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REVIEWS

The Risk of Atrial Fibrillation With Ivabradine Treatment: A Meta-analysis With Trial Sequential Analysis of More Than 40000 Patients

İbrahim Halil Tanboğa MD | Selim Topçu MD | Enbiya Aksakal MD | Oktay Gulcu MD | Emrah Aksakal MD | Uğur Aksu MD | Vecih Oduncu MD | Fatih Rıfat Ulusoy MD | Serdar Sevimli MD | Cihangir Kaymaz MD

Department of Cardiology (Tanboğa, Topçu, Enbiya Aksakal, Gulcu, Emrah Aksakal, Aksu, Sevimli) and Department of Biostatistics (Tanboğa, Topçu), Medical School, Atatürk University, Erzurum, Turkey; Department of Cardiology (Oduncu), Medical School, Bahçeşehir University, Istanbul, Turkey; Department of Cardiology (Ulusoy), Yalova State Hospital, Yalova, Turkey; Department of Cardiology (Kaymaz), Kosuyolu Heart Hospital, Istanbul, Turkey

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corresponding Author: İbrahim Halil Tanboğa, MD, Tıp Fakültesi, Kardiyoloji AD, Atatürk University, Erzurum, Turkey, (haliltanboga@yahoo.com)

Recent trials reported that risk of atrial fibrillation (AF) is increased in patients using ivabradine compared with controls. We performed this meta-analysis to investigate the risk of AF association with ivabradine treatment on the basis of data obtained from randomized controlled trials (RCTs). We searched PubMed, EMBASE, Scopus, and the Cochrane Library for RCTs that comprised >100 patients. The incidence of AF was assessed. We obtained data from European Medicines Agency (EMA) scientific reports for the RCTs in which the incidence of AF was not reported. We used trial sequential analysis (TSA) to provide information on when we had reached firm evidence of new AF based on a 15% relative risk increase (RRI) in ivabradine treatment. Three RCTs and 1 EMA overall oral safety set (OOSS) pooled analysis (included 5 RCTs) were included in the meta-analysis (N = 40 437). The incidence of AF was 5.34% in patients using ivabradine and 4.56% in placebo. There was significantly higher incidence of AF (24% RRI) in the ivabradine group when compared with placebo before (RR: 1.24, 95% confidence interval: 1.08-1.42, $P = 0.003$, $I^2 = 53\%$) and after excluding OOSS (RR: 1.24, 95% confidence interval: 1.06-1.44, $P = 0.008$). In the TSA, the cumulative z-curve crossed both the traditional boundary ($P = 0.05$) and the trial sequential monitoring boundary, indicating firm evidence for ≥15% increase in ivabradine treatment when compared with placebo. Study results indicate that AF is more common in the ivabradine group (24% RRI) than in controls.

KEYWORDS

atrial fibrillation, meta-analysis, Ivabradine

1 | INTRODUCTION

Ivabradine is a heart rate (HR)-lowering drug and acts via specific and selective I_f inhibition.[1] Since 1980 it has been well known that resting HR is both a prognostic indicator and treatment target in coronary artery disease (CAD) and heart failure (HF).[2,3] Early clinical studies of ivabradine, such as the International Trial on the Treatment of Angina With Ivabradine vs Atenolol (INITIATIVE) study[4] and the Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction (BEAUTIFUL)[5] trial, focused on its antianginal effects. It has been shown that selective reduction of HR improves coronary blood flow in ischemic myocardial area. Favorable effects have been more pronounced in patients with HR >70 bpm as determined in the prespecified subgroup analyses. Afterward, the Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial (SHIFT),[6] which included HF patients, was conducted, and in this study it was determined that ivabradine reduced the adverse events in HF patients. In a meta-analysis performed by Martin et al in 2014, it was determined that atrial fibrillation (AF) risk was significantly greater in patients using ivabradine.[7] Recently, the Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease

(SIGNIFY),[8] which is the largest randomized controlled trial (RCT) including CAD patients without HF, was published, and positive effects of ivabradine were not observed in this patient group. Furthermore, it was determined that frequency of AF and bradycardia were significantly higher in the ivabradine arm when compared with placebo. In SIGNIFY subgroup analyses, which were published later, it was claimed that neither AF nor bradycardia were related to adverse events.[9]

Debates about increased AF risk in patients using ivabradine still continue. Therefore, we aimed to perform a meta-analysis to assess the risk of AF in patients using ivabradine on the basis of data obtained from all double-blind RCTs.

2 | METHODS

We followed the preferred reporting items for systematic reviews and meta-analyses guidelines to report our findings.[10]

2.1 | Eligibility Criteria

The study's eligibility criteria were as follows: double-blind RCTs that (1) compared ivabradine with placebo, (2) included the incidence of AF during follow-up, and (3) had ≥50 patients in each group. We did not exclude trials where AF incidence was not reported in the published manuscript, but attempted to identify that data wherever possible.

2.2 | Information Sources and Searching

We searched the MEDLINE, Scopus, EMBASE, and Cochrane Library for RCTs published up to January 2016 in the English language and in humans. Also, European Medicines Agency (EMA) scientific discussion as evidence of licensing was searched for data that were not published in the original trial or unpublished trials. In addition, to find any potential eligible studies, we performed a manual search by checking all the references of RCTs, meta-analyses, and reviews. A computerized search using the terms "ivabradine" and "randomized controlled trial" was made for any indication. All searches were conducted by 2 authors (IHT and ST).

2.3 | Selection and Quality Assessment of Randomized Controlled Trials

Two authors (IHT and ST) independently assessed study eligibility and risk of bias and extracted data. Disagreements were resolved by consensus. The risk of bias was assessed by recommendation of the Cochrane Collaboration: sequence generation of allocation; allocation concealment; blinding of participants, staff, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Trials with high or unclear risk for bias for any 1 of the first 3 components were considered as at high risk of bias; otherwise, they were considered as low risk of bias.

2.4 | Outcome Measure

The primary endpoint of our study was the incidence of AF during follow-up.

2.5 | Trial Sequential Analysis

We applied trial sequential analysis (TSA) to all RCTs included in the meta-analysis. Trial sequential analysis was performed according to the monitoring boundaries approach for the incidence of AF.[11,12] Trial sequential analysis is a statistical method that combines a prior information size calculation for a meta-analysis with adaptation of monitoring boundaries to evaluate the accumulating evidence.[13] Our assumptions included 2-sided testing, type 1 error = 5%, power = 80%. We chose a 15% relative risk increase (RRI) for the incidence of AF. The main result of TSA was expressed through a cumulative z-curve graph; the boundaries in this graph for concluding superiority or inferiority or futility were determined according to the O'Brien-Fleming α spending function. All calculations were carried out using a specific statistical software, TSA version 0.9 beta (User Manual for TSA, Copenhagen Trial Unit 2011; http://www.ctu.dk/tsa).

To assess the magnitude of difference is of clinical importance; we calculated absolute risk reduction/increase (ARR/ARI), relative risk reduction/increase (RRR/RRI), and number needed to treat/harm (NNT/NNH). The ARR/ARI, RRR/RRI, and NNT/NNH were calculated as defined previously.[14,15] Clinical importance was among the criteria defined as ARR/ARI ≥5%, RRR/RRI ≥15%, and NNT <50; and statistical significance was defined as $P < 0.05$.[16]

2.6 | Statistical Analysis

Summary risk ratio (RR) and 95% confidence interval (CI) were calculated between ivabradine and control regarding the incidence of AF using fixed- and random-effects models. The random-effects model was indicated in outcomes with significant heterogeneity ($I^2 > 25\%$). In others, the fixed-effects model was used. The Q together with the resulting degrees of freedom (df), τ^2, and I^2 statistic were used to evaluate heterogeneity. Furthermore, we investigated possible reasons for heterogeneity using a meta-regression, evaluating the impact of prespecified covariates such as age, sex, diabetes mellitus, hypertension (HTN), baseline HR, baseline ejection fraction (EF), previous CAD and stroke, study indication (angina or HF), and ivabradine dose (2.5–10 mg vs >10 mg) on the incidence of AF. Sensitivity analysis was performed by excluding trials one at a time to assess the contribution of each study to the pooled estimates. The EMA–overall oral safety set (OOSS) were excluded and sensitivity analyses were repeated. Statistical significance was defined as $P < 0.05$ (2-tailed tests). Statistical analysis was performed with RevMan 5.3 software (the Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark).

3 | RESULTS

Our initial search strategy identified 43 articles and 1 meta-analysis. We excluded 29 trials that were not RCTs, not double blinded, that

had no follow-up or short duration of follow-up, had duplicate data, and which were not written in English. The meta-analysis performed by Martin et al[7] was examined in detail in terms of references. Four studies in this meta-analysis were not included in our study because the number of patients was <100.[17–20] Two studies were excluded because there were no data about AF.[21,22] Finally we included 8 RCTs in this meta-analysis. Individual AF data were only reported in the SHIFT,[6] BEAUTIFUL,[5] and SIGNIFY trials.[8] However, in the scientific discussion documents of EMA for ivabradine license, 5 RCTs were included as a single dataset in OOSS.[23] In the OOSS, AF frequency during follow-up was given as pooled (2 of these were published before,[4,24] but we could not determine whether the remaining 3 had been published or not) as a single study. In EMA-OOSS pooled analyses, AF frequency in ivabradine 5 to 7.5 mg (n = 1650) and 10 mg (n = 1160), placebo (n = 313), amlodipine (n = 404), and atenolol (n = 408) arms were identified. Data about AF frequency were obtained from the original article in SIGNIFY[8] and SHIFT[6] trials, whereas the AF frequency data in the BEAUTIFUL study were obtained from the EMA website.[25]

Eight RCTs included 40 437 patients. When OOSS was excluded, the remaining patients numbered 36 501. Baseline characteristics are summarized in Table 1. The incidence of AF was 5.34% (n = 1126) in the ivabradine group and 4.56% (n = 885) in the placebo group. There was a significantly higher incidence of AF (24% RRI) in the ivabradine group when compared with placebo (RR: 1.24, 95% CI: 1.08-1.42, P = 0.003; Figure 1A). There was a significant heterogeneity between trials (I^2 = 53%, τ^2 = 0.01, Q [df: 3] = 6.3, and P = 0.10). The NNH, derived from pooled risk difference (0.77%), was 122 over a median of 2 years' follow-up with ivabradine treatment. In the analysis performed after OOSS was excluded, AF frequency was still significantly higher in the ivabradine group (RR: 1.24, 95% CI: 1.06-1.44, P = 0.008; Figure 1B). There was a significant heterogeneity between trials (I^2 = 68%, τ^2 = 0.01, Q [df: 2] = 6.3, and P = 0.04). Similarly, the NNH derived from pooled risk difference (1.22%) was 82.

When the SHIFT and BEAUTIFUL studies were both analyzed in the overall population (Figure 1C) and as previously reported in patients with HR >70 bpm,[26] the AF incidence was found to be higher in the ivabradine group (RR: 1.15, 95% CI: 1.01-1.31, P = 0.04 and RR: 1.25, 95% CI: 1.10-1.42, respectively). In Table 2, we summarized clinical vs statistical importance for individual trials as well as from pairwise combinations to overall pooled combination.

We did not assess small study effects and publication bias using funnel plot because the number of studies was <10.[27] Sensitivity analysis indicated that none of the studies had a significant influential effect on the risk of AF and similar results to main findings, except that the SHIFT trial had a borderline significant effect on the risk of AF (P = 0.064).

After adjusting for baseline covariates (age, diabetes mellitus, HTN, baseline HR, baseline EF, previous CAD and stroke, study indications [angina or HF], and ivabradine doses [2.5–10 mg vs >10 mg]), we determined that previous CAD, baseline EF, study indications, ivabradine doses, previous stroke, and HTN might be the cause of heterogeneity for the development of AF during follow-up.

In the TSA, the cumulative z-curve crossed both the traditional boundary (P = 0.05) and the trial sequential monitoring boundary, indicating that there is firm evidence for ≥15% increase in ivabradine group when compared with placebo (Figure 2).

4 | DISCUSSION

This meta-analysis result showed that ivabradine treatment is associated with increased risk of AF with approximately 24% RRI. Also, TSA indicated that there was firm evidence for increased AF risk in ivabradine treatment.

The studies about ivabradine use in HF and angina started after 2000. Its use in angina pectoris and HF was approved by the EMA in 2005 and 2012, respectively. Increased AF risk related to ivabradine use as shown in the meta-analysis by Martin et al[7] in 2014, and in the SIGNIFY[8] study published in the same year, has drawn attention. We included a total of 8 RCTs in our study. Among these, individual AF data were available only in the SHIFT,[6] BEAUTIFUL,[5] and SIGNIFY trials.[8] However, in the EMA application for ivabradine license, 5 RCTs were included in the OOSS. In the OOSS, AF frequency during follow-up was given as pooled; because of this, we considered the OOSS that included these 5 RCTs as a single study. Also, 2 of these were published before,[4,24] but we could not determine whether the remaining 3 had been published or not. The EMA-OOSS analyzed as a single dataset is likely to result in an overestimation of within-study variance and an underestimation of between-study variance.

TABLE 1 Baseline Characteristics of Included RCTs

Trials	IVA, n	Control, n	Comparator	Indication	IVA Dose, mg	Age, y	EF, %	Previous CAD, %	Male Sex, %	Previous Stroke, %	HR, bpm	DM, %	HTN, %
OOSS	2811	1125	Aten/Aml/ placebo	Angina	5–10	NA	NA	100	NA	NA	NA	NA	NA
BEAUTIFUL	5477	5430	Placebo	HF + angina	5–7.5	65.2	32.4	88	83	18	71.6	37	71
SHIFT	3232	3260	Placebo	HF	2.5–7.5	60.4	29	68	77	8	79.9	31	67
SIGNIFY	9550	9552	Placebo	Angina	10–20	65	56.5	100	72.5	6.6	77.2	43.1	86.2

Abbreviations: Aml, amlodipine; Aten, atenolol; BEAUTIFUL, Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction; CAD, coronary artery disease; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; HR, heart rate; HTN, hypertension; IVA, ivabradine; NA, not available; OOSS, overall oral safety set; RCT, randomized controlled trial; SHIFT, Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial; SIGNIFY, Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease.

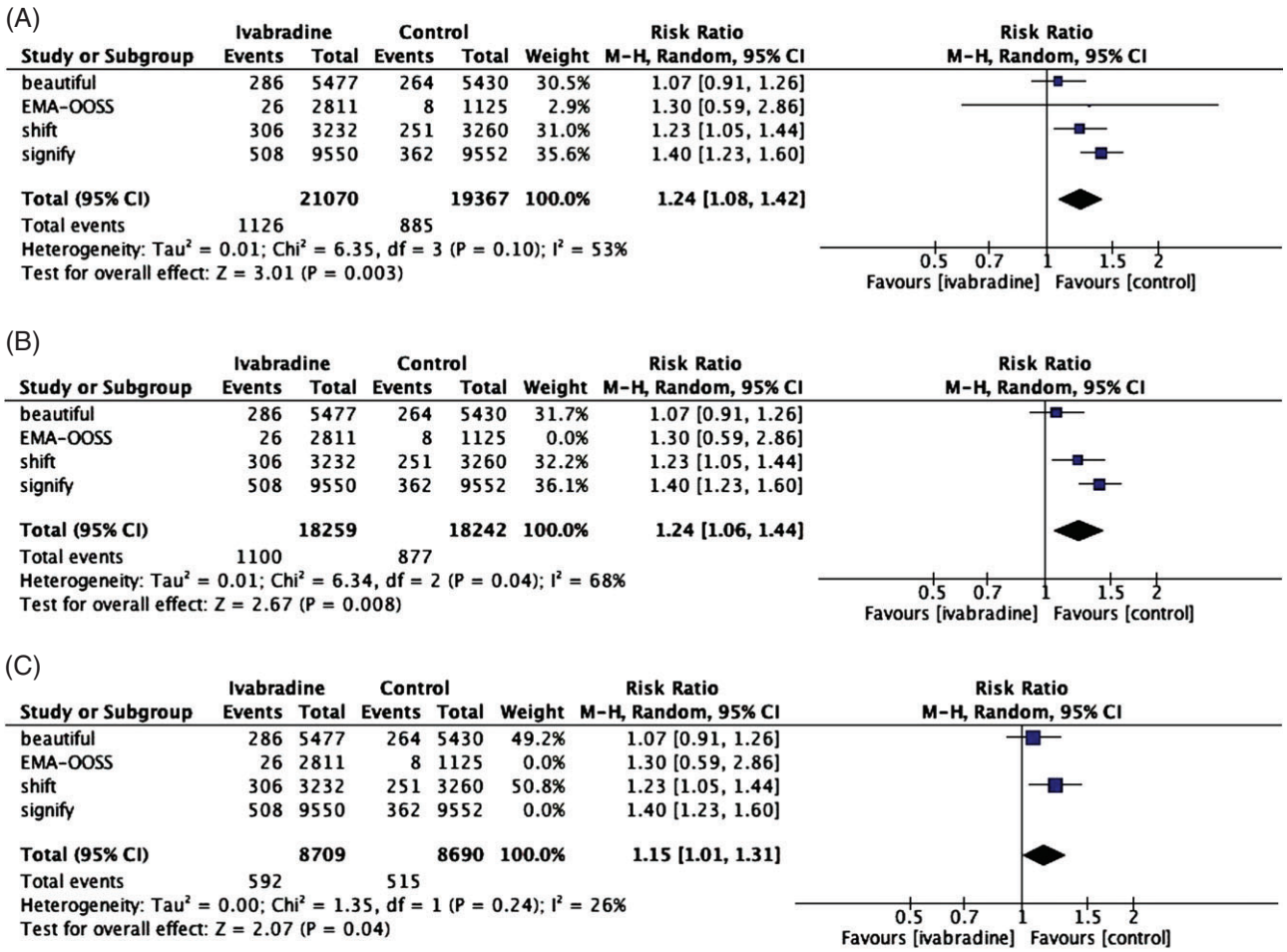

FIGURE 1 Forest plots of AF risk in (A) 8 RCTs; in (B) 3 RCTs, BEAUTIFUL, SHIFT, and SIGNIFY; and in (C) SHIFT and BEAUTIFUL. Abbreviations: AF, atrial fibrillation; BEAUTIFUL, Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction; CI, confidence interval; df, degrees of freedom; EMA-OOSS, European Medicines Agency–overall oral safety set; M-H, Mantel-Haenszel; RCT, randomized controlled trial; SHIFT, Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial; SIGNIFY, Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease.

TABLE 2 Clinical Significance vs Statistical Significance

Results	AF % (IVA)	AF % (Control)	RR (95% CI)	ARI	RRI, %	NNH, n	Clinically Significance?	Statistically Significance?
OOSS	0.9	0.7	1.30 (0.59-2.86)	0.21	30	468	N	N
BEAUTIFUL	5.2	4.9	1.08 (0.91-1.27)	0.36	8	278	N	N
SHIFT	9.5	7.7	1.23 (1.05-1.44)	1.77	23	57	Y	Y
SIGNIFY	5.3	3.8	1.40 (1.23-1.60)	1.53	40	65	Y	Y
BEAUTIFUL + SHIFT	6.8	5.9	1.15 (1.01-1.31)	0.87	15	115	Maybe	Y
BEAUTIFUL + SHIFT with HR >70 bpm	8.4	6.7	1.26 (1.11-1.43)	1.72	26	58	Y	Y
BEAUTIFUL + SHIFT + SIGNIFY	6.0	4.8	1.24 (1.06-1.44)	1.22	24	82	Y	Y
OOSS+ BEAUTIFUL + SHIFT + SIGNIFY	5.3	4.6	1.24 (1.08-1.42)	0.77	24	129	Y	Y

Abbreviations: AF, atrial fibrillation; ARI, absolute risk increase; BEAUTIFUL, Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction; CI, confidence interval; HR, heart rate; IVA, ivabradine; N, no; NNH, number needed to harm; OOSS, overall oral safety set; RR, relative risk; RRI, relative risk increase; SHIFT, Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial; SIGNIFY, Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease; Y, yes.

In the meta-analysis performed by Martin et al,[7] BEAUTIFUL, SHIFT, and EMA-OOSS were included and ivabradine treatment was shown to increase AF risk by 15% (RR: 1.15, 95% CI: 1.05-1.26, P = 0.015). The number of patients in 4 RCTs was <100[17–20] and there were no data related to AF frequency; therefore, they were not included in our study (Martin et al[7] indicated that they obtained the AF data of those studies via personal communication). On the other hand, in our own analysis, we included the SIGNIFY[8] study, which was published after the meta-analysis performed by Martin et al.[7] Additionally, when we combined the SHIFT and BEAUTIFUL studies, which

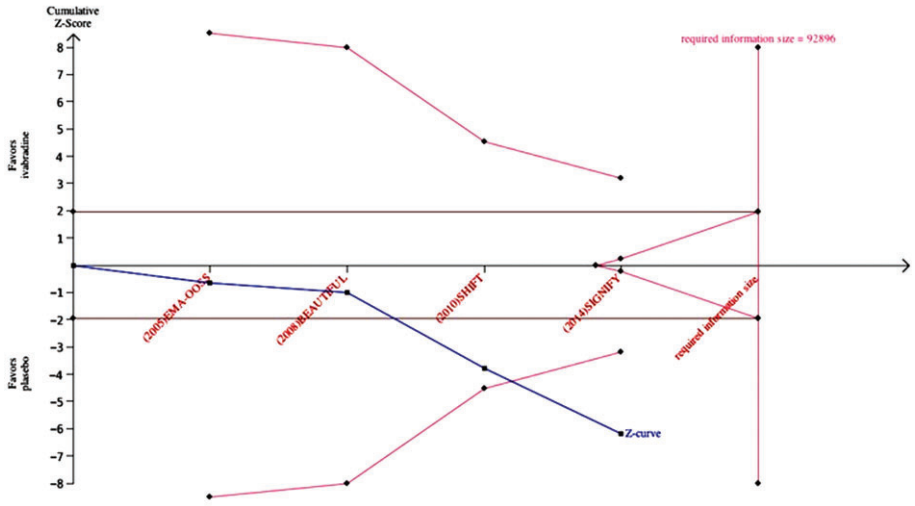

FIGURE 2 Trial sequential analysis evaluating the risk of AF in ivabradine treatment. The expected relative risk increase was assumed to be 15%. Abbreviations: AF, atrial fibrillation; BEAUTIFUL, Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction; EMA-OOSS, European Medicines Agency–overall oral safety set; SHIFT, Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial; SIGNIFY, Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease.

included patients with HF, their analysis demonstrated that the AF incidence was higher in the ivabradine group (RR: 1.15, 95% CI: 1.01-1.31, P = 0.04). Also, Fox et al[26] recently showed that in the pooled subgroup analysis of the SHIFT and BEAUTIFUL studies, there was a significantly increased risk of AF with ivabradine (RR: 1.25, 95% CI: 1.10-1.42) in patients with HR >70 bpm. Finally, we performed a TSA and clinical vs statistical importance analysis in our meta-analysis. In the TSA, we showed that there was firm evidence for a ≥15% increase in ivabradine treatment when compared with placebo. Also, pooled analysis of all study combinations in Table 2 showed that effect magnitude is meaningful both clinically and statistically.

Among studies included in our meta-analysis, only the SHIFT study included patients with a past history of AF[6]; however, in the SIGNIFY and BEAUTIFUL studies, patients with NSR were indicated as an inclusion criteria.[5,8] There was no information about the history of AF in the EMA-OOSS data.[23] This may affect the AF incidence during follow-up. Also, baseline characteristics of the studies may be one of the factors affecting the AF incidence during follow-up. In the meta-regression analysis, we determined that previous CAD, baseline EF, study indications, ivabradine doses, previous stroke, and HTN might be the cause of heterogeneity for the development of AF in follow-up. For instance, the absence of HF patients and the high dose of ivabradine use in the SIGNIFY study may be related to the AF risk.[8]

There is only 1 trial with data about the effect of ivabradine-related AF on the clinical outcomes.[9] It was demonstrated strongly that AF was related to unfavorable clinical events in population-based large clinical trials with long-term follow-up.[28,29] However, even though it was mentioned that there was no difference between patients with and without emergent AF regarding clinical outcomes in the SIGNIFY substudy,[9] the fact that both the number of patients with emergent AF was relatively low and the follow-up period was short might have masked the relation with clinical events.

There might be a few possible explanations regarding the increased risk of AF with ivabradine. First, when the baseline clinical characteristics of patients examined in detail in RCTs were included in this meta-analysis, one might propose that such a group of patients is already prone to AF; however, the randomized design of the included trials makes this assumption weak. Evaluations listed in Table 2 demonstrate that increased AF risk is also clinically important. Another possible mechanism may be the mechanism claimed by Martin et al.[7] As known, ivabradine inhibits I_f channels coded by the HCN4 gene.[30] Also, pulmonary venous myocardium,[31] which is an important source in the initiation and maintenance of AF, contains high rates of I_f channels.[32] Genome-wide association studies have identified associations between genetic variants in the region of the HCN4 gene.[33,34] This might be associated with the possibility that ivabradine treatment may increase AF risk.

4.1 | Study Limitations

An important limitation of our study was that EMA-OOSS was analyzed as a single dataset and there were no detailed data about the studies constituting this dataset. However, we repeated the pooled analyses and performed sensitivity analyses both including and excluding this dataset. In addition, because there were no comprehensive data demonstrating the relationship of newly developed AF during the follow-up with clinical events, we could not analyze the relationship of newly developed AF with clinical events.

5 | CONCLUSION

In this study, we showed that ivabradine treatment is associated with increased risk of AF.

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