Original Research

Incidence and Outcomes of Postoperative Atrial Fibrillation after Coronary Artery Bypass Grafting of a Randomized Controlled Trial: A Blinded End-of-cycle Analysis

Ahmad Farouk Musa[1,2,*], Jeswant Dillon[3], Mohamed Ezani Md Taib[3],
Alwi Mohamed Yunus[3], Abdul Rais Sanusi[3], Mohd Nazeri Nordin[3], Julian A. Smith[4,5]

[1]Jeffrey Cheah School of Medicine & Health Sciences, Monash University Malaysia, 47500 Subang Jaya, Selangor, Malaysia
[2]Victorian Heart Institute, Monash University, 3168 Melbourne, Australia
[3]Department of Cardiothoracic Surgery, National Heart Institute, 50400 Kuala Lumpur, Malaysia
[4]Department of Surgery, School of Clinical Sciences at Monash Health, Monash University, 3168 Melbourne, Australia
[5]Department of Cardiothoracic Surgery, Monash Health, 3168 Melbourne, Australia
*Correspondence: farouk@monash.edu (Ahmad Farouk Musa)
Academic Editors: Giuseppe Santarpino and Giuseppe Nasso
Submitted: 15 December 2021   Revised: 28 February 2022   Accepted: 1 March 2022   Published: 1 April 2022

Abstract

Objective: The objective of this study is to analyse the incidence of postoperative atrial fibrillation (POAF), demography, post-operative outcomes including morbidity and mortality, length of Cardiac Intensive Care Unit (CICU) stay, High Dependency Unit (HDU) stay, and total hospital stay in patients undergoing coronary bypass grafting (CABG) at Institut Jantung Negana (IJN). **Methods**: We conducted a prospective, randomised, controlled trial. We supplied the treatment group with Tocovid capsules and the control group with placebo containing palm superolein. **Results**: Since January 2019, we have recruited the target population of 250 patients. However, the result is still blinded as we are still analysing blood samples for tocotrienol levels. 89.2% of patients completed the study with a 3.6% mortality and a 7.6% attrition rate. 35.2% of the patients developed POAF, the mean time being 46.06 ± 26.96 hours post-CABG. We did not observe any statistically significant difference when we compared left atrial size, New York Heart Association (NYHA) functional class, ejection fraction and premorbid history, besides EuroSCORE II (The European System for Cardiac Operative Risk Evaluation II) status except for older age group, right atrial size, and pleural effusion. There was also no difference in bypass time, cross clamp time or number of anastomoses. However, we noted a significant difference in death ($p = 0.01$) and renal failure requiring dialysis ($p = 0.007$) among patients with POAF; those patients also had a longer CICU stay ($p = 0.005$), HDU stay ($p = 0.02$), and total hospital stay ($p = 0.001$). **Conclusions**: POAF is associated with a higher incidence of renal failure and death while it increases CICU, HDU, and total hospital stay. It remains to be seen whether Tocovid reduces POAF and its associated sequelae. **Clinical Trial Registration**: NCT03807037 (Registered on 16 January 2019).

Keywords: Tocovid; postoperative atrial fibrillation (POAF); CABG; CICU stay; total hospital stay; morbidity; mortality

1. Introduction

One of the commonest complications of cardiac surgery is postoperative atrial fibrillation (POAF). It occurs in about 20% to 40% [1] of patients after isolated coronary bypass grafting (CABG) and more often after combined CABG and valve surgery [2]. In an earlier retrospective study [3], we observed a prolonged Cardiac Intensive Care Unit (CICU) stay, High Dependency Unit (HDU) stay and total hospital stay among these patients, with a projected increase in resource utilisation. This was accompanied by a statistically significant increase in the incidence of stroke and death [3].

There is no single unifying mechanism in the development of POAF. It is generally agreed that both a susceptible substrate and a trigger factor are needed to initiate POAF [4,5]. While multiple factors may initiate POAF, current data suggests that the postoperative inflammatory state after CABG plays a significant role in initiating POAF

[6,7]. More precisely, it is the shed mediastinal blood that serves as a notable source for this inflammation [8–10]. Recent data also showed that the incidence of POAF increased when the pericardium was opened. In contrast when the pericardium remained intact, as in transcatheter aortic valve replacement, a risk reduction of 82% was observed [11,12].

It is currently believed that besides the inflammatory milieu, the presence of oxidative stress also predisposes to POAF [13]. This happens when the reactive oxygen species produced inundates the endogenous antioxidant defences [14]. When the recruited leukocytes are activated to release O_2 (superoxide) by reducing oxygen at the expense of nicotinamide adenine dinucleotide phosphate (NADPH), oxidative stress ensues [15]. The occurrence of a highly inflammatory and pro-oxidant state which generally takes place after CABG predisposes to the development of POAF [16]. As described above, the intrapericardial inflammation and oxidative stress trigger POAF through some patholog-

ical pathways originating from shed mediastinal blood following CABG [17].

In light of this pathogenesis, we postulate that using a potent anti-inflammatory antioxidant might mitigate POAF. We decided on tocotrienol, a compound that has not been commonly investigated, despite its much superior antioxidative and anti-inflammatory effect compared to its cousin, tocopherol [18]. We hypothesise that this may confer a therapeutic advantage in the safety endpoints post-CABG by reducing the incidence of POAF and its adverse sequelae.

2. Aims

To determine the incidence of POAF, demography, post-operative outcomes including morbidity and mortality, length of CICU stay, HDU stay, and total hospital stay.

3. Methods

3.1 Study Design

We designed this study as a prospective, double-blind, randomised, controlled trial involving parallel groups. All patients who were admitted at the Institut Jantung Negana (IJN), Kuala Lumpur, for CABG, or CABG and valve surgery, were automatically recruited into the study.

Patients were divided into two arms using a computer-generated randomisation programme: (1) a Control group with placebo plus standard care, and (2) a Treatment group with Tocovid, plus standard care.

At least two days prior to surgery, the blinded randomised patients were administered daily with either 400 mg Tocovid in two divided doses, or placebo, which was prepared by Hovid Berhad, a company based in Ipoh, Malaysia. Each 200 mg soft-gel Tocovid capsule contained a cocktail of tocotrienol (61.52 mg alpha-Tocotrienol, 112.80 mg gamma-Tocotrienol and 25.68 mg delta-Tocotrienol) and tocopherol (91.60 IU alpha-tocopherol). This regime was continued post-CABG until six weeks follow-up when the study was terminated.

We decided on giving 400 mg of Tocovid daily since many other clinical studies [19,20] have used this regime without any adverse effects. We continued the treatment until the patient was discharged. The patients and the surgeons were blinded throughout the study, as were the research assistants. Only Clinical Research Nurses were not blinded. Onsite cardiothoracic ward nurses monitored and ensured compliance. Postoperatively all patients were observed for any electrocardiogram (ECG) changes via continuous ECG monitoring. All POAF episodes were treated according to the preference of the attending cardiothoracic surgeon.

For the study flow chart, refer to attachment: Fig. 1.

3.2 Inclusion and Exclusion Criteria

Inclusion Criteria:

Males or females over 18 years of age.

Elective, on-pump surgery of coronary artery revascularisation, either isolated or combined with valve surgery.

Exclusion criteria:

Urgent or emergency surgery as well as off-pump surgery.

Poor left ventricular (LV) function (ejection fraction (EF) <30%).

Allergy to palm oil or Vitamin E, or any form of arrhythmia pre-operatively.

Long-term treatment with corticosteroid.

Participation in other clinical trial within three months prior to the study.

Vitamin E or other potent antioxidant supplementation with within one month prior to randomisation.

3.3 Study End Points

The primary end point was POAF occurrence as confirmed on an ECG by the absence of p-wave and irregularly QRS complex of at least 30-second duration. For shorter ECGs, we diagnosed atrial fibrillation (AF)/atrial flutter (AFL) on the arrhythmia present at onset or termination [21]. The secondary end points were the length of hospital stay (LoHS) including both CICU and HDU stay.

3.4 Sample Size Calculation

For sample size calculation, we used the PS Power and Sample Size Calculation Software (Version 3.1.6, Developer: W.D. Dupont & W.D. Plummer. Licensed under a Creative Commons Attribution–NonCommercial-NoDerivs 3.0 United States License).

We estimated sample size based on findings from a prior study by Musa *et al*. [3]. The researchers found POAF incidence at IJN to be 28.7%. Assuming the true relative risk of AF for experimental subjects relative to controls is 0.45 [22], then if we use the PS Power and Sample Size Calculator [23,24] with α equivalent to 0.05 and power $(1-\beta)$ of 0.8, the estimated sample size is 103 in each arm. Assuming a possible attrition rate of 20%, our total sample size is: $103 + 20 (103) \times 2 = 250$ subjects, with 125 controls and 125 experimental subjects.

3.5 Statistical Analysis

For statistical analysis of the data, we used the SPSS software version 27.0 (IBM Inc., Chicago, IL, USA).

4. Ethics Declaration

We conducted this study according to the Malaysian Good Clinical Practice Guideline while abiding by the Helsinki Declaration revised in 2013. Informed written consent was obtained from all subjects prior to their participation in this study.

We sought ethics approvals from three institutions: the Institut Jantung Negara Research Ethics Committee (IJN-REC/201/2017), the Monash University Human Research
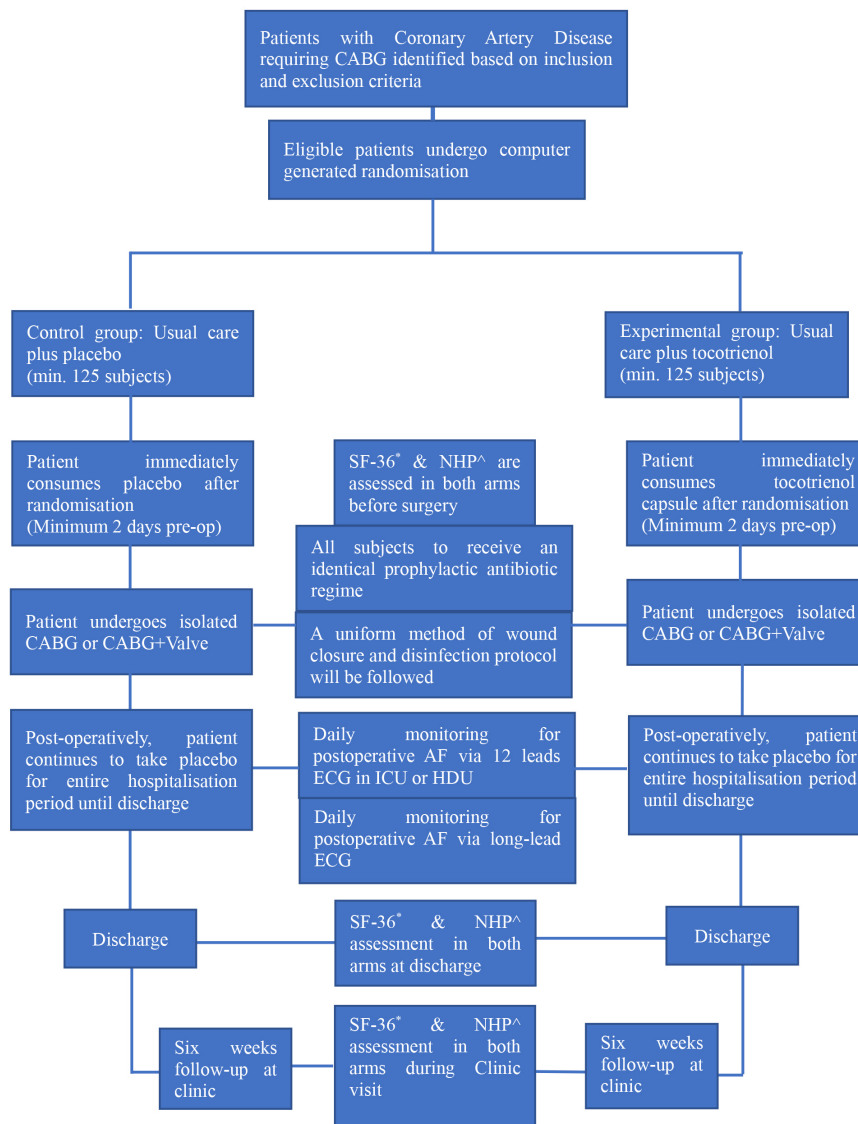
Fig. 1. Study Flow Chart. *SF-36, Short Form 36 Questionnaire; ^NHP, Nottingham Health Profile Questionnaire.

5. Results

Recruitment of patients started on 21 January, 2019 and we reached 250 patients on 30 June, 2021 from a total of 1128 patients screened within that period. The current results are based on patients' data; these were retrieved from patients who have completed the study. The tabulated figures consist of data extracted from both the IJN computer system and physical records.

Our population sample consists of 223 patients (89.2%) who have completed the study. There were 11 withdrawals and another 7 were lost during follow-up. We recorded 9 deaths (3.6%) which was slightly lower compared to our earlier study [25] in 2018 where the mortality rate stood at 4.66%. Therefore, the attrition rate was 7.2%. Eighteen serious adverse events (SAE) were reported but none was related to the investigational product.

The statistical analyses on the results of our study below were on the non-unblinded dataset since we have not completed the collection of all the data. Hence, our analyses were between the POAF group against the non-POAF group–not Tocovid versus control. This final analysis will only be conducted at the end of the study; at that time, all the data would have been completed and the groups unblinded. We also wish to emphasize that our analyses were restricted to patients with complete data. Hence, there might be some variations with regard to the number of patients analysed in each section.

IMR Press

3

Table 1. Characteristics of our sample population and their association with POAF.

Demographic	Total, mean ± SD/n (%)	Non-POAF group, mean ± SD/n (%)	POAF group, mean ± SD/n (%)	p-value
Age (years)	60.88 ± 7.79	59.93 ± 8.54	62.36 ± 6.20	0.02*
Range: 39 to 85 years old				
Gender:				
Male	196	121 (61.7)	75 (38.3)	0.20[a]
Female	46	33 (71.7)	13 (28.3)	
Population:				
Malay	199	122 (61.3)	77 (38.7)	
Chinese	8	6 (75.0)	2 (25.0)	0.40[a]
Indian	34	25 (73.5)	9 (26.5)	
Other	1	1 (100.0)	0 (0.0)	
EuroSCORE II:				
Low risk	102 (42.7)	66 (64.7)	36 (40.9)	
Medium risk	108 (45.2)	70 (64.8)	38 (35.2)	0.39[a]
High risk	29 (12.1)	15 (51.7)	14 (48.3)	

*p-value significant at 0.05 using independent T-test.

[a] Test using Chi-Square test.

5.1 Patients' characteristics

Table 1 below describes the characteristics of our study sample. The mean age was 60.88 ± 7.79 ranging between 39 to 85 years old. Older age group is associated with POAF and this consolidated the fact that age has always been considered the most consistent factor responsible for an increased incidence of POAF [26]. In fact, it is an independent predictor of POAF [27], the higher occurrence of POAF in elderly patients due to age-related co-morbidities [28] where ageing causes degenerative changes in the atrium as well as changes in the atrial physiology. These changes were described by Amar *et al*. [29] as having shorter refractory period, delayed sinoatrial (SA) and atrioventricular (AV) nodal conductivity, atrial stiffening and spluttering of the arial waveform. Cardiac surgery could also cause injury to the sympatho-vagal fibres of the cardiac plexus of elderly patients, leading to POAF [30]. Indeed, Mathew *et al*. [31] noted a 75% increase in the odds of developing POAF in every ten-year increase in age.

As a predictive factor of POAF, gender remains a contentious matter. While it is controversial to assume that male gender is a predictor of POAF, the effect of gender on POAF is definitely an interesting field of study. It has been shown that the female gender is shielded against POAF [32] but other studies have shown poorer outcomes among women after CABG [33–36]. Meanwhile, Filardo *et al*. [37] attested to the poorer late survival in both women and men; however, they also showed that the early burden of POAF was less in women. While the debate continues, our results showed that there was no statistically significant difference between the sexes in developing POAF although the majority (80.9%) of our patients were males.

However, we found no statistically significant difference exists between the different ethnic groups in terms of POAF. However, this is a marked difference from our previous study [25] in which the Indian population had significantly lower odds of developing POAF compared to the other races. It also contrasts with a Singaporean study [38] that found that Malays and Chinese, as compared to Indians, had a higher likelihood of developing this phenomenon post-CABG. Western papers [39–41] showed that Caucasians were more prone to developing POAF compared to blacks, and genetic disparity between the races was thought to be the reason [39]. However, the survival rate of POAF patients after CABG showed that the black race was a significant predictor for decreased survival [40,41]. This finding was definitely useful to both the surgeons and their patients.

Our study cohort showed that most of our patients (87.9%) were in the low and medium risk EuroSCORE II group. We observed no statistically significant difference in the development of POAF in between these groups. However, an earlier study by Chen-Scarabelli *et al*. [42] showed that higher EuroSCORE was associated with POAF though not with mortality after CABG surgery.

5.2 POAF Characteristics of Study Patients

Table 2 below refers to the POAF (post-operative AF) characteristics of our study patients. 35.2% of patients developed POAF which is higher compared to our previous study [25] where 28.7% of the patients developed AF post CABG. However, it would be hasty to conclude that To-covid has no effect in lowering the POAF rate since this is still a blinded analysis. Nevertheless, 35.2% falls within the POAF incidence range cited in the literature [43–45].

The mean time for POAF development of was 46.56 ± 26.96 hours after surgery; in the second postoperative day, and was within the range cited by the literature of 2–3 days after surgery [46]. Its occurrence ranges from 20 minutes

Table 2. Characteristics of POAF.

Characteristics of AF	n (%), mean $\pm$ SD
Occurrence of POAF	88 (35.2)
Time from surgery to POAF (minutes)	2793.61 $\pm$ 1617.36
Range: 10 to 7044 minutes	
Duration (hours):	
$\leq$48	45 (52.9)
>48	40 (47.1)
Number of episodes:	
Single	45 (51.1)
Multiple	43 (48.9)
Atrial fibrillation on discharge	0 (0.0)

to 5.7 days post-CABG. However, this was also within the cited range in the literature [46–48] POAF mainly occurs within the first week post-surgery, with 70% of cases [49] within the first four postoperative days. In addition, we noticed a single episode of POAF in 51.1% of our patients; while the remaining 48.9% had multiple AF episodes post-CABG. Nonetheless, all study patients reverted without exception, and they were all discharged in sinus rhythm.

5.3 Pre-operative Characteristics of Study Patients

Malaysia has the highest rate of obesity and overweight among Asian countries according to World Health Organization (WHO) [50]. Table 3 below indicates that 52.22% of the study sample was overweight and 25.12% was obese according to the Asian guidelines [51]. However, no statistically significant difference was observed between the groups in terms of POAF occurrence. This finding contradicts some reports in the literature [52–55] which suggest that, compared to their non-obese counterparts, obese patients are more prone to develop POAF. An earlier work of Sun X *et al*. [56] together with a most recent study by Vural Ü and Aglar A [57] have suggested that obesity is a predictor for POAF. However, a very recent meta-analysis [58] of 36 prospective studies which has yet to be peer-reviewed found that obesity might not increase the risk of developing POAF after CABG.

We have excluded poor EF (<30%) from our study, so most patients were in New York Heart Functional Class (NYHA) I and II. According to our findings, although the mean left ventricular ejection fraction (EF) for the non-POAF group was slightly better at 51.92% as compared to the POAF group at 50.67%, this was not statistically significant. Additionally, although left atrial size was larger in the POAF group as compared to the non-POAF group, this was also not statistically significant. These two findings contradicted some of the literature [59–62] that established a correlation between poor EF and an increased left atrial size in POAF development. But strikingly, the POAF group had a statistically significant dilated right atrial size as compared to the non-POAF group: this is consistent with

the literature [63] where POAF is believed to be due to dilatation process and the ensuing remodelling process itself [63].

5.4 Medical History

The pre-morbid history of our patients is illustrated in Table 4 below. As expected, the majority were afflicted with hypertension (81%), diabetes mellitus (62%) and hypercholesterolaemia (90.1%) but we noticed no statistically significant difference between the groups. Similarly, our analysis on chronic kidney disease which is normally linked to POAF [64,65], showed no significant difference in between the two groups.

When we compared current or ex-smokers with non-smokers to analyse the relationship between smoking habits and POAF incidence, we observed no statistically significant difference between them ($p = 0.77$). In contrast, a previous study [66] showed smokers tend to have a lower incidence of POAF ($p < 0.05$). However, the authors strongly recommended a ban on smoking for at least 4 weeks before surgery; in view of improving post-operative outcomes. The paper, however, might seem at odds with the presumption that nicotine increases the heart rate by stimulating the release of catecholamines and inducing the electrical instability of the atria by blocking the potassium currents, thereby increasing the risk of AF [67]. Another paper also found an association between smoking and AF-related outcomes such as bleeding, thrombosis and death [68]. Due to these conflicting reports, a meta-analysis which included 36 meta-analysis was conducted recently by Wan *et al*. [69]. They concluded that smoking was neither associated with an increased risk of POAF in CABG patients, nor does it have a protective effect.

5.5 Operative Details

We performed isolated CABG in 92.5% and CABG combined with valve surgery in 7.5% in our study population as shown in Table 5 below. Mitral valve replacement surgery accounts for almost 60% of cases of the combined surgery group; only one case involved mitral valve repair. Aortic valve replacement was performed in the remaining 40% of cases. However, no statistically significant difference was observed between these groups in terms of developing POAF. This contradicts the general belief that a combined valve with CABG would result in a higher occurrence of POAF [70,71] besides the use of heart-lung bypass machine [72,73]. In a recent multicentre prospective study [74] involving a total of 28 centres, it was reconfirmed that combined valve and CABG was significantly correlated with the occurrence of POAF.

The mean cross-clamp time in our study was 75.84 $\pm$ 30 minutes and the mean bypass time was 97 $\pm$ 35.59 minutes. Similarly, no statistically significant difference was observed between the two groups though we knew that both the cross-clamp time and the bypass time had an association

Table 3. Pre-operative characteristics and their association with POAF.

Pre-operative characteristic	Total, mean ± SD/n (%)	Non-POAF group, mean ± SD/n (%)	POAF group, mean ± SD/n (%)	p-value
Body Mass Index (kg/m^2)	27.15 ± 4.39	27.25 ± 4.52	26.86 ± 4.39	
<18.5	2 (0.8)	0 (0.0)	2 (100.0)	
18.5–22.9	57 (23.6)	38 (66.7)	19 (33.3)	0.29[a]
23–29.9	124 (51.2)	79 (63.7)	45 (36.3)	
≥30	59 (24.4)	37 (62.7)	22 (37.3)	
Range: 17.6 to 42.47				
New York Heart Functional Class:				
NYHA I	145 (60.2)	92 (63.4)	53 (36.6)	
NYHA II	94 (39.0)	61 (64.9)	33 (35.1)	0.89[a]
NYHA III	2 (0.8)	1 (50.0)	1 (50.0)	
NYHA IV	0 (0.0)	0 (0.0)	0 (0.0)	
Left ventricular ejection fraction	51.45 ± 9.02	51.92 ± 8.94	50.67 ± 9.09	0.29[b]
Range: 9 to 67				
Left atrial size (mm)	18.09 ± 4.96	17.63 ± 4.34	18.74 ± 5.85	0.09[b]
Range: 9 to 46				
Right atrial size (mm)	13.88 ± 3.09	13.43 ± 2.62	14.51 ± 3.55	0.007*
Range: 7.7 to 31				

*p-value significant at 0.05 using independent T-test.

[a] Test using Chi Square test.

[b] Test using independent T-test.

Table 4. Underlying medical conditions and their association with POAF.

Medical condition	Total, n (%)	Non-POAF group, n (%)	POAF group, n (%)	χ^2	p-value
COPD:					
Yes	3 (1.2)	2 (66.7)	1 (33.3)	-	0.7[b]
No	239 (98.8)	152 (63.6)	87 (36.4)		
Asthma:					
Yes	1 (0.4)	1 (100.0)	0 (0.0)	-	0.64[b]
No	241 (99.6)	153 (63.5)	88 (36.5)		
Hypertension:					
Yes	196 (81.0)	123 (62.8)	73 (37.2)	0.35	0.56[a]
No	46 (19.0)	31 (67.4)	15 (32.6)		
Diabetes mellitus:					
Yes	150 (62.0)	93 (62.0)	57 (38.0)	0.46	0.49[a]
No	92 (38.0)	61 (66.3)	31 (33.7)		
Hypercholesterolemia:					
Yes	218 (90.1)	140 (64.2)	78 (35.8)	0.32	0.57[a]
No	24 (9.9)	14 (58.3)	10 (41.7)		
Chronic kidney disease:					
Yes	23 (9.5)	14 (60.9)	9 (39.1)	0.08	0.77[a]
No	219 (90.5)	140 (63.9)	79 (36.1)		
Current or ex-smoker:					
Yes	127 (54.3)	83 (65.4)	44 (34.6)	0.08	0.77[a]
No	107 (45.7)	68 (63.6)	39 (36.4)		
Alcohol intake:					
Yes	9 (3.9)	4 (44.4)	5 (55.6)	-	0.18[b]
No	219 (96.1)	142 (64.8)	77 (35.2)		

[a] Test using Chi-Square test.

[b] Test using Fisher Exact Test.

Table 5. Patient operative details (CABG, coronary bypass grafting) and their association with POAF.

Operative details	Total, mean ± SD/n (%)	Non-POAF group, mean ± SD/n (%)	POAF group, mean ±SD/n (%)	χ^2/t-value	p-value
Surgery type:					
CABG alone	222 (92.5)	143 (64.4)	79 (35.6)	1.49	0.22[a]
CABG + valve	18 (7.5)	9 (50.0)	9 (50.0)		
Bypass time (in minutes)	97.00 ± 35.59	95.98 ± 38.43	98.91 ± 30.35		0.54[b]
Range: 42 to 304 minutes					
Cross-clamp time (in mins)	75.84 ± 30.05	75.86 ± 32.28	75.81 ± 25.79	0.22	0.99[b]
Range: 17 to 244 minutes					
Number of anastomoses:					
Single	6 (2.5)	2 (33.3)	4 (66.7)	-	0.13[c]
Multiple	234 (97.5)	150 (64.1)	84 (35.9)		

[a]Test using Chi Square test.

[b]Test using Independent T-test.

[c]Test using Fisher exact test.

with POAF development [75–78]. Similarly, we could not find any significant corelation between the number of distal anastomoses with POAF in our study with a similar finding observed in another study by Lotfi *et al*. [79].

5.6 Post-operative Outcomes

Adverse outcomes such as stroke, reoperation, infection, renal failure, respiratory complications and other cerebral insults, besides a twofold increase in mortality [80–82] were always associated with POAF. Admittedly, while this correlation might not be direct, it does contribute to the increase in morbidity and mortality post-CABG. In Table 6 below, although more POAF patients developed stroke as compared to non-POAF, it was not statistically significant. While the mortality rate in our study population was 3.6% as compared to the mortality rate in our earlier publication (4.66%) [25] this was definitely much lower. But we saw a statistically significant difference with a threefold increase in death among patients that developed POAF post-CABG. Our finding concurs with a recent paper by Emma Thorén *et al*. [83] where POAF was associated with mortality with a more recent paper from Taiwan which also concluded that in the Asian population, POAF is significantly correlated with an overall mortality [84].

We also assessed other common complications as depicted in Table 6 but none of them, except pleural effusion, were significantly correlated with POAF. This is consistent with the finding by Brookes *et al*. [85] who found a link between new onset atrial fibrillation and pleural effusion. Similarly, Anderson [86] also showed that self-clearing chest tubes may reduce POAF although a randomized data is still needed to prove this claim. Interestingly a systematic review by Gozdek *et al*. [87] showed that posterior pericardial drainage to minimize any possibility of pericardial tamponade could reduce the odds of POAF by 58% indicating that POAF is possibly associated with pericar-

dial collections. In our study cohort as well, we noticed that statistically significant number of patients with renal failure developed POAF. Similarly, the correlation between renal dysfunction and POAF has been established by Chua *et al*. [88]. While the mechanism was not fully understood, it was thought to be related to fluid overload and activation of renin-angiotensin-aldosterone cascade which would then lead to myocardial fibrosis [89].

5.7 Postoperative Stay

To date, no study in Malaysia has assessed the economic impact of managing POAF patients post cardiac surgery. The closest regional study was conducted in Thailand [90] where it was shown that there was a statistically significant high economic burden in managing POAF patients. Studies conducted elsewhere have demonstrated that POAF was associated with prolonged CICU stay and total hospital stay [91,92]. This would of course be translated into an increased cost of hospitalisation. For instance, US patients who developed POAF would incur additional hospital treatment costs in the range of USD10,000 to USD20,000 [93]. Furthermore, US healthcare expenditures related to POAF management were approximately 1 billion USD per year [94]. Another study [95] demonstrated that POAF led to an increase in the utilisation of hospital resources, with an increase in the direct costs of managing affected patients. No such studies have been conducted locally regarding the financial burden in managing POAF patients. However, it would not be surprising if it yields similar results.

Based on the outcomes tabulated in Table 7 above, there was a statistically significant difference between the two groups with regard in to the mean duration of CICU stay (p = 0.005) and HDU stay (p = 0.02). Similarly, there was also a significant difference in total duration of hospital stay (p = 0.001). Our findings concur with one study

Table 6. Post-operative outcomes and their association with POAF.

Post-operative outcomes	Total, n (%)	Non-POAF group, n (%)	POAF group, n (%)	χ^2	p-value
Stroke:					
Yes	4 (1.7)	1 (25.0)	3 (75.0)	-	0.14[b]
No	232 (98.3)	148 (63.8)	84 (36.2)		
Sternal infection:					
Yes	6 (2.5)	4 (66.7)	2 (33.33)	-	0.6[b]
No	232 (97.5)	146 (62.9)	86 (37.1)		
Respiratory problems:					
Yes	9 (3.8)	4 (44.4)	5 (55.6)	-	0.2[b]
No	229 (96.2)	146 (63.8)	83 (36.2)		
Renal failure requiring dialysis:					
Yes	12 (5.0)	3 (25.0)	9 (75.0)	-	0.007**
No	226 (95.0)	147 (65.0)	79 (35.0)		
Endocrine problems:					
Yes	1 (0.4)	1 (100.0)	0 (0.0)	-	0.63[b]
No	237 (99.6)	149 (62.9)	88 (37.1)		
Pleural effusion:					
Yes	18 (7.6)	7 (38.9)	11 (61.1)	4.79	0.03*
No	219 (92.4)	142 (64.8)	77 (35.2)		
Cardiac Tamponade:					
Yes	22 (9.2)	13 (59.1)	9 (40.9)	0.16	0.69[a]
No	216 (90.8)	137 (63.4)	79 (36.6)		
Fever:					
Yes	12 (5.0)	5 (41.7)	7 (58.3)	-	0.10[b]
No	226 (95.0)	145 (64.2)	81 (35.8)		
Hyperkalaemia:					
Yes	4 (1.7)	1 (25.0)	3 (75.0)	-	0.15[b]
No	233 (98.3)	148 (63.5)	85 (36.5)		
Others:					
Yes	7 (2.9)	2 (28.6)	5 (71.4)	-	0.06[b]
No	231 (97.1)	148 (64.1)	83 (35.9)		
Death:					
Yes	9 (3.75)	2 (22.2)	7 (77.8)	-	0.01*
No	231 (96.25)	150 (64.9)	81 (35.1)		

*p-value significant at 0.05 using Chi Square Test.

**p-value significant at 0.05 using Fisher exact Test.

[a]Test using Chi Square test.

[b]Test using Fisher Exact Test.

[73] that collected data from 28 centres which showed that POAF occurrence was significantly correlated to the length of stay in CICU and total hospital stay with a resultant increase in resource utilisation.

6. Discussion

35.2% of our study population exhibited POAF. This was slightly higher compared to our previous study [2] of about 28.7%. We should note that despite advances in the perioperative cardiac surgery care, the length of stay in the CICU, HDU, and the total hospital stay have remained unchanged over the years [96,97]. At the moment we are unsure whether our prophylactic intervention using Tocovid would reduce the incidence of POAF in the study arm. Despite this uncertainty, we take comfort in the words of Sir William Ramsay, the Chemist Nobel Laureate, who reminds us that progress is made by trial and failure. Therefore, we shall endure until the study is unblinded.

Table 7. The association between POAF and duration of CICU, HDU and total hospital stay, ventilation time and reintubation.

Duration	Total, median ± IQR/n (%)	Non-POAF group, median ± IQR/n (%)	POAF group, median ± IQR/n (%)	p-value
Duration in CICU (minute) Range: 640 to 67740 minutes	1722 ± 2648	1632 ± 1638	2872 ± 5493	0.005*
Duration in HDU (minute) Range: 190 to 14760 minutes	1640 ± 1711	1545 ± 1510	2700 ± 2795	0.02*
Duration of ventilation (minute) Range: 350 to 17120 minutes	1134 ± 380	1110 ± 395	1190 ± 415	0.06[a]
Duration of hosp. stay (day) Range: 5 to 86 days	7.0 ± 3	7.0 ± 2	8.0 ± 4	0.001*
Reintubation:				0.12[b]
Yes	8 (3.4)	3 (37.5)	5 (62.5)	
No	230 (96.6)	148 (64.3)	82 (35.7)	

*p-value significant at <0.05 using Mann-Whitney Test.

[a]Test using Mann-Whitney test.

[b]Test using Fisher Exact test.

As we outlined earlier, oxidative stress and inflammation from the shed mediastinal blood within the pericardium are now thought to be responsible for the pathogenesis of POAF. Cardiac surgery itself inflicts a trauma on the heart, and this is compounded by the use of cardiopulmonary bypass that produces ischaemic injury. Oxidative stress and the production of pro-inflammatory molecules from reperfusion injury after cardioplegic arrest activateds the production of leucocytes, nitrous oxide and reactive oxygen species [79,98]. Human studies have demonstrated that a correlation exists between the development of POAF with systemic inflammation and oxidative stress [99,100].

Studies have shown that longer CICU and hospital stay, and a higher rate of readmission were associated with POAF [95,101]. These outcomes translate into approximately USD 2 billion out of more than USD 6 billion per year related to POAF care in the US [102,103]. Unfortunately, no financial data from IJN of Kuala Lumpur or any other cardiac centres in Malaysia are available with regard to the total cost in managing patients with POAF. Nonetheless, there is no doubt that managing such patients entails higher costs. Therefore, reducing POAF incidence among post-CABG patients would benefit not only patients or hospitals but to the national economy itself.

We are aware that other compounds have been used in research to prevent POAF; for instance, polyunsaturated fatty acids (PUFAs), vitamin C, or a combination of vitamins C and E [104]. PUFAs have been demonstrated to reduce cardiovascular morbidity in animal models [105]. In a study by Rubanenko O and Rubanenko A [106], patients treated with PUFAs not only displayed reduced in inflammation and oxidative stress after CABG, but also exhibited a reduction in POAF after CABG. A meta-analysis [107] of 19 randomised controlled trials (RCTs) conducted in 2017 and a meta-analysis [108] in 2018 that included 14 RCTs also showed that CABG patients treated with PUFAs displayed a significant reduction of POAF compared to controls. In all these cases, an antioxidant prevented POAF, and the results were very promising the more so since our study is based on the same presumption.

Similarly, vitamin C, a known antioxidant, has been studied. A 2016 meta-analysis [109] of 7 RCTs showed that vitamin C treatment reduces the incidence of POAF. However, a more recent RCT [110] in 2018 found no significant difference. But to date, there are no guidelines on the use of vitamin C for POAF prophylaxis. A 2013 study [111] used combined antioxidants with vitamin C, vitamin E and PUFAs, demonstrated a significant reduction in the incidence of POAF among patients receiving these cocktails as compared to controls. However, to date, there are no guidelines regarding this protocol.

With the aforementioned studies and the postulated inflammatory and oxidative pathways in the promotion of POAF, we anticipate that using Tocovid, a strong antioxidant and anti-inflammatory agent, might be useful in mitigating the occurrence of POAF. We understand that it is still too early to make any definite claim. Nonetheless, this study has a scientific rationale, and once completed, it will be unblended for analysis.

7. Limitations

Our main limitation was the patients' recruitment. This is due to the current COVID-19 pandemic which reduced the number of patients that could be enrolled in our study as a result of the limited availability of ICU beds. Similarly, the rate of tracing the patients' medical records at the IJN Record Office dampened the pace of the study since only limited records were available for tracing each week. Not all the required data points were available on the track care, making reference to patients' medical records unavoidable.

8. Conclusions

As a preliminary conclusion, we would like to reiterate that POAF after cardiac surgery was the most common complication after CABG; it occurred in 35.2% of our study population. There was a statistically significant difference among POAF patients with regard to the occurrence of renal failure and death; we observed a three-fold increase in both. Both CICU and HDU time, and also the total hospital stay, were significantly longer among POAF patients. This translates to a heavier economic burden on the patient, the hospital, and the economy, although we have not conducted any cost analysis in this study.

Consent for Publication

All authors of this paper have read and approved the final version submitted.

Availability of Data and Materials

Harvard Dataverse: Replication Data for: A mid-cycle analysis on the role of Tocovid, a tocotrienol-rich vitamin E, in preventing atrial fibrillation after coronary artery bypass grafting (CABG) surgery.

Link: https://doi.org/10.7910/DVN/BZBHGX.
This project contains the following underlying data:
Set 1: Raw Data.
Set 2: Output Data.
CONSORT Checklist.

Author Contributions

AFM—conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, writing-original draft preparation, writing-review and editing; JD, MEMT, AMY, ARS, MNN— provided significant input into the study protocol, performed the bypass surgery on the study patients, and provided the post-operative care; JAS—administration, supervision, validation, writing-review and editing.

Ethics Approval and Consent to Participate

The study protocol was approved by the Institut Jantung Negara Ethics Committee (IJNREC/201/2017), Monash University Human Research Ethics Committee (MUHREC/2017-9227-10263). and the National Pharmaceutical Regulatory Agency (NPRA/CTX-180304). IJN-REC also served as the data safety committee.

We registered the study with the National Medical Research Registry (NMRR-17-1994-34963) and the US National Library of Medicine-Clinical Trials (NCT03807037).

Link: https://clinicaltrials.gov/ct2/show/NCT 03807037.

Written informed consent was obtained from all subjects prior to commencement of the study. A copy of the written consent form is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

Conflict of Interest

The authors declare no conflict of interest.

References

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

[2] D'Agostino RS, Jacobs JP, Badhwar V, Fernandez FG, Paone G, Wormuth DW, et al. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2018 update on outcomes and quality. Annals of Thoracic Surgery. 2018; 105: 15–23.

[3] Farouk Musa A, Quan CZ, Xin LZ, Soni T, et al. A retrospective study on atrial fibrillation after coronary artery bypass grafting surgery at The National Heart Institute, Kuala Lumpur. F1000Research. 2018; 7: 164.

[4] Ferrari R, Bertini M, Blomstrom-Lundqvist C, Dobrev D, Kirchhof P, Pappone C, et al. An update on atrial fibrillation in 2014: From pathophysiology to treatment. International Journal of Cardiology. 2016; 203: 22–29.

[5] Iwasaki YK, Nishida K, Kato T, Nattel S. Atrial fibrillation pathophysiology: Implications for management. Circulation. 2011; 124: 2264–2274.

[6] Ramlawi B, Otu H, Mieno S, Boodhwani M, Sodha NR, Clements RT, et al. Oxidative stress and atrial fibrillation after cardiac surgery: a case-control study. Annals of Thoracic Surgery. 2007; 84: 1166–1173.

[7] Zakkar M, Ascione R, James AF, Angelini GD, Suleiman MS. Inflammation, oxidative stress and postoperative atrial fibrillation in cardiac surgery. Pharmacology and Therapeutics. 2015; 154: 13–20.

[8] Philippou H, Adami A, Davidson SJ, Pepper JR, Burman JF, Lane DA. Tissue factor is rapidly elevated in plasma collected from the pericardial cavity during cardiopulmonary bypass. Thrombosis and Haemostasis. 2000; 84:124–128.

[9] Svenmarker S, Engstrom KG. The inflammatory response to recycled pericardial suction blood and the influence of cell-saving. Scandinavian Cardiovascular Journal. 2003; 37: 158–164.

[10] Kramer PA, Chacko BK, Ravi S, Johnson MS, Mitchell T, Barnes S, et al. Hemoglobin-associated oxidative stress in the

pericardial compartment of postoperative cardiac surgery patients. Laboratory Investigation. 2015; 95: 132–141.

[11] Tanawuttiwat T, O'Neill BP, Cohen MG, Chintakanan O, Heldman AW, Martinez CA, et al. New-onset atrial fibrillation after aortic valve replacement: comparison of transfemoral, transapical, transaortic, and surgical approaches. Journal of the American College of Cardiology. 2014; 63: 1510–1519.

[12] Cuculich PS, Cooper DH. Pericardial invasion: lessons learned from surgical and transcatheter aortic valve replacement. Journal of the American College of Cardiology. 2014; 63: 1520–1521.

[13] Youn JY, Zhang J, Zhang Y, Chen H, Liu D, Ping P, et al. Oxidative stress in atrial fibrillation: an emerging role of NADPH oxidase. Journal of Molecular and Cellular Cardiology. 2013; 62: 72–79.

[14] Wu JH, Marchioli R, Silletta M, Masson S, Sellke SW, Libby P, et al. Oxidative stress biomarkers and incidence of postoperative atrial fibrillation in the Omega-3 Fatty Acids for Prevention of Postoperative Atrial Fibrillation (OPERA) trial. Journal of the American Heart Association. 2015; 4: e001886.

[15] Babior BM. Phagocytes and oxidative stress. American Journal of Medicine. 2000; 109: 33–44.

[16] Elahi MM, Flatman S, Matata BM. Tracing the origins of postoperative atrial fibrillation: the concept of oxidative stress-mediated myocardial injury phenomenon. European Journal of Preventive Cardiology. 2008; 15: 735–741.

[17] St-Onge S, Perrault LP, Demers P, Boyle EM, Gillinov AM, Cox J, Melby S. Pericardial blood as a trigger factor for postoperative atrial fibrillation after cardiac surgery. Annals of Thoracic Surgery. 2018; 105: 321–328.

[18] Ramanathan N, Tan E, Loh LJ, Soh BS, Yap WN. Tocotrienol is a cardioprotective agent against ageing-associated cardiovascular disease and its associated morbidities. Nutrition and Metabolism. 2018; 15: 6.

[19] Gopalan Y, Shuaib IL, Magosso E, Ansari MA, Abu Bakar MR, Wong JW, et al. Clinical investigation of the protective effects of palm vitamin E tocotrienols on brain white matter. Stroke. 2014; 45: 1422–1428.

[20] Magosso E, Ansari MA, Gopalan Y, Shuaib IL, Wong JW, Khan NA, et al. Tocotrienols for normalisation of hepatic echogenic response in non-alcoholic fatty liver: a randomised placebo-controlled trial. Nutrition Journal. 2013; 12: 166–174.

[21] Mozaffarian D, Marchioli R, Gardner T, Ferrazzi P, O'Gara P, Latini R, et al. The ω-3 fatty acids for prevention of postoperative atrial fibrillation trial–rationale and design. American Heart Journal. 2011; 162: 56–63. e3.

[22] Calò L, Bianconi L, Colivicchi F, Lamberti F, Loricchio ML, de Ruvo E, et al. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. Journal of the American College of Cardiology. 2005; 45: 1723–1728.

[23] Dupont WD, Plummer WD. Power and sample size calculations: a review and computer program. Controlled Clinical Trials. 1990; 11: 116–128.

[24] Dupont WD, Plummer WD Jr. Power and sample size calculations for studies involving linear regression. Controlled Clinical Trials. 1998; 19: 589–601.

[25] Musa AF, Cheong XP, Dillon J, Nordin RB. Validation of EuroSCORE II in patients undergoing coronary artery bypass grafting (CABG) surgery at the National Heart Institute, Kuala Lumpur: a retrospective review. F1000Research. 2018; 7: 534.

[26] Echahidi N, Mohty D, Pibarot P, Després JP, O'Hara G, Champagne J, et al. Obesity and metabolic syndrome are independent risk factors for atrial fibrillation after coronary artery bypass graft surgery. Circulation. 2007; 116: I-213–I-219.

[27] Hogue CW Jr, Filos KS, Schuessler RB, Sundt TM. Sinus nodal function and risk for atrial fibrillation after coronary artery by-

pass graft surgery. Anesthesiology. 2000; 92: 1286–1292.

[28] Aranki SF, Shaw DP, Adams DH, Rizzo RJ, Couper GS, VanderVliet M, et al. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. Circulation 1996; 94: 390–397.

[29] Amar D, Zhang H, Leung DHY, Roistacher N, Kadish AH. Older age is the strongest predictor of postoperative atrial fibrillation. Anesthesiology. 2002; 96: 352–356.

[30] Babaev AA, Vloka ME, Sadurski R, Steinberg JS. Influence of age on atrial activation as measured by the P-wave signal-averaged electrocardiogram. American Journal of Cardiology. 2000; 86: 692–695.

[31] Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. Journal of the American Medical Association. 2004; 291: 1720–1729.

[32] Pothineni NV, Vallurupalli S. Gender and atrial fibrillation: differences and disparities. US Cardiology Review. 2018; 12: 24–33.

[33] Chung J, Stevens LM, Ouzounian M, El-Hamamsy I, Bouhout I, Dagenais F, et al. Sex-related differences in patients undergoing thoracic aortic surgery. Circulation. 2019; 139: 1177–1184.

[34] Nicolini F, Vezzani A, Fortuna D, Contini GA, Pacini D, Gabbieri D, et al. Gender differences in outcomes following isolated coronary artery bypass grafting: long-term results. Journal of Cardiothoracic Surgery. 2016; 11: 144.

[35] Saxena A, Dinh D, Smith JA, Shardey G, Reid CM, Newcomb AE. Sex differences in outcomes following isolated coronary artery bypass graft surgery in Australian patients: analysis of the Australasian Society of Cardiac and Thoracic Surgeons cardiac surgery database. European Journal of Cardio-thoracic Surgery. 2012; 41: 755–762.

[36] Arif R, Farag M, Gertner V, Szabó G, Weymann A, Veres G, et al. Female gender and differences in outcome after isolated coronary artery bypass graft surgery: does age play a role? PLoS ONE. 2016; 11: e0145371.

[37] Filardo G, Ailawadi G, Pollock BD, da Graca B, Phan TK, Thourani V, et al. Postoperative atrial fibrillation: sex-specific characteristics and effect on survival. Journal of Thoracic and Cardiovascular Surgery. 2020; 159: 1419–1425.e1.

[38] Zhang W, Liu W, Chew ST, Shen L, Ti LK. A clinical prediction model for post-cardiac surgery atrial fibrillation in an Asian population. Anesthesia and Analgesia. 2016; 123: 283–289.

[39] Nazeri A, Razavi M, Elayda MAA, Lee VV, Massumi AA, Wilson JM. Race/ethnicity and the incidence of new onset atrial fibrillation after isolated coronary artery bypass surgery. Heart Rhythm. 2010; 7: 1458–1463.

[40] Efird JT, Davies SW, O'Neil WT, Anderson CA, Anderson EJ, O'Neil JB, et al. The impact of race and postoperative atrial fibrillation on operative mortality after elective coronary bypass grafting. European Journal of Cardio-thoracic Surgery. 2014; 45: e20–e25.

[41] O'Neil WT, Efird JT, Davies SW, O'Neil JB, Anderson CA, Ferguson TB, et al. The impact of postoperative atrial fibrillation and race on long-term survival after coronary artery bypass grafting. Journal of Cardiac Surgery. 2013; 28: 484–491.

[42] Chen-Scarabelli C, Scarabelli T, Petrilli G, Saravolatz L, Mazzucco A, Faggian G. Postoperative Atrial Fibrillation is Associated with Higher Euroscore, but not with Hospital Mortality after Coronary Artery Bypass Graft Surgery. Journal of Clinical and Experimental Cardiology. 2012, S: 9002.

[43] Benedetto U, Gaudino M, Dimagli A, Gerry S, Gray A, Lees B, et al. Postoperative atrial fibrillation and long-term risk of stroke after isolated coronary artery bypass graft surgery. Circulation. 2020; 142: 1320–1329.

[44] Ismail MF, El-Mahrouk AF, Hamouda TH, Radwan H, Hneef A,

Jamjoon AA. Factors influencing postoperative atrial fibrillation in patients undergoing on-pump coronary artery bypass grafting, single center experience. Journal of Cardiothoracic Surgery. 2017; 12: 40.

[45] Lubitz SA, Yin X, Rienstra M, Schnabel RB, Walkey AJ, Magnani JW, *et al*. Long-term outcomes of secondary atrial fibrillation in the community: the Framingham Heart Study. Circulation. 2015; 131: 1648–1655.

[46] Creswell LL, Schuessler RB, Rosenbloom M, Cox JL. Hazards of postoperative atrial arrhythmias. Annals of Thoracic Surgery. 1993; 56: 539–549.

[47] Nair SG. Atrial fibrillation after cardiac surgery. Annals of Cardiac Anaesthesia. 2010; 13: 196–205.

[48] Almassi GH, Schowalter T, Nicolosi AC, Aggarwal A, Moritz TE, Henderson WG, *et al*. Atrial fibrillation after cardiac surgery. A major morbid event? Annals of Surgery. 1997; 226: 501–511.

[49] Patel D, Gillinov MA, Natale A. Atrial fibrillation after cardiac surgery: where are we now? Indian Pacing and Electrophysiol Journal. 2008; 8: 281–291.

[50] World health Organization. Malaysia and WHO call for more investment in primary health care the 21st century. 2019. Available at: https://www.who.int/malaysia/news/detail/08-04-2019-malaysia-and-who-call-for-more-investment-in-primary-health-care-the-21st-century (Accessed: 25 July 2021).

[51] The Asia-Pacific perspective: Redefining obesity and its treatment. IASO International Association for the study of obesity. World Health Organization, Western Pacific Region. 2000.

[52] Phan K, Khuong JN, Xu J, Kanagaratnam A, Yan TD. Obesity and post-operative atrial fibrillation in patients undergoing cardiac surgery: Systematic review and meta-analysis. International Journal of Cardiology. 2016; 217: 49–57.

[53] Serban C, Arinze JT, Starreveld R, Lanters EAH, Yaksh A, Kik C, *et al*. The impact of obesity on early post-operative atrial fibrillation burden. Journal of Thoracic and Cardiovascular Surgery. 2020; 159: 930–938.e2.

[54] Perrier S, Meyer N, Hoang-Minh T, Announe T, Bentz J, Billaud P, *et al*. Predictors of atrial fibrillation after coronary artery bypass grafting: A Bayesian analysis. Annals of Thoracic Surgery. 2017; 103: 92–97.

[55] Lavie CJ, Pandey A, Lau DH, Alpert MA, Sanders P. Obesity and atrial fibrillation prevalence, pathogenesis, and prognosis: Effects of weight loss and exercise. Journal of the American College of Cardiology. 2017; 70: 2022–2035.

[56] Sun X, Boyce SW, Hill PC, Bafi AS, Xue Z, Lindsay J, *et al*. Association of body mass index with new-onset atrial fibrillation after coronary artery bypass grafting operations. Annals of Thoracic Surgery. 2011; 91: 1852–1859.

[57] Vural Ü, Aglar AA. What is the role of metabolic syndrome and obesity for postoperative atrial fibrillation after coronary bypass grafting? BMC Cardiovascular Disorders. 2019; 19: 147.

[58] Liu M, Mei K, Ma J, YU P, Xie L, Zhao Y, *et al*. Dose-response relationship among body mass index, abdominal adiposity, and atrial fibrillation in patients undergoing cardiac surgery: A meta-analysis of 30 prospective studies. BMJ Yale. 2020. (in press)

[59] Straus S, Kacila M, Omerbasic E, Mujičić E. Atrial fibrillation and coronary bypass surgery–what can be risk factors for its appearance? Bosnian Journal of Basic Medical Sciences. 2010; 10: 78–82.

[60] El-Gendy A, Dabsha MH, Elewa GM, Ali AH. Predictors of post-operative atrial fibrillation after coronary artery bypass grafting: a prospective observational cohort study. Ain-Shams Journal of Anaesthesiology. 2020; 12: 55.

[61] Başaran Ö, Tigen K, Gözübüyük G, Dündar C, Güler A, Taşar O, *et al*. Predictive role of left atrial and ventricular mechanical function in post-operative atrial fibrillation a two-dimensional speckle-tracking echocardiography study. Turk Kardiyoloji Dernegi Arsivi. 2016; 44: 45–52.

[62] Turkkolu ST, Selçuk E, Köksal C. Biochemical predictors of postoperative atrial fibrillation following cardiac surgery. BMC Cardiovascular Disorders. 2021; 21: 167.

[63] Aksu U, Kalkan K, Gulcu O, Aksakal E, Öztürk M, Topcu S. The role of right atrium in development of postoperative atrial fibrillation: A speckle tracking echocardiography study. Journal of Clinical Ultrasound. 2019; 47: 470–476.

[64] Hashemzadeh K, Dehdilani M, Dehdilani M. Postoperative atrial fibrillation following open cardiac surgery: predisposing factors and complications. Journal of Cardiovascular and Thoracic Research. 2013; 5: 103–107.

[65] Sammoud K, Lajmi M, Touhami F, Hfayedh A, Lahdhili H, Chenik S. Predictive factors of new onset atrial fibrillation in cardiac surgery. Archives of Cardiovascular Diseases Supplements. 2019; 11: 141–142.

[66] Benedetto U, Albanese A, Kattach H, Ruggiero D, De Robertis F, Amrani M, *et al*. Smoking cessation before coronary artery bypass grafting improves operative outcomes. Journal of Thoracic and Cardiovascular Surgery. 2014; 148: 468–474.

[67] Zhu W, Yuan P, Shen Y, Wan R, Hong K. Association of smoking with the risk of incident atrial fibrillation: A meta-analysis of prospective studies. International Journal of Cardiology. 2016; 218: 259–266.

[68] Zhu W, Guo L, Hong K. Relationship between smoking and adverse outcomes in patients with atrial fibrillation: A meta-analysis and systematic review. International Journal of Cardiology. 2016; 222: 289–294.

[69] Wan Q, Li S, Hu J. Association of smoking with postoperative atrial fibrillation in patients with cardiac surgery: A PRISMA-compliant article. Medicine. 2021; 100: e26179.

[70] Chebbout R, Heywood EG, Drake TM, Wild JRL, Lee J, Wilson M, Lee MJ. A systematic review of the incidence of and risk factors for postoperative atrial fibrillation following general surgery. Anaesthesia 2018; 73: 490–498.

[71] Rho RW. The management of atrial fibrillation after cardiac surgery. Heart. 2009; 95: 422–429.

[72] Angelini GD, Taylor FC, Reeves BC, Ascione R. Early and midterm outcome after off-pump and on-pump surgery in Beating Heart Against Cardioplegic Arrest Studies (BHACAS 1 and 2): a pooled analysis of two randomised controlled trials. The Lancet. 2002; 359: 1194–1199.23.

[73] Wijeysundera DN, Beattie WS, Djaiani G, Rao V, Borger MA, Karkouti K, *et al*. Off-pump coronary artery surgery for reducing mortality and morbidity: meta-analysis of randomized and observational studies. Journal of the American College of Cardiology. 2005; 46: 872–882.

[74] Akintoye E, Sellke F, Marchioli R, Tavazzi L, Mozaffarian D. Factors associated with postoperative atrial fibrillation and other adverse events after cardiac surgery. Journal of Thoracic and Cardiovascular Surgery. 2018; 155: 242–251.

[75] Villareal RP, Hariharan R, Liu BC, Kar B, Lee W, Elyada M, *et al*. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. Journal of the American College of Cardiology. 2004; 43: 742–748.

[76] Mitchell LB. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: Prevention and treatment of atrial fibrillation after cardiac surgery. Canadian Journal of Cardiology. 2011; 27: 91–97.

[77] Helgadottir S, Sigurdsson MI, Ingvarsdottir IL, Arnar DO, Gudbjartsson T. Atrial fibrillation following cardiac surgery: risk analysis and long-term survival. Journal of Cardiothoracic Surgery. 2012; 19: 87.

[78] Dave S, Nirgude A, Gujjar P, Sharma R. Incidence and risk fac-

tors for development of atrial fibrillation after cardiac surgery under cardiopulmonary bypass. Indian Journal of Anaesthesia. 2018; 62: 887–891.

[79] Lotfi A, Wartak S, Sethi P, Garb J, Guigliano GR. Postoperative atrial fibrillation is not associated with an increase risk of stroke or the type and number of grafts: a single-center retrospective analysis. Clinical Cardiology. 2011; 34: 787–790.

[80] Zakkar M, Ascione R, James AF, Angelini GD, Suleiman MS. Inflammation, oxidative stress, and postoperative atrial fibrillation in cardiac surgery. Pharmacology and Therapeutics. 2015; 154: 13–20.

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

[82] Attaran S, Shaw M, Bond L, Pullman MD, Fadri BM. Atrial fibrillation postcardiac surgery: a common but morbid complication. Interactive Cardiovascular and Thoracic Surgery. 2011; 12: 772–777.

[83] Thorén E, Wernroth M-L, Christersson C, Ginnemo K-H, Jidéus L, Stähle E. Compared with match-controls, patients with postoperative atrial fibrillation (POAF) have increased long-term AF after CABG, and POAF is further associated with increased ischaemic stroke, heart failure, and mortality even after adjustment for AF. Clinical Research in Cardiology. 2020; 109: 1232–1242.

[84] Hsu JC, Huang CY, Chuang SL, Yu HY, Chen YS, Wang CH, Lin LY. Long Term Outcome of Postoperative Atrial Fibrillation After Cardiac Surgery-A Propensity Score-Matched Cohort Analysis. Frontiers in Cardiovascular Medicine. 2021; 8: 650147.

[85] Brookes JDL, Williams M, Matthew M, Yan T, Bannon P. Pleural effusion post coronary artery bypass surgery: associations and complications. Journal of Thoracic Disease. 2021; 13: 1083–1089.

[86] Anderson ND. Active clearance chest tube: Awaiting randomized data. Journal of Thoracic and Cardiovascular Surgery. 2017; 154: 509–510.

[87] Gozdek M, Pawliszak W, Hagner W, Zalewski P, Kowalewski J, Paparella D, et al. Systematic review and meta-analysis of randomized controlled trials assessing safety and efficacy of posterior pericardial drainage in patients undergoing heart surgery. Journal of Thoracic and Cardiovascular Surgery. 2017; 153: 865–875.e12.

[88] Chua SK, Shyu KG, Lu MJ, Hung HF, Cheng JJ, Chiu CZ, et al. Renal dysfunction and the risk of postoperative atrial fibrillation after cardiac surgery: Role beyond the CHA2DS2–VASc score. Europace. 2015; 17: 1363–1370.

[89] Soliman EZ, Prineas RJ, Go AS, Xie D, Lash JP, Rahman M, et al. Chronic kidney disease and prevalent atrial fibrillation: The Chronic Renal Insufficiency Cohort (CRIC). American Heart Journal. 2010; 159: 1102–1107.

[90] Kosuma P, Wachirasrisirkui S, Jedsadayanmata A. Attributable costs of postoperative atrial fibrillation among patients undergoing cardiac surgery. Cardiology Research and Practice. 2018; 2018: 3759238.

[91] Matthew JP, Parks R, Savino JS, Friedman AS, Koch C, Mangano DT, et al. Atrial fibrillation following coronary artery bypass graft surgery: Predictors, outcomes, and resource utilization. Multicenter Study of Perioperative Ischemia Research Group. Journal of the American Medical Association. 1996; 276: 300–306.

[92] Melby SJ, George JF, Picone DJ, Davies JE, George D, et al. A time-related parametric risk factor analysis for postoperative atrial fibrillation after heart surgery. Journal of Thoracic and Cardiovascular Surgery. 2015; 149: 886–892.

[93] Echaidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, pre-

vention, and treatment of atrial fibrillation after cardiac surgery. Journal of the American College of Cardiology. 2008; 51: 793–801.

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

[95] Hernández-Leiva E, Alvarado P, Dennis RJ. Postoperative atrial fibrillation: Evaluation of its economic impact on the cost of cardiac surgery. Brazilian Journal of Cardiovascular Surgery. 2019; 34: 179–186.

[96] Almassi GH, Wagner TH, Carr B, Hattler B, Collins JF, Quin JA, et al. Postoperative atrial fibrillation impacts on costs and one-year clinical outcomes: the Veterans Affairs Randomized On/Off Bypass Trial. Annals of Thoracic Surgery. 2015; 99: 109–114.

[97] Steinberg BA, Zhao Y, He X, Hernandez AF, Fullerton DA, Thomas KL, et al. Management of postoperative atrial fibrillation and subsequent outcomes in contemporary patients undergoing cardiac surgery: Insights from Society of Thoracic Surgeons CAPS-Care Atrial Fibrillation Registry. Clinical Cardiology. 2014; 37: 7–13.

[98] Ishii Y, Schuessler RB, Gaynor SL, Yamada K, Fu AS, Boineau JP, et al. Inflammation of atrium after cardiac surgery is associated with inhomogeneity of atrial conduction and atrial fibrillation. Circulation. 2005; 111: 2881–2888.

[99] Kramer PA, Chacko BK, Ravi S, Johnson MS, Mitchell T, Barnes S, et al. Haemoglobin-associated oxidative stress in the pericardial compartment of postoperative cardiac surgery patients. Laboratory Investigation. 2015; 95: 132–141.

[100] Kramer PA, Chacko BK, George DJ, Zhi D, Wei CC, Dell'Italia LJ, et al. Decreased bioenergetic health index in monocytes isolated from the pericardial fluid and blood of postoperative cardiac surgery patients. Bioscience Reports. 2015; 35: e00237.

[101] LaPar DJ, Speir AM, Crosby IK, Fonner E Jr, Brown M, Rich JB, Quader M, Kern JA, Kron IL, Ailawadi G; Investigators for the Virginia Cardiac Surgery Quality Initiative. Postoperative atrial fibrillation significantly increases mortality, hospital readmission, and hospital costs. Annals of Thoracic Surgery. 2014; 98: 527–533.

[102] Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total health care costs in patients with atrial fibrillation in the United States. Circulation. Cardiovascular quality and outcomes.2011; 4: 313–320.

[103] Wolowacs SE, Samuel M, Brennan VK, Jasso-Mosqueda JG, Van Gelder IC. The cost of illness of atrial fibrillation: a systematic review of the recent literature. Europace. 2011; 13: 1375–1385.

[104] Burrage PS, Low YH, Campbell NG, O'Brien B. New-onset atrial fibrillation in adult patients after cardiac surgery. Current Anesthesiology Reports. 2019; 9: 174–193.

[105] Gorenek B, Pellicia A, Benjamin EJ, Boriani G, Crijns HJ, Fogel RI, Van-Gelder IC, et al. European Heart Rhythm Association (EHRA)/European Association of Cardiovascular Prevention and Rehabilitation (EACPR) position paper on how to prevent atrial fibrillation endorsed by the Heart Rhythm Society (HRS) and the Asia Pacific Heart Rhythm Society (APHRS). European Journal of Preventive Cardiology. 2017; 24: 4–40.

[106] Rubanenko O, Rubanenko A. The effect of Omega-3 polyunsaturated fatty acids in prevention of postoperative atrial fibrillation development in patients undergoing coronary artery bypass graft surgery. European Journal of Preventive Cardiology. 2021; 28: zwab061-005.

[107] Langlois PL, Hardy G, Manzanares W. Omega-3 polyunsaturated fatty acids in cardiac surgery patients: An updated systematic review and meta-analysis. Clinical Nutrition. 2017; 36:

737–746.

[108] Wang H, Chen J, Zhao L. N-3 polyunsaturated fatty acids for prevention of postoperative atrial fibrillation: updated meta-analysis and systematic review. Journal of Interventional Cardiac Electrophysiology. 2018; 51: 105–115.

[109] Ali-Hassan Al-Saegh S, Mirhosseini SJ, Tabernejad M, Mahdavi P, Shahidzadeh A, Karim-Bondarabadi AA, *et al*. Impact of antioxidant supplementation on cardi-renal protection in cardiac surgery: an updated and comprehensive meta-analysis and systematic review. Cardiovascular Therapeutics. 2016; 34: 360–

370.

[110] Mirmohammadsadeghi M, Mirmohammmadsadeghi A, Mahmoudian M. Preventive use of ascorbic acid for atrial fibrillation after coronary artery bypass graft surgery. Heart Surgery Forum. 2018; 21: E415–E417.

[111] Rodrigo R, Korantzopoulos P, Cereceda M, Asenio R, Zamarano J, Vilalabeitia E, *et al*. A randomized controlled trial in prevent post-operative atrial fibrillation by antioxidant reinforcement. Journal of the American College of Cardiology. 2013; 62: 1457–1465.