Prevention of Post–Coronary Artery Bypass Grafting (CABG) Atrial Fibrillation: Efficacy of Prophylactic Beta-Blockers in the Modern Era

A meta-analysis of latest randomized controlled trials

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Background: Atrial fibrillation/flutter (AF) is a common complication of open heart surgery and ACC/AHA guidelines strongly recommend the use of prophylactic beta-blockers (BB) for its prevention. Several recent studies, however, have failed to show the desired protective effects of BB against post–coronary artery bypass grafting (CABG) AF. As the protocols of CABG, medical management of CAD (coronary artery disease) and demographic features of the patients undergoing open heart surgery have evolved significantly over the last two decades, we decided to perform a review of evidence from latest randomized controlled trials (RCTs) to confirm the efficacy of prophylactic BB.

Methods: We searched for RCTs comparing the efficacy of prophylactic BB versus placebo/control against post-CABG AF. We limited our search to 1995 till present to reflect ongoing advancements in the protocols of CABG and the medical management of CAD. Initially, 34 trials were selected; however after certain exclusions only 10 RCTs were included in the final analysis.

Results: Prophylactic BB decreased the incidence of post-CABG AF from 32.8% in the control group to 20% in the prophylactic group with risk ratio (RR) of 0.50 with 95% CI of 0.36–0.69, P value < 0.001. In a subgroup analysis, carvedilol appears to be superior to metoprolol for the prevention of postoperative AF.

Conclusions: Despite several limitations, this analysis confirms the efficacy of prophylactic BB against post-CABG AF in this era. We recommend continuing perioperative BB in the open heart surgery patients in the absence of contraindications.

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Atrial fibrillation/flutter (AF) is the most common arrhythmia following coronary artery bypass grafting (CABG) with or without valve surgery and it adds significantly to morbidity, cost, and length of stay associated with this procedure.^{1,2} Postoperative AF may also identify a subset of

patients with higher in-hospital and long-term mortality.¹

The reported incidence of new onset post-CABG AF in the absence of recommended prophylaxis is about 20–40% after CABG alone and up to 50% after valve surgery.^{2–4}

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Updated American College of Cardiology/American Heart Association (ACC/AHA) 2006 guidelines strongly recommend preoperative or postoperative initiation of oral beta-blocker (BB) therapy for the prevention of post-CABG AF. Other recommended pharmacological prophylactic therapies include Amiodarone and Sotalol.⁵ The largest meta-analysis to assess the efficacy of prophylactic BB against post-CABG AF was performed by Crystal et al.⁶ (2002) and it included 27 randomized controlled trials (RCTs); 21 of which were conducted in 1980s, predating the latest advancements in the protocols of CABG and medical management of coronary artery disease (CAD). Thus, these results are heavily influenced by the earlier studies and might not reflect the true efficacy of prophylactic BB in the recent era. In addition, despite of recommended prophylaxis, few recent studies have failed to confirm the desired protective effects of BB against post-CABG AF⁷⁻⁹ and its incidence is on the rise as compared to past few years.⁵

The protocols and techniques of CABG have evolved considerably over the last two decades with the most notable changes of introduction of off pump CABG (OP CABG), increase in the number of patients undergoing valve surgery, use of new methods for the induction of hypothermia and cardioplegia and increasing age of the patients undergoing open heart surgery. Similarly, recent evidence has suggested judicious use of certain perioperative medications like aspirin (ASA), statins, and angiotensin converting enzyme inhibitors (ACEI) to decrease the risk of postoperative complications. Some of these new measures (OP CABG, use of statins, and ACEI) have been independently shown to minimize peri-CABG inflammation resulting in lower incidence of postoperative arrhythmias including AF.^{4,10-12} These findings along with few recent studies which did not confirm the desired AF protection have created certain doubts regarding the utility of prophylactic BB as some authors think that lower incidence of post-CABG AF might be linked to the factors other than prophylaxis with BB.⁹

To further clarify the role of prophylactic BB in this era of new CABG protocols and to minimize the immeasurable confounding effects of recent advancements in the medical management, we strongly felt the need to redo a meta-analysis from the latest RCTs.

In addition, we also wanted to find the answers to two key issues which were not addressed in the guidelines

- (1) To find the effect of timing of initiation of BB prophylaxis (preoperative vs. postoperative) on the incidence of post-CABG AF and
- (2) To measure the differences among individual BB regarding the prevention of AF.

METHODS

Selection and Characteristics of Studies

- (1) The search was performed in accordance with the recommendations from Cochrane Collaboration using Cochrane CENTRAL database, MEDLINE database of National Library of Medicine, PUBMED and SCOPUS using the initial key terms of "Atrial fibrillation" "Cardiac surgery" and "Beta-Blockers." References from the initially identified articles were hand searched to find additional relevant trials. We also searched the abstract books and CD ROMS of annual scientific meetings of the American Heart Association and American College of Cardiology to find additional relevant manuscripts. No language restrictions were applied.
- (2) We limited our search to 1995 until the present (June 2011) to reflect recent changes in the techniques and protocols of CABG and advancement in the medical management of CAD. The year 1995 was chosen for two main reasons: one is the introduction of OP CABG in late 90s¹³ and the second is the beginning of the wide spread use of peri-CABG cardio-protective medications (ASA, Statins and ACEI).
- (3) The data was gathered by two researchers (authors MFK and MRM) individually and compared at the end to resolve any discrepancies. Attempts were made to contact one author to get relevant data however desired information could not be retrieved.
- (4) Trials were carefully reviewed with particular attention to inclusion/exclusion criteria, method of randomization, exact timing of administration of postoperative and preoperative BB, definition of AF, continuity of telemetry during postoperative period and the duration of follow up and the end point of the studies.

Figure 1. Flow Diagram of the selection process *(including Risk factors for post-CABG AF, treatment of AF, Letters to editor, noncardiac surgery patients). †(Two of these studies were used in a subanalysis).

- (5) RCTs (blinded or unblinded) in which the patients undergoing elective CABG and/or valve replacement were randomized to prophylactic pharmacological intervention with BB versus placebo/no prophylaxis where incidence of post-CABG AF or supra-ventricular tachycardia (SVT) was one of the primary outcome measure were selected. Trials with any combination of prophylactic agents/supplements, use of other antiarrhythmic drugs, and use of BB in both of the randomized arms alone or in combination with other pharmacological agents were excluded.
- (6) Initially, 34 manuscripts evaluating the efficacy of BB for the prevention of post-CABG AF were identified, however 24 were excluded for various reasons (Fig. 1). The remaining ten RCTs were included in the final analysis.
- (7) Although most of the included RCTs have similar exclusion criteria (Absence of sinus rhythm at the time of surgery, atrioventricular (AV) block, chronic obstructive pulmonary disease (COPD) and bronchospasm, hypotension, and congestive heart failure (CHF), individual trials vary from one another in terms of definition

of AF, length/method of monitoring and some demographic features of study population. Individual characteristics of included studies are detailed in Table 1.

Statistical Analysis

We assessed publication bias by generating a funnel plot (not shown) and Begg's rank-correlation method (Kendall's tau),¹⁴ using the "metabias" user-written command in Stata 10.0. RR (Risk ratios) was the meta-analytic measure of association, and was calculated using the number of subjects with AF and number of subjects in each trial group (2×2 tables). For the prospective trials which have a higher incidence of events in controls, use of RR is more appropriate than odds ratio (OR). Meta-analyses were conducted on subgroups of studies involving different types of BB and were performed with the "metan" user-written command in Stata 10.0. We tested statistical heterogeneity across trials with I^2 values and Cochrane's Q statistic, using a P value greater than 0.10 to indicate presence of heterogeneity among trials for each analysis. However, we used a random effects

Table 1. Characteristics of Included Trials

Name	Timing	Pre-op BB% (P-C)	Mean age (years) (P-C)	Male% (P-C)	LVEF (P-C)	AF definition	Exclusion criteria	Limitations
Imren et al.	PREOP	NA	62.2–61.4	59–60	54–52	15 mins	CHF included	IOP Esmolol, OP CABG only
Lucio et al.	POSTOP	65–63	59–62	72–74	NA	Sustained symptom	EF<35%	Continuous ECG for only 3 days, BB WD
Wenke et al.	POSTOP	61–56	63–64	79–75	63–62	NK	EF<30%	BB WD, Continuous ECG for 2 days only
Paull et al.	POSTOP	NK	NK	NK	NK	15 mins	EF<30%	No demographic information available
Yazicioglu et al.	PREOP	NA	57–55	80–75	52–50	NK	EF<30%	Small study group
Bert et al.	POSTOP	76–72	63.6–63.8	76–83	49–49	5 mins	EF<20%, AVR included	BB WD
Connolly et al.	POSTOP	82–79	63–62	78–80	NK	1 min	CHF, Valve surgery included	BB WD
Babin-Ebell et al.	POSTOP	61–65	61–64	76–83	67–62	NK	EF<40%	BB WD, used SVT
Gun et al.	POSTOP	NK	NK	NK	NK	NK	NK	Only abstract is available
Ali et al.	POSTOP	100–100	65–63	74–69	59–56	NK	EF<35%	BB WD, Continuous ECG for 3 days only

Abbreviations as in text. NS = nonspecific; NA = not applicable; NK = not known; min = minutes; IOP = intraoperative; OP = off-pump; WD = withdrawal; P = prophylactic group, C = control group.

model¹⁵ to estimate summary effects, which allows that the true effect could vary from study to study and assumes that the available studies are a random sample of the relevant distribution of effects.

RESULTS

The total number of patients studied in all of the included RCTs was 2556, of which 1280 comprised the prophylactic group and 1276 comprised the placebo group. The mean age of the study population ranged from 55 to 64 years. There was also an obvious male predominance anywhere from 60% to 80% in the individual studies.^{16–23} Most of the authors,^{9,16–18,21–23} except the two,^{19,20} excluded patients with ejection fraction (EF) less than 20–40% and the mean EF of the study population ranged from 50% to 65%. Only two

authors included the patients undergoing valve surgery.^{18,19} Other standard exclusions were the contraindications to BB and prior CABG. Another important thing to notice is the use of pretrial BB; 60–100% of these patients were already taking preenrollment BB.^{16–19,21,22} Timing of initiation for BB prophylaxis was 3–4 days before the surgery in the preoperative prophylaxis studies^{20,23} and within 24 hours of surgery in the postoperative group.^{9,16–19,21,22,24} Definition of post-CABG AF in terms of duration varied slightly among the trials. All the patients were monitored using continuous electrocardiography (ECG) or telemetry,^{9,16–18,20–23} however, the duration of monitoring varied among individual studies.

Marked heterogeneity among the trials was largely explained by the use of different types and dosages of BB, variations in the sample size and use of prestudy BB. The quality of individual

Figure 2. BB prophylaxis versus placebo for the prevention of AF.

studies was assessed using Jaded score.²⁵ Two studies had a score 5 each,^{19,20} and the remaining eight^{9,16–18,21–24} had a score of 3 each. A score of 3 was explained by the lack of double blindness due to a particular study design or yes/no nature of the outcome that is, AF. Funnel plots (Begg’s method) were assessed visually and it displayed no asymmetry to suggest publication bias. Repeating the analysis excluding one trial²⁴ which was reported only in the abstract form did not alter the overall results. Additional subgroup analyses measuring the effects of pre- and postoperative BB, metoprolol (MPL) and propranolol (PPL) against placebo resulted in similar results except for preoperative BB for which the protective effect did not appear statistically significant.

BB versus Placebo

Two hundred fifty-eight of 1280 (20%) in the prophylactic group and 419 of 1276 (32.8%) in the control group developed new onset post-CABG AF. The RR for the individual trials ranged from lowest

of 0.11 to highest of 0.92 confirming the protective effect of BB against post-CABG AF. This protective effect of BB was statistically significant in seven of ten RCTs. None of the trials showed increased incidence of post-CABG AF with BB. Heterogeneity of the effect was indicated by ($I^2 = 67\%$, $P = 0.001$). Overall, patients on prophylactic BB had 50% reduced risk of developing post-CABG AF (RR of 0.50, 95% CI 0.36–0.69 with P value < 0.001 ; Fig. 2). Repeating the analysis after excluding one trial²⁴ resulted in similar values (RR of 0.48, 95% CI of 0.32–0.70 with P value < 0.001).

Preoperative versus Postoperative Initiation of Prophylaxis

Majority of the studies included in this analysis compared postoperative initiation of BB prophylaxis^{9,16–19,21,22,24} with controls and only two authors studied the effects of preoperative initiation of prophylaxis.^{20,23} Preoperative BB prophylaxis initiation ($I^2 = 0\%$, $P = 0.48$) resulted in 51% reduction in the incidence of AF as

Figure 3. Postoperative BB prophylaxis versus placebo for the prevention of AF.

compared to controls, however these results were not statistically significant. (RR 0.49, 95% CI of 0.24–1.0 with P value = 0.06). On the other hand, in the postoperative initiation group ($I^2 = 73.4\%$, $P < 0.001$), BB reduced the incidence up to 50% with statistically significant P value (RR 0.50, 95% CI of 0.35–0.71 with P value < 0.001 ; Fig. 3). Sensitivity analysis for the postoperative group after excluding Gun et al.²⁴ produced slightly stronger values (RR of 0.47, 95% CI of 0.303–0.732 with P value < 0.001).

Efficacy of Different BB

MPL was the most commonly used BB in RCTs after 1990s followed by PPL and atenolol (ATL). Comparison of different BB revealed that PPL and MPL were nearly equally effective in protecting against post-CABG AF. As compared to controls, PPL ($I^2 = 0.0\%$, $P = 0.404$) reduced the incidence of post-CABG AF up to 48% (RR of 0.52, 95% CI of 0.38–0.72 with P value < 0.001 ; Fig. 4) whereas use of MPL ($I^2 = 79.2\%$, $P = 0.001$) as a prophylactic drug resulted in 53% reduction in the incidence of AF (RR of 0.47, 95% CI of 0.25–0.89 with P value < 0.001 ; Fig. 5). Repeat analysis for PPL group after excluding Gun et al.²⁴ resulted in stronger

protection (RR of 0.41, 95% CI of 0.20–0.83 with P value < 0.001).

Although excluded from the initially selected RCTs, for the sake of comparison we included two randomized trials comparing MPL to carvedilol (CRG). In the meta-analysis of two available studies;^{26,27} as compared to MPL, CRG ($I^2 = 0.0\%$, $P = 1.00$) resulted in 55% reduction in the incidence of AF (RR 0.45, 95% CI of 0.28–0.74 with P value < 0.001 ; Fig. 6).

DISCUSSION

AF complicates up to 40% of the 500,000 patients per year undergoing CABG and increases the cost of the procedure by 10,055 per case resulting in incremental cost of about \$2 billion annually.²⁸ It also increases the length of stay to additional 4–5 days and identifies a subset of patients at increased risk of morbidity, strokes and in-hospital and long-term mortality.^{1,4,28} The results of our meta-analysis are similar to those of previous analyses with few exceptions. First of all, of the pooled proportions, reported incidence of postoperative AF in the controls in two previous analyses was 34% and 33%^{6,29} which is similar to that found by

Figure 4. Prophylaxis with propranolol versus placebo for the prevention of AF.

Figure 5. Prophylaxis with metoprolol versus placebo for the prevention of AF.

us (32.8%). This similarity contradicts the verdict of recent increase in the incidence of post-CABG AF mentioned in other articles.⁵ However, reported incidence of post-CABG AF in the prophylactic group was 8.7% in Andrews et al.²⁹ analysis as compared to 20% in this review. Andrews et al. included 18 RCTs (1549 patients) in their meta-analysis and found, as compared to controls, BB prophylaxis reduced the likelihood of post-CABG AF with OR = 0.28, 95% CI of 0.21–0.36. Similarly, Crystal et al.⁶ used 27 RCTs trials with 3840

patients and found reduced incidence of post-CABG AF with BB prophylaxis with OR = 0.39, 95% CI of 0.28–0.52. If we had analyzed the OR, the summary results for all the studies would have been OR = 0.40, 95% CI of 0.27–0.60, indicating results similar to that of Crystal et al. but different from Andrews et al. The exact reason of this difference in the efficacy of BB remains unclear. Although there are several differences between the study populations of the two analyses, however one of the most notable differences is the mean

Figure 6. Prophylaxis with carvedilol versus metoprolol for the prevention of AF.

age of the patients undergoing open heart surgery. The mean age range for the Andrews et al. analysis was 51–60 which is younger to current mean age range of 55–65. Age is one of the strongest risk factor for the development of post-CABG AF and higher age of the patients undergoing open heart surgery accounts for higher risk for postoperative AF.⁴ However, despite of age difference between the two populations, incidence of post-CABG AF is similar between the control groups. Does it mean that age adversely affect prophylactic ability of BB against post-CABG AF? In our opinion, we need further work to clarify the relationship between age and efficacy of prophylactic BB against AF.

Although no previous trial directly compared AF prophylaxis between PPL and MPL, in a subgroup analysis we did not find significant difference between PPL (most commonly used BB in earlier studies) and MPL (most commonly used BB in the recent studies) regarding the protection against post-CABG AF.

In a separate meta-analysis of two randomized comparative studies,^{26,27} CRG appears to be more effective than MPL for the prevention of post-CABG AF; however, the number of patients in both of these studies are small. In addition to its usual alpha and beta blockade effects, CRG has been shown to exert antiinflammatory, antioxidant, and anti-arrhythmic actions in certain clinical settings.^{30–32} As the development of post-CABG AF has been linked with higher levels of inflammation and oxidative stress in the peri-operative period,^{33–35} it is possible that above mentioned properties of CRG might offer an additional protection against post-CABG AF.

Based on the available information, it is difficult to evaluate the relationship between dosages of

Table 2. Dosages of Drugs in Included Trials

Study	Beta-blocker	Dosages	Post-CABG AF in prophylactic arm
Imren et al.	MPL	50 mg daily	8.8%
Lucio et al.	MPL	100–300 mg daily (titrated)	11%
Wenke et al.	MPL	1 mg/kg	4%
Paull et al.	MPL	50–200 mg daily (titrated)	24%
Yazicioglu et al.	ATL	50 mg daily	15.4%
Bert et al.	PPL	40 (10 q6h) mg daily	18%
Connolly et al.	MPL	100–150 mg daily	31%
Babin-Ebell et al.	PPL	40 (10 q6h) mg daily	7%
Gun et al.	PPL	NK	13.2%
Ali et al.	NS	NK	17%

NS = nonspecific; NK = not known.

BB and the incidence of post-CABG AF (Table 2). Two studies which titrated prophylactic BB dosages to heart rates of 60–90 per minute, did not find any correlation between higher dosages and prevention of post-CABG AF.^{9,21} Two other studies which showed the lowest incidence of post-CABG AF among the included RCTs, only used low-to-moderate dosages of BB for prophylaxis.^{17,22} On the other hand, in a study by Connolly et al., incidence of post-CABG AF with BB prophylaxis was 31% even with moderately higher dosages of MPL (100 and 150 mg per day) and increasing the dose from 100 mg per day to 150 mg per day did not affect the outcome.¹⁹

Our data cannot be corrected to adjust for differences in the dosages of BB, and this difference in dosages among the studies, remains one of the main determinants of heterogeneity for this analysis. This issue gets further complicated by the fact that there are no RCTs comparing different dosages of same drug for the prevention of post-CABG AF; and the studies which used titration of BB dosages to lower heart rates in the perioperative period did not show any convincing relationship between lower heart rates and incidence of post-CABG AF.^{9,21}

Previous studies did not show statistically significant difference in protection against post-CABG AF with regard to timing of initiation of prophylaxis.²⁹ Based on our analysis, postoperative initiation of BB prophylaxis appears to be superior to preoperative initiation of prophylaxis for the prevention of post-CABG AF. However, one must realize that this comparison is limited by relatively lower number of patients in the preoperative arm (151 in preoperative prophylaxis group vs. 2405 in postoperative prophylaxis group). We feel that this matter should be further investigated in RCTs to reach a final conclusion.

Most of the included studies^{9,16-18,20-23} used a 24/7 telemetry or continuous ECG monitoring for arrhythmia detection which is in contrast to a previous analysis where many of the studies had used bed side monitoring resulting in potential bias of lower incidence of reported AF.²⁹

Limitations

In addition to usual limitations of a meta-analysis, there are several shortcomings to the results of this paper. One of the most prominent one pertaining to the individual studies is a comparison between group of patients who were continued on their pretrial BB therapy to those where BB were abruptly discontinued before or after the surgery, creating a BB withdrawal.^{16-19,21,22} Deleterious effects of BB withdrawal had been studied in details and are well-known to cause AF.^{2,4,28,36,37} 60–100% of patients (prophylactic and control groups) included in the selected RCTs were taking pre-enrollment BB. Patients with chronic BB therapy have a hyper adrenergic state due to up regulation of beta-adrenergic receptors.³⁸⁻⁴¹ Abrupt discontinuation of BB results in rebound increase in sympathetic activity which may predispose to AF.^{37,42,43} In these studies, discontinuation of BB in

the control group likely created a withdrawal effect resulting in increased incidence of postoperative AF. Thus, the final results are biased and at least partially represent the effects of BB withdrawal rather than true magnitude of protection offered by the prophylactic BB. This withdrawal effect is more prominent with agents of shorter half life like PPL⁴⁴ and MPL which were the most commonly used drugs in the included RCTs. BB withdrawal phenomenon have been shown to last for 8–13 days,³⁹ which means that even preoperative discontinuation of nonstudy BB in controls for at least 7 days before the surgery to enroll in RCT might have created withdrawal effects in the post-CABG period. A previous meta-analysis tried to overcome this issue by performing a subgroup analysis by dividing the available studies into two groups that is, those with and without BB withdrawal. “BB withdrawn” group consisted of the studies where study BB was compared to placebo plus discontinuation of nonstudy BB whereas “BB not withdrawn” group comprised of studies where study BB was compared to placebo plus continuation of nonstudy BB.⁴⁵ Although authors showed that prophylactic BB appeared much less effective in the absence of withdrawal however these results were confounded as “BB not withdrawn” group had BB in both the arms (control and prophylactic) which would have underestimated the protection offered by prophylactic BB. In this article, we could not perform such an analysis as eight of the included trials were cofounded by withdrawal along with two trials where the information on the continuation of nonstudy BB was not clearly stated.

In addition, patients with CHF, COPD, past history of AF and combined CABG and valve surgery who were at higher risk for postoperative AF⁴ were excluded from many of the RCTs. Thus, these results cannot be generalized to nonstudy and higher risk patients.

We could not compare the efficacy of prophylactic BB between OP CABG versus conventional CABG as several RCTs, though included patients with OP CABG, did not separately describe the characteristics of two groups.

Although all of the studies used continuous ECG monitoring for arrhythmia detection, the duration of monitoring in some of the studies was only for 3 days.

Analysis is limited as we did not have access to all the clinically relevant information.

CONCLUSION

Although there are several limitations, results of this analysis represent the efficacy of prophylactic BB in open heart surgery patients of this era. By setting our starting point to 1995, we tried to minimize the confounding factors related to the evolution of protocols of CABG and the medical management of CAD.

We conclude that continuation of perioperative BB in patients without any contraindication to BB therapy is protective against post-CABG AF. Although CRG appears to be a better prophylactic agent than MPL, we need further RCTs to confirm this finding.

To minimize the confounding effects of BB withdrawal, with current standards of care it is difficult to enroll CAD patients who are not taking any pretrial BB, however an RCT involving patients undergoing isolated valve surgery who are naive to BB will give a true measure of protection offered by BB against post-CABG AF.

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