World J Surg (2014) 38:51–59
DOI 10.1007/s00268-013-2284-2

World Journal of Surgery

# Value of Plasma Brain Natriuretic Peptide Levels for Predicting Postoperative Atrial Fibrillation: A Systemic Review and Meta-analysis

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Published online: 16 October 2013


**Abstract**

*Background* Blood natriuretic peptide (NP) levels have been reported to be useful for predicting postoperative atrial fibrillation (AF). We aimed to quantitatively synthesize the current evidence of the accuracy of using NP levels in predicting postoperative AF.

*Methods and Results* Medline, Embase, and reference lists were searched. Studies were included if either brain natriuretic peptide (BNP) or N-terminal pro-b type natriuretic peptide (NT-proBNP) had been evaluated perioperatively to predict postoperative AF. Data were analyzed to obtain summary accuracy estimates. Data from 1,844 patients in 10 studies were analyzed. Summary estimates for the sensitivity and specificity of using NP levels for predicting postoperative AF were 75 % [95 % confidence interval (CI) 67–79 %] and 80 % (95 % CI 62–91 %), respectively. The overall diagnostic odds ratio was 3.28 (95 % CI 2.23–4.84). Subgroup analysis showed that elevated NP levels in the perioperative period were a strong independent predictor of postoperative AF. NT-proBNP appeared to have better predictive value than BNP, as did postoperative assessment over preoperative assessment. BNP had a better correlation with postoperative AF in patients undergoing thoracic surgery than in patients undergoing cardiac surgery.

*Conclusions* Perioperative assessment of the natriuretic peptide level in patients undergoing major cardiothoracic surgery could be a valuable diagnostic aid for identifying patients at high risk of developing postoperative AF, and for providing critical clinical information to guide prophylactic antiarrhythmic therapy in the perioperative period.

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## Introduction

Atrial fibrillation (AF) represents one of the most frequent postoperative cardiac complications, especially in patients undergoing cardiothoracic surgery [1, 2]. The incidence of postoperative AF varies between 10 and 40 % [1, 3]. Although AF is often benign, it has been related to increased morbidity, including hypotension, heart failure, thromboembolic complications, prolonged hospital stay, and increased hospital costs [3–7]. Several pharmacological therapies have been shown to be able to prevent the development of postoperative AF [8, 9], but there is no established method for the preoperative identification of patients at high risk of developing this arrythymia. Because use of preventive medications is not totally without risk, unselective administration of such medications is not justifiable. Several factors, including male gender, age, atrial dimension, low ejection fraction, left ventricular (LV) diastolic dysfunction, history of diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and coronary artery disease, have been reported as predictors of postoperative AF following coronary artery bypass surgery (CABG) or other surgery, but only advanced age has been widely validated.

Recently, a number of observational studies have examined the predictive value of brain natriuretic peptide (BNP) or N-terminal pro-b type natriuretic peptide (NT-proBNP) for identifying patients at risk of AF after a major surgery [10–19]. B-type natriuretic peptide or its inactive cleavage product N-terminal pro-BNP is secreted mainly from the left ventricle in response to pressure and volume overload [20]. Systemic physiologic effects of natriuretic peptides (NPs) include natriuresis, diuresis, and vasodilation [21]. Although most studies have shown an association between elevated NP levels and postoperative AF, the risk estimates vary widely among studies. We therefore carried out a systematic review and meta-analysis to summarize data on the association between NP levels and postoperative AF in adult patients.

## Materials and Methods

### Search Strategy and Selection Criteria

We searched three electronic databases (Medline, Embase, and the Cochrane database) for studies published through January 2012 with the following MeSH terms and free text: "natriuretic peptide," "surgery," "arrhythmia," and "atrial fibrillation." We did not set any time or language restrictions for these searches. We checked the reference lists of relevant review articles. Selection was performed independently by two reviewers. Discrepancies between the selections of the reviewers were resolved by a consensus meeting with the third or fourth co-author.

The title and abstract of the studies were screened in the first round, and potentially relevant articles were retrieved for full-text review in the second round. For inclusion, the studies had to fulfil the following criteria:

- Have a study population of consecutive patients (age >18 years) undergoing cardiac or non-cardiac surgery
- Include results of a BNP or NT-proBNP test in the perioperative period
- Use perioperative AF as one of the endpoints
- Include calculations of sensitivity, specificity, or odds ratio, or have sufficient data to construct a 2 × 2 contingency table.

We excluded case reports, case series, review articles, editorials, and clinical guidelines. Two authors independently assessed all titles and abstracts to determine whether the inclusion criteria were satisfied. Full-text articles were retrieved if any of the reviewers considered the abstract suitable. The study inclusion and exclusion process is summarized in Fig. 1.

### Quality Assessment

The methodological quality of the selected studies was evaluated independently by two reviewers with a validated tool for the quality assessment of diagnostic accuracy studies (Quality Assessment of Diagnostic Accuracy

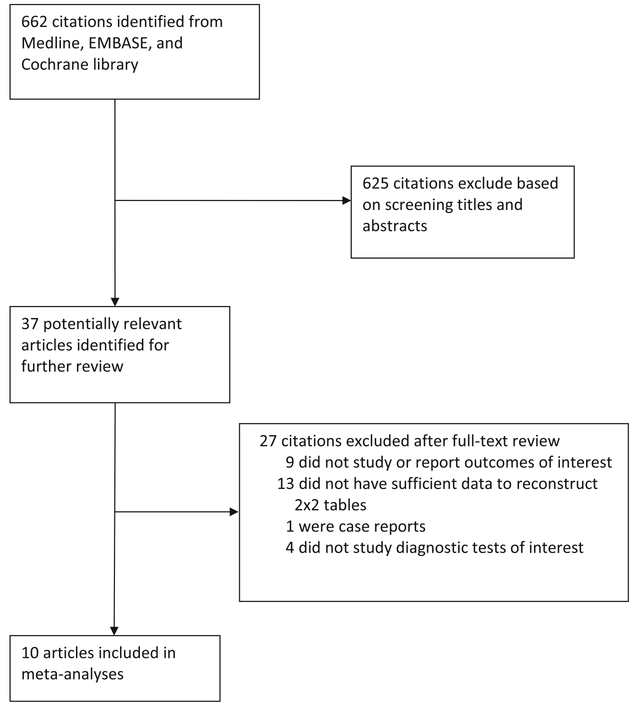


**Fig. 1** Flow chart of study identification and inclusion

Studies, QUADAS) [22]. Discrepancies were resolved by a consensus meeting with the third and fourth co-authors.

### Data Synthesis and Analysis

We calculated the pooled sensitivity, specificity, likelihood ratio, as well as the diagnostic odds ratio for the included studies. Given the inherent negative correlation between sensitivity and specificity, we estimated these parameters with the bivariate model for diagnostic meta-analyses [23]. This approach assumes a bivariate distribution for the log-transformed sensitivity and specificity. In addition to accounting for study size, the bivariate model also estimates and adjusts for the negative correlation between the sensitivity and specificity of the index test that may arise from the different thresholds used in different studies [24]. To compare diagnostic performance between two biomarkers, we calculated the area under the summary receiver operating characteristic (AUROC) curve and diagnostic odds ratio (OR) to summarize the true positive and false positive rates of different diagnostic studies, irrespective of the different cutoff points used in the various studies. To deal with zero observations in 2 × 2 contingency tables, ½ was added to each cell, reducing performance in the small studies. To formally quantify the extent of between-study variation (i.e., heterogeneity), we calculated the inconsistency index $I^2$, which describes the variation of effect estimate that is attributable to heterogeneity across studies [25]. Summary diagnostic odds ratios were estimated by random (DerSimonian-Laird) or fixed (Mantel–Haenszel) effect models, depending on whether $I^2$ was greater or lower than 50 % [26]. Meta-regression was used to evaluate the amount of heterogeneity in the subgroup analysis. We defined a priori the following potential relevant covariates: biomarker, type of surgery, and the age range and underlying disease of the study patients [27]. We tested for publication bias by inspecting the symmetry of funnel plots, and we then assessed the potential for publication bias by performing Begg and Egger tests [28]. Statistical analyses were conducted using STATA 11.0 (Stata Corp, College Station, TX). All statistical tests were two-sided, and statistical significance was defined as a $P$ value less than 0.05.

## Results

A total of 10 primary studies (1 non-English-language study) met the criteria for inclusion. They included 1,844 patients undergoing major operations whose BNP or NT-proBNP levels were measured in the perioperative period (Fig. 1). Four hundred thirty-four patients (24 %) developed postoperative AF. Agreement regarding eligibility was 90 %.

Of these 10 studies, 6 included patients undergoing cardiac valve surgery or CABG, and the remaining 4 included patients undergoing thoracic surgery either for lung cancer or for esophageal cancer. The study settings included hospitalized patients (8 studies) and Intensive Care Unit (ICU) patients [2]. Details of the participants, settings, outcomes, and study quality criteria of the studies selected for meta-analyses are summarized in Table 1. The sensitivity, specificity, and diagnostic odds ratio for the BNP and NT-proBNP tests, and the timing of biomarker measurement are summarized in Table 2. The sensitivity of natriuretic peptides (NPs) in predicting postoperative AF ranged from 67 to 87 %, and the specificities ranged from 29 to 93 %. The diagnostic OR ranged from 1.00 to 27.9, with 8 studies reporting the adjusted effect estimate and 2 derived from crude calculation.

### Study Characteristics

All of the included studies collected data prospectively and provided clear descriptions of patient selection criteria and index tests. All patients underwent standard electrocardiography as a reference test without differential disease ascertainment. None of the included studies provided an explanation for uninterpretable test results or participants' withdrawal from the study. Although none of the studies specified whether they were blinded to index testing in ascertaining outcome, incorporation bias is not likely because the diagnosis of AF is not influenced by knowledge of serum levels of NPs. Figure 2 provides an overall picture of the methodological quality of studies as evaluated with the QUADAS tool.

## Results of Individual Studies

### Sensitivity and Specificity

We identified a total of five studies that reported estimated sensitivity and specificity of NPs in predicting postoperative AF. Overall, the pooled sensitivity was 73 % (95 % CI 67–79 %) and specificity was 80 % (95 % CI 62–91 %) (Table 3). The pooled positive likelihood ratio was 3.69 (95 % CI 1.87–7.26) and the negative likelihood ratio was 0.34 (95 % CI 0.28–0.40). Four studies evaluated NT-proBNP, while only 1 study evaluated BNP. Detailed pooled effect estimates of 5 studies reporting sensitivity and specificity are summarized in Table 3. Figure 3 shows the summary receiver operator characteristic (ROC) curve

**Table 1** Summary of the characteristics of the included studies

| Author, year, country | Mean age | Prevalence (*n*) | Outcomes | Setting | Type of surgery |
|---|---|---|---|---|---|
| Wazni et al. (2004) USA [19] | 65.7 | 0.43 (187) | Postoperative atrial fibrillation | Inpatient | CABG and/or valve surgery |
| Detaint et al. 2005 USA [12] | 63 | 0.09 (124) | Postoperative atrial fibrillation | Inpatient | Cardiac valve surgery |
| Cardinale 2007, Italy [11] | 62 | 0.18 (400) | Postoperative atrial fibrillation | Inpatient | Lung cancer surgery |
| Dogan et al. 2007, Turkey [13] | 60.2 | 0.18 (57) | Postoperative atrial fibrillation | ICU | On-pump CABG |
| Hou et al. 2008, China [15] | 66.5 | 0.08 (142) | Postoperative atrial fibrillation | Inpatient | Esophageal cancer surgery |
| Gibson et al. 2009, UK [14] | 65 | 0.39 (275) | Postoperative atrial fibrillation | Inpatient | CABG and/or valve surgery |
| Nojiri et al. 2010, Japan [17] | 66.1 | 0.28 (80) | Postoperative atrial fibrillation | Inpatient | Lung cancer surgery |
| Salvatici et al. 2010, Italy [18] | 62 | 0.18 (400) | Postoperative atrial fibrillation | Inpatient | Lung cancer surgery |
| Tanaray et al. 2010, Iran [10] | NA | 0.18 (79) | Postoperative atrial fibrillation | Inpatient | CABG and/or valve surgery |
| Krzych et al. 2011, Poland [16] | 65.9 | 0.34 (100) | Postoperative atrial fibrillation | ICU | On-pump CABG |

*BNP* B-type natriuretic peptide, *CABG* coronary artery bypass graft, *NA* not available

**Table 2** Summary of subgroup analysis by different characteristics of the included studies

| Biomarkers tested<br>Author, year, country | Preoperative BNP sensitivity, specificity, odds ratio | Postoperative BNP sensitivity, specificity, odds ratio | Preoperative NT-proBNP sensitivity, specificity, odds ratio | Postoperative NT-proBNP sensitivity, specificity, odds ratio | Adjusted variables | Cutoff (pg/mL) BNP | Cutoff (pg/mL) NT-pro BNP |
|---|---|---|---|---|---|---|---|
| Wazni et al. 2004, USA [19] | NA<br>NA<br>2.45 (1.12–5.39) | NA<br>NA<br>NA | NA<br>NA<br>NA | NA<br>NA<br>NA | Age, gender, type of surgery (CABG only versus valve surgery), Hypertension, LV function, LVH, left atrial size, presence of coronary artery disease, use of β-blockers, plasma BNP | NA | NA |
| Detaint et al. 2005, USA [12] | NA<br>NA<br>5.30 (1.32–21.30) | NA<br>NA<br>NA | NA<br>NA<br>NA | NA<br>NA<br>NA | Age, gender, LA volume, AF, ESVI, NYHA class | 31 | NA |
| Cardinale et al. 2007, Italy [11] | NA<br>NA<br>NA | NA<br>NA<br>NA | 67 %<br>93 %<br>27.90 (13.20–58.90) | NA<br>NA<br>20.10 (5.80–69.40) | Age, gender, major comorbidities, echocardiography parameters, pneumonectomy and medications, both preoperative and postoperative NT-pro BNP values | NA | Multiple cutoff values[a] |
| Dogan et al. 2007, Turkey [13] | NA<br>NA<br>NA | NA<br>NA<br>NA | NA<br>NA<br>1.001 (0.999–1.004) | NA<br>NA<br>NA | Age, lower ejection fraction, prolonged $P_{max}$, prolonged PD and large left atrium | NA | 842 |
| Hou et al. 2008, China [15] | NA<br>NA<br>NA | NA<br>NA<br>NA | NA<br>NA<br>4.711 (1.212–7.646) | NA<br>NA<br>NA | Age, gender, COPD, history of cardiac diseases, hypertension, postoperative hypoxia, and thoracic-gastric dilation | NA | NA |
| Gibson et al. 2009, UK [14] | 81 %<br>39 %<br>2.74 (1.54–4.89) | NA<br>NA<br>NA | 87 %<br>29 %<br>2.74 (1.42–5.26) | NA<br>NA<br>NA | Age, male gender, β-blocker | 31 | 74 |
| Nojiri et al. 2010, Japan [27] | 77 %<br>93 %<br>1.17 (1.04–1.31) | NA<br>NA<br>NA | NA<br>NA<br>NA | NA<br>NA<br>NA | Age, $FEV_1$/FVC, ANP | 30 | NA |
| Salvatici et al. 2010, Italy [18] | NA<br>NA<br>NA | NA<br>NA<br>NA | 69.4 %<br>82.6 %<br>NA | 72.2<br>%<br>86.9 %<br>NA | NA | NA | Preoperative: 128.7<br>Postoperative 182.3 |
| Tanaray et al. 2010, Iran [10] | NA<br>NA<br>NA | NA<br>NA<br>NA | NA<br>NA<br>NA | NA<br>NA<br>15.43 (1.77–132.95) | NA | NA | 854 |
| Krzych et al. 2011, Poland [16] | NA<br>NA<br>NA | NA<br>NA<br>NA | 73.5 %<br>57.6 %<br>NA | NA<br>NA<br>NA | NA | NA | 513 |

*NT-pro BNP* N-terminal pro-brain natriuretic peptide, *CABG* coronary artery bypass graft, *COPD* chronic obstructive pulmonary disease, *AF* atrial fibrillation, *LV* left ventricular, *LVH* LV hypertrophy, *PD* P-wave dispersion, $P_{max}$ maximum P-wave duration, *ANP* atrial natriuretic peptide, $FEV_1/FVC$ forced expiratory volume in 1 s/forced vital capacity, *RR* relative risk, *ESVI* end-systolic volume index, *NYHA* New York Heart Association

[a] Multiple cutoff values (64 and 125 ng/L for men and women 49 years of age, 125 and 186 ng/L for men and women 50–59 years of age, and 194 and 204 ng/L for men and women 60 years of age, respectively)

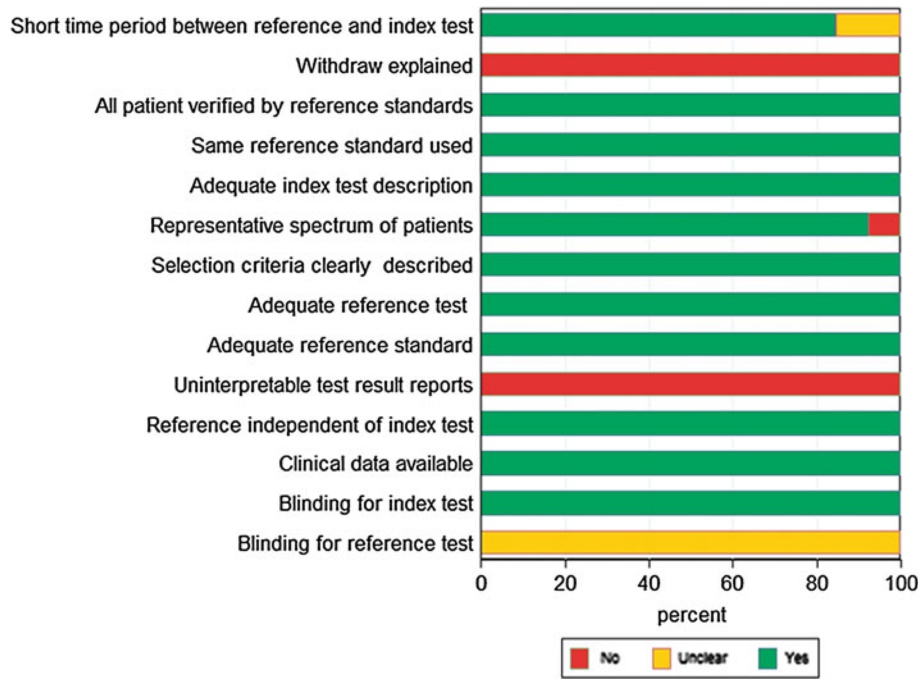


**Fig. 2** The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria for included studies

of the NP test, which revealed an area under the ROC curve of 0.78 (95 % CI 0.74–0.81).

Diagnostic Odds Ratio

We identified a total of 10 studies reporting the estimated diagnostic OR for the use of perioperative NP tests in predicting postoperative AF. The overall diagnostic OR is 3.28 (95 % CI 2.22–4.84) (Fig. 4). A significant degree of heterogeneity ($I^2$: 95.4 %) was observed in either primary or subgroup analysis. Subgroup analysis showed an attenuated effect estimate in adjusted analysis. Comparing the two subtypes of NP, NT-proBNP was associated with a superior diagnostic OR as compared to BNP. Natriuretic peptides can predict postoperative AF more accurately in patients undergoing thoracic surgery (pooled OR 7.07, 95 % CI 1.14–44.04) than in patients undergoing cardiac surgery (pooled OR 1.90, 95 % CI 1.21–2.99). Postoperative measurement of NPs (pooled OR 5.67, 95 % CI 1.05–30.55) was associated with a higher diagnostic value than preoperative measurement (pooled OR 3.90, 95 % CI 1.86–8.19). None of the subgroup analyses were significantly different from the overall meta-regression analysis. There was evidence of publication bias. Detailed pooled effect estimates of 10 studies reporting diagnostic OR are summarized in Table 4.

## Discussion

In this study, elevated plasma BNP or NT-proBNP levels obtained in the perioperative period were strong independent predictors of the occurrence of postoperative AF. NT-proBNP levels appeared to have better predictive power than BNP levels. Similarly, postoperative assessment had better predictive power than preoperative assessment. Brain NP levels showed better correlation with postoperative AF in patients undergoing thoracic surgery than in patients undergoing cardiac surgery. The overall pooled sensitivity and specificity in predicting postoperative AF were 75 % (95 % CI 67–79 %) and 80 % (95 CI 62–91 %), respectively.

Both BNP and NT-proBNP are synthesized and released by an overloaded myocardium with cyclic guanosine monophosphate-mediated natriuretic and vasodilator properties [21]. In addition to serving as indicators of heart failure, BNP and NT-proBNP levels are major biomarkers of risk for several cardiac diseases, such as coronary heart disease, sepsis, and valvular heart disease [29–31]. In major cardiac or thoracic surgery, the natriuretic peptide level reflects the magnitude of hemodynamic change and LV change. Elevated levels of NP have been linked to major adverse cardiac events in previous systematic reviews [29, 32, 33]. In major cardiothoracic surgery, there is a profound need for such a biomarker, because the identification of high-risk patients is essential, both for clinical management and to indicate patients who require close postoperative monitoring and preventive therapy for arrhythmia.

Several preventive medications have shown promise in reducing the incidence of postoperative AF, including beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, amiodarone, magnesium

**Table 3** Summary of pooled diagnostic accuracy indices

| Variables | Number of studies | Sensitivity (95 % CI) | Specificity (95 % CI) | Likelihood ratio+ | Likelihood ratio− | AUROC (95 % CI) | Diagnostic OR (95 % CI) | $I^2$ (95 % CI) | Publication bias (Egger's test P) |
|---|---|---|---|---|---|---|---|---|---|
| Overall [10–19] | 5 | 0.73 (0.67–0.79) | 0.80 (0.62–0.91) | 3.69 (1.87–7.26) | 0.34 (0.28–0.40) | 0.78 (0.74–0.81) | 10.9 (4.83–24.7) | 87.3 (74.7–93.6) | 0.657 |
| NT-proBNP [11, 13–15] | 4 | 0.75 (0.67–0.82) | 0.75 (0.50–0.90) | 3.02 (1.45–6.27) | 0.33 (0.27–0.40) | 0.80 (0.76–0.83) | 8.93 (3.89–20.5) | 87.3 (72.7–94.1) | 0.459 |

*AUROC* area under the receiver operating curve, *OR* odds ratio

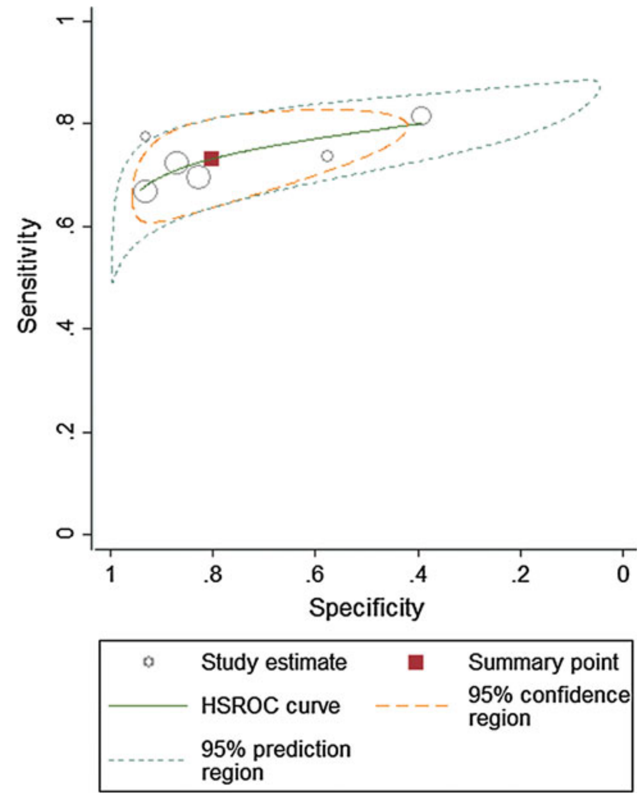


**Fig. 3** Summary receiver operating characteristic (SROC) curve (*solid line*) and the bivariate summary estimate (*solid square*), together with the corresponding 95 % confidence ellipse (*inner dashed line*) and 95 % prediction ellipse (*outer dotted line*). The symbol size for each study is proportional to the study size

sulfate, and non-steroidal anti-inflammatory drugs [8]. However, none of these drugs are totally safe, and their unnecessary use may cause excessive iatrogenic adverse events.

Based on the high accuracy of NPs in predicting postoperative AF, an NP-guided selective preventive strategy is of high interest. To make our results more informative to clinicians, we used pooled likelihood ratio estimates to calculate the post-test probability. In a virtual population with a postoperative prevalence of 25 % (the actual pooled prevalence in this study is 24 %), a positive NP test (LR+: 3.69) would increase the post-test probability to 55 %. Likewise, in the same population, a negative NP test (LR−: 0.34) would reduce the post-test probability to 10 %. Therefore, for patients with a negative preoperative NP test result, avoiding preventive medication carries only a 10 % risk for developing postoperative AF.

In addition to the imperfect sensitivity and specificity, clinical recommendations regarding the utility of NP testing to guide prophylaxis against postoperative AF should consider several other factors. Of note, the threshold value, the timing of measurement, and the type of NP test should

**Fig. 4** Forest plot of diagnostic odds ratio for studies using natriuretic peptide to predict postoperative atrial fibrillation

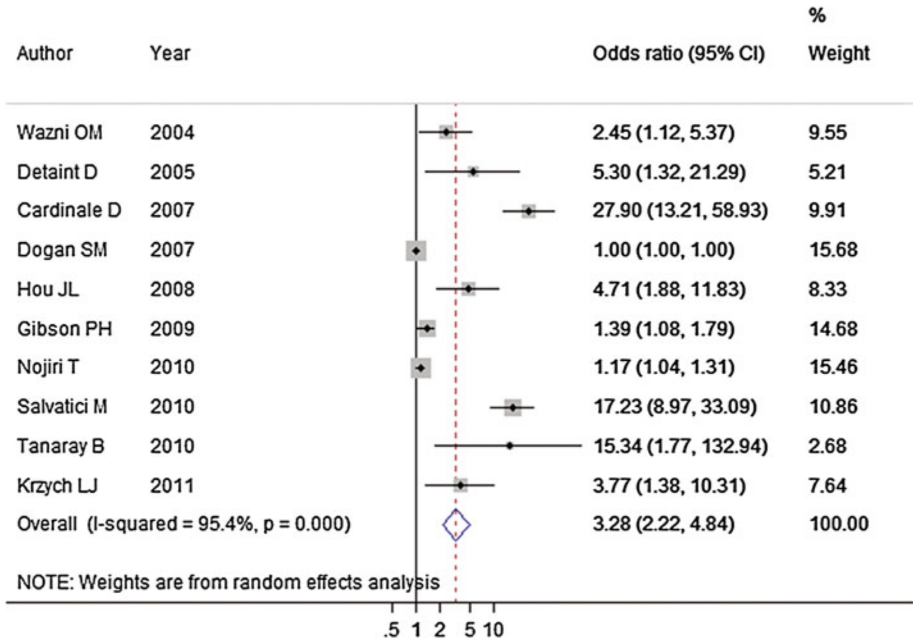


**Table 4** Summary of subgroup analysis of the included studies by the various study characteristics Query ID="Q3" Text="AQ: Again, please verify the accuracy of the reference numbers.

| Variables | Number of studies | Diagnostic OR (95 % CI) | $I^2$ (95 % CI) | Publication bias (Egger's test *P*) | Meta-regression *P* |
|---|---|---|---|---|---|
| Overall [10–19] | 10 | 3.28 (2.23–4.84) | 95.4 (93.3–96.9) | 0.002 | – |
| Adjusted [11–15, 17, 19] | 7 | 2.20 (1.55–3.13) | 94.6 (91.1–96.7) | 0.002 | 0.20 |
| BNP [12, 14, 17, 19] | 4 | 2.13 (1.09–4.18) | 73.8 (26.6–90.6) | 0.001 | 0.38 |
| NT-proBNP [10, 11, 13–16, 18] | 7 | 5.00 (2.19–11.39) | 96.7 (94.9–97.8) | 0.013 | 0.38 |
| Cardiac surgery [10, 12–14, 16, 19] | 6 | 1.90 (1.21–2.99) | 83.2 (64.6–92.0) | 0.000 | 0.23 |
| Thoracic surgery [11, 15, 17, 18] | 4 | 7.07 (1.14–44.04) | 97.8 (96.2–98.7) | 0.079 | 0.23 |
| Preoperative assessment [11–14, 16, 18, 19] | 7 | 3.90 (1.86–8.19) | 96.2 (94.0–97.5) | 0.016 | 0.58 |
| Postoperative assessment [10, 15, 17, 18] | 4 | 5.67 (1.05–30.55) | 96.1 (92.6–97.9) | 0.167 | 0.58 |

be clearly defined. In our analysis, measuring NT-proBNP in the operative period with a threshold level between 180 and 850 pg/mL appeared to be the most accurate combination. However, this finding needs to be confirmed, given the small number of studies and the wide range of threshold values. Moreover, the aforementioned pharmacologic prophylactic therapy was mostly administered in the preoperative setting; whether postoperative administration would be as effective remains unanswered.

One way to resolve the controversy is to enhance the predictive value of preoperative NP measurement. Further efforts to combine established risk factors for postoperative AF, such as age, gender, hypertension, echocardiographic characteristics, and cardiovascular disease, into a risk-prediction instrument may produce a robust algorithm that can further guide selective prevention with fewer false negatives in the preoperative assessment. In addition, prospective randomized controlled trials designed to evaluate both markers in the preoperative and postoperative period would be highly desirable. Results of such trials would help determine the best timing and the appropriate patient population for administration of prophylactic therapy.

The main strength of this meta-analysis is that it highlights the high predictive value of perioperative NP levels for postoperative AF. Our data suggest that use of the NT-proBNP test and measurement in the postoperative period are associated with higher predictive value. The main weaknesses of our report stem from the limitations of the identified studies. The most obvious limitation is the incomplete reporting of diagnostic accuracy parameters, especially sensitivity and specificity, in many of the included articles. The pooled sensitivity and specificity is based on half of the included articles, which may lead to biased results. A high degree of heterogeneity is another issue, where the study settings, case mix, and cutoff levels for NP tests varied greatly among the included studies, limiting the generalizability of their results. Although 7 studies reported adjusted OR that comprehensively adjusted for the comorbidities in each patient population (Table 1), there are multiple factors that may contribute to postoperative AF that may not have been controlled for in each study, and the value of NP tests may have been overevaluated. Studies with small sample sizes also may have allowed for a type II error. We did not find significant publication bias in our analysis, but the limitation of our statistical method in detecting publication bias has been demonstrated. Therefore, we cannot disprove the inflation of accuracy estimates due to the favorable acceptance of papers reporting favorable results.

## Conclusions

Preoperative natriuretic peptide levels predict postoperative AF in patients undergoing cardiothoracic surgery. BNP levels could be used to better stratify patients in this respect. In addition, BNP activation should direct the attention of clinicians toward monitoring cardiac rhythm and hemodynamic variables more closely than as might be suggested by a cursory evaluation.

**Acknowledgments** The authors are grateful to Medical Wisdom Inc. for their help in statistical analysis. This work was funded by the Zhejiang Provincial Program for the Cultivation of High-level Innovative Health talents, the Provincial and Bureau co-construction project (wkj2012-2-020), the Hygiene Bureau project (201202011), and the Zhejiang Traditional Chinese Medicine Science and Technology Project (2009za011). No commercial sponsorship or other external financial support was used in the conduct of this work.

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