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Ivabradine for the Treatment of Heart Failure: A Systematic Review and Meta-Analysis

Hadir Aljohani[1], Hadeel Alkofide[2] and Hanin Aljohani[2]

Abstract

Background: Ivabradine has a pure heart rate reduction. However, the use of ivabradine remains limited due to the conflicting evidence of its safety and efficacy.
Purpose: To determine the efficacy and safety of ivabradine compared to control in subjects with Heart failure (HF).
Data Sources: Medline, Embase, Ovid and the Cochrane Central Register of Controlled Trials from inception through June 2018.
Study Selection: Peer-reviewed, randomized controlled trials of Ivabradine versus control in patients with heart failure with or without low ejection fraction.
Data Extraction: Two investigators independently extracted data from each eligible study and assessed the risk of bias of included studies.
Data Synthesis: Six trials with 17886 patients were included. There was no significant difference among Ivabradine treated group versus control in lowering all-cause mortality, cardiovascular mortality or hospital readmission. Ivabradine had an increase in the mean difference in the percentage of ejection fraction (EF) by 3% as compared with control. Bradycardia, phosphenes and blurred vision were significantly higher with ivabradine by 4 and 5 times as compared with control.
Conclusion: Administration of Ivabradine to adults with HF with or without low EF significantly improved the ejection fraction. However, there was no significant impact on mortality and re-admission rates

Keywords: Ivabradine, heart failure, systematic review, meta-analysis.

[1] Drug Safety Sector, Saudi Food and Drug Authority, Riyadh, Saudi Arabia.
[2] Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
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1. Introduction

Heart failure (HF) "represents a complex clinical syndrome, which is characterized by ventricular dysfunction when the heart is unable to pump adequate blood to meet the body's metabolic needs".(1) The percentage of the adult populace who has HF in the developed countries is between 1 to 2 %, within five years of diagnosis 50% of them will die.(2) In the last few years, there has been a considerable advancement in the management of HF. One therapeutic target is heart rate reduction, which is linked to reduced mortality and cardiovascular incidents.

Beta-blockers have been showed an improvement in the survival in subjects with HF and have an effect on lowering the heart rate.(3) However, just 30-35% of patients in clinical practice reach the target therapeutic dose of beta-blockers , as their utilization is limited in subjects with conduction abnormalities, severe left ventricular (LV) dysfunction, and active bronchospasm.(4) Recently, ivabradine, an anti-anginal and anti-ischemic agent, have been introduced in the treatment of HF. "Ivabradine selectively and specifically inhibits the If current in the sino-atrial (SA) node, and provides pure heart rate reduction without altering other cardiovascular parameters." (5)

Studies have shown that ivabradine might improve the management of subjects with HF. However, only a few trials have explored the beneficial impacts of ivabradine in HF, and the results have not been consistent across several clinical outcomes. Also, the safety of ivabradine in subjects with HF remains unclear. So, our goal is to comprehensively evaluate the literature and determine the relative efficacy and safety of the of ivabradine in subjects with HF. Our long-term goal is to gain a better understanding of the role that ivabradine can provide to subjects with HF, especially those not able to tolerate beta-blockers. We propose the following specific aims to evaluate the efficacy of ivabradine compared to control in subjects with HF on objective and patient-reported outcome measures used in HF management and determine the safety of ivabradine compared to control in subjects with HF with or without low ejection fraction.

2. Research Design and Methods section

2.1 Data Sources and Search

A systematic literature search performed in Medline, Embase, Ovid and the Cochrane Central Register of Controlled Trials. We did the search through reference lists of eligible articles and related existing systematic reviews. To identify any unpublished studies, we searched conference proceedings of the American Heart Association/American Stroke Association, American Diabetes Association, European Society of Cardiology Congress, and World Congress of Cardiology. We developed a search strategy that includes keywords appropriate to study design (randomized, controlled trial), the disease of interest (heart failure), and the intervention of interest (Ivabradine). A list of these keywords is available in (Appendix Table 1 available at www.annals.org). Search terms explored and

properly modified according to each database we were using. Searching was limited to humans, but no language restriction was applied. This systematic review was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.

2.2 Study Selection

Two reviewers were assigned for identified and reviewed all included studies of randomized controlled trials of Ivabradine if they fulfilled the following criteria (Appendix Table 2): comparison of Ivabradine either as monotherapy or add-on therapy to other heart failure treatment with control in patients with heart failure with or without low ejection fraction; at any age and without any dose or follow-up duration restriction; inclusion of at least 1 pre-specified outcome measure. We excluded any non-randomized trials and studies with a significant risk of bias as evaluated by the methods suggested by the Cochrane Collaboration. Our primary outcome was: all- causes mortality, cardiovascular mortality, or hospital admission for new onset or even worsening of heart failure. Secondary outcomes include resting HR from baseline until the end of follow-up, LVEF, and adverse events. Two investigators were independently screen titles and abstracts of the citations for relevant articles by using Abstrackr (Brown University). Also, the same two investigators recovered and rescreen all full-text of relevant articles. Any discrepancies were resolved by consensus.

2.3 Data Extraction and Quality Assessment

Two investigators assigned independently for extraction of data from each eligible study, and any disagreement during data abstraction was recognized and solved consensus. We extracted data on study design and methodology, patient characteristics, interventions, comparators, outcome measures, and adverse events by using a standardized data collection form. The methodological quality of the qualified studies evaluated with" the Cochrane Collaboration's risk-of-bias tool for randomized trials" (Appendix Table 3, available at www.annals.org). Thirteen risk-of-bias items are included in this tool. A decision for the first 7 items (sequence generation, allocation concealment, patients' blinding, caregivers' blinding, outcome assessors' blinding, attrition, and selective outcome reporting) assigned by "low," "high," or "unclear", while the judgment of the remainder (intention-to-treat analysis, baseline balance, co-intervention similarity, compliance, and presence of other biases) assigned by "yes," "no," or "unsure".

After evaluating all risk-of-bias items, to each RCT, we assigned good, fair, or poor as a grade for quality. We considered studies with poor quality if they have one of the following: lack of blinding, differential loss to follow-up, imbalances in the baseline, or lack of a washout period in the crossover studies. Studies that described enough details about the blinding (for example double-blinding and if they used identical capsules) had a low chance of bias while studies with inadequate reporting (such as, reporting of an expression, for example, "double-blind") had an unclear

chance of bias. We looked at the extents of withdrawals in each group by using the chi-square test and for a P value, less than 0.1 will be were used to show the differential loss of follow-up.

2.4 Data Synthesis and Analysis

We assessed the treatment effect on binary outcomes by using the risk ratio (RR) with the corresponding 95% confidence intervals (CIs). On the other hand, for continuous outcomes, the difference in mean changes from baseline between ivabradine and control was calculated for each study included. We estimated the summary treatment effects by using random-effects model that is determined by the empirical Bayes method. We calculated a summary RR, and mean difference, between Ivabradine and control, where suitable. We assessed statistical heterogeneity by using Cochran's Q and I2 statistics. Heterogeneity were classified as I2 values Low <25%, moderate 25% to 50%, and high-level >50%.

3. RESULTS

3.1 Literature Search

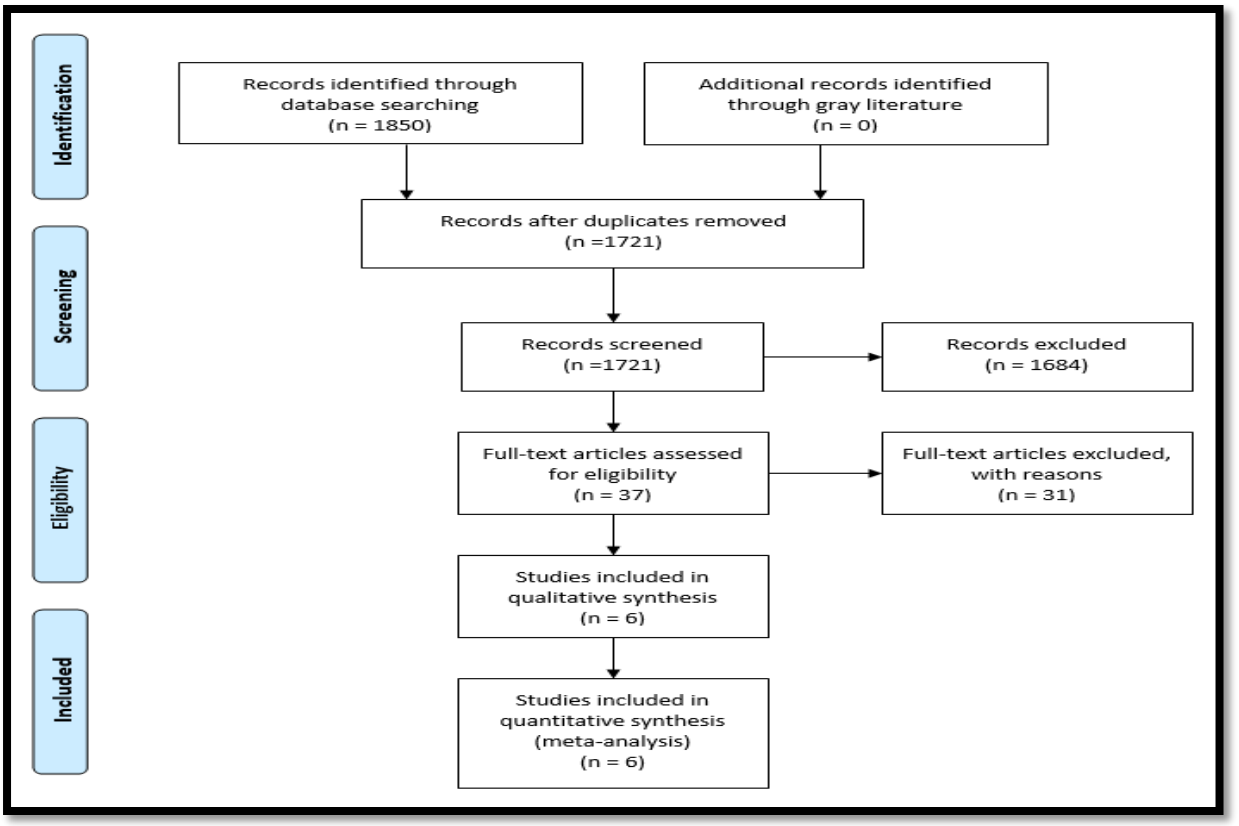

Figure 1: PRISMA flow diagram of evidence search and selection

Figure 1 summarizes our search yield. We screened 1721citations.A total of 37 articles were retrieved for full-text review; of those, 6 RCTs met our inclusion criteria with 17886 patients included in the systematic review and meta-analysis.

3.2 Trial Characteristics

Table 1 summarizes the characteristics of the included RCTs, which were published between 2008 and 2017. Six RCTs met our inclusion criteria. The Six studies (6),(7),(8),(9),(10),(11) included adult patients with mean age between 60 to 73 years. Two studies included heart failure with preserved ejection fraction, and four studies included heart failure patients with reduced ejection fraction, of these two were with coronary artery disease. The main exclusion criteria were all patients with recent myocardial infraction within the previous six months. Overall, 17886 patients were randomly assigned to receive either Ivabradine or control. Beta-blockers, Aspirin, Diuretics, Angiotensin-converting enzyme(ACEI) or Angiotensin II receptor blockers (ARBs) were used as concomitant treatments by all patients in five studies, whereas the sixth study used Abciximab in addition to nitrates, aspirin, clopidogrel, statin and ACEI as concurrent treatment. Mean HR at baseline was between 71bpm and 92 bpm and mean ejection fraction at baseline was between 29% and 69%. We included six RCT, and four RCTs were multicenter. Treatment duration ranged from 7 days to 32 months.

Table 1: Trials characteristics

Study, Year	Population	Treatment Groups	Patients, n	Age, y	EF, %	Treatment Duration
BEAUTIFUL, 2008 [6]	CAD, EF<40%	Ivabradine	5479	65.3	32.4	24 months
		Placebo	5438	65	32.3	
Fasullo, 2009 [7]	STEMI, EF<50%	Ivabradine	78	61.6	41.3	2 months
		Placebo	75	62.1	42.5	
SHIFT, 2010 [8]	HF, EF≤35%	Ivabradine	3241	60.7	29	32 months
		Placebo	3264	60.1	29	
Kosmala,2013[9]	HF,EF ≥50%	Ivabradine	30	66.5	67	7 days
		Placebo	31	68	69	
ETHIC-AHF, 2016 [10]	HF, EF< 40 %	Ivabradine	33	66.2	29.8	12 months
		control	38	67.7	29.9	
EDIFY,2017 [11]	HF, EF ≥45%	Ivabradine	95	72	60	8 months
		Placebo	84	73	61	

3.3 Assessment of Risk of Bias

Six RCTs [6-11] were included and five RCTs assessed to be high quality. Generation of randomized sequence, allocation concealment and double blinding were reported clearly and intention to treat analysis were used in five trials. There was a co-interventions similarity in all trials.

3.4 Mortality and Cardiovascular End Points

Six[6-11] and three trials respectively, reported the effect of ivabradine compared with control on mortality and cardiovascular mortality. Ivabradine did not always lower all-cause mortality (summary RR,0.97 [CI, 0.89 to 1.07]; I^2 =11%) (figure 2) and

cardiovascular mortality (summary RR,1.01 [CI, 0.82 to 1.24]; I^2 =71%) (*Appendix figure 1*) and four trials reported the effect of ivabradine compared with control on hospital readmission (summary RR,0.84[CI, 0.66 to 1.07]; I^2 =73%). (figure 3). A mean difference in change from baseline in percentage of ejection fraction (EF) was calculated for five trials, and overall, patients treated with ivabradine had an increase in EF by 3 % as compared with control (summary RR, 3.27 [CI, 2.08 to 4.45]; I^2 =26%) (figure 4). A mean difference in change from baseline in percentage of heart rate was calculated for four trials, and there was no statistically significant difference between ivabradine and control (summary RR, 0.59 [CI, -0.08 to 1.26]; I^2 =93%) (*Appendix figure 2*).

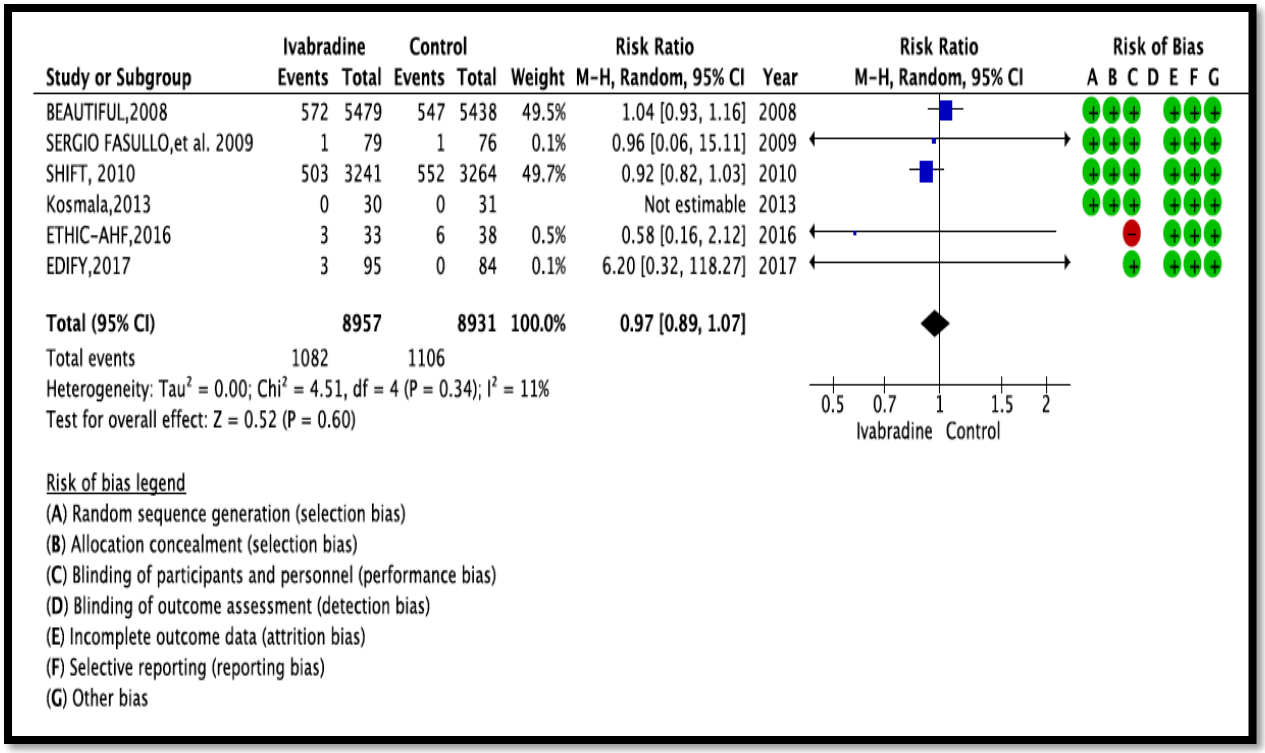

Figure 2: Summary of Relative Risk of Mortality

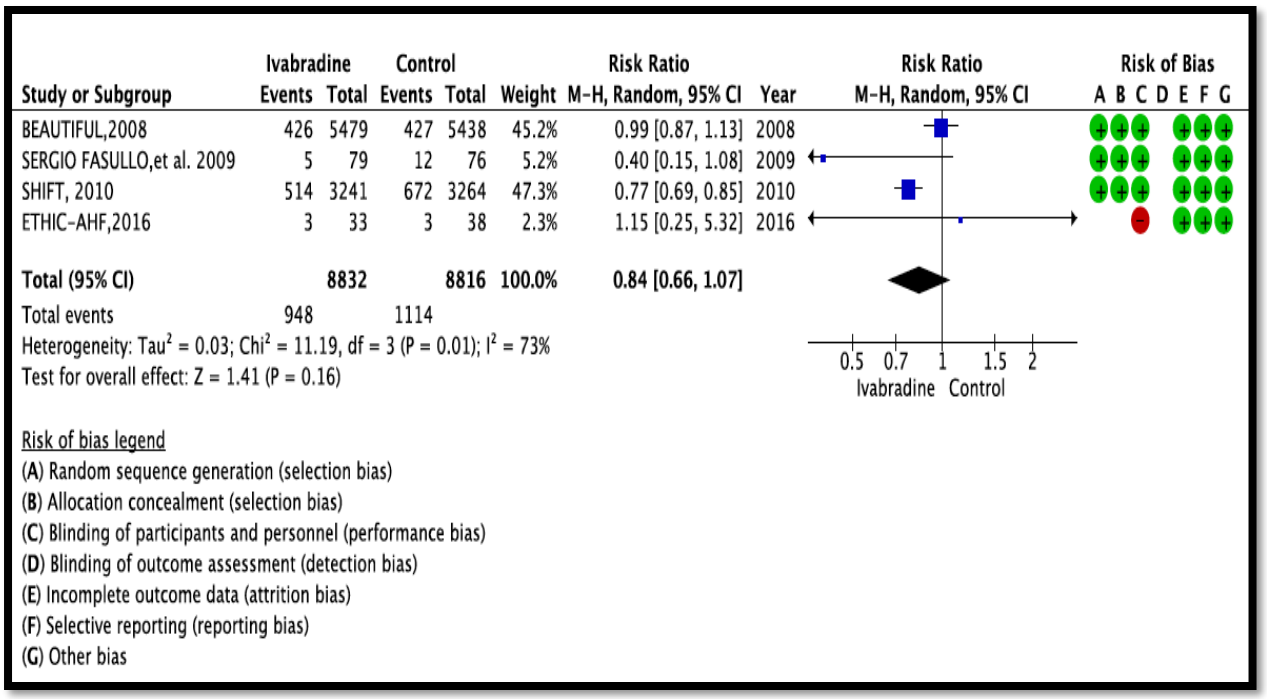

Figure 3: Summary of Relative Risk of Hospital Readmission

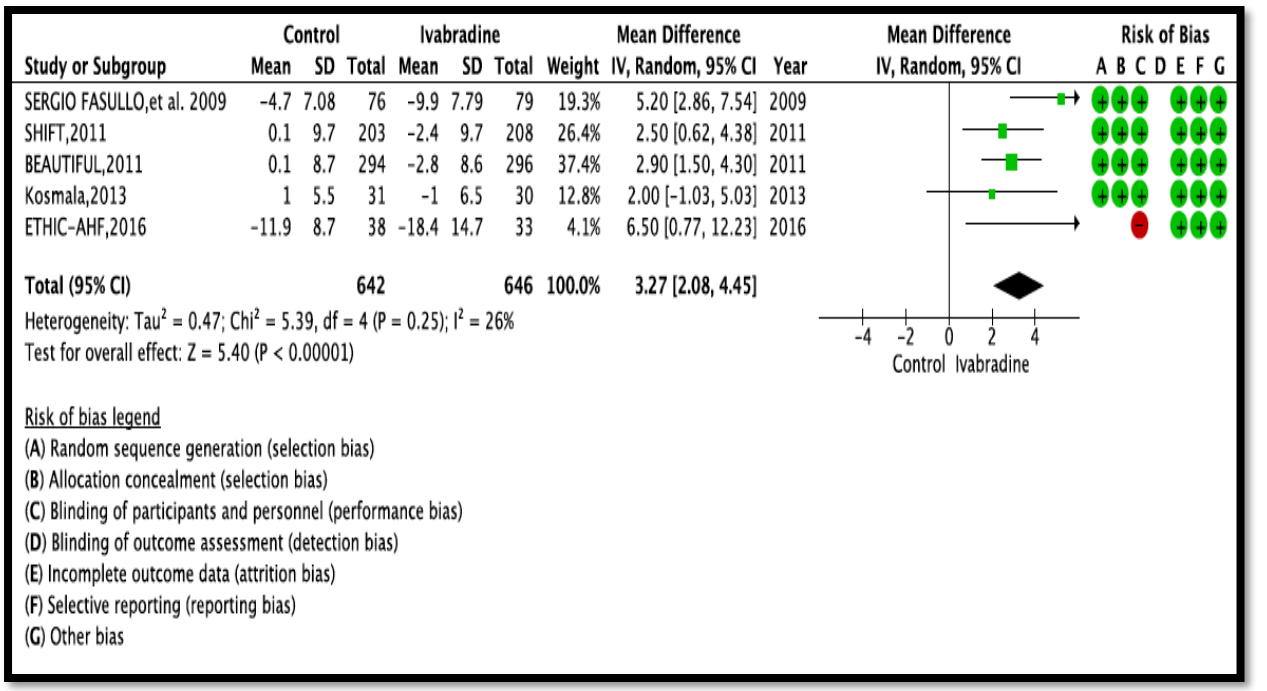

Figure 4: Pre and Post Treatment Mean Difference of EF %

3.5 Safety End Points

Six [6-11] and four trials respectively, reported the incidence of all adverse events and ischemic events of ivabradine compared with control. Ivabradine did not always increase the incidence of all adverse event (summary RR,0.97[CI, 0.91 to 1.02]; I^2 =23%) (figure 5), and ischemic events (summary RR,0.95[CI, 0.89 to 1.02];I^2 =0%) (*Appendix figure 3*).However , the incidence of bradycardia, phosphenes and blurred vision as adverse events were reported in three trials and were significantly higher with ivabradine by 4 and 5 times as compared with control (summary RR,5.04[CI, 2.49 to 10.18];I^2 =85%)(figure 6) and (summary RR,4.08[CI, 2.80 to 5.95];I^2 =0%) (figure 7) respectively. The number of withdrawal patients from six trials in ivabradine were higher compared with control (summary RR,1.12[CI, 1.03 to 1.22] ;I^2 =0%) (figure 8), and the main reasons for withdrawal from ivabradine were symptomatic and asymptomatic bradycardia and phosphenes which are the main adverse events of ivabradine .

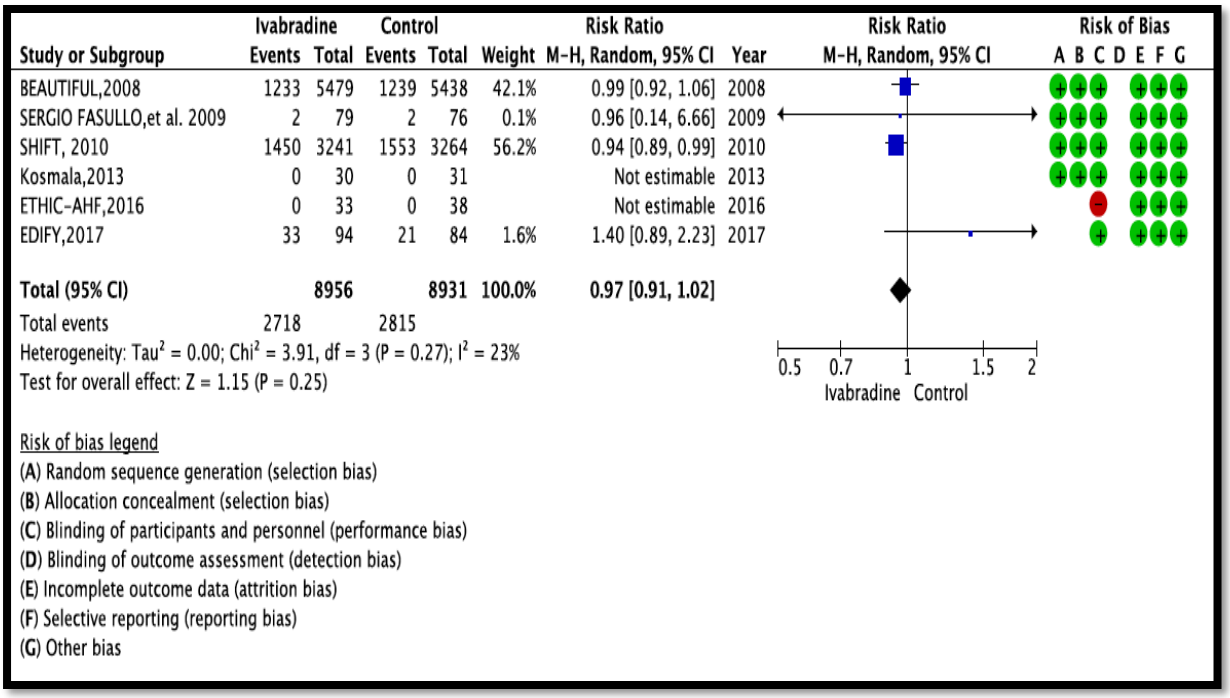

Figure 5: Summary of Relative Risk of All Adverse Events

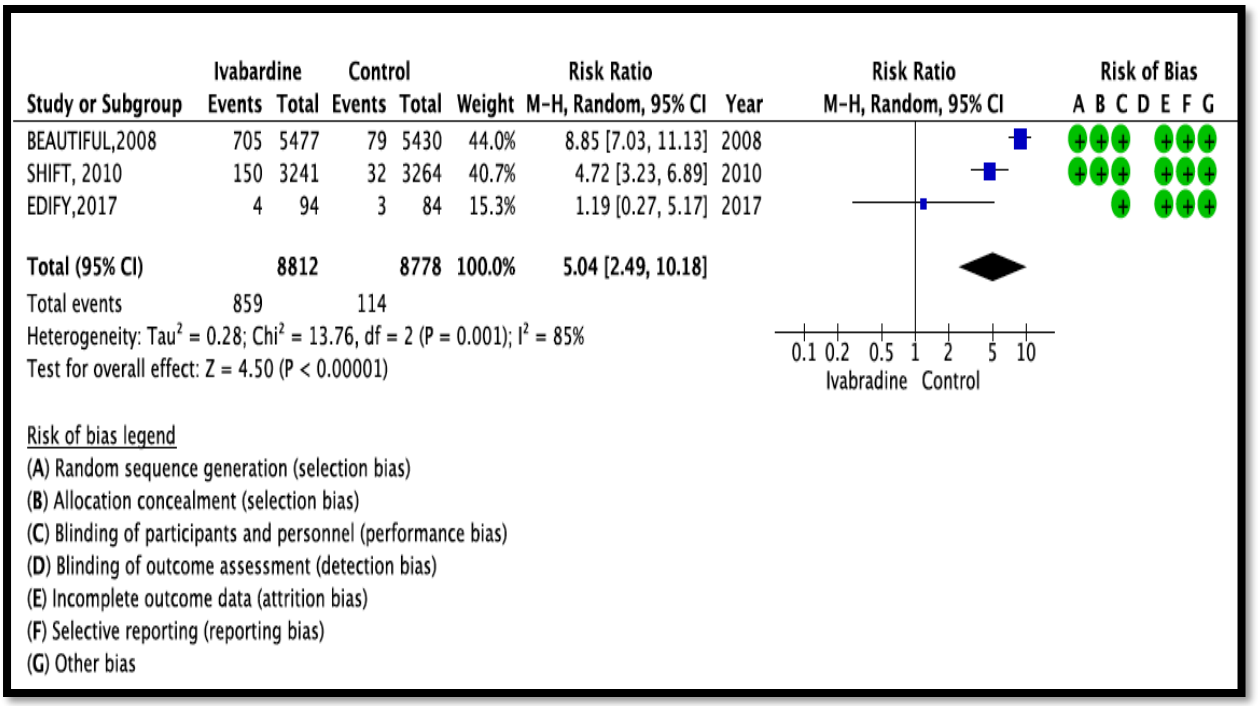

Figure 6: Summary of Relative Risk of bradycardia

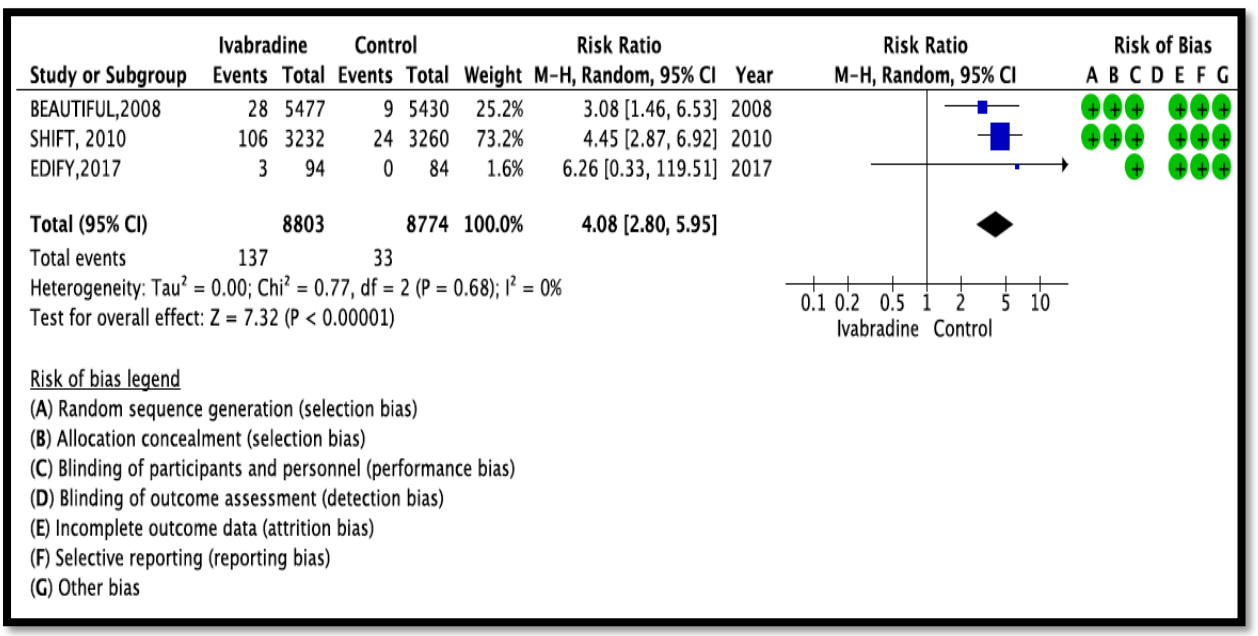

Figure 7: Summary of Relative Risk of phosphenes and blurred vision

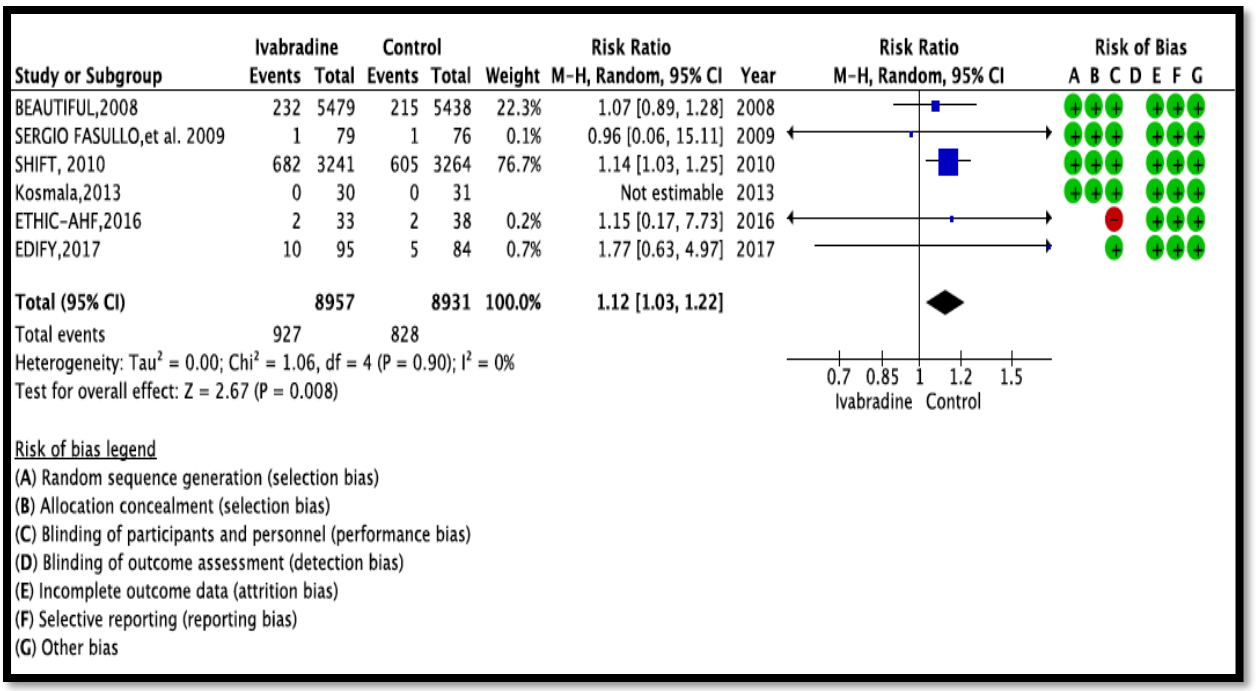

Figure 8: Summary of Relative Risk of withdrawal

4. Discussion

In our study we included RCTs met our inclusion criteria, These RCTs included heart failure patients with reduced and preserved ejection fraction and coronary artery disease with reduced ejection fraction. Overall, 17886 patients were randomly assigned to receive either ivabradine or control with treatment duration ranged from 7 days to 32 months. Ivabradine increased EF by 3% compared with control. However, ivabradine did not lower all-cause mortality or hospital readmission, and there was no significant difference reduction in the mean heart rate from baseline to the follow up compared with control. Ivabradine did not increase the incidence of all adverse events or ischemic events. But the incidence of phosphenes, blurred vision and bradycardia were higher with ivabradine by 4 and 5 times as compared with control. Finally, the number of withdrawal patients from all the included trials were higher in ivabradine as compared with control. Phosphenes, blurred vision and bradycardia were the main reasons for withdrawal.

In a BEAUTIFUL study [(7)] 10917 eligible subjects had coronary artery disease and a left ventricular EF of less than 40% randomly assigned to either ivabradine or placebo. Ivabradine had no significant effect on cardiovascular death, any hospital admission for new onset or worsening heart failure. However, ivabradine was associated with a reduction in the admission to hospital for myocardial infarction

and coronary revascularization. Furthermore, in subjects with baseline heart ≥70 beats/min ivabradine had a significant reduction in the risk of hospitalization for the myocardial infraction by 36%, the risk of coronary revascularization by 30% and coronary events by 22%. In the SHIFT trial [(6)]. 6558 participants were randomly assigned to either ivabradine or placebo. There was an 18% reduction in cardiovascular death or hospital admission for worsening heart failure in subjects who received ivabradine, compared to placebo. Death from HF and most cardiovascular endpoints were significantly reduced in patients treated with ivabradine. This study shows the importance of ivabradine in reducing the heart rate which will improve the clinical outcomes of HF. In 2009, a randomized, double-blind trial [(8)] was conducted to assess the tolerability and the effect of ivabradine versus metoprolol after 30 days in patients with ST-segment elevation myocardial infarction (STEMI) and reperfused by percutaneous coronary intervention (PCI) with LV ejection fraction (EF) < 50%. A total of 155 patients we randomly allocated to receive either metoprolol or ivabradine for 12 months after PCI. Ivabradine as compared to metoprolol, showed a significant reduction after 60 days follow up in readmission for heart failure, the end-systolic volume (ESV) and end-diastolic volume (EDV), (P=.047, P<.0001 and P<.0001, respectively). In addition, a significant increase in EF, P<.0001. However, there was no significant difference in heart rate(HR) reduction between both groups as both showed significant HR reduction between baseline and after 60 days (91± 6 vs. 66±7 and 92±7 vs. 65± 6 beats/min, respectively, P<.0001).In 2013, a randomized, double-blind trial[(9)],was done to assess the effect of ivabradine on exercise capacity and left ventricular filling in patients with HF with HFpEF, 61 patients randomly assigned to either ivabradine or placebo for 7 days, and they found that the short time treatment with ivabradine showed an improvement on exercise capacity and left ventricular filling pressure . In ETHIC-AHF trial[(10)],71 hospitalized patients with HF and HFrEF randomly assigned to either ivabradine and beta-blockers versus beta-blockers alone and followed for 1 year, and they found that early co-administration of ivabradine and beta blocker produced significant improvement in both HR and left ventricular systolic function as compared with beta blocker alone. In EDIFY, [(11)] a recent randomized, double-blind, placebo control trial, 179 patients randomly allocated to either ivabradine or placebo, to assess if HR reduction could improve the cardiac function among HF patients with HFpEF. After following the patients for 8 months they found that among HFpEF patients, HR reduction in the ivabradine group did not improve cardiac outcomes.

In the recent years, there has been an increased number of studies assessing the efficacy and safety of ivabradine in patients with HF with or without low EF. In many international, especially European guidelines, ivabradine is recommended as part of the management of HF. [(2)] In the most current Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, the role of ivabradine for HF management and how it is fit is still unclear, it is only fit on HF on maximum therapy. The guideline says ivabradine has an effect on reducing HF hospitalization which mainly based on SHIFT trial.

However, in our study, we did not find it significant with ivabradine. Furthermore, the use of ivabradine has not been widely adopted yet but many clinicians. This could be due to the high cost of ivabradine, with the limited, and somewhat conflicting evidence on its efficacy and safety. (13-16)

In our meta-analysis some of the limitations at the systematic review level and the other associated with the included trials. Outcomes may be reported differently by each study, at different time points, and some outcomes were not reported. Due to the small number of randomized controlled trials on ivabradine in HF, we had limited data to perform subgroup or sensitivity analyses on different types of HF.

5. Conclusion

This systematic review and meta-analysis investigate that administration of ivabradine to adults with heart failure with or without low ejection fraction significantly improved the ejection fraction. However, there was no significant impact with ivabradine in mortality, cardiovascular mortality, re-admission rates and the mean difference in change of heart rate. Ivabradine did not always increase the incidence of all adverse event or ischemic events. But the incidence of bradycardia, phosphenes and blurred vision as adverse events were higher with ivabradine as compared with control and these were the main reasons for withdrawal which was higher with ivabradine group compared with control. This may indicate a poorer tolerability profile. Our finding suggests that ivabradine may be efficacious and safe as a treatment in its usual doses in adults with heart failure with or without low ejection fraction. Further studies are needed to confirm these results and during this time more studies might show up.

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Appendices

Appendix Table 1. Search strategy

1. Randomized controlled trial.pt.
2. Controlled clinical trial.pt.
3. randomized controlled trials/
4. Random Allocation/
5. Double-blind Method/
6. Single-Blind Method/
7. clinical trial.pt
8. Clinical Trials.mp. or exp Clinical Trials/
9. (clinic$ adj25 trial$).tw.
10. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
11. Placebos/
12. placebo$.tw.
13. random$.tw.
14. trial$.tw.
15. (randomized control trial or clinical control trial).sd.
16. (latin adj square).tw.
17. Comparative Study.tw. or Comparative Study.pt.
18. exp Evaluation studies/
19. Follow-Up Studies/
20. Prospective Studies/
21. (control$ or prospectiv$ or volunteer$).tw.
22. Cross-Over Studies/
23. or/1-22
24. (ivabradine).af.
25. (Procoralan or Corlentor or Coraxan or Coralan or Procoralan or Coralan).af.
26. S-16257 or S-15544 or S-16257-2 or S-16260.af.

27. Selective inhibitor of cardiac If channels.af.
28. or/24-27
29. Heart failure.af.
30. Low ejection fraction or Left ventricular ejection fraction (LVEF) or reduced ejection fraction (HFrEF) or Preserved ejection fraction (HFpEF) .af.
31. 29 or 30

Appendix Table 2. Criteria for inclusion/exclusion of studies in the review

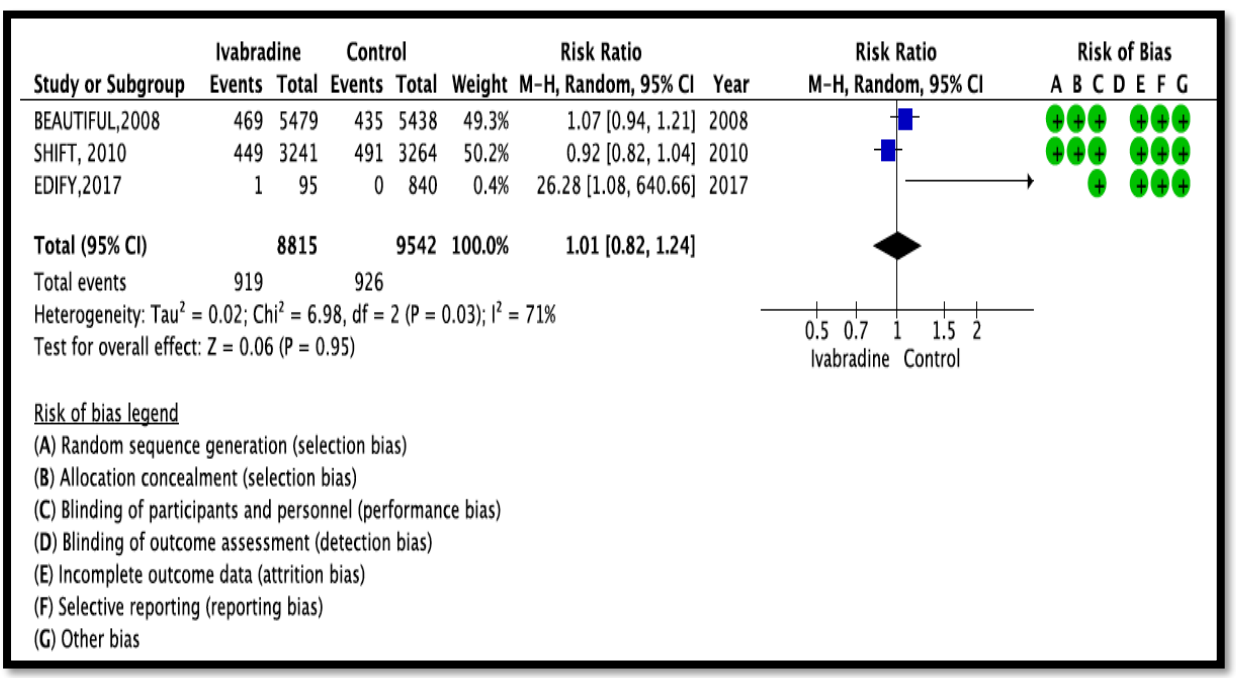
	Description	Comments
Population	All Heart failure patients with or without low ejection fraction	No age restriction will be applied
Intervention	Ivabradine	We plan to include studies on ivabradine alone or in combination with other agents for heart failure management
Comparator	control	Either control alone or in combination with other agents for heart failure management
Outcomes	Benefits: Primary outcomes: all- cause mortality, cardiovascular mortality, cardiac death, admission to hospital for new onset or worsening heart failure. Secondary outcomes: resting HR from baseline till end of follow-up, change in NYHA functional class, LVEF, and concentrations of plasma B-type natriuretic peptide (BNP)	
	Harms: Any adverse drug reactions	
Study Design	Randomized Controlled Double-blind Trials	non-inferiority studies

Appendix Table 3. Risk-of-Bias Items Assessed for Randomized, Controlled Trials

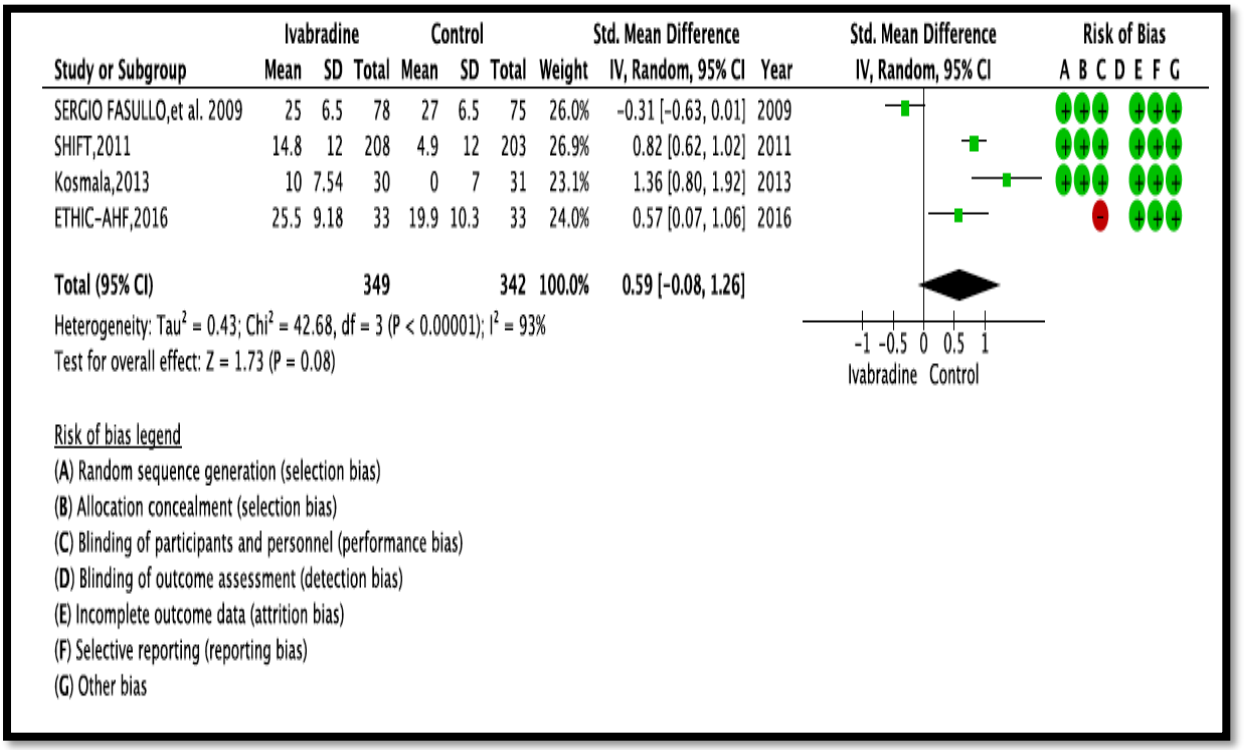
1. What is the risk of selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence? [Low, Unclear, High]
2. What is the risk of selection bias (biased allocation of interventions) due to inadequate concealment of allocations before assignment? [Low, Unclear, High]
3. For each main outcome or class of outcomes, what is the risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study (lack of study participant and personnel blinding)? [Low, Unclear, High]
4. Was the care provider blinded to the intervention? [Low, Unclear, High]
5. For each main outcome or class of outcomes, what is the risk of detection bias due to knowledge of the allocated interventions by outcome assessment (lack of outcome assessor blinding)? [Low, Unclear, High]
6. For each main outcome or class of outcomes, what is the risk of attrition bias due to amount, nature, or handling of incomplete outcome data? [Low, Unclear, High]
7. What is the risk of reporting bias due to selective outcome reporting? [Low, Unclear, High]
8. Were all randomized participants analyzed in the group to which they were allocated? [Yes, No, Unsure]
9. Were the groups similar at baseline regarding the most important prognostic indicators? [Yes, No, Unsure]
10. Were co-interventions avoided or similar? [Yes, No, Unsure]
11. Was the compliance acceptable in all groups? [Yes, No, Unsure]
12. Was the timing of the outcome assessment similar in all groups? [Yes, No, Unsure]
13. Are there other risks of bias? [Yes, No]

Appendix Table 4: Mean heart rate at baseline and follow-up

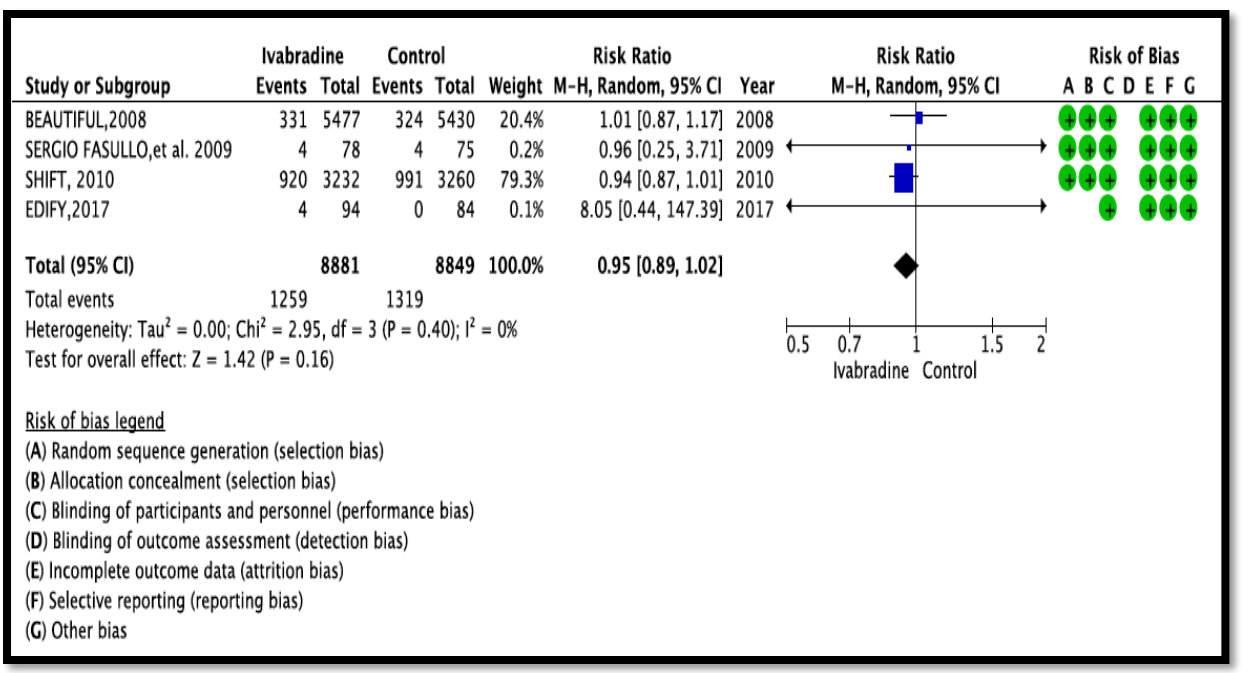
Name of Study	Fox, 2008		Fasullo, 2009		Swedberg, 2010	
Group	Baseline	Follow-up (24 months)	Baseline	Follow-up (2 months)	Baseline	Follow-up (32 months)
Ivabradine	72 bpm	64 bpm	91 bpm	66 bpm	80 bpm	67 bpm
Control group	72 bpm	69 bpm	92 bpm	65 pbm	80 bpm	75 bpm



Appendix Figure 1. Summary of Relative Risk of Cardiovascular Mortality



Appendix Figure 2. Pre and Post Treatment Mean Difference of HR



Appendix Figure 3. Summary of Relative Risk of ischemic events