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ORIGINAL ARTICLE

Atrial fibrillation associated with ivabradine treatment: meta-analysis of randomised controlled trials

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ABSTRACT

Objective To quantify any risk of atrial fibrillation (AF) associated with ivabradine treatment by meta-analysis of clinical trial data.

Methods Medline, Embase, Web of Knowledge and the Cochrane central register of controlled trials were searched for double-blinded randomised controlled trials of ivabradine with a minimum follow-up period of 4 weeks. For studies where AF data were unpublished, safety data were obtained from the European Medicines Agency (EMA) website and personal communications. Studies were appraised for risk of bias using components recommended by the Cochrane Collaboration. Meta-analyses were performed of relative risk of AF and absolute risk difference of AF per year of treatment. The main outcome measure was incident AF during the follow-up period.

Results AF data were available from 11 studies: one from the published report, six from the EMA and four from personal communications. Ivabradine treatment was associated with a relative risk of AF of 1.15 (95% CI 1.07 to 1.24, $p=0.0027$) among 21 571 patients in the meta-analysis. From this we estimated that the number needed to harm for ivabradine would be 208 (95% CI 122 to 667) per year of treatment.

Conclusions AF is a substantially more common side effect of ivabradine treatment than one patient in 10 000, the risk presently reported in the product literature. The incidence of AF has not routinely been reported in clinical trials of ivabradine.

greater than 75 bpm, in combination with standard therapy, including β -blocker therapy, or when β -blockers are contraindicated or not tolerated.³ Use of ivabradine is yet to be approved by the US Food and Drug Administration.

Genome-wide association studies have identified associations between genetic variants in the region of the gene *HCN4*, which codes for the main ion channel responsible for the I_f current, and both heart rate and atrial fibrillation (AF).^{4 5} The pulmonary venous myocardium, which is an important source of AF initiation and maintenance,⁶ demonstrates an I_f current which is affected by ivabradine.⁷ This raises the possibility that ivabradine treatment may affect AF risk. AF is common in patients with coronary artery disease and cardiac failure⁸ and so incident AF in the target population for ivabradine treatment would not necessarily be attributed to the drug. It has been shown that genome-wide association study hits can identify therapeutic targets and provide insight into drug side effects. For example, a single nucleotide polymorphism (SNP) in the tumour necrosis factor receptor 1 gene which is associated with multiple sclerosis (MS) risk has been shown to explain the mechanism whereby antitumour necrosis factor therapies typically exacerbate MS.⁹ We therefore examined whether there was a significant increase in AF risk associated with ivabradine treatment by meta-analysis, and quantified that risk in terms of number needed to harm (NNH) per year.

INTRODUCTION

Ivabradine (Procoralan, Servier) is a heart rate lowering drug which acts by specifically inhibiting the pacemaker I_f current, which causes spontaneous depolarisation in the sino-atrial node that regulates the heart rate.¹ Ivabradine was approved for use by the European Medicines Agency (EMA) in 2005 for use in the treatment of stable angina pectoris in patients with normal sinus rhythm who are not able to tolerate β -blocker therapy. In 2010, the indication was extended to include treatment in patients with uncontrolled angina symptoms and a heart rate in excess of 60 bpm despite β -blocker therapy, following the results of the BEAUTIFUL trial.² A new indication was approved in 2012, following the results of the SHIFT trial, for treatment of chronic heart failure (New York Heart Association class II–IV) with systolic dysfunction, in patients in sinus rhythm and whose heart rate is

METHODS

The study was performed in line with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁰

Eligibility criteria, information sources and search protocol

We included in our analysis all randomised controlled double-blind trials of ivabradine, for any indication and of any size, which followed patients up for at least 4 weeks. We did not exclude studies where AF incidence was not reported in the published manuscript, but attempted to identify that data wherever possible. We included both placebo-controlled studies and non-inferiority studies where an alternative drug treatment was used as a comparator. We excluded open or single-blinded studies, studies where the follow-up period was less



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than 4 weeks and studies where there was significant risk of bias, as assessed by the methods recommended by the Cochrane Collaboration.

We performed a systematic search, without language restriction, for randomised clinical trials of ivabradine treatment for any indication, using the search term 'ivabradine' and the document type 'clinical trial' or 'randomized controlled trial'. We searched Medline, Embase and Web of Knowledge from 1980 to October 2013, and the Cochrane Central Register of Controlled Trials. We also examined the reference lists of published trials, review articles and meta-analyses to identify other eligible trials. We read the scientific discussions of the EMeA to identify safety data that were not published in the original trial report. We also contacted directly the authors and in the case of industry-sponsored trials, the sponsors of studies which did not report the AF incidence in the original manuscript.

Selection and quality assessment

Studies were assessed on the basis of their title or abstract and those studies which appeared to meet the eligibility criteria were selected for full text review. Trials were assessed for eligibility and risk of bias using the components recommended by the Cochrane Collaboration: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias.¹¹ We considered any trial with a high or unclear risk of bias, by the Cochrane criteria, in sequence generation, allocation concealment and blinding to be at high risk of bias; all other studies were considered to be at low risk of bias.

Outcome measures and data collected

The main outcome measure was incident AF reported during the trial follow-up period. Where data on AF incidence were not reported, we contacted the authors by email on at least two occasions. We also identified AF incidence reported in the EMeA scientific discussions where trials were submitted as evidence for licensing and, in the case of trials sponsored by the manufacturer, contacted the manufacturer directly. Study data were collected on data collection forms which recorded

reference data, ethical approval, randomisation, blinding, control agent (placebo or other drug), follow-up duration, inclusion and exclusion criteria and sponsorship and funding information as well as numbers of patients in the ivabradine and control arms with incident AF.

Statistical analyses

We performed meta-analysis of intention to treat outcomes using a random effect model in the metafor package in R statistical software V3.0.2.^{12 13} Detailed statistical methods are available in the online supplement.

RESULTS

Study selection and characteristics of included trials

Our initial search strategy identified 84 published articles. We reviewed titles and abstracts and excluded papers that were not clinical trials, were not of sufficient duration of follow-up or which reported supplementary data from trials published elsewhere. We assessed the full text of the remaining 34 articles for eligibility. Eight papers were translated into English. After studies were excluded on the basis of study design (one), follow-up duration (two), randomisation (nine), study blinding (10) and duplication (two), our search strategy yielded 10 double-blind randomised controlled trials that enrolled 20 022 patients for a mean of 1.5 (range 0.076–1.88) years follow-up, for a total of 30 090 patient-years of follow-up (table 1, figure 1).^{2 3 14–22} Risk of bias of the included studies is summarised in online supplementary table S1. Of the 10 studies identified, AF incidence was only reported in one, the SHIFT trial. We wrote to the authors of the other studies to request the unpublished AF data. Of the five studies not sponsored by the manufacturer, four authors replied with AF data. None of the authors of studies sponsored by the manufacturer provided AF data. We contacted the manufacturer directly who declined to provide the unpublished data, citing ongoing inhouse analyses. Of the missing studies, full AF safety data were provided for the BEAUTIFUL study on the EMeA website. The safety data from the ASSOCIATE study which is reported in the EMeA documentation do not report the incidence of AF. The data from the INITIATIVE

Table 1 Eligible trials for which AF data were sought

Author	Year	Acronym	Number of participants	Indication	Control	Ivabradine dose (bid)	AF data source
Tardif <i>et al</i> ¹⁴	2005	INITIATIVE	939	Angina	Atenolol	7.5 mg/10 mg	Included in OOSS
Ruzyllo <i>et al</i> ¹⁵	2007		1195	Angina	Amlodipine	7.5 mg/10 mg	Included in OOSS
Fox <i>et al</i> ²	2008	BEAUTIFUL	10 907	Heart Failure	Placebo	5 mg/7.5 mg	EMeA
Tardif <i>et al</i> ¹⁶	2009	ASSOCIATE	889	Angina	Placebo	5 mg/7.5 mg	No data
Fasullo <i>et al</i> ¹⁷	2009		155	Anterior STEMI	Metoprolol	5 mg/7.5 mg	No data
Swedberg <i>et al</i> ³	2010	SHIFT	6492	Heart Failure	Placebo	2.5–7.5 mg	Original paper
Nerla <i>et al</i> ¹⁸	2012		61	Type II diabetes	Atenolol/placebo	5 mg	Personal communication
Dominguez-Rodriguez <i>et al</i> ¹⁹	2012		27	NSTE-ACS	Placebo	5 mg	Personal communication
Cappato <i>et al</i> ²¹	2012		21	IST	Placebo	5 mg	Personal communication
Villano <i>et al</i> ²²	2013		46	Microvascular angina	Ranolazine/placebo	5 mg	Personal communication
EMeA	2005	OOSS	3936		Atenolol/amlodipine/placebo	5–10 mg	EMeA

The AF data for the INITIATIVE study and from Ruzyllo *et al* were not available separately, but were included in the OOSS from the EMeA with three other studies.

AF, atrial fibrillation; bid, twice daily; EMeA, European Medicines Agency; IST, inappropriate sinus tachycardia; NSTE-ACS, non-ST elevation acute coronary syndrome; OOSS, overall oral safety set; STEMI, ST elevation myocardial infarction.

Trial acronyms: ASSOCIATE: Efficacy of the If current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4 month, randomized, placebo-controlled trial. BEAUTIFUL: Ivabradine for patients with stable coronary artery disease and left ventricular dysfunction (BEAUTIFUL): a randomized, double-blind, placebo-controlled trial. INITIATIVE: Efficacy of ivabradine, a new selective If inhibitor, compared with atenolol in patients with chronic stable angina. SHIFT: Systolic Heart Failure Treatments with If Inhibitor Ivabradine Trial.

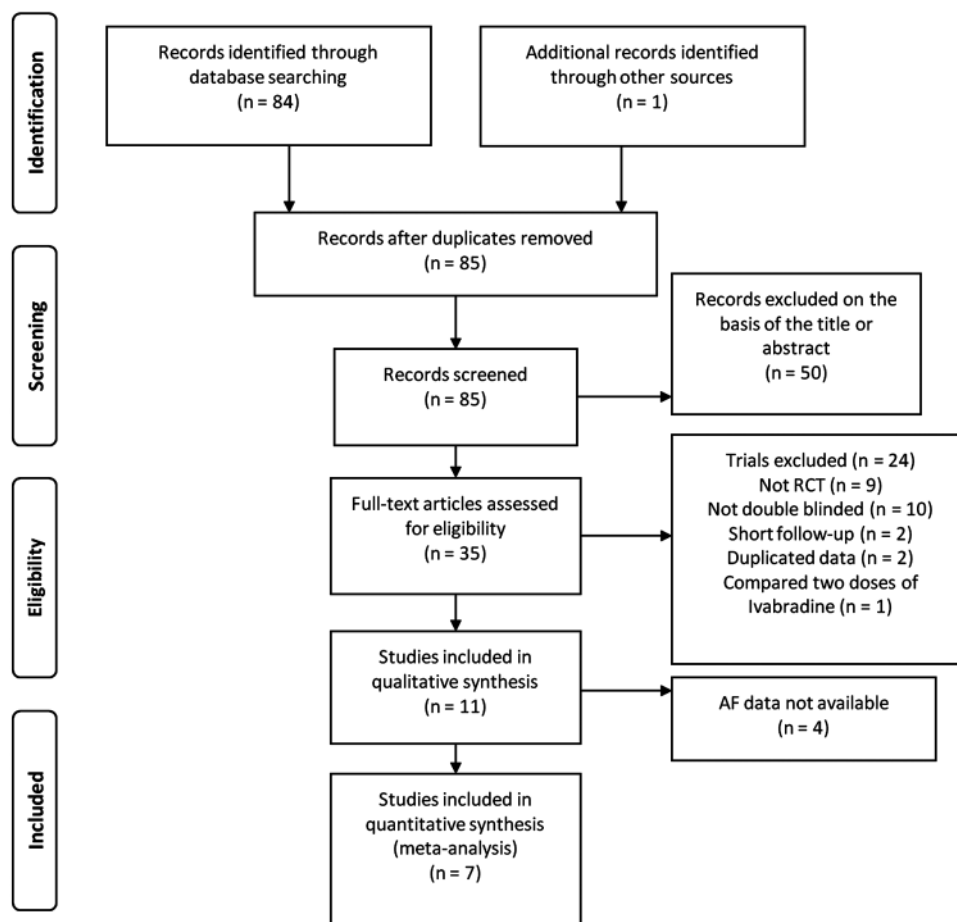


Figure 1 Flow chart of study selection.

study and from Ruzyllo *et al* are included in the analyses performed by the EMeA for licensing of ivabradine. The data are not available for each trial individually, however, but are combined with the safety data from a 3-month phase III clinical trial (for which we were unable to identify a published report) and two very short (four doses and 2 weeks, respectively) dose-ranging phase II studies. All of the studies included in this overall oral safety set (OOSS) were randomised, controlled and double-blinded. None of the trials for which we obtained AF incidence data separately were included in the OOSS. In order to provide the most accurate estimate of the effect of AF, we decided to include the OOSS as a single study in our meta-analysis and also to perform two sensitivity analyses. In the first, the OOSS was excluded and in the second only those trials where the drug treatment was compared with placebo, rather than an alternative such as amlodipine or a β -blocker, were included.

In our full data set for analysis including the OOSS, therefore, there were 21 571 patients, followed up for a mean of 1.43 years to provide a total of 30 755 patient-years of follow-up. When the OOSS was excluded, the data set included 17 635 patients, followed up for a mean of 1.67 years to give a total of 29 385 patient-years of follow-up. In the placebo-controlled trials only data set, there were 17 571 patients followed up for a mean of 1.67 years to give a total of 29 380 patient-years of follow-up.

AF incidence

Compared with controls, treatment with ivabradine was associated with a relative risk (RR) of AF of 1.15 times that of

alternative treatments (95% CI 1.07 to 1.24, $p=0.0027$) (figure 2). The results were largely similar if the OOSS was excluded, RR=1.15 (95% CI 1.06 to 1.25, $p=0.0065$) and if only placebo-controlled trials were examined, RR=1.15 (95% CI 1.05 to 1.26, $p=0.015$). When treatment indication was included in the model, the association between treatment indication and AF risk was not significant ($p=0.99$), although this analysis was limited as the majority of patient-years of follow-up (17 475/17 635) were in the two trials (SHIFT and BEAUTIFUL) for which the main treatment indication was heart failure.

When the absolute risk of AF was compared between ivabradine and control groups, ivabradine treatment was associated with an NNH of 208.3 per year of treatment (95% CI 122.0 to 666.7, $p=0.013$) (figure 3). This corresponds to an absolute risk difference of 0.48%. This effect was very similar when the OOSS was excluded, NNH=208.3 (95% CI 113.6 to 1250, $p=0.028$) and when only placebo-controlled trials were included, NNH=208.3 (95% CI 105.3 to 10 000, $p=0.048$). As ivabradine is indicated for chronic treatment of angina or cardiac failure and treatment is likely to continue for more than 1 year, this NNH represents a substantially greater risk than the very rare (less than 1:10 000) risk of AF reported in the product literature.

The heterogeneity of RR in the trials included was low, $I^2=0.00\%$, with the observed heterogeneity explained by within-study variance ($p=0.96$). The same was true in the analysis of absolute risk difference, $I^2=0.00\%$, where the residual heterogeneity after accounting for length of follow-up was

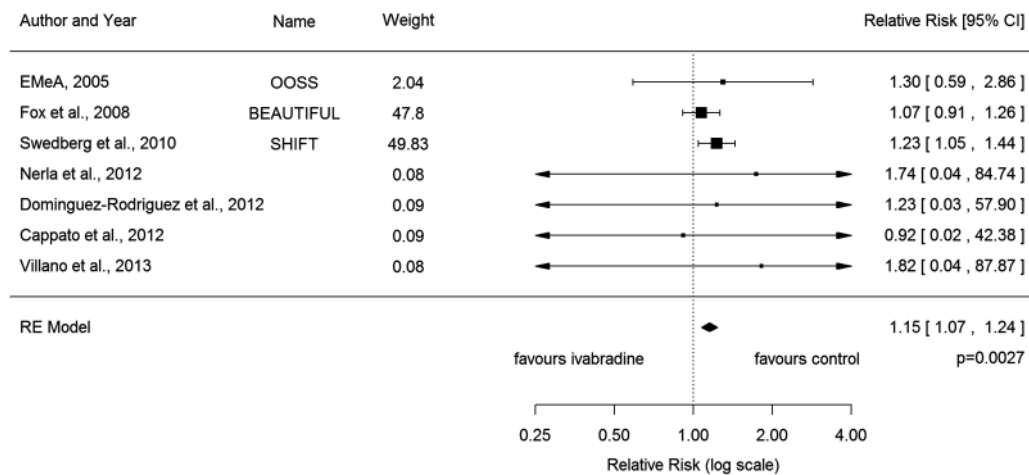


Figure 2 Forest plot of relative risk of atrial fibrillation in all trials with available data. RE Model, random effects model.

explained by within-study variance ($p=0.86$). This explains the similarity of the meta-analysis results between subgroups of trials.

There was no evidence of publication bias, rank test $p=1.00$ and regression test $p=0.64$, and examination of the funnel plots did not suggest any missing data (figure 4).

DISCUSSION

The results of this study, which used as much of the safety data as were available, quantify the risk of AF associated with ivabradine treatment. Use of ivabradine is associated with an approximately 15% increase in the risk of developing AF. This risk is greater than previously reported in the product safety information.

AF is a common complication of coronary artery disease and cardiac failure. Patients with these conditions have a higher rate of complications from AF than patients with AF alone.²³ In addition, ivabradine has not been shown to limit the ventricular rate in patients in AF, and so those patients who develop AF are likely to have higher heart rates, thus negating any benefits of ivabradine as a rate-lowering therapy in treating either angina or cardiac failure. These risks however need to be balanced against the benefits of ivabradine. In the SHIFT study, ivabradine

treatment resulted in a reduction in the composite endpoint of death or hospitalisation with worsening heart failure; the number needed to treat (NNT) was 26, which was largely driven by a reduction in hospitalisations.³ A combined analysis of the individual data from the SHIFT trial and those patients in the BEAUTIFUL trial with a baseline heart rate ≥ 70 bpm also identified a reduction in the same endpoint; the NNT was 40.7.²⁴ Interestingly, in the same analysis, which looked at patients with a higher baseline heart rate, the increase in AF incidence was greater than we found in our meta-analysis; the NNH was 58 (albeit over a longer follow-up of 19–22 months). This raises the possibility that it is the patient group with the most to gain from ivabradine treatment who have the greatest risk of developing AF and that the absolute increase in the risk of AF with ivabradine treatment in this group is of a similar size to the absolute decrease in risk of hospitalisation.

The associations between genetic markers near HCN4, combined with the results of this meta-analysis, which identifies an association between I_f current inhibition and AF, provide further evidence for the role of HCN4 and the I_f current in the pathophysiology of AF. The results of this analysis also highlight the importance of large safety data sets and ongoing postmarketing surveillance of licensed and approved medications to identify side

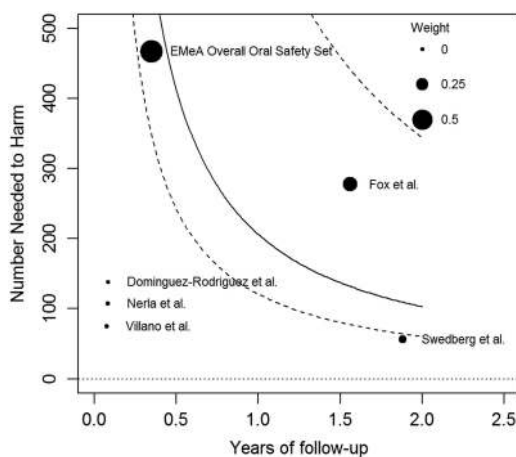


Figure 3 Number needed to harm per year of follow-up. Individual studies are plotted as circles with size proportional to the weighting in the meta-analysis model of absolute risk difference. The best fit line with 95% CI (dashed lines) is shown.

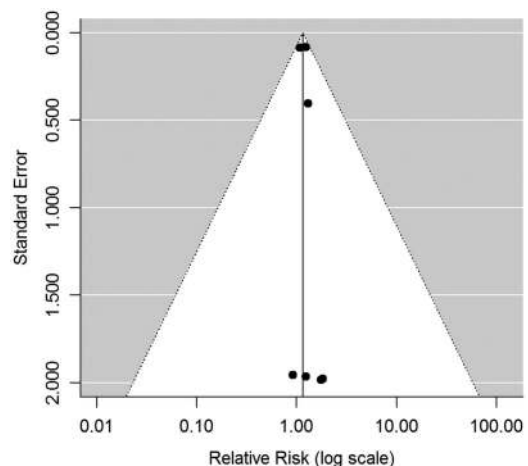


Figure 4 Funnel plot of relative risk versus SE. The plot is largely symmetrical, suggesting that there is no publication bias.

Arrhythmias and sudden death

effects which might otherwise be dismissed as complications of the underlying disease in a patient group with significant comorbidity.

Limitations

We were not able to obtain the incidence of AF for all of the trials which we identified, and the funnel plot shows a relative lack of mid-sized trials, which reflects this. The use of the OOSS from the EMeA scientific discussion may have resulted in an underestimation of the heterogeneity of the data available. Five studies, possibly quite different in various ways from each other, were combined to form a single data set that was treated in the analysis as a single trial. This is likely to result in an overestimation of within-study variance and an underestimation of between-study variance. We have attempted to ameliorate this by performing sensitivity analyses in which the OOSS is excluded.

As the AF data for the largest trials which studied patients with angina, rather than heart failure, were not available separately for each trial, we were unable to definitively assess the effect of treatment indication on AF risk. It is possible that AF is less common as a side effect of ivabradine treatment in patients with angina pectoris rather than heart failure. However, a definitive assessment of this risk would require analysis of the individual trial data from the angina studies and possibly even a prospective study of angina patients similar in size to the SHIFT and BEAUTIFUL studies. Such a trial is unlikely to be conducted.

We are unable to provide data comparing the AF risk profile of patients who developed AF to those who did not in either the ivabradine treatment or control groups. It is possible that the increase in AF risk is restricted to a small high-risk subgroup within the overall study population for each trial.

CONCLUSIONS

Ivabradine treatment is associated with a 15% increase in the RR of AF. We estimate that 208 patient-years of treatment with ivabradine would be required to cause one new case of AF.

Key messages

What is known on this subject?

Ivabradine is an effective heart rate lowering treatment which reduces symptoms in chronic stable angina and reduces hospitalisations in chronic heart failure. Ivabradine may carry an increased risk of atrial fibrillation (AF).

What might this study add?

Ivabradine treatment carries a substantially higher risk of AF than previously thought; we estimate that 208 patient-years of treatment would be required to cause one new case of AF.

How might this impact on clinical practice?

The risk of AF needs to be taken into consideration when weighing the balance of risk and benefits of ivabradine treatment.

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Contributors RIRM and BDK participated in the study design. RIRM performed the search and RIRM and OP extracted the data and translated manuscripts into English. RIRM and MDT performed the analysis. RIRM, BDK and MDT drafted the manuscript. MSK and JPB critically revised the manuscript. All authors participated in the revision and final approval of the manuscript. BDK acts as the guarantor of the manuscript.

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Heart

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