Interventions for prevention of post-operative atrial fibrillation and its complications after cardiac surgery: a meta-analysis

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Aims Atrial fibrillation (AF) is the most common complication after cardiac surgery. We aimed to evaluate, by meta-analysis, all randomized trials testing interventions for preventing AF.

Methods and results Ninety-four trials of prevention of post-operative AF were identified, by standard search methods, and analysed by standard meta-analysis techniques. All five commonly tested interventions, beta-blockers (BBs), sotalol, amiodarone, magnesium, and atrial pacing, were effective in preventing AF. The odds ratio (OR) for the effect of BB on the incidence of AF was 0.36 (95% CI 0.28–0.47, P < 0.001), but after trials confounded by post-operative non-study BB withdrawal were excluded was 0.69 (95% CI 0.54–0.87, P = 0.002). Sotalol reduced AF, compared with placebo (OR 0.34, 95% CI 0.26–0.45, P < 0.001) and compared with conventional BB (OR 0.42, 95% CI 0.26–0.65, P < 0.001). Amiodarone reduced AF (OR 0.48, 95% CI 0.40–0.57, P < 0.001). Magnesium (Mg) also had an effect (OR 0.57, 95% CI 0.42–0.77) but there was significant heterogeneity (P < 0.001), partly explained by concomitant BB. The effect of Mg with BB was less (OR 0.83, 95% CI 0.60–1.16). Pacing reduced AF (OR 0.60, 95% CI 0.47–0.77, P < 0.001), despite wide variations in techniques. Only amiodarone and pacing significantly reduced length of stay, average 20.60 days (95% CI 20.92 to 20.29) and 21.3 days (95% CI 22.55 to 20.08), respectively. Collectively, all treatments analysed together reduced stroke (OR 0.63, 95% CI 0.41–0.98). Amiodarone was the only intervention that alone significantly reduced stroke rate (OR 0.54, 95% CI 0.30–0.95).

Conclusion All five interventions reduced the incidence of AF, though the effect of BBs is less than previously thought. The significant reductions in length of stay and stroke in meta-analysis suggest that there are worthwhile benefits from aggressive prevention. Larger studies to confirm these clinical benefits and evaluate their cost-effectiveness would be worthwhile.

KEYWORDS Atrial fibrillation; Cardiac surgery; Meta-analysis; Prevention

Introduction

Post-operative atrial fibrillation (AF) after cardiac surgery is a growing problem. The rate of AF after cardiac surgery in the 1970s was about 10%, and is now consistently at least 30%, and much higher in older patients or those undergoing valve surgery.1,2 Although AF was always considered a problem, acknowledgment of AF as a potentially serious arrhythmia has increased. There have been more than 100 trials, multiple meta-analyses, and three sets of practice guidelines for prevention of post-operative AF in cardiac surgery. Despite this, the mainstay of therapy remains beta-blockers (BBs) alone, with only a modest influence on overall rates of post-operative AF.

Development of AF immediately after coronary artery bypass surgery (CABG) results in a longer stay in the intensive care unit and in hospital,3–8 together with a significantly higher (two- to three-fold) risk of post-operative stroke.4,8,9 Post-operative AF has also been shown to independently predict post-operative delirium and neurocognitive decline.10,11 Despite previous meta-analyses, there remains confusion about the potential benefits of individual agents, making a comprehensive updated review important; the present meta-analysis adds another 4 years of research and several thousand additional patients to the last comprehensive review.12

Methods

The search was performed in accordance with the recommendations of the Cochrane Collaboration, using Cochrane CENTRAL database, Medline, Premedline, and Embase from the earliest achievable date to December 2005. The initial search terms were 'AF' and 'cardiac surgery'.
Inclusion criteria for studies

Although a variety of agents and procedures have been tested for preventing AF, the aim of this meta-analysis was to include only interventions tested in more than three trials: BBs (excluding sotalol), sotalol, amiodarone, magnesium (Mg), and pacing. Summary statistics for digoxin and calcium channel blockers derived from previous meta-analyses are presented, as there have been no additional trials of these agents since and there is general acceptance that they are less effective interventions.13,14 Studies were included only if they met all of the following criteria: (i) randomized controlled trials (RCTs) using placebo or usual care (including BB) as the comparator; (ii) investigating the prevention of post-operative AF in CABG or valve or combined surgery as a primary aim of the trial; (iii) an adequately detailed published method; and (iv) adequate data on efficacy published.

Double-blind and non-blinded studies were included. Papers published in abstract form were reviewed but qualified only if they included sufficient information to fulfill the above criteria. Trials that did not qualify for the primary analysis as there were three or fewer trials of that treatment strategy have been included in a secondary table for comparison as there were 19 studies of off-pump coronary bypass surgery (OPCAB) in which AF rates were recorded but were not a primary purpose of the trial.

Other outcome measurements that were extracted from the analysis were AF requiring treatment, length of hospital stay (LOS), mortality, major morbidity, bradycardia, withdrawal of treatment, ventricular arrhythmias [tachycardia (VT) or fibrillation (VF)], and stroke. Where information was not published, attempts were made to contact authors.

Two reviewers independently performed the search (N.S., D.B.) and two reviewers independently extracted the data from the published sources (M.K., D.B.). Any discrepancies were resolved by consensus.

Statistics

The occurrence of AF, AF requiring treatment, mortality, major morbidity, bradycardia, treatment withdrawal, VT or VF, and stroke were treated as dichotomous variables. LOS was treated as a continuous variable, for which the sample size-weighted mean difference was calculated as a difference between the mean values of LOS in treatment and control groups.

Analyses were based on the intention-to-treat principle. Pooled effect estimates and heterogeneity between studies were analysed by use of the Reymann 4.2 statistical package, with a random-effects model with results presented as an odds ratio (OR) and 95% CIs. Two-sided P-values ≤ 0.05 were regarded as inferring statistical significance. Heterogeneity was assessed by means of the Cochrane Q heterogeneity test and considered significant when P < 0.05.

Publication bias was assessed using Begg’s funnel plot and examined for signs of asymmetry in the scatter plots of the treatment effects from individual studies (on the x-axis) against standard error (SE) or the variance of the effect estimate (y-axis) plotted on a logarithmic scale. The shape of the plot should resemble a symmetrical inverted funnel if publication bias is absent. Lack of symmetry, in particular the absence of studies in the lower right quadrant (representing small studies with a negative result) would raise suspicion that publication bias was present.

Results

Ninety-four studies evaluating the prevention of post-operative AF were published before January 2006 (Figure 1). Enrolment ranged from 36 to 1000 patients. All studies included patients undergoing CABG or valve surgery (Supplementary material, Table S1). Prevalence of background BB use varied but was higher in the more recent trials. Some studies delivered prophylaxis pre-operatively; in others, it was intra-operative or post-operative.

All trials used continuous ECG or Holter monitoring and either daily ECGs or pre-discharge Holter monitoring. Follow-up was usually restricted to the duration of hospital stay, but was extended to 30 or 90 days in some trials.

There were 31 comparisons evaluating BB against placebo, eight comparisons testing sotalol against placebo, together with seven comparisons of sotalol with conventional beta blockers in 14 trials, 18 comparisons of amiodarone with placebo, 22 comparisons of magnesium with placebo, and 23 comparisons of overdrive pacing against back up pacing in 14 trials (Table 1). There were 19 OPCAB trials in which AF was reported but not a primary outcome of the trial and 17 trials of other interventions with three or less trials each (Table 2).

Beta-blockers

Thirty-one trials evaluated prevention of post-operative AF by BB, comprising 4452 patients (Figure 2, Table 1).15–44 Despite showing an overall reduction in AF, there was significant heterogeneity (P < 0.001) between the trials which could not be explained by dose or drug. As such, it is inappropriate to pool all these study results together.

A significant amount of this heterogeneity was explained by whether each trial required the withdrawal of non-study BB in the control group. In those studies in which non-study BB was withdrawn at the time of surgery in the control group, the reduction in AF was much larger (OR 0.30, 95% CI 0.24–0.40) compared with those trials allowing continuation of non-study BB after surgery in the control group (OR 0.69, 95% CI 0.54–0.87). Some of the residual heterogeneity was explained by the large variation between trials in control group event rate (5–54%), with a higher event rate tending to be associated with a larger effect size. (Figure 2, Table 1, Supplementary material, Figure S1).

Sotalol

Fourteen trials evaluated sotalol for preventing post-operative AF, comprising 2583 patients with 2622 patient comparisons. Five trials used BB in the control arm,45–49 and seven used placebo control50–56 and two trials had both placebo and BB control arms51,54 (Figure 2, Table 1, Supplementary material, Figure S2).

Overall, AF was reduced from 33.7 to 16.9% (OR 0.37, 95% CI 0.29–0.48). In the trials that compared it directly with BB, sotalol reduced AF from 25.7 to 13.7% (OR 0.42, 95% CI 0.30–0.58). In the amiodarone trials, AF was reported but not a primary outcome of the trial and 17 of other interventions with three or less trials each (Table 2).

Amiodarone

Eighteen trials (3295 patients), with a variety of dosing strategies, have evaluated amiodarone for the prevention of post-operative AF (Figure 2, Table 1, Supplementary material, Figure S3).44,57–73 Amiodarone reduced AF from an average incidence of 33.2% in the control group to 19.8% (OR 0.48, 95% CI 0.40–0.57). In the amiodarone
trials, 3.4% in the control groups and 6.8% in the amiodarone groups had bradycardia (OR 1.66, 95% CI 1.73–2.47). Also, 5.2% in the control groups and 2.2% in the amiodarone groups had VT or VF (OR 0.45, 95% CI 0.29–0.69) (Figure 3, Supplementary material, Figures S9 and S10).

**Magnesium**

Twenty-two trials (2896 patients) evaluated prevention of post-operative AF by Mg (Figure 2, Table 1, Supplementary material, Figure S4). These trials varied greatly in dose and timing of delivery. Despite showing an overall reduction in AF (OR 0.57, 95% CI 0.42–0.77), there was significant heterogeneity ($P < 0.001$) between trials not explained by dose, meaning it is inappropriate to pool all these studies together. Some of this heterogeneity was explained by the concomitant use of BB; the largest effect of magnesium was in the two trials with no use of BB (OR 0.05, 95% CI 0.02–0.16) and the smallest effect was in the trials in which BB was recommenced post-operatively in both treatment and control groups (OR 0.83, 95% CI 0.60–1.16).

**Overdrive pacing**

Fourteen trials among 1586 patients with 1885 patient comparisons evaluated overdrive pacing strategies for prevention of post-operative AF (Figure 2, Table 1, Supplementary material, Figure S5). The trials were all small (21–160 patients). The overall effect of pacing was a reduction in AF from 34.8 to 24.6% (OR 0.60, 95% CI 0.47–0.77). Bi-atrial pacing had the only individually significant result, with the greatest effect size, reducing AF from an average of 35.3% in the control group to 17.7% in the paced group (OR 0.44, 95% CI 0.31–0.64). Right atrial pacing
reduced AF from 33.1% in the control group to 27.5% in the paced group (not significant, OR 0.74, 95% CI 0.48–1.12). Left atrial (LA) pacing or Bachmann’s bundle pacing reduced AF from 37.5% in the control group to 30.2% in the paced group (not significant, OR 0.70, 95% CI 0.46–1.07).

**Digoxin**

Digoxin was not found to be effective for AF prevention in the Kowey meta-analysis published in 1992^13^ (OR 0.97, 95% CI 0.62–1.49). No further studies have been identified or published since that analysis (Figure 2, Table 1).

### Table 1  Trials included in primary analysis

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Trials</th>
<th>Comparator</th>
<th>Patients</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value for effect</th>
<th>P-value for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB</td>
<td>31</td>
<td>All</td>
<td>4452</td>
<td>0.36</td>
<td>0.28–0.47</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Placebo + no post-operative non-study BBs 'BB withdrawal'</td>
<td>2600</td>
<td>0.30</td>
<td>0.22–0.40</td>
<td>&lt;0.001</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Placebo + post-operative non-study BB recommended 'No BB withdrawal'</td>
<td>1163</td>
<td>0.69</td>
<td>0.54–0.87</td>
<td>0.002</td>
<td>0.72</td>
</tr>
<tr>
<td>Sotalol</td>
<td>14^a</td>
<td>BB or placebo</td>
<td>2622</td>
<td>0.37</td>
<td>0.29–0.48</td>
<td>&lt;0.001</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Placebo</td>
<td>1382</td>
<td>0.34</td>
<td>0.26–0.45</td>
<td>&lt;0.001</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>BB</td>
<td>1240</td>
<td>0.42</td>
<td>0.26–0.65</td>
<td>&lt;0.001</td>
<td>0.08</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>18</td>
<td>Placebo</td>
<td>3295</td>
<td>0.48</td>
<td>0.40–0.57</td>
<td>&lt;0.001</td>
<td>0.31</td>
</tr>
<tr>
<td>Magnesium</td>
<td>22</td>
<td>All</td>
<td>2896</td>
<td>0.54</td>
<td>0.40–0.74</td>
<td>0.007</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Placebo + no BB allowed pre- or post-operatively</td>
<td>348</td>
<td>0.05</td>
<td>0.02–0.16</td>
<td>&lt;0.001</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Placebo + no BB post-operatively</td>
<td>674</td>
<td>0.67</td>
<td>0.39–1.14</td>
<td>0.14</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Placebo + restart of non-study BB post-operatively</td>
<td>707</td>
<td>0.83</td>
<td>0.60–1.16</td>
<td>0.46</td>
<td>0.47</td>
</tr>
<tr>
<td>Overdrive pacing</td>
<td>14^b</td>
<td>No pacing</td>
<td>1885</td>
<td>0.60</td>
<td>0.47–0.77</td>
<td>&lt;0.001</td>
<td>0.13</td>
</tr>
<tr>
<td>Bi-atrial</td>
<td>10</td>
<td>No pacing</td>
<td>754</td>
<td>0.44</td>
<td>0.31–0.64</td>
<td>&lt;0.001</td>
<td>0.32</td>
</tr>
<tr>
<td>Right atrial</td>
<td>9</td>
<td>No pacing</td>
<td>723</td>
<td>0.74</td>
<td>0.48–1.12</td>
<td>0.15</td>
<td>0.14</td>
</tr>
<tr>
<td>LA or Bachmann’s bundle</td>
<td>4</td>
<td>No pacing</td>
<td>408</td>
<td>0.70</td>
<td>0.46–1.07</td>
<td>0.10</td>
<td>0.74</td>
</tr>
<tr>
<td>Calcium channel blockers^d</td>
<td>15</td>
<td>Placebo</td>
<td>1756</td>
<td>0.73</td>
<td>0.48–1.12</td>
<td>0.15</td>
<td>0.004</td>
</tr>
<tr>
<td>Dihydropyridines</td>
<td>3</td>
<td>Placebo</td>
<td>291</td>
<td>2.69</td>
<td>0.57–12.64</td>
<td>0.2</td>
<td>0.095</td>
</tr>
<tr>
<td>Non-dihydropyridines</td>
<td>12</td>
<td>Placebo</td>
<td>1465</td>
<td>0.62</td>
<td>0.41–0.93</td>
<td>0.02</td>
<td>0.03</td>
</tr>
</tbody>
</table>

^a^Janssen et al.^4^ and Auer et al.^4^ had both BB and placebo control arms, number of patients represents number of patient comparisons.

^b^Goette et al.,^9^ Daoud et al.,^9^ Newman et al.,^9^ Fan et al.,^10^ Greenberg et al.,^10^ and Gerstenfeld et al.,^10^ had two or more active treatment arms in trials; number of patients represent number of patient comparisons.

^'*^Kowey et al.,^1^ and Wijeysundera et al.,^16^ had both BB and placebo control arms, number of patients represents number of patient comparisons.

<table>
<thead>
<tr>
<th>OPCAB</th>
<th>19</th>
<th>All</th>
<th>2671</th>
<th>0.66</th>
<th>0.51–0.85</th>
<th>0.001</th>
<th>0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>On-pump with AF rate ≥45%</td>
<td>252</td>
<td>0.23</td>
<td>0.08–0.63</td>
<td>0.004</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>On-pump with AF rate ≥30 &lt; 45%</td>
<td>656</td>
<td>0.64</td>
<td>0.45–0.90</td>
<td>0.01</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>On-pump with AF rate &lt; 30%</td>
<td>1763</td>
<td>0.80</td>
<td>0.63–1.02</td>
<td>0.07</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>3</td>
<td>Beta-blocker or placebo</td>
<td>597</td>
<td>0.73</td>
<td>0.39–1.38</td>
<td>0.97</td>
<td>0.16</td>
</tr>
<tr>
<td>Procainamide</td>
<td>2</td>
<td>Placebo</td>
<td>146</td>
<td>0.51</td>
<td>0.25–1.04</td>
<td>0.07</td>
<td>0.59</td>
</tr>
<tr>
<td>GIK</td>
<td>3</td>
<td>Placebo</td>
<td>102</td>
<td>0.25</td>
<td>0.06–1.01</td>
<td>0.05</td>
<td>0.12</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1</td>
<td>Placebo</td>
<td>236</td>
<td>0.48</td>
<td>0.26–0.88</td>
<td>0.05</td>
<td>NA</td>
</tr>
<tr>
<td>T3</td>
<td>2</td>
<td>Placebo</td>
<td>296</td>
<td>0.55</td>
<td>0.18–1.67</td>
<td>0.29</td>
<td>0.06</td>
</tr>
<tr>
<td>Quinidine</td>
<td>1</td>
<td>Control</td>
<td>100</td>
<td>1.00</td>
<td>0.34–2.91</td>
<td>1.00</td>
<td>NA</td>
</tr>
<tr>
<td>Alinidine</td>
<td>1</td>
<td>Placebo</td>
<td>32</td>
<td>0.01</td>
<td>0.00–0.29</td>
<td>0.006</td>
<td>NA</td>
</tr>
<tr>
<td>Ventral cardiac denervation</td>
<td>1</td>
<td>Control</td>
<td>416</td>
<td>0.23</td>
<td>0.12–0.42</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>Preservation anterior fat pad</td>
<td>1</td>
<td>Control</td>
<td>55</td>
<td>0.14</td>
<td>0.03–0.69</td>
<td>0.02</td>
<td>NA</td>
</tr>
<tr>
<td>N-3 fatty acids</td>
<td>1</td>
<td>Control</td>
<td>160</td>
<td>0.36</td>
<td>0.17–0.77</td>
<td>0.009</td>
<td>NA</td>
</tr>
<tr>
<td>Intrapericardial blake drain</td>
<td>1</td>
<td>Rigid drain</td>
<td>203</td>
<td>0.41</td>
<td>0.19–0.89</td>
<td>0.02</td>
<td>NA</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>1</td>
<td>Placebo</td>
<td>200</td>
<td>0.41</td>
<td>0.23–0.72</td>
<td>0.002</td>
<td>NA</td>
</tr>
</tbody>
</table>

GIK, glucose–insulin–potassium; T3, tri-iodothyronine.
Calcium channel blockers

Similarly, there has been little new research on calcium channel blockers (CA) since 2000. The 2003 Wijeysundera meta-analysis\textsuperscript{14} provides the most up to date results. Overall, there was no significant effect on supraventricular tachycardias (SVT), OR 0.73, 95% CI 0.48–1.12 but with significant heterogeneity (P = 0.004). Subgroup analyses showed that non-dihydropyridines significantly reduced SVT (OR 0.62, 95% CI 0.41–0.93) but still with significant heterogeneity (P = 0.03), whereas dihydropyridines non-significantly increased SVT (OR 2.69, 95% CI 0.57–12.64) (Figure 2, Table 1).

Trials excluded from primary analysis

Nineteen OPCAB\textsuperscript{109–126} trials reported rates of AF, but did not meet the entry criteria for inclusion in the meta-analysis, as AF was not a primary endpoint of these trials. As such, monitoring, definitions and concomitant therapies vary

\textbf{Table 1}  

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Treatment</th>
<th>Control</th>
<th>OR and 95% CI</th>
<th>P-value for heterogeneity*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-blockers (BB)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(withdrawal or continuation of non-study BB)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB withdrawn</td>
<td>131/1243</td>
<td>390/1357</td>
<td>0.30 (0.22–0.40)</td>
<td></td>
</tr>
<tr>
<td>BB not withdrawn</td>
<td>183/581</td>
<td>234/592</td>
<td>0.69 (0.54–0.87)</td>
<td></td>
</tr>
<tr>
<td>Withdrawal not stated</td>
<td>51/339</td>
<td>88/350</td>
<td>0.53 (0.36–0.79)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>365/2153</td>
<td>712/2289</td>
<td>0.36 (0.28–0.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Sotalol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotalol vs. placebo</td>
<td>134/687</td>
<td>286/695</td>
<td>0.34 (0.26–0.45)</td>
<td></td>
</tr>
<tr>
<td>Sotalol vs. BB</td>
<td>80/583</td>
<td>169/657</td>
<td>0.42 (0.26–0.65)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>214/1270</td>
<td>455/1352</td>
<td>0.37 (0.29–0.48)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Amiodarone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone vs. placebo</td>
<td>331/1670</td>
<td>539/1625</td>
<td>0.48 (0.40–0.57)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Magnesium</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium:continued</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB</td>
<td>93/356</td>
<td>106/351</td>
<td>0.83 (0.60–1.16)</td>
<td></td>
</tr>
<tr>
<td>Magnesium: no post-operative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB</td>
<td>77/341</td>
<td>95/333</td>
<td>0.67 (0.39–1.14)</td>
<td></td>
</tr>
<tr>
<td>Magnesium: no pre-operative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB</td>
<td>4/193</td>
<td>41/155</td>
<td>0.05 (0.02–0.16)</td>
<td></td>
</tr>
<tr>
<td>Magnesium vs. placebo and BB use not stated</td>
<td>106/598</td>
<td>160/569</td>
<td>0.57 (0.41–0.80)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>282/1488</td>
<td>402/1408</td>
<td>0.57 (0.42–0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Overdrive pacing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bi-atrial pacing</td>
<td>69/367</td>
<td>135/387</td>
<td>0.44 (0.31–0.62)</td>
<td></td>
</tr>
<tr>
<td>Right atrial</td>
<td>100/364</td>
<td>119/359</td>
<td>0.74 (0.48–1.12)</td>
<td></td>
</tr>
<tr>
<td>Left atrial</td>
<td>58/192</td>
<td>81/216</td>
<td>0.70 (0.46–1.07)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>227/923</td>
<td>335/962</td>
<td>0.60 (0.47–0.77)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin vs. placebo</td>
<td>34/240</td>
<td>47/267</td>
<td>0.97 (0.62–1.49)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Calcium-channel blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydropyridines vs. placebo</td>
<td>19/145</td>
<td>9/146</td>
<td>2.69 (0.57–12.64)</td>
<td></td>
</tr>
<tr>
<td>Nondihydropyridines vs. placebo</td>
<td>117/719</td>
<td>166/746</td>
<td>0.62 (0.41–0.93)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>130/864</td>
<td>175/892</td>
<td>0.73 (0.48–1.12)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*P-value for heterogeneity displayed is the value tested across all trials of that treatment not by sub-groups displayed.

\textsuperscript{13}Kowey et al.\textsuperscript{13}

\textsuperscript{14}Wijeysundara et al.\textsuperscript{14}

\textbf{Figure 2}  

Effect of all interventions on post-operative occurrence of AF.
widely and the trials have significant heterogeneity (P < 0.001) which is partly explained by the baseline rates of AF in the control groups. There was a larger effect in those trials with an AF rate in the control group of ≥45% (OR 0.20, 95% CI 0.11–0.37) and a non-significant effect in the lowest risk group with AF ≤30% (OR 0.80, 95% CI 0.63–1.02) (Table 2, Supplementary material, Figure S11 and Table S2).

Seventeen trials127–143 did not meet the entry criteria for inclusion in the meta-analysis as the interventions were not tested in more than three trials but provide an overview of treatments, some that have historical interest only such as quinidine and some interventions that are early in the investigative cycle and that will require confirmatory studies (Table 2, Supplementary material, Figure S12 and Table S3).

Length of stay

Twenty-nine trials evaluated LOS: two BB,15,44 ten amiodarone,44,48,50,51,53,55,56 and seven sotalol44,48,50,51,53,55,56 trials (3 trials tested multiple interventions). Only amiodarone and pacing had a significant effect on LOS (Figure 4, Supplementary material, Figure S6). Amiodarone reduced LOS (−0.60 95% CI −0.92 to −0.29) compared with control. Pacing reduced LOS (−1.3 days 95% CI −2.55 to −0.08) compared with control.

Risk of stroke

Twenty-five trials (5479 patients)15,35,40,44,48,51,57,58,61–64,66–69,71–73,76,93,97,102,104,105 reported on the incidence of post-operative stroke (Figure 5, Supplementary material, Figure S7). No individual trial has shown less stroke, but with all trials of all treatments combined, reported stroke rate averaged 1.9% in the control group and 1.1% with treatment (OR 0.63, 95% CI 0.41–0.98). Amiodarone was the only single intervention that showed a significantly reduced stroke rate, from 2.4% in the control group to 1.2% in the treatment group (OR 0.54, 95% CI 0.30–0.95). There was no obvious indication that this finding was subject to important publication bias based on assessment of a funnel plot (Figure 6, Supplementary material, Figure S7).

Discussion

Systematic meta-analysis is an important tool to identify the effects of treatment and differences in effects between subgroups of patients beyond the reach of individual clinical trials.144 This meta-analysis is unique in clarifying the status of AF prophylaxis in contemporary clinical practice by identifying the confounding effect of BB withdrawal in the trials of both BBs and magnesium; additionally, it is the first to find a significant advantage of sotalol over standard BBs and identify a significant overall reduction in both stroke and LOS with prophylaxis. As such, this meta-analysis offers an opportunity to review the current policy guidelines.145–147

The routine use of prophylaxis for preventing AF after cardiac surgery has been adopted slowly, partly because of a perception that post-operative AF is of minor clinical consequence and partly because of the small size of trials, which until recently were unable to document significant benefits on clinical outcomes even when pooled. The absence of comprehensive safety data has also probably slowed clinical uptake.

Reliance on recommencing BB alone after surgery leaves a significant number of patients at risk of post-operative AF. The previous reports of BB effectiveness in preventing AF have been overestimated for contemporary practice due to grouping of heterogenous trials. The trials included subjects with a wide variety of background BB use. The estimates were confounded by the grouping of trials requiring non-study BB withdrawal after surgery (increasing control group AF rate and subsequently the effect size of study BB) with studies allowing continuation of non-study BB (it is thought that acute BB withdrawal increases the risk of post-operative AF beyond that of BB-naive patients). The effectiveness of Mg has previously been similarly overestimated because of pooling all trials together which in this analysis was found to be inappropriate due to heterogeneity, some of which is due to concomitant use of BB. In the Mg trials that most closely reflect current clinical practice, in which BB were recommenced post-operatively, there is no significant reduction in AF (OR 0.83, 95% CI 0.60–1.16) attributable to Mg.
The lower rate of AF when cardiopulmonary bypass is not used (OPCAB) could logically relate to reduced systemic inflammation or reduced trauma to the atrium; but as it was not uniformly studied in the OPCAB trials, it may alternatively relate to confounding effects of less inotrope requirement, earlier recommencement of BBs, or shorter time on electrocardiographic monitoring. However, as more trials are performed in this area, it may provide important insights into the causes of post-operative AF.

Several investigative therapies (Table 2) also look promising but may be subject to considerable publication bias.

The other major barrier to the use of more potent prophylaxis is the perception that post-operative AF does not affect other clinical outcomes; this meta-analysis provides the strongest evidence to date that reduction in AF can improve clinical outcomes, specifically reducing LOS and stroke incidence.

Although the number of stroke events in the meta-analysis was small and the reduction in stroke with AF prophylaxis must be viewed as hypothesis-generating requiring further study, it suggests that the risk of post-operative stroke attributable to AF is sufficiently large for AF prevention to reduce it. There was no evidence that publication bias explained this finding (Figure 6).

Patients after cardiac surgery have several factors leading to a higher risk of thrombo-embolic stroke than non-surgical patients. A thrombotic milieu is often present post-operatively, with impaired left ventricular systolic and diastolic function, subsequent high LA pressure, dilation of LA and the LA appendage (LAA), decreased LAA velocities, increased stasis, and enhanced potential for thrombus formation. These changes are aggravated when post-operative AF occurs and lessened when AF can be prevented.

Anticoagulation is sometimes contraindicated and may be underused. Other plausible mechanisms that may be important in the reduction of stroke by AF prophylaxis are prevention of low output states resulting from rapid AF and prevention of low output or ventricular thrombus formation from complicating VT and VF.

Much larger RCTs would be needed to determine whether stroke reduction with more potent AF prevention can be reproduced.
Our meta-analysis suggests that if sufficiently potent methods are used, both the risk of stroke and LOS may be reduced in patients undergoing cardiac surgery. This could translate to real clinical benefits; for example, if amiodarone is as effective as the analysis suggests treating 1000 similar patients would prevent 134 episodes of AF, 30 episodes of sustained VT, and 12 strokes at the cost of 34 episodes of bradycardia but saving about 600 hospital days.

Limitations
This meta-analysis is limited by the lack of complete availability of all relevant data. Data on stroke rates, VT and VF, treatment withdrawal, and LOS were not available in many included studies. As such, there may be reporting bias in these outcomes. Although no intervention affected mortality due to the low overall death rates, a difference cannot be excluded. In addition, many studies failed to collect or report on comprehensive safety outcomes.

Practical applications
This meta-analysis supports the present recommendation that BBs are not withdrawn in the post-operative period, but suggests, in contrast to previous recommendations, that in those at high risk of AF, BB will not offer great protection when used alone. There is little compelling evidence that BBs are more effective than other therapies or reduce LOS or morbidity. In fact, the largest study of BB showed only a modest reduction in AF incidence, from 39 to 31%, with no change in LOS or costs (though control rates of BB use were probably high reflecting contemporary clinical practice but diluting the effect size). In the comparisons of BB and sotalol, the rate of AF in the BB group was high: 25.9% and significantly reduced by sotalol. Magnesium may offer little or no additional benefit to those using BB therapy and we do not recommend it for prophylaxis in this setting. Amiodarone trials give the most comprehensive information on morbidity, and collectively now show a decrease in AF, LOS, ventricular arrhythmias, and stroke at the expense of increased bradycardia. In contrast to a recent meta-analysis that focuses only on amiodarone, we feel that there is now sufficient evidence to state that amiodarone gives additive protection when used with BB, as there is no heterogeneity across the amiodarone trials, despite widely varying rates of BB use, from 25 to 100%. Additionally, the largest trial of amiodarone also showed a significant reduction in AF in a pre-specified subgroup analysis of subjects on peri-operative BB drug therapy. This was applied exclusively post-operatively without negative inotropic or chronotropic effects. The best strategy or drug dose to follow cannot be concluded from this analysis and is clearly an area for further research. The future of AF prevention is the addition of these more potent strategies to routine BB continuation, although the overall benefits with comprehensive safety data should ideally be confirmed in large-scale multicentre RCTs.

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Conflict of interest: The authors have no conflicts of interest to declare.

References

Supplementary material
Supplementary material is available at European Heart Journal online.
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