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Review Article

Perioperative Biomarkers Predicting Postoperative Atrial Fibrillation Risk After Coronary Artery Bypass Grafting: A Narrative Review

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Postoperative atrial fibrillation (POAF) after cardiac surgery remains a highly prevalent and costly condition that negatively impacts patient quality of life and survival. Numerous retrospective studies, meta-analysis, and review papers have been reported identifying POAF risk based on patients' risk factors and clinical biomarkers. In this narrative review, the authors report significant variations among selected pre- and perioperative biomarkers used to predict POAF incidence in patients without a history of atrial fibrillation (AF). POAF prediction based on B-type natriuretic peptide, N-terminal pro B-type natriuretic peptide, C-reactive protein, interleukin-6, creatinine, and plasminogen activator inhibitor-1 differs significantly among different studies, thereby limiting their clinical utility to predict POAF risk with high accuracy. Conversely, soluble vascular endothelial cells adhesion molecule-1, soluble CD40 ligand, Galectin-3, and aldosterone show promise for better POAF prediction. However, the current datasets for these selected biomarkers are not of sufficient size to validate the broad clinical application specifically for patients with no prior history of AF.

Key Words: atrial fibrillation; biomarkers; coronary artery bypass graft; postoperative atrial fibrillation

CORONARY ARTERY bypass grafting (CABG) is a well-established surgical procedure performed worldwide.[1] However, post-CABG complications are prevalent and difficult to predict.[2] In particular, a sizeable cohort of patients undergoing cardiac surgery develops postoperative atrial fibrillation (POAF).[3] It can be procedure-dependent, with an incidence of POAF of approximately 6% to 40% after CABG alone, 49% after CABG plus aortic valve replacements, and 64% after CABG plus mitral valve replacements.[4-6] After CABG surgery, of the patients who develop POAF, 70% and 94% of patients

Abbreviations and Acronyms: AF, Atrial fibrillation; AVR, Aortic valve replacement; BMI, Body mass index; BNP, B-type natriuretic peptide; CABG, Coronary artery bypass grafting; CAD, Coronary artery disease; COPD, Chronic obstructive pulmonary disease; CPB, Cardiopulmonary bypass; CVD, Cardiovascular disease; Cr, Creatinine; CRP, C-reactive protein; DM, Diabetes mellitus; EF, Ejection fraction; Gal-3, Galectin-3; HF, Heart failure; ICU, Intensive care unit; IL-6, Interleukin-6; IQR, Interquartile range; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; NA, Not available; NT-proBNP, N-terminal pro b-type natriuretic peptide; PAI-1, Plasminogen activator inhibitor-1; PC, Prospective cohort; POAF, Postoperative atrial fibrillation; PVD, Peripheral vascular disease; RC, Retrospective cohort; SD, Standard deviation; sVCAM, Soluble vascular endothelial cells adhesion molecule-1; TNF, Tumor necrosis factor

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developed POAF before the end of the fourth and the sixth postoperative days, respectively, and it is linked to increased complications, financial burden, morbidity, and mortality rate.[7,8]

Different formulas, algorithms, and other predictive methods have been reported to predict clinical outcome and recovery time based on family history, medical conditions, patient lifestyle, and other patient comorbidities.[9-16] Identifying the biomarkers that provide predictive power linked to POAF clinical outcome has greatly affected the field of medicine. Previous reports showed that biomarkers may be used as forecasters of a cardiac patients' status post cardiac surgery, and the applications are numerous.[17-24] In this narrative review, the authors complied preoperative and perioperative biomarker data that have been shown to predict POAF incidence in patients undergoing either on-pump or off-pump CABG surgery with no history of atrial fibrillation (AF). However, significant variation has been noted within biomarkers of interest, and thus the reported comprehensive data have added more questions regarding the clinical utility of these biomarkers to predict POAF incidence. Most importantly, many studies have reported postoperative biomarkers in their protocols as identifying patients at increased risk of POAF incidence, whereas those biomarkers were collected after cardiac surgery at day 1 and afterwards, and this timeline overlaps with the typical onset of POAF. Finding appropriate biomarkers with predictive value and their concentrations preoperatively and intraoperatively will guide changes in cardiac surgery care specifically for those patients who would be at risk of POAF development and also may benefit from increased postsurgical monitoring, pre-emptive antiarrhythmic therapy, and/or additional surgical interventions (such as pulmonary vein isolation or surgical maze), and further developing personalized treatment strategies possibly including prophylactic interventions and closer monitoring to minimizing the risk of developing long-term AF.

Methods

Selection of Studies

The authors aimed to evaluate the studies by examining the quality of the previously reported preoperative and perioperative biomarkers data among patients with no prior AF history during either on-pump or off-pump CABG surgery. Articles were extracted using both PubMed and MEDLINE databases. The search strategy involved the Medical Subject Headings keywords such as "biomarker," "atrial fibrillation," "coronary artery bypass," "creatinine," and the text keywords such as "postoperative atrial fibrillation," "preoperative," "perioperative/intraoperative," "postoperative," "biomarker," "NT-proBNP," "BNP," "CRP," "IL-6," "inflammatory biomarkers," "PAI-1," "VCAM," "aldosterone," "sCD40L," and "Galectin-3".

Data Extraction

Once an abstract's general information had been identified, full articles were assessed and studied to ensure both inclusion and exclusion criteria. Studies not published as full-text articles, single case reports, opinion articles, and articles not written in English were excluded. No article was excluded based on pre-existing antiarrhythmic drug therapy. Patients with history of AF and any prior heart surgical procedure also were excluded from the search. Both prospective and retrospective studies were included. Search was restricted to studies in adults (aged: 18+ years) with and without POAF incidence after cardiac surgery but none of the studies were excluded based on sex, race/ethnicity, body mass index, obesity, diabetes mellitus, and myocardial infarction condition. Finally, studies reported either preoperative biomarker data, perioperative biomarker data, or both have been included. Only CABG procedures were considered. However, to increase the number of studies and patient population, both CABG and CABG + Valve were considered for plasminogen activator inhibitor-1 (PAI-1) and aldosterone. Finally, studies reported that postoperative data also have been included, as long as they also showed preoperative data. Two members (M.S.K. and K.Y.) reviewed the published data in the articles and reached consensus.

Evaluation of Study Quality

The following key points were required to ensure the study quality: clear identification of the study population, clear identification of procedure (CABG/CABG + Valve), clear identification of preoperative data and perioperative data, clear identification of standard units used for individual biomarker such as "mg/L" for C-reactive protein (CRP), "pg/mL" for interleukin-6 (IL-6), "μmol/L" for creatinine (Cr), "ng/mL" for vascular cell adhesion molecule-1 (VCAM), "pg/mL" for N-terminal pro B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP), and "ng/mL" for PAI-1 and soluble CD40 ligand (sCD40L). Units were converted to standard units wherever required. Either standard deviation (SD) or interquartile range (IQR) has been clearly identified for each biomarker data presented as preoperatively and perioperatively. Summary of the articles selection, data extraction and evaluation is shown in Figure 1.

Results and Discussion

Quality of the individual biomarker has been accessed and compared for patients who developed POAF with patients who remained in sinus rhythm (SR). Variations in the biomarker-of-interest predicting POAF in patients with no previous AF episodes have been noted within the individual study and among different studies.

NT-ProBNP and BNP

In response to pressure and volume overload, the myocardium produces natriuretic peptides.[25] Myocyte stretch triggers the release of a precursor molecule (proBNP), which afterwards splits into BNP and an NT-proBNP.[26] Preoperative blood levels for NT-proBNP in patients with cardiovascular disease, particularly those with heart failure (HF), have shown variations in comparison with patients with healthy hearts.[25,26] Thus, preoperative

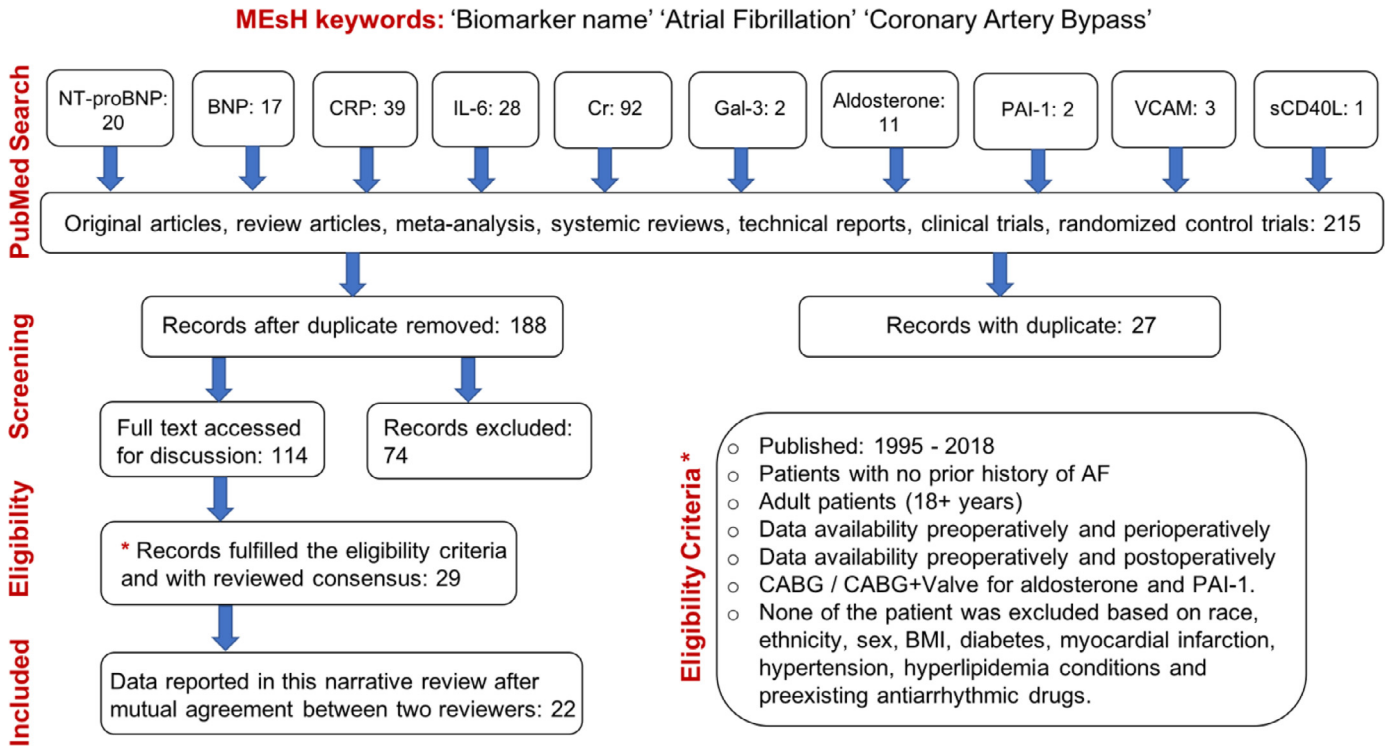

Fig 1. Flow diagram of selected studies included in this narrative review.

measurements of NT-proBNP levels among CABG patients with no prior history of AF may be useful in predicting POAF risk.[27]

Schachner et al. conducted a large patient study (n = 819) and found that patients who had CABG surgery with preoperative NT-proBNP level >502 pg/mL were at higher risk of POAF (n = 306) in comparison with those (<430 pg/mL) who remained in SR (n = 513).[27] Gasparovic et al. measured preoperative NT-ProBNP levels for 215 patients in SR undergoing CABG[20] and noted significantly lower concentration of preoperative NT-ProBNP in the subset of patients that maintained stable SR (273 ± 347 pg/mL, n = 160) in comparison to those who developed POAF (469 ± 629 pg/mL, n = 55; $p < 0.0001$). Pretorius et al. reported the perioperative values for NT-proBNP in 253 patients.[28] NT-proBNP level was low in 73.5% of patients who remained in SR after cardiac surgery, compared with those who developed POAF (182.0 ± 30.6 pg/mL *v* 248.2 ± 63.2 pg/mL, respectively, p = 0.001).[28] Unlike Gasparovic et al., the blood samples collected in the Pretorius et al. study were obtained immediately after separation from cardiopulmonary bypass (CPB) and processed utilizing the multiplex LINCOplex immunoassay. Thus, besides the patient risk factors and demographic information, the time required to process the collected preoperative samples is very critical in order for biomarkers to have practical utility to predict POAF. Cuthbertson et al. reported that the level of LV systolic function highly affects the preoperative NT-proBNP concentration in patients undergoing CABG surgery.[29] They reported that patients (n = 732) with normal LV systolic dysfunction had a median NT-proBNP level of 227 pg/mL (IQR 101-613). In comparison, those with mild systolic dysfunction had a median level of 468 pg/mL (IQR 159-1,136), those with moderate dysfunction had median levels of 614 pg/mL (IQR 263-1,356), and those with severe dysfunction had median levels of 818 pg/mL (IQR 565-9,098).

BNP is a well-known predictive biomarker in both acute coronary syndrome and ambulatory HF patients and thus, also has been recognized as an indicator of cardiac function.[30] In the setting of CABG surgery specifically, increased BNP is significantly associated with more recurrent unfavorable in-hospital cardiovascular events, and all-cause mortality after discharge.[31] Other studies reported that preoperative BNP levels among CABG patients may be valuable in predicting postoperative HF hospitalization or death and decreased longer-term physical function.[32,33] However, these reports did not elaborate on whether the patients had any pre-existing AF. Cuthbertson et al. reported a small study with 40 patients who had no prior record of AF.[34] They found a high preoperative BNP level in 27.5% of patients who developed POAF, compared with those who remained in SR after CABG procedure (310 pg/mL [IQR 177-443] *v* 82 pg/mL [IQR 51-149], respectively, p = 0.001).[34] In another study (n = 187) conducted in patients with no AF history by Wazni et al., preoperative BNP concentration for CABG patients was measured to be 615 pg/mL (IQR 265-940) and 444 pg/mL (IQR 107-707) for patients with and without POAF, respectively (p = 0.005).[35] BNP levels reported by Wazni et al. are about 2 times higher in comparison with the study reported by Cuthbertson et al. These differences could be owing to patients' clinical risk factors including age, left atrial diameter, left ventricular ejection fraction, chronic obstructive pulmonary disease, hypertension, and myocardial infarction, as identified by Yamashita et al. in their meta-analysis study of POAF in cardiac surgery patients.[36]

CRP and Il-6

Both CRP and IL-6 are inflammatory biomarkers and were claimed as independent POAF predictors among CABG patients. CRP is a plasma protein found in secretory cells (monocytes) and migrates to the injury site upon stimulation from stress or trauma.[37] The risk of developing POAF in both CPB and off-pump CABG surgery is significantly higher in patients with a high baseline CRP level (>3 mg/L).[38] A large study (n = 5,491) including patients with no prior AF history reported by Aviles et al. revealed the possibility of utilizing the CRP level as a predictor for the presence of AF after off-pump CABG.[39] The median CRP value of 1.92 mg/L (IQR 0.97-3.41) was measured based on 897 subjects who developed POAF. It has been noted that subjects in higher quartiles of CRP had a more adverse event risk profile. In their report, the risk for AF was progressively higher with increasing CRP quartiles. For instance, the CRP level was higher among subjects with AF (median 2.41 mg/L, IQR 1.29-5.02 *v* 1.89 mg/L, IQR 0.95-3.37; $p < 0.001$). Further, elevated levels for CRP (>1.5 mg/L) and IL-6 (>2.2 pg/mL) were found to be a significant independent risk factor for the occurrence of POAF among patients with an increased waist circumference (>102 cm).[40]

IL-6 is a proinflammatory cytokine that plays an important role in the inflammatory cascade and also is associated with the higher risk of POAF.[41] Pretorius et al. examined biomarkers in 253 patients who underwent on-pump CABG and 26% of patients who developed POAF incidence.[28] In their work, perioperative IL-6 level was almost twice in the POAF group than in those patients who did not develop POAF (380.6 ± 151.1 pg/mL *v* 174.8 ± 16.9 pg/mL). These perioperative samples were obtained immediately after separation from CPB and analyzed using multiplex LINCOplex biomarker immunoassays. In a smaller study with 71 patients with no prior history of AF conducted by Canbaz et al.,[23] the preoperative level of CRP was found to be 23 ± 17 mg/L in 18% of patients who developed POAF, compared with those who stayed in SR after CABG procedure POAF (17 ± 14 mg/L, $p < 0.05$). The same study also reported the preoperative IL-6 level in POAF patients and was found to be 11 ± 19 mg/L, which also was slightly higher in comparison with those who did not develop any POAF (9 ± 11 mg/L), $p < 0.05$.[23] However, the data reported in their study was significantly higher in comparison with the study conducted by Ucar et al. with 49 patients.[22] The preoperative CRP concentration in Ucar et al. was measured to be 0.3 ± 0.2 mg/L and 0.6 ± 0.2 mg/L for patients without POAF and with POAF, $p = 0.03$, respectively. The preoperative IL-6 concentration was measured to be 6.2 ± 2.9 pg/mL and 7.4 ± 3.6 pg/mL for patients without POAF and with POAF ($p = 0.24$), respectively. They also have reported postoperative CRP and IL-6 levels before POAF onset (16.9 ± 1.9 mg/L and 36.9 ± 15.9 mg/L for no-POAF *v* 22.4 ± 4.1 pg/mL and 100.7 ± 65.8 pg/mL for POAF). Cut-off points for postoperative first day IL-6, preoperative CRP, and postoperative first day CRP were 46.4 pg/mL with sensitivity of 92.9% and specificity of 80%, 0.46 mg/L with sensitivity of 71% and specificity of 75%, and 17.9 mg/L with sensitivity of 92.9% and specificity of 78%, respectively. A stepwise multivariate analysis conducted by Choi et al. demonstrated that continuously elevated perioperative levels of CRP and IL-6 over the time immediately after surgery also can be used as a predictor for the possible development of POAF at day 1.[21] In this study, among 315 CABG patients, 21% of patients developed POAF and their preoperative level of CRP was higher in comparison with those who remained in SR after surgery (0.66 ± 1.27 *v* 0.47 ± 1.14 mg/dL, $p = 0.25$). On the other hand, a small study (n = 19) conducted by Bruins et al. reported a low preoperative CRP level of 0.23 mg/L (IQR 0.15-0.47) among CABG patients who developed POAF (37%) in comparison with 0.33 mg/L (IQR 0.15-0.47) in those who did not develop POAF.[42] Another clinical study reported by Gasparovic et al. measured both the preoperative and postoperative CRP levels for 215 patients.[20] They noted CRP values increased from 6 ± 13 to 163 ± 88 mg/L ($p < 0.0001$) in the SR group and 6 ± 16 to 163 ± 104 mg/L ($p < 0.0001$) in the POAF group. All samples were analyzed using the Olympus AU 2700 clinical chemistry platform. However, their data did not show any significant difference in both cases (POAF *v* no-POAF).

There are other reported studies that determined that the elevated CRP levels were independent risk factors for the incidence of POAF.[39,43] However, based on aforementioned reports, a large standard deviation has been noted in both CRP and IL-6 levels and a significant variation also has been identified among different reports. Further, postoperative biomarker data presented in these and many other studies could be helpful from a research perspective but may not provide any predictive utility, as in many cases this timeline overlaps the onset of POAF. More research with a large patient cohort will likely be needed in CABG patients with no prior history of AF to determine conclusively if CRP and IL-6 can be utilized as effective POAF risk predictors.

Serum Cr

With the increasing age of cardiac surgery patients, and with increasing amounts of diabetes, hypertension, congestive heart failure, and arteriosclerotic disease, the amount of patients with decreased renal function is inevitably increasing.[44] Patients with a mildly increased preoperative level of serum Cr have a higher risk of developing POAF risk in the intensive care unit, and consequently, prolonged stay in the hospital as a result from POAF.[44] Previous studies have shown that preoperative renal failure with Cr level >2.5 mg/dL (>221 μmol/L) has a significant impact on early and late AF in patients undergoing CABG surgery.[45] Studies have shown that in-hospital mortality has been associated with high preoperative and postoperative Cr.[46] Alexandre et al. conducted a study with 137 patients undergoing CABG to evaluate the effectiveness of preoperative serum Cr level predicting POAF risk.[24] In their work, 24.8% patients developed POAF and the reported preoperative Cr level among POAF patients was 1.15 ± 0.45 mg/dL (101.4 ± 39.8 μmol/L) in comparison with those who did not develop POAF (0.96 ± 0.26 mg/dL [84.6 ± 23.2 μmol/L], $p < 0.05$). Another study conducted by Gasparovic et al. measured preoperative Cr level

for 215 patients in SR undergoing CABG and found lower concentration in the subset of patients that maintained stable SR after cardiac surgery (1.16 ± 0.28 mg/dL [103 ± 25 μmol/L]) in comparison to those who went on to develop immediate POAF (1.29 ± 0.41 mg/dL [114 ± 36 μmol/L], p = 0.12).[20] Thoren et al. reported one of the largest studies on the prediction of POAF in 7,115 CABG patients based on Cr level and other factors such as male sex, New York Heart Association class III/IV, current smoking, prior myocardial infarction, and the absence of hyperlipidemia. Among 2,270 (32%) patients who developed POAF condition, about 43% showed a much higher preoperative serum Cr level of ≥1.69 mg/dL (150 μmol/L) in comparison to 3.2% of the total patient population. Further, from 4,845 (68%) patients who were at SR after cardiac surgery, only 129 patients (2.7%) showed a high preoperative Cr level of 1.69 mg/dL. Based on preoperative cut-off value of Cr ≥1.69 mg/dL (150 μmol/L), receiver operating characteristic curve for POAF prediction after CABG showed the area under the curve of 0.62.[47] Mirhosseini et al. conducted a cross-sectional study in 200 nondiabetic male patients undergoing elective off-pump CABG surgery. Patients with POAF (n = 100) and without POAF (n = 100) were included in the study.[48] Their preoperative serum Cr (3 days before surgery) was 1.8 ± 0.3 mg/dL (159.12 ± 26.52 μmol/L) and 1.0 ± 0.2 mg/dL (88.4 ± 17.68 μmol/L) in POAF and no-POAF groups. However, they did not observe the increased level in Cr on the day of surgery, and reported as 1.6 ± 0.2 mg/dL (141.44 ± 17.68 μmol/L) and 1.1 ± 0.5 mg/dL (97.24 ± 44.2 μmol/L), respectively. Radmehr et al. conducted a study with 892 patients[49] and they indicated that 21.8% of patients with the mild increased level of Cr 1.3-2.2 mg/dL (114.92-194.48 μmol/L) were at the high POAF risk in comparison with those who did not develop POAF and maintained lower Cr level of 0.5-1.2 mg/dL (44.2-106.08 μmol/L), p = 0.001. Although high serum Cr level has been shown to be a good candidate for prediction of POAF among patients with no prior AF history, further research is required in a large CABG patient cohort to study the significance of preoperative and perioperative Cr levels.

PAI-1

PAI-1 is an acute-phase reactant and serves as the primary inhibitor of a tissue-type plasminogen activator.[50] The increased PAI-1 promotes fibrosis and reduces extracellular matrix turnover, which can alter the physiology of atrial substrate and possibly lead to a high risk of POAF after cardiac surgery.[51] In a study of 100 patients conducted by Fawzy et al., preoperative PAI-1 level was significantly higher in patients who developed POAF (28%) than those with no POAF (8.5 ng/mL, IQR 2.3-17.5 *v* 21 ng/mL, IQR 12-34, p < 0.01).[52] PAI-1 showed a sensitivity of 71.43% and a specificity of 70.83% at preoperative cut-off value of 15 ng/mL in predicting POAF. Pretorius et al. enrolled 253 adult patients with normal SR before on-pump CABG.[28] In their study, in patients who developed POAF (26.5%), the level of preoperative PAI-1 was slightly higher in collected blood samples in comparison with patients who stayed in SR (29.0 ± 2.1 ng/mL *v* 24.3 ± 0.9 ng/mL, p = 0.036). The PAI-1 level among patients who developed POAF is almost 3.2 times higher (29.0 ± 2.1 *v* 8.5 ng/mL) in comparison with the study published by Fawzy et al.[52] Based on these small patient cohort studies, it is not possible to determine the predictive power of PAI-1 levels to identify patients at highest risk for POAF. A large patient cohort study will add more power to determine the usefulness of PAI-1 in both preoperative and perioperative serum samples of those with no prior history of AF.

Soluble Vascular Endothelial Cells Adhesion Molecule-1

Soluble vascular endothelial cells adhesion molecule-1 (sVCAM-1) gene expression is regulated by the transcription factor nuclear factor-kappa B, which may be activated by tumor necrosis factor-α and reactive oxygen species.[53] The release of sVCAM-1 into the circulation has been associated with a number of cardiovascular disease processes including human POAF.[54] Harling et al. conducted a study with 34 patients with no prior history of AF to investigate whether the recorded changes in serum sVCAM-1 follow the development of POAF.[55] Preoperative sVCAM-1 level was significantly higher (>763.5 pg/mL) in 38.2% of patients developing POAF when compared with no-POAF (587.7 pg/mL), p = 0.022. However, no significant difference was observed in postoperative sVCAM-1 levels between the POAF and no-POAF groups (p = 0.073 and 0.135, respectively).[55] Receiver operating characteristic analysis revealed that at cut-off of 763.5 ng/mL, sVCAM-1 had a sensitivity of 60.0% and specificity of 77.27%, with an overall diagnostic accuracy of 75.2% in predicting POAF. Thus, it would be beneficial to establish a new study to record sVCAM-1 level preoperatively and immediately after the cardiac surgery. In another small study conducted by Canbaz et al. with 71 patients, 13 patients (18.3%) developed POAF after on-pump CABG surgery.[23] The preoperative sVCAM-1 level was higher in POAF patients than those who remained in SR (902 ± 320 ng/mL *v* 797 ± 293 ng/mL, p < 0.05). The presented data showed significant variations and did not reveal any details whether the samples were collected immediately after the surgery. Based on these evidences, a large patient cohort study is highly recommended to validate the broad clinical applicability of sVCAM-1 as an independent predictor of POAF in CABG patients with no prior AF history.

sCD40L

sCD40L is a proinflammatory and prothrombotic molecule, belonging to the tumor necrosis factor superfamily.[56] Elevated sCD40L has been found in various cardiovascular conditions that are associated with AF.[57] Indeed, evidence suggests that sCD40L reflects overall platelet activation, in particular, in patients with coronary atherosclerosis.[58] Increased levels of sCD40L would be associated with an increased risk of microthrombi formation and related ischemia after surgery.[59] In those patients with pre-existing AF, sCD40L level surpassing 476 pg/mL had a nearly 5-fold higher likelihood of suffering a vascular event.[60] However, the association between an increased sCD40L concentration and the postsurgery AF development was not consistently demonstrated in case-control studies.[61] To find the sCD40L levels in patients

with no prior record of AF and who underwent off-pump CABG surgery, Antoniades et al. measured sCD40L levels in 144 patients the day before the surgery.[62] Preoperative sCD40L levels were significantly higher in 29.9% of patients who developed POAF, compared with those who remained in SR (1.89 ng/mL with IQR 1.21-2.97 *v* 0.98 ng/mL with IQR 0.63-1.31). Nevertheless, this was the only study that reported sCD40L levels of patients undergoing off-pump CABG surgery with no prior record of AF. Thus, increased sCD40L level might be used as an independent predictor of POAF development after CABG. However, further work is needed to acquire preoperative and perioperative sCD40L levels in a large patient population and compare the outcome of the 2 groups (patients with POAF *v* without POAF).

Aldosterone and Galectin-3

Aldosterone promotes myocardial inflammation and fibrosis, modulation of ionic currents and induces oxidative stress, and therefore can create a substrate for the development of POAF.[63] Similarly, Galectin-3 (Gal-3), a galactoside-binding lectin, has gained much attention as a novel biomarker of cardiac fibrosis and myocardium remodeling in HF.[24] Chequel et al. presented evidence that the renin–angiotensin-aldosterone system and Gal-3 could be very useful predictive biomarkers of POAF and potentially interesting therapeutic targets to prevent POAF occurrence.[64] Alexandre et al. conducted a study with 137 patients (109 with CABG and 28 with CABG + aortic valve replacement) in which POAF occurred in 34 (24.8%) patients.[24] Preoperative aldosterone levels were higher in the POAF group compared with the no-POAF group (183 pmol/L [IQR 138-300] *v* 143 pmol/L [IQR 96.5-216.5] with $p < 0.01$) respectively. With a cut-off value of >155 pmol/L, aldosterone revealed 67.0% specificity and 79.4% sensitivity to predict POAF. In the same study, they further evaluated the usefulness of preoperative plasma Gal-3 levels among patients with no prior AF history and identified the risk of predicting POAF. In their finding, they concluded that Gal-3 levels were only available in a subgroup of 29 patients (14 with POAF, 15 with no-POAF). In the POAF group (48.3%), the median preoperative Gal-3 level was 14.5 ng/mL (IQR 9.2-15.6), whereas, in the no-POAF group, the median Gal-3 level was 7.4 ng/mL (IQR 5.5-8.3) with $p < 0.002$.[24] Interestingly, in this subgroup, plasma aldosterone levels also were higher in the POAF group in comparison with the no-POAF group, 294.5 pmol/L (IQR 190.5-381) *v* 96.0 pmol/L (66.5-120.0), $p < 0.0001$. Thus, carefully conducted studies involving a larger number of patients, excluding those with a history of AF, to confirm whether Gal-3 and aldosterone reflect the prediction of POAF are highly recommended. Further, the differences in methods utilized in analyzing the samples could cause intrainstitutional variability. In addition to drawing the preoperative blood at different time intervals, underpowered studies with a small patient cohort could cause major differences in the results.

Conclusion

This review compiles available literature on selected preoperative and perioperative biomarkers that were used to evaluate patient POAF risk after either on-pump or off-pump CABG surgery. As shown in Table 1, studies summarized in this review were those that only included patients with no previous history of AF. However, a large standard deviation in dataset within the individual studies and a significant variation among different studies were seen in most of the investigated biomarkers, thereby limiting their clinical utility to predict POAF risk with high accuracy. Preoperative cut-off values of selected biomarkers in patients who did not develop POAF condition after cardiac surgery are shown in Table 2. Antiarrhythmic therapy for all patients undergoing cardiac surgery has been proposed as a justifiable precaution given the risks associated with POAF. Various studies have investigated the use of b-blockers, amiodarone, or magnesium to prevent POAF,[66,67] but these approaches have not been adopted widely owing to the risk of giving these drugs with known side effects to a particularly vulnerable population of cardiac surgery patients. POAF remains a substantially morbid, mortal, and socioeconomic problem, and it is critical that improved strategies with high accuracy be developed to identify patients at high risk in order to develop personalized treatment strategies possibly including prophylactic interventions, closer monitoring, and minimizing the risk of developing long-term AF. Rate control and rhythm control also have been studied to investigate POAF and may provide information to improve clinical decision-making for this highly prevalent condition.[68]

Though numerous studies have been reported and claimed that NT-ProBNP, BNP, CRP, IL-6, Cr, and PAI-1 could be utilized as POAF risk predictors, their preoperative results differed significantly. Conversely, VCAM-1, sCD40L, Gal-3, and aldosterone have shown promise for better POAF prediction. Unfortunately, the current dataset for these biomarkers are not of sufficient size to validate the broad clinical application of these biomarkers specifically for patients with no prior history of AF. It also was noted that recording these biomarkers postoperatively during POAF on days 2 and 3 do not provide predictive value because this timeline overlaps with the typical onset of POAF.

Furthermore, the authors suggest the following steps for future clinical trials to test the validity of aldosterone, NT-proBNP, Cr, sVCAM, Gal-3, and sCD40L:

1. Multivariate and multicenter analyses are warranted to develop large CABG patient datasets (>1,000).
2. Patients with no prior history of AF must be enrolled prospectively.
3. Patients must have consented regardless of race, ethnicity, sex, body mass index, diabetes, chronic obstructive pulmonary disease, hypertension, hyperlipidemia, peripheral vascular disease, peripheral artery disease, myocardial infarction, percutaneous coronary intervention, transient ischemic attack, and coronary artery disease.
4. For each patient, preoperative antiarrhythmic drug and left ventricular ejection fraction must be reported.
5. Patient blood samples must be collected preoperatively (24 h and 6 h before surgery) and perioperatively (during surgery before bypass).
6. Same technique (enzyme-linked immunosorbent assay, flow cytometry, etc) must be utilized to process and analyze the patient samples.

Table 1
Preoperative and Perioperative Biomarkers Collected From CABG Patients With No Prior History of AF

Ref.	Biomarker Type	Total Patients	POAF Patients (%)	Surgery (CABG)	Preoperative		Postoperative/Perioperative	
					Patients Without POAF	Patients With POAF	Patients Without POAF	Patients With POAF
[27]	NT-proBNP	819	37.4	On-pump	<430 ng/mL	>502 pg/mL	NA	NA
[20]	NT-proBNP	215	26	On-pump	273 ± 347 pg/mL	469 ± 629 pg/mL	3,110 ± 3,600 pg/mL	4,625 ± 5,640 pg/mL
[65]	NT-proBNP	253	26.5	On-pump	NA	NA	182.0 ± 30.6 pg/mL*	248.2 ± 63.2 pg/mL*
[29]	NT-proBNP	252	29.8	Off-pump	120-289 pg/mL	NA	246 pg/mL (IQR105-747)	388 pg/mL (IQR 150-1004)
[35]	BNP	187	42.8	NA	444 pg/mL (IQR 107-707)	615 pg/mL (IQR 265-940)	NA	NA
[34]	BNP	40	27.5	NA	82 pg/mL (IQR 51-149)	310 pg/mL (IQR 177-443)	157 pg/mL (IQR 82-225)	214 pg/mL (IQR 89-433)
[42]	CRP	19	36.8	On-pump	0.33 mg/L (IQR 0.15-0.47)	0.23 mg/L (IQR 0.15-0.47)	65 mg/mL (IQR 50-75)	51 mg/L (IQR 42-76)
[23]	CRP	71	18.3	On-pump	17 ± 14 mg/L	23 ± 17 mg/L	45 ± 17 mg/L	53 ± 17 mg/L
[21]	CRP	315	20.9	Off-pump	0.47 ± 1.14 mg/dL	0.66 ± 1.27 mg/dL	NA	NA
[22]	CRP	49	28.5	On-pump	0.3 ± 0.2 mg/L	0.6 ± 0.2 mg/L	16.9 ± 1.9 mg/L	22.4 ± 4.1 mg/L
[20]	CRP	215	25.6	On-pump	6 ± 13 mg/L	6 ± 16 mg/L	163 ± 188 mg/L	163 ± 104 mg/L
[40]	CRP	294	50†	On-pump	NA	>1.5 mg/mL†	NA	NA
[22]	IL-6	49	28.5	On-pump	6.2 ± 2.9 pg/mL	7.4 ± 3.6 pg/mL	36.9 ± 15.9 pg/mL	100.7 ± 65.8 pg/mL
[23]	IL-6	71	18.3	On-pump	9 ± 11 pg/mL	11 ± 19 pg/mL	27 ± 37 pg/mL	38 ± 36 pg/mL
[40]	IL-6	294	50†	On-pump	NA	>2.2 pg/mL†	NA	NA
[65]	IL-6	253	26.5	On-pump	3.3 ± 0.9 pg/mL	2.7 ± 0.5 pg/mL	174.8 ± 16.9 pg/mL*	380.6 ± 151.1 pg/mL*
[24]	Creatinine	137	24.8	On-pump	84.6 ± 23.2 μmol/L	101.4 ± 39.8 μmol/L	NA	NA
[47]	Creatinine	7115	32	On/Off-pump	NA	≥150 μmol/L	NA	NA
[49]	Creatinine	892	27.8	On-pump	44.2-106 μmol/L	114.9-194.5 μmol/L	NA	NA
[20]	Creatinine	215	25.6	On-pump	103 ± 25 μmol/L	114 ± 36 μmol/L	NA	NA
[52]	PAI-1‡	100	28	On-pump	8.5 ng/mL (IQR 2.3-17.5)	21 ng/mL (IQR 12-34)	12 ng/mL (IQR 6.7-23.0)	43 ng/mL (IQR 29.5-54.5)
[65]	PAI-1	253	26.5	On-pump	24.3 ± 0.9 ng/mL	29.0 ± 2.1 ng/mL	14.6 ± 0.7 ng/mL*	17.2 ± 1.2 ng/mL*
[55]	VCAM-1	34	38.2	On-pump	<587.7 ng/L	765.5 ng/L	NA	NA
[28]	VCAM-1	253	26.5	On-pump	NA	NA	476.4 ± 12.4 ng/mL*	514.5 ± 28.8 ng/mL*
[23]	VCAM-1	71	18.3	On-pump	797 ± 293 ng/mL	902 ± 320 ng/mL	924 ± 424 ng/mL	1,021 ± 351 ng/mL
[24]	Aldosterone§	137	24.8	On-pump	143 pmol/L (IQR 96.5-216.5)	183 pmol/L (IQR 138-300)	NA	NA
[24]	Galectin-3‖,	29	48.3	On-pump	7.4 ng/mL (IQR 5.5-8.3)	14.5 ng/mL (IQR 9.2-15.6)	NA	NA
[24]	Aldosterone‖,	29	48.3	On-pump	96 pmol/L (IQR 66.5-120)	294.5 pmol/L (IQR 190.5-381)	NA	NA
[62]	sCD40L	144	29.9	Off-pump	0.98 ng/mL (IQR 0.63-1.31)	1.89 ng/mL (IQR 1.21-2.97)	1.97 ng/mL (IQR 1.21-3.22)	5.62 ng/mL (IQR 3.93-5.94)

Abbreviations: BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CRP, C-reactive protein; Il-6, interleukin-6; Gal-3, Galectin-3; IQR, interquartile range; NA, data not available; NT-proBNP, N-terminal pro B-type natriuretic peptide; PAI-1, plasminogen activator inhibitor-1; POAF, postoperative atrial fibrillation; sCD40L, soluble CD40 ligand; VCAM-1, vascular cell adhesion molecule-1.

* Indicates data were recorded from blood samples collected immediately after separation from CPB.

† Indicates nested case study: 147 patients among 2,214 were recruited who developed POAF. The presented data were compared with 147 patients as control (no POAF). Thus, 50% designated as POAF group with waist circumference of >102 cm.

‡ Indicates CABG: 59 patients (20 with POAF), Valve (mitral/aortic/tricuspid): 38 patients (7 with POAF) and CABG + Valve patients: 3 (1 with POAF).

§ Indicates total patients: 137, CABG patients: 109 (27 with POAF), CABG + aortic valve replacement patients: 28 (7 with POAF).

‖ Indicates a subgroup of 29 patients who were considered in to access the outcome for Gal-3 and aldosterone.

Table 2
Preoperative Cut-off Value of Selected Biomarkers in Patients Who Did Not Develop POAF Condition After Cardiac Surgery

Ref.	Biomarker Type	Preoperative Cut-off Value
[29]	NT-proBNP	204 (120-289) ng/L
[34]	BNP	82 (51-149) pg/mL
[42]	CRP	0.33 (0.15-0.47) mg/L
[22]	IL-6	6.2 (3.3-9.1) pg/mL
[49]	Creatinine	44.2-106 μmol/L
[55]	sVCAM	587.7 ng/mL
[24]	Gal-3	7.4 (5.5-8.3) ng/mL
[52]	PAI-1	8.5 (2.3-17.5) ng/mL
[24]	Aldosterone	143 (96.5-216.5) pmol/L
[62]	sCD40L	0.98 (0.63-1.31)

Abbreviations: BNP, B-type natriuretic peptide; CRP, C-reactive protein; Gal-3, Galectin-3; IL-6, interleukin-6; NT-proBNP, N-terminal pro B-type natriuretic peptide; PAI-1, plasminogen activator inhibitor-1; sCD40L, soluble CD40 ligand; sVCAM, soluble vascular endothelial cells adhesion molecule-1.

7. Pre- and perioperative data must be reported in SI units for consistency.
8. At the end of each study, positive/negative predictive value for all the biomarkers must be highlighted.
9. Patients must be classified as "POAF" for those who will develop AF within 6 days after cardiac surgery and "no-POAF" for those who will remain at SR after cardiac surgery.
10. A regression model must be developed to study the outcome of these biomarkers individually and collectively.

In addition, more comprehensive models will need to be developed that could create risk scores based on the compilation of clinical characteristics and, perhaps, an array of biologic markers.

Conflict of Interest

Authors declare no conflict of interest.

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