Review Article
The effects of ranolazine monotherapy on the incidence of atrial fibrillation in heart disease: a meta-analysis of randomized controlled trials

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Abstract: As the most common cardiac arrhythmia, atrial fibrillation (AF) increases health-care costs and morbidity. Ranolazine, a novel anti-angina drug, has unique antiarrhythmic properties, which have aroused interest in its use in AF prevention. To evaluate the effects of ranolazine monotherapy on the incidence of AF, randomized controlled trials (RCTs) that reported the effects of monotherapy with ranolazine on the incidence of AF and that were published up through May 2017 were searched in the Cochrane library, PubMed, and EMBASE databases. Data are expressed as the odds ratio (OR) with a 95% confidence interval (CI). Five RCTs involving 7003 patients (3580 in the ranolazine group, 3423 in the controls group) were included in the meta-analysis. Ranolazine monotherapy significantly reduced the incidence of AF (OR 0.66, 95% CI 0.50 to 0.87; P<0.01) compared with the controls, especially for postoperative (OR 0.33, 95% CI 0.13 to 0.79; P<0.05) or non-surgical patients (OR 0.72, 95% CI 0.53 to 0.98; P<0.05). Further analysis showed that a high dose of ranolazine could effectively prevent AF (OR 0.68, 95% CI 0.50 to 0.93; P<0.05), but a low dose group didn’t have the effect of preventing AF (OR 0.46, 95% CI 0.14 to 1.56; P=0.08). Ranolazine monotherapy may prove beneficial in AF prevention in heart disease. However, not all doses of ranolazine can be effective in the prevention of AF. Therefore, further studies with large RCTs are warranted to confirm the effects of different doses of ranolazine monotherapy in AF therapy.

Keywords: Ranolazine, atrial fibrillation, meta-analysis, arrhythmia

Introduction
As the most common complication of heart disease, atrial fibrillation (AF) increases health-care costs and morbidity [1]. Therefore, AF prevention is of great importance.

Ranolazine, a novel anti-anginal drug in patients with chronic stable angina and coronary artery disease, has the characteristic properties of a selective inhibitor of the inward sodium current, which also imparts unique antiarrhythmic properties, including atrial and ventricular arrhythmias [2]. Recent studies show that a combination of ranolazine and amiodarone can effectively prevent atrial fibrillation [3-6]. However, the role of ranolazine monotherapy on the incidence of AF remains unclear. We therefore undertook a meta-analysis of all published RCTs to evaluate the effects of ranolazine monotherapy on AF prevention.

Methods

Search strategy
The RCTs published up through May 2017 that reported the effects of ranolazine monotherapy on AF prevention were searched in the Cochrane library, PubMed, and EMBASE databases. The following key words were used in our search strategies: “Ranolazine”, “Ranolazine Hydrochloride”, “Ranolazine Dihydrochloride”, and “atrial fibrillation”, “Auricular Fibrillation”, and “Randomized controlled trial”, “Randomized”, “placebo”, “Retrospective”.

Eligibility criteria
Studies were selected for the meta-analysis if they fulfilled the following entry criteria [7]:

(1) Participants: patients with heart disease; (2) Intervention: ranolazine (no matter what regi-
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(1) Intervention: ranolazine (200 mg bid); (2) Comparator: ranolazine (200 mg bid) + placebo (200 mg bid); (3) Control: control (placebo or no ranolazine); (4) Outcome: the incidence of AF. (5) Study design: randomized design; No language restriction was applied.

Data extraction and outcome measures

All data were independently abstracted in duplicate by two investigators (Z.L. and Z.Y.J.). Discrepancies were resolved by consensus. When necessary, the original authors were contacted for supplementary information. The following data were extracted from each study: first author’s last name, year, study design, intervention group, control group, endpoint, method of AF detection, follow up period, country, study population, number of patients, cohort mean age, gender, left atrial diameter, mean ejection fraction. Extracted data were entered into a standardized Excel file.

Risk of bias assessments

The risk of bias was evaluated on the basis of Cochrane Risk of Bias Methods [8] by two authors (H.M. and L.M.Y.) and assigned a value of ‘high’, ‘low’, or ‘unclear’ based on the following: random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome assessment, incomplete outcome data.

Grading quality of evidence

The GRADE system was used to assess the quality of evidence. Evidence from cohort studies begins with a grade of “Low”. The quality of the evidence was upgraded for large magnitude of effect, a plausible residual confounding that would not reduce the effect size, and a dose response gradient, or downgraded for inconsistency, indirectness, imprecision, and publication bias. Finally, the quality of the evidence is categorized as high, moderate, low, and very low [9].

Statistical analysis

All of the statistical analyses were conducted with Review Manager version 5.3 and the GRADE system. A P-value < 0.05 was considered statistically significant. The results were expressed as odds ratios (OR) with 95% confidence intervals (CI) (using a fixed-effect approach unless there was significant heterogeneity, in which case a random-effects statistical model was used). Heterogeneity across studies was tested by using the I^2 statistic. I^2 statistics of 25% to 50%, 50% to 75% and 75% to 100% were respectively considered to have low heterogeneity, moderate heterogeneity, and a high degree of heterogeneity. An I^2 value greater than 50% indicates significant heterogeneity. A fixed-effects model was used (I^2<50%), and a random-effects model was used in the case of significant heterogeneity (I^2>50%) [10]. The potential publication bias was assessed using Begg’s funnel plot test.

Results

Study identification and selection

The initial search yielded 200 relevant publications of which 186 were excluded for various reasons (47 duplications, 97 reviews, 33 irrelevant to the current analysis, 6 combination therapy, or 3 not human based on the titles and abstracts). The remaining 14 were then retrieved for full text review; nine of them were also excluded because they did not describe randomized studies. Thus, 5 studies were included in the final analysis [11-15]. A flow chart of the studies included in meta-analysis is shown in Figure 1.

Study and patient characteristics

The basic characteristics of the studies and patients included in the meta-analysis are
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### Table 1. Study characteristics of the 5 RCTs included

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Design</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Endpoint</th>
<th>Method of AF detection</th>
<th>Follow up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bekeith, 2015</td>
<td>DB, PC</td>
<td>1000 mg p.o bid</td>
<td>Placebo</td>
<td>POAF</td>
<td>Holter monitor</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Tagarakis, 2013</td>
<td>SB, SC</td>
<td>375 mg p.o bid for 3 days prior to surgery and until discharge</td>
<td>NR</td>
<td>POAF</td>
<td>Holter monitor for the first 24 hours and ECG monitor every 4 hours until discharge</td>
<td>10 days</td>
</tr>
<tr>
<td>Scirica, 2015</td>
<td>DB, PC</td>
<td>200 mg bolus iv, subsequently 80 mg/h infusion for 12-96 h, followed by 1000 mg p.o bid</td>
<td>Placebo</td>
<td>Cardiovascular death, MI, or recurrent ischemia</td>
<td>cECG monitor for the first 7 days</td>
<td>12 months</td>
</tr>
<tr>
<td>DeFerrari, 2015</td>
<td>DB, PC, MC</td>
<td>375 mg p.o bid, 500 mg p.o bid, 750 mg p.o bid</td>
<td>Placebo</td>
<td>AF recurrence</td>
<td>TT-ECG monitor</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Sendón, 2014</td>
<td>DB, PC, MC</td>
<td>750 mg p.o bid, 1000 mg p.o bid</td>
<td>Placebo</td>
<td>Times to angina onset and to 1 mm ST segment depression after 12 weeks</td>
<td>ECG monitor</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial; SR = sinus rhythm; DB = double-blind; PC = placebo control; P.O. = Per os; bid = Eis in die; h = hour; NR = not reported; POAF = postoperative atrial fibrillation; SB = single blind; SC = single center; ECG = electrocardiography; IV = intravenous; MI = myocardial infarction; cECG = continuous electrocardiography; MC = multicenter; AF = atrial fibrillation; TT-ECG = transtelephonic electrocardiography.

### Table 2. Characteristics of patients in 5 RCTs included

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Country</th>
<th>Study population</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Female (%)</th>
<th>LAD (mm)</th>
<th>LVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bekeith, 2015</td>
<td>USA</td>
<td>Isolated CABG (44, 81%); AVR (4, 7%); Combined AVR/CABG (3, 6%), SR</td>
<td>27/27</td>
<td>64.3±11.4</td>
<td>18.5%</td>
<td>NR</td>
<td>46.4±14.6</td>
</tr>
<tr>
<td>Tagarakis, 2013</td>
<td>Greece</td>
<td>CABG, SR</td>
<td>34/68</td>
<td>69±7/67±8</td>
<td>29.4/33.8</td>
<td>34.9±3.4/33.8±2.7</td>
<td>52.6±8.6/53.8±9.4</td>
</tr>
<tr>
<td>Scirica, 2015</td>
<td>USA</td>
<td>NSTEACS, SR</td>
<td>3162/3189</td>
<td>63±11/63±11</td>
<td>33.8/36.3</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>DeFerrari, 2015</td>
<td>Germany, Italy, Spain, UK</td>
<td>Post-ECV, PAF</td>
<td>183/55</td>
<td>65.4±10.7/65.2±9.5</td>
<td>21.9/25.5</td>
<td>44.1±7.7/44±7</td>
<td>56.0±10.7/57±9</td>
</tr>
<tr>
<td>Sendón, 2014</td>
<td>USA</td>
<td>CEA, SR</td>
<td>174/84</td>
<td>65.5±10.4/64.8±9.3</td>
<td>14.9/22.6</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Values are given as n or mean ± SD (Ranolazine group/Control group). RCT = randomized controlled trial; LAD = Left atrial diameter; LVEF = Left ventricular rejection fraction; USA = United States of America; CABG = coronary artery bypass graft surgery; AVR = aortic valve replacement; SR = sinus rhythm; NR = not reported; NSTEACS = Non-ST elevation acute coronary syndromes; ECV = electrical cardioversion; UK = United Kingdom; PAF = persistent atrial fibrillation; CEA = chronic exertional angina.
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Table 3. Baseline clinical characteristics in 5 RCTs included

<table>
<thead>
<tr>
<th></th>
<th>Ranolazine (n=3580)</th>
<th>Placebo (n=3423)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>63.3±11.0 (n=3553)</td>
<td>63.2±10.9 (n=3396)</td>
<td>0.70</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>55.5±10.5 (n=217)</td>
<td>55.2±9.4 (n=123)</td>
<td>0.79</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2550 (n=3519)</td>
<td>2454 (n=3328)</td>
<td>0.23</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1118 (n=3519)</td>
<td>1102 (n=3328)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Values are given as n or mean ± SD (Ranolazine group/Control group). RCT = randomized controlled trial; LVEF = Left ventricular rejection fraction.

The details of the risks of biases of the included studies according to the Cochrane assessment tool are listed in Figure 2. The overall quality was good, but only one study in the context of other biases was under a high risk of bias, and it was for an inconsistency in patient baseline characteristics [13]. These items: blinding of random sequence generation, participants and personnel, blinding of the outcome assessment, incomplete outcome data, and selective reporting regarding studies were almost all under a low risk of bias. Most studies had not clearly illustrated the method of allocation concealment, except 2 trials that had a low risk of this bias [11, 15].

Effect of ranolazine on the incidence of AF

Overall, five studies including 7003 patients were included in this analysis (3580 in the ranolazine group and 3423 in the control group). The meta-analysis of the five studies using a fixed effects model suggested that ranolazine significantly reduced the incidence of AF (OR 0.66, 95% CI 0.50 to 0.87; P<0.01) in patients with heart disease compared with the control. There was no heterogeneity among the studies (I²=0%, heterogeneity P=0.49; Figure 3). Further analysis of the effects of different doses of ranolazine (>500 mg as the high dose group, ≤500 mg as the low dose group) on the incidence of AF showed that a high dose of ranolazine could effectively prevent AF (OR 0.68, 95% CI 0.50 to 0.93; P<0.05), but the low dose group didn’t have the effect of preventing AF (OR 0.46, 95%
Figure 3. Forest plots from the meta-analysis for the effects of ranolazine monotherapy on the incidence of atrial fibrillation in various clinical settings. The effect size of each study is proportional to the statistical weight. The diamond indicates the overall summary estimate for the analysis; the width of the diamond represents the 95% CI. CI, confidence interval.

Figure 4. Forest plots from the subgroup meta-analysis for the effects of ranolazine monotherapy on the incidence of atrial fibrillation in POAF and non-POAF. The effect size of each study is proportional to the statistical weight. The diamond indicates the overall summary estimate for the analysis; the width of the diamond represents the 95% CI. POAF, postoperative atrial fibrillation; CI, confidence interval.

CI 0.14 to 1.56; P=0.08), compared with the control (Figure 5). In addition, we also found that not only POAF (OR 0.33, 95% CI 0.13 to 0.79; P<0.05) but also non-POAF (OR 0.72, 95% CI 0.53 to 0.98; P<0.05), can be prevented by ranolazine (Figure 4).

Quality of evidence

Following the GRADE system, the study design for all the trials included in the review of evidence for ranolazine was RCT, and the evidence quality was assessed by reviewing whether the studies had limitations or flaws. The outcomes that ranolazine prevents POAF and a high dose of ranolazine prevents AF are strong evidence (Table 4). One study downgraded the quality of evidence in the “indirect” context, for its post-hoc analysis of the CARISA trial [11], which leads to the outcomes that ranolazine prevents AF and non-POAF to be moderately strong evidence (Table 4). The other one downgraded the quality of evidence for this outcome that ranolazine prevents AF in the context of “inconsistency”, for $I^2$>50%, which leads to the outcomes that a low dose of ranolazine prevents AF to be moderately strong evidence (Table 4).

Publication biases

Begg's funnel plot of the included studies did not suggest any significant publication biases.
## Table 4. Summary of findings table using GRADE methodology for ranolazine on the AF prevention

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**Patient or population:** patients with cardiovascular disease  
**Settings:** The effects of ranolazine monotherapy on the incidence of atrial fibrillation in heart disease  
**Intervention:** Ranolazine monotherapy

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Assumed risk</th>
<th>Corresponding risk</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **The Effect of Ranolazine on Incidence of Atrial Fibrillation: A Meta-Analysis of Randomized Controlled Trials**  
Follow-up: 7-180 days | | | | | | | |
| Control | | Study population | 40 per 1000 | 27 per 1000 (20 to 35) | OR 0.66 (0.5 to 0.87) | 7003 (5 studies) | ⊕⊕⊕⊝ moderate ||
| | | | 296 per 1000 | 217 per 1000 (174 to 268) | | | |
| **Subgroup-1.2.1 POAF; 1.2.2 NON-POAF**  
Follow-up: 10-14 | | Study population | 305 per 1000 | 127 per 1000 (54 to 258) | OR 0.33 (0.13 to 0.79) | 156 (2 studies) | ⊕⊕⊕⊕ high ||
| | | | 303 per 1000 | 125 per 1000 (53 to 256) | | | |
| **Subgroup-1.2.1 POAF; 1.2.2 NON-POAF**  
Follow-up: 7-180 | | Study population | 32 per 1000 | 23 per 1000 (17 to 32) | OR 0.72 (0.53 to 0.98) | 6847 (3 studies) | ⊕⊕⊕ moderate ||
| | | | 24 per 1000 | 17 per 1000 (13 to 24) | | | |
| **Subgroup-Ranolazine dosage-Ranolazine dosage ≤500 mg**  
Follow-up: 10-180 | | Study population | 423 per 1000 | 252 per 1000 (93 to 533) | OR 0.46 (0.14 to 1.56) | 282 (2 studies) | ⊕⊕⊕ moderate ||
| | | | 436 per 1000 | 262 per 1000 (98 to 547) | | | |
| **Subgroup-Ranolazine dosage-Ranolazine dosage >500 mg**  
Follow-up: 7-180 | | Study population | 34 per 1000 | 24 per 1000 (17 to 32) | OR 0.68 (0.5 to 0.93) | 6776 (4 studies) | ⊕⊕⊕⊕ high ||
| | | | 160 per 1000 | 115 per 1000 (87 to 150) | | | |

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; OR: Odds ratio; GRADE Working Group grades of evidence:High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. *Post-hoc analysis of the CARISA trial in Sendón 2014; †I² >50%.
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Discussion

To the best of our knowledge, this is the first comprehensive meta-analysis to assess the efficacy of ranolazine monotherapy on the incidence of the AF in heart disease. Strong evidence from 5 RCT studies supports a significant anti-AF effect of ranolazine monotherapy, which also imparts unique antiarrhythmic properties, including atrial and ventricular arrhythmias [2]. Recently, several studies regarding effects of ranolazine in AF prevention have been published [11-17]. However, the role of ranolazine in AF prevention remains unknown.

To evaluate the effects of ranolazine in AF prevention, several retrospective studies have first reported the efficacy of ranolazine in AF pre-
vention. Miles et al. assessed the effects of ranolazine vs. amiodarone therapy (1500 mg preoperative loading, followed by 1000 mg twice daily thereafter) for POAF prevention in 393 patients. POAF occurred in 18% of the patients on ranolazine (P=0.035), compared with 27% of the patients on amiodarone [16]. Hammond et al. reported their findings on patients who were treated with a 1000 mg twice daily dose of ranolazine in addition to standard therapy vs. standard therapy alone in 205 patients. POAF was significantly reduced in the ranolazine group (10.1% vs. 41.9%, P<0.0001) [17]. In recent years, the role of ranolazine in the prevention of AF has received increasing attention. The corresponding number of randomized controlled trials also increased. In the combination therapy aspect of ranolazine, Fragakis et al. found that conversion of recent-onset AF within 24 hours (primary end point) was achieved in 22 patients (88%) in the ranolazine + amiodarone group versus 17 patients (65%) in the amiodarone group (P=0.056) [6]. Koskinas, et al. reported that patients in the amiodarone plus ranolazine group compared with the amiodarone-only group showed significantly higher conversion rates of recent-onset atrial fibrillation at 24 h (87 vs. 70%, respectively; P=0.024) and at 12 h (52 vs. 32%; P=0.021) [5]. Simopoulos et al. believed that, compared to amiodarone alone, the ranolazine-amiodarone combination had a superior antiarrhythmic effect against POAF [4].

In the monotherapy therapy aspect of ranolazine, Tagarakis found that a significant reduction in the incidence of POAF was noted in the patients who were treated with ranolazine 375 mg twice daily for 3 days prior to surgery, and until hospital discharge (8.8% vs. 30.8%, P<0.001) in 102 patients [13]. Bekeith further evaluates the efficacy of ranolazine in preventing AF after cardiac surgery in 54 patients [14]. Although not statistically significant, a trend showed that ranolazine can be used safely in patients to reduce postoperative AF by 38%. De Ferrari et al. reveal the reduction in overall AF recurrence in the combined 500-mg and 750-mg groups was of borderline significance compared to the placebo group (P=.053) and significant compared to 375-mg group (P=.035) [12]. Scirica et al. showed ranolazine reduced the overall 1-year incidence of clinical AF events [15]. In addition, in a recent meta-analysis study [18], ranolazine monotherapy and combination therapy were analyzed, but the type of prevention of AF was not further elucidated. The other two meta-analysis studies [19, 20] found that, although the classification of AF was analyzed, the studies included were not completely randomized. Therefore, the role of ranolazine monotherapy in AF prevention still has not been elucidated.

We therefore undertook a comprehensive meta-analysis of published studies to assess the efficacy of ranolazine monotherapy in AF prevention for patients with heart disease. Ranolazine significantly reduced the incidence of AF (OR 0.66, 95% CI 0.50 to 0.87; P<0.01) in patients with heart disease compared with control. There was no heterogeneity among the studies (I²=0%, heterogeneity P=0.49; Figure 3). Further analysis of the effects of different doses of ranolazine (>500 mg as the high dose group, ≤500 mg as the low dose group) on the incidence of AF showed that a high dose of ranolazine could effectively prevent AF (OR 0.68, 95% CI 0.50 to 0.93; P<0.05), but a low dose group didn’t have the effect of preventing AF (OR 0.46, 95% CI 0.14 to 1.56; P=0.08), compared with the control (Figure 5). In addition, we also found that not only POAF (OR 0.33, 95% CI 0.13 to 0.79; P<0.05) but also non-POAF (OR 0.72, 95% CI 0.53 to 0.98; P<0.05), can be prevented by ranolazine (Figure 4).

**Limitations**

Several potential limitations of this meta-analysis merit consideration. First, an overestimation of the treatment effect is more likely in smaller studies than it is in larger samples. Second, the included studies in the low doses of ranolazine group were limited and lacked homogeneity, potentially leading to an underestimation and/or overestimation of the true incidence of AF. Finally, it was possible that some missing and unpublished data may have led to a bias in the effect size.

**Conclusion**

In conclusion, despite its various limitations, our study is clinically valuable because it revealed that ranolazine leads to a lower incidence of AF in patients with heart disease. However, not all doses of ranolazine can effectively prevent AF. Additional large-scale, multi-
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center, randomized controlled parallel trials are necessary to confirm these positive results.

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Disclosure of conflict of interest

None.

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