Review

Determinants of atrial fibrillation after cardiac surgery

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Post-operative Atrial fibrillation (POAF) is a common complication post cardiac surgery. It can result in detrimental short- and long-term outcomes due to the increased risk of stroke, cardiac arrest and congestive heart failure in addition to prolonged intensive care and total hospital stay raising the overall healthcare cost. Accurately identifying predictors and biomarkers for POAF ensures that patients at greatest risk can be given the appropriate prophylactic measures; resources can be distributed to the groups who are most in need and where they will gain the optimum effect. Commonly recurring predictors can be investigated further to unveil the pathophysiology behind POAF, which has yet to be fully understood. This literature review aims to examine relevant studies on the proposed predictors of POAF: increased age, gender, history of atrial fibrillation, hypertension, cardiopulmonary bypass time and the use of beta blockers amongst others. This paper will discuss the significance of both the well-known and newfound risk factors to consolidate the areas that require further exploration in order to highlight those at risk and to unravel the mechanism behind POAF.

Keywords

Heart; Surgery; Outcome; Results

1. Introduction

Post-operative atrial fibrillation (POAF) refers to a new onset of atrial fibrillation, developing immediately post-surgery [1]. POAF can be classified into different groups: acute, paroxysmal, persistent or permanent [2], depending on the character of the tachycardia. It is estimated that 20–40% of cardiac surgeries are complicated by POAF [1, 3, 4] and it has contributed to increased hospital stays and increased risk of morbidities and mortality rate [5]. Typically, post-operative atrial fibrillation presents within the first four hours of the peri-operative period [1]. However, two time periods have been identified as maximum risk for onset of POAF. The first is thought to be within 18 hours of the surgery [6] and the second is two days post-surgery [6], with a decline in the incidence four to seven days [6] post-surgery. It is believed that there are different predictors for the two peaks with advanced age being a common risk factor. Trauma and inflammation during surgery are assumed to create the first peak, whilst it is speculated that obesity and ethnicity contribute to the development of POAF in the second peak [6]. It should be noted that the way POAF is defined and monitored can significantly impact its detection which influences the reported incidence of POAF. As such, there is a greater detection rate of POAF when using continuous holter compared to a 12-lead ECG [2].

Despite the advances in surgical techniques and perioperative prophylactic drug trials, POAF remains the "most common adverse event" following cardiac surgery [7, 8]. CABG and valvular surgeries hold the greatest risk of developing POAF at 60–80%; they cause a greater scale of damage to the structural integrity of the heart via fibrosis and dilation of the valves and subsequently of the heart's chambers [3, 9]. Furthermore, the nature of CABG and valvular surgeries is such that they're more extensive and invasive so there is a greater likelihood of impinging on the electrophysiological network of the heart, leading to POAF [9]. The tachycardia consequently results in an increased risk of cardiac complications and thrombus formation, thus leading to an increased risk of stroke [10, 11]. Prevention of POAF is possible if appropriate predictors are monitored and managed through prophylactic therapies and lifestyle alterations. Fig. 1 is a summary of the predictors for POAF.

2. General pathophysiology

Understanding the pathophysiology of POAF is imperative in order to guide management and possible prophylaxis options. The underlying mechanisms behind POAF are not yet well understood, but it is widely accepted to be multifactorial, attributing it to factors such as inflammation, sympathetic activation, cardiac ischemia and electrolyte imbalances [1]. Surgery is a taxing feat on the body, it renders patients in a hypercoagulable state with an increased risk of bleeding and it leaves the body in a highly stressed state [3]. This leads to sympathetic activation with a subsequent increase in heart rate and catecholamine release, which leaves the myocardium in a more vulnerable state, more susceptible to arrhythmias [3]. Furthermore, administration of fluids intraoperatively and postoperatively, especially when creating a hypervolemic state, may lead to atrial stretching which may cause POAF

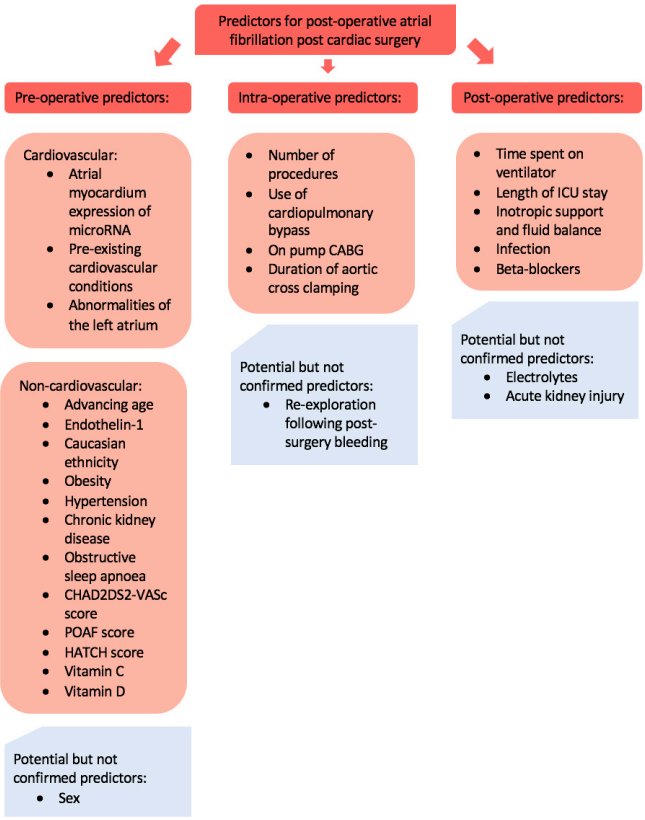

Fig. 1. Diagram categorising the predictors for POAF.

[3, 10]. POAF can arise as a result of hypoxia by two possible mechanisms: ischemia of the myocardium, reducing perfusion to the conduction system and pulmonary vein vasoconstriction which increases the pressure in the right atria and ventricle, leading to atrial stretch [10]. Fig. 2 is summary of the pathophysiology of POAF.

3. Cardiovascular pre-operative predictors

3.1 Atrial myocardium expression of microRNA

MicroRNAs(miRNA) regulate gene expression by binding to segments on the mRNA and preventing translation into the relevant protein [12]. Some miRNAs are involved with regulating the metabolic pathways in cardiomyocytes and so when these levels rise, they cause disruption to the cellular homeostasis and may predispose to an arrhythmia [12].

One study has discussed testing for atrial tissue microRNAs as a potential biomarker for POAF [12]. It was found that sixteen microRNAs in the atrial myocardium were expressed significantly differently (FC >1.5, $p < 0.05$) in those who acquired POAF compared to those who maintained sinus rhythm after undergoing an on- pump coronary artery bypass grafting procedure (CABG) [12]. However, only two of these sixteen microRNAs were investigated further, and so more widespread investigations need to be carried out in order to evaluate the impact of each of the sixteen microRNAs.

Using the microarray analysis technique, it was found that miR-483-5p was the most overexpressed (FC = 1.804, p = 0.0193) and miR-208a was the most under expressed (FC = 2.458, p = 0.0205) in the atrial tissue of the patients who developed POAF [12].

In order to verify these findings, a quantitative reverse transcription polymerase chain reaction (PCR) was carried out for the expression of miR-483-5p and miR-208a alone in serum samples taken pre-operatively, 48 hours post-operatively and 96 hours post-operatively [12].

In the preoperative serum samples taken, miR-483-5p was notably higher in those that went on to develop POAF when compared with the other cohort that maintained sinus rhythm (p = 0.0137) [12]. However, miR-208a was not detected at any point during the PCR analysis of the serum samples as it is specific to cardiomyocytes. This can exclude miR-208a as a potential serum biomarker for POAF. Moreover, miR-483-5p expression significantly increased 48 hours postoperatively in the group that developed POAF (p = 0.046) compared to the other group that displayed no significant change (p = 0.9507), showcasing the prolonged effects of a raised miR-483-5p preoperatively [12].

Receiver Operating Characteristic analysis has revealed that testing for the expression of miR-483-5p in preoperative serum, to predict the development of POAF has a 78% diagnostic accuracy (sensitivity and specificity of 77.78% and 77.27%) [12].

Other specific miRNAs that have been associated with the development of POAF include miRNA-23a and miRNA-26a. Samples were taken pre-operatively and post-operatively from patients undergoing a CABG procedure. It was found that circulating levels of miRNA-23a and miRNA-26a in the pre-operative serum were similar across those who did not develop POAF and those that did. However, there were significantly lower circulating levels of miRNA-23a (p = 0.02) and miRNA-26a (p = 0.01) in the post-operative serum of those that developed POAF [13]. Despite this study demonstrating that circulating miRNA can be used to identify those at risk of POAF, there was only a difference seen in the post-operative serums. Therefore, it may be able to categorise risk of POAF after surgery but not prior.

Therefore, a serum blood test prior to surgery screening for elevated plasma micro-RNA 483-5p may be valuable in identifying those who are more susceptible to developing POAF. This can be performed alongside other preoperative biomarkers that have been identified such as C-reactive protein (which has a lower diagnostic accuracy of 68%) [12].

One important limitation of the Receiver Operating Characteristic analysis is the relatively small patient cohort of thirty four patients [12]. A larger patient cohort should be recruited in order to strengthen the reliability of the study [12]. Further inquiry into the potential mechanism of POAF should be conducted to find the cause in expression which would further validate the findings [12].

3.2 Pre-existing cardiovascular conditions

Understanding the past medical history of a patient prior to cardiac surgery is crucial when evaluating the risk of devel-

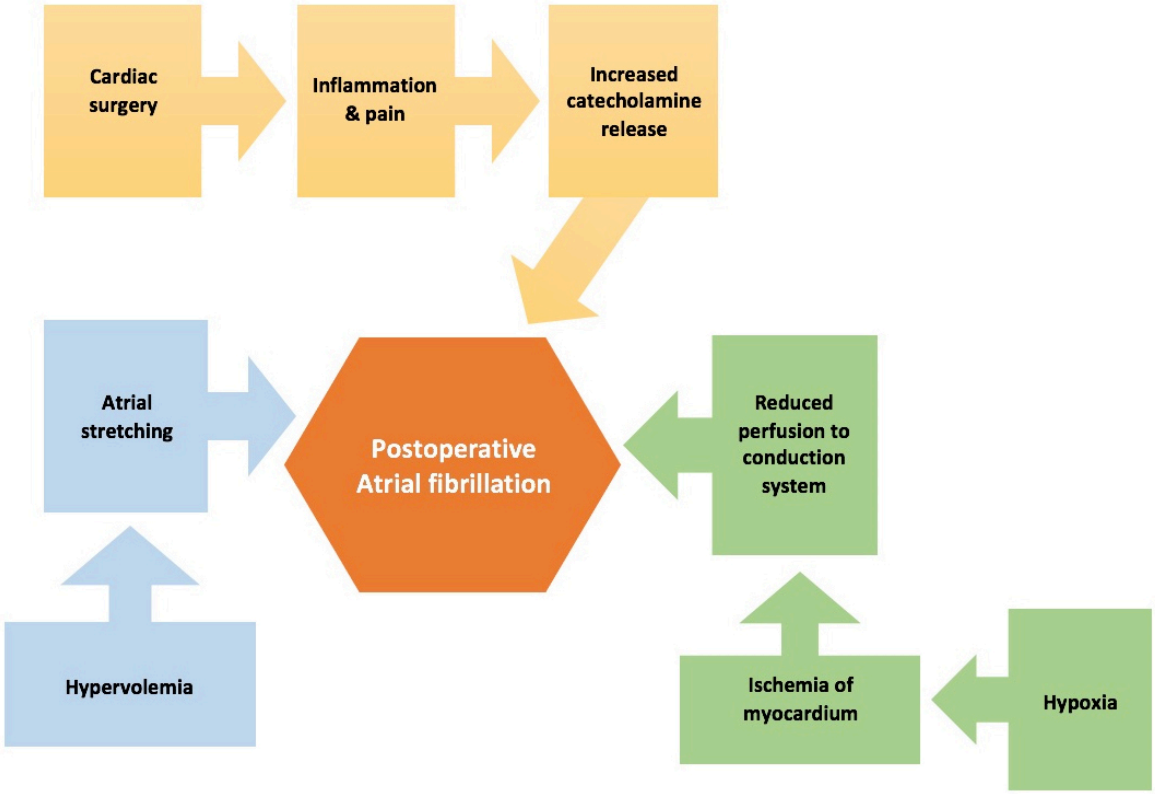

Fig. 2. Diagram outlining the pathophysiology of POAF.

oping POAF. This will identify pre-existing cardiovascular conditions such as heart failure, hypertension and myocardial infarction which have been found to be significant predictors of POAF incidence in a meta-analysis [14]. The study analysed 36,834 subjects from twenty-four studies: with a 28% incidence of POAF. The odds ratio for a history of heart failure were combined across eight studies to get a value of 1.56 (95% confidence interval (CI)) [14], in favour of the patients that did not have a history of heart failure. This suggests that a population with a history of heart failure are 56% more likely to develop POAF than their counterparts [14]. The pooling of odds ratios for hypertension and a history of myocardial infarction was then performed. Nineteen studies were analysed for hypertension data and found an average of 29% higher odds of POAF occurring in hypertensive patients compared to those without hypertension [14]. A history of myocardial infarction across ten studies found patients with a history of myocardial infarction are expected to have an 18% higher odd of POAF than those without [14].

Based on the odds ratios alone, heart failure is the best predictor of POAF to note from a medical history out of these three variables. However, the meta- analysis across the eight studies for history of heart failure has a high heterogeneity value (I^2 = 62%) [14] which means that there was a high variability between the studies. There was also a moderate heterogeneity in the meta-analysis analysing hypertension (I^2 = 39%) [14]. This proves that when generalising the cumulative results, it can prove difficult to obtain a conclusion which supports all individual findings. For example, one study found that a greater percentage of patients with hypertension developed POAF in comparison to the patients without hypertension, (73.3% vs. 42.6%, p = 0.029), suggesting hypertension to be an independent risk factor towards the development of POAF [15]. Other cardiovascular risk factors that have been identified include non-coronary vascular disease, coronary artery disease, left atrial enlargement [16], left ventricular dysfunction and a prior history of atrial fibrillation (AF) [5].

3.3 Abnormalities of the left atrium and ventricles

There were a multitude of risk factors that were found across the papers for POAF involving the left atrium such as: left atrial enlargement or an increased diameter of the left atrium [5, 14, 16, 17], higher left atrial volume index of $\geq$36 mL/m^2 (sensitivity of 84.6% and specificity of 68.6% in the cohort p = 0.006) [18] and reduced longitudinal left atrial strain [19, 20]. One study found that left atrial strain was significantly associated with the occurrence of POAF in those that had a normal left atrial volume index. The echocardiogram analysis found that the peak atrial contraction strain (PACS) and peak atrial longitudinal strain (PALS) were the only variables to have a strong correlation with the development of post-operative arrhythmias. In the multivariate analysis of PALS and PACS, the odds ratios were 0.73 and 0.72 respectively [20]. Other factors such as mean atrial or ven-

tricular volumes and left atrial enlargement were not deemed to be statistically significant predictors POAF [20]. This implies that PALS and PACS indexes can be strongly predictable of POAF undergoing an aortic valve replacement and can be routinely tested for using an echocardiogram [20].

In a retrospective study, pre-operative and post-operative ECGs were obtained along with an echocardiographic assessment to evaluate various functions of the heart. Many of the variables tested for were associated with POAF when the univariate analysis was performed, with right atrial volume index (RAVi) (odds ratio (OR): 5.7, 95% CI: 2.5–8.5, $p < 0.001$) and left atrium volume index (LAVI) (OR: 6.3, 95% CI: 4.2–8.3, $p < 0.001$) having the greatest odds ratios with POAF patients having higher volume indices [21]. This is closely followed by left atrial strain (LASr) (OR: 0.81, 95% CI: 0.69–0.95, $p < 0.001$) and right atrial reservoir function strain (RASr) (OR: 0.72, 95% CI: 0.61–0.84, $p < 0.001$) which tends to be reduced in POAF patients. On a further multivariate analysis; RAVI (OR: 3.1, 95% CI: 2.2–6.3, $p = 0.033$) and RASr (OR: 0.82, 95% CI: 0.67–0.93, $p = 0.048$) were both independently associated with POAF [21]. RAVi demonstrated a sensitivity of 86% and a specificity of 77% for the prediction of POAF in receiver operating characteristics (ROC) analysis [21]. In contrast to the previous study, a higher cohort sensitivity and specificity was recorded for LAVi [18]. This study indicates that it is not only left atrial dysfunction that can help predict the occurrence of POAF, but right atrial function and structure are just as important risk factors and could be screened for pre-operatively [21].

In a long term follow up of an ablation procedure, the documentation of AF before the procedure (OR: 3.53) along with previous use of flecainide (OR: 3.33) were independent risk factors for the occurrence of POAF after the procedure [17]. The previous use of flecainide (OR: 2.43) and pre- and intra-procedural AF (OR 3.81) also predicted additional need for ablation [17]. Flecainide is an antiarrhythmic medicine that is used to treat irregular heartbeats and has been found to be particularly effective in the treatment of Atrial fibrillation [22]. Using this evidence, it should be considered that any flecainide course of treatment should be stopped at least 5 half-lives prior to cardiac surgery or procedure [17], particularly ablation, to minimise the risk of POAF occurring. The same study also supports that left atrial diameter (OR: 2.96) is an independent risk factor for POAF. These variables all have a p value below 0.05 so are considered statistically significant [17]. A meta-analysis of sixteen papers has supported the claim that a history of atrial fibrillation, particularly a long duration and persistent AF, is a significant predictor for the occurrence following surgery in addition to increased left atrial diameter [16]. The hazard ratio, when compared to a reference group was 1.25 (95% CI: 1.12–1.3, $p < 0.0001$) [16] for increased left diameter and 1.10 (95% CI: 1.04–1.17, $p < 0.0009$) [16] for a long duration of AF. However, it should be noted that both of these studies investigated the occurrence of AF after an ablation procedure for atrial flutter so it should not be assumed that a history of AF is a predictor of POAF in all cardiac surgeries or procedures. However, supporting research that an increased atrial diameter is a predictor for POAF has been shown in an aforementioned meta-analysis. The standardised mean difference (SMD) between those who developed POAF and those who did not was significantly different for the variable 'left atrial diameter' (SMD = 0.45, 95% CI: 0.15–0.75) [14].

These papers suggest that left atrial function is likely to be impaired in those that are more at risk of developing POAF; one paper specifically finds that it is impaired excitation-contraction coupling in atrial myocytes that contributes to this [23]. A key finding was that the SERCA2a protein content was significantly reduced in those patients that developed AF after open-heart surgery compared to those that did not [23]. This was indicative of "reduced SERCA- mediated Ca^{2+} uptake into the sarcoplasmic reticulum" which may contribute to an increased susceptibility to atrial arrhythmogenesis as well as reducing atrial contractile function [23]. As a reduced SERCA protein content is recognised at reducing atrial contractility, this could be assessed prior to surgery as an independent risk factor for POAF. If there is reduced activity of SERCA channels detected, it could act as a potential target for drugs that can act as SERCA agonists; this will amplify SERCA activity, increase atrial contractility and therefore possibly reduce the chances of developing POAF [23].

Due to the large volume of supporting evidence that left atrial abnormalities are risk factors for developing atrial fibrillation post cardiac surgery [5, 14, 16, 18, 19, 23], it would be valuable to test for any abnormalities prior to surgery using an electrocardiograph [18, 23]. The importance of Speckle Tracking Echocardiography (STE) in prognosis and diagnosis is crucial as it can be used to evaluate myocardial function in many different clinical scenarios. Using this technique, the degree of myocardial deformation and dysfunction can be assessed. It is particularly valuable at assessing the atrial contractile function and the left atrial reservoir [24]. This is performed by evaluating peak atrial longitudinal strain (shown to be decreased in those who develop POAF) [19, 20] and peak atrial contractile strain (shown to be decreased in those who develop POAF) [23]. The technique can also identify any left atrial dilation and fibrosis which are often linked to the generation of AF [24].

A biomarker miRNA has been identified which suggests that a simple serum blood test can be performed on patients undergoing cardiac surgery to look for this predictor [12]. This combined with the research on 'altered atrial cytosolic calcium handling' [23] will contribute towards understanding the pathophysiology behind arrythmias, including POAF [25]. Fig. 3 outlines the association between left atria (LA) strain and development of POAF.

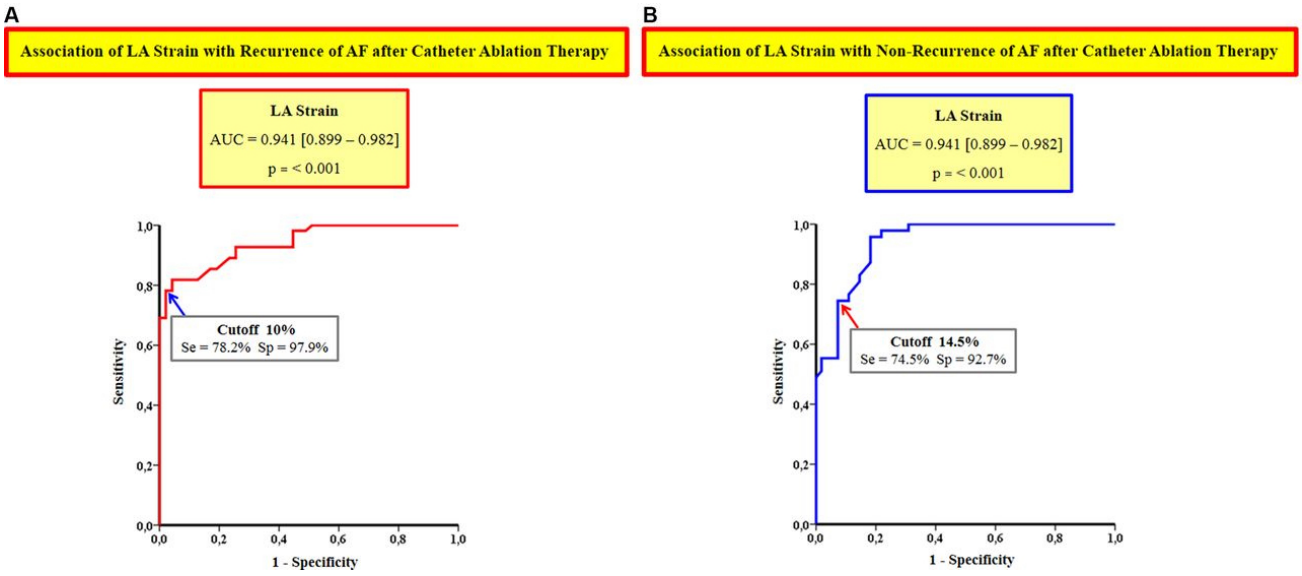

Fig. 3. Graphs displaying the association between left atria (LA) strain and POAF after catheter ablation therapy [26].

4. Pre-operative: non-cardiovascular predictors

4.1 Age

Advancing age is the most widely proven major predictor in the occurrence of POAF [27–31]. In patients aged 72 years or older, the risk of POAF is approximately five times greater than in patients who are aged 55 or younger [2]. In a study of 999 patients Todorov *et al.* [31] found age to be the most powerful predictor of POAF (OR = 1.448 per decade increase ($p < 0.0001$)). There are several theories that contribute to the theory behind increased incidence of POAF with advancing age: reduced efficacy in cardiac conduction; atrial fibrosis; increased likelihood of ischemia and reperfusion injury; build-up of oxidative stress and scarring from cardiac surgeries [2, 30].

4.2 Gender

Sex has also been found to play a role in POAF. Fragão-Marques *et al.* [32] conducted a study of 379 patients who underwent isolated AVR surgery. They used multiple logistic regression to look at gender-specific predictors of POAF and found an independent association between increased postoperative peak lactate and POAF in men and a lower mean aortic valve gradient with POAF in women (area under the curve (AUC) for the model = 0.77 [0.68–0.86] and 0.69 [0.60–0.78] for men and women, respectively) [32]. At a 4-year follow-up Fragão-Marques *et al.* [32] found that POAF was linked to increased risk of death in men but not in women. Conflicting results were obtained by Filardo *et al.* [33] who discovered that the effect of POAF on long-term survival after CABG surgery did not differ between the sexes. Filardo *et al.* [33] also found that the incidence of POAF after CABG surgery was 32.8% in men, and 27.4% in women. Over the 9-year period of their study they found that women had a significantly lower risk of POAF after CABG surgery (absolute difference, –5.3% (95% CI: –10.5% to –0.6%)), and that they had significantly shorter first (–2.9 hours, 95% CI: –5.8 to 0.0), and longest (–4.3 hours, 95% CI: –8.3 to –0.3) AF duration [33]. Evidence into male sex as a predictor for POAF is controversial. Thus, further research is required to explore the influence of gender on development of POAF before a conclusion is drawn [2].

4.3 Endothelin-1

A study of 80 people by Lu *et al.* [34] found that preoperative levels of plasma endothelin-1 (ET-1) were found to be significantly higher in patients who developed POAF compared to those who did not develop POAF (2.23 $\pm$ 0.67 vs. 1.68 $\pm$ 0.59 pg/mL, $p < 0.001$). They also found a positive correlation between left atrial diameter and plasma concentrations of ET-1 (Pearson's r = 0.421, $p < 0.001$) [34]. In a larger study of 118 patients by Song *et al.* [35], it was found that patients with higher plasma big endothelin-1 levels were significantly more likely to develop POAF (0.41 $\pm$ 0.19 vs. 0.27 $\pm$ 0.14 pmol/L, $p = 0.001$). These initial studies look promising, but they are less representative of a population due to their small participant group; to strengthen the association between serum ET-1 levels and POAF further research is required on greater cohorts.

4.4 Ethnicity

Caucasian ethnicity has been found to be a predictor for POAF [5, 7, 36, 37]. A study by Efird *et al.* [37] of 13,594 patients undergoing first-time, isolated CABG found that POAF is significantly associated with white race (95% CI, $p < 0.0001$). Furthermore, there has been substantial evidence to suggest that there is a large genetic component to a person's risk of POAF, opening the potential for biomarkers to be used to predict POAF [38]. However, while the evidence is promising, the cohort sizes used for these studies are too small to be representative of a true population size thus more

Table 1. Potential biomarkers significant as predictors for POAF [12, 13, 19, 38–41].

Biomarker	Study referenced	Statistical significance (p value)
miRNA-483-5p	Elevated serum microRNA 483-5p levels may predict patients at risk of post-operative atrial fibrillation [12]	When compared to preoperative samples, there was a significant increase in the expression of miRNA-483-5p at the 48 hour postoperative time point in the POAF-group (p = 0.046). While in the non-POAF group, there was no significant change in serum expression in the samples collected preoperatively and 2 days postoperatively [12]
miRNA-29a	Non-invasive biomarker-based risk stratification for development of new onset atrial fibrillation after coronary artery bypass surgery [19]	Preoperative amino-terminal-procollagen-III-peptide (103.1 $\pm$ 39.7 vs. 35.1 $\pm$ 19.3; p = 0.041) and carboxy-terminal-procollagen-I-peptide levels were elevated in PoAF patients compared to non-PoAF patients with a reduction in miR-29 levels [19]
miRNA-23a and miRNA-26a	Analysis of Circulating miR-1, miR-23a, and miR-26a in Atrial Fibrillation Patients Undergoing Coronary Bypass Artery Grafting Surgery [13]	There were reduced expression levels for miRNA-23a (p = 0.02) and -26a (p = 0.01) in the POAF group during the postoperative period in comparison to preoperative results with receiver operating curve of 0.63 (confidence interval [CI]: 0.51–0.74) and 0.66 (95% CI: 0.55–0.77), respectively [13]
miRNA-199a	Altered expression of micro-RNA 199a and increased levels of cardiac SIRT1 protein are associated with the occurrence of atrial fibrillation after coronary artery bypass graft surgery [39]	miRNA-199a was lowered in 29 patients that developed POAF after surgery in comparison to 20 patients that remained in sinus (p = 0.022) [39]
Mitochondrial DNA (mtDNA)	Relation of Mitochondrial DNA Copy Number in Peripheral Blood to Postoperative Atrial Fibrillation After Isolated Off-Pump Coronary Artery Bypass Grafting [40]	In patients with POAF the mtDNA copy number was drastically higher (n = 101, 21%) than in those who remained in sinus following CABG procedure ($p < 0.001$) [40]
Single nucleotide polymorphisms (SNPs)	Polymorphism rs2200733 at chromosome 4q25 is associated with atrial fibrillation recurrence after radiofrequency catheter ablation in the Chinese Han population [41]	Allelic analysis was conducted and a strong association was found between rs2200733 and AF recurrence after ablation (p = 0.011) [41]

trials must be carried out with larger cohorts before a definitive conclusion is drawn (Table 1, Ref. [12, 13, 19, 38–41]) [38].

4.5 Modifiable risk factors

In the case of POAF, modifiable predictors include diseases such as obesity and a high BMI [29, 42, 43]. A meta-analysis by Phan *et al.* [43] found that patients who were obese were significantly more likely to develop POAF than the non-obese patients they were compared to (p = 0.006). Yamashita *et al.* [14] conducted a systematic review and meta-analysis and found a significant link between COPD and POAF (pooled odds ratio 1.36: 1.13–1.64). Yamashita *et al.* [14] also identified hypertension as a significant risk factor for POAF (pooled odds ratio 1.29: 1.12–1.48) [44]. Chronic kidney disease has also been found to be a significant risk factor by Musa *et al.* [45] who examined 637 patient records (adjusted OR: 2.124, 95% CI: 1.057–4.268, p = 0.034). Obstructive sleep apnoea has also been found to be a risk factor for POAF as a retrospective cohort study of 506,604 patients found that patients with OSA were more likely than non-OSA patients to develop POAF (OR = 1.04, 95% CI: 1.01–1.08) [46].

Chen *et al.* [47] conducted a meta-analysis including 18,086 patients and found that the CHAD2DS2-VASc score is an independent predictor of POAF (OR: 1.46; 95% CI: 1.25–1.72). Furthermore, Burgos *et al.* [48] led a study of 3113 patients and compared the performance of three scoring systems in calculating risk of developing POAF: HATCH score, POAF score and CHAD2DS2-VASc. It was found that the CHAD2DS2-VASc score had the greatest diagnostic ability (AUC-ROC was 0.77 (95% CI: 0.75–0.79)),whereas the POAF score had a moderate diagnostic ability, (AUC-ROC, 0.71 (95% CI: 0.69–0.73)) [48]. The HATCH score had the lowest diagnostic ability out of the three scoring systems contrasted (AUC-ROC = 0.70 (95% CI: 0.67–0.72))[48]. This signifies that the most discriminative test to use was the CHAD2DS2-VASc score. Moreover, inferring from this study, it can be concluded that implementing the CHAD2DS2-VASc score in clinical practice would be most useful as it was the most sensitive scoring system with sensitivity of 80% (95% CI: 76.85%–83.12%) in comparison to the POAF score (sensitivity of 62%, CI 95%: 58.38%–65.96%) and HATCH score (sensitivity of 58%, 95% CI: 53.75%–61.47%) [48]. Further studies critiquing and comparing the three scoring systems are required to identify the most useful scoring model.

Vitamin C has been found to be a predictor of POAF. In a systematic review and meta-analysis by Shi *et al.* [49] including thirteen trials involving 1956 patients Vitamin C was found to significantly reduce incidence of POAF both when used alone (RR: 0.75, 95% CI: 0.63–0.90, p = 0.002) and when used in addition to other therapies (statins or beta-blockers) (RR: 0.32, 95% CI: 0.20–0.53, $p < 0.001$). Taking Vitamin C

Table 2. Significant scoring models and their respected risk factors [48, 52, 53].

Risk factor	CHADSVASc score given	HATCH score given	POAF score given
Age 60–69			1
Age 65–74	1		
Age 70–79			2
Age >75	2	1	
Age ≥80			3
Female sex	1		
Stroke	2	2	
Congestive heart failure	1	2	
Hypertension	1	1	
Chronic obstructive pulmonary disease		1	1
Diabetes mellitus	1		
Vascular disease	1		
eGFR <15 mL/min per 1.73 m^2 or dialysis			1
Valve surgery			1
Preoperative Intra-aortic balloon pump (IABP)			1
Emergency operation			1
Left ventricular ejection fraction <30%			1

was also found to significantly decrease length of stay in the ICU unit, length of stay in the hospital and reduce the risk of adverse effects [49].

Vitamin D level has also been found to be a predictor of POAF and it has been suggested that lower vitamin D levels contributes to the development of POAF [50]. A randomized clinical trial by Özsin *et al.* [50] of 100 patients found vitamin D level to be an independent predictor of POAF after CABG surgery (OR: 0.855, 95% CI: 0.780–0.938, $p = 0.001$). However, this finding has not been replicated in all studies, as it was found in Cerit *et al.*'s [51] study of 128 patients that while Vitamin D levels do significantly negatively correlate with left atrial diameter, it was not an independent predictor for POAF. Table 2 (Ref. [48, 52, 53]) is summary of the risk scoring models.

5. Intraoperative predictors for POAF

Establishing causation of POAF through intra-operative predictors such as: type of procedure, need of reopening for exploration post-surgery, durations of cardiopulmonary bypass (CPB) and aortic cross clamp is pivotal in order to reduce the incidence of post-operative atrial fibrillation (Table 3, Ref. [44, 54–56]).

5.1 Correlation between types of procedures and incidence of POAF

Several studies suggest valvular surgeries have a greater incidence of POAF. A recent paper following patients with congenital heart disease suggested that the incidence of POAF is greatest post surgeries involving mitral valve interventions [44]. A comparison between interventions in the four different valves showed that the greatest risk of developing POAF was after mitral valve intervention (OR: 3.38, 95% CI , $p = 0.009$) [44], compared with the lowest risk being associated with pulmonary valve interventions (OR: 0.72, 95% CI , $p = 0.464$) [44]. Additional papers [54, 55] have supported the claim, with it being reported that incidence of POAF was 48.8% following mitral valve replacement [54]. However, the pathological or structural abnormalities of the mitral valve requiring surgery which lead to left atrial enlargement alongside the trauma and inflammation during surgery contribute to the development of post-operative atrial fibrillation [54]. The combination of CABG and valve surgery has been reported to have the greatest risk of developing POAF [55, 57, 58].

A study by Emmanuel Akintoye *et al.* [55] suggests the risk of POAF triples when patients undergo an extensive operation combining CABG, valvular and one other procedure (OR: 2.9, $p = 0.01$) [55]. It can be thought that the increased risk of developing POAF when multiple procedures are combined is due to the increased surgical trauma and longer time under cardiopulmonary bypass.

5.2 Cardiopulmonary bypass and extensive inflammation

Cardiopulmonary bypass (CPB) use during surgery has long been associated with POAF. A paper focusing on 1462 patients found a greater incidence of POAF in patients undergoing CPB (OR: 2.4, 95% CI, $p = < 0.001$) [55]. The OR demonstrates that the risk of developing POAF is more than double in cohorts undergoing CPB [55].

It is thought that exposure of plasma proteases to the nonendothelial lining of the CPB circuit and the increased production of tissue factor due to vascular injury leads to all aspects of the complement system becoming activated. Furthermore, the ischemia and reperfusion during CPB contributes to the inflammation as the local response to reperfusion moves into the systemic circulation resulting in increased serum cytokine [59]. The inflammatory response is thought to contribute to the development of POAF.

Table 3. Summary of intraoperative predictors with proposed cut off values [44, 54–56].

Predictor	Comment	Proposed cut off values/modifications to reduce incidence of POAF
Aortic cross clamping duration	Association between duration of aortic cross clamping and POAF development has been noted. Duration of aortic cross clamping of >60 minutes has been statistically proven as a predictor towards the development of POAF.	Aortic cross clamping time should be kept under 60 minutes.
Cardiopulmonary bypass (CPB)	The risk of developing POAF has been found to be double in patients undergoing CPB due to the activation of the complement system which causes extensive inflammation. The longer a patient spends under CPB, the greater the risk of developing POAF. Statistically significant relationship has been noted in patients who spent over 100 minutes under CPB and the development of POAF.	CPB duration should be kept under 100 minutes.
On pump CABG	A greater incidence of POAF was found in cohorts undergoing on pump CABG as opposed to off pump CABG in patients under sixty-five.	CABG procedures should be done off pump, especially in patients under sixty-five.
Mitral valve intervention	Procedures involving mitral valve interventions have be found to have the greatest incidence of POAF post procedure. Incidence of POAF after mitral valve replacement has been noted to be 48.8%.	-
Combing procedures	Combing valve surgery and CABG has been reported to have the greatest risk of developing POAF.	Patients should not undergo multiple procedures in one surgery.
	Additionally, the risk of developing POAF triples if a patient undergoes three procedures within one surgery.	In particular, valve surgery and CABG should not be combined.

Several studies suggest that there is a correlation between longer times of CPB and the development of POAF [18, 54, 60].

A study by Ming Ann Sim *et al.* [60] following 1743 patients undergoing on pump CABG saw a relationship between longer CPB duration and the development of POAF, (114.7 min vs. 97.9 mins, $p \leq 0.001$, OR = 1.007) [60]. Moreover, Sona Dave *et al.* [54], noted a statistically significant relationship between CPB duration >100 minutes and the incidence of POAF ($p = 0.001$) [54]. The incidence of POAF following CPB times longer than 100 minutes was calculated to be 60% [54]; further strengthening the association between POAF and longer duration of CPB.

However, some studies have suggested that there is no relationship between duration of CPB and development of POAF as the data has been deemed statically unsignificant [45, 61].

5.3 Off pump CABG verses on pump CABG

It is understood that the activation of the complement system is highest on days two and three post operation in patients undergoing on pump CABG, the increased inflammatory response has been assumed to contribute to the greater development of post-operative atrial fibrillation in patients undergoing on pump CABG [56, 62].

Many studies have been conducted into whether off pump CABG (OPCAB) reduces the incidence of POAF based on the theory that there is less activation of the complement system [56]. However, a recent study following 1836 patients monitoring the incidence of POAF between OPCAB and CABG showed no significant difference between the cohorts, reporting an incidence of (19.3% vs. 18.3%) [56] respectively. The slightly higher incidence of POAF in the OPCAB group was due to a greater population within the OPCAB group having hypertension [56]—an independent predictor of POAF. Further studies similarly showed that there was no significant difference in reduced incidence of POAF following OPCAB [63, 64].

Overall, evidence suggesting no correlation between OPCAB and reduced incidence of POAF outweighs evidence suggesting OPCAB can reduce cases of post-operative atrial fibrillation. In one study, multivariate adjustment showed that there was a lower risk of POAF in men (OR: 0.53; 95% CI, 0.33–0.85) [55] following OPCAB compared to women (OR: 1.7; 95% CI: 0.61–4.5) [55]. Similarly, under sixty-five (OR: 0.35; 95% CI: 0.16–0.75) [55] benefited more from OPCAB than over sixty-five (OR: 0.88; 95% CI: 0.52–1.5) [55], however univariate analysis of OPCAB did not affect cases of POAF suggesting that the development of POAF is multifactorial.

5.4 Duration of Aortic cross clamping

Aortic cross clamping has been associated with greater levels of pro inflammatory markers, in particular IL6 due to hypoxia [65], the proinflammatory state contributes to the development of POAF.

Evidence on aortic cross clamp time impacting the development of POAF is diverse.

The largest cohort study focusing on 637 patients [45] found the aortic cross clamp duration to be the same in both study groups (64 minutes) [45], thus showing no significant relationship [45]. Further studies analysing smaller populations also showed no statistically significant link [18, 63].

In contrast, Michael A Brock *et al.* [44] discovered a significant relationship between duration of aortic cross clamp >60 minutes and POAF in univariate analysis(OR: 2.43, p = 0.03) [44], however to ensure that there is a strong association between duration of aortic cross clamp and POAF, multivariate analysis would be required. Similarly, smaller studies showed significant correlation between aortic cross clamp time and POAF [54, 66].

6. Post-operative predictors for POAF

6.1 Time spent on ventilator

Patients undergoing cardiac surgery are routinely put onto a ventilator until they have recovered from the sedative effects of the anaesthesia [67]. Thereafter, they are able to regain their ability to ventilate independent of any external source. However, in critically unwell patients, often with numerous comorbidities, they'll require the assistance of a ventilator for longer in order to wholly regain lung function [67].

Multiple papers have proven the significance of prolonged ventilation with the subsequent diagnosis of POAF, often as the most prominent post-operative risk factor [2, 5, 7, 31, 45, 67–70]. Prolonged ventilation may be necessitated by hypoxia, hypovolemia, sepsis and electrolyte imbalances that occurs post operatively, each of which contributes towards POAF [71]. Sona Dave *et al.* [54] found the odds of developing POAF in these patients were 12.28 times higher (p = 0.023). A retrospective study consisting of a larger cohort of 637 patients found that the median duration spent on ventilation was 1155 minutes (19.25 hours) in their non-POAF patients, compared to 1277.5 minutes (21.29 hours) in their POAF patients [42]. Although this implies a narrow gap between the groups, this study also concluded that ventilatory support was a significant predictor of POAF [45].

6.2 Length of ICU stays

POAF is associated with a multitude of postoperative factors that may contribute towards a longer ICU stay for these patients: prolonged ventilation, prolonged ionotropic support, electrolyte imbalances, pulmonary pathologies, AKI, hemodynamic instability and fluid overload. Consequently, longer ICU stays are recognised as a risk factor of POAF due to the need to further observe, manage and stabilise these patients [67, 68]. The aforementioned retrospective study echoed this finding (ICU stay $p < 0.001$) and states that 54.9% (100) of their patients with POAF could be attributed to this group, in contrast with only 30.2% (136) of the non-POAF patients [45]. The median ICU stay in the POAF group was 9.0 days, compared to 7.2 days in the non-POAF group [45]. This complements Hristo Todrov *et al.*'s [31] conclusion of a median increase in approximately 2 days spent in ICU between the POAF and non-POAF groups.

6.3 Inotropic support and fluid imbalance

Cardiac surgery is a strenuous feat on the human body; it can lead to predisposing factors of POAF such as pericardial inflammation, fluid imbalance as well as an excess of catecholamines due to sympathetic activation during this state of increased stress [67]. In regard to fluid balance, a postoperative volume overload has been associated with POAF, especially when there's a positive fluid balance detected in the first two days after cardiac surgery [2, 31, 69].

Notably, patients with POAF are more likely to have a postoperative autonomic imbalance which necessitates the use of more aggressive or longer periods of ionotropic support; it is not yet clear whether this is a causative mechanism or if the association is due to inotropes being used as a management strategy in unstable patients at higher risk of POAF [67, 68]. Ionotropic support is indicated when there's considerable preoperative myocardial dysfunction or if intraoperative technical difficulties occur [67].

Sona Dave *et al.* pointed out that although it was not statistically significant, the incidence of POAF was greater in those that required more than 30 minutes of ionotropic support, but other studies were able to determine that prolonged ionotropic support was statistically significant, such as A.Omar *et al.* (p = 0.04) [54, 68]. Sona Dave *et al.* may not have been able to reach this conclusion due to their notably smaller sample size of 150 patients compared to 267 in A.Omar *et al.*'s study [54, 68].

6.4 Electrolytes

Current guidelines may dictate intraoperative and postoperative magnesium and potassium supplementation, yet both of these electrolytes been linked to POAF [5, 36, 45].

Electrolyte supplementation is used as a prophylactic means to combat the hypomagnesemia that commonly occurs post surgically and may lead to POAF as "magnesium regulates calcium mobility, influences cardiomyocyte contractility, and has been shown to have anti-ischemic effects" [5]. However, Jason W Greenberg *et al.* [5] signposted that high levels of magnesium may also contribute towards POAF, despite the apparent anti arrhythmic properties of magnesium. This may be clarified by Jeroen Boons *et al.* [36], who states that the association between hypomagnesemia and POAF has been widely studied and accepted, but rather it's the use of magnesium supplementation as prophylaxis that is doubted, and this was later clarified by a meta-analysis that it did not prevent POAF.

One study deduced that where prophylactic magnesium supplementation was used, it only prevented POAF in patients with hypomagnesemia and not those who had normal serum magnesium levels [45].

This same study found that of the patients who developed POAF, 69% had hypokalaemia whereas only 24% from the non POAF group had hypokalaemia [45]. However, the association between serum potassium levels and POAF has been scrutinised in other studies who've concluded that there is no association between the two [5].

6.5 Acute kidney injury (AKI)

"Up to one in every three patients develop renal dysfunction" post cardiac surgery [42].

AKI as a common form of renal dysfunction post cardiac surgery has been heavily related to POAF [42, 45, 69]. Upon adjusting for preoperative variables, one study found considerable statistical significance (adjusted odds ratio: 1.572; 95% CI: 1.295–1.908; $p < 0.001$) and calculated that their post-operative AKI patients had a 57% greater risk of developing POAF [42]. Despite this apparent strong association, they showed caution by refraining from labelling AKI as a cause of POAF as it's possible that the two are related because of other risk factors that they share [42]. The causative mechanism could be attributed to the electrolyte imbalance and fluid overload occurring during an AKI that then leads to atrial distension [42]. It's possible that POAF may in turn cause AKI "due to reduced cardiac output and tissue perfusion" [42]. Thus, as the mechanism and timing of onset is not easily discernible, more research needs to be carried out to understand the mechanism and establish whether POAF is a risk factor for AKI or vice versa.

6.6 Infection

Similarly, there have been findings that link postoperative infections to the development of POAF, but there is no clarity in the onset of POAF and whether it occurred as a consequence of the infection or if they are unrelated [2, 7, 45, 72]. Nonetheless, studies have found that patients who develop postsurgical infections are more likely to be diagnosed with POAF ($p = 0.008$) with one study listing postoperative pneumonia in particular as a prominent postoperative risk factor [2, 72]. Other pathologies alongside infection have been associated with POAF such as pleural effusion and cardiac tamponade as they lead to "an increased inflammatory response" which is one of the proposed pathophysiological mechanisms behind POAF [7]. One study discovered that pulmonary complications ($p = 0.018$) and post-operative fever ($p = 0.018$) led to POAF, but the paper failed to describe what the pulmonary complications entailed of so it cannot be assumed to be infection-based pathology [45].

6.7 Re-exploration following post-surgery bleeding

Re-opening for exploration following surgery can be considered towards contributing to the development of atrial fibrillation post cardiac surgery [63, 73]. A study following 16793 patients investigated the detrimental effects of re-exploration surgery. 661 patients required reopening for re-exploration and 36.3% of patients developed new onset of atrial fibrillation, compared with 26% of patients in the cohort who did not require re-exploration [73]. Whilst a smaller population required re-opening for exploration, a greater population developed POAF, suggesting that there is an increase in surgical trauma contributing to increased inflammation leading to POAF. Moreover, Mohamed F. Ismail *et al.* [63] followed 252 adult patients post CABG surgery which saw a greater percentage of patients in the POAF group requiring re-exploration following bleeding than in the non POAF group (9.5% vs. 1.2%, $p = 0.0003$) [63]. It was suggested that patients requiring re-exploration are twice as likely to develop POAF [63], however other factors were thought to contribute to the development of POAF. Further research is required to establish re-exploration for bleeding as a significant predictor of post-operative atrial fibrillation following cardiac surgery.

6.8 Beta blockers

Major guidelines such as The European Association for Cardio-Thoracic Surgery (EACTS) recommends beta blockers and other antiarrhythmics postcardiac surgery, in order to combat the surge in adrenaline and noradrenaline [2, 5, 71]. The profound prophylactic effects of beta blockers in reducing the incidence of POAF was showcased in a meta-analysis (OR: 0.33, 95% CI: 0.26–0.43, $I^2 = 55\%$) that consisted of 601 participants [2]. Moreover, a study by Musa *et al.* [45] of 637 patients undergoing CABG procedures found that taking beta blockers significantly reduced the risk of having POAF (adjusted OR: 1.611, 95% CI: 1.049–2.467, $p = 0.029$). However, it appears that to sustain its prophylactic effect it must be continued postoperatively as the immediate withdrawal of beta blockers may lead to a 91% increased chance in developing POAF [36]. Additionally, in the aforementioned study by Mohamed F. Ismail *et al.* [63], it was suggested that the delayed postoperative beta blocker therapy post CABG surgery contributed to the development of POAF in the cohort. Comparatively, in patients where beta blocker treatment was continued postoperatively the odds of developing POAF were 68%, proving the detriment of beta blocker withdrawal [36]. Hiroki Kohno *et al.* [74] conducted a study comprising of 157 patients and found that giving beta blockers postoperatively, whether it was a continued or new therapy, showed a 5-fold decreased incidence in developing POAF ($p < 0.001$).

7. Clinical implications

Adaptations within the management of patients throughout their care would assist in reducing the incidence of POAF and subsequently reduce the incidence of the morbidity and mortality associated with the arrythmia.

An additional blood test added into the pre-operation assessment to test for the biomarker microRNA 483-5p and endotherlin-1 would assist in differentiating between patient groups more susceptible towards developing POAF [12, 34, 35]. Knowing the results of these biomarkers would ensure patients start prophylactic therapy, such as beta-blockers and assist in planning after care for patients. Baseline magnesium levels should be detected from preoperative blood tests and prophylactic magnesium supplements should be given to patients with hypomagnesemia, as it is accepted that magnesium supplements assist in reducing the incidence of POAF in cohorts with hypomagnesemia [45].

Additionally, prophylaxis supplements of vitamin D and vitamin C pre-surgery would assist in reducing the incidence

of POAF in susceptible patient groups [49, 50]. Ensuring patient cohorts appropriately manage their health conditions such as hypertension may also reduce the risk of POAF development.

Modifications to cardiac procedures by reducing the duration a patient spends under cardiopulmonary bypass or aortic cord clamping may contribute to reducing the risk of POAF development post cardiac surgery [44, 60]. However, it would make procedures more challenging as they would need to be conducted in less time.

Additionally, the suggestion to reduce the number of procedures done within one operation in order to reduce the risk of POAF would increase the strain on healthcare services and patients [55]. Patients would require multiple surgeries to treat conditions resulting in longer hospital stays and longer time under general anaesthetic.

Longer ICU stays and ventilator times have been indicated as predictors towards the development of POAF, ideally modifications in patient care should be conducted in order to reduce the time patients stay in ICU [42, 45]. Moreover, it has been noted that inotropic support of longer than 30 minutes has a correlation with the development of POAF; modifications should be attempted to reduce the length of inotropic support [68].

Surgical teams should attempt to reduce the incidence of re-exploration following post-surgery bleeding as it contributes to further trauma and inflammation, thus contributing to an increased incidence of POAF [63]. Furthermore, patients should be given beta blocker therapy immediately post-surgery as delayed postoperative beta blocker therapy can contribute towards the development of POAF [63].

Whilst the aetiology of POAF is multifactorial, these adaptions to patient care will assist in reducing incidence of the tachycardia.

8. Complications associated with POAF

Many complications have been noted as a consequence of POAF. Increased risk of thrombus formation within the left atria, leading to a greater risk of stroke is a significant adverse effect. In patients undergoing cardiac surgery, the risk of stoke following onset of POAF increased by "20%" [11].

Additionally, a "stroke risk of 1.47% at 1 year post-discharge in POAF patients was noted, in comparison to 0.36% in controls without AF" [3].

Patients have reported to be a at greater risk of haemodynamic instability post-surgery following the development of POAF, consequently resulting in longer intensive care unit stays [1]. Besides stroke, patients developing post-operative atrial fibrillation are at a greater risk of suffering from additional cardiac conditions, such as: congestive heart failure, myocardial infarctions and cardiac arrests [10]. Damage to the kidneys is also prevalent with both acute kidney injury and chronic kidney injuries being noted as adverse outcomes of POAF [2, 75].

9. Conclusions

POAF is a great psychological and physiological burden for a patient as well as the healthcare system. Thus, it is important to identify high risk patients in order to implement prevention strategies in a timely manner.

Although the mechanism behind POAF is not fully understood, risk factors such as: atrial abnormalities, obesity, obstructive sleep apnoea, inflammation caused by cardiopulmonary bypass, electrolyte imbalances and acute kidney injury post cardiac surgery alongside others have been consistently linked to the development of POAF. Further exploration into these factors may reveal the precise pathophysiology of POAF and subsequently, establish more effective treatment options.

Author contributions

MQ, AA, EM, VM contributed to the writing of this paper. MQ, AA, EM, VM researched the topic and selected appropriate papers for the review. MQ and AA edited and proofread the manuscript. MQ referenced the paper. AH proposed review title, reviewed and critically edited the paper. All authors have approved the final form of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

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References

[1] Dobrev D, Aguilar M, Heijman J, Guichard J, Nattel S. Postoperative atrial fibrillation: mechanisms, manifestations and management. Nature Reviews Cardiology. 2019; 16: 417–436.

[2] Rezaei Y, Peighambari MM, Naghshbandi S, Samiei N, Ghavidel AA, Dehghani MR, *et al.* Postoperative atrial fibrillation following cardiac surgery: from pathogenesis to potential therapies. American Journal of Cardiovascular Drugs. 2020; 20: 19–49.

[3] Jagadish PS, Kirolos I, Khare S, Rawal A, Lin V, Khouzam RN. Post-operative atrial fibrillation: should we anticoagulate? Annals of Translational Medicine. 2019; 7: 407.

[4] Yadava M, Hughey AB, Crawford TC. Postoperative atrial fibrillation: incidence, mechanisms, and clinical correlates. Heart Failure Clinics. 2016; 12: 299–308.

[5] Greenberg JW, Lancaster TS, Schuessler RB, Melby SJ. Postoperative atrial fibrillation following cardiac surgery: a persistent complication. European Journal of Cardio-Thoracic Surgery. 2017; 52: 665–672.

[6] Melby SJ, George JF, Picone DJ, Wallace JP, Davies JE, George DJ, *et al.* A time-related parametric risk factor analysis for postopera-

tive atrial fibrillation after heart surgery. Journal of Thoracic and Cardiovascular Surgery. 2015; 149: 886–892.
[7] Gudbjartsson T, Helgadottir S, Sigurdsson MI, Taha A, Jeppsson A, Christensen TD, *et al.* New-onset postoperative atrial fibrillation after heart surgery. Acta Anaesthesiologica Scandinavica. 2020; 64: 145–155.
[8] Maesen B, Nijs J, Maessen J, Allessie M, Schotten U. Post-operative atrial fibrillation: a maze of mechanisms. Europace. 2012; 14: 159–174.
[9] Bidar E, Bramer S, Maesen B, Maessen JG, Schotten U. Post-operative atrial fibrillation—pathophysiology, treatment and prevention. Journal of Atrial Fibrillation. 2013; 5: 781.
[10] Bessissow A, Khan J, Devereaux PJ, Alvarez-Garcia J, Alonso-Coello P. Postoperative atrial fibrillation in non-cardiac and cardiac surgery: an overview. Journal of Thrombosis and Haemostasis. 2015; 13: S304–S312.
[11] Lin M, Kamel H, Singer DE, Wu Y, Lee M, Ovbiagele B. Perioperative/postoperative atrial fibrillation and risk of subsequent stroke and/or mortality. Stroke. 2019; 50: 1364–1371.
[12] Harling L, Lambert J, Ashrafian H, Darzi A, Gooderham NJ, Athanasiou T. Elevated serum microRNA 483-5p levels may predict patients at risk of post-operative atrial fibrillation. European Journal of Cardio-Thoracic Surgery. 2017; 51: 73–78.
[13] Feldman A, Moreira DAR, Gun C, Wang HL, Hirata MH, de Freitas Germano J, *et al.* Analysis of circulating miR-1, miR-23a, and miR-26a in atrial fibrillation patients undergoing coronary bypass artery grafting surgery. Annals of Human Genetics. 2017; 81: 99–105.
[14] Yamashita K, Hu N, Ranjan R, Selzman C, Dosdall D. Clinical risk factors for postoperative atrial fibrillation among patients after cardiac surgery. Thoracic and Cardiovascular Surgeon. 2019; 67: 107–116.
[15] Gode S, Aksu T, Demirel A, Sunbul M, Gul M, Bakır I, *et al.* Effect of vitamin D deficiency on the development of postoperative atrial fibrillation in coronary artery bypass patients. Journal of Cardiovascular and Thoracic Research. 2016; 8: 140–146.
[16] Quan D, Huang H, Kong B, Li Q, Liao J, Wang G. Predictors of late atrial fibrillation recurrence after cryoballoon-based pulmonary vein isolation: a meta-analysis. Kardiologia Polska. 2017; 75: 376–385.
[17] De Bortoli A, Shi L, Ohm O, Hoff PI, Schuster P, Solheim E, *et al.* Incidence and clinical predictors of subsequent atrial fibrillation requiring additional ablation after cavotricuspid isthmus ablation for typical atrial flutter. Scandinavian Cardiovascular Journal. 2017; 51: 123–128.
[18] Ozben B, Akaslan D, Sunbul M, Filinte D, Ak K, Sari İ, *et al.* Postoperative atrial fibrillation after coronary artery bypass grafting surgery: a two-dimensional speckle tracking echocardiography study. Heart, Lung & Circulation. 2016; 25: 993–999.
[19] Rizvi F, Mirza M, Olet S, Albrecht M, Edwards S, Emelyanova L, *et al.* Noninvasive biomarker-based risk stratification for development of new onset atrial fibrillation after coronary artery bypass surgery. International Journal of Cardiology. 2020; 307: 55–62.
[20] Pernigo M, Benfari G, Geremia G, Noni M, Borio G, Mazzali G, *et al.* Atrial function as an independent predictor of postoperative atrial fibrillation in patients undergoing aortic valve surgery for severe aortic stenosis. Journal of the American Society of Echocardiography. 2017; 30: 956–965.e1.
[21] Aksu U, Kalkan K, Gulcu O, Aksakal E, Öztürk M, Topcu S. The role of the right atrium in development of postoperative atrial fibrillation: a speckle tracking echocardiography study. Journal of Clinical Ultrasound. 2019; 47: 470–476.
[22] Echt DS, Ruskin JN. Use of flecainide for the treatment of atrial fibrillation. American Journal of Cardiology. 2020; 125: 1123–1133.
[23] Fakuade FE, Steckmeister V, Seibertz F, Gronwald J, Kestel S, Menzel J, *et al.* Altered atrial cytosolic calcium handling contributes to the development of postoperative atrial fibrillation. Cardiovascular Research. 2021; 117: 1790–1801.
[24] Pastore MC, De Carli G, Mandoli GE, D'Ascenzi F, Focardi M, Contorni F, *et al.* The prognostic role of speckle tracking echocardiography in clinical practice: evidence and reference values from the literature. Heart Failure Reviews. 2020.
[25] Ad N. MicroRNAs and post-operative atrial fibrillation: a step in the understanding of the mechanism and identifying reliable biomarkers. European Journal of Cardio-Thoracic Surgery. 2017; 51: 78–79.
[26] Parwani AS, Morris D, Blaschke F, Huemer M, Pieske B, Haverkamp W, *et al.* Left atrial strain predicts recurrence of atrial arrhythmias after catheter ablation of persistent atrial fibrillation. Open Heart. 2017; 4: e000572.
[27] Gorczyca I, Michta K, Pietrzyk E, Wożakowska-Kapłon B. Predictors of post-operative atrial fibrillation in patients undergoing isolated coronary artery bypass grafting. Kardiologia Polska. 2018; 76: 195–201.
[28] Kharbanda RK, Lodder L, Ragab AAY, de Jong PL, Kik C, Brundel BJJM, *et al.* Early and late post-operative arrhythmias after surgical myectomy: 45 years of follow-up. International Journal of Cardiology. 2021; 328: 63–68.
[29] Stefano PL, Bugetti M, Del Monaco G, Popescu G, Pieragnoli P, Ricciardi G, *et al.* Overweight and aging increase the risk of atrial fibrillation after cardiac surgery independently of left atrial size and left ventricular ejection fraction. Journal of Cardiothoracic Surgery. 2020; 15: 316.
[30] Sood A, Toth A, Abdallah M, Gillinov M, Milind D, Allan K, *et al.* Temporal trend and associated risk factors for new-onset atrial fibrillation following cardiac valve surgery. Journal of Atrial Fibrillation. 2020; 12: 2129.
[31] Todorov H, Janssen I, Honndorf S, Bause D, Gottschalk A, Baasner S, *et al.* Clinical significance and risk factors for new onset and recurring atrial fibrillation following cardiac surgery—a retrospective data analysis. BMC Anesthesiology. 2017; 17: 163.
[32] Fragão-Marques M, Mancio J, Oliveira J, Falcão-Pires I, Leite-Moreira A. Gender differences in predictors and long-term mortality of new-onset postoperative atrial fibrillation following isolated aortic valve replacement surgery. Annals of Thoracic and Cardiovascular Surgery. 2020; 26: 342–351.
[33] Filardo G, Ailawadi G, Pollock BD, da Graca B, Phan TK, Thourani V, *et al.* Postoperative atrial fibrillation: sex-specific characteristics and effect on survival. Journal of Thoracic and Cardiovascular Surgery. 2020; 159: 1419–1425.e1.
[34] Lu R, Ma N, Jiang Z, Mei J. Endothelin-1 is associated with dilatation of the left atrium and can be an independent predictor of atrial fibrillation after mitral valve surgery. Interactive Cardiovascular and Thoracic Surgery. 2018; 26: 66–70.
[35] Song C, Wang S, Guo Y, Zheng X, Lu J, Fang X, *et al.* Plasma big endothelin-1 predicts new-onset atrial fibrillation after surgical septal myectomy in patients with hypertrophic cardiomyopathy. BMC Cardiovascular Disorders. 2019; 19: 122.
[36] Boons J, Van Biesen S, Fivez T, de Velde MV, Al Tmimi L. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery: a narrative review. Journal of Cardiothoracic and Vascular Anesthesia. 2020. (in press)
[37] Efird JT, Gudimella P, O'Neal WT, Griffin WF, Landrine H, Kindell LC, *et al.* Comparison of risk of atrial fibrillation in black versus white patients after coronary artery bypass grafting. American Journal of Cardiology. 2016; 117: 1095–1100.
[38] Khan MS, Yamashita K, Sharma V, Ranjan R, Dosdall DJ. RNAs and gene expression predicting postoperative atrial fibrillation in cardiac surgery patients undergoing coronary artery bypass grafting. Journal of Clinical Medicine. 2020; 9: 1139.
[39] Yamac AH, Kucukbuzcu S, Ozansoy M, Gok O, Oz K, Erturk M, *et al.* Altered expression of micro-RNA 199a and increased levels of cardiac SIRT1 protein are associated with the occurrence of atrial fibrillation after coronary artery bypass graft surgery. Cardiovascular Pathology. 2016; 25: 232–236.
[40] Zhang J, Xu S, Xu Y, Liu Y, Li Z, Zhang Y, *et al.* Relation of mitochondrial DNA copy number in peripheral blood to postoperative atrial fibrillation after isolated off-pump coronary artery bypass grafting. American Journal of Cardiology. 2017; 119: 473–477.

[41] Chen F, Yang Y, Zhang R, Zhang S, Dong Y, Yin X, *et al.* Polymorphism rs2200733 at chromosome 4q25 is associated with atrial fibrillation recurrence after radiofrequency catheter ablation in the Chinese Han population. American Journal of Translational Research. 2016; 8: 688–697.
[42] Cole OM, Tosif S, Shaw M, Lip GYH. Acute kidney injury and postoperative atrial fibrillation in patients undergoing cardiac surgery. Journal of Cardiothoracic and Vascular Anesthesia. 2020; 34: 1783–1790.
[43] Phan K, Khuong JN, Xu J, Kanagaratnam A, Yan TD. Obesity and postoperative atrial fibrillation in patients undergoing cardiac surgery: systematic review and meta-analysis. International Journal of Cardiology. 2016; 217: 49–57.
[44] Brock MA, Coppola J, Reid J, Moguillansky D. Atrial fibrillation in adults with congenital heart disease following cardiac surgery in a single center: analysis of incidence and risk factors. Congenital Heart Disease. 2019; 14: 924–930.
[45] Farouk Musa A, Quan CZ, Xin LZ, Soni T, Dillon J, Hay YK, *et al.* A retrospective study on atrial fibrillation after coronary artery bypass grafting surgery at the National Heart Institute, Kuala Lumpur. F1000Research. 2018; 7: 164.
[46] Feng TR, White RS, Ma X, Askin G, Pryor KO. The effect of obstructive sleep apnea on readmissions and atrial fibrillation after cardiac surgery. Journal of Clinical Anesthesia. 2019; 56: 17–23.
[47] Chen Y, Zeng M, Liu Y, Xu Y, Bai Y, Cao L, *et al.* CHA2DS2-VASc score for identifying patients at high risk of postoperative atrial fibrillation after cardiac surgery: a meta-analysis. Annals of Thoracic Surgery. 2020; 109: 1210–1216.
[48] Burgos LM, Seoane L, Parodi JB, Espinoza J, Galizia Brito V, Benzadón M, *et al.* Postoperative atrial fibrillation is associated with higher scores on predictive indices. Journal of Thoracic and Cardiovascular Surgery. 2019; 157: 2279–2286.
[49] Shi R, Li Z, Chen D, Wu Q, Zhou X, Tie H. Sole and combined vitamin C supplementation can prevent postoperative atrial fibrillation after cardiac surgery: a systematic review and meta-analysis of randomized controlled trials. Clinical Cardiology. 2018; 41: 871–878.
[50] Özsin KK, Sanrı US, Toktaş F, Kahraman N, Yavuz Ş. Effect of plasma level of vitamin d on postoperative atrial fibrillation in patients undergoing isolated coronary artery bypass grafting. Brazilian Journal of Cardiovascular Surgery. 2018; 33: 217–223.
[51] Cerit L, Kemal H, Gulsen K, Ozcem B, Cerit Z, Duygu H. Relationship between Vitamin D and the development of atrial fibrillation after on-pump coronary artery bypass graft surgery. Cardiovascular Journal of Africa. 2017; 28: 104–107.
[52] Mariscalco G, Biancari F, Zanobini M, Cottini M, Piffaretti G, Saccocci M, *et al.* Bedside tool for predicting the risk of postoperative atrial fibrillation after cardiac surgery: the POAF score. Journal of the American Heart Association. 2014; 3: e000752.
[53] de Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, Coelen RJ, *et al.* Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. Journal of the American College of Cardiology. 2010; 55: 725–731.
[54] Dave S, Nirgude A, Gujjar P, Sharma R. Incidence and risk factors for development of atrial fibrillation after cardiac surgery under cardiopulmonary bypass. Indian Journal of Anaesthesia. 2019; 62: 887–891.
[55] Akintoye E, Sellke F, Marchioli R, Tavazzi L, Mozaffarian D. Factors associated with postoperative atrial fibrillation and other adverse events after cardiac surgery. Journal of Thoracic and Cardiovascular Surgery. 2018; 155: 242–251.e10.
[56] Lewicki Ł, Siebert J, Rogowski J. Atrial fibrillation following off-pump versus on-pump coronary artery bypass grafting: Incidence and risk factors. Cardiology Journal. 2018; 66: 518–523.
[57] Weymann A, Ali-Hasan-Al-Saegh S, Popov A, Sabashnikov A, Mirhosseini SJ, Liu T, *et al.* Haematological indices as predictors of atrial fibrillation following isolated coronary artery bypass grafting, valvular surgery, or combined procedures: a systematic review with meta-analysis. Kardiologia Polska. 2018; 76: 107–118.
[58] Qi W, Zhang N, Korantzopoulos P, Letsas KP, Cheng M, Di F, *et al.* Serum glycated hemoglobin level as a predictor of atrial fibrillation: a systematic review with meta-analysis and meta-regression. PLoS ONE. 2017; 12: e0170955.
[59] Bronicki RA, Hall M. Cardiopulmonary bypass-induced inflammatory response: pathophysiology and treatment. Pediatric Critical Care Medicine. 2017; 17: S272–S278.
[60] Sim MA, Liu W, Chew STH, Ti LK. Wider perioperative glycemic fluctuations increase risk of postoperative atrial fibrillation and ICU length of stay. PLoS ONE. 2018; 13: e0198533.
[61] Akça B, Erdil N, Colak MC, Disli OM, Battaloglu B, Colak C. Is there any difference in risk factors between male and female patients in new-onset atrial fibrillation after coronary artery bypass grafting? Thoracic and Cardiovascular Surgeon. 2018; 66: 483–490.
[62] Bruins P, Velthuis HT, Yazdanbakhsh AP, Jansen PGM, van Hardevelt FWJ, de Beaumont EM, *et al.* Activation of the complement system during and after cardiopulmonary bypass surgery. Circulation. 1997; 96: 3542–3548.
[63] Ismail MF, El-Mahrouk AF, Hamouda TH, Radwan H, Haneef A, Jamjoom AA. Factors influencing postoperative atrial fibrillation in patients undergoing on-pump coronary artery bypass grafting, single center experience. Journal of Cardiothoracic Surgery. 2017; 12: 40.
[64] Kadric N, Osmanovic E. Rhythm disturbance after myocardial revascularization. Medical Archives. 2017; 71: 400–403.
[65] Jalkanen J, Maksimow M, Jalkanen S, Hakovirta H. Hypoxia-induced inflammation and purinergic signaling in cross clamping the human aorta. SpringerPlus. 2016; 5: 2.
[66] Carter-Storch R, Dahl JS, Christensen NL, Pecini R, Søndergård EV, Øvrehus KA, *et al.* Postoperative atrial fibrillation after aortic valve replacement is a risk factor for long-term atrial fibrillation. Interactive CardioVascular and Thoracic Surgery. 2019; 29: 378–385.
[67] Trouillet J, Combes A, Vaissier E, Luyt C, Ouattara A, Pavie A, *et al.* Prolonged mechanical ventilation after cardiac surgery: outcome and predictors. Journal of Thoracic and Cardiovascular Surgery. 2009; 138: 948–953.
[68] Bateman RM, Sharpe MD, Jagger JE, Ellis CG, Solé-Violán J, López-Rodríguez M, *et al.* 36th international symposium on intensive care and emergency medicine : Brussels, Belgium. 15–18 March 2016. Crit Care. 2016; 20: 94.
[69] Woldendorp K, Farag J, Khadra S, Black D, Robinson B, Bannon P. Postoperative atrial fibrillation after cardiac surgery: a meta-analysis. Annals of Thoracic Surgery. 2021. (in press)
[70] Iliescu AC, Salaru DL, Achitei I, Grecu M, Floria M, Tinica G. Postoperative atrial fibrillation prediction following isolated surgical aortic valve replacement. The Anatolian Journal of Cardiology. 2018; 19: 394–400.
[71] Nyström U, Edvardsson N, Berggren H, Pizzarelli GP, Rådegran K. Oral sotalol reduces the incidence of atrial fibrillation after coronary artery bypass surgery. Thoracic and Cardiovascular Surgeon. 1993; 41: 34–37.
[72] Khan J, Khan N, Loisa E, Sutinen J, Laurikka J. Increasing occurrence of postoperative atrial fibrillation in contemporary cardiac surgery. Journal of Cardiothoracic and Vascular Anesthesia. 2016; 30: 1302–1307.
[73] Ruel M, Chan V, Boodhwani M, McDonald B, Ni X, Gill G, *et al.* How detrimental is reexploration for bleeding after cardiac surgery? Journal of Thoracic and Cardiovascular Surgery. 2019; 154: 927–935.
[74] Kohno H, Ueda H, Matsuura K, Tamura Y, Watanabe M, Matsumiya G. Long-term consequences of atrial fibrillation after aortic valve replacement. Asian Cardiovascular and Thoracic Annals. 2017; 25: 179–191.
[75] Harky A, Bithas C, Chan JSK, Snosi M, Pousios D, Muir AD. Surgical Treatment of Atrial Fibrillation: Cutting Through the Edges. Brazilian Journal of Cardiovascular Surgery. 2020; 35: 375–386.