The Use of Preoperative B-Type Natriuretic Peptide as a Predictor of Atrial Fibrillation After Thoracic Surgery: Systematic Review and Meta-Analysis

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Objective: To determine whether elevated preoperative B-type natriuretic peptide (NP) measurements are an independent predictor of atrial fibrillation (AF) in patients having thoracic surgery.

Design: Systematic review and meta-analysis.

Setting: In-hospital and 30 days after thoracic surgery.

Participants: The 742 patients who participated in the 5 observational studies.

Interventions: None.

Measurements and Main Results: EMBASE, OVID Health Star, Ovid Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and ProQuest Dissertations and Theses A&I databases were searched for all studies of noncardiac thoracic surgery patients in whom a preoperative NP was measured up to 1 month before surgery, and that measured the incidence of postoperative AF. Studies were included regardless of their language, sample size, publication status, or study design. Study quality was evaluated using the Newcastle Ottowa Scale.

The combined incidence of postoperative AF was 14.5% (n = 108/742), and the NP thresholds used to predict AF varied among studies. An elevated preoperative NP measurement was associated with an OR of 3.13 (95% CI 1.38-7.12; I² = 87%) for postoperative AF, with the sensitivity analysis reporting an OR of 9.51 (95% CI 4.66-19.40; I² = 0).

Conclusion: Patients with an elevated preoperative NP measurement are at an increased risk of postoperative AF. There may be value in incorporating NP measurement into existing AF risk prediction models.

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KEY WORDS: BNP, NT-proBNP, natriuretic peptides, atrial fibrillation, noncardiac surgery, thoracic surgery

I t is estimated that 5 million major thoracic surgical procedures are undertaken annually around the world. Atrial fibrillation (AF) is a common major postoperative complication, with an incidence as high as 40% after certain thoracic procedures (eg, pneumonectomy). AF is associated with increased hospital morbidity and poorer long-term survival.1,2

The B-type natriuretic peptide (NP) biomarkers (ie, B-type natriuretic peptide [BNP] or N-terminal fragment of proBNP [NT-proBNP]) are secreted by cardiac myocytes and fibroblasts in response to myocyte stretch. Elevations in these hormones have been associated with increased adverse cardiovascular events (death, myocardial infarction, and heart failure) in the postoperative period.3 Further, studies have suggested that NP elevation may be predictive of AF, particularly in patients undergoing thoracic surgery.4 Preoperative NP measurement may allow the early identification of patients at risk of AF and thereby facilitate early intervention and the possibility of improving patient outcomes.

In this systematic review and meta-analysis, the authors aimed to determine whether an elevated preoperative NP measurement was an independent predictor of AF in patients who underwent thoracic surgery.

METHODS

Trial Eligibility and Identification

All studies of noncardiac thoracic surgery patients in whom a preoperative NP was measured up to 1 month before surgery and that measured the incidence of postoperative AF were included. Studies were included regardless of their language, sample size, publication status, or study design. Six databases were searched (EMBASE, OVID Health Star, Ovid Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, ProQuest Dissertations, and Theses A&I). An example of the search strategy used is shown in Appendix 1 and associated table.

Eligibility Assessment

The title and abstract of each citation was screened independently by both D.S. and D.P. to identify potentially eligible studies. If either reviewer believed the citation may contain a relevant study, the article was retrieved to undergo full text evaluation. Full texts of all citations identified as being potentially relevant then were evaluated independently by both D.S. and D.P. to determine eligibility. Disagreements were solved by consensus. If disagreements were not resolved during this process, an independent third adjudicator (R.R.) resolved disagreements. Chance-corrected interobserver agreement for study eligibility was tested using kappa statistics to quantify interobserver chance-corrected agreement.

Data Collection, Assessment of Study Quality, and Outcomes

Data were extracted to an Excel spreadsheet recording principal author, year of publication, study design, total number of study patients, mean age of study patients, type of NP assay, NP manufacturer, timing of preoperative NP sampling, and length of follow-up. Authors were contacted to provide original patient data when it was insufficient for meta-analysis. Study quality was evaluated using the Newcastle Ottowa Scale† (Table 3).

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1053-0770/2601-0001$36.00/0
http://dx.doi.org/10.1053/j.jvca.2014.05.015

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For each eligible study, the definition and incidence of postoperative AF were extracted. In addition, the adjusted odds ratios (OR) and 95% confidence interval (CI) associated with an elevated preoperative NP measurement for the outcome of AF were extracted, and all reported hazard ratios and relative risk statistics were converted to odds ratios for meta-analysis. Meta-analysis was conducted using a random effects model in Review Manager Version 5.1. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Heterogeneity was assessed using $I^2$ and chi-square analysis. Pooled dichotomous outcomes were reported as OR and 95% CI. A funnel plot was constructed to assess for the possibility of publication bias. Heterogeneity was explored in the results by conducting a sensitivity analysis. In this analysis, the studies that used their NP measurement as a continuous variable (nonthreshold studies) in their regression analysis were examined. Using the post-hoc NP thresholds determined by these studies, an unadjusted OR was calculated, which was used in the sensitivity analysis.

RESULTS

The study selection process is shown in Fig 1. A total of 1,008 citations were identified, from which 94 were selected for full-text evaluation. From these, 56 were excluded because they did not record AF as a study outcome (references in Appendix 2), 9 because patients did not have thoracic surgery, 7–15 9 because the publications contained retracted or fraudulent data, 16–24 4 that had no preoperative NP measurement, 25–28 4 that had no surgery being conducted, 29–32 3 that were editorials or letters, 33–35 2 that dealt with cardiac surgery, 36,37 1 that was a meta-analysis, 38 and 1 that represented a duplicate cohort. 39–43 Interobserver agreement for study eligibility was good (kappa = 0.7).

The characteristics of the 5 included studies, representing 742 patients (63 pneumonectomies and 86 reported video-assisted thoracoscopic surgery) who underwent elective thoracic surgery, are reported in Tables 1 and 2. Most studies examined in-hospital AF, with only the study by Hoksch et al conducting 30-day follow-up. 40 Three studies made use of an NT-proBNP assay, 39,41,42 and the remaining two used BNP assays. 30,43 All studies measured preoperative NPs within at least a month before surgery.

The quality characteristics of the 5 included trials are reported in Table 3. All studies were prospective observational studies and excluded patients in chronic AF, renal failure, on antiarrhythmics, or in cardiac failure.

The combined incidence of postoperative AF was 14.5% ($n = 108/742$), and the NP thresholds used to predict AF varied among studies (Table 1). Importantly, both the studies by Lee et al and Nojiri et al did not calculate a NP threshold but used their NP measurement as a continuous variable in the logistic regression. These two studies undertook a post-hoc analysis, defining an optimal NP threshold using ROC statistics after conducting their regression analysis (i.e., NT-proBNP of 160 ng/L for Lee et al; BNP of 30 ng/L for Nojiri et al). Multiple unsuccessful attempts were made to contact both authors to obtain further study details. The studies by Cardinale et al and Nojiri et al 39,43 reported an adjusted relative risk for postoperative AF associated with an elevated NP measurement, and this was converted to an OR and 95% CI.

Fig 2 presents the results of the meta-analysis of the adjusted ORs for all 5 studies, performed to determine the risk of postoperative AF associated with an elevated preoperative BNP. Fig 3 presents the associated funnel plot.

<table>
<thead>
<tr>
<th>Records identified through search strategy (n = 1008)</th>
<th>Records excluded during screening process (n = 912)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-text articles excluded (n = 89)</td>
<td></td>
</tr>
<tr>
<td>56 – No AF outcome</td>
<td></td>
</tr>
<tr>
<td>9 – No thoracic surgery</td>
<td></td>
</tr>
<tr>
<td>9 – Publications retracted / fraudulent</td>
<td></td>
</tr>
<tr>
<td>4 – No preoperative BNP measured</td>
<td></td>
</tr>
<tr>
<td>4 – No surgery conducted</td>
<td></td>
</tr>
<tr>
<td>3 – Editorial / letter to the editor not</td>
<td></td>
</tr>
<tr>
<td>presenting original data</td>
<td></td>
</tr>
<tr>
<td>2 – Cardiac surgery</td>
<td></td>
</tr>
<tr>
<td>1 – Meta-analysis</td>
<td></td>
</tr>
<tr>
<td>1 – Duplicate cohort</td>
<td></td>
</tr>
</tbody>
</table>

Fig 1. The study selection process.
An elevated preoperative NP measurement was associated with an OR of 3.13 (95% CI 1.38-7.12) for postoperative AF, but the results showed significant heterogeneity ($I^2 = 87\%$) as well as significant publication bias.

Two studies used their NP measurement as a continuous variable (nonthreshold studies) in their regression analyses (ie, Lee et al\textsuperscript{42} and Nojiri et al\textsuperscript{43}). Using the post-hoc BNP threshold of 30 ng/L published by Nojiri et al, the continuous NP measurement was converted into a dichotomous variable and an unadjusted OR of 8.91 (95% CI 2.71-29.27) associated with an elevated preoperative BNP was calculated for the prediction of postoperative AF. Sufficient data could not be extracted to calculate the unadjusted OR in the study by Lee et al. The sensitivity analysis, using the unadjusted OR for the Nojiri et al study, showed that patients with an elevated preoperative NP measurement were at increased risk of postoperative AF (OR 9.51, 95% CI 4.66-19.40). This sensitivity analysis reported no heterogeneity ($I^2 = 0$) (Figs 4 and 5) and dramatically improved the perception of publication bias.

**DISCUSSION**

This analysis found that an elevated preoperative NP measurement was associated with an OR of 3.13 (95% CI

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### Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patient population, type of surgery</th>
<th>Pneumonectomies (n)</th>
<th>Patient (n)</th>
<th>Mean age (SD)</th>
<th>AF incidence (%)</th>
<th>AF definition</th>
<th>Surveillance time period</th>
<th>Length of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardinale, 2007</td>
<td>Elective, thoracic, lung cancer</td>
<td>49</td>
<td>400</td>
<td>62.10</td>
<td>17.75</td>
<td>New onset with an episode &gt;5 min or requiring intervention</td>
<td>Continuous ECG monitoring for 72 h, daily follow-up thereafter</td>
<td>In-hospital</td>
</tr>
<tr>
<td>Hoksch, 2007</td>
<td>Elective, thoracic</td>
<td>6</td>
<td>22</td>
<td>67.11</td>
<td>22.72</td>
<td>New onset</td>
<td>ECG criteria, clinical (not further defined)</td>
<td>30 days postoperatively</td>
</tr>
<tr>
<td>Hou, 2008</td>
<td>Elective, thoracic, esophageal carcinoma</td>
<td>0</td>
<td>142</td>
<td>66.5 (13.15)*</td>
<td>7.74</td>
<td>New onset. Absent P wave before QRS with irregular ventricular rhythm on rhythm strip</td>
<td>Continuous ECG monitoring 48 h then cardiology review daily</td>
<td>In-hospital</td>
</tr>
<tr>
<td>Lee, 2011</td>
<td>Elective, thoracic, lung resection</td>
<td>8</td>
<td>98</td>
<td>61.1 (12)</td>
<td>3.06</td>
<td>T-wave inversion of greater than 2 mm, and ST-segment deviation of greater than 2 mm in at least two contiguous chest leads or greater than 1 mm in at least two contiguous limb leads. Arrhythmia was defined as a new sustained abnormal cardiac rhythm</td>
<td>24 hour ECG monitoring then daily follow-up</td>
<td>In-hospital</td>
</tr>
<tr>
<td>Nojiri, 2011</td>
<td>Elective, thoracic, pulmonary resection, lung cancer</td>
<td>0</td>
<td>80</td>
<td>77.9 (2.9)</td>
<td>22.5</td>
<td>New onset</td>
<td>Continuous ECG monitoring</td>
<td>In-hospital</td>
</tr>
</tbody>
</table>

**Abbreviations:** AF, atrial fibrillation; ECG, electrocardiogram; SD, standard deviation.

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### Table 2. Characteristics of NP Assays

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Natriuretic Peptide</th>
<th>Threshold(s)</th>
<th>Assay, Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardinale, 2007</td>
<td>NT-proBNP</td>
<td>≤ 49 years: Male - 64 ng/L; Female - 125 ng/L; 50-59 years: Male, 125 ng/L; Female, 186 ng/L; &gt;60 years: Male, 194 ng/mL; Female, 204 ng/L</td>
<td>Elecsys ProBNP, Roche Diagnostics</td>
</tr>
<tr>
<td>Hoksch, 2007</td>
<td>BNP</td>
<td>30 ng/L</td>
<td>Triage BNP-Test, Biosite Diagnostic</td>
</tr>
<tr>
<td>Hou, 2008</td>
<td>NT-proBNP</td>
<td>Not defined</td>
<td>Elecsys ProBNP, Roche Diagnostics</td>
</tr>
<tr>
<td>Lee, 2011</td>
<td>NT-proBNP</td>
<td>160 ng/L</td>
<td>Elecsys ProBNP, Roche Diagnostics</td>
</tr>
<tr>
<td>Nojiri, 2011</td>
<td>BNP</td>
<td>30 ng/L</td>
<td>Shionogi BNP, Shionogi Pharmaceutical</td>
</tr>
</tbody>
</table>

**Abbreviations:** NT-proBNP, N-terminal proBNP; BNP, B-type natriuretic peptide.
1.38-7.12; \( I^2 = 87\% \) for postoperative AF, with the sensitivity analysis reporting an OR of 9.51 (95% CI 4.66-19.40; \( I^2 = 0 \)).

AF is defined as an irregular, atrial rhythm that usually is rapid and is a common complication after major thoracic surgery. When defined as an electrocardiographically documented episode that lasts ≥30 minutes, the incidence after lung transplantation has been reported to be as high as 40% after pneumonectomy, with an incidence ranging between 10% to 40%.[10,15] AF is associated with increased hospital morbidity, poorer long-term (5-year) survival and increased mortality. The proposed mechanism in this unique form of AF is postulated to be a combination of pericardial inflammation, myocardial ischemia, catecholamine surge, autonomic imbalance, and interstitial fluid mobilization.

Medications such as amiodarone, magnesium sulphate, beta-blockers, and anti-inflammatory drugs have been shown to reduce the incidence of postoperative AF.[44,45] These drugs are not without their own side effects, some of which may be life-threatening. However, most patients who undergo thoracic surgery will not suffer postoperative AF, and it is, therefore, inappropriate to administer prophylactic AF drugs to all thoracic surgery patients. Therefore, the ability to identify patients at risk of postoperative AF and thereby institute preventative therapy or allocate the patient to high-care areas is very appealing. It is also likely that incorporating NP measurement into existing prediction rules would further improve risk stratification.[46] This would assist in identifying high-risk patients who would stand to benefit most from prophylactic interventions.

For such a strategy to be effective, the prognostic threshold for the prediction of AF should be associated with a high enough odds ratio to result in a post-test probability sufficient to change the perception of clinical risk. In the primary analysis of the present study, the OR associated with an elevated NP was 3.13 (95% CI 1.38-7.12) and the sensitivity analysis found an OR of 9.51 (95% CI 4.66-19.40). The large difference in the point estimate of these two results, driven solely in the manner by which the NP thresholds were determined, highlights the importance of how these thresholds are determined. A recent publication has highlighted different preoperative thresholds in patients undergoing vascular compared with noncardiac surgery. In vascular surgery, BNP thresholds of 0 to 29, 30 to 115, 116 to 371, and >372 ng/L showed a 30-day major adverse cardiovascular event rate (MACE) of 1.2%, 6.5%, 20.9%, and 36.5%, respectively, and thresholds for mixed noncardiac surgery ranged from 0 to 99, 100 to 250, and >250 and demonstrated MACE rates of 5.3%, 11.6%, and 26.9%, respectively. In meta-analysis, the NP thresholds centered on a BNP measurement of 30 ng/L, and ranged from 64 to 204 ng/L for NT-proBNP-adjusted thresholds for age. Large prospective studies are required in thoracic patients to allow the identification of robust NP thresholds able to reliably predict postoperative AF.

As age increases, BNP measurements increase; however, in studies that have evaluated BNP for the prediction of mortality and MI after noncardiac surgery—and that have adjusted for age—BNP has remained an independent predictor.[48] Unfortunately, only one of the studies included in this meta-analysis (ie, Cardinale et al) adjusted for age in their regression analysis. In this study, BNP measurement remained predictive of AF, even after adjusting for age.

### Table 3. Newcastle-Ottawa Scale Assessment of Study Quality

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Selection (Maximum = 4 Stars)</th>
<th>Comparability (Maximum = 2 Stars)</th>
<th>Outcome (Maximum = 3 Stars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardinale, 2007</td>
<td>Prospective</td>
<td>****</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Hoksch, 2007</td>
<td>Prospective</td>
<td>****</td>
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<tr>
<td>Hou, 2008</td>
<td>Prospective</td>
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</tr>
<tr>
<td>Lee, 2011</td>
<td>Prospective</td>
<td>****</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>Nojiri, 2011</td>
<td>Prospective</td>
<td>****</td>
<td>*</td>
<td>***</td>
</tr>
</tbody>
</table>

**Fig 2.** Adjusted odds ratios for elevated preoperative NP and the associated risk of postoperative AF.

**Fig 3.** Funnel plot for studies reporting the risk of postoperative AF associated with elevated preoperative BNP.
Previous studies have suggested that pneumonectomy is associated with a higher incidence of AF; however, this meta-analysis was not able to show this association as none of the studies adjusted for type of surgery.

Larger studies will afford the opportunity to determine whether NP measurement remains clinically useful when adjusted for the type of surgical procedure (ie, pneumonectomy or lobectomy).

In addition to allowing preoperative intervention, improved risk stratification would allow physicians to institute intensive postoperative monitoring for high-risk patients. This could entail admission to areas with continuous electrocardiogram monitoring what would facilitate early identification and intervention.

The primary strength of this analysis was the extensive literature research and high degree of agreement on study eligibility between members of the team. However, the analysis was constrained by the small number of studies conducted in this population. Despite this, the present results were in broad agreement with previous studies in this field.47 Although there was significant heterogeneity in the primary analysis, much of this could be explained by the sensitivity analysis, despite not being able to obtain additional data from two of the studies.

CONCLUSION

Elevated preoperative NP measurement was associated with an OR of 3.13 (95% CI 1.38-7.12; I² = 87%) for postoperative AF, with the sensitivity analysis reporting an OR of 9.51 (95% CI 4.66-19.40; I² = 0). NP measurement holds the promise of improved AF risk stratification in this patient population and could assist in identifying patients who would benefit from preoperative intervention and intensive postoperative monitoring.

APPENDIX 1. SEARCH STRATEGY AND DATABASES

The search terms, including validated prognostic search terms (Appendix Table 1) and databases used, are shown here. Database searches were conducted on July 15, 2013 using the OvidSP search engine (Ovid Technologies, Inc., New York, NY) for the following databases:

1. (1) EMBASE 1980 to 2012 Week 28, (2) OVID Health Star (1966 to June 2013), (3) Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and AVID MEDLINE(R) 1946 to present, (4) Cochrane Central Register of Controlled Trials (June 2012), (5) Cochrane Database of Systematic Reviews (June 2012), (6) ProQuest Dissertations and Theses A&I (June 2012)

Table. Appendix 1. Example of Search Conducted on MEDLINE

Search terms | Number
--- | ---
1 (Natriuretic peptide OR natriureti*).mp. | 90064
2 (BNP OR B type natriureti* OR B-type natriureti* OR Brain natriureti*).mp. | 42364
3 (NT-pro BNP OR NT-proBNP OR NT-pro-BNP OR N terminal proBNP OR N terminal pro-BNP OR N-terminal proBNP N terminal pro-BNP OR N-terminal pro-brain natriureti* OR N-terminal pro-B-type natriureti* OR N-terminal pro-B type natriureti*).mp | 13484
4 (Surgery OR operative OR noncardiac).mp. | 3308271
5 1 or 2 or 3 | 94975
6 4 and 5 | 4456
7 prognosis.sh. or diagnosed.tw. or cohort:.mp. or predictor:.tw. or death.tw. or exp models, statistical/ | 4837473
8 6 and 7 | 1433
9 remove duplicates from 8 | 876

NOTE: No additional search filters were used. For the EMBASE search the EMTree term “Brain natriuretic peptide” was used.

APPENDIX A. SUPPORTING INFORMATION

Supplementary material cited in this article is available online at doi:10.1053/j.jvca.2014.05.015.
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