Are prophylactic β-blockers of benefit in reducing the incidence of AF following coronary bypass surgery?

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Received 16 July 2004; accepted 22 July 2004,

Summary

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was whether prophylactic beta-blockers effectively reduces the incidence of atrial fibrillation post-cardiac surgery. Altogether 113 papers were found using the reported search, of which 8 represented the best evidence on this topic. The author, journal, date and country of publication, patient group studied, study type, relevant outcomes, results, and study weaknesses were tabulated. We conclude that prophylactic beta-blockers clearly reduce the incidence of AF with a number needed to treat of only seven to prevent one episode of AF. The optimal beta-blocker or the benefits to patients with impaired ejection fraction are less clear.

Keywords: Beta-blockers; Thoracic surgery; Prophylactic drug therapy; Atrial fibrillation; Review

1. Introduction

A best evidence topic was constructed according to a structures protocol. This protocol is fully described in the ICVTS [1].

2. Clinical scenario

You are seeing a 75-year-old diabetic man with triple vessel disease, for whom you are going to perform triple vessel coronary arterial bypass tomorrow. He has been suffering with angina for the past 9 years but it has got progressively worse. His left ventricular ejection fraction is 45%.

You note that he is on 25 mg of atenolol pre-operatively and his heart rate is 80 today. He reports that he has had palpitations occasionally in the past but not recently. You feel that he is almost destined to go into atrial fibrillation post-operatively but there is a wide variation in the hospital with regard to beta-blocker prophylaxis with some patients being changed to sotalol pre-operatively, some having atenolol started on the day after surgery, and many patients with any impairment of their ejection fraction having all beta-blockers withdrawn for at least 4 days. You wonder whether there is any consensus in the literature.

3. Three-part question

In [patients undergoing cardiac surgery] are [prophylactic β-blockers] of benefit in reducing the incidence of [post-operative AF]?

4. Search strategy

[cardiac surgery.mp OR exp thoracic surgery OR bypass.mp OR CABG.mp OR exp coronary artery bypass OR cardiopulmonary bypass.mp OR exp cardiovascular surgical procedures] AND [exp adrenergic beta-antagonists OR exp beta-blockers OR beta-adrenoceptor blocker.mp OR prophylactic drug therapy.mp] AND [exp atrial fibrillation OR post-operative AF.mp OR post-operative atrial fibrillation.mp OR supraventricular arrhythmia.mp OR supraventricular arrhythmias.mp].
Table 1  
Summary of best evidence papers

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Andrews et al., 1991, Circulation, USA [2]</td>
<td>Meta-analysis of 18 RCTs addressing the efficacy of beta-blockers as prophylaxis after CABG, and 24 RCTs found looking at all drugs</td>
<td>Meta-analysis (level 1a)</td>
<td>Incidence of supraventricular arrhythmia in the various study subgroups</td>
<td>All beta-blocker patients 8.7% Control patients 34% ($P&lt;0.0001$)</td>
<td>In this meta-analysis supraventricular arrhythmia included atrial fibrillation, atrial flutter, paroxysmal reentrant supraventricular tachycardia or paroxysmal atrial tachycardia. The patients in these studies were highly selected, predominantly young males with well preserved left ventricular function. Most beta-blocker trials either included patients on beta-blockers before surgery or excluded patients with ejection fractions below 30–50%. Trials also excluded patients with insulin-dependent diabetes, history of AV block, sick sinus syndrome, bronchospastic lung disease or hypotension at the time of randomization.</td>
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<td>A total of 1549 patients on beta-blockers were analysed</td>
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<td>Pre-operative beta-blockers 8.1% Control patients 40.1% ($P&lt;0.00001$)</td>
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<td>Subgroup analysis of pre-operative treatment groups, post-operative treatment groups, patients treated with either low dose or high dose propranolol and patients treated with either propranolol or non-propranolol beta-blockers was also performed</td>
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<td>Post-operative beta-blockers 8.9% Control patients 32.3% ($P&lt;0.00001$)</td>
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<td>Verapamil patients 18.2% Control patients 18.2% ($P=0.69$)</td>
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<td>Digoxin patients 14.2% Control patients 17.6% ($P=0.88$)</td>
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<td>Kowey et al., 1992, Am J Cardiol, USA [3]</td>
<td>Meta-analysis of 7 randomized trials investigating the effectiveness of prophylactic beta-blockers in preventing supraventricular arrhythmia early after CABG</td>
<td>Meta-analysis (level 1a)</td>
<td>Supraventricular arrhythmia early after CABG</td>
<td>Beta-blocker patients 66/675 (9.8%) Control patients 150/743 (20.2%) $P&lt;0.001$</td>
<td>Drug selection, dosing and monitoring were all variable in individual trial. Despite that most cases of post-operative SVA were due to AF, some were attributed to atrial flutter. Variables that may have contributed to the results of individual trials were not taken into account. Data used in the study was 5–15 years old. Mean age of patients 55, male to female 4.5:1</td>
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<td>A total of 1418 patients were analyzed: 743 controls vs 675 patients who received beta-blocker therapy</td>
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<td></td>
<td>Combination of beta-blocker and digoxin 3/139 (2.2%) Control patients 45/153 (29.4%) $P&lt;0.001$</td>
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Table 1 (continued)

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<td>American College of Cardiology/American Heart Association Task Force on Practice Guidelines, 1999, J Am Coll Cardiol, USA [4]</td>
<td>Systematic review of various issues regarding coronary artery bypass grafting</td>
<td>Systematic review (level 1a)</td>
<td>Prevention of post-operative atrial fibrillation</td>
<td>Withdrawal of pre-operative beta-blockers in the post-operative period doubles the risk of atrial fibrillation after CABG. Thus, early re-initiation of beta-blockers is critical for avoidance of this complication.</td>
<td>Only highly selected papers referenced. No search strategy given. No level of evidence or grade of recommendation given.</td>
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<td>Crystal et al., 2002, Circulation, USA [6]</td>
<td>27 RCTs evaluating the role of beta-blockers in the prevention of post-operative AF were analyzed, involving a total of 3840 patients</td>
<td>Meta-analysis (level 1a)</td>
<td>Primary outcome measure was the incidence of post-operative AF or atrial flutter. Two other outcome measures LOS and incidence of stroke were also analyzed</td>
<td>All beta-blocker patients 19% Control patients 33% (OR=0.39, P&lt;0.00001) Sotalol patients 17% Control patients 37% (OR=0.35, P&lt;0.00001) no significant heterogeneity between trials P=0.25 Sotalol patients 12% Other beta-blockers 22% (OR, 0.50; 95% CI, 0.34–0.74) Amiodarone patients 22.5% Control patients 37% (OR=0.48, P&lt;0.00001) with no significant heterogeneity between trials (P=0.55) Beta-blockers did not significantly reduced LOS (−0.66 day, 95% CI, −2.04 to 0.72) Incidence of stroke was 1.2% in all the treatment groups combined and 1.4% in controls (P=NS)</td>
<td>There was significant heterogeneity between individual beta-blocker trials (P=0.00001). However, analysis of the role of specific beta-blockers used, individual sample size, the proportion of patients taking beta-blockers pre-operatively, method of ECG monitoring, and source where the information for this meta-analysis was obtained from, revealed no reasons for heterogeneity. Individual studies included span 3 decades (1979–2001) Most studies excluded patients with impaired EF. Mean EF ranged from 43 to 68%</td>
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5. Search outcome

A total of 113 papers were found from which five meta-analyses and systematic reviews represented the best evidence. In addition, The American Heart Association guidelines were reviewed. Cross-checking reference lists and journal club suggestions provided an additional two papers. These papers are listed in Table 1.

6. Results

Andrews et al. [2] performed the first meta-analysis in this area. They found that 13 or 18 studies investigating the benefit of prophylactic beta-blockers showed a significant benefit in favor of giving prophylaxis. Pooling all these results showed a reduction in AF from 34% to 8.7% from studies involving 1549 patients. Interestingly, no difference was shown when pre-operative beta-blocker studies were compared to post-operative studies. No benefit was shown in eight studies assessing either verapamil or digoxin as AF prophylaxis. They also showed that the mean ventricular rate was significantly lower in beta-blocked patients when they did go into AF, with a mean rate 24 bpm slower than controls. They did caution that most patients in these studies were young, male and had good ejection fractions and had been on beta-blockers pre-operatively.

Kowey et al. [3] in 1992 pooled data from seven studies containing 1418 patients, and found a reduction in AF from 20.2% to 9.8%. In addition, they pooled data from two studies containing 292 patients that looked at prophylaxis with both digoxin and beta-blockers and concluded that combination therapy was better than beta-blockers alone with a $P$ value of less than 0.01.

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<td>Wurdeman et al., 2002, Chest, USA [7]</td>
<td>10 RCTs that studied either amiodarone ($n=764$) or sotalol ($n=539$) as prophylaxis for AF (5 RCTs for each drug, no direct comparative studies)</td>
<td>Meta-analysis (level 1a)</td>
<td>Incidence of AF</td>
<td>Sotalol group 21.5% reduction in AF compared to placebo ($P&lt;0.001$)</td>
<td>Neither drug reduced LOS</td>
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<td>Ferguson et al., 2002, J Am Med Assoc, USA [8]</td>
<td>The use of pre-operative B-blockers was assessed in the STS database from 1996 to 1999, among 629,877 patients from 497 sites for mortality and morbidity</td>
<td>Retrospective Cohort study (level 2b)</td>
<td>Unadjusted mortality</td>
<td>B-blocker patients 2.8% Control patients 3.4% (OR 0.8, CI 0.78–0.82)</td>
<td>6.4% of patients did not have any record of whether B-blockers were used</td>
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<td>Zimmer et al., 2003, Am J Cardiol, USA [9]</td>
<td>13 RCTs identified including 1783 patients that specifically looked at prophylactic antiarrhythmic studies that reported data on Length of stay (LOS) costs, CVA, or mortality</td>
<td>Meta-analysis (level 1a)</td>
<td>Odds of AF</td>
<td>Odds of AF in all studies was reduced by 0.52 (0.41–0.65)</td>
<td>65 trials excluded due to incomplete reporting of data. Only one of the 13 RCTs looked at beta-blockers, 6 were in amiodarone, 5 were in atrial pacing, and one was in procainamide</td>
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Downloaded from https://academic.oup.com/icvts/article-abstract/3/4/641/677693 by guest on 31 December 2018
Zimmer et al. [9] performed a meta-analysis of all anti-arrhythmic strategies to look at the length of stay, costs, stroke and mortality. They found that the use of beta-blockers reduced AF from 33% to 19% from pooled data from 27 RCTs that recruited 3840 patients. This corresponds to a number needed to treat of 7. Pooling all strategies to reduce AF, they concluded that hospital stay could be reduced by half a day, but no reduction in the incidence of stroke could be found. In sub-analyses they found that four trials with 900 patients compared sotalol with other beta-blockers and found that sotalol significantly reduced the incidence of AF compared to other beta-blockers. However, they caution that sotalol also has the potential to cause proarrhythmic side effects despite this reduction in AF, but provide no figures to back this up. They also investigated the effect of either pre-operative or post-operative commencement of beta-blocker prophylaxis and found no difference between the two strategies. As a final note they found that both prophylactic amiodarone and biatrial pacing also significantly reduces the incidence of AF.

Wurdeman et al. [7] in 2002 compared studies investigating sotalol with studies investigating amiodarone. They found no studies that directly compared the drugs. They found that sotalol reduced the incidence of AF by 21.5% compared to a reduction of 14% with amiodarone, but this difference between the drugs was not statistically significant. In addition a significantly higher percentage of patients receiving sotalol had their treatment stopped due to side-effects. No differences in length of stay were found. They concluded that both drugs were comparable in terms of their efficacy in reducing AF but amiodarone had fewer side-effects.

Maisel et al. [5] performed a systematic review in 2001 and concluded that all patients should receive both pre-operative and post-operative beta-blockers prior to cardiac surgery, unless contraindicated, in which case amiodarone or biatrial pacing should be used. Of note they mainly quoted the meta-analysis from Andrews et al. in making these recommendations [2].

Ferguson et al. [8] performed a large retrospective analysis of the STS surgical database containing 629,877 patients to look at the mortality and morbidity associated with pre-operative beta-blocker use. This was not a randomized trial and therefore patients had not received beta-blockers randomly, so the authors used a propensity score for the risk of receiving a beta-blocker, derived from patient and centre-associated risk factors. After adjustment they found that there was a slightly lower mortality in the pre-operative beta-blocker group, and a lower incidence of stroke ventilation and renal failure. They also found that patients with an EF less than 30% had a slightly increased mortality. This study was also not considering the effect of reduction in AF but only the benefit of beta-blockers by any mechanism.


In summary, the results of five meta-analyses show that prophylactic beta-blockers clearly reduce the incidence of AF. In addition some benefits in terms of reducing length of stay, costs, mortality and morbidity have been shown in patients with a good ejection fraction, although the evidence for this is far less strong. In addition the benefits of pre-operative administration over early post-operative administration have not been clearly demonstrated or the relative benefits of any one beta-blocker over another.

7. Clinical bottom line

Prophylactic beta-blockers clearly reduce the incidence of AF with a number needed to treat of only 7 to prevent one episode of AF. The optimal beta-blocker or the benefits to patients with impaired ejection fraction are less clear.

References


