvastatin 20-40mg/day (or equivalent dose of other statins). Concomitant therapy: People were treated with optimized current medication and interventional therapy for acute coronary syndromes, in that angiotensin-converting enzyme inhibitors, beta-blockers, aspirin and clopidogrel were administered to the majority of people when indicated. All people received ongoing counselling on therapeutic lifestyle modifications. People were not permitted to be treated with any lipid-modifying agent other than the study drug.
Population subgroups	Different agents/doses within each intensity class: High intensity vs. medium intensity Primary versus secondary prevention: Secondary prevention Presence versus absence of chronic kidney disease: Not stated/unclear Age (<75 versus ≥75): <75 (mean was 60.8 in the high intensity group, 60.4 in the medium intensity group)) Sex: Predominantly male (76.7% in the high intensity group, 77.0% in the medium intensity group) Ethnicity/family origin (black, Asian, white, mixed, other): Not stated/unclear Presence versus absence of autoimmune disease: Not stated/unclear
Comparator	Statins - Atorvastatin (medium intensity) N=675 Oral atorvastatin 10mg/day (or equivalent dose of other statins). Concomitant therapy: People were treated with optimized current medication and interventional therapy for acute coronary syndromes, in that angiotensin-converting enzyme inhibitors, beta-blockers, aspirin and clopidogrel were administered to the majority of people when indicated. All people received ongoing counselling on therapeutic lifestyle modifications. People were not permitted to be treated with any lipid-modifying agent other than the study drug.
Number of participants	1355
Duration of follow-up	Median follow up for 2 years
Indirectness	No additional information
Additional comments	Method of analysis unclear.

Study arms

Statins - Atorvastatin (high intensity) (N = 680)

Oral atorvastatin 20-40mg/day (or equivalent dose of other statins). Concomitant therapy: People were treated with optimized current medication and interventional therapy for acute coronary syndromes, in that angiotensin-converting enzyme inhibitors, beta-blockers, aspirin and clopidogrel were administered to the majority of people when indicated. All people received ongoing counselling on therapeutic lifestyle modifications. People were not permitted to be treated with any lipid-modifying agent other than the study drug.

Statins - Atorvastatin (medium intensity) (N = 675)

Oral atorvastatin 10mg/day (or equivalent dose of other statins). Concomitant therapy: People were treated with optimized current medication and interventional therapy for acute coronary syndromes, in that angiotensin-converting enzyme inhibitors, beta-blockers, aspirin and clopidogrel were administered to the majority of people when indicated. All people received ongoing counselling on therapeutic lifestyle modifications. People were not permitted to be treated with any lipid-modifying agent other than the study drug.

Characteristics

Arm-level characteristics

Characteristic	Statins - Atorvastatin (high intensity) (N = 680)	Statins - Atorvastatin (medium intensity) (N = 675)
% Female Sample size	n = 158 ; % = 23.2	n = 155 ; % = 23
Mean age (SD) (years) Mean (SD)	60.8 (10.4)	60.4 (10.6)
Age over 75 years Sample size	NR	NR
Ethnicity Sample size	NR	NR
Existing CVD diagnoses Sample size	-	-
ST-elevation Sample size	n = 278 ; % = 40.9	n = 273 ; % = 40.4
Non-ST-elevation Sample size	n = 402 ; % = 59.1	n = 402 ; % = 59.6
Congestive heart failure Sample size	n = 24 ; % = 4	n = 29 ; % = 4.9
Coronary artery bypass graft Sample size	n = 2 ; % = 0.3	n = 2 ; % = 0.3
Percutaneous transluminal coronary angioplasty Sample size	n = 372 ; % = 64.2	n = 366 ; % = 63.6
Hypertension	n = 369 ; % = 61	n = 364 ; % = 60

Sample size		
Type 2 diabetes Sample size	n = 123 ; % = 21	n = 144 ; % = 24
Chronic kidney disease Sample size	NR	NR
Family history of CVD Sample size	n = 30 ; % = 4.54	n = 29 ; % = 4
Autoimmune disease Sample size	NR	NR
Serious mental illness Sample size	NR	NR
Socioeconomic group Sample size	NR	NR
LDL cholesterol level at baseline (mmol/L) Mean (SD)	2.72 (0.82)	2.71 (0.91)
LDL cholesterol level at the end of follow-up (mmol/L) Mean (SD)	1.99 (0.74)	2.17 (0.75)
Reduction in LDL cholesterol (absolute) Sample size	NR	NR

Outcomes

Study timepoints

- Baseline
- 2 year (Median follow up)

Efficacy - dichotomous outcome

Outcome	Statins - Atorvastatin (high intensity), Baseline, N = 680	Statins - Atorvastatin (high intensity), 2 year, N = 680	Statins - Atorvastatin (medium intensity), Baseline, N = 675	Statins - Atorvastatin (medium intensity), 2 year, N = 675

Combined major adverse cardiovascular events Includes cardiac death, non-fatal acute myocardial infarction, revascularisation with either PCI or CABG at least 30 days after randomisation, documented unstable angina or severe heart failure requiring emergency rehospitalisation, ischaemic stroke. No of events	-	n = 28 ; % = 5.5	-	n = 20 ; % = 3.9

Combined major adverse cardiovascular events - Polarity - Lower values are better

Efficacy - time to event outcome

Outcome	Statins - Atorvastatin (high intensity) vs Statins - Atorvastatin (medium intensity), Baseline, N2 = 680, N1 = 675	Statins - Atorvastatin (high intensity) vs Statins - Atorvastatin (medium intensity), 2 year, N2 = 680, N1 = 675
Combined major cardiovascular adverse events Includes cardiac death, non-fatal acute myocardial infarction, revascularisation with either PCI or CABG at least 30 days after randomisation, documented unstable angina or severe heart failure requiring emergency rehospitalisation, ischaemic stroke. Hazard ratio	NA	1.39
Combined major cardiovascular adverse events Includes cardiac death, non-fatal acute myocardial infarction, revascularisation with either PCI or CABG at least 30 days after randomisation, documented unstable angina or severe heart failure requiring emergency rehospitalisation, ischaemic stroke. Mean (95% CI)	NA (NA to NA)	NA (0.78 to 2.46)

Combined major cardiovascular adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (efficacy)
Efficacy-MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Efficacy-time-to-event outcome-MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Outcomes

Study timepoints

- Baseline
- 2 year (Median follow up)

Adverse effects - Dichotomous outcomes

Outcome	Statins - Atorvastatin (high intensity), Baseline, N = 680	Statins - Atorvastatin (high intensity), 2 year, N = 680	Statins - Atorvastatin (medium intensity) , Baseline, N = 675	Statins - Atorvastatin (medium intensity) , 2 year, N = 675
Rhabdomyolysis (CK >10 times normal) No of events	-	n = 0 ; % = 0	-	n = 0 ; % = 0
Liver (transaminases >3 times normal level) ALT >3 times upper limit of normal No of events	-	n = 13 ; % = 1.9	-	n = 10 ; % = 1.5
Haemorrhagic stroke (cerebral haemorrhage) No of events	-	n = 0 ; % = 0	-	n = 2 ; % = 0.3

Rhabdomyolysis (CK >10 times normal) - Polarity - Lower values are better

Liver (transaminases >3 times normal level) - Polarity - Lower values are better

Haemorrhagic stroke (cerebral haemorrhage) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (adverse effects)

Rhabdomyolysis(CK>10timesnormal) - Atorvastatin (high vs medium intensity)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Liver (transaminases>3timesnormallevel)- Atorvastatin (high vs medium intensity)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Haemorrhagic stroke (cerebral haemorrhage)-Atorvastatin (high vs medium intensity)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

D.3 Systematic reviews

Blazing, 2022

Bibliographic Reference

Blazing, Michael; Braunwald, Eugene; de Lemos, James; Murphy, Sabina; Pedersen, Terje; Pfeffer, Marc; White, Harvey; Wiviott, Stephen; Clearfield, Michael; Downs, John R; Gotto; Jr, Antonio; Weis, Stephen; Fellström, Bengt; Holdaas, Hallvard; Jardine, Alan; Gordon, David; Davis, Barry; Furberg, Curt; Grimm, Richard; Pressel, Sara; Probstfield, Jeffrey; Rahman, Mahboob; Simpson, Lara; Koren, Michael; Dahlöf, Björn; Gupta, Ajay; Poulter, Neil; Sever, Peter; Wedel, Hans; Knopp, Robert; Cobbe, Stuart; Schmieder, Roland; Zannad, Faiez; Betteridge, D John; Colhoun, Helen; Durrington, Paul; Fuller, John; Hitman, Graham A; Neil, Andrew; Hawkins, C Morton; Moyé, Lemuel; Sacks, Frank; Kjekshus, John; Wikstrand, John; Wanner, Christoph; Krane, Vera; Franzosi, Maria Grazia; Latini, Roberto; Lucci, Donata; Maggioni, Aldo; Marchioli, Roberto; Nicolis, Enrico; Tavazzi, Luigi; Tognoni, Gianni; Bosch, Jackie; Lonn, Eva; Yusuf, Salim; Armitage, Jane; Bowman, Louise; Collins, Rory; Keech, Anthony; Landray, Martin; Parish, Sarah; Peto, Richard; Sleight, Peter; Kastelein, John; Glynn, Robert; Koenig, Wolfgang; MacFadyen, Jean; Ridker, Paul; MacMahon, Stephen; Marschner, Ian; Tonkin, Andrew; Shaw, John; Simes, John; Serruys, Patrick; Knatterud, Genell; Ford, Ian; MacFarlane, Peter; Packard, Chris; Sattar, Naveed; Shepherd, James; Trompet, Stella; Cannon, Christopher P; Amarenco, Pierre; Welch, K Michael; Wilhelmsen, Lars; Barter, Philip; LaRosa, John; Kean, Sharon; Robertson, Michele; Young, Robin; Arashi, Hiroyuki; Clarke, Robert; Flather, Marcus; Goto, Shinya; Goldbourt, Uri; Hopewell, Jemma; Hovingh, Kees; Kitas, George; Newman, Connie; Sabatine, Marc S; Schwartz, Greg; Smeeth, Liam; Tobert, Jonathan; Varigos, John; Yamaguchi, Junichi; Kearney, Patricia; Jukema, J Wouter; Byington, Robert; Effect of statin therapy on muscle symptoms: an individual participant data meta-analysis of large-scale, randomised, double-blind trials; The Lancet; 2022; vol. 400 (no. 10355); 832-845

Study Characteristics

Study design	Systematic review
Study details	Dates searched No details given Databases searched No details given Sources of funding British Heart Foundation, Medical Research Council, Australian National Health and Medical Research Council
Study and participant inclusion criteria	All RCTs of statin therapy with more than 1000 participants and a scheduled mean follow-up of 2 years or more Double-blind comparison of statin versus placebo or of more intensive statin versus less intensive statin regimens
Study and participant exclusion criteria	Not reported
Intervention(s)	Statin Placebo Higher intensity statin

	Lower intensity statin
Outcome(s)	Any muscle pain Myalgia, limb pain, other musculoskeletal pain, muscle cramp or spasm
Number of studies included in the systematic review	Statin vs placebo: 19 RCTs Higher intensity statin vs lower intensity statin: 4 RCTs
Studies from the systematic review that are relevant for use in the current review	4S 1989 Statin vs placebo WOSCOPS 1991 Statin vs placebo CARE 1991 Statin vs placebo LIPID 1992 Statin vs placebo HPS 1997 Statin vs placebo LIPS 1998 Statin vs placebo PROSPER 1999 Statin vs placebo ASPEN 1999 Statin vs placebo ASCOT-LLA 2000 Statin vs placebo CARDS 2001 Statin vs placebo SPARCL 2001 Statin vs placebo JUPITER 2006 Statin vs placebo HOPE-3 2010 Statin vs placebo

	TNT 1999 Higher intensity vs lower intensity statin PROVE-IT 2001 Higher intensity vs lower intensity statin IDEAL 2005
Studies from the systematic review that are not relevant for use in the current review	AFCAPS/TexCAPS 1993 Statin vs placebo ALERT 1997 Statin vs placebo 4D 2002 Statin vs placebo AURORA 2004 Statin vs placebo CORONA 2005 Statin vs placebo GISSI-HF 2005 Statin vs placebo A to Z 2003 Higher intensity vs lower intensity statin SEARCH 2001 Higher intensity vs lower intensity statin

Study arms
Statin (N = 62028)
Placebo (N = 61912)

Higher intensity statin (N = 15390)

Lower intensity statin (N = 15334)

Outcomes

Study timepoints

- 5.9 year (From equal to or greater then 2 years up to 5.9 years for relevant studies in SR)

Any muscle pain

Outcome	Statin, 5.9 year, N = 62028	Placebo, 5.9 year, N = 61912	Higher intensity statin, 5.9 year, N = 15390	Lower intensity statin, 5.9 year, N = 15334
4S 1989 No of events	n = 307 ; % = 13.8	n = 311 ; % = 14	n = NA	n = NA
WOSCOPS 1991 No of events	n = 2067 ; % = 62.6	n = 2052 ; % = 62.3	n = NA	n = NA
CARE 1991 No of events	n = 1307 ; % = 62.8	n = 1292 ; % = 62.2	n = NA	n = NA
LIPID 1992 No of events	n = 137 ; % = 3	n = 146 ; % = 3.2	n = NA	n = NA
HPS 1997 No of events	n = 3561 ; % = 34.7	n = 3574 ; % = 34.8	n = NA	n = NA
LIPS 1998 No of events	n = 46 ; % = 5.5	n = 51 ; % = 6.2	n = NA	n = NA
PROSPER 1999 No of events	n = 1889 ; % = 65.3	n = 1850 ; % = 63.5	n = NA	n = NA
ASPEN 1999 No of events	n = 324 ; % = 26.8	n = 281 ; % = 23.4	n = NA	n = NA
ASCOT-LLA 2000 No of events	n = 916 ; % = 17.8	n = 911 ; % = 17.8	n = NA	n = NA
CARDS 2001 No of events	n = 544 ; % = 38.1	n = 533 ; % = 37.8	n = NA	n = NA
SPARCL 2001 No of events	n = 598 ; % = 25.3	n = 616 ; % = 26	n = NA	n = NA
JUPITER 2006 No of events	n = 1815 ; % = 21.7	n = 1627 ; % = 19.5	n = NA	n = NA

HOPE-3 2010 No of events	n = 417 ; % = 6.6	n = 351 ; % = 5.5	n = NA	n = NA
TNT 1999 No of events	n = NA	n = NA	n = 1944 ; % = 38.9	n = 1857 ; % = 37.1
PROVE-IT 2001 No of events	n = NA	n = NA	n = 623 ; % = 29.7	n = 609 ; % = 29.5
4S 1989 No of events	n = 2 ; % = 0.09	n = 4 ; % = 0	n = NA	n = NA
WOSCOPS 1991 No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = NA	n = NA
CARE 1991 No of events	n = 2 ; % = 0.096	n = 0 ; % = 0	n = NA	n = NA
LIPID 1992 No of events	n = 5 ; % = 0.089	n = 2 ; % = 0.044	n = NA	n = NA
HPS 1997 No of events	n = 10 ; % = 0.097	n = 4 ; % = 0	n = NA	n = NA
LIPS 1998 No of events	n = 1 ; % = 0.12	n = 1 ; % = 0.12	n = NA	n = NA
PROSPER 1999 No of events	n = 1 ; % = 0.035	n = 1 ; % = 0.034	n = NA	n = NA
ASPEN 1999 No of events	n = 0 ; % = 0	n = 1 ; % = 0.083	n = NA	n = NA
ASCOT-LLA 2000 No of events	n = 1 ; % = 0.019	n = 0 ; % = 0	n = NA	empty data
CARDS 2001 No of events	n = 1 ; % = 0.07	n = 0 ; % = 0	n = NA	n = NA
SPARCL 2001 No of events	n = 6 ; % = 0.25	n = 5 ; % = 0.21	n = NA	n = NA
JUPITER 2006 No of events	n = 3 ; % = 0.034	n = 0 ; % = 0	n = NA	n = NA

HOPE-3 2010 No of events	n = 2 ; % = 0.031	n = 1 ; % = 0.016	n = NA	n = NA
TNT 1999 No of events	n = NA	n = NA	n = 11 ; % = 0.22	n = 11 ; % = 0.22
PROVE-IT 2001 No of events	n = NA	n = NA	n = 2 ; % = 0.95	n = 0 ; % = 0

Any muscle pain - Polarity - Lower values are better

Myalgia, limb pain, other musculoskeletal pain, muscle cramp or spasm

Critical appraisal - ROBIS checklist (adverse effects)

Section	Question	Answer
Overall study ratings	Overall risk of bias	Moderate (Unclear how studies were selected for inclusion (no details in main study and protocol publication)
Overall study ratings	Applicability as a source of data	Fully applicable

Swerdlow, 2015

Bibliographic Reference

Swerdlow, D. I.; Preiss, D.; Kuchenbaecker, K. B.; Holmes, M. V.; Engmann, J. E.; Shah, T.; Sofat, R.; Stender, S.; Johnson, P. C.; Scott, R. A.; Leusink, M.; Verweij, N.; Sharp, S. J.; Guo, Y.; Giambartolomei, C.; Chung, C.; Peasey, A.; Amuzu, A.; Li, K.; Palmen, J.; Howard, P.; Cooper, J. A.; Drenos, F.; Li, Y. R.; Lowe, G.; Gallacher, J.; Stewart, M. C.; Tzoulaki, I.; Buxbaum, S. G.; van der, A. Dl; Forouhi, N. G.; Onland-Moret, N. C.; van der Schouw, Y. T.; Schnabel, R. B.; Hubacek, J. A.; Kubinova, R.; Baceviciene, M.; Tamosiunas, A.; Pajak, A.; Topor-Madry, R.; Stepaniak, U.; Malyutina, S.; Baldassarre, D.; Sennblad, B.; Tremoli, E.; de Faire, U.; Veglia, F.; Ford, I.; Jukema, J. W.; Westendorp, R. G.; de Borst, G. J.; de Jong, P. A.; Algra, A.; Spiering, W.; Maitland-van der Zee, A. H.; Klungel, O. H.; de Boer, A.; Doevendans, P. A.; Eaton, C. B.; Robinson, J. G.; Duggan, D.; Kjekshus, J.; Downs, J. R.; Gotto, A. M.; Keech, A. C.; Marchioli, R.; Tognoni, G.; Sever, P. S.; Poulter, N. R.; Waters, D. D.; Pedersen, T. R.; Amarenco, P.; Nakamura, H.; McMurray, J. J.; Lewsey, J. D.; Chasman, D. I.; Ridker, P. M.; Maggioni, A. P.; Tavazzi, L.; Ray, K. K.; Seshasai, S. R.; Manson, J. E.; Price, J. F.; Whincup, P. H.; Morris, R. W.; Lawlor, D. A.; Smith, G. D.; Ben-Shlomo, Y.; Schreiner, P. J.; Fornage, M.; Siscovick, D. S.; Cushman, M.; Kumari, M.; Wareham, N. J.; Verschuren, W. M.; Redline, S.; Patel, S. R.; Whittaker, J. C.; Hamsten, A.; Delaney, J. A.; Dale, C.; Gaunt, T. R.; Wong, A.; Kuh, D.; Hardy, R.; Kathiresan, S.; Castillo, B. A.; van der Harst, P.; Brunner, E. J.; Tybjaerg-Hansen, A.; Marmot, M. G.; Krauss, R. M.; Tsai, M.; Coresh, J.; Hoogeveen, R. C.; Psaty, B. M.; Lange, L. A.; Hakonarson, H.; Dudbridge, F.; Humphries, S. E.; Talmud, P. J.; Kivimäki, M.; Timpson, N. J.; Langenberg, C.; Asselbergs, F. W.; Voevoda, M.; Bobak, M.; Pikhart, H.; Wilson, J. G.; Reiner, A. P.; Keating, B. J.; Hingorani, A. D.; Sattar, N.; HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials; Lancet; 2015; vol. 385 (no. 9965); 351-61

Study Characteristics

Study design	Systematic review
Study details	Dates searched No details given Databases searched No details given Sources of funding Academy of Finland, British Heart Foundation, Chest, Heart and Stroke Scotland, Chief Physician Johan Boserup and Lise Boserup's Fund, Danish Medical Research Council, Diabetes UK, EU/EFPIA Innovative Medicines Initiative Joint Undertaking, Foundation for Old Servant, Magnus Bergvall Foundation, Medical Research Council, Ministry of Health, Czech Republic, National Heart, Lung and Blood Institute, National Institutes of Health, National Institute on Aging, National Institute on Minority Health and Health Disparities of the NIH, Netherlands Organisation for Health Research and Development, Research Fund at Rigshospitalet, Copenhagen University Hospital, University College London NIHR Biomedical Research Centre, Wellcome Trust
Study and participant inclusion criteria	RCTs of at least 1000 participants, followed up for at least 1 year
Study and participant exclusion criteria	RCTs of participants with organ transplants or on dialysis RCTs with differences in participant follow-up between treatment arms RCTs investigating dual lipid-lowering therapy
Intervention(s)	Statin Placebo Higher intensity statin Lower intensity statin
Outcome(s)	New-onset type 2 diabetes Diagnostic criteria for type 2 diabetes varied among the 20 contributing RCTs, but included one or more of, (i) physician-reported diagnosis of type 2 diabetes; (ii) commencement of glucose-lowering medication; or, (iii) fasting glucose >7.0mmol/L (on at least one occasion, and (iv) type 2 diabetes defined according to World Health Organisation 1999 criteria
Number of studies included in the systematic review	Statin vs placebo: 15 RCTs Higher intensity statin vs lower intensity statin: 5 RCTs
Studies from the systematic review that are relevant for	4S 1989 Statin vs placebo WOSCOPS 1991

use in the current review	Statin vs placebo LIPID 1992 Statin vs placebo HPS 1997 Statin vs placebo LIPS 1998 Statin vs placebo PROSPER 1999 Statin vs placebo ASCOT-LLA 2000 Statin vs placebo SPARCL 2001 Statin vs placebo JUPITER 2006 Statin vs placebo HOPE-3 2010 TNT 1999 Higher intensity statin vs lower intensity statin PROVE-IT 2001 Higher intensity statin vs lower intensity statin IDEAL 2005
Studies from the systematic review that are not relevant for use in the current review	AFCAPS/TexCAPS 1993 Statin vs placebo CORONA 2005 Statin vs placebo GISSI-HF 2005 Statin vs placebo A to Z 2003 High intensity vs lower intensity statin SEARCH 2001 High intensity vs lower intensity statin GISSI-Prevenzione 2000

	Statin vs placebo ALLHAT-LLT 2002 Statin vs placebo MEGA 2006 Statin vs placebo
Additional comments	

Study arms
Statin (N = 48150)

Placebo (N = 48268)

Higher intensity statin (N = 16408)

Lower intensity statin (N = 16344)

Outcomes
Study timepoints
- 4.2 year (Range: 1·9 to 6·7 years)

Type 2 diabetes

Outcome	Statin, 4.2 year, N = 48150	Placebo, 4.2 year, N = 48268	Higher intensity statin, 4.2 year, N = 16408	Lower intensity statin, 4.2 year, N = 16344
New onset type 2 diabetes Diagnostic criteria for type 2 diabetes varied among the 20 contributing RCTs, but included one or more of, (i) physician-reported diagnosis of type 2 diabetes; (ii) commencement of glucose-lowering medication; or, (iii) fasting glucose >7.0mmol/L (on at least one occasion, and (iv) type 2 diabetes defined according to World Health Organisation 1999 criteria No of events	n = 2409 ; % = 5	n = 2181 ; % = 4.5	n = 1448 ; % = 8.8	n = 1300 ; % = 8

4S 1989 No of events	n = 198 ; % = 10.32	n = 193 ; % = 9.98	n = NA	n = NA
WOSCOPS 1991 No of events	n = 75 ; % = 2.56	n = 93 ; % = 3.23	n = NA	n = NA
LIPID 1992 No of events	n = 198 ; % = 3.74	n = 138 ; % = 4.1	n = NA	n = NA
LIPS 1998 No of events	n = 17 ; % = 2.4	n = 14 ; % = 1.9	n = NA	n = NA
PROSPER 1999 No of events	n = 165 ; % = 7.03	n = 127 ; % = 5.32	n = NA	n = NA
ASCOT-LLA 2000 No of events	n = 154 ; % = 4.1	n = 134 ; % = 3.59	n = NA	n = NA
SPARCL 2001 No of events	n = 166 ; % = 9.55	n = 115 ; % = 6.45	n = NA	n = NA
JUPITER 2006 No of events	n = 270 ; % = 3.13	n = 216 ; % = 2.49	n = NA	n = NA
HOPE-3 2010 No of events	n = 232 ; % = 3.88	n = 226 ; % = 3.77	n = NA	n = NA
TNT 1999 No of events	n = NA	n = NA	n = 418 ; % = 11	n = 358 ; % = 9.43
PROVE-IT 2001 No of events	n = NA	n = NA	n = 101 ; % = 5.92	n = 99 ; % = 5.86
IDEAL 2005 No of events	empty data	empty data	n = 240 ; % = 6.42	n = 209 ; % = 5.61

New onset type 2 diabetes - Polarity - Lower values are better

Diagnostic criteria for type 2 diabetes varied among the 20 contributing RCTs, but included one or more of, (i) physician-reported diagnosis of type 2 diabetes; (ii) commencement of glucose-lowering medication; or, (iii) fasting glucose >7.0mmol/L (on at least one occasion, and (iv) type 2 diabetes defined according to World Health Organisation 1999 criteria

Critical appraisal - ROBIS checklist (adverse effects)

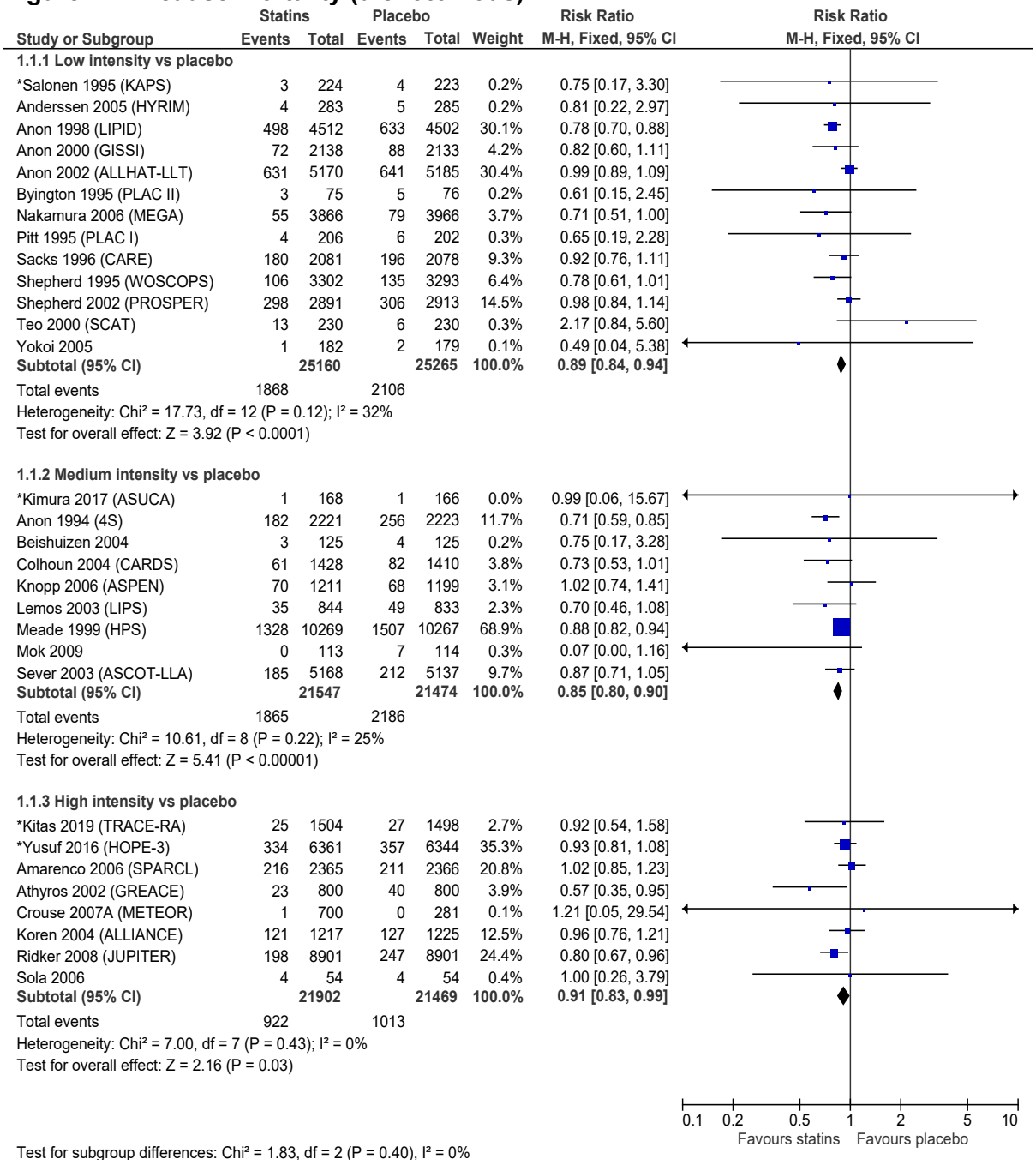
Section	Question	Answer
Overall study ratings	Overall risk of bias	Moderate
Overall study ratings	Applicability as a source of data	Fully applicable

Appendix E – Forest plots

E.1 Efficacy

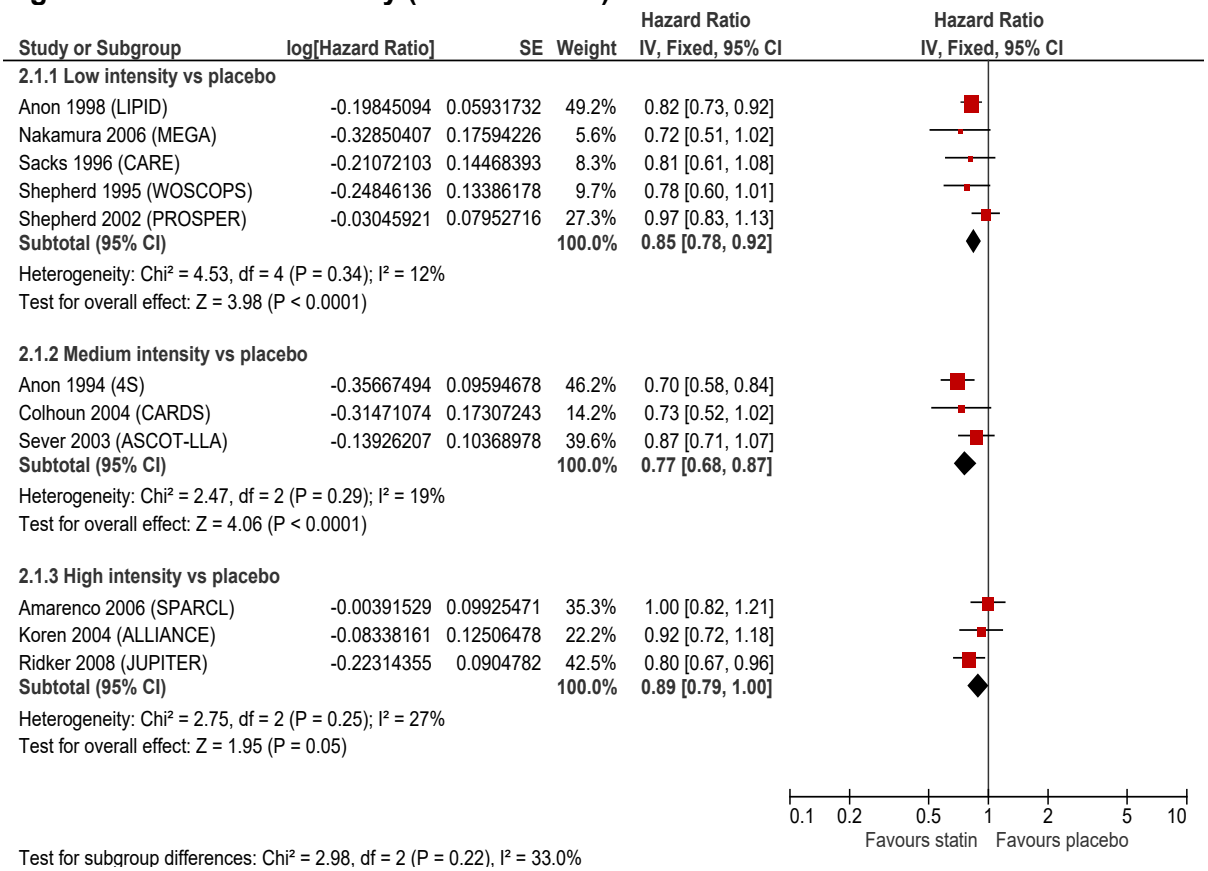
E.1.1 Statins versus placebo

Figure 2: All-cause mortality (dichotomous)



**Indicates studies added during the 2023 update*

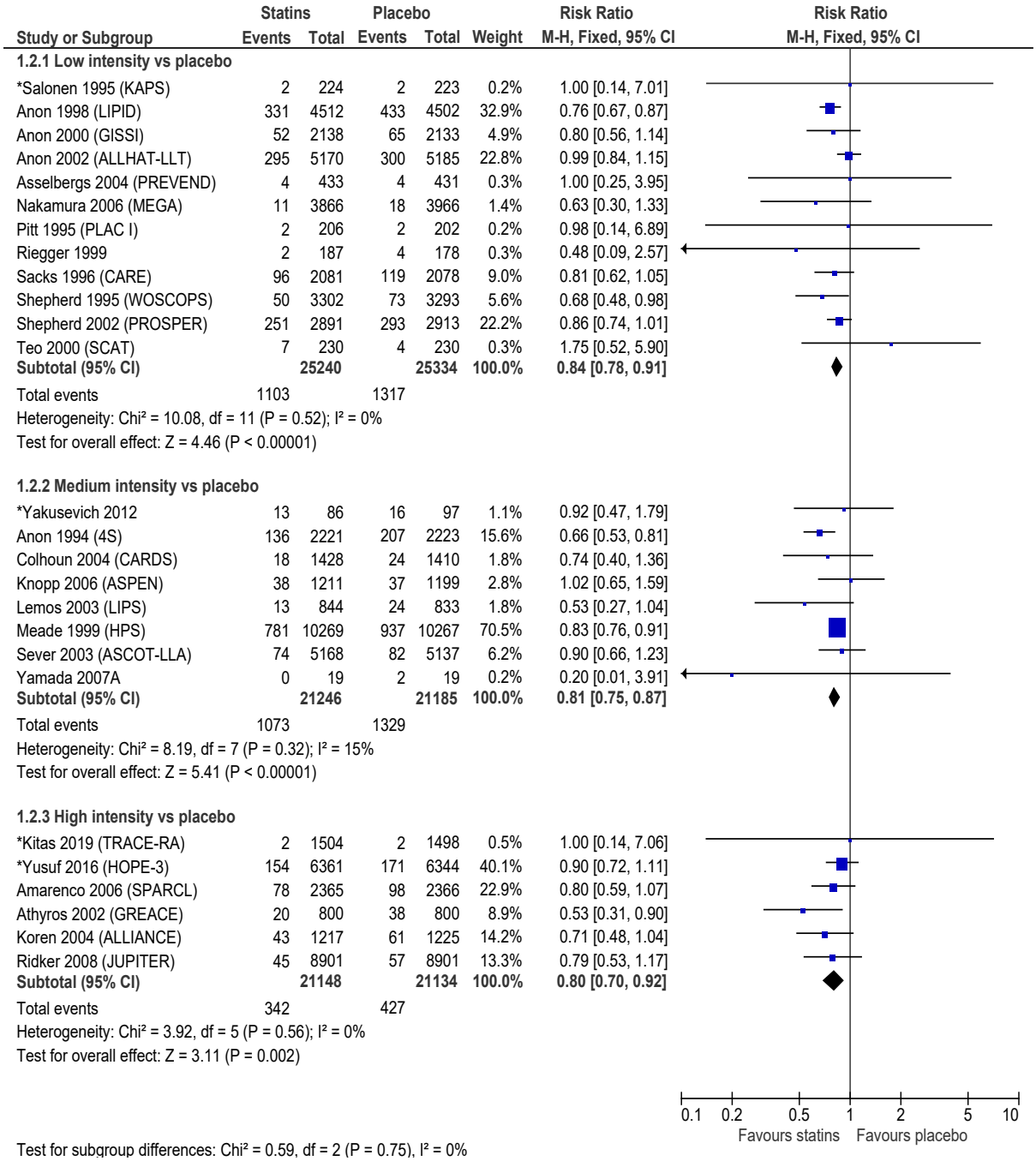
Figure 3: All-cause mortality (time-to-event)



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
2.1.1 Low intensity vs placebo				
Anon 1998 (LIPID)	-0.19845094	0.05931732	49.2%	0.82 [0.73, 0.92]
Nakamura 2006 (MEGA)	-0.32850407	0.17594226	5.6%	0.72 [0.51, 1.02]
Sacks 1996 (CARE)	-0.21072103	0.14468393	8.3%	0.81 [0.61, 1.08]
Shepherd 1995 (WOSCOPS)	-0.24846136	0.13386178	9.7%	0.78 [0.60, 1.01]
Shepherd 2002 (PROSPER)	-0.03045921	0.07952716	27.3%	0.97 [0.83, 1.13]
Subtotal (95% CI)			**100.0%**	**0.85 [0.78, 0.92]**
Heterogeneity: Chi² = 4.53, df = 4 (P = 0.34); I² = 12%				
Test for overall effect: Z = 3.98 (P < 0.0001)				
2.1.2 Medium intensity vs placebo				
Anon 1994 (4S)	-0.35667494	0.09594678	46.2%	0.70 [0.58, 0.84]
Colhoun 2004 (CARDS)	-0.31471074	0.17307243	14.2%	0.73 [0.52, 1.02]
Sever 2003 (ASCOT-LLA)	-0.13926207	0.10368978	39.6%	0.87 [0.71, 1.07]
Subtotal (95% CI)			**100.0%**	**0.77 [0.68, 0.87]**
Heterogeneity: Chi² = 2.47, df = 2 (P = 0.29); I² = 19%				
Test for overall effect: Z = 4.06 (P < 0.0001)				
2.1.3 High intensity vs placebo				
Amarenco 2006 (SPARCL)	-0.00391529	0.09925471	35.3%	1.00 [0.82, 1.21]
Koren 2004 (ALLIANCE)	-0.08338161	0.12506478	22.2%	0.92 [0.72, 1.18]
Ridker 2008 (JUPITER)	-0.22314355	0.0904782	42.5%	0.80 [0.67, 0.96]
Subtotal (95% CI)			**100.0%**	**0.89 [0.79, 1.00]**
Heterogeneity: Chi² = 2.75, df = 2 (P = 0.25); I² = 27%				
Test for overall effect: Z = 1.95 (P = 0.05)				

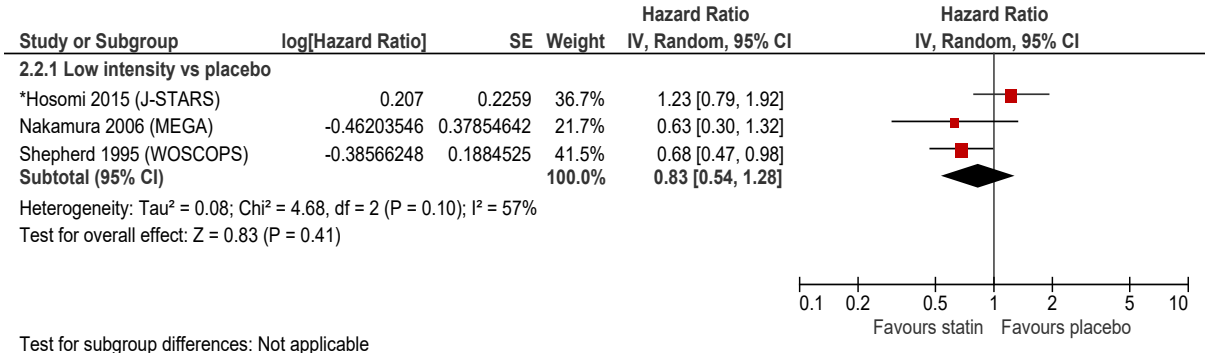
Test for subgroup differences: Chi² = 2.98, df = 2 (P = 0.22), I² = 33.0%

Figure 4: Cardiovascular mortality (dichotomous)



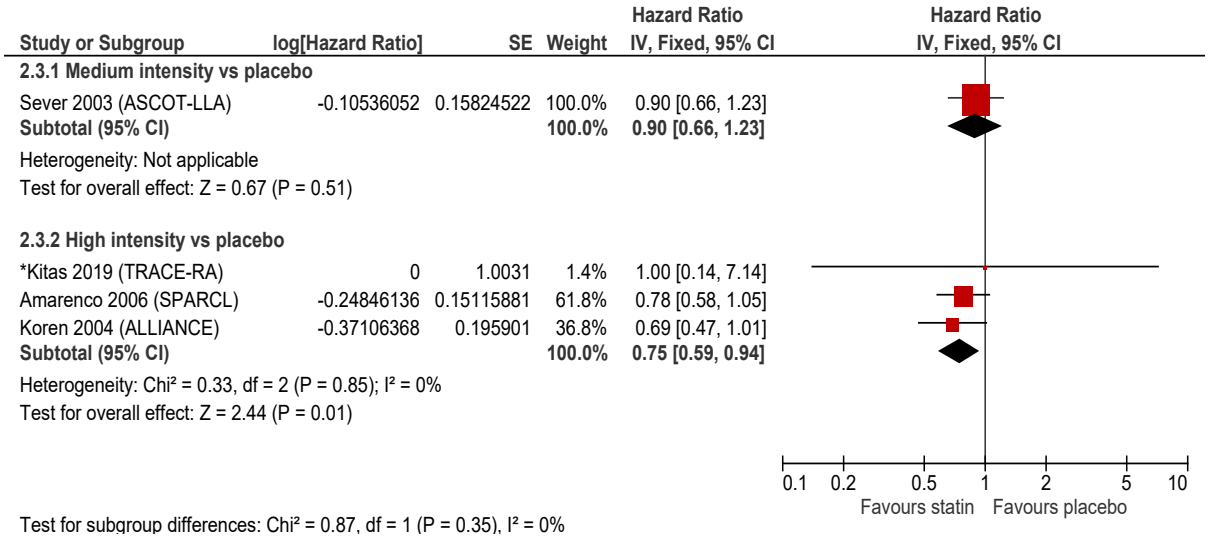
**Indicates studies added during the 2023 update*

Figure 5: Cardiovascular mortality (time-to-event)



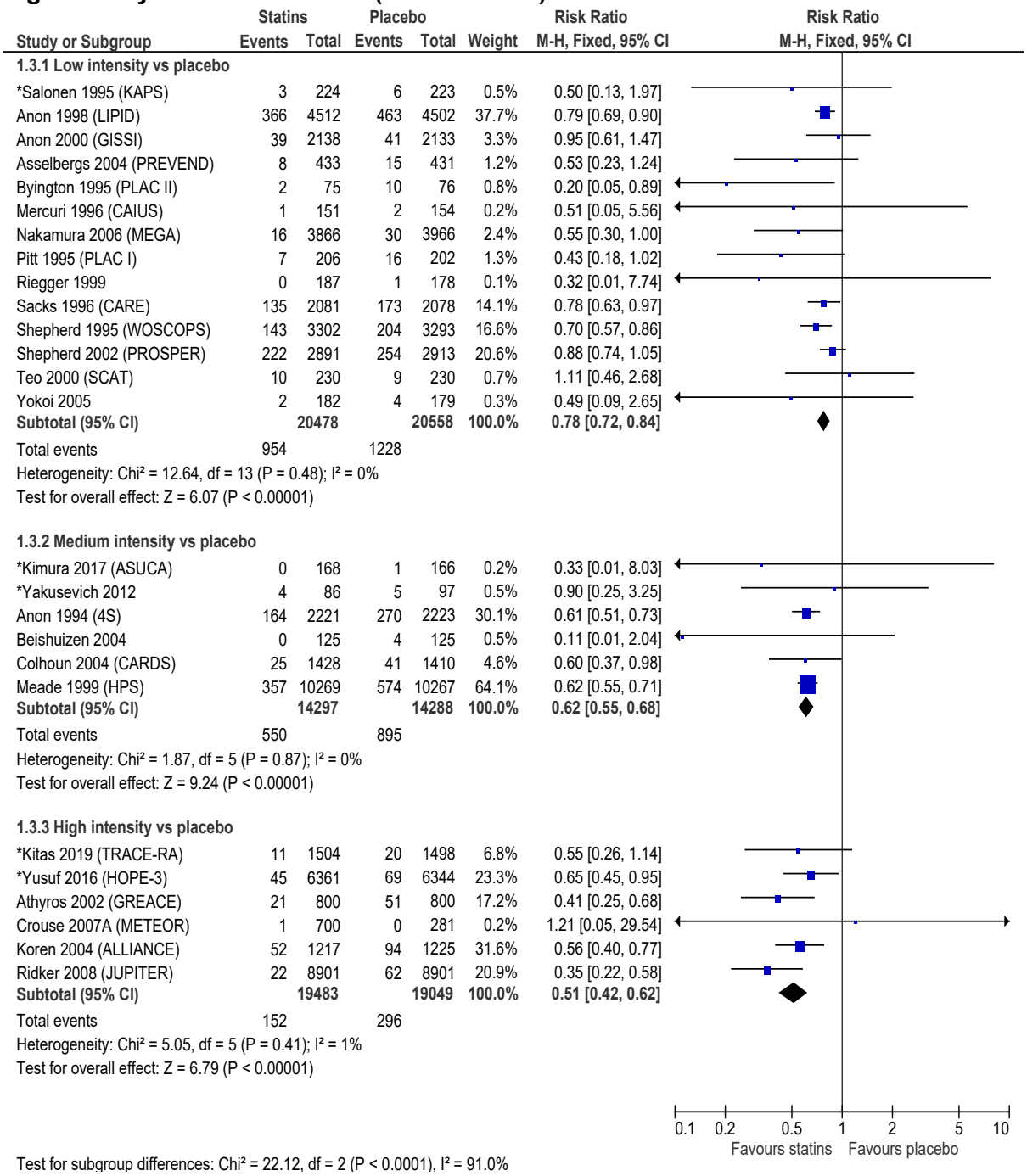
**Indicates studies added during the 2023 update*

Figure 6: Cardiovascular mortality (time-to-event)



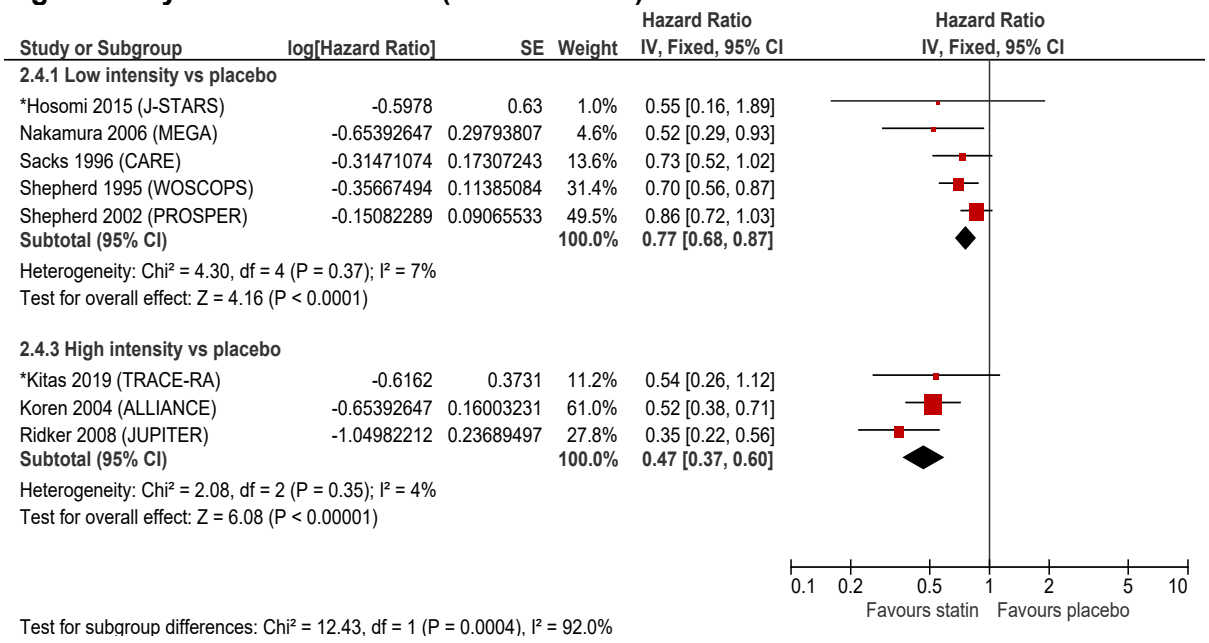
**Indicates studies added during the 2023 update*

Figure 7: Myocardial infarction (dichotomous)



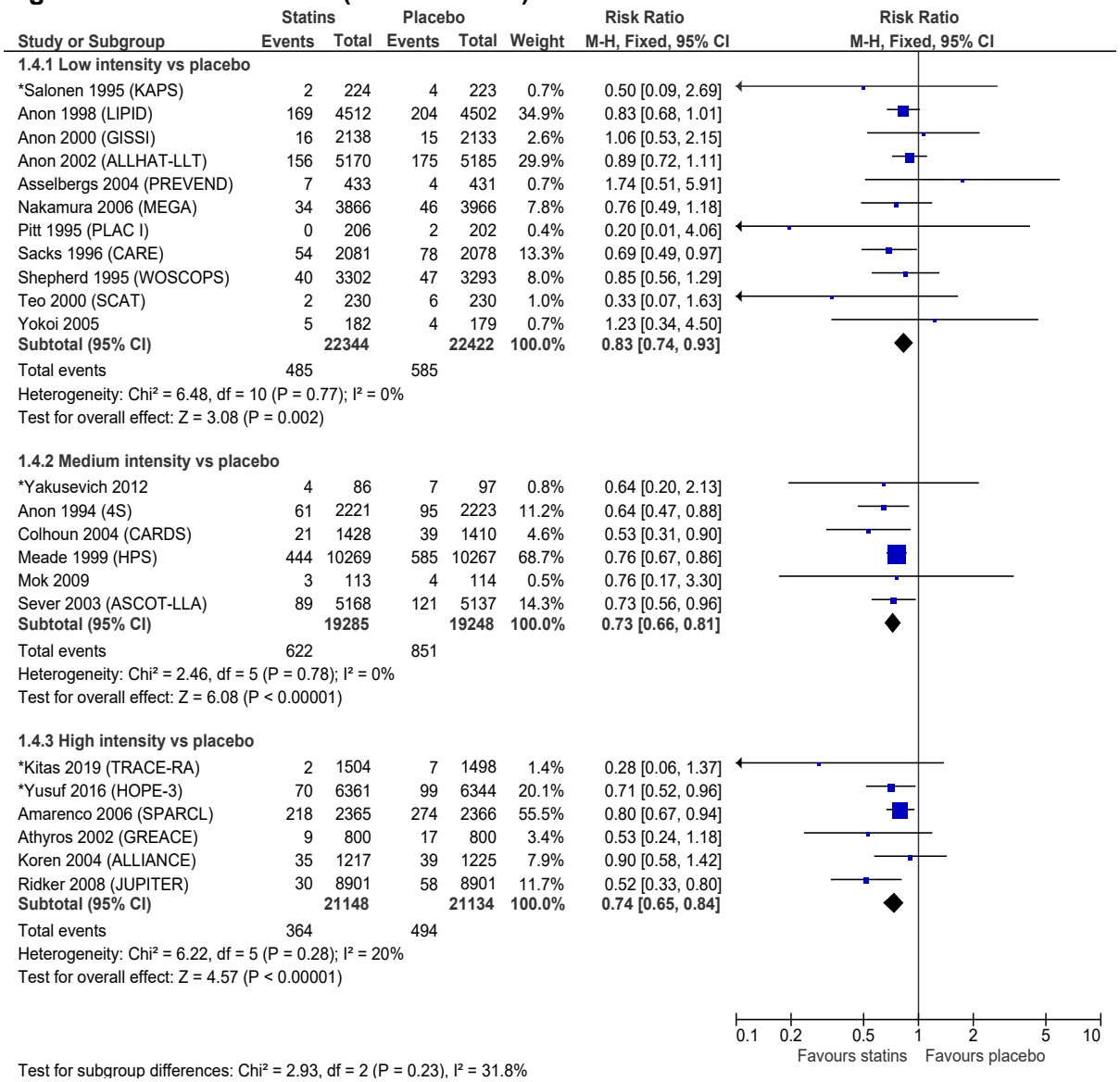
**Indicates studies added during the 2023 update*

Figure 8: Myocardial infarction (time-to-event)



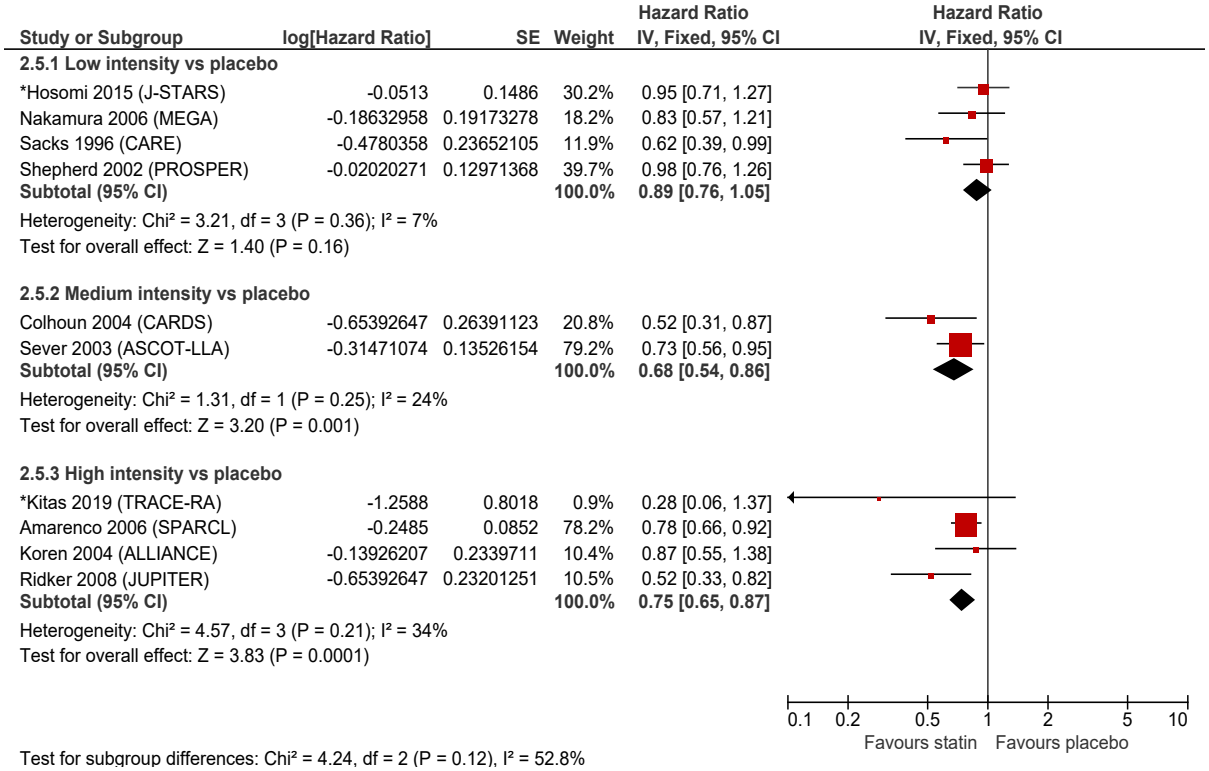
**Indicates studies added during the 2023 update*

Figure 9: Non-fatal stroke (dichotomous)



**Indicates studies added during the 2023 update*

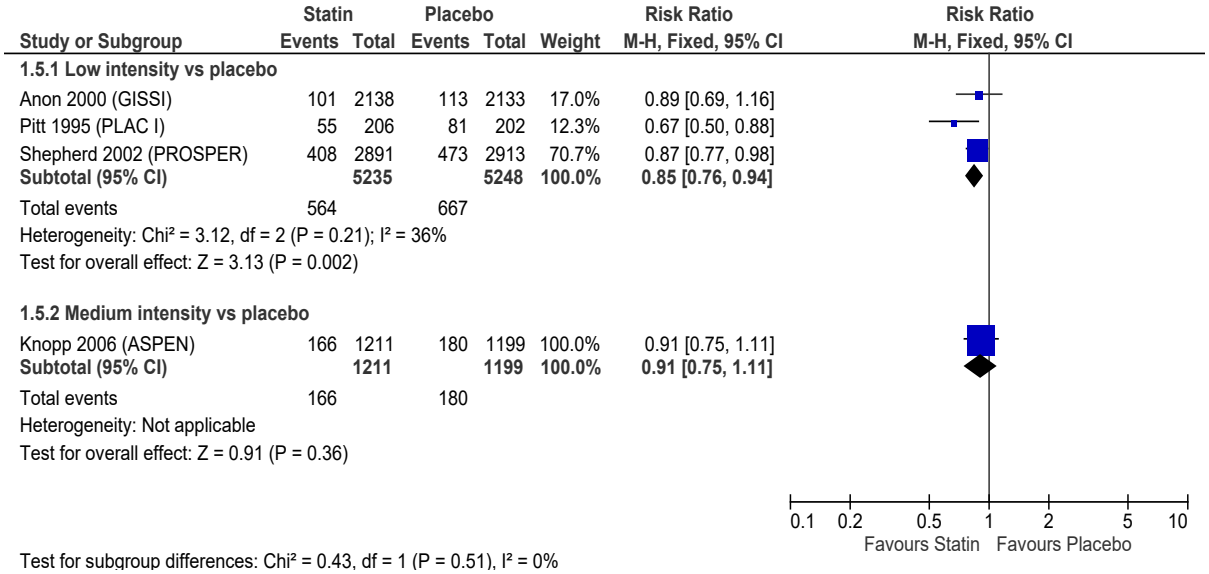
Figure 10: Non-fatal stroke (time-to-event)



Test for subgroup differences: Chi² = 4.24, df = 2 (P = 0.12), I² = 52.8%

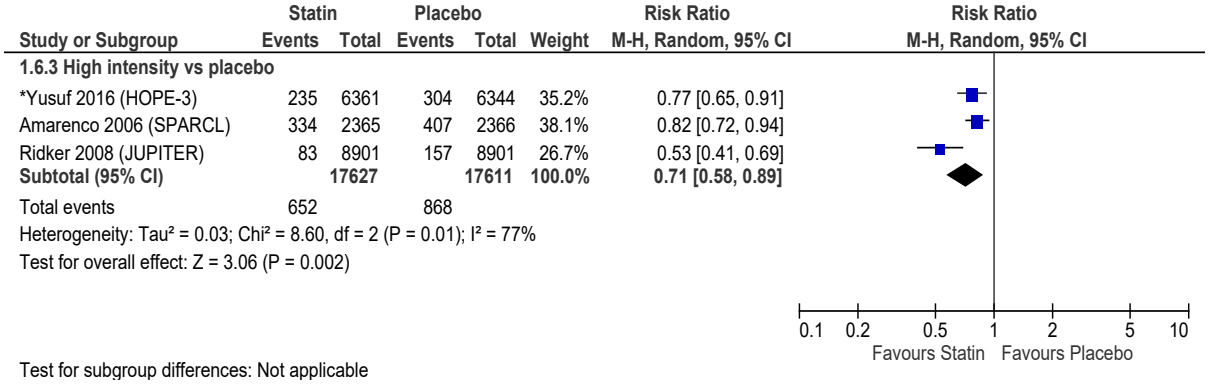
**Indicates studies added during the 2023 update*

Figure 11: Major adverse cardiovascular events (dichotomous)



Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%

Figure 12: Major adverse cardiovascular events (dichotomous)



**Indicates studies added during the 2023 update*

Figure 13: Major adverse cardiovascular events (time-to-event)

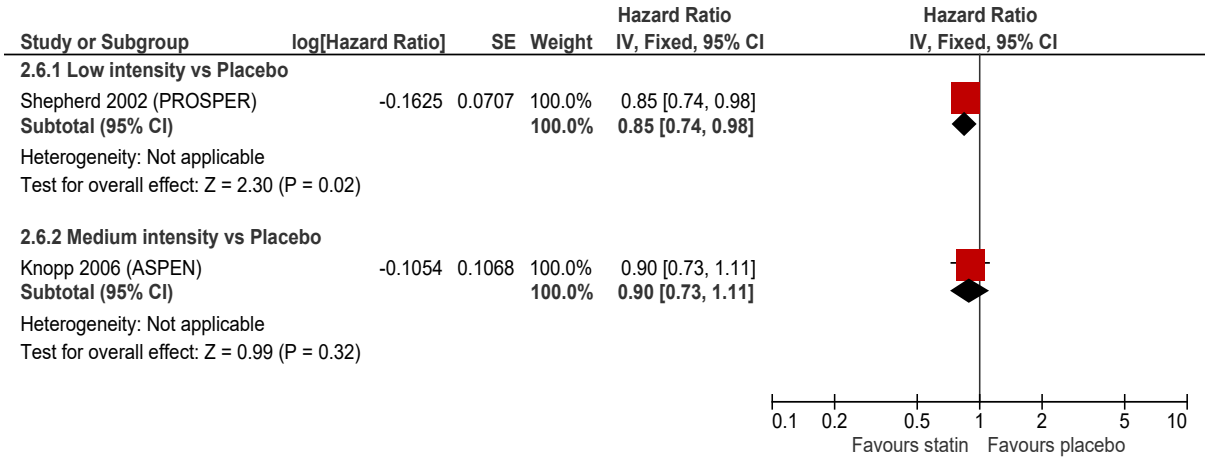
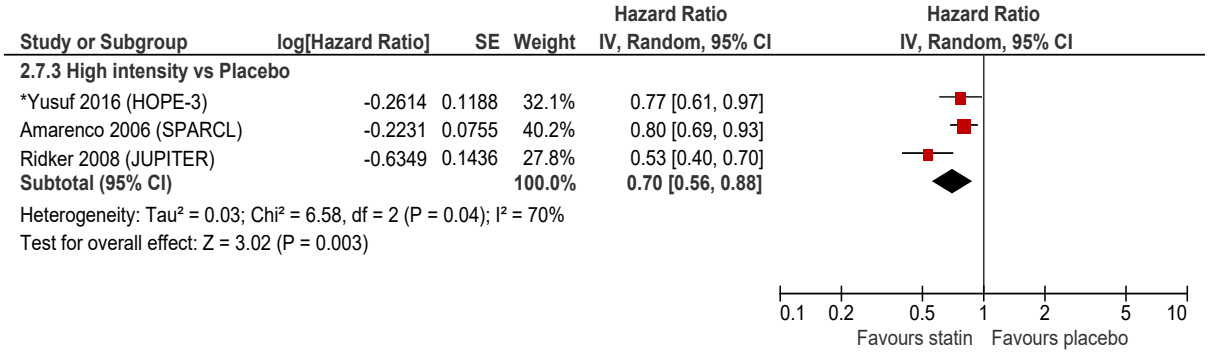


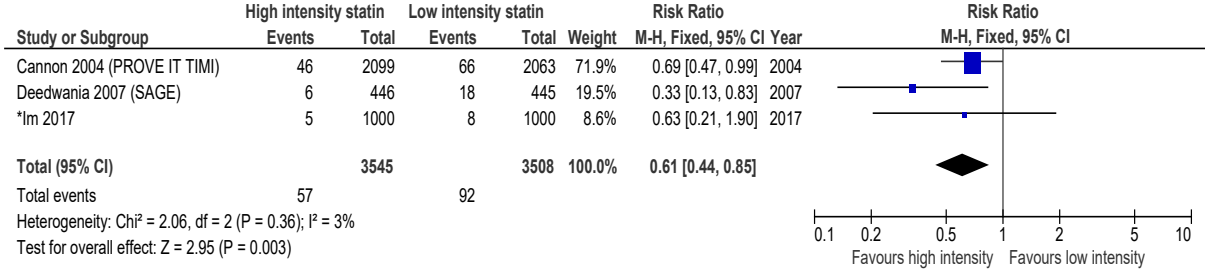
Figure 14: Major adverse cardiovascular events (time-to-event)



**Indicates studies added during the 2023 update*

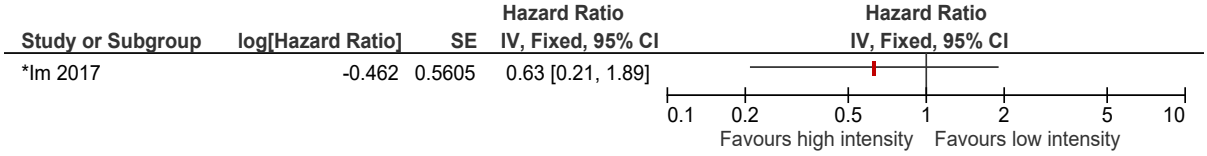
E.1.2 High versus low intensity statins

Figure 15: All-cause mortality (dichotomous)



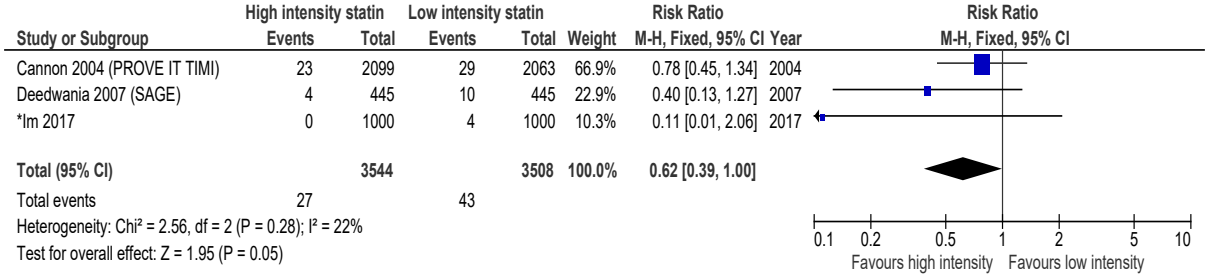
**Indicates studies added during the 2023 update*

Figure 16: All-cause mortality (time-to-event)



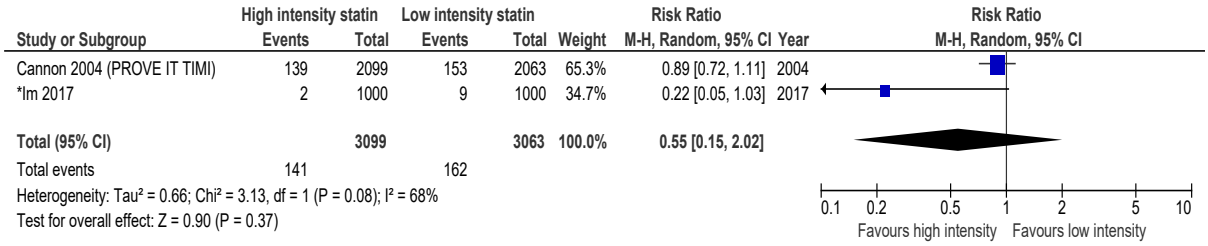
**Indicates studies added during the 2023 update*

Figure 17: Cardiovascular mortality (dichotomous)



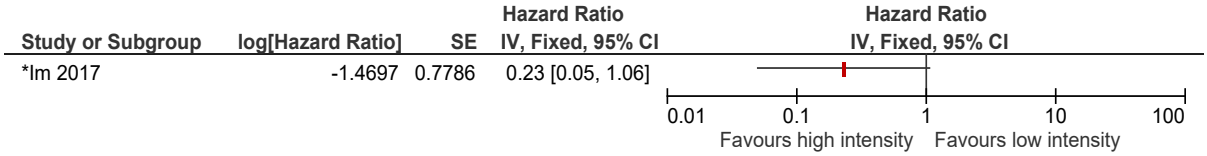
**Indicates studies added during the 2023 update*

Figure 18: Myocardial infarction (dichotomous)



**Indicates studies added during the 2023 update*

Figure 19: Myocardial infarction (time-to-event)



**Indicates studies added during the 2023 update*

Figure 20: Stroke (dichotomous)

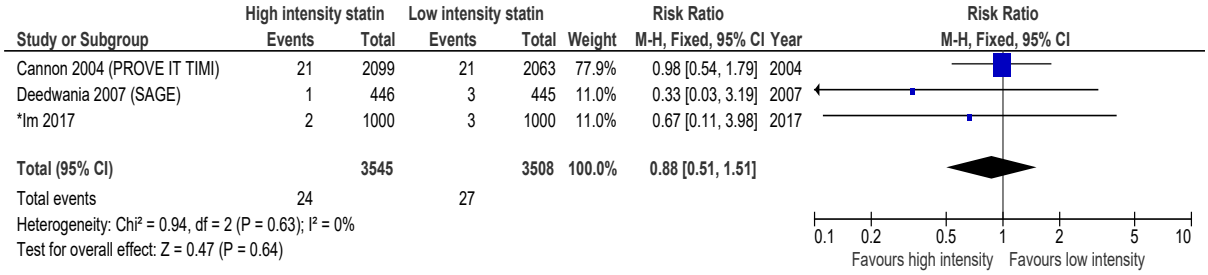
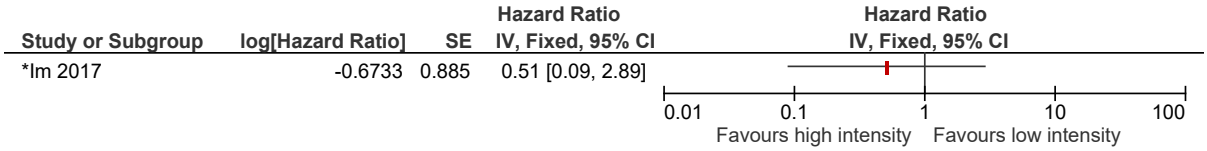
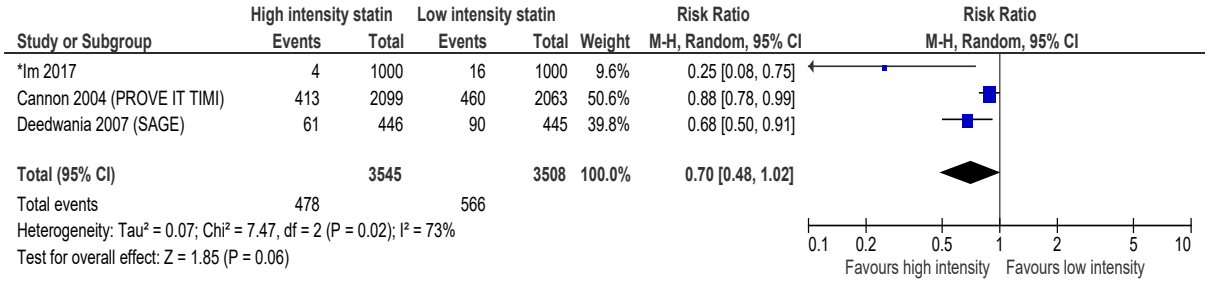


Figure 21: Stroke (time-to-event)



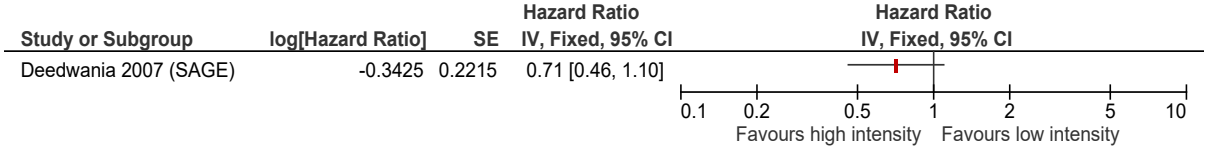
**Indicates studies added during the 2023 update*

Figure 22: Major adverse cardiovascular events (dichotomous)



**Indicates studies added during the 2023 update*

Figure 23: Major adverse cardiovascular events (time-to-event)



E.1.3 High versus medium intensity statins

Figure 24: All-cause mortality (dichotomous)

Figure 25: All-cause mortality (time-to-event)

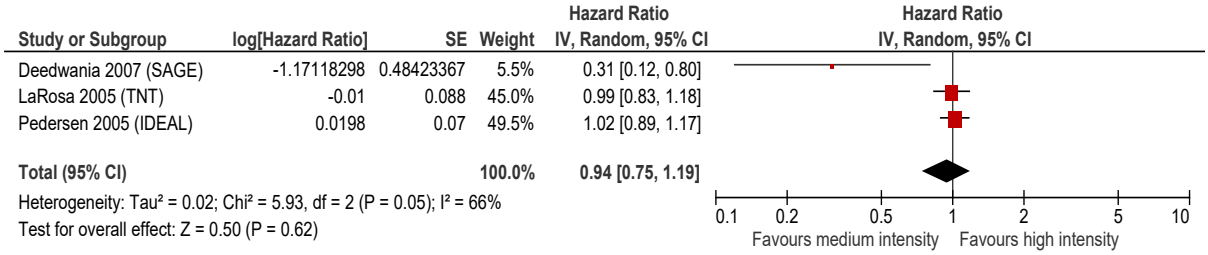


Figure 26: Cardiovascular mortality (dichotomous)

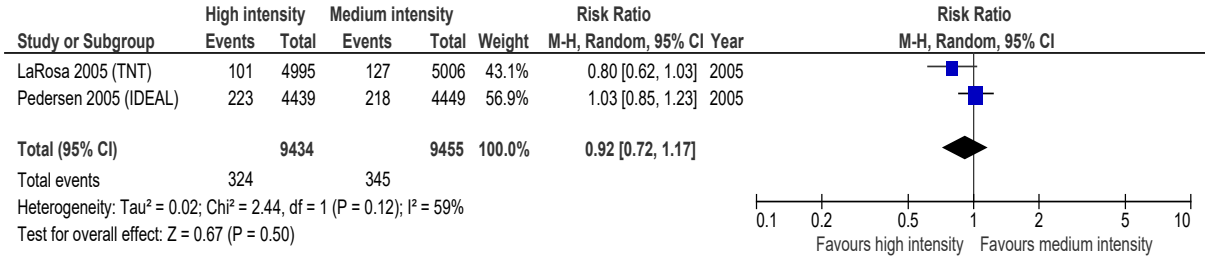


Figure 27: Cardiovascular mortality (time-to-event)

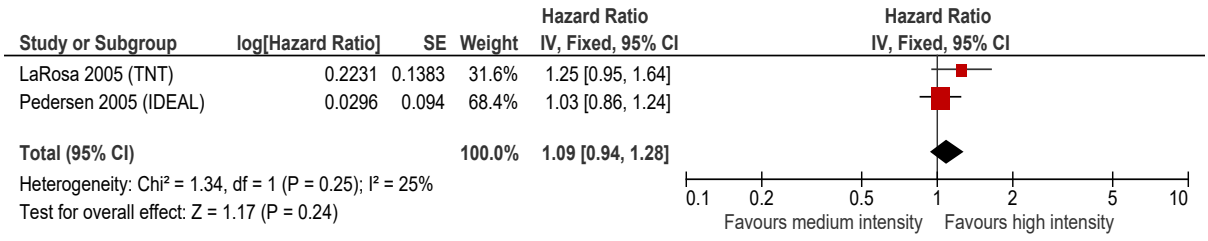


Figure 28: Myocardial infarction (dichotomous)

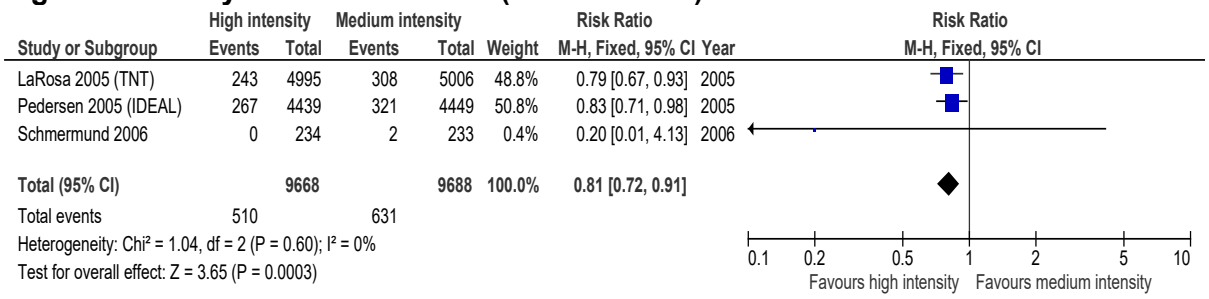


Figure 29: Myocardial infarction (time-to-event)

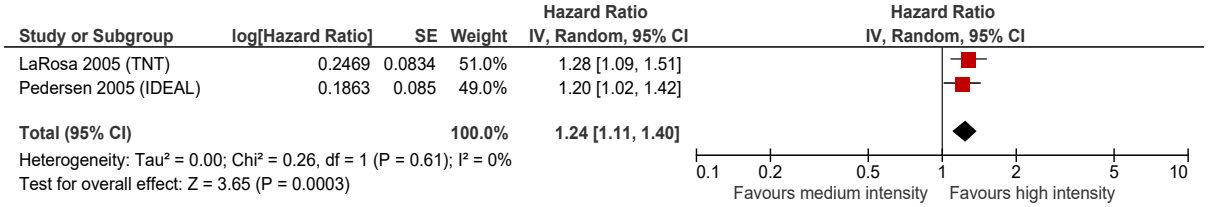
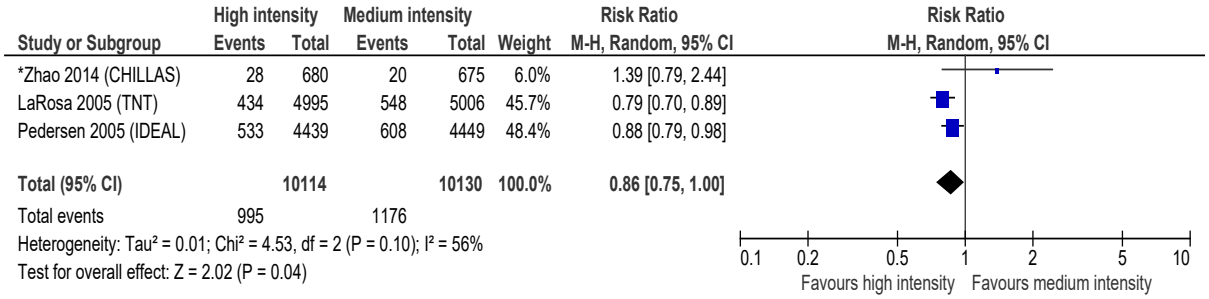


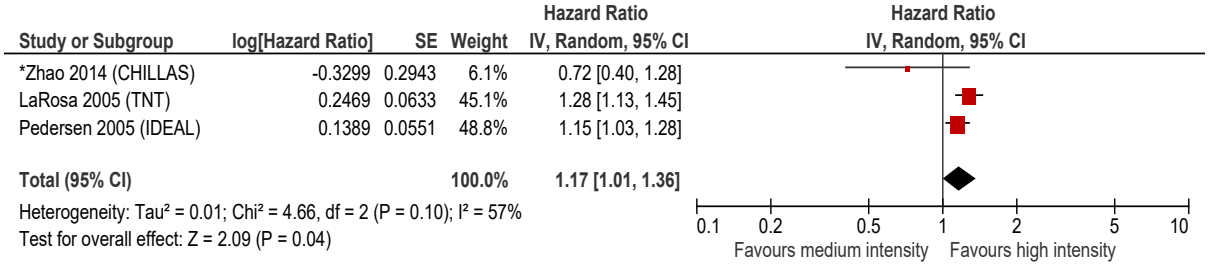
Figure 30: Stroke (dichotomous)

Figure 31: Major adverse cardiovascular events (dichotomous)



**Indicates studies added during the 2023 update*

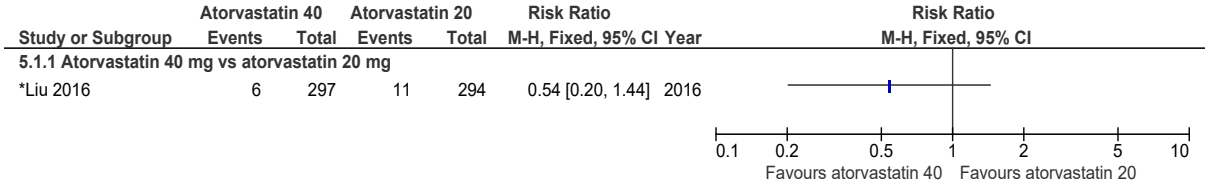
Figure 32: Major adverse cardiovascular events (time-to-event)



**Indicates studies added during the 2023 update*

E.1.4 High versus high intensity statins

Figure 33: All-cause mortality (dichotomous)



**Indicates studies added during the 2023 update*

Figure 34: Cardiovascular mortality (dichotomous)

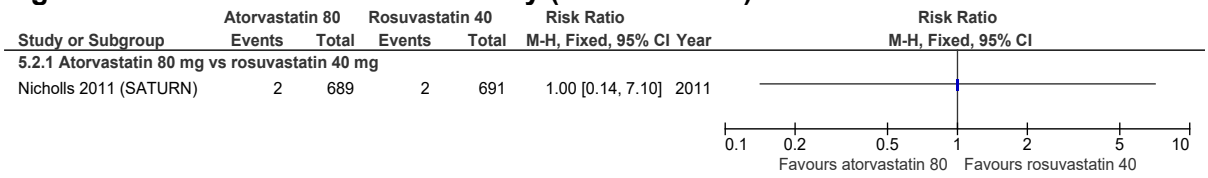
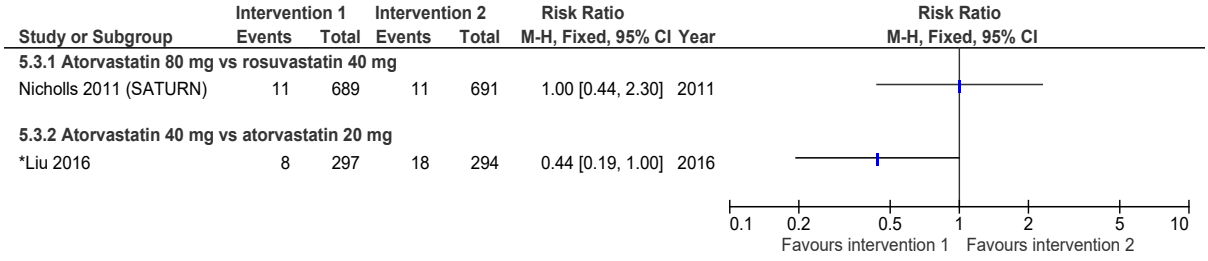
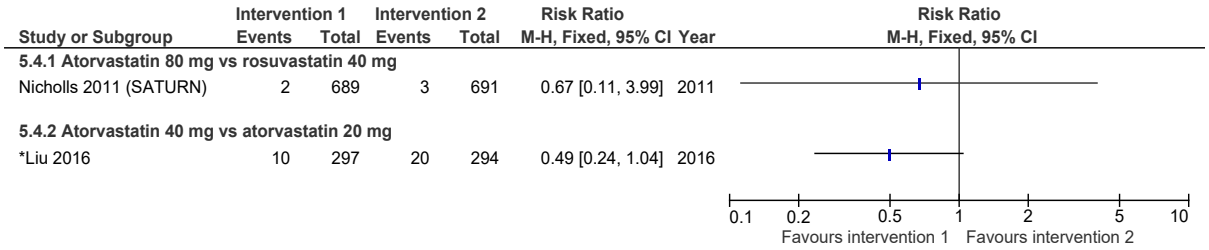


Figure 35: Myocardial infarction (dichotomous)



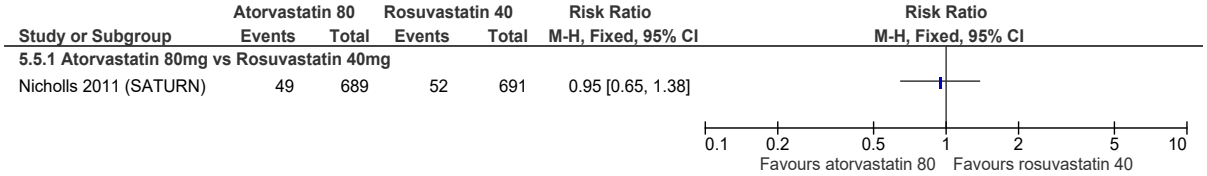
**Indicates studies added during the 2023 update*

Figure 36: Stroke (dichotomous)



**Indicates studies added during the 2023 update*

Figure 37: Major adverse cardiovascular events (dichotomous)



E.1.5 Medium versus low intensity statins

Figure 38: Cardiovascular mortality (dichotomous)

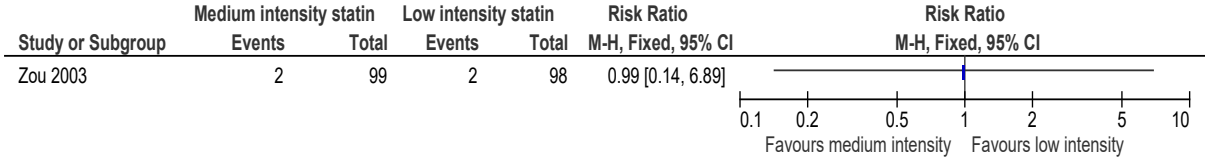
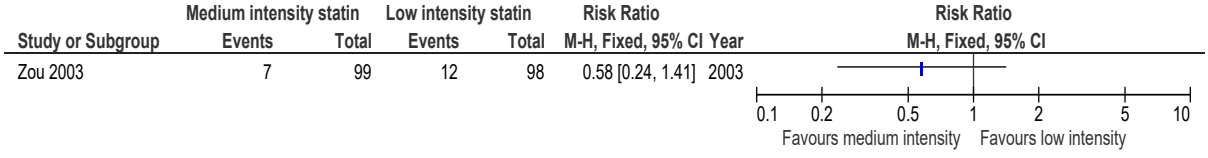


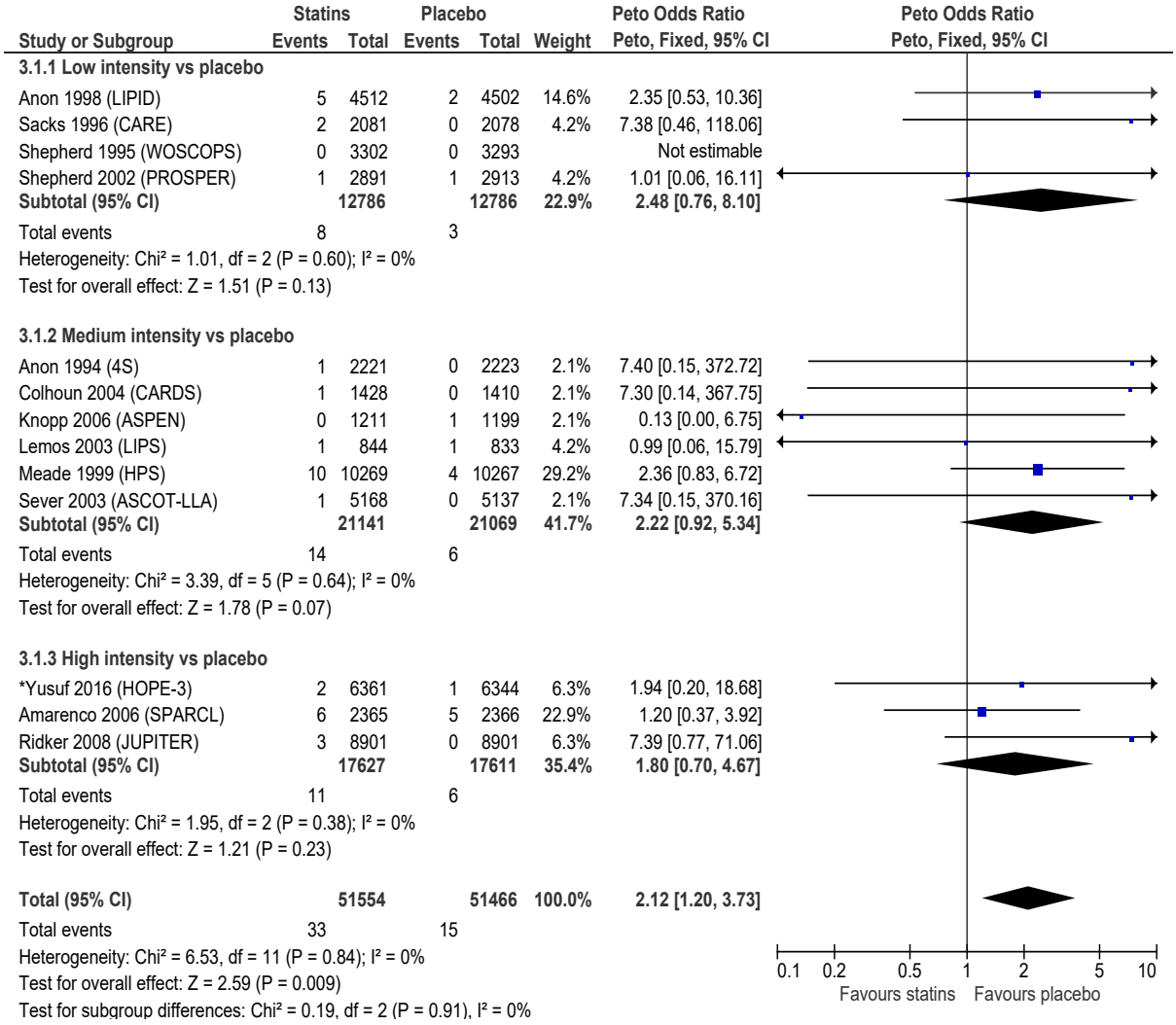
Figure 39: Myocardial infarction (dichotomous)



E.2 Adverse effects

E.2.1 Statins versus placebo

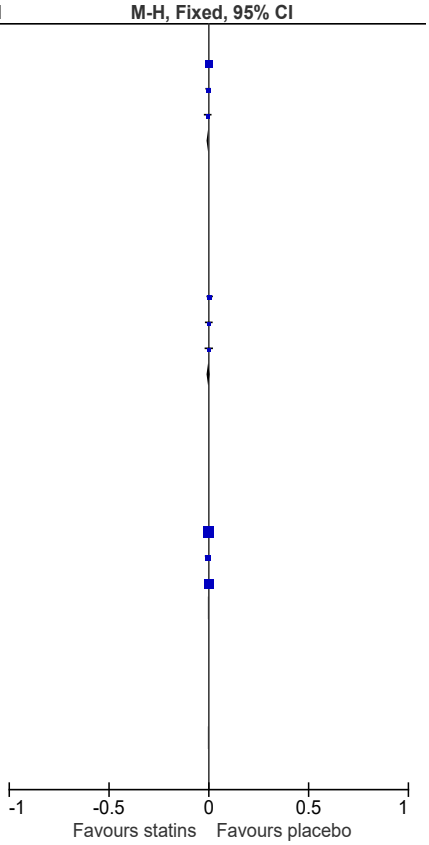
Figure 40: Rhabdomyolysis (from IPD)



**Indicates studies added during the 2023 update*

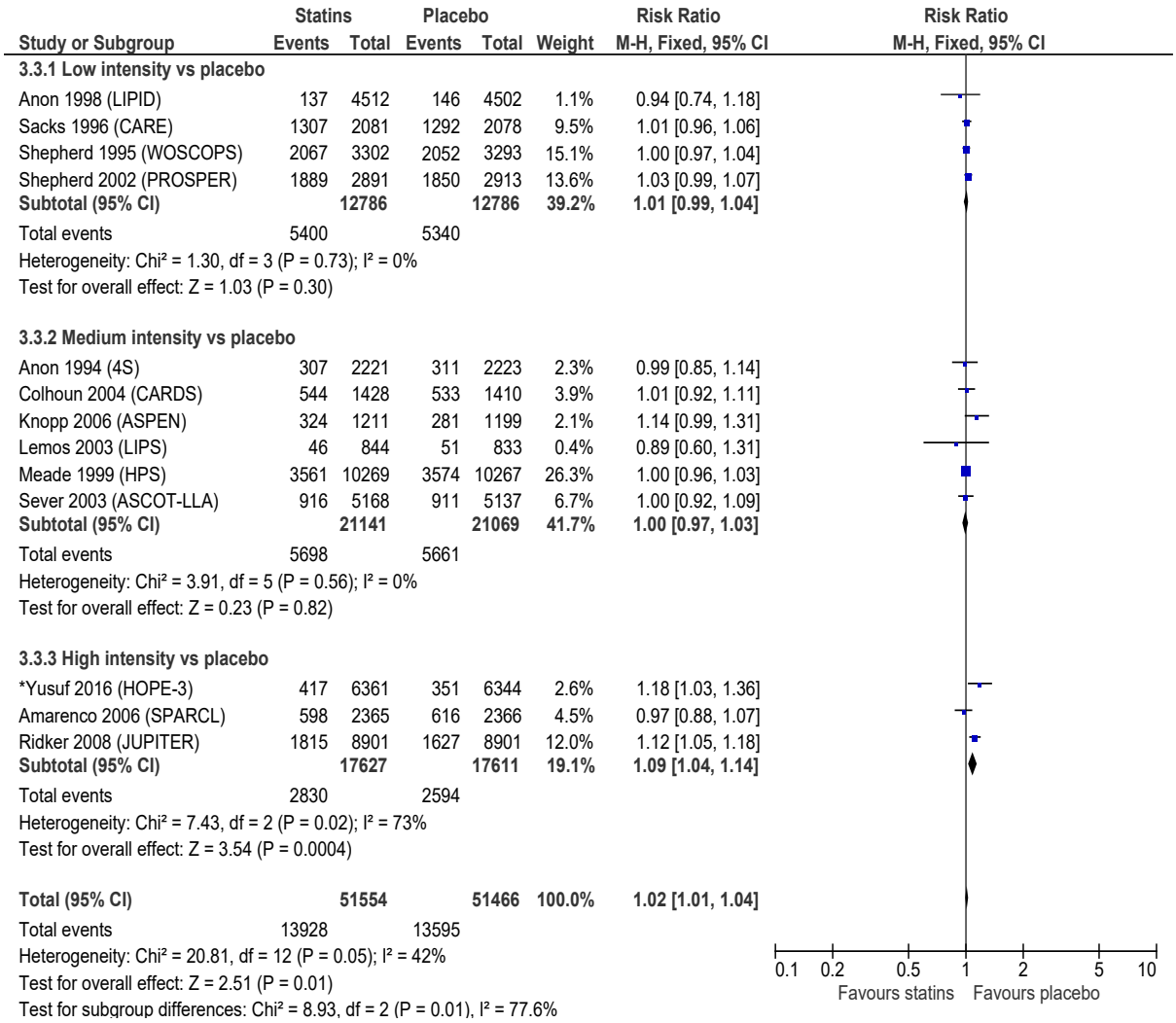
Figure 41: Rhabdomyolysis (from studies not in IPD analysis)

Study or Subgroup	Statins Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
3.2.1 Low intensity vs placebo						
*Hosomi 2015 (J-STARS)	2	780	1	785	16.2%	0.00 [-0.00, 0.01]
Anderssen 2005 (HYRIM)	0	283	1	285	5.9%	-0.00 [-0.01, 0.01]
Riegger 1999	0	187	1	178	3.8%	-0.01 [-0.02, 0.01]
Subtotal (95% CI)		**1250**		**1248**	**25.8%**	**-0.00 [-0.00, 0.00]**
Total events	2		3			
Heterogeneity: Chi² = 1.58, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.38 (P = 0.70)						
3.2.2 Medium intensity vs placebo						
Baigent 2005 (UK-HARP-I)	1	224	0	224	4.6%	0.00 [-0.01, 0.02]
Beishuizen 2004	0	125	0	125	2.6%	0.00 [-0.02, 0.02]
Mok 2009	0	113	0	114	2.3%	0.00 [-0.02, 0.02]
Subtotal (95% CI)		**462**		**463**	**9.6%**	**0.00 [-0.01, 0.01]**
Total events	1		0			
Heterogeneity: Chi² = 0.27, df = 2 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.50 (P = 0.62)						
3.2.3 High intensity vs placebo						
*Kitas 2019 (TRACE-RA)	0	1504	0	1498	31.0%	0.00 [-0.00, 0.00]
Crouse 2007A (METEOR)	1	700	2	281	8.3%	-0.01 [-0.02, 0.00]
Koren 2004 (ALLIANCE)	0	1217	0	1225	25.3%	0.00 [-0.00, 0.00]
Subtotal (95% CI)		**3421**		**3004**	**64.6%**	**-0.00 [-0.00, 0.00]**
Total events	1		2			
Heterogeneity: Chi² = 2.91, df = 2 (P = 0.23); I² = 31%						
Test for overall effect: Z = 0.90 (P = 0.37)						
Total (95% CI)		**5133**		**4715**	**100.0%**	**-0.00 [-0.00, 0.00]**
Total events	4		5			
Heterogeneity: Chi² = 3.92, df = 8 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.55 (P = 0.58)						
Test for subgroup differences: Chi² = 0.44, df = 2 (P = 0.80), I² = 0%						



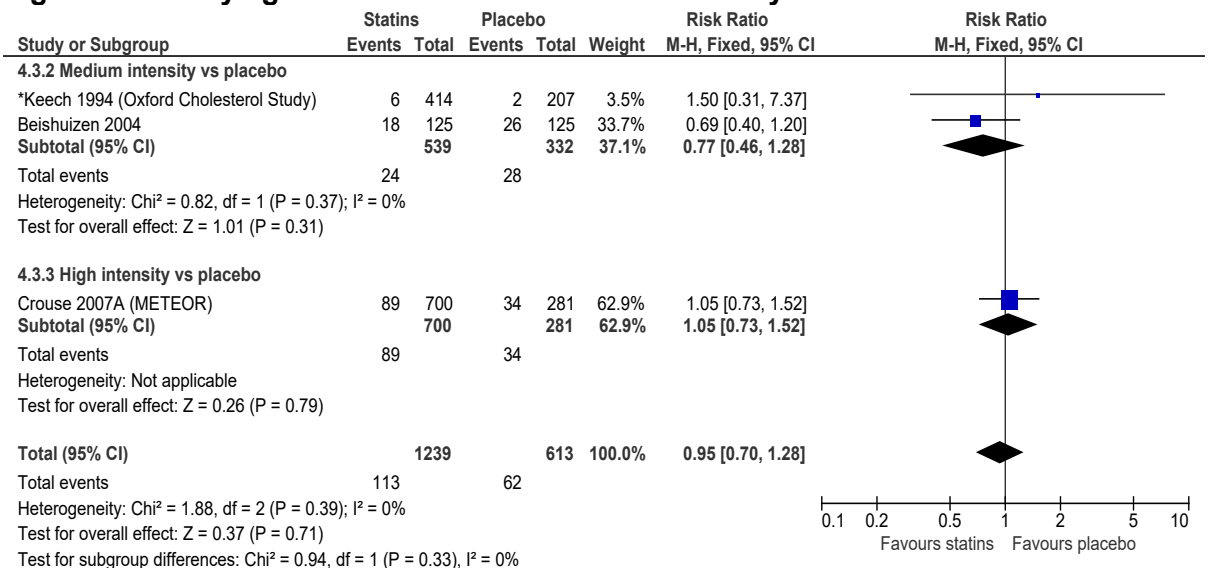
**Indicates studies added during the 2023 update*

Figure 42: Myalgia (any muscle pain from IPD)



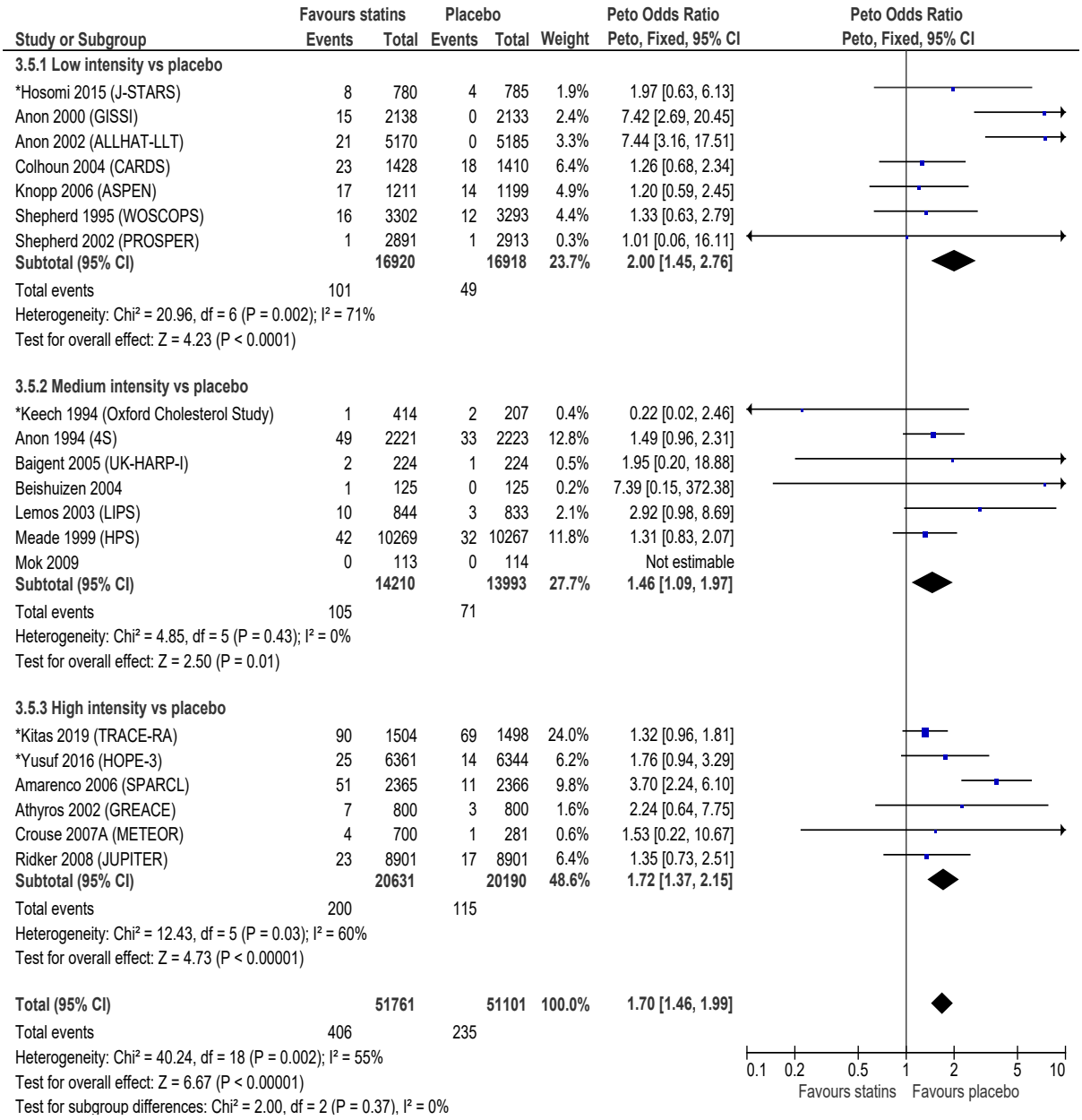
**Indicates studies added during the 2023 update*

Figure 43: Myalgia data from studies not in IPD analysis



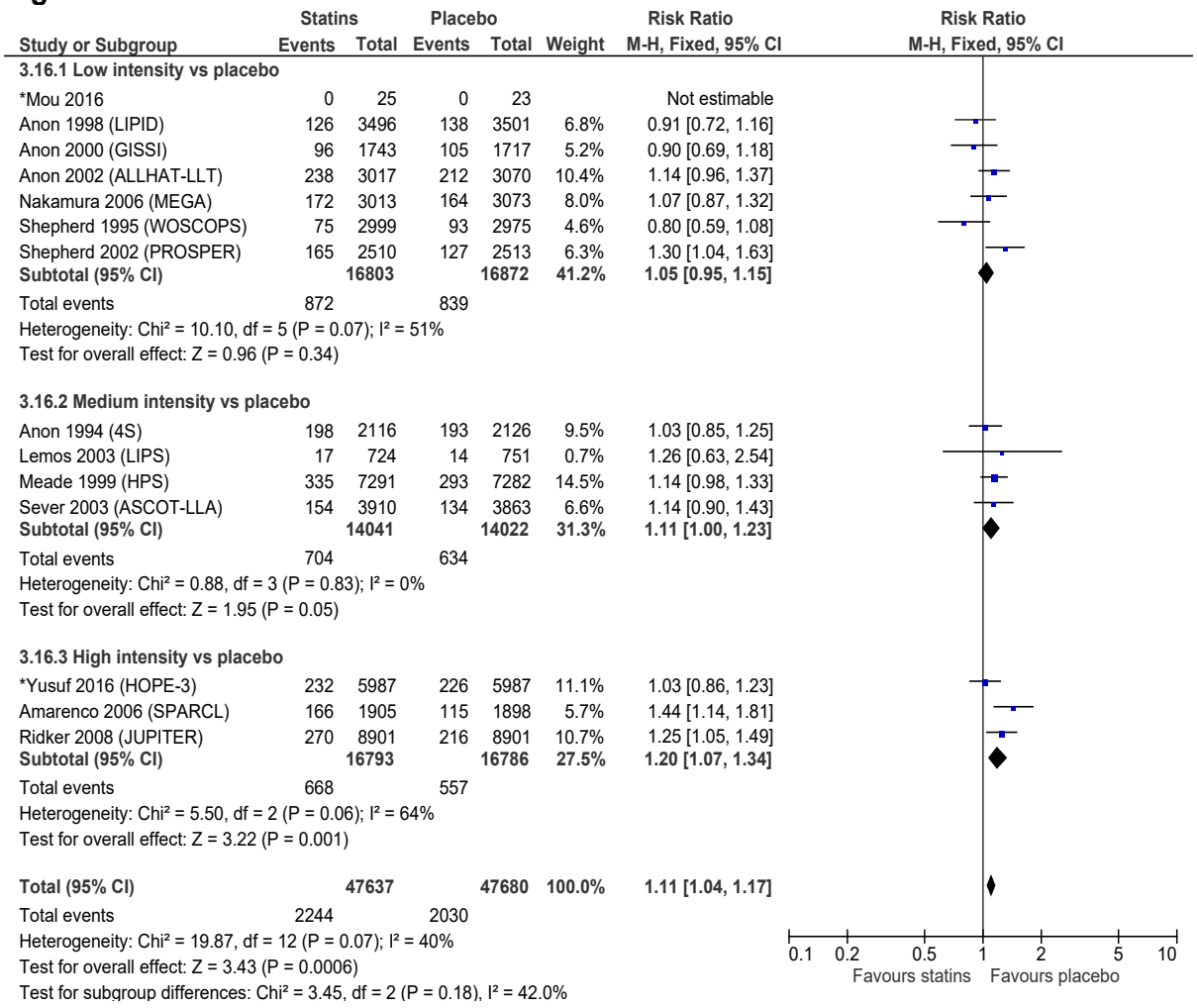
**Indicates studies added during the 2023 update*

Figure 44: Liver adverse events



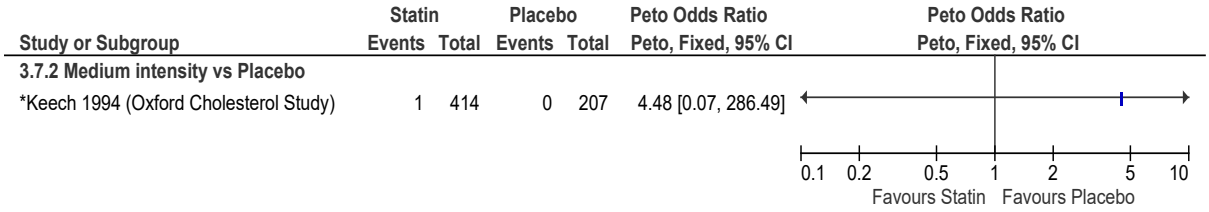
**Indicates studies added during the 2023 update*

Figure 45: New-onset diabetes



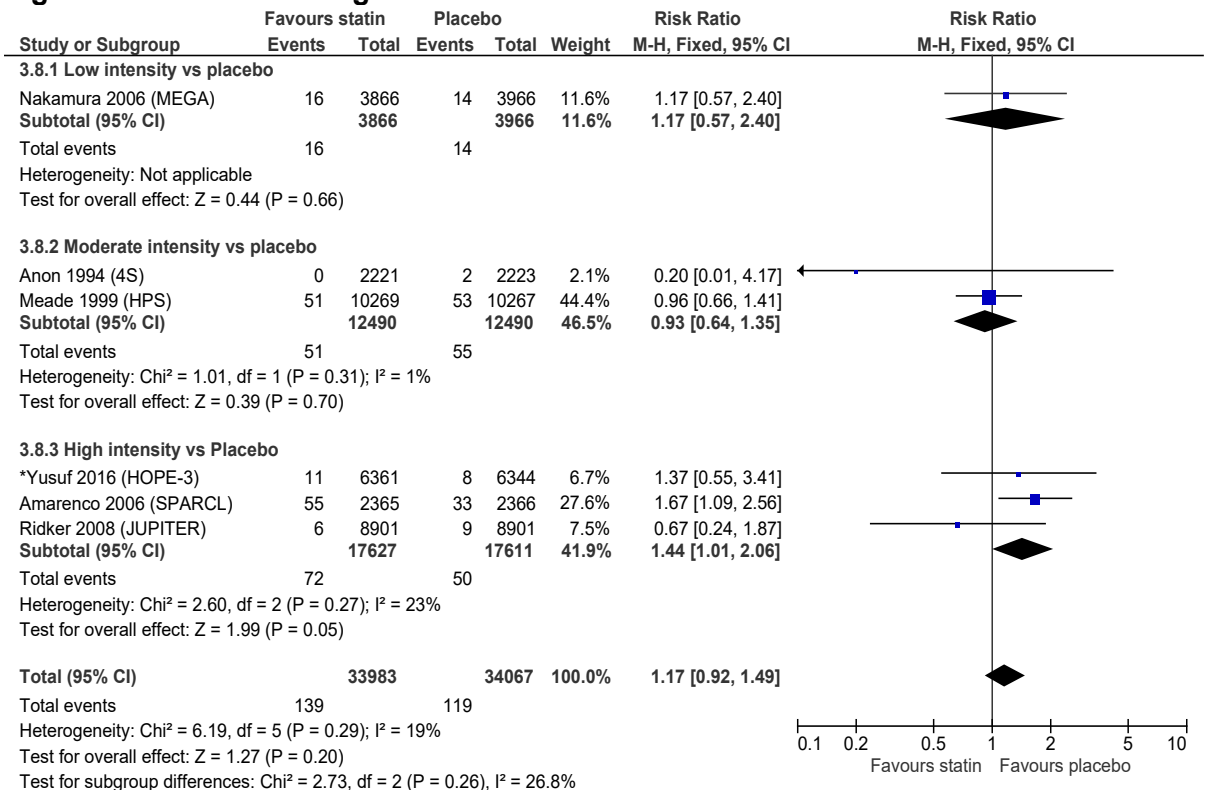
**Indicates studies added during the 2023 update*

Figure 46: Worsening of diabetes



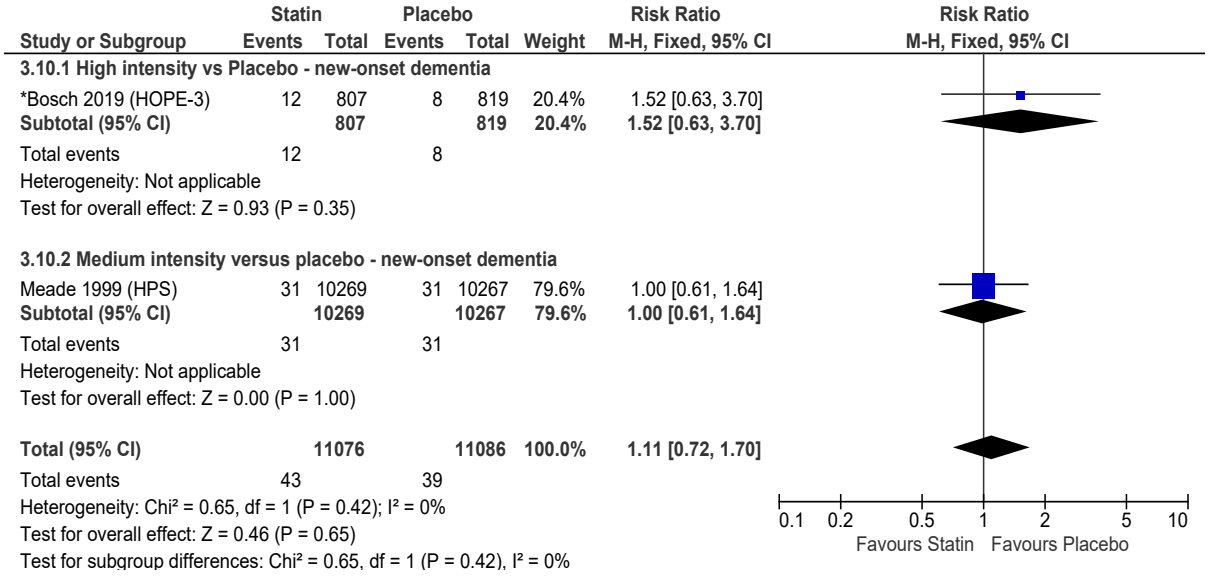
**Indicates studies added during the 2023 update*

Figure 47: Haemorrhagic stroke



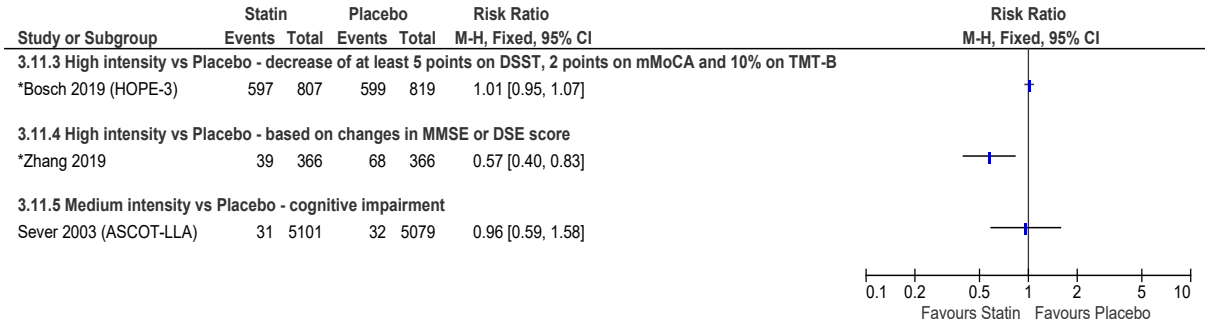
**Indicates studies added during the 2023 update*

Figure 48: Dementia



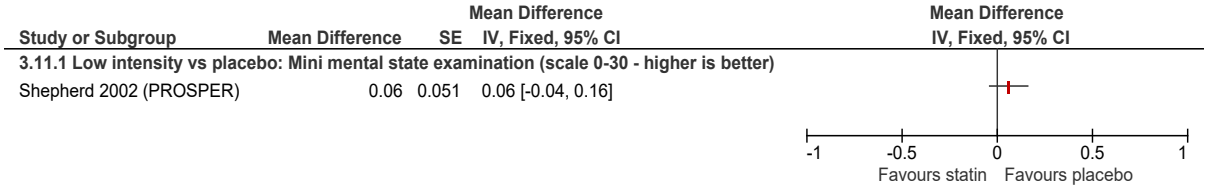
**Indicates studies added during the 2023 update*

Figure 49: Cognitive decline (dichotomous)



**Indicates studies added during the 2023 update*

Figure 50: Cognitive decline (change from baseline)



Appendix F – GRADE tables

F.1 Efficacy

Table 27: Clinical evidence profile: statins versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	placebo (by intensity)	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality - Low intensity vs placebo												
13	randomised trials	not serious	not serious	not serious	not serious[a]	none	1868/25160 (7.4%)	2106/25265 (8.3%)	**RR 0.89** (0.84 to 0.94)	**9 fewer per 1,000** (from 13 fewer to 5 fewer)	⊕⊕⊕⊕ High	CRITICAL
All-cause mortality - Medium intensity vs placebo												
9	randomised trials	not serious	not serious	not serious	not serious[a]	none	1865/21547 (8.7%)	2186/21474 (10.2%)	**RR 0.85** (0.80 to 0.90)	**15 fewer per 1,000** (from 20 fewer to 10 fewer)	⊕⊕⊕⊕ High	CRITICAL
All-cause mortality - High intensity vs placebo												
8	randomised trials	not serious	not serious	not serious	not serious[a]	none	922/21902 (4.2%)	1013/21469 (4.7%)	**RR 0.91** (0.83 to 0.99)	**4 fewer per 1,000** (from 8 fewer to 0 fewer)	⊕⊕⊕⊕ High	CRITICAL
CV mortality - Low intensity vs placebo												
12	randomised trials	not serious	not serious	not serious	not serious[a]	none	1103/25240 (4.4%)	1317/25334 (5.2%)	**RR 0.84** (0.78 to 0.91)	**8 fewer per 1,000** (from 11 fewer to 5 fewer)	⊕⊕⊕⊕ High	CRITICAL
CV mortality - Medium intensity vs placebo												
8	randomised trials	not serious	not serious	not serious	not serious[a]	none	1073/21246 (5.1%)	1329/21185 (6.3%)	**RR 0.81** (0.75 to 0.87)	**12 fewer per 1,000** (from 16 fewer to 8 fewer)	⊕⊕⊕⊕ High	CRITICAL
CV mortality - High intensity vs placebo												
6	randomised trials	not serious	not serious	not serious	not serious[a]	none	342/21148 (1.6%)	427/21134 (2.0%)	**RR 0.80** (0.70 to 0.92)	**4 fewer per 1,000** (from 6 fewer to 2 fewer)	⊕⊕⊕⊕ High	CRITICAL
Non-fatal MI - Low intensity vs placebo												
14	randomised trials	not serious	not serious	not serious	serious[b]	none	954/20478 (4.7%)	1228/20558 (6.0%)	**RR 0.78** (0.72 to 0.84)	**13 fewer per 1,000** (from 17 fewer to 10 fewer)	⊕⊕⊕◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	placebo (by intensity)	Relative (95% CI)	Absolute (95% CI)		
Non-fatal MI - Medium intensity vs placebo												
6	randomised trials	not serious	not serious	not serious	not serious	none	550/14297 (3.8%)	895/14288 (6.3%)	**RR 0.62** (0.55 to 0.68)	**24 fewer per 1,000** (from 28 fewer to 20 fewer)	⨁⨁⨁⨁ High	CRITICAL
Non-fatal MI - High intensity vs placebo												
6	randomised trials	not serious	not serious	not serious	not serious	none	152/19483 (0.8%)	296/19049 (1.6%)	**RR 0.51** (0.42 to 0.62)	**8 fewer per 1,000** (from 9 fewer to 6 fewer)	⨁⨁⨁⨁ High	CRITICAL
Non-fatal ischaemic stroke - Low intensity vs placebo												
11	randomised trials	not serious	not serious	not serious	serious[b]	none	485/22344 (2.2%)	585/22422 (2.6%)	**RR 0.83** (0.74 to 0.93)	**4 fewer per 1,000** (from 7 fewer to 2 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Non-fatal ischaemic stroke - Medium intensity vs placebo												
6	randomised trials	not serious	not serious	not serious	serious[b]	none	622/19285 (3.2%)	851/19248 (4.4%)	**RR 0.73** (0.66 to 0.81)	**12 fewer per 1,000** (from 15 fewer to 8 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Non-fatal ischaemic stroke - High intensity vs placebo												
6	randomised trials	not serious	not serious	not serious	serious[b]	none	364/21134 (1.7%)	494/21134 (2.3%)	**RR 0.74** (0.65 to 0.84)	**6 fewer per 1,000** (from 8 fewer to 4 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Major adverse cardiovascular events (MACE) - Low intensity vs placebo												
3	randomised trials	not serious	not serious	not serious	serious[b]	none	564/5235 (10.8%)	667/5248 (12.7%)	**RR 0.85** (0.76 to 0.94)	**19 fewer per 1,000** (from 31 fewer to 8 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Major adverse cardiovascular events (MACE) - Medium intensity vs placebo												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	166/1211 (13.7%)	180/1199 (15.0%)	**RR 0.91** (0.75 to 1.11)	**14 fewer per 1,000** (from 38 fewer to 17 more)	⨁⨁⨁◯ Moderate	CRITICAL
Major adverse cardiovascular events (MACE) - High intensity vs placebo												
3	randomised trials	not serious	very serious[c]	not serious	serious[b]	none	652/17627 (3.7%)	868/17611 (4.9%)	**RR 0.71** (0.58 to 0.89)	**14 fewer per 1,000** (from 21 fewer to 5 fewer)	⨁◯◯◯ Very low	CRITICAL
Quality of life (assessed with: EQ5D; Scale from: 0 to 1)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	placebo (by intensity)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[d]	not serious	not serious	serious[e]	none	1062	1079	-	median **0.04 points lower** (0 to 0)	⨁⨁◯◯ Low	CRITICAL

a. For mortality imprecision was assessed on the basis of the whether the confidence intervals crossed the line of no effect

b. 95% confidence interval crosses one MID (0.8)

c. Very serious inconsistency (I2 = 77%): too few studies to investigate subgroups

d. Baseline differences in EQ-5D score

e. Imprecision could not be assessed

Table 28: Clinical evidence profile: high versus low intensity statin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High intensity	low intensity statin	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
3	randomised trials	not serious	not serious	not serious	not serious[a]	none	57/3545 (1.6%)	92/3508 (2.6%)	**RR 0.61** (0.44 to 0.85)	**10 fewer per 1,000** (from 15 fewer to 4 fewer)	⨁⨁⨁⨁ High	CRITICAL
CV mortality												
3	randomised trials	not serious	not serious	not serious	not serious[a]	none	27/3544 (0.8%)	43/3508 (1.2%)	**RR 0.62** (0.39 to 1.00)	**5 fewer per 1,000** (from 7 fewer to 0 fewer)	⨁⨁⨁⨁ High	CRITICAL
Non-fatal MI												
2	randomised trials	not serious	serious[b]	not serious	very serious[c]	none	141/3099 (4.5%)	162/3063 (5.3%)	**RR 0.55** (0.15 to 2.02)	**24 fewer per 1,000** (from 45 fewer to 54 more)	⨁◯◯◯ Very low	CRITICAL
Stroke												
3	randomised trials	not serious	not serious	not serious	very serious[c]	none	24/3545 (0.7%)	27/3508 (0.8%)	**RR 0.88** (0.51 to 1.51)	**1 fewer per 1,000** (from 4 fewer to 4 more)	⨁⨁◯◯ Low	CRITICAL
Major adverse cardiovascular event (MACE)												
1	randomised trials	serious[d]	not serious	not serious	serious[e]	none	61/446 (13.7%)	90/445 (20.2%)	**RR 0.68** (0.50 to 0.91)	**65 fewer per 1,000** (from 101 fewer to 18 fewer)	⨁⨁◯◯ Low	CRITICAL

a. For mortality imprecision was assessed on the basis of the whether the confidence intervals crossed the line of no effect

b. Serious inconsistency (I2 = 66%): too few studies to investigate subgroups

c. 95% confidence interval crosses both MIDs (0.8, 1.25)

d. High rate of missing data and unclear allocation concealment

e. 95% confidence interval crosses one MID (0.8)

Table 29: Clinical evidence profile: high versus medium intensity statin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High intensity	medium intensity statin	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
2	randomised trials	serious[a]	not serious	not serious	serious[b]	none	650/9434 (6.9%)	656/9455 (6.9%)	**RR 0.99** (0.89 to 1.10)	**1 fewer per 1,000** (from 8 fewer to 7 more)	⨁⨁◯◯ Low	CRITICAL
CV mortality												
2	randomised trials	serious[a]	serious[c]	not serious	serious[b]	none	324/9434 (3.4%)	345/9455 (3.6%)	**RR 0.92** (0.72 to 1.17)	**3 fewer per 1,000** (from 10 fewer to 6 more)	⨁◯◯◯ Very low	CRITICAL
Non-fatal MI												
3	randomised trials	serious[a]	not serious	not serious	serious[d]	none	510/9668 (5.3%)	631/9688 (6.5%)	**RR 0.81** (0.72 to 0.91)	**12 fewer per 1,000** (from 18 fewer to 6 fewer)	⨁⨁◯◯ Low	CRITICAL
Stroke												
2	randomised trials	serious[a]	not serious	not serious	serious[d]	none	152/4673 (3.3%)	175/4682 (3.7%)	**RR 0.87** (0.70 to 1.08)	**5 fewer per 1,000** (from 11 fewer to 3 more)	⨁⨁◯◯ Low	CRITICAL
Major adverse cardiovascular event (MACE)												
3	randomised trials	serious[e]	serious[f]	not serious	serious[d]	none	995/10114 (9.8%)	1176/10130 (11.6%)	**RR 0.86** (0.75 to 1.00)	**16 fewer per 1,000** (from 29 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL

a. Majority of the evidence at high risk of performance bias: Additional interventions not balanced between groups: additional statins

b. For mortality imprecision was assessed on the basis of the whether the confidence intervals crossed the line of no effect

c. Serious inconsistency (I2 = 59%): too few studies to investigate subgroups

d. 95% CI crosses one MID (0.8)

e. Evidence at high risk of bias (unbalanced additional interventions, or unclear allocation concealment)

f. Serious inconsistency (I2 = 56%): too few studies to investigate subgroups

Table 30: Clinical evidence profile: high versus high intensity statin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High intensity	high intensity	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality: Atorvastatin 40 mg vs atrovastatin 20 mg												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	6/297 (2.0%)	11/294 (3.7%)	**RR 0.54** (0.20 to 1.44)	**17 fewer per 1,000** (from 30 fewer to 16 more)	⨁⨁◯◯ Low	CRITICAL
CV mortality: Atorvaostatin 80 mg vs rosuvastatin 40 mg												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	2/689 (0.3%)	2/691 (0.3%)	**RR 1.00** (0.14 to 7.10)	**0 fewer per 1,000** (from 2 fewer to 18 more)	⨁⨁◯◯ Low	CRITICAL
Non-fatal MI - Atorvaostatin 80 mg vs rosuvastatin 40 mg												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	11/689 (1.6%)	11/691 (1.6%)	**RR 1.00** (0.44 to 2.30)	**0 fewer per 1,000** (from 9 fewer to 21 more)	⨁⨁◯◯ Low	CRITICAL
Non-fatal MI - Atorvastatin 40 mg vs atrovastatin 20 mg												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	8/297 (2.7%)	18/294 (6.1%)	**RR 0.44** (0.19 to 1.00)	**34 fewer per 1,000** (from 50 fewer to 0 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Non-fatal stroke - Atorvaostatin 80 mg vs rosuvastatin 40 mg												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	2/689 (0.3%)	3/691 (0.4%)	**RR 0.67** (0.11 to 3.99)	**1 fewer per 1,000** (from 4 fewer to 13 more)	⨁⨁◯◯ Low	CRITICAL
Non-fatal stroke - Atorvastatin 40 mg vs atrovastatin 20 mg												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	10/297 (3.4%)	20/294 (6.8%)	**RR 0.49** (0.24 to 1.04)	**35 fewer per 1,000** (from 52 fewer to 3 more)	⨁⨁⨁◯ Moderate	CRITICAL
Major adverse cardiovascular events (MACE) - Atorvastatin 80mg vs Rosuvastatin 40mg												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	49/689 (7.1%)	52/691 (7.5%)	**RR 0.95** (0.65 to 1.38)	**4 fewer per 1,000** (from 26 fewer to 29 more)	⨁⨁◯◯ Low	CRITICAL

a. 95% confidence interval crosses both MIDs (0.8, 1.25)

b. 95% confidence interval crosses one MID (0.8)

Table 31: Clinical evidence profile: medium versus low intensity statin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Medium intensity	low intensity statin	Relative (95% CI)	Absolute (95% CI)		
CV mortality												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	2/99 (2.0%)	2/98 (2.0%)	**RR 0.99** (0.14 to 6.89)	**0 fewer per 1,000** (from 18 fewer to 120 more)	⨁◯◯◯ Very low	CRITICAL
Non-fatal MI												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	7/99 (7.1%)	12/98 (12.2%)	**RR 0.58** (0.24 to 1.41)	**51 fewer per 1,000** (from 93 fewer to 50 more)	⨁◯◯◯ Very low	CRITICAL

a. High rate of missing data

b. 95% confidence interval crosses both MIDs (0.8, 1.25)

F.2 Adverse effects

Table 32: Clinical evidence profile: statins versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	placebo	Relative (95% CI)	Absolute (95% CI)		
Rhabdomyolysis ('myopathy' from IPD analysis)												
13	randomised trials	not serious	not serious	serious[a]	not serious	none	33/51554 (0.1%)	15/51466 (0.0%)	**OR 2.12** (1.20 to 3.73)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)[b]	⨁⨁⨁◯ Moderate	CRITICAL
Rhabdomyolysis from studies not in IPD analysis												
9	randomised trials	not serious	not serious	not serious	very serious[c]	none	4/5133 (0.1%)	5/4715 (0.1%)	not estimable	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
Myalgia ('Any muscle pain' from IPD analysis)												
13	randomised trials	not serious	not serious	not serious	not serious	none	13928/51554 (27.0%)	13595/51466 (26.4%)	**RR 1.02** (1.01 to 1.04)	**5 more per 1,000** (from 3 more to 11 more)	⨁⨁⨁⨁ High	CRITICAL
Myalgia data from studies not in IPD analysis												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	placebo	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[d]	not serious	not serious	very serious[e]	none	113/1239 (9.1%)	62/613 (10.1%)	**RR 0.95** (0.70 to 1.28)	**5 fewer per 1,000** (from 30 fewer to 28 more)	⊕◯◯◯ Very low	CRITICAL

Liver adverse events

20	randomised trials	not serious	serious[f]	not serious	not serious	none	406/51761 (0.8%)	235/51101 (0.5%)	**OR 1.70** (1.46 to 1.99)	**0 more per 1,000** (from 0 more to 0 more) [b]	⊕⊕⊕◯ Moderate	CRITICAL

New onset diabetes

14	randomised trials	not serious	not serious	not serious	not serious	none	2244/47637 (4.7%)	2030/47680 (4.3%)	**RR 1.11** (1.04 to 1.17)	**5 more per 1,000** (from 2 more to 7 more)	⊕⊕⊕⊕ High	CRITICAL

Worsening of diabetes

1	randomised trials	very serious[g]	not serious	serious[h]	very serious[e]	none	1/414 (0.2%)	0/207 (0.0%)	**OR 4.48** (0.07 to 286.49)	**0 fewer per 1,000** (from 10 fewer to 10 more) [b]	⊕◯◯◯ Very low	CRITICAL

Haemorrhagic stroke

6	randomised trials	not serious	not serious	not serious	serious[i]	none	139/33983 (0.4%)	119/34067 (0.3%)	**RR 1.17** (0.92 to 1.49)	**1 more per 1,000** (from 0 fewer to 2 more)	⊕⊕⊕◯ Moderate	CRITICAL

Dementia

2	randomised trials	serious[j]	not serious	not serious	very serious[e]	none	43/11076 (0.4%)	39/11086 (0.4%)	**RR 1.11** (0.72 to 1.70)	**0 fewer per 1,000** (from 1 fewer to 2 more)	⊕◯◯◯ Very low	CRITICAL

Cognitive decline or dementia - High intensity vs Placebo - decrease of at least 5 points on DSST, 2 points on mMoCA and 10% on TMT-B

1	randomised trials	very serious[k]	not serious	not serious	not serious	none	597/807 (74.0%)	599/819 (73.1%)	**RR 1.01** (0.95 to 1.07)	**7 more per 1,000** (from 37 fewer to 51 more)	⊕⊕◯◯ Low	CRITICAL

Cognitive decline or dementia - High intensity vs Placebo - based on changes in MMSE or DSE score

1	randomised trials	not serious	not serious	not serious	serious[l]	none	39/366 (10.7%)	68/366 (18.6%)	**RR 0.57** (0.40 to 0.83)	**80 fewer per 1,000** (from 111 fewer to 32 fewer)	⊕⊕⊕◯ Moderate	CRITICAL

Cognitive decline or dementia - Medium intensity vs Placebo - cognitive impairment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[m]	not serious	serious[n]	very serious[g]	none	31/5101 (0.6%)	32/5079 (0.6%)	**RR 0.96** (0.59 to 1.58)	**0 fewer per 1,000** (from 3 fewer to 4 more)	⨁◯◯◯ Very low	CRITICAL

Cognitive decline (change from baseline) - Low intensity vs placebo: Mini mental state examination (scale 0-30 - higher is better)

1	randomised trials	very serious[o]	not serious	not serious	not serious[p]	none	2891	2913	-	MD **0.06 points higher** (0.04 lower to 0.16 higher)	⨁⨁◯◯ Low	CRITICAL

a. Serious outcome indirectness: creatine kinase levels not used in the definition

b. Absolute effect estimate based on risk difference

c. Sample size <80% of optimal information size

d. Majority of evidence at high risk of attrition bias

e. 95% confidence interval crosses both MIDs (0.8 and 1.25)

f. Serious heterogeneity (I2 = 55%) not explained by statin intensity subgroups

g. High risk of attrition bias (number missing greater than event rate) and high risk of outcome reporting bias (self-reported)

h. Serious outcome indirectness: definition does not match the protocol

i. 95% confidence interval crosses one MID (1.25)

j. Serious risk of outcome reporting bias: unclear how defined or if consistently recorded for all participants, and not prespecified

k. Serious risk of selection bias: prespecified subgroup analysis among those aged >70 years but not stratified at randomisation for this variable, and not all participants agreed to the cognitive assessment. Serious risk of outcome reporting bias: not prespecified. For baseline and change scores on the assessment tools see full evidence table.

l. 95% CI crosses one MID (0.8)

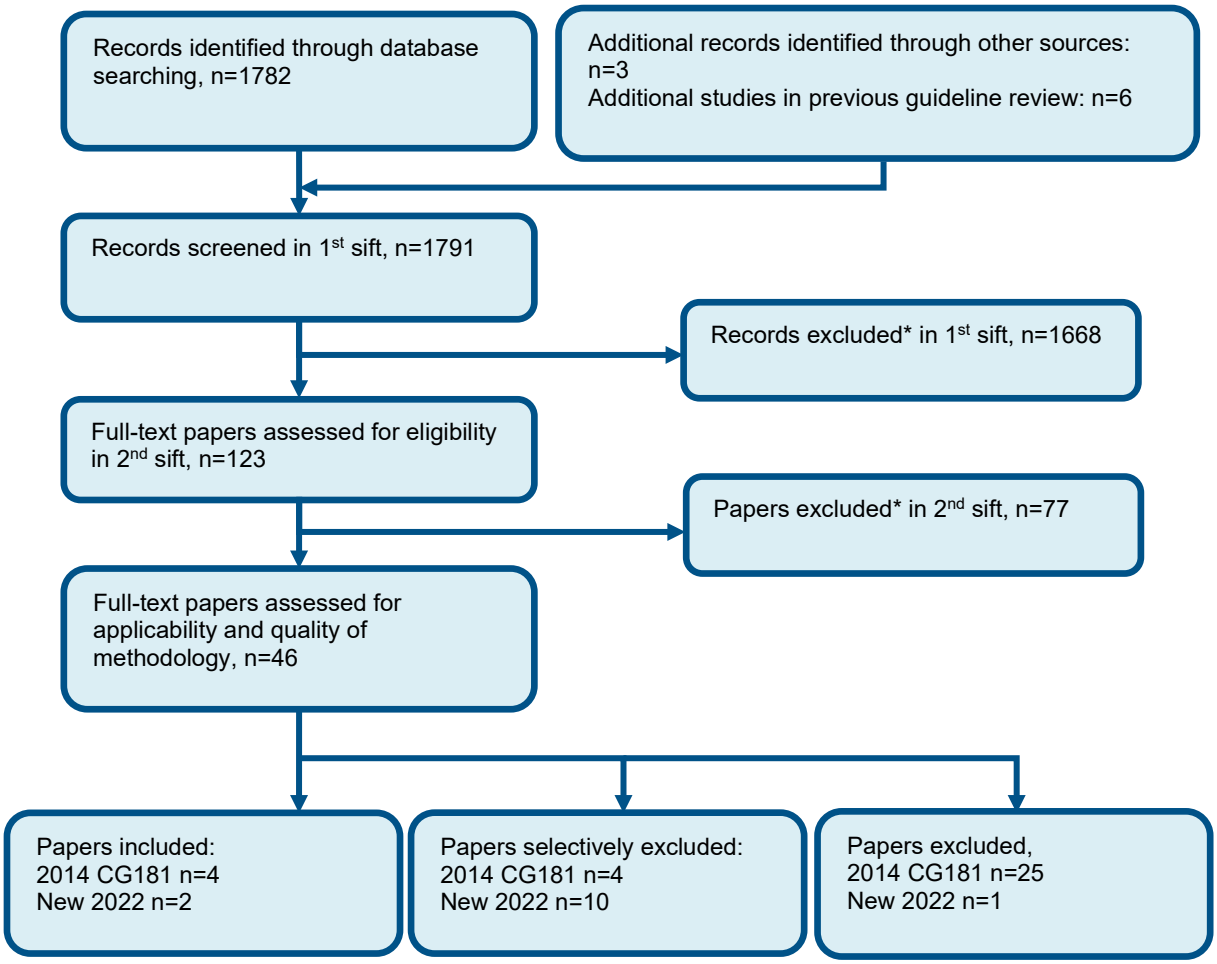
m. Unclear allocation concealment and outcome definition

n. Serious outcome indirectness: unclear if a validated questionnaire was used

o. Final scores not reported, only the difference in change from baseline, with the direction of effect unclear.

p. MID = 0.775 (0.5 x median baseline SD for MMSE score)

Appendix G – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

H.1 New studies since CG181

Study	Guthrie 2023[68]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model Updated version of CG181 model **Approach to analysis:** Markov model with cardiovascular disease states (no event, MI, unstable angina, stable angina, stroke, TIA, PAD, heart failure). No adverse effects. 1 year cycles. Relative treatment effects from CG181 meta-analysis of placebo controlled trials reporting hard outcomes. **Perspective:** UK NHS **Time horizon:** lifetime	**Population:** people without establish CVD – analysed by CV risk (QRISK3) **Cohort settings:** Start age: 60 **Intervention 1:** No statin **Intervention 2:** Low intensity statins[(b)] **Intervention 3:** Medium intensity statins[(b)] **Intervention 3:** High intensity statins[(b)]	**Total costs men/women (mean per patient):** **CVD risk 10% (da)** 1.£6,943/£6,013 2.£7,868/ £6,933 3.£7,336/£6,463 4.£7,353/£6,443 Incremental (2−1): £925/£920 (95% CI: NR; p=NR) Incremental (3−1): £393/£450 (95% CI: NR; p=NR) Incremental (4−1): £410/430 (95% CI: NR; p=NR) **Currency & cost year:** 2019-21 UK pounds **Cost components incorporated:** Statin costs and monitoring costs, CVD acute and ongoing costs. Lowest cost statin in each intensity category used in base case: S10, S20, A20.	**QALYs men/women (mean per patient):** **CVD risk 10% (da)** 1.13.460/12.057 2.13.616/12.191 3.13.724/12.284 4.13.797/12.350 Incremental (2−1): 0.156/0.134 (95% CI: NR; p=NR) Incremental (3−1): 0.264/0.227 (95% CI: NR; p=NR) Incremental (4−1): 0.337/0.293 (95% CI: NR; p=NR)	**Men/women, CVD risk 10%:** • 4 vs 1 £1,441/ £1,228 per QALY gained (da); 95% CI: NR • Interventions 2 and 3 ruled out by dominance or extended dominance • Probability Intervention 4 cost effective (£20K/30K threshold): 100%/100% **Analysis of uncertainty:** • Conclusions not sensitive to wide range of one-way sensitivity analyses except when a risk reduction was applied for non-CV death for low or medium statin only **CV risk threshold** Two-way combinations of age (40-80 years) and 10-year CV risk (2-40%) were analysed. High intensity statins were cost effective across all age/risk subgroups except men aged 74 to 80 years with 2% risk, men aged 80 years with 4% risk and women older than 76yrs with 2% risk. In these cases medium intensity statins were cost effective.

Treatment effect duration:[(a)] lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%				**Additional sensitivity analyses (ran for this guideline update – for details see Appendix H.1.1)** • Running sensitivity analysis reducing secondary CVD event probabilities by 10% and 20% as done in 2014 CG181 model did not change conclusions. • Including a diabetes adverse effect as in 2014 CG181 model base case did not change conclusions. • Applying minor changes to RRs based on systematic review for this update and Sept 2022 statin costs did not change conclusions. • Threshold analysis for cost effectiveness of A40 vs A20 found that with only a small increase in effectiveness A40 would be cost-effective due to very small differences in cost. **Direct treatment disutility** • Exploratory analysis where direct treatment disutility (a type of process utility aiming to reflect the inconvenience of taking medication) was incorporated changed the conclusion that high intensity statins were cost effective in some age/risk subgroups.
Data sources				
Health outcomes: Mortality was based on 2017-2019 ONS life tables for England and Wales and ONS 2019 mortality data by cause of death. Overall first cardiovascular event probabilities are defined by the specified 10 year QRISK3 predicted risk. The proportions of people experiencing different CVD events was derived from a novel analysis of CPRD data that used a multinomial logistic regression model to estimate the relative probabilities of a cardiovascular event being of each type according to sex, age at event and baseline QRISK3 predicted risk. Cardiovascular risk is assumed to increase linearly in the first 10 years; after this accelerating risk increase is incorporated based on the QRISK3 derivation study. Relative treatment effects were				

based on 2014 CG181 systematic review and meta analyses of studies with CVD event outcomes as done in the 2014 CG181 model. However, the non-cardiovascular risk benefit and risk of diabetes was removed. It is assumed that the risk ratios given for treatment with each class of statins are constant regardless of the baseline CV risk. It is also assumed that risk ratios are constant regardless of baseline LDL-cholesterol levels. The way relative treatment effects were applied was revised compared to the 2014 CG181 model as it was found the original methods sometimes led to anomalous results in later model cycles. The adverse effect of diabetes included in the 2014 CG181 model was removed based on a published meta analysis that found no association. Improved specification of competing risk of non-cardiovascular mortality was also incorporated. **Quality-of-life weights:** underlying utilities were based on a novel analysis of data from the Health Survey for England and were dependent on age and sex and non-linearity. CVD utility multiplier for the first year and subsequent years were EQ-5D-3L collected in mostly British populations, UK tariff, identified from a systematic literature review. **Cost sources:** standard national cost sources and published UK estimates from a rapid review.	
Comments	
Source of funding: NIHR **Limitations:** Transition probabilities after CVD first event are potentially out of date however conclusions weren't sensitive to this. Does not include diabetes adverse effect in but additional sensitivity analysis found conclusions not sensitive to this. **Other:** none.	
Overall applicability:(c) Directly applicable	**Overall quality:**(d) Minor limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Low intensity = F20-40, P10-40 and S10; medium intensity = A10, F80, R5 and S20-40; high intensity = A20-80, R10-40 and S80.

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Schlackow 2019[157]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model with CKD stages (3B, 4, 5, on dialysis, with kidney transplant) and	**Population:** CKD stages 3B, 4 and 5 not on dialysis. Mean age in SHARP study was 63 years; 62% were male; 23% had diabetes; and 15% had a prior history of (noncoronary) vascular disease.	**Total costs (mean per patient):** **By CKD stage** **3B** Intervention 1: £60,100 Intervention 2: £61,000 Intervention 3: £61,100 Incremental (2−1): £900 (95% CI: -£1,100 to £2,600; p=NR)	**QALYs (mean per patient):** **By CKD stage** **3B** Intervention 1: 12.73 Intervention 2: 12.96 Intervention 3: 12.98 Incremental (2−1): 0.23 (95% CI: 0.04 to 0.39; p=NR) Incremental (3−2): 0.02	**ICER:** **By CKD stage** **3B** • 2 vs 1 £3,700 per QALY gained (pa); 95% CI: -£13,800 to £8,100 • 3 vs 2 £5,400 per QALY gained (pa); 95% CI: -£11,100 to £9,600 Probability Intervention 2 cost effective (£20K/30K threshold): NR **4**

cardiovascular events (major atherosclerotic events, haemorrhagic stroke, vascular death). 1 year cycles. Relative treatment effects with statins estimated using LDL lowering and applied to major atherosclerotic events and vascular death. **Perspective:** UK NHS (note that a US perspective is also reported but not included here) **Time horizon:** lifetime **Treatment effect duration:**[(a)] lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	People with a history of MI or revascularisation were excluded. **Cohort settings:** Start age: Male: **Intervention 1:** No lipid-lowering treatment **Intervention 2:** Atorvastatin 20mg daily **Intervention 3:** Atorvastatin 40mg daily Note that ezetimibe 10mg and combinations of ezetimibe and atorvastatin were also incorporated but are not presented here as are not included in the review protocol.	Incremental (3−2): £100 (95% CI: -£100 to £200; p=NR) **4** Intervention 1: £77,900 Intervention 2: £81,000 Intervention 3: £81,300 Incremental (2−1): £3,100 (95% CI: £500 to £5,600; p=NR) Incremental (3−2): £300 (95% CI: £0 to £500; p=NR) **5 not on dialysis** Intervention 1: £121,700 Intervention 2: £126,400 Intervention 3: £126,800 Incremental (2−1): £4,700 (95% CI: £1,100 to £8,000; p=NR) Incremental (3−2): £400 (95% CI: £100 to £700; p=NR) **<u>By 5-year risk of cardiovascular disease at baseline</u>** **Low (<10%)** Intervention 1: £107,900 Intervention 2: £109,900 Intervention 3: £110,100 Incremental (2−1): £2,000 (95% CI: £400 to £3,400; p=NR)	(95% CI: 0.00 to 0.03; p=NR) **4** Intervention 1: 10.23 Intervention 2: 10.54 Intervention 3: 10.56 Incremental (2−1): 0.30 (95% CI: 0.11 to 0.48; p=NR) Incremental (3−2): 0.03 (95% CI: 0.01 to 0.04; p=NR) **5 not on dialysis** Intervention 1: 8.59 Intervention 2: 8.86 Intervention 3: 8.88 Incremental (2−1): 0.27 (95% CI: 0.10 to 0.43; p=NR) Incremental (3−2): 0.02 (95% CI: 0.01 to 0.03; p=NR) **<u>By 5-year risk of cardiovascular disease at baseline</u>** **Low (<10%)** Intervention 1: 16.49 Intervention 2: 16.75 Intervention 3: 16.77 Incremental (2−1): 0.27 (95% CI: 0.12 to 0.40; p=NR) Incremental (3−2): 0.02	• 2 vs 1 £10,400 per QALY gained (pa); 95% CI: £3,600 to £16,900 • 3 vs 2 £11,400 per QALY gained (pa); 95% CI: £5,600 to £18,500 Probability Intervention 2 cost effective (£20K/30K threshold): NR **5 not on dialysis** • 2 vs 1 £18,800 per QALY gained (pa); 95% CI: £12,300 to £25,200 • 3 vs 2 £19,800 per QALY gained (pa); 95% CI: £14,500 to £26,700 Probability Intervention 2 cost effective (£20K/30K threshold): NR **<u>By 5-year risk of cardiovascular disease at baseline</u>** **Low (<10%)** • 2 vs 1 £7,800 per QALY gained (pa); 95% CI: £3,000 to £11,400 • 3 vs 2 £9,500 per QALY gained (pa); 95% CI: £6,000 to £13,500 Probability Intervention 2 cost effective (£20K/30K threshold): NR **Medium (10%-20%)** • 2 vs 1 £9,300 per QALY gained (pa); 95% CI: £3,800 to £13, 900 • 3 vs 2 £10,300 per QALY gained (pa); 95% CI: £5,800 to £15,100 Probability Intervention 2 cost effective (£20K/30K threshold): NR **High (≥20%)** • 2 vs 1 £14,100 per QALY gained (pa); 95% CI: £6,500 to £20,100

		Incremental (3−2): £200 (95% CI: £0 to £300; p=NR) **Medium (10%-20%)** Intervention 1: £75,500 Intervention 2: £79,100 Intervention 3: £79,300 Incremental (2−1): £2,500 (95% CI: £500 to £4,300; p=NR) Incremental (3−2): £200 (95% CI: £0 to £300; p=NR) **High (≥20%)** Intervention 1: £61,000 Intervention 2: £65,000 Intervention 3: £65,300 Incremental (2−1): £3,900 (95% CI: £900 to £6,600; p=NR) Incremental (3−2): £300 (95% CI: £100 to £600; p=NR) **Currency & cost year:** 2019 (drug costs) 2011 (hospitalisation costs) UK pounds **Cost components incorporated:** Statin costs, hospitalisation costs related to CKD and CVD.	(95% CI: 0.01 to 0.03; p=NR) **Medium (10%-20%)** Intervention 1: 9.74 Intervention 2: 10.00 Intervention 3: 10.02 Incremental (2−1): 0.27 (95% CI: 0.12 to 0.40; p=NR) Incremental (3−2): 0.02 (95% CI: 0.01 to 0.03; p=NR) **High (≥20%)** Intervention 1: 5.46 Intervention 2: 5.73 Intervention 3: 5.75 Incremental (2−1): 0.27 (0.11 to 0.40) (95% CI: NR; p=NR) Incremental (3−2): 0.02 (95% CI: 0.01 to 0.03; p=NR)	• 3 vs 2 £14,900 per QALY gained (pa); 95% CI: £8,000 to £21,100 Probability Intervention 2 cost effective (£20K/30K threshold): NR Authors note that in all patient subgroups, rosuvastatin 20mg was dominated by cheaper, and with the same effectiveness, atorvastatin 40mg although results are not reported. Results are not shown for options including ezetimibe however note that atorvastatin 40mg plus ezetimibe was the most cost effective option except in CKD stage 5. Uncertainty from probabilistic analysis not available for only comparators relevant to review protocol (only for all comparators including those with ezetimibe). **Analysis of uncertainty:** Conclusions were not sensitive to inclusion of potential adverse effects or reduced compliance with treatment. ICERs were substantially reduced when the annual treatment costs for RRT was assumed similar to those for CKD stage 5 not on dialysis.
Data sources				

Health outcomes: baseline transition probabilities for CKD progression and CVD events were based on analysis of data from the SHARP study. UK non-vascular mortality data was used. **Quality-of-life weights:** utilities were based on EQ-5D-3L data from the SHARP study, UK tariff. **Cost sources:** Resource use (in terms of annual hospital care) for each model state was based on an analysis of data from the SHARP study. Standard UK national sources were used (Drug Tariff and NHS reference costs).
Comments
Source of funding: The SHARP study, including the analyses presented here, was funded by Merck & Co., Inc., Kenilworth, NJ USA, with additional support from the British Heart Foundation (CH/1996001/9454), and the UK Medical Research Council (A310). SHARP was initiated, conducted, and interpreted independently of the principal study funder (Merck & Co.) **Limitations:** 2003-2011 resource use from international trial and 2009/2011 UK unit costs may not reflect current UK context. Reduction in CV risk modelled via LDL reduction rather than via risk ratios for hard outcomes. **Other:** none.
Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(e) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(f) Directly applicable / Partially applicable / Not applicable

(g) Minor limitations / Potentially serious limitations / Very serious limitations

H.1.1 Guthrie 2023 – additional sensitivity analyses

The authors of Guthrie 2023 provided the executable model file for their updated version of the 2014 CG181 model and some additional sensitivity analyses were conducted by the guideline development team to explore uncertainties not already addressed by existing analyses in the study report. [68] For pragmatic reasons, deterministic analysis was conducted but this would have no bearing on the cost-effectiveness ratios, as the base case deterministic and probabilistic estimates were closely aligned.

For comparison, Guthrie 2023 reported:

- the base case ICERs for 60-year-old men/women with 10% 10-year CV risk were £1,217/£1,469 per QALY gained.

Guthrie 2023 also reported two-way results where age was varied between 40 and 80 years and 10-year risk was varied between 2% and 40%. This found that high intensity statins were cost effective for every age/risk combination except the following (which were agreed to be non-plausible age/risk combinations):

- Men aged 74 to 80 years with 2% risk
- Men aged 80 years with 4% risk
- Women aged 76 to 80 years with 2% risk

Lower secondary CVD event probabilities

In the 2104 CG181 model, sensitivity analyses were done where secondary CVD event probabilities were reduced by 10% and 20% to account for potential improvements in outcomes over time. The Guthrie 2023 model uses the same secondary CVD event probabilities and the authors noted that they should be updated and so this sensitivity analysis was done by the guideline team to explore whether cost-effectiveness conclusions might be affected. [68] This functionality was not in the Guthrie 2023 model and so an additional switch was added that multiplied secondary event probabilities by 90% or 80% as was done in the 2014 CG181 analysis.

ICERs for 60 year old men/women with 10% 10-year CV risk were changed from £1,217/£1,469 per QALY gained to £1,207/£1,467 (90% applied) and £1,196/£1,465 (80% applied) and conclusions across age/risk subgroups did not change.

Diabetes adverse effect

The Guthrie 2023 model for primary prevention removed the diabetes adverse effect included in the 2014 CG181 model. [68] The updated clinical review for this guideline found a small increase in diabetes that did not meet the criteria for a clinically important harm however the relative risks were very similar to those in the 2014 CG181 review and so the guideline team ran the model adding this adverse affect back in to see if it affects conclusions about cost effectiveness.

The Guthrie 2023 model already included the functionality to include the diabetes adverse event on the same basis as in the 2014 CG181 base-case analysis. This was that additional diagnoses represent cases of diabetes being brought forward in people who would otherwise still have been expected to contract diabetes later in life by an average of 4 years. The costs of the first 4 years of diabetes treatment for these people were added to all statin arms of the model compared with no treatment. The number of people diagnosed earlier was estimated assuming that with no treatment 5% of individuals without CVD would be diagnosed during primary prevention and applying risk ratios for low, medium and high intensity statins from the clinical review. Costs were applied in years 3, 4, 5 and 6 of the model.

The committee agreed that statin induced cases of diabetes were most likely to relate to a shift in biochemical markers that mean people meet the definition for a diagnosis of diabetes but the change is not great enough to expose people to additional risks in terms of macro- and micro-vascular complications. Given this, the approach taken in this sensitivity analysis where additional treatment costs are incurred but QALYs are not impacted was deemed appropriate. It was noted that the 2014 CG181 model also undertook at sensitivity analysis that incorporated longer term treatment cost implications and cost and QALY losses due to diabetes complications however the committee agreed this was not likely to reflect a real world impact and so didn't need to also be reran.

Relative risks for diabetes were based on the updated clinical review (Table 33). The inputs used in the 2014 CG181 analysis are also shown for comparison. Resource use and costs used are shown in Table 34 with 2014 CG181 inputs for comparison. Resource use was based on the assumptions used in the 2014 CG181 analysis with the following changes. GP and nurse visits were reduced as it was identified that the original assumption was based on a study that measured total visits not additional visits compared to someone without diabetes. GP and nurse visits were instead based on the estimates reported in NICE guideline PH38 about prevention of type 2 diabetes and annual eye screening was also added.[123] The model already assumes that everyone on statins will have 1 HbA1c test per year but as people with diabetes will have HbA1c measured at least every 6 months an additional test cost was also added. It was assumed that 20% of people would use an SGLT2 inhibitor based on committee expert opinion. Unit costs were also updated; sources are listed in the table footnote. The committee noted that the annual costs are somewhat approximate and highlighted that not everyone will receive the drug treatments specified early in management.

Table 33: Relative risks for diabetes

	2014 CG181 data	Updated clinical review
Low intensity	1.05 (0.95 to 1.15)	1.05 (0.96 to 1.15)
Medium intensity	1.11 (1.00 to 1.23)	1.11 (1.00 to 1.24)
High intensity	1.25 (1.05 to 1.49)	1.21 (1.08 to 1.35)

Table 34: Early diabetes costs (first 4 years)

	2014 CG181 costs		Updated 2022 costs	
Component	**Resource use**	**Unit cost**	**Resource use**	**Unit cost**
GP appointment	4 a year	£45.00	2 a year	£36.55[(a)]
Nurse appointment	5 a year	£13.43	2 a year	£15.04[(a)]
HbA1c test	n/a	n/a	Additional 1 a year	£3[(b)]
Eye screening	n/a	n/a	1 a year	£38[(b)]
Diet management programme	1 per 4 years	£87.96	1 per 4 years	£101[(c)]
Metformin (500 mg tablets x84)	4 a day	£1.00	4 a day	£2.13[(d)]
ACE inhibitor (ramipril 10 mg capsules x 28)	1 a day	£1.19	1 a day	£1.07[(d)]
Calcium-channel blocker (amlodipine 10 mg tablets x 28)	1 a day	£0.94	1 a day	£0.70[(d)]
SGLT2 inhibitor (empagliflozin tablets x28)	n/a	n/a	1 a day; 20% of people	£36.59[(d)]
Total annual cost		**£314.33**		**£325.03**

Abbreviations: ACE = angiotensin-converting enzyme; SGLT2 = sodium glucose co-transporter-2

(a) PSSRU Unit Costs for Health and Social Care 2021, including direct care staff costs and qualifications (excluding individual and productivity costs)[48]

(b) Cost from 2014 CG181 report inflated to 2020/21 using inflation indices from PSSRU Unit Costs for Health and Social Care 2021[48, 120]
(c) Cost from 2011 PH38 report inflated to 2020/21 using inflation indices from PSSRU Unit Costs for Health and Social Care 2021[48, 123]
(d) NHS Drug Tariff September 2022 online[126]

ICERs for 60 year old men/women with 10% 10-year CV risk were changed from £1,217/£1,469 per QALY gained to £1,245/£1,501 and conclusions across age/risk subgroups did not change.

Updated treatment effects and statin costs

The Guthrie 2023 model uses relative risks from the 2014 CG181 guideline clinical review. This review was updated as part of this guideline update. [68] Relative risks did not change substantially but for completeness a sensitivity analysis was done with the updated data as well as September 2022 statin costs.[126]

Table 35: Treatment effects

RR vs placebo	2014 CG181 data	Updated clinical review
Non-fatal MI		
Low intensity	0.78 (0.72 to 0.84)	0.78 (0.72 to 0.84)
Medium intensity	0.61 (0.55 to 0.68)	0.62 (0.55 to 0.68)
High intensity	0.46 (0.37 to 0.59)	0.51 (0.42 to 0.62)
Stroke		
Low intensity	0.84 (0.75 to 0.94)	0.83 (0.74 to 0.93)
Medium intensity	0.73 (0.66 to 0.81)	0.73 (0.66 to 0.81)
High intensity	0.80 (0.70 to 0.91)	0.74 (0.65 to 0.84)
Cardiovascular death		
Low intensity	0.84 (0.78 to 0.91)	0.84 (0.78 to 0.91)
Medium intensity	0.81 (0.75 to 0.87)	0.81 (0.75 to 0.87)
High intensity	0.73 (0.61 to 0.88)	0.80 (0.70 to 0.92)

Table 36: Statin costs

Statin	Guthrie 2023[68] (November 2021 NHS Drug Tariff)	September 2022 NHS Drug Tariff
Low intensity - simvastatin 10 mg/day	£0.92	£0.74
Medium intensity simvastatin 20 mg/day	£0.96	£0.77
High intensity – atorvastatin 20mg/day	£1.10	£0.89
High intensity – atorvastatin 80mg/day	£1.68	£1.35

ICERs for 60 year old men/women changed from £1,217/£1,469 per QALY gained to £922/£1,248 and high intensity statins were now cost effective for all age/risk subgroups.

Atorvastatin 40 mg

In the model statins are grouped by intensity and the underlying assumption is that treatment effect is the same within the group and so the lowest cost option within the group will be the most cost effective. In the 2014 CG181 update there was not considered enough data to model comparisons within the high intensity group. However, results were presented where the cost of atorvastatin 20 mg was replaced with cost of higher doses. In addition, in the secondary prevention analysis threshold analyses were undertaken to assess how much more effective higher doses of atorvastatin would need to be for it to be cost effective to help inform discussions about starting dose. These threshold analyses were not done in the 2014 CG181 primary prevention analysis.

A new study was identified in the clinical review for this update that compared a high intensity statin (atorvastatin 40 mg) with another high intensity statin (atorvastatin 20 mg). The committee agreed this evidence had some limitations but that it supported greater effect with the higher dose as would be expected. In addition, the current cost of atorvastatin 40mg is very similar to atorvastatin 20 mg (A20 £0.89, A40 £0.97 per pack of 28; annual cost difference £1.04 per person). Therefore some additional sensitivity analyses were added with atorvastatin 40 mg.

The guideline team first ran the analysis where the cost of a high intensity statin was changed to the atorvastatin 40 mg cost of £0.97 per pack of 28. ICERs for 60 year old men/women with 10% 10-year CV risk were changed from £922/£1,232 (analysis above with update relative risks and September 2022 costs) to £971/£1,285 and high intensity statins remained cost effective for all age/risk subgroups.

The updated CG181 model already included functionality to include a higher dose high intensity comparator (A80) programmed with higher costs (in addition to high dose statin with A20) but did not include a variable to specify improved treatment effects. The cost of A40 was added and used for the higher dose high intensity comparator. Three additional variables for the RR of A40 vs A20 for MI, stroke and CV death. Transition probabilities for high intensity statin were then multiplied by these additional relative risks to calculate the higher dose high intensity statin comparator transition probabilities.

In this analysis, even if the RRs for A40 vs A20 were only 0.99 (for MI, stroke and CV death), A40 was cost effective compared to A20 with an ICER of £883/£1,214 per QALY gained for men/women aged 60 years with 10% 10-year CV risk compared to no statin treatment.

H.2 Evidence from the 2014 CG181 update

H.2.1 CG181 2014 model

Study	CG181 2014 model[120] The full methods and results for the CG181 2014 model are available in appendix L of the CG181 2014 guideline report: https://www.nice.org.uk/guidance/cg181/evidence/lipid-modification-update-appendices-pdf-243786638.			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model with cardiovascular disease states (no event, MI, unstable angina, stable angina, stroke, TIA, PAD, heart failure). Diabetes adverse effect incorporated 4 years additional costs. 1-year cycles. Relative treatment effects from 2104 CG181 meta-analysis of placebo controlled trials reporting hard outcomes. **Perspective:** UK NHS **Time horizon:** lifetime	**Populations:** • People with established CVD • People without established CVD – analysis by CV risk (QRISK2)[(b)] **Cohort settings:** Start age: 60 years Male **Intervention 1:** No statin **Intervention 2:** Low intensity statins[(c)] **Intervention 3:** Medium intensity statins[(c)] **Intervention 4:** High intensity statins[(c)]	**Total costs men (mean per patient):** **Established CVD (pa)** 1.£9,404 2.£11,116 3.£11,057 4.£11,057 Incremental (2−1): £1,712 (95% CI: NR; p=NR) Incremental (3−1): £1,653 (95% CI: NR; p=NR) Incremental (4−1): £1,903 (95% CI: NR; p=NR) **Without established CVD – CVD risk 10% (pa)** 1.£3,013 2.£4,353 3.£4,199 4.£4,285 Incremental (2−1): £1,340 (95% CI: NR; p=NR)	**QALYs men (mean per patient):** **Established CVD (pa)** 1.6.293 2.6.579 3.6.675 4.6.841 Incremental (2−1): 0.372 (95% CI: NR; p=NR) Incremental (3−1): 0.465 (95% CI: NR; p=NR) Incremental (4−1): 0.643 (95% CI: NR; p=NR) **Without established CVD – CVD risk 10% (pa)** 1.11.414 2.11.619 3.11.698 4.11.723 Incremental (2−1): 0.205 (95% CI: NR; p=NR)	**Established CVD (pa)** • High intensity vs no treatment: £2,959 per QALY gained • Low and medium intensity ruled out by dominance or extended dominance • Probability cost effective (£20K/30K threshold): high 86.6%, medium 11.7%, low 1.7%, no treatment 0%/NR. **Analysis of uncertainty:** • High intensity statin was the most cost-effective option for all age (40, 50, 60, 70) and gender subgroups. • ICER using A80 instead of A20 cost for high intensity: £3,275 per QALY gained (pa). • Conclusions not sensitive to a wide range of sensitivity analyses except when all risk ratios are taken at end of range and if rate of non-CV death not constant between statin categories. • Conclusions not sensitive to removal of all-cause mortality affect (additional 2022).[(d)] • Threshold analysis within high intensity class: A40/A80 cost effective compared to A20 if 1%/2% more effective.[(e)]

Treatment effect duration:[(a)] lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%		Incremental (3−1): £1,186 (95% CI: NR; p=NR) Incremental (4−1): £1,272 (95% CI: NR; p=NR) **Currency & cost year:** 2014 UK pounds **Cost components incorporated:** Statin costs and monitoring costs, CVD acute and ongoing costs, diabetes adverse effect costs. Lowest cost statin in each intensity category used in base case: S10, S20, A20.	Incremental (3−1): 0.284 (95% CI: NR; p=NR) Incremental (4−1): 0.309 (95% CI: NR; p=NR)	**<u>Without established CV</u>** **CVD risk 10% (pa)** • High intensity vs no treatment: £4,125 per QALY gained • Low and medium intensity ruled out by dominance or extended dominance • Probability cost effective (£20K/30K threshold): high 74.5%, medium 25.5%, low 0% and no treatment 0%/NR **CV risk threshold** High intensity remains CE: 6.8% **Analysis of uncertainty:** • At 10% CV risk high intensity statins were the most cost-effective option for all age (40, 50, 60, 70) and gender subgroups. • Conclusions not sensitive to a wide range of sensitivity analyses except when all risk ratios are taken to be at the end of their range, if the rate of non-CV death was not constant between statin categories and when baseline TPs reduced by 20%. • Using A80 cost instead of A20 for high intensity it remains most cost-effective option for men age 60 years; ICER vs medium £12,769 per QALY gained (medium no longer ruled out by extended dominance); ICER vs no statin £4,875. • Costs and QALYs vary by CV risk. High intensity statins are increasingly cost-effective with increasing CV risk. • Risk threshold high intensity remains CE is 5.2% for women age 60 years.

				• Risk threshold high intensity remains CE varies with age for both men and women: to a max of 6.8% and 7.3% at age 70 years) (see Table 37 below). • Medium intensity was CE to a lower risk threshold.
Data sources				
Health outcomes: Mortality was based on 2010-2012 ONS life tables for England and Wales and ONS 2012 mortality data by cause of death. First cardiovascular event probabilities are defined by the specified 10-year QRISK2 predicted risk. Baseline event rates for initial and subsequent CVD events taken from analyses developed for previous NICE technology appraisals or guidelines (Ward 2005[184] and NCCPC 2008[121]) updated by 2014 CG181 guideline update using a range of sources. Relative treatment effects based on 2014 CG181 systematic review and meta analysis of studies with CVD event outcomes. Cardiovascular risk assumed to increase linearly with time. It is assumed that the risk ratios given for treatment with each class of statins are constant regardless of the baseline CV risk. It is also assumed that risk ratios are constant regardless of baseline LDL-cholesterol levels and LDL. **Quality-of-life weights:** Utility multipliers for health states were based on statins NICE technology appraisal model by Ward 2005[184] (these were determined following a systematic review), supplemented with values used by NCCPC 2008[121] for states not included in Ward model – these used a variety of published sources. The instrument and values sets used are not reported. **Cost sources:** standard national cost sources and published UK estimates.				
Comments				
Source of funding: NICE. **Limitations:** 2012-14 costs may not reflect current costs and updating costs has been shown to improve cost effectiveness in a more recent update of this model and this could affect conclusions about the threshold for cost effectiveness for primary prevention; rosuvastatin has since become available generically although is not used in the base case analysis and is not the lowest cost high intensity statin. The instrument and value sets are not reported for utility weights used to estimate QALYs. Transition probabilities after CVD first event are potentially out of date however sensitivity analyses were done with lower rates. Inclusion of an effect of statins on non-CV mortality may not be appropriate. Based on subsequently published update of 2014 CG181 model for primary prevention (Guthrie 2023)[68] some other inputs could be more up to date. However, conclusions are not considered likely to change for the established CVD population; conclusions about the CVD risk threshold may be affected for the primary prevention population. **Other:** None.				
Overall applicability:[(f)] Partially applicable **Overall quality:**[(g)] Minor limitations (established CVD analysis) / Potentially serious limitations (without established CVD analysis)				

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NCCPC = National Collaborating Centre for Primary Care; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(c) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(d) A separate analysis was also run for people with type two diabetes with CV risk based on UKPDS however, as QRISK2 was recommended for use in people with type 2 diabetes in CG181 only the main analysis using QRISK2 is presented here.

(e) Low intensity = F20-40, P10-40 and S10; medium intensity = A10, F80, R5 and S20-40; high intensity = A20-80, R10-40 and S80.

(f) Risk ratios for non-cardiovascular mortality were changed to 1 for all statin comparators. Low and medium intensity options remained ruled out by dominance or extended dominance. The ICER for high intensity (A20) compared to no treatment increased to £3171 from £3077 (deterministic analysis).

*(g) 1% increase in effectiveness is applied as: revised RR for high vs placebo = 1 - ((1-original RR) * 1.01). For example, RR with 1% increase in effectiveness if original RR 0.8: revised RR = 1 – ((1-0.8)*1.01)) = 0.798.*
(h) Directly applicable / Partially applicable / Not applicable
(i) Minor limitations / Potentially serious limitations / Very serious limitations

Table 37: 2014 CG181 model: 10-year CV risk thresholds using QRISK2 at which high intensity primary prevention treatment was cost effective compared to medium intensity treatment (simvastatin 20 mg) for different cost-effectiveness thresholds

	Risk threshold above which high-intensity statins are cost effective					
	£20,000 per QALY gained			£30,000 per QALY gained		
	A20	A40	A80	A20	A40	A80
Men age 40	3.1%	3.3%	4.0%	2.9%	3.0%	3.5%
Men age 50	5.0%	5.3%	6.3%	4.8%	5.0%	5.7%
Men age 60	6.8%	7.1%	8.7%	6.4%	6.7%	7.8%
Men age 70	6.8%	7.5%	10.1%	6.4%	6.8%	8.6%
Women age 40	2.4%	2.6%	3.4%	2.2%	2.3%	2.9%
Women age 50	3.5%	3.8%	4.8%	3.3%	3.5%	4.2%
Women age 60	5.2%	5.6%	7.2%	4.8%	5.1%	6.3%
Women age 70	7.3%	8.1%	11.6%	6.7%	7.3%	9.6%

Source: Reproduced from 2014 CG181 guideline report, Appendix L Cost-effectiveness analysis: low intensity, medium intensity and high-intensity statin treatment for the primary and secondary prevention of CVD.[120] The authors note that the primary prevention model does not work at very low levels of CV risk due to the effect of the negative component of age-related risk which is added to early years of the model. Values written in lighter type denote risks below the level at which the model is entirely accurate; these values are indicative of the likely risk thresholds, but should not be relied on.

H.2.2 Published studies included in the 2014 CG181 update

Ara 2009/Ara 2012[15, 16]				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model of CVD states with 1-year cycles (adaptation of model in Ward 2005[184]) **Perspective:** UK NHS **Time horizon:** lifetime **Treatment effect duration**[(a)]**:** lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** UK patients with existing ACS (angina, MI, revascularisation) **Cohort settings:** Start age: 60 Male: NR **Intervention 1:** Medium intensity statin: simvastatin 40 mg daily **Intervention 2:** High intensity statins • **2a:** Simvastatin 80 mg daily • **2b:** Atorvastatin 80 mg daily • **2c:** Rosuvastatin 40 mg daily Note that simvastatin 80 mg is not included in the 2022 review protocol as it is no longer used.	**Total costs (mean per patient):** Intervention 1: £14,522 Intervention 2a: £15,110 Intervention 2b: NR[(b)] Intervention 2c: £18,464 Incremental (2a−1): £588 Incremental (2b−1): NR[(b)] Incremental (2c−1): £3,941 (95% CI: NR; p=NR in all cases) **Currency & cost year:** 2007 UK pounds **Cost components incorporated:** Statins. Consultations and monitoring tests. CVD event health states for Markov model (first and subsequent years): unstable angina, MI,	**QALYs (mean per patient):** Intervention 1: 7.546 Intervention 2a: 7.657 Intervention 2b: NR[(b)] Intervention 2c: 7.862 Incremental (2a−1): 0.111 Incremental (2b−1): NR[(b)] Incremental (2c−1): 0.316 (95% CI: NR; p=NR in all cases)	**ICERs** **Intervention 2a versus Intervention 1:** £5,319 per QALY gained (pa) (95% CI: £5,229 to £5,408) **Intervention 2b versus Intervention 1:** £3,172 per QALY gained (pa/da – unclear) (95% CI: NR) **Intervention 2c versus Intervention 1:** £12,484 per QALY gained (pa) (95% CI: £12,372 to £12,595) **Intervention 2b versus Intervention 2a:** Atorvastatin 80 mg dominates simvastatin 80 mg **Intervention 2c versus Intervention 2b:** ICER cannot be calculated using data reported,[(f)] but it is stated that atorvastatin 80 mg is the preferred, cost effective treatment where the cost-effectiveness threshold is between £5000 and £30,000 per QALY gained. **Analysis of uncertainty:** The base case scenario, with a high cost of atorvastatin (in which it was found that all 3 high intensity statins were cost effective compared to simvastatin 40 mg, with rosuvastatin 40 mg dominating atorvastatin 80 mg and cost

		revascularisation, stroke.		effective compared to simvastatin 80 mg), was subject to one-way sensitivity analyses with regard to discounting (0%), starting age (50, 70), health state costs (±50%) and utility values (±20%) and was robust to all these – the ICER for rosuvastatin (£12,484 in the base case) remained below £20,000 in each case. High-intensity statins were however dominated by medium-intensity statins when the relative clinical effectiveness of medium- and high-intensity statins was varied substantially. These sensitivity analyses were not applied when the cost of atorvastatin was reduced (as that was itself a sensitivity analysis), though it could be predicted that the results would similarly be relatively robust to varying most parameters apart from clinical effectiveness. Different patterns of adherence to statins were also studied, but these also had only moderate effect on cost effectiveness, both in the base case and for reduced cost (£92) atorvastatin – with the ICER varying between £3,155 and £7,331 with different assumptions regarding adherence to statins. The analysis was also repeated with a third, lower possible atorvastatin cost of £20.78 per year. The ICER was not stated, but at this cost atorvastatin was the preferred, cost-effective intervention at all cost-effectiveness thresholds.
Data sources				
Health outcomes: Baseline event rates taken from large UK registry studies (NHAR, RITA-2, SLSR), similar to Ward 2005. Effectiveness from meta-analysis and network meta-analysis of 28 phase III trials measuring effect of statins on LDL cholesterol. Cholesterol reduction converted into CVD events using published analysis of statin RCT data from the Cholesterol Treatment Trialists (CTT) collaborators 2005. **Quality-of-life weights:** Various published sources using EQ-5D in UK. **Cost sources:** Health state costs from Ward 2005 or calculated from BNF prices using new assumptions on resource use. Simvastatin and rosuvastatin costs from BNF (2008). Atorvastatin cost estimated future cost for generic drug.				

Comments
Source of funding: UK National Coordinating Centre for Health Technology Assessment. **Limitations:** Based on UK ACS population, following NICE reference case. Model does not account for any adverse events. Effectiveness of statins in reducing CVD events is based on a meta-analysis of effectiveness in reducing LDL cholesterol, linked to relationship between cholesterol reduction and CVD event reduction - necessary at the time due to lack of direct evidence for rosuvastatin, but not direct evidence of CVD event reduction. Cost of atorvastatin 80 mg assumed to fall to £92 or £20.78 annually once off patent; actual current cost is lower. **Other:** None.
Overall applicability[(c)]**:** Partially applicable **Overall quality**[(d)]**:** Potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; ACS: acute coronary syndrome; CUA: cost–utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; MI: myocardial infarction; NR: not reported; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Costs and outcomes were given for the intervention (£18,572, 7.778 QALYs) and incrementally (£4,050, 0.232 QALYs – ICER £17,469) for the base case used in the paper (atorvastatin 80 mg at full price: £367.76 per year), but not for the sensitivity analysis for atorvastatin 80 mg at £92 per year (or the additional analysis using £20.78 per year), which are the analyses of primary interest to this review.

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

McConnachie 2014[111]				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** within-trial analysis **Approach to analysis:** 10-year follow up of participants in 5-year WOSCOPS trial[165], looking at healthcare usage **Perspective:** UK NHS **Follow-up:** 15 years	**Population:** Men in West Scotland with raised cholesterol but no previous MI (primary prevention) Start age: 45–64 Male: 100% **Intervention 1:** No statins during trial (4.9 years); after 5 years additional follow up 35.2% taking LLT	**Total costs (mean per patient):** Intervention 1: £3,550 Intervention 2: £2,840 Incremental (2−1): −£710 (95% CI: −£1,090 to −£320; p<0.001) **Currency & cost year:** 2012 UK pounds **Cost components incorporated:** Statins (pravastatin 40 mg).	**QALYs (mean per patient):** Intervention 1: 11.057 Intervention 2: 11.193 Incremental (2−1): 0.136 (95% CI: 0.025 to 0.247; p=0.017)	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominates Intervention 1 (is cheaper and more effective) – cost saving of £710 per person over 15 years. Probability Intervention 2 cost-effective (£20K/30K threshold): N/A **Analysis of uncertainty:** One-way sensitivity analyses showed that the intervention was still cost saving if hospital costs or ongoing costs of CVD events were varied by

Treatment effect duration[(a)]**:** 5 years **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Intervention 2:** Pravastatin 40 mg daily during trial (4.9 years); after 5 years additional follow up 38.7% taking LLT	Consultations and monitoring tests. Healthcare: costs of hospital admissions for any CV or diabetes-related cause; costs of continuing treatment for people with CV conditions		±25%. If statin and monitoring costs were increased by 400% then it was no longer cost saving but still highly cost effective.
Data sources				
Health outcomes: CVD events and hospital admissions based on linked healthcare records for WOSCOPS participants for control and intervention groups. **Quality-of-life weights:** Uses disutilities of CV conditions from Ward 2005 – various sources. **Cost sources:** Used 2012 UK annual cost of generic pravastatin 40 mg (£36), similar to current UK cost (£23). Hospital costs based on NHS Scotland Tariff costs for HRGs. Continuing costs of CV conditions based on Ward 2005.				
Comments				
Source of funding: Original WOSCOPS trial and first 5 years follow up funded by Bristol-Myers Squibb (manufacturer of pravastatin). This further follow-up study was not funded by manufacturer (Wellcome Trust, Celera Diagnostics). **Limitations:** Looks at Scottish men aged 45–54 at start. Follows NICE reference case where possible. Utility values taken from Ward 2005. Baseline event rate based on the WOSCOPS study not a meta-analysis or whole UK epidemiology – reflects men aged 45–54 in West Scotland, but likely to be relatively similar to men throughout UK. Effectiveness of pravastatin based on WOSCOPS not meta-analysis of multiple trials, but WOSCOPS was carried out in UK and so is highly relevant. Uses real-life NHS resource use over 15 year follow up, applying current NHS HRG costs and recent cost of pravastatin. **Other:** None.				
Overall applicability[(b)]**:** Directly applicable **Overall quality**[(c)]**:** Minor limitations				

Abbreviations: CUA: cost–utility analysis; CV: cardiovascular; da: deterministic analysis; HRG: healthcare resource group; ICER: incremental cost-effectiveness ratio; LLT: lipid-lowering therapy; N/A: not applicable; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

NICE CG67[121]				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs)	**Population:** UK secondary prevention. Separate analyses for: A: ACS (high risk)	**Total costs (mean per patient):** A: ACS Intervention 1: £10,165	**QALYs (mean per patient):** A: ACS	**ICER (Intervention 2 versus Intervention 1):** A: ACS

Study design: Probabilistic decision analytic model **Approach to analysis:** Markov model of CVD states with 6-month cycles (adaptation of model in Ward 2005) **Perspective:** UK NHS **Time horizon:** lifetime **Treatment effect duration**[(a)]**:** lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	B: CHD (lower risk) **Cohort settings:** Start age: 65 Male: NR **Intervention 1:** Lower-intensity statins (effectiveness data from atorvastatin 10 mg, simvastatin 20 mg (both medium intensity) and pravastatin 40 mg (low intensity)) **Intervention 2:** High-intensity statins: atorvastatin 80 mg (or simvastatin 80 mg)	Intervention 2: £11,583 Incremental (2−1): £1,418 (95% CI: NR; p=NR) B: CHD Intervention 1: £7,692 Intervention 2: £10,081 Incremental (2−1): £2,389 (95% CI: NR; p=NR) **Currency & cost year:** 2007 UK pounds **Cost components incorporated:** Statins. Consultations and monitoring tests. CVD event health states for Markov model (first and subsequent years): unstable angina, MI, TIA, stroke, PAD, HF, revascularisation.	Intervention 1: 5.52 Intervention 2: 5.84 Incremental (2−1): 0.32 (95% CI: NR; p=NR) B: CHD Intervention 1: 5.61 Intervention 2: 5.70 Incremental (2−1): 0.08 (95% CI: NR; p=NR)	£4,397 per QALY gained (da) (95% CI: NR) Probability Intervention 2 cost-effective (£20K/30K threshold): 94%/NR B: CHD £28,361 per QALY gained (da) (95% CI: NR) Probability Intervention 2 cost-effective (£20K/30K threshold): 42%/NR **Analysis of uncertainty:** Both conclusions (high-intensity statins are cost effective at a threshold of £20,000 per QALY for ACS but not for CHD) were robust to one-way sensitivity analyses varying effectiveness of treatment (varying one outcome at a time) apart from CV death, age, cost of CVD event states, utilities, and number of consultations. The results were sensitive to the cost of statins, with high-intensity treatment dominating lower-intensity statins for CHD patients when the cost of simvastatin 80 mg is used instead of atorvastatin 80 mg, assuming equal effectiveness.
Data sources				
Health outcomes: Baseline data from combination of UK epidemiology, UK cohort studies (including NHAR, SLSR) and international trials. Generally best available sources at the time, though may now be partially out of date due to developments in standard treatment for CVD events. Effectiveness based on meta-analysis of the available head-to-head trials (PROVE IT and A to Z for ACS; IDEAL and TNT for CHD). **Quality-of-life weights:** Various published sources, mainly patient-reported using EQ-5D in UK, identified in a systematic review (by Ward 2005). **Cost sources:** Statins UK 2008 costs. Health state costs based on Ward 2005, other NICE guidelines and NHS reference costs.				
Comments				

Source of funding: NICE. **Limitations:** Designed in accordance with NICE reference case. The costs used, especially for statins, are now out of date, making the results unreliable. This is unlikely to affect the conclusion favouring high-intensity statins for higher risk (ACS) secondary prevention patients, but is likely to change the conclusion favouring lower-intensity statins for lower risk (CHD) secondary prevention patients. **Other:** None.

Overall applicability[(b)]**:** Partially applicable **Overall quality**[(c)]**:** Potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; ACS: acute coronary syndrome; CHD: coronary heart disease; CUA: cost–utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HF: heart failure; ICER: incremental cost-effectiveness ratio; MI: myocardial infarction; NR: not reported; PAD: peripheral artery disease; QALYs: quality-adjusted life years; TIA: transient ischaemic attack

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I – Health economic model

New health economic modelling was not prioritised for this update.

Appendix J – Excluded studies

Clinical studies

Table 38: Studies excluded from the clinical review

Study	Reason for exclusion
(2004) Atorvastatin is more effective than pravastatin in preventing recurrent cardiac events. Evidence-based healthcare and public health 8(5): 296-297	- Data not reported in an extractable format or a format that can be analysed
(2004) Simvastatin reduces stroke and major vascular events in people at high-risk. Evidence-based healthcare and public health 8(5): 294-295	- Secondary publication of an included study that does not provide any additional relevant information
(2005) Intensive lipid lowering with atorvastatin: the TNT study. Merec extra	- Full text paper not available
(2008) Justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER). ACC cardiosource review journal 17(12): 64	- Full text paper not available
(2007) Controlled rosuvastatin multinational trial in heart failure (CORONA). ACC cardiosource review journal 16(12): 31	- Study excluded in CG181 2014 update
(2007) High-dose atorvastatin after stroke or transient ischemic attack. Current atherosclerosis reports 9(2): 96	- Conference abstract
(2005) The effects of cholesterol lowering with simvastatin on cause-specific mortality and on cancer incidence in 20,536 high-risk people: a randomised placebo-controlled trial. BMC medicine 3: 6	- Study already included in CG181 2014 update
(2011) C-reactive protein concentration and the vascular benefits of statin therapy: an analysis of 20 536 patients in the Heart Protection Study. Lancet 377(9764): 469-476	- Secondary publication of an included study that does not provide any additional relevant information
(1995) Protocol for a prospective collaborative overview of all current and planned randomized trials of cholesterol treatment regimens. Cholesterol Treatment Trialists' (CTT) Collaboration. The American journal of cardiology 75(16): 1130-1134	- Protocol paper for excluded study
Abid Shah, M.; Suleman, S.; Hussain Munir, A. (2013) Comparative efficacy and safety profile of 5 MG rosuvastatin versus 10 MG rosuvastatin in patients with ischemic heart disease. Journal of Medical Sciences (Peshawar) 21(1): 35-39	- Insufficient follow-up time
Adams, S. P.; Sekhon, S. S.; Wright, J. M. (2014) Lipid-lowering efficacy of rosuvastatin. Cochrane Database of Systematic Reviews: cd010254	- Systematic review does not match the protocol Outcomes not relevant to protocol
Adams, S. P.; Tsang, M.; Wright, J. M. (2015) Lipid-lowering efficacy of atorvastatin. Cochrane Database of Systematic Reviews: cd008226	- Systematic review does not match the protocol Outcomes not relevant to protocol

Study	Reason for exclusion
Adams, Sp, Sekhon, Ss, Tsang, M et al. (2018) Fluvastatin for lowering lipids. Cochrane Database of Systematic Reviews	- Outcomes not relevant to the protocol
Adams, Sp; Sekhon, Ss; Wright, Jm (2014) Rosuvastatin for lowering lipids. Cochrane Database of Systematic Reviews	- Outcomes not relevant to the protocol
Adams, Sp; Tsang, M; Wright, Jm (2015) Atorvastatin for lowering lipids. Cochrane Database of Systematic Reviews	- Outcomes not relevant to the protocol
Agrawal, D, Manchanda, Sc, Sawhney, Jps et al. (2018) To study the effect of high dose Atorvastatin 40mg versus 80mg in patients with dyslipidemia. Indian heart journal 70suppl3: S8-s12	- Insufficient follow-up time
Ahrens, J (1995) Results of the 4-S study. Cholesterol lowering with simvastatin lowers the mortality rate in patients with coronary heart disease. Therapiewoche schweiz 11(1): 19-22	- Study not reported in English
Alkhalil, M., Kuzemczak, M., Whitehead, N. et al. (2021) Meta-Analysis of Intensive Lipid-Lowering Therapy in Patients With Polyvascular Disease. Journal of the American Heart Association 10(5): e017948	- Comparator in study does not match that specified in this review protocol Some of the studies included in systematic review are not relevant to the protocol
Alkhenizan, A (2003) Effect of statin therapy on total mortality. Trial in a more varied population. Canadian family physician médecin de famille canadien 49: 757-759	- Study excluded in CG181 2014 update
Amarenco, P, Bogousslavsky, J, Callahan, A et al. (1999) Effect of atorvastatin compared with placebo on cerebrovascular end points in patients with previous stroke or transient ischemic attack - The SPARCL Study. Cerebrovascular diseases (basel, switzerland) 9suppl1: 108	- Conference abstract
Amirov, Nb, Potapova, Mv, Ishkineev, Fi et al. (2007) Dyslipidemia correction with atorvastatin in patients with coronary heart disease and arterial hypertension. Cardiovascular therapy and prevention 6(7): 55-58	- Study not reported in English
Anderssen, S. A., Hjelstuen, A. K., Hjermann, I. et al. (2005) Fluvastatin and lifestyle modification for reduction of carotid intima-media thickness and left ventricular mass progression in drug-treated hypertensives. Atherosclerosis 178(2): 387-97	- Study already included in CG181 2014 update
Armitage, J., Bowman, L., Collins, R. et al. (2009) Effects of simvastatin 40 mg daily on muscle and liver adverse effects in a 5-year randomized placebo-controlled trial in 20,536 high-risk people. BMC Clin Pharmacol 9: 6	- Secondary publication of an included study that does not provide any additional relevant information
Arshad, A. R. (2014) Comparison of low-dose rosuvastatin with atorvastatin in lipid-lowering efficacy and safety in a high-risk pakistani cohort: an open-label randomized trial. Journal of Lipids 2014: 875907	- Outcomes not relevant to the protocol

Study	Reason for exclusion
Athyros, Vg, Kakafika, Ai, Papageorgiou, Aa et al. (2007) Atorvastatin decreases triacylglycerol-associated risk of vascular events in coronary heart disease patients. Lipids 42(11): 999-1009	- Study design not relevant to this review protocol: post hoc analysis
Bangalore, S., Fayyad, R., Hovingh, G. K. et al. (2014) Statin and the risk of renal-related serious adverse events: Analysis from the IDEAL, TNT, CARDS, ASPEN, SPARCL, and other placebo-controlled trials. American Journal of Cardiology 113(12): 2018-2020	- Outcomes not relevant to the protocol
Bangalore, S., Fayyad, R., Laskey, R. et al. (2014) Lipid lowering in patients with treatment-resistant hypertension: an analysis from the Treating to New Targets (TNT) trial. European Heart Journal 35(27): 1801-8	- Secondary publication of an included study that does not provide any additional relevant information - Study design not relevant to this review protocol: post hoc analysis
Bangalore, S, Fayyad, R, Laskey, R et al. (2012) Intensive lipid lowering with atorvastatin in patients with treatment resistant hypertension: an analysis from the treating to new targets (TNT) trial. Circulation 126(21suppl1)	- Conference abstract
Barylski, M., Nikfar, S., Mikhailidis, D. P. et al. (2013) Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy--a meta-analysis of 11 randomized controlled trials involving 21,295 participants. Pharmacological Research 72: 35-44	- Systematic review used as source of primary studies: all relevant studies included in 2014 update
Behounek, Bd (1994) Pravastatin in patients with cardiovascular risk factors. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. Fortschritte der medizin 112(5): 45-54	- Study not reported in English
Bohara, S., Gaonkar, V. B., Garg, K. et al. (2021) Effect of statins on functional outcome and mortality following aneurysmal subarachnoid hemorrhage - Results of a meta-analysis, metaregression and trial sequential analysis. Clinical Neurology & Neurosurgery 207: 106787	- Systematic review does not contain a comparison relevant to this review protocol
Bonsu, K. O.; Reidpath, D. D.; Kadirvelu, A. (2016) Lipophilic Statin Versus Rosuvastatin (Hydrophilic) Treatment for Heart Failure: a Meta-Analysis and Adjusted Indirect Comparison of Randomised Trials. Cardiovascular Drugs & Therapy 30(2): 177-88	- Systematic review does not contain a comparison relevant to this review protocol
Bosch, J (2016) HOPE-3: effects of rosuvastatin on cardiovascular disease in moderate risk primary prevention in diverse ethnic groups.	- Full text paper not available
Bosch, J., Lonn, E. M., Jung, H. et al. (2021) Lowering cholesterol, blood pressure, or both to prevent cardiovascular events: results of 8.7 years of follow-up of Heart Outcomes Evaluation	- Study design not relevant to this review protocol: non-randomised follow-up

Study	Reason for exclusion
Prevention (HOPE)-3 study participants. European Heart Journal 42(31): 2995-3007	
Bulbulia, R, Bowman, L, Wallendszus, K et al. (2011) Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial. Lancet 378(9808): 2013-2020	- Study excluded in CG181 2014 update
Byington, Rp; Furberg, Cd; Crouse, Jr (1993) PLAC 2: effects of pravastatin on progression of carotid atherosclerosis and clinical events. European heart journal 14(s): 20	- Conference abstract
Byington, Rp, Jukema, Jw, Salonen, Jt et al. (1996) Reduction of cardiovascular events with pravastatin. A pooled analysis of clinical events within the scope of the Pravastatin Atherosclerosis Intervention Program. Fortschritte der Medizin 114(8): 91-98	- Study not reported in English
Byrne, P., Cullinan, J., Smith, A. et al. (2019) Statins for the primary prevention of cardiovascular disease: an overview of systematic reviews. BMJ Open 9(4): e023085	- Overview of systematic reviews used as source of primary studies: insufficient detail on included studies and outcome data to include
Byrne, P., Demasi, M., Jones, M. et al. (2022) Evaluating the Association Between Low-Density Lipoprotein Cholesterol Reduction and Relative and Absolute Effects of Statin Treatment: A Systematic Review and Meta-analysis. JAMA Internal Medicine 14: 14	- Systematic review does not match the protocol: all statins versus placebo for efficacy outcomes, not sub-grouped by statin intensity - Systematic review: used as a source of primary studies
Cai, T., Abel, L., Langford, O. et al. (2021) Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. BMJ 374: n1537	- Systematic review does not contain a comparison relevant to this review protocol (control group pooled placebo/no treatment with active control groups)
Campese, Vm, Callahan, A, Rudolph, Ae et al. (2007) Effect of high-dose atorvastatin on changes in renal function: a secondary analysis of the Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trial. Circulation 116(16supplement): 471	- Conference abstract
Cannon, Cp, McCabe, Ch, Belder, R et al. (2002) Design of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) - TIMI 22 trial. American journal of cardiology 89(7): 860-861	- Protocol paper - Study already included in CG181 2014 update
Chan, Jcn, Kong, Aps, Bao, W et al. (2016) Safety of atorvastatin in Asian patients within clinical trials. Cardiovascular therapeutics 34(6): 431-440	- Study design not relevant to this review protocol: post hoc analysis
Chen, J., Li, M., Zhu, X. et al. (2020) Atorvastatin reduces cerebral vasospasm and infarction after aneurysmal subarachnoid hemorrhage in elderly Chinese adults. Aging 12(3): 2939-2951	- Insufficient follow-up time

Study	Reason for exclusion
Chen, Q., Chen, L. Z., Guo, X. H. et al. (2018) Clinical efficacy of statins in the prevention and treatment of coronary heart disease. Biomedical Research (India) 29(2): 309-312	- Study does not contain an intervention classification relevant to this review protocol - Insufficient follow-up time
Cheng, Y., Qiao, L., Jiang, Z. et al. (2020) Significant reduction in the LDL cholesterol increases the risk of intracerebral hemorrhage: a systematic review and meta-analysis of 33 randomized controlled trials. American Journal Of Translational Research 12(2): 463-477	- Systematic review: all relevant trials already included in CG181 2014 update
Choi, Hj, Lee, W, Han, Kw et al. (2002) Comparison of Efficacy and Safety of Simvastatin, 10 mg and 20 mg in the Treatment of Hypercholesterolemia Patients Over 60-Year Old. Journal of the korean geriatrics society 6(4): 320-329	- Full text paper not available
Cholesterol Treatment Trialists, Collaboration (2019) Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet 393(10170): 407-415	- Systematic review does not contain a comparison relevant to this review protocol - Systematic review used as a source of primary studies
Cholesterol Treatment Trialists, Collaboration, Fulcher, J., O'Connell, R. et al. (2015) Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 385(9976): 1397-405	- Systematic review does not contain a comparison relevant to this review protocol - Systematic review used as a source of primary studies
Cholesterol Treatment Trialists, Collaboration, Herrington, W. G., Emberson, J. et al. (2016) Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. The Lancet Diabetes & Endocrinology 4(10): 829-39	- Systematic review does not contain a comparison relevant to this review protocol - Systematic review used as a source of primary studies
Clearfield, M (2006) Reduction in cardiovascular events with atorvastatin in type 2 diabetes. Current atherosclerosis reports 8(1): 9-10	- Secondary publication of an included study that does not provide any additional relevant information
Colhoun, Hm, Betteridge, Dj, Durrington, Pn et al. (2004) Cholesterol lowering with atorvastatin for the primary prevention of cardiovascular disease in diabetic adults. Journal of clinical outcomes management 11(11): 682-685	- Study already included in CG181 2014 update
Colivicchi, F., Tubaro, M., Mocini, D. et al. (2010) Full-dose atorvastatin versus conventional medical therapy after non-ST-elevation acute myocardial infarction in patients with advanced non-revascularisable coronary artery disease. Curr Med Res Opin 26(6): 1277-84	- Comparator in study does not match that specified in this review protocol
Colivicchi, F, Guido, V, Tubaro, M et al. (2002) Effects of atorvastatin 80 mg daily early after onset of unstable angina pectoris or non-Q-wave	- Comparator in study does not match that specified in this review protocol

Study	Reason for exclusion
myocardial infarction. American journal of cardiology 90(8): 872-4	
Collins, R., Reith, C., Emberson, J. et al. (2016) Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 388(10059): 2532-2561	- Non-systematic review with narrative style that could not be directly incorporated into our analysis: used as source of primary studies
Cui, J. Y., Zhou, R. R., Han, S. et al. (2018) Statin therapy on glycemic control in type 2 diabetic patients: A network meta-analysis. Journal of Clinical Pharmacy & Therapeutics 43(4): 556-570	- Systematic review does not match the protocol: outcomes not relevant to the protocol - Systematic review used as source of primary studies
Dalla Nora, E., Passaro, A., Zamboni, P. F. et al. (2003) Atorvastatin improves metabolic control and endothelial function in type 2 diabetic patients: a placebo-controlled study. J Endocrinol Invest 26(1): 73-8	- Outcomes not relevant to the protocol
Davis, K. A. S., Bishara, D., Perera, G. et al. (2020) Benefits and Harms of Statins in People with Dementia: A Systematic Review and Meta-Analysis. Journal of the American Geriatrics Society 68(3): 650-658	- Systematic review does not match the review protocol: statins used to treat dementia not for CVD risk reduction
De Luca, G., Verdoia, M., Savonitto, S. et al. (2020) Impact of diabetes on clinical outcome among elderly patients with acute coronary syndrome treated with percutaneous coronary intervention: insights from the ELDERLY ACS 2 trial. Journal of Cardiovascular Medicine 21(6): 453-459	- Study does not contain an intervention relevant to this review protocol - Comparator in study does not match that specified in this review protocol
de Vries, F. M., Kolthof, J., Postma, M. J. et al. (2014) Efficacy of standard and intensive statin treatment for the secondary prevention of cardiovascular and cerebrovascular events in diabetes patients: a meta-analysis. PLoS ONE [Electronic Resource] 9(11): e111247	- Systematic review: all relevant trials already included in CG181 2014 update
Delluc, A, Ghanima, W, Kovacs, Mj et al. (2022) Statins for venous event reduction in patients with venous thromboembolism: A multicenter randomized controlled pilot trial assessing feasibility. Journal of thrombosis and haemostasis : JTH 20(1): 126-132	- Insufficient follow-up time
Deng, Y., Zou, W., Chen, G. et al. (2019) Comparative studies on the effects of different doses of atorvastatin combined with aspirin on inflammatory cytokines and carotid plaques in patients with ischemic cerebrovascular disease. International Journal of Neuroscience 129(11): 1133-1138	- Insufficient follow-up time
Eun, M. Y., Jung, J. M., Choi, K. H. et al. (2020) Statin Effects in Atrial Fibrillation-Related Stroke: A Systematic Review and Meta-Analysis. Frontiers in neurology [electronic resource]. 11: 589684	- Systematic review does not match the protocol Does not include RCTs
Everett, Bm, Glynn, Rj, MacFadyen, Jg et al. (2009) Rosuvastatin in the prevention of stroke	- Study already included in CG181 2014 update

Study	Reason for exclusion
among men and women with elevated levels of C-reactive protein: justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER). Circulation 121: 143-150	
Fang, J and Zhang, X (2022) Effect of various doses of rosuvastatin in the treatment of elderly patients with unstable angina pectoris. American journal of translational research 14(1): 594-602	- Outcomes not relevant to the protocol
Farmer, Ja (2005) Intensive versus moderate lipid lowering with statins in acute coronary syndromes. Current atherosclerosis reports 7(2): 85-86	- Secondary publication of an included study that does not provide any additional relevant information
Fassett, Robert G., Robertson, Iain K., Ball, Madeleine J. et al. (2010) Effect of atorvastatin on kidney function in chronic kidney disease: A randomised double-blind placebo-controlled trial. Atherosclerosis 213(1): 218-224	- Outcomes not relevant to the protocol *CVD events not recorded as part of trial just unadjudicated events from historical records*
Feinstein, M. J., Jhund, P., Kang, J. et al. (2015) Do statins reduce the risk of myocardial infarction in patients with heart failure? A pooled individual-level reanalysis of CORONA and GISSI-HF. European Journal of Heart Failure 17(4): 434-41	- Population not relevant to this review protocol: heart failure
Ford, I., Murray, H., McCowan, C. et al. (2016) Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol With Statin Therapy: 20-Year Follow-Up of West of Scotland Coronary Prevention Study. Circulation 133(11): 1073-80	- Study design not relevant to this review protocol: non-randomised follow-up
Gencer, B., Marston, N. A., Im, K. et al. (2020) Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. Lancet 396(10263): 1637-1643	- Systematic review does not match the protocol 45.3% participants included from non statin trials
Ghalaut, P. S. and Tarun (2015) Comparative evaluation of the efficacy and safety of rosuvastatin vs atorvastatin in patients of dyslipidemia with coronary heart disease in Indian Scenario. Journal International Medical Sciences Academy 28(3): 135-137	- Insufficient follow-up time - Outcomes not relevant to the protocol
Ghayda, R. A., Lee, J. Y., Yang, J. W. et al. (2021) The effect of statins on all-cause and cardiovascular mortality in patients with non-dialysis chronic kidney disease, patients on dialysis, and kidney transplanted recipients: an umbrella review of meta-analyses. European Review for Medical & Pharmacological Sciences 25(6): 2696-2710	- Overview of systematic reviews used as source of primary studies: insufficient detail on included studies and outcome data to include
Gupta, A, Chang, Cl, Collier, D et al. (2011) The relationship between statin therapy and progression of renal damage among 10305 hypertensive patients randomised in the ascot-Lipid-Lowering Arm (LLA). Atherosclerosis. Supplements 12(1): 158-159	- Conference abstract

Study	Reason for exclusion
Gupta, Ak, Chang, Cl et al. (2011) Cardiovascular and all-cause mortality outcomes among hypertensive patients with moderate renal dysfunction in the ASCOT-LLA, and its extended follow-up. European heart journal 32: 220	- Conference abstract
Haffner, Sm (1997) The Scandinavian Simvastatin Survival Study (4S) subgroup analysis of diabetic subjects: implications for the prevention of coronary heart disease. Diabetes care 20(4): 469-471	- Secondary publication of an included study that does not provide any additional relevant information
Han, B. H., Sutin, D., Williamson, J. D. et al. (2017) Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults: The ALLHAT-LLT Randomized Clinical Trial. JAMA Internal Medicine 177(7): 955-965	- Secondary publication of an included study that does not provide any additional relevant information - Study design not relevant to this review protocol: post hoc analysis
Han, X., Zhang, Y., Yin, L. et al. (2018) Statin in the treatment of patients with myocardial infarction: A meta-analysis. Medicine 97(12): e0167	- Systematic review does not match the protocol Most of the included studies had less than 1 year follow up
He, W.; Cao, M.; Li, Z. (2020) Effects of different doses of atorvastatin, rosuvastatin, and simvastatin on elderly patients with ST-elevation acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI). Drug Development Research 81(5): 551-556	- Insufficient follow-up time
Heo, J. H., Song, D., Nam, H. S. et al. (2016) Effect and Safety of Rosuvastatin in Acute Ischemic Stroke. Journal of Stroke 18(1): 87-95	- Outcomes not relevant to the protocol
Heo, Jh (2011) The Effects of Very Early Use of Rosuvastatin in Preventing Recurrence of Ischemic Stroke (EUREKA).	- Not a peer-reviewed publication: clinical trials registry
Herd, J. A., Ballantyne, C. M., Farmer, J. A. et al. (1997) Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). Am J Cardiol 80(3): 278-86	- Study does not contain an intervention relevant to this review protocol Open label cholestyramine permitted in addition to randomised treatment if indicated.
Herrett E, Williamson E, Brack K et al. (2021) The effect of statins on muscle symptoms in primary care: the StatinWISE series of 200 N-of-1 RCTs. Health technology assessment (Winchester, England) 25(16): 1-62	- N-of-1 trial: sufficient data available from standard RCTs
Herrett, E., Williamson, E., Beaumont, D. et al. (2017) Study protocol for statin web-based investigation of side effects (StatinWISE): a series of randomised controlled N-of-1 trials comparing atorvastatin and placebo in UK primary care. BMJ Open 7(12): e016604	- Protocol for an n-of-1 trial
Hitman, Ga, Colhoun, H, Newman, C et al. (2009) Stroke prediction and stroke prevention with atorvastatin in the Collaborative Atorvastatin Diabetes Study (CARDS). Diabetic medicine 24(12): 1313-1321	- Study already included in CG181 2014 update

Study	Reason for exclusion
Hjalmarson, A (2008) CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). Clinical cardiology 31(2): 90	- Conference abstract
Holdaas, H, Wanner, C, Abletshauser, C et al. (2007) The effect of fluvastatin on cardiac outcomes in patients with moderate to severe renal insufficiency: a pooled analysis of double-blind, randomized trials. International journal of cardiology 117(1): 64-74	- Study excluded in CG181 2014 update
Hong, Y. J., Jeong, M. H., Hyun, D. W. et al. (2005) Prognostic significance of simvastatin therapy in patients with ischemic heart failure who underwent percutaneous coronary intervention for acute myocardial infarction. Am J Cardiol 95(5): 619-22	- Population not relevant to this review protocol: heart failure
Horng, Ms (2007) Effect of high-dose atorvastatin on cardiovascular outcomes in elderly coronary patients. Journal of clinical outcomes management 14(9): 496498	- Secondary publication of an included study that does not provide any additional relevant information
Howard JP, Wood FA, Finegold JA et al. Side Effect Patterns in a Crossover Trial of Statin, Placebo, and No Treatment. Journal of the American College of Cardiology 78(12): 1210-1222	- N-of-1 trial: sufficient data available from standard RCTs
Hsue, P. Y., Bittner, V. A., Betteridge, J. et al. (2015) Impact of female sex on lipid lowering, clinical outcomes, and adverse effects in atorvastatin trials. American Journal of Cardiology 115(4): 447-53	- Study design not relevant to this review protocol: post hoc analysis
Hwang, S. D., Kim, K., Kim, Y. J. et al. (2020) Effect of statins on cardiovascular complications in chronic kidney disease patients: A network meta-analysis. Medicine 99(22): e20061	- Systematic review and network meta-analysis: CVD event outcome does not match the protocol
Isaacsohn, Jl, Davidson, Mh, Hunninghake, D et al. (2000) Aggressive lipid-lowering initiation abates new cardiac events (ALLIANCE)-rationale and design of atorvastatin versus usual care in hypercholesterolemic patients with coronary artery disease. American journal of cardiology 86(2): 250-252	- Secondary publication of an included study that does not provide any additional relevant information
Izawa, A., Kashima, Y., Miura, T. et al. (2015) Assessment of lipophilic vs. hydrophilic statin therapy in acute myocardial infarction - ALPS-AMI study. Circulation Journal 79(1): 161-8	- Study does not contain an intervention classification relevant to this review protocol
Jukema, Jw, Bruschke, Avg, Van, Boven Aj et al. (1996) Retarding progression of coronary atherosclerosis with pravastatin. Cardiology review 13(3): 9-14	- Population not relevant to this review protocol: heart failure
Kabaklic, A. and Fras, Z. (2017) Moderate-dose atorvastatin improves arterial endothelial function in patients with angina pectoris and normal coronary angiogram: a pilot study. Archives of Medical Science 13(4): 827-836	- Insufficient follow-up time
Kadota, S, Matsuda, M, Izuhara, M et al. (2008) Long-term effects of early statin therapy for	- Insufficient follow-up time

Study	Reason for exclusion
patients with acute myocardial infarction treated with stent implantation. Journal of cardiology 51(3): 171-178	
Kamran, H., Kupferstein, E., Sharma, N. et al. (2018) Statins and New-Onset Diabetes in Cardiovascular and Kidney Disease Cohorts: A Meta-Analysis. Cardiorenal Medicine 8(2): 105-112	- Data not reported in an extractable format or a format that can be analysed
Karam, Jg; Loney-Hutchinson, L; McFarlane, Si (2008) High-dose atorvastatin after stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. Journal of the cardiometabolic syndrome 3(1): 68-69	- Study excluded in CG181 2014 update
Kaste, M (2003) Statins in threatened stroke. Stroke; a journal of cerebral circulation 34(2): 351-353	- Secondary publication of an included study that does not provide any additional relevant information
Kaul, U., Varma, J., Kahali, D. et al. (2013) Post-marketing study of clinical experience of atorvastatin 80 mg vs 40 mg in Indian patients with acute coronary syndrome- a randomized, multi-centre study (CURE-ACS). Journal of the Association of Physicians of India 61(2): 97-101	- Insufficient follow-up time
Khan, S Abrar A Rafique A Abid AJan T (2010) Efficacy and safety of rosuvastatin compared to simvaststin in coronary artery disease. Gomal j med sci 8(1): 64-69	- Insufficient follow-up time
Kim, B. H., Cho, K. I., Jang, J. S. et al. (2014) Efficacy and safety of statins for primary prevention of cardiovascular events in women and men: Systemic review and up-to-date meta-analysis. Experimental and Clinical Cardiology 20(1): 1222-1227	- Full text paper not available
Kim, J. B., Song, W. H., Park, J. S. et al. (2021) A randomized, open-label, parallel, multi-center Phase IV study to compare the efficacy and safety of atorvastatin 10 and 20 mg in high-risk Asian patients with hypercholesterolemia. PLoS ONE [Electronic Resource] 16(1): e0245481	- Insufficient follow-up time
Kitas, Gd, Nightingale, P, Armitage, J et al. (2019) Trial of atorvastatin for the primary prevention of cardiovascular events in patients with rheumatoid arthritis (TRACE RA): a multicenter, randomized, placebo controlled trial. Arthritis & rheumatology	- Duplicate reference
Kochsiek, K, Lehmacher, W, Stiefelhagen, P et al. (2000) Complementary evaluation of the CARE study. Stroke incidence in patients after myocardial infarction under therapy with pravastatin. Internist 41(10): 1120-1123	- Study not reported in English
Kohli, P, Waters, Dd, Nemr, R et al. (2015) Risk of new-onset diabetes and cardiovascular risk reduction from high-dose statin therapy in pre-diabetics and non-pre-diabetics: an analysis	- Secondary publication of an included study that does not provide any additional relevant information

Study	Reason for exclusion
from TNT and IDEAL. Journal of the American College of Cardiology 65(4): 402-404	- Study design not relevant to this review protocol: post hoc analysis
Kohli-Lynch, C. N., Lewsey, J., Boyd, K. A. et al. (2022) Beyond Ten-Year Risk: A Cost-Effectiveness Analysis of Statins for the Primary Prevention of Cardiovascular Disease. Circulation. 07	- Study does not contain an intervention relevant to this review protocol
Kohriyama, T, Nomura, E, Matsumoto, M et al. (2006) J-STARS (Japan statin treatment against recurrent stroke). Nippon rinsho. Japanese journal of clinical medicine 64suppl7: 511-518	- Study not reported in English
Koizumi, J and Yoshida, I (2001) 4S [Scandinavian Simvastatin Survival Study. Nippon rinsho. Japanese journal of clinical medicine 59suppl3: 410-415	- Study not reported in English
Kones, R (2009) The JUPITER study, CRP screening and agressive statin therapy-implications for the primary prevention of cardiovascular disease. Therapeutic advances in cardiovascular disease 3(4): 309-315	- Secondary publication of an included study that does not provide any additional relevant information
Krishnan, S and Jacobson, Ta (2013) Statins in patients with CKD prove beneficial in reducing cardiovascular events and mortality but show no benefit in patients on dialysis. Evidence based medicine 18(5): 175-176	- Study design not relevant to this review protocol Commentary on a published systematic review
Kristiansen, O., Vethe, N. T., Peersen, K. et al. (2021) Effect of atorvastatin on muscle symptoms in coronary heart disease patients with self-perceived statin muscle side effects: a randomized, double-blinded crossover trial. European Heart Journal Cardiovascular Pharmacotherapy 7(6): 507-516	- Insufficient follow-up time
Kuznar, W (2008) No effect of statin on cardiovascular outcomes in older patients with advanced systolic heart failure. Geriatrics 63(1): 34-35	- Conference abstract
Lai, G-K; Zhu, L; Tang, J-M (2019) Effects of short-term intensive statin therapy on blood lipid level, cardiac function and MACE events in patients after percutaneous coronary intervention. Journal of Xi'an Jiaotong University (Medical Sciences) 40(5): 732-735 and 754	- Study not reported in English
Lampl, Y, Lorberboym, M, Gilad, R et al. (2010) Early outcome of acute ischemic stroke in hyperlipidemic patients under atorvastatin versus simvastatin. Clinical neuropharmacology 33(3): 129-134	- Study design not relevant to this review protocol: not randomised
Lee, Cw, Kang, Sj, Ahn, Jm et al. (2012) Comparison of effects of atorvastatin (20 mg) versus rosuvastatin (10 mg) therapy on mild coronary atherosclerotic plaques (from the ARTMAP trial). American journal of cardiology 109(12): 1700-1704	- Insufficient follow-up time
Lee, Jg, Kim, Hm, Lee, Hh et al. (2002) Comparison of efficacy and safety of	- Study not reported in English

Study	Reason for exclusion
simvastatin, 10 mg and 20 mg in the treatment of hypercholesterolemia. Korean journal of medicine 63(1): 46-53	
Lee, M., Cheng, C. Y., Wu, Y. L. et al. (2022) Association Between Intensity of Low-Density Lipoprotein Cholesterol Reduction With Statin-Based Therapies and Secondary Stroke Prevention: A Meta-analysis of Randomized Clinical Trials. JAMA Neurology 79(4): 349-358	- Systematic review: limited to studies in people with prior stroke and most relevant trials included in 2014 update, so no benefit of including this review - Systematic review used as source of primary studies
Lemos, Marcelo M., Watanabe, Renato, Carvalho, Aluizio B. et al. (2013) Effect of rosuvastatin and sevelamer on the progression of coronary artery calcification in chronic kidney disease: a pilot study. Clinical Nephrology 80(1): 1-8	- Study already included in CG181 2014 update
Leoncini, M., Toso, A., Maioli, M. et al. (2013) High-dose atorvastatin on the pharmacodynamic effects of double-dose clopidogrel in patients undergoing percutaneous coronary interventions: The ACHIDO (Atorvastatin and Clopidogrel HIgh DOse in stable patients with residual high platelet activity) study. Jacc: Cardiovascular Interventions 6(2): 169-79	- Comparator in study does not match that specified in this review protocol
Li, H., Wang, C., Zhang, S. et al. (2016) Safety Profile of Atorvastatin 80 mg: A Meta-Analysis of 17 Randomized Controlled Trials in 21,910 Participants. Drug Safety 39(5): 409-19	- Systematic review does not match the protocol: includes studies with follow-up <12 months - Systematic review used as source of primary studies: all relevant studies included in the 2014 update
Li, L, Zhang, P, Tian, Jh et al. (2014) Statins for primary prevention of venous thromboembolism. Cochrane Database of Systematic Reviews	- Systematic review: all relevant trials already included in CG181 2014 update
Li, M., Wang, X., Li, X. et al. (2019) Statins for the Primary Prevention of Coronary Heart Disease. BioMed Research International 2019: 4870350	- Systematic review: most relevant trials included in CG181, so no benefit of including this review. One additional relevant study already identified in search and added into this review analysis. - Systematic review used as source of primary studies
Li, W., Zhang, Y., Tian, Z. et al. (2020) Statin treatment for unruptured intracranial aneurysms study: a study protocol for a double-blind, placebo-controlled trial. Stroke & Vascular Neurology 5(4): 410-415	- Outcomes not relevant to the protocol
Liang, X.; He, Q.; Zhao, Q. (2018) Effect of Stains on LDL Reduction and Liver Safety: A Systematic Review and Meta-Analysis. BioMed Research International 2018: 7092414	- Systematic review: most relevant trials included in CG181, so no benefit of including this review. Two additional relevant studies already identified in search and added into this guideline review analysis.

Study	Reason for exclusion
	- Systematic review used as source of primary studies
Liping, Z, Xiufang, L, Tao, Y et al. (2018) Efficacy comparison of rosuvastatin and atorvastatin in the treatment of atherosclerosis and drug safety analysis. Pakistan journal of pharmaceutical sciences 31(5): 2203-2208	- Insufficient follow-up time
Liu, G., Zheng, X. X., Xu, Y. L. et al. (2014) Effects of lipophilic statins for heart failure: a meta-analysis of 13 randomised controlled trials. Heart, Lung & Circulation 23(10): 970-7	- Systematic review does not match the protocol: incorrect population (heart failure)
Liu, Z-L and Jia, G-Q (2016) Effect of sequential therapy of atorvastatin on the levels of ischemia modified albumin in patients undergoing emergency percutaneous coronary intervention for acute st-segment elevation myocardial infarction. Journal of interventional radiology (china) 25(9): 755-758	- Study not reported in English
Lloyd, S. M., Stott, D. J., de Craen, A. J. et al. (2013) Long-term effects of statin treatment in elderly people: extended follow-up of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PLoS ONE [Electronic Resource] 8(9): e72642	- Study design not relevant to this review protocol: non-randomised follow-up
Lou, M (2017) The Safety and Efficacy Study of High Dose Atorvastatin After Thrombolytic Treatment in Acute Ischemic Stroke (SEATIS).	- Not a peer-reviewed publication: clinical trials registry
Mach, F., Ray, K. K., Wiklund, O. et al. (2018) Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. European Heart Journal 39(27): 2526-2539	- Systematic review with narrative synthesis of results that could not be directly incorporated into our analysis: used as a source of primary studies
Macin, Sm, Perna, Er, Farias, Ef et al. (2005) Atorvastatin has an important acute anti-inflammatory effect in patients with acute coronary syndrome: results of a randomized, double-blind, placebo-controlled study. American heart journal 149(3): 451-7	- Outcomes not relevant to the protocol Insufficient follow up time of relevant outcomes
Maerz, W, Wollschlaeger, H, Klein, G et al. (1999) Safety of low-density lipoprotein cholestrol reduction with atorvastatin versus simvastatin in a coronary heart disease population (the TARGET TANGIBLE trial). American journal of cardiology 84(1): 7-13	- Insufficient follow-up time
Mahatme, Ms, Bargade, Mb, Hiware, Sk et al. (2021) Effect of atorvastatin and rosuvastatin on the glycemic control in patients with type II diabetes mellitus: a Comparative, randomized, double-blind study. Journal of pharmacology & pharmacotherapeutics 12(2): 54-60	- Insufficient follow-up time
Manzato, E, Roselli, Della Rovere G, Romanato, G et al. (2003) New evidences about the reduction of cardiovascular diseases in the	- Study not reported in English

Study	Reason for exclusion
elderly: the PROSPER study. Giornale di gerontologia 51(5): 408-412	
Margolis, K. L., Davis, B. R., Baimbridge, C. et al. (2013) Long-term follow-up of moderately hypercholesterolemic hypertensive patients following randomization to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). Journal of Clinical Hypertension 15(8): 542-54	- Study design not relevant to this review protocol: non-randomised follow-up
Marz, W, Wollschlager, H, Klein, G et al. (1999) Safety of low-density lipoprotein cholesterol reduction with atorvastatin versus simvastatin in a coronary heart disease population (the TARGET TANGIBLE Trial). Perfusion 12(10): 427-436	- Study not reported in English
Masson, W., Lobo, M., Masson, G. et al. (2021) Statin use in patients with elevated serum hepatic transaminases at baseline: A meta-analysis. Nutrition Metabolism & Cardiovascular Diseases 31(5): 1357-1364	- Systematic review does not contain a comparison relevant to this review protocol
McMurray, J and Slattery, J (1994) Scandinavian simvastatin study (4S). Lancet 344(89398940): 1765-1766; author reply 1767	- Not a peer-reviewed publication: letter to the editor
Mihaylova, B, Emberson, J, Blackwell, L et al. (2012) The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 380(9841): 581-590	- Study excluded in CG181 2014 update
Milionis, H., Ntaios, G., Korompoki, E. et al. (2020) Statin-based therapy for primary and secondary prevention of ischemic stroke: A meta-analysis and critical overview. International Journal of Stroke 15(4): 377-384	- Systematic review: most relevant trials included in CG181 2014 update, so no benefit of including this review. One additional relevant study already identified in search and added in to this guideline review analysis. - Systematic review used as source of primary studies
Montaner, J., Bustamante, A., Garcia-Matas, S. et al. (2016) Combination of Thrombolysis and Statins in Acute Stroke Is Safe: Results of the STARS Randomized Trial (Stroke Treatment With Acute Reperfusion and Simvastatin). Stroke 47(11): 2870-2873	- Outcomes not relevant to the protocol
Mora, S, Wenger, Nk, Demicco, Da et al. (2012) Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. Circulation 125(16): 1979-1987	- Outcomes not relevant to the protocol
Mori, T (2012) Pharmacological intervention of Atorvastatin vs. Rosvastatin in patients with acute Ischemic Stroke (ARIS study).	- Not a peer-reviewed publication: clinical trials registry
Mostafa, S. A., Elrabat, K., Mahrous, M. et al. (2018) Short term comparison between safety	- Full text paper not available

Study	Reason for exclusion
and efficacy of rosuvastatin 40 mg and atorvastatin 80 mg in patients with acute coronary syndrome. Rational Pharmacotherapy in Cardiology 14(5): 636-645	
Munkhaugen, J., Vethe, N. T., Fagerland, M. W. et al. (2019) Statin-associated muscle symptoms in coronary patients: design of a randomized study. Scandinavian Cardiovascular Journal 53(3): 162-168	- Protocol paper for excluded study
Munoz, O. M., Reyna Carrasco, O. A., Castelblanco, S. M. et al. (2019) Therapeutic impact of statins on the lipid profile and cardiovascular risk in patients with rheumatoid arthritis: Systematic review of the literature and a meta-analysis. Revista Colombiana de Reumatologia 26(1): 40-47	- Study not reported in English
Muscari, A (2008) High dose atorvastatin in acute ischemic stroke – Monocenter pilot study.	- Not a peer-reviewed publication: clinical trials registry
Naci, H., Brugts, J. J., Fleurence, R. et al. (2013) Comparative effects of statins on major cerebrovascular events: a multiple-treatments meta-analysis of placebo-controlled and active-comparator trials. Qjm 106(4): 299-306	- Systematic review does not contain a comparison relevant to this review protocol - Systematic review used as source of primary studies
Naci, H., Brugts, J. J., Fleurence, R. et al. (2013) Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. European Journal of Preventive Cardiology 20(4): 641-57	- Systematic review does not contain a comparison relevant to this review protocol - Systematic review used as source of primary studies
Naci, H.; Brugts, J.; Ades, T. (2013) Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. Circulation. Cardiovascular Quality & Outcomes 6(4): 390-9	- Systematic review does not contain a comparison relevant to this review protocol - Systematic review used as source of primary studies
Nakamura, M., Fukukawa, T., Kitagawa, K. et al. (2018) Ten-year standardization of lipids and high-sensitivity C-reactive protein in a randomized controlled trial to assess the effects of statins on secondary stroke prevention: Japan Statin Treatment Against Recurrent Stroke. Annals of Clinical Biochemistry 55(1): 128-135	- Outcomes not relevant to the protocol
Nakaya, N, Mizuno, K, Ohashi, Y et al. (2011) Low-dose pravastatin and age-related differences in risk factors for cardiovascular disease in hypercholesterolaemic Japanese: analysis of the management of elevated cholesterol in the primary prevention group of adult Japanese (MEGA study). Drugs & aging 28(9): 681-692	- Secondary publication of an included study that does not provide any additional relevant information
Namal, E, Sener, N, Ulaş, T et al. (2011) Effects of different statins, ezetimibe/simvastatin combination on hsCRP levels in unstable angina pectoris and non-ST elevation myocardial	- Study not reported in English

Study	Reason for exclusion
infarction patients: a randomized trial. Anadolu kardiyoloji dergisi [Anatolian journal of cardiology] 11(8): 703-710	
Nilsson, P and Erhardt, L (2001) An extensive English study: reduced cardiovascular mortality and morbidity by statin. Läkartidningen 98(5152): 5846-5850	- Study not reported in English
Orkaby, A. R., Gaziano, J. M., Djousse, L. et al. (2017) Statins for Primary Prevention of Cardiovascular Events and Mortality in Older Men. Journal of the American Geriatrics Society 65(11): 2362-2368	- Study design not relevant to this review protocol: not randomised
Osborn, D., Burton, A., Walters, K. et al. (2019) Primary care management of cardiovascular risk for people with severe mental illnesses: the Primrose research programme including cluster RCT. NIHR Journals Library. Programme Grants for Applied Research 4: 4	- Study does not contain an intervention relevant to this review protocol
Ostadal, P, Alan, D, Hajek, P et al. (2005) Fluvastatin in the therapy of acute coronary syndrome: rationale and design of a multicenter, randomized, double-blind, placebo-controlled trial (The FACS Trial). Current controlled trials in cardiovascular medicine 6(1): 4	- Insufficient follow-up time
Ott, B. R., Daiello, L. A., Dahabreh, I. J. et al. (2015) Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. J Gen Intern Med 30(3): 348-58	- Systematic review: all relevant studies already included in 2014 update - Systematic review used as source of primary studies
Palmer, Sc, Navaneethan, Sd, Craig, Jc et al. (2014) HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database of Systematic Reviews	- Full text paper not available
Pandit, A. K., Kumar, P., Kumar, A. et al. (2016) High-dose statin therapy and risk of intracerebral hemorrhage: a meta-analysis. Acta Neurologica Scandinavica 134(1): 22-8	- Systematic review: all relevant studies already included in 2014 update - Systematic review used as source of primary studies
Pedersen, Tr, Kjekshus, J, Berg, K et al. (2004) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). 1994. Atherosclerosis. Supplements 5(3): 81-87	- Duplicate reference Same article as the original 4S trial publication
Pedersen, Tr, Kjekshus, J, Pyorala, K et al. (1998) Effect of Simvastatin on ischemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). American journal of cardiology 81(3): 333-335	- Secondary publication of an included study that does not provide any additional relevant information
Pfeffer, Ma, Keech, A, Sacks, Fm et al. (2002) Safety and tolerability of Pravastatin in long-term clinical trials: prospective Pravastatin Pooling (PPP) project. Circulation 105(20): 2341-2346	- Systematic review: all relevant studies already included in 2014 update - Systematic review used as source of primary studies

Study	Reason for exclusion
Pitt, B, Loscalzo, J, Monyak, J et al. (2012) Comparison of lipid-modifying efficacy of Rosuvastatin versus Atorvastatin in patients with acute coronary syndrome (from the LUNAR study). American journal of cardiology 109(9): 1239-1246	- Insufficient follow-up time
Pose, E., Napoleone, L., Amin, A. et al. (2020) Safety of two different doses of simvastatin plus rifaximin in decompensated cirrhosis (LIVERHOPE-SAFETY): a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet. Gastroenterology & Hepatology 5(1): 31-41	- Insufficient follow-up time
Poulter, Nr; Caulfield, M; Feder, G (2001) Ethnic variations in response to a statin (EVIREST). Journal of human hypertension 15(suppl1): S87-s89	- Secondary publication of an included study that does not provide any additional relevant information
Preorazhenskii, Dv (2009) Rosuvastatin has no effect on clinical outcomes in patients with heart failure. Results of the GISSI-HF trial. Kardiologiia 49(4): 64-65	- Study not reported in English
Prescott, Lm (1996) Pravastatin recommended for MI survivors with normal cholesterol levels. P and t 21(6): 338-341	- Conference abstract
Puri, R., Nissen, S. E., Shao, M. et al. (2014) Antiatherosclerotic effects of long-term maximally intensive statin therapy after acute coronary syndrome: insights from Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin. Arteriosclerosis, Thrombosis & Vascular Biology 34(11): 2465-72	- Secondary publication of an included study that does not provide any additional relevant information
Qi, W. W., Liu, T., Xu, G. et al. (2015) Upstream therapeutic strategies of Valsartan and Fluvastatin on Hypertensive patients with non-permanent Atrial Fibrillation (VF-HT-AF): study protocol for a randomized controlled trial. Trials [Electronic Resource] 16: 336	- Protocol paper for excluded study
Rajpathak, Sn, Kumbhani, Dj, Crandall, J et al. (2009) Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes care 32(10): 1924-1929	- Systematic review: all relevant trials already included in CG181 2014 update
Ribeiro, R. A., Ziegelmann, P. K., Duncan, B. B. et al. (2013) Impact of statin dose on major cardiovascular events: a mixed treatment comparison meta-analysis involving more than 175,000 patients. International Journal of Cardiology 166(2): 431-9	- Network meta-analysis including some studies that do not match this review protocol (follow-up <12 months; incorrect population; statins not licenced in the UK) - Systematic review used as source of primary studies
Richardson, K., Schoen, M., French, B. et al. (2013) Statins and cognitive function: a systematic review. Ann Intern Med 159(10): 688-97	- Systematic review: all relevant studies already included in 2014 update - Systematic review used as source of primary studies

Study	Reason for exclusion
Ridker, P. M., Lonn, E., Paynter, N. P. et al. (2017) Primary Prevention With Statin Therapy in the Elderly: New Meta-Analyses From the Contemporary JUPITER and HOPE-3 Randomized Trials. Circulation 135(20): 1979-1981	- Secondary publication of an included study that does not provide any additional relevant information
Ridker, Pm, Pradhan, A, MacFadyen, Jg et al. (2012) Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet (london, england) 380(9841): 565-571	- Study already included in CG181 2014 update
Rompler, A; Unger, H; Henrichs, Hr (1995) Secondary prevention by lipid lowering: scandinavian simvastatin survival study. Diabetes und stoffwechsel 4(4): 374-378	- Study not reported in English
Rutter, M. K., Prais, H. R., Charlton-Menys, V. et al. (2011) Protection Against Nephropathy in Diabetes with Atorvastatin (PANDA): a randomized double-blind placebo-controlled trial of high- vs. low-dose atorvastatin(1). Diabet Med 28(1): 100-8	- Study population not relevant to this review protocol: statins not used for CVD risk reduction
Sacks, F. M., Pfeffer, M. A., Moye, L. A. et al. (1996) The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 335(14): 1001-9	- Study already included in CG181 2014 update
Sadeghi, R., Asadpour-Piranfar, M., Asadollahi, M. et al. (2014) The effects of different doses of atorvastatin on serum lipid profile, glycemic control, and liver enzymes in patients with ischemic cerebrovascular accident. Arya Atherosclerosis 10(6): 298-304	- Insufficient follow-up time
Sakamoto, T, Kojima, S, Ogawa, H et al. (2006) Multicenter Study for Aggressive Lipid-Lowering Strategy by HMG-CoA Reductase Inhibitors in Patients With Acute Myocardial Infarction Investigators. Effects of early statin treatment on symptomatic heart failure and ischemic events after acute myocardial infarction in Japanese. American journal of cardiology 97(8): 1165-1171	- Study does not contain an intervention classification relevant to this review protocol
Samaras, K.; Brodaty, H.; Sachdev, P. S. (2016) Does statin use cause memory decline in the elderly?. Trends in Cardiovascular Medicine 26(6): 550-65	- Systematic review: all relevant trials already included in CG181
Sanchez, P., Toro-Trujillo, E., Munoz-Velandia, O. M. et al. (2019) Therapeutic Impact of Statins on the Lipid Profile and Cardiovascular Risk in Patients With Systemic Lupus Erythematosus: Systematic Review of the Literature and a Meta-analysis. Reumatologia Clinica 15(6): e86-e91	- Systematic review does not contain any outcome data relevant to this review protocol - Systematic review used as source of primary studies
Sandwith, L. and Forget, P. (2021) Statins in Healthy Adults: A Meta-Analysis. Medicina 57(6): 07	- Systematic review: all relevant trials already included in CG181 2014 update

Study	Reason for exclusion
Sanguankeo, A., Upala, S., Cheungpasitporn, W. et al. (2015) Effects of Statins on Renal Outcome in Chronic Kidney Disease Patients: A Systematic Review and Meta-Analysis. PLoS ONE [Electronic Resource] 10(7): e0132970	- Outcomes not relevant to the protocol
Sarma, A., Cannon, C. P., de Lemos, J. et al. (2014) The incidence of kidney injury for patients treated with a high-potency versus moderate-potency statin regimen after an acute coronary syndrome. Journal of the American Heart Association 3(3): e000784	- Outcomes not relevant to the protocol
Sato, H, Kinjo, K, Ito, H et al. (2008) Effect of early use of low-dose pravastatin on major adverse cardiac events in patients with acute myocardial infarction: the OACIS-LIPID study. Circulation 72(1): 17	- Insufficient follow-up time
Savarese, G., Gotto, A. M., Jr., Paolillo, S. et al. (2013) Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. Journal of the American College of Cardiology 62(22): 2090-9	- Systematic review: all relevant trials already included in CG181 2014 update
Schrott, H, Fereshetian, Ag, Knopp, Rh et al. (1998) A multicenter, placebo-controlled, dose-ranging study of atorvastatin. Journal of cardiovascular pharmacology and therapeutics 3(2): 119-124	- Insufficient follow-up time
Schwartz, G. G., Fayyad, R., Szarek, M. et al. (2017) Early, intensive statin treatment reduces 'hard' cardiovascular outcomes after acute coronary syndrome. European Journal of Preventive Cardiology 24(12): 1294-1296	- Insufficient follow-up time
Schwartz, Gg, Olsson, Ag, Ezekowitz, Md et al. (2001) Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. Jama 285(13): 1711	- Insufficient follow-up time
Serebruany, Vl (2008) Controlled Rosuvastatin Multinational Trial in Heart Failure (The Positive Negative Trial). American journal of cardiology 101(12): 1808-1809	- Review article but not a systematic review
Serruys, P. W., de Feyter, P., Macaya, C. et al. (2002) Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. Jama 287(24): 3215-22	- Study excluded in CG181 2014 update
Server, Ps; Dahlof, B; Poulter, Nr (2003) Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac outcomes Trial - Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 361: 1149-1158	- Study already included in CG181 2014 update
Sever, Ps, Dahlof, B, Poulter, Nr et al. (2003) Prevention of coronary and stroke events with	- Study not reported in English

Study	Reason for exclusion
atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cariac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Zeitschrift fur kardiologie 92: 613	
Shen, J., Shen, J., Zhu, K. et al. (2019) Efficacy of Statins in Cerebral Vasospasm, Mortality, and Delayed Cerebral Ischemia in Patients with Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. World Neurosurgery 131: e65-e73	- Systematic review does not match the protocol: incorrect population
Shepherd, J., Breazna, A., Deedwania, P. C. et al. (2016) Relation Between Change in Renal Function and Cardiovascular Outcomes in Atorvastatin-Treated Patients (from the Treating to New Targets [TNT] Study). American Journal of Cardiology 117(8): 1199-205	- Secondary publication of an included study that does not provide any additional relevant information
Shepherd, J, Vidt, Dg, Miller, E et al. (2007) Safety of rosuvastatin: update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. Cardiology 107(4): 433-443	- Systematic review does not match the protocol Participant with heterozygous or homozygous familial hypercholesterolemia were included
Shukla, A Sharma M Jain AGoel P (2005) Prevention of Atherosclerosis Progression Using Atorvastatin in Normolipidemic Coronary Artery Disease Patients - A Controlled Randomized Trial. Indian heart journal 57(6): 675-680	- Study already included in CG181 2014 update
Silva, M, Matthews, MI, Jarvis, C et al. (2007) Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. Clinical therapeutics 29(2): 253-260	- Systematic review: all relevant trials already included in CG181 2014 update
Singh, B. M., Lamichhane, H. K., Srivatsa, S. S. et al. (2020) Role of Statins in the Primary Prevention of Atherosclerotic Cardiovascular Disease and Mortality in the Population with Mean Cholesterol in the Near-Optimal to Borderline High Range: A Systematic Review and Meta-Analysis. Advances in Preventive Medicine 2020: 6617905	- Systematic review used as source of primary studies - Systematic review: most relevant trials included in 2014 update, so no benefit of including this review. Two additional relevant studies published since the 2014 update already identified in search and added in to this guideline review analysis.
Singh, H., Gill, B. S., Bajaj, V. K. et al. (2013) An open prospective, randomized controlled study to evaluate the antianginal effect of atorvastatin in patients of coronary artery disease with dyslipidemia. Journal of Pharmaceutical Sciences and Research 5(3): 72-75	- Study does not contain an intervention relevant to this review protocol
Soedamah-Muthu, S. S., Livingstone, S. J., Charlton-Menys, V. et al. (2015) Effect of atorvastatin on C-reactive protein and benefits for cardiovascular disease in patients with type 2 diabetes: analyses from the Collaborative Atorvastatin Diabetes Trial. Diabetologia 58(7): 1494-502	- Secondary publication of an included study that does not provide any additional relevant information

Study	Reason for exclusion
Suwaidi, J. A. (2016) Hope for primary cardiovascular prevention with the HOPE (Heart Outcomes Prevention Evaluation)-3 trial findings. Global Cardiology Science & Practice 2016(2): e201613	- Secondary publication of an included study that does not provide any additional relevant information
Szarek, M., Amarenco, P., Callahan, A. et al. (2020) Atorvastatin Reduces First and Subsequent Vascular Events Across Vascular Territories: The SPARCL Trial. Journal of the American College of Cardiology 75(17): 2110-2118	- Secondary publication of an included study that does not provide any additional relevant information - Study design not relevant to this review protocol: post hoc analysis
Szarek, M, Amarenco, P, Callahan, A et al. (2020) Atorvastatin reduces total events overall and across vascular beds in the sparcl trial. Journal of the American College of Cardiology 75(11): 2202	- Secondary publication of an included study that does not provide any additional relevant information
Taylor, F, Huffman, Md, Macedo, Af et al. (2013) Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews	- Systematic review: most relevant trials already included in 2014 update, so no benefit of including this review. One additional relevant study already identified in search and added in to this review analysis. - Systematic review used as source of primary studies
Teng, M., Lin, L., Zhao, Y. J. et al. (2015) Statins for Primary Prevention of Cardiovascular Disease in Elderly Patients: Systematic Review and Meta-Analysis. Drugs & Aging 32(8): 649-61	- Systematic review: all relevant trials already included in CG181
Teoh, R. J. J., Huang, C. J., Chan, C. P. et al. (2019) Does statin increase the risk of intracerebral hemorrhage in stroke survivors? A meta-analysis and trial sequential analysis. Therapeutic Advances in Neurological Disorders 12: 1756286419864830	- Systematic review: most relevant trials already included in 2014 update, so no benefit of including this review. One additional relevant study published since the 2014 update already identified in search and added in to this review analysis. - Systematic review used as source of primary studies
Thakker, D., Nair, S., Pagada, A. et al. (2016) Statin use and the risk of developing diabetes: A network meta-analysis. Pharmacoepidemiology and Drug Safety.	- Conference abstract
Thiago, L, Tsuji, Sr, Nyong, J et al. (2016) Statins for aortic valve stenosis. Cochrane Database of Systematic Reviews	- Systematic review does not match the protocol Purpose of statins is not for CVD risk reduction
Thomas, J (2009) Rosuvastatin significantly reduces incidence of major cardiovascular events. Australian journal of pharmacy 90(1072): 73	- Secondary publication of an included study that does not provide any additional relevant information
Tonelli, M, Isles, C, Curhan, Gc et al. (2004) Effect of pravastatin on cardiovascular events in people with chronic kidney disease. Circulation 110(12): 1557-1563	- Study design not relevant to this review protocol: post hoc analysis
Toyota, T., Morimoto, T., Yamashita, Y. et al. (2019) More- Versus Less-Intensive Lipid-	- Systematic review: all relevant trials already included in CG181 2014 update

Study	Reason for exclusion
Lowering Therapy. Circulation. Cardiovascular Quality & Outcomes 12(8): e005460	
Tramacere, I., Boncoraglio, G. B., Banzi, R. et al. (2019) Comparison of statins for secondary prevention in patients with ischemic stroke or transient ischemic attack: a systematic review and network meta-analysis. BMC Medicine 17(1): 67	- Network meta-analysis including some studies that do not match this review protocol (follow-up <12 months) - Systematic review: limited to studies in people with prior stroke and most relevant trials included in 2014 update, so no benefit of including this review. Two additional relevant studies published since the 2014 update already identified in search and added in to the guideline review analysis. - Systematic review used as source of primary studies
Tran, A. V., Nguyen, T. T., Tran, L. N. T. et al. (2021) Efficacy of Rosuvastatin and Atorvastatin in Vietnamese Patients with Acute Coronary Syndrome: A randomized trial. Pharmaceutical Sciences Asia 48(5): 413-419	- Outcomes not relevant to the protocol
Trevillyan, J. M., Dart, A., Paul, E. et al. (2021) Impact of rosuvastatin on atherosclerosis in people with HIV at moderate cardiovascular risk: a randomised, controlled trial. AIDS 35(4): 619-624	- Outcomes not relevant to the protocol
Tsujimoto, T. and Kajio, H. (2018) Favorable effects of statins in the treatment of heart failure with preserved ejection fraction in patients without ischemic heart disease. International Journal of Cardiology 255: 111-117	- Study design not relevant to this review protocol: not randomised
Tsunoda, R, Sakamoto, T, Kojima, S et al. (2011) Recurrence of angina pectoris after percutaneous coronary intervention is reduced by statins in Japanese patients. Journal of cardiology 58(3): 208-215	- Study does not contain an intervention classification relevant to this review protocol
Ueshima, K., Itoh, H., Kanazawa, N. et al. (2016) Rationale and Design of the Standard Versus Intensive Statin Therapy for Hypercholesterolemic Patients with Diabetic Retinopathy (EMPATHY) Study: a Randomized Controlled Trial. Journal of Atherosclerosis & Thrombosis 23(8): 976-90	- Study design not relevant to this review protocol: treat-to-target trial
Vale, N, Nordmann, Aj, Schwartz, Gg et al. (2014) Statins for acute coronary syndrome. Cochrane Database of Systematic Reviews	- Systematic review: all relevant studies already included in CG181 2014 update
Vallejo-Vaz, A. J., Robertson, M., Catapano, A. L. et al. (2017) Low-Density Lipoprotein Cholesterol Lowering for the Primary Prevention of Cardiovascular Disease Among Men With Primary Elevations of Low-Density Lipoprotein Cholesterol Levels of 190 mg/dL or Above: Analyses From the WOSCOPS (West of Scotland Coronary Prevention Study) 5-Year	- Secondary publication of an included study that does not provide any additional relevant information

Study	Reason for exclusion
Randomized Trial and 20-Year Observational Follow-Up. Circulation 136(20): 1878-1891	
Vollmer, H (1998) The Lipoprotein and Coronary Atherosclerosis Study (LCAS) confirms the benefit of lipid lowering for example with fluvastatin. Therapie und erfolg 2(1): 76-77	- Study not reported in English
Wan, M.; Yi, S.; Yi, X. (2020) Effects of atorvastatin on elderly patients with acute myocardial infarction. International Journal of Clinical and Experimental Medicine 13(3): 1712-1719	- Insufficient follow-up time - Study design not relevant to this review protocol: not randomised
Wang, J., Chen, D., Li, D. B. et al. (2016) Comparison of the efficacy and safety of intensive-dose and standard-dose statin treatment for stroke prevention: A meta-analysis. Medicine 95(39): e4950	- Systematic review: all relevant trials already included in CG181 2014 update
Wang, W. and Zhang, B. (2014) Statins for the prevention of stroke: a meta-analysis of randomized controlled trials. PLoS ONE [Electronic Resource] 9(3): e92388	- Secondary publication of an included study that does not provide any additional relevant information
Wardle, J., Armitage, J., Collins, R. et al. (1996) Randomised placebo controlled trial of effect on mood of lowering cholesterol concentration. Oxford Cholesterol Study Group. Bmj 313(7049): 75-8	- Outcomes not relevant to the protocol
Welty, F. K., Lewis, S. J., Friday, K. E. et al. (2016) A Comparison of Statin Therapies in Hypercholesterolemia in Women: A Subgroup Analysis of the STELLAR Study. Journal of Women's Health 25(1): 50-6	- Insufficient follow-up time
Wiviott, Sd, Cannon, Cp, Morrow, Da et al. (2005) Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: a PROVE IT-TIMI 22 substudy. Journal of the american college of cardiology 46(8): 1411-1416	- Study does not contain an intervention relevant to this review protocol
Wong, G. K., Liang, M., Tan, H. et al. (2013) High-dose simvastatin for aneurysmal subarachnoid hemorrhage: a multicenter, randomized, controlled, double-blind clinical trial protocol. Neurosurgery 72(5): 840-4	- Insufficient follow-up time
Xie, C., Zhu, M., Hu, Y. et al. (2020) Effect of Intensive and Standard Lipid-Lowering Therapy on the Progression of Stroke in Patients With Coronary Artery Syndromes: A Meta-Analysis of Randomized Controlled Trials. Journal of Cardiovascular Pharmacology 75(3): 222-228	- Systematic review: all relevant trials already included in CG181 2014 update
Xie, J, Wang, Y-K, Shao, Y et al. (2015) Comparison of efficacy of two statins for peripheral artery atherosclerosis. Chinese journal of new drugs 24(7): 808-812	- Study not reported in English
Xie, R. Q., Cui, W., Liu, F. et al. (2010) Statin therapy shortens QTc, QTcd, and improves	- Population not relevant to this review protocol: heart failure

Study	Reason for exclusion
cardiac function in patients with chronic heart failure. Int J Cardiol 140(2): 255-7	
Xie, W., Huang, H., Xiao, S. et al. (2020) Effect of statin use on cardiovascular events and all-cause mortality in immune-mediated inflammatory diseases: A systematic review and meta-analysis involving 148,722 participants. Pharmacological Research 160: 105057	- Systematic review: insufficient quality assessment of included studies and all relevant studies already included in 2014 update
Xu, J. Y., Qian, H. Y., Huang, P. S. et al. (2019) Transplantation efficacy of autologous bone marrow mesenchymal stem cells combined with atorvastatin for acute myocardial infarction (TEAM-AMI): rationale and design of a randomized, double-blind, placebo-controlled, multi-center, Phase II TEAM-AMI trial. Regenerative Medicine 14(12): 1077-1087	- Study does not included an intervention relevant to the review protocol. - Protocol paper: trial results not yet published
Yakusevich, Vv; Malygin, Ay; Kabanov, Av (2013) Effect of simvastatin on the prognosis and the changes of the clinical status in patients with acute ischemic stroke. The results of the 12 month randomized, open comparative study. Rational pharmacotherapy in cardiology 9(4): 379-385	- Study not reported in English
Yan, Y. L., Qiu, B., Wang, J. et al. (2015) High-intensity statin therapy in patients with chronic kidney disease: a systematic review and meta-analysis. BMJ Open 5(5): e006886	- Systematic review: limited to studies in people with CKD and all relevant trials included in 2014 update. - Systematic review used as source of primary studies
Yao, R, Du, Y, Zhang, Y et al. (2016) Comparison of clinical efficacy of different statins on cardiovascular events following percutaneous coronary intervention. International journal of clinical and experimental medicine 9(2): 4356-4363	- Full text paper not available
Yebyo, H. G., Aschmann, H. E., Kaufmann, M. et al. (2019) Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: A systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants. American Heart Journal 210: 18-28	- Network meta-analysis does not contain a comparison relevant to the review protocol - Systematic review: does not contain a comparison relevant to the efficacy review protocol and includes open-label trials for subjective outcomes. - Systematic review used as source of primary studies
Yokote, K, Saito, Y, Bujo, H et al. (2009) Influence of statins on glucose tolerance in patients with type 2 diabetes mellitus: subanalysis of the collaborative study onhypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA Study). Journal of atherosclerosis and thrombosis 16(3): 297-298	- Full text paper not available

Study	Reason for exclusion
Yourman, L. C., Cenzer, I. S., Boscardin, W. J. et al. (2021) Evaluation of Time to Benefit of Statins for the Primary Prevention of Cardiovascular Events in Adults Aged 50 to 75 Years: A Meta-analysis. JAMA Internal Medicine 181(2): 179-185	- Systematic review: all relevant trials already included in CG181 2014 update
Yu, S., Jin, J., Chen, Z. et al. (2020) High-intensity statin therapy yields better outcomes in acute coronary syndrome patients: a meta-analysis involving 26,497 patients. Lipids in Health & Disease 19(1): 194	- Systematic review does not contain a comparison relevant to the protocol - Systematic review used as source of primary studies
Yun, Kh, Park, Hy, Choi, Jh et al. (2007) Comparison of Efficacy and Safety after Administering High Potency Statin to High Risk Patients: rosuvastatin 10 mg versus Atorvastatin 20 mg. Korean circulation journal 37(4): 154-160	- Insufficient follow-up time
Yusuf, S., Lonn, E., Pais, P. et al. (2016) Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease. New England Journal of Medicine 374(21): 2032-43	- Secondary publication of an included study that does not provide any additional relevant information
Zhai, C., Hou, K., Li, R. et al. (2020) Efficacy of statin treatment based on cardiovascular outcomes in elderly patients: a standard meta-analysis and Bayesian network analysis. Journal of International Medical Research 48(6): 300060520926349	- Network meta-analysis does not contain a comparison relevant to this review protocol - Systematic review: all relevant trials included in CG181 2014 update
Zhang, F-F (2018) Clinical Comparative Study and Securitt Analysis on Different Doses of Atorvastatin and Rosuvastatin for Patients with Chronic Heart Failure. Chinese journal of pharmaceutical biotechnology 25(2): 153-156	- Study not reported in English
Zhang, H., Jiang, M., Hou, H. et al. (2021) Efficacy of simvastatin on carotid atherosclerotic plaque and its effects on serum inflammatory factors and cardiocerebrovascular events in elderly patients. Experimental and Therapeutic Medicine 22(2)	- Outcomes not relevant to the protocol
Zhang, X., Xiang, C., Zhou, Y. H. et al. (2014) Effect of statins on cardiovascular events in patients with mild to moderate chronic kidney disease: a systematic review and meta-analysis of randomized clinical trials. BMC Cardiovascular Disorders 14: 19	- Systematic review: all relevant trials already included in CG181 2014 update
Zhao, S, Wang, F, Yang, K et al. (2014) Efficacy and safety of fluvastatin extended-release tablets in Chinese patients with hyperlipidemia: a multi-center, randomized, double-blind, double dummy, active-controlled, parallel-group study. Zhonghua nei ke za zhi [Chinese journal of internal medicine] 53(6): 455-459	- Study not reported in English
Zhao, Z., Niu, X., Dong, Z. et al. (2018) Upstream therapeutic strategies of valsartan and fluvastatin on hypertensive patients with non-permanent atrial fibrillation. Cardiovascular therapeutics 36(6): e12478	- Data not reported in an extractable format or a format that can be analysed

Study	Reason for exclusion
Zhao, Z., Yang, Y., Wang, J. et al. (2020) Combined treatment with valsartan and fluvastatin to delay disease progression in nonpermanent atrial fibrillation with hypertension: A clinical trial. Clinical Cardiology 43(12): 1592-1600	- Outcomes not relevant to the protocol
Zhong, P., Wu, D., Ye, X. et al. (2017) Secondary prevention of major cerebrovascular events with seven different statins: a multi-treatment meta-analysis. Drug design, development & therapy 11: 2517-2526	- Systematic review used as source of primary studies - Study does not contain an intervention classification relevant to this review protocol - Systematic review: all relevant trials already included in CG181 2014 update
Zhou, T.; Mei, J.; Hou, M. (2021) Clinical study of double anti-platelet therapy combined with different doses of statin in the treatment of acute cerebral infarction complicated with microhemorrhage. American Journal of Translational Research 13(10): 12043-12050	- Insufficient follow-up time
Zhou, Z., Albarqouni, L., Curtis, A. J. et al. (2020) The Safety and Tolerability of Statin Therapy in Primary Prevention in Older Adults: A Systematic Review and Meta-analysis. Drugs & Aging 37(3): 175-185	- Systematic review: all relevant trials already included in CG181 2014 update
Zhou, Z., Ofori-Asenso, R., Curtis, A. J. et al. (2020) Association of Statin Use With Disability-Free Survival and Cardiovascular Disease Among Healthy Older Adults. Journal of the American College of Cardiology 76(1): 17-27	- Study design does not match the protocol Observational analysis of data from an RCT
Ziff, O. J., Banerjee, G., Ambler, G. et al. (2019) Statins and the risk of intracerebral haemorrhage in patients with stroke: systematic review and meta-analysis. Journal of Neurology, Neurosurgery & Psychiatry 90(1): 75-83	- Systematic review: all relevant studies included in 2014 update

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2007 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 39 lists new studies identified since the 2014 CG181 update search cut offs (November 2013) and Table 40 lists studies selectively excluded from CG181 (that were published 2007 or later and not from a non-OECD country or USA) with the reasons given at the time.

Table 39: Studies excluded from the 2022 update health economic review

Reference	Reason for exclusion
Aarnio 2015[1]	Primary prevention. This study was assessed as partially applicable (2011 Finnish setting may not reflect current UK NHS context; some differences

Reference	Reason for exclusion
	to NICE reference case); however, given that a more applicable UK analysis was available this study was selectively excluded.
Anouk 2021[14]	Primary prevention. This study was assessed as partially applicable (Swiss setting may not reflect current UK NHS context; some differences to NICE reference case); however, given that a more applicable UK analysis was available this study was selectively excluded.
Dakin 2020[49]	Primary prevention. This study was assessed as partially applicable; however, given that a more applicable UK analysis was available this study was selectively excluded.
De Vries 2014[51]	Primary prevention. This study was assessed as partially applicable (Netherlands setting may not reflect current UK NHS context); however, given that a more applicable UK analysis was available this study was selectively excluded.
Jeong 2017[81]	Unclear if primary or secondary prevention or mixed. Selectively excluded due to a combination of applicability and methodological limitations. These included: 2009-2015 Korean costs may not reflect the current NHS context; QALYs not estimated; only drug costs considered; population unclear.
Kim 2021[86]	Primary prevention. Selectively excluded due to a combination of applicability and methodological limitations. These included: 2009-2015 Korean costs may not reflect the current NHS context; QALYs not estimated; unclear what costs were incorporated.
Lamy 2019[98]	Primary prevention. Selectively excluded due to a combination of applicability and methodological limitations. These included: combined European/Canadian/Australian costs may not reflect the current NHS context; only costs analysed.
Macchia 2015[107]	Primary prevention. This study was assessed as partially applicable (Italian setting may not reflect current UK NHS context; QALYs not calculated); however, given that a more applicable UK analysis was available this study was selectively excluded.
Romanens 2017[153]	Primary prevention. This study was assessed as partially applicable (Swiss setting may not reflect current UK NHS context); however, given that a more applicable UK analysis was available this study was selectively excluded.
Romanens 2021[152]	Primary prevention. Primary prevention. This study was assessed as partially applicable (Swiss setting may not reflect current UK NHS context and unclear if discounting and QALY estimation methods are in line with the NICE reference case); however, given that a more applicable UK analysis was available this study was selectively excluded.
Stam-Slob 2017[171]	Secondary prevention. Excluded as rated not applicable. The intervention group included ezetimibe as well as statins with regard to treatment effects and costs and so did not meet the review protocol. In additional 2014 Netherlands perspective may not reflect current UK context.

Table 40: Studies excluded from the health economic review in 2014 CG181 update

Reference	Reason for exclusion
Annemans 2010[13]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Barrios 2012[26]	This study was assessed as having limited applicability and potentially serious limitations. Evidence from the UK was identified which was more applicable.

Reference	Reason for exclusion
Cobiac 2012[38]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Conly 2011[44]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Costa 2008[45]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Fragoulakis 2012[58]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Gandhi 2012[62]	This study was assessed as partially applicable with potentially serious limitations. However, the GDG judged that other available evidence was of greater applicability, and therefore this study was selectively excluded.
Grover 2008[67]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Herregods 2008[70]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Ito 2011[80]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Kang 2009[82]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Khoury 2009[85]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Lachaine 2007[96]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Lafuma 2008[97]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Lindgren 2007[104]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
National Collaborating Centre for Primary Care 2008, model C[122]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Ohsfeldt 2010[131]	This study was assessed as partially applicable with potentially serious limitations. However, the GDG judged that other available evidence was of greater applicability, and therefore this study was selectively excluded.
Ohsfeldt 2012[132]	This study was assessed as partially applicable with potentially serious limitations. However, the GDG judged that other available evidence was of greater applicability, and therefore this study was selectively excluded.
Onishi 2013[133]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Peura 2008[135]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Pinto 2008[136]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.

Reference	Reason for exclusion
Raikou 2007[142]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Soini 2010[169]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Taylor 2009[174]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Thanh 2012[178]	This study was assessed as not applicable. Evidence using QALYs was identified which was more applicable.
Tran 2007[180]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Wagner 2009[182]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Wagner 2009[183]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Zechmeister 2008[193]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.

Appendix K – Call for evidence submissions

Table 41: Call for evidence submissions – exclusion reasons

Submission	Title	Identified in statins review search?	Rationale for exclusion
Bytyci 2022	Prevalence of statin intolerance: a meta-analysis	Yes	Outcomes not relevant to the review protocol
Collins 2016	Interpretation of the evidence for the efficacy and safety of statin therapy	Yes	Systematic review already identified in the search and used as source of primary studies
CTT 2019	Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials	Yes	Historical comparison arm does not meet review protocol
Ference 2017	Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic and clinical studies. A Consensus Statement from the European Atherosclerosis Society Consensus Panel.	Yes	Interventions not relevant to the protocol (lipoproteins)
Ginsberg 2021	Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies—a consensus statement from the European Atherosclerosis Society	Yes	Interventions not relevant to the protocol (lipoproteins)
Goodman 2022	Longer-term safety of alirocumab with 24,610 patient-years of placebo-controlled observation: Further insights from the ODYSSEY OUTCOMES trial	N/A [Embargo]	Interventions not relevant to the protocol (alicromab)
Hageman 2022	Estimation of recurrent atherosclerotic cardiovascular event risk in patients with established cardiovascular disease: the updated SMART2 algorithm	Yes	Study design not relevant to protocol (prognostic model, non-RCT)
Hegele 2019	Rare dyslipidaemias, from phenotype to genotype to management: a European Atherosclerosis Society task force consensus statement	Yes	Interventions not relevant to the protocol (lipoproteins)
Jan Boren 2020	Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel	Yes	Interventions not relevant to the protocol (lipoproteins)
Landmesser 2017	2017 Update of ESC/EAS Task force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia.	Yes	Interventions not relevant to the protocol (proprotein convertase subtilisin/kexin type 9 inhibition)

Submission	Title	Identified in statins review search?	Rationale for exclusion
Law 2003	Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials.	Yes	Interventions not relevant to the protocol (beta blockers, ACE inhibitors, calcium channel blockers)
Law 2003	. Quantifying the effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis.	Yes	Already included in CG181 2014 update
Mach 2018	Adverse effects of statin therapy: perception vs. the evidence – focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract	Yes	Systematic review already identified in the search and used as source of primary studies
McKay 2022	Is the SMART risk prediction model ready for real-world implementation? A validation study in a routine care setting of approximately 380 000 individuals	Yes	Study design not relevant to protocol (prognostic model, non-RCT)
Mihaylova 2022	Cost-effectiveness of statin therapy in categories of patients in the UK	N/A [Embargoed version provided in advance of publication]	Not included as abstract not full paper
Newman 2018	Statin Safety and Associated Adverse Events	Yes	Study design not relevant to protocol (scientific statement, non-RCT)
Office for Health Improvement and Disparities	Preventing illness and improving health for all: a review of the NHS Health Check programme and recommendations	Yes	Study design not relevant to protocol (scientific statement, non-RCT)
Patel 2021	Assessing Cardiovascular Risk to Altering Risk Trajectories: Opportunities Revealed by England's NHS Health Check Programme	Yes	Study design not relevant to protocol (Programme evaluation, non-RCT)
Ray 2019	Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial.	Yes	Interventions not relevant to the protocol (alicromab)
Ray 2021	The DA VINCI study, EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care	Yes	Interventions not relevant to the protocol (lipoproteins)
Ray 2022	Low-density lipoprotein cholesterol levels exceed the recommended European threshold for PCSK9i initiation: lessons from the HEYMANS study	Yes	Interventions not relevant to the protocol (lipoproteins)
Schlackow 2017 [158]	A policy model of cardiovascular disease in moderate-to-advanced chronic kidney disease	Yes	Already identified as a source reference for a

Submission	Title	Identified in statins review search?	Rationale for exclusion
			study included in statin economic review
Schlackow 2019 [157]	Cost-effectiveness of lowering LDL cholesterol with statins and ezetimibe in chronic kidney disease.	Yes	Already identified and included in statin economic review
Schmidt 2020	PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease	Yes	Interventions not relevant to the protocol (PCSK9 inhibitor)
Schwartz 2018	Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome	Yes	Interventions not relevant to the protocol (alicromab)
Simmonds 2012	Risk estimation versus screening performance: a comparison of six risk algorithms for cardiovascular disease.	Yes	Already included in CG181 2014 update
Steg 2019	Effect of Alirocumab on Mortality After Acute Coronary Syndromes. Circulation	Yes	Interventions not relevant to the protocol (alicromab)
Taylor 2013 [175]	Statins for Primary Prevention of Cardiovascular Disease. Cochrane Database of Systematic Reviews	Yes	Systematic review, already identified in the search and used as source of primary studies; all relevant trials included in CG181 2014 update
Thalmann 2020	Determinants of statin initiation and discontinuation in the secondary prevention of atherosclerotic cardiovascular disease in Scotland during 2009-2017	No	Not included as abstract not full paper
Tunon 2020	Effect of alirocumab on major adverse cardiovascular events according to renal function in patients with a recent acute coronary syndrome: prespecified analysis from the ODYSSEY OUTCOMES randomized clinical trial	Yes	Interventions not relevant to the protocol (alicromab)
Vallejo-Vaz 2022	Implications of ACC/AHA Versus ESC/EAS LDL-C Recommendations for Residual Risk Reduction in ASCVD: A Simulation Study From DA VINCI	Yes	Study design not relevant to protocol (simulation model, non-RCT)
Wald 2003	A strategy to reduce cardiovascular disease by more than 80%.	Yes	Interventions not relevant to the protocol (Polypill, statin combination therapy)
Wald 2011	Screening for Future Cardiovascular Disease Using Age Alone Compared with Multiple Risk Factors and Age.	Yes	Already included in CG181 2014 update
Wald 2012	Randomized Polypill crossover trial in people aged 50 and over.	Yes	Interventions not relevant to the protocol (Polypill, statin combination therapy)
Wald 2014	Quantifying the health benefits of chronic disease prevention: a fresh approach using cardiovascular disease as an example.	Yes	Interventions not relevant to the protocol (Polypill, statin combination therapy)

Submission	Title	Identified in statins review search?	Rationale for exclusion
Wald 2016	Cost-benefit analysis of the polypill in the primary prevention of myocardial infarction and stroke.	Yes	Interventions not relevant to the protocol (Polypill, statin combination therapy)
Wu 2021	Gaps in antihypertensive and statin treatments and benefits of optimisation: a modelling study in a 1 million ethnically diverse urban population in UK.	No	Not included as assessing suboptimal treatment and impact of change (rather than cost effectiveness) - passed on to committee for information about current practice
Wu 2021[188]	A model of lifetime health outcomes in cardiovascular disease based on clinical trials and large cohorts	No	Not included as abstract not full paper
Wu 2022	Benefit accrual with cardiovascular disease prevention and effects of discontinuation: a modelling study	N/A [Embargoed version provided in advance of publication]	Not included as abstract not full paper
Wu 2022[187]	Calibrating Cardiovascular Disease Policy Model Using Large Cohort Data	No	Not included as abstract not full paper
Zhou 2022	Impact of cardiovascular events on primary and hospital care costs: findings from UK Biobank study	N/A [Embargoed version provided in advance of publication]	Not included as abstract not full paper

Appendix L Patient decision aid – Methods

The patient decision aid (PDA) produced for the 2014 NICE guideline, CG181, was updated for this guideline update. It was developed in line with the NICE process guide for decision aids, with an oversight group that included clinical and patient experts. A wide range of stakeholders, including patient and professional groups, has been invited to comment on a draft. This document serves as a technical appendix to the PDA and explains the evidence used in its production.

Benefits

The method used was the same as for the 2014 PDA, updated with risk ratios from the updated evidence review.

The QRISK3 outcome

The QRISK3 outcome is the same as the QRISK2 outcome: the composite outcome of ischaemic stroke, transient ischaemic attack (TIA) or coronary heart disease (angina or myocardial infarction [MI]).[71]

The relative distribution of first cardiovascular events within this composite used in the health economic model for the 2014 guideline was taken from table 49 of the systematic review by Ward et al. (2007)[184], and this was used in the preparation of this PDA (Table 42).

Modelling

As in the 2014 PDA, risk ratios for the effects of statins versus no treatment were taken from the guideline evidence review C. In keeping with the recommendation in the guideline to use a high-intensity statin for primary prevention, the risk ratios for high-intensity statins compared with no treatment were used, taken from table 7 and forest plots E1 in the evidence review. As in the health economic model for the guideline, the relative risk from a related outcome was used for outcomes which were not meta-analysed in the guideline systematic review (for example, the risk ratio for stroke was also applied for TIA). The risk ratios used are given in Table 43. The risk ratio for each event was assumed to be constant over time and for all age and sex groups.

Table 42: Relative distribution of first cardiovascular events, excluding heart failure and peripheral arterial disease

Age (years)	Stable angina	Unstable angina	MI	TIA	Stroke	CVD death	Total
Men							
45–54	0.31	0.11	0.30	0.06	0.13	0.10	1.00
55–64	0.33	0.07	0.17	0.09	0.21	0.13	1.00
65–74	0.21	0.08	0.17	0.10	0.27	0.16	1.00
75–84	0.19	0.08	0.16	0.08	0.34	0.14	1.00
Women							
45–54	0.33	0.12	0.08	0.16	0.23	0.09	1.00
55–64	0.35	0.07	0.09	0.10	0.29	0.11	1.00
65–74	0.20	0.05	0.12	0.07	0.38	0.17	1.00
75–84	0.15	0.03	0.10	0.10	0.46	0.15	1.00
Age (years)	Stable angina	Unstable angina	MI	TIA	Stroke	CVD death	Total

In the table, column headings for stable and unstable angina, MI (myocardial infarction), TIA (transient ischaemic attack) and stroke refer to nonfatal events; CVD (cardiovascular disease) death is the sum of death from coronary and cerebrovascular causes.

Table 43: Relative risks for high-intensity statins versus no treatment

Outcome	Relative risk	95%CI	GRADE
CVD death	0.80	0.70 to 0.92	High
Non-fatal MI	0.51	0.42 to 0.62	High
Non-fatal ischaemic stroke	0.74	0.65 to 0.84	Moderate
Non-fatal stable angina	As MI	-	-
Non-fatal unstable angina	As MI	-	-
TIA	As stroke	-	-

The effect of high-intensity statins was calculated for each age and sex group and for 8 levels of 10-year cardiovascular disease risk by applying the appropriate risk ratio to each of the outcomes in the composite QRISK3 outcome and then multiplying the sum of the products by the baseline 10-year risk to obtain an estimated on-treatment 10-year risk. The number of first cardiovascular events per 100 people on high-intensity statin treatment over 10 years for a given baseline 10-year cardiovascular disease risk is given by:

Events per 100 over 10 years = R x (0.51UA+0.51SA+0.51MI+0.74TIA+0.74ST+0.80CVDD)

Where

R = events per 100 people not on treatment over 10 years

UA = relative proportion of non-fatal unstable angina

SA = relative proportion of non-fatal stable angina

MI = relative proportion of non-fatal MI

TIA = relative proportion of non-fatal TIA

ST = relative proportion of non-fatal stroke

CVDD = relative proportion of death from cardiovascular causes

Data were manipulated in Microsoft Excel.

Limitations

The PDA is intended to give some sense of the magnitude of risks and benefits from high-intensity statins in primary prevention of cardiovascular disease, but the figures provided have a measure of uncertainty. The modelling relied on a number of assumptions as described above and is also subject to the limitations of the data on which it is built. These limitations should be considered when using the PDA.

In particular, it was only practicable to use point estimates of the relative distribution of first cardiovascular events. It is not practicable to indicate in an icon array the uncertainty indicated by 95% confidence intervals around relative risks. Moreover, for a given QRISK score, the differences in distribution of first events by age and sex resulted in the calculated point estimates of absolute effects of high-intensity statins being slightly different in different

age and sex groups. In absolute terms, for a given QRISK score, the estimated total number of events prevented was highest in men aged 45–54 years and lowest in women aged 75–84 years, with greater differences at greater 10-year QRISK scores. It should be noted that these point estimates have a measure of uncertainty and the statistical significance of the differences has not been tested. For simplicity in representing the benefits from statin therapy, and taking into account the limitations arising from using point estimates as above, the PDA project group agreed that the mean absolute effect on first cardiovascular events should be represented.

At stakeholder review of the guideline, an alternative modelling approach was proposed by the authors of the updated economic model used for the 2023 guideline. This produced extremely similar absolute benefits and so the original modelling for the PDA was retained.

Harms

The outcomes considered in evidence review C were:

- Rhabdomyolysis (creatine kinase (CK)>10 times normal)
- Myalgia
- Liver (transaminases>3 times normal level)
- New onset diabetes
- Worsening of diabetes:
- Cognitive decline (by validated questionnaire) or dementia
- Haemorrhagic stroke

Results are presented in appendix E.2.1, forest plots 40 to 50

Rhabdomyolysis

From the IPD analysis, the pooled control event rate from all studies was 0.03%. The odds ratio for high-intensity statins versus placebo was not statistically significant (1.80, 95%CI 0.70 to 4.67) but the pooled odds ratio for all statins was 2.12 (95%CI 1.20 to 3.73). This indicates an absolute increase of 0.03% (95%CI 0.01% to 0.08%). Applying the odds ratio for high-intensity statins versus placebo gives a similar point estimate absolute risk increase (0.02%). This risk is discussed in the PDA.

Myalgia

From the IPD analysis, the pooled control event rate from all studies was 26.4%. The relative risk for high-intensive statins versus placebo was 1.09 (95%CI 1.04 to 1.14). This indicates an absolute increase of 2.38% (95%CI 1.06% to 3.70%). This risk is discussed in the PDA.

New onset or worsening of diabetes

Only one small study reported on worsening of diabetes, but this evidence was rated as very low quality; it was not thought sufficient to form the basis of any conclusion by the committee and so this is not mentioned in the PDA. For new-onset diabetes the relative risk with high-intensity statins was 1.20 (95%CI 1.07 to 1.34). With a pooled control event rate from all studies of 4.26%, this is an absolute increase of 0.85% (0.30% to 1.45%). This risk is discussed in the PDA.

Liver transaminases

Although the review found evidence of an increased risk of raised transaminases, it is not clear what the clinical impact of this would be and the guideline committee did not attach any significance to it. This risk is not mentioned in the PDA.

Cognitive decline and dementia

The guideline committee also noted that there does not appear to be any evidence of an effect on cognitive decline and dementia, and any declines observed are likely to reflect normal age-related decline. The relative risks were not statistically significant for all outcomes except for a reduction in risk of cognitive decline based on changes in MMSE or DSE score (relative risk for high intensity statins versus placebo 0.57, 95%CI 0.40 to 0.83). Based on their experience that this is a possible harm that patients sometimes ask about, the project group decided, to include a statement that there is no good evidence that statins cause dementia.

Haemorrhagic stroke

Regarding haemorrhagic stroke, there was a suggestion from the evidence review of a possible harm based on an increased relative risk. However, the event rate was judged by the guideline committee as very low, and they agreed that the absolute risk difference did not represent a clinically important harm. Moreover, for the purposes of the PDA, the increased relative risk was not statistically significant for all statin intensities versus placebo (relative risk 1.17, 95%CI 0.92 to 1.49) and the confidence intervals were wide for high intensity statins versus placebo (1.44, 95%CI 1.01 to 2.06). With a pooled control event rate from all studies of 3.5 per 1000, the relative risk for high intensity statins indicated an increased risk of an additional 1.5 events per 1000 (95%CI 0.03 to 3.7). Haemorrhagic stroke is not listed as an adverse effect of statins in the BNF. This risk is therefore not mentioned in the PDA.