Ivabradine for coronary artery disease - supplemental

Supplement 1 – List of databases

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

Supplement 2 – Search strategy

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

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

Supplement 3 – PRISMA flow chart

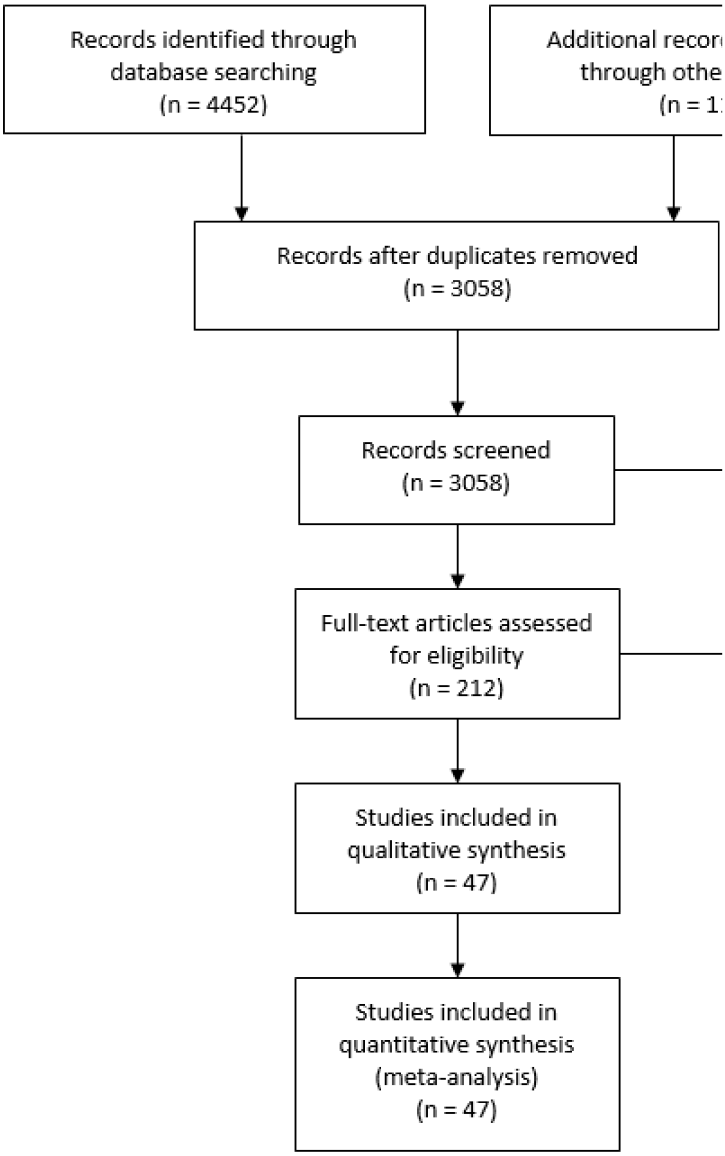

Figure 1 – PRISMA flowchart.

Supplement 4 - Risk of bias

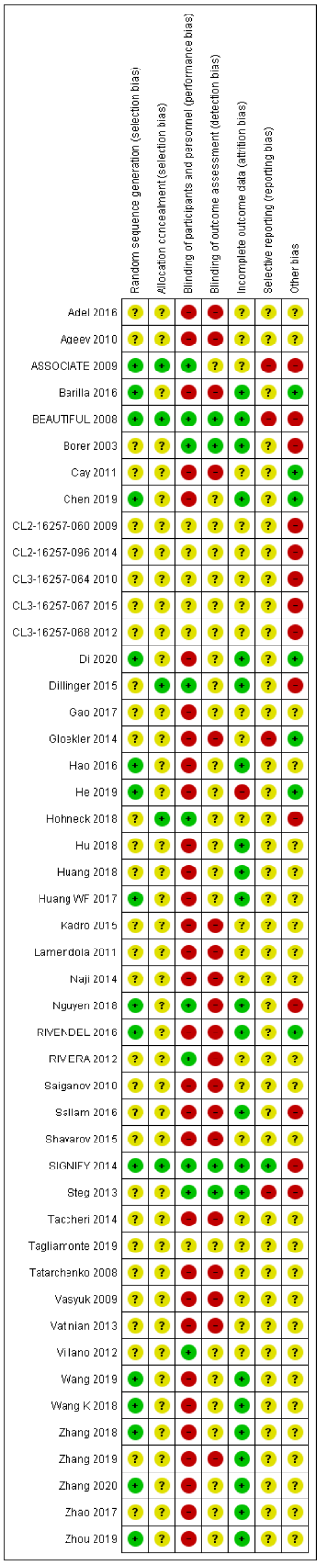

Figure 2 – Risk of bias graph. Green: low risk of bias; yellow: unclear risk of bias; red: high risk of bias.

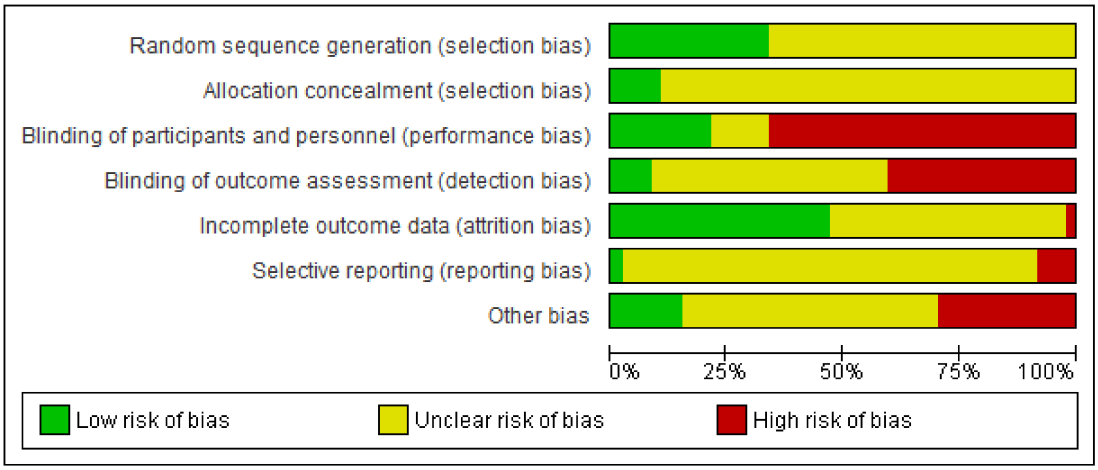

Figure 3 – Risk of bias summary. Green: low risk of bias; yellow: unclear risk of bias; red: high risk of bias.

Supplement 5 - All-cause mortality

Main analyses

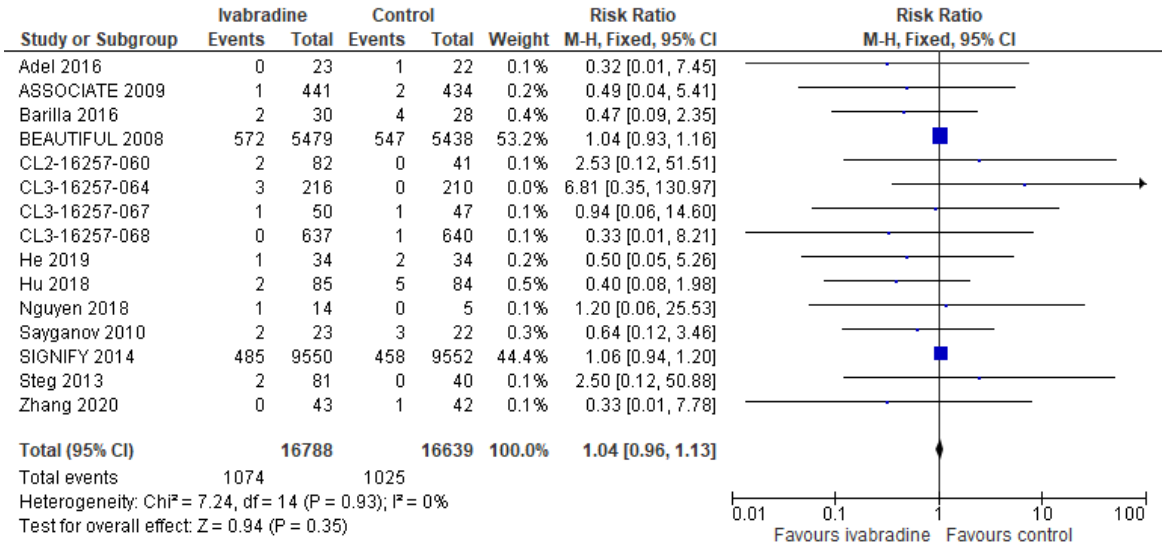

Figure 4 - Forest plot of the meta-analysis of all-cause mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

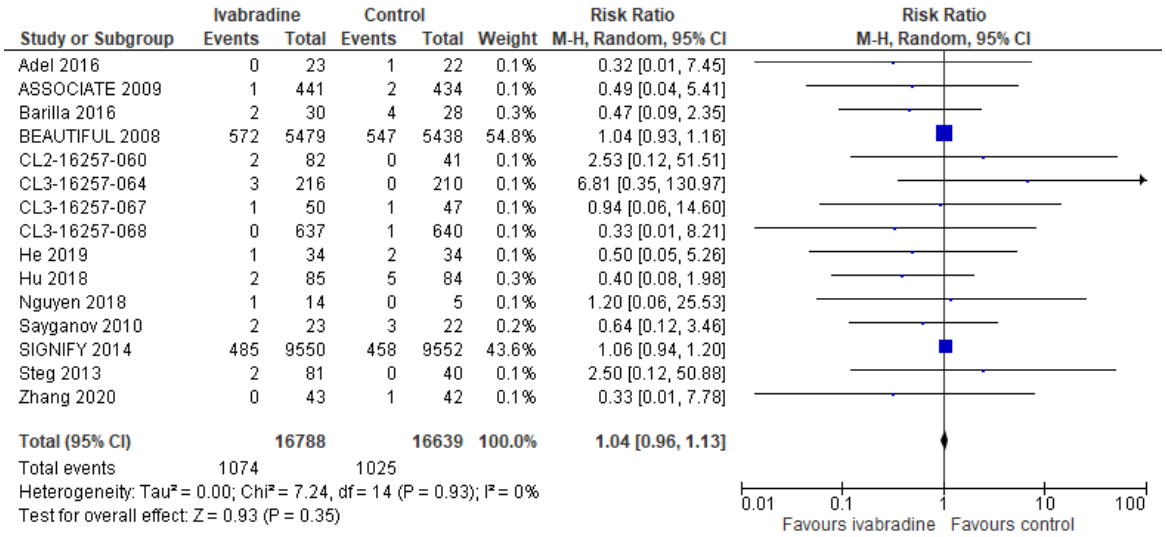

Figure 5 - Forest plot of the meta-analysis of all-cause mortality using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

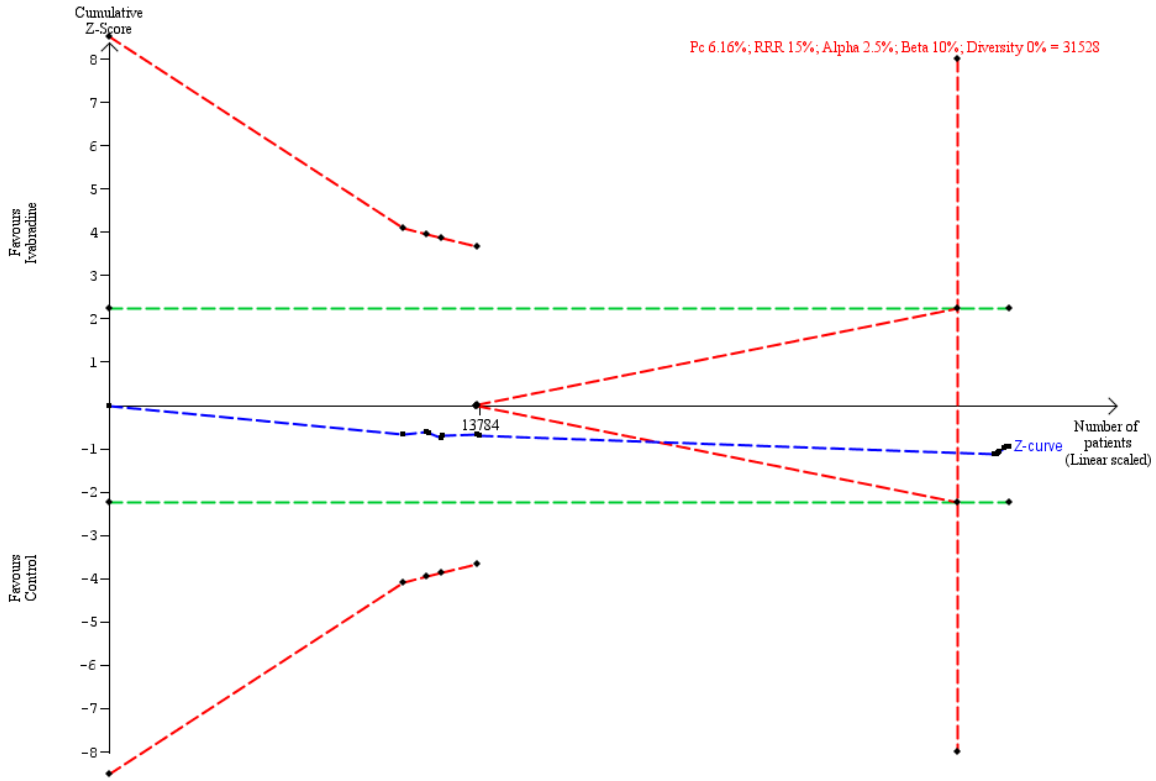

Figure 6 - Trial Sequential Analysis graph of all-cause mortality. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine. The cumulative z-curve (the blue line) breaches the boundary of futility and the required information size.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

Sensitivity analyses

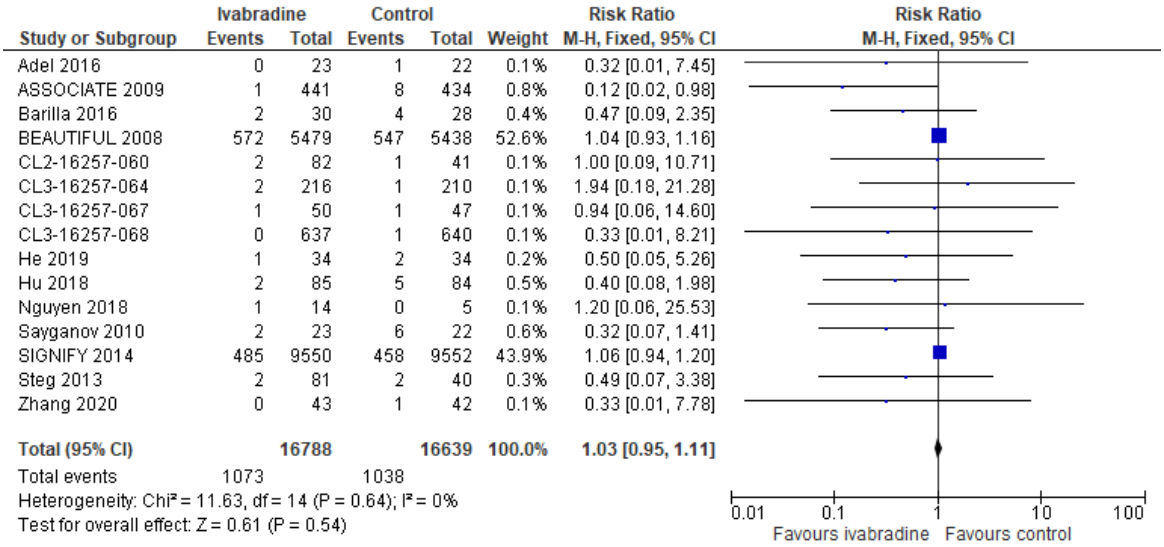

Figure 7 - Forest plot of the sensitivity analysis of all-cause mortality using best/worst-case scenario. The sensitivity analysis showed that missing data did not seem to have the potential to influence the results.

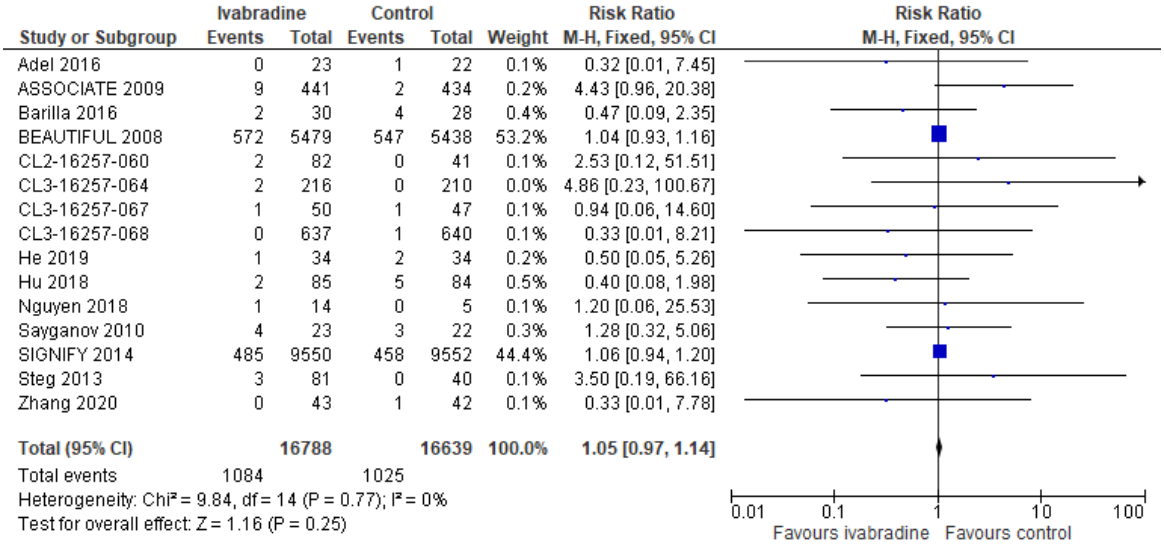

Figure 8 - Forest plot of the sensitivity analysis of all-cause mortality using worst/best-case scenario. The sensitivity analysis showed that missing data did not seem to have the potential to influence the results.

Subgroup analyses

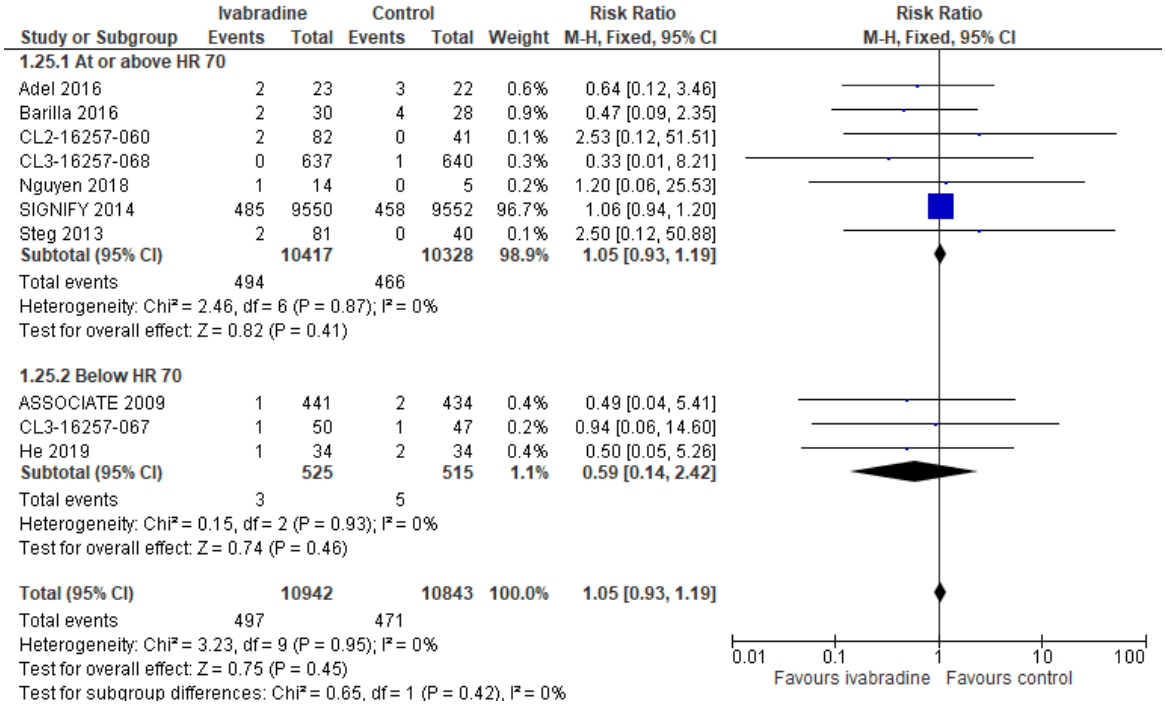

Figure 9 – Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute versus trials randomising participants with heart rate below 70 beats per minute. Test for subgroup differences showed that there was no difference between trials randomising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

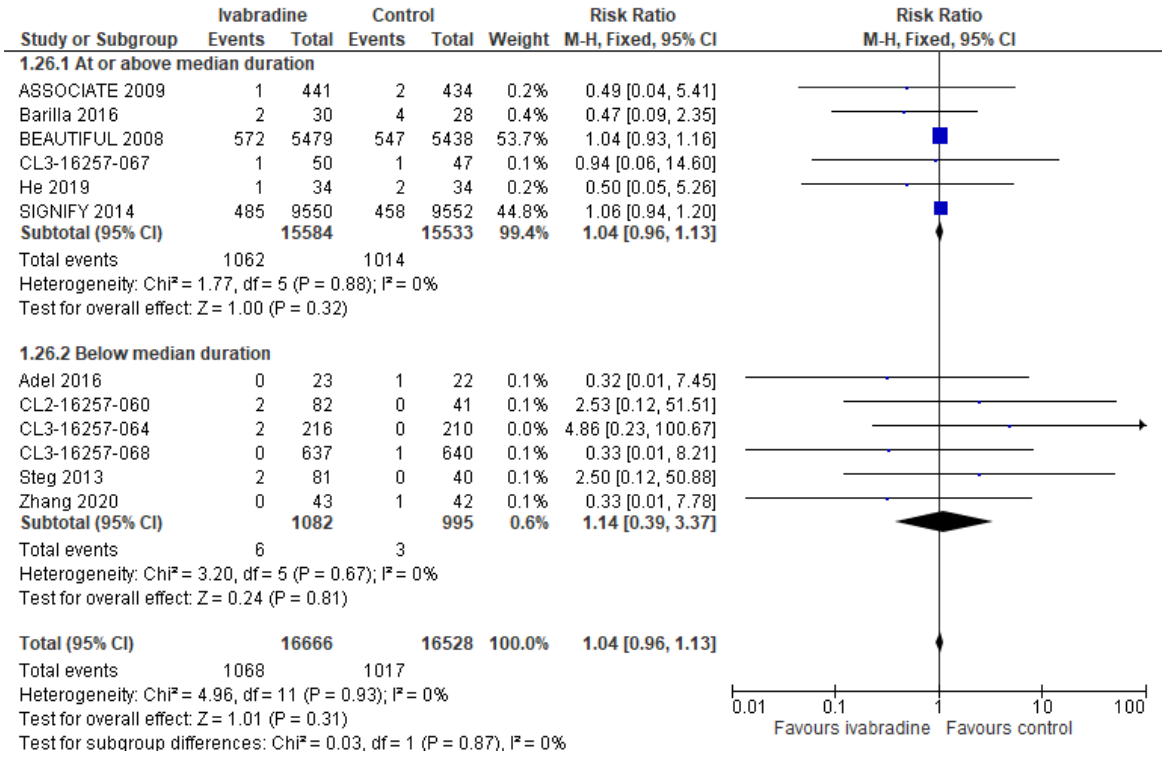

Figure 10 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration versus trials administering ivabradine below median duration. Test for subgroup differences showed that there was no difference between trials administering ivabradine at or above median duration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

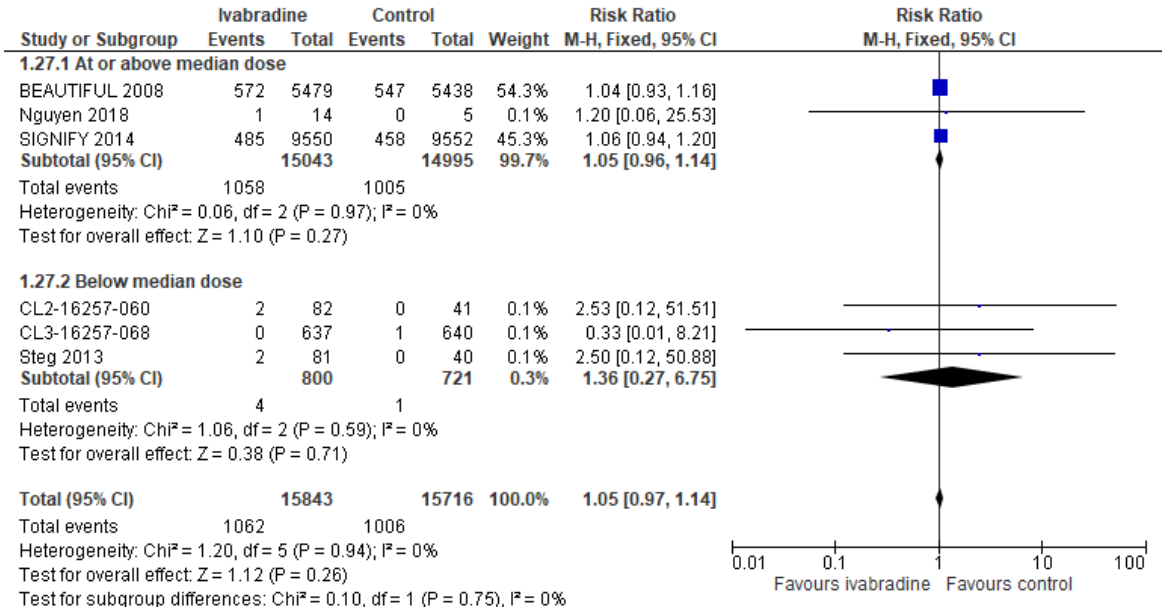

Figure 11 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose versus trials administering ivabradine below median daily dose. Test for subgroup differences showed that there was no difference between trials administering ivabradine at or above median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

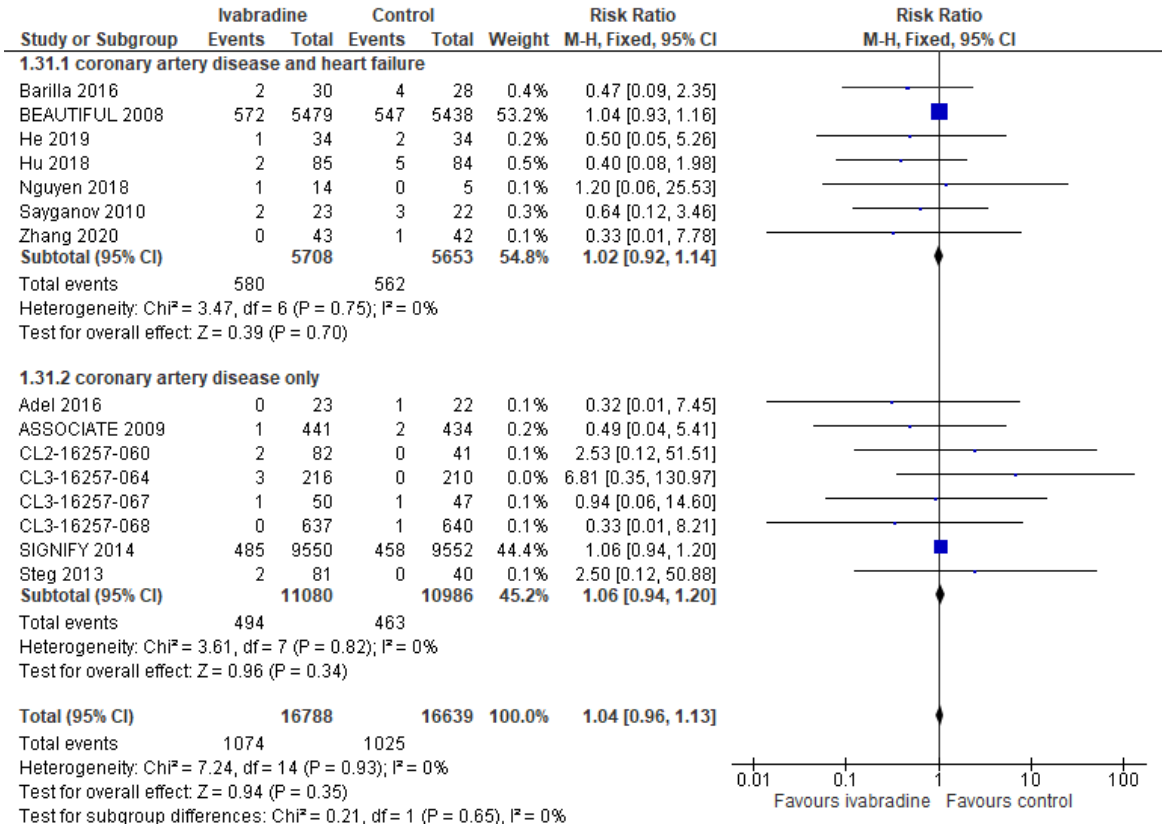

Figure 12 – Forest plot of the subgroup analyses of trials randomising participants with both coronary artery disease and heart failure versus trials randomising participants with coronary artery disease only. Test for subgroup differences showed that there was no difference between trials randomising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

Supplement 6 - Serious adverse events

Main analyses

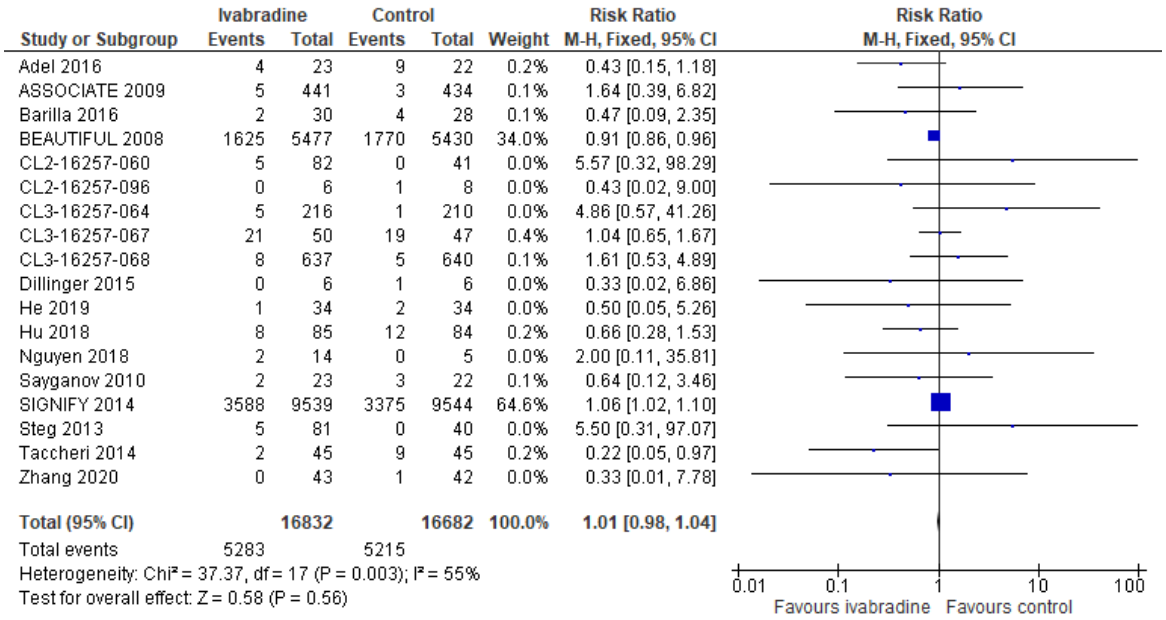

Figure 13 - Forest plot of the meta-analysis of serious adverse events using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

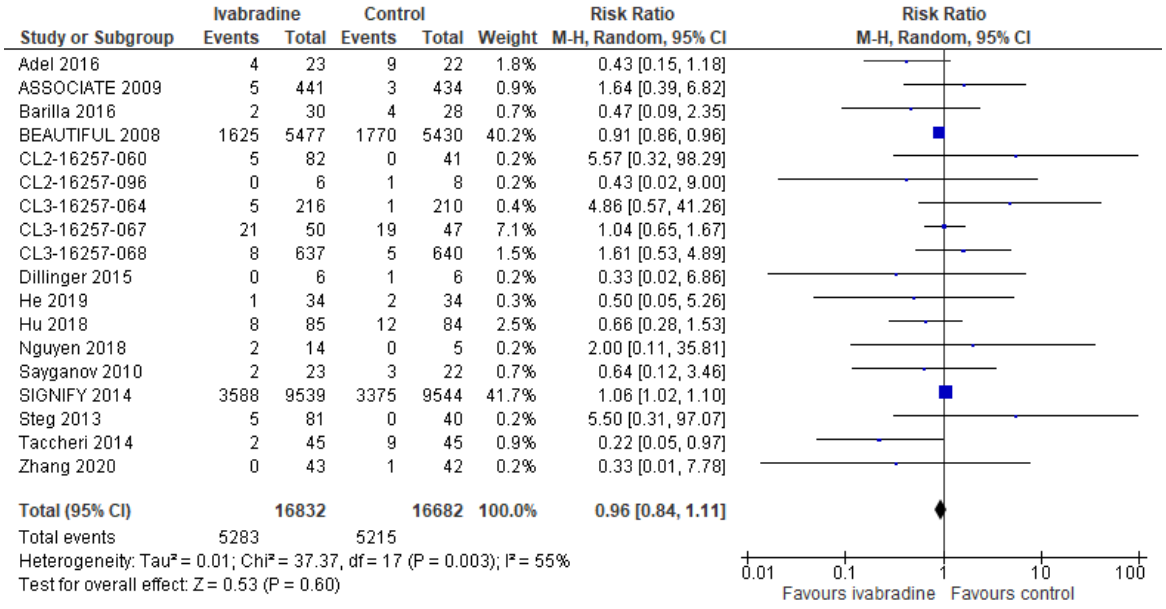

Figure 14 – Forest plot of the meta-analysis of serious adverse events using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

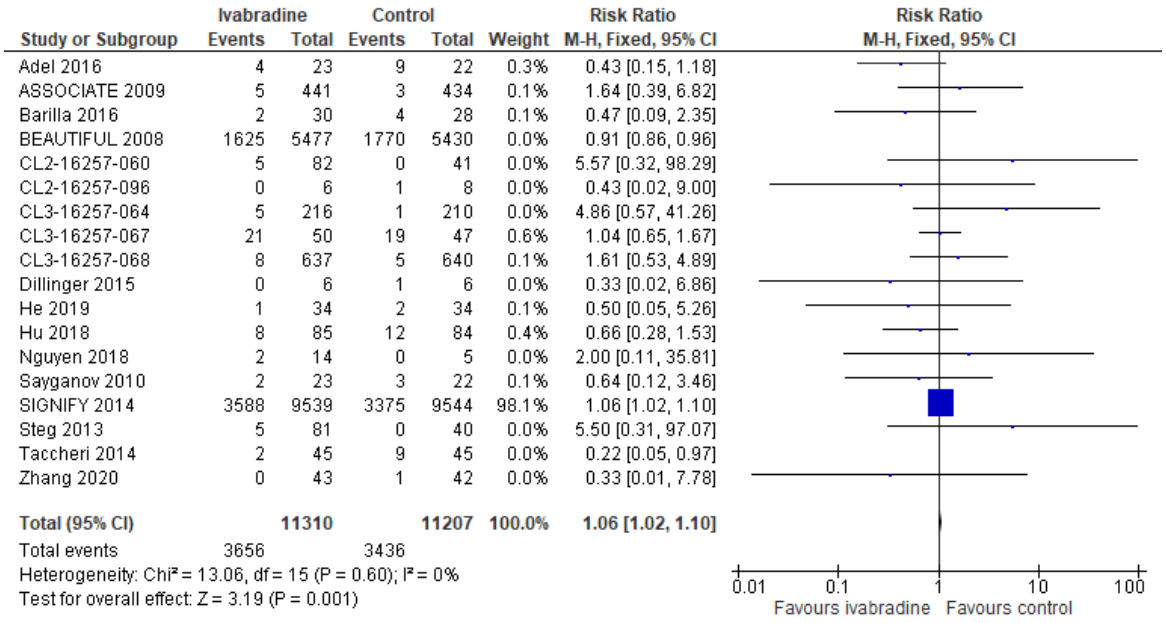

Figure 15 - Forest plot of the meta-analysis of serious adverse events using fixed-effect meta-analysis after excluding outliers. The meta-analysis showed evidence of a harmful effect of ivabradine

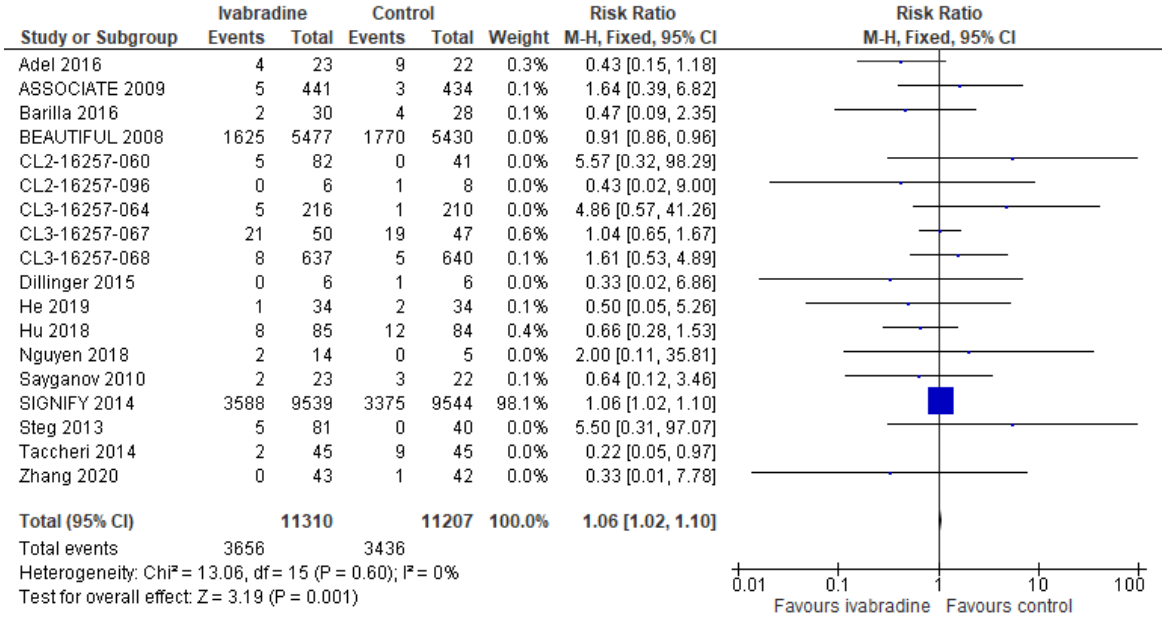

Figure 16 - Forest plot of the meta-analysis of serious adverse events using random-effects meta-analysis after excluding outliers. The meta-analysis showed evidence of a harmful effect of ivabradine

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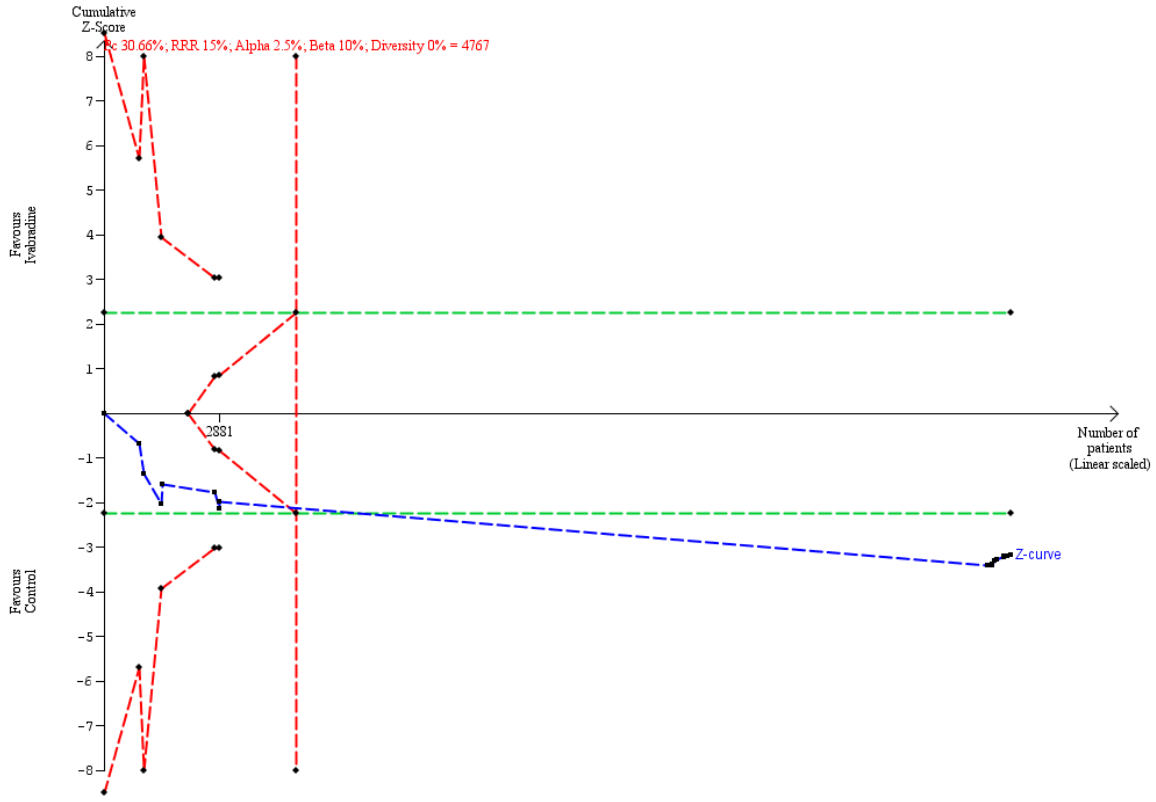


Figure 17 - Trial Sequential Analysis graph of serious adverse events after removing outliers. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine. The cumulative z-curve (the blue line) breaches the boundary of futility before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

Sensitivity analyses

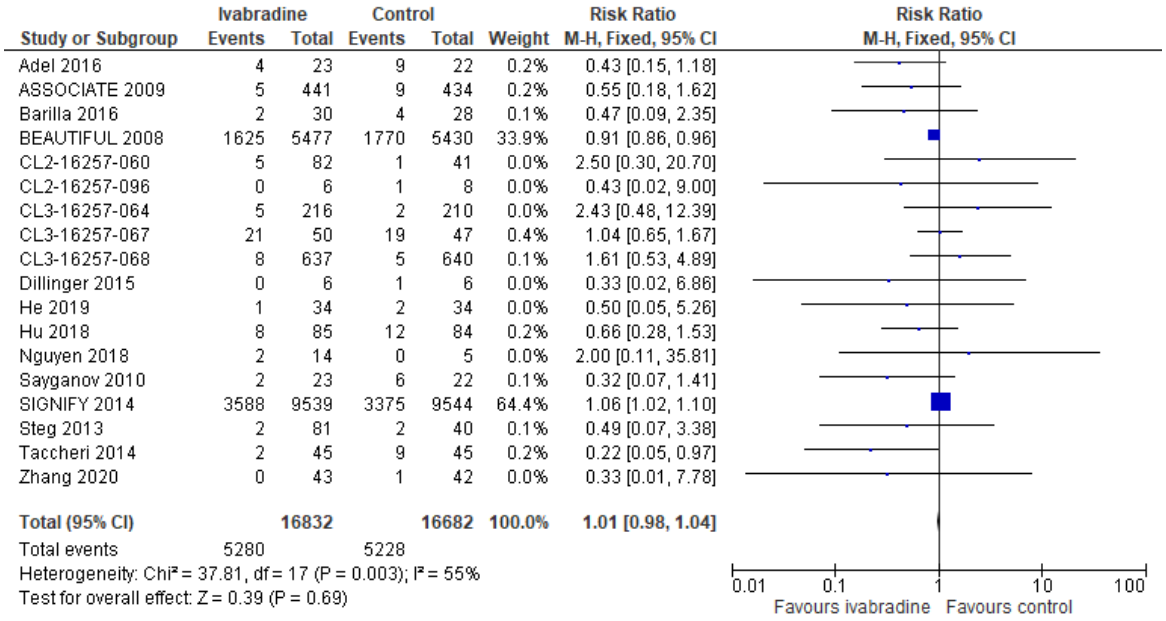


Figure 18 - Forest plot of the sensitivity analysis of serious adverse events using best/worst-case scenario. The sensitivity analysis showed that missing data did not seem to have the potential to influence the results.

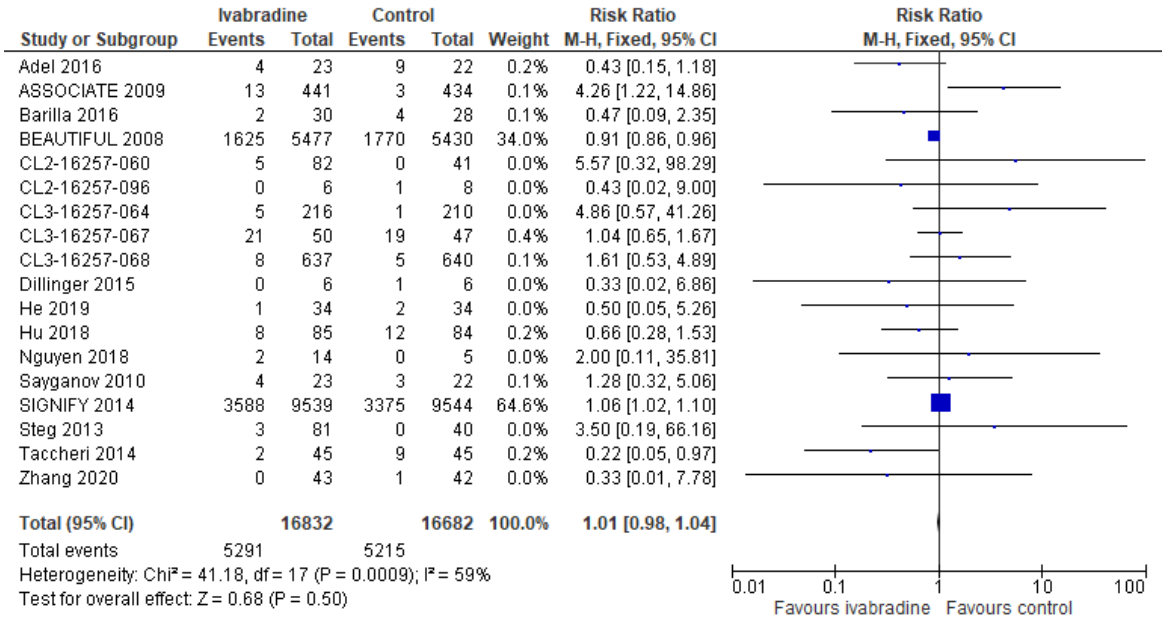


Figure 19 - Forest plot of the sensitivity analysis of serious adverse events using worst/best-case scenario. The sensitivity analysis showed that missing data did not seem to have the potential to influence the results.

Subgroup analyses

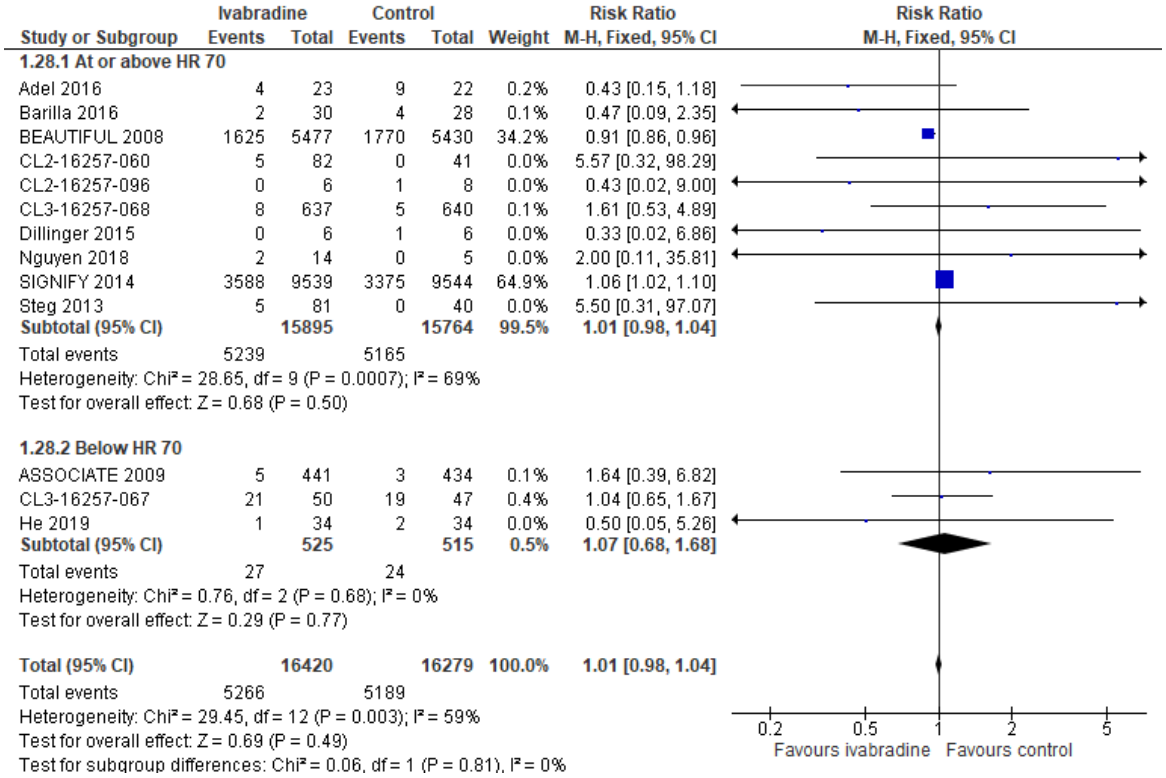


Figure 20 - Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute versus trials randomising participants with heart rate below 70 beats per minute. Test for subgroup differences showed that there was no difference between trials randomising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

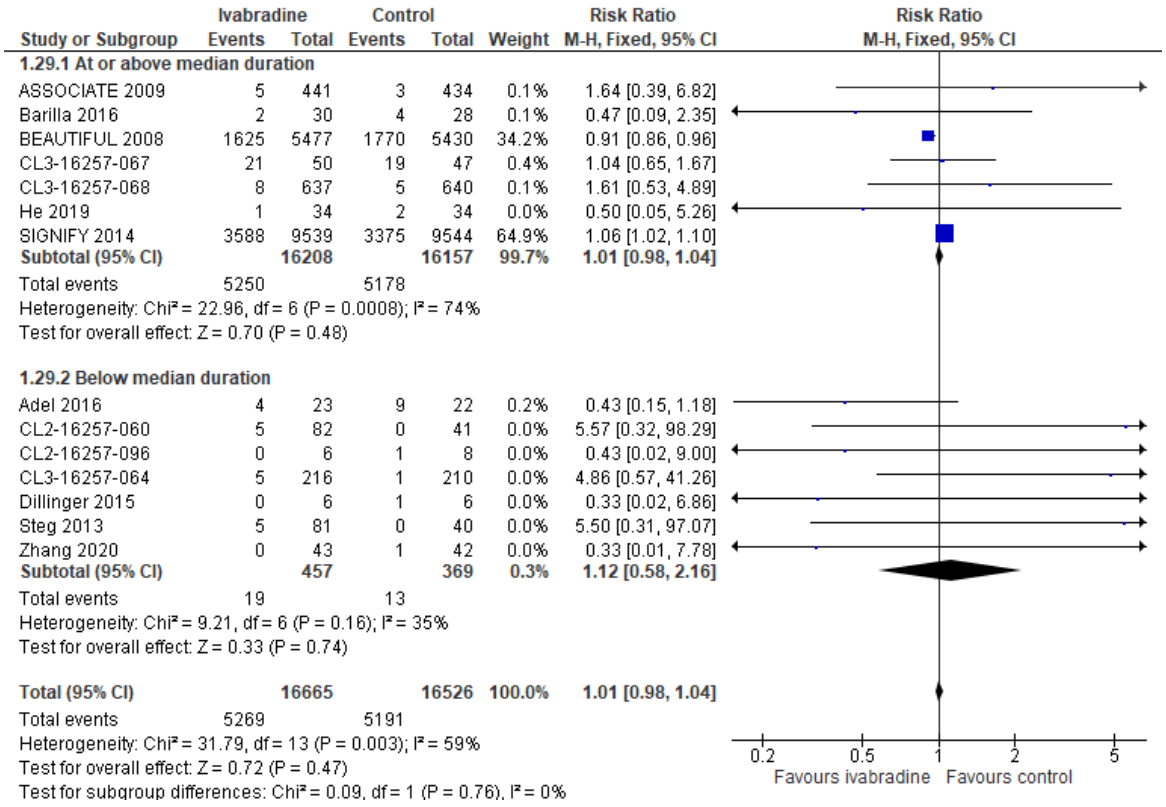


Figure 21 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration versus trials administering ivabradine below median duration. Test for subgroup differences showed that there was no difference between trials administering ivabradine at or above median duration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

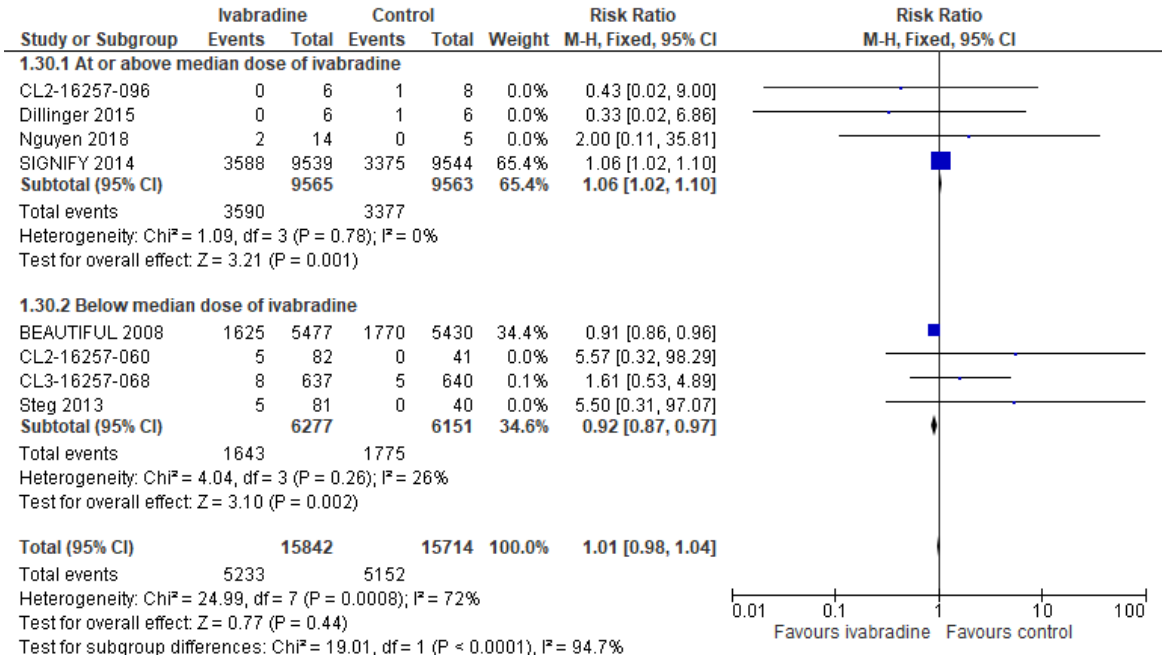


Figure 22 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose versus trials administering ivabradine below median daily dose. Test for subgroup differences showed evidence of between trials administering ivabradine at or above median daily dose versus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

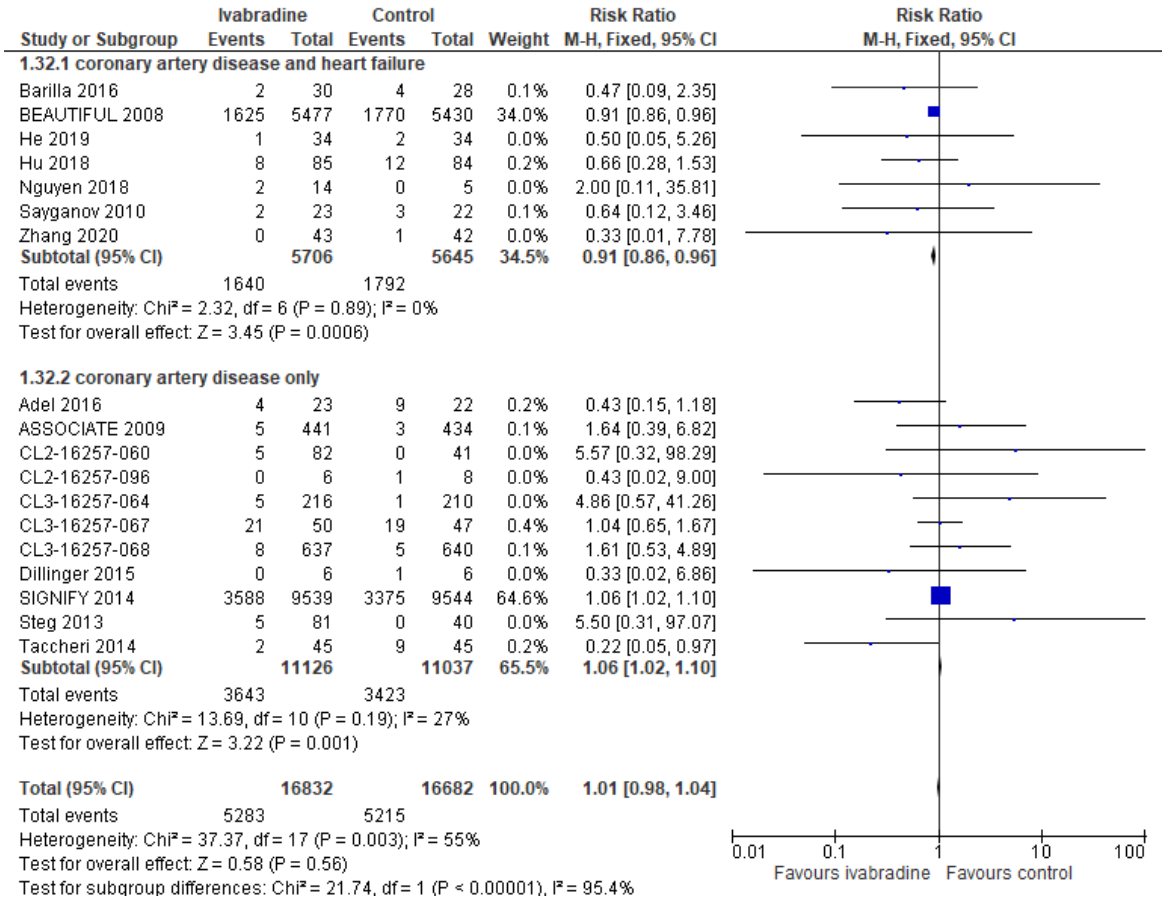


Figure 23 – Forest plot of the subgroup analyses of trials randomising participants with both coronary artery disease and heart failure versus trials randomising participants with coronary artery disease only. Test for subgroup differences showed evidence of a difference (p<0.00001) between trials randomising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

Supplement 7 - Quality of life

Main analyses

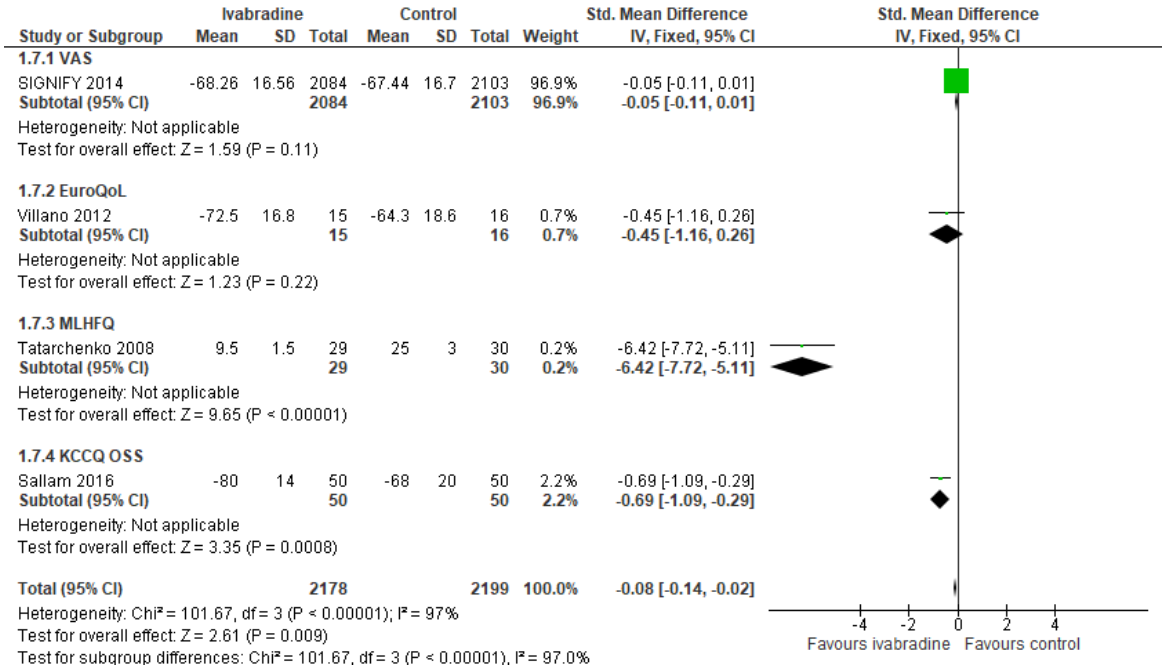


Figure 24 - Forest plot of the meta-analysis of quality of life using standardised mean differences in a fixed-effect meta-analysis. The meta-analysis showed no evidence of a beneficial effect of ivabradine.

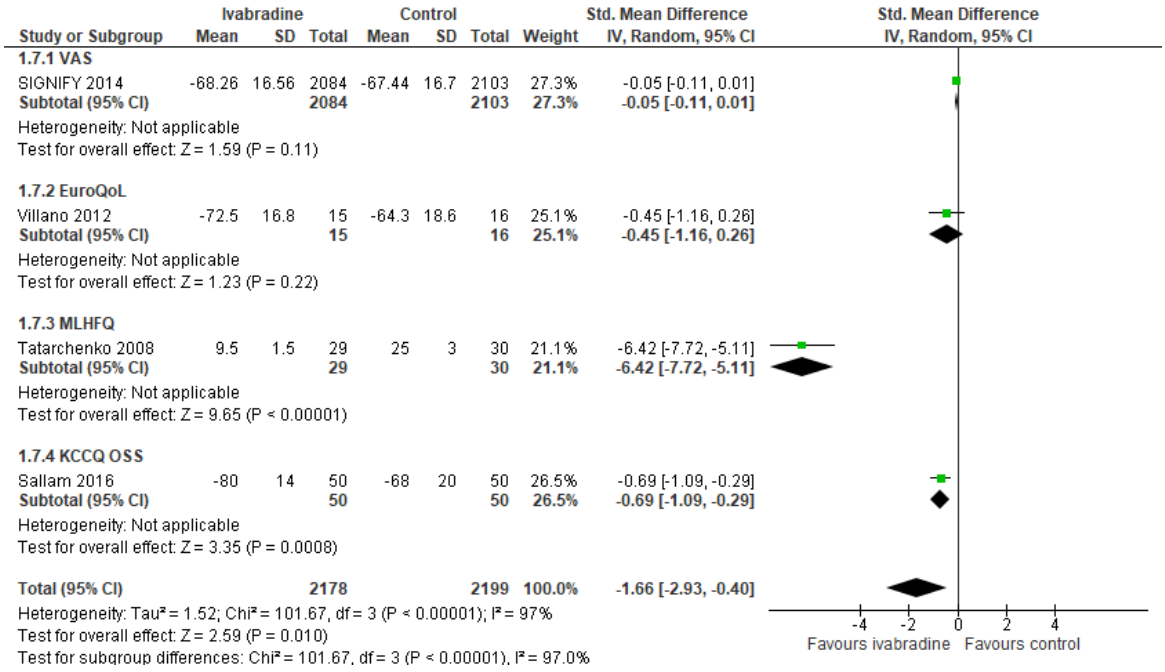


Figure 25 - Forest plot of the meta-analysis of quality of life using standardised mean differences in a random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine.

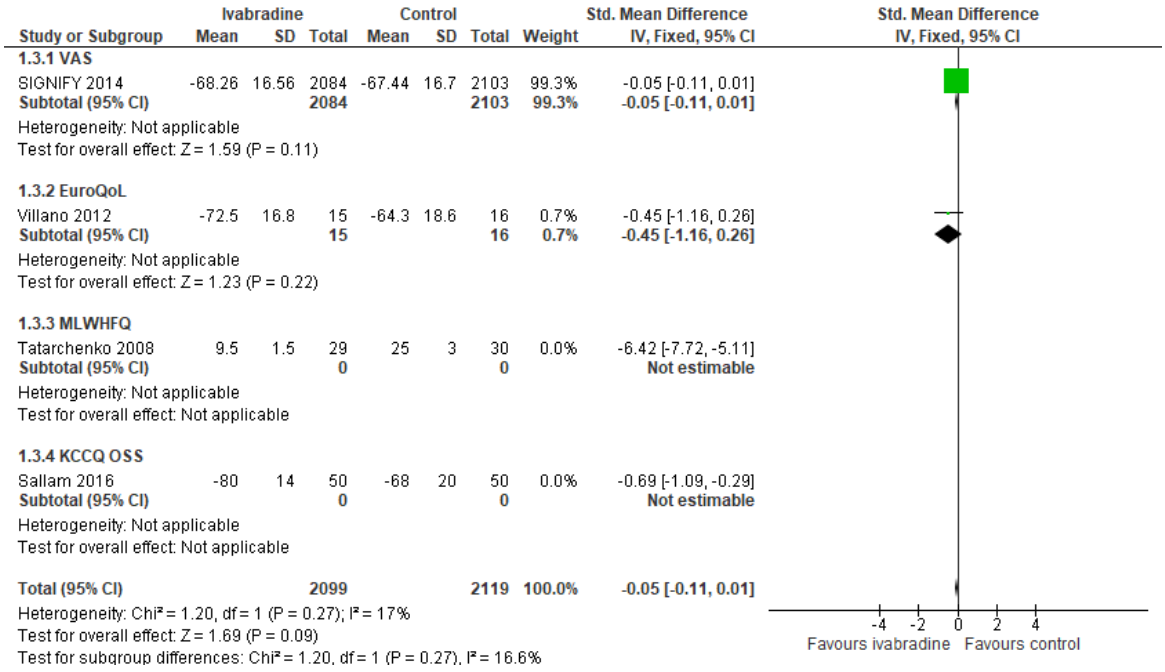


Figure 26 – Forest plot of the meta-analysis of quality of life using standardised mean differences in a fixed-effect meta-analysis after relieving heterogeneity. The meta-analysis showed no evidence of a difference between ivabradine and control.

Sensitivity analyses

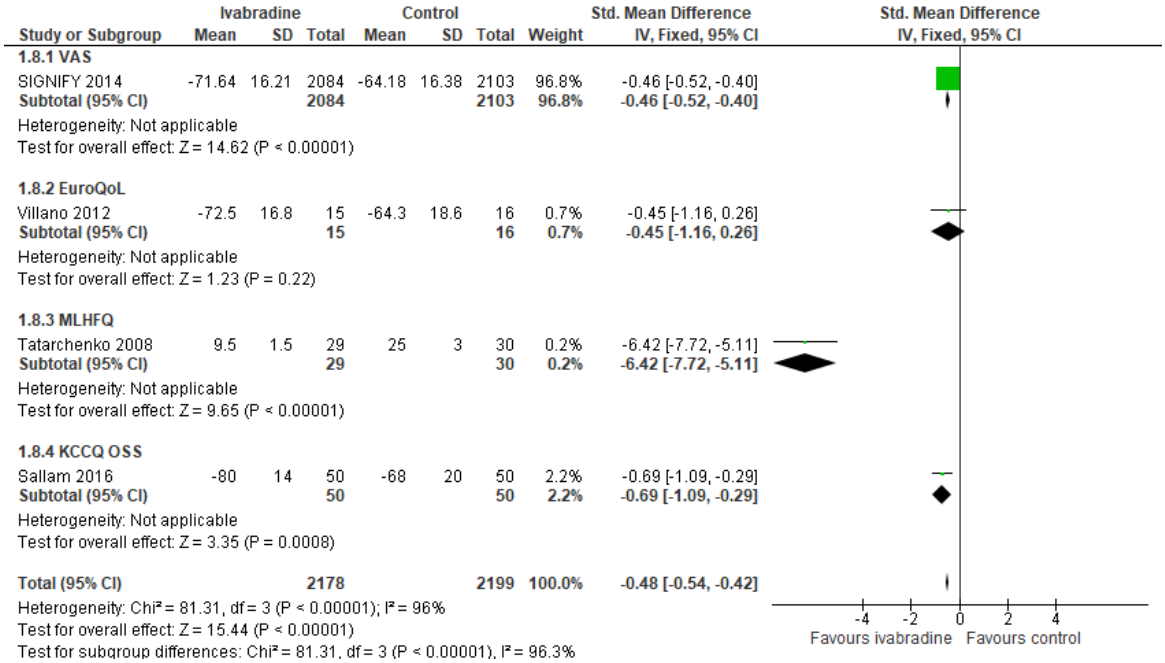


Figure 27 - Forest plot of the sensitivity analysis of quality of life using best/worst-case scenario. The sensitivity analysis showed that missing data did seem to have the potential to change the result.

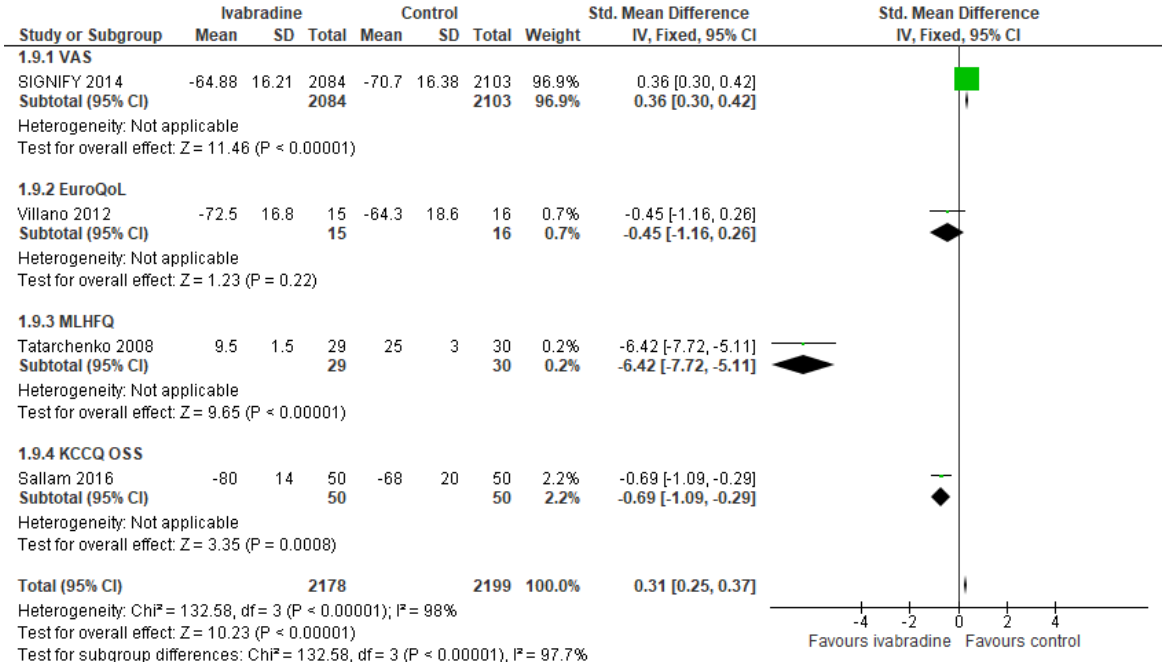


Figure 28 - Forest plot of the sensitivity analysis of quality of life using worst/best-case scenario. The sensitivity analysis showed that missing data did seem to have the potential to change the result.

Minimal important difference

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

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

Subgroup analyses

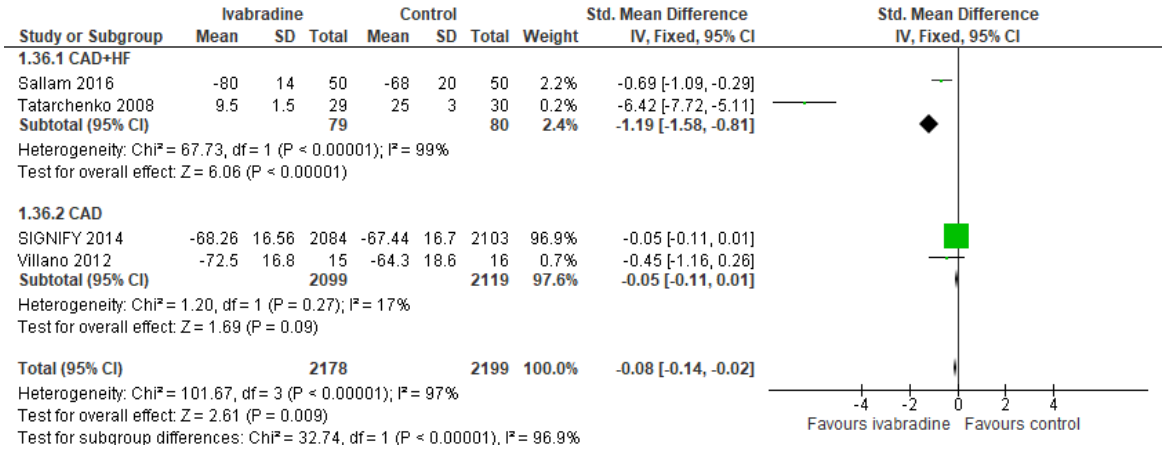


Figure 29 – Forest plot of the subgroup analyses of trials randomising participants with both coronary artery disease and heart failure versus trials randomising participants with coronary artery disease only. Test for subgroup differences showed evidence of a difference (p<0.00001) between trials randomising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

Supplement 8 - Cardiovascular mortality

Main analyses

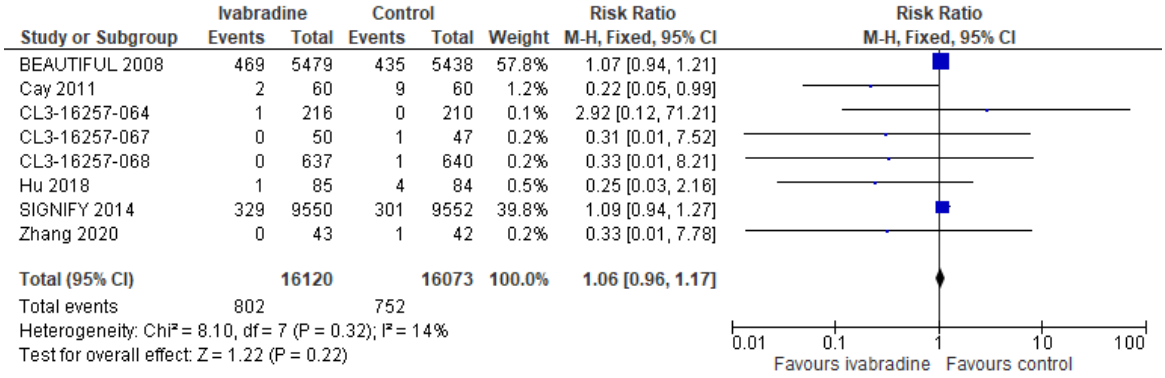


Figure 30 – Forest plot of the meta-analysis of cardiovascular mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

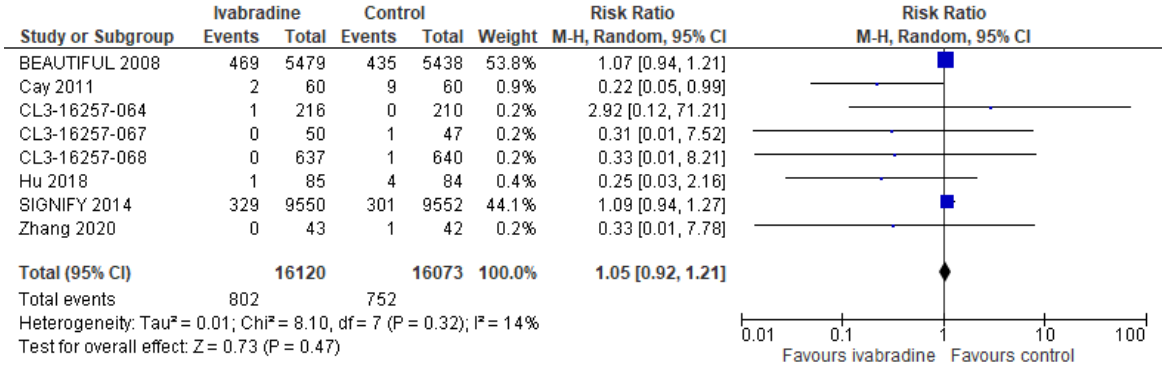


Figure 31 - Forest plot of the meta-analysis of cardiovascular mortality using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

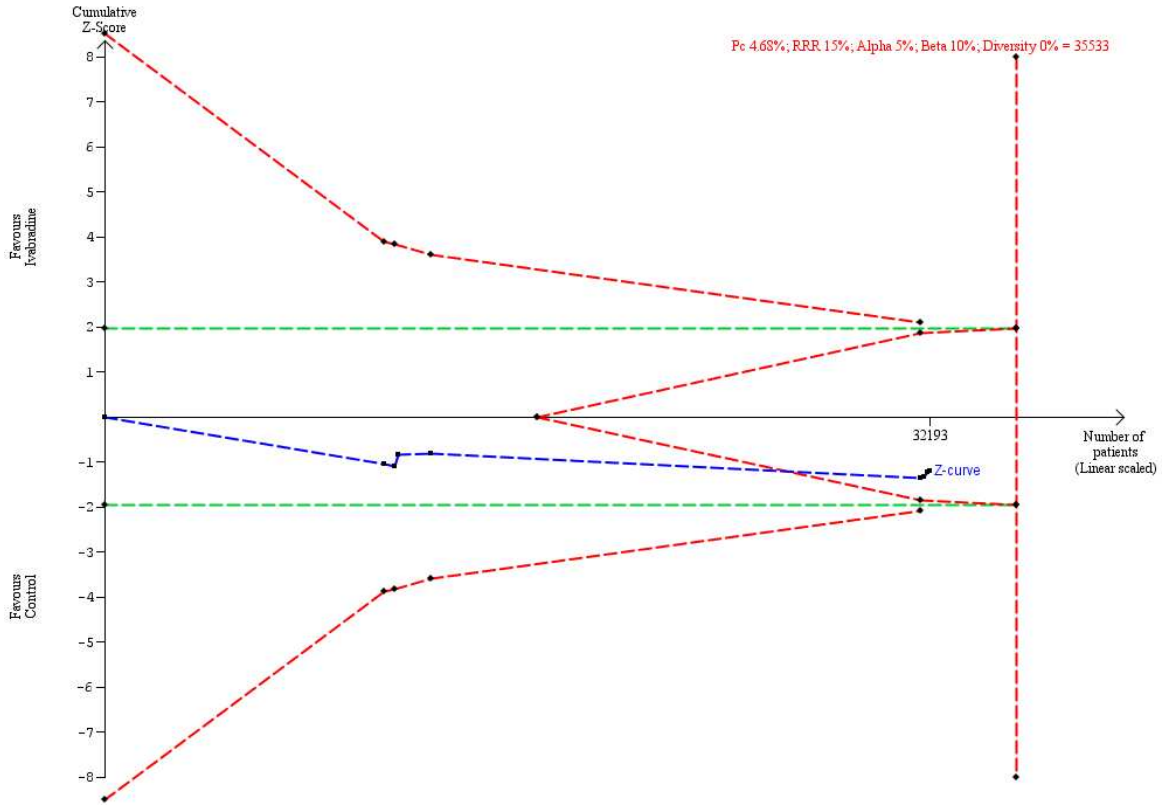
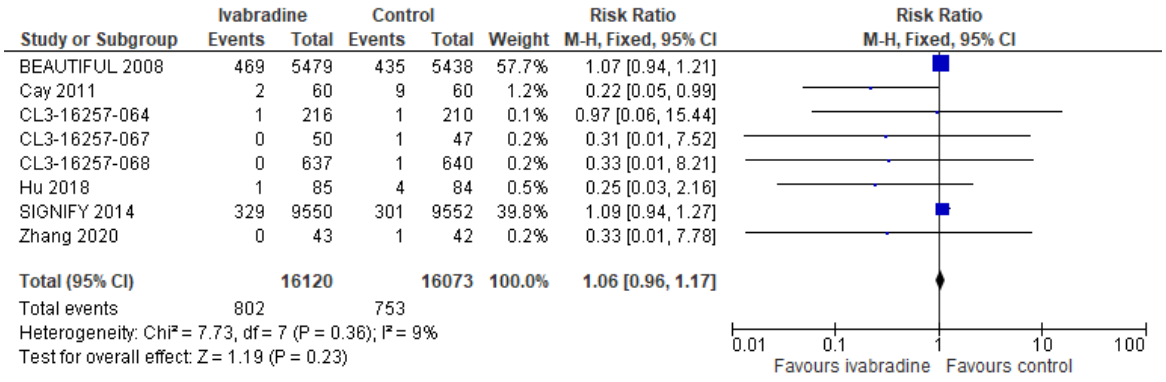


Figure 32 - Trial Sequential Analysis graph of cardiovascular mortality. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine. The cumulative z-curve (the blue line) breaches the boundary of futility. Pc: prevalence in control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

Sensitivity analyses



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

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

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

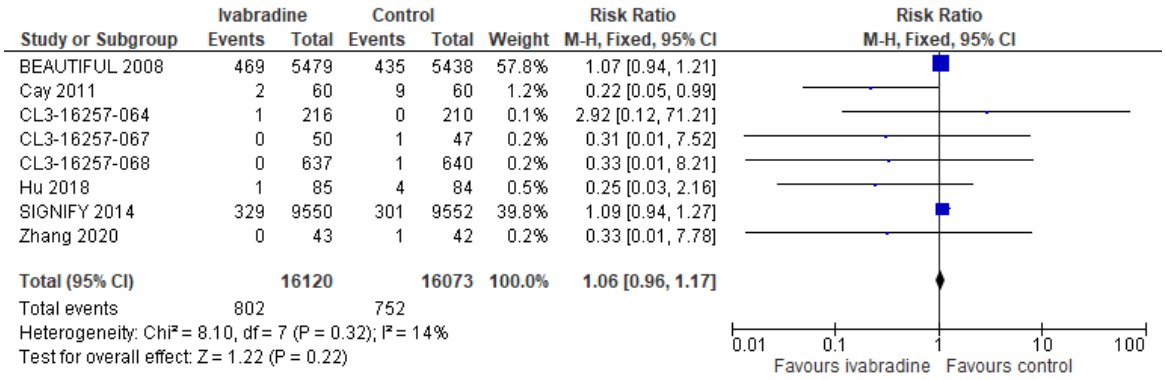


Figure 34 – Forest plot of the sensitivity analysis of cardiovascular mortality using worst/best-case scenario. The sensitivity analysis showed that missing data did not seem to have the potential to change the result.

Supplement 9 - Myocardial infarction

Main analyses

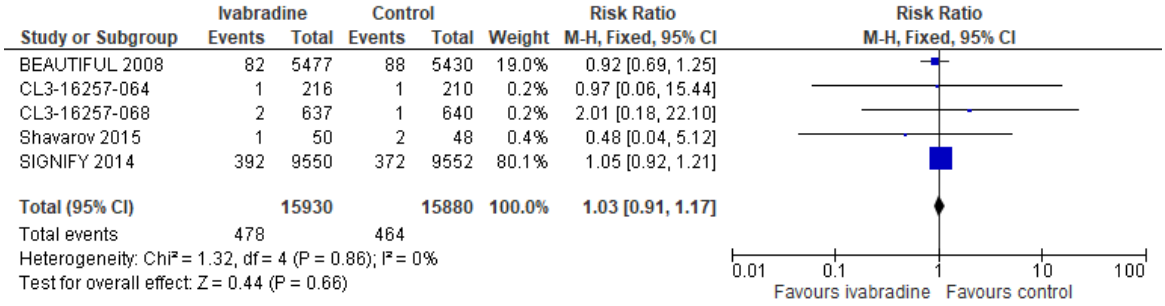


Figure 35 - Forest plot of the meta-analysis of myocardial infarction using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

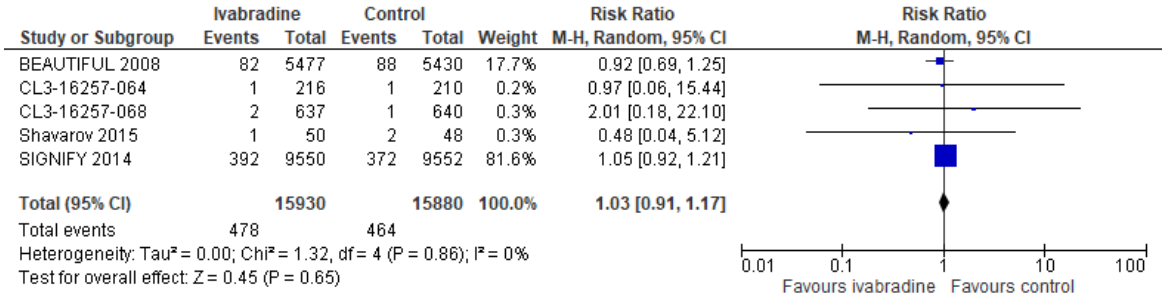


Figure 36 - Forest plot of the meta-analysis of myocardial infarction using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine and control.

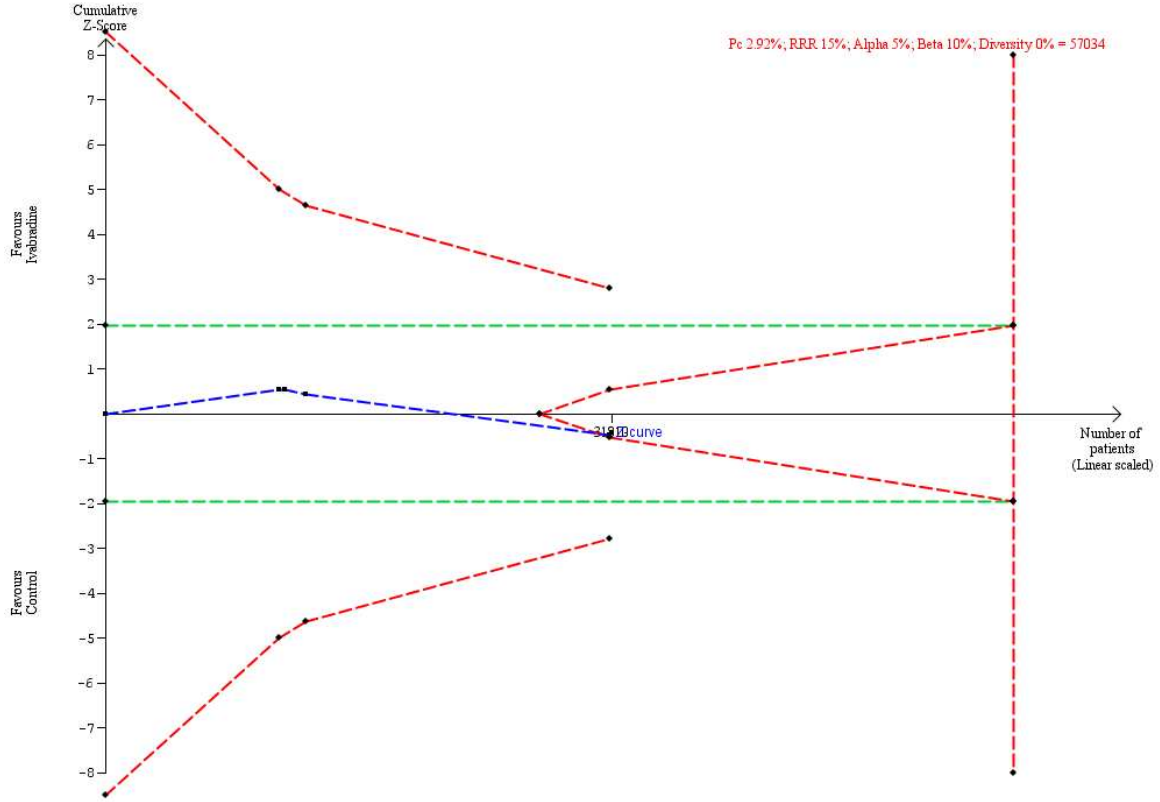


Figure 37 - Trial Sequential Analysis graph of myocardial infarction. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine. The cumulative z-curve (the blue line) breaches the boundary of futility. Pc: prevalence in control group;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

Sensitivity analyses

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

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

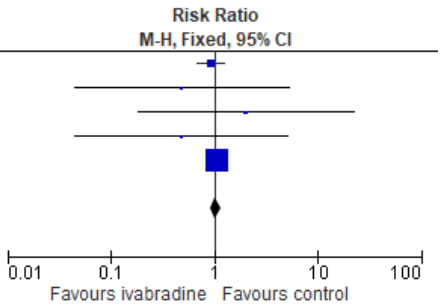


Figure 38 – Forest plot of the sensitivity analysis of myocardial infarction using a best/worst-case scenario. The meta-analysis showed that missing data did not seem to have the potential to influence the result.

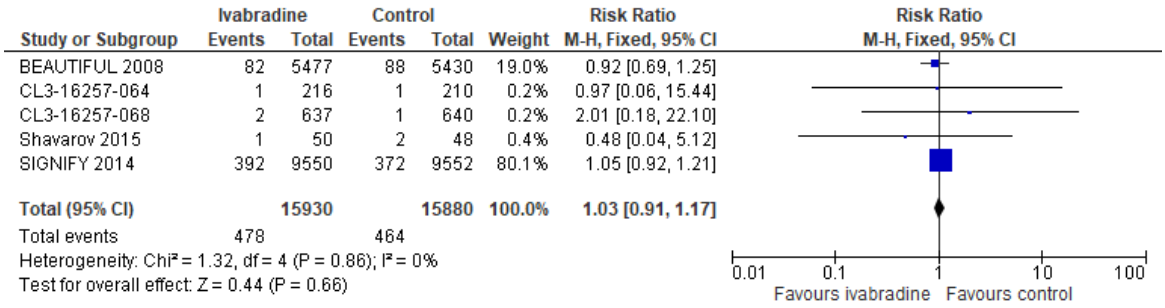


Figure 39 - Forest plot of the sensitivity analysis of myocardial infarction using a worst/best-case scenario. The meta-analysis showed that missing data did not seem to have the potential to influence the result.

Supplement 10 - Non-serious adverse events

Main analyses

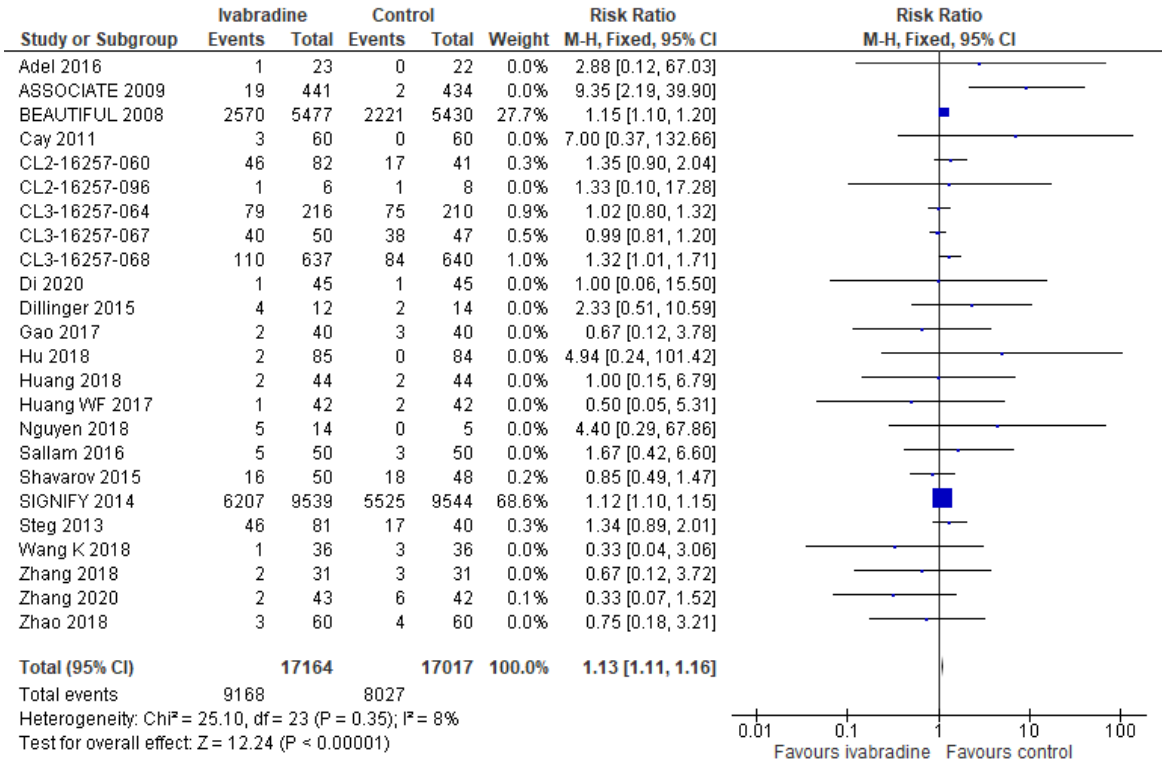


Figure 40 - Forest plot of the meta-analysis of non-serious adverse events using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to increase the risk of non-serious adverse events by 13%.

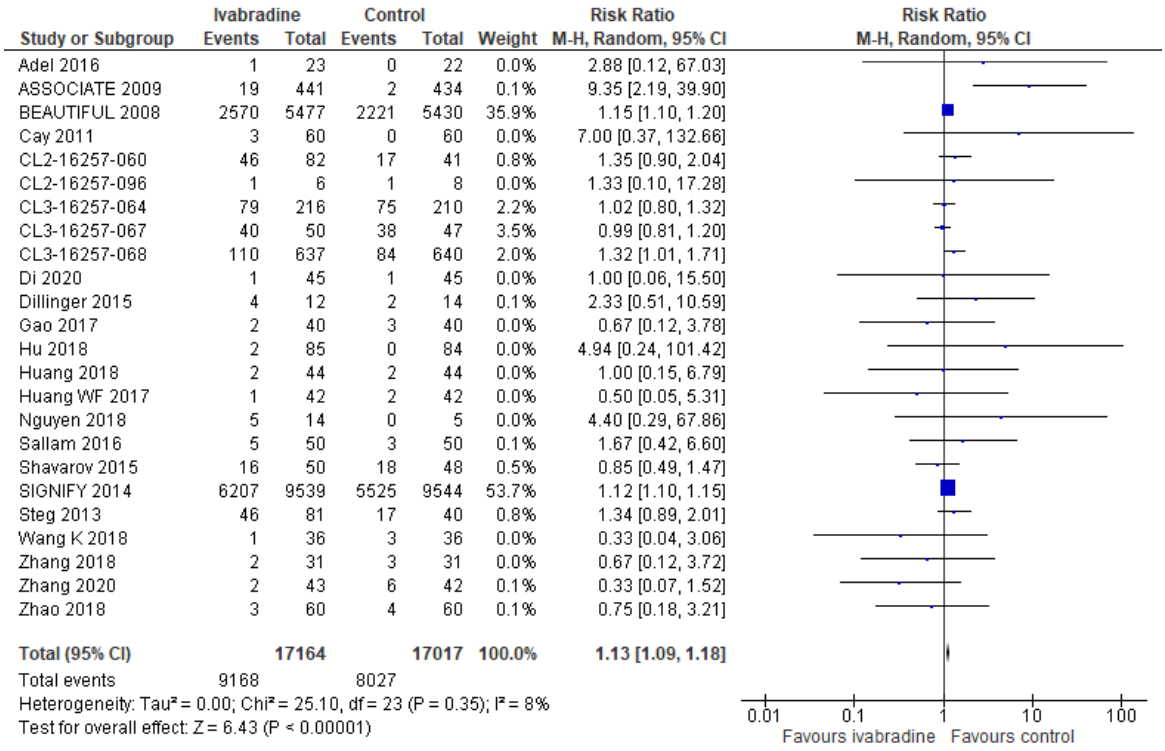


Figure 41 - Forest plot of the meta-analysis of non-serious adverse events using random-effects meta-analysis. The meta-analysis showed that ivabradine seemed to increase the risk of non-serious adverse events by 13%.

Sensitivity analyses

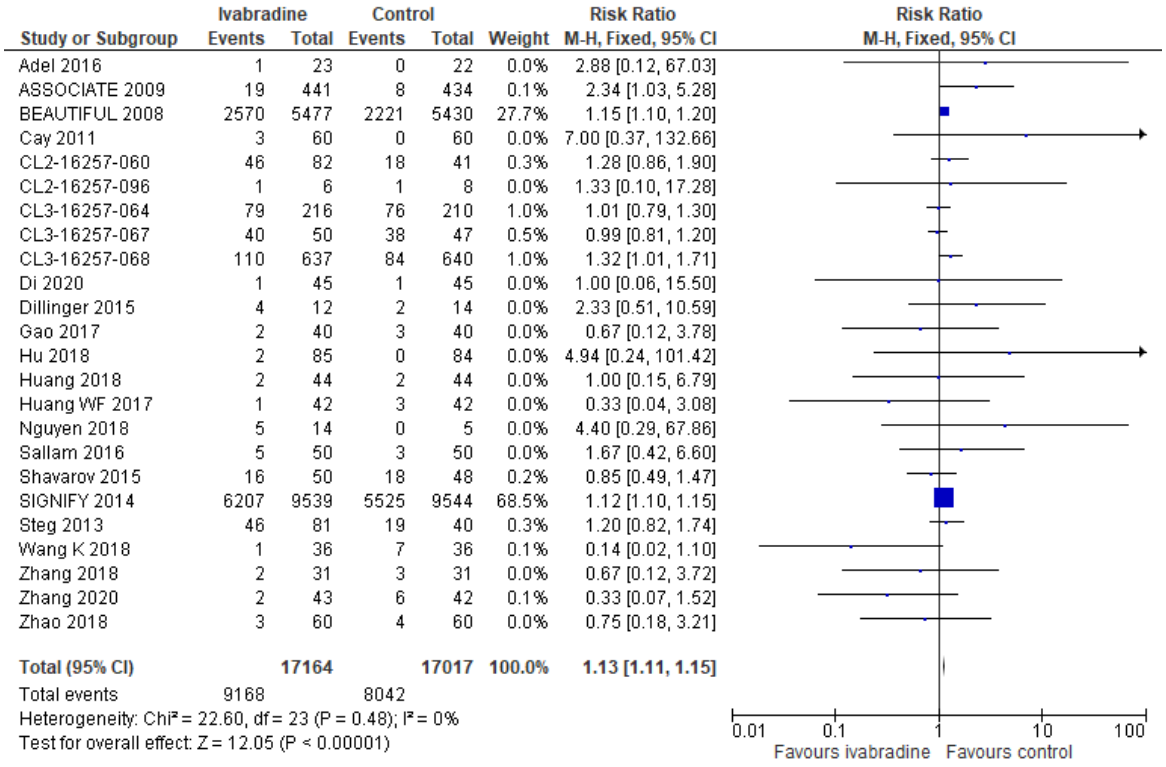


Figure 42 – Forest plot of the meta-analysis of non-serious adverse events using a best/worst-case scenario. The meta-analysis showed that missing data did not seem to have the potential to change the result.

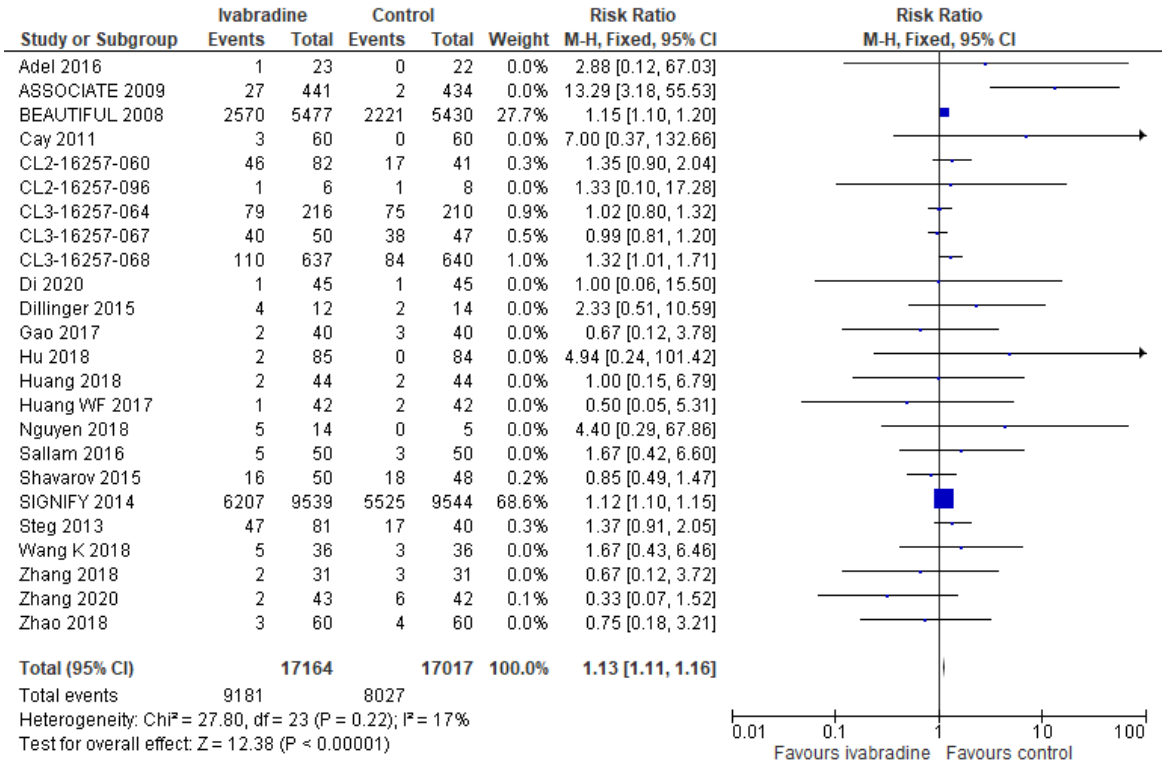


Figure 43 - Forest plot of the meta-analysis of non-serious adverse events using a worst/best-case scenario. The meta-analysis showed that missing data did not seem to have the potential to change the result.

Supplement 11 – Discrepancy in safety data

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

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

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

Supplement 12 – Exploratory outcomes

Resting heart rate at follow-up

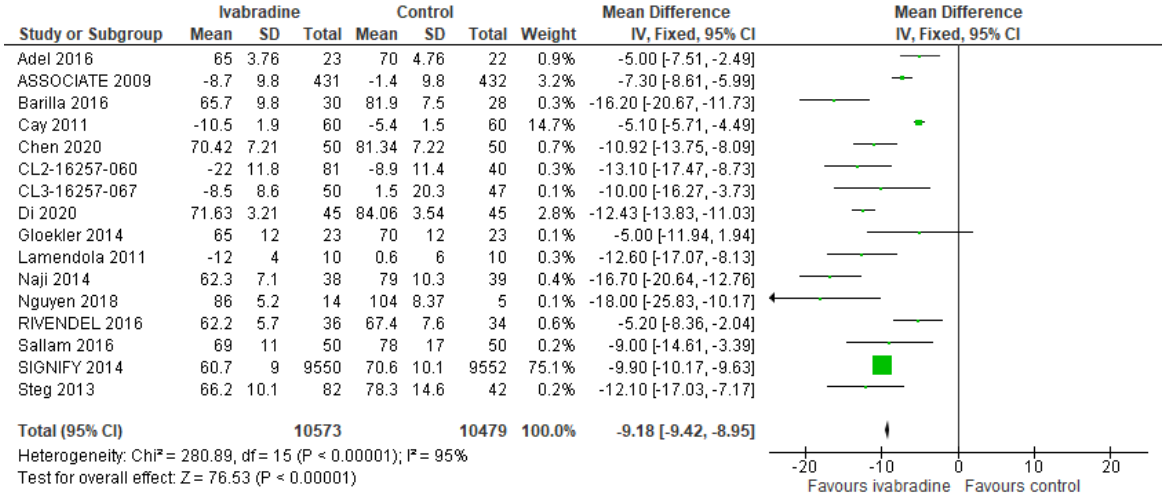


Figure 44 – Forest plot of the meta-analysis of resting heart rate at follow-up using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to decrease the resting heart rate at follow-up by 9·05 beats per minute.

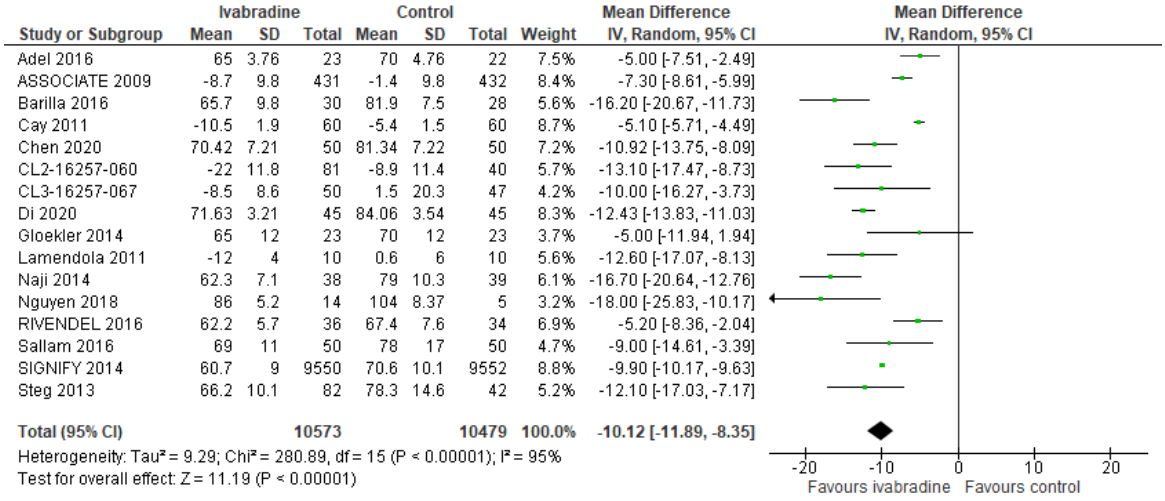


Figure 45 - Forest plot of the meta-analysis of resting heart rate at follow-up using random-effects meta-analysis. The meta-analysis showed that ivabradine seemed to decrease the resting heart rate at follow-up by 9·01 beats per minute.

Left ventricular ejection fraction

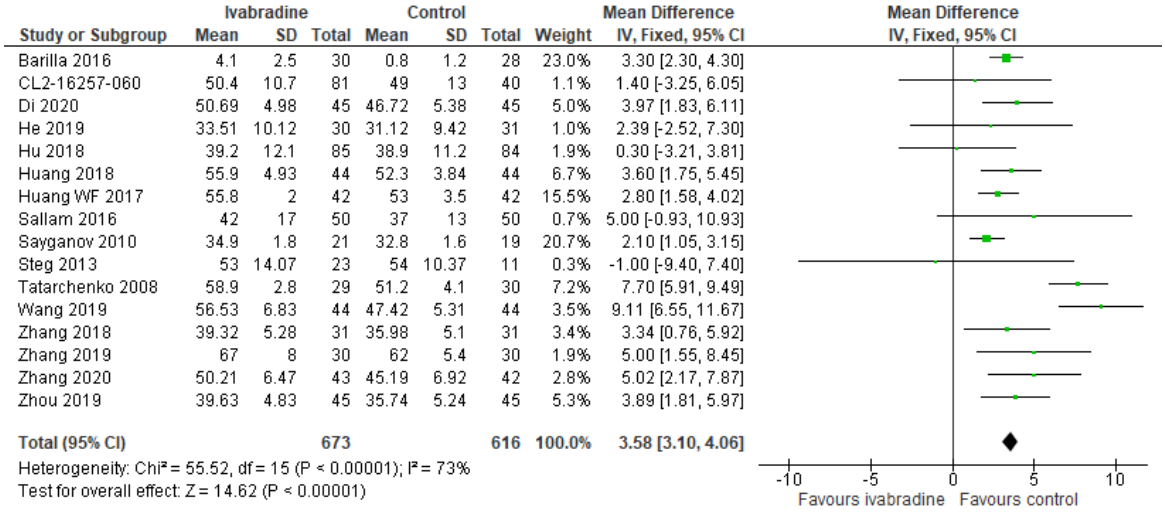


Figure 46 - Forest plot of the meta-analysis of left ventricular ejection fraction using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to increase the left ventricular ejection fraction by 2·59%.

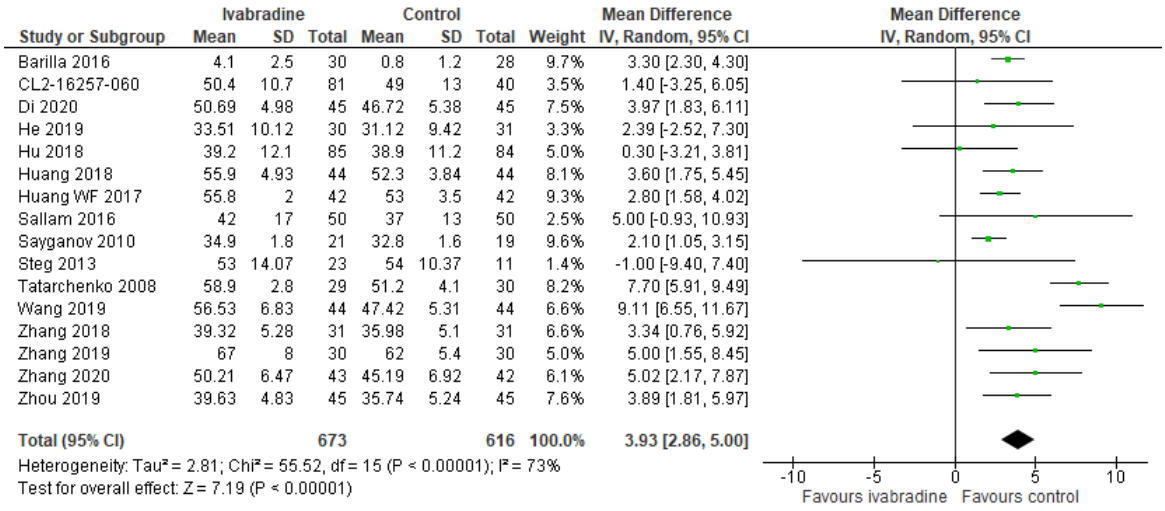


Figure 47 - Forest plot of the meta-analysis of left ventricular ejection fraction using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to increase the left ventricular ejection fraction by 2·59%.

Angina pectoris
Angina frequency

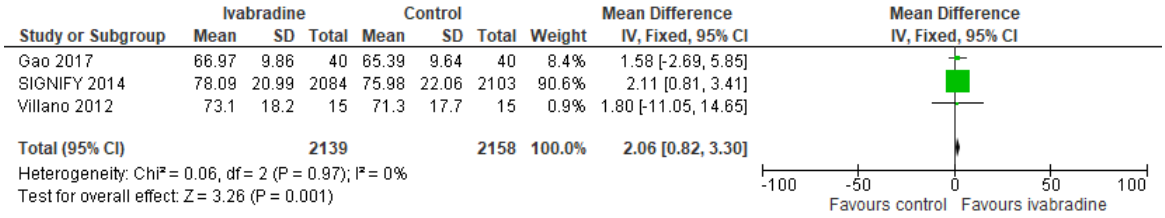


Figure 48 – Forest plot of the meta-analysis of angina frequency using fixed-effect meta-analysis. The meta-analysis shows that ivabradine seems to increase angina frequency (a positive outcome) by 2·06 points.

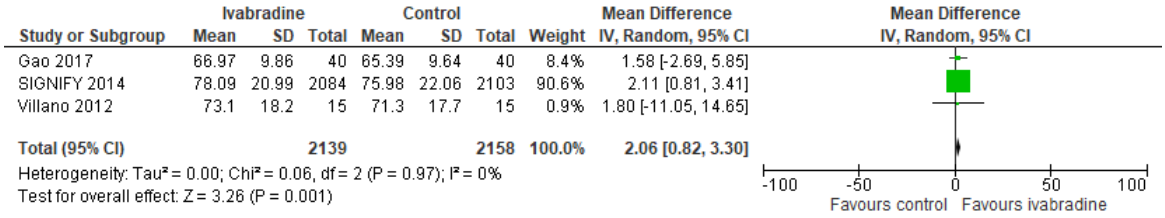


Figure 49 - Forest plot of the meta-analysis of angina frequency using random-effects meta-analysis. The meta-analysis shows that ivabradine seems to increase angina frequency (a positive outcome) by 2·06 points.

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

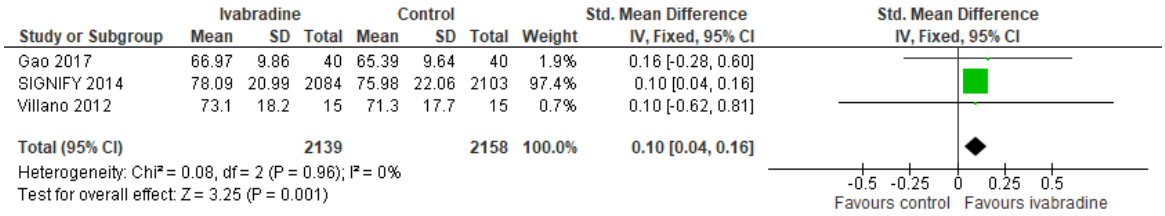


Figure 50 – Forest plot of the meta-analysis of angina frequency using standardised mean differences. The meta-analysis showed evidence of a beneficial effect of ivabradine.

Angina stability

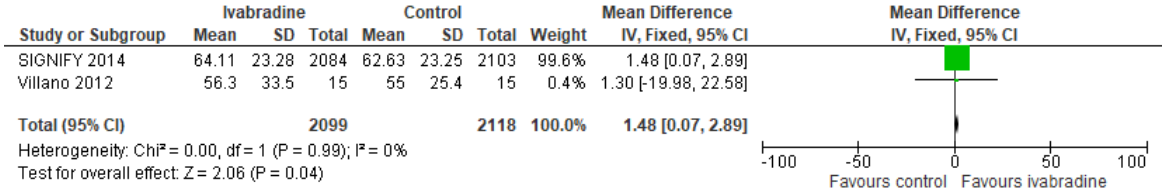


Figure 51 - Forest plot of the meta-analysis of angina frequency using fixed-effect meta-analysis. The meta-analysis shows that ivabradine seems to increase angina stability by 1·48 points.

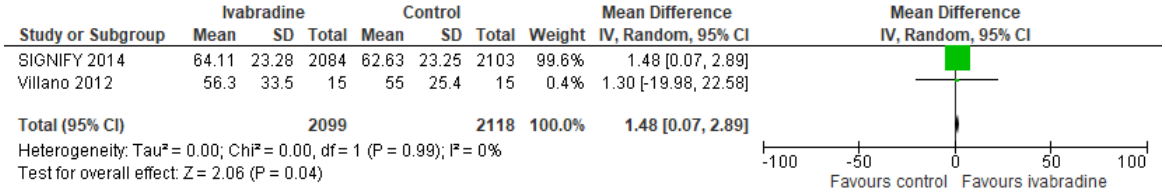


Figure 52 - Forest plot of the meta-analysis of angina frequency using random-effects meta-analysis. The meta-analysis shows that ivabradine seems to increase angina stability by 1·48 points.

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

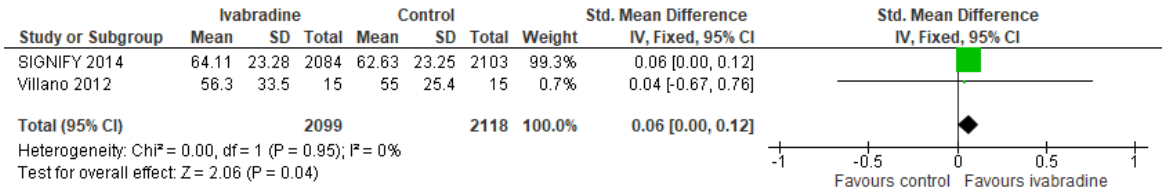


Figure 53 – Forest plot of the meta-analysis of angina stability using standardised mean differences. The meta-analysis showed evidence of a beneficial effect of ivabradine.

Exercise tolerance test

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

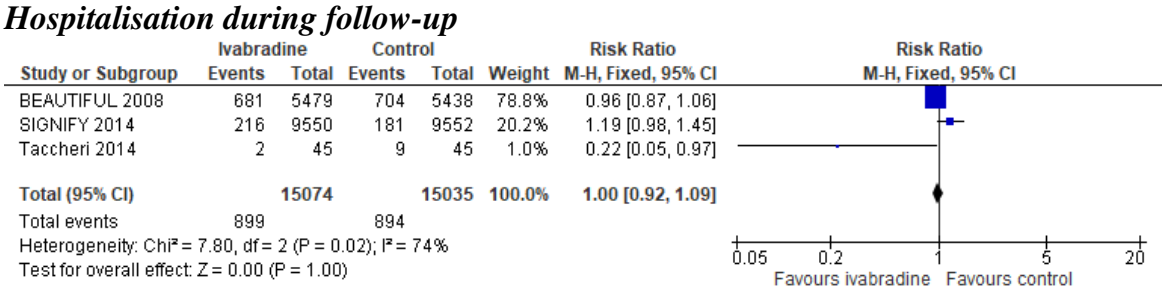


Figure 54 – Forest plot of the meta-analysis of hospitalisation during follow-up using fixed-effect meta-analysis. The meta-analysis shows no evidence of a difference between ivabradine and control.

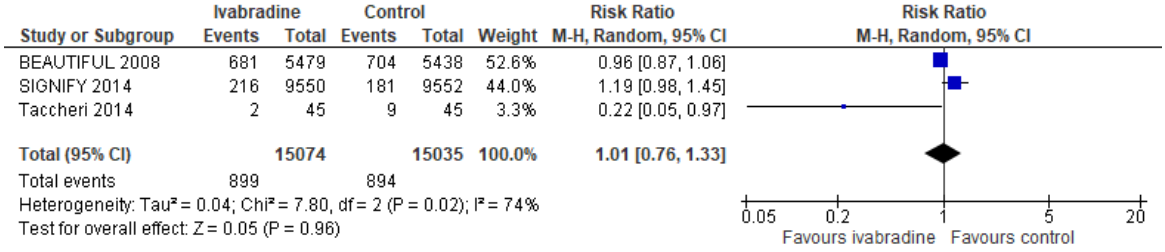


Figure 55 - Forest plot of the meta-analysis of hospitalisation during follow-up using random-effects meta-analysis. The meta-analysis shows no evidence of a difference between ivabradine and control.

Supplement 13 – 'Summary of findings'-table

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

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

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

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