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

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Supplement 1 – List of databases

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

Supplement 2 – Search strategy

MEDLINE 31/05/2021, n = 422

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

EMBASE 31/05/2021, n = 1401

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

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

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

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

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

LILACS 31/05/2021, n = 25

- 1. Ivabradine
- 2. Ivabradina
- 3. 1 or 2

CENTRAL 31/05/2021, n = 638

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

EudraCT 31/05/2021, n = 46

1. ivabradine OR corlanor OR procoralan OR corlentor

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

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

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

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

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

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

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

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

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

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

Chinese Science Journal Database (VIP), n = 165

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

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

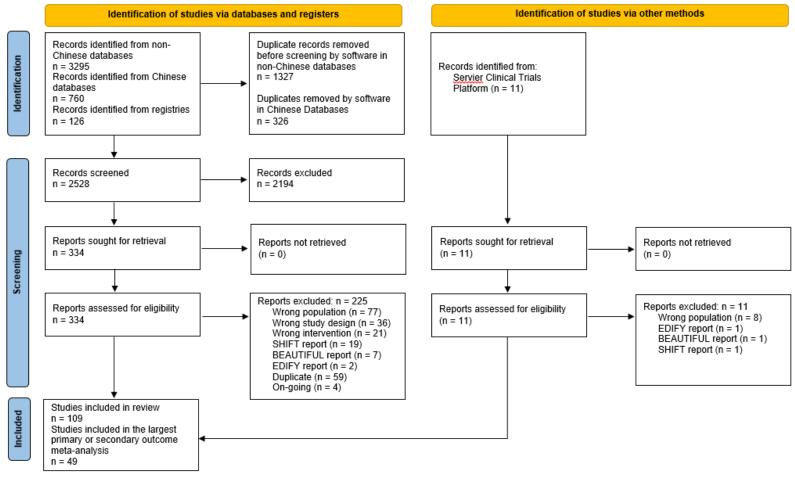
China National Knowledge Infrastructure (CNKI), n = 255

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

Wanfang, n = 200

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

Supplement 3 – PRISMA flow chart



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

Figure 1 – PRISMA flowchart.

Supplement 4 - Risk of bias

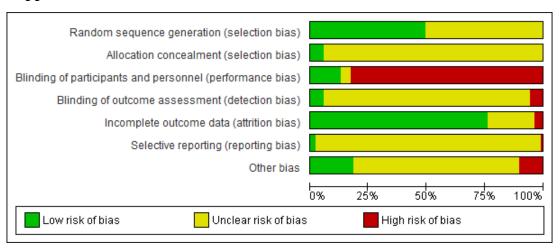


Figure 2 - Risk of bias graph.



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

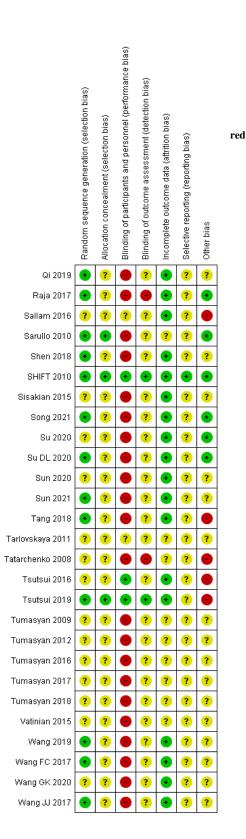




Figure 3 – Risk of bias summary. Green circles = low risk of bias; yellow circles = unclear risk of bias; circles = high risk of bias.

Supplement 5 - All-cause mortality *Main analyses*

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

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

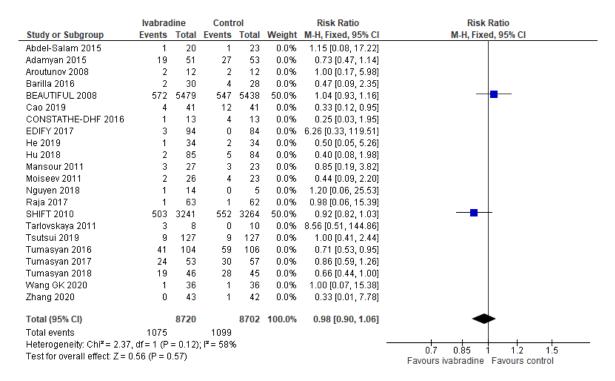


Figure 5 – Forest plot of the meta-analysis of all-cause mortality using fixed-effect meta-analysis including only trials at low risk of bias, except for for-profit bias. The meta-analysis showed no evidence of a difference between ivabradine versus placebo.

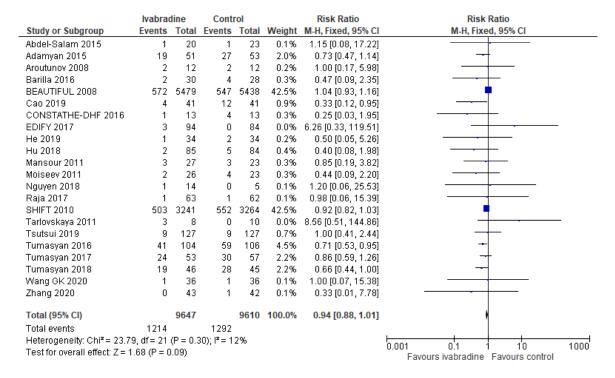


Figure 6 - Forest plot of the meta-analysis of all-cause mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

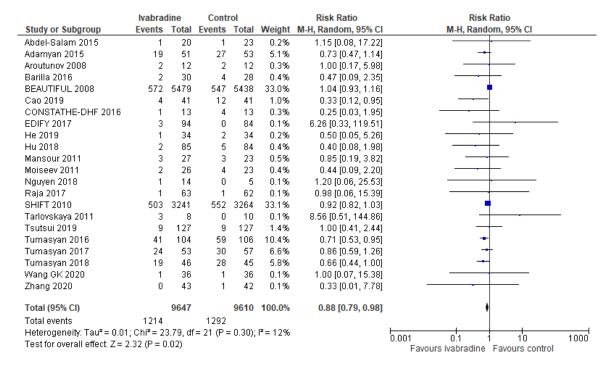


Figure 7 - Forest plot of the meta-analysis of all-cause mortality using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

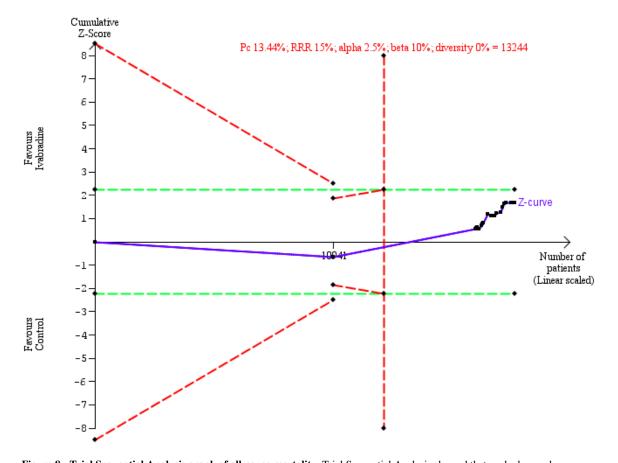
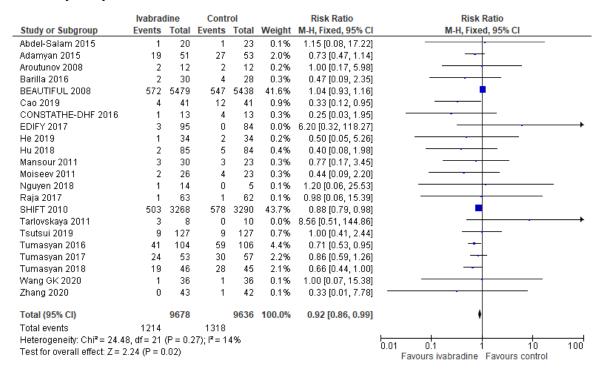


Figure 8 - Trial Sequential Analysis graph of all-cause mortality. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) breaches the boundary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

Sensitivity analyses



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

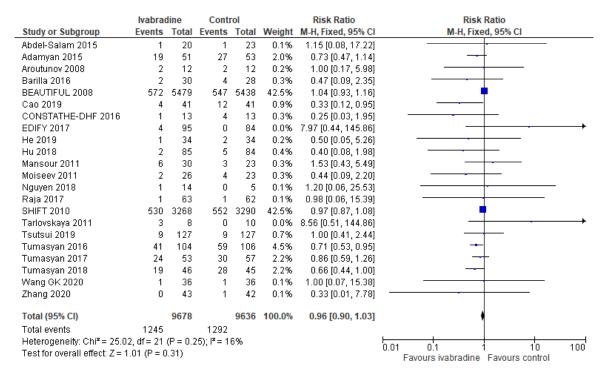
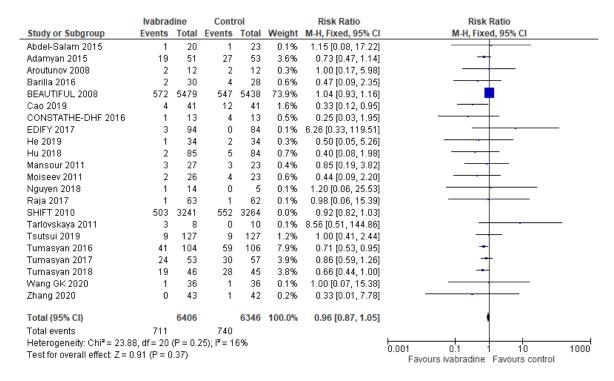


Figure 10 - Forest plot of the sensitivity analysis of all-cause mortality using worst- compared with best-case scenario.

	lvabrad	line	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Abdel-Salam 2015	1	20	1	23	0.1%	1.15 [0.08, 17.22]	
Adamyan 2015	19	51	27	53	3.6%	0.73 [0.47, 1.14]	
Aroutunov 2008	2	12	2	12	0.3%	1.00 [0.17, 5.98]	
Barilla 2016	2	30	4	28	0.6%	0.47 [0.09, 2.35]	
BEAUTIFUL 2008	572	5479	547	5438	0.0%	1.04 [0.93, 1.16]	
Cao 2019	4	41	12	41	1.6%	0.33 [0.12, 0.95]	
CONSTATHE-DHF 2016	1	13	4	13	0.5%	0.25 [0.03, 1.95]	
EDIFY 2017	3	94	0	84	0.1%	6.26 [0.33, 119.51]	
He 2019	1	34	2	34	0.3%	0.50 [0.05, 5.26]	
Hu 2018	2	85	5	84	0.7%	0.40 [0.08, 1.98]	
Mansour 2011	3	27	3	23	0.4%	0.85 [0.19, 3.82]	
Moiseev 2011	2	26	4	23	0.6%	0.44 [0.09, 2.20]	
Nguyen 2018	1	14	0	5	0.1%	1.20 [0.06, 25.53]	
Raja 2017	1	63	1	62	0.1%	0.98 [0.06, 15.39]	
SHIFT 2010	503	3241	552	3264	73.9%	0.92 [0.82, 1.03]	
Tarlovskaya 2011	3	8	0	10	0.1%	8.56 [0.51, 144.86]	
Tsutsui 2019	9	127	9	127	1.2%	1.00 [0.41, 2.44]	
Tumasyan 2016	41	104	59	106	7.9%	0.71 [0.53, 0.95]	-
Tumasyan 2017	24	53	30	57	3.9%	0.86 [0.59, 1.26]	
Tumasyan 2018	19	46	28	45	3.8%	0.66 [0.44, 1.00]	
Wang GK 2020	1	36	1	36	0.1%	1.00 [0.07, 15.38]	
Zhang 2020	0	43	1	42	0.2%	0.33 [0.01, 7.78]	
Total (95% CI)		4168		4172	100.0%	0.87 [0.79, 0.95]	•
Total events	642		745				
Heterogeneity: Chi² = 16.83	7, df = 20	(P = 0.6)	66); I ^z = 0	%			0.001 0.1 1 10 1000
Test for overall effect: Z = 2	.95 (P = 0	.003)					Favours ivabradine Favours control

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



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

Subgroup analyses

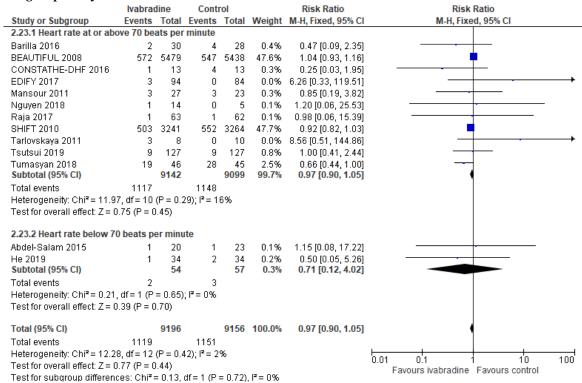


Figure 13 – Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared to trials randomising participants with heart rate below 70 beats per minute on all-cause mortality.

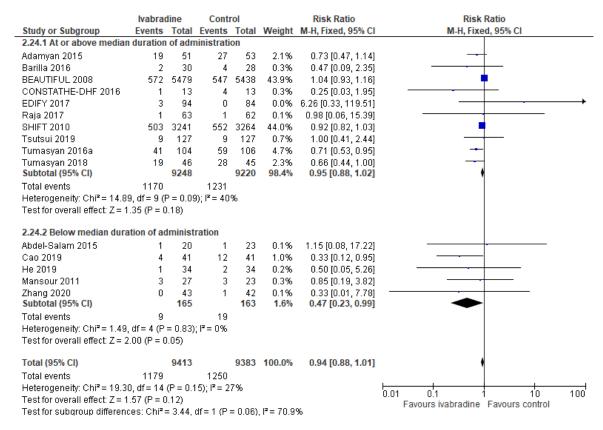


Figure 14 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (182.64 days) versus trials administering ivabradine below median duration on all-cause mortality.

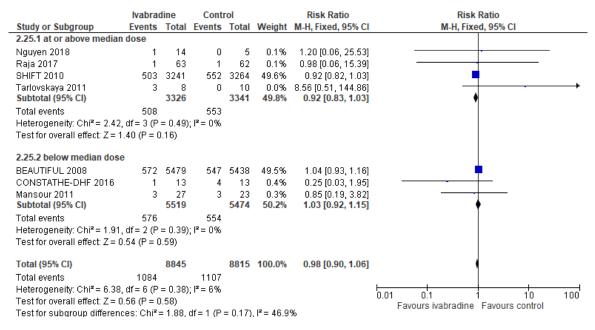


Figure 15 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose (12.7 mg) compared to trials administering ivabradine below median daily dose on all-cause mortality.

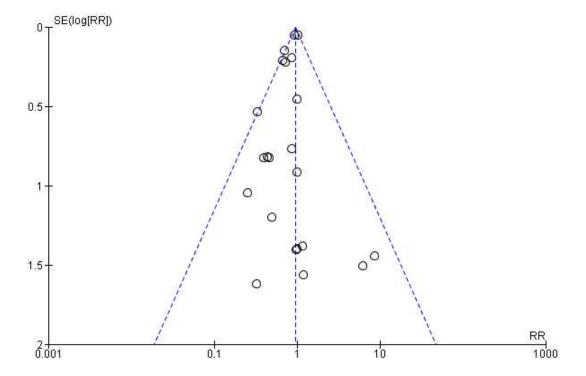


Figure 16 - Funnel plot of the analyses of all-cause mortality. The funnel plot did not indicate small study bias.

Supplement 6 - Serious adverse events *Main analyses*

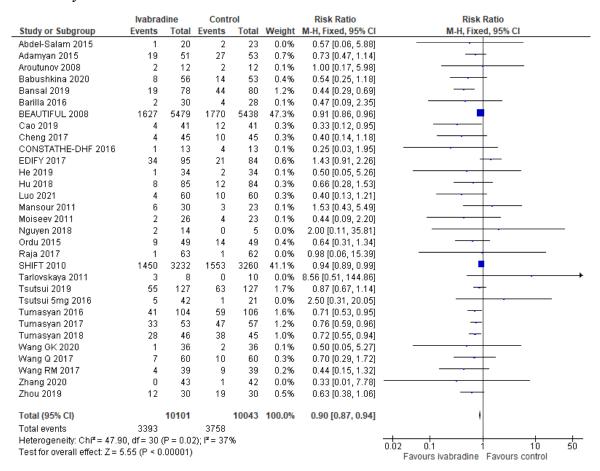


Figure 17 - Forest plot of the meta-analysis of serious adverse events using fixed-effect meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

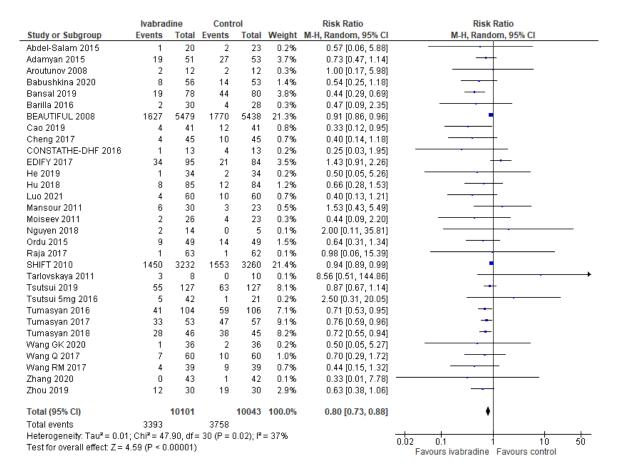


Figure 18 – Forest plot of the meta-analysis of serious adverse events using random-effects meta-analysis. The meta-analysis showed evidence of a beneficial effect of ivabradine versus control (placebo or no intervention).

Sensitivity analyses

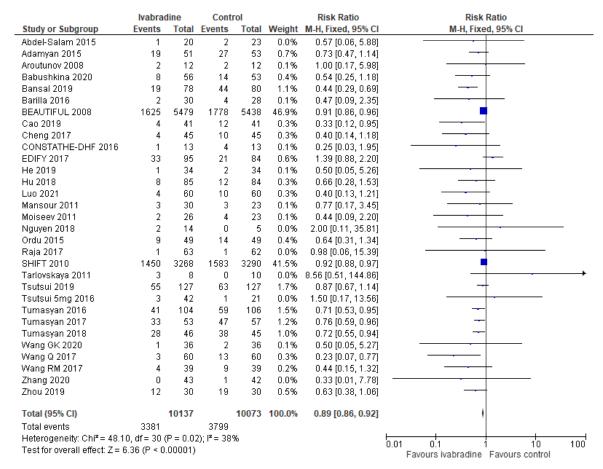


Figure 19 - Forest plot of the sensitivity analysis of serious adverse events using best- compared with worst-case scenario.

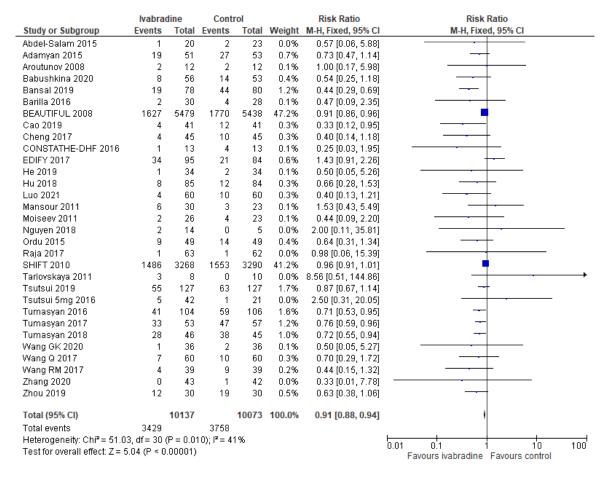


Figure 20 - Forest plot of the sensitivity analysis of serious adverse events using worst- compared with best-case scenario.

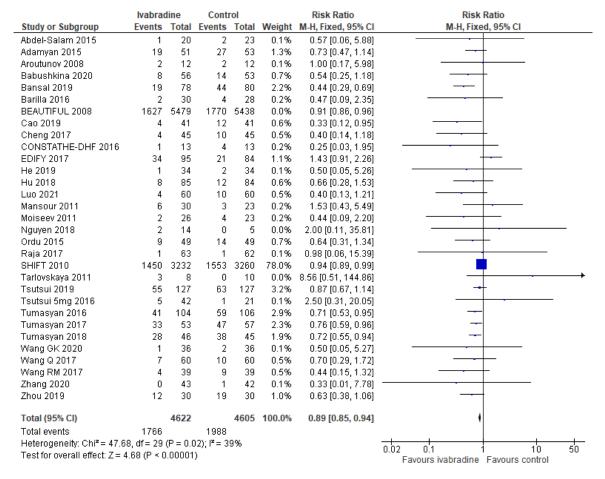


Figure 21 – Forest plot of the sensitivity analysis of serious adverse events removing the BEAUTIFUL trial.

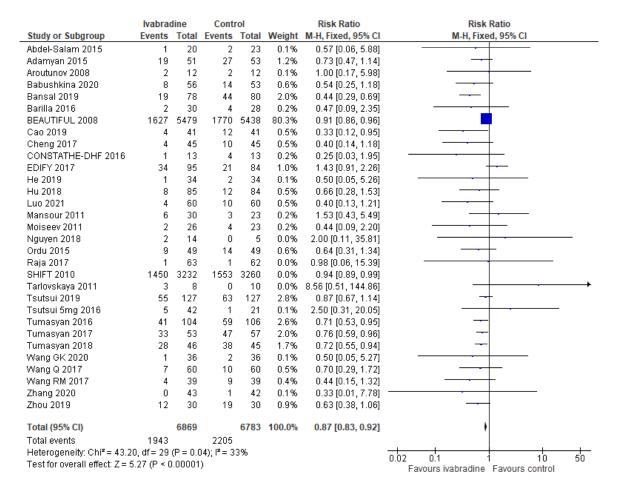
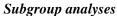


Figure 22 - Forest plot of the sensitivity analysis of serious adverse events removing the SHIFT trial.



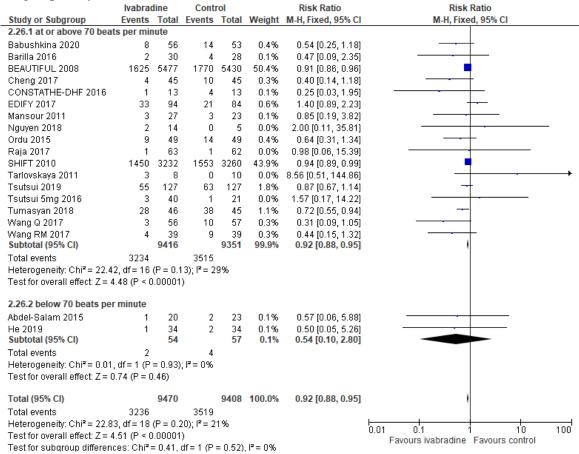


Figure 23 - Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared to trials randomising participants with heart rate below 70 beats per minute on all-cause mortality.

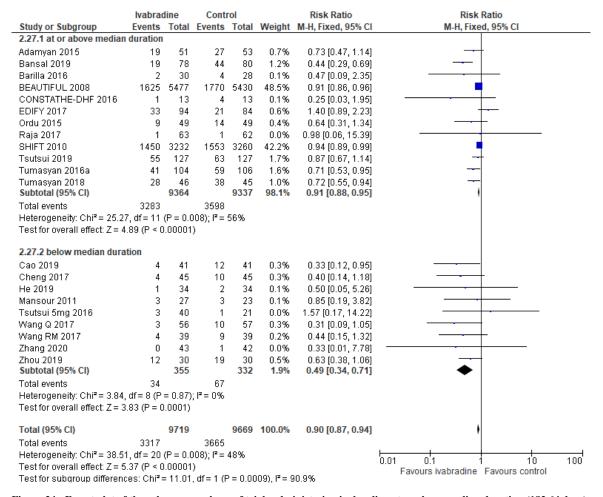


Figure 24 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median duration (182.64 days) compared to trials administering ivabradine below median duration on serious adverse events.

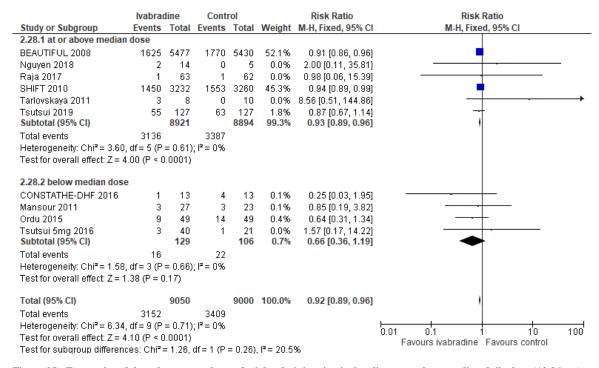


Figure 25 - Forest plot of the subgroup analyses of trials administering ivabradine at or above median daily dose (12.36 mg) compared to trials administering ivabradine below median daily dose on serious adverse events.

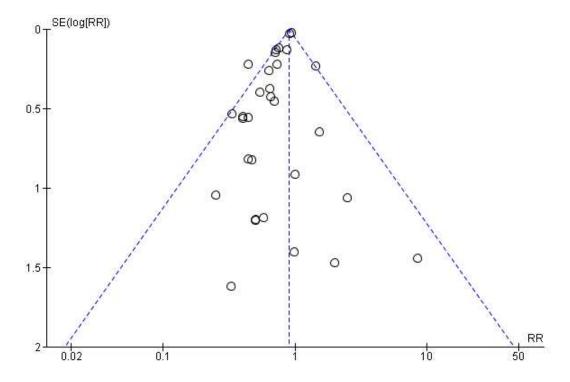


Figure 26 – Funnel plot of the analysis of serious adverse events. The funnel plot did not indicate small study bias.

Supplement 7 - Quality of life

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

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

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

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

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

Sensitivity analyses for trials using KCCQ.

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

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

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

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

Subgroup analyses for trials using the KCCQ

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

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

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

	Ival	bradin	e	C	Control			Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI				
2.50.1 MLWHFQ mea	an score												
Abdel-Salam 2015	46.4	7.3	20	51.7	6.6	23	8.8%	-5.30 [-9.48, -1.12]					
Sarullo 2010	31.2	2.6	30	37.5	1.9	30	46.3%	-6.30 [-7.45, -5.15]					
Zeng FC 2019 Subtotal (95% CI)	27.44	4.26	33 83	32.21	4.79	32 85	23.9% 79.0%	-4.77 [-6.98, -2.56] - 5.93 [-6.93, -4.94]	<u>→</u>				
Heterogeneity: Tau ² =	0.00; C	hi² = 1	.55, df=	= 2 (P =	0.46);	$I^2 = 0\%$,						
Test for overall effect:	•												
2.50.2 MLWHFQ cha	nge sco	re											
Mansour 2011	-12.3	3.3	30	-8.7	5.2	23	21.0%	-3.60 [-6.03, -1.17]					
Subtotal (95% CI)			30			23	21.0%	-3.60 [-6.03, -1.17]	•				
Heterogeneity: Not ap	oplicable												
Test for overall effect:	Z = 2.90	(P=0	0.004)										
Total (95% CI)			113			108	100.0%	-5.28 [-6.60, -3.96]	•				
Heterogeneity: Tau ² =	0.64; C	hi² = 4	.58, df=	3 (P =	0.21);	l ² = 35°	%	-	10 5 10				
Test for overall effect:	Z = 7.82	(P < 0	0.00001	1)					-10 -5 0 5 10 Favours ivabradine Favours control				
Test for subgroup diff	ferences	: Chi²:	= 3.04.	df = 1 (F	o.0 = 0	8), I²=	67.1%		Favours Ivabraume Favours Control				

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

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

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

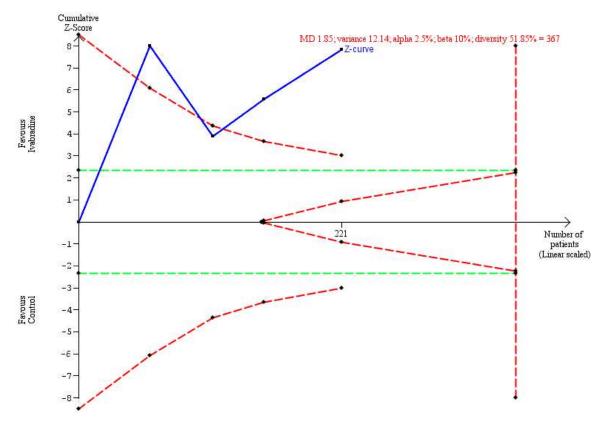


Figure 34 – Trial Sequential Analysis graph of quality of life from trials using the MLWHFQ. Trial Sequential Analysis showed that we had enough information to detect a mean difference of -5.60 points of ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) breached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

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

	Ival	bradin	е	C	Control			Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI				
2.51.1 MLWHFQ mea	an score												
Abdel-Salam 2015	46.4	7.3	20	51.7	6.6	23	8.8%	-5.30 [-9.48, -1.12]					
Sarullo 2010	31.2	2.6	30	37.5	1.9	30	46.3%	-6.30 [-7.45, -5.15]	-				
Zeng FC 2019 Subtotal (95% CI)	27.44	4.26	33 83	32.21	4.79	32 85	23.9% 79.0%	-4.77 [-6.98, -2.56] - 5.93 [-6.93, -4.94]	<u>→</u>				
Heterogeneity: Tau ² =	= 0.00; CI	hi² = 1	.55, df :	= 2 (P =	0.46);	$I^2 = 0\%$,						
Test for overall effect			•										
2.51.2 MLWHFQ cha	nge scoi	re											
Mansour 2011	-12.3	3.3	30	-8.7	5.2	23	21.0%	-3.60 [-6.03, -1.17]					
Subtotal (95% CI)			30			23	21.0%	-3.60 [-6.03, -1.17]	•				
Heterogeneity: Not ap	pplicable												
Test for overall effect	: Z= 2.90	(P = 0	0.004)										
Total (95% CI)			113			108	100.0%	-5.28 [-6.60, -3.96]	•				
Heterogeneity: Tau ² =	= 0.64; CI	hi² = 4	.58, df :	= 3 (P =	0.21);	$I^2 = 35^{\circ}$	%	-	-10 -5 0 5 10				
Test for overall effect	Z = 7.82	(P < 0	0.00001	1)					Favours ivabradine Favours control				
Test for subgroup dif	ferences	: Chi²:	= 3.04.	df = 1 (I	= 0.0	18), I ^z =	67.1%		Favours (vabradine Favours control				

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

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

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



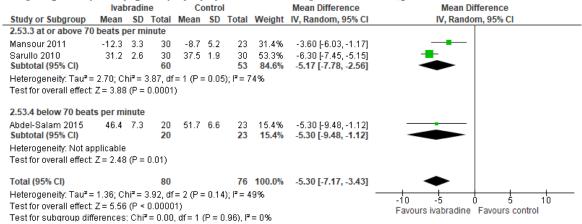


Figure 37 - Forest plot of the subgroup analyses of trials randomising participants with a heart rate at or above 70 beats per minute compared trials randomising participants with heart rate below 70 beats per minute on quality of life using the MLWHFQ.

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

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

Supplement 8 - Cardiovascular mortality *Main analyses*

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

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

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

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

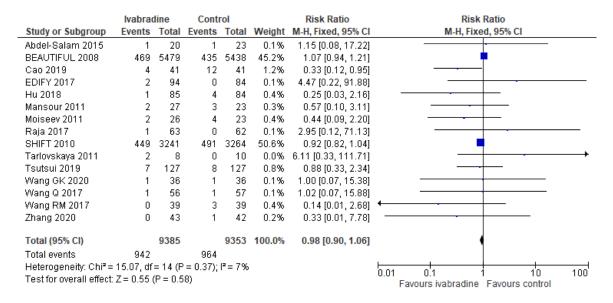


Figure 41 – Forest plot of the meta-analysis of cardiovascular mortality using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

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

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

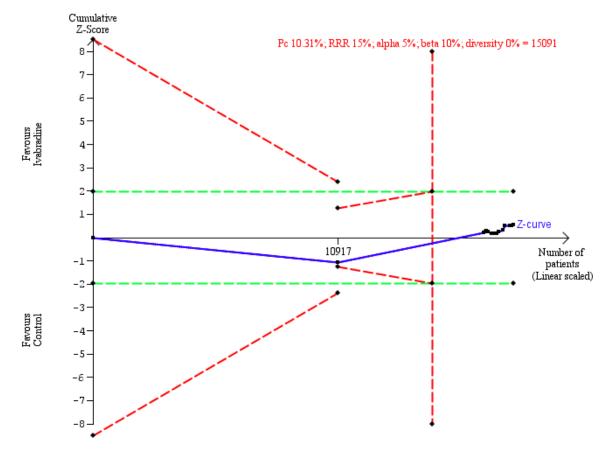


Figure 43 - Trial Sequential Analysis graph of cardiovascular mortality. Trial Sequential Analysis showed that we had enough information to reject a relative risk reduction of 15% or more by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) breaches the boundary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

Sensitivity analyses

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

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

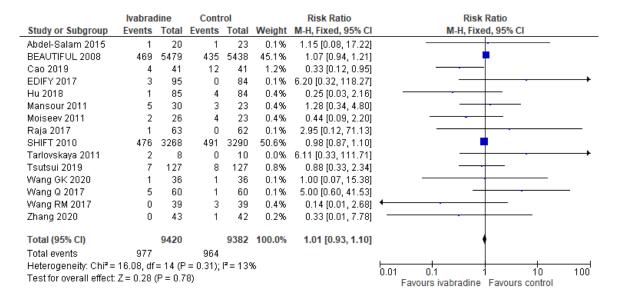


Figure 45 - Forest plot of the sensitivity analysis of cardiovascular mortality using worst compared with best-case scenario.

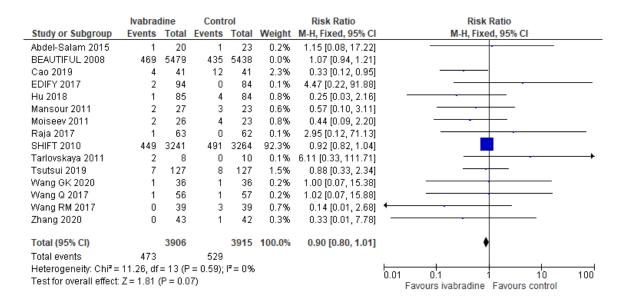


Figure 46 - Forest plot of the sensitivity analysis of cardiovascular mortality removing the BEAUTIFUL trial.

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

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

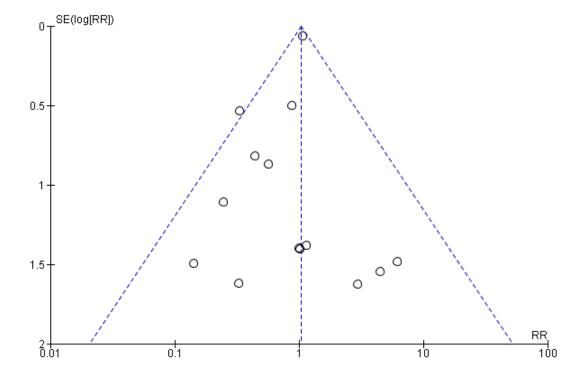


Figure 48 – Funnel plot of the analysis of cardiovascular mortality. The funnel plot did not indicate small study bias.

Supplement 9 - Myocardial infarction

Main analyses

		lvabrad	line	Contr	ol		Risk Ratio	Risk Ratio
_	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
	Babushkina 2020	0	56	3	53	0.0%	0.14 [0.01, 2.56]	
	BEAUTIFUL 2008	82	5477	88	5430	62.2%	0.92 [0.69, 1.25]	#
	EDIFY 2017	2	94	0	84	0.0%	4.47 [0.22, 91.88]	
	Liu YY 2020	4	61	5	61	0.0%	0.80 [0.23, 2.84]	
	Moiseev 2011	2	26	3	23	0.0%	0.59 [0.11, 3.22]	
	SHIFT 2010	62	3232	54	3260	37.8%	1.16 [0.81, 1.66]	+
	Tarlovskaya 2011	2	8	0	10	0.0%	6.11 [0.33, 111.71]	
	Tsutsui 2019	2	127	1	127	0.0%	2.00 [0.18, 21.78]	
	Tsutsui 5mg 2016	0	40	1	21	0.0%	0.18 [0.01, 4.21]	
	Total (95% CI)		8709		8690	100.0%	1.01 [0.80, 1.27]	•
	Total events	144		142				
	Heterogeneity: Chi² = I	0.89, df=	1 (P =	0.34); l ² =	: 0%			0.01 0.1 1 10 100
	Test for overall effect: .	Z = 0.11 ((P = 0.9)	2)				0.01 0.1 1 10 100 Favours ivabradine Favours control
								Tavours trabiadine Tavours control

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

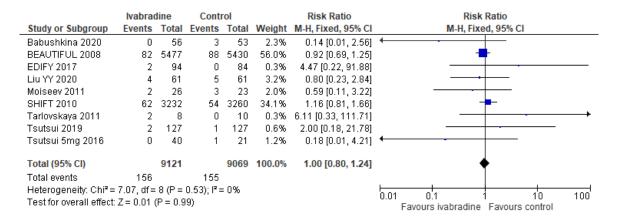


Figure 50 - Forest plot of the meta-analysis of myocardial infarction using fixed-effect meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

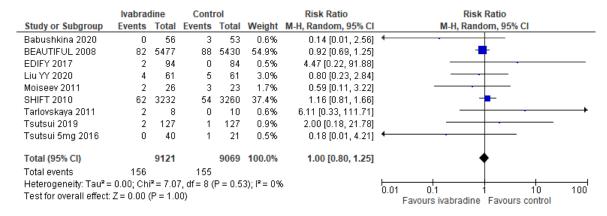


Figure 51 - Forest plot of the meta-analysis of myocardial infarction using random-effects meta-analysis. The meta-analysis showed no evidence of a difference between ivabradine versus control (placebo or no intervention).

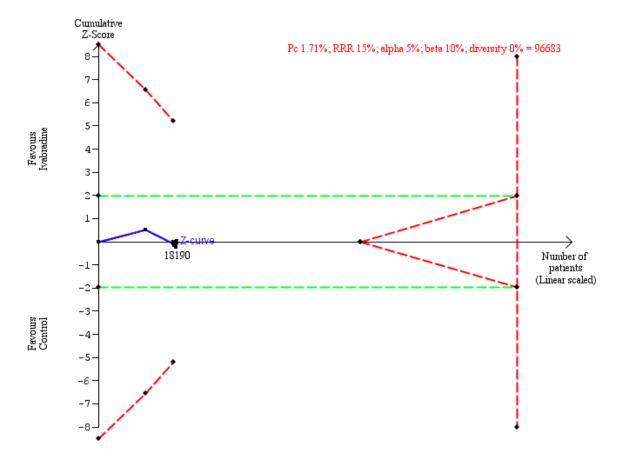


Figure 52 - Trial Sequential Analysis graph of myocardial infarction. Trial Sequential Analysis showed that we did not have enough information to detect or reject a relative risk reduction of 15% or more by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line)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

Sensitivity analyses

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

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

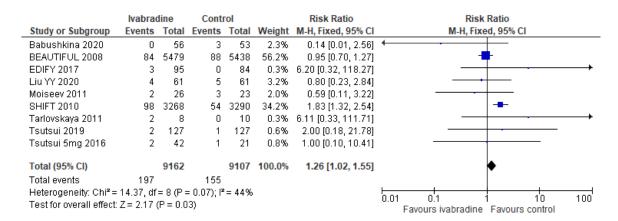
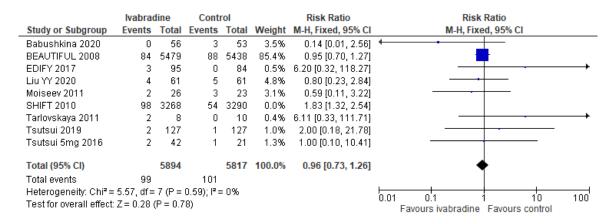


Figure 54 - Forest plot of the sensitivity analysis of myocardial infarction using a worst- compared with best-case scenario.

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

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



 $Figure\ 56-Forest\ plot\ of\ the\ sensitivity\ analysis\ of\ myocardial\ infarction\ removing\ the\ SHIFT\ trial.$

Supplement 10 - Non-serious adverse events *Main analyses*

Ctudu or Cubarous	Ivabra		Conti		Moight	Risk Ratio	Risk Ratio
Study or Subgroup	Events				weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Abdel-Salam 2015	3	20	0	23		Not estimable	
Bansal 2019	3	78 5477	1	80	40.00	Not estimable	
BEAUTIFUL 2008	2570	5477	2221	5430	48.3%	1.15 [1.10, 1.20]	•
ao 2019	2	41	3	41		Not estimable	
Cheng 2017	2	45	1	45		Not estimable	
Cong 2018	1	45	1	45		Not estimable	
Deng 2017	1	41	1	41		Not estimable	
Di 2020	3	63	2	63		Not estimable	
EDIFY 2017	57	94	51	84		Not estimable	
Fu 2021	2	32	1	32		Not estimable	
Hu 2018	2	85	0	84		Not estimable	
Huang J 2017	5	52	0	50		Not estimable	
Li 2020	2	48	1	48		Not estimable	
_iu YY 2020	3	61	4	61		Not estimable	
Lu 2019	1	30	0	30		Not estimable	
Luo 2021	4	60 25	3	60		Not estimable	
Lu YH 2020	1	35	0	35		Not estimable	
Ma 2020	2	43	2	43		Not estimable	
Manz 2003	9	27	2	11		Not estimable	
Mao 2018	2	30	2	30		Not estimable	
Nguyen 2018	5	14	0	5		Not estimable	
Pan 2020	2	25	1	25		Not estimable	
Qi 2019	0	48	2	48		Not estimable	
Raja 2017	2	63	0	62		Not estimable	
Sallam 2016	5	50	3	50		Not estimable	_
SHIFT 2010	2694	3232	2577	3260	51.7%	1.05 [1.03, 1.08]	
Sun 2020	1	50	4	50		Not estimable	
Tang 2018	1	31	3	31		Not estimable	
Tsutsui 2.5mg 2016	23	42	6	20		Not estimable	
Tsutsui 2019	119	127	116	127		Not estimable	
Tsutsui 5mg 2016	27	42	6	21		Not estimable	
Wang FC 2017	2	53	6	43		Not estimable	
Wang JJ 2017	2	20	3	20		Not estimable	
Wang Q 2017	6	56	4	57		Not estimable	
Wang RM 2017	3	39	3	39		Not estimable	
Wei 2019	1	32	0	32		Not estimable	
Xia 2016	1	39	1	39		Not estimable	
Xing 2018	1	10	3	10		Not estimable	
Xu 2019	3	38	0	39		Not estimable	
Xue 2020	2	45	1	45		Not estimable	
Yang WT 2019	1	40	0	40		Not estimable	
Yu 2018	1	10	3	10		Not estimable	
Yue 2016	2	43	1	43		Not estimable	
Zeng FC 2019	0	33	1	32		Not estimable	
Zeng XM 2019	3	45	4	45		Not estimable	
Zhang 2020	2	43	6	42		Not estimable	
Zhang 2021	1	47	2	47		Not estimable	
Zhang XJ 2019	1	55	1	55		Not estimable	
Zhou 2019	3	30	2	30		Not estimable	
Zhou 2020	2	43	5	43		Not estimable	
Total (95% CI)		8709		8690	100.0%	1.10 [1.00, 1.21]	
Total events	5264		4798				
					$001); I^2 =$		

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)

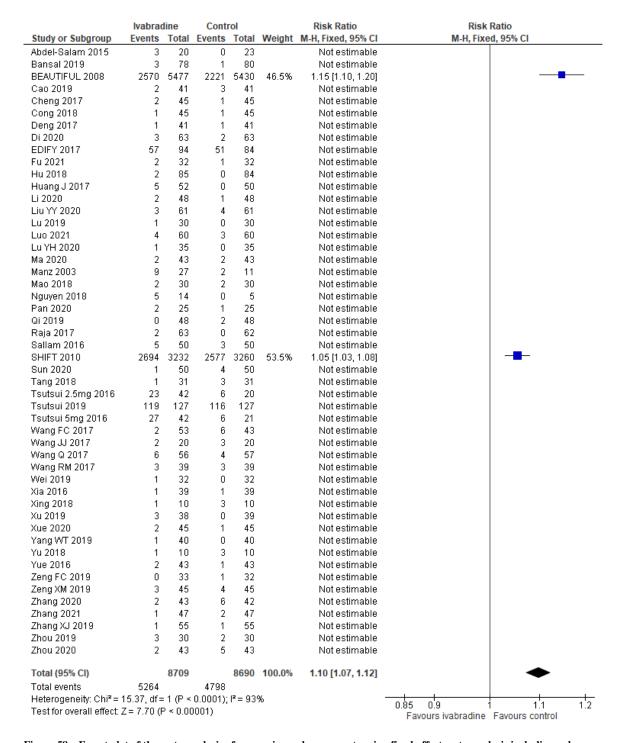


Figure 58 – Forest plot of the meta-analysis of non-serious adverse events using fixed-effect meta-analysis including only trials at low risk of bias. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention).

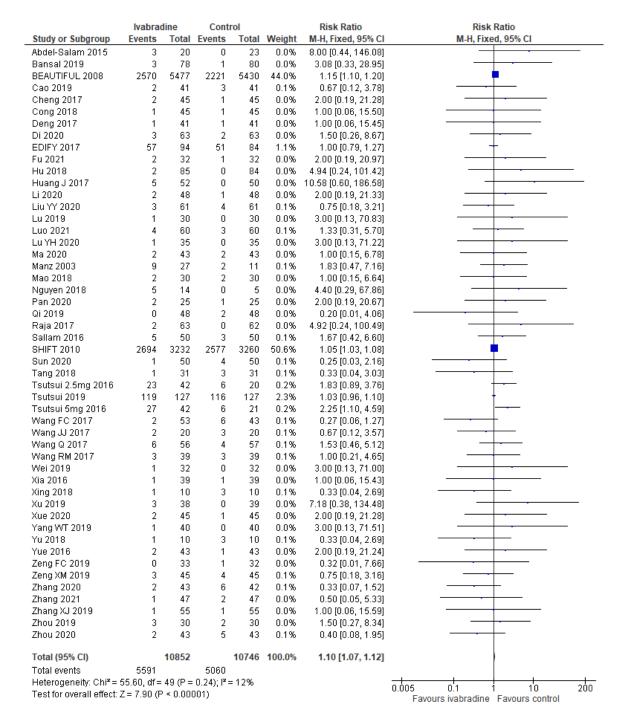


Figure 59 - Forest plot of the meta-analysis of non-serious adverse events using fixed-effect meta-analysis. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention).

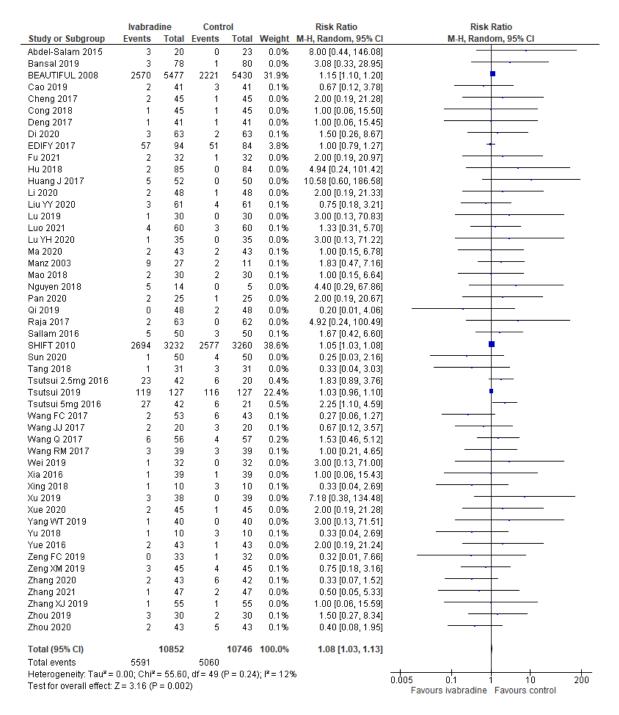


Figure 60 - Forest plot of the meta-analysis of non-serious adverse events using random-effects meta-analysis. The meta-analysis showed evidence of a harmful effect of ivabradine versus control (placebo or no intervention)

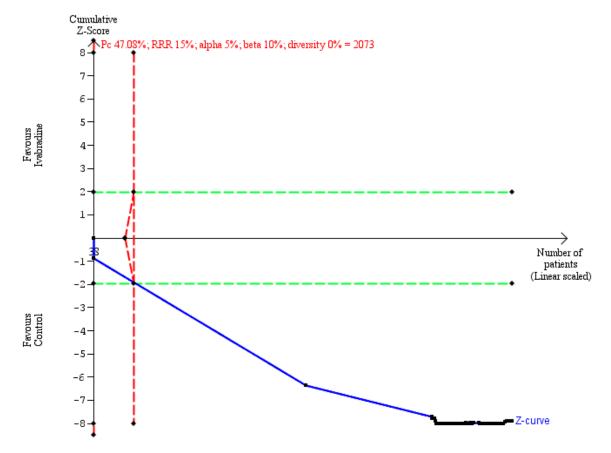


Figure 61 – **Trial Sequential Analysis graph of non-serious adverse events.** Trial Sequential Analysis showed that we had enough information to detect a relative risk increase of 10% by ivabradine versus control (placebo or no intervention). The cumulative z-curve (the blue line) reached the required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

Sensitivity analyses

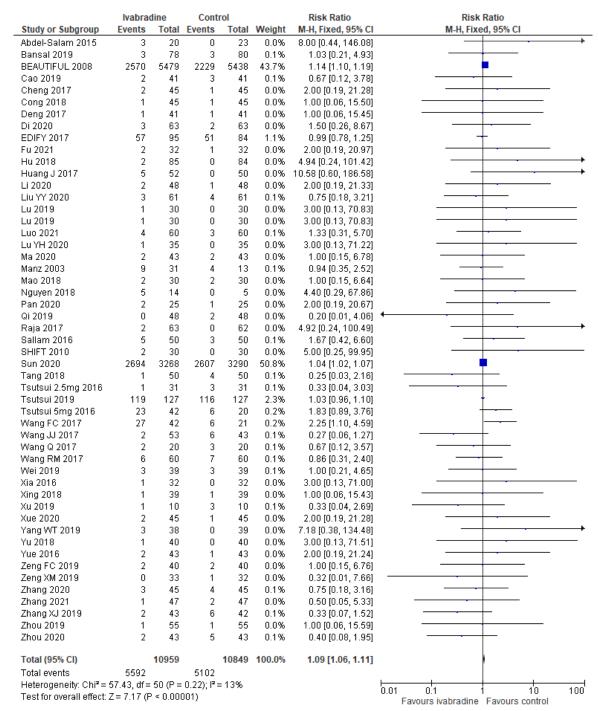


Figure 62 - Forest plot of the meta-analysis of non-serious adverse events using a best- compared with worst-case scenario.

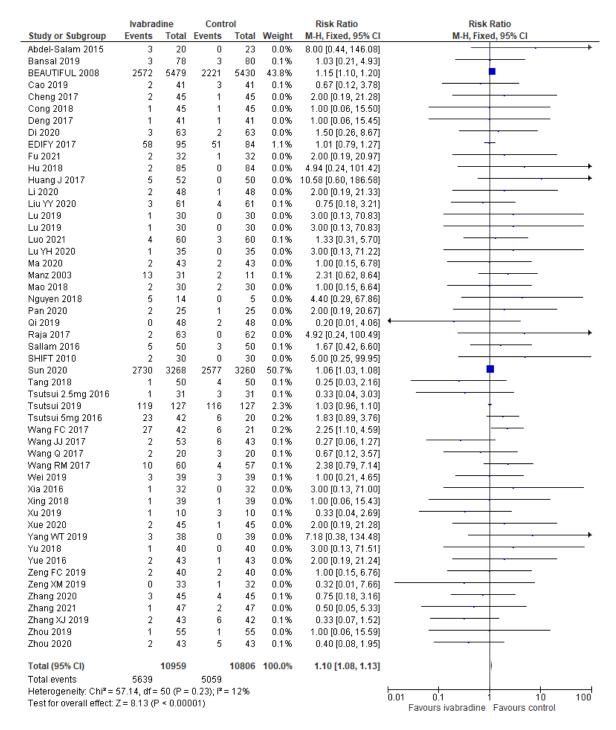


Figure 63 - Forest plot of the meta-analysis of non-serious adverse events using a worst- compared with best-case scenario.

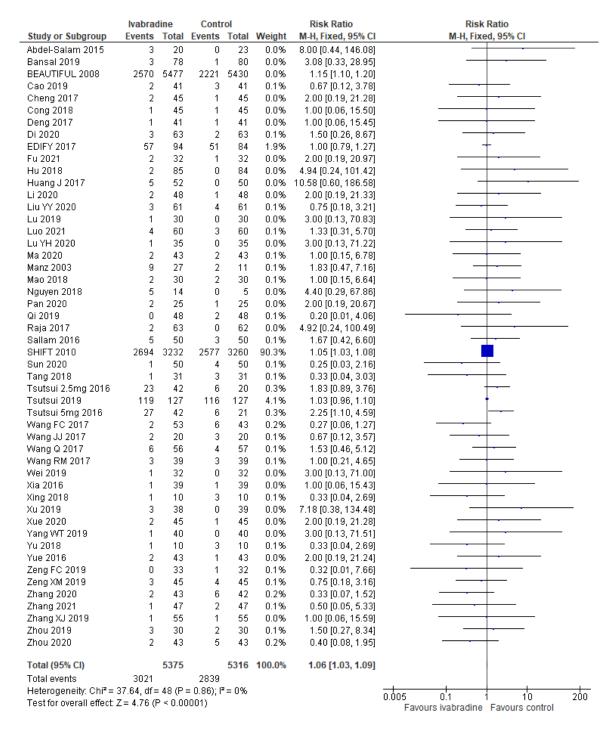


Figure 64 - Forest plot of the sensitivity analysis of non-serious adverse events removing the BEAUTIFUL trial.

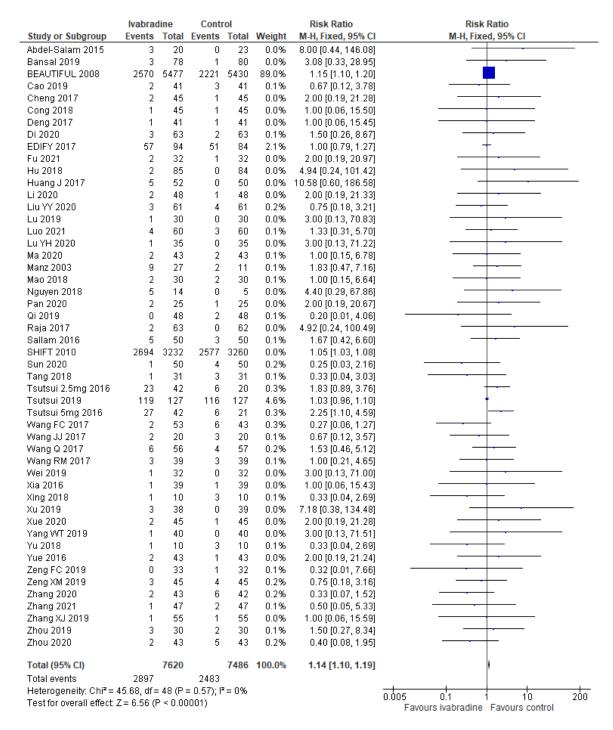


Figure 65 - Forest plot of the sensitivity analysis of non-serious adverse events removing the SHIFT trial.

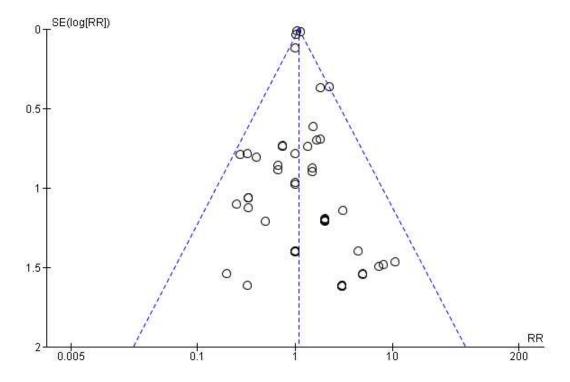


Figure 66 – Funnel plot of the analysis of non-serious adverse events. The funnel plot did not indicate small study bias.

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*

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

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

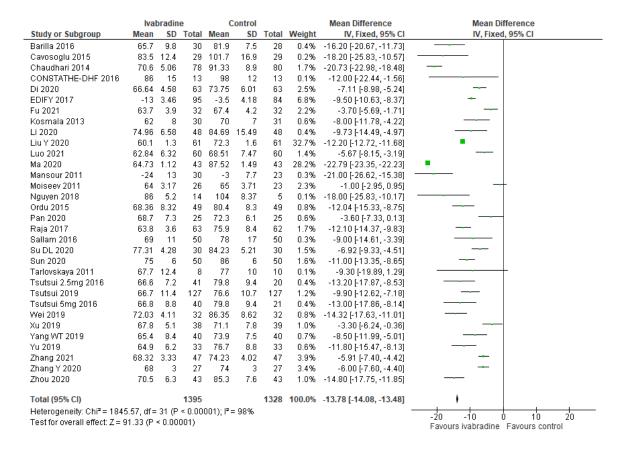


Figure 68 - Forest plot of the meta-analysis of resting heart rate at follow-up using fixed-effect meta-analysis. The meta-analysis showed that ivabradine seemed to decrease the resting heart rate at follow-up by 13.78 beats per minute at follow-up.

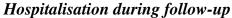
Left ventricular ejection fraction

Study or Subgroup	lval Mean	bradine SD	Total	Co Mean	ntrol SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Abdel-Salam 2015	39	7	20	33	10	23	1.0%	6.00 [0.89, 11.11]	
Bansal 2019	35	3.71	78		4.24	80	1.5%	2.00 [0.76, 3.24]	
Barilla 2016	4.1	2.5	30	0.8	1.2	28	1.5%	3.30 [2.30, 4.30]	—
3i 2020	63.06	9.85	99	44.27	7.16	99	1.4%	18.79 [16.39, 21.19]	
Cao 2019	52.39	5.32	41	39.89	4.98	41		12.50 [10.27, 14.73]	
Cavosoglu 2015	26.4	5.3	29	28.4	4.3	29	1.4%	-2.00 [-4.48, 0.48]	
Chaudhari 2014	35	3.71	78		4.24	80	1.5%	2.00 [0.76, 3.24]	-
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		30	1.4%	8.82 [6.35, 11.29]	
Chen HX 2021	41.77	6.02	30		5.13	30	1.3%	6.85 [4.02, 9.68]	
CONSTATHE-DHF 2016	29	4.00	13	25	8	13	0.9%	4.00 [-2.15, 10.15]	
Di 2020	49.98	4.98	63	44.67	4.5	63	1.5%	5.31 [3.65, 6.97]	
Fu 2021	51.6	5.3	32	49 32.603	4.8	32	1.4%	2.60 [0.12, 5.08] 9.70 [5.82, 13.57]	
3uo 2017 He 2019	42.301 33.51	6.358 10.12	16 30	31.12	4.7	16 31	1.2%	2.39 [-2.52, 7.30]	
не 2019 Ни 2017	48.31	6.54	30	41.73		30	1.3%	6.58 [3.41, 9.75]	
Tu 2017 Hu 2018	39.2	12.1	85		11.2	84	1.3%	0.30 [-3.21, 3.81]	
luang J 2017	40	6	52	34	7	50	1.4%	6.00 [3.47, 8.53]	
Kosmala 2013	68	6	30	68	5	31	1.4%	0.00 [-2.78, 2.78]	
i 2018	52.5	2.5	45	41.9	2.6	44	1.5%	10.60 [9.54, 11.66]	
i 2020	39.84	3.69	48		2.47	48	1.5%	3.58 [2.32, 4.84]	
i B 2020	50.09	5.32	55		4.83	55	1.5%	4.15 [2.25, 6.05]	
iu 2019	57.6	6.7	48	47.9	8.7	48	1.3%	9.70 [6.59, 12.81]	
iu 2020	51.54	1.18	49	41.29		49	1.5%	10.25 [9.83, 10.67]	-
_u 2019	41.27	4.65	28	38.1		27	1.4%	3.17 [0.84, 5.50]	
_uo 2021	48.29	5.32	60	45.31		60	1.5%	2.98 [1.21, 4.75]	
/la 2016	36	3.11	30	32.3		30	1.5%	3.70 [2.16, 5.24]	
/la 2020	58.01	8.39	43	46.32		43	1.3%	11.69 [8.40, 14.98]	
Mansour 2011	6.2	8.3	27	1.8	6.7	23	1.2%	4.40 [0.24, 8.56]	
/lanz 2003	37.2	10.01	27	38.4	9.3	11	0.8%	-1.20 [-7.87, 5.47]	
/lao 2018	44.3	7.9	30	39.3	7.1	30	1.2%	5.00 [1.20, 8.80]	
doiseev 2011	36.5	8.19	26	35.7	5.51	23	1.2%	0.80 [-3.07, 4.67]	
°an 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]	
3hen 2018	51.2	1.6	56	43.2	1.3	56	1.5%	8.00 [7.46, 8.54]	_
3HIFT 2010	34.7	10.2	204	31.5	10	199	1.4%	3.20 [1.23, 5.17]	
3ong 2021	63.16	3.17	48		3.46	48		11.49 [10.16, 12.82]	
3u 2020	52.1	4.2	40	46.2	5	30	1.4%	5.90 [3.69, 8.11]	
Bu DL 2020	45.28	4.14	30	39.56		30	1.4%	5.72 [3.34, 8.10]	
Bun 2021	50.2	5.6	59 31	43.4	5.5 4.59	59	1.4%	6.80 [4.80, 8.80]	<u> </u>
Fang 2018 Fatarchenko 2008	41.1 58.9	4.93 2.8	29	38 51.2	4.09	31 30	1.4% 1.5%	3.10 [0.73, 5.47] 7.70 [5.91, 9.49]	
rsutsui 2.5mg 2016	33.8	8.7	41	31.2	8.8	20	1.1%	2.80 [-1.89, 7.49]	
rsutsui 2.5111g 2010 Fsutsui 2019	38.9	12.8	127	33.3	13	127	1.3%	5.60 [2.43, 8.77]	<u> </u>
rsutsui 5mg 2016	35	10.4	40	31	8.8	21	1.1%	4.00 [-0.96, 8.96]	
atinian 2015/	51.2	2.1	26	45.3	1.9	26	1.5%	5.90 [4.81, 6.99]	
Vang 2019	37.79	5.23	35		4.86	33	1.4%	0.47 [-1.93, 2.87]	
Vang FC 2017	42.51	6.03	53	36.78	7.4	43	1.4%	5.73 [2.99, 8.47]	
Vang GK 2020	55.3	10.4	36	52.2		36	1.1%	3.10 [-1.87, 8.07]	
Vang لیا 2020	58.63	4.25	35	52.34		35	1.4%	6.29 [4.35, 8.23]	
Vang RM 2017	49.06	7.05	39	43.03		39	1.3%	6.03 [2.94, 9.12]	
Vang YH 2018	55.35	7.1	34	52.86		34	1.3%	2.49 [-0.68, 5.66]	+
Vei 2019	48.14	2.62	32	41.69	1.06	32	1.5%	6.45 [5.47, 7.43]	-
(ia 2016	48.25	6.65	39	41.57		39	1.4%	6.68 [3.88, 9.48]	
(u 2019	46.2	3.8	38	43.9	3.4	39	1.5%	2.30 [0.69, 3.91]	
(u 2020	49.83	3.25	61	45.01	2.76	61	1.5%	4.82 [3.75, 5.89]	
/ang WT 2019	48.3	5.4	40	43.2	6.5	40	1.4%	5.10 [2.48, 7.72]	
/ang Z 2019	46.87	6.38	67	43.61		68	1.4%	3.26 [1.03, 5.49]	
/ao 2016	38.22	4.86	36		3.52	36	1.4%	3.99 [2.03, 5.95]	
/i 2017	37.72	7.6	43		6.08	42	1.3%	5.88 [2.96, 8.80]	
/u 2019	29.3	3	33	27.7	3.4	33	1.5%	1.60 [0.05, 3.15]	_
/ue 2016	39.78	3.44	40		3.28	40	1.5%	2.08 [0.61, 3.55]	
Zeng FC 2019	59.36	6.25	33		5.52	32	1.3%	6.19 [3.33, 9.05]	
Zeng XM 2019 Zhang 2010	57.6	4.2	45	45.2	4.7	45		12.40 [10.56, 14.24]	
Thang 2019	67 50.24	8	30	62	5.4	30	1.3%	5.00 [1.55, 8.45]	
Thang 2020 Thang 2021	50.21	6.47	43	45.19		42	1.3%	5.02 [2.17, 7.87]	
Thang 2021	48.32	4.23	47	43.76		47	1.5%	4.56 [2.87, 6.25]	
Thang J 2019	35.16 51.77	2.68	45 55	35.34 20.02		41 55	1.5%	-0.18 [-1.35, 0.99]]
Thang XJ 2019	51.77	3.84	55 27	38.02 51		55 27		13.75 [12.52, 14.98]	
Thang Y 2020	57 47 00	7 00	27	51 24.24	12	27	0.9%	6.00 [-0.40, 12.40]	
Ihou 2019 Ihou 2020	47.89 46.8	7.89 6.3	30 43	34.34 36.7	7.6	30 43	1.3% 1.3%	13.55 [10.07, 17.03]	l
.110u 2020	40.6	0.3	43	30.7	7.0	43	1.370	10.10 [7.15, 13.05]	
otal (95% CI)			3323			3230	100.0%	5.43 [4.52, 6.34]	•
(00.00)				0 (D = 0 0	00041			ST. IS [NOZ. OIST]	
leterogeneity: Tau ^z = 13.8	(5 · C b i≠ − 1								-10 -5 0 5 10

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

Study or Subarana		oradine	Total		ntrol	Total	Weight	Mean Difference	Mean Difference
Study or Subgroup Abdel-Salam 2015	Mean 39	7	Total 20	Mean 33	10	23	Weight 0.1%	IV, Fixed, 95% CI 6.00 [0.89, 11.11]	IV, Fixed, 95% CI
Bansal 2019	35	3.71	78	33	4.24	80	2.3%	2.00 [0.76, 3.24]	
Barilla 2016	4.1	2.5	30	0.8	1.2	28	3.6%	3.30 [2.30, 4.30]	
Bi 2020	63.06	9.85	99		7.16	99	0.6%	18.79 [16.39, 21.19]	-
Cao 2019	52.39	5.32	41	39.89	4.98	41	0.7%	12.50 [10.27, 14.73]	
Cavosoglu 2015	26.4	5.3	29	28.4	4.3	29	0.6%	-2.00 [-4.48, 0.48]	
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		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		31	0.1%	2.39 [-2.52, 7.30]	
Hu 2017	48.31	6.54	30	41.73		30	0.4%	6.58 [3.41, 9.75]	
Hu 2018	39.2 40	12.1 6	85 52	38.9 34	11.2	84 50	0.3% 0.6%	0.30 [-3.21, 3.81]	
Huang J 2017 Kosmala 2013	68	6	30	54 68	5	31	0.5%	6.00 [3.47, 8.53] 0.00 [-2.78, 2.78]	
Kusiiiaia 2013 Li 2018	52.5	2.5	45	41.9	2.6	44	3.2%	10.60 [9.54, 11.66]	<u> </u>
Li 2020	39.84	3.69	48	36.26		48	2.3%	3.58 [2.32, 4.84]	
Li B 2020	50.09	5.32	55	45.94	4.83	55	1.0%	4.15 [2.25, 6.05]	
Liu 2019	57.6	6.7	48	47.9	8.7	48	0.4%	9.70 [6.59, 12.81]	<u></u>
Liu 2020	51.54	1.18	49	41.29		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		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		48		11.49 [10.16, 12.82]	
Su 2020	52.1	4.2 4.14	40	46.2 39.56	5.21	30 30	0.7%	5.90 [3.69, 8.11]	
Su DL 2020 Sun 2021	45.28 50.2	5.6	30 59	43.4	5.5	59	0.6% 0.9%	5.72 [3.34, 8.10] 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		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		32	3.7%	6.45 [5.47, 7.43]	+
Xia 2016	48.25	6.65	39	41.57		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		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		68	0.7%	3.26 [1.03, 5.49]	
Yao 2016	38.22	4.86	36	34.23		36	0.9%	3.99 [2.03, 5.95]	-
Yi 2017	37.72	7.6	43	31.84		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]	<u> </u>
Yue 2016 Zong EC 2010	39.78	3.44	40	37.7		40	1.6%	2.08 [0.61, 3.55]	<u> </u>
Zeng FC 2019 Zeng VM 2010	59.36 57.6	6.25	33	53.17		32 45	0.4%	6.19 [3.33, 9.05]	
Zeng XM 2019 Zhang 2019	57.6	4.2	45	45.2	4.7	45		12.40 [10.56, 14.24]	l
Zhang 2019 Zhang 2020	67 60.21	8 6 4 7	30	62 45 10	5.4	30	0.3%	5.00 [1.55, 8.45]	
Zhang 2020 Zhang 2021	50.21	6.47	43	45.19		42	0.4%	5.02 [2.17, 7.87]	
Zhang 2021 Zhang 12019	48.32	4.23	47 45	43.76		47	1.3%	4.56 [2.87, 6.25]	
Zhang J 2019 Zhang V I 2019	35.16	2.68	45 55	35.34		41	2.6%	-0.18 [-1.35, 0.99]	T
Zhang XJ 2019 Zhang V 2020	51.77	3.84	55 27	38.02		55 27		13.75 [12.52, 14.98]	
Zhang Y 2020 Zhou 2019	57 47.89	12 7.89	27 30	51 34.34	12 5.67	27 30	0.1% 0.3%	6.00 [-0.40, 12.40]	
Znou 2019 Zhou 2020	47.89	6.3	43	34.34	7.6	43	0.4%	13.55 [10.07, 17.03]	
L1104 2020	40.6	0.3	43	30.7	7.0	43	0.470	10.10 [7.15, 13.05]	
Total (95% CI)			3323			3230	100.0%	6.63 [6.44, 6.82]	1
		72 /0 ~ (V IZ = 0.5	ov.	0200		0.00 [0.74, 0.02]	
Heterogeneity: Chi ^z = 1459									-10 -5 0 5 10

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%.



	_	00 1						
		lvabradine		Control		Risk Ratio		Risk Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ξ.	Abdel-Salam 2015	1	20	2	23	0.1%	0.57 [0.06, 5.88]	
	Adamyan 2008	4	70	11	75	0.4%	0.39 [0.13, 1.17]	
	Babushkina 2020	8	56	14	53	0.6%	0.54 [0.25, 1.18]	
	Bansal 2019	19	78	44	80	1.8%	0.44 [0.29, 0.69]	
	BEAUTIFUL 2008	681	5479	704	5438	29.9%	0.96 [0.87, 1.06]	•
	CONSTATHE-DHF 2016	1	13	0	13	0.0%	3.00 [0.13, 67.51]	
	Luo 2021	4	60	10	60	0.4%	0.40 [0.13, 1.21]	
	Moiseev 2011	3	26	6	23	0.3%	0.44 [0.12, 1.57]	
	SHIFT 2010	1231	3241	1356	3264	57.2%	0.91 [0.86, 0.97]	•
	Tsutsui 2019	55	127	63	127	2.7%	0.87 [0.67, 1.14]	+
	Tumasyan 2016	17	53	29	53	1.2%	0.59 [0.37, 0.93]	
	Tumasyan 2017	33	53	47	57	1.9%	0.76 [0.59, 0.96]	~
	Tumasyan 2018	28	46	38	45	1.6%	0.72 [0.55, 0.94]	
	Wang GK 2020	1	36	2	36	0.1%	0.50 [0.05, 5.27]	· · ·
	Wang Q 2017	3	56	10	57	0.4%	0.31 [0.09, 1.05]	-
	Wang RM 2017	4	39	9	39	0.4%	0.44 [0.15, 1.32]	
	Zhou 2019	12	30	19	30	0.8%	0.63 [0.38, 1.06]	
	Total (95% CI)		9483		9473	100.0%	0.89 [0.85, 0.94]	•
	Total events	2105		2364				
	Heterogeneity: Chi ^z = 34.25	5, df = 16	(P = 0.0)	06); l ² = :	53%			0.01 0.1 1 10 100
	Test for overall effect: $Z = 4$.	.57 (P < 0	.00001)				'0.01 0.1 1 1'0 100' Favours ivabradine Favours control
		•						ravours ivabradine ravours control

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

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

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



	Ivabradine			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Cavosoglu 2015	195	96	29	166	52	29	1.1%	29.00 [-10.74, 68.74]	
Cheng 2017	322.33	175.15	45	235.56	171.25	45	0.3%	86.77 [15.20, 158.34]	
Cong 2018	522.19	52.35	45	442.14	42.12	45	4.4%	80.05 [60.42, 99.68]	
EDIFY 2017	4.3	50	84	7.9	67.9	84	5.2%	-3.60 [-21.63, 14.43]	
Fu 2021	284.3	45	32	346.1	60.5	32	2.5%	-61.80 [-87.92, -35.68]	
Gou 2017	198.7	56.31	30	162.01	57.36	30	2.0%	36.69 [7.93, 65.45]	
Guo 2017	454.752	35.173	16	415.375	52.456	16	1.8%	39.38 [8.43, 70.32]	
He 2019	428.1	25.52	30	350.8	26.8	31	9.8%	77.30 [64.17, 90.43]	-
Huang J 2017	386.41	101.75	52	306.24	135.87	50	0.8%	80.17 [33.45, 126.89]	
Li 2018	421.1	31.5	45	382.1	31.2	44	9.9%	39.00 [25.97, 52.03]	
Liu 2019	523.27	45.46	49	446.25	39.23	49	6.0%	77.02 [60.21, 93.83]	
Liu Y 2020	386	38	61	331	45	61	7.7%	55.00 [40.22, 69.78]	
Lu 2019	427.57	46.61	28	367.27	52.23	27	2.5%	60.30 [34.10, 86.50]	
Luo 2021	357.57	70.86	60	303.12	72.13	60	2.6%	54.45 [28.87, 80.03]	
Ma 2016	336	53.66	30	344.3	42.71	30	2.8%	-8.30 [-32.84, 16.24]	
Manz 2003	379	117	30	307	98	30	0.6%	72.00 [17.39, 126.61]	
Mao 2018	379	117	30	307	98	30	0.6%	72.00 [17.39, 126.61]	
Pan 2020	378.6	48.5	19	366.2	42.8	18	1.9%	12.40 [-17.04, 41.84]	
Raja 2017	493.5	4.6	63	367	82	62	4.0%	126.50 [106.06, 146.94]	·
Song 2021	340.62	65.69	48	289.62	45.66	48	3.3%	51.00 [28.37, 73.63]	
Su DL 2020	422.54	51.24	30	378.76	39.67	30	3.1%	43.78 [20.59, 66.97]	_
Wang FC 2017	384.2	43	53	278.5	82.7	43	2.3%	105.70 [78.41, 132.99]	\rightarrow
Wang GK 2020	347.9	80.8	36	299.1	87.2	36	1.1%	48.80 [9.97, 87.63]	
Xu 2020	396.52	36	61	341	30	61	12.2%	55.52 [43.76, 67.28]	
Yu 2019	402.2	53.7	33	351.3	44.5	33	3.0%	50.90 [27.11, 74.69]	
Yue 2016	341.7	76.69	40	313.83	72.98	40	1.6%	27.87 [-4.94, 60.68]	
Zhang J 2019	336.19	47.02	36	308.75	60.33	28	2.3%	27.44 [0.32, 54.56]	
Zhang XJ 2019	411.47	123.49	55	324.21	102.55	55	0.9%	87.26 [44.84, 129.68]	
Zhou 2019	270.24	43.34	30	256.9	47.65	30	3.2%	13.34 [-9.71, 36.39]	 •
Zhou 2020	361.7	97.5	43	294.6	104.8	43	0.9%	67.10 [24.32, 109.88]	
Total (95% CI)			1243			1220	100.0%	50.62 [46.52, 54.72]	•
Heterogeneity: Chi ² =	266.41, df	= 29 (P <	0.000	01); I ² = 89	%				-100 -50 0 50 100
Test for overall effect:	Z = 24.19	(P < 0.00)	001)						-100 -50 0 50 100 Favours control Favours ivabradine
			,						Favours control Favours Madradine

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

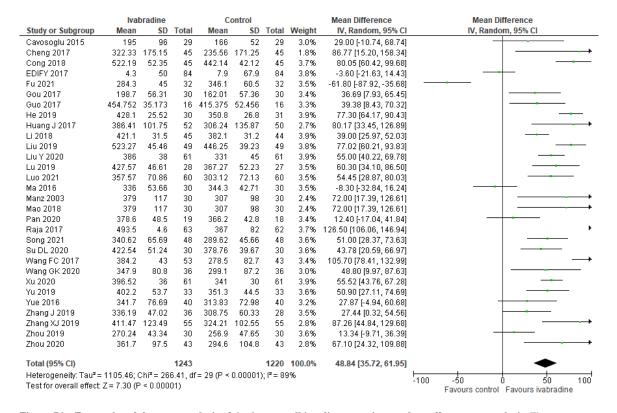


Figure 74 – Forest plot of the meta-analysis of 6-minutes walking distance using random-effects meta-analysis. The meta-analysis shows evidence of a beneficial effect of ivabradine versus control (placebo or no intervention) of 48.84 meters per 6 minutes.