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

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Supplement 1 – List of databases

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

Supplement 2 – Search strategy

MEDLINE 31/05/2021, n = 422

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

EMBASE 31/05/2021, n = 1401

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

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

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

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

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

LILACS 31/05/2021, n = 25

1. Ivabradine
2. Ivabradina
3. 1 or 2

CENTRAL 31/05/2021, n = 638

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

EudraCT 31/05/2021, n = 46

1. ivabradine OR corlanor OR procoralan OR corlentor

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

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

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

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

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

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

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

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

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

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

Chinese Science Journal Database (VIP), n = 165

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

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

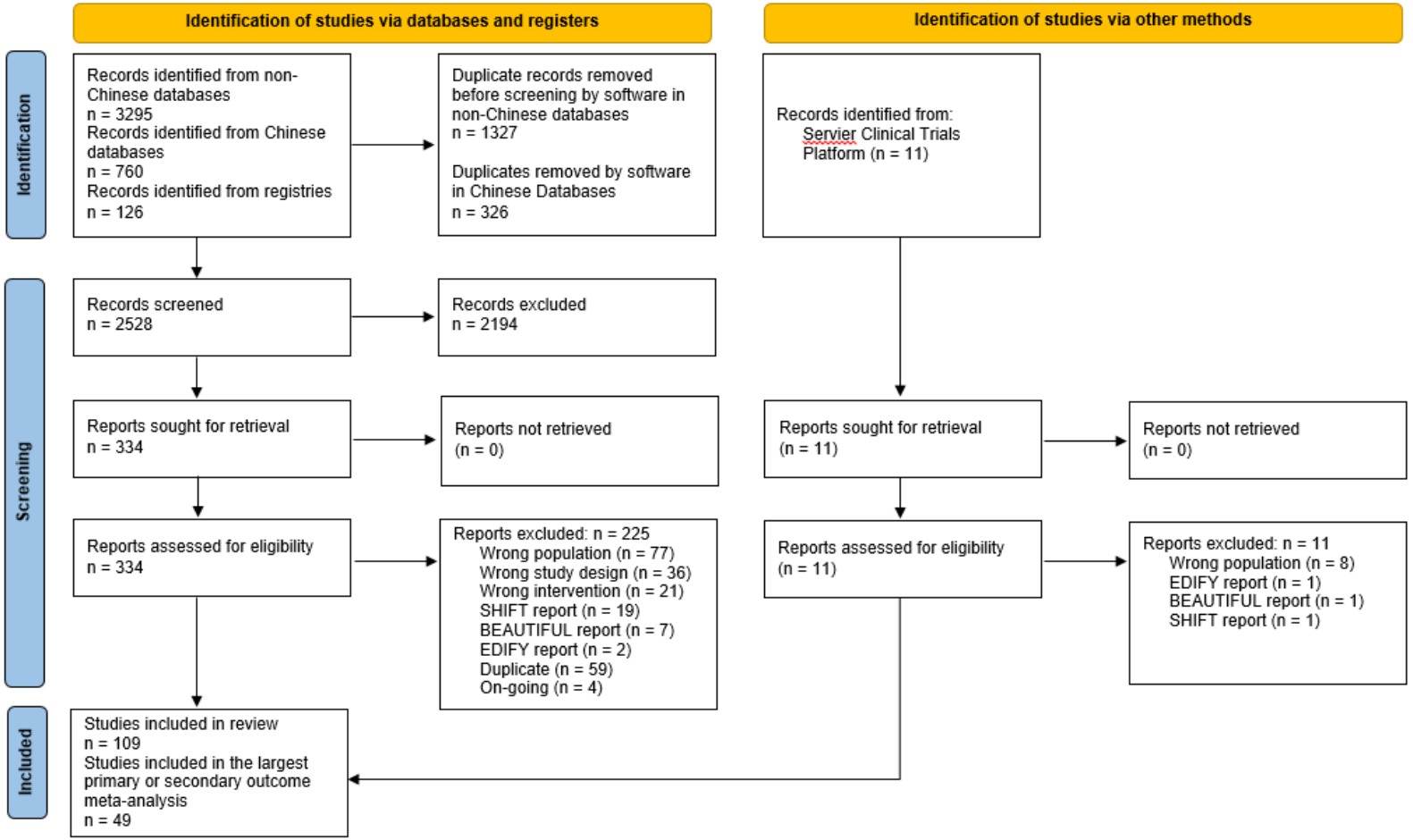
China National Knowledge Infrastructure (CNKI), n = 255

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

Wanfang, n = 200

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

Supplement 3 – PRISMA flow chart



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

Figure 1 – PRISMA flowchart.

Supplement 4 - Risk of bias

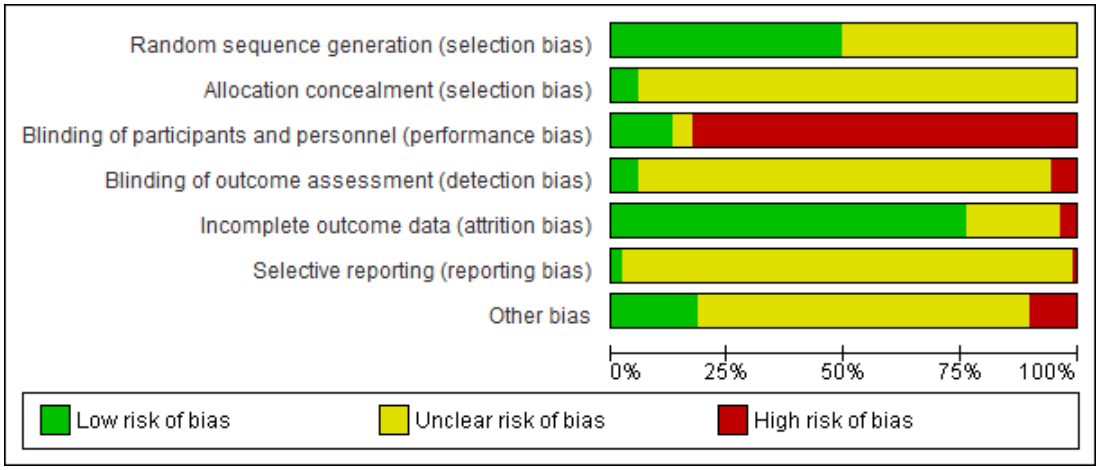
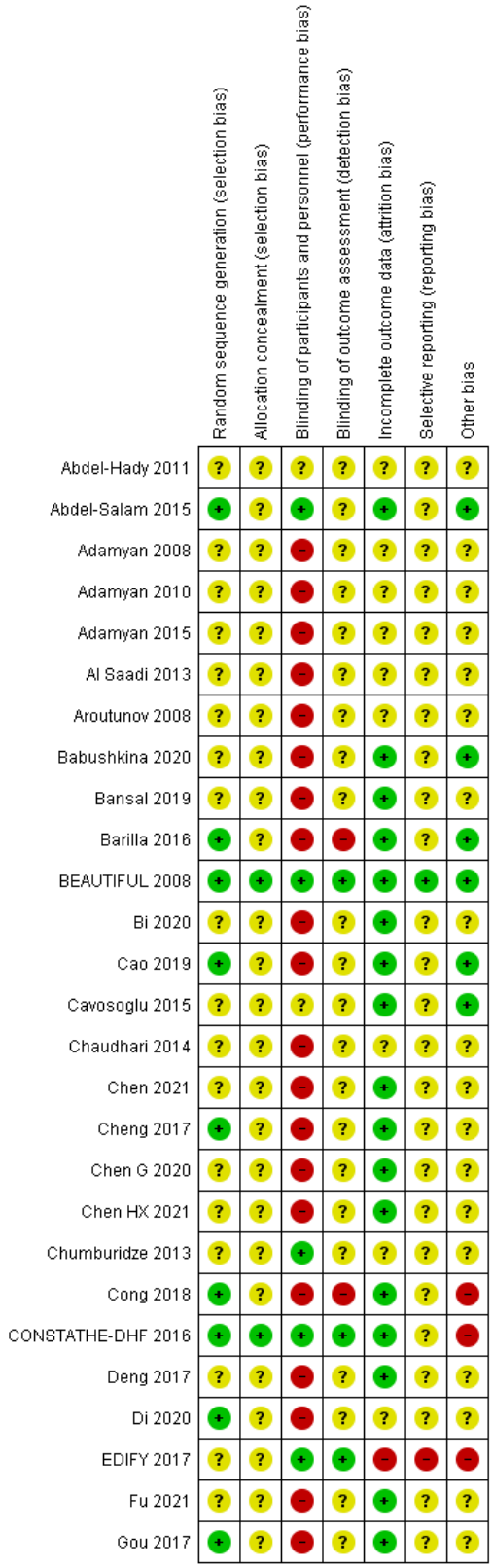
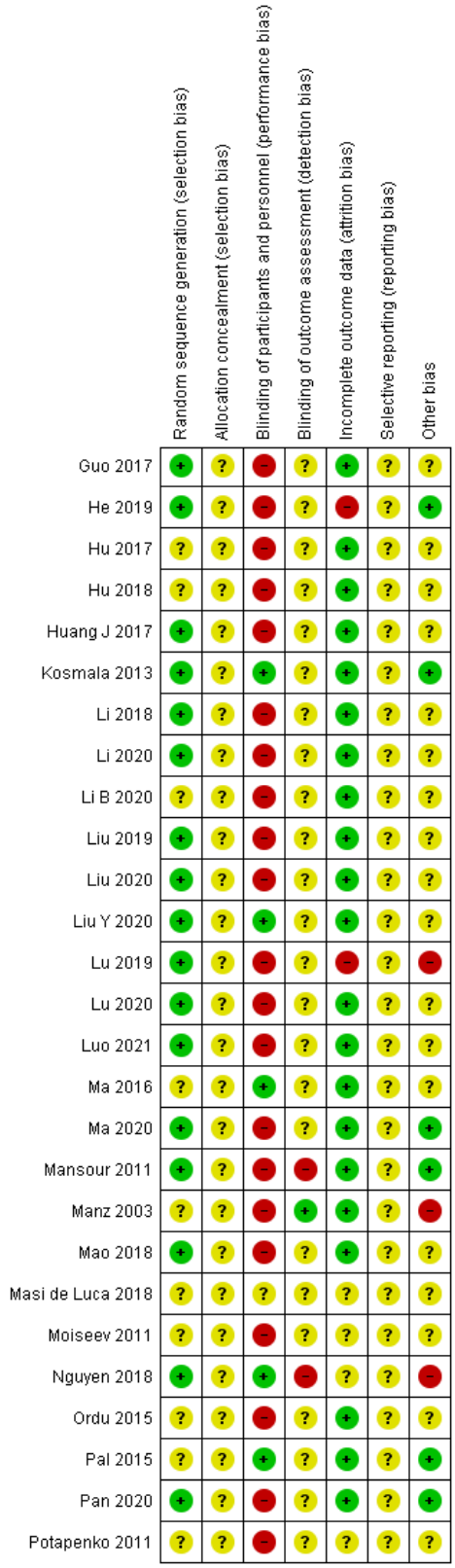
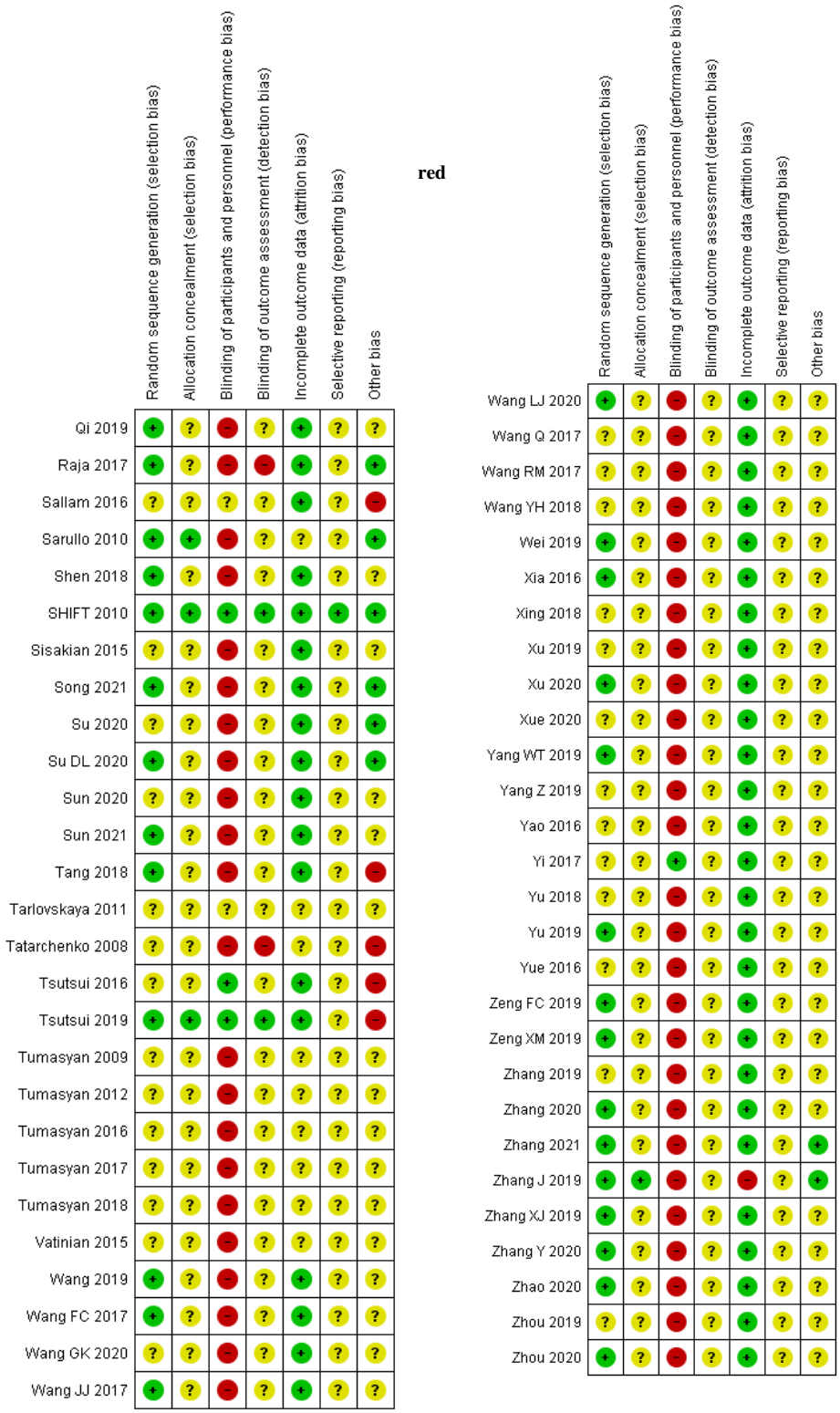


Figure 2 – Risk of bias graph.


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


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



red

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

Supplement 5 - All-cause mortality

Main analyses

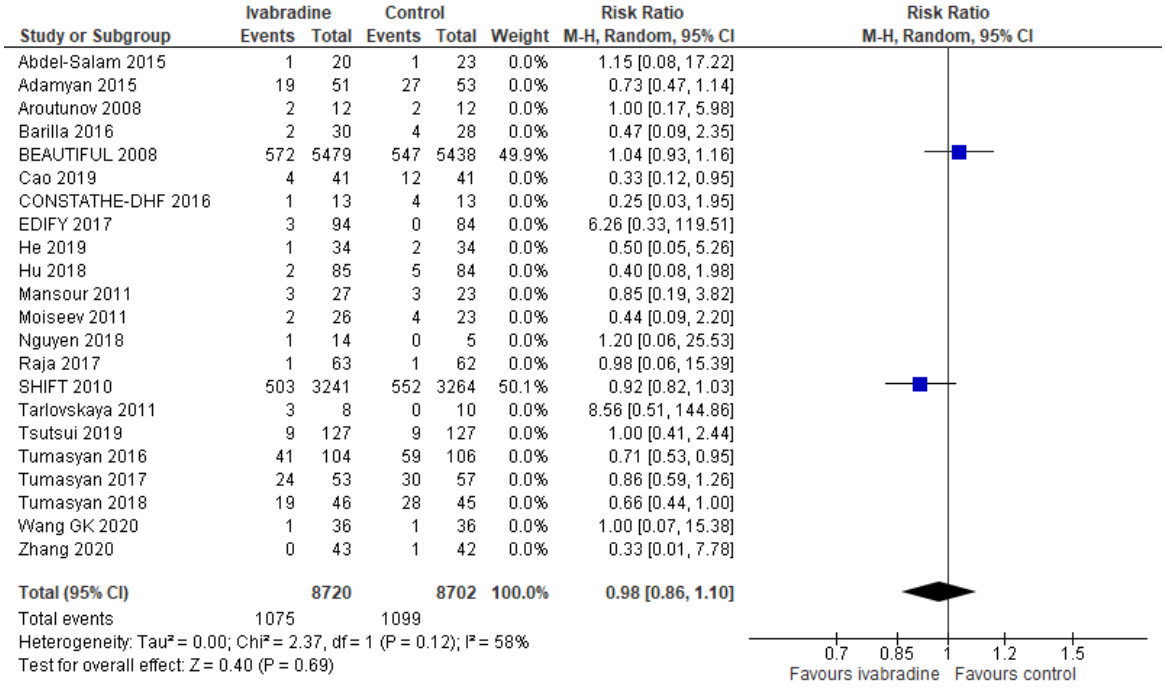


Figure 4 – Forest plot of the meta-analysis of all-cause mortality using random-effecs meta-analysis including only trials at low risk of bias, except for for-profit bias. The meta-analysis showed no evidence of an difference between ivabradine versus placebo.

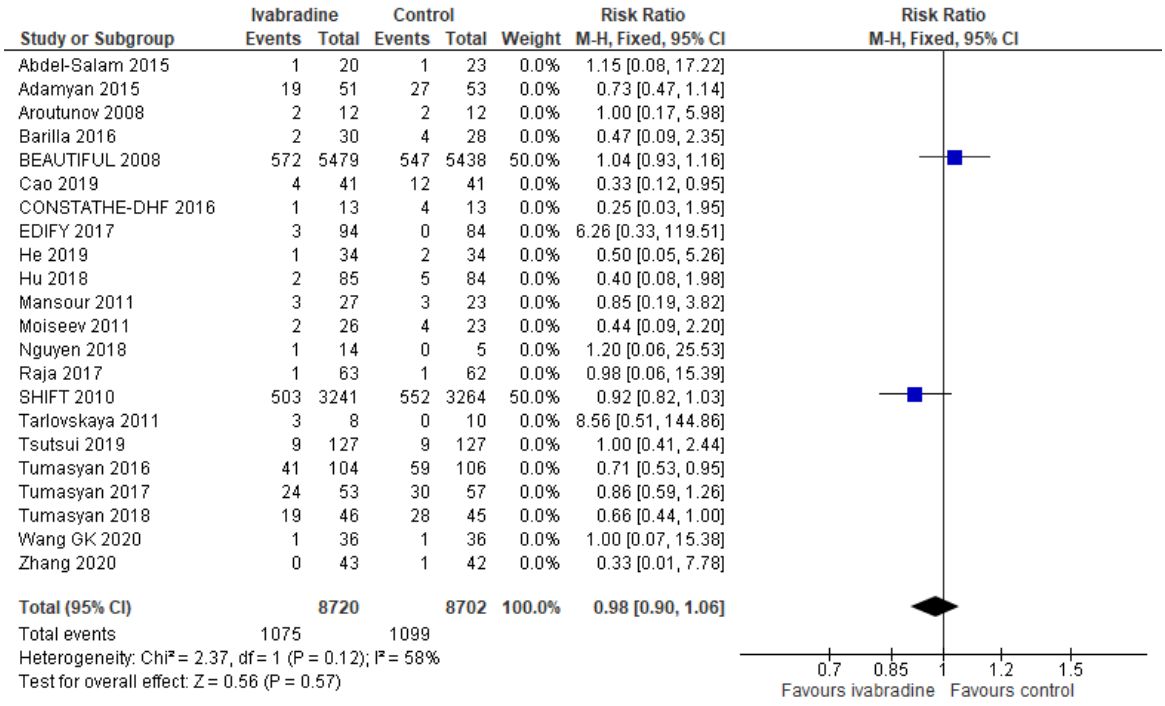


Figure 5 – Forest plot of the meta-analysis of all-cause mortality using fixed-effect meta-analysis including only trials at low risk of bias, except for for-profit bias. The meta-analysis showed no evidence of a difference between ivabradine versus placebo.

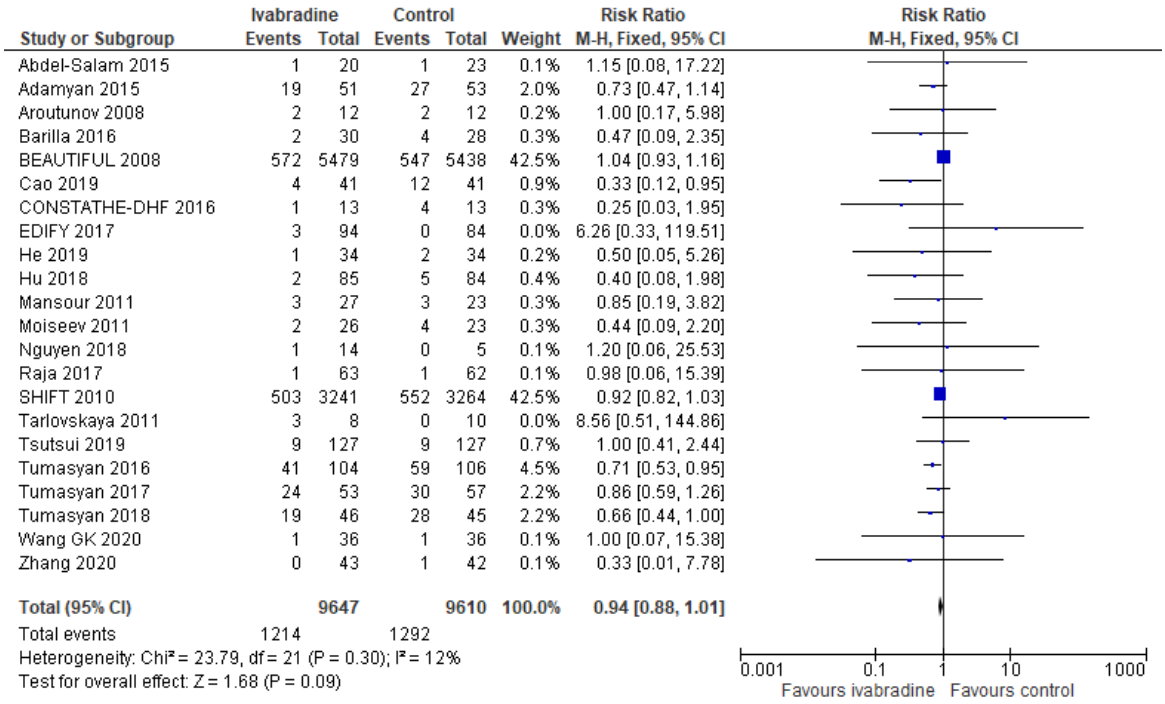


Figure 6 - Forest plot of the meta-analysis of all-cause mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

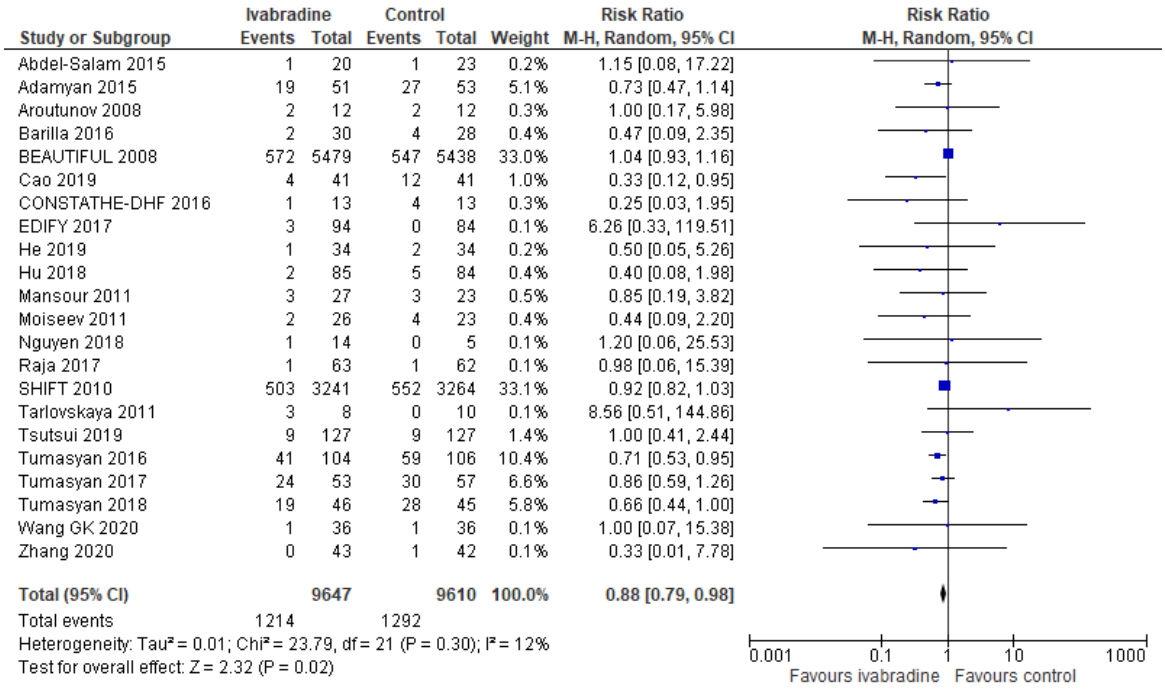


Figure 7 - Forest plot of the meta-analysis of all-cause mortality using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

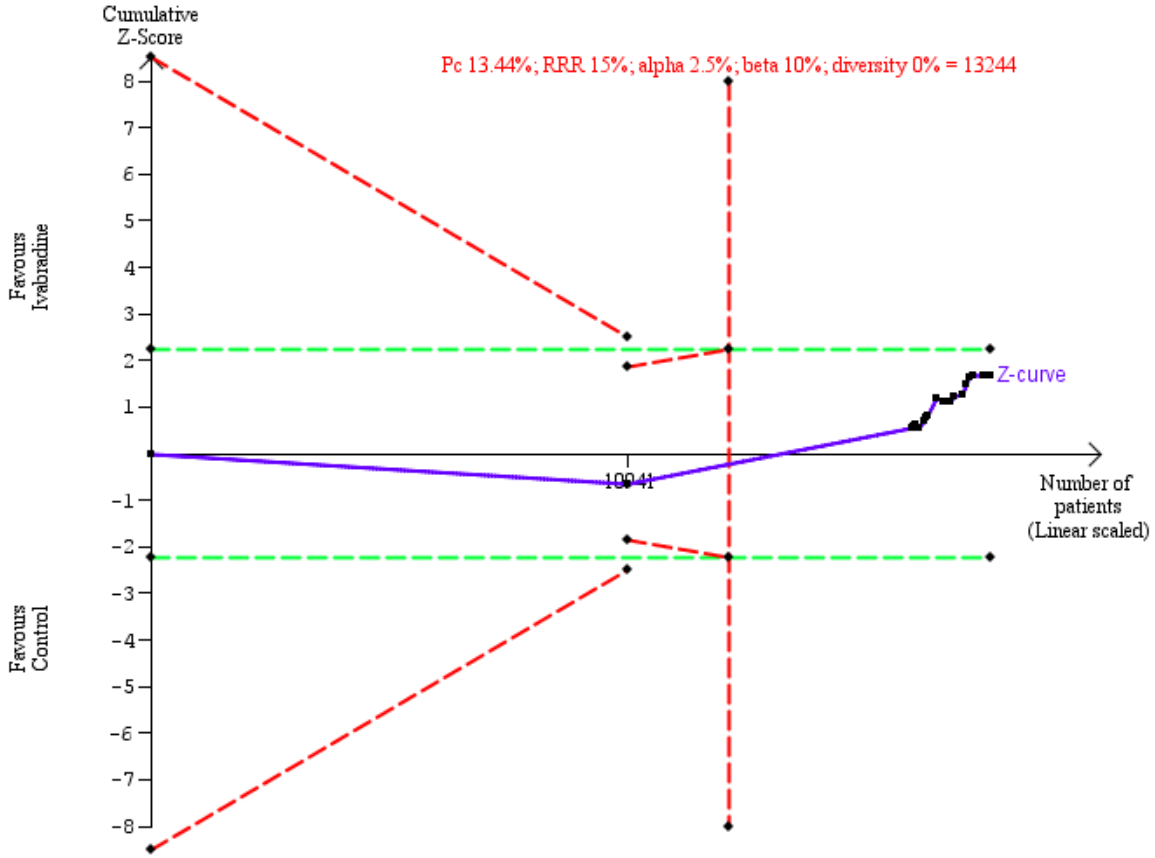


Figure 8 - Trial Sequential Analysis graph of all-cause mortality. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) breaches the boundary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

Sensitivity analyses

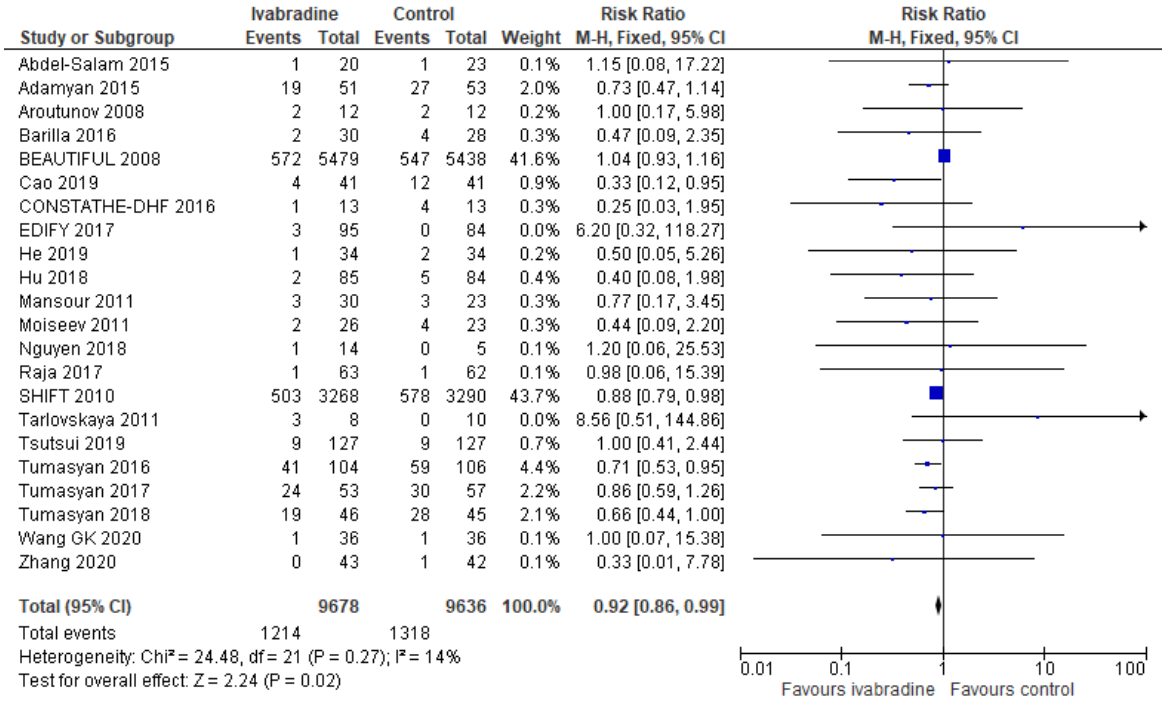


Figure 9 - Forest plot of the sensitivity analysis of all-cause mortality using best- compared with worst-case scenario.

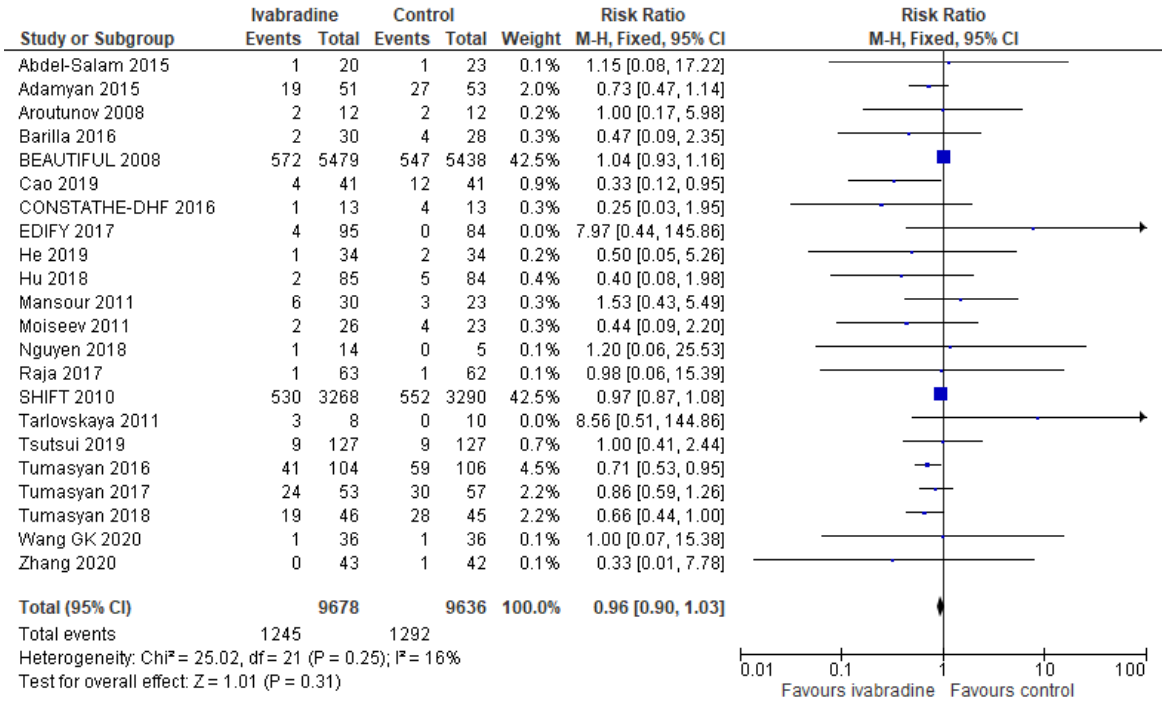


Figure 10 - Forest plot of the sensitivity analysis of all-cause mortality using worst- compared with best-case scenario.

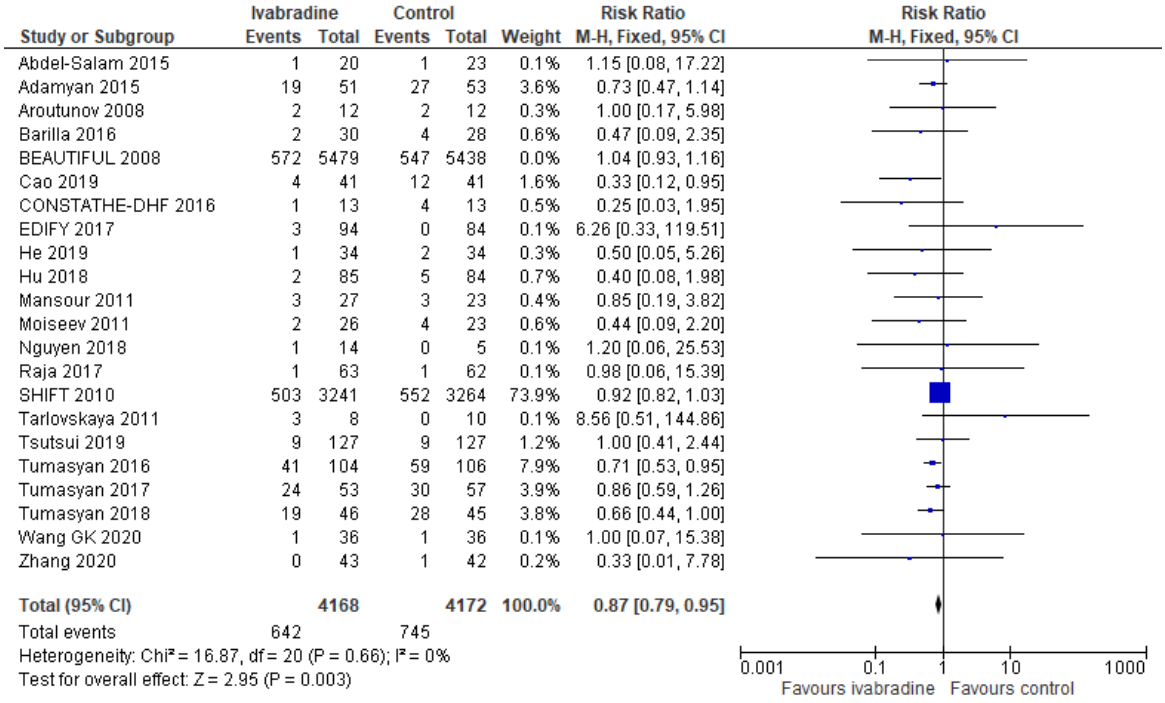


Figure 11 – Forest plot of the sensitivity analysis of all-cause mortality removing the BEAUTIFUL trial.

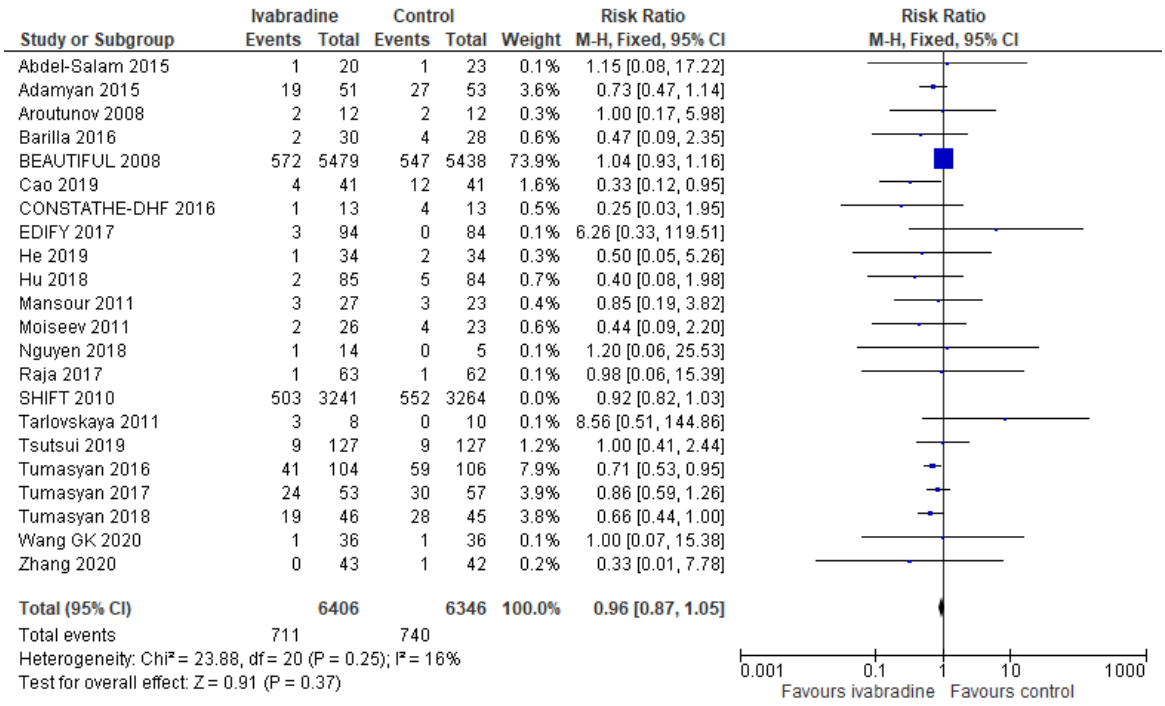


Figure 12 – Forest plot of the sensitivity analysis of all-cause mortality removing the SHIFT trial.

Subgroup analyses

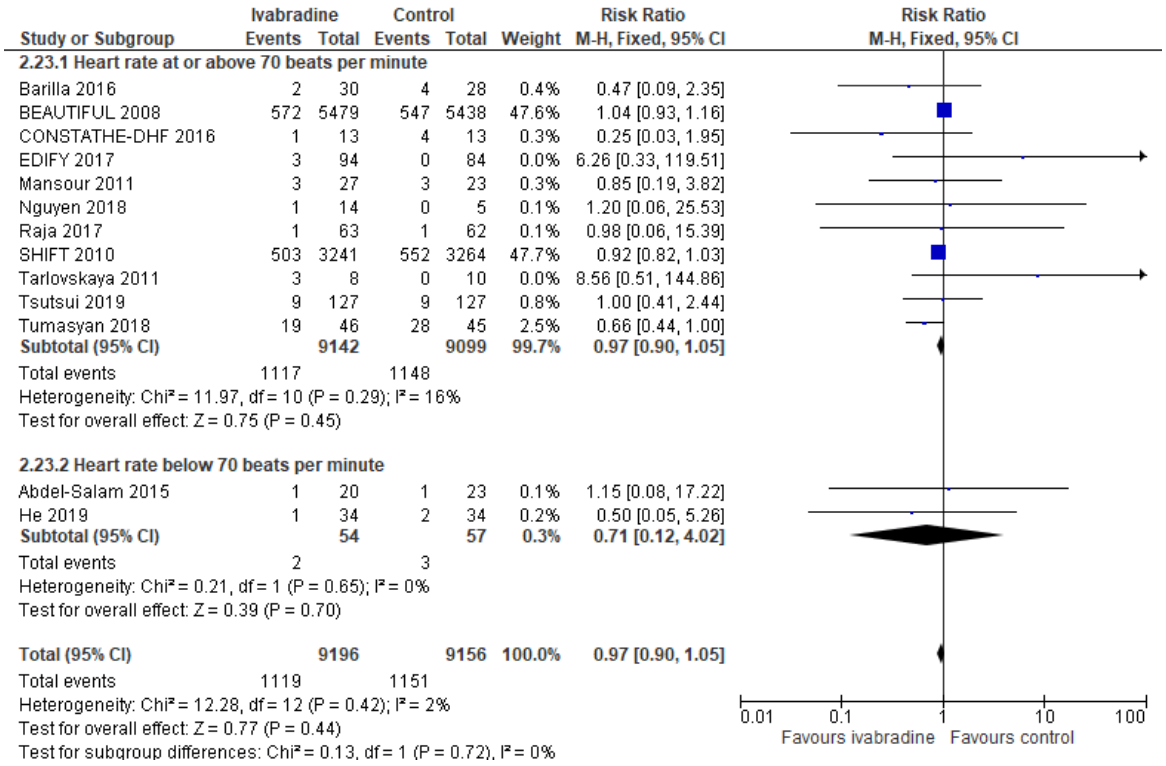


Figure 13 – Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared to trials randomising participants with heart rate below 70 beats per minute on all-cause mortality.

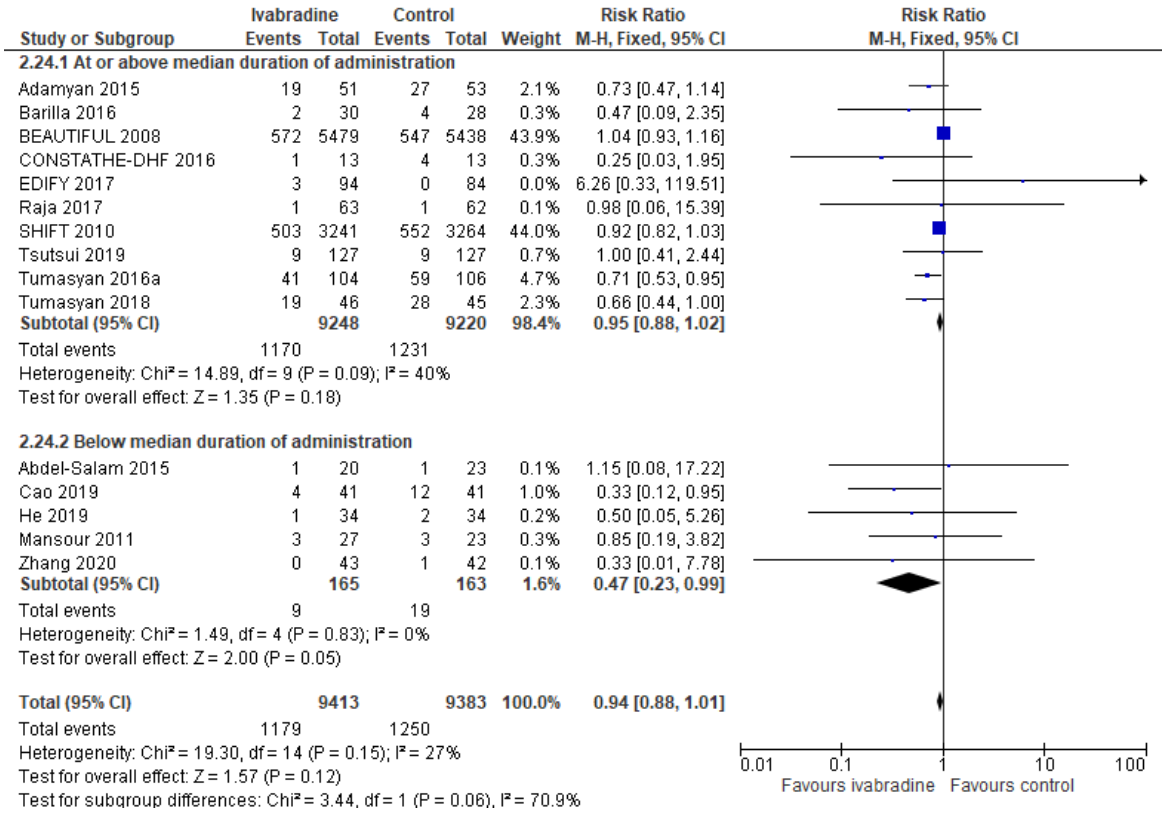


Figure 14 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (182.64 days) versus trials administering ivabradine below median duration on all-cause mortality.

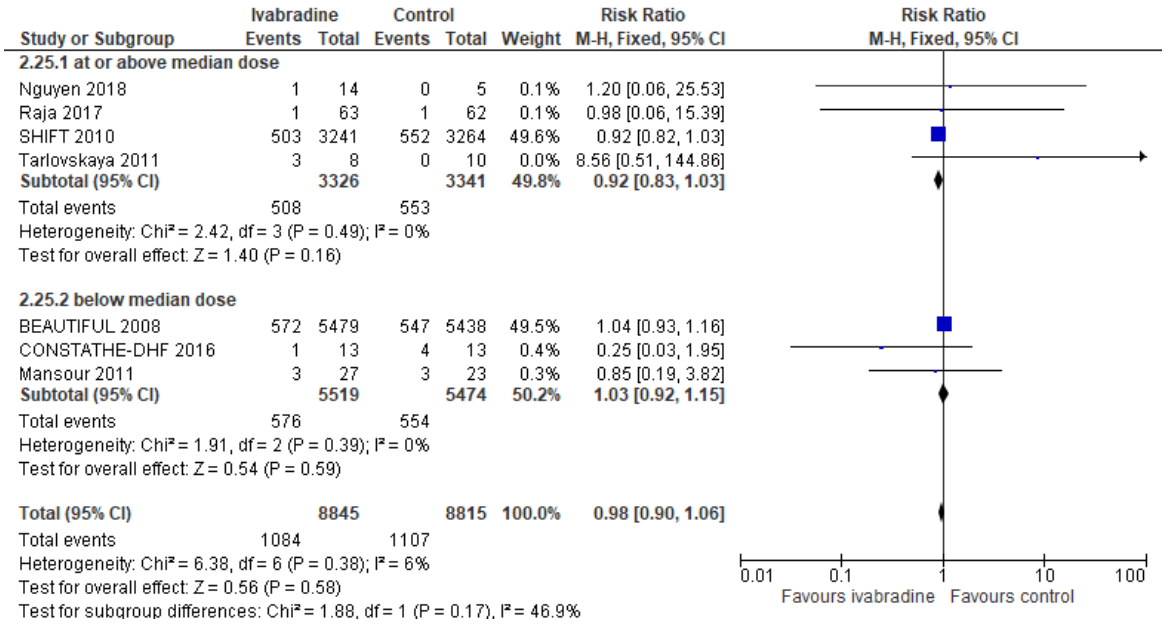


Figure 15 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose (12.7 mg) compared to trials administering ivabradine below median daily dose on all-cause mortality.

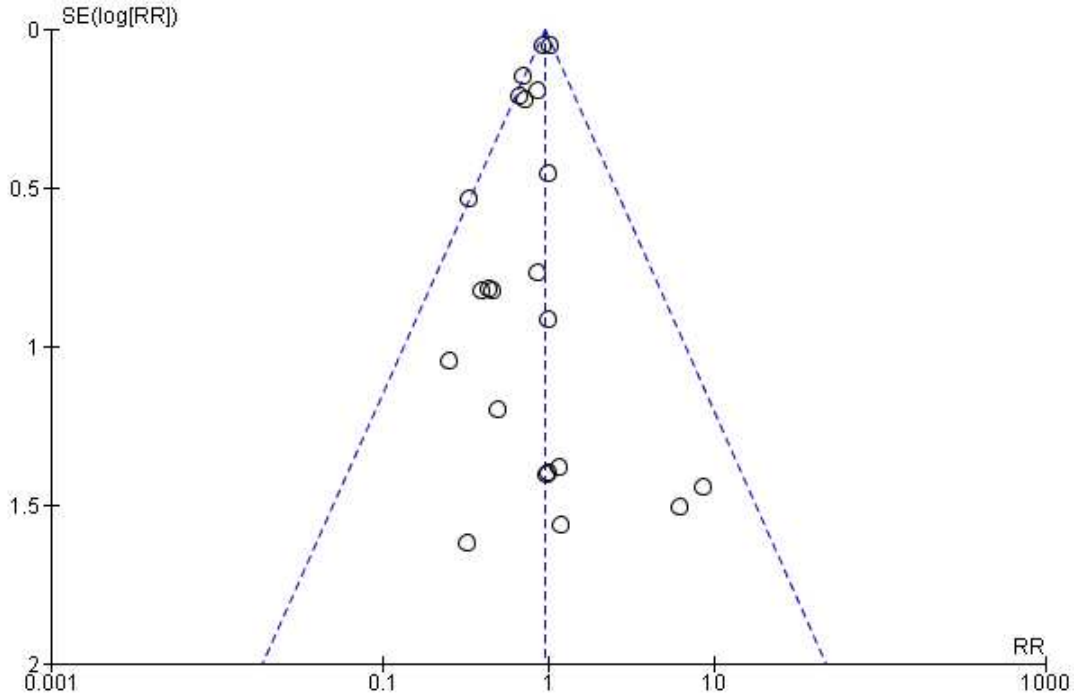


Figure 16 – Funnel plot of the analyses of all-cause mortality. The funnel plot did not indicate small study bias.

Supplement 6 - Serious adverse events

Main analyses

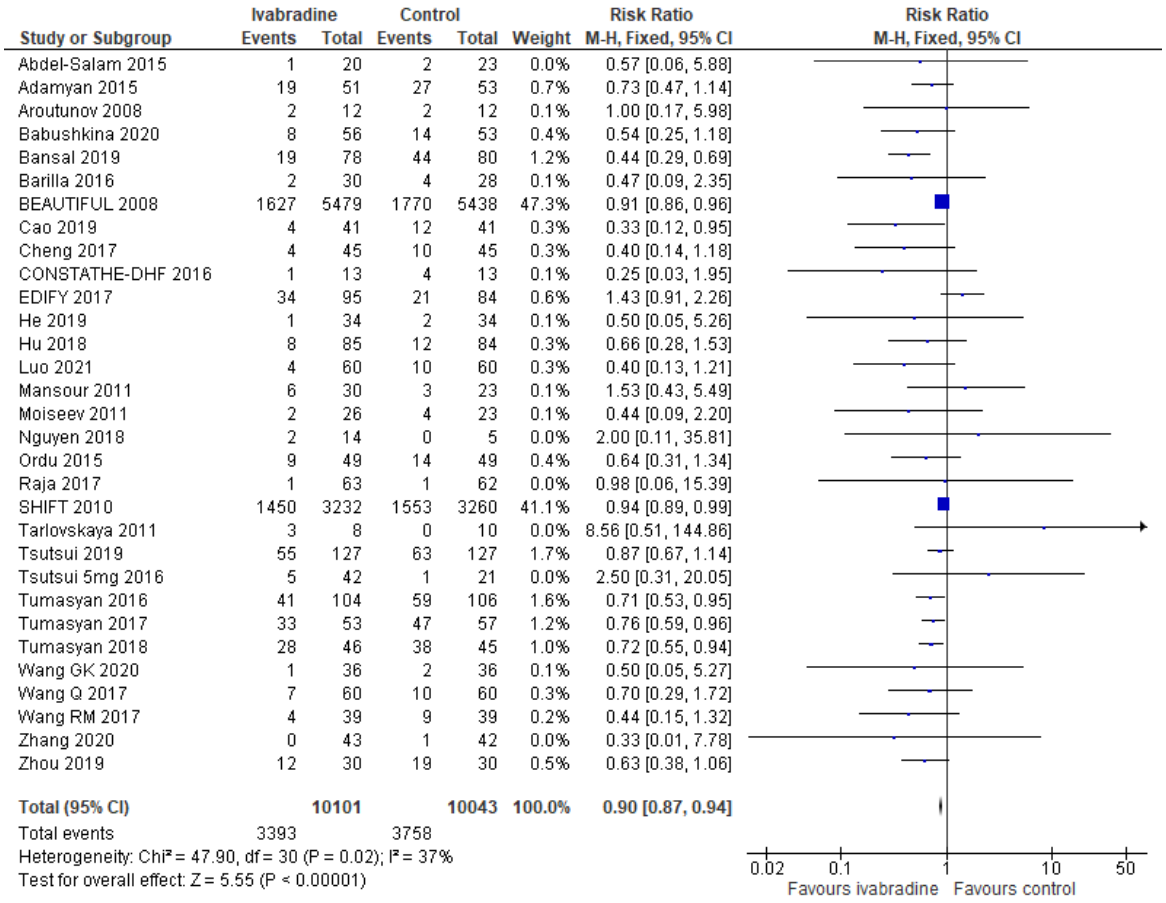


Figure 17 - Forest plot of the meta-analysis of serious adverse events using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

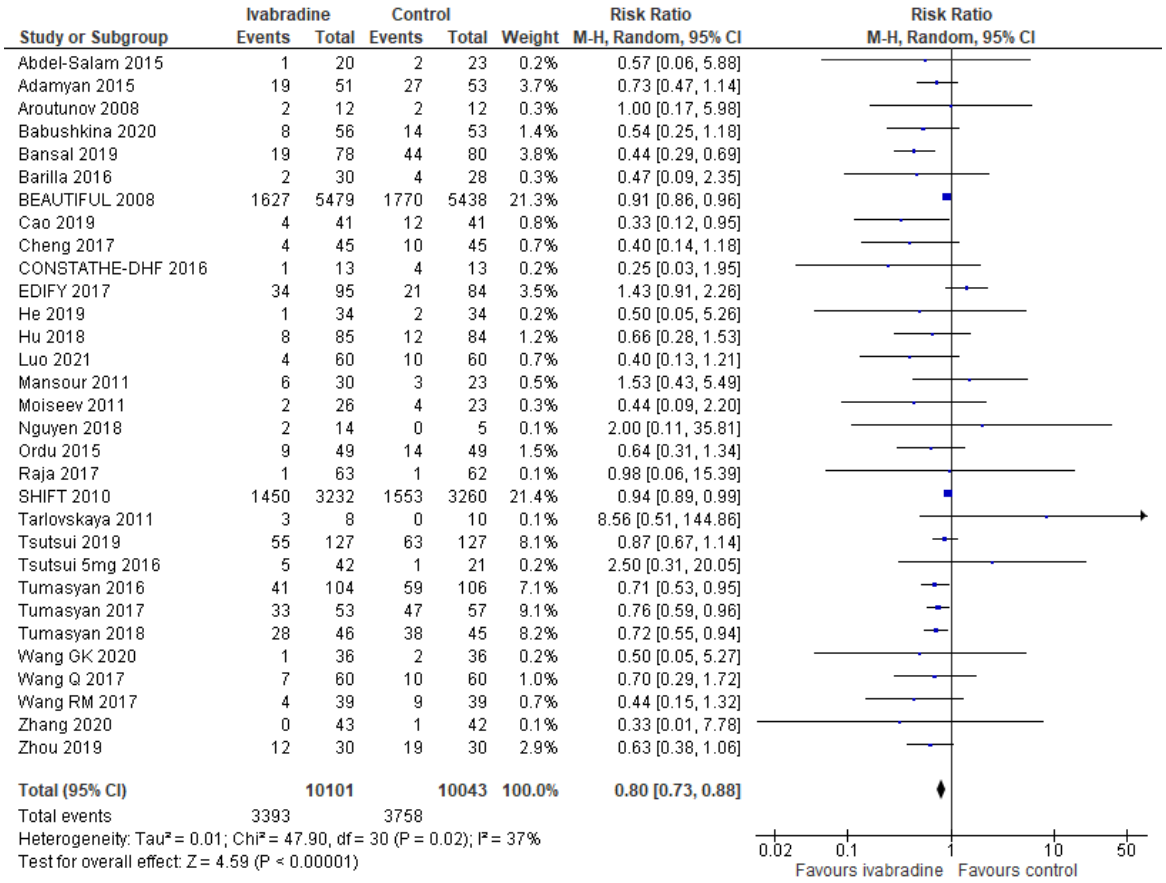


Figure 18 – Forest plot of the meta-analysis of serious adverse events using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

Sensitivity analyses

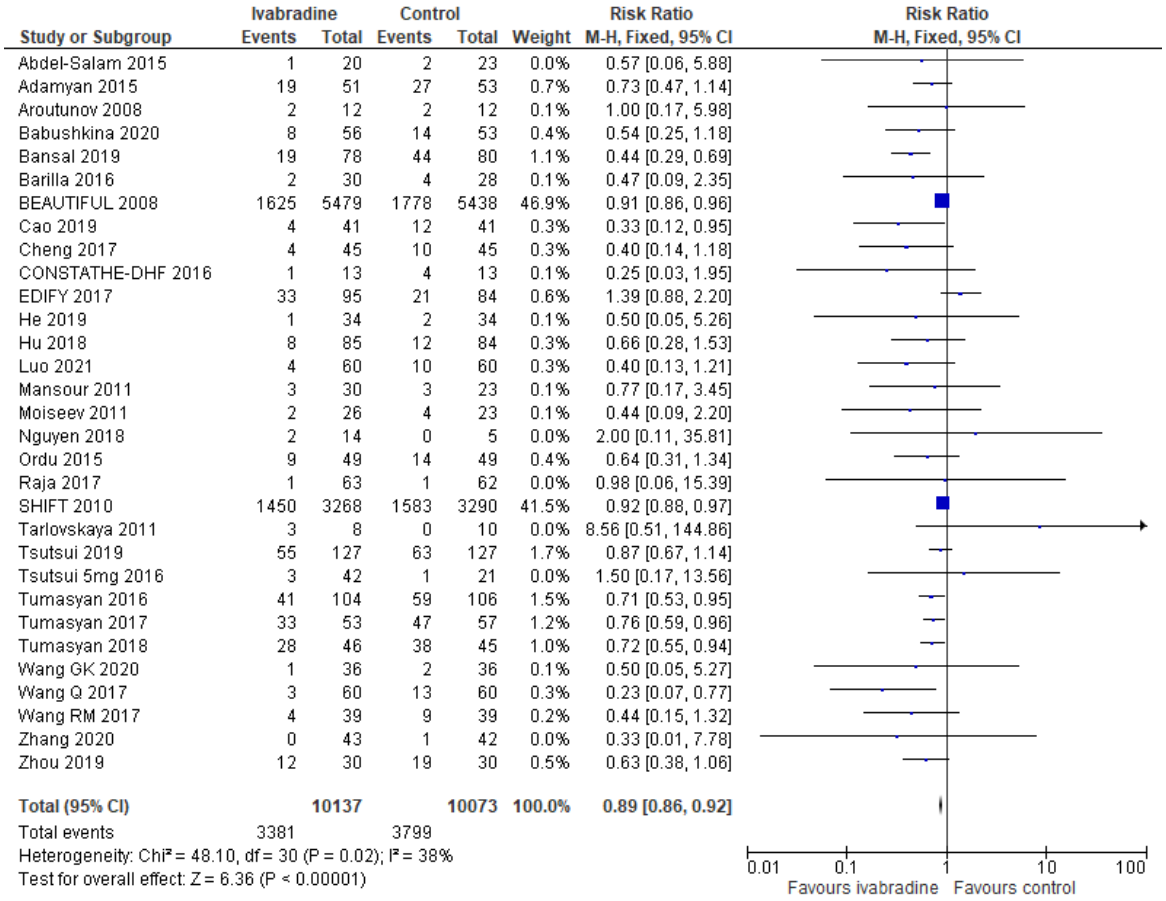


Figure 19 - Forest plot of the sensitivity analysis of serious adverse events using best- compared with worst-case scenario.

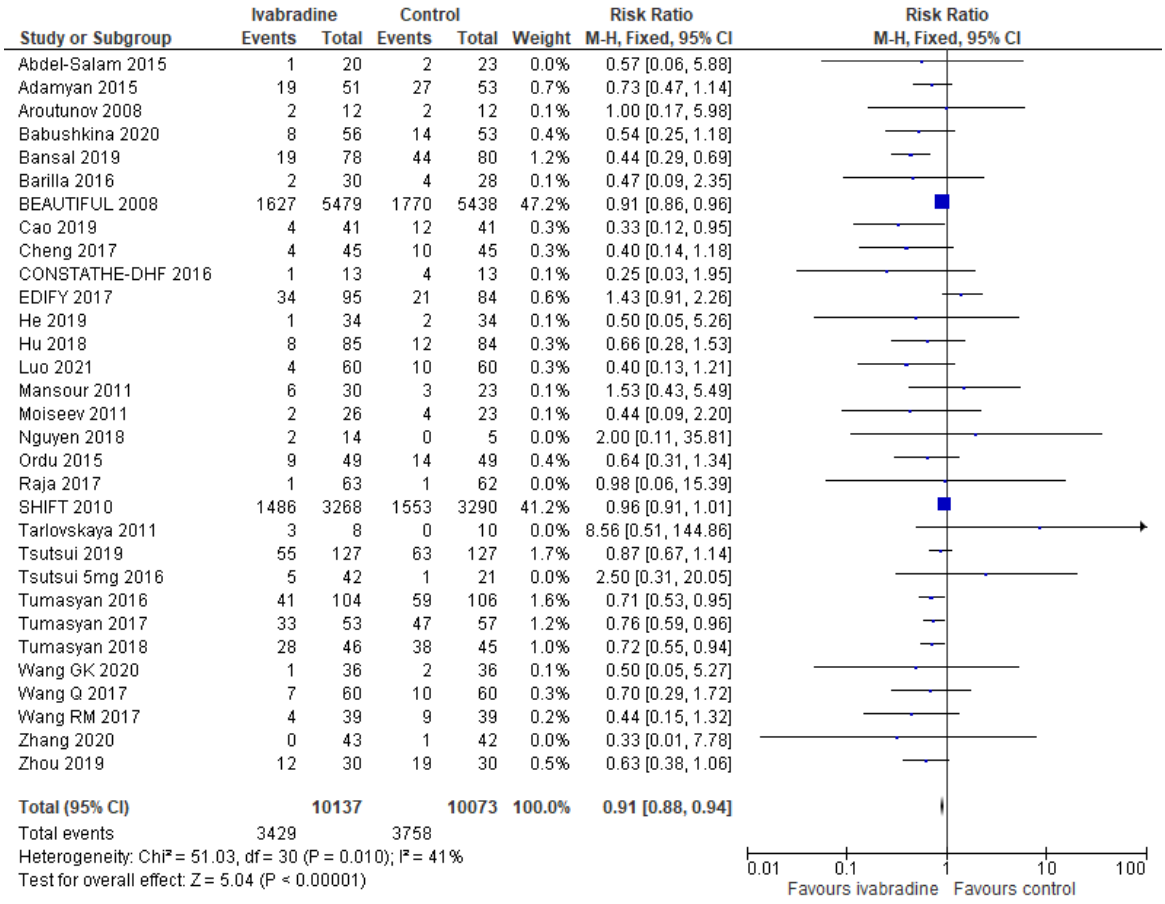


Figure 20 - Forest plot of the sensitivity analysis of serious adverse events using worst- compared with best-case scenario.

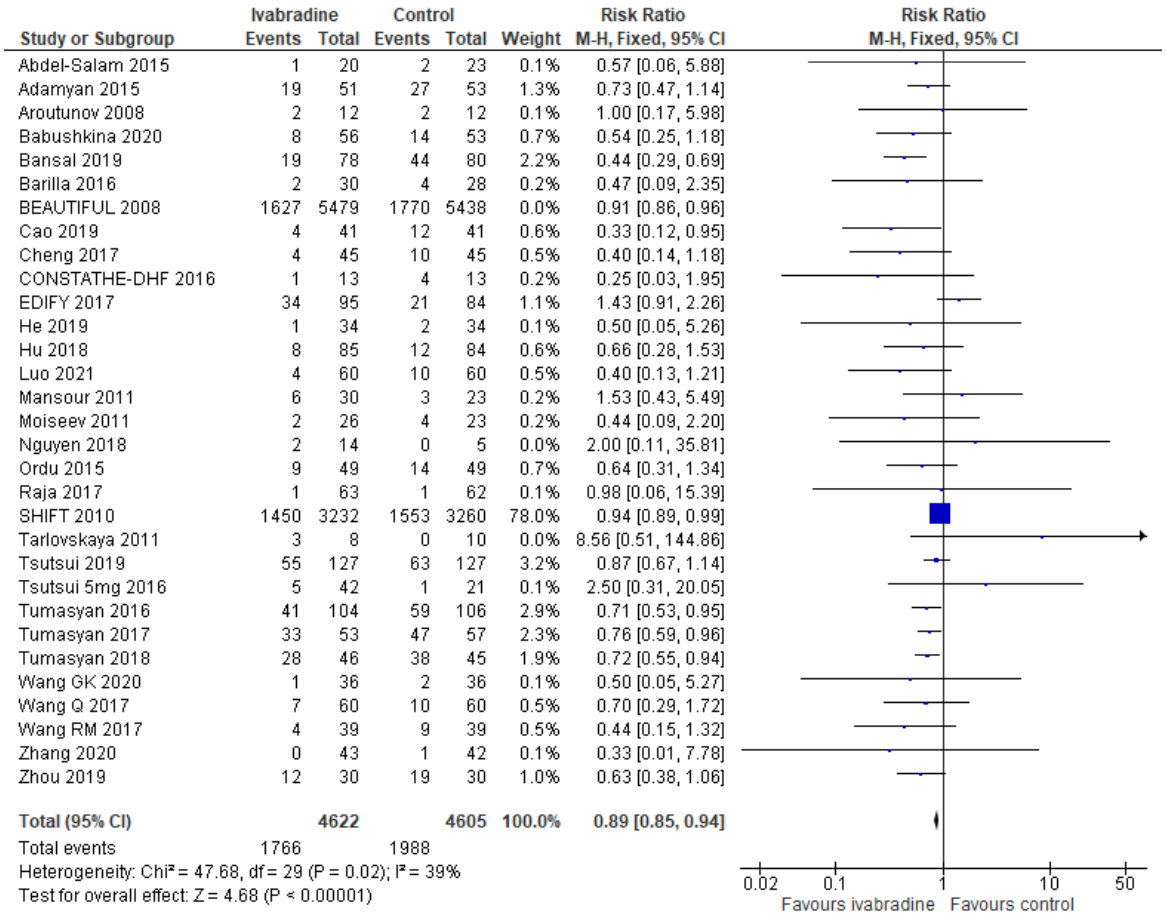


Figure 21 – Forest plot of the sensitivity analysis of serious adverse events removing the BEAUTIFUL trial.

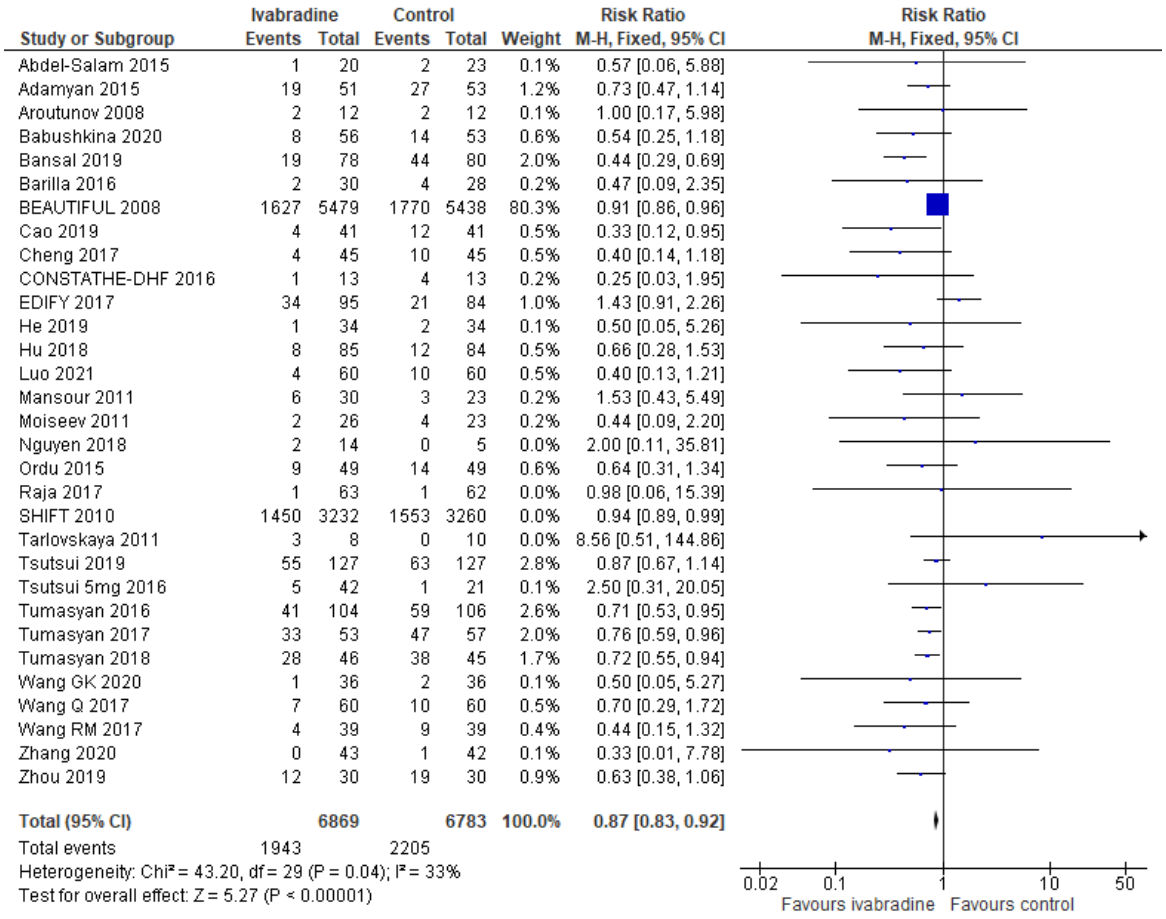


Figure 22 – Forest plot of the sensitivity analysis of serious adverse events removing the SHIFT trial.

Subgroup analyses

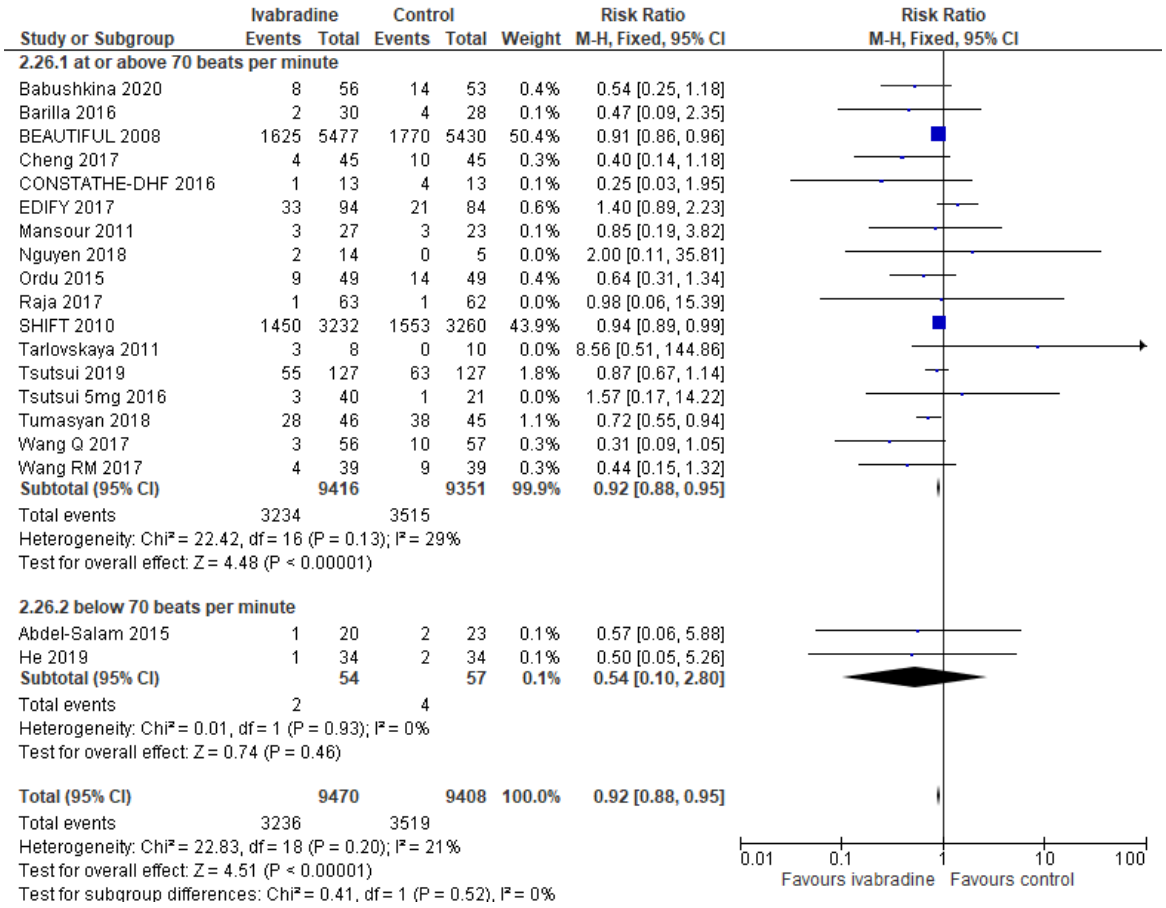


Figure 23 - Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared to trials randomising participants with heart rate below 70 beats per minute on all-cause mortality.

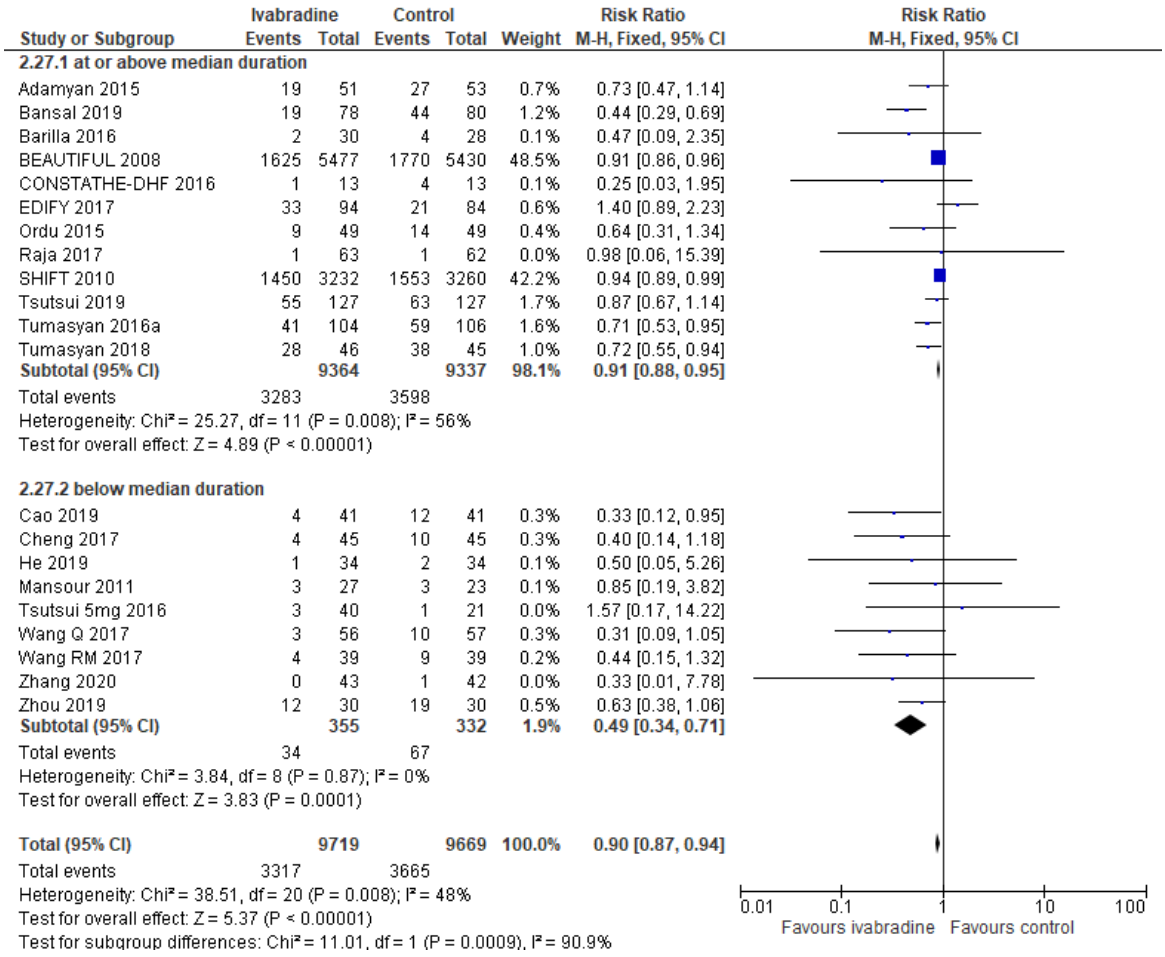


Figure 24 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (182.64 days) compared to trials administering ivabradine below median duration on serious adverse events.

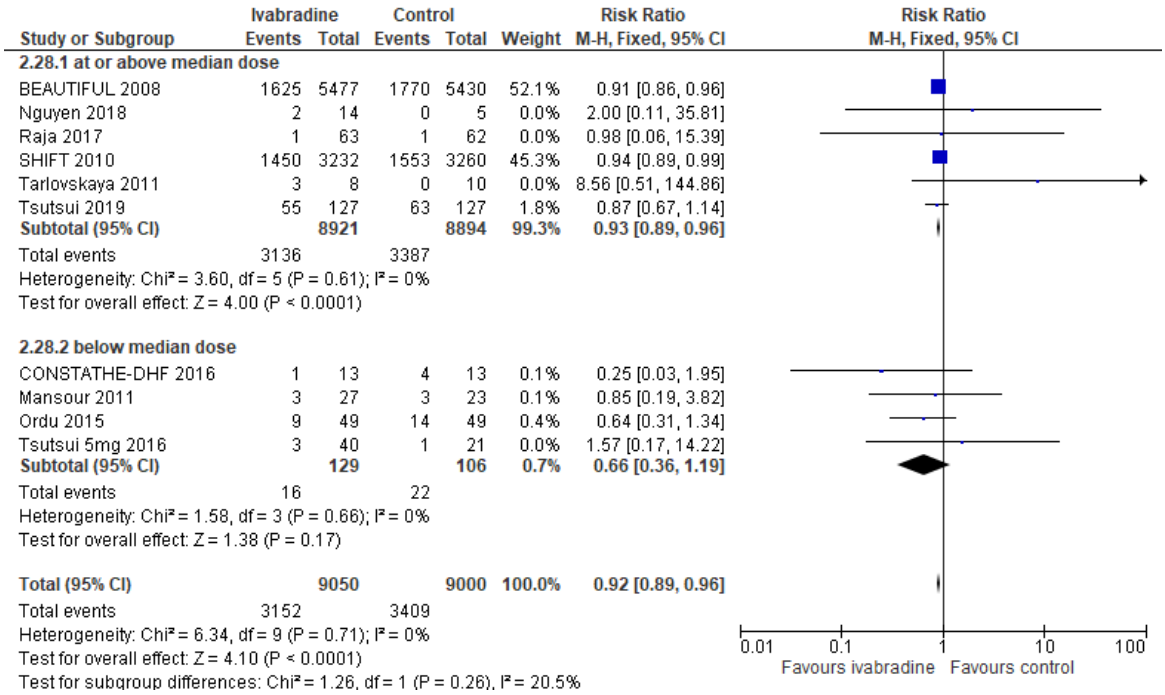


Figure 25 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose (12.36 mg) compared to trials administering ivabradine below median daily dose on serious adverse events.

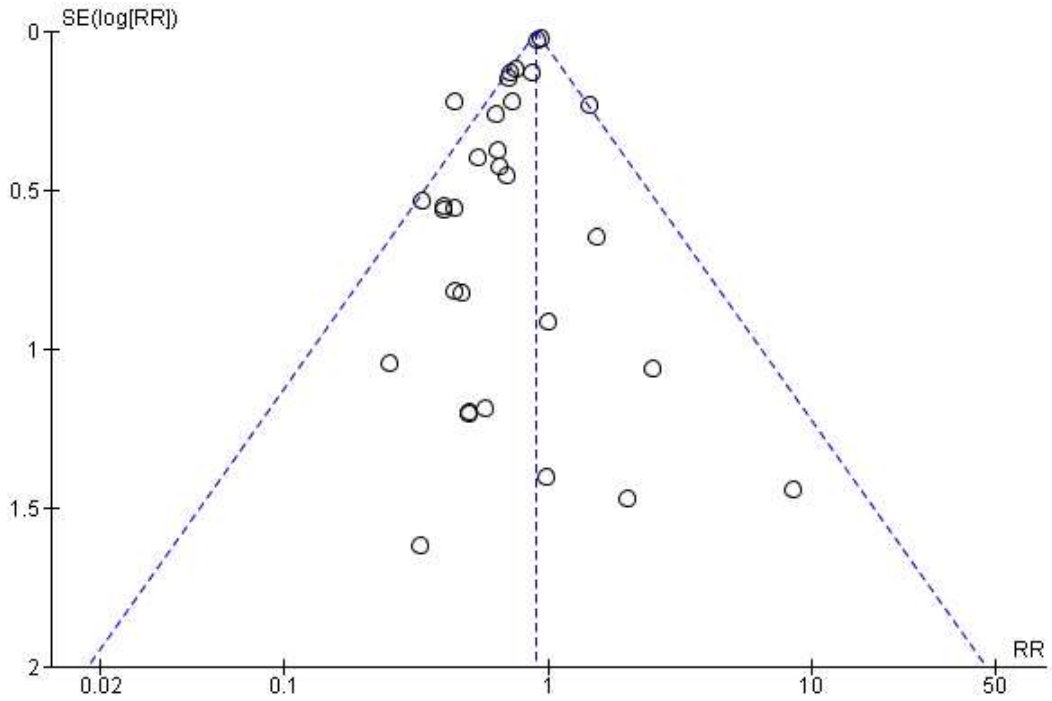


Figure 26 – Funnel plot of the analysis of serious adverse events. The funnel plot did not indicate small study bias.

Supplement 7 - Quality of life

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

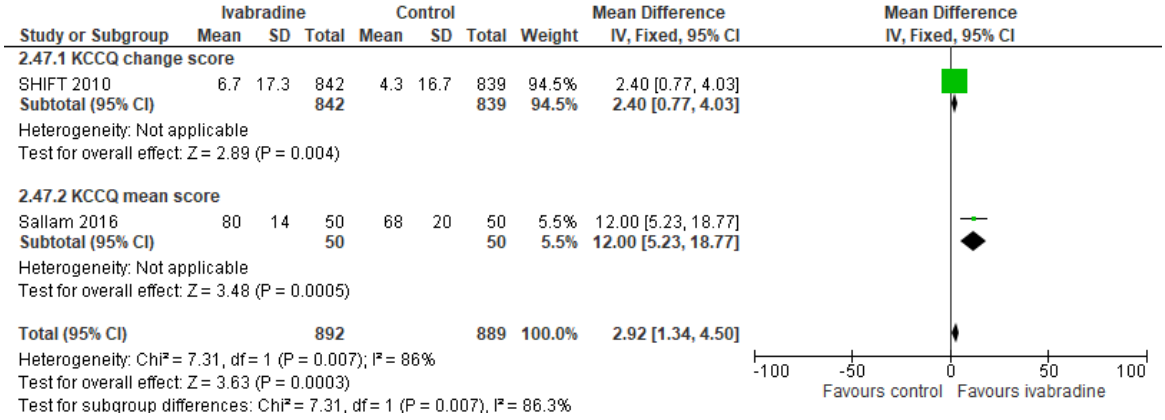


Figure 27 – Forest plot of the meta-analysis of quality of life from trials using the KCCQ using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine.

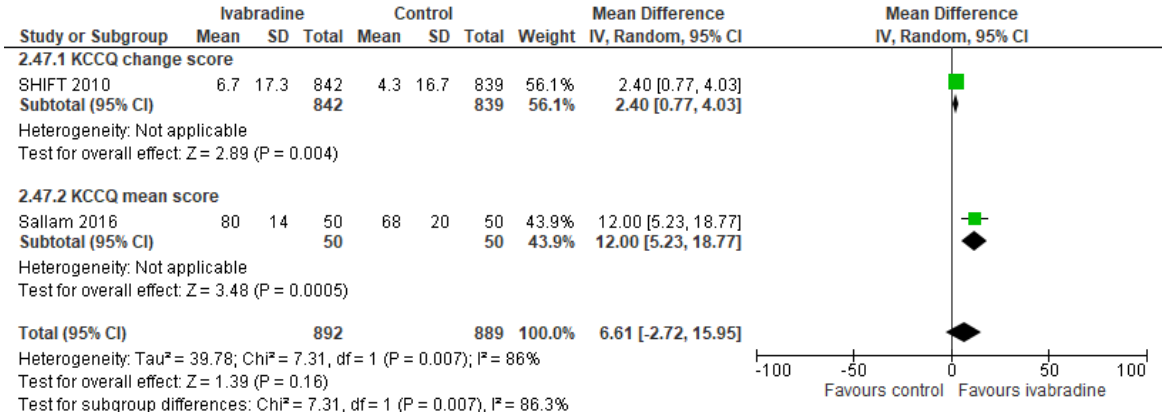


Figure 28 – Forest plot of the meta-analysis of quality of life from trials using the Kansas City Cardiomyopathy Questionnaire (KCCQ) using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

Sensitivity analyses for trials using KCCQ.

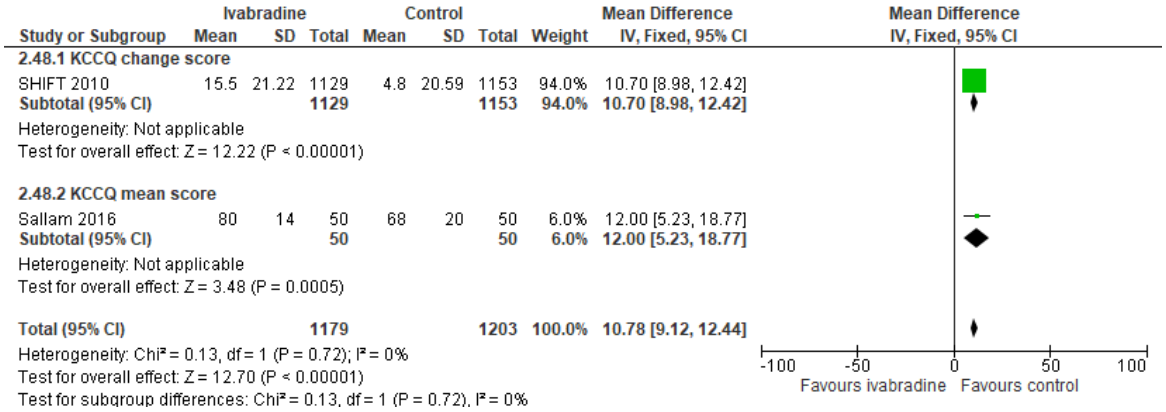


Figure 29 – Forest plot of the sensitivity analysis of quality of life (KCCQ) using best- compared with worst-case scenario.

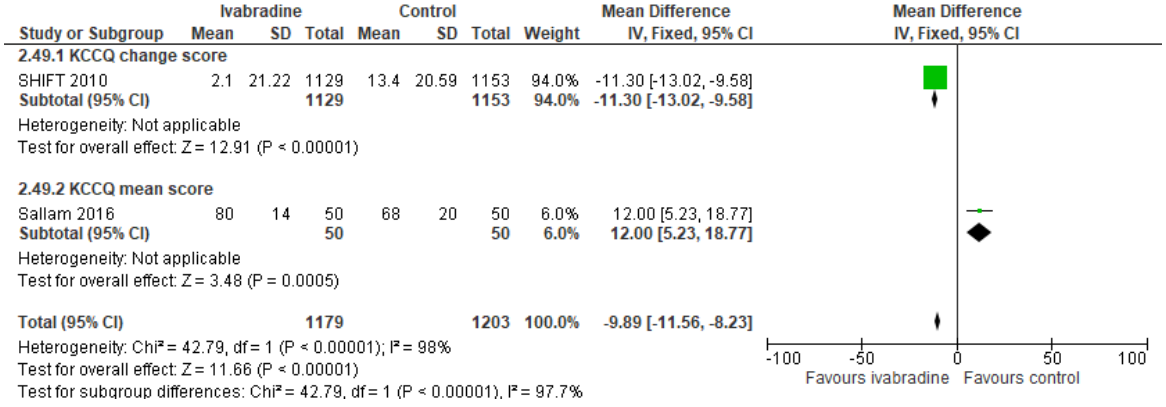


Figure 30 – Forest plot of the sensitivity analysis of quality of life (MLWHFQ) using worst- compared with best-case scenario.

Subgroup analyses for trials using the KCCQ

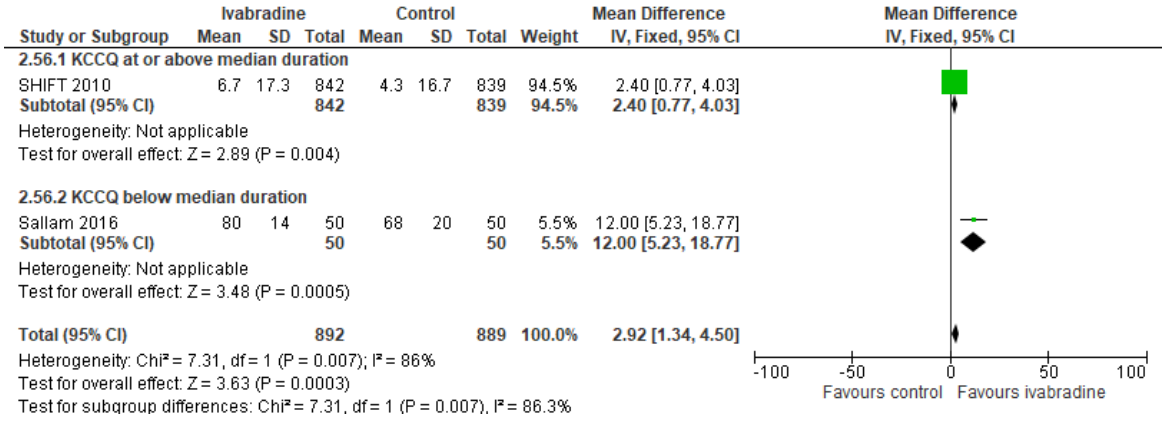


Figure 31 – Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (90.66 days) compared to trials administering ivabradine below median duration on quality of life using the KCCQ.

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

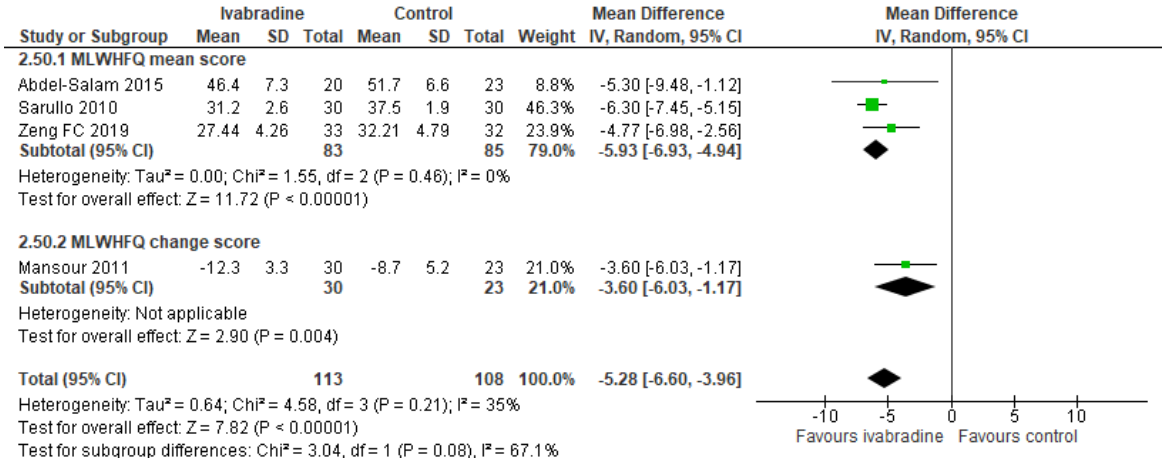


Figure 32 – Forest plot of the meta-analysis of quality of life from trials using the MLWHFQ using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

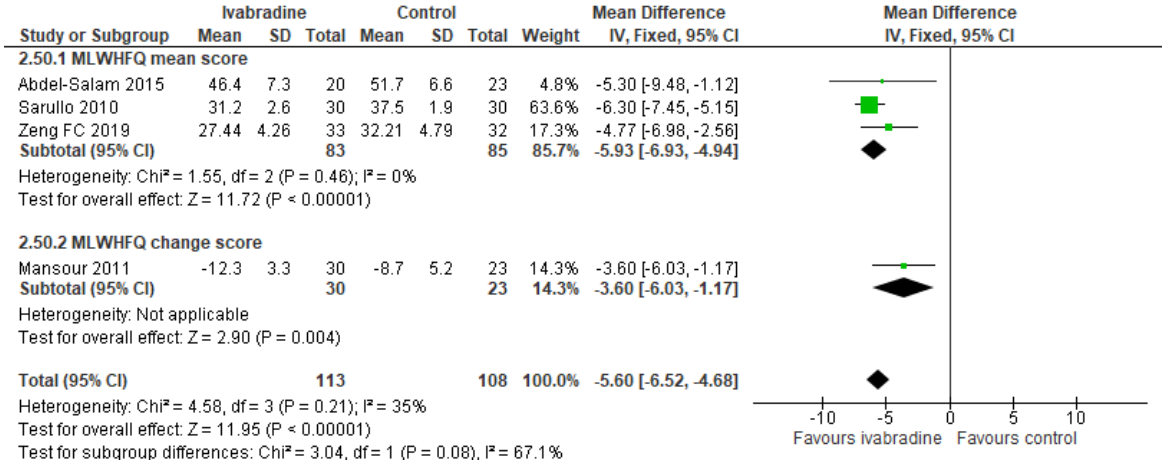


Figure 33 – Forest plot of the meta-analysis of quality of life from trials using the MLWHFQ using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine.

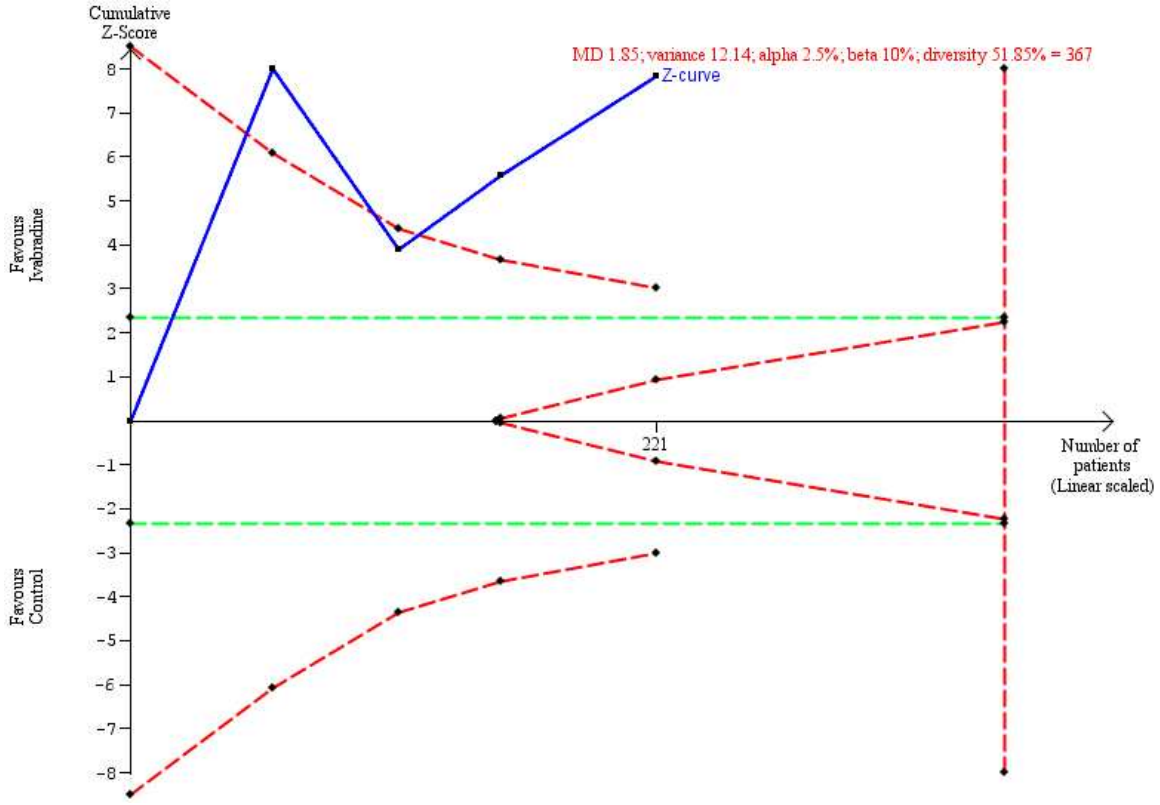


Figure 34 – Trial Sequential Analysis graph of quality of life from trials using the MLWHFQ. Trial Sequential Analysis showed that we had enough information to detect a mean difference of -5.60 points of ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) breached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

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

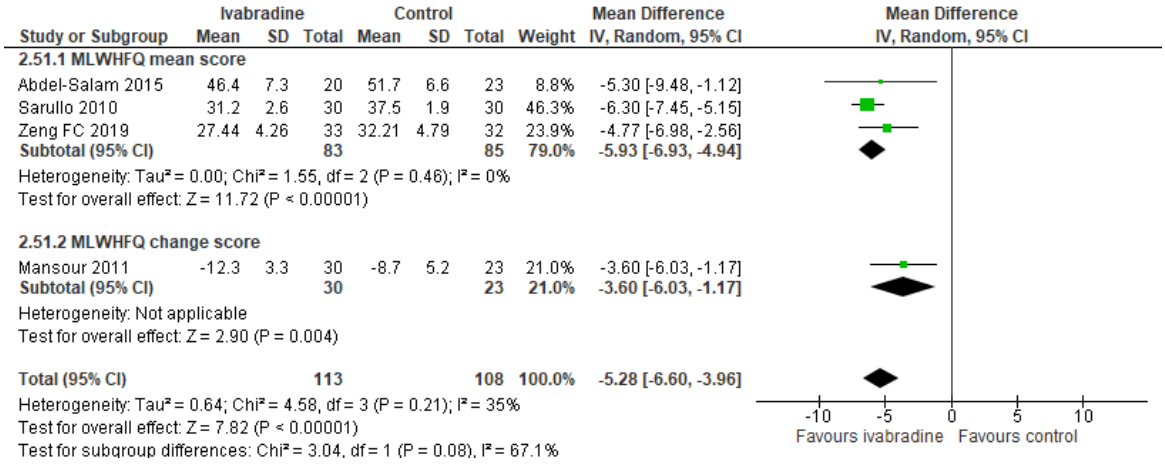


Figure 35 – Forest plot of the sensitivity analysis of quality of life (MLWHFQ) using best- compared with worst-case scenario.

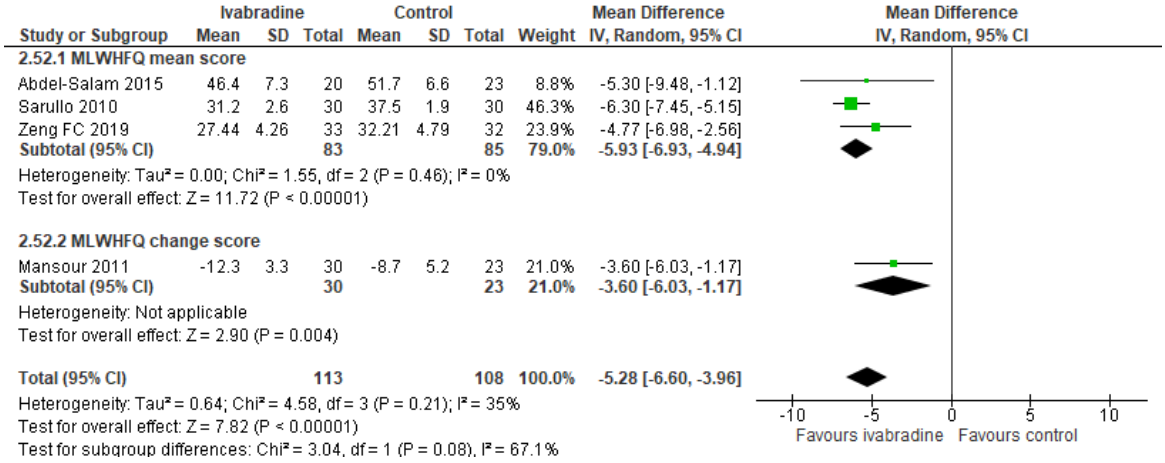


Figure 36 – Forest plot of the sensitivity analysis of quality of life (MLWHFQ) using worst- compared with best-case scenario.

Subgroup analyses of quality of life from trials using the MLWHFQ

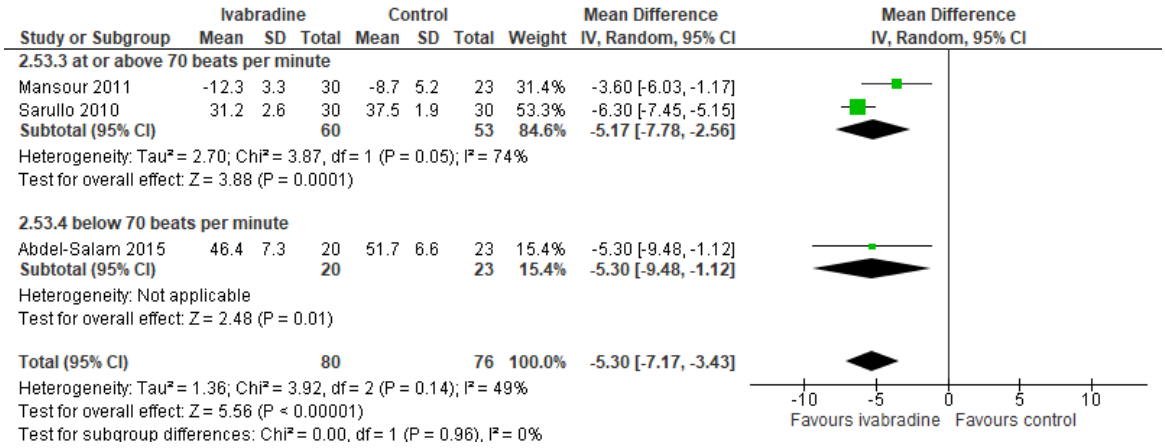


Figure 37 - Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared trials randomising participants with heart rate below 70 beats per minute on quality of life using the MLWHFQ.

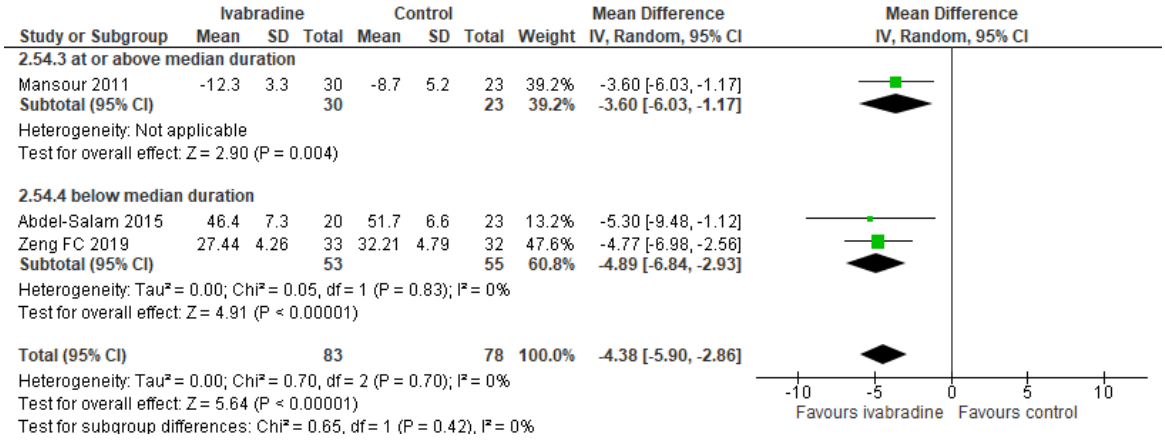


Figure 38 – Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (90.66 days) compared to trials administering ivabradine below median duration on quality of life using the MLWHFQ.

Supplement 8 - Cardiovascular mortality

Main analyses

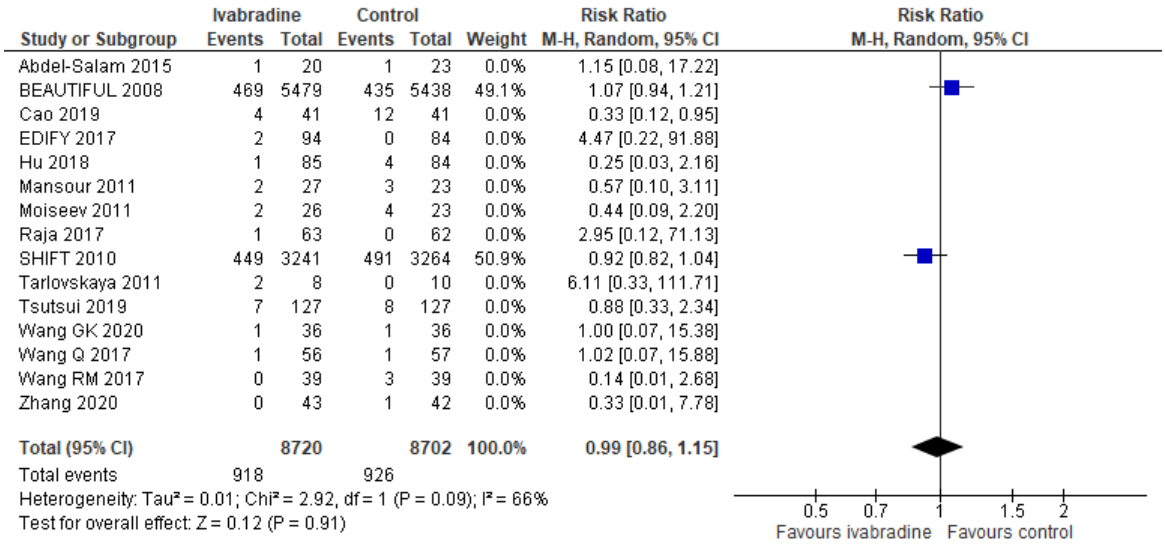


Figure 39 – Forest plot of the meta-analysis of cardiovascular mortality using random-effects meta-analysis including only trials at low risk of bias. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

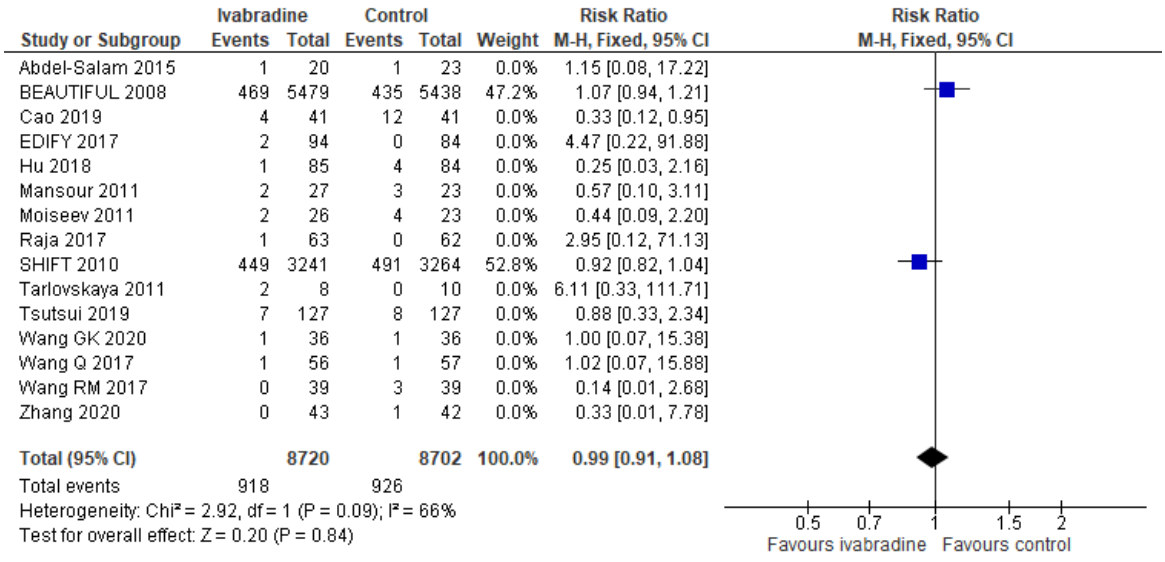


Figure 40 – Forest plot of the meta-analysis of cardiovascular mortality using fixed-effect meta-analysis including only trials at low risk of bias. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

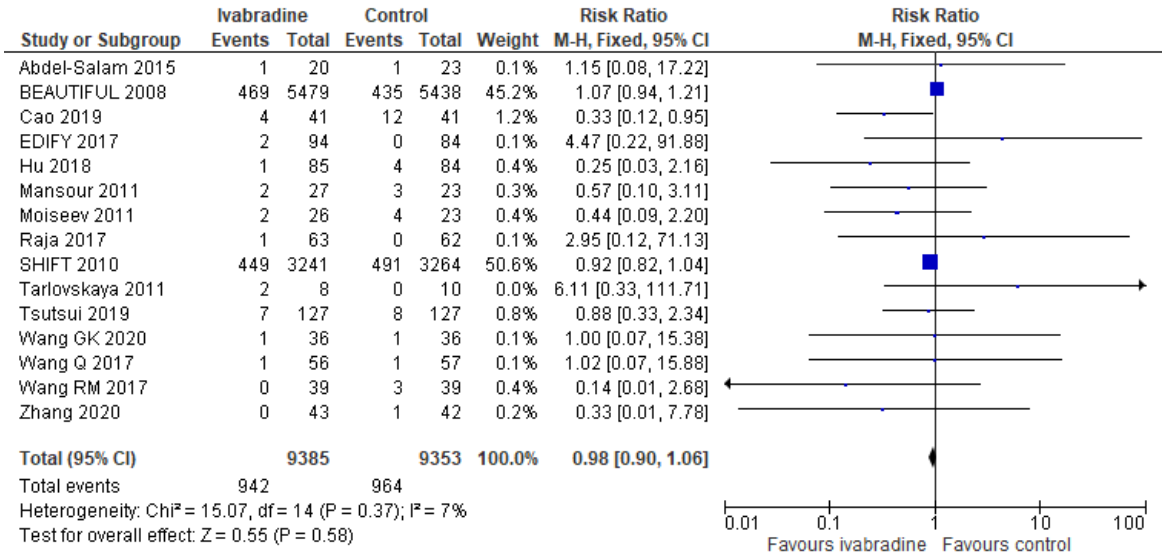


Figure 41 – Forest plot of the meta-analysis of cardiovascular mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

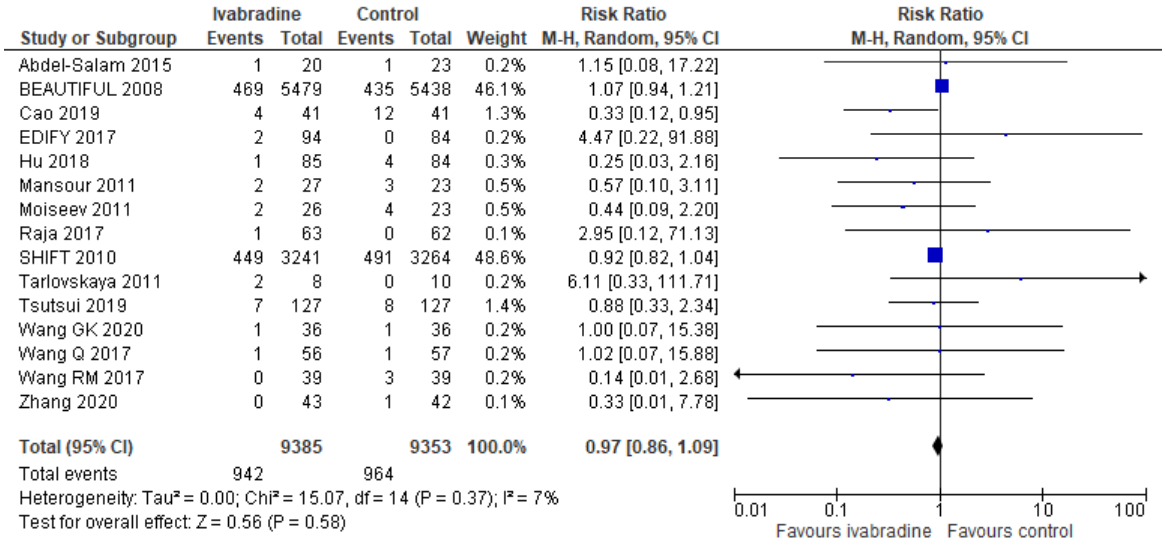


Figure 42 - Forest plot of the meta-analysis of cardiovascular mortality using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

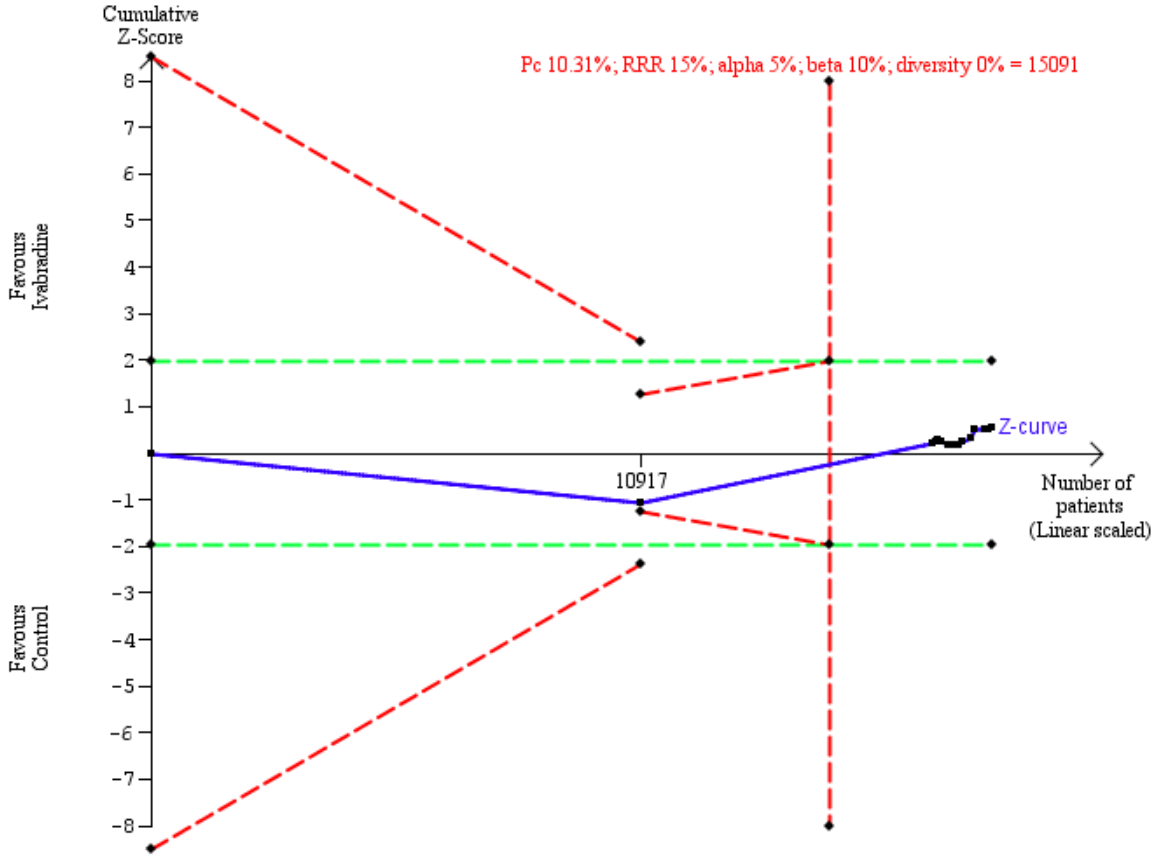


Figure 43 - Trial Sequential Analysis graph of cardiovascular mortality. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) breaches the boundary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

Sensitivity analyses

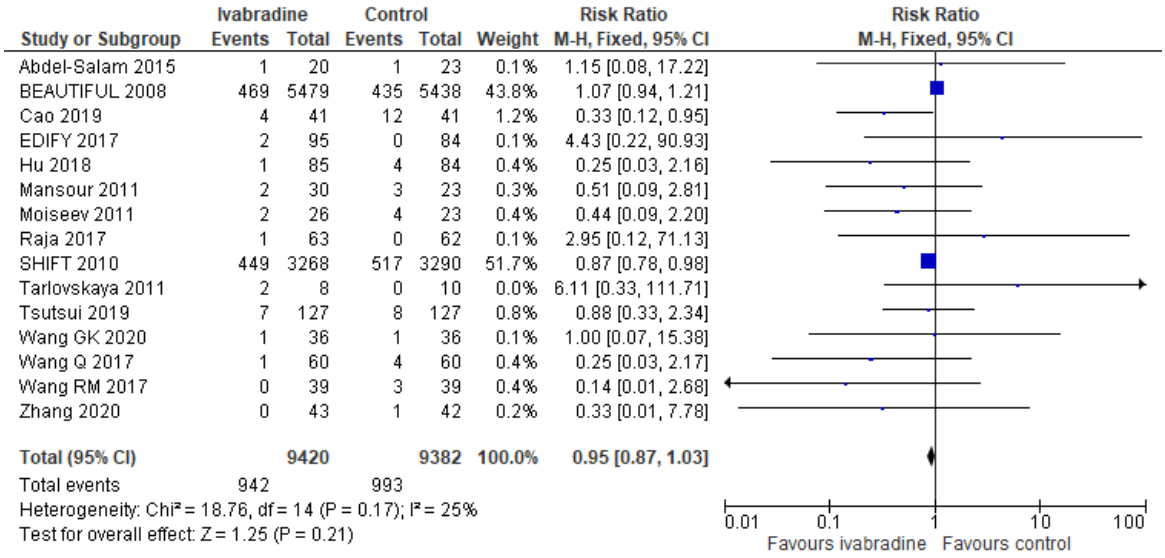


Figure 44 - Forest plot of the sensitivity analysis of cardiovascular mortality using best- compared with worst-case scenario.

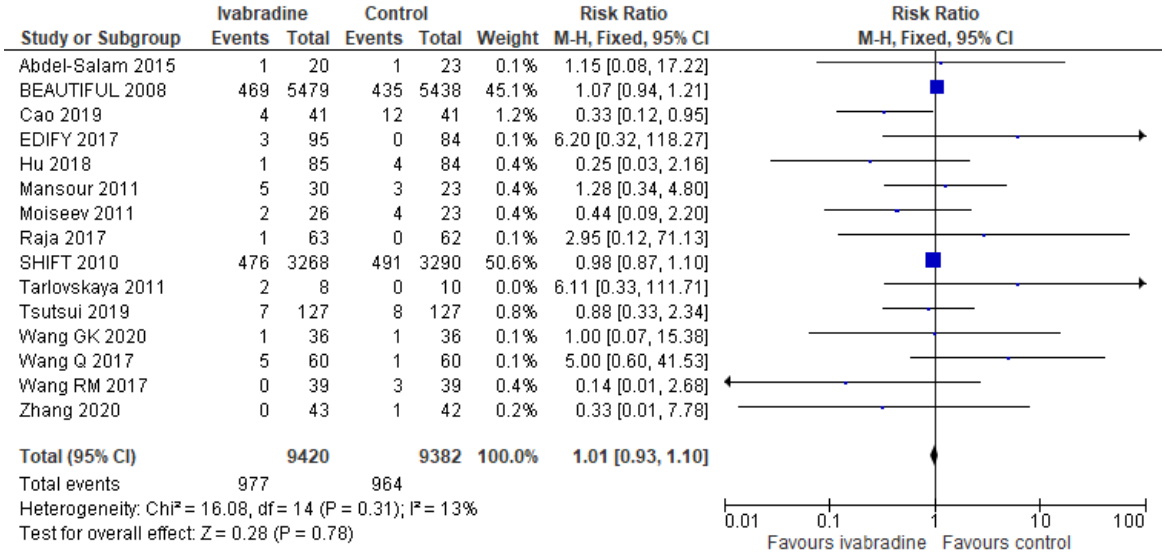


Figure 45 – Forest plot of the sensitivity analysis of cardiovascular mortality using worst compared with best-case scenario.

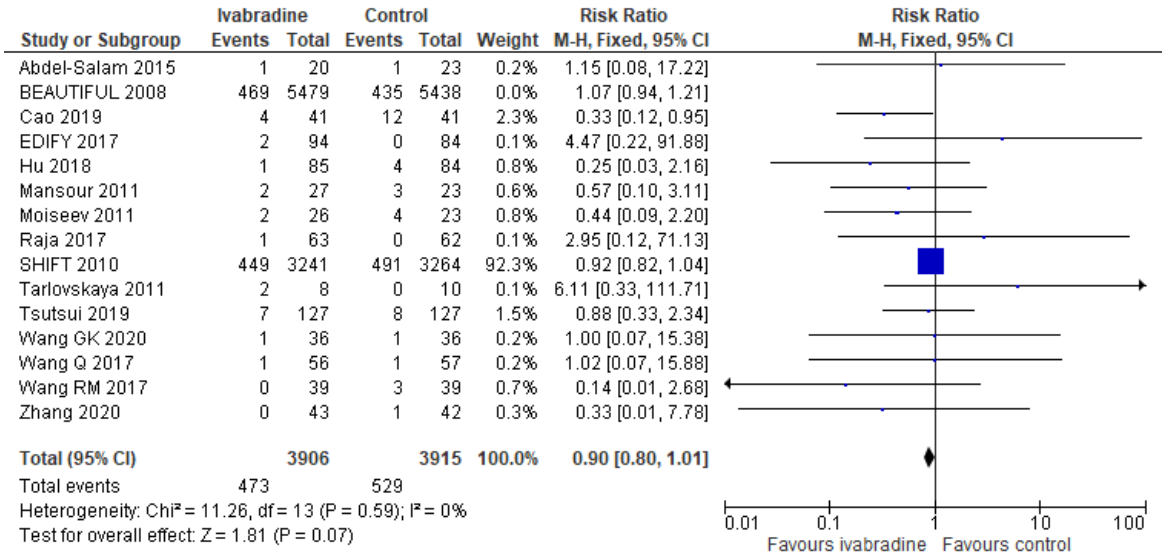


Figure 46 – Forest plot of the sensitivity analysis of cardiovascular mortality removing the BEAUTIFUL trial.

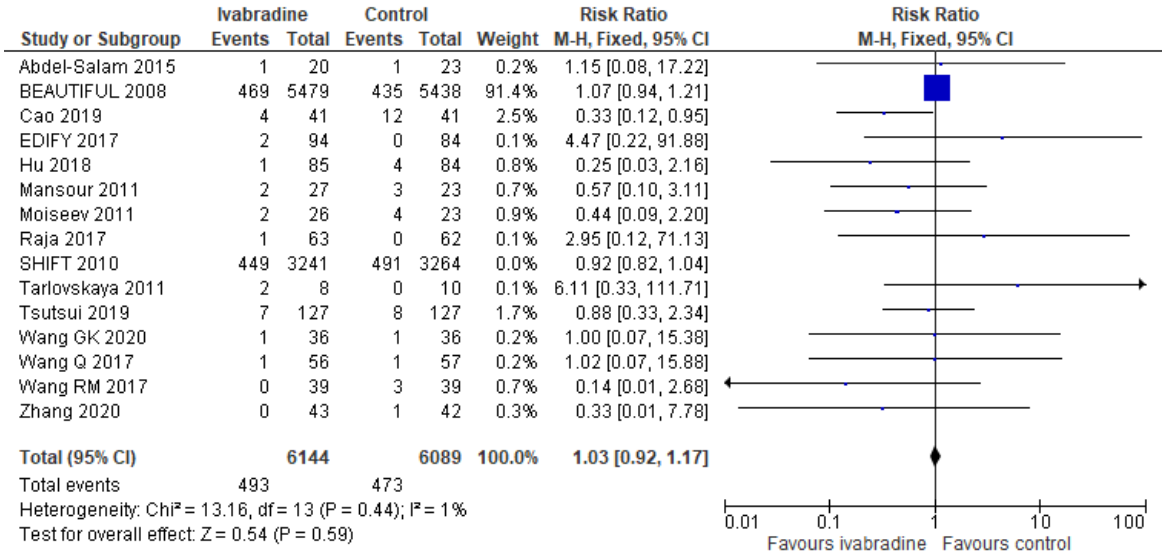


Figure 47 – Forest plot of the sensitivity analysis of cardiovascular mortality removing the SHIFT trial.

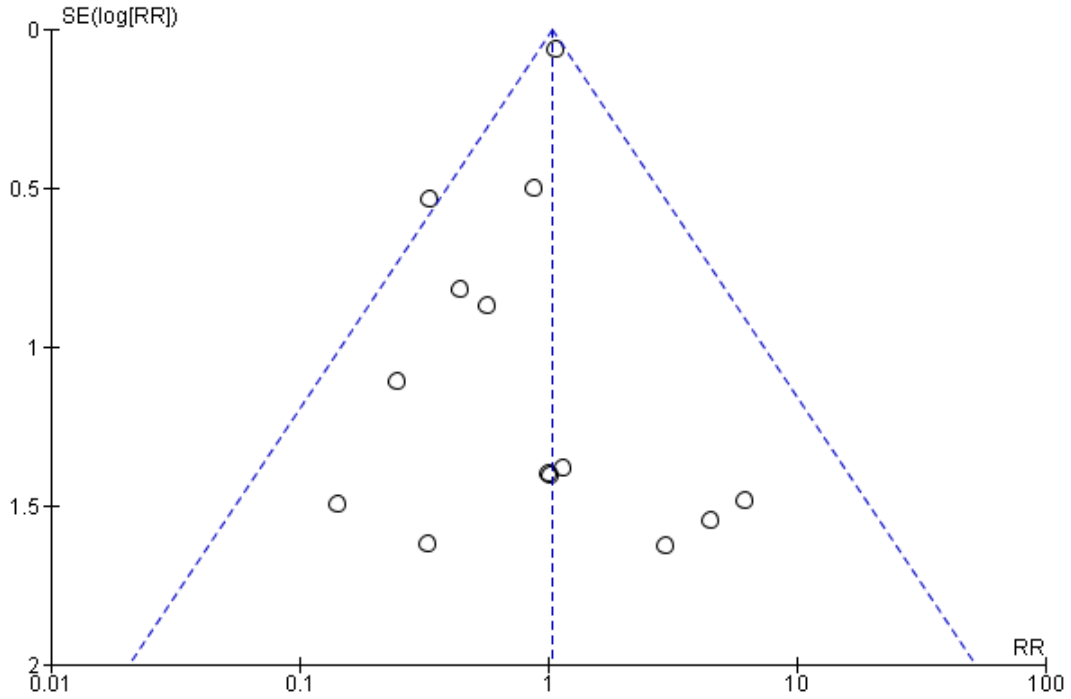


Figure 48 – Funnel plot of the analysis of cardiovascular mortality. The funnel plot did not indicate small study bias.

Supplement 9 - Myocardial infarction

Main analyses

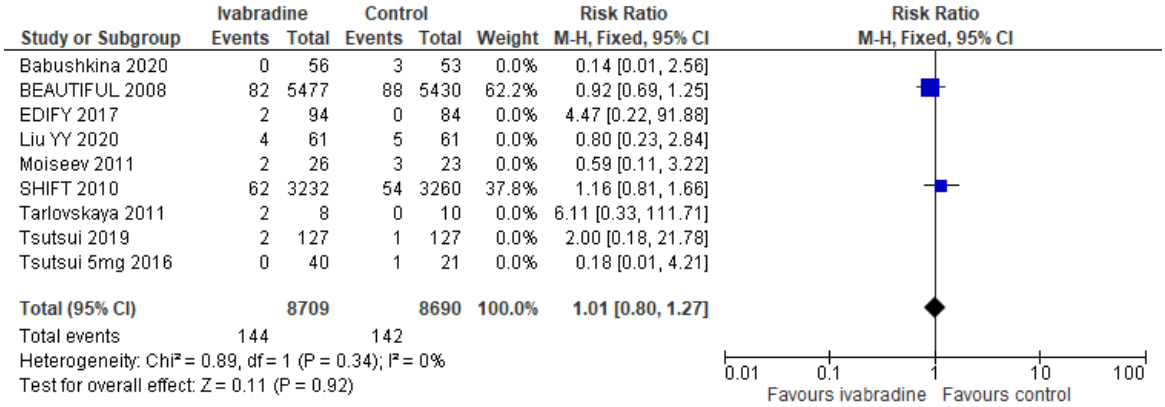


Figure 49 – Forest plot of the meta-analysis of myocardial infarction using fixed-effect meta-analysis including only trial results at low risk of bias. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

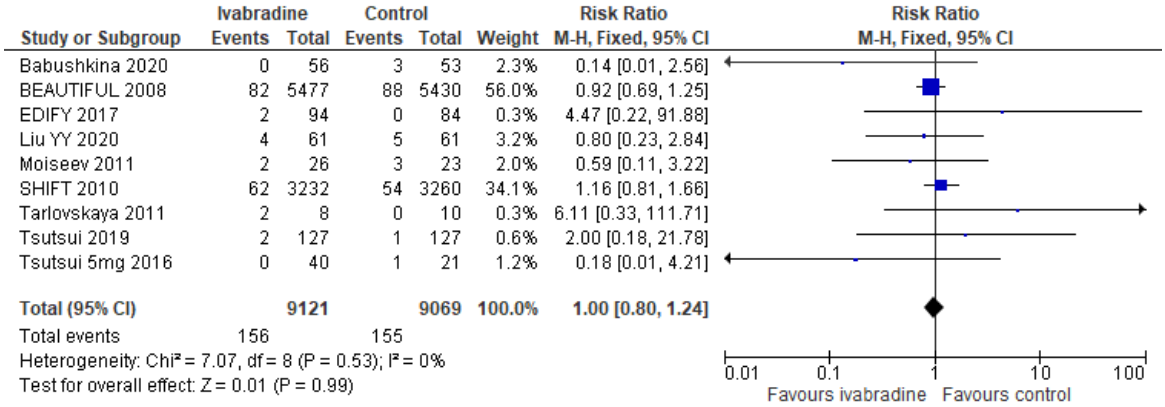


Figure 50 - Forest plot of the meta-analysis of myocardial infarction using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

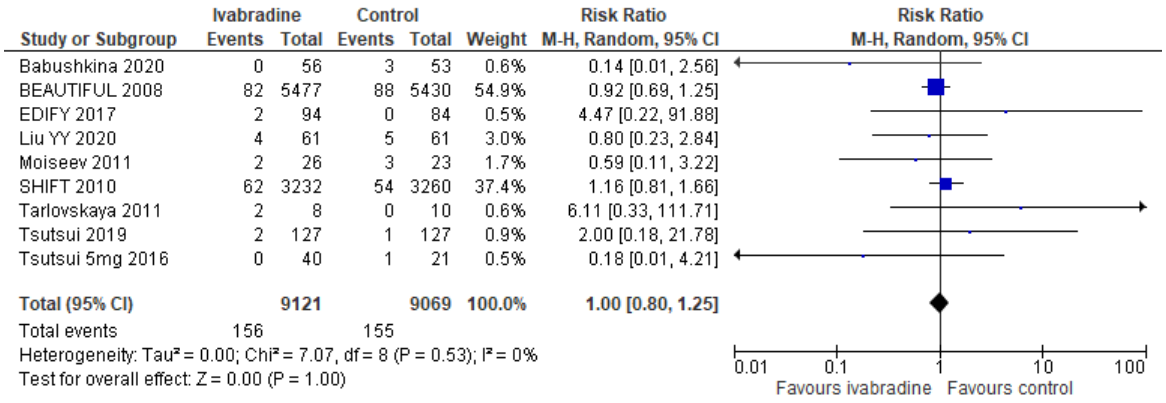


Figure 51 - Forest plot of the meta-analysis of myocardial infarction using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

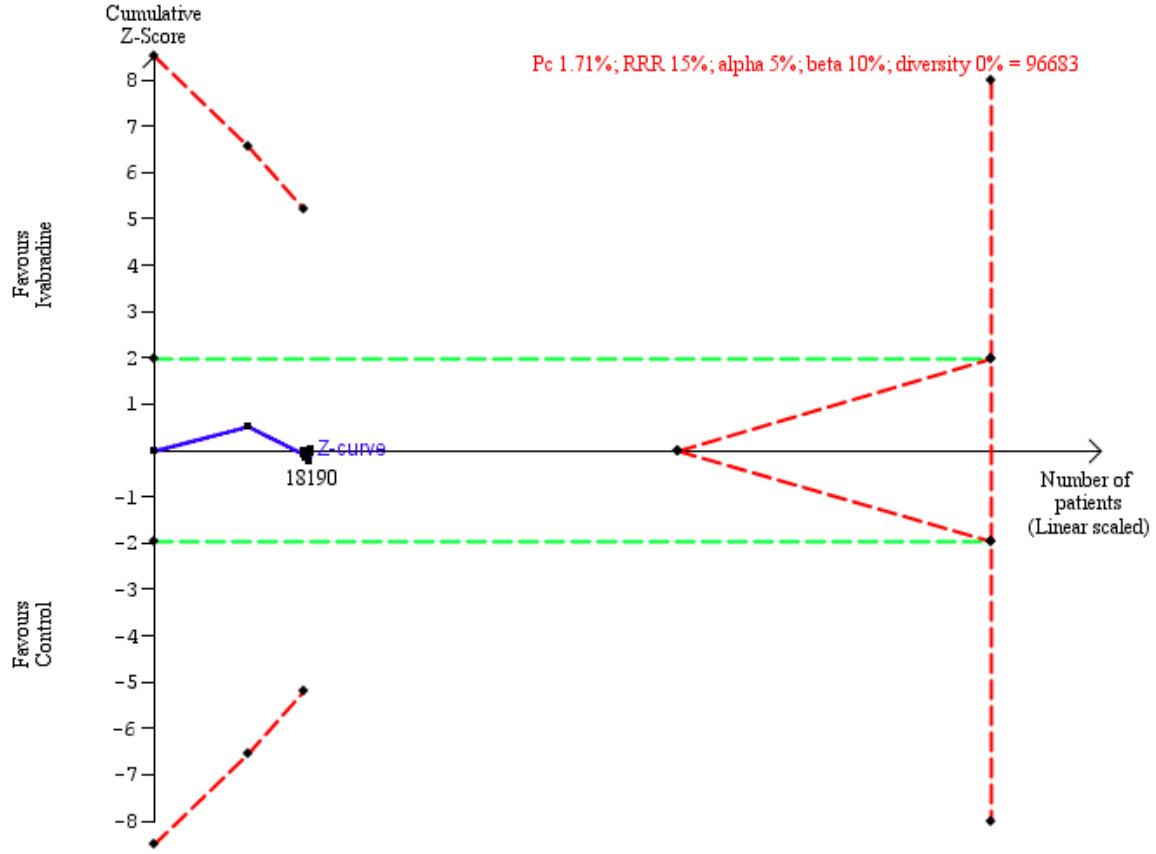


Figure 52 - Trial Sequential Analysis graph of myocardial infarction. Trial Sequential Analysis showed that we did not have enough information to detect or reject a relative risk reduction of 15% or more by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line)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

Sensitivity analyses

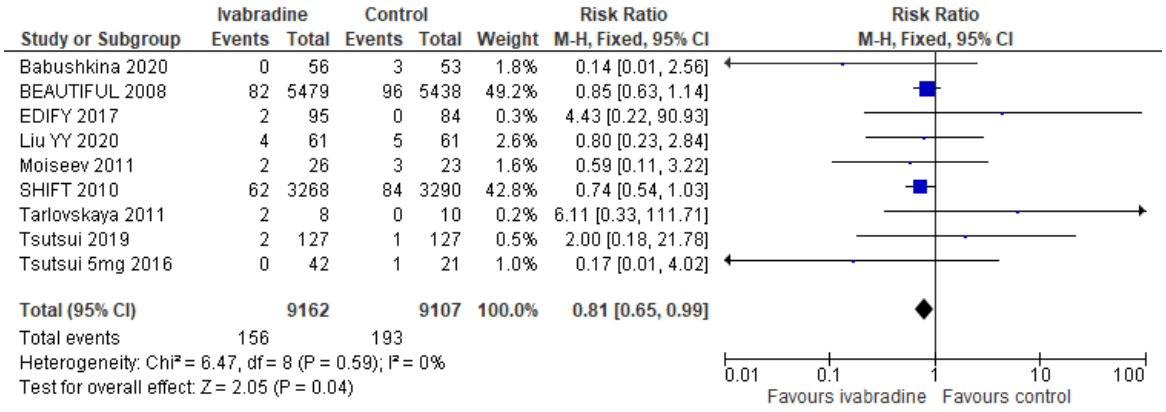


Figure 53 – Forest plot of the sensitivity analysis of myocardial infarction using a best- compared with worst-case scenario.

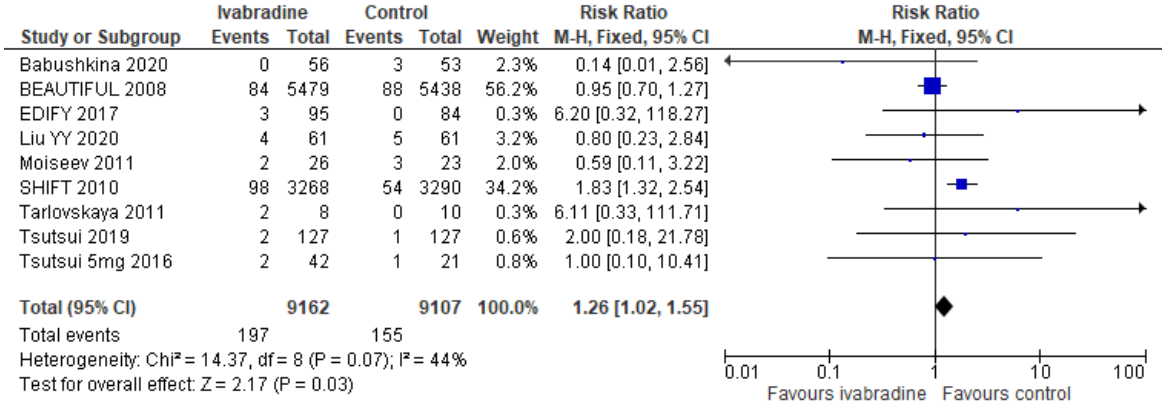


Figure 54 - Forest plot of the sensitivity analysis of myocardial infarction using a worst- compared with best-case scenario.

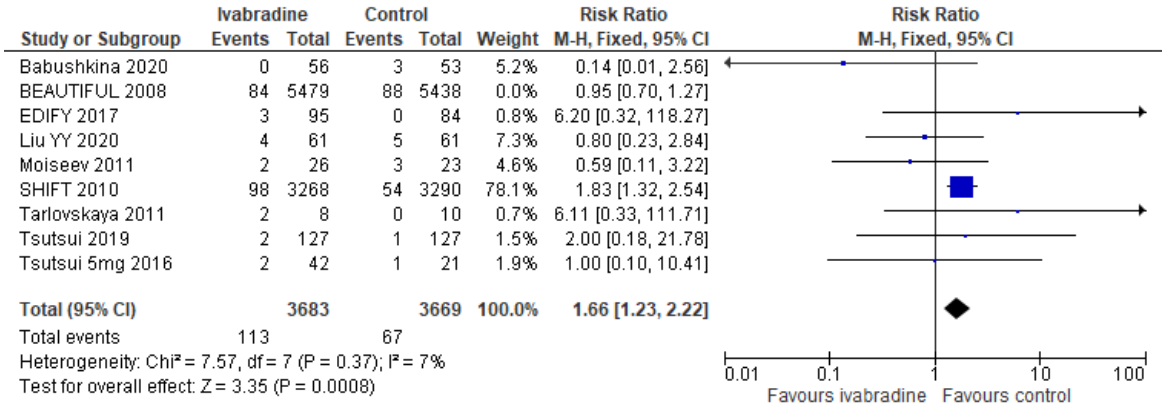


Figure 55 – Forest plot of the sensitivity analysis of myocardial infarction removing the BEAUTIFUL trial.

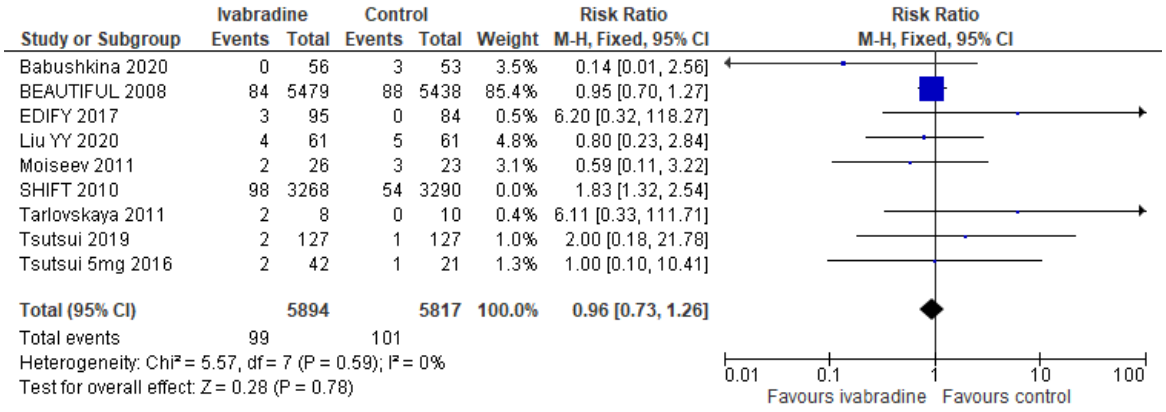


Figure 56 – Forest plot of the sensitivity analysis of myocardial infarction removing the SHIFT trial.

Supplement 10 - Non-serious adverse events

Main analyses

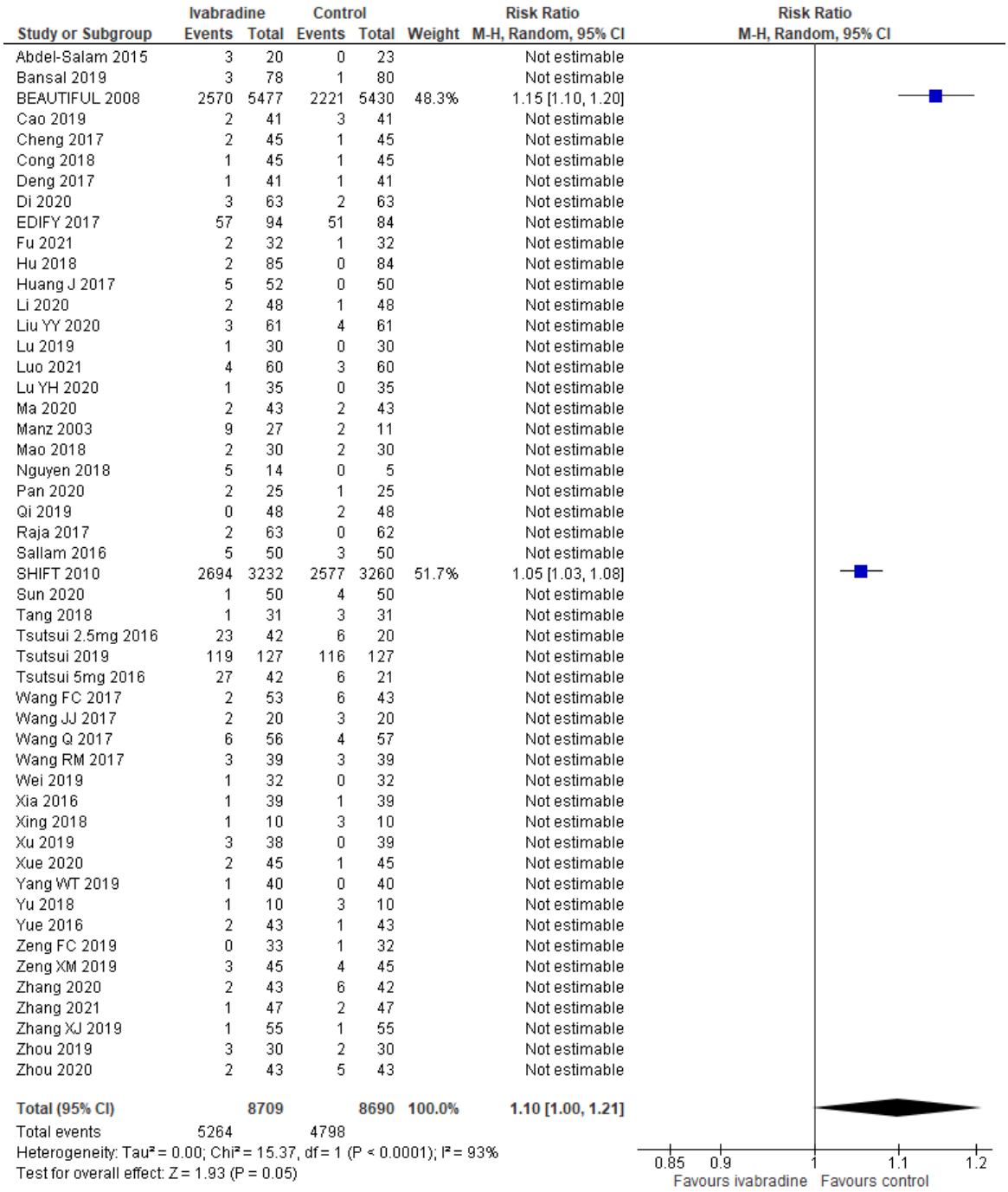


Figure 57 – Forest plot of the meta-analysis of non-serious adverse events using random-effects meta-analysis including only trials at low risk of bias. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention)

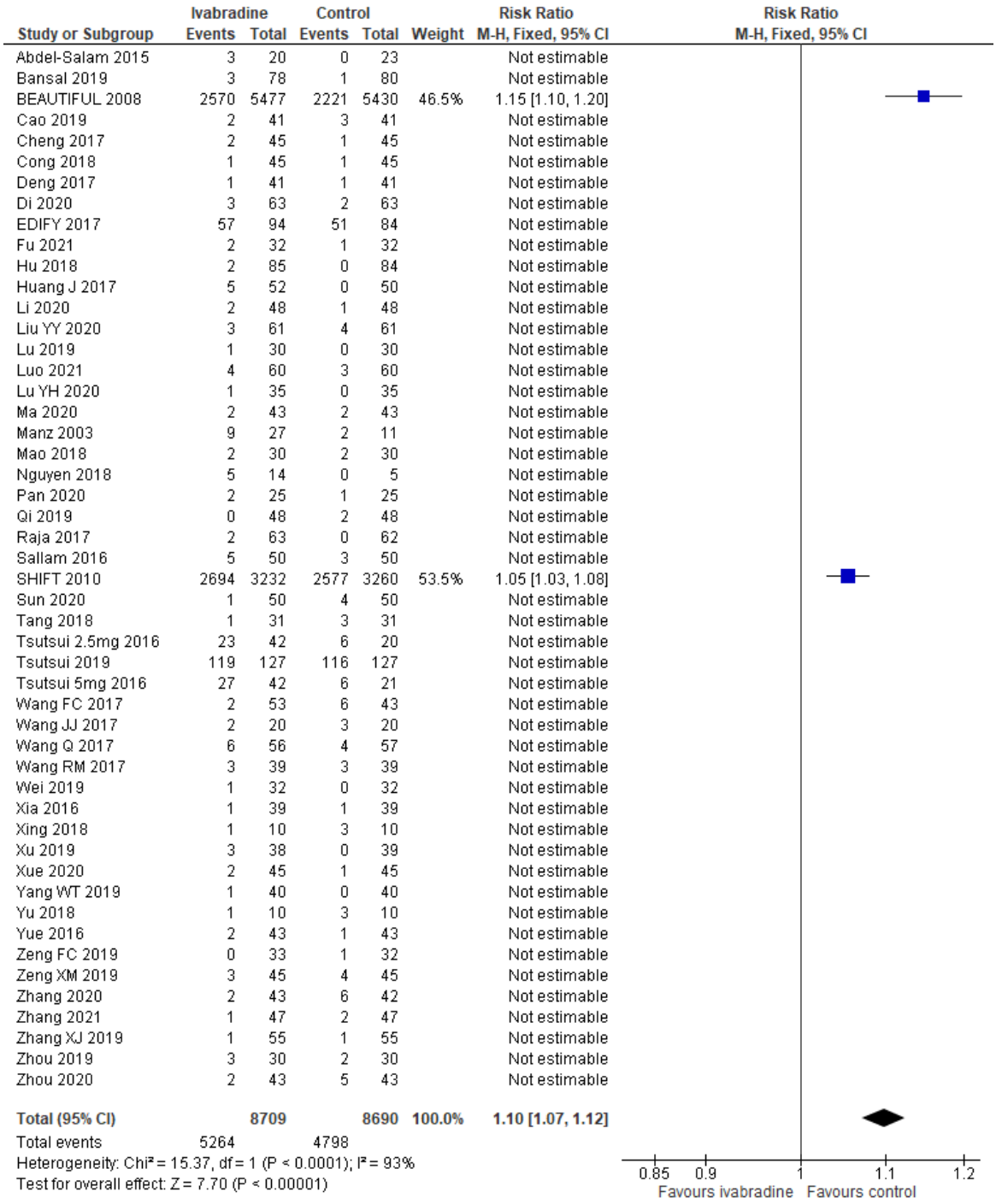


Figure 58 – Forest plot of the meta-analysis of non-serious adverse events using fixed-effect meta-analysis including only trials at low risk of bias. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention).

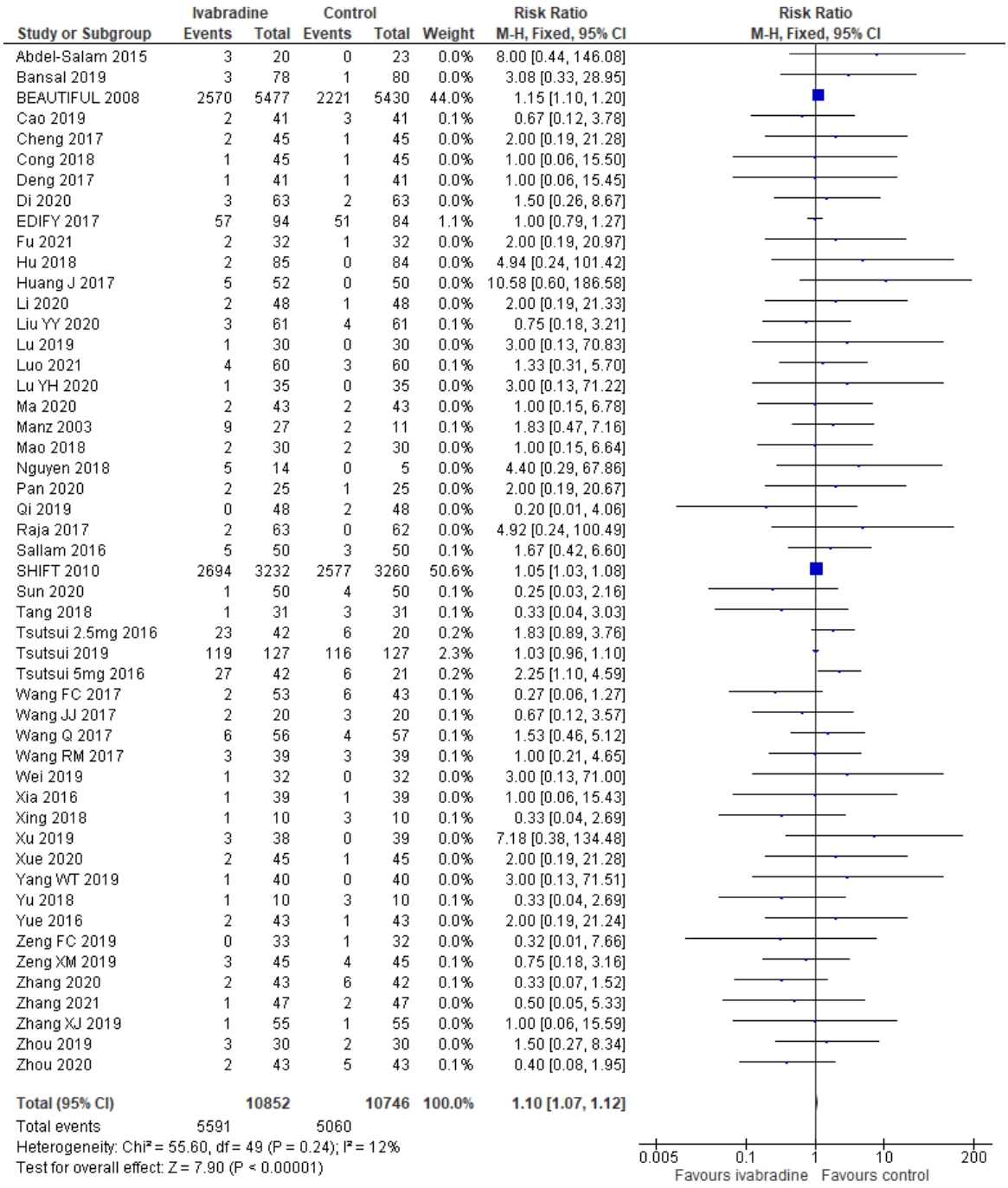


Figure 59 - Forest plot of the meta-analysis of non-serious adverse events using fixed-effect meta-analysis. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention).

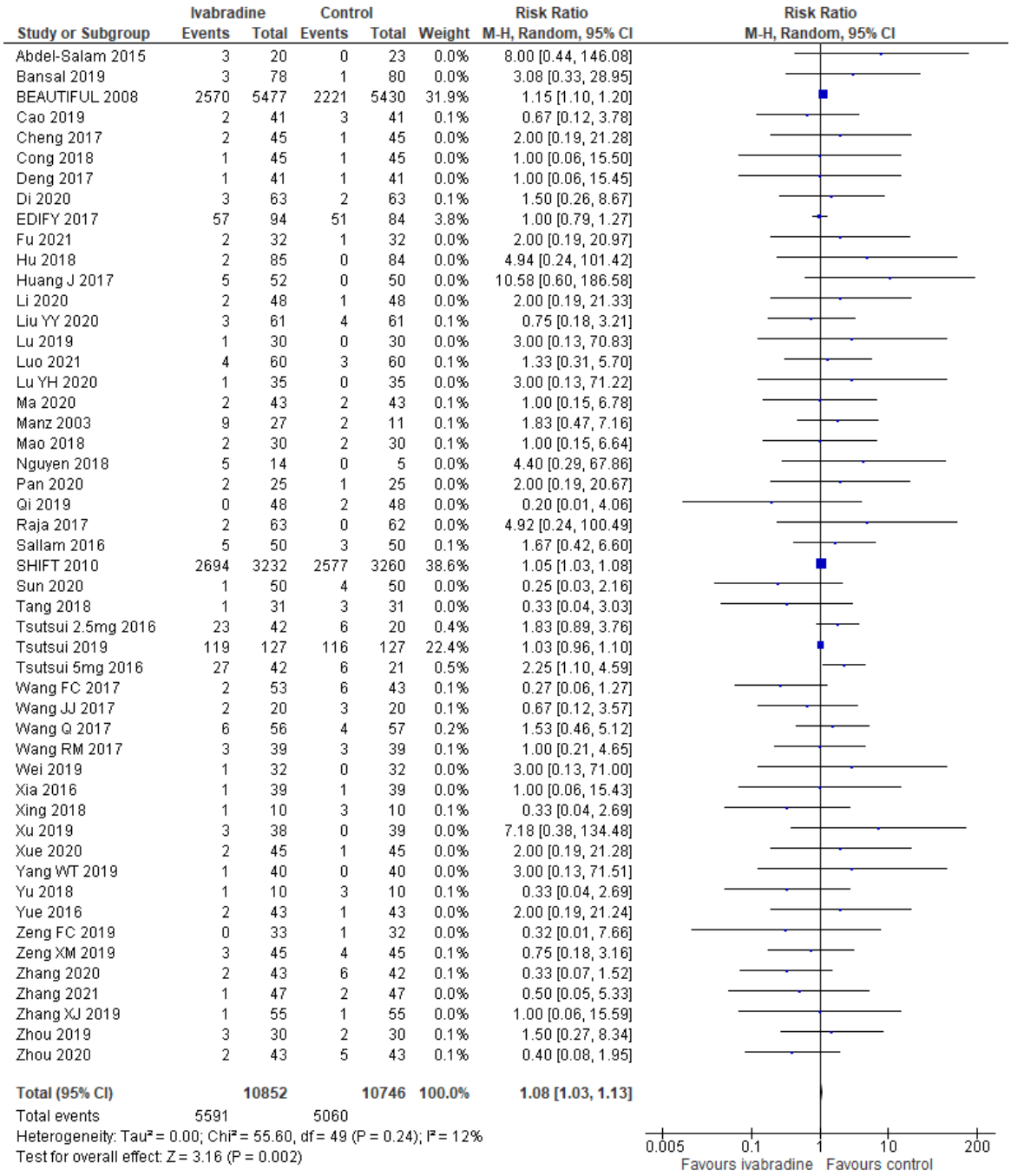


Figure 60 - Forest plot of the meta-analysis of non-serious adverse events using random-effects meta-analysis. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention)

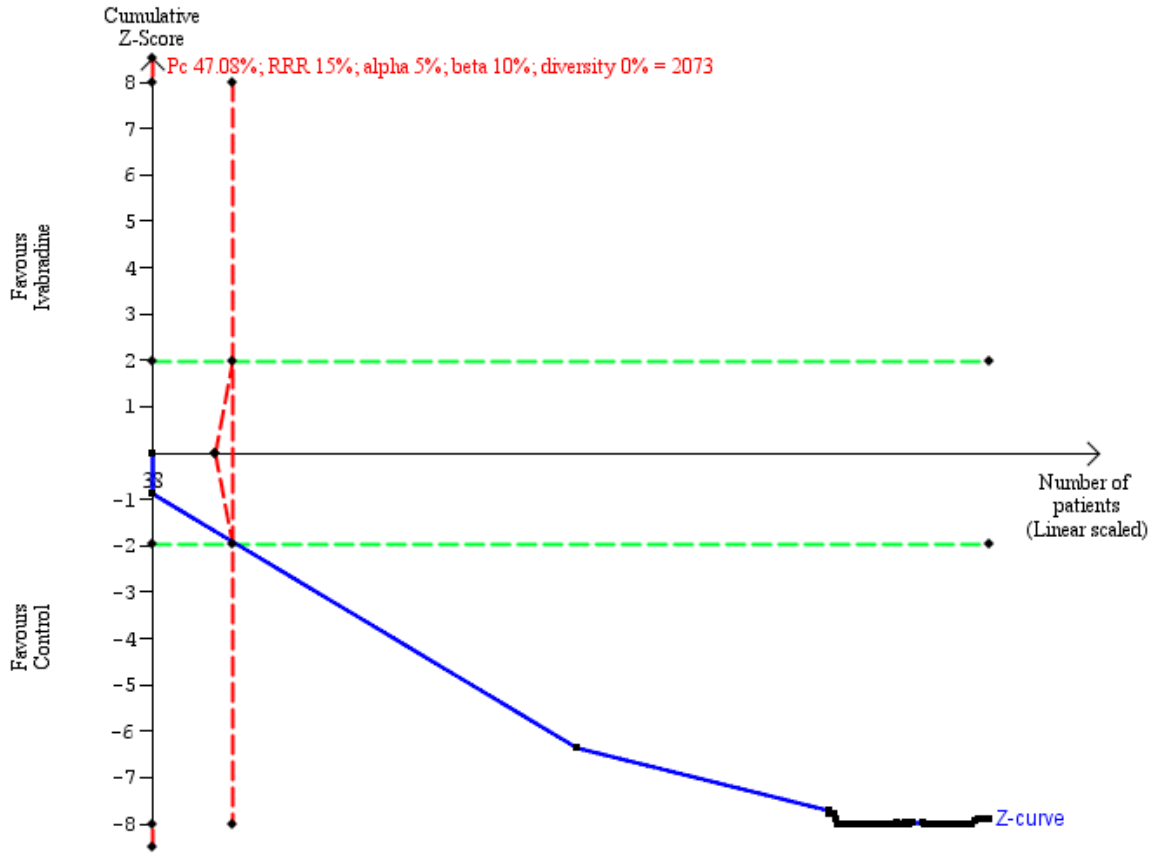


Figure 61 – Trial Sequential Analysis graph of non-serious adverse events. Trial Sequential Analysis showed that we had enough information to detect a relative risk increase of 10% by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) reached the required information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

Sensitivity analyses

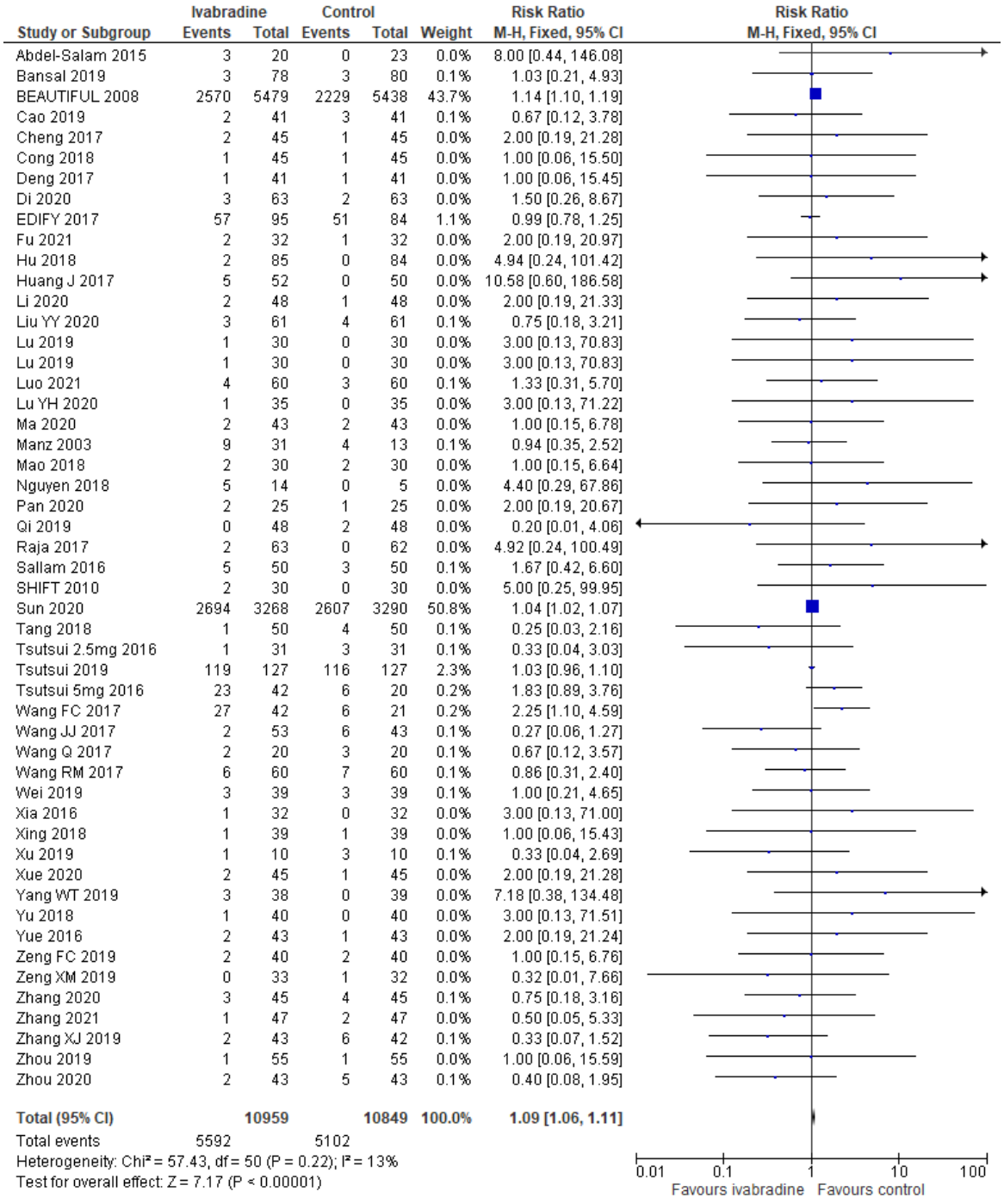


Figure 62 – Forest plot of the meta-analysis of non-serious adverse events using a best- compared with worst-case scenario.

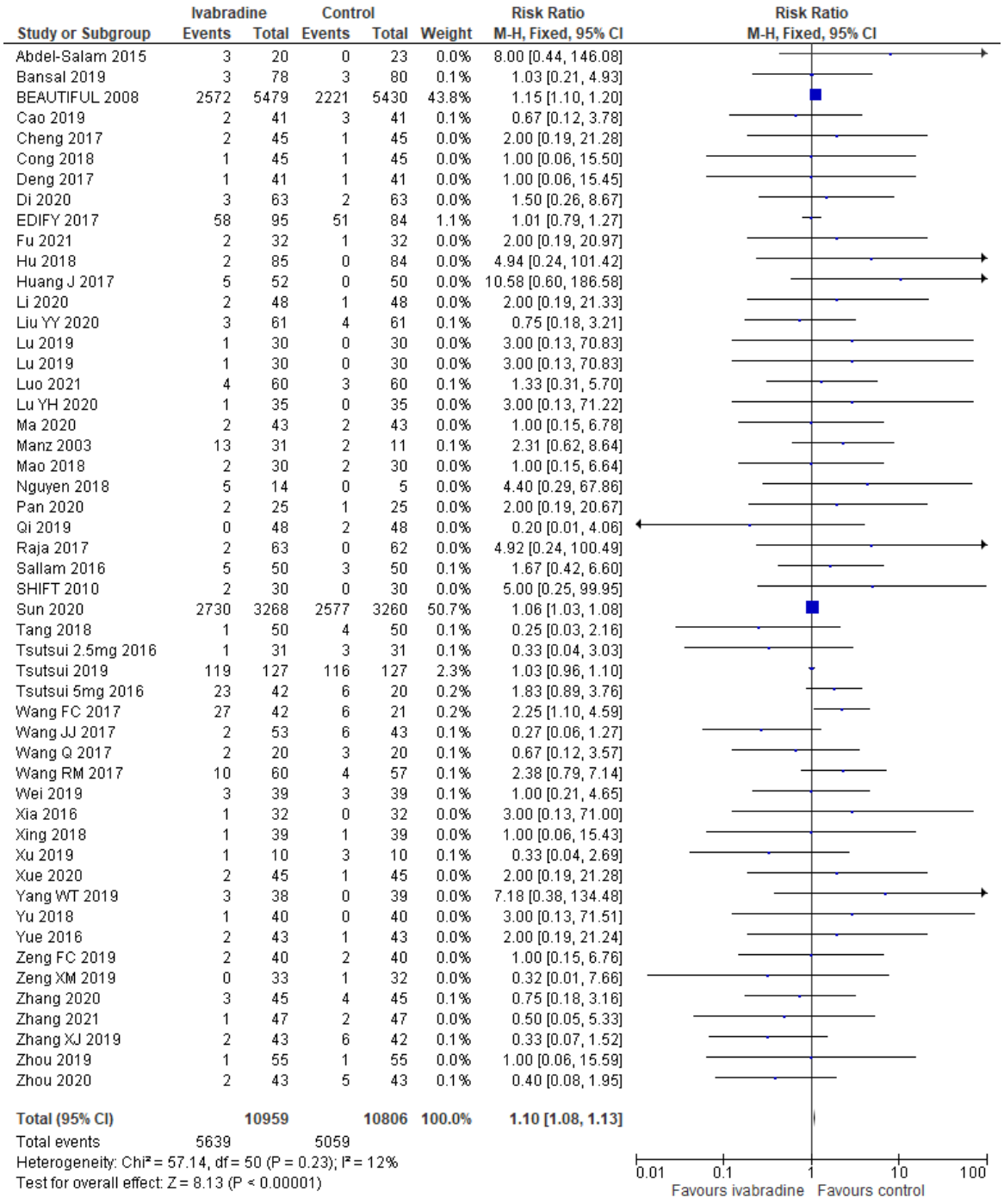


Figure 63 - Forest plot of the meta-analysis of non-serious adverse events using a worst- compared with best-case scenario.

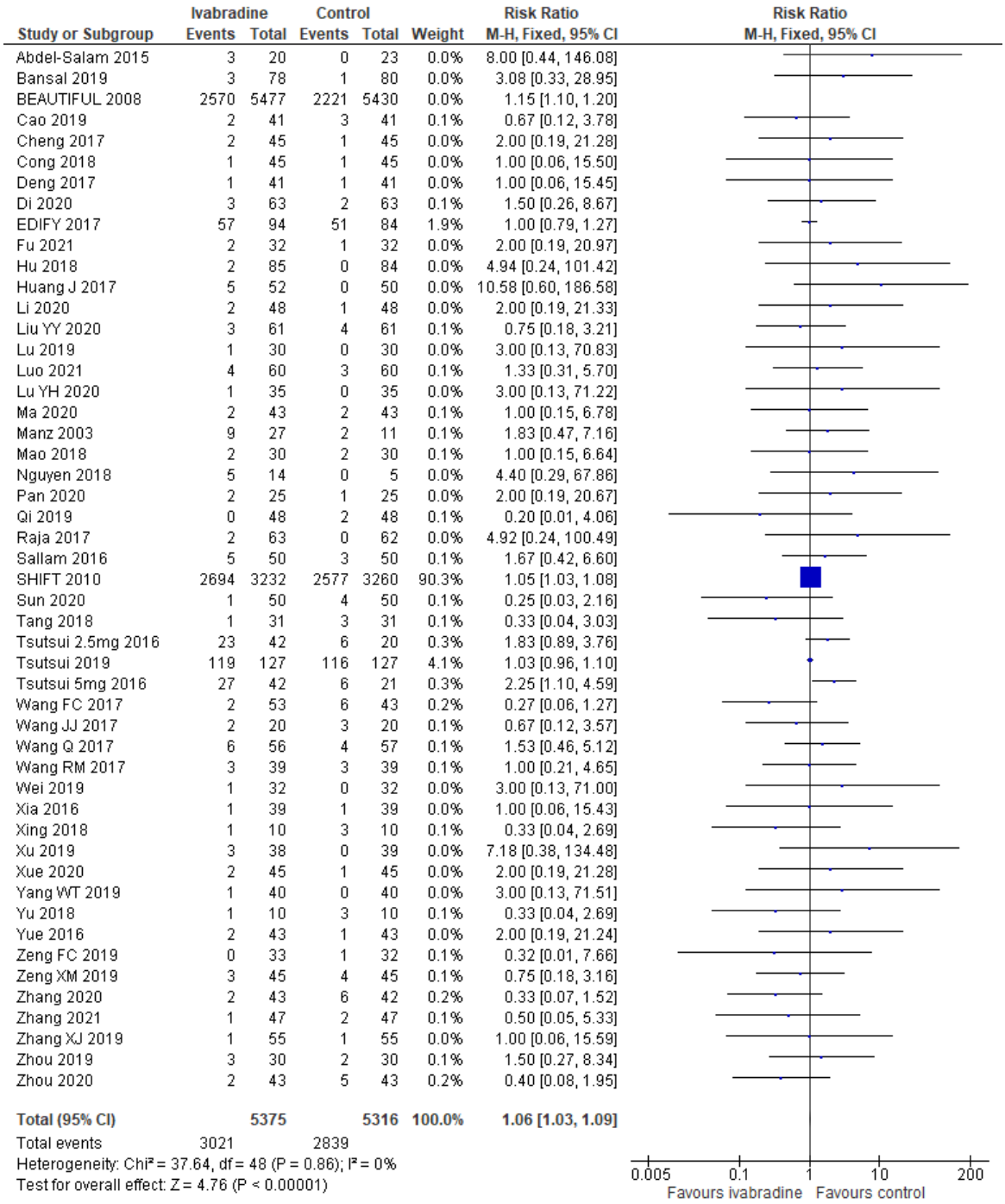


Figure 64 – Forest plot of the sensitivity analysis of non-serious adverse events removing the BEAUTIFUL trial.

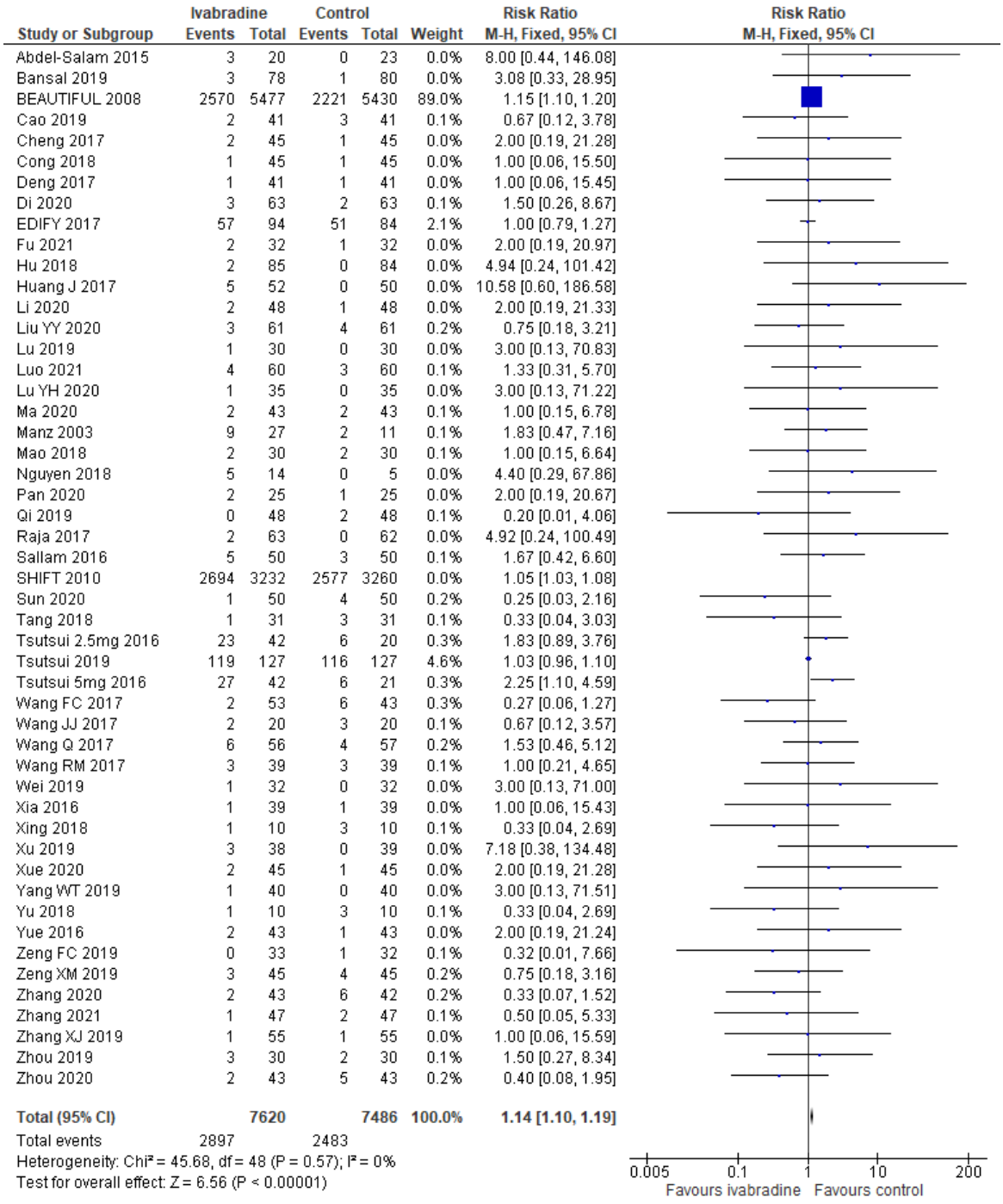


Figure 65 – Forest plot of the sensitivity analysis of non-serious adverse events removing the SHIFT trial.

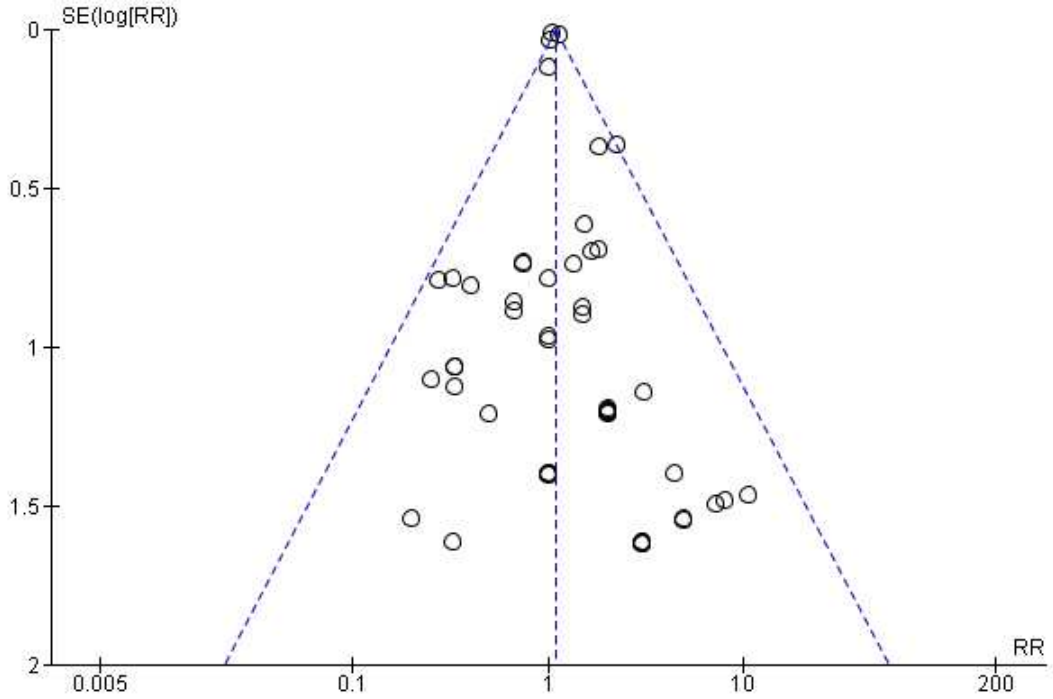


Figure 66 – Funnel plot of the analysis of non-serious adverse events. The funnel plot did not indicate small study bias.

Supplement 11 – Discrepancy in safety data

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

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

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

Supplement 12 – Exploratory outcomes

Resting heart rate at follow-up

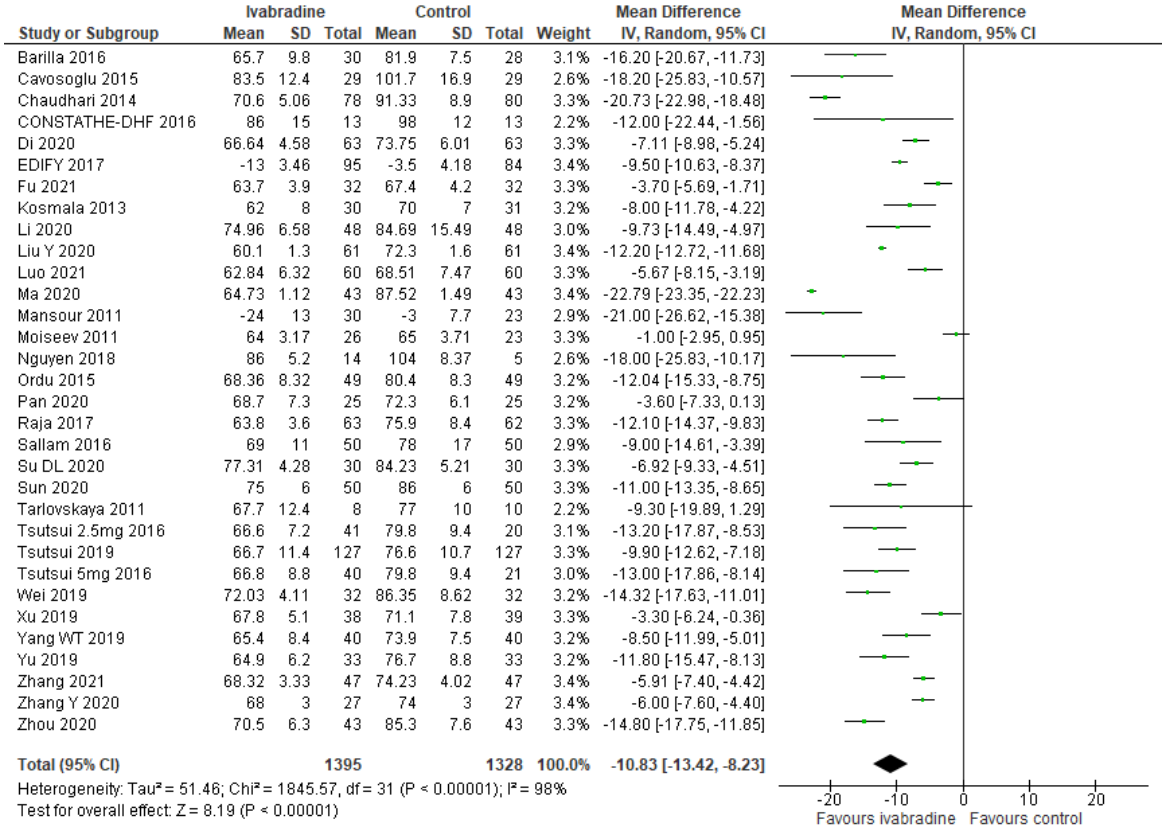


Figure 67 – Forest plot of the meta-analysis of resting heart rate at follow-up using random-effects meta-analysis. The meta-analysis showed that ivabradine seemed to decrease the resting heart rate at follow-up by 10.83 beats per minute at follow-up.

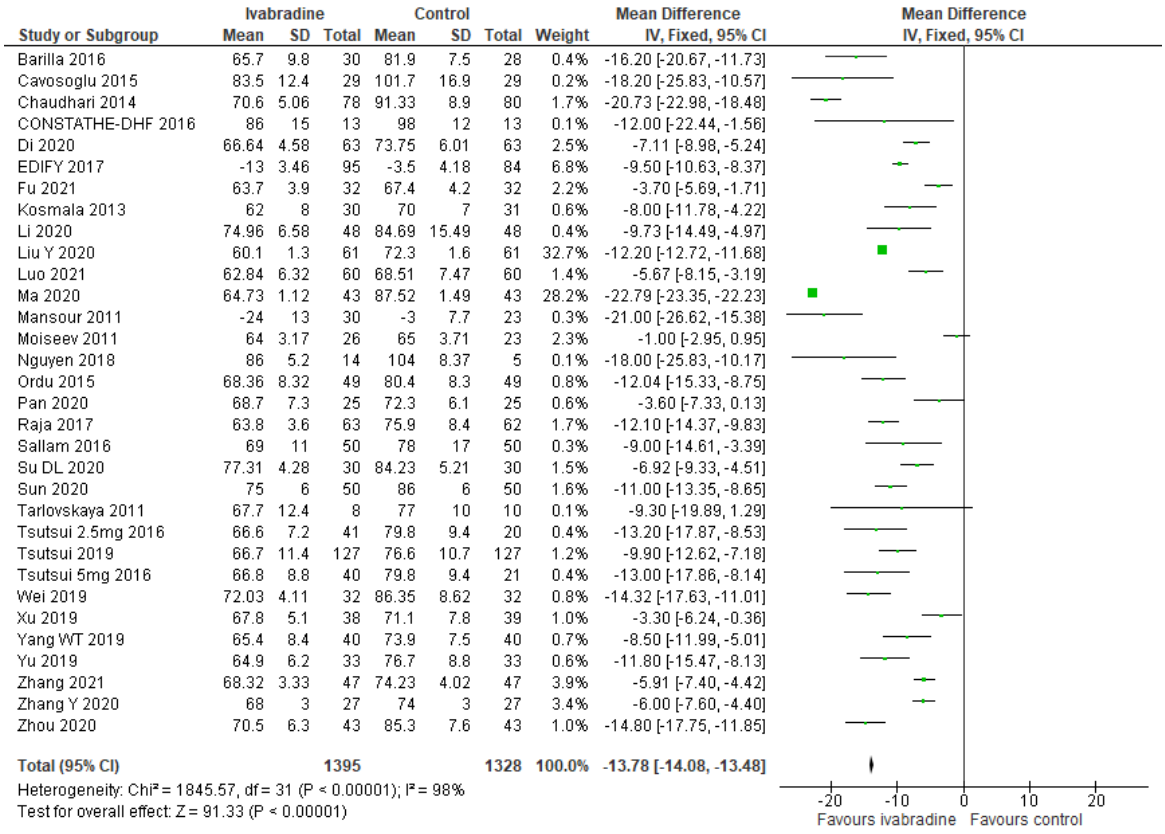


Figure 68 - Forest plot of the meta-analysis of resting heart rate at follow-up using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to decrease the resting heart rate at follow-up by 13.78 beats per minute at follow-up.

Left ventricular ejection fraction

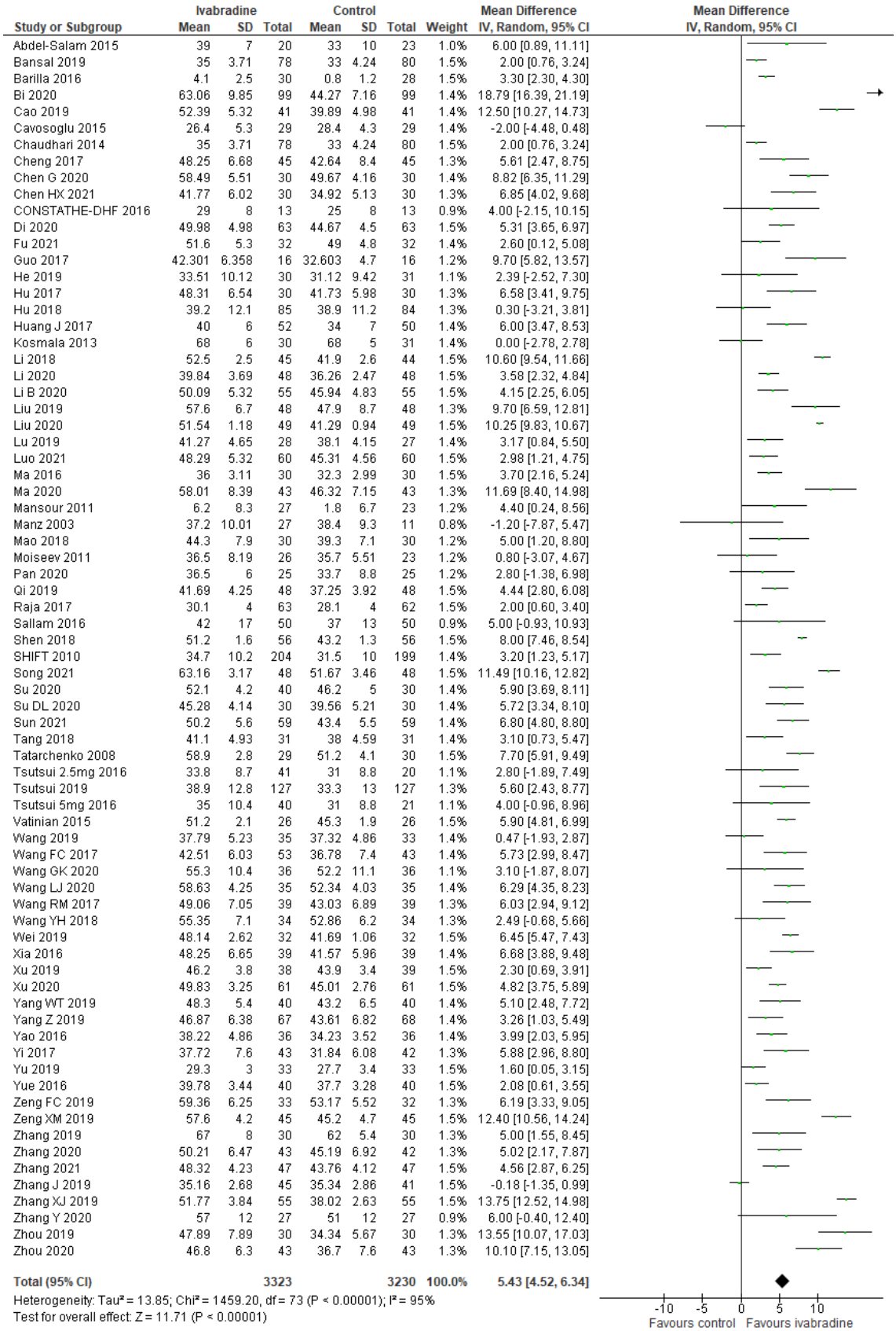

Ivabradine
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Abdel-Salam 2015 39 7 20 33 10 23 1.0% 6.00 [0.89, 11.11]
Bansal 2019 35 3.71 78 33 4.24 80 1.5% 2.00 [0.76, 3.24]
Barilla 2016 4.1 2.5 30 0.8 1.2 28 1.5% 3.30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

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

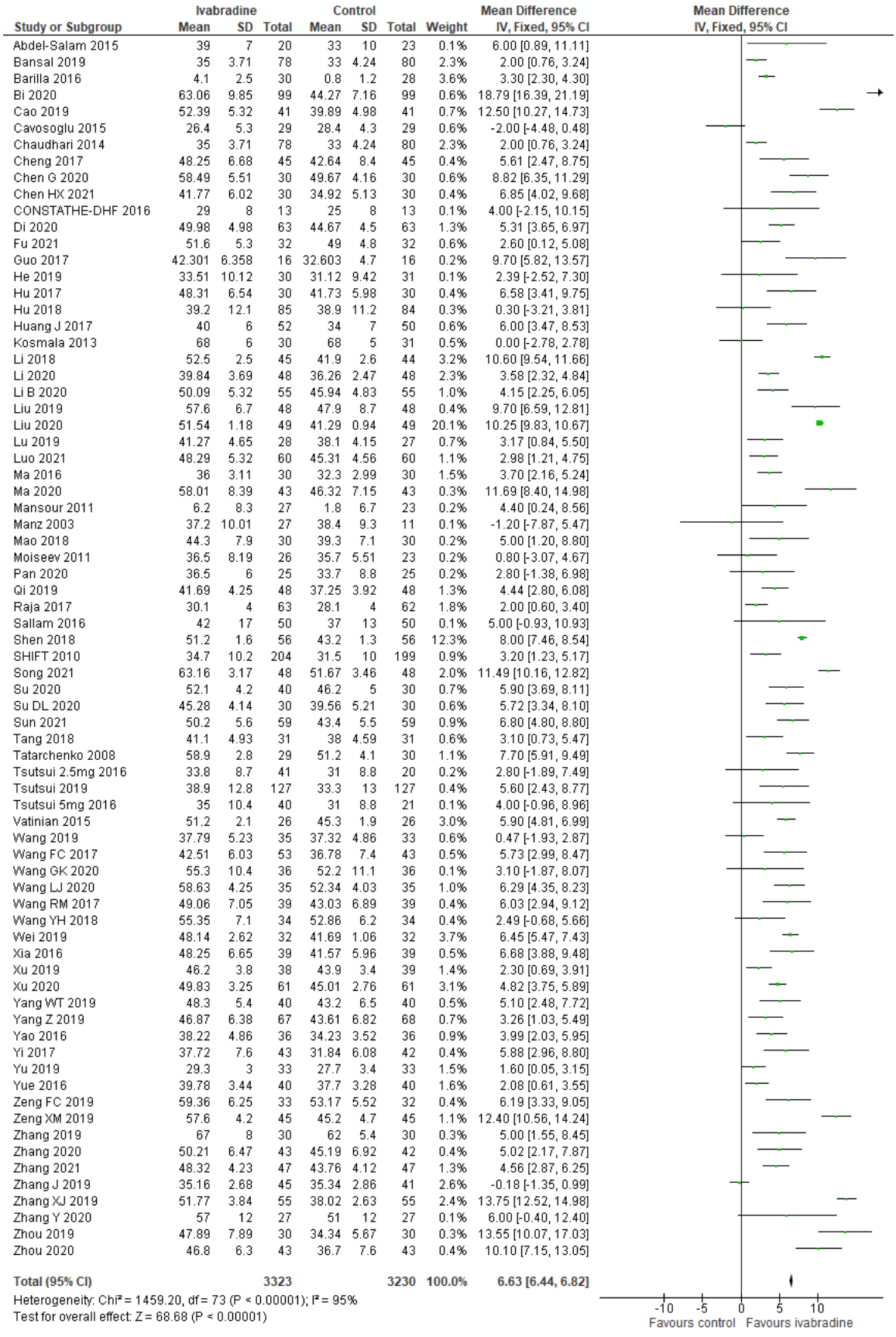

Ivabradine
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Abdel-Salam 2015 39 7 20 33 10 23 0.1% 6.00 [0.89, 11.11]
Bansal 2019 35 3.71 78 33 4.24 80 2.3% 2.00 [0.76, 3.24]
Barilla 2016 4.1 2.5 30 0.8 1.2 28 3.6% 3.30 [2.30,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

Figure 70 - Forest plot of the meta-analysis of left ventricular ejection fraction using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to increase the left ventricular ejection fraction by 6.63%.

Hospitalisation during follow-up

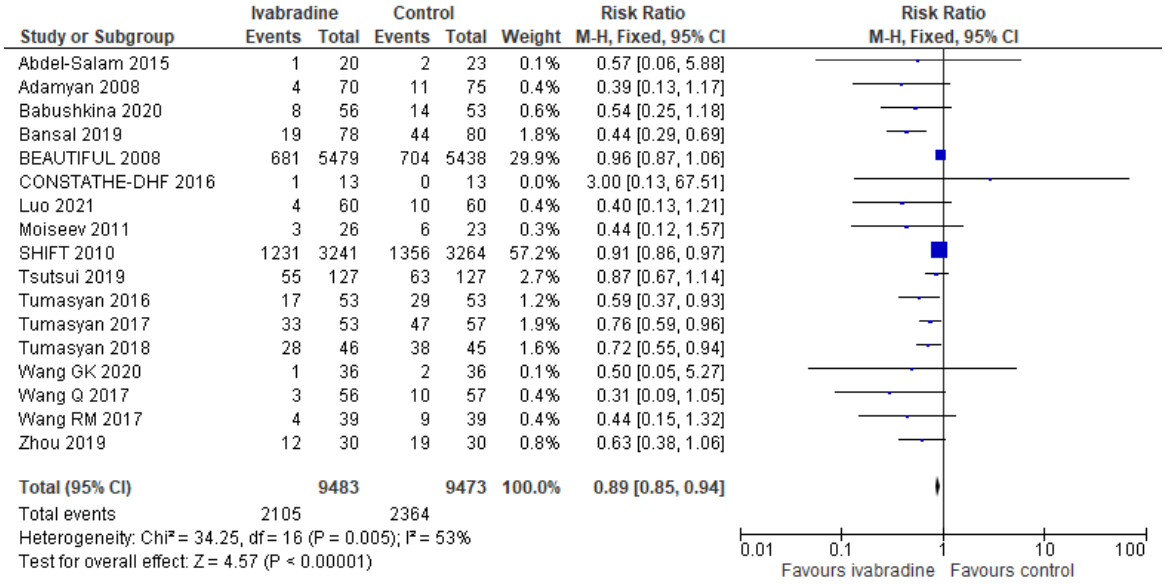


Figure 71 – Forest plot of the meta-analysis of hospitalisation during follow-up using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect ivabradine versus control (placebo or no intervention) of a risk ratio of 0.89.

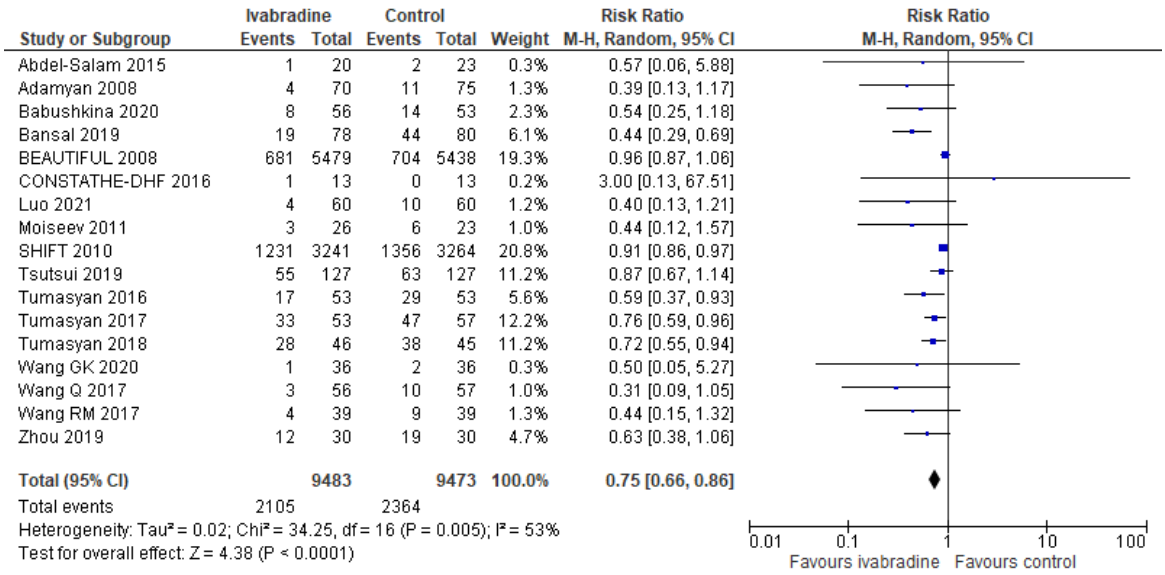


Figure 72 - Forest plot of the meta-analysis of hospitalisation during follow-up using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention) of a risk ratio of 0.75.

6-minutes walking distance

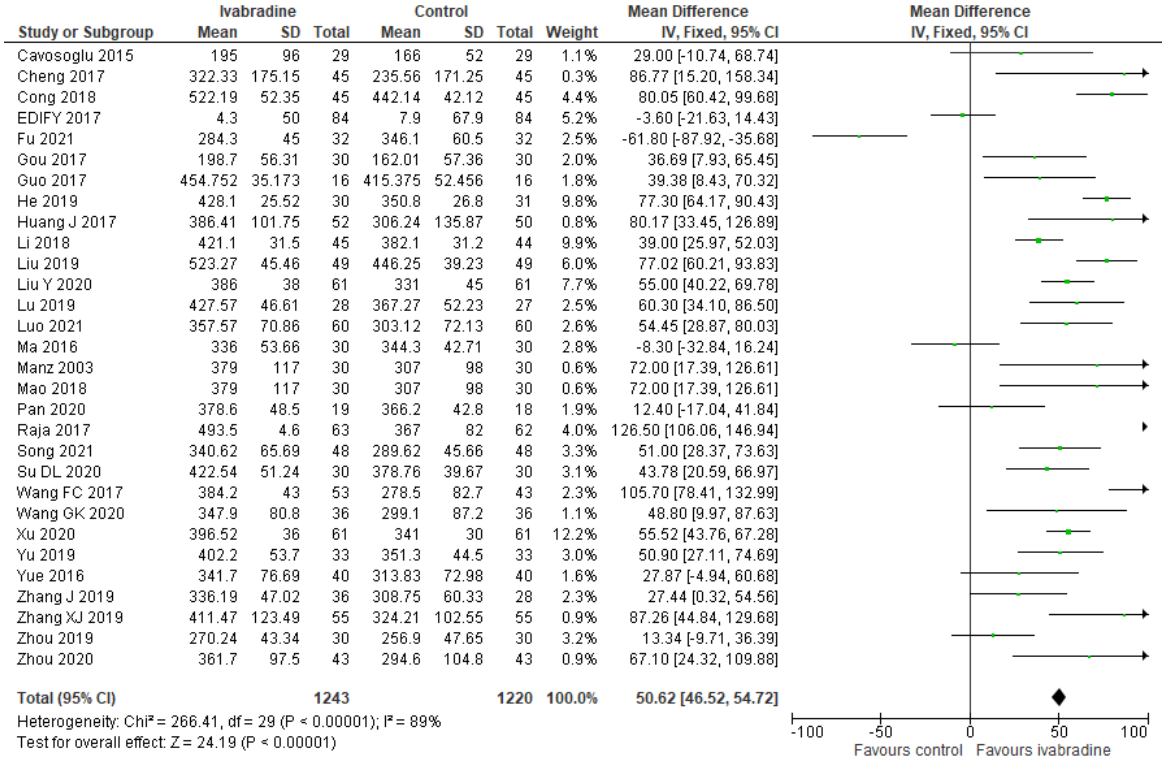


Figure 73 – Forest plot of the meta-analysis of 6-minutes walking distance using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention) of 50.62 meters per 6 minutes.

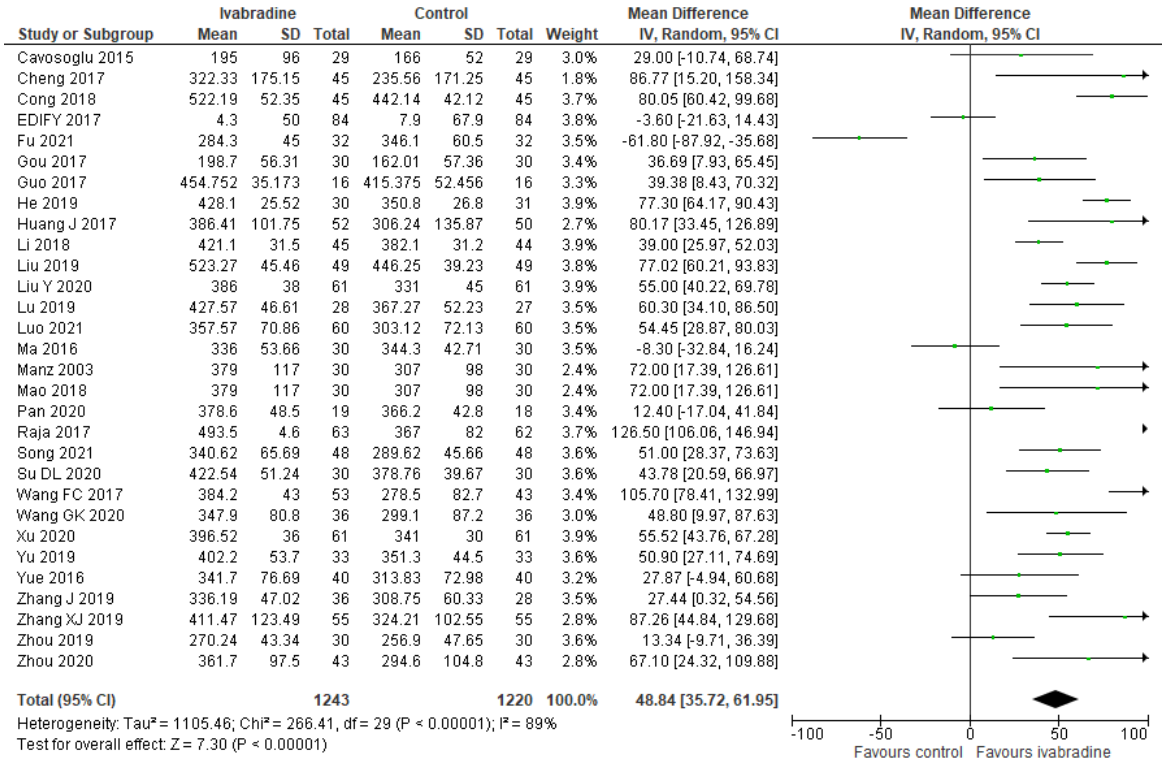


Figure 74 – Forest plot of the meta-analysis of 6-minutes walking distance using random-effects meta-analysis. The meta-analysis shows evidence of a beneficial effect of ivabradine versus control (placebo or no intervention) of 48.84 meters per 6 minutes.