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Effects of adding ivabradine to usual care in patients with angina pectoris: a systematic review of randomised clinical trials with meta-analysis and Trial Sequential Analysis

Mathias Maagaard ,[1] Emil Eik Nielsen ,[2] Naqash Javaid Sethi,[1] Liang Ning,[3,4] Si-hong Yang,[4] Christian Gluud,[5] Janus Christian Jakobsen[1,6]

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For numbered affiliations see end of article.

Correspondence to
Dr Mathias Maagaard; mathias.maagaard@ctu.dk

ABSTRACT

Objective To determine the impact of ivabradine on outcomes important to patients with angina pectoris caused by coronary artery disease.

Methods We conducted a systematic review. We included randomised clinical trials comparing ivabradine versus placebo or no intervention for patients with angina pectoris due to coronary artery disease published prior to June 2020. We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, Cochrane methodology, Trial Sequential Analysis, Grading of Recommendations Assessment, Development, and Evaluation, and our eight-step procedure. Primary outcomes were all-cause mortality, serious adverse events and quality of life.

Results We included 47 randomised clinical trials enrolling 35 797 participants. All trials and outcomes were at high risk of bias. Ivabradine compared with control did not have effects when assessing all-cause mortality (risk ratio [RR] 1.04; 95% CI 0.96 to 1.13), quality of life (standardised mean differences −0.05; 95% CI −0.11 to 0.01), cardiovascular mortality (RR 1.07; 95% CI 0.97 to 1.18) and myocardial infarction (RR 1.03; 95% CI 0.91 to 1.16). Ivabradine seemed to increase the risk of serious adverse events after removal of outliers (RR 1.07; 95% CI 1.03 to 1.11) as well as the following adverse events classified as serious: bradycardia, prolonged QT interval, photopsia, atrial fibrillation and hypertension. Ivabradine also increased the risk of non-serious adverse events (RR 1.13; 95% CI 1.11 to 1.16). Ivabradine might have a statistically significant effect when assessing angina frequency (mean difference (MD) 2.06; 95% CI 0.82 to 3.30) and stability (MD 1.48; 95% CI 0.07 to 2.89), but the effect sizes seemed minimal and possibly without any relevance to patients, and we identified several methodological limitations, questioning the validity of these results.

Conclusion Our findings do not support that ivabradine offers significant benefits on patient important outcomes, but rather seems to increase the risk of serious adverse events such as atrial fibrillation and non-serious adverse events. Based on current evidence, guidelines need reassessment and the use of ivabradine for angina pectoris should be reconsidered.

Key questions

What is already known about this subject?

► Ivabradine is recommended in European Society of Cardiology guidelines on chronic coronary syndromes. In the 'ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction' (BEAUTIFUL) trial, ivabradine seemed to reduce the incidence of coronary artery disease outcomes in patients with a heart rate of 70 beats/min or higher. In the 'ivabradine in stable coronary artery disease without clinical heart failure' (SIGNIFY) trial, ivabradine did not improve clinical outcomes. Previous studies have shown a beneficial effect of ivabradine on angina pectoris symptoms. To our knowledge, no previous systematic review has assessed the effects of ivabradine compared with placebo or no intervention, searching all relevant databases, and considering both risks of systematic errors and random errors.

What does this study add?

► Our findings do not support that ivabradine offers significant benefits on patient important outcomes, but rather seems to increase the risk of serious adverse events such as atrial fibrillation and non-serious adverse events.

How might this impact on clinical practice?

► Based on current evidence, guidelines need reassessment and the use of ivabradine for angina pectoris should be reconsidered.

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INTRODUCTION

Cardiovascular diseases accounts for 30% of all deaths worldwide.[1] Ischaemic heart disease is associated with an increased risk of mortality and morbidity with an estimated global prevalence over 110 million in 2015.[2]

Coronary artery disease is characterised by recurrent episodes of a mismatch between myocardial oxygen supply and demand, resulting in myocardial ischaemia and chest discomfort known as angina pectoris.[3]

Ivabradine is a selective sinus node inhibitor, exerting its effect by decreasing heart rate, thereby decreasing myocardial oxygen demand and increasing myocardial oxygen supply.[4] Theoretically, ivabradine might be an effective intervention for angina pectoris caused by coronary artery disease.[4–7] To our knowledge, no previous systematic review has assessed the effects of ivabradine compared with usual care (ie, placebo or no intervention) for angina pectoris, searching all relevant databases, and considering both risk of systematic errors and random errors.[8–12]

METHODS

Our methodology is described in detail in our protocol published prior to conducting the literature search.[13 14]

In short, we carried out this systematic review following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12] We included all trials comparing ivabradine versus placebo or no intervention (ie, usual care plus ivabradine vs usual care alone) for participants with angina pectoris. We searched various databases for randomised clinical trials published prior to June 2020, see 'online supplemental 1' for a detailed list of databases. Out search strategy is shown in 'online supplemental 2'. We included randomised clinical trials regardless of trial design, setting, publication status, year, language and reporting of outcomes. Two authors (MM and EEN) independently screened for randomised clinical trials in all non-Chinese databases. The Chinese databases were independently screened by two other authors (LN and SY). Three authors independently extracted data and assessed the risks of bias in the non-Chinese trials (MM all included trials, EEN and NS half each) and two other authors independently extracted data and assessed the risk of bias in the Chinese trials (LN and SY). We attempted to contact trial authors if data were unclear or missing. Disagreements were resolved through discussion or by consulting another author (JCJ).[14]

We assessed three primary outcomes: all-cause mortality, serious adverse events and quality of life. We also assessed three secondary outcomes and eight exploratory outcomes.[14] For all outcomes, we used the trial results reported at maximal follow-up. We chose to assess quality of life using standardised mean differences (SMD), due to the trials reporting on quality of life using different scales. As a 'rule of thumb', an effect below 0.4 is a small effect, 0.4 to 0.7 is a moderate effect and above 0.7 is a large effect.[15]

We predefined several subgroup analyses for the primary outcomes, and we conducted sensitivity analyses when assessing both primary and secondary outcomes (see the Results section for sensitivity analyses and see 'online supplemental material' for subgroup analyses).[14]

Assessment of statistical and clinical significance

We performed all meta-analyses using Review Manager V.5.3.[16] To control for random errors, we used Trial Sequential Analysis and adjusted the threshold for statistical significance as suggested by Jakobsen and colleagues.[8 10 17] We used three primary outcomes and therefore considered a p value of 0.025 as the threshold for statistical significance.[10] When analysing secondary and exploratory outcomes, we considered a p value of 0.05 as the threshold for statistical significance.[10] We reported the Trial Sequential Analysis-adjusted confidence intervals and if the cumulative Z-curves crossed any of the Trial Sequential Analysis boundaries (benefit, harm or futility). In order to control the risk of random error when assessing the individual serious and non-serious adverse events, we further adjusted our thresholds for statistical significance according to the large number of comparisons (see 'Serious adverse events' and 'Non-serious adverse events'). Hence, we post-hoc considered a p value of 0.001 as threshold for statistical significance when analysing individual serious and non-serious adverse events.

We used a 'best-worst case' and a 'worst-best case' analysis to assess the impact of missing data.[15] We used GRADE to assess the certainty of evidence.[18 19]

RESULTS

Our literature search identified 4452 records from databases. We also identified 11 unpublished trials on the trial platform of the company, Servier, that developed ivabradine.[20] After removing duplicates, 3058 records remained. We excluded 2846 records based on title or abstract. We excluded another 165 records based on full text, see 'online supplemental 3'. We included 42 randomised clinical trials from databases. We included five unpublished, randomised clinical trials from Servier.[21–25] Therefore, we included a total of 47 randomised clinical trials randomising 35 797 participants.[21–67] Twenty trials compared ivabradine with placebo[21–25 28–32 34 36 39 40 44 46 50 54 55 58] and 27 trials compared ivabradine with 'no intervention'. Of the 16 trials comparing ivabradine with 'no intervention', 14 trials used guideline-based therapy in both trial groups[26 41 42 45 47 56 60 62–68] and 13 trials used various cointerventions other than guideline-based therapy in both trial groups (12 trials used specific beta-blockers[27 35 38 43 48 51–53 57 59 61 69] and one used a calcium-channel blocker).[33] For baseline characteristics, see table 1. For all primary and secondary outcomes, we chose to analyse data using fixed-effect meta-analysis due to two trials accounting for more than 97% of weight (see paragraph below).[10 32 54]

The two largest trials, the SIGNIFY trial and the BEAUTIFUL trial, contributed with more than 97% of weight

Table 1 Baseline characteristics of the included trials

Trial ID	Year	Condition(s)	Max follow-up	Number randomised	Mean age	%-Female	% on beta-blockers	% on calcium channel blockers
Adel	2016	CAD	30 days	45	57.3	35.6	35.6	NR
Ageev	2010	CAD	6 mo	50	63.8	8.0	NR	NR
ASSOCIATE	2009	CAD	4 mo	889	59.9	15.6	NR	NR
Barilla	2016	CAD +HF	6 mo	58	55.4	32.8	NR	NR
BEAUTIFUL	2008	CAD +HF	35 mo	10917	65.2	17.1	86.9	NR
Borer	2003	CAD	2 wks	360	NR	NR	NR	NR
Cay	2011	CAD	30 days	120	NR	NR	NR	NR
Chen	2019	CAD	NR	100	64.2	44.0	NR	NR
CL2-16257-060	2009	AMI	24 hours	75	59.4	21.8	34.9	NR
CL2-16257-096	2014	CAD	3 wks	14	62.9	14.3	100.0	NR
CL3-16257-064	2010	CAD	6 wks	427	59.4	31.2	NR	23.1
CL3-16257-067	2015	CAD	36 mo	97	63.5	42.2	73.2	NR
CL3-16257-068	2012	CAD	6 wks	1277	60.9	12.5	NR	100.0
Di	2020	CAD	3 mo	90	69.3	37.8	NR	NR
Dillinger	2015	CAD	3 wks	12	63.3	8.3	100.0	16.7
Gao	2017	CSA	3 mo	80	NR	NR	NR	NR
Gloekler	2014	CAD	6 mo	46	64.0	10.9	58.7	17.4
Hao	2016	CAD	3 mo	32	NR	NR	NR	NR
He	2019	CAD +HF	6 mo	68	64.8	47.1	NR	NR
Hohneck	2018	CAD	6 mo	26	61.8	26.9	73.1	15.4
Hu	2018	CAD +HF	NR	169	NR	NR	NR	NR
Huang	2018	CAD	3 mo	88	NR	NR	NR	NR
Huang (WF)	2017	CAD	3 mo	85	NR	NR	NR	NR
Kadro	2015	CAD	6 mo	50	NR	NR	NR	NR
Lamendola	2011	CAD	1 mo	20	50.0	75.0	NR	NR
Naji	2014	CAD	1 mo	78	NR	NR	60.3	NR
Nguyen	2018	CAD +HF	NR	19	57.5	15.8	94.7	NR
RIVENDEL	2016	CAD	2 mo	70	69.5	22.9	58.6	10.0
RIVIERA	2012	CAD	30 days	27	61.5	7.4	0.0	0.0
Sallam	2016	CAD +HF	3 mo	100	63.5	30.0	NR	NR
Sayganov	2010	CAD +HF	NR	40	66.5	40.0	NR	NR
Shavarov	2015	AMI	14 days	98	68.3	36.7	100.0	NR
SIGNIFY	2014	CAD	27.8 mo	19102	65.0	27.6	83.1	26.8
Steg	2013	CAD	4 mo	124	59.4	22.5	32.3	NR

Continued

Table 1 Continued

Trial ID	Year	Condition(s)	Max follow-up	Number randomised	Mean age	%-Female	% on beta-blockers	% on calcium channel blockers
Taccheri	2014	CAD	12 mo	90	NR	NR	NR	NR
Tagliamonte	2019	CAD	1 mo	41	66.0	39.0	NR	NR
Tatarchenko	2008	CAD +HF	6 mo	59	57.3	NR	NR	NR
Vasyuk	2009	CAD	6 mo	22	56.2	NR	NR	NR
Vatinian	2015	CAD	6 mo	52	NR	NR	NR	NR
Villano	2012	CAD	1 mo	31	NR	NR	NR	NR
Wang	2019	CAD +HF	6 mo	88	65.0	44.3	NR	NR
Wang	2018	CAD	3 mo	80	NR	NR	NR	NR
Zhang	2018	CAD	4 mo	62	NR	NR	NR	NR
Zhang	2019	CAD +HF	2 mo	60	64.2	57.0	NR	NR
Zhang	2020	CAD +HF	6 mo	85	64.4	36.5	NR	NR
Zhao	2017	CAD	3 mo	120	NR	NR	NR	NR
Zhou	2019	CAD	4 mo	90	61.4	42.2	NR	NR

AMI, acute myocardial infarction; ASSOCIATE, Efficay of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial (reference 46); CAD, coronary artery disease; HF, heart failure; mo, months; NR, not reported; RIVENDEL, Heart rate reduction by ivabradine for improvement of endothelial function in patients with coronary artery disease: the RIVENDEL study (reference 41); RIVIERA, Anti-inflammatory effects of ivabradine in patients with acute coronary syndrome: a pilot study (reference 31); wks, weeks.

in all primary and secondary outcome meta-analyses. We identified several methodological limitations regarding these two trials. First, both trials were not prospectively registered before randomisation began.[32 54] The BEAUTIFUL trial randomised the first participant in January 2005 and was first registered with ClinicalTrials.gov in September 2005 and sent their rationale article for peer review in November 2005.[54 70 71] The SIGNIFY trial randomised the first participant in October 2009 and was first registered with Clinicaltrials.gov in May 2015 and first sent their rationale article for peer review in April 2013.[32 72 73] Therefore, it was not documented that the methodology, including outcomes and participating centres, was predefined before randomisation began. This is especially problematic when assessing composite outcomes consisting of individual components with very different degrees of severity (ie, in the SIGNIFY trial, the primary composite outcome was death from cardiovascular causes or non-fatal myocardial infarction. In the BEAUTIFUL trial, the primary composite outcome was cardiovascular death, admission to hospital for acute myocardial infarction, or admission to hospital for new onset or worsening heat failure). There is a high risk of selective outcome reporting bias, if the composite outcomes are not clearly predefined before randomisation begins.[15] Furthermore, during the course of the BEAUTIFUL trial, the investigators incorporated a subgroup analysis on participants with a baseline heart rate at or above 70 beats/min (one of the inclusion criteria in the SIGNIFY trial).[32 54] However, there is no documentation for this subgroup analysis being prespecified prior to initiation of the BEAUTIFUL trial.[54 70 71] Second, in the SIGNIFY trial assessing quality of life and angina pectoris, 13 871 (72.6%) of the 19 102 participants included in the main study were not included in the analysis.[32 74] It was briefly described in the publication that the reasons were either that some countries did not have a translation of the quality of life scale or it was due to 'lack of consent'.[74] Third, for serious and non-serious adverse events, there were considerable discrepancies between the data reported in the publication of the SIGNIFY trial as compared with the raw data reported on ClinicalTrials.gov, see 'online supplemental 11'.[32 73] Fourth, both the SIGNIFY trial and the BEAUTIFUL trial, as well as all other included trials, were at high risk of bias. Therefore, there is a risk that our results overestimate beneficial effects and underestimate harmful effects.[75–80]

We have contacted the trial authors and the company that produced ivabradine, Servier, but we have not received additional information regarding some of these issues.

See 'online supplemental 4' for a detailed description of the bias risk assessment.

All-cause mortality

Fifteen trials randomising 33 427 participants reported on all-cause mortality. Meta-analysis showed no evidence of a difference between ivabradine and control (RR 1.04; 95% CI 0.96 to 1.13; p=0.35; moderate certainty of evidence). Visual inspection of the forest plot and I^2-statistics (I^2=0%) indicated no heterogeneity. Trial Sequential Analysis showed that we had enough information to reject that ivabradine versus control reduced the risk of all-cause mortality by 15% or more (RR 1.03; 95% CI 0.88 to 1.20; p=0.46; I^2=0%; D^2=0%). This outcome result was assessed at high risk of bias. Incomplete outcome data alone did not seem to have the potential to influence the results. See 'Summary of findings-table' and 'online supplemental 5'.

Serious adverse events

Eighteen trials randomising 33 514 participants reported on serious adverse events. Meta-analysis showed no evidence of a difference between ivabradine and control (RR 1.01; 95% CI 0.98 to 1.04; p=0.56; moderate certainty of evidence). Visual inspection of the forest plot and I^2-statistics (I^2=55%) indicated substantial heterogeneity which could be resolved by removing the BEAUTIFUL trial and the trial by Taccheri *et al* from the analysis (RR 1.06; 95% CI 1.02 to 1.10; p=0.001; I^2=0%). Trial Sequential Analysis, after removing outliers, showed that we had enough information to reject that ivabradine decreased the risk of serious adverse events by 15% or more (RR 1.06; 95% CI 1.00 to 1.13; p=0.0014; I^2=0%; D^2=0%). This outcome result was assessed at high risk of bias. Incomplete outcome data alone did not seem to have the potential to influence the results. See 'Summary of findings-table' and 'online supplemental 6'.

Individual serious adverse events

The trials reported on 1749 different serious adverse events, where the SIGNIFY and the BEAUTIFUL trials reported on the majority of those. To limit problems with multiplicity and type 1 errors caused by the unexpected large number of individual serious adverse events, we post-hoc adjusted the threshold for statistical significance to 0.001 when assessing individual serious adverse events.[10]

Ivabradine increased the risk of the following adverse events classified as serious by the trialists: bradycardia (event classified as 'bradycardia' (RR 4.53; 95% CI 2.99 to 6.87; p<0.0001; two trials); event classified as 'heart rate decreased' (RR 8.22; 95% CI 3.85 to 17.54; p<0.0001; two trials); event classified as 'sinus bradycardia' (RR 6.86; 95% CI 3.11 to 15.15; p<0.0001; one trial)); prolonged QT interval (RR 3.21; 95% CI 1.90 to 5.40; p<0.0001; two trials); photopsia (RR 9.34; 95% CI 2.84 to 30.71; p=0.0002; one trial); atrial fibrillation (RR 1.26; 95% CI 1.10 to 1.44; p=0.0008; three trials); and hypertension (RR 1.42; 95% CI 1.15 to 1.75; p=0.001; one trial).

Ivabradine did not seem to decrease the risk of any individual serious adverse events at the threshold of statistical significance of 0.001.

Quality of life

Four trials randomising 4377 participants reported on quality of life analysed as a continuous outcome. One trial used EuroQoL score (0–100 points),[50] one trial used the Kansas City Cardiomyopathy Questionnaire,[59] one trial used Minnesota Living with Heart Failure Questionnaire[60] and the SIGNIFY trial reported on quality of life using the Seattle Angina Questionnaire (which does not result in a combined end-score) and a generic visual analogue scale (0–100 points).[32] Meta-analysis showed evidence of a beneficial effect of ivabradine (SMD −0.08; 95% CI −0.14 to −0.02; p=0.009; low certainty of evidence). Visual inspection of the forest plot and I^2-statistics (I^2=97%) indicated substantial heterogeneity, which could be resolved by removing the trials by Sallam *et al*[59] and Tatarchenko *et al*[60] (SMD −0.05; 95% CI −0.11 to 0.01; p=0.09; I^2=17%). It was not possible to conduct Trial Sequential Analysis using SMD.[81] This outcome result was assessed as at high risk of bias. We assessed the risk of incomplete outcome data bias to be substantial since 70% of the participants in the SIGNIFY trial were excluded from the analysis of quality of life, see first section of 'Results'. See 'Summary of findings-table' and 'online supplemental 7'.

Cardiovascular mortality

Eight trials randomising 32 193 participants reported on cardiovascular mortality. Meta-analysis showed no evidence of a difference between ivabradine and control (RR 1.06; 95% CI 0.96 to 1.17; p=0.22; moderate certainty of evidence). Visual inspection of the forest plot and I^2-statistics (I^2=14%) indicated low heterogeneity. Trial Sequential Analysis showed that we had enough information to reject that ivabradine versus control reduced the risk of cardiovascular mortality by 15% or more (RR 1.066; 95% CI 0.95 to 1.18; p=0.22; I^2=14%; D^2=53%). This outcome result was assessed at high risk of bias. Incomplete outcome data alone did not seem to have the potential to influence the results. See 'Summary of findings-table' and 'online supplemental 8'.

Myocardial infarction

Five trials randomising 31 810 participants reported on myocardial infarction. Meta-analysis showed no evidence of a difference between ivabradine and control (RR 1.02; 95% CI 0.90 to 1.16; p=0.71; moderate certainty of evidence). Visual inspection of the forest plot and I^2-statistics (I^2=0%) indicated no heterogeneity. Trial Sequential Analysis showed that we had enough information to reject that ivabradine versus control reduced the risk of myocardial infarction by 15% or more (RR 1.02; 95% CI 0.85 to 1.23; p=0.71; I^2=0%; D^2=0%). This outcome result was assessed at high risk of bias. Incomplete outcome data alone did not seem to have the potential to influence the results. See 'Summary of findings-table' and 'online supplemental 9'.

Non-serious adverse events

Twenty-four trials randomising 34 181 participants reported on non-serious adverse events. Meta-analysis showed evidence of a harmful effect of ivabradine (RR 1.13; 95% CI 1.11 to 1.16; p<0.00001; moderate certainty of evidence). Visual inspection of the forest plot and I^2-statistics (I^2=8%) indicated low heterogeneity. Trial Sequential Analysis showed that we had enough information to detect that ivabradine versus control increased the risk of non-serious adverse events by 13% or more (RR 1.13; 95% CI 1.11 to 1.16; p<0.0001; I^2=8%; D^2=73%). This outcome result was assessed at high risk of bias. Incomplete outcome data alone did not seem to have the potential to influence the results. See 'Summary of findings-table' and 'online supplemental 10'.

Individual non-serious adverse events

The trials reported 54 different non-serious adverse events; the SIGNIFY and the BEAUTIFUL trials reported on the majority of those. To limit problems with multiplicity and type 1 errors caused by the unexpected large number of individual serious adverse events, we post-hoc adjusted the threshold for statistical significance to 0.001 when assessing individual non-serious adverse events.[10]

Ivabradine seemed to increase the risk of bradycardia (event classified as 'bradycardia' (RR 4.54; 95% CI 3.78 to 5.46; p<0.0001; nine trials); event classified as 'heart rate decreased' (RR 8.05; 95% CI 6.76 to 9.59; p<0.0001; two trials); event classified as 'sinus bradycardia' (RR 9.61; 5.65 to 16.33; p<0.0001; one trial)); phosphenes (RR 6.58; 95% CI 5.34 to 8.10; p<0.0001; seven trials); vision blurred (RR 3.39; 95% CI 2.32 to 4.93; p<0.0001; five trials); QT interval prolonged (RR 2.65; 95% CI 1.85 to 3.81; p<0.0001; one trial); hypertension (RR 1.19; 95% CI 1.09 to 1.30; p=0.0001; four trials); and dizziness (RR 1.32; 95% CI 1.13 to 1.54; p=0.0003; four trials).

Ivabradine seemed to decrease the risk of sinus tachycardia (RR 0.25; 95% CI 0.18 to 0.35; p=0.0001; one trial).

Exploratory outcomes

Ivabradine seemed to increase the score of angina frequency (0–100 points, higher score represents a positive outcome; MD 2.06; 95% CI 0.82 to 3.30; p=0.001; I^2=0%; 3 trials; 4297 participants) and angina stability, both on the Seattle Angina Questionnaire score (0–100 points, higher score represents a positive outcome; MD 1.48; 95% CI 0.07 to 2.89; p=0.04; I^2=0%; 2 trials; 4217 participants). However, the effect sizes were minimal (SMD 0.1 for angina frequency and SMD 0.06 for angina stability) and both were more than five times below our predefined minimal important difference (SMD 0.5). Furthermore, the SIGNIFY trial accounted for more than 97% of the total weight in both analyses and used questionable methodology (see the first section of the Results section). We assessed the risk of incomplete outcome data bias to be substantial since 70% of the participants in the SIGNIFY trial were excluded from the analysis of

angina, see the first section of the Results section and 'online supplemental 11'.

Four trials assessed exercise tolerance tests. In the ASSOCIATE trial, ivabradine versus control did not reach the minimal important difference in any of the outcome measures in exercise tolerance testing (time to angina onset, time to limiting angina, time to 1 mm ST depression and total exercise duration).[46] In the trial by Borer *et al*,[28] ivabradine treatment reached the minimal important difference for time to angina onset and time to 1 mm ST depression in the 10 mg ivabradine twice daily group, which is a higher dose than recommended.[28 82] The participants had discontinued any other anti-ischaemic drug two to 7 days prior to randomisation and the primary outcome was measured after 14 days of treatment.[28] In two of the unpublished trials, there seemed to be no difference between ivabradine and control in regard to exercise tolerance testing.[22 23]

The results of the remaining exploratory outcomes are reported in the online supplemental material, see 'online supplemental 12' and the Discussion section.

Subgroup analyses

We post-hoc decided to conduct a subgroup analysis of trials randomising participants with coronary artery disease alone compared to trials randomising participants with both coronary artery disease *and* heart failure with reduced ejection fraction. We identified 11 trials including participants with both coronary artery disease and heart failure with an ejection fraction of 40% or less[49 54 56–59 61 63 64 67 68] and one trial including participants with an ejection fraction of 45% or more.[60] We judged trials as being 'coronary artery disease only' trials, if heart failure was not an inclusion criterion, if heart failure was an exclusion criterion, or if there was no mention of heart failure. For serious adverse events, test for subgroup differences showed evidence of a difference (p<0.00001). When analysed separately, we found evidence of a harmful effect of ivabradine in trials randomising participants with coronary artery disease only (RR 1.06; 95% CI 1.02 to 1.10; p=0.001; I^2=27%; 11 trials) and evidence of a beneficial effect of ivabradine in trials randomising participants with both coronary artery disease and heart failure (RR 0.91; 95% CI 0.86 to 0.96; p=0.0009; I^2=0%; two trials). For quality of life, test for subgroup differences showed evidence of a difference (p<0.00001). When analysed separately, we found no evidence of a difference between ivabradine and control in trials randomising participants with coronary artery disease only (SMD −0.05; 95% CI −0.11 to 0.01; p=0.27; I^2=17%; two trials) and evidence of a beneficial effect of ivabradine in trials randomising participants with both coronary artery disease and heart failure (SMD −1.19; 95% CI −1.58 to −0.81; p<0.00001; I^2=99%; two trials).

For serious adverse events, test for subgroup differences showed evidence of a difference (p<0.0001) when comparing trials administering ivabradine at or above median daily dose with trials adminstering ivabradine below median daily dose. When analysed separately, we found evidence of a harmful effect of ivabradine in trials administering ivabradine at or above median daily dose (RR 1.06; 95% CI 1.02 to 1.10; p=0.001; I^2=0%; four trials) and evidence of a beneficial effect of ivabradine in trials administering ivabradine below median daily dose (RR 0.92; 95% CI 0.87 to 0.97; p=0.002; I^2=26%; four trials)

For the remaining subgroup analyses, test for subgroup differences showed no evidence of a difference between ivabradine and control. The results of all subgroup analyses can be found in 'online supplemental 5–7'.

DISCUSSION

We included a total of 47 randomised clinical trials enrolling 35 797 participants. All trials and outcomes were at high risk of bias.[21–67]

Meta-analyses and Trial Sequential Analysis showed that there was no evidence of a difference between ivabradine and placebo or no intervention when assessing all-cause mortality, quality of life, cardiovascular mortality and myocardial infarction.

Meta-analysis showed that ivabradine potentially increased the risk of serious adverse events after removal of outliers from the analyses as well as the following adverse events classified as serious: bradycardia, prolonged QT interval, photopsia, atrial fibrillation and hypertension. Meta-analysis and Trial Sequential Analysis showed that ivabradine seemed to increase the risk of non-serious adverse events.

Ivabradine seemed to increase the score of angina frequency and angina stability on the Seattle Angina Questionnaire. However, we identified several methodological limitations regarding these outcomes (see the Results section). Furthermore, the observed effect sizes seemed minimal as they were more than five times lower than our predefined minimal important difference.[14]

See 'Summary of findings-table' in 'online supplemental 13'.

In a post-hoc subgroup analyses, ivabradine seemed to increase the risk of serious adverse events in trials randomising participants with only coronary artery disease and to decrease the risk of serious adverse events in trials randomising participants with both coronary artery disease and heart failure. Post-hoc analyses need to be interpreted with caution.

Our systematic review has several strengths. Our methodology was predefined and was described in detail in our published protocol.[13 14] We identified 47 trials, whereas the largest of the previous (non-systematic) reviews only included eights trials.[83–86] To control the risk of random error, we used Trial Sequential Analysis[8] and adjusted our thresholds for statistical significance.[10] To control the risk of systematic error, we assessed the risk of bias of all included trials.[18 19] To assess if the thresholds for statistical and clinical significance were crossed, we used our eight-step procedure.[10] We included all randomised clinical trials regardless of publication type, status, language and outcomes. We attempted to

contact trialists if there were incomplete outcome data or additional information was required.

Our review also has several limitations. All trials were at high risk of bias, including a substantial risk of for-profit bias.[80] Fourteen of the trials were sponsored by the company that developed ivabradine, including the two largest trials, the SIGNIFY and the BEAUTIFUL trials, that randomised 30 019 participants (91%).[21–25 28 30 32 36 44 46 54 58 59] Five of the included trials were unpublished and non-peer reviewed trials of the company that produced ivabradine.[21–25] Sponsorship of drug trials by manufacturing companies leads to more favourable efficacy results than trials sponsored by other sources.[80] The BEAUTIFUL and the SIGNIFY trials both used composite outcomes that did not seem to be predefined prior to randomising participants, see the Results section.[32 54 70–73] The results of 11 trials were reported only as abstracts, which made the assessment of the methodology and results problematic.[27 29 39 40 42 45 47 48 50 55] Therefore, there is a risk that our present results overestimate the beneficial effects and underestimate the harmful effects of ivabradine.[80 87–92] Last, to limit problems with multiplicity and type 1 errors caused by the unexpected large number of individual serious adverse events, we post-hoc adjusted the threshold for statistical significance to 0.001 when assessing individual serious and non-serious adverse events. This threshold was not predefined, and these results should therefore be interpreted with caution. Nevertheless, several of the harmful outcomes may indeed be increased by ivabradine.

Ivabradine was recommended as an effective second-line treatment for angina relief in the 2013 and the 2019 European Society of Cardiology guidelines on the management of chronic coronary artery syndromes.[3 82] However, we did not identify any valid evidence supporting that ivabradine should reduce angina symptoms in a clinically significant way. On the contrary, our results show that ivabradine does not seem to have beneficial effects on all-cause mortality, serious adverse events, quality of life, cardiovascular mortality and myocardial infarction. Moreover, ivabradine increases the risk of both serious and non-serious adverse events. The lack of benefit has previously been discussed as being partly due to the decrease in heart rate caused by ivabradine resulting in an increase in systolic blood pressure and left ventricular overload.[93]

CONCLUSION

Our findings do not support that ivabradine offers significant benefits on patient important outcomes, but rather seems to increase the risk of serious adverse events such as atrial fibrillation and non-serious adverse events. Based on current evidence, guidelines need reassessment and the use of ivabradine for angina pectoris should be reconsidered.

Differences between protocol and review

We conducted our literature search in parallel with another review on the effects of adding ivabradine to usual care in participants with heart failure. We originally planned to report and analyse the results including participants with angina and participants with heart failure in one review, but due to clinical and statistical heterogeneity and reviewer recommendations, we decided to report the results in two separate reviews.[14]

Author affiliations
[1]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Copenhagen, Denmark
[2]Department of Internal Medicine, Holbæk Hospital, Holbæk, Denmark
[3]Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences Guanganmen Hospital, Xicheng District, China
[4]Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China
[5]The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Copenhagen, Denmark
[6]Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

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Contributors MM: conceived the systematic review, conducted literature search, data extraction, data analysis, data interpretation and wrote the article. EEN, LN and S-hY: conducted literature search, data extraction and amended the article. NJS: conducted data extraction and amended the article. CG: helped conceive the systematic review, provided invaluable comments and amended the article. JCJ: conceived the systematic review, aided in data interpretation and amended the article.

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ORCID iDs
Mathias Maagaard http://orcid.org/0000-0002-9037-7295
Emil Eik Nielsen http://orcid.org/0000-0003-1108-9533

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Ivabradine for coronary artery disease - supplemental

Supplement 1 – List of databases

- Cochrane Central Register of Controlled Trials (CENTRAL),
- Medical Literature Analysis and Retrieval System Online (MEDLINE),
- Excerpta Medica database (EMBASE),
- Latin American and Carribean Health Sciences Literature (LILACS),
- Science Citation Index Expanded on Web of Science,
- BIOSIS,
- ClinicalTrials.gov,
- Google Scholar,
- Turning Research into Practice (TRIP) Database,
- European Medicines Agency (EMA), United States Food and Drug Administration (FDA),
- China Food and Drug Administration (CFDA),
- Medicines and Healthcare products Regulatory Agency,
- World Health Organization (WHO), and
- International Clinical Trials Registry Platform (ICTRP).
- Chinese Biomedical Literature Database (CBM),
- Wanfang, China National Knowledge Infrastructure (CNKI),
- Chinese Science Journal Database (VIP)

Supplement 2 – Search strategy

This was the search strategy that we used in MEDLINE and corrected to fit other databases as needed. We used a minimally excluding search strategy to ensure that we did not miss any relevant trials.

1. (ivabradin* or corlanor or procoralan or corlentor).af
2. (random* or blind* or placebo* or meta-analys* or systematic review).af
3. 2 and 3

Supplement 3 – PRISMA flow chart

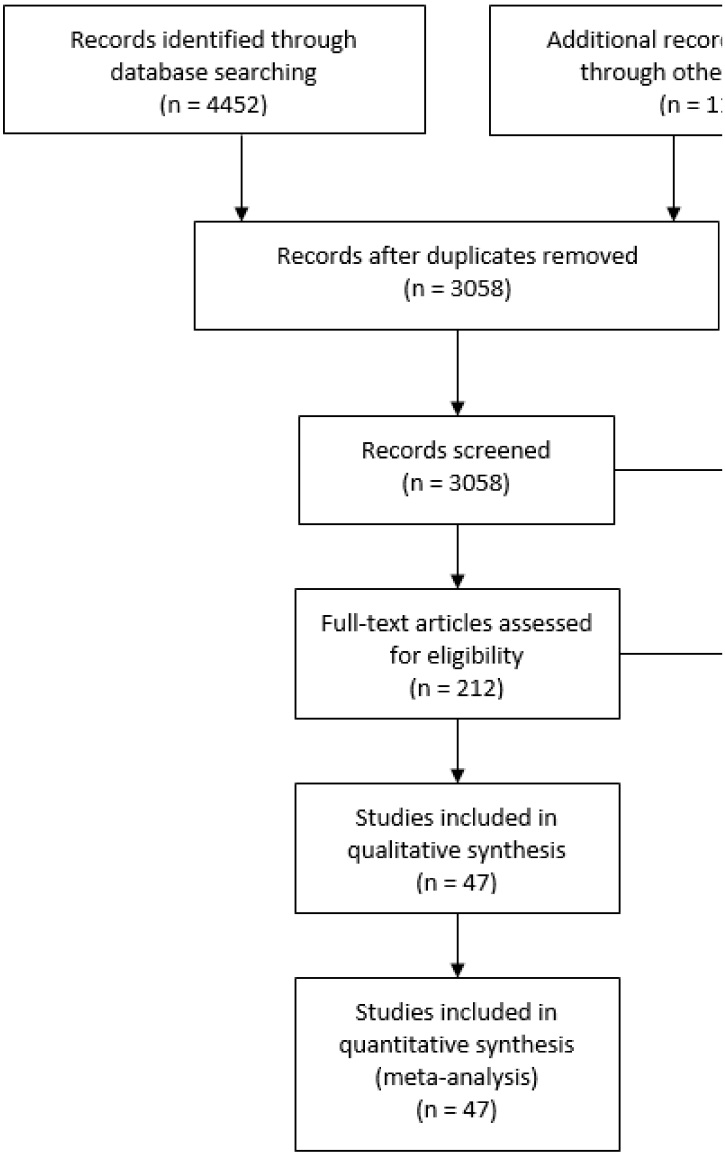

Figure 1 – PRISMA flowchart.

Supplement 4 - Risk of bias

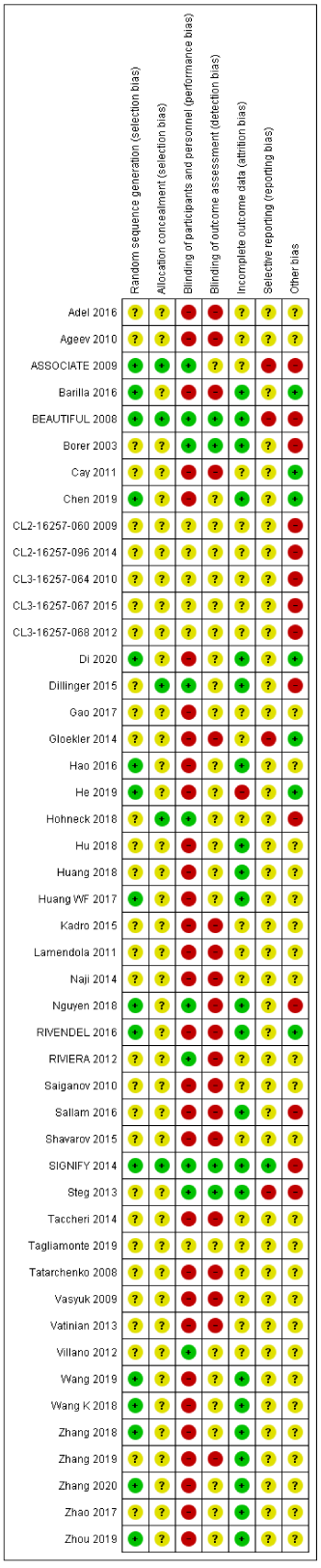

Figure 2 – Risk of bias graph. Green: low risk of bias; yellow: unclear risk of bias; red: high risk of bias.

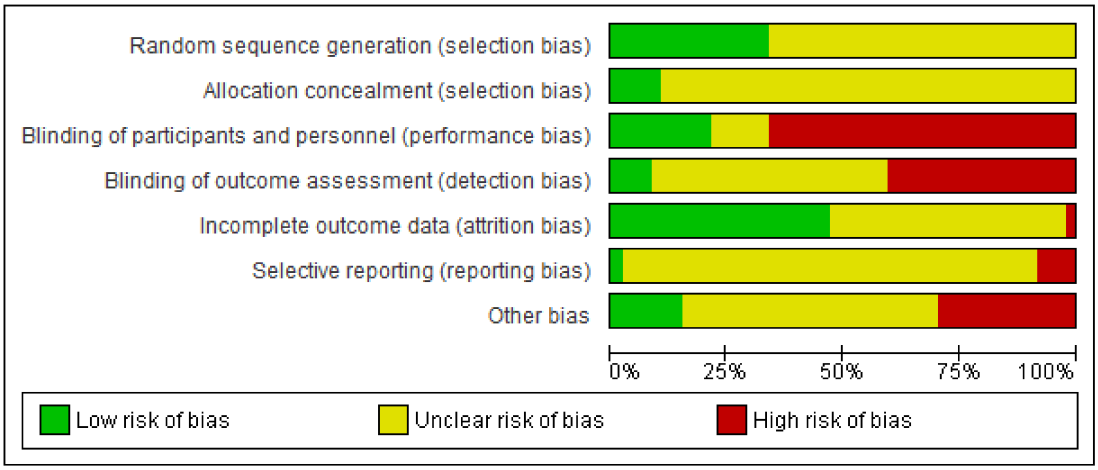

Figure 3 – Risk of bias summary. Green: low risk of bias; yellow: unclear risk of bias; red: high risk of bias.

Supplement 5 - All-cause mortality

Main analyses

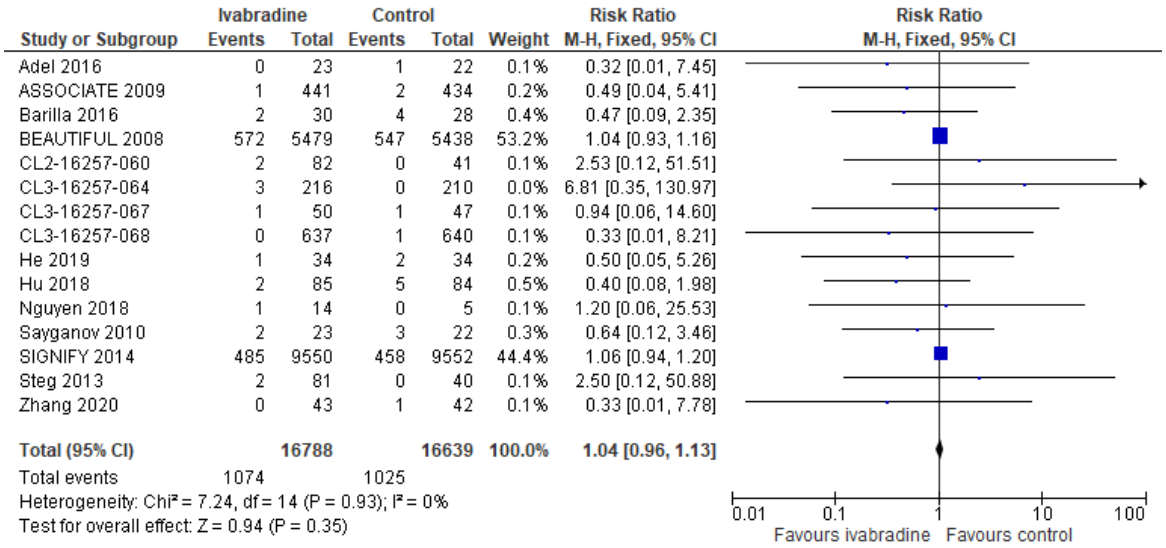

Figure 4 - Forest plot of the meta-analysis of all-cause mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

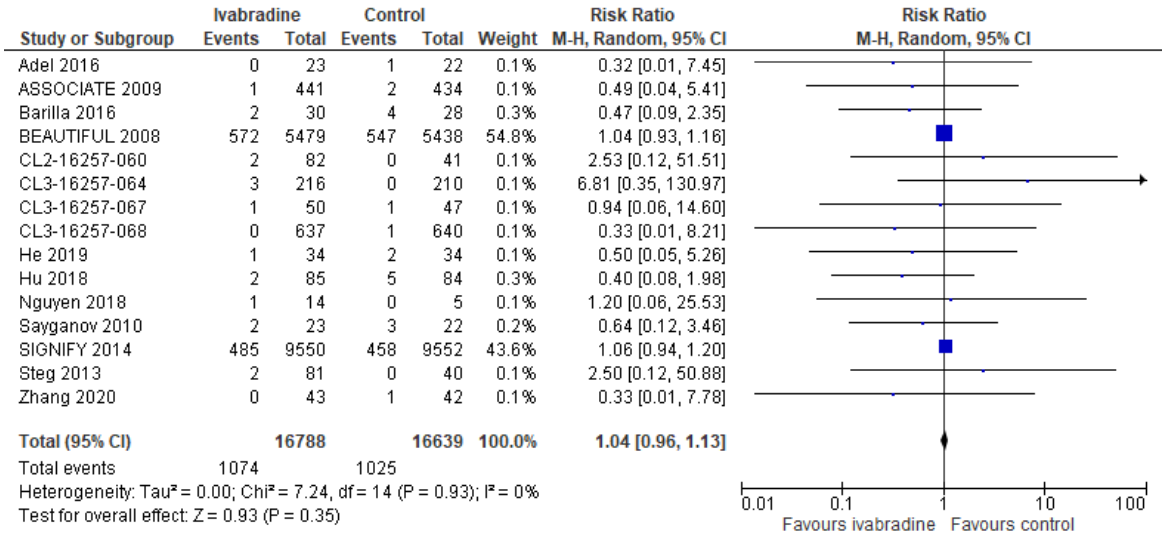

Figure 5 - Forest plot of the meta-analysis of all-cause mortality using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

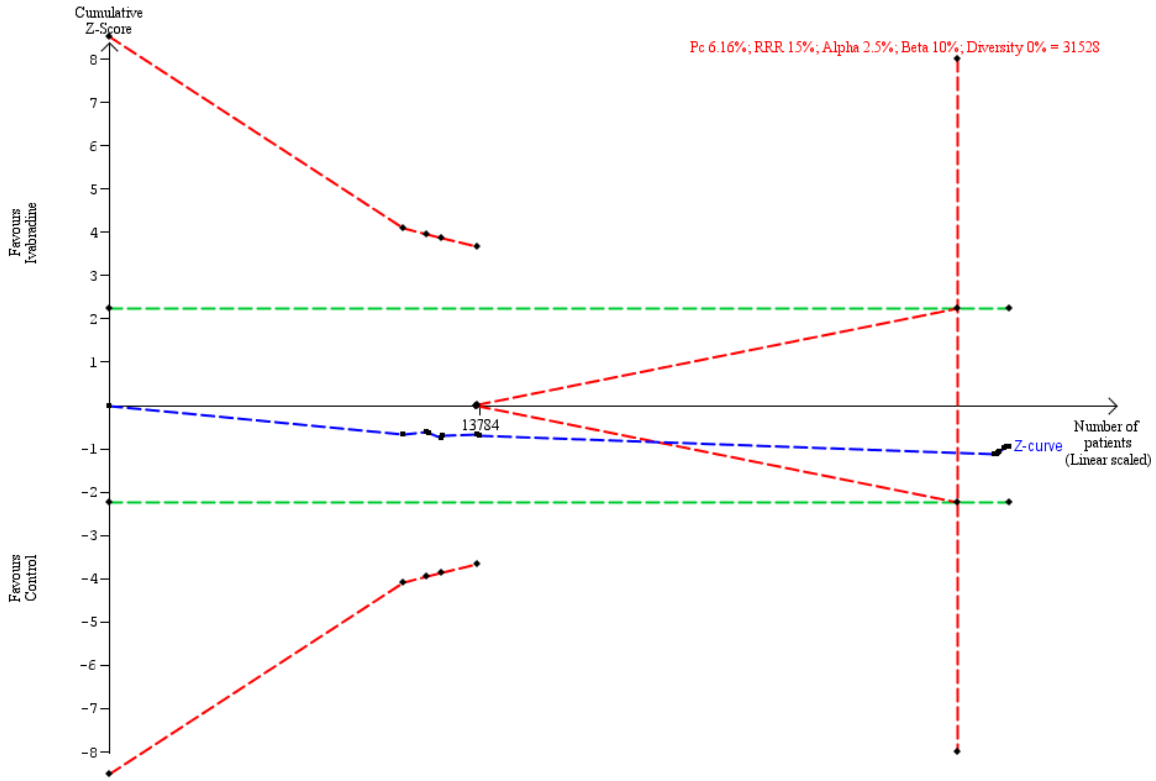

Figure 6 - Trial Sequential Analysis graph of all-cause mortality. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine. The cumulative z-curve (the blue line) breaches the boundary of futility and the required information size. Pc: prevalence in control group; RRR: relative risk ratio.

Sensitivity analyses

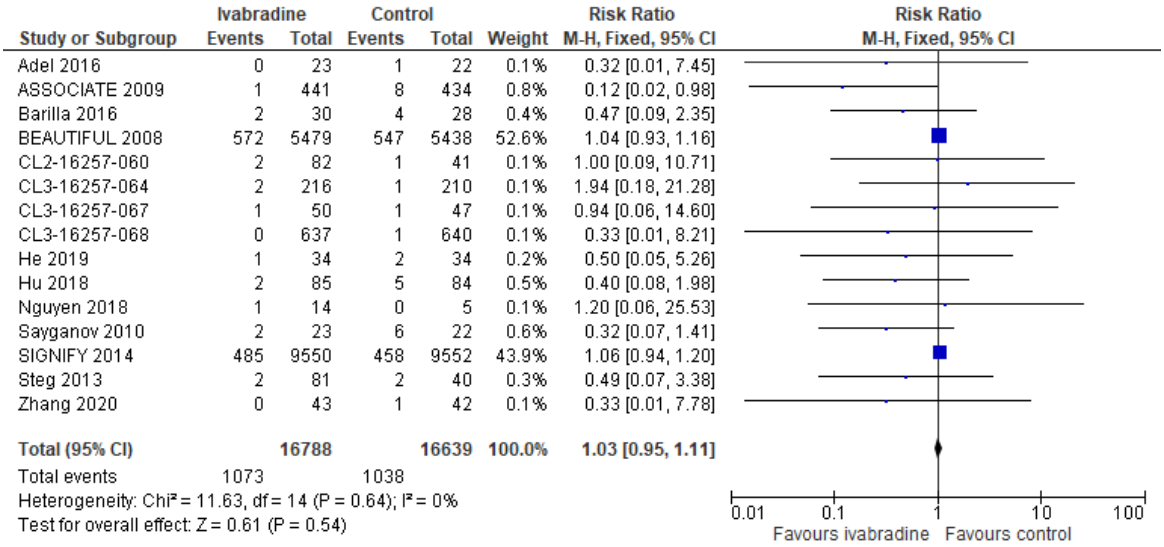

Figure 7 - Forest plot of the sensitivity analysis of all-cause mortality using best/worst-case scenario. The sensitivity analysis showed that missing data did not seem to have the potential to influence the results.

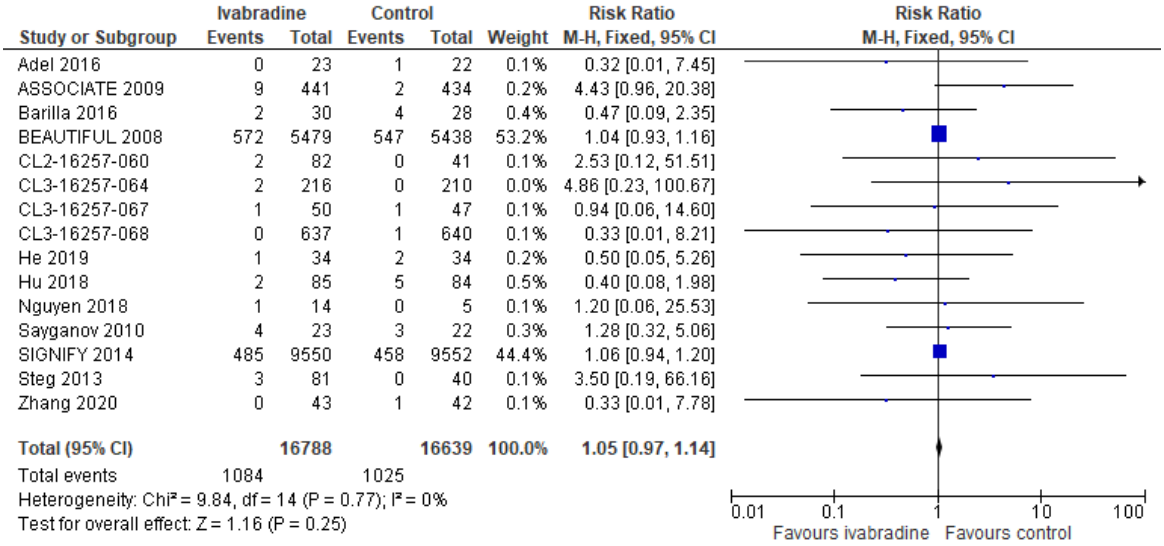

Figure 8 - Forest plot of the sensitivity analysis of all-cause mortality using worst/best-case scenario. The sensitivity analysis showed that missing data did not seem to have the potential to influence the results.

Subgroup analyses

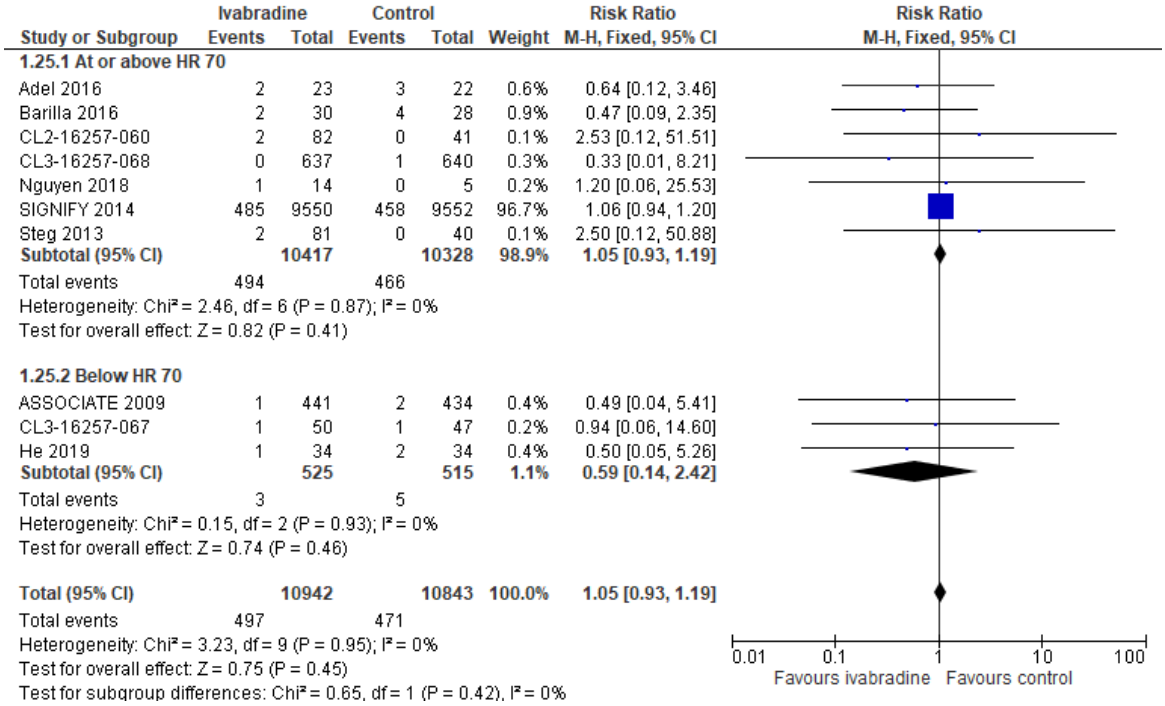

Figure 9 – Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute versus trials randomising participants with heart rate below 70 beats per minute. Test for subgroup differences showed that there was no difference between trials randomising participants with a heart rate at or above 70 beats per minute and trials randomising participants with a heart rate below 70 beats per minute.

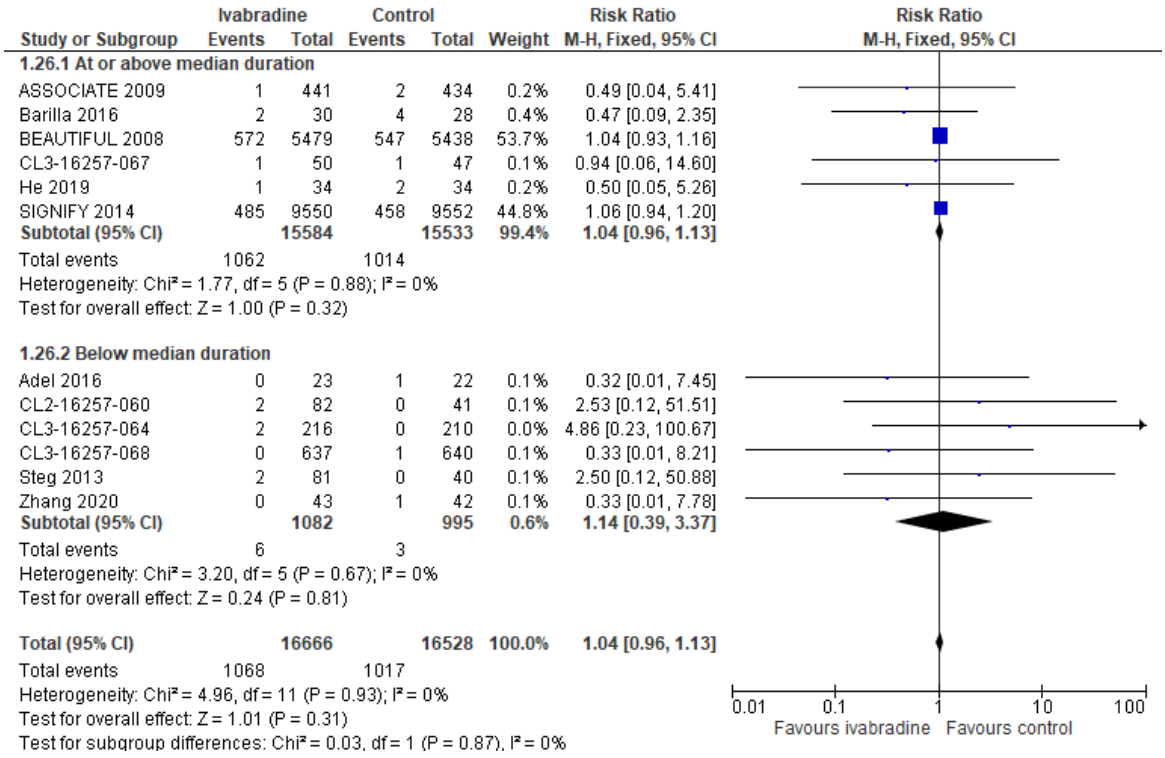

Figure 10 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration versus trials administering ivabradine below median duration. Test for subgroup differences showed that there was no difference between trials administering ivabradine at or above median duration and trials administering ivabradine below median duration.

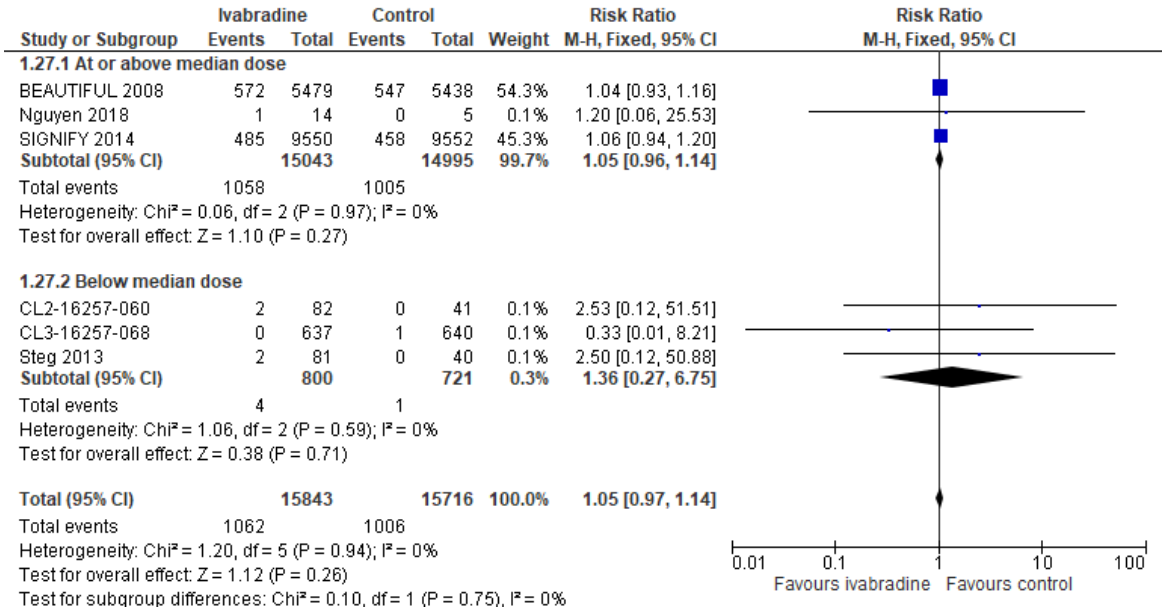

Figure 11 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose versus trials administering ivabradine below median daily dose. Test for subgroup differences showed that there was no difference between trials administering ivabradine at or above median daily dose and trials administering ivabradine below median daily dose.

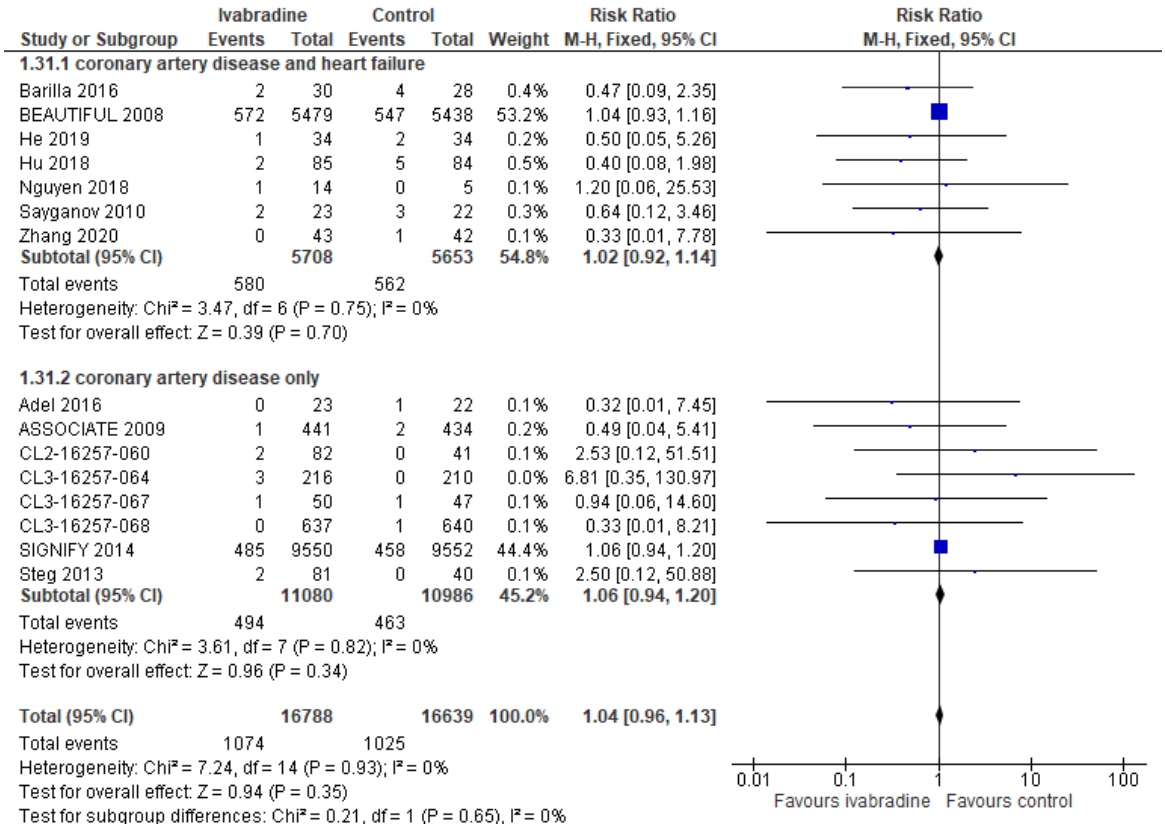

Figure 12 – Forest plot of the subgroup analyses of trials randomising participants with both coronary artery disease and heart failure versus trials randomising participants with coronary artery disease only. Test for subgroup differences showed that there was no difference between trials randomising participants with both coronary artery disease and heart failure versus trials randomising participants with coronary artery disease only.

Supplement 6 - Serious adverse events

Main analyses

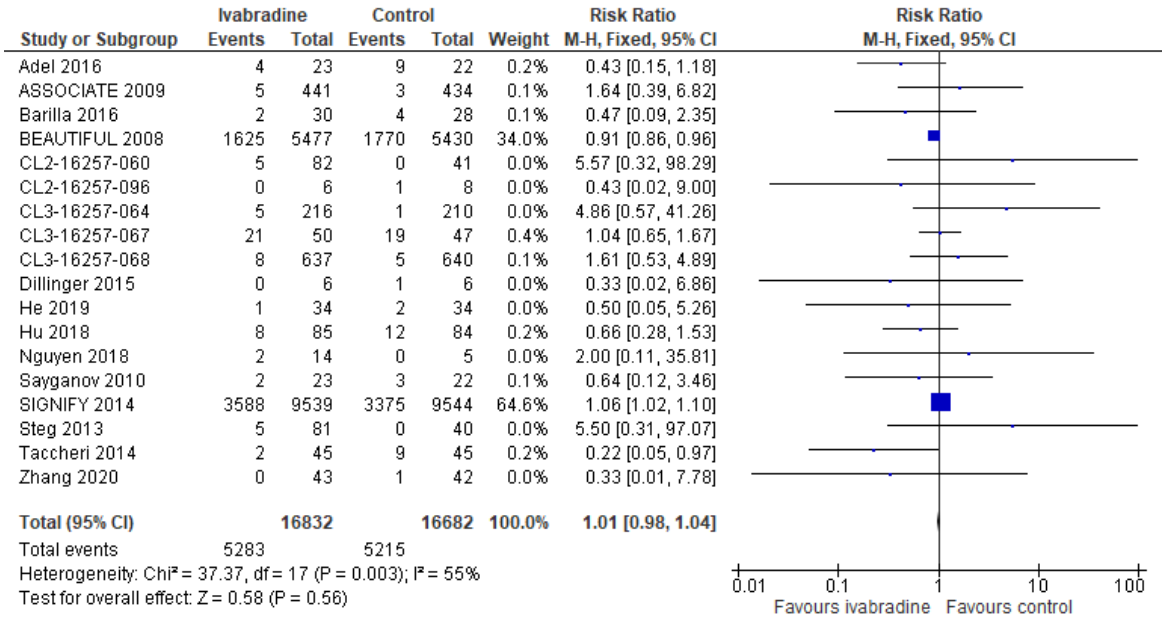

Figure 13 - Forest plot of the meta-analysis of serious adverse events using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

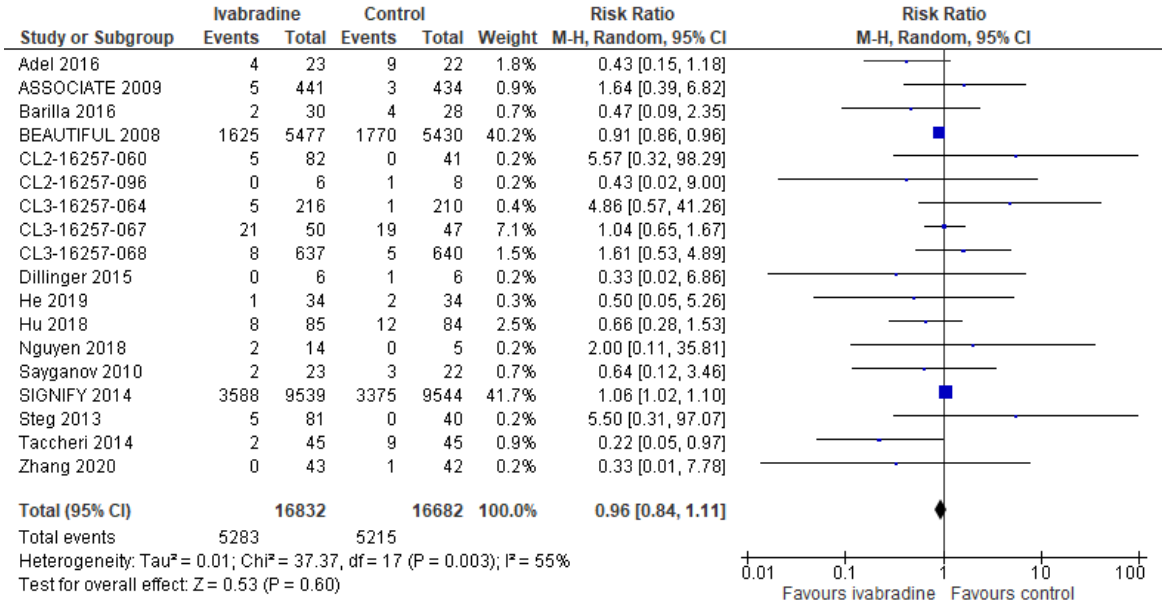

Figure 14 – Forest plot of the meta-analysis of serious adverse events using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

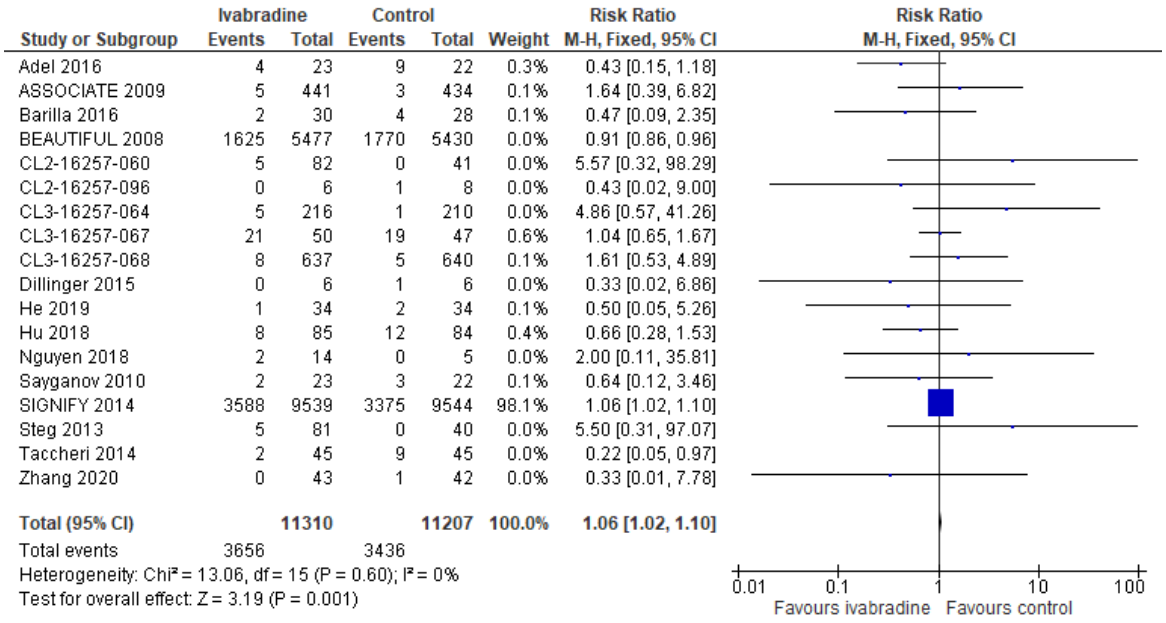

Figure 15 - Forest plot of the meta-analysis of serious adverse events using fixed-effect meta-analysis after excluding outliers. The meta-analysis showed evidence of a harmful effect of ivabradine

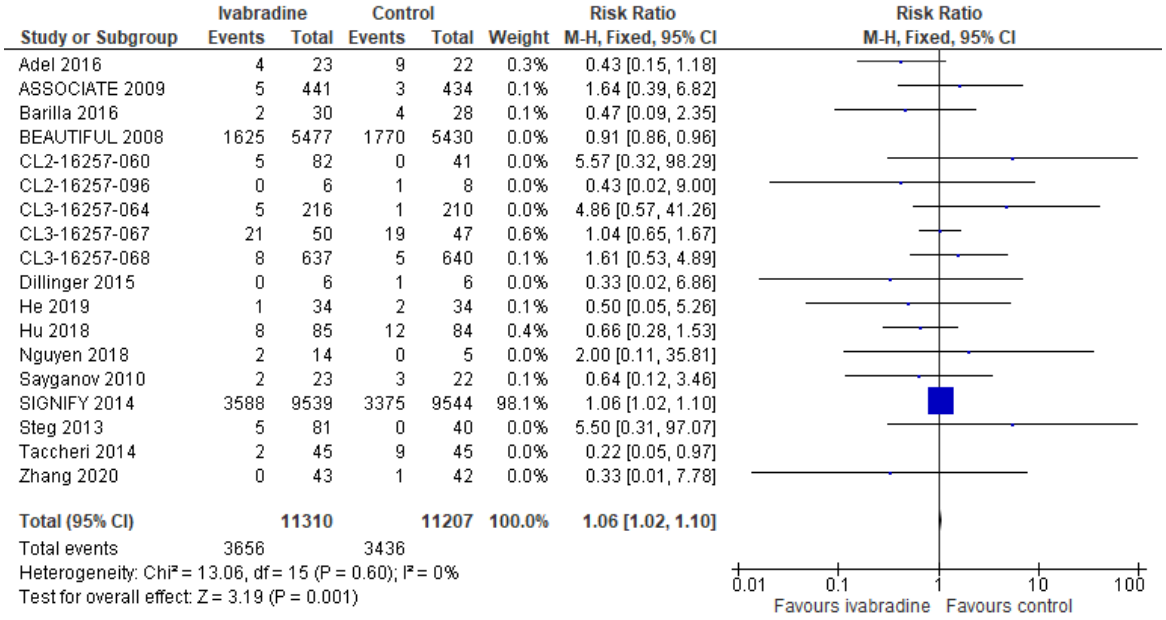

Figure 16 - Forest plot of the meta-analysis of serious adverse events using random-effects meta-analysis after excluding outliers. The meta-analysis showed evidence of a harmful effect of ivabradine

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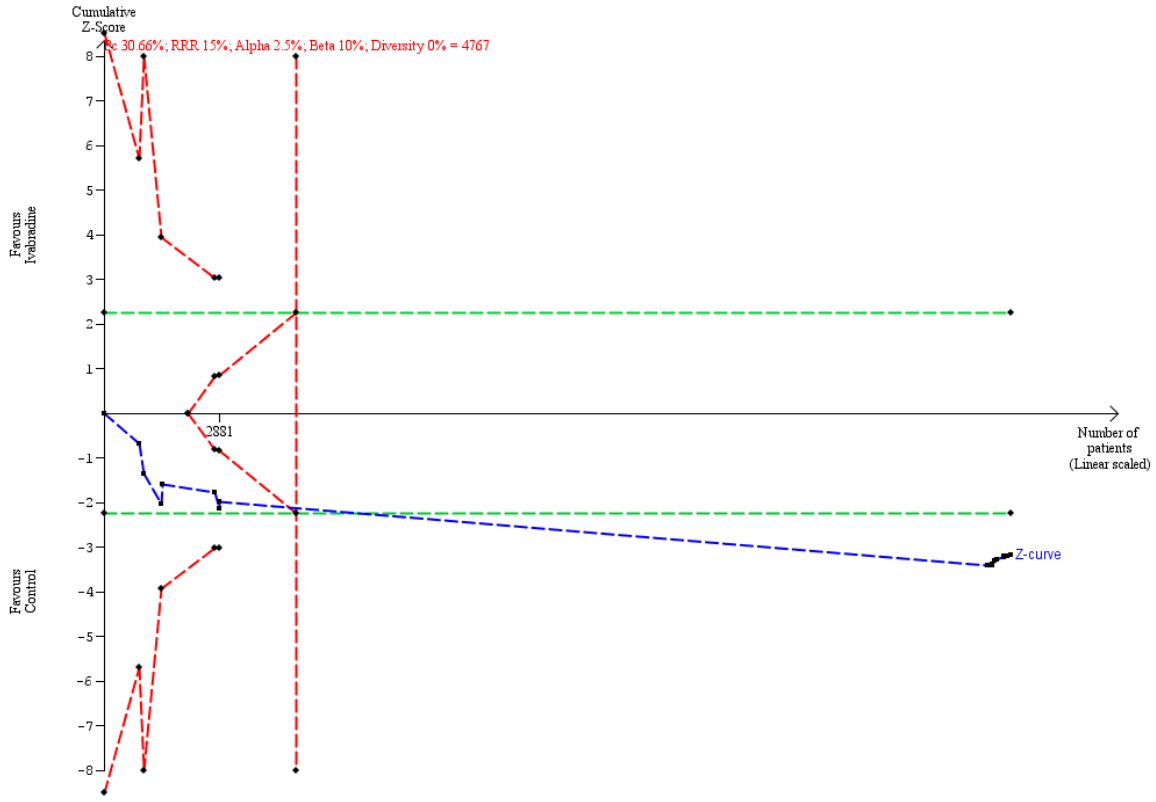


Figure 17 - Trial Sequential Analysis graph of serious adverse events after removing outliers. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine. The cumulative z-curve (the blue line) breaches the boundary of futility before breaching the conventional threshold for significance (the green line). Pc: prevalence in control group; RRR: relative risk ratio.

Sensitivity analyses

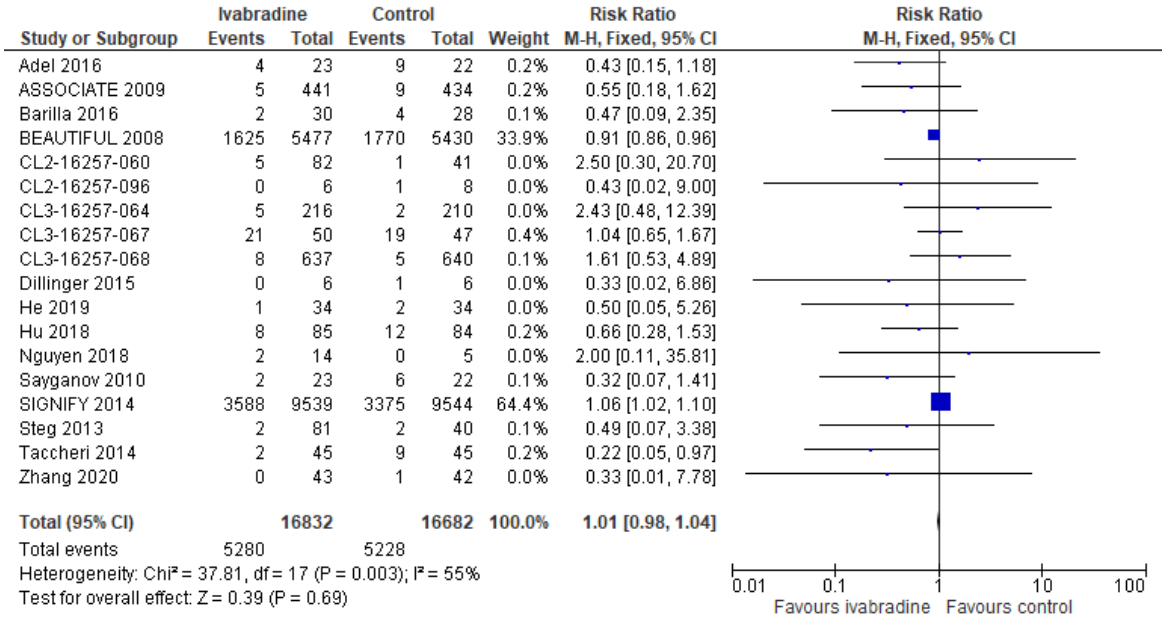


Figure 18 - Forest plot of the sensitivity analysis of serious adverse events using best/worst-case scenario. The sensitivity analysis showed that missing data did not seem to have the potential to influence the results.

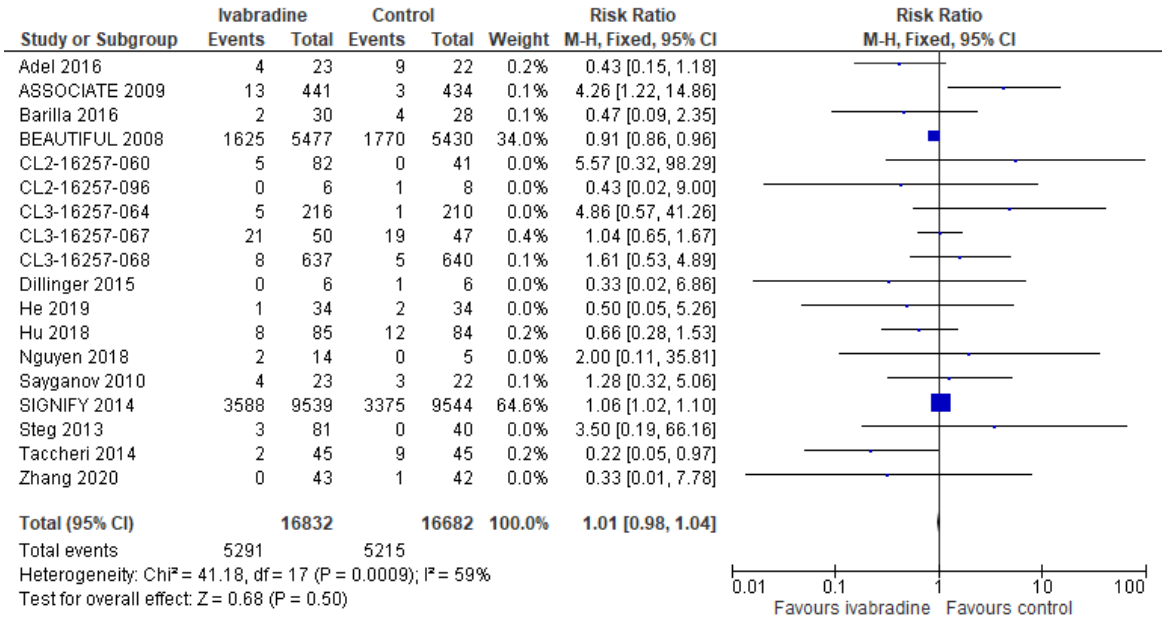


Figure 19 - Forest plot of the sensitivity analysis of serious adverse events using worst/best-case scenario. The sensitivity analysis showed that missing data did not seem to have the potential to influence the results.

Subgroup analyses

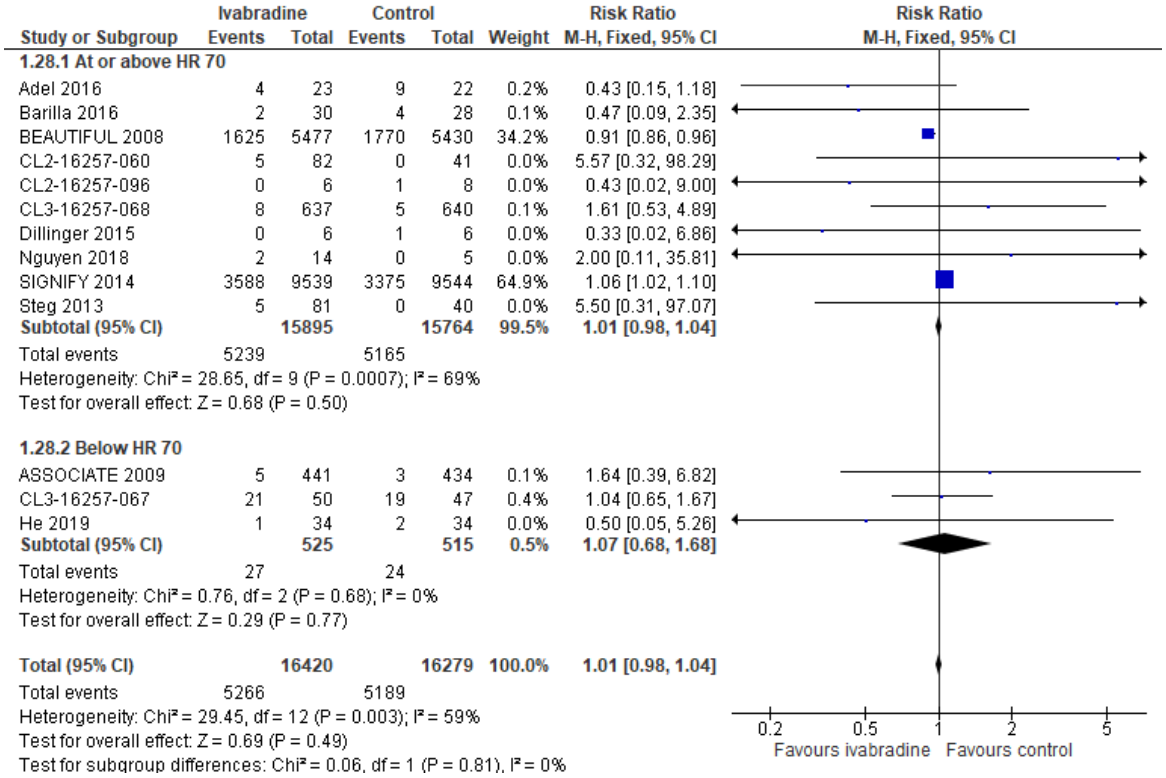


Figure 20 - Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute versus trials randomising participants with heart rate below 70 beats per minute. Test for subgroup differences showed that there was no difference between trials randomising participants with a heart rate at or above 70 beats per minute and trials randomising participants with a heart rate below 70 beats per minute.

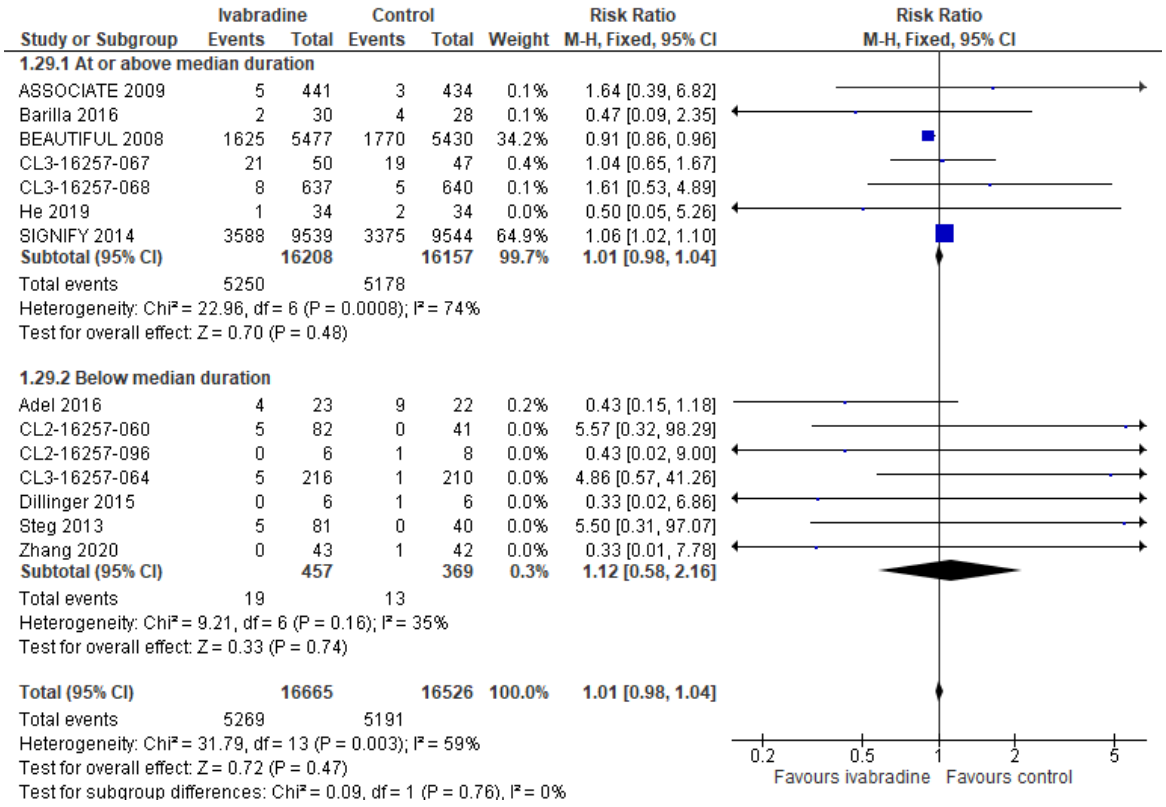


Figure 21 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration versus trials administering ivabradine below median duration. Test for subgroup differences showed that there was no difference between trials administering ivabradine at or above median duration and trials administering ivabradine below median duration.

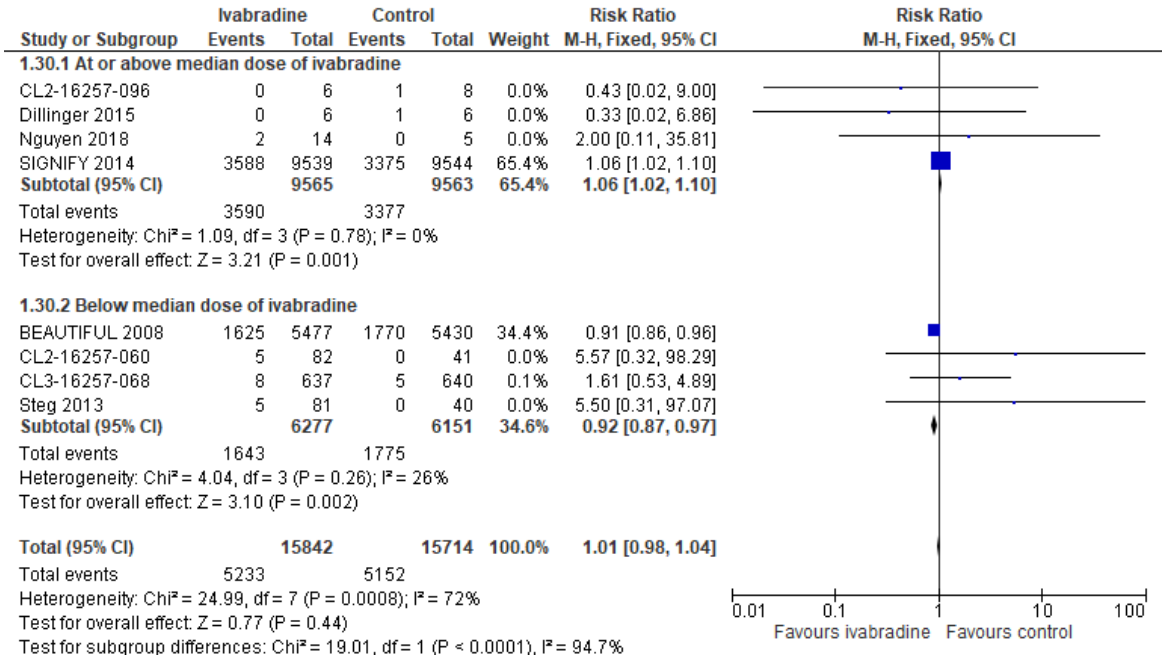


Figure 22 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose versus trials administering ivabradine below median daily dose. Test for subgroup differences showed evidence of between trials administering ivabradine at or above median daily dose versus trials administering ivabradine below median daily dose. When analysed separately, there was evidence of a harmful effect of ivabradine in trials administering ivabradine at or above median daily dose and evidence of a beneficial effect of ivabradine in trials administering ivabradine below median daily dose.

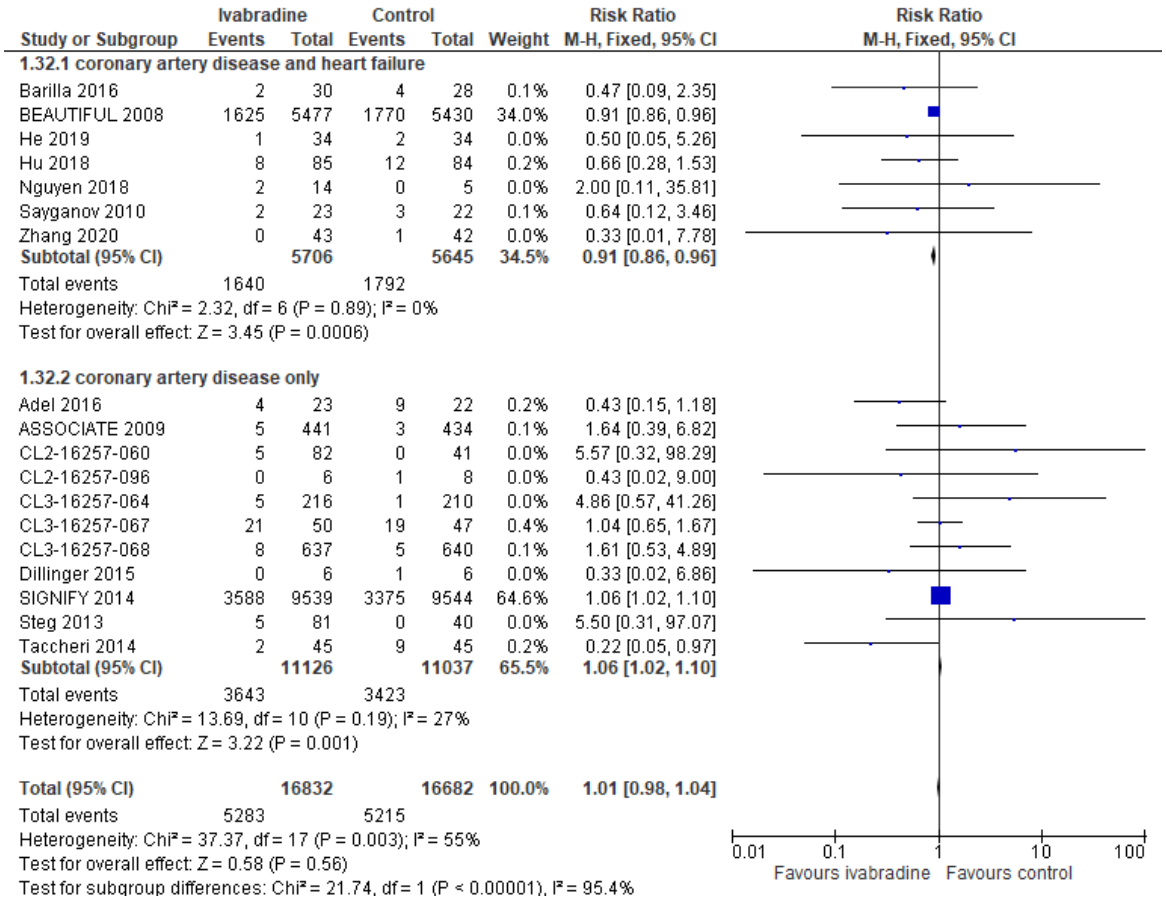


Figure 23 – Forest plot of the subgroup analyses of trials randomising participants with both coronary artery disease and heart failure versus trials randomising participants with coronary artery disease only. Test for subgroup differences showed evidence of a difference (p<0.00001) between trials randomising participants with both coronary artery disease and heart failure versus trials randomising participants with coronary artery disease only. When analysed separately, there was evidence of a beneficial effect of ivabradine in trials randomising participants with both coronary artery disease and heart failure and evidence of a harmful effect of ivabradine in trials randomising participants with coronary artery disease only.

Supplement 7 - Quality of life

Main analyses

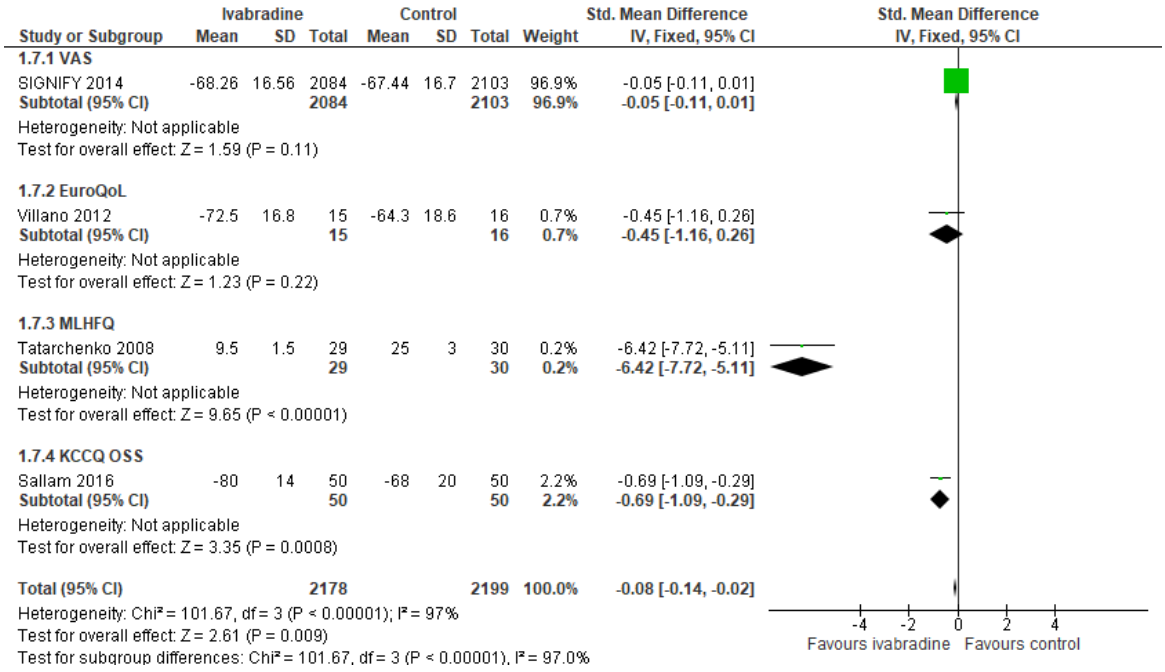


Figure 24 - Forest plot of the meta-analysis of quality of life using standardised mean differences in a fixed-effect meta-analysis. The meta-analysis showed no evidence of a beneficial effect of ivabradine.

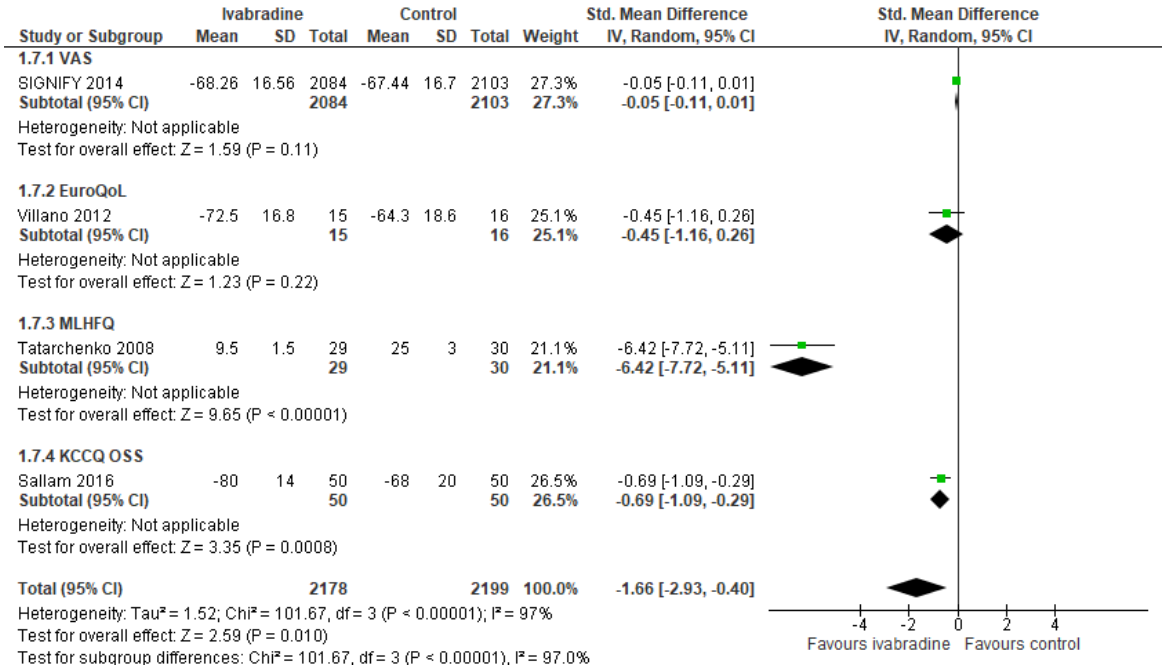


Figure 25 - Forest plot of the meta-analysis of quality of life using standardised mean differences in a random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine.

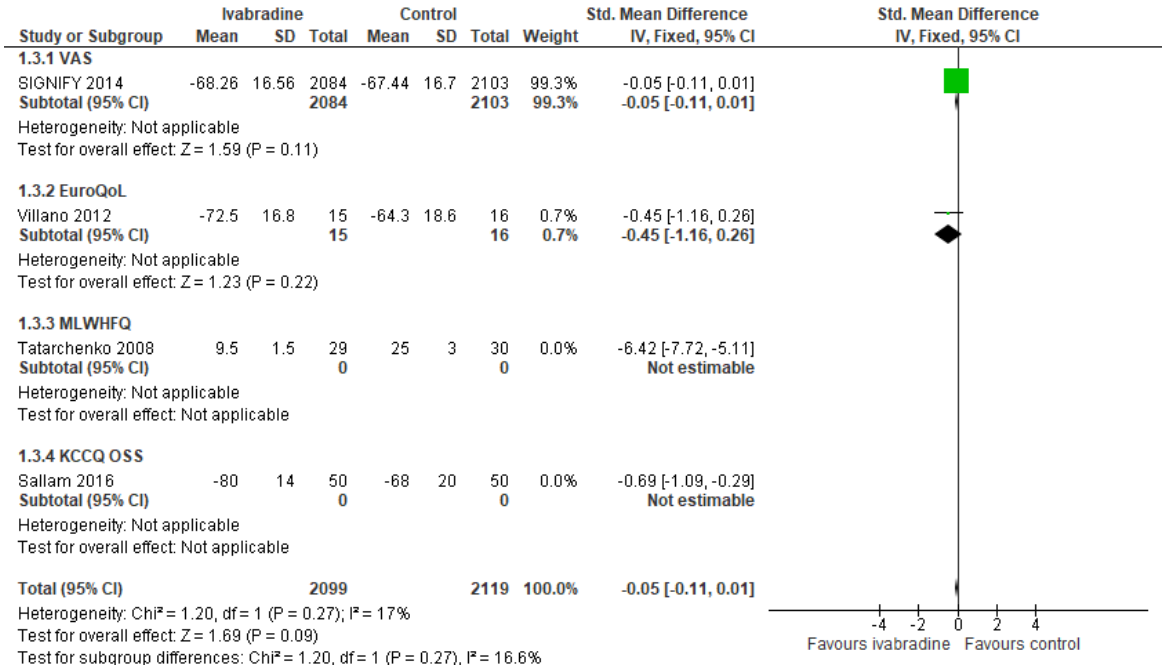


Figure 26 – Forest plot of the meta-analysis of quality of life using standardised mean differences in a fixed-effect meta-analysis after relieving heterogeneity. The meta-analysis showed no evidence of a difference between ivabradine and control.

Sensitivity analyses

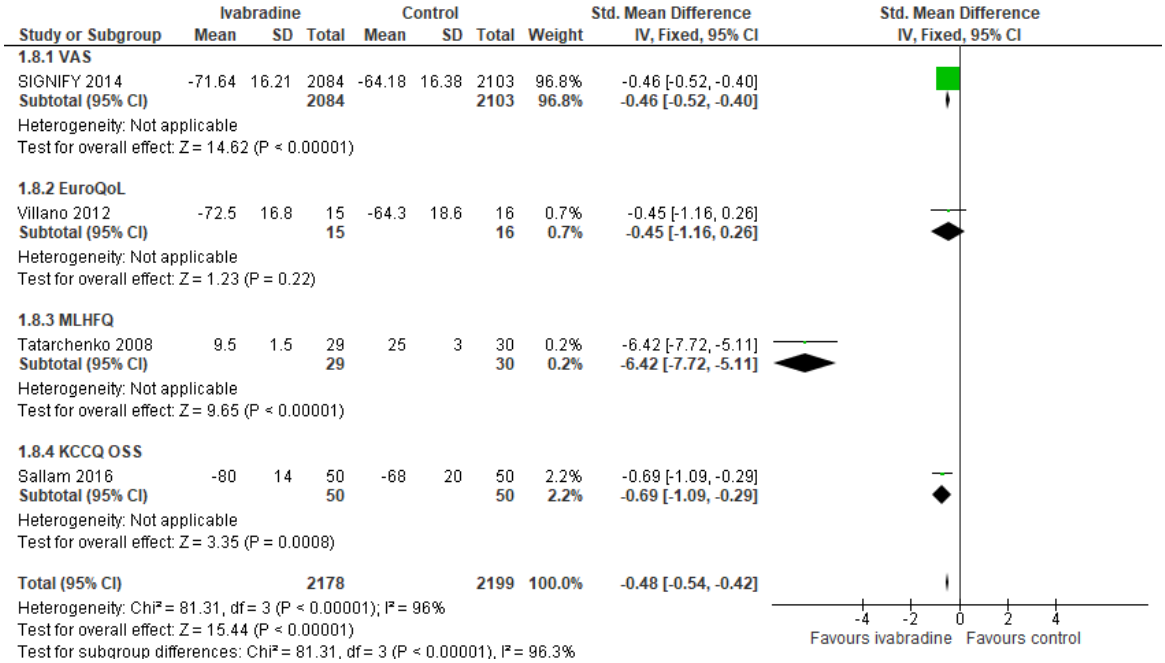


Figure 27 - Forest plot of the sensitivity analysis of quality of life using best/worst-case scenario. The sensitivity analysis showed that missing data did seem to have the potential to change the result.

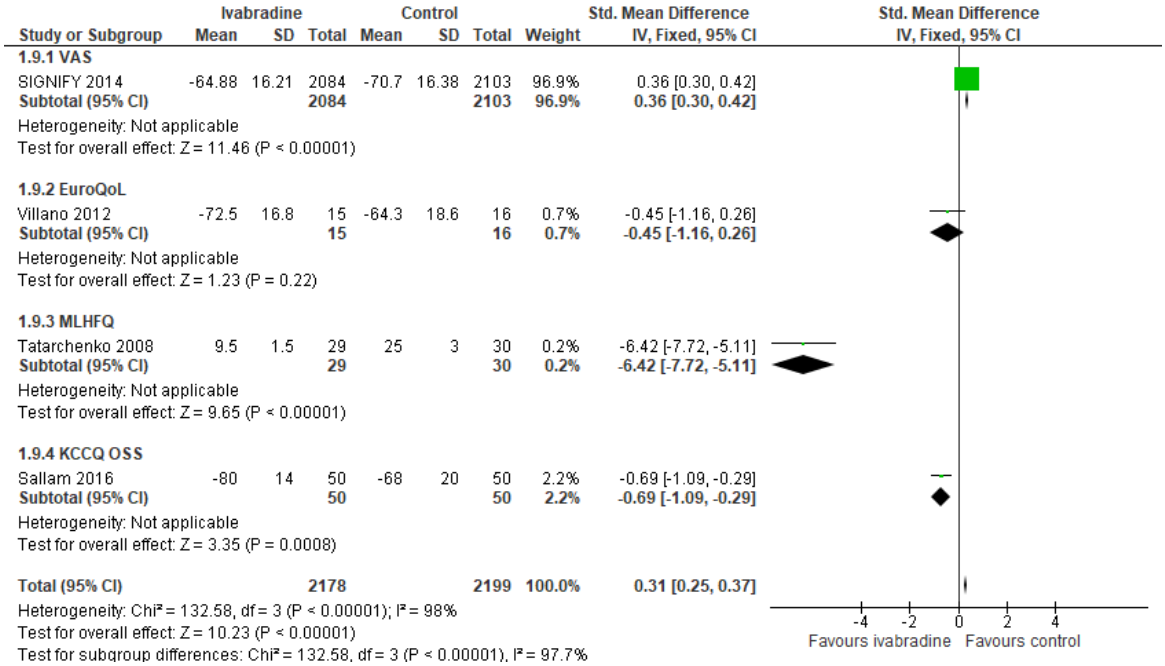


Figure 28 - Forest plot of the sensitivity analysis of quality of life using worst/best-case scenario. The sensitivity analysis showed that missing data did seem to have the potential to change the result.

Minimal important difference

In the SIGNIFY trial, the observed difference between ivabradine and control was 0·82 points at follow-up. The observed mean standard deviation (SD) of the intervention groups was SD 16·63 points. We pre-defined that we would consider the standard deviation divided by '2' (SD/2) as the minimal important difference. Therefore, the minimal important difference in the SIGNIFY trial was 8·32 points. Thus, the difference at follow-up of 0·82 points was 10·15 times lower than the minimal important difference. In the SIGNIFY trial, the analysis of quality of life change using the visual analogue scale achieved statistical significance, favouring ivabradine. However, the effect size was minimal and possibly without any relevance to patients.

In the trial by Villano et al., the difference between ivabradine and control was 8·2 points at follow-up. The combined SD of the intervention groups was 17·7 points. Thus, the minimal important difference was 8·85 points. Therefore, the difference at follow-up did not reach the minimal important difference.

Subgroup analyses

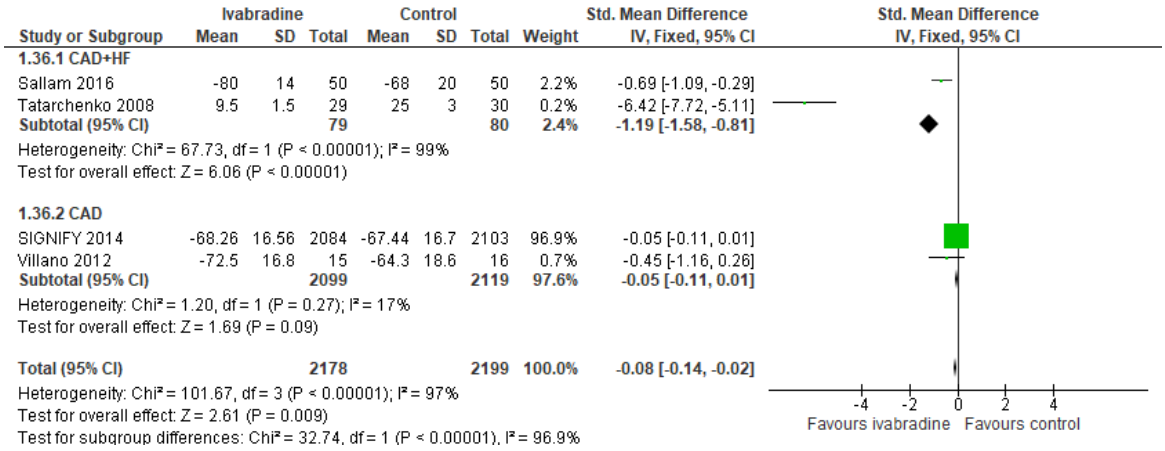


Figure 29 – Forest plot of the subgroup analyses of trials randomising participants with both coronary artery disease and heart failure versus trials randomising participants with coronary artery disease only. Test for subgroup differences showed evidence of a difference (p<0.00001) between trials randomising participants with both coronary artery disease and heart failure versus trials randomising participants with coronary artery disease only. When analysed separately, there was evidence of a beneficial effect of ivabradine in trials randomising participants with both coronary artery disease and heart failure and no evidence of a difference between ivabradine and control in trials randomising participants with coronary artery disease only.

Supplement 8 - Cardiovascular mortality

Main analyses

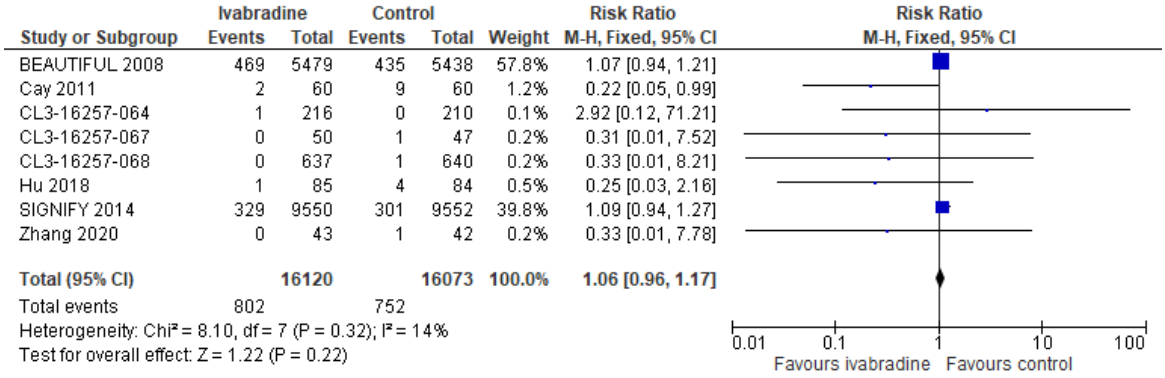


Figure 30 – Forest plot of the meta-analysis of cardiovascular mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

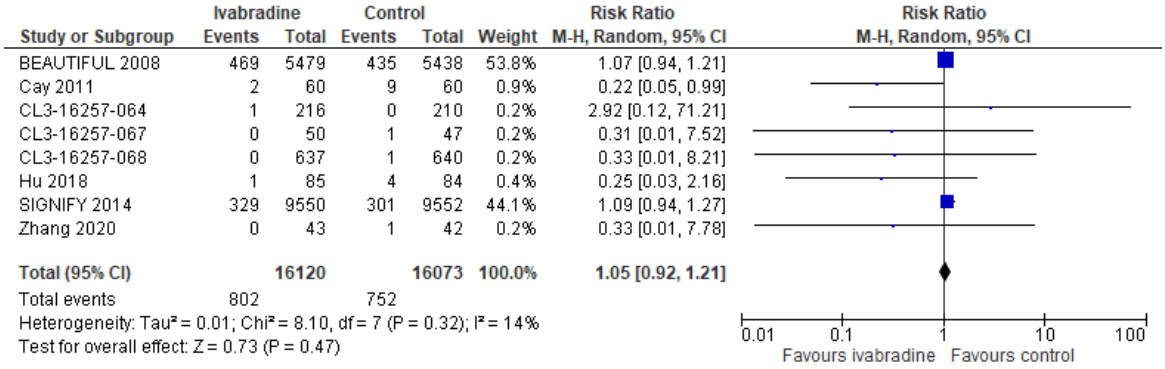


Figure 31 - Forest plot of the meta-analysis of cardiovascular mortality using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

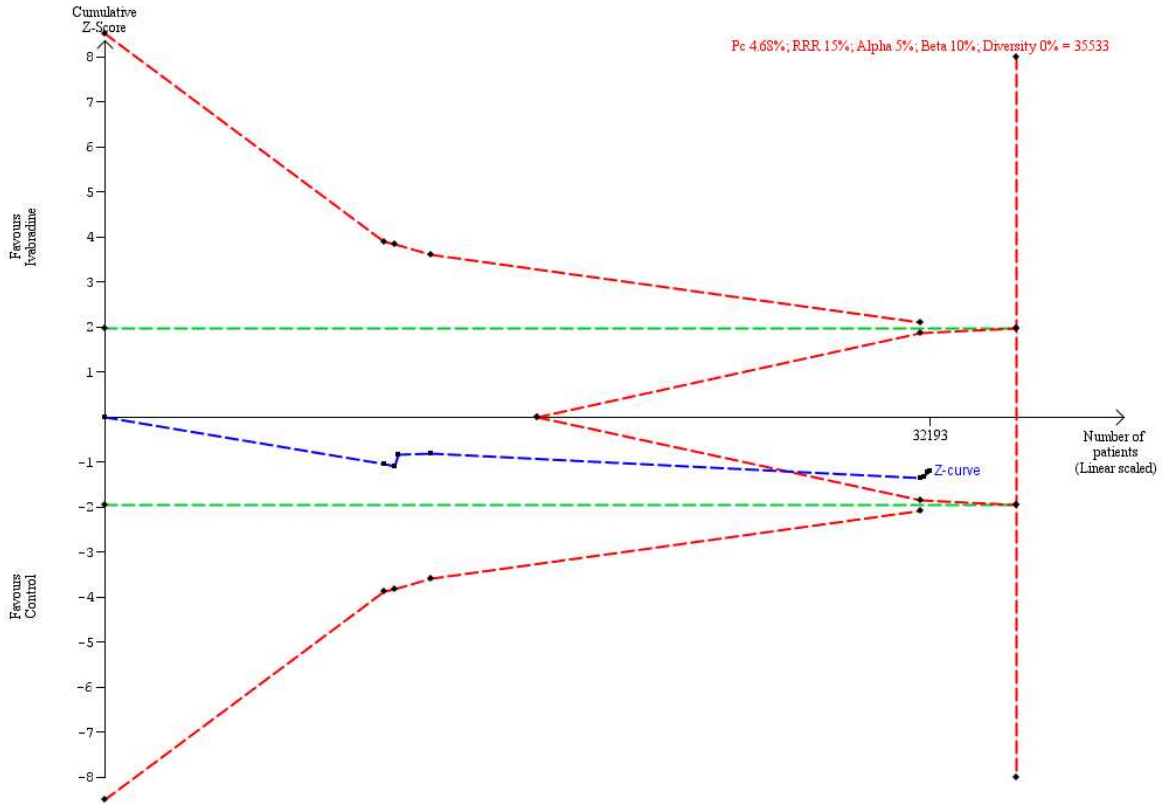
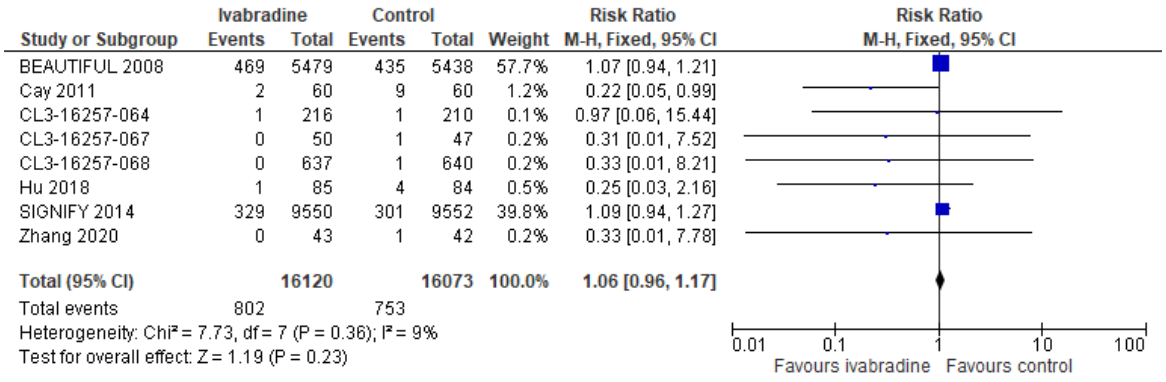


Figure 32 - Trial Sequential Analysis graph of cardiovascular mortality. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine. The cumulative z-curve (the blue line) breaches the boundary of futility. Pc: prevalence in control group; RRR: relative risk ratio.

Sensitivity analyses



Study or Subgroup	Ivabradine Events	Ivabradine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BEAUTIFUL 2008	469	5479	435	5438	57.7%	1.07 [0.94, 1.21]
Cay 2011	2	60	9	60	1.2%	0.22 [0.05, 0.99]
CL3-16257-064	1	216	1	210	0.1%	0.97 [0.06, 15.44]
CL3-16257-067	0	50	1	47	0.2%	0.31 [0.01, 7.52]
CL3-16257-068	0	637	1	640	0.2%	0.33 [0.01, 8.21]
Hu 2018	1	85	4	84	0.5%	0.25 [0.03, 2.16]
SIGNIFY 2014	329	9550	301	9552	39.8%	1.09 [0.94, 1.27]
Zhang 2020	0	43	1	42	0.2%	0.33 [0.01, 7.78]
Total (95% CI)		**16120**		**16073**	**100.0%**	**1.06 [0.96, 1.17]**
Total events	802		753			

Heterogeneity: Chi² = 7.73, df = 7 (P = 0.36); I² = 9%
Test for overall effect: Z = 1.19 (P = 0.23)

Figure 33 - Forest plot of the sensitivity analysis of cardiovascular mortality using best/worst-case scenario. The sensitivity analysis showed that missing data did not seem to have the potential to change the result.

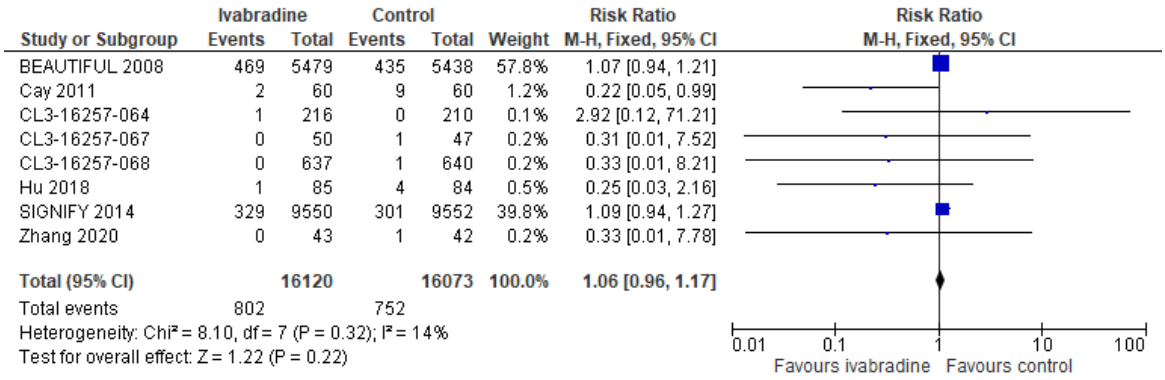


Figure 34 – Forest plot of the sensitivity analysis of cardiovascular mortality using worst/best-case scenario. The sensitivity analysis showed that missing data did not seem to have the potential to change the result.

Supplement 9 - Myocardial infarction

Main analyses

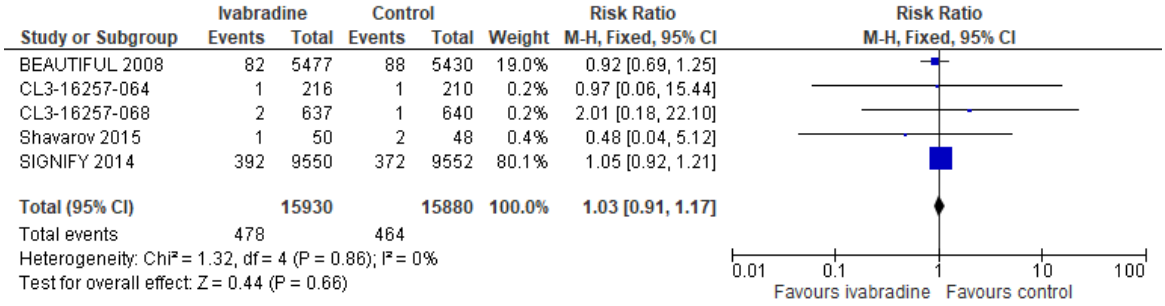


Figure 35 - Forest plot of the meta-analysis of myocardial infarction using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

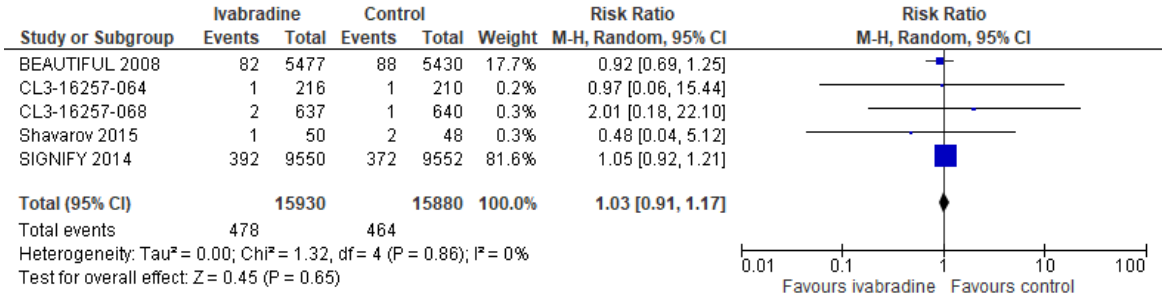


Figure 36 - Forest plot of the meta-analysis of myocardial infarction using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

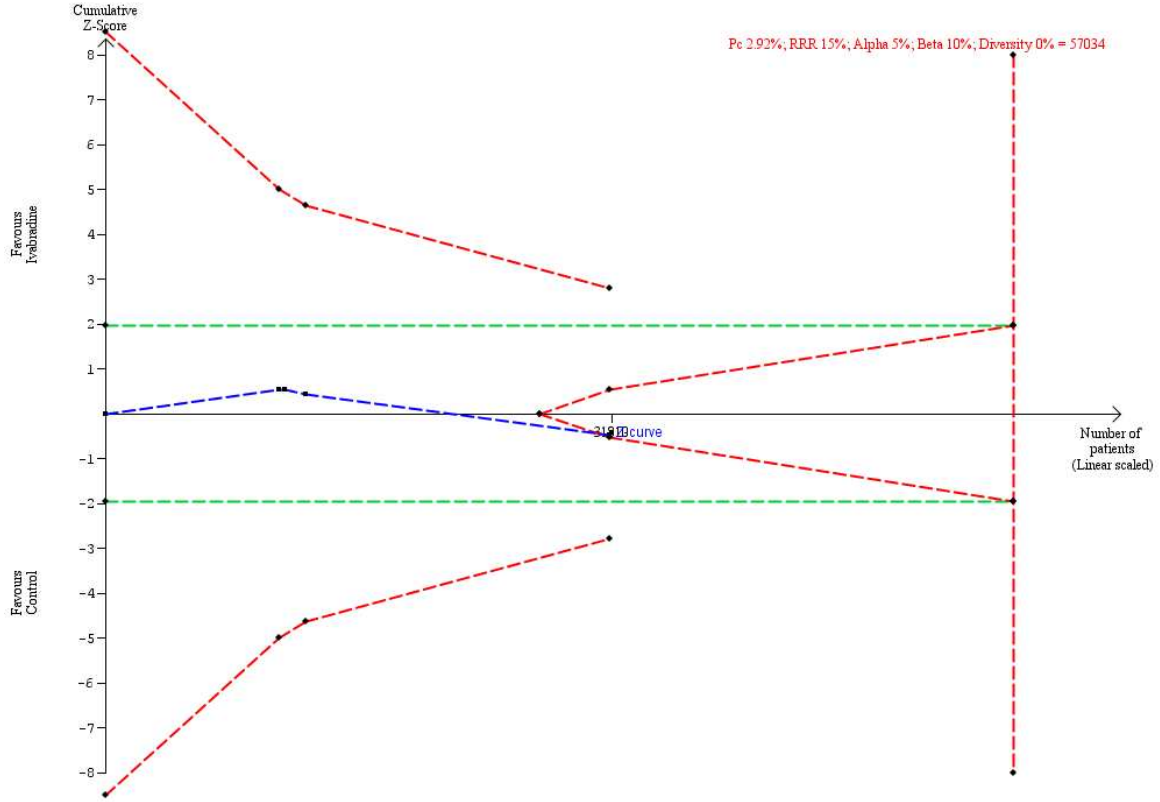


Figure 37 - Trial Sequential Analysis graph of myocardial infarction. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine. The cumulative z-curve (the blue line) breaches the boundary of futility. Pc: prevalence in control group; RRR: relative risk ratio.

Sensitivity analyses

Study or Subgroup	Ivabradine Events	Ivabradine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BEAUTIFUL 2008	82	5477	88	5430	19.0%	0.92 [0.69, 1.25]
CL3-16257-064	1	216	2	210	0.4%	0.49 [0.04, 5.32]
CL3-16257-068	2	637	1	640	0.2%	2.01 [0.18, 22.10]
Shavarov 2015	1	50	2	48	0.4%	0.48 [0.04, 5.12]
SIGNIFY 2014	392	9550	372	9552	79.9%	1.05 [0.92, 1.21]
Total (95% CI)		**15930**		**15880**	**100.0%**	**1.03 [0.91, 1.16]**
Total events	478		465			

Heterogeneity: Chi² = 1.69, df = 4 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.41 (P = 0.68)

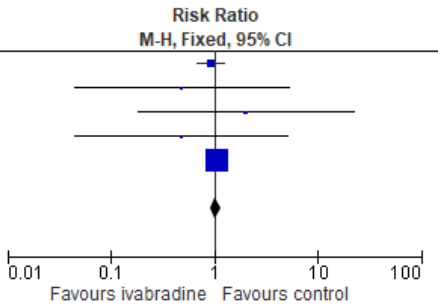


Figure 38 – Forest plot of the sensitivity analysis of myocardial infarction using a best/worst-case scenario. The meta-analysis showed that missing data did not seem to have the potential to influence the result.

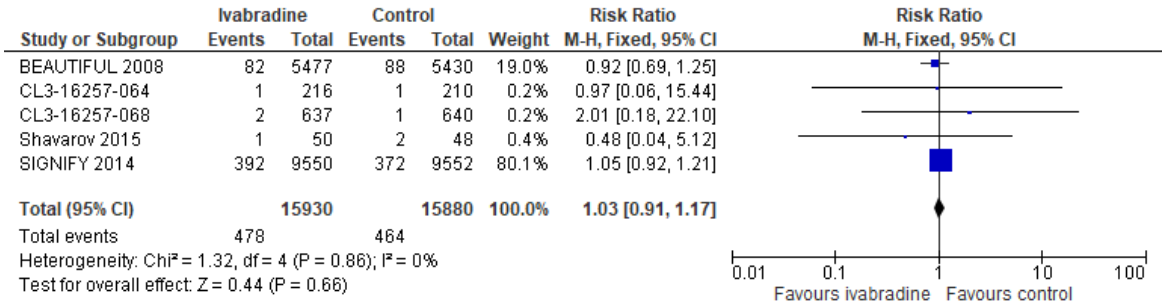


Figure 39 - Forest plot of the sensitivity analysis of myocardial infarction using a worst/best-case scenario. The meta-analysis showed that missing data did not seem to have the potential to influence the result.

Supplement 10 - Non-serious adverse events

Main analyses

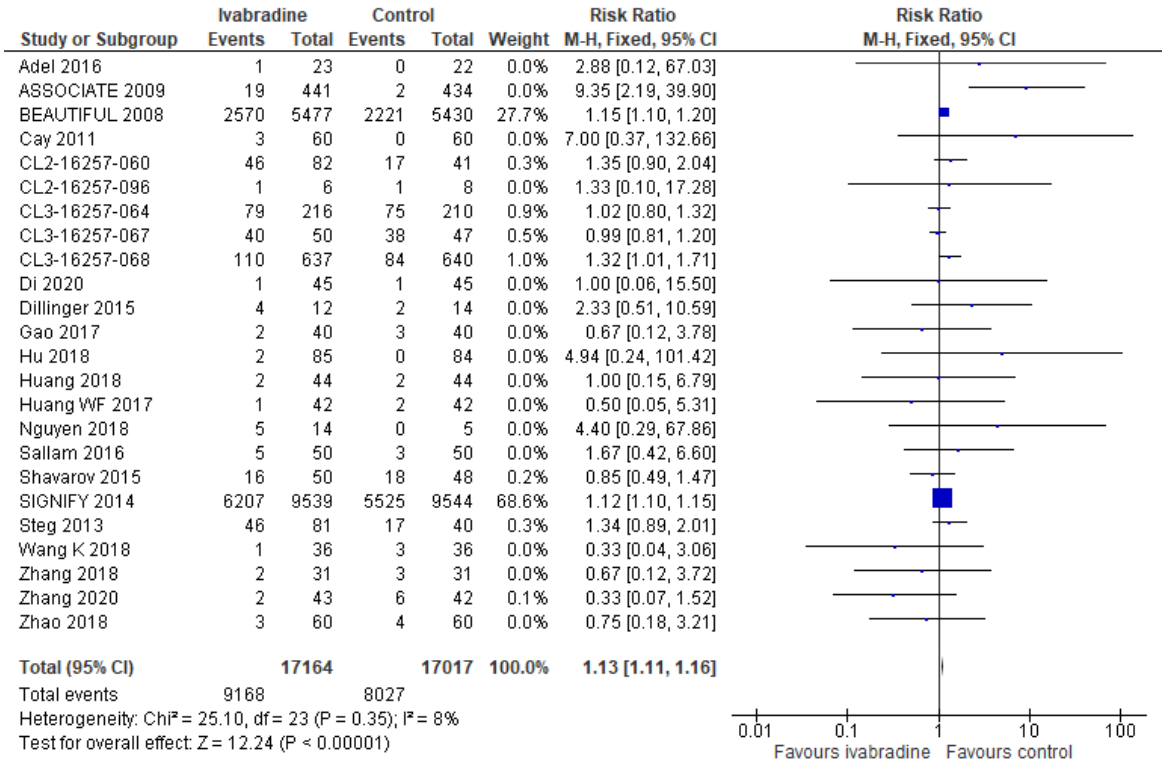


Figure 40 - Forest plot of the meta-analysis of non-serious adverse events using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to increase the risk of non-serious adverse events by 13%.

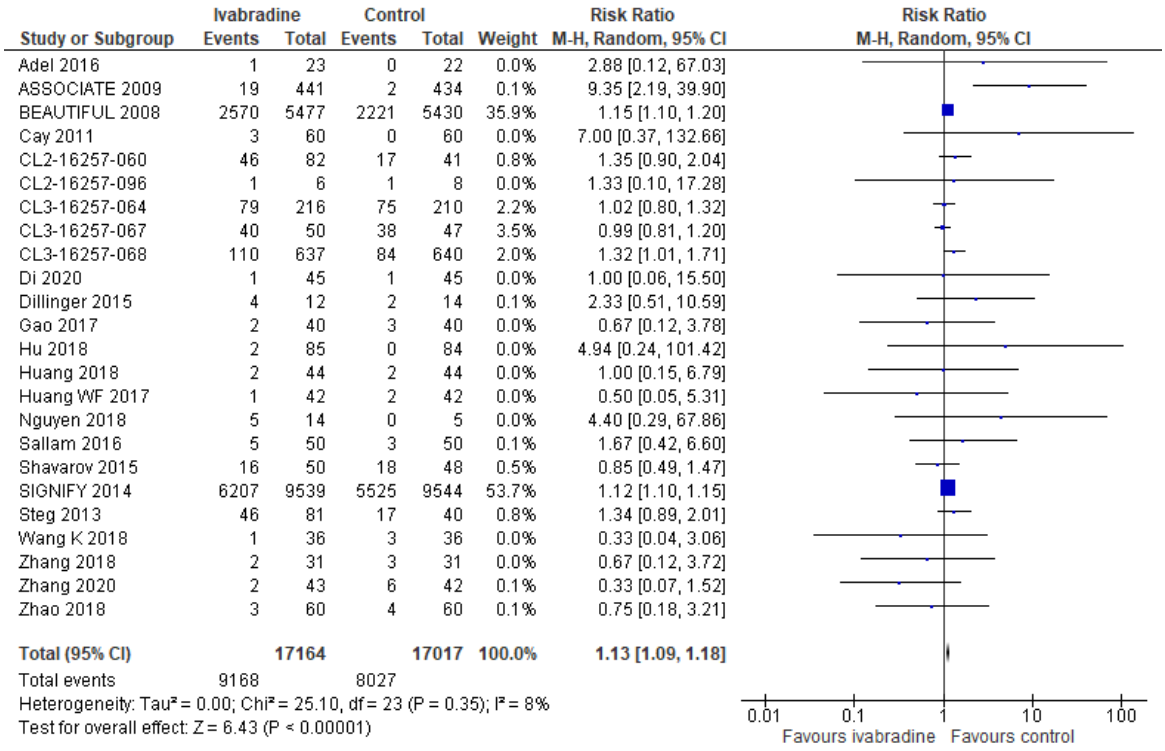


Figure 41 - Forest plot of the meta-analysis of non-serious adverse events using random-effects meta-analysis. The meta-analysis showed that ivabradine seemed to increase the risk of non-serious adverse events by 13%.

Sensitivity analyses

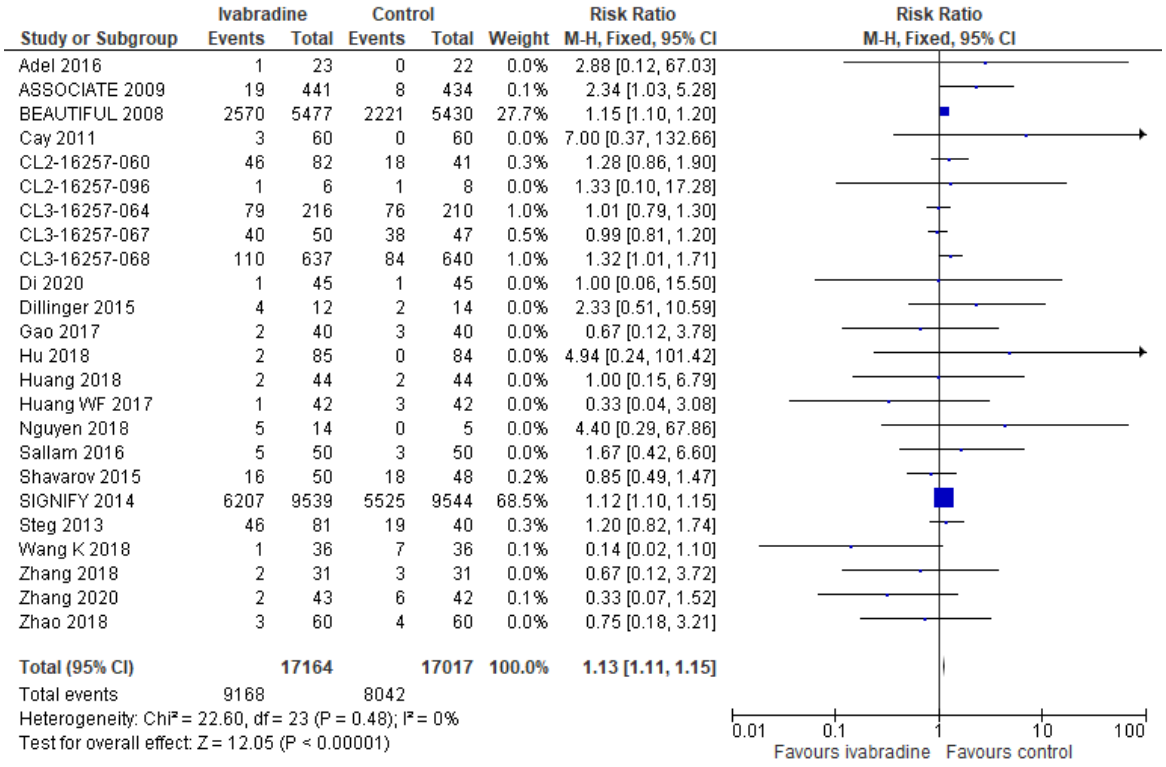


Figure 42 – Forest plot of the meta-analysis of non-serious adverse events using a best/worst-case scenario. The meta-analysis showed that missing data did not seem to have the potential to change the result.

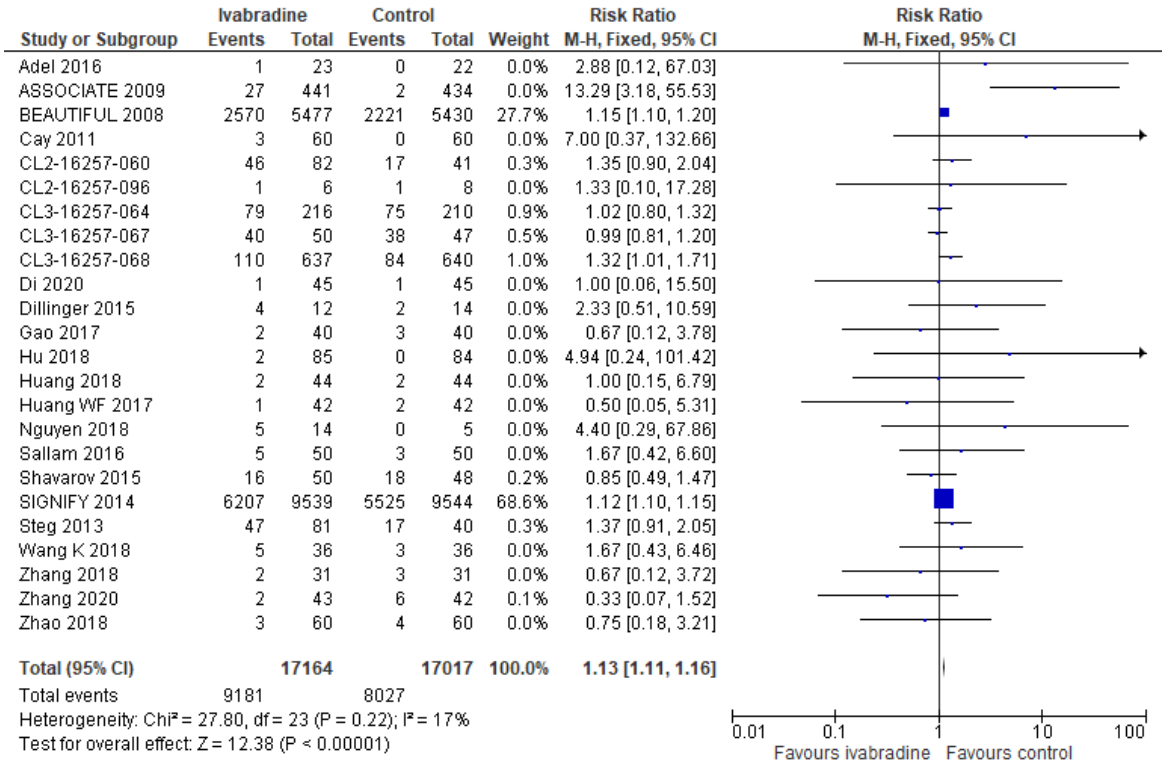


Figure 43 - Forest plot of the meta-analysis of non-serious adverse events using a worst/best-case scenario. The meta-analysis showed that missing data did not seem to have the potential to change the result.

Supplement 11 – Discrepancy in safety data

For serious and non-serious adverse events, there were considerable discrepancies between the data reported in the publication in the SIGNIFY trial as compared to the raw data reported on ClinicalTrials.gov.[32,69]

In the published article of the SIGNIFY trial it was reported that 3,588/9,539 (37·6%) participants in the ivabradine group and 3,375/9,544 (35·4%) in the control group experienced one or more serious adverse events.[32] However, in the raw data it was reported that 3,379/9,539 (35·4%) in the ivabradine group and 3,263/9,544 (34·2%) in the control group experienced one or more serious adverse events.[69] In our analyses, we have used the highest proportion of participants at risk.

In the published article of the SIGNIFY trial it was reported that 6,990/9,539 (73·3%) participants in the ivabradine group and 6,382/9,544 (66·9%) in the control group experienced one or more non-serious adverse events.[32] However, in the original entry of raw data on ClinicalTrials.gov it was reported that 9,360/9,539 (98·1%) in the ivabradine group and 7,311/9,544 (76·6%) in the control group experienced one or more non-serious adverse events.[69] This has since been changed by the company, so that now it is reported on ClinicalTrials.gov that 6,207/9,539 in the ivabradine group and 5,525/9,544 in the control group experienced one or more non-serious adverse events. In our analyses, we have used the new entry on ClinicalTrials.gov. The company that developed ivabradine, Servier, have informed us that in the publication, the data given for serious and non-serious adverse events 'are given during the study' while the data on ClinicalTrials.gov 'are given on treatment'.

Supplement 12 – Exploratory outcomes

Resting heart rate at follow-up

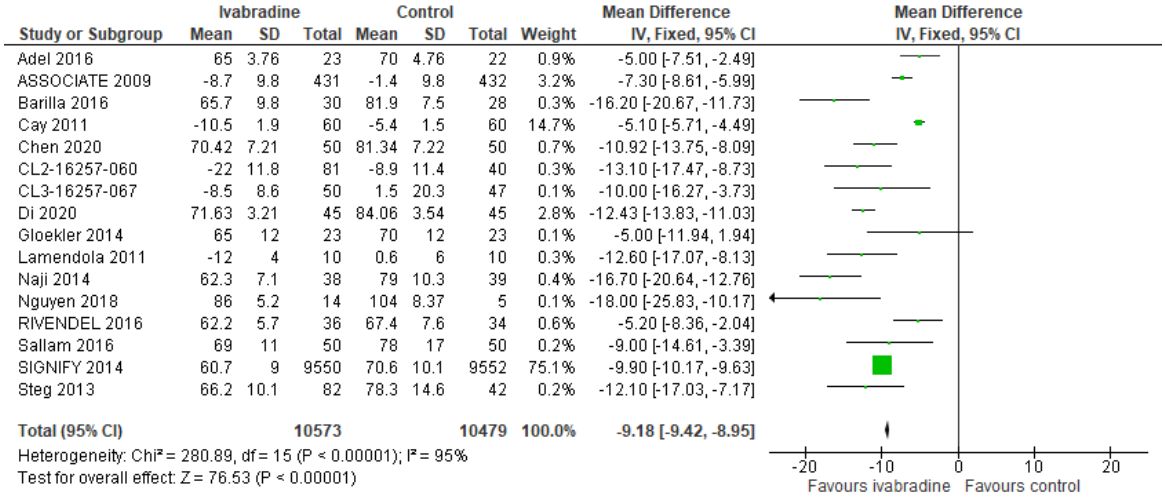


Figure 44 – Forest plot of the meta-analysis of resting heart rate at follow-up using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to decrease the resting heart rate at follow-up by 9·05 beats per minute.

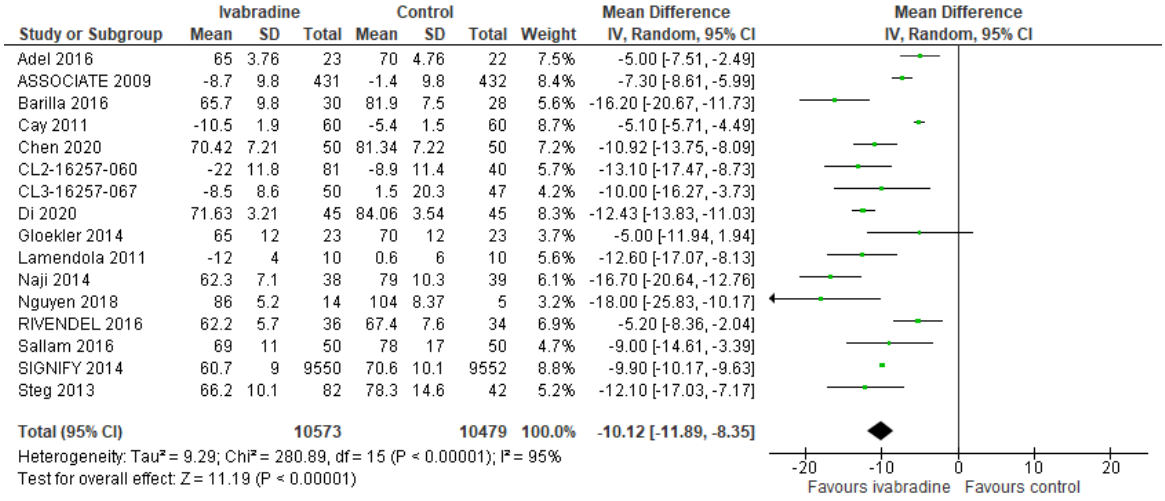


Figure 45 - Forest plot of the meta-analysis of resting heart rate at follow-up using random-effects meta-analysis. The meta-analysis showed that ivabradine seemed to decrease the resting heart rate at follow-up by 9·01 beats per minute.

Left ventricular ejection fraction

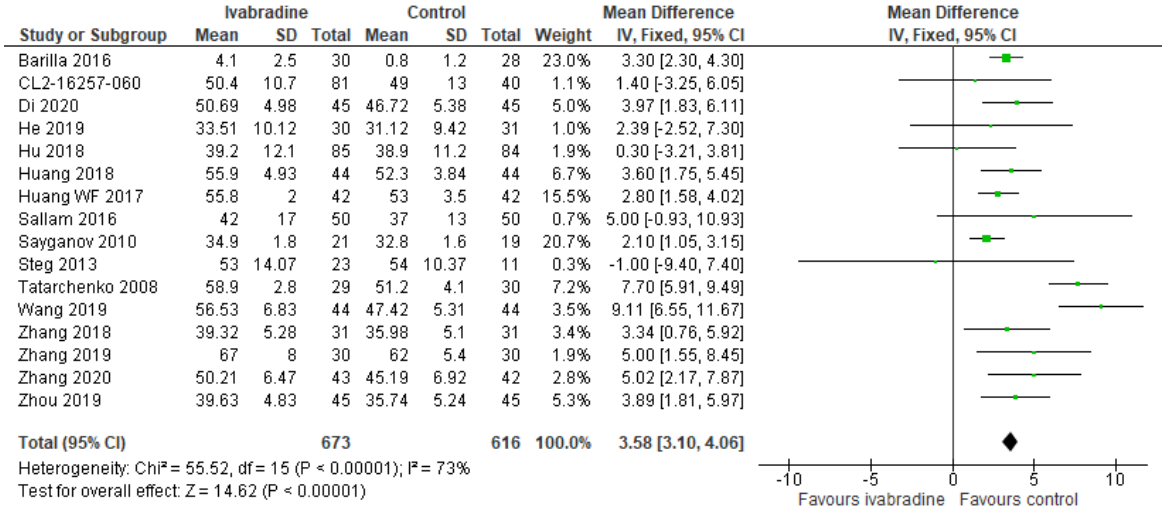


Figure 46 - Forest plot of the meta-analysis of left ventricular ejection fraction using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to increase the left ventricular ejection fraction by 2·59%.

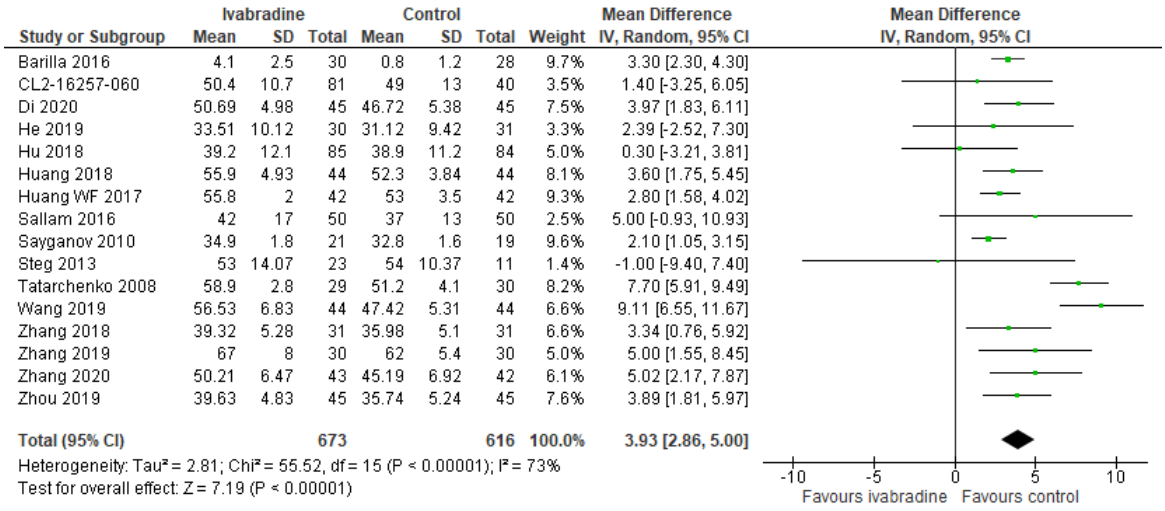


Figure 47 - Forest plot of the meta-analysis of left ventricular ejection fraction using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to increase the left ventricular ejection fraction by 2·59%.

Angina pectoris
Angina frequency

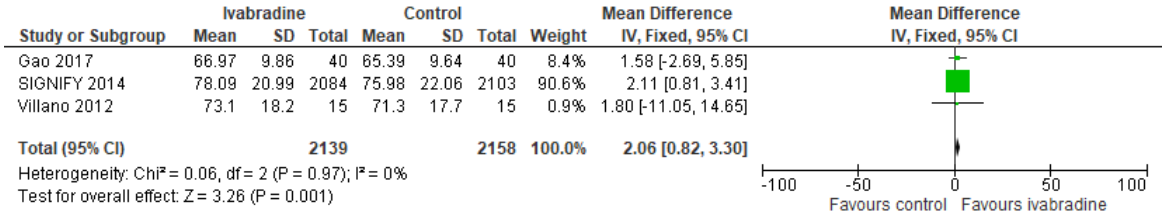


Figure 48 – Forest plot of the meta-analysis of angina frequency using fixed-effect meta-analysis. The meta-analysis shows that ivabradine seems to increase angina frequency (a positive outcome) by 2·06 points.

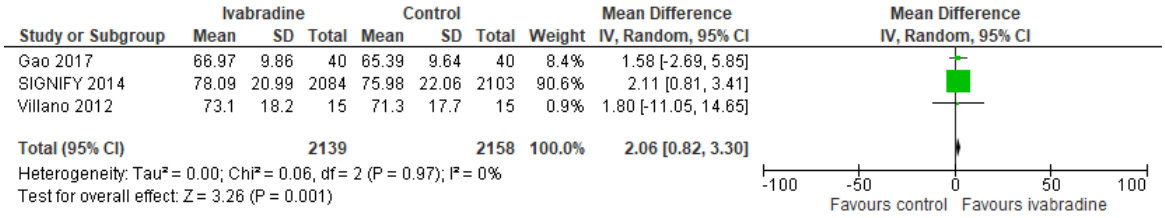


Figure 49 - Forest plot of the meta-analysis of angina frequency using random-effects meta-analysis. The meta-analysis shows that ivabradine seems to increase angina frequency (a positive outcome) by 2·06 points.

In the SIGNIFY trial, the difference between ivabradine and control was 2·11 points at follow-up. The combined standard deviation was SD 20·53 points. Thus, the minimal important difference was 10·27 points. The difference of 2·11 points at follow-up was 4·87 times lower than the minimal important difference. In the SIGNIFY trial, a statistically significant effect of ivabradine on angina frequency was reported. However, when analysing continuous outcomes including a large sample size (almost 4 200 participants), small and clinically insignificant effects become statistically significant. The effect size in this case seems small and possibly without any relevance to patients.

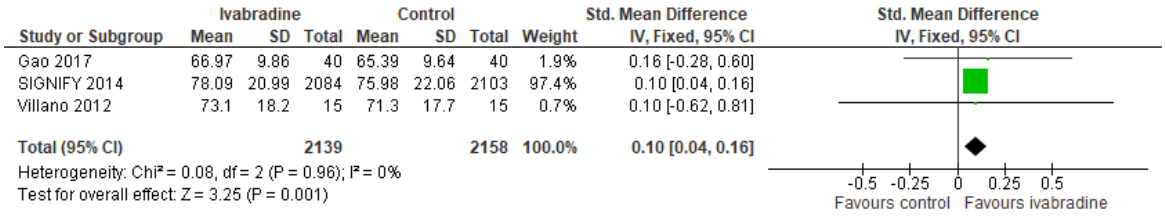


Figure 50 – Forest plot of the meta-analysis of angina frequency using standardised mean differences. The meta-analysis showed evidence of a beneficial effect of ivabradine.

Angina stability

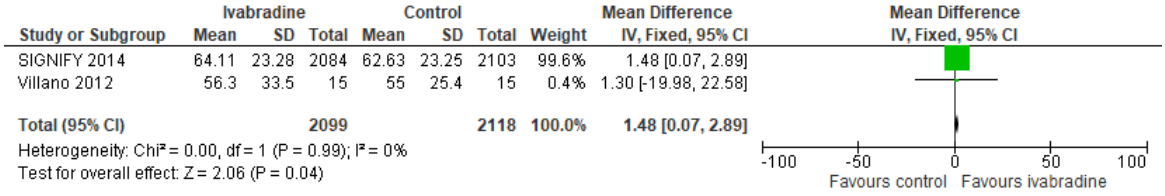


Figure 51 - Forest plot of the meta-analysis of angina frequency using fixed-effect meta-analysis. The meta-analysis shows that ivabradine seems to increase angina stability by 1·48 points.

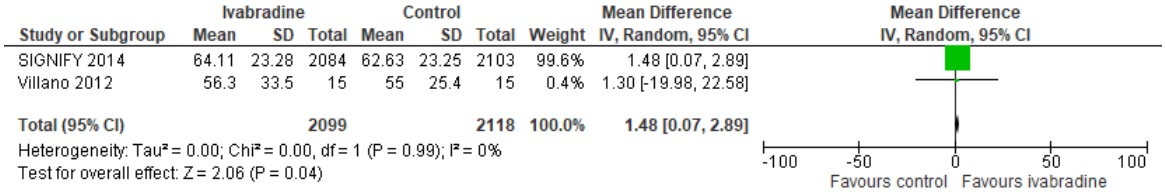


Figure 52 - Forest plot of the meta-analysis of angina frequency using random-effects meta-analysis. The meta-analysis shows that ivabradine seems to increase angina stability by 1·48 points.

In the SIGNIFY trial, the difference between ivabradine and control was 1·48 points at follow-up. The combined standard deviation was SD 23·24 points. Thus, the minimal important difference was 11·62 points. The difference of 1·48 points at follow-up was 7·85 times lower than the minimal important difference. In the SIGNIFY trial, a statistically significant effect of ivabradine on angina stability was reported. However, when analysing continuous outcomes including a large sample size (almost 4 200 participants), small and clinically insignificant effects become statistically significant. The effect size in this case seems small and possibly without any relevance to patients.

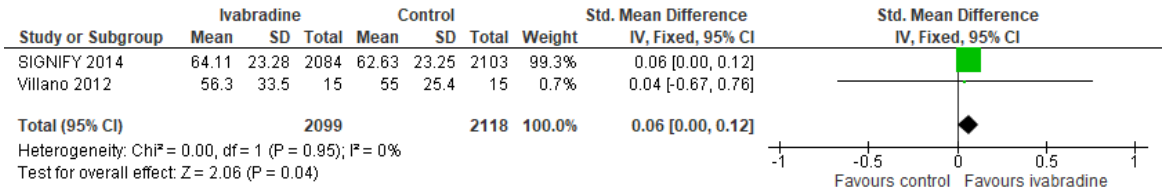


Figure 53 – Forest plot of the meta-analysis of angina stability using standardised mean differences. The meta-analysis showed evidence of a beneficial effect of ivabradine.

Exercise tolerance test

In the trial by Borer et al., the table shows that the minimal important difference was only reached in the 10mg twice daily ivabradine group for time to angina onset and time to 1mm ST depression.

Time to limiting angina						
	Effect	**SD**	**Diff.eff.**	**Combined SD**	**MID**	**Ratio MID/diff.eff**
Placebo	12·7	51·3				
Iva 2.5mg	22·5	55·4	9·8	53·35	26·68	2·72
Iva 5mg	27·2	56·8	14·5	54·05	27·03	1·86
Iva 10mg	40·8	69·3	28·1	60·3	30·15	1·07

Time to angina onset						
	Effect	**SD**	**Diff.eff.**	**Combined SD**	**MID**	**Ratio MID/diff.eff**
Placebo	24·7	64·2				
Iva 2.5mg	37·6	57·7	12·9	60·95	30·48	2·36
Iva 5mg	38·8	81·7	14·1	72·95	36·58	2·59
Iva 10mg	69·4	74·8	44·7	69·5	34·75	0·78

Time to 1mm ST-depression						
	Effect	**SD**	**Diff.eff.**	**Combined SD**	**MID**	**Ratio MID/diff.eff**
Placebo	9·0	63·6				
Iva 2.5mg	32·0	74·3	23·0	68·95	34·48	1·50
Iva 5mg	44·1	80·1	35·1	71·85	35·93	1·02
Iva 10mg	46·2	78·2	37·2	70·9	35·45	0·95

Table 1-3: Tables of the minimal important difference in the trial by Borer et al. Effect: the change between day 0 and day 14; SD: standard deviation; Diff Eff: difference in effect between placebo and ivabradine; Combined SD: the mean of the standard deviation of placebo and ivabradine; MID: minimal important difference, SD/2; Ratio MID/diff.eff: the ratio between minimal important difference and the difference in effect between ivabradine and placebo. The MID/diff.eff ratio has to be below 1·00 for the given effect size to be larger than the minimal important difference.

In the ASSOCIATE trial, the table shows that the minimal important difference was not reached for any of the outcome measures.

Total exercise duration						
	Effect	**SD**	**Diff.eff**	**Combined SD**	**MID**	**Ratio MID/diff.eff**
Placebo	458·4	111·1				
Ivabradine	469·9	119·2	11·5	115·15	57·58	5·01

Time to limiting angina						
	Effect	**SD**	**Diff.eff**	**Combined SD**	**MID**	**Ratio MID/diff.eff**
Placebo	456·0	111·1				
Ivabradine	467·9	119·8	11·9	115·45	57·73	4·85

Time to angina onset						
	Effect	**SD**	**Diff.eff**	**Combined SD**	**MID**	**Ratio MID/diff.eff**
Placebo	379·9	115·8				
Ivabradine	401·6	125·5	21·7	120·65	60·33	2·78

Time to 1mm ST-depression						
	Effect	**SD**	**Diff.eff**	**Combined SD**	**MID**	**Ratio MID/diff.eff**
Placebo	362·6	122·5				
Ivabradine	383·5	123·2	20·9	122·85	61·43	2·94

Table 4-7 – Table of the minimal important difference in the ASSOCIATE trial. Effect: the change between day 0 and the end of study; SD: standard deviation; Diff Eff: difference in effect between placebo and ivabradine; Combined SD: the mean of the standard deviation of placebo and ivabradine; MID: minimal important difference, SD/2; Ratio MID/diff.eff: the ratio between minimal important difference and the difference in effect between ivabradine and placebo. The MID/diff.eff ratio has to be below 1·00 for the given effect size to be larger than the minimal important difference.

In the CL3-16257-068 trial, the table shows that the minimal important difference was not reached for any of the outcome measures.

Total exercise duration						
	Effect	**SD**	**Diff.eff**	**Combined SD**	**MID**	**Ratio MID/diff.eff**
Placebo	63·5	105·9				
Ivabradine	80·1	103·6	16·6	104·75	52·38	3·16

Time to limiting angina						
	Effect	**SD**	**Diff.eff**	**Combined SD**	**MID**	**Ratio MID/diff.eff**
Placebo	64·6	105·4				
Ivabradine	81·5	103·7	16·9	104·55	52·28	3·09

Time to angina onset						
	Effect	**SD**	**Diff.eff**	**Combined SD**	**MID**	**Ratio MID/diff.eff**
Placebo	92·8	122·3				
Ivabradine	108·3	119·2	15·5	120·75	60·38	3·90

Total 1mm ST-depression						
	Effect	**SD**	**Diff.eff**	**Combined SD**	**MID**	**Ratio MID/diff.eff**
Placebo	83·6	139·0				
Ivabradine	112·2	146·3	28·6	142·65	71·33	2·49

Table 8-11 - Table of the minimal important difference in the CL3-16257-068 trial. Effect: the change at peak of drug activity; SD: standard deviation; Diff Eff: difference in effect between placebo and ivabradine; Combined SD: the mean of the standard deviation of placebo and ivabradine; MID: minimal important difference, SD/2; Ratio MID/E: the ratio between minimal important difference and the difference in effect between ivabradine and placebo. The MID/E ratio has to be below 1·00 for the given effect size to be larger than the minimal important difference

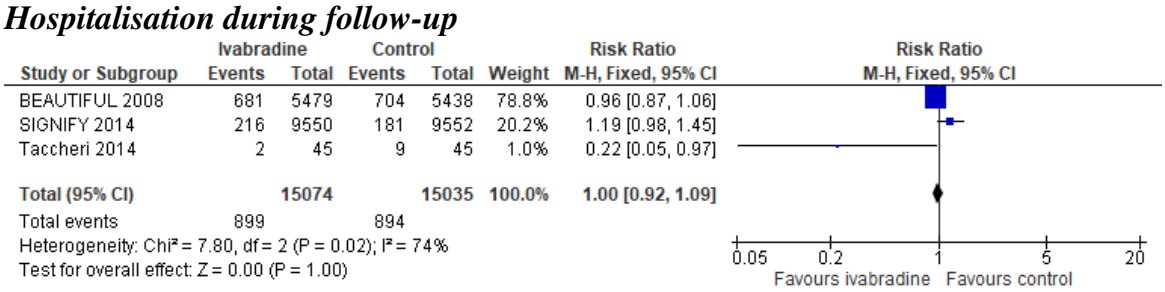


Figure 54 – Forest plot of the meta-analysis of hospitalisation during follow-up using fixed-effect meta-analysis. The meta-analysis shows no evidence of a difference between ivabradine and control.

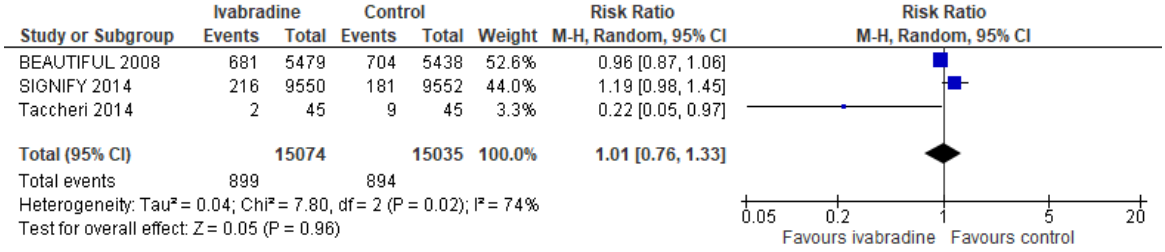


Figure 55 - Forest plot of the meta-analysis of hospitalisation during follow-up using random-effects meta-analysis. The meta-analysis shows no evidence of a difference between ivabradine and control.

Supplement 13 – 'Summary of findings'-table

Outcomes	**Control intervention at risk**	**Intervention at risk**	**Relative effect (TSA-adjusted 95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
All-cause mortality	62 per 1000	64 per 1000	RR 1·04 (0·88 to 1·20)	33 427 (15 trials)	⨁⨁⨁⨀ Moderate[1]	All trials were at high risk of bias. Trial Sequential Analysis showed that we had enough information to reject a 15% relative risk reduction by ivabradine
Serious adverse events	307 per 1000	324 per 1000	RR 1·06 (1·00 to 1·13)	33 514 (18 trials)	⨁⨁⨁⨀ Moderate[2]	All trials were at high risk of bias. Trial Sequential Analysis showed that we had enough information to reject a 15% relative risk reduction by ivabradine.
Quality of life	-	-	SMD -0·05 (-0·11 to 0·01)	4 218 (Two trials)	⨁⨁⨀⨀ Low[3]	All trials were at high risk of bias. The effect was 10 times lower than the minimal

						important difference of SMD 0·5.
Cardiovascular mortality	47 per 1000	50 per 1000	RR 1·05 (0·95 to 1·18)	32 193 (8 trials)	⨁⨁⨁⊖ Moderate[4]	All trials were at high risk of bias. Trial Sequential Analysis showed that we had enough information to reject a 15% relative risk reduction by ivabradine
Myocardial infarction	30 per 1000	30 per 1000	RR 1·03 (0·85 to 1·23)	31 810 (5 trials)	⨁⨁⨁⊖ Moderate[5]	All trials were at high risk of bias. Trial Sequential Analysis showed that we had enough information to reject a 15% relative risk reduction by ivabradine
Non-serious adverse events	472 per 1000	534 per 1000	RR 1·13 (1·11 to 1·16)	34 181 (24 trials)	⨁⨁⨁⊖ Moderate[6]	All trials were at high risk of bias. One trials under reported the number of participants with one or more non-serious

						adverse events. Trial Sequential Analysis showed that we had enough information to detect a relative risk increase of 15% by ivabradine

1. Downgraded by one due to all trials being at high risk of bias.
2. Downgraded by one due to all trials being at high risk of bias.
3. Downgraded by one due to all trials being at high risk of bias and by one due to inconsistency.
4. Downgraded by one due to all trials being at high risk of bias.
5. Downgraded by one due to all trials being at high risk of bias.
6. Downgraded by one due to all trials being at high risk of bias.