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Ranolazine for stable angina pectoris (Review)

Salazar CA, Basilio Flores JE, Veramendi Espinoza LE, Mejia Dolores JW, Rey Rodriguez DE, Loza Munárriz C

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[Intervention Review]

Ranolazine for stable angina pectoris

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ABSTRACT

Background

Stable angina pectoris is a chronic medical condition with significant impact on mortality and quality of life; it can be macrovascular or microvascular in origin. Ranolazine is a second-line anti-anginal drug approved for use in people with stable angina. However, the effects of ranolazine for people with angina are considered to be modest, with uncertain clinical relevance.

Objectives

To assess the effects of ranolazine on cardiovascular and non-cardiovascular mortality, all-cause mortality, quality of life, acute myocardial infarction incidence, angina episodes frequency and adverse events incidence in stable angina patients, used either as monotherapy or as add-on therapy, and compared to placebo or any other anti-anginal agent.

Search methods

We searched CENTRAL, MEDLINE, Embase and the Conference Proceedings Citation Index - Science in February 2016, as well as regional databases and trials registers. We also screened reference lists.

Selection criteria

Randomised controlled trials (RCTs) which directly compared the effects of ranolazine versus placebo or other anti-anginals in people with stable angina pectoris were eligible for inclusion.

Data collection and analysis

Two authors independently selected studies, extracted data and assessed risk of bias. Estimates of treatment effects were calculated using risk ratios (RR), mean differences (MD) and standardised mean differences (SMD) with 95% confidence intervals (CI) using a fixed-effect model. Where we found statistically significant heterogeneity (Chi^2 $P < 0.10$), we used a random-effects model for pooling estimates. Meta-analysis was not performed where we found considerable heterogeneity ($I^2 \geq 75\%$). We used GRADE criteria to assess evidence quality and the GRADE profiler (GRADEpro GDT) to import data from Review Manager 5.3 to create 'Summary of findings' tables.

Main results

We included 17 RCTs (9975 participants, mean age 63.3 years). We found very limited (or no) data to inform most planned comparisons. Summary data were used to inform comparison of ranolazine versus placebo. Overall, risk of bias was assessed as unclear.

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For add-on ranolazine compared to placebo, no data were available to estimate cardiovascular and non-cardiovascular mortality. We found uncertainty about the effect of ranolazine on: all-cause mortality (1000 mg twice daily, RR 0.83, 95% CI 0.26 to 2.71; 3 studies, 2053 participants; low quality evidence); quality of life (any dose, SMD 0.25, 95% CI -0.01 to 0.52; 4 studies, 1563 participants; I^2 = 73%; moderate quality evidence); and incidence of non-fatal acute myocardial infarction (AMI) (1000mg twice daily, RR 0.40, 95% CI 0.08 to 2.07; 2 studies, 1509 participants; low quality evidence). Add-on ranolazine 1000 mg twice daily reduced the fervour of angina episodes (MD -0.66, 95% CI -0.97 to -0.35; 3 studies, 2004 participants; I^2 = 39%; moderate quality evidence) but increased the risk of non-serious adverse events (RR 1.22, 95% CI 1.06 to 1.40; 3 studies, 2053 participants; moderate quality evidence).

For ranolazine as monotherapy compared to placebo, we found uncertain effect on cardiovascular mortality (1000 mg twice daily, RR 1.03, 95% CI 0.56 to 1.88; 1 study, 2604 participants; low quality evidence). No data were available to estimate non-cardiovascular mortality. We also found an uncertain effect on all-cause mortality for ranolazine (1000 mg twice daily, RR 1.00, 95% CI 0.81 to 1.25; 3 studies, 6249 participants; low quality evidence), quality of life (1000 mg twice daily, MD 0.28, 95% CI -1.57 to 2.13; 3 studies, 2254 participants; moderate quality evidence), non-fatal AMI incidence (any dose, RR 0.88, 95% CI 0.69 to 1.12; 3 studies, 2983 participants; I^2 = 50%; low quality evidence), and frequency of angina episodes (any dose, MD 0.08, 95% CI -0.85 to 1.01; 2 studies, 402 participants; low quality evidence). We found an increased risk for non-serious adverse events associated with ranolazine (any dose, RR 1.50, 95% CI 1.12 to 2.00; 3 studies, 947 participants; very low quality evidence).

Authors' conclusions

We found very low quality evidence showing that people with stable angina who received ranolazine as monotherapy had increased risk of presenting non-serious adverse events compared to those given placebo. We found low quality evidence indicating that people with stable angina who received ranolazine showed uncertain effect on the risk of cardiovascular death (for ranolazine given as monotherapy), all-cause death and non-fatal AMI, and the frequency of angina episodes (for ranolazine given as monotherapy) compared to those given placebo. Moderate quality evidence indicated that people with stable angina who received ranolazine showed uncertain effect on quality of life compared with people who received placebo. Moderate quality evidence also indicated that people with stable angina who received ranolazine as add-on therapy had fewer angina episodes but increased risk of presenting non-serious adverse events compared to those given placebo.

PLAIN LANGUAGE SUMMARY

Ranolazine for people with stable angina pectoris

Review question

We wanted to find out if ranolazine (a drug to prevent angina) was more effective than a fake drug (placebo) or other drugs to treat stable angina.

Background

Angina pectoris is sudden chest pain caused when the heart does not get enough oxygen or from other stresses. People with stable angina have a predictable pattern of when they experience angina symptoms. Angina is made worse by physical effort and relieved by rest or some medications. Ranolazine is a relatively new drug for people with angina pectoris who are already taking other drugs to treat angina.

Search date

The evidence is current to February 2016.

Study funding sources

Most studies were either fully (9/17) or partly (3/17) funded by drug companies, two received no external funding, and three did not declare sources of funding.

Study characteristics

We included 17 studies that involved a total of 9975 adult participants and lasted between 1 and 92 weeks.

Key results

We only compared ranolazine and placebo because there were few data for other comparisons. The evidence was uncertain about the effect of ranolazine 1000 mg given alone twice daily to people with stable angina pectoris on the chance of dying from heart-related causes. There was no evidence about whether ranolazine changed the risk of dying from causes that were not heart-related.

Although the evidence was uncertain about the effect of ranolazine 1000 mg twice daily on the chance of dying from any cause, quality of life, the possibility of heart attack or the frequency of angina attacks (for ranolazine taken alone), ranolazine did modestly reduce the numbers of angina attacks per week when given with other anti-angina drugs. Ranolazine 1000 mg twice daily increased the risk for experiencing dizziness, nausea and constipation from taking the drug (mild adverse events).

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Quality of evidence

Overall, evidence quality was assessed as very low for the chance of mild adverse events (for people who took ranolazine alone). Evidence was also low for estimating the chance of death from heart-related (when ranolazine is taken alone) or any causes, having a heart attack, and how often angina attacks occur (when ranolazine is taken alone). We found moderate quality evidence about quality of life, frequency of angina attacks and the chance of experiencing mild adverse events (for people who took ranolazine together with other anti-angina drugs),

Low evidence quality related to problems and reporting of study methods and too few data to calculate precise estimates.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Ranolazine (add-on therapy) versus placebo for stable angina pectoris

Ranolazine (add-on therapy) versus placebo for stable angina pectoris*

Patient or population: patients with stable angina pectoris
Settings: not specified
Intervention: ranolazine (add-on therapy)
Comparison: placebo (add-on therapy)

Outcomes	Illustrative comparative risks** (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Ranolazine				
Cardiovascular mortality - not reported	See comment	See comment	Not estimable	-	See comment	No data were available for this outcome
Non-cardiovascular mortality - not reported	See comment	See comment	Not estimable	-	See comment	No data were available for this outcome
All-cause mortality Follow-up: 42 to 84 days	**6 per 1000**	**5 per 1000** (2 to 16)	**RR 0.83** (0.26 to 2.71)	2053 (3 studies)	⊕⊕⊝⊝ **low**[1 2]	Ranolazine 1000 mg twice daily
Quality of life Scale: 0 to 100. Follow-up: 28 to 56 days	Mean quality of life in control group participants was **44.3 points**	Mean quality of life in intervention group participants was **0.25 standard deviations higher** (0.01 lower to 0.52 higher)		1563 (4 studies)	⊕⊕⊕⊝ **moderate**[3]	Ranolazine any dose (SMD 0.25, 95% CI -0.01 to 0.52)
AMI incidence Follow-up: 42 to 56 days	**7 per 1000**	**3 per 1000** (1 to 14)	**RR 0.40** (0.08 to 2.07)	1509 (2 studies)	⊕⊕⊝⊝ **low**[4]	Ranolazine 1000 mg twice daily
Angina episodes frequency Follow-up: 42 to 84 days	Mean angina episode frequency in control group participants was **4.1 episodes per week**	Mean angina episodes frequency in intervention group participants was **0.66 lower** (0.97 to 0.35 lower)		2004 (3 studies)	⊕⊕⊕⊝ **moderate**[1]	Ranolazine 1000 mg twice daily (MD -0.66, 95% CI -0.97 to -0.35)
Adverse events incidence Follow-up: 42 to 84 days	**241 per 1000**	**294 per 1000** (256 to 337)	**RR 1.22** (1.06 to 1.4)	2123 (3 studies)	⊕⊕⊕⊝ **moderate**[5]	Ranolazine 1000 mg twice daily

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*Add-on therapy: refers to the addition of ranolazine to an antianginal regimen already in course. The results reported correspond to the comparisons (data and analyses) 3 and 4 of the review (involving ranolazine given at 1000mg twice daily or any dosage); this is specified in the Comments column.

The **assumed risk is based on the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Quality of evidence was downgraded one level due to unclear risk of bias regarding blinding of outcome assessment and incomplete outcome data
[2] Quality of evidence was downgraded one level due to insufficient number of events (less than 300), and the 95% confidence interval around the pooled effect includes both 1) no effect and 2) appreciable benefit/harm
[3] Quality of evidence was downgraded one level due to substantial heterogeneity
[4] Quality of evidence was downgraded two levels due to insufficient number of events (less than 300), and the 95% confidence interval around the pooled effect includes both 1) no effect and 2) appreciable benefit/harm
[5] Quality of evidence was downgraded one level due to unclear risk of bias regarding blinding of outcome assessment and selective reporting

Summary of findings 2. Ranolazine (monotherapy) versus placebo for stable angina pectoris

Ranolazine (monotherapy) versus placebo for stable angina pectoris*

Patient or population: patients with stable angina pectoris
Settings: not specified
Intervention: ranolazine (monotherapy)
Comparison: placebo (monotherapy)

Outcomes	Illustrative comparative risks** (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Ranolazine				
Cardiovascular mortality Follow-up: mean 643 days	**16 per 1000**	**16 per 1000** (9 to 29)	**RR 1.03** (0.56 to 1.88)	2604 (1 study)	⊕⊕⊝⊝ **low**[1 2]	Ranolazine 1000 mg twice daily
Non-cardiovascular mortality - not reported	See comment	See comment	Not estimable	-	See comment	No data were available for this outcome

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All-cause mortality Follow-up: 37 to 643 days	**49 per 1000**	**49 per 1000** (39 to 61)	**RR 1.00** (0.81 to 1.25)	6249 (3 studies)	⊕⊕⊝⊝ **low**[2 3]	Ranolazine 1000 mg twice daily
Quality of life Scale: 0 to 100 Follow-up: 14 to 643 days	Mean quality of life in control group participants was **68.6 points**	Mean quality of life in intervention group participants was **0.28 higher** (1.57 lower to 2.13 higher)		2256 (3 studies)	⊕⊕⊕⊝ **moderate**[4]	Ranolazine 1000 mg twice daily (MD 0.28. 95% CI -1.57 to 2.13)
AMI incidence Follow-up: 7 to 643 days	**85 per 1000**	**75 per 1000** (59 to 96)	**RR 0.88** (0.69 to 1.12)	2983 (3 studies)	⊕⊕⊝⊝ **low**	Ranolazine any dose
Angina episodes frequency Follow-up: 14 to 28 days	Mean angina episode frequency in control group participants was **2.08 episodes per week**	Mean angina episode frequency in intervention group participants was **0.08 higher** (0.85 lower to 1.01 higher)		402 (2 studies)	⊕⊕⊝⊝ **low**[3 5]	Ranolazine any dose (MD 0.08, 95% CI -0.85 to 1.01)
Adverse events incidence Follow-up: 7 to 14 days	**131 per 1000**	**197 per 1000** (147 to 262)	**RR 1.50** (1.12 to 2)	947 (3 studies)	⊕⊝⊝⊝ **very low**[3 5 6]	Ranolazine any dose

*Monotherapy: refers to the administration of ranolazine as the only antianginal drug. The results reported correspond to the comparisons (data and analyses) 1 and 2 of the review (involving ranolazine given at 1000mg twice daily or any dosage); this is specified in the Comments column.

The **assumed risk is based on the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Quality of evidence was downgraded one level due to unclear risk of bias regarding allocation concealment and high risk of bias regarding selective reporting
[2] Quality of evidence was downgraded one level due to insufficient numbers of events (< 300), and the 95% CI around the pooled effect includes both 1) no effect and 2) appreciable benefit/harm
[3] Quality of evidence was downgraded one level because a group of participants (not quantified) in one or more included studies received ranolazine in addition to usual anti-anginals (i.e. not as monotherapy)
[4] Quality of evidence was downgraded one level because the 95% CI around the pooled effect included both 1) no effect and 2) appreciable benefit/harm
[5] Quality of evidence was downgraded one level due to unclear risk of bias for most criteria
[6] Quality of evidence was downgraded one level due to insufficient numbers of events (< 300)

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BACKGROUND

Description of the condition

Stable angina pectoris is a chronic medical condition which is generally regarded as the main symptomatic manifestation of coronary artery disease (CAD) (NICE 2011). It has been estimated that stable angina affects 58% of people with CAD (Ohman 2016), with an annual mortality rate ranging between 1.2% and 2.4% (ESC 2013). Apart from its associated risk of cardiovascular death and recurrent myocardial infarction, stable angina pectoris has a significant impact on functional capacity and quality of life (Scirica 2009). Mortality is higher among people with angina than those with no history of CAD at baseline (O'Toole 2008). Factors associated with a poorer prognosis include more severe symptoms, male sex, abnormal resting electrocardiogram (ECG) and previous myocardial infarction (O'Toole 2008).

A universal definition for stable angina has not been agreed internationally, but it is usually recognised clinically by its character, location and relationship to provocative stimuli (NICE 2010). Angina pain is identified by: constricting discomfort in the chest or neck, shoulders, jaw or arms; precipitated by physical exertion; and relieved by rest or nitrates within about 5 to 10 minutes. Typical angina is defined by the presence of all of these features (NICE 2010). The underlying cause is of angina pectoris is usually macrovascular CAD, but may be microvascular in some people (ESC 2013). Importantly, other (non CAD) cardiac conditions may be responsible for typical anginal pain, including aortic valve disease and hypertrophic cardiomyopathy (NICE 2010). Macrovascular CAD refers to dysfunction of the coronary arteries and their main branches, as opposed to microvascular CAD in which dysfunction involves the small coronary arterioles (< 500 µm) (Jones 2012).

Diagnosis of stable angina due to CAD can be established based solely on clinical assessment or with the aid of additional diagnostic testing (NICE 2010). Basic tests usually involve biochemical tests, resting ECG, echocardiography, etc. Non-invasive diagnostic tests include exercise ECG, stress imaging testing and coronary computed-tomography angiography (CTA). The only invasive test is invasive coronary angiography (ESC 2013). The choice of diagnostic test (functional or structural, invasive or non-invasive) is guided by the estimated likelihood of CAD (from clinical assessment) and consideration of coronary revascularisation (NICE 2010). Although current NICE guidelines do not recommend exercise ECG to evaluate people with suspected stable angina, it remains a useful option because of its simplicity and widespread availability (ESC 2013). Furthermore, according to American (ACC/AHA 2012) and European (SIGN 2007; ESC 2013) guidelines, exercise ECG is recommended as an option to impose stress during imaging for people with intermediate pre-test probability of CAD. Some people with stable angina have microvascular coronary disorders, which can be detected on normal coronary angiography only (Di Fiore 2013). Since evaluation of a person with stable angina does not always include coronary angiography (either invasive or non-invasive), people with microvascular coronary dysfunction would remain unidentified using this approach.

Description of the intervention

Management options for people with stable angina include lifestyle modifications, pharmacological therapy, and revascularisation interventions. Treatment is aimed at improving prognosis (by preventing myocardial infarction and death) and minimising or abolishing symptoms. All management options have potential to meet both treatment aims (ESC 2013). However, the main aim of anti-anginal drug treatment is to prevent episodes of angina; the secondary aim is to prevent cardiovascular events such as heart attack and stroke (NICE 2011). Anti-anginal drugs are classified as first-line (adrenergic beta antagonists, calcium channel blockers) or second-line (long-acting nitrates, ivabradine, nicorandil, ranolazine, trimetazidine) (Tarkin 2012). Anti-angina treatment is recommended to begin using one of the first-line drugs as monotherapy. If symptoms are not controlled satisfactorily, a combination of two first-line drugs is recommended. Second-line drugs are recommended as add-on therapy when a combination of two first-line drugs cannot be accomplished, or as monotherapy when none of the first-line drugs can be used (ESC 2013; NICE 2011). Adding a third anti-angina drug can be considered only when revascularisation is not an option or as a temporary measure while the patient awaits revascularisation (NICE 2011). However, since ranolazine is the only second-line drug approved by the US Food and Drug Administration (FDA) (Hawwa 2013), American guidelines (ACC/AHA 2012) recommend use of ranolazine in a similar way to second-line drugs in European guidelines (ESC 2013).

Ranolazine was approved by the US FDA in 2007 for use in a maximum dose (extended release) of 1000 mg twice daily (FDA 2016), and by the European Medicines Agency (EMA) in 2008 for use in a maximum dose (prolonged release) of 750 mg twice daily (EMA 2008). The immediate release presentation shows peak plasma concentrations within one hour, with an estimated half-life of 1.4 hours to 1.9 hours (Jerling 2006); for the extended release presentation, values are 2 hours to 6 hours and 7 hours, respectively (Cattaneo 2015; Jerling 2006). The ranolazine extended release preparation reduces the frequency of angina episodes, improves exercise performance, and delays the development of exercise-induced angina and ST-segment depression (ACC/AHA 2012). Although these effects are considered to be dose-related (Chaitman 2011), they have been observed to be modest (EMA 2008) and of uncertain clinical significance (NICE 2011). Furthermore, there is no evidence about the effects of ranolazine on long-term outcomes in people with stable angina, or for the addition of ranolazine to a calcium channel blocker (NICE 2011). Conversely, an advantage of ranolazine is that it does not cause significant haemodynamic changes, with an average of less than 2 beats per minute reduction in heart rate and less than 3 mm Hg decrease in systolic blood pressure (ACC/AHA 2012). However, ranolazine is associated with a dose-dependant increase in QT-interval, with a mean increase of 6 ms at the maximum recommended dosing (ACC/AHA 2012). More recently, an anti-arrhythmic (antifibrillatory) effect of ranolazine has been proposed, but current evidence is based on small, non-controlled trials (Hawwa 2013). Contra-indications to ranolazine are prolonged QT-interval and co-administration with other QT-prolonging drugs, previous history of ventricular tachycardia and moderate to severe kidney impairment or severe liver failure (Tarkin 2012). The most common adverse events related to use of ranolazine are headache (5.5%), dizziness (1% to 6%), constipation (5%) and nausea (≤ 4%; dose related). Although there is concern

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about QT prolongation on ECG, its prevalence has been estimated to be less than 1% (Ranexa PI 2013).

How the intervention might work

Ranolazine is a selective inhibitor of the late sodium current (INaL) in cardiomyocytes, which is thought to be an important contributor to the pathogenesis of angina through calcium overload and increase in oxygen consumption in the cardiomyocytes (Codolosa 2014). Although most studies have focused on its role in macrovascular angina, some findings suggest that ranolazine also has anti-inflammatory or antioxidant effects which may improve glycometabolic homeostasis, which are more important in microvascular angina (Cattaneo 2015).

Early studies on the effects of ranolazine in people with stable angina have been undertaken using the drug's immediate release formulation. However, given that its action was deemed significant only in the peak measurements, an extended release formulation was developed, which was approved for use in people with stable angina (Keating 2008). Overall, ranolazine has been shown to improve exercise tolerance test (ETT) parameters and angina frequency in people with stable angina without substantial haemodynamic effect (Savarese 2013). However, ranolazine has also been related to prolongation of the QTc interval, although not pro-arrhythmic at therapeutic doses (Thadani 2012). Moreover, ranolazine has been shown to have anti-arrhythmic effects by reducing atrial and ventricular arrhythmias (Hawwa 2013).

A number of subgroup analyses have been performed for ranolazine in people with stable angina. The effects of ranolazine on ETT parameters have been found to be greater among women. However, the effects of ranolazine on decreased angina frequency and nitroglycerin consumption were comparable among the gender groups (Wenger 2007). Differences among age groups have been evaluated. Although ranolazine efficacy is similar among people aged 70 years or older and patients younger than 70 years, its safety profile was better in the younger age group (Rich 2007). Differences between diabetic and non-diabetic patients have also been sought. Although ranolazine has not been found to have a different effect for people with diabetes regarding ETT parameters, angina frequency and nitroglycerin consumption, it was related to a significant reduction in HbA1c levels (Patel 2008).

Why it is important to do this review

Although ranolazine reduces angina episodes and improves ETT parameters, its impact on the long-term prognosis in people with stable angina remains unclear. Moreover, the clinical significance of those effects is a matter of debate (NICE 2011). Even though the main indication for ranolazine in people with stable angina is as add-on therapy, the evidence regarding its use in combination with some first-line drugs is lacking (NICE 2011). More evidence is needed on the use of ranolazine as monotherapy, given that it may provide an option for people who cannot use any of the first-line drugs (ESC 2013; NICE 2011) or recommended as a first-line drug given its apparently better side effects profile compared with classical anti-anginal agents (ACC/AHA 2012). In view of these gaps in the knowledge of the role of ranolazine for the management of people with stable angina, a systematic analysis of relevant, high quality, and up-to-date evidence was needed.

OBJECTIVES

To assess the effects of ranolazine on cardiovascular and non-cardiovascular mortality, all-cause mortality, quality of life, acute myocardial infarction incidence, angina episodes frequency and adverse events incidence in stable angina patients, used either as monotherapy or as add-on therapy, and compared to placebo or any other anti-anginal agent.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised, controlled, parallel-group and cross-over trials, with double blinding (of participants and trial personnel) that assessed the effects of ranolazine in the management of stable angina pectoris, irrespective of the number of groups and the length of follow-up. However, for safety outcomes, we also included trials regardless of blinding so long as other criteria were met. We included studies reported as full-text, those published only as abstracts, and unpublished data.

Types of participants

We included adults (aged 18 years or over) diagnosed with stable angina pectoris, irrespective of gender, country of enrolment, setting, previous treatment status, comorbidities and symptom severity. The diagnosis of stable angina pectoris could be established based on clinical history, myocardial ischaemia demonstrated by functional tests or significant obstructive coronary artery disease (CAD) demonstrated by angiography. We considered studies which included a subset of relevant participants if results were reported separately for people with stable angina.

Types of interventions

We included trials comparing ranolazine (given orally for at least one week as either monotherapy or add-on therapy, irrespective of dose, presentation (immediate or extended release) and daily frequency) with placebo or other anti-anginal agent. We included the following co-interventions provided they were not part of the randomised treatment: other anti-anginal agents (long-acting nitrates, adrenergic beta antagonists and/or calcium channel blockers), statins, antiplatelet agents, antihypertensive agents and surgical interventions for CAD. We included trials that applied the following designs.

Monotherapy

- Ranolazine versus placebo.
- Ranolazine versus first-line anti-anginal drugs, grouped by class: 1) adrenergic beta antagonists and 2) calcium channel blockers.
- Ranolazine versus other second-line anti-anginal drugs, grouped as: 1) long-acting nitrates, 2) ivabradine, 3) nicorandil and 4) trimetazidine.

Add-on therapy

- Ranolazine added to first-line anti-anginal drugs (grouped by class as for monotherapy) versus placebo added to first-line anti-anginal drugs (grouped by class).

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- Ranolazine added to other second-line anti-anginal drugs (grouped as for monotherapy) versus placebo added to other second-line anti-anginal drug (grouped).
- Ranolazine added to first-line anti-anginal drugs (grouped as for monotherapy) versus other second-line anti-anginal drugs (grouped as mentioned before) added to first-line anti-anginal drugs (grouped).
- Ranolazine added to other second-line anti-anginal drugs (grouped as for monotherapy) versus first-line anti-anginal drugs (grouped) added to other second-line anti-anginal drugs (grouped).

Types of outcome measures

We considered effectiveness and safety outcome measures, and only measures taken at the longest follow-up within each study. For the outcomes considered, we included only results measured with a follow-up of at least one week. Studies were included irrespective of whether or not they assessed the outcomes listed below.

Primary outcomes

Effectiveness

- Cardiovascular mortality, expressed as a proportion of the total study population.

Safety

- Non-cardiovascular mortality, expressed as a proportion of the total study population.

Secondary outcomes

Effectiveness

1. All-cause mortality, expressed as a proportion of the total study population.
2. Quality of life, measured using general scales: Medical Outcomes Study Short Form-36 (SF-36), World Health Organization Quality of Life tool (WHOQOL), Illness Perception Questionnaire (IPQ) and Nottingham Health Profile (NHP) (Silva 2011); or specific scales: Seattle Angina Questionnaire (SAQ), MacNew Heart Disease Health-Related QoL Questionnaire, Ferrans and Powers QoL Index and Speak from the Heart Chronic Angina Checklist (Young 2013); all were expressed as mean differences (MDs).
3. Acute myocardial infarction (AMI) incidence (fatal and non-fatal), defined as the proportion of participants who experienced one or more AMI episodes, expressed separately for fatal and non-fatal AMI.
4. Need for revascularisation procedure, expressed as a proportion of the total study population.
5. Angina episodes frequency, measured as a weekly average, expressed as MDs.
6. Costs of health care. We considered any information regarding costs of study interventions and related medical care (hospitalisations, additional interventions and outpatient health care).
7. Time to 1-mm ST-segment depression on exercise electrocardiogram (ECG) at peak, measured in seconds, expressed as MDs.

Safety

- Adverse events incidence, defined as the proportion of participants who experienced one or more serious (non-cardiac life-threatening) or non-serious events, expressed as a whole but separately for each category. Serious adverse events were defined as those that threaten life, require or prolong hospitalisation, result in permanent disability, or cause birth defects (Cochrane Glossary).

Search methods for identification of studies

Electronic searches

We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 1, 2016, searched 9 February 2016);
- MEDLINE In-Process and Other Non-Indexed Citations and MEDLINE (Ovid, 1946 to 9 February 2016);
- Embase (Ovid, 1980 to 2016 week 6, searched 9 February 2016); and
- Conference Proceedings Citation Index - Science (CPCI-S Web of Science, 1990 to 9 February 2016).

The detailed MEDLINE search strategy is presented in Appendix 1. We adapted the MEDLINE search strategy for other databases (Appendix 1). The Cochrane highly sensitive search strategy for identifying randomised trials, sensitivity-maximising version, was applied to MEDLINE and adapted for Embase and CPCI-S (Lefebvre 2011). We searched these databases from dates of inception to 9 February 2016 and did not apply language restrictions.

Searching other resources

In an effort to identify further ongoing, unpublished and published trials (Van Enst 2012) we also searched the following resources (Higgins 2011):

1. National and regional databases:
   a. African Index Medicus (AIM, Africa) (http://indexmedicus.afro.who.int/) (1966 to 24 April 2016);
   b. Informit Health Collection (Australasia) (http://www.informit.com.au/health.html) (1846 to 24 April 2016);
   c. VIP Information/Chinese Scientific Journals Database (CSJD-VIP, China) (http://www.cqvip.com/) (from inception to 24 April 2016);
   d. Index Medicus for the Eastern Mediterranean Region (IMEMR, Eastern Mediterranean); (http://www.emro.who.int/information-resources/imemr-database/) (1966 to 24 April 2016);
   e. IndMED (India) (http://indmed.nic.in/indmed.html) (1980 to 24 April 2016);
   f. KoreaMed (Korea) (http://www.koreamed.org/SearchBasic.php) (1959 to 24 April 2016);
   g. LILACS (Latin America and the Caribbean) (http://lilacs.bvsalud.org/es/) (1980 to 24 April 2016);
   h. Index Medicus for South-East Asia Region (IMSEAR, DSpace, South-East Asia) (http://imsear.hellis.org/) (1871 to 24 April 2016); and
   i. Western Pacific Region Index Medicus (WPRIM, Western Pacific) (http://www.wprim.org/) (1950 to 24 April 2016).

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2. Grey literature databases:
   a. OpenGrey (Europe, formerly OpenSIGLE (Stock 2011)) (http://www.opengrey.eu/) (1973 to 24 April 2016); and
   b. National Technical Information Service (NTIS, U.S.) (http://www.ntis.gov/) (1851 to 24 April 2016).
3. Prospective trial registers search portals:
   a. WHO International Clinical Trials Registry Platform (WHO ICTRP) (http://www.who.int/ictrp/en/) (1 January 1990 to 24 April 2016);
   b. MetaRegister of Current Controlled Trials (*m*RCT) (http://www.controlled-trials.com/mrct/) (6 April 2000 to 24 April 2016); and
   c. ClinicalTrials.gov (http://www.clinicaltrials.gov/) (3 November 1999 to 24 April 2016).
4. Conference abstracts:
   a. American Heart Association Scientific Sessions from 2009 to February 2016 (http://my.americanheart.org/professional/Sessions/ScientificSessions/Archive/Archive-Scientific-Sessions_UCM_316935_SubHomePage.jsp); and
   b. European Society of Cardiology Congresses from 2007 to February 2016 (http://www.escardio.org/congresses/past_congresses/Pages/Past-Congresses.aspx).
5. Other reviews: checking studies included in other relevant reviews retrieved from searches of:
   a. Database of Abstracts of Reviews of Effects (DARE) through the Centre for Reviews and Dissemination (CRD) (http://www.crd.york.ac.uk/CRDWeb/) (1975 to 24 April 2016);
   b. NHS Economic Evaluation Database (NHS EED) through the CRD (http://www.crd.york.ac.uk/CRDWeb/) (1975 to 24 April 2016); and
   c. Health Technology Assessment Database (HTA Database) through the CRD (http://www.crd.york.ac.uk/CRDWeb/) (1975 to 24 April 2016).
6. Approval documents from the US Food and Drrug Administration (FDA) (http://www.fda.gov/) and the European Medcines Agency (EMA) (http://www.ema.europa.eu/), checked on 24 April 2016.
7. Checking reference lists of included studies and other relevant papers identified through the search process.
8. The website of Gilead Sciences (http://www.gilead.com/), the company which discovered, developed and commercialised ranolazine, checked on 24 April 2016.

Data collection and analysis

Selection of studies

Two review authors (LV, JM) independently screened titles and abstracts for inclusion identified from searches, and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. Disagreements were resolved by arbitration involving a third review author (JB). We retrieved full-text study reports and publications; two review authors (LV, JM) then independently screened the studies for inclusion, and recorded reasons for exclusion of ineligible studies. Disagreements were resolved through discussion, or if required, the participation of a third review author (JB or CS). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in this Cochrane review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1) and Characteristics of excluded studies table.

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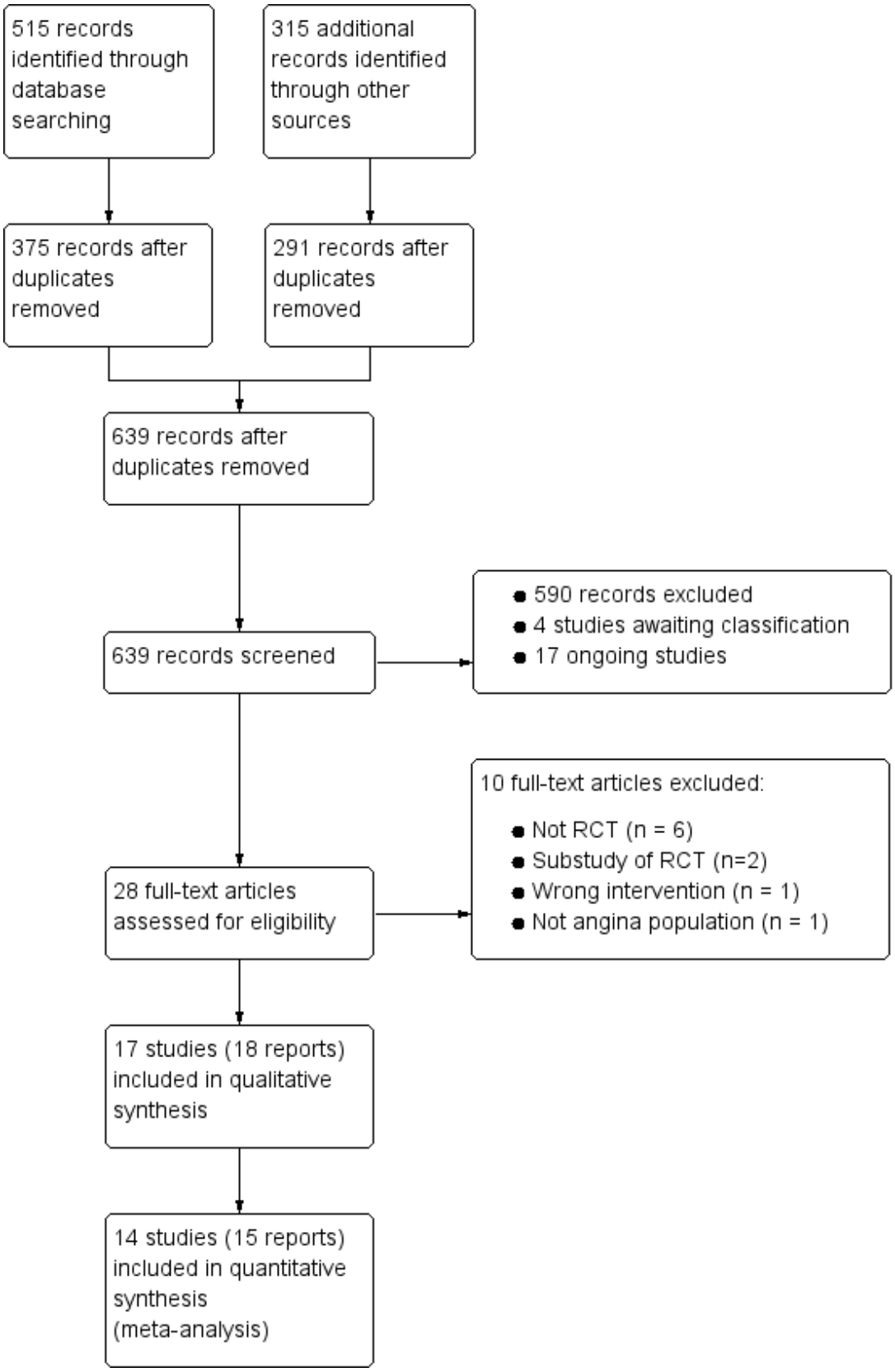
Figure 1. Study flow diagram †Two included articles report data from the RIVER-PCI trial



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Data extraction and management

We used a data collection form for study characteristics and outcome data which had been piloted on one study included in the review. Four review authors (JB, LV, JM, DR) were involved in both processes so that two review authors independently analysed each included study. We resolved disagreements by consensus or by involving a fifth review author (CS). One review author (JB) entered data into RevMan 2014. We double-checked that study characteristics and outcome data were entered correctly by comparing the data presented in the systematic review with the study reports. We extracted the following study characteristics:

1. Methods: date of study, study design, method of randomisation, method of concealment of allocation, blinding, power calculation, duration of follow-up, number of patients randomised, exclusions post-randomisation, withdrawals (and reasons).
2. Participants: N, countries of enrolment, setting/location, mean age/age range, gender (male %), severity of condition, diagnostic criteria, comorbidities, inclusion and exclusion criteria.
3. Interventions: intervention (including type of formulation), comparison, concomitant medications, excluded medications and duration of treatment.
4. Outcomes: primary and secondary outcomes (efficacy and safety) specified and collected, and time points reported. For each outcome: outcome definition, method of measurement and unit of measurement. Results: number of patients analysed (according to type of analysis) and main results.
5. Notes: source of funding and notable conflicts of interest of trial authors.

Assessment of risk of bias in included studies

Two review authors (JB, LV) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving a third review author (CS). We assessed the risk of bias according to the following domains:

1. Random sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants and personnel (performance bias).
4. Blinding of outcome assessment (detection bias).
5. Incomplete outcome data (attrition bias).
6. Selective outcome reporting (reporting bias).
7. Other bias: source of funding.

We graded each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification for our judgment in 'Risk of bias' tables. We took into account the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) regarding 'Risk of bias' assessment of cross-over studies. We summarised the risk of bias judgements across different studies for each domain. We did not obtain information on risk of bias related to unpublished data or correspondence with trial authors. We performed an additional handsearch to identify published study protocols to check for selective reporting bias. When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted this Cochrane Review according to the published protocol and reported deviations in Differences between protocol and review.

Measures of treatment effect

We analysed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs) and continuous data as mean differences (MDs) with 95% CIs. We used standardised mean differences (SMD) for quality of life meta-analyses if included data were measured using different tools. We entered data presented as a scale with a consistent direction of effect (with higher scores indicating better quality of life). We did not use skewed data for the quantitative analysis.

Unit of analysis issues

We included randomised controlled trials (RCTs) with either parallel-group or cross-over designs. Cross-over studies were suitable for this Cochrane review because stable angina pectoris is a relatively stable chronic manifestation of disease and the interventions we assessed have only a temporal effect. We took into account the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) regarding statistical analysis of cross-over studies.

Dealing with missing data

We contacted trial authors to obtain missing numerical outcome data where possible. Where this was not possible, we performed analyses only with the available data.

Assessment of heterogeneity

We statistically assessed the presence of heterogeneity among study results by means of the Chi^2 test with a P value < 0.10 as cut-off point. We further assessed the degree of heterogeneity by using the I^2 statistic (McNamara 2015), considering the following thresholds for interpretation: 0% to 40%: not important heterogeneity; 30% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; and 75% to 100%: considerable heterogeneity (in which case meta-analyses were not performed) (Higgins 2011).

Assessment of reporting biases

We planned to perform statistical tests for funnel plot asymmetry only for those meta-analyses which included 10 or more studies (Sterne 2011). Since none of the meta-analyses performed met this criterion, we used only visual inspection of funnel plots to assess for publication bias.

Data synthesis

We used Review Manager software, version 5.3 (RevMan 2014) for data synthesis and analysis. We undertook meta-analyses only where this was meaningful, that is, if the treatments, participants and underlying clinical question were sufficiently similar for pooling to make sense. We used fixed-effect meta-analyses to calculate effect estimates if there was no statistically significant heterogeneity (Chi^2 P < 0.10). For results with statistically significant but not considerable heterogeneity ($I^2 \geq 75\%$), we used random-effects meta-analyses to calculate effect estimates.

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Subgroup analysis and investigation of heterogeneity

We planned to carry out subgroup analyses based on the following variables:

- age;
- gender;
- previous AMI status;
- patients undergoing percutaneous coronary intervention (PCI); and
- number of revascularisation procedures.

Subgroup analyses for these variables could be carried out because we found insufficient data. However, we decided to add another variable: type of stable angina diagnosis (macrovascular versus microvascular). This subgroup analysis was performed for incidence of non-serious adverse events for ranolazine given as monotherapy compared to placebo, and for quality of life for add-on ranolazine compared to placebo.

Sensitivity analysis

We undertook sensitivity analyses to explore the effects of decisions we made throughout the review process, including:

1. Restriction to trials with low risk of bias (those which had at least three domains graded as low risk of bias).
2. Exchanging the statistical approach for data synthesis (random-effects versus fixed-effect models).
3. Changing the measures of treatment effects for dichotomous (RRs to ORs) and continuous data (SMDs to MDs and vice versa).
4. Changing the method of dealing with missing data (ignoring versus imputing with replacement values for poor outcomes). This sensitivity analysis was not performed because we decided not to impute any missing data; however, we calculated some data included in the quantitative synthesis from the available information published in reports of the included studies.
5. Those relevant issues identified during the analyses of studies: we decided to pool the available data irrespective of the duration of follow-up and perform an additional sensitivity analysis based on this variable (< 6 weeks versus ≥ 6 weeks).

Summary of Findings table and quality of evidence (GRADE)

We created 'Summary of findings' tables for the following outcomes: cardiovascular mortality, non-cardiovascular mortality, all-cause mortality, quality of life, AMI incidence, angina episodes frequency and adverse events incidence. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it relates to the studies which contributed data to the meta-analyses for the prespecified outcomes. We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software (GRADEpro GDT 2015). We provided justifications for all decisions to downgrade the quality of evidence in footnotes and included comments to aid readers' understanding of the review where necessary.

Reaching conclusions

We based our conclusions only on findings from the quantitative or narrative synthesis of included studies for this Cochrane review. The Implications for research sections suggests priorities for future research and outlines remaining uncertainties in the area.

RESULTS

Description of studies

See the Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies and Characteristics of studies awaiting classification tables for detailed descriptions.

Results of the search

We identified 515 records through searching electronic databases and 315 additional records from other sources. After removing duplicates, 639 records remained for screening of titles and abstracts. We deemed 611 to be irrelevant and the remaining 28 records were obtained in full-text for eligibility assessment. We excluded 10 reports. We included 17 RCTs (18 records) in the qualitative analysis; of these, 14 studies (15 reports) were also included in the quantitative synthesis (CARISA 2004; ERICA 2006; MARISA 2004; Mehta 2011; MERLIN-TIMI 36 2007; Pelliccia 2012; Pepine 1999; RAN080 2005; RIVER-PCI 2016; RWISE 2016; Shammas 2015; TERISA 2013; Thadani 1994; Villano 2013) (see Figure 1).

The MERLIN-TIMI 36 2007 trial included patients with non ST-elevation acute coronary syndrome; a subgroup of those patients had also a history of stable angina, and the results regarding these patients were reported in the sub study included in this review. The RIVER-PCI 2016 trial considered three sub studies in its protocol, all of which were of interest for this review; however, only the results of two have been published in separate reports included in this review.

Included studies

We included 17 randomised controlled trials (RCTs) that enrolled a total of 9975 participants. Two RCTs (MERLIN-TIMI 36 2007; RIVER-PCI 2016) provided data for 61.8% of participants.

Of the 17 RCTs, 11 were parallel-group and six were cross-over design studies. Most studies were performed in high-income regions such as North America, Europe and Australia; five studies included participants from Asia, Russia, Israel, India (CARISA 2004; MERLIN-TIMI 36 2007; RIVER-PCI 2016; Sandhiya 2015; TERISA 2013) and Africa (MERLIN-TIMI 36 2007). All but three studies included mostly female participants; Mehta 2011, RWISE 2016 and Villano 2013 reported percentages of male participants as 0%, 4% and 19.6%, respectively. Most participants' ages ranged from 60 years to 80 years. Although all studies included people with angina, some considered additional inclusion criteria that enabled discrimination between people with macrovascular angina (Babalis 2015; CARISA 2004; ERICA 2006; MARISA 2004; RAN080 2005; Sandhiya 2015; Shammas 2015; TERISA 2013) and microvascular angina (Mehta 2011; RWISE 2016; Tagliamonte 2015; Villano 2013). Notably, three of four studies that included people with microvascular angina were also those that included mostly female participants. Only four studies enrolled participants with comorbidities such as acute coronary syndrome (ACS) (MERLIN-TIMI 36 2007), incomplete revascularisation post-percutaneous

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coronary intervention (PCI) (RIVER-PCI 2016) and type 2 diabetes mellitus (Sandhiya 2015; TERISA 2013). Intervention durations ranged from 1 to 92 weeks.

Ranolazine was used as both extended and immediate release formulations; however, the formulation was not specified in nine studies (Babalis 2015; Mehta 2011; Pelliccia 2012; RIVER-PCI 2016; Sandhiya 2015; Shammas 2015; Tagliamonte 2015; Thadani 1994; Villano 2013). Ranolazine was administered as add-on therapy in seven studies. Co-medications included adrenergic beta antagonists (Shammas 2015), calcium channel blockers (ERICA 2006) or both (Babalis 2015; CARISA 2004; Pepine 1999; TERISA 2013; Villano 2013). However, several other studies (Mehta 2011; MERLIN-TIMI 36 2007; Pelliccia 2012; RAN080 2005; RIVER-PCI 2016; RWISE 2016) permitted concomitant anti-angina medications to be administered to some participants.

Most studies compared ranolazine only with placebo; other comparators included atenolol (RAN080 2005), ivabradine (Villano 2013) and trimetazidine (Sandhiya 2015).

Seven included studies evaluated mainly parameters related to exercise electrocardiogram (ECG) (Babalis 2015; CARISA 2004; MARISA 2004; MERLIN-TIMI 36 2007; Pepine 1999; RAN080 2005; Thadani 1994), which were added (time to 1-mm ST-segment depression at peak) to the review outcomes. Three studies reported data relevant only for a secondary safety outcome (incidence of adverse events) (Babalis 2015; MARISA 2004; Pepine 1999). Only one study reported data for the primary outcomes of this review and collected data on the costs of health care (a secondary outcome). However, results are not yet published (RIVER-PCI 2016).

Most included studies (n = 12) reported commercial sources of funding including: CV Therapeutics (CARISA 2004; ERICA 2006; MARISA 2004; MERLIN-TIMI 36 2007; RAN080 2005; RWISE 2016); Syntex Research (Pepine 1999; Thadani 1994); Gilead Sciences (RIVER-PCI 2016; Shammas 2015; TERISA 2013); and other (Mehta 2011). Two studies reported no external sources of funding (Sandhiya 2015; Pelliccia 2012) and three did not state sources of funding (Babalis 2015; Tagliamonte 2015; Villano 2013).

Excluded studies

We excluded 10 studies after retrieving and assessing full-text reports. Six studies were excluded because their design did not correspond to a RCT. Four of these studies were economic analyses for which the health economics data provided did not come from studies conducted alongside a RCT (Coleman 2015; Hidalgo-Vega 2014; Kohn 2014; Lucioni 2009). Another of these studies was a safety study on ranolazine without comparator (ROLE 2007). The remaing study was a one-group cross-over trial and it did not state if the treatment order was randomised (Jain 1990). Two studies were excluded because of corresponding to substudies of already included studies (Arnold 2014, Rich 2007). One study was excluded because the duration of the intervention was shorter than the 1-week period established as a minimum for inclusion (Cocco 1992). Another study was excluded because its population did not match inclusion criteria for participants (Rehberger-Likozar 2015).

Studies awaiting classification

Four studies await classification (Characteristics of studies awaiting classification). Available data were insufficient to determine if these studies met the inclusion criteria for this review. In three studies, population characteristics were not described in sufficient detail to determine if they were restricted to people with stable angina (NCT01304095; Tagarakis 2013; Tian 2012). The fourth study (Wang 2012) did not provide information about randomisation and blinding. The full-text reports for three studies (Tagarakis 2013; Tian 2012; Wang 2012) could not be obtained.

Ongoing studies

We identified 17 ongoing trials which met the review eligibility criteria (Characteristics of ongoing studies). Of those, 15 studies are parallel-group designs and two are cross-over studies (NCT01754259, NCT01495520). Most studies are being performed in high-income regions, such as North America and Europe, two studies in Asia (India) (CTRI/2014/01/004332; Gupta 2014); and six did not state locations (Calcagno 2014; Calcagno 2015; NCT02147067; NCT02252406; NCT02423265; Šebeštjen 2014). All but one study includes a mixed population regarding gender; Šebeštjen 2014 includes only males. Seven studies restricted the population to people with macrovascular angina (EUCTR 2011-001278-24; EUCTR 2012-001584-77; NCT01495520; NCT01754259; NCT01948310; NCT02252406; NCT02423265) and two restricted participants to people with microvascular angina (NCT02052011; NCT02147067). Some studies consider comorbidities or important antecedents such as PCI-stent implantation (Calcagno 2014; Calcagno 2015; NCT02423265), sustained STEMI (CTRI/2014/01/004332), diabetes mellitus (Gupta 2014; NCT01754259), metabolic syndrome (NCT02252406) and other cardiac conditions (NCT01558830). Intervention durations range from 4 weeks to 12 months.

The evaluation of ranolazine as add-on therapy is explicitly stated in two studies (Gupta 2014; NCT02423265); the remainder provide insufficient information to determine how ranolazine is being administered. Ranolazine doses range from 375 mg twice daily to 1000 mg twice daily. The comparator for most studies is placebo or no treatment, with only three studies comparing ranolazine with other second-line anti-angina treatments such as ivabradine (Calcagno 2015) and trimetazidine (CTRI/2014/01/004332; Šebeštjen 2014).

Five studies assess quality of life (NCT02052011; NCT02147067; NCT02147834; NCT02265796; NCT02423265); two assess frequency of angina episodes (EUCTR 2011-001278-24; Gupta 2014); two assess need for revascularisation procedure (NCT02147834; NCT02265796); five assess exercise ECG parameters (Calcagno 2014; Calcagno 2015; EUCTR 2011-001278-24; NCT02147067; NCT02423265). Eight studies do not assess any of the effectiveness outcomes of this review (CTRI/2014/01/004332; EUCTR 2012-001584-77; NCT01495520; NCT01558830; NCT01754259; NCT01948310; NCT02252406; Šebeštjen 2014). Eight studies state commercial sources of funding (at least partially) from pharmaceutical companies such as Gilead Sciences (NCT01558830; NCT01948310; NCT02052011; NCT02147067; NCT02147834; NCT02265796) and Menarini International Operations (EUCTR 2011-001278-24; EUCTR 2012-001584-77).

Risk of bias in included studies

Risk of bias is illustrated in Figure 2 and Figure 3. Also see Characteristics of included studies.

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Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

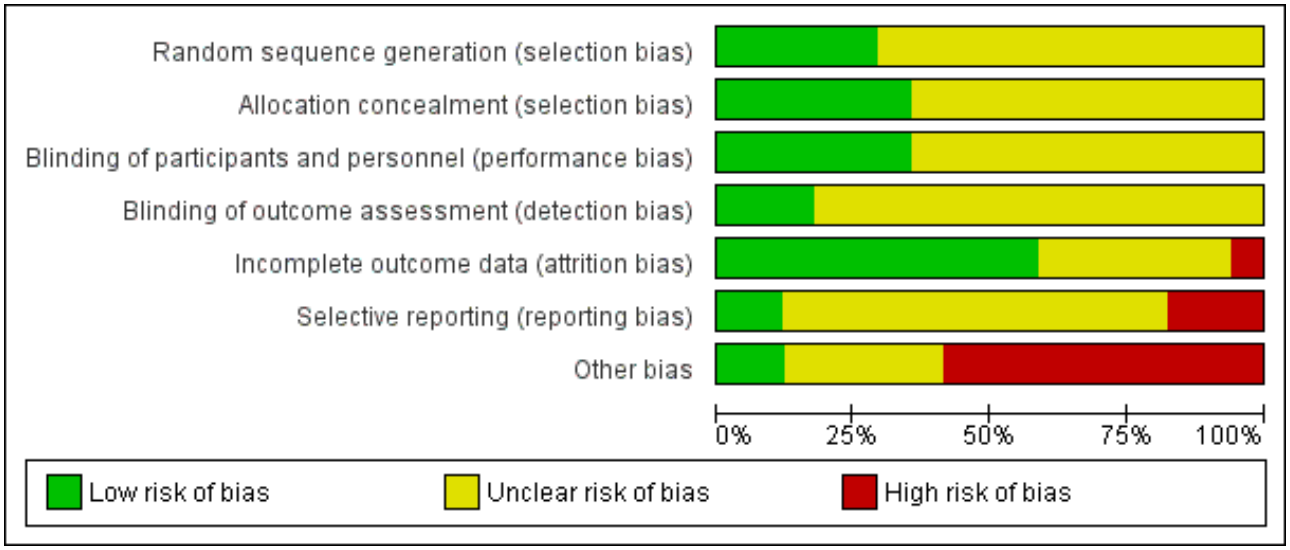

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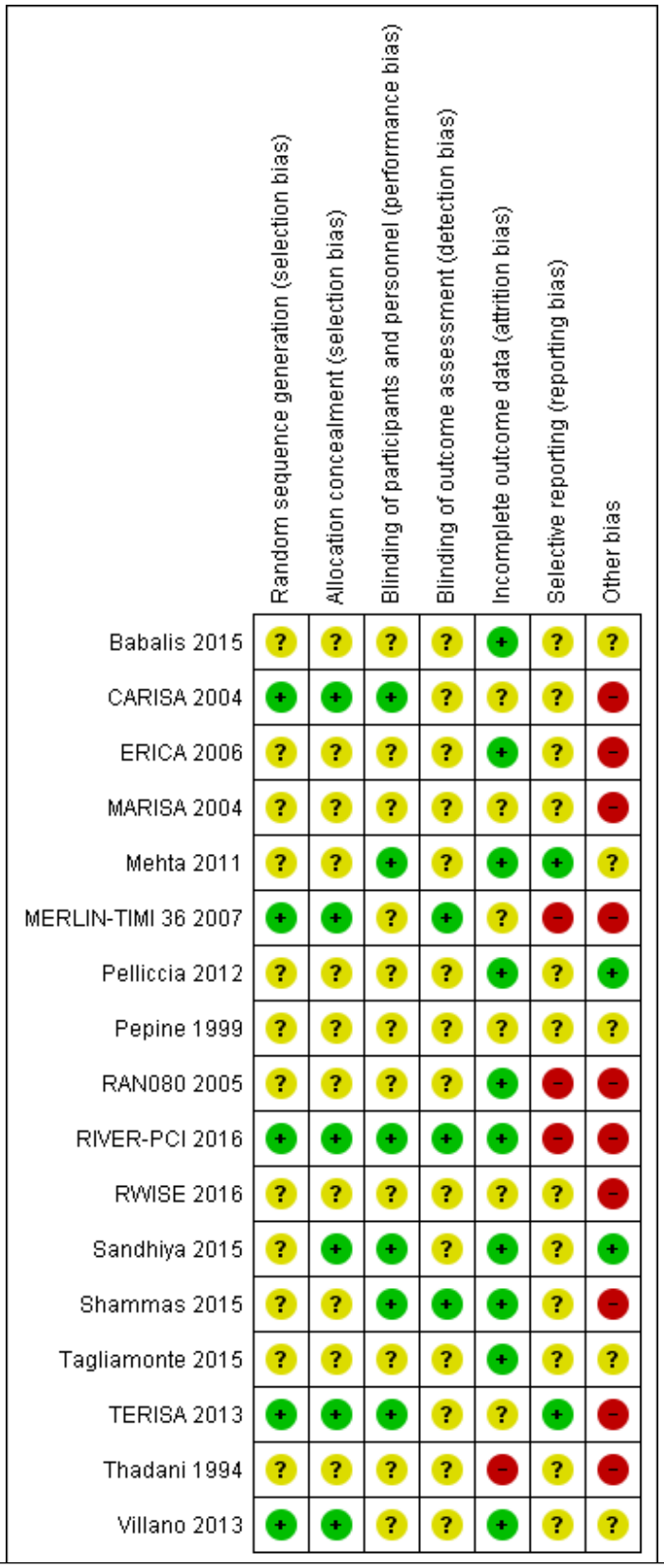
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Other bias criteria: we considered the source of funding in this section, we scored high risk of bias if the source of funding was solely from private organisations, unclear risk of bias if it was mixed (private and public) and low risk of bias if it was solely not external or from public organisations.



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Allocation

All included studies randomly assigned participants to treatment groups using either computer-generated sequences (CARISA 2004; MERLIN-TIMI 36 2007; RIVER-PCI 2016; TERISA 2013; Villano 2013) or other methods that were described with insufficient detail to enable assessment (Babalis 2015; ERICA 2006; MARISA 2004; Mehta 2011; Pelliccia 2012; Pepine 1999; RAN080 2005; RWISE 2016; Sandhiya 2015; Shammas 2015; Tagliamonte 2015; Thadani 1994).

Adequate concealment of allocation methods were described in four studies (CARISA 2004; Sandhiya 2015; TERISA 2013; Villano 2013). Two additional studies (MERLIN-TIMI 36 2007; RIVER-PCI 2016) did not describe in detail their method for allocation concealment, but it was considered to be adequate given the use of a centralised randomization system. One study stated that investigators had been blinded to treatment allocation (Shammas 2015); this was not considered to be sufficiently detailed to inform assessment.

Blinding

Most studies reported using a double-blind design for the treatment phase. However, only one study explicitly indicated who were blinded (Shammas 2015). This was established from information provided in five other studies (CARISA 2004; Mehta 2011; RIVER-PCI 2016; Sandhiya 2015; TERISA 2013). Blinding was not stated in two study reports (Babalis 2015; Villano 2013).

Blinding of outcome assessment was reported in seven studies (CARISA 2004; MARISA 2004; Mehta 2011; MERLIN-TIMI 36 2007; RIVER-PCI 2016; Shammas 2015; Villano 2013). However, for outcomes considered in this review, only three studies reported blinding measures for outcome assessment (MERLIN-TIMI 36 2007; RIVER-PCI 2016; Shammas 2015).

Incomplete outcome data

Six studies did not report any withdrawals or exclusions of participants, but of these, only three explicitly stated that no participants withdrew or were excluded (Babalis 2015; Mehta 2011; Tagliamonte 2015). Five studies did not describe reasons for exclusions or withdrawal in sufficient detail to inform assessment (CARISA 2004; MERLIN-TIMI 36 2007; Pepine 1999; RWISE 2016; TERISA 2013). One study did not report the allocated groups of excluded or withdrawn participants (MARISA 2004). The five studies in which numbers, reasons and allocated group of participants who withdrew or were excluded were reported, inconsistencies in data were identified for one or two participants in three studies (ERICA 2006; RAN080 2005; Shammas 2015). The number of exclusions and withdrawals approached 10% of the total study population in one study (Thadani 1994).

The type of analysis was not stated in eight studies (Babalis 2015; ERICA 2006; RWISE 2016; Sandhiya 2015; Shammas 2015; Tagliamonte 2015; TERISA 2013; Villano 2013). Seven studies reported performing intention-to-treat analyses (CARISA 2004; MARISA 2004, Mehta 2011; MERLIN-TIMI 36 2007; Pelliccia 2012; RAN080 2005; RIVER-PCI 2016); two studies reported performing intention-to-treat and per-protocol analyses (Pepine 1999; Thadani 1994). Pepine 1999 and Thadani 1994 reported results from intention-to-treat analyses, and stated that no significant differences were found among intention-to-treat and per-protocol analyses.

Selective reporting

We assessed selective reporting by cross-checking study outcomes with published protocols. We found protocols for only five included studies (Mehta 2011; MERLIN-TIMI 36 2007; RIVER-PCI 2016; RWISE 2016; TERISA 2013). The protocol for the MERLIN-TIMI 36 trial (Morrow 2006) did not consider the sub study (MERLIN-TIMI 36 2007) we included in this review (post-hoc analyses), and thus was considered to be at high risk of bias. Of note, the report of this sub study met our pre-specified inclusion criteria, and it takes part of only one of our analyses (Analysis 1.2), whose result do not change if the MERLIN TIMI 36 sub study is not considered.

We used information presented in studies' Methods sections as a proxy for protocols. We found that three studies did not report data for some outcomes (Babalis 2015; MERLIN-TIMI 36 2007; RIVER-PCI 2016) and four studies reported data for additional outcomes (CARISA 2004; MERLIN-TIMI 36 2007; RAN080 2005; RIVER-PCI 2016). Selective reporting affected outcomes considered in this review in three studies (CARISA 2004; RAN080 2005; RIVER-PCI 2016).

Other potential sources of bias

We considered the source of funding and conflicts of interest as potential sources of bias. Most studies reported funding from commercial pharmaceutical companies. Sources of funding were reported to be partially supported by commercial pharmaceutical companies in three studies, no conflicts of interest were reported in two of these (Mehta 2011, Pepine 1999) and conflicts of interest were reported for some of the authors in the other one (RWISE 2016). Three studies (Babalis 2015; Tagliamonte 2015; Villano 2013) reported neither funding source nor authors' conflicts of interest. Two studies reported no external source of funding and absence of conflicts of interest (Pelliccia 2012; Sandhiya 2015).

Effects of interventions

See: **Summary of findings for the main comparison** Ranolazine (add-on therapy) versus placebo for stable angina pectoris; **Summary of findings 2** Ranolazine (monotherapy) versus placebo for stable angina pectoris

Summary of findings for the main comparison presents ranolazine compared to placebo (add-on therapy) and Summary of findings 2 presents ranolazine compared to placebo (monotherapy).

Primary outcomes

Cardiovascular mortality

Only RIVER-PCI 2016 reported data on cardiovascular mortality for ranolazine 1000 mg twice daily administered as monotherapy compared to placebo. We observed uncertain effect on cardiovascular mortality from the 20/1287 cardiovascular deaths in the placebo group and 21/1317 cardiovascular deaths in the ranolazine group (RR 1.03, 95% CI 0.56 to 1.88; low quality evidence) (Analysis 1.1).

Non-cardiovascular mortality

None of the included studies reported non-cardiovascular mortality.

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Secondary outcomes

Effectiveness

The main results are summarised in analyses for ranolazine as monotherapy compared to placebo (Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 2.1; Analysis 2.2) and as add-on therapy compared to placebo (Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5; Analysis 4.1; Analysis 4.2).

Data were reported for ranolazine as monotherapy compared to placebo for quality of life (Tagliamonte 2015) and frequency of angina episodes (RAN080 2005; Thadani 1994). These data could not be pooled in a meta-analysis due to incompleteness.

Ranolazine was compared to other first- (RAN080 2005, atenolol 100 mg once daily) and second-line anti-anginals (Sandhiya 2015; Villano 2013; trimetazidine 35 mg twice daily and ivabradine 5 mg twice daily respectively), either as monotherapy (RAN080 2005; Sandhiya 2015) or add-on therapy (Villano 2013). Data could not be meta-analysed because, for any outcome, only one trial provided data. Study authors were contacted to obtain missing data. Additional data were provided by Dr Noel Bairey Merz (Mehta 2011) and Dr Nicolas W Shammas (Shammas 2015) and included in the quantitative synthesis.

All-cause mortality

Three studies reported all-cause mortality for ranolazine 1000 mg monotherapy administered twice daily compared to placebo (MERLIN-TIMI 36 2007; Pelliccia 2012; RIVER-PCI 2016). Low quality evidence showed that intervention and placebo group participants were at similar risk of death from all causes (RR 1.00, 95% CI 0.81 to 1.25; 3 studies, 6249 participants; Analysis 1.2). There was no heterogeneity (Chi^2 P = 0.64, I^2 = 0%).

Three studies reported all-cause mortality for ranolazine 1000 mg as add-on therapy administered twice daily (co-medications: adrenergic beta antagonists and calcium channel blockers) compared to placebo (CARISA 2004; ERICA 2006; TERISA 2013). Low quality evidence showed that intervention and placebo group participants were at similar risk of death from all causes (RR 0.83, 95% CI 0.26 to 2.71; 3 studies, 2053 participants; Analysis 3.1). There was no heterogeneity (Chi^2 P = 0.57, I^2 = 0%).

Quality of life

Three studies evaluated quality of life for ranolazine 1000 mg monotherapy administered twice daily compared to placebo (Mehta 2011; RIVER-PCI 2016, RWISE 2016). Moderate quality evidence showed that quality of life did not differ between intervention and placebo group participants (MD 0.28, 95% CI -1.57 to 2.13; 3 studies, 2254 participants; Analysis 1.3). There was no heterogeneity (Chi^2 P = 0.38, I^2 = 0%). Data were assessed using the quality of life dimension of the Seattle Angina Questionnaire (SAQ) in the three trials. The score for this dimension ranged between 0 and 100, with a higher score indicating a better quality of life.

Three studies evaluated quality of life for ranolazine 1000 mg as add-on therapy administered twice daily (co-medications: adrenergic beta antagonists and calcium channel blockers) compared to placebo (ERICA 2006; Shammas 2015; TERISA 2013). Moderate quality evidence showed that quality of life did not differ between intervention and control group participants (SMD 0.13, 95% CI -0.05 to 0.32; 3 studies, 1533 participants; Analysis 3.2). Since there was statistically significant, but not considerable, heterogeneity (Chi^2 P = 0.09, I^2 = 58%) we used a random-effects model to calculate the pooled estimate. We observed that studies differed in risk of selection and detection bias and population size (fewer than 30 participants versus more than 400 participants), which may explain heterogeneity. Pooled data were reported for quality of life assessed using different scales: the angina frequency and quality of life dimensions of the SAQ, and the physical component of SF-36. Scores range from 0 to 100, with higher scores indicating better quality of life.

One additional study evaluated quality of life for ranolazine given as add-on therapy (to adrenergic beta antagonists and calcium channel blockers) compared to placebo (Villano 2013), making a total of four trials for the ranolazine any dose (375mg twice daily and 1000mg twice daily) comparison. Moderate quality evidence showed that quality of life did not differ between intervention and placebo group participants (ranolazine any dose, SMD 0.25, 95% CI -0.01 to 0.52; 4 studies, 1563 participants, Analysis 4.1). Since there was statistically significant, but not considerable, heterogeneity (Chi^2 P = 0.01, I^2 = 73%) we used a random-effects model to calculate the pooled estimate. We observed that trials in this analysis differed in risk of selection and detection bias and population size (fewer than 40 versus more than 400) and type of stable angina diagnosis (macrovascular angina versus microvascular angina), which may explain heterogeneity.

Acute myocardial infarction (AMI) incidence

Fatal AMI incidence

We found no data on fatal AMI for ranolazine given as monotherapy compared to placebo. Two studies reported data on fatal AMI events for ranolazine 1000 mg twice daily given as add-on therapy compared to placebo (ERICA 2006; TERISA 2013). Low quality evidence showed uncertain effect for the risk of fatal AMI between intervention and placebo group participants (RR 1.51, 95% CI 0.25 to 9.05; 2 studies, 1509 participants; Analysis 3.3). There was no statistically significant heterogeneity (Chi^2 P = 0.23, I^2 = 31%).

Non-fatal AMI incidence

Two studies reported non-fatal AMI incidence for ranolazine 1000 mg twice daily given as monotherapy compared to placebo (Pelliccia 2012; RIVER-PCI 2016). Very low quality evidence showed that participants in both intervention and control groups were at similar risk of non-fatal AMI (RR 0.55, 95% CI 0.14 to 2.15; 2 studies, 2674 participants; Analysis 1.4). Since there was statistically significant, but not considerable, heterogeneity (Chi^2 P = 0.06, I^2 = 73%) we used a random-effects model to calculate the pooled estimate. We observed that studies in this analysis differed in risk of performance and detection bias and duration of follow-up (30 days versus 643 days), which may explain heterogeneity.

One study reported non-fatal AMI incidence for ranolazine given as monotherapy compared to placebo (RAN080 2005), making a total of three studies for ranolazine any dose (400 mg three times daily and 1000 mg twice daily) comparison. Low quality evidence showed that intervention and control group participants were at a similar risk of non-fatal AMI (RR 0.88, 95% CI 0.69 to 1.12; 2983 participants, Analysis 2.1). There was no statistically significant heterogeneity (Chi^2 P = 0.13, I^2 = 50%).

Two other studies reported non-fatal AMI incidence for ranolazine 1000 mg twice daily given as add-on therapy compared to placebo

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(ERICA 2006; TERISA 2013). Low quality evidence showed that participants in both groups were at a similar risk of suffering a non-fatal AMI (RR 0.40, 95% CI 0.08 to 2.07, 1509 participants, Analysis 3.4). There was no heterogeneity (Chi² P = 0.81, I² = 0%).

Need for revascularisation procedure

Two studies reported incidence of revascularisation procedures for ranolazine 1000 mg twice daily given as monotherapy compared to placebo (Pelliccia 2012; RIVER-PCI 2016). Moderate quality evidence showed that ranolazine has no effect on the risk of undergoing a revascularisation procedure (RR 0.98, 95% CI 0.82 to 1.18, 2674 participants, Analysis 1.5). There was no heterogeneity (Chi² P = 0.99, I² = 0%).

Angina episodes frequency

Two studies evaluated angina episodes frequency for ranolazine any dose (120 mg 3 times daily and 1000 mg twice daily) given as monotherapy compared to placebo (RWISE 2016; Thadani 1994). Low quality evidence showed that the average number of angina episodes per week did not differ in the participants in both groups (MD 0.08, 95% CI -0.85 to 1.01, 402 participants, Analysis 2.2). There was no heterogeneity (Chi² P = 0.84, I² = 0%).

Three studies evaluated angina episodes frequency for ranolazine 1000 mg twice daily given as add-on therapy (to adrenergic beta antagonists and calcium channel blockers) compared to placebo (CARISA 2004; ERICA 2006; TERISA 2013). Moderate quality evidence showed that the average number of angina episodes per week was lower in the participants who received ranolazine (MD -0.66, 95% CI -0.97 to -0.35, 2004 participants, Analysis 3.5). There was no statistically significant heterogeneity (Chi² P = 0.19, I² = 39%).

Costs of healthcare

None of the included trials reported data on costs and resource use of the management of stable angina participants. We found that only one trial (RIVER-PCI 2016) reported a planned health economics sub-study (Weisz 2013), but results have not yet been published.

Time to 1-mm ST-segment depression

Three studies evaluated time to 1-mm ST-segment depression in exercise ECG at peak for ranolazine any dose (375 mg twice daily, 400 mg three times daily and 1000 mg twice daily) given as add-on therapy compared to placebo (CARISA 2004; Pepine 1999; Villano 2013). Moderate quality evidence showed that the average time to 1-mm ST-segment depression in seconds was higher in participants who received ranolazine (MD 34.62, 95% CI 33.08 to 36.16, 1198 participants, Analysis 4.2). There was no statistically significant heterogeneity (Chi² P = 0.23, I² = 31%).

Data were also available for ranolazine given as monotherapy compared to placebo; however, pooled estimates showed substantial heterogeneity (I² = 90% to 99%) which precluded us from including those results in the quantitative synthesis. We observed that studies included in this analysis differed notably in design (parallel-group versus cross-over), duration of follow-up (< 1 month versus ~12 months), number of participants (< 200 versus > 3000), and baseline 1-mm ST-segment depression (< 260 s versus > 430 s).

Safety

The main results are summarised in forest plots for ranolazine given as monotherapy compared to placebo (Analysis 1.6, Analysis 2.3) and as add-on therapy compared to placebo (Analysis 3.6). Data from other trials are also reported for ranolazine given as monotherapy compared to placebo for adverse events incidence (Pepine 1999; Thadani 1994) which could not be pooled for meta-analysis due to incompleteness. Similarly, data for ranolazine given as add-on therapy compared to placebo for adverse events incidence (Shammas 2015, Villano 2013) could not be pooled for meta-analysis due to incompleteness. Missing data have been requested from the study contact authors. Although no quantitative analysis could be performed for specific events, it was observed that the most frequently reported events were dizziness, nausea and constipation. 'Other' which included peripheral oedema, headache, asthenia, palpitations, dyspepsia, weakness and postural hypotension, was the most commonly re[ported category.

Adverse events incidence

Serious adverse events

We found insufficient data on serious adverse events to perform quantitative synthesis. Although the included studies reported types of serious adverse events inconsistently, we summarised data into three categories:

1. Cerebrovascular events: Two studies (RIVER-PCI 2016; RWISE 2016) reported data for ranolazine 1000 mg twice daily given as monotherapy compared to placebo. RIVER-PCI 2016 reported 22/1317 and 20/1287 events of stroke and 13/1317 and 3/1287 events of transitory ischaemic attack among participants who received ranolazine and placebo respectively. RWISE 2016 reported 2/128 and 0/128 events of pre-syncope and 1/128 and 0/128 events of syncope among participants who received ranolazine and placebo respectively. Three other studies (ERICA 2006; Shammas 2015; TERISA 2013) reported data for ranolazine 1000 mg twice daily given as add-on therapy compared to placebo. ERICA 2006 reported that there were no events of stroke in any treatment groups. Shammas 2015 reported 1/24 and 0/24 events of stroke among participants given ranolazine and placebo respectively. TERISA 2013 reported 1/470 and 4/474 events of stroke among participants given ranolazine and placebo respectively. Pooling data resulted in RR of 0.56 (95% CI 0.12 to 2.60, 3 studies, 1557 participants, Chi² P = 0.21, I² = 38%).
2. Heart failure: Only RIVER-PCI 2016 reported data for ranolazine 1000 mg twice daily given as monotherapy compared to placebo. RIVER-PCI 2016 reported heart failure events requiring hospitalisation (further classified as ischaemia and non-ischemia-related) in 38/1317 and 25/1287 of participants given ranolazine and placebo respectively.
3. Arrhythmias: None of the included studies reported arrhythmia-related hospitalisations. However two trials reported symptomatic documented arrhythmias for ranolazine 1000 mg twice daily given as monotherapy (MERLIN-TIMI 36 2007) and as add-on therapy (ERICA 2006) compared to placebo. MERLIN-TIMI 36 2007 (stable angina patients subgroup) reported 52/1785 and 52/1775 symptomatic documented arrhythmias among participants given ranolazine and placebo respectively. ERICA 2006 reported 8/281 and 10/284 arrhythmias (ventricular extrasystoles, sinus bradycardias, sinus tachycardias and

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atrioventricular blockages) among participants given ranolazine and placebo respectively. Of note, Shammas 2015 and MERLIN-TIMI 36 2007 conducted separate recordings of arrhythmias over short periods of the total study duration, which we considered did not fit the purposes of this review.

Some other events were labelled as major or serious adverse events in some trials (RIVER-PCI 2016; TERISA 2013) but these were not reported in sufficient detail to determine their suitability to meet the definition for this outcome.

Non-serious adverse events

Two studies reported the incidence of non-serious adverse events for ranolazine 1000 mg twice daily given as monotherapy compared to placebo (MARISA 2004; RWISE 2016). Very low quality evidence showed that participants in both groups were at similar risk of presenting non-serious adverse events (RR 1.33, 95% CI 0.90 to 1.98, 638 participants, Analysis 1.6). There was no heterogeneity (Chi^2 P = 0.79, I^2 = 0%).

RAN080 2005 reported non-fatal AMI incidence for ranolazine given as monotherapy compared to placebo. Very low quality evidence showed that the participants treated with ranolazine were at a higher risk of presenting non-serious adverse events (RR 1.50, 95% CI 1.12 to 2.00, 947 participants, Analysis 2.3). There was no heterogeneity (Chi^2 P = 0.67, I^2 = 0%).

Three studies reported incidence of non-serious adverse events for ranolazine 1000 mg twice daily given as add-on therapy (to adrenergic beta antagonists and calcium channel blockers) compared to placebo (CARISA 2004; ERICA 2006; TERISA 2013). Moderate quality evidence showed that participants treated with ranolazine were at higher risk of presenting non-serious adverse events (RR 1.22, 95% CI 1.06 to 1.40; 3 studies, 2053 participants, Analysis 3.6). There was no heterogeneity (Chi^2 P = 0.68, I^2 = 0%). Two studies reported incidence of non-serious adverse events for ranolazine given as add-on therapy (to adrenergic beta antagonists and calcium channel blockers) compared to placebo (Babalis 2015; Villano 2013). However, since these studies reported no events for each treatment group, individual RRs were not estimable, and could not be pooled with the other studies. Therefore, meta-analysis for these five studies (Babalis 2015; CARISA 2004; ERICA 2006; TERISA 2013. Villano 2013) was not performed.

Subgroup analysis

We performed subgroup analysis for type of stable angina diagnosis. There were insufficient data to conduct other planned subgroup analyses. This subgroup analysis was performed for non-serious adverse events incidence for ranolazine given as monotherapy compared to placebo (Analysis 2.3) and for quality of life for ranolazine given as add-on therapy compared to placebo (Analysis 4.1). The direction and magnitude of the treatment effects for the macrovascular angina subgroups were similar to those of the overall pooled estimates. We observed difference (Chi^2 P = 0.01) in the pooled estimates between subgroups only for quality of life (Analysis 4.1).

Sensitivity analysis

We performed sensitivity analyses to assess the effects of including only studies at low risk of bias, by switching statistical models for data synthesis (fixed-effect to random-effects and vice versa) and changing measures of treatment effects (RRs to ORs, MDs to SMDs and vice versa).

We could not perform sensitivity analysis for change of the measure of treatment effect (MD to SMD) for time to 1-mm ST-segment depression because there were insufficient data to inform calculation. We were unable to conduct sensitivity analysis for restriction to trials with low risk of bias for some outcomes because none of the studies initially included was regarded as having low risk of bias. Such outcomes are: adverse events incidence (for ranolazine given as monotherapy at 1000mg twice daily or any dosage versus placebo) and quality of life (for any dose ranolazine given as monotherapy versus placebo).

Overall, we found no major differences in either the direction or magnitude of treatment effects except for the quality of life outcome for ranolazine 1000 mg twice daily given as add-on therapy versus placebo (Analysis 6.10) or any dose ranolazine given as add-on therapy versus placebo (Analysis 6.15). For these two analyses, the measure of treatment effect became statistically significant after changing the model (random-effects to fixed-effect).

We also performed a sensitivity analysis to assess the effect of including only studies with follow-up duration of at least six weeks. We were unable to conduct this sensitivity analysis for some outcomes because none of the studies initially included reported results from follow-up ≥ 6 weeks (leaving 0 trials for analysis). Such outcomes are: adverse events incidence (for ranolazine given as monotherapy at 1000mg twice daily or any dosage versus placebo), quality of life (for any dose ranolazine given as monotherapy versus placebo) and time to 1-mm ST-segment depression (Microvascular angina subgroup, for any dose ranolazine given as add-on therapy versus placebo).

We found no major differences in either the direction or magnitude of treatment effects except for quality of life with ranolazine 1000 mg monotherapy administered twice daily versus placebo (Analysis 8.2). For this analysis, the measure of treatment effect changed direction from favouring ranolazine to favouring placebo, but remained not statistically significant. We observed that heterogeneity in Analysis 1.4 (2 studies) may be explained by differences in duration of follow-up (1 week versus 643 days). Heterogeneity in Analysis 4.1 (4 studies) was not explained by differences in duration of follow-up.

DISCUSSION

Summary of main results

We included 17 randomised controlled trials (RCTs). We found evidence on the effects of ranolazine compared to placebo given as monotherapy and as add-on therapy for people with stable angina pectoris from 14 RCTs. Three studies did not provide data for quantitative analysis.

For ranolazine given as add-on therapy (Summary of findings for the main comparison), we found no evidence for the effect on cardiovascular and non-cardiovascular mortality. We also found low quality evidence of uncertain effect on all-cause mortality (for ranolazine 1000mg twice daily), moderate quality evidence of uncertain effect on quality of life (for any dose ranolazine), and low quality evidence of uncertain effect on AMI incidence (for

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ranolazine 1000mg twice daily). We assessed moderate quality evidence for reduced frequency of angina episodes with the use of ranolazine 1000mg twice daily. There was moderate quality evidence for increased time to 1-mm ST-segment depression in exercise electrocardiogram (ECG) associated with the use of any dose ranolazine. There was moderate quality evidence of increased risk of non-serious adverse events with the use of ranolazine 1000mg twice daily.

In relation to ranolazine as monotherapy (Summary of findings 2), we found low quality evidence of uncertain effect on cardiovascular mortality (for ranolazine 1000mg twice daily) and no evidence of the effect on non-cardiovascular mortality. We also found low quality evidence of uncertain effect on all-cause mortality (for ranolazine 1000mg twice daily), moderate quality evidence of uncertain effect on quality of life (for ranolazine 1000mg twice daily), low quality evidence of uncertain effect on non-fatal acute myocardial infarction (AMI) incidence (for any dose ranolazine), and frequency of angina episodes (for any dose ranolazine). We found moderate quality evidence of no effect on need for revascularisation procedures (for ranolazine 1000mg twice daily), and very low quality evidence for increased risk of non-serious adverse events (for any dose ranolazine).

Overall, we found evidence of clinical benefit from the use of ranolazine as add-on therapy by reducing the frequency of angina episodes and increasing the time to 1-mm ST-segment depression. However, we found also evidence of clinical harm from the use of ranolazine as either monotherapy or add-on therapy by increasing the risk of non-serious adverse events.

We found evidence on the effects of ranolazine compared to other anti-angina agents (atenolol, ivabradine and trimetazidine) for people with stable angina from three RCTs, but these data were insufficient to perform quantitative synthesis.

We found evidence of differential effect on quality of life for any dose ranolazine given as add-on therapy compared to placebo according to the type of stable angina (macrovascular versus microvascular).

The sensitivity analyses generally showed no major differences in the results we obtained. For any dose ranolazine given as monotherapy, no trials left after restricting to studies with low risk of bias or follow-up ≥ 6 weeks for angina episodes frequency and adverse events incidence. For ranolazine given as add-on therapy, a modest increase in quality of life was obtained with a fixed-effect model (exchange of model for data synthesis).

Overall completeness and applicability of evidence

Several gaps in the evidence remain. Data were available for the primary effectiveness outcome (cardiovascular mortality) from only one study (RIVER-PCI 2016). None of the included studies reported results on the primary safety outcome (non-cardiovascular mortality). Similarly, no data were available for healthcare costs; RIVER-PCI 2016 included a sub study on health economics but results have not yet been published. No data from head-to-head comparisons on ranolazine versus other anti-anginals were available for quantitative synthesis. Only three trials reported data on these later comparisons (ranolazine versus other anti-anginals); all had small population sizes (40 participants to 158 participants). Notably, we found no studies that compared ranolazine with a calcium channel blocker, long-acting nitrate or nicorandil. We therefore present findings for ranolazine compared to placebo only.

Assessment of external validity of our results should consider the following.

1. The included studies varied in several important aspects: (a) ranolazine dosage and type of formulation, (b) the presence of comorbidity (type 2 diabetes mellitus, acute coronary syndrome, incomplete revascularisation); (c) concomitant medication (permitted), with some participant groups labelled as 'monotherapy' actually receiving concomitant anti-anginal drugs at varying proportions; and (d) duration of follow-up ranged from one week to more than two years.
2. The diagnostic criteria for stable angina varied among included studies. Three studies included in the quantitative analysis restricted study populations to people with microvascular angina. Diagnostic criteria roughly fell into either of two categories for the remaining studies: clinical diagnosis (history of exertional angina) and angiographic diagnosis (evidence of macrovascular coronary disease). Studies applying clinical diagnosis enabled enrolment of people with macrovascular and microvascular angina.
3. Taken together, the included studies enrolled participants from multiple sites mainly in North America, Europe and Australia, with less contribution from people in Asia and Africa, and no representation of Central and South American region peoples.

The marked heterogeneity among the included studies regarding the characteristics listed above, along with paucity of data for most planned comparisons and subgroup analyses meant that some components of review questions remain unresolved.

Quality of the evidence

We included data from 14 RCTs (9292 participants) to the 'Summary of findings' tables. Although studies were heterogeneous in individual quality assessments, most shared important characteristics such as a parallel-group (8/14), double-blind design (11/14), macrovascular angina population (6/14), 1000 mg twice daily dosage for ranolazine (10/14) and intention-to-treat analysis approach (9/14, explicitly stated). Fewer than 10% of participants randomised to all studies were lost to follow-up. However, allocation concealment and blinding of study personnel were not described for most studies, rendering unclear risk of bias. Of note, an important part of the evidence in this review came from trials deemed at high risk of bias related to the source of funding and conflicts of interest, since every analysis we report includes at least one trial with that characteristic.

None of the results obtained were deemed to be high quality. Evidence quality was low for the primary outcomes (cardiovascular mortality). In relation to secondary outcomes, evidence quality was lower for ranolazine given as monotherapy than as add-on therapy. This was due in part to the indirectness of the comparison for ranolazine given as monotherapy (a group of participants actually received ranolazine as add-on therapy).

Overall, evidence quality was low for all-cause mortality, moderate for quality of life, low for non-fatal AMI incidence, low to moderate for frequency of angina episodes (low for ranolazine as monotherapy and moderate for ranolazine as add-on therapy) and

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very low to moderate for non-serious adverse events incidence (very low for ranolazine as monotherapy and moderate for ranolazine as add-on therapy).

We downgraded quality of life evidence by one level due to indirectness concerns or substantial heterogeneity. We downgraded evidence quality for non-fatal AMI incidence due to risk of bias concerns (by one level) or imprecision of the estimate (by one or two levels). We downgraded evidence quality for frequency of angina episodes due to risk of bias or indirectness concerns. We also downgraded evidence quality for non-serious adverse events incidence due to risk of bias and indirectness concerns or small number of events.

Potential biases in the review process

The risk of having introduced bias throughout the review process was limited given that study selection, data extraction and assessment of risk of bias were performed by pairs of authors who worked independently to reach consensus. Comprehensive electronic and other resources searches were performed to identify all potentially relevant studies for this review. Nevertheless, there are a number of potential biases in the review process given the presence of some limitations: 1) few additional data were obtained apart from published data; 2) all available data were summarised irrespective of study quality; and 3) insufficient data to perform planned subgroup analyses. We also made some deviations from the published protocol during the review process (see Differences between protocol and review) which we considered to be appropriate and did not change the conclusions of the review.

Agreements and disagreements with other studies or reviews

The available evidence regarding the use of ranolazine in people with stable angina pectoris has been systematically analysed in some studies. Two systematic reviews (Banon 2014; Savarese 2013) studied the effects of ranolazine given as monotherapy or as add-on therapy for people with stable angina. Another systematic review (Belsey 2015) focused on the effects of ranolazine given as add-on therapy for people with stable angina. These reviews focused on exercise ECG parameters (duration, time to angina, time to ST-segment depression). Of these, two also studied weekly frequency of angina attacks and nitroglycerin use (Banon 2014; Savarese 2013). Banon 2014 also assessed quality of life and incidence of adverse events. Although differing in numbers of included studies, these reviews arrived at similar conclusions about the effects of ranolazine compared to placebo for people with stable angina. Results from these reviews show beneficial effect for ranolazine (mainly given as add-on therapy) on quality of life (data not pooled), frequency of angina attacks, exercise ECG parameters and a harmful effect on adverse events incidence.

Our results regarding quality of life showed that ranolazine (either as monotherapy or add-on therapy) had uncertain effects for people with stable angina. In relation to other outcomes, our results show a similar direction and magnitude of treatment effect for ranolazine given as add-on therapy. Notably, our results include data from a greater number of studies, especially for ranolazine given as monotherapy, and data on other relevant outcomes, such as all-cause mortality, AMI incidence, and need for revascularisation procedure.

AUTHORS' CONCLUSIONS

Implications for practice

There was uncertain evidence of the effect from treatment with ranolazine given as monotherapy compared to placebo in people with stable angina pectoris in regard to cardiovascular mortality. Similarly, there was uncertain evidence of the effect from treatment with ranolazine (given either as monotherapy or add-on therapy) compared to placebo in people with stable angina pectoris in regard to all-cause mortality, quality of life and non-fatal AMI incidence. There was also uncertain evidence of the effect from treatment with ranolazine given as monotherapy in regard to the weekly frequency of angina episodes.

There is evidence of clinical benefit from treatment with ranolazine given as add-on therapy compared to placebo in people with stable angina pectoris in regard to the weekly frequency of anginal episodes.

There is evidence of clinical harm from ranolazine treatment (either as monotherapy or add-on therapy) compared to placebo in people with stable angina pectoris in regard to non-serious adverse events incidence.

There was insufficient evidence of clinical benefit or harm from ranolazine treatment compared to placebo in people with stable angina pectoris in regard to non-cardiovascular mortality and healthcare costs. Similarly, there was limited evidence of clinical benefit or harm from treatment with ranolazine compared to other anti-anginals.

Implications for research

Future RCTs should consider aiming to:

- Further determine the effectiveness and safety of ranolazine compared to first-line anti-anginals, particularly calcium channel blockers, and other second-line anti-anginals in a population of people with stable angina pectoris.
- Further determine differences in the effect of ranolazine in subgroups of people with stable angina pectoris with macrovascular and microvascular angina.
- Provide more long-term data (beyond two years) on mortality, quality of life, acute myocardial infarction incidence, need for revascularisation procedures and cost-effectiveness of treatment with ranolazine in people with stable angina pectoris.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Babalis 2015

Methods	Study design: parallel-group trial

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Babalis 2015 *(Continued)*

	Total study duration: 3 months Duration of follow-up: no follow-up beyond treatment phase Method of randomisation: not described Method of concealment of allocation: not mentioned Blinding: not mentioned Power calculation: not mentioned Phases of the study: 1 (treatment phase) Number of patients randomised: 40 (20/20 for placebo/ranolazine group) Exclusions post-randomisation: not reported Withdrawals (and reasons): not reported
Participants	Total number: 40 Country of enrolment: Greece Setting/location: not specified Diagnostic criteria (stable angina pectoris): symptoms of stable angina and coronary artery disease (CAD) established by coronary stenosis > 70% in one or more vessels documented by angiography (macrovascular angina) Comorbidities: none (non suitability for invasive treatment) Age (mean): 69 ± 7 years Gender (male %): 75% Inclusion criteria: • Adult patient • Symptomatic stable angina despite optimised anti-anginal treatment, not suitable for further invasive treatment • Coronary disease (coronary stenosis > 70% in one or more vessels, as documented by angiography) Exclusion criteria: • Severe ischaemic heart failure (New York Heart Association class [NYHA] III or IV) • Unstable angina • Recent (< 1 month) myocardial infarction • Ongoing treatment with drugs that might prolong the QT interval on the ECG
Interventions	Number of intervention groups: 2 Concomitant medications: optimised anti-anginal treatment (not further specified) Excluded medications: none **Placebo group** Intervention: placebo Duration of intervention: 3 months **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 500 mg twice daily

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Babalis 2015 *(Continued)*

	Duration of intervention: 3 months
Outcomes	Total number of outcomes: 1 • According to study protocol: no published protocol; according to the "Patients and Methods" section: 3 (exercise treadmill test (ETT) measurements, left ventricular (LV) function measurements, safety evaluations) • Reported: 2 (results for ETT measurements were not reported) **OUTCOMES** **Adverse events incidence** • Outcome definition: events related to medications • Method and unit of measurement: number of patients • Time points reported: 3 months **RESULTS** **Adverse events incidence** • Sample size: 40 (intention-to-treat analysis) • Missing participants: none • Summary data: 0/20-0/20 for Placebo group-Ranolazine group (type of analysis not specified) • Subgroup analyses: not performed
Notes	Relevant observations for the data provided before: It is worth mentioning that two ranolazine group participants and four placebo group participants were not eligible for revascularisation because of complicated coronary anatomy or lack of grafts Source of funding: not stated Notable conflicts of interest: the authors declare that they have no conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation is stated but described only as "in a 1:1 ratio"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusion or withdrawal is reported, it is stated that no patient withdrew from the study because of ranolazine-related adverse reactions. We assume that all patients completed the study
Selective reporting (reporting bias)	Unclear risk	There is no published protocol. Exercise capacity and duration and time to appearance of angina results were not reported in spite they were mentioned among the study benchmarks

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Babalis 2015 *(Continued)*

Other bias	Unclear risk	The authors declare that they have no conflict of interest. However, the source of funding is not stated. Furthermore, editorial assistance for the preparation of the manuscript was provided by Luca Giacomelli, PhD, on behalf of Content Ed Net; this assistance was funded by Menarini International, an Italian pharmaceutical company.

CARISA 2004

Methods	Study design: parallel-group trial Total study duration: 14 weeks plus follow-up (around 14 months). Patients were enrolled from July 1999 to August 2001 Duration of follow-up: from August 2001 to 31 October 2002 Method of randomisation: randomisation schedules generated by Quintiles (UK) Limited in SAS version 6.12, stratified by the 3 background anti-anginal therapies using a block size of 6 Method of concealment of allocation: drug packaging with code break envelopes provided by Brecon Pharmaceuticals Ltd. Blinding: double-blind, not described but presumably referred to participants and study personnel Power calculation: 90% to detect a difference of 30s in the primary end point Phases of the study: 3 (qualifying phase, treatment phase, open-label follow-up phase) Number of patients randomised: 823 (269/279/275 for placebo/ranolazine 750 mg/ranolazine 1000 mg group) Exclusions post-randomisation (for each phase): Qualifying phase: 32 (11/7/14 from placebo/ranolazine 750 mg/ranolazine 1000 mg group). Treatment phase: 54 (14/18/22 from placebo/ranolazine 750 mg/ranolazine 1000 mg group) Withdrawals (and reasons): not reported (excluded patients were reported only as "dropped out")
Participants	Total number: 823 Country of enrolment: 15 (Canada, Czech Republic, Georgia, Greece, Ireland, Israel, Italy, New Zealand, Poland, Romania, Russia, Spain, United Kingdom, United States) Setting/location: ambulatory outpatient Diagnostic criteria (stable angina pectoris): minimum 3 month history of exertional angina with CAD confirmed by angiography, documented prior myocardial infarction, or a diagnostic stress myocardial imaging study (macrovascular angina) Comorbidities: none Age (mean, SD): 63.7(8.9)/64.3(9.3)/63.9(9.3) for placebo/ranolazine 750 mg/ranolazine 1000 mg group Gender (male %): 75.1/77.8/79.6 for placebo/ranolazine 750 mg/ranolazine 1000 mg group Inclusion criteria: • Minimum 3-month history of exertional angina • Coronary artery disease • Reproducible angina on exercise treadmill test while receiving required background anti-anginal treatment Exclusion criteria:

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CARISA 2004 *(Continued)*

- Factors that precluded satisfactory interpretation of the ECG
- Class III or IV heart failure
- Acute coronary syndrome or coronary revascularisation procedure within the prior two months

Interventions	Number of intervention groups: 3 Concomitant medications: background anti-anginal treatment (atenolol 50 mg once daily, diltiazem 180 mg once daily, or amlodipine 5m g once daily) Excluded medications: none **Placebo group** Intervention: placebo twice daily Duration of intervention: 12 weeks **Ranolazine 750 mg group** Intervention: ranolazine ER 750 mg twice daily Duration of intervention: 12 weeks **Ranolazine 1000 mg group** Intervention: ranolazine ER 1000 mg twice daily Duration of intervention: 12 weeks
Outcomes	Total number of outcomes: • According to study protocol: no published protocol; according to the "Methods" section: 9 (exercise duration at through levels, exercise duration at peak levels, time to angina at peak and trough levels, time to 1-mm ST segment depression at peak and through levels, frequency of angina attacks, frequency of nitroglycerin use, drug tolerability and safety) • Reported: 11 (including heart rate and blood pressure, mortality deemed to be part of the safety outcome) **All-cause mortality** Outcome definition: number of deaths Method and unit of measurement: absolute frequency, survival rate Time points reported: 12 weeks (plus the 14-day safety follow-up), 17 months (including follow-up phase) **Angina episodes frequency** • Outcome definition: average angina attacks per week • Method and unit of measurement: number per week • Time points reported: 12 weeks **Adverse events incidence** • Outcome definition: not described • Method and unit of measurement: percentage • Time points reported: 12 weeks **RESULTS** **All-cause mortality** • Sample size: 823 (intention-to-treat analysis), 750 (open-label follow-up phase)

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CARISA 2004 *(Continued)*

- Missing participants: none
- Summary data: 3/269-2/279-1/275 for placebo-ranolazine 750 mg ranolazine 1000 mg group. Survival rates are reported for the open-label long-term follow-up phase
- Subgroup analyses: not performed

Angina episodes frequency

- Sample size: 791 (intention-to-treat analysis)
- Missing participants: 32 (exclusion post-randomisation during the qualifying phase)
- Summary data: mean (SE) 3.3(0.3) / 2.5(0.2) / 2.1 (0.2) for placebo/ranolazine 750 mg/ranolazine 1000 mg group
- Subgroup analyses: not performed

Adverse events incidence

- Sample size: 823 (intention-to-treat analysis)
- Missing participants: none
- Summary data: 26.4%/31.2%/32.7% for placebo/ranolazine 750 mg/ranolazine 1000 mg group. The most common dose-related adverse effects were constipation, dizziness, nausea and asthenia (≤ 7.3% in both ranolazine groups; ≥ 0.7% in the placebo group)
- Subgroup analyses: not performed

Notes

Relevant observations for the data provided before: none

Source of funding: CV Therapeutics Inc.

Notable conflicts of interest: six of the authors have financial relationships with CV Therapeutics

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence. Randomisation schedules generated by Quintiles (UK) Limited in SAS version 6.12, stratified by the 3 background anti-anginal therapies using a block size of 6
Allocation concealment (selection bias)	Low risk	Drug packaging with code break envelopes made by Brecon Pharmaceuticals Ltd. The medication assignment was provided to the principal investigator in a sealed envelope.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment phase is declared to be double-blinded, but no description is provided. Drug packages were made with code break envelopes and provided to the clinical units, so patients and personnel were not aware of the treatment assigned.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Exercise treadmill test ECGs were interpreted by a core EGC laboratory blinded to treatment assignment using customised software. Although this is stated only for the single-blind qualifying phase, we assume it also applies for the double-blind treatment phase. However, for outcomes such as all-cause mortality, angina frequency and adverse events incidence blinding measures have not been described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of patients dropped out during the qualifying and treatment phases are reported, but reasons and explanations are not provided
Selective reporting (reporting bias)	Unclear risk	There is no published protocol. Results for all the outcomes stated in the "Methods" section of the paper are reported, but results for some additional outcomes (haemodynamics) are also reported.

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CARISA 2004 *(Continued)*

Other bias	High risk	The study was supported by CV Therapeutics Inc. Furthermore, six of the authors have financial relationships with CV Therapeutics.

ERICA 2006

Methods	Study design: parallel-group trial Total study duration: 9 weeks; recruitment from July 30, 2004 to February 16, 2005 Duration of follow-up: no follow-up beyond treatment phase Method of randomisation: randomisation in a 1:1 ratio, centralised and not stratified by centre Method of concealment of allocation: not mentioned Blinding: double-blind, not described Power calculation: not mentioned Phases of the study: 2 (qualifying phase, treatment phase), treatment phase made up by 1-week run-in phase and 6-week full-dose treatment phase Number of patients randomised: 565 (284/281 for placebo/ranolazine group) Exclusions post-randomisation: run-in phase: 1 withdrawal before study drug treatment (placebo group), 3 exclusions from placebo group because not beginning full-dose treatment phase, 4 exclusions from ranolazine group, 1 because not beginning full-dose treatment phase, 3 because not having any diary data in the full-dose treatment phase Withdrawals (and reasons): ranolazine group (3 adverse events, 1 death, 3 withdrew consent), placebo group (5 adverse events (4 according to the text), 1 death)
Participants	Total number: 564 Country of enrolment: Eastern Europe, United States, Canada Setting/location: not specified Diagnostic criteria (stable angina pectoris): history of chronic stable angina ≥3 months, documented history of CAD (macrovascular angina) Comorbidities: none Age (mean ± SD): 61.3±9.0 / 62.0±8.7 for placebo / ranolazine group Gender (male %): 73% / 72% for placebo / ranolazine group Inclusion criteria: • Age ≥ 18 years • Chronic stable angina ≥ 3 months, and ≥ 3 episodes of angina per week during a ≥2-week qualification period despite treatment with 10 mg/day amlodipine • Documented history of CAD (angiographic evidence of ≥ 60% stenosis of at least 1 major coronary artery, history of previous myocardial infarction and/or a stress-induced reversible perfusion defect identified by radionuclide or echocardiographic imaging) Exclusion criteria: • NYHA functional class IV congestive heart failure • History of myocardial infarction or unstable angina within the previous 2 months • Active acute myocarditis, pericarditis, hypertrophic cardiomyopathy, or uncontrolled hypertension

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ERICA 2006 *(Continued)*

- History of torsades de pointes
- Receiving agents known to prolong the QTc interval
- QTc interval measurement > 500 ms at study entry
- Clinically significant hepatic disease, creatinine clearance < 30 mL/min, or chronic illness likely to interfere with protocol compliance

Interventions	Number of intervention groups: 2 Concomitant medications: amlodipine 10 mg/day; LANs and sublingual nitroglycerin as required Excluded medications: inhibitors of cytochrome P450-3A4, digitalis preparation, perhexiline, trimetazidine, beta-blockers, calcium cannel blockers other than amlodipine **Placebo group** • Intervention: placebo • Duration of intervention: 6 weeks (full-dose treatment phase) **Ranolazine group** • Intervention: ranolazine ER 1000 mg twice daily • Duration of intervention: 6 weeks (full-dose treatment phase)
Outcomes	Total number of outcomes: • According to study protocol: no published protocol (registered data in clinicaltrials.gov is not available any more); according to the "Methods" section: 7 (average weekly frequency of self-reported angina episodes, average weekly nitroglycerin consumption, change from baseline of the 5 dimensions of the Seattle Angina Questionnaire (SAQ), reported adverse events, haemodynamics, routine clinical laboratory measures, 12-lead electrocardiograms) • Reported: 7 **All-cause mortality** • Outcome definition: number of deaths • Method and unit of measurement: absolute frequency • Time points reported: 9 weeks **Quality of life** • Outcome definition: change from baseline of the 5 dimensions of the Seattle Angina Questionnaire (SAQ), reported separately • Upper and lower limits and whether a high or low score is good: each dimension (anginal frequency, physical limitation, anginal stability, disease perception, and treatment satisfaction) was scored on a scale of 0 to 100 • Method and unit of measurement: score difference • Time points reported: 6 weeks **Acute myocardial infarction incidence (fatal and non-fatal)** • Outcome definition: not described • Method and unit of measurement: percentage • Time points reported: 9 weeks **Angina episodes frequency** • Outcome definition: average weekly angina episodes frequency • Method and unit of measurement: number per week • Time points reported: 6 weeks **Adverse events incidence**

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ERICA 2006 *(Continued)*

- Outcome definition: number of patients that reported any adverse event
- Method and unit of measurement: percentage
- Time points reported: 9 weeks

RESULTS

All-cause mortality

- Sample size: 565 (Intention-to-treat analysis)
- Missing participants: none
- Summary data: 1/284-1/281 for placebo-ranolazine group
- Subgroup analyses: not performed

Quality of life

- Sample size: 558 (Intention-to-treat analysis)
- Missing participants: 7 (3 from placebo group, 4 from ranolazine group)
- Summary data: SAQ dimension 1 (anginal frequency) 22.5 ± 19.0/18.5 ± 18.8 for ranolazine/placebo group
- Subgroup analyses: significant improvement of SAQ anginal frequency only for patients with baseline angina frequency > 4.5 per week

Acute myocardial infarction incidence (fatal and non-fatal)

- Sample size: 565 (Intention-to-treat analysis)
- Missing participants: none
- Summary data: 0.7%/0.4% for placebo/ranolazine group
- Subgroup analyses: not performed

Angina episodes frequency

- Sample size: 558 (intention-to-treat analysis)
- Missing participants: 7 (3 from placebo group, 4 from ranolazine group)
- Summary data: arithmetic means ± SE: 4.3 ± 0.64/3.29 ± 0.26 for placebo/ranolazine group; trimmed means ± SE: 3.31 ± 0.22/2.88 ± 0.19 for placebo/ranolazine group
- Subgroup analyses: significant reductions of angina frequency for patients with baseline angina frequency > 4.5 per week and for ≤ 4.5 per week

Adverse events incidence

- Sample size: 565 (Intention-to-treat analysis)
- Missing participants: none
- Summary data: 35.3%/39.9% for placebo/ranolazine group. The most frequently reported adverse events in the ranolazine group were constipation (25/281), peripheral edema (16/281), dizziness (11/281), nausea (8/281) and headache (8/281); in the placebo group were peripheral edema (8/284), dizziness (7/284), headache (7/284), constipation (5/284) and nausea (2/284).
- Subgroup analyses: performed for the following variables: long acting nitrates (LAN) user state, gender, age

Notes

Relevant observations for the data provided before: given that 4 placebo patients and 3 ranolazine patients discontinued the study because of adverse events but 5 placebo patients are reported not to have terminated the trial because of adverse events and 3 more ranolazine patients are reported not to have terminated the trial because of withdrawing consent, it is not clear which patients were finally included in the efficacy analysis

Source of funding: CV Therapeutics

Notable conflicts of interest: all the authors have received some kind of reward or support for participating in this trial from several pharmaceutical companies

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ERICA 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation is stated but described only as "in a 1:1 ratio, centralized but not stratified"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Treatment phase is declared to be double-blinded, but not description is provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Treatment phase is declared to be double-blinded, but not description is provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patients who did not complete the trial are described clearly, however, there is an inconsistency in the data provided for terminating patients in the placebo group for only one case and it is not clear which patients were finally included in the efficacy analysis
Selective reporting (reporting bias)	Unclear risk	There is no published protocol. Results for all the outcomes mentioned in the "Methods" section of the paper are reported
Other bias	High risk	The study was supported by CV Therapeutics Inc. All the authors have received some kind of reward or support for participating in this trial from several pharmaceutical companies

MARISA 2004

Methods	Study design: cross-over trial Total study duration: 6 weeks plus follow-up, the study began in December 1997 and ended in May 1999 Duration of follow-up: about 2 years; to October 15, 2001 Method of randomisation: not described Method of concealment of allocation: not mentioned Blinding: double-blind, not described Power calculation: not mentioned Phases of the study: 3 (qualifying phase, treatment phase, open-label follow-up phase) Number of patients randomised: 191 Exclusions post-randomisation: 16 (treatment phase, those who did not complete at least three treatment periods) Withdrawals (and reasons): 23 patients (12%) discontinued the study before completing all treatment periods: 15 patients (7.9%) for adverse events, 4 patients (2.1%) by elective withdrawal, 2 patients

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MARISA 2004 *(Continued)*

	(1.0%) for other reasons, 1 patient (< 1%) because of death and 1 patient (< 1%) because of inappropriate enrolment
Participants	Total number: 191 Country of enrolment: 4 (Canada, Czech Republic, Poland, United States) Setting/location: not specified Diagnostic criteria (stable angina pectoris): at least a three-month history of effort angina responding to beta-blockers, calcium channel blockers and/or long-acting nitrates with well-documented CAD (macrovascular angina) Comorbidities: none Age (mean ± SD): 64.3 ± 9.4 years Gender (male %): 73.3% Inclusion criteria: • Patients were at least 21 years of age • Well-documented coronary artery disease • At least a three-month history of effort angina responding to beta-blockers, calcium channel blockers, and/or long-acting nitrates • All patients discontinued anti-anginal treatment during the study (except sublingual nitroglycerin as needed) and provided written informed consent Exclusion criteria: • Conditions that might compromise electrocardiogram (ECG) or ETT interpretation (e.g. treatment with digoxin, 1 mm ST-segment depression at rest, left bundle branch block, pacemaker rhythm) • New York Heart Association functional class III or IV congestive heart failure • Unstable angina • Myocardial infarction • Any coronary revascularisation procedure within two months of enrolment • Corrected QT interval (QTc) > 500 ms or any medication known to prolong the QTc interval • Requirement for medication or food known to affect metabolism by cytochrome P450 3A4
Interventions	Number of intervention groups: 4 Concomitant medications: sublingual nitroglycerin Excluded medications: anti-anginal treatment except sublingual nitroglycerin **Placebo group** Intervention: placebo twice daily Duration of intervention: 1 week **Ranolazine 500 mg group** Intervention: ranolazine SR 500 mg twice daily Duration of intervention: 1 week **Ranolazine 1000 mg group** Intervention: ranolazine SR 1000 mg twice daily Duration of intervention: 1 week

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MARISA 2004 *(Continued)*

	Ranolazine 1500 mg group Intervention: ranolazine SR 1500 mg twice daily Duration of intervention: 1 week
Outcomes	Total number of outcomes: • According to study protocol: no published protocol; according to the "Methods" section: 10 (ETT duration (through and peak), ETT time to onset of angina (through and peak), ETT time to 1mm ST-segment depression (through and peak), haemodynamics (through and peak), laboratory, safety evaluations) • Reported: 10 **Adverse events incidence** Outcome definition: number of patients who report any adverse event Method and unit of measurement: percentage Time points reported: 1 week **RESULTS** **Adverse events incidence** Sample size: 191 (intention-to-treat analysis) Missing participants: none Summary data: 15.6%/16.0%/21.7%/34.2% for placebo/ranolazine 500 mg/ranolazine 1000 mg/ranolazine 1500 mg group. Over a total of 191 participants, the adverse events most frequently reported were dizziness (2/2/10/23), nausea (0/1/2/16), asthenia (4/0/3/12), constipation (0/0/3/8), angina (10/10/3/6), headache (4/1/2/5) and sweating (0/0/0/5) for placebo/ranolazine 500 mg/ranolazine 1000 mg/ranolazine 1500 mg group. Subgroup analyses: not performed
Notes	Relevant observations for the data provided before: none Source of funding: CV Therapeutics Notable conflicts of interest: three of the authors have financial relationships with CV Therapeutics

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation is stated but not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study is declared to be double-blinded, but no description is provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Exercise treadmill test ECGs were interpreted by a core EGC laboratory blinded to treatment assignment using customised software. However, for outcomes such as adverse events incidence, blinding measures have not been described

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MARISA 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Patients who did not complete the trial are described, but the treatment they were receiving is not specified
Selective reporting (reporting bias)	Unclear risk	There is no published protocol. Results for all the outcomes stated in the "Methods" section of the paper are reported
Other bias	High risk	The study was supported by CV Therapeutics. Three of the authors have financial relationships with CV Therapeutics

Mehta 2011

Methods	Study design: cross-over trial Total study duration: 10 weeks plus up to 24 months of qualifying phase Duration of follow-up: no follow-up beyond treatment phase Method of randomisation: not described Method of concealment of allocation: not mentioned Blinding: double-blind, not described Power calculation: not mentioned Phases of the study: 2 (qualifying phase, treatment phase) Number of patients randomised: 20 Exclusions post-randomisation: not reported Withdrawals (and reasons): not reported
Participants	Total number: 20 Country of enrolment: United States Setting/location: not specified Diagnostic criteria (stable angina pectoris): chest pain and abnormal routine stress testing without obstructive CAD (< 50% epicardial coronary stenosis in all epicardial coronary arteries) on clinically indicated coronary angiography (microvascular angina) Comorbidities: none Age (mean): 57 ± 11 years Gender (male %): 0% Inclusion criteria: • Women with signs and symptoms of myocardial ischaemia (chest pain and abnormal routine stress testing) • No obstructive CAD (< 50% epicardial coronary stenosis in all epicardial coronary arteries) on clinically indicated coronary angiography • Abnormal adenosine stress CMR (≥ 10% ischaemic myocardium) within the previous 12 months Exclusion criteria:

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Mehta 2011 *(Continued)*

- Contraindications to withholding nitrates, calcium channel agents, and alpha and beta-adrenergic blockers for 24 hours before testing
- Contraindications to CMR including implantable cardioverter-defibrillators, pacemakers, and severe claustrophobia
- Hepatic insufficiency, prolonged QT, renal failure
- Use of drugs that inhibit CYP3A such as diltiazem, verapamil, ketoconazole, macrolides, and HIV protease inhibitors
- Women younger than 18 years of age, pregnant, or breastfeeding
- Taking drugs that prolong the QT interval
- Life expectancy < 6 months

Interventions	Number of intervention groups: 2 Concomitant medications: usual anti-anginal medication Excluded medications: none (apart from those mentioned in the exclusion criteria) **Placebo group** Intervention: placebo twice daily Duration of intervention: 4 weeks (plus 2 weeks of washout) **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 500/1000 mg twice daily (the dose was increased from 500 mg to 1000 mg twice daily during the second half of treatment period if tolerated) Duration of intervention: 4 weeks (plus 2 weeks of washout)
Outcomes	Total number of outcomes: • According to study protocol (published in clinicaltrials.gov): 3 (quality of life assessed by the Seattle Angina Questionnaire -SAQ and Duke Activity Status Index-DASI; cardiac magnetic resonance (CMR) studies) • Reported: 3 **Quality of life** **1. Seattle Angina Questionnaire (SAQ)** Outcome definition: score in the 5 sub-scales, reported separately (For scales) upper and lower limits and whether a high or low score is good: higher scores are better, upper and lower limits are not described Method and unit of measurement: score Time points reported: 4 weeks **2. Duke Activity Status Index (DASI)** Outcome definition: functional capacity scale, not further described (For scales) upper and lower limits and whether a high or low score is good: not described Method and unit of measurement: score Time points reported: 4 weeks **RESULTS** **Quality of life**

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Mehta 2011 *(Continued)*

	1. Seattle Angina Questionnaire (SAQ) Sample size: 47 (intention-to-treat analysis) Missing participants: none Summary data: reported as mean (minimum, maximum) i) Physical functioning: 83.3 (66.6, 97.2) /91.7 (79.2, 97.9) for placebo/ranolazine group; ii) Angina stability: 50.0 (25.0, 75.0)/75.0 (50.0, 100.0) for placebo/ranolazine group; iii) angina frequency: 75.0 (60.0, 87.5)/80.0 (50.0, 100.0) for placebo/ranolazine group; iv) Treatment satisfaction: 93.8 (75.0, 100.0)/87.5 (75.0, 100.0) for placebo/ranolazine group v) Quality of life: 66.7 (58.3, 75.0)/75.0 (60.4, 83.3) for placebo/ranolazine group Subgroup analyses: not performed **2. Duke Activity Status Index (DASI)** Sample size: 20 (intention-to-treat analysis) Missing participants: none Summary data: 8.9 (5.4 minimum, 12.1 maximum) METS / 8.6 (3.7 minimum, 11.5 maximum) METS for placebo/ranolazine group Subgroup analyses: not performed
Notes	Relevant observations for the data provided before: details about the qualifying phase are not provided Source of funding: grants and contracts from several public and private organisations in the United States. Notable conflicts of interest: the authors reported they have no relationships to disclose.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation is stated, but no description is provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study is declared to be double-blinded. Participants and investigators.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Cardiac magnetic resonance imaging outcomes were measured by readers blinded to treatment assignment. However, for outcomes such as quality of life, blinding measures have not been described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study.
Selective reporting (reporting bias)	Low risk	There is published protocol in clinical trials. Results for all the outcomes stated in the "Methods" section of the paper are reported.

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Mehta 2011 *(Continued)*

Other bias	Unclear risk	The study received grants and contracts from several public and private organisations in the United States. The authors reported they have no relationships to disclose.

MERLIN-TIMI 36 2007

Methods	Study design: parallel-group trial Total study duration: mean of 350 days Duration of follow-up: no follow-up beyond treatment phase Method of randomisation: via a central computerised telephone system with stratification by the responsible physician's intended management strategy (early invasive versus conservative) Method of concealment of allocation: not mentioned Blinding: double-blind, not described Power calculation: 90% to detect a significant difference between treatment groups at 2-sided 5% significance level Phases of the study: 1, treatment phase Number of patients randomised: 6560 in the original trial, 3565 in the sub-study on stable angina patients (1789/1776 for ranolazine/placebo group) Exclusions post-randomisation: 5 lost to follow-up Withdrawals (and reasons): 8.1%/4.1% discontinued ranolazine due to an adverse event in ranolazine/placebo group
Participants	Total number: 3565 Country of enrolment: 17 (Australia, France, Germany, Poland, United Kingdom, United States, Spain, Israel, Austria, Switzerland, Italy, The Netherlands, South Africa, Hungary, Czech Republic, Canada, Belgium) Setting/location: hospitalisation Diagnostic criteria (stable angina pectoris): history of prior stable angina before and separate from the presenting ACS Comorbidities: Acute coronary syndrome: clinical presentation consistent with an ACS with at least 1 indicator of moderate to high risk of death or recurrent ischaemic events Age (mean (25th, 75th)): 65 (57,73)/66 (56/73) for ranolazine/placebo group Gender (male %): 1149/1789(64.2%)-1083/1776(61.0%) for ranolazine-placebo group Inclusion criteria: • Aged ≥ 18 years • Hospitalised with NSTE-ACS defined as chest discomfort or anginal equivalent occurring at rest, lasting ≥ 10 min and consistent with myocardial ischaemia • Presence of ischaemic symptoms (≥ 5 minutes) at rest within 48 hours of enrolment (may include index episode) • At least one indicator of moderate to high risk (elevated cardiac troponin or CK-MB, ST depression ≥ 0.1 mV, diabetes mellitus, TIMI risk score for UA/NSTEMI ≥ 3) • Willing and able to provide written informed consent

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MERLIN-TIMI 36 2007 *(Continued)*

	Exclusion criteria: • Persistent (> 20 minutes) acute ST-segment elevation ≥ 0.1 mV in ≥ 2 continuous leads • Successful revascularisation of the culprit stenosis during qualifying hospitalisation before randomisation • Acute pulmonary edema requiring endotracheal intubation, sustained systolic blood pressure < 90 mm Hg, or evidence of cardiogenic shock • Left bundle branch block, electronic pacemaker, or left ventricular hypertrophy with severe repolarisation abnormality that would interfere with the interpretation of the Holter • Pregnant or lactating women • Use at randomisation of agents that are strong inhibitors of cytochrome P450 pathway isoform 3A4 • Need for ongoing or anticipated need for chronic treatment during the study period with any of the following agents that might interfere with the evaluation of the therapeutic response or safety of the study drug: agents known to prolong the QT interval, any digitalis preparation • Clinically significant hepatic disease • End-stage kidney disease requiring dialysis • Participation in another trial of an investigational drug or device within 30d (or longer as per local requirements) or treatment with ranolazine or previous participation in MERLIN • Inability to comply with the protocol and follow-up visits • Any serious medical comorbidity such the patients life expectancy is < 12 months • Any condition that might increase the risk to the patient or decrease the chance of obtaining satisfactory data to achieve the objectives of the study
Interventions	Number of intervention groups: 2 Concomitant medications: intravenous ranolazine 12 hours to 96 hours before intervention Excluded medications: none (apart from those mentioned in the exclusion criteria) **Placebo group** Intervention: placebo twice daily Duration of intervention: mean of 350 days **Ranolazine group** Intervention: ranolazine ER 1000 mg twice daily (500 mg twice daily for renal insufficiency patients) Duration of intervention: mean of 350 days
Outcomes	Total number of outcomes: • According to study protocol: 7 (composite of cardiovascular (CV) death, myocardial infarction (MI) and recurrent ischaemia, rate of major cardiovascular events (composite of CV death, MI and severe recurrent ischaemia), rate of failure of therapy (composite of CV death, MI, recurrent ischaemia, positive Holter for ischaemia, hospitalisation for new/worsening heart failure, or early positive ETT), rate of CV death, MI, severe recurrent ischaemia or positive Holter for ischaemia through 30 days, quality of life at 4 months, duration of exercise on ETT at 8 months, total duration of ischaemia on Holter monitoring between randomisation and 72 h, death from any cause, composite of death from any cause or any cardiovascular hospitalisation, frequency of symptomatic documented arrhythmia, frequency of clinically significant arrhythmias detected during protocol-related Holter monitoring, serious adverse events related to study drug and clinically significant laboratory abnormalities) • Reported: 6 (composite of cardiovascular death, myocardial infarction, or recurrent ischaemia; worsening angina; need for an increase of anti-anginal therapy; exercise duration on ETT; Holted-detected arrhythmias; adverse events) **All-cause mortality** Outcome definition: number of deaths

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MERLIN-TIMI 36 2007 *(Continued)*

Method and unit of measurement: absolute frequency

Time points reported: overall study duration (mean of 350 days)

RESULTS

All-cause mortality

Sample size: 3560 (1785 + 1775) (intention-to-treat analysis)

Missing participants: 5

Summary data: 114/1775 - 111/1785 for placebo-ranolazine group

Subgroup analyses: not performed

Adverse events

The most common adverse effects that were more frequent in the ranolazine group compared with placebo were dizziness (12.4% versus 7.4%), nausea (9.7% versus 6.1%) and constipation (8.5% versus 3,3%).

Notes

Relevant observations for the data provided before: sub-study of the MERLIN TIMI 36 trial not considered in the protocol

Source of funding: CV Therapeutics (CVT), Inc.

Notable conflicts of interest: five of the authors have financial relationships with CVT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Via a central computerised telephone system
Allocation concealment (selection bias)	Low risk	Not mentioned. However, given the use of a centralised telephone system for randomization (and allocation), it can be assumed that study personnel was blinded until the moment of assignment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study is declared to be double-blinded, but no description is provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All elements of the primary composite and major secondary efficacy end points as well as hospitalisation for new or worsening heart failure were adjudicated by members of a Clinical Events Committee blinded to treatment allocation. Exercise treadmill test results were also interpreted by a core laboratory blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Patients who did not complete the trial are described, but the treatment they were receiving or the reasons for withdrawal are not specified
Selective reporting (reporting bias)	High risk	This sub-study of the MERLIN TIMI 36 trial included in this review was not prespecified in the published protocol. Furthermore, results for some outcomes (laboratory abnormalities) included in the protocol are not reported in the paper while results for some other outcomes (worsening angina, need for an increase of anti-anginal therapy) not mentioned in the protocol are reported in the paper.

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MERLIN-TIMI 36 2007 *(Continued)*

Other bias	High risk	The study was supported by CV Therapeutics (CVT), Inc. Five of the authors have financial relationships with CVT

Pelliccia 2012

Methods	Study design: parallel-group trial Total study duration: 37 days Duration of follow-up: 30 days Method of randomisation: not described Method of concealment of allocation: not mentioned Blinding: double-blind, not described Power calculation: not mentioned Phases of the study: 2 (treatment phase, 30-day follow-up phase) Number of patients randomised: 70 (35/35 for placebo/ranolazine group) Exclusions post-randomisation: not reported Withdrawals (and reasons): not reported
Participants	Total number: 70 Country of enrolment: Italy Setting/location: not specified Diagnostic criteria (stable angina pectoris): typical stable effort angina with positive stress test, with indication for PCI Comorbidities: none Age (mean ± SD): 60 ± 18/64 ± 17 for placebo/ranolazine group Gender (male %): 57%/63% for placebo/ranolazine group Inclusion criteria: • Presence of typical stable effort angina • Positive stress test (exercise stress test, stress myocardial scintigraphy, or dobutamine stress echocardiography) • Indication for PCI Exclusion criteria: • Acute myocardial infarction (< 3 months) • Unstable angina • Any increase in CK-MB, troponin I, or myoglobin above ULN at the time of randomisation • Any increase in liver enzymes • Left ventricular ejection fraction < 40% • Renal failure with estimated glomerular filtration rate < 60 mL/min per 1.73 m^2 • History of liver or muscle disease
Interventions	Number of intervention groups: 2

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Pelliccia 2012 *(Continued)*

Concomitant medications: aspirin 100 mg/d, loading dose of clopidogrel 600 mg or ticlopidine 250 mg bid (before the procedure), and clopidogrel 75 mg/d or ticlopidine 250 mg bid for 1 or 12 months. Other medications such as β-blockers, calcium antagonists, statins, and angiotensin-converting enzyme inhibitors given as appropriate

Excluded medications: none

Placebo group

Intervention: placebo as pretreatment for PCI

Duration of intervention: 1 week

Ranolazine group

Intervention: ranolazine (type of formulation not specified) 1000 mg twice daily as pretreatment for PCI

Duration of intervention: 1 week

Outcomes

Total number of outcomes:

- According to study protocol: no published protocol; according to the "Methods" section: 2 (periprocedural myocardial infarction, incidence of MACE by 30 days (death, myocardial infarction, target-vessel revascularisation))
- Reported: 2

All-cause mortality

Outcome definition: number of deaths

Method and unit of measurement: absolute frequency

Time points reported: 37 days

Acute myocardial infarction incidence (fatal and non-fatal)

Outcome definition: (periprocedural) postprocedural increase of CK-MB ≥ 3 times above the upper limit of normal, number of cases

Method and unit of measurement: absolute frequency

Time points reported: 7 days (periprocedural), 37 days (periprocedural plus spontaneous)

Need for revascularisation procedure

Outcome definition: target-vessel revascularisation, number of cases

Method and unit of measurement: absolute frequency

Time points reported: 37 days

RESULTS

All-cause mortality

Sample size: 70 (intention-to-treat analysis)

Missing participants: none

Summary data: 1/35-0/35 for placebo-ranolazine group

Subgroup analyses: not performed

Acute myocardial infarction incidence (fatal and non-fatal)

Sample size: 70 (intention-to-treat analysis)

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Pelliccia 2012 *(Continued)*

	Missing participants: none
	Summary data: 9/35-2/35 for placebo/ranolazine group (37 days)
	Subgroup analyses: not performed
	Need for revascularisation procedure
	Sample size: 70 (intention-to-treat analysis)
	Missing participants: none
	Summary data: 1/35-1/35 for placebo-ranolazine group
	Subgroup analyses: not performed
Notes	Relevant observations for the data provided before: none
	Source of funding: no extramural funding
	Notable conflicts of interest: no conflicts of interest to declare.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation is stated but not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study declared to be double-blinded, but no description is provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study declared to be double-blinded, but no description is provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusion or withdrawal is reported, we assume that all patients completed the study
Selective reporting (reporting bias)	Unclear risk	There is no published protocol. Results for all the outcomes stated in the "Methods" section of the paper are reported
Other bias	Low risk	The authors declare that the study was not supported by any external source of funding. Furthermore, there were no conflicts of interest to declare.

Pepine 1999

Methods	Study design: cross-over trial
	Total study duration: 8 weeks
	Duration of follow-up: no follow-up beyond treatment phase

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Pepine 1999 *(Continued)*

	Method of randomisation: not described Method of concealment of allocation: not mentioned Blinding: double-blind (with "double dummy" technique) Power calculation: not mentioned Phases of the study: 2 (qualifying phase, treatment phase) Number of patients randomised: 318 Exclusions post-randomisation: 6 (not described) Withdrawals (and reasons): premature withdrawals due to adverse events are declared to have been very similar for all treatments, but no details are provided
Participants	Total number: 312 Country of enrolment: United States, Canada. Setting/location: not specified Diagnostic criteria (stable angina pectoris): chronic (≥ 3 months) stable angina pectoris that had responded to conventional anti-anginal therapy Comorbidities: none Age (mean, range): 64.3 (33-85) years Gender (male %): 226 (72%) Inclusion criteria: • Chronic (≥ 3 months) stable angina pectoris that had responded to conventional anti-anginal therapy • Exercise-induced ischaemia, defined as horizontal or down-sloping ≥1 mm ST-segment depression persisting in 3 consecutive beats Exclusion criteria: • Left ventricular hypertrophy • Preexcitation • Conduction abnormalities • Pacemaker rhythm • Unstable angina • Myocardial infarction within the preceding 3 months • Heart failure (New York Heart Association class III or IV) • Uncorrected valvular • Congenital heart disease • Need for digoxin or long-acting nitrates • Labile diabetes • Conditions that would confuse follow-up evaluation
Interventions	Number of intervention groups: 4 Concomitant medications: β-blockers and/or calcium antagonists (minimum medication needed during qualifying phase) Excluded medications: long-acting nitrates **Placebo group** Intervention: placebo

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Pepine 1999 *(Continued)*

	Duration of intervention: 1 week (5 double-blind treatment periods in an extended period Latin square design) **Ranolazine 400 mg bid group** Intervention: ranolazine IR 400 mg twice daily Duration of intervention: 1 week (5 double-blind treatment periods in an extended period Latin square design) **Ranolazine 267 mg tid group** Intervention: ranolazine IR 267 mg thrice daily Duration of intervention: 1 week (5 double-blind treatment periods in an extended period Latin square design) **Ranolazine 400 mg tid group** Intervention: ranolazine IR 400 mg thrice daily Duration of intervention: 1 week (5 double-blind treatment periods in an extended period Latin square design)
Outcomes	Total number of outcomes: • According to study protocol: no published protocol; according to the "Methods" section: 9 (ETT time to onset of angina (peak and through), ETT duration of exercise (peak and through), ETT time to onset of ischaemic-type ST-segment depression (peak and through), haemodynamic, laboratory, adverse events) • Reported: 9 **Adverse events incidence** Outcome definition: number of patients experiencing an adverse event Method and unit of measurement: percentage Time points reported: 1 week **RESULTS** **Adverse events incidence** Sample size: 312 (intention-to-treat) Missing participants: 6 Summary data: it is stated that adverse events rates were similar for all ranolazine and placebo regimens and approximately 25%, but data for each group is not reported. It is stated that only minor gastrointestinal complaints tended to occur more often with ranolazine (6.6% to 10.7%) than with placebo (3,2%). Subgroup analyses: not performed
Notes	Relevant observations for the data provided before: "all patients" (intention-to-treat) (N = 312) and per-protocol (N = 260) analysis were performed for ETT variables Source of funding: in part by a grant from Syntex Research Notable conflicts of interest: not stated
Risk of bias	

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Pepine 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation is stated but no described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study is declared to be double-blinded, but no description is provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study is declared to be double-blinded, but no description is provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Exclusions and withdrawals are reported, but no reasons or explanations are provided
Selective reporting (reporting bias)	Unclear risk	There is no published protocol. Results for all the outcomes stated in the "Methods" section of the paper are reported
Other bias	Unclear risk	The study was supported in part by a grant from Syntex Research. The authors did not stated any conflicts of interest.

RAN080 2005

Methods	Study design: cross-over trial Total study duration: 28 to 40 days Duration of follow-up: no follow-up beyond treatment phase Method of randomisation: not described Method of concealment of allocation: not mentioned Blinding: double-blind (with 'double-dummy' technique), not described Power calculation: not mentioned Phases of the study: 2 (qualifying phase, treatment phase) Number of patients randomised: 158 Exclusions post-randomisation: 4 (did not perform ≥ 1 exercise test in the treatment phase) Withdrawals (and reasons): 6, 4 withdrawals attributed to adverse events (2 during ranolazine therapy, 1 because of hematologic abnormality, 1 because of asthenia, nausea and chest pain; 2 during placebo therapy, due to exacerbation of angina)
Participants	Total number: 158 Country of enrolment: Europe and Canada Setting/location: not specified

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RAN080 2005 *(Continued)*

Diagnostic criteria (stable angina pectoris): symptoms and exercise test results that support the diagnosis of chronic angina with evidence of CAD (macrovascular angina)

Comorbidities: none

Age (mean ± SD): 59 ± 8 years

Gender (male %): 89%

Inclusion criteria:

- Age 18 to 75 years
- Evidence of coronary artery disease consisting of a well-documented medical history of myocardial infarction or significant coronary artery disease (defined by the presence of ≥ 50% diameter stenosis accompanied by ischaemic electrocardiographic signs and angina during exercise), ideally within 12 months of study entry
- Symptoms that supported the diagnosis of chronic angina and a bicycle or modified Bruce's protocol treadmill exercise electrocardiogram that showed ≥1-mm ST-segment depression 3 to 9 min after the start of exercise
- Documented improvement in anginal symptoms and ST-segment depression during exercise testing after administration of standard anti-anginal medical therapy (β blockers, long-acting nitrates, and/or calcium channel blockers)

Exclusion criteria:

- Clinically significant arrhythmias
- Implanted pacemaker
- Pre-exercise ST-segment depression ≥1mm in any lead, left bundle branch block, digoxin therapy, or other factors that could reasonably interfere with exercise electrocardiographic interpretation
- History of congestive heart failure, unstable angina, or myocardial infarction at any time ≤1 month before study entry
- Clinically significant comorbidities, including hepatic or renal dysfunction, pulmonary hypertension, chronic obstructive pulmonary disease, a history of cerebral haemorrhage, or seizure disorder that required anticonvulsant medication
- Pregnancy or lactation
- Verapamil therapy
- Inability to discontinue β-blocker therapy

Interventions	Number of intervention groups: 3 Concomitant medications: (permitted) short-acting nitrates, calcium cannel blockers (except those that are cardiodepressants) Excluded medications: β-blockers, verapamil **Placebo group** Intervention: Placebo Duration of intervention: 7 to 10 days **Atenolol group** Intervention: atenolol 100 mg/d Duration of intervention: 7 to 10 days **Ranolazine group** Intervention: ranolazine IR 400 mg thrice daily Duration of intervention: 7 to 10 days

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RAN080 2005 *(Continued)*

Outcomes

Total number of outcomes:

- According to study protocol: no published protocol; according to the "Methods" section: 6 (time to onset of angina, time to 1-mm ST segment depression, total exercise duration, heart rate x systolic blood pressure, angina frequency, nitroglycerin consumption)
- Reported: 9 (including heart rate, blood pressure, and safety and adverse events)

Acute myocardial infarction incidence (fatal and non-fatal)

Outcome definition: mentioned as “serious adverse events”, number of cases

Method and unit of measurement: absolute frequency

Time points reported: 28 to 40 days (total study duration)

Angina episodes frequency

Outcome definition: average number of episodes per week

Method and unit of measurement: number per week

Time points reported: 28 to 40 days (total study duration)

Adverse events incidence

Outcome definition: number of patients that reported ≥ 1 adverse event

Method and unit of measurement: absolute frequency

Time points reported: 28 to 40 days

RESULTS

Acute myocardial infarction incidence (fatal and non-fatal)

Sample size: 155 (intention-to-treat analysis)

Missing participants: 3

Summary data (for each intervention group) (according to type of analysis) (for the largest time point): 1/154 – 0/154 – 0/155 for placebo – atenolol – ranolazine group

Subgroup analyses: not performed

Angina episodes frequency

Sample size: not specified (presumably 154)

Missing participants: not specified (presumably 4)

Summary data: numerical data not reported

Subgroup analyses: not performed

Adverse events incidence

Sample size: 155 (intention-to-treat analysis)

Missing participants: 3

Summary data: 26/154 – 39/154 – 45/155 for placebo – atenolol – ranolazine group. The most frequently reported adverse events were asthenia (19/26/4), dizziness (2/9/4), headache (6/0/5), nausea (6/0/2), palpitations (4/2/3), dyspepsia (7/0/2), pain (1/2/2), constipation (5/0/1), malaise (1/1/2) and dyspnoea (0/1/3) for ranolazine/atenolol/placebo group.

Subgroup analyses: not performed

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RAN080 2005 *(Continued)*

Notes	Relevant observations for the data provided before: none Source of funding: CV Therapeutics, Inc. Notable conflicts of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation is stated but not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study declared to be double-blinded, but no description is provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study declared to be double-blinded, but no description is provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Six patients are reported not to have completed the study. Reasons for withdrawal and treatment assigned are not described for two of them
Selective reporting (reporting bias)	High risk	There is no published protocol. Results for all the outcomes stated in the "Methods" section of the paper are reported, but results for some additional outcomes (haemodynamics and safety and adverse events) are also reported
Other bias	High risk	The study was supported by CV Therapeutics, Inc. Conflicts of interest were not stated.

RIVER-PCI 2016

Methods	Study design: parallel-group trial Total study duration: about 3.5 years Duration of follow-up: mean of 643 days Method of randomisation: interactive web-based block randomisation system (block sizes of 10), with randomisation stratified by diabetes history (presence versus absence) and acute coronary syndrome presentation (acute versus non-acute) Method of concealment of allocation: not described in enough detail, it is just mentioned that investigators and patients were masked to treatment allocation Blinding: double-blind, referred to participants, clinicians ("masked to treatment allocation"), data collectors (independent Data Safety Monitoring Board, independent on-site clinical monitors, independent angiographic core laboratory), outcome adjudicators (independent Clinical Endpoint Committee) and data analysts (independent statistical data analysis group, Duke Clinical Research Institute for quality of life and economic analyses)

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RIVER-PCI 2016 *(Continued)*

Power calculation: 85% power using a 2-sided log-rank test at the 5% significance level, with regard to the primary end point events

Phases of the study: 1 (treatment phase, including a 7-day run-in period)

Number of patients randomised: 2651 (1319/1332 for placebo/ranolazine group)

Exclusions post-randomisation: 32 exclusions in the placebo group (19 not treated, 3 scientific misconduct, 10 no qualifying PCI), 15 exclusions in the ranolazine group (7 not treated, 3 scientific misconduct, 5 no qualifying PCI). Additionally, for the quality of life sub-study, there were 105 exclusions in the placebo group (97 questionnaires invalid, 8 questionnaires not done) and 110 exclusions in the ranolazine group (103 questionnaires invalid, 7 questionnaires not done)

Withdrawals (and reasons): 463/1287 - 529/1317 for placebo - ranolazine group, reasons detailed in the appendix of the study report

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Participants

Total number: 2651

Country of enrolment: 15 countries (Europe, Israel, Russia, USA)

Setting/location: inpatient and outpatient

Diagnostic criteria (stable angina pectoris): symptoms of stable angina

Comorbidities: incomplete revascularisation (ICR) post-PCI

Age (mean): 63.3±10 / 63.3±10.4 years for placebo/ranolazine group

Gender (male %): 80.3% / 79.7% for placebo/ranolazine group

Inclusion criteria:

- Men and women aged ≥18 years
- History of chronic angina, defined as ≥ 2 episodes of angina pain or discomfort in the chest, jaw, shoulder, back, neck, or arm that is precipitated by exertion or emotional stress and relieved by rest or sublingual nitroglycerin, occurring on ≥ 2 separate days and ≥14 d before PCI (in the case of staged PCI procedures, a history of angina has to have occurred at least 14 days before the first PCI in the series)
- PCI for any indication (ACS or non-ACS)
- Evidence of ICR post-PCI. ICR is defined as the presence of ≥ 1 lesion with visually estimated ≥50% diameter stenosis in any coronary artery (including branch vessels) with reference vessel diameter ≥2.0 mm, whether in the target vessel or in a non-target vessel. In the case of a participant post-CABG, ICR is defined as the presence of ≥ 1 lesion with visually estimated ≥ 50% diameter stenosis in a non bypassed epicardial vessel ≥ 2.0 mm in diameter, or ≥1 visually estimated ≥ 50% diameter stenosis in a bypass graft supplying an otherwise non revascularised myocardial territory
- Clinically stable post-PCI. Participants randomised in hospital on the day of planned discharge or in clinic are considered stable. Participants randomised in hospital before the day of planned discharge must meet all of the following criteria:
  - CK-MB < 3 times the upper limit of normal (ULN) ≥3 hours after PCI, or with evidence of decreasing CK-MB (by at least 20% from the prior measurement) if ≥3 times the ULN, each as reported by local laboratory. If CK-MB is not available, the participant must have evidence of normal or decreasing troponin levels (by at least 20% from the prior measurement) ≥3 hours after PCI, as reported by local laboratory
  - Systolic blood pressure ≥ 90 mm Hg and not receiving pressors or inotropes
  - No current requirement for an intra-aortic balloon pump or any left ventricular assist device
  - No current requirement for intravenous (IV) nitroglycerin
- Women of childbearing potential must have a negative pregnancy test result at screening (unless surgically sterile or postmenopausal) and must agree to use highly effective contraception methods from screening throughout the duration of study treatment and for 14 d after the last dose of study drug
- Ability and willingness to comply with all study procedures during the course of the study

Exclusion criteria:

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RIVER-PCI 2016 *(Continued)*

- Any future planned revascularisation (including staged procedures) or possible planned revascularisation (e.g. planned stress test to assess the imminent need for additional revascularisation). Future planned stress tests for purposes of monitoring are permitted but strongly discouraged. Participants may be enrolled after the last PCI in the staged series or once a decision is made not to perform a follow-up PCI, as long as randomisation occurs within 14 d from the last PCI. If a participant has had a stress test after PCI and before randomisation and no further intervention is planned, the participant may be enrolled within 14 days from the last PCI.
- Unrevascularised left main coronary artery lesion with diameter stenosis ≥ 50%. Participants with a history of CABG to the left coronary system will be considered to have a revascularised left main if at least 1 graft is patent.
- Major complication during or after the index PCI (in the case of staged PCI, the last in the series) including any of the following:
  - TIMI major bleeding or any bleeding requiring blood transfusion of ≥ 2 units of red blood cells
  - Coronary perforation requiring treatment
  - Procedural complication requiring surgery (including CABG or peripheral vascular surgery)
- Stroke within 90 days before randomisation or any history of stroke with permanent major neurologic disability Cardiogenic shock within 90 d before randomisation (transient decreases in blood pressure without clinical sequelae are not considered to be cardiogenic shock)
- New York Heart Association class III or IV heart failure
- Severe renal insufficiency as defined by an estimated GFR 30 mL/min per 1.73 m^2 using the 4 variable modification of diet in renal disease equation (based on the last available measurement before randomisation, collected within 1 mo before the index PCI [or in the case of staged PCI, the last in the series])
- Liver cirrhosis
- Use of class Ia, Ic, or class III anti-arrhythmic agents, except for amiodarone
- Current treatment with strong inhibitors of CYP3A
- Current treatment with cytochrome P450 3A4 inducers or P-gp inducers
- Participants taking > 20 mg simvastatin daily or > 40 mg lovastatin daily who cannot reduce the dose to 20 mg once daily for simvastatin or 40 mg once daily for lovastatin, or who cannot switch to another statin
- Participants taking > 1000 mg daily of metformin who cannot reduce the dose to a maximum total of 1000 mg daily (additional antidiabetic medications may be added as clinically indicated to allow participants to decrease their metformin dose and maintain glycaemic control)
- Previous treatment with ranolazine for > 7 consecutive days within 30 d before randomisation, or known hypersensitivity or intolerance to ranolazine or to any of the excipients
- Participation in another investigational drug or investigational device study within 30 d before randomisation (participation in registries is allowed)
- Women who are pregnant or breast-feeding
- Non–coronary artery disease–related comorbid conditions (e.g. advanced malignancy, severe aortic stenosis), which are likely to result in death within 2 years of randomisation

Interventions	Number of intervention groups: 2 Concomitant medications: per the discretion of the investigator Excluded medications: those mentioned in exclusion criteria **Placebo group** Intervention: placebo Duration of intervention: mean (IQR) of 642 (575-561) days **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 1000 mg twice daily Duration of intervention: mean (IQR) of 644 (575-757) days

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RIVER-PCI 2016 *(Continued)*

Outcomes

Total number of outcomes: 1

- According to study protocol: 14 (time from randomisation to the occurrence of ischemia-driven revascularisation/hospitalisation, sudden cardiac death, cardiovascular death, myocardial infarction; all-cause mortality; incidence of major adverse cardiovascular events: stroke, transient ischaemic attack, hospitalisation for heart failure; SAQ score, DASI score, symptoms by Rose Dyspnea Scale score (quality of life sub-study);cumulative total US medical costs, health care costs and resource use, cost per life-year added and cost per quality-adjusted life-year added (health economics sub study))
- Reported: 16 (including incidence of ischemia-driven revascularisation/hospitalisation, sudden cardiac death, cardiovascular death, myocardial infarction, missing time to event for sudden cardiac death, cardiovascular death and myocardial infarction)

Cardiovascular mortality

- Outcome definition: death from cardiac disease, stroke, pulmonary embolism (in the absence of conditions such as malignancy), peripheral artery disease or cardiovascular intervention/surgery
- Method and unit of measurement: absolute frequency
- Time points reported: overall study duration

All-cause mortality

- Outcome definition: number of deaths
- Method and unit of measurement: absolute frequency
- Time points reported: overall study duration

Quality of life

1. Seattle Angina Questionnaire (SAQ)

- Outcome definition: includes 5 domains: angina frequency, angina stability, angina-related treatment satisfaction, angina-related physical functioning and QOL
- Upper and lower limits and whether a high or low score is good: each domain is scored separately from 0 to 100, with higher scores indicating better health status
- Method and unit of measurement: score for each domain
- Time points reported: 1, 6, 12 months

2. Duke Activity Satuts Index (DASI)

- Outcome definition:12-item scale which focuses on physical activity ranging from self-care to strenuous physical work; each activity is weighted by the metabolic output associated with its performance, and a final score weights the performed activities
- Upper and lower limits and whether a high or low score is good: score ranges from 0 (worst) to 58.2 (best)
- Method and unit of measurement: score
- Time points reported: 1, 6, 12 months

3. Mental Health Inventory-5 (MHI-5)

- Outcome definition: 5-question scale derived from the 36-item Short Form Health Survey (SF-36) version 2.0
- Upper and lower limits and whether a high or low score is good: not described
- Method and unit of measurement: score
- Time points reported: 1, 6, 12 months

4. European QOL Five Dimension Three-Level Scale (EuroQOL-5D-3 L)

- Outcome definition: 5-item instrument assessing specific domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
- Upper and lower limits and whether a high or low score is good: not described
- Method and unit of measurement: score

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RIVER-PCI 2016 *(Continued)*

- Time points reported: 1, 6, 12 months

5. Rose Dyspnea Scale (RDS)

- Outcome definition: not described
- Upper and lower limits and whether a high or low score is good: not described
- Method and unit of measurement: score
- Time points reported: 1, 6, 12 months

Acute myocardial infarction incidence (fatal and non-fatal)

- Outcome definition: episodes defined by symptoms suggestive of ischaemia/infarction in association with ECG, cardiac biomarker, or pathologic evidence of infarction
- Method and unit of measurement: absolute frequency
- Time points reported: overall study duration

Need for revascularisation procedure

- Outcome definition: any PCI or CABG surgery occurring after randomisation for angina or angina equivalent symptoms, with or without documented ischaemia. PCI is defined as an attempt to cross a lesion with a wire with the intention of performing revascularisation
- Method and unit of measurement: absolute frequency
- Time points reported: overall study duration

RESULTS

Cardiovascular mortality

- Sample size: 2604 (intention-to-treat analysis)
- Missing participants: 47 (32/15 for placebo/ranolazine group)
- Summary data: 20/1287 - 21/1317 for placebo - ranolazine group
- Subgroup analyses: not performed

All-cause mortality

- Sample size: 823 (intention-to-treat analysis)
- Missing participants: 32 (22/10 for placebo/ranolazine group)
- Summary data: 36/1297 - 42/1322 for placebo - ranolazine group
- Subgroup analyses: not performed

Quality of life 1182 1207

1. Seattle Angina Questionnaire (SAQ)

- Sample size: 1958 (980/978 for the placebo/ranolazine group) (intention-to-treat analysis)
- Missing participants: 202/229 for placebo/ranolazine group
- Summary data: baseline/12-month (mean ± SD) score in the QOL domain: 49.5 ± 22.8 / 70.4 ± 22.2 for placebo group, 48.3 ± 22.3 / 70.3 ± 22.5 for ranolazine group
- Subgroup analyses: performed for the following variables: age, sex, indication for the qualifying PCI, baseline anti-anginal use, diabetes mellitus, baseline angina

2. Duke Activity Satuts Index (DASI)

- Sample size: 1957 (980/977 for the placebo/ranolazine group) (intention-to-treat analysis)
- Missing participants: 202/230 for the placebo/ranolazine group
- Summary data: baseline/12-month (mean±SD) score: 18.7±14.3 / 23.3±16.1 for placebo group, 18.7±14.9 / 22.5±15.8 for ranolazine group
- Subgroup analyses: performed for the following variables: age, sex, indication for the qualifying PCI, baseline anti-anginal use, diabetes mellitus, baseline angina

3. Mental Health Inventory-5 (MHI-5)

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RIVER-PCI 2016 *(Continued)*

- Sample size: 1954 (978/976 for the placebo/ranolazine group) (intention-to-treat analysis)
- Missing participants: 204/231 for placebo/ranolazine group
- Summary data: baseline/12-month (mean±SD) score: 64.1 ± 19.6 / 70.4 ± 18.0 for placebo group, 64.9±19.2 / 70.3 ± 18.1 for ranolazine group
- Subgroup analyses: performed for the following variables: age, sex, indication for the qualifying PCI, baseline anti-anginal use, diabetes mellitus, baseline angina

4. European QOL Five Dimension Three-Level Scale (EuroQOL-5D-3 L)

- Sample size: 1934 (973/961 for the placebo/ranolazine group) (intention-to-treat analysis)
- Missing participants: 209/246 for placebo/ranolazine group
- Summary data: baseline/12-month (mean±SD) score: 0.75 ± 0.23 / 0.78 ± 0.23 for placebo group, 0.75 ± 0.23 / 0.79 ± 0.22 for ranolazine group
- Subgroup analyses: performed for the following variables: age, sex, indication for the qualifying PCI, baseline anti-anginal use, diabetes mellitus, baseline angina

5. Rose Dyspnea Scale (RDS)

- Sample size: 1939 (971/968 for the placebo/ranolazine group) (intention-to-treat analysis)
- Missing participants: 211/239 for placebo/ranolazine group
- Summary data: baseline/12-month (mean ± SD) score: 1.7 ± 1.4 / 1.0 ± 1.3 for placebo group, 1.7±1.4 / 1.1 ± 1.3 for ranolazine group
- Subgroup analyses: performed for the following variables: age, sex, indication for the qualifying PCI, baseline anti-anginal use, diabetes mellitus, baseline angina

Acute myocardial infarction incidence (fatal and non-fatal)

- Sample size: 2604 (intention-to-treat analysis)
- Missing participants: 47 (32/15 for placebo/ranolazine group)
- Summary data: 116/1287 - 111/1317 for placebo - ranolazine group
- Subgroup analyses: not performed

Need for revascularisation procedure

- Sample size: 2604 (intention-to-treat analysis)
- Missing participants: 47 (32/15 for placebo/ranolazine group)
- Summary data: 200/1287 - 201/1317 for placebo - ranolazine group
- Subgroup analyses: performed for the following variables: sex, age, precedence, diabetes mellitus, indication for PCI, type of vessel disease, residual SYNTAX score, type of PCI device, total occlusion, previous CABG, baseline BNP and baseline LVEF

Adverse events

Dizziness, constipation, nausea, hypotension, vomiting and vertigo were reported more often in the ranolazine group than in the placebo group.

Notes

Relevant observations for the data provided before: none

Source of funding: Gilead Sciences, Menarini Group

Notable conflicts of interest: seven of the authors declare current of past financial relationships with Gilead Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence. Random sequence generated by an interactive web-based block randomisation system with block sizes of ten

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RIVER-PCI 2016 *(Continued)*

Allocation concealment (selection bias)	Low risk	Described for participants and clinicians as "masked to treatment allocation". The use of a web-based system for randomization (and allocation) can be considered sufficient to mantain blinded the study personnel until the momment of assignment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment phase is declared to be double-blinded, but no description for participants and personnel is provided. However, the subjects idea about study arm was measured, and study data was collected by independent groups, then presumably both participants and investigators were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data for events and quality of life/economic analyses were collected by independent outcome adjudication groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions and withdrawals are described, and reason are reported
Selective reporting (reporting bias)	High risk	There are two sub studies (quality of life and health economics) besides the main study for the RIVER-PCI trial, and all the main endpoints considered in the protocol were reported (the health economics sub study has not yet been published). Of note, for the events under study, time to event occurrence was stated to be the endpoint rather than the rate/incidence of the event; however, results for the secondary endpoint events were reported only as rate/incidence, and no data about time to event occurrence was provided
Other bias	High risk	The study was supported by Gilead Sciences and Menarini Group. Seven of the authors declare current or past financial relationships with Gilead Sciences.

RWISE 2016

Methods	Study design: cross-over trial Total study duration: recruitment was undertaken since 12 May 2011 to 10 Aug 2015, treatment phase duration was of 6 weeks (including 2 periods of treatment of 2 weeks and 1 period of washout of 1 week) Duration of follow-up: 2 weeks Method of randomisation: performed at a 1:1 ratio blocked by clinical site, not further described Method of concealment of allocation: not mentioned Blinding: double-blind, not described Power calculation: 90% power to detect a mean difference of 15 in SAQ score using a two-sided t-test at the 0.017 Holm-Bonferroni corrected level of significance Phases of the study: 1 (treatment phase) Number of patients randomised: 142 Exclusions post-randomisation: 4 participants were excluded because they received incomplete treatment Withdrawals (and reasons): number differ between the text (subject characteristics) and figure 1, data from the later was deemed to be more coherent. Five participants dropped-out during ranolazine treatment and 4 during placebo washout (no dropouts during ranolazine washout), reasons not described

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RWISE 2016 *(Continued)*

Participants	Total number: 128 Country of enrolment: USA Setting/location: not specified Diagnostic criteria (stable angina pectoris): chronic angina or its equivalent with coronary angiogram revealing coronary microvascular dysfunction (CMD) with no obstructive CAD (microvascular angina) Comorbidities: none Age (mean ± SD): 55.2 ± 9.2 years Gender (male %): 4% Inclusion criteria: 1. Men or women age > 18 years from diverse racial/ethnic groups; 2. Competent to give informed consent; 3. Patients with chronic angina or its equivalent; 4. Coronary angiogram revealing CMD with no obstructive CAD (epicardial coronary stenosis <50% luminal diameter stenosis); or measured noninvasively using the Society of Cardiovascular Computed Tomography threshold of < 50% stenosis. 5. Left ventricular ejection fraction ≥ 45%; 6. Objective evidence of ischaemia by noninvasive methods such as exercise stress test, stress Echo, CMRI or single photon emission tomography (SPECT); 7. Patients with CMD defined as an invasive measured CFR < 2.5 or acetylcholine (ACH) response of no dilation or constriction, determined by local site read, or a CMRI derived MPRI ≤ 2.0**. 8. Patients must have withdrawn from ranolazine at least 2 weeks prior to study entry. 9. Either a qualifying WISE or clinical CMRI scan must be completed within 2.5 years ± 1 month of study participation. 10. Qualifying angiograms must have been within 2.5 years ± 1 month of study enrolment. Exclusion criteria: 1. Acute coronary syndrome (defined by World Health Organization [WHO]), cardiogenic shock or requiring inotropic or intra-aortic balloon support; 2. Planned percutaneous coronary intervention or coronary bypass surgery or established obstructive CAD with ischaemia eligible for revascularisation, acute myocardial infarction (MI); 3. Prior non-cardiac illness with estimated life expectancy < 4 years; 4. Unable to give informed consent; 5. Allergy or contra-indication to CMRI testing, including renal failure, claustrophobia, and asthma, uncontrolled moderate hypertension (sitting blood pressure (BP) > 160/95 mm Hg with measurements recorded on at least 2 occasions), other conditions likely to influence outcomes: Severe lung, creatinine > 1.8 or creatinine clearance [CrCl] ≤ 50 mL/min) or hepatic disease; 6. Surgically uncorrected significant congenital or valvular heart disease and other disease likely to be fatal or require frequent hospitalisation within the next six months; 7. Adherence or retention reasons; 8. Unwilling to complete follow-up evaluation including repeat testing, documented obstructive hypertrophic cardiomyopathy; 9. Aortic stenosis (valve area < 1.5 cm); 10. LV dysfunction (ejection fraction < 45%); 11. History of significant cocaine or amphetamine abuse; 12. Taking potent CYP3A4 inhibitors (ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir) 13. Women who are pregnant
Interventions	Number of intervention groups: 2

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RWISE 2016 *(Continued)*

Concomitant medications: (permitted) anti-anginals, antihypertensives, statins, hormone replacement therapy

Excluded medications: those mentioned in exclusion criteria

Placebo group

Intervention: placebo twice daily

Duration of intervention: 2 weeks

Ranolazine group

Intervention: ranolazine ER 500/1000 mg twice daily

Duration of intervention: 2 weeks

Outcomes

Total number of outcomes:

- According to study protocol (published in clinicaltrials.gov; published as Online Exhibit A): 7 (angina frequency, nitroglycerine use frequency, quality of life, healthcare costs, cardiac MRI perfusion and diastolic function, biochemical parameters, correlation between quality of life and cardiac MRI myocardial ischaemia improvements)
- Reported: 6 (missing healthcare costs and biochemical parameters, including adverse events incidence)

Quality of life

1. Seattle Angina Questionnaire (SAQ and SAQ-7)

- Outcome definition: includes 5 domains: angina frequency, angina stability, treatment satisfaction, physical limitation and QoL
- Upper and lower limits and whether a high or low score is good: not described
- Method and unit of measurement: score for each domain and overall
- Time points reported: 2 weeks

2. Duke Activity Satuts Index (DASI)

- Outcome definition: measure of functional status
- Upper and lower limits and whether a high or low score is good: not described
- Method and unit of measurement: score
- Time points reported: 2 weeks

3. QOL

- Outcome definition: selected questions from the Medical Outcomes Study(MOS)-Short Form-36 Health Survey (SF-36, energy/fatigue and emotional domains), the MOS-116 (moody and low spirits domains), and the HIS-GWB Mental Health (depressed and strain domains)
- Method and unit of measurement: score separately for each domain
- Time points reported: 2 weeks

Angina episodes frequency

- Outcome definition: average number of episodes per week
- Method and unit of measurement: number per week
- Time points reported: 2 weeks

Adverse events incidence

- Outcome definition: number of patients that reported ≥1 adverse event
- Method and unit of measurement: absolute frequency
- Time points reported: 2 weeks

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RWISE 2016 *(Continued)*

RESULTS

Quality of life

1. Seattle Angina Questionnaire (SAQ)

- Sample size: 128 (per-protocol analysis)
- Missing participants: 5/5 for placebo/ranolazine group
- Summary data: score (mean±SD) in the QOL domain: 54.17±23.31 / 56.05±23.09 for placebo / ranolazine group
- Subgroup analyses: not reported

2. Duke Activity Satuts Index (DASI)

- Sample size: 128 (per-protocol analysis)
- Missing participants: 5/5 for placebo/ranolazine group
- Summary data: score (mean±SD): 6.20±5.05 / 6.35±4.83 for placebo / ranolazine group
- Subgroup analyses: not reported

3. QOL

- Sample size: 128 (per-protocol analysis)
- Missing participants: 5/5-6 for placebo/ranolazine group
- Summary data: score (mean±SD) for each scale and domain mentioned above
- Subgroup analyses: not reported

Angina episodes frequency

- Sample size: 128 (per-protocol analysis)
- Missing participants: 5/5 for placebo/ranolazine group
- Summary data: number/week (mean ± SD): 4.88 ± 7.75 / 4.78 ± 8.20 for placebo/ranolazine group
- Subgroup analyses: not performed

Adverse events incidence

- Sample size: 128 (per-protocol analysis)
- Missing participants: 5/5 for placebo/ranolazine group
- Summary data: 6/128 – 7/128 for placebo – ranolazine group. The adverse events reported for the ranolazine treatment group were nausea and dizziness (3/128), arm shaking (1/128), back pain (1/128), renal abnormality (1/128) and throat swelling (1/128), for the placebo treatment group were chest pain (3(128), throat swelling (1/128), cough (1/128) and sinus infection (1/128).
- Subgroup analyses: not performed

Notes

Relevant observations for the data provided before: none

Source of funding: unrestricted research grant from Gilead and contracts from several public (USA) entities

Notable conflicts of interest: seven of the authors declare financial relationships with private pharmaceutical organisations (Gilead among others) and public (USA) entities

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation is stated but described only as "in a 1:1 ratio, blocked by clinical site"

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RWISE 2016 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study declared to be double-blinded, but no description is provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study declared to be double-blinded, but no description is provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Exclusions and withdrawals are reported, but no reasons or explanations are provided. Furthermore, inconsistencies among the data provided were observed
Selective reporting (reporting bias)	Unclear risk	Protocol published in clinicaltrials.gov and as Online Exhibit adjoined to the results publication. Healthcare costs and biochemical parameters were not reported, adverse events incidence was reported but not included among the study outcomes in protocol
Other bias	High risk	The study was supported by Gilead and several public organisations. Seven authors declared financial relationships with private pharmaceutical organisations

Sandhiya 2015

Methods	Study design: parallel-group trial Total study duration: from 1 January 2012 to 11 April 2013 Duration of follow-up: no follow-up beyond treatment phase Method of randomisation: not described, performed in a 1:1 ratio Method of concealment of allocation: drugs distributed using sequentially numbered opaque sealed envelopes Blinding: not mentioned Power calculation: not mentioned Phases of the study: 1 (treatment phase) Number of patients randomised: 47 (24/23 for trimetazidine/ranolazine group) Exclusions post-randomisation: not reported Withdrawals (and reasons): not reported
Participants	Total number: 40 Country of enrolment: Greece Setting/location: outpatient Diagnostic criteria (stable angina pectoris): history of exertional angina and CAD documented by coronary angiography (macrovascular angina) Comorbidities: diabetes mellitus

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Sandhiya 2015 *(Continued)*

	Age (mean): 57.4 ± 9.1 / 58 ± 8.1 years for trimetazidine/ranolazine group Gender (male %): 83% (87.5/78.3 for trimetazidine/ranolazine group) Inclusion criteria: • Aged ≥ 18 years • Diagnosis of CAD: documented by coronary angiography/minimum three months history of exertional angina • Diagnosis of diabetes mellitus with HbA_{1c}>7% Exclusion criteria: • History of myocardial infarction in the previous three months • Heart failure • Valvular heart diseases • Alcoholic cardiomyopathy • Renal failure • Chronic lung diseases • Hepatic failure • Baseline ECG abnormalities • Hyperthyroidism • Secondary causes of angina • Pregnancy/absence of contraceptive use in women of childbearing age/lactating mothers • Patients on P-glycoprotein inhibitors, drugs known to prolong QT interval, CYP3A4 inhibitors, CYP3A4 inducers, pacemaker • Patients participating in other clinical trials or those who participated in any clinical trial within the last three months
Interventions	Number of intervention groups: 2 Concomitant medications: statins Excluded medications: those mentioned in exclusion criteria **Trimetazidine group** • Intervention: trimetazidine 35 mg twice daily • Duration of intervention: 3 months **Ranolazine group** • Intervention: ranolazine (type of formulation not specified) 500 mg twice daily • Duration of intervention: 3 months
Outcomes	Total number of outcomes: 1 • According to study protocol: no published protocol; according to the "Materials and Methods" section: 5 (angina episodes frequency, adverse events, biochemical diabetes assessment, QTc interval, haemodynamic parameters) • Reported: 6 (including sublingual nitrate consumption frequency) **Angina episodes frequency** • Outcome definition: average angina attacks per week • Method and unit of measurement: number per week • Time points reported: 12 weeks **RESULTS**

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Sandhiya 2015 *(Continued)*

Angina episodes frequency

- Sample size: 47 (intention-to-treat analysis)
- Missing participants: none
- Summary data: mean (SD) 1.4(2.2) / 1.2(1.7) for trimetazidine/ranolazine group (baseline values are also reported)
- Subgroup analyses: not performed

Adverse events

The adverse events reported for the ranolazine group included angina, constipation, postural hypotension, headache, dizziness, nausea and weakness; for the trimetazidine group were constipation, weakness, palpitations, angina, dizziness, nausea, dyspepsia, headache, gastric discomfort and joint pain.

Notes	Relevant observations for the data provided before: none Source of funding: no external source of funding Notable conflicts of interest: the authors declare that they have no conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation is stated but described only as "in a 1:1 ratio"
Allocation concealment (selection bias)	Low risk	Study drugs were provided in sequentially numbered opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study declared to be double-blinded, but no description is provided. However, it can be presumed that participants and personnel were blinded since drugs were provided in sealed envelopes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study declared to be double-blinded, but no description is provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusion or withdrawal is reported, we assume that all patients completed the study
Selective reporting (reporting bias)	Unclear risk	There is no published protocol. Results for all the outcomes stated in the "Methods" section of the paper are reported
Other bias	Low risk	The authors declare that the study was not supported by external source of funding. Also, they declared that they had no conflict of interest.

Shammas 2015

Methods	Study design: cross-over trial Total study duration: 16 weeks Duration of follow-up: no follow-up beyond treatment phase Method of randomisation: not described

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Shammas 2015 *(Continued)*

	Method of concealment of allocation: not described Blinding: double-blind, it is stated that the investigators and the patient remained blinded to the treatment until the completion of the trial, but no details are provided Power calculation: not performed (pilot study) Phases of the study: 1 (treatment phase) Number of patients randomised: 28 Exclusions post-randomisation: 4 Withdrawals (and reasons): 5 (3 withdrew voluntarily, 1 lost to follow-up, 1 withdrew involuntarily) (only 4 patients were excluded from the analysis)
Participants	Total number: 28 Country of enrolment: United States Setting/location: not specified Diagnostic criteria (stable angina pectoris): symptomatic (exertional angina or dyspnoea) ischaemic cardiomyopathy (ICM) with angiographic documentation of CAD (macrovascular angina) Comorbidities: none (not treatable by further revascularisation) Age (mean ± SD): 71.5 ± 8.4 years Gender (male %): 82.1% Inclusion criteria: • ICM with continued symptoms on guideline-directed medical treatment, where optimal medical treatment was defined as treatment with two anti-ischaemic agents (amlodipine or long-acting nitrates on top of beta blockers) as well as an ACEI/ARB unless contraindicated, and continued symptoms defined as significant exertional angina or dyspnoea, interfering with the patient's daily activity • Angiographic documentation of coronary artery disease that was not amenable to treatment by coronary intervention (already treated or non treatable) • A recent ejection fraction (EF) of less than or equal to 40% within 6 months of enrolment, as assessed by echocardiography or isotope ventriculography • Able to sign an informed consent before enrolment Exclusion criteria: • Dyalisis patients • There was no prespecified exclusion based on QTc or renal function
Interventions	Number of intervention groups: 2 Concomitant medications: angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), a beta blocker, and at least one additional anti-ischaemic drug (amlodipine or long-acting nitrate) Excluded medications: none **Placebo group** Intervention: placebo Duration of intervention: 6 weeks (plus 2 weeks of washout) **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 500 mg/1000 mg twice daily

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Shammas 2015 *(Continued)*

Duration of intervention: 6 weeks (plus 2 weeks of washout)

Outcomes

Total number of outcomes:

- According to study protocol: no published protocol; according to the "Methods" section: 2 (SAQ and Rose Dyspnea Scale (RDS) scores)
- Reported: 3 (including adverse events incidence)

Quality of life

1. Seattle Angina Questionnaire (SAQ)

- Outcome definition: level of functioning scale, measured by the scores in the 5 sub scales, reported separately and as a mean score
- Upper and lower limits and whether a high or low score is good: higher scores are better, upper and lower limits are not described
- Method and unit of measurement: score
- Time points reported: 6 weeks

2. Rose Dyspnea Scale (RDS)

- Outcome definition: scale for dyspnoea with regular activities, measured by a total score
- Upper and lower limits and whether a high or low score is good: higher scores indicate dyspnoea leading to more physical limitation (worse)
- Method and unit of measurement: change from baseline, score
- Time points reported: 6 weeks

Adverse events incidence

- Outcome definition: number of adverse events (serious and non serious) reported
- Method and unit of measurement: frequency
- Time points reported: 6 weeks

RESULTS

Quality of life

1. Seattle Angina Questionnaire (SAQ)

- Sample size: 24 (intention-to-treat analysis)
- Missing participants: 4
- Summary data: baseline/post-intervention score:
  * i) physical limitation 62.35/58.02 - 62.19/64.35,
  * ii) anginal stability 50/63.89 - 61.11/61.11,
  * iii) anginal frequency 74.44/74.44 - 71.11/86.67,
  * iv) treatment satisfaction 89.58/87.5 - 88.89/92.36,
  * v) quality of life 68.52/66.67 - 58.33/72.22 for placebo-ranolazine group
- Subgroup analyses: not performed

2. Rose Dyspnea Scale (SAQ)

- Sample size: 20 (intention-to-treat analysis)
- Missing participants: 8 (4 because of not having dyspnoea)
- Summary data: -0.34/-0.45 for placebo/ranolazine group
- Subgroup analyses: not performed

Adverse events incidence

- Sample size: 24 (intention-to-treat analysis)
- Missing participants: 4

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Shammas 2015 *(Continued)*

- Summary data: neither the frequency of each adverse event nor the number of patients who report any adverse event were reported, but it is stated that the most common side effects reported in the ranolazine arm included nausea, dizziness, constipation, headache, hypotension and dyspepsia; while in the placebo patients, dizziness was reported.
- Subgroup analyses: not performed

Notes	Relevant observations for the data provided before: none Source of funding: research grant from Gilead Notable conflicts of interest: Dr Shammas is a speaker for and is on the advisory board of Gilead

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation is stated but not described
Allocation concealment (selection bias)	Unclear risk	It is stated that the investigators remained blinded to the treatment (allocation) until the completion of the trial, but no details are provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study declared to be double-blinded, with blinding corresponding to investigators and patients
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A core laboratory blinded to patient treatment determined the SAQ scores
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals and reasons are described; however, there is an inconsistency in the number of patients who did not complete the trial (5) and the number of patients excluded from the analysis (4)
Selective reporting (reporting bias)	Unclear risk	There is no published protocol. Results for all the outcomes stated in the "Methods" section of the paper are reported
Other bias	High risk	The study was supported by a research grant from Gilead Science. Dr Shammas is a speaker for and is on the advisory board of Gilead.

Tagliamonte 2015

Methods	Study design: parallel-group trial Total study duration: 8 weeks Duration of follow-up: no follow-up beyond treatment phase Method of randomisation: not described Method of concealment of allocation: not mentioned Blinding: double-blind, not described Power calculation: not mentioned Phases of the study: 1 (treatment phase)

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Tagliamonte 2015 *(Continued)*

	Number of patients randomised: 58 (29/29 for placebo/ranolazine group) Exclusions post-randomisation: none Withdrawals (and reasons): none
Participants	Total number: 58 Country of enrolment: Italy Setting/location: not specified Diagnostic criteria: sings and symptoms of myocardial ischaemia without obstructive CAD (microvascular angina) Comorbidities: none Age (mean ± SD): 66 ± 10 years Gender (male %): 67% Inclusion criteria: • Signs and symptoms of myocardial ischaemia but no obstructive CAD (< 70% coronary stenosis in all epicardial coronary arteries) Exclusion criteria: • Hepatic insufficiency • Prolonged QT • Renal failure • Use of drugs that inhibit CYP3A such as diltiazem, verapamil, ketoconazole, macrolides, HIV protease inhibitors • life expectancy < 6 months • Atrial fibrillation, left bundle branch block on ECG, primary valvular heart disease, hypertrophic cardiomyopathy, previous acute coronary syndrome, left ventricular systolic dysfunction with ejection fraction < 55%
Interventions	Number of intervention groups: 2 Concomitant medications: aspirin Excluded medications: those mentioned in exclusion criteria **Placebo group** • Intervention: placebo twice daily • Duration of intervention: 8 weeks **Ranolazine group** • Intervention: ranolazine (type of formulation not specified) 500 mg twice daily (increased from 350 mg twice daily for 4 weeks) • Duration of intervention: 8 weeks
Outcomes	Total number of outcomes: 3 According to study protocol: no published protocol; according to the "Methods" section: 3 (coronary flow reserve, left ventricular ejection fraction, SAQ score) Reported: 3 **Quality of life**

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Tagliamonte 2015 *(Continued)*

- Outcome definition: score in the 5 dimensions of the Seattle Angina Questionnaire (SAQ), reported separately
- Upper and lower limits and whether a high or low score is good: not described
- Method and unit of measurement: average score
- Time points reported: 8 weeks

RESULTS

Quality of life

- Sample size: 58 (Intention-to-treat analysis)
- Missing participants: 0
- Summary data: reported as mean (minimum, maximum) i) Physical functioning: 82.2 (71.1, 88.9) / 87.4 (73.3, 97.9) for placebo / ranolazine group; ii) Angina stability: 58.6 (25.0, 75.0) / 77.6 (50.0, 100.0) for placebo/ranolazine group; iii) Angina frequency: 64.8 (40.0, 80.0) / 80.7 (50.0, 100.0) for placebo / ranolazine group; iv) Treatment satisfaction: 90.3 (76.5, 100.0) / 86.4 (70.6, 100.0) for placebo / ranolazine group v) Quality of life: 62.9 (50.0, 75.0) / 77.6 (58.3, 91.7) for placebo / ranolazine group. Baseline data measured but not reported

Notes	Relevant observations for the data provided before: none Source of funding: not stated Notable conflicts of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation is stated but not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study declared to be double-blinded, but no description is provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study declared to be double-blinded, but no description is provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	It is reported that no patient withdrew the study
Selective reporting (reporting bias)	Unclear risk	There is no published protocol. Results for all the outcomes stated in the "Methods" section of the paper are reported
Other bias	Unclear risk	The source of funding was not stated. Conflicts of interest were not stated.

TERISA 2013

Methods	Study design: parallel-group trial

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TERISA 2013 *(Continued)*

	Total study duration: 12 weeks Duration of follow-up: no follow-up beyond treatment phase Method of randomisation: Interactive Voice/Web Response System (IVRS/IWRS) Method of concealment of allocation: blinded study drug bottle assigned by the IVRS/IWRS Blinding: double-blind, participants and clinicians were blinded by using study drug bottles assigned by the IVRS/IWRS Power calculation: 90% to show a relative reduction of 20% in weekly angina frequency Phases of the study: 2 (qualifying phase, treatment phase) Number of patients randomised: 949 (476/473 for placebo/ranolazine group) Exclusions post-randomisation: 22 (11 in the ranolazine arm, 11 in the placebo arm) Withdrawals (and reasons): 20 (9 withdrawals, 3 deaths in the ranolazine group, 11 withdrawals, 2 deaths in the placebo group)

Participants	Total number: 949
	
	Country of enrolment: 14 (United States, Belarus, Bulgaria, Canada, Czech Republic, Georgia, Germany, Israel, Poland, Russian Federation, Serbia, Slovakia, Slovenia, Ukraine)
	
	Setting/location: not specified
	
	Diagnostic criteria (stable angina pectoris): at least a three-month history of chronic stable angina that remain symptomatic despite treatment with 1 or 2 anti-anginal, with documented history of CAD (macrovascular angina)
	
	Comorbidities: type 2 diabetes mellitus
	
	Age (mean ± SD): 64 ± 8.5 years
	
	Gender (male %): 61%
	
	Inclusion criteria:
	
	• Aged at least 18 years
	• At least a 3-month history of chronic stable angina triggered by physical effort and relieved by rest and/or sublingual nitroglycerin
	• CAD documented by one or more of the following:
	  • Angiographic evidence of ≥ 50% stenosis of one or more major coronary arteries
	  • History of myocardial infarction (MI) documented by positive myocardial muscle creatine kinase (CK-MB) enzymes, troponins, or electrocardiogram (ECG) changes
	  • Cardiac imaging study or exercise test diagnostic for CAD
	• Treatment with up to 2 anti-anginal therapies at a stable dose for at least 2 weeks prior to the qualifying period.
	• Documented history of T2DM
	• Willing to maintain stable tobacco usage habits throughout the study
	• Willing to maintain stable activity levels throughout the study
	• Females of childbearing potential must agree to use highly effective contraception methods from Screening throughout the duration of study treatment and for 14 days following the last dose of study drug
	
	Exclusion criteria:
	
	• New York Heart Association (NYHA) Class III and IV
	• Acute coronary syndrome in the prior 2 months or planned coronary revascularisation during the study period

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TERISA 2013 *(Continued)*

- Stroke or transient ischaemic attack within 6 months prior to screening
- QTc > 500 ms
- Uncontrolled hypertension (seated systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg)
- Systolic blood pressure < 100 mm Hg
- Clinically significant hepatic impairment
- Prior treatment with ranolazine, or known hypersensitivity or intolerance to ranolazine
- Females who are breastfeeding
- Positive serum pregnancy test
- Participation in another investigational drug or device study within 1 month prior to Screening
- Current treatment with trimetazidine, ivabradine, or nicorandil. Subjects will need to discontinue these medications 2 weeks prior to the qualifying period
- Current treatment with potent inhibitors of cytochrome (CYP)3A (e.g. ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir)
- Current treatment with CYP3A and P glycoprotein (Pgp) inducers (e.g. rifampicin/rifampin, carbamazepine, and St. John's wort [Hypericum perforatum])
- Current treatment with CYP3A4 substrates with a narrow therapeutic range (e.g. cyclosporine, tacrolimus, and sirolimus)
- Subjects taking simvastatin who cannot reduce the dose to 20 mg once daily or who cannot switch to another statin
- Current treatment with Class I or III anti-arrhythmic medications
- History of illicit drug use or alcohol abuse within 1 year of Screening
- Any other conditions that, in the opinion of the investigator, are likely to prevent compliance with the study protocol or pose a safety concern if the subject participates in the study

Interventions	Number of intervention groups: 2 Concomitant medications: Anti-anginal: beta blockers, calcium channel blockers, long-acting nitrates; other cardiovascular medications: statins, antiplatelet agents, ACE-I/ARB; antidiabetic medications: glucose-lowering medications, insulin Excluded medications: none (apart from those mentioned in the exclusion criteria) **Placebo group** • Intervention: placebo • Duration of intervention: 8 weeks **Ranolazine group** • Intervention: ranolazine ER 1000 mg twice daily • Duration of intervention: 8 weeks
Outcomes	Total number of outcomes: • According to study protocol: 6 (angina episodes frequency, sublingual nitroglycerin use frequency, number of angina-free days, proportion of subjects with ≥50% reduction in average weekly angina frequency, health-related quality of life, adverse events incidence) • Reported: 6 **All-cause mortality** • Outcome definition: number of deaths • Method and unit of measurement: absolute frequency • Time points reported: 8 weeks **Quality of life** **1. Medical Outcomes Short Form-36 (SF-36)**

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TERISA 2013 *(Continued)*

- Outcome definition: health state scale, change from baseline in the Mental and Physical Components
- Upper and lower limits and whether a high or low score is good: the range of each health domain score is 0-100, with 0 indicating a poorer health state and 100 indicating a better health state
- Method and unit of measurement: change from baseline, score
- Time points reported: 8 weeks

2. Patient's Global Impression of Change (PGIC)

- Outcome definition: change in overall status scale, total score
- Upper and lower limits and whether a high or low score is good: ranging from 1 (no change or worse) to 7 (very much improved)
- Method and unit of measurement: score
- Time points reported: 8 weeks

Acute myocardial infarction incidence (non-fatal)

- Outcome definition: number non-fatal myocardial infarction cases
- Method and unit of measurement: absolute frequency
- Time points reported: 8 weeks

Angina episodes frequency

- Outcome definition: average number of angina episodes per week from weeks 2 to 8 of treatment
- Method and unit of measurement: number of angina episodes per week
- Time points reported: 8 weeks

Adverse events incidence

- Outcome definition: number of patients who report any non serious adverse event
- Method and unit of measurement: absolute frequency
- Time points reported: 8 weeks plus 30 days

RESULTS

All-cause mortality

- Sample size: 944 (intention-to-treat analysis)
- Missing participants: 5
- Summary data: 2/474-3/470 for placebo-ranolazine group
- Subgroup analyses: not performed

Quality of life

1. Medical Outcomes Short Form-36 (SF-36)

- Sample size: 927 (intention-to-treat analysis)
- Missing participants: 22
- Summary data: Physical component: 1.9 (1.3-2.5) / 2.9 (2.3-3.5) for placebo/ranolazine group; mental component: 1.1 (0.28-1.92) / 1.0 (0.18-1.82) for placebo/ranolazine group
- Subgroup analyses: not performed

2. Patient's Global Impression of Change (PGIC)

- Sample size: 927 (intention-to-treat analysis)
- Missing participants: 22
- Summary data: 3.9 (3.74-4.10) / 4.0 (3.82-4.19) for placebo/ranolazine group
- Subgroup analyses: not performed

Acute myocardial infarction incidence (non-fatal)

- Sample size: 944 (intention-to-treat analysis)

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TERISA 2013 *(Continued)*

- Missing participants: 5
- Summary data: 3/474 - 1/470 for placebo-ranolazine group
- Subgroup analyses: not performed

Angina episodes frequency

- Sample size: 927 (intention-to-treat analysis)
- Missing participants: 22
- Summary data: 4.3 (4.01-4.52) / 3.8 (3.57-4.05) for placebo/ranolazine group
- Subgroup analyses: several pre-specified subset analyses, all are reported, significant interaction in the effect of ranolazine versus placebo was found only by the geographic region of enrolment (Russia, Ukraine, Belarus versus Other, $p_{interaction}$ = 0.016). Russia, Ukraine and Belarus: 4.3 (4.1-4.6) / 4.1 (3.9-4.4) for placebo/ranolazine group; Other: 4.1 (3.7-4.6) / 3.1 (2.8-3.5) for placebo/ranolazine group

Adverse events incidence:

- Sample size: 944 (intention-to-treat analysis)
- Missing participants: 5
- Summary data: 85/474 - 110/470 for placebo-ranolazine group. The most common adverse events reported in the ranolazine group were dizziness (17/462), nausea (17/462), headache (7/462), constipation (8/462), hypoglycaemia (3/462); and in the placebo group were dizziness (6/465), nausea (2/465), headache (9/465) and constipation (2/465), hypoglycaemia = 0/465.
- Subgroup analyses: not performed

Notes	Relevant observations for the data provided before: none Source of funding: Gilead Sciences Notable conflicts of interest: all the authors have financial relationships with Gilead Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation undertaken by the IVRS/IWRS
Allocation concealment (selection bias)	Low risk	Intervention was provided to personnel in blinded study drug bottles assigned by the IVRS/IWRS
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study declared to be double-blinded, but no description is provided. Intervention was provided to personnel and patients in blinded drug bottles, so they were unaware of the treatment assigned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study declared to be double-blinded, but no description about the blinding of data collectors/outcome adjudicators is provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals are reported, but no description is provided
Selective reporting (reporting bias)	Low risk	According to the protocol published in Clinicaltrials.gov, results for all the outcomes are reported
Other bias	High risk	The study was supported by Gilead Sciences. All the authors have financial relationships with Gilead Sciences

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Thadani 1994

Methods	Study design: parallel-group trial Total study duration: 35-40 days Duration of follow-up: no follow-up beyond treatment phase Method of randomisation: not described Method of concealment of allocation: not mentioned Blinding: double-blind, not described Power calculation: not mentioned Phases of the study: 2 (qualifying phase, treatment phase) Number of patients randomised: 319 (79, 81, 81 and 78 for placebo, ranolazine 30 mg, ranolazine 60 mg and ranolazine 120 mg groups) Exclusions post-randomisation: 20 Withdrawals (and reasons): 31 (15 because of adverse events, new intercurrent illnesses, or new laboratory abnormalities, 4 because of unsatisfactory therapeutic response, 2 because of study administration problems, 10 for 'other' reasons (4 did not take study medication in compliance with the protocol, 2 elected to have surgical intervention, 2 declined to finish the study, 1 violated the protocol, and 1 required medication to control ventricular ectopy)). Withdrawals were similarly distributed among the study groups: 9/79, 9/81, 7/81 and 6/78 for placebo, ranolazine 30 mg, ranolazine 60 mg and ranolazine 120 mg groups

Participants	Total number: 319
	
	Country of enrolment: United States
	
	Setting/location: not specified
	
	Diagnostic criteria: at least a 3-month history of symptomatic chronic stable angina triggered by physical effort and relieved by rest or nitroglycerin
	
	Comorbidities: none
	
	Age (mean ± SD): 65 ± 8 years
	
	Gender (male %): 74.7%/80.2%/81.5%/79.5% for placebo/ranolazine 30 mg/ranolazine 60 mg/ranolazine 120 mg group
	
	Inclusion criteria:
	
	• At least a 3-month history of symptomatic chronic stable angina triggered by physical effort and relieved by rest or nitroglycerin
	• Having ECG evidence of exercise-induced myocardial ischaemia (ST segment depression of >1 mm from baseline) and a resting ECG pattern that would not interfere with the interpretation of ST changes during exercise.
	• Patients entered the 4-week double-blind phase if they met the following entry criteria:
	  * The duration of exercise for each of two qualifying ETTs had been 3 to 9 minutes
	  * The difference between the two qualifying ETTs was not more than 15% of the duration of the longer ETT
	  * All qualifying ETTs had evidence of myocardial ischaemia, as diagnosed by ST depression of 1 mm or more, measured 80 milliseconds from the J point
	  * The Holter monitor had at least 36 hours of readable ECG tracings
	  * The patient reported at least one anginal episode during the week before randomisation

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Thadani 1994 *(Continued)*

	Exclusion criteria: • Patients with pacemakers • Standing systolic blood pressure < 95 mm Hg • Patients with conditions that would hinder or confuse follow-up evaluations • Patients unable to undergo the protocol requirements for the study (e.g. stress testing)
Interventions	Number of intervention groups: 4 Concomitant medications: (permitted) sublingual nitroglycerin (0.4mg tablets), taken for anginal pain and not as a prophylactic agent; hydrochlorothiazide and potassium supplementation for the treatment of hypertension Excluded medications: all anti-anginal medication with the exception of sublingual nitroglycerin **Placebo group** • Intervention: placebo thrice daily • Duration of intervention: 4 weeks **Ranolazine 30 mg group** • Intervention: ranolazine (type of formulation not specified) 30 mg thrice daily • Duration of intervention: 4 weeks **Ranolazine 60 mg group** • Intervention: ranolazine (type of formulation not specified) 60 mg thrice daily • Duration of intervention: 4 weeks **Ranolazine 120 mg group** • Intervention: ranolazine (type of formulation not specified) 120 mg thrice daily • Duration of intervention: 4 weeks
Outcomes	Total number of outcomes: 6 According to study protocol: no published protocol; according to the "Methods" section: 10 (change from baseline in ETT total exercise duration, time to onset of angina and time to 1-mm ST segment depression (peak and through), change from baseline in the number and duration of ST segment depression episodes (by Holter monitoring), change from baseline in the weekly rate of NTG consumption and anginal attacks, adverse events incidence) Reported: 12 (including circulatory data at peak and through) **Angina episodes frequency** • Outcome definition: weekly rate of anginal attacks, change from baseline • Method and unit of measurement: number per week • Time points reported: 4 weeks **Adverse events incidence** • Outcome definition: number of adverse events reported • Method and unit of measurement: absolute frequency • Time points reported: 4 weeks **RESULTS** **Angina episodes frequency** • Sample size: 283 (intention-to-treat analysis)

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Thadani 1994 *(Continued)*

- Missing participants: 36
- Summary data (mean, 95% CI -2.24 -3.04 to -1.58) / -2.32 (-3.34 to -1.71) / -2.67 (-3.38 to -2.05) / -2.11 (-3.03 to -1.50) for placebo/ranolazine 30 mg/ranolazine 60 mg/ranolazine 120 mg group
- Subgroup analyses: not performed

Adverse events incidence

- Sample size: 299 (intention-to-treat analysis)
- Missing participants: 20
- Summary data: it is stated that the rates of adverse events were similar among the study groups, but incidence for each one is not reported. It is stated that the 3 adverse events reported most frequently in the ranolazine groups were headache, dizziness and asthenia. No description is provided for the ranolazine group.
- Subgroup analyses: not performed

Notes	Relevant observations for the data provided before: 'all patients' (intention-to-treat) (N = 299) and per-protocol (N = 258) analysis were performed for ETT variables Source of funding: Syntex Research, Palo Alto, CA, USA Notable conflicts of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation is stated but not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study declared to be double-blinded, but no description is provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study declared to be double-blinded, but no description is provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals and reasons are provided and similarly distributed among the study groups, however, number of withdrawals is nearly 10% of total number of randomised patients
Selective reporting (reporting bias)	Unclear risk	There is no published protocol. Results for all the outcomes stated in the "Methods" section of the paper are reported
Other bias	High risk	The study was supported by Syntex Research. Authors did not state conflicts of interest.

Villano 2013

Methods	Study design: parallel-group trial Total study duration: 4 weeks

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Villano 2013 *(Continued)*

	Duration of follow-up: no follow-up beyond treatment phase Method of randomisation: computer-generated table of random numbers Method of concealment of allocation: drugs were given to patients in anonymous drug packages by three of the authors who were not involved in the clinical assessment of patients. Cardiologists involved in the clinical and laboratory assessment of patients and/or analyses of data were blinded to the allocation of treatment Blinding: not mentioned, but presumably involving participants and data collectors/outcome adjudicators Power calculation: 90% to detect a significant difference of 15 points (SD 10) between each active drug versus placebo in any SAQ item and in the EuroQoL score Phases of the study: 1 (treatment phase) Number of patients randomised: 46 Exclusions post-randomisation: not reported Withdrawals (and reasons): not reported

Participants	Total number: 46
	
	Country of enrolment: Italy
	
	Setting/location: ambulatory patients
	
	Diagnostic criteria (stable angina pectoris): history of typical effort angina with exercise-induced ST-segment depression ≥ 1 mm, normal coronary angiography and absence of any specific cardiac disease including vasospastic angina (microvascular angina) which remains symptomatic despite anti-ischaemic therapy
	
	Comorbidities: none
	
	Age (mean, interval): 57 ± 12/57 ± 11/60 ± 9 years for ivabradine/ranolazine/placebo group
	
	Gender (male %): 2/16, 3/15, 4/15 for ivabradine-ranolazine-placebo group
	
	Inclusion criteria:
	
	• Diagnosis of stable primary MVA based on the presence of
	  * A history of typical effort angina
	  * Exercise-induced ST-segment depression ≥ 1 mm
	  * Normal coronary angiography
	  * Absence of any specific cardiac disease including vasospastic angina
	  * Normal echocardiographic examination including absence of left ventricular hypertrophy
	  * A coronary flow reserve < 2.5 in the left anterior descending coronary artery
	• Suboptimal control of symptoms on conventional anti-ischaemic therapy, as indicated by the occurrence of ≥1 episode per week of angina
	• No previous consumption of the drugs under investigation
	• No apparent contraindications to ivabradine and ranolazine administration
	
	Exclusion criteria: Not described

Interventions	Number of intervention groups: 3 Concomitant medications: anti-anginals, antihypertensives, anti-aggregants, statins Excluded medications: none **Placebo group**

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Villano 2013 *(Continued)*

- Intervention: placebo twice daily
- Duration of intervention: 4 weeks

Ivabradine group

- Intervention: ivabradine 5 mg twice daily
- Duration of intervention: 4 weeks

Ranolazine group

- Intervention: ranolazine (type of formulation not specified) 375 mg twice daily
- Duration of intervention: 4 weeks

Outcomes

Total number of outcomes:

- According to study protocol: no published protocol; according to the "Methods" section: 5 (angina status, quality of life, exercise stress tests, coronary microvascular dilation, peripheral vascular dilation)
- Reported: 5

Quality of life

1. Seattle Angina Questionnaire (SAQ)

- Outcome definition: angina status scale, five components
- Upper and lower limits and whether a high or low score is good: each component is scored on a 0 to 100 scale, with higher scores indicating better functional status
- Method and unit of measurement: score
- Time points reported: 4 weeks

2. EuroQoL visual analogue scale (VAS)

- Outcome definition: quality of life scale, measured as a total score
- Upper and lower limits and whether a high or low score is good: scored from 0 (worst condition) to 100 (best condition)
- Method and unit of measurement: score
- Time points reported: 4 weeks

Adverse events incidence

- Outcome definition: number of adverse events reported
- Method and unit of measurement: absolute frequency
- Time points reported: 4 weeks

RESULTS

Quality of life

1. Seattle Angina Questionnaire (SAQ)

- Sample size: 46 (intention-to-treat analysis)
- Missing participants: none
- Summary data: baseline/post-intervention for placebo-ivabradine-ranolazine group
  - (i) physical limitation: 68.2 ± 20/67.0 ± 21 - 65.4 ± 15/76.5 ± 16 - 69.8 ± 16/84.1 ± 12,
  - (ii) angina stability: 56.7 ± 26/55.0 ± 25 - 43.8 ± 30/56.3 ± 33 - 40.0 ± 25/90.0 ± 18,
  - (iii) angina frequency: 72.7 ± 17/71.3 ± 18 - 64.4 ± 14/73.1 ± 18 - 61.3 ± 12/81.3 ±1 7,
  - (iv) treatment satisfaction: 75.8 ± 15/74.2 ± 14 - 75.8 ± 15/84.4 ± 14 - 68.8 ± 16/90.8 ± 9,
  - (v) disease perception: 60.0 ± 22/57.2 ± 23 - 49.5 ± 23/62.5 ± 26 - 45.0 ± 17/79.4 ± 14
- Subgroup analyses: not performed

2. EuroQoL visual analogue scale (VAS)

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Villano 2013 *(Continued)*

- Sample size: 46 (intention-to-treat analysis)
- Missing participants: none
- Summary data: baseline/post-intervention for placebo-ivabradine-ranolazine group 65.7 ± 17/64.3 ± 19 - 66.6 ± 14/72.5 ± 17 - 61.3 ± 17/79.3 ± 13
- Subgroup analyses: not performed

Adverse events incidence

- Sample size: 46 (intention-to-treat analysis)
- Missing participants: none
- Summary data: 0/15 - 0/16 - 0/15 for placebo-ivabradine-ranolazine group
- Subgroup analyses: not performed

Notes

Relevant observations for the data provided before: none

Source of funding: not stated

Notable conflicts of interest: no conflicts of interest to disclose

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated table of random numbers
Allocation concealment (selection bias)	Low risk	Drugs were given to patients in anonymous drug packages by three of the authors who were not involved in the clinical assessment of patients.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding design is not stated. It is mentioned that study drugs were provided in anonymous packages, so it could be assumed that patients and personnel were blinded to the allocation of treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding design is not stated. It is mentioned that the cardiologists involved in the clinical and laboratory assessment of patients and/or analyses of data were blinded to the allocation of treatment. However, for outcomes such as quality of life, blinding measures have not been described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions or withdrawals were reported. We assumed that all patients completed the study
Selective reporting (reporting bias)	Unclear risk	There was no published protocol. Results for all outcomes in the 'Methods' section were reported
Other bias	Unclear risk	Funding source not stated. The authors declared no conflicts of interest

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arnold 2014	Substudy of RCT: substudy of the TERISA 2013 trial on quality of life
Cocco 1992	Wrong intervention: ranolazine given in single dose

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Study	Reason for exclusion
Coleman 2015	Not RCT: health economics study not conducted alongside a RCT
Hidalgo-Vega 2014	Not RCT: health economics study not conducted alongside a RCT
Jain 1990	Not RCT: three-period cross-over trial with only one group of participants, no randomisation method stated
Kohn 2014	Not RCT: health economics study not conducted alongside a RCT
Lucioni 2009	Not RCT: health economics study not conducted alongside a RCT
Rehberger-Likozar 2015	No angina population: condition studied did not meet inclusion criteria
Rich 2007	Substudy of RCT: subgroup analysis of the CARISA 2004 and ERICA 2006 trials
ROLE 2007	Not RCT: open-label follow-up study of the CARISA 2004 and MARISA 2004 trials, including only participants treated with ranolazine (without comparator)

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT01304095

Methods	Study design: parallel-group trial Duration of follow-up: 6 months Method of randomisation: not described Method of concealment of allocation: not described Blinding: open-label Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Total number: 160 (estimated) Country of enrolment: USA Setting/location: not specified Diagnostic criteria (stable angina pectoris): symptoms of angina with evidence of stable CAD (macrovascular angina) Comorbidities: metabolic syndrome Inclusion criteria: • Evidence of stable Coronary Artery Disease • * MI > 30 days prior to enrolment * PCI > 30 days prior to enrolment * CABG > 30 days prior to enrolment * Angiography showing > 50% stenosis in a major vessel, branch or bypass graft > 30 days prior to enrolment • Metabolic Syndrome as evidenced by at least one of the following risk factors:

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NCT01304095 *(Continued)*

	• Abdominal Obesity (elevated waist circumference)
	  * Men - waist circumference ≥ 40 inches (102 cm) Asians/Asian Americans ≥ 35.5 inches (90 cm)
	  * Women - waist circumference ≥ 35 inches (88 cm) Asians/Asian Americans ≥ 31.5 inches (80 cm)
	• Atherogenic dyslipidaemia (either one or both)
	  * Triglycerides ≥ 150 mg/dL
	  * Reduced HDL Men - HDL ≤ 40 mg/dL Women - HDL ≤ 50 mg/dL
	• Elevated Blood Pressure (equal to or greater than 130/85)
	• Elevated fasting glucose (equal to or greater than 100 mg/dL)

Interventions	Number of intervention groups: 2 Concomitant medications: standard medical therapy Excluded medications: those mentioned in exclusion criteria **Control group** Intervention: no treatment Duration of intervention: 6 months **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 500/1000 mg twice daily Duration of intervention: 6 months
Outcomes	Total number of outcomes: 6 (ETT parameters, fasting glucose, angina (SAQ scale), concomitant medications, lipid profile, HbA1c) **OUTCOMES** No outcome meets inclusion criteria
Notes	

Tagarakis 2013

Methods	Study design: parallel-group trial Duration of follow-up: not reported Method of randomisation: not described Method of concealment of allocation: not described Blinding: single-blind (outcome assessors) Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Country of enrolment: Greece Setting/location: inpatient Diagnostic criteria (stable angina pectoris): not described Comorbidities: patients scheduled for elective on-pump CABG

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Tagarakis 2013 *(Continued)*

	Inclusion criteria: not described Exclusion criteria: not described
Interventions	Number of intervention groups: 2 Concomitant medications: not described Excluded medications: not described **Control group** Intervention: no treatment Duration of intervention: not reported **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 375 mg twice daily for 3 days prior to surgery and until discharge Duration of intervention: not reported
Outcomes	Total number of outcomes: 3 (post-operative atrial fibrillation, left atrial diameter, left ventricular ejection fraction) **OUTCOMES** No outcome meets the inclusion criteria
Notes	

Tian 2012

Methods	Study design: parallel-group trial Duration of follow-up: Method of randomisation: not described Method of concealment of allocation: not described Blinding: not mentioned Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Total number: 86 Country of enrolment: China Setting/location: not specified Diagnostic criteria (stable angina pectoris): not described Comorbidities: none Inclusion criteria: not described Exclusion criteria: not described

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Tian 2012 *(Continued)*

Interventions	Number of intervention groups: 2 Concomitant medications: diltiazem Excluded medications: not described **Control group** Intervention: no treatment Duration of intervention: not reported **Ranolazine group** Intervention: ranolazine (type of formulation not specified) (dosage not reported) Duration of intervention: not reported
Outcomes	Total number of outcomes: 2 (ECG total effective rate, adverse events incidence) **OUTCOMES** **Adverse events incidence** Outcome definition: not described Method and unit of measurement: absolute frequency Time points to report: not reported
Notes	

Wang 2012

Methods	Study design: parallel-group trial Duration of follow-up: 8 weeks Method of randomisation: not described Method of concealment of allocation: not described Blinding: not mentioned Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Country of enrolment: China Setting/location: not specified Diagnostic criteria (stable angina pectoris): stable angina with coronary heart disease (macrovascular angina) Comorbidities: none Inclusion criteria: not described Exclusion criteria: not described
Interventions	Number of intervention groups: 3

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Wang 2012 *(Continued)*

	Concomitant medications: conventional therapy (aspirin, cholesterol lowering agents, metoprolol) Excluded medications: not described **Placebo group** Intervention: placebo Duration of intervention: 8 weeks **Ranolazine 500 mg group** Intervention: ranolazine SR 500 mg twice daily Duration of intervention: 8 weeks **Ranolazine 1000 mg group** Intervention: ranolazine SR 1000 mg twice daily Duration of intervention: 8 weeks
Outcomes	Total number of outcomes: 5 (angina frequency, nitroglycerin consumption frequency, ECG total effective rate, ADR, liver/kidney function) **OUTCOMES** **Angina episodes frequency** Outcome definition: not described Method and unit of measurement: not described Time points to report: 8 weeks
Notes	

Characteristics of ongoing studies *[ordered by study ID]*

Calcagno 2014

Trial name or title	Not stated
Methods	Study design: parallel-group trial Duration of follow-up: 12 months Method of randomisation: not described Method of concealment of allocation: not described Blinding: not mentioned Power calculation: not mentioned Phases of the study: 2 (treatment phase, follow-up phase)
Participants	Country of enrolment: not described Setting/location: not specified Diagnostic criteria (stable angina pectoris): not described

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Calcagno 2014 *(Continued)*

	Comorbidities: percutaneous coronary intervention plus stent implantation Inclusion criteria: not described Exclusion criteria: not described
Interventions	Number of intervention groups: 2 Concomitant medications: medical therapy (not described) Excluded medications: not mentioned **No treatment group** Intervention: none Duration of intervention: 30 days **Ranolazine group** Intervention: ranolazine (type of formulation not specified) (dose not reported) Duration of intervention: 30 days
Outcomes	Total number of outcomes: 5 (ETT parameters, symptoms, arrhythmia, angina during moderate exercises, re-hospitalisation) **OUTCOMES** No outcome appears to meet the inclusion criteria
Starting date	Not reported
Contact information	Not provided
Notes	

Calcagno 2015

Trial name or title	Not stated
Methods	Study design: parallel-group trial Duration of follow-up: 12 months Method of randomisation: not described Method of concealment of allocation: not described Blinding: not mentioned Power calculation: not mentioned Phases of the study: 2 (treatment phase, follow-up phase)
Participants	Country of enrolment: not described Setting/location: not specified Diagnostic criteria (stable angina pectoris): not described Comorbidities: percutaneous coronary intervention plus stent implantation

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Calcagno 2015 *(Continued)*

	Inclusion criteria: not described Exclusion criteria: not described
Interventions	Number of intervention groups: 3 Concomitant medications: standard therapy (not described) Excluded medications: not mentioned **No treatment group** Intervention: none Duration of intervention: 30 days **Ivabradine group** Intervention: ivabradine (dose not reported) Duration of intervention: 30 days **Ranolazine group** Intervention: ranolazine (type of formulation not specified) (dose not reported) Duration of intervention: 30 days
Outcomes	Total number of outcomes: 3 (ETT parameters, weekly angina during daily moderate exercises, re-hospitalisation) **OUTCOMES** No outcome meets the inclusion criteria
Starting date	Not reported
Contact information	Not provided
Notes	

CTRI/2014/01/004332

Trial name or title	CTRI/2014/01/004332
Methods	Study design: parallel-group trial Duration of follow-up: 8 weeks Method of randomisation: computer generated randomisation Method of concealment of allocation: sequentially numbered, sealed, opaque envelopes Blinding: not specified ("Investigator Blinded") Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Total number: 50 (estimated) Country of enrolment: India

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CTRI/2014/01/004332 *(Continued)*

	Setting/location: not specified Diagnostic criteria (stable angina pectoris): not described Comorbidities: sustained STEMI Inclusion criteria: • Age from 18 to 75 years • Patients who have sustained STEMI more than 12 weeks ago • Left ventricular ejection fraction ≤40% Exclusion criteria: • H/o undergoing CABG or stenting procedure within the last 12 weeks • Co-existing end-stage pulmonary, or hepatic disease • Valvular heart disease • Patient consumed other study medication in the last 3 months • Unwilling to comply with study related procedures
Interventions	Number of intervention groups: 2 Concomitant medications: those indicated by the patient's cardiologist Excluded medications: not mentioned **Trimetazidine group** Intervention: trimetazidine 35 mg twice daily Duration of intervention: 8 weeks **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 500 mg twice daily Duration of intervention: 8 weeks
Outcomes	Total number of outcomes: 3 (changes in LV systolic and diastolic function, improvement in angina symptoms, ADR) **OUTCOMES** No outcome meets the inclusion criteria
Starting date	28/10/2013
Contact information	Dr Melvin George Assistant Professor Cardiac Research SRM Medical College Hospital Dept of Cardiology SRM MCH RC Kattankulathur Kancheepuram Kancheepuram TAMIL NADU 603203 India 9894133697 melvingeorge2003@gmail.com

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CTRI/2014/01/004332 *(Continued)*

Notes	Source of funding: SRM Medical College Hospital

EUCTR 2011-001278-24

Trial name or title	2011-001278-24 / MEIN/10/Ran-Cad/003
Methods	Study design: parallel-group trial Duration of follow-up: 24 weeks Method of randomisation: not described Method of concealment of allocation: not described Blinding: double-blind Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Total number: 1460 (estimated) Country of enrolment: Greece, Switzerland Setting/location: not specified Diagnostic criteria (stable angina pectoris): exercise angina in patients with CAD (macrovascular angina) Comorbidities: none Inclusion criteria: • Male and female patients (females of childbearing potential must be using adequate contraceptive precautions such as implants, injectables, combined oral contraceptives, intrauterine devices, sexual abstinence or vasectomised partner) • Patients aged ≥ 18 years • Patients with coronary artery disease confirmed by angiography, prior MI, prior revascularisation (PCI, CABG) and with exercise angina not controlled by the standard therapy • ST-segment depression ≥ 1mm during exercise ECG • Capacity to perform the exercise test • Able and willing to sign informed consent and to comply with study procedures • Females of childbearing potential or within two years from the menopause must have a negative urine pregnancy test • Reproducible ST-segment depression ≥ 1mm during two exercise tests performed 1 week apart (difference in exercise no more than 20%) (at first visit) Exclusion criteria: • Angina at rest • ECG abnormalities at rest (left bundle-branch block, resting ST-segment depression ≥ 1mm, tachyarrhythmia) • Presence of factors that preclude satisfactory interpretation of the ECG (e.g. resting ST-segment depression ≥ 1 mm in any lead, left bundle-branch block, digoxin therapy) or repolarisation and conduction abnormalities • Heart failure (class III or IV NYHA) • Moderate-severe hypertension (SBP > 160 mmHg and/or DBP > 100 mmHg) • Hypotension

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EUCTR 2011-001278-24 *(Continued)*

	• Acute coronary syndrome or coronary revascularisation procedure within the prior 3 months before enrolment • Females who are pregnant or nursing • Any clinically relevant haematological or biochemical abnormality on routine screening, according to Investigator's judgment • Severe concurrent pathology, including terminal illness (cancer, AIDS, etc.) • Renal impairment defined as creatinine clearance< 30 mL/min • Mild, moderate or severe hepatic impairment or hepatic insufficiency defined as: SGOT or SGPT > 3 times ULN or total serum bilirubin > 1.5 times greater than normal upper limit • Pre-existing QT prolongation (including congenital long QT syndrome, uncorrected hypokalaemia) • Patients on QT-prolonging drugs such as Class Ia (e.g. quinidine) and Class III (e.g. dofetilide, sotalol, dronedarone) anti-arrhythmics, and antipsychotics (e.g. thioridazine, ziprasidone) • Existing contraindications for exercise testing (e.g. acute myocarditis or pericarditis, DVT, severe aortic stenosis) • Dementia, psychosis, alcoholism (>350 g ethanol/week) or chronic abuse of medicines, drugs or psychoactive substances • Conditions which in the Investigator's opinion may interfere with the study's execution or due to which the patient should not participate for safety reasons • Risk of low patient cooperation
Interventions	Number of intervention groups: 2 Concomitant medications: not described Excluded medications: those mentioned in exclusion criteria **Placebo group** Intervention: placebo Duration of intervention: 24 weeks **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 750 mg twice daily Duration of intervention: 24 weeks
Outcomes	Total number of outcomes: 5 (ETT parameters, angina frequency, nitroglycerin consumption frequency, adverse events incidence, laboratory findings) **OUTCOMES** **Angina episodes frequency** Outcome definition: weekly frequency Method and unit of measurement: number/week Time points to report: 4, 12 and 24 weeks **Adverse events incidence** Outcome definition: not described Method and unit of measurement: absolute frequency Time points to report: 4, 12 and 24 weeks
Starting date	Not reported

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EUCTR 2011-001278-24 *(Continued)*

Contact information	Study Medical Expert (SME) Via Walter Tobagi, 8 Peschiera Borromeo - Italy 003902516555236 dzava@lusofarmaco.it
Notes	Source of funding: Menarini International Operations Luxembourg SA

EUCTR 2012-001584-77

Trial name or title	EUCTR2012-001584-77-DE / MEIN/10/Ran-PCI/005
Methods	Study design: parallel-group trial Duration of follow-up: 5 weeks Method of randomisation: not described Method of concealment of allocation: not described Blinding: double-blind Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Country of enrolment: Germany Setting/location: not specified Diagnostic criteria (stable angina pectoris):history of chronic stable angina and coronary stenosis by angiography (macrovascular angina) Comorbidities: none Inclusion criteria: • Male and female patients (females of childbearing potential must have a negative urine pregnancy test and must be using adequate contraceptive precautions • Performed coronary angiography with or without initial PCI more than 24 hours before MRI • Remaining ≥ 70% stenosis of a coronary artery bigger than 2 mm diameter (not corrected by PCI) • Indication of further interventional treatment • Wall motion abnormalities in at least one segment; if segment 17 is affected, an additional segment has to show wall motion abnormalities • History of chronic angina pectoris • Age ≥ 18 years • Normalised blood pressure < 140/90 mmHg and heart rate < 70 bpm and ≥ 50 bpm at rest • Sinus rhythm • Standard therapy: beta-blocker and/or calcium channel blocker (stable for 4 weeks) Exclusion criteria: • Cardiac instability, e.g. acute coronary syndrome as indication for the coronary angiography (ST-elevation or positive troponin testing)

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EUCTR 2012-001584-77 *(Continued)*

	• Contraindication for MRI (e.g. implanted pace maker, internal defibrillator, MRI incompatible devices or metals) • Contraindication for dobutamine, atropine, gadolinium based contrast agent, or metoprolol • Patients with heart failure classification NYHA III and NYHA IV • Myocardial infarction during the last 3 days prior to treatment with ranolazine • Severe renal impairment (GFR < 30 ml/min) • Moderate or severe hepatic impairment (ALT or AST > 2.5 × upper normal limit) • Allergic asthma bronchiale • Hyperthyroidism or Hashimoto thyroiditis • Myocarditis or inflammatory heart disease • Concomitant administration of class Ia (e.g. quinidine) or class III (e.g. dofetilide, sotalol) anti-arrhythmics, except for amiodarone • Long acting nitrates • Concomitant treatment with potent inhibitors of CYP3A • Concomitant treatment with CYP3A inducers • Dronedarone • Use of greater than 1000 mg daily dose of metformin during the study • Hypersensitivity to the active substance or to any of the excipients • Hypersensitivity to dobutamine, atropine, gadolinium based contrast agent, or metoprolol • Concomitant administration of > 20 mg simvastatin/day • History of ECG abnormalities that, in the opinion of the investigator, render the patient unsuitable for the trial, e.g. history of long QT syndrome or significant prolonged QT interval (> 120%) • Participation in another trial of an investigational drug or device within 30 days prior to screening • Pregnant and breast-feeding women (females of childbearing potential or within two years from the menopause must have a negative urine pregnancy test) • Less than 3 months since delivery, abortion, or lactation before the first screening/examination vis • Severe psychiatric disorders/neurological disorders • Suspected abuse of alcohol, analgesics or psychotropic drugs • Disabling or terminal illness
Interventions	Number of intervention groups: 2 Concomitant medications: standard therapy (beta-blocker and/or calcium channel blocker) Excluded medications: those mentioned in exclusion criteria **Placebo group** Intervention: film-coated tablet Duration of intervention: 5 weeks **Ranolazine group** Intervention: ranolazine ER (dose not reported) Duration of intervention: 5 weeks
Outcomes	Total number of outcomes: 2 (changes of the wall motion abnormalities, heart's perfusion deficit and related variables) **OUTCOMES** No outcome meets the inclusion criteria
Starting date	Not reported
Contact information	Dr. Notghi Contract Research GmbH

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EUCTR 2012-001584-77 *(Continued)*

	Zimmerstraße 55 - Berlin 004903046064780 eraser@notghi.com
Notes	Source of funding: Menarini International Operations Luxembourg S.A. Reported as Prematurely ended

Gupta 2014

Trial name or title	Not stated
Methods	Study design: parallel-group Duration of follow-up: 6 weeks Method of randomisation: not described Method of concealment of allocation: not described Blinding: not specified Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Total number: 185 Country of enrolment: India Setting/location: not specified Diagnostic criteria (stable angina pectoris): not described Comorbidities: type 2 diabetes Inclusion criteria: not described Exclusion criteria: not described
Interventions	Number of intervention groups: 2 Concomitant medication: 1 or 2 anti-anginals Excluded medications: not described **Placebo group** Intervention: placebo Duration of intervention: 6 weeks **Ranolazine group** Intervention: ranolazine (type of formulation not specified) (dose not reported) Duration of intervention: 6 weeks
Outcomes	Total number of outcomes: 2 (weekly angina frequency, weekly sublingual nitrate use) **OUTCOMES**

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Gupta 2014 *(Continued)*

	Angina episodes frequency Outcome definition: not described Method and unit of measurement: number per week Time points reported: 6 weeks
Starting date	Not reported
Contact information	Not provided
Notes	

NCT01495520

Trial name or title	NCT01495520
Methods	Study design: cross-over trial Duration of follow-up: 30 days Method of randomisation: not described Method of concealment of allocation: not described Blinding: double-blind (Subject, Caregiver, Investigator) Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Total number: 100 (estimated) Country of enrolment: Italy Setting/location: not specified Diagnostic criteria (stable angina pectoris): coronary artery disease (macrovascular angina) Comorbidities: none Inclusion criteria: • Symptoms of palpitations • Angiographically-proven coronary artery disease • Stable conditions • No recent acute coronary syndromes • Able to understand and willing to sign the informed consent form • Symptomatic patients (palpitation) with stable angina pectoris already on therapy with beta-blockers and/or calcium antagonists Exclusion criteria: • Women of child bearing potential patients must demonstrate a negative pregnancy test performed within 24 hours • Severe renal failure • Severe hepatic failure
Interventions	Number of intervention groups: 2

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NCT01495520 *(Continued)*

	Concomitant medications: not described Excluded medications: not described **Placebo group** Intervention: placebo Duration of intervention: 30 days **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 750 mg twice daily Duration of intervention: 30 days
Outcomes	Total number of outcomes: 2 (occurrence of symptoms of palpitations, occurrence of arrhythmia in case of symptoms of palpitations) **OUTCOMES** No outcome meets the inclusion criteria
Starting date	January 2014
Contact information	Francesco Pelliccia, MD +39064997 f.pelliccia@mclink.it
Notes	Source of funding: University of Roma La Sapienza

NCT01558830

Trial name or title	NCT01558830
Methods	Study design: parallel-group Duration of follow-up: 3 months Method of randomisation: not described Method of concealment of allocation: not described Blinding: single-blind (subject) Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Country of enrolment: United States Setting/location: not specified Diagnostic criteria (stable angina pectoris): history of stable angina Comorbidities: other cardiac conditions (such as atrial fibrillation) Inclusion criteria: • Ischemic cardiac disease

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NCT01558830 *(Continued)*

	• Chronic anginal symptoms • On amiodarone therapy for other cardiac conditions Exclusion criteria: • Pregnant • Non-English speaking • Unstable angina • Baseline electrocardiogram (EKG) corrected QT (QTc)>490ms • Severe thyroid dysfunction • Heart block without a pacer system • Liver disease
Interventions	Number of intervention groups: 2 Concomitant medications: amiodarone Excluded medications: not described **Placebo group** Intervention: sugar pill Duration of intervention: 3 months **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 500/1000 mg twice daily Duration of intervention: 3 months
Outcomes	Total number of outcomes: 6 (ventricular arrhythmia burden, atrial arrhythmia burden, QTc interval measurement, hospitalisation rate, syncope hospitalisation rate, liver function assay) **OUTCOMES** No outcomes meets inclusion criteria
Starting date	Not reported
Contact information	Erik J Sirulnick, MD 702-731-8224 erikmd@me.com
Notes	Source of funding: Cardiovascular Consultants of Nevada, Gilead Sciences

NCT01754259

Trial name or title	NCT01754259
Methods	Study design: cross-over trial Duration of follow-up: 4 weeks Method of randomisation: not described Method of concealment of allocation: "labelled" bottles provided by the sponsor

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NCT01754259 *(Continued)*

	Blinding: double-blind (Subject, Investigator) Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Total number: 70 (estimated) Country of enrolment: United States Setting/location: not specified Diagnostic criteria (stable angina pectoris): symptoms of stable angina and CAD (criteria for diagnosis not described) (macrovascular angina) Comorbidities: type 1 and 2 diabetes mellitus Inclusion criteria: • Type 1 or 2 diabetes mellitus • Anginal symptoms and/or exertional dyspnoea • Ability to exercise and achieve an exercise tolerance of at least 3 METS but not higher than 9 METS either on a treadmill or bicycle exercise tolerance test • Perfusion sum stress score (SSS) ≤ 6, as assessed by initial PET Exclusion criteria: • Patients not fulfilling inclusion criteria • Patients with evidence of unprotected left main coronary artery stenosis >50% • Patients with evidence of new obstructive CAD not on optimal medical therapy • Evidence of angiographic disease and/or inducible myocardial ischaemia on stress testing planning to undergo revascularisation within the following 3 months • History of cardiomyopathy (LVEF <40%) or significant valvular heart disease • Uncontrolled hypertension (SBP >180 mm Hg at screening) • Gait instability, lower extremity amputations preventing exercise • Significant liver dysfunction (LFTs >3x upper limits of normal), including cirrhosis • Prolonged QT (QTc >450 and >470 ms for men and women, respectively) or concomitant use of drugs that prolong QT interval (including methadone and anti-arrhythmics such as sotalol, amiodarone, and quinidine) • Use of drugs that inhibit CYP3A such as ketoconazole, itraconazole, fluconazole, clarithromycin, erythromycin, diltiazem, verapamil, nefazodone, nelfinavir, ritonavir, lopinavir, ritonavir, indinavir, and saquinavir • Use of drugs that induce CYP3A such rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, and St. John's wort 13. atrial fibrillation / inability to hold breath for ≥ 10 seconds (in patients in whom CTA will be performed) • eGFR < 50 ml/min or end stage renal disease on dialysis • Allergy to intravenous contrast • Pregnant or lactating women, or women of childbearing potential not using an acceptable form of birth control (negative pregnancy test also required) • Inability to fit safely in PET/CT scanner
Interventions	Number of intervention groups: 2 Concomitant medications: anti-anginals (not described) Excluded medications: those mentioned in exclusion criteria **Placebo group** Intervention: placebo

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NCT01754259 *(Continued)*

	Duration of intervention: 4 weeks **Ranolazine group** Intervention: ranolazine (type of formulation not specified) (dosage not reported) Duration of intervention: 4 weeks
Outcomes	Total number of outcomes: 9 (post-exercise coronary vasodilator reserve, symptoms of exertional angina and/or dyspnoea (SAQ/RDS scales), left ventricular systolic function, post-exercise global myocardial blood flow, post-exercise global coronary vascular resistance, serum biomarkers of myocardial strain, LV diastolic function, correlation between multimodality imaging parameters) **OUTCOMES** No outcome meets the inclusion criteria
Starting date	April 2013
Contact information	Ron Blankstein, MDBrigham and Women's Hospital
Notes	Source of funding: Brigham and Women's Hospital

NCT01948310

Trial name or title	NCT01948310
Methods	Study design: parallel-group Duration of follow-up: not stated Method of randomisation: not described Method of concealment of allocation: not described Blinding: double-blind (Subject, Caregiver, Investigator, Outcomes Assessor) Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Total number: 40 (estimated) Country of enrolment: United States Setting/location: not specified Diagnostic criteria (stable angina pectoris): stable angina for at least 3 months with documented CAD (macrovascular angina) Comorbidities: none Inclusion criteria: • Documented CAD diagnosis • Stable angina ≥ 3 months Exclusion criteria: • Class III or IV heart failure • Myocardial Infarction or coronary revascularisation procedure within 2 months

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NCT01948310 *(Continued)*

	• QT interval > 500 ms or prescribed medication known to prolong the QTc interval Contraindicated medications • Metformin dose > 1700 mg/day • Class Ia, Ic and III anti-arrhythmics • CYP3A inhibitors • Simvastatin > 20 mg/day • Severe renal disease (< 30ml/min creatinine clearance) • Currently on dialysis • Lack of transportation to the exercise and testing facilities • Implanted pacemaker that is not rate responsive
Interventions	Number of intervention groups: 2 Concomitant therapy: aerobic exercise three times per week, 45 minutes per session at an intensity of 10-20 beats per minute below the angina threshold Excluded medications: those mentioned in exclusion criteria **Placebo group** Intervention: placebo Duration of intervention: 13 weeks (not explicitly stated) **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 1000 mg twice daily Duration of intervention: 13 weeks (not explicitly stated)
Outcomes	Total number of outcomes: 3 (change in peak oxygen consumption, change in treatment satisfaction (SAQ scale), change in total daily energy expenditure) **Adverse events incidence** No outcome meets the inclusion criteria
Starting date	December 2013
Contact information	Leslie H Willis, MS 9196606782 leslie.willisduke.edu
Notes	Source of funding: Duke University, Gilead Sciences

NCT02052011

Trial name or title	NCT02052011
Methods	Study design: parallel-group trial Duration of follow-up: 4 weeks Method of randomisation: not described Method of concealment of allocation: not described

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NCT02052011 *(Continued)*

	Blinding: double-blind (Subject, Caregiver, Investigator, Outcomes Assessor) Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Total number: 30 (estimated) Country of enrolment: United States Setting/location: emergency patients Diagnostic criteria (stable angina pectoris): microvascular angina Comorbidities: none Inclusion criteria: • Patients admitted to the Yale ED CPC • ≥ 30 years age • Chest pain or angina equivalent as their chief complaint within 24 hours of enrolment • Coronary Flow Reserve(CFR) <2.5 on PET scan in the ED Exclusion criteria: • Acute coronary syndrome • Prior evidence of obstructive heart disease (history of Percutaneous Transluminal Coronary Angioplasty (PTCA), Coronary Artery Bypass Grafting (CABG) or calcium score > 10 on PET scan) • Resting blood pressure of systolic >180/110 mm Hg or <100/40 • Known cardiomyopathy or heart failure • Currently on dialysis • Creatinine clearance <30 ml/min • Liver cirrhosis • Significant aortic stenosis (murmur on exam) • Active use of cocaine or amphetamine • Current use of potent CYP3A4 inducers or inhibitors (such as ketoconazole, clarithromycin, HIV protease inhibitors) • Baseline QTc > 580 msec • Use of drugs that prolong QTc (Haldol, erythromycin) • Pregnancy • Inability to read or understand English • Suffering from a condition that precludes interview (i.e. cognitive or communication impairment)
Interventions	Number of intervention groups: 2 Concomitant medications: not mentioned Excluded medications: those mentioned in exclusion criteria **Placebo group** Intervention: placebo Duration of intervention: 4 weeks **Ranolazine group** Intervention: ranolazine ER 1000 mg twice daily (up-titrated from 500 mg twice daily for 1 week) Duration of intervention: 4 weeks

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NCT02052011 *(Continued)*

Outcomes	Total number of outcomes: 3 (Coronary Flow Reserve, quality of life (SAQ scale), return visits) **OUTCOMES** **Quality of life** Outcome definition: not described Method and unit of measurement: score Time points reported: 4 weeks
Starting date	April 2014
Contact information	Matthew Naftilan, MS 203-785-4676 matthew.naftilan@yale.edu
Notes	Source of funding: Yale University, Gilead Sciences

NCT02147067

Trial name or title	NCT02147067
Methods	Study design: parallel-group trial Duration of follow-up: 12 weeks Method of randomisation: not described Method of concealment of allocation: not described Blinding: double-blind (Subject, Caregiver, Investigator, Outcomes Assessor) Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Total number: 50 (estimated) Country of enrolment: not described Setting/location: not specified Diagnostic criteria (stable angina pectoris): symptoms of stable angina and no evidence of CAD (microvascular angina) Comorbidities: none Inclusion criteria: • History of typical angina or effort-induced anginal symptoms and are currently experiencing angina at least once per week • Abnormal stress ECG, exercise stress imaging, or pharmacological stress imaging • Non-obstructive coronary artery disease as defined by lesion stenosis ≤ 50% in any artery as visualised by diagnostic angiography Exclusion criteria:

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NCT02147067 *(Continued)*

	• Inability to provide informed consent • Active Myocardial Infarction • History of coronary artery bypass grafting • Diagnosis of other specific cardiac disease such as severe valvular heart disease, cardiomyopathy, or variant angina • Left Ventricular Ejection Fraction (LVEF) < 30% • Known renal insufficiency (CrCl < 30 mL/min) or on dialysis • Contraindications to the use of Ranolazine
Interventions	Number of intervention groups: 2 Concomitant medications: not described Excluded medications: not described **Placebo group** Intervention: placebo Duration of intervention: 12 weeks **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 1000 mg twice daily Duration of intervention: 12 weeks
Outcomes	Total number of outcomes: 5 (quality of life (SAQ scale), peak rate of oxygen consumption, ETT parameters, Coronary Flow Velocity Reserve (CFR), Hyperemic Microcirculatory Resistance (HMR)) **OUTCOMES** **Quality of life** Outcome definition: Seattle Angina Questionnaire score regarding angina frequency, physical functioning, treatment satisfaction, angina stability, and quality of life Method and unit of measurement: score (change from baseline) Time points reported: 12 weeks
Starting date	September 2014
Contact information	Habib Samady, MD (404) 778-1237 hsamady@emory.edu
Notes	Source of funding: Emory University, Gilead Sciences

NCT02147834

Trial name or title	NCT02147834
Methods	Study design: parallel-group trial Duration of follow-up: 4 months Method of randomisation: not described

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NCT02147834 *(Continued)*

	Method of concealment of allocation: not described Blinding: double-blind (Subject, Caregiver, Investigator, Outcomes Assessor) Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Total number: 250 (estimated) Country of enrolment: United States Setting/location: not specified Diagnostic criteria (stable angina pectoris): not described, patients deferred from having a PCI Comorbidities: none Inclusion criteria: • Stable patients aged ≥ 18 years referred for cardiac catheterisation for evaluation of cardiac symptoms (angina, fatigue, or shortness of breath) • At least 1 indeterminate stenosis (20% to 80%), fractional flow reserve (FFR) ≥ 0.8 and PCI deferred Exclusion criteria: • Coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting) during the index procedure or anticipated within the next month • Acute coronary syndrome or cardiogenic shock • Use of strong inhibitors of CTP3A (i.e. ketoconazole, itraconazole, clarithromycin,nefazodone, nelfinavir, ritonavir, indinavir and saquinavir) • Use of inducers of CYP3A (i.e. rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, and St. John's wort) • Liver cirrhosis • Severe renal insufficiency (i.e. creatinine clearance < 30 mL/min/1.73 m^2) • QTc > 500 milliseconds
Interventions	Number of intervention groups: 2 Concomitant medications: not described Excluded medications: those mentioned in exclusion criteria **Placebo group** Intervention: sugar pill twice daily Duration of intervention: 16 weeks **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 1000 mg twice daily (up-titrated from 500 mg twice daily for 1 week) Duration of intervention: 16 weeks
Outcomes	Total number of outcomes: 3 (quality of life (SAQ scale), subjective well being, ischemia-driven revascularisation or hospitalisation) **OUTCOMES** **Quality of life**

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NCT02147834 *(Continued)*

	Outcome definition: the Seattle Angina Questionnaire is a valid and reliable instrument that measures five clinically important dimensions of health in patients with CAD (physical limitation, anginal stability, anginal frequency, treatment satisfaction, and disease perception) Method and unit of measurement: score (change from baseline) Time points reported: 4 months **Need for revascularisation procedure** Outcome definition: frequency of the number of reported adverse events for ischaemia driven revascularisation Method and unit of measurement: absolute frequency Time points reported: 4 months
Starting date	August 2015
Contact information	Anthony A Bavry, MD MPH 352-376-1611 ext 4726 anthony.bavry@va.gov
Notes	Source of funding: North Florida Foundation for Research and Education, Gilead Sciences, University of Florida

NCT02252406

Trial name or title	NCT02252406
Methods	Study design: parallel-group Duration of follow-up: 24 weeks Method of randomisation: not described Method of concealment of allocation: not described Blinding: double-blind (Subject, Caregiver, Investigator, Outcomes Assessor) Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Total number: 40 (estimated) Country of enrolment: not described Setting/location: not specified Diagnostic criteria (stable angina pectoris): symptoms of chronic stable angina and evidence of CAD (macrovascular angina) Comorbidities: Metabolic Syndrome Inclusion criteria: • Patients with chronic stable angina (> 3 months) and symptomatic >=3 attacks/week on evidence based adequate therapy • Evidence of stable coronary artery disease by any of these:

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NCT02252406 *(Continued)*

- MI, PCI or CABG > 30 days prior to enrolment or
- Angiography showing > 50% stenosis in major vessel, branch or bypass graft > 30 days of Enrollment or
- Abnormal stress MPI nuclear study, or DBA stress echo where the decision has been to treat medically and where angina has remained stable for >= 3 months

- Evidence of the Metabolic Syndrome: As defined by ATP III criteria i.e. 3/5 of following Abdominal circumference F > 88 cm (35 in), M > 102 cm (40 in) Hypertriglyceridemia ≥ 150 mg/dl HDL F < 50 mg/dl M < 40 mg/dl Blood Pressure ≥130/85 Fasting Glucose ≥100 mg/dl For reproductive age women, a negative urine pregnancy test is required if all other inclusion criteria are met

Exclusion criteria:

- Contraindications to use of Ranexa, including patients on CYP3A4 inducers/potent inhibitors, and patients with liver cirrhosis
- Patients with CrCl < 30 mL/min
- Limit dose of Ranexa to 500 mg BID in patients on concurrent diltiazem/verapamil
- Limit concurrent simvastatin to 20 mg/day
- Limit concurrent metformin to 1000 mg/day

Additional exclusion

- Patients with variable -inconsistent symptoms
- Patients with unstable coronary artery disease or revascularisation within 30 days of enrolment
- Patients who have known severe liver disease
- Patients already receiving maximal ranolazine therapy for more than 4 weeks
- Presence of diabetes, hypothyroidism, active infection, cancer and/or recent major surgery or illness
- Patients with any contraindication to ranolazine see above
- Women of reproductive age are excluded if they are planning to become pregnant in the next 6 -12 months after randomisation
- Patients who are pregnant or lactating
- Documented allergic reaction to ranolazine in the past
- Unexplained prolongation of the QTc > 500 milliseconds
- Current or planned co-administration of moderate CYP3A inhibitors (e.g. diltiazem, verapamil, aprepitant, erythromycin, fluconazole, and grapefruit juice or grapefruit-containing products) is not a full contraindication, if meet inclusion criteria otherwise, these patients could be accepted in trial but dose will be limited to 500 mg BID as stated previously
- Current or planned co-administration of strong CYP3A inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir) OR strong CYP3A inducers (e.g. rifampin, rifabutin, rifapentine, phenobarbital, phenytoin,carbamazepine, and St. John's Wort) is a contraindication

Interventions	Number of intervention groups: 2 Concomitant medications: not described Excluded medications: those mentioned in exclusion criteria **Placebo group** Intervention: placebo Duration of intervention: 24 weeks **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 500 mg twice daily Duration of intervention: 24 weeks

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NCT02252406 *(Continued)*

Outcomes	Total number of outcomes: (angina frequency (SAQ scale), biomarkers) **OUTCOMES** No outcome meets the inclusion criteria
Starting date	September 2015
Contact information	Gladys Velarde, MD 904-244-43095 gladys.velarde@jax.ufl.edu
Notes	Source of funding: University of Florida

NCT02265796

Trial name or title	NCT02265796
Methods	Study design: parallel-group trial Duration of follow-up: 16 weeks Method of randomisation: not described Method of concealment of allocation: not described Blinding: double-blind (Subject, Caregiver, Investigator, Outcomes Assessor) Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Total number: 50 (estimated) Country of enrolment: United States Setting/location: not specified Diagnostic criteria (stable angina pectoris): not described Comorbidities: none Inclusion criteria: • Adult patients aged ≥ 18 years referred for cardiac catheterisation for evaluation of cardiac symptoms (angina, fatigue, or shortness of breath) • At least 1 indeterminate stenosis (20% to 80%) • Fractional flow reserve (FFR) ≤ 0.8 and PCI deferred Exclusion criteria: • Coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting) during the index procedure or anticipated within the next month • Acute coronary syndrome or cardiogenic shock • QTc > 500 milliseconds • Use of strong inhibitors of CTP3A (i.e. ketoconazole, itraconazole, clarithromycin,nefazodone, nelfinavir, ritonavir, indinavir and saquinavir)

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NCT02265796 *(Continued)*

	• Use of inducers of CYP3A (i.e. rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, and St. John's wort) • Liver cirrhosis • Severe renal insufficiency (i.e. creatinine clearance < 30mL/min/1.73 m^2)
Interventions	Number of intervention groups: 2 Concomitant medications: not described Excluded medications: those mentioned in exclusion criteria **Placebo group** Intervention: sugar pill twice daily Duration of intervention: 16 weeks **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 1000 mg twice daily (up-titrated from 500 mg twice daily for 1 week) Duration of intervention: 16 weeks
Outcomes	Total number of outcomes: 3 (quality of life (SAQ scale), subjective well being, ischemia-driven revascularisation or hospitalisation) **OUTCOMES** **Quality of life** Outcome definition: the Seattle Angina Questionnaire is a valid and reliable instrument that measures five clinically important dimensions of health in patients with coronary artery disease (physical limitation, anginal stability, anginal frequency, treatment satisfaction, and disease perception) Method and unit of measurement: score (change from baseline) Time points reported: 16 weeks **Need for revascularisation procedure** Outcome definition: frequency of the number of reported adverse events for ischaemia driven revascularisation Method and unit of measurement: absolute frequency Time points reported: 16 weeks
Starting date	September 2014
Contact information	Anthony A Bavry, MD, MPH 352-376-1611 ext 4726 anthon.bavry@va.gov
Notes	Source of funding: North Florida Foundation for Research and Education, Gilead Sciences

NCT02423265

Trial name or title	NCT02423265

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NCT02423265 *(Continued)*

Methods	Study design: parallel-group trial Duration of follow-up: 9 weeks Method of randomisation: not described Method of concealment of allocation: not described Blinding: Double-blind (Subject, Investigator, Outcomes Assessor) Power calculation: not mentioned Phases of the study: 2 (treatment phase, follow-up phase)
Participants	Country of enrolment: not described Setting/location: not specified Diagnostic criteria (stable angina pectoris): not described Comorbidities: percutaneous coronary intervention plus stent implantation Inclusion criteria: • Angiographically proven coronary artery disease with chronic stable angina for at least 3 months. • Abnormal stress test (treadmill ECG, nuclear stress test, dobutamine stress echocardiogram or stress perfusion cardiac MRI) • ≥ 1 chronically occluded coronary artery of a dominant coronary vessel or the left anterior descending artery and/or ≥ 1 occluded vein graft to chronically occluded native coronary vessel • Subjects must be taking a minimum of 2 anti-anginal agents Exclusion criteria: • LVEF < 40 • Terminal illness such as cancer • Occluded recessive coronary vessel • Hepatic insufficiency, • Liver cirrhosis, • Prolonged QT interval on ECG, • Severe renal failure (see below), Excluding patients with CrCl < 30 • Drugs that are strong inhibitors of CYP3A such as, ketoconazole, macrolide antibiotics and HIV protease inhibitors. • Limit Ranolazine to 500 mg BID in patients on concurrent diltiazem/verapamil • Limit concurrent simvastatin to 20 mg/day • Limit concurrent metformin to 1700 mg/day • Inability to have an MRI scan/known claustrophobia
Interventions	Number of intervention groups: 3 Concomitant medications: standard therapy (not described) Excluded medications: not mentioned **Placebo group** Intervention:placebo with up-titration after 1 week Duration of intervention: 9 weeks **Ranolazine group**

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NCT02423265 *(Continued)*

	Intervention: ranolazine (type of formulation not specified) 1000 mg twice daily (up-titrated after 1-week 500 mg twice daily) Duration of intervention: 9 weeks
Outcomes	Total number of outcomes: 4 (cardiac MRI strain, dobutamine wall motion scoring index, quality of life, ETT parameters) **OUTCOMES** **Quality of life** Outcome definition: measured with 3 scales (SAQ, DASI, SF-12) Method and unit of measurement: total score Time points to report: 9 weeks
Starting date	June 2015
Contact information	Ashesh N Buch, MB.ChB, M.D. bucha@ecu.edu
Notes	

Šebeštjen 2014

Trial name or title	
Methods	Study design: parallel-group trial Duration of follow-up: 12 weeks Method of randomisation: not described Method of concealment of allocation: not described Blinding: double-blind Power calculation: not mentioned Phases of the study: 1 (treatment phase)
Participants	Total number: 52 Country of enrolment: not mentioned Setting/location: not specified Diagnostic criteria (stable angina pectoris): not described Comorbidities: none Inclusion criteria: not described Exclusion criteria: not described
Interventions	Number of intervention groups: 2 Concomitant medications: not described Excluded medications: not described

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Šebeštjen 2014 *(Continued)*

	Trimetazidine group Intervention: trimetazidine 35 mg twice daily Duration of intervention: 12 weeks **Ranolazine group** Intervention: ranolazine (type of formulation not specified) 375/500 mg twice daily Duration of intervention: 12 weeks
Outcomes	Total number of outcomes: 2 (flow-mediated (endothelium-dependent) dilation (FMD) of brachial artery, nitroglycerin-induced (endothelium-independent) (GTN) dilation of brachial artery) **OUTCOMES** No outcomes meets inclusion criteria
Starting date	Not reported
Contact information	Not provided
Notes	

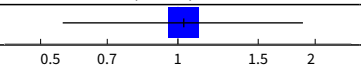
DATA AND ANALYSES

Comparison 1. Ranolazine (monotherapy) 1000 mg twice daily versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiovascular mortality	1	2604	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.56, 1.88]
2 All-cause mortality	3	6249	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.81, 1.25]
3 Quality of life	3	2254	Mean Difference (IV, Fixed, 95% CI)	0.28 [-1.57, 2.13]
4 AMI incidence	2	2674	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.14, 2.15]
5 Need for revascularisation procedure	2	2674	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.82, 1.18]
6 Adverse events incidence	2	638	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.90, 1.98]

Analysis 1.1. Comparison 1 Ranolazine (monotherapy) 1000 mg twice daily versus placebo, Outcome 1 Cardiovascular mortality.

Study or subgroup	Ranolazine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
RIVER-PCI 2016	21/1317	20/1287		100%	1.03[0.56,1.88]



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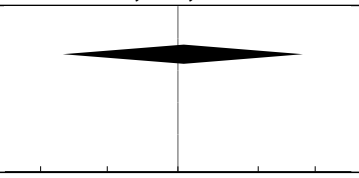
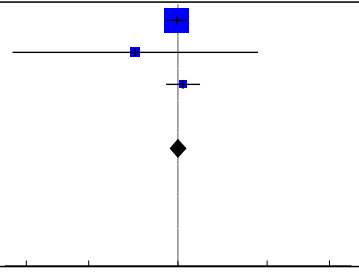
Study or subgroup	Ranolazine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)	**1317**	**1287**		**100%**	**1.03[0.56,1.88]**
Total events: 21 (Ranolazine), 20 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.08(P=0.93)					



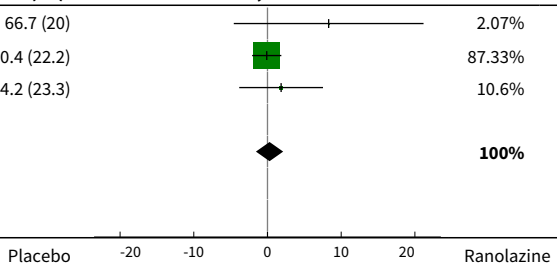
Analysis 1.2. Comparison 1 Ranolazine (monotherapy) 1000 mg twice daily versus placebo, Outcome 2 All-cause mortality.

Study or subgroup	Ranolazine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
MERLIN-TIMI 36 2007	111/1785	114/1775		75.13%	0.97[0.75,1.25]
Pelliccia 2012	0/35	1/35		0.99%	0.33[0.01,7.91]
RIVER-PCI 2016	42/1322	36/1297		23.88%	1.14[0.74,1.77]
Total (95% CI)	**3142**	**3107**		**100%**	**1[0.81,1.25]**
Total events: 153 (Ranolazine), 151 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.89, df=2(P=0.64); I^2=0%					
Test for overall effect: Z=0.04(P=0.97)					



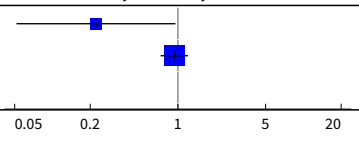
Analysis 1.3. Comparison 1 Ranolazine (monotherapy) 1000 mg twice daily versus placebo, Outcome 3 Quality of life.

Study or subgroup	Ranolazine N	Ranolazine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Mehta 2011	20	75 (21.6)	20	66.7 (20)		2.07%	8.3[-4.57,21.17]
RIVER-PCI 2016	978	70.3 (22.5)	980	70.4 (22.2)		87.33%	-0.1[-2.08,1.88]
RWISE 2016	128	56.1 (23.1)	128	54.2 (23.3)		10.6%	1.85[-3.83,7.53]
Total ***	**1126**		**1128**			**100%**	**0.28[-1.57,2.13]**
Heterogeneity: Tau^2=0; Chi^2=1.93, df=2(P=0.38); I^2=0%							
Test for overall effect: Z=0.3(P=0.77)							



Analysis 1.4. Comparison 1 Ranolazine (monotherapy) 1000 mg twice daily versus placebo, Outcome 4 AMI incidence.

Study or subgroup	Ranolazine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Pelliccia 2012	2/35	9/35		37.03%	0.22[0.05,0.96]
RIVER-PCI 2016	111/1317	116/1287		62.97%	0.94[0.73,1.2]



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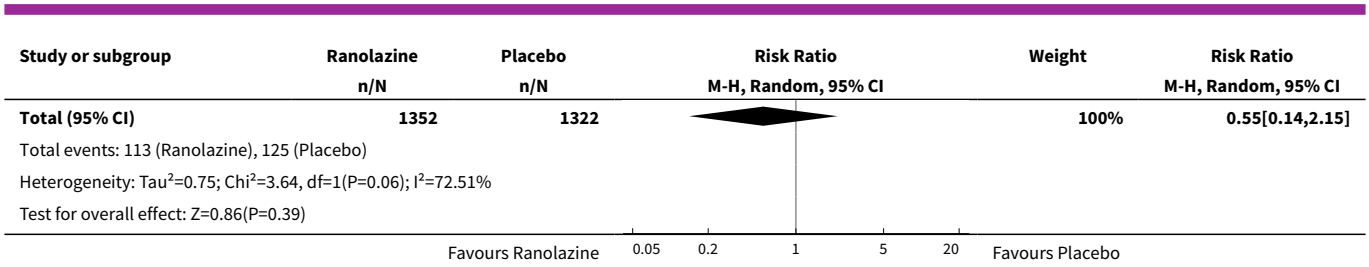
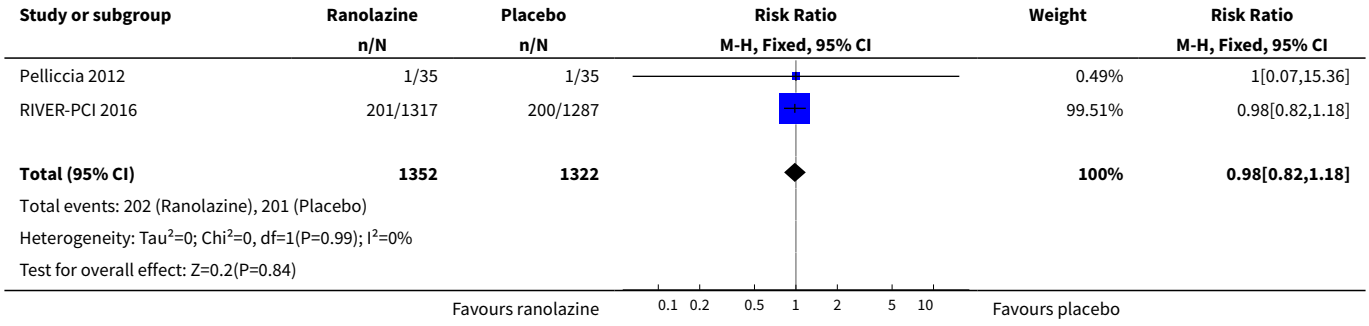
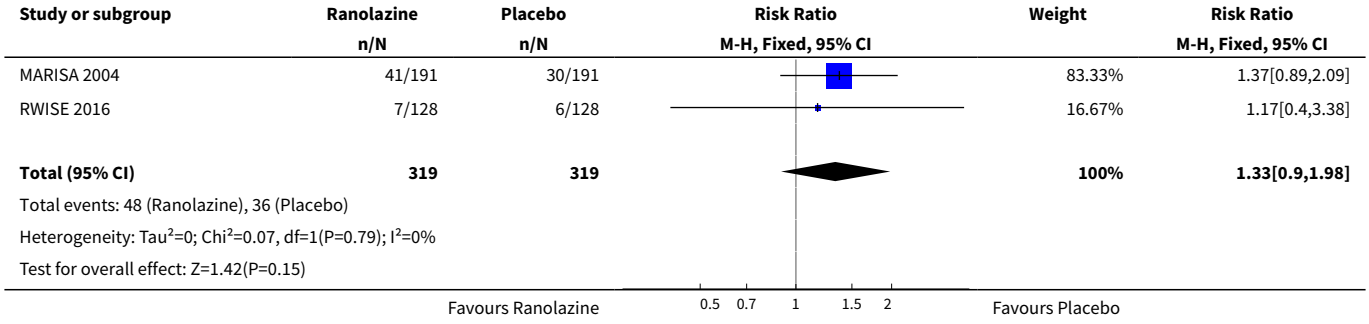


Analysis 1.5. Comparison 1 Ranolazine (monotherapy) 1000 mg twice daily versus placebo, Outcome 5 Need for revascularisation procedure.



Analysis 1.6. Comparison 1 Ranolazine (monotherapy) 1000 mg twice daily versus placebo, Outcome 6 Adverse events incidence.



Comparison 2. Ranolazine (monotherapy) any dose versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 AMI incidence	3	2983	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.69, 1.12]
2 Angina episodes frequency	2	402	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.85, 1.01]
3 Adverse events incidence	3	947	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.12, 2.00]

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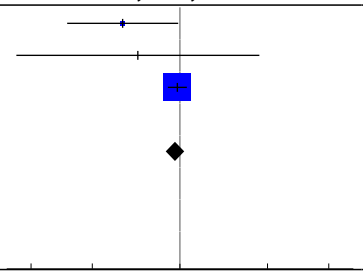
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Macrovascular angina	2	691	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.13, 2.07]
3.2 Microvascular angina	1	256	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.40, 3.38]

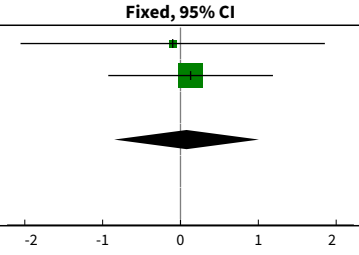
Analysis 2.1. Comparison 2 Ranolazine (monotherapy) any dose versus placebo, Outcome 1 AMI incidence.

Study or subgroup	Ranolazine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Pelliccia 2012	2/35	9/35		7.04%	0.22[0.05,0.96]
RAN080 2005	0/155	1/154		1.18%	0.33[0.01,8.07]
RIVER-PCI 2016	111/1317	116/1287		91.78%	0.94[0.73,1.2]
Total (95% CI)	**1507**	**1476**		**100%**	**0.88[0.69,1.12]**
Total events: 113 (Ranolazine), 126 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.01, df=2(P=0.13); I^2=50.16%					
Test for overall effect: Z=1.05(P=0.29)					



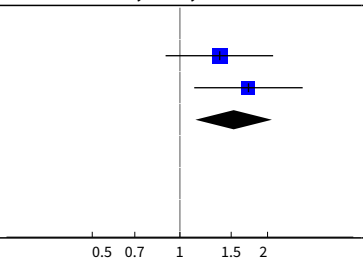
Analysis 2.2. Comparison 2 Ranolazine (monotherapy) any dose versus placebo, Outcome 2 Angina episodes frequency.

Study or subgroup	Ranolazine N	Ranolazine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
RWISE 2016	128	4.8 (8.2)	128	4.9 (7.8)		22.65%	-0.1[-2.05,1.85]
Thadani 1994	75	-2.1 (3.4)	71	-2.2 (3.1)		77.35%	0.13[-0.93,1.19]
Total ***	**203**		**199**			**100%**	**0.08[-0.85,1.01]**
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.84); I^2=0%							
Test for overall effect: Z=0.16(P=0.87)							



Analysis 2.3. Comparison 2 Ranolazine (monotherapy) any dose versus placebo, Outcome 3 Adverse events incidence.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Macrovascular angina					
MARISA 2004	41/191	30/191		48.32%	1.37[0.89,2.09]
RAN080 2005	45/155	26/154		42.01%	1.72[1.12,2.64]
Subtotal (95% CI)	**346**	**345**		**90.34%**	**1.53[1.13,2.07]**
Total events: 86 (Experimental), 56 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.56, df=1(P=0.46); I^2=0%					
Test for overall effect: Z=2.77(P=0.01)					



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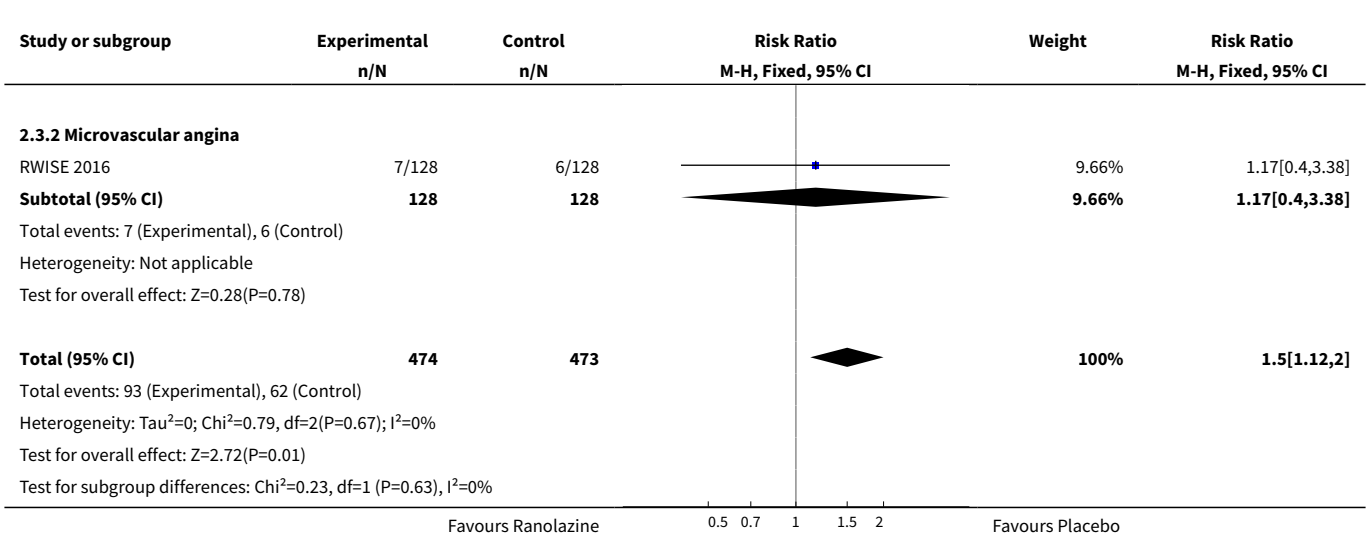
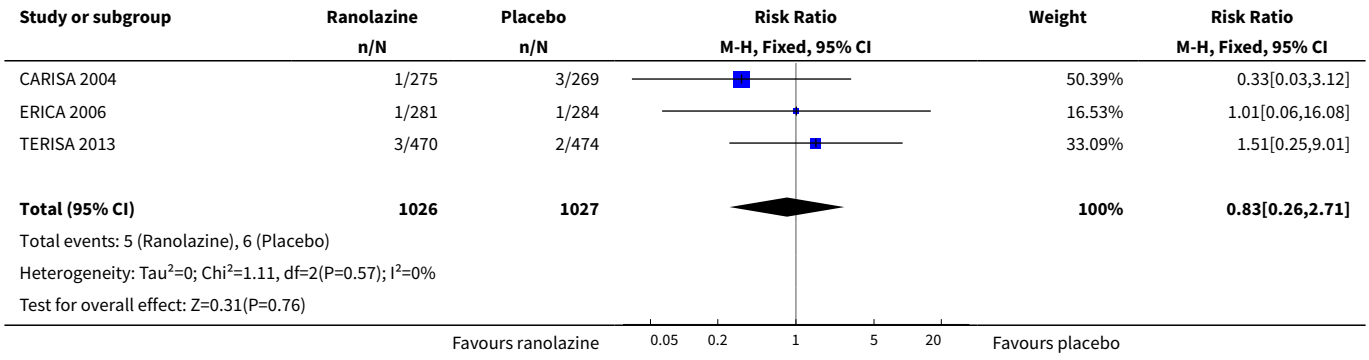


Comparison 3. Ranolazine (add-on therapy) 1000 mg twice daily versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	3	2053	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.26, 2.71]
2 Quality of life	3	1533	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.05, 0.32]
3 AMI incidence (fatal)	2	1509	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.25, 9.05]
4 AMI incidence (non-fatal)	2	1509	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.07]
5 Angina episodes frequency	3	2004	Mean Difference (IV, Fixed, 95% CI)	-0.66 [-0.97, -0.35]
6 Adverse events incidence	3	2053	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.06, 1.40]

Analysis 3.1. Comparison 3 Ranolazine (add-on therapy) 1000 mg twice daily versus placebo, Outcome 1 All-cause mortality.



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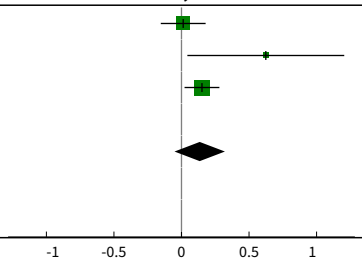
Analysis 3.2. Comparison 3 Ranolazine (add-on therapy) 1000 mg twice daily versus placebo, Outcome 2 Quality of life.

Study or subgroup	Ranolazine N	Ranolazine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
ERICA 2006	277	22.5 (316.2)	281	18.5 (315)		42.32%	0.01[-0.15,0.18]
Shammas 2015	24	13.9 (33.5)	24	-1.8 (10.4)		8.9%	0.62[0.04,1.2]
TERISA 2013	462	2.9 (6.6)	465	1.9 (6.6)		48.78%	0.15[0.02,0.28]
Total ***	**763**		**770**			**100%**	**0.13[-0.05,0.32]**

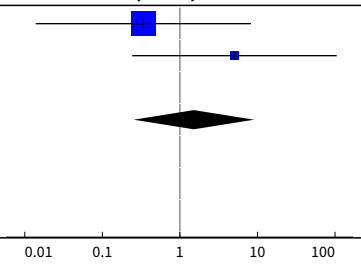
Heterogeneity: Tau^2=0.01; Chi^2=4.73, df=2(P=0.09); I^2=57.67%
Test for overall effect: Z=1.42(P=0.16)



Analysis 3.3. Comparison 3 Ranolazine (add-on therapy) 1000 mg twice daily versus placebo, Outcome 3 AMI incidence (fatal).

Study or subgroup	Ranolazine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ERICA 2006	0/281	1/284		74.98%	0.34[0.01,8.23]
TERISA 2013	2/470	0/474		25.02%	5.04[0.24,104.75]
Total (95% CI)	**751**	**758**		**100%**	**1.51[0.25,9.05]**

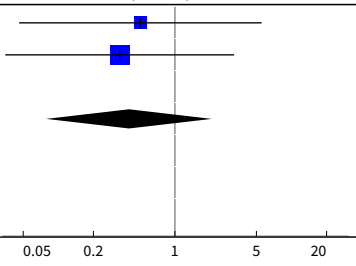
Total events: 2 (Ranolazine), 1 (Placebo)
Heterogeneity: Tau^2=0; Chi^2=1.45, df=1(P=0.23); I^2=31.19%
Test for overall effect: Z=0.45(P=0.65)



Analysis 3.4. Comparison 3 Ranolazine (add-on therapy) 1000 mg twice daily versus placebo, Outcome 4 AMI incidence (non-fatal).

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ERICA 2006	1/281	2/284		39.97%	0.51[0.05,5.54]
TERISA 2013	1/470	3/474		60.03%	0.34[0.04,3.22]
Total (95% CI)	**751**	**758**		**100%**	**0.4[0.08,2.07]**

Total events: 2 (Experimental), 5 (Control)
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.81); I^2=0%
Test for overall effect: Z=1.09(P=0.28)



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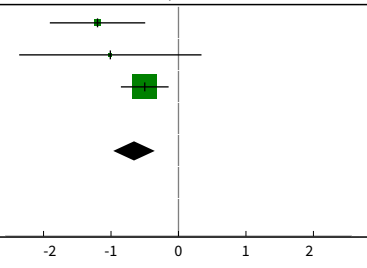
Analysis 3.5. Comparison 3 Ranolazine (add-on therapy) 1000 mg twice daily versus placebo, Outcome 5 Angina episodes frequency.

Study or subgroup	Ranolazine N	Ranolazine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
CARISA 2004	261	2.1 (3.2)	258	3.3 (4.8)		18.97%	-1.2[-1.91,-0.49]
ERICA 2006	277	3.3 (4.3)	281	4.3 (10.7)		5.19%	-1.01[-2.36,0.34]
TERISA 2013	462	3.8 (2.7)	465	4.3 (2.8)		75.83%	-0.5[-0.85,-0.15]
Total ***	**1000**		**1004**			**100%**	**-0.66[-0.97,-0.35]**

Heterogeneity: Tau²=0; Chi²=3.29, df=2(P=0.19); I²=39.15%

Test for overall effect: Z=4.2(P<0.0001)



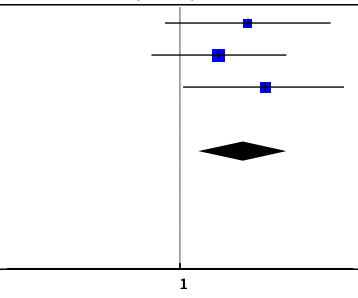
Analysis 3.6. Comparison 3 Ranolazine (add-on therapy) 1000 mg twice daily versus placebo, Outcome 6 Adverse events incidence.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
CARISA 2004	90/275	71/269		28.05%	1.24[0.95,1.61]
ERICA 2006	112/281	100/284		38.87%	1.13[0.91,1.4]
TERISA 2013	110/470	85/474		33.08%	1.31[1.01,1.68]
Total (95% CI)	**1026**	**1027**		**100%**	**1.22[1.06,1.4]**

Total events: 312 (Experimental), 256 (Control)

Heterogeneity: Tau²=0; Chi²=0.76, df=2(P=0.68); I²=0%

Test for overall effect: Z=2.8(P=0.01)



Comparison 4. Ranolazine (add-on therapy) any dose versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life	4	1563	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.01, 0.52]
1.1 Macrovascular angina	3	1533	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.05, 0.32]
1.2 Microvascular angina	1	30	Std. Mean Difference (IV, Random, 95% CI)	1.13 [0.36, 1.91]
2 Time to 1-mm ST-segment depression	3	1165	Mean Difference (Fixed, 95% CI)	34.62 [33.08, 36.16]

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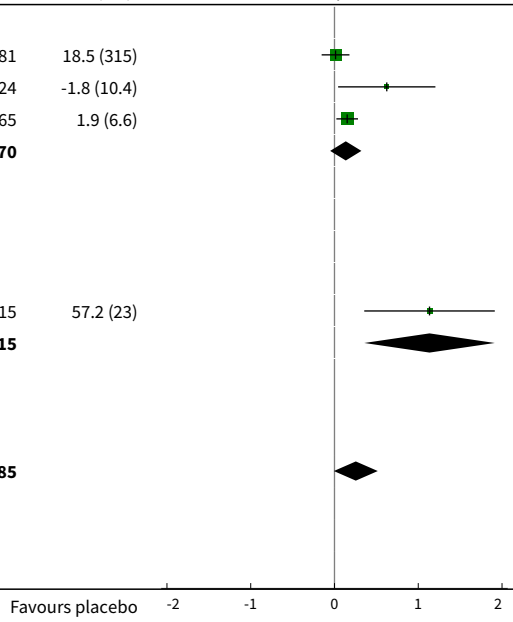
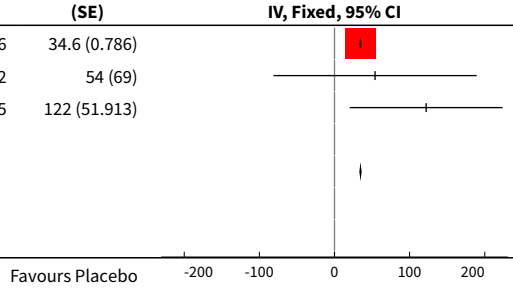
Analysis 4.1. Comparison 4 Ranolazine (add-on therapy) any dose versus placebo, Outcome 1 Quality of life.

Study or subgroup	Ranolazine N	Ranolazine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
4.1.1 Macrovascular angina							
ERICA 2006	277	22.5 (316.2)	281	18.5 (315)		37.34%	0.01[-0.15,0.18]
Shammas 2015	24	13.9 (33.5)	24	-1.8 (10.4)		13.96%	0.62[0.04,1.2]
TERISA 2013	462	2.9 (6.6)	465	1.9 (6.6)		39.68%	0.15[0.02,0.28]
Subtotal ***	**763**		**770**			**90.97%**	**0.13[-0.05,0.32]**
Heterogeneity: Tau²=0.01; Chi²=4.73, df=2(P=0.09); I²=57.68%							
Test for overall effect: Z=1.42(P=0.16)							
4.1.2 Microvascular angina							
Villano 2013	15	79.4 (14)	15	57.2 (23)		9.03%	1.13[0.36,1.91]
Subtotal ***	**15**		**15**			**9.03%**	**1.13[0.36,1.91]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.85(P=0)							
Total ***	**778**		**785**			**100%**	**0.25[-0.01,0.52]**
Heterogeneity: Tau²=0.04; Chi²=11.2, df=3(P=0.01); I²=73.2%							
Test for overall effect: Z=1.9(P=0.06)							
Test for subgroup differences: Chi²=5.98, df=1 (P=0.01), I²=83.28%							



Analysis 4.2. Comparison 4 Ranolazine (add-on therapy) any dose versus placebo, Outcome 2 Time to 1-mm ST-segment depression.

Study or subgroup	Ranolazine N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
CARISA 2004	255	256	34.6 (0.786)		99.96%	34.6[33.06,36.14]
Pepine 1999	312	312	54 (69)		0.01%	54[-81.24,189.24]
Villano 2013	15	15	122 (51.913)		0.02%	122[20.25,223.75]
Total (95% CI)					**100%**	**34.62[33.08,36.16]**
Heterogeneity: Tau²=0; Chi²=2.91, df=2(P=0.23); I²=31.33%						
Test for overall effect: Z=44.07(P<0.0001)						



Comparison 5. Sensitivity analysis 1: Studies at low risk of bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparison 1 - All-cause mortality	2	6179	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.26]
2 Comparison 1 - Quality of life	2	1998	Mean Difference (IV, Fixed, 95% CI)	0.09 [-1.86, 2.05]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Comparison 1 - AMI incidence	1	2604	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.73, 1.20]
4 Comparison 1 - Need for revascularisation procedure	1	2604	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.82, 1.18]
5 Comparison 2 - AMI incidence	1	2604	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.73, 1.20]
6 Comparison 3 - All-cause mortality	2	1488	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.22, 2.95]
7 Comparison 3 - Quality of life	2	975	Std. Mean Difference (IV, Random, 95% CI)	0.30 [-0.13, 0.73]
8 Comparison 3 - AMI incidence (fatal)	1	944	Risk Ratio (M-H, Fixed, 95% CI)	5.04 [0.24, 104.75]
9 Comparison 3 - AMI incidence (non-fatal)	1	944	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.04, 3.22]
10 Comparison 3 - Angina episodes frequency	2	1446	Mean Difference (IV, Fixed, 95% CI)	-0.64 [-0.96, -0.32]
11 Comparison 3 - Adverse events incidence	2	1488	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.06, 1.53]
12 Comparison 4 - Quality of life	3	1005	Std. Mean Difference (IV, Random, 95% CI)	0.54 [-0.03, 1.10]
12.1 Macrovascular angina	2	975	Std. Mean Difference (IV, Random, 95% CI)	0.30 [-0.13, 0.73]
12.2 Microvascular angina	1	30	Std. Mean Difference (IV, Random, 95% CI)	1.13 [0.36, 1.91]
13 Comparison 4 - Time to 1-mm ST-segment depression	2		Mean Difference (Fixed, 95% CI)	34.62 [33.08, 36.16]

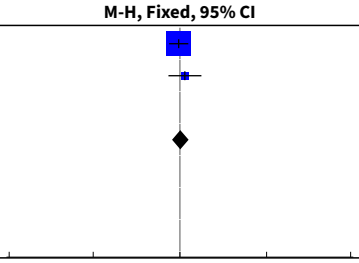
Analysis 5.1. Comparison 5 Sensitivity analysis 1: Studies at low risk of bias, Outcome 1 Comparison 1 - All-cause mortality.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
MERLIN-TIMI 36 2007	111/1785	114/1775		75.88%	0.97[0.75,1.25]
RIVER-PCI 2016	42/1322	36/1297		24.12%	1.14[0.74,1.77]
Total (95% CI)	**3107**	**3072**		**100%**	**1.01[0.81,1.26]**

Total events: 153 (Experimental), 150 (Control)

Heterogeneity: Tau^2=0; Chi^2=0.42, df=1(P=0.52); I^2=0%

Test for overall effect: Z=0.1(P=0.92)



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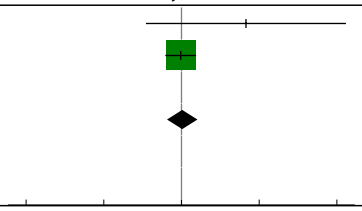
Analysis 5.2. Comparison 5 Sensitivity analysis 1: Studies at low risk of bias, Outcome 2 Comparison 1 - Quality of life.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Mehta 2011	20	75 (21.6)	20	66.7 (20)		2.31%	8.3[-4.57,21.17]
RIVER-PCI 2016	978	70.3 (22.5)	980	70.4 (22.2)		97.69%	-0.1[-2.08,1.88]
Total ***	**998**		**1000**			**100%**	**0.09[-1.86,2.05]**

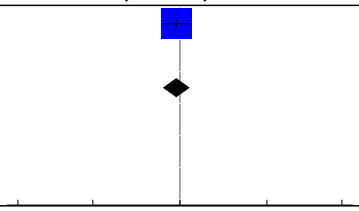
Heterogeneity: Tau²=0; Chi²=1.6, df=1(P=0.21); I²=37.41%
Test for overall effect: Z=0.09(P=0.92)



Analysis 5.3. Comparison 5 Sensitivity analysis 1: Studies at low risk of bias, Outcome 3 Comparison 1 - AMI incidence.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
RIVER-PCI 2016	111/1317	116/1287		100%	0.94[0.73,1.2]
Total (95% CI)	**1317**	**1287**		**100%**	**0.94[0.73,1.2]**

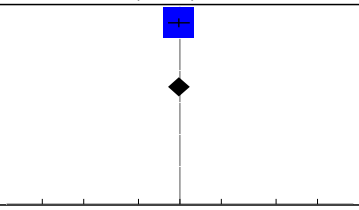
Total events: 111 (Experimental), 116 (Control)
Heterogeneity: Not applicable
Test for overall effect: Z=0.53(P=0.6)



Analysis 5.4. Comparison 5 Sensitivity analysis 1: Studies at low risk of bias, Outcome 4 Comparison 1 - Need for revascularisation procedure.

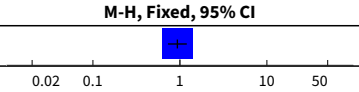
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
RIVER-PCI 2016	201/1317	200/1287		100%	0.98[0.82,1.18]
Total (95% CI)	**1317**	**1287**		**100%**	**0.98[0.82,1.18]**

Total events: 201 (Experimental), 200 (Control)
Heterogeneity: Not applicable
Test for overall effect: Z=0.2(P=0.84)



Analysis 5.5. Comparison 5 Sensitivity analysis 1: Studies at low risk of bias, Outcome 5 Comparison 2 - AMI incidence.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
RIVER-PCI 2016	111/1317	116/1287		100%	0.94[0.73,1.2]



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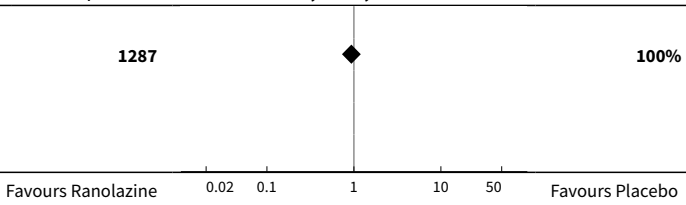
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)	**1317**	**1287**		**100%**	**0.94[0.73,1.2]**
Total events: 111 (Experimental), 116 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.53(P=0.6)					

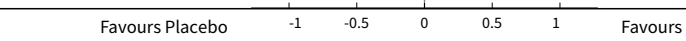


Analysis 5.6. Comparison 5 Sensitivity analysis 1: Studies at low risk of bias, Outcome 6 Comparison 3 - All-cause mortality.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
CARISA 2004	1/275	3/269		60.36%	0.33[0.03,3.12]
TERISA 2013	3/470	2/474		39.64%	1.51[0.25,9.01]
Total (95% CI)	**745**	**743**		**100%**	**0.8[0.22,2.95]**
Total events: 4 (Experimental), 5 (Control)					
Heterogeneity: Tau²=0; Chi²=1.1, df=1(P=0.29); I²=8.92%					
Test for overall effect: Z=0.34(P=0.73)					

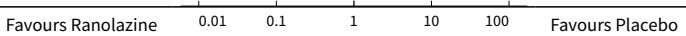
Analysis 5.7. Comparison 5 Sensitivity analysis 1: Studies at low risk of bias, Outcome 7 Comparison 3 - Quality of life.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Shammas 2015	24	13.9 (33.5)	24	-1.8 (10.4)		31.32%	0.62[0.04,1.2]
TERISA 2013	462	2.9 (6.6)	465	1.9 (6.6)		68.68%	0.15[0.02,0.28]
Total ***	**486**		**489**			**100%**	**0.3[-0.13,0.73]**
Heterogeneity: Tau²=0.07; Chi²=2.43, df=1(P=0.12); I²=58.76%							
Test for overall effect: Z=1.37(P=0.17)							



Analysis 5.8. Comparison 5 Sensitivity analysis 1: Studies at low risk of bias, Outcome 8 Comparison 3 - AMI incidence (fatal).

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
TERISA 2013	2/470	0/474		100%	5.04[0.24,104.75]
Total (95% CI)	**470**	**474**		**100%**	**5.04[0.24,104.75]**
Total events: 2 (Experimental), 0 (Control)					
Heterogeneity: Not applicable					



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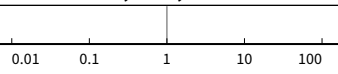
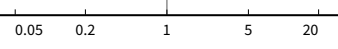
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=1.05(P=0.3)					



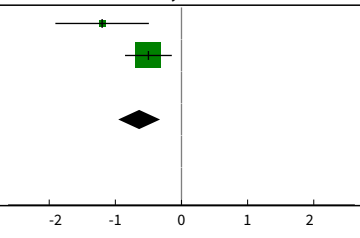
Analysis 5.9. Comparison 5 Sensitivity analysis 1: Studies at low risk of bias, Outcome 9 Comparison 3 - AMI incidence (non-fatal).

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
TERISA 2013	1/470	3/474		100%	0.34[0.04,3.22]
Total (95% CI)	**470**	**474**		**100%**	**0.34[0.04,3.22]**
Total events: 1 (Experimental), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.95(P=0.34)					



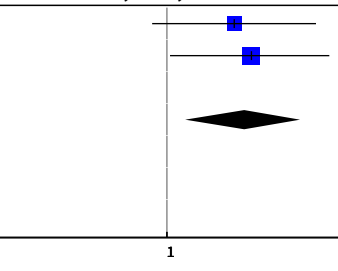
Analysis 5.10. Comparison 5 Sensitivity analysis 1: Studies at low risk of bias, Outcome 10 Comparison 3 - Angina episodes frequency.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
CARISA 2004	261	2.1 (3.2)	258	3.3 (4.8)		20.01%	-1.2[-1.91,-0.49]
TERISA 2013	462	3.8 (2.7)	465	4.3 (2.8)		79.99%	-0.5[-0.85,-0.15]
Total ***	**723**		**723**			**100%**	**-0.64[-0.96,-0.32]**
Heterogeneity: Tau^2=0; Chi^2=3.01, df=1(P=0.08); I^2=66.82%							
Test for overall effect: Z=3.97(P<0.0001)							



Analysis 5.11. Comparison 5 Sensitivity analysis 1: Studies at low risk of bias, Outcome 11 Comparison 3 - Adverse events incidence.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
CARISA 2004	90/275	71/269		45.89%	1.24[0.95,1.61]
TERISA 2013	110/470	85/474		54.11%	1.31[1.01,1.68]
Total (95% CI)	**745**	**743**		**100%**	**1.28[1.06,1.53]**
Total events: 200 (Experimental), 156 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=1(P=0.78); I^2=0%					
Test for overall effect: Z=2.62(P=0.01)					



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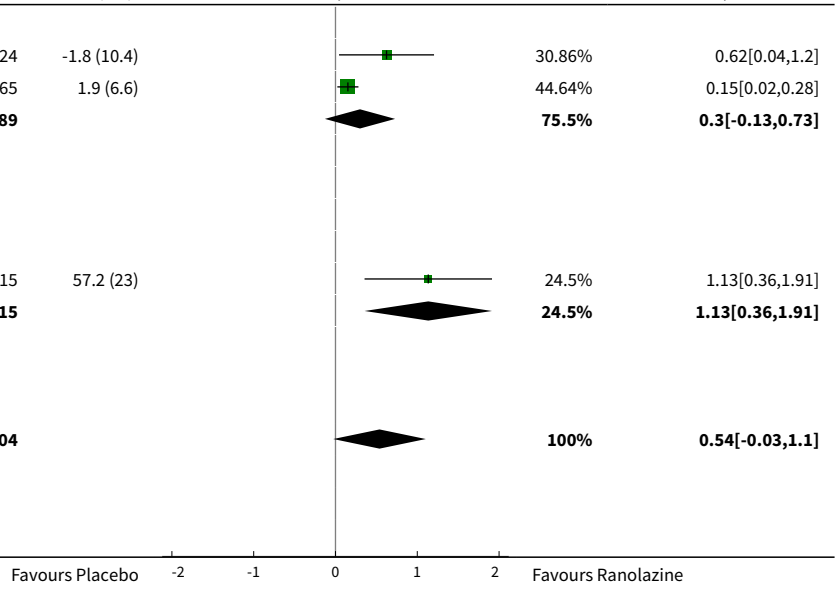
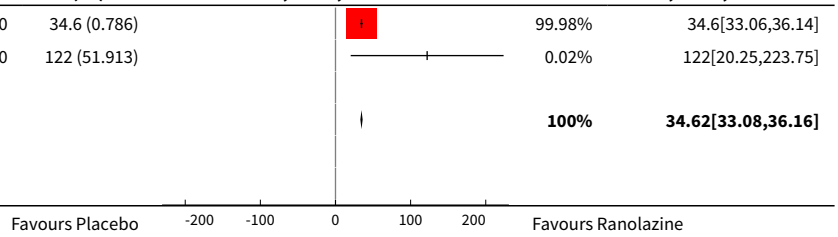
Analysis 5.12. Comparison 5 Sensitivity analysis 1: Studies at low risk of bias, Outcome 12 Comparison 4 - Quality of life.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
5.12.1 Macrovascular angina							
Shammas 2015	24	13.9 (33.5)	24	-1.8 (10.4)		30.86%	0.62[0.04,1.2]
TERISA 2013	462	2.9 (6.6)	465	1.9 (6.6)		44.64%	0.15[0.02,0.28]
Subtotal ***	**486**		**489**			**75.5%**	**0.3[-0.13,0.73]**
Heterogeneity: Tau²=0.07; Chi²=2.43, df=1(P=0.12); I²=58.77%							
Test for overall effect: Z=1.37(P=0.17)							
5.12.2 Microvascular angina							
Villano 2013	15	79.4 (14)	15	57.2 (23)		24.5%	1.13[0.36,1.91]
Subtotal ***	**15**		**15**			**24.5%**	**1.13[0.36,1.91]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.85(P=0)							
Total ***	**501**		**504**			**100%**	**0.54[-0.03,1.1]**
Heterogeneity: Tau²=0.18; Chi²=8.12, df=2(P=0.02); I²=75.36%							
Test for overall effect: Z=1.86(P=0.06)							
Test for subgroup differences: Chi²=3.38, df=1 (P=0.07), I²=70.43%							



Analysis 5.13. Comparison 5 Sensitivity analysis 1: Studies at low risk of bias, Outcome 13 Comparison 4 - Time to 1-mm ST-segment depression.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
CARISA 2004	0	0	34.6 (0.786)		99.98%	34.6[33.06,36.14]
Villano 2013	0	0	122 (51.913)		0.02%	122[20.25,223.75]
Total (95% CI)					**100%**	**34.62[33.08,36.16]**
Heterogeneity: Tau²=0; Chi²=2.83, df=1(P=0.09); I²=64.71%						
Test for overall effect: Z=44.07(P<0.0001)						



Comparison 6. Sensitivity analysis 2: Exchange of model for data synthesis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparison 1 - All-cause mortality	3	6249	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.81, 1.25]
2 Comparison 1 - Quality of life	3	2254	Mean Difference (IV, Random, 95% CI)	0.28 [-1.57, 2.13]
3 Comparison 1 - AMI incidence	2	2674	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.69, 1.13]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Comparison 1 - Need for revascularisation procedure	2	2674	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.82, 1.18]
5 Comparison 1 - Adverse events incidence	2	638	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.90, 1.99]
6 Comparison 2 - AMI incidence	3	2983	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.19, 1.63]
7 Comparison 2 - Angina episodes frequency	2	402	Mean Difference (IV, Random, 95% CI)	0.08 [-0.85, 1.01]
8 Comparison 2 - Adverse events incidence	3	947	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.12, 2.01]
8.1 Macrovascular angina	2	691	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.13, 2.07]
8.2 Microvascular angina	1	256	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.40, 3.38]
9 Comparison 3 - All-cause mortality	3	2053	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.25, 3.04]
10 Comparison 3 - Quality of life	3	1533	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [0.01, 0.22]
11 Comparison 3 - AMI incidence (fatal)	2	1509	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.10, 19.46]
12 Comparison 3 - AMI incidence (non-fatal)	2	1509	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.08, 2.11]
13 Comparison 3 - Angina episodes frequency	3	2004	Mean Difference (IV, Random, 95% CI)	-0.78 [-1.28, -0.27]
14 Comparison 3 - Adverse events incidence	3	2053	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.06, 1.39]
15 Comparison 4 - Quality of life	4	1563	Std. Mean Difference (IV, Fixed, 95% CI)	0.13 [0.03, 0.23]
15.1 Macrovascular angina	3	1533	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [0.01, 0.22]
15.2 Microvascular angina	1	30	Std. Mean Difference (IV, Fixed, 95% CI)	1.13 [0.36, 1.91]
16 Comparison 4 - Time to 1-mm ST-segment depression	3		Mean Difference (Random, 95% CI)	51.05 [4.05, 98.04]

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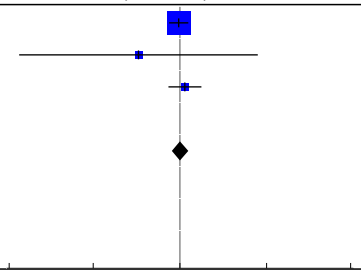
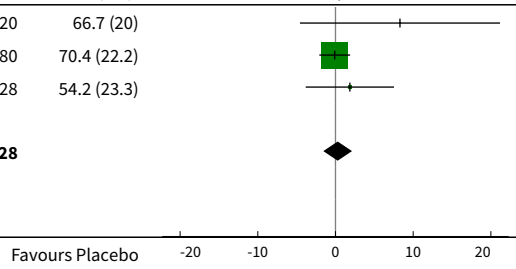
Analysis 6.1. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 1 Comparison 1 - All-cause mortality.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
MERLIN-TIMI 36 2007	111/1785	114/1775		74.68%	0.97[0.75,1.25]
Pelliccia 2012	0/35	1/35		0.48%	0.33[0.01,7.91]
RIVER-PCI 2016	42/1322	36/1297		24.85%	1.14[0.74,1.77]
Total (95% CI)	**3142**	**3107**		**100%**	**1[0.81,1.25]**
Total events: 153 (Experimental), 151 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.89, df=2(P=0.64); I^2=0%					
Test for overall effect: Z=0.04(P=0.97)					



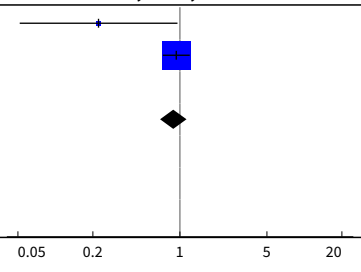
Analysis 6.2. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 2 Comparison 1 - Quality of life.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Mehta 2011	20	75 (21.6)	20	66.7 (20)		2.07%	8.3[-4.57,21.17]
RIVER-PCI 2016	978	70.3 (22.5)	980	70.4 (22.2)		87.33%	-0.1[-2.08,1.88]
RWISE 2016	128	56.1 (23.1)	128	54.2 (23.3)		10.6%	1.85[-3.83,7.53]
Total ***	**1126**		**1128**			**100%**	**0.28[-1.57,2.13]**
Heterogeneity: Tau^2=0; Chi^2=1.93, df=2(P=0.38); I^2=0%							
Test for overall effect: Z=0.3(P=0.77)							



Analysis 6.3. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 3 Comparison 1 - AMI incidence.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Pelliccia 2012	2/35	9/35		7.12%	0.22[0.05,0.96]
RIVER-PCI 2016	111/1317	116/1287		92.88%	0.94[0.73,1.2]
Total (95% CI)	**1352**	**1322**		**100%**	**0.88[0.69,1.13]**
Total events: 113 (Experimental), 125 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.64, df=1(P=0.06); I^2=72.51%					
Test for overall effect: Z=0.99(P=0.32)					



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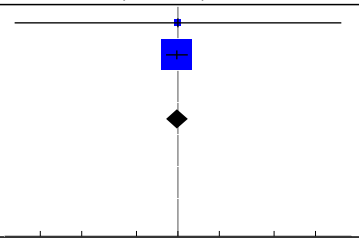
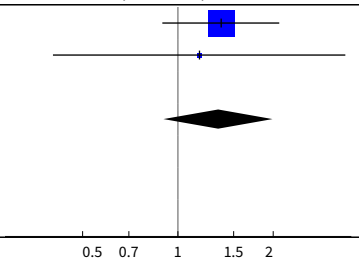
Analysis 6.4. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 4 Comparison 1 - Need for revascularisation procedure.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Pelliccia 2012	1/35	1/35		0.43%	1[0.07,15.36]
RIVER-PCI 2016	201/1317	200/1287		99.57%	0.98[0.82,1.18]
Total (95% CI)	**1352**	**1322**		**100%**	**0.98[0.82,1.18]**
Total events: 202 (Experimental), 201 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=0.2(P=0.84)					



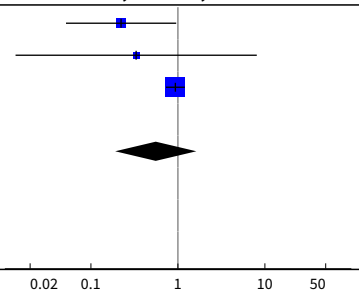
Analysis 6.5. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 5 Comparison 1 - Adverse events incidence.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
MARISA 2004	41/191	30/191		86.15%	1.37[0.89,2.09]
RWISE 2016	7/128	6/128		13.85%	1.17[0.4,3.38]
Total (95% CI)	**319**	**319**		**100%**	**1.34[0.9,1.99]**
Total events: 48 (Experimental), 36 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.79); I^2=0%					
Test for overall effect: Z=1.44(P=0.15)					



Analysis 6.6. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 6 Comparison 2 - AMI incidence.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Pelliccia 2012	2/35	9/35		29.21%	0.22[0.05,0.96]
RAN080 2005	0/155	1/154		9.61%	0.33[0.01,8.07]
RIVER-PCI 2016	111/1317	116/1287		61.19%	0.94[0.73,1.2]
Total (95% CI)	**1507**	**1476**		**100%**	**0.56[0.19,1.63]**
Total events: 113 (Experimental), 126 (Control)					
Heterogeneity: Tau^2=0.48; Chi^2=4.01, df=2(P=0.13); I^2=50.16%					
Test for overall effect: Z=1.07(P=0.28)					



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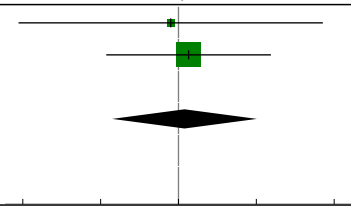
Analysis 6.7. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 7 Comparison 2 - Angina episodes frequency.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
RWISE 2016	128	4.8 (8.2)	128	4.9 (7.8)		22.65%	-0.1[-2.05,1.85]
Thadani 1994	75	-2.1 (3.4)	71	-2.2 (3.1)		77.35%	0.13[-0.93,1.19]
Total ***	**203**		**199**			**100%**	**0.08[-0.85,1.01]**

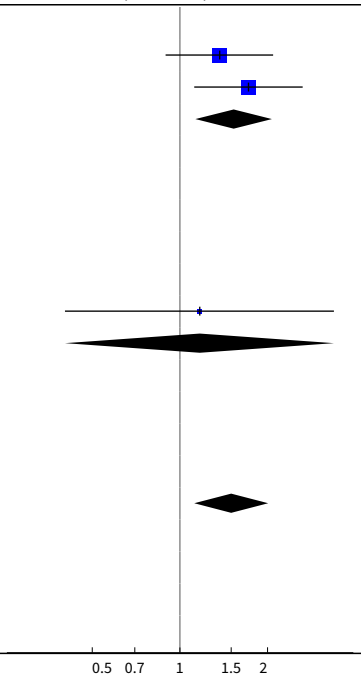
Heterogeneity: Tau²=0; Chi²=0.04, df=1(P=0.84); I²=0%

Test for overall effect: Z=0.16(P=0.87)



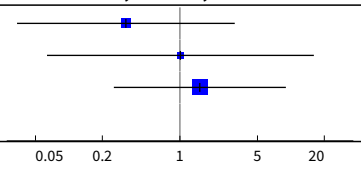
Analysis 6.8. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 8 Comparison 2 - Adverse events incidence.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.8.1 Macrovascular angina					
MARISA 2004	41/191	30/191		46.5%	1.37[0.89,2.09]
RAN080 2005	45/155	26/154		46.03%	1.72[1.12,2.64]
Subtotal (95% CI)	**346**	**345**		**92.52%**	**1.53[1.13,2.07]**
Total events: 86 (Experimental), 56 (Control)					
Heterogeneity: Tau²=0; Chi²=0.56, df=1(P=0.46); I²=0%					
Test for overall effect: Z=2.77(P=0.01)					
6.8.2 Microvascular angina					
RWISE 2016	7/128	6/128		7.48%	1.17[0.4,3.38]
Subtotal (95% CI)	**128**	**128**		**7.48%**	**1.17[0.4,3.38]**
Total events: 7 (Experimental), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.28(P=0.78)					
Total (95% CI)	**474**	**473**		**100%**	**1.5[1.12,2.01]**
Total events: 93 (Experimental), 62 (Control)					
Heterogeneity: Tau²=0; Chi²=0.79, df=2(P=0.67); I²=0%					
Test for overall effect: Z=2.74(P=0.01)					
Test for subgroup differences: Chi²=0.23, df=1 (P=0.63), I²=0%					



Analysis 6.9. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 9 Comparison 3 - All-cause mortality.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
CARISA 2004	1/275	3/269		30.63%	0.33[0.03,3.12]
ERICA 2006	1/281	1/284		20.38%	1.01[0.06,16.08]
TERISA 2013	3/470	2/474		48.99%	1.51[0.25,9.01]



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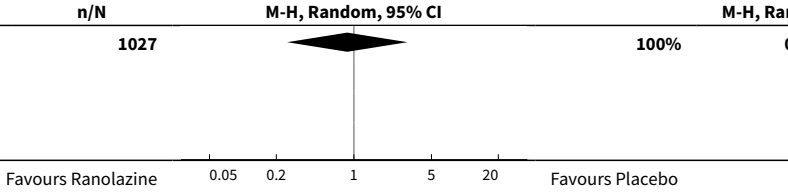
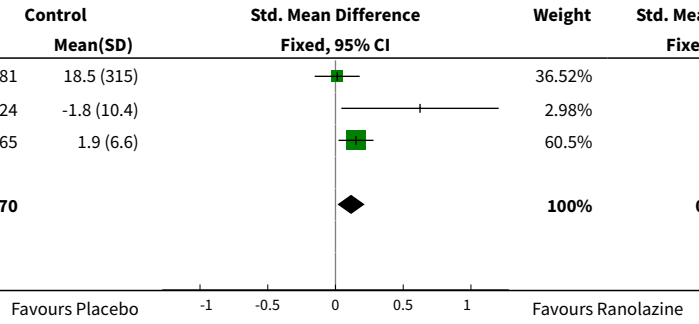
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**1026**	**1027**		**100%**	**0.87[0.25,3.04]**
Total events: 5 (Experimental), 6 (Control)					
Heterogeneity: Tau²=0; Chi²=1.11, df=2(P=0.57); I²=0%					
Test for overall effect: Z=0.22(P=0.83)					



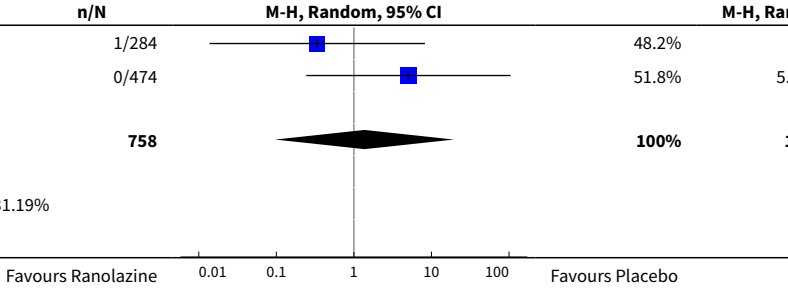
Analysis 6.10. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 10 Comparison 3 - Quality of life.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
ERICA 2006	277	22.5 (316.2)	281	18.5 (315)		36.52%	0.01[-0.15,0.18]
Shammas 2015	24	13.9 (33.5)	24	-1.8 (10.4)		2.98%	0.62[0.04,1.2]
TERISA 2013	462	2.9 (6.6)	465	1.9 (6.6)		60.5%	0.15[0.02,0.28]
Total ***	**763**		**770**			**100%**	**0.11[0.01,0.22]**
Heterogeneity: Tau²=0; Chi²=4.73, df=2(P=0.09); I²=57.67%							
Test for overall effect: Z=2.25(P=0.02)							



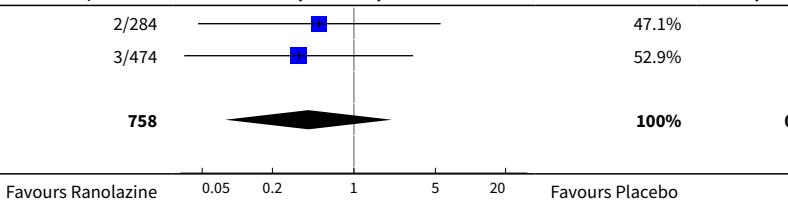
Analysis 6.11. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 11 Comparison 3 - AMI incidence (fatal).

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ERICA 2006	0/281	1/284		48.2%	0.34[0.01,8.23]
TERISA 2013	2/470	0/474		51.8%	5.04[0.24,104.75]
Total (95% CI)	**751**	**758**		**100%**	**1.37[0.1,19.46]**
Total events: 2 (Experimental), 1 (Control)					
Heterogeneity: Tau²=1.15; Chi²=1.45, df=1(P=0.23); I²=31.19%					
Test for overall effect: Z=0.23(P=0.82)					



Analysis 6.12. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 12 Comparison 3 - AMI incidence (non-fatal).

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ERICA 2006	1/281	2/284		47.1%	0.51[0.05,5.54]
TERISA 2013	1/470	3/474		52.9%	0.34[0.04,3.22]
Total (95% CI)	**751**	**758**		**100%**	**0.41[0.08,2.11]**
Total events: 2 (Experimental), 5 (Control)					



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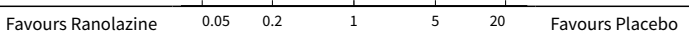
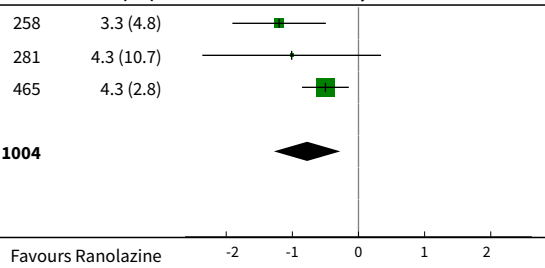
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=0.06, df=1(P=0.81); I²=0%					
Test for overall effect: Z=1.07(P=0.28)					



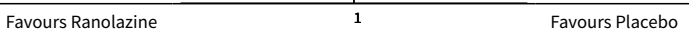
Analysis 6.13. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 13 Comparison 3 - Angina episodes frequency.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
CARISA 2004	261	2.1 (3.2)	258	3.3 (4.8)		30.95%	-1.2[-1.91,-0.49]
ERICA 2006	277	3.3 (4.3)	281	4.3 (10.7)		11.79%	-1.01[-2.36,0.34]
TERISA 2013	462	3.8 (2.7)	465	4.3 (2.8)		57.26%	-0.5[-0.85,-0.15]
Total ***	**1000**		**1004**			**100%**	**-0.78[-1.28,-0.27]**
Heterogeneity: Tau²=0.08; Chi²=3.29, df=2(P=0.19); I²=39.15%							
Test for overall effect: Z=3.03(P=0)							



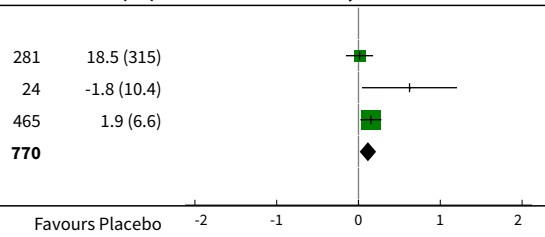
Analysis 6.14. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 14 Comparison 3 - Adverse events incidence.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
CARISA 2004	90/275	71/269		27.94%	1.24[0.95,1.61]
ERICA 2006	112/281	100/284		42.07%	1.13[0.91,1.4]
TERISA 2013	110/470	85/474		29.99%	1.31[1.01,1.68]
Total (95% CI)	**1026**	**1027**		**100%**	**1.21[1.06,1.39]**
Total events: 312 (Experimental), 256 (Control)					
Heterogeneity: Tau²=0; Chi²=0.76, df=2(P=0.68); I²=0%					
Test for overall effect: Z=2.72(P=0.01)					



Analysis 6.15. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 15 Comparison 4 - Quality of life.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
6.15.1 Macrovascular angina							
ERICA 2006	277	22.5 (316.2)	281	18.5 (315)		35.92%	0.01[-0.15,0.18]
Shammas 2015	24	13.9 (33.5)	24	-1.8 (10.4)		2.93%	0.62[0.04,1.2]
TERISA 2013	462	2.9 (6.6)	465	1.9 (6.6)		59.51%	0.15[0.02,0.28]
Subtotal ***	**763**		**770**			**98.37%**	**0.11[0.01,0.22]**
Heterogeneity: Tau²=0; Chi²=4.73, df=2(P=0.09); I²=57.68%							



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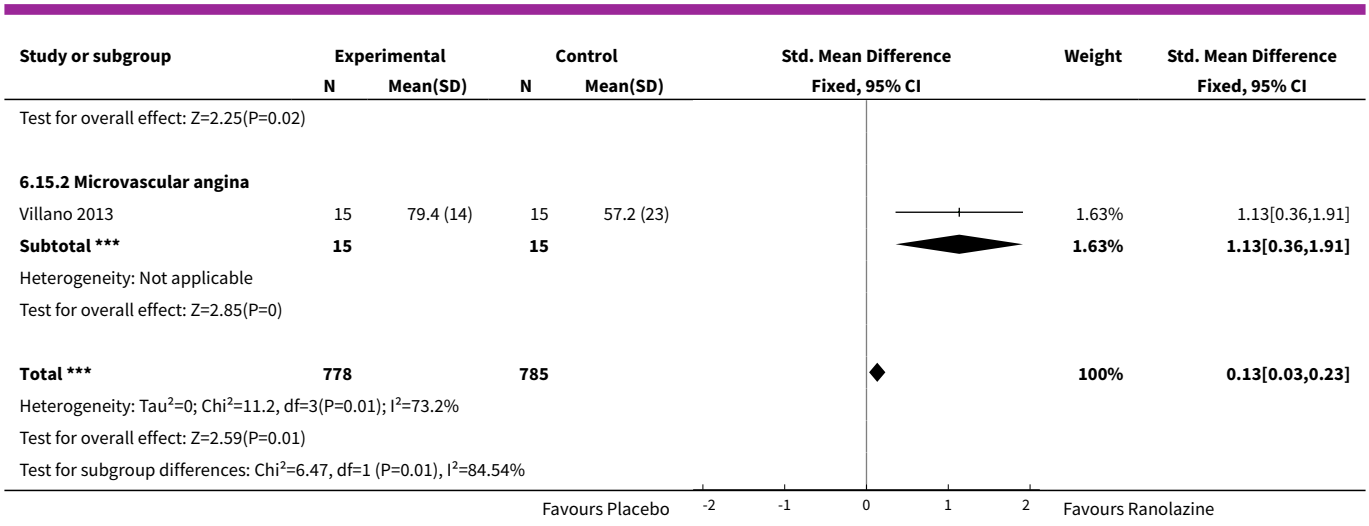
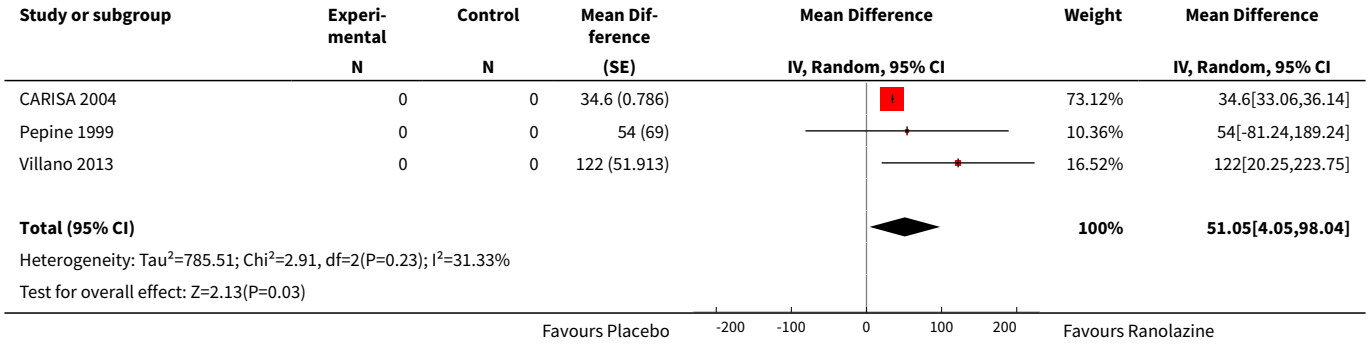


Analysis 6.16. Comparison 6 Sensitivity analysis 2: Exchange of model for data synthesis, Outcome 16 Comparison 4 - Time to 1-mm ST-segment depression.



Comparison 7. Sensitivity analysis 3: Change of the measure of treatment effect

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparison 1 - All-cause mortality	3	6249	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.80, 1.27]
2 Comparison 1 - Quality of life	3	2254	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.07, 0.09]
3 Comparison 1 - AMI incidence	2	2674	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.10, 2.41]
4 Comparison 1 - Need for revascularisation procedure	2	2674	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.79, 1.21]
5 Comparison 1 - Adverse events incidence	2	638	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.88, 2.26]

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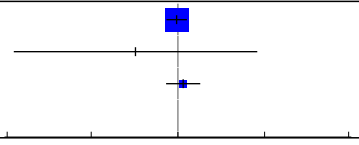
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Comparison 2 - AMI incidence	3	2983	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.67, 1.13]
7 Comparison 2 - Angina episodes frequency	2	402	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.19, 0.20]
8 Comparison 2 - Adverse events incidence	3	947	Odds Ratio (M-H, Fixed, 95% CI)	1.64 [1.15, 2.35]
8.1 Macrovascular angina	2	691	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [1.17, 2.49]
8.2 Microvascular angina	1	256	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.38, 3.60]
9 Comparison 3 - All-cause mortality	3	2053	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.25, 2.73]
10 Comparison 3 - Quality of life	3	1533	Mean Difference (IV, Random, 95% CI)	5.91 [-5.52, 17.34]
11 Comparison 3 - AMI incidence (fatal)	2	1509	Odds Ratio (M-H, Fixed, 95% CI)	1.52 [0.25, 9.09]
12 Comparison 3 - AMI incidence (non-fatal)	2	1509	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.08]
13 Comparison 3 - Angina episodes frequency	3	2004	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.28, -0.11]
14 Comparison 3 - Adverse events incidence	3	2053	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [1.09, 1.61]
15 Comparison 4 - Quality of life	4	1563	Mean Difference (IV, Random, 95% CI)	11.17 [-2.54, 24.87]
15.1 Macrovascular angina	3	1533	Mean Difference (IV, Random, 95% CI)	5.91 [-5.52, 17.34]
15.2 Microvascular angina	1	30	Mean Difference (IV, Random, 95% CI)	22.20 [8.57, 35.83]

Analysis 7.1. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 1 Comparison 1 - All-cause mortality.

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
MERLIN-TIMI 36 2007	111/1785	114/1775		74.51%	0.97[0.74,1.27]
Pelliccia 2012	0/35	1/35		1.03%	0.32[0.01,8.23]
RIVER-PCI 2016	42/1322	36/1297		24.46%	1.15[0.73,1.81]



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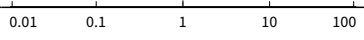
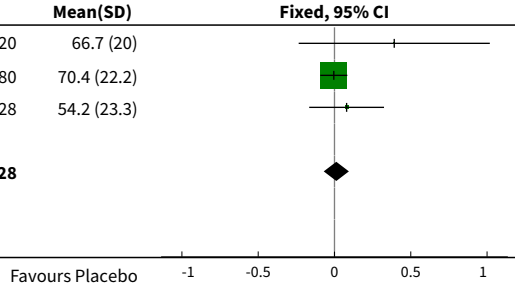
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Total (95% CI)	**3142**	**3107**		**100%**	**1[0.8,1.27]**
Total events: 153 (Experimental), 151 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.89, df=2(P=0.64); I^2=0%					
Test for overall effect: Z=0.04(P=0.97)					



Analysis 7.2. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 2 Comparison 1 - Quality of life.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Mehta 2011	20	75 (21.6)	20	66.7 (20)		1.74%	0.39[-0.23,1.02]
RIVER-PCI 2016	978	70.3 (22.5)	980	70.4 (22.2)		86.91%	-0[-0.09,0.08]
RWISE 2016	128	56.1 (23.1)	128	54.2 (23.3)		11.35%	0.08[-0.17,0.32]
Total ***	**1126**		**1128**			**100%**	**0.01[-0.07,0.09]**
Heterogeneity: Tau^2=0; Chi^2=1.84, df=2(P=0.4); I^2=0%							
Test for overall effect: Z=0.28(P=0.78)							

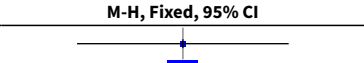


Analysis 7.3. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 3 Comparison 1 - AMI incidence.

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Pelliccia 2012	2/35	9/35		38.18%	0.18[0.03,0.88]
RIVER-PCI 2016	111/1317	116/1287		61.82%	0.93[0.71,1.22]
Total (95% CI)	**1352**	**1322**		**100%**	**0.49[0.1,2.41]**
Total events: 113 (Experimental), 125 (Control)					
Heterogeneity: Tau^2=1.05; Chi^2=4, df=1(P=0.05); I^2=74.98%					
Test for overall effect: Z=0.88(P=0.38)					

Analysis 7.4. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 4 Comparison 1 - Need for revascularisation procedure.

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Pelliccia 2012	1/35	1/35		0.56%	1[0.06,16.65]
RIVER-PCI 2016	201/1317	200/1287		99.44%	0.98[0.79,1.21]
Total (95% CI)	**1352**	**1322**		**100%**	**0.98[0.79,1.21]**
Total events: 202 (Experimental), 201 (Control)					



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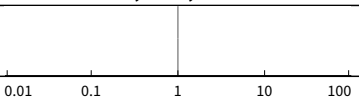
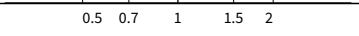
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.99); I²=0%					
Test for overall effect: Z=0.2(P=0.84)					



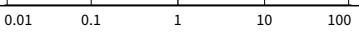
Analysis 7.5. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 5 Comparison 1 - Adverse events incidence.

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
MARISA 2004	41/191	30/191		80.6%	1.47[0.87,2.47]
RWISE 2016	7/128	6/128		19.4%	1.18[0.38,3.6]
Total (95% CI)	**319**	**319**		**100%**	**1.41[0.88,2.26]**
Total events: 48 (Experimental), 36 (Control)					
Heterogeneity: Tau²=0; Chi²=0.12, df=1(P=0.73); I²=0%					
Test for overall effect: Z=1.43(P=0.15)					



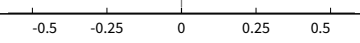
Analysis 7.6. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 6 Comparison 2 - AMI incidence.

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Pelliccia 2012	2/35	9/35		7.23%	0.18[0.03,0.88]
RAN080 2005	0/155	1/154		1.28%	0.33[0.01,8.14]
RIVER-PCI 2016	111/1317	116/1287		91.5%	0.93[0.71,1.22]
Total (95% CI)	**1507**	**1476**		**100%**	**0.87[0.67,1.13]**
Total events: 113 (Experimental), 126 (Control)					
Heterogeneity: Tau²=0; Chi²=4.36, df=2(P=0.11); I²=54.16%					
Test for overall effect: Z=1.06(P=0.29)					



Analysis 7.7. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 7 Comparison 2 - Angina episodes frequency.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
RWISE 2016	128	4.8 (8.2)	128	4.9 (7.8)		63.7%	-0.01[-0.26,0.23]
Thadani 1994	75	-2.1 (3.4)	71	-2.2 (3.1)		36.3%	0.04[-0.28,0.36]
Total ***	**203**		**199**			**100%**	**0.01[-0.19,0.2]**
Heterogeneity: Tau²=0; Chi²=0.06, df=1(P=0.8); I²=0%							
Test for overall effect: Z=0.06(P=0.95)							



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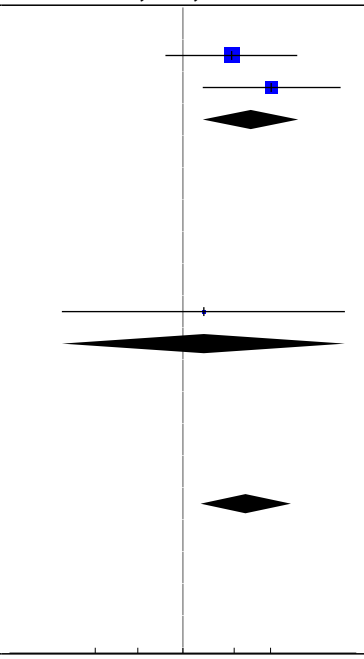
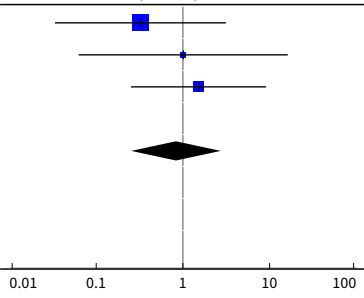
Analysis 7.8. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 8 Comparison 2 - Adverse events incidence.

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
7.8.1 Macrovascular angina					
MARISA 2004	41/191	30/191		49.35%	1.47[0.87,2.47]
RAN080 2005	45/155	26/154		38.77%	2.01[1.17,3.48]
Subtotal (95% CI)	**346**	**345**		**88.12%**	**1.71[1.17,2.49]**
Total events: 86 (Experimental), 56 (Control)					
Heterogeneity: Tau²=0; Chi²=0.68, df=1(P=0.41); I²=0%					
Test for overall effect: Z=2.79(P=0.01)					
7.8.2 Microvascular angina					
RWISE 2016	7/128	6/128		11.88%	1.18[0.38,3.6]
Subtotal (95% CI)	**128**	**128**		**11.88%**	**1.18[0.38,3.6]**
Total events: 7 (Experimental), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.28(P=0.78)					
Total (95% CI)	**474**	**473**		**100%**	**1.64[1.15,2.35]**
Total events: 93 (Experimental), 62 (Control)					
Heterogeneity: Tau²=0; Chi²=1.06, df=2(P=0.59); I²=0%					
Test for overall effect: Z=2.74(P=0.01)					
Test for subgroup differences: Chi²=0.38, df=1 (P=0.54), I²=0%					



Analysis 7.9. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 9 Comparison 3 - All-cause mortality.

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
CARISA 2004	1/275	3/269		50.43%	0.32[0.03,3.13]
ERICA 2006	1/281	1/284		16.54%	1.01[0.06,16.24]
TERISA 2013	3/470	2/474		33.02%	1.52[0.25,9.11]
Total (95% CI)	**1026**	**1027**		**100%**	**0.83[0.25,2.73]**
Total events: 5 (Experimental), 6 (Control)					
Heterogeneity: Tau²=0; Chi²=1.11, df=2(P=0.57); I²=0%					
Test for overall effect: Z=0.31(P=0.76)					



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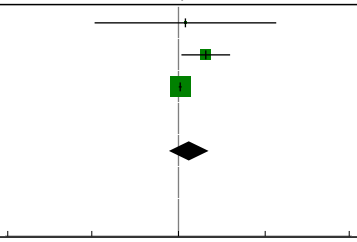
Analysis 7.10. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 10 Comparison 3 - Quality of life.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
ERICA 2006	277	22.5 (316.2)	281	18.5 (315)		4.43%	4[-48.37,56.37]
Shammas 2015	24	13.9 (33.5)	24	-1.8 (10.4)		32.41%	15.74[1.71,29.77]
TERISA 2013	462	2.9 (6.6)	465	1.9 (6.6)		63.16%	1[0.15,1.85]
Total ***	**763**		**770**			**100%**	**5.91[-5.52,17.34]**

Heterogeneity: Tau^2=53.64; Chi^2=4.23, df=2(P=0.12); I^2=52.77%

Test for overall effect: Z=1.01(P=0.31)



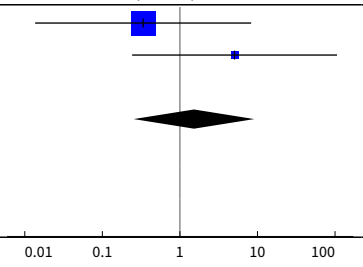
Analysis 7.11. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 11 Comparison 3 - AMI incidence (fatal).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
ERICA 2006	0/281	1/284		75.05%	0.34[0.01,8.28]
TERISA 2013	2/470	0/474		24.95%	5.06[0.24,105.76]
Total (95% CI)	**751**	**758**		**100%**	**1.52[0.25,9.09]**

Total events: 2 (Experimental), 1 (Control)

Heterogeneity: Tau^2=0; Chi^2=1.46, df=1(P=0.23); I^2=31.27%

Test for overall effect: Z=0.45(P=0.65)



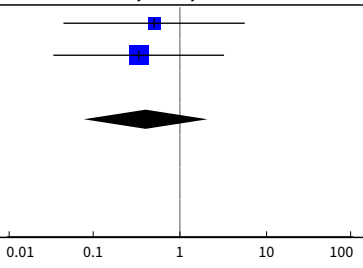
Analysis 7.12. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 12 Comparison 3 - AMI incidence (non-fatal).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
ERICA 2006	1/281	2/284		39.94%	0.5[0.05,5.59]
TERISA 2013	1/470	3/474		60.06%	0.33[0.03,3.23]
Total (95% CI)	**751**	**758**		**100%**	**0.4[0.08,2.08]**

Total events: 2 (Experimental), 5 (Control)

Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.81); I^2=0%

Test for overall effect: Z=1.09(P=0.28)



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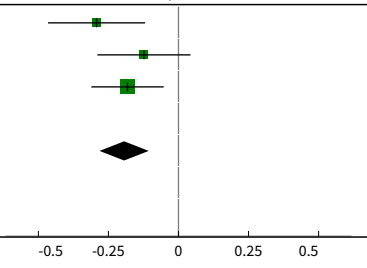
Analysis 7.13. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 13 Comparison 3 - Angina episodes frequency.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
CARISA 2004	261	2.1 (3.2)	258	3.3 (4.8)		25.76%	-0.29[-0.47,-0.12]
ERICA 2006	277	3.3 (4.3)	281	4.3 (10.7)		27.94%	-0.12[-0.29,0.04]
TERISA 2013	462	3.8 (2.7)	465	4.3 (2.8)		46.31%	-0.18[-0.31,-0.05]
Total ***	**1000**		**1004**			**100%**	**-0.19[-0.28,-0.11]**

Heterogeneity: Tau^2=0; Chi^2=1.97, df=2(P=0.37); I^2=0%

Test for overall effect: Z=4.33(P<0.0001)



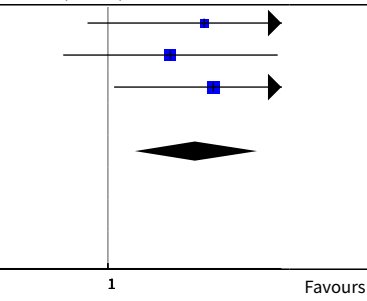
Analysis 7.14. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 14 Comparison 3 - Adverse events incidence.

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
CARISA 2004	90/275	71/269		27.92%	1.36[0.94,1.96]
ERICA 2006	112/281	100/284		34.59%	1.22[0.87,1.72]
TERISA 2013	110/470	85/474		37.49%	1.4[1.02,1.92]
Total (95% CI)	**1026**	**1027**		**100%**	**1.32[1.09,1.61]**

Total events: 312 (Experimental), 256 (Control)

Heterogeneity: Tau^2=0; Chi^2=0.35, df=2(P=0.84); I^2=0%

Test for overall effect: Z=2.8(P=0.01)



Analysis 7.15. Comparison 7 Sensitivity analysis 3: Change of the measure of treatment effect, Outcome 15 Comparison 4 - Quality of life.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
7.15.1 Macrovascular angina							
ERICA 2006	277	22.5 (316.2)	281	18.5 (315)		5.82%	4[-48.37,56.37]
Shammas 2015	24	13.9 (33.5)	24	-1.8 (10.4)		27.53%	15.74[1.71,29.77]
TERISA 2013	462	2.9 (6.6)	465	1.9 (6.6)		38.65%	1[0.15,1.85]
Subtotal ***	**763**		**770**			**72%**	**5.91[-5.52,17.34]**

Heterogeneity: Tau^2=53.64; Chi^2=4.23, df=2(P=0.12); I^2=52.77%

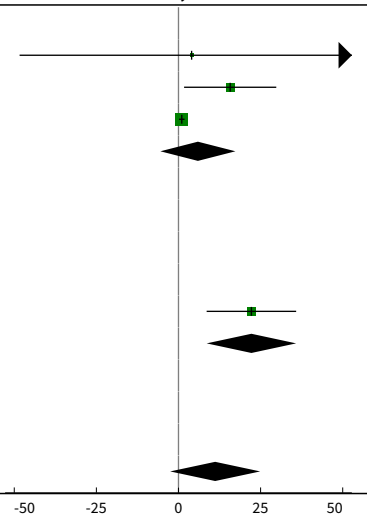
Test for overall effect: Z=1.01(P=0.31)

7.15.2 Microvascular angina							
Villano 2013	15	79.4 (14)	15	57.2 (23)		28%	22.2[8.57,35.83]
Subtotal ***	**15**		**15**			**28%**	**22.2[8.57,35.83]**

Heterogeneity: Not applicable

Test for overall effect: Z=3.19(P=0)

Total ***	**778**		**785**			**100%**	**11.17[-2.54,24.87]**



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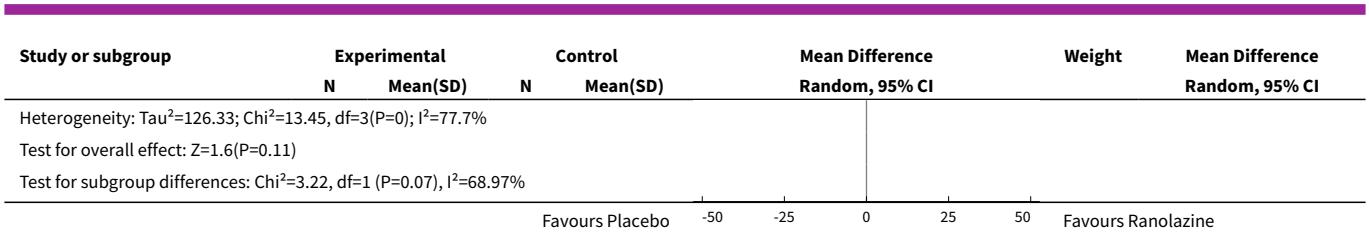

Comparison 8. Sensitivity analysis 4: follow-up ≥ 6 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparison 1 - All-cause mortality	2	6179	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.26]
2 Comparison 1 - Quality of life	1	1958	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-2.08, 1.88]
3 Comparison 1 - AMI incidence	1	2604	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.73, 1.20]
4 Comparison 1 - Need for revascularisation procedure	1	2604	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.82, 1.18]
5 Comparison 2 - AMI incidence	1	2604	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.73, 1.20]
6 Comparison 3 - All-cause mortality	3	2053	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.26, 2.71]
7 Comparison 3 - Quality of life	3	1533	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.05, 0.32]
8 Comparison 3 - AMI incidence (fatal)	2	1509	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.25, 9.05]
9 Comparison 3 - AMI incidence (non-fatal)	2	1509	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.07]
10 Comparison 3 - Angina episodes frequency	3	2004	Mean Difference (IV, Fixed, 95% CI)	-0.66 [-0.97, -0.35]
11 Comparison 3 - Adverse events incidence	3	2053	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.06, 1.40]
12 Comparison 4 - Quality of life	3	1533	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.05, 0.32]
12.1 Macrovascular angina	3	1533	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.05, 0.32]
13 Comparison 4 - Time to 1-mm ST-segment depression	1		Mean Difference (Fixed, 95% CI)	34.6 [33.06, 36.14]

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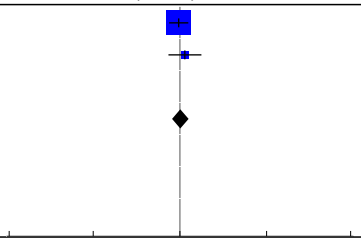
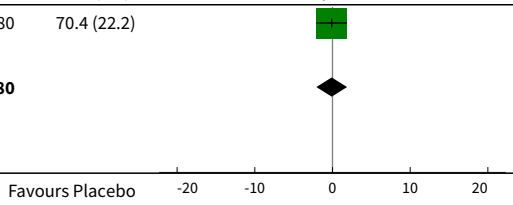
Analysis 8.1. Comparison 8 Sensitivity analysis 4: follow-up ≥ 6 weeks, Outcome 1 Comparison 1 - All-cause mortality.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
MERLIN-TIMI 36 2007	111/1785	114/1775		75.88%	0.97[0.75,1.25]
RIVER-PCI 2016	42/1322	36/1297		24.12%	1.14[0.74,1.77]
Total (95% CI)	**3107**	**3072**		**100%**	**1.01[0.81,1.26]**
Total events: 153 (Experimental), 150 (Control)					
Heterogeneity: Tau²=0; Chi²=0.42, df=1(P=0.52); I²=0%					
Test for overall effect: Z=0.1(P=0.92)					



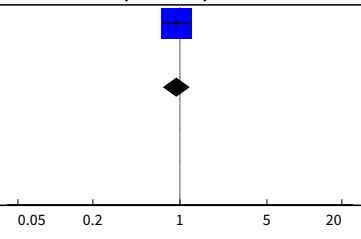
Analysis 8.2. Comparison 8 Sensitivity analysis 4: follow-up ≥ 6 weeks, Outcome 2 Comparison 1 - Quality of life.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
RIVER-PCI 2016	978	70.3 (22.5)	980	70.4 (22.2)		100%	-0.1[-2.08,1.88]
Total ***	**978**		**980**			**100%**	**-0.1[-2.08,1.88]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.1(P=0.92)							



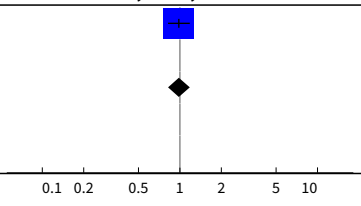
Analysis 8.3. Comparison 8 Sensitivity analysis 4: follow-up ≥ 6 weeks, Outcome 3 Comparison 1 - AMI incidence.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
RIVER-PCI 2016	111/1317	116/1287		100%	0.94[0.73,1.2]
Total (95% CI)	**1317**	**1287**		**100%**	**0.94[0.73,1.2]**
Total events: 111 (Experimental), 116 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.53(P=0.6)					



Analysis 8.4. Comparison 8 Sensitivity analysis 4: follow-up ≥ 6 weeks, Outcome 4 Comparison 1 - Need for revascularisation procedure.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
RIVER-PCI 2016	201/1317	200/1287		100%	0.98[0.82,1.18]
Total (95% CI)	**1317**	**1287**		**100%**	**0.98[0.82,1.18]**
Total events: 201 (Experimental), 200 (Control)					
Heterogeneity: Not applicable					



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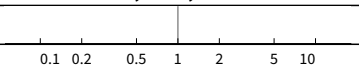
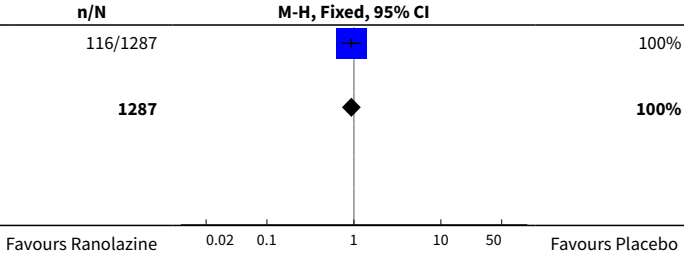
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.2(P=0.84)					



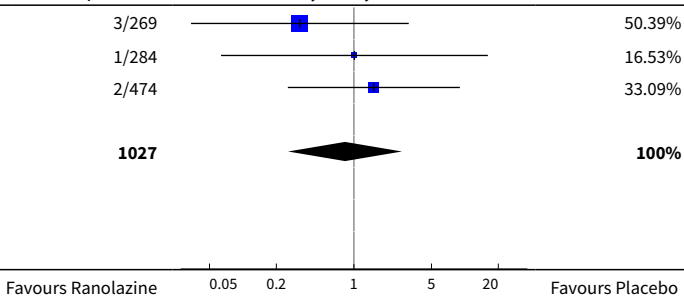
Analysis 8.5. Comparison 8 Sensitivity analysis 4: follow-up ≥ 6 weeks, Outcome 5 Comparison 2 - AMI incidence.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
RIVER-PCI 2016	111/1317	116/1287		100%	0.94[0.73,1.2]
Total (95% CI)	**1317**	**1287**		**100%**	**0.94[0.73,1.2]**
Total events: 111 (Experimental), 116 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.53(P=0.6)					



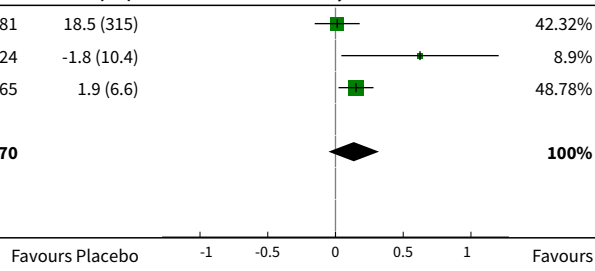
Analysis 8.6. Comparison 8 Sensitivity analysis 4: follow-up ≥ 6 weeks, Outcome 6 Comparison 3 - All-cause mortality.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
CARISA 2004	1/275	3/269		50.39%	0.33[0.03,3.12]
ERICA 2006	1/281	1/284		16.53%	1.01[0.06,16.08]
TERISA 2013	3/470	2/474		33.09%	1.51[0.25,9.01]
Total (95% CI)	**1026**	**1027**		**100%**	**0.83[0.26,2.71]**
Total events: 5 (Experimental), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.11, df=2(P=0.57); I^2=0%					
Test for overall effect: Z=0.31(P=0.76)					



Analysis 8.7. Comparison 8 Sensitivity analysis 4: follow-up ≥ 6 weeks, Outcome 7 Comparison 3 - Quality of life.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
ERICA 2006	277	22.5 (316.2)	281	18.5 (315)		42.32%	0.01[-0.15,0.18]
Shammas 2015	24	13.9 (33.5)	24	-1.8 (10.4)		8.9%	0.62[0.04,1.2]
TERISA 2013	462	2.9 (6.6)	465	1.9 (6.6)		48.78%	0.15[0.02,0.28]
Total ***	**763**		**770**			**100%**	**0.13[-0.05,0.32]**
Heterogeneity: Tau^2=0.01; Chi^2=4.73, df=2(P=0.09); I^2=57.67%							
Test for overall effect: Z=1.42(P=0.16)							



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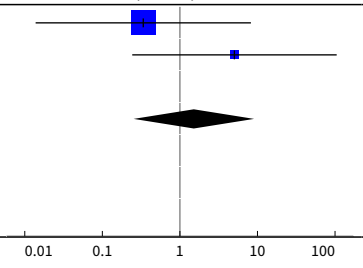
Analysis 8.8. Comparison 8 Sensitivity analysis 4: follow-up ≥ 6 weeks, Outcome 8 Comparison 3 - AMI incidence (fatal).

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ERICA 2006	0/281	1/284		74.98%	0.34[0.01,8.23]
TERISA 2013	2/470	0/474		25.02%	5.04[0.24,104.75]
Total (95% CI)	**751**	**758**		**100%**	**1.51[0.25,9.05]**

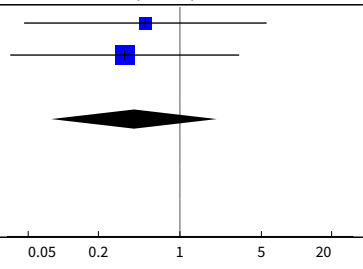
Total events: 2 (Experimental), 1 (Control)
Heterogeneity: Tau^2=0; Chi^2=1.45, df=1(P=0.23); I^2=31.19%
Test for overall effect: Z=0.45(P=0.65)



Analysis 8.9. Comparison 8 Sensitivity analysis 4: follow-up ≥ 6 weeks, Outcome 9 Comparison 3 - AMI incidence (non-fatal).

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ERICA 2006	1/281	2/284		39.97%	0.51[0.05,5.54]
TERISA 2013	1/470	3/474		60.03%	0.34[0.04,3.22]
Total (95% CI)	**751**	**758**		**100%**	**0.4[0.08,2.07]**

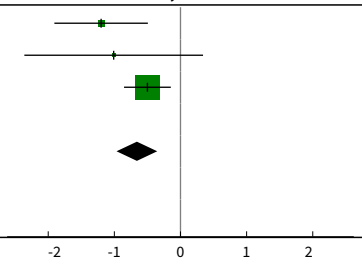
Total events: 2 (Experimental), 5 (Control)
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.81); I^2=0%
Test for overall effect: Z=1.09(P=0.28)



Analysis 8.10. Comparison 8 Sensitivity analysis 4: follow-up ≥ 6 weeks, Outcome 10 Comparison 3 - Angina episodes frequency.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
CARISA 2004	261	2.1 (3.2)	258	3.3 (4.8)		18.97%	-1.2[-1.91,-0.49]
ERICA 2006	277	3.3 (4.3)	281	4.3 (10.7)		5.19%	-1.01[-2.36,0.34]
TERISA 2013	462	3.8 (2.7)	465	4.3 (2.8)		75.83%	-0.5[-0.85,-0.15]
Total ***	**1000**		**1004**			**100%**	**-0.66[-0.97,-0.35]**

Heterogeneity: Tau^2=0; Chi^2=3.29, df=2(P=0.19); I^2=39.15%
Test for overall effect: Z=4.2(P<0.0001)



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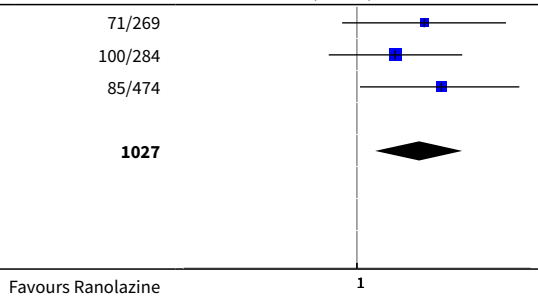
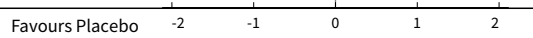
Analysis 8.11. Comparison 8 Sensitivity analysis 4: follow-up ≥ 6 weeks, Outcome 11 Comparison 3 - Adverse events incidence.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
CARISA 2004	90/275	71/269		28.05%	1.24[0.95,1.61]
ERICA 2006	112/281	100/284		38.87%	1.13[0.91,1.4]
TERISA 2013	110/470	85/474		33.08%	1.31[1.01,1.68]
Total (95% CI)	**1026**	**1027**		**100%**	**1.22[1.06,1.4]**
Total events: 312 (Experimental), 256 (Control)					
Heterogeneity: Tau²=0; Chi²=0.76, df=2(P=0.68); I²=0%					
Test for overall effect: Z=2.8(P=0.01)					



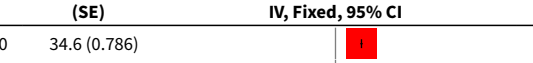
Analysis 8.12. Comparison 8 Sensitivity analysis 4: follow-up ≥ 6 weeks, Outcome 12 Comparison 4 - Quality of life.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
8.12.1 Macrovascular angina							
ERICA 2006	277	22.5 (316.2)	281	18.5 (315)		42.32%	0.01[-0.15,0.18]
Shammas 2015	24	13.9 (33.5)	24	-1.8 (10.4)		8.9%	0.62[0.04,1.2]
TERISA 2013	462	2.9 (6.6)	465	1.9 (6.6)		48.78%	0.15[0.02,0.28]
Subtotal ***	**763**		**770**			**100%**	**0.13[-0.05,0.32]**
Heterogeneity: Tau²=0.01; Chi²=4.73, df=2(P=0.09); I²=57.68%							
Test for overall effect: Z=1.42(P=0.16)							
Total ***	**763**		**770**			**100%**	**0.13[-0.05,0.32]**
Heterogeneity: Tau²=0.01; Chi²=4.73, df=2(P=0.09); I²=57.68%							
Test for overall effect: Z=1.42(P=0.16)							



Analysis 8.13. Comparison 8 Sensitivity analysis 4: follow-up ≥ 6 weeks, Outcome 13 Comparison 4 - Time to 1-mm ST-segment depression.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
CARISA 2004	0	0	34.6 (0.786)		100%	34.6[33.06,36.14]
Total (95% CI)					**100%**	**34.6[33.06,36.14]**
Heterogeneity: Not applicable						
Test for overall effect: Z=44.04(P<0.0001)						



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APPENDICES

Appendix 1. Search strategies

CENTRAL

#1 MeSH descriptor: [Angina Pectoris] explode all trees
#2 angina*:ti,ab,kw (Word variations have been searched)
#3 stenocardia*:ti,ab,kw (Word variations have been searched)
#4 angor pectoris:ti,ab,kw (Word variations have been searched)
#5 #1 or #2 or #3 or #4
#6 ranolazine:ti,ab,kw (Word variations have been searched)
#7 ranexa:ti,ab,kw (Word variations have been searched)
#8 latixa:ti,ab,kw (Word variations have been searched)
#9 (rs next "43285"):ti,ab,kw (Word variations have been searched)
#10 #6 or #7 or #8 or #9
#11 #5 and #10

MEDLINE OVID

1. exp Angina Pectoris/
2. angina*.tw.
3. stenocardia*.tw.
4. angor pectoris.tw.
5. or/1-4
6. ranolazine.mp.
7. ranexa.mp.
8. latixa.mp.
9. (rs adj "43285").mp.
10. 110445-25-5.rn.
11. or/6-10
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. randomized.ab.
15. placebo.ab.
16. drug therapy.fs.
17. randomly.ab.
18. trial.ab.
19. groups.ab.
20. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp animals/ not humans.sh.
22. 20 not 21
23. 5 and 11
24. 22 and 23

EMBASE OVID

1. exp Angina Pectoris/
2. angina*.tw.
3. stenocardia*.tw.
4. angor pectoris.tw.
5. or/1-4
6. ranolazine.mp.
7. ranexa.mp.
8. latixa.mp.
9. (rs adj "43285").mp.
10. ranolazine/
11. or/6-10
12. random$.tw.
13. factorial$.tw.
14. crossover$.tw.
15. cross over$.tw.
16. cross-over$.tw.

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17. placebo$.tw.
18. (doubl$ adj blind$).tw.
19. (singl$ adj blind$).tw.
20. assign$.tw.
21. allocat$.tw.
22. volunteer$.tw.
23. crossover procedure/
24. double blind procedure/
25. randomized controlled trial/
26. single blind procedure/
27. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. (animal/ or nonhuman/) not human/
29. 27 not 28
30. 5 and 11 and 29

Web of Science

#12 #11 AND #10
Indexes=CPCI-S Timespan=All years

#11 TOPIC: ((random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*))
Indexes=CPCI-S Timespan=All years

#10 #9 AND #4
Indexes=CPCI-S Timespan=All years

#9 #8 OR #7 OR #6 OR #5
Indexes=CPCI-S Timespan=All years

#8 TOPIC: (("rs 43285"))
Indexes=CPCI-S Timespan=All years

#7 TOPIC: (latixa)
Indexes=CPCI-S Timespan=All years

#6 TOPIC: (ranexa)
Indexes=CPCI-S Timespan=All years

#5 TOPIC: (ranolazine)
Indexes=CPCI-S Timespan=All years

#4 #3 OR #2 OR #1
Indexes=CPCI-S Timespan=All years

#3 TOPIC: ("angor pectoris")
Indexes=CPCI-S Timespan=All years

#2 TOPIC: (stenocardia*)
Indexes=CPCI-S Timespan=All years

#1 TOPIC: (angina*)
Indexes=CPCI-S Timespan=All years

Other sources

Since several of the searched databases did not have an "advanced search" tool, we used only the term "ranolazine" as the search strategy.

WHAT'S NEW

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Date	Event	Description
24 January 2019	Amended	Minor correction in Characteristics of included studies table - intervention for CARISA 2004 corrected to 'Ranolazine 1000 mg group'.

CONTRIBUTIONS OF AUTHORS

- CS: selection of studies, data extraction, risk of bias assessment, data analysis, writing the final review.
- JB: selection of studies, data extraction, risk of bias assessment, data analysis, writing the final review.
- JM: selection of studies, data extraction.
- LV: selection of studies, data extraction, risk of bias assessment, writing the final review.
- DR: data extraction.
- CL: data analysis.

DECLARATIONS OF INTEREST

None of the authors received any payment or service from a third party (government, private foundation, other) for any aspect of the submitted work. Relationships that were present during the 36 months prior to publication are reported. None of the authors have any patent, either planned, pending or issued, broadly relevant to the work or have any other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, this review.

SOURCES OF SUPPORT

Internal sources

- None, Other.

  No sources of support supplied

External sources

- None, Other.

  No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the minimal duration of follow-up of outcome measures for inclusion in analysis to one week from six weeks in the protocol, and performed an additional sensitivity analysis restricting to results of outcomes measured with a follow-up of at least six weeks. We included an additional outcome regarding exercise electrocardiogram (time to 1-mm ST-segment depression, measured at peak) as a secondary effectiveness outcome. We added type of stable angina diagnosis (macrovascular versus microvascular) as an additional variable for subgroup analysis. We calculated some missing data using formulae from the Cochrane Handbook, but did not perform imputation of any missing data. Thus, we did not perform sensitivity analysis regarding the method of dealing with missing data.

INDEX TERMS

Medical Subject Headings (MeSH)

Angina, Stable [*drug therapy] [mortality] [prevention & control]; Cardiovascular Agents [administration & dosage] [adverse effects] [*therapeutic use]; Cause of Death; Incidence; Myocardial Infarction [epidemiology]; Quality of Life; Randomized Controlled Trials as Topic; Ranolazine [administration & dosage] [adverse effects] [*therapeutic use]

MeSH check words

Humans; Middle Aged

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