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Ivabradine added to usual care in patients with heart failure: a systematic review with meta-analysis and trial sequential analysis

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10.1136/bmjebm-2021-111724

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjebm-2021-111724).

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To cite: Maagaard M, Nielsen EE, Sethi NJ, *et al*. *BMJ Evidence-Based Medicine* 2022;**27**:224–234.

Abstract

Objectives To assess the beneficial and harmful effects of adding ivabradine to usual care in participants with heart failure.

Design A systematic review with meta-analysis and trial sequential analysis.

Eligibility criteria Randomised clinical trials comparing ivabradine and usual care with usual care (with or without) placebo in participants with heart failure.

Information sources Medline, Embase, CENTRAL, LILACS, CNKI, VIP and other databases and trial registries up until 31 May 2021.

Data extraction Primary outcomes were all-cause mortality, serious adverse events and quality of life. Secondary outcomes were cardiovascular mortality, myocardial infarction and non-serious adverse events. We performed meta-analysis of all outcomes. We used trial sequential analysis to control risks of random errors, the Cochrane risk of bias tool to assess the risks of systematic errors and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess the certainty of the evidence.

Results We included 109 randomised clinical trials with 26 567 participants. Two trials were at low risk of bias, although both trials were sponsored by the company that developed ivabradine. All other trials were at high risk of bias. Meta-analyses and trial sequential analyses showed that we could reject that ivabradine versus control reduced all-cause mortality (risk ratio (RR)=0.94; 95% CI 0.88 to 1.01; p=0.09; high certainty of evidence). Meta-analysis and trial sequential analysis showed that ivabradine seemed to reduce the risk of serious adverse events (RR=0.90; 95% CI 0.87 to 0.94; p<0.00001; number needed to treat (NNT)=26.2; low certainty of evidence). This was primarily due to a decrease in the risk of 'cardiac failure' (RR=0.83; 95% CI 0.71 to 0.97; p=0.02; NNT=43.9), 'hospitalisations' (RR=0.89; 95% CI 0.85 to 0.94; p<0.0001; NNT=36.4) and 'ventricular tachycardia' (RR=0.59; 95% CI 0.43 to 0.82; p=0.001; NNT=212.8). However, the trials did not describe how these outcomes were defined and assessed during follow-up. Meta-analyses showed that ivabradine increased the risk of atrial fibrillation (RR=1.19; 95% CI 1.04 to 1.35; p=0.008; number needed to harm (NNH)=116.3) and bradycardia (RR=3.95; 95% CI 1.88 to 8.29; p=0.0003; NNH=303). Ivabradine seemed to increase quality of life on the Kansas City Cardiomyopathy Questionnaire (KCCQ) (mean difference (MD)=2.92; 95% CI 1.34 to 4.50; p=0.0003; low certainty of evidence), but the effect size was small and possibly without relevance to patients, and on the Minnesota Living With Heart Failure Questionnaire (MLWHFQ) (MD=−5.28; 95% CI −6.60 to −3.96; p<0.00001; very low certainty of evidence), but the effects were uncertain. Meta-analysis showed no evidence of a difference between ivabradine and control when assessing cardiovascular mortality and myocardial infarction. Ivabradine seemed to increase the risk of non-serious adverse events.

Conclusion and relevance High certainty evidence shows that ivabradine does not seem to affect the risks of all-cause mortality and cardiovascular mortality. The effects on quality of life were small and possibly without relevance to patients on the KCCQ and were very uncertain for the MLWHFQ. The effects on serious adverse events, myocardial infarction and hospitalisation are uncertain. Ivabradine seems to increase the

SUMMARY BOX

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

⇒ Ivabradine is recommended in patients with symptoms of heart failure despite optimal background therapy for reducing heart failure hospitalisation in the 2017 American guidelines on heart failure.
⇒ Ivabradine is recommended for reducing cardiovascular mortality and heart failure hospitalisation in the 2016 European guidelines on heart failure.
⇒ A recent Cochrane review did not find evidence of a difference between ivabradine and placebo/no intervention on cardiovascular mortality and serious adverse events.

SUMMARY BOX

WHAT ARE THE NEW FINDINGS?

⇒ In our systematic review, including 109 randomised clinical trials with 26 567 participants, ivabradine did not seem to reduce all-cause mortality, cardiovascular mortality or myocardial infarction.
⇒ Ivabradine seemed to decrease the risk of serious adverse events, mainly due to a reduction in cardiac failure and hospitalisations, but these outcomes were poorly defined and poorly assessed.
⇒ The effect on quality of life was small and probably without relevance to patients.
⇒ Ivabradine seemed to increase the risk of atrial fibrillation, bradycardia and non-serious adverse events.

HOW MIGHT IT IMPACT CLINICAL PRACTICE IN THE FORESEEABLE FUTURE?

⇒ Based on the evidence, the guideline recommendations on the treatment of heart failure with ivabradine should be reconsidered.

risk of atrial fibrillation, bradycardia and non-serious adverse events.
PROSPERO registration number: CRD42018112082.

Introduction

Of all deaths worldwide, 30% are attributable to cardiovascular disease.[1] Heart failure is characterised by symptoms related to fluid retention such as peripheral oedema, breathlessness and dyspnoea.[2] Heart failure can be caused by either functional cardiac disease (eg, a decrease in the function of the myocardium) or structural cardiac disease (eg, disease of the cardiac valves).[3 4] Medical management of heart failure includes the use of beta-blockers, angiotensin receptor blockers, ACE inhibitors and diuretics (loop diuretics, thiazides and potassium-sparing diuretics). Ivabradine is a relatively new drug that was first introduced into heart failure guidelines in Europe in 2012 and in America in 2017.[5 6]

Ivabradine selectively inhibits the sinus node, thereby decreasing the heart rate. The decrease in heart rate, results in a decreased myocardial oxygen demand and an increased myocardial oxygen supply, thereby improving the mismatch seen in heart failure.[7] Therefore, ivabradine might be an effective intervention in people with heart failure.[7 8] A recently published Cochrane review assessed the beneficial and harmful effects of ivabradine in people with heart failure and included 19 trials with 19 628 participants and did not find evidence of a difference between ivabradine and control in regard to cardiovascular mortality and serious adverse events.[9] Another systematic review included 10 trials with 18 036 participants, did not search all relevant databases, did not consider the risk of random error and did not assess the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[10] To the best of our knowledge, no previous systematic review has assessed the beneficial and harmful effects of ivabradine compared with usual care (ie, placebo or no intervention) for people with heart failure, searching all relevant databases while considering the risks of both systematic errors and random errors.[9 11–15]

Methods

We described our methodology in detail in our protocol that was published before conducting the literature search.[2 16] We reported this systematic review according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15] We included all trials comparing ivabradine with placebo or no intervention in patients with heart failure. Four authors (MM, EEN, S-HY and NL) independently searched and screened for trials published prior to 31 May 2021 in Medline, Embase, CENTRAL, LILACS, CNKI, VIP and other databases and trial registries, see supplement 1 in online supplemental file 1 for a detailed list of databases and trial registries. Detailed search strategies are presented in supplement 2 in online supplemental file 2. We included randomised clinical trials regardless of their design, the trial setting, the publication status, year, language or reporting of outcomes. Five authors (MM, EEN, NJS, NL and S-HY) worked in pairs and independently extracted data and assessed the risks of bias in the included trials. If data were missing or unclear, we attempted to contact the trial authors by email. We resolved disagreements through discussion or by consulting a third author (JCJ).[2] We planned to include non-randomised studies identified during the literature search for the reporting of serious and non-serious adverse events. However, we did not identify such studies during the literature search, and we did not systematically search for such studies. Therefore, there is a risk that we have not identified and reported on all relevant serious and non-serious adverse events, especially those that are rare or only associated with long-term treatment.

We predefined three primary outcomes: all-cause mortality, serious adverse events and quality of life. We also predefined three secondary outcomes and eight exploratory outcomes.[2] We used the trial results reported at maximal follow-up for all our outcomes.

We predefined several subgroup analyses for the assessment of the primary outcomes:

- Trials at high risk of bias compared with trials at low risk of bias
- Men compared with women
- Participants with a resting heart rate at or above 70 beats/min compared with below 70 beats/min.
- Trials administering ivabradine at or above median daily dose compared with below median daily dose
- Trials administering ivabradine at or above median duration compared with below median duration

Assessment of risk of bias

To assess the risks of systematic errors, we assessed the risk of bias for each included trial. The risk of bias was assessed individually by five reviewers working in pairs (MM, EEN, NJS, S-HY and NL).[17] We assessed the risk of small study bias using funnel plots and funnel plot asymmetry tests. We planned to assess the risk of for-profit bias as part of the risk of bias assessment but post-hoc decided to only acknowledge for-profit bias throughout the review in line with the Cochrane Handbook.[18]

Assessment of statistical and clinical significance

We used Review Manager V.5.4 for all meta-analyses.[19] We chose to analyse all primary and secondary outcome meta-analyses using fixed effect due to the BEAUTIFUL and the SHIFT trials accounting for more than 85%wt in all primary and secondary

meta-analyses (excluding the quality of life assessment with the Minnesota Living With Heart Failure Questionnaire (MLWHFQ), see the Quality of life section).[13 20 21] Random-effects meta-analyses were also performed as sensitivity analyses. We used trial sequential analysis to control random errors (see below) and we adjusted the thresholds for statistical significance, as suggested by Jakobsen and colleagues, to control for the risks of random errors.[11 13 22] We used three primary outcomes and, therefore, adjusted the p value to 0.025 as the threshold for statistical significance. When analysing our secondary and exploratory outcomes, we used a p value of 0.05 as the threshold for statistical significance, since these outcomes were meant to be hypothesis generating.

For continuous outcome data, we converted medians and IQRs to means and SDs and we converted SEs to SDs. Continuous outcomes were reported using mean differences (MDs) with 95% CIs. Dichotomous outcomes were reported using risk ratios (RRs) with 95% CIs. We visually inspected forest plots for the presence of heterogeneity and quantified heterogeneity using I^2 statistics. Meta-analyses results are presented in forest plots (see supplement 5 to 12 in online supplemental file 1).

Meta-analyses might include too few participants to obtain enough statistical power for the reliable assessment of intervention effects. Even with statistically significant results, the credibility is poor when too few participants are included, and the intervention effects may be overestimated or underestimated. Trial sequential analysis calculates the required information size (the number of participants) needed to confirm or reject predefined anticipated intervention effects.[13] Furthermore, trial sequential analysis expands the CIs when the accrued information size has not reached the required information size. Trials included in meta-analyses might introduce heterogeneity, which is also accounted for in trial sequential analysis by increasing the required information size with increasing heterogeneity.[11] In an empirical review, false positive results were present in 7 out of 100 of Cochrane meta-analyses with a total of 14 false-positive meta-analytic results. Trial sequential analysis would have prevented 13 of those, had it been implemented.[23] Trial sequential analysis reduces the risk of false positive results and inaccurate effect estimates in systematic reviews of interventions.[22] We reported the Trial Sequential Analysis adjusted-confidence intervals (CIs) that accounts for the uncertainty of the effect when the accumulating data in the meta-analysis had not yet reached the required information size. We also reported trial sequential analysis-adjusted CIs, if the cumulative Z-curve crossed any of the trial sequential analysis boundaries of either benefit, harm or futility.

To assess the impact of missing data, we used 'best–worst case' and 'worst–best case' analyses.[17] We used GRADE to assess the certainty of evidence.[24 25] We downgraded the certainty of evidence by two levels due to imprecision in GRADE if the accrued number of participants was below 50% of the diversity-adjusted required information size (DARIS) and by one level if the accrued number of participants was between 50% and 100% of DARIS. We did not downgrade if the cumulative Z-curve crossed the monitoring boundaries for benefit, harm or futility, or the DARIS was reached.

Results

From our literature search, we identified 4192 records. Additionally, 11 trials were identified from other sources. After the removal of duplicates, a total of 2539 records remained. We excluded a total of 2194 records based on their title or abstract. We excluded another 236 records based on their full text, see supplement 3 in online supplemental file 1. Therefore, we included a total of 109 clinical trials randomising 26 567 participants.[20 21 26–132] Eighteen trials compared ivabradine with placebo[20 21 26 27 44 55 56 63 68 70 72 74 76 82 91 93 94 118] and 91 trials compared ivabradine with 'no intervention'. Of the 91 trials comparing ivabradine with 'no intervention', 48 trials used guideline-based therapy in both groups,[28 30 32–36 38–40 48 51 60–62 64 66 67 69 73 75 77 78 80 84–87 89 92 95–99 101 103 109 112 113 115 116 120 122 123 125 128 132] 37 trials used various beta-blockers at an equal dose in both groups other than guideline-based therapy,[29 31 41 43 45–47 49 50 52–54 57–59 71 81 83 88 90 100 102 104 106–108 110 111 114 117 119 121 124 126 127 129 131] 1 trial used cyclic AMP analogue other than guideline-based therapy,[79] 4 trials used levosimendan other than guideline-based therapy[42 65 105 130] and 1 trial used trimetazidine other than guideline-based therapy.[37] See online supplemental file 2, baseline characteristics.

The BEAUTIFUL and the SHIFT trials contributed with more than 85% wt in all primary and secondary outcome meta-analyses.[20 21] For both trials, we identified methodological limitations. First, neither of the trials were adequately registered prior to randomising the first participants in 2004 and 2006, respectively.[20 21 133–136] Therefore, it was not adequately documented that the methodology used in the trials, including some outcomes and participating centres, was predefined. Second, primarily based on the results of these two trials, we found indications of a beneficial effect of ivabradine when assessing serious adverse events (see the Results section), primarily due to ivabradine decreasing the risk of 'cardiac failure' and 'hospitalisations' (see the Serious adverse events section). However, in the two trials, it was not described how 'cardiac failure' and 'hospitalisation' were assessed during follow-up or how 'cardiac failure' and 'hospitalisation' were defined. In the BEAUTIFUL trial, all-cause hospitalisation was not reported, which raises concerns of selective outcome reporting.[20] Third, in the SHIFT substudy assessing quality of life using the Kansas City Cardiomyopathy Questionnaire (KCCQ), only 1944 participants (29.9%) of the 6505 participants analysed in the main trial were included.[137] The reason was because some countries did not participate or did not have a translated version of the KCCQ, but otherwise it was unclear how this selection of participants was conducted.[137] Fourth, for serious and non-serious adverse events, there were discrepancies between the data reported in the publication of the SHIFT trial when compared with the raw data presented on ClinicalTrials.gov, see supplement 11 in online supplemental file 1.[21 135] The BEAUTIFUL and the SHIFT trials and its authors were sponsored by the company that developed ivabradine, but the trials were otherwise judged to be at low risk of bias. All other included trials were judged to be at high risk of bias, see online supplemental file 1, risk of bias. Due to these limitations, there is a risk that we overestimate the beneficial effects and underestimate the harmful effects of ivabradine.[2 16 17]

See supplement 4 online supplemental file 1 for risk of bias graph and summary.

Primary outcomes

All-cause mortality

Two trial results were judged to be at low risk of bias (but at risk of for-profit bias).[20 21] In trials at low risk of bias, mortality occurred in 1075 (12.3 %) of 8720 in the ivabradine groups compared with 1099 (12.6 %) of 8702 in the control groups. Meta-analysis showed no evidence of a difference between ivabradine and control on all-cause mortality (RR=0.98; 95% CI 0.86 to 1.10; I^2=58%; figure 4 in online supplemental file 1). Meta-analysis of all trials showed a similar result (RR=0.94; 95% CI 0.88 to 1.01; p=0.09; 22 trials;

high certainty of evidence; figure 6 in online supplemental file 1). Visual inspection of the forest plot and I^2 statistics (I^2=12%) indicated heterogeneity that might not be important. Trial sequential analysis showed that we had enough information to reject that ivabradine reduced the risk of all-cause mortality by 15% (RR=0.94; 95% CI 0.86 to 1.03; p=0.09; I^2=16%; D^2=61%; figure 8 in online supplemental file 1). This outcome result was judged to be at low risk of bias (but at risk of for-profit bias). Incomplete outcome data alone seemed to have the potential to influence the results. Visual inspection of the funnel plot and Harbord's test (p=0.51) did not indicate funnel plot asymmetry. See summary of findings table (figure 1) and supplement 5 in online supplemental file 1.

Serious adverse events

Serious adverse events occurred in 3393 of 10 101 participants in the ivabradine groups compared with 3758 of 10 043 in the control

Patient or population: patients with heart failure
Setting: any setting
Intervention: Ivabradine
Comparison: placebo/no intervention/usual care

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo/no intervention/usual care	Risk difference with Ivabradine
All-cause mortality	19257 (22 RCTs)	⨁⨁⨁⨁ High [a,b,c]	**RR 0.94** (0.88 to 1.01)	134 per 1.000	**8 fewer per 1.000** (16 fewer to 1 more)
Serious adverse events	20144 (31 RCTs)	⨁⨁◯◯ Low [b,c,d]	**RR 0.90** (0.87 to 0.94)	374 per 1.000	**37 fewer per 1.000** (49 fewer to 22 fewer)
Quality of life (KCCQ)	1781 (2 RCTs)	⨁⨁◯◯ Low [b,e,f]	-		MD **2.92 higher** (1.34 higher to 4.5 higher)
Quality of life (MLWHFQ)	221 (4 RCTs)	⨁◯◯◯ Very low [b,g,h]	-		MD **5.28 lower** (6.6 lower to 3.96 lower)
Cardiovascular mortality	18738 (15 RCTs)	⨁⨁⨁⨁ High [a,b,c]	**RR 0.98** (0.90 to 1.06)	103 per 1.000	**2 fewer per 1.000** (10 fewer to 6 more)
Myocardial infarction	18190 (9 RCTs)	⨁⨁◯◯ Low [a,c,i]	**RR 1.00** (0.80 to 1.24)	17 per 1.000	**0 fewer per 1.000** (3 fewer to 4 more)
Non-serious adverse events	21598 (49 RCTs)	⨁⨁⨁⨁ High [a,b,c]	**RR 1.10** (1.07 to 1.12)	471 per 1.000	**47 more per 1.000** (33 more to 57 more)

*__The risk in the intervention group__ (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; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. The two largest trials weighing more than 85% in all primary and secondary outcome meta-analyses and its authors were sponsored by the company that developed ivabradine. Therefore, there was a substantial risk of for-profit bias. However, the two largest trials were otherwise at low risk of bias and the certainty of the evidence has not been downgraded due to risk of bias.
b. The accrued information size reached the required information size in Trial Sequential Analysis. Therefore, imprecision was not present.
c. I2 statistics showed no heterogeneity or heterogeneity that might not be important. Therefore, there was no inconsistency.
d. The reporting of serious adverse events was heterogeneous. The effect was mainly attributable to a reduction in hospitalisations. However, how hospitalisations were defined and assessed was not adequately reported or pre-defined. Therefore, the certainty of the evidence was downgraded by two.
e. The study accounting for 95% of weight in the meta-analysis excluded 70% of the participants originally included in the main study from the quality of life substudy due to "countries not participating or not having a translated version of the quality of life measure, otherwise it was unclear how this selection of participants was conducted. Therefore, we downgraded the certainty of the evidence by one due to risk of bias.
f. The individual effect estimates had high variability and I2 statistics showed substantial heterogeneity. Therefore, the certainty of evidence was downgraded by one due to inconsistency.
g. All trials were small and at high risk of bias. Therefore, the certainty of the evidence was downgraded by two due to risk of bias.
h. I2 statistics indicated moderate heterogeneity and two trials included an effect that was below the minimal important difference. Therefore, the certainty of the evidence was downgraded by one due to inconsistency.
i. The accrued information size was below 50% of the required information size. Therefore, severe imprecision was present and the certainty of the evidence downgraded by two.

Figure 1 Summary of findings. RR, risk ratio. RCTs, randomised clinical trials. GRADE, Grading of Recommendations Assessment, Development and Evaluation.

groups. Meta-analysis showed evidence of a beneficial effect of ivabradine versus control on serious adverse events (RR=0.90; 95% CI 0.87 to 0.94; p<0.00001; 31 trials; number needed to treat (NNT)=26.3; low certainty of evidence; figure 17 in online supplemental file 1). Visual inspection of the forest plot and I^2=37% indicated heterogeneity that might not be important. Trial sequential analysis showed that we had enough information to confirm that ivabradine decreased the risk of serious adverse events by 10% (RR=0.90; 95% CI 0.87 to 0.94; p<0.0001; I^2=37%; D^2=85%; Trial sequential analysis graph not produced due to the first trial exceeding the required information size). This outcome result was judged to be at high risk of bias. Incomplete outcome data alone did not seem to have the potential to influence the results. Visual inspection of the funnel plot and Harbord's test (p=0.32) did not indicate funnel plot asymmetry. See Summary of findings table (figure 1) and supplement 6 in online supplemental file 1.

Individual serious adverse events

The 31 trials reported on 1033 individual serious adverse events. The majority of these serious adverse events were primarily reported in the BEAUTIFUL and the SHIFT trials. For all types of individual serious adverse events, we calculated RRs, 95% CIs and p values.

Ivabradine may decrease the risk of the following adverse events classified as serious by the trialists: cardiac failure (RR=0.83; 95% CI 0.76 to 0.90; p<0.00001; I^2=41%; NNT=43.9; 5 trials), ventricular tachycardia (RR=0.59; 95% CI 0.43 to 0.81; I^2=0%; NNT=212.8; 3 trials) and hospitalisation (RR 0.89; 95% CI 0.85 to 0.94; p<0.0001; I^2=56%; NNT=37; 17 trials).

Ivabradine may increase the risk of bradycardia (RR=3.95; 95% CI 1.88 to 8.29; p=0.0003; I^2=0%; number needed to harm (NNH)=303; 3 trials).

We regarded atrial fibrillation as a serious adverse event regardless of how it was reported in the included trials. Therefore, we conducted a meta-analysis, including the highest proportion of participants with atrial fibrillation as reported in the trials. Ivabradine may increase the risk of atrial fibrillation (RR=1.17; 95% CI 1.03 to 1.32; p=0.02; I^2=0%; NNH=129.9; 10 trials).

Quality of life

Quality of life was reported using the KCCQ in two trials, including the SHIFT trial, analysing 1781 participants. Meta-analysis showed evidence of a beneficial effect of ivabradine versus control on quality of life using the KCCQ (MD=2.92; 95% CI 1.34 to 4.50; p=0.0003; low certainty of evidence; figure 27 in online supplemental figure 1). Visual inspection of the forest plot and I^2=86% indicated substantial heterogeneity. Trial sequential analysis showed that we had enough information to confirm that ivabradine increased the quality of life by 2.92 points (TSA graph not produced due to the first trial exceeding the required information size). This outcome result was judged to be at high risk of bias. Incomplete outcome data seemed to have the potential to influence the results. We predefined that we would consider the observed SD divided by '2' as the minimal important difference.[2] In the trials using the KCCQ, the observed difference between ivabradine and control was 2.92 points at follow-up. The SD was approximately 16.8 points; hence, the minimal important clinical difference was 8.4 points. Therefore, the observed difference of 2.92 points at follow-up was only one-third of the minimal important difference.

Quality of life was reported using the MLWHFQ in 4 trials randomising 221 participants. In three trials, it was unclear whether SDs or SEs were reported and these were excluded from the analyses.[33 80 92] Meta-analysis showed evidence of a difference between ivabradine and control on quality of life using the MLWHFQ (MD=−5.28; 95% CI −6.60 to −3.96; p<0.00001; very low certainty of evidence; figure 32 in online supplemental figure 1). Visual inspection of the forest plot and I^2=35% indicated moderate heterogeneity. Trial sequential analysis showed that we had enough information to confirm MD of 5.28 points by ivabradine (MD=−5.28; 95% CI −7.32 to −3.24; p<0.0001; I^2=35%; D^2=52%; figure 34 in online supplemental figure 1). This outcome result was judged to be at high risk of bias. Incomplete outcome data alone did not seem to have the potential to influence the results. In the trials using MLWHFQ, the observed difference between ivabradine and control was 5.28 points at follow-up. The SD was 3.70; hence, the minimal important difference was 1.85 points. The observed difference of 5.28 points was above the minimal important difference. However, the evidence was very uncertain. See Summary of findings table (figure 1) and supplement 7 in online supplemental file 1.

Secondary outcomes

Cardiovascular mortality

Two trial results were judged to be at low risk of bias (but at risk of for-profit bias).[20 21] In trials at low risk of bias, cardiovascular mortality occurred in 918 (10.6 %) of 8720 in the ivabradine groups compared with 926 (10.6%) of 8702 in the control groups. Meta-analysis showed no evidence of a difference between ivabradine and control on cardiovascular mortality (RR=0.99; 95% CI 0.86 to 1.15; p=0.91; I^2=66%; figure 39 in online supplemental file 1). Meta-analysis of all trials showed showed a similar result (RR=0.98; 95% CI 0.90 to 1.06; p=0.58; 15 trials; high certainty of evidence; figure 41 in online supplemental file 1). Visual inspection of the forest plot and I^2=7% indicated heterogeneity that might not be important. Trial sequential analysis showed that we had enough information to reject that ivabradine reduced the risk of cardiovascular mortality by 15% when compared with control (RR=0.98; 95% CI 0.88 to 1.08; p=0.58; I^2=7%; D^2=49%; figure 43 in online supplemental file 1). This outcome result was judged to be at low risk of bias (but at risk of for-profit bias). Incomplete outcome data alone did not seem to have the potential to influence the results. Visual inspection of the funnel plot and Harbord's test (p=0.36) did not indicate funnel plot asymmetry. See Summary of findings table (figure 1) and supplement 8 in online supplemental file 1.

Myocardial infarction

Two trial results were judged to be at low risk of bias (but at risk of for-profit bias).[20 21] In trials at low risk of bias, myocardial infarction occurred in 144 (1.7%) of 8709 in the ivabradine groups compared with 142 (1.6%) of 8690 in the control groups. Meta-analysis showed no evidence of a difference between ivabradine and control on myocardial infarction (RR=1.01; 95% CI 0.80 to 1.27; p=0.92; I^2=0%; figure 49 in online supplemental file 1). Meta-analysis of all trials showed a similar result (RR=1.00; 95% CI 0.80 to 1.24; p=0.96; 9 trials; low certainty of evidence; figure 50 in online supplemental file 1). Visual inspection of the forest plot and I^2=0% indicated no heterogeneity. Trial sequential analysis showed that we did not have enough information to reject that ivabradine reduced the risk of myocardial infarction by 15% when compared with control (RR=1.01; 95% CI 0.41 to 2.43; p=0.83; I^2=0%; D^2=0%; figure 52 in online supplemental file 1). This outcome result was judged to be at low risk of bias (but at risk of for-profit bias). Incomplete outcome data alone seemed to have

the potential to influence the results. See Summary of findings table (figure 1) and supplement 9 in online supplemental file 1.

Non-serious adverse events

Two trial results were judged to be at low risk of bias (but at risk of for-profit bias).[20 21] In trials at low risk of bias, non-serious adverse events occurred in 5264 (60.4%) of 8709 participants in the ivabradine groups compared with 4798 (55.2%) of 8690 participants in the control groups. Meta-analysis showed evidence of a harmful effect of ivabradine versus control on non-serious adverse events (RR=1.10; 95% CI 1.00 to 1.21; p=0.05; I^2=93%; figure 57 in online supplemental file 1). Meta-analysis of all trials showed a similar result (RR=1.10; 95% CI 1.07 to 1.12; p<0.00001; NNH=22.5; 49 trials; high certainty of evidence; figure 59 in online supplemental file). Visual inspection of the forest plot and I^2=12% indicated heterogeneity that might not be important. Trial sequential analysis showed that we had enough information to confirm that ivabradine increased the risk of non-serious adverse events by 10% when compared with control (RR=1.10; 95% CI 1.07 to 1.12; p<0.0001; I^2=12%; D^2=83%; figure 61 in online supplemental file 1). This outcome result was judged to be at low risk of bias (but at risk of for-profit bias). Incomplete outcome data alone did not seem to have the potential to influence the results. Visual inspection of the funnel plot and Harbord's test (p=0.21) did not indicate funnel plot asymmetry. See Summary of findings table (figure 1) and supplement 10 in online supplemental file 1.

Individual non-serious adverse events

Ivabradine may increase the risk of 'bradycardia' (RR=1.62; 95% CI 1.01 to 2.60; p=0.05; I^2=45%; NNH=39.4; 25 trials), 'heart rate decreased' (RR=4.32; 95% CI 3.39 to 5.50; I^2=0%; NNH=33; 3 trials), and phosphenes (RR=4.71; 95% CI 3.67 to 6.04; p<0.00001; I^2=0%; NNH=33.8; 20 trials).

Ivabradine may decrease the risk of 'sinus tachycardia' (RR=0.39; 95% CI 0.27 to 0.56; p<0.00001; NNT=52.4; 2 trials) and 'hypotension' (RR=0.70; 95% CI 0.55 to 0.90; I^2=0%; NNT=192.3; 5 trials).

Exploratory outcomes

The results of our exploratory outcomes are reported in supplement 12 in online supplemental file 1.

Subgroup analyses

We predefined several subgroup analyses for the primary outcomes.[2]

When assessing all-cause mortality, test for subgroup differences (p=0.06) suggested a difference between trials administering ivabradine at or above median duration (RR=0.95; 95% CI 0.88 to 1.02) compared with trials administering ivabradine below median duration (RR=0.47; 95% CI 0.23 to 0.99).

When assessing serious adverse events, test for subgroup differences (p=0.005) suggested a difference between trials administering ivabradine at or above median duration (RR=0.92; 95% CI 0.88 to 0.95) compared with trials administering ivabradine below median duration (RR=0.53; 95% CI 0.36 to 0.77).

When assessing quality of life on the KCCQ, test for subgroup differences (p=0.007) suggested a potential difference between trials administering ivabradine at or above median duration (MD=2.40; 95% CI 0.77 to 4.03) compared with trials administering ivabradine below median duration (MD=12.00; 95% CI 5.23 to 18.77). When assessing quality of life on the MLWHFQ, test for subgroup differences (p=0.05) suggested a potential difference between trials administering ivabradine at or above median duration (MD=−13.80; 95% CI −23.17 to −4.44) compared with trials administering ivabradine below median duration (MD=−1.14; 95% CI −9.90 to 7.61).

See the respective supplementary sections for all-cause mortality, serious adverse events and quality of life for all subgroup analyses.

For all other subgroup analyses, test for subgroup differences did not show evidence of a difference between the subgroups or the subgroup analyses could not be conducted.

Discussion

The objective of our systematic review was to assess both the beneficial and harmful effects of adding ivabradine to usual care versus usual care with or without placebo in people with heart failure. We included 109 randomised clinical trials randomising 26 567 people with heart failure. All trials were judged to be at high risk of bias, except for the BEAUTIFUL and the SHIFT trials that were judged to be at low risk of bias (but at risk of for-profit bias).[18 20 21] The BEAUTIFUL and the SHIFT trials accounted for more than 85% of weight in most meta-analysis and we did, therefore, now downgrade the certainty of the evidence due to risk of bias for most outcomes. However, we downgraded the certainty of the evidence for serious adverse events due to methodological limitations regarding the reporting of serious adverse events (see second paragraph of the Results section). Our results must be interpreted in the light of the high risks of bias and risks of for-profit bias that might result in overestimation of beneficial effects and underestimation of harmful effect of ivabradine. Due to the BEAUTIFUL and the SHIFT trials contributing with more than 85% of weight in all primary and secondary outcome meta-analyses, the results and conclusions presented in this systematic review can mostly be applied to people matching the populations in the BEAUTIFUL and the SHIFT trials.

Our results showed that ivabradine does not seem to affect the risks of all-cause mortality, cardiovascular mortality and myocardial infarction. Ivabradine seemed to decrease the risk of serious adverse events, primarily due to a decrease in the risk of 'cardiac failure', 'hospitalisations' and 'ventricular tachycardia'. However, in the BEAUTIFUL and the SHIFT trials, and in the other trials reporting these outcomes, it was not described how these outcomes were assessed during follow-up or how the outcomes were defined. The effects on quality of life using the KCCQ were small and possibly without relevance to patients. The effects on quality of life using the MLWHFQ were very uncertain. Ivabradine seemed to increase the risk of atrial fibrillation, bradycardia, and non-serious adverse events. See Summary of findings table (figure 1).

Our systematic review has strengths. First, we predefined our methodology in detail in a protocol that was published prior to conducting the literature search.[2 16] Second, we identified a total of 109 trials, which is more than any other previous systematic review on the topic. This has increased our precision and, therefore, strengthened our results. The recently published Cochrane review only identified 19 trials with 19 628 participants (90 trials less than ours).[9] Third, we used trial sequential analysis on both primary and secondary outcomes[11] and we adjusted our thresholds for statistical significance for the primary outcomes[13] to control the risks of random errors. Fourth, we judged the risk of bias of all included trials to assess the risks of systematic errors.[24 25]

Fifth, we used our eight-step procedure to assess if the thresholds for statistical and clinical significance were crossed.[13] Moreover, we included all randomised clinical trials identified through our literature search without imposing restrictions on their publication type, status, language and their reporting of outcomes. We attempted to contact the authors of the trials if data were incomplete or additional information was needed.

Our review also has limitations. First, all the included trials were judged to be at a high risk of bias as well as having a high risk of selective outcome reporting bias and for-profit bias.[18] Nine of the trials were in some way sponsored by the company that developed ivabradine, including the BEAUTIFUL and the SHIFT trials that randomised 17 475 participants, accounting for more than 85% in all primary and secondary meta-analysis.[20 21 55 63 70 74 81 93] Research has shown that drug trials funded by manufacturing companies tend to show more favourable efficacy results than trials funded by other sources.[18] Moreover, 18 trials were reported only as abstracts which made the interpretation of methodology and results problematic.[26 28–32 34 39 44 73 91 95 96 99 100 138–140] Therefore, there is a risk that our results are also biased and, therefore, overestimate the beneficial effects of ivabradine and underestimate the harmful effects.[18 141–146]

Conclusion and relevance

High certainty evidence shows that ivabradine does not seem to affect the risks of all-cause mortality and cardiovascular mortality. The effects on quality of life were small and possibly without relevance to patients on the KCCQ and were very uncertain for the MLWHFQ. The effects on serious adverse events, myocardial infarction and hospitalisation are uncertain. Ivabradine seems to increase the risk of atrial fibrillation, bradycardia and non-serious adverse events,

Differences between the protocol and the systematic review

We conducted our literature search in parallel with another systematic review on the effects of adding ivabradine to usual care in participants with angina pectoris due to coronary artery disease.[147] We originally planned to analyse and report the results, including participants with coronary artery disease and participants with heart failure into one review, but due to clinical and statistical heterogeneity, we decided to report the results in two separate reviews.[2]

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Acknowledgements We would like to thank Liliya Ziganshina for assisting us with screening and data extracting articles in Russian.

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Funding This study was funded by the Copenhagen Trial Unit, Centre for Clinical Intervention Research, through wages paid to JCJ and CG. The funding is through the Danish Finance Act and the funding source had no influence on the systematic review.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. All data in the systematic review will be made available upon reasonable request to the corresponding author.

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Ivabradine added to usual care in patients with heart failure: a systematic review with meta-analysis and Trial Sequential Analysis – supplementary material

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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)
- Web of Science Core Collection
- Web of Science BIOSIS
- ClinicalTrials.gov
- Google Scholar
- 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)
- 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

MEDLINE 31/05/2021, n = 422

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

EMBASE 31/05/2021, n = 1401

4. (ivabradin* or corlanor or procoralan or corlentor).af
5. (random* or blind* or placebo* or meta-analys* or systematic review).af.
6. 1 and 2

Web of Science Core Collection 31/05/2021, n = 633

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

Web of Science BIOSIS previews 31/05/2021, n = 50

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

LILACS 31/05/2021, n = 25

1. Ivabradine
2. Ivabradina
3. 1 or 2

CENTRAL 31/05/2021, n = 638

1. (Ivabradin* or corlanor or Procoralan or corlentor)

EudraCT 31/05/2021, n = 46

1. ivabradine OR corlanor OR procoralan OR corlentor

ClinicalTrials.gov 31/05/2021, n = 80

1. Ivabradine (also searched for Procoralan Corlanor, Ivabradin, Corlentor, S 16257)
2. Interventional studies

Chinese Biomedical Literature Database (CBM/Sinomed), n = 140

#1 (((“伊伐布雷定”[全字段:智能]) OR “可兰特”[全字段:智能]) OR “依伐布雷定”[全字段:智能]) OR “伊法布雷定”[全字段:智能]

#2 ((“心衰”[全字段:智能]) OR “心脏衰竭”[全字段:智能]) OR “心力衰竭”[全字段:智能]

#3 (((“冠状动脉”[全字段:智能]) OR “冠脉疾病”[全字段:智能]) OR “冠脉病”[全字段:智能]) OR “冠心病”[全字段:智能]

#4 ((((((“心绞痛”[全字段:智能]) OR “心肌梗死”[全字段:智能]) OR “心肌梗塞”[全字段:智能]) OR “心肌缺血”[全字段:智能]) OR “缺血性心肌病”[全字段:智能]) OR “心源性水肿”[全字段:智能]) OR “心肾综合征”[全字段:智能]

#5 (#4) OR (#3) OR (#2)

#6 (((((((“随机”[全字段:智能]) OR “meta-分析”[全字段:智能]) OR “meta分析”[全字段:智能]) OR “系统综述”[全字段:智能]) OR “荟萃分析”[全字段:智能]) OR “系统评价”[全字段:智能]) OR “安慰剂”[全字段:智能]) OR “盲法”[全字段:智能]

#7 (#6) OR (#5) OR (#1)

Chinese Science Journal Database (VIP), n = 165

(U=伊伐布雷定 OR 可兰特 OR 依伐布雷定 OR 伊法布雷定) AND (U=(心衰 OR 心脏衰竭 OR 心力衰竭 OR 心源性水肿 OR 心肾综合征 OR 冠状动脉 OR 冠心病 OR 冠脉病 OR 冠脉疾病 OR 心肌缺血 OR 缺血性心肌病 OR 心绞痛 OR 心肌梗死 OR 心肌梗塞 OR 心功能不全) OR R=(心衰 OR 心脏衰竭 OR 心力衰竭 OR 心源性水肿 OR 心肾综合征 OR 冠状动脉 OR 冠心病 OR 冠脉病 OR 冠脉疾病 OR 心肌缺血 OR 缺血性心肌病 OR 心绞痛 OR 心肌梗死 OR 心肌梗塞 OR 心功能不全)) AND (R=(随机 OR meta-分析 OR meta分析 OR 荟萃分析 OR 系统评价

OR 系统综述 OR 安慰剂 OR 盲法) OR U=(随机 OR meta-分析 OR meta分析 OR 荟萃分析 OR 系统评价 OR 系统综述 OR 安慰剂 OR 盲法))

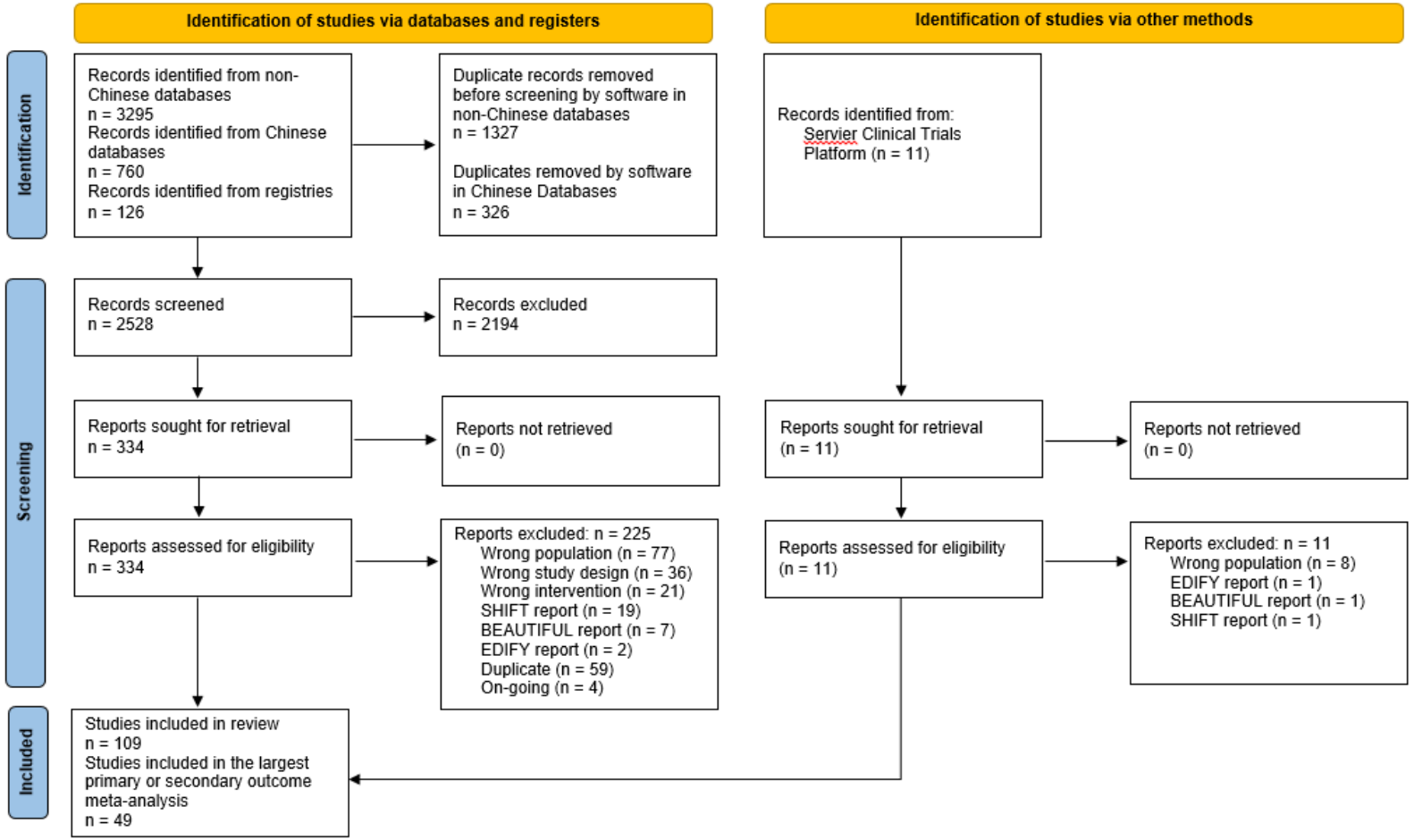
China National Knowledge Infrastructure (CNKI), n = 255

SU=('伊伐布雷定'+'可兰特'+'依伐布雷定'+'伊法布雷定') AND SU=('心衰'+'心脏衰竭'+'心力衰竭'+'心源性水肿'+'心肾综合征'+'冠状动脉*'+'冠心病'+'冠脉病'+'冠脉疾病'+'心肌缺血'+'缺血性心肌病'+'心绞痛'+'心肌梗死'+'心肌

Wanfang, n = 200

主题:(伊伐布雷定 + 可兰特 + 依伐布雷定 + 伊法布雷定) * 主题:(心衰 + 心脏衰竭 + 心力衰竭 + 心源性水肿 + 心肾综合征 + 冠状动脉 + 冠心病 + 冠脉疾病 + 冠脉病 + 心肌缺血 + 心绞痛 + 心肌梗死 + 缺血性心肌病 + 心肌梗塞 + 心功能不全) * 全部:(随机 + meta-分析 + meta分析 + 荟萃分析 + 系统评价 + 系统综述 + 安慰剂 + 盲法)

Supplement 3 – PRISMA flow chart



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 1 – PRISMA flowchart.

Supplement 4 - Risk of bias

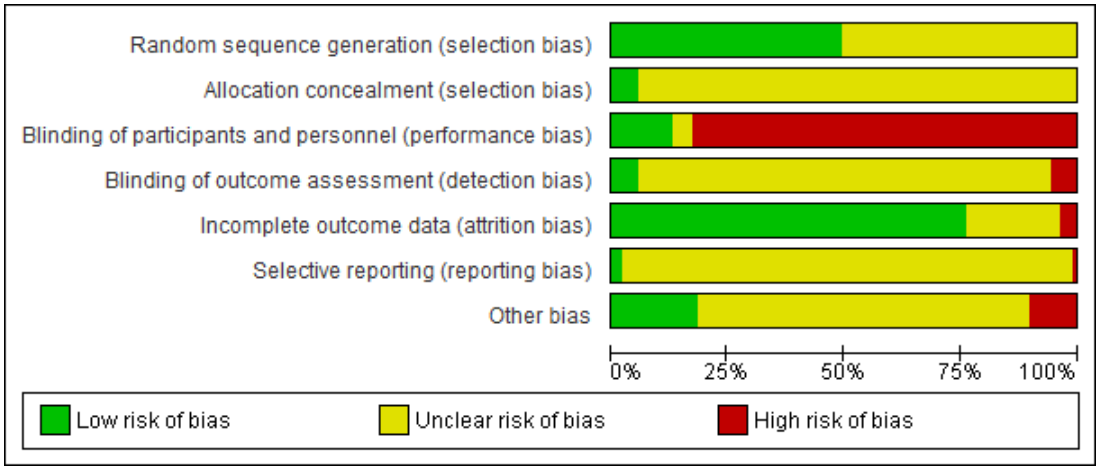
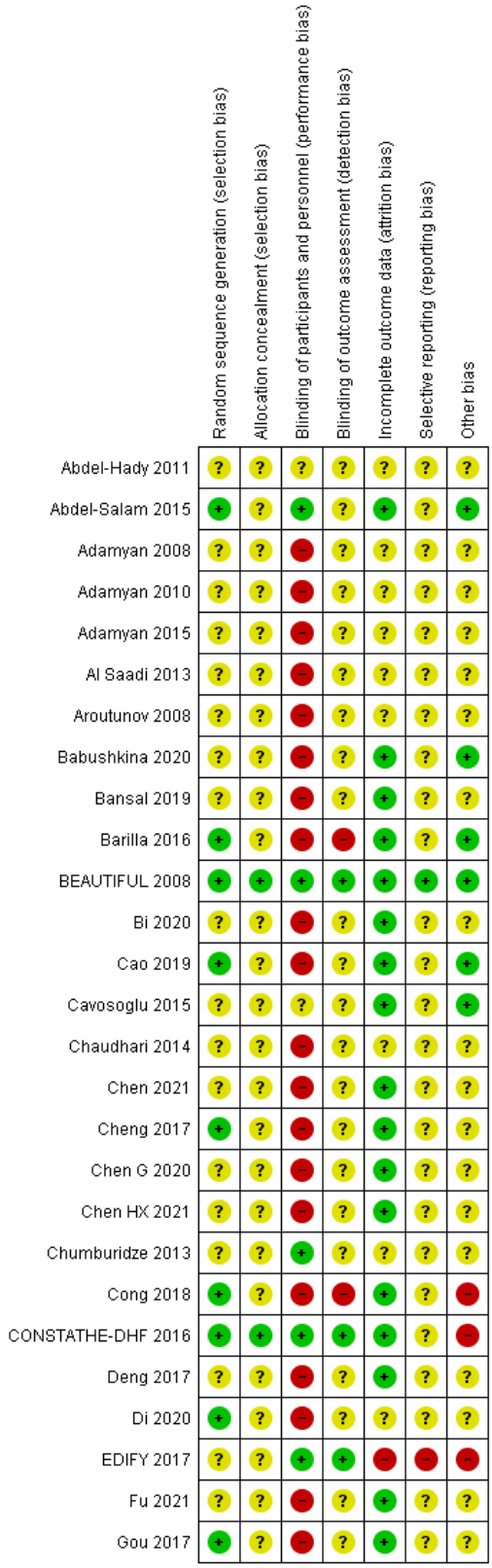
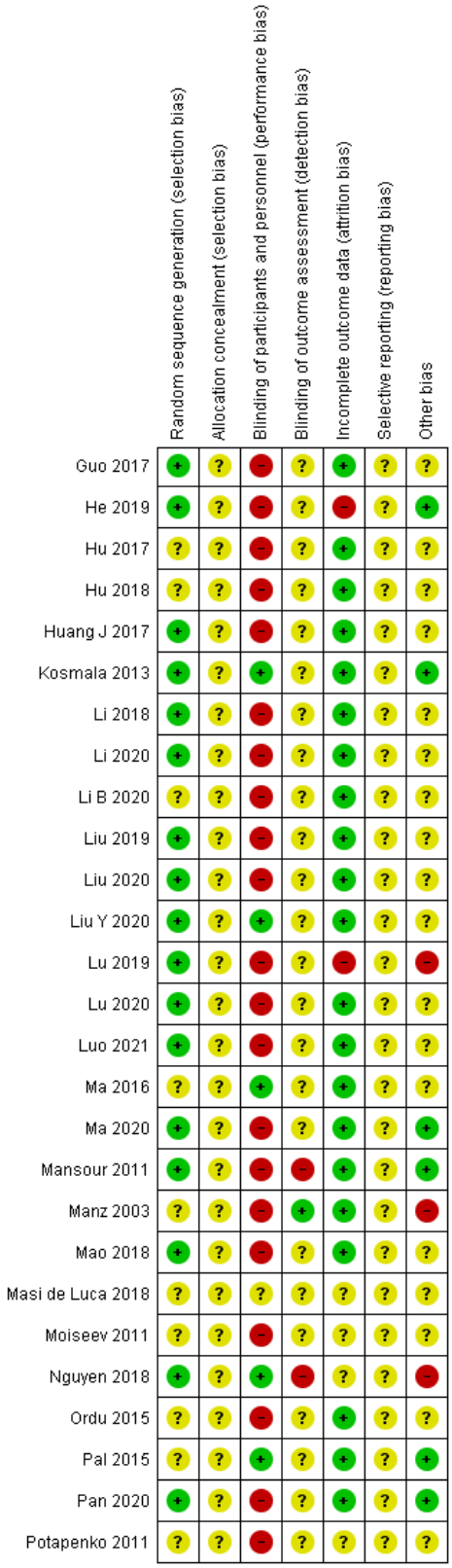


Figure 2 – Risk of bias graph.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Abdel-Hady 2011
Abdel-Salam 2015
Adamyan 2008
Adamyan 2010
Adamyan 2015
Al Saadi 2013
Aroutunov 2008
Babushkina 2020
Bansal 2019
Barilla 2016
BEAUTIFUL 2008
Bi 2020
Cao 2019
Cavosoglu 2015
Chaudhari 2014
Chen 2021
Cheng 2017
Chen G 2020
Chen HX 2021
Chumburidze 2013
Cong 2018
CONSTATHE-DHF 2016
Deng 2017
Di 2020
EDIFY 2017
Fu 2021
Gou 2017


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Guo 2017
He 2019
Hu 2017
Hu 2018
Huang J 2017
Kosmala 2013
Li 2018
Li 2020
Li B 2020
Liu 2019
Liu 2020
Liu Y 2020
Lu 2019
Lu 2020
Luo 2021
Ma 2016
Ma 2020
Mansour 2011
Manz 2003
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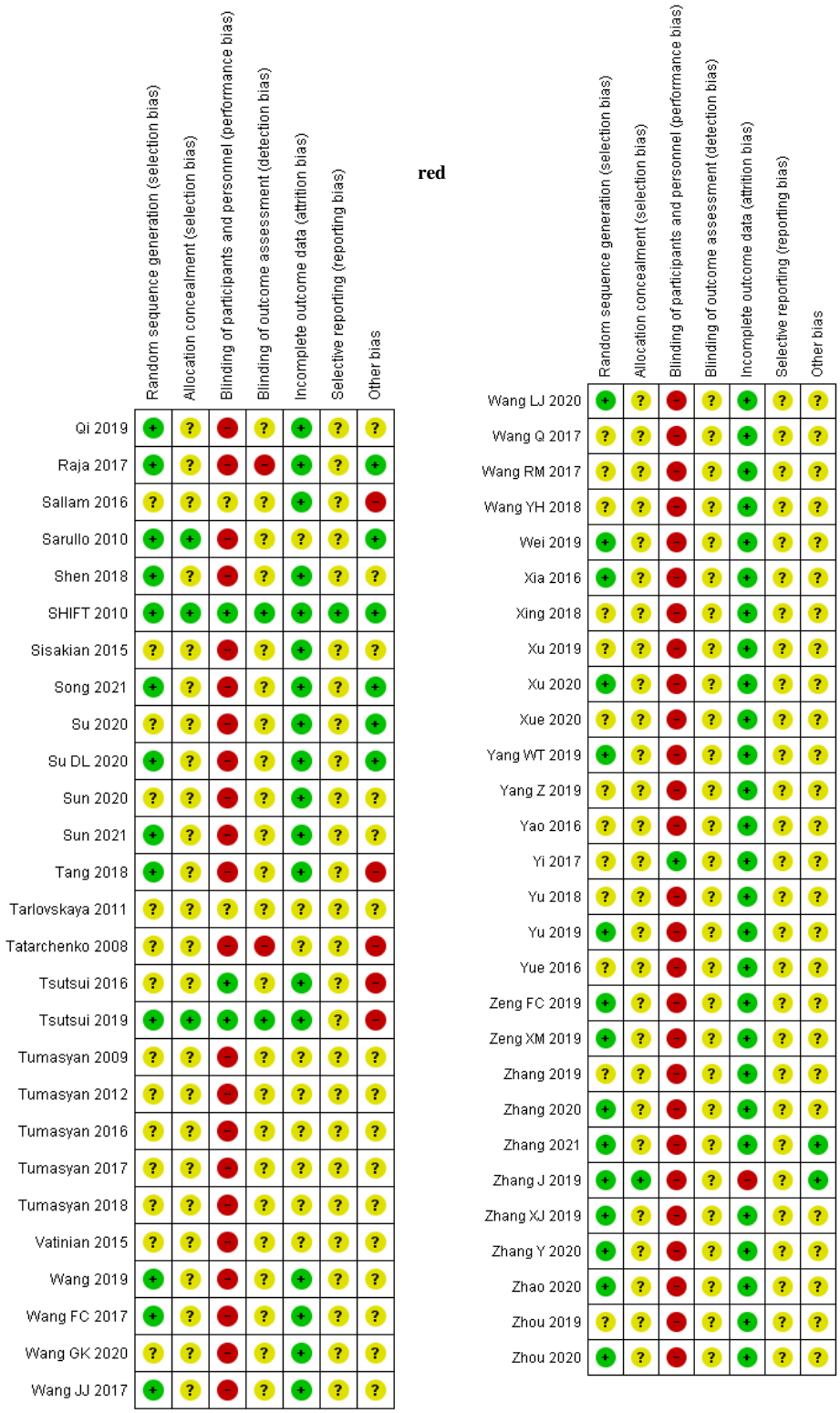
Masi de Luca 2018
Moiseev 2011
Nguyen 2018
Ordu 2015
Pal 2015
Pan 2020
Potapenko 2011



red

Figure 3 – Risk of bias summary. Green circles = low risk of bias; yellow circles = unclear risk of bias; circles = high risk of bias.

Supplement 5 - All-cause mortality

Main analyses

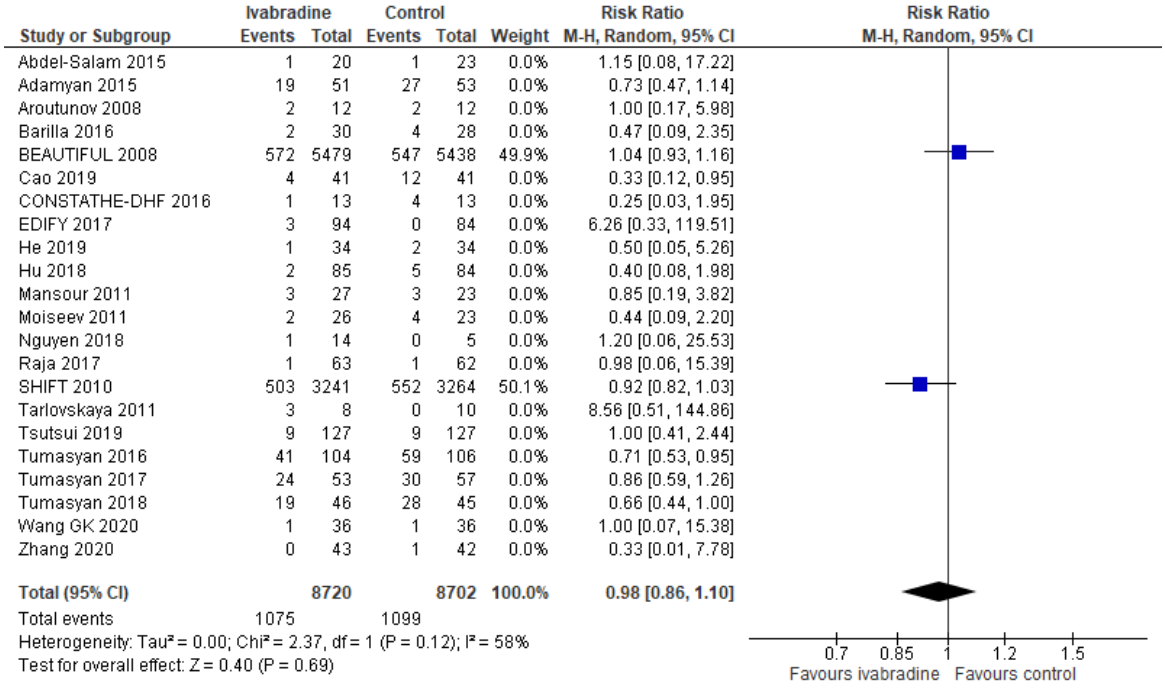


Figure 4 – Forest plot of the meta-analysis of all-cause mortality using random-effecs meta-analysis including only trials at low risk of bias, except for for-profit bias. The meta-analysis showed no evidence of an difference between ivabradine versus placebo.

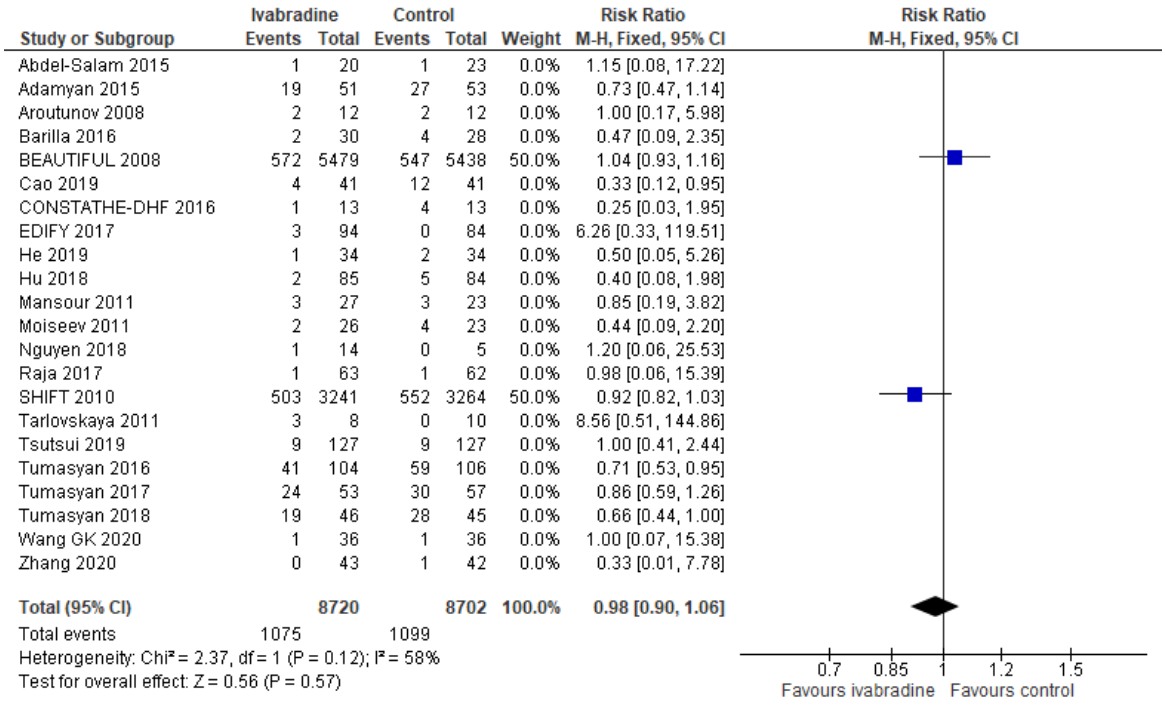


Figure 5 – Forest plot of the meta-analysis of all-cause mortality using fixed-effect meta-analysis including only trials at low risk of bias, except for for-profit bias. The meta-analysis showed no evidence of a difference between ivabradine versus placebo.

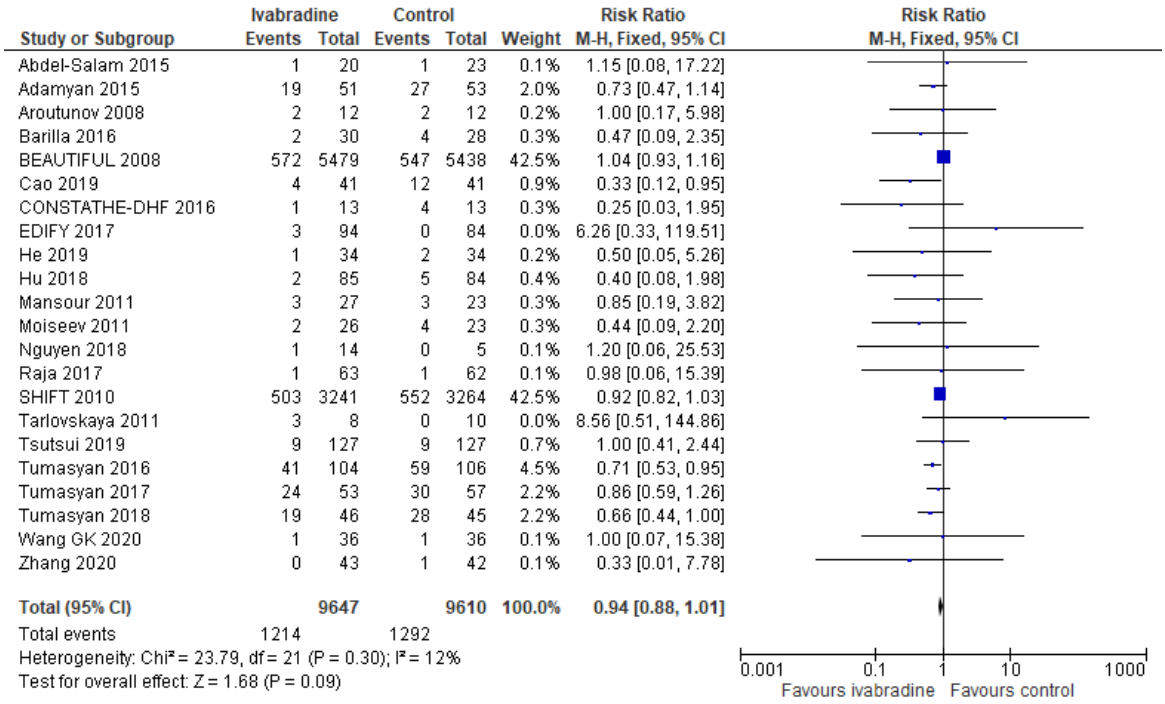


Figure 6 - Forest plot of the meta-analysis of all-cause mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

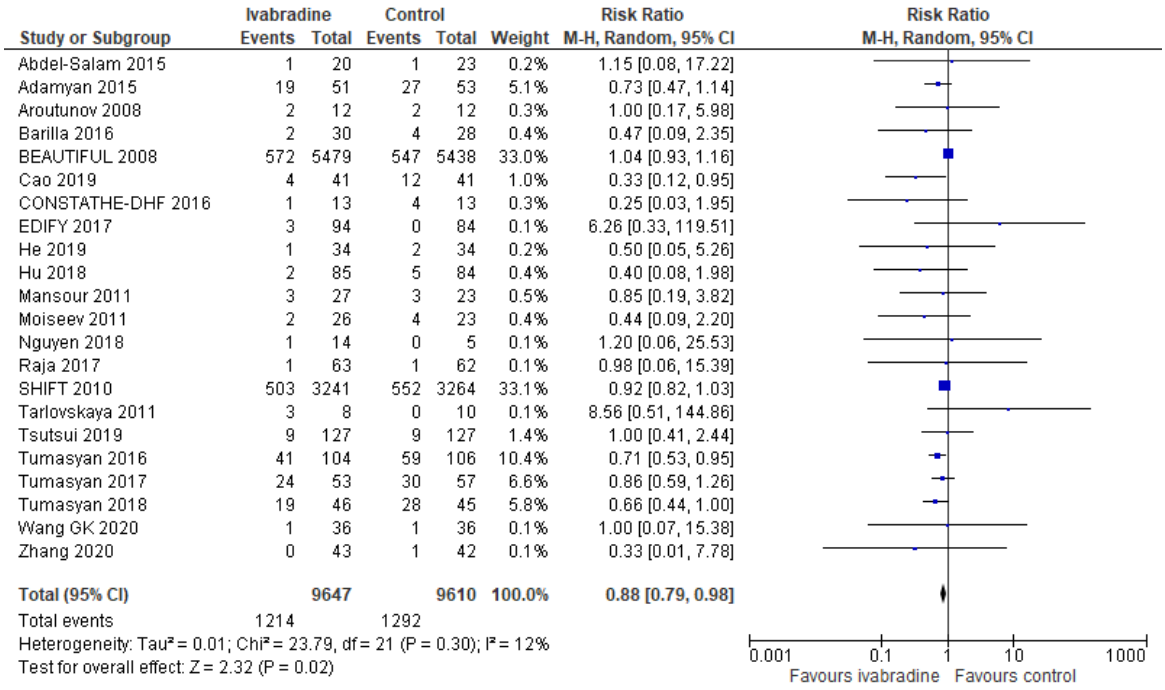


Figure 7 - Forest plot of the meta-analysis of all-cause mortality using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

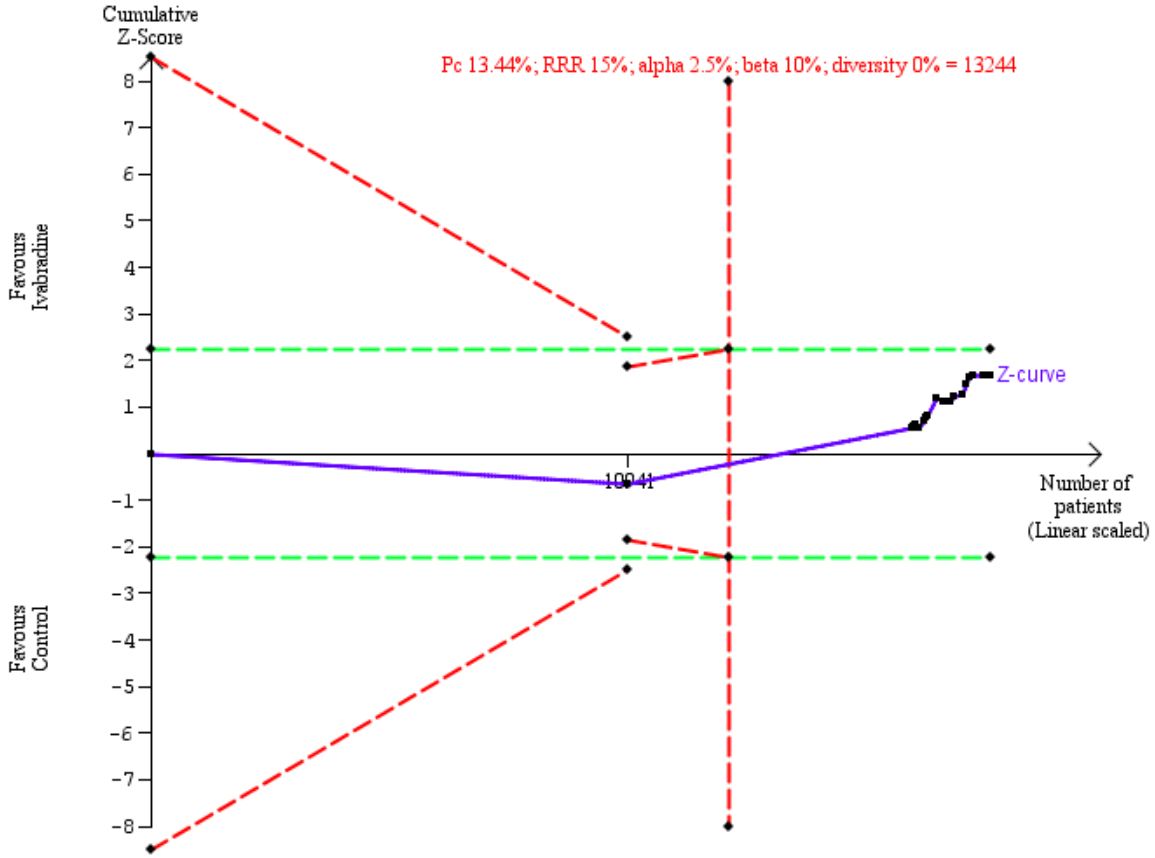


Figure 8 - Trial Sequential Analysis graph of all-cause mortality. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) breaches the boundary of futility and the required information size. Pc: prevalence in control group; RRR: relative risk ratio.

Sensitivity analyses

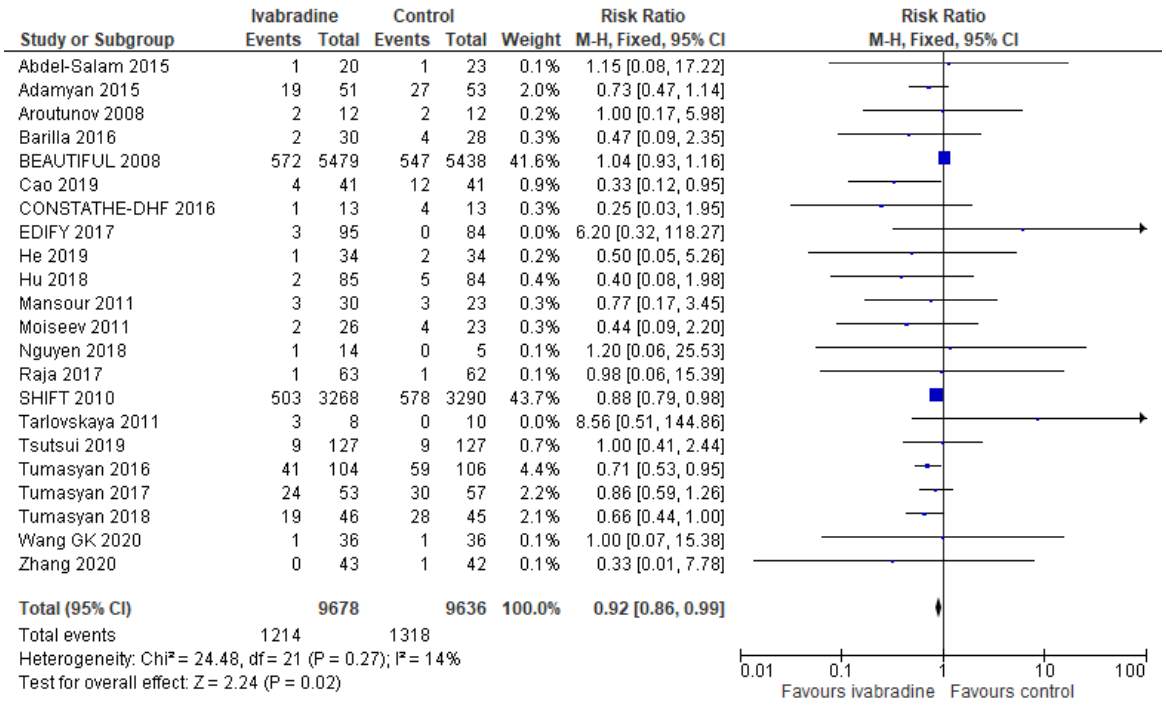


Figure 9 - Forest plot of the sensitivity analysis of all-cause mortality using best- compared with worst-case scenario.

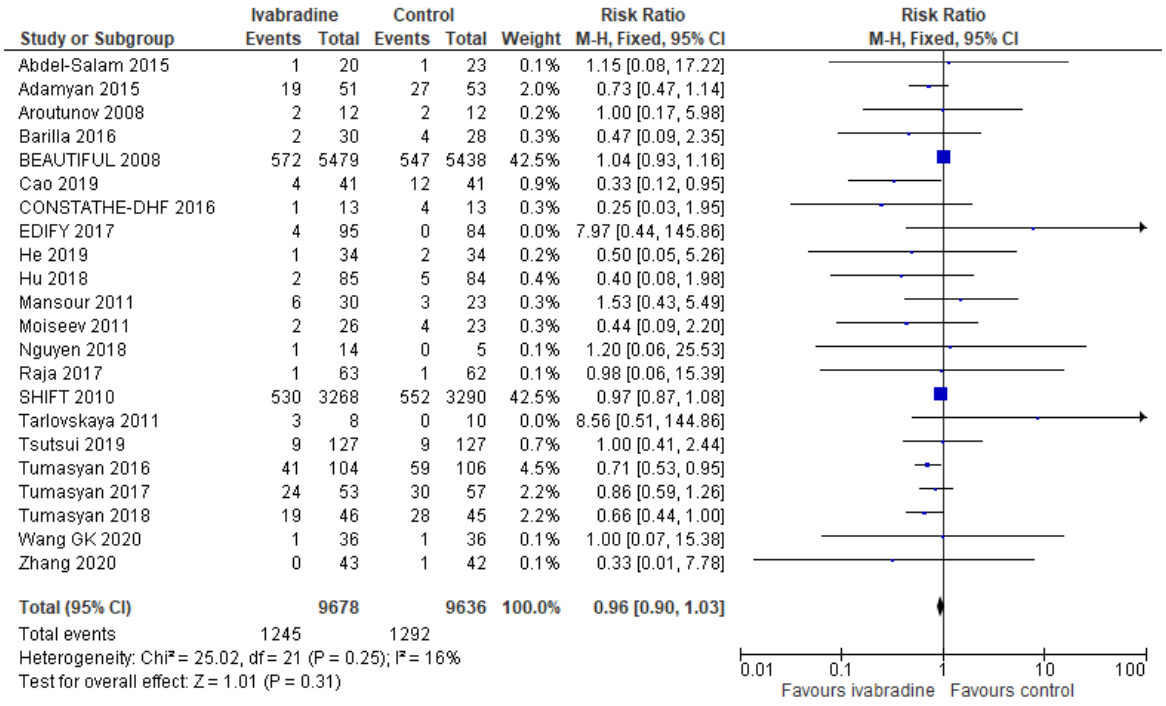


Figure 10 - Forest plot of the sensitivity analysis of all-cause mortality using worst- compared with best-case scenario.

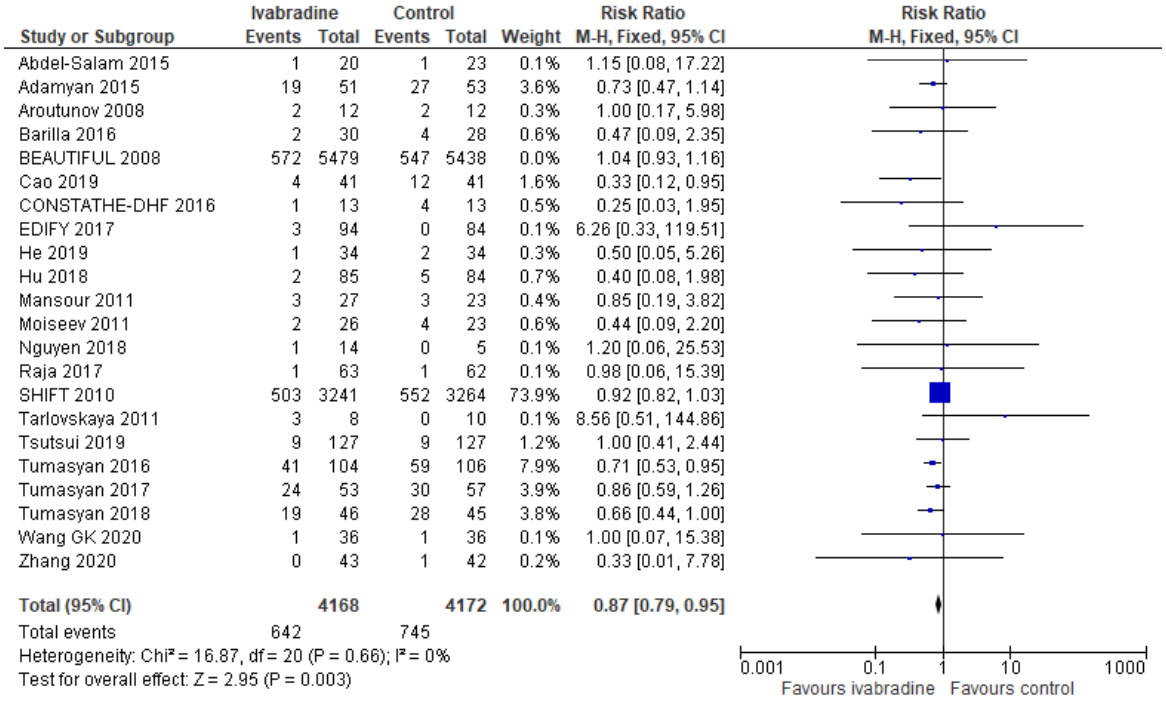


Figure 11 – Forest plot of the sensitivity analysis of all-cause mortality removing the BEAUTIFUL trial.

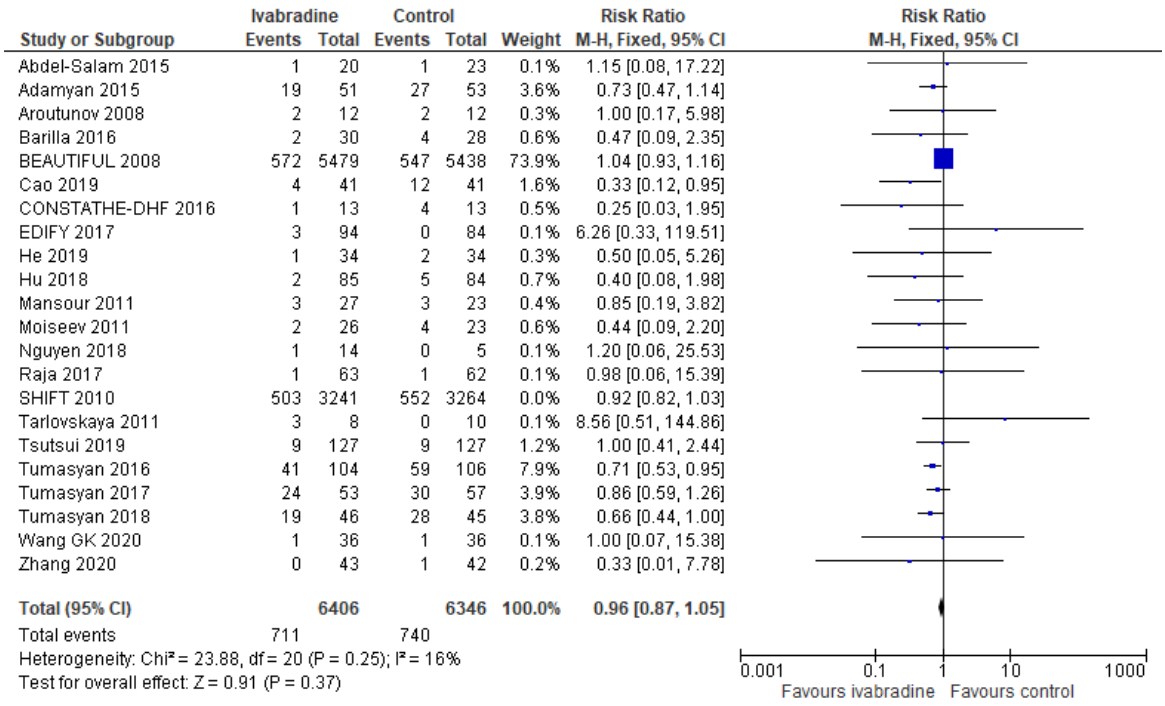


Figure 12 – Forest plot of the sensitivity analysis of all-cause mortality removing the SHIFT trial.

Subgroup analyses

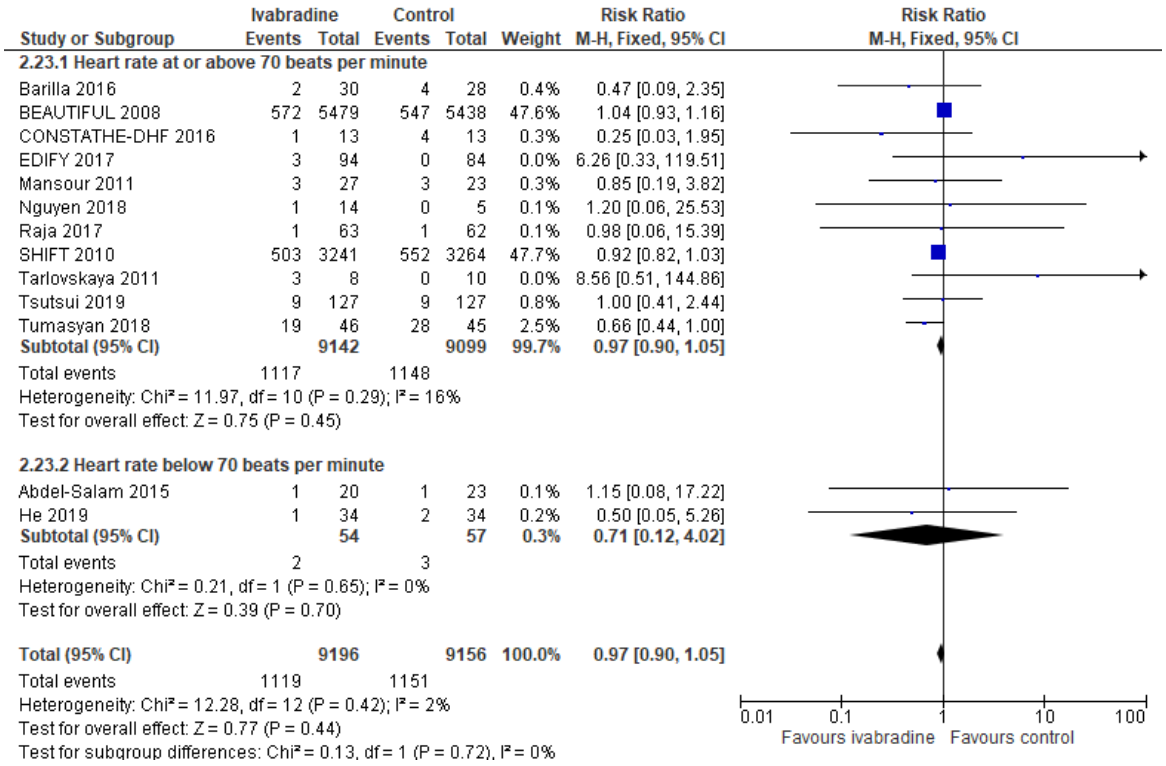


Figure 13 – Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared to trials randomising participants with heart rate below 70 beats per minute on all-cause mortality.

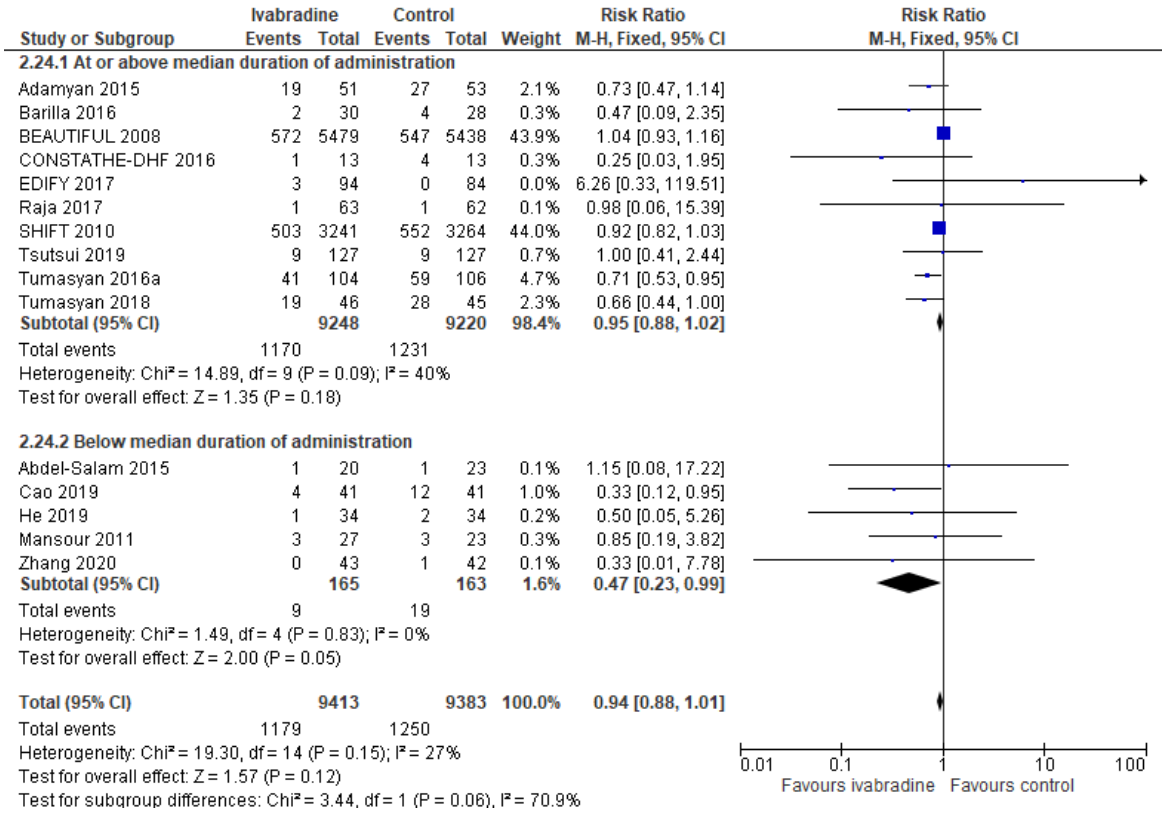


Figure 14 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (182.64 days) versus trials administering ivabradine below median duration on all-cause mortality.

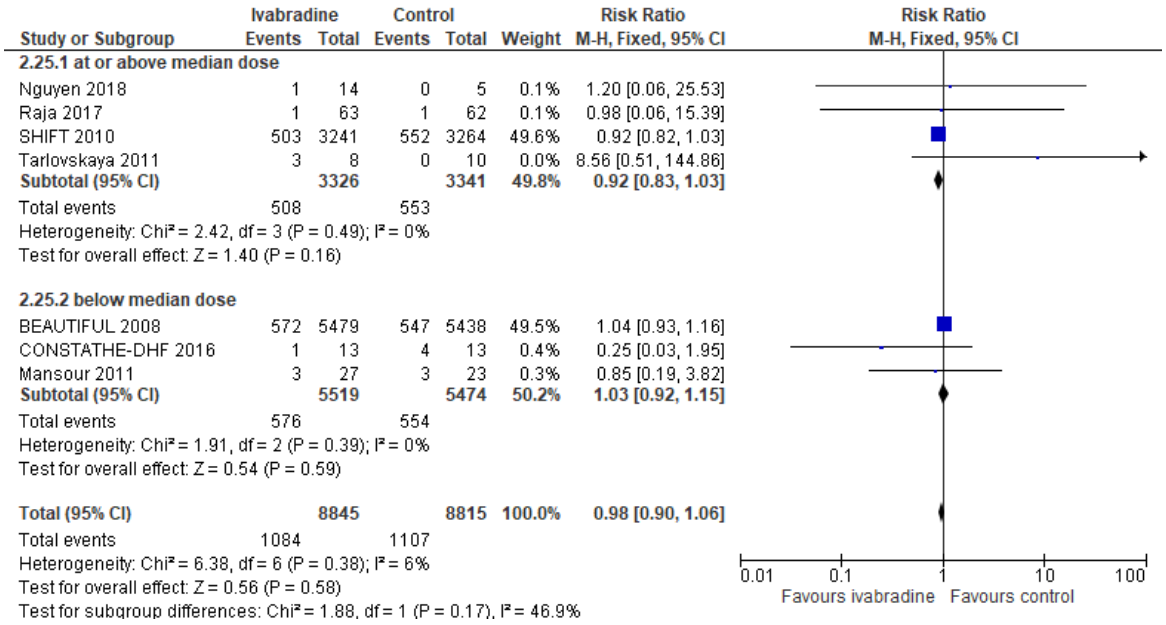


Figure 15 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose (12.7 mg) compared to trials administering ivabradine below median daily dose on all-cause mortality.

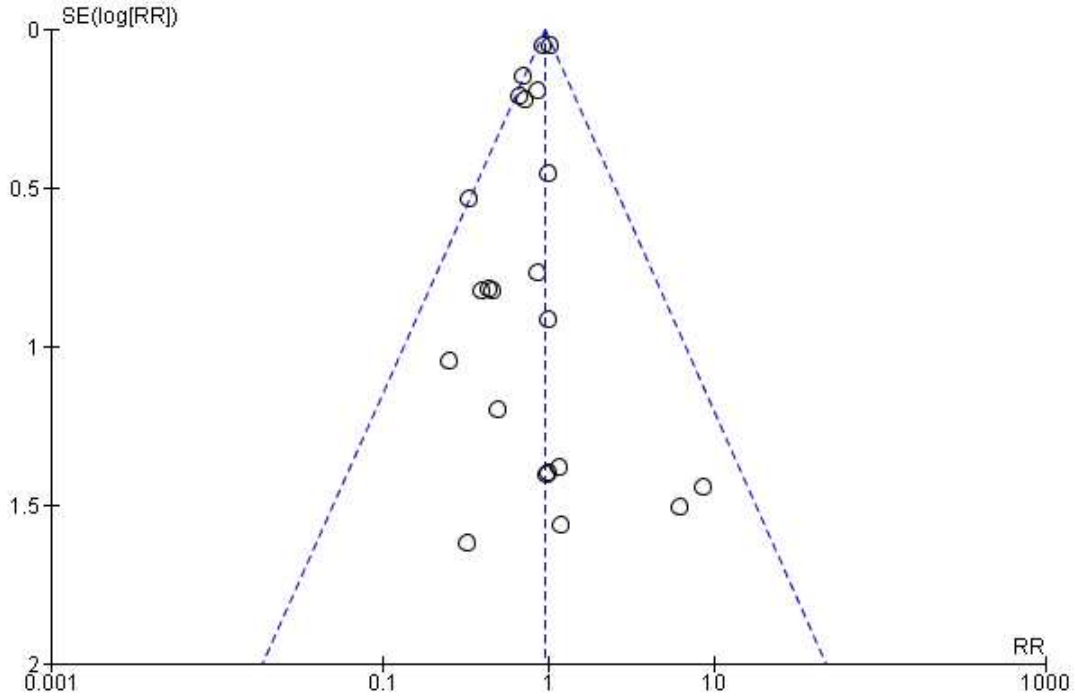


Figure 16 – Funnel plot of the analyses of all-cause mortality. The funnel plot did not indicate small study bias.

Supplement 6 - Serious adverse events

Main analyses

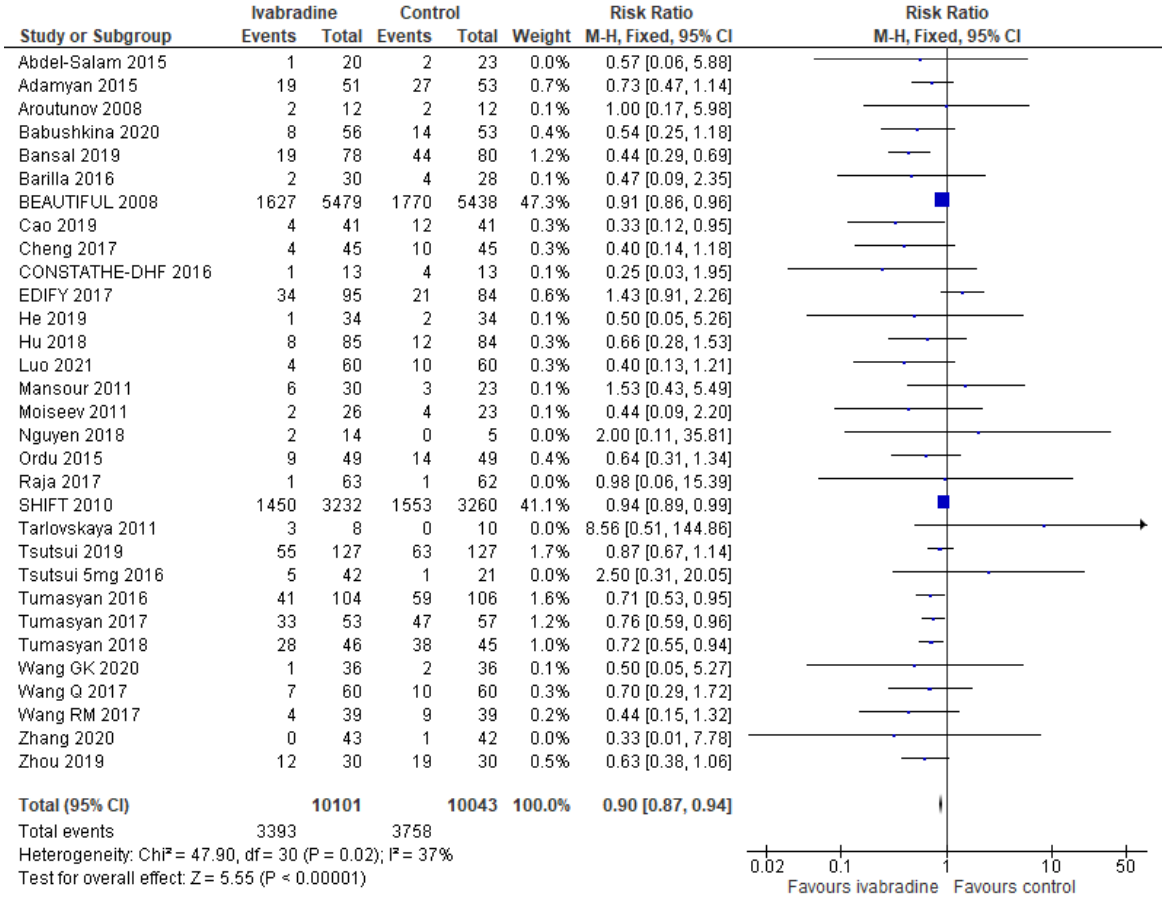


Figure 17 - Forest plot of the meta-analysis of serious adverse events using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

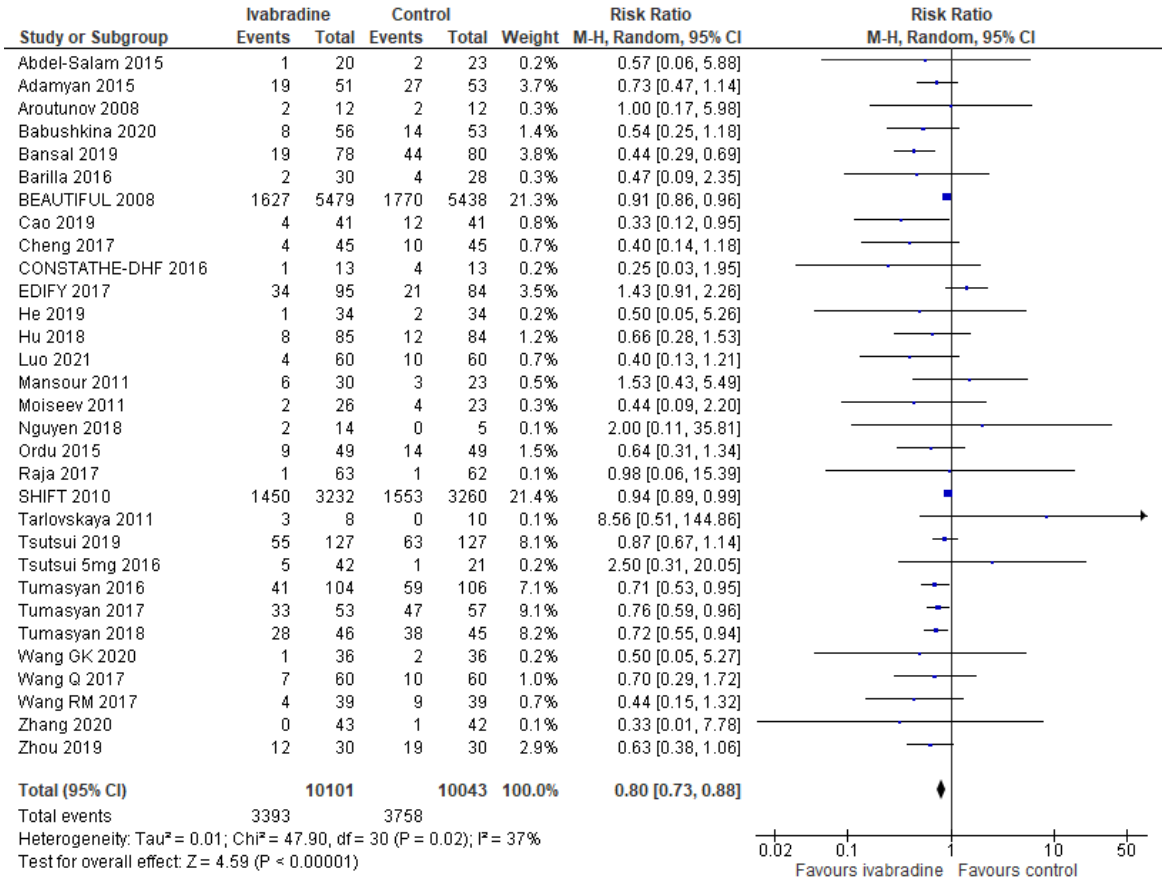


Figure 18 – Forest plot of the meta-analysis of serious adverse events using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

Sensitivity analyses

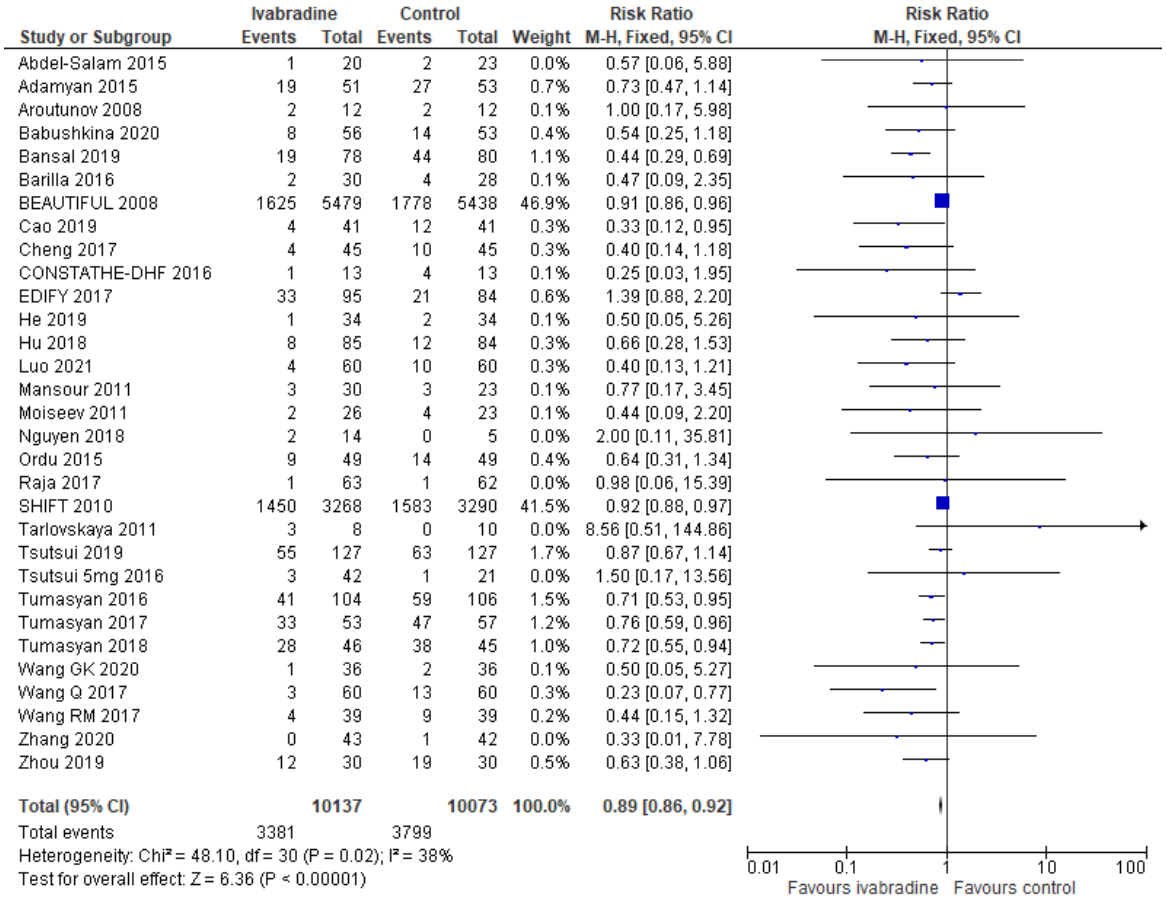


Figure 19 - Forest plot of the sensitivity analysis of serious adverse events using best- compared with worst-case scenario.

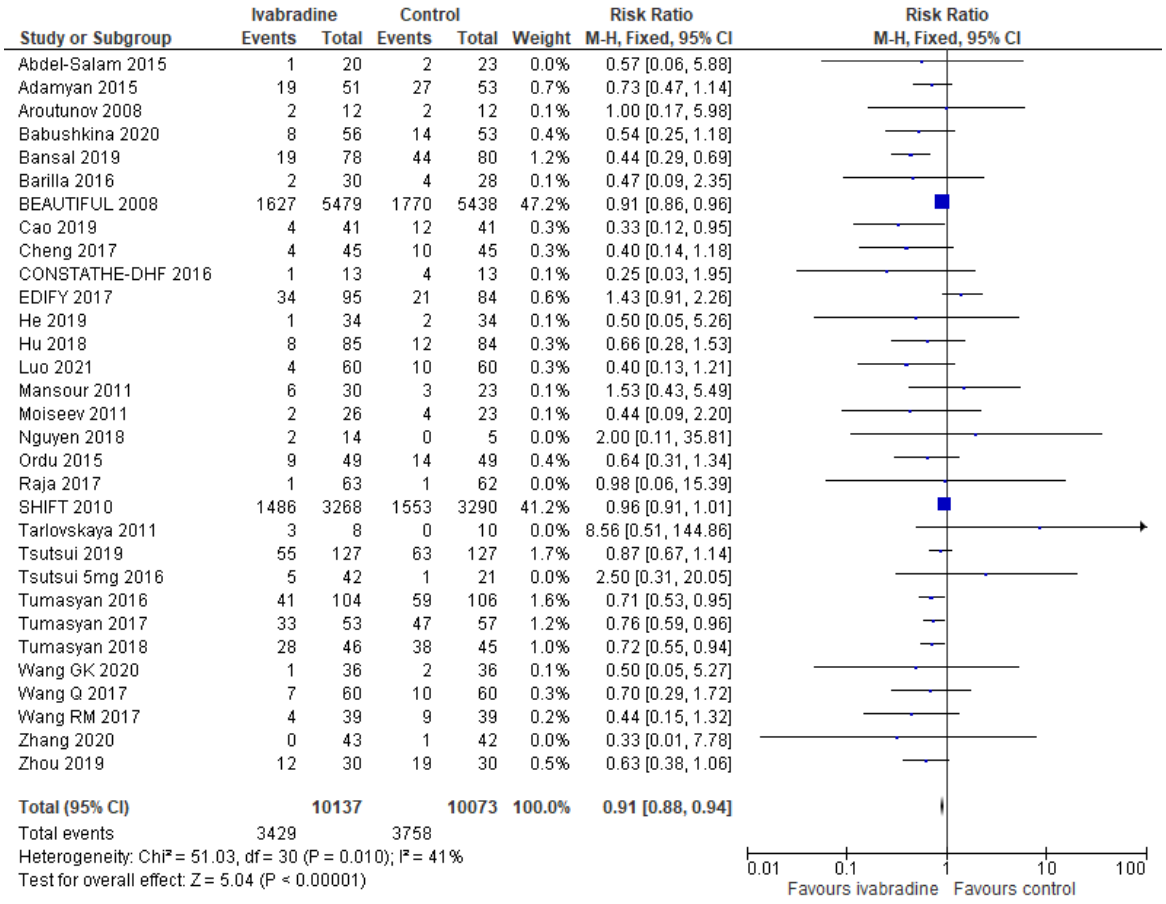


Figure 20 - Forest plot of the sensitivity analysis of serious adverse events using worst- compared with best-case scenario.

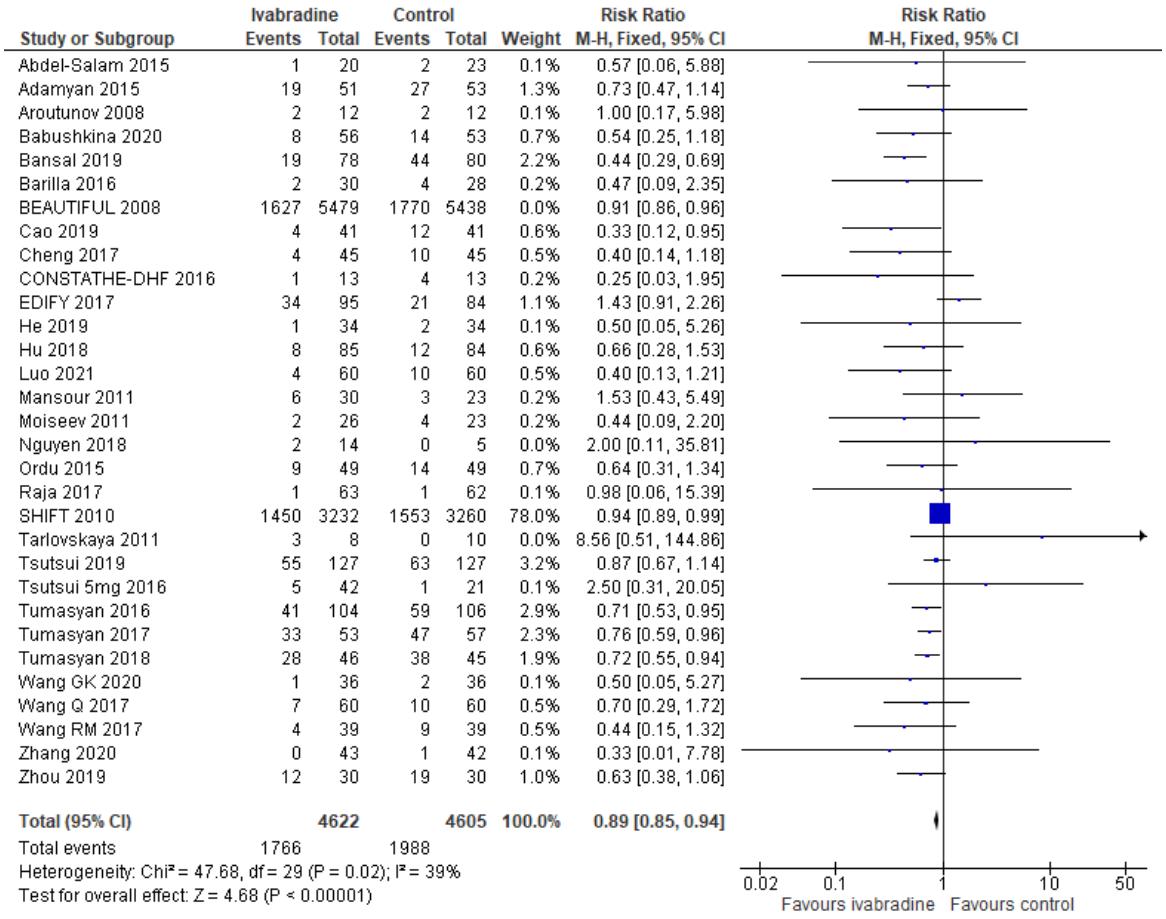


Figure 21 – Forest plot of the sensitivity analysis of serious adverse events removing the BEAUTIFUL trial.

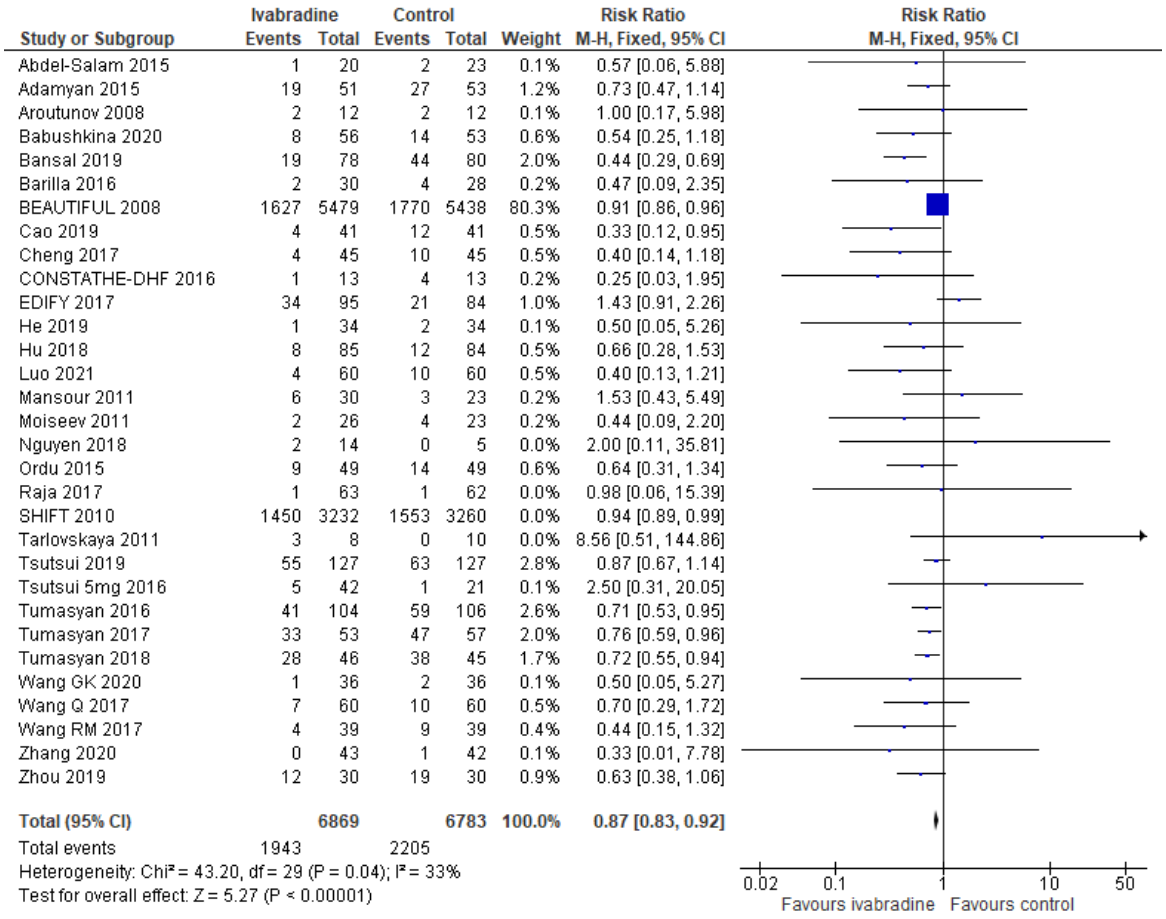


Figure 22 – Forest plot of the sensitivity analysis of serious adverse events removing the SHIFT trial.

Subgroup analyses

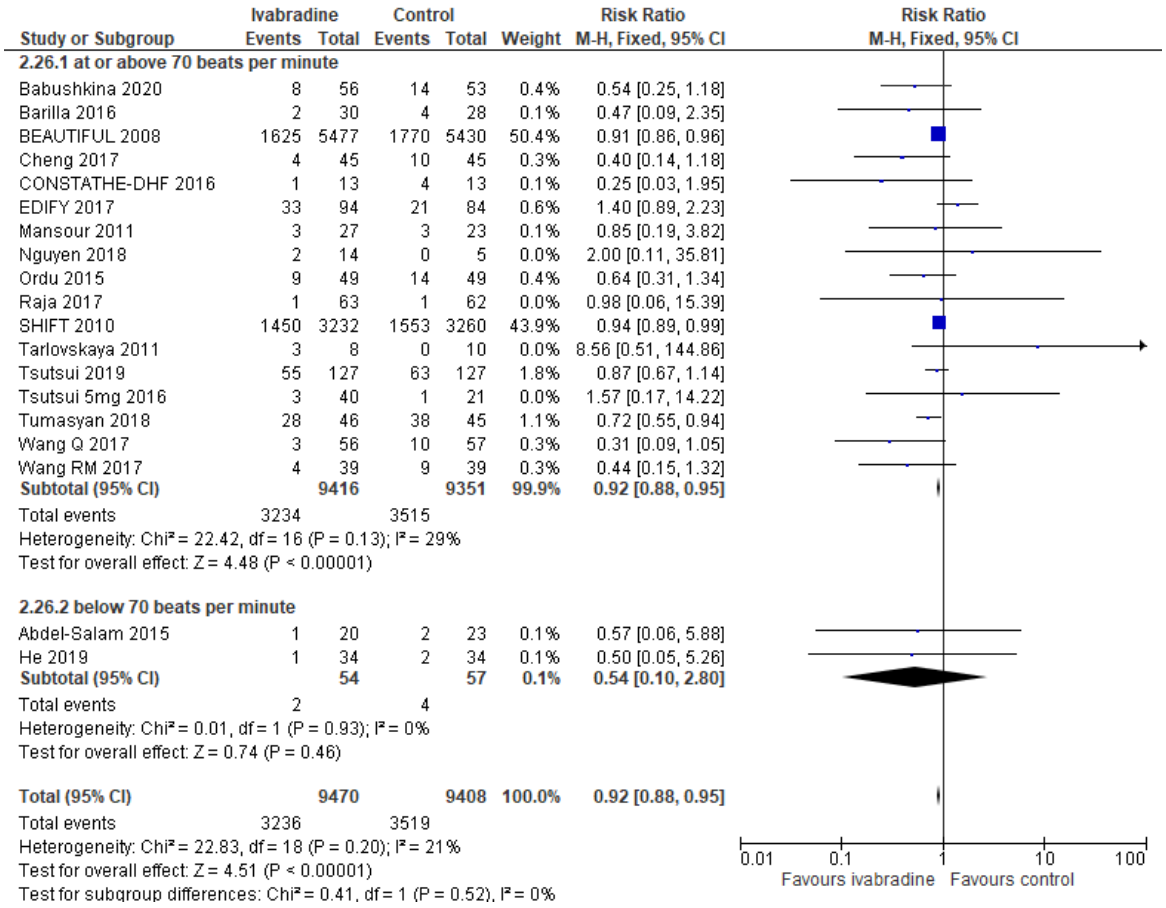


Figure 23 - Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared to trials randomising participants with heart rate below 70 beats per minute on all-cause mortality.

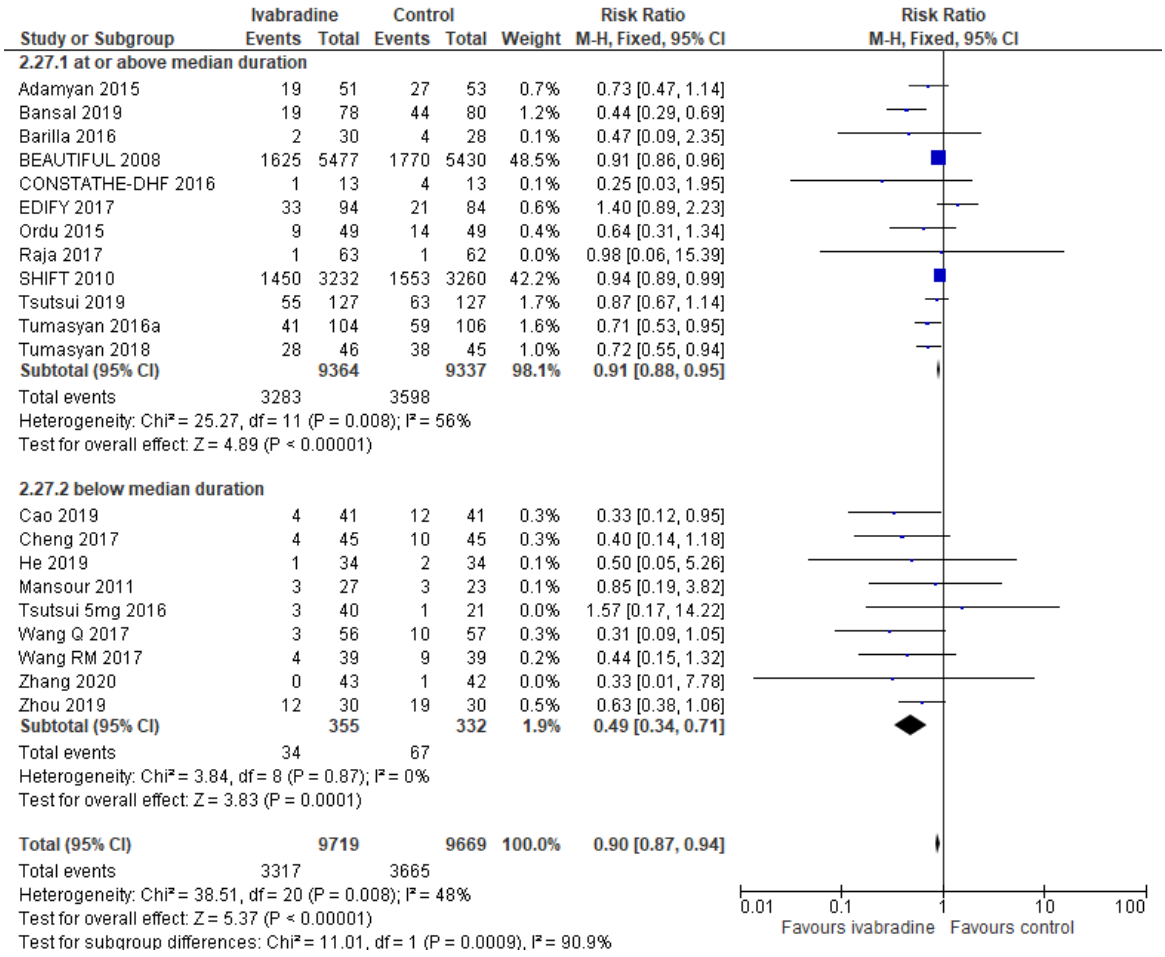


Figure 24 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (182.64 days) compared to trials administering ivabradine below median duration on serious adverse events.

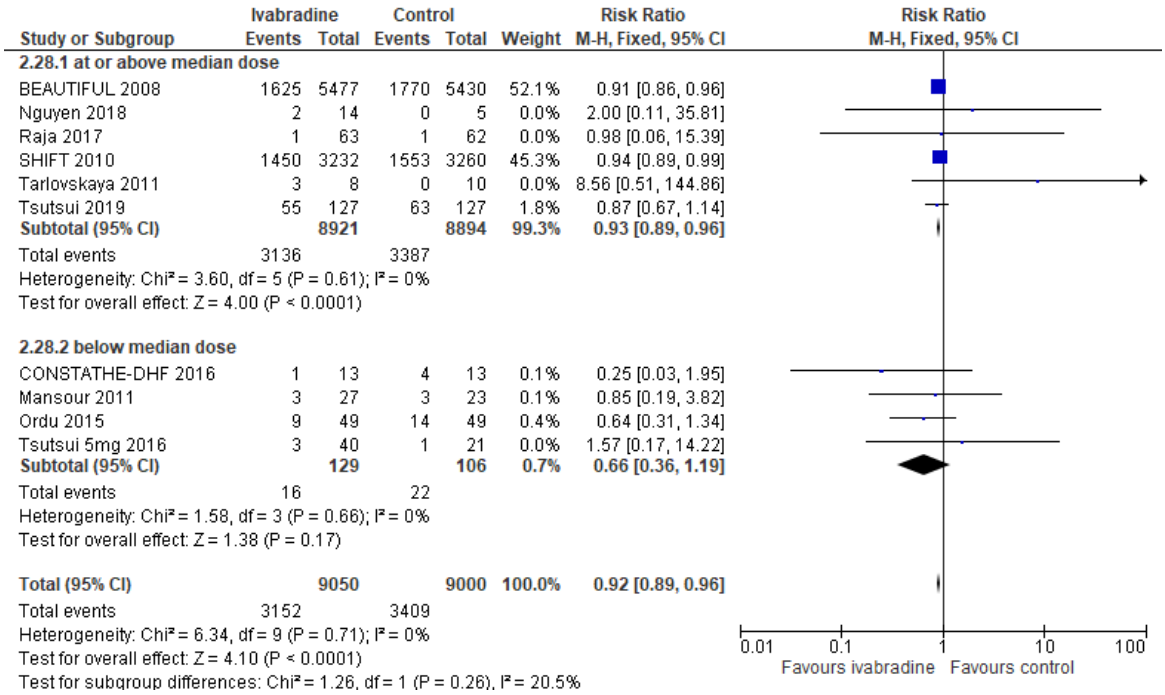


Figure 25 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose (12.36 mg) compared to trials administering ivabradine below median daily dose on serious adverse events.

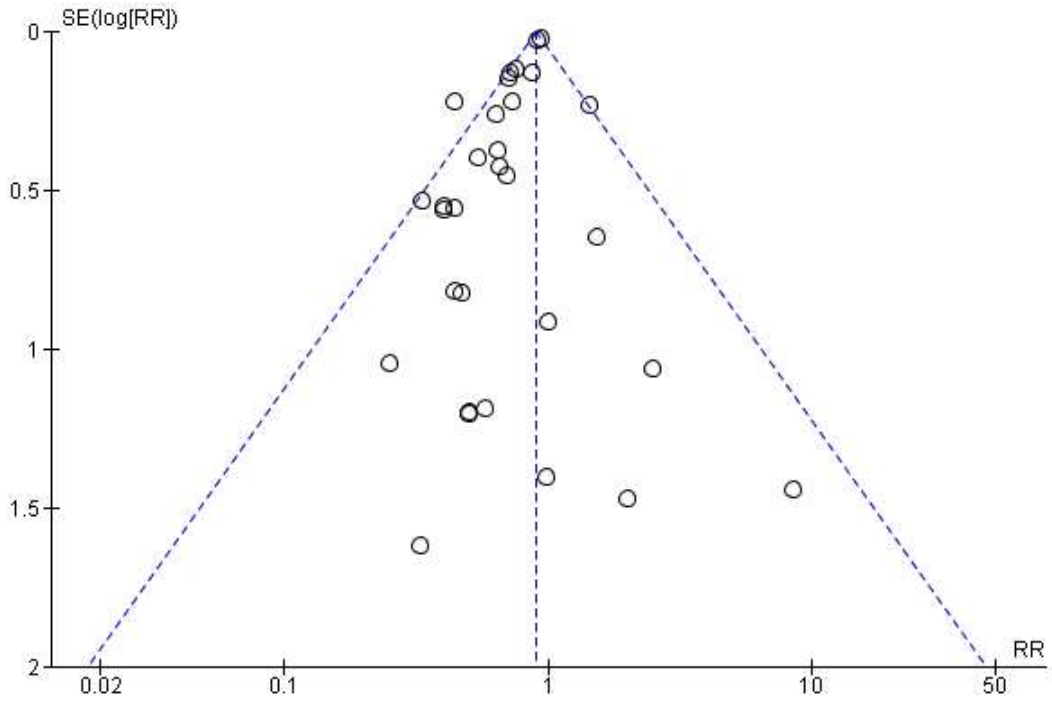


Figure 26 – Funnel plot of the analysis of serious adverse events. The funnel plot did not indicate small study bias.

Supplement 7 - Quality of life

Main analyses for trials using Kansas City Cardiomyopathy Questionnaire (KCCQ)

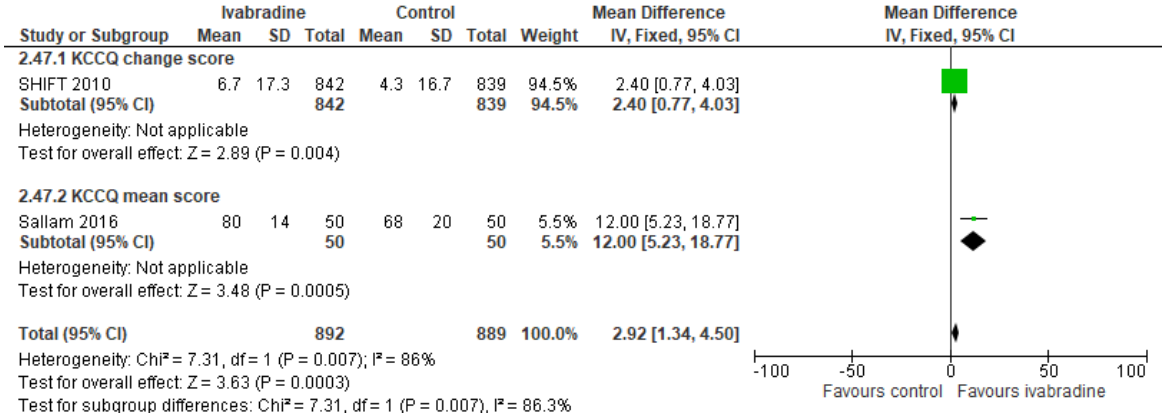


Figure 27 – Forest plot of the meta-analysis of quality of life from trials using the KCCQ using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine.

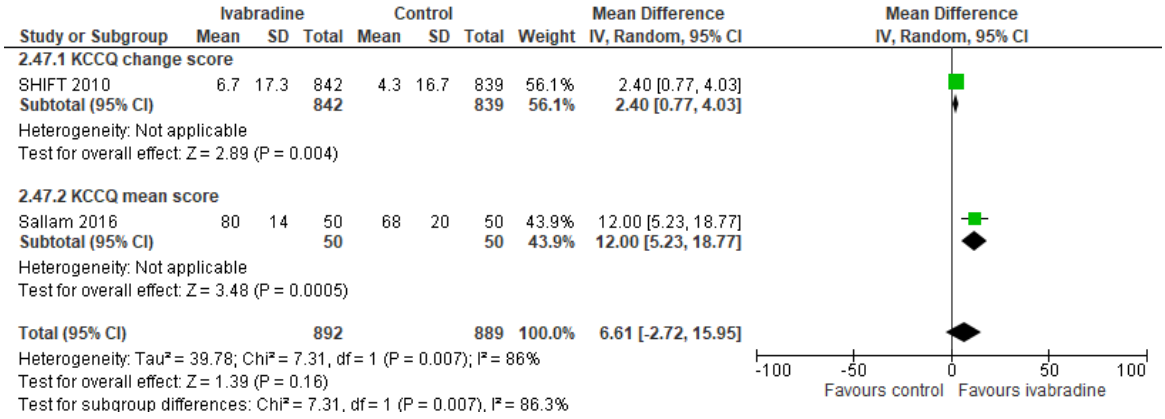


Figure 28 – Forest plot of the meta-analysis of quality of life from trials using the Kansas City Cardiomyopathy Questionnaire (KCCQ) using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

Sensitivity analyses for trials using KCCQ.

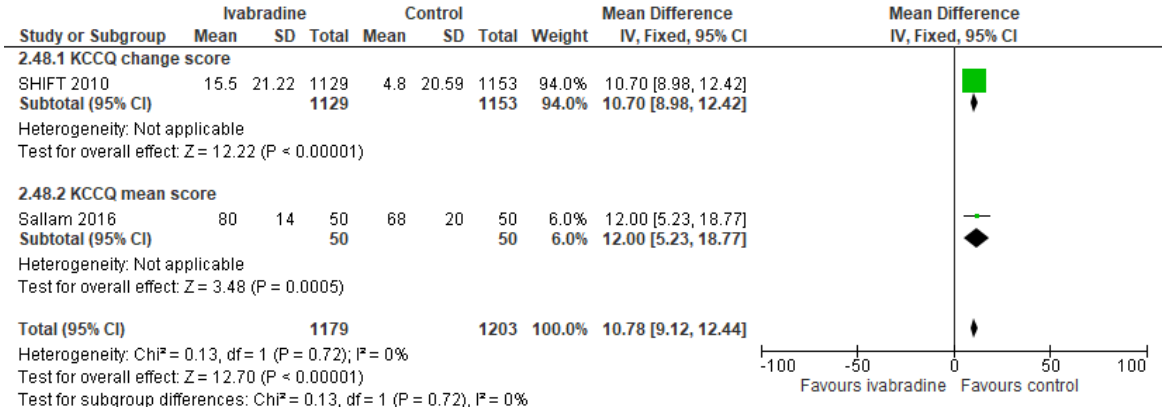


Figure 29 – Forest plot of the sensitivity analysis of quality of life (KCCQ) using best- compared with worst-case scenario.

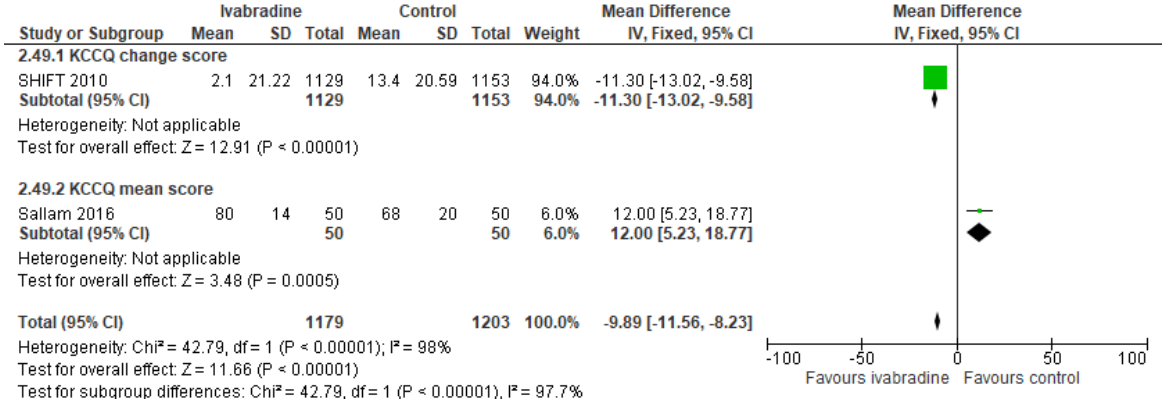


Figure 30 – Forest plot of the sensitivity analysis of quality of life (MLWHFQ) using worst- compared with best-case scenario.

Subgroup analyses for trials using the KCCQ

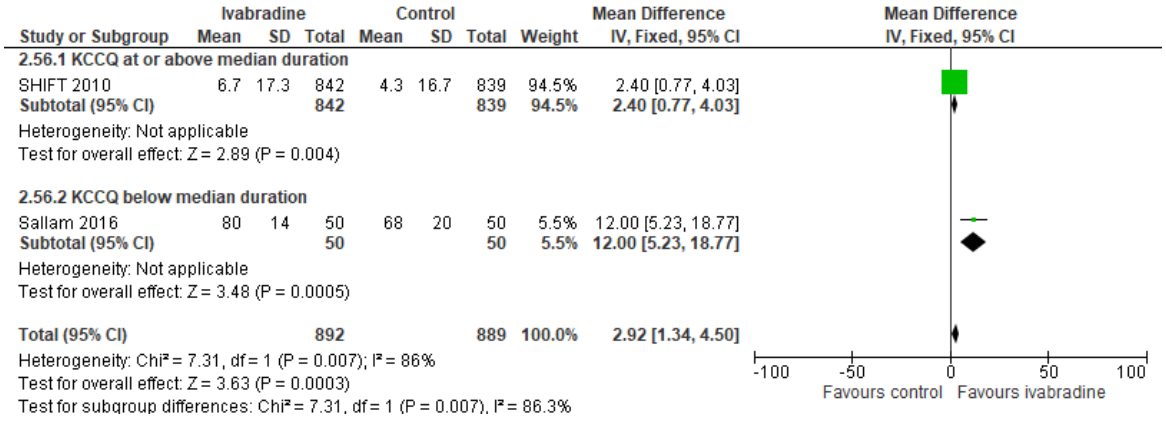


Figure 31 – Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (90.66 days) compared to trials administering ivabradine below median duration on quality of life using the KCCQ.

Main analyses for trials using Minnesota Living With Heart Failure Questionnaire (MLWHFQ)

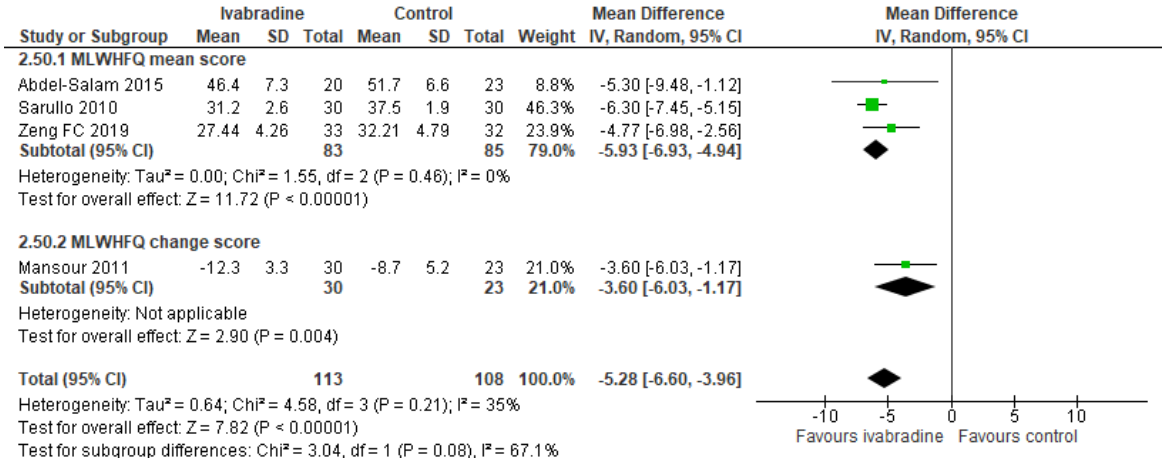


Figure 32 – Forest plot of the meta-analysis of quality of life from trials using the MLWHFQ using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

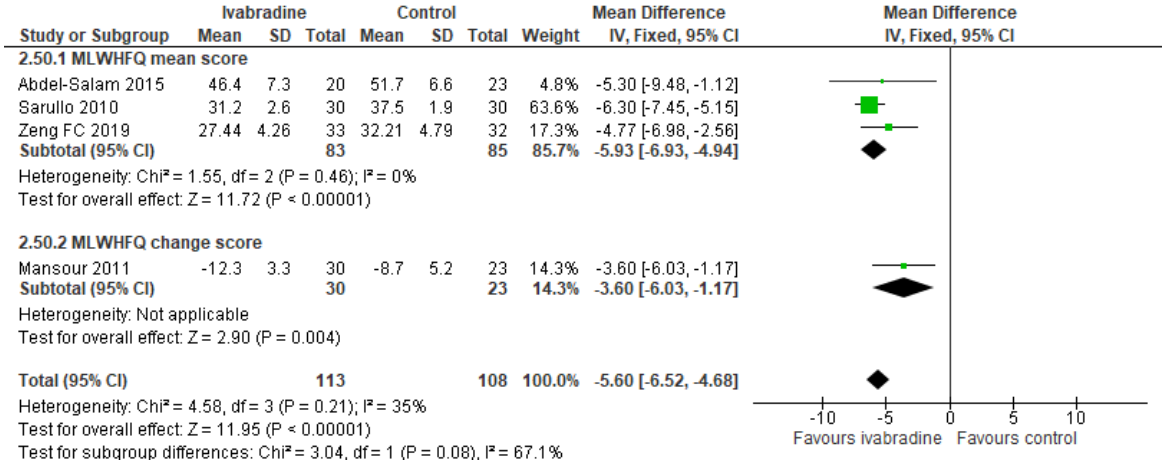


Figure 33 – Forest plot of the meta-analysis of quality of life from trials using the MLWHFQ using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine.

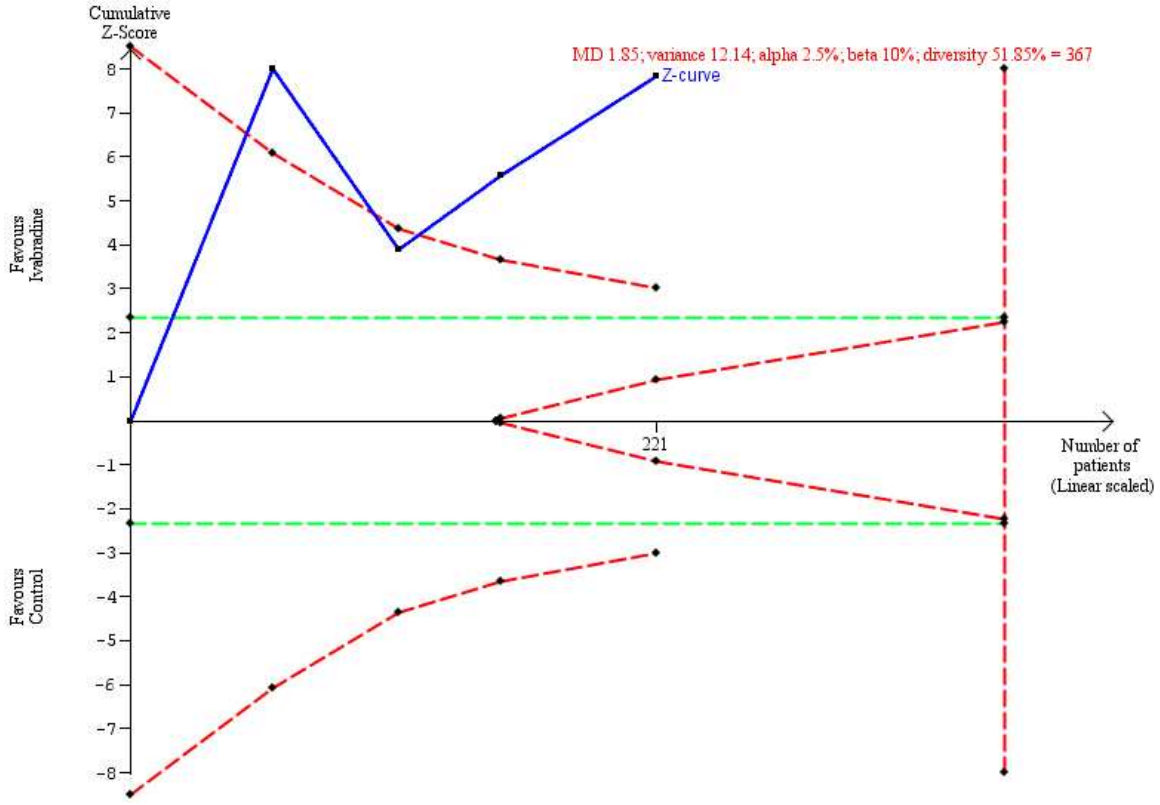


Figure 34 – Trial Sequential Analysis graph of quality of life from trials using the MLWHFQ. Trial Sequential Analysis showed that we had enough information to detect a mean difference of -5.60 points of ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) breached the boundary of benefit. MD: mean difference (SD/2 from the control group).

Sensitivity analyses of quality of life from trials using the MLWHFQ.

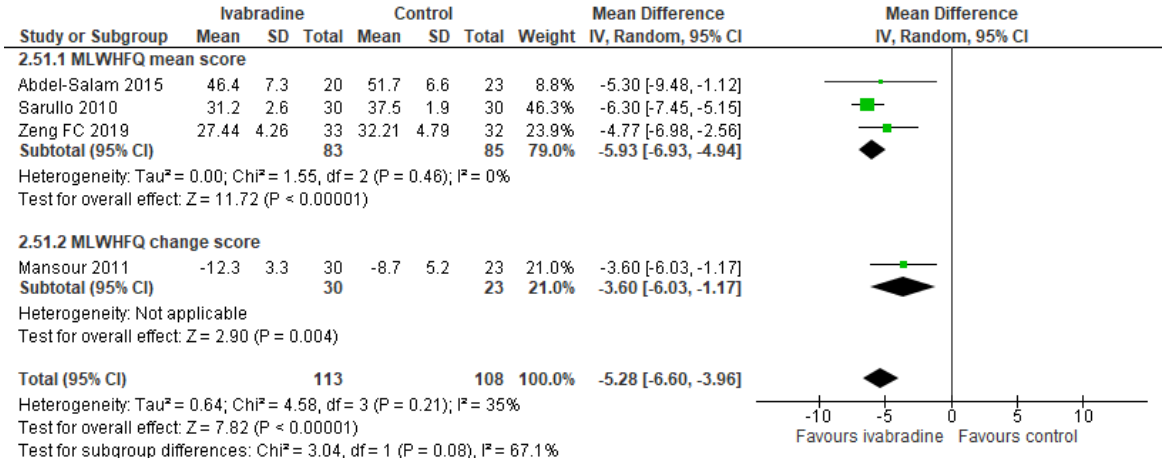


Figure 35 – Forest plot of the sensitivity analysis of quality of life (MLWHFQ) using best- compared with worst-case scenario.

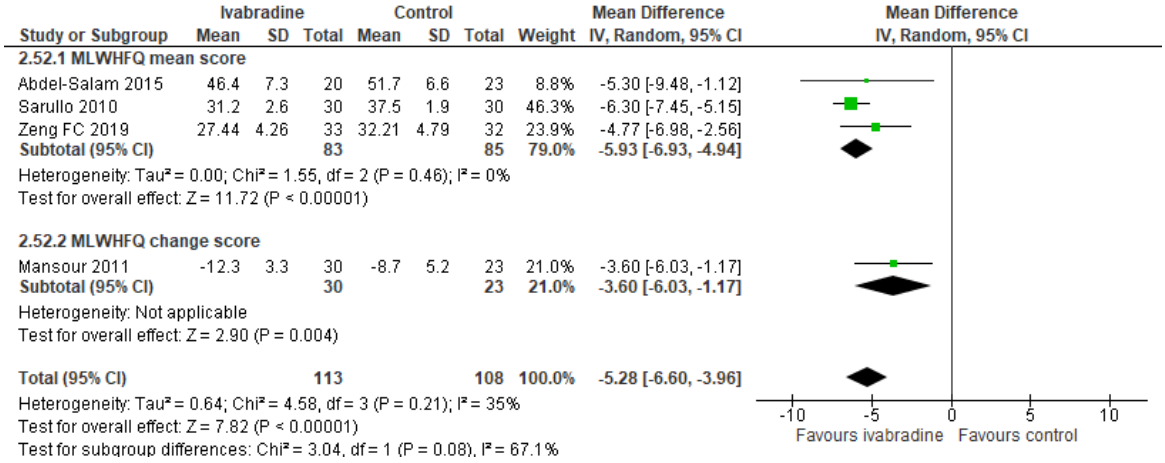


Figure 36 – Forest plot of the sensitivity analysis of quality of life (MLWHFQ) using worst- compared with best-case scenario.

Subgroup analyses of quality of life from trials using the MLWHFQ

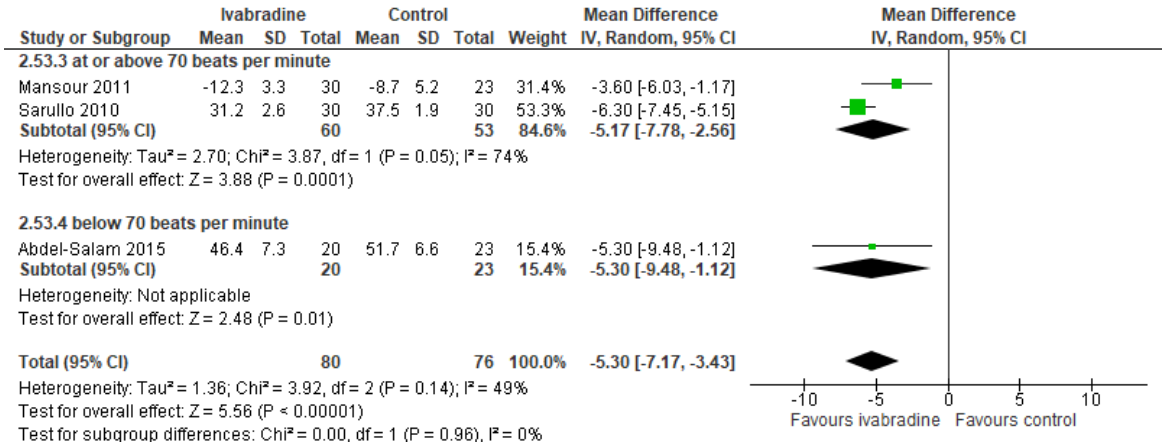


Figure 37 - Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared trials randomising participants with heart rate below 70 beats per minute on quality of life using the MLWHFQ.

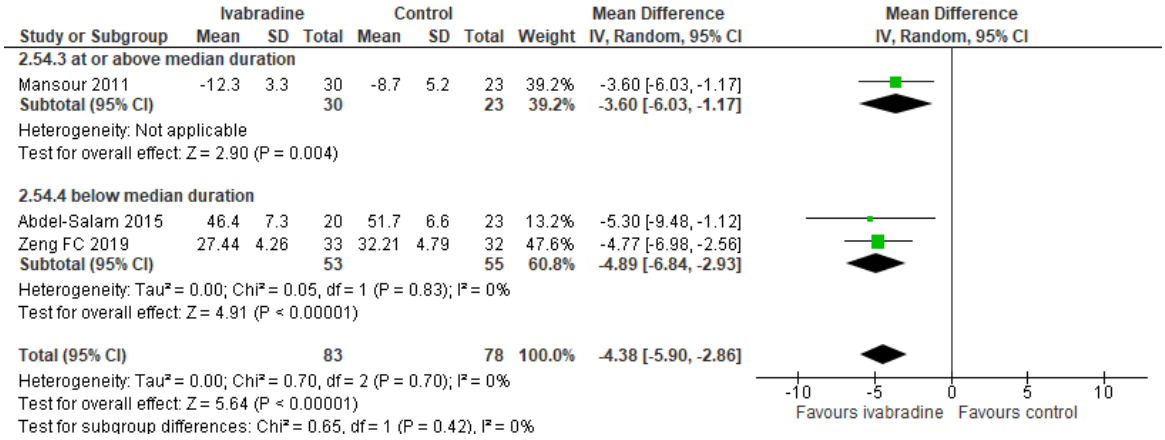


Figure 38 – Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (90.66 days) compared to trials administering ivabradine below median duration on quality of life using the MLWHFQ.

Supplement 8 - Cardiovascular mortality

Main analyses

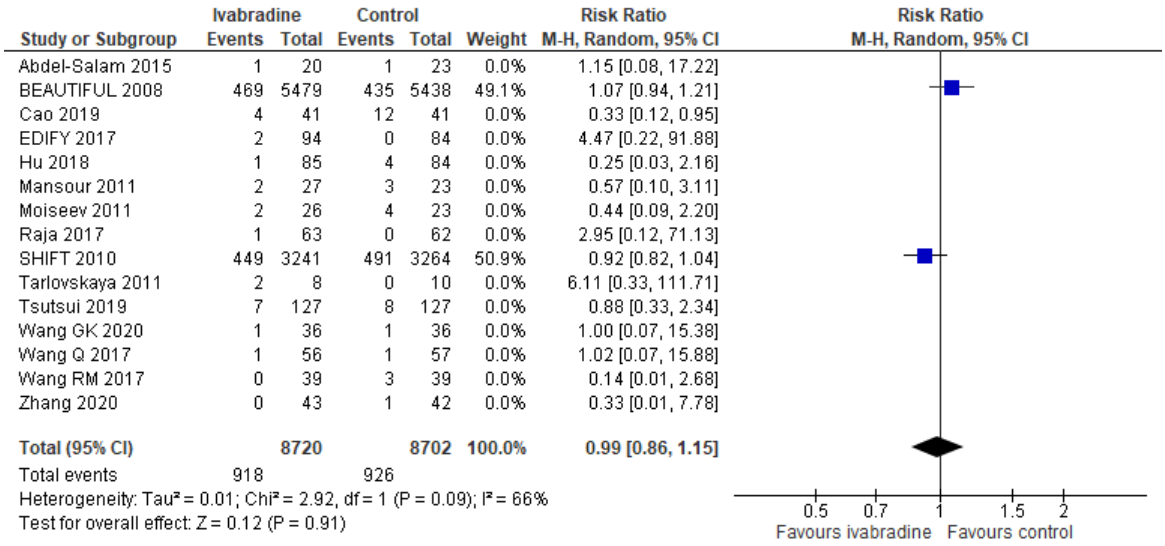


Figure 39 – Forest plot of the meta-analysis of cardiovascular mortality using random-effects meta-analysis including only trials at low risk of bias. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

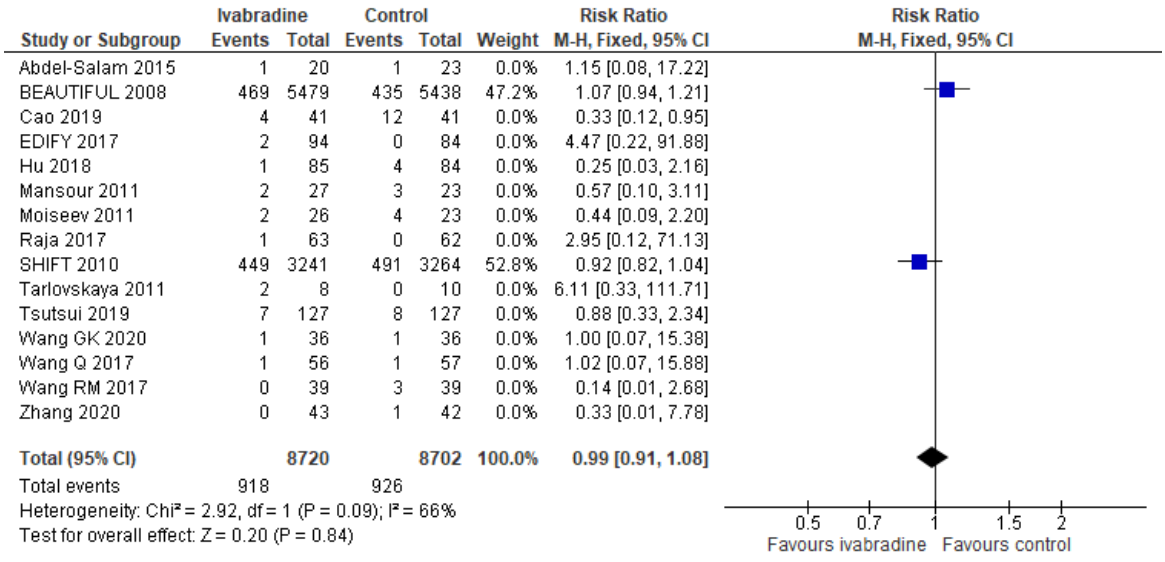


Figure 40 – Forest plot of the meta-analysis of cardiovascular mortality using fixed-effect meta-analysis including only trials at low risk of bias. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

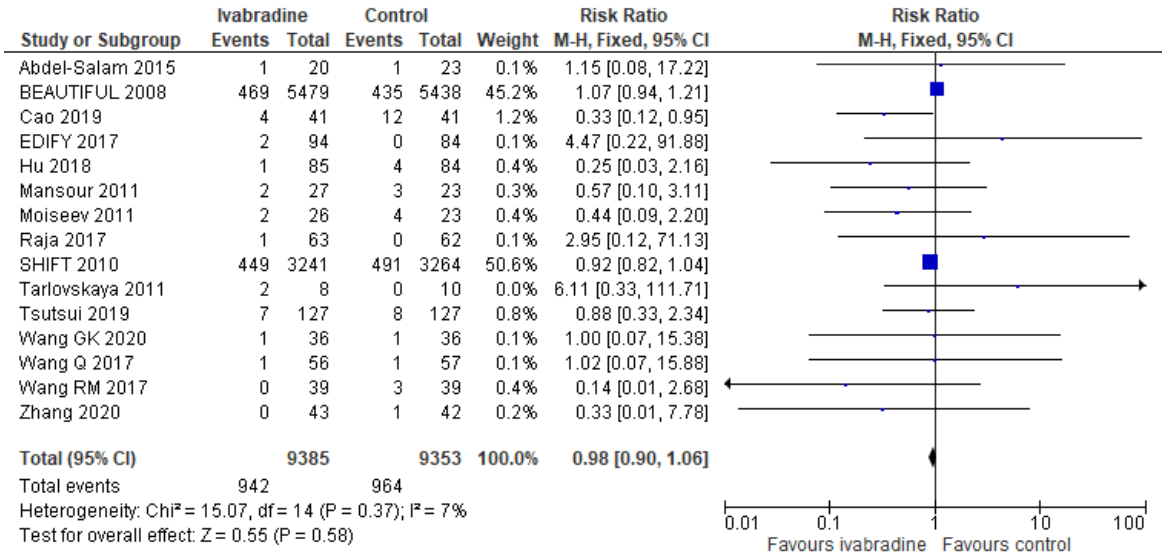


Figure 41 – Forest plot of the meta-analysis of cardiovascular mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

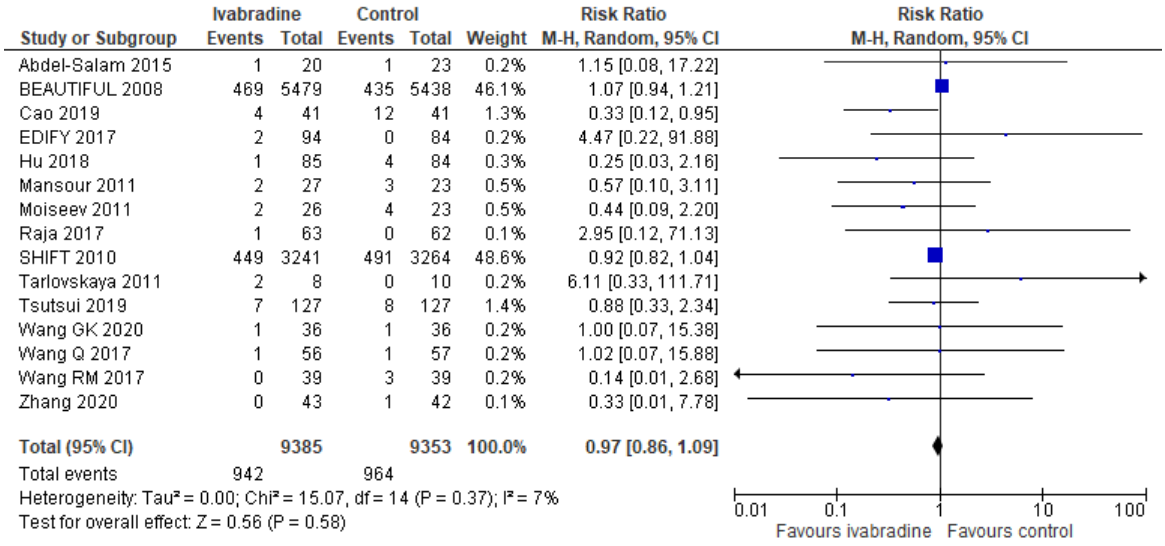


Figure 42 - Forest plot of the meta-analysis of cardiovascular mortality using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

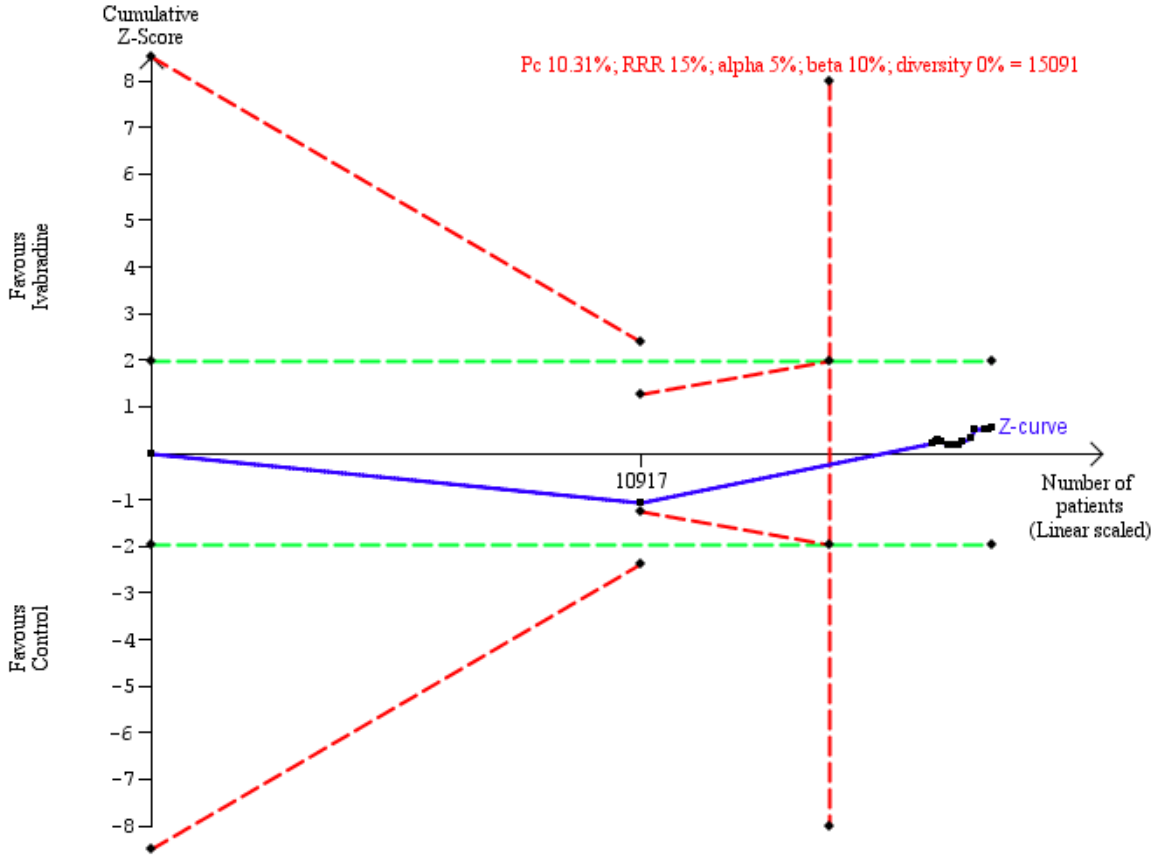


Figure 43 - Trial Sequential Analysis graph of cardiovascular mortality. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) breaches the boundary of futility and the required information size. Pc: prevalence in control group; RRR: relative risk ratio.

Sensitivity analyses

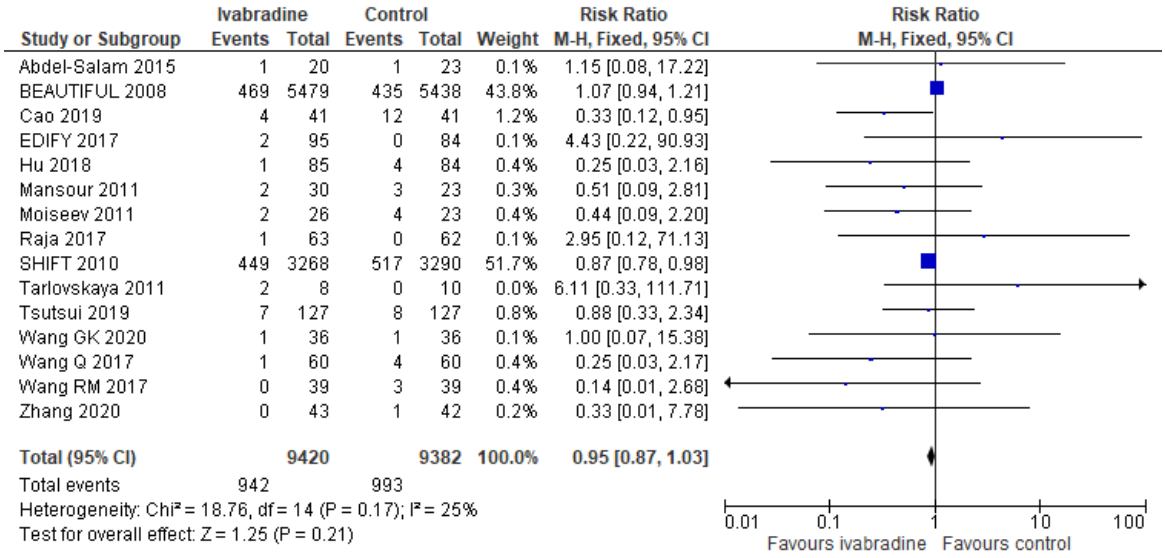


Figure 44 - Forest plot of the sensitivity analysis of cardiovascular mortality using best- compared with worst-case scenario.

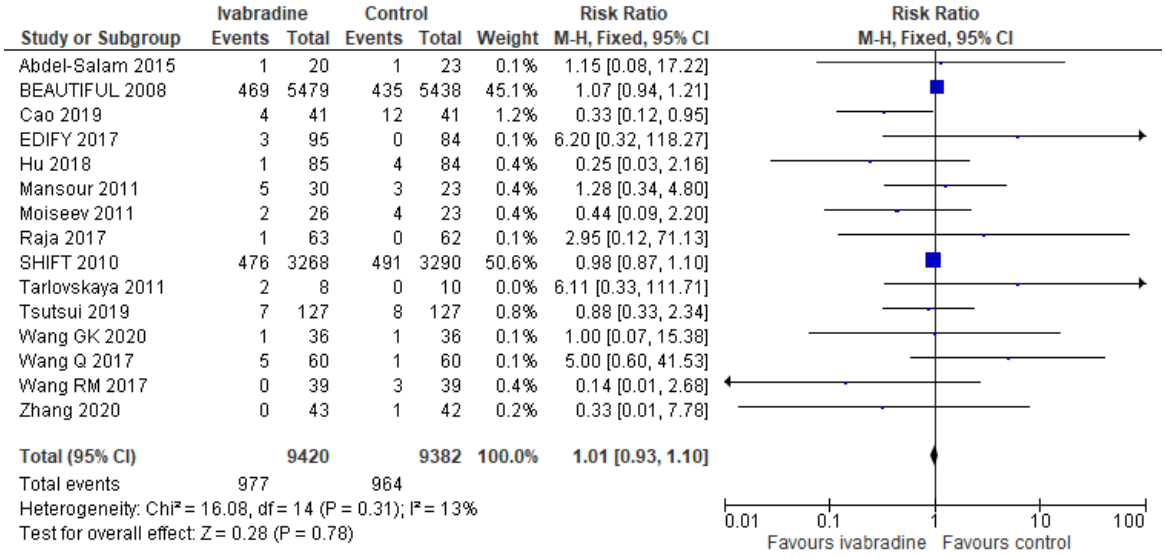


Figure 45 – Forest plot of the sensitivity analysis of cardiovascular mortality using worst compared with best-case scenario.

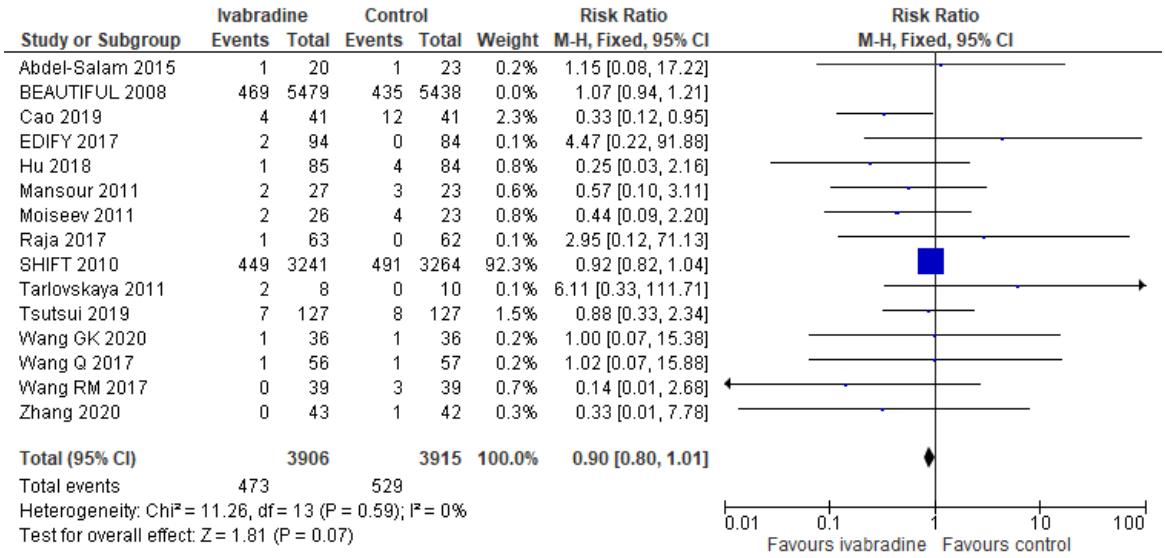


Figure 46 – Forest plot of the sensitivity analysis of cardiovascular mortality removing the BEAUTIFUL trial.

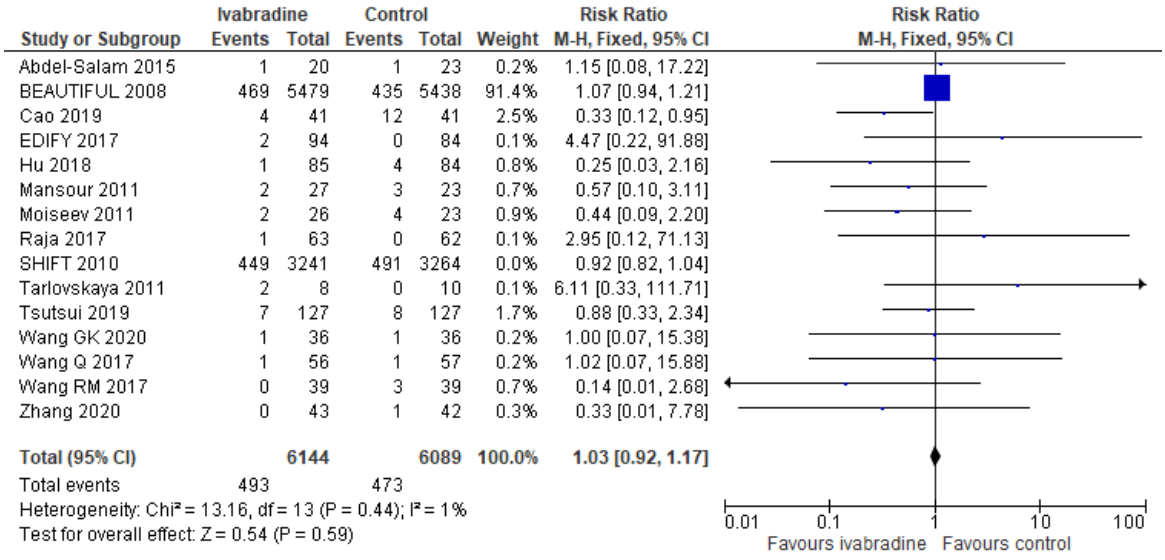


Figure 47 – Forest plot of the sensitivity analysis of cardiovascular mortality removing the SHIFT trial.

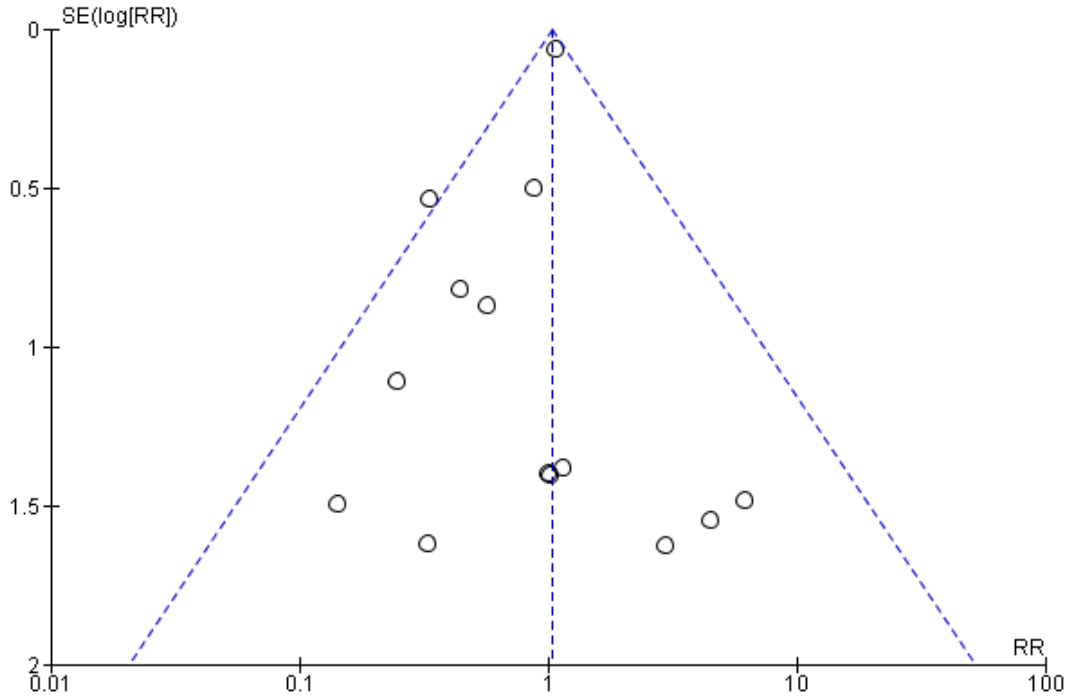


Figure 48 – Funnel plot of the analysis of cardiovascular mortality. The funnel plot did not indicate small study bias.

Supplement 9 - Myocardial infarction

Main analyses

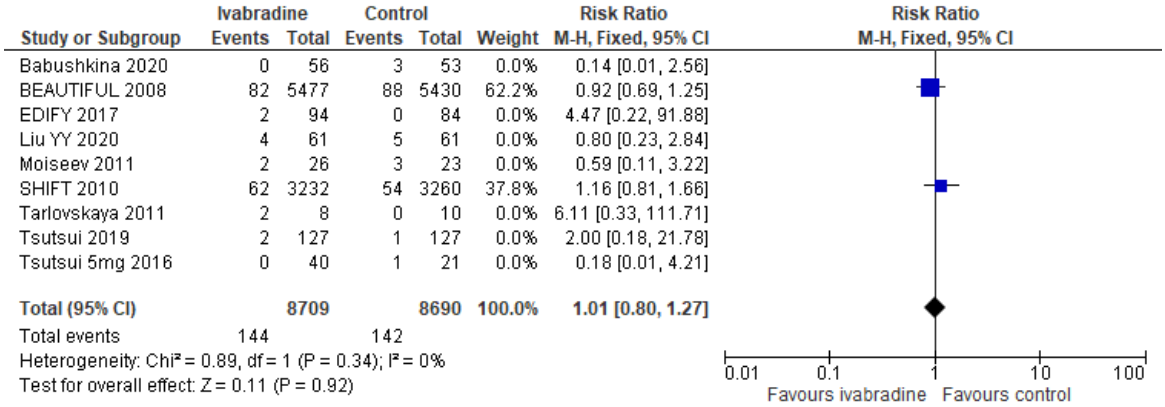


Figure 49 – Forest plot of the meta-analysis of myocardial infarction using fixed-effect meta-analysis including only trial results at low risk of bias. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

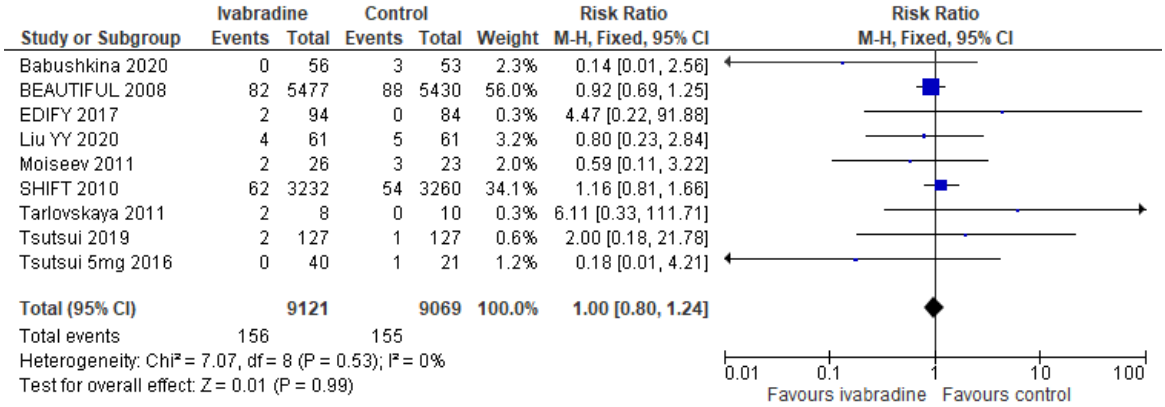


Figure 50 - Forest plot of the meta-analysis of myocardial infarction using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

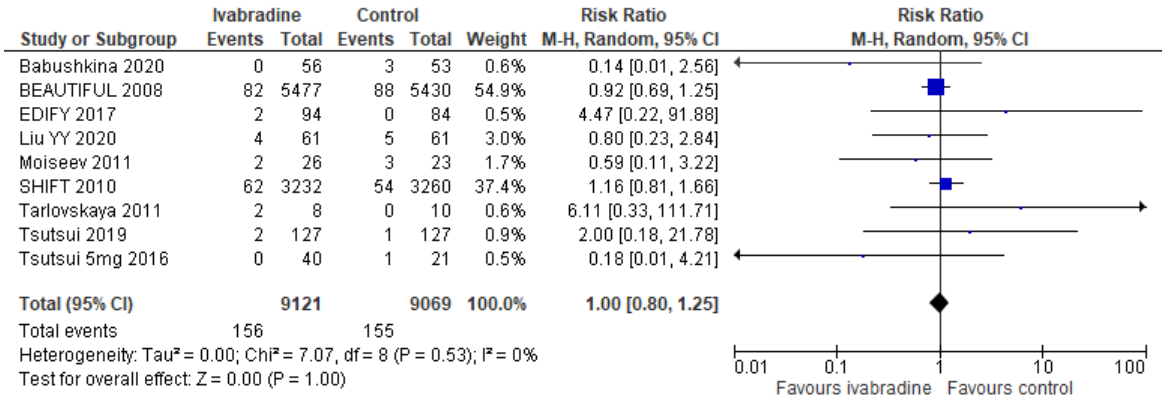


Figure 51 - Forest plot of the meta-analysis of myocardial infarction using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

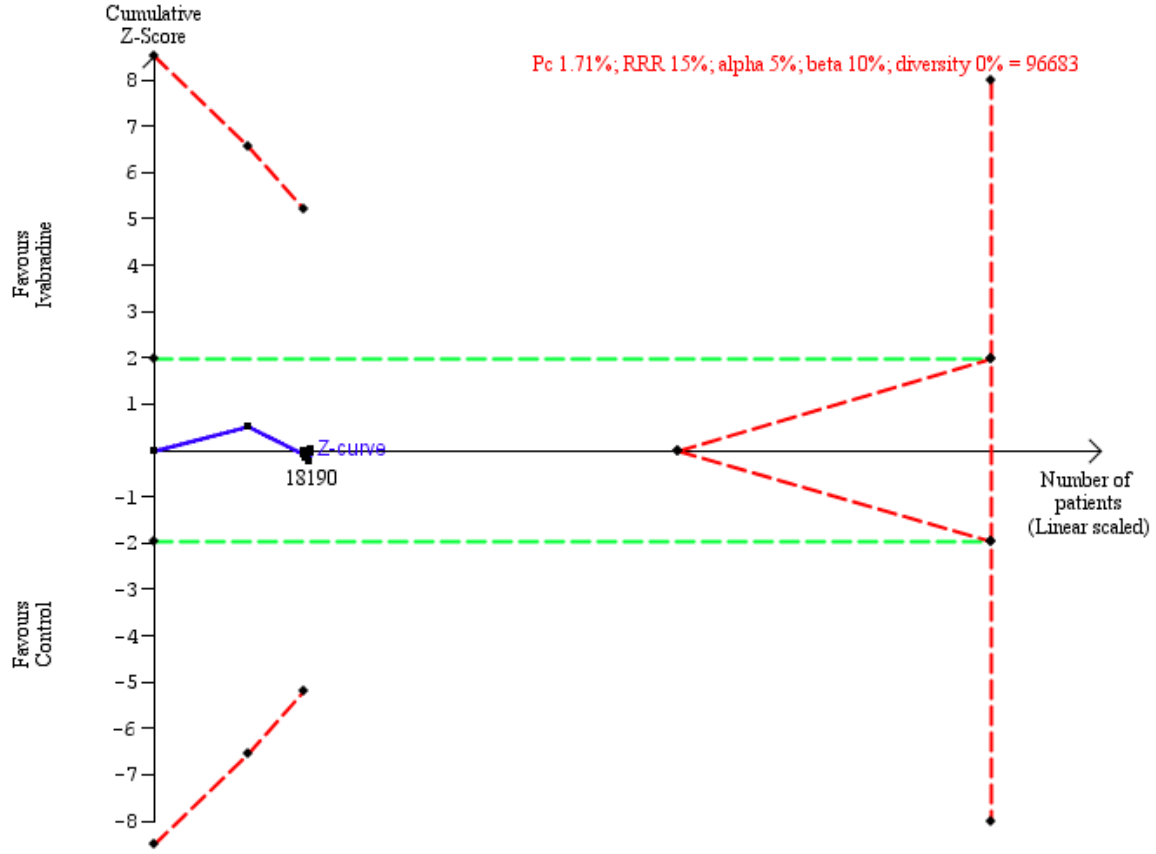


Figure 52 - Trial Sequential Analysis graph of myocardial infarction. Trial Sequential Analysis showed that we did not have enough information to detect or reject a relative risk reduction of 15% or more by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) does not breach any boundaries. Pc: prevalence in control group; RRR: relative risk ratio.

Sensitivity analyses

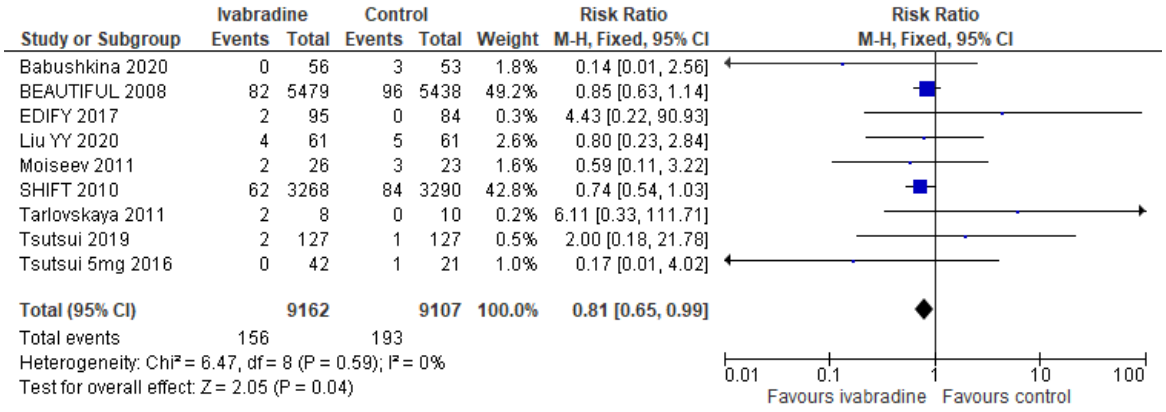


Figure 53 – Forest plot of the sensitivity analysis of myocardial infarction using a best- compared with worst-case scenario.

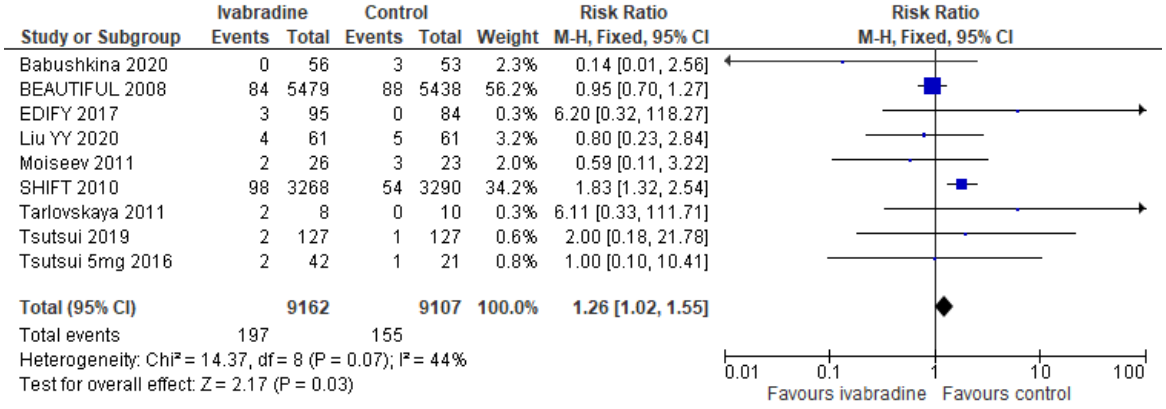


Figure 54 - Forest plot of the sensitivity analysis of myocardial infarction using a worst- compared with best-case scenario.

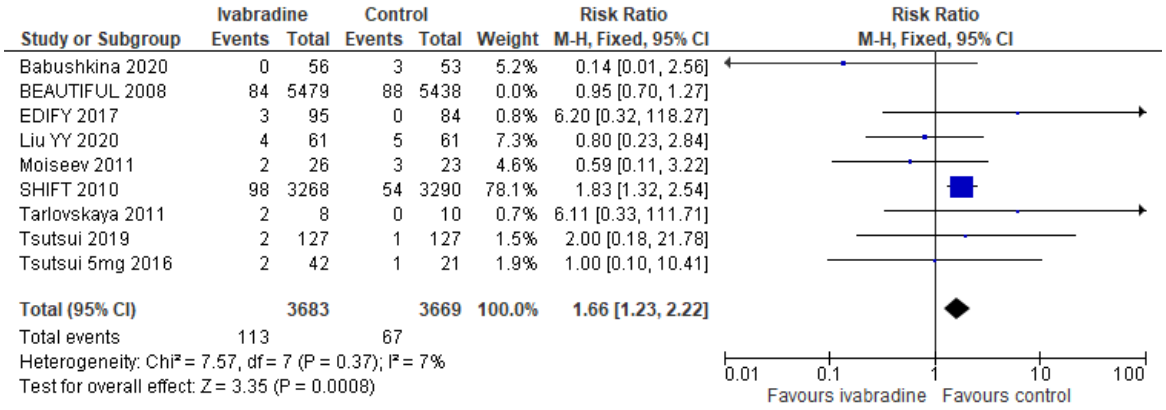


Figure 55 – Forest plot of the sensitivity analysis of myocardial infarction removing the BEAUTIFUL trial.

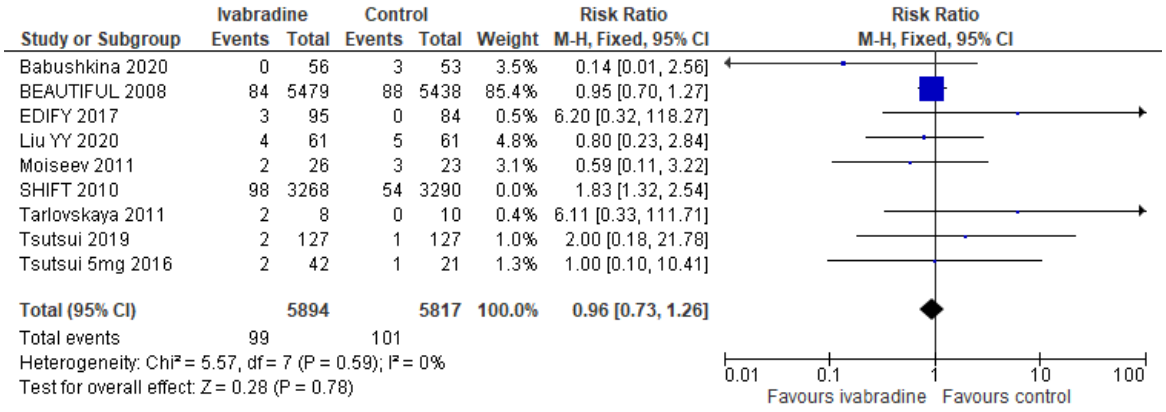


Figure 56 – Forest plot of the sensitivity analysis of myocardial infarction removing the SHIFT trial.

Supplement 10 - Non-serious adverse events

Main analyses

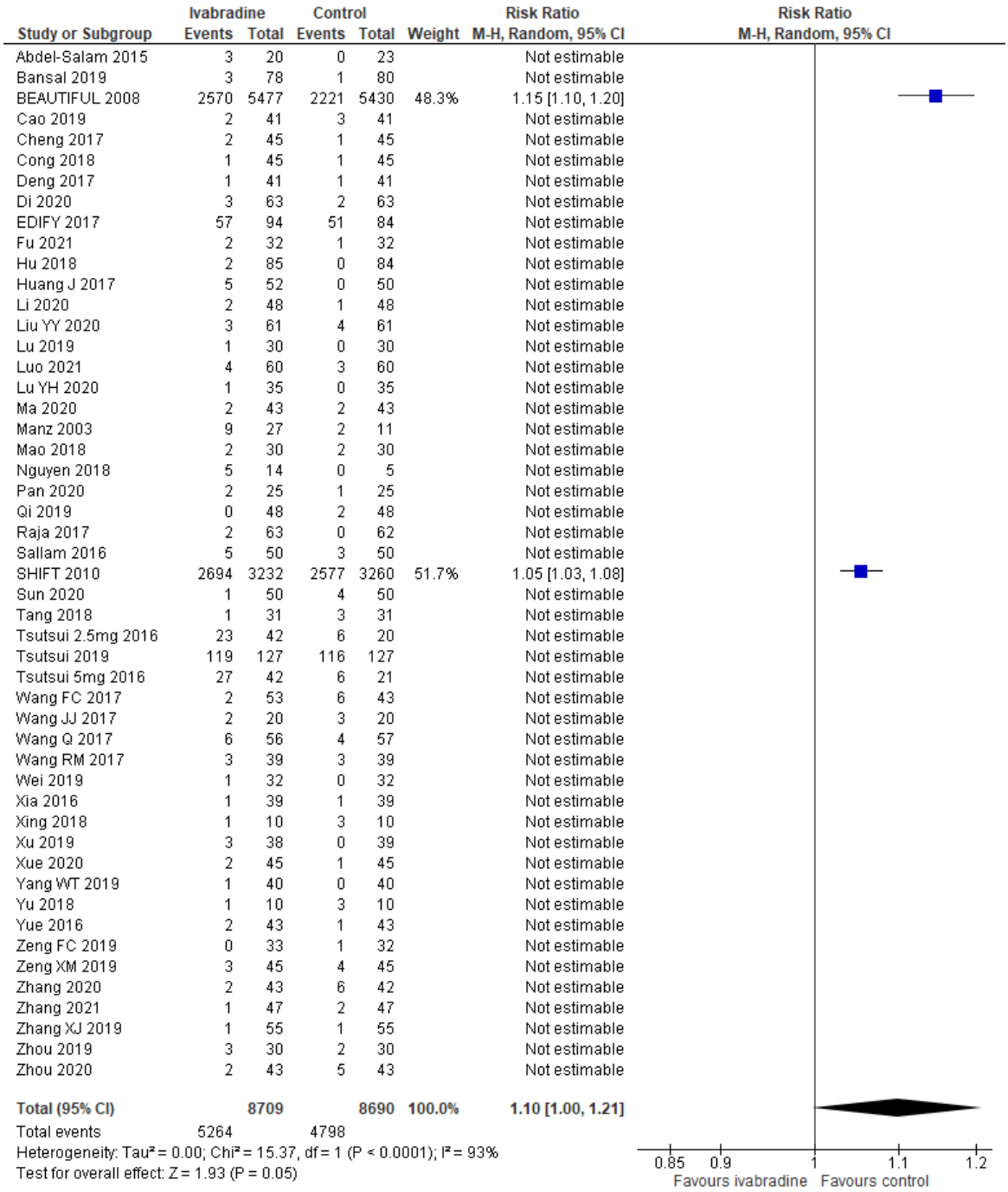


Figure 57 – Forest plot of the meta-analysis of non-serious adverse events using random-effects meta-analysis including only trials at low risk of bias. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention)

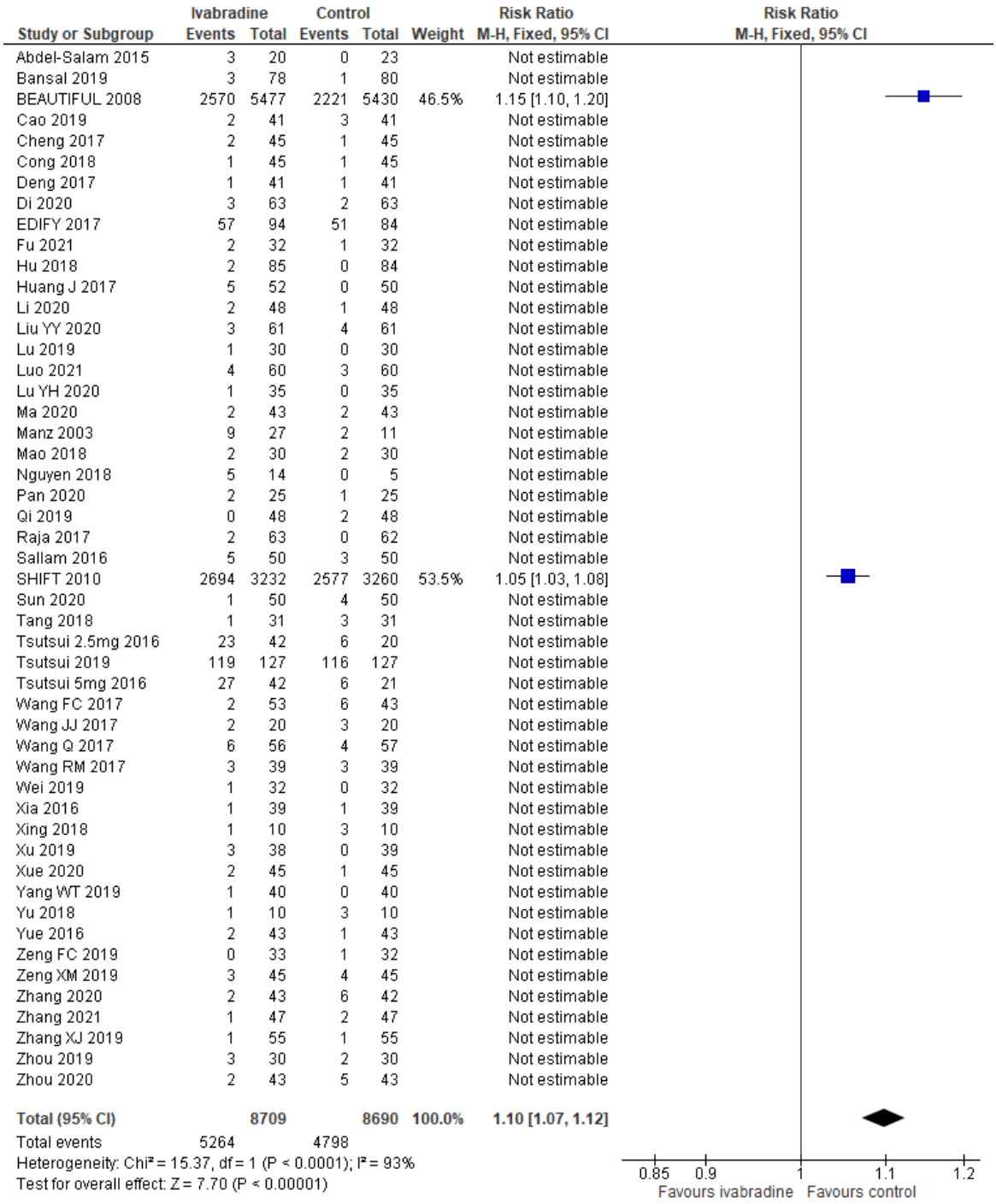


Figure 58 – Forest plot of the meta-analysis of non-serious adverse events using fixed-effect meta-analysis including only trials at low risk of bias. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention).

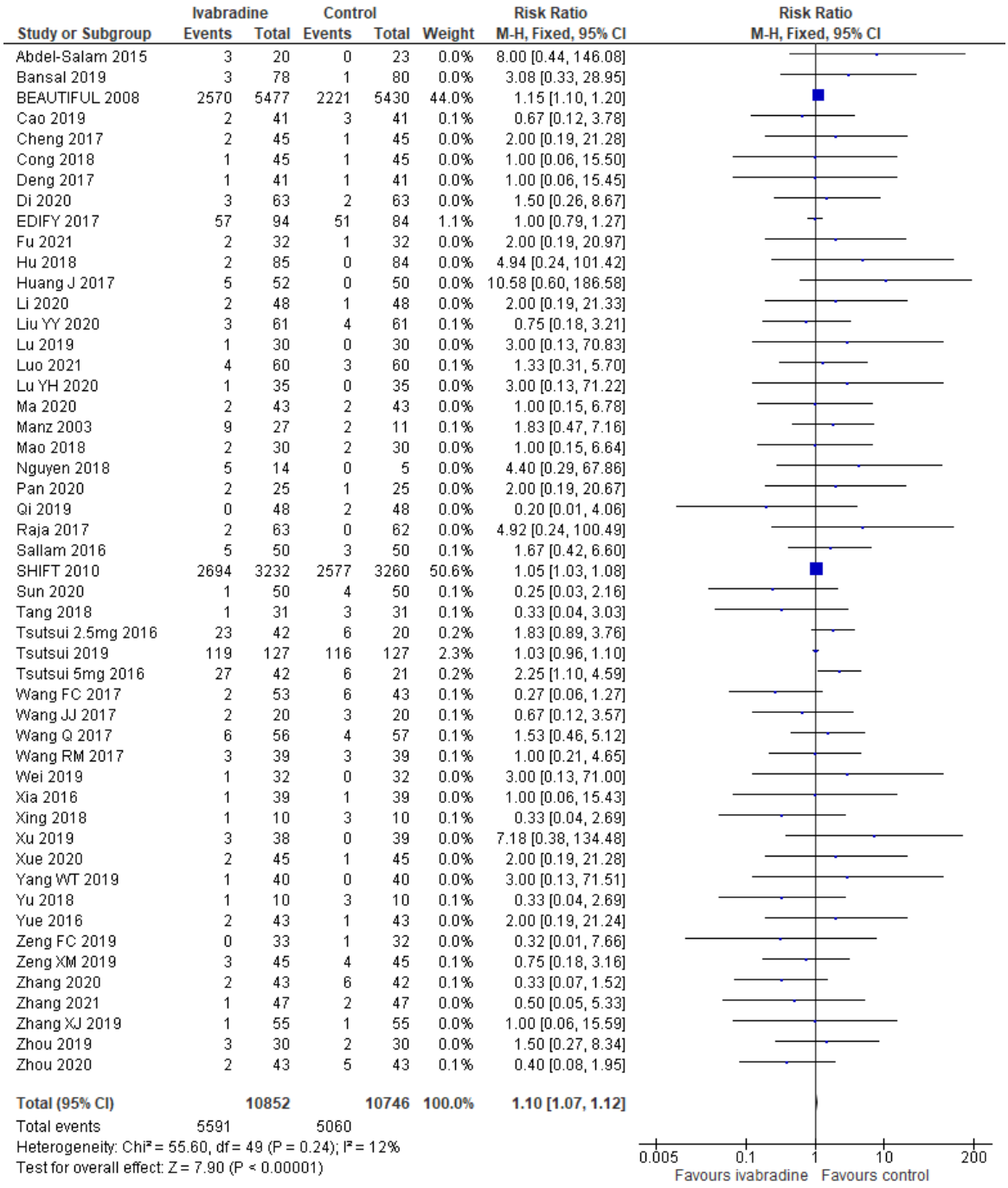


Figure 59 - Forest plot of the meta-analysis of non-serious adverse events using fixed-effect meta-analysis. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention).

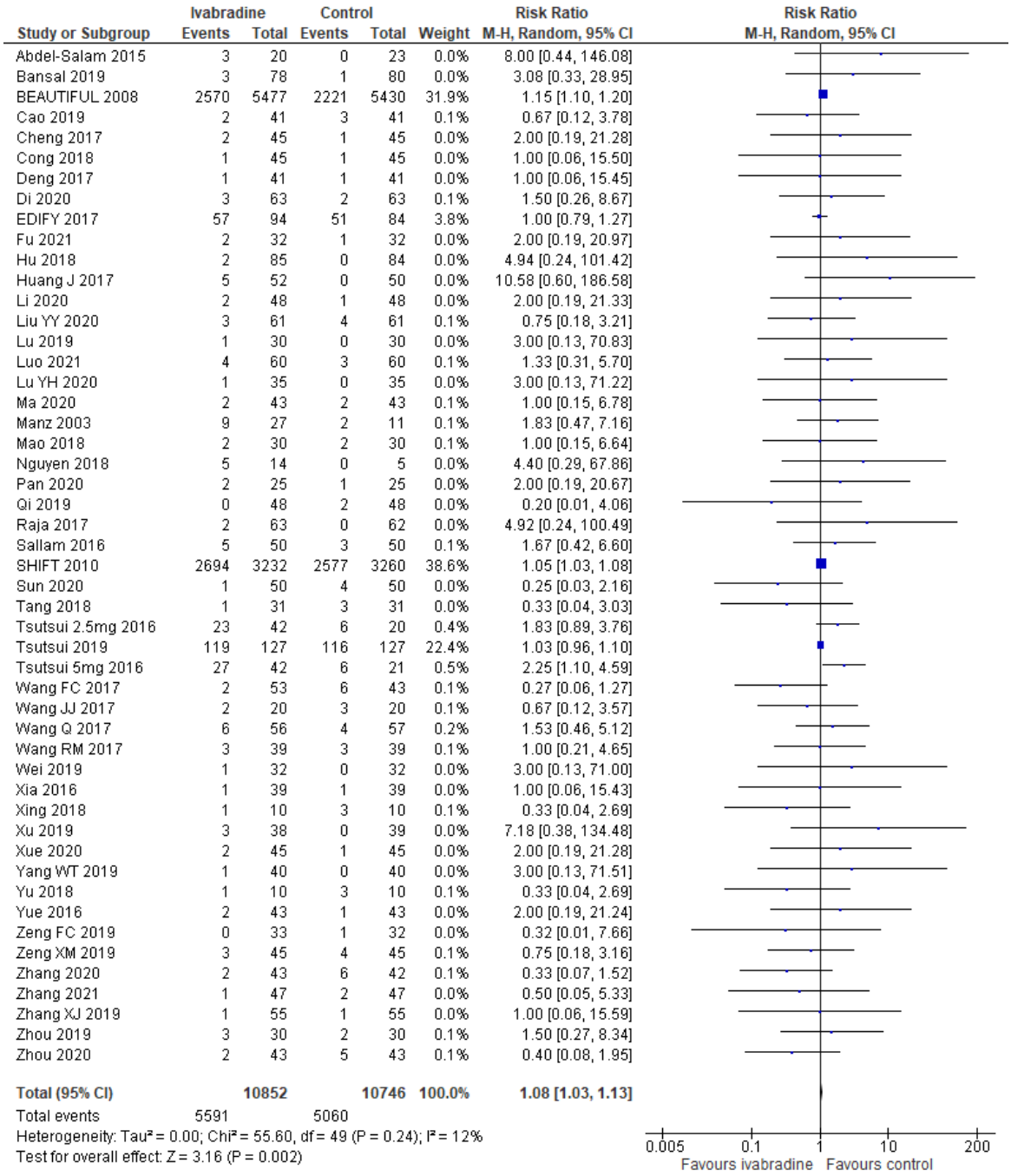


Figure 60 - Forest plot of the meta-analysis of non-serious adverse events using random-effects meta-analysis. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention)

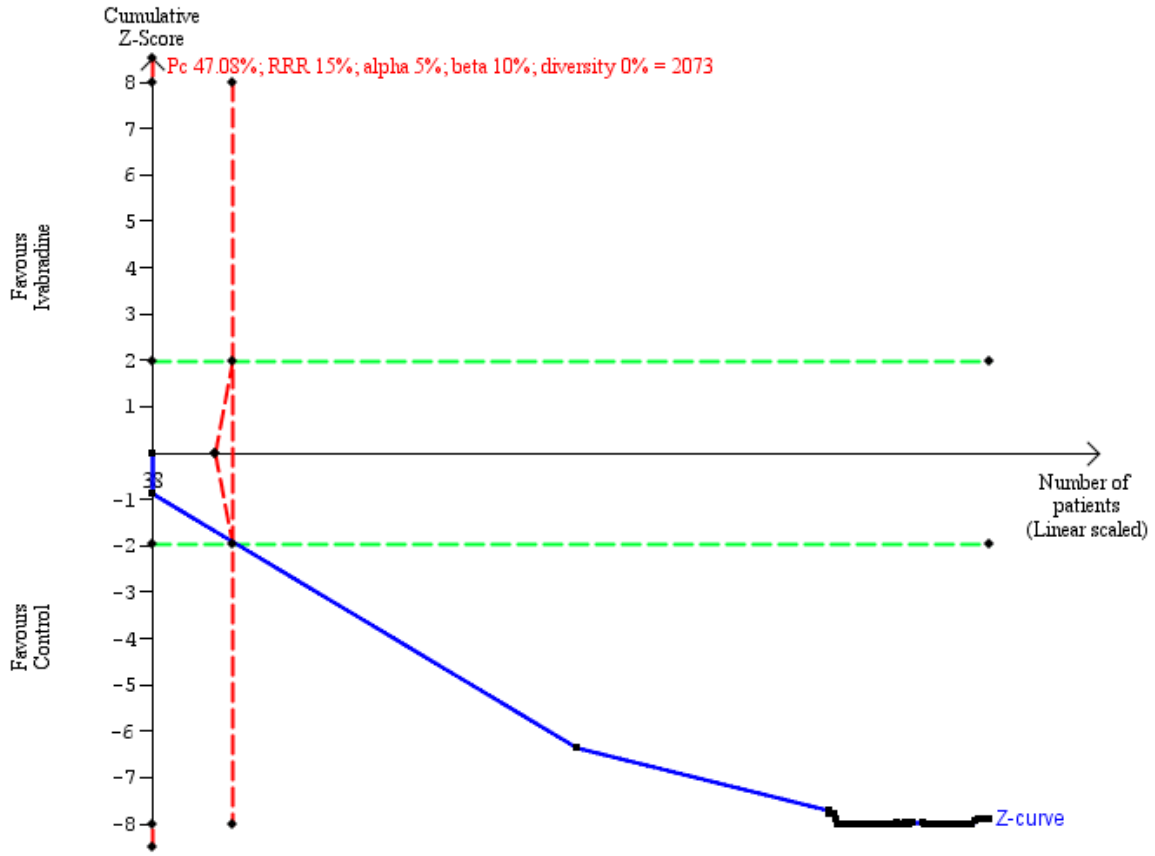


Figure 61 – Trial Sequential Analysis graph of non-serious adverse events. Trial Sequential Analysis showed that we had enough information to detect a relative risk increase of 10% by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) reached the required information size and crossed the conventional boundary of statistical significance. Pc: prevalence in control group; RRR: relative risk ratio.

Sensitivity analyses

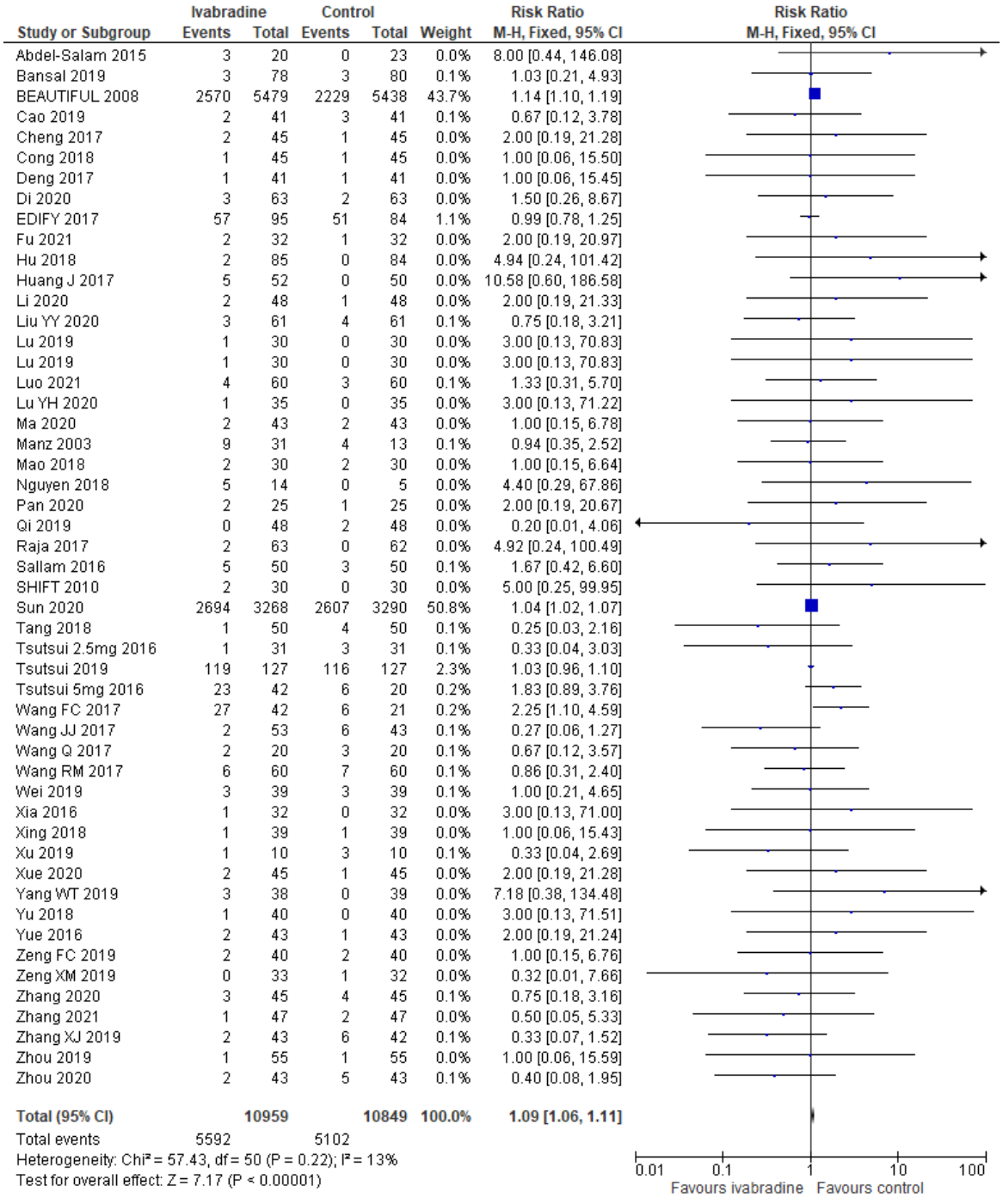


Figure 62 – Forest plot of the meta-analysis of non-serious adverse events using a best- compared with worst-case scenario.

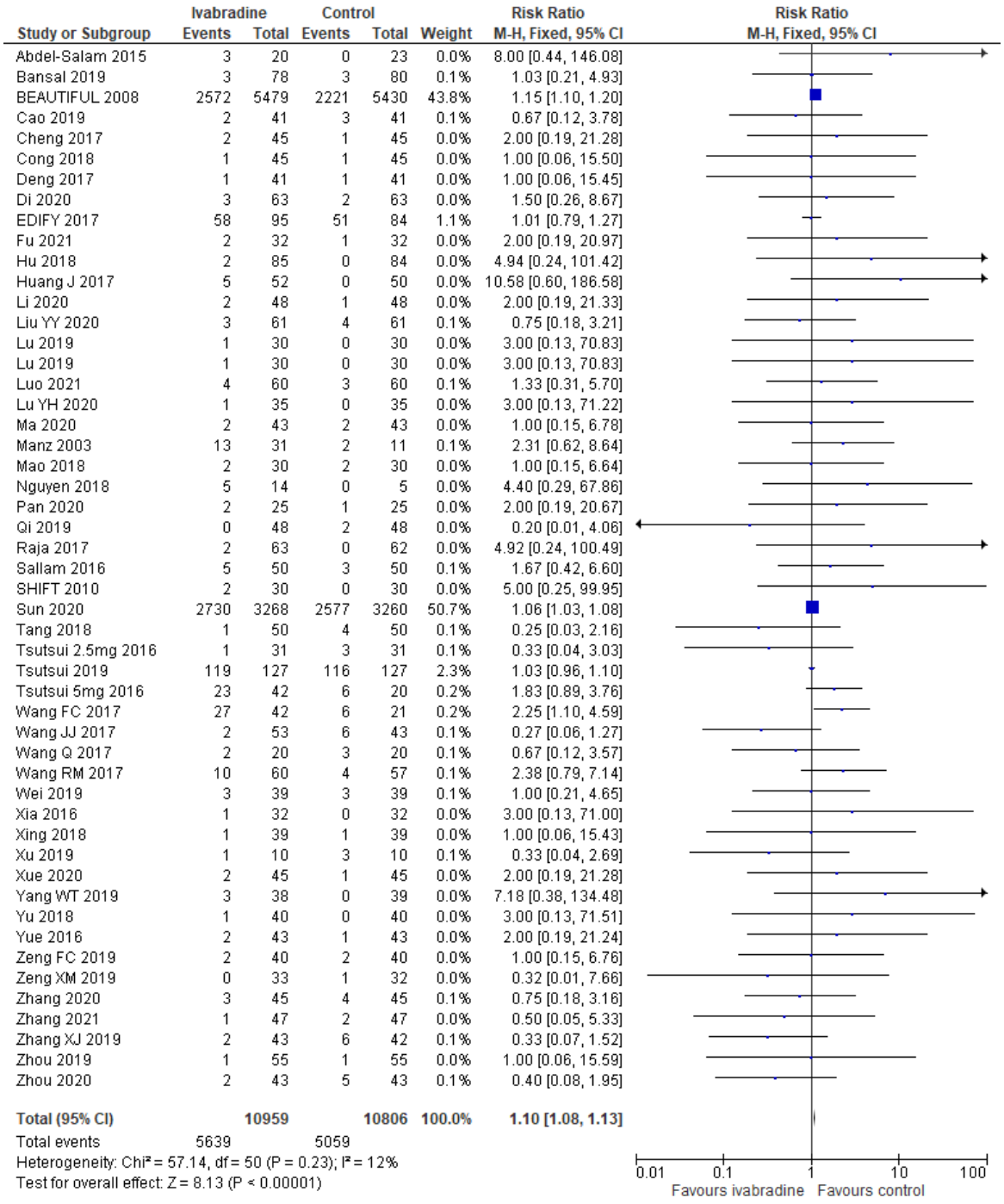


Figure 63 - Forest plot of the meta-analysis of non-serious adverse events using a worst- compared with best-case scenario.

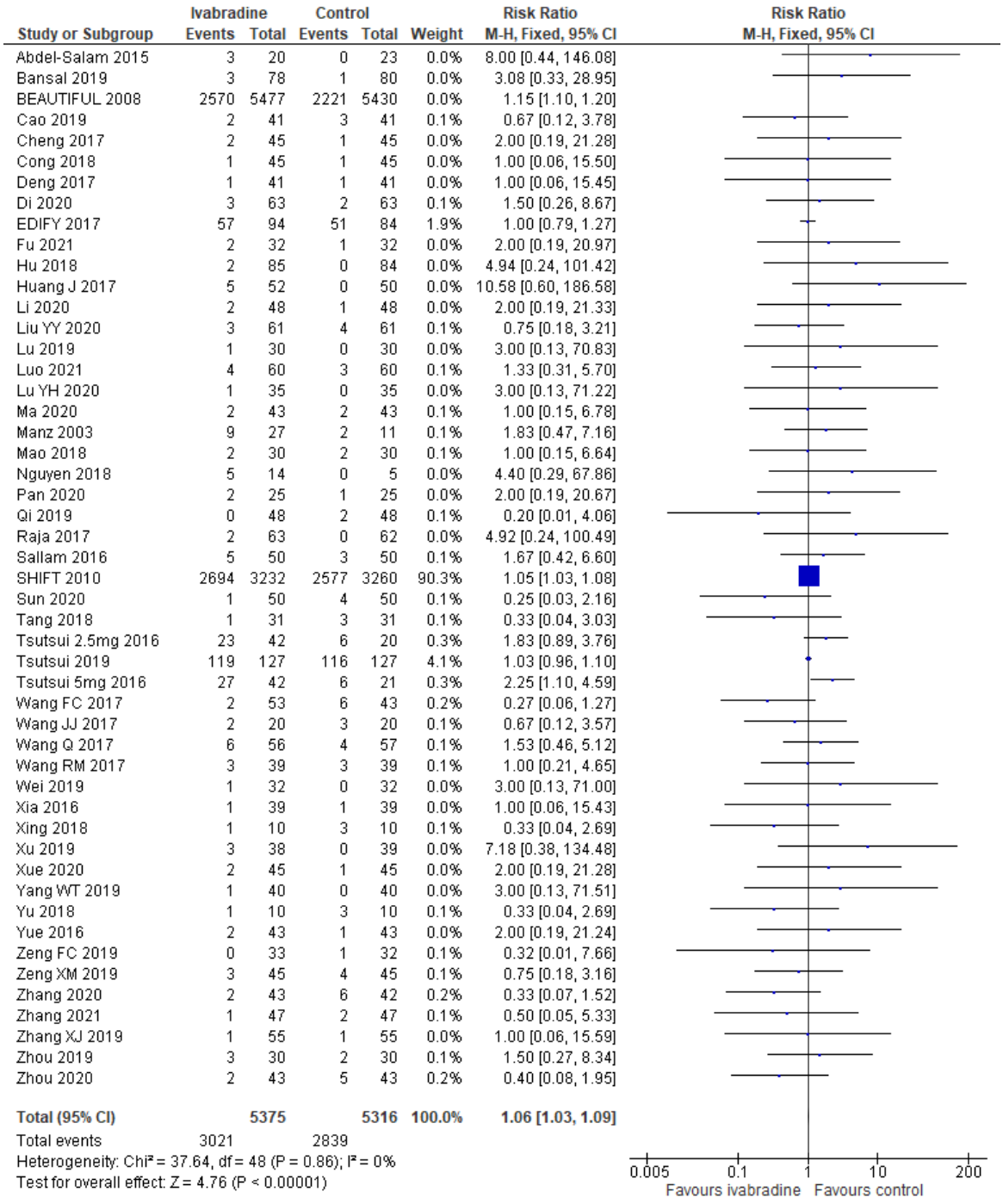


Figure 64 – Forest plot of the sensitivity analysis of non-serious adverse events removing the BEAUTIFUL trial.

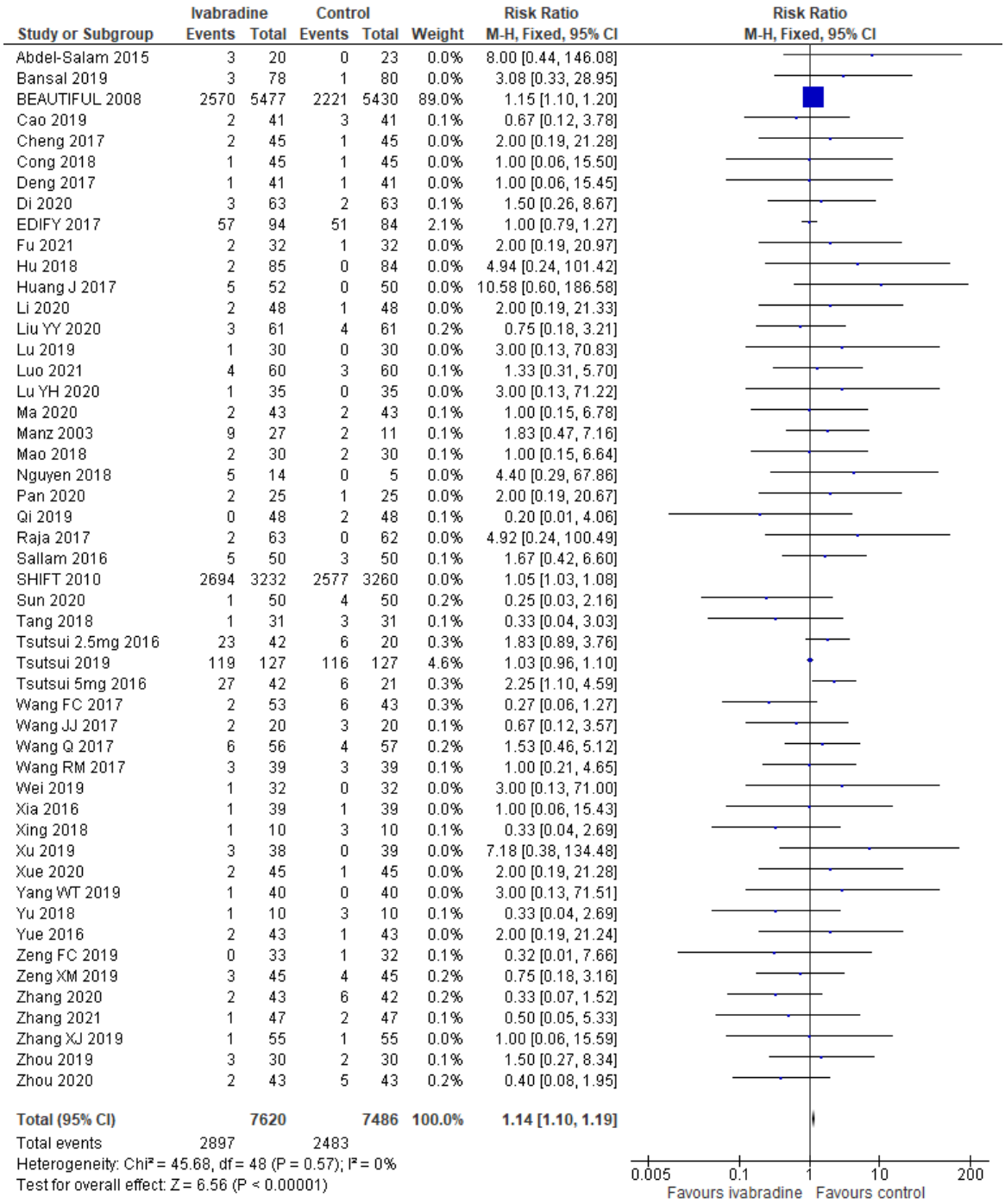


Figure 65 – Forest plot of the sensitivity analysis of non-serious adverse events removing the SHIFT trial.

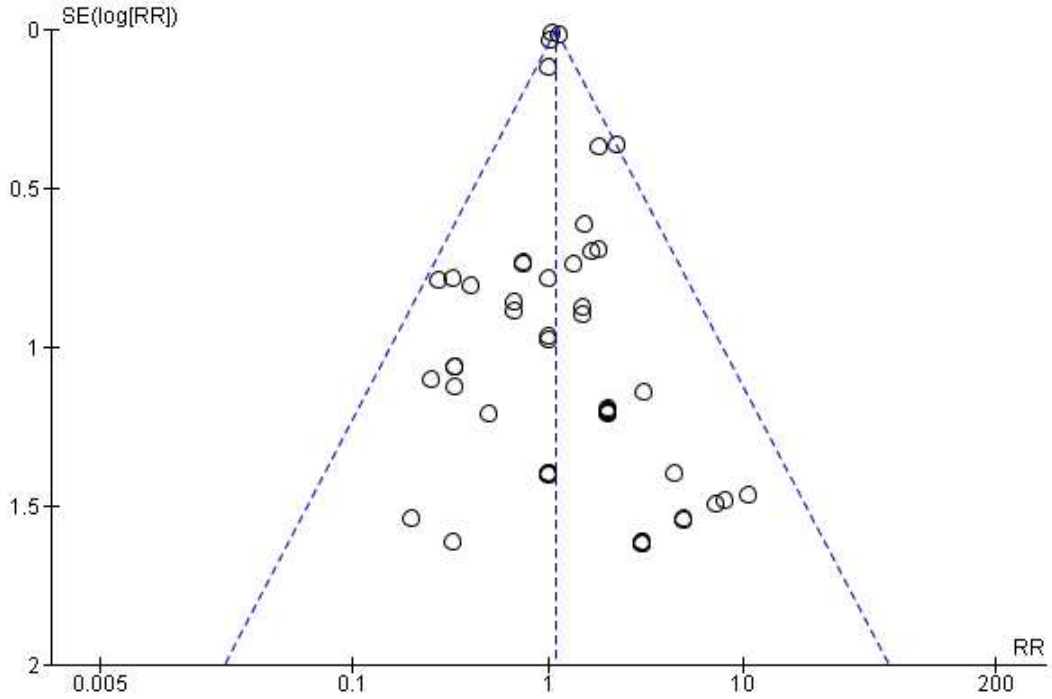


Figure 66 – Funnel plot of the analysis of non-serious adverse events. The funnel plot did not indicate small study bias.

Supplement 11 – Discrepancy in safety data

For serious and non-serious adverse events, there were discrepancies between the data reported in the publication in the SHIFT trial as compared to the raw data reported on ClinicalTrials.gov.

In the published article of the SHIFT trial, it was reported that 1450/3232 (44.86%) participants in the ivabradine group and 1553/3260 (47.6%) in the control group experienced one or more serious adverse events. However, in the raw data it was reported that 1369/3232 (42.4%) in the ivabradine group versus 1481/3260 (45.4%) in the control group experienced one or more serious adverse events. In our analyses, we have used the highest proportion of participants at risk.

In the published article of the SHIFT trial it was reported that 2439/3232 (75.5%) participants in the ivabradine group and 2423/3260 (74.3%) in the control group experienced one or more non-serious adverse events. However, in the raw data it was reported that 2062/3232 (63.8%) in the ivabradine group versus 2020/3260 (62.0%) in the control group experienced one or more non-serious adverse events. In our analyses, we have used the highest proportion of participants at risk. The company that developed ivabradine, Servier, has 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

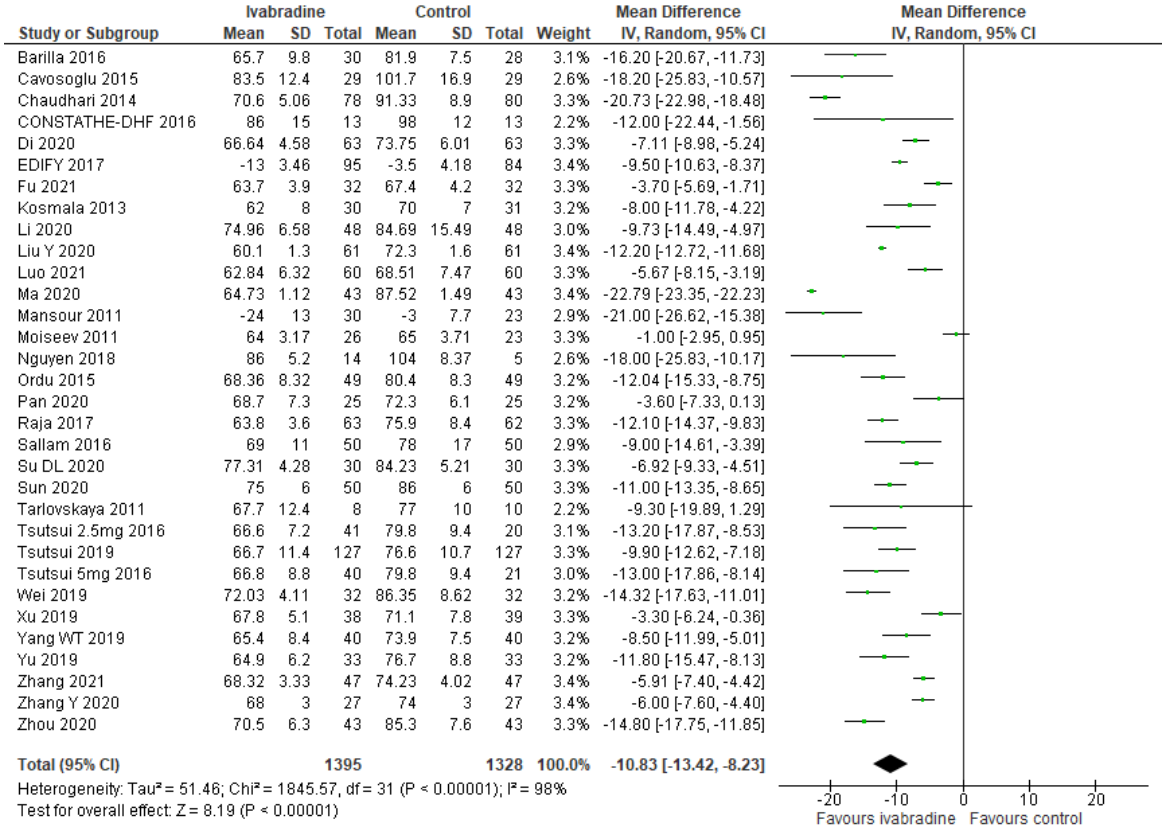


Figure 67 – Forest plot of the meta-analysis of resting heart rate at follow-up using random-effects meta-analysis. The meta-analysis showed that ivabradine seemed to decrease the resting heart rate at follow-up by 10.83 beats per minute at follow-up.

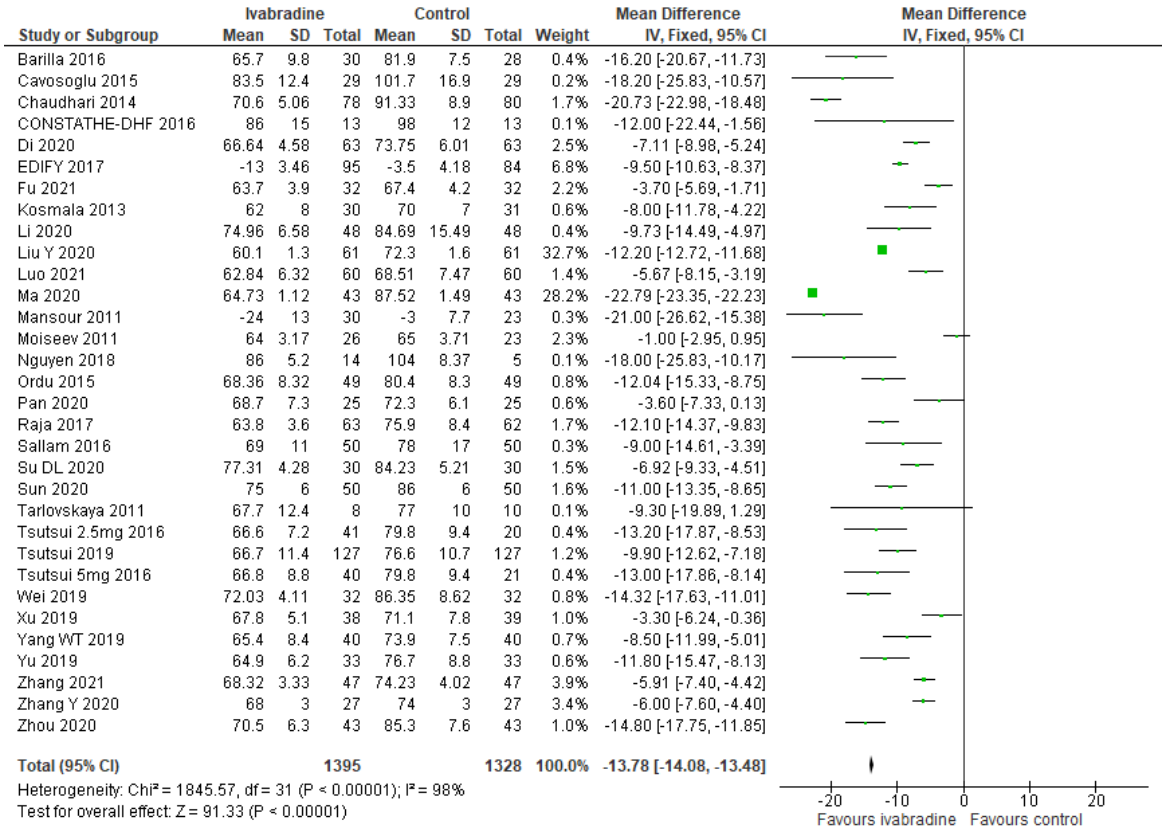


Figure 68 - Forest plot of the meta-analysis of resting heart rate at follow-up using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to decrease the resting heart rate at follow-up by 13.78 beats per minute at follow-up.

Left ventricular ejection fraction

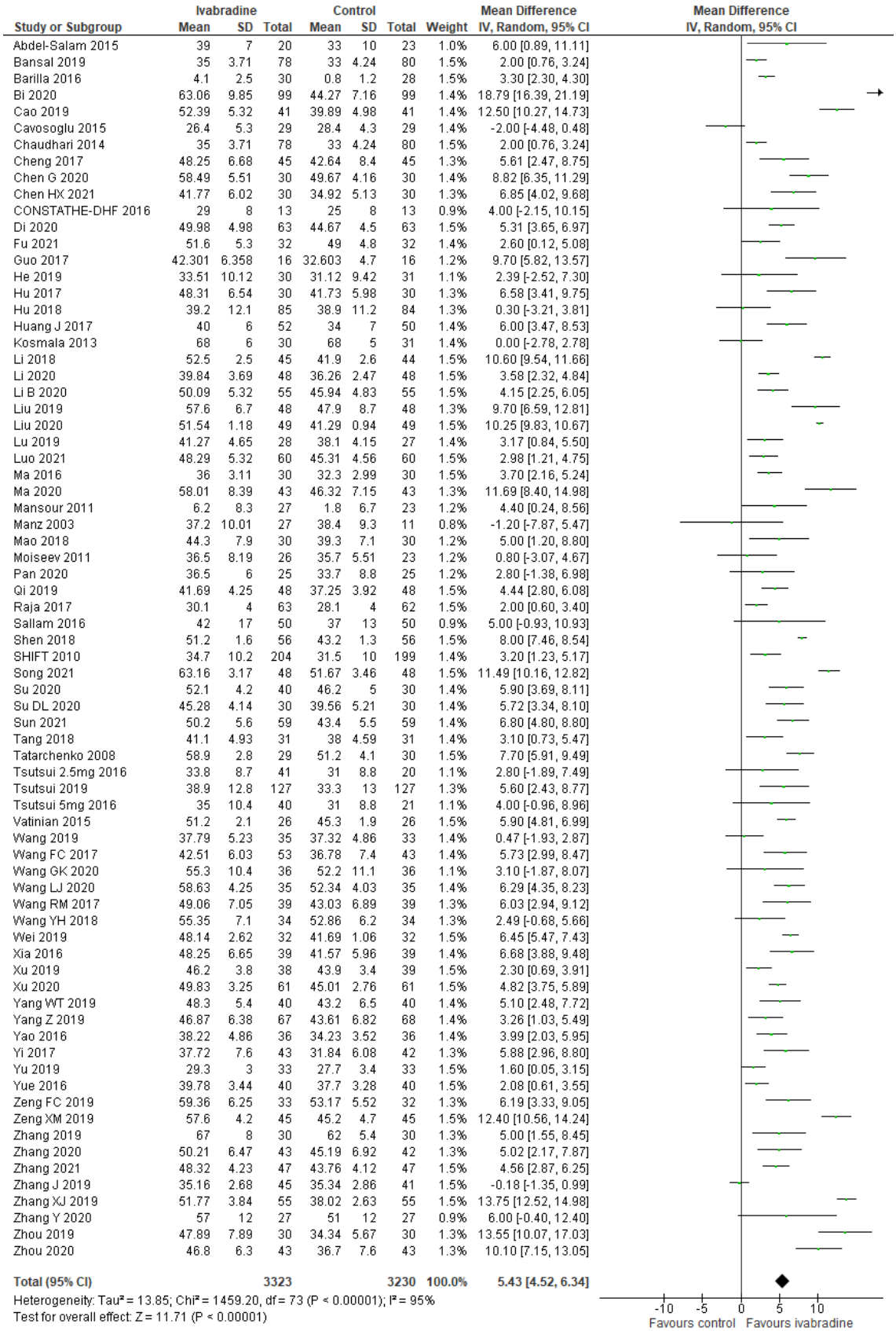

Ivabradine
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Abdel-Salam 2015 39 7 20 33 10 23 1.0% 6.00 [0.89, 11.11]
Bansal 2019 35 3.71 78 33 4.24 80 1.5% 2.00 [0.76, 3.24]
Barilla 2016 4.1 2.5 30 0.8 1.2 28 1.5% 3.30 [2.30, 4.30]
Bi 2020 63.06 9.85 99 44.27 7.16 99 1.4% 18.79 [16.39, 21.19]
Cao 2019 52.39 5.32 41 39.89 4.98 41 1.4% 12.50 [10.27, 14.73]
Cavosoglu 2015 26.4 5.3 29 28.4 4.3 29 1.4% -2.00 [-4.48, 0.48]
Chaudhari 2014 35 3.71 78 33 4.24 80 1.5% 2.00 [0.76, 3.24]
Cheng 2017 48.25 6.68 45 42.64 8.4 45 1.3% 5.61 [2.47, 8.75]
Chen G 2020 58.49 5.51 30 49.67 4.16 30 1.4% 8.82 [6.35, 11.29]
Chen HX 2021 41.77 6.02 30 34.92 5.13 30 1.3% 6.85 [4.02, 9.68]
CONSTATHE-DHF 2016 29 8 13 25 8 13 0.9% 4.00 [-2.15, 10.15]
Di 2020 49.98 4.98 63 44.67 4.5 63 1.5% 5.31 [3.65, 6.97]
Fu 2021 51.6 5.3 32 49 4.8 32 1.4% 2.60 [0.12, 5.08]
Guo 2017 42.301 6.358 16 32.603 4.7 16 1.2% 9.70 [5.82, 13.57]
He 2019 33.51 10.12 30 31.12 9.42 31 1.1% 2.39 [-2.52, 7.30]
Hu 2017 48.31 6.54 30 41.73 5.98 30 1.3% 6.58 [3.41, 9.75]
Hu 2018 39.2 12.1 85 38.9 11.2 84 1.3% 0.30 [-3.21, 3.81]
Huang J 2017 40 6 52 34 7 50 1.4% 6.00 [3.47, 8.53]
Kosmala 2013 68 6 30 68 5 31 1.4% 0.00 [-2.78, 2.78]
Li 2018 52.5 2.5 45 41.9 2.6 44 1.5% 10.60 [9.54, 11.66]
Li 2020 39.84 3.69 48 36.26 2.47 48 1.5% 3.58 [2.32, 4.84]
Li B 2020 50.09 5.32 55 45.94 4.83 55 1.5% 4.15 [2.25, 6.05]
Liu 2019 57.6 6.7 48 47.9 8.7 48 1.3% 9.70 [6.59, 12.81]
Liu 2020 51.54 1.18 49 41.29 0.94 49 1.5% 10.25 [9.83, 10.67]
Lu 2019 41.27 4.65 28 38.1 4.15 27 1.4% 3.17 [0.84, 5.50]
Luo 2021 48.29 5.32 60 45.31 4.56 60 1.5% 2.98 [1.21, 4.75]
Ma 2016 36 3.11 30 32.3 2.99 30 1.5% 3.70 [2.16, 5.24]
Ma 2020 58.01 8.39 43 46.32 7.15 43 1.3% 11.69 [8.40, 14.98]
Mansour 2011 6.2 8.3 27 1.8 6.7 23 1.2% 4.40 [0.24, 8.56]
Manz 2003 37.2 10.01 27 38.4 9.3 11 0.8% -1.20 [-7.87, 5.47]
Mao 2018 44.3 7.9 30 39.3 7.1 30 1.2% 5.00 [1.20, 8.80]
Moiseev 2011 36.5 8.19 26 35.7 5.51 23 1.2% 0.80 [-3.07, 4.67]
Pan 2020 36.5 6 25 33.7 8.8 25 1.2% 2.80 [-1.38, 6.98]
Qi 2019 41.69 4.25 48 37.25 3.92 48 1.5% 4.44 [2.80, 6.08]
Raja 2017 30.1 4 63 28.1 4 62 1.5% 2.00 [0.60, 3.40]
Sallam 2016 42 17 50 37 13 50 0.9% 5.00 [-0.93, 10.93]
Shen 2018 51.2 1.6 56 43.2 1.3 56 1.5% 8.00 [7.46, 8.54]
SHIFT 2010 34.7 10.2 204 31.5 10 199 1.4% 3.20 [1.23, 5.17]
Song 2021 63.16 3.17 48 51.67 3.46 48 1.5% 11.49 [10.16, 12.82]
Su 2020 52.1 4.2 40 46.2 5 30 1.4% 5.90 [3.69, 8.11]
Su DL 2020 45.28 4.14 30 39.56 5.21 30 1.4% 5.72 [3.34, 8.10]
Sun 2021 50.2 5.6 59 43.4 5.5 59 1.4% 6.80 [4.80, 8.80]
Tang 2018 41.1 4.93 31 38 4.59 31 1.4% 3.10 [0.73, 5.47]
Tatarchenko 2008 58.9 2.8 29 51.2 4.1 30 1.5% 7.70 [5.91, 9.49]
Tsutsui 2.5mg 2016 33.8 8.7 41 31 8.8 20 1.1% 2.80 [-1.89, 7.49]
Tsutsui 2019 38.9 12.8 127 33.3 13 127 1.3% 5.60 [2.43, 8.77]
Tsutsui 5mg 2016 35 10.4 40 31 8.8 21 1.1% 4.00 [-0.96, 8.96]
Vatinian 2015 51.2 2.1 26 45.3 1.9 26 1.5% 5.90 [4.81, 6.99]
Wang 2019 37.79 5.23 35 37.32 4.86 33 1.4% 0.47 [-1.93, 2.87]
Wang FC 2017 42.51 6.03 53 36.78 7.4 43 1.4% 5.73 [2.99, 8.47]
Wang GK 2020 55.3 10.4 36 52.2 11.1 36 1.1% 3.10 [-1.87, 8.07]
Wang LJ 2020 58.63 4.25 35 52.34 4.03 35 1.4% 6.29 [4.35, 8.23]
Wang RM 2017 49.06 7.05 39 43.03 6.89 39 1.3% 6.03 [2.94, 9.12]
Wang YH 2018 55.35 7.1 34 52.86 6.2 34 1.3% 2.49 [-0.68, 5.66]
Wei 2019 48.14 2.62 32 41.69 1.06 32 1.5% 6.45 [5.47, 7.43]
Xia 2016 48.25 6.65 39 41.57 5.96 39 1.4% 6.68 [3.88, 9.48]
Xu 2019 46.2 3.8 38 43.9 3.4 39 1.5% 2.30 [0.69, 3.91]
Xu 2020 49.83 3.25 61 45.01 2.76 61 1.5% 4.82 [3.75, 5.89]
Yang WT 2019 48.3 5.4 40 43.2 6.5 40 1.4% 5.10 [2.48, 7.72]
Yang Z 2019 46.87 6.38 67 43.61 6.82 68 1.4% 3.26 [1.03, 5.49]
Yao 2016 38.22 4.86 36 34.23 3.52 36 1.4% 3.99 [2.03, 5.95]
Yi 2017 37.72 7.6 43 31.84 6.08 42 1.3% 5.88 [2.96, 8.80]
Yu 2019 29.3 3 33 27.7 3.4 33 1.5% 1.60 [0.05, 3.15]
Yue 2016 39.78 3.44 40 37.7 3.28 40 1.5% 2.08 [0.61, 3.55]
Zeng FC 2019 59.36 6.25 33 53.17 5.52 32 1.3% 6.19 [3.33, 9.05]
Zeng XM 2019 57.6 4.2 45 45.2 4.7 45 1.5% 12.40 [10.56, 14.24]
Zhang 2019 67 8 30 62 5.4 30 1.3% 5.00 [1.55, 8.45]
Zhang 2020 50.21 6.47 43 45.19 6.92 42 1.3% 5.02 [2.17, 7.87]
Zhang 2021 48.32 4.23 47 43.76 4.12 47 1.5% 4.56 [2.87, 6.25]
Zhang J 2019 35.16 2.68 45 35.34 2.86 41 1.5% -0.18 [-1.35, 0.99]
Zhang XJ 2019 51.77 3.84 55 38.02 2.63 55 1.5% 13.75 [12.52, 14.98]
Zhang Y 2020 57 12 27 51 12 27 0.9% 6.00 [-0.40, 12.40]
Zhou 2019 47.89 7.89 30 34.34 5.67 30 1.3% 13.55 [10.07, 17.03]
Zhou 2020 46.8 6.3 43 36.7 7.6 43 1.3% 10.10 [7.15, 13.05]
Total (95% CI) 3323 3230 100.0% 5.43 [4.52, 6.34]
Heterogeneity: Tau² = 13.85; Chi² = 1459.20, df = 73 (P < 0.00001); I² = 95%
Test for overall effect: Z = 11.71 (P < 0.00001)
-10 -5 0 5 10
Favours control Favours ivabradine

Figure 69 - Forest plot of the meta-analysis of left ventricular ejection fraction using random-effects meta-analysis. The meta-analysis showed that ivabradine seemed to increase the left ventricular ejection fraction by 5.43%.

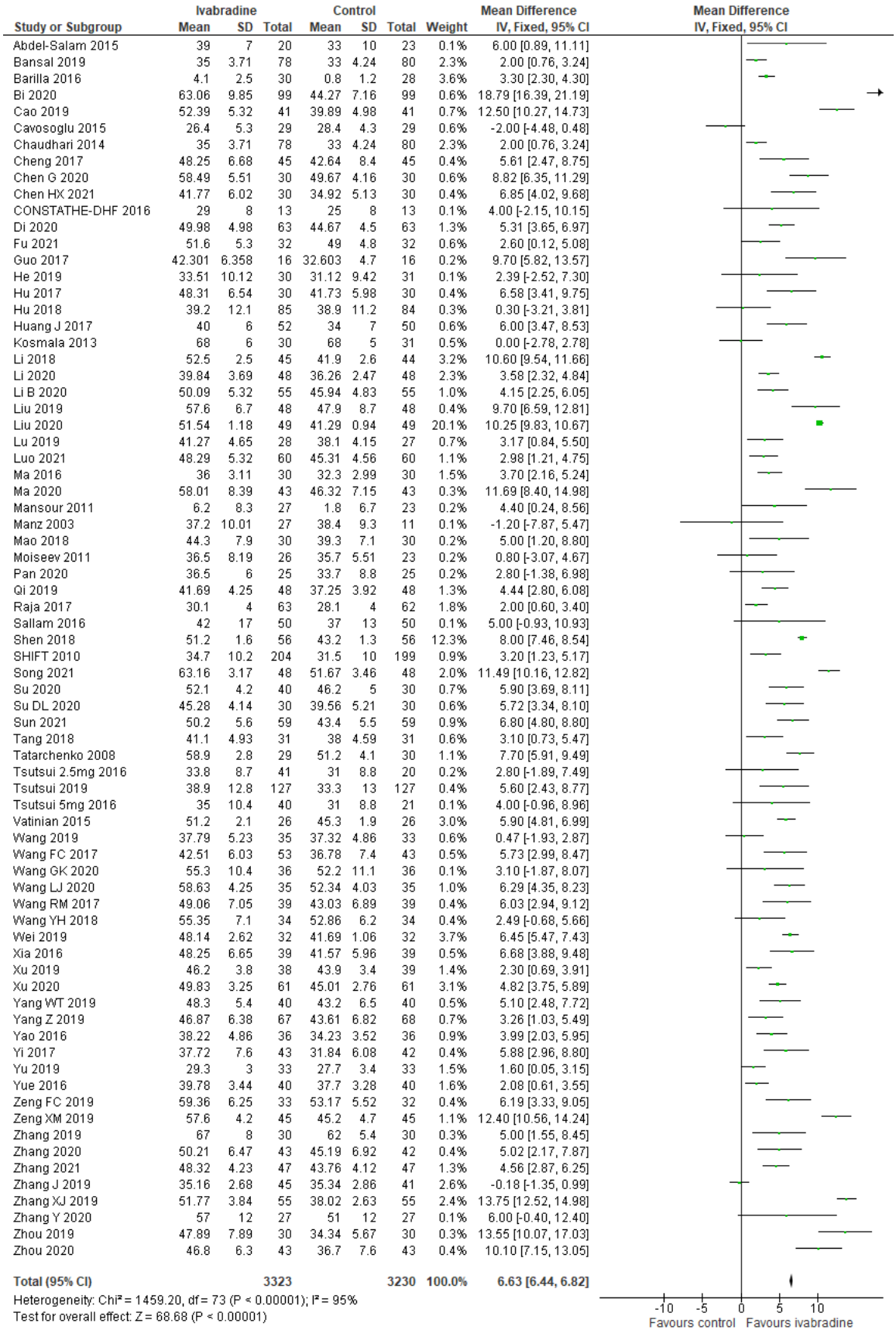

Ivabradine
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Abdel-Salam 2015 39 7 20 33 10 23 0.1% 6.00 [0.89, 11.11]
Bansal 2019 35 3.71 78 33 4.24 80 2.3% 2.00 [0.76, 3.24]
Barilla 2016 4.1 2.5 30 0.8 1.2 28 3.6% 3.30 [2.30, 4.30]
Bi 2020 63.06 9.85 99 44.27 7.16 99 0.6% 18.79 [16.39, 21.19]
Cao 2019 52.39 5.32 41 39.89 4.98 41 0.7% 12.50 [10.27, 14.73]
Cavosoglu 2015 26.4 5.3 29 28.4 4.3 29 0.6% -2.00 [-4.48, 0.48]
Chaudhari 2014 35 3.71 78 33 4.24 80 2.3% 2.00 [0.76, 3.24]
Cheng 2017 48.25 6.68 45 42.64 8.4 45 0.4% 5.61 [2.47, 8.75]
Chen G 2020 58.49 5.51 30 49.67 4.16 30 0.6% 8.82 [6.35, 11.29]
Chen HX 2021 41.77 6.02 30 34.92 5.13 30 0.4% 6.85 [4.02, 9.68]
CONSTATHE-DHF 2016 29 8 13 25 8 13 0.1% 4.00 [-2.15, 10.15]
Di 2020 49.98 4.98 63 44.67 4.5 63 1.3% 5.31 [3.65, 6.97]
Fu 2021 51.6 5.3 32 49 4.8 32 0.6% 2.60 [0.12, 5.08]
Guo 2017 42.301 6.358 16 32.603 4.7 16 0.2% 9.70 [5.82, 13.57]
He 2019 33.51 10.12 30 31.12 9.42 31 0.1% 2.39 [-2.52, 7.30]
Hu 2017 48.31 6.54 30 41.73 5.98 30 0.4% 6.58 [3.41, 9.75]
Hu 2018 39.2 12.1 85 38.9 11.2 84 0.3% 0.30 [-3.21, 3.81]
Huang J 2017 40 6 52 34 7 50 0.6% 6.00 [3.47, 8.53]
Kosmala 2013 68 6 30 68 5 31 0.5% 0.00 [-2.78, 2.78]
Li 2018 52.5 2.5 45 41.9 2.6 44 3.2% 10.60 [9.54, 11.66]
Li 2020 39.84 3.69 48 36.26 2.47 48 2.3% 3.58 [2.32, 4.84]
Li B 2020 50.09 5.32 55 45.94 4.83 55 1.0% 4.15 [2.25, 6.05]
Liu 2019 57.6 6.7 48 47.9 8.7 48 0.4% 9.70 [6.59, 12.81]
Liu 2020 51.54 1.18 49 41.29 0.94 49 20.1% 10.25 [9.83, 10.67]
Lu 2019 41.27 4.65 28 38.1 4.15 27 0.7% 3.17 [0.84, 5.50]
Luo 2021 48.29 5.32 60 45.31 4.56 60 1.1% 2.98 [1.21, 4.75]
Ma 2016 36 3.11 30 32.3 2.99 30 1.5% 3.70 [2.16, 5.24]
Ma 2020 58.01 8.39 43 46.32 7.15 43 0.3% 11.69 [8.40, 14.98]
Mansour 2011 6.2 8.3 27 1.8 6.7 23 0.2% 4.40 [0.24, 8.56]
Manz 2003 37.2 10.01 27 38.4 9.3 11 0.1% -1.20 [-7.87, 5.47]
Mao 2018 44.3 7.9 30 39.3 7.1 30 0.2% 5.00 [1.20, 8.80]
Moiseev 2011 36.5 8.19 26 35.7 5.51 23 0.2% 0.80 [-3.07, 4.67]
Pan 2020 36.5 6 25 33.7 8.8 25 0.2% 2.80 [-1.38, 6.98]
Qi 2019 41.69 4.25 48 37.25 3.92 48 1.3% 4.44 [2.80, 6.08]
Raja 2017 30.1 4 63 28.1 4 62 1.8% 2.00 [0.60, 3.40]
Sallam 2016 42 17 50 37 13 50 0.1% 5.00 [-0.93, 10.93]
Shen 2018 51.2 1.6 56 43.2 1.3 56 12.3% 8.00 [7.46, 8.54]
SHIFT 2010 34.7 10.2 204 31.5 10 199 0.9% 3.20 [1.23, 5.17]
Song 2021 63.16 3.17 48 51.67 3.46 48 2.0% 11.49 [10.16, 12.82]
Su 2020 52.1 4.2 40 46.2 5 30 0.7% 5.90 [3.69, 8.11]
Su DL 2020 45.28 4.14 30 39.56 5.21 30 0.6% 5.72 [3.34, 8.10]
Sun 2021 50.2 5.6 59 43.4 5.5 59 0.9% 6.80 [4.80, 8.80]
Tang 2018 41.1 4.93 31 38 4.59 31 0.6% 3.10 [0.73, 5.47]
Tatarchenko 2008 58.9 2.8 29 51.2 4.1 30 1.1% 7.70 [5.91, 9.49]
Tsutsui 2.5mg 2016 33.8 8.7 41 31 8.8 20 0.2% 2.80 [-1.89, 7.49]
Tsutsui 2019 38.9 12.8 127 33.3 13 127 0.4% 5.60 [2.43, 8.77]
Tsutsui 5mg 2016 35 10.4 40 31 8.8 21 0.1% 4.00 [-0.96, 8.96]
Vatinian 2015 51.2 2.1 26 45.3 1.9 26 3.0% 5.90 [4.81, 6.99]
Wang 2019 37.79 5.23 35 37.32 4.86 33 0.6% 0.47 [-1.93, 2.87]
Wang FC 2017 42.51 6.03 53 36.78 7.4 43 0.5% 5.73 [2.99, 8.47]
Wang GK 2020 55.3 10.4 36 52.2 11.1 36 0.1% 3.10 [-1.87, 8.07]
Wang LJ 2020 58.63 4.25 35 52.34 4.03 35 1.0% 6.29 [4.35, 8.23]
Wang RM 2017 49.06 7.05 39 43.03 6.89 39 0.4% 6.03 [2.94, 9.12]
Wang YH 2018 55.35 7.1 34 52.86 6.2 34 0.4% 2.49 [-0.68, 5.66]
Wei 2019 48.14 2.62 32 41.69 1.06 32 3.7% 6.45 [5.47, 7.43]
Xia 2016 48.25 6.65 39 41.57 5.96 39 0.5% 6.68 [3.88, 9.48]
Xu 2019 46.2 3.8 38 43.9 3.4 39 1.4% 2.30 [0.69, 3.91]
Xu 2020 49.83 3.25 61 45.01 2.76 61 3.1% 4.82 [3.75, 5.89]
Yang WT 2019 48.3 5.4 40 43.2 6.5 40 0.5% 5.10 [2.48, 7.72]
Yang Z 2019 46.87 6.38 67 43.61 6.82 68 0.7% 3.26 [1.03, 5.49]
Yao 2016 38.22 4.86 36 34.23 3.52 36 0.9% 3.99 [2.03, 5.95]
Yi 2017 37.72 7.6 43 31.84 6.08 42 0.4% 5.88 [2.96, 8.80]
Yu 2019 29.3 3 33 27.7 3.4 33 1.5% 1.60 [0.05, 3.15]
Yue 2016 39.78 3.44 40 37.7 3.28 40 1.6% 2.08 [0.61, 3.55]
Zeng FC 2019 59.36 6.25 33 53.17 5.52 32 0.4% 6.19 [3.33, 9.05]
Zeng XM 2019 57.6 4.2 45 45.2 4.7 45 1.1% 12.40 [10.56, 14.24]
Zhang 2019 67 8 30 62 5.4 30 0.3% 5.00 [1.55, 8.45]
Zhang 2020 50.21 6.47 43 45.19 6.92 42 0.4% 5.02 [2.17, 7.87]
Zhang 2021 48.32 4.23 47 43.76 4.12 47 1.3% 4.56 [2.87, 6.25]
Zhang J 2019 35.16 2.68 45 35.34 2.86 41 2.6% -0.18 [-1.35, 0.99]
Zhang XJ 2019 51.77 3.84 55 38.02 2.63 55 2.4% 13.75 [12.52, 14.98]
Zhang Y 2020 57 12 27 51 12 27 0.1% 6.00 [-0.40, 12.40]
Zhou 2019 47.89 7.89 30 34.34 5.67 30 0.3% 13.55 [10.07, 17.03]
Zhou 2020 46.8 6.3 43 36.7 7.6 43 0.4% 10.10 [7.15, 13.05]
Total (95% CI) 3323 3230 100.0% 6.63 [6.44, 6.82]
Heterogeneity: Chi² = 1459.20, df = 73 (P < 0.00001); I² = 95%
Test for overall effect: Z = 68.68 (P < 0.00001)
-10 -5 0 5 10
Favours control Favours ivabradine

Figure 70 - 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 6.63%.

Hospitalisation during follow-up

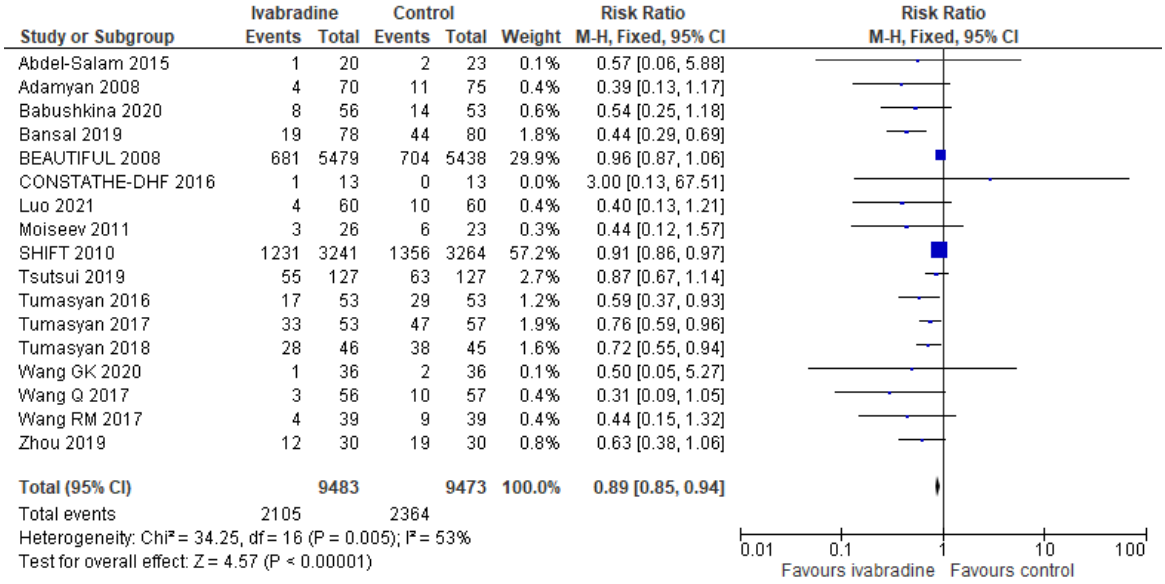


Figure 71 – Forest plot of the meta-analysis of hospitalisation during follow-up using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect ivabradine versus control (placebo or no intervention) of a risk ratio of 0.89.

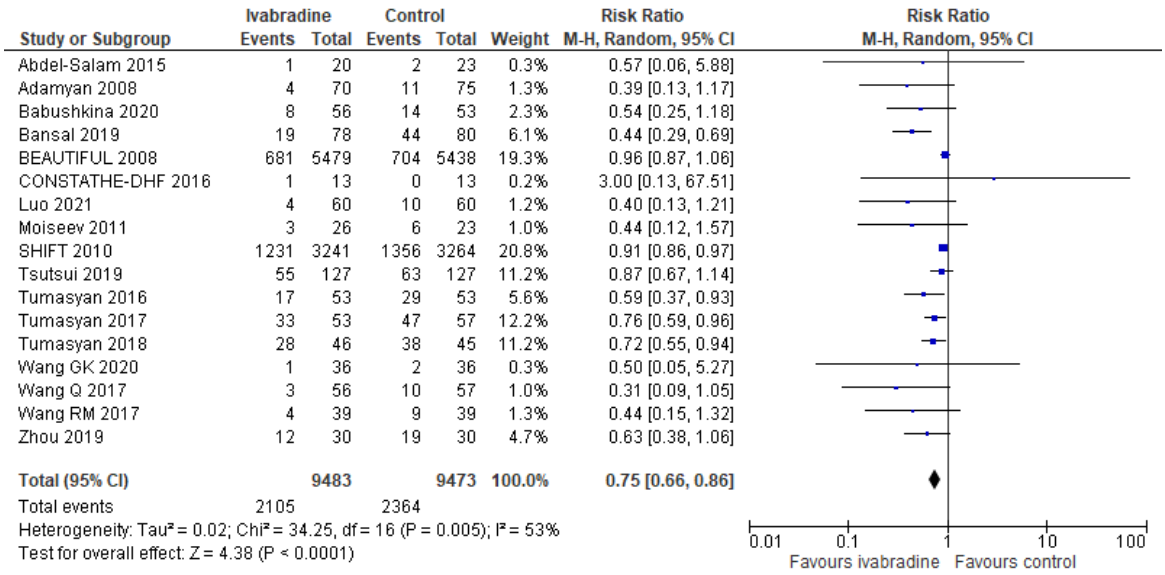


Figure 72 - Forest plot of the meta-analysis of hospitalisation during follow-up using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention) of a risk ratio of 0.75.

6-minutes walking distance

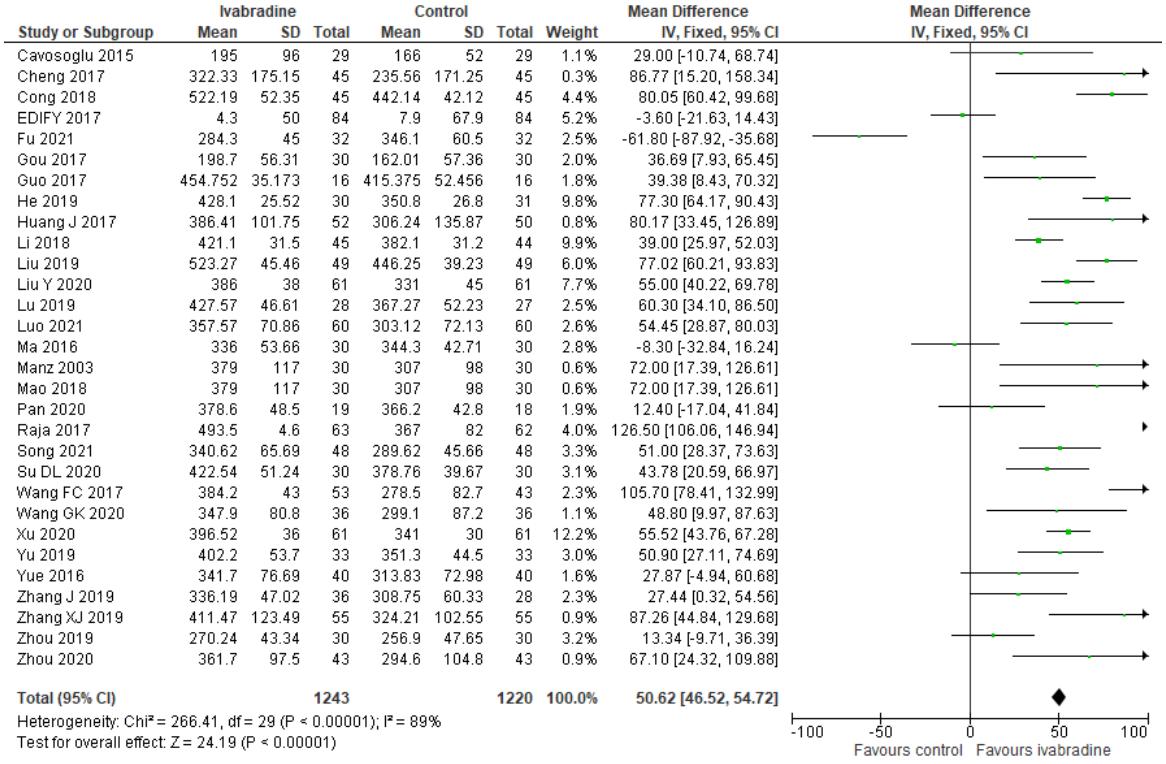


Figure 73 – Forest plot of the meta-analysis of 6-minutes walking distance using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention) of 50.62 meters per 6 minutes.

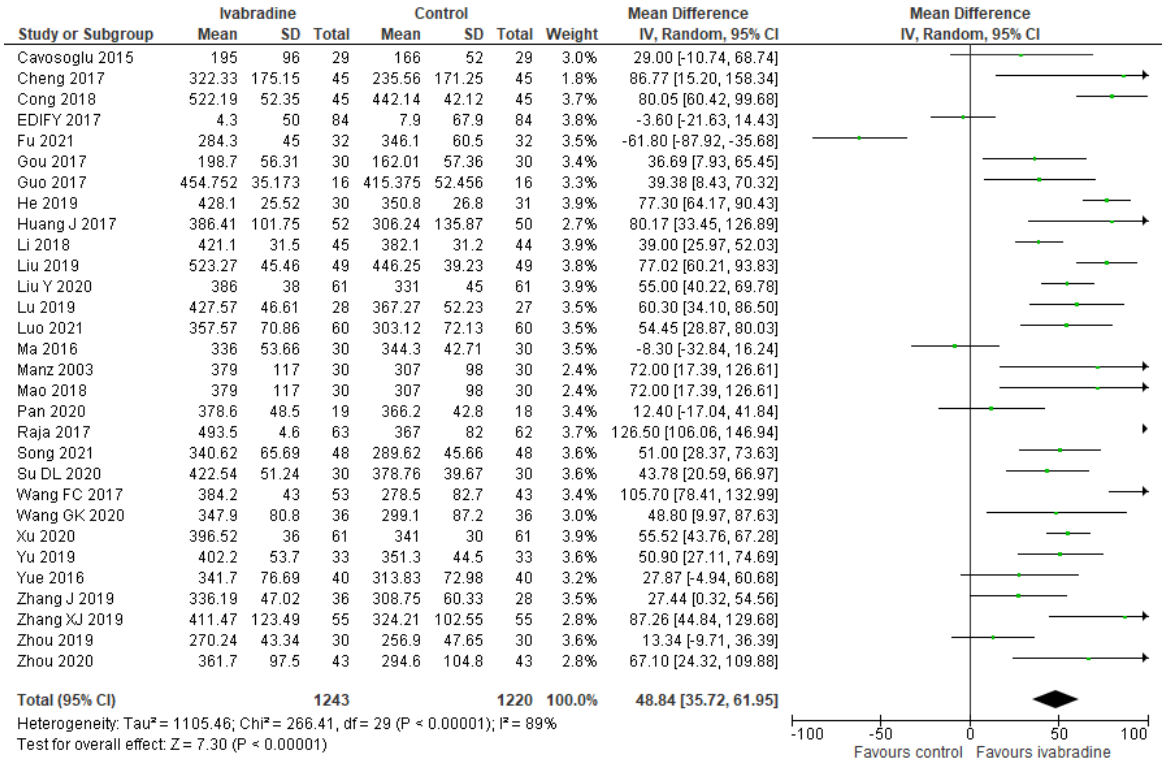


Figure 74 – Forest plot of the meta-analysis of 6-minutes walking distance using random-effects meta-analysis. The meta-analysis shows evidence of a beneficial effect of ivabradine versus control (placebo or no intervention) of 48.84 meters per 6 minutes.

First author	Year	Publication type	No. randomised	Clinical condition(s)	Age	%-female	Interventions	
							Experimental	Control
Abdel-Hady	2011	Abstract	100	Heart failure, EF<35%	NR	NR	Ivabradine	Placebo
Abdel-Salam	2015	Paper	43	Dilated cardiomyopathy, EF<40%	50.8	46.5	Ivabradine	Placebo
Adamyan	2010	Abstract	118	Heart failure, EF>50%	58.0	24.8	Ivabradine	No intervention
Adamyan	2008	Abstract	145	Heart failure, EF<35%	58.0	30.0	Ivabradine	No intervention
Adamyan	2015	Abstract	104	Heart failure, EF>50%	63.2	NR	Ivabradine	No intervention
Al Saadi	2013	Abstract	NR	Stable ischemic heart failure	NR	NR	Ivabradine	No intervention
Aroutunov	2008	Abstract	24	Decompensated heart failure	NR	NR	Ivabradine	No intervention
Babushkina	2020	Article	109	Heart failure, EF>50%	57.7	37	Ivabradine	No intervention
Bansal	2019	Abstract	309	Stable ischemic heart failure	NR	NR	Ivabradine	No intervention
Barilla	2016	Paper	58	Acute myocardial infarction, cardiogenic shock	55.4	32.8	Ivabradine	No intervention
Bi	2020	Paper	198	Heart failure	56.8	46.0	Ivabradine	No intervention
Cao	2019	Paper	82	Heart failure, EF<35%	69.3	50.0	Ivabradine	No intervention
Cavosoglu	2015	Paper	58	Decompensated heart failure, EF<35%	65.6	25.7	Ivabradine	No intervention
Chaudhari	2014	Abstract	158	Ischemic heart failure	NR	NR	Ivabradine	No intervention
Chen	2020	Paper	60	Chronic heart failure	62.5	35	Ivabradine	No intervention
Chen	2021	Paper	100	Chronic heart failure	57.8	42	Ivabradine	No intervention
Chen HX	2021	Paper	60	Severe chronic heart failure	70.5	45	Ivabradine	No intervention
Cheng	2017	Paper	90	Heart failure, EF<45%	71.0	44.4	Ivabradine	No intervention
Chumburidze	2013	Abstract	30	Dilated cardiomyopathy EF<35%	54.0	NR	Ivabradine	Placebo
Cong	2018	Paper	90	Heart failure	64.6	60.0	Ivabradine	No intervention
Deng	2017	Paper	82	Heart failure	61.8	40.2	Ivabradine	No intervention
Di	2020	Paper	126	Heart failure, EF<40%, HR>70	66.4	43.4	Ivabradine	No intervention
Fox (BEAUTIFUL)	2008	Paper	10917	Stable coronary artery disease, heart failure, EF<40%	65.2	17.1	Ivabradine	Placebo
Fu	2021	Paper	64	Chronic heart failiure, EF 40-50%, HR>70	NR	NR	Ivabradine	No intervention
Gou	2017	Paper	60	Decompensated heart failure, EF<40%	63.7	48.3	Ivabradine	No intervention
Guo	2017	Paper	32	Heart failure, EF<40%	NR	0.0	Ivabradine	No intervention
He	2019	Paper	68	Coronary artery disease, heart failure, EF 40-49%	64.8	47.1	Ivabradine	No intervention
Hu	2017	Paper	60	Heart failure, EF<35%	68.0	45.0	Ivabradine	No intervention
Hu	2018	Paper	169	Acute myocardial infarction, heart failure	63.0	3.6	Ivabradine	No intervention
Huang J	2017	Paper	102	Heart failure	71.5	41.2	Ivabradine	No intervention
Komajda (EDIFY)	2017	Paper	179	Heart failure, EF>45%	72.5	64.8	Ivabradine	Placebo

Kosmala	2013	Paper	61	Heart failure, EF >50%	67.3	82.0	Ivabradine	Placebo
Li	2018	Paper	89	Heart failure	57.5	47.2	Ivabradine	No intervention
Li B	2020	Paper	110	Chronic heart failure, HR>100	64.2	35.4	Ivabradine	No intervention
Li Q	2020	Paper	96	Chronic heart failure, EF<50%, HR>75	65.3	33.6	Ivabradine	No intervention
Liu	2019	Paper	96	Heart failure	63.8	51.0	Ivabradine	No intervention
Liu	2020	Paper	98	Heart failure	67.4	60.2	Ivabradine	Placebo
Liu Y	2020	Paper	122	Heart failure, EF>50%, HR>70	65	34.4	Ivabradine	No intervention
Lofrano-Alves	2016	Paper	26	Heart failure, EF<40%	42.0	46.2	Ivabradine	Placebo
Lu	2019	Thesis	60	Dilated cardiomyopathy, EF<40%	47.2	43.3	Ivabradine	No intervention
Lu	2020	Paper	70	Chronic heart failure, EF 30-50%	69.9	34.3	Ivabradine	No intervention
Luo	2021	Paper	120	Heart failure, HR>70	84.2	42.5	Ivabradine	No intervention
Ma	2016	Thesis	60	Heart failure, EF<40%	NR	NR	Ivabradine	Placebo
Ma	2020	Paper	86	Heart failure	58.1	41.9	Ivabradine	Placebo
Mansour	2011	Paper	53	Dilated cardiomyopathy, EF<40%	49.0	40.0	Ivabradine	No intervention
Manz	2003	Paper	44	Cardiomyopathy, EF 20-50%	59.9	NR	Ivabradine	Placebo
Mao	2018	Paper	60	Heart failure	53.1	31.7	Ivabradine	No intervention
Masi de Luca	2018	Abstract	111	Heart failure, EF>50%	61.0	30.0	Ivabradine	Placebo
Moiseev	2011	Abstract	49	Heart failure, EF<40%	63.0	18.4	Ivabradine	No intervention
Nguyen	2018	Paper	19	Planned CABG, EF 20-40%	57.5	15.8	Ivabradine	Placebo
Ordu	2015	Paper	98	Heart failure, EF<35%	65.8	66.3	Ivabradine	No intervention
Pal	2015	Paper	22	Heart failure, EF>50%	74.6	65.0	Ivabradine	Placebo
Pan	2020	Paper	50	Decompensated heart failure, EF<40%	60.1	44.0	Ivabradine	No intervention
Potapenko	2011	Paper	49	Systolic, chronic heart failure	63.1	18.4	Ivabradine	No intervention
Qi	2019	Paper	96	Heart failure	59.7	45.8	Ivabradine	No intervention
Raja	2017	Paper	125	Dilated cardiomyopathy, EF<40%	47.2	43.1	Ivabradine	No intervention
Sallam	2016	Paper	100	Coronary artery disease, heart failure, EF<40%	63.5	30.0	Ivabradine	No intervention
Sarullo	2010	Paper	60	Stable, ischemic heart failure, EF<40%	52.7	25.0	Ivabradine	Placebo
Shen	2018	Paper	112	Heart failure	70.0	41.1	Ivabradine	No intervention
Sisakian	2015	Paper	54	Heart failure, EF<40%	59.9	18.5	Ivabradine	No intervention
Song	2021	Paper	96	Heart failure	69.4	43.8	Ivabradine	No intervention
Su	2020	Paper	70	Heart failure	69.0	44.3	Ivabradine	No intervention
Su D	2020	Paper	60	Chronic heart failure, EF<50%	61.8	48.3	Ivabradine	No intervention
Sun	2020	Paper	100	Heart failure	62.0	42.0	Ivabradine	No intervention

Sun	2021	Paper	118	Chronic heart failure	67.6	43.2	Ivabradine	No intervention
Swedberg (SHIFT)	2010	Paper	6558	Heart failure, EF<35%	60.4	23.4	Ivabradine	Placebo
Tang	2018	Paper	62	Heart failure, EF<40%	63.2	29.0	Ivabradine	No intervention
Tarlovskaya	2011	Abstract	18	Heart failure, EF<35%	53.5	NR	Ivabradine	Placebo
Tatarchenko	2008	Paper	59	Coronary artery disease, heart failure, EF>45%	57.3	NR	Ivabradine	No intervention
Tsutsui	2019	Paper	254	Heart failure, EF<35%	60.7	18.0	Ivabradine	Placebo
Tsutsui	2016	Paper	125	Heart failure, EF<35%	59.0	14.3	Ivabradine	Placebo
Tumasyan	2009	Abstract	126	Severe heart failure	NR	NR	Ivabradine	No intervention
Tumasyan	2012	Abstract	76	Heart failure	57.4	NR	Ivabradine	No intervention
Tumasyan	2016	Abstract	210	Severe heart failure	57.4	NR	Ivabradine	No intervention
Tumasyan	2017	Abstract	110	Heart failure	63.2	NR	Ivabradine	No intervention
Tumasyan	2018	Abstract	91	Heart failure, mid range EF	50.1	NR	Ivabradine	No intervention
Vatinian	2015	Abstract	52	Coronary artery disease, heart failure, EF<35%	NR	NR	Ivabradine	No intervention
Wang	2019	Paper	68	Heart failure, EF <35%	55.8	0.5	Ivabradine	No intervention
Wang FC	2017	Paper	96	Heart failure	70.6	43.8	Ivabradine	No intervention
Wang JJ	2017	Paper	40	Heart failure	52.9	55.0	Ivabradine	No intervention
Wang Q	2017	Paper	120	Heart failure	62.3	35.0	Ivabradine	No intervention
Wang RM	2017	Paper	78	Heart failure	59.9	28.3	Ivabradine	No intervention
Wang YH	2018	Paper	68	Heart failure	66.0	42.3	Ivabradine	No intervention
Wang GK	2020	Paper	72	Chronic heart failure	68.5	48.6	Ivabradine	No intervention
Wang LJ	2020	Paper	70	Chronic heart failure	57.0	22.9	Ivabradine	No intervention
Wei	2019	Paper	64	Heart failure, EF<45%	60.6	39.7	Ivabradine	No intervention
Xia	2016	Paper	78	Heart failure	60.7	44.9	Ivabradine	No intervention
Xing	2018	Paper	20	Heart failure	52.7	55.0	Ivabradine	No intervention
Xu	2019	Paper	77	Heart failure, EF<50%	68.1	0.5	Ivabradine	No intervention
Xu	2020	Paper	122	Heart failure, EF<45%	71.0	56.6	Ivabradine	No intervention
Xue	2020	Paper	90	Chronic heart failure	59.2	45.6	Ivabradine	No intervention
Yang WT	2019	Paper	80	Heart failure, EF<45%	62.2	0.4	Ivabradine	No intervention
Yang Z	2019	Paper	135	Heart failure	65.7	0.3	Ivabradine	No intervention
Yao	2016	Paper	72	Heart failure, EF<40%	NR	NR	Ivabradine	No intervention
Yi	2017	Paper	90	Heart failure, EF<45%	66.6	32.2	Ivabradine	Placebo
Yu	2019	Paper	66	Dilated cardiomyopathy, EF<40%	46.8	0.4	Ivabradine	No intervention
Yu	2018	Paper	86	Heart failure	62.5	43.0	Ivabradine	No intervention

Yue	2016	Thesis	80	Heart failure, EF<40%	68.3	50.0	Ivabradine	No intervention
Zeng FC	2019	Paper	65	Heart failure	72.0	0.6	Ivabradine	No intervention
Zeng XM	2019	Paper	90	Heart failure	70.6	0.5	Ivabradine	No intervention
Zhang	2018	Paper	60	Coronary artery disease, heart failure	64.2	48.3	Ivabradine	No intervention
Zhang J	2019	Paper	86	Heart failure	66.2	0.5	Ivabradine	No intervention
Zhang XJ	2019	Paper	110	Heart failure	61.6	0.4	Ivabradine	No intervention
Zhang	2020	Paper	85	Coronary heart disease, heart failure	64.4	0.4	Ivabradine	No intervention
Zhang Y	2020	Paper	54	Chronic heart failure	NR	51.9	Ivabradine	No intervention
Zhang	2021	Paper	94	Chronic heart failure	70.9	44.7	Ivabradine	No intervention
Zhao	2020	Paper	80	Chronic heart failure	68.3	46.3	Ivabradine	No intervention
Zhou	2019	Thesis	60	Heart failure	54.8	0.4	Ivabradine	No intervention
Zhou	2020	Paper	86	Heart failure, EF<35%, HR>100	65	47.7	Ivabradine	No intervention

Ivabradine added to usual care in patients with heart failure: systematic review with meta-analysis and Trial Sequential Analysis

Detailed risk of bias judgements.

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Abdel-Hady 2011		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	No information
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No protocol available
Other bias	Unclear	No mention of funding or conflicts of interest

Abdel-Salam 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "Randomization was performed by computer-generated allocation schedule drawn by an independent statistician."
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "Study drugs were identical in appearance. Both the patients and the investigators performing the baseline and follow-up assessment were blinded to the treatment allocation."
Blinding of outcome assessment	Unclear	Not mentioned
Incomplete outcome data	Low	No loss to follow-up.
Selective reporting	Unclear	No protocol and serious adverse events reported inadequately
Other bias	Low	Funded by university. No conflicts of interest

Adamyan 2008		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information

Other bias	Unclear	No mention of funding or conflicts of interest

Adamyan 2010		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Adamyan 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Al Saadi 2013		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to carvedilol. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information

Other bias	Unclear	No mention of funding. No conflicts of interest.

Aroutunov 2008		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Babushkina 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine and bisoprolol was compared to bisoprolol alone. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	No funding or conflicts of interest

Bansal 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of

		interest

Barilla 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "patients were assigned to the two treatment groups according to a computer-generated list of randomisation"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	High	Only the echocardiographer was blinded to treatment allocation.
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	No funding received. No conflicts of interest.

BEAUTIFUL 2008 (Fox 2008)		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "the random-allocation schedule was computer-generated by non-adaptive balanced randomisation"
Allocation concealment	Low	Quote: "central interactive voice-response system and an interactive web-response system."
Blinding of participants and personnel	Low	Quote: "double-blind" and "randomised to ivabradine or matched placebo"
Blinding of outcome assessment	Low	Quote: "prespecified events were adjudicated by a central endpoint validation committee blinded to the allocation of randomized study medication"
Incomplete outcome data	Low	Intention-to-treat data presented.
Selective reporting	Low High for serious adverse events and hospitalisations	Protocol registered retrospectively. However, serious adverse events and all-cause mortality was reported. All-cause hospitalisation was not reported and this raises serious concerns of selective outcome reporting related to hospitalisations and serious adverse events.
Other bias	Low	Funded by the company that produced ivabradine (Servier).

Bi 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Cao 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Yan 'An Science and Technology Research Project. No conflicts of interest.

Cavosoglu 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	Reported as placebo-controlled, but no mention of blinding
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	No mention of funding. No conflicts of interest.

Chaudhari 2014		
Bias domain	**Authors' judgement**	**Support for judgement**

Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Chen 2021		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Chen G 2020		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Chen HX 2020		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information

Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Cheng 2017		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Low	Quote: “random-number table”
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Chumburidze 2013		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: “double-blind”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Cong 2018		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Low	Quote: “random-number table”
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome	Unclear	No information

assessment		
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

CONSTATHE-DHF 2016 (Lofrano-Alves)		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "randomly assigned via computer-generated sequence into two groups"
Allocation concealment	Low	Quote: "the randomisation sequence was held by an independent pharmacy"
Blinding of participants and personnel	Low	Quote: "Commercially available IVA tablets were encapsulated in hard gelatin capsules. To create a PLA, capsules were filled with starch; they were indistinguishable from the IVA-containing capsules. Patient, caregivers, outcome assessors, and researched remained blinded to the intervention."
Blinding of outcome assessment	Low	Quote: "outcome assessors remained blinded to the intervention."
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Low	Protocol not registered prospectively. All-cause mortality and serious adverse events reported.
Other bias	High	An author (EAB) received consulting fees and travel/hotel/registration fee subsidies from Servier. EAB also performed contracted research from Servier, received honoraria from Servier, and was a member of the steering comittee of Servier.

Deng 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of

		interest

Di 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

EDIFY 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	Quote: "the randomisation was balanced 1:1 and stratified on centres". No information on the procedure of generating the random sequence
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "double-blind" and "study investigators and participants were masked to treatment for the duration of the trial
Blinding of outcome assessment	Low	Quote: "The trial was conducted under the supervision of an independent executive committee (Supplementary material online, Appendix S3), the members of which were blinded to study medication. After the study unblinding, this committee was given full access to the data and analyses and was responsible for the interpretation of the results and review of the manuscript"
Incomplete outcome data	High	95 were assigned to ivabradine and 84 to placebo. 87 were analysed for efficacy in the ivabradine group and 84 were analysed for efficacy in the placebo group. Hence, 8 patients are unaccounted for in the ivabradine group. 76 participants in the ivabradine group and 77 in the placebo group completed the 8 months follow-up.

Selective reporting	High	Protocol not registered prospectively. Quality of life on the Kansas City Cardiomyopathy Questionnaire not reported.
Other bias	High	The trial was funded by the company that developed ivabradine (Servier). Servier was responsible for data management, analysis, interpretation, and writing of the article.

Fu 2021		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Gou 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Guo 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "computer-generated random number"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"

Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

He 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	High	Unaccounted missing data
Selective reporting	Unclear	No information
Other bias	Low	Funded by Guangdong Traditional Chinese Medicine Supervision Bureau. No conflicts of interest.

Hu 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Hu 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information

Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Huang J 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Kosmala 2013		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "The procedure of randomization to receive either ivabradine 5 mg or placebo twice daily was performed by computerized sequence generation."
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "The hospital pharmacies were responsible for drug randomization and dispensing, and both the investigators and patients were blinded to the treatment option."
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	Retrospectively registered protocol.
Other bias	Low	Funded by Wroclaw Medical University and Brisbane University. No conflicts of interest.

Li 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"

personnel		
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Li 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Li B 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Liu 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information

Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Liu 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Liu YY 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "participants and researchers were unaware of allocation"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Lu 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of

		interest
Lu 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Luo 2021		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Ma 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "double-blind, placebo-controlled"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Ma 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Scientific Research Project of Anhui Provincial Health and Family Planning Commision

Mansour 2011		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "A computer-driven randomization program was used to allocate"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participant and personnel were probably unblinded.
Blinding of outcome assessment	High	No information. Only echocardiographer mentioned as being blinded to treatment allocation.
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	"This work was supported by the Faculty of Medicine at Ain Shams University, and Ain Shams University Hospitals." No conflicts of interest.

Manz 2003		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "single-blind, placebo-controlled study" and "the investigators were aware of the nature of each patient's treatment"
Blinding of outcome	Low	Quote: "The cross-reading investigator

assessment		was blinded to the identity of the patient, the treatment administered, the timing of the recording (Echo 0, 1 or 2) and the assessment of the other investigator. Only the results of the blinded cross-readings were used for statistical analysis of efficacy."
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	High	Funded by the company that developed ivabradine (Servier)

Mao 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Masi de Luca 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	No information
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Moiseev 2011		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to standard

personnel		care. Therefore, the participants and personnel were probably not blinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Nguyen 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote "computer-generated list"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote "patients and physicians were blinded to the study treatment"
Blinding of outcome assessment	High	Quote "an independent sponsor staff was aware of the allocation groups in order to analyze data and monitor adverse events"
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	An inadequate protocol was registered with the European Clinical Trials Database in 2010 (EUDRACT 2009–018175-14). Only the primary endpoint is mentioned in the protocol.
Other bias	High	Two authors were employed by Servier, the study was funded by Servier, and Servier provided statistical support.

Ordu 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No conflicts of interest. No mention of funding.

Pal 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence	Unclear	No information

generation		
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: “double-blind”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	Trial retrospectively registered on clinicaltrials.gov (NCT02354573)
Other bias	Low	No conflicts of interest. Funding by the Chest, Heart and Stroke Society

Pan 2020		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Low	Quote: “random-number table”
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Nantong Scientific Project

Potapenko 2011		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therfore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Qi 2019		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	Quote: “lottery”
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: “open-label”

personnel		
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Raja 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"Computerized random number generation protocol"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Only echocardiographer blinded
Blinding of outcome assessment	High	Only echocardiographer blinded
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by the Department of Cardiology, SGPGIMS, Lucknow, India. No conflicts of interest.

Sallam 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	No information
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	High	The Kansas City Cardiomyopathy Questionnaire was funded by the company that developed ivabradine (Servier)

Sarullo 2010		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "computerized sequence generation"
Allocation concealment	Low	Quote: "ivabradine and placebo were prepared in numbered anonymous

		bottles”
Blinding of participants and personnel	High	Quote: “single-blind”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Low	No funding and no conflicts of interest

Shen 2018		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Low	Quote: “random-number table”
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

SHIFT 2010 (Swedberg)		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "Patients were randomly to treatment groups by computer-generated assignment through a telephone interactive voice response system."
Allocation concealment	Low	Quote: “The allocation sequence was generated at the sponsor level through validated in-house application software; access was restricted to people responsible for study therapeutic units production until database lock."
Blinding of participants and personnel	Low	Quote: "Eligible patients were allocated to receive ivabradine or placebo" and "Patients and investigators were masked to treatment allocation. The study drugs (ivabradine or placebo) were identical in appearance."
Blinding of outcome assessment	Low	Quote: "An endpoint validation committee, masked to study treatment, reviewed and adjudicated all prespecified events according to definitions included in the charter."

Incomplete outcome data	Low	Quote: "Analysis was by intention to treat". "6658 patients were randomly assigned to treatment groups (3268 ivabradine, 3290 placebo)." 3241 was included in the ivabradine group and 3264 was included in the placebo group for the analysis of the primary and secondary outcomes.
Selective reporting	Low	The first patient was randomised in 2006. Prospectively registered with ISRCTN with limited information on methodology. The rationale and design article was published on November the 5th 2009. The trial was first registered on ClinicalTrials.gov in 2015.
Other bias	Low High for serious adverse events.	Most authors have received funding from the company that developed ivabradine (Servier). Servier was the sole sponsor of the study. Quote: "There IS an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed." There was an effect on serious adverse events, primarily due to a decrease in hospitalisations. However, the definition of hospitalisations was not pre-defined and the assessment of hospitalisations was not described.

Sisakian 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	Quote: "empirically allocated"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably not blinded to treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Song 2021		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Beijing Dongcheng District Excellent Talents Training Funding

Su 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Guangdong Health Bureau Projects

Su DL 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Fund Project of Zhongshan City Health Bureau of Guangdong Province

Sun 2020		
Bias domain	**Authors' judgement**	**Support for judgement**

Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Sun 2021		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Tang 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Tarlovskaya 2011		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	Reported as "placebo-controlled", but no information on blinding

Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Tatarchenko 2008		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open randomised controlled study"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Tsutsui 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "The patients and investigators were masked to the treatment allocation"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	Outcome data for most participants
Selective reporting	Unclear	No protocol available in English.
Other bias	High	Trial designed and conducted by Ono Pharmaceutical, a partner of the company that developed ivabradine (Servier). The data were collected and analysed and the first draft manuscript was written by the sponsor.

Tsutsui 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "A minimization method for dynamic allocation was used with adjustment for study site, baseline resting HR (≥85 and <85 beats/min), and β-

		blocker dose before study treatment (0, >0–<50, and ≥50% of the target dose of carvedilol 20 mg/day and bisoprolol 5 mg/day) to balance baseline covariates."
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: “Patients and investigators were masked to treatment allocation, and study medications (ivabradine or placebo) were the same size and color.”
Blinding of outcome assessment	Low	Quote: “"An endpoint adjudication committee, independent from the sponsor and ivestigators, evaluated all clinical events according to prespecified definitions in a blinded manner"
Incomplete outcome data	Low	Almost data for all participants
Selective reporting	Unclear	No protocol was prospectively registered
Other bias	High	Trial designed and conducted by Ono Pharmaceutical, a partner of the company that developed ivabradine (Servier). The data were collected and analysed and the first draft manuscript was written by the sponsor.

Tumasyan 2009		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Tumasyan 2012		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants

		and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Tumasyan 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Tumasyan 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest
Tumasyan 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to no

personnel		intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Vatinian 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang FC 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information

Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang JJ 2017		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Low	Quote: “random-number table”
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang Q 2017		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang RM 2017		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome	Unclear	No information

assessment		
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang YH 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang GK 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang LJ 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information

Other bias	Unclear	No mention of funding or conflicts of interest

Wei 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xia 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xing 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xu 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xu 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xue 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yang WT 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence	Low	Quote: "random-number table"

generation		
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yang Z 2019		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yao 2016		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yi 2017		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: “double-blind, placebo-

personnel		controlled"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yu 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yu 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yue 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information

Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zeng FC 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zeng XM 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zhang 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of

		interest

Zhang J 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Low	Quote: "sequential opaque envelopes"
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	High	Unaccounted missing data.
Selective reporting	Unclear	No information
Other bias	Low	Funded by Tianjin Natural Science Foundation

Zhang XJ 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Zhang 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zhang Y 2020

Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zhang 2021		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Hubei Province Science and Technology Plan Project

Zhao 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Zhou 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information

Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Zhou 2020		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Low	Quote: “random-number table”
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Ivabradine added to usual care in patients with heart failure: a systematic review with meta-analysis and Trial Sequential Analysis – supplementary material

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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)
- Web of Science Core Collection
- Web of Science BIOSIS
- ClinicalTrials.gov
- Google Scholar
- 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)
- 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

MEDLINE 31/05/2021, n = 422

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

EMBASE 31/05/2021, n = 1401

4. (ivabradin* or corlanor or procoralan or corlentor).af
5. (random* or blind* or placebo* or meta-analys* or systematic review).af.
6. 1 and 2

Web of Science Core Collection 31/05/2021, n = 633

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

Web of Science BIOSIS previews 31/05/2021, n = 50

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

LILACS 31/05/2021, n = 25

1. Ivabradine
2. Ivabradina
3. 1 or 2

CENTRAL 31/05/2021, n = 638

1. (Ivabradin* or corlanor or Procoralan or corlentor)

EudraCT 31/05/2021, n = 46

1. ivabradine OR corlanor OR procoralan OR corlentor

ClinicalTrials.gov 31/05/2021, n = 80

1. Ivabradine (also searched for Procoralan Corlanor, Ivabradin, Corlentor, S 16257)
2. Interventional studies

Chinese Biomedical Literature Database (CBM/Sinomed), n = 140

#1 (((“伊伐布雷定”[全字段:智能]) OR “可兰特”[全字段:智能]) OR “依伐布雷定”[全字段:智能]) OR “伊法布雷定”[全字段:智能]

#2 ((“心衰”[全字段:智能]) OR “心脏衰竭”[全字段:智能]) OR “心力衰竭”[全字段:智能]

#3 (((“冠状动脉”[全字段:智能]) OR “冠脉疾病”[全字段:智能]) OR “冠脉病”[全字段:智能]) OR “冠心病”[全字段:智能]

#4 ((((((“心绞痛”[全字段:智能]) OR “心肌梗死”[全字段:智能]) OR “心肌梗塞”[全字段:智能]) OR “心肌缺血”[全字段:智能]) OR “缺血性心肌病”[全字段:智能]) OR “心源性水肿”[全字段:智能]) OR “心肾综合征”[全字段:智能]

#5 (#4) OR (#3) OR (#2)

#6 (((((((“随机”[全字段:智能]) OR “meta-分析”[全字段:智能]) OR “meta分析”[全字段:智能]) OR “系统综述”[全字段:智能]) OR “荟萃分析”[全字段:智能]) OR “系统评价”[全字段:智能]) OR “安慰剂”[全字段:智能]) OR “盲法”[全字段:智能]

#7 (#6) OR (#5) OR (#1)

Chinese Science Journal Database (VIP), n = 165

(U=伊伐布雷定 OR 可兰特 OR 依伐布雷定 OR 伊法布雷定) AND (U=(心衰 OR 心脏衰竭 OR 心力衰竭 OR 心源性水肿 OR 心肾综合征 OR 冠状动脉 OR 冠心病 OR 冠脉病 OR 冠脉疾病 OR 心肌缺血 OR 缺血性心肌病 OR 心绞痛 OR 心肌梗死 OR 心肌梗塞 OR 心功能不全) OR R=(心衰 OR 心脏衰竭 OR 心力衰竭 OR 心源性水肿 OR 心肾综合征 OR 冠状动脉 OR 冠心病 OR 冠脉病 OR 冠脉疾病 OR 心肌缺血 OR 缺血性心肌病 OR 心绞痛 OR 心肌梗死 OR 心肌梗塞 OR 心功能不全)) AND (R=(随机 OR meta-分析 OR meta分析 OR 荟萃分析 OR 系统评价

OR 系统综述 OR 安慰剂 OR 盲法) OR U=(随机 OR meta-分析 OR meta分析 OR 荟萃分析 OR 系统评价 OR 系统综述 OR 安慰剂 OR 盲法))

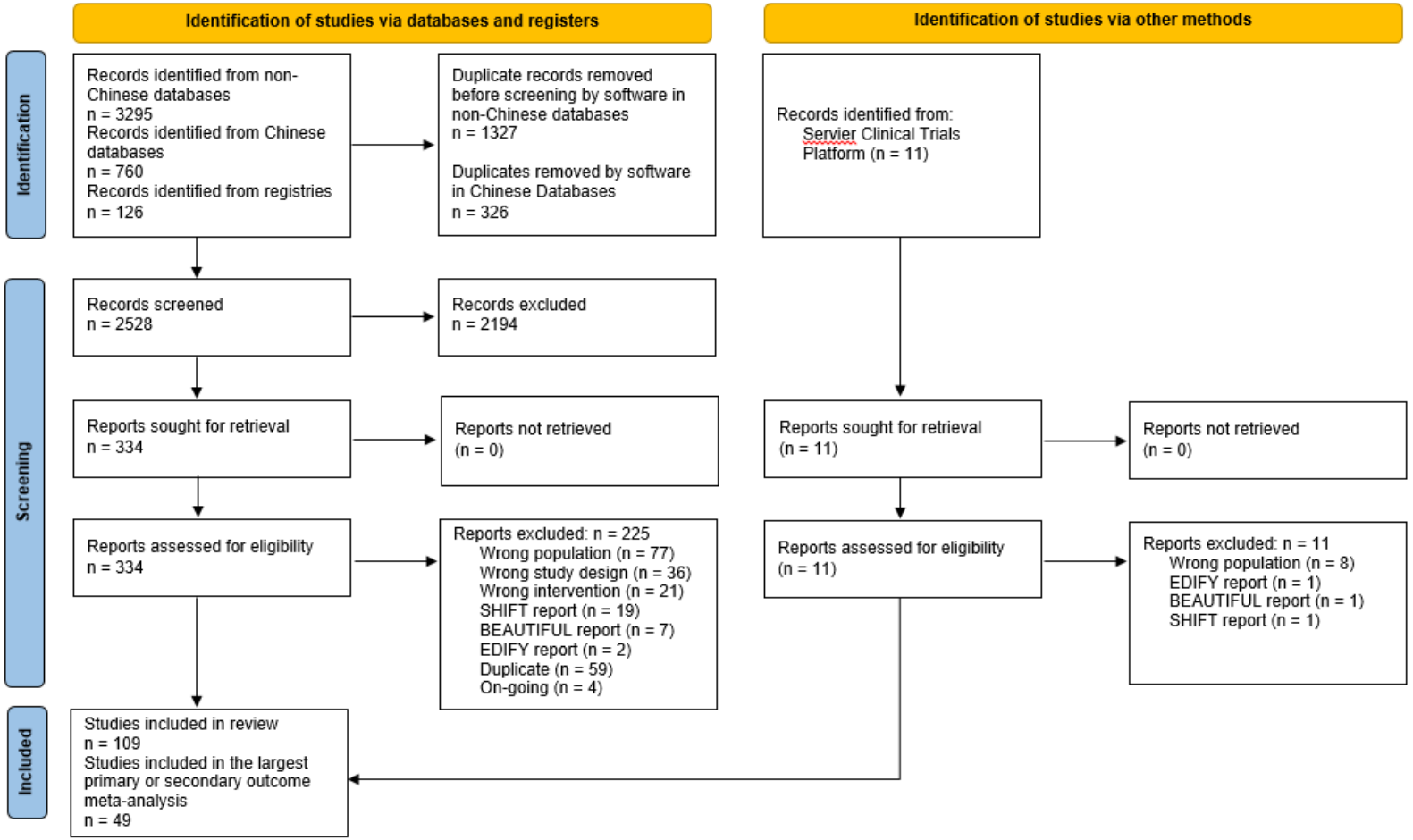
China National Knowledge Infrastructure (CNKI), n = 255

SU=('伊伐布雷定'+'可兰特'+'依伐布雷定'+'伊法布雷定') AND SU=('心衰'+'心脏衰竭'+'心力衰竭'+'心源性水肿'+'心肾综合征'+'冠状动脉*'+'冠心病'+'冠脉病'+'冠脉疾病'+'心肌缺血'+'缺血性心肌病'+'心绞痛'+'心肌梗死'+'心肌

Wanfang, n = 200

主题:(伊伐布雷定 + 可兰特 + 依伐布雷定 + 伊法布雷定) * 主题:(心衰 + 心脏衰竭 + 心力衰竭 + 心源性水肿 + 心肾综合征 + 冠状动脉 + 冠心病 + 冠脉疾病 + 冠脉病 + 心肌缺血 + 心绞痛 + 心肌梗死 + 缺血性心肌病 + 心肌梗塞 + 心功能不全) * 全部:(随机 + meta-分析 + meta分析 + 荟萃分析 + 系统评价 + 系统综述 + 安慰剂 + 盲法)

Supplement 3 – PRISMA flow chart



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 1 – PRISMA flowchart.

Supplement 4 - Risk of bias

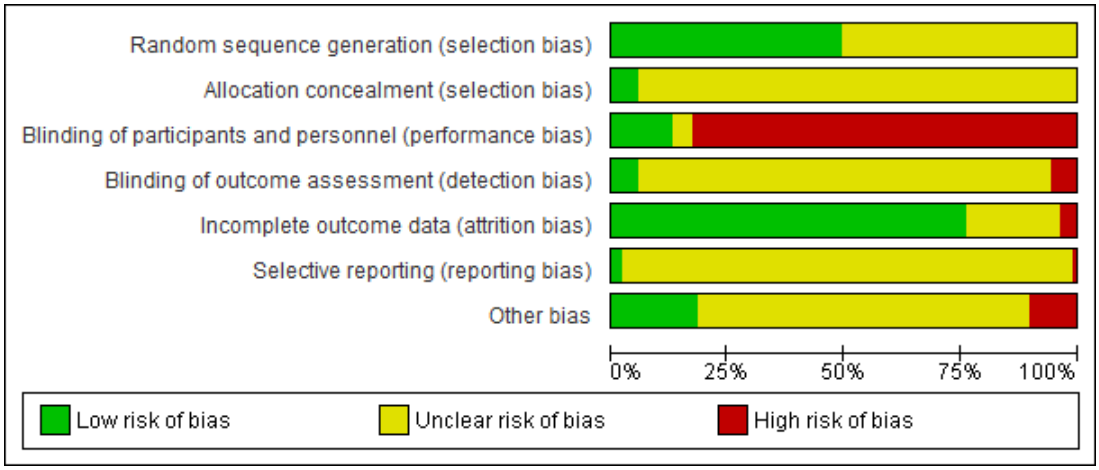
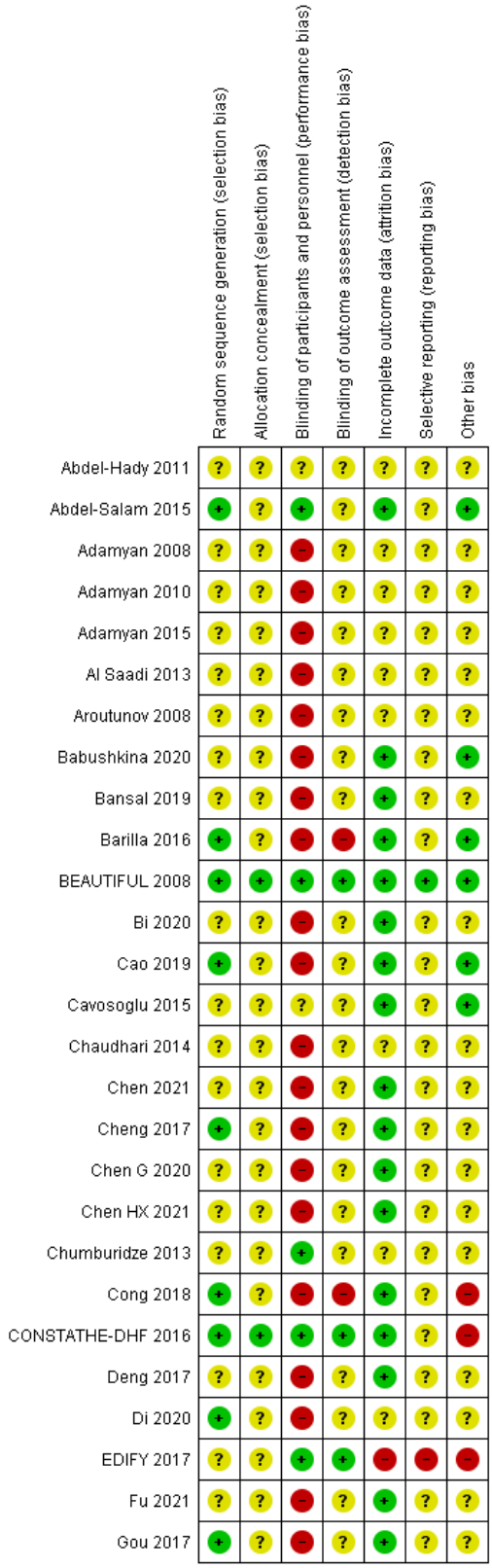
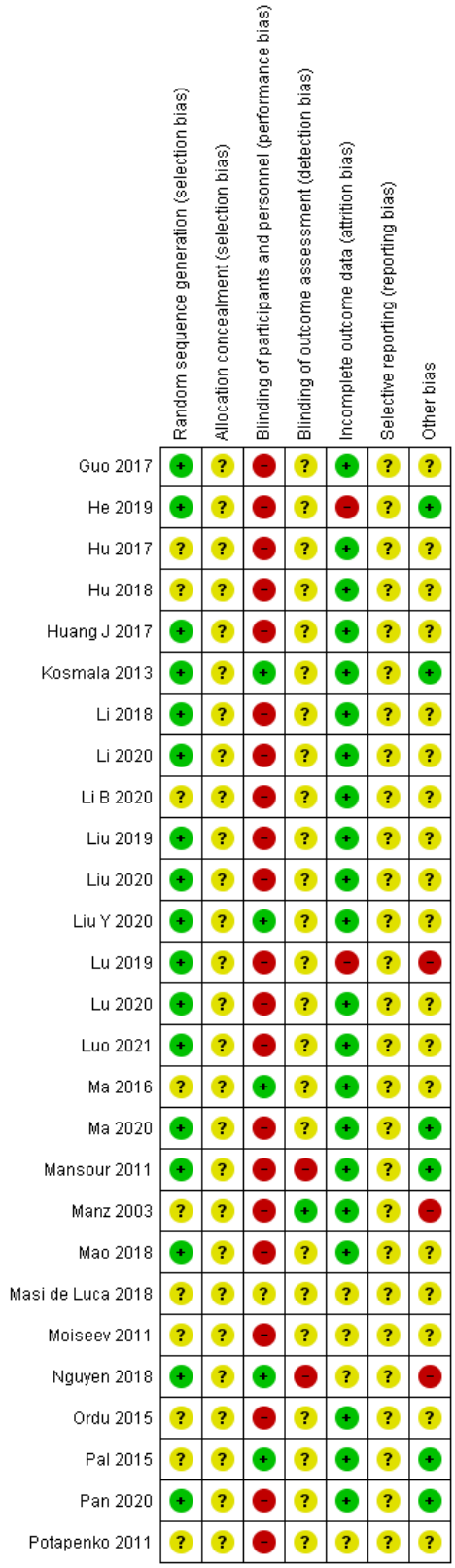
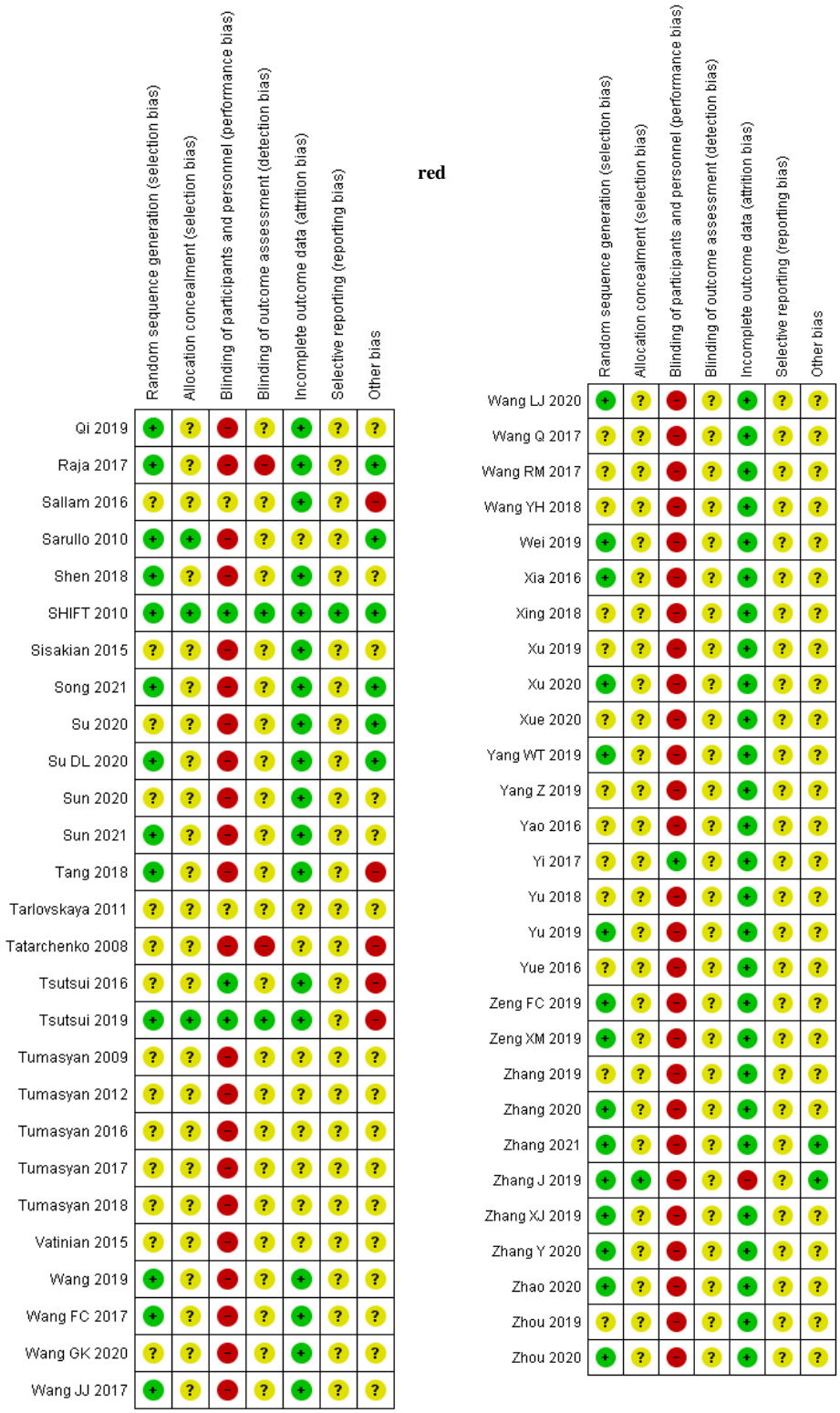


Figure 2 – Risk of bias graph.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Abdel-Hady 2011
Abdel-Salam 2015
Adamyan 2008
Adamyan 2010
Adamyan 2015
Al Saadi 2013
Aroutunov 2008
Babushkina 2020
Bansal 2019
Barilla 2016
BEAUTIFUL 2008
Bi 2020
Cao 2019
Cavosoglu 2015
Chaudhari 2014
Chen 2021
Cheng 2017
Chen G 2020
Chen HX 2021
Chumburidze 2013
Cong 2018
CONSTATHE-DHF 2016
Deng 2017
Di 2020
EDIFY 2017
Fu 2021
Gou 2017


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Guo 2017
He 2019
Hu 2017
Hu 2018
Huang J 2017
Kosmala 2013
Li 2018
Li 2020
Li B 2020
Liu 2019
Liu 2020
Liu Y 2020
Lu 2019
Lu 2020
Luo 2021
Ma 2016
Ma 2020
Mansour 2011
Manz 2003
Mao 2018
Masi de Luca 2018
Moiseev 2011
Nguyen 2018
Ordu 2015
Pal 2015
Pan 2020
Potapenko 2011



red

Figure 3 – Risk of bias summary. Green circles = low risk of bias; yellow circles = unclear risk of bias; circles = high risk of bias.

Supplement 5 - All-cause mortality

Main analyses

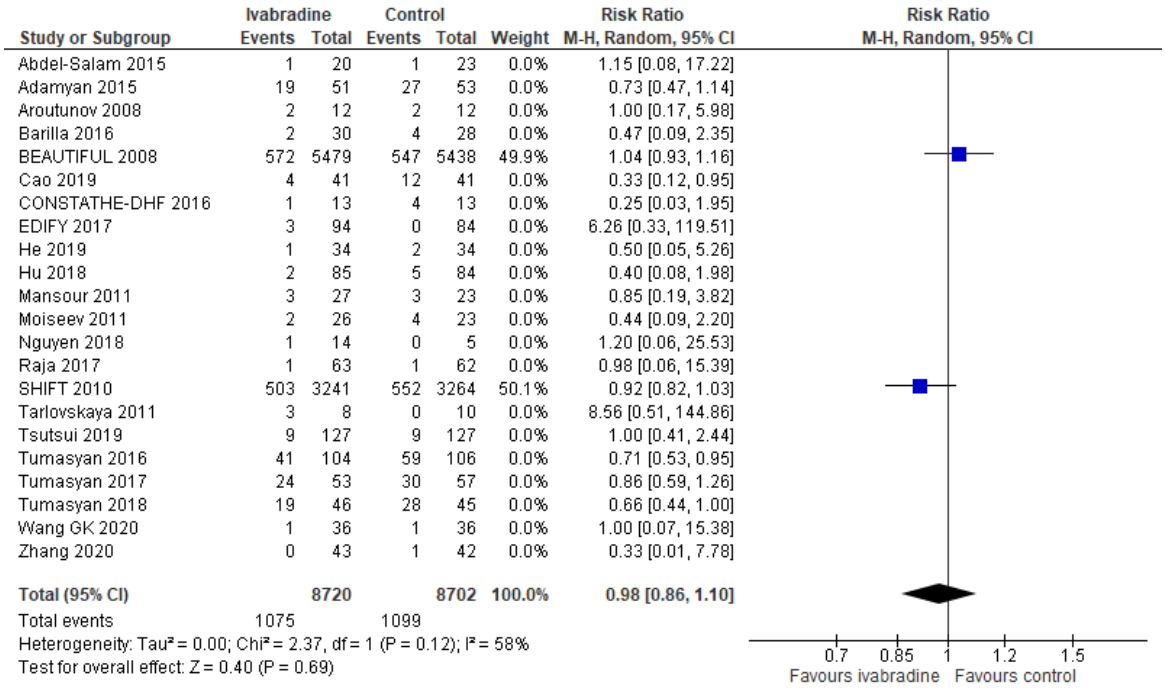


Figure 4 – Forest plot of the meta-analysis of all-cause mortality using random-effecs meta-analysis including only trials at low risk of bias, except for for-profit bias. The meta-analysis showed no evidence of an difference between ivabradine versus placebo.

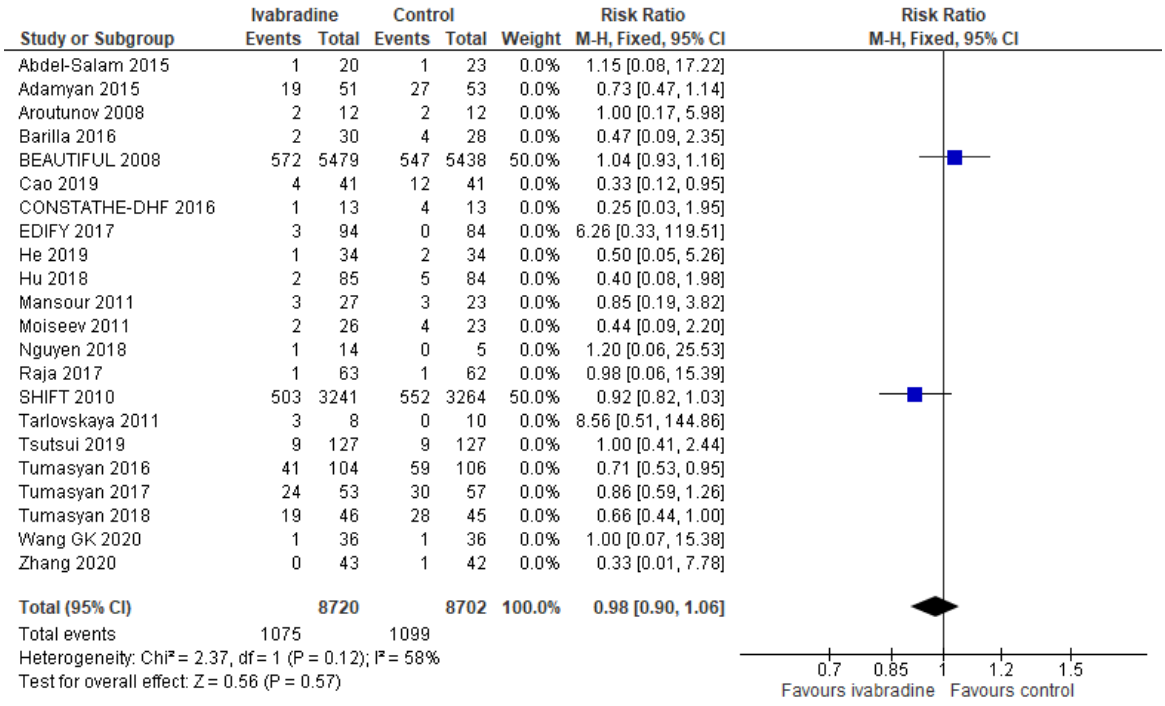


Figure 5 – Forest plot of the meta-analysis of all-cause mortality using fixed-effect meta-analysis including only trials at low risk of bias, except for for-profit bias. The meta-analysis showed no evidence of a difference between ivabradine versus placebo.

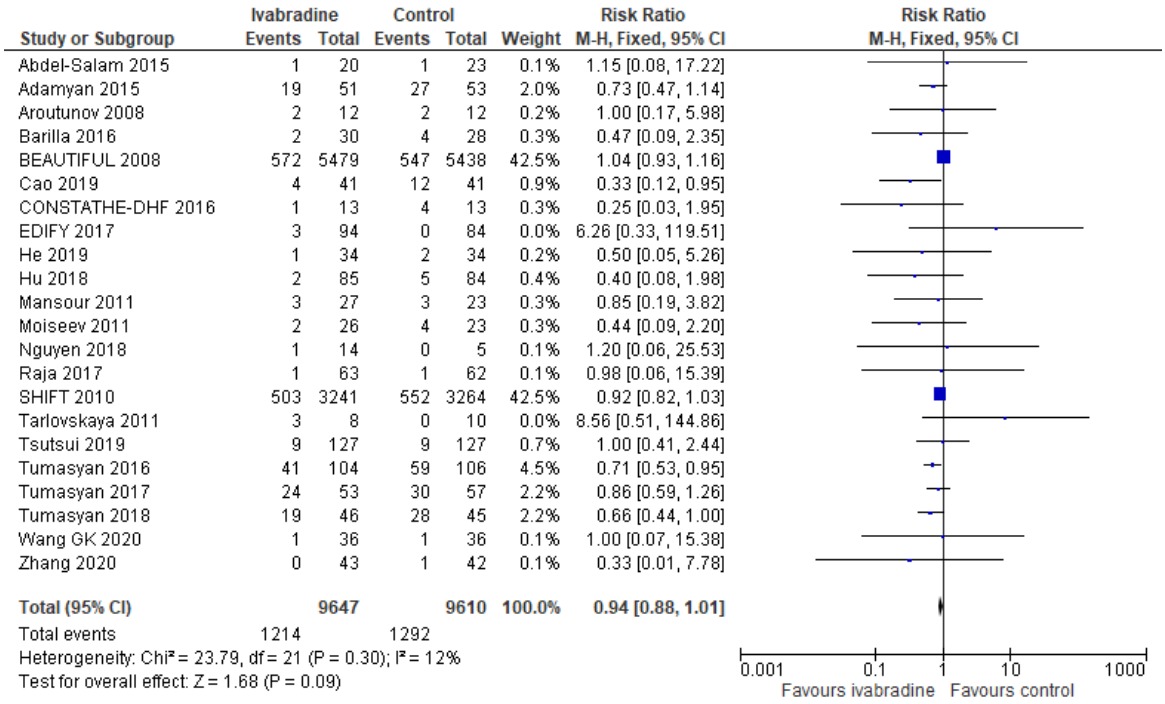


Figure 6 - Forest plot of the meta-analysis of all-cause mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

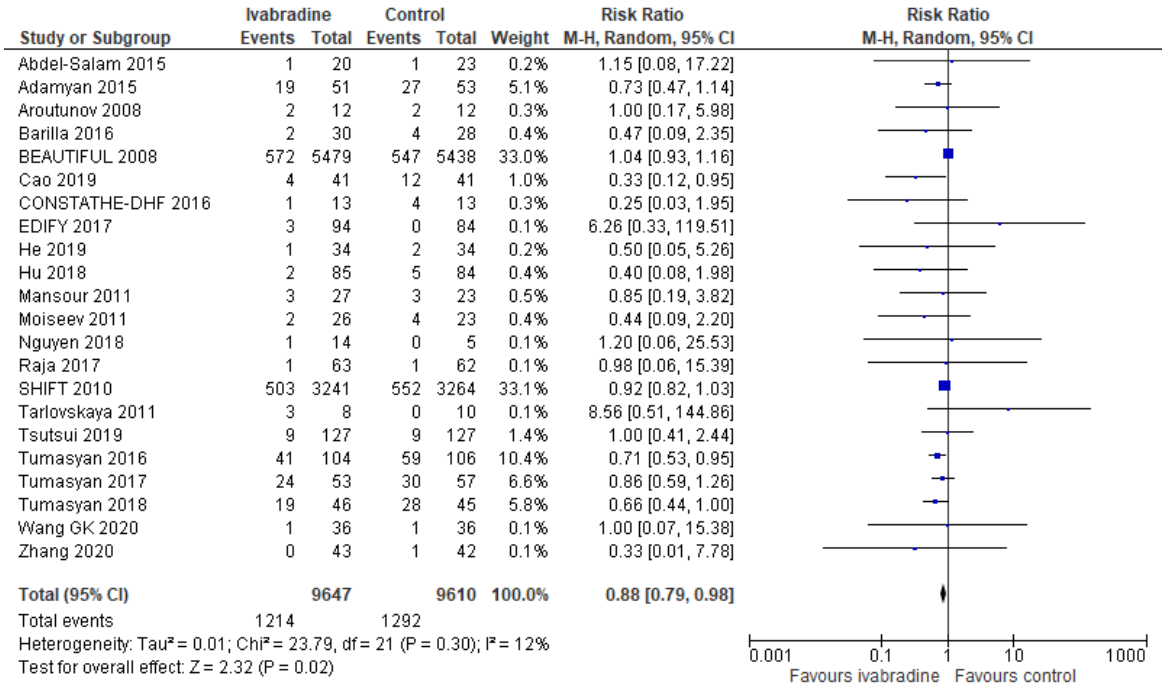


Figure 7 - Forest plot of the meta-analysis of all-cause mortality using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

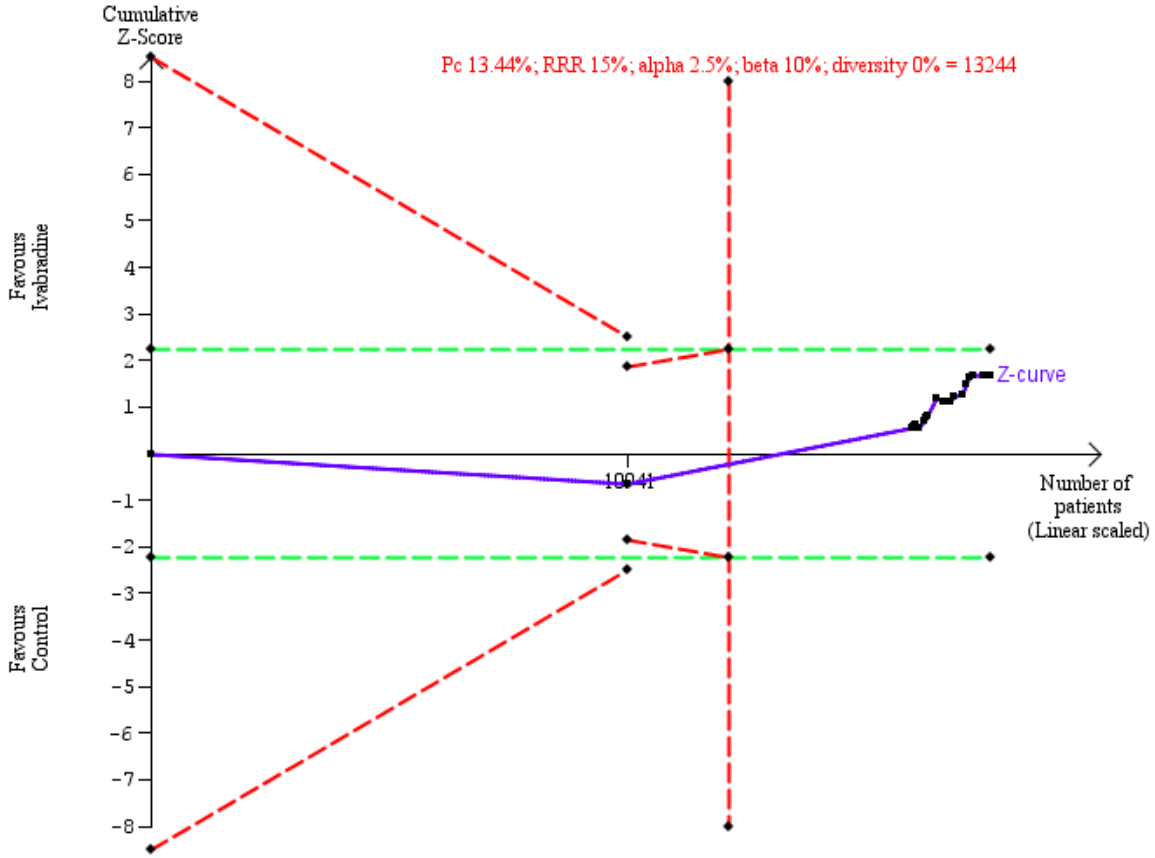


Figure 8 - Trial Sequential Analysis graph of all-cause mortality. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) breaches the boundary of futility and the required information size. Pc: prevalence in control group; RRR: relative risk ratio.

Sensitivity analyses

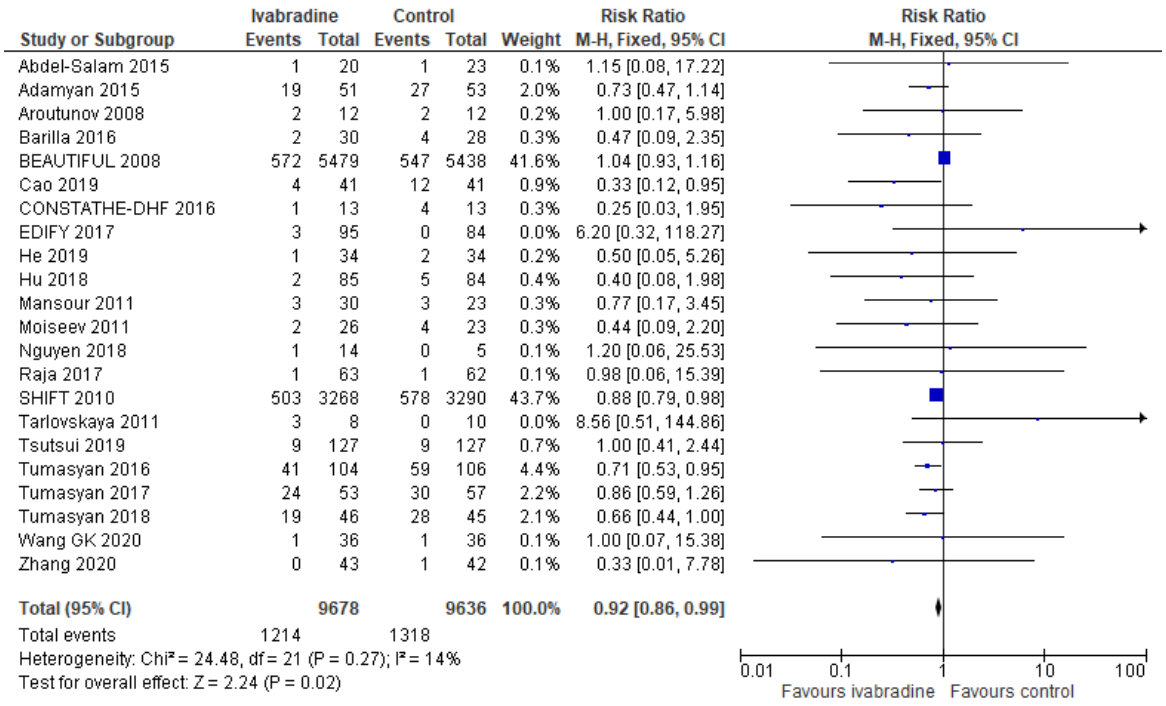


Figure 9 - Forest plot of the sensitivity analysis of all-cause mortality using best- compared with worst-case scenario.

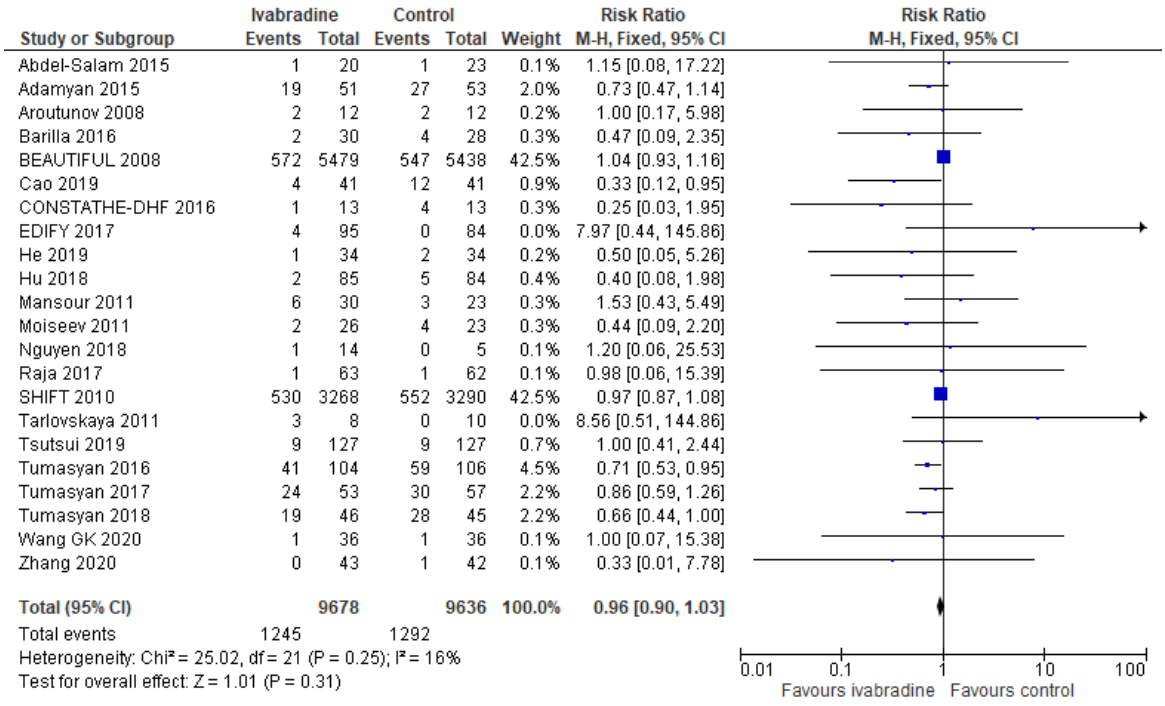


Figure 10 - Forest plot of the sensitivity analysis of all-cause mortality using worst- compared with best-case scenario.

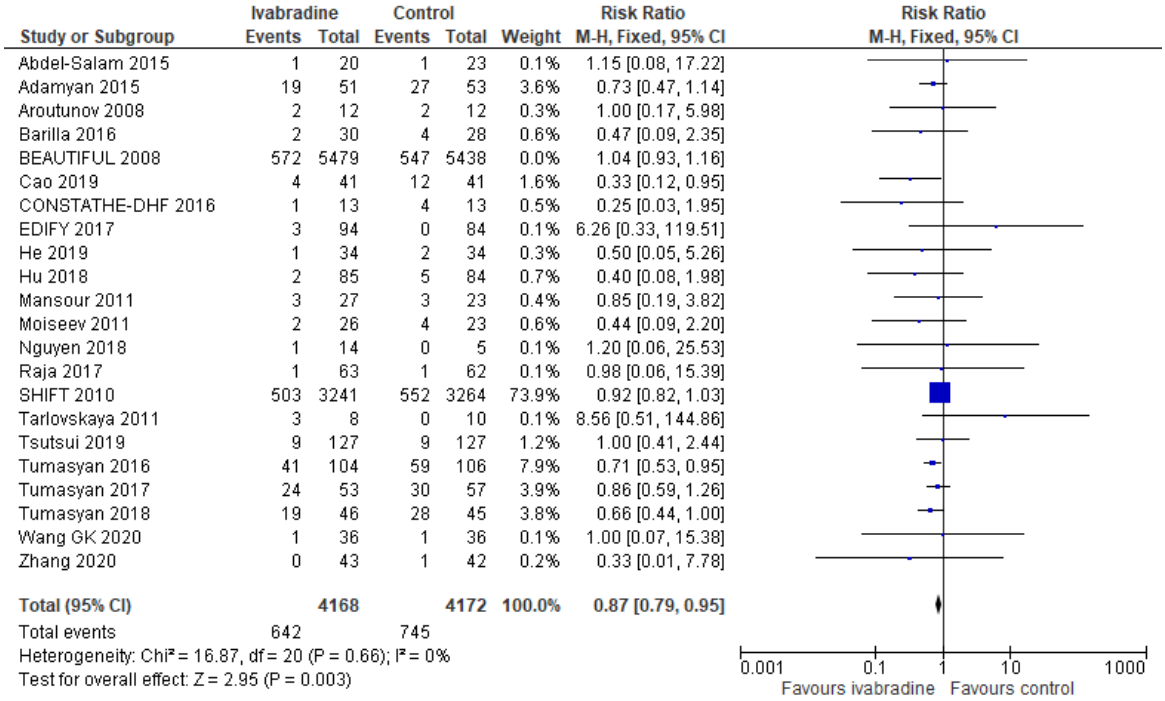


Figure 11 – Forest plot of the sensitivity analysis of all-cause mortality removing the BEAUTIFUL trial.

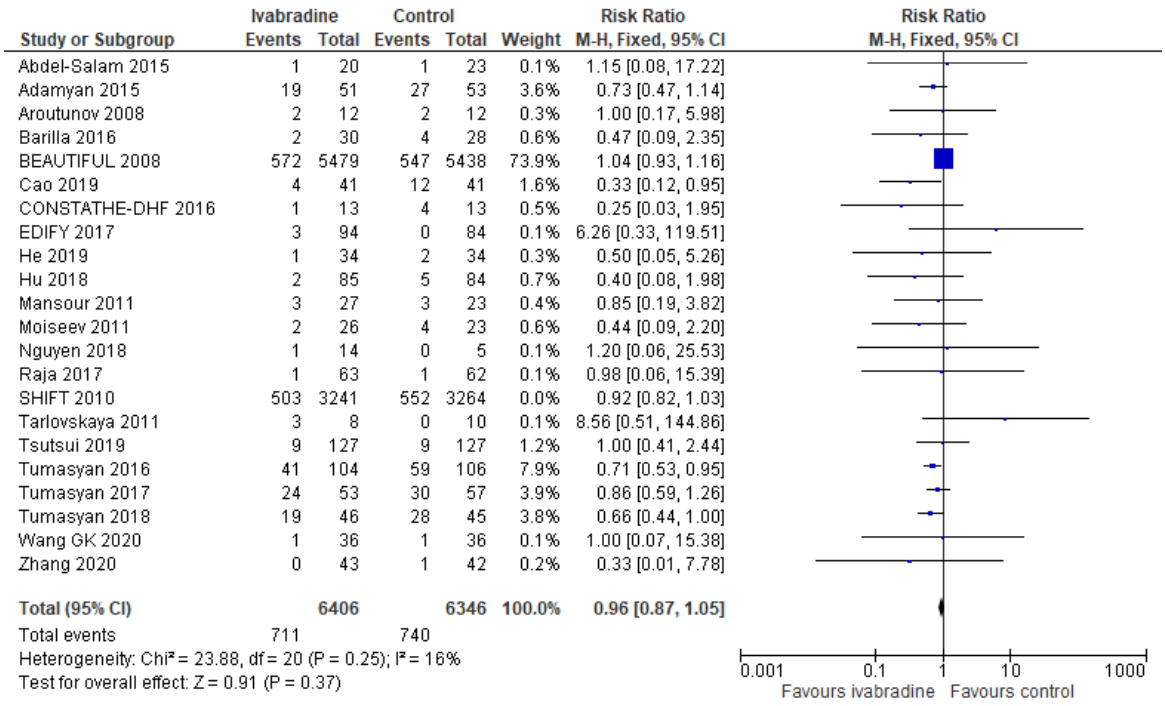


Figure 12 – Forest plot of the sensitivity analysis of all-cause mortality removing the SHIFT trial.

Subgroup analyses

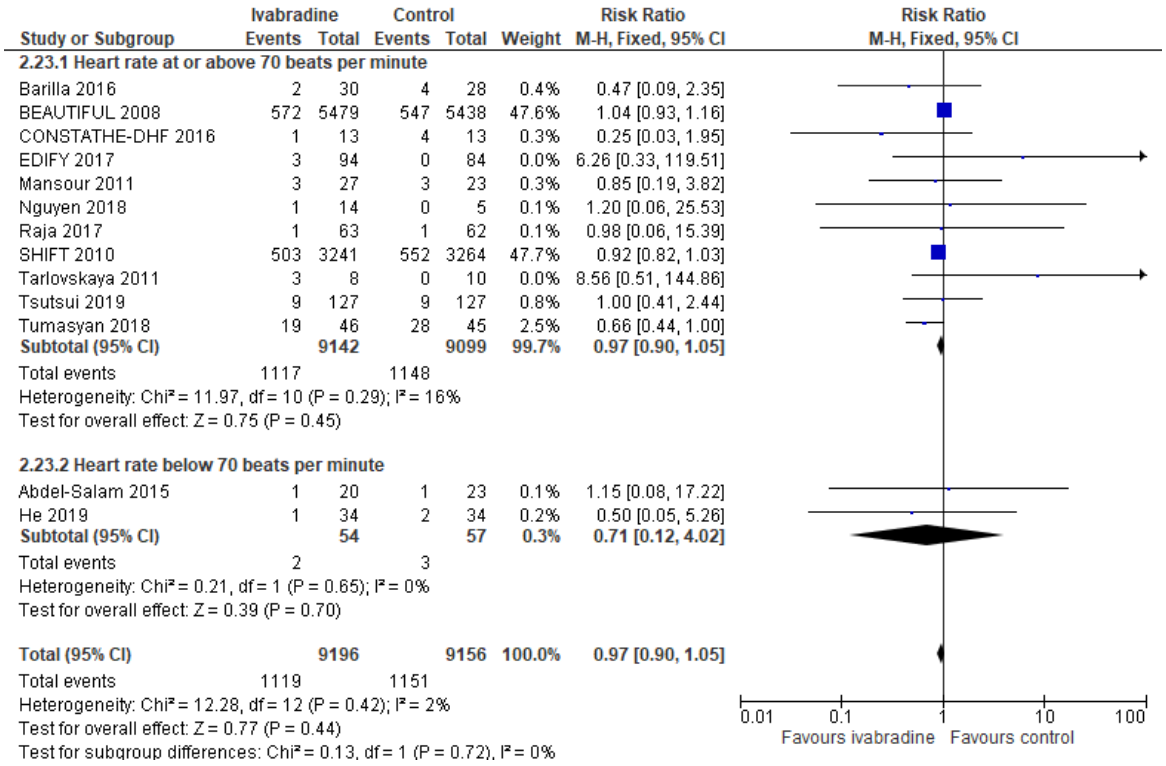


Figure 13 – Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared to trials randomising participants with heart rate below 70 beats per minute on all-cause mortality.

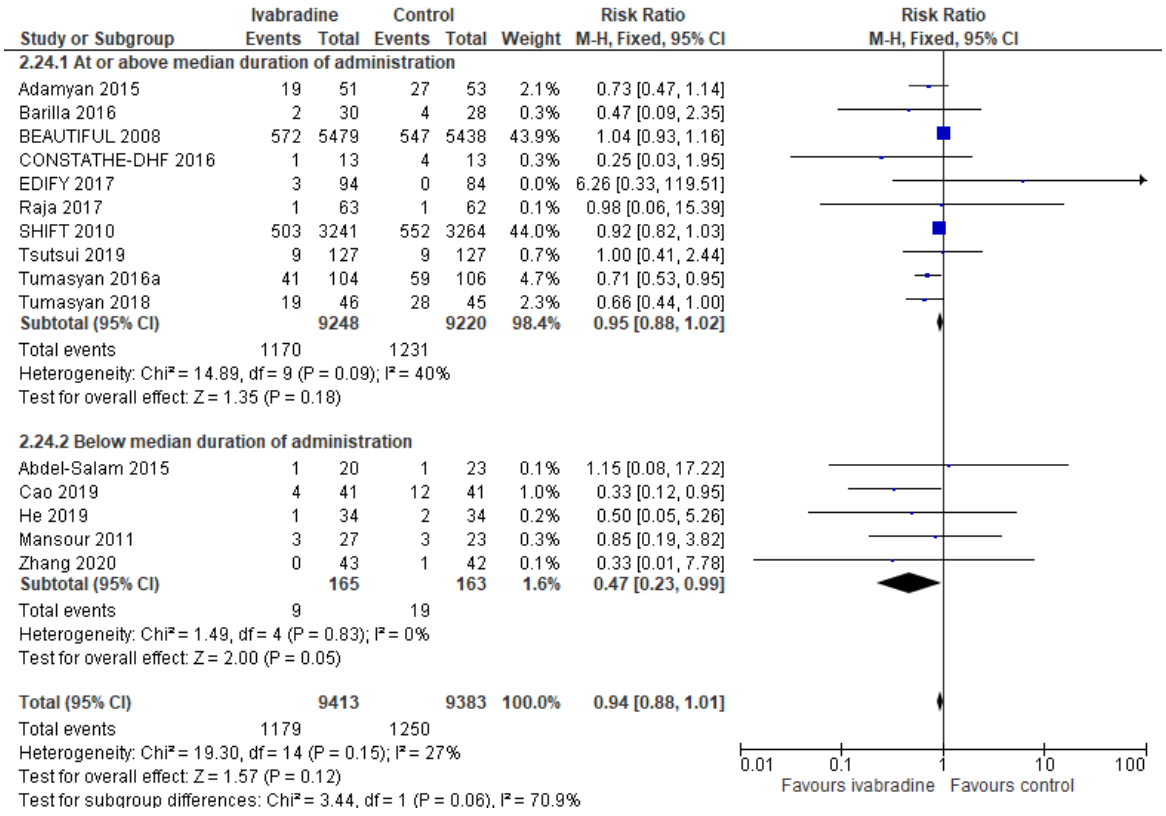


Figure 14 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (182.64 days) versus trials administering ivabradine below median duration on all-cause mortality.

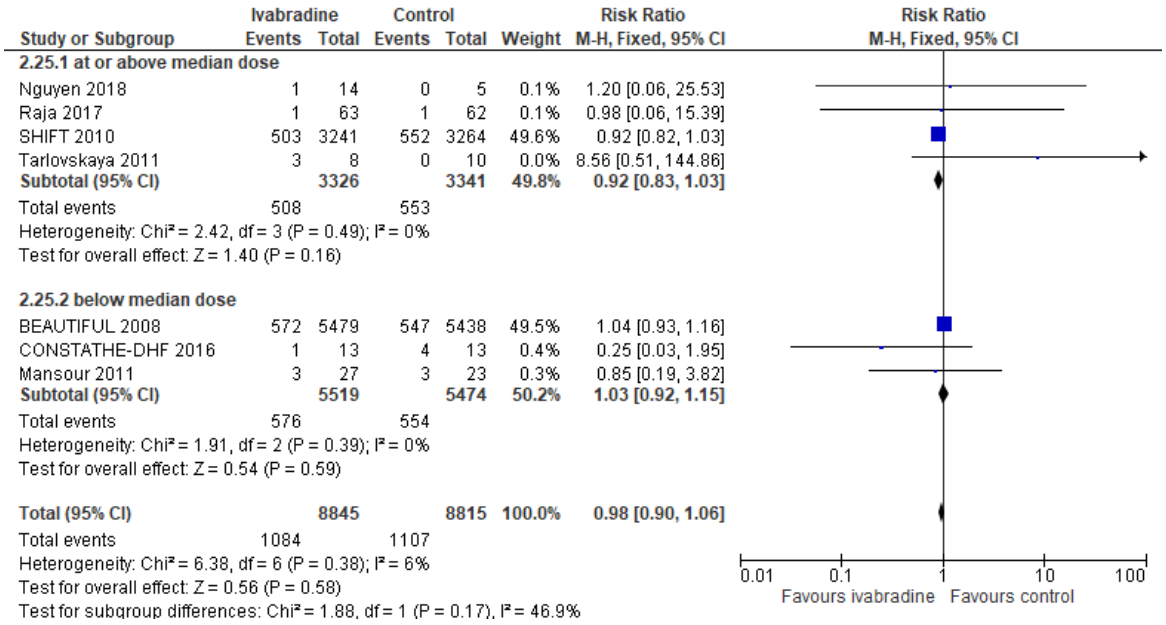


Figure 15 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose (12.7 mg) compared to trials administering ivabradine below median daily dose on all-cause mortality.

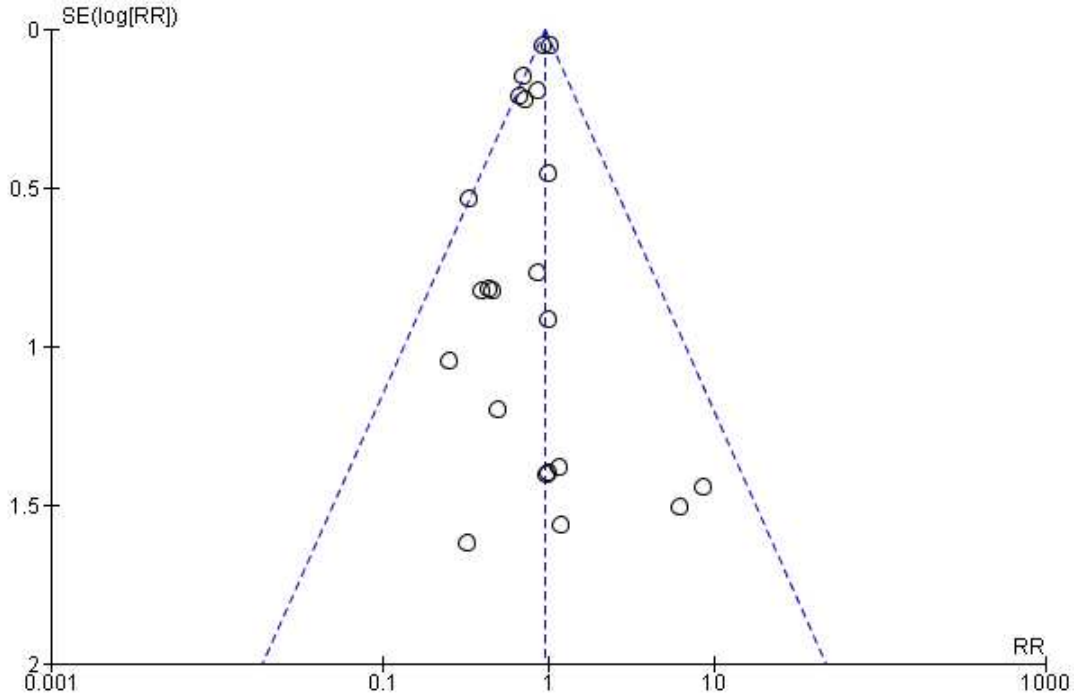


Figure 16 – Funnel plot of the analyses of all-cause mortality. The funnel plot did not indicate small study bias.

Supplement 6 - Serious adverse events

Main analyses

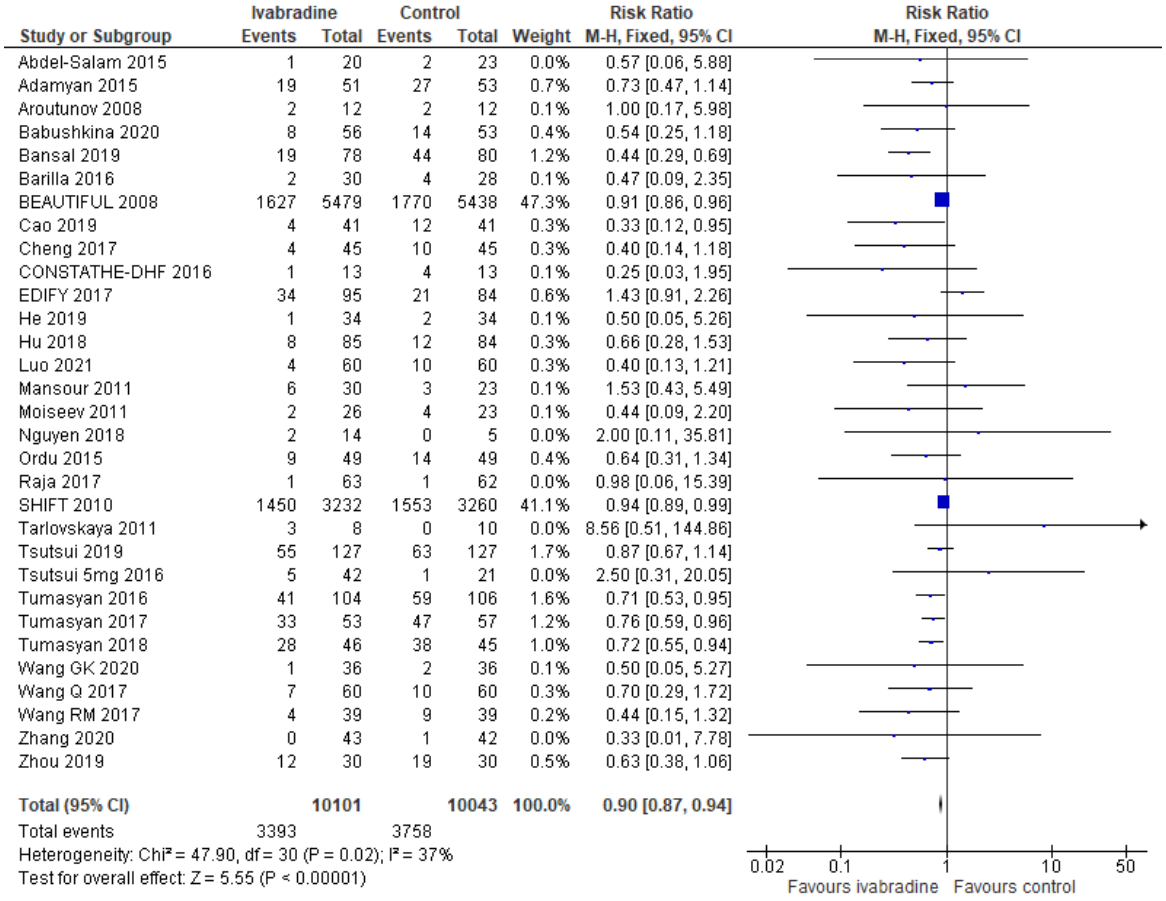


Figure 17 - Forest plot of the meta-analysis of serious adverse events using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

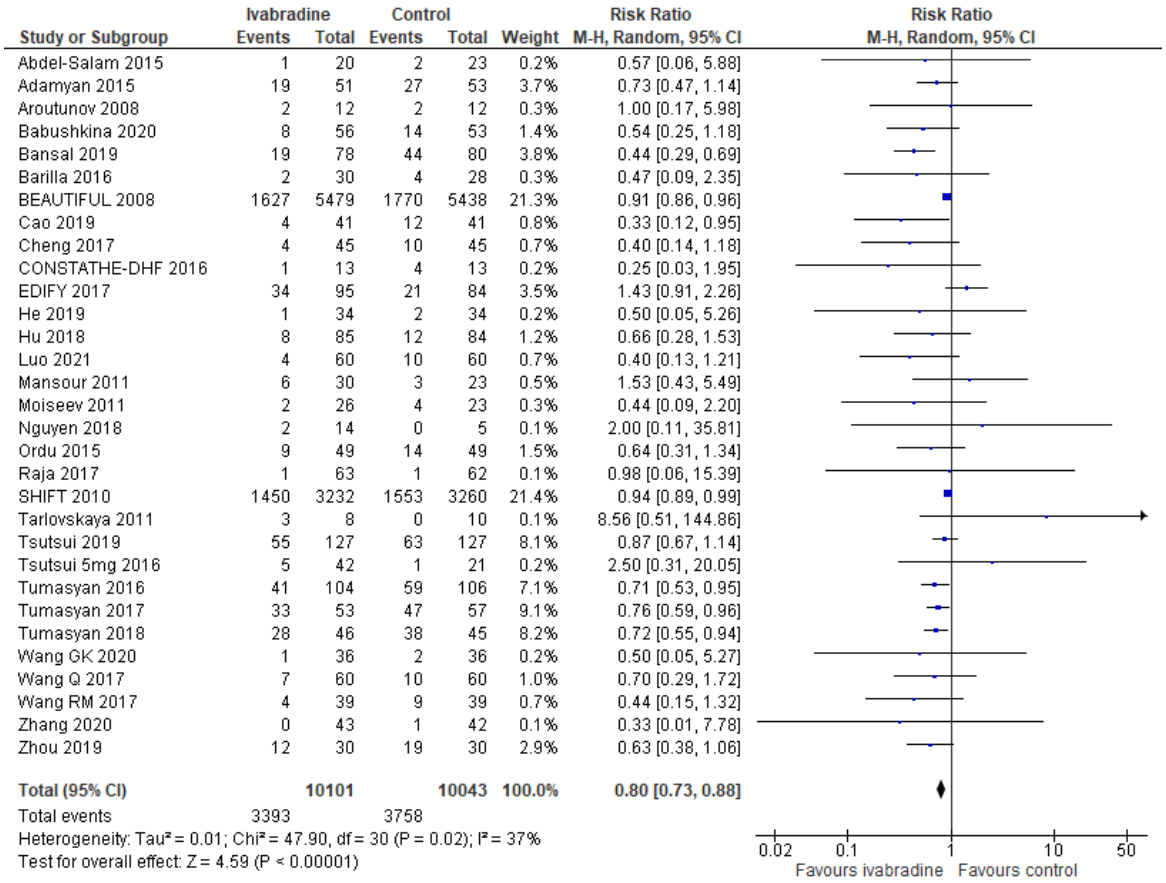


Figure 18 – Forest plot of the meta-analysis of serious adverse events using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

Sensitivity analyses

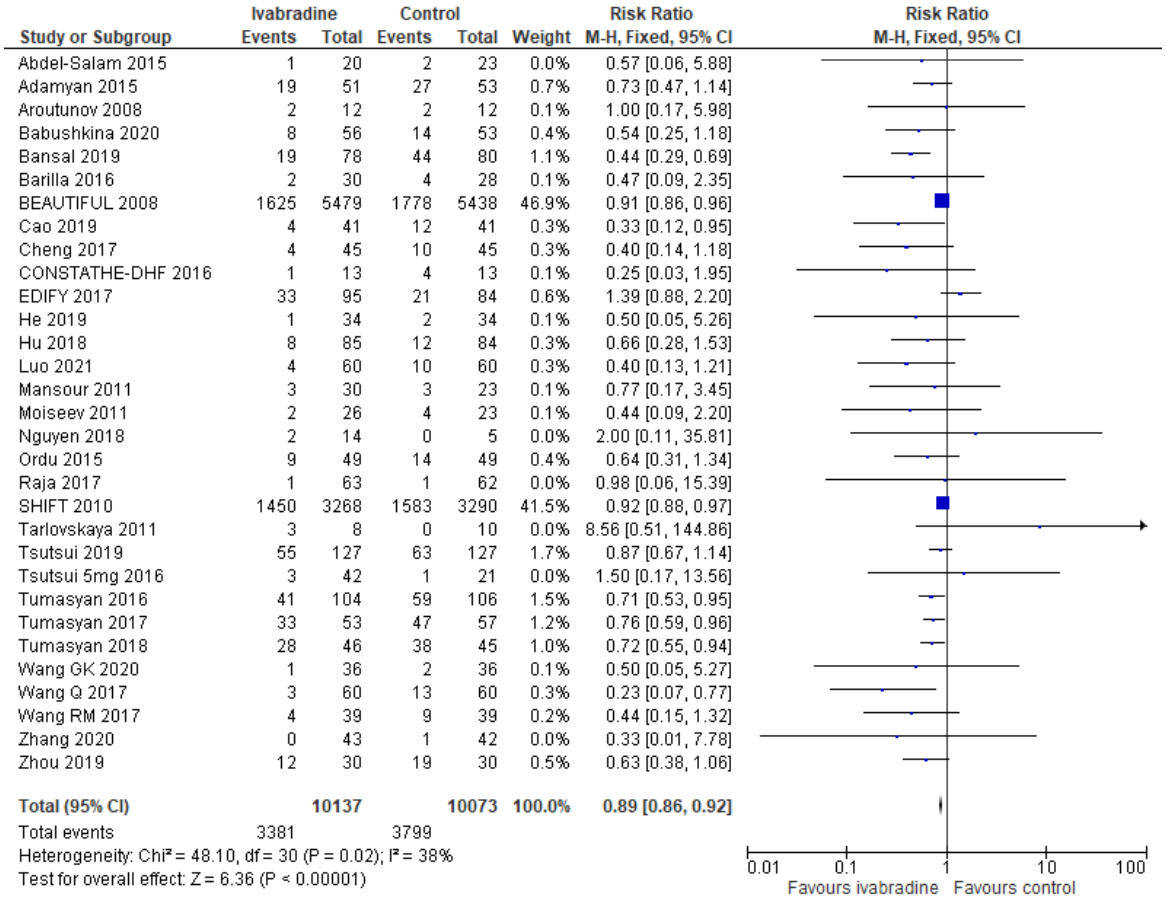


Figure 19 - Forest plot of the sensitivity analysis of serious adverse events using best- compared with worst-case scenario.

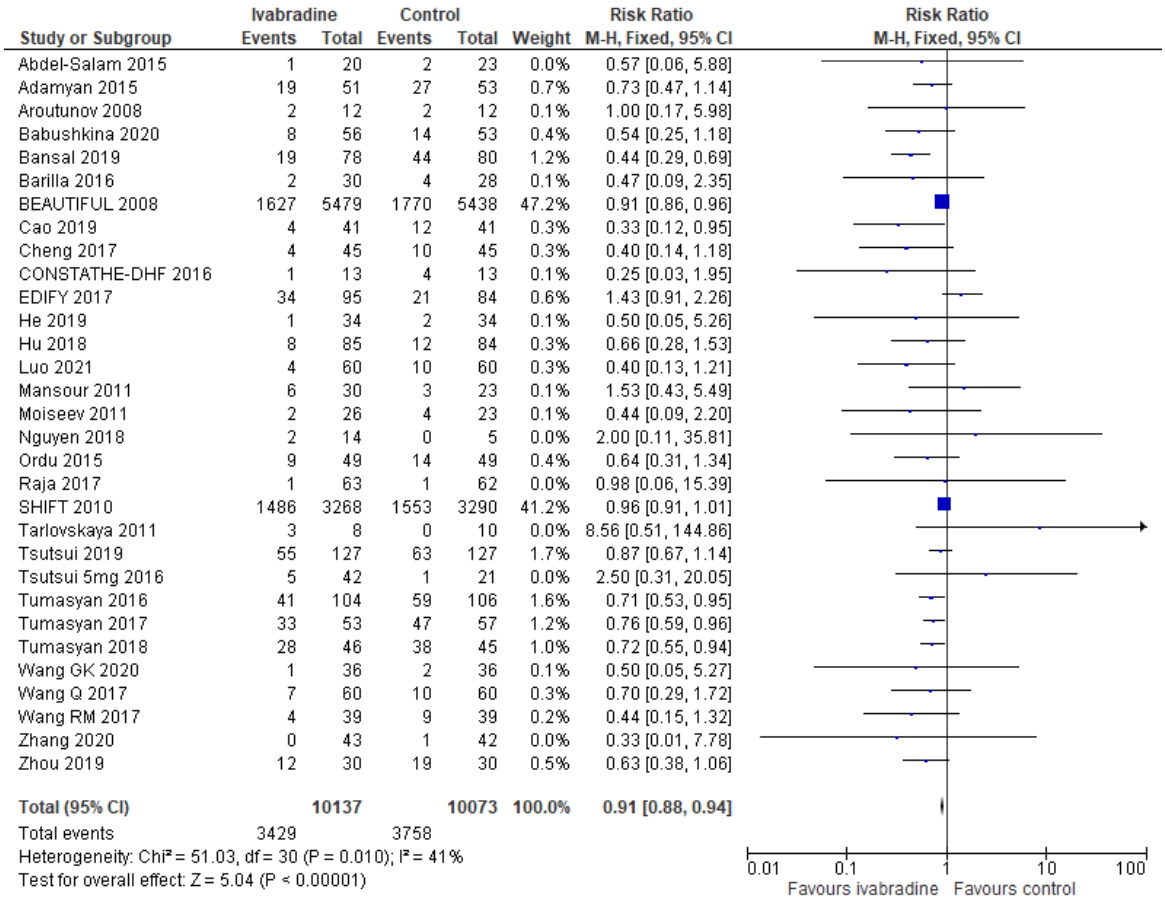


Figure 20 - Forest plot of the sensitivity analysis of serious adverse events using worst- compared with best-case scenario.

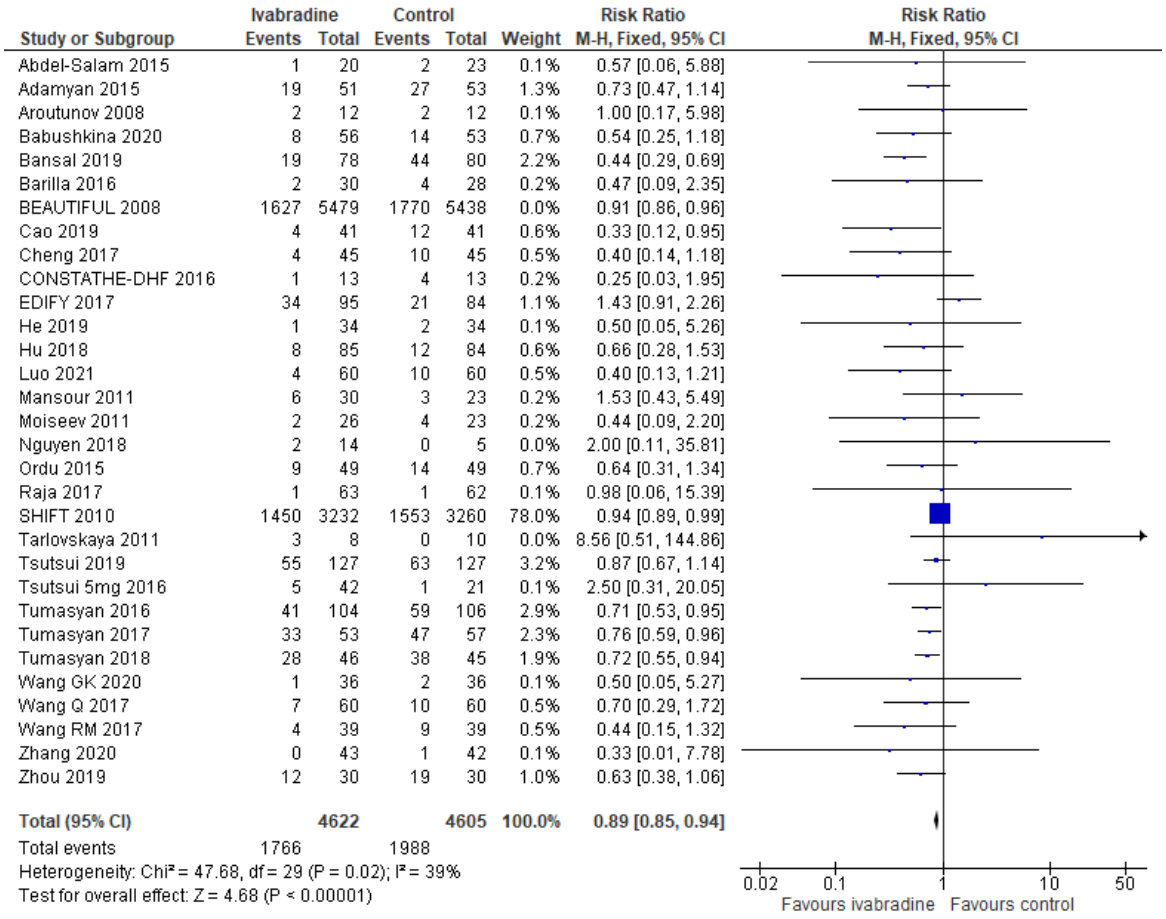


Figure 21 – Forest plot of the sensitivity analysis of serious adverse events removing the BEAUTIFUL trial.

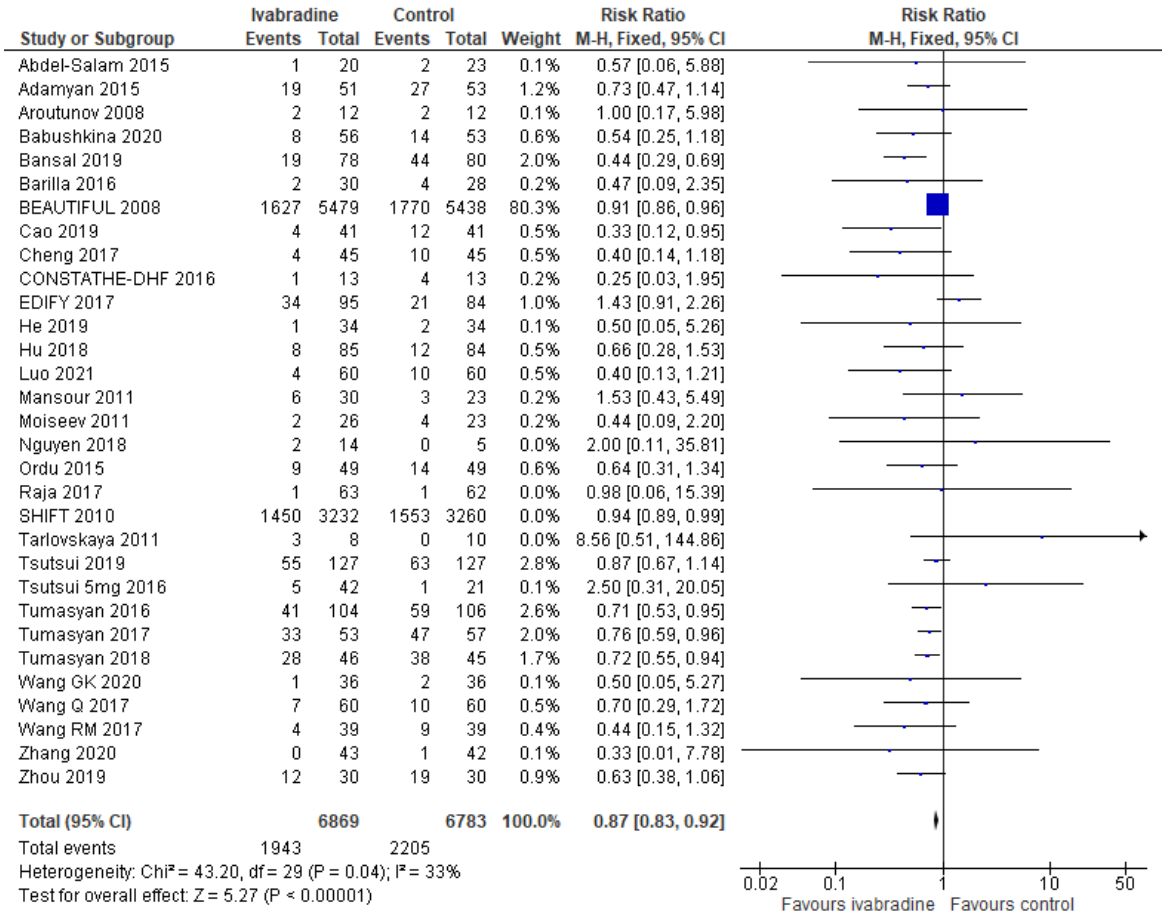


Figure 22 – Forest plot of the sensitivity analysis of serious adverse events removing the SHIFT trial.

Subgroup analyses

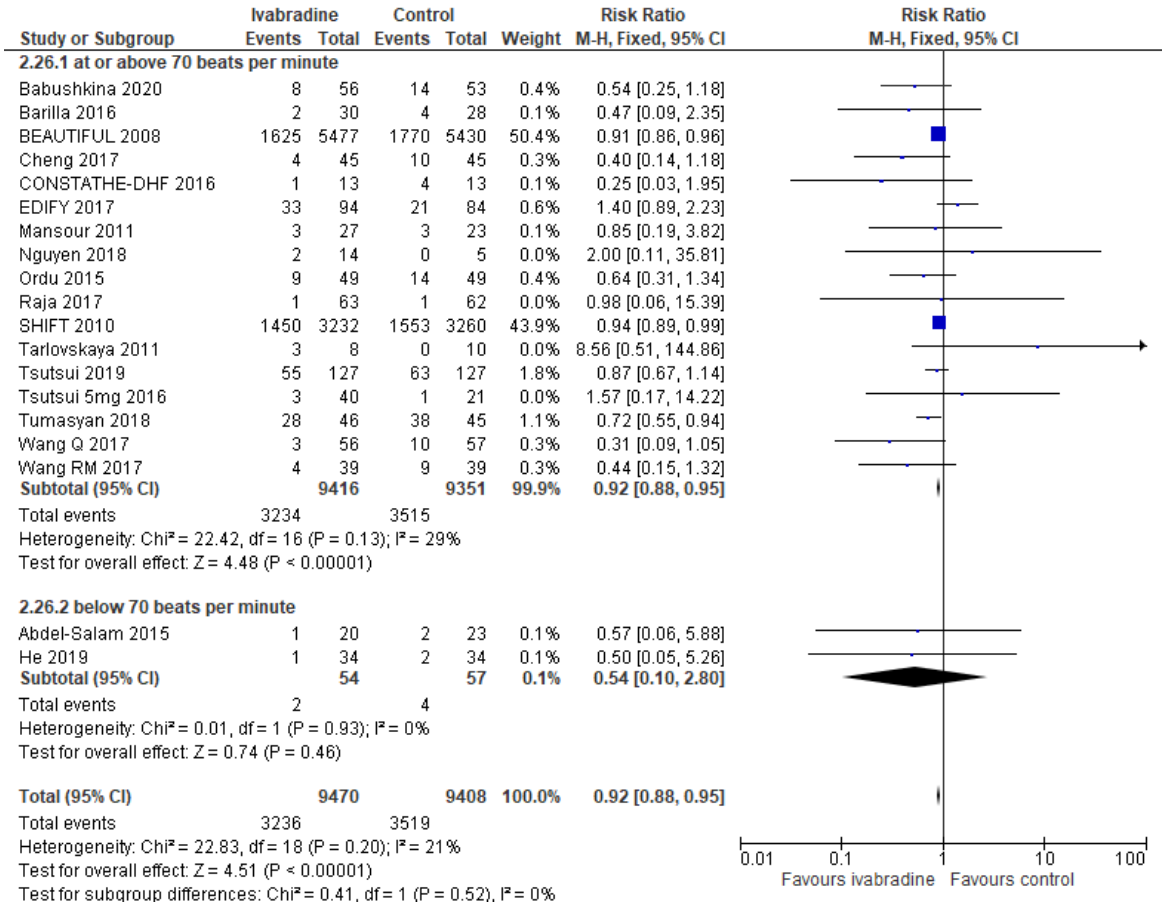


Figure 23 - Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared to trials randomising participants with heart rate below 70 beats per minute on all-cause mortality.

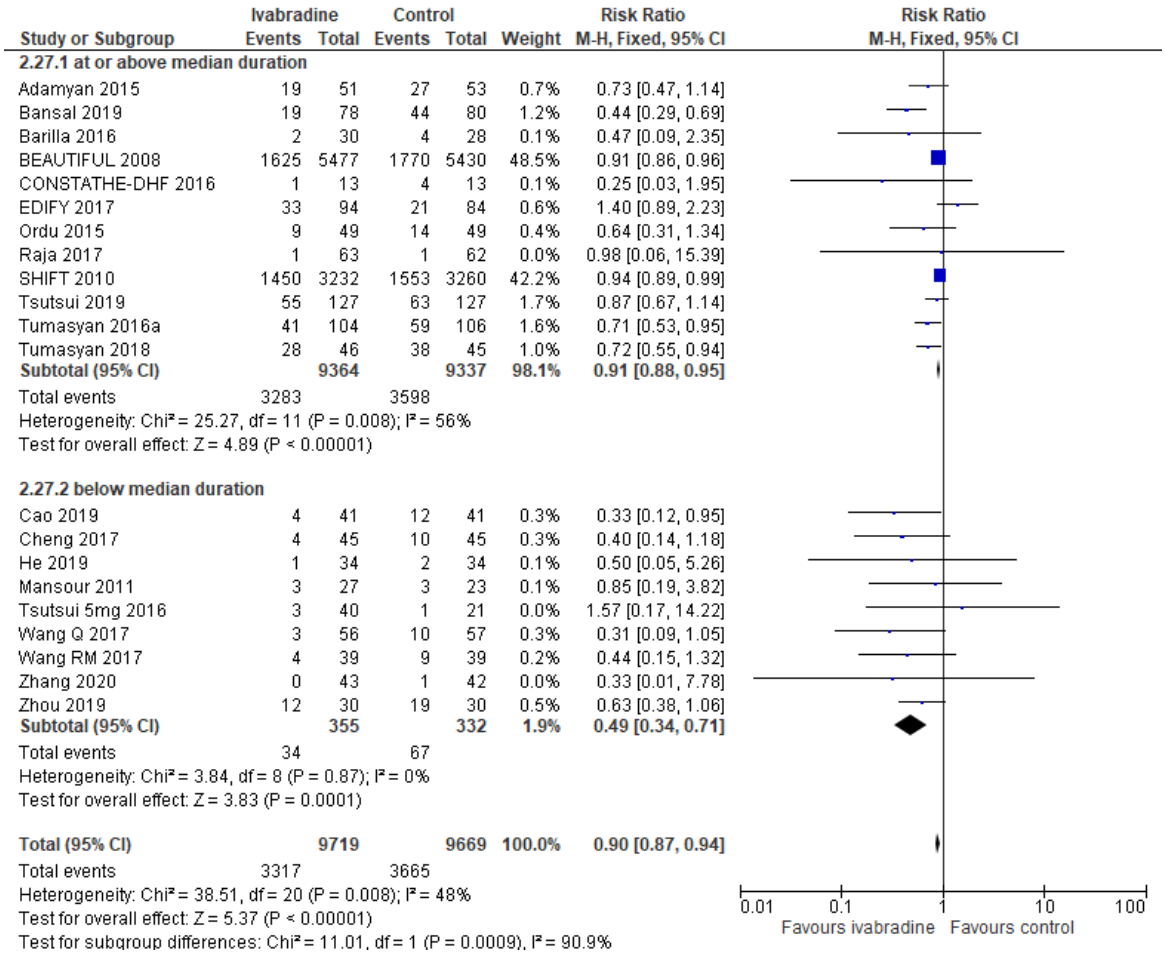


Figure 24 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (182.64 days) compared to trials administering ivabradine below median duration on serious adverse events.

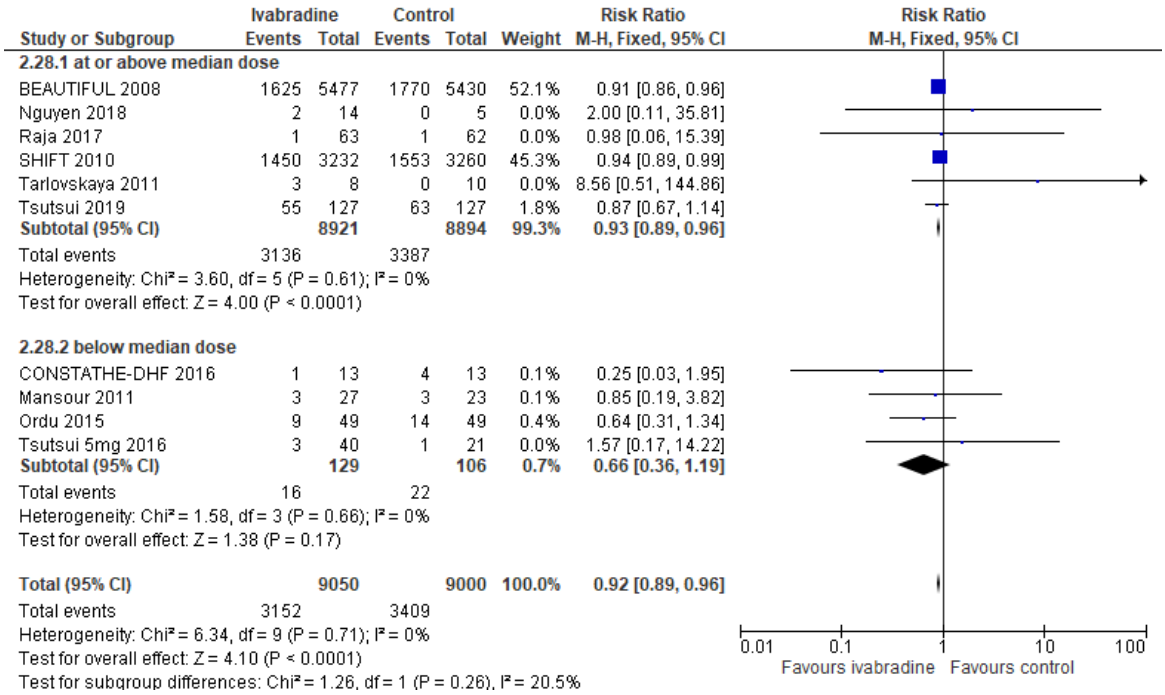


Figure 25 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose (12.36 mg) compared to trials administering ivabradine below median daily dose on serious adverse events.

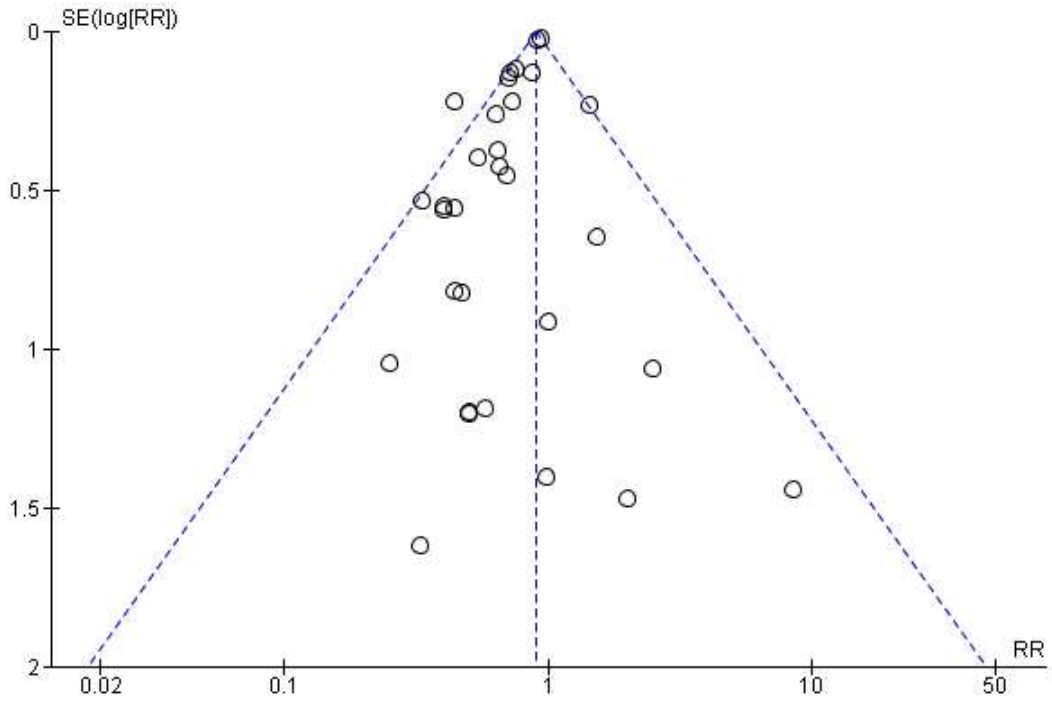


Figure 26 – Funnel plot of the analysis of serious adverse events. The funnel plot did not indicate small study bias.

Supplement 7 - Quality of life

Main analyses for trials using Kansas City Cardiomyopathy Questionnaire (KCCQ)

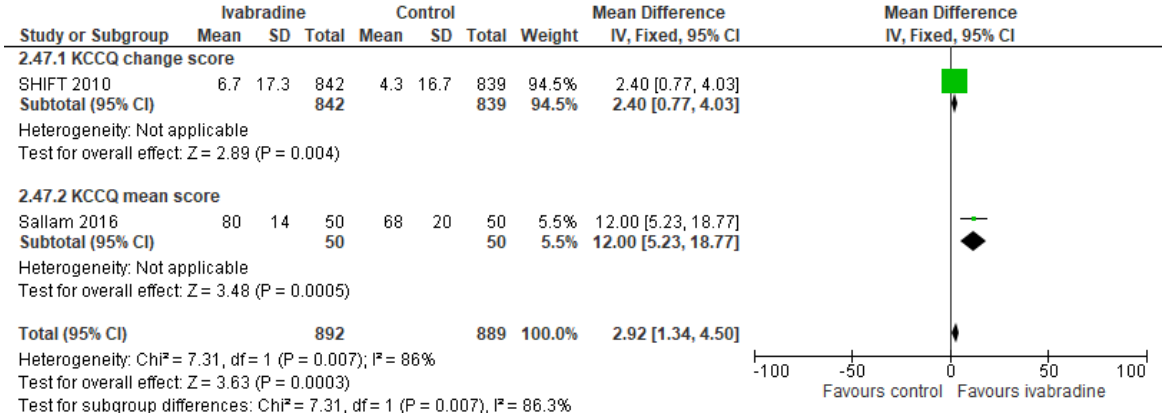


Figure 27 – Forest plot of the meta-analysis of quality of life from trials using the KCCQ using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine.

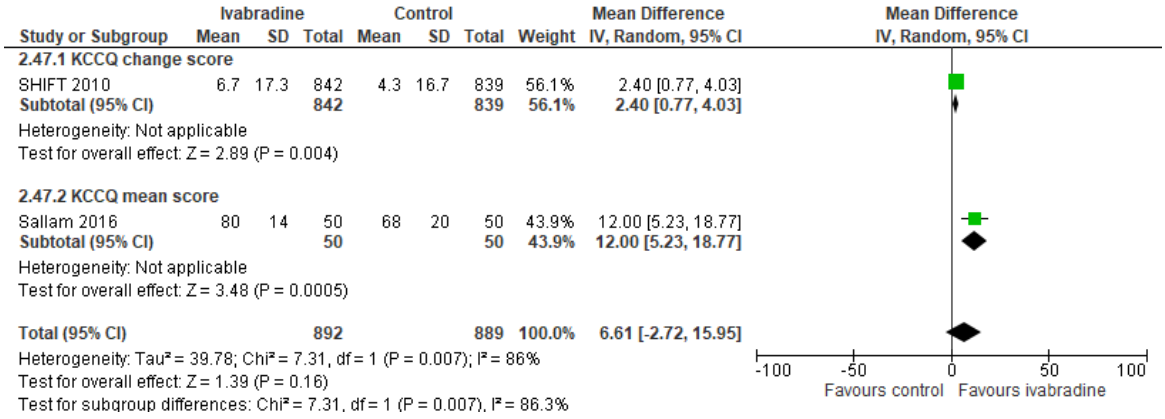


Figure 28 – Forest plot of the meta-analysis of quality of life from trials using the Kansas City Cardiomyopathy Questionnaire (KCCQ) using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

Sensitivity analyses for trials using KCCQ.

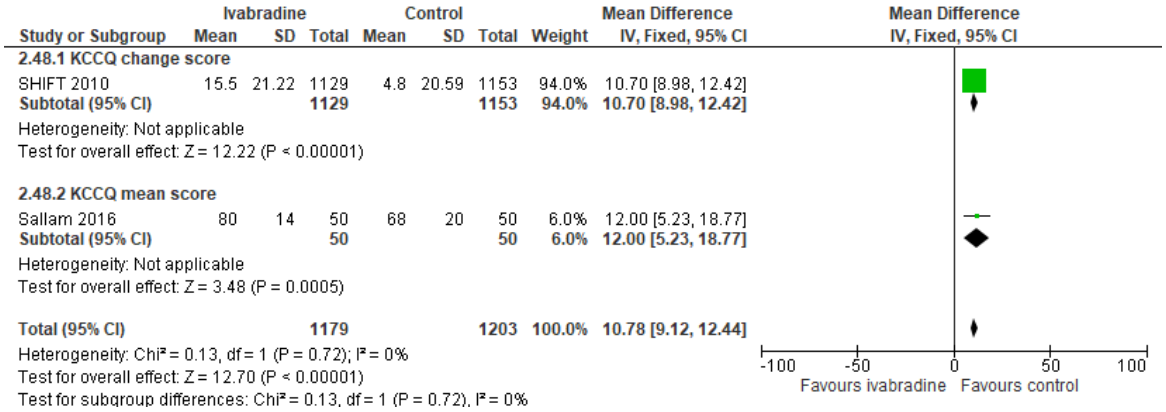


Figure 29 – Forest plot of the sensitivity analysis of quality of life (KCCQ) using best- compared with worst-case scenario.

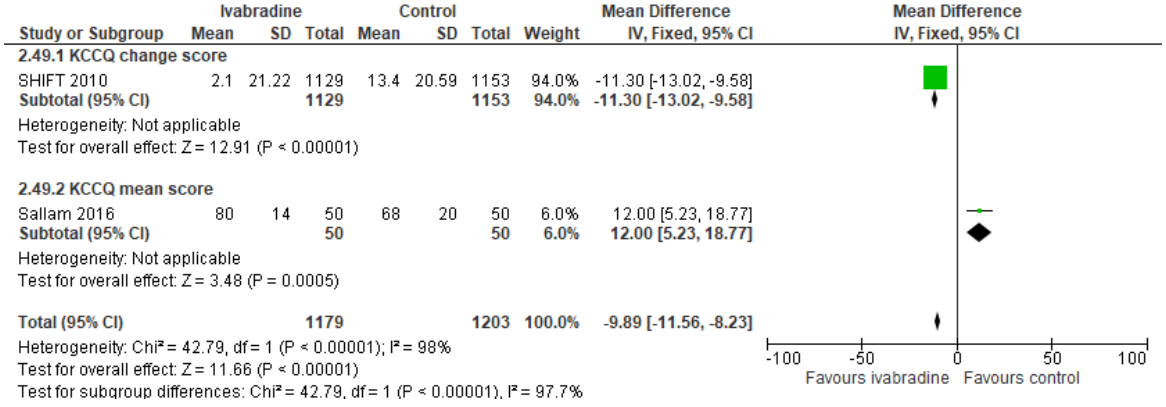


Figure 30 – Forest plot of the sensitivity analysis of quality of life (MLWHFQ) using worst- compared with best-case scenario.

Subgroup analyses for trials using the KCCQ

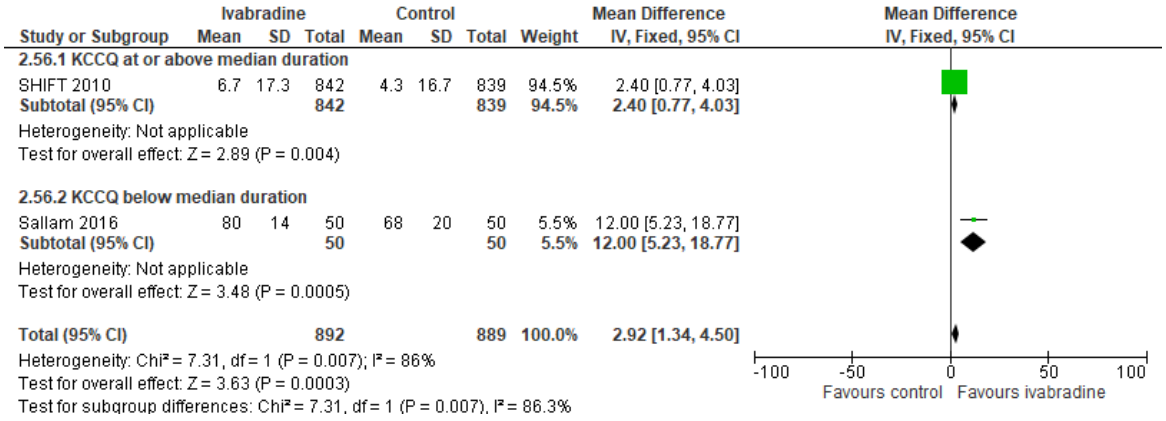


Figure 31 – Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (90.66 days) compared to trials administering ivabradine below median duration on quality of life using the KCCQ.

Main analyses for trials using Minnesota Living With Heart Failure Questionnaire (MLWHFQ)

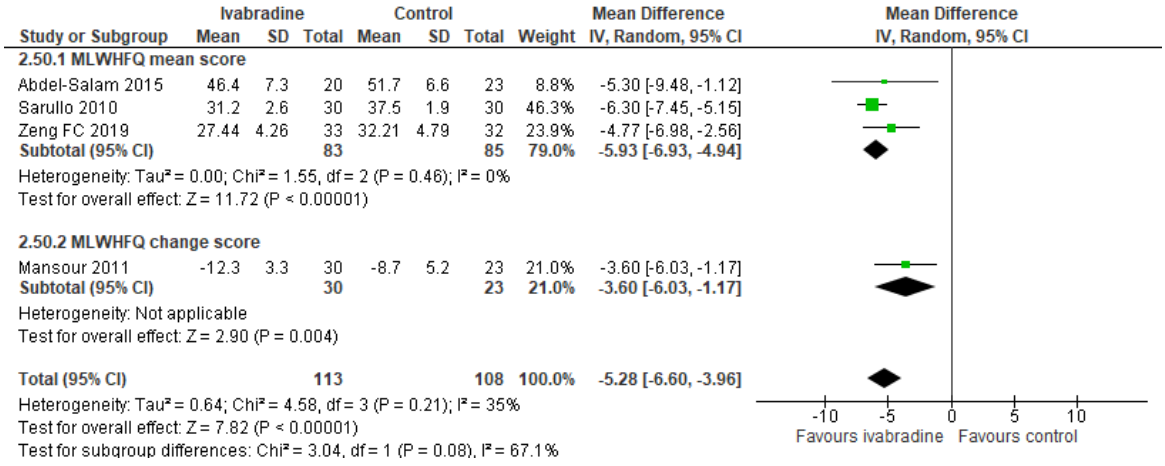


Figure 32 – Forest plot of the meta-analysis of quality of life from trials using the MLWHFQ using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

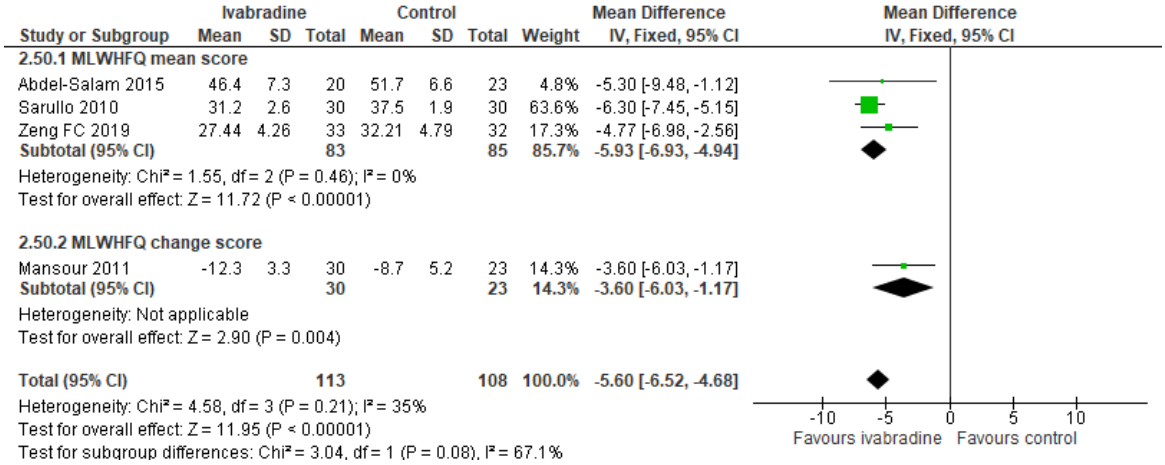


Figure 33 – Forest plot of the meta-analysis of quality of life from trials using the MLWHFQ using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine.

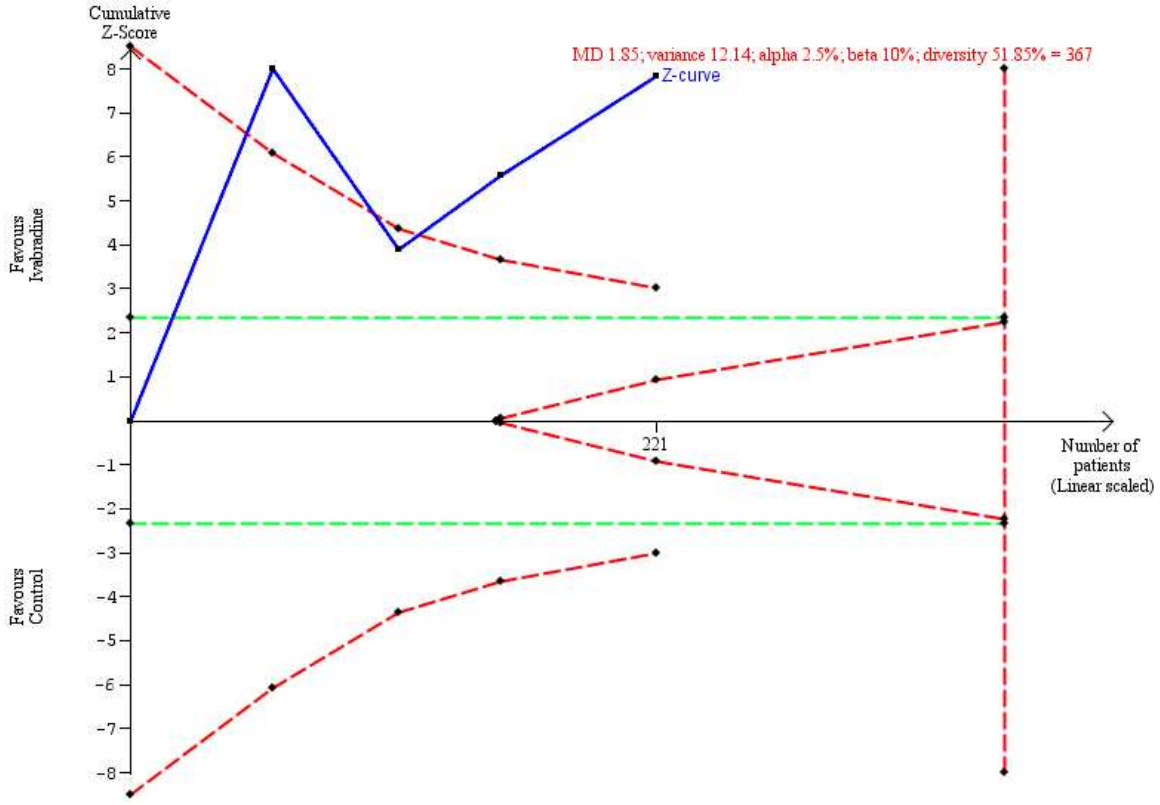


Figure 34 – Trial Sequential Analysis graph of quality of life from trials using the MLWHFQ. Trial Sequential Analysis showed that we had enough information to detect a mean difference of -5.60 points of ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) breached the boundary of benefit. MD: mean difference (SD/2 from the control group).

Sensitivity analyses of quality of life from trials using the MLWHFQ.

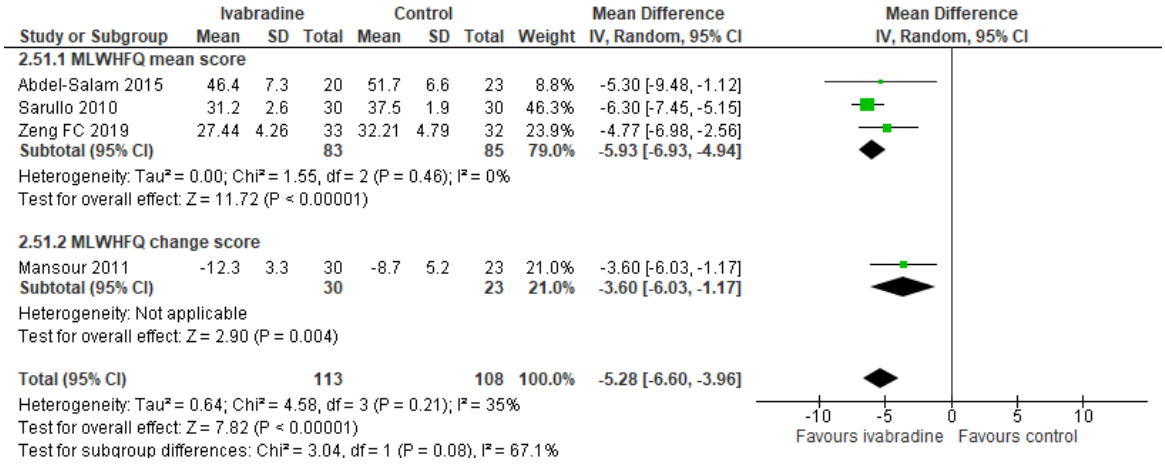


Figure 35 – Forest plot of the sensitivity analysis of quality of life (MLWHFQ) using best- compared with worst-case scenario.

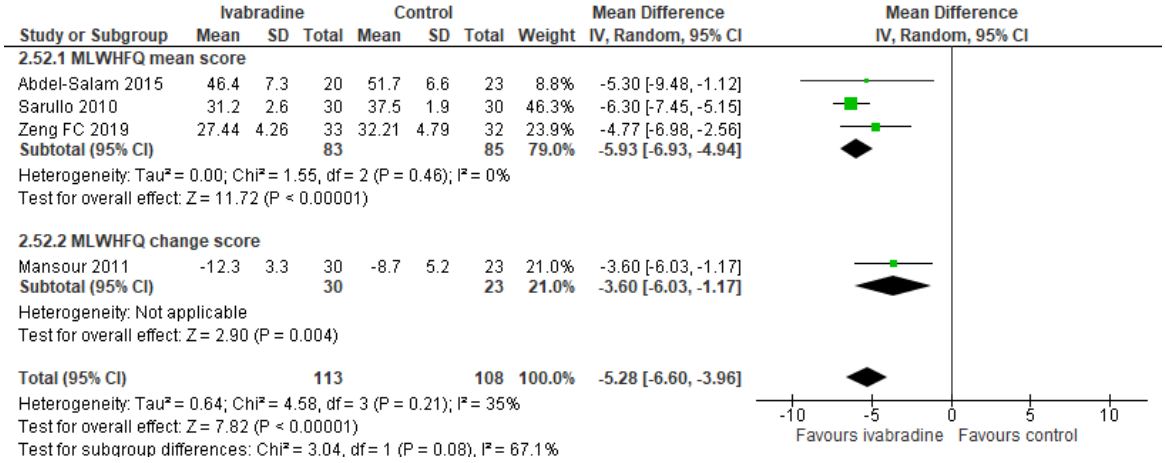


Figure 36 – Forest plot of the sensitivity analysis of quality of life (MLWHFQ) using worst- compared with best-case scenario.

Subgroup analyses of quality of life from trials using the MLWHFQ

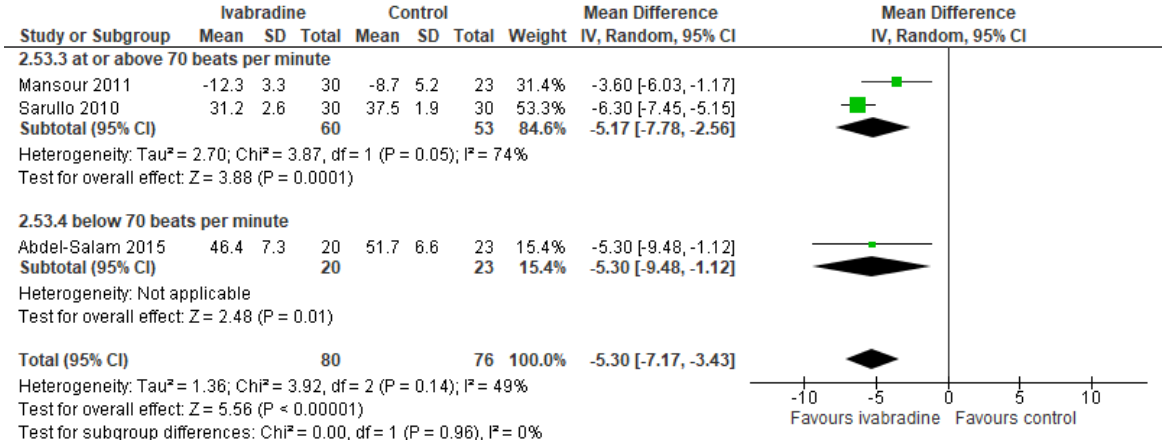


Figure 37 - Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared trials randomising participants with heart rate below 70 beats per minute on quality of life using the MLWHFQ.

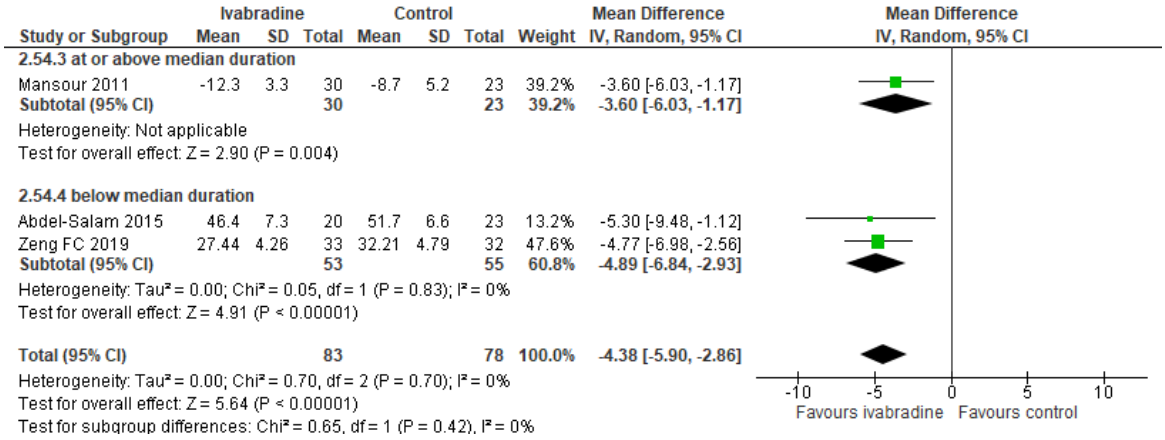


Figure 38 – Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (90.66 days) compared to trials administering ivabradine below median duration on quality of life using the MLWHFQ.

Supplement 8 - Cardiovascular mortality

Main analyses

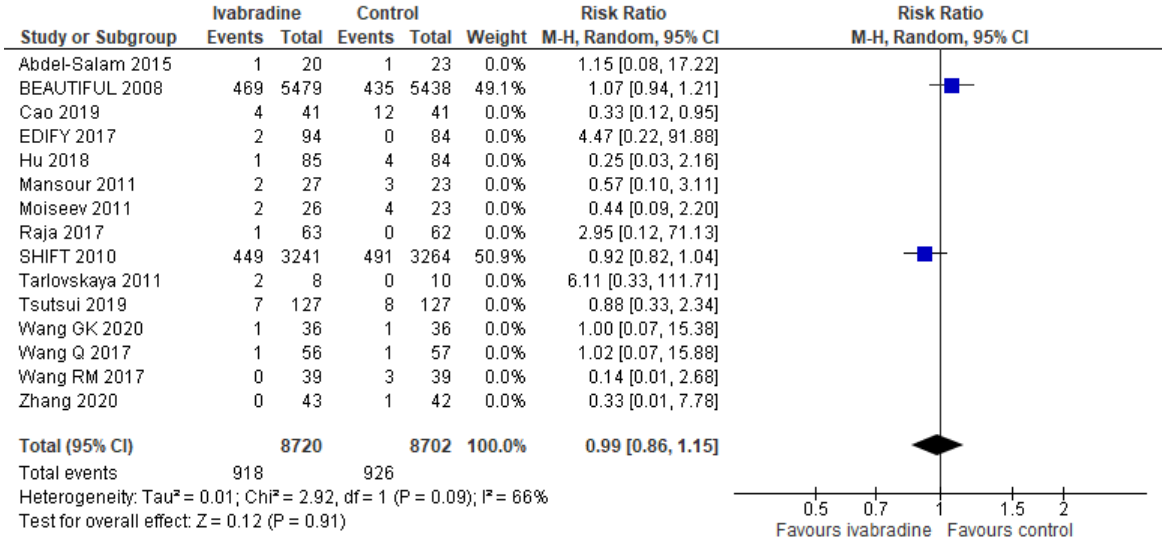


Figure 39 – Forest plot of the meta-analysis of cardiovascular mortality using random-effects meta-analysis including only trials at low risk of bias. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

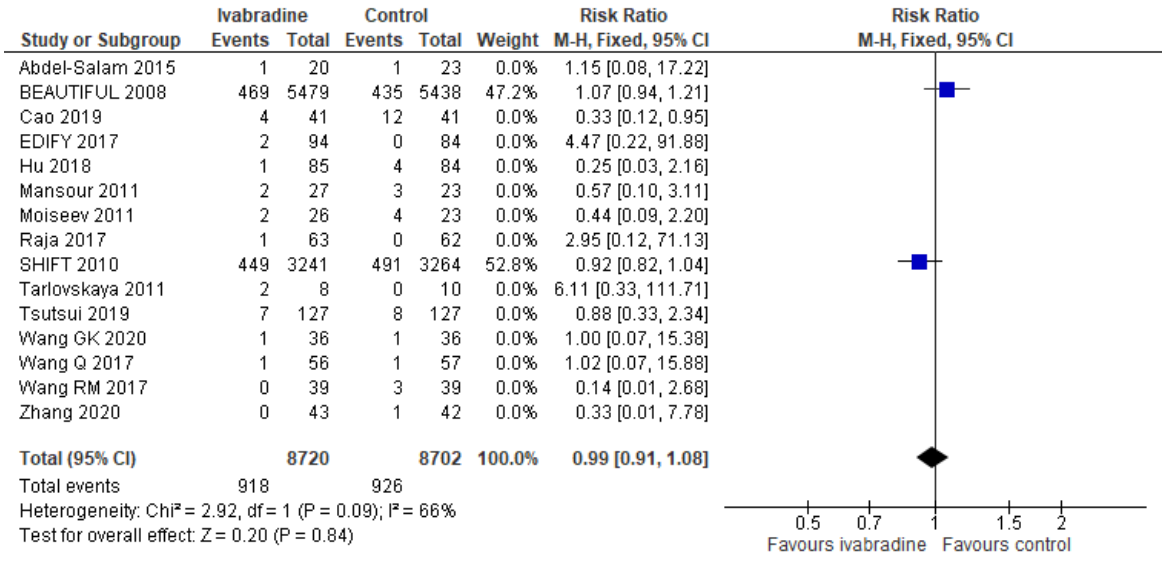


Figure 40 – Forest plot of the meta-analysis of cardiovascular mortality using fixed-effect meta-analysis including only trials at low risk of bias. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

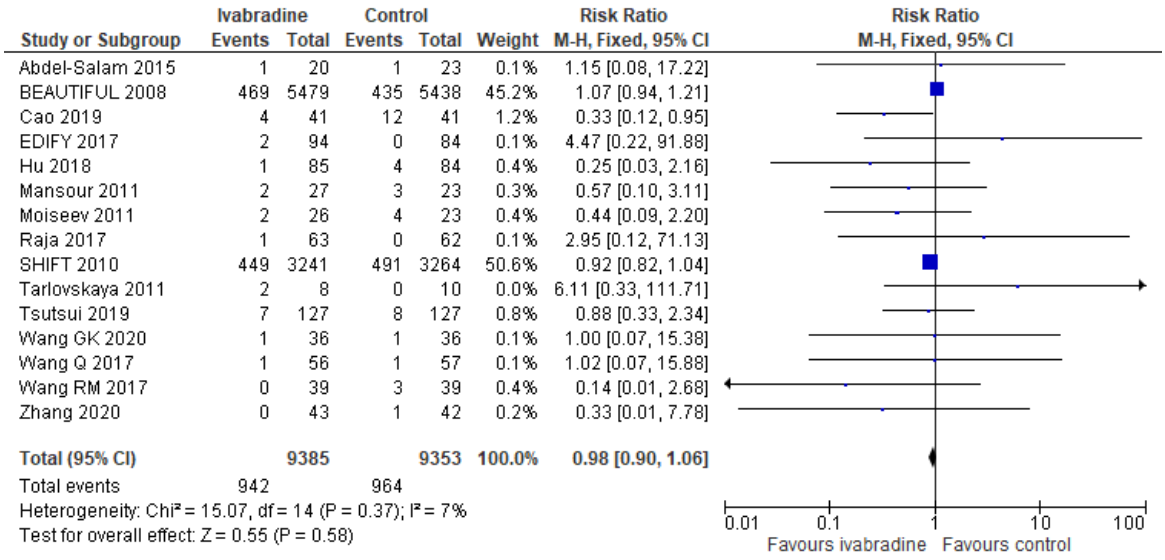


Figure 41 – Forest plot of the meta-analysis of cardiovascular mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

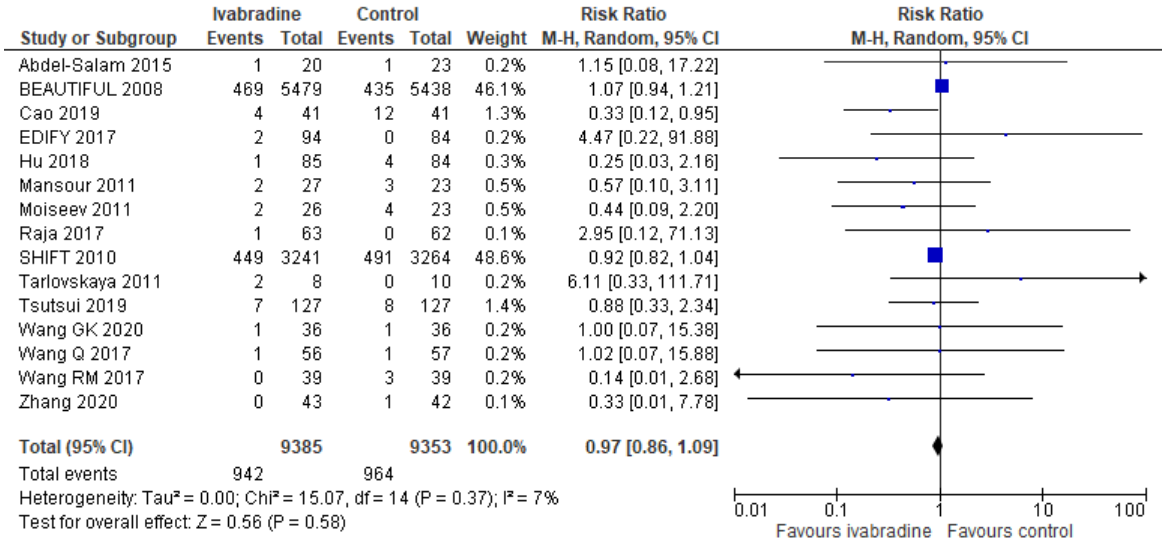


Figure 42 - Forest plot of the meta-analysis of cardiovascular mortality using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

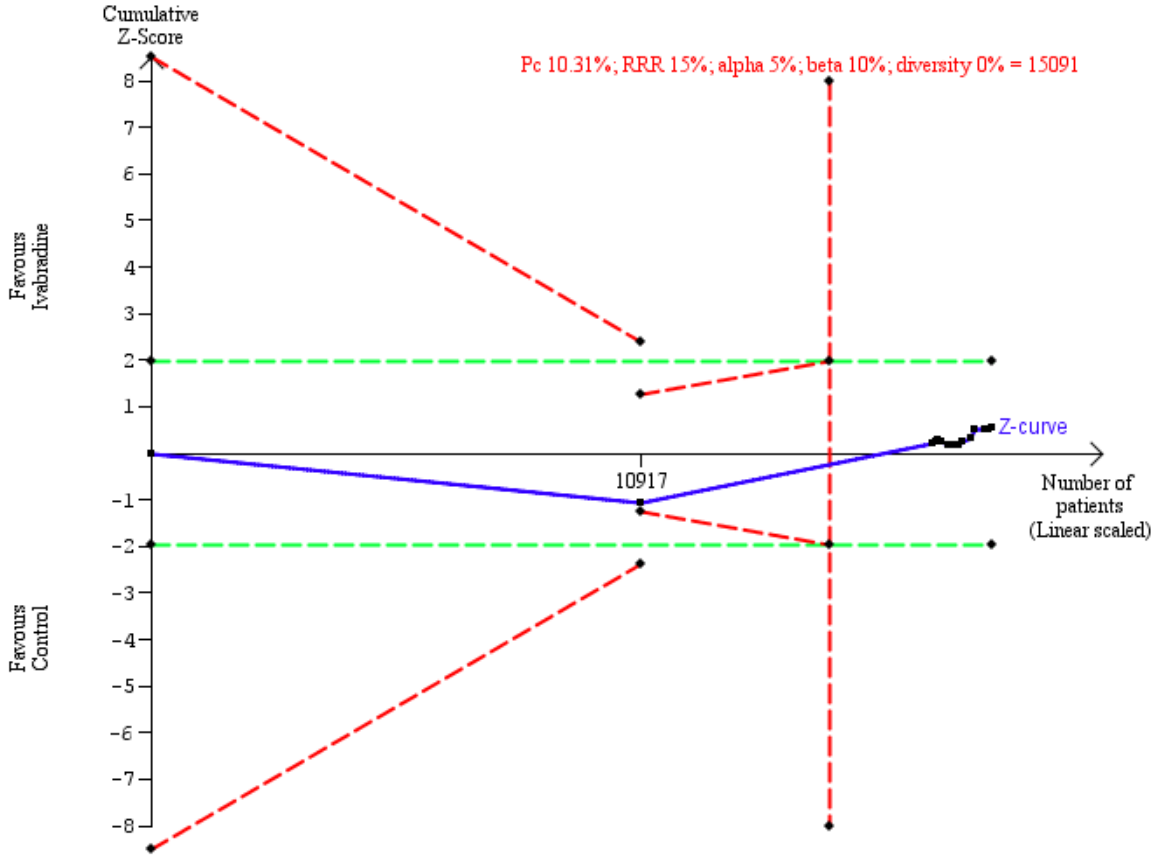


Figure 43 - Trial Sequential Analysis graph of cardiovascular mortality. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) breaches the boundary of futility and the required information size. Pc: prevalence in control group; RRR: relative risk ratio.

Sensitivity analyses

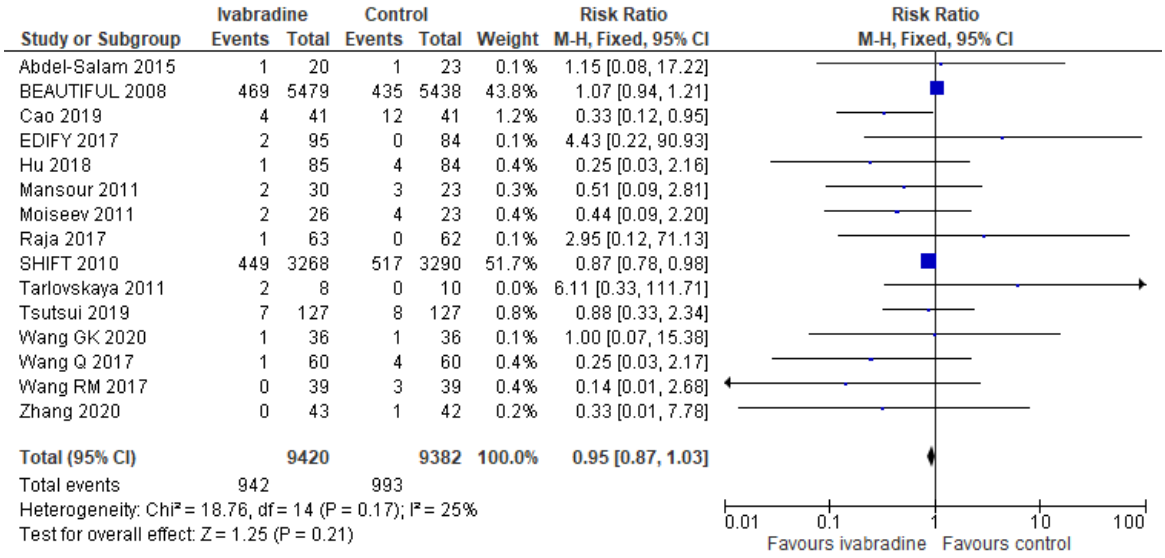


Figure 44 - Forest plot of the sensitivity analysis of cardiovascular mortality using best- compared with worst-case scenario.

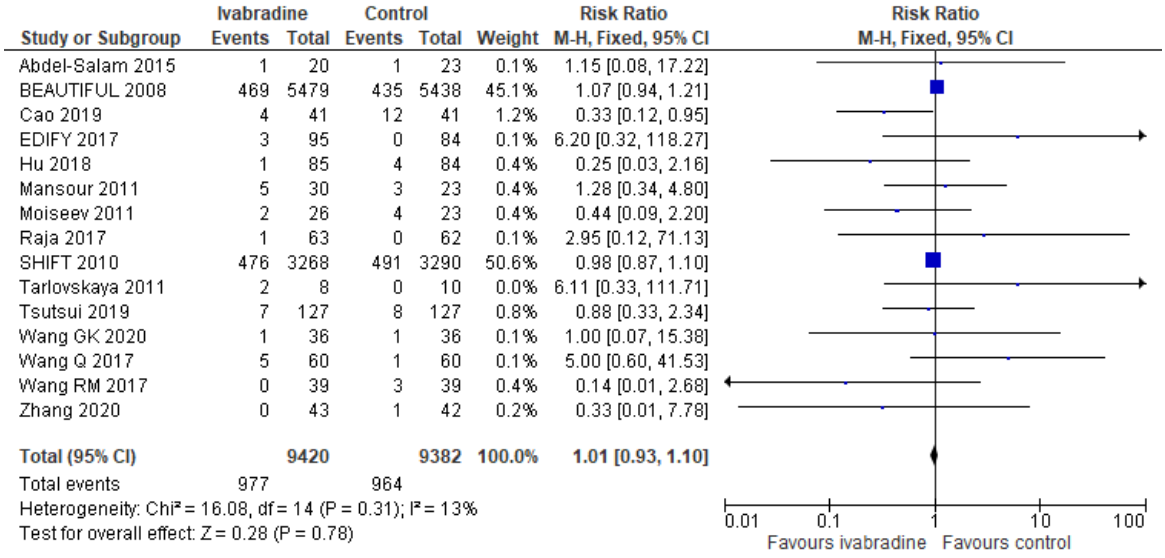


Figure 45 – Forest plot of the sensitivity analysis of cardiovascular mortality using worst compared with best-case scenario.

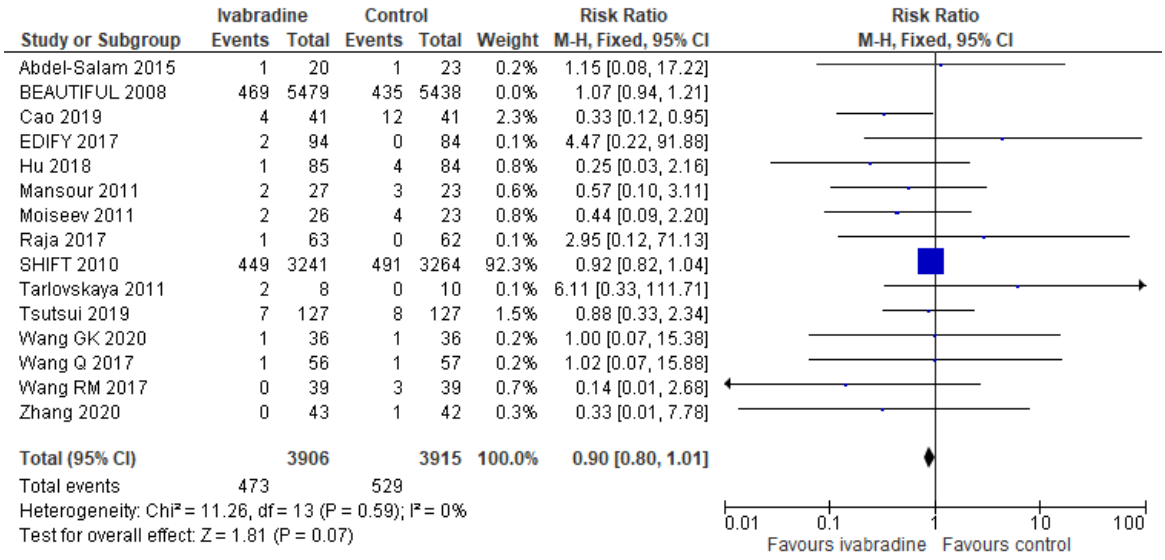


Figure 46 – Forest plot of the sensitivity analysis of cardiovascular mortality removing the BEAUTIFUL trial.

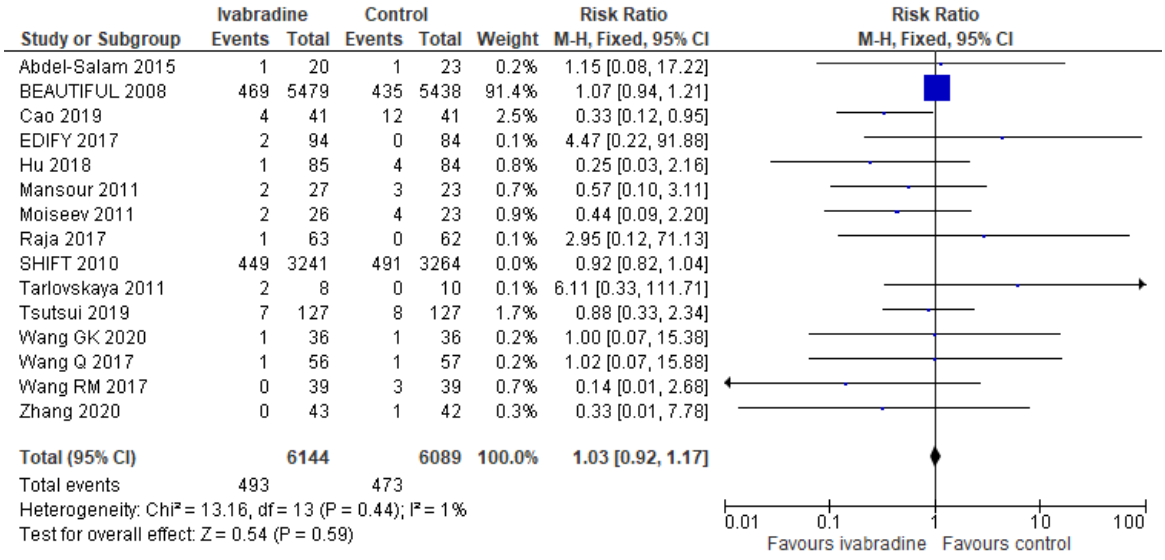


Figure 47 – Forest plot of the sensitivity analysis of cardiovascular mortality removing the SHIFT trial.

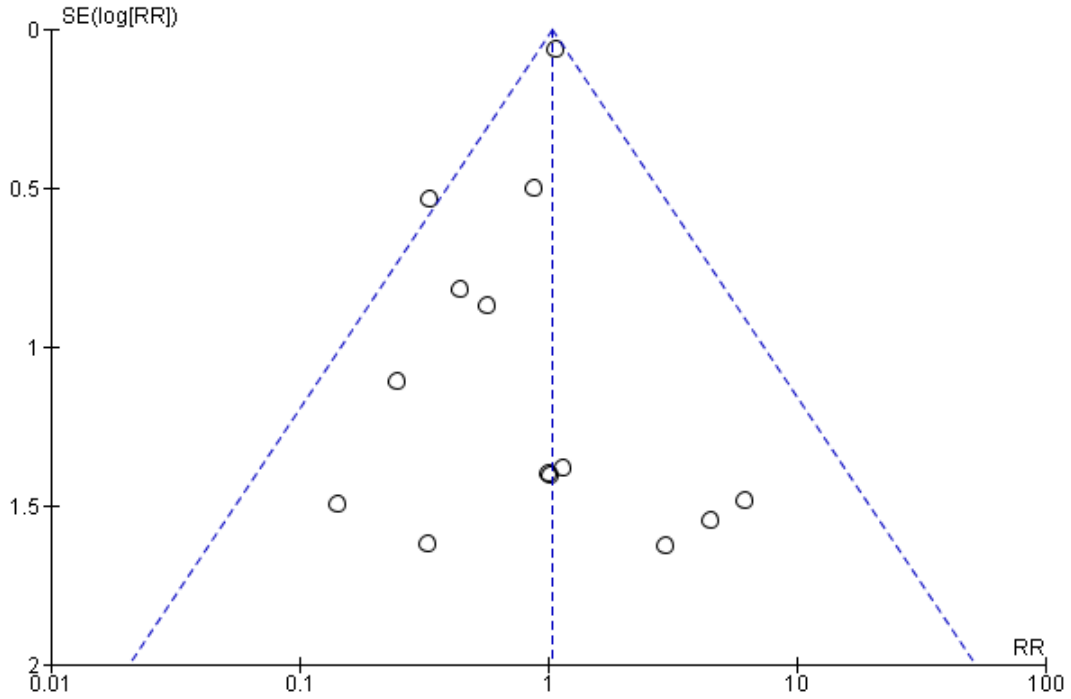


Figure 48 – Funnel plot of the analysis of cardiovascular mortality. The funnel plot did not indicate small study bias.

Supplement 9 - Myocardial infarction

Main analyses

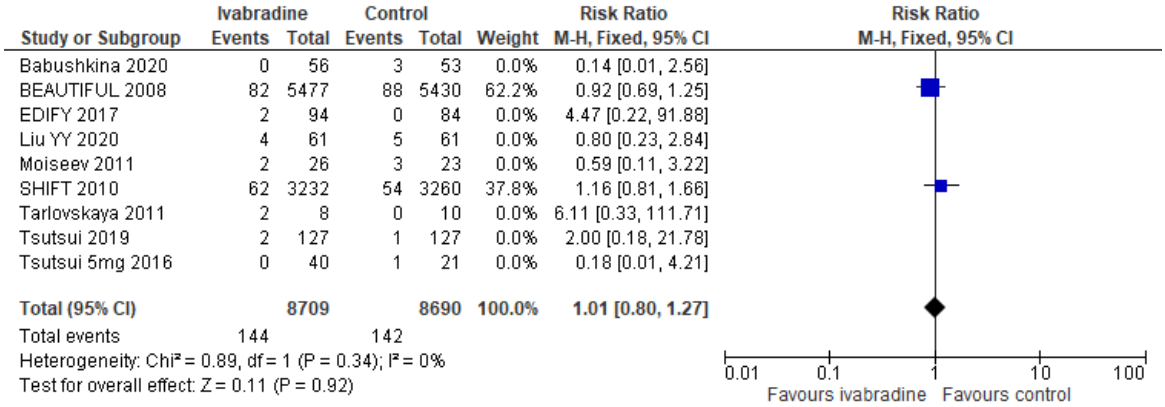


Figure 49 – Forest plot of the meta-analysis of myocardial infarction using fixed-effect meta-analysis including only trial results at low risk of bias. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

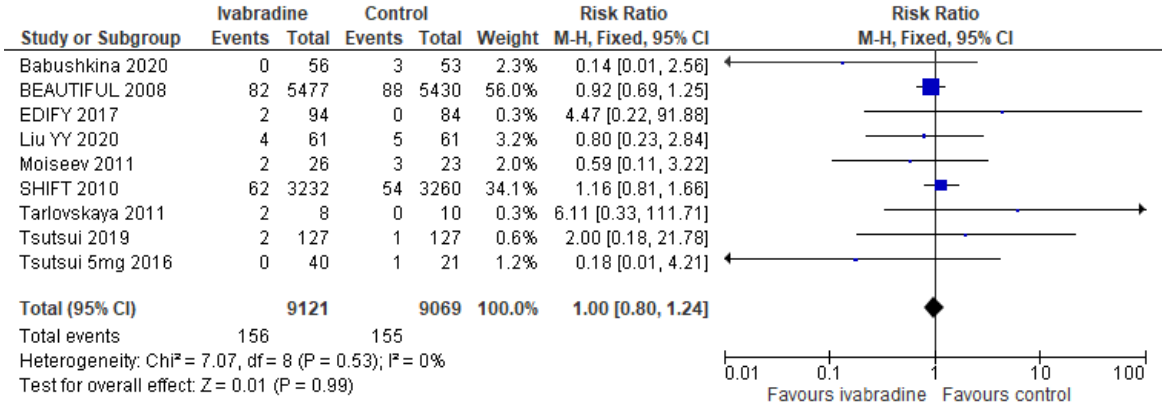


Figure 50 - Forest plot of the meta-analysis of myocardial infarction using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

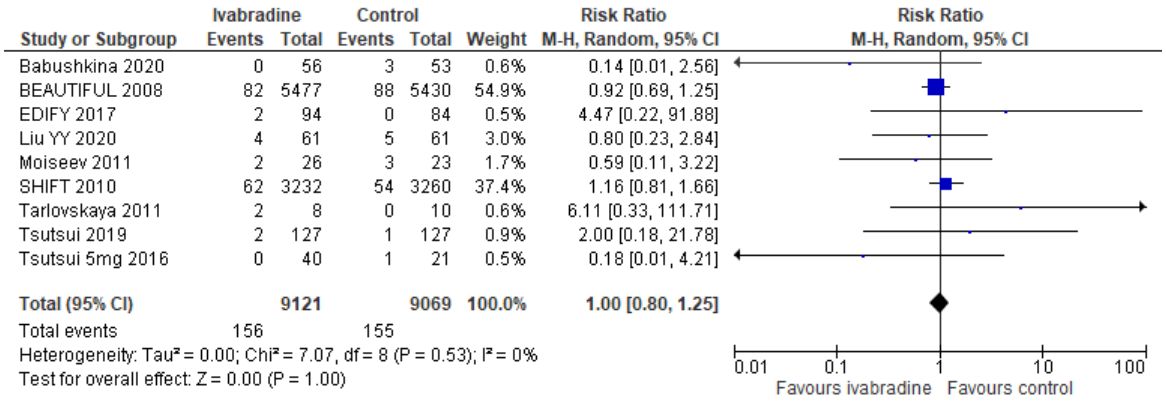


Figure 51 - Forest plot of the meta-analysis of myocardial infarction using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

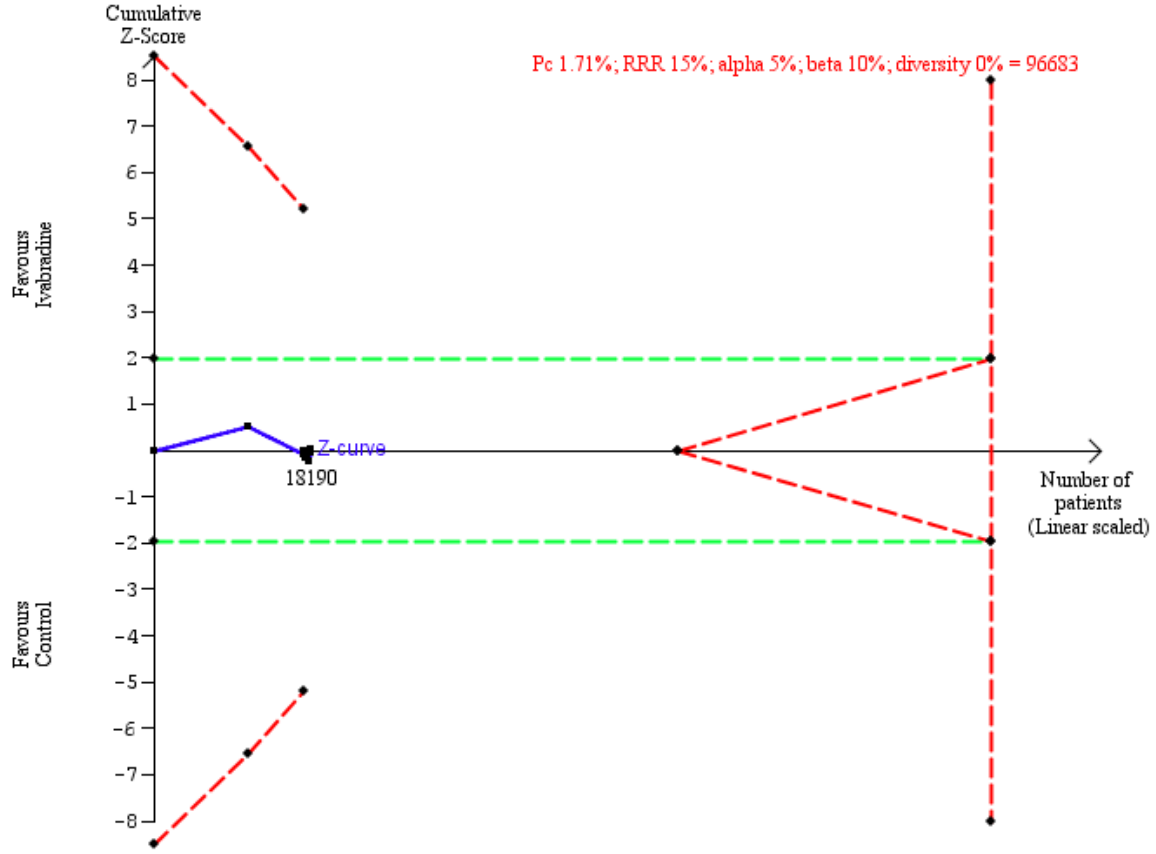


Figure 52 - Trial Sequential Analysis graph of myocardial infarction. Trial Sequential Analysis showed that we did not have enough information to detect or reject a relative risk reduction of 15% or more by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) does not breach any boundaries. Pc: prevalence in control group; RRR: relative risk ratio.

Sensitivity analyses

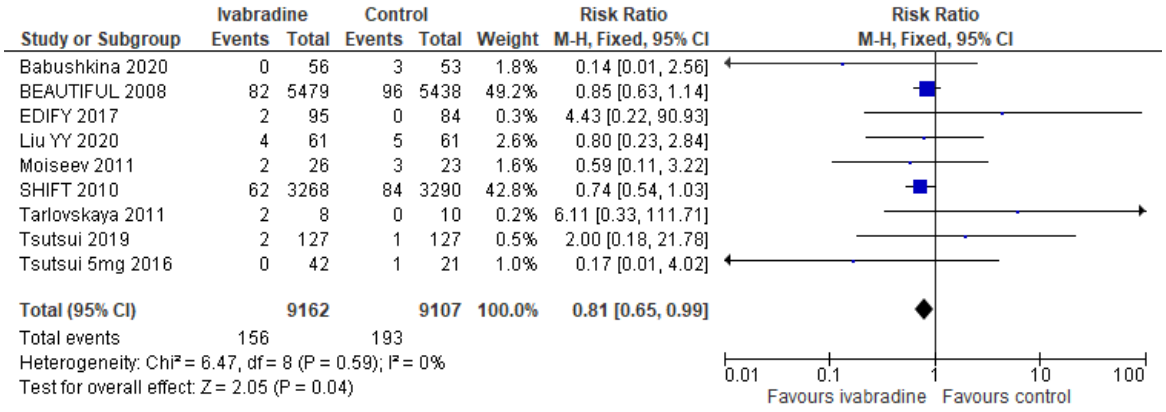


Figure 53 – Forest plot of the sensitivity analysis of myocardial infarction using a best- compared with worst-case scenario.

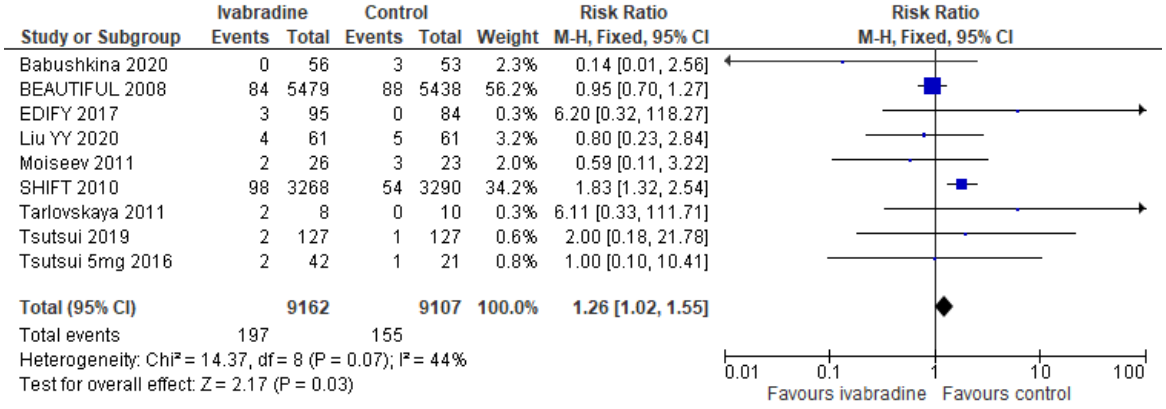


Figure 54 - Forest plot of the sensitivity analysis of myocardial infarction using a worst- compared with best-case scenario.

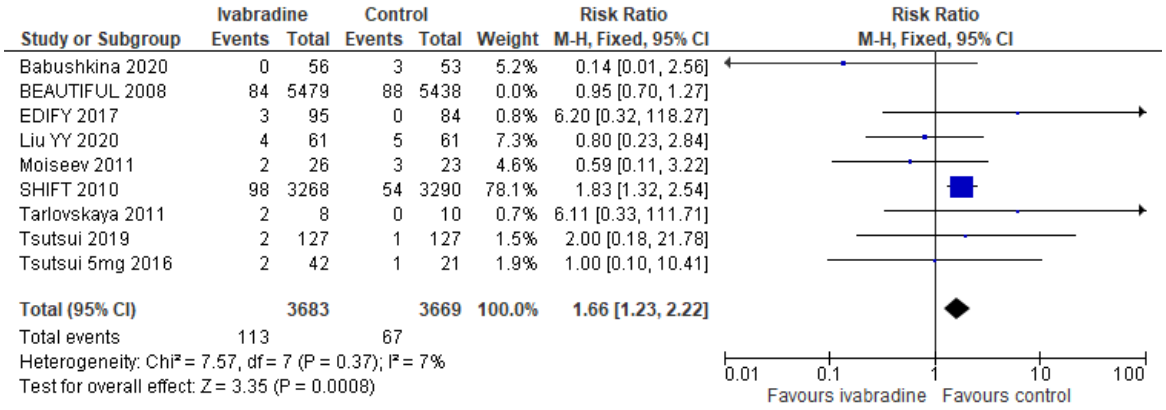


Figure 55 – Forest plot of the sensitivity analysis of myocardial infarction removing the BEAUTIFUL trial.

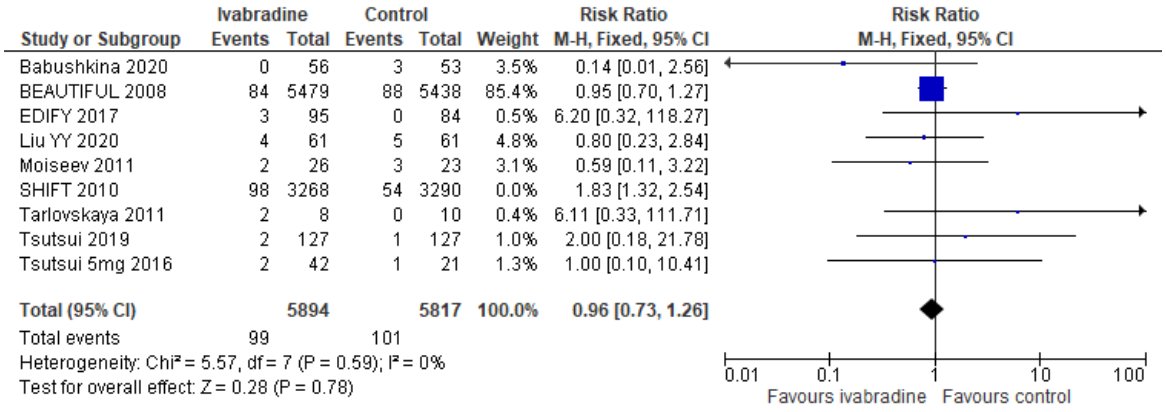


Figure 56 – Forest plot of the sensitivity analysis of myocardial infarction removing the SHIFT trial.

Supplement 10 - Non-serious adverse events

Main analyses

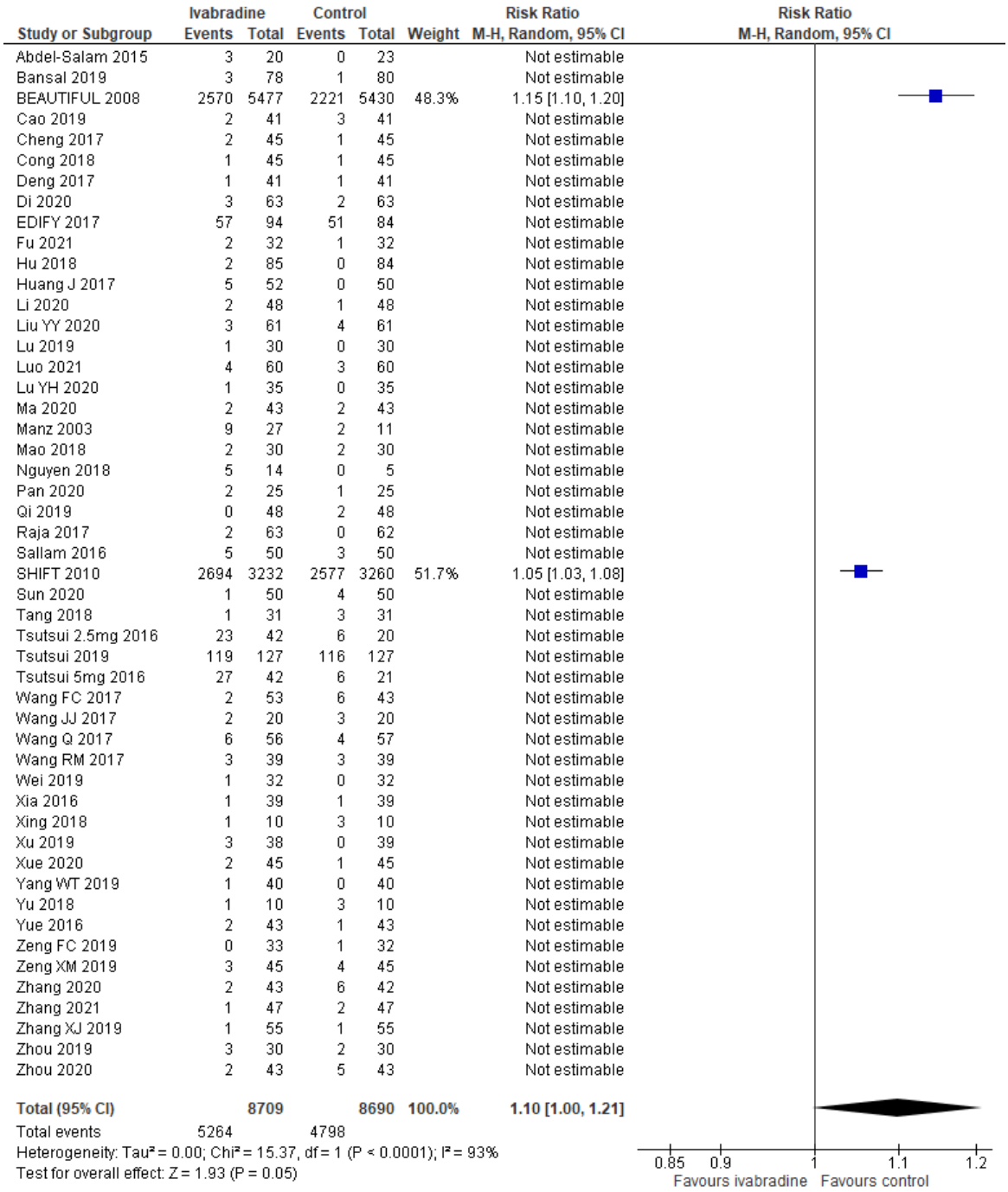


Figure 57 – Forest plot of the meta-analysis of non-serious adverse events using random-effects meta-analysis including only trials at low risk of bias. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention)

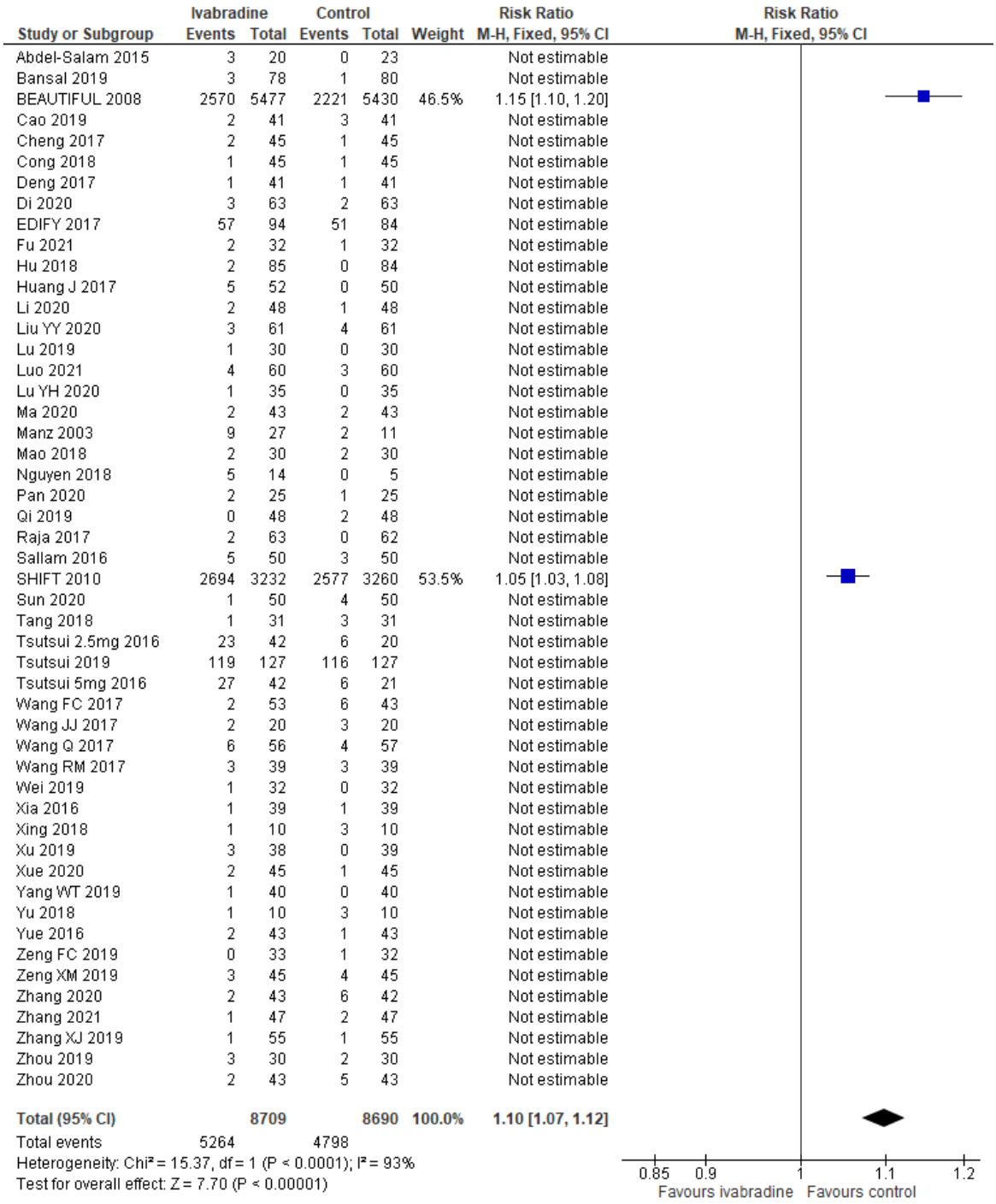


Figure 58 – Forest plot of the meta-analysis of non-serious adverse events using fixed-effect meta-analysis including only trials at low risk of bias. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention).

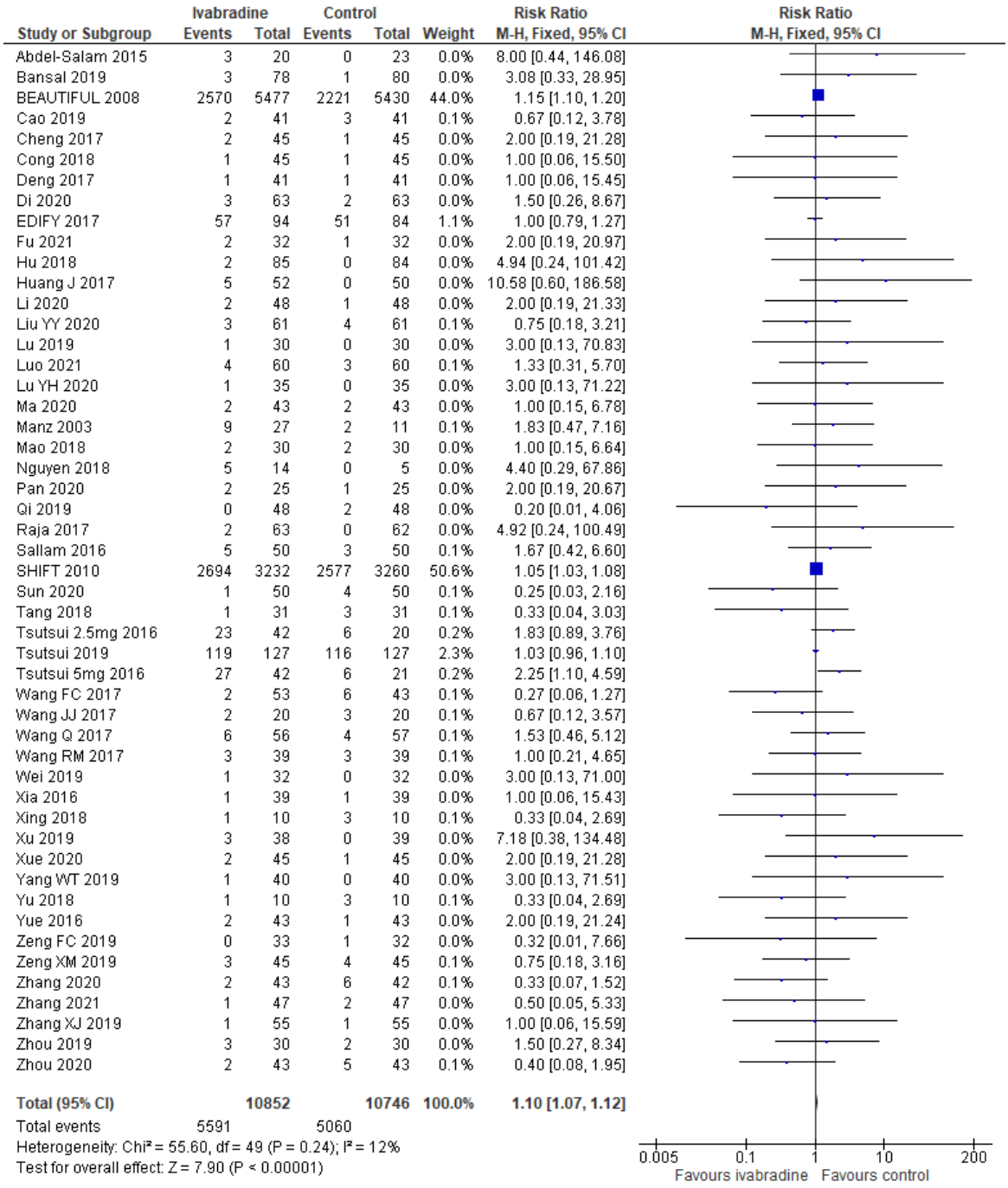


Figure 59 - Forest plot of the meta-analysis of non-serious adverse events using fixed-effect meta-analysis. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention).

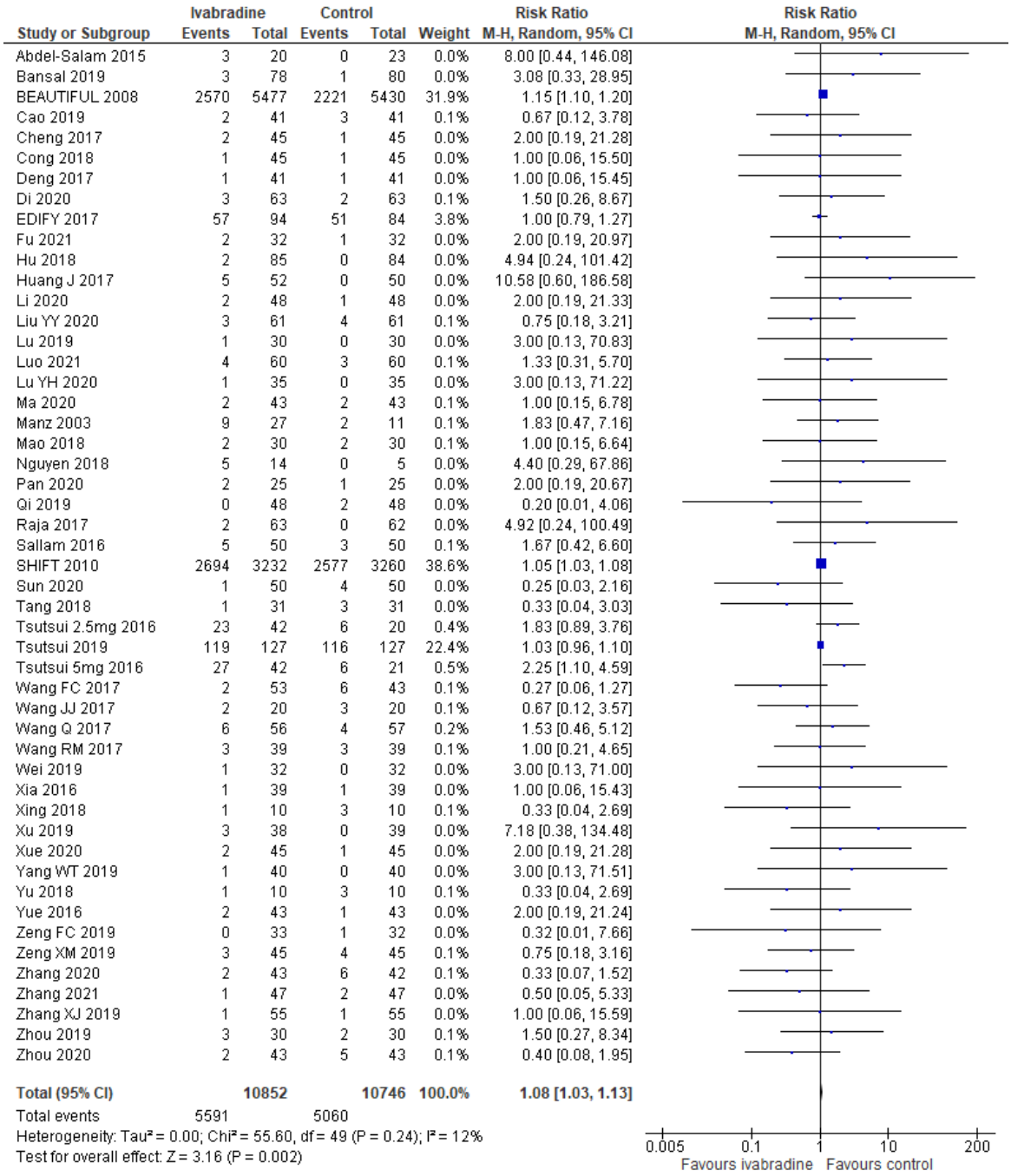


Figure 60 - Forest plot of the meta-analysis of non-serious adverse events using random-effects meta-analysis. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention)

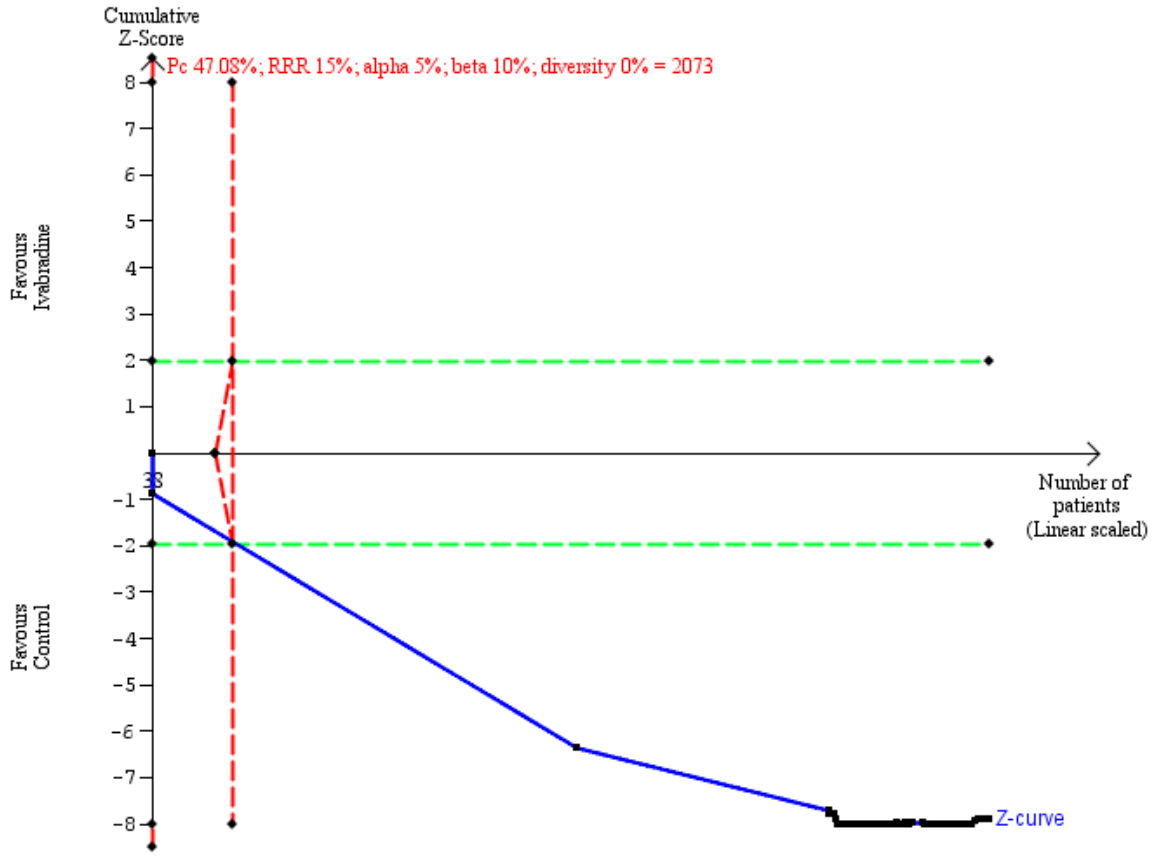


Figure 61 – Trial Sequential Analysis graph of non-serious adverse events. Trial Sequential Analysis showed that we had enough information to detect a relative risk increase of 10% by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) reached the required information size and crossed the conventional boundary of statistical significance. Pc: prevalence in control group; RRR: relative risk ratio.

Sensitivity analyses

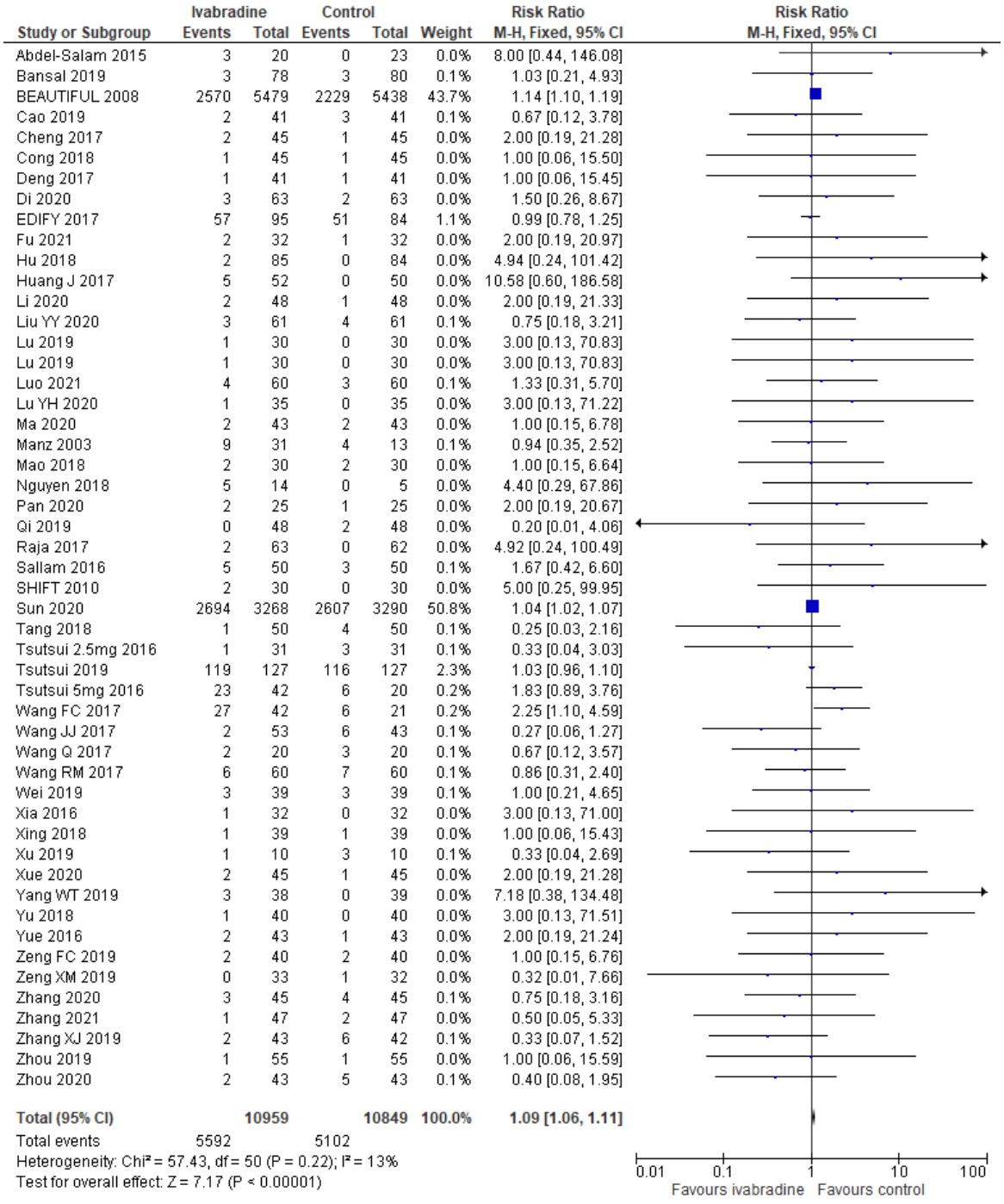


Figure 62 – Forest plot of the meta-analysis of non-serious adverse events using a best- compared with worst-case scenario.

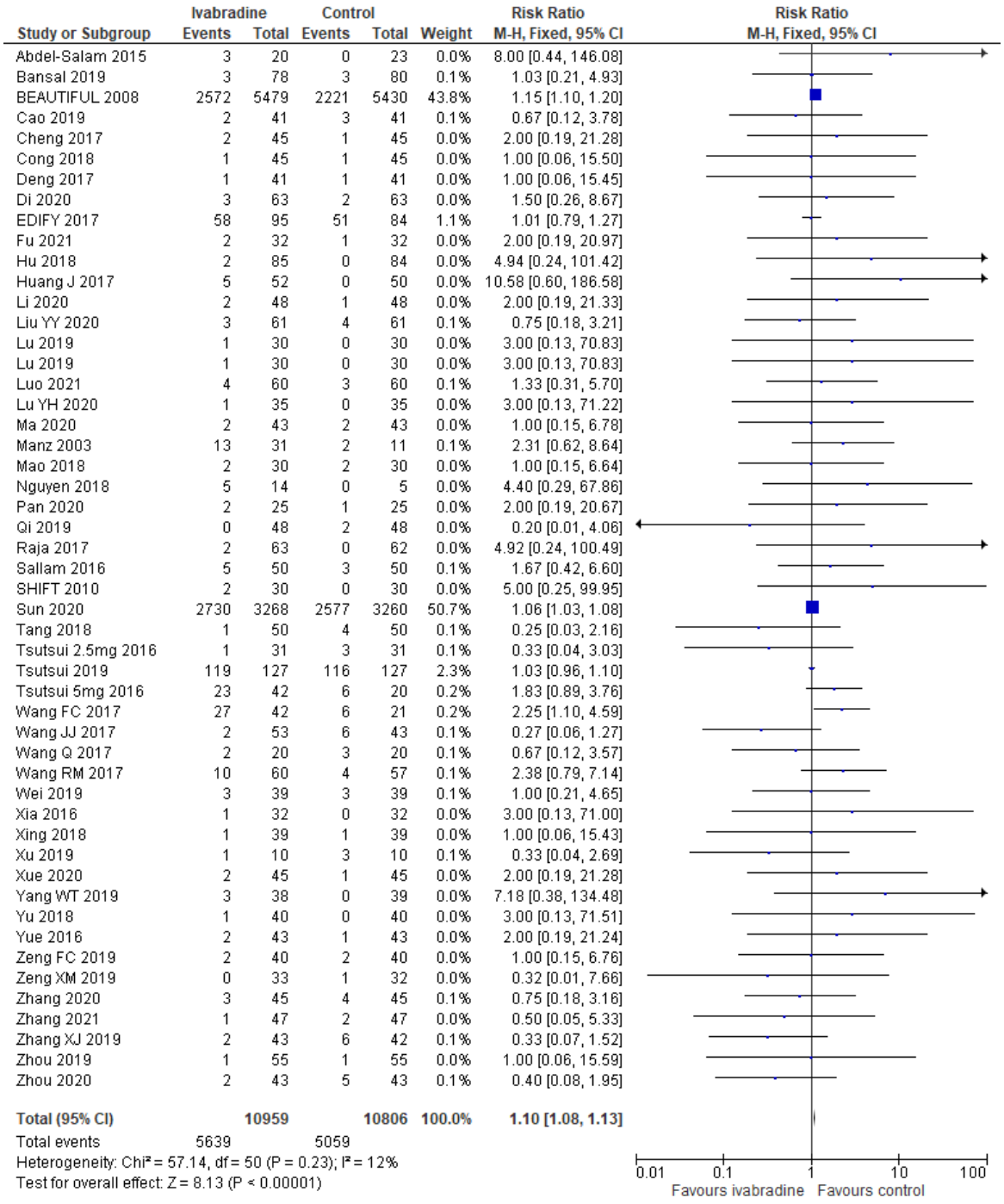


Figure 63 - Forest plot of the meta-analysis of non-serious adverse events using a worst- compared with best-case scenario.

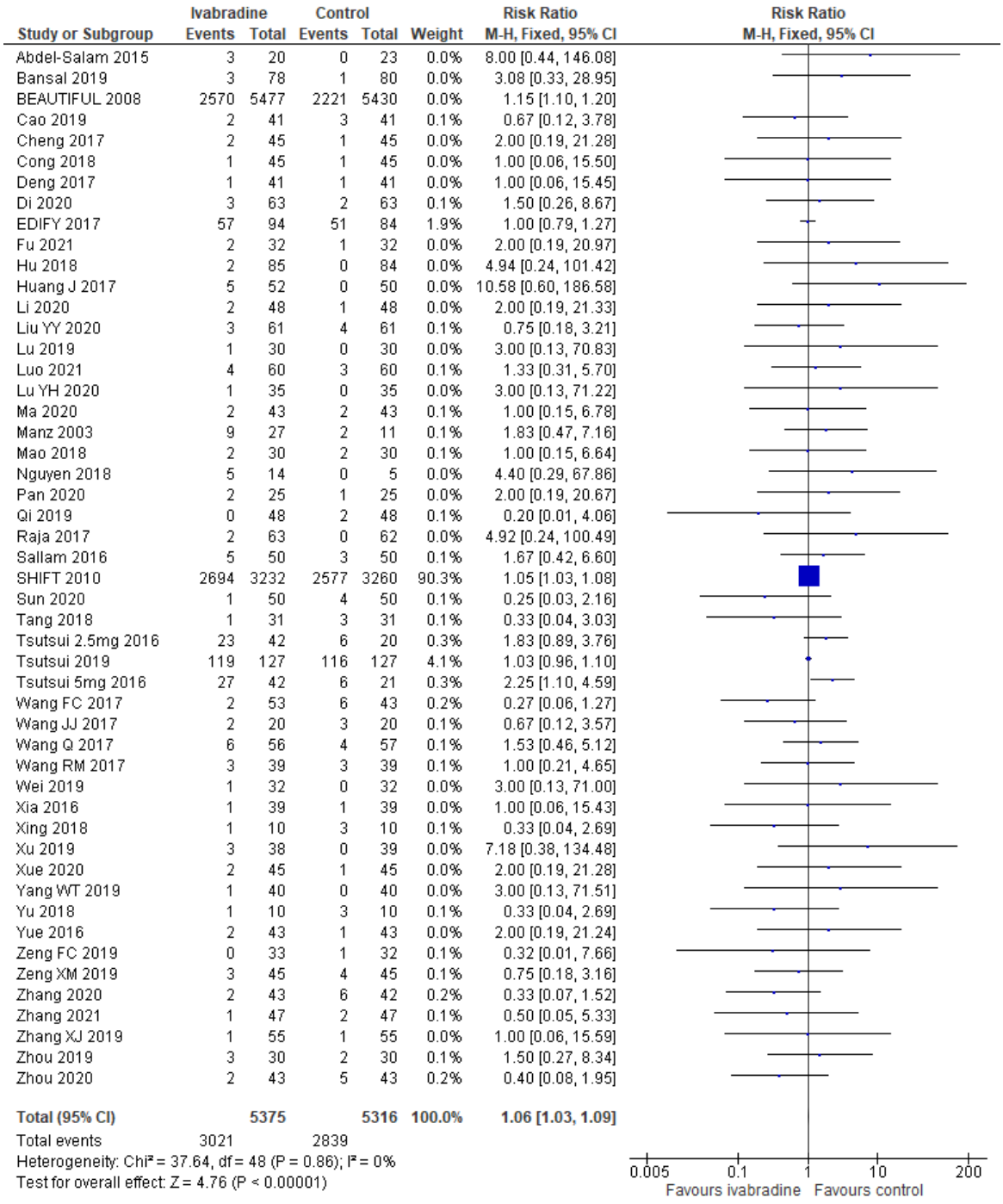


Figure 64 – Forest plot of the sensitivity analysis of non-serious adverse events removing the BEAUTIFUL trial.

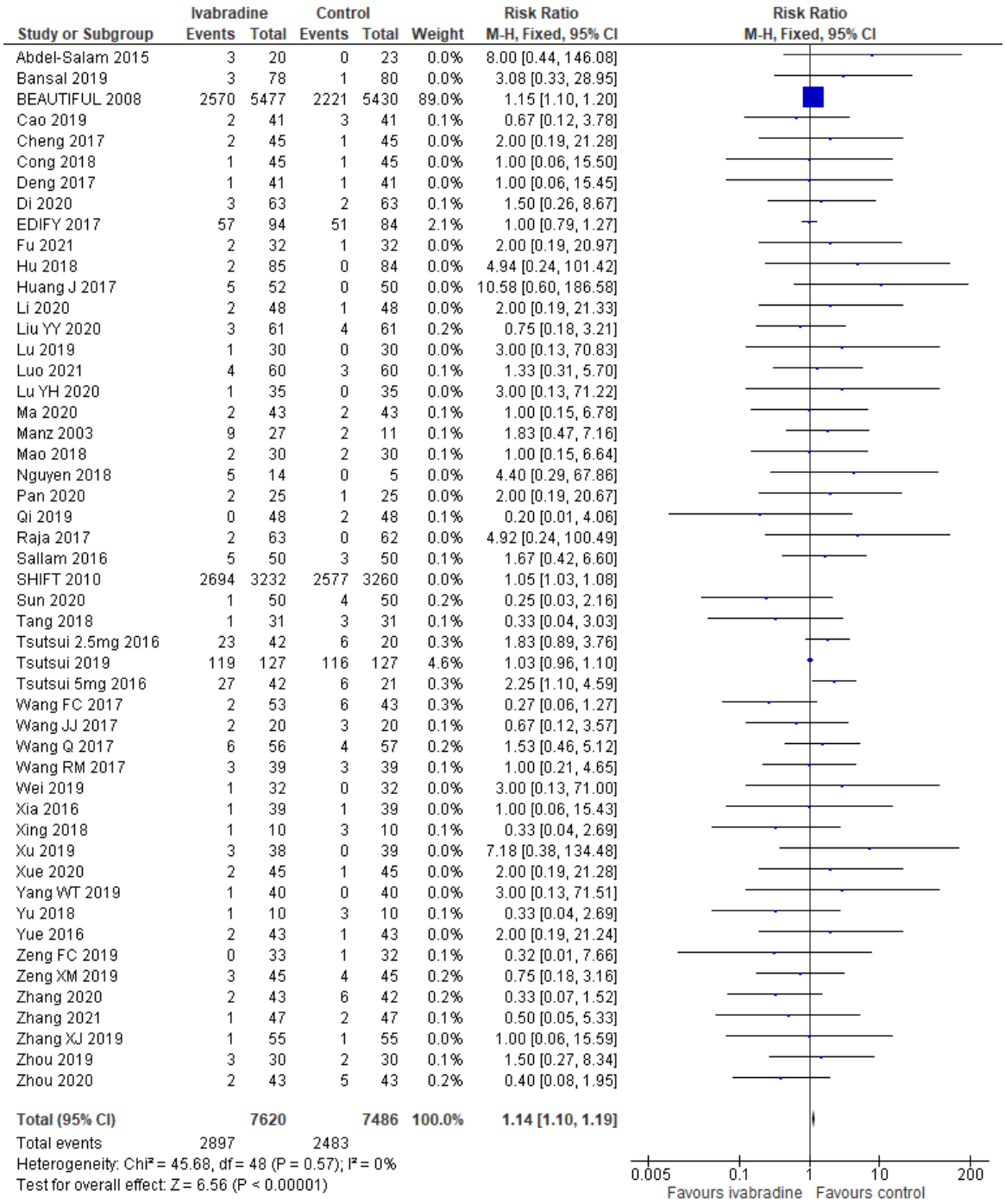


Figure 65 – Forest plot of the sensitivity analysis of non-serious adverse events removing the SHIFT trial.

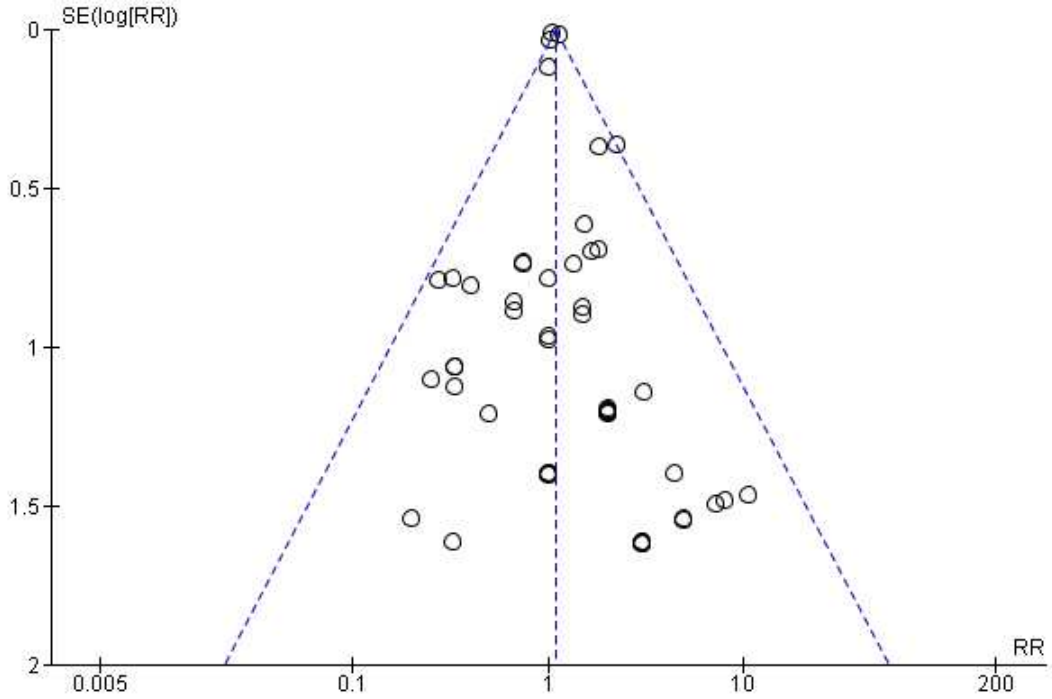


Figure 66 – Funnel plot of the analysis of non-serious adverse events. The funnel plot did not indicate small study bias.

Supplement 11 – Discrepancy in safety data

For serious and non-serious adverse events, there were discrepancies between the data reported in the publication in the SHIFT trial as compared to the raw data reported on ClinicalTrials.gov.

In the published article of the SHIFT trial, it was reported that 1450/3232 (44.86%) participants in the ivabradine group and 1553/3260 (47.6%) in the control group experienced one or more serious adverse events. However, in the raw data it was reported that 1369/3232 (42.4%) in the ivabradine group versus 1481/3260 (45.4%) in the control group experienced one or more serious adverse events. In our analyses, we have used the highest proportion of participants at risk.

In the published article of the SHIFT trial it was reported that 2439/3232 (75.5%) participants in the ivabradine group and 2423/3260 (74.3%) in the control group experienced one or more non-serious adverse events. However, in the raw data it was reported that 2062/3232 (63.8%) in the ivabradine group versus 2020/3260 (62.0%) in the control group experienced one or more non-serious adverse events. In our analyses, we have used the highest proportion of participants at risk. The company that developed ivabradine, Servier, has 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

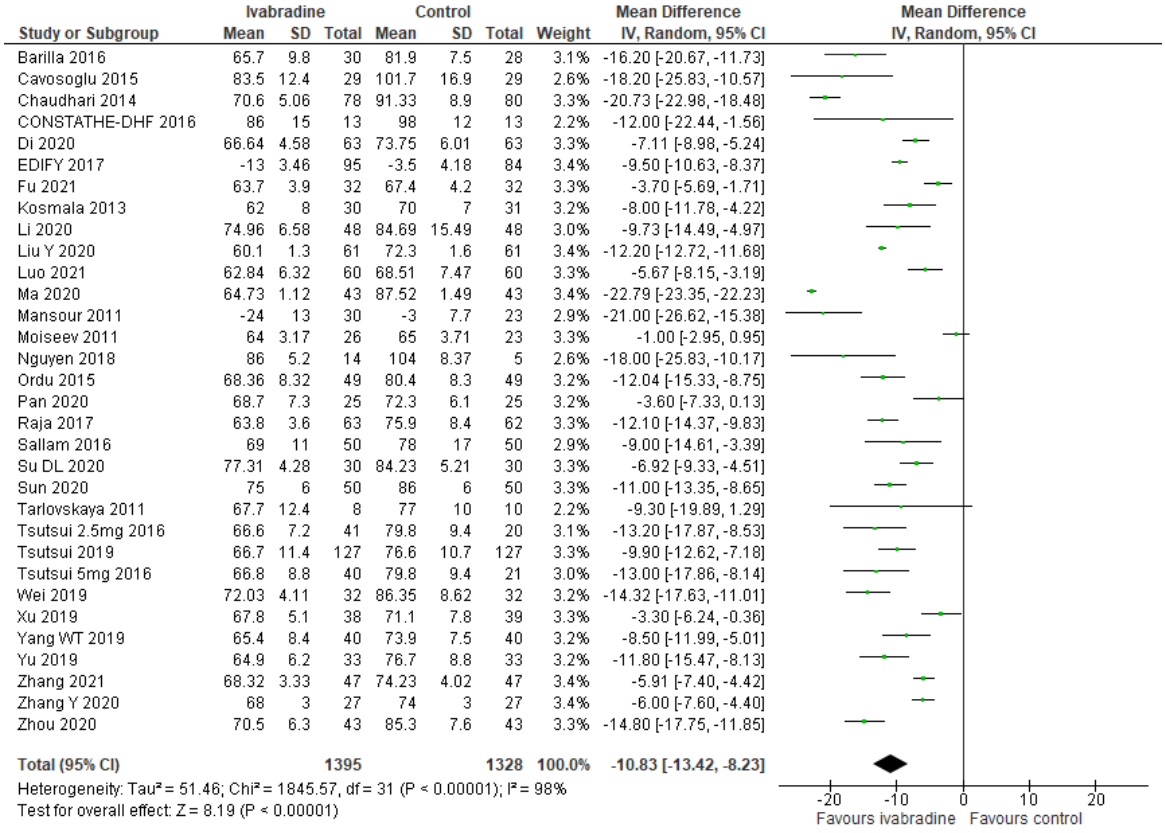


Figure 67 – Forest plot of the meta-analysis of resting heart rate at follow-up using random-effects meta-analysis. The meta-analysis showed that ivabradine seemed to decrease the resting heart rate at follow-up by 10.83 beats per minute at follow-up.

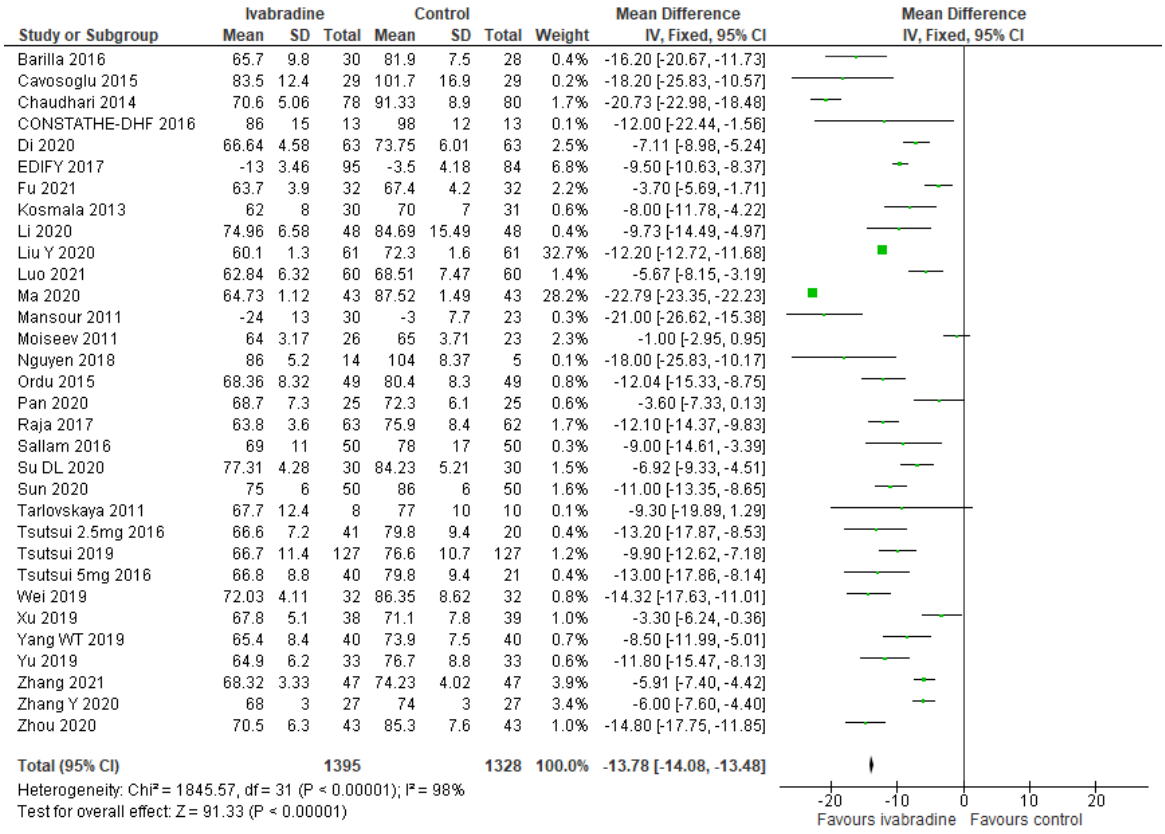


Figure 68 - Forest plot of the meta-analysis of resting heart rate at follow-up using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to decrease the resting heart rate at follow-up by 13.78 beats per minute at follow-up.

Left ventricular ejection fraction

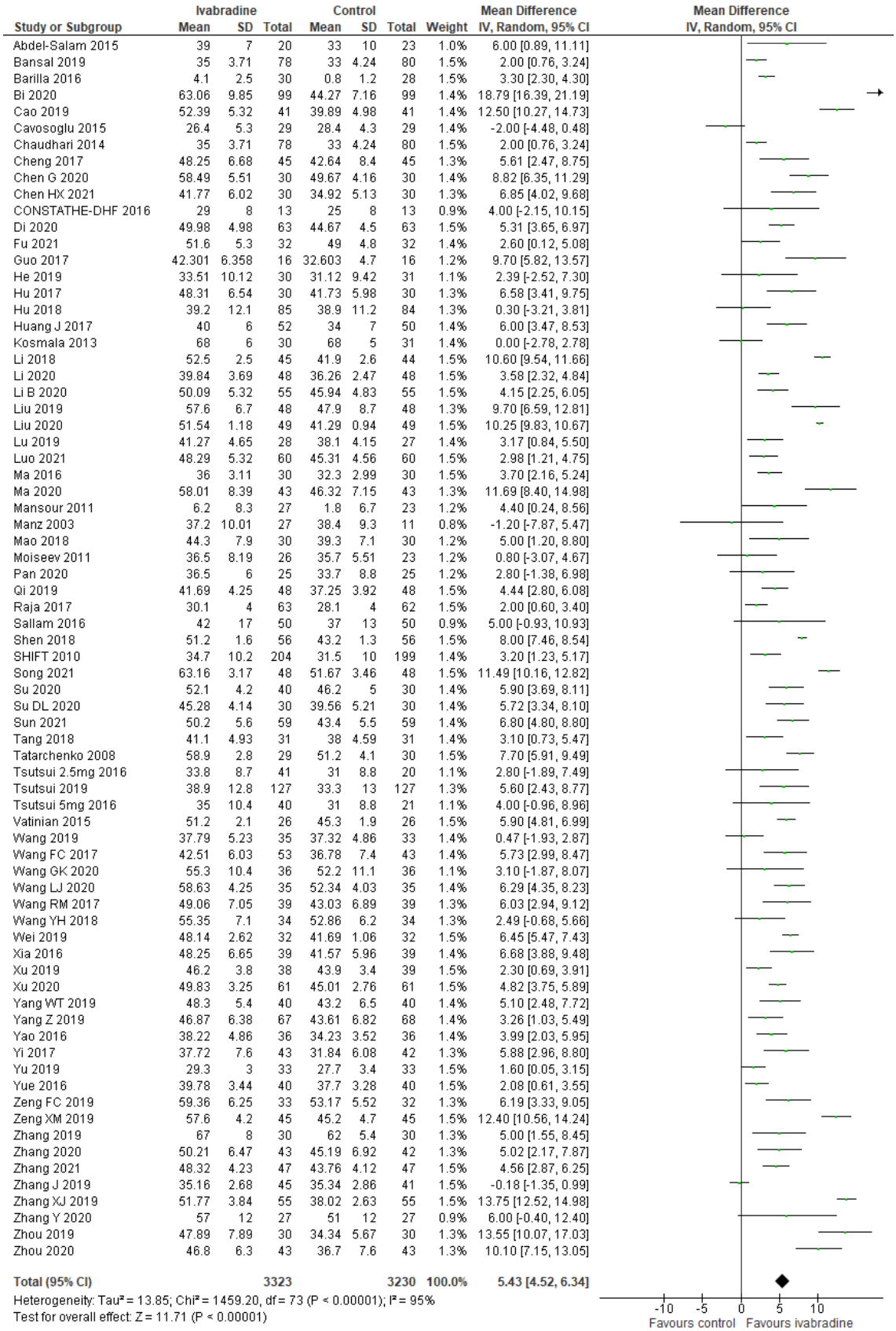

Ivabradine
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Abdel-Salam 2015 39 7 20 33 10 23 1.0% 6.00 [0.89, 11.11]
Bansal 2019 35 3.71 78 33 4.24 80 1.5% 2.00 [0.76, 3.24]
Barilla 2016 4.1 2.5 30 0.8 1.2 28 1.5% 3.30 [2.30, 4.30]
Bi 2020 63.06 9.85 99 44.27 7.16 99 1.4% 18.79 [16.39, 21.19]
Cao 2019 52.39 5.32 41 39.89 4.98 41 1.4% 12.50 [10.27, 14.73]
Cavosoglu 2015 26.4 5.3 29 28.4 4.3 29 1.4% -2.00 [-4.48, 0.48]
Chaudhari 2014 35 3.71 78 33 4.24 80 1.5% 2.00 [0.76, 3.24]
Cheng 2017 48.25 6.68 45 42.64 8.4 45 1.3% 5.61 [2.47, 8.75]
Chen G 2020 58.49 5.51 30 49.67 4.16 30 1.4% 8.82 [6.35, 11.29]
Chen HX 2021 41.77 6.02 30 34.92 5.13 30 1.3% 6.85 [4.02, 9.68]
CONSTATHE-DHF 2016 29 8 13 25 8 13 0.9% 4.00 [-2.15, 10.15]
Di 2020 49.98 4.98 63 44.67 4.5 63 1.5% 5.31 [3.65, 6.97]
Fu 2021 51.6 5.3 32 49 4.8 32 1.4% 2.60 [0.12, 5.08]
Guo 2017 42.301 6.358 16 32.603 4.7 16 1.2% 9.70 [5.82, 13.57]
He 2019 33.51 10.12 30 31.12 9.42 31 1.1% 2.39 [-2.52, 7.30]
Hu 2017 48.31 6.54 30 41.73 5.98 30 1.3% 6.58 [3.41, 9.75]
Hu 2018 39.2 12.1 85 38.9 11.2 84 1.3% 0.30 [-3.21, 3.81]
Huang J 2017 40 6 52 34 7 50 1.4% 6.00 [3.47, 8.53]
Kosmala 2013 68 6 30 68 5 31 1.4% 0.00 [-2.78, 2.78]
Li 2018 52.5 2.5 45 41.9 2.6 44 1.5% 10.60 [9.54, 11.66]
Li 2020 39.84 3.69 48 36.26 2.47 48 1.5% 3.58 [2.32, 4.84]
Li B 2020 50.09 5.32 55 45.94 4.83 55 1.5% 4.15 [2.25, 6.05]
Liu 2019 57.6 6.7 48 47.9 8.7 48 1.3% 9.70 [6.59, 12.81]
Liu 2020 51.54 1.18 49 41.29 0.94 49 1.5% 10.25 [9.83, 10.67]
Lu 2019 41.27 4.65 28 38.1 4.15 27 1.4% 3.17 [0.84, 5.50]
Luo 2021 48.29 5.32 60 45.31 4.56 60 1.5% 2.98 [1.21, 4.75]
Ma 2016 36 3.11 30 32.3 2.99 30 1.5% 3.70 [2.16, 5.24]
Ma 2020 58.01 8.39 43 46.32 7.15 43 1.3% 11.69 [8.40, 14.98]
Mansour 2011 6.2 8.3 27 1.8 6.7 23 1.2% 4.40 [0.24, 8.56]
Manz 2003 37.2 10.01 27 38.4 9.3 11 0.8% -1.20 [-7.87, 5.47]
Mao 2018 44.3 7.9 30 39.3 7.1 30 1.2% 5.00 [1.20, 8.80]
Moiseev 2011 36.5 8.19 26 35.7 5.51 23 1.2% 0.80 [-3.07, 4.67]
Pan 2020 36.5 6 25 33.7 8.8 25 1.2% 2.80 [-1.38, 6.98]
Qi 2019 41.69 4.25 48 37.25 3.92 48 1.5% 4.44 [2.80, 6.08]
Raja 2017 30.1 4 63 28.1 4 62 1.5% 2.00 [0.60, 3.40]
Sallam 2016 42 17 50 37 13 50 0.9% 5.00 [-0.93, 10.93]
Shen 2018 51.2 1.6 56 43.2 1.3 56 1.5% 8.00 [7.46, 8.54]
SHIFT 2010 34.7 10.2 204 31.5 10 199 1.4% 3.20 [1.23, 5.17]
Song 2021 63.16 3.17 48 51.67 3.46 48 1.5% 11.49 [10.16, 12.82]
Su 2020 52.1 4.2 40 46.2 5 30 1.4% 5.90 [3.69, 8.11]
Su DL 2020 45.28 4.14 30 39.56 5.21 30 1.4% 5.72 [3.34, 8.10]
Sun 2021 50.2 5.6 59 43.4 5.5 59 1.4% 6.80 [4.80, 8.80]
Tang 2018 41.1 4.93 31 38 4.59 31 1.4% 3.10 [0.73, 5.47]
Tatarchenko 2008 58.9 2.8 29 51.2 4.1 30 1.5% 7.70 [5.91, 9.49]
Tsutsui 2.5mg 2016 33.8 8.7 41 31 8.8 20 1.1% 2.80 [-1.89, 7.49]
Tsutsui 2019 38.9 12.8 127 33.3 13 127 1.3% 5.60 [2.43, 8.77]
Tsutsui 5mg 2016 35 10.4 40 31 8.8 21 1.1% 4.00 [-0.96, 8.96]
Vatinian 2015 51.2 2.1 26 45.3 1.9 26 1.5% 5.90 [4.81, 6.99]
Wang 2019 37.79 5.23 35 37.32 4.86 33 1.4% 0.47 [-1.93, 2.87]
Wang FC 2017 42.51 6.03 53 36.78 7.4 43 1.4% 5.73 [2.99, 8.47]
Wang GK 2020 55.3 10.4 36 52.2 11.1 36 1.1% 3.10 [-1.87, 8.07]
Wang LJ 2020 58.63 4.25 35 52.34 4.03 35 1.4% 6.29 [4.35, 8.23]
Wang RM 2017 49.06 7.05 39 43.03 6.89 39 1.3% 6.03 [2.94, 9.12]
Wang YH 2018 55.35 7.1 34 52.86 6.2 34 1.3% 2.49 [-0.68, 5.66]
Wei 2019 48.14 2.62 32 41.69 1.06 32 1.5% 6.45 [5.47, 7.43]
Xia 2016 48.25 6.65 39 41.57 5.96 39 1.4% 6.68 [3.88, 9.48]
Xu 2019 46.2 3.8 38 43.9 3.4 39 1.5% 2.30 [0.69, 3.91]
Xu 2020 49.83 3.25 61 45.01 2.76 61 1.5% 4.82 [3.75, 5.89]
Yang WT 2019 48.3 5.4 40 43.2 6.5 40 1.4% 5.10 [2.48, 7.72]
Yang Z 2019 46.87 6.38 67 43.61 6.82 68 1.4% 3.26 [1.03, 5.49]
Yao 2016 38.22 4.86 36 34.23 3.52 36 1.4% 3.99 [2.03, 5.95]
Yi 2017 37.72 7.6 43 31.84 6.08 42 1.3% 5.88 [2.96, 8.80]
Yu 2019 29.3 3 33 27.7 3.4 33 1.5% 1.60 [0.05, 3.15]
Yue 2016 39.78 3.44 40 37.7 3.28 40 1.5% 2.08 [0.61, 3.55]
Zeng FC 2019 59.36 6.25 33 53.17 5.52 32 1.3% 6.19 [3.33, 9.05]
Zeng XM 2019 57.6 4.2 45 45.2 4.7 45 1.5% 12.40 [10.56, 14.24]
Zhang 2019 67 8 30 62 5.4 30 1.3% 5.00 [1.55, 8.45]
Zhang 2020 50.21 6.47 43 45.19 6.92 42 1.3% 5.02 [2.17, 7.87]
Zhang 2021 48.32 4.23 47 43.76 4.12 47 1.5% 4.56 [2.87, 6.25]
Zhang J 2019 35.16 2.68 45 35.34 2.86 41 1.5% -0.18 [-1.35, 0.99]
Zhang XJ 2019 51.77 3.84 55 38.02 2.63 55 1.5% 13.75 [12.52, 14.98]
Zhang Y 2020 57 12 27 51 12 27 0.9% 6.00 [-0.40, 12.40]
Zhou 2019 47.89 7.89 30 34.34 5.67 30 1.3% 13.55 [10.07, 17.03]
Zhou 2020 46.8 6.3 43 36.7 7.6 43 1.3% 10.10 [7.15, 13.05]
Total (95% CI) 3323 3230 100.0% 5.43 [4.52, 6.34]
Heterogeneity: Tau² = 13.85; Chi² = 1459.20, df = 73 (P < 0.00001); I² = 95%
Test for overall effect: Z = 11.71 (P < 0.00001)
-10 -5 0 5 10
Favours control Favours ivabradine

Figure 69 - Forest plot of the meta-analysis of left ventricular ejection fraction using random-effects meta-analysis. The meta-analysis showed that ivabradine seemed to increase the left ventricular ejection fraction by 5.43%.

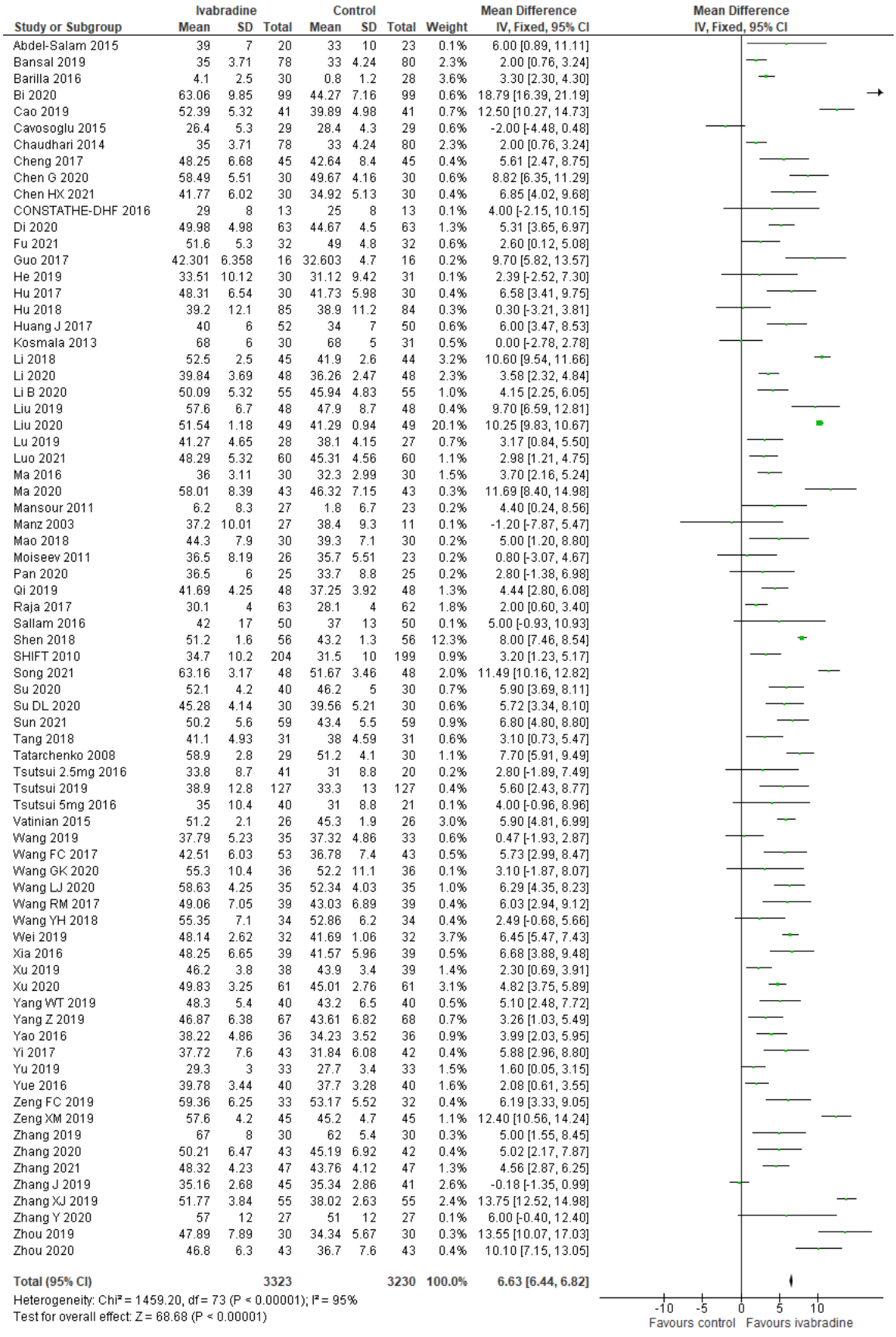

Ivabradine
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Abdel-Salam 2015 39 7 20 33 10 23 0.1% 6.00 [0.89, 11.11]
Bansal 2019 35 3.71 78 33 4.24 80 2.3% 2.00 [0.76, 3.24]
Barilla 2016 4.1 2.5 30 0.8 1.2 28 3.6% 3.30 [2.30, 4.30]
Bi 2020 63.06 9.85 99 44.27 7.16 99 0.6% 18.79 [16.39, 21.19]
Cao 2019 52.39 5.32 41 39.89 4.98 41 0.7% 12.50 [10.27, 14.73]
Cavosoglu 2015 26.4 5.3 29 28.4 4.3 29 0.6% -2.00 [-4.48, 0.48]
Chaudhari 2014 35 3.71 78 33 4.24 80 2.3% 2.00 [0.76, 3.24]
Cheng 2017 48.25 6.68 45 42.64 8.4 45 0.4% 5.61 [2.47, 8.75]
Chen G 2020 58.49 5.51 30 49.67 4.16 30 0.6% 8.82 [6.35, 11.29]
Chen HX 2021 41.77 6.02 30 34.92 5.13 30 0.4% 6.85 [4.02, 9.68]
CONSTATHE-DHF 2016 29 8 13 25 8 13 0.1% 4.00 [-2.15, 10.15]
Di 2020 49.98 4.98 63 44.67 4.5 63 1.3% 5.31 [3.65, 6.97]
Fu 2021 51.6 5.3 32 49 4.8 32 0.6% 2.60 [0.12, 5.08]
Guo 2017 42.301 6.358 16 32.603 4.7 16 0.2% 9.70 [5.82, 13.57]
He 2019 33.51 10.12 30 31.12 9.42 31 0.1% 2.39 [-2.52, 7.30]
Hu 2017 48.31 6.54 30 41.73 5.98 30 0.4% 6.58 [3.41, 9.75]
Hu 2018 39.2 12.1 85 38.9 11.2 84 0.3% 0.30 [-3.21, 3.81]
Huang J 2017 40 6 52 34 7 50 0.6% 6.00 [3.47, 8.53]
Kosmala 2013 68 6 30 68 5 31 0.5% 0.00 [-2.78, 2.78]
Li 2018 52.5 2.5 45 41.9 2.6 44 3.2% 10.60 [9.54, 11.66]
Li 2020 39.84 3.69 48 36.26 2.47 48 2.3% 3.58 [2.32, 4.84]
Li B 2020 50.09 5.32 55 45.94 4.83 55 1.0% 4.15 [2.25, 6.05]
Liu 2019 57.6 6.7 48 47.9 8.7 48 0.4% 9.70 [6.59, 12.81]
Liu 2020 51.54 1.18 49 41.29 0.94 49 20.1% 10.25 [9.83, 10.67]
Lu 2019 41.27 4.65 28 38.1 4.15 27 0.7% 3.17 [0.84, 5.50]
Luo 2021 48.29 5.32 60 45.31 4.56 60 1.1% 2.98 [1.21, 4.75]
Ma 2016 36 3.11 30 32.3 2.99 30 1.5% 3.70 [2.16, 5.24]
Ma 2020 58.01 8.39 43 46.32 7.15 43 0.3% 11.69 [8.40, 14.98]
Mansour 2011 6.2 8.3 27 1.8 6.7 23 0.2% 4.40 [0.24, 8.56]
Manz 2003 37.2 10.01 27 38.4 9.3 11 0.1% -1.20 [-7.87, 5.47]
Mao 2018 44.3 7.9 30 39.3 7.1 30 0.2% 5.00 [1.20, 8.80]
Moiseev 2011 36.5 8.19 26 35.7 5.51 23 0.2% 0.80 [-3.07, 4.67]
Pan 2020 36.5 6 25 33.7 8.8 25 0.2% 2.80 [-1.38, 6.98]
Qi 2019 41.69 4.25 48 37.25 3.92 48 1.3% 4.44 [2.80, 6.08]
Raja 2017 30.1 4 63 28.1 4 62 1.8% 2.00 [0.60, 3.40]
Sallam 2016 42 17 50 37 13 50 0.1% 5.00 [-0.93, 10.93]
Shen 2018 51.2 1.6 56 43.2 1.3 56 12.3% 8.00 [7.46, 8.54]
SHIFT 2010 34.7 10.2 204 31.5 10 199 0.9% 3.20 [1.23, 5.17]
Song 2021 63.16 3.17 48 51.67 3.46 48 2.0% 11.49 [10.16, 12.82]
Su 2020 52.1 4.2 40 46.2 5 30 0.7% 5.90 [3.69, 8.11]
Su DL 2020 45.28 4.14 30 39.56 5.21 30 0.6% 5.72 [3.34, 8.10]
Sun 2021 50.2 5.6 59 43.4 5.5 59 0.9% 6.80 [4.80, 8.80]
Tang 2018 41.1 4.93 31 38 4.59 31 0.6% 3.10 [0.73, 5.47]
Tatarchenko 2008 58.9 2.8 29 51.2 4.1 30 1.1% 7.70 [5.91, 9.49]
Tsutsui 2.5mg 2016 33.8 8.7 41 31 8.8 20 0.2% 2.80 [-1.89, 7.49]
Tsutsui 2019 38.9 12.8 127 33.3 13 127 0.4% 5.60 [2.43, 8.77]
Tsutsui 5mg 2016 35 10.4 40 31 8.8 21 0.1% 4.00 [-0.96, 8.96]
Vatinian 2015 51.2 2.1 26 45.3 1.9 26 3.0% 5.90 [4.81, 6.99]
Wang 2019 37.79 5.23 35 37.32 4.86 33 0.6% 0.47 [-1.93, 2.87]
Wang FC 2017 42.51 6.03 53 36.78 7.4 43 0.5% 5.73 [2.99, 8.47]
Wang GK 2020 55.3 10.4 36 52.2 11.1 36 0.1% 3.10 [-1.87, 8.07]
Wang LJ 2020 58.63 4.25 35 52.34 4.03 35 1.0% 6.29 [4.35, 8.23]
Wang RM 2017 49.06 7.05 39 43.03 6.89 39 0.4% 6.03 [2.94, 9.12]
Wang YH 2018 55.35 7.1 34 52.86 6.2 34 0.4% 2.49 [-0.68, 5.66]
Wei 2019 48.14 2.62 32 41.69 1.06 32 3.7% 6.45 [5.47, 7.43]
Xia 2016 48.25 6.65 39 41.57 5.96 39 0.5% 6.68 [3.88, 9.48]
Xu 2019 46.2 3.8 38 43.9 3.4 39 1.4% 2.30 [0.69, 3.91]
Xu 2020 49.83 3.25 61 45.01 2.76 61 3.1% 4.82 [3.75, 5.89]
Yang WT 2019 48.3 5.4 40 43.2 6.5 40 0.5% 5.10 [2.48, 7.72]
Yang Z 2019 46.87 6.38 67 43.61 6.82 68 0.7% 3.26 [1.03, 5.49]
Yao 2016 38.22 4.86 36 34.23 3.52 36 0.9% 3.99 [2.03, 5.95]
Yi 2017 37.72 7.6 43 31.84 6.08 42 0.4% 5.88 [2.96, 8.80]
Yu 2019 29.3 3 33 27.7 3.4 33 1.5% 1.60 [0.05, 3.15]
Yue 2016 39.78 3.44 40 37.7 3.28 40 1.6% 2.08 [0.61, 3.55]
Zeng FC 2019 59.36 6.25 33 53.17 5.52 32 0.4% 6.19 [3.33, 9.05]
Zeng XM 2019 57.6 4.2 45 45.2 4.7 45 1.1% 12.40 [10.56, 14.24]
Zhang 2019 67 8 30 62 5.4 30 0.3% 5.00 [1.55, 8.45]
Zhang 2020 50.21 6.47 43 45.19 6.92 42 0.4% 5.02 [2.17, 7.87]
Zhang 2021 48.32 4.23 47 43.76 4.12 47 1.3% 4.56 [2.87, 6.25]
Zhang J 2019 35.16 2.68 45 35.34 2.86 41 2.6% -0.18 [-1.35, 0.99]
Zhang XJ 2019 51.77 3.84 55 38.02 2.63 55 2.4% 13.75 [12.52, 14.98]
Zhang Y 2020 57 12 27 51 12 27 0.1% 6.00 [-0.40, 12.40]
Zhou 2019 47.89 7.89 30 34.34 5.67 30 0.3% 13.55 [10.07, 17.03]
Zhou 2020 46.8 6.3 43 36.7 7.6 43 0.4% 10.10 [7.15, 13.05]
Total (95% CI) 3323 3230 100.0% 6.63 [6.44, 6.82]
Heterogeneity: Chi² = 1459.20, df = 73 (P < 0.00001); I² = 95%
Test for overall effect: Z = 68.68 (P < 0.00001)
-10 -5 0 5 10
Favours control Favours ivabradine

Figure 70 - 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 6.63%.

Hospitalisation during follow-up

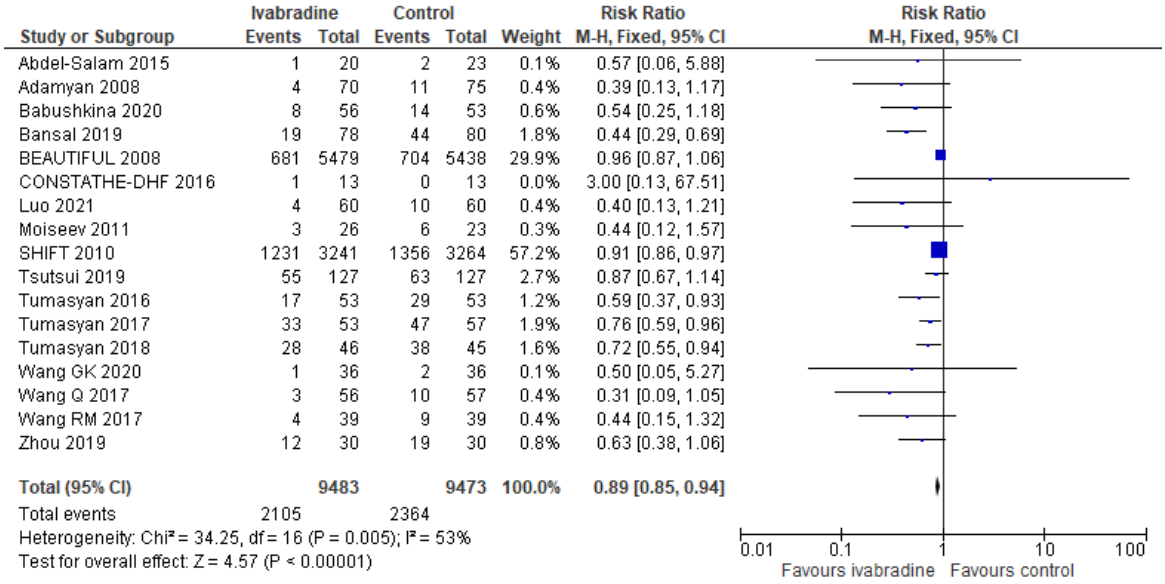


Figure 71 – Forest plot of the meta-analysis of hospitalisation during follow-up using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect ivabradine versus control (placebo or no intervention) of a risk ratio of 0.89.

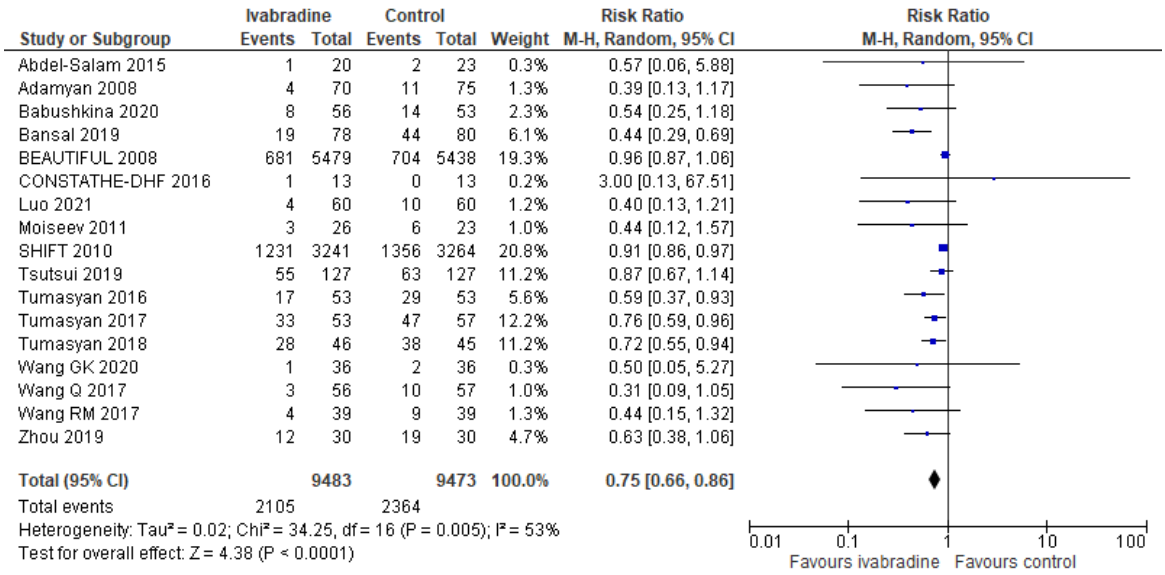


Figure 72 - Forest plot of the meta-analysis of hospitalisation during follow-up using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention) of a risk ratio of 0.75.

6-minutes walking distance

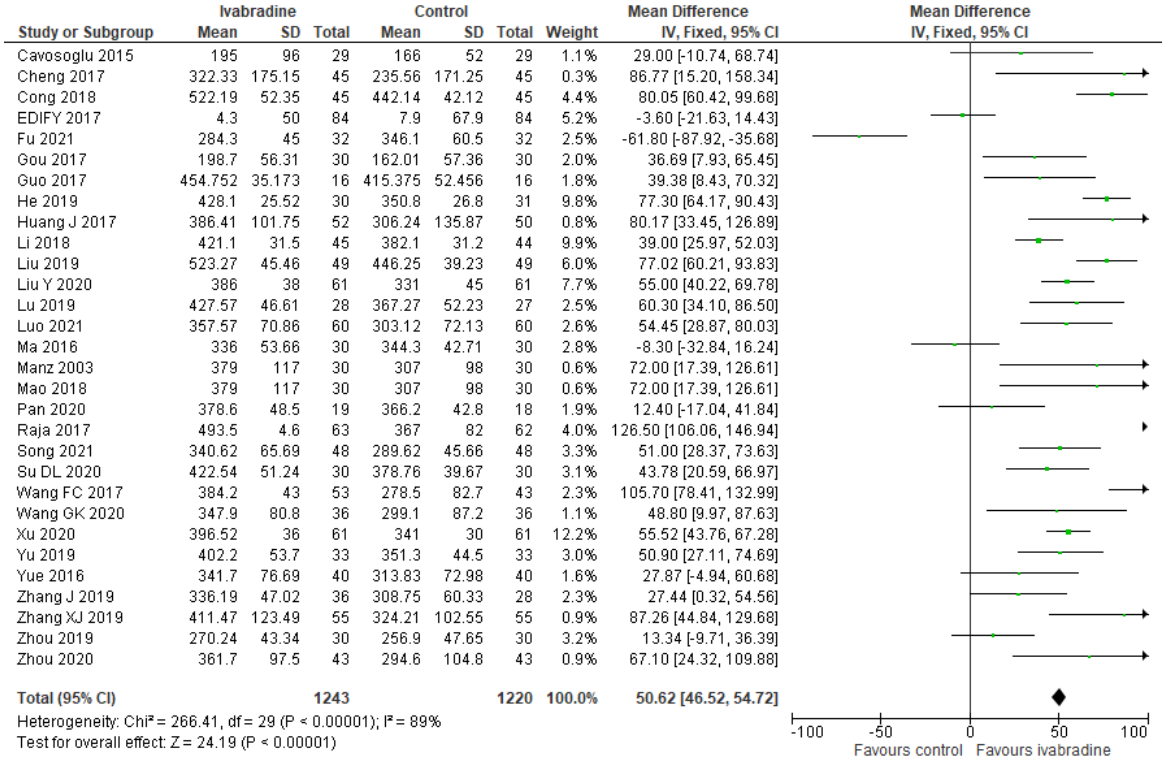


Figure 73 – Forest plot of the meta-analysis of 6-minutes walking distance using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention) of 50.62 meters per 6 minutes.

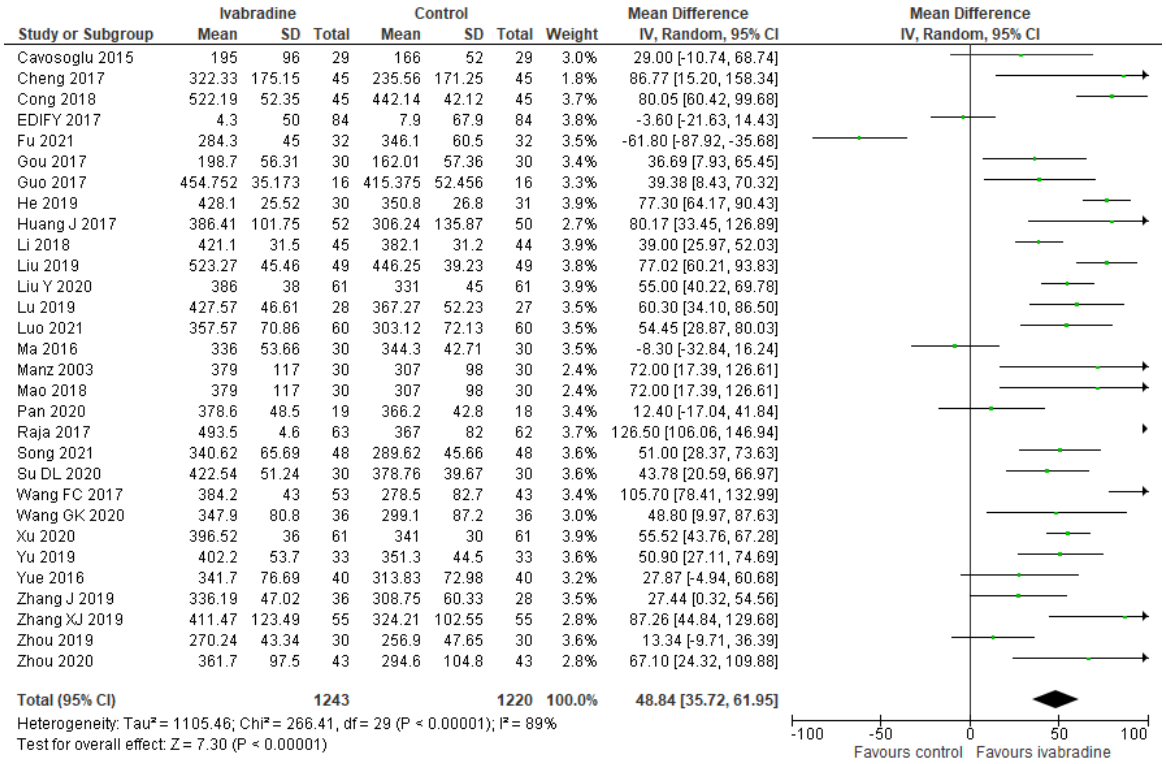


Figure 74 – Forest plot of the meta-analysis of 6-minutes walking distance using random-effects meta-analysis. The meta-analysis shows evidence of a beneficial effect of ivabradine versus control (placebo or no intervention) of 48.84 meters per 6 minutes.

First author	Year	Publication type	No. randomised	Clinical condition(s)	Age	%-female	Interventions	
							Experimental	Control
Abdel-Hady	2011	Abstract	100	Heart failure, EF<35%	NR	NR	Ivabradine	Placebo
Abdel-Salam	2015	Paper	43	Dilated cardiomyopathy, EF<40%	50.8	46.5	Ivabradine	Placebo
Adamyan	2010	Abstract	118	Heart failure, EF>50%	58.0	24.8	Ivabradine	No intervention
Adamyan	2008	Abstract	145	Heart failure, EF<35%	58.0	30.0	Ivabradine	No intervention
Adamyan	2015	Abstract	104	Heart failure, EF>50%	63.2	NR	Ivabradine	No intervention
Al Saadi	2013	Abstract	NR	Stable ischemic heart failure	NR	NR	Ivabradine	No intervention
Aroutunov	2008	Abstract	24	Decompensated heart failure	NR	NR	Ivabradine	No intervention
Babushkina	2020	Article	109	Heart failure, EF>50%	57.7	37	Ivabradine	No intervention
Bansal	2019	Abstract	309	Stable ischemic heart failure	NR	NR	Ivabradine	No intervention
Barilla	2016	Paper	58	Acute myocardial infarction, cardiogenic shock	55.4	32.8	Ivabradine	No intervention
Bi	2020	Paper	198	Heart failure	56.8	46.0	Ivabradine	No intervention
Cao	2019	Paper	82	Heart failure, EF<35%	69.3	50.0	Ivabradine	No intervention
Cavosoglu	2015	Paper	58	Decompensated heart failure, EF<35%	65.6	25.7	Ivabradine	No intervention
Chaudhari	2014	Abstract	158	Ischemic heart failure	NR	NR	Ivabradine	No intervention
Chen	2020	Paper	60	Chronic heart failure	62.5	35	Ivabradine	No intervention
Chen	2021	Paper	100	Chronic heart failure	57.8	42	Ivabradine	No intervention
Chen HX	2021	Paper	60	Severe chronic heart failure	70.5	45	Ivabradine	No intervention
Cheng	2017	Paper	90	Heart failure, EF<45%	71.0	44.4	Ivabradine	No intervention
Chumburidze	2013	Abstract	30	Dilated cardiomyopathy EF<35%	54.0	NR	Ivabradine	Placebo
Cong	2018	Paper	90	Heart failure	64.6	60.0	Ivabradine	No intervention
Deng	2017	Paper	82	Heart failure	61.8	40.2	Ivabradine	No intervention
Di	2020	Paper	126	Heart failure, EF<40%, HR>70	66.4	43.4	Ivabradine	No intervention
Fox (BEAUTIFUL)	2008	Paper	10917	Stable coronary artery disease, heart failure, EF<40%	65.2	17.1	Ivabradine	Placebo
Fu	2021	Paper	64	Chronic heart failiure, EF 40-50%, HR>70	NR	NR	Ivabradine	No intervention
Gou	2017	Paper	60	Decompensated heart failure, EF<40%	63.7	48.3	Ivabradine	No intervention
Guo	2017	Paper	32	Heart failure, EF<40%	NR	0.0	Ivabradine	No intervention
He	2019	Paper	68	Coronary artery disease, heart failure, EF 40-49%	64.8	47.1	Ivabradine	No intervention
Hu	2017	Paper	60	Heart failure, EF<35%	68.0	45.0	Ivabradine	No intervention
Hu	2018	Paper	169	Acute myocardial infarction, heart failure	63.0	3.6	Ivabradine	No intervention
Huang J	2017	Paper	102	Heart failure	71.5	41.2	Ivabradine	No intervention
Komajda (EDIFY)	2017	Paper	179	Heart failure, EF>45%	72.5	64.8	Ivabradine	Placebo

Kosmala	2013	Paper	61	Heart failure, EF >50%	67.3	82.0	Ivabradine	Placebo
Li	2018	Paper	89	Heart failure	57.5	47.2	Ivabradine	No intervention
Li B	2020	Paper	110	Chronic heart failure, HR>100	64.2	35.4	Ivabradine	No intervention
Li Q	2020	Paper	96	Chronic heart failure, EF<50%, HR>75	65.3	33.6	Ivabradine	No intervention
Liu	2019	Paper	96	Heart failure	63.8	51.0	Ivabradine	No intervention
Liu	2020	Paper	98	Heart failure	67.4	60.2	Ivabradine	Placebo
Liu Y	2020	Paper	122	Heart failure, EF>50%, HR>70	65	34.4	Ivabradine	No intervention
Lofrano-Alves	2016	Paper	26	Heart failure, EF<40%	42.0	46.2	Ivabradine	Placebo
Lu	2019	Thesis	60	Dilated cardiomyopathy, EF<40%	47.2	43.3	Ivabradine	No intervention
Lu	2020	Paper	70	Chronic heart failure, EF 30-50%	69.9	34.3	Ivabradine	No intervention
Luo	2021	Paper	120	Heart failure, HR>70	84.2	42.5	Ivabradine	No intervention
Ma	2016	Thesis	60	Heart failure, EF<40%	NR	NR	Ivabradine	Placebo
Ma	2020	Paper	86	Heart failure	58.1	41.9	Ivabradine	Placebo
Mansour	2011	Paper	53	Dilated cardiomyopathy, EF<40%	49.0	40.0	Ivabradine	No intervention
Manz	2003	Paper	44	Cardiomyopathy, EF 20-50%	59.9	NR	Ivabradine	Placebo
Mao	2018	Paper	60	Heart failure	53.1	31.7	Ivabradine	No intervention
Masi de Luca	2018	Abstract	111	Heart failure, EF>50%	61.0	30.0	Ivabradine	Placebo
Moiseev	2011	Abstract	49	Heart failure, EF<40%	63.0	18.4	Ivabradine	No intervention
Nguyen	2018	Paper	19	Planned CABG, EF 20-40%	57.5	15.8	Ivabradine	Placebo
Ordu	2015	Paper	98	Heart failure, EF<35%	65.8	66.3	Ivabradine	No intervention
Pal	2015	Paper	22	Heart failure, EF>50%	74.6	65.0	Ivabradine	Placebo
Pan	2020	Paper	50	Decompensated heart failure, EF<40%	60.1	44.0	Ivabradine	No intervention
Potapenko	2011	Paper	49	Systolic, chronic heart failure	63.1	18.4	Ivabradine	No intervention
Qi	2019	Paper	96	Heart failure	59.7	45.8	Ivabradine	No intervention
Raja	2017	Paper	125	Dilated cardiomyopathy, EF<40%	47.2	43.1	Ivabradine	No intervention
Sallam	2016	Paper	100	Coronary artery disease, heart failure, EF<40%	63.5	30.0	Ivabradine	No intervention
Sarullo	2010	Paper	60	Stable, ischemic heart failure, EF<40%	52.7	25.0	Ivabradine	Placebo
Shen	2018	Paper	112	Heart failure	70.0	41.1	Ivabradine	No intervention
Sisakian	2015	Paper	54	Heart failure, EF<40%	59.9	18.5	Ivabradine	No intervention
Song	2021	Paper	96	Heart failure	69.4	43.8	Ivabradine	No intervention
Su	2020	Paper	70	Heart failure	69.0	44.3	Ivabradine	No intervention
Su D	2020	Paper	60	Chronic heart failure, EF<50%	61.8	48.3	Ivabradine	No intervention
Sun	2020	Paper	100	Heart failure	62.0	42.0	Ivabradine	No intervention

Sun	2021	Paper	118	Chronic heart failure	67.6	43.2	Ivabradine	No intervention
Swedberg (SHIFT)	2010	Paper	6558	Heart failure, EF<35%	60.4	23.4	Ivabradine	Placebo
Tang	2018	Paper	62	Heart failure, EF<40%	63.2	29.0	Ivabradine	No intervention
Tarlovskaya	2011	Abstract	18	Heart failure, EF<35%	53.5	NR	Ivabradine	Placebo
Tatarchenko	2008	Paper	59	Coronary artery disease, heart failure, EF>45%	57.3	NR	Ivabradine	No intervention
Tsutsui	2019	Paper	254	Heart failure, EF<35%	60.7	18.0	Ivabradine	Placebo
Tsutsui	2016	Paper	125	Heart failure, EF<35%	59.0	14.3	Ivabradine	Placebo
Tumasyan	2009	Abstract	126	Severe heart failure	NR	NR	Ivabradine	No intervention
Tumasyan	2012	Abstract	76	Heart failure	57.4	NR	Ivabradine	No intervention
Tumasyan	2016	Abstract	210	Severe heart failure	57.4	NR	Ivabradine	No intervention
Tumasyan	2017	Abstract	110	Heart failure	63.2	NR	Ivabradine	No intervention
Tumasyan	2018	Abstract	91	Heart failure, mid range EF	50.1	NR	Ivabradine	No intervention
Vatinian	2015	Abstract	52	Coronary artery disease, heart failure, EF<35%	NR	NR	Ivabradine	No intervention
Wang	2019	Paper	68	Heart failure, EF <35%	55.8	0.5	Ivabradine	No intervention
Wang FC	2017	Paper	96	Heart failure	70.6	43.8	Ivabradine	No intervention
Wang JJ	2017	Paper	40	Heart failure	52.9	55.0	Ivabradine	No intervention
Wang Q	2017	Paper	120	Heart failure	62.3	35.0	Ivabradine	No intervention
Wang RM	2017	Paper	78	Heart failure	59.9	28.3	Ivabradine	No intervention
Wang YH	2018	Paper	68	Heart failure	66.0	42.3	Ivabradine	No intervention
Wang GK	2020	Paper	72	Chronic heart failure	68.5	48.6	Ivabradine	No intervention
Wang LJ	2020	Paper	70	Chronic heart failure	57.0	22.9	Ivabradine	No intervention
Wei	2019	Paper	64	Heart failure, EF<45%	60.6	39.7	Ivabradine	No intervention
Xia	2016	Paper	78	Heart failure	60.7	44.9	Ivabradine	No intervention
Xing	2018	Paper	20	Heart failure	52.7	55.0	Ivabradine	No intervention
Xu	2019	Paper	77	Heart failure, EF<50%	68.1	0.5	Ivabradine	No intervention
Xu	2020	Paper	122	Heart failure, EF<45%	71.0	56.6	Ivabradine	No intervention
Xue	2020	Paper	90	Chronic heart failure	59.2	45.6	Ivabradine	No intervention
Yang WT	2019	Paper	80	Heart failure, EF<45%	62.2	0.4	Ivabradine	No intervention
Yang Z	2019	Paper	135	Heart failure	65.7	0.3	Ivabradine	No intervention
Yao	2016	Paper	72	Heart failure, EF<40%	NR	NR	Ivabradine	No intervention
Yi	2017	Paper	90	Heart failure, EF<45%	66.6	32.2	Ivabradine	Placebo
Yu	2019	Paper	66	Dilated cardiomyopathy, EF<40%	46.8	0.4	Ivabradine	No intervention
Yu	2018	Paper	86	Heart failure	62.5	43.0	Ivabradine	No intervention

Yue	2016	Thesis	80	Heart failure, EF<40%	68.3	50.0	Ivabradine	No intervention
Zeng FC	2019	Paper	65	Heart failure	72.0	0.6	Ivabradine	No intervention
Zeng XM	2019	Paper	90	Heart failure	70.6	0.5	Ivabradine	No intervention
Zhang	2018	Paper	60	Coronary artery disease, heart failure	64.2	48.3	Ivabradine	No intervention
Zhang J	2019	Paper	86	Heart failure	66.2	0.5	Ivabradine	No intervention
Zhang XJ	2019	Paper	110	Heart failure	61.6	0.4	Ivabradine	No intervention
Zhang	2020	Paper	85	Coronary heart disease, heart failure	64.4	0.4	Ivabradine	No intervention
Zhang Y	2020	Paper	54	Chronic heart failure	NR	51.9	Ivabradine	No intervention
Zhang	2021	Paper	94	Chronic heart failure	70.9	44.7	Ivabradine	No intervention
Zhao	2020	Paper	80	Chronic heart failure	68.3	46.3	Ivabradine	No intervention
Zhou	2019	Thesis	60	Heart failure	54.8	0.4	Ivabradine	No intervention
Zhou	2020	Paper	86	Heart failure, EF<35%, HR>100	65	47.7	Ivabradine	No intervention

Ivabradine added to usual care in patients with heart failure: systematic review with meta-analysis and Trial Sequential Analysis

Detailed risk of bias judgements.

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Abdel-Hady 2011		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	No information
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No protocol available
Other bias	Unclear	No mention of funding or conflicts of interest

Abdel-Salam 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "Randomization was performed by computer-generated allocation schedule drawn by an independent statistician."
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "Study drugs were identical in appearance. Both the patients and the investigators performing the baseline and follow-up assessment were blinded to the treatment allocation."
Blinding of outcome assessment	Unclear	Not mentioned
Incomplete outcome data	Low	No loss to follow-up.
Selective reporting	Unclear	No protocol and serious adverse events reported inadequately
Other bias	Low	Funded by university. No conflicts of interest

Adamyan 2008		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information

Other bias	Unclear	No mention of funding or conflicts of interest

Adamyan 2010		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Adamyan 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Al Saadi 2013		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to carvedilol. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information

Other bias	Unclear	No mention of funding. No conflicts of interest.

Aroutunov 2008		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Babushkina 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine and bisoprolol was compared to bisoprolol alone. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	No funding or conflicts of interest

Bansal 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of

		interest

Barilla 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "patients were assigned to the two treatment groups according to a computer-generated list of randomisation"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	High	Only the echocardiographer was blinded to treatment allocation.
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	No funding received. No conflicts of interest.

BEAUTIFUL 2008 (Fox 2008)		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "the random-allocation schedule was computer-generated by non-adaptive balanced randomisation"
Allocation concealment	Low	Quote: "central interactive voice-response system and an interactive web-response system."
Blinding of participants and personnel	Low	Quote: "double-blind" and "randomised to ivabradine or matched placebo"
Blinding of outcome assessment	Low	Quote: "prespecified events were adjudicated by a central endpoint validation committee blinded to the allocation of randomized study medication"
Incomplete outcome data	Low	Intention-to-treat data presented.
Selective reporting	Low High for serious adverse events and hospitalisations	Protocol registered retrospectively. However, serious adverse events and all-cause mortality was reported. All-cause hospitalisation was not reported and this raises serious concerns of selective outcome reporting related to hospitalisations and serious adverse events.
Other bias	Low	Funded by the company that produced ivabradine (Servier).

Bi 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Cao 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Yan 'An Science and Technology Research Project. No conflicts of interest.

Cavosoglu 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	Reported as placebo-controlled, but no mention of blinding
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	No mention of funding. No conflicts of interest.

Chaudhari 2014		
Bias domain	**Authors' judgement**	**Support for judgement**

Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Chen 2021		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Chen G 2020		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Chen HX 2020		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information

Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Cheng 2017		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Low	Quote: “random-number table”
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Chumburidze 2013		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: “double-blind”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Cong 2018		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Low	Quote: “random-number table”
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome	Unclear	No information

assessment		
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

CONSTATHE-DHF 2016 (Lofrano-Alves)		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "randomly assigned via computer-generated sequence into two groups"
Allocation concealment	Low	Quote: "the randomisation sequence was held by an independent pharmacy"
Blinding of participants and personnel	Low	Quote: "Commercially available IVA tablets were encapsulated in hard gelatin capsules. To create a PLA, capsules were filled with starch; they were indistinguishable from the IVA-containing capsules. Patient, caregivers, outcome assessors, and researched remained blinded to the intervention."
Blinding of outcome assessment	Low	Quote: "outcome assessors remained blinded to the intervention."
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Low	Protocol not registered prospectively. All-cause mortality and serious adverse events reported.
Other bias	High	An author (EAB) received consulting fees and travel/hotel/registration fee subsidies from Servier. EAB also performed contracted research from Servier, received honoraria from Servier, and was a member of the steering comittee of Servier.

Deng 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of

		interest

Di 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

EDIFY 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	Quote: "the randomisation was balanced 1:1 and stratified on centres". No information on the procedure of generating the random sequence
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "double-blind" and "study investigators and participants were masked to treatment for the duration of the trial
Blinding of outcome assessment	Low	Quote: "The trial was conducted under the supervision of an independent executive committee (Supplementary material online, Appendix S3), the members of which were blinded to study medication. After the study unblinding, this committee was given full access to the data and analyses and was responsible for the interpretation of the results and review of the manuscript"
Incomplete outcome data	High	95 were assigned to ivabradine and 84 to placebo. 87 were analysed for efficacy in the ivabradine group and 84 were analysed for efficacy in the placebo group. Hence, 8 patients are unaccounted for in the ivabradine group. 76 participants in the ivabradine group and 77 in the placebo group completed the 8 months follow-up.

Selective reporting	High	Protocol not registered prospectively. Quality of life on the Kansas City Cardiomyopathy Questionnaire not reported.
Other bias	High	The trial was funded by the company that developed ivabradine (Servier). Servier was responsible for data management, analysis, interpretation, and writing of the article.

Fu 2021		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Gou 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Guo 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "computer-generated random number"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"

Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

He 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	High	Unaccounted missing data
Selective reporting	Unclear	No information
Other bias	Low	Funded by Guangdong Traditional Chinese Medicine Supervision Bureau. No conflicts of interest.

Hu 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Hu 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information

Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Huang J 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Kosmala 2013		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "The procedure of randomization to receive either ivabradine 5 mg or placebo twice daily was performed by computerized sequence generation."
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "The hospital pharmacies were responsible for drug randomization and dispensing, and both the investigators and patients were blinded to the treatment option."
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	Retrospectively registered protocol.
Other bias	Low	Funded by Wroclaw Medical University and Brisbane University. No conflicts of interest.

Li 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"

personnel		
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Li 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Li B 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Liu 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information

Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Liu 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Liu YY 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "participants and researchers were unaware of allocation"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Lu 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of

		interest
Lu 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Luo 2021		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Ma 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "double-blind, placebo-controlled"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Ma 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Scientific Research Project of Anhui Provincial Health and Family Planning Commision

Mansour 2011		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "A computer-driven randomization program was used to allocate"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participant and personnel were probably unblinded.
Blinding of outcome assessment	High	No information. Only echocardiographer mentioned as being blinded to treatment allocation.
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	"This work was supported by the Faculty of Medicine at Ain Shams University, and Ain Shams University Hospitals." No conflicts of interest.

Manz 2003		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "single-blind, placebo-controlled study" and "the investigators were aware of the nature of each patient's treatment"
Blinding of outcome	Low	Quote: "The cross-reading investigator

assessment		was blinded to the identity of the patient, the treatment administered, the timing of the recording (Echo 0, 1 or 2) and the assessment of the other investigator. Only the results of the blinded cross-readings were used for statistical analysis of efficacy."
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	High	Funded by the company that developed ivabradine (Servier)

Mao 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Masi de Luca 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	No information
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Moiseev 2011		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to standard

personnel		care. Therefore, the participants and personnel were probably not blinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Nguyen 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote "computer-generated list"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote "patients and physicians were blinded to the study treatment"
Blinding of outcome assessment	High	Quote "an independent sponsor staff was aware of the allocation groups in order to analyze data and monitor adverse events"
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	An inadequate protocol was registered with the European Clinical Trials Database in 2010 (EUDRACT 2009–018175-14). Only the primary endpoint is mentioned in the protocol.
Other bias	High	Two authors were employed by Servier, the study was funded by Servier, and Servier provided statistical support.

Ordu 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No conflicts of interest. No mention of funding.

Pal 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence	Unclear	No information

generation		
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: “double-blind”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	Trial retrospectively registered on clinicaltrials.gov (NCT02354573)
Other bias	Low	No conflicts of interest. Funding by the Chest, Heart and Stroke Society

Pan 2020		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Low	Quote: “random-number table”
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Nantong Scientific Project

Potapenko 2011		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therfore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Qi 2019		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	Quote: “lottery”
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: “open-label”

personnel		
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Raja 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"Computerized random number generation protocol"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Only echocardiographer blinded
Blinding of outcome assessment	High	Only echocardiographer blinded
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by the Department of Cardiology, SGPGIMS, Lucknow, India. No conflicts of interest.

Sallam 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	No information
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	High	The Kansas City Cardiomyopathy Questionnaire was funded by the company that developed ivabradine (Servier)

Sarullo 2010		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "computerized sequence generation"
Allocation concealment	Low	Quote: "ivabradine and placebo were prepared in numbered anonymous

		bottles”
Blinding of participants and personnel	High	Quote: “single-blind”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Low	No funding and no conflicts of interest

Shen 2018		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Low	Quote: “random-number table”
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

SHIFT 2010 (Swedberg)		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "Patients were randomly to treatment groups by computer-generated assignment through a telephone interactive voice response system."
Allocation concealment	Low	Quote: “The allocation sequence was generated at the sponsor level through validated in-house application software; access was restricted to people responsible for study therapeutic units production until database lock."
Blinding of participants and personnel	Low	Quote: "Eligible patients were allocated to receive ivabradine or placebo" and "Patients and investigators were masked to treatment allocation. The study drugs (ivabradine or placebo) were identical in appearance."
Blinding of outcome assessment	Low	Quote: "An endpoint validation committee, masked to study treatment, reviewed and adjudicated all prespecified events according to definitions included in the charter."

Incomplete outcome data	Low	Quote: "Analysis was by intention to treat". "6658 patients were randomly assigned to treatment groups (3268 ivabradine, 3290 placebo)." 3241 was included in the ivabradine group and 3264 was included in the placebo group for the analysis of the primary and secondary outcomes.
Selective reporting	Low	The first patient was randomised in 2006. Prospectively registered with ISRCTN with limited information on methodology. The rationale and design article was published on November the 5th 2009. The trial was first registered on ClinicalTrials.gov in 2015.
Other bias	Low High for serious adverse events.	Most authors have received funding from the company that developed ivabradine (Servier). Servier was the sole sponsor of the study. Quote: "There IS an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed." There was an effect on serious adverse events, primarily due to a decrease in hospitalisations. However, the definition of hospitalisations was not pre-defined and the assessment of hospitalisations was not described.

Sisakian 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	Quote: "empirically allocated"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably not blinded to treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Song 2021		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Beijing Dongcheng District Excellent Talents Training Funding

Su 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Guangdong Health Bureau Projects

Su DL 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Fund Project of Zhongshan City Health Bureau of Guangdong Province

Sun 2020		
Bias domain	**Authors' judgement**	**Support for judgement**

Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Sun 2021		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Tang 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Tarlovskaya 2011		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	Reported as "placebo-controlled", but no information on blinding

Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Tatarchenko 2008		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open randomised controlled study"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Tsutsui 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "The patients and investigators were masked to the treatment allocation"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	Outcome data for most participants
Selective reporting	Unclear	No protocol available in English.
Other bias	High	Trial designed and conducted by Ono Pharmaceutical, a partner of the company that developed ivabradine (Servier). The data were collected and analysed and the first draft manuscript was written by the sponsor.

Tsutsui 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "A minimization method for dynamic allocation was used with adjustment for study site, baseline resting HR (≥85 and <85 beats/min), and β-

		blocker dose before study treatment (0, >0–<50, and ≥50% of the target dose of carvedilol 20 mg/day and bisoprolol 5 mg/day) to balance baseline covariates."
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: “Patients and investigators were masked to treatment allocation, and study medications (ivabradine or placebo) were the same size and color.”
Blinding of outcome assessment	Low	Quote: “"An endpoint adjudication committee, independent from the sponsor and ivestigators, evaluated all clinical events according to prespecified definitions in a blinded manner"
Incomplete outcome data	Low	Almost data for all participants
Selective reporting	Unclear	No protocol was prospectively registered
Other bias	High	Trial designed and conducted by Ono Pharmaceutical, a partner of the company that developed ivabradine (Servier). The data were collected and analysed and the first draft manuscript was written by the sponsor.

Tumasyan 2009		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Tumasyan 2012		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants

		and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Tumasyan 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Tumasyan 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest
Tumasyan 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to no

personnel		intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Vatinian 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang FC 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information

Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang JJ 2017		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Low	Quote: “random-number table”
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang Q 2017		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang RM 2017		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome	Unclear	No information

assessment		
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang YH 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang GK 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang LJ 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information

Other bias	Unclear	No mention of funding or conflicts of interest

Wei 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xia 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xing 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xu 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xu 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xue 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yang WT 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence	Low	Quote: "random-number table"

generation		
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yang Z 2019		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yao 2016		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yi 2017		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: “double-blind, placebo-

personnel		controlled"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yu 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yu 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yue 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information

Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zeng FC 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zeng XM 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zhang 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of

		interest

Zhang J 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Low	Quote: "sequential opaque envelopes"
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	High	Unaccounted missing data.
Selective reporting	Unclear	No information
Other bias	Low	Funded by Tianjin Natural Science Foundation

Zhang XJ 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Zhang 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zhang Y 2020

Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zhang 2021		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Hubei Province Science and Technology Plan Project

Zhao 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Zhou 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information

Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Zhou 2020		
Bias domain	**Authors’ judgement**	**Support for judgement**
Random sequence generation	Low	Quote: “random-number table”
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: “open-label”
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information