

# 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 26567 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). Metaanalysis 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

#### **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.

(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 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.<sup>7</sup> 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 19628 participants and did not find evidence of a difference between ivabradine and control in regard to cardiovascular mortality and serious adverse events. Another systematic review included 10 trials with 18036 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.<sup>2</sup> <sup>16</sup> 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). We planned to include non-randomised studies identified during the literature search for the reporting of serious and nonserious 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 longterm 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.<sup>2</sup> 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).<sup>17</sup> 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.<sup>18</sup>

#### Assessment of statistical and clinical significance

We used Review Manager V.5.4 for all meta-analyses. <sup>19</sup> 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). <sup>13</sup> <sup>20</sup> <sup>21</sup> 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. <sup>11</sup> <sup>13</sup> <sup>22</sup> 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<sup>2</sup> 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 metaanalyses 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 metaanalytic results. Trial sequential analysis would have prevented 13 of those, had it been implemented.<sup>23</sup> Trial sequential analysis reduces the risk of false positive results and inaccurate effect estimates in systematic reviews of interventions.<sup>22</sup> 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.<sup>17</sup> We used GRADE to assess the certainty of evidence.<sup>24</sup> <sup>25</sup> 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. <sup>20 21 26-132</sup> Eighteen trials compared ivabradine with placebo <sup>20 21 26 27 44 55 56 63 68 70 72 74 76 82 91 93 94 118</sup> 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, <sup>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, <sup>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, <sup>79</sup> 4 trials used levosimendan other than guideline-based therapy, <sup>37</sup> See online supplemental file 2, baseline characteristics.</sup></sup>

The BEAUTIFUL and the SHIFT trials contributed with more than 85% wt in all primary and secondary outcome metaanalyses. 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.<sup>20 21 133–136</sup> 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.<sup>20</sup> 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.<sup>137</sup> 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.<sup>2</sup> 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). <sup>20</sup> <sup>21</sup> 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<sup>2</sup>=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<sup>2</sup> 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 10043 in the control

Patient or population: patients with heart failure

Setting: any setting Intervention: Ivabradine

Comparison: placebo/no intervention/usual care

	Nº of	Certainty of		Anticipated absolute effects		
Outcomes	participants (studies) Follow-up	the evidence (GRADE)	Relative effect (95%CI)	Risk with placebo <i>f</i> no intervention <i>f</i> usual care	Risk difference with Ivabradine	
All-cause mortality	19257 (22 RCTs)	⊕⊕⊕ High <sup>a,b,c</sup>	<b>RR 0.94</b> (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 <sup>b,c,d</sup>	<b>RR 0.90</b> (0.87 to 0.94)	374 per 1.000	<b>37 fewer per 1.000</b> (49 fewer to 22 fewer)	
Quality of life (KCCQ)	1781 (2 RCTs)	⊕⊕⊖⊖ Low <sup>b,e,f</sup>	-		MD <b>2.92 higher</b> (1.34 higher to 4.5 higher)	
Quality of life (MLWHFQ)	221 (4 RCTs)	⊕○○○ Very low <sup>b,g,h</sup>	\-		MD <b>5.28 lower</b> (6.6 lower to 3.96 lower)	
Cardiovascular mortality	18738		103 per 1.000	2 fewer per 1.000 (10 fewer to 6 more)		
Myocardial infarction	18190 (9 RCTs)	⊕⊕⊖ Low <sup>a,c,i</sup>	<b>RR 1.00</b> (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 <sup>a,b,c</sup>	<b>RR 1.10</b> (1.07 to 1.12)	471 per 1.000	<b>47 more per 1.000</b> (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. IZ 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
- 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 🛭 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. 12 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

Summary of findings. RR, risk ratio. RCTs, randomised clinical trials. GRADE, Grading of Recommendations Assessment, Development and Figure 1 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. Metaanalysis showed evidence of a beneficial effect of ivabradine versus control on quality of life using the KCCO (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<sup>2</sup>=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.<sup>2</sup> 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<sup>2</sup>=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 I2=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).<sup>20 21</sup> 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. Metaanalysis 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 I2=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).<sup>20 21</sup> 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<sup>2</sup>=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.<sup>2</sup>

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 26567 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.<sup>2</sup> <sup>16</sup> 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).<sup>9</sup> Third, we used trial sequential analysis on both primary and secondary outcomes<sup>11</sup> and we adjusted our thresholds for statistical significance for the primary outcomes<sup>13</sup> 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.<sup>24</sup> <sup>25</sup>

#### **Evidence** synthesis

Fifth, we used our eight-step procedure to assess if the thresholds for statistical and clinical significance were crossed. 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. <sup>18</sup> 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. <sup>20 21 55 63 70 74 81 93</sup> Research has shown that drug trials funded by manufacturing companies tend to show more favourable efficacy results than trials funded by other sources. <sup>18</sup> Moreover, 18 trials were reported only as abstracts which made the interpretation of methodology and results problematic. <sup>26 28-32 34 39 44 73 91 95 96 99 100 138-140</sup> Therefore, there is a risk that our results are also biased and, therefore, overestimate the beneficial effects of ivabradine and underestimate the harmful effects. <sup>18 141-146</sup>

#### **Conclusion and relevance**

High certainty evidence shows that ivabradine does not seem to affect the risks of all-cause mortality and cardio-vascular 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. <sup>147</sup> 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. <sup>2</sup>

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

Contributors Guarantors: MM and JCJ.MM: conceived the systematic review, conducted literature search, data extraction, data analysis and data interpretation and wrote the article. EEN, NL and S-HY: conducted literature search and data extraction and amended the article. NJS: conducted data extraction and amended the article. CG: helped conceive the systematic review,

provided invaluable comments and amended the article. JCJ: conceived the systematic review, aided in data interpretation and amended the article.

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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<sup>\*</sup>Corresponding author

#### **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 心则梗死 OR 心则能不全)) 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))

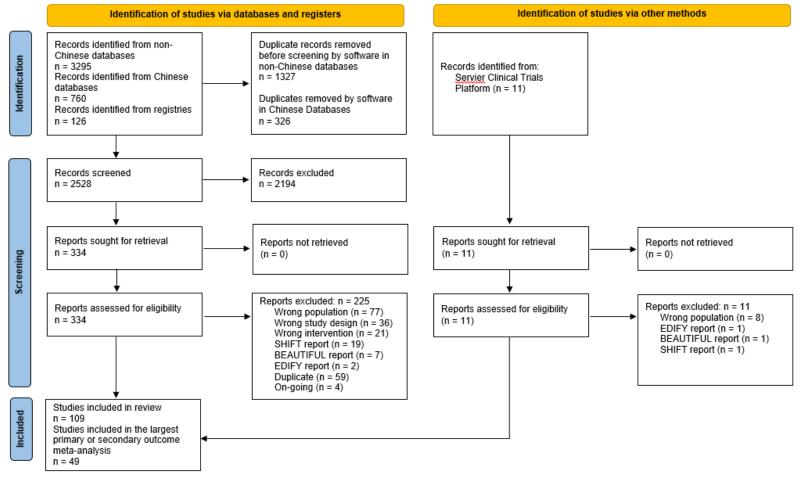
#### China National Knowledge Infrastructure (CNKI), n = 255

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, doj: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 1 – PRISMA flowchart.

#### Supplement 4 - Risk of bias

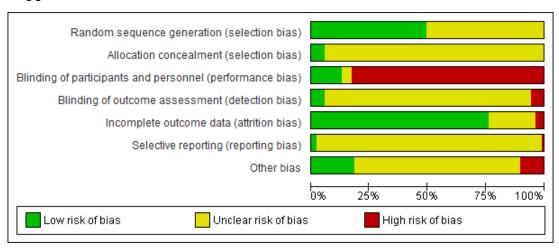


Figure 2 - Risk of bias graph.



	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
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	?	?	•	?	?	?	?

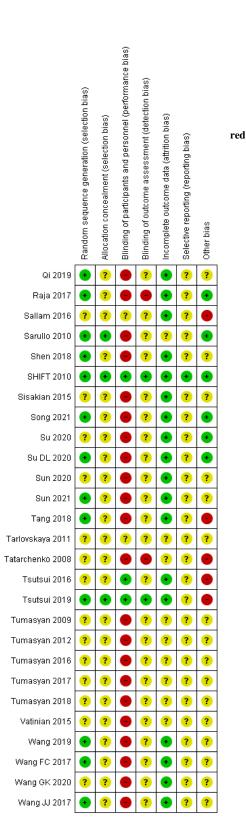




Figure 3 – Risk of bias summary. Green circles = low risk of bias; yellow circles = unclear risk of bias; circles = high risk of bias.

## **Supplement 5 - All-cause mortality** *Main analyses*

	lvabrad	line	Contr	rol	Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Abdel-Salam 2015	1	20	1	23	0.0%	1.15 [0.08, 17.22]	
Adamyan 2015	19	51	27	53	0.0%	0.73 [0.47, 1.14]	
Aroutunov 2008	2	12	2	12	0.0%	1.00 [0.17, 5.98]	
Barilla 2016	2	30	4	28	0.0%	0.47 [0.09, 2.35]	
BEAUTIFUL 2008	572	5479	547	5438	49.9%	1.04 [0.93, 1.16]	<del>-</del> -
Cao 2019	4	41	12	41	0.0%	0.33 [0.12, 0.95]	
CONSTATHE-DHF 2016	1	13	4	13	0.0%	0.25 [0.03, 1.95]	
EDIFY 2017	3	94	0	84	0.0%	6.26 [0.33, 119.51]	
He 2019	1	34	2	34	0.0%	0.50 [0.05, 5.26]	
Hu 2018	2	85	5	84	0.0%	0.40 [0.08, 1.98]	
Mansour 2011	3	27	3	23	0.0%	0.85 [0.19, 3.82]	
Moiseev 2011	2	26	4	23	0.0%	0.44 [0.09, 2.20]	
Nguyen 2018	1	14	0	5	0.0%	1.20 [0.06, 25.53]	
Raja 2017	1	63	1	62	0.0%	0.98 [0.06, 15.39]	
SHIFT 2010	503	3241	552	3264	50.1%	0.92 [0.82, 1.03]	<del></del>
Tarlovskaya 2011	3	8	0	10	0.0%	8.56 [0.51, 144.86]	
Tsutsui 2019	9	127	9	127	0.0%	1.00 [0.41, 2.44]	
Tumasyan 2016	41	104	59	106	0.0%	0.71 [0.53, 0.95]	
Tumasyan 2017	24	53	30	57	0.0%	0.86 [0.59, 1.26]	
Tumasyan 2018	19	46	28	45	0.0%	0.66 [0.44, 1.00]	
Wang GK 2020	1	36	1	36	0.0%	1.00 [0.07, 15.38]	
Zhang 2020	0	43	1	42	0.0%	0.33 [0.01, 7.78]	
Total (95% CI)		8720		8702	100.0%	0.98 [0.86, 1.10]	-
Total events	1075		1099				
Heterogeneity: Tau <sup>2</sup> = 0.00	Chi2 = 2.	37, df=	1 (P = 0	.12); l² :	= 58%	-	
Test for overall effect: $Z = 0$	•		,				0.7 0.85 1 1.2 1.5
							Favours ivabradine Favours control

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.

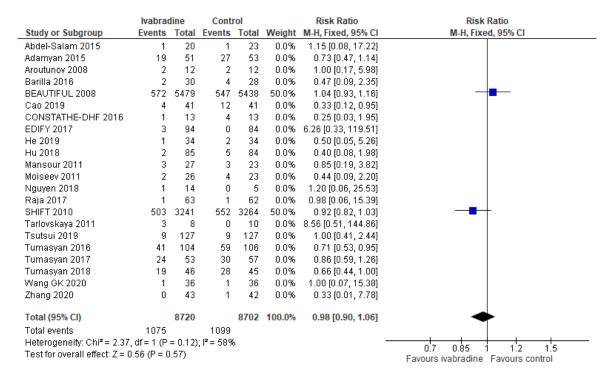


Figure 5 – Forest plot of the meta-analysis of all-cause mortality using fixed-effect meta-analysis including only trials at low risk of bias, except for for-profit bias. The meta-analysis showed no evidence of a difference between ivabradine versus placebo.

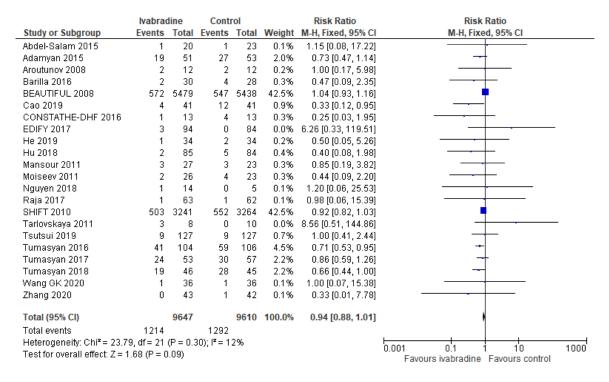


Figure 6 - Forest plot of the meta-analysis of all-cause mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

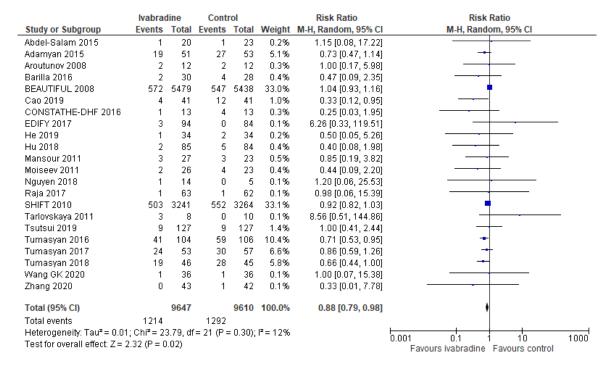
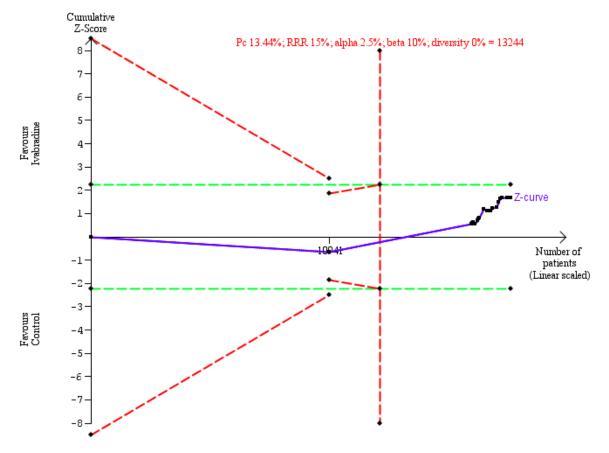
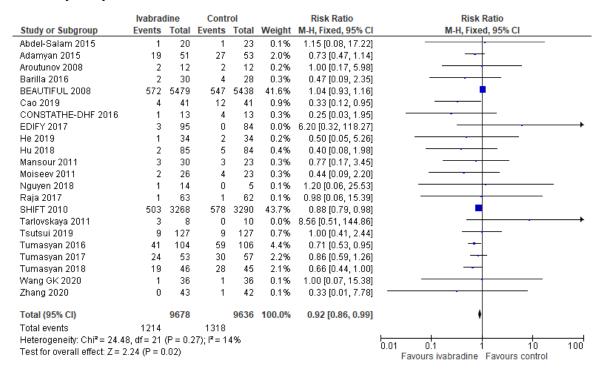


Figure 7 - Forest plot of the meta-analysis of all-cause mortality using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).



**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



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

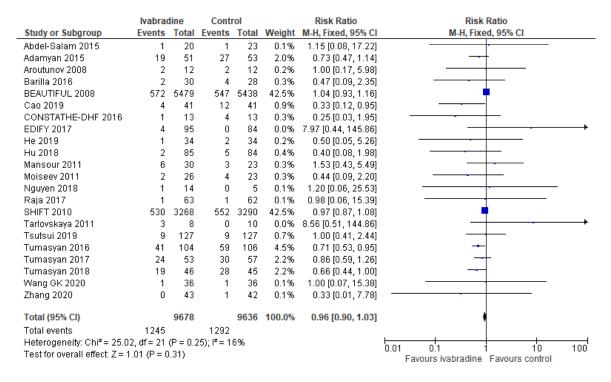
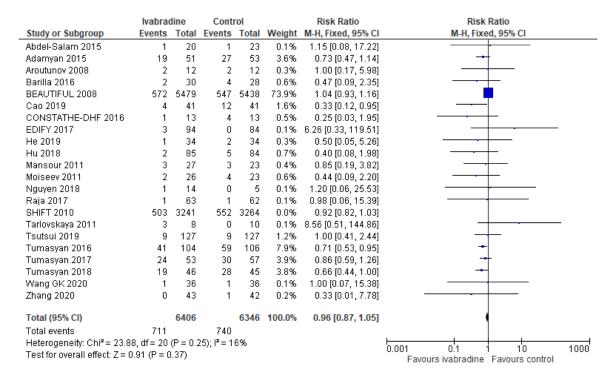


Figure 10 - Forest plot of the sensitivity analysis of all-cause mortality using worst- compared with best-case scenario.

lvabrad	dine	Contr	rol	Risk Ratio		Risk Ratio
Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1	20	1	23	0.1%	1.15 [0.08, 17.22]	<del></del>
19	51	27	53	3.6%	0.73 [0.47, 1.14]	<del> </del>
2	12	2	12	0.3%	1.00 [0.17, 5.98]	
2	30	4	28	0.6%	0.47 [0.09, 2.35]	<del></del>
572	5479	547	5438	0.0%	1.04 [0.93, 1.16]	
4	41	12	41	1.6%	0.33 [0.12, 0.95]	<del></del>
1	13	4	13	0.5%	0.25 [0.03, 1.95]	<del></del>
3	94	0	84	0.1%	6.26 [0.33, 119.51]	<del></del>
1	34	2	34	0.3%	0.50 [0.05, 5.26]	<del></del>
2	85	5	84	0.7%	0.40 [0.08, 1.98]	<del></del>
3	27	3	23	0.4%	0.85 [0.19, 3.82]	<del></del>
2	26	4	23	0.6%	0.44 [0.09, 2.20]	<del></del>
1	14	0	5	0.1%	1.20 [0.06, 25.53]	<del></del>
1	63	1	62	0.1%	0.98 [0.06, 15.39]	
503	3241	552	3264	73.9%	0.92 [0.82, 1.03]	
3	8	0	10	0.1%	8.56 [0.51, 144.86]	<del>                                     </del>
9	127	9	127	1.2%	1.00 [0.41, 2.44]	<del></del>
41	104	59	106	7.9%	0.71 [0.53, 0.95]	-
24	53	30	57	3.9%	0.86 [0.59, 1.26]	
19	46	28	45	3.8%	0.66 [0.44, 1.00]	<del></del>
1	36	1	36	0.1%	1.00 [0.07, 15.38]	
0	43	1	42	0.2%	0.33 [0.01, 7.78]	
	4168		4172	100.0%	0.87 [0.79, 0.95]	•
642		745				
7, df = 20	(P = 0.8)	66); I² = 0	%			0.001 0.1 10 1000
.95 (P = 0	0.003)					0.001 0.1 1 10 1000 Favours ivabradine Favours control
	Events  1 19 2 572 4 13 3 1 2 3 2 1 1 503 3 9 41 24 19 1 0 642 7, df= 20	1 20 19 51 2 12 2 30 572 5479 4 41 1 13 3 94 1 34 2 85 3 27 2 26 1 1 14 1 63 503 3241 3 8 9 127 41 104 24 53 19 46 1 36 0 43	Events         Total         Events           1         20         1           19         51         27           2         12         2           2         30         4           572         547         547           4         41         12           1         13         4           3         94         0           1         34         2           2         85         5           3         27         3           2         26         4           1         14         0           1         63         1           503         3241         552           3         8         0           9         127         9           41         104         59           24         53         30           19         46         28           1         36         1           0         43         1           41         28           1         36         1           0         43         1	Events         Total         Events         Total           1         20         1         23           19         51         27         53           2         12         2         12           2         30         4         28           572         5479         547         5438           4         41         12         41           1         13         4         13           3         94         0         84           1         34         2         34           2         85         5         84           3         27         3         23           2         26         4         23           1         14         0         5           1         63         1         62           503         3241         552         3264           3         8         0         10           9         127         9         127           41         104         59         106           24         53         30         57           19         46         2	Events         Total         Events         Total         Weight           1         20         1         23         0.1%           19         51         27         53         3.6%           2         12         2         12         0.3%           2         30         4         28         0.6%           572         5479         547         5438         0.0%           4         41         12         41         1.6%           1         13         4         13         0.5%           3         94         0         84         0.1%           1         34         2         34         0.3%           2         85         5         84         0.7%           3         27         3         23         0.4%           2         26         4         23         0.6%           1         14         0         5         0.1%           503         3241         552         3264         73.9%           41         104         59         106         7.9%           41         104         59         106	Events         Total         Events         Total         Weight         M-H, Fixed, 95% CI           1         20         1         23         0.1%         1.15 [0.08, 17.22]           19         51         27         53         3.6%         0.73 [0.47, 1.14]           2         12         2         12         0.3%         1.00 [0.17, 5.98]           2         30         4         28         0.6%         0.47 [0.09, 2.35]           572         5479         547         5438         0.0%         1.04 [0.93, 1.16]           4         41         12         41         1.6%         0.33 [0.12, 0.95]           1         13         4         13         0.5%         0.25 [0.03, 1.95]           3         94         0         84         0.1%         0.26 [0.33, 1.95]           1         34         2         34         0.3%         0.50 [0.05, 5.26]           2         85         5         84         0.7%         0.40 [0.08, 1.98]           3         27         3         23         0.4%         0.85 [0.19, 3.82]           2         26         4         23         0.6%         0.44 [0.09, 2.20]

 $Figure\ 11-Forest\ plot\ of\ the\ sensitivity\ analysis\ of\ all\text{-}cause\ mortality\ removing\ the\ BEAUTIFUL\ trial.$ 



 $Figure \ 12-Forest\ plot\ of\ the\ sensitivity\ analysis\ of\ all\text{-}cause\ mortality\ removing\ the\ SHIFT\ trial.$ 

#### Subgroup analyses

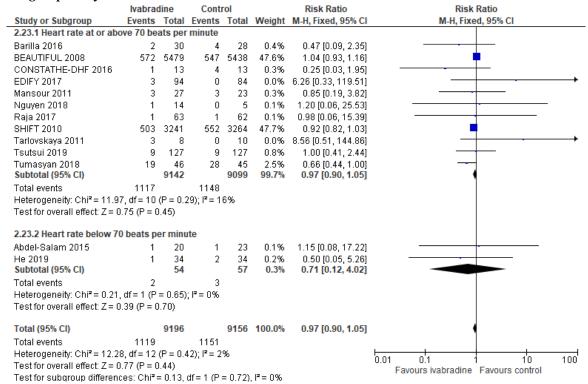


Figure 13 – Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared to trials randomising participants with heart rate below 70 beats per minute on all-cause mortality.

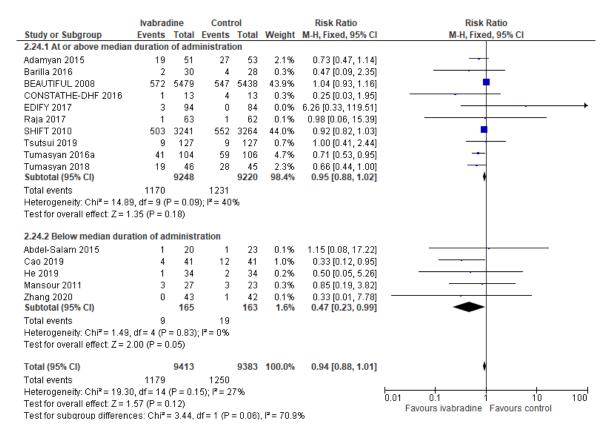


Figure 14 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (182.64 days) versus trials administering ivabradine below median duration on all-cause mortality.

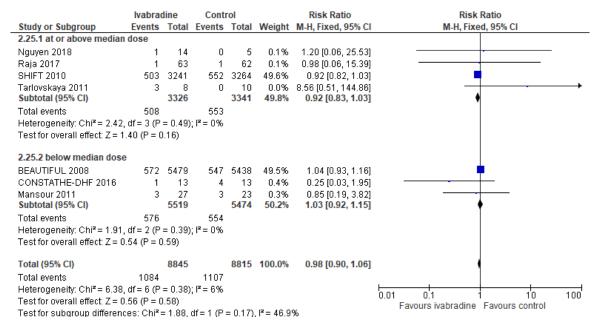


Figure 15 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose (12.7 mg) compared to trials administering ivabradine below median daily dose on all-cause mortality.

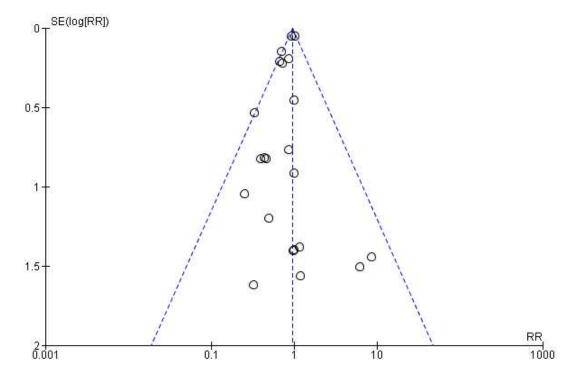


Figure 16 - Funnel plot of the analyses of all-cause mortality. The funnel plot did not indicate small study bias.

## **Supplement 6 - Serious adverse events** *Main analyses*

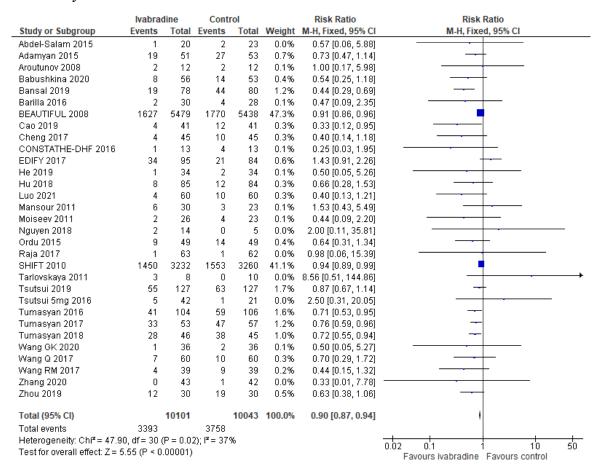


Figure 17 - Forest plot of the meta-analysis of serious adverse events using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

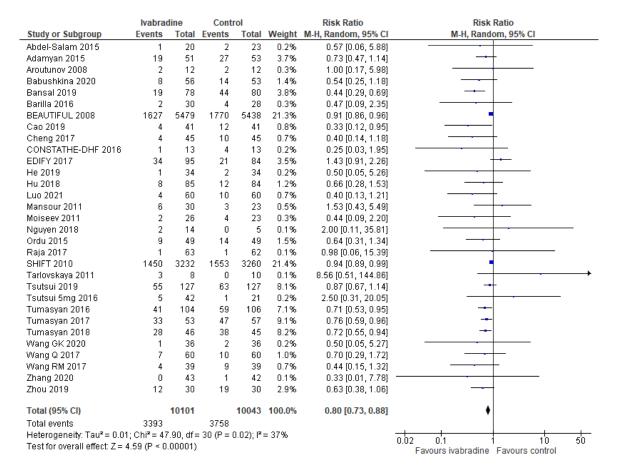


Figure 18 – Forest plot of the meta-analysis of serious adverse events using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

#### Sensitivity analyses

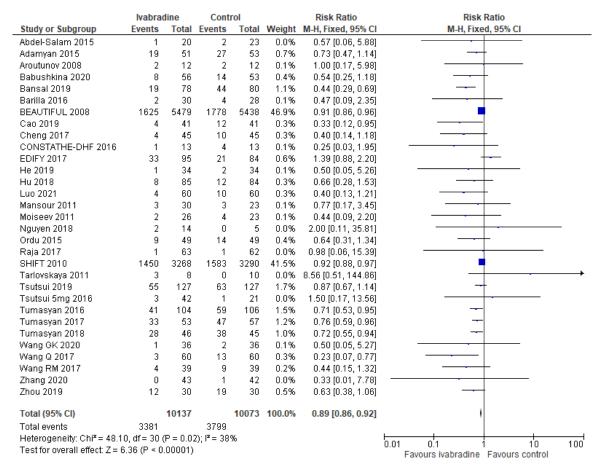


Figure 19 - Forest plot of the sensitivity analysis of serious adverse events using best- compared with worst-case scenario.

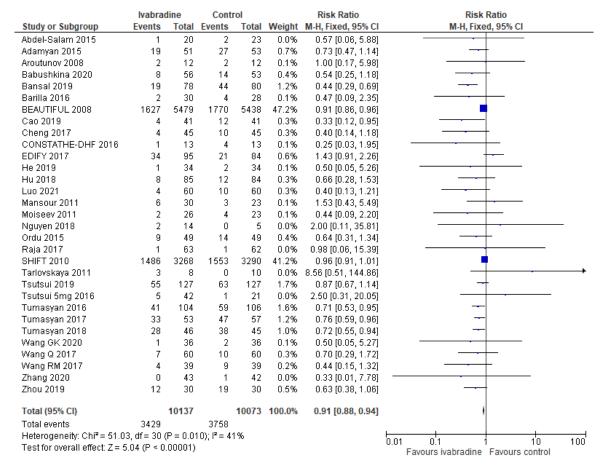
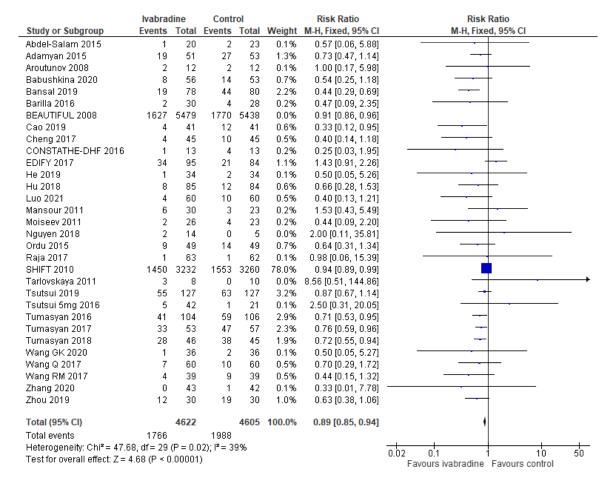


Figure 20 - Forest plot of the sensitivity analysis of serious adverse events using worst- compared with best-case scenario.



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

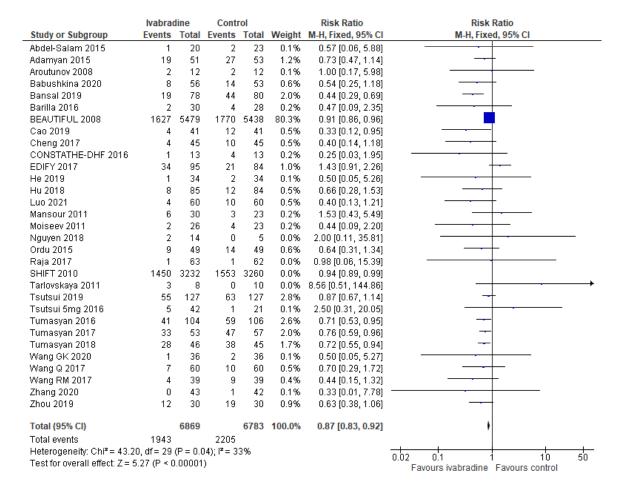


Figure 22 - Forest plot of the sensitivity analysis of serious adverse events removing the SHIFT trial.

### Subgroup analyses

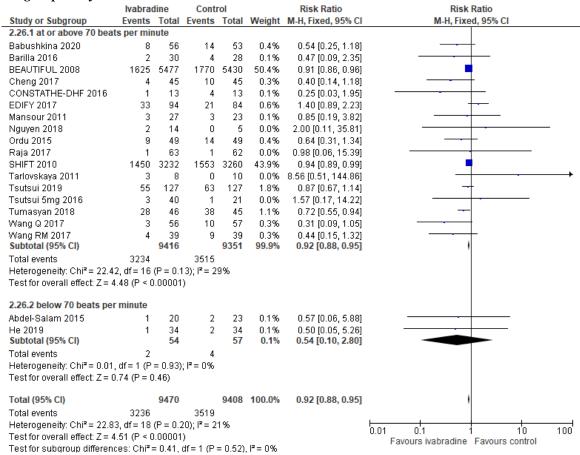


Figure 23 - Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared to trials randomising participants with heart rate below 70 beats per minute on all-cause mortality.

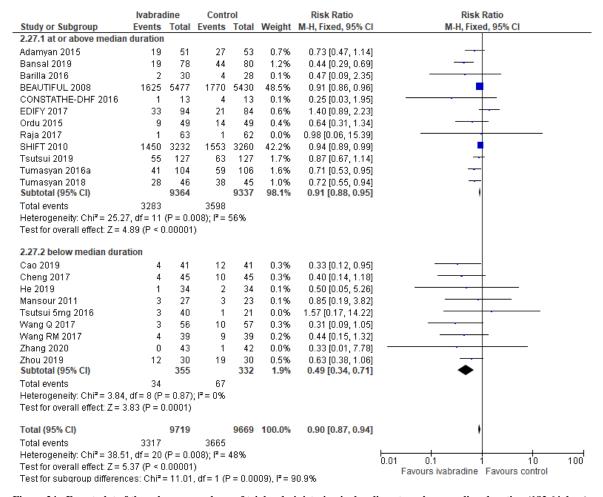


Figure 24 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (182.64 days) compared to trials administering ivabradine below median duration on serious adverse events.

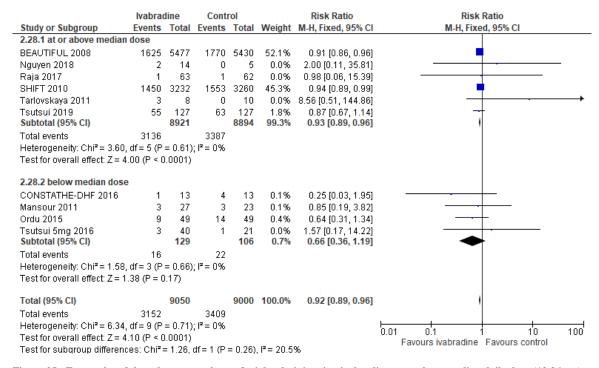


Figure 25 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose (12.36 mg) compared to trials administering ivabradine below median daily dose on serious adverse events.

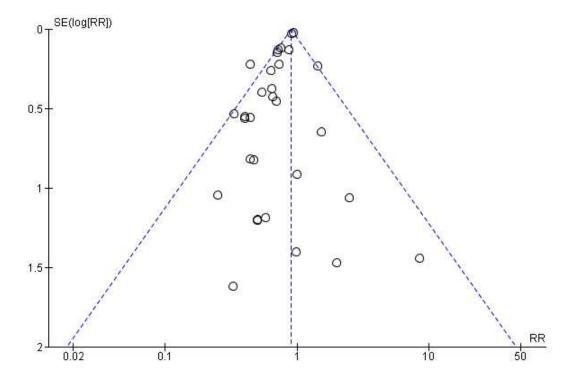


Figure 26 – Funnel plot of the analysis of serious adverse events. The funnel plot did not indicate small study bias.

# **Supplement 7 - Quality of life**

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

	Ival	Ivabradine			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.47.1 KCCQ change	score								
SHIFT 2010 Subtotal (95% CI)	6.7	17.3	842 <b>842</b>	4.3	16.7	839 <b>839</b>	94.5% <b>94.5</b> %	2.40 [0.77, 4.03] <b>2.40 [0.77, 4.03</b> ]	<b>,</b>
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 2.89	(P = 0	0.004)						
2.47.2 KCCQ mean so	соге								
Sallam 2016 Subtotal (95% CI)	80	14	50 <b>50</b>	68	20	50 <b>50</b>	5.5% <b>5.5%</b>	12.00 [5.23, 18.77] <b>12.00 [5.23, 18.77]</b>	<b>→</b>
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 3.48	(P = 0	).0005)						
Total (95% CI)			892			889	100.0%	2.92 [1.34, 4.50]	•
Heterogeneity: Chi²= Test for overall effect: Test for subgroup diff	Z = 3.63	(P = 0	).0003)			07), I² =	= 86.3%		-100 -50 0 50 100 Favours control Favours ivabradine

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.

	Ival	bradin	е	C	ontrol			Mean Difference	Mean Dif	ference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Randoi	m, 95% CI	
2.47.1 KCCQ change	score										
SHIFT 2010 Subtotal (95% CI)	6.7	17.3	842 <b>842</b>	4.3	16.7	839 <b>839</b>	56.1% <b>56.1</b> %	2.40 [0.77, 4.03] <b>2.40 [0.77, 4.03]</b>		•	
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 2.89	(P = 0	0.004)								
2.47.2 KCCQ mean so	core										
Sallam 2016 Subtotal (95% CI)	80	14	50 <b>50</b>	68	20	50 <b>50</b>	43.9% <b>43.9</b> %	12.00 [5.23, 18.77] <b>12.00 [5.23, 18.77]</b>		•	
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z= 3.48	(P = 0	0.0005)								
Total (95% CI)			892			889	100.0%	6.61 [-2.72, 15.95]	-	•	
Heterogeneity: Tau² = Test for overall effect: Test for subgroup diffe	Z = 1.39	(P = 0	0.16)	,					 50 0 ours control	) 50 Favours ivabi	100 adine

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.

	Iva	lvabradine			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.48.1 KCCQ change	score								<u></u>
SHIFT 2010 Subtotal (95% CI)	15.5	21.22	1129 <b>1129</b>	4.8	20.59	1153 <b>1153</b>			1 <del></del>
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 12.2	2 (P < 0	0.0000	1)					
2.48.2 KCCQ mean s	соге								
Sallam 2016 Subtotal (95% CI)	80	14	50 <b>50</b>	68	20	50 <b>50</b>	6.0% <b>6.0</b> %		<b>→</b>
Heterogeneity: Not ap			0005						
Test for overall effect:	∠= 3.48	i (P = U.	0005)						
Total (95% CI)			1179			1203	100.0%	10.78 [9.12, 12.44]	•
Heterogeneity: Chi <sup>z</sup> = Test for overall effect:									-100 -50 0 50 100
Test for subgroup diff		,		*	= 0.72)	I <sup>2</sup> = 0.9	6		Favours ivabradine Favours control

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

	lva	abradin	е	(	Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.49.1 KCCQ change	score								_
SHIFT 2010 Subtotal (95% CI)	2.1	21.22	1129 <b>1129</b>		20.59	1153 <b>1153</b>		-11.30 [-13.02, -9.58] - <b>11.30 [-13.02</b> , - <b>9.58]</b>	<b>-</b>
Heterogeneity: Not ap	plicable	!							
Test for overall effect:	Z=12.9	91 (P < 0	0.0000	1)					
2.49.2 KCCQ mean s	соге								
Sallam 2016 Subtotal (95% CI)	80	14	50 <b>50</b>	68	20	50 <b>50</b>	6.0% <b>6.0%</b>	12.00 [5.23, 18.77] <b>12.00 [5.23, 18.77]</b>	<b>→</b>
Heterogeneity: Not ap Test for overall effect:	•		0005)						
Total (95% CI)			1179			1203	100.0%	-9.89 [-11.56, -8.23]	•
Heterogeneity: Chi² = Test for overall effect:	Z=11.8	66 (P < 0	0.0000	1)					-100 -50 0 50 100
Test for subgroup diff	ferences	: Chi²=	42.79.	df = 1 (1)	P < 0.00	001), P	= 97.7%		Tavouis Ivabiaumo Tavouis Comio

 $\label{eq:figure 30-Forest plot of the sensitivity analysis of quality of life (MLWHFQ) using worst-compared with best-case scenario.$ 

# Subgroup analyses for trials using the KCCQ

	Ival	lvabradine			ontrol			Mean Difference		Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, I	ixed, 95% (	CI	
2.56.1 KCCQ at or ab	ove med	dian dı	uration										
SHIFT 2010 Subtotal (95% CI)	6.7	17.3	842 <b>842</b>	4.3	16.7	839 <b>839</b>	94.5% <b>94.5%</b>	2.40 [0.77, 4.03] <b>2.40 [0.77, 4.03]</b>			•		
Heterogeneity: Not ap	oplicable	!											
Test for overall effect:	Z= 2.89	(P = 0	0.004)										
2.56.2 KCCQ below r	nedian d	luratio	n										
Sallam 2016 Subtotal (95% CI)	80	14	50 <b>50</b>	68	20	50 <b>50</b>		12.00 [5.23, 18.77] <b>12.00 [5.23, 18.77]</b>			•		
Heterogeneity: Not ap	pplicable	!											
Test for overall effect:	Z= 3.48	(P = 0	0.0005)										
Total (95% CI)			892			889	100.0%	2.92 [1.34, 4.50]			•		
Heterogeneity: Chi²=	7.31, df	= 1 (P	= 0.00	7); I <sup>2</sup> = 8	6%				100		<del>                                     </del>		
Test for overall effect:	Z = 3.63	(P = 0	0.0003)						-100	-50 Favours cor	utrol Eavou	50 ire ivabradii	100
Test for subgroup diff	ferences	: Chi²:	= 7.31.	df = 1 (6)	= 0.0	07), <b>i²</b> :	= 86.3%			i avouis coi	ilioi Favou	io ivabiauli	ii c

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)

	Ival	bradin	е	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.50.1 MLWHFQ me	an score								
Abdel-Salam 2015	46.4	7.3	20	51.7	6.6	23	8.8%	-5.30 [-9.48, -1.12]	
Sarullo 2010	31.2	2.6	30	37.5	1.9	30	46.3%	-6.30 [-7.45, -5.15]	
Zeng FC 2019 Subtotal (95% CI)	27.44	4.26	33 <b>83</b>	32.21	4.79	32 <b>85</b>	23.9% <b>79.0%</b>		<b>→</b>
Heterogeneity: Tau <sup>2</sup> :	= 0.00; CI	hi² = 1.	.55, df=	= 2 (P =	0.46);	$l^2 = 0\%$	)		
Test for overall effect	t: Z= 11.7	'2 (P <	0.0000	01)					
2.50.2 MLWHFQ cha	inge scoi	re							
Mansour 2011	-12.3	3.3	30	-8.7	5.2	23	21.0%	-3.60 [-6.03, -1.17]	
Subtotal (95% CI)			30			23	21.0%	-3.60 [-6.03, -1.17]	•
Heterogeneity: Not a	pplicable								
Test for overall effect	:: Z = 2.90	(P = 0	0.004)						
Total (95% CI)			113			108	100.0%	-5.28 [-6.60, -3.96]	•
Heterogeneity: Tau <sup>2</sup> :	= 0.64; CI	$hi^2 = 4$	.58, df=	= 3 (P =	0.21);	$I^2 = 35^{\circ}$	%	-	-10 -5 0 5 10
Test for overall effect	: Z = 7.82	(P < 0	0.00001		Favours ivabradine Favours control				
Test for subgroup di	fferences	: Chi <sup>z</sup> :	= 3.04	df = 1/8		i avouis ivabiaulile Favouis Colliloi			

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.

	Ival	oradin	е	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.50.1 MLWHFQ mea	n score								
Abdel-Salam 2015	46.4	7.3	20	51.7	6.6	23	4.8%	-5.30 [-9.48, -1.12]	<del></del>
Sarullo 2010	31.2	2.6	30	37.5	1.9	30	63.6%	-6.30 [-7.45, -5.15]	-
Zeng FC 2019 Subtotal (95% CI)	27.44	4.26	33 <b>83</b>	32.21	4.79	32 <b>85</b>	17.3% <b>85.7</b> %	-4.77 [-6.98, -2.56] -5.93 [-6.93, -4.94]	<b>→</b>
Heterogeneity: Chi²=	1.55, df	= 2 (P	= 0.46)	; I <sup>2</sup> = 09	6				
Test for overall effect:									
2.50.2 MLWHFQ chan	ige scoi	re							
Mansour 2011 Subtotal (95% CI)	-12.3	3.3	30 <b>30</b>	-8.7	5.2	23 <b>23</b>		-3.60 [-6.03, -1.17] - <b>3.60 [-6.03, -1.17]</b>	<del>-</del>
Heterogeneity: Not ap Test for overall effect:			0.004)						
Total (95% CI)			113			108	100.0%	-5.60 [-6.52, -4.68]	•
Heterogeneity: Chi²= Test for overall effect:					%			_	-10 -5 0 5 10 Favours ivabradine Favours control
Test for subgroup diff	erences	: Chi²:	= 3.04,	df = 1 (F	P = 0.0	8), I²=	67.1%		. arodio irazi adino ir divolio 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.

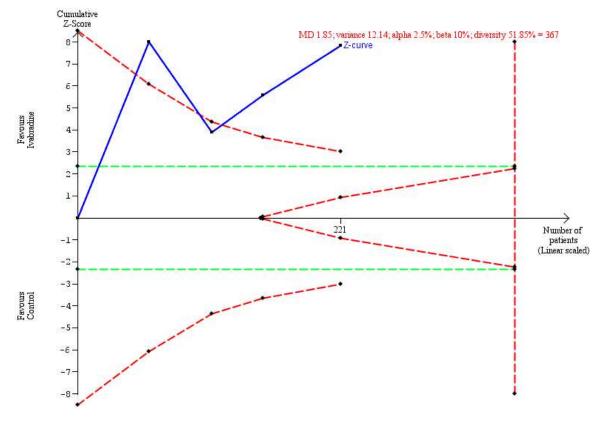


Figure 34 – Trial Sequential Analysis graph of quality of life from trials using the MLWHFQ. Trial Sequential Analysis showed that we had enough information to detect a mean difference of -5.60 points of ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) breached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

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

	lvabradine		C	ontrol			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.51.1 MLWHFQ mea	an score								
Abdel-Salam 2015	46.4	7.3	20	51.7	6.6	23	8.8%	-5.30 [-9.48, -1.12]	<del></del>
Sarullo 2010	31.2	2.6	30	37.5	1.9	30	46.3%	-6.30 [-7.45, -5.15]	-
Zeng FC 2019 Subtotal (95% CI)	27.44	4.26	33 <b>83</b>	32.21	4.79	32 <b>85</b>	23.9% <b>79.0%</b>	-4.77 [-6.98, -2.56] - <b>5.93 [-6.93, -4.94]</b>	<b>→</b>
Heterogeneity: Tau <sup>2</sup> :	= 0.00; C	hi² = 1	.55, df :	= 2 (P =	0.46);	$I^2 = 0\%$	,		
Test for overall effect									
2.51.2 MLWHFQ cha	nge sco	re							
Mansour 2011	-12.3	3.3	30	-8.7	5.2	23	21.0%	-3.60 [-6.03, -1.17]	
Subtotal (95% CI)			30			23	21.0%	-3.60 [-6.03, -1.17]	•
Heterogeneity: Not a	pplicable	!							
Test for overall effect	: Z = 2.90	(P=(	0.004)						
Total (95% CI)			113			108	100.0%	-5.28 [-6.60, -3.96]	•
Heterogeneity: Tau <sup>2</sup> :	= 0.64; C	hi² = 4	.58, df :	= 3 (P =	0.21);	l <sup>2</sup> = 35	%	-	-10 -5 0 5 10
Test for overall effect	Z = 7.82	(P < 0		-10 -5 0 5 10 Favours ivabradine Favours control					
Test for subgroup dif	fferences	: Chi²	= 3.04.	df = 1 (1)	P = 0.0	18), I² =	67.1%		Favours (vabraulite Favours Control

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

	Ival	bradin	e	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.52.1 MLWHFQ mea	n score								
Abdel-Salam 2015	46.4	7.3	20	51.7	6.6	23	8.8%	-5.30 [-9.48, -1.12]	<del></del>
Sarullo 2010	31.2	2.6	30	37.5	1.9	30	46.3%	-6.30 [-7.45, -5.15]	-
Zeng FC 2019 Subtotal (95% CI)	27.44	4.26	33 <b>83</b>	32.21	4.79	32 <b>85</b>	23.9% <b>79.0%</b>	-4.77 [-6.98, -2.56] - <b>5.93 [-6.93, -4.94]</b>	<b>→</b>
Heterogeneity: Tau <sup>2</sup> =	0.00; CI	$hi^2 = 1$	.55, df=	2 (P =	0.46);	$l^2 = 0\%$	,		
Test for overall effect:	Z = 11.7	'2 (P <	0.0000	)1)					
2.52.2 MLWHFQ char	ige scoi	re							
Mansour 2011 Subtotal (95% CI)	-12.3	3.3	30 <b>30</b>	-8.7	5.2	23 <b>23</b>	21.0% <b>21.0%</b>	-3.60 [-6.03, -1.17] - <b>3.60 [-6.03, -1.17]</b>	<del></del>
Heterogeneity: Not ap Test for overall effect:	•		0.004)						
Total (95% CI)			113			108	100.0%	-5.28 [-6.60, -3.96]	•
Heterogeneity: Tau² = Test for overall effect: Test for subgroup diff	Z = 7.82	(P < 0	0.00001	)					-10 -5 0 5 10 Favours ivabradine Favours control

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



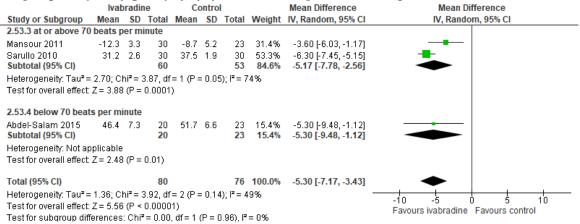


Figure 37 - Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared trials randomising participants with heart rate below 70 beats per minute on quality of life using the MLWHFQ.

	Ival	Ivabradine			ontrol			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
2.54.3 at or above m	edian du	ıration										
Mansour 2011 Subtotal (95% CI)	-12.3	3.3	30 <b>30</b>	-8.7	5.2	23 <b>23</b>	39.2% <b>39.2%</b>	-3.60 [-6.03, -1.17] - <b>3.60 [-6.03, -1.17]</b>	<b>-</b>			
Heterogeneity: Not ap	pplicable											
Test for overall effect:	Z = 2.90	(P=0	0.004)									
2.54.4 below median	duratio	n										
Abdel-Salam 2015	46.4	7.3	20	51.7	6.6	23	13.2%	-5.30 [-9.48, -1.12]				
Zeng FC 2019	27.44	4.26	33	32.21	4.79	32	47.6%	-4.77 [-6.98, -2.56]	<del></del>			
Subtotal (95% CI)			53			55	60.8%	-4.89 [-6.84, -2.93]	•			
Heterogeneity: Tau² =	= 0.00; CI	hi² = 0	.05, df :	= 1 (P =	0.83);	$I^2 = 0\%$						
Test for overall effect:	Z= 4.91	(P < 0	0.0000	)								
Total (95% CI)			83			78	100.0%	-4.38 [-5.90, -2.86]	•			
Heterogeneity: Tau <sup>2</sup> =	= 0.00; CI	hi²= 0	70, df	2 (P =	0.70);	$I^2 = 0\%$			-10 -5 0 5 10			
Test for overall effect:	Z = 5.64	(P < 0	0.0000	)		-10 -5 0 5 10 Favours ivabradine Favours control						
Test for subgroup diff	ferences	: Chi <sup>z</sup> :	= 0.65.	df = 1 (i	P = 0.4	2), l <sup>2</sup> =	0%		1 avours (vabraume   avours control			

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*

	lvabrad	line	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Abdel-Salam 2015	1	20	1	23	0.0%	1.15 [0.08, 17.22]	
BEAUTIFUL 2008	469	5479	435	5438	49.1%	1.07 [0.94, 1.21]	+
Cao 2019	4	41	12	41	0.0%	0.33 [0.12, 0.95]	
EDIFY 2017	2	94	0	84	0.0%	4.47 [0.22, 91.88]	
Hu 2018	1	85	4	84	0.0%	0.25 [0.03, 2.16]	
Mansour 2011	2	27	3	23	0.0%	0.57 [0.10, 3.11]	
Moiseev 2011	2	26	4	23	0.0%	0.44 [0.09, 2.20]	
Raja 2017	1	63	0	62	0.0%	2.95 [0.12, 71.13]	
SHIFT 2010	449	3241	491	3264	50.9%	0.92 [0.82, 1.04]	<del></del>
Tarlovskaya 2011	2	8	0	10	0.0%	6.11 [0.33, 111.71]	
Tsutsui 2019	7	127	8	127	0.0%	0.88 [0.33, 2.34]	
Wang GK 2020	1	36	1	36	0.0%	1.00 [0.07, 15.38]	
Wang Q 2017	1	56	1	57	0.0%	1.02 [0.07, 15.88]	
Wang RM 2017	0	39	3	39	0.0%	0.14 [0.01, 2.68]	
Zhang 2020	0	43	1	42	0.0%	0.33 [0.01, 7.78]	
Total (95% CI)		8720		8702	100.0%	0.99 [0.86, 1.15]	<b>*</b>
Total events	918		926				
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi	$i^2 = 2.93$	2, df = 1 (	P = 0.0	9); I <sup>z</sup> = 66	% -	05 07 1 15 2
Test for overall effect:	Z = 0.12 (	(P = 0.9)	1)				Favours ivabradine Favours control

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).

lvabrad	line	Conti	rol		Risk Ratio	Risk Ratio					
<b>Events</b>	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI					
1	20	1	23	0.0%	1.15 [0.08, 17.22]						
469	5479	435	5438	47.2%	1.07 [0.94, 1.21]	<b>- </b> -					
4	41	12	41	0.0%	0.33 [0.12, 0.95]						
2	94	0	84	0.0%	4.47 [0.22, 91.88]						
1	85	4	84	0.0%	0.25 [0.03, 2.16]						
2	27	3	23	0.0%	0.57 [0.10, 3.11]						
2	26	4	23	0.0%	0.44 [0.09, 2.20]						
1	63	0	62	0.0%	2.95 [0.12, 71.13]						
449	3241	491	3264	52.8%	0.92 [0.82, 1.04]	<del>-■</del> †					
2	8	0	10	0.0%	6.11 [0.33, 111.71]						
7	127	8	127	0.0%	0.88 [0.33, 2.34]						
1	36	1	36	0.0%	1.00 [0.07, 15.38]						
1	56	1	57	0.0%	1.02 [0.07, 15.88]						
0	39	3	39	0.0%	0.14 [0.01, 2.68]						
0	43	1	42	0.0%	0.33 [0.01, 7.78]						
	8720		8702	100.0%	0.99 [0.91, 1.08]	<b>*</b>					
918		926									
Heterogeneity: Chi <sup>2</sup> = 2.92, df = 1 (P = 0.09); i <sup>2</sup> = 66%											
Z = 0.20 (	(P = 0.8)	4)				0.5 0.7 1 1.5 2 Favours ivabradine Favours control					
	1 469 4 2 1 1 2 2 1 1 449 2 7 1 1 0 0 0 918 2.92, df =	1 20 469 5479 4 41 2 94 1 85 2 27 2 26 1 63 449 3241 2 8 7 127 1 36 1 56 0 39 0 43  8720  918 2.92, df = 1 (P =	Events         Total         Events           1         20         1           469         5479         435           4         41         12           2         94         0           1         85         4           2         27         3           2         26         4           1         63         0           449         3241         491           2         8         0           7         127         8           1         36         1           1         56         1           0         39         3           0         43         1           918         8         926	Events         Total         Events         Total           469         5479         435         5438           4         41         12         41           2         94         0         84           1         85         4         84           2         27         3         23           2         26         4         23           1         63         0         62           449         3241         491         3264           2         8         0         10           7         127         8         127           1         36         1         36           1         56         1         57           0         39         3         39           0         43         1         42           918         926         926         292, df = 1 (P = 0.09); P = 66%	Events         Total         Events         Total         Weight           1         20         1         23         0.0%           469         5479         435         5438         47.2%           4         41         12         41         0.0%           2         94         0         84         0.0%           1         85         4         84         0.0%           2         27         3         23         0.0%           1         63         0         62         0.0%           449         3241         491         3264         52.8%           42         8         0         10         0.0%           4         127         0.0%         0.0%           4         136         1         36         0.0%           4         136         1         36         0.0%           1         36         1         36         0.0%           1         56         1         57         0.0%           2         39         3         39         0.0%           4         30         1         42         0.0% <td>Events         Total         Events         Total         Weight         M-H, Fixed, 95% CI           469         5479         435         5438         47.2%         1.07 [0.94, 1.21]           4         41         12         41         0.0%         0.33 [0.12, 0.95]           2         94         0         84         0.0%         4.47 [0.22, 91.88]           1         85         4         84         0.0%         0.25 [0.03, 2.16]           2         27         3         23         0.0%         0.57 [0.10, 3.11]           2         26         4         23         0.0%         0.57 [0.10, 3.11]           449         3241         491         3264         52.8%         0.92 [0.82, 1.04]           449         3241         491         3264         52.8%         0.92 [0.82, 1.04]           42         8         0         10         0.0%         6.11 [0.33, 111.71]           7         127         8         127         0.0%         0.88 [0.33, 2.34]           1         36         1         57         0.0%         1.02 [0.07, 15.88]           1         56         1         57         0.0%         0.14 [0.01, 2.68]</td>	Events         Total         Events         Total         Weight         M-H, Fixed, 95% CI           469         5479         435         5438         47.2%         1.07 [0.94, 1.21]           4         41         12         41         0.0%         0.33 [0.12, 0.95]           2         94         0         84         0.0%         4.47 [0.22, 91.88]           1         85         4         84         0.0%         0.25 [0.03, 2.16]           2         27         3         23         0.0%         0.57 [0.10, 3.11]           2         26         4         23         0.0%         0.57 [0.10, 3.11]           449         3241         491         3264         52.8%         0.92 [0.82, 1.04]           449         3241         491         3264         52.8%         0.92 [0.82, 1.04]           42         8         0         10         0.0%         6.11 [0.33, 111.71]           7         127         8         127         0.0%         0.88 [0.33, 2.34]           1         36         1         57         0.0%         1.02 [0.07, 15.88]           1         56         1         57         0.0%         0.14 [0.01, 2.68]					

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).

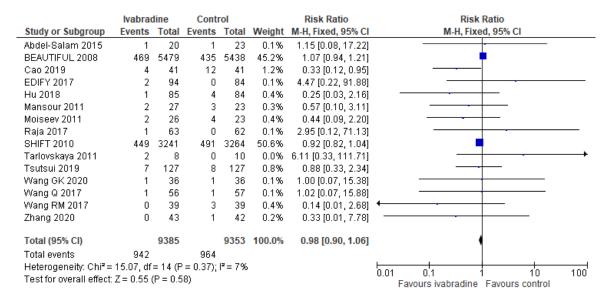
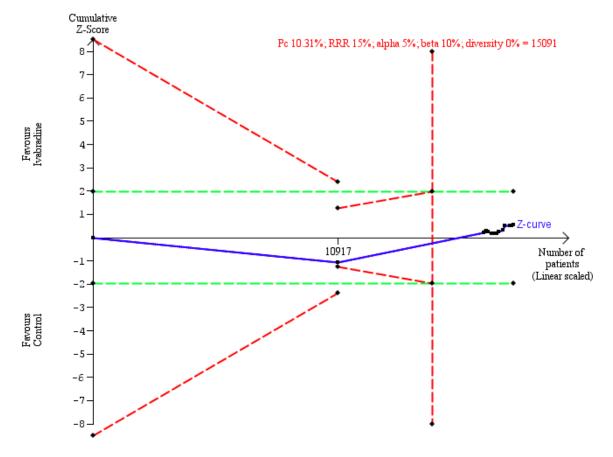


Figure 41 – Forest plot of the meta-analysis of cardiovascular mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

	Ivabra	line	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Abdel-Salam 2015	1	20	1	23	0.2%	1.15 [0.08, 17.22]	<del></del>
BEAUTIFUL 2008	469	5479	435	5438	46.1%	1.07 [0.94, 1.21]	•
Cao 2019	4	41	12	41	1.3%	0.33 [0.12, 0.95]	
EDIFY 2017	2	94	0	84	0.2%	4.47 [0.22, 91.88]	<del> </del>
Hu 2018	1	85	4	84	0.3%	0.25 [0.03, 2.16]	<del></del>
Mansour 2011	2	27	3	23	0.5%	0.57 [0.10, 3.11]	-
Moiseev 2011	2	26	4	23	0.5%	0.44 [0.09, 2.20]	<del></del>
Raja 2017	1	63	0	62	0.1%	2.95 [0.12, 71.13]	<del> </del>
SHIFT 2010	449	3241	491	3264	48.6%	0.92 [0.82, 1.04]	•
Tarlovskaya 2011	2	8	0	10	0.2%	6.11 [0.33, 111.71]	<del></del>
Tsutsui 2019	7	127	8	127	1.4%	0.88 [0.33, 2.34]	
Wang GK 2020	1	36	1	36	0.2%	1.00 [0.07, 15.38]	
Wang Q 2017	1	56	1	57	0.2%	1.02 [0.07, 15.88]	
Wang RM 2017	0	39	3	39	0.2%	0.14 [0.01, 2.68]	<del>  </del>
Zhang 2020	0	43	1	42	0.1%	0.33 [0.01, 7.78]	
Total (95% CI)		9385		9353	100.0%	0.97 [0.86, 1.09]	•
Total events	942		964				
Heterogeneity: Tau² =	0.00; Ch	$i^2 = 15.0$	07, df = 1	4 (P = 0)	0.37); (2=	7%	0.01 0.1 1 10 100
Test for overall effect:	Z = 0.56	(P = 0.5)	8)				0.01 0.1 1 10 100 Favours ivabradine Favours control
							i avouis ivabilaulile Favouis colliloi

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

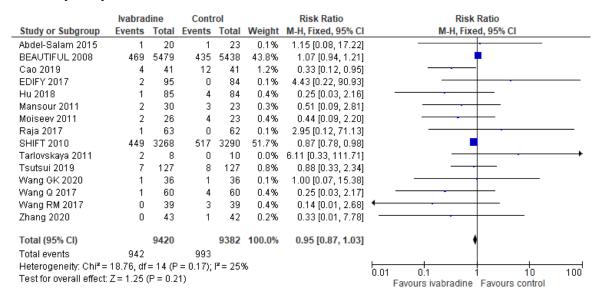


Figure 44 - Forest plot of the sensitivity analysis of cardiovascular mortality using best- compared with worst-case scenario.

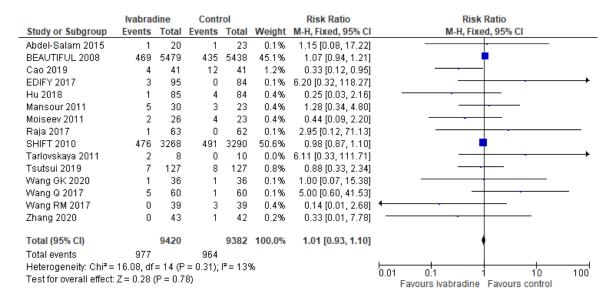


Figure 45 - Forest plot of the sensitivity analysis of cardiovascular mortality using worst compared with best-case scenario.

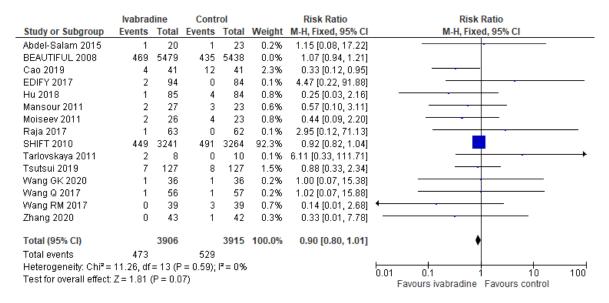


Figure 46 - Forest plot of the sensitivity analysis of cardiovascular mortality removing the BEAUTIFUL trial.

	Ivabra	dine	Cont	rol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Abdel-Salam 2015	1	20	1	23	0.2%	1.15 [0.08, 17.22]		<u>-</u>	
BEAUTIFUL 2008	469	5479	435	5438	91.4%	1.07 [0.94, 1.21]			
Cao 2019	4	41	12	41	2.5%	0.33 [0.12, 0.95]		<del></del>	
EDIFY 2017	2	94	0	84	0.1%	4.47 [0.22, 91.88]		<del>-   ·</del>	
Hu 2018	1	85	4	84	0.8%	0.25 [0.03, 2.16]			
Mansour 2011	2	27	3	23	0.7%	0.57 [0.10, 3.11]		<del></del>	
Moiseev 2011	2	26	4	23	0.9%	0.44 [0.09, 2.20]		<del></del>	
Raja 2017	1	63	0	62	0.1%	2.95 [0.12, 71.13]		<del> </del>	
SHIFT 2010	449	3241	491	3264	0.0%	0.92 [0.82, 1.04]			
Tarlovskaya 2011	2	8	0	10	0.1%	6.11 [0.33, 111.71]		<del> </del>	$\longrightarrow$
Tsutsui 2019	7	127	8	127	1.7%	0.88 [0.33, 2.34]			
Wang GK 2020	1	36	1	36	0.2%	1.00 [0.07, 15.38]			
Wang Q 2017	1	56	1	57	0.2%	1.02 [0.07, 15.88]			
Wang RM 2017	0	39	3	39	0.7%	0.14 [0.01, 2.68]	<b>—</b>	•	
Zhang 2020	0	43	1	42	0.3%	0.33 [0.01, 7.78]	_	•	
Total (95% CI)		6144		6089	100.0%	1.03 [0.92, 1.17]		<b>•</b>	
Total events	493		473						
Heterogeneity: Chi <sup>2</sup> =	13.16, df	= 13 (P	= 0.44);	l <sup>2</sup> = 1%			0.04	0.1 1 10	400
Test for overall effect:	Z = 0.54	(P = 0.5)	i9)				0.01	Favours ivabradine Favours control	100
		-						ravours ivabraume Favours control	

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

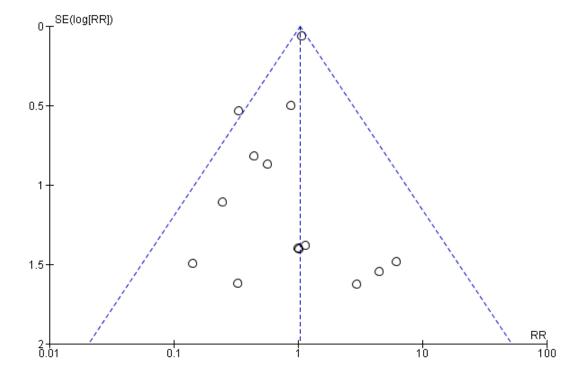


Figure 48 – Funnel plot of the analysis of cardiovascular mortality. The funnel plot did not indicate small study bias.

# **Supplement 9 - Myocardial infarction**

### Main analyses

	lvabrad	line	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Babushkina 2020	0	56	3	53	0.0%	0.14 [0.01, 2.56]	
BEAUTIFUL 2008	82	5477	88	5430	62.2%	0.92 [0.69, 1.25]	#
EDIFY 2017	2	94	0	84	0.0%	4.47 [0.22, 91.88]	
Liu YY 2020	4	61	5	61	0.0%	0.80 [0.23, 2.84]	
Moiseev 2011	2	26	3	23	0.0%	0.59 [0.11, 3.22]	
SHIFT 2010	62	3232	54	3260	37.8%	1.16 [0.81, 1.66]	<b>+</b>
Tarlovskaya 2011	2	8	0	10	0.0%	6.11 [0.33, 111.71]	
Tsutsui 2019	2	127	1	127	0.0%	2.00 [0.18, 21.78]	
Tsutsui 5mg 2016	0	40	1	21	0.0%	0.18 [0.01, 4.21]	
Total (95% CI)		8709		8690	100.0%	1.01 [0.80, 1.27]	<b>•</b>
Total events	144		142				
Heterogeneity: Chi <sup>2</sup> =	0.89, df=	1 (P =	0.34); l² =	: 0%			0.01 0.1 1 10 100
Test for overall effect:	Z = 0.11 (	(P = 0.9)	2)				0.01 0.1 1 10 100 Favours ivabradine Favours control
							. areare made and a drouge control

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).

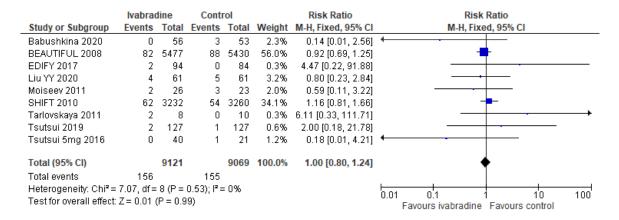


Figure 50 - Forest plot of the meta-analysis of myocardial infarction using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

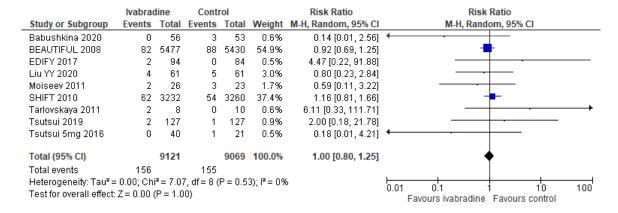
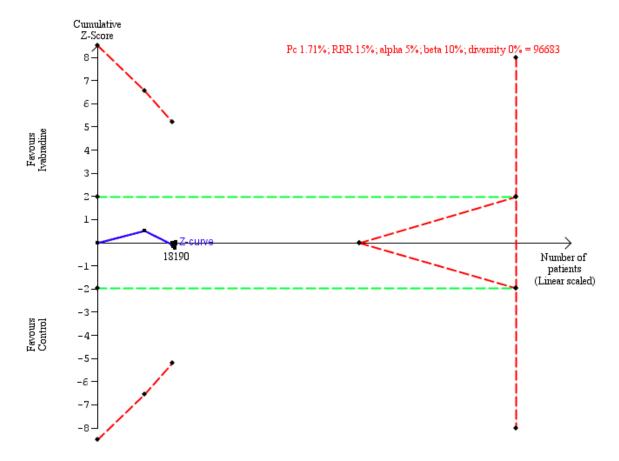


Figure 51 - Forest plot of the meta-analysis of myocardial infarction using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).



**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

	lvabrad	dine	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Babushkina 2020	0	56	3	53	1.8%	0.14 [0.01, 2.56]	<del></del>
BEAUTIFUL 2008	82	5479	96	5438	49.2%	0.85 [0.63, 1.14]	=
EDIFY 2017	2	95	0	84	0.3%	4.43 [0.22, 90.93]	<del></del>
Liu YY 2020	4	61	5	61	2.6%	0.80 [0.23, 2.84]	<del></del>
Moiseev 2011	2	26	3	23	1.6%	0.59 [0.11, 3.22]	<del></del>
SHIFT 2010	62	3268	84	3290	42.8%	0.74 [0.54, 1.03]	<del></del>
Tarlovskaya 2011	2	8	0	10	0.2%	6.11 [0.33, 111.71]	<del></del>
Tsutsui 2019	2	127	1	127	0.5%	2.00 [0.18, 21.78]	<del></del>
Tsutsui 5mg 2016	0	42	1	21	1.0%	0.17 [0.01, 4.02]	<del></del>
Total (95% CI)		9162		9107	100.0%	0.81 [0.65, 0.99]	•
Total events	156		193				
Heterogeneity: Chi²=	6.47, df=	8 (P=	0.59); l <sup>2</sup> =	= 0%			0.01 0.1 1 10 100
Test for overall effect:	Z = 2.05 (	(P = 0.0)	14)				Favours ivabradine Favours control

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

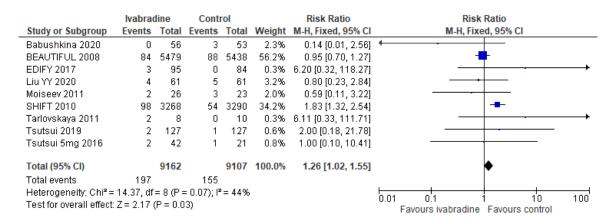
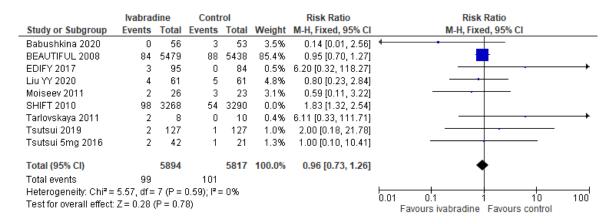


Figure 54 - Forest plot of the sensitivity analysis of myocardial infarction using a worst- compared with best-case scenario.

	lvabrad	dine	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	<b>Events</b>	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Babushkina 2020	0	56	3	53	5.2%	0.14 [0.01, 2.56]	· · ·
BEAUTIFUL 2008	84	5479	88	5438	0.0%	0.95 [0.70, 1.27]	
EDIFY 2017	3	95	0	84	0.8%	6.20 [0.32, 118.27]	<del></del>
Liu YY 2020	4	61	5	61	7.3%	0.80 [0.23, 2.84]	<del></del>
Moiseev 2011	2	26	3	23	4.6%	0.59 [0.11, 3.22]	
SHIFT 2010	98	3268	54	3290	78.1%	1.83 [1.32, 2.54]	<del>   </del>
Tarlovskaya 2011	2	8	0	10	0.7%	6.11 [0.33, 111.71]	<del></del>
Tsutsui 2019	2	127	1	127	1.5%	2.00 [0.18, 21.78]	<del></del>
Tsutsui 5mg 2016	2	42	1	21	1.9%	1.00 [0.10, 10.41]	
Total (95% CI)		3683		3669	100.0%	1.66 [1.23, 2.22]	<b>*</b>
Total events	113		67				
Heterogeneity: Chi <sup>2</sup> =	7.57, df=	7 (P=	0.37); l² =	- 7%			
Test for overall effect:	Z = 3.35 (	(P = 0.0)	008)				0.01 0.1 1 10 100 Favours ivabradine Favours control
							ravouis ivabiaulile ravouis colliloi

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*

	Fuente	Total	Fuente	Total	Moinbt	MIII Dandom OFN CL	MIII Dandom OFW CI
Study or Subgroup	Events				weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Abdel-Salam 2015	3	20	0	23		Not estimable	
Bansal 2019	3	78 5477	1	80	40.00	Not estimable	
BEAUTIFUL 2008	2570	5477	2221	5430	48.3%	1.15 [1.10, 1.20]	•
Cao 2019	2	41	3	41 45		Not estimable	
Cheng 2017	2 1	45 45	1	45		Not estimable	
Cong 2018	1	41	1	41		Not estimable	
Deng 2017	3		1			Not estimable	
Di 2020		63 94		63		Not estimable	
EDIFY 2017 Fu 2021	57 2	32	51 1	84 32		Not estimable	
	2	32 85	0	32 84		Not estimable	
Hu 2018	5	52	0	50		Not estimable	
Huang J 2017	2	48	1	48		Not estimable	
_i 2020 xx 2020	3	40 61	4	61		Not estimable	
_iu YY 2020						Not estimable	
_u 2019 _uo 2021	1 4	30 60	0	30 60		Not estimable	
_uo 2021 _u YH 2020	1	35	0	35		Not estimable Not estimable	
.u rH 2020 Ma 2020	2	43	2	43		Not estimable	
wa 2020 Manz 2003	9	27	2	11		Not estimable	
Man2 2003 Mao 2018	2	30	2	30		Not estimable	
	5	14	0	5			
Nguyen 2018 Pan 2020	2	25	1	25		Not estimable Not estimable	
an 2020 Qi 2019	0	48	2	48			
	2	63	0	62		Not estimable	
Raja 2017	5	50	3	50		Not estimable	
Ballam 2016 BHIFT 2010	2694	3232	2577	3260	51.7%	Not estimable	
Bun 2020	2034	50	4	50	31.770	1.05 [1.03, 1.08] Not estimable	_
Fang 2018	1	31	3	31		Not estimable	
rang 2010 Fsutsui 2.5mg 2016	23	42	6	20		Not estimable	
rsutsui 2.3111g 2010 Fsutsui 2019	119	127	116	127		Not estimable	
rsutsui 5mg 2016	27	42	6	21		Not estimable	
Vang FC 2017	2	53	6	43		Not estimable	
Vang JJ 2017	2	20	3	20		Not estimable	
Vang Q 2017	6	56	4	57		Not estimable	
Vang & 2011 Vang RM 2017	3	39	3	39		Not estimable	
Vei 2019	1	32	0	32		Not estimable	
(ia 2016	1	39	1	39		Not estimable	
(ing 2018	1	10	3	10		Not estimable	
(u 2019	3	38	0	39		Not estimable	
(ue 2020	2	45	1	45		Not estimable	
ang WT 2019	1	40	Ö	40		Not estimable	
/u 2018	1	10	3	10		Not estimable	
/ue 2016	2	43	1	43		Not estimable	
Zeng FC 2019	0	33	1	32		Not estimable	
Zeng XM 2019	3	45	4	45		Not estimable	
Zhang 2020	2	43	6	42		Not estimable	
Thang 2020 Thang 2021	1	47	2	47		Not estimable	
Zhang XJ 2019	1	55	1	55		Not estimable	
Zhou 2019	3	30	2	30		Not estimable	
Zhou 2019 Zhou 2020	2	43	5	43		Not estimable	
Гotal (95% CI)		8709		8690	100.0%	1.10 [1.00, 1.21]	
Total events	5264		4798				
		- 45 00		D ~ O O	001); l²=	0.20%	

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)

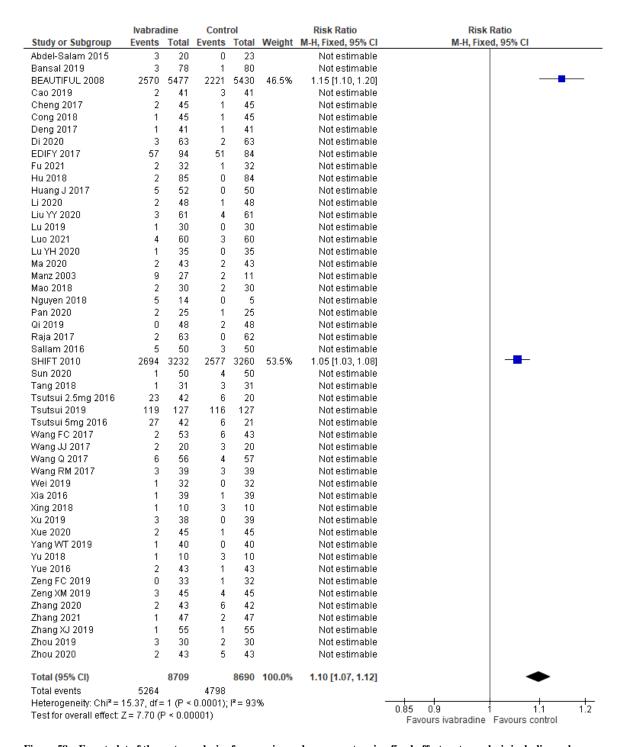


Figure 58 – Forest plot of the meta-analysis of non-serious adverse events using fixed-effect meta-analysis including only trials at low risk of bias. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention).

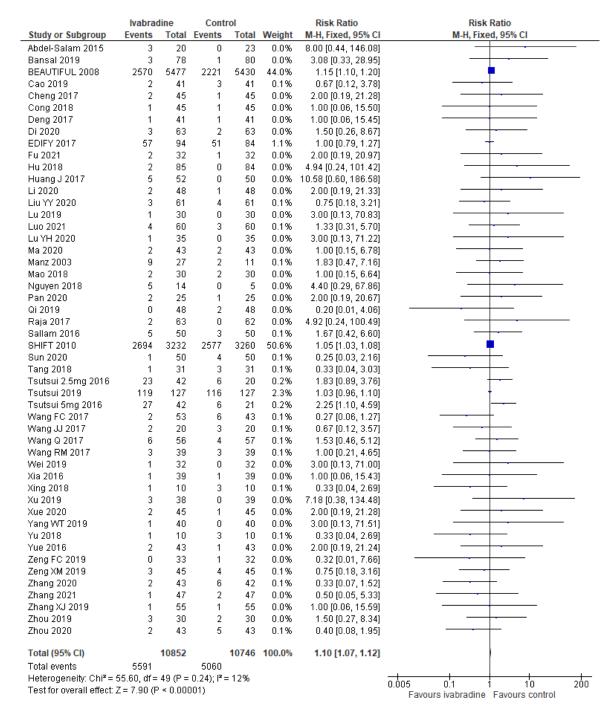


Figure 59 - Forest plot of the meta-analysis of non-serious adverse events using fixed-effect meta-analysis. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention).

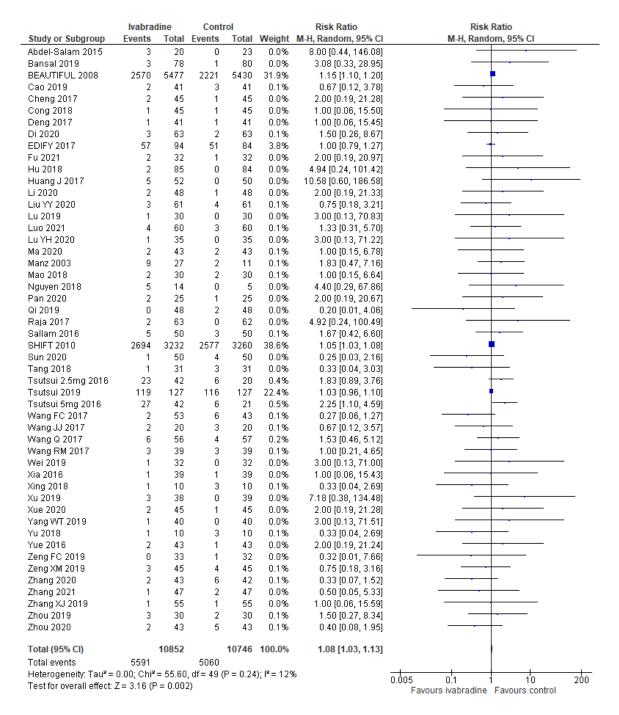
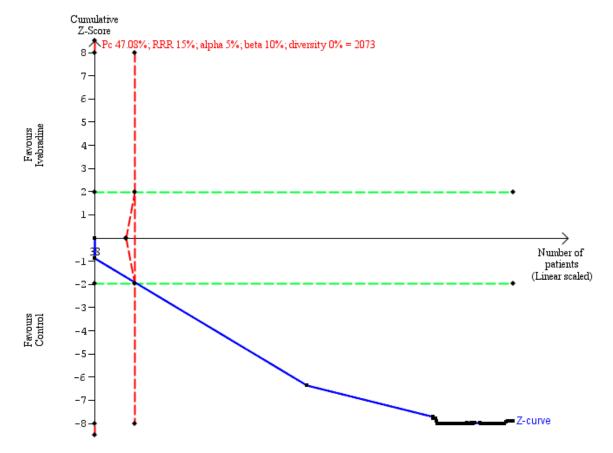


Figure 60 - Forest plot of the meta-analysis of non-serious adverse events using random-effects meta-analysis. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention)



**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

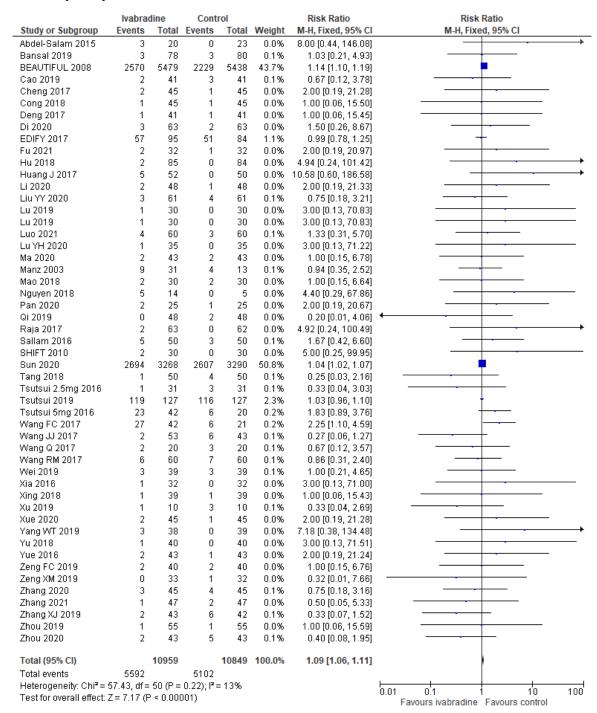


Figure 62 - Forest plot of the meta-analysis of non-serious adverse events using a best- compared with worst-case scenario.

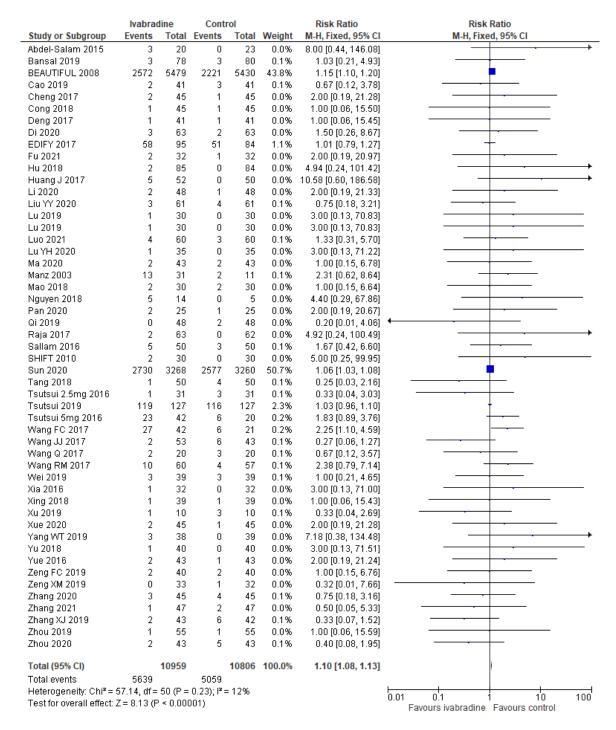


Figure 63 - Forest plot of the meta-analysis of non-serious adverse events using a worst- compared with best-case scenario.

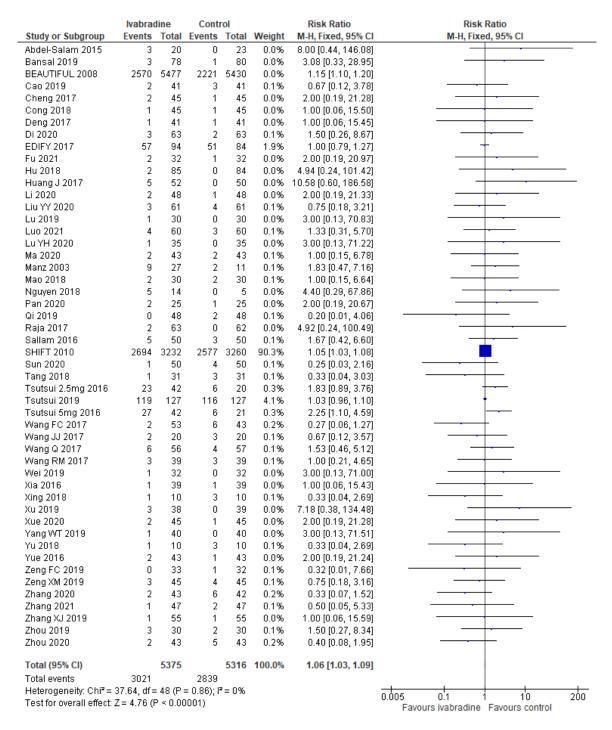


Figure 64 - Forest plot of the sensitivity analysis of non-serious adverse events removing the BEAUTIFUL trial.

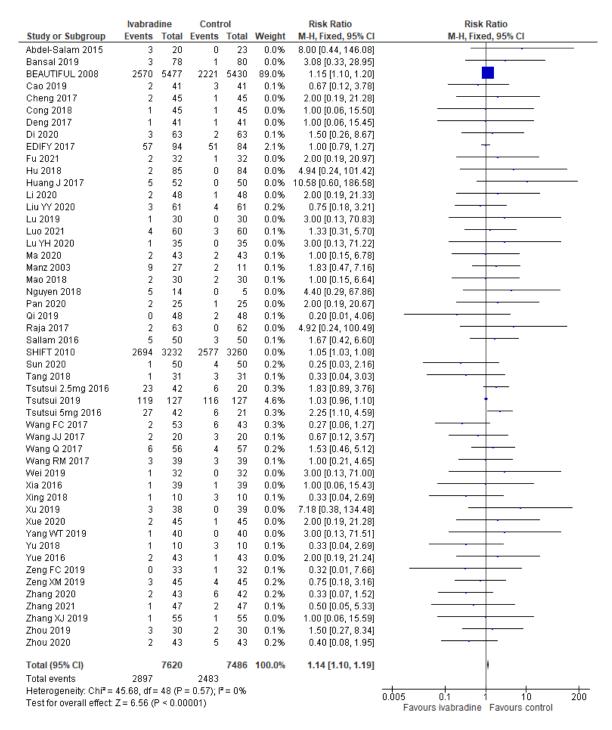


Figure 65 - Forest plot of the sensitivity analysis of non-serious adverse events removing the SHIFT trial.

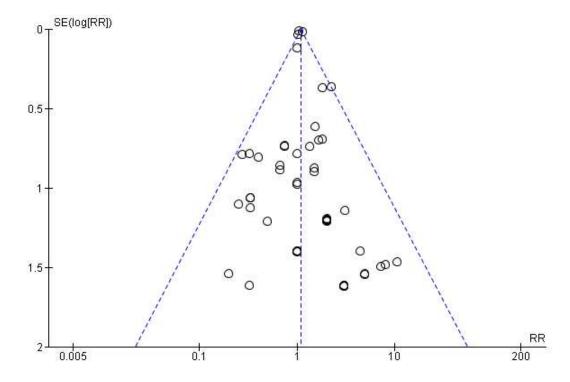


Figure 66 – Funnel plot of the analysis of non-serious adverse events. The funnel plot did not indicate small study bias.

# 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*

G		J							
		bradin			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean		Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Barilla 2016	65.7	9.8	30	81.9	7.5	28	3.1%	-16.20 [-20.67, -11.73]	<del></del>
Cavosoglu 2015	83.5	12.4	29	101.7	16.9	29	2.6%	-18.20 [-25.83, -10.57]	
Chaudhari 2014	70.6	5.06		91.33	8.9	80	3.3%	-20.73 [-22.98, -18.48]	
CONSTATHE-DHF 2016	86	15	13	98	12	13	2.2%	-12.00 [-22.44, -1.56]	<del></del>
Di 2020	66.64	4.58	63	73.75	6.01	63	3.3%	-7.11 [-8.98, -5.24]	-
EDIFY 2017	-13	3.46	95	-3.5	4.18	84	3.4%	-9.50 [-10.63, -8.37]	+
Fu 2021	63.7	3.9	32	67.4	4.2	32	3.3%	-3.70 [-5.69, -1.71]	
Kosmala 2013	62	8	30	70	7	31	3.2%	-8.00 [-11.78, -4.22]	<del></del>
Li 2020	74.96	6.58	48	84.69	15.49	48	3.0%	-9.73 [-14.49, -4.97]	<del></del>
Liu Y 2020	60.1	1.3	61	72.3	1.6	61	3.4%	-12.20 [-12.72, -11.68]	•
Luo 2021	62.84			68.51	7.47	60	3.3%	-5.67 [-8.15, -3.19]	<del></del>
Ma 2020	64.73			87.52	1.49	43	3.4%	-22.79 [-23.35, -22.23]	•
Mansour 2011	-24	13	30	-3	7.7	23	2.9%	-21.00 [-26.62, -15.38]	
Moiseev 2011	64	3.17	26	65	3.71	23	3.3%	-1.00 [-2.95, 0.95]	+
Nguyen 2018	86	5.2	14	104	8.37	5	2.6%	-18.00 [-25.83, -10.17]	
Ordu 2015	68.36	8.32	49	80.4	8.3	49	3.2%	-12.04 [-15.33, -8.75]	
Pan 2020	68.7	7.3	25	72.3	6.1	25	3.2%	-3.60 [-7.33, 0.13]	<del></del>
Raja 2017	63.8	3.6	63	75.9	8.4	62	3.3%	-12.10 [-14.37, -9.83]	<del></del>
Sallam 2016	69	11	50	78	17	50	2.9%	-9.00 [-14.61, -3.39]	
Su DL 2020	77.31	4.28		84.23	5.21	30	3.3%	-6.92 [-9.33, -4.51]	
Sun 2020	75	6	50	86	6	50	3.3%	-11.00 [-13.35, -8.65]	<del></del>
Tarlovskaya 2011	67.7		8	77	10	10	2.2%	-9.30 [-19.89, 1.29]	
Tsutsui 2.5mg 2016	66.6	7.2	41	79.8	9.4	20	3.1%	-13.20 [-17.87, -8.53]	
Tsutsui 2019	66.7		127	76.6	10.7	127	3.3%	-9.90 [-12.62, -7.18]	<del></del>
Tsutsui 5mg 2016	66.8	8.8	40	79.8	9.4	21	3.0%	-13.00 [-17.86, -8.14]	
Wei 2019	72.03			86.35	8.62	32		-14.32 [-17.63, -11.01]	<del></del>
Xu 2019	67.8	5.1	38	71.1	7.8	39	3.3%	-3.30 [-6.24, -0.36]	
Yang WT 2019	65.4	8.4	40	73.9	7.5	40	3.2%	-8.50 [-11.99, -5.01]	<del></del>
Yu 2019	64.9	6.2	33	76.7	8.8	33	3.2%	-11.80 [-15.47, -8.13]	<del></del>
Zhang 2021	68.32			74.23	4.02	47	3.4%	-5.91 [-7.40, -4.42]	-
Zhang Y 2020	68	3	27	74	3	27	3.4%	-6.00 [-7.60, -4.40]	<del></del>
Zhou 2020	70.5	6.3	43	85.3	7.6	43	3.3%	-14.80 [-17.75, -11.85]	
Total (95% CI)			1395			1328	100.0%	-10.83 [-13.42, -8.23]	•
Heterogeneity: Tau <sup>2</sup> = 51.4	16; Chi²=	1845	.57, df=	= 31 (P ·	< 0.000	01); l² =	98%		-20 -10 0 10 20
Test for overall effect: $Z = 0$	3.19 (P ≤	0.000	01)						Favours ivabradine Favours control

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.

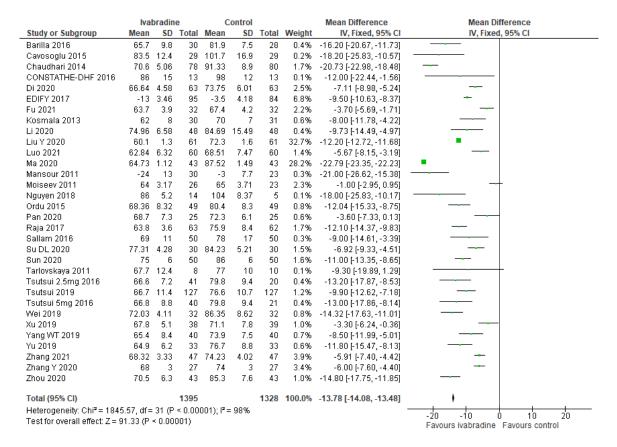


Figure 68 - Forest plot of the meta-analysis of resting heart rate at follow-up using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to decrease the resting heart rate at follow-up by 13.78 beats per minute at follow-up.

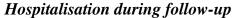
Left ventricular ejection fraction

Study or Subgroup	lval Mean	bradine SD	Total	Co Mean	ontrol SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference 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]	<del></del>
Barilla 2016	4.1	2.5	30	0.8	1.2	28	1.5%	3.30 [2.30, 4.30]	-
3i 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		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]	<del></del>
Chaudhari 2014	35	3.71	78	33	4.24	80	1.5%	2.00 [0.76, 3.24]	<del></del>
Cheng 2017	48.25	6.68	45	42.64	8.4	45	1.3%	5.61 [2.47, 8.75]	<del></del>
Chen G 2020	58.49	5.51	30	49.67	4.16	30	1.4%	8.82 [6.35, 11.29]	<del></del>
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]	<del></del>
Di 2020	49.98	4.98	63	44.67	4.5	63	1.5%	5.31 [3.65, 6.97]	<del></del>
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]	<del></del>
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]	<del></del>
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]	<del></del>
.i 2018	52.5	2.5	45	41.9	2.6	44	1.5%	10.60 [9.54, 11.66]	
.i 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]	
.iu 2019	57.6	6.7	48	47.9	8.7	48	1.3%	9.70 [6.59, 12.81]	
.iu 2020	51.54	1.18	49	41.29	0.94	49	1.5%	10.25 [9.83, 10.67]	-
_u 2019	41.27	4.65	28	38.1		27	1.4%	3.17 [0.84, 5.50]	<del></del>
_uo 2021	48.29	5.32	60	45.31		60	1.5%	2.98 [1.21, 4.75]	
1a 2016	36	3.11	30	32.3		30	1.5%	3.70 [2.16, 5.24]	
/la 2020	58.01	8.39	43	46.32		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]	<del></del>
Manz 2003	37.2	10.01	27	38.4	9.3	11	0.8%	-1.20 [-7.87, 5.47]	<del></del>
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]	<del></del>
an 2020	36.5	6	25	33.7	8.8	25	1.2%	2.80 [-1.38, 6.98]	<del>                                     </del>
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]	<del></del>
Sallam 2016	42	17	50	37	13	50	0.9%	5.00 [-0.93, 10.93]	<del>                                     </del>
3hen 2018	51.2	1.6	56	43.2	1.3	56	1.5%	8.00 [7.46, 8.54]	-
3HIFT 2010	34.7	10.2	204	31.5	10	199	1.4%	3.20 [1.23, 5.17]	<del></del>
3ong 2021	63.16	3.17	48	51.67	3.46	48	1.5%	11.49 [10.16, 12.82]	<del></del>
3u 2020	52.1	4.2	40	46.2	5	30	1.4%	5.90 [3.69, 8.11]	
3u DL 2020	45.28	4.14	30	39.56	5.21	30	1.4%	5.72 [3.34, 8.10]	
3un 2021	50.2	5.6	59	43.4	5.5	59	1.4%	6.80 [4.80, 8.80]	
Гang 2018	41.1	4.93	31	38	4.59	31	1.4%	3.10 [0.73, 5.47]	<del></del>
Fatarchenko 2008	58.9	2.8	29	51.2	4.1	30	1.5%	7.70 [5.91, 9.49]	
Fsutsui 2.5mg 2016	33.8	8.7	41	31	8.8	20	1.1%	2.80 [-1.89, 7.49]	<del></del>
rsutsui 2019	38.9	12.8	127	33.3	13	127	1.3%	5.60 [2.43, 8.77]	
rsutsui 5mg 2016	35	10.4	40	31	8.8	21	1.1%	4.00 [-0.96, 8.96]	<del> </del>
/atinian 2015	51.2	2.1	26	45.3	1.9	26	1.5%	5.90 [4.81, 6.99]	<del></del>
Wang 2019	37.79	5.23	35	37.32	4.86	33	1.4%	0.47 [-1.93, 2.87]	<del></del>
Wang FC 2017	42.51	6.03	53	36.78	7.4	43	1.4%	5.73 [2.99, 8.47]	
Vang GK 2020	55.3	10.4	36	52.2		36	1.1%	3.10 [-1.87, 8.07]	<del> </del>
Vang ليا 2020	58.63	4.25	35	52.34		35	1.4%	6.29 [4.35, 8.23]	
Vang RM 2017	49.06	7.05	39	43.03		39	1.3%	6.03 [2.94, 9.12]	
Vang YH 2018	55.35	7.1	34	52.86	6.2	34	1.3%	2.49 [-0.68, 5.66]	+
Vei 2019	48.14	2.62	32	41.69		32	1.5%	6.45 [5.47, 7.43]	-
(ia 2016	48.25	6.65	39	41.57	5.96	39	1.4%	6.68 [3.88, 9.48]	
(u 2019	46.2	3.8	38	43.9	3.4	39	1.5%	2.30 [0.69, 3.91]	
(u 2020	49.83	3.25	61	45.01		61	1.5%	4.82 [3.75, 5.89]	
ang WT 2019	48.3	5.4	40	43.2	6.5	40	1.4%	5.10 [2.48, 7.72]	
/ang Z 2019	46.87	6.38	67	43.61	6.82	68	1.4%	3.26 [1.03, 5.49]	
′ao 2016	38.22	4.86	36	34.23		36	1.4%	3.99 [2.03, 5.95]	
/i 2017	37.72	7.6	43	31.84	6.08	42	1.3%	5.88 [2.96, 8.80]	
/u 2019	29.3	3	33	27.7	3.4	33	1.5%	1.60 [0.05, 3.15]	<del></del>
/ue 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]	
hang 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]	
Thang 2021	48.32	4.23	47	43.76		47	1.5%	4.56 [2.87, 6.25]	
Zhang J 2019	35.16	2.68	45	35.34		41	1.5%	-0.18 [-1.35, 0.99]	+
Zhang XJ 2019	51.77	3.84	55	38.02	2.63	55		13.75 [12.52, 14.98]	-
Thang Y 2020	57	12	27	51	12	27	0.9%	6.00 [-0.40, 12.40]	<del>                                     </del>
Zhou 2019	47.89	7.89	30	34.34		30		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]	
otal (95% CI)			3323			3230	100.0%	5.43 [4.52, 6.34]	•
	5: Chi <b>3</b> = 1	1459 20		3 (P < n ∩	000011				-10 -5 0 5 10
eterogeneity: Tau² = 13.8									

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%.

Study or Subarons		oradine	Total	Co Mean	ntrol SD	Total	Weight	Mean Difference	Mean Difference IV, Fixed, 95% CI
Study or Subgroup Abdel-Salam 2015	Mean 39	7	Total 20	33	10	23	Weight 0.1%	IV, Fixed, 95% CI 6.00 [0.89, 11.11]	IV, Fixed, 95% CI
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]	-
3i 2020	63.06	9.85	99		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]	<del></del>
Chaudhari 2014	35	3.71	78	33	4.24	80	2.3%	2.00 [0.76, 3.24]	<del></del>
Cheng 2017	48.25	6.68	45	42.64	8.4	45	0.4%	5.61 [2.47, 8.75]	<del></del>
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]	<del></del>
CONSTATHE-DHF 2016	29	8	13	25	8	13	0.1%	4.00 [-2.15, 10.15]	<del>+</del>
Di 2020	49.98	4.98	63	44.67	4.5	63	1.3%	5.31 [3.65, 6.97]	
u 2021	51.6	5.3	32	49	4.8	32	0.6%	2.60 [0.12, 5.08]	<del></del>
3uo 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		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]	<del></del>
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		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]	
_iu 2019	57.6	6.7	48	47.9	8.7	48	0.4%	9.70 [6.59, 12.81]	
_iu 2020	51.54	1.18	49	41.29		49	20.1%	10.25 [9.83, 10.67]	
_u 2019	41.27	4.65	28	38.1	4.15	27	0.7%	3.17 [0.84, 5.50]	
_uo 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		30	1.5%	3.70 [2.16, 5.24]	—
/la 2020 /lanagus 2011	58.01	8.39	43	46.32		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		10.01	27	38.4	9.3	11	0.1%	-1.20 [-7.87, 5.47]	<u> </u>
Mao 2018 Maio agu 2011	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	4.25	25	33.7	8.8	25	0.2%	2.80 [-1.38, 6.98]	<u></u>
Qi 2019 Paia 2017	41.69 30.1	4.25 4	48 63	37.25 28.1	3.92	48 62	1.3%	4.44 [2.80, 6.08]	<u> </u>
Raja 2017 Ballam 2016	42	17	50	37	13	50	1.8% 0.1%	2.00 [0.60, 3.40] 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	1.3	199	0.9%	3.20 [1.23, 5.17]	<u> </u>
30ng 2021	63.16	3.17	48	51.67		48		11.49 [10.16, 12.82]	
3u 2020	52.1	4.2	40	46.2	5.40	30	0.7%	5.90 [3.69, 8.11]	
3u DL 2020	45.28	4.14	30	39.56	5.21	30	0.6%	5.72 [3.34, 8.10]	
3un 2021	50.2	5.6	59	43.4	5.5	59	0.9%	6.80 [4.80, 8.80]	
Fang 2018	41.1	4.93	31	38	4.59	31	0.6%	3.10 [0.73, 5.47]	<del></del> -
Tatarchenko 2008	58.9	2.8	29	51.2	4.1	30	1.1%	7.70 [5.91, 9.49]	<del></del>
rsutsui 2.5mg 2016	33.8	8.7	41	31	8.8	20	0.2%	2.80 [-1.89, 7.49]	<del></del>
rsutsui 2019	38.9	12.8	127	33.3	13	127	0.4%	5.60 [2.43, 8.77]	<del></del>
rsutsui 5mg 2016	35	10.4	40	31	8.8	21	0.1%	4.00 [-0.96, 8.96]	<del></del>
/atinian 2015	51.2	2.1	26	45.3	1.9	26	3.0%	5.90 [4.81, 6.99]	<del>-</del>
Vang 2019	37.79	5.23	35	37.32		33	0.6%	0.47 [-1.93, 2.87]	<del></del>
Vang FC 2017	42.51	6.03	53	36.78	7.4	43	0.5%	5.73 [2.99, 8.47]	
Vang GK 2020	55.3	10.4	36	52.2		36	0.1%	3.10 [-1.87, 8.07]	+
2020 ليا Vang	58.63	4.25	35	52.34		35	1.0%	6.29 [4.35, 8.23]	
Vang RM 2017	49.06	7.05	39	43.03		39	0.4%	6.03 [2.94, 9.12]	
Vang YH 2018	55.35	7.1	34	52.86	6.2	34	0.4%	2.49 [-0.68, 5.66]	<del> </del>
Vei 2019	48.14	2.62	32	41.69		32	3.7%	6.45 [5.47, 7.43]	-
(ia 2016	48.25	6.65	39	41.57	5.96	39	0.5%	6.68 [3.88, 9.48]	
(u 2019	46.2	3.8	38	43.9	3.4	39	1.4%	2.30 [0.69, 3.91]	<del></del>
(u 2020	49.83	3.25	61	45.01		61	3.1%	4.82 [3.75, 5.89]	
ang WT 2019	48.3	5.4	40	43.2	6.5	40	0.5%	5.10 [2.48, 7.72]	
/ang Z 2019	46.87	6.38	67	43.61		68	0.7%	3.26 [1.03, 5.49]	
/ao 2016	38.22	4.86	36	34.23		36	0.9%	3.99 [2.03, 5.95]	
/i 2017	37.72	7.6	43	31.84		42	0.4%	5.88 [2.96, 8.80]	
/u 2019	29.3	3	33	27.7	3.4	33	1.5%	1.60 [0.05, 3.15]	<del> </del>
/ue 2016	39.78	3.44	40	37.7		40	1.6%	2.08 [0.61, 3.55]	
Zeng FC 2019	59.36	6.25	33	53.17		32	0.4%	6.19 [3.33, 9.05]	
Zeng XM 2019	57.6	4.2	45	45.2	4.7	45		12.40 [10.56, 14.24]	
Zhang 2019	67	8	30	62	5.4	30	0.3%	5.00 [1.55, 8.45]	<del></del>
Zhang 2020	50.21	6.47	43	45.19		42	0.4%	5.02 [2.17, 7.87]	
Zhang 2021	48.32	4.23	47	43.76		47	1.3%	4.56 [2.87, 6.25]	
Zhang J 2019	35.16	2.68	45	35.34		41	2.6%	-0.18 [-1.35, 0.99]	<b>T</b>
Zhang XJ 2019	51.77	3.84	55	38.02		55		13.75 [12.52, 14.98]	-
Zhang Y 2020	57	12	27	51	12	27	0.1%	6.00 [-0.40, 12.40]	<u> </u>
Zhou 2019	47.89	7.89	30	34.34		30		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 (05% CI)			3333			3330	100.0%	6 63 16 44 6 021	1
otal (95% CI)			3323		.,	JZ30	100.0%	6.63 [6.44, 6.82]	
leterogeneity: Chi² = 1459	100 44 -								

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%.



-	lvabrad	dine	Conti	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Abdel-Salam 2015	1	20	2	23	0.1%	0.57 [0.06, 5.88]	
Adamyan 2008	4	70	11	75	0.4%	0.39 [0.13, 1.17]	<del></del>
Babushkina 2020	8	56	14	53	0.6%	0.54 [0.25, 1.18]	<del></del>
Bansal 2019	19	78	44	80	1.8%	0.44 [0.29, 0.69]	<del></del>
BEAUTIFUL 2008	681	5479	704	5438	29.9%	0.96 [0.87, 1.06]	•
CONSTATHE-DHF 2016	1	13	0	13	0.0%	3.00 [0.13, 67.51]	<del></del>
Luo 2021	4	60	10	60	0.4%	0.40 [0.13, 1.21]	
Moiseev 2011	3	26	6	23	0.3%	0.44 [0.12, 1.57]	<del></del>
SHIFT 2010	1231	3241	1356	3264	57.2%	0.91 [0.86, 0.97]	•
Tsutsui 2019	55	127	63	127	2.7%	0.87 [0.67, 1.14]	<del>-</del>
Tumasyan 2016	17	53	29	53	1.2%	0.59 [0.37, 0.93]	<del></del>
Tumasyan 2017	33	53	47	57	1.9%	0.76 [0.59, 0.96]	<del></del>
Tumasyan 2018	28	46	38	45	1.6%	0.72 [0.55, 0.94]	<del></del>
Wang GK 2020	1	36	2	36	0.1%	0.50 [0.05, 5.27]	· · ·
Wang Q 2017	3	56	10	57	0.4%	0.31 [0.09, 1.05]	-
Wang RM 2017	4	39	9	39	0.4%	0.44 [0.15, 1.32]	<del></del>
Zhou 2019	12	30	19	30	0.8%	0.63 [0.38, 1.06]	<del></del>
Total (95% CI)		9483		9473	100.0%	0.89 [0.85, 0.94]	•
Total events	2105		2364				
Heterogeneity: Chi² = 34.25	5, df = 16	(P = 0.0)	005); I² =	53%			0.01 0.1 1 10 100
Test for overall effect: Z = 4	.57 (P < 0	.00001	)				0.01 0.1 1 10 100 Favours ivabradine Favours control
							i avours ivabraume   Favours Common

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.

	lvabrad	line	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Abdel-Salam 2015	1	20	2	23	0.3%	0.57 [0.06, 5.88]	<del></del>
Adamyan 2008	4	70	11	75	1.3%	0.39 [0.13, 1.17]	<del></del>
Babushkina 2020	8	56	14	53	2.3%	0.54 [0.25, 1.18]	<del></del>
Bansal 2019	19	78	44	80	6.1%	0.44 [0.29, 0.69]	
BEAUTIFUL 2008	681	5479	704	5438	19.3%	0.96 [0.87, 1.06]	•
CONSTATHE-DHF 2016	1	13	0	13	0.2%	3.00 [0.13, 67.51]	<del></del>
Luo 2021	4	60	10	60	1.2%	0.40 [0.13, 1.21]	<del></del>
Moiseev 2011	3	26	6	23	1.0%	0.44 [0.12, 1.57]	<del></del>
SHIFT 2010	1231	3241	1356	3264	20.8%	0.91 [0.86, 0.97]	•
Tsutsui 2019	55	127	63	127	11.2%	0.87 [0.67, 1.14]	<del></del>
Tumasyan 2016	17	53	29	53	5.6%	0.59 [0.37, 0.93]	
Tumasyan 2017	33	53	47	57	12.2%	0.76 [0.59, 0.96]	
Tumasyan 2018	28	46	38	45	11.2%	0.72 [0.55, 0.94]	
Wang GK 2020	1	36	2	36	0.3%	0.50 [0.05, 5.27]	
Wang Q 2017	3	56	10	57	1.0%	0.31 [0.09, 1.05]	-
Wang RM 2017	4	39	9	39	1.3%	0.44 [0.15, 1.32]	<del></del>
Zhou 2019	12	30	19	30	4.7%	0.63 [0.38, 1.06]	<del></del>
Total (95% CI)		9483		9473	100.0%	0.75 [0.66, 0.86]	<b>•</b>
Total events	2105		2364				
Heterogeneity: Tau² = 0.02;	Chi <sup>2</sup> = 3	4.25, df	= 16 (P =	0.005	); I <sup>z</sup> = 53%	5	0.01 0.1 1 10 100
Test for overall effect: Z = 4	.38 (P < 0	.0001)					0.01 0.1 1 10 100 Favours ivabradine Favours control
							Favours ivabraume Favours Control

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.



		bradine		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Cavosoglu 2015	195	96	29	166	52	29	1.1%	29.00 [-10.74, 68.74]	<del></del>
Cheng 2017	322.33	175.15	45	235.56	171.25	45	0.3%	86.77 [15.20, 158.34]	
Cong 2018	522.19	52.35	45	442.14	42.12	45	4.4%	80.05 [60.42, 99.68]	
EDIFY 2017	4.3	50	84	7.9	67.9	84	5.2%	-3.60 [-21.63, 14.43]	<del></del>
Fu 2021	284.3	45	32	346.1	60.5	32	2.5%	-61.80 [-87.92, -35.68]	
Gou 2017	198.7	56.31	30	162.01	57.36	30	2.0%	36.69 [7.93, 65.45]	<del></del>
Guo 2017	454.752	35.173	16	415.375	52.456	16	1.8%	39.38 [8.43, 70.32]	<del></del>
He 2019	428.1	25.52	30	350.8	26.8	31	9.8%	77.30 [64.17, 90.43]	<del></del>
Huang J 2017	386.41	101.75	52	306.24	135.87	50	0.8%	80.17 [33.45, 126.89]	
Li 2018	421.1	31.5	45	382.1	31.2	44	9.9%	39.00 [25.97, 52.03]	
Liu 2019	523.27	45.46	49	446.25	39.23	49	6.0%	77.02 [60.21, 93.83]	
Liu Y 2020	386	38	61	331	45	61	7.7%	55.00 [40.22, 69.78]	
Lu 2019	427.57	46.61	28	367.27	52.23	27	2.5%	60.30 [34.10, 86.50]	
Luo 2021	357.57	70.86	60	303.12	72.13	60	2.6%	54.45 [28.87, 80.03]	
Ma 2016	336	53.66	30	344.3	42.71	30	2.8%	-8.30 [-32.84, 16.24]	<del></del>
Manz 2003	379	117	30	307	98	30	0.6%	72.00 [17.39, 126.61]	
Mao 2018	379	117	30	307	98	30	0.6%	72.00 [17.39, 126.61]	
Pan 2020	378.6	48.5	19	366.2	42.8	18	1.9%	12.40 [-17.04, 41.84]	<del></del>
Raja 2017	493.5	4.6	63	367	82	62	4.0%	126.50 [106.06, 146.94]	·
Song 2021	340.62	65.69	48	289.62	45.66	48	3.3%	51.00 [28.37, 73.63]	
Su DL 2020	422.54	51.24	30	378.76	39.67	30	3.1%	43.78 [20.59, 66.97]	_ <del></del>
Wang FC 2017	384.2	43	53	278.5	82.7	43	2.3%	105.70 [78.41, 132.99]	
Wang GK 2020	347.9	80.8	36	299.1	87.2	36	1.1%	48.80 [9.97, 87.63]	
Xu 2020	396.52	36	61	341	30	61	12.2%	55.52 [43.76, 67.28]	
Yu 2019	402.2	53.7	33	351.3	44.5	33	3.0%	50.90 [27.11, 74.69]	
Yue 2016	341.7	76.69	40	313.83	72.98	40	1.6%	27.87 [-4.94, 60.68]	<del>                                     </del>
Zhang J 2019	336.19	47.02	36	308.75	60.33	28	2.3%	27.44 [0.32, 54.56]	
Zhang XJ 2019	411.47	123.49	55	324.21	102.55	55	0.9%	87.26 [44.84, 129.68]	
Zhou 2019	270.24	43.34	30	256.9	47.65	30	3.2%	13.34 [-9.71, 36.39]	<del>  • • •</del>
Zhou 2020	361.7	97.5	43	294.6	104.8	43	0.9%	67.10 [24.32, 109.88]	<del></del>
Total (95% CI)			1243			1220	100.0%	50.62 [46.52, 54.72]	•
Heterogeneity: Chi² = Test for overall effect:				01); I² = 89	%				-100 -50 0 50 100 Favours control Favours ivabradine

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.

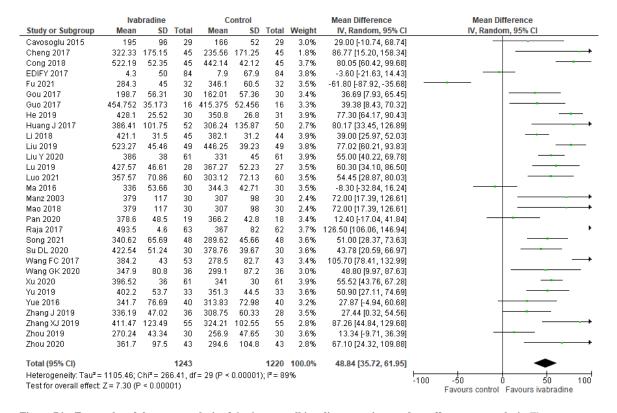


Figure 74 – Forest plot of the meta-analysis of 6-minutes walking distance using random-effects meta-analysis. The meta-analysis shows evidence of a beneficial effect of ivabradine versus control (placebo or no intervention) of 48.84 meters per 6 minutes.

Einst andh an	Vacan	Publication	No nondenical	Clinical 1:4:(-)	A	0/ famala	Interv	entions
First author	Year	type	No. randomised	Clinical condition(s)	Age	%-female	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
Не	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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Unclear	No information
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "Randomization was performed
generation		by computer-generated allocation
		schedule drawn by an independent
		statistician."
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: "Study drugs were identical in
personnel		appearance. Both the patients and the
		investigators performing the baseline and
		follow-up assessment were blinded to the
		treatment allocation."
Blinding of outcome	Unclear	Not mentioned
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to standard
personnel		care. Therefore, the participants and
		personnel were probably unblinded.
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to standard
personnel		care. Therefore, the participants and
		personnel were probably unblinded.
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to standard
personnel		care. Therefore, the participants and
		personnel were probably unblinded.
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to carvedilol.
personnel		Therefore, the participants and personnel
•		were probably unblinded.
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to standard
personnel		care. Therefore, the participants and
		personnel were probably unblinded.
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine and bisoprolol was compared
personnel		to bisoprolol alone. Therefore, the
		participants and personnel were probably
		unblinded.
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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
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Barilla 2016		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "patients were assigned to the two
generation		treatment groups according to a
		computer-generated list of
		randomisation"
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	High	Only the echocardiographer was blinded
assessment		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	Low	Quote: "the random-allocation schedule
generation		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	Low	Quote: "double-blind" and "randomised
personnel		to ivabradine or matched placebo"
Blinding of outcome	Low	Quote: "prespecified events were
assessment		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	Protocol registered retrospectively.
		However, serious adverse events and all-
	High for serious	cause mortality was reported.
	adverse events and	
	hospitalisations	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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Unclear	Reported as placebo-controlled, but no
personnel		mention of blinding
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Chen G 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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

Blinding of participants and	High	Quote: "open-label"
personnel		
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

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

Chumburidze 2013		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: "double-blind"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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
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Di 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

<b>EDIFY 2017</b>		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	Quote: "the randomisation was balanced
generation		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	Low	Quote: "double-blind" and "study
personnel		investigators and participants were
		masked to treatment for the duration of
		the trial
Blinding of outcome	Low	Quote: "The trial was conducted under
assessment		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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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

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

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

He 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	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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.

Kosmala 2013		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "The procedure of randomization
generation		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	Low	Quote: "The hospital pharmacies were
personnel		responsible for drug randomization and
		dispensing, and both the investigators and
		patients were blinded to the treatment
		option."
Blinding of outcome	Unclear	No information
assessment		
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	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

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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Liu YY 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: "participants and researchers were
personnel		unaware of allocation"
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

Lu 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	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Luo 2021		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Ma 2016		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: "double-blind, placebo-
personnel		controlled"
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

Ma 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "A computer-driven
generation		randomization program was used to
		allocate"
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to no
personnel		intervention. Therefore, the participant
		and personnel were probably unblinded.
Blinding of outcome	High	No information. Only echocardiographer
assessment		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	Unclear	No information
generation		
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	Unclear	No information
assessment		
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	Low	Quote: "double-blind"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	Quote: "lottery"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"

personnel		
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

Raja 2017		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	"Computerized random number
generation		generation protocol"
Allocation concealment	Unclear	No information
Blinding of participants and	High	Only echocardiographer blinded
personnel		
Blinding of outcome	High	Only echocardiographer blinded
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Unclear	No information
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "computerized sequence
generation		generation"
Allocation concealment	Low	Quote: "ivabradine and placebo were
		prepared in numbered anonymous

		bottles"
Blinding of participants and personnel	High	Quote: "single-blind"
1		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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
Selective reporting	Low	secondary outcomes.  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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 information

Sun 2021		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Unclear	Reported as "placebo-controlled", but no
personnel		information on blinding

Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open randomised controlled
personnel		study"
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: "The patients and investigators
personnel		were masked to the treatment allocation"
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "A minimization method for
generation		dynamic allocation was used with
		adjustment for study site, baseline resting
		HR ( $\geq$ 85 and $\leq$ 85 beats/min), and β-

		blocker dose before study treatment (0,
		>0–<50, and $\geq$ 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	Low	Quote: "Patients and investigators were
personnel		masked to treatment allocation, and study
		medications (ivabradine or placebo) were
		the same size and color."
Blinding of outcome	Low	Quote: ""An endpoint adjudication
assessment		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	Unclear	No information
generation		
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	Unclear	No information
assessment		
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	Unclear	No information
generation		
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.

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.

Tumagyan 2017		
Tumasyan 2017	Ι	
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
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	Unclear	No information
assessment		
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	Unclear	No information
generation		
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	Unclear	No information
assessment	Unclear	No information
Incomplete outcome data		- 10
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	Unclear	No information
generation		
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	Unclear	No information
assessment		
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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 FC 2017		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information

Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
Incomplete outcome data	Low	No loss to follow-up
Incomplete outcome data Selective reporting	Low Unclear	No loss to follow-up No information
	_ · · ·	*

Wang JJ 2017		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 Q 2017		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 GK 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		_
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 LJ 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Wei 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	High	Quote: "open-label"
personnel		
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

Xia 2016		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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

Xu 2019		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Xu 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Xue 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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	High	Quote: "open-label"
personnel		
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

Yang Z 2019		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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
<u> </u>		
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: "double-blind, placebo-

personnel		controlled"
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

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

Yu 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	High	Quote: "open-label"
personnel		
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

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

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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Zhang 2019		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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
----------

<b>Zhang J 2019</b>		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Low	Quote: "sequential opaque envelopes"
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 information

<b>Zhang 2020</b>		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		_
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

# **Zhang Y 2020**

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

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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 information

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

Blinding of participants and	High	Quote: "open-label"
personnel		
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 information

Zhou 2020					
Bias domain	Authors' judgement	Support for judgement			
Random sequence	Low	Quote: "random-number table"			
generation					
Allocation concealment	Unclear	No information			
Blinding of participants and	High	Quote: "open-label"			
personnel					
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 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 心则梗死 OR 心则能不全)) 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))

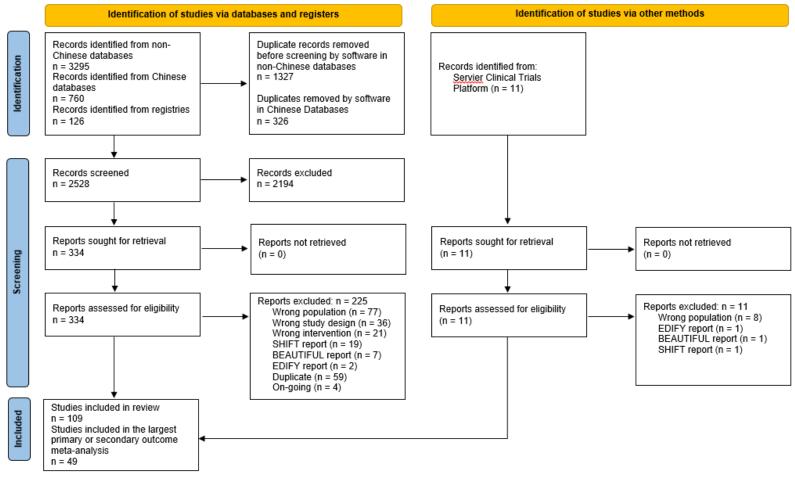
#### China National Knowledge Infrastructure (CNKI), n = 255

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, doj: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 1 – PRISMA flowchart.

# Supplement 4 - Risk of bias

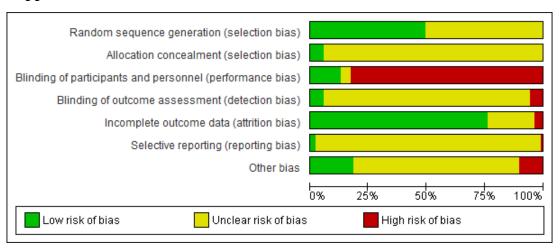


Figure 2 - Risk of bias graph.



	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
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	?	?	•	?	?	?	?

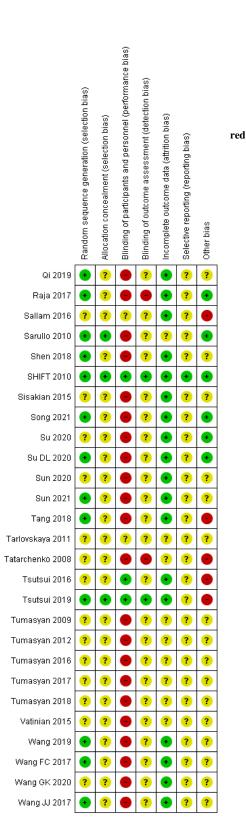




Figure 3 – Risk of bias summary. Green circles = low risk of bias; yellow circles = unclear risk of bias; circles = high risk of bias.

# **Supplement 5 - All-cause mortality** *Main analyses*

lvabrad	line	Contr	ol	Risk Ratio		Risk	Ratio
Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	om, 95% CI
1	20	1	23	0.0%	1.15 [0.08, 17.22]		
19	51	27	53	0.0%	0.73 [0.47, 1.14]		
2	12	2	12	0.0%	1.00 [0.17, 5.98]		
2	30	4	28	0.0%	0.47 [0.09, 2.35]		
572	5479	547	5438	49.9%	1.04 [0.93, 1.16]	_	<del>                                     </del>
4	41	12	41	0.0%	0.33 [0.12, 0.95]		
1	13	4	13	0.0%	0.25 [0.03, 1.95]		
3	94	0	84	0.0%	6.26 [0.33, 119.51]		
1	34	2	34	0.0%	0.50 [0.05, 5.26]		
2	85	5	84	0.0%	0.40 [0.08, 1.98]		
3	27	3	23	0.0%	0.85 [0.19, 3.82]		
2	26	4	23	0.0%	0.44 [0.09, 2.20]		
1	14	0	5	0.0%	1.20 [0.06, 25.53]		
1	63	1	62	0.0%	0.98 [0.06, 15.39]		
503	3241	552	3264	50.1%	0.92 [0.82, 1.03]		+
3	8	0	10	0.0%	8.56 [0.51, 144.86]		
9	127	9	127	0.0%	1.00 [0.41, 2.44]		
41	104	59	106	0.0%	0.71 [0.53, 0.95]		
24	53	30	57	0.0%	0.86 [0.59, 1.26]		
19	46	28	45	0.0%	0.66 [0.44, 1.00]		
1	36	1	36	0.0%	1.00 [0.07, 15.38]		
0	43	1	42	0.0%	0.33 [0.01, 7.78]		
	8720		8702	100.0%	0.98 [0.86, 1.10]	<	
1075		1099					
Chi <sup>2</sup> = 2.	37, df=	1 (P = 0	.12); l <sup>z</sup> =	= 58%			1 1.2 1.5
.40 (P = 0	.69)						
	1 19 2 2 572 4 1 1 3 3 1 1 2 2 3 3 2 2 1 1 503 3 9 9 41 1 24 19 1 0 0 1075 ; Chi₹= 2.	1 20 19 51 2 12 2 30 572 5479 4 41 1 13 3 94 1 34 2 85 3 27 2 26 1 1 64 1 63 503 3241 3 8 9 127 41 104 24 53 19 46 1 36 0 43	Events         Total         Events           1         20         1           19         51         27           2         12         2           2         30         4           572         5479         547           4         41         12           1         13         4           3         94         0           1         34         2           2         85         5           3         27         3           2         26         4           1         14         0           1         63         1           503         3241         552           3         8         0           9         127         9           41         104         59           24         53         30           19         46         28           1         36         1           0         43         1           8         1         1           1075         1099         107           1076         1076         1076	Events         Total         Events         Total           1         20         1         23           19         51         27         53           2         12         2         12           2         30         4         28           572         5479         547         5438           4         41         12         41           1         13         4         13           3         94         0         84           1         34         2         34           2         85         5         84           3         27         3         23           2         26         4         23           1         63         1         62           503         3241         552         3264           3         8         0         10           9         127         9         127           41         104         59         106           24         53         30         57           19         46         28         45           1         36	Events         Total         Events         Total         Weight           1         20         1         23         0.0%           19         51         27         53         0.0%           2         12         2         12         0.0%           572         5479         547         5438         49.9%           4         41         12         41         0.0%           3         94         0         84         0.0%           1         34         2         34         0.0%           2         85         5         84         0.0%           2         26         4         23         0.0%           2         26         4         23         0.0%           1         14         0         5         0.0%           3         321         552         3264         50.1%           41         104         59         106         0.0%           41         104         59         106         0.0%           44         104         59         106         0.0%           45         3         30         57	Events         Total         Events         Total         Weight         M-H, Random, 95% CI           1         20         1         23         0.0%         1.15 [0.08, 17.22]           19         51         27         53         0.0%         0.73 [0.47, 1.14]           2         12         2         12         0.0%         1.00 [0.17, 5.98]           572         5479         547         5438         49.9%         0.47 [0.09, 2.35]           4         41         12         41         0.0%         0.33 [0.12, 0.95]           1         13         4         13         0.0%         0.25 [0.03, 1.95]           3         94         0         84         0.0%         0.25 [0.03, 1.95]           3         94         0         84         0.0%         0.25 [0.03, 1.95]           3         94         0         84         0.0%         0.50 [0.05, 5.26]           2         85         5         84         0.0%         0.40 [0.08, 1.98]           3         27         3         23         0.0%         0.44 [0.09, 2.20]           1         14         0         5         0.0%         0.44 [0.09, 2.20]	Events         Total         Events         Total         Weight         M-H, Random, 95% CI         M-H, Rand           1         20         1         23         0.0%         1.15 [0.08, 17.22]           19         51         27         53         0.0%         0.73 [0.47, 1.14]           2         12         2         12         0.0%         1.00 [0.17, 5.98]           2         30         4         28         0.0%         0.47 [0.09, 2.35]           572         5479         547         5438         49.9%         1.04 [0.93, 1.16]           4         41         12         41         0.0%         0.33 [0.12, 0.95]           1         13         4         13         0.0%         0.25 [0.03, 1.95]           3         94         0         84         0.0%         0.50 [0.05, 5.26]           2         85         5         84         0.0%         0.40 [0.08, 1.98]           3         27         3         23         0.0%         0.40 [0.08, 1.98]           3         27         3         23         0.0%         0.44 [0.09, 2.20]           1         14         0         5         0.0%         0.98 [0.06, 15.

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.

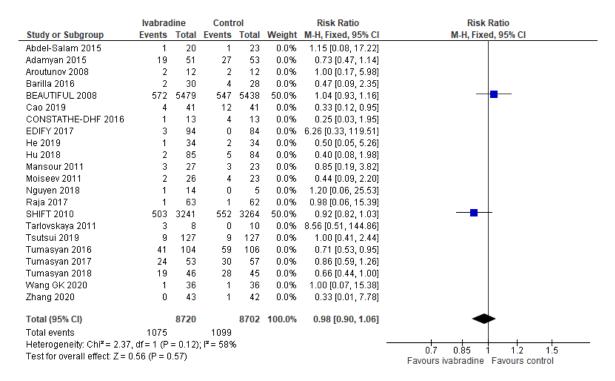


Figure 5 – Forest plot of the meta-analysis of all-cause mortality using fixed-effect meta-analysis including only trials at low risk of bias, except for for-profit bias. The meta-analysis showed no evidence of a difference between ivabradine versus placebo.

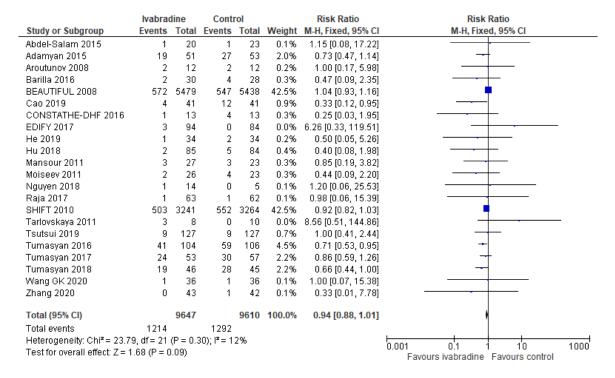


Figure 6 - Forest plot of the meta-analysis of all-cause mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

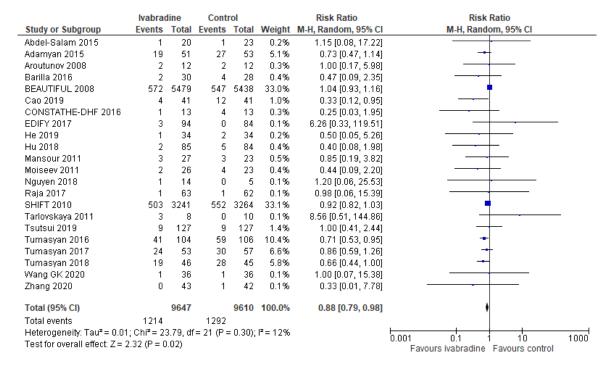
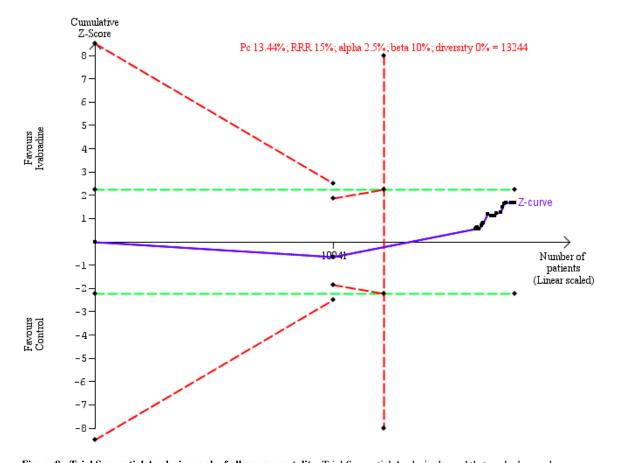
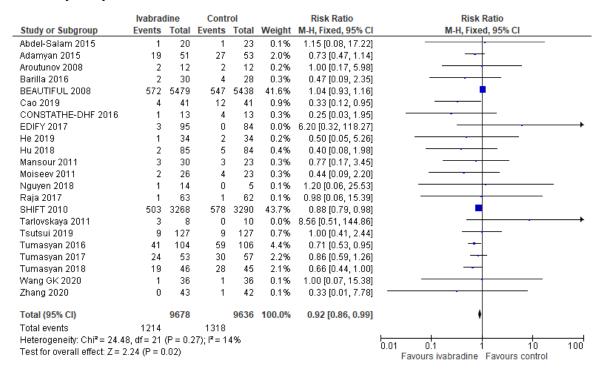


Figure 7 - Forest plot of the meta-analysis of all-cause mortality using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).



**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



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

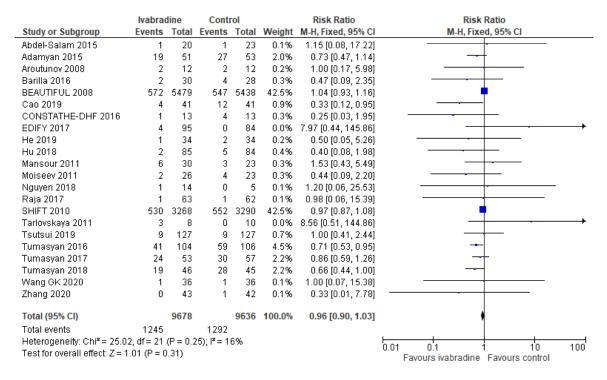
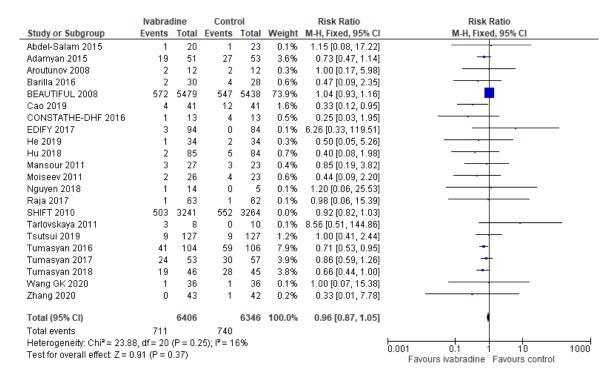


Figure 10 - Forest plot of the sensitivity analysis of all-cause mortality using worst- compared with best-case scenario.

lvabrad	dine	Contr	rol	Risk Ratio		Risk Ratio
Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1	20	1	23	0.1%	1.15 [0.08, 17.22]	<del></del>
19	51	27	53	3.6%	0.73 [0.47, 1.14]	<del> </del>
2	12	2	12	0.3%	1.00 [0.17, 5.98]	
2	30	4	28	0.6%	0.47 [0.09, 2.35]	<del></del>
572	5479	547	5438	0.0%	1.04 [0.93, 1.16]	
4	41	12	41	1.6%	0.33 [0.12, 0.95]	<del></del>
1	13	4	13	0.5%	0.25 [0.03, 1.95]	<del></del>
3	94	0	84	0.1%	6.26 [0.33, 119.51]	<del></del>
1	34	2	34	0.3%	0.50 [0.05, 5.26]	<del></del>
2	85	5	84	0.7%	0.40 [0.08, 1.98]	<del></del>
3	27	3	23	0.4%	0.85 [0.19, 3.82]	<del></del>
2	26	4	23	0.6%	0.44 [0.09, 2.20]	<del></del>
1	14	0	5	0.1%	1.20 [0.06, 25.53]	<del></del>
1	63	1	62	0.1%	0.98 [0.06, 15.39]	
503	3241	552	3264	73.9%	0.92 [0.82, 1.03]	
3	8	0	10	0.1%	8.56 [0.51, 144.86]	<del>                                     </del>
9	127	9	127	1.2%	1.00 [0.41, 2.44]	<del></del>
41	104	59	106	7.9%	0.71 [0.53, 0.95]	-
24	53	30	57	3.9%	0.86 [0.59, 1.26]	
19	46	28	45	3.8%	0.66 [0.44, 1.00]	<del></del>
1	36	1	36	0.1%	1.00 [0.07, 15.38]	
0	43	1	42	0.2%	0.33 [0.01, 7.78]	
	4168		4172	100.0%	0.87 [0.79, 0.95]	•
642		745				
7, df = 20	(P = 0.8)	66); I² = 0	%			0.001 0.1 10 1000
.95 (P = 0	0.003)					0.001 0.1 1 10 1000 Favours ivabradine Favours control
	Events  1 19 2 572 4 13 3 1 2 3 2 1 1 503 3 9 41 24 19 1 0 642 7, df= 20	1 20 19 51 2 12 2 30 572 5479 4 41 1 13 3 94 1 34 2 85 3 27 2 26 1 1 14 1 63 503 3241 3 8 9 127 41 104 24 53 19 46 1 36 0 43	Events         Total         Events           1         20         1           19         51         27           2         12         2           2         30         4           572         547         547           4         41         12           1         13         4           3         94         0           1         34         2           2         85         5           3         27         3           2         26         4           1         14         0           1         63         1           503         3241         552           3         8         0           9         127         9           41         104         59           24         53         30           19         46         28           1         36         1           0         43         1           41         28           1         36         1           0         43         1	Events         Total         Events         Total           1         20         1         23           19         51         27         53           2         12         2         12           2         30         4         28           572         5479         547         5438           4         41         12         41           1         13         4         13           3         94         0         84           1         34         2         34           2         85         5         84           3         27         3         23           2         26         4         23           1         14         0         5           1         63         1         62           503         3241         552         3264           3         8         0         10           9         127         9         127           41         104         59         106           24         53         30         57           19         46         2	Events         Total         Events         Total         Weight           1         20         1         23         0.1%           19         51         27         53         3.6%           2         12         2         12         0.3%           2         30         4         28         0.6%           572         5479         547         5438         0.0%           4         41         12         41         1.6%           1         13         4         13         0.5%           3         94         0         84         0.1%           1         34         2         34         0.3%           2         85         5         84         0.7%           3         27         3         23         0.4%           2         26         4         23         0.6%           1         14         0         5         0.1%           503         3241         552         3264         73.9%           41         104         59         106         7.9%           41         104         59         106	Events         Total         Events         Total         Weight         M-H, Fixed, 95% CI           1         20         1         23         0.1%         1.15 [0.08, 17.22]           19         51         27         53         3.6%         0.73 [0.47, 1.14]           2         12         2         12         0.3%         1.00 [0.17, 5.98]           2         30         4         28         0.6%         0.47 [0.09, 2.35]           572         5479         547         5438         0.0%         1.04 [0.93, 1.16]           4         41         12         41         1.6%         0.33 [0.12, 0.95]           1         13         4         13         0.5%         0.25 [0.03, 1.95]           3         94         0         84         0.1%         0.26 [0.33, 1.95]           1         34         2         34         0.3%         0.50 [0.05, 5.26]           2         85         5         84         0.7%         0.40 [0.08, 1.98]           3         27         3         23         0.4%         0.85 [0.19, 3.82]           2         26         4         23         0.6%         0.44 [0.09, 2.20]

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



 $Figure\ 12-Forest\ plot\ of\ the\ sensitivity\ analysis\ of\ all\text{-}cause\ mortality\ removing\ the\ SHIFT\ trial.$ 

#### Subgroup analyses

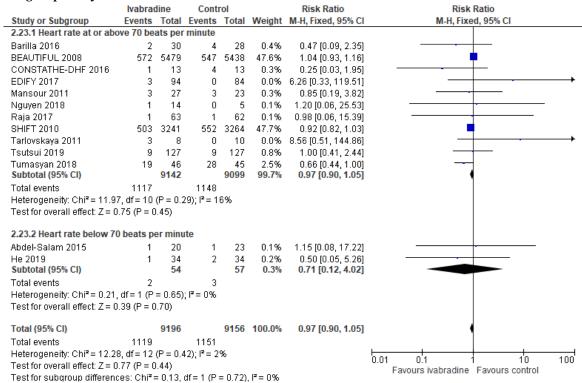


Figure 13 – Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared to trials randomising participants with heart rate below 70 beats per minute on all-cause mortality.

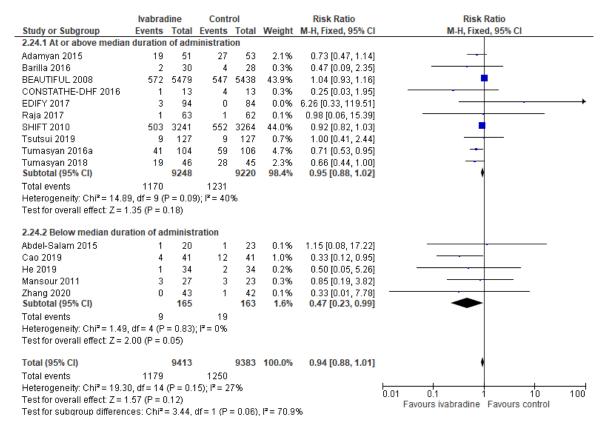


Figure 14 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (182.64 days) versus trials administering ivabradine below median duration on all-cause mortality.

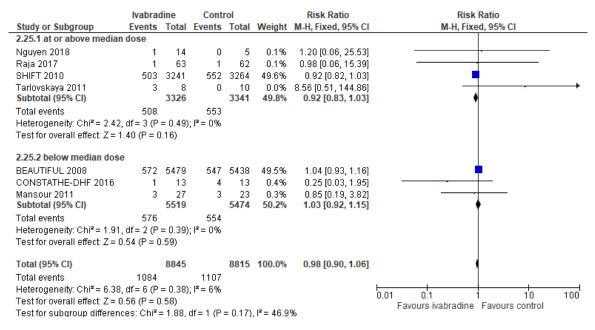


Figure 15 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose (12.7 mg) compared to trials administering ivabradine below median daily dose on all-cause mortality.

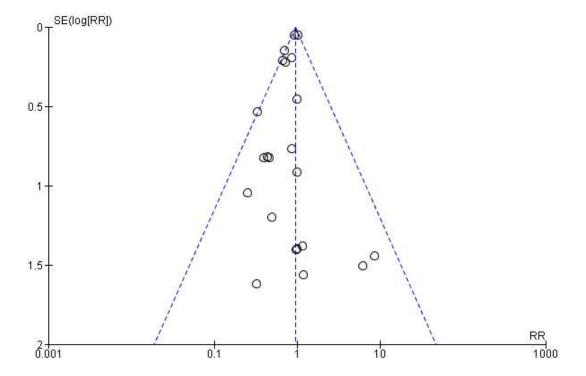


Figure 16 - Funnel plot of the analyses of all-cause mortality. The funnel plot did not indicate small study bias.

# **Supplement 6 - Serious adverse events** *Main analyses*

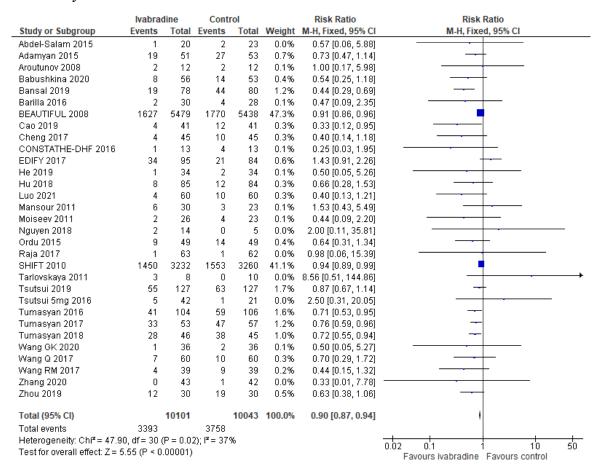


Figure 17 - Forest plot of the meta-analysis of serious adverse events using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

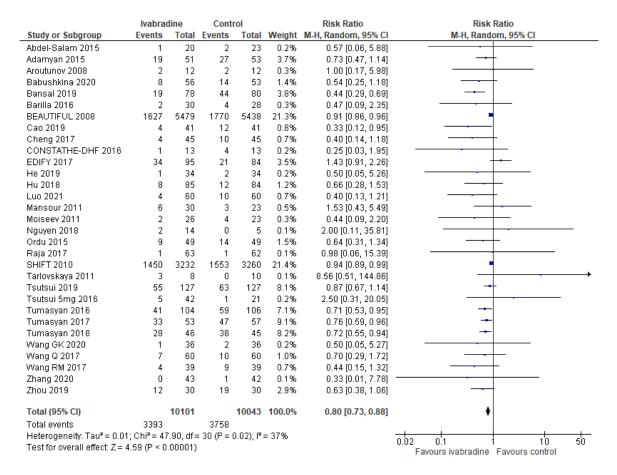


Figure 18 – Forest plot of the meta-analysis of serious adverse events using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

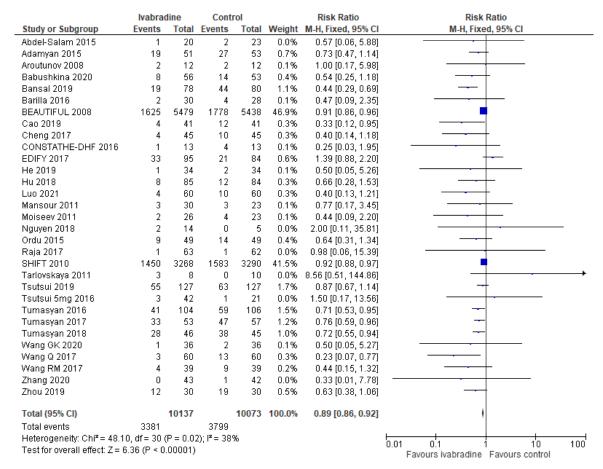


Figure 19 - Forest plot of the sensitivity analysis of serious adverse events using best- compared with worst-case scenario.

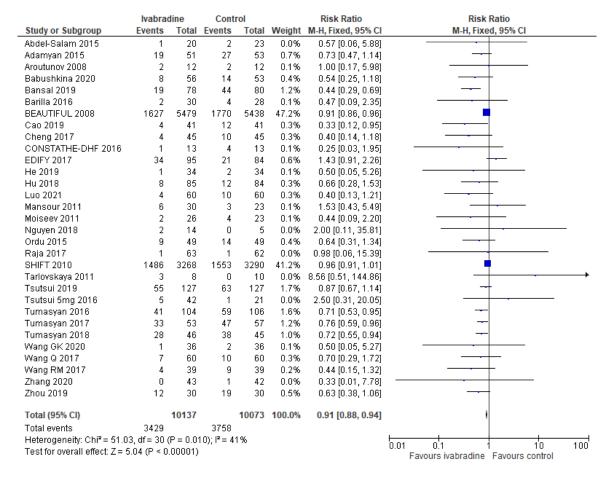


Figure 20 - Forest plot of the sensitivity analysis of serious adverse events using worst- compared with best-case scenario.

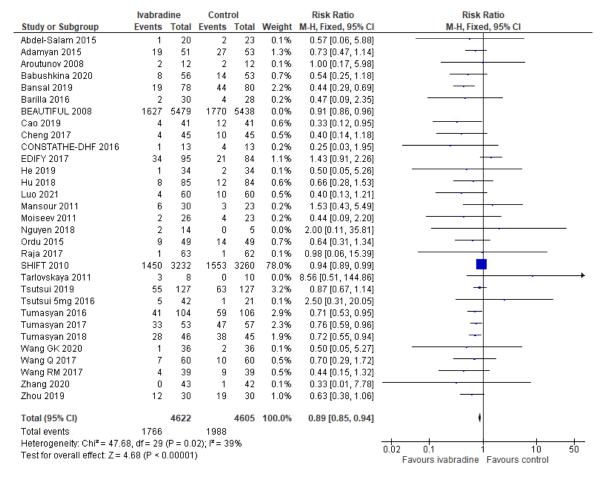


Figure 21 – Forest plot of the sensitivity analysis of serious adverse events removing the BEAUTIFUL trial.

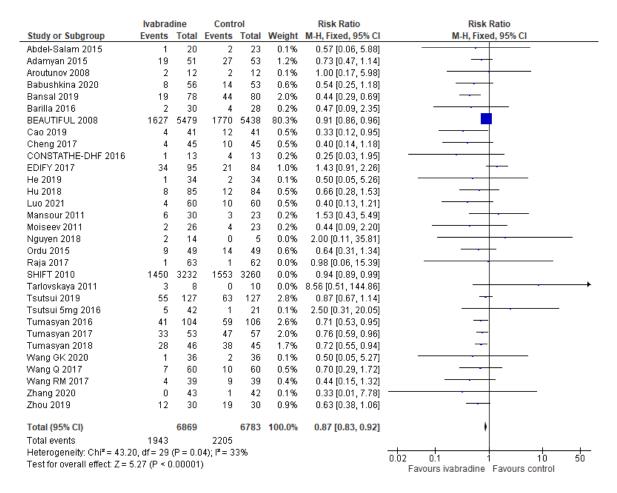
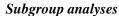


Figure 22 - Forest plot of the sensitivity analysis of serious adverse events removing the SHIFT trial.



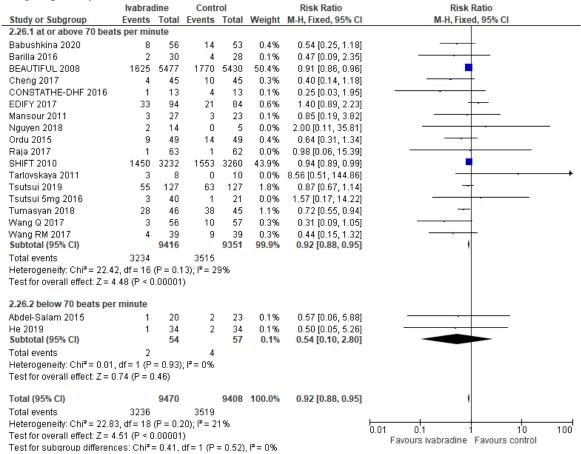


Figure 23 - Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared to trials randomising participants with heart rate below 70 beats per minute on all-cause mortality.

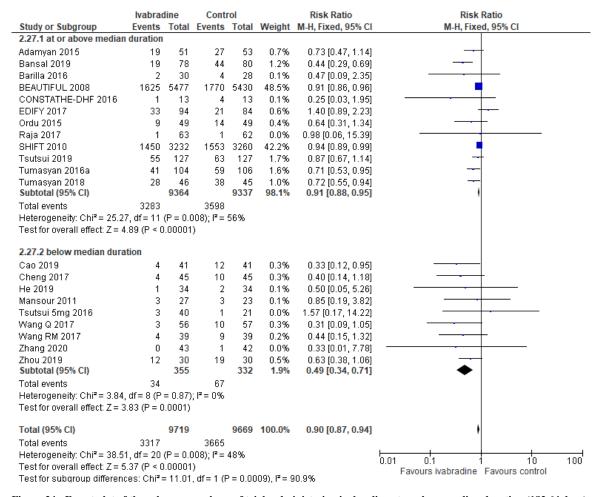


Figure 24 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (182.64 days) compared to trials administering ivabradine below median duration on serious adverse events.

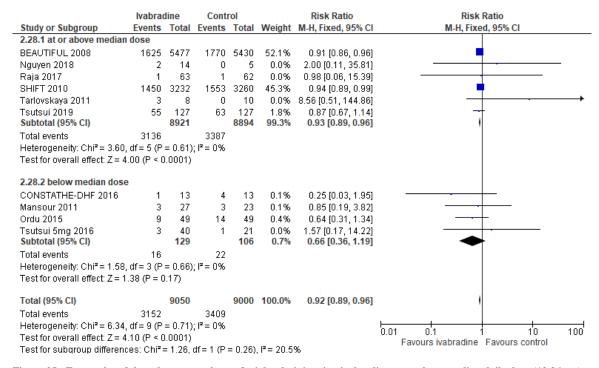


Figure 25 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose (12.36 mg) compared to trials administering ivabradine below median daily dose on serious adverse events.

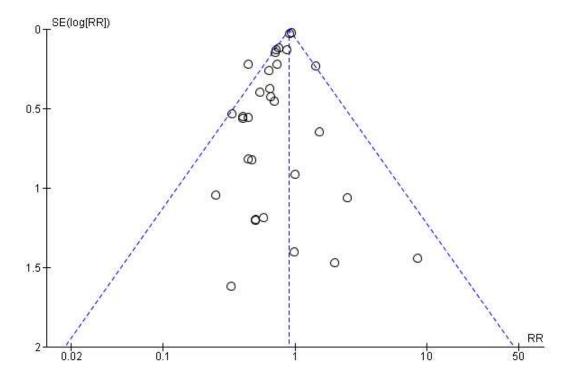


Figure 26 – Funnel plot of the analysis of serious adverse events. The funnel plot did not indicate small study bias.

# **Supplement 7 - Quality of life**

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

	lvabradine			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.47.1 KCCQ change	score								
SHIFT 2010 Subtotal (95% CI)	6.7	17.3	842 <b>842</b>	4.3	16.7	839 <b>839</b>	94.5% <b>94.5%</b>	2.40 [0.77, 4.03] <b>2.40 [0.77, 4.03</b> ]	· <del></del>
Heterogeneity: Not ap	plicable	!							
Test for overall effect:	Z = 2.89	(P = 0	0.004)						
2.47.2 KCCQ mean s	core								
Sallam 2016 Subtotal (95% CI)	80	14	50 <b>50</b>	68	20	50 <b>50</b>		12.00 [5.23, 18.77] <b>12.00 [5.23, 18.77]</b>	I .
Heterogeneity: Not ap	plicable	!							
Test for overall effect:	Z = 3.48	(P = 0	).0005)						
Total (95% CI)			892			889	100.0%	2.92 [1.34, 4.50]	•
Heterogeneity: Chi²=	7.31, df	= 1 (P	= 0.00	7); I² = 8	6%				100 50 100
Test for overall effect:	Z = 3.63	(P = 0	0.0003)						-100 -50 0 50 100 Favours control Favours ivabradine
Test for subgroup diff	ferences	: Chi²:	= 7.31,	df = 1 (F	o.0 = 9	07), l <sup>2</sup> :	= 86.3%		Tavours control Tavours Ivabraume

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.

	lval	Ivabradine Control						Mean Difference			erence		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random	n, 95% CI		
2.47.1 KCCQ change	score												
SHIFT 2010 Subtotal (95% CI)	6.7	17.3	842 <b>842</b>	4.3	16.7	839 <b>839</b>	56.1% <b>56.1</b> %	2.40 [0.77, 4.03] <b>2.40 [0.77, 4.03</b> ]		•	ı		
Heterogeneity: Not ap	plicable												
Test for overall effect:	Z= 2.89	(P = 0	0.004)										
2.47.2 KCCQ mean s	соге												
Sallam 2016 Subtotal (95% CI)	80	14	50 <b>50</b>	68	20	50 <b>50</b>	43.9% <b>43.9</b> %	12.00 [5.23, 18.77] 12.00 [5.23, 18.77]			<b>+</b>		
Heterogeneity: Not ap	plicable												
Test for overall effect:	Z= 3.48	(P = 0	0.0005)										
Total (95% CI)			892			889	100.0%	6.61 [-2.72, 15.95]		•	•		
Heterogeneity: Tau <sup>2</sup> =	39.78; 0	Chi²=	7.31, d	f=1 (P:	= 0.00	7); $I^2 = 8$	B6%		-100 -5	<del></del>		50	100
Test for overall effect:	Z = 1.39	(P = 0	0.16)							ours control f			
Test for subgroup diff	erences	: Chi²:	= 7.31,	df = 1 (F	o.0 = 9	107), l <sup>z</sup> =	= 86.3%		Tavo	ruis contitor i	avours iv	abraume	1

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.

	Iva	bradin	е	(	Control			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI			
2.48.1 KCCQ change	score								<u></u>			
SHIFT 2010 Subtotal (95% CI)	15.5	21.22	1129 <b>1129</b>	4.8	20.59	1153 <b>1153</b>			1 <del></del>			
Heterogeneity: Not ap	plicable											
Test for overall effect:	Z = 12.2	2 (P < 0	0.0000	1)								
2.48.2 KCCQ mean s	соге											
Sallam 2016 Subtotal (95% CI)	80	14	50 <b>50</b>	68	20	50 <b>50</b>	6.0% <b>6.0</b> %		<b>→</b>			
Heterogeneity: Not ap			0005									
Test for overall effect:	∠= 3.48	i (P = U.	0005)									
Total (95% CI)			1179			1203	100.0%	10.78 [9.12, 12.44]	•			
Heterogeneity: Chi <sup>z</sup> = Test for overall effect:									-100 -50 0 50 100			
Test for subgroup diff		,		*	= 0.72)	I <sup>2</sup> = 0.9	6		Favours ivabradine Favours control			

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

	lva	abradin	е	(	Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.49.1 KCCQ change	score								_
SHIFT 2010 Subtotal (95% CI)	2.1	21.22	1129 <b>1129</b>		20.59	1153 <b>1153</b>		-11.30 [-13.02, -9.58] - <b>11.30 [-13.02</b> , - <b>9.58]</b>	<b>-</b>
Heterogeneity: Not ap	plicable	!							
Test for overall effect:	Z = 12.9	91 (P < 0	0.0000	1)					
2.49.2 KCCQ mean s	соге								
Sallam 2016 Subtotal (95% CI)	80	14	50 <b>50</b>	68	20	50 <b>50</b>	6.0% <b>6.0%</b>	12.00 [5.23, 18.77] <b>12.00 [5.23, 18.77]</b>	<b>→</b>
Heterogeneity: Not ap Test for overall effect:	•		0005)						
Total (95% CI)			1179			1203	100.0%	-9.89 [-11.56, -8.23]	•
Heterogeneity: Chi² = Test for overall effect:	Z=11.8	66 (P < 0	0.0000	1)					-100 -50 0 50 100
Test for subgroup diff	ferences	: Chi²=	42.79.	df = 1 (1)	P < 0.00	001), P	= 97.7%		Tavouis Ivabiaumo Tavouis Comio

 $\label{eq:figure 30-Forest plot of the sensitivity analysis of quality of life (MLWHFQ) using worst-compared with best-case scenario.$ 

# Subgroup analyses for trials using the KCCQ

	lvabradine				ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.56.1 KCCQ at or ab	ove med	dian dı	uration						<u>L</u>
SHIFT 2010 Subtotal (95% CI)	6.7	17.3	842 <b>842</b>	4.3	16.7	839 <b>839</b>	94.5% <b>94.5</b> %	2.40 [0.77, 4.03] <b>2.40 [0.77, 4.03</b> ]	<b>,</b>
Heterogeneity: Not ap	plicable	!							
Test for overall effect:	Z = 2.89	(P = 0	0.004)						
2.56.2 KCCQ below r	nedian d	luratio	n						
Sallam 2016 Subtotal (95% CI)	80	14	50 <b>50</b>	68	20	50 <b>50</b>		12.00 [5.23, 18.77] <b>12.00 [5.23, 18.77]</b>	<b>→</b>
Heterogeneity: Not as	plicable	!							
Test for overall effect:	Z= 3.48	(P = 0	0.0005)						
Total (95% CI)			892			889	100.0%	2.92 [1.34, 4.50]	•
Heterogeneity: Chi²=	7.31, df	= 1 (P	= 0.00	7); I² = 8	6%				100 50 100
Test for overall effect:	Z = 3.63	(P = 0	0.0003)						-100 -50 0 50 100 Favours control Favours ivabradine
Test for subgroup diff	erences	: Chi²:	= 7.31,	df = 1 (i	o.0 = 9	07), l <sup>2</sup> :	= 86.3%		i avours control. Pavours Ivabilaurile

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)

	Ivabradine Control				ontrol			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
2.50.1 MLWHFQ mea	an score										
Abdel-Salam 2015	46.4	7.3	20	51.7	6.6	23	8.8%	-5.30 [-9.48, -1.12]			
Sarullo 2010	31.2	2.6	30	37.5	1.9	30	46.3%	-6.30 [-7.45, -5.15]			
Zeng FC 2019 Subtotal (95% CI)	27.44	4.26	33 <b>83</b>	32.21	4.79	32 <b>85</b>	23.9% <b>79.0%</b>	-4.77 [-6.98, -2.56] - <b>5.93 [-6.93, -4.94]</b>	<u>→</u>		
Heterogeneity: Tau <sup>2</sup> =	= 0.00; C	hi² = 1	.55, df=	= 2 (P =	0.46);	$I^2 = 0\%$	,				
Test for overall effect:	•										
2.50.2 MLWHFQ cha	nge sco	re									
Mansour 2011	-12.3	3.3	30	-8.7	5.2	23	21.0%	-3.60 [-6.03, -1.17]			
Subtotal (95% CI)			30			23	21.0%	-3.60 [-6.03, -1.17]	•		
Heterogeneity: Not ap	oplicable										
Test for overall effect:	Z = 2.90	(P=0	0.004)								
Total (95% CI)			113			108	100.0%	-5.28 [-6.60, -3.96]	•		
Heterogeneity: Tau <sup>2</sup> =	0.64; C	hi² = 4	.58, df=	3 (P =	0.21);	l <sup>2</sup> = 35°	%	-	10 5 10		
Test for overall effect:	Z = 7.82	(P < 0		-10 -5 0 5 10 Favours ivabradine Favours control							
Test for subgroup diff	ferences	: Chi²:	= 3.04.	df = 1 (F	o.0 = □	8), I² =	67.1%		Favours ivabraume Favours Control		

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.

	Ival	oradin	е	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.50.1 MLWHFQ mea	n score								
Abdel-Salam 2015	46.4	7.3	20	51.7	6.6	23	4.8%	-5.30 [-9.48, -1.12]	<del></del>
Sarullo 2010	31.2	2.6	30	37.5	1.9	30	63.6%	-6.30 [-7.45, -5.15]	-
Zeng FC 2019 Subtotal (95% CI)	27.44	4.26	33 <b>83</b>	32.21	4.79	32 <b>85</b>	17.3% <b>85.7</b> %	-4.77 [-6.98, -2.56] -5.93 [-6.93, -4.94]	<b>→</b>
Heterogeneity: Chi²=	1.55, df	= 2 (P	= 0.46)	; I <sup>2</sup> = 09	6				
Test for overall effect:									
2.50.2 MLWHFQ chan	ige scoi	re							
Mansour 2011 Subtotal (95% CI)	-12.3	3.3	30 <b>30</b>	-8.7	5.2	23 <b>23</b>		-3.60 [-6.03, -1.17] - <b>3.60 [-6.03, -1.17]</b>	<del>-</del>
Heterogeneity: Not ap Test for overall effect:			0.004)						
Total (95% CI)			113			108	100.0%	-5.60 [-6.52, -4.68]	•
Heterogeneity: Chi²= Test for overall effect:					%			_	-10 -5 0 5 10 Favours ivabradine Favours control
Test for subgroup diff	erences	: Chi²:	= 3.04,	df = 1 (F	P = 0.0	8), I²=	67.1%		. arodio irazi adino ir divolio 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.

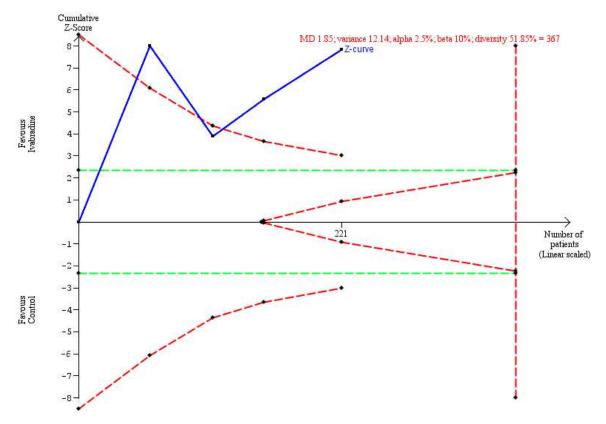


Figure 34 – Trial Sequential Analysis graph of quality of life from trials using the MLWHFQ. Trial Sequential Analysis showed that we had enough information to detect a mean difference of -5.60 points of ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) breached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

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

	Ivabradine			C	ontrol			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
2.51.1 MLWHFQ mea	an score										
Abdel-Salam 2015	46.4	7.3	20	51.7	6.6	23	8.8%	-5.30 [-9.48, -1.12]	<del></del>		
Sarullo 2010	31.2	2.6	30	37.5	1.9	30	46.3%	-6.30 [-7.45, -5.15]	-		
Zeng FC 2019 Subtotal (95% CI)	27.44	4.26	33 <b>83</b>	32.21	4.79	32 <b>85</b>	23.9% <b>79.0%</b>	-4.77 [-6.98, -2.56] - <b>5.93 [-6.93, -4.94]</b>	<u>→</u>		
Heterogeneity: Tau <sup>2</sup> =	= 0.00; CI	hi² = 1	.55, df :	= 2 (P =	0.46);	$I^2 = 0\%$	,				
Test for overall effect			•								
2.51.2 MLWHFQ cha	nge scoi	re									
Mansour 2011	-12.3	3.3	30	-8.7	5.2	23	21.0%	-3.60 [-6.03, -1.17]			
Subtotal (95% CI)			30			23	21.0%	-3.60 [-6.03, -1.17]	•		
Heterogeneity: Not ap	pplicable										
Test for overall effect	: Z= 2.90	(P = 0	0.004)								
Total (95% CI)			113			108	100.0%	-5.28 [-6.60, -3.96]	•		
Heterogeneity: Tau <sup>2</sup> =	= 0.64; CI	hi² = 4	.58, df :	-	-10 -5 0 5 10						
Test for overall effect	Z = 7.82	(P < 0	0.00001	1)					Favours ivabradine Favours control		
Test for subgroup dif	ferences	: Chi²:	= 3.04.	df = 1 (I	= 0.0	18), I <sup>z</sup> =	67.1%		Favours (vabradine Favours control		

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

	Ivabradine Control							Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.52.1 MLWHFQ mea	n score								
Abdel-Salam 2015	46.4	7.3	20	51.7	6.6	23	8.8%	-5.30 [-9.48, -1.12]	<del></del>
Sarullo 2010	31.2	2.6	30	37.5	1.9	30	46.3%	-6.30 [-7.45, -5.15]	-
Zeng FC 2019 Subtotal (95% CI)	27.44	4.26	33 <b>83</b>	32.21	4.79	32 <b>85</b>	23.9% <b>79.0%</b>	-4.77 [-6.98, -2.56] - <b>5.93 [-6.93, -4.94]</b>	•
Heterogeneity: Tau <sup>2</sup> =			•	•	0.46);	I <sup>2</sup> = 0%	ı		
Test for overall effect:	Z= 11.7	2 (F S	0.0000	)))					
2.52.2 MLWHFQ char	ige sco	re							
Mansour 2011 Subtotal (95% CI)	-12.3	3.3	30 <b>30</b>	-8.7	5.2	23 <b>23</b>	21.0% <b>21.0</b> %	-3.60 [-6.03, -1.17] - <b>3.60 [-6.03, -1.17]</b>	•
Heterogeneity: Not ap Test for overall effect:			0.004)						
Total (95% CI)			113			108	100.0%	-5.28 [-6.60, -3.96]	•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Test for subgroup diff	Z = 7.82	(P < 0	0.0000	l) `					-10 -5 0 5 10 Favours ivabradine Favours control

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



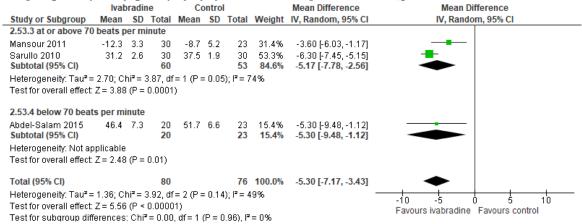


Figure 37 - Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared trials randomising participants with heart rate below 70 beats per minute on quality of life using the MLWHFQ.

	Ival	Ivabradine Control						Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
2.54.3 at or above m	edian du	ration										
Mansour 2011 Subtotal (95% CI)	-12.3	3.3	30 <b>30</b>	-8.7	5.2	23 <b>23</b>	39.2% <b>39.2%</b>	-3.60 [-6.03, -1.17] - <b>3.60 [-6.03, -1.17]</b>	•			
Heterogeneity: Not ap	oplicable											
Test for overall effect:	Z = 2.90	(P = 0	.004)									
2.54.4 below median	duratio	n										
Abdel-Salam 2015	46.4	7.3	20	51.7	6.6	23	13.2%	-5.30 [-9.48, -1.12]	<del></del>			
Zeng FC 2019 Subtotal (95% CI)	27.44	4.26	33 <b>53</b>	32.21	4.79	32 <b>55</b>	47.6% 60.8%	-4.77 [-6.98, -2.56] -4.89 [-6.84, -2.93]	<b>*</b>			
Heterogeneity: Tau <sup>2</sup> =	= 0.00; CI	$hi^2 = 0.$	05, df=	= 1 (P =	0.83);	l² = 0%						
Test for overall effect:	Z= 4.91	(P < 0	1.00001	)								
Total (95% CI)			83			78	100.0%	-4.38 [-5.90, -2.86]	•			
Heterogeneity: Tau <sup>2</sup> =	= 0.00; CI	hi² = 0.	70, df=	2 (P =	0.70);	$l^2 = 0\%$			-10 -5 0 5 10			
Test for overall effect:	Z = 5.64	(P < 0	1.00001	)		-10 -5 0 5 10 Favours ivabradine Favours control						
Test for subgroup dif	ferences	: Chi²÷	= 0.65,	df = 1 (f	o = 0.4	2), I²=	0%		ravours ivabilaunie Pavours control			

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*

	lvabrad	line	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Abdel-Salam 2015	1	20	1	23	0.0%	1.15 [0.08, 17.22]	
BEAUTIFUL 2008	469	5479	435	5438	49.1%	1.07 [0.94, 1.21]	+
Cao 2019	4	41	12	41	0.0%	0.33 [0.12, 0.95]	
EDIFY 2017	2	94	0	84	0.0%	4.47 [0.22, 91.88]	
Hu 2018	1	85	4	84	0.0%	0.25 [0.03, 2.16]	
Mansour 2011	2	27	3	23	0.0%	0.57 [0.10, 3.11]	
Moiseev 2011	2	26	4	23	0.0%	0.44 [0.09, 2.20]	
Raja 2017	1	63	0	62	0.0%	2.95 [0.12, 71.13]	
SHIFT 2010	449	3241	491	3264	50.9%	0.92 [0.82, 1.04]	<del></del>
Tarlovskaya 2011	2	8	0	10	0.0%	6.11 [0.33, 111.71]	
Tsutsui 2019	7	127	8	127	0.0%	0.88 [0.33, 2.34]	
Wang GK 2020	1	36	1	36	0.0%	1.00 [0.07, 15.38]	
Wang Q 2017	1	56	1	57	0.0%	1.02 [0.07, 15.88]	
Wang RM 2017	0	39	3	39	0.0%	0.14 [0.01, 2.68]	
Zhang 2020	0	43	1	42	0.0%	0.33 [0.01, 7.78]	
Total (95% CI)		8720		8702	100.0%	0.99 [0.86, 1.15]	<b>*</b>
Total events	918		926				
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi	$i^2 = 2.93$	2, df = 1 (	P = 0.0	9); I <sup>z</sup> = 66	% -	05 07 1 15 2
Test for overall effect:	Z = 0.12 (	(P = 0.9)	1)				Favours ivabradine Favours control

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).

	lvabrad	line	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Abdel-Salam 2015	1	20	1	23	0.0%	1.15 [0.08, 17.22]	
BEAUTIFUL 2008	469	5479	435	5438	47.2%	1.07 [0.94, 1.21]	<b>-</b>  ■-
Cao 2019	4	41	12	41	0.0%	0.33 [0.12, 0.95]	
EDIFY 2017	2	94	0	84	0.0%	4.47 [0.22, 91.88]	
Hu 2018	1	85	4	84	0.0%	0.25 [0.03, 2.16]	
Mansour 2011	2	27	3	23	0.0%	0.57 [0.10, 3.11]	
Moiseev 2011	2	26	4	23	0.0%	0.44 [0.09, 2.20]	
Raja 2017	1	63	0	62	0.0%	2.95 [0.12, 71.13]	
SHIFT 2010	449	3241	491	3264	52.8%	0.92 [0.82, 1.04]	<del>-■</del> +
Tarlovskaya 2011	2	8	0	10	0.0%	6.11 [0.33, 111.71]	
Tsutsui 2019	7	127	8	127	0.0%	0.88 [0.33, 2.34]	
Wang GK 2020	1	36	1	36	0.0%	1.00 [0.07, 15.38]	
Wang Q 2017	1	56	1	57	0.0%	1.02 [0.07, 15.88]	
Wang RM 2017	0	39	3	39	0.0%	0.14 [0.01, 2.68]	
Zhang 2020	0	43	1	42	0.0%	0.33 [0.01, 7.78]	
Total (95% CI)		8720		8702	100.0%	0.99 [0.91, 1.08]	<b>*</b>
Total events	918		926				
Heterogeneity: Chi²=	2.92, df=	1 (P=	0.09); l² =	66%			0.5 0.7 1 1.5 2
Test for overall effect:	Z = 0.20 (	P = 0.8	4)				Favours ivabradine Favours control

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).

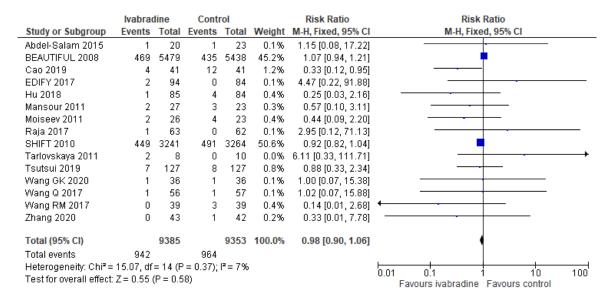
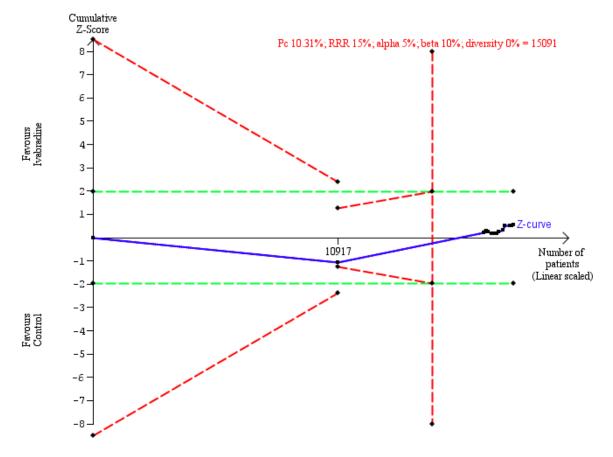


Figure 41 – Forest plot of the meta-analysis of cardiovascular mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

	Ivabra	line	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Abdel-Salam 2015	1	20	1	23	0.2%	1.15 [0.08, 17.22]	<del></del>
BEAUTIFUL 2008	469	5479	435	5438	46.1%	1.07 [0.94, 1.21]	•
Cao 2019	4	41	12	41	1.3%	0.33 [0.12, 0.95]	
EDIFY 2017	2	94	0	84	0.2%	4.47 [0.22, 91.88]	<del> </del>
Hu 2018	1	85	4	84	0.3%	0.25 [0.03, 2.16]	<del></del>
Mansour 2011	2	27	3	23	0.5%	0.57 [0.10, 3.11]	-
Moiseev 2011	2	26	4	23	0.5%	0.44 [0.09, 2.20]	<del></del>
Raja 2017	1	63	0	62	0.1%	2.95 [0.12, 71.13]	
SHIFT 2010	449	3241	491	3264	48.6%	0.92 [0.82, 1.04]	•
Tarlovskaya 2011	2	8	0	10	0.2%	6.11 [0.33, 111.71]	<del></del>
Tsutsui 2019	7	127	8	127	1.4%	0.88 [0.33, 2.34]	
Wang GK 2020	1	36	1	36	0.2%	1.00 [0.07, 15.38]	
Wang Q 2017	1	56	1	57	0.2%	1.02 [0.07, 15.88]	
Wang RM 2017	0	39	3	39	0.2%	0.14 [0.01, 2.68]	<del>  </del>
Zhang 2020	0	43	1	42	0.1%	0.33 [0.01, 7.78]	
Total (95% CI)		9385		9353	100.0%	0.97 [0.86, 1.09]	•
Total events	942		964				
Heterogeneity: Tau² =	0.00; Ch	$i^2 = 15.0$	07, df = 1	4 (P = 0)	0.37); (2=	7%	0.01 0.1 1 10 100
Test for overall effect:	Z = 0.56	(P = 0.5)	8)				0.01 0.1 1 10 100 Favours ivabradine Favours control
							i avouis ivabilaulile Favouis colliloi

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.

	lvabrad	dine	Contr	rol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Abdel-Salam 2015	1	20	1	23	0.1%	1.15 [0.08, 17.22]			
BEAUTIFUL 2008	469	5479	435	5438	43.8%	1.07 [0.94, 1.21]		•	
Cao 2019	4	41	12	41	1.2%	0.33 [0.12, 0.95]		<del></del>	
EDIFY 2017	2	95	0	84	0.1%	4.43 [0.22, 90.93]			
Hu 2018	1	85	4	84	0.4%	0.25 [0.03, 2.16]			
Mansour 2011	2	30	3	23	0.3%	0.51 [0.09, 2.81]		<del></del>	
Moiseev 2011	2	26	4	23	0.4%	0.44 [0.09, 2.20]		<del></del>	
Raja 2017	1	63	0	62	0.1%	2.95 [0.12, 71.13]		<del></del>	
SHIFT 2010	449	3268	517	3290	51.7%	0.87 [0.78, 0.98]		•	
Tarlovskaya 2011	2	8	0	10	0.0%	6.11 [0.33, 111.71]		<del> </del>	$\longrightarrow$
Tsutsui 2019	7	127	8	127	0.8%	0.88 [0.33, 2.34]			
Wang GK 2020	1	36	1	36	0.1%	1.00 [0.07, 15.38]			
Wang Q 2017	1	60	4	60	0.4%	0.25 [0.03, 2.17]			
Wang RM 2017	0	39	3	39	0.4%	0.14 [0.01, 2.68]	-	· -	
Zhang 2020	0	43	1	42	0.2%	0.33 [0.01, 7.78]	_	•	
Total (95% CI)		9420		9382	100.0%	0.95 [0.87, 1.03]		•	
Total events	942		993						
Heterogeneity: Chi²=	18.76, df	= 14 (P	= 0.17);	l <sup>2</sup> = 259	%		L-04		400
Test for overall effect:							0.01	0.1 1 10 Favours ivabradine Favours control	100
								r avours ivabraume   Favours control	

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

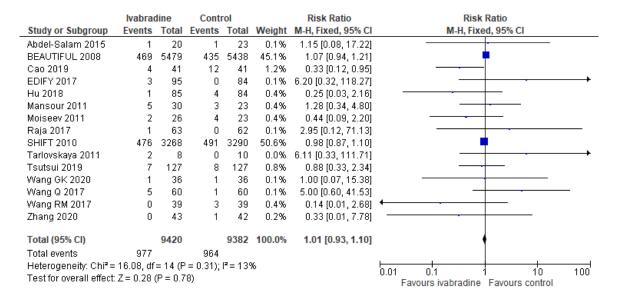


Figure 45 - Forest plot of the sensitivity analysis of cardiovascular mortality using worst compared with best-case scenario.

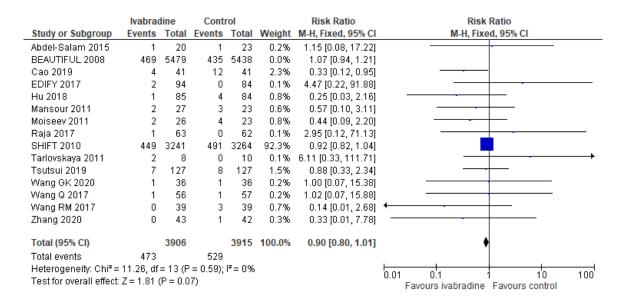


Figure 46 - Forest plot of the sensitivity analysis of cardiovascular mortality removing the BEAUTIFUL trial.

	lvabrad	dine	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Abdel-Salam 2015	1	20	1	23	0.2%	1.15 [0.08, 17.22]	<u> </u>
BEAUTIFUL 2008	469	5479	435	5438	91.4%	1.07 [0.94, 1.21]	
Cao 2019	4	41	12	41	2.5%	0.33 [0.12, 0.95]	
EDIFY 2017	2	94	0	84	0.1%	4.47 [0.22, 91.88]	<del></del>
Hu 2018	1	85	4	84	0.8%	0.25 [0.03, 2.16]	<del></del>
Mansour 2011	2	27	3	23	0.7%	0.57 [0.10, 3.11]	<del></del>
Moiseev 2011	2	26	4	23	0.9%	0.44 [0.09, 2.20]	<del></del>
Raja 2017	1	63	0	62	0.1%	2.95 [0.12, 71.13]	<del></del>
SHIFT 2010	449	3241	491	3264	0.0%	0.92 [0.82, 1.04]	
Tarlovskaya 2011	2	8	0	10	0.1%	6.11 [0.33, 111.71]	<del></del>
Tsutsui 2019	7	127	8	127	1.7%	0.88 [0.33, 2.34]	<del></del>
Wang GK 2020	1	36	1	36	0.2%	1.00 [0.07, 15.38]	
Wang Q 2017	1	56	1	57	0.2%	1.02 [0.07, 15.88]	
Wang RM 2017	0	39	3	39	0.7%	0.14 [0.01, 2.68]	<del></del>
Zhang 2020	0	43	1	42	0.3%	0.33 [0.01, 7.78]	-
Total (95% CI)		6144		6089	100.0%	1.03 [0.92, 1.17]	<b>↓</b>
Total events	493		473				
Heterogeneity: Chi <sup>2</sup> =	13.16, df	= 13 (P	= 0.44);	l <sup>2</sup> = 1%			
Test for overall effect:	Z = 0.54 (	(P = 0.5)	9)				0.01 0.1 1 10 100 Favours ivabradine Favours control
		-	-				ravours ivabraunie ravours control

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

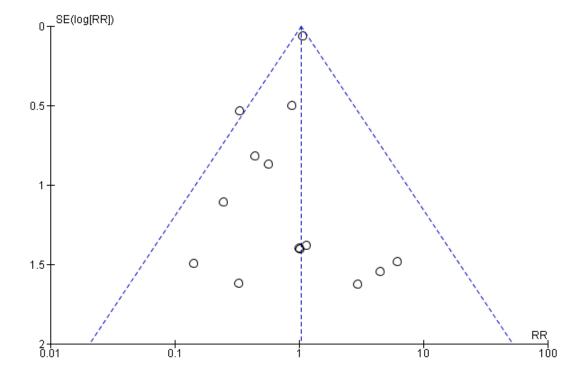


Figure 48 – Funnel plot of the analysis of cardiovascular mortality. The funnel plot did not indicate small study bias.

# **Supplement 9 - Myocardial infarction**

#### Main analyses

	lvabrad	line	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Babushkina 2020	0	56	3	53	0.0%	0.14 [0.01, 2.56]	
BEAUTIFUL 2008	82	5477	88	5430	62.2%	0.92 [0.69, 1.25]	#
EDIFY 2017	2	94	0	84	0.0%	4.47 [0.22, 91.88]	
Liu YY 2020	4	61	5	61	0.0%	0.80 [0.23, 2.84]	
Moiseev 2011	2	26	3	23	0.0%	0.59 [0.11, 3.22]	
SHIFT 2010	62	3232	54	3260	37.8%	1.16 [0.81, 1.66]	<b>+</b>
Tarlovskaya 2011	2	8	0	10	0.0%	6.11 [0.33, 111.71]	
Tsutsui 2019	2	127	1	127	0.0%	2.00 [0.18, 21.78]	
Tsutsui 5mg 2016	0	40	1	21	0.0%	0.18 [0.01, 4.21]	
Total (95% CI)		8709		8690	100.0%	1.01 [0.80, 1.27]	<b>•</b>
Total events	144		142				
Heterogeneity: Chi <sup>2</sup> =	0.89, df=	1 (P =	0.34); l² =	: 0%			0.01 0.1 1 10 100
Test for overall effect:	Z = 0.11 (	(P = 0.9)	2)				0.01 0.1 1 10 100 Favours ivabradine Favours control
							. areare made and a drouge control

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).

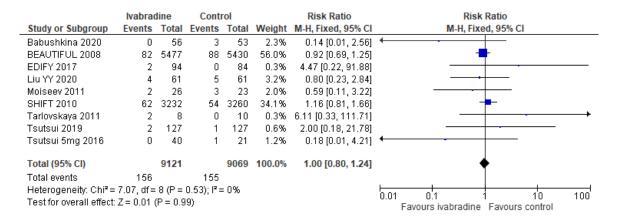


Figure 50 - Forest plot of the meta-analysis of myocardial infarction using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

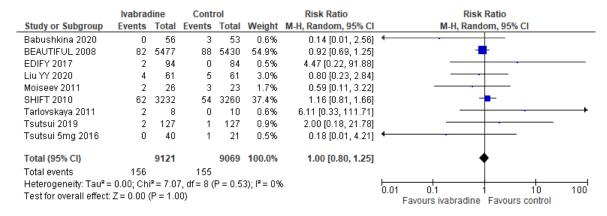
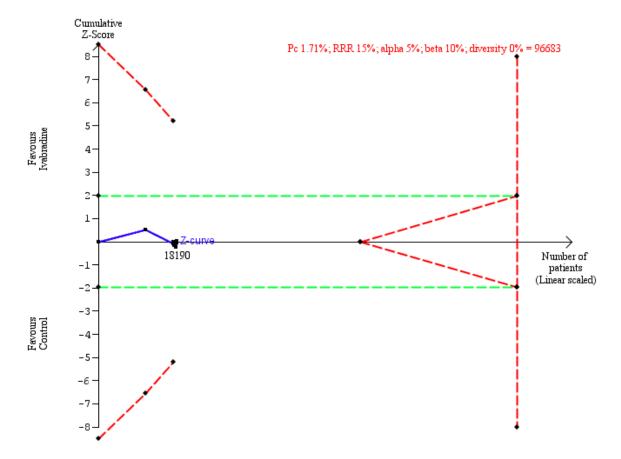


Figure 51 - Forest plot of the meta-analysis of myocardial infarction using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).



**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.

	Ivabrad	dine	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Babushkina 2020	0	56	3	53	1.8%	0.14 [0.01, 2.56]	<del></del>
BEAUTIFUL 2008	82	5479	96	5438	49.2%	0.85 [0.63, 1.14]	<b>=</b>
EDIFY 2017	2	95	0	84	0.3%	4.43 [0.22, 90.93]	<del></del>
Liu YY 2020	4	61	5	61	2.6%	0.80 [0.23, 2.84]	<del></del>
Moiseev 2011	2	26	3	23	1.6%	0.59 [0.11, 3.22]	<del></del>
SHIFT 2010	62	3268	84	3290	42.8%	0.74 [0.54, 1.03]	
Tarlovskaya 2011	2	8	0	10	0.2%	6.11 [0.33, 111.71]	<del></del>
Tsutsui 2019	2	127	1	127	0.5%	2.00 [0.18, 21.78]	<del></del>
Tsutsui 5mg 2016	0	42	1	21	1.0%	0.17 [0.01, 4.02]	<del></del>
Total (95% CI)		9162		9107	100.0%	0.81 [0.65, 0.99]	•
Total events	156		193				
Heterogeneity: Chi²=	6.47, df=	8 (P =	0.59);	= 0%			
Test for overall effect:	Z = 2.05 (	(P = 0.0)	14)				0.01 0.1 1 10 100 Favours ivabradine Favours control

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

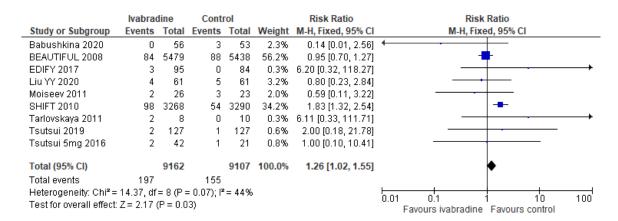
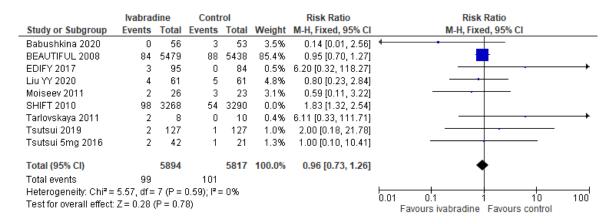


Figure 54 - Forest plot of the sensitivity analysis of myocardial infarction using a worst- compared with best-case scenario.

	lvabrad	dine	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Babushkina 2020	0	56	3	53	5.2%	0.14 [0.01, 2.56]	· ·
BEAUTIFUL 2008	84	5479	88	5438	0.0%	0.95 [0.70, 1.27]	
EDIFY 2017	3	95	0	84	0.8%	6.20 [0.32, 118.27]	<del></del>
Liu YY 2020	4	61	5	61	7.3%	0.80 [0.23, 2.84]	<del></del>
Moiseev 2011	2	26	3	23	4.6%	0.59 [0.11, 3.22]	<del></del>
SHIFT 2010	98	3268	54	3290	78.1%	1.83 [1.32, 2.54]	-
Tarlovskaya 2011	2	8	0	10	0.7%	6.11 [0.33, 111.71]	<del></del>
Tsutsui 2019	2	127	1	127	1.5%	2.00 [0.18, 21.78]	<del></del>
Tsutsui 5mg 2016	2	42	1	21	1.9%	1.00 [0.10, 10.41]	
Total (95% CI)		3683		3669	100.0%	1.66 [1.23, 2.22]	•
Total events	113		67				
Heterogeneity: Chi²=	7.57, df=	7 (P=	0.37); l² =	7%			0.01 0.1 1 10 100
Test for overall effect:	Z = 3.35 (	(P = 0.0)	008)				Favours ivabradine Favours control

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*

	Fuente	Total	Fuente	Total	Moinbt	MIII Dandom OFN CL	MIII Dandom OFW CI
Study or Subgroup	Events				weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Abdel-Salam 2015	3	20	0	23		Not estimable	
Bansal 2019	3	78 5477	1	80	40.00	Not estimable	
BEAUTIFUL 2008	2570	5477	2221	5430	48.3%	1.15 [1.10, 1.20]	•
Cao 2019	2	41	3	41 45		Not estimable	
Cheng 2017	2 1	45 45	1	45		Not estimable	
Cong 2018	1	41	1	41		Not estimable	
Deng 2017	3		1			Not estimable	
Di 2020		63 94		63		Not estimable	
EDIFY 2017 Fu 2021	57 2	32	51 1	84 32		Not estimable	
	2	32 85	0	32 84		Not estimable	
Hu 2018	5	52	0	50		Not estimable	
Huang J 2017	2	48	1	48		Not estimable	
_i 2020 xx 2020	3	40 61	4	61		Not estimable	
_iu YY 2020						Not estimable	
_u 2019 _uo 2021	1 4	30 60	0	30 60		Not estimable	
_uo 2021 _u YH 2020	1	35	0	35		Not estimable Not estimable	
.u rH 2020 Ma 2020	2	43	2	43		Not estimable	
wa 2020 Manz 2003	9	27	2	11		Not estimable	
Man2 2003 Mao 2018	2	30	2	30		Not estimable	
	5	14	0	5			
Nguyen 2018 Pan 2020	2	25	1	25		Not estimable Not estimable	
an 2020 Qi 2019	0	48	2	48			
	2	63	0	62		Not estimable	
Raja 2017	5	50	3	50		Not estimable	
Ballam 2016 BHIFT 2010	2694	3232	2577	3260	51.7%	Not estimable	
Bun 2020	2034	50	4	50	31.770	1.05 [1.03, 1.08] Not estimable	_
Fang 2018	1	31	3	31		Not estimable	
rang 2010 Fsutsui 2.5mg 2016	23	42	6	20		Not estimable	
rsutsui 2.3111g 2010 Fsutsui 2019	119	127	116	127		Not estimable	
rsutsui 5mg 2016	27	42	6	21		Not estimable	
Vang FC 2017	2	53	6	43		Not estimable	
Vang JJ 2017	2	20	3	20		Not estimable	
Vang Q 2017	6	56	4	57		Not estimable	
Vang & 2011 Vang RM 2017	3	39	3	39		Not estimable	
Vei 2019	1	32	0	32		Not estimable	
(ia 2016	1	39	1	39		Not estimable	
(ing 2018	1	10	3	10		Not estimable	
(u 2019	3	38	0	39		Not estimable	
(ue 2020	2	45	1	45		Not estimable	
ang WT 2019	1	40	Ö	40		Not estimable	
/u 2018	1	10	3	10		Not estimable	
/ue 2016	2	43	1	43		Not estimable	
Zeng FC 2019	0	33	1	32		Not estimable	
Zeng XM 2019	3	45	4	45		Not estimable	
Zhang 2020	2	43	6	42		Not estimable	
Thang 2020 Thang 2021	1	47	2	47		Not estimable	
Zhang XJ 2019	1	55	1	55		Not estimable	
Zhou 2019	3	30	2	30		Not estimable	
Zhou 2019 Zhou 2020	2	43	5	43		Not estimable	
Гotal (95% CI)		8709		8690	100.0%	1.10 [1.00, 1.21]	
Total events	5264		4798				
		- 45 00		D ~ O O	001); l²=	0.20%	

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)

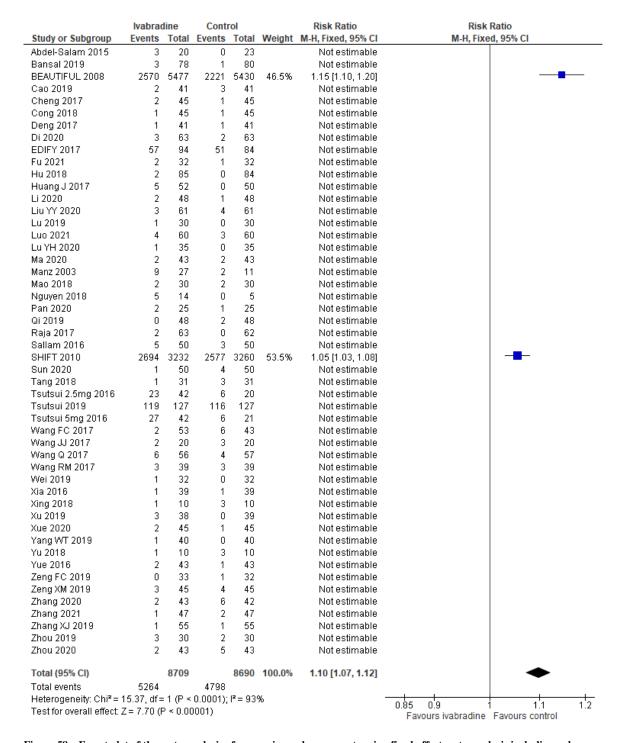


Figure 58 – Forest plot of the meta-analysis of non-serious adverse events using fixed-effect meta-analysis including only trials at low risk of bias. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention).

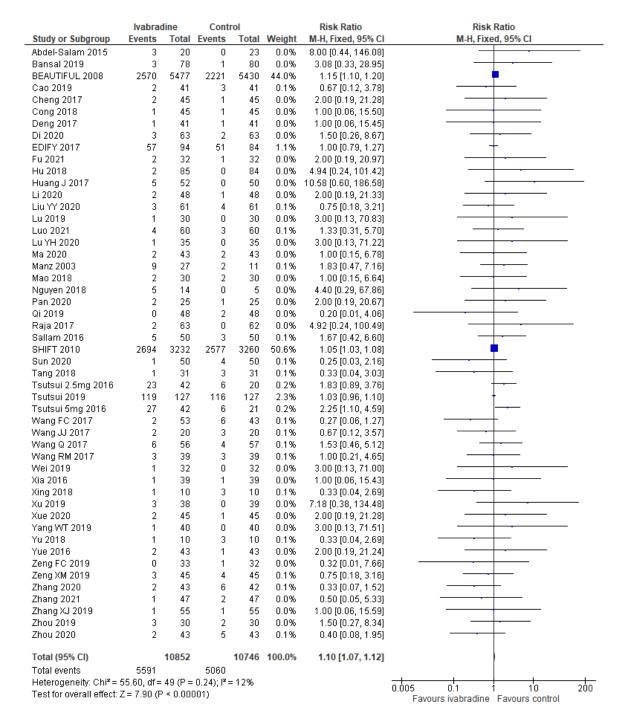


Figure 59 - Forest plot of the meta-analysis of non-serious adverse events using fixed-effect meta-analysis. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention).

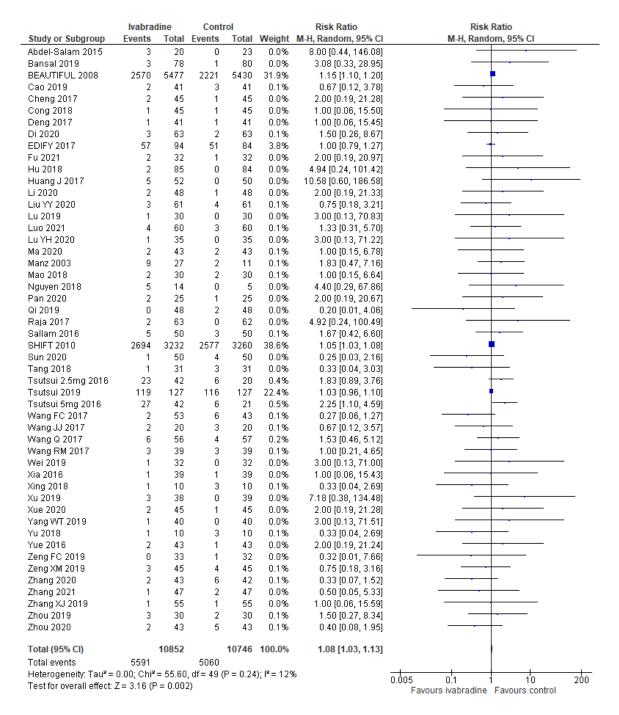
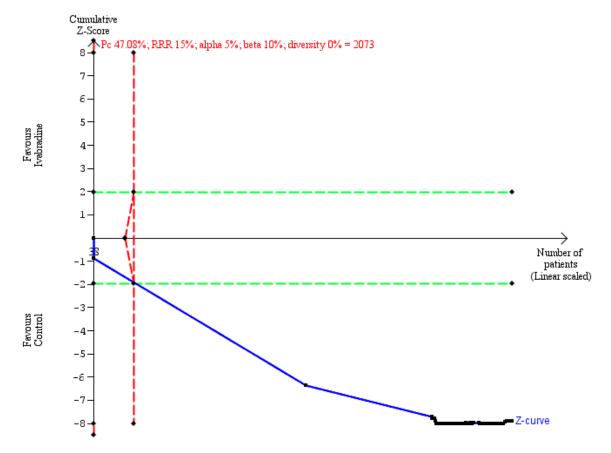


Figure 60 - Forest plot of the meta-analysis of non-serious adverse events using random-effects meta-analysis. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention)



**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.

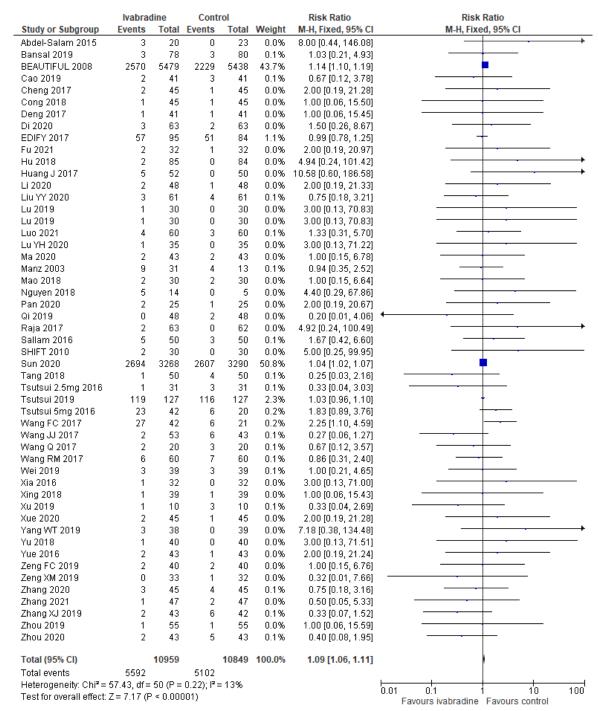


Figure 62 - Forest plot of the meta-analysis of non-serious adverse events using a best- compared with worst-case scenario.

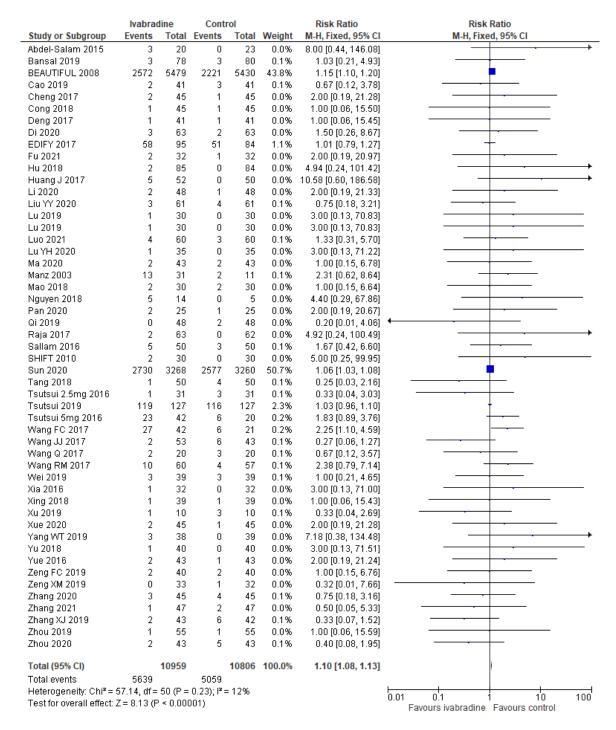


Figure 63 - Forest plot of the meta-analysis of non-serious adverse events using a worst- compared with best-case scenario.

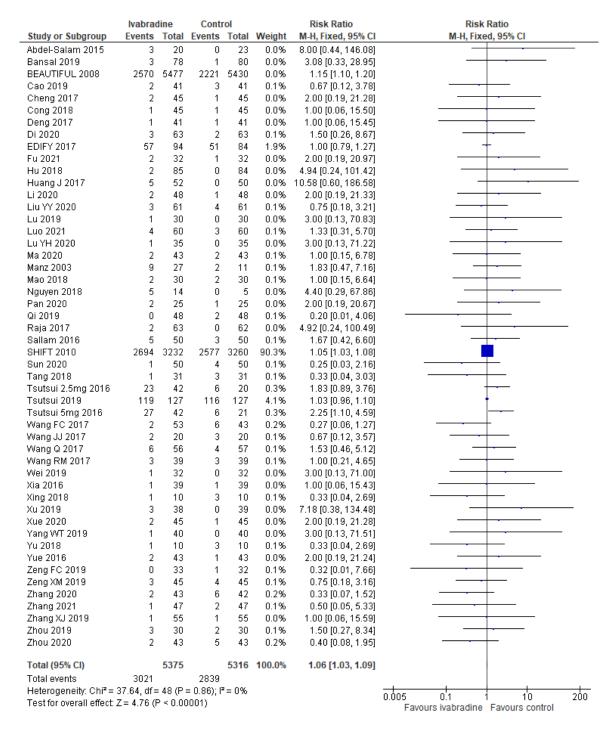


Figure 64 - Forest plot of the sensitivity analysis of non-serious adverse events removing the BEAUTIFUL trial.

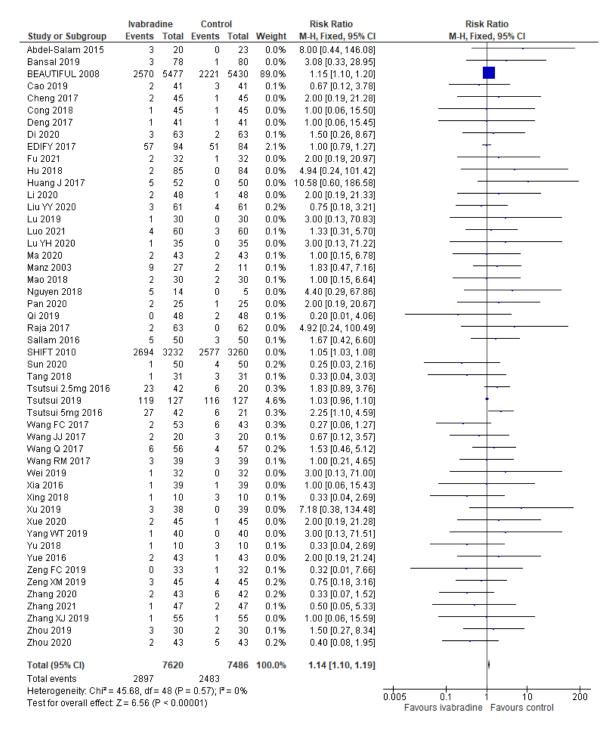


Figure 65 - Forest plot of the sensitivity analysis of non-serious adverse events removing the SHIFT trial.

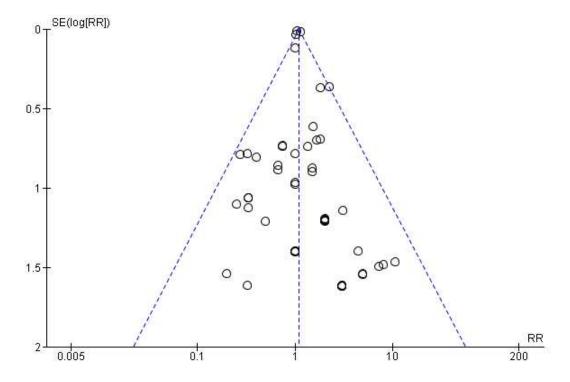


Figure 66 – Funnel plot of the analysis of non-serious adverse events. The funnel plot did not indicate small study bias.

# 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*

8	lval	oradin	•	•	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean		Total			Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Barilla 2016	65.7	9.8	30	81.9	7.5	28		-16.20 [-20.67, -11.73]	
Cavosoglu 2015	83.5			101.7	16.9	29		-18.20 [-25.83, -10.57]	
Cavosogiu 2015 Chaudhari 2014		5.06		91.33	8.9	80		-20.73 [-22.98, -18.48]	
CONSTATHE-DHF 2016	86	15	13	98	12	13	2.2%	-12.00 [-22.44, -1.56]	
Di 2020	66.64			73.75	6.01	63	3.3%	-7.11 [-8.98, -5.24]	-
EDIFY 2017		3.46	95	-3.5	4.18	84	3.4%	-9.50 [-10.63, -8.37]	<b>+</b>
Fu 2021	63.7	3.9	32	67.4	4.2	32	3.3%	-3.70 [-5.69, -1.71]	<b>→</b>
Kosmala 2013	62	8	30	70	7.2	31	3.2%	-8.00 [-11.78, -4.22]	<u> </u>
Li 2020	74.96			84.69	15.49	48	3.0%	-9.73 [-14.49, -4.97]	
Liu Y 2020	60.1	1.3	61	72.3	1.6	61		-12.20 [-12.72, -11.68]	•
Luo 2021	62.84		60	68.51	7.47	60	3.3%	-5.67 [-8.15, -3.19]	<u> </u>
Ma 2020	64.73			87.52	1.49	43		-22.79 [-23.35, -22.23]	•
Mansour 2011	-24	13	30	-3	7.7	23		-21.00 [-26.62, -15.38]	
Moiseev 2011	64	3.17	26	65	3.71	23	3.3%	-1.00 [-2.95, 0.95]	<del></del>
Nguyen 2018	86	5.2	14	104	8.37	5		-18.00 [-25.83, -10.17]	
Ordu 2015	68.36		49	80.4	8.3	49	3.2%	-12.04 [-15.33, -8.75]	
Pan 2020	68.7	7.3	25	72.3	6.1	25	3.2%	-3.60 [-7.33, 0.13]	<del></del>
Raja 2017	63.8	3.6	63	75.9	8.4	62	3.3%	-12.10 [-14.37, -9.83]	<del></del>
Sallam 2016	69	11	50	78	17	50	2.9%	-9.00 [-14.61, -3.39]	<del></del>
Su DL 2020	77.31	4.28	30	84.23	5.21	30	3.3%	-6.92 [-9.33, -4.51]	<del></del>
Sun 2020	75	6	50	86	6	50	3.3%	-11.00 [-13.35, -8.65]	<del></del>
Tarlovskaya 2011	67.7	12.4	8	77	10	10	2.2%	-9.30 [-19.89, 1.29]	<del></del>
Tsutsui 2.5mg 2016	66.6	7.2	41	79.8	9.4	20	3.1%	-13.20 [-17.87, -8.53]	
Tsutsui 2019	66.7	11.4	127	76.6	10.7	127	3.3%	-9.90 [-12.62, -7.18]	<del></del>
Tsutsui 5mg 2016	66.8	8.8	40	79.8	9.4	21	3.0%	-13.00 [-17.86, -8.14]	
Wei 2019	72.03	4.11	32	86.35	8.62	32	3.2%	-14.32 [-17.63, -11.01]	<del></del>
Xu 2019	67.8	5.1	38	71.1	7.8	39	3.3%	-3.30 [-6.24, -0.36]	
Yang WT 2019	65.4	8.4	40	73.9	7.5	40	3.2%	-8.50 [-11.99, -5.01]	<del></del>
Yu 2019	64.9	6.2	33	76.7	8.8	33	3.2%	-11.80 [-15.47, -8.13]	<del></del>
Zhang 2021	68.32	3.33	47	74.23	4.02	47	3.4%	-5.91 [-7.40, -4.42]	
Zhang Y 2020	68	3	27	74	3	27	3.4%	-6.00 [-7.60, -4.40]	<del></del>
Zhou 2020	70.5	6.3	43	85.3	7.6	43	3.3%	-14.80 [-17.75, -11.85]	<del></del>
Total (95% CI)			1395			1328	100.0%	-10.83 [-13.42, -8.23]	•
Heterogeneity: Tau² = 51.4 Test for overall effect: Z = (				31 (P	< 0.0000	01); I²=	98%		-20 -10 0 10 20 Favours ivabradine Favours control

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.

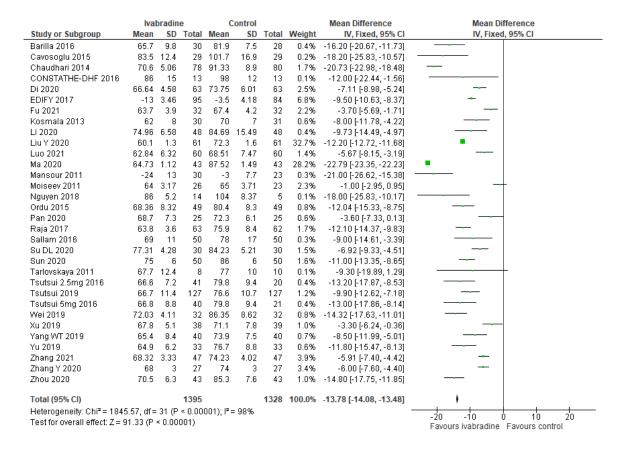


Figure 68 - Forest plot of the meta-analysis of resting heart rate at follow-up using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to decrease the resting heart rate at follow-up by 13.78 beats per minute at follow-up.

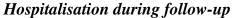
Left ventricular ejection fraction

Study or Subgroup	lval Mean	bradine SD	Total	Co Mean	ntrol SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference 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		4.24	80	1.5%	2.00 [0.76, 3.24]	<del></del>
Barilla 2016	4.1	2.5	30	0.8	1.2	28	1.5%	3.30 [2.30, 4.30]	—
3i 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		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		4.24	80	1.5%	2.00 [0.76, 3.24]	<del>-</del>
Cheng 2017	48.25	6.68	45	42.64	8.4	45	1.3%	5.61 [2.47, 8.75]	<del></del>
Chen G 2020	58.49	5.51	30	49.67		30	1.4%	8.82 [6.35, 11.29]	
Chen HX 2021	41.77	6.02	30		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 32.603	4.8	32	1.4%	2.60 [0.12, 5.08] 9.70 [5.82, 13.57]	
3uo 2017 He 2019	42.301 33.51	6.358 10.12	16 30	31.12	4.7	16 31	1.2%	2.39 [-2.52, 7.30]	
не 2019 Ни 2017	48.31	6.54	30	41.73		30	1.3%	6.58 [3.41, 9.75]	
Tu 2017 Hu 2018	39.2	12.1	85		11.2	84	1.3%	0.30 [-3.21, 3.81]	
luang 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]	
i 2018	52.5	2.5	45	41.9	2.6	44	1.5%	10.60 [9.54, 11.66]	
i 2020	39.84	3.69	48		2.47	48	1.5%	3.58 [2.32, 4.84]	
i B 2020	50.09	5.32	55		4.83	55	1.5%	4.15 [2.25, 6.05]	
iu 2019	57.6	6.7	48	47.9	8.7	48	1.3%	9.70 [6.59, 12.81]	
iu 2020	51.54	1.18	49	41.29		49	1.5%	10.25 [9.83, 10.67]	-
_u 2019	41.27	4.65	28	38.1		27	1.4%	3.17 [0.84, 5.50]	
_uo 2021	48.29	5.32	60	45.31		60	1.5%	2.98 [1.21, 4.75]	
/la 2016	36	3.11	30	32.3		30	1.5%	3.70 [2.16, 5.24]	
/la 2020	58.01	8.39	43	46.32		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]	<del></del>
/lanz 2003	37.2	10.01	27	38.4	9.3	11	0.8%	-1.20 [-7.87, 5.47]	<del></del>
/lao 2018	44.3	7.9	30	39.3	7.1	30	1.2%	5.00 [1.20, 8.80]	<del></del>
doiseev 2011	36.5	8.19	26	35.7	5.51	23	1.2%	0.80 [-3.07, 4.67]	<del></del>
°an 2020	36.5	6	25	33.7	8.8	25	1.2%	2.80 [-1.38, 6.98]	<del> </del>
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]	<del>                                     </del>
3hen 2018	51.2	1.6	56	43.2	1.3	56	1.5%	8.00 [7.46, 8.54]	_
3HIFT 2010	34.7	10.2	204	31.5	10	199	1.4%	3.20 [1.23, 5.17]	—
3ong 2021	63.16	3.17	48		3.46	48		11.49 [10.16, 12.82]	
3u 2020	52.1	4.2	40	46.2	5	30	1.4%	5.90 [3.69, 8.11]	
Bu DL 2020	45.28	4.14	30	39.56		30	1.4%	5.72 [3.34, 8.10]	
Bun 2021	50.2	5.6	59 31	43.4	5.5 4.59	59	1.4%	6.80 [4.80, 8.80]	<u> </u>
Fang 2018 Fatarchenko 2008	41.1 58.9	4.93 2.8	29	38 51.2	4.09	31 30	1.4% 1.5%	3.10 [0.73, 5.47] 7.70 [5.91, 9.49]	
rsutsui 2.5mg 2016	33.8	8.7	41	31.2	8.8	20	1.1%	2.80 [-1.89, 7.49]	
rsutsui 2.5111g 2010 Fsutsui 2019	38.9	12.8	127	33.3	13	127	1.3%	5.60 [2.43, 8.77]	<u> </u>
rsutsui 5mg 2016	35	10.4	40	31	8.8	21	1.1%	4.00 [-0.96, 8.96]	
atinian 2015/	51.2	2.1	26	45.3	1.9	26	1.5%	5.90 [4.81, 6.99]	
Vang 2019	37.79	5.23	35		4.86	33	1.4%	0.47 [-1.93, 2.87]	<del></del>
Vang FC 2017	42.51	6.03	53	36.78	7.4	43	1.4%	5.73 [2.99, 8.47]	<del></del>
Vang GK 2020	55.3	10.4	36	52.2		36	1.1%	3.10 [-1.87, 8.07]	<del> </del>
Vang لیا 2020	58.63	4.25	35	52.34		35	1.4%	6.29 [4.35, 8.23]	
Vang RM 2017	49.06	7.05	39	43.03		39	1.3%	6.03 [2.94, 9.12]	
Vang YH 2018	55.35	7.1	34	52.86		34	1.3%	2.49 [-0.68, 5.66]	+
Vei 2019	48.14	2.62	32	41.69	1.06	32	1.5%	6.45 [5.47, 7.43]	-
(ia 2016	48.25	6.65	39	41.57		39	1.4%	6.68 [3.88, 9.48]	
(u 2019	46.2	3.8	38	43.9	3.4	39	1.5%	2.30 [0.69, 3.91]	
(u 2020	49.83	3.25	61	45.01	2.76	61	1.5%	4.82 [3.75, 5.89]	
/ang WT 2019	48.3	5.4	40	43.2	6.5	40	1.4%	5.10 [2.48, 7.72]	
/ang Z 2019	46.87	6.38	67	43.61		68	1.4%	3.26 [1.03, 5.49]	
/ao 2016	38.22	4.86	36		3.52	36	1.4%	3.99 [2.03, 5.95]	
/i 2017	37.72	7.6	43		6.08	42	1.3%	5.88 [2.96, 8.80]	
/u 2019	29.3	3	33	27.7	3.4	33	1.5%	1.60 [0.05, 3.15]	_
/ue 2016	39.78	3.44	40		3.28	40	1.5%	2.08 [0.61, 3.55]	
Zeng FC 2019	59.36	6.25	33		5.52	32	1.3%	6.19 [3.33, 9.05]	
Zeng XM 2019 Zhang 2010	57.6	4.2	45	45.2	4.7	45		12.40 [10.56, 14.24]	
Thang 2019	67 50.24	8	30	62	5.4	30	1.3%	5.00 [1.55, 8.45]	
Thang 2020 Thang 2021	50.21	6.47	43	45.19		42	1.3%	5.02 [2.17, 7.87]	
Thang 2021	48.32	4.23	47	43.76		47	1.5%	4.56 [2.87, 6.25]	
Thang J 2019	35.16 51.77	2.68	45 55	35.34 20.02		41 55	1.5%	-0.18 [-1.35, 0.99]	]
Thang XJ 2019	51.77	3.84	55 27	38.02 51		55 27		13.75 [12.52, 14.98]	
Thang Y 2020	57 47 00	7 00	27	51 24.24	12	27	0.9%	6.00 [-0.40, 12.40]	
Ihou 2019 Ihou 2020	47.89 46.8	7.89 6.3	30 43	34.34 36.7	7.6	30 43	1.3% 1.3%	13.55 [10.07, 17.03]	l
.110u 2020	40.6	0.3	43	30.7	7.0	43	1.370	10.10 [7.15, 13.05]	
otal (95% CI)			3323			3230	100.0%	5.43 [4.52, 6.34]	•
(00.00)				0 (D = 0 0	00041			ST. IS [ NOZ.   SIST]	
leterogeneity: Tau <sup>z</sup> = 13.8	(5 · (*) b /# − *								-10 -5 0 5 10

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%.

Study or Subarons		oradine	Total	Co Mean	ntrol SD	Total	Weight	Mean Difference	Mean Difference IV, Fixed, 95% CI
Study or Subgroup Abdel-Salam 2015	Mean 39	7	Total 20	33	10	23	Weight 0.1%	IV, Fixed, 95% CI 6.00 [0.89, 11.11]	IV, Fixed, 95% CI
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]	-
3i 2020	63.06	9.85	99		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]	<del></del>
Chaudhari 2014	35	3.71	78	33	4.24	80	2.3%	2.00 [0.76, 3.24]	<del></del>
Cheng 2017	48.25	6.68	45	42.64	8.4	45	0.4%	5.61 [2.47, 8.75]	<del></del>
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]	<del></del>
CONSTATHE-DHF 2016	29	8	13	25	8	13	0.1%	4.00 [-2.15, 10.15]	<del>+</del>
Di 2020	49.98	4.98	63	44.67	4.5	63	1.3%	5.31 [3.65, 6.97]	
u 2021	51.6	5.3	32	49	4.8	32	0.6%	2.60 [0.12, 5.08]	<del></del>
3uo 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		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]	<del></del>
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		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]	
_iu 2019	57.6	6.7	48	47.9	8.7	48	0.4%	9.70 [6.59, 12.81]	
_iu 2020	51.54	1.18	49	41.29		49	20.1%	10.25 [9.83, 10.67]	
_u 2019	41.27	4.65	28	38.1	4.15	27	0.7%	3.17 [0.84, 5.50]	
_uo 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		30	1.5%	3.70 [2.16, 5.24]	—
/la 2020 /lanagus 2011	58.01	8.39	43	46.32		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		10.01	27	38.4	9.3	11	0.1%	-1.20 [-7.87, 5.47]	<u> </u>
Mao 2018 Maio agu 2011	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	4.25	25	33.7	8.8	25	0.2%	2.80 [-1.38, 6.98]	<u></u>
Qi 2019 Paia 2017	41.69 30.1	4.25 4	48 63	37.25 28.1	3.92	48 62	1.3%	4.44 [2.80, 6.08]	<u> </u>
Raja 2017 Ballam 2016	42	17	50	37	13	50	1.8% 0.1%	2.00 [0.60, 3.40] 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	1.3	199	0.9%	3.20 [1.23, 5.17]	<u> </u>
30ng 2021	63.16	3.17	48	51.67		48		11.49 [10.16, 12.82]	
3u 2020	52.1	4.2	40	46.2	5.40	30	0.7%	5.90 [3.69, 8.11]	
3u DL 2020	45.28	4.14	30	39.56	5.21	30	0.6%	5.72 [3.34, 8.10]	
3un 2021	50.2	5.6	59	43.4	5.5	59	0.9%	6.80 [4.80, 8.80]	
Fang 2018	41.1	4.93	31	38	4.59	31	0.6%	3.10 [0.73, 5.47]	<del></del> -
Tatarchenko 2008	58.9	2.8	29	51.2	4.1	30	1.1%	7.70 [5.91, 9.49]	<del></del>
rsutsui 2.5mg 2016	33.8	8.7	41	31	8.8	20	0.2%	2.80 [-1.89, 7.49]	<del></del>
rsutsui 2019	38.9	12.8	127	33.3	13	127	0.4%	5.60 [2.43, 8.77]	<del></del>
rsutsui 5mg 2016	35	10.4	40	31	8.8	21	0.1%	4.00 [-0.96, 8.96]	<del></del>
/atinian 2015	51.2	2.1	26	45.3	1.9	26	3.0%	5.90 [4.81, 6.99]	<del>-</del>
Vang 2019	37.79	5.23	35	37.32		33	0.6%	0.47 [-1.93, 2.87]	<del></del>
Vang FC 2017	42.51	6.03	53	36.78	7.4	43	0.5%	5.73 [2.99, 8.47]	
Vang GK 2020	55.3	10.4	36	52.2		36	0.1%	3.10 [-1.87, 8.07]	+
2020 ليا Vang	58.63	4.25	35	52.34		35	1.0%	6.29 [4.35, 8.23]	
Vang RM 2017	49.06	7.05	39	43.03		39	0.4%	6.03 [2.94, 9.12]	
Vang YH 2018	55.35	7.1	34	52.86	6.2	34	0.4%	2.49 [-0.68, 5.66]	<del> </del>
Vei 2019	48.14	2.62	32	41.69		32	3.7%	6.45 [5.47, 7.43]	-
(ia 2016	48.25	6.65	39	41.57	5.96	39	0.5%	6.68 [3.88, 9.48]	
(u 2019	46.2	3.8	38	43.9	3.4	39	1.4%	2.30 [0.69, 3.91]	<del></del>
(u 2020	49.83	3.25	61	45.01		61	3.1%	4.82 [3.75, 5.89]	
ang WT 2019	48.3	5.4	40	43.2	6.5	40	0.5%	5.10 [2.48, 7.72]	
/ang Z 2019	46.87	6.38	67	43.61		68	0.7%	3.26 [1.03, 5.49]	
/ao 2016	38.22	4.86	36	34.23		36	0.9%	3.99 [2.03, 5.95]	
/i 2017	37.72	7.6	43	31.84		42	0.4%	5.88 [2.96, 8.80]	
/u 2019	29.3	3	33	27.7	3.4	33	1.5%	1.60 [0.05, 3.15]	<del> </del>
/ue 2016	39.78	3.44	40	37.7		40	1.6%	2.08 [0.61, 3.55]	
Zeng FC 2019	59.36	6.25	33	53.17		32	0.4%	6.19 [3.33, 9.05]	
Zeng XM 2019	57.6	4.2	45	45.2	4.7	45		12.40 [10.56, 14.24]	
Zhang 2019	67	8	30	62	5.4	30	0.3%	5.00 [1.55, 8.45]	<del></del>
Zhang 2020	50.21	6.47	43	45.19		42	0.4%	5.02 [2.17, 7.87]	
Zhang 2021	48.32	4.23	47	43.76		47	1.3%	4.56 [2.87, 6.25]	
Zhang J 2019	35.16	2.68	45	35.34		41	2.6%	-0.18 [-1.35, 0.99]	<b>T</b>
Zhang XJ 2019	51.77	3.84	55	38.02		55		13.75 [12.52, 14.98]	-
Zhang Y 2020	57	12	27	51	12	27	0.1%	6.00 [-0.40, 12.40]	<u> </u>
Zhou 2019	47.89	7.89	30	34.34		30		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 (05% CI)			3333			3330	100.0%	6 63 16 44 6 021	1
otal (95% CI)			3323		.,	JZ30	100.0%	6.63 [6.44, 6.82]	
leterogeneity: Chi² = 1459	100 44 -								

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%.



	_		, ,		_			
		lvabrad	dine	Contr	rol		Risk Ratio	Risk Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ξ.	Abdel-Salam 2015	1	20	2	23	0.1%	0.57 [0.06, 5.88]	
	Adamyan 2008	4	70	11	75	0.4%	0.39 [0.13, 1.17]	<del></del>
	Babushkina 2020	8	56	14	53	0.6%	0.54 [0.25, 1.18]	<del></del>
	Bansal 2019	19	78	44	80	1.8%	0.44 [0.29, 0.69]	<del></del>
	BEAUTIFUL 2008	681	5479	704	5438	29.9%	0.96 [0.87, 1.06]	•
	CONSTATHE-DHF 2016	1	13	0	13	0.0%	3.00 [0.13, 67.51]	<del></del>
	Luo 2021	4	60	10	60	0.4%	0.40 [0.13, 1.21]	<del></del>
	Moiseev 2011	3	26	6	23	0.3%	0.44 [0.12, 1.57]	
	SHIFT 2010	1231	3241	1356	3264	57.2%	0.91 [0.86, 0.97]	•
	Tsutsui 2019	55	127	63	127	2.7%	0.87 [0.67, 1.14]	+
	Tumasyan 2016	17	53	29	53	1.2%	0.59 [0.37, 0.93]	<del></del>
	Tumasyan 2017	33	53	47	57	1.9%	0.76 [0.59, 0.96]	~
	Tumasyan 2018	28	46	38	45	1.6%	0.72 [0.55, 0.94]	<del></del>
	Wang GK 2020	1	36	2	36	0.1%	0.50 [0.05, 5.27]	· · ·
	Wang Q 2017	3	56	10	57	0.4%	0.31 [0.09, 1.05]	<del></del>
	Wang RM 2017	4	39	9	39	0.4%	0.44 [0.15, 1.32]	
	Zhou 2019	12	30	19	30	0.8%	0.63 [0.38, 1.06]	
	Total (95% CI)		9483		9473	100.0%	0.89 [0.85, 0.94]	•
	Total events	2105		2364				
	Heterogeneity: Chi <sup>z</sup> = 34.25	5, df = 16	(P = 0.0)	06); l <sup>2</sup> = :	53%			0.01 0.1 1 10 100
	Test for overall effect: $Z = 4$ .	.57 (P < 0	.00001	)				'0.01 0.1 1 1'0 100' Favours ivabradine Favours control
		•						ravours ivabradine ravours control

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.

	Ivabra	line	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Abdel-Salam 2015	1	20	2	23	0.3%	0.57 [0.06, 5.88]	
Adamyan 2008	4	70	11	75	1.3%	0.39 [0.13, 1.17]	· · ·
Babushkina 2020	8	56	14	53	2.3%	0.54 [0.25, 1.18]	· <del>  </del>
Bansal 2019	19	78	44	80	6.1%	0.44 [0.29, 0.69]	· · · · · · · · · · · · · · · · · · ·
BEAUTIFUL 2008	681	5479	704	5438	19.3%	0.96 [0.87, 1.06]	· •
CONSTATHE-DHF 2016	1	13	0	13	0.2%	3.00 [0.13, 67.51]	l — — — — —
Luo 2021	4	60	10	60	1.2%	0.40 [0.13, 1.21]	· <del>  </del>
Moiseev 2011	3	26	6	23	1.0%	0.44 [0.12, 1.57]	· · · · · · · · · · · · · · · · · · ·
SHIFT 2010	1231	3241	1356	3264	20.8%	0.91 [0.86, 0.97]	· •
Tsutsui 2019	55	127	63	127	11.2%	0.87 [0.67, 1.14]	<del>-• </del>
Tumasyan 2016	17	53	29	53	5.6%	0.59 [0.37, 0.93]	· ·
Tumasyan 2017	33	53	47	57	12.2%	0.76 [0.59, 0.96]	· · ·
Tumasyan 2018	28	46	38	45	11.2%	0.72 [0.55, 0.94]	<del></del>
Wang GK 2020	1	36	2	36	0.3%	0.50 [0.05, 5.27]	· · ·
Wang Q 2017	3	56	10	57	1.0%	0.31 [0.09, 1.05]	· · · · · · · · · · · · · · · · · · ·
Wang RM 2017	4	39	9	39	1.3%	0.44 [0.15, 1.32]	· · · · · · · · · · · · · · · · · · ·
Zhou 2019	12	30	19	30	4.7%	0.63 [0.38, 1.06]	· ·
Total (95% CI)		9483		9473	100.0%	0.75 [0.66, 0.86]	•
Total events	2105		2364				
Heterogeneity: Tau² = 0.02 Test for overall effect: Z = 4			•	0.005	); I <sup>z</sup> = 53%	5	0.01 0.1 1 10 100  Favours ivabradine Favours control

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.



	Ival	bradine		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Cavosoglu 2015	195	96	29	166	52	29	1.1%	29.00 [-10.74, 68.74]	<del></del>
Cheng 2017	322.33	175.15	45	235.56	171.25	45	0.3%	86.77 [15.20, 158.34]	
Cong 2018	522.19	52.35	45	442.14	42.12	45	4.4%	80.05 [60.42, 99.68]	
EDIFY 2017	4.3	50	84	7.9	67.9	84	5.2%	-3.60 [-21.63, 14.43]	<del></del>
Fu 2021	284.3	45	32	346.1	60.5	32	2.5%	-61.80 [-87.92, -35.68]	
Gou 2017	198.7	56.31	30	162.01	57.36	30	2.0%	36.69 [7.93, 65.45]	<del></del>
Guo 2017	454.752	35.173	16	415.375	52.456	16	1.8%	39.38 [8.43, 70.32]	
He 2019	428.1	25.52	30	350.8	26.8	31	9.8%	77.30 [64.17, 90.43]	-
Huang J 2017	386.41	101.75	52	306.24	135.87	50	0.8%	80.17 [33.45, 126.89]	
Li 2018	421.1	31.5	45	382.1	31.2	44	9.9%	39.00 [25.97, 52.03]	<del></del>
Liu 2019	523.27	45.46	49	446.25	39.23	49	6.0%	77.02 [60.21, 93.83]	<del></del>
Liu Y 2020	386	38	61	331	45	61	7.7%	55.00 [40.22, 69.78]	
Lu 2019	427.57	46.61	28	367.27	52.23	27	2.5%	60.30 [34.10, 86.50]	
Luo 2021	357.57	70.86	60	303.12	72.13	60	2.6%	54.45 [28.87, 80.03]	
Ma 2016	336	53.66	30	344.3	42.71	30	2.8%	-8.30 [-32.84, 16.24]	<del></del>
Manz 2003	379	117	30	307	98	30	0.6%	72.00 [17.39, 126.61]	
Mao 2018	379	117	30	307	98	30	0.6%	72.00 [17.39, 126.61]	
Pan 2020	378.6	48.5	19	366.2	42.8	18	1.9%	12.40 [-17.04, 41.84]	<del></del>
Raja 2017	493.5	4.6	63	367	82	62	4.0%	126.50 [106.06, 146.94]	·
Song 2021	340.62	65.69	48	289.62	45.66	48	3.3%	51.00 [28.37, 73.63]	
Su DL 2020	422.54	51.24	30	378.76	39.67	30	3.1%	43.78 [20.59, 66.97]	_ <del></del>
Wang FC 2017	384.2	43	53	278.5	82.7	43	2.3%	105.70 [78.41, 132.99]	$\rightarrow$
Wang GK 2020	347.9	80.8	36	299.1	87.2	36	1.1%	48.80 [9.97, 87.63]	
Xu 2020	396.52	36	61	341	30	61	12.2%	55.52 [43.76, 67.28]	<del></del>
Yu 2019	402.2	53.7	33	351.3	44.5	33	3.0%	50.90 [27.11, 74.69]	
Yue 2016	341.7	76.69	40	313.83	72.98	40	1.6%	27.87 [-4.94, 60.68]	<del>                                     </del>
Zhang J 2019	336.19	47.02	36	308.75	60.33	28	2.3%	27.44 [0.32, 54.56]	<del></del>
Zhang XJ 2019	411.47	123.49	55	324.21	102.55	55	0.9%	87.26 [44.84, 129.68]	
Zhou 2019	270.24	43.34	30	256.9	47.65	30	3.2%	13.34 [-9.71, 36.39]	<del>  •</del>
Zhou 2020	361.7	97.5	43	294.6	104.8	43	0.9%	67.10 [24.32, 109.88]	
Total (95% CI)			1243			1220	100.0%	50.62 [46.52, 54.72]	•
Heterogeneity: Chi <sup>2</sup> =	266.41, df	= 29 (P <	< 0.0001	01); <b>I</b> ² = 89	%				-100 -50 0 50 100
Test for overall effect:	Z = 24.19	(P < 0.00)	001)						-100 -50 0 50 100 Favours control Favours ivabradine
			,						Favours control Favours Madradine

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.

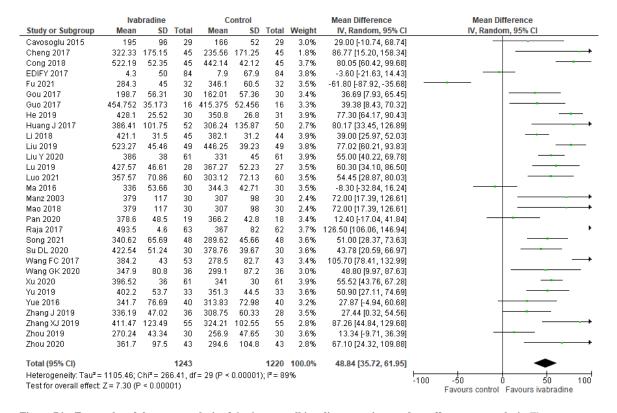


Figure 74 – Forest plot of the meta-analysis of 6-minutes walking distance using random-effects meta-analysis. The meta-analysis shows evidence of a beneficial effect of ivabradine versus control (placebo or no intervention) of 48.84 meters per 6 minutes.

E' and an discussion	*7	Publication	N	CP 1-1 P41-(-)		<i>6</i> /	Interv	entions
First author	Year	type	No. randomised	Clinical condition(s)	Age	%-female	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
Не	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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Unclear	No information
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "Randomization was performed
generation		by computer-generated allocation
		schedule drawn by an independent
		statistician."
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: "Study drugs were identical in
personnel		appearance. Both the patients and the
		investigators performing the baseline and
		follow-up assessment were blinded to the
		treatment allocation."
Blinding of outcome	Unclear	Not mentioned
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to standard
personnel		care. Therefore, the participants and
		personnel were probably unblinded.
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to standard
personnel		care. Therefore, the participants and
		personnel were probably unblinded.
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to standard
personnel		care. Therefore, the participants and
		personnel were probably unblinded.
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to standard
personnel		care. Therefore, the participants and
		personnel were probably unblinded.
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine and bisoprolol was compared
personnel		to bisoprolol alone. Therefore, the
		participants and personnel were probably
		unblinded.
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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
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Barilla 2016		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "patients were assigned to the two
generation		treatment groups according to a
		computer-generated list of
		randomisation"
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	High	Only the echocardiographer was blinded
assessment		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	Low	Quote: "the random-allocation schedule
generation		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	Low	Quote: "double-blind" and "randomised
personnel		to ivabradine or matched placebo"
Blinding of outcome	Low	Quote: "prespecified events were
assessment		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	Protocol registered retrospectively.
		However, serious adverse events and all-
	High for serious	cause mortality was reported.
	adverse events and	
	hospitalisations	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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Cao 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	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Chen G 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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

Blinding of participants and	High	Quote: "open-label"
personnel		
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

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

Chumburidze 2013		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: "double-blind"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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	Low	Quote: "randomly assigned via computer-
generation		generated sequence into two groups"
Allocation concealment	Low	Quote: "the randomisation sequence was
		held by an independent pharmacy"
Blinding of participants and	Low	Quote: "Commercially available IVA
personnel		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	Low	Quote: "outcome assessors remained
assessment		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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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
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Di 2020		
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

EDIFY 2017		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	Quote: "the randomisation was balanced
generation		1:1 and stratified on centres". No
		information on the procedure of
A 11	TT 1	generating the random sequence
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: "double-blind" and "study
personnel		investigators and participants were
		masked to treatment for the duration of
		the trial
Blinding of outcome	Low	Quote: "The trial was conducted under
assessment		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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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

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

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

He 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	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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.

Kosmala 2013		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "The procedure of randomization
generation		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	Low	Quote: "The hospital pharmacies were
personnel		responsible for drug randomization and
		dispensing, and both the investigators and
		patients were blinded to the treatment
		option."
Blinding of outcome	Unclear	No information
assessment		
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	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

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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Liu 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	High	Quote: "open-label"
personnel		
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

Liu 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Liu YY 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: "participants and researchers were
personnel		unaware of allocation"
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

Lu 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	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Luo 2021		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Ma 2016		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: "double-blind, placebo-
personnel		controlled"
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

Ma 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "A computer-driven
generation		randomization program was used to
		allocate"
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to no
personnel		intervention. Therefore, the participant
		and personnel were probably unblinded.
Blinding of outcome	High	No information. Only echocardiographer
assessment		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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Masi de Luca 2018		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Unclear	No information
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
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	Unclear	No information
assessment		
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	Low	Quote: "double-blind"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	Quote: "lottery"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"

personnel		
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

Raja 2017		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	"Computerized random number
generation		generation protocol"
Allocation concealment	Unclear	No information
Blinding of participants and	High	Only echocardiographer blinded
personnel		
Blinding of outcome	High	Only echocardiographer blinded
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Unclear	No information
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "computerized sequence
generation		generation"
Allocation concealment	Low	Quote: "ivabradine and placebo were
		prepared in numbered anonymous

		bottles"
Blinding of participants and	High	Quote: "single-blind"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	High	Quote: "open-label"	
personnel			
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	

SHIFT 2010 (Swedberg)				
Bias domain	Authors' judgement	Support for judgement		
Random sequence	Low	Quote: "Patients were randomly to		
generation		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	Low	Quote: "Eligible patients were allocated		
personnel		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	Low	Quote: "An endpoint validation		
assessment		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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
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 information

Sun 2021		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 information

<b>Tang 2018</b>		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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

Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open randomised controlled
personnel		study"
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: "The patients and investigators
personnel		were masked to the treatment allocation"
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "A minimization method for
generation		dynamic allocation was used with
		adjustment for study site, baseline resting
		HR ( $\geq$ 85 and $\leq$ 85 beats/min), and β-

		blocker dose before study treatment (0,
		>0–<50, and $\geq$ 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	Low	Quote: "Patients and investigators were
personnel		masked to treatment allocation, and study
		medications (ivabradine or placebo) were
		the same size and color."
Blinding of outcome	Low	Quote: ""An endpoint adjudication
assessment		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	Unclear	No information
generation		
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	Unclear	No information
assessment		
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	Unclear	No information
generation		
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.
Diadias of sections	I I and a su	
Blinding of outcome	Unclear	No information
assessment		
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	Unclear	No information
generation		
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	Unclear	No information
assessment		
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	Unclear	No information
generation		
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	Unclear	No information
assessment		
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	Unclear	No information
generation		
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	Unclear	No information
assessment	Unclear	No information
Incomplete outcome data		- 10
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	Unclear	No information
generation		
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	Unclear	No information
assessment		
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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 FC 2017		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information

Blinding of participants and	High	Quote: "open-label"
personnel		
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 JJ 2017		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 Q 2017		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 RM 2017		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
1	T. 1	NT 1 C 11
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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 GK 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 LJ 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Wei 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	High	Quote: "open-label"
personnel		
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

Xia 2016		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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

Xu 2019		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Xu 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

Xue 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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	High	Quote: "open-label"
personnel		
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

Yang Z 2019		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

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	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: "double-blind, placebo-

personnel		controlled"
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

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

Yu 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	High	Quote: "open-label"
personnel		
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

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

Zeng FC 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	High	Quote: "open-label"
personnel		
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

Zeng XM 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	High	Quote: "open-label"
personnel		
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

Zhang 2019		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Unclear	No information
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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
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<b>Zhang J 2019</b>		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Low	Quote: "sequential opaque envelopes"
Blinding of participants and	High	Quote: "open-label"
personnel		
Blinding of outcome	Unclear	No information
assessment		
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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 information

Zhang 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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

## Zhang Y 2020

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

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	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 information

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

Blinding of participants and	High	Quote: "open-label"
personnel		
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 information

Zhou 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"
generation		
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"
personnel		
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 information