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Ivabradine has a neutral effect on mortality in randomized controlled trials

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Abstract

Background: It has long been a controversial hotspot whether resting heart rate (RHR) is a risk factor or a marker for death. Ivabradine, a specific inhibitor of the If current in the sinoatrial node, is a pure RHR lowering agent. The study was aimed to investigate whether ivabradine would reduce more RHR, cardiovascular disease (CVD) mortality, and all-cause mortality than those placebo or beta-blockers.

Methods: The authors performed a meta-analysis of 8 randomized controlled clinical studies (with 40,357 participants), and 3 studies of those which were ivabradine versus placebo (36,069 participants) and other 5 studies ivabradine versus beta-blockers (4288 participants) were available. The authors compared the association of the RHR reduction with death from CVD causes (2674 in 40,285 participants) and the rate of all-cause death (3143 deaths in 38,037 participants), and assessed improvement in death rates with the use of ivabradine.

Results: The change of RHR from baseline to endpoint was 8 to 16 beats/min (bpm) in ivabradine group, 1 to 8 bpm in placebo group, and 4 to 24 bpm in beta-blockers group. In ivabradine versus placebo, the reduced risks of CVD mortality and all-cause morbidity were not significantly (risk ratio [RR] 1.02; 95% confidence interval [CI] 0.91–1.14, $P = .737$; RR: 1.00, 95% CI: 0.92–1.09, $P = .992$, respectively). CVD and all-cause morbidity were similar for ivabradine versus beta-blockers (RR: 1.04; 95% CI: 0.80–1.37, $P = .752$; RR: 1.17, 95% CI: 0.53–2.60, $P = .697$, respectively).

Conclusions: Ivabradine had a neutral effect on mortality, suggesting that a pure RHR lowering agent did not reduce CVD mortality, all-cause mortality and improve the lifespan.

Abbreviations: bpm = beats/min, CAD = coronary artery disease, CI = confidence interval, CVD = cardiovascular disease, HR = heart rate, ISA = intrinsic sympathetic activity, LVEF = left ventricular ejection fraction, RCT = randomized controlled clinical trial, RHR = resting heart rate, RR = risk ratio.

Keywords: all-cause death, cardiovascular disease death, ivabradine, randomized controlled trials

1. Introduction

The pursuit of longevity is a dream of people since ancient times. Resting heart rate (RHR) is the heart rate (HR) when people keep on quiet or inactive. HR reflects the status of cardiovascular system and is an indicator of autonomic nervous system activity and body metabolic rate.[1] HR can be affected by many factors, for example, physical fitness, psychological status, diet, drugs, and the interaction of genetics and the environment.[1]

Early biologists discovered faster HR, the shorter life, for example, the RHR of Galapagos tortoise was 6 beats/min (bpm), and it had the lifespan of 177 years, the RHR of mouse was 500 bpm, and its lifespan only lasted for 2 years.[2] The slower, the better?[3] Medical researchers also found that the beta-blockers without intrinsic sympathetic activity (ISA) significantly decreased the cardiovascular disease death (CVD death) and all-cause death than those with ISA,[4,5] which brought about relative prolongation of the patients' lifespan. Recently, a new drug called ivabradine is a hyperpolarization-activated cyclic nucleotide-gated channel blocker, which selectively inhibits the If current to reduce the spontaneous pacemaker activity, but it presents no effect on ventricular repolarization and no effect on myocardial contractility.[6,7] Thereby ivabradine appears to be an ideal drug for investigating pure HR effects on lifespan and validating the concept of heart-beats-per-life.

Therefore, we investigated whether ivabradine would reduce more RHR, CVD mortality, and all-cause mortality than placebo or beta-blockers in randomized controlled trials (RCTs).

2. Methods

2.1. Data sources

We conducted a meta-analysis by using the approach recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for meta-analyses of interventional studies.[8] Relevant studies were identified in Embase, Medline, Cochrane library database, and PubMed by the way of studies

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assessing treatment differences in mortality among patients who underwent ivabradine versus placebo or beta-blockers (all kinds of beta-blockers). We did restrict the search by language in English. The last search was performed on May 31, 2016.

2.2. Study selection and data extraction

The title and abstract were initially reviewed. Then full texts of those citations were appraised for eligibility for inclusion. Inclusion criteria included the following: the RCTs that involved patients who had the treatment with ivabradine versus placebo or ivabradine versus beta-blockers; including baseline RHR, endpoint RHR, and change of RHR; to present the CVD death data (all deaths from coronary causes, cardiovascular procedures, fatal stroke, other cardiovascular causes, nonsudden death of unknown cause, and unclassifiable deaths) and/or all-cause death data (any cause death or total death); and to report follow-up period and death endpoint.

We excluded relevant abstracts with incomplete data in conference, case reports, pool analysis, and subgroup analysis of included studies. All search results were assessed by 2 individuals, with minor differences resolved by discussion and consultation with a third researcher.

The potential information was abstracted: the research abbreviation or the last name of the first author, publication year, country where the study was performed, study design, total participants in the study, numbers of male participants, coronary artery disease (CAD), hypertension, diabetes, dyslipidemia, stroke, smoker, baseline left ventricular ejection fraction (LVEF), follow-up period, intervention participants, control participants, baseline RHR, endpoint RHR, CVD death participants, and all-cause death participants.

2.3. Statistical analysis

Abstracted data from the included studies were analyzed by Stata/MP 11.0 statistical software (StataCorp).[9] Four analyses were performed: the risk ratios (RRs) for CVD mortality (ivabradine vs. placebo), using numbers of CVD death and specific participants to each treatment; the RRs for CVD mortality (ivabradine vs. beta-blockers), using numbers of CVD death and specific participants to each treatment; the RRs for all-cause mortality (ivabradine vs. placebo), using numbers of all-cause death and specific participants to each treatment; and the RRs for all-cause mortality (ivabradine vs. beta-blockers), using numbers of all-cause death and specific participants to each treatment.

If the event of interest is rare, odds ratios tend to overestimate the strength of association,[10] here RRs were used. Hazard ratios were used interchangeably with RRs. Data were combined using the DerSimonian and Laird random-effects model with inverse variance weighting for clinical and statistical heterogeneity between studies.[11] Estimates were reported as RRs comparing ivabradine with placebo or beta-blockers, with 95% confidence intervals (CIs). Differences were considered statistically significant at $P < .05$ (2-sided). Heterogeneity across studies was assessed with the Cochran Q statistic (χ^2), with $P < .10$ considered significant, and with the I^2 test.[12] The I^2 statistic, which indicated the percentage of variation attributable to between-study heterogeneity, was shown in the forest plot figures for the primary analyses.

The potential sources were evaluated for differences in age, male sex, CAD prevalence, hypertension prevalence, diabetes prevalence, dyslipidemia prevalence, stroke prevalence, smoker prevalence, LVEF (%), and follow-up period (Table 1). In

Table 1

Summary of baseline characteristics of included trials.

Study	Country	Design	No. of participants	Mean age, y	No. of male sex	No. of CAD	No. of hypertension	No. of diabetes	No. of dyslipidemia	No. of stroke	No. of smoker	Baseline LVEF, %	Follow-up, mo
Ivabradine vs placebo													
BEAUTIFUL[15]	33 countries	Randomized, double-blind, placebo-controlled trial	10,917	65	9047	10,917	7720	4036	8567	1991	1647	32.4 ± 5.5	19 (16–24)
SHIFT[16]	37 countries	Randomized, double-blind, placebo-controlled trial	6050	60	4970	4418	4314	1979	NA	523	1118	29.0 ± 5.1	22.9 (18–28)
SIGNIFY[17]	51 countries	Randomized, double-blind, placebo-controlled trial	19,102	65	13,839	19,102	16,466	8230	13,697	1265	4605	56.4 ± 8.5	27.8 (21.0–35.2)
Ivabradine vs beta-blockers													
INITIATIVE[18]	21 countries	Randomized, double-blind, parallel-controlled trial	939	61	798	939	NA	NA	NA	NA	NA	NA	4
Fasullo et al[19]	Italy	Randomized, double-blind,	155	62	105	155	70	54	75	NA	55	41.35 ± 4.7	2
Iliuta et al[20]	Romania	Open-label, randomized trial	527	63	311	356	351	151	NA	NA	NA	NA	1
Bocchi et al[13]	Brazil	Randomized trial	2596	59	1991	1561	1617	820	NA	199	406	28.1 ± 5.4	19.2 ± 9.0
ETHIC-AHF[14]	Spain	Comparative, randomized trial	71	66	29	30	52	42	30	7	35	29.8 ± 7.5	4

Age was expressed in means (decimals were rounded into numbers). Follow-up period was expressed in median and interquartile or means ± SD. LVEF (%) was expressed as means ± SD.
CAD = coronary artery disease, LVEF = left ventricular ejection fraction, NA = not available, SD = standard deviation.

Table 2

Summary of clinical outcomes of included trials.

Study	Intervention	Baseline RHR, bpm	Endpoint RHR, bpm	No. of CVD death	No. of all-cause death	Control	Baseline RHR, bpm	Endpoint RHR, bpm	No. of CVD death	No. of all-cause death
Ivabradine vs placebo										
BEAUTIFUL[15]	Ivabradine: n=5479	72	64	469	572	Placebo: n=5438	72	69	435	547
SHIFT[16]	Ivabradine: n=3241	80	67	449	503	Placebo: n=3264	80	75	491	552
SIGNIFY[17]	Ivabradine: n=9550	77	61	329	485	Placebo: n=9552	77	71	301	458
Ivabradine vs beta-blockers										
INITIATIVE[18]	Ivabradine: n=632	78	64	5	5	Atenolol: n=307	79	63	1	1
Fasullo et al[19]	Ivabradine: n=79	91	66	1	1	Metoprolol: n=76	92	65	1	1
Iliuta et al[20]	Ivabradine: n=172	79	NA	NA	7	Metoprolol: n=176	81	NA	NA	7
Bocchi et al[13]	Carvedilol+ ivabradine: n=1318	80	64	98	NA	Carvedilol + placebo: n=1278	80	74	93	NA
ETHIC-AHF[14]	Ivabradine + carvedilol or bisoprolol: n=33	87	61	1	2	Carvedilol or bisoprolol: n=38	88	68	0	2

RHR was expressed in means (decimals were rounded into numbers).
bpm=beats/min, CVD=cardiovascular disease, NA=not available, RHR=resting heart rate.

addition, RHR was expressed in means, and decimals were rounded into numbers in order to calculate the change of RHR from baseline to endpoint (Table 2 and Fig. 1).

Further, we performed a combination of 2 subgroup analyses, which combined data of ivabradine versus placebo with ivabradine versus beta-blockers, these analyses would explore for possible trends in the ivabradine versus comparators. Also, we performed the sensitivity analyses: while a study was removed from the meta-analysis,[13] the reanalysis of the combined effect on CVD mortality was performed. Similarly, another study was removed,[14] the reanalysis of the combined effect on all-cause morbidity was redone. Begg test and Egger test for publication bias were completed for the included studies.

3. Results

3.1. Literature search

Study selection was described in Fig. 2. A total of 348 citations were identified. Of these, 8 randomized controlled studies (3 trials were ivabradine vs. placebo[15–17]; other 5 trials were ivabradine vs. beta-blockers[13,14,18–20]) were included for meta-analysis of CVD mortality and all-cause mortality.

3.2. Participant characteristics in the included studies and follow-up period

The 8 included studies involved 40,357 patients were treated by ivabradine versus comparators (placebo or beta-blockers).[13–20] The higher age and higher prevalences of CAD, hypertension, diabetes, dyslipidemia, and lower LVEF (%) were reported in the included participants (Table 1). The follow-up period was more than 12 months in half of studies (Table 1).

3.3. Baseline RHR, endpoint RHR, and change of RHR

The baseline and endpoint average of RHR in ivabradine group, placebo group, ivabradine + beta-blockers group, and beta-blockers group were presented in Table 2. Further, the changes of RHR from baseline to endpoint were shown in Fig. 1. Ivabradine appeared to be

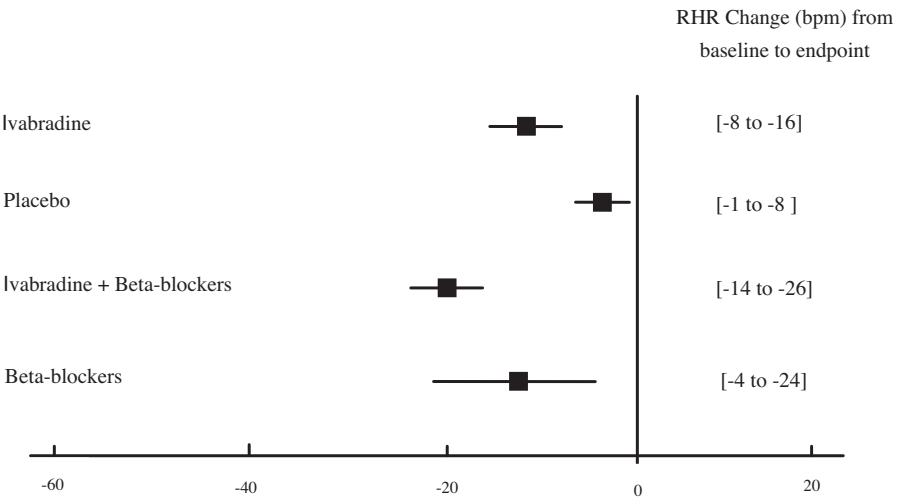

Figure 1. The change of resting heart rate comparing ivabradine versus comparators.

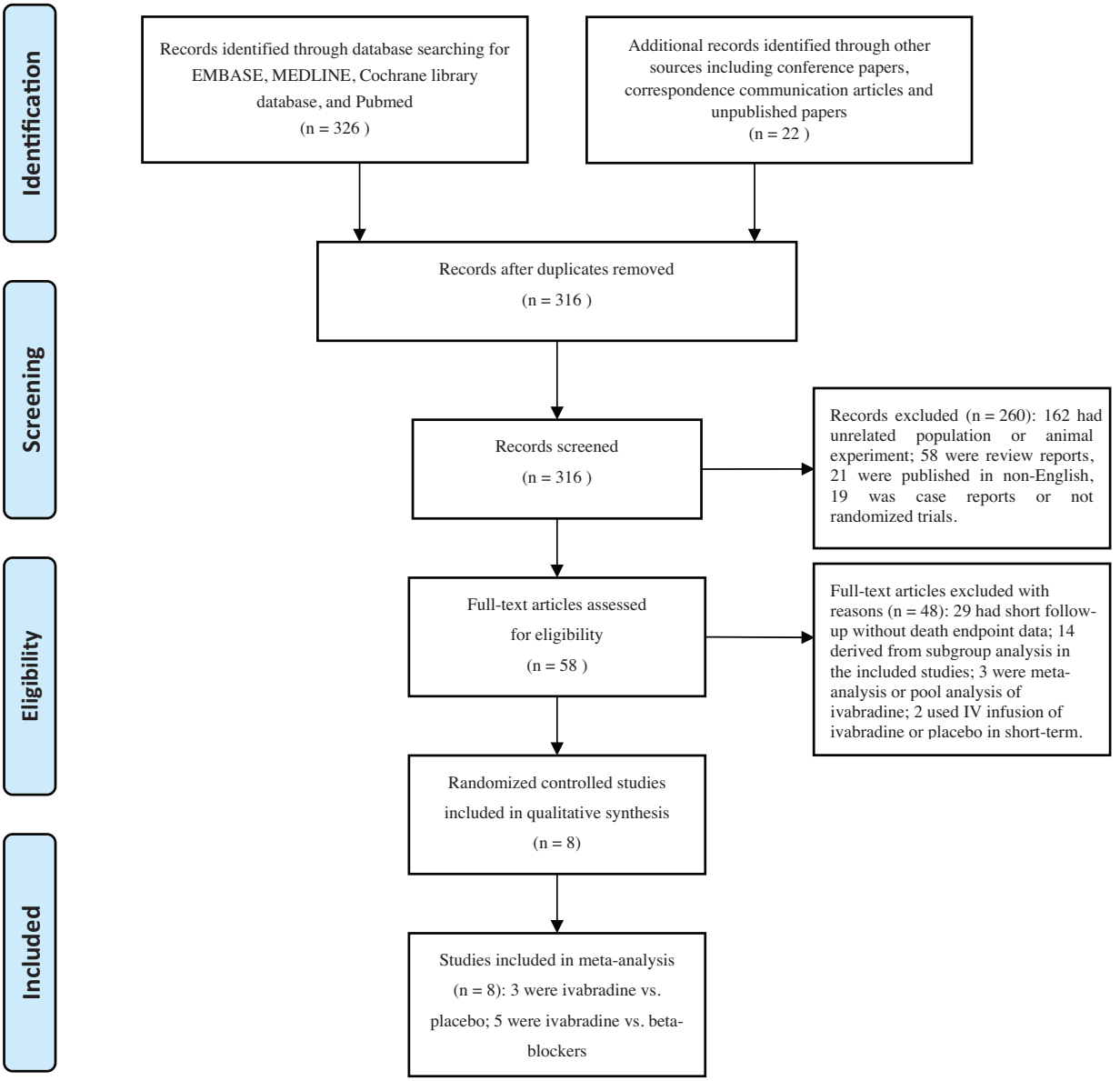

Figure 2. Flowchart of trial identification for meta-analysis.

more decreasing RHR than placebo, but it had less decreasing RHR than ivabradine + beta-blockers or beta-blockers.

3.4. CVD death and all-cause death

Eight studies reported the number of CVD death and all-cause death comparing ivabradine with placebo or beta-blockers,[13–20] and involved 20,504 patients using ivabradine (group), 18,254 patients using placebo (group), and 1875 patients using beta-blockers (group) (Table 2).

There were 1247 (3.41% rate) and 1227 (3.36% rate) CVD deaths in ivabradine and placebo, respectively. In the subgroup analysis, ivabradine had not a significantly lower risk of CVD mortality compared with placebo (RR: 1.02; 95% CI: 0.91–1.14, $P=.737$; [$I^2=52.1\%$; χ^2 for heterogeneity = 4.17, $P=.124$]) (Fig. 3). On the other hand, there were 105 (2.79% rate) and 95 (2.53% rate) CVD mortality in ivabradine and beta-blockers, respectively. In this subgroup analysis, ivabradine also had not a significantly lower risk of CVD mortality compared with beta-blockers (RR: 1.04; 95% CI: 0.80–1.37, $P=.752$; [$I^2=0.0\%$; χ^2 for heterogeneity = 1.17, $P=.761$]) (Fig. 3).

Further we performed a reclassified analysis to combine the subgroup (ivabradine vs. placebo) with another subgroup (ivabradine vs. beta-blockers) from 8 studies[13–20]; however, across all ivabradine versus comparators, the reclassification of ivabradine was not associated with a reduced risk of CVD mortality in all included study outcomes (RR: 1.01; 95% CI: 0.94–1.09, $P=.688$; [$I^2=0.0\%$; χ^2 for heterogeneity = 5.39, $P=.495$]) (Fig. 3).

With regard to all-cause death, ivabradine still had not any significantly lower risk of all-cause morbidity in comparison to placebo or beta-blockers (RR: 1.00, 95% CI: 0.92–1.09, $P=.992$ in ivabradine vs. placebo; RR: 1.17, 95% CI: 0.53–2.60, $P=.697$ in ivabradine vs. beta-blockers; RR: 1.00, 95% CI: 0.94–1.07, $P=.995$ in ivabradine vs. comparators) (Fig. 4).

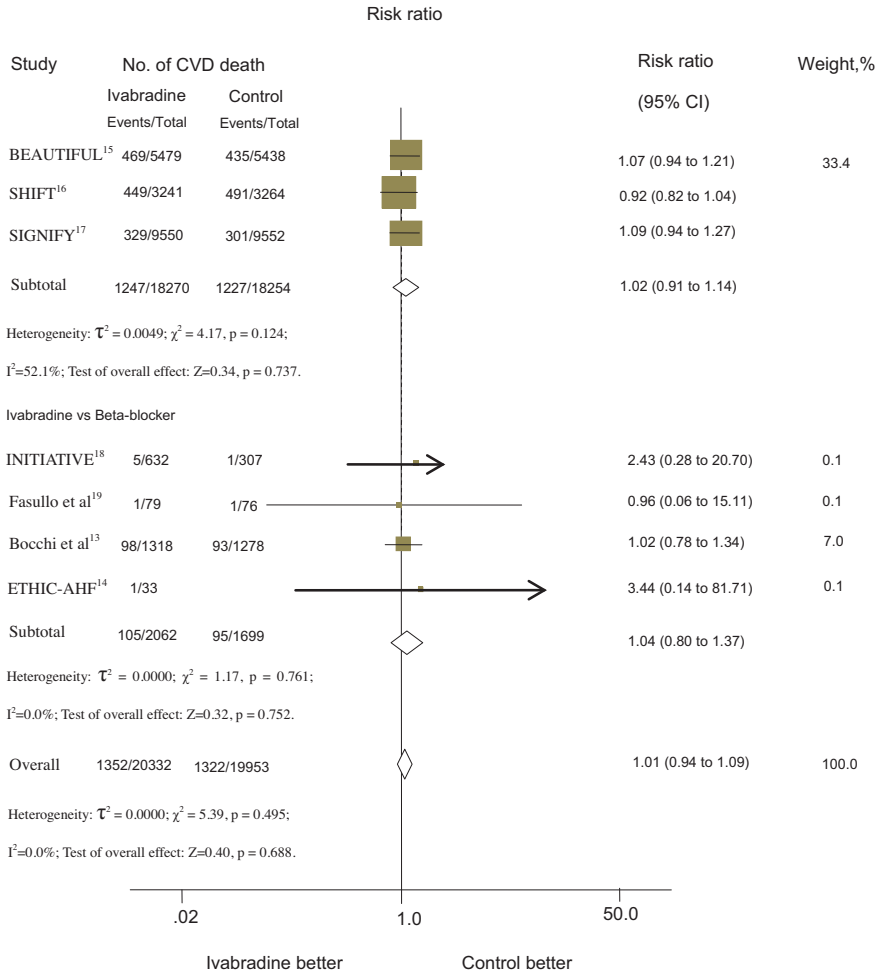

Figure 3. The risk of CVD mortality when ivabradine was compared with comparators. Shown are values for the risk of CVD mortality based on the treatment of ivabradine, as compared with comparators, and the study outcomes of CVD death from coronary causes, death related to cardiovascular procedures, fatal stroke, other deaths from cardiovascular causes, nonsudden death of unknown cause, and unclassifiable deaths. Data were combined using the DerSimonian and Laird random-effects model with inverse variance weighting. The horizontal line indicates the 95% confidence interval. CVD = cardiovascular disease.

3.5. Sensitivity analysis

In the 2 sensitivity analyses, after removal of a study,[13] ivabradine had not significantly lower the risk of CVD mortality in compared with beta-blockers (RR: 2.00, 95% CI: 0.45–8.89, $P=.363$) and in the reclassified analysis (RR: 1.02, 95% CI: 0.94–1.10, $P=.694$ in ivabradine vs. comparators). Similarly after removal of another study,[14] ivabradine also had not significantly lower the risk of all-cause mortality in compared with beta-blockers (RR: 1.18, 95% CI: 0.49–2.83, $P=.718$) and in the reclassified analysis (RR: 1.00, 95% CI: 0.94–1.07, $P=.991$ in ivabradine vs. comparators). Thus our sensitive analysis demonstrated that when respective removal of 2 studies did not alter the effect estimate in the meta-analysis, and the conclusion was stable and unchanged. In addition, Begg test and Egger test did not find for publication bias in the included studies (Fig. 5), z value for Begg test was 0.87, $P=.386$; t value for Egger test was 1.53, $P=.177$.

4. Discussion

It has long been a controversial hotspot whether RHR is a risk factor or a marker for death. Early the Framingham heart study in patients free of CVD, but cardiovascular and coronary mortality increased progressively with rising RHR.[21] Further there was a J-shaped curve for the relationship between RHR and all-cause death.[22] Slowing RHR could decrease the mortality of myocardial infarction.[23]

Despite that women have a little longer lifespan than men, when adjusted for age, HR in women averages 2 to 7 bpm higher than in men,[24,25] similarly, in the MERIT-HF study, Metoprolol CR/XL significantly reduced mortality independent of change in HR, [26] suggesting that HR was not exclusive mechanism to improve lifespan. In our meta-analysis indicated that compared with placebo, ivabradine could decrease more RHR (Fig. 1), however, which was not significantly lower risks of CVD mortality and all-cause mortality (Figs. 3 and 4). Thereby, our findings suggested that an elevated RHR would be one of intermediate links and risk factors in causal relationships of death, the sympathetic activity and body metabolic demand would be determining factor for lifespan. However, our conclusion needs several potential mechanisms to explain: First, ivabradine, a specific inhibitor of the If current in the sinoatrial node, is a pure RHR lowering agent, and it does not affect myocardial contractility, blood pressure, intracardiac conduction, or ventricular repolarization.[6,7,27] However, RHR serves

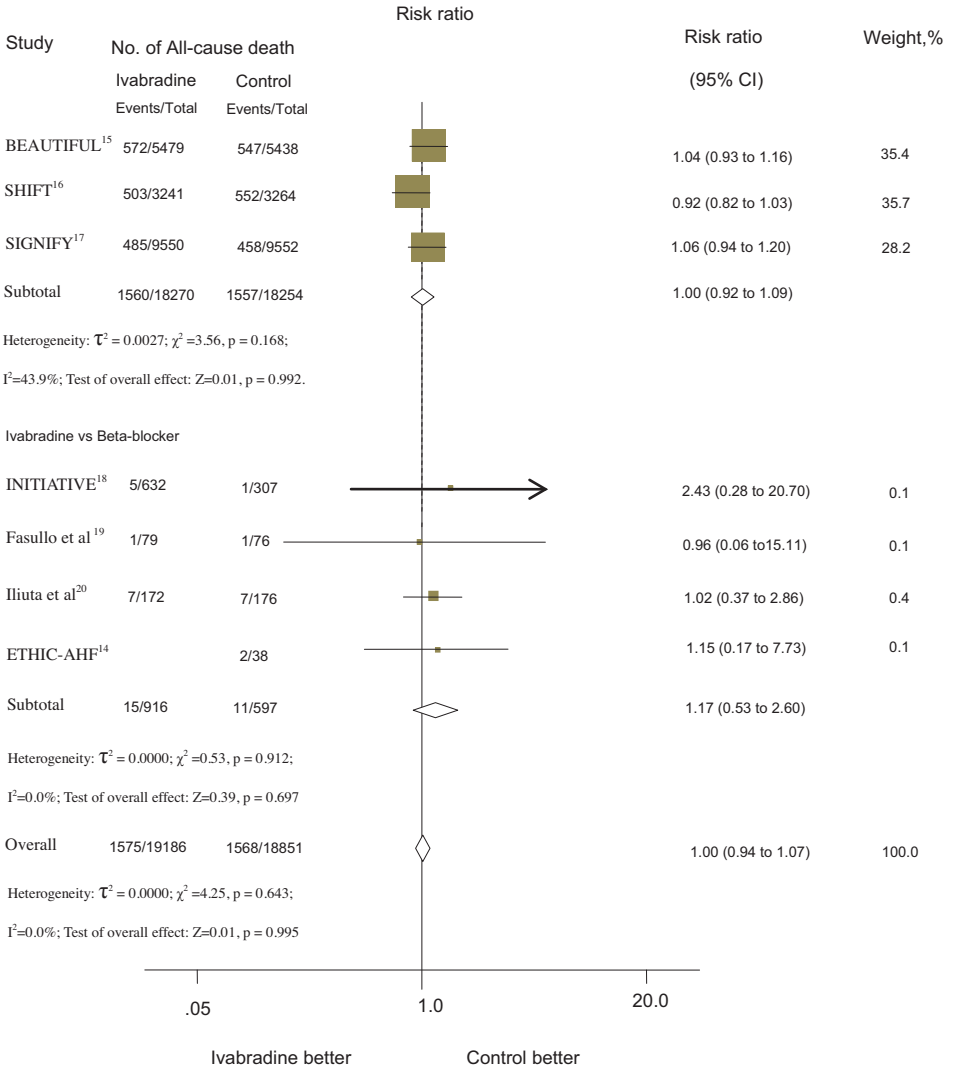

Figure 4. The risk of all-cause mortality when ivabradine was compared with comparators. Shown are values for the risk of all-cause mortality based on the treatment of ivabradine, as compared with comparators, and the study outcomes of all-cause death from any cause death or total death. Data were combined using the DerSimonian and Laird random-effects model with inverse variance weighting. The horizontal line indicates the 95% confidence interval.

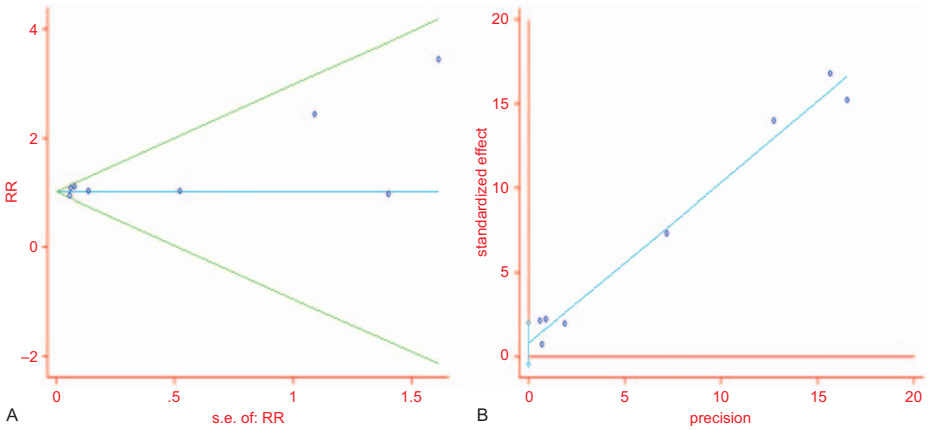

Figure 5. Begg test and Egger test for publication bias in the included studies. (A). Begg funnel plot with pseudo 95% confidence limits. (B). Egger publication bias plot.

as a marker of autonomic nervous system activity. The depolarization rate of sinoatrial node is largely determined by the activity of autonomic nervous system. Early studies showed that the sustained autonomic imbalance (a relative or absolute decrease in vagal activity or an increase in sympathetic activity) has been associated with arrhythmia, hypertension, myocardial hypertrophy, CAD, heart failure, and death,[28–31] and its potential mechanisms might be involved in endothelial dysfunction, atherosclerosis, plaque rupture, thrombosis, and activated renin–angiotensin–aldosterone system.[32–35] On the other hand, the elevated plasma norepinephrine levels, which reflect sympathetic nervous system activity, are directly related to prognosis; for example, patients with levels >900 pg/mL have a poor prognosis and the shortened life expectancy.[36]

Although beta-blockers inhibit the adrenergic beta receptor sites for the endogenous catecholamines epinephrine and norepinephrine of sympathetic nervous system, some beta-blockers exhibit ISA (e.g., oxprenolol, pindolol, penbutolol, labetalol, acebutolol). Considering that the beta-blockers' agents with ISA increase CVD mortality, thus they are not used in the management of CAD, heart failure, and tachyarrhythmia.[5,6] It is inescapably clear that the endogenous long-lasting sympathetic hyperactivity play an key role on increasing CVD mortality and all-cause mortality.

Second, RHR also is a marker of oxygen consumption and metabolic demand.[37] In smaller animals, higher RHR is derived from higher basal metabolic rate , which is correlated with body surface area.[38] Surprisingly, the total number of heart beats/lifetime is remarkably constant among mammals,[2] suggesting that a basic characteristic of the energetics of living matter drives this phenomenon. It is calculated that the basal O_2 consumption/body atom of all animals is ~10 O_2 molecules/lifetime and in those animals with a heart ~10^{-8} O_2 molecules/heart beat.[39]

Importantly, caloric restriction increases lifespan and delays the occurrence of pathophysiological changes in various mammalian species.[40] Caloric restriction by 40% may change the balance of sympathetic and parasympathetic nervous system, thus decrease HR by ~10% and diastolic arterial pressure by ~10 mm Hg,[41] in addition to reduce reactive oxygen species production and its damage on mitochondria,[42] and improve insulin sensitivity.

Third, an average human HR is assumed to 60 to 100 bpm, we should have lifespans about 20 years.[43] For a majority of human history, average lifespan has been <30 years.[44] A life expectancy of 70 to 80 years in humans is only presented in recent decades. Developments of health care, disease prevention, and modern medical treatment are primarily responsible for the increase in human lifespan from other mammals[45,46]; for example, sinus node and cardiac conduction system disorders result in severe bradycardia and arrhythmia, subsequently cardiac origin of syncope is occurred, it is necessary for prophylactic implantation of artificial cardiac pacemaker to prolong lifespan.

4.1. Limitations

The study was an attempt to evaluate the impact of a sinus node selective drug induced HR decrease on mortality, thus the different CVD populations were selected in the study. Because the meta-analysis data were based on the published studies and reports, we could not detailed analyze that ivabradine would be possible trend of improved survival in heart failure population while the cutoff of HR >70/min. Certainly, we also noticed that ivabradine improved heart failure mortality than placebo (3% vs. 5%), but it did not further decrease CVD mortality and all-cause mortality than placebo in the same heart failure population.[16] Considering that ivabradine reduced only 2% heart failure death rate than placebo, and ivabradine was not the same as beta-blockers, it was necessary for several large samples trials to prove the 2% value and significant in real world. Simultaneously, the concept of heart-beats-per-life is necessary to be used as a background of the specific disease study in future. Inevitably, the primary endpoint of the SHIFT trial was the composite of cardiovascular death or hospital admission for worsening heart failure and the effect was driven mainly by hospital admissions for worsening heart failure. In that situation, when patients are admitted to the hospital, follow-up is ended. Not followed until death. We can never tell that these patients are alive or dead if ivabradine is continued. We can only know the effects of ivabradine on cardiovascular mortality when the patients die before the first hospitalization for worsening heart failure. On the other hand, ivabradine had the similar decreasing death rate compared with beta-blockers in small samples and short follow-up period; however, 3 of those studies showed that ivabradine was partly combined with beta-blockers in the intervention group,[13,14,16] when the 2 study[13,14] was deleted in our sensitivity analysis, the conclusion of the meta-analysis was stable and unchanged. In addition, in SHIFT study,[16] beta-blockers were administered to 2897 (89%) in ivabradine group and 2923 (90%) in placebo group, at 32 months follow-up, mean HR was 67 bpm versus 75 bpm in the 2 group, all-cause mortality was 503 (16%) versus 552 (17%), $P=.092$; CVD mortality was 449 (14%) versus 491 (19%), $P=.128$; thus ivabradine + beta-blocker could more decrease RHR than beta-blocker; however, the diminishing RHR did not further significantly minimize the risk of death between the 2 groups. Thereafter, it was necessary for several large samples of population studies and longer follow-up to explore head to head comparison of ivabradine and beta-blockers in future.

5. Conclusion

Ivabradine had a neutral effect on mortality, suggesting that a pure RHR lowering agent did not reduce CVD mortality, all-cause mortality and improve the lifespan.

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