Research Article

Does Tocovid, a Tocotrienol-rich Vitamin E, Mitigate Postoperative Atrial Fibrillation after Coronary Artery Bypass Grafting (CABG) Surgery? A Single-Centre Double-blind Randomised Controlled Trial

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

1. Jeffrey Cheah School of Medicine and Health Sciences, Monash University, Victoria, Australia; 2. Department of Cardiothoracic Surgery, Institut Jantung Negara - National Heart Institute, Kuala Lumpur, Malaysia; 3. Monash University, Victoria, Australia; 4. Department of Cardiothoracic Surgery, Monash Health, Melbourne, Australia

Objective: 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) patients; and in improving their quality of life (QOL).

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

Results: The recruitment of patients started 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.

No statistically significant difference was observed 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 probability of occurrence of POAF was 36.4% with no

 doi.org/10.32388/GL22XT.2

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 POAF development was 47-hours post-CABG. The quality of life as measured by the 36-Item Short Form Survey (SF-36) and Nottingham Health Profile (NHP) did not show any significant difference except in role physical and role emotional on SF-36 and sleep quality on NHP.

Conclusion: POAF was not mitigated by Tocovid presumably from low tocotrienol level post-surgery; however, the CICU stay was shortened with reduced pleural effusion, and an improvement in the physical and emotional state with better sleep quality.

Corresponding author: Ahmad Farouk Musa, farouk@monash.edu

1.0 Introduction

Despite 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 which is demonstrably reduced in off-pump surgery.[12][13][14] On the one hand, CPB and cardiac surgery itself can lead to the production of pro-inflammatory mediators such as 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 most probably 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 single-centre, prospective, randomised, 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 12-lead electrocardiogram (ECG) monitoring on one-patient-one-nurse basis; they were subsequently transferred to High Dependency Unit (HDU) or direct to the ward if their condition was stable. The ECG monitoring was continued for at least the first three postoperative days on the normal cardiothoracic wards via Long Lead II 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 were followed-up six weeks after discharge through physical examination, ECG and blood tests for tocotrienol levels. For study flow chart, see attachment: Figure 2.

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 POAF. AF was detected by ECG during the group's hospitalisation period with a continuous monitoring using a 12-lead ECG postoperatively in CICU, and again throughout the group's stay in the ward post-surgery via long lead II. 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- β) 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) X 2 = 250 subjects. Of this total, there will be 125 controls and 125 experimental subjects.

4.7 Statistical Analysis

Statistical analysis was undertaken using SPSS version 28.0, IBM® SPSS® Statistics (SPSS Inc., Chicago, IL, USA). Level of statistical significance was set at 0.05.

Mean (±SD) was calculated for continuous variables, and frequencies (percentages) were measured for categorical variables. Differences between groups were analysed by an unpaired Student-*t* test for continuous variables; for categorical variables, group differences were examined by the Chi-Square or Fisher Exact test, as appropriate. In particular, the Fisher Exact test was applied in case of an expected frequency of less than 5 in any cell in a 2x2 table. A *p* value of less than 0.05 will be considered statistically significant. The primary analysisfor all outcomes used the intention-to-treat (ITT) analysis. Theoccurrence of POAF in the two treatmentgroups was tested with the Relative Risk (95% CI) of the two-binomial proportion.

To examine the mean (+SD) QoL (SF36 and NHP) score differences between the two groups (pre-operative, six weeks and three months), the one-way mixed-mode repeated measure ANOVA with

post-hoc multiple comparison test (between and within subject) of the two groups was performed. Before performing the test, seven assumptions have to be considered: (1) the dependent variable should be measured at the continuous level; (2) the within-subjects factor (i.e., within-subjects independent variable) should consist of at least two categorical, "related groups" or "matched pairs"; (3) the between-subjects factor (i.e., between-subjects factor independent variable) should each consist of at least two categorical, "independent groups"; (4) no significant outliers in any group of the within-subjects factor or between-subjects factor should be present; (5) the dependent variable should be approximately normally distributed for each combination of the groups of the two factors; (6) the variances for each combination of the groups of the two factors (i.e., within-subjects factor and between-subjects factor) should be homogeneous (Levene's test for homogeneity of variances); and (7) sphericity, the variances of the differences between the related groups of the within-subject factor for all groups of the between-subjects factor (i.e., within-subjects factor and between-subjects factor) must be equal (Mauchly's Test of Sphericity). For a statistically significant interaction, to determine the difference between the two groups at each level of each factor (known as simple main effects rather than main effects). In the absence of a statistically significant interaction, to interpret and report the main effects for both factors (i.e., the "within-subjects" factor and "between-subjects" factor). In addition, if either of these main effects is statistically significant, to interpret the relevant post hoc tests using the pairwise comparisons table.

For this study, if the drop-out rate was less than 20 per cent and found to be similar in both the treatment group and placebo group, we will consider the missing values as treatment failures after dichotomization of the endpoint.

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 to parcipants before their consent was obtained; 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 last follow-up was done on 26 August 2021. The CONSORT Flow Diagram is shown below in Figure 1:

CONSORT Flow Diagram

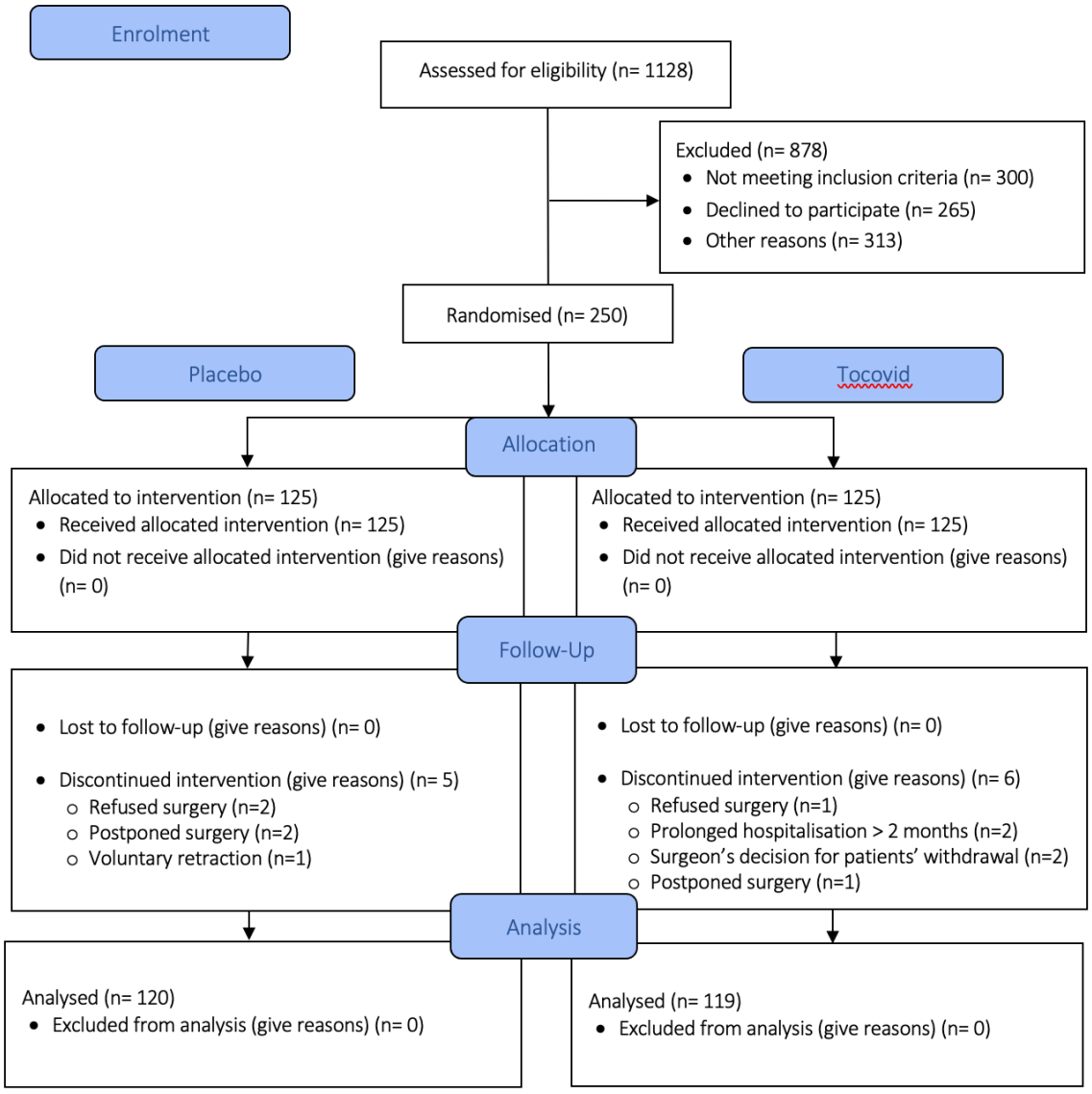


Figure 1. CONSORT Flow Diagram

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. This is despite age being considered the most consistent factor with an increased incidence of POAF[35] and an independent predictor of POAF.[36]

Demographic	Total	Tocovid group, mean ± SD/n (%)	Placebo group, mean ± SD/n (%)
Age (years)	60.88 ± 7.79	61.08 ± 8.27	60.67 ± 7.30
Range: 39 to 85 years old			
Gender:			
Male	201	101 (50.2)	100 (49.8)
Female	49	24 (49)	25 (51)
Population:			
Malay	205	101 (49.3)	104 (50.7)
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)
Medium Risk	109 (44.9)	49 (45)	60 (55)
High Risk	30 (12.3)	14 (46.7)	16 (53.3)

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

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 noted 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 probability of occurrence of POAF in our study was 36.4% with equal occurrence in both the Tocovid and placebo arms. This is slightly higher than in our previous study[32] where 28.7% of patients developed POAF. However, this figure is within the cited range in the literatures[39][40][41] that put the POAF probability of occurrence ranges between 20% and 40%. However, it was obvious that Tocovid did not reduce the probability of occurrence of POAF; we shall discuss the possible reasons for this phenomenon later.

Characteristics of AF	**n* (%), mean ± SD**	**Tocovid group, n (%)**	**Placebo group, n (%)**	**Relative Risk (95% CI)**	***p*-value**
Occurrence of POAF Yes	88 (36.4)	44 (50)	44 (50)	1.026 (0.608-1.733)	0.923[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	1.000 (1.000-1.000)	0.485[b]
Range: 10 to 7044 minutes					
Duration (hours):					
≤48	45 (52.9)	24 (53.3)	21 (46.7)	1.397 (0.594-3.284)	0.443[a]
>48	40 (47.1)	18 (45)	22 (55)		
Number of episodes:					
Single	45 (51.1)	21 (46.7)	24 (53.3)	0.761 (0.329-1.759)	0.522[a]
Multiple	43 (48.9)	23 (53.5)	20 (46.5)		

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

[a] *Test using Chi-Square test*

[b] *Test using Independent t-test*

**RR = Risk Ratio*

***CI = Confidence Interval*

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.

Pre-operative characteristic	Total*, n (%)	Tocovid group, n (%)	Placebo group, n (%)
Body Mass Index (kg/m^2)	27.15 ± 4.39	27.06 ± 4.37	27.24 ± 4.42
<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:			
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)
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
Range: 9 to 46			
Right atrial size (mm)	13.88 ± 3.09	13.82 ± 3.1	13.94 ± 3.1
Range: 7.7 to 31			

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

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.

doi.org/10.32388/GL22XT.2

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)	-	0.561[b]
	No	247 (98.8)	123 (49.8)	124 (50.2)		
Asthma:	Yes	1 (0.4)	1 (100)	0 (0)	-	0.500[b]
	No	249 (99.6)	124 (49.8)	125 (50.2)		
Hypertension:	Yes	204 (81.6)	100 (49)	104 (51)	0.43	0.514[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	0.314[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	0.827[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	0.505[a]
	No	111 (46.3)	59 (53.2)	52 (46.8)		
Alcohol intake:	Yes	10 (4.3)	4 (40.0)	6 (60.0)	-	0.554[b]
	No	224 (95.7)	111 (49.6)	113 (50.4)		

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

** 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 shown 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.

doi.org/10.32388/GL22XT.2

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)	0.416[a]
Calcium Channel Blocker	71 (29.8)	31 (43.7)	40 (56.3)	0.149[a]
Beta-Blocker	158 (66.4)	78 (49.4)	80 (50.6)	0.523[a]
Other Anti-hypertensives	4 (1.7)	3 (75)	1 (25)	0.324[b]
Anti-platelet				
Aspirin	199 (83.6)	99 (49.7)	100 (50.3)	0.447[a]
Clopidogrel	156 (65.5)	83 (53.2)	73 (46.8)	0.314[a]
Other anti-platelets	31 (13)	15 (48.4)	16 (51.6)	0.770[a]
Anti-lipid				
HMG CoA Inhibitor (statins)	211 (88.7)	111 (52.6)	100 (47.4)	0.128[a]
Fibrates	5 (2.1)	3 (60)	2 (40)	0.516[b]
Ezetimibe	13 (5.5)	6 (46.2)	7 (53.8)	0.728[a]
Anti-diabetic				
Biguanide	101 (42.4)	54 (53.5)	47 (46.5)	0.487[a]
Sulphonylurea	53 (22.3)	30 (56.6)	23 (43.4)	0.341[a]
Alpha Glucosidase Inhibitor	0	0	0	0
DPP-4 Inhibitor	20 (8.4)	11 (55)	9 (45)	0.697[a]
Sodium-glucose co-transporter (SGLT)	40 (16.8)	17 (42.5)	23 (57.5)	0.247[a]
Insulin	60 (25.2)	28 (46.7)	32 (53.3)	0.455[a]
Inhaled agents				
Inhaled Beta Agonist	4 (1.7)	3 (75)	1 (25)	0.324[b]

Preoperative medication	Total*, n (%)	Tocovid group, n (%)	Placebo group, n (%)	*p*-value
Inhaled Anti Muscarinic	1 (0.4)	0 (0)	1 (100)	0.492[b]
Inhaled Steroids	2 (0.8)	2 (100)	0 (0)	0.257[b]
Anti-angina	162 (68.1)	84 (51.9)	78 (48.1)	0.649[a]
Diuretics	41 (17.2)	18 (43.9)	23 (56.1)	0.329[a]
Amiodarone	2 (0.8)	1 (50.0)	1 (50.0)	0.743[b]
Proton Pump Inhibitor	131 (55.0)	65 (49.6)	66 (50.4)	0.676[a]
Anti-Coagulant (Warfarin)	1 (0.4)	1 (100)	0 (0)	0.508[b]

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

* *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 involved 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.

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	0.231[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	0.619[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]

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

[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 serositic inflammation unrelated to pericarditis. Pleural effusion also accounts for an increase in resource utilisation and a further intervention for drainage.[51]

We postulated that 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]

Postoperative outcomes		Total*, n (%)	Tocovid group, n (%)	Placebo group, n (%)	χ^2	*p*-value
Stroke:	Yes	4 (1.7)	2 (1.7)	2 (1.7)	-	0.683[b]
	No	232 (98.3)	117 (50.4)	115 (49.6)		
Sternal infection:	Yes	6 (2.5)	2 (33.3)	4 (66.7)	-	0.330[b]
	No	233 (97.5)	119 (51.1)	114 (48.9)		
Respiratory problems:	Yes	9 (3.8)	4 (44.4)	5 (55.6)	-	0.484[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	0.964[a]
	No	227 (95.0)	115 (50.7)	112 (49.3)		
Endocrine problems:	Yes	1 (0.4)	1 (100.0)	0 (0)	-	0.506[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	0.046*
	No	220 (92.4)	115 (52.3)	105 (47.7)		
Cardiac Tamponade:	Yes	22 (9.2)	9 (40.9)	13 (59.1)	0.916	0.339[a]
	No	217 (90.8)	112 (51.6)	105 (48.4)		
Fever:	Yes	12 (5.0)	7 (58.3)	5 (41.7)	0.300	0.584[a]
	No	227 (95.0)	114 (50.2)	113 (49.8)		
Hyperkalaemia:	Yes	4 (1.7)	1 (25)	3 (75)	-	0.297[b]
	No	234 (98.3)	120 (51.3)	114 (48.7)		
Others:	Yes	7 (2.9)	6 (85.7)	1 (14.3)	-	0.064[b]
	No	232 (97.1)	115 (49.6)	117 (50.4)		

doi.org/10.32388/GL22XT.2

Postoperative outcomes		Total*, n (%)	Tocovid group, n (%)	Placebo group, n (%)	χ^2	*p*-value
Death:	Yes	9 (3.6)	6 (66.7)	3 (33.3)	-	0.250[b]
	No	241 (96.4)	119 (49.4)	122 (50.6)		

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

** 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.

Duration	**Total, median ± IQR / n (%)**	**Tocovid group, n (%), median ± IQR / n (%)**	**Placebo group, median ± IQR /n (%)**	***p*-value**
Duration in ICU (mins)	1722.50± 2648	1605 ± 1768	2565 ± 3900	0.041*
Range: 640 to 67740 minutes				
Duration in HDU (mins)	1640 ± 1711	1920 ± 1770	1620 ± 1685	0.900[a]
Range: 190 to 14760 minutes				
Duration of ventilation (mins)	1134 ± 380	1110 ± 372	1145 ± 384	0.477[a]
Range: 350 to 17120 minutes				
Duration of hosp. stay (days)	7.0 ± 3	7.0 ± 2	7.0 ± 4	0.331[a]
Range: 5 to 86 days				
Reintubation: Yes	8 (3.4)	3 (37.5)	5 (62.5)	0.361[b]
No	230 (96.6)	116 (50.4)	114 (49.6)	

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.

** 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: (1) preoperative or upon admission and approximately two days before surgery; (2) postoperative or approximately one day post-surgery when the patients are still in the ICU; (3) before discharge, normally on the day of discharge itself; and (4) 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 ⊠-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.

Alpha	**Tocotrienol (ng/ml), mean ± SD**	**Placebo(ng/ml), 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*

Table 9a. Mean Plasma Alpha Tocotrienols Levels vs placebo

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

doi.org/10.32388/GL22XT.2

Gamma	Tocotrienol (ng/ml), mean ± SD	Placebo (ng/ml), 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*

Table 9b. Mean Plasma Gamma Tocotrienols Levels vs placebo

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

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

Table 9c. Mean Plasma Delta Tocotrienols Levels vs placebo

**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.

doi.org/10.32388/GL22XT.2

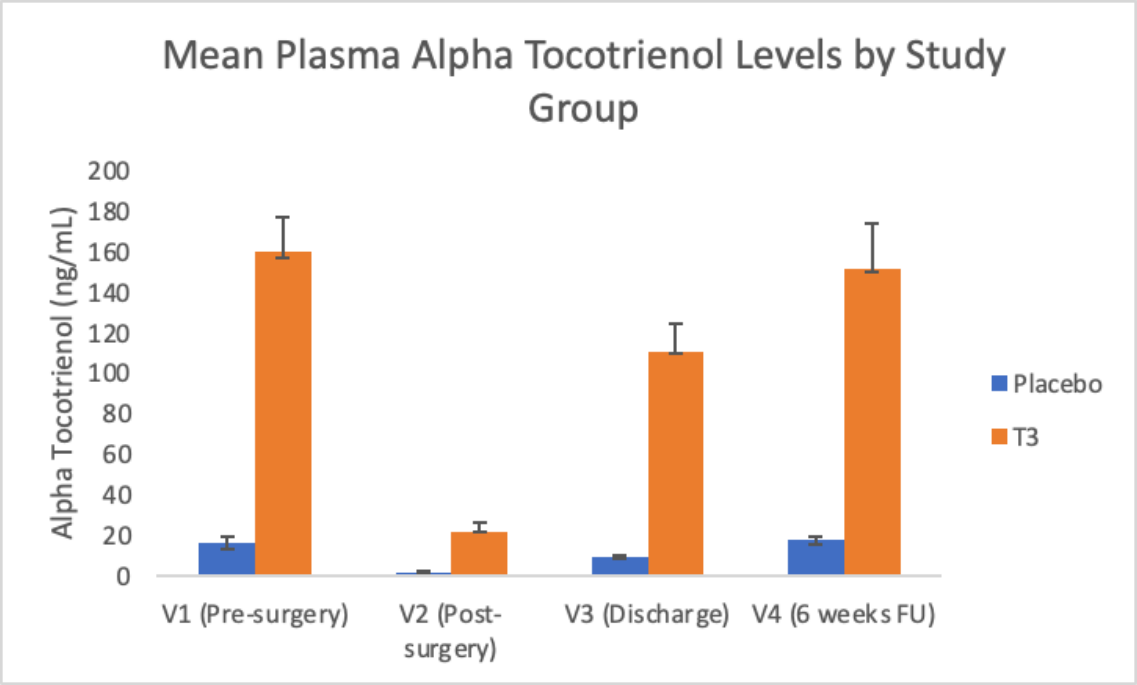


Figure 3a. Levels of alpha-tocotrienol at pre-surgery, post-surgery, discharge, and six-week follow up visit.

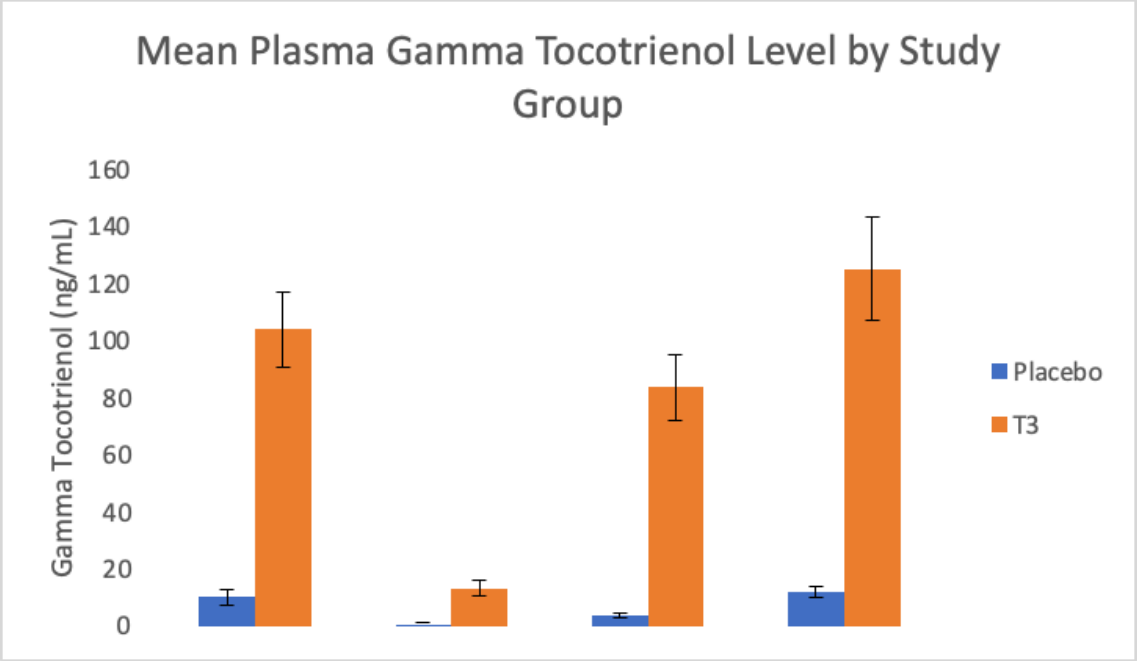


Figure 3b. Levels of gamma-tocotrienol at pre-surgery, post-surgery, discharge, and six-week follow up visit.

doi.org/10.32388/GL22XT.2

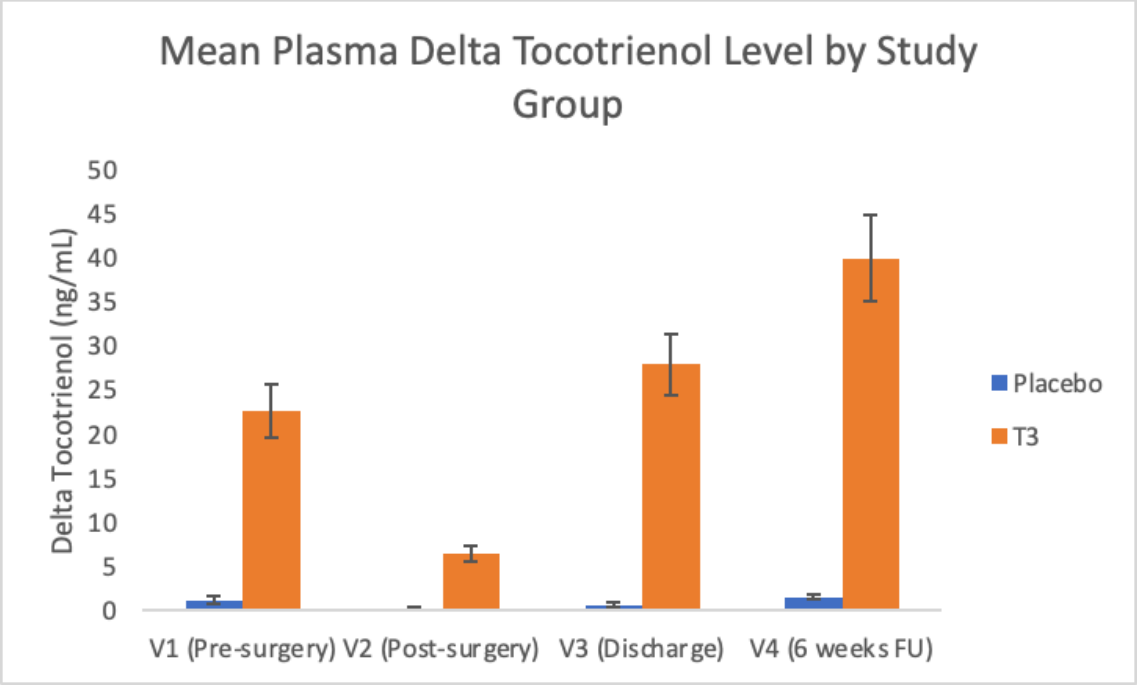


Figure 3c. Levels of delta-tocotrienol at pre-surgery, post-surgery, discharge, and six-week follow up visit.

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). Essentially, 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.

Similarly in assessing the quality of life, we used another instrument: the Nottingham Health Profile (NHP) – Part I. 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 other circumstances, SF-36 may show greater responsivity to treatment.[57]

To show whether there were any changes in the quality of life of patients, we have done repeated measures ANOVA test on these two instruments. Table 10 below indicates the results of this repeated measures ANOVA.

Variables	Timepoints	Tocotrienol	Placebo	F stat. (df)[a]	*p*-value
		Mean (SD)	Mean (SD)		
SF36 (overall health)	Pre	68.73 (10.63)	71.32 (13.00)	1.655 (2, 218)	0.192
	Discharge	72.53 (13.15)	73.63 (12.34)		
	Follow-up	81.27 (14.78)	80.05 (16.09)		
SF36 (physical health)	Pre	64.22 (11.52)	66.77 (13.73)	1.390 (2, 218)	0.250
	Discharge	67.47 (14.32)	67.71 (14.48)		
	Follow-up	76.11 (17.43)	74.76 (18.36)		
SF36 (mental health)	Pre	78.70 (8.65)	80.22 (10.41)	2.158 (2, 218)	0.124
	Discharge	82.71 (10.46)	84.50 (9.01)		
	Follow-up	88.36 (10.67)	87.00 (12.34)		
NHP	Pre	11.24 (7.04)	12.07 (6.89)	0.673 (2, 205)	0.511
	Discharge	17.90 (13.11)	18.61 (11.74)		
	Follow-up	8.05 (9.89)	10.79 (13.49)		

Table 10. Comparing mean scores for SF36 and NHP between Tocovid and placebo group

[a] *time-group interaction effect*

From Table 10 above, there are no apparent differences in the quality of life of patients from both groups, Tocovid and placebo. We have also drawn graphical descriptions below to illustrate the mean

scores for SF-36 between Tocovid and placebo groups at three-time point.

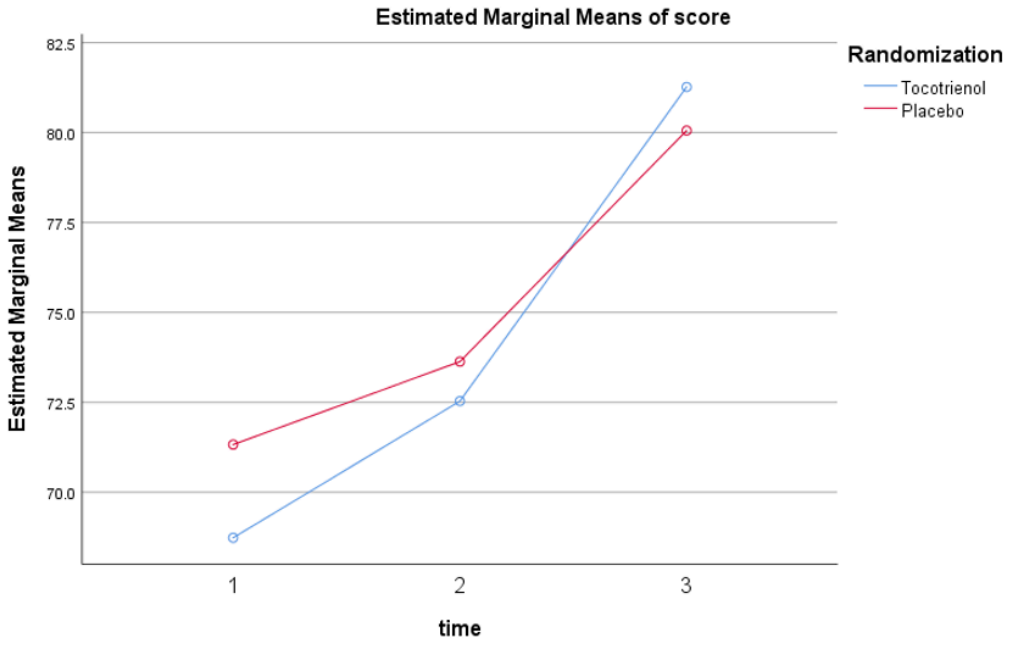


Figure 4. Comparing mean scores for total SF-36 between Tocovid and placebo groups at 3-timepoint.

The subsequent graphical illustrations as in Figure 5 and 6 below, describe the mean scores for physical health and the mean scores for mental health in SF-36 between Tocovid and placebo groups.

doi.org/10.32388/GL22XT.2

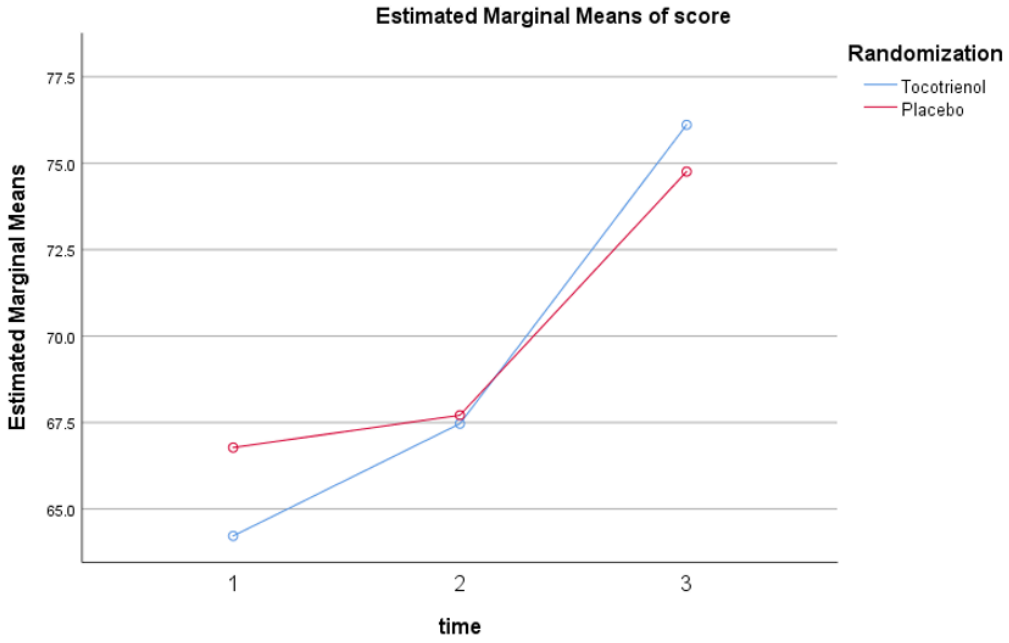


Figure 5. Comparing mean scores for physical health in SF-36 between Tocovid and placebo groups at 3-timepoint.

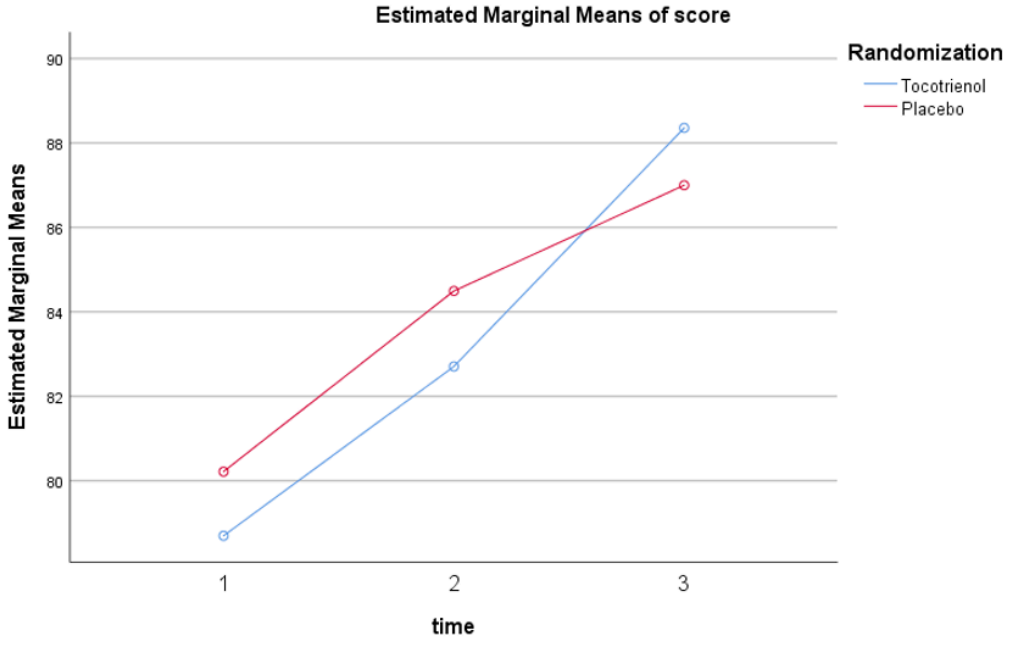


Figure 6. Comparing mean scores for mental health in SF-36 between tocotrienol and placebo groups in 3 timepoints.

doi.org/10.32388/GL22XT.2

The graphical illustration below meanwhile, illustrates the mean scores of NHP between Tocovid and placebo groups at three-time point.

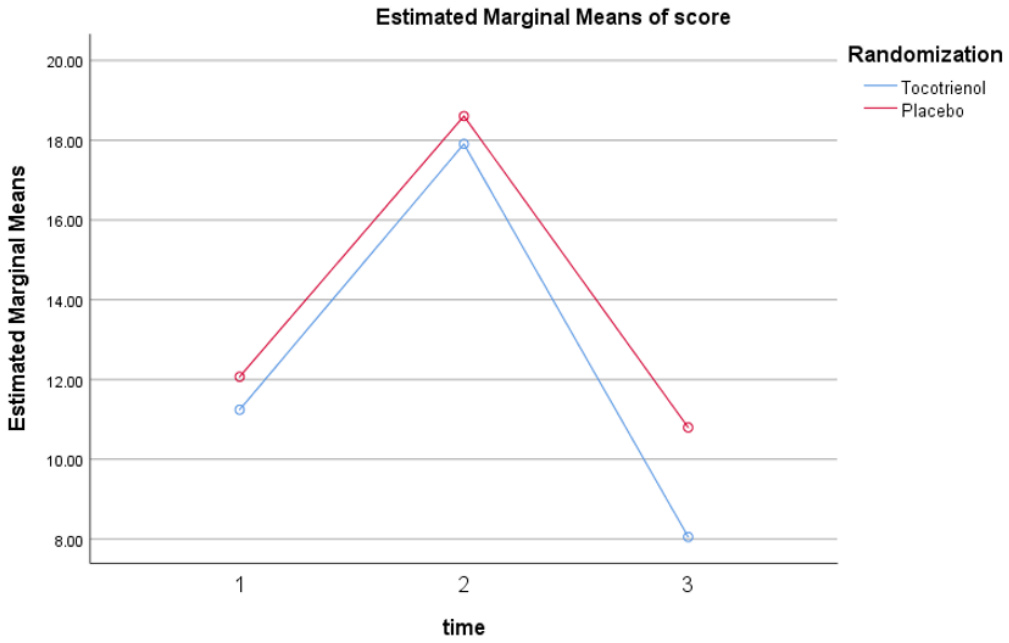


Figure 7. Comparing mean scores for NHP between Tocovid and placebo groups in 3 timepoints.

Considering that there were no significant difference when looking at the total score of SF-36, we performed an individual analysis according to the different domains. The table below describes the results.

doi.org/10.32388/GL22XT.2

SF36 Domains	Timepoints	Tocotrienol	Placebo	F stat. (df)[a]	*p*-value
		Mean (SD)	Mean (SD)		
Physical Functioning	Pre	63.85 (17.52)	62.79 (18.84)	0.811 (2, 218)	0.445
	Discharge	61.97 (28.39)	57.39 (27.79)		
	Follow-up	70.37 (19.83)	70.00 (23.70)		
Role Physical	Pre	22.25 (37.63)	38.53 (46.96)	3.382 (2, 218)	0.035*
	Discharge	36.24 (45.19)	42.20 (48.19)		
	Follow-up	67.43 (43.24)	64.90 (44.89)		
Role Emotional	Pre	51.24 (31.38)	62.46 (34.85)	4.364 (2, 218)	0.013*
	Discharge	65.12 (35.41)	71.77 (34.29)		
	Follow-up	92.90 (24.14)	89.19 (26.65)		
Vitality	Pre	94.68 (12.37)	93.69 (11.13)	0.377 (2, 218)	0.686
	Discharge	88.11 (14.98)	88.29 (15.89)		
	Follow-up	88.21 (14.09)	86.44 (15.90)		
Mental Health	Pre	94.09 (8.85)	91.49 (13.85)	0.414 (2, 218)	0.661
	Discharge	95.89 (7.35)	94.92 (9.17)		
	Follow-up	95.78 (7.75)	94.16 (10.91)		
Social Functioning	Pre	84.14 (14.46)	82.39 (17.78)	0.850 (2, 218)	0.428
	Discharge	80.90 (20.82)	83.52 (16.84)		
	Follow-up	80.56 (24.49)	82.50 (24.55)		
Bodily Pain	Pre	74.61 (17.18)	73.06 (18.87)	0.055 (2, 218)	0.947
	Discharge	71.95 (18.19)	71.06 (19.99)		
	Follow-up	73.92 (21.45)	73.45 (20.64)		
General Health	Pre	68.15 (17.70)	68.87 (18.70)	0.471 (2, 218)	0.625
	Discharge	81.15 (14.49)	81.98 (13.92)		
	Follow-up	82.82 (15.59)	81.31 (16.85)		

Table 11. Comparing mean scores for SF-36 according to domains between tocotrienol and placebo group.

[a] *time-group interaction effect*

**p-value significant at <0.05*

The above table clearly shows that there were statistically significant difference in both the role physical and role emotional domains in SF-36. Role physical basically measures limitations in various roles, including work and daily activities, while role emotional measures role limitations due to mental health difficulties. However these differences were not huge enough to influence the entire domains in SF-36. This explains the absence of any noticeable significant difference in the overall results in Table 10.

For the analysis which yielded statistically significant difference in the above table namely role physical and role emotional, we performed a post hoc test to identify exactly which groups differ from each other. Below are the results from our post hoc test in both Table 12 and 13.

(I) time	(J) time	Mean difference (I-J)	Std. Error	Sig	95% Confidence	
					Lower bound	Upper bound
Pre	Discharge	-8.830*	3.041	0.012	-16.166	-1.494
	Follow-up	-35.780*	3.935	0.000	-45.275	-26.285
Discharge	Pre	8.830*	3.041	0.012	1.494	16.166
	Follow-up	-26.950*	3.823	0.000	-36.175	-17.724
Follow-up	Pre	35.780*	3.935	0.000	26.285	45.274
	Discharge	26.950*	3.823	0.000	17.724	36.175

Table 12. Post hoc test on Role Physical in SF-36.

**mean difference is significant at <0.05 using Bonferroni comparison*

doi.org/10.32388/GL22XT.2

(I) time	(J) time	Mean difference (I-J)	Std. Error	Sig	95% Confidence	
					Lower bound	Upper bound
Pre	Discharge	-11.599*	2.478	0.000	-17.578	-5.620
	Follow-up	-34.197*	2.709	0.000	-40.733	-27.660
Discharge	Pre	11.599*	2.478	0.000	5.620	17.578
	Follow-up	-22.598*	2.580	0.000	-28.823	-16.372
Follow-up	Pre	34.197*	2.709	0.000	27.660	40.733
	Discharge	22.598*	2.580	0.000	16.372	28.823

Table 13. Post hoc test on Role Emotional in SF-36.

**mean difference is significant at <0.05 using Bonferroni comparison*

We also performed an individual domain analysis in NHP to determine whether there were any statistically significant difference individually. The results are tabulated in Table 14 below.

NHP Domains	Timepoints	Tocotrienol	Placebo	F stat. (df)[a]	p-value
		Mean (SD)	Mean (SD)		
Energy Level	Pre	46.67 (24.91)	49.38 (26.38)	0.289 (2, 210)	0.749
	Discharge	44.13 (31.93)	45.77 (33.27)		
	Follow-up	15.07 (22.79)	20.48 (28.11)		
Pain	Pre	3.04 (12.49)	3.02 (10.86)	0.351 (2, 208)	0.704
	Discharge	11.51 (14.72)	13.55(13.68)		
	Follow-up	6.74 (13.16)	8.46 (17.05)		
Emotional Reactions	Pre	2.38 (7.24)	2.41 (8.41)	0.993 (2, 208)	0.371
	Discharge	2.98 (9.54)	2.41 (8.17)		
	Follow-up	1.42 (7.45)	2.92 (9.98)		
Sleep	Pre	13.09 (12.52)	13.48 (17.09)	3.036 (2, 210)	0.049*
	Discharge	26.74 (28.77)	32.68 (28.62)		
	Follow-up	10.72 (20.38)	22.09 (31.98)		
Social Isolation	Pre	1.11 (5.17)	0.84 (4.26)	2.363 (2, 209)	0.095
	Discharge	2.24 (10.79)	0.62 (3.61)		
	Follow-up	0.79 (4.04)	1.82 (9.55)		
Physical Mobility	Pre	1.75 (7.26)	3.12 (9.09)	0.569 (2, 209)	0.566
	Discharge	18.25 (20.84)	17.24 (18.03)		
	Follow-up	12.33 (19.62)	10.71 (18.59)		

Table 14. Comparing mean scores for NHP according to domains between Tocovid and placebo group.

[a] *time-group interaction effect*

**p-value significant at <0.05*

doi.org/10.32388/GL22XT.2

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.

Similarly we performed the post hoc test on the positive result from the table above and depicted below in Table 15.

(I) time	(J) time	Mean difference (I-J)	Std. Error	Sig	95% Confidence	
					Lower bound	Upper bound
Pre	Discharge	-16.423*	2.043	0.000	-21.355	-11.492
	Follow-up	-3.122	2.041	0.383	-8.047	1.803
Discharge	Pre	16.423*	2.043	0.000	11.492	21.355
	Follow-up	13.301*	2.561	0.000	7.121	19.482
Follow-up	Pre	3.122	2.041	0.383	-1.803	8.047
	Discharge	-13.301*	2.561	0.000	-19.482	-7.121

Table 15. Post hoc test on Sleep in NHP.

**mean difference is significant at <0.05 using Bonferroni comparison*

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 peroxyl 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 a 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 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, 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 α-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 judgement 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. To remove attrition bias, analysis of data uses the intention-to-treat (ITT) analysis. Considering the actual attrition rate was 9.56% which was less than 20% as initially predicted when calculating the sample size, the slightly overpowered sample size was a bias. An overpowered study is considered a waste in resources but since the attrition rate was 9.56% in our study, it was a mere 10.44% extra in the sample size calculation.

9.0 Conclusion

This double-blind, randomised controlled trial among CAD patients undergoing isolated CABG or CABG and valve surgery took three years to complete at the National Heart Institute, a centre of excellence in Kuala Lumpur,. The most important lesson learnt from this study is 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 it to the maintenance level. Although Tocovid that comprises mainly of tocotrienols, an isomer of vitamin E, was not effective enough in our study to prevent the occurrence of POAF after CABG, this can be attributed 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 reduced 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, their HRQOL improved in terms of role physical that measures limitations in various roles, including work and daily activities, and role emotional that measures role limitations due to mental health difficulties as measured by SF-36 instruments; moreover, they had a better quality of sleep after discharge from the hospital as proven from the Nottingham Health Profile analysis.

10.0 Future Directions

We have a few recommendations to ensure that this research is replicable if not 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 formulations; 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: Does Tocovid, a Tocotrienol-rich Vitamin E, Mitigate Postoperative Atrial Fibrillation after Coronary Artery Bypass Grafting (CABG) Surgery? A Single-Centre Double-blind Randomised Controlled Trial.

Link: https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/DBAZ7C

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: Raw Data – SF-36 & NHP Scores

Set 6: Output Data – Repeated Measures ANOVA

11.5 Competing interests

The authors declare that they have no competing interests.

11.6 Funding

This project was funded by HOVID Berhad: MMRD-MS-1801 and Malaysian Palm Oil Berhad (MPOB): MMRD-MS-2001. However, the funders had no role in the design of the project nor in the preparation of this manuscript.

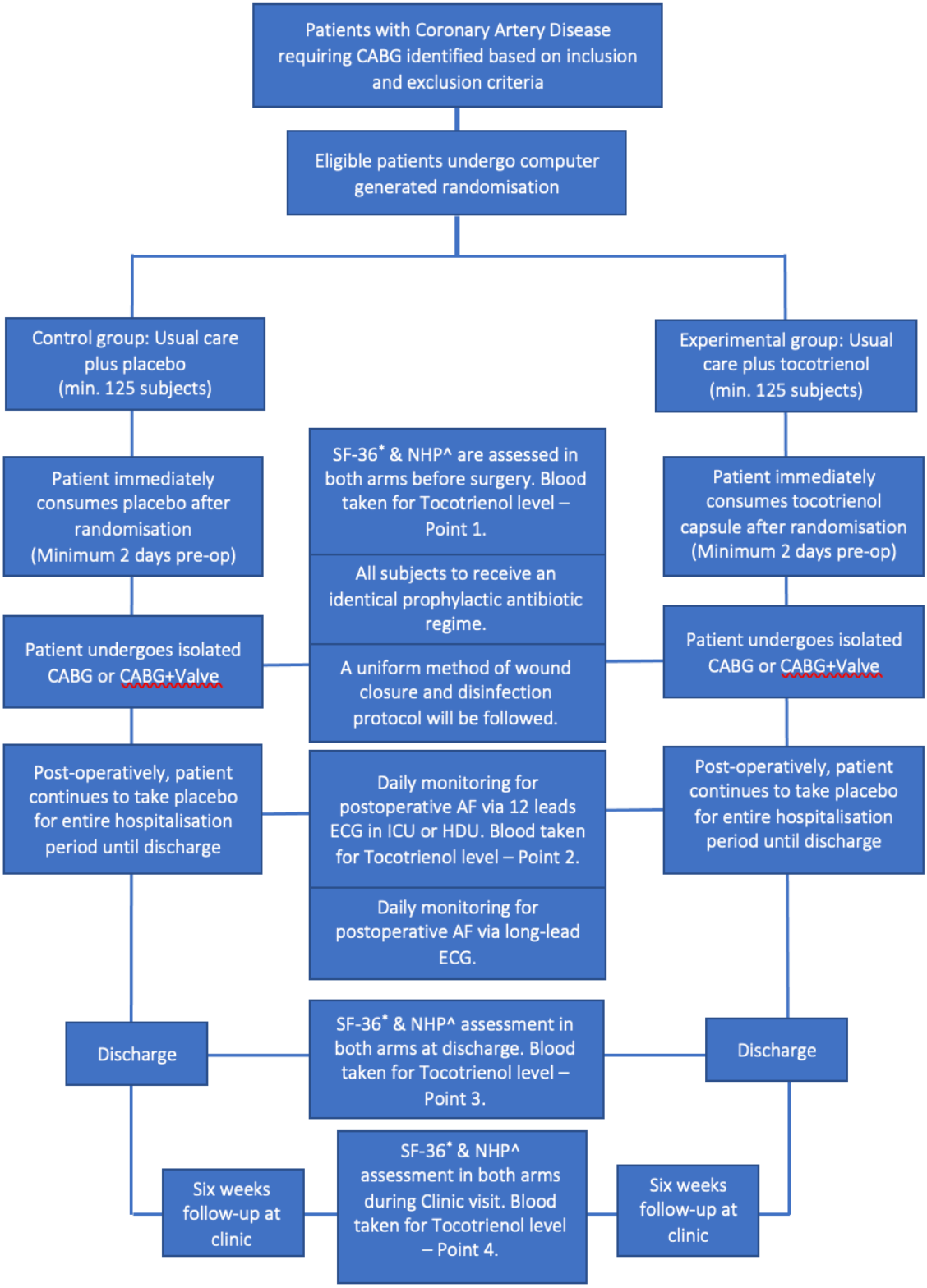
11.7 Authors' contributions

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; Nordin RB & Smith J: Project Administration, Supervision, Validation, Writing – Review & Editing

11.8 Acknowledgements

The authors would like to extend their heartfelt gratitude to Madam Irni Yusnida Mohd Rashid, Senior Study Coordinator, Clinical Research Department, National Heart Institute; the Clinical Research nurses; and our dedicated research assistants namely Mohd Ikhmal Othman, Anisah Zahirah Nor Aripin and Ahmad Muziru Idham Adnan for making this study possible. We also thank Nageeb Gounjaria for proofreading and editing the manuscript.

Appendix



doi.org/10.32388/GL22XT.2

Figure 2. Study Flow Chart

SF-36 - Short Form 36 Questionnaire

^NHP - Nottingham Health Profile Questionnaire

References

1. *Hernandez-Romero D, Vilchez JA, Lahoz A, Romero-Aniorte AI, Orenes-Pinero E, Caballero L, et al. High-sensitivity troponin T as a biomarker for the development of atrial fibrillation after cardiac surgery. Eur J Cardiothorac Surg 2014; 45:733-78.*
2. *Orenes-Pinero E, Montoro-Garcia S, Banarjee A, Valdes M, Lip GY, Martin F. Pre- and postoperative treatments for prevention of atrial fibrillation after cardiac surgery. Mini Rev Med Chem 2012; 12:1419-31.*
3. *Mostafa A, El-Haddad MA, Shenoy M, Tuliani T. Atrial fibrillation post cardiac bypass surgery. Avicenna J Med 2012; 2:65-70.*
4. *El-Chiami MF, Kilgo P, Thourani V, Lattouf OM, Delurgio DB, Guyton RA, et al. New-onset atrial fibrillation predicts long-term mortality after coronary artery bypass graft. J Am Coll Cardiol 2010; 55:1370-76.*
5. *Brooks DC, Schindler JL. Perioperative stroke: risk assessment, prevention and treatment. Curr Treat Options Cardiovasc Med 2014; 16:282.*
6. *Philip F, Becker M, Galla J, Blackstone E, Kapadia SR. Transient postoperative atrial fibrillation predicts short and long-term adverse events following CABG. Cardiovasc Diagn Ther 2014; 4:365-72.*
7. *Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery 2001; 135:1061-73.*
8. *Ferro CR, Oliveira DC, Nunes FP, Piegas LS. Postoperative atrial fibrillation after cardiac surgery. Arq Bras Cardiol 2009; 93:59-63.*
9. *Maesen B, Nijs J, Maessen J, Allessie M, Schotten U. Postoperative atrial fibrillation: a maze of mechanisms. Europace 2012; 14:159-74.*
10. *Anogeianaki A, Angelucci D, Cianchetti E, D'Alessandro M, Maccauro G, Saggini A, et al. Artheroscleros is: a classic inflammatory disease. Int J Immunopathol Pharmacol 2011; 24:817-25.*

11. ^Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and t reatment. An update. Eur J Cardiothorac Surg 2002; 21:232-44.

12. ^Ascione R, Lloyd CT, Underwood MJ, Lotto AA, Pitsis AA, Angelini GD, et al. Inflammatory response afte r coronary revascularization with or without cardiopulmonary bypass. Ann Thorac Surg 2000; 69: 1198 -1204.

13. ^Caputo M, Yeatman M, Narayan P, Marchetto G, Ascione R, Reeves BC, et al. Effect of off-pump corona ry surgery with right ventricular assist deise on organ function and inflammatory response: a randomis ed controlled trial. Ann Thorac Surg 2002; 74:2088-95.

14. ^Nesher N, Frolkis I, Vardi M, Sheinberg N, Bakir I, Caselman F et al. Higher levels of serum cytokines an d myocardial tissue markers during on-pump versus off-pump coronary artery bypass surgery. J Card S urg 2006; 395-402.

15. ^Ucar HI, Tok M, Atalar E, Dogan OF, Oc M, Farsak B, et al. Predictive significance of plasma levels of int erleukin-6 and high-sensitivity of C-reactive protein in atrial fibrillation after coronary artery bypass s urgery. Heart Surg Forum 2007; 10: E131-E135.

16. ^Elahi MMM< Flatman S, Matata BM. Tracing the origins of postoperative atrial fibrillation: the concep t of oxidative-stress-mediated myocardial injury phenomenon. Eur J Cardiovasc Prev Rehabil 2008; 15: 735-41.

17. ^Wu N, Xu B, Xiang Y, Wu L, Zhang Y, Ma X et al. Association of inflammatory factors with occurrence a nd recurrence of atrial fibrillation: a meta-analysis. Int J Cardiol 2013; 169: 62-72.

18. ^Giustarini D, Dallle-Donne I, Tsikas D, Rossi R. Oxidative stress and human diseases: origin, link, meas urement, mechanism, and biomarkers. Crit Rev Clin Lab Sci 2009; 46:241-81.

19. ^McDonald CI, Fraser JF, Coombes JS, Fung YI. Oxidative stress during extracorporeal circulation. Eur J C ardiothroc Surg 2014; 46:937-43.

20. ^Suleiman MS, Zacharowski K, Angelini GD. Inflammatory response and cardioprotection during open- heart surgery: the importance of anaesthetics. Br J Pharmacol 2008; 153:21-33.

21. a, bSuleiman MS, Hancock M, Shukia R, Rajakaruna C, Angelini GD. Cardioplegic strategies to protect th e hypertrophic heart during cardiac surgery. Perfusion 2011; 26(Supp 1): 48-56.

22. ^Kim YM, Guzik TJ, Zhang YH, Zhang MH, Kattach H, Ratnatunga C, et al. A myocardial Nox2 containin g NAD(P)H oxidase contributes to oxidative stress in human atrial fibrillation. Circ Res 2005; 97:629-3 6.

23. ^Kim YM, Kattach H, Ratnatunga C, Pillai R, Channon KM, Casadei B. Association of atrial nicotinamide adenine dinucleotide phosphate oxidase activity with the development of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 2008; 51:68-74.

24. ^Gopalan Y, Shuaib IB, Magosso E, Ansari MA, et al. Clinical Investigation of the Protective Effects of Pal m Vitamin E Tocotrienols On Brain White Matter. Stroke 2014; 45: 1422-28./}

25. ^Magosso E, Ansari MA, Gopalan Y, Shuhaib IB, et al. Tocotrienols for Normalisation of Hepatic Echoge nic Response In Non-Alcoholic Fatty Liver: A Randomised Placebo-Controlled Trial. Nutr J 2013; 12: 166 -74.

26. ^Mozaffarian D, Marchioli R, Gardner T, Ferrazzi P, O'Gara P, Latini R, Libby P, Lombardi F, Macchia A, Page R, Santini M, Tavazzi L, Tognoni G. The ω-3 Fatty Acids for Prevention of Post-Operative Atrial Fi brillation trial—rationale and design. Am Heart J. 2011; 162(1): 56-63.

27. ^Jenkinson C. The S-36 physical and mental health summary measures: an example of how to interpret scores. J Health Serv Res Policy 1998; 3: 92-6.

28. ^Lukkaranen H, Hentine M. Assessment and quality of life with the Nottingham Health Profile among women with coronary artery disease. Heart & Lung 1998; 3:188-99.

29. a, bDupont WD, Plummer WD. Power and sample size calculations: a review and computer program. Con trol Clinical Trials 1990; 11:116-28.

30. a, bDupont WD, Plummer WD. Power and sample size calculations for studies involving linear regressio n. Control Clinical Trials 1998; 19:589-601.

31. ^Wittes J. Sample size calculations for randomized controlled trials. Epidemiologic Reviews 2002; 24(1): 39-56.

32. a, bMusa AF, Chao ZQ, Low ZX, Soni T, Dillon J, Yuen KH, Nordin R. A retrospective study on atrial fibrill ation after coronary artery bypass grafting surgery at the National Heart Institute, Kuala Lumpur. F100 oResearch 2018; 7:164.

33. ^Saravanan P, Bridgewater B, West AL, O'Neill SC, Calder PC, Davidson NC. Omega-3 fatty acid supple mentation does not reduce risk of atrial fibrillation after coronary artery bypass surgery: a randomized, double-blind, placebo controlled clinical trial. Circulation: Arrythmia and Electrophysiology 2009; 3:46 -53.

34. ^Calo L, Bianconi L, Colivicchi F, Lamberti F, Loricchio ML, de Ruvo E, Meo A, Pandozi C, Staibano M, S antini M. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a r andomized, controlled trial. Journal of the American College of Cardiology 2005; 45: 1723–1728.

35. ^Echahidi N, Mohty D, Pibarot P, Despre's JP, O'Hara G, Champagne J, Philippon F, Daleau P, Voisine P, Mathieu P. Obesity and metabolic syndrome are independent risk factors for atrial fibrillation after coro nary artery bypass graft surgery. Circulation 2007; 116(11 Suppl):I-213: I-219.

36. ^Hogue Jr CW, Filos KS, Schuessler RB, Sundt TM. Sinus nodal function and risk for atrial fibrillation afte r coronary artery bypass graft surgery. Anesthesiology 2000; 92:1286–92.

37. ^George J, Rapsomaniki E, Pujades-Rodriguez M, Shah AD, Denaxas S, Herrett M, Smeeth L, Timmins A, Hemingway H. How does cardiovascular disease first present in women and men? Incidence of 12 car diovascular diseases in a contemporary cohort of 1,937,360 people. Circulation 2015; 132:1320-8.

38. ^Leening MJ, Ferket BS, Steyerberg EW, Kavousi M, Deckers JW, Nieboer D, Heeringa J, Portegies MLP, H ofman A, Ikram MA, Hunink MGM, Franco OH, Stricker BH, Witteman JCM, Roos-Hesselink JW. Sex diffe rences in lifetime risk and first manifestation of cardiovascular disease: prospective population based co hort study. BMJ 2014; 349:g5992.

39. ^Benedetto U, Gaudino M, Dimagli A, Gerry S, Gray A, Lees B et al. Postoperative atrial fibrillation and l ong-term risk of stroke after isolated coronary artery bypass graft surgery. Circulation 2020; 142:1320-29.

40. ^Ismail MF, El-Mahrouk AF, Hamouda TH, Radwan H, Hneef A, Jamjoon AA. Factors influencing posto perative atrial fibrillation in patients undergoing on-pump coronary artery bypass grafting, single cent er experience. J Cardiothorac Surg 2017; 12:40.

41. ^Lubitz SA, Yin X, Rienstra M, Schnabel RB, Walkey AJ, Magnani JW, Rahman F, McManus DD, Tadros T M, Levy D, et al. Long-term outcomes of secondary atrial fibrillation in the community: the Framingha m Heart Study. Circulation 2015; 131:1648–1655.

42. ^Creswell LL, Schuessler RB, Rosenbloom M, Cox JL. Hazards of postoperative atrial arrhythmias. Ann T horac Surg 1993; 56:539–49.

43. ^Greenberg JW, Lancaster TS, Schuessler SB, Melby SJ. Postoperative atrial fibrillation following cardiac surgery: A persistent complication. Eur J Cardiothorac Surg 2017; 52(4):665-72./}

44. ^Aranki SF, Shaw DP, Adams DH, Rizzo RJ, Couper GS, VanderVliet M, Collins JJ, Cohn LH, Burstin HR. Pr edictors of atrial fibrillation after coronary artery surgery. Circulation 1996; 94:390–7.

45. ^Almassi GH, Schowalter T, Nicolosi AC, Aggarwal A, Moritz TE, Henderson WG, Tarazi R, Shroyer AL, S ethi GK, Grover FL, Hammermeister KE. Atrial fibrillation after cardiac surgery. A major morbid event? Ann Surg 1997; 226:501–11.

46. ^Patel D, Gillinov MA, Natale A. Atrial fibrillation after cardiac surgery: Where are we now? Indian Paci ng Electrophysiol J 2008; 8(4):281-91.

47. ^The Asia-Pacific perspective: Redefining obesity and its treatment. IASO International Association for t he study of obesity; World Health Organization, Western Pacific Region. 2000.

48. ^WHO International: 2019; Link: 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 on 25 July 2021.

49. ^Labidi M, Baillot R, Donne B, Lacasse Y, Maltais F, Boulet LP. Pleural effusion following cardiac surger y: prevalence, risk factors, and clinical features. Chest 2009; 136(6):1604-11.

50. ^Brookes JDL, Williams M, Matthew M, Yan T, Bannon P. Pleural effusion post coronary artery bypass su rgery: association and complications. J Thorac Dis 2021; 13(2):1083-89.

51. a, bPapageorgiou E, Kostikas K, Kiropoulos T, Karetsi E, Mpatavanis G, Gourgoulianis KI. Increased oxid ative stress in exudative pleural effusions: a new marker in differentiation between exudates and transu dates. Chest 2005; 128(5):3291-7.

52. ^Light RW. Pleural effusions following cardiac injury and coronary artery bypass graft surgery. Semin R espir Crit Care Med 2001; 22(6):657-64.

53. ^St-Onge S, Perrault LP, Demers P, Boyle EM, Gillinov AM, Melby S. Pericardial blood as a trigger for po stoperative atrial fibrillation after cardiac surgery. Ann Thorac Surg 2018; 105:321-8.

54. ^Xiong T, Pu L, Ma YF, Zhu YL, Li H, Cui X, Li YX. Posterior pericardiotomy to prevent new-onset atrial f ibrillation after coronary artery bypass grafting: a systematic review and meta-analysis of 10 randomis ed controlled trials. J Cardiothorac Surg 2021; 16:233.

55. ^Klevsgård R, Fröberg BL, Risberg B, Hallberg IR. Nottingham Health Profile and Short-Form 36 Health Survey questionnaires in patients with chronic lower limb ischaemia. J Cardiovasc Surg 2002; 36(2):310 -7.

56. ^Meyer-Rosberg K, Burckhardt C, Huizar K, Kvanström A, Nordfors LO, Kristofferson A. A comparison of the SF-36 and Nottingham Health Profile in patients with chronic neuropathic pain. Eur J Pain 2001; 5 (4):391-403.

57. ^Beaton DE, Hogg-Johnson S, Bombardier C. Evaluating changes in health status: reliability and respon siveness of five generic health status measures in workers with musculoskeletal disorders. J Clin Epidem iol 1997; 50(1):79-93.

58. ^a, ^b*Alzoubi KH, Khabour OF, Rashid BA, Damaj IM, Salah HA. The neuroprotective effect of vitamin E on chronic sleep deprivation-induced memory impairment: the role of oxidative stress. Bahav Brain Res 20 12; 226(1):205-10.*

59. ^a, ^b*Hemilä H, Suonsyrjä T. Vitamin C for preventing atrial fibrillation in high risk patients: a systematic review and meta-analysis. BMC Cardiovasc Dis 2017; 17:49.*

60. ^^*Ballmer PE, Reinhart WH, Jordan P, Buhler E, Moser UK, Gey KF. Depletion of plasma vitamin C but not of vitamin E in response to cardiac operations [corrections in 1995; 110:1972]. J Thorac Cardiovasc Surg 1994; 108:311.*

61. ^a, ^b, ^c*Lassnigg A, Punz A, Barker R, Keznicki P, Manhart N, Roth E, Hesmayr M. Influence of intravenous vitamin E supplementation in cardiac surgery on oxidative stress : a double-blinded, randomized, contr olled study. Br J Anaesthesia 2003; 90:148-54.*

62. ^*. Rodemeister S, Duquesne M, Adolph M, Nohr D, Biesalski HK, Unertl K. Massive and long-lasting decr ease in vitamin C plasma levels as a consequence of extracorporeal circulation. Nutrition 2014; 30:673-8.*

63. ^a, ^b*Serbinova E, Kagan V, Han D, Packer L. Free radical recycling and intramembrane mobility in the an tioxidant properties of alpha-tocopherol and alpha-tocotrienol. Free Radic Biol Med 1991; 10:263-75.*

64. ^^*Sen CK, Khanna S, Roy S. Tocotrienols: Vitamin E beyond tocopherols. Life Sci 2006; 78(18):2088-98.*

65. ^^*Packer L, Weber SU, Rimbach G. Molecular aspects of alpha-tocotrienol antioxidant action and cell sig nalling. J Nutr 2001; 131:369S-373S.*

66. ^^*Suzuki YJ, Tsuchiya M, Wassall SR, Govil G, Kagan VE, Packer L. Structural and dynamic membrane pro perties of alpha-tocopherol and alpha-tocotrienol: implication to the molecular mechanism of their ant ioxidant potency. Biochemistry 1993; 32:10692-99.*

67. ^^*Ahsan H, Ahad A, Iqbal J, Siddiqui WA. Pharmacological potential of tocotrienols: a review. Nutr & Met ab 2014; 11:52.*

68. ^^*Lee SP, Mar GY, Ng LT. Effects of tocotrienol-rich fraction on exercise endurance capacity and oxidativ e stress in forced swimming rats. Eur J Appl Physiol 2009; 107(5):587-95.*

69. ^^*Newaz MA, Nawal NN. Effect of gamma-tocotrienol on blood pressure, lipid peroxidation and total an tioxidant status in spontaneously hypertensive rats (SHR). Clin Exp Hypertens 1999; 21(8):1297-1313.*

70. ^^*Hsieh TC, Wu JM. Suppression of cell proliferation and gene expression by combinatorial synergy of EG CG, resveratrol and gamma-tocotrienol in estrogen receptor-positive MCF-7 breast cancer cells. Int J O ncol 2008; 33(4):851-59.*

71. ^Adam A, Marzuki A, Ngah WZ, Top GM. Nitrofurantoin-induced hepatic and pulmonary biochemical c hanges in mice fed different vitamin E doses. Pharmacol Toxicol 1996; 79(6):334-39.

72. ^Renuka Devi R, Arumughan C: Antiradical efficacy of phytochemical extracts from defatted rice bran. F ood Chem Toxicol. 2007, 45 (10): 2014-2021.

73. ^Ong FB, Wan Ngah WZ, Shamaan NA, Md Top AG, Marzuki A, Khalid AK. Glutathione S-transferase an d gamma-glutamyl transpeptidase activities in cultured rat hepatocytes treated with tocotrienol and to copherol. Comp Biochem Physiol Part C Pharmacol Toxicol Endocrinol. 1993; 106(1):237-40.

74. ^Palozza P, Verdecchia S, Avanzi L, Vertuani S, Serini S, Iannone A, Manfredini S. Comparative antioxid ant activity of tocotrienols and the novel chromanyl-polyisoprenyl molecule FeAox-6 in isolated memb ranes and intact cells. Mol Cell Biochem 2006; 287(1–2):21-32.

75. ^Osakada F, Hashino A, Kume T, Katsuki H, Kaneko S, Akaike A. Alpha-tocotrienol provides the most po tent neuroprotection among vitamin E analogues on cultured striatal neurons. Neuropharmacology 200 4; 47(6):904-15.

76. ^Wong SK, Kamisah Y, Mohamed N, Muhammad N, Masbah N, Fahami NAM, Mohamed IN, Shuid AN, Saad QM, Abdullah A, Mohamad NV, Ibrahim NR, Pang KL, Chow YY, Thong BKS, Subramaniam S, Chin KY. Potential Role of Tocotrienols on Non-Communicable Diseases: A Review of Current Evidence. Nutri ents 2020; 12(1):259.

77. ^Zhao L, Fang X, Marshall MR, Chung S. Regulation of obesity and metabolic complications by gamma and delta tocotrienols. Molecules 2016; 21:344.

78. ^Khor BH, Tiong HC, Tan SC, Wong SK, Chin KY, Karupiah T, Ima-Nirwana S, Gafor AHA. Effects of toco trienols supplementation on markers of inflammation and oxidative stress: A systematic review and me ta-analysis of randomized controlled trials. Plos One 2021; 14:56.

79. ^Gershengorn HB, Garland A. Patterns of daily costs differ for medical and surgical intensive care unit p atients. Ann Am Thorac Soc 2015; 12:1831-36.

80. ^Aung YN, Nur AM, Ismail A, Aljunid SM. Determining the cost and length of stay at Intensive Care Units and the factors influencing them in a teaching hospital in Malaysia. Econ Eval 2020; 21:149-58.

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.