Tocovid, a tocotrienol-rich vitamin E in preventing atrial fibrillation in post-coronary artery bypass grafting (CABG) surgery: A preliminary result

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Abstract

Introduction: Post-operative atrial fibrillation (POAF) is associated with poor outcome, increased resource utilisation, morbidity and mortality. Its pathogenesis is initiated by systemic inflammation and oxidative stress. It is hypothesised that a potent antioxidant and anti-inflammatory agent such as tocotrienol, an isomer of Vitamin E, could prevent POAF.

Aims: The aim of this study is to determine whether a potent antioxidative and anti-inflammatory agent, Tocovid, a tocotrienol-rich capsule, could reduce the incidence of POAF and affect the mortality and morbidity as well as the duration of ICU, HDU and hospital stay.

Methods: This study was planned as a prospective, randomised, controlled trial with parallel groups. The control group received placebo containing palm superolein while the treatment group received Tocovid capsules. We investigated the incidence of POAF, the length of hospital stay (LoHS) after surgery and the health-related quality of life (HRQoL).

Results: The recruitment started in January 2019 but the preliminary results are unblinded since the study is still ongoing. 202 patients have been recruited out of a target sample size of 250 as of January 2021. About 75% have completed the study and 6.4% were either lost during follow-up or withdrawn; 4% of them died. The mean age group was 61.44 ± 7.30 with no statistical difference between them, with males having a preponderance for AF. The incidence rate of POAF was 24.36% and the mean time for developing POAF was 55.38 ± 29.9 hours post-CABG. Obesity is not a predictive factor. No statistically significant difference was observed when comparing left atrial size, NYHA group, ejection fraction and the premorbid history. The mean cross-clamp time was 71 ± 34 minutes and the mean bypass time was 95 ± 46 minutes, with no statistical difference. There was a three-fold increase in death among patients with POAF (p=0.008) and an increase in the duration of ICU stay (p=0.01), the total duration of hospital stay (p=0.04) and reintubation (p=0.045).

Conclusion: A relatively lower incidence rate of POAF was noted though the study is still ongoing. It remains to be seen if our prophylactic intervention using Tocovid would reduce the incidence of AF.

1.0 Introduction

Post-operative Atrial fibrillation (POAF) following cardiac surgery is the most common heart arrhythmia; it occurs in about 25% of patients after isolated CABG but can double to between 40%-50% in combined CABG and valve surgery. In our own retrospective study² conducted on post-CABG patients at the National Heart Institute (IJN), Kuala Lumpur, it was demonstrated that patients who developed POAF had a prolonged Intensive Care Unit (ICU) stay, High Dependency Unit (HDU) stay and total hospital stay, with a concomitant accretion in resource utilisation. There was also a six-fold surge in strokes and a three-fold increase in deaths during our study.
The arrhythmogenic foci of AF begin in the muscular sleeves of the pulmonary veins. However, current evidence suggests that the pathogenesis of POAF is multifactorial, with inflammation and oxidative stress playing important roles. Oxidative stress results from excessive reactive oxygen species (ROS-) that are involved in multiple pathological processes; these radicals are released during cardiac surgery. Extracorporeal circulation during CABG also increases oxidative stress. CABG causes ischaemic reperfusion that stimulates the production of these free radicals, leading to the depletion of endogenous antioxidants.

At present, guidelines exist in Europe and the USA on the pharmacological prophylaxis and management of POAF. However, such therapies are subject to a number of limitations such as toxicity and pro-arrhythmogenicity. Thanks to antioxidant vitamins, we now have a better understanding of the role of oxidative stress in the promotion of POAF. Carnes et al demonstrated a reduction in the incidence of POAF following antioxidant vitamin C therapy while in their meta-analysis, Harling et al demonstrated a reduction in both the ICU and overall hospital stay in the antioxidant group compared to the controls. Similarly, after conducting an extensive MEDLINE and EMBASE search, Rasoli et al concluded that antioxidant vitamins have a role in the risk reduction of POAF. It cannot be overlooked that the weak antioxidant effects of both vitamins C and E had an impact on their study.

All previous research on vitamin E used tocopherols instead of tocotrienols which are proven to possess a more potent antioxidant activity. Tocotrienols also have the ability to scavenge peroxyl radicals in liposomes besides showing anti-inflammatory properties by inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase). The HMG-CoA reductase inhibitory effect of tocotrienols have been established in several previous in-vitro and in-vivo studies. Tocotrienols have also demonstrated a post-transcriptional suppression of HMG-CoA reductase. Kumagai et al have shown that atorvastatin, another HMG-CoA reductase inhibitor, prevented the maintenance of AF by inhibiting inflammation in a canine model.

In view of emerging evidence on the HMG-CoA reductase inhibitory role in the incidence of AF and the established inhibitory properties of tocotrienols, we postulate that supplementation with Tocovid, a tocotrienol-rich Vitamin E, may confer therapeutic advantage in the safety endpoints of post-CABG. Consequently, we adopted this strategy with the hope that it would reduce the incidence of POAF and mitigate its deleterious outcomes.

2.0 Aims

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

3.0 Methods
3.1 Study design

We planned this study as a prospective, randomised, controlled trial with parallel groups. The main goal was to assess the effect of Tocovid on the occurrence of POAF. The study protocol was approved by the National Heart Institute Ethics Committee (IJNREC). IJNREC also served as the data safety committee. We obtained a similar approval from the Monash University Human Research Ethics Committee (MUHREC).

We recruited all patients admitted for CABG or CABG and Valve surgery. The IJN's CABG pathway has a 72-hour maximum admission time prior to surgery which was deemed adequate for a minimal treatment duration with Tocovid before CABG.

We assigned the eligible patients to one of the two study arms through a computer-generated randomisation list:

1) Control group with standard care plus palm superolein as placebo, or

2) Treatment group with standard care plus Tocovid.

Immediately after randomisation at least two days prior to surgery, we administered either Tocovid in two divided doses of 200mg per day or placebo. Hovid Berhad produces and markets Tocovid as Tocovid Suprabio, with each 200mg soft-gel capsule containing 61.52mg alpha-Tocotrienol, 112.80mg gamma-Tocotrienol, 25.68mg delta-Tocotrienol and 91.60IU alpha-tocopherol. We continued this regime for a minimum of five days after surgery until the follow-up visit at six weeks after discharge.

We estimated the dosage of Tocovid based on the regime used by Olaf Stanger et al which consisted of three ampoules of 45IE Vitamin E; this is equivalent to 30mg per ampoule or 90mg in total. Since the oral preparation of Tocovid has a lower and incomplete absorption compared to IV, we decided on a higher dosing. In fact, the bioavailability of oral administration can be as low as 10–30%. Given that many other clinical studies used 400mg daily without any adverse effects, we decided on the same dosing.

The treatment was continued until the patient was discharged. Compliance was monitored by the cardiothoracic ward nurses. Blood was taken for tocotrienol level testing pre-operatively on admission: at day-4 post-op, just before discharge and during the first follow-up six weeks later – the termination date of the study. After discharge, all patients were asked to report to the outpatient department of our institution in case of any relevant symptoms. ECG was also be taken at follow-up. All POAF episodes were treated under the direction of the attending cardiothoracic surgeon.

For the study flow chart, see attachment: Fig. 1

3.2 Inclusion and Exclusion Criteria

Inclusion Criteria:
Males or females more than 18 years of age.

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

Exclusion Criteria:

Any urgent or emergency surgery and off-pump surgery.

Poor LV (EF < 30%).

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

Long-term corticosteroid treatment.

Participation in other clinical trial within the previous three months.

Supplementation with Vitamin E or other potent antioxidants within one month prior to randomisation.

3.3 Study End Points

The primary end point is the occurrence of POAF similar to any electrocardiographically confirmed episode of AF/Atrial Flutter (AFL) post CABG of at least 30-second duration. If a shorter duration ECG was available, we diagnosed AF/AFL on the arrhythmia present at onset or termination.

The secondary end points are the length of hospital stay (LoHS) post-surgery which include ICU and HDU stay and the health-related quality of life (HRQoL) of patients; the latter will be determined at the end of the study using the validated Malay Short-Form 36 Questionnaire (SF-36) and Nottingham Health Profile Part I. The attending surgeon blinded to treatment assignment adjudicated all the end points based on the clinical records and ECG tracings.

3.4 Sample size calculation

We used the PS Power and Sample Size Calculation Software for sample size calculation.

Calculation of sample size in the present study requires precise specification of the primary hypothesis of the study (Tocovid consumption reduces the incidence of POAF in subjects that had undergone CABG) and the method of analysis (using Relative Risk: RR). In addition, the study has taken into account the possibility of “loss to follow-up” (attrition bias) of subjects by analysing all subjects from the start to completion of the study according to the groups in which they were originally randomised [Intention-To-Treat (ITT) analysis]. To calculate the desired sample size, we used the PS Power and Sample Size Calculation Software.

In the present RCT, the estimated sample size for the primary end point (incidence of POAF) was computed on the basis of findings from a prior study by Musa et al\(^2\) who found the incidence of POAF at IJN to be 28.7%. This RCT was planned with experimental subjects and controls with one control(s) per
If the true relative risk of AF for experimental subjects relative to controls is 0.45, then using the PS Power and Sample Size Calculator\textsuperscript{30,31} with \(\alpha\) equivalent to 0.05 and power (1 - \(\beta\)) is 0.8, the estimated sample size is 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 was: 103 + .20 (103) X 2 = 250 subjects of which there will be 125 controls and 125 experimental subjects.

### 3.5 Statistical Analysis

We used SPSS version 24.0 for statistical analysis.

### 4.0 Ethical Consideration

The study was conducted in compliance with ethical principles outlined in the Malaysian Good Clinical Practice Guideline; it also abides by the Helsinki Declaration revised in 2013. Written informed consent was obtained from potential study participants and/or legally acceptable representative prior to their enrolment into the study.

Ethical approval was obtained from both the National Heart Institute Research Ethics Committee (IJNREC/201/2017), the Monash University Human Research Ethics Committee (2017-9227-10263) and the National Pharmaceutical Regulatory Agency (NPRA) (CTX-180304). The study was also registered with the National Medical Research Register (NMRR-17-1994-34963) and the US National Library of Medicine - Clinical Trials (NCT03807037).

### 5.0 Results

The recruitment of patients for this study started on 21st January 2019. The current results are based on patients recruited as of 31st January 2021 and the research is ongoing since our target sample size is 250 patients. However, the tabulated data are based on details extracted from both the IJN track care and the patients’ medical records (PMR). This ongoing process is dependent on the efficiency of the IJN Record Office in providing the PMRs since not all information could be obtained from the computer track care system.

The total number of patients recruited as of 31st January 2021 is 202 patients (80.8% recruitment rate). Of these, 151 (60.4%) have completed the study, that is, they have at least been followed up to their first post-operative clinic visit. There are currently 28 patients who have yet to complete their enrolment in this study. They include patients who have been discharged but are awaiting their first post-operative clinic appointment. Five patients were lost during follow-up and ten patients withdrew from the study. There were eight deaths, equivalent to 3.96% of the study population; this is slightly lower as compared to the study we conducted in 2018. Among a total of 1718 CABG patients who were operated for the whole year of 2016, the mortality rate was 4.66%. In other words, our current overall attrition rate stands at 12.4%. 18
serious adverse events (SAE) were reported but none were related to the investigational product. These were mainly due to surgical site infection, pericardial tamponade and pleural effusion.

We would like to stress that, at this point in time, the statistical analyses conducted on the results of our study below were limited to the non-unblinded data set since the study is still ongoing. Hence, the analyses compared the post-operative AF group against the non-POAF group – not the group that received Tocovid versus the control group; this analysis will only be done at the end of the study when the groups will be unblinded. It is also noteworthy that the current analyses were done on patients with complete information as traced from the track care and the medical records. Consequently, we expect be variations with regard to the total number of patients analysed in each section.

5.1 Patients’ characteristics

Referring to Table 1 below on the characteristics of our sample population, we found that the study sample follows a normal distribution with a minimum and maximum age of 39 and 85 respectively. As expected, the majority of the patients were Malays (69.8%) followed by Chinese (3.7%) who are in fact under-represented if we were to consider the Malaysian cohort; 8.5% were Indians who are actually over-represented in our study sample.
### Table 1
Characteristics of the sample population in our study and their association with POAF.

| Demographic | Total          | Non-POAF group, n (%) | POAF group, n (%) | p-value |
|-------------|----------------|-----------------------|-------------------|---------|
| Age (years) | 61.44 ± 7.30   | 61.30 ± 7.62          | 61.87 ± 6.24      | 0.68#   |
| Gender:     |                |                       |                   |         |
| Male        | 130            | 94 (72.31)            | 36 (27.69)        | 0.03*   |
| Female      | 26             | 24 (92.31)            | 2 (7.69)          |         |
| Population: |                |                       |                   | 0.94    |
| Malay       | 132            | 100 (75.8)            | 32 (24.2)         |         |
| Chinese     | 7              | 5 (71.4)              | 2 (28.6)          |         |
| Indian      | 16             | 12 (75)               | 4 (25)            |         |
| Other       | 1              | 1 (100)               | 0 (0)             |         |

# Test using Independent t-test

*p-value significant at 0.05 using the Chi-Square test

There was no statistically significant difference (p = 0.68) between the mean age group of patients with AF (61.87) to those without (61.30) though patients with POAF tended to be slightly older. This observation is at odds with existing literatures where advanced age is considered the most consistent risk factor for POAF, a condition attributed to a loss in myocardial fibres coupled with an increase in fibrosis and collagen deposition near the SA node in the atrium which alters the atrial electrical conductivity. One retrospective study with almost 15,000 patients over two decades revealed that the chance of developing POAF increases at a higher rate after the age of 55; those who are 72 or older are five times more likely to develop POAF than those who are 55 years old.

However, the current data analysis showed a statistically significant difference (p = 0.03) between males and females in developing POAF. Males (27.69%) tended to have a higher preponderance for this phenomenon compared to females (7.69%). This is in line with a study by Filardo G et al who showed over a nine-year study period that women had a statistically significant lower risk of developing POAF with an absolute difference of -5.3% (95% confidence interval CI, -10.5% to -0.6%).

Our current preliminary result also revealed no statistically significant difference between the various ethnic groups with respect to POAF. This differs from our earlier study that saw the Indian population, as compared to the other races, having a significantly lower odds of developing POAF. It also contrasted with a Singaporean study which found that, compared to Indians, Malays and Chinese were more prone to develop this condition post-CABG.

### 5.2 Post-operative AF (POAF) characteristics

Table 2 below refers to the characteristics of POAF. 38 of our study patients corresponding to 24.36% of the sample developed AF. This figure is slightly lower than in our previous study where 28.7% of patients developed POAF. However, this is an unblinded result and at this point in time, we do not know for certain
if Tocovid managed to lower down the POAF rate significantly. Indeed, this incidence rate is within the cited range in the literature that puts the POAF incidence range between 20% and 40%.

| Characteristics of POAF among 156 subjects |
|-------------------------------------------|
| **Characteristics of AF**                  | n* (%) | mean ± SD |
| Occurrence of POAF                        | 38 (24.36) |
| Time from surgery to POAF (minutes)       | 55.38 ± 29.9 |
| Duration (hours):                         |         |
| ≤48                                       | 13 (41.94) |
| >48                                       | 18 (58.06) |
| Number of episodes:                       |         |
| Single                                    | 17 (53.13) |
| Multiple                                  | 15 (46.87) |
| Atrial fibrillation on discharge          | 0 (0)    |

• Total n varies slightly for each item due to a small amount of missing data in each

The median time for the development of POAF was 54 hours after surgery, which was slightly delayed than the oft-cited 48 hours post-surgery. The mean time was 55.38 ± 29.9 hours post-CABG or on the third day after CABG. We also noticed that in our preliminary results, slightly more than half of the cases (58.06%) developed AF after more than 48 hours post-surgery. However, this was within the range cited by many literatures about POAF mainly occurring within the first week post-surgery at a median time of two days post-CABG. Moreover, slightly more than half of our study patients (53.13%) had a single episode of POAF while the remaining 46.87% had multiple episodes. Nonetheless, all of them were discharged with sinus rhythm.

5.3 Pre-operative characteristics

According to the WHO, Malaysia has the highest rate of obesity and overweight among Asian countries: about 65% of the female and 64% of the male population are either obese or overweight. Referring to our Table 3 below, it is therefore not surprising that 53.2% of the study sample was categorised as overweight and 27.56% as obese according to the Asian guidelines. However, obesity is not a predictive factor for POAF and we found no statistically significant difference between the groups. This does not conform to some literatures suggesting that obese patients have significant higher odds in developing POAF compared to non-obese ones. This suggestion of obesity as a significant independent predictor for postoperative AF is also supported by an earlier work of Sun et al.
Table 3
Association between POAF and pre-operative characteristics that were recorded.

| Pre-operative characteristic                  | Total*, n (%) | Non-POAF group, n (%) | POAF group, n (%) | p-value |
|----------------------------------------------|--------------|----------------------|------------------|---------|
| Body Mass Index (kg/m²)                      | 27.23 ± 4.61 | 27.43 ± 4.55         | 27.03 ± 5.20     | 0.50²   |
| <18.5                                        | 2 (1.29)     | 1 (50)               | 1 (50)           |         |
| 18.5–22.9                                    | 28 (17.95)   | 19 (67.90)           | 9 (32.10)        |         |
| 23-29.9                                      | 83 (53.20)   | 66 (79.50)           | 17 (20.50)       |         |
| ≥30                                          | 43 (27.56)   | 32 (74.40)           | 11 (25.60)       |         |
| New York Heart Functional Class:             |              |                      |                  | 0.57²   |
| NYHA I                                       | 58 (53.71)   | 43 (74.14)           | 15 (25.86)       |         |
| NYHA II                                      | 48 (44.44)   | 32 (66.70)           | 16 (33.30)       |         |
| NYHA III                                     | 2 (1.85)     | 1 (50)               | 1 (50)           |         |
| NYHA IV                                      | 0 (0)        | (0)                  | (0)              |         |
| Left ventricular Ejection Fraction           | 46.35 ± 15.82| 46.96 ± 15.26        | 44.87 ± 17.25    | 0.49ᵇ   |
| Left atrial size (mm)                        | 18.43 ± 5.48 | 18.11 ± 5.89         | 19.16 ± 4.43     | 0.10ᶜ   |
| Right atrial size (mm)                       | 13.83 ± 4.02 | 13.58 ± 3.99         | 14.36 ± 4.09     | 0.14ᶜ   |

*Test using Chi Square test

**Test using independent T-test

*Test using Mann-Whitney test

- Total n varies slightly for each item due to a small amount of missing data in each.

Since our study has omitted poor EF<30% based on our Exclusion Criteria, most of the patients in the study cohort belong to the relatively normal functional status with 53.71% of them in New York Heart Functional Class (NYHA) I and 44.44% in NYHA Class II. We found the mean left ventricular ejection fraction to be approximately 46%; we also noted that the POAF group has a poorer EF (about 45%) compared to the non-POAF group (about 47%). However, this was not statistically significant. Similarly, we observed no statistically significant difference between the POAF group that had a larger left atrial size compared to the non-POAF group. These two findings were at odds with some literatures that established a correlation between poor EF and left atrial size dilatation to the development of POAF.

5.4 Medical History
We analysed the pre-morbid history of our patients as shown in Table 4 below. We found that the majority of them had the three most common pre-morbid conditions: hypertension (82.76%), diabetes mellitus (70.09%), and hypercholesterolaemia (85.09%). However, no statistically significant difference between the groups was detected. Similarly, we analysed the history of chronic kidney disease which has been associated with POAF in a few literatures. Again, we found no significant difference between the two groups.

### Table 4
Association between POAF and underlying medical conditions on admission.

| Medical condition               | Total*, n (%) | Non-POAF group, n (%) | POAF group, n (%) | $\chi^2$ | p-value |
|---------------------------------|---------------|-----------------------|-------------------|---------|---------|
| COPD Yes                        | 2 (1.7)       | 2 (100)               | 0 (0)             | -       | 1.00#   |
| COPD No                         | 114 (98.3)    | 79 (69.3)             | 35 (30.7)         |         |         |
| Asthma: Yes                     | 1 (0.9)       | 1 (100)               | 0 (0)             | -       | 1.00#   |
| Asthma: No                      | 115 (99.1)    | 80 (69.6)             | 35 (30.4)         |         |         |
| Hypertension: Yes               | 96 (82.8)     | 67 (69.8)             | 29 (30.2)         | 0.000   | 0.97    |
| Hypertension: No                | 20 (17.2)     | 14 (70.0)             | 6 (30.0)          |         |         |
| Diabetes Mellitus: Yes          | 82 (70.1)     | 59 (72)               | 23 (28)           | 0.952   | 0.33    |
| Diabetes Mellitus: No           | 35 (29.9)     | 22 (62.9)             | 13 (37.1)         |         |         |
| Hypercholesterolemia: Yes       | 97 (85.1)     | 69 (71.1)             | 28 (28.90)        | 1.030   | 0.31    |
| Hypercholesterolemia: No        | 17 (14.9)     | 10 (58.8)             | 7 (41.2)          |         |         |
| Chronic kidney disease: Yes     | 15 (13.0)     | 10 (66.7)             | 5 (33.33)         | -       | 0.77#   |
| Chronic kidney disease: No      | 100 (87.0)    | 70 (70.0)             | 30 (30.0)         |         |         |
| Current or ex-smoker: Yes       | 63 (58.9)     | 41 (65.1)             | 22 (34.9)         | 6.074   | 0.014*  |
| Current or ex-smoker: No        | 44 (41.1)     | 38 (86.4)             | 6 (13.6)          |         |         |
| Alcohol intake: Yes             | 6 (6.1)       | 3 (50)                | 3 (50)            | -       | 0.173#  |
| Alcohol intake: No              | 93 (93.9)     | 70 (75.3)             | 23 (24.)          |         |         |

*Test using Fisher Exact Test

*p-value significant at $p < 0.05$ using Chi-Square test

- Total n varies slightly for each item due to a small amount of missing data in each. COPD: Chronic obstructive pulmonary disease
In our analysis on smoking habits, we observed that the current or ex-smoker group had a lower incidence of POAF compared to the non-smoker group, with a statistically significant difference ($p = 0.0014$). This is mirrored by another study that showed a statistically significant difference between the groups where smokers tended to have a lower incidence of POAF ($p < 0.05$). That study also uncovered that the postoperative complications incidence did not differ significantly among smoking status groups. Nevertheless, the researchers strongly recommended cessation of smoking for at least 4 weeks before surgery in order to improve post-operative outcomes and reduce the risk of post-operative pulmonary complications.

**5.5 Operative Details**

Since we have excluded Off-pump surgery in the Exclusion Criteria, and taking into account that IJN is an On-pump centre, we mainly performed isolated CABG (91.55%) while combined valve surgery was only 8.45% as depicted in Table 5 below. Only the mitral valve was involved in the combined valve surgery, with two-third being mitral valve repair and the other one-third consisting of mitral valve replacement. However, there was no statistically significant difference between them in terms of developing POAF.

### Table 5
Association between post-operative atrial fibrillation (POAF) and patient operative details. CABG, coronary bypass grafting.

| Operative details        | Total*, n (%) | Non-POAF group, n (%) | POAF group, n (%) | $p$-value |
|--------------------------|---------------|-----------------------|-------------------|-----------|
| Surgery type:            |               |                       |                   |           |
| CABG alone               | 130 (91.55)   | 96 (73.80)            | 34 (26.20)        | 0.59      |
| CABG + valve             | 12 (8.45)     | 8 (66.67)             | 4 (33.33)         |           |
| Bypass time (in minutes) | 95 ± 46       | 96 ± 57               | 94 ± 38           | 0.87      |
| Cross-clamp time (in mins) | 71 ± 34     | 70 ± 36               | 73 ± 31           | 0.81      |

* Total n varies slightly for each item due to a small amount of missing data in each

We observed that the mean cross-clamp time was 71 ± 34 minutes ranging from 22 to 244 minutes, and the mean bypass time was 95 ± 46 minutes ranging from 49 to 304 minutes. Similarly, there was no statistically significant difference between the two groups though it is an established fact that both cross-clamp and bypass time were associated with the development of POAF.

**5.6 Post-operative Outcomes**

The discussion on the post-operative outcome is perhaps the most intriguing where POAF has been associated with numerous adverse outcomes; that includes a two to four-fold increase in stroke, reoperation, infection, renal failure, respiratory complications and cerebral insults in addition to a two-fold increase in all-cause thirty-day mortality. While this might not be a direct correlation, it is certainly
contributory and plays a part in the increase in morbidity and mortality after cardiac surgery.\textsuperscript{58} Based on Table 6 below, the most significant association was the three-fold increase in deaths among patients with POAF ($p = 0.008$). The mortality rate in our study population stood at 3.96\% which was slightly lower than the mortality rate (around 4.66\%) in our earlier publication.\textsuperscript{34} However, our finding on the increase in mortality rate among POAF patients not only confirmed the previous literature findings but also the most recent paper by Emma Thorén et al that associated POAF with mortality even after adjustment for AF during follow-up.
Table 6
Association between POAF and post-operative outcomes in 156 subjects.

| Post-operative outcomes               | Total*, n (%) | Non-POAF group, n (%) | POAF group, n (%) | p-value |
|---------------------------------------|---------------|-----------------------|-------------------|---------|
| Stroke: Yes                           | 4 (4.0)       | 2 (50)                | 2 (50)            | 0.58    |
| No                                    | 97 (96.0)     | 69 (71.1)             | 28 (28.9)         |         |
| Sternal infection: Yes                | 3 (3.0)       | 3 (100)               | 0 (0)             | 0.55    |
| No                                    | 98 (97.0)     | 68 (69.4)             | 30 (30.6)         |         |
| Respiratory problems: Yes             | 6 (5.9)       | 3 (50)                | 3 (50)            | 0.36    |
| No                                    | 95 (94.1)     | 68 (71.6)             | 27 (28.4)         |         |
| Renal failure requiring dialysis: Yes | 5 (5.0)       | 4 (80)                | 1 (20)            | 1.00    |
| No                                    | 96 (95.0)     | 67 (69.8)             | 29 (30.2)         |         |
| Endocrine problems: Yes               | 1 (1.0)       | 1 (100.0)             | 0 (0)             | 1.00    |
| No                                    | 100 (99.0)    | 70 (70.0)             | 30 (30.0)         |         |
| Pleural effusion: Yes                 | 5 (5.0)       | 3 (60)                | 2 (40)            | 0.63    |
| No                                    | 96 (95.0)     | 68 (70.8)             | 28 (29.2)         |         |
| Cardiac Tamponade: Yes                | 14 (13.9)     | 13 (92.9)             | 1 (7.1)           | 0.06    |
| No                                    | 87 (86.1)     | 58 (66.7)             | 29 (33.3)         |         |
| Fever: Yes                            | 6 (5.9)       | 4 (66.7)              | 2 (33.3)          | 1.00    |
| No                                    | 95 (94.1)     | 67 (70.5)             | 28 (29.5)         |         |
| Hyperkalaemia: Yes                    | 4 (4.0)       | 3 (75)                | 1 (25)            | 1.00    |
| No                                    | 97 (96.0)     | 68 (70.1)             | 29 (29.9)         |         |
| Others: Yes                           | 3 (3.0)       | 1 (33.33)             | 2 (66.7)          | 0.21    |
| No                                    | 98 (97.0)     | 70 (71.4)             | 28 (28.6)         |         |
| Death: Yes                            | 8 (7.9)       | 2 (25)                | 6 (75)            | 0.008*  |
| No                                    | 93 (92.1)     | 69 (74.2)             | 24 (25.8)         |         |

* p-value significant at < 0.05 using the Fisher Exact test

- Others: Low blood pressure, Multiple premature ventricular complexes
- Total n varies slightly for each item due to a small amount of missing data in each
We also looked at all the other common complications such as stroke, sternal wound infection, respiratory problems, renal failure requiring dialysis, endocrine problems, pleural effusion, cardiac tamponade, fever and hyperkalaemia; none of them were significantly correlated.

### 5.7 Postoperative Stay

Studies elsewhere have shown that POAF have a prolonged ICU stay, with an additional two to five days in the hospital. In the US, patients who develop POAF would be utilising an average of USD10,000 – USD20,000 in additional hospital treatment costs. Furthermore, the healthcare expenditures related to the management of POAF in the US were estimated at over USD 1 billion per year. Another study conducted at the Instituto de Cardiologia, Bogota DC, Colombia, also demonstrated that the occurrence of POAF is associated with a significant increase in the utilisation of hospital resources and in direct cost in patient management. Unfortunately, to date, no study has been conducted in Malaysia on the financial burden in managing POAF patients. Nevertheless, we believe that the results would not be much different.

| Duration                    | Total, median ± IQR / n (%) | Non-POAF group, median ± IQR / n (%) | POAF group, median ± IQR / n (%) | p-value |
|-----------------------------|------------------------------|-------------------------------------|----------------------------------|---------|
| Duration in ICU (min)       | 2767.50 ± 3927              | 1742 ± 2354                         | 3847.50 ± 4773                  | 0.01*   |
| Duration in HDU (min)       | 1522.50 ± 1584              | 1480 ± 1514                         | 1755 ± 2743                     | 0.33    |
| Duration of ventilation (min) | 1187.50 ± 442              | 1157 ± 391                          | 1230 ± 875                      | 0.22    |
| Duration of hosp. stay (day)| 8.0 ± 3                     | 7.0 ± 3                             | 9.0 ± 3                         | 0.04*   |
| Reintubation:Yes            | 4 (2.6)                     | 1 (25)                              | 3 (75)                          | 0.045** |
| No                          | 152 (97.4)                  | 117 (77.0)                          | 35 (23.0)                       |         |

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

** p-value significant at < 0.05 using Fisher Exact test

- Total n varies slightly for each item due to a small amount of missing data in each

The results tabulated in Table 7 above reflect what we actually expected. We noted a statistically significant difference in the mean duration of ICU stay (p = 0.01), the total duration of hospital stay (p = 0.04) and reintubation (p = 0.045). Our findings were similar to one study that collected and evaluated data from 28 centres across the United States, Italy and Argentina via multivariate adjusted models. The researchers found that the occurrence of POAF was significantly correlated with an increase in resource
utilisation, including length of stay in ICU and total hospital stay. In another study that compared on-pump versus off-pump surgery, a statistically significant higher rate of reintubation and adverse outcome with POAF was observed.

6.0 Discussion

Without doubt, atrial fibrillation after cardiac surgery is the most common complication in 24.36% of our study population. This is definitely lower than in our previous study\textsuperscript{2} that reported an incidence rate of 28.7%. Nonetheless, this current study is still ongoing and the results will definitely change. What we anticipate even more eagerly is whether our prophylactic intervention using Tocovid, a tocotrienol-rich compound, would reduce the incidence of AF in the study arm.

It is also noteworthy that the increase in mortality rate and the length of stay in the intensive care unit and the total hospital stay, apart from the increased rate of reintubation, have remained almost unchanged over the years. This is despite advancement in post-operative care of cardiac patients. Consequently, in trying to alleviate this situation by providing a possible solution via prophylactic means, our project is intriguing. While we are unsure if our intervention would work, the scientific theory propelling our endeavour cannot be doubted. As Danish physicist Niels Bohr aptly puts it, “It’s very difficult to make predictions, especially about the future.”

We mentioned about the pathogenesis of POAF which is now thought to be due to oxidative stress and inflammation. Cardiac surgery itself inflicts a trauma on the heart, and the use of cardiopulmonary bypass produces ischaemic injury. Reperfusion injury that happens after an artery is grafted leads to oxidative stress and the production of pro-inflammatory molecules, resulting in leucocyte activation and the production of nitrous oxide and reactive oxygen species.\textsuperscript{60} It has also been demonstrated in human studies that a correlation exists between systemic inflammation and oxidative stress and the development of POAF. Guided by all this information, we ventured into this research project. If our hypothesis is proven correct, we would be able to reduce the morbidity and mortality associated with POAF together with the total time spent in ICU and the overall hospital stay – this alone would reduce the cost in patient management and lessen the strain on the healthcare system.

Research has shown that POAF was correlated with longer and costlier lengths of stay both in the ICU and also the total hospital stay, besides the rate of readmission.\textsuperscript{70,71} In the USA, these outcomes translate into a substantial financial impact amounting to approximately USD 2 billion per year\textsuperscript{39} out of a total expenditure of more than USD 6 billion related to AF care in the country.\textsuperscript{39} Despite the absence of any data either at the IJN of Kuala Lumpur or elsewhere countrywide regarding the total cost incurred in managing patients with this type of complication, it is predicted that the total costs would be huge if not monstrous. Hence, it is undeniable that improving the health condition of patients would have a positive effect on their economic activity, and subsequently, the national economy itself.
In devising ways to contend with this issue, we are fully cognizant of the fact that several non-drugs or non-pharmacological compounds have been used in the research to prevent POAF – namely polyunsaturated fatty acids (PUFAs), vitamin C, or a combination of vitamins C and E. While focusing on the non-pharmacological compounds, we noticed that as a known dietary antioxidant, PUFAs have been shown to confer potential benefits in reducing cardiovascular morbidity in animal models despite limited evidence for their use as prophylaxis for POAF. However, a very recent paper by Rubanenko O and Rubanenko A shows that patients treated with PUFAs had less activation of inflammation and oxidative stress after CABG, with a significant decrease in the prevalence of POAF after CABG. A 2017 meta-analysis of 19 randomised controlled trials (RCTs) found a reduction in POAF. Similarly, a 2018 meta-analysis that included 14 RCTs also showed a significant reduction of POAF with PUFAs as compared to controls, although this effect was found only in CABG, not valve surgery. It is very promising that an antioxidant had been shown to have an effect in preventing POAF, especially when our hypothesis is built upon a similar promise that tocotrienol-rich Tocovid, itself a powerful anti-oxidant, could ameliorate and prevent the occurrence of POAF.

Another compound which has been studied quite extensively is vitamin C, a compound known to reduce oxidative stress. In a 2016 meta-analysis of 7 RCTs, the incidence of POAF was found to be reduced as compared to controls. However, a more recent RCT involving 314 on-pump patients found to have no difference in POAF, ICU stay and the total hospital stay, and to date, there are still no guidelines referring its use for POAF prophylaxis. However, when we look at a combined antioxidants use where vitamin C is combined with vitamin E and PUFAs, a 2013 study showed that there was a significant reduction in the incidence of POAF among patients receiving antioxidants as compared to controls. It was therefore not surprising then when the authors recommended the use of a combination of these antioxidants as an effective, safe and cheap prophylaxis against the onset of POAF. However, until today, no guidelines reference of such a protocol is available.

Based on all the above-mentioned studies, it is highly likely that a powerful antioxidant and anti-inflammatory agent such as Tocovid might be able to mitigate the occurrence of POAF; this is exactly where this study might be able to pave the way in finding such a solution. While it is still too early to make any conclusion, the scientific basis to pursue such a study is well established and it will take a few more months before this study is concluded and the study groups unblinded.

7.0 Limitations

The main limitation in the study is with regard to the current COVID-19 pandemic that made it difficult to recruit patients for enrolment in the study. There was a reduction in the numbers of patients enrolled due to the limited number of ICU beds.

8.0 Conclusion
At this point in time, we can conclude that the incidence for the occurrence of POAF remains high (slightly above 20%), exacting a high toll in terms of worse outcome; it increases both the mortality rate and hospital care costs since we observed a statistically significant increase in ICU stay and total hospital stay. Consequently, a non-invasive, highly effective, low-risk and cheaper alternative in preventive therapy to reduce the incidence of POAF would be a huge step forward in managing this common problem. It still remains uncertain whether this prophylactic intervention for reducing POAF should be limited to high-risk patients or if it should be extended to all patients. A knowledge gap persists in this area, as is the mechanism of the development of POAF; it is highly unlikely that there is a single unifying mechanism for the development of this arrhythmia although the inflammatory and oxidative pathways are most likely involved in exacting the common outcome of this major complication of CABG.

Declarations

9.0 Data Availability

Harvard Dataverse: Replication Data for: Tocovid, a tocotrienol-rich vitamin E in preventing atrial fibrillation in post-coronary artery bypass grafting (CABG) surgery: A preliminary result.

Https: https://doi.org/10.7910/DVN/HX0AVU

This project contains the following underlying data:

Set 1: Raw Data
Set 2: Output Data

10.0 Competing interests

No competing interests were disclosed.

11.0 Author roles

Musa AF: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Visualization, Writing – Original Draft Preparation, Writing - Review & Editing; DillonJ, MdTaib ME, YunusMA, SanusiAR, NordinN, NordinRB: Resources, Software, Visualisation, Project Administration; NordinRB: Supervision, Validation, Writing – Review & Editing
12.0 Grant information

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Figures
Figure 1

Study Flow Chart

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
• OutputData.pdf
• RawData.csv