ONLINE SUPPLEMENT

Benefits and harms of lower blood pressure treatment targets – systematic review and meta-analysis of randomized placebo-controlled trials

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eMethods - Search strategy for previous systematic review

The previous systematic review used a two-stage approach. First, we searched for systematic reviews of randomized controlled trials assessing antihypertensive treatment. All trials included in any previous systematic review were judged in full text against our eligibility criteria. We then performed an additional search for randomized controlled trials published after the latest previous search (with a few months overlap to account for time lag in indexing).

Search strategy systematic reviews
We used the phrase ("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND (mortality OR myocardial OR stroke) in all databases, adding the filter for meta-analyses in PubMed.

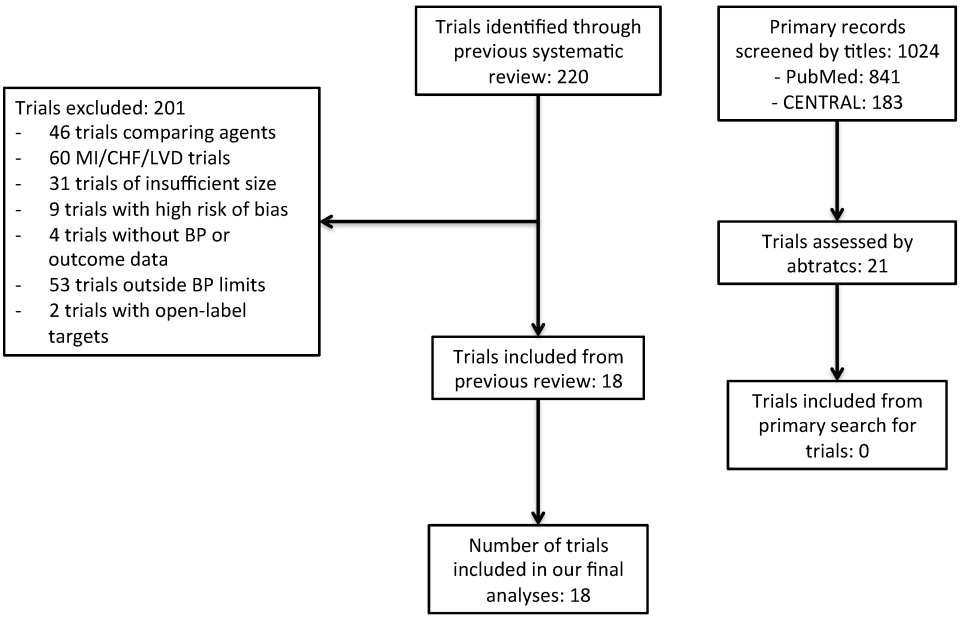
The titles of the retrieved articles were browsed to identify reviews concerning the effect of BP lowering on death, cardiovascular events and renal disease. Reviews concerning treatment of other conditions, effects of specific agents, or the effect of BP lowering on other outcomes, were discarded. All randomized controlled trials included in any of the reviews deemed relevant were retrieved in full text and judged according to the above eligibility criteria.

Search strategy for randomized controlled trials
We used the phrase ("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND (mortality OR myocardial OR stroke), adding ("2015/11/01"[Date – Publication] : "3000"[Date – Publication]) to the PubMed search and limiting the CENTRAL search to 2015-2017.

We also performed an alternative PubMed search, using the phrase (("blood pressure lowering" OR "blood-pressure lowering" OR "blood pressure-lowering" OR antihypertensive) AND ("2015/11/01"[Date - Publication] : "3000"[Date - Publication])) with RCT filter.

Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

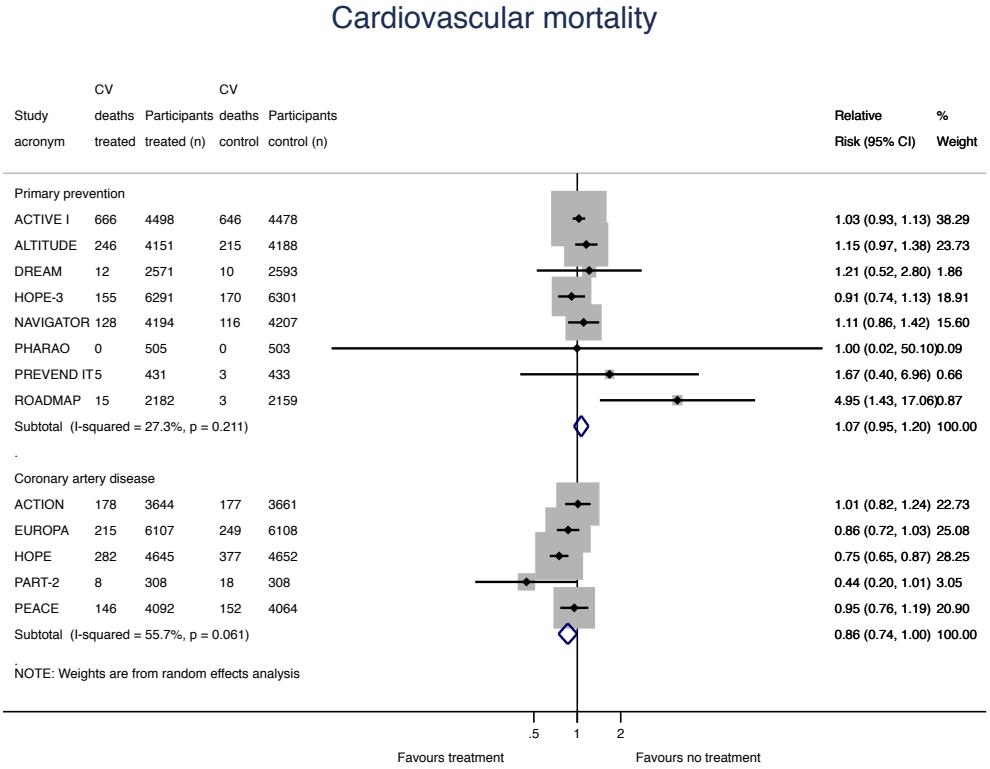
eFigure 1 - PRISMA flow chart



CENTRAL = Cochrane Central Register for Controlled Trials. MI = myocardial infarction. CHF = congestive heart failure. LVD = left ventricular dysfunction. BP = blood pressure.

Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 2 – Forest plot for cardiovascular mortality

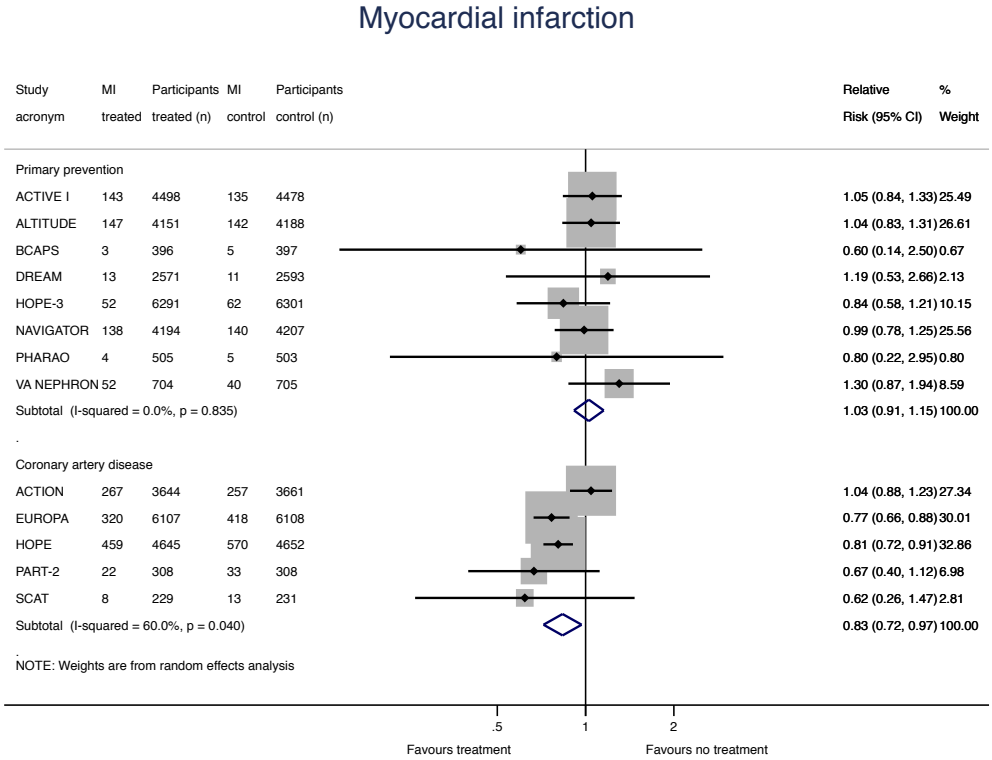


CV = cardiovascular.

Random-effects metaregression for interaction (p=0.047)

Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 3 – forest plot for myocardial infarction

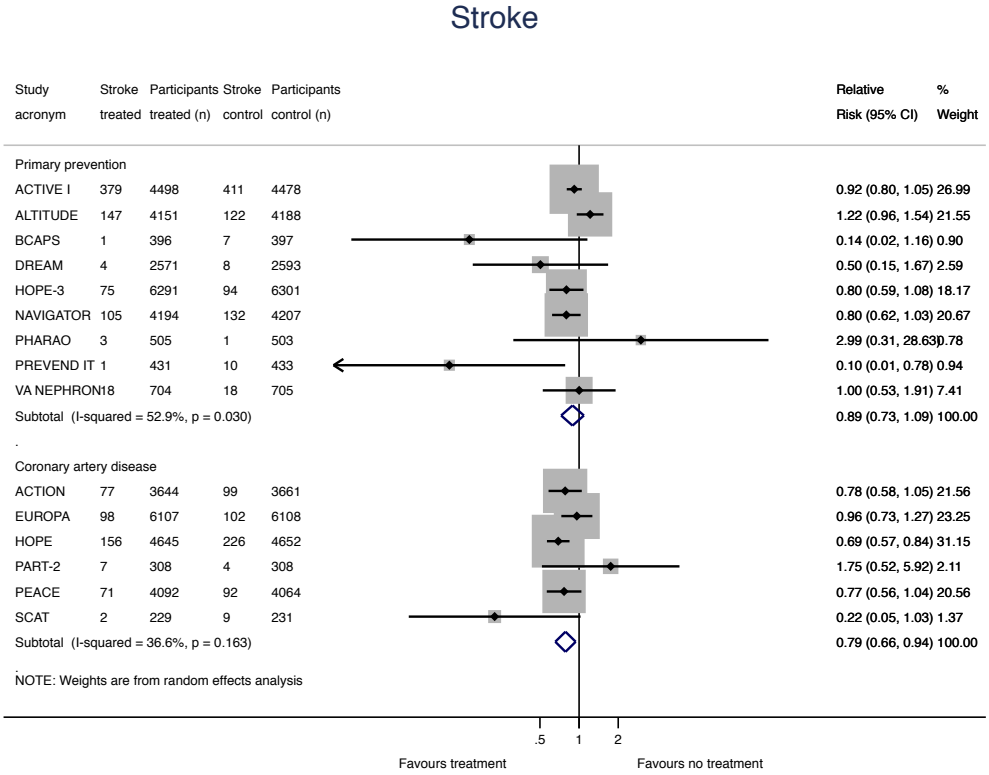


MI = myocardial infarction.

Random-effects metaregression for interaction (p=0.061)

Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

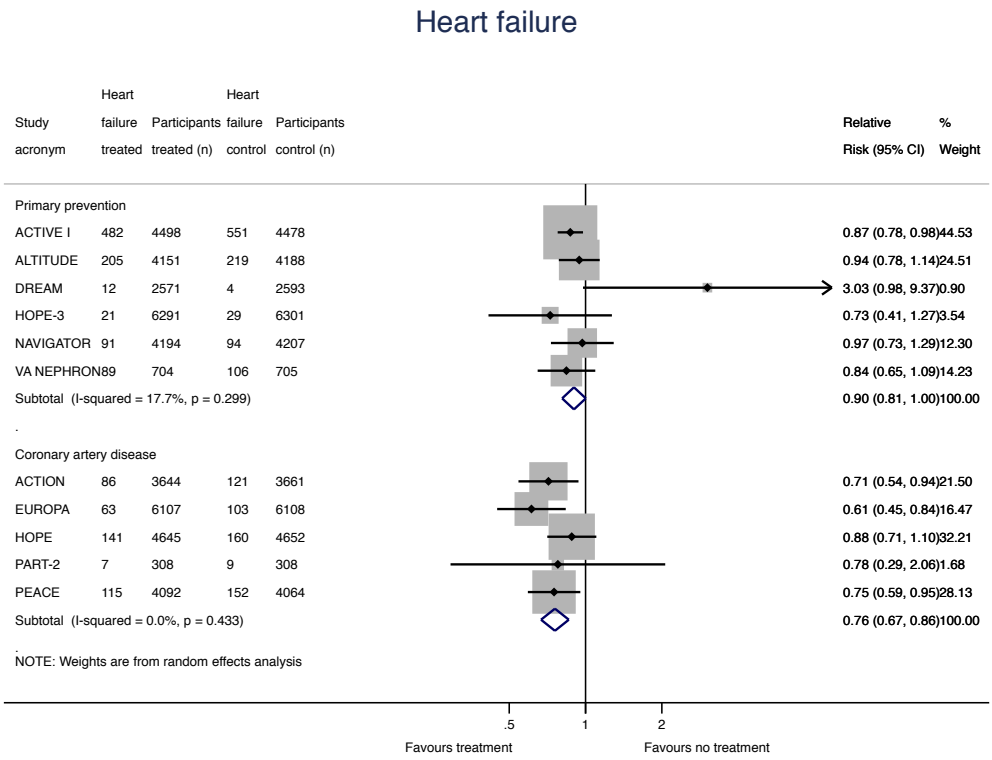
eFigure 4 – forest plot for stroke



Random-effects metaregression for interaction (p=0.329)

Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

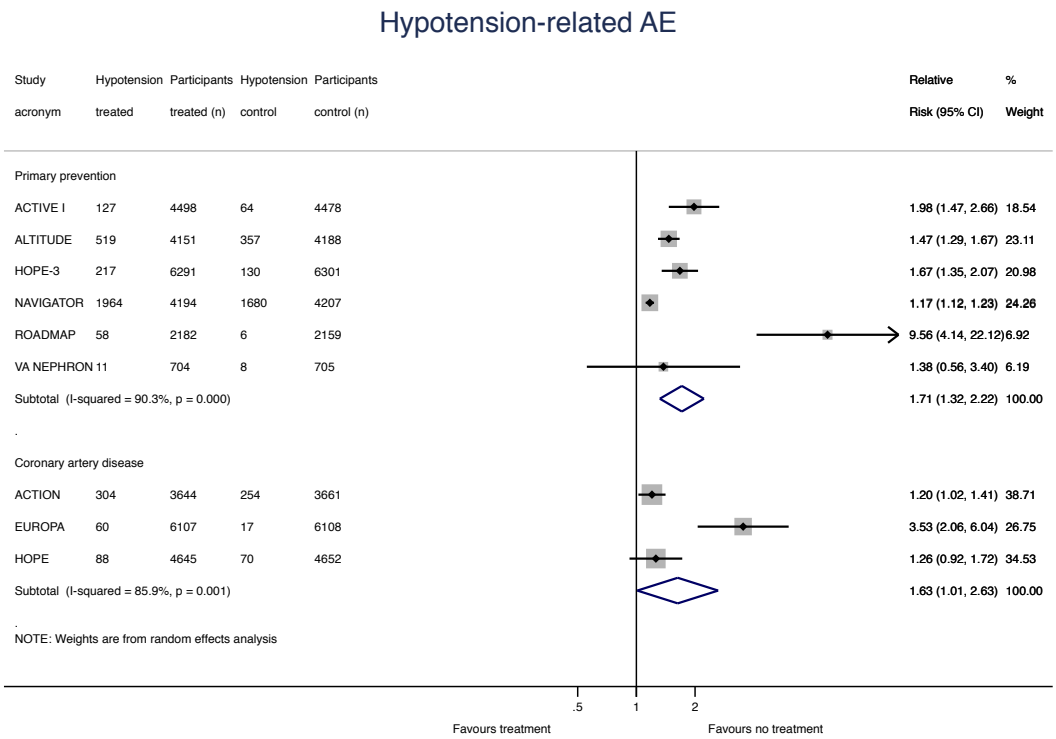
eFigure 5 – forest plot for heart failure



Random-effects metaregression for interaction (p=0.072)

Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 6 – forest plot for hypotension-related AEs

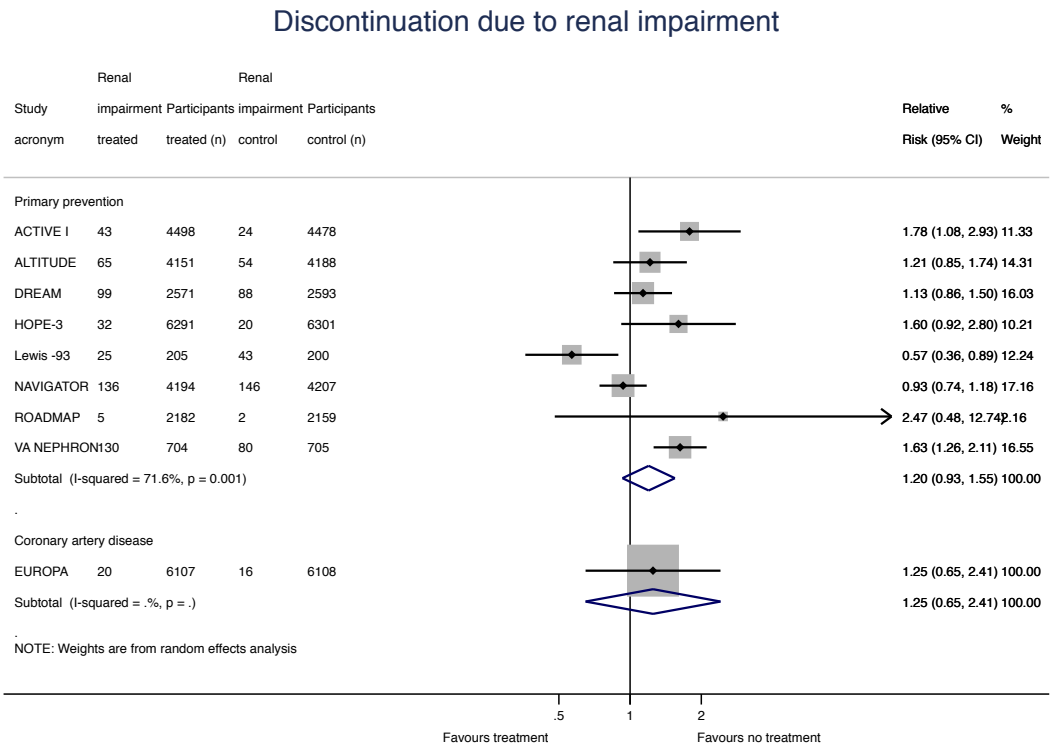


AEs = adverse events

Random-effects metaregression for interaction (p=0.798)

Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 7 – forest plot for renal impairment

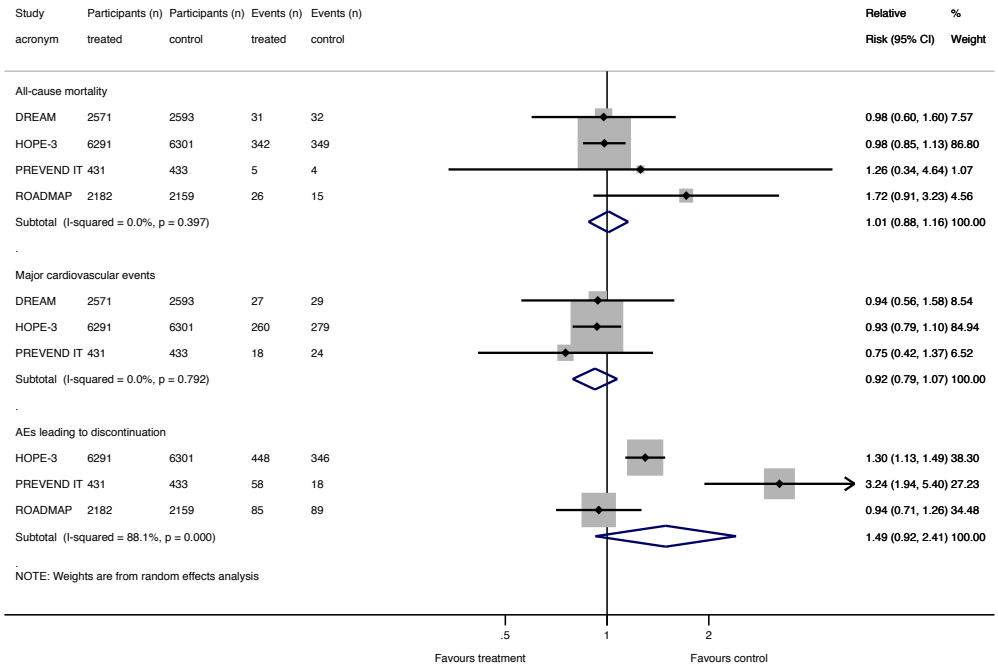


Random-effects metaregression for interaction (p=0.936)

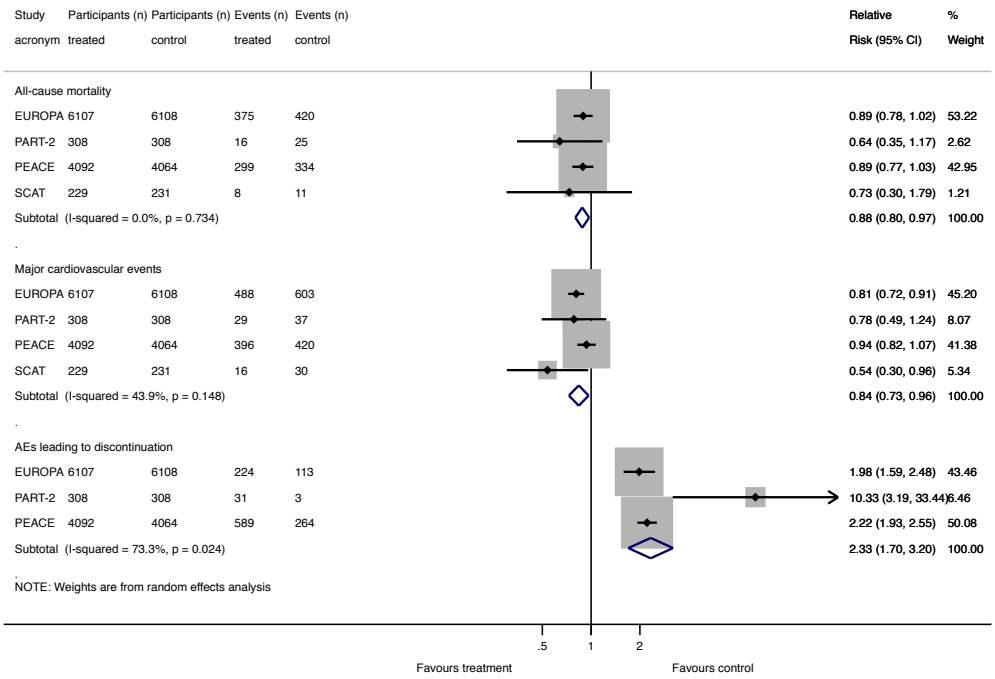
Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 8 – Sensitivity analysis excluding trials not reaching < 130 mm Hg

Primary prevention - restricted to trials reaching < 130 mm Hg

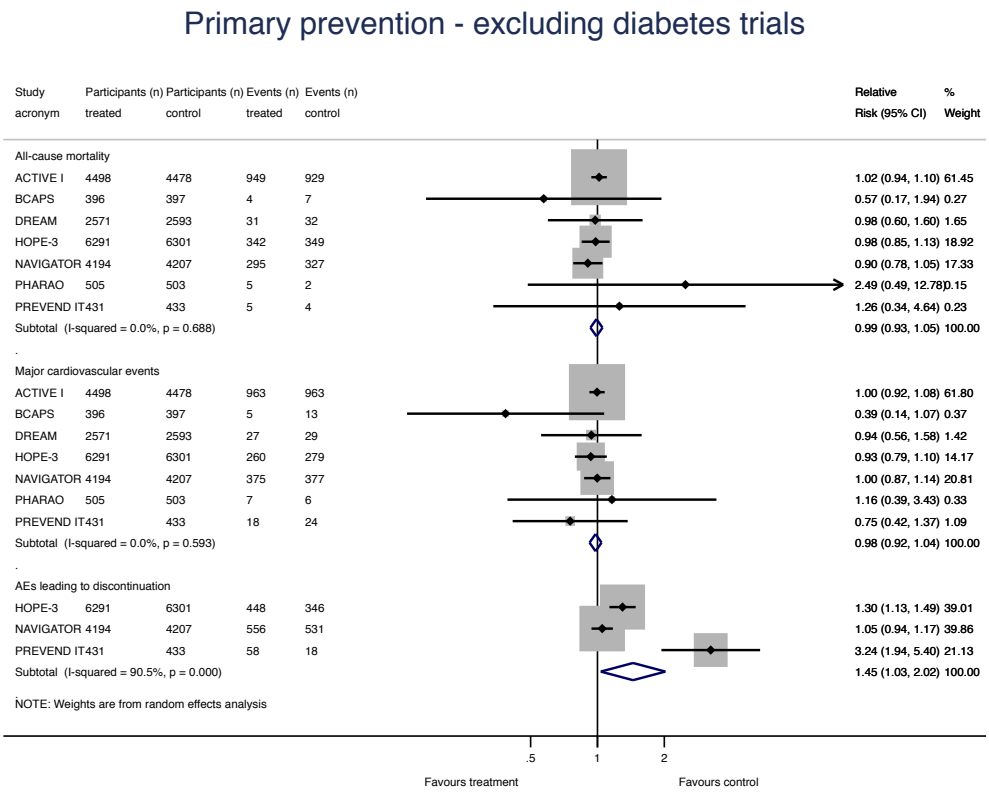


Coronary artery disease - restricted to trials reaching < 130 mm hg



Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

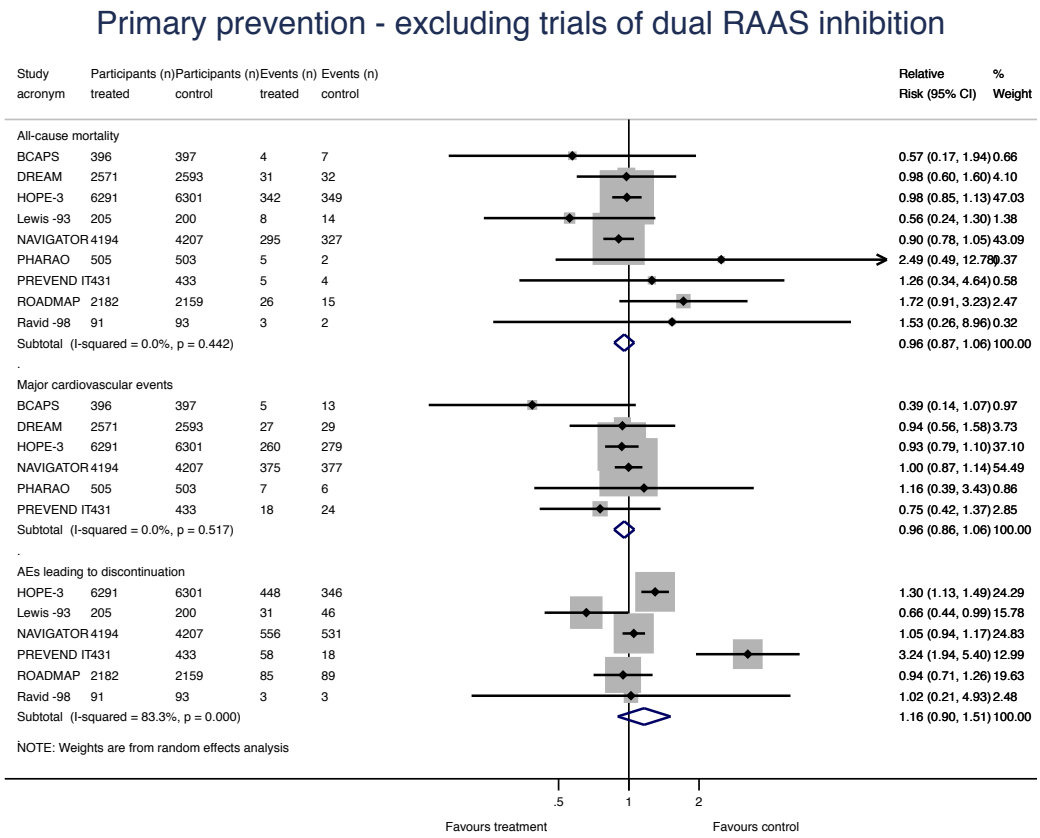
eFigure 9 – sensitivity analysis excluding trials in people with diabetes



Note: None of CAD trials were primarily in people with diabetes. Hence, no sensitivity analysis was performed.

Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 10 – sensitivity analysis excluding trials of dual RAAS-inhibition

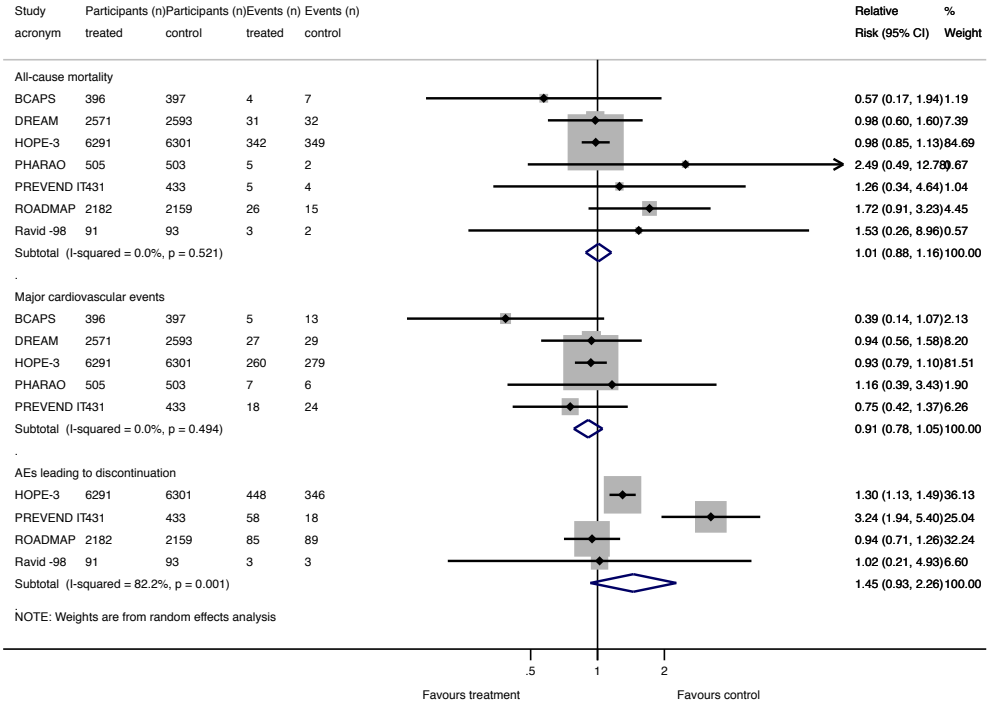


Note: None of CAD trials were testing dual RAAS inhibition. Hence, no sensitivity analysis was performed.

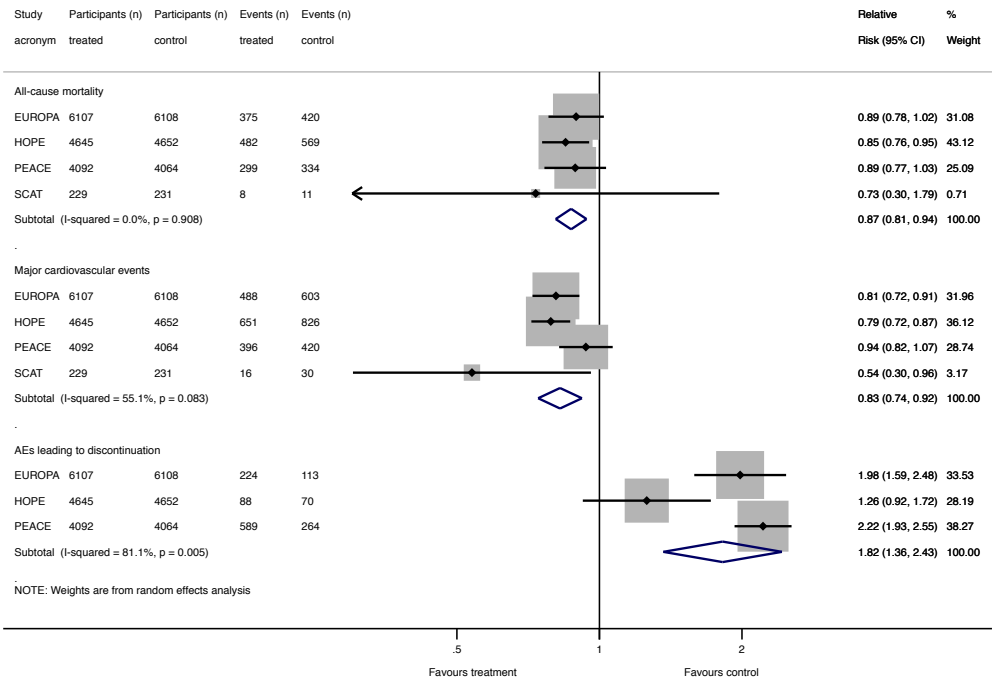
Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 11 – sensitivity analysis excluding trials in people with hypertension

Primary prevention - excluding previous hypertension



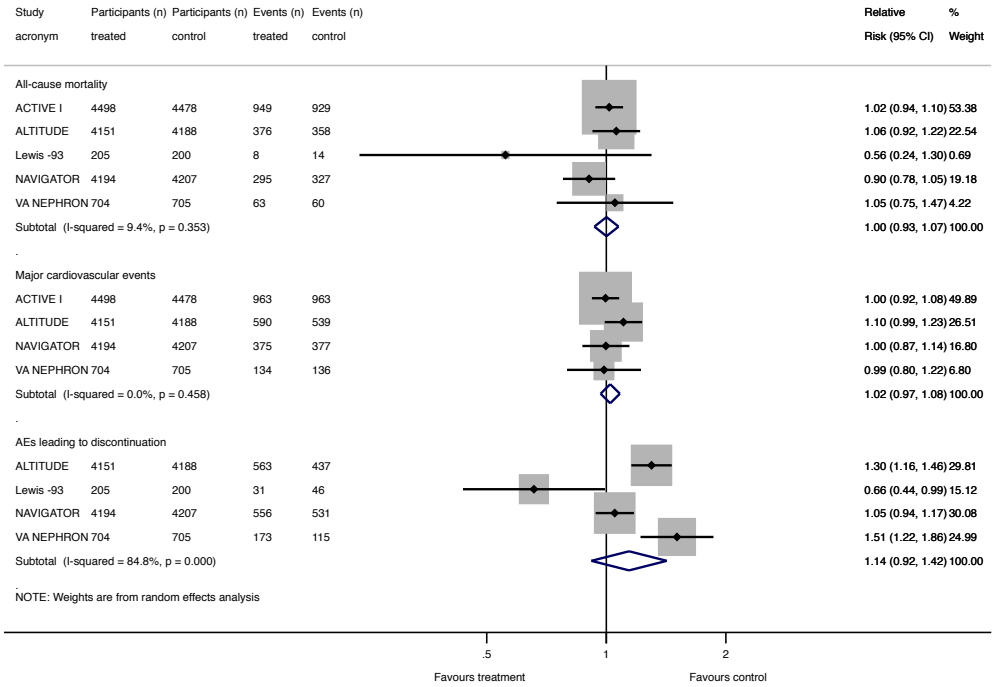
Coronary artery disease - excluding previous hypertension



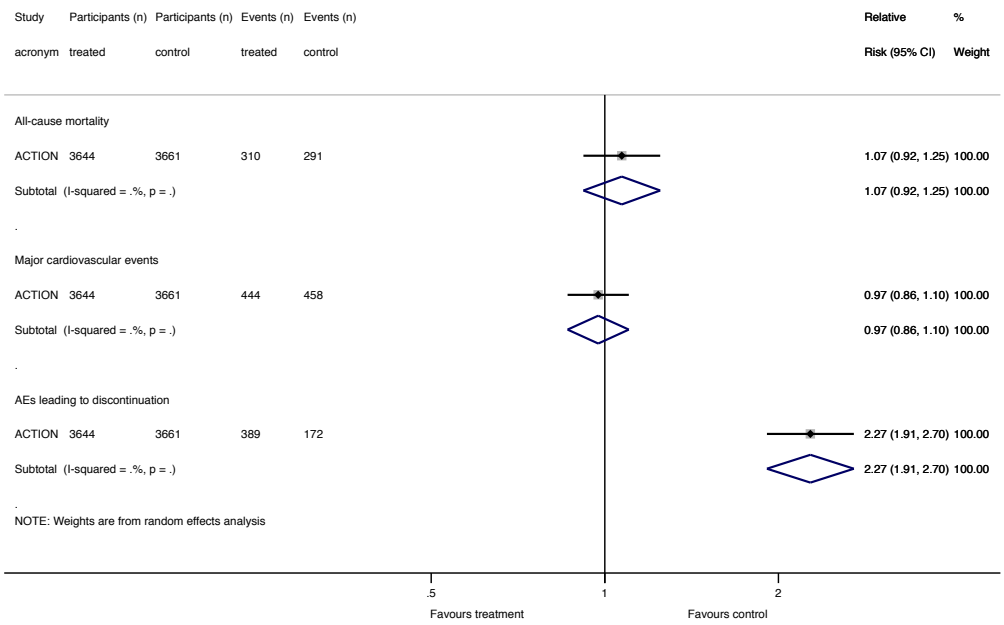
Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 12 – sensitivity analysis restricted to trials in people with hypertension

Primary prevention - restricted to previous hypertension

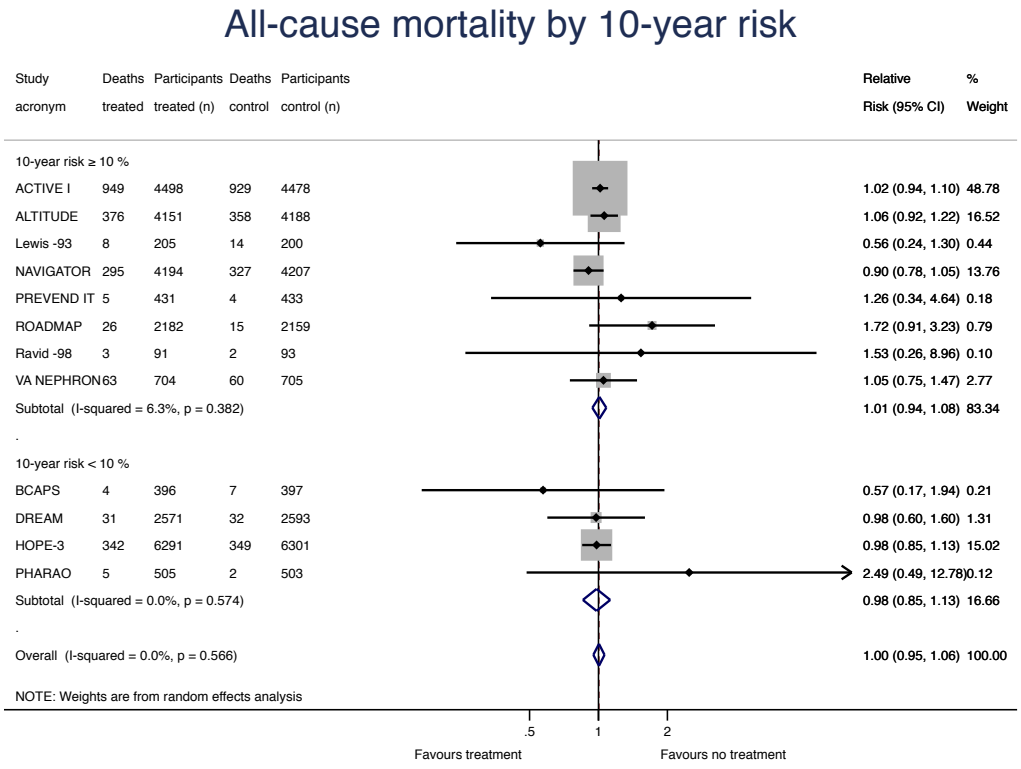


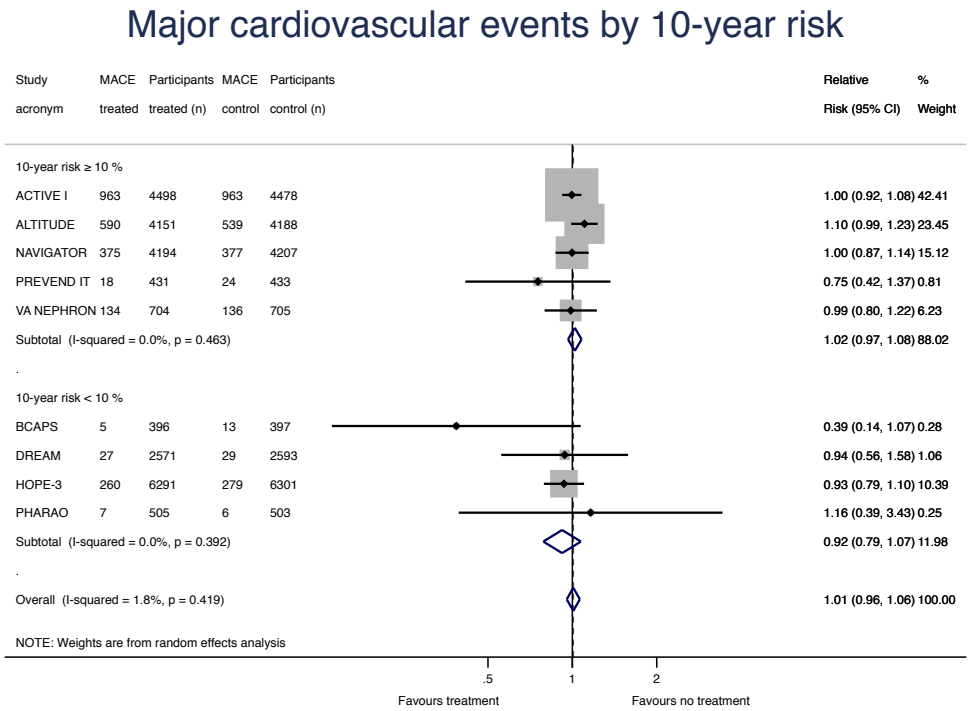
Coronary artery disease - restricted to previous hypertension



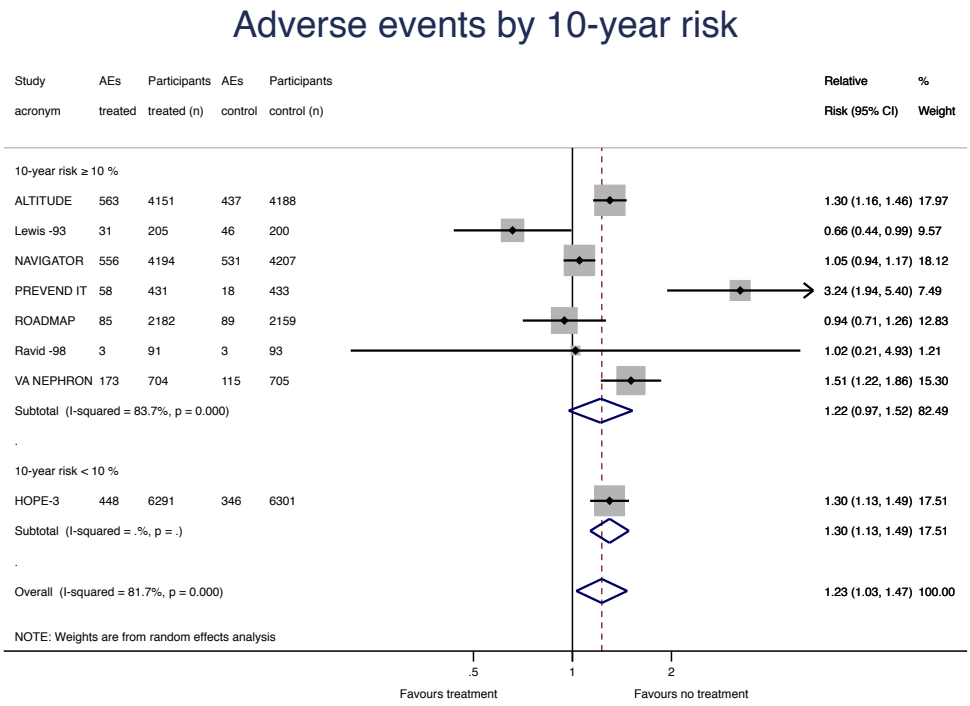
Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 13 – Primary preventive trials stratified by 10-year cardiovascular risk





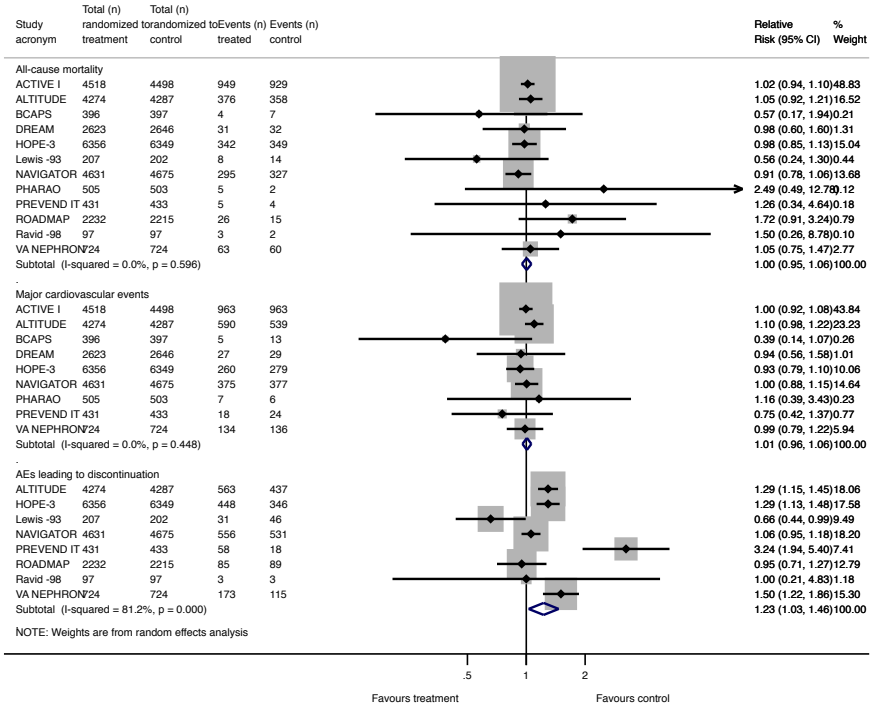
Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686



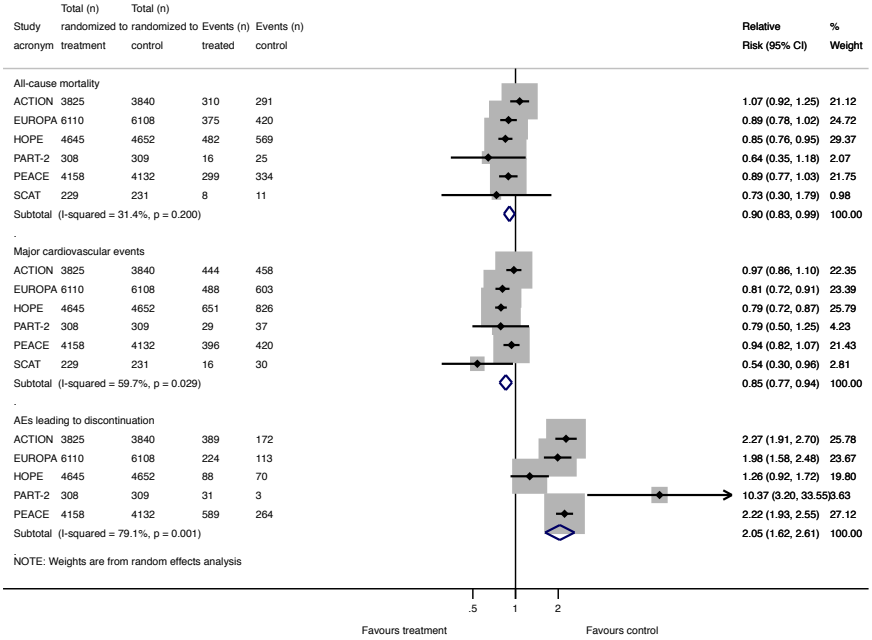
Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 14 - Lost to follow-up imputed as event-free

Primary prevention - all lost event-free



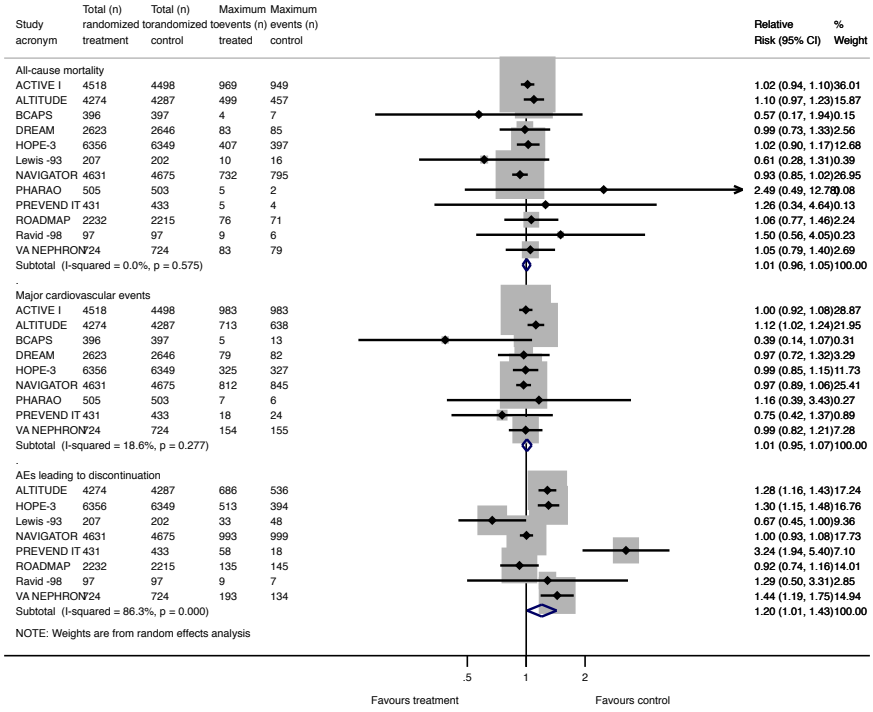
Coronary artery disease - all lost event-free



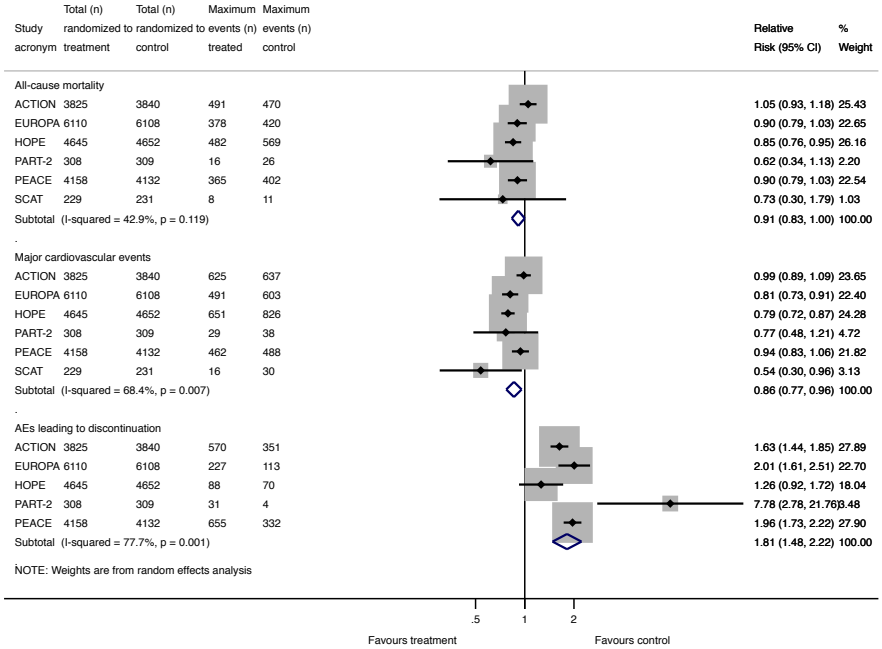
Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 15 - lost to follow-up imputed as having an event

Primary prevention - all lost with event



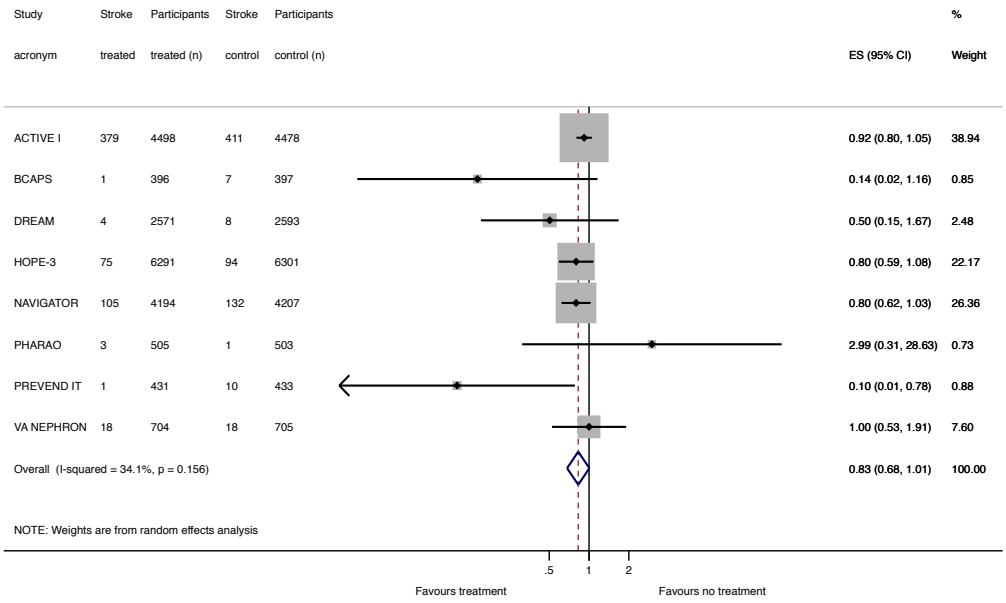
Coronary artery disease - all lost with event



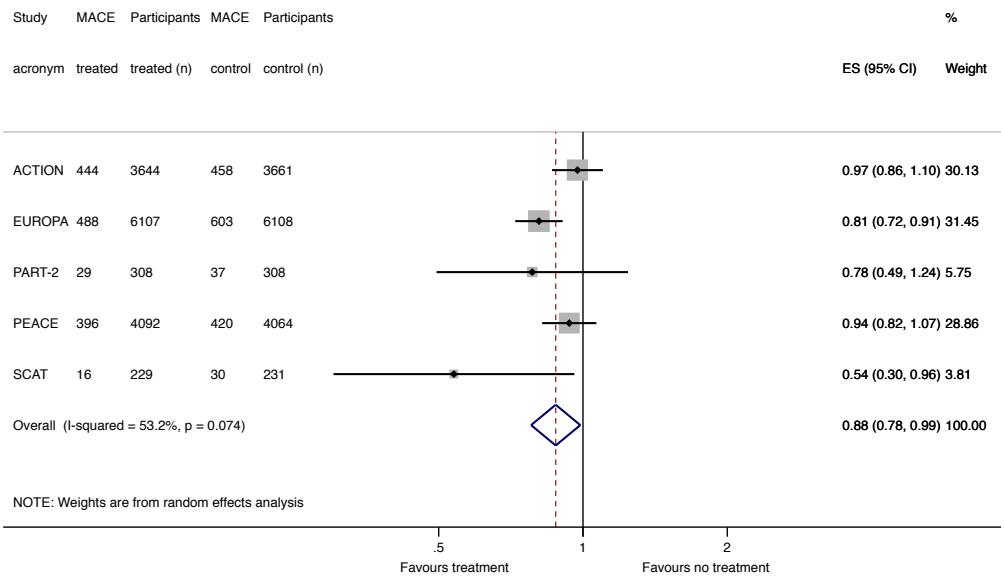
Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 16 - Ad hoc sensitivity analyses based on risk of bias assessment

Stroke - primary prevention excl. ALTITUDE

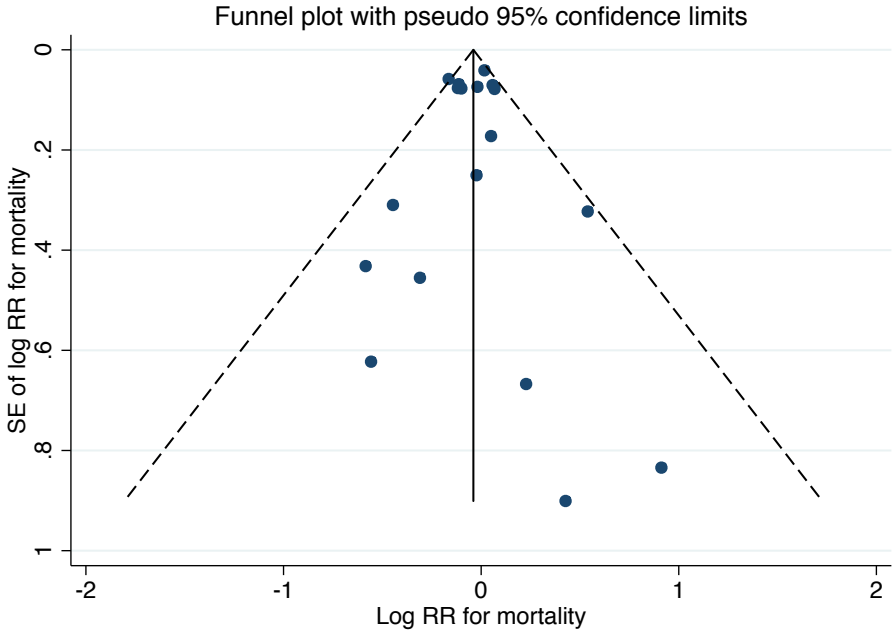


MACE - CAD trials excl. HOPE



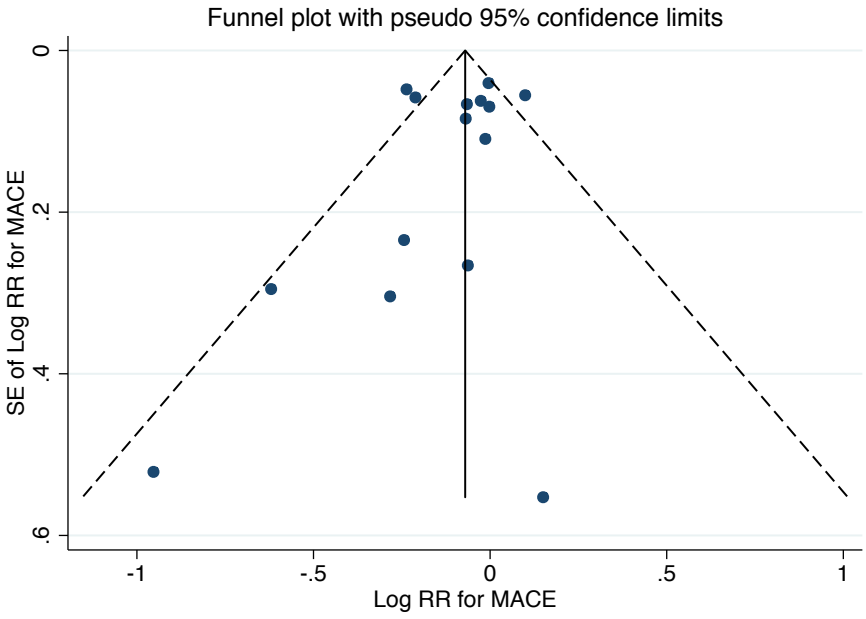
Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 17 – Funnel plot for all-cause mortality



RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.938

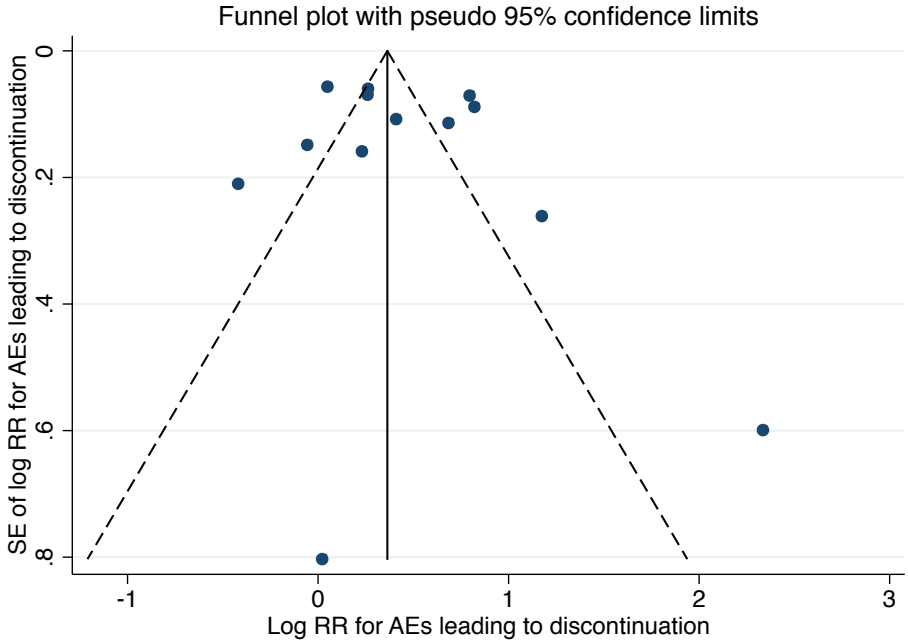
eFigure 18 – Funnel plot for major cardiovascular events



RR = relative risk. SE = standard error. MACE = major cardiovascular events.
Harbord's test for small-study effects p = 0.410

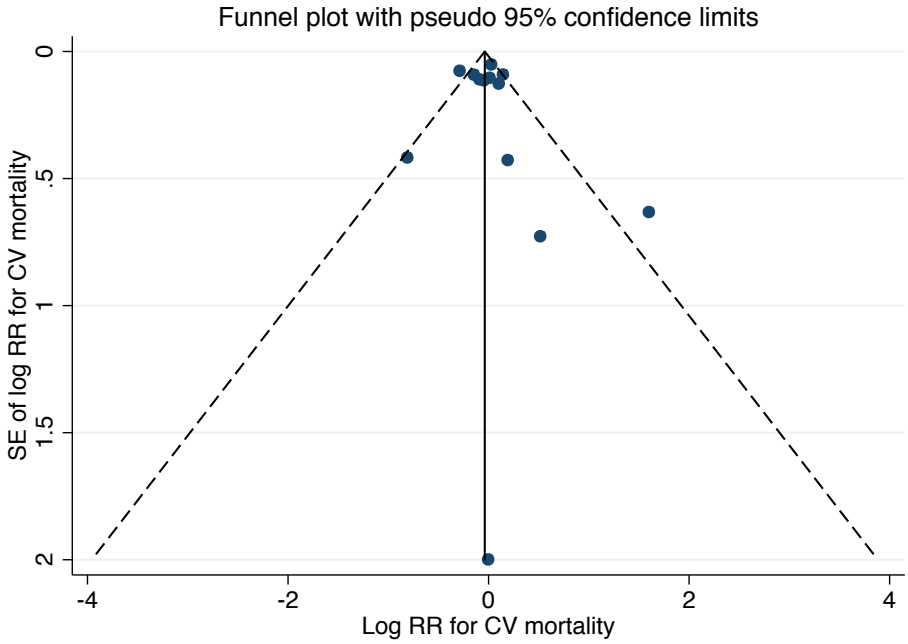
Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 19 – Funnel plot for adverse events leading to discontinuation



RR = relative risk. SE = standard error. AEs = adverse events.
Harbord's test for small-study effects p = 0.712

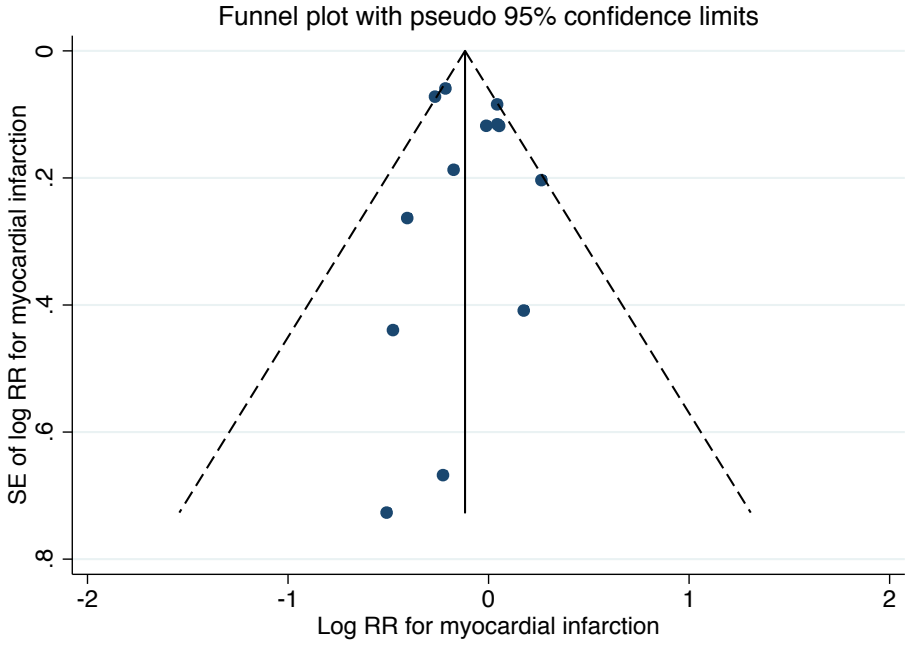
eFigure 20 – Funnel plot for cardiovascular mortality



RR = relative risk. SE = standard error. CV = cardiovascular.
Harbord's test for small-study effects p = 0.507

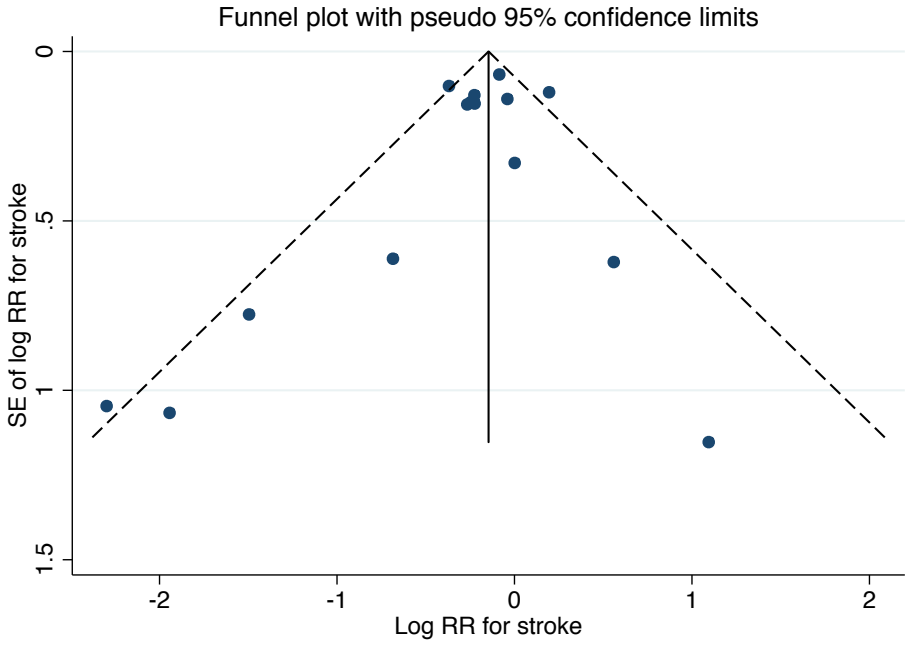
Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 21 – Funnel plot for myocardial infarction



RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.599

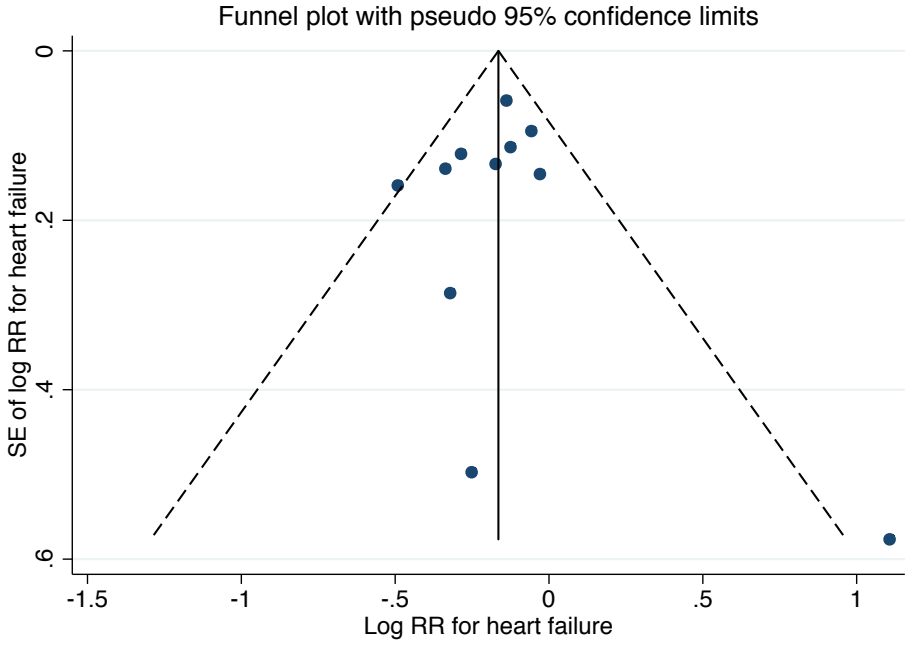
eFigure 22 – Funnel plot for stroke



RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.267

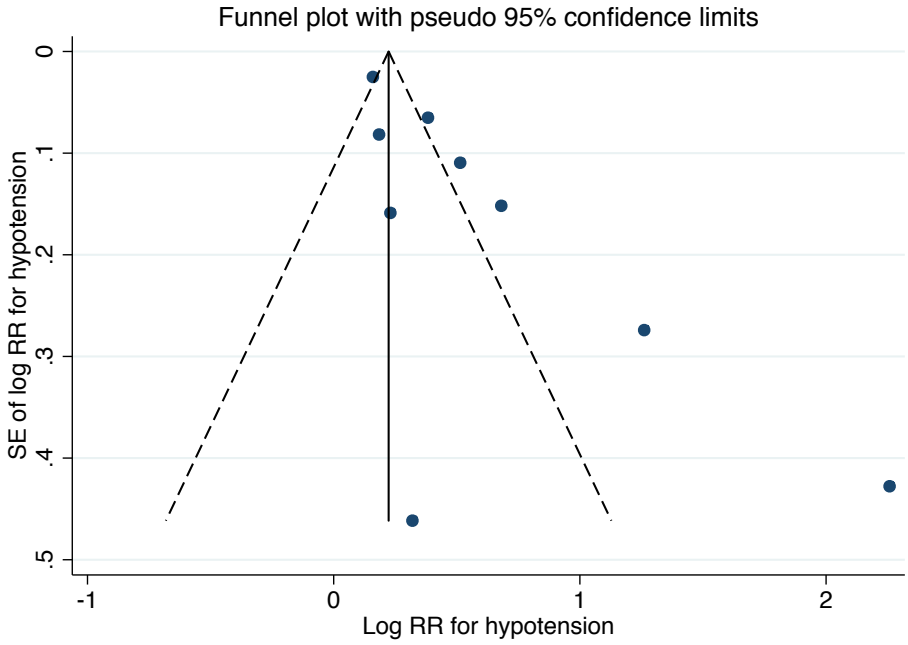
Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 23 – Funnel plot for heart failure



RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.854

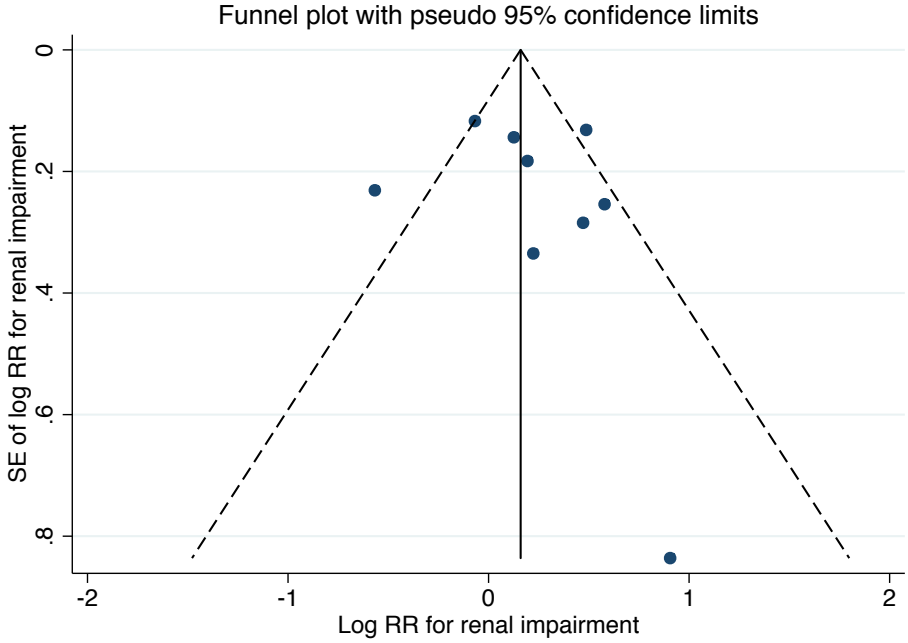
eFigure 24 – Funnel plot for hypotension-related adverse events



RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.060

Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eFigure 25 – Funnel plot for renal impairment



RR = relative risk. SE = standard error.
Harbord's test for small-study effects p = 0.655

Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eTable 1 – Studies excluded due to high risk of bias or missing data

Study ID	Reason for exclusion
DIRECT Prevent 1[1] DIRECT Protect 1[1] DIRECT Protect 2 [1,2]	Cardiovascular events were evaluated as adverse events, and therefore not blinded. Also, cardiovascular events were not followed-up in people who discontinued treatment, meaning that > 700 patients were lost to follow-up regarding these events. Based on the above, we judge the DIRECT trials to be at high risk of both detection bias and attrition bias.
EUCLID [3]	No outcome data
HDFP [4]	Patients in the intervention group and patients in the control group were treated at different clinics. We therefore judge this trial to be at high risk of performance bias.
Hunan study [5]	Original publication could not be retrieved. Data from previous meta-analyses were of uncertain quality. For example number of strokes differed by tenfold in the analyses by Ettehad et al. and Law et al. Risk of bias assessment could not be made.
INTACT [6]	No blood pressure difference between groups.
MDRD [7]	No outcome data.
NICOLE [8]	No blood pressure data.
PATS [9]	30 % of patients were lost to follow-up. This was about five times the number of events, which means this trial is at high risk of attrition bias.
STONE [10]	Randomisation likely to have failed based on large difference in number of participants in each treatment arm. We judged this trial to be at high risk of selection bias.
Suzuki -08 [11]	All patients received hemodialysis and there was no difference in blood pressure between treatment groups. Although hemodialysis was not a pre-specified exclusion criteria, it alters physiology, affecting blood pressure and drug pharmacokinetics in such a way that the results in these patients are not applicable to the general population.
Syst-China [12]	Treatment allocation was not random. Therefore this trial is at high risk of selection bias and does not fulfil the inclusion criteria of this systematic review.
USPHS [13]	> 30 % of patients dropped out, not specified how many were lost to follow-up respectively followed for outcomes. Vital status not known for 26 patients, compared to 6 deaths. This suggests high risk of attrition bias. Furthermore, treatment groups differed by 2 mm Hg in systolic blood pressure at baseline, and 60 % vs 40 % on prior antihypertensive therapy.

Note: Several of the studies presented above were outside the eligible blood pressure range. They are presented here because exclusions based of risk of bias were done before selection on blood pressure data.

Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eTable 2 - Absolute risk of MACE in primary preventive trials

Study ID	Pts (n)	MACE (n)	Follow-up (y)	10-year MACE-rate (%) *
ACTIVE I	9016	1926	4.1	52
ALTITUDE	8561	1129	2.7	49
BCAPS	793	18	3.0	7.6
DREAM	5269	56	3.0	3.5
HOPE-3	12705	539	5.6	7.6
Lewis -93	409	-	3.0	-
NAVIGATOR	9306	752	6.5	12
PHARAO	1008	13	3.0	4.3
PREVEND-IT	864	42	3.8	13
ROADMAP	4447	-	3.2	-
Ravid -98	194	-	6.0	-
VA-NEPHRON	1448	270	2.2	85

Pts = participants. MACE = major cardiovascular events.

* 10-year MACE-rate was calculated as (MACE/Pts)x(10/duration).

Brunström M, Carlberg B. *BMJ Open* 2019; 9:e026686. doi: 10.1136/bmjopen-2018-026686

eTable 3 - Risk of bias table

Study acronym	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other sources of bias
ACTION [14]	Low	Low	Low	Unclear	Low	Low	Low
ACTIVE I [15]	Low	Low	Low	Low	Low	Low	Low
ALTITUDE [16]	Low	Low	Low	Low	Unclear	Low	High
BCAPS [17]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
DREAM [18]	Low	Low	Low	Low	Unclear	Low	Low
EUROPA [19]	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
HOPE [20]	Low	Low	Low	Low	Low	Low	High
HOPE-3 [21]	Low	Low	Unclear	Low	Low	Low	Low
Lewis -93 [22]	Low	Low	Low	Low	Low	High	Low
NAVIGATOR [23]	Low	Low	Low	Low	Unclear	Low	Low
PART-2 [24]	Low	Low	Low	Unclear	Low	Low	Low
PEACE [25]	Low	Low	Low	Unclear	Low	Low	Low
PHARAO [26]	Low	Low	Unclear	Low	Low	Low	Low
PREVEND-IT [27]	Low	Low	Low	Low	Unclear	Low	Low
Ravid -98 [28]	Low	Low	Low	Low	Unclear	Low	Low
ROADMAP [29]	Low	Low	Low	Unclear	Low	Low	Low
SCAT [30]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
VA-NEPHRON [31]	Low	Low	Low	Unclear	Unclear	Low	Low

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eTable 4 - Hypotension-related adverse events

Study ID	Pts (n)	Events (n)	RR for hypotension
NAVIGATOR	8 401	3 644	1.17
ACTION	7 305	558	1.20
HOPE	9 297	158	1.26
VA NEPHRON	1 409	19	1.38
ALTITUDE	8 339	876	1.47
HOPE-3	12 592	347	1.67
ACTIVE I	8 976	191	1.98
EUROPA	12 215	77	3.53
ROADMAP	4 341	64	9.56

Note: the apparent asymmetry in the funnel plots is not primarily due to smaller studies having extreme results; rather studies with few events show larger relative risks. This should be interpreted cautiously, but might represent different thresholds for reporting adverse events in different trials, with larger relative risks for more severe events.

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eResults - Risk of bias assessment and description

Risk of bias was judged as low when we found a clear description that fulfilled the criteria for low risk of bias according to Cochrane Collaborations risk of bias assessment tool. Risk of bias was judged as unclear if we could not find an adequate description, or if the described methods did not fulfil the criteria for either low or high risk of bias. High risk of bias was assigned when we found a description of a study characteristic of methodological feature known to be associated with biased effect estimates.

All included studies were described as randomized double-blind placebo-controlled trials. Studies judged be at unclear risk of bias for the first three domains generally provided no further description of how randomization and/or blinding was achieved, yet we have no reason to believe it failed. Trials judged to be at unclear risk of bias in the forth domain generally described that outcomes were assessed by a separate committee, but did not explicitly describe this committee as blinded.

Several trials were judged to be at unclear risk of bias for incomplete outcome data. We used this label when attrition was small and asymmetric (ALTITUDE), or when loss to follow-up-rates were higher than event-rates (others). None of the included trials had large and asymmetric loss to follow-up.

Lewis -93 reported myocardial infarction, stroke, and heart failure for both groups combined, and is therefore judged to be at high risk of bias for these outcomes. This is not likely to affect overall results, however, because Lewis -93 was a small study with very few events compared to overall analyses.

We assessed early termination, changes in protocol and sponsor involvement as other potential sources of bias. In EUROPA, the definition of the primary outcome changed during follow-up. Although this might affect the interpretation of the study findings, outcomes used in our analyses where based on pre-defined criteria and not on whether they were primary or secondary in individual studies. Thus it should have little impact on our analyses.

ALTITUDE and HOPE were stopped pre-term due to interim findings. ALTITUDE was stopped due to an increased risk of stroke in the intervention group, whereas HOPE was stopped due to decreased risk of major cardiovascular events in the intervention group. To test the impact of these trials on overall results, we performed ad-hoc sensitivity analyses where they were excluded. Exclusion of ALTITUDE from the primary preventive stroke analysis moved the estimate slightly more towards benefit (relative risk 0.83, 95 % confidence interval 0.68-1.01, compared to 0.89, 0.73-1.09 when ALTITUDE was included). Exclusion of HOPE from the MACE analysis for CAD trials moved the estimate slightly towards neutrality (0.88, 0.78-0.99, compared to 0.85, 0.77-0.94 when HOPE was included).

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