Review of the evidence supports role for routine prophylaxis against postoperative supraventricular arrhythmia in patients undergoing pulmonary resection

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Abstract

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was ‘Is there an indication for routine prophylaxis against postoperative supraventricular arrhythmia in patients undergoing pulmonary resection surgery?’ Altogether almost 150 papers were found as a result of the reported search, of which 14 represented the best evidence to reach conclusions regarding the issues of interest for this review. The major outcome of interest that was investigated was the incidence of supraventricular arrhythmia (SVA), notably atrial fibrillation (AF). The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes, results and study weakness of the papers were tabulated. Current guidance from the Society of Thoracic Surgeons (STS) supports the use of diltiazem and amiodarone in most patients undergoing major pulmonary resection. Robust data from a large randomized, controlled trial (RCT) showed a reduction from 25 to 15% in the incidence of clinically significant atrial arrhythmia with diltiazem; $P<0.03$. Moreover, numerous RCTs have shown that there is a clear benefit with the use of amiodarone in reducing the incidence of postoperative SVA. Of note, one prospective clinical trial randomized 242 patients into a treatment group with amiodarone ($n=122$) and a placebo group ($n=120$). The incidence of postoperative AF was reduced from 32 to 9% in the active arm; $P<0.001$. The risk of acute lung injury with amiodarone has not been substantiated further in more recent clinical trials and has in fact been shown to be safe. The STS guidelines do, however, advise against the use of amiodarone in extensive lung resection such as pneumonectomy. We conclude that there is an indication for routine prophylaxis against postoperative supraventricular arrhythmia in patients undergoing pulmonary resection. However, further data are needed to ascertain the impact of said anti-arrhythmic medications on the length of postoperative hospital stay, intensive care unit stay and cost. Those patients deemed high-risk need to be promptly identified, so the anti-arrhythmic therapy can be tailored to the cohort thus optimizing on cost and safety.

Keywords: Supraventricular arrhythmia • Atrial fibrillation • Anti-arrhythmic prophylaxis • Pulmonary resection

INTRODUCTION

A best evidence topic was constructed according to a structured protocol as outlined in the Best BETS document, which is fully described in the ICVTS [1].

THREE-PART QUESTION

In [adult patients undergoing pulmonary resection surgery], is there an indication for [routine prophylaxis] to prevent [postoperative supraventricular arrhythmias]?

CLINICAL SCENARIO

I am working in a thoracic surgical unit with an incidence of postoperative supraventricular tachycardia of around 10–15% following major lung resection. You have noticed that from previous centres sometimes prophylaxis was used and other times nothing was used.

SEARCH STRATEGY


SEARCH OUTCOMES

The search yielded 142 papers; all relevant papers were screened and their reference lists were cross-checked. This process extracted 14 papers that were deemed to offer the best evidence. The papers are detailed in Table 1.
### Table 1: Details of included studies

<table>
<thead>
<tr>
<th>Author, date, journal and country</th>
<th>Study type (level of evidence)</th>
<th>Patient group characteristics</th>
<th>Outcomes measured</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amar et al. (1997), Ann Thorac Surg, USA [2]</td>
<td>Prospective randomized study (level Ib evidence)</td>
<td>70 consecutive patients post-pneumonectomy or extrapleural pneumonectomy were randomized to receive diltiazem (n = 35) or digoxin (n = 35)</td>
<td>Incidence of SVA in the postoperative period</td>
<td>Diltiazem group—14%, digoxin group—31%, untreated group—28% (P &lt; 0.005)</td>
<td>No randomized control arm</td>
</tr>
<tr>
<td>Amar et al. (2000) J Thorac Cardiovasc Surg, USA [3]</td>
<td>Randomized control trial (level Ib evidence)</td>
<td>330 patients post-lobectomy or pneumonectomy</td>
<td>Incidence of a sustained (&gt;15 min) or clinically significant atrial arrhythmia</td>
<td>Diltiazem group—25/167 (15%), placebo group—40/163 (25%) (P = 0.03)</td>
<td>Younger average age in the pneumonectomy group coupled with a smaller sample size interfered with the study’s ability to meaningfully compare the control and test groups</td>
</tr>
<tr>
<td>Borgeat et al. (1991), Ann Thorac Surg, Switzerland [4]</td>
<td>Prospective, randomized study (level Ib evidence)</td>
<td>30 patients undergoing thoracotomy for lung resection</td>
<td>Incidence of SVA for &gt;10 beats or complex ventricular arrhythmia</td>
<td>Flecainide group—1/15 (7), digoxin group—7/15 (47%), P &lt; 0.05</td>
<td>Failure was defined as the appearance of AF or flutter or the development of complex ventricular arrhythmias</td>
</tr>
<tr>
<td>Ciszewski et al. (2013), Thorac Cardiovasc Surg, Poland [5]</td>
<td>Randomized control trial (level Ib evidence)</td>
<td>117 pneumonectomy or lobectomy patients</td>
<td>Incidence of postoperative AF</td>
<td>5, 23 and 20% in Groups 1, 2 and 3, respectively</td>
<td>This study concluded that acebutolol and diltiazem were non-effective for the treatment or prevention of AF</td>
</tr>
<tr>
<td>Fernando et al. (2011), Ann Thorac Surg, USA [6]</td>
<td>Executive summary on report from the STS workforce</td>
<td>Executive report highlighting the evidence and current guidance/recommendations on the use of anti-arrhythmic prophylaxis in patients undergoing general thoracic surgery</td>
<td>Beta-blockers</td>
<td>Patients taking beta-blockers pre-surgery should have it continued in the postoperative period. Initiating new beta-blockers for prophylaxis is less favoured when compared with diltiazem owing to their side-effects</td>
<td>Evidence-based guidelines created by a taskforce panel following review of all identifiable published reports relating to prophylaxis and management of AF</td>
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<td></td>
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<td>Diltiazem</td>
<td>This is reasonable in most patients who are not taking a preoperative beta-blocker</td>
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<tr>
<td></td>
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<td></td>
<td>Amiodarone</td>
<td>This is reasonable in most patients (excluding pneumonectomy). For lobectomy patients, 1050 mg as a continuous IV infusion over the first 24 h after surgery and then 400 mg twice daily orally for 6 days is the recommended regimen</td>
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<td></td>
<td></td>
<td></td>
<td>Magnesium</td>
<td>Useful in augmenting the effects of other agents</td>
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<td></td>
<td></td>
<td></td>
<td>Flecainide</td>
<td>Not recommended</td>
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<td></td>
<td></td>
<td></td>
<td>Digoxin</td>
<td>Not recommended</td>
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<tr>
<td>Author, date, journal and country</td>
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<td><strong>Table 1:</strong> (Continued)</td>
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<td>Jakobsen et al. (1997), J Cardiothorac Vasc Anesth, Denmark [7]</td>
<td>Prospective randomized controlled, double-blinded trial (level 1b evidence)</td>
<td>30 patients undergoing elective thoracotomy for lung resection equally randomized to receive metoprolol or placebo</td>
<td>Incidence of AF</td>
<td>Metoprolol group—1/15 (6.7), placebo group—6/15 (40%), <em>P</em> &lt; 0.05</td>
<td>Study limited by the small sample size</td>
</tr>
<tr>
<td>Khalil et al. (2013) J Anesth, Egypt [8]</td>
<td>Randomized controlled trial (level Ib evidence)</td>
<td>438 patients undergoing lobectomy prospectively analysed</td>
<td>Incidence of AF in the postoperative period</td>
<td>Group A: 21/219 (10%), Group M: 27/219 (12.5%), <em>P</em> = NS. Group C: 44/219 (20.5%)</td>
<td>Lack of placebo control</td>
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<tr>
<td>Lanza et al. (2003), Ann Thorac Surg, USA [9]</td>
<td>Retrospective study (level IIb evidence)</td>
<td>31 patients received prophylactic LDOA (200 mg orally 8 hourly)</td>
<td>Incidence of postoperative AF</td>
<td>20/83 (24%) with prophylaxis, 17/52 (33%) without prophylaxis</td>
<td>The retrospective, non-randomized nature of the study may contribute bias to the results</td>
</tr>
<tr>
<td>Nojiri et al. (2012) J Thorac Cardiovasc Surg, Osaka, Japan [10]</td>
<td>Prospective randomized study (level Ib evidence)</td>
<td>40 patients with raised preoperative titres of BNP (&gt;30 pg/ml) who underwent pulmonary resection for lung cancer</td>
<td>Primary end-point; incidence of postoperative AF</td>
<td>ANP group—10% incidence, placebo group—60% incidence, <em>P</em> &lt; 0.001</td>
<td>Single-site clinical study with restricted patient numbers</td>
</tr>
<tr>
<td>Riber et al. (2012), Ann Thorac Surg, Denmark [11]</td>
<td>Randomized control trial (level Ib evidence)</td>
<td>254 consecutive patients undergoing surgery for lung cancer were randomized to receive amiodarone prophylaxis (n = 122) or placebo (n = 120)</td>
<td>Incidence of postoperative AF</td>
<td>Amiodarone group—11/122 (9%) vs 38/120 (32%) in the placebo group (<em>P</em> &lt; 0.001)</td>
<td>Reliable study design</td>
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<td>5 patients in each arm discontinued their intervention leaving 117 and 115 for per-protocol analysis in the treatment and placebo groups, respectively</td>
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</table>
The Society of Thoracic Surgeons guidelines recommend the use of diltiazem and amiodarone in most patients undergoing major pulmonary resection; however, the latter is not recommended for pneumonectomy patients owing to the toxicity risk [6]; former Best Evidence Topic data support the use of diltiazem and magnesium [19]. However, in spite of this, there is no well-defined strategy and as such routine use of anti-arrhythmics is highly variable.

A randomized prospective trial recruited 70 patients undergoing pneumonectomy or extrapleural pneumonectomy. The cohort was randomized to receive either diltiazem or digoxin in equal numbers per arm, in order to ascertain the impact on the incidence of postoperative SVAs. The incidence of SVA was 14 and 31% in the diltiazem and digoxin cohorts, respectively, $P < 0.005$. The study concluded that diltiazem is both safe and effective in decreasing the incidence of SVD after pneumonectomy [2].

A further randomized controlled study with double blinding and placebo control recruited 330 pneumonectomy or lobectomy patients. They were randomized to receive diltiazem prophylaxis ($n = 167$) or placebo ($n = 163$). The incidence of clinically
significant or sustained atrial arrhythmias was 15 and 25% in the treatment and placebo groups, respectively (P < 0.03) [3].

Borgeat et al. [4] prospectively analysed the effects of flecainide on thoracotomy patients randomized to receive this anti-arrhythmic. The incidence of AF between the two groups was found to be insignificant, but flecainide reduced the incidence of overall SVA when compared with control (digoxin in this study); P < 0.05. The small sample sizes (n = 15) in the groups limited the reliability of the data, however.

Ciszewski et al. [5] conducted a prospective, randomized, controlled trial (RCT), where 117 pneumonectomy or lobectomy patients were equally randomized to one of three groups: Group 1 (n = 39)—acebutolol, Group 2 (n = 39)—diltiazem and Group 3 (n = 39)—no anti-arrhythmics (placebo). AF occurred at rates of 5, 23 and 20% in Groups 1, 2 and 3, respectively.

Jakobsen’s group [7] found that metoprolol signiﬁcantly reduces the incidence of AF in post-thoracotomy patients, P < 0.05; however, the small sample size (n = 15) limited the reliability of the data.

Khalil et al. conducted a trial involving 438 patients undergoing lobectomy whereby patients were equally randomized to receive amiodarone or magnesium sulphate prophylaxis. Both agents were effective in decreasing the incidence of postoperative AF compared with control; however, there was no significant difference between the two treatment arms. Postoperative AF occurred in 21 of 219 (9.6%) patients in the amiodarone group and in 27 of 219 (12.3%) patients in the magnesium group [8].

Lanza et al. retrospectively analysed patients over 60 who underwent pulmonary resection in a 30-month period. Thirty-one patients received low-dose oral amiodarone (LDOA) and 52 received no prophylaxis. The incidence of postoperative AF was 9.7 and 33% in the treatment and no prophylaxis groups, respectively, P = 0.02. Furthermore, the study found that prophylactic therapy was associated with a slower rate of accumulation of hospital charges during the inpatient stay [9].

Nojiri et al. examined the prophylactic effects of low-dose atrial natriuretic peptide (ANP) on the incidence of postoperative AF in 40 patients who underwent pulmonary resection with raised preoperative titres of B-type natriuretic peptide (BNP) (>30 pg/ml). The patients were equally randomized to receive ANP or placebo. The incidence of postoperative AF was 10 and 60% in the treatment and placebo groups, respectively. Raised preoperative BNP titres confer an increased risk for postoperative SVAs, and this study concluded that continuous low human ANP infusion exerts a prophylactic effect against postoperative SVAs in this group of higher-risk patients [10].

Riber et al. [11] randomized lung cancer patients undergoing pulmonary resection into a treatment group with amiodarone (n = 122) and a placebo group (n = 120); the incidence of postoperative AF was 9 and 32%, respectively, P < 0.001.

Ritchie et al. [12] concluded that there is no role for digoxin in the prevention of post-lung resection arrhythmias.

Terzi et al. [13] randomized 193 patients to a magnesium arm (n = 93) and control arm (n = 101). The incidence of AF in the active group was reduced from 26.7 to 10.3%, without side-effects.

Tisdale et al. [14] randomized 130 patients undergoing lobectomy or pneumonectomy equally to a treatment arm with amiodarone and to a control arm (no prophylaxis). The incidence of AF was 13.8 and 32.3% in the treatment and control arms, respectively, P = 0.02. The median of intensive care stay was significantly shorter (P = 0.03) in the amiodarone group 46 vs 84 h.

Van Mieghem et al. [15] randomized 199 post-lung resection patients to receive verapamil (n = 100) and placebo (n = 99). The incidence of AF was reduced from 15 to 8% in the active group; however, these findings were insignificant.

RCT data have effectively demonstrated the safety and efficacy of diltiazem in decreasing the overall incidence of SVA post-pneumonectomy [3]. Similarly, RCT evidence exists to illustrate the efficacy of amiodarone in preventing clinically significant post-thoracotomy SVA [8, 11, 14]; the concern of lung injury associated with amiodarone use [20] has not been conﬁrmed in follow-up studies where its use has been deemed to be safe [21, 22]. Indeed, the best evidence exists to support the use of amiodarone [8, 9, 11, 14], and then diltiazem [2, 3] and finally beta-blockers [5, 7]; however, there are no recent robust RCT data to further explore the use of beta-blockers.

**CLINICAL BOTTOM LINE**

There is good evidence to support the routine use of prophylactic agents in pulmonary resection patients with centres reporting up to a 45% overall risk reduction in the incidence of clinically signiﬁcant SVA [3]. However, further RCT evidence is needed to delineate whether administration results in decreased costs and length of hospital or intensive care unit stay. Furthermore, the identiﬁcation of high-risk patient subsets is warranted such that particular classes of anti-arrhythmic can be tailored to these groups thus optimizing cost and patient safety [23].

**Conflict of interest:** none declared.

**REFERENCES**


