Prevention of atrial fibrillation onset by beta-blocker treatment in heart failure: a meta-analysis

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Aims Atrial fibrillation (AF) is an important morbidity–mortality risk factor, especially in patients with heart failure (HF). Beta-blockers reduce morbidity and mortality in HF. The study was designed to estimate the preventive efficacy of beta-blocker treatment on AF occurrence in patients with HF.

Methods and results A systematic review of the literature was performed to identify all clinical trials evaluating beta-blockers’ efficacy in HF. Eligible studies had to be randomized, placebo-controlled and providing information on the incidence of AF during follow-up among those with sinus rhythm at baseline. A total of seven studies which included 11 952 patients receiving a background treatment with angiotensin-converting enzyme-inhibitors could be found. Overall, beta-blockers significantly reduced incidence of onset of AF from 39 to 28 per 1000 patient-years: relative risk reduction = 27% (95% confidence interval 14–38, P < 0.001); heterogeneity test: P = 0.096. A same trend of efficacy was observed in all trials except the SENIORS study. In this trial which included aged patients (>70 years) with systolic or diastolic HF, a higher prevalence of AF at baseline (35%) was observed compared with the mean baseline prevalence (13%).

Conclusion Beta-blockers appear to effectively prevent occurrence of AF in patients with systolic HF.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia found in clinical practice. Its prevalence dramatically increases with age.1 Chronic heart failure (HF) predisposes to AF, and data from the Framingham study indicated that chronic HF was associated with a 4.5 to 6-fold risk of AF for men and women.1

In congestive HF (CHF) patients, the presence of AF leads to increased morbidity and mortality.2,3 In addition, AF causes a significant economic burden which has grown in the past decades and is expected to grow even further in the upcoming period.4,5 The treatment of AF relies traditionally on two different strategies: rhythm or rate control. Many studies have shown no difference between the two strategies.6 Interestingly, there was a trend favoring rhythm control in patients with pre-existing HF.7

Preventing primary onset of AF could be an important goal to decrease its burden on CHF patients and to eliminate the need for potentially harmful agents (both antiarrhythmics and anticoagulations). Thus, there is some evidence to suggest that both ACE-inhibitors and angiotensin receptor blockers prevent or delay onset of AF, with a greatest benefit on patients with HF.8

Beta-blockers reduce morbidity and mortality in patients with HF.9–11 The mechanisms of these benefits are still disputed but may involve prevention of AF. Only one randomized trial suggests such an effect; recent post hoc analyses from the CAPRICORN trial indicated that an early treatment with carvedilol reduced the incidence of atrial arrhythmias following myocardial infarction in patients with LV systolic dysfunction.12 It is not known whether beta-blockers, added to ACE-inhibitor treatment, will further reduce AF occurrence in chronic HF patients.

A systematic review of published and unpublished data is timely and could allow estimating the effectiveness of beta-blockers to prevent chronic HF-related AF.

Methods

Literature search

The search was performed in accordance with the recommendations of the Cochrane collaboration using Cochrane CENTRAL database and PubMed. The initial search terms were ‘beta-blocker’, the individual name of all drugs used for CHF in this class, and ‘AF’. The search was limited to randomized, controlled clinical trials and English-language publications. Additional publications were sought...
using the reference lists of identified papers, the published reviews on the topic, and a manual search of abstracts from the scientific sessions of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology. The result sections and tables of these studies were then examined to see whether data on AF at baseline and during follow-up were reported. Attempts were made to contact authors of beta-blocker trials that did not report AF incidence.

Two reviewers (I.A. and A.B.) then independently evaluated identified titles, and manuscripts were retrieved for any publication that either reviewer felt was potentially relevant.

Two blinded reviewers re-evaluated all of the abstracts and manuscripts identified as potentially relevant, and publications were selected for this review. Relevant study data were independently abstracted, in duplicate, using a standardized form. Discrepancies during data abstraction were resolved by consensus.

Inclusion criteria for studies

Studies were included only if they met all of the following criteria: (i) randomized, controlled trials with parallel design; (ii) comparing beta-blockers with placebo; (iii) including patients with CHF; and (iv) providing adequate data on AF incidence during follow-up. For each trial analysis, patients with AF at baseline were excluded.

The results of all studies included in this meta-analysis for were post hoc analyses and not specifically intended for AF evaluation.

Primary outcome for comparison was the number of patients with occurrence of AF during follow-up among those with sinus rhythm at baseline.

Cardiac atrial arrhythmias were not a pre-specified endpoint in the different trials included. Arrhythmias were identified and characterized according to the adverse event reports. Indeed, AF onset was notified in each trial as an adverse event notified by investigators and blindly assessed by independent committee of critical event in these large-scale trials (except for the Waagstein trial).

### Statistical methods

The meta-analysis was performed using the relative risk (RR) as parameter of efficacy with a fixed effect model. Different techniques were used: the combined logarithm of the RR, Mantel–Haenszel, Greenland–Robins, and Peto. The results obtained from the different methods were very similar, and therefore only the results from the combined logarithm of the RR with the corresponding 95% confidence interval (CI) are presented in this article. A χ² association and χ² heterogeneity tests were performed. P-value for significance of association and heterogeneity tests was set, respectively, at 0.05 and 0.10. Graphic representation of RR and their 95% CI were performed with use of linear scale.

For robustness, the analysis was realized by adding studies for which no effect is obtained (RR = 1) and whose size and risk in the control group are equal to the average of the values obtained in the included trials.

The statistical analysis for the meta-analysis was performed using EASYMA software.

### Results

**Identified studies**

Our database search identified a total of 26 randomized, controlled, double-blind human trials since 1985 comparing beta-blockers with placebo in the field of HF, representing a total of 19 170 patients. Ten of them were performed with carvedilol, seven with metoprolol, four with bucindolol, three with nebivolol, and two with bisoprolol. Among these trials, seven studies provided information on the number of patients with occurrence of AF during follow-up and were included in the meta-analysis. The characteristics of studies included are summarized in Tables 1 and 2. There were 13 715 patients in the identified studies. After exclusion of patients on AF

<table>
<thead>
<tr>
<th>Author/study, year</th>
<th>Drug</th>
<th>Number of patients</th>
<th>Mean age (years)</th>
<th>Follow-up (years)</th>
<th>Aetiology of HF</th>
<th>Mean LVEF(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS I, 35 1994</td>
<td>Bisoprolol</td>
<td>641</td>
<td>60</td>
<td>2</td>
<td>CAD/DCM</td>
<td>25</td>
</tr>
<tr>
<td>MERIT HF, 11 1999</td>
<td>Metoprolol</td>
<td>3991</td>
<td>64</td>
<td>1</td>
<td>CAD/DCM</td>
<td>28</td>
</tr>
<tr>
<td>BEST, 31 2001</td>
<td>Bucindolol</td>
<td>2708</td>
<td>60</td>
<td>2</td>
<td>CAD/DCM</td>
<td>23</td>
</tr>
<tr>
<td>COPERNICUS, 47 2002</td>
<td>Carvedilol</td>
<td>2289</td>
<td>63</td>
<td>0.9</td>
<td>CAD/DCM</td>
<td>20</td>
</tr>
<tr>
<td>Waagstein, 26 2003</td>
<td>Metoprolol</td>
<td>169</td>
<td>57</td>
<td>0.5</td>
<td>CAD/DCM</td>
<td>28</td>
</tr>
<tr>
<td>SENIORS, 34 2004</td>
<td>Nebivolol</td>
<td>2128</td>
<td>76</td>
<td>1.8</td>
<td>CAD/DCM</td>
<td>36</td>
</tr>
<tr>
<td>CAPRICORN, 37 2005</td>
<td>Carvedilol</td>
<td>1789</td>
<td>63</td>
<td>1.3</td>
<td>CAD</td>
<td>33</td>
</tr>
</tbody>
</table>

*CAD, coronary artery disease; DCM, idiopathic dilated cardiomyopathy.*

<table>
<thead>
<tr>
<th>Author/study, date</th>
<th>Rate of AF at baseline (%)</th>
<th>NYHA class</th>
<th>ACE-I or ARB, placebo group (%)</th>
<th>ACE-I or ARB, beta-blockers group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS I, 35 1994</td>
<td>13</td>
<td>III–IV</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>MERIT HF, 11 1999</td>
<td>16</td>
<td>II–IV</td>
<td>90</td>
<td>89</td>
</tr>
<tr>
<td>BEST, 31 2001</td>
<td>11</td>
<td>III–IV</td>
<td>91</td>
<td>91</td>
</tr>
<tr>
<td>COPERNICUS, 47 2002</td>
<td>NA</td>
<td>IV</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Waagstein, 26 2003</td>
<td>0</td>
<td>II–III</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>SENIORS, 34 2004</td>
<td>35</td>
<td>I–IV</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>CAPRICORN, 37 2005</td>
<td>9</td>
<td>NA</td>
<td>97</td>
<td>98</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor antagonists; NA, not applicable.
at baseline, data from 11,952 patients were used for the analysis.

Primary prevention of AF

During an average follow-up of 1.35 years, the incidence of AF was 28 per 1000 patient-years in the beta-blockers arm and 39 per 1000 patient-years in the placebo arm, with, respectively, 227 and 313 events.

Beta-blockers significantly reduced incidence of onset of AF (Table 3, Figure 1) with an RR reduction of 27% (95% CI 14–38, $P = 0.001$). There were differences in treatment effect between individual trials, as indicated by the statistical test of heterogeneity ($P = 0.096$). These beneficial effects are added to those of ACE-inhibitors and angiotensin receptor blockers, since 90% of the patients received this background treatment as well in the placebo group and in the beta-blockers group (Table 2).

The robustness analysis showed that more than 18 trials (including more than 800 patients by trial) had to be added to obtain a non-significant result of the meta-analysis for the primary endpoint.

Statistical test of heterogeneity shows significant difference in the treatment effect ($P = 0.096$). A same trend of efficacy was observed in all trials except the SENIORS study. Absence of nebivolol effect in the SENIORS trial is responsible for this finding, since the withdrawal of the study suppresses such heterogeneity ($P = 0.58$). This trial included older patients (>70 years) and was the only one to include diastolic HF. In addition, we observe in the SENIORS trial a higher prevalence of AF at baseline (35%) compared with the mean baseline prevalence of 13% in the others (11–15%).

Furthermore, we performed an effect model analysis comparing annual incidence on AF onset between the two groups (with or without beta-blockers) and excluding the SENIORS study. It shows, with trials having studied similar patients, a multiplicative model which means that the beneficial effect of beta-blockers is constant whatever baseline risk evaluated with the annual incidence of AF in the placebo groups (Figure 2). The weight of the Waagstein et al. trial is relatively small, which explains the position of the regression line close to the largest trials.

Subgroup analysis according to the pharmacological profile of drugs (Figure 3) showed an RR reduction of 17% (95% CI 4–35) of the AF occurrence with selective compounds (metoprolol, nebivolol, and bisoprolol); however, this reduction was not significant ($P = 0.11$). When SENIORS is withdrawn from this subgroup, the reduction becomes significant (RR reduction = 41%; $P = 0.006$; Figure 4) and similar to that obtained with non-selective beta-blockers. Non-selective beta-blockers ( bucindolol, carvedilol) showed a significant RR reduction of 36% (95% CI 18–49, $P < 0.001$).

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**Table 3** Incidence of onset of AF in each trial in HF

<table>
<thead>
<tr>
<th>Data source</th>
<th>Beta-blockers (events/number of patients)</th>
<th>Placebo (events/number of patients)</th>
<th>Weight (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS [b]</td>
<td>9/280</td>
<td>13/276</td>
<td>4</td>
<td>0.68 (0.29–1.57)</td>
</tr>
<tr>
<td>MERIT HF (metoprol)</td>
<td>33/1677</td>
<td>54/1681</td>
<td>15</td>
<td>0.61 (0.39–0.94)</td>
</tr>
<tr>
<td>BEST (bucindolol)</td>
<td>78/1208</td>
<td>111/1197</td>
<td>36</td>
<td>0.69 (0.52–0.92)</td>
</tr>
<tr>
<td>COPERNICUS (carvedilol)</td>
<td>12/1156</td>
<td>22/1133</td>
<td>5.7</td>
<td>0.53 (0.26–1.07)</td>
</tr>
<tr>
<td>Waagstein (metoprol)</td>
<td>1/86</td>
<td>8/79</td>
<td>0.7</td>
<td>0.11 (0.01–0.89)</td>
</tr>
<tr>
<td>SENIORS (nebivolol)</td>
<td>78/706</td>
<td>74/684</td>
<td>30.8</td>
<td>1.02 (0.75–1.37)</td>
</tr>
<tr>
<td>CAPRICORN (carvedilol)</td>
<td>16/894</td>
<td>31/895</td>
<td>7.8</td>
<td>0.51 (0.28–0.93)</td>
</tr>
<tr>
<td>Total</td>
<td>227/6007 (3.8%)</td>
<td>313/5944 (5.3%)</td>
<td>100</td>
<td>0.73 (0.61–0.86)</td>
</tr>
</tbody>
</table>

*Complementary data from the investigators.
The study of the heterogeneity between the two groups did not find any significant difference (\( P = 0.15 \)).

**Discussion**

This meta-analysis based on seven randomized, placebo-controlled trials and including \( >70\% \) of the total patients’ population having taken part in HF studies with beta-blockers indicates that this therapy is effective in preventing the development of AF in HF whatever baseline risk. These results are highly significant, and the robustness analysis makes unlikely the possibility of publication bias, owing to unpublished neutral trials.

Among the large-scale trials realized in the field of HF, CIBIS II (not included in this meta-analysis) provided additional data on hospitalizations related to supraventricular arrhythmias (most often AF) showing a trend (although non-significant) towards the reduction of such hospitalizations from 2.5% in the placebo group to 1.7% in the beta-blocker group.

While considering pharmacological profile, the benefit of beta-blocker therapy seems to be similar with selective and non-selective beta-blockers when the SENIORS study is excluded from the analysis. The old age of included patients, the higher prevalence of AF at baseline, and the high proportion (one-third) of patients with diastolic HF may partly explain the absence of effect of nebivolol in SENIORS.

In the other trials, beta-blocker therapy provides an additional benefit to that already induced with ACE-inhibitors and ARB since meta-analysis of Healey et al. \(^8\) demonstrated that they both reduce the risk of occurrence of AF by 28%.

**Mechanism of action**

Although conventional beta-blockers do not possess atrial stabilizing properties, there are several possible biological, direct or indirect mechanisms by which they might reduce the development of AF. They may prevent or improve adverse ventricular remodelling with a consequent decrease in LV and atrial end-diastolic pressure. \(^{36}\) Their anti-arrhythmic effects could also be due to attenuation of the actions of the sympathetic nervous system on automaticity and conduction in the heart. Indeed, an increased sympathetic drive has been shown to induce atrial tachyarrhythmias. \(^{37}\) In addition, beta-adrenergic stimulation shortens the action potential duration by increasing the magnitude of \( I_K \). \(^{38}\) In pacing-induced AF, shortening of the atrial refractoriness is thought to be an important mechanism by which AF perpetuates itself. \(^{39}\) Furthermore, it has been shown recently that the ultrarapid delayed rectifier K1 current (IKUR) plays an important role in human atrial repolarization. \(^{40}\) An increase in IKUR decreases action potential duration, and it was shown that this current effect is reversed by the addition of propranolol. \(^{41}\) Hence, there is evidence from experimental observations that stimulation of adrenoceptors might facilitate the induction and perpetuation of AF. Beta-blockers may also protect against AF by the prevention of atrial ischaemia \(^{42}\), \(^{43}\) and fibrosis in those with underlying ischaemic heart disease.

**Clinical implications**

Beta-blockers generally have not been considered to be atrial-stabilizing agents except in few well-defined situations. First, a small population of patients with adrenergically mediated AF associated with stress or anxiety \(^ {37}\), these patients may well respond to beta-blockade. Secondly, and more common, is the use of beta-blockers in prevention of AF for patients following cardiothoracic surgery, in which AF occurs in \( \approx 30\% \) of patients. \(^ {44}\) Kuhlkamp et al. \(^ {45}\) demonstrated in a third situation, a significant although small effect in reducing relapse rates of AF following cardioversion, although the majority of patients did not suffer from HF. But these results suggest especially that the preventive effect cannot be solely attributed to a better control of the underlying cardiac disease.

Quinidine, disopyramide, flecainide, propafenone, D,L-sotalol, and amiodarone have all shown efficacy in reducing AF recurrence in patients with paroxysmal and/or persistent AF. Unfortunately, these agents are associated with serious side effects, and class I agents are classically contraindicated among patients with LV dysfunction.
Our meta-analysis suggests that beta-blockers should be used as the first-line agents on preventing occurrence or recurrence of HF-related AF, with a similar and additional benefit in comparison with ACE-inhibitors and Angiotensin II receptor antagonists. It will be interesting to see the place of beta-blocker therapy in the AF-CHF trial which is ongoing. 10 This trial compares rhythm and rate control strategies in patients with HF.

In addition to the different potential mechanisms of beta-blockers-induced benefit in HF, our results show that prevention of onset of AF could play an important role in the overall reduction in mortality and morbidity in HF.

Limitations

The trials included in this analysis were post hoc reports of randomized trials designed to assess outcomes other than AF.

In this meta-analysis, the presence of arrhythmia was identified and characterized on the basis of adverse event reports. It is possible that frequency of asymptomatic AF may be underestimated, especially in the group taking beta-blocker, compared with the placebo group because of lower ventricular rates.

Conclusion

Beta-blockers appear to effectively prevent occurrence of AF in patients with systolic HF.

Conflict of interest: none declared.

References
