RESEARCH

Preoperative levels of natriuretic peptides and the incidence of postoperative atrial fibrillation after noncardiac surgery: a prospective cohort study

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ABSTRACT

BACKGROUND: Postoperative atrial fibrillation (POAF) is associated with clinically significant short- and long-term complications after noncardiac surgery. Our aim was to describe the incidence of clinically important POAF after noncardiac surgery and establish the prognostic value of N-terminal pro–brain-type natriuretic peptide (NT-proBNP) in this context.

METHODS: The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study was a prospective cohort study involving patients aged 45 years and older who had inpatient noncardiac surgery that was performed between August 2007 and November 2013. We determined 30-day incidence of clinically important POAF (i.e., resulting in angina, congestive heart failure, symptomatic hypotension or requiring treatment) using logistic regression models to analyze the association between preoperative NT-proBNP and POAF.

RESULTS: In 37 664 patients with no history of atrial fibrillation, we found that the incidence of POAF was 1.0% (95% confidence interval [CI] 0.9%–1.1%; 369 events); 3.2% (95% CI 2.3%–4.4%) in patients undergoing major thoracic surgery, 1.3% (95% CI 1.2%–1.5%) in patients undergoing major nonthoracic surgery and 0.2% (95% CI 0.1%–0.3%) in patients undergoing low-risk surgery. In a subgroup of 9789 patients with preoperative NT-proBNP measurements, the biomarker improved the prediction of POAF risk over conventional prognostic factors (likelihood ratio test $p < 0.001$; fraction of new information from NT-proBNP was 16%). Compared with a reference NT-proBNP measurement set at 100 ng/L, adjusted odds ratios for the occurrence of POAF were 1.31 (95% CI 1.15–1.49) at 200 ng/L, 2.07 (95% CI 1.27–3.36) at 1500 ng/L and 2.39 (95% CI 1.26–4.51) at 3000 ng/L.

INTERPRETATION: We determined that the incidence of clinically important POAF after noncardiac surgery was 1.0%. We also found that preoperative NT-proBNP levels were associated with POAF independent of established prognostic factors. **Trial registration:** ClinicalTrials.gov, no. NCT00512109

Postoperative atrial fibrillation (POAF) is the most common arrhythmia that occurs after noncardiac surgery[1] and is associated with prolonged hospital stays and an increased risk of stroke and death,[2–8] both of which raise societal costs.[9] The reported incidence of POAF ranges from 3.7% to 21.0% in patients undergoing thoracic surgery[3,10] and from less than 0.5% to 10.0% in patients undergoing noncardiac, nonthoracic surgery (Appendix 1, Supplementary Table 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.200840/tab-related-content).[6,11]

Brain-type natriuretic peptide (BNP) is a neurohormone released by cardiomyocytes in response to volume and pressure overload.[12] This biomarker has an established role in the diagnosis and management of heart failure and in predicting cardiovascular morbidity and mortality.[13] Although natriuretic peptides have been shown to predict new-onset atrial fibrillation (AF) in the nonsurgical setting reliably,[14–18] their value in predicting POAF after noncardiac surgery is unclear.[19–21]

The Vascular events In non-cardiac Surgery patIents cOhort evaluatioN (VISION) Study was a prospective international cohort

study involving a representative sample of adults who underwent noncardiac surgery that required an overnight hospital stay. One of the predefined objectives in VISION was to determine the incidence of new-onset, clinically important POAF. We aimed to describe the overall and surgery-specific incidence of POAF after noncardiac surgery and to investigate the association between preoperative N-terminal pro–brain-type natriuretic peptide (NT-proBNP) and POAF. We hypothesized that measurement of NT-proBNP would improve POAF risk prediction beyond conventional prognostic factors.

Methods

Study population

The international VISION study included 40 004 patients from 28 centres in 14 countries (Canada, the United States, Peru, Brazil, Colombia, South Africa, India, Malaysia, China, Australia, the United Kingdom, Spain, Poland and France) who underwent various noncardiac surgeries from August 2007 to November 2013 (ClinicalTrials.gov NCT00512109). All participating centres were university hospitals (Appendix 1, Supplementary Table 2). Informed consent was obtained before (in most cases) or within 24 hours of surgery from patients or their designated decision-makers. Seven centres used a deferred consent process for patients who were unable to provide consent and for whom no designated decision-maker was available.

To ensure the representativeness of the study sample population, research personnel were responsible for daily screening of patient lists in preoperative assessment clinics and daily surgical lists to identify patients undergoing elective or urgent or emergent surgery during weekdays and weekends, as well as during the day and the night.[22–24] Eligible patients were those aged 45 years or older who had inpatient noncardiac surgery. Preoperative blood samples were collected for NT-proBNP measurement from a subset of patients within selected centres.

Data sources

The selection of centres involved in the NT-proBNP substudy was based on their willingness to participate and the availability of the infrastructure to perform the collection, centrifugation and shipment of samples to our facility or to test locally. Five centres measured NT-proBNP locally: 1 centre performed NT-proBNP measurements in real time, whereas the other 4 sites batched their samples and later ran the assays at the same time. The remaining 11 centres centrifuged the collected samples, and shipped them to the Clinical Research Laboratory and Biobank in Hamilton, Ontario, Canada, where the samples were frozen and then later thawed to perform NT-proBNP measurements at the same time. Each laboratory performed its own quality control as a part of its standard procedures. Health care providers and study personnel were blinded to NT-proBNP measurements.

We calculated the Birmingham 2009 schema (CHA_2DS_2-VASc) score[25] to stratify the risk of thromboembolic events in patients who developed POAF. This tool is recommended by the American College of Cardiology, American Heart Association and European Society of Cardiology to assess indications for anticoagulation in patients with AF. The score incorporates age (1 point for age 65–74 yr, 2 points for age ≥ 75 yr) and sex (1 point for female sex), as well as history of congestive heart failure (1 point), hypertension (1 point), diabetes mellitus (1 point), vascular diseases (1 point) and previous thromboembolic events (2 points).[26,27] A follow-up telephone call was conducted with patients or their relatives or caregivers 30 days after surgery, and we obtained outcome documentation in cases of new-onset POAF.

Outcomes

Our primary outcome was clinically important POAF within 30 days after surgery. There was no electrocardiogram (ECG) screening protocol to detect POAF, other than local clinical practice. Recorded POAF events were adjudicated by 2 expert physicians according to the VISION definition and using all available source documents.[24] Clinically important POAF was defined as AF (ECG-documented) that resulted in angina, congestive heart failure or symptomatic hypotension or that required treatment with a rate-controlling drug, an antiarrhythmic drug or electrical cardioversion. This definition has previously been shown to be associated with an increased length of hospital stay, stroke and death.[4,24,28] Patients were prospectively observed throughout the hospital stay by the medical staff, who recorded any event of clinically important POAF. Study personnel phoned each patient or patient's relative 30 days after the procedure to gather data concerning study outcomes.

Statistical analysis

We used data from a large cohort study (VISION) where sample size calculations were based on the expected incidence of major cardiac complications after noncardiac surgery.[22] We performed a complete-case analysis owing to a relatively small fraction of missing data reported for the overall VISION cohort.[22,24] We determined the proportion of patients who presented with POAF up to 30 days after surgery and the associated 95% confidence intervals (CIs). We described the association between preoperative NT-proBNP modelled as a continuous variable and POAF using univariable and multivariable logistic regression models derived using data from 9789 patients who participated in the VISION preoperative NT-proBNP substudy.

We tested the added prognostic value of NT-proBNP over and above (i.e., independent of, after adjustment for) other potential predictors of POAF that were identified in the existing literature. Variable selection was guided by the authors' knowledge of the subject matter and the number of events available for analysis. The full list of variables that we identified through a literature search and initially considered as potential predictors of POAF is listed in Appendix 2, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.200840/tab-related-content. We focused on features that are routinely measured before surgery, to build the baseline model. After choosing the final list of variables to include in the multivariable logistic regression model, we applied no further model selection procedures.

Our final model included age, sex, history of hypertension, history of coronary artery disease, history of congestive heart failure, history of chronic obstructive pulmonary disease and type of surgery (divided into 3 categories: low risk, major nonthoracic and major thoracic). We modelled age and NT-proBNP using restricted cubic splines, allowing for nonlinear relationships and avoiding

the known problems resulting from categorization of continuous variables.[29] We used Wald tests to assess departures from linearity of log-odds. Splines are best interpreted using a figure, but they also allow comparison of any 2 desired values of the predictor that can be easily interpreted as an odds ratio (OR) without the need to refit the model.[30] We summarized the added prognostic value of NT-proBNP as the fraction of new information (proportion of explainable variation that is explained by the biomarker; ratio of variances of predicted values before and after adding the biomarker to the model). In addition, we visualized the information provided by NT-proBNP measurement by analyzing pre- and post-test probabilities (Appendix 1). All analyses were performed using R version 3.6.0 (R Project) using the rms, givitiR and ggplot2 packages. Reporting of the data conforms to the STROBE statement (Appendix 1, Supplementary Table 3).

Ethics approval

The study complied with the Declaration of Helsinki and its protocol was approved by the institutional ethics board at each site.

Results

From the full VISION cohort, we excluded 2189 (5.5%) patients with a history of AF, or with AF present before surgery, and 151 (0.4%) patients with missing information on AF, leaving 37 664 patients for the final analysis (Figure 1).

Table 1 reports demographic, clinical and surgical characteristics for the included patients, as well as laboratory measurement values stratified by the occurrence of POAF. Appendix 1, Supplementary Table 4 provides the same information in the subgroup of patients who had NT-proBNP measured before surgery.

The incidence of clinically important POAF after noncardiac surgery was 1.0% (95% CI 0.9–1.1). It was the highest after major thoracic surgery (3.2%; 95% CI 2.3–4.4), followed by major nonthoracic surgery (1.3%; 95% CI 1.2–1.5) and low-risk surgery (0.2%; 95% CI 0.1–0.3). Most cases of POAF occurred during the initial hospital stay (357, 96.7%), with a median time to event of 2 days.

Treatment prompted by POAF occurred in 349 (94.6%) patients, 67.7% of whom were treated with rate-controlling drugs, 55.7% with antiarrhythmic drugs and 6.5% with electrical cardioversion. A histogram showing distribution of CHA_2DS_2-VASc scores in this group is presented in Appendix 1, Supplemental Figure 1. After subtracting points for sex from the total score, 336 of 369 (91.1%) patients still had at least 1 point. Anticoagulation therapy was started in 21.8% of patients with POAF, and 2.7% were discharged home with such treatment.

We obtained preoperative NT-proBNP measurements for 9789 patients (26.0%). A comparison of demographic and clinical characteristics of patients with and without preoperative NT-proBNP measurements is presented in Appendix 1, Supplementary Table 5. We observed 109 POAF events in this subgroup. The median (interquartile range [IQR]) preoperative level of NT-proBNP was 258 ng/L (IQR 108–679) in patients who developed POAF and 86 ng/L (IQR 37–220) in those who did not develop POAF ($p < 0.001$). Histograms of preoperative NT-proBNP values stratified by the occurrence of POAF are provided in Figure 2. The unadjusted association

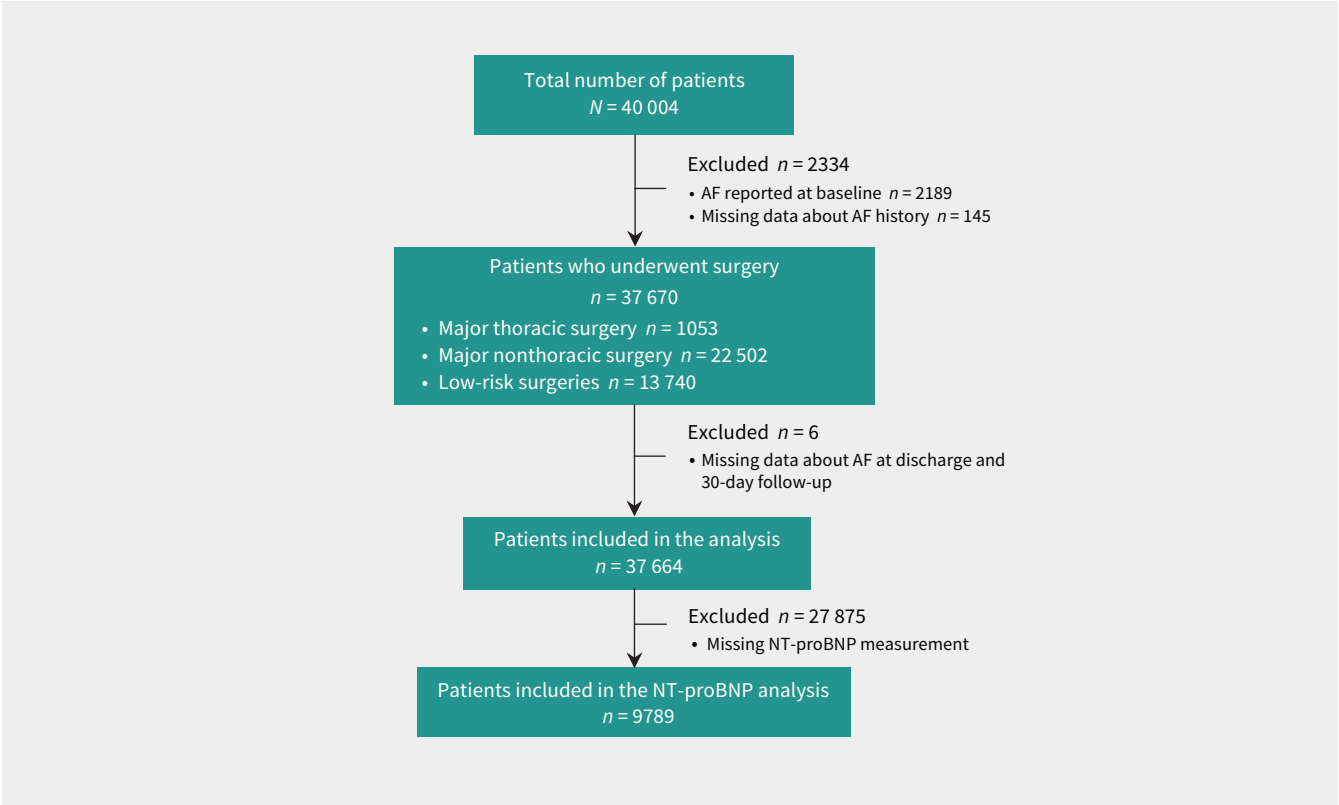

Figure 1: Flow chart for selection of study patients. Note: AF = atrial fibrillation, NT-proBNP = N-terminal pro–brain-type natriuretic peptide.

Table 1: Patient demographic and clinical characteristics stratified by occurrence of new-onset, clinically important postoperative atrial fibrillation*

Characteristic	No. (%) of patients without POAF within 30 d after surgery† *n* = 37 295	No. (%) of patients with POAF within 30 d after surgery† *n* = 369	*p* value for difference
Age, yr; mean ± SD	63.4 ± 11.1	73.1 ± 10.2	< 0.001
Female	18 724 (50.2)	169 (45.8)	0.09
Frail‡	2052 (5.5)	36 (9.8)	0.001
Smoking history			
Current smoker	20 069 (53.9)	143 (38.8)	< 0.001
Former smoker	11 916 (32.0)	182 (49.3)	
Medical history			
Coronary artery disease	4250 (11.4)	68 (18.4)	< 0.001
Recent high-risk CAD	310 (0.8)	3 (0.8)	> 0.99
Congestive heart failure	895 (2.4)	17 (4.6)	0.02
Aortic stenosis	283 (0.8)	10 (2.7)	< 0.001
Peripheral vascular disease	2759 (7.4)	44 (11.9)	0.002
History of CVE	2134 (5.7)	38 (10.3)	< 0.001
History of DVT/PE	1150 (3.1)	11 (3.0)	> 0.99
Hypertension	18 197 (48.8)	247 (66.9)	< 0.001
Diabetes	7657 (20.5)	73 (19.8)	0.8
Chronic obstructive pulmonary disease	2683 (7.2)	62 (16.8)	< 0.001
Obstructive sleep apnea	1743 (4.7)	18 (4.9)	0.8
Preoperative medications ≤ 24 h before surgery			
β-blockers	5386 (14.5) *n* =37 260	71 (19.2) *n* = 369	0.01
Rate-controlling calcium channel blocker	694 (1.9) *n* = 37 264	12 (3.3) *n* = 369	0.08
Preoperative medications > 24 h to 7 d before surgery			
β-blockers	6032 (16.2)	84 (22.8)	0.001
Rate-controlling calcium-channel blocker	819 (2.2)	15 (4.1)	0.03
Urgent/emergent surgery	3792 (10.2)	62 (16.8)	< 0.001
Surgery			
Thoracic surgery	1053 (2.8)	35 (9.5)	
Major nonthoracic surgery	22 502 (60.3)	306 (82.9)	< 0.001
Other surgeries	13 740 (36.8)	28 (7.6)	
Type of anesthesia			
General anesthesia	22 961 (61.7)	187 (50.7)	
Regional anesthesia	10 145 (27.2)	75 (20.3)	< 0.001
Combined general and regional anesthesia	4137 (11.1)	107 (29.0)	
Preoperative hemoglobin, g/L			
Mean ± SD	130.4 ± 19.4 *n* = 35 978	125.8 ± 21.1 *n* = 364	
Median (IQR)	132 (120–143) *n* = 35 978	128 (113–140) *n* = 364	< 0.001
Preoperative eGFR, mL/min/1.73 m^2			
Mean ± SD	80.5 ± 24.2 *n* = 34 696	68.6 ± 25.4 *n* = 361	
Median (IQR)	84.7 (67.8–97.2) *n* = 34 696	73.3 (52.2–88.3) *n* = 361	< 0.001

Note: CAD = coronary artery disease, CHF = congestive heart failure, CVE = cerebrovascular events, DVT/PE = deep venous thrombosis/pulmonary embolism, eGFR = estimated glomerular filtration rate, IQR = interquartile range, POAF = postoperative atrial fibrillation, SD = standard deviation.
*All outcome definitions are available in Appendix 2. When data are missing, denominators are specified.
†Unless specified otherwise.
‡We defined "frail" as a person living in a assisted living facility or who requires assistance with activities of daily living.

between NT-proBNP levels and POAF is shown in Figure 3. We used an NT-proBNP level of 100 ng/L as a reference value to obtain ORs from logistic regression models. We found that preoperative NT-proBNP levels of 200, 1500 and 3000 ng/L were associated with unadjusted ORs for POAF equal to 1.50 (95% CI 1.33–1.69), 2.75 (95% CI 1.81–4.20) and 3.32 (95% CI 1.90–5.80), respectively. The

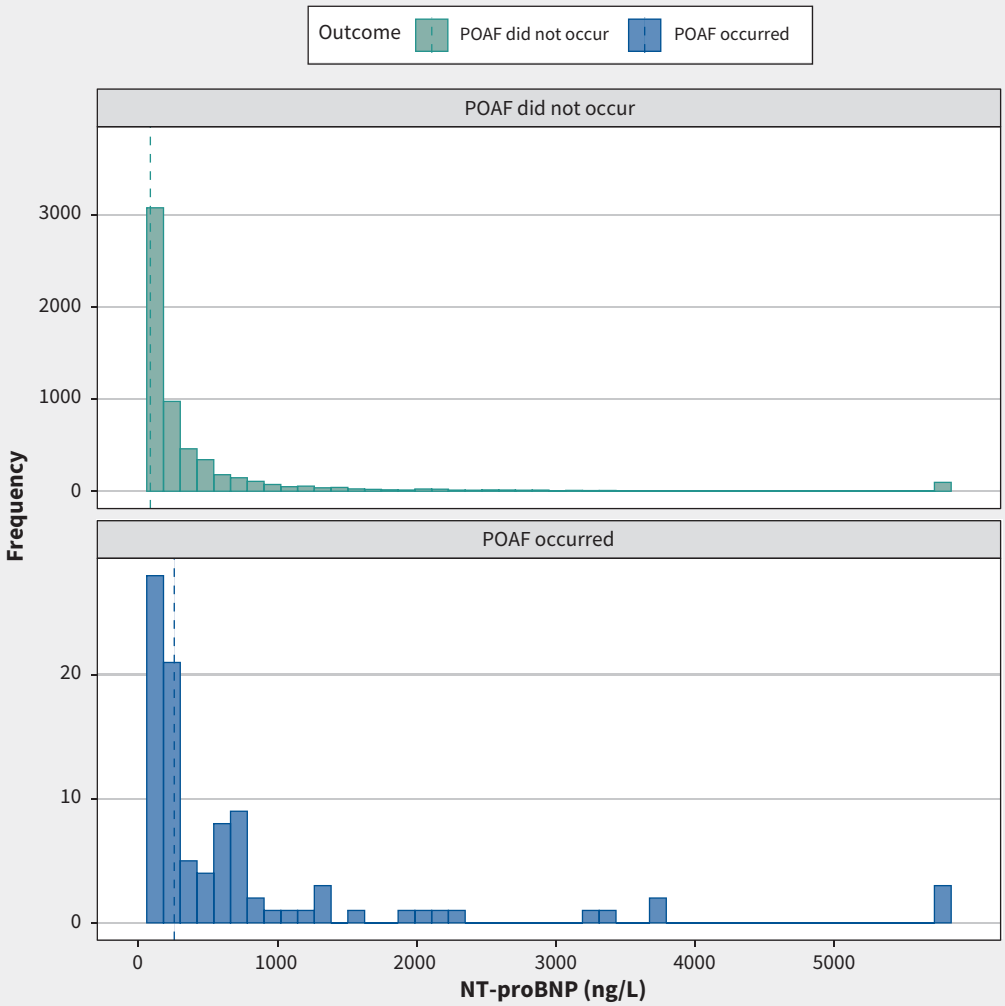

Figure 2: Histograms presenting distributions of values of N-terminal pro–brain-type natriuretic peptide (NT-proBNP) stratified by the occurrence of postoperative atrial fibrillation (POAF). Median values of NT-proBNP in both groups are marked with broken lines. Values of NT-proBNP winsorized at the 99th percentile (i.e., 98 most extreme values replaced with 5732 ng/L) for increased readability.

multivariable adjusted associations are shown in Figure 3 and Table 2. We determined that preoperative NT-proBNP levels of 200, 1500 and 3000 ng/L were associated with adjusted ORs for POAF of 1.31 (95% CI 1.15–1.49), 2.07 (95% CI 1.27–3.36) and 2.39 (95% CI 1.26–4.51), respectively. The fraction of new information from NT-proBNP over and above other prognostic factors was equal to 16%. Graphical representation of information provided by the biomarker can be seen in Appendix 1, along with model internal validation and goodness-of-fit measures.

Interpretation

We found that new, clinically important POAF complicates 1 in 100 major noncardiac surgeries, with a rate of 2 events per 1000 patients after low-risk surgery and 32 events per 1000 patients after major thoracic surgery. Importantly, these numbers represent the incidence of overt AF events that manifested with clinical symptoms or required treatment in the postoperative period. We also found that elevated levels of preoperative NT-proBNP were associated with increased odds of POAF and provided additional information independent of other established prognostic factors. Postoperative atrial fibrillation prompted anticoagulation treatment in only 22% of patients, and only a small fraction of these patients continued the treatment after hospital discharge.

The reported incidence of POAF varies across different studies (Appendix 1, Supplementary Table 1). Our results are consistent with those of large registry-based studies. A retrospective cohort study of administrative data from a cohort of more than 1.6 million patients in California showed an incidence of POAF equal to 3.7% in patients undergoing thoracic procedures and 0.7% in patients after nonthoracic procedures,[3] whereas a retrospective review involving 363 092 patients who underwent major noncardiac surgery, 2.2% of whom underwent thoracic surgery, in 375 hospitals in the United States found that POAF complicated 1% of all procedures.[2] In a 2018 Danish registry study that included more than 1.5 million patients undergoing both thoracic and nonthoracic noncardiac surgery, the incidence of POAF

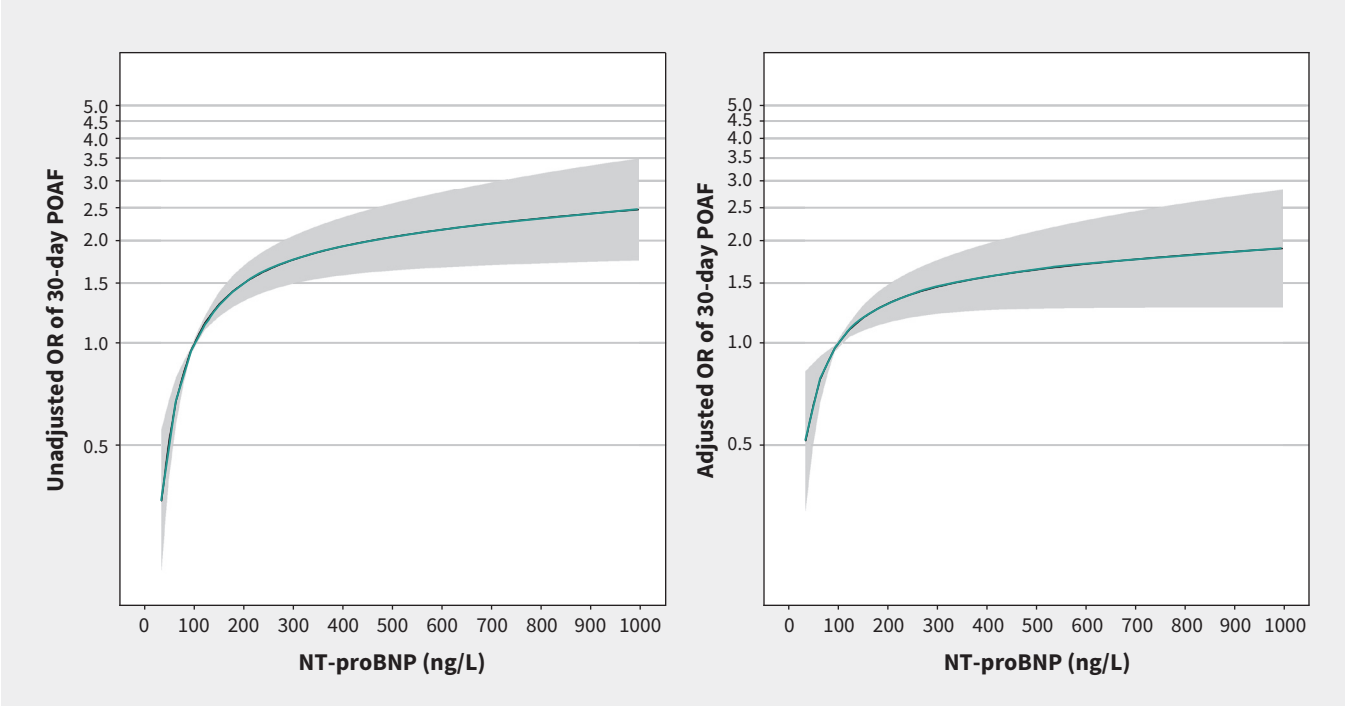

Figure 3: Unadjusted (left) and adjusted (right) relation between N-terminal pro–brain-type natriuretic peptide (NT-proBNP) measurement and postoperative atrial fibrillation (POAF). The test for nonlinearity of the estimated unadjusted relation between NT-proBNP and POAF had a *p* value = 0.01. The test for nonlinearity of the estimated relation had a *p* value = 0.2 in the multivariable analysis. The grey area represents 95% confidence intervals. Note: OR = odds ratio.

was 2.7% and 0.4%, respectively.[7] The similar incidence of POAF in administrative database studies and the VISION study may reflect that only postoperative AF with symptoms or requiring treatment is recorded in administrative databases (i.e., the VISION definition of POAF).

Preoperative NT-proBNP measurements were available in almost 10 000 patients. Our study adds to the current understanding of the association between NT-proBNP and POAF by displaying the entire relation between preoperative levels of this biomarker and the occurrence of POAF without any arbitrary categorization. The prospective design and representative sample of our study provided an opportunity to assess the prognostic value of NT-proBNP measurement for the occurrence of clinically important POAF after noncardiac surgery. We found that NT-proBNP provided important new information for POAF prediction independent of other prognostic factors.

The use of NT-proBNP is likely to increase. Elevated NT-proBNP before surgery is associated with increased risk of major perioperative cardiovascular outcomes after noncardiac surgery (e.g., vascular death, nonfatal myocardial infarction or myocardial injury), and the biomarker was shown to improve the predictive performance of the Revised Cardiac Risk Index.[31,32] The association between NT-proBNP and POAF after cardiac surgery has been researched extensively.[19,33–36] Our results confirm the prognostic value of this biomarker in the setting of noncardiac surgery.

In our study, only 22% of the patients with POAF received anticoagulation therapy during the index hospital stay, which is consistent with other published studies.[7,37] Less than 3% of patients with POAF were prescribed therapeutic anticoagulation therapy at the time of discharge from hospital, despite more than 90% of these patients having baseline CHA_2DS_2-VASc scores that would likely prompt the start of such therapy in a nonsurgical setting.[27] There are no high-quality data on the proportion of patients with POAF who develop recurrent or chronic AF, which limits physicians' ability to make informed decisions on anticoagulation treatment for these patients. Data from the PeriOperative ISchemic Evaluation (POISE)-1 and POISE-2 trials showed an increased 1-year risk of stroke among patients who developed POAF, which suggests that such patients may benefit from anticoagulation therapy.[28] A recent meta-analysis confirmed these findings.[8] However, no randomized controlled trials to date have assessed the efficacy and safety of providing anticoagulation treatment for patients with POAF, and we believe that there is a clear need for such a trial.[38]

Limitations

We used the definition of clinically important POAF to capture new postoperative events that have immediate clinical consequences. It is likely that shorter episodes of mainly asymptomatic POAF are more frequent among noncardiac surgery patients and would have been detected more often with active screening.[21] Similarly, extended monitoring after hospital discharge with remote devices could have shown a substantially higher rate of AF in the 30-day postoperative period. Continuous cardiac monitoring is, however, rarely used outside operating rooms and intensive care units, and the clinical consequences of asymptomatic POAF are not clear. Despite showing the added prognostic value of NT-proBNP, our analyses did not address the question about causal relations between various cardiovascular diseases leading to cardiac wall stress and, in turn, elevated levels of the biomarker and POAF.

Table 2: Multivariable logistic regression model used to predict postoperative atrial fibrillation (*n* = 109) in a subgroup of 9789 patients who had NT-proBNP measured before surgery*

Variable	OR (95% CI)
NT-proBNP, ng/L	
100	1 (Ref.)
200	1.31 (1.15–1.49)
1500	2.07 (1.27–3.36)
3000	2.39 (1.26–4.51)
Age, yr	
50	1 (Ref.)
65	2.06 (0.92–4.61)
80	4.37 (1.91–9.98)
Type of surgery	
Low-risk	1 (Ref.)
Major nonthoracic	3.23 (1.67–6.25)
Major thoracic	4.71 (1.57–14.14)
Demographic and clinical characteristics	
Male sex	1.20 (0.81–1.78)
Hypertension	0.93 (0.61–1.43)
Diabetes mellitus	1.21 (0.76–1.92)
Coronary artery disease	1.12 (0.69–1.81)
Chronic obstructive pulmonary disease	2.04 (1.24–3.33)

Note: CI = confidence interval, NT-proBNP = N-terminal pro–brain-type natriuretic peptide, OR = odds ratio, Ref. = reference category.
*We modelled NT-proBNP and age as continuous variables using restricted cubic splines. Splines are best interpreted using a figure, but they also allow the comparison of any 2 desired values of the predictor that can be easily interpreted as an OR without the need to refit the model. We used previously established thresholds for NT-proBNP and clinically meaningful increments for age. Odds ratios presented in the table can be interpreted as relative risks owing to the low baseline risk of the outcome.

Conclusion

We found that incidence of clinically important POAF after noncardiac surgery was 1%. We also determined that preoperative NT-proBNP measurement was an independent prognostic factor for POAF. More research is needed to establish evidence-based prevention and treatment strategies for POAF in patients undergoing noncardiac surgery.

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