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Effect of Tocovid - a Tocotrienol-rich Vitamin E - in Mitigating Post-Operative Atrial Fibrillation (POAF) after Coronary Artery Bypass Grafting (CABG) Surgery: A Double-blind Randomised Controlled Trial

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Abstract

Objective: The objective of this study was to determine whether tocotrienol-rich Tocovid has any effect in reducing the incidence of postoperative atrial fibrillation (POAF), mortality and morbidity, length of Cardiac Intensive Care Unit (CICU), High Dependency Unit (HDU) and total hospital stay among post coronary artery bypass grafting (CABG) surgery patients; and in improving their quality of life.

Methods: A prospective randomised controlled trial was conducted at the National Heart Institute, Kuala Lumpur. The treatment group received Tocovid capsules while the control group was given placebo containing palm superolein.

Results: We started our recruitment of patients in January 2019 and reached the target population of 250 patients in December 2021. 95.6% of patients completed the study with a 4.4% attrition rate. We did not observe any statistically significant difference between the age group, gender, race, EuroSCORE II status, body mass index, NYHA class, left or right atrial size, ejection fraction, preoperative medications, and premorbid history (except hypercholesterolaemia). There was also no difference in cardiopulmonary bypass time, aortic cross clamp time or number of anastomoses. In terms of outcomes, we noted a significant difference in the occurrence of pleural effusion and a longer CICU stay ($p=0.04$) among the placebo groups. The incidence of POAF was 36.4% with no difference between the two groups and this was reflected in the low blood levels of tocotrienols at day one post-surgery whence the median time for the POAF development was 47 hours post-CABG. The 36-Item Short Form Survey (SF-36) that measures the quality of life showed no significant difference between the two groups but the Nottingham Health Profile (NHP) analysis showed better sleep quality on 6-week follow-up among the study group.

Conclusion: Tocovid did not mitigate the occurrence of POAF mainly due to the low tocotrienols levels post-CABG;

however, it conferred better sleep quality and reduced pleural effusion.

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1.0 Introduction

Despite the advances in cardiac surgery and perioperative care, the incidence of the commonest complication after coronary artery bypass surgery, namely postoperative atrial fibrillation (POAF), remains high with an incidence of up to 60%.^{[1][2][3]} Throughout the years, these patients have been shown to have a higher rates of morbidity and mortality.^{[4][5][6]} Operative trauma, ischaemic reperfusion injury, chemical and nervous stimulation, and the premorbid condition of the patients, have all been associated with this complication.^{[7][8][9]} However, in recent years, POAF has been linked to the presence of oxidative stress and inflammatory mediators. Pre-existing co-morbidities such as atherosclerosis

can trigger an inflammatory response,^[10] although the main inflammatory response is from the cardiac surgery itself. This is mainly from cardiopulmonary bypass (CPB) and reperfusion injury following bypass.^[11] CPB is believed to be the source of inflammatory response since off-pump surgery demonstrably reduces inflammatory response.^{[12][13][14]} On the one hand, CPB and cardiac surgery itself can lead to the production of pro-inflammatory mediators like IL-6, TNF- α , and CRP.^{[15][16][17]} On the other hand, oxidative stress occurs when the generation of reactive oxygen species (ROS) overwhelms the antioxidant capabilities endogenously. Similar to the inflammatory response, premorbid conditions of patients such as ischaemia or atherosclerosis are also known to be associated with oxidative stress.^[18] Open heart surgery involving CPB generates ROS that augments oxidative stress.^[19] ROS is also increased from reperfusion injury stemming from cardiac bypass surgery.^{[20][21]} The pathogenesis of POAF has been linked to the ROS generating system, NADPH oxidase. It has been suggested that the NADPH oxidase activity is the most significant independent predictor for the development of POAF.^{[22][23]}

This understanding that both inflammation and oxidative stress can initiate POAF that leads to an increase in morbidity and mortality among coronary bypass patients led us to undertake this prospective study in using a potent anti-inflammatory and antioxidant agent, namely Tocovid, which predominantly consists of tocotrienol, an isomer of Vitamin E.

2.0 Aim

- To determine whether the intake of tocotrienol-rich Tocovid capsules before and immediately following CABG is safe, reduces the incidence of POAF, improves the quality of life of patients, and shortens the length of hospital stay of patients post-CABG.

3.0 Hypothesis

- Tocovid is safe and it reduces the incidence of POAF when taken before and immediately following CABG, improves the quality of life of patients, and shortens the duration of hospital stay post-CABG.

4.0 Methodology

4.1 Study design

The study was a prospective, randomized, controlled trial with parallel groups. The main goal was to assess the effects of Tocovid in the occurrence of POAF post-CABG. The National Heart Institute Ethics Committee (IJNREC) and Monash University Human Research Ethics Committee (MUHREC) approved the study protocol. The ethics committee also served as the data safety committee. All patients admitted for CABG or CABG and valve surgery under the co-researchers were recruited into this study upon consent. We assigned patients to one of the two study arms according to a computer-

generated randomisation list:

1. control group: usual care plus placebo containing palm superolein or
2. treatment group: usual care plus Tocovid capsules

Patients were started on two capsules of 200mg per day in divided doses immediately after randomisation at least two days prior to surgery. We continued this regimen for the entire duration in the hospital until the first follow-up visit at 6 weeks after discharge. We chose this regimen since many clinical studies with tocotrienol have used 400mg daily in two divided doses and have been proven to be safe.^{[24][25]} Treatment was continued until the patients' discharge. Compliance was monitored by the intensive care and cardiothoracic ward nurses. Tocotrienol level was measured at four time points. Blood was taken for tocotrienol level preoperatively, at day-4 post-op, before discharge and during the first follow-up six weeks later.

Only on-pump surgery using cold potassium cardioplegia was included. Procedures were done using the usual midline sternotomy or midcab. After surgery, all patients were admitted to the Cardiac Intensive Care Unit (CICU) with close monitoring on one-patient-one-nurse basis and were subsequently transferred to High Dependency Unit (HDU) or direct to the ward if their condition was stable. The monitoring was continued for at least the first three postoperative days on the normal cardiothoracic wards until the patients were discharged. The electrocardiographic data was stored and reviewed on a daily basis by the cardiothoracic team involved in the research. The printouts of all abnormal rhythms were also reviewed for any episodes of arrhythmia. All printouts were included in the clinical records. Additionally, an ECG was recorded in case of symptoms or when arrhythmia is suspected on clinical grounds; AF episodes were treated under the direction of the attending cardiothoracic surgeon using either amiodarone or digoxin.

After discharge, all patients were asked to report to the outpatient department of our institution in case of any relevant symptoms. Additionally, all patients was followed-up six weeks after discharge through physical examination, ECG and blood tests for tocotrienol levels. For study flow chart, see Figure 1 below.

Study Flow Chart

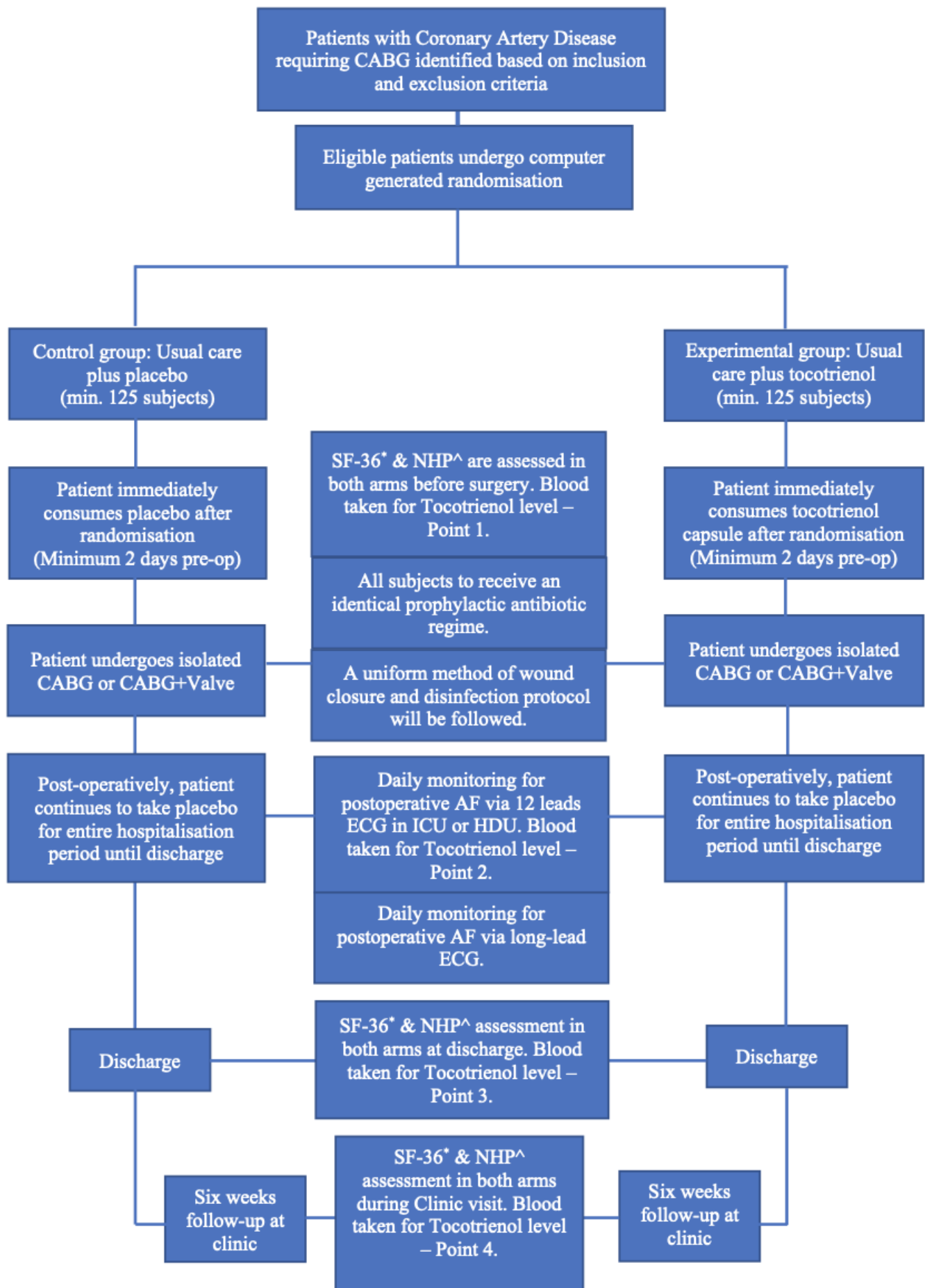


Figure 1. Study Flow Chart

Figure 1: Study flow chart

* SF-36 - Short Form 36 Questionnaire

^ NHP - Nottingham Health Profile Questionnaire

4.2 Randomisation, Blinding & Concealment

The study patients were prospectively and randomly divided into two parallel groups by means of computer-generated numbers in a block of 10 experimental to 10 matching controls at enrolment. The experimental group received Tocovid capsules whilst the control group received identical placebo capsules containing palm superolein oil.

The National Heart Institute pharmacy was given the responsibility for dispensing both the trial drug and placebo based on the unique randomisation codes for the patients. Neither the patients nor the surgeons or investigators knew the treatment arm to which the patients were randomised. Allocation concealment was ensured where the randomisation allocation sequence was generated by an independent research nurse using an offsite computer. The research nurse also prepared the study product and placebo with allocated coding and subject unique identification number. The randomisation and allocation were fully concealed from the principal investigator and co-researchers, surgeons, research officers and participants until the end of the study.

4.3 Inclusion & Exclusion Criteria

Inclusion Criteria:

1. Males or females
2. More than 18 years of age
3. Elective, on-pump surgery of coronary artery revascularisation, isolated or combined valve surgery

Exclusion Criteria:

1. Less than 18 years of age
2. Refusal to have surgery
3. Urgent or emergency surgery
4. Off-pump surgery
5. Poor LV (EF < 30%)
6. Inability to give informed consent
7. Documented allergy to palm oil or Vitamin E
8. Documented AF or any form of arrhythmia preoperatively
9. Currently on or indicated for long-term corticosteroid treatment
10. Patients who have been included in any other clinical trial within the previous three months
11. Patients who were on supplementation of Vitamin E or other potent antioxidants up to one month before randomisation

4.4 Study End-points

The primary end point of the study was the safety of endpoint in atrial fibrillation (AF) after CABG, measured as between group incidence of postoperative AF. AF is detected by ECG during the hospitalisation period. POAF was defined as any electrocardiographically confirmed episode of AF/Atrial Flutter (AFL) post-CABG of at least 30 seconds duration and documented by rhythm strip or 12-lead ECG. If only a shorter duration ECG is available, then the diagnosis of AF/AFL is based on the arrhythmia being present at onset or termination.^[26]

The secondary end points included the length of hospital stay (LoHS) after surgery, which was obtained from the National Heart Institute hospital register and the health-related quality of life (HRQoL). Three measurements were used to determine the LoHS: (1) Total Intensive/coronary care unit length of stay, (2) Total days of High Dependency Unit stay; and (3) Total hospital length of stay.^[21] The HRQoL of patients were measured using the validated Malay Short-Form 36 Questionnaires (SF-36) and Nottingham Health Profile Part I.^{[27][28]}

All end points were independently adjudicated after discharge by two surgeons blinded to treatment assignment on the basis of clinical records and electrocardiographic tracings.

4.5 Withdrawal Criteria

A patient was considered withdrawn from the study when the trial-related therapy, follow-up and also documentation were terminated prematurely. All participants had the right to withdraw from the clinical trial at any time, without the need to give any specific reasons for the termination of their informed consent. Patients were withdrawn if the investigators deemed it detrimental or risky for the subject to continue. Withdrawn subjects were not replaced.

We reserved the right to withdraw a trial participant in the following events:

- i. Assessment by investigators that premature termination of participant from the trial is necessary
- ii. Incidence of Adverse Events/Serious Adverse Events (AEs/SAEs) that warrants the termination of participant's participation in the trial
- iii. Non-compliance of the participant
- iv. Loss of contact with the participant

4.6 Sample size estimation

The PS Power and Sample Size Calculation Software^{[29][30]} was used for sample size calculation.

We took into account the possibility of "loss to follow-up" or attrition bias of subjects by analysing all subjects from the start to the completion of the study according to the groups that they were originally randomised [Intention-To-Treat (ITT) analysis].^[31]

The estimated sample size for the primary end point, namely POAF incidence, was computed based on findings from a prior study by Musa et al.^[32] that indicated the incidence of POAF at the National Heart Institute to be 28.7%. We planned

this study with experimental subjects and controls with one control per experimental subject similar to the study by Saravanan et al.^[33] If the true relative risk of POAF for experimental subjects relative to controls is 0.45,^[34] using the PS Power and Sample Size Calculator^{[29][30]} with α equivalent to 0.05 and power ($1 - \beta$) is 0.8, the estimated sample size will be 103 experimental subjects and 103 control subjects in order to be able to reject the null hypothesis that this relative risk equals 1 with probability (power) of 0.8. We used the uncorrected chi-squared statistics to evaluate this null hypothesis. Taking into account a possible attrition rate of 20%, the total sample size will be: $103 + .20 (103) \times 2 = 250$ subjects. Of this total, there will be 125 controls and 125 experimental subjects.

4.7 Statistical Analysis

Statistical analysis was done using SPSS version 28.0 by IBM® SPSS® Statistics.

5.0 Ethical Consideration

The study was conducted in compliance with ethical principles outlined in the Malaysian Good Clinical Practice Guideline and the Helsinki Declaration. Written informed consent was obtained from study participants and/or legally acceptable representative prior to their enrolment into the study. Detailed explanation of the study was given before they were asked for consent to participate; these include purpose of study, nature of interventions and investigational products, expected duration of the study, reasonable expected benefits and participant's responsibility.

6.0 Results

The recruitment of patients for this study started on 21 January, 2019. We achieved our sample size of 250 patients as of 30 June, 2021 from a total of 1128 patients screened within that period. The CONSORT Flow Diagram is shown below in Figure 2:

CONSORT Flow Diagram

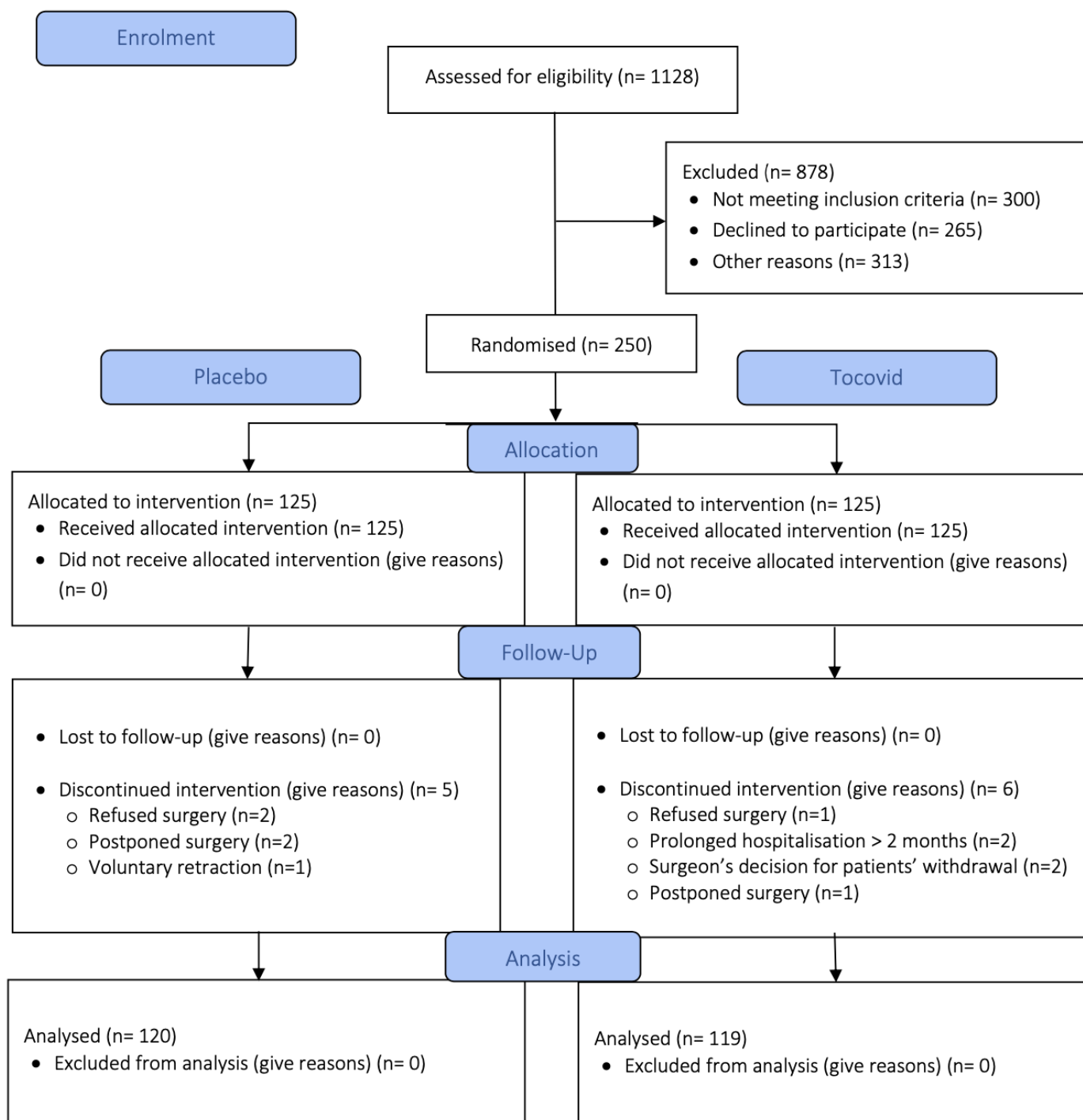


Figure 2. CONSORT Flow Diagram

Of this population sample, 250 patients were randomised into two groups with 125 patients in each group. Five patients from the placebo group and 6 patients from the Tocovid group were lost during follow-up, which gives an attrition rate of 9.56%. A total of 18 serious adverse events (SAE) were reported but none of them were related to the investigational product; they were mainly due to surgical site infection, pericardial tamponade and pleural effusion.

6.1 Patients' characteristics

Table 1 below describes the characteristics of our sample population. The mean age in the placebo group was 61.08 ± 7.79 and that of Tocovid was 60.67 ± 7.30 with a range between 39 to 85 years old. It shows that there was no statistically significant difference in between the groups. While we understand that age is considered the most consistent factor with an increased incidence of POAF^[35] and an independent predictor of POAF,^[36] this non-significance in the age group difference was the result of randomisation.

Table 1. Characteristics of the sample population in our study between Tocovid and placebo group.

Demographic	Total	Tocovid group, mean \pm SD/n (%)	Placebo group, mean \pm SD/n (%)	p-value
Age (years)	60.88 ± 7.79	61.08 ± 8.27	60.67 ± 7.30	0.68 ^b
Range: 39 to 85 years old				
Gender:				
Male	201	101 (50.2)	100 (49.8)	0.87 ^a
Female	49	24 (49)	25 (51)	
Population:				
Malay	205	101 (49.3)	104 (50.7)	0.25 ^a
Chinese	9	7 (77.8)	2 (22.2)	
Indian	35	16 (45.7)	19 (54.3)	
Other	1	1 (100)	0 (0)	
EUROScore II				
Low Risk	104 (42.8)	59 (56.7)	43 (43.3)	0.21 ^a
Medium Risk	109 (44.9)	49 (45)	60 (55)	
High Risk	30 (12.3)	14 (46.7)	16 (53.3)	

^a Test using Chi-Square test

^b Test using Independent t-test

In our cohort, there were more males than females who underwent CABG in both groups with 80.8% in the Tocovid group and 80% in the control group. This is consistent with findings elsewhere which indicate that men have a higher propensity to develop coronary artery disease (CAD);^{[37][38]} however, in our study, no statistically significant difference was observed between the Tocovid and placebo groups. Similarly, there was no statistically significant difference observed in between the races of the two groups. While most patients in both groups were of low and medium risk EuroSCORE II with 88.5% in the Tocovid group and 86.5% in the placebo group, no statistical significant difference was recorded.

6.2 Postoperative AF (POAF) characteristics

Table 2 below refers to the characteristics of POAF. The incidence of POAF in our study was 36.4% with equal incidence in both the Tocovid and placebo arms. This is slightly higher than in our previous study^[32] where 28.7% of patients

developed AF post-CABG. However, this incidence rate is within the cited range in the literatures^{[39][40][41]} that put the POAF incidence ranges between 20% and 40%. But what is clear is that Tocovid did not seem to reduce the incidence of POAF; we shall discuss the possible reasons for this phenomenon later.

Table 2. Characteristics of POAF in our study between Tocovid and placebo group.

Characteristics of AF		n* (%), mean ± SD	Tocovid group, n (%)	Placebo group, n (%)	p-value
Occurrence of POAF	Yes	88 (36.4)	44 (50)	44 (50)	0.92 ^a
	No	154 (63.6)	78 (50.6)	76 (49.4)	
Time from surgery to POAF (minutes)		2793.61 ± 1617.36	2918.55 ± 1599.60	2671.58 ± 1644.11	0.49 ^b
Range: 10 to 7044 minutes					
Duration (hours):					
≤48		45 (52.9)	24 (53.3)	21 (46.7)	0.443 ^a
>48		40 (47.1)	18 (45)	22 (55)	
Number of episodes:					
Single		45 (51.1)	21 (46.7)	24 (53.3)	0.52 ^a
Multiple		43 (48.9)	23 (53.5)	20 (46.5)	

^a Test using Chi-Square test

^b Test using Independent t-test

The median time for the development of POAF was 47 hours after surgery, which was within the range cited by the literature of 2-3 days after surgery.^[42] The mean time was 46.56 ± 27.85 hours post-CABG or on the second day after CABG ranging from 10 minutes to 4.89 days post-CABG. We also noticed that slightly more than half of the cases (52.9%) developed AF within 48 hours post-surgery. This was consistent with the observation by Greenberg et al.^[43] that indicated a peak incidence of POAF on postoperative day 2 although the range cited by many literatures^{[44][45]} stated that POAF mainly occurs within the first week post-surgery with 70% of cases^[46] observed within the first four postoperative days. We noticed that slightly less than half of the patients on Tocovid (46.7%) had a single episode of POAF whereas the incidence was reverse in the control group where slightly more than half (53.3%) developed a single episode although it was not statistically significant. Nonetheless, all patients were discharged with sinus rhythm.

6.3 Preoperative characteristics

Table 3 below showed that 75.6% of the study sample was categorised as either overweight or obese according to the Asian guidelines;^[47] this concurs with the WHO report^[48] that Malaysia has the highest rate of obesity and overweight among Asian countries. But there was no statistical difference between the two groups.

Table 3. Comparison between preoperative characteristics of Tocovid and placebo group.

Pre-operative characteristic	Total*, n (%)	Tocovid group, n (%)	Placebo group, n (%)	p-value
Body Mass Index (kg/m ²)	27.15 ± 4.39	27.06 ± 4.37	27.24 ± 4.42	0.96 ^a
<18.5	2 (0.8)	1 (50)	1 (50)	
18.5-22.9	59 (23.6)	28 (47.5)	31 (52.5)	
23-29.9	128 (51.2)	66 (51.6)	62 (48.4)	
≥30	61 (24.4)	30 (49.2)	31 (50.8)	
Range: 17.6 to 42.47				
New York Heart Functional Class:				0.54 ^a
NYHA I	145 (59.7)	77 (53.1)	68 (46.9)	
NYHA II	96 (39.5)	44 (45.8)	52 (54.2)	
NYHA III	2 (0.8)	1 (50)	1 (50)	
NYHA IV	0 (0)	(0)	(0)	0.98 ^b
Left ventricular Ejection Fraction	51.29 ± 9.37	51.29 ± 9.82	51.28 ± 8.93	
Range: 9 to 67				
Left atrial size (mm)	18.09 ± 4.96	17.63 ± 5.3	18.54 ± 4.56	0.15 ^b
Range: 9 to 46				
Right atrial size (mm)	13.88 ± 3.09	13.82 ± 3.1	13.94 ± 3.1	0.76 ^b
Range: 7.7 to 31				

^aTest using Chi Square test

^bTest using independent T-test

Similarly there was no statistical difference in New York Heart Functional Class, left ventricular ejection fraction and left atrial size or right atrial size. That is, the population was evenly distributed in terms of preoperative characteristics.

6.4 Medical History

The pre-morbid history of our patients in both groups was analysed as shown in Table 4 below. As expected, the majority of them had the three most common pre-morbid conditions: hypertension (81.6%), diabetes mellitus (62.4%) and hypercholesterolaemia (89.6%). We analysed all the other pre-morbid conditions such as Chronic Obstructive Pulmonary Disease (COPD), asthma, Chronic kidney disease (CKD), smoking habit and alcohol intake, but none showed any statistical difference between the two groups. The only statistically significant difference was in hypercholesterolaemia where those receiving Tocovid were more hypercholesterolaemic than the placebo group.

Table 4. Comparison between underlying medical conditions on admission of Tocovid and placebo group.

Medical condition		Total*, n (%)	Tocovid group, n (%)	Placebo group, n (%)	χ^2	p-value
COPD	Yes	3 (1.2)	2 (66.7)	1 (33.3)	-	0.5 ^b
	No	247 (98.8)	123 (49.8)	124 (50.2)		
Asthma:	Yes	1 (0.4)	1 (100)	0 (0)	-	0.5 ^b
	No	249 (99.6)	124 (49.8)	125 (50.2)		
Hypertension:	Yes	204 (81.6)	100 (49)	104 (51)	0.43	0.51 ^a
	No	46 (18.4)	25 (54.3)	21 (45.7)		
Diabetes Mellitus:	Yes	153 (62.4)	73 (47.7)	80 (52.3)	1.012	0.31 ^a
	No	92 (37.6)	50 (54.3)	42 (45.7)		
Hypercholesterolemia:	Yes	224 (89.6)	117 (52.2)	107 (47.8)	4.29	0.038 [*]
	No	26 (10.4)	8 (30.8)	18 (69.2)		
Chronic kidney disease:	Yes	23 (9.2)	11 (47.8)	12 (52.2)	0.048	0.83 ^a
	No	227 (90.8)	114 (50.2)	113 (49.8)		
Current or ex-smoker:	Yes	129 (53.8)	63 (48.8)	66 (51.2)	0.45	0.51 ^a
	No	111 (46.3)	59 (53.2)	52 (46.8)		
Alcohol intake:	Yes	10 (4.3)	4 (40.0)	6 (60.0)	-	0.55 ^b
	No	224 (95.7)	111 (49.6)	113 (50.4)		

* p-value significant at 0.05 using Chi Square Test

^a Test using Chi-Square test

^b Test using Fisher Exact Test

The list of preoperative medications in between the two groups is listed in Table 5 below. The table indicates the absence of any statistical difference in between the two groups irrespective of the preoperative medications that they received, such as anti-hypertensives, anti-platelets, anti-lipid, anti-diabetic, insulin, inhalers, diuretics, amiodarone, proton-pump inhibitors or Warfarin. It shows that both groups were randomly distributed with no evidence of bias.

Table 5. List of patient medications on admission, classified into groups – comparison between Tocovid and placebo group.

Preoperative medication	Total*, n (%)	Tocovid group, n (%)	Placebo group, n (%)	p-value
Anti-hypertensive				
ACE inhibitor	130 (54.6)	60 (46.2)	70 (53.8)	0.113 ^a
Angiotensin Receptor Blocker	22 (9.2)	13 (59.1)	9 (40.9)	0.42 ^a
Calcium Channel Blocker	71 (29.8)	31 (43.7)	40 (56.3)	0.15 ^a
Beta-Blocker	158 (66.4)	78 (49.4)	80 (50.6)	0.52 ^a
Other Anti-hypertensives	4 (1.7)	3 (75)	1 (25)	0.32 ^b
Anti-platelet				
Aspirin	199 (83.6)	99 (49.7)	100 (50.3)	0.45 ^a
Clopidogrel	156 (65.5)	83 (53.2)	73 (46.8)	0.31 ^a
Other anti-platelets	31 (13)	15 (48.4)	16 (51.6)	0.77 ^a
Anti-lipid				
HMG CoA Inhibitor (statins)	211 (88.7)	111 (52.6)	100 (47.4)	0.13 ^a
Fibrates	5 (2.1)	3 (60)	2 (40)	0.52 ^b
Ezetimibe	13 (5.5)	6 (46.2)	7 (53.8)	0.73 ^a
Anti-diabetic				
Biguanide	101 (42.4)	54 (53.5)	47 (46.5)	0.49 ^a
Sulphonylurea	53 (22.3)	30 (56.6)	23 (43.4)	0.34 ^a
Alpha Glucosidase Inhibitor	0	0	0	0
DPP-4 Inhibitor	20 (8.4)	11 (55)	9 (45)	0.7 ^a
Sodium-glucose co-transporter (SGLT)	40 (16.8)	17 (42.5)	23 (57.5)	0.25 ^a
Insulin	60 (25.2)	28 (46.7)	32 (53.3)	0.46 ^a
Inhaled agents				
Inhaled Beta Agonist	4 (1.7)	3 (75)	1 (25)	0.32 ^b
Inhaled Anti Muscarinic	1 (0.4)	0 (0)	1 (100)	0.49 ^b
Inhaled Steroids	2 (0.8)	2 (100)	0 (0)	0.26 ^b
Anti-angina	162 (68.1)	84 (51.9)	78 (48.1)	0.65 ^a
Diuretics	41 (17.2)	18 (43.9)	23 (56.1)	0.33 ^a
Amiodarone	2 (0.8)	1 (50.0)	1 (50.0)	0.74 ^b
Proton Pump Inhibitor	131 (55.0)	65 (49.6)	66 (50.4)	0.67 ^a
Anti-Coagulant (Warfarin)	1 (0.4)	1 (100)	0 (0)	0.51 ^b

* p-value significant at 0.05 using Chi Square Test

^a Test using Chi-Square test

^b Test using Fisher Exact Test

6.5 Operative Details

IJN is known as an on-pump centre, and we mainly performed isolated CABG (92.6%) compared to combined valve surgery (7.4%) as depicted in Table 6 below. Of the combined surgery, mitral valve surgery accounts for almost 60% of cases with only one case involving mitral valve repair. The others were mitral valve replacement. Aortic valve replacement was done in the remaining 40% of cases. However, there was no statistically significant difference in between the two groups in both CABG alone or in CABG & Valve surgery.

Table 6. Comparison between Tocovid and placebo group in operative details.

Operative details	Total*, n (%)	Tocotrienol group, n (%)	Placebo group, n (%)	χ^2/t -value	p-value
Surgery type:					
CABG alone	224 (92.6)	118 (52.7)	106 (47.3)	4.133	0.042 ^{a*}
CABG + valve	18 (7.4)	5 (27.8)	13 (72.2)	4.133	0.042 ^{a*}
Bypass time (in minutes)	97.05 ± 35.65	94.31 ± 32.53	99.82 ± 38.49	-1.201	0.23 ^b
Range: 42 to 304 minutes					
Cross-clamp time (in mins)	75.84 ± 30.05	74.88 ± 25.67	76.82 ± 33.99	-0.498	0.62 ^b
Range: 17 to 244 minutes					
Number of anastomoses					
Single	6 (2.5)	3 (50.0)	3 (50.0)	1.000	0.650 ^c
Multiple	234 (97.5)	118 (50.4)	116 (46.9)	1.000	0.650 ^c

^a Test using Chi Square test

^b Test using Independent T-test

^c Test using Fisher exact test

* p-value significant at 0.05 using Chi Square Test

We found that the mean cross-clamp time was 75 ± 84 minutes ranging from 17 to 244 minutes while the mean bypass time was 97 ± 05 minutes ranging from 42 to 304 minutes. Similarly, there was no statistically significant difference between the two groups of Tocovid and placebo. With regard to the number of anastomoses in between the groups, we observed no statistically significant difference as well.

6.6 Postoperative Outcomes

Based on Table 7 below, we noticed that there was no significant difference in terms of mortality or morbidity in both groups except for pleural effusion. Patients on Tocovid had a reduced incidence of pleural effusion compared to those on placebo. Although pleural effusion has been associated with POAF^[49], this is not reflected in our study. This association between pleural effusion and POAF was also noted by Brookes et al.^[50] who postulated that this was due to poor oxygen saturation, an overall fluid state and atrial stretch, or a serositis inflammation unrelated to pericarditis. Pleural effusion also accounts for an increase in resource utilisation and a further intervention for drainage.^[51]

We postulated that somehow the significant difference between the occurrence of pleural effusion between the two groups was mainly due to the antioxidative action of Tocovid since oxidative stress has been implicated in exudative pleural effusion^[51] that happens following CABG.^[52]

Table 7. Comparison between Tocovid and placebo group in terms of postoperative outcomes.

Postoperative outcomes		Total*, n (%)	Tocovid group, n (%)	Placebo group, n (%)	χ^2	p-value
Stroke:	Yes	4 (1.7)	2 (50)	2 (50)	-	0.68 ^b
	No	232 (98.3)	117 (50.4)	115 (49.6)		
Sternal infection:	Yes	6 (2.5)	2 (33.3)	4 (66.7)	-	0.33 ^b
	No	233 (97.5)	119 (51.1)	114 (48.9)		
Respiratory problems:	Yes	9 (3.8)	4 (44.4)	5 (55.6)	-	0.48 ^b
	No	230 (96.2)	117 (50.9)	113 (49.1)		
Renal failure requiring dialysis:	Yes	12 (5.0)	6 (50)	6 (50)	0.002	0.96 ^a
	No	227 (95.0)	115 (50.7)	112 (49.3)		
Endocrine problems:	Yes	1 (0.4)	1 (100.0)	0 (0)	-	0.51 ^b
	No	238 (99.6)	120 (50.4)	118 (49.6)		
Pleural effusion:	Yes	18 (7.6)	5 (27.8)	13 (72.2)	3.994	0.05*
	No	220 (92.4)	115 (52.3)	105 (47.7)		
Cardiac Tamponade:	Yes	22 (9.2)	9 (40.9)	13 (59.1)	0.916	0.34 ^a
	No	217 (90.8)	112 (51.6)	105 (48.4)		
Fever:	Yes	12 (5.0)	7 (58.3)	5 (41.7)	0.300	0.58 ^a
	No	227 (95.0)	114 (50.2)	113 (49.8)		
Hyperkalaemia:	Yes	4 (1.7)	1 (25)	3 (75)	-	0.30 ^b
	No	234 (98.3)	120 (51.3)	114 (48.7)		
Others:	Yes	7 (2.9)	6 (85.7)	1 (14.3)	-	0.06 ^b
	No	232 (97.1)	115 (49.6)	117 (50.4)		
Death:	Yes	9 (3.6)	6 (66.7)	3 (33.3)	-	0.25 ^b
	No	241 (96.4)	119 (49.4)	122 (50.6)		

* p-value significant at 0.05 using Chi Square Test

^a Test using Chi Square test

^b Test using Fisher Exact Test

We also looked at all the other common complications such as sternal wound infection, respiratory problems, renal failure requiring dialysis, endocrine problems, cardiac tamponade, fever, hyperkalaemia and others including low blood

pressure – none of them showed any statistical difference in between the two groups. It was noted that although more patients on placebo developed cardiac tamponade than on Tocovid, the statistical difference was not significant. Interestingly, a paper by St-Onge et al.^[53] showed that shed mediastinal blood, not necessarily restricted to cardiac tamponade, could initiate POAF by inducing both the inflammatory and oxidative damage to the heart surface. For this reason, some surgeons^[54] advocated posterior pericardiotomy to prevent POAF by making a longitudinal incision parallel and posterior to the phrenic nerve to drain the pericardial effusion to the left pleural cavity.

6.7 Postoperative Stay

The outcomes of our study as tabulated in Table 8 below showed a statistically significant difference in the mean duration of ICU stay ($p=0.04$) in between the Tocovid and placebo groups. This is also reflected in the reduction of ventilation time among the Tocovid group although it did not achieve statistical significance. However, there was no statistically significant difference in the total duration of hospital stay. What we can infer is that the increase in ICU stay among the placebo group of patients was associated with an increase in hospital care although there was no difference in the total hospital stay. Admittedly, no study has been conducted either in IJN or in Malaysia on the economic impact of managing such patients.

Table 8. Comparison between Tocovid and placebo group in terms of Intensive Care Unit (ICU), High dependency Unit (HDU), and Hospital stay as well as duration of ventilation and reintubation.

Duration	Total, median \pm IQR / n (%)	Tocovid group, n (%), median \pm IQR / n (%)	Placebo group, median \pm IQR / n (%)	p-value
Duration in ICU (mins)	1722.50 \pm 2648	1605 \pm 1768	2565 \pm 3900	0.04*
Range: 640 to 67740 minutes				
Duration in HDU (mins)	1640 \pm 1711	1920 \pm 1770	1620 \pm 1685	0.9 ^a
Range: 190 to 14760 minutes				
Duration of ventilation (mins)	1134 \pm 380	1110 \pm 372	1145 \pm 384	0.48 ^a
Range: 350 to 17120 minutes				
Duration of hosp. stay (days)	7.0 \pm 3	7.0 \pm 2	7.0 \pm 4	0.33 ^a
Range: 5 to 86 days				
Reintubation: Yes	8 (3.4)	3 (37.5)	5 (62.5)	0.36 ^b
No	230 (96.6)	116 (50.4)	114 (49.6)	

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

^a Test using Mann-Whitney test

^b Test using Fisher Exact test

6.8 Blood Plasma Levels of Tocotrienols

The tables below summarize the blood plasma levels of the three different isomers of tocotrienols and placebo taken at

four different time points: preoperative or upon admission and approximately two days before surgery; postoperative or approximately one day post-surgery when the patients are still in the ICU; before discharge, normally on the day of discharge itself; and on six-week follow-up, which is the first follow-up date after discharge. The blood samples were initially stored at IJN at a temperature below -27° C and later analysed using High Performance Liquid Chromatography (HPLC) machine. Below are the level of the isomers of tocotrienols analysed except for b-tocotrienols which was too low to be detected on HPLC.

Table 9. Comparison between blood plasma levels of Tocotrienols and Placebo pre-operation, post-operation, at discharge and on six-week follow-up.

Table 9a. Mean Plasma Alpha Tocotrienols Levels vs placebo			
Alpha	Tocotrienol, mean ± SD	Placebo, mean ± SD	p-value
Pre-surgery (V1)	160.02 ± 192.11	16.84 ± 35.28	0.0001*
Post-surgery (V2)	22.29 ± 44.47	1.82 ± 6.91	0.0001*
Discharge (V3)	110.97 ± 147.94	9.49 ± 10.23	0.0001*
6-week follow up (V4)	151.73 ± 226.90	17.78 ± 18.0	0.0001*

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

Table 9b. Mean Plasma Gamma Tocotrienols Levels vs placebo			
Gamma	Tocotrienol, mean ± SD	Placebo, mean ± SD	p-value
Pre-surgery (V1)	103.99 ± 144.26	10.05 ± 27.85	0.0001*
Post-surgery (V2)	13.28 ± 30.91	0.69 ± 5.38	0.0001*
Discharge (V3)	83.77 ± 123.62	3.81 ± 8.43	0.0001*
6-week follow up (V4)	126.26 ± 188.08	11.84 ± 18.95	0.0001*

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

Table 9c. Mean Plasma Delta Tocotrienols Levels vs placebo

Delta	Tocotrienol, mean \pm SD	Placebo, mean \pm SD	p-value
Pre-surgery (V1)	22.72 \pm 33.49	1.23 \pm 5.16	0.0001*
Post-surgery (V2)	6.48 \pm 8.97	0.23 \pm 1.44	0.0001*
Discharge (V3)	27.92 \pm 38.35	0.62 \pm 2.96	0.0001*
6-weeks follow up (V4)	39.99 \pm 49.74	1.56 \pm 2.93	0.0001*

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

Based on the HPLC analysis of the different isomers of Tocotrienols which form the main component of Tocovid, the compliance to medication was good and the levels of each and every isomer of tocotrienols showed statistically significant levels as compared to placebo. The preoperative blood samples were taken approximately two days before surgery, while the postoperative blood samples were taken while patients were in ICU. Both Tocovid and placebo were dispensed by the nurses. We learnt that patients might have missed their Tocovid or placebo on the day of surgery when they were transferred into the operation theatre (OT) since they were kept fasting at least six hours before surgery; after approximately four hours in the OT, they were transferred back to the Cardiac Intensive Care Unit (CICU) while still intubated. The nurses will dispense Tocovid and placebo again only when they were allowed orally after extubation from an overnight ventilation. This explains the lower levels of both tocotrienols and placebo post-surgery. Given the short half-life of tocotrienols of about 4.4, 4.3 and 2.3 hours for alpha-, gamma-, and delta-tocotrienols respectively, this might not be sufficient enough to ward off the POAF since we know that the median time for the occurrence of POAF was 47 hours after surgery or 46.56 ± 26.56 hours mean time. This was compounded by the fact that the absorption of Tocovid was compromised by an empty stomach. This would explain the non-significant difference in between the two groups. However, the higher levels of Tocovid during this period – though not adequately high – was enough to merit a significant shorter stay in ICU. Hence, we assume that it might have helped to reduce the cost of managing CABG patients.

Below are bar charts on the different isomers of tocotrienols at different time points for a clearer depiction. The low-level of both tocotrienols and placebo post-surgery is better appreciated with the bar charts below as in Figure 3a, 3b, and 3c.

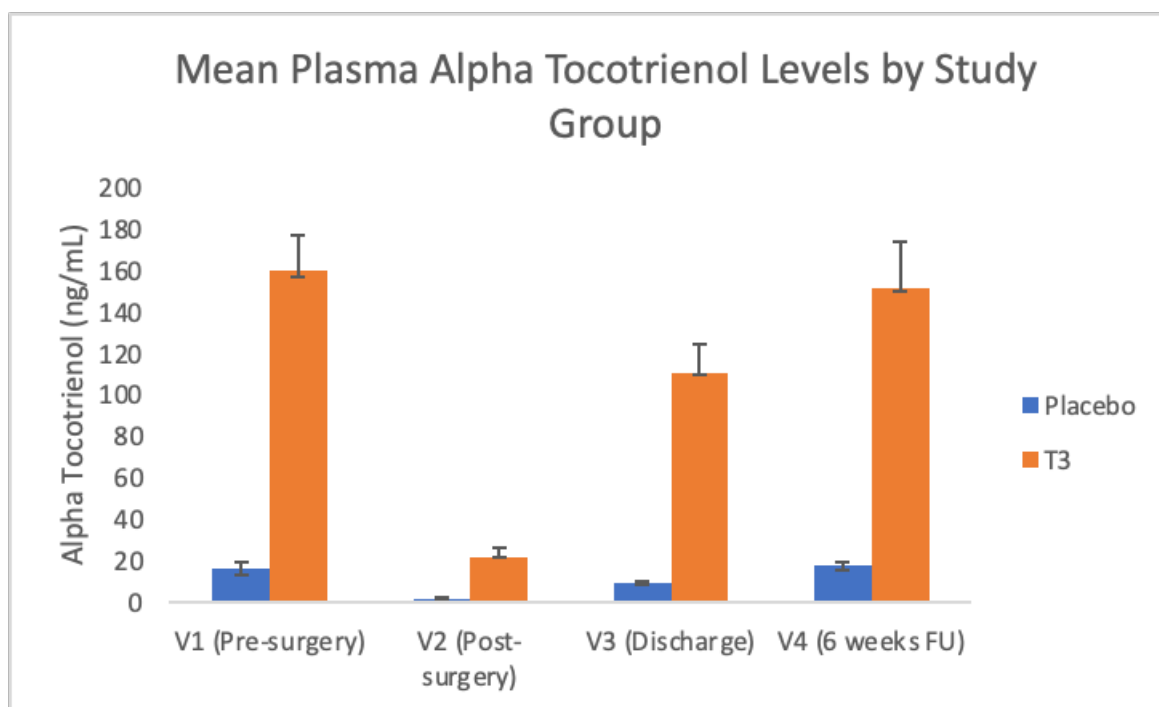


Figure 3a. Levels of alpha-tocotrienol at pre-surgery, post-surgery, discharge, and six-week follow up visit.

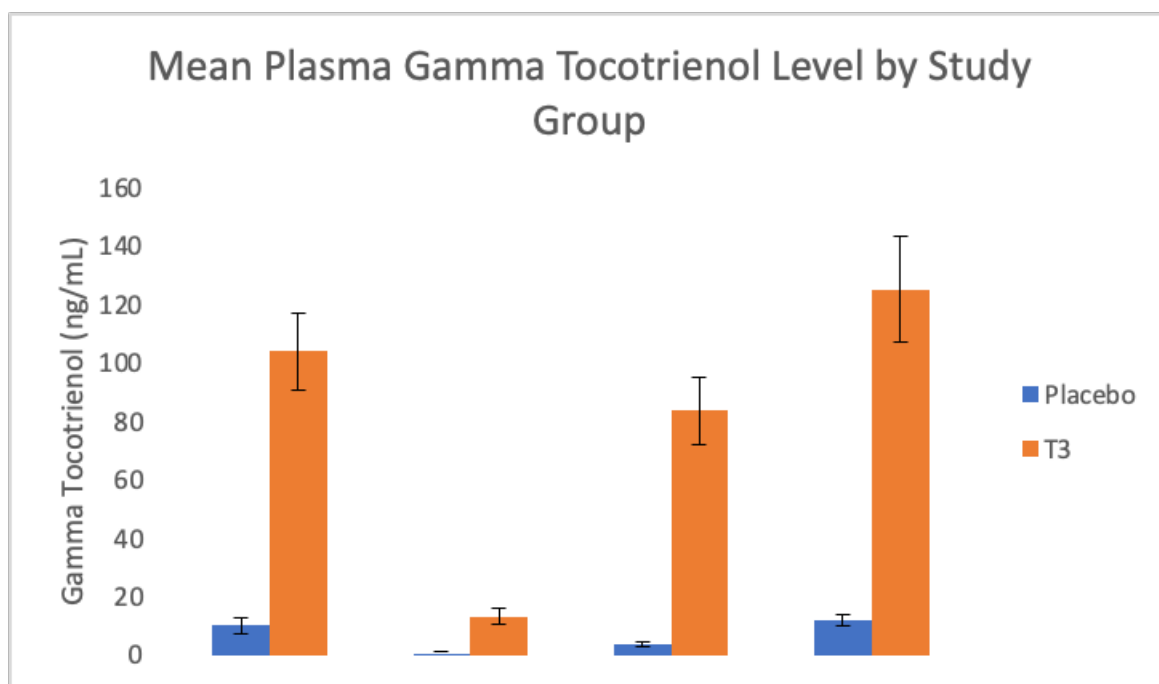


Figure 3b. Levels of gamma-tocotrienol at pre-surgery, post-surgery, discharge, and six-week follow up visit.

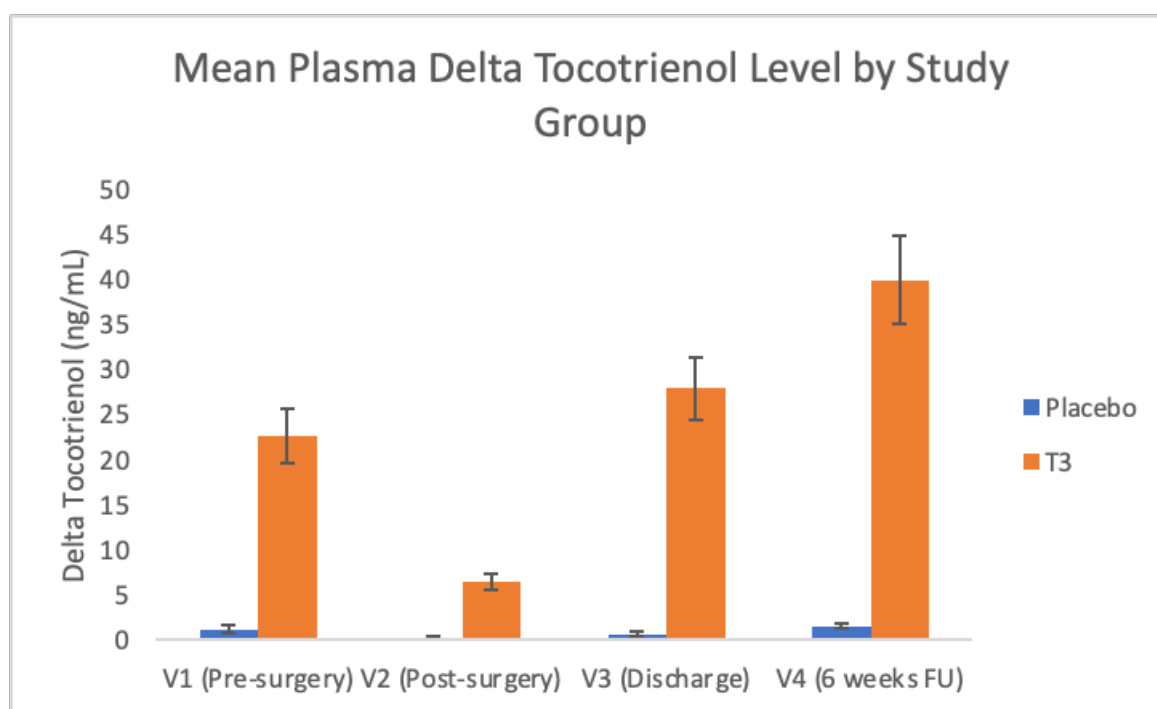


Figure 3c. Levels of delta-tocotrienol at pre-surgery, post-surgery, discharge, and six-week follow up visit.

6.9 Health-related Quality of Life (HRQOL) of patients

As we are aware, the SF-36 measures eight scales: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). It measures two distinct components, namely the physical and the mental. The PF, RP, BP, and GH represent the cluster of physical subscales, while the mental cluster includes MH, RE, SF and VT. Each subscale is transformed into a 0-100 scale where a score of zero is equivalent to maximum disability while a score of 100 represents no disability. That is, the lower the score, the greater the disability, and vice versa.

Table 10. SF-36 assessment at four time points: pre-operation, post-operation, at discharge, and at 6-week follow up post-CABG after oral administration of Tocovid and placebo.

Variable	Capsules	Preoperative	Discharge	6-week follow up
Physical Functioning (PF)	Tocovid	64.23 ± 18.13	62.42 ± 29.12	70.37 ± 19.83
	Placebo	63.13 ± 18.39	57.61 ± 27.59	70.0 ± 23.7
	p-value	0.64	0.19	0.9
Role-Physical (RP)	Tocovid	24.79 ± 38.48	35.38 ± 44.97	67.43 ± 43.24
	Placebo	36.48 ± 45.92	42.46 ± 48.14	65.09 ± 44.63
	p-value	0.03*	0.25	0.69
Bodily Pain (BP)	Tocovid	73.94 ± 17.85	72.20 ± 18.73	73.92 ± 21.45
	Placebo	73.0 ± 18.98	71.47 ± 19.89	73.45 ± 20.64
	p-value	0.69	0.77	0.87
General Health (GH)	Tocovid	69.35 ± 17.36	80.59 ± 15.17	82.82 ± 15.59
	Placebo	69.63 ± 18.55	81.97 ± 13.86	81.31 ± 16.85
	p-value	0.9	0.47	0.49
Vitality (VT)	Tocovid	93.74 ± 13.51	87.5 ± 15.90	88.21 ± 14.09
	Placebo	93.17 ± 12.5	87.56 ± 16.96	86.44 ± 15.90
	p-value	0.73	0.97	0.38
Social Functioning (SF)	Tocovid	83.64 ± 15.12	80.93 ± 20.19	80.56 ± 24.49
	Placebo	82.58 ± 18.08	83.55 ± 16.79	82.66 ± 24.49
	p-value	0.62	0.28	0.53
Role-Emotional (RE)	Tocovid	52.46 ± 31.76	64.12 ± 35.45	92.97 ± 24.03
	Placebo	61.25 ± 34.51	72.65 ± 34.08	89.19 ± 26.65
	p-value	0.04*	0.06	0.27
Mental Health (MH)	Tocovid	93.49 ± 9.57	95.21 ± 8.26	95.78 ± 7.75
	Placebo	91.74 ± 13.46	94.94 ± 9.06	94.16 ± 10.91
	p-value	0.24	0.81	0.21

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

Table 10 above shows no apparent difference in the quality of life of patients from both groups, Tocovid and placebo, although patients on Tocovid had a worse condition preoperatively on two domains namely role-physical and role-emotional which represents both components of physical and mental. However, their quality of life improved after surgery with Tocovid although when compared to placebo, there was no statistically significant difference in between the two groups post-surgery.

To assess the quality of life, we used another instrument: the Nottingham Health Profile (NHP) – Part I. As depicted in Table 11 below, it comprises 38 questions arranged in six categories, namely sleep, physical mobility, energy, pain, emotional reactions and social isolation; zero score indicates no distress and 100 severe distress. The NHP is simple, comprehensive and widely used; in some circumstances it may be more sensitive than the SF-36.^[55] It includes a specific sleep scale and more pain items compared to the SF-36 instrument^[56]. However, in some circumstances, SF-36 may show greater responsivity to treatment.^[57]

The NHP analysis showed statistically significant difference in the sleep quality at 6 weeks on follow-up, which indicates a better sleep quality in patients receiving Tocovid. It is unclear how Tocovid would effect this; Alzoubi et al.^[58] hypothesised that this might be due to its effect on the hippocampus. This better sleep quality correlated well with the high levels of Tocovid in the blood as depicted in Figure 3c.

Table 11. NHP assessment pre-operation, post-operation, discharge, and at 6-week follow up post-CABG after oral administration of Tocovid and placebo.

Variable	Capsules	Pre-operative	Discharge	6-weeks follow up
Energy Level	Tocovid	45.76 ± 24.27	45.80 ± 31.69	14.99 ± 22.66
	Placebo	49.67 ± 26.85	44.94 ± 32.99	20.11 ± 28.01
	<i>p</i> -value	0.23	0.84	0.13
Pain	Tocovid	3.55 ± 12.99	12.04 ± 14.73	6.86 ± 13.08
	Placebo	2.71 ± 10.19	13.73 ± 13.73	8.41 ± 16.94
	<i>p</i> -value	0.57	0.34	0.45
Emotional Reaction	Tocovid	2.29 ± 7.17	2.88 ± 9.33	1.36 ± 7.29
	Placebo	2.11 ± 7.91	2.39 ± 7.91	2.79 ± 9.77
	<i>p</i> -value	0.85	0.67	0.22
Sleep	Tocovid	11.89 ± 12.25	27.19 ± 28.75	11.14 ± 21.14
	Placebo	13.71 ± 16.56	31.69 ± 28.79	21.10 ± 31.58
	<i>p</i> -value	0.33	0.23	0.007*
Social interaction	Tocovid	1.33 ± 5.55	2.31 ± 10.69	0.77 ± 3.98
	Placebo	0.73 ± 3.96	0.56 ± 3.44	1.92 ± 9.50
	<i>p</i> -value	0.32	0.09	0.24
Physical Activity	Tocovid	1.79 ± 7.34	19.59 ± 21.88	12.09 ± 19.41
	Placebo	3.23 ± 9.01	17.98 ± 18.85	11.13 ± 19.31
	<i>p</i> -value	0.17	0.55	0.71

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

7.0 Discussion

From this randomised, double-blind, controlled trial, we would like to emphasise that POAF after cardiac surgery is still the most common complication that occurred in 36.4% of our study population with no difference in between the group treated with Tocovid or placebo. Consequently, our current findings do not support our postulated hypothesis regarding the potent antioxidative effect of Tocovid in reducing the incidence of POAF by inhibiting the pathogenesis of such incidence. This is in contrast to a meta-analysis^[59] on vitamin C that shows that it prevents POAF, and shortens the duration of ICU stay

and hospital stay in cardiac surgery patients. The studies were also designed on a presumption that vitamin C possesses antioxidative activity^[59] and it was also noted in some studies^{[60][61][62]} that cardiac surgery reduces vitamin C levels consistent with the increase in oxidative stress.

It has to be stressed here that the presumed antioxidant property of tocotrienol is not new. Serbinova et al.^[63] noticed that the activity of α -tocotrienol in scavenging peroxy radicals was 1.5 times higher in liposomes as compared to α -tocopherol. In rat liver microsomes, the efficacy was 40 times higher in α -tocotrienol to protect against Fe(II)+ NADPH-induced lipid peroxidation than that of α -tocopherol. The superior antioxidant properties of tocotrienols was said to be due to the presence of the unsaturated side chain which allows more efficient incorporation into tissues, especially those with saturated fatty layers.^[64]

Serbinova^[63] also noted that α -tocotrienol was 6.5 times more potent in preventing cytochrome P-450 against oxidative damage. The postulation was that the chromanol radical of α -tocotrienol was recycled faster in the membranes and lipoproteins than the α -tocopherol radicals.^[61] Studies with nuclear magnetic resonance have indicated that α -tocotrienol is located closer to the membrane surface, which may facilitate recycling.^[65] They also show that α -tocotrienol is distributed more evenly within the membrane than α -tocopherol. These properties enhance the interaction of chromanols with the lipid radicals.^{[61][66]}

It has been established that cellular damage is closely related to the generation of free radicals (O^- , H_2O_2 , and OH^-) from the incomplete reduction of molecular oxygen during aerobic respiration.^[67] It is said that the normal physiological processes are maintained via the cellular process regulation of the balance between production of reactive oxygen species (ROS) and its removal by the antioxidant system. The tocotrienols antioxidant activities are mediated via the induction of antioxidant enzymes such as superoxide dismutase,^{[68][69]} quinone-oxide-reductase,^[70] and glutathione peroxidase,^[71] which swallow free radicals such as superoxide radicals.^[72] Interestingly, the effects of tocotrienol-rich fraction (TRF) on exercise endurance and oxidative stress in forced swimming rats was investigated by another group of researchers.^[73] They found that the TRF-treated rats swam significantly longer than the control. The TRF-treated rats also showed lower levels of blood lactate and liver thiobarbituric acid reactive substances (TBARS) – a by-product of lipid peroxidation, i.e. degradation products of fat, and muscle protein carbonyl – whereas the levels of superoxide dismutase, catalase, and glutathione peroxidase were increased. Their results suggested that the physiological condition in forced swimming rats was improved and it significantly reduced the exercise-induced oxidative stress.^{[74][75]}

Several factors can explain the discouraging result in our study which was essentially a clinical translation from bench to bedside. One is, as mentioned earlier, the short half-life and bioavailability of tocotrienols, and also its oral absorption which is highly dependent on the consumption of dietary fat due to their lipid solubility.^[76] Also, after surgery in the ICU, patients were initially intubated and even right after extubation, they were normally permitted only sips of clear fluids. Therefore, the poor absorption of tocotrienols on an empty stomach led to the low blood levels as depicted in the V2 bar charts above (Figures 3a, 3b, and 3c). This is made worse by the shorter elimination half-time of tocotrienols by 4.5 to 8.7

times as compared to a-tocopherol.^[77]

In the most recent systematic review and meta-analysis on the effects of tocotrienol supplementation on markers of inflammation and oxidative stress by Khor et al.^[78], the authors concluded that their systematic review of clinical trials was unable to make a conclusive judgment on the anti-inflammatory and antioxidative effects of tocotrienols. It appeared that laboratory findings on animals were insufficient to provide conclusive evidence of the anti-inflammatory and antioxidative effects of tocotrienols, besides not being reproducible in human trials. They recommended more randomised, controlled trials to confirm these effects by assessing validated inflammatory and oxidative stress biomarkers using state-of-the-art technologies.

Nonetheless, we should not ignore the finding that, in our study, CICU stay was significantly lower in the Tocovid group, as depicted in Table 8. This translates into cost savings although there is no difference in the duration of hospital stay. A study in the US^[79] showed that the cost of care at the Cardiac Intensive Care Unit (CICU) was the highest due to high postoperative resources for cardiac surgical cases. In one local study at a teaching hospital in Malaysia,^[80] it was noted that while the unit cost per day at the ICU was dependent on the type of ICU, the cost for CICU was approximately USD1154 per day. A shorter stay in CICU will definitely provide an economic benefit in terms of cost savings in whichever hospital the patients were admitted for CABG.

It should also be noted that the NHP analysis of the quality of life of our CABG patients showed an improvement in the quality of sleep postoperatively. Although there are no human clinical trials on this aspect, an animal study by Alzoubi et al.^[58] (as mentioned earlier) showed the possible antioxidant role of tocotrienol in manifesting its properties via the hippocampus. As discussed earlier, the statistically significant difference in the level of Tocovid six weeks after discharge showed that this was not a coincidental finding but an effect from Tocovid considering the fact that all other factors remained constant during recovery. The reason why this effect was not observed preoperatively was most likely due to the condition of all patients before surgery, a time when they are highly anxious. The effect was only appreciated when all the patients were at ease in a familiar home environment a few weeks after surgery.

Overall, although the study did not confirm the efficacy of Tocovid in reducing POAF after CABG from the postulated hypothesis that its potent antioxidative properties might play a role in mitigating the oxidative process that leads to POAF; we were able to postulate on its failure. Nonetheless, we witnessed the benefit of Tocovid in reducing the cost of hospitalisation. Though this was done without any direct evidence, it still suggests that tocotrienol is beneficial for patients undergoing CABG for CAD.

8.0 Limitations

The main limitations of our study was that it was conducted during the COVID-19 pandemic. This compromised patients

recruitment rate while decreasing the availability of CICU beds and the number of surgery performed. Moreover, since the HRQOL assessment of patients were interviewer-dependent, we cannot rule out biases on the part of the interviewers in transcribing, analysing, providing feedback and reporting. In addition, the patients themselves may also have been biased since they believed they were on a supplement that might have an effect on them although they were simply consuming placebos.

9.0 Conclusion

This double-blind, randomised controlled trial took three years to be completed at the National Heart Institute, a centre of excellence in Kuala Lumpur, among CAD patients undergoing isolated CABG or CABG and valve surgery. The most important lesson learnt from this study was that tocotrienol is safe to be taken pre-surgery and post-surgery together with other medications. There is no evidence of increased bleeding in the perioperative period though tocotrienol is thought to have a blood-thinning effect. We can also confidently say that dosing for two or three days before surgery is adequate to raise to the maintenance level. Although Tocovid that comprises mainly of tocotrienols, an isomer of vitamin E, is not effective enough to prevent the occurrence of POAF after CABG, this was mainly due to the relatively short half-life of tocotrienol and more importantly to its reduced bioavailability in the blood stream in an empty stomach, and the omitted consumption on the night before surgery, and subsequently on the first day in CICU. As shown from the blood levels of tocotrienols, this simply reduces the blood level significantly. Post-CABG patients who were initially ventilated in the CICU definitely were kept nil by mouth. This prevented them from getting the protective effect of tocotrienol. Any tocotrienol that was given to them orally after extubation from an overnight ventilation had a poor chance of being absorbed into the blood circulation from the empty stomach. Considering that the occurrence of POAF was predominantly on day-2 post-CABG, the CICU phase was the most critical in ensuring adequate level of tocotrienol in the bloodstream. Hence, continuous dosing is required; otherwise the blood serum levels will fall and no protective effect is conferred. It is also interesting to note that while the tocotrienol levels in the bloodstream were not high enough to prevent POAF, it did confer some benefits to the patients in CICU. More specifically, the patients had a shorter CICU stay which translates into lower hospitalisation cost. Additionally, they had a better quality of sleep after discharge from the hospital.

10.0 Future Directions

We have a few recommendations to ensure that this research is replicable and would perhaps show a better result. One is on improving the efficacy of the current formulation of Tocovid. This is mainly due to its poor bioavailability and relatively shorter $t_{1/2}$ that can somehow affect its potency. Future research should also look into other possibilities such as a higher stat dose prior to surgery to ensure that the serum concentration of tocotrienols remain high even during the first few hours post-surgery when the patients are in CICU; nano-formulations since lipid-based nanovesicles are promising for delivery of lipophilic compounds like tocotrienols; self-emulsifying; and the possibility of non-oral route such as intravenous preparation of tocotrienols at least for the perioperative period. This would keep tocotrienol levels sustainable throughout

that critical period.

11.0 Declarations

11.1 Ethics approval

The study protocol was approved by the National Heart Institute Ethics Committee (IJNREC/201/2017). IJNREC also served as the data safety committee. We obtained a similar approval from the Monash University Human Research Ethics Committee (MUHREC/2017-9227-10263) and the National Pharmaceutical Regulatory Agency (NPRA/CTX-180304). The trial was registered 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/NCT03807037>

11.2 Consent

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.

11.3 Consent for publication

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

11.4 Availability of data and materials

Harvard Dataverse: Replication Data for: Effect of Tocovid - a tocotrienol-rich Vitamin E - in mitigating postoperative atrial fibrillation (POAF) after coronary artery bypass grafting (CABG) surgery: A double-blind randomised controlled trial

Link: <https://doi.org/10.7910/DVN/XGDWG5>

This project contains the following underlying data:

Set 1: Raw Data

Set 2: Output Data

Set 3: Tocotrienol Levels – Raw Data

Set 4: Tocotrienol levels – Output Data

Set 5: HRQOL – SF-36

Pre-op – Raw Data & Output Data

Discharge – Raw Data & Output Data

Follow-up – Raw Data & Output Data

Set 6: HRQOL – NHP

Pre-op – Raw Data & Output Data

Discharge – Raw Data & Output Data

Follow-up – Raw Data & Output Data

11.5 Competing interests

The authors declare that they have no competing interests.

11.6 Funding

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11.7 Authors' contributions

Musa AF: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Dillon J, MdTaib ME, Yunus MA, Sanusi AR, Nordin MN: Provided significant input into the study protocol, performed the bypass surgery on the study patients, and provided the postoperative care; Smith J: Project Administration, Supervision, Validation, Writing – Review & Editing

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