

Risk Factors for Post-Coronary Artery Bypass Grafting (CABG) Atrial Fibrillation and the Role of Aspirin and Beta Blockers in its Prevention

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Abstract

Background: Atrial fibrillation/flutter (AF) is the most common arrhythmia following coronary artery bypass grafting (CABG) and it increases morbidity and mortality associated with this procedure. The purpose of this study was to evaluate the predictability of this arrhythmia using previously identified risk factors and to assess the efficacy of recommended prophylactic beta blocker (BB) therapy in the prevention of post CABG AF.

Methods: We performed a retrospective chart analysis of consecutive patients undergoing elective CABG during 1 year period. Patients who developed new onset AF after the surgery were designated as cases and those who did not, as controls. 41 different variables were analyzed using Chi-square test and independent sample t-test. Multivariate analysis was carried out using logistic regression model.

Results: 23% patients undergoing CABG developed AF during post-operative period. Statistically significant differences were observed between the two groups in terms of age, use of peri-operative Aspirin (ASA), current smoking, previous history of AF, left atrial size, history of congestive heart failure (CHF) and brain natriuretic peptide (BNP) levels. In terms of prophylactic therapy, preoperative BB did not independently protect against post CABG AF. On multivariate analysis, only age, use of ASA and previous history of AF remained as independent predictors of post CABG AF.

Conclusion: In our study population, the use of preoperative BB did not independently decrease the risk of post-CABGAF. Age, peri-operative ASA use and previous history of AF remained strong independent predictors of post-operative AF.

Introduction

Atrial fibrillation/flutter (AF) is a common complication of coronary artery bypass grafting (CABG) with or without valve surgery that increases the morbidity, cost and the length of stay associated

with this procedure.^{1,2} Post-CABG AF also identifies a subset of patients with increased in-hospital and long-term mortality.¹

The incidence of new onset post- CABG AF without recommended prophylaxis is anywhere between 20 to 50% depending on the type of open

heart surgery i.e., CABG or the valve surgery.^{2,4}

American Heart Association (AHA) and American College of Cardiology (ACC) 2006 and 2011 guide lines recommend preoperative or post-operative oral BB (beta blocker) therapy for the prevention of post- CABG AF (Class 1a). Other recommended pharmacological prophylactic therapies include sotalol (Class IIb) and amiodarone (Class IIa).^{5, 6} These guide- lines are mainly based on the results of previous studies and meta-analyses which have shown that prophylactic BB significantly decrease the incidence of post-CABG AF as compared to the controls.^{7,8}

However, several later studies failed to show the desired protective effect of BB against the development of post- CABG AF.⁹⁻¹¹ Additionally the overall incidence of post- CABG AF is on the rise over the past few years.⁵

The risk factors predisposing to the development of post- operative AF have been identified in previous studies and include advanced age, previous history of AF, COPD (chronic obstructive pulmonary disease), valvular heart disease, enlarged LA (left atrium), CHF (congestive heart failure), withdrawal of BB or ACE (angiotensin converting enzyme) inhibitors,⁴ on-pump CABG¹² obesity,¹³ higher preoperative plasma concentration of BNP (brain natriuretic peptide),¹⁴ hypokalemia,¹⁵ hypomagnesemia,¹⁶ severe right coronary artery stenosis,¹⁷ and preoperative increase in P wave duration on surface EKG (>116 msec).¹⁸

As the techniques of CABG and the demographic features of the patients undergoing open heart surgery have evolved significantly over the last two decades, we decided to perform a retrospective study to confirm previously identified risk factors and the effectiveness of prophylactic BB therapy in the current era.

The purpose of this study is twofold

1. To evaluate the predictability of post-CABG AF using previously identified risk factors.
2. To assess the efficacy of recommended prophylactic BB therapy.

Study Design and Methodology

We performed a retrospective case control study of consecutive patients undergoing elective CABG with or without valve surgery during 1 year period. The protocol was approved by our Institutional Review Board (09/2007). Informed Consent was waived as this was a retrospective chart review study.

All consecutive patients who had elective CABG (off-pump or on-pump) with or without valve surgery between 1/1/06 and 12/31/06 were included in the study. Total of 247 patients were screened for inclusion. The patients who underwent isolated valve surgery (3 patients) and those who were in AF or other arrhythmia (13 patients) at the time of surgery were excluded leaving 231 patients in the final analysis.

AF was defined as a rhythm with irregular QRS complexes without identifiable P waves. Atrial flutter was defined as a rhythm with regular QRS complexes with flutter waves. All patients were monitored using 24 hour telemetry throughout the post-operative period. AF was diagnosed on the review of EKG and telemetry strips and confirmed with physician's notes. Postoperative period was defined as the time spent in the hospital after the open heart surgery.

The patients who either developed new onset post-operative AF for more than 30 minutes in duration or had hemodynamic compromise due to AF episodes of any duration were designated as cases; and those who did not meet these criteria were designated as controls. The duration of 30 minutes was selected based on the previous studies and it seems appropriate as shorter lived episodes are likely clinically insignificant. Electronic and paper charts were reviewed to obtain the relevant data. We collected detailed patient information with particular attention to demographics, the presence of previously documented risk factors for post- CABG AF, laboratory data including electrolytes, co-morbidities, preoperative medications, P-wave length on preoperative EKG, and , pertinent intra-operative and post-operative variables. These 41 different preoperative, and intra-operative post-operative variables were derived from previous studies with similar objectives.

Statistical Analysis

The data were gathered by two researchers (MFK and AH) separately which was later checked and corrected for any discrepancies. It was initially recorded in Microsoft excel 2007 and subsequently entered into SPSS for further analysis.

Categorical variables were analyzed using Chi-square test and Fisher's Exact test, whereas Continuous variables were expressed as mean \pm SD (standard deviation) and were analyzed using independent sample t-test. Statistical significance was defined as a p-value of <0.05 . Multivariate analysis was carried out using step wise Logistic regression model. Variables seeming to predict post CABG AF on the univariate analysis were included in the Logistic regression model. All the statistical analysis was carried out using SPSS. (Chicago, IL.

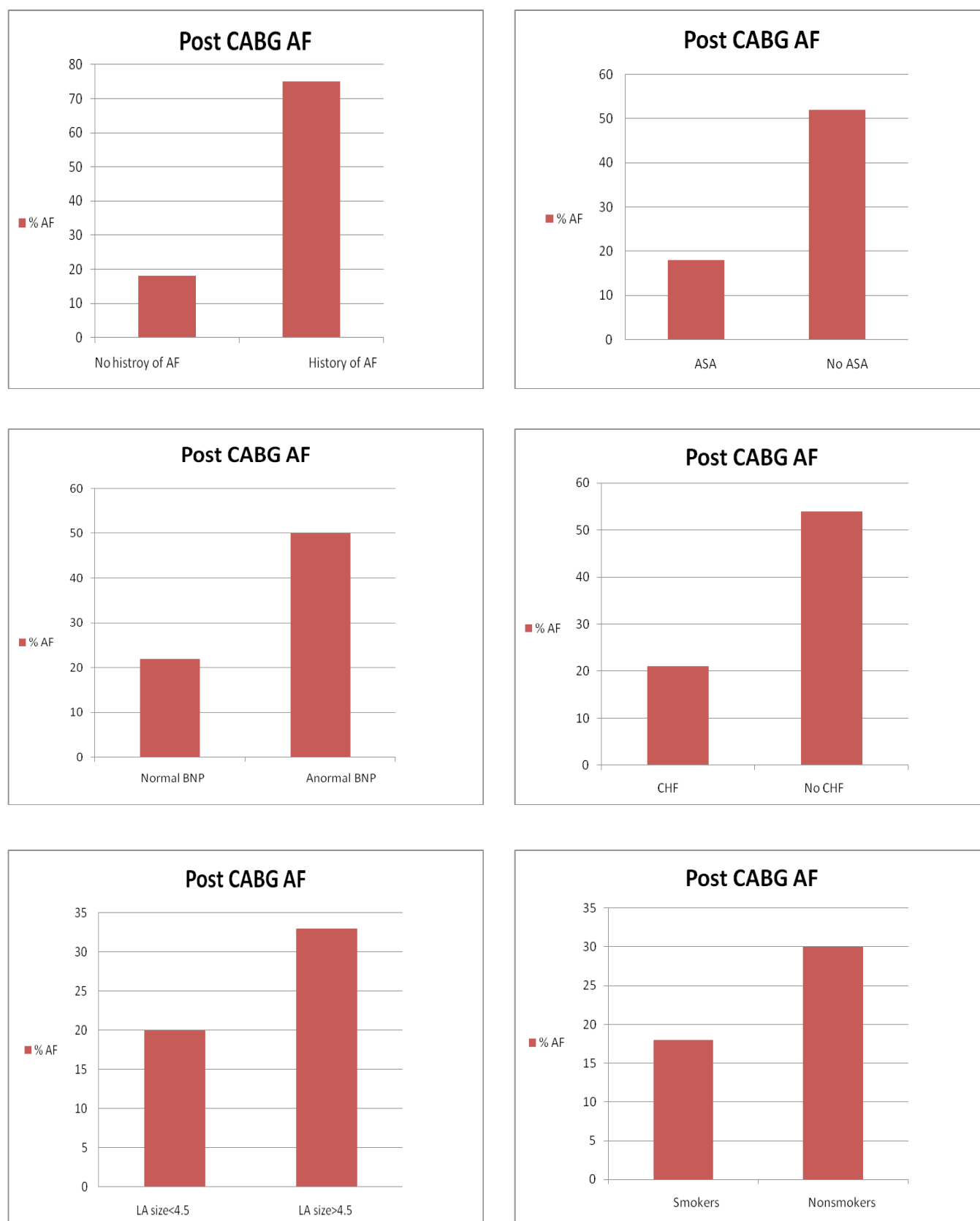
2nd and 4th post- operative day. On univariate analysis, risk factors for post- operative AF included advanced age, previous history of AF, enlarged LA size (more than 4.5 cm diameter), history of CHF, elevated BNP levels ($>500\text{pg/ml}$), preoperative BB or digoxin administration, and the absence of peri-operative ASA (Table 1 and Graphs 1-6). According to these results, age, previous history of AF and the use of ASA were identified as the most significant predictors for the development of post- CABG AF. The mean age of the patients who developed AF was 72 ± 9.2 years as compared to 64 ± 11.5 years for that of controls (p-value < 0.001). Additionally 28% of the cases had a history of AF as compared to only 2.8% for that of controls (p-value < 0.001). Similarly the use of ASA was associated with reduced incidence of post- CABG AF. Seventeen out of 33 patients (52%) who were not on ASA at the time of surgery developed AF

Table 1

Risk Factors for Post CABG AF

Variables	Post-op AF n=53 (%)	No Post-op AF n=178 (%)	p-value	OR (95% CI)
Age, yrs (mean \pm SD)	72 ± 9.2	64 ± 11.5	<0.001	3 (1.6 -5.8)
Male sex	36(68)	123(69.1)	0.5	1.05 (0.55-2.0)
Abnormal BNP	6 (11.3)	6 (3.4)	0.03	3.7 (1.1-11.9)
History of CHF	7 (13.2)	6 (3.4)	0.013	4.4 (1.4-13.6)
History of AF	15 (28.3)	5 (2.8)	<0.001	13.6 (4.7-39.9)
EF ≤ 40 %	12 (22.6)	24 (13.5)	0.84	1.8 (0.8 4.0)
Abnormal LA size	19 (38.8)	38 (23.5)	0.03	2 (1.1-4)
Pre-op Beta Blockers	35 (66)	87 (47.9)	0.02	2 (1.1-3.9)
Pre-op Digoxin	3 (5.7)	1 (0.6)	0.04	10.6 (1.1-104)
Off pump CABG	27(51)	97(54)	0.649	1.1 (0.6-2.1)
CABG plus AVR	4(7.5)	7(4)	0.23	2(0.56-7.0)
Clamp time (min \pm SD)	72.8 ± 51.5	68.9 ± 30.5	0.42	1.0 (0.9-1.01)
Number of Anastomoses	3.3 ± 1.2	3.7 ± 1.1	0.1	0.82 (0.6-1.07)
Active Smoking	25(48)	113(64)	0.028	0.5 (0.27-0.96)
Hypertension	42(79)	127(72)	0.168	1.5(0.73-3.2)
Dyslipidemia	36(68)	124(70)	0.46	0.9(0.5-1.8)
Diabetes mellitus	15(28)	55(31)	0.429	0.9(0.45-1.74)
COPD	5(9.4)	16(9)	0.55	1(0.37-3)
CAD	22(42)	73(41)	0.55	1(0.54-1.9)
Pre-op Statin	29(56)	103(59)	0.40	0.9(0.5-1.6)
ASA	34(67)	160(91)	<0.001	0.2 (0.09-0.44)
Pre-op ACEI/ARB	23(47)	97(55)	0.197	0.7(0.39-1.35)

*Patients received ASA on the morning of surgery and within 24 hours after arrival to SICU, †All patients on pre-operative BB received 1st postoperative dose within 24 hours of surgery

Figure: Graphs 1-6: Analysis of Individual Risk Factors Except BB and Digoxin (Univariate Analysis)

For history of AF: p-value < 0.001, OR 13.6 and 95% CI (4.6-39.8), For ASA : p-value < 0.001, OR 0.2 and 95% CI (0.09-0.44), For history of CHF: p-value = 0.013, OR 4.3 and 95% CI (1.4-13.6), For LA size >4.5 cm: p-value = 0.029, OR 2 and 95% CI (1.04-4.0), For Smokes: p-value = 0.028, OR 0.5 and 95% CI (0.27-0.96), For BNP >500: p-value = 0.03, OR 3.6 and 95% CI (1.1-11.8)

as compared to 34 out of 194 (18%) who developed AF were taking ASA at the time of surgery (p -value<0.001) (ASA use could not be confirmed for 4 patients). Use of logistic regression model showed that advanced Age (>70 years) OR (odds ratio) of 1.06 (p -value=0.007, 95% CI, 1.015-1.102), previous history of AF OR of 5.0 (p -value=0.015, 95% CI, 1.37-17.57) and the use of peri-operative ASA OR of 0.35 (p -value=0.03, 95% CI, 0.13-0.91) independently predicted the development of post CABG AF.

One twenty four out of 231 patients underwent off-pump (OP) CABG while remaining 107 patients had on-pump CABG. The incidence of post-CABG AF in patients with OP-CABG and on-pump CABG was 22% and 24% respectively but this difference was not statistically different between the two groups.

In terms of prophylactic therapy, on univariate analysis, preoperative BB administration appears to be associated with higher incidence of post-CABG AF. In this study group, 122/231 (52.8%) of the patients entered into the surgery on oral BB. 70 % of the patients were taking metoprolol tartrate or succinate, 24.5% were taking atenolol and the rest were on carvedilol, propranolol or labetalol. The remaining 109/231 (47.18%) of the patients did not get preoperative BB due to various contraindications including bronchospasm, bradycardia, hypotension or the use of other AV nodal blocking/anti arrhythmic agents. However, 101 out of 109 patients were ultimately started on BB in the post-operative period before the discharge. The typical starting time for new post-operative BB therapy was after 2nd post-operative day, so these were not considered as prophylactic for the prevention of post-operative AF.

To further clarify relationship between preoperative BB use and post-CABG AF, we performed a secondary analysis to compare patients with BB prophylaxis to those without prophylaxis.

This sub-analysis (Table 2) showed that 35 of 122 (28.6%) developed AF while on prophylactic BB whereas only 18 of 109 (16.5%) developed post-operative AF in the absence of preoperative BB (p -value<0.05). However, these two groups had statistically significant differences between them

in terms of other co-morbidities. Despite more cases being on preoperative BB, they were older, had higher incidence of history of AF, history of CAD, higher rate of previous CABG, HTN and dyslipidemia, all of which are well known risk factors for AF. The difference, in incidence of post-CABG AF between these two groups, did not remain statistically significant after adjustment of these risk factors with logistic regression model.

Regarding other anti-arrhythmics, eleven out of 231(5%) patients were on amiodarone preoperatively. Four out of 53 patients (7.5%) who developed post-CABG AF while seven out of 178 patients (4%) who did not develop AF were taking preoperative amiodarone. Postoperative amiodarone was used in 30 patients who developed post CABG AF while diltiazem was used in 18 patients who developed post-operative AF.

Discussion

Post-operative AF affects up to 40 % of the 500,000 patients per year undergoing CABG and results in \$10,055 increase in cost per patient with incremental cost of about \$2 billion annually.¹⁹ It increases the length of stay by 4 to 5 days and identifies a subset of patients with increased risk of strokes and in-hospital and long term mortality.^{1,4,19}

Although the exact mechanisms leading to the development of post-CABG AF are not entirely clear, however several studies indicate that increased level of oxidative stress secondary to ischemia,^{20, 21} heightened sympathetic tone,^{22,23} abnormal atrial conduction^{24,25} and inflammation²⁶ associated with CABG leads to post-operative AF. Bruins et al²⁷ found maximum levels of inflammatory markers including CRP (C-reactive protein) on the second post-CABG day correlating with the occurrence of arrhythmias on the same day. Another study found a significant association between new onset AF and the elevation of white blood cell counts in post-CABG period.²⁸ On-pump CABG has been associated with higher incidence of post-operative AF due to higher levels of inflammation resulting from cardiopulmonary bypass.¹² In our study a direct relationship between the markers of inflammation and post-operative AF was not evaluated, however, indirectly there was no difference in the incidence of AF between OP-CABG and on-pump CABG.

Age has been consistently shown as the most significant risk factor for post-CABG AF,⁴ confirmed by this study as well. In a study of 915 patients who underwent isolated valve surgeries, the risk of development of post-operative AF increased with each decade of life (odds ratio of 1.51 per decade).²⁹ The reasons for this predisposition are not entirely clear, however advanced age related changes in the atria including fibrosis, increased collagen content and loss of the atrial muscle mass appear to predispose to AF.^{7, 30}

Similar to earlier studies,⁴ previous history of AF was also confirmed as one of the stronger predisposing factors for the development of post- CABG AF. Patients with a previous history of AF likely have underlying atrial abnormalities which are exacerbated by the insults from cardiac surgery, resulting in the recurrence of this arrhythmia.

Use of ASA in the peri-operative period has been an area of controversy till 2004-2005 when major guidelines strongly recommended the use of ASA before and after the CABG.^{31,32,33} Beneficial effects of ASA in CABG patients include reduced inpatient mortality, lower risk of peri-operative MI and stroke.^{34,35}

A role of ASA in the prevention of post CABG

AF has not been determined due to the lack of literature in this regard. Risk factors for the development of post- CABG AF has been very well studied however protective effects of ASA against post-operative AF have never been documented and ours is the first study to show this association.

The underlying mechanisms for this protection against post- CABG AF are not entirely clear. As mentioned above, onset of post- CABG AF has been shown to be associated with higher levels of peri-operative inflammation, oxidative stress and ischemia; it is quite possible that ASA by virtue of its anti-inflammatory and anti-ischemic effects may offer additional protection against AF. Furthermore, ASA, even in a lower dose inhibits cyclo-oxygenase enzyme resulting in an anti-thrombotic state due to decreased production of thromboxane A2. Similarly, steroids, which exert anti-inflammatory effects by inhibiting initial step in the same pathway (Phospholipase A2), and other NSAIDs have been shown to protect against post- CABG AF.^{4,36}

Certain variables including large LA size, history of CHF and elevated BNP levels which appeared to predict post- CABG AF on univariate analysis, have been confirmed in previous studies as well. On the other hand, we could not confirm few of

Table 2 Comparison of Patients with BB Prophylaxis Versus without Prophylaxis

Variable	Prophylactic BB (122)	No Prophylactic BB (109)	p- value (2 Sided)
Age, yrs (mean \pm SD)	67.34 \pm 10.6	64.3 \pm 12.2	0.041
Abnormal BNP	7	5	0.77
EF <40%	16	20	0.28
Post op AF	35	18	0.029
CABG + AVR	5	6	0.9
Preoperative Digoxin	2	2	1
Anti-arrhythmic drugs	5	6	0.9
Statin	91	41	<0.001
Previous CABG	5	0	<0.001
History of AF	18	2	<0.001
CHF	7	6	1
CAD	60	35	0.008
COPD	11	10	1
Dyslipidemia	97	63	<0.001
HTN	105	64	<0.001
Smoking	69	69	0.3
Sex (male)	78	81	1
Death	2	2	1

the previously known risk factors like male gender, HTN, peripheral vascular disease, CAD, duration/length of aortic cross clamp time, number of anastomoses and COPD as the predictors of post-CABG AF in our population. Surprisingly, for unknown reasons, active smoking seems to be associated with lower incidence of post-CABG AF; a finding shown by other authors as well.¹³

Preoperative BB are routinely recommended for the prevention of post-CABG AF, however these agents have failed to show consistency among several previous studies.^{9-11,37,38} ACC/AHA recommendation of starting BB as a prophylactic therapy for post-CABG AF is mainly based on the results of three meta-analyses.^{7,8,39} Majority of the randomized controlled trials (RCTs) included in these analyses were conducted in 1980s, predating the major advancements in techniques and protocols of CABG and the medical management of CAD. And there are several obvious differences between those RCTs and our study which could explain the relative inefficacy of preoperative BB found in this analysis. In many of the previous RCTs, patients with moderate to severe CHF (LVEF < 40%), history of arrhythmias, severe COPD, combined CABG and valve surgery, were excluded.^{37,40-46} Exclusion of these known risk factors for post-operative AF might have led to underestimation of AF incidence and possible overestimation of the protective ability of prophylactic BB. On the other hand, subgroup analysis of our study population confirms that as compared to no-preoperative BB group, patient who were taking preoperative BB were actually at higher risk for developing post-operative AF (higher rates of known AF risk factors) which partially explains the relative inefficacy of prophylactic BB.

In most of the previous studies, authors compared patients who were continued on post-operative BB to those patients whose BB were discontinued post-operatively. 70-100% of these patients (prophylactic and control groups) were taking preoperative BB,^{41,44,46-52} and the abrupt discontinuation of BB in the control groups created a BB withdrawal phenomenon. BB withdrawal has been extensively studied and is well known to cause AF.^{2,4,19,24,53} So, results of such studies likely represent the effects of BB withdrawal rather than the true magnitude of protection offered by the prophylac-

tic BB. The withdrawal effect is more prominent with agents of shorter half-life like propranolol,⁵⁴ which was the most commonly used prophylactic BB in previous RCTs. meta-analyses.^{37,38,42,45,48,50,51,55-57} This withdrawal phenomenon has been shown to last for 8-13 days,⁴⁰ which means that preoperative discontinuation of a BB (within seven days before the surgery) in a patient to be enrolled in an RCT may create a BB withdrawal state in the post-operative period. Abrupt discontinuation of BB results in rebound increase in sympathetic activity which may predispose to post-operative AF.^{23,24,58}

The mean age of our study group is higher than the mean ages of the study populations of the most of the previous trials.^{37,38,41-52,55-57} Age has been shown to be the most significant risk factor for post-CABG AF. Advanced age of the patients in our study group may partially explain the relative ineffectiveness of BB.

Further RCTs with elimination of BB withdrawal are needed in this era of advanced techniques of CABG to prove prophylactic efficacy of BB against AF.

Limitations

In addition to usual limitations of a retrospective study there are several other shortcomings to these results. We studied only a limited number of patients at one cardiac surgery center and the data and population characteristics might not reflect other facilities, thus results cannot be generalized to other cardiac surgery centers in the US. Incidence of supra-ventricular arrhythmias other than AF was not studied. During the study period, three surgeons independently performed CABG and/or valve surgeries and the data was not corrected for the performance of an individual surgeon. The exact timing of administration of the drugs (especially BB or ASA) in the postoperative period was not known, however per the protocol, patients (already on BB or ASA) were supposed to get their medications within 24 hours of SICU arrival. Regarding prophylactic BB use, it is possible that we could not find the desired protective effect due to a small sample size. The relationship between the dosages of BBs and the incidence of post-CABG AF was not evaluated in this study. Similarly we did not evaluate the relationship be-

tween ASA dose (81mg vs. 325mg) and AF protection. Retrospective nature of this study along with smaller number of patients predispose to a selection bias which cannot be completely eliminated even with logistic regression model.

Conclusions

In this analysis, we confirmed advanced age, the use of peri-reoperative ASA and a previous the history of AF as the strongest predictors of post-CABG AF. Further RCTs are needed to confirm the efficacy of prophylactic BB in higher risk patients of this era. In accordance with current guidelines, we strongly suggest continuing peri-operative ASA, as in addition to other benefits, it appears to protect against AF; however this finding needs to be confirmed in larger studies.

Disclosures

No disclosures relevant to this article were made by the authors.

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