Efficacy of N-Acetylcysteine Plus Beta-Blocker Versus Beta-Blocker Alone in Preventing Postoperative Atrial Fibrillation After Cardiac Surgery: A Meta-Analysis of Randomized Controlled Trials

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DISCLOSURE: None

Abstract

BACKGROUND: Postoperative atrial fibrillation (POAF) is the most common arrythmia to occur after cardiovascular surgery. Inflammation being pivotal in POAF perpetuation has been utilized as a therapeutic target. Owing to their anti-inflammatory and anti-oxidant effects, beta-blockers (BB) and N-acetylcysteine (NAC) became research interests in the pursuit for an effective POAF prevention strategy.

OBJECTIVE: To determine the efficacy of NAC plus BB versus BB alone in preventing POAF in cardiac surgery patients.

METHODOLOGY: A literature search using the following search engines: PubMed/Medline, Cochrane Review Central, Clinical Trials Registry, ResearchGate, Mendeley and Google Scholar for relevant randomized trials were conducted. Published and unpublished studies indexed from inception until 2023 were included. Three independent reviewers evaluated the randomized clinical trials (RCTs) for eligibility. The pooled estimates for POAF prevention as primary outcome and MACE, mortality, myocardial infarction, stroke, ICU LOS and hospital LOS as secondary outcomes were measured using the RStudio statistical software.

Results: Seven eligible RCTs allocated 1069 cardiac surgery patients to NAC + BB (n=539) and BB alone (N = 530) treatment arms. The effect estimate using random effect model disclosed significantly reduced POAF events (RR 0.62, 95% CI [0.44, 0.86], $p = 0.005$) in those on NAC + BB. While no statistical difference between the study arms were demonstrated in reducing mortality (RR 0.63, 95% CI [0.23, 1.73], $p = 0.37$); myocardial infarction (RR 1.02, 95% CI [0.49, 2.13], $p = 0.96$); stroke (RR 0.95, 95% CI [0.24, 3.68], $p = 0.94$); ICU LOS (std. mean difference 0.14, 95% CI [-0.43, 0.70], $p = 0.41$), and hospital LOS (std. mean difference 0.08, 95% CI [-0.06, 0.21], $p = 0.19$).

CONCLUSION: Among cardiac surgery patients, the use of NAC in combination with BB compared with BB alone significantly reduced POAF.

INTRODUCTION

Rationale

Postoperative atrial fibrillation (POAF) can potentially complicate any surgery. Cardiac surgery accounts for 30% of its overall incidence, but rates vary depending on the type of cardiac operation. Its incidence can go to a high of 40%-50% following valve replacement surgeries, 30% for those who underwent aortic surgery, 20% post coronary artery bypass graft (CABG) and 4% following cardiac transplant.[1]

The incidence of POAF has remained stable through the years and this is despite a better understanding of its pathophysiology and impact on clinical outcomes and development of newer preventive measures. Thus, there is continued research interest in pursuit for and development of more effective preventive POAF strategies.

While traditionally defined as new-onset atrial fibrillation in the immediate (peaking at 2-4 days) postoperative period, there is actually no consensus as to the definition used in clinical trials.[2] Authors' definition varied to include POAF requiring treatment (thus, discounting self-terminating AF) or any POAF that lasted more than 30 seconds and in others longer than 10 minutes as well [3-5]

Despite its transient nature, patients who developed POAF have longer in-hospital and ICU length of stays (LOS) translating to higher hospitalization costs and higher rates of adverse cardiovascular events including stroke, heart failure, myocardial infarction, acute renal failure and mortality.[6-7] There is also a link to an 8-fold increase in risk of developing atrial fibrillation beyond the postoperative period.[8]

While patients' inherent cardiovascular risk factors and comorbidities may contribute to the risk of POAF, cardiac surgery may itself facilitate POAF. Cardiopulmonary bypass may increase cytosolic calcium levels that stimulate oxidative stress and inflammation [9-12] Right atriotomy during venous cannulation or manipulation of the perivalvular atrial tissue can lead to atrial structural alterations and inhomogeneity in conduction that will favor dynamic reentry and POAF.[13]

Pericardial effusion, ion channel modifications, periatrial fat metabolic activity and autonomic neuromodulation, gap junction uncoupling and ectopic pulmonary vein activity have been implicated as pathophysiological mechanisms underlying POAF as well.[14-20]

It is believed that the key mechanism promoting POAF is inflammation and this has been corroborated with peak increase of inflammatory markers coincident with the peak incidence of POAF.[21] Anti-inflammatory interventions with statins, corticosteroids and colchicine therapies utilized this as a therapeutic target. [22-25]

Since sympathetic activation has been identified to play an important role in POAF initiation and perpetuation, perioperative beta-blocker (BB) therapy remains a mainstay in pharmacopeia of POAF. However, a Cochrane meta-analysis of 33 RCTs attested that the reduction of POAF does not necessarily translate in reduction in perioperative stroke or mortality and length of stay.[26]

Owing to its anti-inflammatory and antioxidant properties, interest in mucolytic, N-acetylcysteine (NAC) was heightened when promising results of POAF prevention from observational studies and small RCTs were demonstrated. [27-28]

RCTs investigating the combined NAC + BB in the POAF demographic are sparse with small number of study population.

This meta-analysis therefore aims to delve into the current collective data comparing the efficacy of NAC and BB with BB alone in preventing POAF after cardiac surgery.

Research Question

Among cardiac surgery patients, how effective is NAC plus BB in preventing POAF as compared to BB alone?

OBJECTIVES

General Objective

To determine the efficacy of NAC plus BB versus BB alone in preventing POAF in cardiac surgery patients.

Specific Objectives

1. To describe the baseline characteristics of cardiac surgery patients.
2. To compare the POAF events in cardiac surgery patients treated with NAC plus BB versus BB alone.
3. To determine the risk of major adverse cardiovascular events in cardiac surgery patients treated with NAC plus BB versus BB alone.
4. To determine the mortality in cardiac surgery patients treated with NAC plus BB versus BB alone.
5. To determine the myocardial infarction events in cardiac surgery patients treated with NAC plus BB versus BB alone.
6. To determine the cerebrovascular events in cardiac surgery patients treated with NAC plus BB versus BB alone.
7. To compare the length of intensive care unit stay in cardiac surgery patients treated with NAC plus BB versus BB alone.
8. To compare the length of hospitalization in cardiac surgery patients treated with NAC plus BB versus BB alone.

Materials and Methods

This meta-analysis was executed according to a predetermined protocol outlined by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) using standard systematic review procedures

Eligibility Criteria

Type of Studies: Only RCTs evaluating NAC plus BB as prevention of POAF among cardiac surgery patients were included. BB therapy may include maintenance BB or preoperative BB started days prior to cardiac surgery.

Population: Studies were limited to patients who underwent coronary artery bypass grafting with or without valve surgery.

Language: Publications with English language was considered.

Types of Intervention: NAC plus BB versus BB alone among cardiac surgery patients. NAC plus BB arm included patients with preoperative NAC added on top of a maintenance BB or a preoperatively initiated BB.

Time Frame: The publication status restrictions were imposed. Published and unpublished studies indexed from inception until 2023 were included.

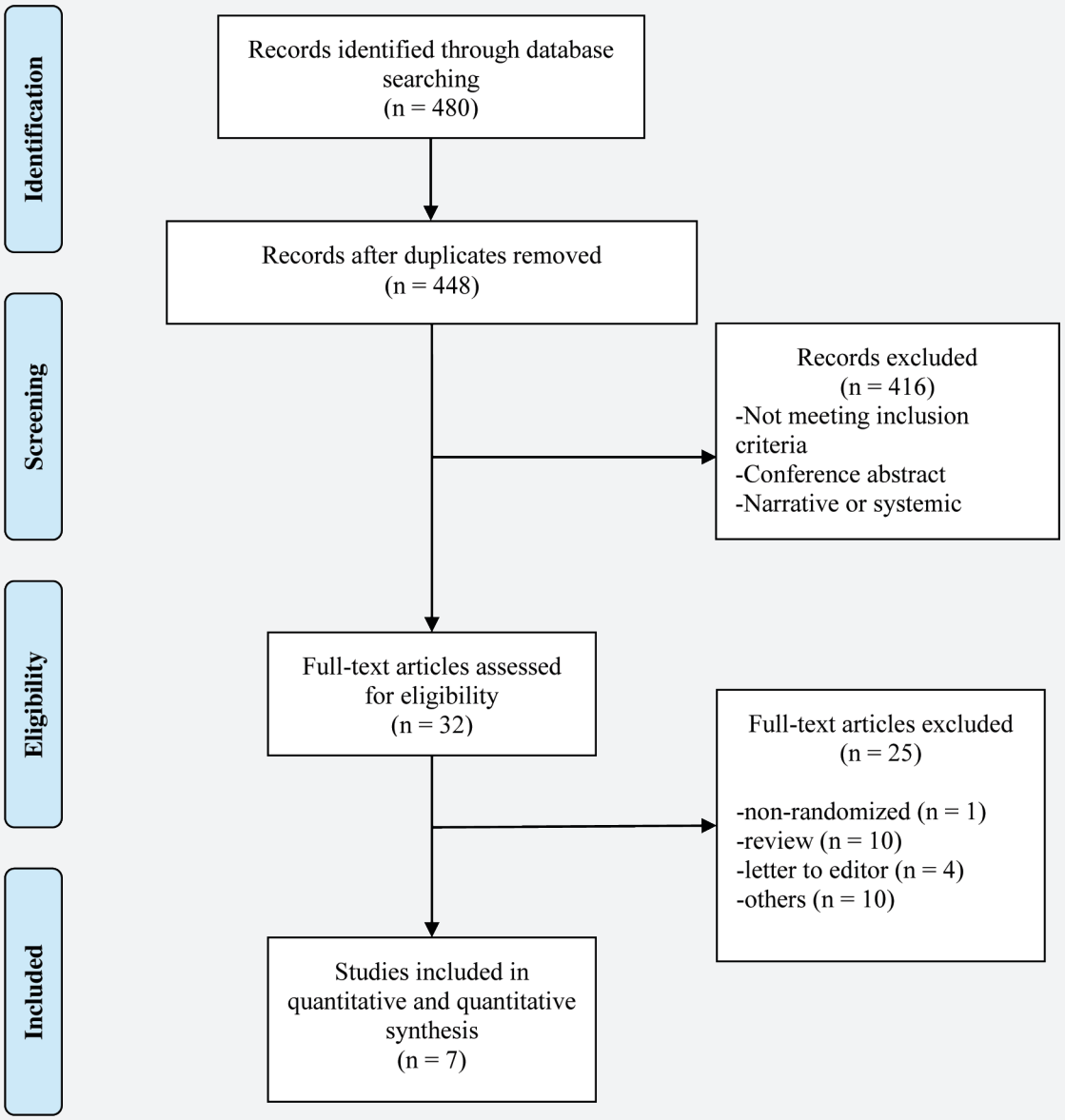


Figure 1. PRISMA flow diagram of study selection

Exclusion Criteria

All non-randomized trials, observational studies, abstract, review and letter to editor were excluded.

Types of Outcome Measures:

Primary Outcome

1. POAF

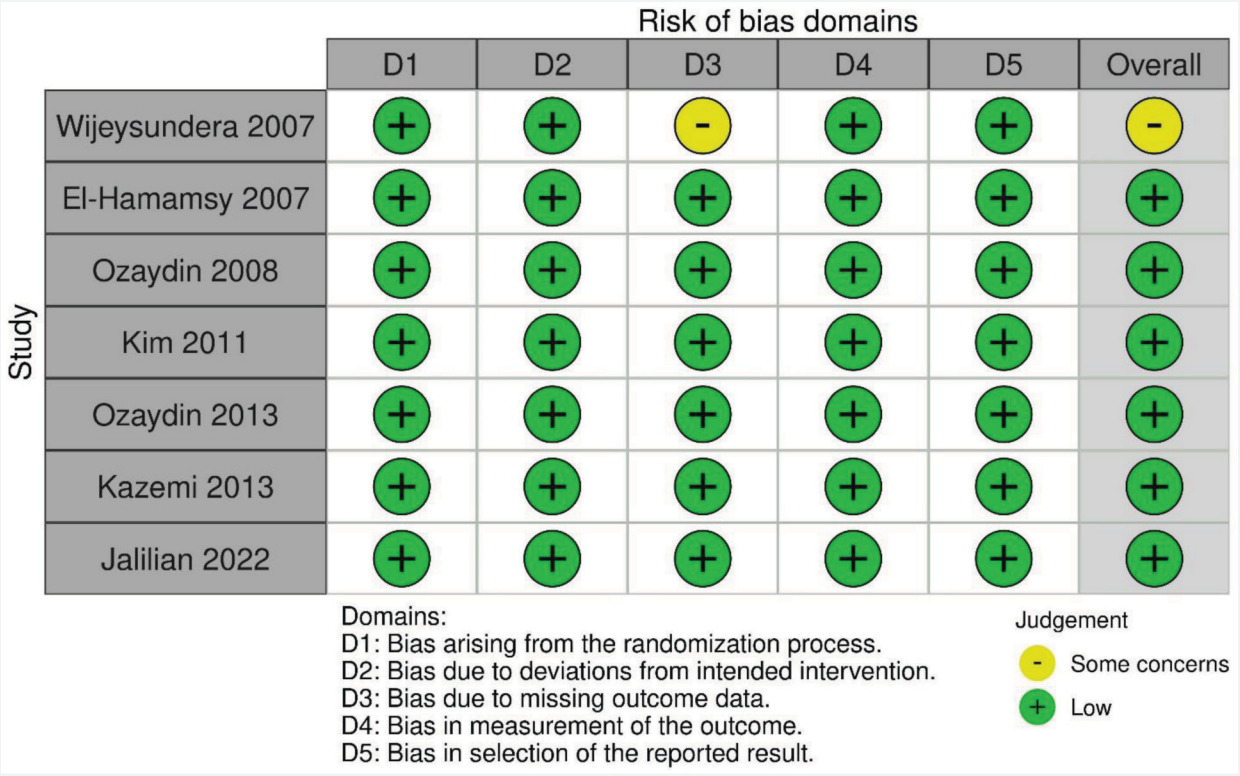
Secondary Outcomes

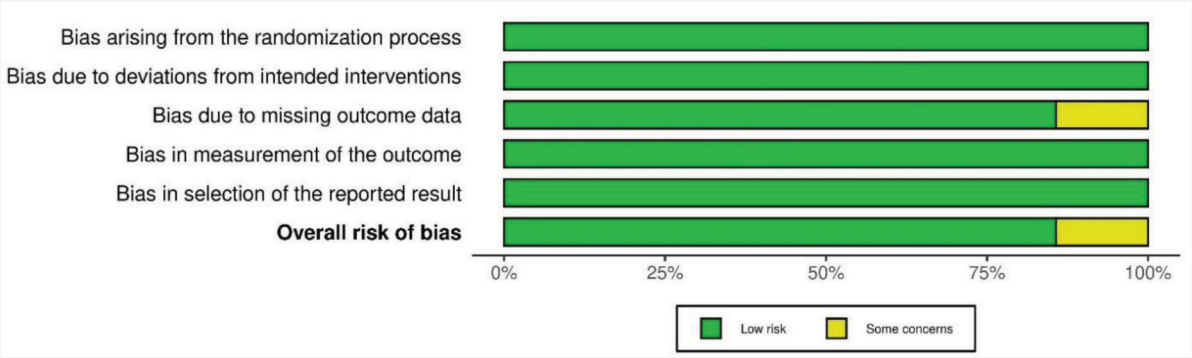
1. Mortality
2. Myocardial infarction
3. Stroke
4. Length of ICU stay
5. Length of hospitalization

Operational Definition of Terms

- ***Atrial fibrillation (AF)*** – a supraventricular tachyarrhythmia described on the electrocardiogram (ECG) as rapid oscillations or fibrillatory waves that vary in size, shape, and timing, associated with an irregular, frequently rapid ventricular response when atrioventricular conduction is intact.
- ***Postoperative atrial fibrillation (POAF)*** – any postoperative atrial fibrillation lasting at least 5 minutes
- ***N-acetylcysteine*** – an acetylated form of the amino acid L-cysteine, which has an antioxidant, anti-inflammatory and mucus thinning properties.
- ***Beta-adrenergic receptor antagonists or Beta-blockers*** – group of medications mainly used to treat cardiovascular conditions like hypertension, angina pectoris and cardiac arrhythmias. These include carvedilol, metoprolol, bisoprolol and nebivolol.

Table 1. Risk of bias summary





Search Methods for Identification of Studies

Three reviewers independently searched both published and unpublished studies. Studies were identified by searching through electronic databases PubMed/Medline (http://www.ncbi.nlm.nih.gov/pubmed), Cochrane Review Central (http://www.cochranelibrary.com), Clinical Trials Registry (https://clinicaltrials.gov), ResearchGate (https://www.researchgate.net), Mendeley (https://www.mendeley.com) and Google Scholar (http://scholar.google.com), indexed from inception up to 2023, using the following search terms: "Postoperative Atrial Fibrillation" OR "POAF" AND "N-Acetylcysteine" OR "NAC." Reference lists of original articles identified were also hand searched for additional eligible studies. Only data accessible in peer-reviewed journals were included to minimize potential sources of bias and inaccuracy.

DATA COLLECTION AND DATA ANALYSIS

Study Selection and Appraisal of Study Quality

Each title and abstract of individual studies was screened initially to exclude irrelevant reports. Eligibility assessment was performed independently and potentially relevant studies retrieved. In case of disagreement, discrepancies were resolved by reaching a consensus between reviewers. The reviewers started with a large number of identified records, then sequentially excluded records according to the eligibility criteria. Those who passed the eligibility criteria were reviewed in its full text publication.

Quality assessment of the studies was performed using the Cochrane Collaboration's Risk of Bias tool. CASP RCT standard checklist was also utilized to assess the quality of evidence.

An extensive search was made via PubMed/Medline, Cochrane Review Central, Clinical Trials Registry, ResearchGate, Mendeley, Google Scholar and reference lists of relevant trial databases which yielded 480 articles. After an initial assessment, 32 studies were included, however, only seven study trials were included in the final analysis.

Data Extraction and Management

Data from different relevant studies were extracted by two independent reviewers to an electronic data collection form (Appendix A). Full manuscripts of all potentially relevant studies were obtained from an eligible published and unpublished randomized trial. A letter was sent via email to all main authors of each included study for extraction of additional pertinent data. The following data were extracted: author's name, year of publication, study design, study duration, population size, intervention, type of surgery and outcome. Inclusion criteria and follow-up duration were also extracted. The included studies were independently reviewed by two separate reviewers (GV and VT). Disagreements between data extractors/review authors were resolved after a thorough review and discussion of eligibility criteria with third party technical and content experts (MV and SC, respectively) before getting into a consensus.

Assessment of Risk of Bias

Methodological quality assessment using the Cochrane Risk of Bias Tool was independently performed by two of the authors. Risk of bias was assessed by performing a full text review of each included study and identifying statements that describes a particular domain. Any disagreement was resolved by consensus.

Measures of Effect

For incidence of POAF, MACE, mortality, myocardial infarction and stroke, the outcome measures were presented using risk ratio together with 95% confidence intervals (CI). The length of ICU and hospital stay, which are continuous outcomes, were presented using means and standard deviations. Therefore, mean difference (and standard mean difference for data that are transformed) together with the corresponding 95% CI were effective measures used for these outcomes. For dichotomous data (events and non-events), Mantel Haenszel (MH) was used for pooling effect sizes from individual studies while for continuous data (mean and standard deviation), inverse variance (IV) was used. The pooled estimates for POAF prevention as primary outcome and MACE, mortality, myocardial infarction, stroke, ICU LOS and hospital LOS

Table 2. Eligible RCTs study characteristics

STUDY / YEAR	STUDY DESIGN	STUDY DURATION	NUMBER OF NAC + BB/ BB	INTERVENTION	SURGERY TYPE	DEFINITION OF POAF	NAC PROTOCOL
Wijeysundera 2007[33]	RCT Single-center	2003-2005	88/87	Preoperative NAC added to maintenance BB vs. maintenance BB	CABG ± valve	NEW ONSET AF detected by continuous telemetry or 12-lead electrocardiograms.	100 mg/kg IV over 30 mins after induction of anesthesia, then 20mg/kg/h for 4 h after CPB
El Hamamsy 2007[34]	RCT Single-center	2003-2004	50/50	Preoperative NAC added to maintenance BB vs. maintenance BB	CABG	ANY POSTOPERATIVE AF Documented from all electrocardiograms interpreted by 2 independent observers (ICU physicians) who were blinded to the study groups	600mg orally the day before and the morning of the operation, 150mg/kg IV before skin incision, then 12.5mg/kg/h over 24 hours
Ozaydin 2008[35]	RCT, Single-center	2005-2006	58/57	Preoperative NAC added to maintenance BB vs. maintenance BB	CABG ± valve	ANY POSTOPERATIVE AF Confirmed by 12L ECG	50mg/kg IV for 1 hour before surgery, then 50 mg/kg/day after operation
Kim 2011[36]	RCT Single-center	2010	24/24	Preoperative NAC added to maintenance BB vs. maintenance BB	CABG	ANY POSTOPERATIVE AF	100mg/kg IV bolus after anesthetic induction, then 40mg/kg/day IV for 24 hours
Ozaydin 2013[37]	RCT Single-center	2008-2011	104/104	NAC plus Carvedilol vs. Carvedilol	CABG ± valve	ANY POSTOPERATIVE AF lasting at least 5 minutes	50mg/kg IV for 1 hour before and at the same dose for 48 hours after surgery
Kazemi 2013[38]	RCT Single-center	2010-2011	120/120	Preoperative NAC added to maintenance BB vs. maintenance BB	CABG ± valve	ANY POSTOPERATIVE AF lasting at least 5 minutes Or Hemodynamically significant AF within 72 hours of post operative monitoring (resulting to hypotension or heart failure)	1200mg orally 2 times per day from 48 hours before and upto 72 hours after heart surgery
Jalilian 2022[39]	RCT Single-center	2016-2017	150/150	NAC plus Carvedilol vs. Carvedilol	CABG	ANY POSTOPERATIVE AF	After starting cardiopulmonary bypass, cardioplegic solution was enriched with NAC (4 mmol/l)

RCT, randomized controlled trial; NAC, N-acetylcysteine; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; MI, myocardial infarction; CK-MB, creatine-kinase myocardial band; POAF, postoperative atrial fibrillation; ALI, acute lung injury; ICU, intensive care unit

Table 3. Study Population Baseline Characteristics

	Total / Ave.	Wijeysundera 2007		El Hamamsy 2007		Ozaydin 2008		Kim 2011		Ozaydin 2013		Kazemi 2013		Jalilian 2022	
	N = 1069 (%)	NAC +BB	BB	NAC + BB	BB	NAC + BB	BB	NAC + BB	BB	NAC + BB	BB	NAC + BB	BB	NAC + BB	BB
		n=88	*n=87*	*n=50*	*n=50*	*n=58*	*n=57*	*n=24*	*n=24*	*n=104*	*n=104*	*n=120*	*n=120*	*n=150*	*n=150*
Age (years)	62.7 ± 13	74 ± 8	73 ± 9	59.8 ± 7.8	61.3 ± 7.4	57± 11	59 ± 9	60.8 ± 8.4	65.3 ± 7.6	63 ± 9	62 ± 9	61.3 ± 9.8	58.2 ± 12.7	61.1	61.5
Male	803 (75.11)	53	51	43	46	47	44	21	22	81	76	79	76	87	77
Preoperative status:															
CHF	201 (18.8)	17	16	20	25	-	-	24	24	15	18	4	5	15	18
Ejection Fraction (%)	45.95 ± 9.8	-	-	-	-	53 ± 9	49 ± 11	34.8 ± 7.6	33.1 ± 6.2	49 ± 12	49 ± 13	47.4 ± 9.5	47.2 ± 10.4	48.6	48.4
CAD presentations															
Stable Angina	481 (44.99)	-	-	-	-	26	20	-	-	40	51	36	84	119	105
ACS UA/MI	529 (49.5)	-	-	22	22	30	35	10	12	64	53	71	49	79	82
Previous MI	146 (13.66)	-	-	17	23	-	-	-	-	-	-	52	54	-	-
Serum creatinine	1.29	1.48	1.39	-	-	-	-	1.1	1.2	-	-	-	-	-	-
LA diameter (mm)	38.7 ± 4.5	-	-	-	-	38 ± 5	40 ± 5	-	-	41 ± 5	41 ± 4	34.5 ± 5	36.7 ± 2.8	39	39
Comorbidities															
HPN	660 (61.74)	72	64	-	-	31	35	15	18	64	62	55	70	86	88
Diabetes	437 (40.88)	31	26	-	-	19	18	14	14	44	45	40	42	70	74
Dyslipidemia	256 (23.95)	-	-	-	-	-	-	-	-	-	-	61	43	78	74
PAD	30 (0.03)	15	15	-	-	-	-	-	-	-	-	-	-	-	-
Stroke	32 (0.03)	12	20	-	-	-	-	-	-	-	-	-	-	-	-
COPD	74 (0.07)	8	13	-	-	-	-	-	-	13	12	5	8	7	8
CKD	79 (0.07)	-	-	-	-	-	-	-	-	-	-	11	7	19	42
Coronary involvement															
Three-vessel	331 (0.31)	-	-	41	41	20	18	20	20	-	-	82	89	-	-
Left main	79 (0.07)	-	-	11	13	7	6	6	5	-	-	12	19	-	-
Preop. meds:															
Beta-blocker	1000 (93.54)	61	57	44	38	51	53	11	12	80	91	102	100	150	150
CCB	121 (	35	29	22	21	-	-	8	6	-	-	-	-	-	-
ACEi or ARBs	521	57	49	28	24	39	37	17	21	47	42	81	79	-	-
Aspirin	243	67	62	-	-	57	57	-	-	-	-	-	-	-	-
Statin	359	-	-	-	-	48	49	-	-	30	34	100	98	-	-
Diuretics	90	-	-	-	-	-	-	8	10	15	16	17	24	-	-

NAC, N-acetylcysteine; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome; UA, unstable angina; MI, myocardial infarction; LA, left atrium; PVD, peripheral vascular disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; BB, beta-blocker; CCB, calcium channel blocker; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker

as secondary outcomes were measured using the RStudio Statistical software.

Moreover, Chi square was used to test the association between studies and after that is pooled analysis. Risk of bias assessment was used for the RCTs included in this study.

RESULTS

Selection and Characteristic of the Study

Table 2 summarized the characteristics of the seven eligible RCTs which allocated 1069 cardiac surgery patients to NAC + BB (n=539) and BB alone (n=530) treatment arms. All were single center RCTs investigating patients who underwent CABG with or without valve replacement surgery. The type of BB used were not specified in five of these studies, while two used carvedilol as the study BB. The POAF definition varied but most studies used any POAF, either detected by continuous telemetry or 12-lead ECG as the event criterion with some authors specifying a duration requisite of at least 5 minutes. The NAC initiation protocols also varied as to the manner of drug administration (intravenous or per orem), loading and maintenance dosages and timing of initiation.

The study population (Table 3) was predominantly male (75.11%) with a mean age of 62.7 ± 13 years and average LVEF of 45.95 ± 9.8%. Coronary artery disease, hypertension, diabetes and congestive heart failure were the prevailing comorbidities.

Study Outcome

A. Postoperative Atrial Fibrillation

The POAF prevalence among the study population was 19.08% (204/1069) wherein those given NAC + BB had 80/539 (14.84%) events, while those on BB alone had 124/530 (23.40%). The effect estimate using random effect model disclosed a significant 38% reduction of POAF events (RR 0.62, 95% CI [0.44, 0.86], $p = 0.005$) afforded by NAC + BB over BB alone with an overall moderate heterogeneity of 35%.

B. Mortality

Five of the seven eligible RCTs reported a total of 19 deaths, seven in NAC + BB versus 12 in BB arms. While there is a trend in survival advantage favoring NAC + BB (0.63 [0.32;1.73] p = 0.37, $I^2 = 9\%$) the difference between treatment arms did not reach statistical significance.

C. Myocardial Infarction

A total of 27 myocardial infarction events: 14/173 (8.09%) in the NAC + BB and 13/166 (7.83%) in BB arms were reported in three of the seven RCTs. The difference between treatment arms were not statistically significant.

D. Stroke

Only eight events were reported in four RCTs investigating a predefined stroke outcome. However, two of these studies

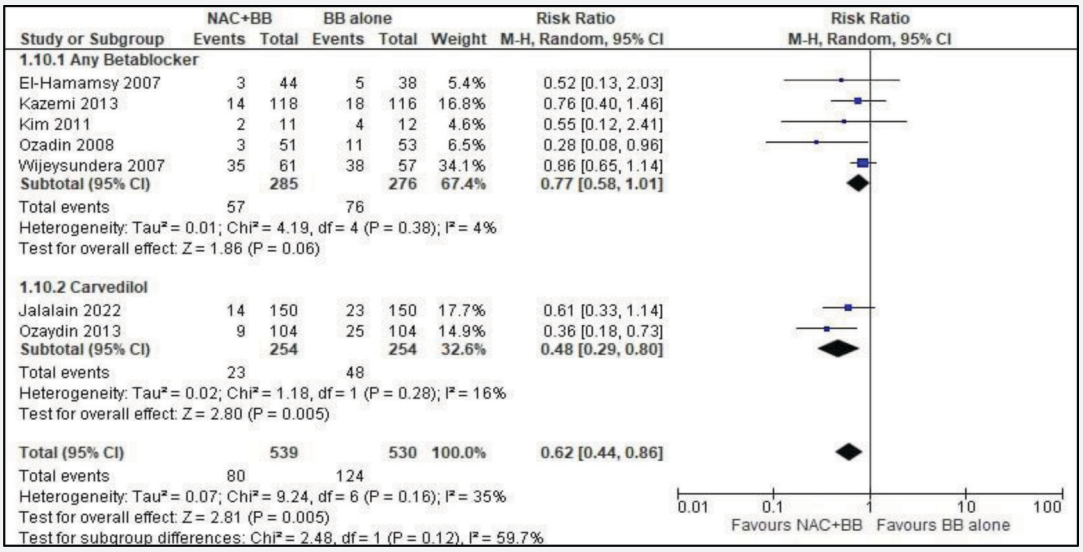


Figure 2. Forest Plot of POAF risk among patients undergoing cardiac surgery allocated to received NAC+ BB vs. BB alone

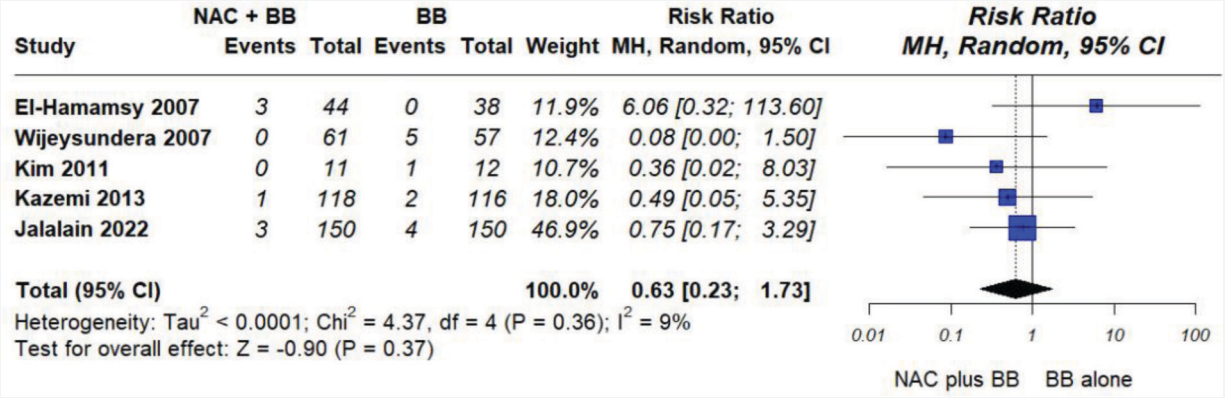


Figure 3. Forest plot of mortality risk in patients undergoing cardiac surgery allocated to received NAC+ BB vs. BB alone

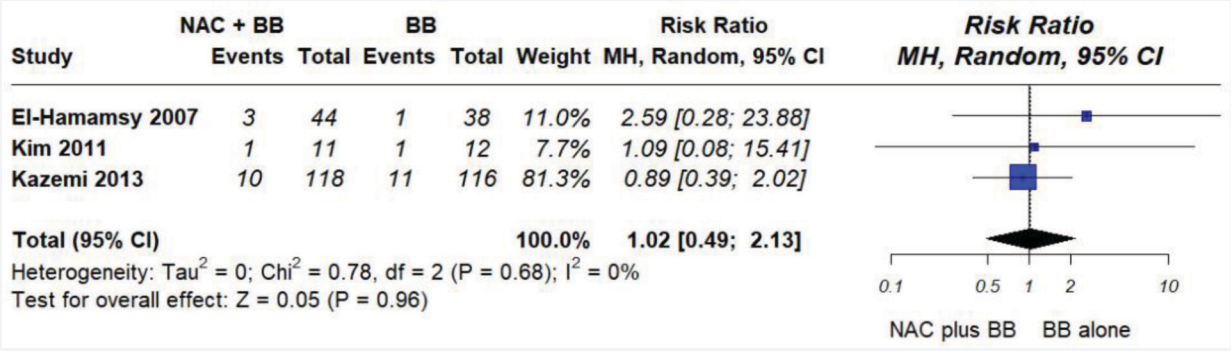


Figure 4. Forest plot of myocardial infarction risk in patients undergoing cardiac surgery allocated to received NAC + BB versus BB alone

reported zero events rendering the pool estimates to be imprecise for adequate interpretation.

E. Length of ICU Stay

F. Length of Hospitalization

The pooled estimate analyses showed a trend of longer ICU and hospital stay with NAC + BB but the difference between treatment arms did not reach statistical significance.

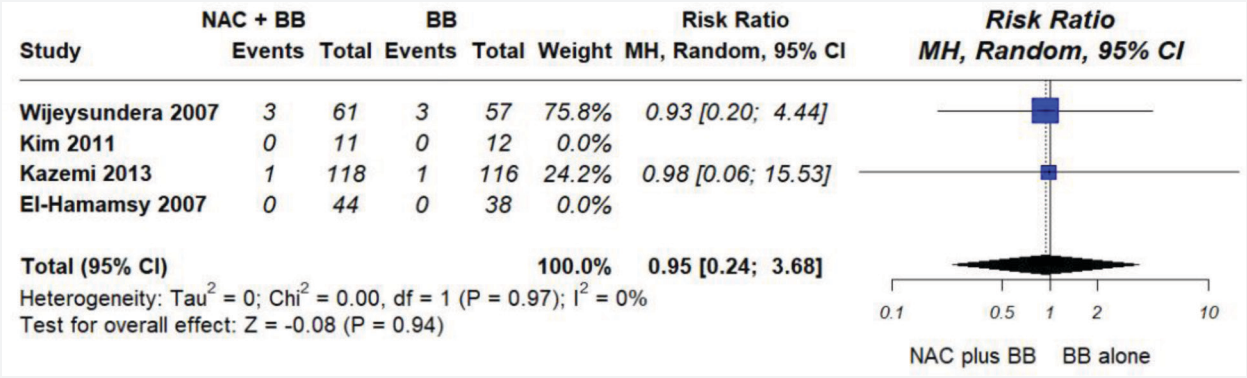


Figure 5. Forest plot of mortality in patients undergoing cardiac surgery allocated to received NAC + BB vs. BB alone

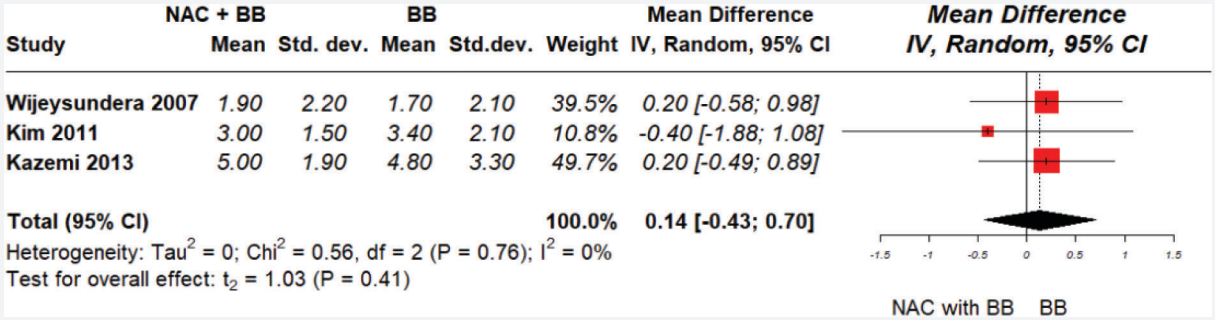


Figure 6. Forest plot of the length of ICU stay in patients undergoing cardiac surgery allocated to received NAC + BB versus BB alone

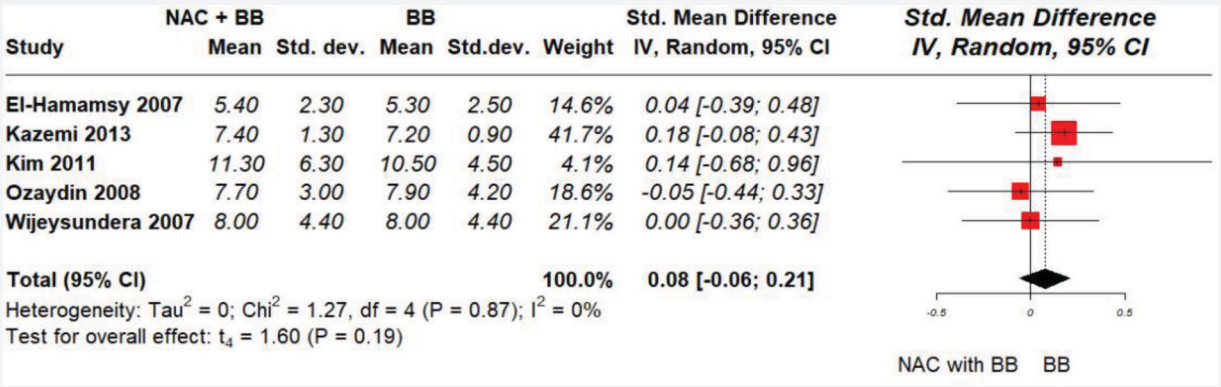


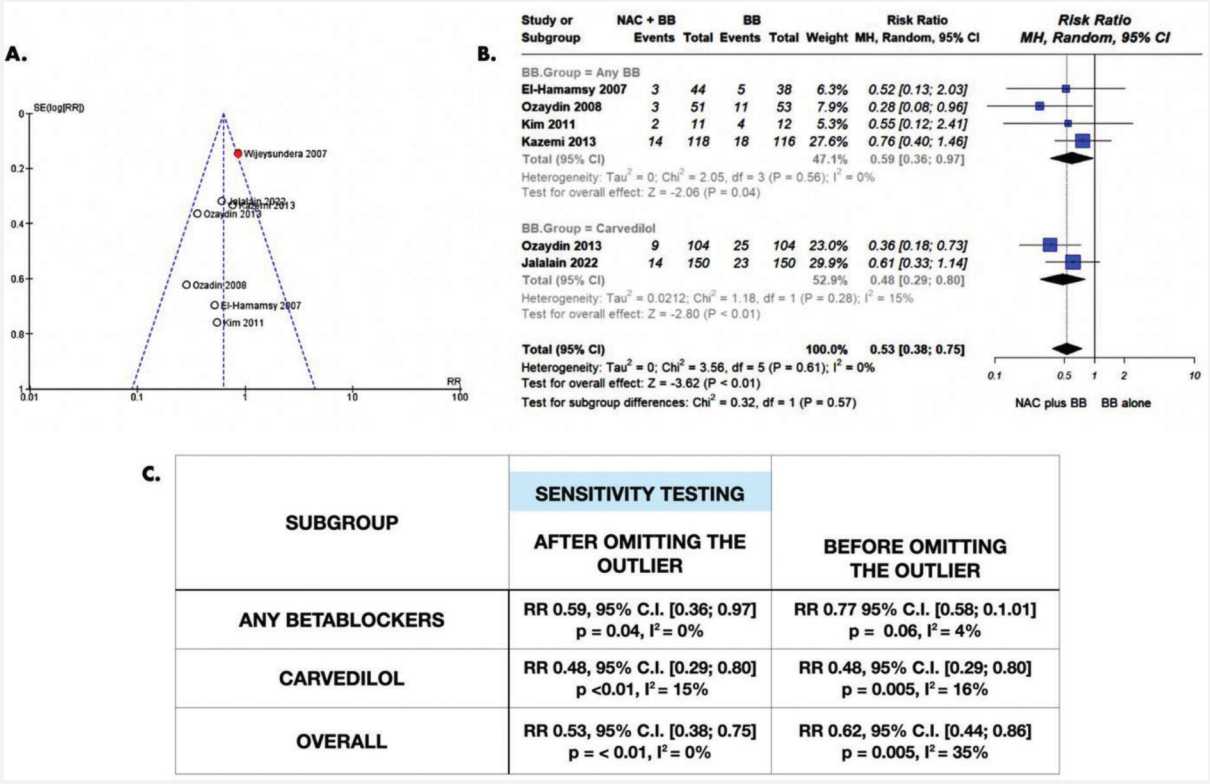
Figure 7. Forest plot of the length of hospital stay in patients undergoing cardiac surgery allocated to received NAC + BB versus BB alone

Whether this unexpected trend is due to small event rates, data outliers or bias, random chance, or unmeasured confounders remained to be ascertained.

DISCUSSION

The pooled random analysis of the seven eligible RCTs demonstrated a 38% reduction of POAF events favoring the use of NAC + BB. With a moderate heterogeneity of 35%, a sensitivity analysis was run to determine the presence of publication bias. In the funnel plot of the primary outcome, the study of Wijeysundra, 2007[33] (Figure 8A) was found touching the significant dash line making it a potential outlier. Excluding this study in the analysis (Figure 8B) dropped the overall heterogeneity to 0% and lowered further the risk for POAF to 47% (0.53, 95% CI [0.38;0.75] p<0.01). This study accounted for 57% of pooled estimates for the endpoint of POAF which were not consistent with the former values in the "ANY Betablockers" subcategory and the subgroups' overall effect, (Figure 8C) suggesting the presence of publication bias.

To determine the potential source of heterogeneity, the Pearson's Chi-Square Test for Independence (Table 4) was



C.

SUBGROUP	SENSITIVITY TESTING: AFTER OMITTING THE OUTLIER	BEFORE OMITTING THE OUTLIER
ANY BETABLOCKERS	RR 0.59, 95% C.I. [0.36; 0.97] p = 0.04, I^2 = 0%	RR 0.77 95% C.I. [0.58; 0.1.01] p = 0.06, I^2 = 4%
CARVEDILOL	RR 0.48, 95% C.I. [0.29; 0.80] p <0.01, I^2 = 15%	RR 0.48, 95% C.I. [0.29; 0.80] p = 0.005, I^2 = 16%
OVERALL	RR 0.53, 95% C.I. [0.38; 0.75] p = < 0.01, I^2 = 0%	RR 0.62, 95% C.I. [0.44; 0.86] p = 0.005, I^2 = 35%

Figure 8. Sensitivity analysis for the primary outcome of POAF

Table 4. Pearson's test for independence

	Wijeysundera 2007	El Hamamsy 2007	Ozaydin 2008	Kim 2011	Ozaydin 2013	Kazemi 2013	Jalilian 2022	P-value
Total Population	175	100	115	48	208	240	300	
Age (years)	73 ± 8.5	60 ± 7.6	58 ± 10	63 ± 8	62.5 ± 9	59.6 ± 11	61.3	0.4232
Male	104 (59%)	89 (89%)	91 (79%)	43 (90%)	157 (75%)	155 (65%)	164 (55%)	0.0000*
Congestive heart failure	33 (19%)	45 (45%)	No data	48 (100%)	33 (16%)	9 (04%)	33 (11%)	0.0000*
Ejection Fraction (%)	No data	No data	51 ± 10	33.95 ± 6.9	49 ± 12.5	47.3 ± 10	48.5	0.3071
Coronary artery disease	141 (81%)	100 (100%)	115 (100%)	48 (100%)	208 (100%)	206 (86%)	300 (100%)	0.0000*
LA diameter (mm)	No data	No data	39 ± 5	No data	41 ± 4.5	35.6 ± 3.9	39	0.3916
Comorbid conditions								
HPN	136 (78%)	No data	66 (57%)	33 (69%)	126 (61%)	125 (52%)	174 (58%)	0.0000*
Diabetes	57 (33%)	No data	37 (32%)	28 (58%)	89 (43%)	82 (34%)	144 (48%)	0.0000*
Dyslipidemia	No data	No data	No data	No data	No data	104 (43%)	152 (51%)	0.1076
Stroke	32 (18%)	No data	No data	No data	No data	No data	No data	NA
Procedure								
CABG	93 (53%)	100 (100%)	107 (93%)	48 (100%)	195 (94%)	203 (85%)	300 (100%)	0.0000*
CABG + valve	48 (27%)	No data	8 (07%)	No data	13 (6%)	3 (01%)	No data	0.0000*
Valve only	34 (19%)	No data	No data	No data	No data	15 (6%)	No data	0.0000*
BYPASS TIME (min)	105 ± 37	70.5 ± 23.5	99 ± 26.5	No data	105.5 ± 29	88.98 ± 41.45	77.45	0.4159
CROSS CLAMP TIME (min)	80 ± 30	42.5 ± 18.5	54.5 ± 16	No data	61 ± 24.5	55.5 ± 40.3	48.3	0.4159

Highlighted in gray in the table are parameters that reach statistical significance. This means that the frequency of these variables were significantly different from study to study.

run using Kruskal-Wallis and Chi-square Tests for continuous and categorical variables, respectively. Clinical parameters that reached statistical significance were the baseline risk profiles (male gender, CAD, HPN, T2DM and CHF) and type of cardiac surgery (CABG, CABG + Valve, Valve only). This means that the frequency of these variables was significantly different from study to study and as such, these variables can potentially contribute to heterogeneity.

The differences in POAF definition, preoperative NAC protocols and the type of BB used can also potentially contribute to the heterogeneity of the primary outcome.

When meta-analyses comparing different BB showed that carvedilol was best tolerated and may be more effective in reducing POAF, questions as to the ideal BB for POAF prevention were raised.[29-31]

Unlike metoprolol, bisoprolol and atenolol, carvedilol inhibits the postsynaptic cardiac B1, B2 and alpha-1 receptors, presynaptic B2 receptors and upregulates muscarinic M2 receptors and effects an antioxidant and free radicals scavenging properties on top of its vasodilatory effect.[32]

Together with the theoretic anti-inflammatory and antioxidant effect of NAC, it is hypothesized that combined NAC + carvedilol may have an advantage to further reduce POAF compared to NAC + any other BB.

In this meta-analysis, the pooled estimates of dedicated carvedilol studies [Jalalain 2022 and Ozaydin 2013][37,39], showed a higher risk reduction in POAF (0.48 [0.29, 0.80] p = 0.005, I^2 =16%) afforded by carvedilol + NAC over carvedilol alone and in comparison to "ANY Betablocker" subgroup (0.77 [0.58, 1.01] p = 0.06, I^2=4%). These favorable results suggest that carvedilol can be considered as a candidate preferred BB but it still needs validation in large-scale phase III trials as a standard comparator with or without NAC for wider applicability as a POAF preventive strategy.

In a relatively recent Cochrane meta-analysis of 33 RCTs in 2020, preoperative BB among patients undergoing cardiac surgery affirmed reduction of POAF events but did not translate to reduction in perioperative stroke or mortality and length of stay.[26]

Similarly, this meta-analysis also demonstrated significant POAF reduction favoring NAC + BB regimen over BB alone, but did not impact a reduction in all the secondary outcomes of mortality, stroke, myocardial infarction and length of ICU and hospital stay. The neutral effect of NAC + BB on the secondary endpoints was likely due to the small number of events which may render the pool estimates to be imprecise for adequate interpretation.

Limitation of the Study

The eligible RCTs were single center experience and most did not provide adequate information about randomization and allocation concealment. Similarly, most trials have relatively small population size and event rates for predefined secondary outcomes. And not all studies included the same covariates (comorbidities and concomitant medications) nor provided data for predefined secondary endpoints.

CONCLUSION

In conclusion, this meta-analysis showed that the use of NAC in combination with BB compared with BB alone significantly reduced POAF in cardiac surgery patients.

In consideration of the inherent limitations of eligible RCTs, a large scale well designed phase III trial validation on the efficacy of combined effects of NAC + BB on POAF prevention and reduction of MACE and LOS is recommended.

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APPENDIX A: DATA COLLECTION FORMS

	Postoperative Atrial Fibrillation			
	NAC plus BB		BB alone	
Study	Events	Total	Events	Total
Wijeysundera 2007	35	61	38	57
El-Hamamsy 2007	3	44	5	38
Ozaydin 2008	3	51	11	53
Kim 2011	2	11	4	12
Ozaydin 2013	9	104	25	104
Kazemi 2013	14	118	18	116
Jalalain 2022	14	150	23	150
Total:		**539**		**530**
Total events:	**80**		**124**	

	Major Adverse Cardiovascular Events			
	NAC plus BB		BB alone	
Study	Events	Total	Events	Total
Kim 2011	1	11	2	12
Kazemi 2013	12	118	14	116
El-Hamamsy 2007	6	44	1	38
Total:		**173**		**166**
Total events:	**19**		**17**	

	Mortality			
	NAC plus BB		BB alone	
Study	Events	Total	Events	Total
El-Hamamsy 2007	3	44	0	38
Wijeysundera 2007	0	61	5	57
Kim 2011	0	11	1	12
Kazemi 2013	1	118	2	116
Jalalain 2022	3	150	4	150
Total:		**384**		**373**
Total events:	7		12	

	Myocardial Infarction			
	NAC plus BB		BB alone	
Study	Events	Total	Events	Total
El-Hamamsy 2007	3	44	1	38
Kim 2011	1	11	1	12
Kazemi 2013	10	118	11	116
Total:		**173**		**166**
Total events:	14		13	

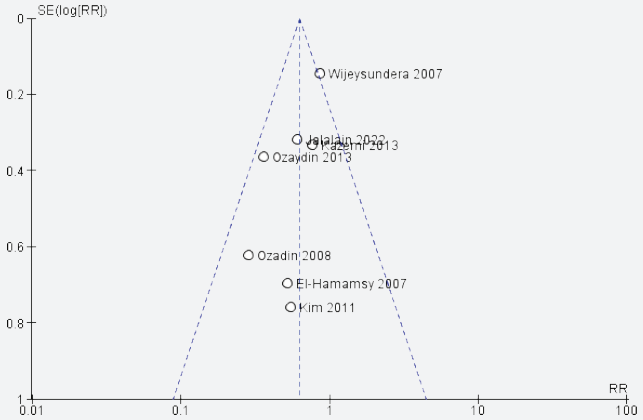
	Stroke			
	NAC plus BB		BB alone	
Study	Events	Total	Events	Total
Wijeysundera 2007	3	61	3	57
Kim 2011	0	11	0	12
Kazemi 2013	1	118	1	116
El-Hamamsy 2007	0	44	0	38
Total:		**234**		**223**
Total events:	4		4	

	Length of ICU stay			
	NAC plus BB		BB alone	
Study	Mean (SD)	Total	Mean (SD)	Total
Wijeysundera 2007	1.9 (2.2)	61	1.7 (2.1)	57
Kim 2011	3 (1.5)	11	3.4 (2.1)	12
Kazemi 2013	5 (1.9)	118	4.8 (3.3)	116
Total:		**129**		**128**

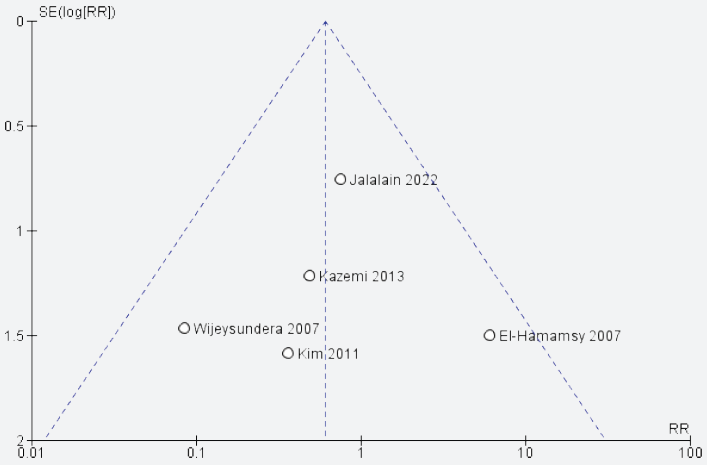
	Length of Hospitalization			
	NAC plus BB		BB alone	
Study	Mean (SD)	Total	Mean (SD)	Total
El-Hamamsy 2007	5.4 (2.3)	44	5.3 (2.5)	38
Kazemi 2013	7.4 (1.3)	118	7.2 (0.9)	116
Kim 2011	11.3 (6.3)	11	10.5 (4.5)	12
Ozaydin 2008	7.7 (3)	51	7.9 (4.2)	53
Ozaydin 2013	8.6	104	7.6	104
Wijeysundera 2007	8 (4.4)	61	8 (4.4)	57
Total:		**224**		**219**

APPENDIX B: FUNNEL PLOT

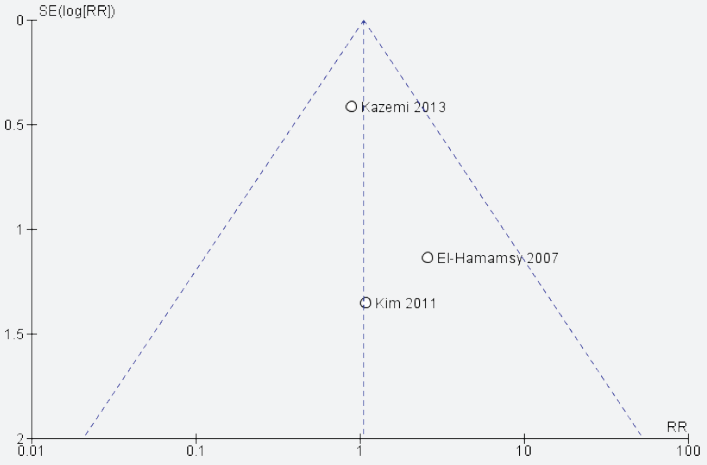
Postoperative atrial fibrillation



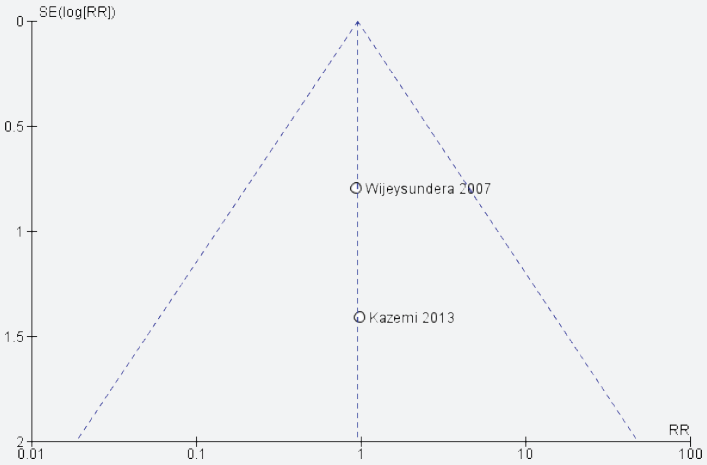
Mortality



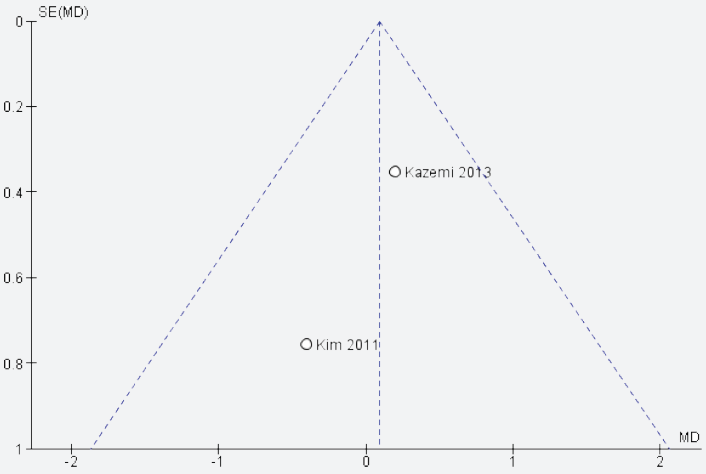
Myocardial infarction



Stroke



Length of ICU stay



Length of hospitalization