COMPARATIVE ANALYSIS OF LONG-TERM OUTCOME IN POST CORONARY ARTERY BYPASS SURGERY WITH AND WITHOUT NEW-ONSET ATRIAL FIBRILLATION

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DM (CARDIOLOGY) THESIS

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DEPARTMENT OF CARDIOLOGY

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND

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A THESIS SUBMITTED BY

Dr. Karthikeyan T

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

DM (CARDIOLOGY)

2023

DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr Karthikeyan T, hereby certify that I had personally carried out the work in the thesis titled, “Comparative analysis of long-term outcome in post coronary artery bypass surgery with and without new-onset atrial fibrillation.”

Before this date, no part of this thesis has been submitted for the award of any other degree or diploma.

Signature

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Date: 28/08/2023

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The thesis entitled "Comparative analysis of long-term outcome in post coronary artery bypass surgery with and without new-onset atrial fibrillation" was carried out under my direct supervision. Before this date, no part of the thesis was submitted for awarding any degree or diploma.

*Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

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APPROVAL OF THE THESIS

The thesis entitled

"Comparative analysis of long-term outcome in post coronary artery bypass surgery with and without new-onset atrial fibrillation"

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for the degree of

DM Cardiology

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Dr. K M Krishnamoorthy

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"Alone we can do so little; together we can do so much".

-Hellen Keller

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Dr. Karthikeyan T

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LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1.	CVA	Cerebrovascular accident
2.	TIA	Transient Ischemic attack
3.	ACS	Acute coronary syndrome
4.	NYHA	New York Heart Association
5.	RRT	Renal Replacement Therapy
6.	POAF	Post-operative Atrial Fibrillation
7.	OSA	Obstructive Sleep Apnoea
8.	CBT	Cardiopulmonary Bypass time
9.	LVEF	Left ventricular ejection fraction
10.	LA	Left Atrium
11.	AF	Atrial Fibrillation
12.	DC cardioversion	Direct current cardioversion
13.	MI	Myocardial Infarction
14.	PVD	Peripheral vascular disease
15.	CABG	Coronary Artery Bypass Surgery
16.	CAD	Coronary artery disease
17.	MACE	major adverse cardiovascular events
18.	CHADSVASc	Congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or TIA or

		thromboembolism, vascular disease, age, sex category
19.	CI	Confidence interval
20.	OR	Odds ratio
21.	ECG	Electrocardiogram
22.	COPD	Chronic Obstructive Pulmonary Disease
23.	CKD	Chronic Kidney Disease
24.	FEV1	Forced Expiratory Volume in first Second
25.	IL-1β	Interleukin 1 beta
26.	ESC	European Society of Cardiology
27.	RCT	Randomized Controlled Trial
28.	RR	Risk Ratio
29.	HR	Hazard Ratio
30.	PUFA	Polyunsaturated fatty acid
31.	$CaCl_2$	Calcium chloride
32.	USA	United States of America
33.	ICU	Intensive Care Unit
34.	aHR	Adjusted Hazard ratio
35.	IABP	Intra-aortic balloon pump
36.	CPB time	Cardio-pulmonary bypass time
37.	AHA	American Heart Association
38.	HRS	Heart Rhythm Society
39.	ACC	American College of Cardiology

40.	OAC	Oral anticoagulants
41.	RWMA	Regional wall motion abnormality
42.	IBM SPSS	International Business Machines Corporation - Statistical Package for Social Sciences, New York, USA) software
43.	SD	Standard deviation
44.	ANOVA	Analysis of Variance
45.	MR	Mitral regurgitation
46.	HF	Heart failure
47.	PCI	Percutaneous coronary intervention
48.	LVH	Left Ventricular Hypertrophy
49.	LM disease	Left main coronary artery disease
50.	LAD	Left anterior descending artery
51.	LCx	Left circumflex coronary artery
52.	RCA	Right coronary artery
53.	SR	Sinus rhythm
54.	AUC	Area under curve
55.	ROC	Receiver Operating characteristic curve
56.	mm	Millimetre
57.	LR	Likelihood ratio
58.	PV	Predictive value
59.	eGFR	Estimated Glomerular filtration rate

SYNOPSIS

COMPARATIVE ANALYSIS OF LONG-TERM OUTCOME IN POST CORONARY ARTERY BYPASS SURGERY WITH AND WITHOUT NEW-ONSET ATRIAL FIBRILLATION

SYNOPSIS

BY

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SYNOPSIS

Introduction: After Coronary Artery Bypass Surgery (CABG), atrial fibrillation (AF) is the most common arrhythmia in the postoperative period. This new onset post-operative AF is reported to have an incidence of 11 – 40% (Long-term Thromboembolic Risk in Patients With Postoperative Atrial Fibrillation After Coronary Artery Bypass Graft Surgery and Patients With Nonvalvular Atrial Fibrillation - PubMed, n.d.). Post-operative AF is a new onset AF within the first 30 postoperative days (New-Onset Atrial Fibrillation After Coronary Artery Bypass Grafting and Long-Term Outcome: A Population-Based Nationwide Study From the SWEDEHEART Registry - PubMed, n.d.). It has been traditionally thought that postoperative AF is benign and transient. There is increasing evidence that they face greater peri and post-operative consequences. They have a higher risk of stroke, prolonged postoperative hospital stays, and in-hospital mortality than those who remain in sinus rhythm postoperatively. This is also associated with postoperative delirium and neurocognitive decline in some patients (Incidence and risk factors for development of atrial fibrillation after cardiac surgery under cardiopulmonary bypass - PubMed, n.d.). The risk factors for developing postoperative AF are increasing age, renal dysfunction, prior heart failure, those who underwent surgery for valvular heart disease along with CABG, and post-operative complications like infections, stroke and unstable hemodynamics (Auer et al., 2005).

Aim: To study the long-term outcomes of new-onset atrial fibrillation in post-coronary artery bypass surgery in comparison with those patients without atrial fibrillation and to study the risk factors responsible for the development of new-onset atrial fibrillation in post-coronary artery bypass surgery patients

Methods: This is a retrospective cohort of 1002 patients who underwent CABG primarily for CAD. These patients were divided into two cohorts based on whether they had developed Atrial Fibrillation post-operatively or not. The baseline clinical and Echocardiographic parameters were taken for analysing the risk factors for the development of POAF. All these patients were assessed for long-term outcomes like the development of MACE events and mortality.

Results: Among 1002 patients, 110 (11%) developed Post-operative Atrial Fibrillation. The median follow-up of the study population is 7 ± 4.5 Years. The mean age at the time of surgery was higher in the POAF group, 58.8 ± 9 years than those who have not developed Atrial fibrillation (54.1 ± 8.6 years). 87.4% of the study population is male. There is a higher association of POAF in males. In the POAF group, 67.3% are diabetic, 81.8% are hypertensive, whereas in the no POAF group, only 53.1% are diabetic ($p = 0.005$), and 65.5% are hypertensive ($p = 0.001$). 4.5% of patients in the POAF group had peripheral vascular disease, and 29.1% of patients in the POAF group had Left ventricular hypertrophy, whereas only 1.2% in no POAF group had peripheral vascular disease and only 16.8% in the no POAF group had Left ventricular hypertrophy with p-value of 0.009 and 0.002 respectively. Patients in the POAF had a larger LA size of 38.0 ± 4.5mm than those without POAF (35.4 ± 4.4mm) with a significant p-value of <0.001. There is no statistical difference between the groups in terms of CBT time, Aortic cross-clamp time and mean LV ejection fraction.

Patients in the POAF group had higher CHADSVASc scores than those without POAF. Most of the patients in the POAF group had CHADSVASc score ≥2 (77.3%), whereas only 54.1% of the patients in the No POAF group had CHADSVASc score

≥2, which is statistically significant (p = 0.041) with Odds Ratio = 2.9 (95% CI for OR = 1.8-4.6).

84% developed Atrial fibrillation within the first four days of the post-operative period, with the maximum onset in the day one post-operative period (27%). No patient has developed AF beyond ten days of the post-operative period.

One hundred six patients (96%) reverted to sinus rhythm. 2 patients did not revert, and two patients initially reverted to sinus rhythm; however, prior to discharge, they went back to atrial fibrillation.

Overall, 96.3% of the patients who developed POAF reverted to sinus rhythm within 72 hours of the development of AF. Almost two-thirds of the POAF patients (68.9%) of the POAF patients were reverted to Sinus Rhythm within 24 hours of development of AF. Most of the patients were reverted with either medications or DC cardioversion or a combination of medical therapy and DC (Direct current) cardioversion. Only 22% (24 patients) who had POAF reverted spontaneously.

Factors associated with POAF in the univariate analysis were Diabetes Mellitus (p=0.005), Hypertension (p=0.001), CHADSVASC SCORE ≥ 2 (p<0.001), Prior AF (p=0.001), presence of Left ventricular Hypertrophy (p=0.002), presence of prior Atrial fibrillation (p=0.001), Post-operative MI (p=0.004) and post-operative Heart failure (p<0.001). However, CHADSVASC SCORE ≥ 2 (p<0.001), History of Prior AF (p=0.016), presence of Left ventricular Hypertrophy (p=0.012), and post-operative Heart failure (p<0.001) remained statistically significant in the multivariate logistic regression analysis.

MACE events occurred more in the POAF group (25.5%), whereas it occurred only 20.6% in the no POAF group. However, it is not statistically significant (P = 0.242). ACS events on follow-up occurred in 15.5% of the POAF group, whereas in only 13.5% of the population in the no POAF group, but not statistically significant. There is also no statistical difference between both groups in terms of heart failure admissions between POAF and no POAF group (4.5% vs 2.7%, p = 0.274). There is also no statistical significance between both groups for CVA events.

There is no statistically significant difference in the all-cause mortality between the groups (12.7% in the POAF group and 8.2% in the no POAF group). However, mortality due to ischemic CVA (Malignant stroke) is significantly higher in the POAF group (3.6%) than those without POAF (1.1%), with a p-value of 0.034. Death due to major bleeding is also higher in the POAF group. The mean duration of survival among the POAF group and the no POAF group was 14.98 (95% CI, 14.03 to 15.9 years) and 16.6 (95% CI, 16.3 to 16.9 years), respectively. The overall survival rate at the end of 5 years for the POAF group was 95%, and that for the no POAF group was 96.4%.

In the POAF group, nine patients (8.2%) had a recurrence, whereas in the no POAF group, 14 patients (1.6%) had a recurrence of AF, which is statistically significant with a p-value of <0.001.

Conclusion: CHADSVASC SCORE ≥ 2, History of Prior Atrial fibrillation, presence of Left ventricular Hypertrophy and occurrence of post-operative Heart failure were the strong predictors for the development of Atrial fibrillation. There is no significant difference in MACE events and overall mortality between those patients who developed Atrial fibrillation post-op and those without. However, there is an increased

risk of death due to malignant stroke in patients with POAF. The risk factors identified in this study for the development of POAF can be used as a comprehensive screening tool for high-risk patients who undergo CABG to predict the occurrence of atrial fibrillation postoperatively.

INTRODUCTION

Introduction:

Atrial arrhythmias are also common after cardiac surgery. Atrial fibrillation (AF) and Atrial flutter are the most common atrial arrhythmia postoperatively. The incidence of AF after any non-cardiac surgery ranges from 0.4-15% (Gaudino, Di Franco, Lisa Q. Rong, et al., 2023; Hsu et al., 2021). Acute or new onset Atrial fibrillation is the most occurs in almost 11-40% of cardiac surgery, especially coronary artery bypass surgery, and its incidence is even higher in valvular surgery patients reported up to >50% (Greenberg et al., 2017). With the recently available continuous electrocardiographic monitoring systems, the incidence of postoperative AF (POAF) has been reported up to 62% after Coronary artery bypass surgery. It is associated with numerous detrimental sequelae. Most of the time it is benign and transient. However, it may also be associated with a prolonged hospital stay, increased morbidity and mortality and increased the financial burden on health care system. Reports suggested that it is also associated with an increased risk of cerebrovascular accidents. It is also associated with increased re-hospitalisation risk after discharge (Mathew et al., 2004a; Tzoumas et al., 2022). Recent evidence suggests that there is an increased risk of cerebrovascular events even ten years after the surgery. It is also found to be associated with an increased risk of late-onset recurrence of atrial fibrillation and heart failure hospitalisations. The major pathophysiological theories that lead to the development of POAF are injury to atrial structures during surgery, increased inflammatory markers postoperatively, myocardial ischemia, alterations in peri atrial adipose tissue metabolic activity and autonomic neuromodulation (Gaudino, Di Franco, Lisa Q. Rong, et al., 2023). The peak incidence of POAF is between days 2 and 4 after surgery. There are higher chance of recurrence especially during first postoperative week. Most often

return to sinus rhythm is spontaneous. Some may require rate or rhythm strategy (Dobrev et al., 2019a).

REVIEW OF LITERATURE

Review of Literature:

Definition:

Atrial fibrillation is defined as a supraventricular tachycardia that is due to uncoordinated atrial electrical activation and consequently ineffective atrial contraction. Electrocardiographic characteristics of Atrial fibrillation is irregularly irregular R-R interval when atrioventricular conduction is not impaired, absence of distinct P waves in ECG, Irregular atrial activations. Clinical AF is defined as any AF that is symptomatic or asymptomatic AF that is documented in surface ECG. The minimum duration if an ECG tracing fir diagnosing clinical AF is at least 30 seconds duration or entire 12 lead ECG (Hindricks et al., 2021a). Post operative Atrial fibrillation is in general defined as newly occurring AF immediately after surgery. There is no proper consensus for the details of the definition. Different authors define it in different way in their studies. Some define as post operative AF that requires treatment as POAF, Others defines as AF episode lasting for > 30 seconds or any new onset AF that occurs postoperative irrespective of duration. Some studies used definition of POAF when the AF episode lasts for > 10min (Gaudino, Di Franco, Lisa Q. Rong, et al., 2023). The most acceptable definition is development of new onset atrial fibrillation occurring within 30 days postoperatively that lasts for more than 30 seconds (McIntyre, 2023). POAF usually peaks around second to third post-operative day and then decreases by end of third or fourth week after surgery. In a study by Bidar et al, almost 40.5% of patients developed POAF within 0-5 post operative days. The incidence remained almost at this level till 16th post operative day. However, beyond 16 post operative days there is drastic decline in incidence of POAF i.e., 2% in the

remaining 14 days (Bidar et al., 2014). In SEARCH-AF trial, with continuous ECG monitoring it is found that 73.3% developed AF in first week, 20% in second week, 6.7% developed in third week, 0.03% in fourth week of surgery. This indicates that there is no significant increase in incidence of AF beyond fourth week postoperatively (Ha et al., 2021). There is also another study which showed that POAF occurring mainly within first 5 days of post operative day (A. G. Zaman et al., 2000). With all these observations its justifiable to label Post operative AF as any new onset AF occurring within first 30 postoperative days. The incidence of POAF varies from the type of surgery whether cardiac or non-cardiac and the type of cardiac surgery.

	Incidence **(Gaudino, Di Franco, Lisa Q. Rong, et al., 2023)**
AFTER CARDIAC SURGERY	
Overall	~30%
CABG	~20%
Valve surgery	40%–50%
Aortic surgery	~30%
Heart transplant	~4%
AFTER THORACIC SURGERY	
Overall	~15%
Pneumonectomy	~30%
AFTER OTHER TYPES OF SURGERY	0.4% - 15%

Table 1: Review of Incidence of POAF (Reproduced from Gaudino et al)

The patients who undergo valve surgery has the highest incidence of development of POAF. The development of POAF among those patients who undergo primarily only CABG is around 20%. Non cardiac surgeries have the least incidence of development of POAF.

Risk Factors:

Post operative AF is an important surgical complication and it is increased in those patients with comorbidities. The risk factors for the development of POAF mainly depend on:

1. The underlying abnormality that exists in atrial substrate preoperatively (Like Preoperative history of AF or Hypertension)
2. Abnormalities in the atrial substrate that appear after the surgery (Like valvular surgery, atrial cannulation technique).
3. The factors that increase the presence of potential triggers for arrhythmia (like electrolyte disturbance, increased sympathetic tone, etc.)

The risk factors can be categorised into patient–related, perioperative, and post-operative factors (Tzoumas et al., 2022).

Patient-related factors	Peri-operative factors	Post-operative factors
Higher Age	Operative Trauma	Electrolyte imbalances
Male	Ischemic injury	Post-operative pneumonia

Obesity	Intra-aortic balloon pump	Increased afterload
Hypertension	Pericardial trauma	Volume overload
COPD	Atrial dilation	Pericardial effusions
CKD	Reperfusion injury	Hypotension
Structural heart abnormalities	Volume changes	
Increased markers of fibrosis	Inotropic usage	
Prior heart surgery	Extracorporeal circulation	
	Left ventricular venting	

Table 2: Risk factors for development of POAF (Reproduced from Tzoumas A et al)

Preoperative Clinical Risk Factors:

Prior Arrhythmia:

In general, prior atrial arrhythmias are strongly associated with the subsequent AF recurrence, which holds true even after cardiac surgery. This is due to the postoperative persistence of preoperative changes in the atrial structural substrate and sensitivity of the same triggers, which made AF possible previously can result in AF postoperatively. The effect of electrical remodelling should also be considered. Moto et al. in a large, single-centre study from the Mayo Clinic, demonstrated that in a consecutive 800 patients undergoing isolated coronary artery bypass grafting (CABG), POAF occurred in 45% (21/47) with prior atrial arrhythmias that those without pre-

operative evidence of AF 22% (165/749) [P<.001]. It is also found that preoperative premature atrial beats are also associated with increased risk of post-operative AF (Hashimoto et al., 1991). As the definition of 'prior AF' is not clearly defined in most of the studies, and some of the studies exclude the prior arrhythmia the actual risk of prior Atrial fibrillation in development of POAF is to be established in multiple studies.

Age:

Increasing age is an independent factor for development of post operative AF. Leitch et al in a large study that recruited 5807 consecutive patients who underwent CABG alone found that POAF occurred in 17.2%. The prevalence of AF is directly proportional to the age at operation. It varies from 3.7% in patients aged less than 40 years and 27.7% in patients aged more than or equal to 70 years (Leitch et al., 1990). In a study by Almassi et al, which included 3855 patients from veterans administration hospital across united states demonstrated that an on odds ratio of 1.6 for each additional 10 years of age above 50 years for development of POAF (Almassi et al., 1997). Similar age distribution for development of atrial fibrillation occurred in the general population as shown in the Framingham population (Benjamin et al., 1994). In another study by Zaman et al which included 358 elective CABG patients found that the incidence of AF progressively increased with age such hat the incidence of POAF is 3.4% in patients aged between 50 to 54 years whereas the incidence is almost 42.2% in patients aged 70 to 74 years (A. G. Zaman et al., 2000). Age related changes in the atrial substrate, such as dilatation, myocardial atrophy and fibrosis, decreased conduction velocity, as well as related co-morbidities has been hypothesized as the

reason for association of higher age with AF (Aranki et al., 1996).These changes in the atrial substrate occur independently of the event of cardiac surgery. The age-related incidence of development of POAF could theoretically parallel with the age-related incidence of AF in general population.

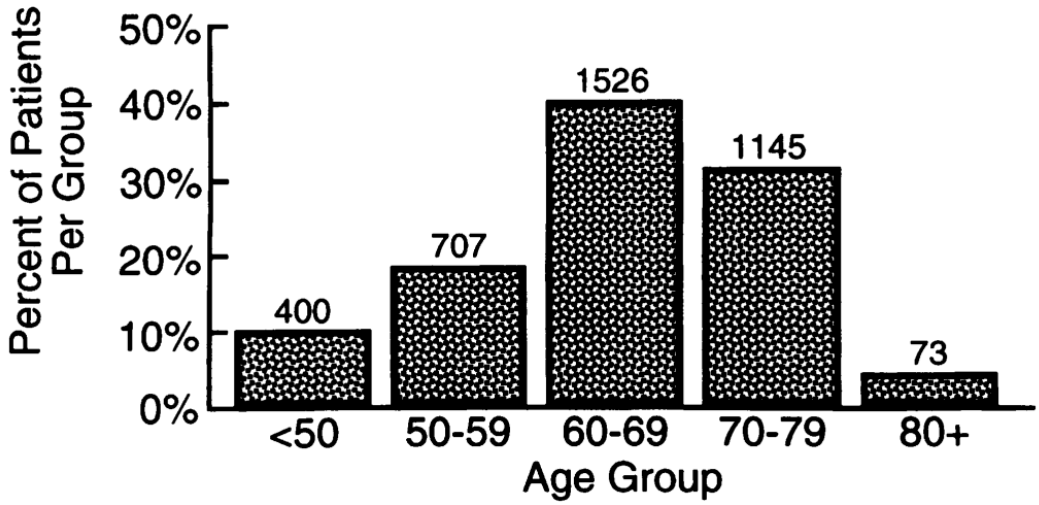

Figure 1: Age Vs POAF risk
(Reproduced from Almassi et al) (18)

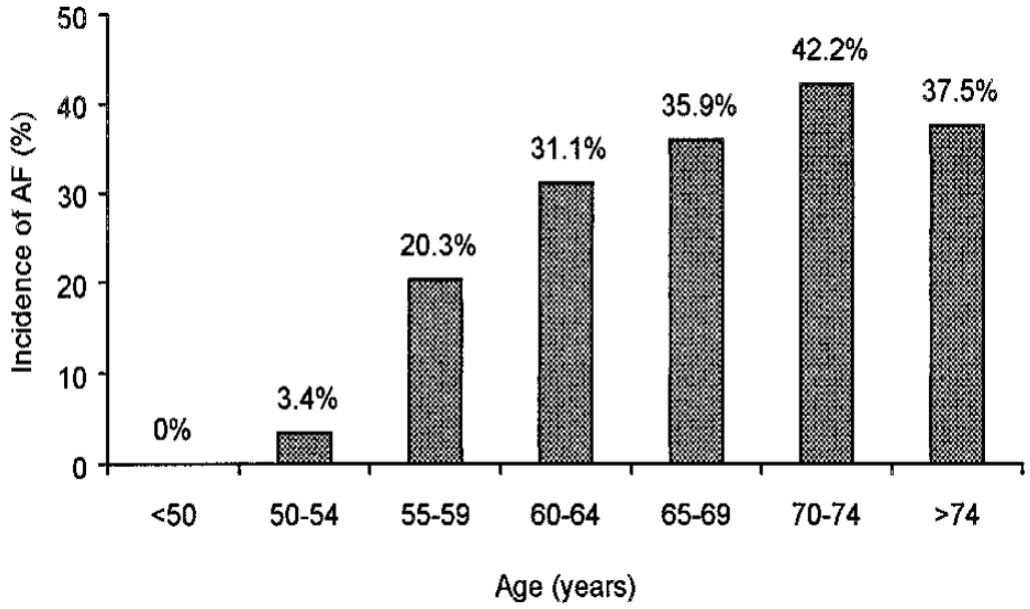

Figure 2: Graphical report demonstrating the risk of POAF with increasing age. Reproduced from Zaman et al (15)

Gender:

There is strong association between male gender and AF is established in general population the association remains still controversial in POAF. Most of the studies showed similar incidence of POAF between men and women. A study by Aranki et al [12] with 175 women of 570 total patients (31%) demonstrated a significant association of AF to male gender with odds ratio of 1.7 (95% CI: 1.1-2.7)(Aranki et al., 1996). Harmone related protective mechanism may account for this gender difference.

Other preoperative medical conditions:

Congestive heart failure:

The association of preoperative history of congestive heart failure with development of POAF is controversial. In single centre studies done by Hashimoto et al and Aranki et al failed to demonstrate association between preoperative symptoms of congestive heart failure and post operative AF. However, it was found elevated left ventricular end-diastolic pressure (> 20mmHg) was associated with POAF (Aranki et al., 1996; Hashimoto et al., 1991).

Hypertension:

In general population there is strong association of development of AF in patients with systemic hypertension. Its association with development of POAF remains controversial. In the data from Leitch et al POAF occurred in 18.2% with history of hypertension whereas it occurred in 16.2% without hypertension ($P<0.05$) (Leitch et al., 1990). Another study done by Almassi et al predominantly in male veterans among those who developed POAF 61.4% had prior hypertension whereas only 58% had prior hypertension (Almassi et al., 1997). Another study by Aranki et al also noted borderline significance of association of Post operative AF and hypertension. 65% of patients with POAF had prior history of hypertension where as 56% of patients doesn't have prior hypertension history (Aranki et al., 1996). Resting systolic blood pressure > 120mmHg was found to an independent predictor of POAF. However, some studies have proven that there is no association of prior systemic hypertension and development of POAF. A study by Hashimoto et al failed to demonstrate any significant association between systemic hypertension and POAF (Hashimoto et al., 1991). Similarly, another study by Steinberg et al also demonstrated that there is no significant association between POAF and hypertension. However, in

the same study it is demonstrated that presence of left ventricular hypertrophy on surface ECG is associated with development POAF. Since ECG changes of hypertrophy occur most often in setting of long standing hypertension these findings suggest that the alteration in myocardial substrate resulting from hypertension may plan an important role in development of POAF (Steinberg et al., 1993).

Chronic lung disease:

There are conflicting data to prove association between preoperative lung disease with post operative AF. Study by Almassi et al showed that 19.57% of patients had prior chronic obstructive lung disease (COPD) that is defined by FEV1 < 1.5Lit whereas prior COPD was present only in 13.57 % who developed POAF (Almassi et al., 1997). In another study by Leitch et al clinical chronic lung disease was present in 25.5% who developed POAF whereas only 16.8% who haven't developed POAF had prior chronic lung disease. Though this finding is not statistically significant it there is trend towards the development of POAF if the patient has prior chronic lung disease (Leitch et al., 1990). Also, another study by Aranki et also demonstrated the trend towards the development of AF postoperatively if the patient had prior chronic lung disease (Aranki et al., 1996).

Adrenergic stimulation:

In the postoperative period, it is found that there is increased norepinephrine levels in patients with development of post operative AF. Kalman et al prospectively studied 131 consecutive patients undergoing CABG of which 65 (50%) developed AF. Serum norepinephrine levels were determined immediately after surgery and every 4 hours for 48 hours following the surgery in sample drawn from the right atrial cavity

via a central venous catheter. Patients who developed AF had significantly higher serum norepinephrine levels immediately following surgery (5.78±2.83 nmol/L vs. 3.57±1.31 nmol/L, $p<0.0001$). In addition, the elevation in norepinephrine levels remained significant for every 4-hour sampling interval in the immediate postoperative period. While this type of sampling represented only generalized sympathetic activity, it clearly documented differences in those patients who developed AF. It is also found that serum norepinephrine levels were significantly higher in those patients on beta-blockers preoperatively (Kalman et al., 1995).

Left atrial size:

The increased left atrial (LA) size is associated with development of post operative AF. In a cohort of 205 patients undergoing cardiac surgery at the Mayo Clinic, it was shown that preoperative indexed LA volume was an independent predictor of postoperative AF, with an LA volume index >32 ml/m^2 conferring an almost 5-fold elevated risk of postoperative AF (compared with the LA volume index ≤ 32 ml/m^2) (Osranek et al., 2006). It is not clear whether LA volume is superior to LA size is predicting the risk of post operative AF. In a retrospective cohort study, which included 3047 isolated CABG patients for risk factor assessment of development of Post operative AF. LA enlargement was defined as an LA diameter of ≥ 41 mm in men or ≥ 39 mm in women. LA diameter below these values was defined as normal LA size. LA enlargement was further categorized as mild (LA diameter 41 to 46 mm in men or 39 to 42 mm in women), moderate (47 to 51 mm in men or 43 to 46 mm in women) or severe (≥ 52 mm in men or ≥ 47 mm in women) according to the recommendations of the American Society of Echocardiography. Moderate to severe

LA enlargement had an odds ratio of 2.176 (95% CI: 1.240-3.820, p = 0.013) for developing AF (Karimi et al., 2020).

Left ventricular ejection fraction (LVEF):

Reduced left ventricular function is associated with the occurrence of AF in the general population. However, its association following cardiac surgery is unclear. In most of the studies the method of assessment of LVEF is poorly defined and is not standardized. One of the largest study is from Hashimoto et al (Hashimoto et al., 1991) at the Mayo Clinic. Here, LVEF data from cardiac catheterization was obtained in 719 of 800 patients undergoing isolated coronary artery bypass surgery; the LVEF was 57±13% in the 553 patients without postoperative AF as compared to 56±13% in the 166 with postoperative AF. A systematic review conducted by Seo et al which included 9 studies with a total of 4798 patients, among them 1555 (32.4%) developed POAF after CABG. The presence of lower left ventricular ejection fraction in Asian patients is a significant risk factor for development of AF (P = 0.001) but not in European population (Seo et al., 2021).

Cardiopulmonary Bypass time (CBT time):

Cardiopulmonary bypass is established prior to the initiation of cardioplegia. It represents a period of time when the myocardium is faced with potential ischemic compromise. Majority of the available studies in the literature showed that there is no association between CBT time and development of POAF. The PSOCS (Processes,

Structures and Outcomes of Care in Cardiac Surgery) trial with 3855 patients from 14 VA (Veterans Affairs) hospitals around the US, demonstrated no difference in duration of cardiopulmonary bypass undergoing all types of cardiac surgery (Almassi et al., 1997).

Aortic Cross-Clamp Time:

Aortic Cross-Clamp Time reflects the period of time of the actual cardiac surgery. That is, after cardiopulmonary bypass and cardioplegia have been established. This is the actual period of time when physiologic antegrade blood flow through the coronary arteries has ceased and during which the proximal and distal graft anastomoses are performed. As such, it most precisely reflects the time of greatest ischemic potential for the myocardium. As with CBT time majority of reports in the literature suggest that there is no association between the aortic cross-clamp time and the development of POAF. In a study by Creswell and colleagues though patients with higher aortic cross – clamp time had higher incidence of development of POAF it became non-significant in multi variate analysis (Creswell et al., 1993). In small study by Caretta et al the patients who developed POAF had higher aortic cross clamp time (Caretta et al., 1991).

Peri- and postoperative myocardial infarction:

In a general cardiology population, AF occurs in 10-15% of patients with acute myocardial infarction (Ellis et al., 1980). Hence it is reasonable to expect that

perioperative myocardial infarction would be associated with an increased incidence of AF. Almassi et al in the PSOCS trial noted perioperative myocardial infarction in 84 of 1133 (7.4%) of patients with postoperative AF as compared to infarction in 91 of 2709 (3.4%) patients without AF ($p<0.001$) (Almassi et al., 1997).

Postoperative pericarditis:

Post op pericarditis is frequently discussed as an important risk factor for the development of postoperative AF. It is proven in some animal studies. n. By definition, all patients undergoing cardiac surgery require pericardial interruption and many patients demonstrate some degree of pericarditis postoperatively. However, some of the studies failed to prove association of post op pericarditis with development of POAF. In a single centre study by Crosby et al (Crosby et al., 1990), found pericarditis in only 8 of 122 (6.6%) patients who developed postoperative AF as compared to its occurrence in 23 of the 296 (7.8%) who did not (p = Not significant). However, in this study, the strict definition of pericarditis ("an audible pericardial friction rub after the removal of all chest tubes" occurring with "associated symptomatology" and requiring treatment with anti-inflammatory agents) limited the number of patients so diagnosed. Using a less strict definition, Rubin and colleagues (Rubin et al., 1987) noted pericarditis in 61 of 123 (50%) total patients in their study of potential risk factors for the development of postoperative AF. Twelve of 36 (33%) patients who developed AF had pericarditis as compared to 49 of 87 (56%) without AF, this difference as not statistically significant.

Pathophysiology of Atrial fibrillation:

Most of the information regarding POAF pathophysiology is derived from cardiac surgery series. It has its unique pathophysiology compared to those patients who develop AF outside post operative period.

The main pathophysiological theories for POAF are (Gaudino, Di Franco, Lisa Q. Rong, et al., 2023):

- Atrial structural alterations
- Pericardial effusion and inflammation
- Gap junction uncoupling
- Peri-atrial adipose tissue metabolic activity
- Myocardial ischemia
- Ion channels modifications
- Autonomic neuromodulation
- Re-entry and ectopic activity in the pulmonary veins

Atrial structural alterations:

Though cardiovascular risk factors and comorbidity burden contribute to the risk of POAF, cardiac surgery imposes a unique set of circumstances that facilitate POAF occurrence. Direct atrial myocardial injury occurring at the time of surgery like venous cannulation via right atriotomy or manipulation and suturing of the perivalvular atrial tissue in mitral and tricuspid surgery can cause occurrence of POAF. The inhomogeneity of conduction and anisotropic conduction occurring after myocardial injury may favour dynamic re-entry circuits in the atrium and finally leading to development of POAF (Ishii et al., 2005).

Pericardial effusion and inflammation:

The key mechanism that can promote POAF is inflammation. Certain studies have shown that the peak concentrations of inflammatory markers like C-reactive protein correlates with the same time as the peak incidence of POAF (Bruins et al., 1997). The ability of anti-inflammatory interventions to reduce the risk of POAF highlights the critical role of inflammation in the development of this arrhythmia. In some studies, it is found that corticosteroid and colchicine can cause reduction in the occurrence of POAF.

Gap junction uncoupling:

With the help of animal models of sterile pericarditis show that inflammation of pericardium lead to induction of atrial arrythmia. Pre-clinical work is suggestive of changes in connexins and loss in epicardial myocyte by activation of fibroblast in epicardium of atrium (Siontis et al., 2022; Walsh et al., 2007). Once there is decrease in connexin in midmyocardium and epicardium, it will lead to slowing in conduction, which in turn is not uniform and proarrhythmic(Ryu et al., 2007). Interestingly, in pre-clinical models of pericarditis, the use of gap-junction modifiers has shown improvement in conduction and helped in prevention of AF(Rossman et al., 2009). Even the shed mediastinal blood remaining in pericardial space leads to oxidation and inflammation(St-Onge et al., 2018).

Peri-atrial adipose tissue metabolic activity:

Adipose tissue in epicardium has been illustrated as a source of pro-inflammatory paracrine effects that increased both risk and severity of AF(Wong et al.,

2016, 2017). This is linked to secretome of adipose tissue in epicardium seems to promote electrical changes like increased conduction heterogenicity in cardiac myocyte and decreased conduction velocity, which directly favours AF(Ernault et al., 2022). Some recent studies have shown that interleukin (IL)-1β secretion by epicardial adipose tissue is significantly more in individuals who develop POAF as compared to those not developing POAF(Cabaro et al., 2022). After CABG, in individuals developing POAF and not developing POAF, when epicardial adipose tissue was subjected to proteomic and genetic analysis revealed association between protein involved in inflammation and regulation of ion channel in individuals developing POAF(Viviano et al., 2018). In epicardial adipose tissue both inflammatory mediators and alteration in conduction appears to be therapeutic target as localized strategy for preventing POAF as it can be easily accessed at time of cardiac surgery. Decline in incidence of POAF was also observed with strategies aimed towards pericardial drainage after cardiac surgery(Gozdek et al., 2017).

Myocardial ischemia:

There is evidence suggestive of role of myocardial ischemia in development of POAF. Outside surgery, obstruction in atrial branches of coronary artery is associated with AF development. After cardioplegic arrest ischemic-reperfusion injury occurring to myocardium of atrium also plays role in pathogenesis of POAF(Tchervenkov et al., 1983). Among on-pump and off-pump coronary artery bypass, on-pump bypass has shown to be associated with higher incidence of myocardial ischemia and inflammation, hence with more risk of developing POAF(Gaudino, Di Franco, Lisa Q Rong, et al., 2023).

Ion channels modifications:

Although altered atrial substrates and conventional risk factors predispose to all varieties of AF, the extent to which conventional factors and acute factors contribute in pathogenesis of POAF is not completely clear. There is increased probability of POAF as age and comorbidity increases(Gaudino, Di Franco, Lisa Q Rong, et al., 2023). In contrast, although differences in activity and expression of ion channel are involved in pathogenesis of non-surgical AF, it is unclear if these changes are critical for POAF induction. In patients with and without POAF, the collective evidence does not strongly corroborate key differences in potassium channel activity or intracellular levels of calcium channels(Gaudino, Di Franco, Lisa Q Rong, et al., 2023; Workman et al., 2006).

Autonomic neuromodulation:

Effect of autonomic system appears to be crucial in pathogenesis of both surgical and non-surgical POAF(Dimmer et al., 1998; Karatela et al., 2023). Specifically, activation of sympathetic system proves to play a critical role in initiation of POAF and elevation of catecholamines play an important role in predicting onset of POAF(Gaudino, Di Franco, Lisa Q Rong, et al., 2023). Sympathetic stimulation with concomitant activation of parasympathetic system, results in increased gradient of calcium ion and afterdepolarization which in turn trigger arrythmia. There is shortening of effective refractory period in atrium in response to parasympathetic stimulation(Patterson et al., 2006).

Excluding perioperative setting, one of the important triggers in development of AF is pulmonary vein ectopy. Henceforth, there is paramount reduction in recurrent

AF by isolating pulmonary veins with catheter ablation (Gaudino, Di Franco, Lisa Q Rong, et al., 2023).

Given the importance of influence of autonomic and sympathetic activity in pathogenesis of POAF, it is evident why treatment with beta-blocker protective against POAF. There is decreased risk of POAF after cardiac denervation(Pokushalov et al., 2015). Likewise, suppressing ganglionated plexi of in epicardium by injecting botulinum toxin (reversible) or calcium chloride (irreversible injury) has proved to reduce severity and risk of POAF (Pokushalov et al., 2015; Waldron et al., 2019; Wang et al., 2021). By improving our understanding of autonomic changes inducing POAF, we can improve our ability to prevent and treat it.

The main pathophysiological theories for POAF are summarized in Figure 3 (Gaudino, Di Franco, Lisa Q Rong, et al., 2023).

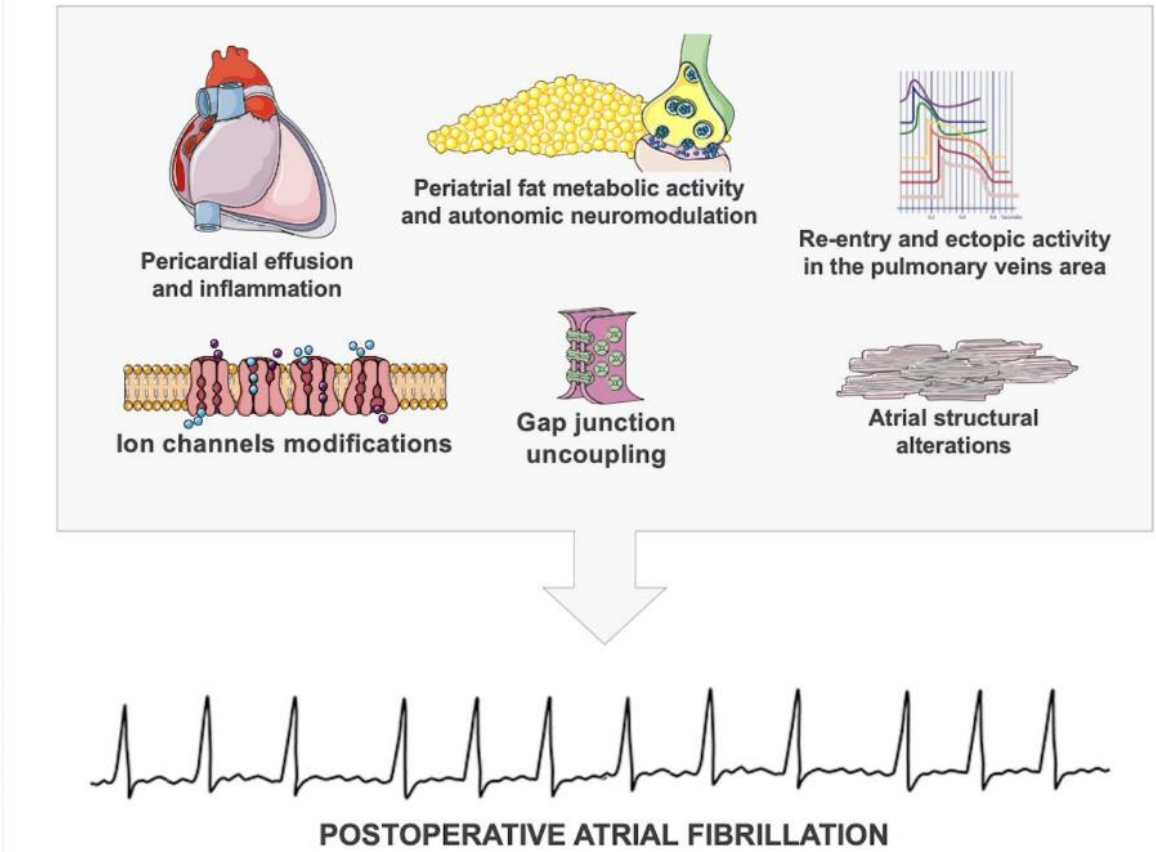

Figure 3: Summary of theories of pathophysiology for POAF

Figure adapted from "Postoperative Atrial Fibrillation: from mechanism to treatment" article by Gaudino et al.(45)

The possible overlap in risk factors for POAF following cardiac vs. non-cardiac surgery is summarized in Figure 4 (Gaudino, Di Franco, Lisa Q Rong, et al., 2023).

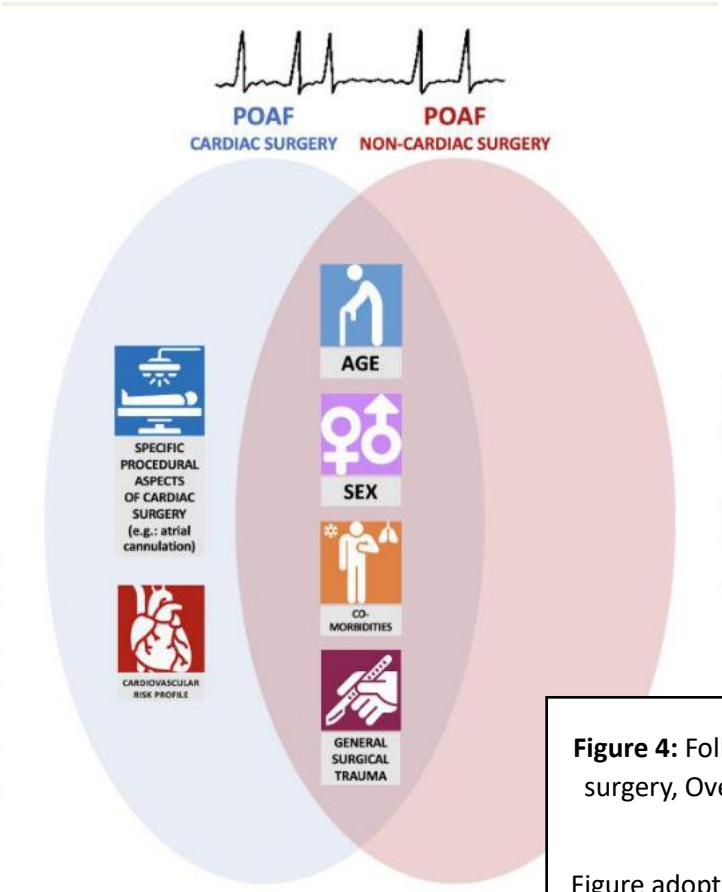

Figure 4: Following cardiac vs. noncardiac surgery, Overlap in risk factors for POAF (45)

Figure adopted from "Postoperative Atrial Fibrillation: from mechanism to treatment" article by Gaudino et al.

Prevention:

1) **Beta blockers:**

According to recommendation by international guidelines (European Society of Cardiology [ESC] guidelines in year 2020, level A of evidence and Recommendation of class I), in patients undergoing cardiac surgery, perioperative beta blockers are cornerstone for prophylaxis of POAF(Hindricks et al., 2021b). Yet available evidence suggests limited use of beta blocker in clinical practice due to improper utilization and high rates of withdrawal in post operative period, approximately 25%(Mathew et al., 2004b).

In a meta-analysis, by Kim et al. involving 25496 patients from 13 studies, who were undergoing cardiac surgery, revealed that incidence of POAF is significantly lower in patients receiving perioperative beta blocker (OR 0.70, 95%CI 0.55–0.91 and OR 0.56, 95% CI 0.35–0.91 in non-randomized and randomized studies, respectively)(Kim et al., 2021). As perioperative incidence of stroke and hospital stay did not show any difference in between two groups, reduced POAF did not render improvement in clinical outcomes. Similar findings were observed in Cochrane meta-analysis including 33 RCTs, which reported decrease in incidence of POAF in patients undergoing cardiac surgery who were randomized to beta blockers (0.33, 95%CI 0.26–0.43), with no effect observed on rate of perioperative stroke, duration of hospital stay or mortality rate(Arsenault et al., 2013). These findings were consistent with a meta-analysis of 10 RCTs involving 2556 patients in total, which reported significantly reduced incidence of POAF in patients who received beta blocker prophylactically (20% vs. 32.8% in control subjects; $P<0.001$)(Khan et al., 2013). It also reported that Carvedilol, among other beta blockers was the most effective drug for prophylaxis of POAF (55% RR reduction vs. metoprolol; $P< 0.001$).

The use of beta blockers prophylactically in patients not undergoing cardiac surgery has been associated with higher rates of adverse events and hence international guidelines discourage their use (ESC guidelines for the diagnosis and management of AF, 2020, B level of Evidence and Class III Recommendation)(Hindricks et al., 2021b). A Cochrane review involving 14,967 patients (not undergoing cardiac surgery) from 83 RCTs, reported

decreased incidence of postoperative AF or flutter (RR 0.41, 95%CI 0.21–0.79) and myocardial ischemia (RR 0.72, 95%CI 0.60–0.87) in patients receiving beta blocker, whereas it showed no significant variation in patient receiving beta blocker vs. control group in terms of cerebrovascular events (RR 1.65, 95%CI 0.97–2.81) and postoperative mortality (RR 1.17, 95%CI 0.89–1.54)(Blessberger et al., 2019).

2) **Amiodarone**:

Amiodarone may play a role in prevention of POAF by multiple mechanism involving re-entrant activity and suppression of ectopic triggers(Gaudino, Di Franco, Lisa Q Rong, et al., 2023). In cardiac surgery patients, it's use is supported by multiple RCTs. Largest among all was PAPABEAR (Prophylactic Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair) trial, involving 601 patients, which reported significantly reduce incidence of atrial tachyarrhythmias in patients who were given oral amiodarone as compared to patients who received placebo (16.1% vs. 29.5%; HR 0.52; 95%CI 0.34– 0.69; $P < 0.001$), but no difference was reported for in-hospital mortality or post op complications(Mitchell et al., 2005). Whereas a Cochrane metanalysis(Arsenault et al., 2013), reported decreased duration of hospital stay and incidence of POAF in patients who received amiodarone as compared to patients who received placebo [(−0.95 days, 95%CI −1.37 to −0.52 days); (OR 0.43, 95%CI 0.34–0.54) respectively], but no difference was observed in rate of stroke or mortality. However, a meta-analysis including 14 RCTs involving 2864 patients, it was found that there was no significant difference

in decreasing incidence of POAF after cardiac surgery when amiodarone was initiated preoperatively rather than postoperatively (OR 0.50, 95%CI 0.39–0.63 for pre-op initiation vs. OR 0.48, 95%CI 0.37–0.63 for post op initiation, p= 0.86) (Gaudino, Di Franco, Lisa Q Rong, et al., 2023).

The use of Amiodarone is limited by its inherent risks including acute lung injury, infusion-related hypotension and bradyarrhythmia(Gaudino, Di Franco, Lisa Q Rong, et al., 2023).

3) **Sotalol:**

The evidence of use of Sotalol is derived from a meta-analysis involving 5205 patients from 14 RCTs, which reported patients undergoing cardiac surgery who received Sotalol had significant decrease in incidence of POAF as compared to patient who received beta blocker (OR 0.42, 95%CI 0.26–0.65) and placebo (OR 0.37, 95%CI 0.29–0.48)(Burgess et al., 2006). Although no significant difference was observed in REDUCE trial in risk of POAF among 160 patients who underwent cardiac surgery and were randomized to receive Sotalol (25%) or amiodarone (17%), (p= 0.21)(Gaudino, Di Franco, Lisa Q Rong, et al., 2023).

The limiting factor for routine clinical use of Sotalol in cardiac surgery patients is renal clearance and tendency for QT prolongation(Dobrev et al., 2019b; Gaudino, Di Franco, Lisa Q Rong, et al., 2023).

4) **Other antiarrhythmic drugs:**

At present there is limited evidence for use of other antiarrhythmic drug in prevention of POAF. For use of calcium channel blocker, there is weak supporting evidence (Dobrev et al., 2019b; Wijeysundera et al., 2003).

A meta-analysis involving 3327 patients from 41 studies concluded that in patients undergoing cardiac surgery, there is no significant effect of calcium channel clockers on development of supraventricular tachycardia (OR 0.73, 95%CI 0.48–1.12); on further subgroup analysis dihydropyridine drugs were found to increase the incidence of arrythmia (OR 2.69, 95%CI 0.57–12) whereas no dihydropyridine drugs reduced the incidence (OR 0.62, 95%CI 0.41–0.93) (Wijeysundera et al., 2003).

There is paucity of evidence on use of other antiarrhythmic drugs belonging to class Ia, Ic or III. It is a general belief that caution should be kept while using antiarrhythmic drugs in postoperative period, as they have proarrhythmic adverse effects, which could worsen with presence of myocardial ischemia, simultaneous administration of inotropes, hemodynamic instability, abnormal renal/liver function and electrolyte disorder (Dobrev et al., 2019b).

5) **Magnesium:**

There is incongruity in data for efficacy of magnesium used intravenously in prevention of POAF(Gaudino, Di Franco, Lisa Q Rong, et al., 2023). In a RCT that randomized 389 cardiac surgery patients to receive magnesium after anaesthesia induction as regime of 50 mg/kg bolus of magnesium followed by 50 mg/kg intravenous infusion of magnesium over 3 hours and placebo group, concluded that incidence of POAF was not reduced in arm receiving magnesium (Klinger et al., 2015). A meta-analysis was conducted for 20 RCTs involving 2490 patients in total reported decrease in incidence of POAF after magnesium administration (OR 0.54, 95%CI 0.38–

0.75), but showed no difference in duration of hospital stay or mortality of patients (Miller et al., 2005). The findings were consistent with Cochrane meta-analysis done over 22 RCTs(Gaudino, Di Franco, Lisa Q Rong, et al., 2023). On the contrary, meta-analysis that included high quality five RCTs, concluded no significant reduction in incidence of POAF after administration of magnesium (OR 0.94, 95%CI 0.61–1.44; P = 0.77) (Cook et al., 2013).

6) **Colchicine:**

At present there is variegated evidence that support the use of colchicine in prophylaxis of POAF. A trial named; The Effect of Low-dose Colchicine on the Incidence of Atrial Fibrillation in Open Heart Surgery Patients trial (END-AF trial), though was closed prematurely in view of slow recruitment of participants and restricted statistical power reported that use of low dose Colchicine has no role in prevention of POAF in patients deemed to undergo cardiac surgery (OR 0.85, 95%CI 0.37–1.99)(Tabbalat et al., 2020). On the contrary, COPPS (Colchicine for the Prevention of the Post-Pericardiotomy Syndrome) POAF sub study, use of colchicine for 1 month period after cardiac surgery showed reduction in incidence of POAF (12.0% vs. 22.0%; P = 0.021), along with reduction in stay in rehabilitation (12.1 ± 6.1 vs. 13.9 ± 6.5 days; P = 0.009) and duration of hospital stay (9.4 ± 3.7 vs. 10.3 ± 4.3 days; P = 0.040) (Imazio et al., 2011). Important data about prevention of POAF using Colchicine is expected to be derived from the ongoing trial COP-AF (Colchicine For The Prevention Of Perioperative Atrial Fibrillation In Patients Undergoing Thoracic Surgery) (NCT03310125).

7) **Statins, glucocorticoids, and polyunsaturated fatty acids:**

Based on anti-inflammatory properties of glucocorticoids and statins; electrophysiological effects of PUFA, they have been suggested to used in prevention of POAF. However, due to paucity of current evidence over efficacy of these agents, present guidelines do not support to use them routinely in clinical practice(Hindricks et al., 2021b).

8) Overdrive atrial pacing:

Various RCTs have proven the role of Overdrive atrial pacing in prevention of POAF (Gaudino, Di Franco, Lisa Q Rong, et al., 2023). Arsenault et al. conducted a Cochrane meta-analysis across 21 trials involving 2933 patients reported that incidence of POAF in paced group (18,7%) as compared to non-paced group (32.8%) (OR 0.47, 95%CI 0.36–0.61) (Arsenault et al., 2013). A network meta-analysis that was conducted over 14 RCTs and involved 1727 patients, showed that there is decrease in incidence of POAF with atrial pacing after CABG (OR 0.49, 95%CI 0.35–0.69) and largest risk reduction was seen after bi- atrial pacing (OR 0.36, 95%CI 0.20–0.64 vs. OR 0.64, 95%CI 0.38–1.07 for right-atrial pacing and OR 0.59, 95%CI 0.34–1.02 for left-atrial pacing) (Ruan et al., 2020).

As it is well known that it is logistically difficult to implement Overdrive atrial pacing routinely in clinical setting. So also, it may also hinder activities of patients' in post operative period. Therefore, at present it's use is limited to clinical studies for research purposes.

9) Left posterior pericardiotomy:

The surgical procedure which involves drainage of the pericardial space into pleural space of left side is known as left posterior pericardiotomy.

Posterior pericardiotomy as a prophylactic strategy for POAF has been tested by various RCTs and most of them showed significant effect, but the quality of RCT in terms of methodology was low to medium(Gaudino, Di Franco, Lisa Q Rong, et al., 2023). Nonetheless, similar findings were reported by a meta-analysis done for 10 RCTs involving 1829 CABG patients in total, i.e, in group who underwent posterior pericardiotomy, there was significant reduction in POAF incidence (RR 0.45, 95%CI 0.29–0.64; P< 0.0001)(Xiong et al., 2021). A recent single centre, good-powered RCT reported significant reduction in POAF incidence in intervention arm (17% vs. 32%; P< 0.001; OR: 0.44, 95%CI 0.27–0.70; P< 0.001)(Gaudino et al., 2021).

10) **Intraoperative epicardial fat removal, pulmonary vein ablation, ganglionated Plexi and Botulinum toxin injection:**

As mentioned above, Autonomic effect and pericardial adipocyte dysfunction (secretion of cytokines and adipocytokines) plays a key role in atrial rhythm modulation. However, a meta-analysis done for seven RCTs involving 991 patients of CABG suggested that removal of anterior pad of fat is not associated with reduction in incidence of POAF (RR 1.34, 95%CI 0.88–2.03; P= 0.18) (Liu et al., 2015).

In animal models, promising results have been shown by use of Botulinum toxin as an agent to prevent POAF. Similar findings were reported by a small RCT that involved 60 patients who had history of paroxysm AF and underwent CABG (POAF incidence: 7% vs. 30% in the intervention group vs. controls, respectively; P= 0.024)(Pokushalov et al., 2014).

A pilot study tested role of map-guided ablation of autonomic ganglionated plexi in preventing POAF in coronary surgery trial, reported decrease in incidence of POAF by 32% with map guided ablation (13).

63% reduction (P= 0.001) in incidence of POAF was observed following $CaCl_2$ injection in four major ganglionated plexi in atrium and reported by Wang et al (Gaudino, Di Franco, Lisa Q Rong, et al., 2023).

In Cardiac surgery patients, there is only minute role of systemic pulmonary vein ablation as a preventive strategy for POAF, as suggested by current evidence. A RCT that randomized 175 patients in two arms, one who underwent CABG with radiofrequency pulmonary vein ablation bilaterally and other arm with CABG only, reported no significant variation in incidence of POAF in both arms (37.1% vs. 36.1%; P= 0.88) (Kiaii et al., 2015).

Outcomes:

POAF is considered as an asymptomatic event which usually occurs 2 to 4 days after cardiac surgery and resolves by self. Yet it forms an important clinical entity not only due to episode of arrythmia but also due to associated complications both in short term and long term, like heart failure, myocardial infarction, prolonged duration of stay in hospital and mortality.

Patients who are prone to develop POAF belong to older age group and are known to have multiple comorbidities. Moreover, POAF shares risk factors with risk factors for any adverse cardiovascular event. POAF shows strong association with raised morbidity and mortality when confounders are not adjusted (LaPar et al., 2014). This association is proven by many published

series even after adjustment of multiple variable (Benedetto et al., 2020; LaPar et al., 2014).

Many studies have reported association of non-surgical AF with structural remodelling of atrium specifically of extracellular matrix occurring as a result of changes in genetic expression(Gaudino, Di Franco, Lisa Q Rong, et al., 2023). However, majority of patients (83%) who develop non-surgical AF, also encounter POAF. It highlights that though non-surgical AF and POAF have different pathophysiology and are considered to be two separate entities, POAF can be considered as an entity to predict development of non-surgical AF earlier in years following surgery(Gaudino, Di Franco, Lisa Q Rong, et al., 2023). It could also be the mode of association between adverse cardiovascular event and POAF (Dobrev et al., 2019b; Gaudino, Di Franco, Lisa Q Rong, et al., 2023).

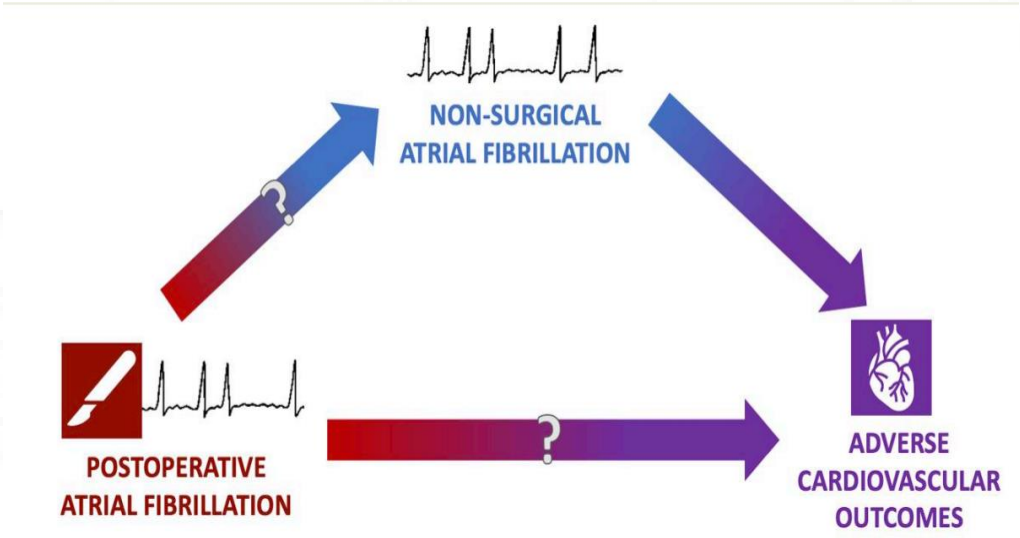

FIGURE 5: Association of POAF with adverse cardiac outcomes

Figure adopted from "Postoperative Atrial Fibrillation: from mechanism to treatment" article by Gaudino et al.

Clinical events associated with POAF after cardiac surgery:

Clinical events with POAF after cardiac surgery range from prolonged duration of stay in hospital to mortality, including, myocardial infarction, stroke, heart failure, non-surgical AF among others.

A strong statically significant association between hospitalization in view of heart failure and POAF (hazard ratio [HR] 1.33, 95% confidence interval [CI] 1.25–1.41) by a cohort study conducted in USA claiming data across 11 states and included 76,536 patients who underwent cardiac surgery(Goyal et al., 2022). A meta-analysis that included 57 studies (246340 patients) observed positive association of POAF with stroke (OR 2.17, 95% CI 1.90– 2.49), acute renal failure (OR 2.74, 95% CI 2.42–3.11), myocardial infarction (OR 1.28, 95% CI 1.06–1.54), perioperative mortality (OR 1.92, 95%CI 1.58–2.33) along with long term mortality (Caldonazo et al., 2023). The findings are consistent with another meta-analysis of 32 studies including 155575 patients, which reported even after adjustment of confounding factors, there was significantly high mortality in patients with POAF (HR 1.25, 95% CI 1.2– 1.3; $P < 0.01$); when splitted across years, 1 year-, 5 year- and 10 year- mortality was found to be 6% vs. 4% (OR 1.69, 95% CI 1.1–2.6; $P = 0.02$), 15% vs. 10% (OR 1.6, 95% CI 1.52–1.68; $P < 0.0001$) and 29% vs. 23% (OR 1.51, 95% CI 1.43–1.60; $P < 0.0001$) respectively. Moreover, patients with POAF developed stroke with four times higher frequency (1% vs. 4%; OR 4.09, 95%CI 2.49–6.72; $P < 0.00001$)(Eikelboom et al.,

2021). In patients who developed POAF, risk of experiencing non-surgical AF has been reported to increase by 8 times (Ahlsson et al., 2010).

Hence, POAF have significant economic impact. In Veterans Affairs Randomized On/Off Bypass Follow-up Study, when sub-analysis was done which included 2203 patients, it was found that for patients who developed POAF, adjusted costs for first year were more by $15 300 (Almassi et al., 2021). The extra cost that is related to POAF can exceed $2 billion/year only in the USA, if extrapolating to number of cardiac surgery and taking into account the reported POAF incidence (Gaudino, Di Franco, Lisa Q Rong, et al., 2023; Rosamond et al., 2007).

S. No.	Study	Year	Type of Study	Study population	Results
1.	LaPar et al. (LaPar et al., 2014)	2014	Retrospective observational study	49,264	• Higher unadjusted incidence of hospital readmission, morbidity, longer ICU stay, prolonged duration of hospital stay, increased hospital costs and mortality was observed in patients with POAF. • There was two times increase in odds of mortality (adjusted OR 2.04, P<0.001) in patients with POAF, after risk adjustment. • After risk adjustment, POAF was also found associated with increased resource utilization in hospital and higher costs

2.	Benedetto et al.(Benedetto et al., 2020)	2020	Post hoc analysis	3023	• The cumulative incidence of cerebrovascular accidents at 10 years was found to be 3.7% (2.9-4.5%) in sinus rhythm vs. 6.3% (4.6-8.1%) in patients who developed POAF • Even after excluding cerebrovascular accidents episodes at time of first admission, POAF was found to be an independent predictor of occurrence of cerebrovascular accidents even at 10 years with (HR 1.53, 95%CI 1.06–2.23; P=0.025, when not excluded vs. HR 1.47, 95%CI 1.02–2.11; P=0.04, when excluded)
3.	Goyal et al. (Goyal et al., 2022)	2022	Retrospective cohort study	76,536 cardiac surgery patients	• There was increased hospitalization in patients with POAF (HR 1.33, 95%CI 1.25–1.41) among patients who underwent cardiac surgery.

				2,929,854 non-cardiac surgery patients	
4.	Caldonazo et al. (Caldonazo et al., 2023)	2021	Meta-analysis	2,46,340	• Positive association was present between POAF and MI (OR 1.28, 95% CI 1.06–1.54), stroke (IRR,1.33, 95%CI 1.21–1.46), acute renal failure (OR 2.74, 95%CI 2.42–3.11), mortality in perioperative period (OR 1.92, 95% CI 1.58–2.33) and long-term mortality (IRR 1.54, 95%CI 1.40–1.69)
5.	Eikelboom et al.	2021	Meta-analysis	1,55,575	• After adjustment of confounding factors, POAF was associated with significantly high long-term mortality (HR 1.25, 95%CI 1.2–1.3; P< 0.01) in patients with POAF

	(Eikelboom et al., 2021)				• 1year mortality was 6% vs. 4% (OR 1.69, 95%CI 1.1–2.6; P=0.02) in patients with and without POAF • 5year mortality was 15% vs. 10% (OR 1.6, 95%CI 1.52–1.68; P<0.00001) in patients with and without POAF
6.	Almassi et al. (Almassi et al., 2021)	2021	Post hoc analysis	2203	• Adjusted costs for first-year after CABG was greater for patients with POAF and were $15,300
7.	Lin et al.(Lin et al., 2019)	2019	Meta-analysis	2,458,010	• Association of POAF was reported to be stronger in patients who underwent non-cardiac surgery as compared to patients who underwent cardiac surgery (HR 2.00; 95%CI 1.70–2.35 vs. HR 1.20; 95%CI 1.07–1.34; respectively)

8.	Amar Taha et al (A et al., 2021)	2007-2015	observational, nationwide, population based, longitudinal registry-based cohort study (SWEDEHEART Registry)	24,523 patients Follow-up - Median 4.5 years (Range 0–9 years)	• POAF developed in 7368 patients, i.e, 30% • They reported increased risk of- o ischemic stroke [aHR] 1.18 [95% CI, 1.05–1.32]) in patients with POAF o Any thromboembolism (ischemic stroke, transient ischemic attack, or peripheral arterial embolism) (aHR 1.16, 1.05–1.28) o Heart failure hospitalization (aHR 1.35, 1.21–1.51) o Recurrent atrial fibrillation (aHR 4.16, 3.76–4.60) o Not with all-cause mortality (aHR 1.08, 0.98–1.18)
9.	Anders Ahlsson a et. al. (Ahlsson et al., 2010)	1999-2000	Single center, observational, cohort study.	N=571 patients	• 165/571, i.e, 28.9% patients developed POAF • 25.4% patients developed AF at time of follow up as compared with 3.6% of patients with no AF at surgery, in POAF patients ($p<0.001$)

			(O¨rebro University Hospital, O¨rebro, Sweden)	Follow-up - Median 6 years	• POAF episode was found to be an independent risk factor for occurrence of late onset POAF, with adjusted risk ratio of 8.31 (95% CI 4.20—16.43) • Mortality rate: 29.7% (AF) vs 4.8% ($p < 0.001$) • Reported death due to- - cerebral ischemia (4.2% vs 0.2%, $p < 0.001$) - MI (6.7% vs 3.0%, $p = 0.041$) • For late-mortality, postoperative AF was found to be an age-independent risk factor, with an adjusted hazard ratio of 1.57 (95% CI 1.05—2.34),
10.	Seung-Hyun Lee et. al. (Lee et al., 2014)	2005-2009	Single center, observational, cohort study.	1171 patients Follow-up - 41 ± 23 months	• POAF- new onset AF which was documented by ECG findings or continuous monitoring for the first 10 days following surgery

			(Severance Cardiovascular Hospital, Yonsei University Health System)	(range 0-87 months)	• Higher incidence of total-AF (20/927 [2.2%] vs 46/244 [18.9%], P < 0.001) and long term recurrence of AF (13/927 [1.4%] vs 25/244 [10.2%], P < 0.001) was reported in POAF group • POAF was found to be an independent predictor of newly developed long-term AF (hazard ratio 4.99, 95% CI 1.68-14.84, P = .004)
11.	Emma Thorén et. al. (Thorén et al., 2020)	1996-2012	Observational cohort study. The Department of Cardiothoracic Surgery, Uppsala University Hospital, Sweden	7145 patients Follow-up -. Median follow-up 9.8 years	• POAF was found to be associated with- - long-term AF recurrence (adjusted HR 3.20; 95% CI 2.73–3.76) - Ischemic stroke (1.23; 1.06–1.42) - Heart failure (1.44; 1.27–1.63) - Cardiac mortality (1.35; 1.18–1.54) - Cerebrovascular mortality (1.54; 1.17–2.02)

					- Overall mortality (1.21; 1.11–1.32)
12.	Malhotra et. al. (Malhotra et al., 2021a)	January 2018 and April 2019	Single center, observational, Retrospective case control study	263 patients	• 24 patients (9.12%) developed POAF • IABP high in POAF group (5 in group I vs. 10 in group II, p = 0.001) • Mortality: 4 deaths in POAF and 7 in non-POAF (P = 0.002)
13.	Dave et al (Dave et al., 2018)		Topiwala National Medical College, Mumbai	N=150 patients	• POAF - 40.7% (61 patients) • Preoperative LVEF <0.4, prior MI, CPB time >100 min and extended ventilation for >24 h were significantly associated with POAF
14.	Ghurram et al (Ghurram et al., 2020)	January 2015 to December 2016	AIMS Kochi	748 OPCABG	• POAF – 127 (16.7%) • Sepsis and age >60 years were found to be an independent predictor of POAF

				Median follow-up - 630 days	• 30-day mortality was found to be high in POAF (7.1% vs. 1.4%; p value < 0.001) • In patients with POAF, 3-year survival was 81.3% vs. 94.4% in the NSR group; Hazard ratio (HR) 3.867 (1.989–7.516)
15.	Alfehaid et. al. (Kashani et al., 2015a)	2008 - 2014	University of California	2385 patients	• Patients who developed POAF- 380 / 2385 (15.9%) • In patients with and without POAF, Mean CHA2DS2-VASc scores were found to be 3.6 ± 1.7 and 2.8 ± 1.7, respectively (P < 0.0001) • Probability of developing POAF increased from 8.2%→42.3% (P < 0.0001) as CHA2DS2-VASc score increased from 0→9

Table 3: Outcomes of POAF from various studies

Treatment:

1) **Rate vs. rhythm control:**

Variable treatment options are available for POAF ranging from control of heart rate, antiarrhythmic drugs and cardioversion (Gaudino, Di Franco, Lisa Q Rong, et al., 2023). When cardiac surgery is complicated by POAF and there is hemodynamic instability, to restore the sinus rhythm patient requires immediate cardioversion. In patients who are hemodynamically stable, rate or rhythm control is used to treat POAF. For patients having preserved left ventricular ejection fraction (LVEF), calcium channel blockers, beta blockers and or digoxin is recommended for rate control. While for patients with decreased LVEF digoxin or beta blockers are recommended for rate control. While attempting pharmacological cardioversion, antiarrhythmic drugs belonging to class IC or class III is preferred in patients having normal LVEF, while in patients with reduced LVEF amiodarone should be used(Hindricks et al., 2021b).

Earlier, the evidence that supported control of rate or rhythm originated from predominantly from observational studies and was limited. Decreased duration for in hospital stay with use of rhythm control was reported in a pilot trial published in 2003 (Lee et al., 2003). However, in a RCT conducted by Cardiothoracic Surgical Trials Network over 523 patients who developed POAF after cardiac surgery, that compared rate vs. rhythm control reported no superiority with either approach (Gillinov et al., 2016). They predominantly used beta blockers for rate control (Target heart rate <100bpm) and amiodarone

(3g loading dose followed by 200 mg maintenance dose daily) for rhythm control and cardioversion, when required. No significant difference was observed between the two strategies in terms of in survival (P=0.64), in hospital stay (P=0.76) or serious adverse events (P=0.64) at end of 60-day follow up. Strikingly, in approximately 1 in 4 patients treatment deviation occurred in both arms, emphasizing the struggle with the use of above medications probably due to ineffective rate control or adverse effects, specifically with amiodarone. Notably, majority patients had sinus rhythm at time of discharge and at 60-days follow up (98% in rhythm control and 94% in rate control), which highlighted the transient nature of POAF in majority of patients. Hence, the current approach to manage POAF can be any of the two, i.e, either rhythm control or rate control strategy.

2) **Prevention of stroke:**

Plenty of data available from RCTs support use of systemic oral anticoagulant medications in patient with established AF who are ambulatory (Carnicelli et al., 2022; Gaudino, Di Franco, Lisa Q Rong, et al., 2023). On the contrary, use of oral anticoagulant drugs so as to prevent stroke in patients who developed POAF is controversial,

in patients with POAF to prevent stroke is controversial and there is incongruity in the evidence.

The recent European Society of Cardiology guidelines recommend the use of oral anticoagulation for long term after POAF complicating cardiac surgery (Level of evidence B, class of recommendation IIb) and non-cardiac surgery (Level of evidence B, class of recommendation IIa), after informed patient

decision(Hindricks et al., 2021b). Current US guidelines similarly recommend using oral anticoagulants in patients developing POAF (Level of Evidence B, class of recommendation IIa) (January et al., 2014).

In patients developing POAF after cardiac surgery, use of oral anticoagulation is based on observational studies which reports significantly increased risk of stroke in patients developing POAF (Lin et al., 2019). Lower risk of stroke was observed patients who were given oral anticoagulation, in a study that included over 10,000 patients (2108 patients developed POAF after cardiac surgery) (adjusted HR 0.55, 95%CI 0.32–0.95; P= 0.03)(Butt et al., 2018a). In contrast, a recent data from Society of Thoracic Surgeons Adult Cardiac Surgery Database including 38,936 patients with POAF reported that use of anticoagulation at discharge was associated with increased mortality (HR 1.16, 95%CI 1.06–1.26) (Fs et al., 2022). Numerous patients who develop new-onset POAF, proceed to develop established AF during follow up. Additionally, with use of anticoagulants, no apparent benefit was observed in patients having CHA2DS2-VASc scores of 2–4 or ≥5.

Given the diverse data, it is difficult to say oral anticoagulants have more benefit or harm when used for POAF.

TABLE 4: Summary of Recommendations from international guidelines for management of postoperative atrial fibrillation

Recommendation	**Class of recommendation**	**Level of evidence**
POAF PREVENTION		
ESC GUIDELINES, 2020 (Hindricks et al., 2021b)		
For patients who underwent cardiac surgery, perioperative beta blocker or amiodarone are recommended drugs for prevention of POAF	I	A
For patients who underwent non-cardiac surgery, beta blockers are not recommended for routine use for preventing POAF	III	B
AHA/HRS/ACC Guidelines, US 2014 (updated- 2019) (January et al., 2014, 2019)		
Administration of Amiodarone preoperatively for patients undergoing cardiac surgery, there is decrease in incidence of AF and hence it is a reasonable preventive strategy for patients who are prone for POAF	IIa	A

For patients undergoing cardiac surgery and are at risk of developing AF, administration of Sotalol can be considered prophylactically	IIb	B
For patients who underwent cardiac surgery, Colchicine administration can be considered postoperatively to reduce AF	IIb	B
POAF TREATMENT		
AHA/ACC/HRS Guidelines (updated 2019) (January et al., 2014, 2019)		
For patients who develop AF after cardiac surgery, Beta blocker is a recommended treatment unless contraindicated	I	A
In patients with POAF when rate control could not be achieved adequately with beta blocker, treatment with non-dihydropyridine calcium channel blocker is recommended	I	B
As advised for non-surgical candidates, for patients who develop POAF it is a reasonable strategy to restore sinus rhythm either pharmacologically using ibutilide or DC-cardioversion	IIa	B
In patients with recurrent or refractory POAF, administration of antiarrhythmic medications so as to maintain sinus rhythm is considered a reasonable strategy	IIa	B

It is reasonable to manage well-tolerated, new-onset POAF with rate control and anticoagulation with cardioversion if Atrial fibrillation does not revert spontaneously to sinus rhythm during follow-up.	IIa	
STROKE PREVENTION		
ESC GUIDELINES, 2020 (Hindricks et al., 2021b)		
For patients undergoing cardiac surgery, using long term anticoagulation can be considered in an attempt to prevent thromboembolic events in patients who are prone to develop stroke along with POAF, after informed patient decision and consideration of clinical benefit after OAC therapy	IIb	B
AHA/ACC/HRS Guidelines (updated 2019) (January et al., 2014, 2019)		
In patients who develop POAF, administration of antithrombotic medications can be considered a reasonable strategy	IIa	B

MATERIALS AND METHODS

3.1 *HYPOTHESIS*

Post coronary artery bypass surgery new onset Atrial fibrillation is associated with a higher risk of long-term mortality and morbidity.

3.2 AIMS AND OBJECTIVES OF THE STUDY

1. Study the long-term outcomes of new-onset atrial fibrillation in post-coronary artery bypass surgery in comparison with those patients without atrial fibrillation.

2. Study the risk factors responsible for the development of new-onset atrial fibrillation in post-coronary artery bypass surgery patients.

3.3 METHODOLOGY

Study Design: Retrospective cohort study

Study Setting: Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Trivandrum

Study period:01/07/2021 to 30/06/2023 after Ethical clearance

Inclusion criteria:

1. All patients who underwent CABG primarily for CAD with age > 18 years

Exclusion criteria:

1. Patients having valvar heart disease

2. Patients who are known case of Atrial Fibrillation

3. Patients who underwent valve replacement surgeries along with CABG

4. Patients who had prior cardiac surgery

5. Patient with congenital heart disease

The study participants were recruited from electronic medical records of the cardiology and cardiothoracic and vascular surgery departments. In the electronic medical records first one thousand patients who underwent CABG during the study period (Jan 1, 2005 – Dec 31 2015) and those fulfilling inclusion and exclusion criteria were enrolled in the study.

1002 patients were recruited for the study, and they were divided into two cohorts. One cohort contains those patients with post-operative atrial fibrillation (Post-operative AF is defined as new onset AF within the first 30 postoperative days). Another cohort contains those without atrial fibrillation. These patients were then assessed for outcome till December 2022.

The baseline clinical details and Lab parameters are entered in a pre-designed Case Record Form and later updated in an Excel sheet for further analysis.

The baseline clinical details are as follows:

Sex	Any previous peripheral systemic embolism
Age	Peripheral vascular disease
History of acute coronary syndrome (ACS)	CHA2DS2-VASc score

History of previous percutaneous coronary intervention	Prior renal insufficiency
Hypertension	Need of Renal replacement therapy
Prior heart failure admissions	Chronic respiratory disease
Prior history of any ischemic or haemorrhagic stroke	Chronic liver disease
Alcoholism	History of any cancer
Obstructive sleep apnoea	Diabetes Mellitus

The Echo parameters that will be included are:

1. LA size
2. Any left ventricular hypertrophy
3. Presence of mitral regurgitation and its severity
4. New onset RWMA

The method of termination of Atrial fibrillation is noted by drugs or cardioversion is noted.

The other parameters that were included are:

- The NYHA functional class
- Post-operative myocardial infarction
- Post-operative Pericarditis
- Post-operative Heart failure

- Cardiopulmonary bypass time
- Aortic cross-clamp time

Primary Outcome:

- 1. Major adverse cardiac event (MACE) during follow-up.
- 2. All-cause mortality

Secondary Outcome:

- 1. Death from any cause
- 2. Ischemic stroke
- 3. Thromboembolism (TIA / Ischemic stroke / Peripheral embolism)
- 4. Heart failure
- 5. Major bleeding
- 6. Episodes of acute coronary syndromes on follow up
- 7. The number of patients who had a recurrence of Atrial fibrillation
- 8. Rhythm on follow-up.

Statistical analysis:

Statistical analyses were performed using IBM SPSS statistics version 20 (**International Business Machines Corporation -** Statistical Package for Social Sciences, New York, USA) software. All tests were two-sided, and a $P < 0.05$ was considered statistically significant. Continuous variables were expressed as mean ± 2 SD if normally distributed or as medians (25th and 75th percentiles) if not normally distributed. Categorical variables were expressed as counts and percentages. Comparisons between groups were made by ANOVA, chi-square test,

paired/ unpaired sample *t-test* wherever appropriate for continuous variables with normal distribution, Wilcoxon signed-rank test for continuous variables with nonnormal distribution, and Fisher exact test for categorical variables. The potential risk factors for the development of post-operative AF were evaluated using a Cox regression model and multiple regression analyses were performed for outcomes with P values less than 0.1. The correlation of variables was expressed by the Pearson correlation coefficient. Differences in long-term survival were analyzed by Kaplan-Meier analysis and compared using the log-rank test. A P-value of less than 0.05 was considered to indicate statistical significance.

3.4 ETHICAL JUSTIFICATION

The present study entails the long-term outcome of post-operative atrial fibrillation in post-CABG patients. There is a dearth of data in this field from the Indian subcontinent, and this study will help immensely in upgrading the quality of care currently available to them.

It is a retrospective study that will analyze the events that are happening postoperatively long term. There is no extra visit or cost needed for the patient. No invasive or non-invasive investigation is required for the patients.

This study was approved by the Institutional Ethics Committee, SCTIMST Trivandrum.

RESULTS

Results:

1002 patients who underwent coronary artery bypass surgery (CABG) from 2005 to 2009 and fulfilled the inclusion and exclusion criteria were included in the study.

Among 1002 patients, 110 (11%) developed Post-operative Atrial Fibrillation (Table 5 and Figure 6). The Mean age at the time of surgery of the study population is 55 ± 8.7 years. Patients who developed POAF had higher age at the surgery of 58.8 ± 9 years than those have not developed POAF 54.1 ± 8.6 years which is statistically significant (P<0.001) (Figure 7 and Table 6).

Presence of POAF	N	%
Yes	110	11%
No	892	89%

Table 5: Incidence of POAF

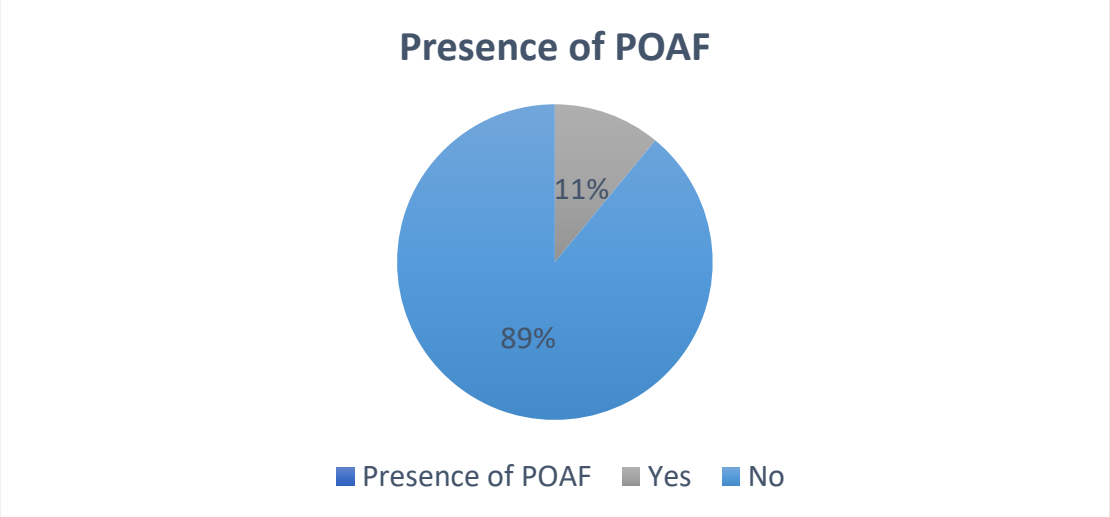

Figure 6: Incidence of POAF

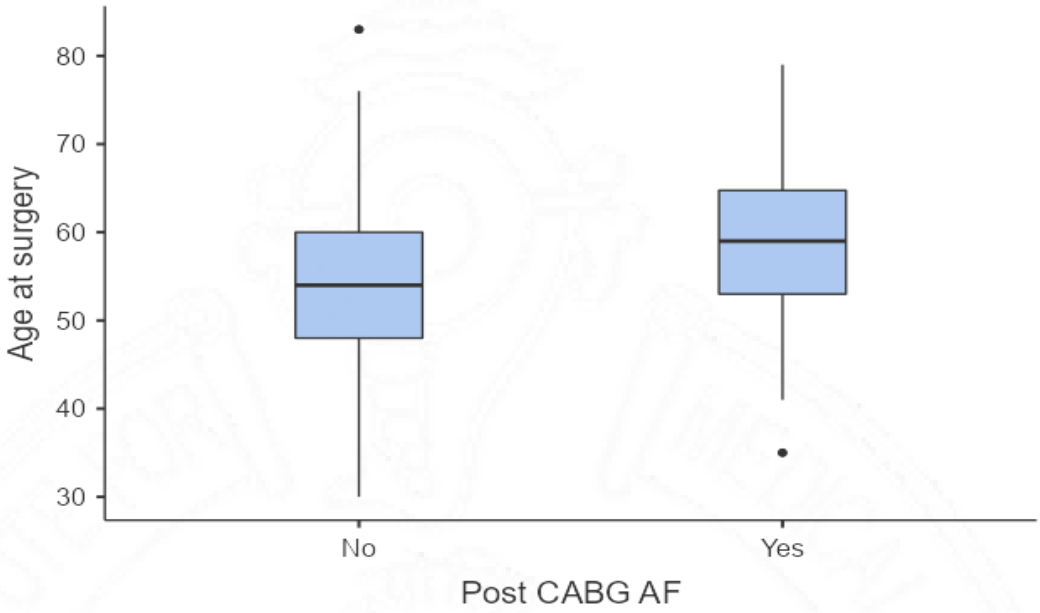

Figure 7: POAF Vs Age at Surgery

	POAF (n=110) Mean ± SD (In Years)	No POAF (n=892) Mean ± SD (In Years)	Total Mean ± SD (In Years)	P Value
Age at surgery	58.8 ± 9.0	54.1±8.6	54.6 +/- 8.73	<0.001

Table 6: POAF Vs Age at Surgery

	POAF (n=110) n (%)	**No POAF (n=892) n (%)**	**Total N (%)**	**P Value**
Male	105 **(95.5%)**	771 (86.4%)	876 (87.4%)	0.007
Female	5(4.5%)	121 **(13.6%)**	126 (12.6%)	NS

Table 7: POAF Vs Sex difference

There is male predominance who constituted 876 (87.4%) of the study population. 12% of males developed POAF while 4% of females developed POAF. P value of 0.007 is between males with and without POAF (Table 7 and Figure 8).

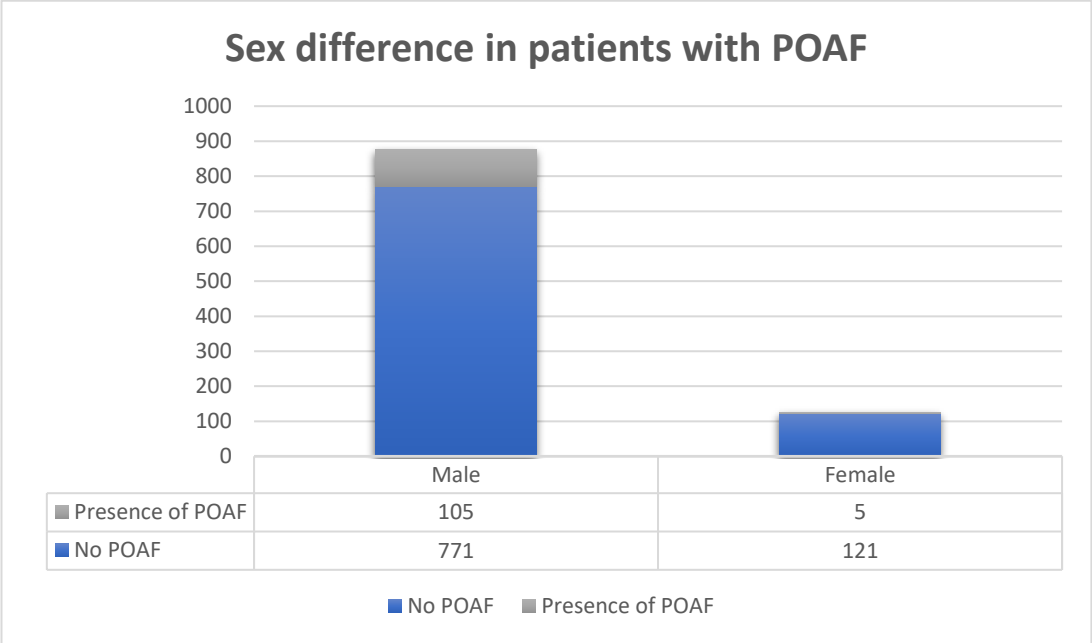

Figure 8: POAF Vs Sex difference

Among the risk factors for the development of Atrial fibrillation in the general population, Diabetes Mellitus is present in 54.7%, Hypertension in 67.5%, Alcoholism in 0.6%, Obstructive sleep apnoea in 1%, history of any renal insufficiency prior to surgery in 9.1%, Chronic respiratory illness (Obstructive and Restrictive airway disease) in 2.2% of the study population. History of any admission for heart failure prior to surgery is present in 7.5%, History of Acute coronary syndrome (ACS) prior to surgery is present in 69.5%, History of Cerebrovascular accident (CVA) including both stroke and TIA (Transient ischemic attacks) in 4% of the study population.

Among those patients who developed POAF 67.3% had Diabetes Mellitus whereas only 53.1% of patients who haven`t developed POAF had Diabetes which is statistically significant (p = 0.005). Similarly, 81.8% of POAF had Hypertension whereas 65.5% of the patients in no POAF group had hypertension which is also statistically significant (p=0.001). History of heart failure admission prior to surgery is seen more in the No POAF group (8.4% vs 0%, P = 0.002) and history of CVA prior to surgery is more in the no POAF group (4.5% vs 0%, P=0.023). Patients with renal insufficiency prior to surgery are more in the no POAF group (10.2%) than in the POAF group (0%) which is statistically significant with P < 0.001. However, the need for RRT is so low and there is no difference between the groups. There is no statistical significance between both groups in terms of prior ACS history, Alcoholism, OSA, presence of hypothyroidism and history of peripheral embolism prior to surgery.

The predominant population is in NYHA functional class II (73.9%), 23.8% of the population is in NYHA functional class III and 1.4% of the population is in NYHA functional class IV. There is no statistical difference in the NYHA functional class between both groups.

69.3% of the study population who underwent CABG had triple vessel disease and 26.5% of the study population had Left main coronary artery involvement. There is no statistical difference between both groups in means of number of vessels involved and the vessels involved.

The baseline characteristics of both cohorts are summarised in the table below (Table 8)

	POAF (n=110) N (%)	***No POAF (n=892) N (%)***	***Total Patients N (%)***	***P value***
Diabetes Mellitus	74 **(67.3%)**	474 (53.1%)	548 (54.7%)	**0.005**
Hypertension	90 **(81.8%)**	584 (65.5%)	674 (67.3%)	**0.001**
History of ACS prior	69 (62.7%)	627 (70.3%)	696 (69.5%)	0.104
Prior HF admission	0 (0%)	75 **(8.4%)**	75 (7.5%)	**0.002**
Prior CVA (Stroke / TIA)	0 (0%)	40 **(4.5%)**	40 (4%)	**0.023**
Alcoholism	0 (0%)	6 (0.7%)	6 (0.6%)	0.388
Obstructive sleep Apnoea	0 (0%)	10 (1.1%)	10 (1%)	0.264
History of % PCI	0 (0%)	30 **(3.4%)**	30 (3%)	**0.051**
History of peripheral embolism	0 (0%)	4 (0.4%)	4 (0.4%)	0.482
Prior renal insufficiency	0 (0%)	91 (10.2%)	91 (9.1%)	<0.001
Need of RRT	0 (0%)	8 (0.9%)	8 (0.8%)	0.319
Chronic respiratory disease	4 (3.6%)	18 (2%)	22 (2.2%)	0.274
Chronic liver disease	1 (0.9%)	1 (0.1%)	2 (0.2%)	0.077
Cancer	1 (0.9%)	7 (0.8%)	8 (0.8%)	0.890
PVD	5 (4.5%)	11 (1.2%)	16 (1.6%)	**0.009**
LVH	32 (29.1%)	150 (16.8%)	182 (18.2%)	**0.002**
Presence of any MR	67 (60.9%)	511 (57.5%)	580 (57.9%)	0.496
Trivial MR	35 (31.8%)	273 (30.6%)	308 (30.7%)	

Mild MR	26 (23.6%)	194 (21.7%)	220 (22%)	
Moderate MR	6 (5.5%)	44 (4.9%)	50 (5%)	
Hypothyroidism	5 (4.5%)	27 (3%)	32 (3.2%)	0.393
NYHA Functional Class				
I	0 (0%)	10 (1.1%)	10 (1%)	
II	73 (66.4%)	667 (74.8%)	740 (73.9%)	
III	34 (30.9%)	204 (22.9%)	238 (23.8%)	
IV	3 (2.7%)	11 (1.2%)	14 (1.4%)	
Number of vessels involved				
1	8 (7.3%)	46 (5.2%)	54 (5.4%)	
2	22 (20%)	232 (26%)	254 (25.3%)	
3	80 (72.7%)	614 (68.8%)	694 (69.3%)	
LM Disease	35 (31.8%)	231 (25.9%)	266 (26.5%)	0.185
LAD involvement	109 (99.1%)	883 (99%)	992 (99%)	0.921
LCx involvement	89 (80.9%)	712 (79.8%)	801 (79.9%)	0.788
RCA involvement	95 (86.4%)	743 (83.3%)	838 (83.6%)	0.412

Table 8: Baseline characteristics of the study population

The mean LA size by Echocardiography prior to surgery is 38 ± 4.5 mm in the POAF group whereas the mean LA size is 35.4 ± 4.4 mm in no POAF surgery which is statistically significant with p value < 0.001 (Figure 9). The patients who had POAF

have higher Cardiopulmonary Bypass time (CBT) and aortic cross-clamp time than those who haven't developed POAF. However, it was not statistically significant. There is no significant difference in baseline Left ventricular ejection fraction (LVEF) between both cohorts.

	POAF (n=110) ***Mean ± SD***	***No POAF(n=892)*** ***Mean ± SD***	***P value***
LA size (mm)	38.0 ± 4.5	35.4 ± 4.4	**<0.001**
LVEF (%)	62.6 ± 14	62.5 ± 12.8	0.921
CBT TIME (min)	91.6 ± 22.8	90.5 ± 25.6	0.700
Aortic cross-clamp time (min)	52.0 ± 14.2	50.6 ± 16	0.375

Table 9: Baseline characteristics of the study population

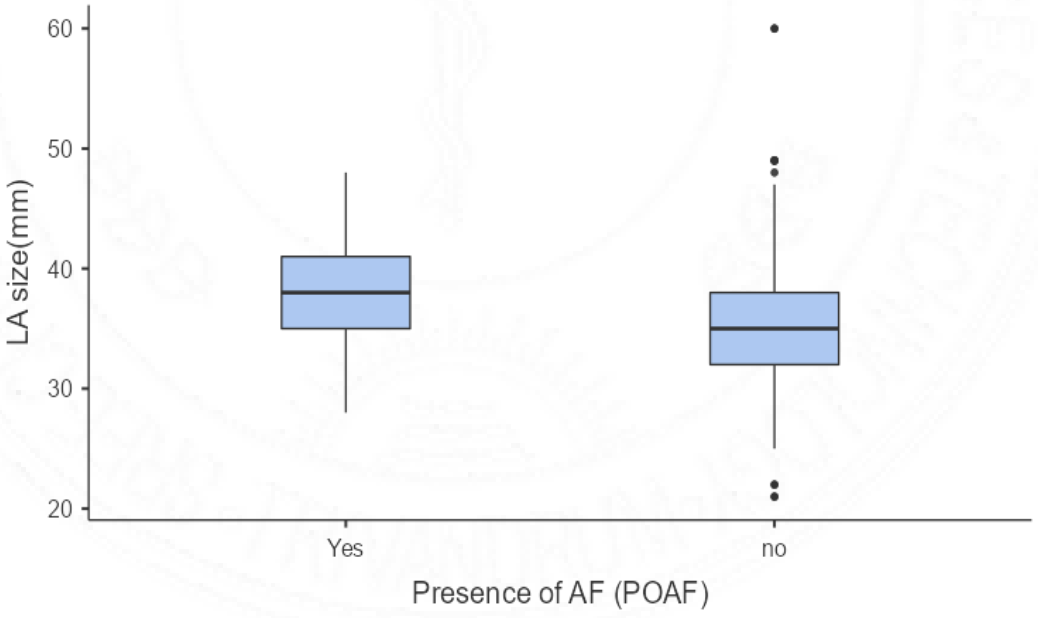

Figure 9: LA diameter between POAF vs No POAF

The basal CHADSVASC score at the time of surgery is higher in the POAF group. It is also found that there is a trend in the development of POAF as the CHADSVASc score increases. Most of the patients in our study had a CHADSVASc score of 2 (39.9%). [Figure 10, Table 10]

		POAF (n=110) ***N (%)***	***No POAF(n=892)*** ***N (%)***	***Total Patients*** ***N (%)***
CHADSVASC score at Surgery	**0**	**9 (8.2%)**	**147 (16.5%)**	**156 (15.6%)**
	1	16 (14.5%)	262 (29.4%)	278 (27.7%)
	2	54 (49.1%)	346 (38.8%)	400 (39.9%)
	3	21 (19.1%)	91 (10.2%)	112 (11.2%)
	4	8 (7.3%)	38 (4.3%)	46 (4.6%)
	5	2 (1.8%)	8 (0.9%)	10 (1%)

Table 10: CHADSVASC score at surgery between POAF and No POAF

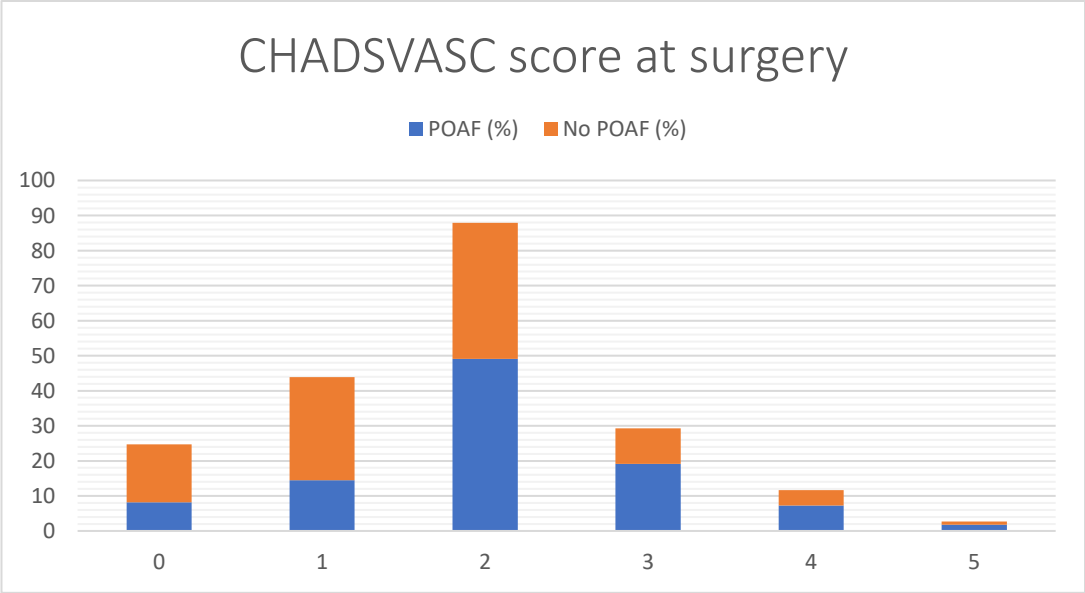

Figure 10: CHADSVASC score at surgery between both groups.

When we separate the population into two groups with CHADSVASc scores < 2 or ≥2 it is found that most of the population (56.7%) is in the ≥2 score group. It is also found that most of the patients in POAF group had CHADSVASc score ≥2 (77.3%) whereas only 54.1% of the patients in No POAF group have CHADSVASc score ≥2 which is statistically significant (p = 0.041) with Odds Ratio = 2.9 (95% CI for OR = 1.8-4.6) [Table 11 and Figure 11].

CHADSVASc Score	***POAF (n=110) N (%)***	***No POAF (n=892) N (%)***	***Total Patients N (%)***	***P value***	***Odds Ratio***
<2	25 (22.7%)	409 (45.9%)	434 (43.3%)	0.041	OR=2.9 [95% CI for OR=1.8-4.6]
≥2	85 (77.3%)	483 (54.1%)	568 (56.7%)		

Table 11: CHADSVASC score <2 vs ≥2

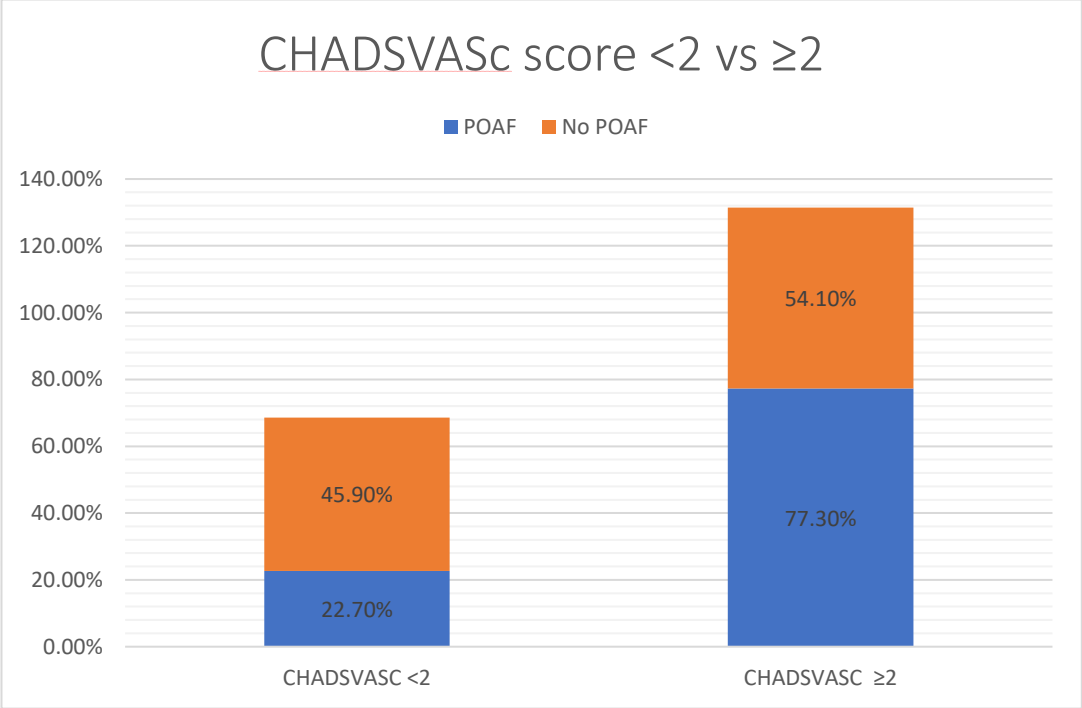

Figure 11: CHADSVASC score <2 vs ≥2

Total of 13 patients had history of previous history of AF which were reverted to sinus rhythm spontaneously in 11 patients and with Amiodarone in 2 patients. All these 13 patients were in sinus rhythm prior to surgery. It is found that 5 patients who had prior AF developed POAF whereas 8 patients who had prior AF had not developed POAF. Most of the patients who had previous AF were paroxysmal and reverted spontaneously. Only 2 patients required Amiodarone to revert to sinus rhythm.

	POAF (n=110) ***N (%)***	***No POAF(n=892)*** ***N (%)***	***Total Patients*** ***N (%)***	***P value***
Prior history of AF	5 (4.5%)	8 (0.9%)	13 (1.3%)	0.001

Table 12: Prior AF and development of POAF

Prior AF reversion	Number of patients (% of prior AF)
Amiodarone	2 (15%)
Spontaneous	11(85%)

Table 13: Method of reversion of prior AF

Most of the patients (84%) developed Atrial fibrillation within the first 4 days of the post-operative period with the maximum onset in the day 1 post-operative period (27%). In our study, no patient has developed AF beyond 10 days of post-operative period. The distribution of POAF patients based on the time of development of AF in the post-operative period is given in the following table 14 and figure 12.

Day of POAF	Number of patients	% of POAF (N=110)
1	30	27%
2	27	25%
3	24	22%
4	11	10%
5	6	5%
6	3	3%
8	1	1%
9	4	4%
10	4	4%

Table 14: POAF patients' distribution based on the day of occurrence of POAF

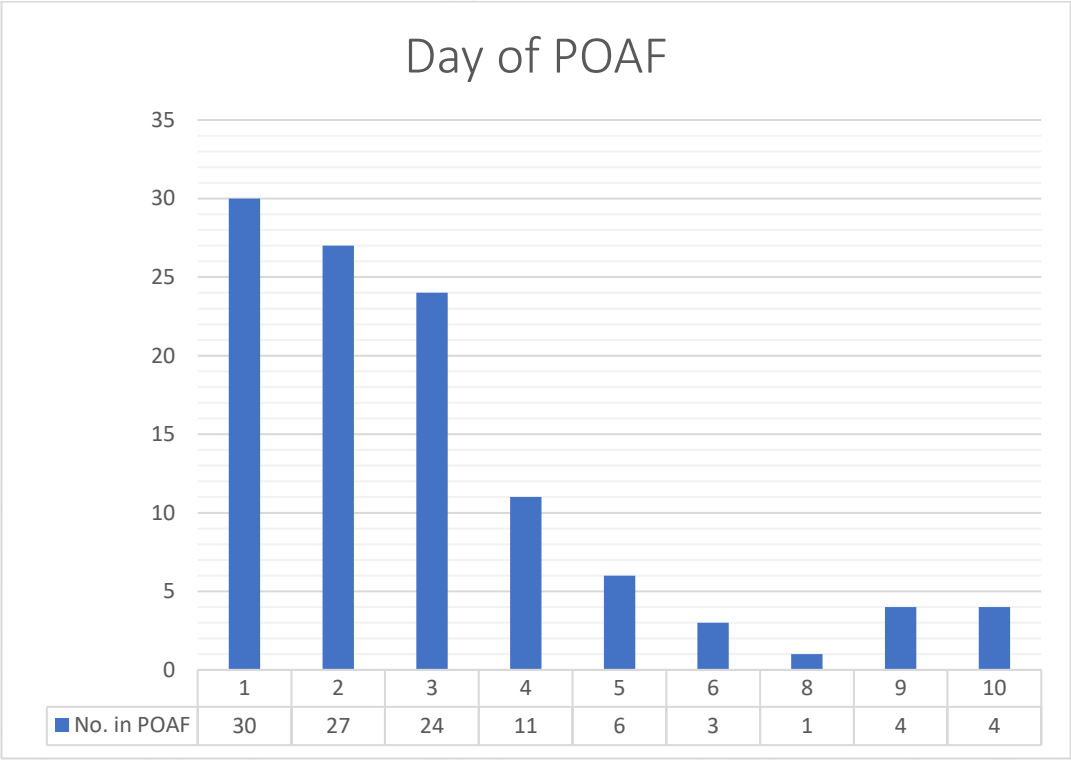

Figure 12: POAF patients' distribution based on the day of occurrence of POAF.

Among 110 patients who developed POAF 106 patients (96%) reverted to sinus rhythm. 2 patients did not revert, and 2 patients initially reverted to sinus rhythm however prior to discharge they went back to atrial fibrillation. Overall, 96.3% of the patients who developed POAF reverted to sinus rhythm within 72 hours of development of AF. Almost two-thirds of the POAF patients (68.9%) of the POAF patients were reverted to Sinus Rhythm within 24 hours of development of AF. Almost every patient who reverted to sinus rhythm has reverted within four days of the development of AF (Table 15, Figure 13,14)

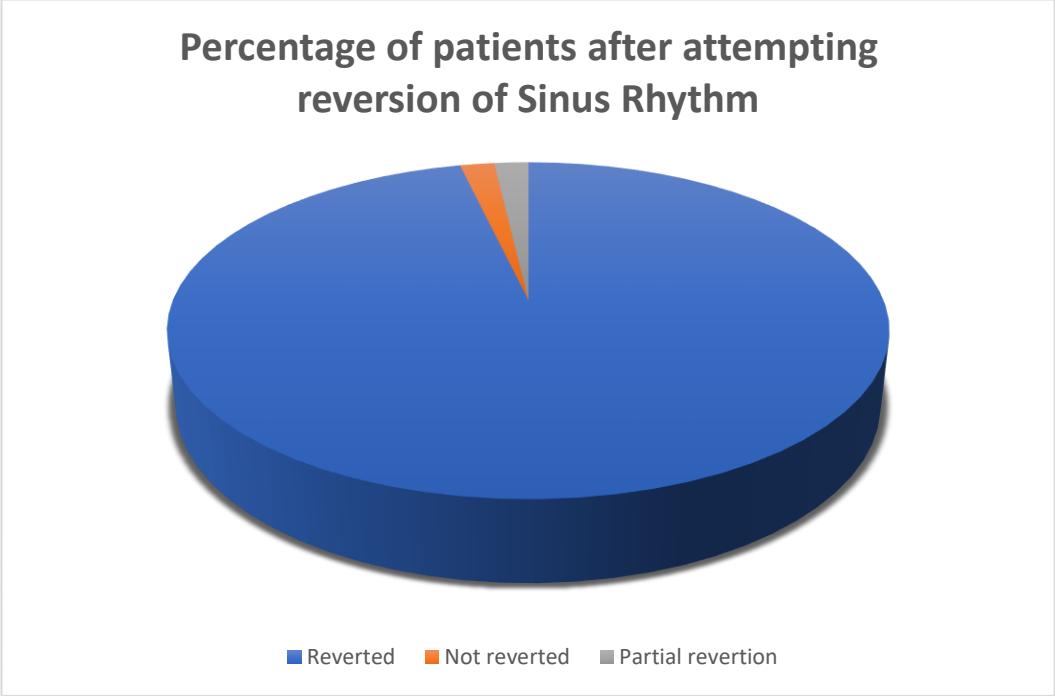

Figure 13: Outcome of patients after attempting reversion of Sinus Rhythm

Number of days to revert to SR	Number of patients	%
< 24 hours	73	68.90%
24-48 hours	15	14.20%
48-72 hours	14	13.20%
72-96 hours	2	1.90%
96-120 hours	2	1.90%

Table 15: POAF patients' distribution based on the day of reversion of POAF.

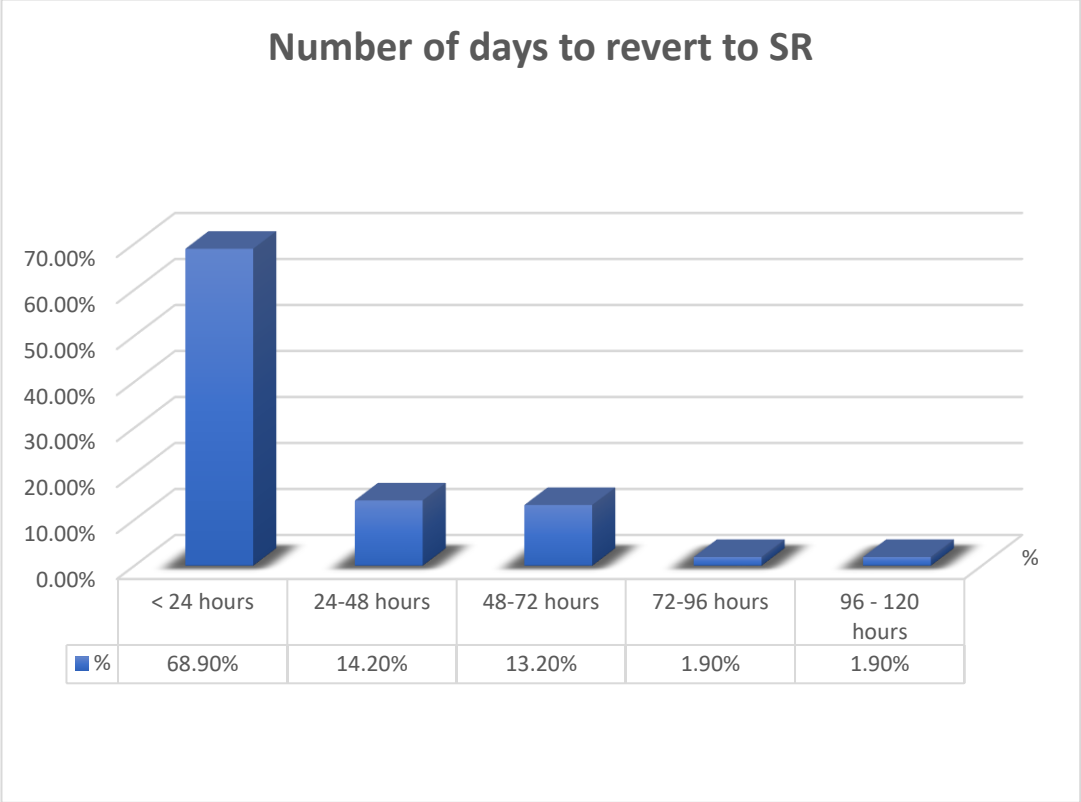

Figure 14: POAF patients' distribution based on the day of reversion of POAF.

Most of the patients were reverted with either medications or DC cardioversion or a combination of medical therapy and DC (Direct current) cardioversion. Only 22% (24 patients) who had POAF reverted spontaneously. 64% required only Amiodarone bolus therapy followed by infusion therapy to revert to sinus rhythm. 9% of the patients reverted to SR by the DC version, Combined Amiodarone and DC cardioversion are used in 4% of the patients. (Table 16 and Figure 15)

Mode of Reversion	Number of patients	% of POAF (N=110)
Amiodarone	70	64%
Spontaneous	24	22%
DC version	10	9%
DC + Amiodarone	4	4%
Verapamil + DC version	2	2%

Table 16: POAF patients' distribution based on the Mode of reversion.

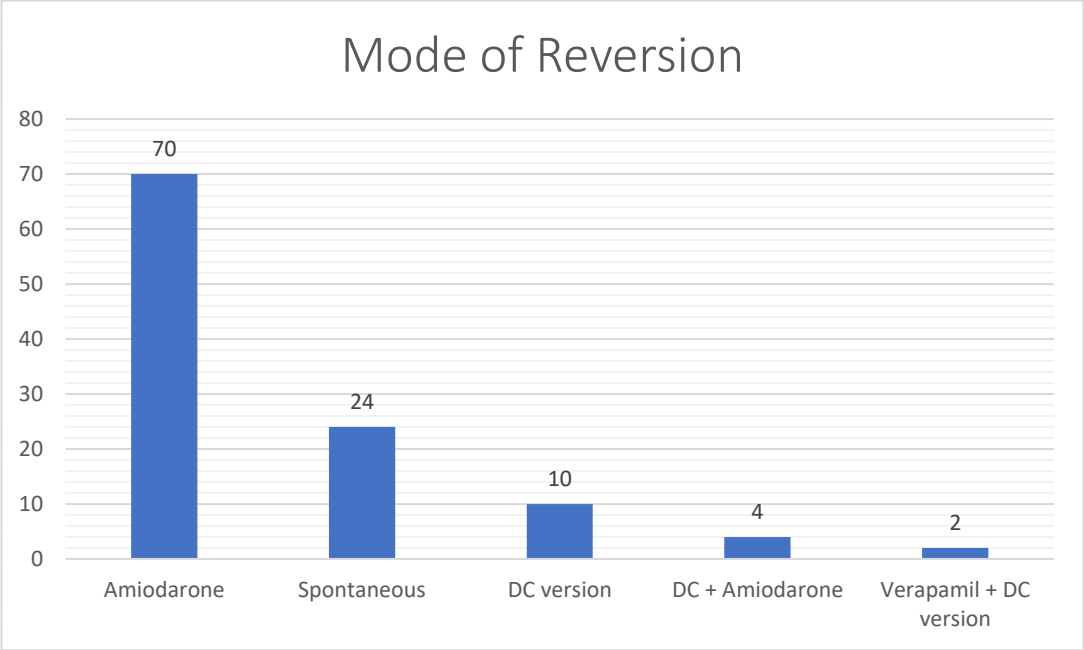

Figure 15: POAF patients' distribution based on the Mode of reversion.

Factors associating with POAF in the univariate analysis were Diabetes Mellitus (p=0.005), Hypertension (p=0.001), CHADSVASC SCORE ≥ 2 (p<0.001), Prior AF (p=0.001), presence of Left ventricular Hypertrophy (p=0.002), presence of

prior Atrial fibrillation (p=0.001), Post-operative MI (p=0.004) and post-operative Heart failure (p<0.001) (Table 17).

Variable	*POAF (n=110) N (%)*	*No POAF (n=892) N (%)*	*Total Patients N (%)*	*P value*	*OR*	*95% CI for OR*
Diabetes Mellitus	74 (67.3%)	474 (53.1%)	548 (54.7%)	0.005	1.8	1.2 - 2.8
Hypertension	90 (81.8%)	584 (65.5%)	674 (67.3%)	0.001	2.4	1.4 - 3.9
CHADSVASC Score ≥2	85 (77.3%)	483 (54.1%)	568 (56.7%)	<0.001	2.9	1.8 - 4.6
Prior AF	5 (4.5%)	8 (0.9%)	13 (1.3%)	0.001	5.3	1.7 - 16.4
LVH	32 (29.1%)	150 (16.8%)	182 (18.2%)	0.002	2	1.3 - 3.2
Post-op MI	8 (7.3%)	21 (2.4%)	29 (2.9%)	0.004	3.3	1.4 - 7.5
Post-op Heart failure	14 (12.7%)	32 (3.6%)	46 (4.6%)	<0.001	3.9	2 - 7.6

Table 17: Univariate Analysis of risk factors for the development of POAF

However, CHADSVASC SCORE ≥ 2 (p<0.001), History of Prior AF (p=0.016), presence of Left ventricular Hypertrophy (p=0.012), and post-operative

Heart failure (p<0.001) remained statistically significant in the multivariate logistic regression analysis (Table 18). These factors were included in the predictive model. The model produced a P value of 0.947 for the Hosmer–Lemeshow goodness-of-fit test indicating a good fit and calibration of the model. The AUC for the predicted probability was 0.673 (95 % confidence interval [CI] 0.643 to 0.702), which suggests a moderate level of discrimination. A mathematical model was generated from the logistic regression analysis to predict the risk of AF, with p denoting the probability of AF.

Logit(p)= -2.931+0.872*a+1.418*b+.596*c +1.272*d

The letters in the equation denote the variables: a = CHADSVASC SCORE (1 if score ≥2, 0 if score <2); b = Prior AF (1 if yes, 0 if not); c = LVH (1 if yes, 0 if not); and d= post operative Heart failure (1 if yes, 0 if not).

Variable	*P value*	*OR*	*95% CI for OR*
CHADSVASC SCORE ≥ 2	<0.001	2.391	1.49 - 3.85
Prior AF	0.016	4.13	1.3 - 13.12
LVH	0.012	1.814	1.14 - 2.88
Post-op Heart failure	<0.001	3.568	1.8 - 7.06

Table 18: Multivariate Analysis of risk factors for the development of POAF

ROC curve of predicted probability to discriminate POAF (Figure 16 and Table 19)

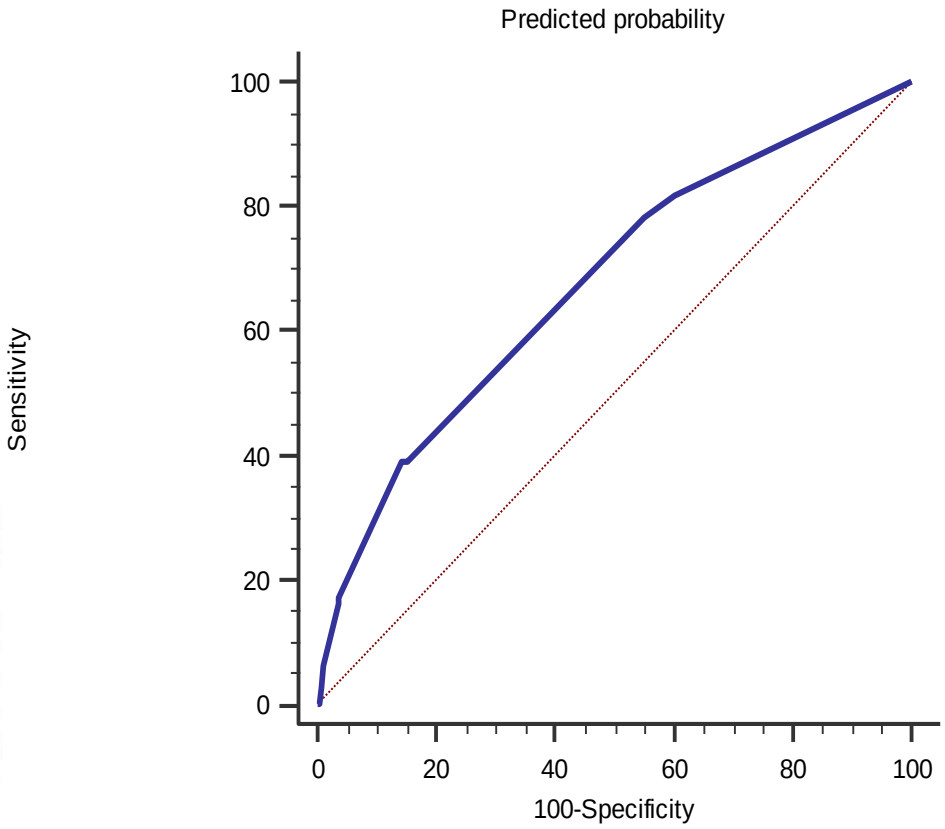

Figure 16: ROC curve of predicted probability to discriminate POAF.

Area under the ROC curve (AUC)	0.673
Standard Error	0.0269
95% Confidence interval	0.643 to 0.702
Significance level P (Area=0.5)	<0.001
Sensitivity	39.09
Specificity	85.65

Table 19: Sensitivity and specificity of predicted probability in the development of POAF

ROC curve for predicting POAF using Age and LA size in mm is shown below.

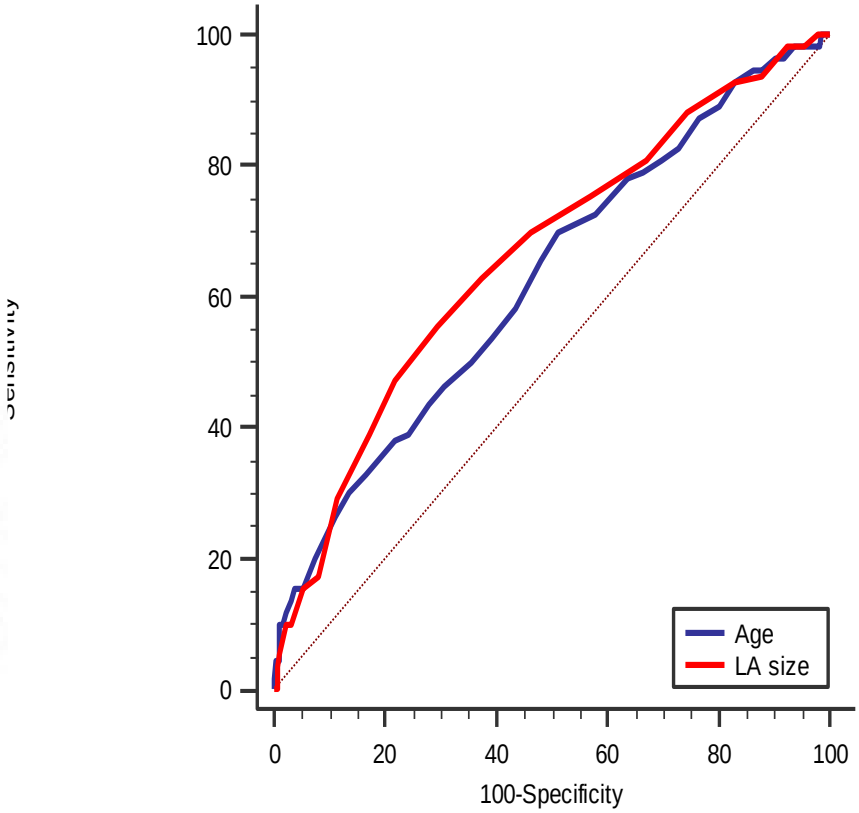

Figure 17: ROC curve of age and LA size to discriminate POAF.

Variable	Age	LA size (mm)
Area under the ROC curve (AUC)	0.622	0.662
Standard Error	0.0291	0.0283
95% Confidence interval	0.591 to 0.652	0.631 to 0.691
Significance level P (Area=0.5)	<0.0001	<0.0001
Sensitivity	70	55.45
Specificity	48.43	70.34
+LR	1.36	1.87
-LR	0.62	0.63
+PV	14.3	18.9
-PV	92.9	92.7

Table 20: Sensitivity and specificity of Age and LA size in the development of POAF

The median follow-up of the study population is 7 ± 4.5 Years.

After the median follow-up of 7 ± 4.5 Years. MACE events were observed in 21.2% of the total study population. MACE events occurred more in the POAF group (25.5%) whereas it occurred only 20.6% in the no POAF group. However, it is not statistically significant. Coming to the individual components of MACE events, ACS events on follow-up occurred in 15.5% of the POAF group whereas in only 13.5% of the population in the no POAF group but not statistically significant. There is also no statistical difference between both groups in terms of heart failure admissions between POAF and no POAF group (4.5% vs 2.7%, p = 0.274). There is also no statistical significance between both the groups for CVA events. (Table 21), Figure 18,19,20)

	POAF (n=110) *N (%)*	*No POAF(n=892)* *N (%)*	*Total Patients* *N (%)*	*P value*
MACE	**28 (25.5%)**	**184 (20.6%)**	**212 (21.2%)**	**0.242**
ACS	**17 (15.5%)**	**120 (13.5%)**	**137 (13.7%)**	**0.564**
Heart failure	**5 (4.5%)**	**24 (2.7%)**	**29 (2.9%)**	**0.274**
CVA	**6 (5.5%)**	**30 (3.4%)**	**36 (3.6%)**	**0.266**

Table 21: MACE Events between both groups

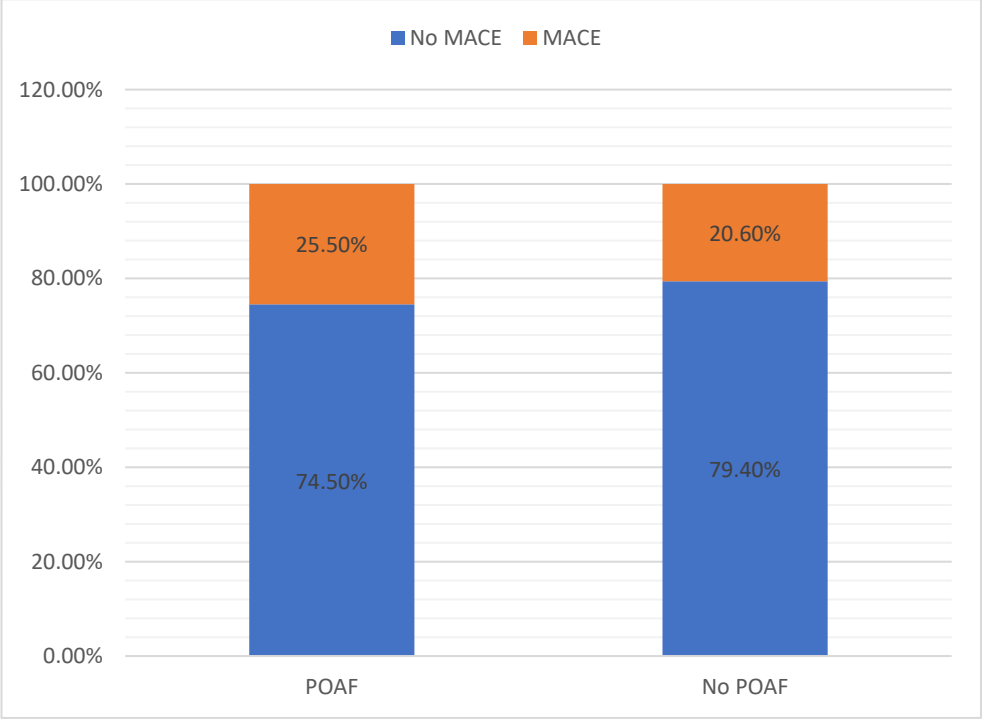

Figure 18: MACE events between POAF and No POAF group

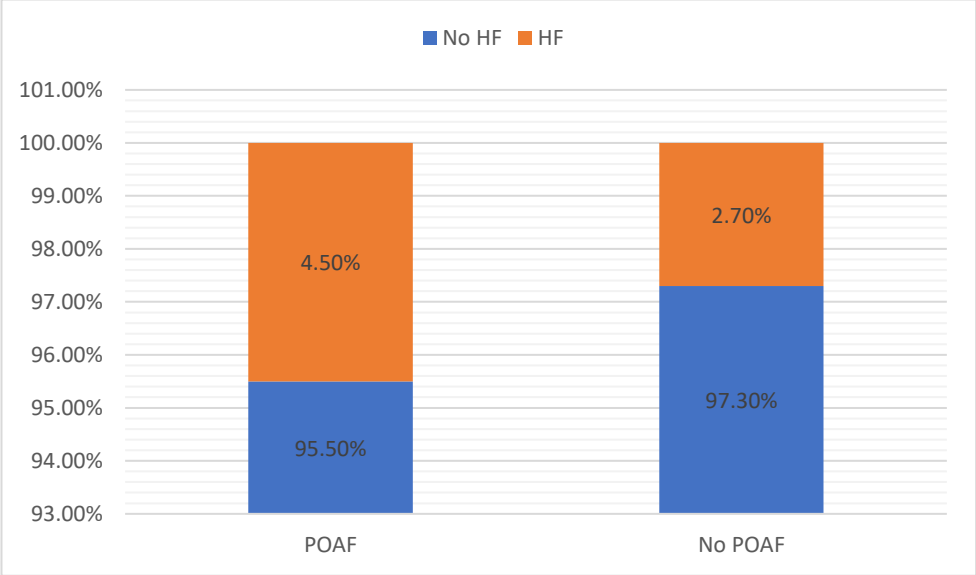

Figure 19: Heart failure events between POAF and No POAF group

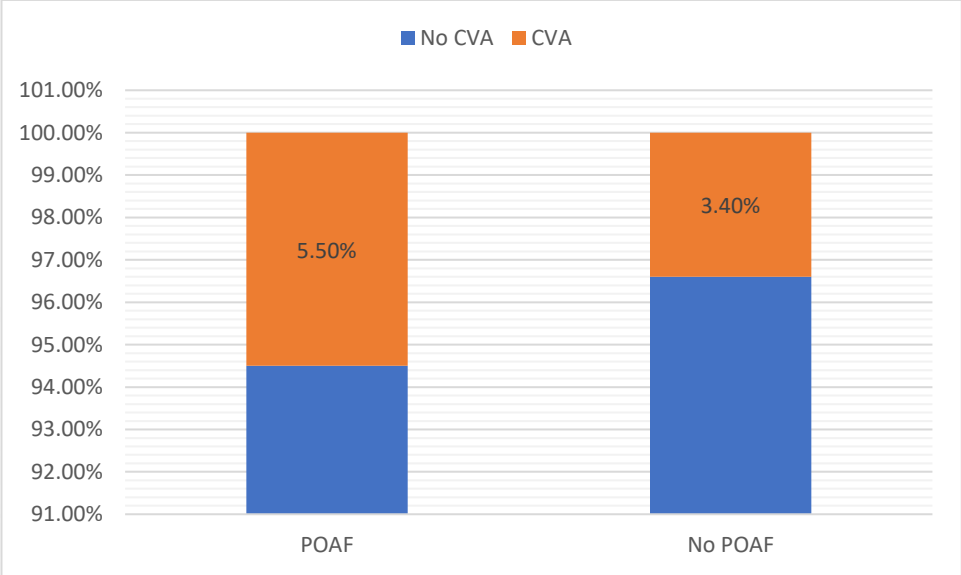

Figure 20: CVA events between POAF and No POAF group

The overall all-cause mortality in the study population is 8.7%, however, there is no statistically significant difference in the all-cause mortality between the groups (12.7% in the POAF group and 8.2% in the no POAF group). However, mortality due to ischemic CVA (Malignant stroke) is significantly higher in the POAF group (3.6%) than those without POAF (1.1%) with a p-value of 0.034. Death due to major bleeding is also higher in the POAF group. There is no difference in mortality due to Heart failure between the groups. In the POAF group 10/14 (71%) is due to cardiovascular causes whereas in the no POAF group, 32/73 (44%) is due to cardiovascular causes. (Table 22 and Figure 21)

	POAF (n=110) N (%)	***No POAF (n=892) N (%)***	***Total Patients N (%)***	***P value***
All-cause Mortality	**14 (12.7%)**	**73 (8.2%)**	**87 (8.7%)**	**0.110**
Death due to CVA	**4 (3.6%)**	**10 (1.1%)**	**14 (1.4%)**	**0.034**
Death due to Heart failure	**4 (3.6%)**	**20 (2.2%)**	**24 (2.4%)**	**0.367**
Death due to Major bleeding	**2 (1.8%)**	**2 (0.2%)**	**4 (0.4%)**	**0.012**

Table 22: Mortality Events

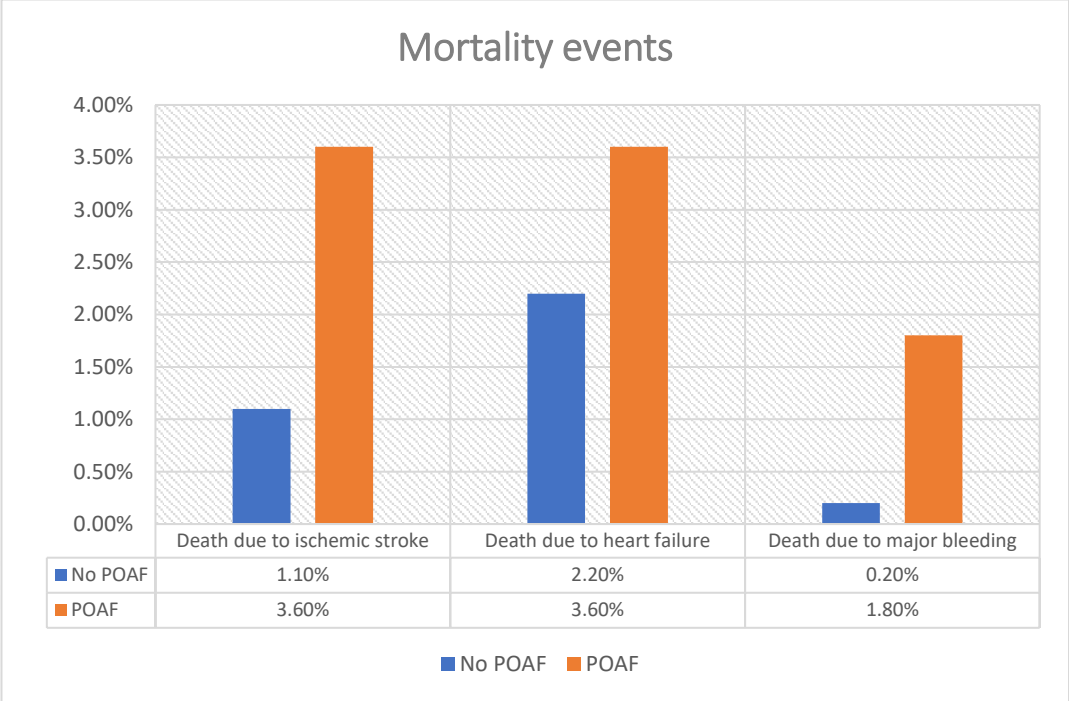

Figure 21: Mortality events between POAF and No POAF group

Survival analysis:

A total of 73 patients (8.18%) in the no POAF group and 14 (12.7%) in the POAF group have died. The hazard ratio for death in the POAF group as compared with the no POAF group is 1.8 [(95% confidence interval [CI], 0.9 to 3.6) P = 0.095]. The overall mean duration of survival was 16.5 years (95% CI, 16.2 to 16.8 years), Mean duration of survival among the POAF group and the no POAF group was 14.98 (95% CI, 14.03 to 15.9 years) and 16.6 (95% CI, 16.3 to 16.9 years) respectively. The overall survival rate at the end of 5 years for the POAF group was 95% and that for the no POAF group was 96.4%. The survival rate at the end of 10 years for the POAF group was 89% and that for the no POAF group was 92.5%. The survival rate at the

end of 15 years for the POAF group was 72.8% and that for the no POAF group was 83%. (Table 23, 24, Figure 22)

Duration of survival:

Duration of survival	Mean ± SE (In Years)	95% CI for the mean
POAF	14.98 ± 0.48	14.029 to 15.925
No POAF	16.61 ± 0.16	16.300 to 16.915
Overall	16.51 ± 0.15	16.209 to 16.808

Table 23: Mean duration of survival

	POAF		No POAF		Overall	
Survival Time (In Years)	Survival Proportion	Standard Error	Survival Proportion	Standard Error	Survival Proportion	Standard Error
5 years	0.950	0.0220	0.964	0.00643	0.963	0.00623
10 years	0.893	0.0345	0.925	0.0110	0.921	0.0105
15 years	0.728	0.0724	0.833	0.0231	0.822	0.0220

Table 24: 5-, 10- and 15-year survival probability

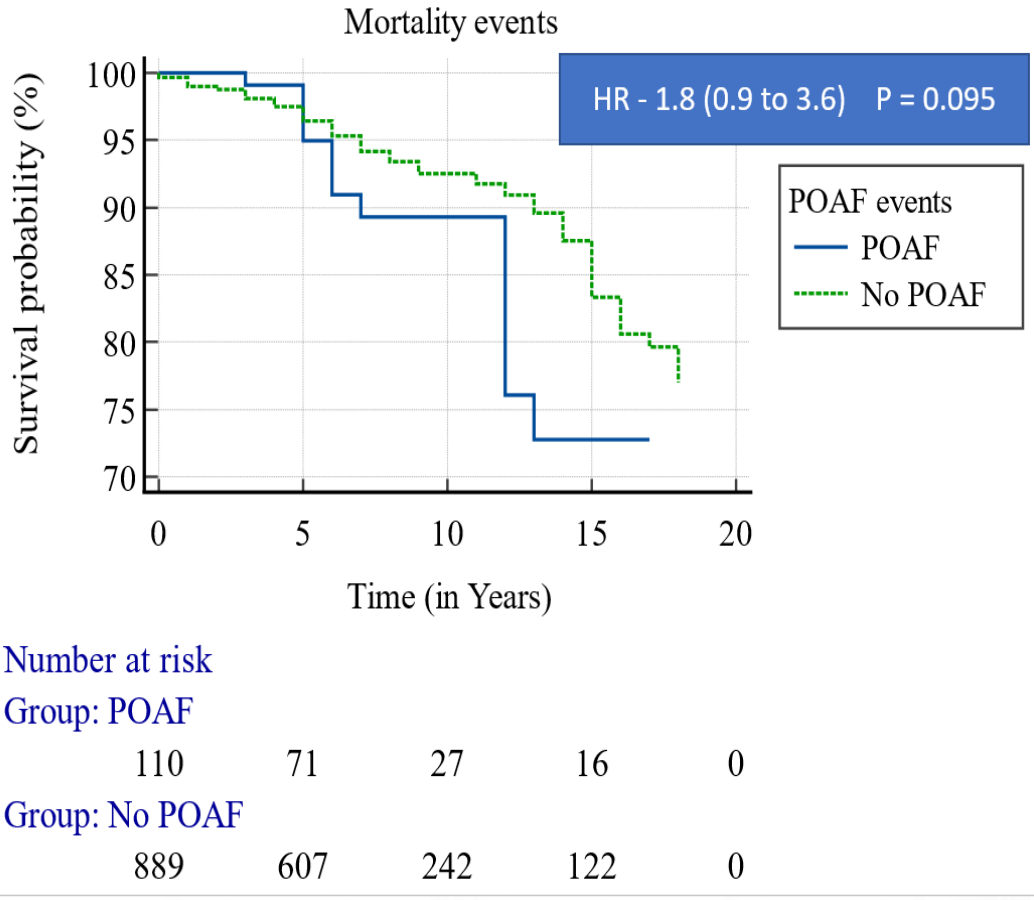

Figure 22: Kaplan-Meier curve for survival analysis

MACE events:

A total of 184 patients (20.6%) in the no POAF group and 28 (25.5%) in the POAF group have MACE events. The hazard ratio for death in the POAF group as compared with the no POAF group is 1.4 [(95% confidence interval [CI], 0.9 to 2.2) P = 0.138] (Figure 23).

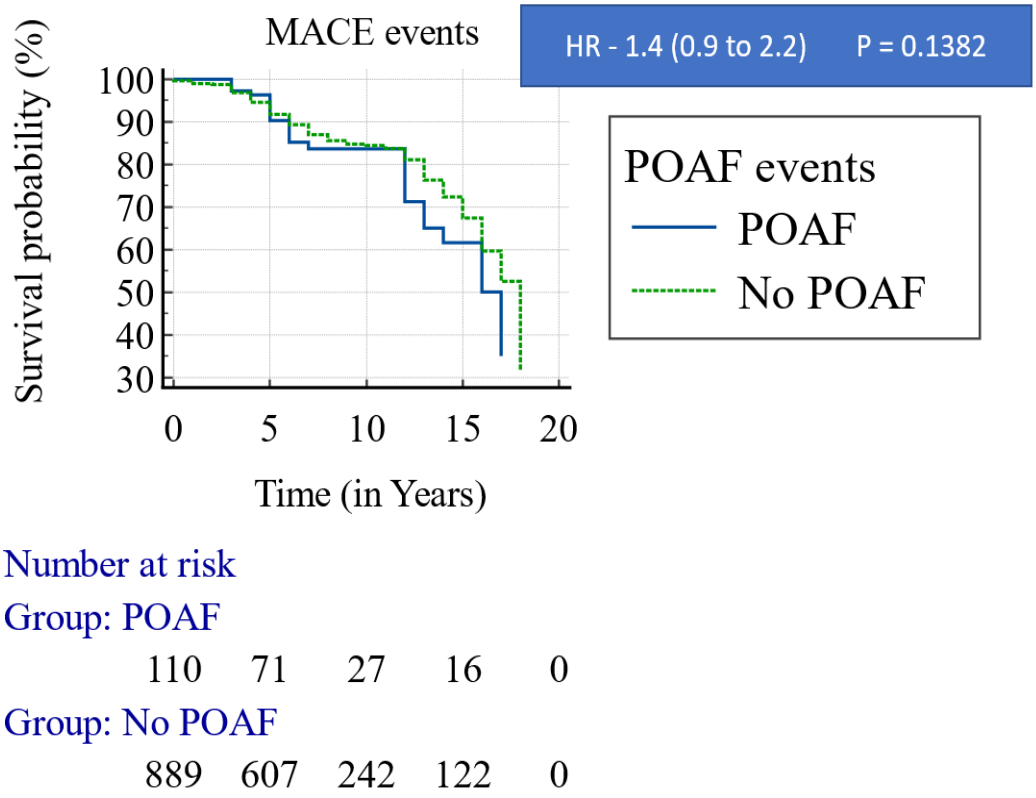

Figure 23: Kaplan-Meier curve for MACE events

Recurrence of AF:

23 patients (2.3%) had a recurrence of Atrial fibrillation on follow-up. In the POAF group, 9 patients (8.2%) had recurrence whereas in the no POAF group, 14 patients (1.6%) had a recurrence of AF which is statistically significant with p-value of <0.001 (Table 25, Figure 24)

	POAF (n=110) *N (%)*	*No POAF(n=892)* *N (%)*	*Total Patients* *N (%)*	*P value*
Recurrence of AF	**9 (8.2%)**	**14 (1.6%)**	**23 (2.3%)**	**< 0.001**

Table 25: Long-term AF recurrence

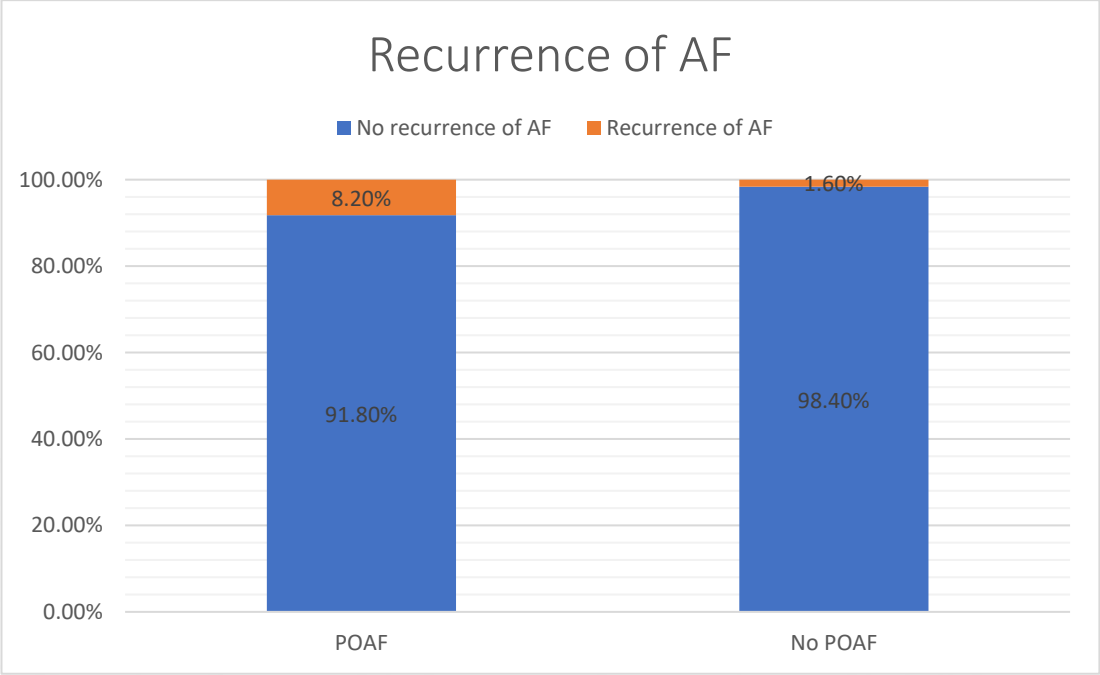

Figure 24: Long-term AF recurrence

DISCUSSION

Discussion:

This is one of the largest cohort studies from our country. In our study, post-operative atrial fibrillation is observed in 11% of the study population. Various studies have reported the incidence of POAF ranging from 11-40% depending on the individual subsets of surgery (Butt et al., 2018b). In a review by ESC, it is shown that the incidence of POAF after isolated Coronary Artery Bypass graft surgery is approximately 20% (Gaudino, Di Franco, Lisa Q. Rong, et al., 2023). An Indian study has also shown the incidence of POAF is around 9.2% (Malhotra et al., 2021b). Our study has shown similar incidence of POAF as compared to previous studies.

One of the independent risk factors for the development of atrial fibrillation is the increasing age in the general population. It holds true even postoperatively, especially post-cardiac surgery. Studies by Almassi et al (Almassi et al., 1997) and Zaman et al (Azfar G. Zaman et al., 2000) have also found that there is an increase in the incidence of the development of atrial fibrillation post-operatively. In our study, it was found that patients who developed POAF had a higher age at the surgery of 58.8 ± 9 years than those who had not developed POAF (54.1 ± 8.6 years) which is statistically significant ($P<0.001$). This strongly indicates that age at the time of surgery is an important risk factor for the development of atrial fibrillation post-operatively and hence it can help in risk stratifying the patients at risk of development of POAF.

The predominant population in our study is males constituting 87.4% of the study population. Males had higher risk of development of POAF with significant P value of 0.007. This is similar to the incidence of AF in general population where male

gender has higher association with AF. However, its incidence in POAF is still unclear. Similar to our study results one study by Aranki et al (Aranki et al., 1996) showed higher association of male gender with POAF.

In our overall study population, 57.4% were diabetic, 67.5% were hypertensive, and chronic respiratory disease was observed in 2.2% of the study population. A history of any heart failure prior to surgery was observed in 7.5% of the study population. History of CVA (both stroke and TIA) in 4% of the study population. However, we can observe that patients with diabetes and Hypertension are observed more in patients who developed POAF (67% were diabetic in the POAF cohort and 65.5% were hypertensive in the POAF group) indicating that diabetes and hypertension are important risk factors for the development of Atrial fibrillation as observed in the general population. In the western studies conducted by Leitch et al (Leitch et al., 1990) and Almassi et al (Almassi et al., 1997) it was found that hypertension as an significant risk factor for the development of POAF. Though there were conflicting evidences as observed by Hashimoto et al (Hashimoto et al., 1991) and Steinberg et al (Steinberg et al., 1993) where there is no statistically demonstratable evidence of association between hypertension and POAF. However, in the same study it was found that ECG changes suggestive of LVH is a risk factor for development of POAF – indicating that alteration in the myocardial substrate that occurs as a consequence of hypertension plays an important role in development of AF. Similar findings were observed in our study population.

In our study it was found that the history of any prior treated heart failure admission is more in no POAF group and similarly the history of prior CVA is seen

more in no POAF group. It could be an incidental finding as only 4% had CVA prior and moreover the data regarding documentation of AF in those CVA patients were not available at the time of study. Similarly, the prior heart failure admissions were also more in the no POAF group. It could be due to the fact that these patients might be on well controlled HF or heart failure might have recovered after an acute event. These risk factors like heart failure and history of CVA were not present immediately prior to the surgery. Some of the studies conducted by Hashimoto et al (Hashimoto et al., 1991) and Aranki et al (Aranki et al., 1996) also failed to demonstrate the association between preoperative congestive heart failure and POAF. Most of the studies used immediate preoperative heart failure as a risk factor for POAF. Even in these studies it was found that elevated left ventricular end diastolic pressure (>20mmHg) is associated with POAF (Aranki et al., 1996; Hashimoto et al., 1991). In our study no patients had immediate preoperative heart failure.

10.2% of the patients in no POAF group had mild renal insufficiency prior to surgery whereas none of the POAF group had renal insufficiency. However, there is no statistically significant difference in the need of renal replacement therapy between the groups. In a study by chua et al found that those patients with eGFR < 60 ml/min/1.73 m2 had statistically significant risk factor for development of POAF (Chua et al., 2015). In another study by Auer et al which included patients from elective cardiac surgery in the absence of Left ventricular dysfunction found that POAF group had lower eGFR than the no POAF group (Auer et al., 2007). In our study renal dysfunction included all patients with eGFR < 90 ml/min/1.73 m2. This might be the reason why there is no difference between the 2 groups. In severe renal dysfunction patients requiring RRT there is no statistically difference between both the groups.

In our study there is no significant difference in both the cohorts in terms of chronic respiratory illness obstructive sleep apnoea. Similar studies by Almassi et al (Almassi et al., 1997), Leitch et al (Leitch et al., 1990) and Aranki et al (Aranki et al., 1996) found that there is a trend towards development of POAF if the patient is having chronic respiratory illness however it was not statistically significant.

As the mean Left ventricular ejection fraction between both the groups were similar there is no significant difference in the incidence of post-operative atrial fibrillation between both the groups in terms of Left ventricular ejection fraction. Some European studies have shown that though the patients who developed POAF had relatively lower LVEF but was not statistically significant (Hashimoto et al., 1991).

In our study the presence of increased LA size is associated with increased risk for development of POAF. The mean LA size in POAF group is 38 ± 4.5 mm whereas in the no POAF group it is 35.4 ± 4.4 mm with significant p-value of < 0.001. It is similar to the various studies which assessed LV size by either assessment of LA volume or LA dimension found similar results (Karimi et al., 2020; Osranek et al., 2006)

Though statistically not significant the patients who developed POAF had prolonged CBT time and Aortic cross-clamp time 91.6 ± 22.8 min and 52.0 ± 14.2 min respectively than those who haven't developed POAF with CBT and Aortic cross-clamp time of 90.5 ± 25.6 min and 50.6 ± 16 min. Similar results were observed in previous studies. In PSOCS trial which includes 3855 patients found that there is no difference in cardiopulmonary bypass time in patients with and without POAF. In studies which assessed the significance of prolonged aortic cross-clamp time in

patients with and without POAF have found similar results. Studies from creswell and colleagues showed higher aortic cross-clamp time in patients who developed POAF only in the univariate analysis. However, when multivariate analysis was done there was no significant difference (Creswell et al., 1993). In contrast an Indian study conducted in Mumbai by Dave et al (Dave et al., 2018) observed that CBT time > 100min is significantly associated with development of POAF. The risk of prolonged CBT time and development of POAF is yet to be established.

The basal CHADSVASc score prior to surgery is higher in the POAF group than in the no POAF group. We can see that the proportion of patients with particular CHADSVASc score group is higher in no POAF group when the score is < 2. Once the CHADSVASc score crosses 2 I.e., ≥ 2 the proportion of patients in the POAF group is more. In a study by Kashani et at it is found that the mean CHA2DS2-VASc scores with POAF and without POAF were 3.6 ± 1.7 and 2.8 ± 1.7, respectively (P< 0.0001) and as the score increases from 0 to 9 the probability of developing POAF increased from 8.2% to 42.3% (P<0.0001) (Kashani et al., 2015b). In our study we have also found that when we divide the population into two groups based on CHADSVASc score < 2 or ≥2 we have found that 77.3% of the study population in POAF group had higher CHADSVASc score of ≥2. However, in no POAF group only 54.1% had CHADSVASc score of ≥2. It had odds Ratio of 2.9 (95% CI for OR = 1.8-4.6] and P value = 0.041. This indicates that patients with CHADSVASc score of ≥2 is 2.9 times more prone for developing AF post operatively than those with CHADSVASc score of <2. This is similar to the study by Kashani et al where it is found that patients with CHADSVASc score of ≥2 were 5 times more prone to develop POAF (P <0.0001).

In our study 4.5% in the POAF group had prior history of AF whereas only 0.9% of the patients in no POAF group had prior history of AF. This has been observed in previous studies as well. The presence of postoperative persistence of preoperative changes in the atrial substrate and the insult or the triggers that occur postoperatively can lead to increased incidence AF post operatively. In a study by Moto et al from Mayo clinic it was found that 45% of the patients in the POAF group had prior atrial arrhythmia whereas only 22% of the patients in the no POAF had prior atrial arrhythmia.

84% of the patients developed Atrial fibrillation within the first 4 days of the post-operative period with the maximum onset in the day 1 post-operative period (27%). In our study, no patient has developed AF beyond 10 days of post-operative period. This observation is similar to the previously established studies. In a study by Bidar et al, almost 40.5% of patients developed POAF within 0-5 post operative days and most of the patients developed AF within 16 post operative day. Beyond 16 post operative days there is drastic decline in incidence of POAF i.e., 2% in the remaining 14 days (Bidar et al., 2013). Similarly, the studies that used continuous ECG monitoring like SEARCH-AF trial similar findings were observed. Here 73.3% developed AF in the first week, 20% in the second week, 6.7% developed in the third week, 0.03% in the fourth week of surgery (Ha et al., 2021).

96% of the POAF patients reverted to sinus rhythm. 69% of the patients were reverted to sinus rhythm within 24 hours of onset of AF. 102/106 patients were reverted to SR within 72 hours of onset of AF. Only 4 patients were reverted after 72 hours of onset of POAF. Among 4 patients who were not reverted to sinus rhythm – 2 were

transiently reverted to SR however they continued to be in AF at the time of discharge. 2 patients never reverted to SR. All these 4 patients had moderate to severe Left ventricular dysfunction.

22% of the patients who developed AF were reverted spontaneously to sinus rhythm. Most of the patients required antiarrhythmic medications alone or DC cardioversion alone or combination of both to revert to sinus rhythm. As most of these patients require maintenance of optimal hemodynamic status in the immediate post operative period most of the patients required some intervention to revert to sinus rhythm.

In our study univariate analysis showed that presence of diabetes Mellitus, Hypertension, higher CHADSVASc score (≥ 2), prior history of Atrial fibrillation, presence of Left ventricular hypertrophy, presence of post operative Myocardial infarction, post operative heart failure were associated with increased occurrence of POAF. Only CHADSVASC SCORE ≥ 2 ($p<0.001$), History of Prior AF ($p=0.016$), presence of Left ventricular Hypertrophy ($p=0.012$), and post-operative Heart failure ($p<0.001$) remained statistically significant in the multivariate logistic regression analysis. Using this logistic regression analysis, a formula to predict development of atrial fibrillation is developed.

Probability of development of POAF = -2.931+0.872*a+1.418*b+.596*c +1.272*d.

The letters in the equation denote the variables: a = CHADSVASC SCORE (1 if score ≥2, 0 if score <2); b = Prior AF (1 if yes, 0 if not); c = LVH (1 if yes, 0 if not); and d= post operative Heart failure (1 if yes, 0 if not).

The median follow-up duration in our study is 7 ± 4.5 Years. In our study patients who developed POAF had trend towards higher MACE (Includes Mortality, ACS, Heart failure and CVA) events (25.5%) in comparison to no POAF group (20.6%) however it was not statistically significant. There is also no difference in the ACS, heart failure and CVA events in between the groups on follow up though there is a trend towards higher ACS, heart failure and CVA events in POAF group. The all-cause mortality in the POAF group is 12.7% which is higher than the no POAF group (8.2%) though statistically not significant. However, while evaluating the cause of death, it is found that the death due to malignant stroke is more in POAF group (3.6%) than in the no POAF group (1.1%) that is statistically significant with p = 0.034. There is no statistically difference in death due to heart failure between both groups. Death due to major bleeding is more in POAF group (1.8%) than the no POAF group (0.2%).

Our observation is similar to a large meta-analysis by Caldonazo et al.that included 57 studies (246340 patients) observed positive association of POAF with stroke (OR 2.17, 95% CI 1.90– 2.49), myocardial infarction (OR 1.28, 95% CI 1.06–1.54), perioperative mortality (OR 1.92, 95%CI 1.58–2.33) along with long term mortality (Caldonazo et al., 2023). In another it is observed that patients with POAF developed stroke with four times higher frequency (1% vs. 4%; OR 4.09, 95%CI 2.49–6.72; P < 0.00001)(Eikelboom et al., 2021). In a study by Benedetto et al.(Benedetto et al., 2020) it was found that the cumulative incidence of cerebrovascular accidents at 10 years was found to be 3.7% (2.9-4.5%) in sinus rhythm vs 6.3% (4.6-8.1%) in patients who developed POAF. Studies by Anders Ahlsson a et. al. (Ahlsson et al., 2010), Emma Thorén et. al. (Thorén et al., 2020), Amar Taha et al (A et al., 2021) also showed higher risk of ischemic stroke, any thromboembolism, heart failure

hospitalisation, higher death due to CVA and Myocardial infarction and overall mortality. Some of the Indian studies by Malhotra et. al. (Malhotra et al., 2021a) and Ghurram et al (Ghurram et al., 2020) have also shown that patients with POAF had significantly higher short term and long term mortality. Though statistically not significant in our study we can find the trend towards higher incidence of stroke in POAF patients. There is highlighting evidence in our study is that there is higher risk of mortality due to CVA in POAF group.

The Kaplan-Meier curve for the survival analysis showed that there is no difference in mortality between POAF and no POAF group with Hazard ratio of 1.8 (0.9-3.6) with p value of 0.095.

In our study the survival proportion at 5 years is 95% in POAF group and 96% in no POAF group, at 10 years the survival proportion is 89% and 92% in POAF and no POAF group respectively. At 15 years the survival proportion between POAF group and no POAF group is 72% and 83%. Overall duration of survival in POAF group is 14.98 ± 0.48 years where as for no POAF group is 16.61 ± 0.16 years. Though there is trend towards higher mortality and reduced survival time in POAF group it is not statistically significant. In a similar study by Eikelboom et al. (Eikelboom et al., 2021) observed that POAF was associated with significantly high long-term mortality (HR 1.25, 95%CI 1.2–1.3; P< 0.01) in patients with POAF. In this study 1year mortality was 6% vs. 4% (OR 1.69, 95%CI 1.1–2.6; P=0.02) in patients with and without POAF and 5-year mortality was 15% vs. 10% (OR 1.6, 95%CI 1.52–1.68; P < 0.00001) in patients with and without POAF.

Total 23 patients (2.3%) had recurrence of AF on follow up. 8.2% of the POAF group and 1.6% in the no POAF group had recurrence on follow up which is statistically significant ($P < 0.001$), Hence, the development of POAF is a risk factor for recurrence of atrial fibrillation. Similar results were observed in various studies by Anders Ahlsson a et. al. (Ahlsson et al., 2010), Seung-Hyun Lee et. al. (Lee et al., 2014), Emma Thorén et. al. (Thorén et al., 2020).

Limitations:

It is a retrospective observational study from 2005. The timeline from 2005 was taken to assess the long-term follow-up. Hence lost to follow-up rates were high.

The data is collected from out Electronic Medical records. Underreporting of the AF can be there. So, the overall incidence of Post-operative AF might be low in our study.

CONCLUSIONS

Conclusions:

- The incidence of Post operative Atrial fibrillation is 11%
- Higher age at surgery is associated with a higher incidence of post-operative Atrial fibrillation.
- Males are at high risk for development of POAF.
- Diabetes Mellitus, Hypertension, left ventricular hypertrophy and peripheral vascular disease are more prone to develop post-operative Atrial fibrillation.
- Larger the LA size higher the incidence of POAF.
- The baseline CHADSVASC score is a significant predictor for the development of POAF. The higher the score at baseline, the higher the risk for the development of POAF. CHADSVASc score especially if ≥2 has 2.9 times the higher risk of development of AF postoperatively.
- Most of the patients (84%) develop Atrial Fibrillation within the first 4 post-operative days. No patient developed AF beyond 10 days of post-operative period. 96% of patients who developed POAF has been reverted to sinus rhythm. 22% reverted spontaneously, 64% with Amiodarone alone, 9% with DC version alone. Among those patients who were reverted to sinus rhythm. 68.9% of the patients reverted to sinus rhythm within the first 24 hours. Almost every patient who reverted to sinus rhythm has reverted within four days of the development of AF.
- CHADSVASC SCORE ≥ 2, History of Prior Atrial fibrillation, presence of Left ventricular Hypertrophy and occurrence of post-operative Heart failure were the strong predictors for development of Atrial fibrillation.

- There is no significant difference in the Major Adverse Cardiovascular Events (MACE) between those patients who have and have not developed POAF.
- There is no significant difference in long-term overall mortality between those patients who have and have not developed POAF.
- However, increased mortality due to malignant stroke and major bleeding is seen in patients who developed post-operative Atrial Fibrillation.
- Patients who have developed post-operative Atrial fibrillation are more prone to develop atrial fibrillation in the long term.
- The risk factors identified in this study for the development of POAF can be used as a comprehensive screening tool for high-risk patients.

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ANNEXURES

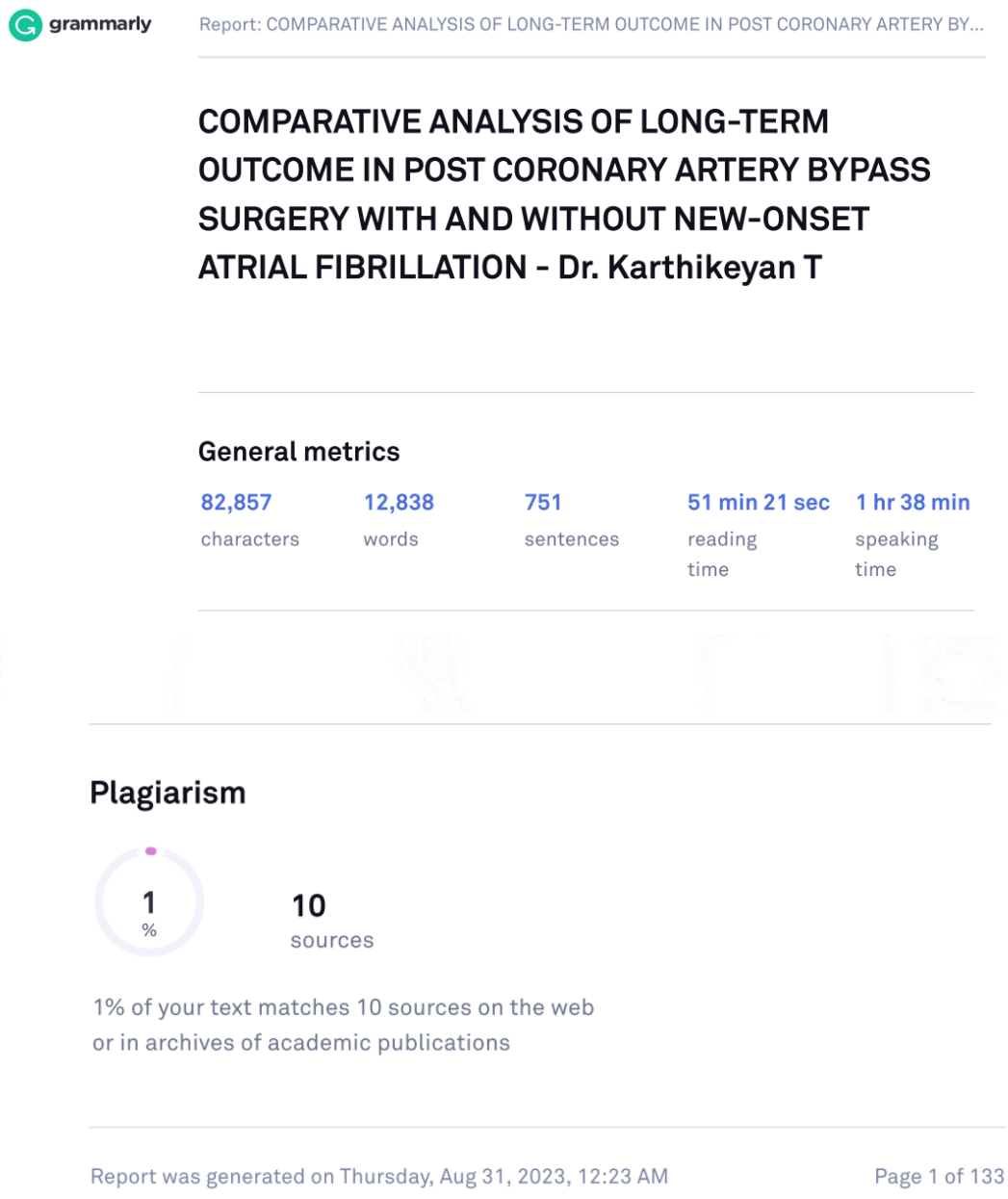
ANNEXURE 1

CURRICULUM VITAE

KARTHIKEYAN	T	
Date of Birth (dd/mm/yy) : 08/04/1992		Sex: Male
Study Site Affiliation (eg. Principal Investigator, Co-investigator, Coordinator): Principal Investigator		
Professional mailing Address (include institution name)		Study site Address (Include institution name)
Dr Karthikeyan T. Room no. PG 12, Sree Chitra Staff Quarters, Kumara Puram, Thiruvananthapuram, 695011		Department of Cardiology SCTIMST
Mobile No. : 9789040614		Email: karthithangaraju91@gmail.com karthithangaraj@sctimst.ac.in
Academic Qualifications (more recent qualification first)		
Degree/Certificate	Year	Institution, Country
SR General Medicine	June 2020	All India Institute of Medical Sciences, Jodhpur, India
MD (General Medicine)	June 2017-2020	All India Institute of Medical Sciences, Jodhpur, India
MBBS	2015	Madras Medical College, Chennai, India
Details of Professional Registration (MCI/State Registration/ Bar council/ DCI etc including registration no. and year of registration) Travancore Cochin Council Reg no.: 79423 Date of Registration: 09/02/2021		
Current and Previous Position (More recent position first)		
Month and year	Title	Institution/ Company, Country
From Jan 2021- till now	Senior Resident, Department of Cardiology	SCTIMST, India
June 2020	SR General Medicine	All India Institute Of Medical Sciences, Jodhpur, India
Brief Summary of Relevant Research Experience 1) MD Thesis: A study of platelet indices with clinical and laboratory parameters of patients with Dengue in Western Rajasthan 2) Current Project/s at hand: DM Thesis - Comparative analysis of long-term outcome in post-coronary artery bypass surgery with and without new-onset atrial fibrillation		
Signature: 		Date: 28/08/2023 Place: Thiruvananthapuram

ANNEXURE 2

Plagiarism Report



ANNEXURE 3

THESIS PROFORMA

S. No. –

AGE –

SEX –

HOMETOWN –

Base line characteristics:

Diabetes Mellitus	
Hypertension	
Prior heart failure admissions	
Prior history of any ischemic or haemorrhagic stroke	
Alcoholism	
Obstructive sleep apnoea	
History of acute coronary syndrome (ACS)	
History of previous percutaneous coronary intervention	
Any previous peripheral systemic embolism	
Prior renal insufficiency	
Need of Renal replacement therapy	
Chronic respiratory disease	
Chronic liver disease	
History of any cancer	
Peripheral vascular disease	
CHA2DS2-VASc score	
Hypothyroidism	

Date for CABG	
ACS / CSA prior	
Number of vessels involved	
Number of grafts	
Presence of Atrial fibrillation	
If yes, Day of AF Drugs / DC version Beta blockers CCBs Amiodarone	

ECHO

LA size	
Any left ventricular hypertrophy	
Presence of mitral regurgitation and its severity	
Any new onset RWMA	
NYHA functional class	

Post operative myocardial infarction	
Pericarditis	
Heart failure	
Cardiopulmonary bypass time	
Aortic cross-clamp time	

OUTCOMES:

Major adverse cardiac event (MACE)	
All-cause mortality	
Death from any cause	
Specific cause of Mortality	
Ischemic stroke	
Thromboembolism (TIA / Ischemic stroke / Peripheral embolism)	
Heart failure	
Major bleeding	
Coronary events – Acute coronary syndromes	
Any recurrence of AF on follow up	

ANNEXURE 4

IEC CLEARANCE CERTIFICATE

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1886/MAY-2022 04.06.2022

Dr. Karthikeyan T
Senior Resident
Department of Cardiology
SCTIMST, Thiruvananthapuram

Dear Dr. Karthikeyan,

The project proposal with the title **"LONG TERM OUTCOME OF NEW ONSET ATRIAL FIBRILLATION IN POST CORONARY ARTERY BYPASS SURGERY"** submitted to Institutional Ethics Committee (IEC) has been reviewed in the IEC Meeting held on 13th May, 2022 and assigned number as IEC/1886.

List of documents submitted:

1. Covering letter addressed to the Chairperson, IEC, SCTIMST
2. Checklist Form
3. Declaration form
4. IEC Application form
5. Project Proposal
6. Participant consent form
7. Information Sheet for study participant
8. Data collection sheet
9. SRC Recommendation Letter

IEC Recommendations

1. The title may be changed as the investigator is comparing two groups those with and without AF.
2. The information provided by the investigators in section IV of the consent process is not correct as it is planned as a retrospective study. Please clarify
3. Patient consent and information sheet is provided. This needs to be justified.
4. Data collection sheet has name and hospital number to be removed.
5. There is a bit of a contradiction on the benefit of this study as is seen on Pages 13 and 14 in that, "(f) BENEFITS: Describe benefits to the subject/participant in participating in the study. Also describe the benefits, if any, to the society. Taking part in this research study is unlikely to benefit subjects immediately in any manner. However, we do hope that this study will shed light on the management of patients withPOAF. (g) RISK/BENEFIT: Analyse the extent to which the benefits of the study out-weigh the risk to the subjects/participants. This study has no inherent risk and essentially provides **scientific benefit to the individual** as well as society in analysing the management and follow up plans for POAF."
6. The consent form is only in English. Clarity is sought on whether that is sufficient.

One set of all the documents including those revised may be submitted. The covering letter should indicate the revisions made.

Sincerely,

Dr. G. Srinivas
Member Secretary, IEC

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM