The Influence of New-Onset Atrial Fibrillation After Coronary Artery Bypass Grafting on Three-Year Survival

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ABSTRAK

Latar belakang: *fibrilasi atrium (FA) awitan dini pascabedah pintas arteri koroner (BPAK) merupakan salah satu komplikasi pascaoperasi yang sering terjadi. Aritmia ini merupakan fenomena sementara dan mayoritas pasien akan mengalami konversi ke irama sinus saat dipulangkan. Meskipun bersifat sementara, FA awitan baru pasca-BPAK berpotensi mengalami rekurensi sehingga meningkatkan risiko mortalitas jangka panjang. Penelitian ini bertujuan untuk mengetahui peran FA awitan baru pasca-BPAK dalam mempengaruhi kesintasan tiga tahun.* ***Metode:*** *studi kohort retrospektif menggunakan analisis kesintasan yang meneliti 196 pasien yang menjalani BPAK di Rumah Sakit Cipto Mangunkusumo sejak Januari 2012 sampai Desember 2015. Eksklusi dilakukan pada pasien dengan riwayat FA sebelum operasi, menjalani operasi tanpa mesin pintas jantung-paru, dan yang meninggal dalam 30 hari pascaoperasi. Subyek penelitian dibagi menjadi 2 kelompok berdasarkan ada tidaknya FA awitan baru pasca-BPAK dan kemudian ditelusuri status kematiannya dalam tiga tahun sejak operasi. Kurva Kaplan-Meier digunakan untuk menilai kesintasan tiga tahun dan dilakukan uji regresi Cox sebagai uji multivariat terhadap variabel perancu untuk mendapatkan nilai adjusted hazard ratio (HR).* ***Hasil:*** *sebanyak 29,59% pasien mengalami FA awitan baru pasca-BPAK. Mortalitas tiga tahun pasien yang mengalami FA awitan baru pasca-BPAK baru lebih tinggi (15,52% vs 3,62%) dan secara signifikan menurunkan kesintasan tiga tahun (p=0,008; HR 4,42; IK 95% 1,49-13,2). Pada analisis multivariat, FA awitan dini pasca-BPAK merupakan faktor independen penurunan kesintasan tiga tahun (adjusted HR 4,04; IK 95% 1,34-12,14). Kesimpulan: FA awitan baru pasca-BPAK secara independen menurunkan kesintasan tiga tahun.*

Kata kunci: *awitan baru, bedah pintas arteri koroner, fibrilasi atrium, kesintasan.*

ABSTRACT

Background: *new-onset atrial fibrillation after coronary artery bypass grafting (CABG) is a common postoperative complication. This arrhytmia considered as temporary phenomenon which the majority are converted back to sinus rhytm when the patients discharged from the hospital. Despite its transience, those arrhytmia can recur and increasing the long term mortality. This study aims to determine the role of new-onset atrial fibrillation after CABG in three year survival.* ***Methods:*** *retrospective cohort study using survival analysis of patients who underwent coronary artery bypass grafting since January 2012 to December 2015 at Cipto Mangunkusumo Hospital. Patients with atrial fibrillation before surgery, who had surgery without cardiopulmonary bypass machine, and who died*

in 30 days after surgery are excluded. Subjects are divided into two category based of the presence of new-onset atrial fibrillation after CABG and the mortality status is followed up until 3 years post-surgery. The Kaplan-Meier curve is used to determine the three-year survival of the patients who had new-onset atrial fibrillation after CABG and Cox regression test used as multivariate analysis with confounding variables in order to get adjusted hazard ratio (HR). ***Results:*** *new-onset atrial fibrillation after-CABG occurred in 29,59% patients. Patients with new-onset atrial fibrillation after CABG have higher three-year mortality (15,52% vs 3,62%) and significantly decreases three-year survival (p=0,008; HR 4,42; 95% CI 1,49-13,2). In multivariate analysis, new-onset atrial fibrillation after CABG is an independent factor of the three-year survival decline (adjusted HR 4,04; 95% CI; 1,34-12,14).* ***Conclusion:*** *new-onset atrial fibrillation after CABG independently decreases three-year survival.*

Keywords: *atrial fibrillation, coronary artery bypass grafting, new-onset, survival.*

INTRODUCTION

Coronary artery bypass grafting (CABG) is one of methods of revascularization therapy in coronary artery disease (CAD). Despite its decline in past decade accompanied by the increasing numbers of percutaneous coronary intervention, CABG still considered better in certain conditions to prolong patients' survival. In United States, about 400.000 operations performed anually.[1]

Older age accompanied by increasing comorbidites of candidates of CABG contributed to difficulties in preventing postoperative complications. One of the complication is postoperative arrhytmia which is dominated by new-onset atrial fibrillation (AF). The incidence of new-onset AF can reach 40% and can be doubled if the procedure combined with the valve surgery.[2,3] Majority of new-onset AF occurred in four days postoperatively and already converted back to sinus rhytm when the patients discharged.[4] Because of its characteristics, new-onset AF after CABG often considered to have no important clinical consequenses.[5]

Meta-analysis reported by Phan et al shows the influence of new-onset AF after CABG to the increasing risk of in-hospital complications and 30-days mortality. Patients with new-onset AF after CABG has lower survival in 1,5, and 10 years.[6] The EXCEL Study (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) concluded that new-onset AF after CABG is an independent predictor of three-year mortality with hazard ratio (HR) 3,02 (p=0,0006, CI 95% 1,6-5,7).[7]

The AF rhytm of patients with history of new-onset AF after CABG can recur in long-term period. Using the most sensitive detector, AF recurrence in that group can reach 60,9% in 2 years postoperatively. Majority of those recurent cases are asymptomatic.[8] Those conditions are related with increasing mortality through cardiac death, fatal stroke, and fatal arrhytmia caused by anti-arrhytmic drugs.[9]

The influence of new-onset AF after CABG to long-term mortality had never been published in Indonesia. Several studies abroad can not be just generalized because some characteristics differences. Patients who underwent CABG in Indonesia are younger and have better left ventricular ejection fraction.[10,11] Several preoperative factors that can influence survival of patients after CABG are patients aged 60 years old and over, the presence of diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD)[12], renal dysfunction (estimated glomerular filtration rate <60 mL/minute/m^2)[13], and low ejection fraction (<40%).[14]

The aim of this study is to determine the role of new-onset atrial AF after CABG on three-year survival so can affect the evaluation and management and resulting in positive impact to patients' survival.

METHODS

This is a retrospective cohort study with survival analysis to study the role of new-onset AF after CABG on three-year survival. The minimum sample size in this study was 248 patients. New-onset AF after CABG is defined as AF rhythm occurred for the first time

postoperatively, with or without symptoms, and documented in hospital care or in ≤30 days if the patients are discharged. This study has been approved by the Ethics Committee of the Faculty of Medicine Universitas Indonesia (Reference no. 1007/UN2.F1/ETIK/2018).

This study analyzed the secondary data with inclusion criteria as follows : patients ≥18 years old who underwent CABG (single or combined with valve surgery) at Cipto Mangunkusumo Hospital since January 2012 to December 2015, and subjects with complete data of heart rhytm in hospital care postoperatively. Exclusion criteria as follows: subjects with history of AF before surgery, subjects operated without cardiopulmonary bypass machine, and patients who died in 30 days postoperatively.

Subjects then divided into the group with and without new-onset AF after CABG. In three years since the surgery date, all cause mortality status will be searched. The subjects will be censored if the mortality status unknown or still alive in three years after surgery. The studied variable and confounding preoperative variables (aged 60 years old and over, DM, COPD, renal dysfunction, low ejection fraction) will be analyzed using proportional hazard test. Variables which fullfill proportional hazard assumption are included in bivariate analysis and then variables with the p value<0,25 will be analyzed in multivariate analysis using Cox regression. STATA 15.0 was used to analyze the data.

RESULTS

Among 196 subjects in this study (**Table 1**), 58 subjects (29.59%) had history of new onset AF after CABG. The characteristics of the groups based on the presence of new-onset AF after CABG can be seen in **Table 2**. The most common episode of new-onset AF on occurred at operative day and 87.9% cases are converted back to sinus rhytm in ≤24 hours. Intravenous amiodarone is the most common therapy given in treating new-onset AF after CABG.

In this study, the three years mortality status of 14 patients (7.14%) are unknown. Patients with history of new-onset AF after CABG has higher mortality rate (15.52% vs 3.62%). The three-year survival curve between groups of patients with and without new-onset AF can be seen in **Figure 1**. New-onset AF after CABG, age 60 years old and over, and DM fullfilled proportonal hazard assumption and then analyzed with Cox regression. Bivariate analysis is shown in **Table 3**. It is concluded that new-onset AF after CABG is the only significant factor influencing the three-year mortality with HR 4.42 (CI 95%) 1.49-13.2). Multivariate analysis with confounding variables resulted in adjusted HR 4.04 (CI 95% 1.34-12.14) as shown in **Table 4**.

Table 1. Characteristics of subjects.

Variables	Description (N = 196)
Age, years - mean (SD)	58.05 (8.24)
Age ≥60 years old - n (%)	94 (47.96)
Male - n (%)	163 (83.16)
Body Mass Index, kg/m^2 - (mean, SD)	25.03 (3.64)
Ejection fraction, % - (mean, SD)	54.14 (14.99)
Low ejection fraction - n (%)	37 (18.88)
Diabetes mellitus - n (%)	75 (38.27)
Renal dysfunction - n (%)	38 (19.39)
CAD three-vessel disease - n (%)	177 (90.31)
Left main disease - n (%)	79 (40.31)
Combination with valve surgery - n (%)	34 (17.35)
New-onset AF after CABG - n (%)	58 (29.59)
Left atrial enlargement - n (%)	45 (22.96)
Diastolic dysfunction - n (%)	93 (47.45)
COPD - n (%)	4 (2.04)
Smoking - n (%)	90 (45.92)
EuroSCORE additive (median, min-max)	3 (0-16)
Beta-blocker usage - n (%)	179 (91.33)
CPB time, minutes (median, min-max)	121 (54-353)
Aortic cross clamp time, minutes - (median, min-max)	92 (32-199)

DISCUSSION

The mean age of this study is 58,05 years old. The result is almost similar with the prior study which was held in Indonesia,[10] although is younger when compared with several studies abroad.[9,12] The mean of fraction ejection in this study is 54,11%, which is better if compared with abroad studies.[9,12] The incidence of new-onset AF after CABG in this study is 29.59%, in range of the reported before.[2] The variation in number

Table 2. Subjects' characteristics based on the presence of new-onset AF after CABG.

Variables	New-Onset AF After CABG	
	Yes (n=58)	No (n=138)
Age ≥60 years old - n (%)	33 (56.9)	61 (44.2)
Male - n (%)	46 (79.31)	117 (84.78)
Body Mass Index, kg/m^2 - mean (SD)	24.84 (3.56)	25.08 (3.68)
Low ejection fraction - n (%)	12 (20.92)	29 (21.01)
Diastolic dysfunction - n (%)	27 (46.55)	66 (47.83)
Left atrial enlargement - n (%)	18 (31.03)	27 (19.57)
COPD - n (%)	1 (1.72)	3 (2.17)
Diabetes mellitus - n (%)	25 (43.1)	50 (36.23)
Renal dysfunction - n (%)	10 (17.24)	28 (20.29)
Smoking - n (%)	23 (39.66)	67 (48.55)
CAD three-vessel disease - n (%)	53 (91.38)	124 (89.86)
Left main disease - n (%)	23 (39.66)	56 (40.58)
Beta blocker usage - n (%)	54 (93.1)	125 (90.58)
Combination with valve surgery - n (%)	12 (20.69)	23 (16.67)
CPB time (minutes), median (min-max)	128,5 (69-284)	118 (54-353)
Aortic cross clamp time (minutes), median (min-max)	93 (52-199)	90.5 (32-186)
Potassium correction - n (%)	48 (82.76)	98 (71.01)
Magnesium correction - n (%)	25 (43.1)	33 (23.91)
Anticoagulant when discharged - n (%)	14 (24.14)	22 (15.94)
EuroSCORE additive (median, min-max)	3 (0-13)	3 (0-16)
Three-year mortality - n (%)		
- Yes	9 (15.52)	5 (3.62)
- Unknown	3 (5.17)	11 (7.97)

Table 3. Influence of new-onset AF after CABG, age ≥60 years old, and diabetes mellitus to three-year survival.

Variables	Hazard Ratio	CI 95%	P value
New-onset AF after CABG	4.42	1.49-13.2	0.008
Age ≥60 years old	1.95	0.65-5.8	0.23
Diabetes mellitus	2.38	0.82-6.86	0.11

of incidence caused by different definition of new-onset AF after CABG which has not been agreed, especially about the minimum duration. New-onset AF after CABG most often occurred at operative day (32.8%) which is related with ischemia, and postoperative day-2 (24.1%) which is influenced by inflammatory response and oxidative stress after using of cardiopulmonary bypass machine.[15] Majority of cases of AF are ended in first 24 hours after surgery because most of patients have normal left atrial diameter and ejection fraction. It is known that the greater the change of heart's structure, the more likely AF become persistent.[5]

Table 4. Hazard ratio of new-onset AF after CABG.

Variables	Hazard ratio (CI 95%)
Crude HR	
- New-onset AF after CABG	4.42(1.49-13.2)
Adjusted HR	
- DM	4.23 (1.42-12.66)
- Age ≥60 years old	4.04 (1.34-12.14)

In this study, the group with new-onset AF after CABG has older age. It is reported in prior study in Indonesia that age is the only significant factor which can increase the incidence of new-onset AF after CABG.[10] More patients with

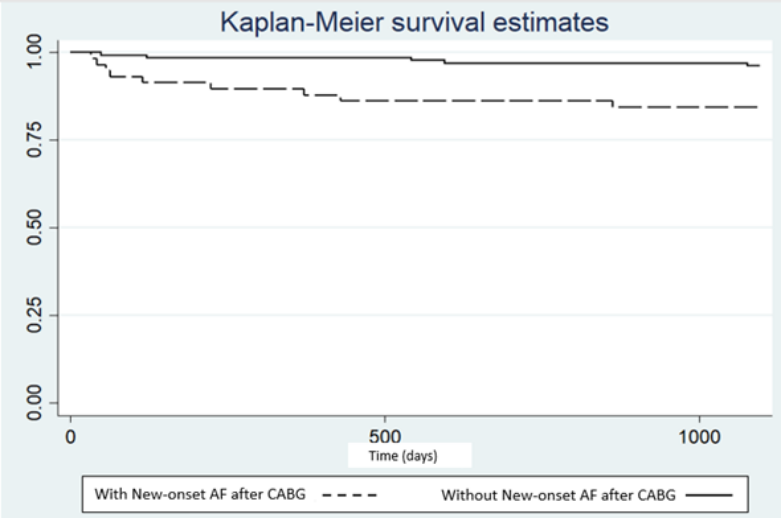

Figure 1. Kaplan-Meier curve of survival analysis between patients with and without new-onset AF after CABG.

new-onset AF after CABG sent home with anticoagulant therapy, although the indications mosly as part of postoperative valve surgery management. Proportion of renal dysfunction is smaller in the group of new-onset AF after CABG. That result can be influenced by the exclusion of patients with 30 days postoperative mortality which also consists of more patients with renal dysfunction.

We do not get median survival data because this study is limited in three-years observation. Mariscalco et al.[9] reported the median survival of patients with new-onset AF after CABG can reach seven years. The influence of new-onset AF after CABG to survival in this study is consistent with prior studies which resulting the value of OR 3.4 (p=0.018, CI 95% 1.58-7.45)[12] and HR 3.02 (p=0.0006, CI 95% 1.6-5.7).[7]

In contrast to other studies, the preoperative ejection fraction is not proven to influence the survival. There are no myocardial viability data in these patients that can make the improvement of ejection fraction after CABG still possible. We also can not find the significant association between variable of age ≥60 year old to the survival. That can be caused by characteristics difference which is influenced by the patients with age of ≥70 years old. Those patients may have significantly lowe survival compared to younger groups. Nicolini et al.[11] in their study had proportion of patients with age of ≥70 years old reaching 24.9% while in this study just only 6.12%.

Patients with history of new-onset AF after CABG usually have severe comorbidities which can increase the possibility to die earlier.[9] Despite of that possibility, new-onset AF after CABG can also thought to have direct association with long-term mortality. This is shown by consistent association although the characteristics between the groups are matched.[9,12]

Causal relationship between new-onset AF and mortality in this study can be assessed by Hill's criteria which shown strength of association, consistency, spesificity, temporality, biological gradient, biological plausibility, and analogy. Like paroxysmal AF in general population, new-onset AF after CABG over time can cause electrophysiological remodelling which can end to progressivity or death.

The strength of this study was the difference of study subjects, which were reported younger and had better ejection fraction than prior studies abroad. The exclusion of 30-day mortality is crucial to evaluate the direct role of new-onset AF after CABG to long-term mortality. The 30-day mortality is agreed as surgery-related mortality, which may not be directly related to AF itself. Although the minimum sample in this study cannot be achieved, the power of study is 96.7% which is good.

The limitation of this study is the using of

secondary data which negates the measurement control that can make the paroxysmal AF cannot be detected. Another limitation is we cannot get the information about patient's cause of death.

CONCLUSION

New onset AF after CABG independently decreases three-year survival, so it necessary to make careful evaluation about the possibility of AF recurence in patients with history of new-onset AF after CABG that can be related to increasing of long-term mortality. Further prospective study using more sensitive AF detector is needed to evaluate the role of new-onset AF in long-term mortality.

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