

# Effect of ivabradine in heart failure: a meta-analysis of heart failure patients with reduced versus preserved ejection fraction

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**Abstract:** In clinical trials of heart failure reduced ejection fraction (HFrEF), ivabradine seemed to be an effective heart rate lowering agent associated with lower risk of cardiovascular death. In contrast, ivabradine failed to improve cardiovascular outcomes in heart failure preserved ejection fraction (HFpEF) despite the significant effect on heart rate. This meta-analysis is the first to compare the effects of ivabradine on heart rate and mortality parameters in HFpEF versus HFrEF. We screened three databases: PubMed, Embase, and Cochrane Library. The outcomes of these studies were mortality, reduction in heart rate, and left ventricular function improvement. We compared the efficacy of ivabradine treatment in HFpEF versus HFrEF. Heart rate analysis of pooled data showed decrease in both HFrEF (−17.646 beats/min) and HFpEF (−11.434 beats/min), and a tendency to have stronger bradycardic effect in HFrEF ( $p = 0.094$ ) in randomized clinical trials. Left ventricular ejection fraction analysis revealed significant improvement in HFrEF (5.936, 95% CI: [4.199–7.672],  $p < 0.001$ ) when compared with placebo ( $p < 0.001$ ). We found that ivabradine significantly improves left ventricular performance in HFrEF, at the same time it exerts a tendency to have improved bradycardic effect in HFrEF. These disparate effects of ivabradine and the higher prevalence of non-cardiac comorbidities in HFpEF may explain the observed beneficial effects in HFrEF and the unchanged outcomes in HFpEF patients after ivabradine treatment.

**Key words:** heart failure, heart failure preserved ejection fraction, heart failure reduced ejection fraction, ivabradine, heart rate, left ventricular function.

**Résumé :** Dans les essais cliniques portant sur l'insuffisance cardiaque à fraction d'éjection réduite (HFrEF), l'ivabradine semblait constituer un agent efficace pour abaisser la fréquence cardiaque et associé avec une réduction du risque de mort cardiovasculaire. En revanche, l'ivabradine n'est pas parvenue à entraîner une amélioration des résultats sur le plan cardiovasculaire dans l'insuffisance cardiaque à fraction d'éjection préservée (HFpEF), en dépit d'un effet notable sur la fréquence cardiaque. La présente méta-analyse est la première à présenter une comparaison entre les effets de l'ivabradine sur la fréquence cardiaque et les paramètres de la mortalité dans l'HFpEF par rapport à l'HFrEF. Nous avons passé au crible trois bases de données (PubMed, Embase, Cochrane Library). Les paramètres de l'étude étaient la mortalité, la diminution de la fréquence cardiaque et l'amélioration de la fonction ventriculaire gauche. Nous avons comparé l'efficacité du traitement par l'ivabradine dans l'HFpEF par rapport à l'HFrEF. PROSPERO: CRD42019141406. L'analyse de données de fréquence cardiaque regroupées a montré une diminution dans l'HFrEF (−17,646 battements/min) comme dans l'HFpEF (−11,434 battements/min), ainsi qu'une tendance vers un effet bradycardisant plus marqué dans l'HFrEF ( $p = 0.094$ ) dans le cadre d'essais avec répartition aléatoire. L'étude de la fraction d'éjection ventriculaire gauche a révélé une amélioration marquée dans l'HFrEF (5,936, IC à 95 % : [4,199–7,672],  $p < 0,001$ ), ainsi que par rapport au placebo ( $p < 0,001$ ). Nous avons observé que l'ivabradine entraîne une amélioration notable de la performance du ventricule gauche dans l'HFrEF, et en même temps une tendance vers une amélioration de l'effet bradycardisant dans l'HFrEF. Ces effets disparates de l'ivabradine et une augmentation de la fréquence des comorbidités non cardiaques dans l'HFpEF pourraient expliquer les bienfaits observés dans l'HFrEF de même que les résultats inchangés après un traitement par l'ivabradine chez les patients atteints d'HFpEF. [Traduit par la Rédaction]

**Mots-clés :** insuffisance cardiaque, insuffisance cardiaque à fraction d'éjection préservée, insuffisance cardiaque à fraction d'éjection réduite, ivabradine, fréquence cardiaque, fonction ventriculaire gauche.

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## 1. Introduction

Chronic heart failure (HF) is a common, complex, and progressive cardiovascular clinical syndrome affecting millions of people worldwide, caused by several conditions including coronary artery disease, myocardial infarction, systemic and pulmonary hypertension, valvular heart diseases, cardiomyopathies, and congenital cardiovascular disorders (Inamdar and Inamdar 2016). These conditions result in the impairment of left ventricular (LV) filling or ejection of blood, causing inadequate perfusion and oxygenation to the tissues (Yancy et al. 2013). HF is always accompanied with serious structural and electrical remodeling causing myocardial hypertrophy, fibrosis, and alterations in different cardiac ion channel protein expression levels (Wang et al. 2010). According to the impairment of LV function, HF is now classified with preserved ejection fraction (HFpEF), with mid-range ejection fraction (HFmrEF) and with reduced ejection fraction (HFrEF) (Ponikowski et al. 2016). HFrEF is referred to as systolic HF, resulting from the impairment of LV function, thus reduced ejection of blood, causing  $\leq 40\%$  LV ejection fraction (LVEF). HFmrEF represents a 'grey area' including patients with LVEF in the range of 40%–49%, characterized by signs of HF with modest LV systolic dysfunction and with features of diastolic dysfunction. HFpEF is known as diastolic HF with  $\geq 50\%$  LVEF, however, recent studies suggest more heterogeneous pathophysiology including the stiffening of ventricular tissue, atrial dysfunction, ventricular systolic and diastolic reserve abnormalities, or endothelial dysfunction (Borlaug 2014). In general, all types of HF are a subject of structural and functional remodeling, however, these changes may differ in HFrEF versus HFpEF.

Heart rate is a modifiable risk factor with prognostic value in HF and increased heart rate is associated with increased risk of cardiovascular mortality and serious life-long cardiovascular diseases (Palatini and Julius 2004; Bohm et al. 2010). The Framingham study demonstrated the association between increased heart rate and increased cardiovascular risk showing that both the healthy population and patients with HF were subjected to a higher risk in mortality outcomes with increased heart rate (Kannel et al. 1987).

Ivabradine (Procoralan) is a heart rate lowering drug that inhibits the pacemaker ("funny") current ( $I_f$ ) (DiFrancesco 1993) and was first known as an antianginal agent in the treatment of chronic stable angina pectoris (Borer et al. 2003). In clinical trials involving HFrEF patients, ivabradine seemed to be a selective and effective heart rate lowering agent, associated with lower risk of cardiovascular death and hospital readmissions, emphasizing that heart rate reduction should be an important target in the therapy of HF (Swedberg et al. 2010). In clinical conditions, the European Society of Cardiology (ESC) guidelines recommend ivabradine treatment to reduce the risk of cardiovascular death and HF hospitalization in symptomatic patients with LVEF  $\leq 35\%$  in sinus rhythm with resting heart rate at 70 bpm or higher, in spite of treatment with an evidence-based dose of  $\beta$ -blocker, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker (Ponikowski et al. 2016). It should also be considered in symptomatic patients to whom the  $\beta$ -blockers are contraindicated or not tolerated (Ponikowski et al. 2016). It is important to note that ivabradine was found to increase the risk of atrial fibrillation (Tanboğa et al. 2016). In the meta-analysis including eight randomized clinical trials (RCTs), ivabradine increased the relative risk of atrial fibrillation by 24% (Tanboğa et al. 2016). In a HFpEF rabbit model, ivabradine was able to reduce cardiac fibrosis (Busseuil et al. 2010) and also improved LV systolic and diastolic function in mouse (Reil et al. 2013); however, in human HFpEF patients, ivabradine also decreased the heart rate, but it was not associated with improvements in LV relaxation and filling pressure (Komajda et al. 2017). As ivabradine failed to improve outcomes in a clinical trial of HFpEF, heart rate reduction with ivabradine may not be beneficial in HFpEF (Komajda et al. 2017). The exact

reason of different actions and the underlying mechanism is not understood. Our hypothesis is that the different stages and progression of electrical remodeling between HFpEF and HFrEF may explain this discrepancy, however, there is no study directly comparing the ivabradine effects between HFpEF and HFrEF thus far. This meta-analysis is the first to investigate the effect of ivabradine in HFpEF compared to HFrEF patients focusing on HF hospitalization, mortality, and cardiovascular outcome parameters, particularly heart rate reduction and LV function in HFrEF versus HFpEF.

## 2. Materials and methods

The protocol of this meta-analysis was registered a priori on the international prospective register of systematic reviews (PROSPERO) database under CRD42019141406.

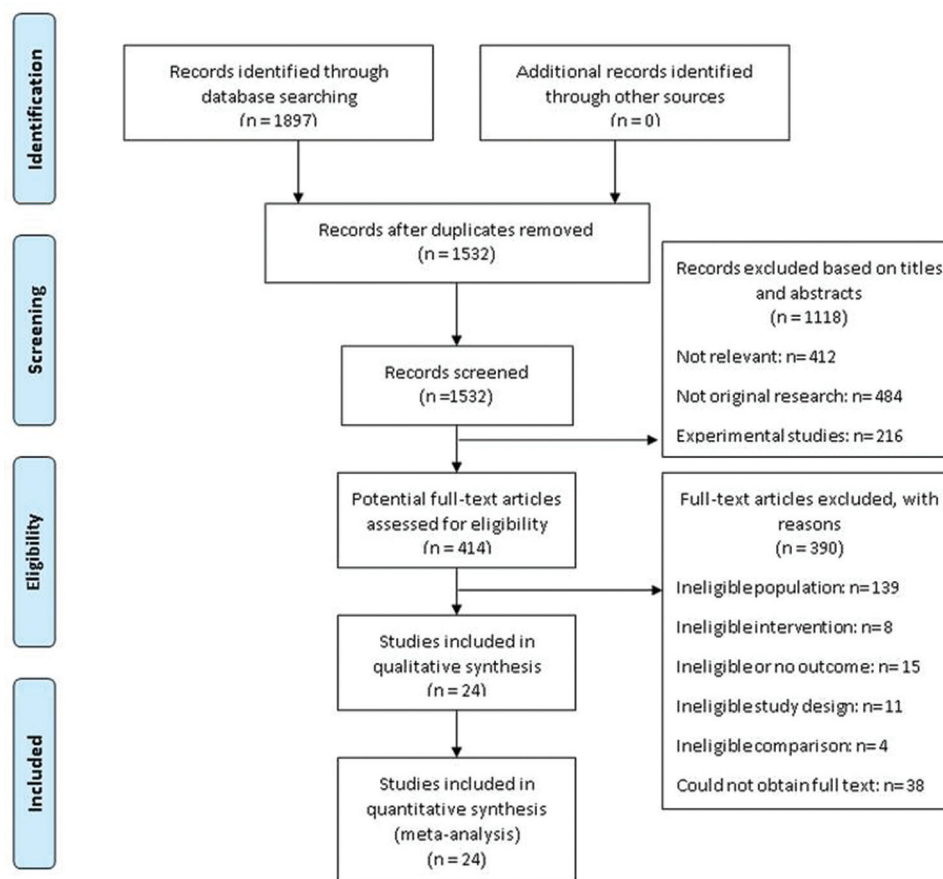
### 2.1. Search

A systematic electronic search was conducted up to 4th of April 2019 in Medline, Embase, and Cochrane Library databases for relevant publications reporting cardiovascular outcomes after ivabradine treatment in HF, without any language restrictions or filters, and was re-conducted at the end of 2020 to avoid omission of recent publications, though none were found. To perform a precise search in the databases the following search term was used: (ivabradine OR procoralan) AND (heart failure OR haemodynamic OR ejection fraction OR heart function OR reduced cardiac function OR ventricular dysfunction OR cardiac failure OR heart decompensation OR myocardial failure). The search was performed using the following PICO format: (P) HF patients treated with ivabradine, (I-C) HFrEF and HFpEF, (O) cardiovascular outcomes (heart rate, LVEF). The reference lists and citations of relevant publications were also checked manually for additional eligible studies. PROSPERO was checked for ongoing and completed meta-analyses and systematic reviews.

### 2.2. Selection and eligibility

This meta-analysis includes all available randomized or non-randomized, controlled or uncontrolled clinical trials and observational cohort studies conducted to determine the effect of ivabradine in patients with HFrEF or HFpEF. The selection criteria were followed to include all studies involving HFrEF or HFpEF patients where ivabradine was used to reduce cardiovascular symptoms. Enrolled studies should show data for either one or more of the following outcomes: (i) mortality outcomes (hospital readmission for worsening HF, all-cause mortality, cardiovascular mortality), (ii) heart rate reduction or (iii) LVEF improvement. Based on the fact that there is no available study in the literature which includes both types of HF in the same population, we defined two populations (HFrEF and HFpEF) by dividing the publications. Since the new classification and terminology of HF has been introduced in 2016 in the ESC Guidelines (Ponikowski et al. 2016), the studies involved in this meta-analysis could not distinguish HFpEF from HFmrEF. Based on this and on the similarity of the symptoms and diagnostic criteria, we included HFmrEF and HFpEF patients in the same group (for the sake of simplicity we refer this group as HFpEF from here on). As the purpose of this meta-analysis is to compare the effect of ivabradine in HFrEF versus HFpEF patients, this study omits the comparison with placebo (with exception for mortality outcomes), which has been described previously in patients with HFrEF (Hartmann et al. 2018). Studies eligible for inclusion required cardiovascular outcomes measured after ivabradine treatment. Only studies on adults were included. The articles focusing on children or adolescents were excluded. Animal experiments and non-clinical studies were also excluded. Further exclusion criteria were case reports, comments, letters, abstracts, conference abstracts, or ivabradine use in other populations of focus (e.g., stable angina or atrial fibrillation).

**Fig. 1.** PRISMA flow diagram for study selection and inclusion. The initial search identified 1897 articles. After removing the overlapping publications by electronic software and manual methods, 1532 studies were screened first by title and abstract, then by full text. A total of 24 eligible studies met the inclusion criteria of this meta-analysis. [Colour online.]



After the search, all the studies were imported into a reference manager software (EndNote X7, Clarivate Analytics, PA, USA) to remove duplicates by searching for studies with overlapping publication date, author, and (or) title.

After the software controlled duplicate removal, authors checked the remaining publications to remove all the duplicates, which were not detected by the software. Studies were screened against pre-identified eligibility criteria first by title, abstract, and then full text. Each step was done by two authors (N.T. and A.P.) independently, and in the case of disagreement the discrepancy was solved by a third reviewer (N.N.).

### 2.3. Data extraction

Data extraction from the selected articles was also done by two authors independently (N.T. and A.P.). Numerical and texted data were manually entered onto a standardized Excel 2010 sheet (Microsoft Office 365, Microsoft, WA, USA) designed a priori. Data were collected as follows: first author, publication year, study design, countries, number of centers, recruitment period, geographical location, number of patients and basic demographics (age, sex ratio), all the abovementioned mortality, cardiovascular outcome parameters before ivabradine treatment, and the duration of intervention.

### 2.4. Quality assessment

The risk of bias was assessed using the Cochrane risk of bias tool (Higgins 2019) for RCTs, and the Newcastle–Ottawa Scale

(Wells 2013) has been edited to our study design and was used to assess the quality of observational cohort studies. Each RCT was assessed for random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias — all with ratings of low, high, or uncertain risk of bias. Cohort studies were judged by the following items: representativeness of the intervention group, selection of the control group, demonstration that the outcomes of interest were not present at start of the study, comparability of cohorts on the basis of the design or analysis controlled for confounders, assessment of outcome, adequacy of the length of follow-up, and adequacy of quality of follow-up. Each item was rated as ‘high risk’ (equals to 0), ‘low risk’ (equals to 1), or ‘unclear risk’ (equals to 0) corresponding to the definitions.

### 2.5. Statistical analysis

Statistical analysis was performed by experienced biostatisticians (A.S. and A.V.) using Comprehensive Meta-analysis software version 3 (Biostat, Englewood) for all analyses. For continuous outcomes, differences in means with 95% confidence intervals (CIs) and with standard error were calculated. For dichotomous outcomes, event rates with 95% CI were calculated. Statistical significance was defined as  $p < 0.05$ . Pooled estimates were calculated with random effects model by using the DerSimonian–Laird method. Statistics provided in this meta-analysis refer to the comparison between

**Table 1.** Baseline characteristics of the included studies and populations in HFREF group.

Study (year)	Design	Country	Centers	Recruitment period	No. of patients	Male (%)	Age (years)	LVEF (%)	Baseline heart rate (bpm)	Duration – follow up
Swedberg et al. (2010)	RCT	Multiple	677	October 2006–June 2009	3241	76	60.7 (11.2)	29 (5.1)	79.7 (9.5)	1 month, 1 year
Fox et al. (2008)	RCT	Multiple	781	December 2004–December 2006	2699	82	64.8 (8.6)	32 (5.6)	79.1 (8.5)	1, 3, 6 months, 1, 2 year
Darabantiu et al. (2016)	Cohort study	Romania	1	–	50	80	60 (12)	26 (7)	89 (10)	3, 6 months
Tsutsui et al. (2016)	RCT	Japan	73	December 2013–February 2015	62				84 (7.5)	6 weeks
Villacorta et al. (2019)	RCT	Brasil	1	–	10	90	56.2 (13.7)	33 (8.1)	89.1 (13.5)	6 months
Volterrani et al. (2011)	RCT	Italy	1	4 months	41	68	67.2 (9.5)	26.4 (4.7)	79.6 (11.2)	3 months
Hidalgo and Anguita (2017)	RCT	Spain	1	November 2013–April 2015	33	72	66.2 (15.4)	32.9 (8.7)	87.3 (10.6)	1 month
Sarullo et al. (2010)	RCT	Italy	1	–	30	75	52.7 (5.3)	30.6 (6)	75.7 (5)	3 months
Abdel-Salam et al. (2015)	RCT	Egypt	1	July 2011–March 2012	20	50	49.1 (15.7)	34 (4)	85 (12)	3 months
Sargento et al. (2013)	Cohort study	Portugal	1	October 2010–December 2010	25	68	63.8 (6.9)	30 (8)	79.2 (7.1)	3 months
Mansour et al. (2011)	RCT	Egypt	1	–	30	60	47 (13)	32.1 (6.1)	96 (15)	3 months, 1 year
Bagriy et al. (2015)	Cohort study	Ukraine	1	April 2011	33	64	63.2 (12.3)	37.4 (6.3)	82.7 (11.3)	5 months
Sisakian et al. (2016)	RCT	Armenia	1	–	27	81	58.3 (12.2)	30.6 (6.7)	81.3 (not shown)	3 months
Rayan et al. (2011)	Cohort study	Egypt	1	2009	35	60	44.2 (7.5)	32.6 (6.7)	101.5 (14.8)	3 months
Ordu et al. (2015)	Cohort study	Turkey	1	October 2013–August 2014	49	33	65.2 (8.7)	26.4 (5.3)	84.1 (8.8)	6 months
Jirak et al. (2018)	Cohort study	Germany	1	–	50	80	not shown	32.8 (1.7)	79.7 (1.1)	3, 6 months

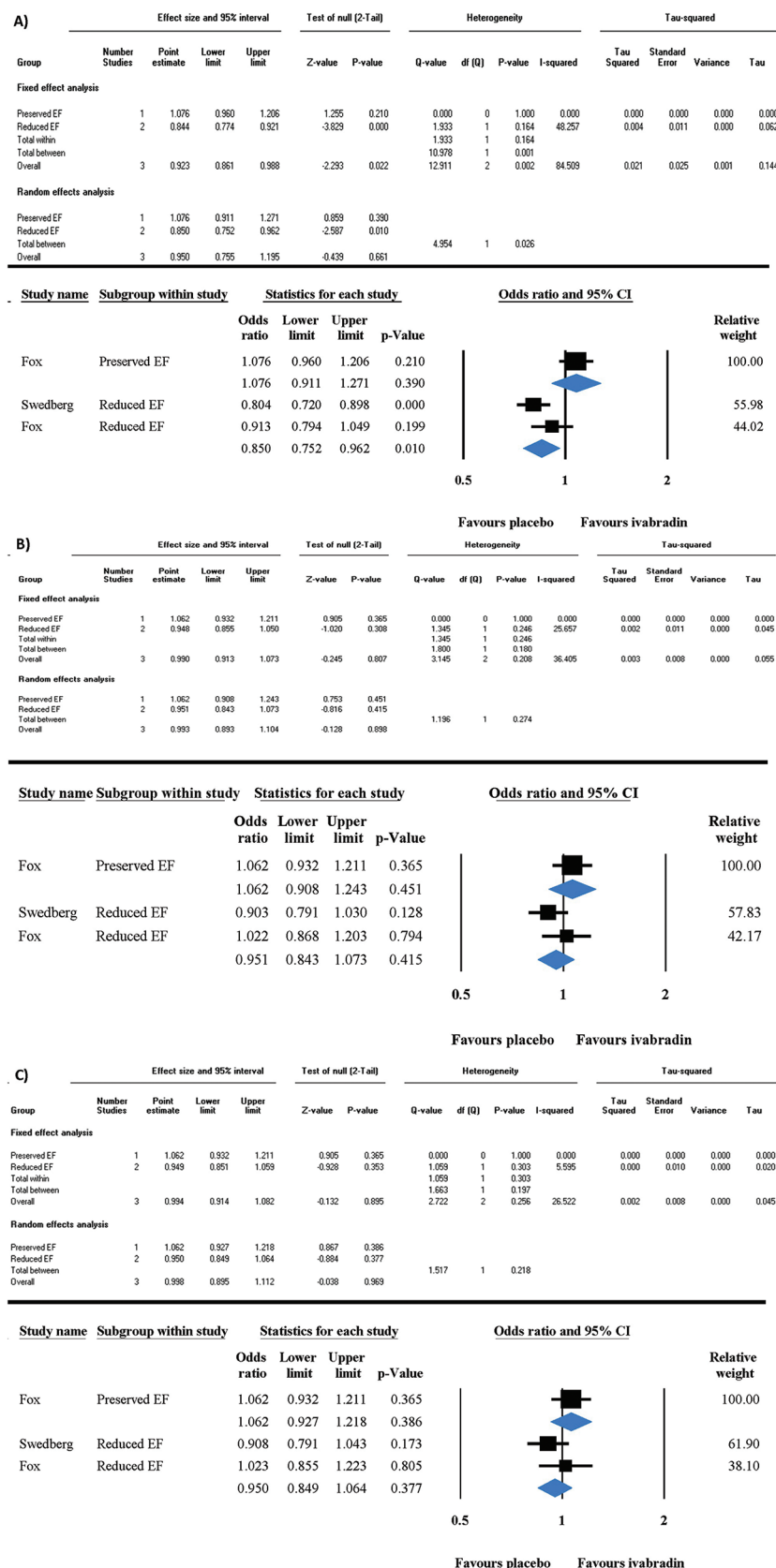
**Note:** For every study, the intervention was ivabradine (7.5 mg) given twice daily. HFREF, heart failure with reduced ejection fraction; RCT, randomized clinical trial; LVEF, left ventricular ejection fraction.

**Table 2.** Baseline characteristics of the included studies and populations in HFpEF group.

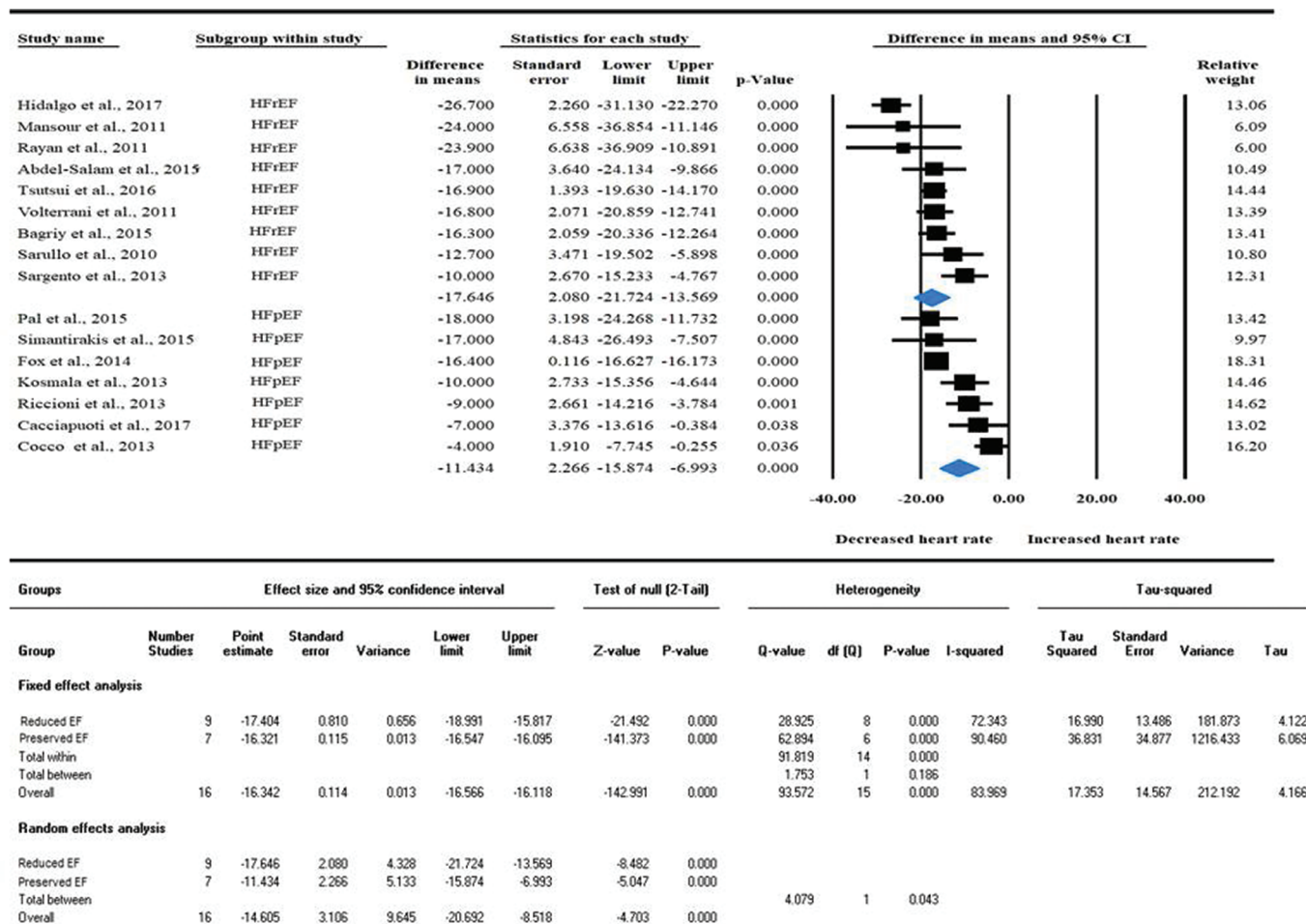
Study (year)	Design	Country	Centers	Recruitment period	No. of patients	Male (%)	Age (years)	LVEF (%)	Baseline heart rate (bpm)	Intervention	Duration – follow up
Komajda et al. (2017)	RCT	Multiple	86	June 2013–July 2015	95	38	72 (66–78)*	60 (54–66)*	75 (72–78)*	Ivabradine 7.5 mg BID	8 months
Cocco and Jerie (2013)	RCT	Switzerland	1	–	20	50	58.9 (2.3)	66 (5)	81 (3)	Ivabradine 7.5 mg BID	3 months
Kosmala et al. (2013)	RCT	Multiple	2	December 2011–December 2012	30	23	66.5 (8.5)	67 (7)	72 (7)	Ivabradine 5 mg BID	7 days
Cacciapuoti et al. (2017)	Cohort study	Italy	1	October 2014–February 2016	25	64	67 (4)	48 (0.2)	81 (2)	Ivabradine 5 mg BID	3 months
Pal et al. (2015)	RCT	United Kingdom	2	December 2011–January 2014	22	35	74.6 (5.9)	64.5 (7.9)	75 (12)	Ivabradine 7.5 mg BID	2, 4 weeks
Fox et al. (2014)	RCT	Multiple	1139	October 2009–April 2012	9550	73	65 (7.2)	56.4 (8.5)	77.1 (6.9)	Ivabradine 7.5 mg BID	1, 2, 3, 6 months
Simantirakis et al. (2015)	Cohort study	Greece	1	–	48	35	55 (10)	60 (4)	85 (5)	Ivabradine 7.5 mg BID	1, 6, 12 months
Riccioni et al. (2013)	Cohort study	Italy		2012	110	49	63 (5)	44 (5)	72 (4)	Ivabradine 5 mg BID	1 month

**Note:** HFpEF, heart failure with preserved ejection fraction; RCT, randomized clinical trial; LVEF, left ventricular ejection fraction; BID, bis in die, twice daily. \*, interquartile range (IQR).

**Fig. 2.** The effect of ivabradine on hospital admission for (A) worsening heart failure, (B) all-cause mortality, and (C) cardiovascular mortality in HFpEF compared to HFrEF. Forest plots represent the odds ratios (95% CI) of the outcomes. CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; EF, ejection fraction. [Colour online.]



**Fig. 3.** The effect of ivabradine on heart rate in HFpEF compared to HFrEF in pooled randomized and non-randomized clinical trials. Heart rate analysis of pooled data showed significant difference among HFrEF vs. HFpEF. Data are presented in difference in means with 95% CI. CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction. [Colour online.]



HFpEF and HFrEF. In the case of heart rate reduction and LVEF improvement, we also performed the comparisons separately including only RCT or just non-RCT studies. In the heart rate analysis, sensitivity analysis and meta-regression was also conducted to examine the potential confounding effect of the following factors: baseline heart rate values, age, and sex (%male). Results of the meta-analysis are displayed graphically using forest plots. Heterogeneity was tested by using the Cochrane's Q and the  $I^2$  statistics, where  $I^2 = 100\% \times (Q - df)/Q$ , and represents the magnitude of the heterogeneity (moderate: 30%–60%, substantial: 50%–90%, considerable: 75%–100%) (Higgins 2019). A  $p$  value  $< 0.1$  was considered to indicate significant heterogeneity. Publication bias and small study effect was illustrated on funnel-plots and tested by Egger's test,  $p < 0.1$  indicating sign of bias.

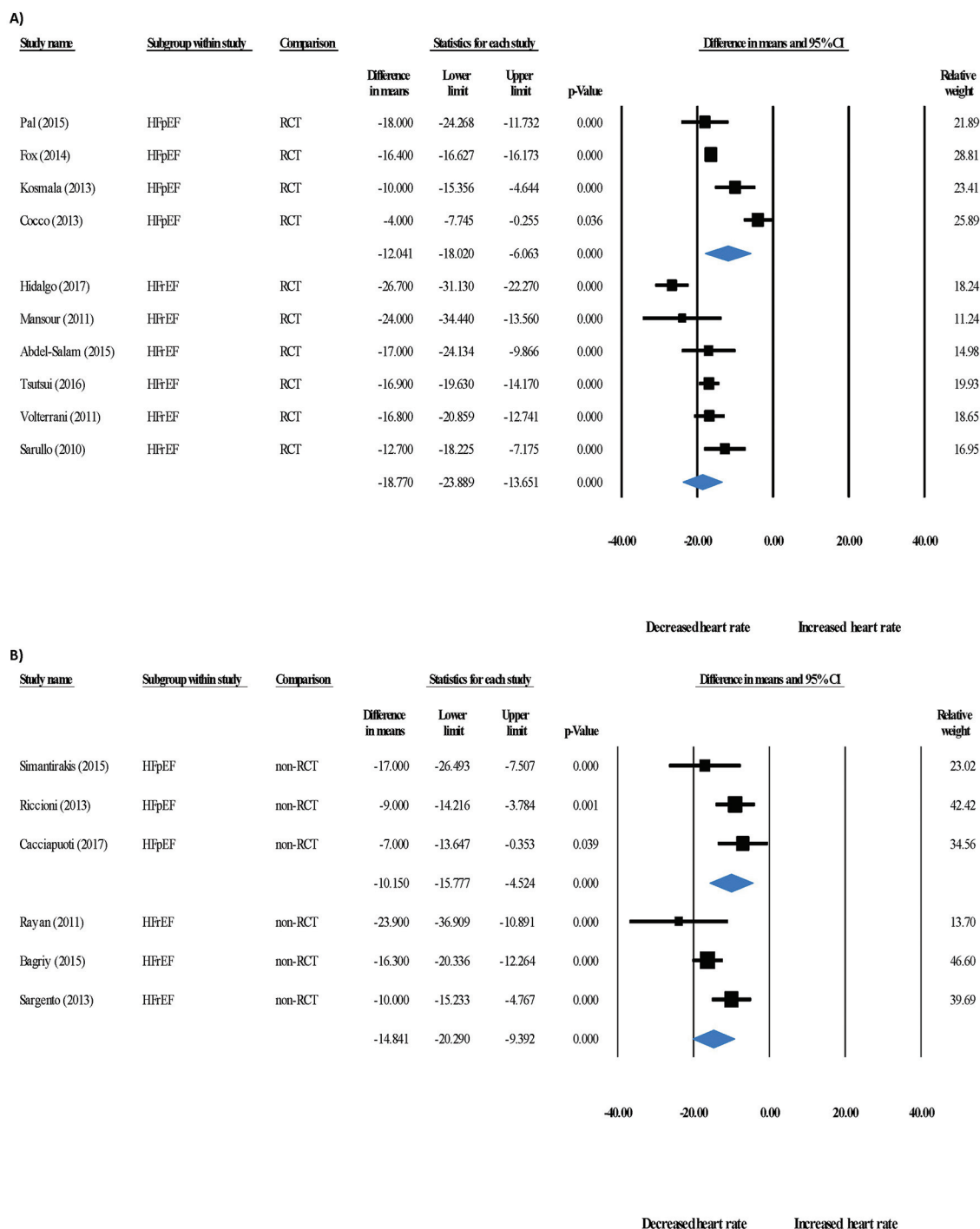
### 3. Results

#### 3.1. Study selection and characteristics

The electronic search conducted in the databases resulted in 1897 potential abstracts. After removing the duplicates, 1532 publications were selected first by title and abstracts, then 414 articles were screened by full text. The reference lists and citations of relevant publications were also checked manually for additional eligible studies, but we could not find any further suitable publications. The flowchart of search and selection process is shown in Fig. 1. Based on the inclusion criteria and full text selection, a total

number of 24 studies were included in the meta-analysis (Fox et al. 2008, 2014; Sarullo et al. 2010; Swedberg et al. 2010; Mansour 2011; Rayan et al. 2011; Volterrani et al. 2011; Cocco and Jerie 2013; Kosmala et al. 2013; Riccioni et al. 2013; Sargento et al. 2013; Abdel-Salam et al. 2015; Bagriy et al. 2015; Ordu et al. 2015; Pal et al. 2015; Simantirakis et al. 2015; Darabantiu 2016; Sisakian et al. 2016; Tsutsui et al. 2016; Cacciapuoti et al. 2017; Hidalgo and Anguita 2017; Komajda et al. 2017; Jirak et al. 2018; Villacorta et al. 2019). Among these articles there were only two studies in the HFrEF group (Fox et al. 2008; Swedberg et al. 2010), and one in the HFpEF group (Fox et al. 2014) that reported outcomes of hospital admission for worsening HF, all-cause mortality, and cardiovascular mortality. Statistics were provided for these data, but because of the low number of articles including mortality outcomes thorough conclusions could not be accomplished. Other articles did not include these data, but reported the most important cardiovascular outcomes of interest, such as resting heart rate before and after the intervention with ivabradine as well as LVEF. The selected articles have different durations of ivabradine effect and follow-up of focus; however, the majority of the included studies and this analysis focus on the short-term effect of ivabradine treatment. Cardiovascular death or hospital admission for worsening HF, all-cause mortality, and cardiovascular mortality are investigated after a 1 year follow-up. The main baseline characteristics of the studies and the population included in the meta-analysis are summarized in Table 1 and Table 2, in HFrEF and HFpEF respectively.

**Fig. 4.** Subgroup analysis of randomized clinical trials and non-randomized clinical trials on the effect of ivabradine on heart rate in HFpEF compared to HFrEF. Significant difference in heart rate reduction disappeared when subgroup analysis was performed by the design of the selected studies, however, it also showed a marked tendency that ivabradine could have stronger bradycardic effect in HFrEF. Data are presented in difference in means with 95% CI. CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction. [Colour online.]

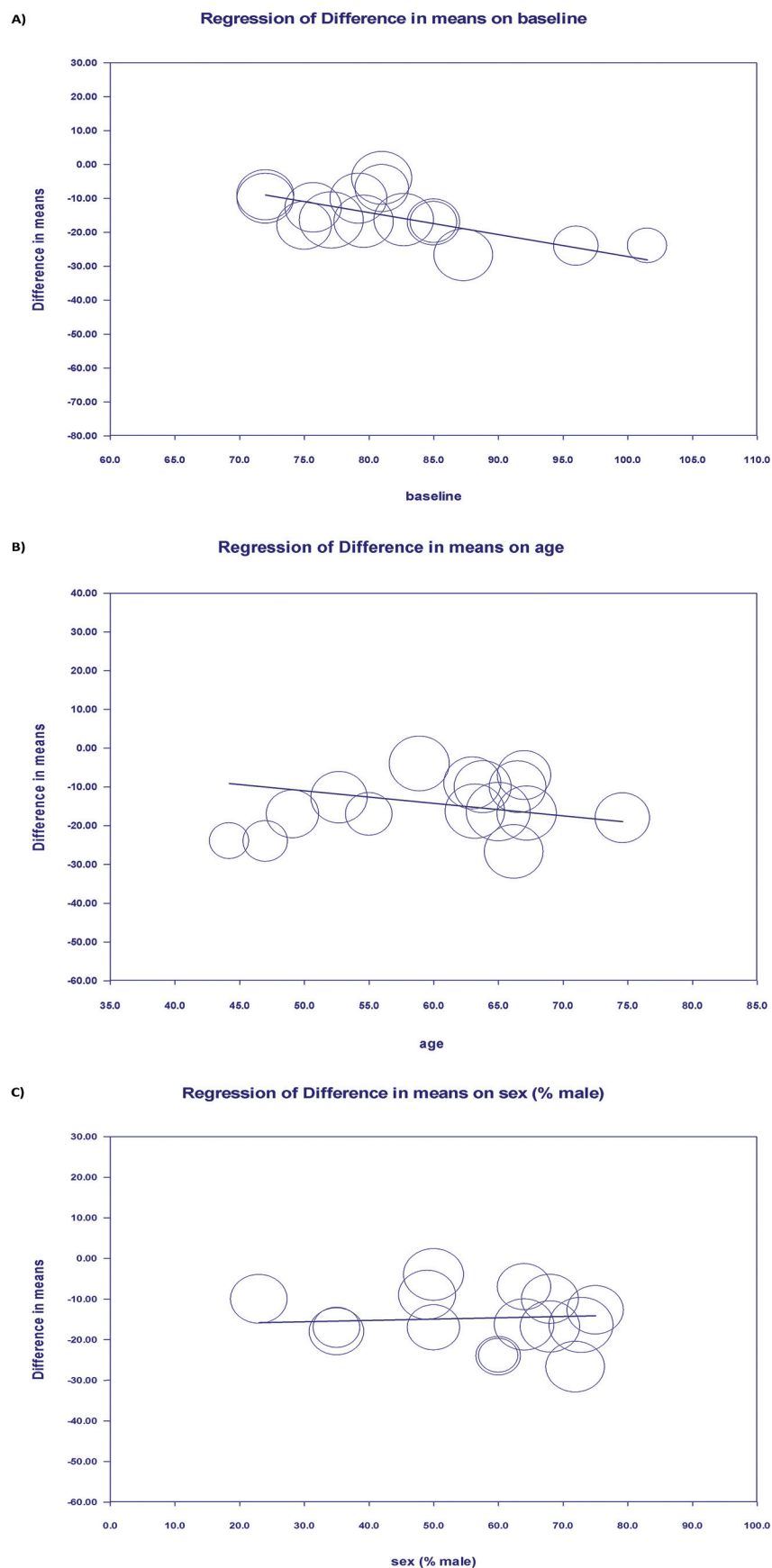


### 3.2. Mortality endpoints

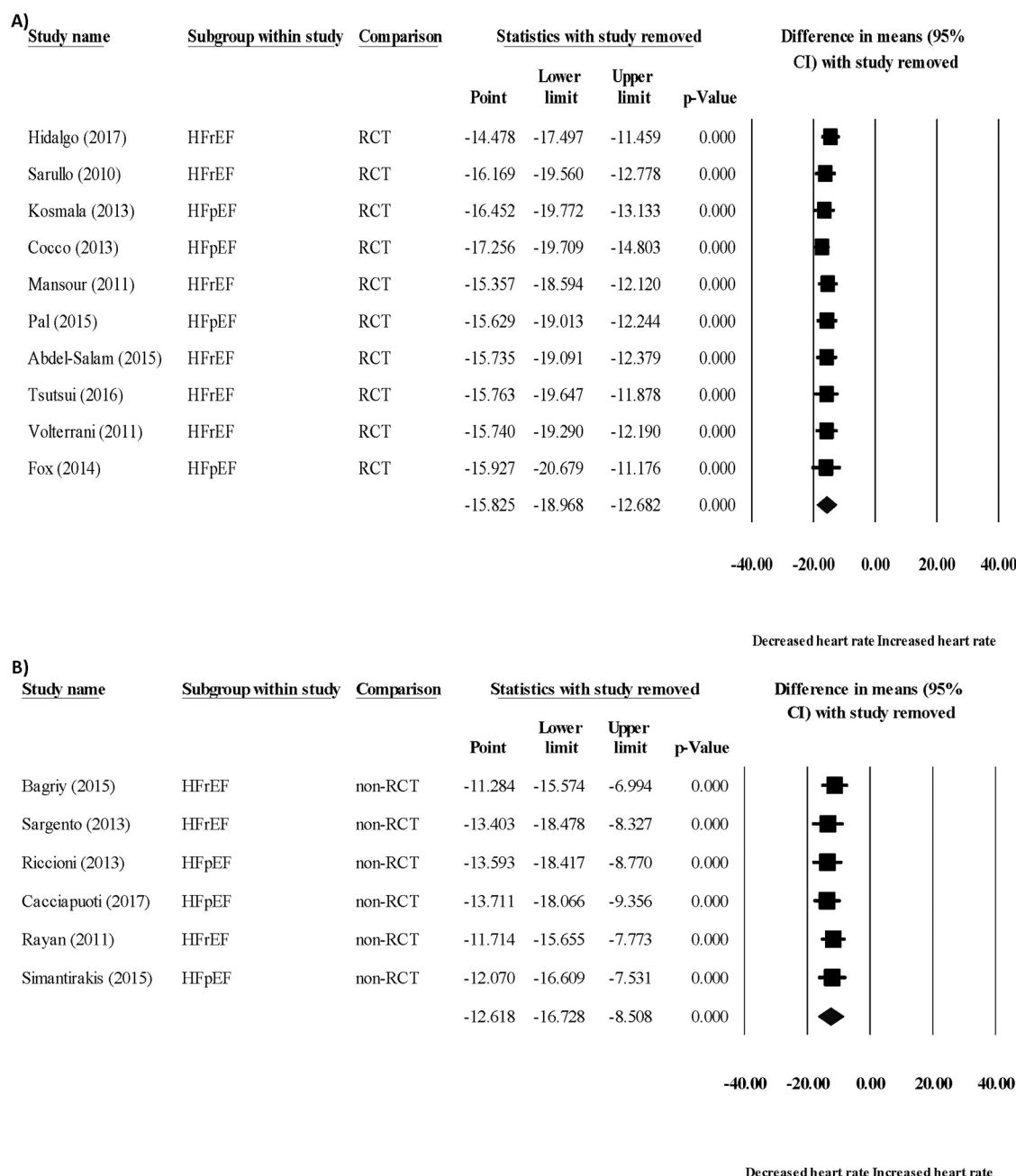
Mortality endpoints of this study were all-cause mortality, cardiovascular mortality, and hospital admission for worsening HF, which were reported only in three of the selected articles (Fox et al. 2008, 2014; Swedberg et al. 2010). We found two studies in the HFrEF population and one in the HFpEF population, thus the low amount of studies prevented us from providing detailed, and

presumably inappropriate, conclusions. To achieve reliable data, the effect of ivabradine treatment on mortality outcomes was compared with placebo in both HF types. Odds ratio (OR) ([95% CI],  $I^2$  test  $p$  value) of cardiovascular death or hospital admission for worsening HF in HFrEF was 0.85 ([0.752 to 0.962];  $I^2$ : 48%,  $p = 0.01$ ), which means ivabradine significantly reduces the risk of rehospitalization in HFrEF (Fig. 2A). In contrast, OR in HFpEF was 1.076

**Fig. 5.** Sensitivity analysis of randomized clinical trials and non-randomized clinical trials on the effect of ivabradine on heart rate. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction. [Colour online.]



**Fig. 6.** Meta-regression of baseline heart rate, age, and sex (%male) on heart rate reduction with ivabradine. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; CI, confidence interval; RCT, randomized clinical trial.



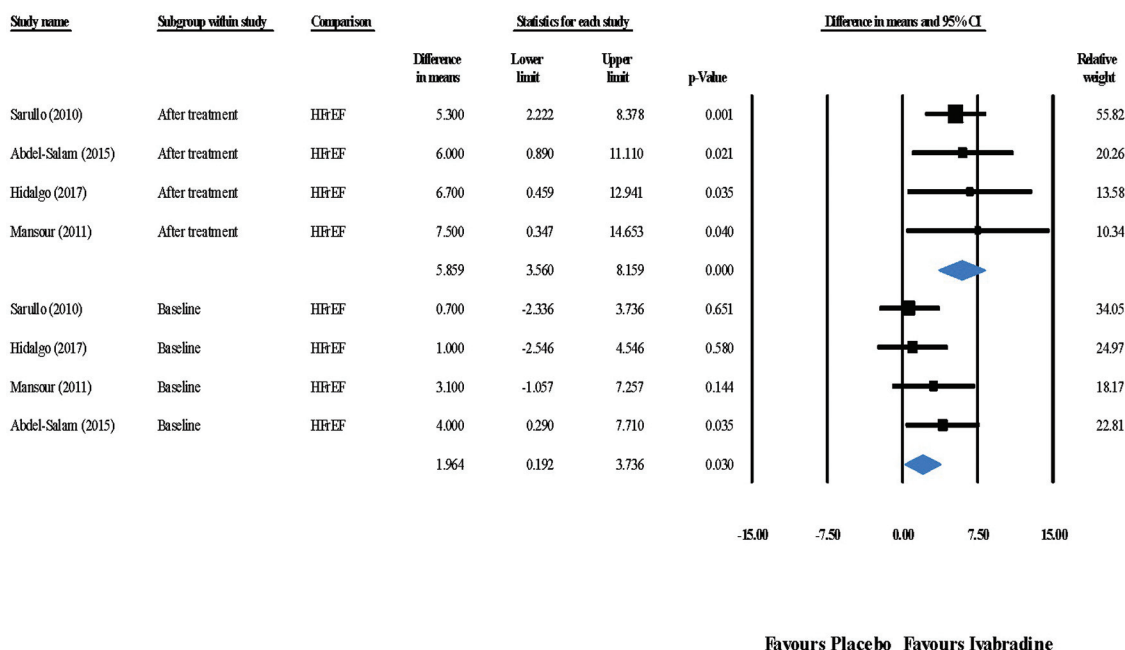
([0.911 to 0.1271];  $I^2$ : 0%,  $p$  = 0.39) resulting in no beneficial effect of ivabradine in HFpEF and highlighting a significant difference between HFrEF and HFpEF ( $p$  = 0.026) (Fig. 2A). A randomized controlled trial of beta-blockers treatment in HFpEF patients showed no improvement in cardiovascular mortality or HF hospitalizations (Yamamoto 2015). The underlying mechanism of the beta-blocker-induced failure to improve cardiovascular mortality and exercise tolerance in HFpEF was probably the resultant negative inotropy. This hypothesis suggests that pure heart rate reduction with ivabradine could be able to improve outcomes as it has no negative inotropic effect. In contrast, OR of all-cause mortality and cardiovascular mortality were 1.062 ([0.908 to 1.243];  $I^2$ : 0%,  $p$  = 0.451) and 1.062 ([0.927 to 1.218];  $I^2$ : 0%,  $p$  = 0.386) in HFpEF, supporting that heart rate reduction with ivabradine was also not associated

with a reduction in all-cause mortality and cardiovascular mortality (Figs. 2B and 2C). It seems that heart rate reduction alone may be not enough to improve outcomes in HFpEF. Surprisingly, the OR risk of all-cause mortality 0.951 ([0.943 to 1.073];  $I^2$ : 25%,  $p$  = 0.415) and cardiovascular mortality 0.95 ([0.849 to 1.064];  $I^2$ : 5%,  $p$  = 0.377) was also unchanged in HFrEF (Fig. 2B and 2C); however, individual RCTs demonstrated a favourable decrease in cardiovascular mortality (Swedberg et al. 2010).

### 3.3. Cardiovascular endpoints

Altogether, we found data for heart rate before and after short-term ivabradine treatment in 16 publications (Fox et al. 2008; Sarullo et al. 2010; Mansour 2011; Rayan et al. 2011; Volterrani et al. 2011; Cocco and Jerie 2013; Kosmala et al. 2013; Riccioni et al.

**Fig. 7.** The effect of ivabradine on left ventricular ejection fraction in HFrEF. Data are presented in difference in means with 95% CI. CI, confidence interval; HFrEF, heart failure with reduced ejection fraction. [Colour online.]



2013; Sargento et al. 2013; Abdel-Salam et al. 2015; Bagriy et al. 2015; Pal et al. 2015; Simantirakis et al. 2015; Tsutsui et al. 2016; Cacciapuoti et al. 2017; Hidalgo and Anguita 2017). Heart rate analysis (difference in means [95% CI];  $I^2$  test,  $p$  value) showed a large decrease in both HFrEF ( $-17.646$  beats/min [ $-21.724$  to  $-13.569$ ];  $I^2$ : 69%,  $p = 0.001$ ) and HFpEF group ( $-11.434$  beats/min [ $-15.874$  to  $-6.993$ ];  $I^2$ : 90%,  $p < 0.001$ ) (Fig. 3). Our results show that together, for all the studies that report heart rate before and after ivabradine treatment, the magnitude of heart rate reduction following ivabradine adjustment is significantly larger in HFrEF compared to HFpEF ( $p = 0.043$ , Fig. 3). As the design of the included studies are different, subgroup analyses were performed to compare the effect of ivabradine separately in RCTs and non-RCT studies. Interestingly, subgroup analysis showed no difference in heart rate reduction between HFpEF and HFrEF (Fig. 4A and 4B). Ivabradine effectively decreased baseline heart rates in non-RCTs in both HFrEF ( $-14.841$  beats/min [ $-20.29$  to  $-9.391$ ];  $I^2$ : 64%,  $p < 0.001$ ) and HFpEF ( $-10.15$  beats/min [ $-15.777$  to  $-4.524$ ];  $I^2$ : 32%,  $p < 0.001$ ) (Figs. 4A and 4B), although the difference was not statistically significant ( $p = 0.241$ ). In RCTs also, heart rate reduction analysis showed a decrease in both HFrEF ( $-18.770$  beats/min [ $-23.889$  to  $-13.651$ ];  $I^2$ : 75%,  $p < 0.001$ ) and HFpEF ( $-12.041$  beats/min [ $-18.02$  to  $-6.062$ ];  $I^2$ : 93%,  $p < 0.001$ ) (Figs. 4A and 4B). The magnitude of heart rate reduction showed a tendency to differ between HFrEF and HFpEF in the RCTs, however it did not reach the statistical significance ( $p = 0.094$ ). Statistical analysis revealed high heterogeneity between the studies. To identify the reason and possible studies which can be responsible for the high heterogeneity, meta-regressions on baseline parameters were done to examine the possible impact of other variables on the effect size. Meta-regression showed that baseline heart rate could be an underlying reason of the high heterogeneity, as the intervention effect increases as the baseline heart rate is higher showing a significant linear correlation (Fig. 5A). Other potential explanatory variables (i.e.: age, sex) did not affect the magnitude of heart rate reduction by ivabradine treatment (Figs. 5B and 5C). Sensitivity analysis did not find any study that was out of line and that could influence the results of the statistics (Figs. 6A and 6B). LVEF analysis revealed a significant improvement in HFrEF (5.936, [4.199 to 7.672],  $I^2$ : 23%,  $p < 0.001$ ), also when compared with placebo

( $p < 0.001$ , Fig. 7). Ivabradine caused no significant change on LVEF in HFpEF (1.247,  $[-0.845$  to  $3.343]$ ,  $I^2$ : 27%,  $p = 0.242$ ). Regarding this negligible effect in HFpEF and the fact that improvement of LVEF in HFpEF could be detrimental, statistical comparison in respect of LVEF between HFrEF and HFpEF is unnecessary.

### 3.4. Risk of bias within studies and publication bias

Risk of bias was assessed in 9 non-RCT studies (Rayan et al. 2011; Riccioni et al. 2013; Sargento et al. 2013; Bagriy et al. 2015; Ordu et al. 2015; Simantirakis et al. 2015; Darabantiu et al. 2016; Cacciapuoti et al. 2017; Jirak et al. 2018) and 15 RCTs (Swedberg et al. 2010; Fox et al. 2008; Mansour 2011; Cocco and Jerie 2013; Kosmala et al. 2013; Pal et al. 2015; Sisakian et al. 2016; Komajda et al. 2017; Tsutsui et al. 2016; Villacorta et al. 2019; Volterrani et al. 2011; Hidalgo and Anguita 2017; Sarullo et al. 2010; Abdel-Salam et al. 2015; Fox et al. 2014). Results of the Cochrane Risk of Bias Assessment Tool for RCTs and the results of the Newcastle–Ottawa quality assessment scale for cohort studies are shown in Fig. 8 and Fig. 9 in both populations. Because of the low number of publications for LVEF outcomes, funnel plots were constructed only for heart rate outcome in HFrEF and HFpEF population. In studies involving HFrEF patients, the funnel plot showed symmetry on visual inspection with  $p = 0.79$  in Egger's test, and studies on HFpEF population showed a little asymmetry with  $p = 0.082$ ; however, publication bias was not large and was unlikely to alter conclusions in both group (Fig. 10).

## 4. Discussion

RCTs (e.g., SHIFT-, BEAUTIFUL-, and EDIFY-trials; Fox et al. 2008; Swedberg et al. 2010; Komajda et al. 2017) found significant effect of ivabradine on heart rate both in HFpEF and HFrEF compared with control, however ivabradine failed to improve cardiovascular outcomes in HFpEF for unknown reasons (Fox et al. 2008; Komajda et al. 2017). In this meta-analysis, we compared the effect of ivabradine in the treatment of HF between HFpEF and HFrEF patients. When RCTs and non-RCTs were pooled, we found significantly improved bradycardic effect of ivabradine in HFrEF patients (Fig. 3). In contrast, when RCTs and non-RCTs were analyzed separately, statistically identical heart rate lowering effect of ivabradine was

**Fig. 8.** Results of the Cochrane Risk of Bias Assessment Tool for randomized clinical trials in (A) HFrEF and (B) HFpEF population. Studies were judged by the following items where letters refer to: (A) Random sequence generation, (B) allocation concealment, (C) selective reporting, (D) blinding of participants and personnel, (E) blinding of outcome assessment, (F) Incomplete outcome data, and (G) other sources of bias. Green: low risk of bias; yellow: uncertain risk of bias; red: high risk of bias. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction. [Colour online.]

A) Included studies (HFrEF)	Items						
	A)	B)	C)	D)	E)	F)	G)
Swedberg et al. (2010)							
Fox et al. (2008)							
Tsutsui et al. (2016)							
Villacorta et al. (2018)							
Volterrani et al. (2011)							
Hidalgo et al. (2017)							
Sarullo et al. (2010)							
Abdel-Salam et al. (2015)							
Mansour et al. (2011)							
Sisakian et al. (2015)							

B) Included studies (HFpEF)	Items						
	A)	B)	C)	D)	E)	F)	G)
Komajda et al. (2017)							
Cocco et al. (2013)							
Kosmala et al. (2013)							
Pal et al. (2015)							
Fox et al. (2014)							

**Fig. 9.** Results of the edited Newcastle–Ottawa quality assessment scale for cohort studies in (A) HFrEF and (B) HFpEF population. Studies were judged by the following items where numbers refer to: (1) representativeness of the intervention group; (2) selection of the control group; (3) demonstration that the outcomes of interest were not present at start of the study; (4) comparability of cohorts on the basis of the design or analysis controlled for confounders; (5) assessment of outcome; (6) adequacy of the length of follow-up; (7) adequacy of quality of follow-up. Each item was rated as ‘high risk’ (equals to 0), ‘low risk’ (equals to 1), or ‘unclear risk’ (equals to 0) corresponding to the definitions. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction. [Colour online.]

A) Included studies (HFrEF)	Items							Total
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	
Darabantiu et al. (2016)	1	0	1	0	1	1	0	4
Sargento et al. (2013)	1	0	1	0	1	1	0	4
Bagriy et al. (2015)	1	0	1	0	1	1	0	4
Rayan et al. (2011)	1	0	1	0	1	1	0	4
Ordu et al. (2015)	1	1	1	0	1	1	1	6
Jirak et al. (2018)	1	0	1	0	1	1	1	5

B) Included studies (HFpEF)	Items							Total
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	
Cacciapuoti et al. (2017)	1	0	1	0	1	1	1	5
Simantirakis et al. (2015)	0	0	1	0	1	1	0	3
Riccioni et al. (2013)	0	0	1	0	1	1	1	4

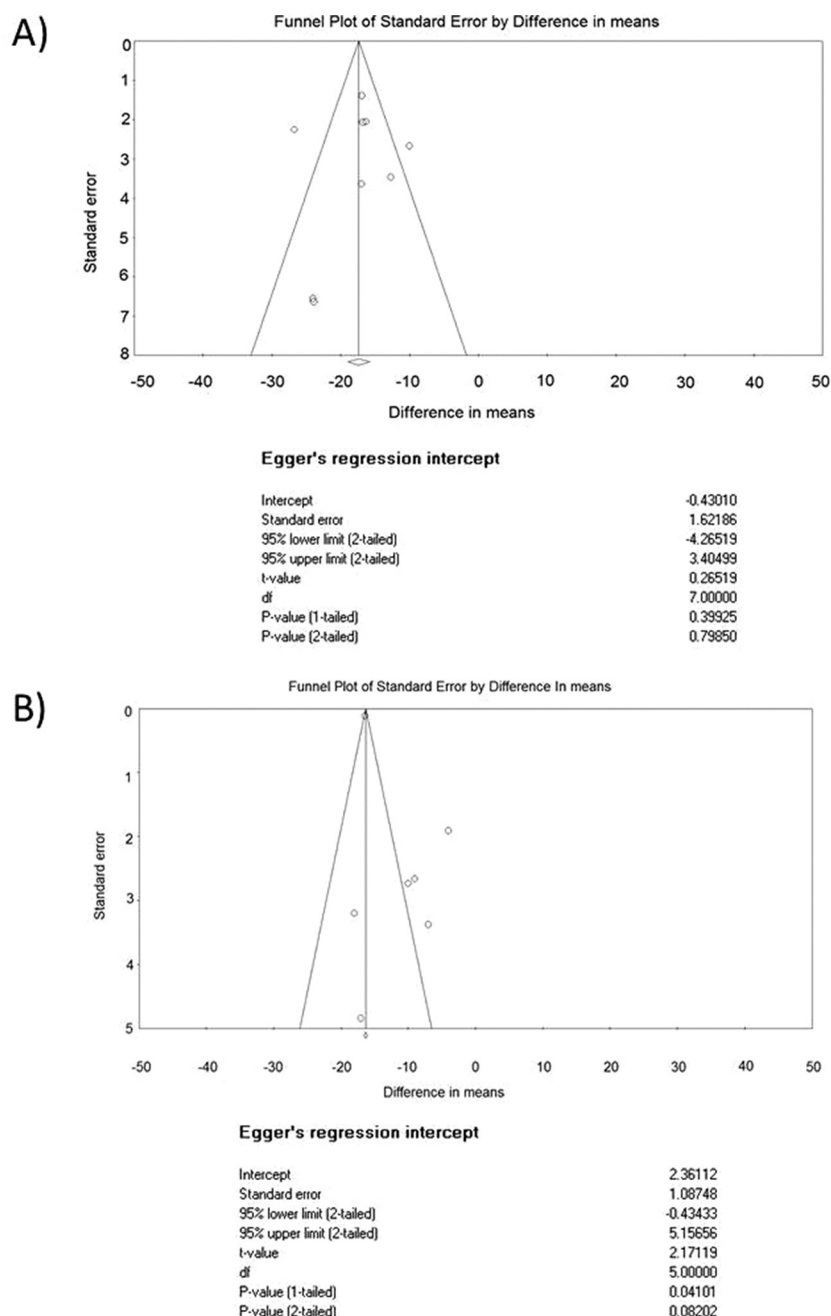
found between HFpEF and HFrEF (Fig. 4); however, a clear tendency of increased bradycardic effect of ivabradine in HFrEF still exists. It was also found that ivabradine significantly improved the LVEF in HFrEF patients (Fig. 7).

#### 4.1. Pharmacological properties of ivabradine

Experimental studies on ivabradine have demonstrated that at a concentration of 3  $\mu\text{M}$  it reduces the pacemaker frequency in isolated rabbit SA node by decreasing the slope of the diastolic depolarization without any effect on action potential (AP) duration or on AP amplitude (Thollon et al. 1994). The the half maximal inhibitory concentration ( $\text{IC}_{50}$ ) for the  $\text{I}_f$  blockade is 2.8  $\mu\text{M}$

(Bois et al. 1996); however, Koncz et al. (2011) demonstrated that ivabradine exerts a considerable inhibiting effect on  $\text{I}_{\text{Kr}}$  (delayed rectifier potassium current), having  $\text{IC}_{50}$  of 3.5  $\mu\text{M}$ . At this concentration, ivabradine provides approximately 60%–65% of  $\text{I}_f$  inhibition. Furthermore, a marked  $\text{I}_{\text{Kr}}$  current inhibition will contaminate the  $\text{I}_f$  inhibiting effect. The study by Koncz et al. (2011) also demonstrated that in normal undiseased dog and in healthy human ventricular myocardium, even 10  $\mu\text{M}$  ivabradine has only marginal AP lengthening effect. In contrast, when the repolarization reserve was attenuated (by 30  $\mu\text{M}$   $\text{BaCl}_2$ ), even 1  $\mu\text{M}$  ivabradine caused marked AP lengthening, indicating the  $\text{I}_{\text{Kr}}$  channel inhibiting role of ivabradine which is prominent in the presence of attenuated repolarization.

**Fig. 10.** Funnel plots for studies in heart rate in HFpEF and HFrEF groups. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



#### 4.2. Structural and electrical remodeling in HFrEF vs. HFpEF

Structurally, HFpEF can be characterized by concentric LV hypertrophy with high LV mass/volume ratio and interstitial fibrosis. In contrast, HFrEF is characterized by progressive ventricular dilatation, eccentric LV remodeling, low LV mass/volume ratio, and decreasing amount of cardiomyocytes replaced with fibrosis (Konstantinou et al. 2013; Asrar Ul Haq et al. 2014; Borlaug 2014). Electrical remodeling is a common feature of HF (Table 3), however, it manifests differently between HFrEF and HFpEF. A modeling study demonstrated longer AP duration in HFrEF via the increased late  $\text{Na}^+$  current and the decreased outward  $\text{K}^+$  currents (Glitsch 2001; Workman et al. 2003; Bueno-Orovio et al. 2014; Adeniran et al. 2015).  $I_{\text{to}}$  (transient outward potassium current) was also found to be decreased in HFrEF causing considerable AP

prolongation in human (Tomaselli et al. 1994; Tomaselli and Marban 1999; Tomaselli and Zipes 2004). The hallmark of HFpEF is the impaired diastolic relaxation, which can be attributable to the decreased  $\text{Na}^+/\text{Ca}^{2+}$  exchanger (NCX) current activity in the presence of reduced sarcoplasmic reticulum (SR)  $\text{Ca}^{2+}$  content and smaller release, compared with healthy control. In contrast, in HFrEF, the NCX activity is increased, causing significant diastolic  $\text{Ca}^{2+}$  leak and markedly decreased SR  $\text{Ca}^{2+}$  content (Table 3). Taken altogether, the released  $\text{Ca}^{2+}$  is lower in the case of HFrEF compared with HFpEF, while the  $I_{\text{CaL}}$  (L-type calcium current) does not differ significantly between the two types of HF. It is important to note that the decreased NCX current in HFpEF contributes in AP duration shortening while the increased exchanger function in HFrEF lengthens the AP duration. Previous

**Table 3.** Summary of results of ion channel expression changes in HFrEF in sinus node and in ventricular muscle.

Ion channel	Sinus node (or atrial myocytes*)			Ventricle		
	Results	Model	Reference	Results	Model	Reference
$I_{CaL}$	Decreased*	Human	(Oquadid et al. 1995)	Decreased	Human	(Oquadid et al. 1995)
	Decreased*	Dog	(Li et al. 2000)	Not altered	Human	(Beuckelmann et al. 1992)
	Not altered	Rabbit	(Verkerk et al. 2003)	Not altered	Human	(Mewes and Ravens 1994)
$I_{CaT}$	Not altered*	Dog	(Li et al. 2000)	Not altered	Human	(Beuckelmann et al. 1991, 1992)
	Not altered	Rabbit	(Verkerk et al. 2003)			
$I_f$	Decreased	Rabbit	(Verkerk et al. 2003)	Increased	Rabbit	(Nattel et al. 2007)
	Decreased	Dog	(Zicha et al. 2005)	Not altered	Human	(Hoppe et al. 1998)
	Increased*	Dog	(Zicha et al. 2005)			
$I_{Kr}$	Not altered	Rabbit	(Verkerk et al. 2003)	Not altered	Dog	(Li et al. 2002)
	Not altered*	Dog	(Li et al. 2000)	Decreased	Rabbit	(Tsuiji et al. 2000)
$I_{to}$	Not altered	Rabbit	(Verkerk et al. 2003)	Decreased	Human	(Beuckelmann et al. 1993)
	Decreased*	Dog	(Li et al. 2000)			
$I_{NCX}$	Not altered	Rabbit	(Verkerk et al. 2003)	Increased	Human	(Flesch et al. 1996)
	Increased*	Dog	(Li et al. 2000)	Increased	Human	(Studer et al. 1994)

Note: Ion channel expression likely differ in HFpEF vs. HFrEF, however, there is still hardly any experimental data on ion channel expression and ionic current changes in HFpEF, thus this table demonstrates only the electrophysiological changes in HFrEF. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction;  $I_{CaL}$ , L-type calcium current;  $I_{CaT}$ , T-type calcium current;  $I_f$ , pacemaker ("funny") current;  $I_{Kr}$ , delayed rectifier potassium current;  $I_{to}$ , transient outward potassium current;  $I_{NCX}$ , sodium-calcium exchanger current.

study demonstrated the important role of NCX in setting the actual length of the AP (Hurtado et al. 2005). The important role of the NCX in HF raises the possibility that selective NCX inhibition could effectively control the actual duration of the AP. Cho et al. (2017) in rat HFpEF model demonstrated  $I_{to}$  downregulation and consequently AP prolongation and prolonged electrocardiogram (ECG) QT interval. The late  $Na^+$  current, and the inward rectifier  $K^+$  current were also remodeled (Borbély et al. 2005; Selby et al. 2011; Zile and Gaasch 2011; Trenor et al. 2012; Gomez et al. 2014). Two studies compared the continuous QT intervals between HFpEF and HFrEF. Both papers demonstrated larger continuous QT in the case of HFrEF ( $454 \pm 42$  vs.  $427 \pm 42$  ms and  $499 \pm 50$  vs.  $453 \pm 43$  ms) (Cenkerova et al. 2016; Hendry et al. 2016) indicating more attenuated repolarization reserve in HFrEF patients compared with HFpEF.

### 4.3. Identical effects of ivabradine on heart rate in HFrEF versus HFpEF

Separation of RCTs and non-RCTs resulted in identical bradycardic effect of ivabradine in HFpEF and HFrEF; however, despite the lack of statistical significance in heart rate reduction, there is a mild difference between the two groups, which needs further investigation. When the available data were pooled (i.e., RCT and non-RCT) statistical analysis revealed significantly enhanced bradycardic effect of ivabradine in HFrEF, therefore, it is plausible that ivabradine could have stronger bradycardic effect in HFrEF, which could be the result of two synergistic mechanisms established by the electrical remodeling. (i) It was found that the expression level of HCN channels is decreased in HFrEF providing reduced pacemaker  $I_f$  during diastolic depolarization of the sinus node cells. In this case the effect of ivabradine is larger because of the increased susceptibility (i.e., decreased current density) of the diastolic depolarization (Rocchetti et al. 2000; Zaza and Lombardi 2001; Kohajda et al. 2019). (ii) The  $I_{Kr}$  inhibitory effect of ivabradine is not negligible as the dose causing 60%–70% inhibition of  $I_f$  also exerts an inhibition of 50% on the  $I_{Kr}$  (Koncz et al. 2011). As  $I_{Kr}$  inhibition also lengthens the sinus node cycle length it could also contribute in the frequency decrease (Boyett et al. 2000). The initial hypothesis, suggesting that the efficacy of ivabradine treatment would be progression dependent, was not confirmed. Nevertheless, the large heterogeneities between studies may considerably limit more precise statistical analysis.

### 4.4. Improved ejection fraction in HFrEF after ivabradine treatment

Structural or functional impairment of LV filling and ejection of blood in HF patients results in symptomatic LV dysfunction causing impaired LVEF in HFrEF. The aim in the treatment of HF is to improve symptoms, slow the progression of the cardiac failure, and to decrease the HF associated mortality in patients. Heart rate reduction accompanied by LVEF improvement should be beneficial in HFrEF patients. All four RCT studies reported that ejection fraction is improved in HFrEF patients after ivabradine treatment. As reduced LVEF is a hallmark characteristic of HFrEF, this secondary effect of ivabradine could be beneficial and may contribute to the improved symptoms and the decreased mortality observed in HFrEF. As previously mentioned, HFrEF patients have significantly longer ECG QT interval due to the downregulation of  $I_{Kr}$ ,  $I_{to}$ , and  $I_{Ks}$  currents, causing impaired repolarization reserve (Beuckelmann et al. 1993; Tsuiji et al. 2000; Cenkerova et al. 2016; Hendry et al. 2016) (Table 3). It is feasible that the additional  $I_{Kr}$  inhibition effect of ivabradine could cause larger QT-lengthening via the attenuated repolarization reserve. The prolonged QT interval and the prolonged plateau phase of the ventricular AP provide increased  $Ca^{2+}$  influx, enhancing the available  $Ca^{2+}$  for sarcoplasmic-endoplasmic reticulum calcium ATPase. As the SR  $Ca^{2+}$  content is increased, the magnitude of the released  $Ca^{2+}$  is also enhanced providing increased LV performance.

### 4.5. Differences in comorbidities in HFpEF and HFrEF

HFrEF and HFpEF exerts some important differences in comorbidities. HFrEF patients are predominantly males having increased susceptibility to myocardial infarction and cardiomyocytes loss (Ho et al. 2013). In contrast, HFpEF patients are more likely to be older with a 2-fold predominance of females (Lee et al. 2009). It is important to note that HFpEF patients have higher incidence of different comorbidities such as pulmonary disease, stroke, hypertension, type-2 diabetes mellitus, anaemia, stroke, gout, and cancer of any type (Ergatoudes et al. 2019). The mortality risk of comorbidities, however, are similar between HFpEF and HFrEF (Felker et al. 2006; Ather et al. 2012; Smith et al. 2013), the incidence of hospitalization caused by comorbidities are higher in HFpEF (Streng et al. 2018). This important difference may indicate that ivabradine has limited efficacy in HFpEF because of the higher rate of comorbidities-related illness.

## 5. Study limitations

Our study has the following limitations: (i) The comparison was performed on two populations, as we could not find any paper comparing HFpEF and HFrEF in one study. This lack of information indicates the necessity of parallel elucidation of ivabradine effect on HFpEF and HFrEF patients in clinical trials. (ii) Since the new classification of HF by the ESC was introduced in 2016 (Ponikowski et al. 2016), the studies involved in this meta-analysis could not distinguish HFpEF from HFmrEF. Based on this and the similarity of the symptoms, two articles that included HFpEF populations which now are considered HFmrEF were merged into those with HFpEF. (iii) Based on the low number of clinical studies in HF treated with ivabradine, this meta-analysis includes different study types: randomized or non-randomized, controlled or uncontrolled clinical trials and observational cohort studies, and there was significant heterogeneity in some of the outcomes that were analyzed in this meta-analysis.

## 6. Conclusions

In this study we found that ivabradine significantly increases the LV performance in HFrEF and exerts a possible tendency to have stronger bradycardic effect in HFrEF compared with HFpEF. These effects, coupled with the previously reported higher prevalence of non-cardiac comorbidities in HFpEF, may contribute to the observed disparate results of ivabradine between HFpEF and HFrEF.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Authors contribution

Norbert Nagy, Attila Farkas, Péter Hegyi and András Varró contributed conception and design of the study. Noémi Tóth and Alexandra Polyák performed the literature search and data extraction from the enrolled studies and assessed the risks of bias in the studies involved. Alexandra Soós and Alex Váradi performed the statistical analysis and created the forest plot and funnel plot figures. Margit Solymár made substantial help registering the study in PROSPERO database. Benedek Tinusz, Anna Vágvolgyi, Andrea Orosz made substantial contributions to the analysis. Noémi Tóth, Norbert Nagy, and Attila Farkas drafted the manuscript. All the authors edited, read, and approved the final version of the manuscript.

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