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REVIEW

# Carvedilol *versus* metoprolol in preventing post-operative atrial fibrillation: a systematic review and meta-analysis

Amir Askarinejad,[1] Erfan Kohansal,[1] Soudabeh Shafiee Ardestani,[1] Mohammadhossein Mozafarybazargany,[1] Hamed Hesami,[1] Amirreza Sabahizadeh,[2] Seyed Abbas Pakmehr,[2] Majid Haghjoo[3,4]

[1]Rajaie Cardiovascular Medical and Research Institute, Tehran; [2]School of Medicine, Shiraz University of Medical Sciences, Shiraz; [3]Department of Electrophysiology, Rajaie Cardiovascular Medical and Research Institute, Tehran; [4]Cardiac Electrophysiology Research Center, Rajaie Cardiovascular Medical and Research Institute, Tehran, Iran

## Abstract

**Background**: The American Heart Association suggests considering amiodarone, sotalol, and/or beta-blockers for the prevention of postoperative atrial fibrillation (POAF). However, managing POAF remains an area of uncertainty despite its high incidence and potential severity. While beta-blockers are generally effective, their efficacy can vary due to class-related differences. We aim to conduct a systematic review and meta-analysis comparing two recommended beta-blockers for the prevention of POAF.

**Methods**: We searched PubMed/Medline, EMBASE, Web of Science, Scopus, and Cochrane Central for studies comparing metoprolol and carvedilol in the prevention of POAF in patients undergoing CABG. Primary outcome was to compare the incidence of POAF in two groups. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the ID: CRD42023469364.

**Results**: This meta-analysis included 691 patients across four clinical trials. The mean age of participants ranged from 5 ±10 to 63±9 years. Carvedilol was associated with a significantly lower incidence of POAF compared to metoprolol (RR: 0.628; 95% CI: 0.473-0.834, p<0.001). Risk difference analysis demonstrated a 13.95% absolute reduction in POAF with carvedilol (RD: -0.1395; 95% CI: -0.2 to -0.06). There were no significant differences between the groups in mortality (0.3% *vs* 0.7%), stroke (0% *vs* 0.3%), MI (0.3% *vs* 0.3%), or bradycardia (2.9% *vs* 3.3%) (all p>0.05).

**Conclusions**: Carvedilol proves more effective than metoprolol in preventing POAF in CABG patients. Furthermore, patients on both beta-blockers showed minimal mortality, low perioperative myocardial infarction, rare bradycardia incidents, and an infrequent need for electrical cardioversion.

**Key words:** atrial fibrillation; post-operative atrial fibrillation; carvedilol; metoprolol; beta-blocker.

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**Correspondence to: Majid Haghjoo, Cardiac Electrophysiology Research Center, Rajaie Cardiovascular Medical and Research Institute, Tehran, Iran.*
*Tel. +98.2.2392 2931 -Fax: +98.21.2204 8174. E-mail: majid.haghjoo@gmail.com*

## Introduction

Post-operative atrial fibrillation (POAF) is a common and debilitating complication of coronary artery bypass graft (CABG) surgery, occurring in up to 40% of patients.[1] While typically self-limiting, this arrhythmia can lead to hemodynamic instability, thromboembolic events, extended hospital stays, and higher health care expenses.[2,3] For the prevention of POAF, the American Heart Association currently recommends the administration of amiodarone, sotalol, and/or beta blockers.[4] Despite the prevalence and severity of POAF, there is considerable uncertainty and variation in practice regarding its prevention and treatment.[5] Beta blockers may reduce POAF risk due to class effects; however, significant variances may impact their efficacy.[6] Two regularly recommended beta blockers for CABG patients are metoprolol and carvedilol.[7]

In 2014, a meta-analysis compared the efficacy of metoprolol and carvedilol in preventing POAF. However, subsequent studies have been published, further examining the effectiveness of these drugs in POAF prevention.[8,9] Our objective is to conduct a comprehensive systematic review and meta-analysis to arrive at a more conclusive understanding of this subject.

## Methods

This study adhered to the standard methodology outlined in the Cochrane Handbook[10] and followed the reporting guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[11] Before starting the systematic review, our protocol, which includes the search strategy, inclusion and exclusion criteria, and the primary and secondary outcomes, was properly registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration ID: CRD42023469364).

### Search strategy

We searched PubMed, EMBASE, Web of Science, Cochrane, and Scopus for studies comparing the efficacy of carvedilol versus metoprolol for POAF prevention in patients who undergo CABG, published up to September 1, 2023. Search syntaxes are demonstrated in Tables A 1-5 (*Appendix A*). Backward and forward citation searching was performed.

### Study selection

The process of eligibility assessment was performed by SSA, EK, and HH, who independently assessed the titles, abstracts, inclusion and exclusion criteria, as well as the full text. In the event of potential disagreements, a panel discussion was utilized to achieve a settlement, while any unresolved problems were deferred to a third-party reviewer (AA). In this systematic review, we included comparative studies (including cohorts, case-controls, and trials) that examined the effectiveness of metoprolol and carvedilol in preventing POAF among patients who underwent CABG. Reviews, editorials, case reports, and case series were excluded.

The present study incorporated studies that investigated the comparative effectiveness of metoprolol and carvedilol in adult patients aged 18 years and older who had undergone CABG surgery. We excluded studies that assessed individuals with a prior medical history of atrial fibrillation/flutter, class III or IV heart failure, second- or third-degree atrioventricular block, a permanent pacemaker, or chronic obstructive pulmonary disease.

The primary outcome of this study was to assess and compare the occurrence of POAF across two groups: those treated with metoprolol and those treated with carvedilol. Secondary outcomes included death, myocardial infarction (MI), stroke, bradycardia, and requiring electrical cardioversion.

### Data extraction

The data extraction form was designed by SSA, AA, and AS. The reviewers extracted data from each article that met the predefined criteria for inclusion and resolved any discrepancies through consensus. The subsequent information was extracted: First author, publication year, study population, country, blinding (double-blind or single-blind), percentage of female participants, initiation time of treatment for POAF, duration of beta-blocker therapy, follow-up duration, AF detection method, number of study arms, dose, other arms, type of surgery, disease type of study population, cardio-pulmonary bypass, off-pump surgery, incidence of POAF in group, postoperative systolic blood pressure, postoperative diastolic blood pressure, postoperative heart rate, prevalence of hypotension requiring dose adjustment, incidence of bradycardia, mortality rate, incidence of electrical cardioversion, length of hospital stay, length of ICU stay, incidence of stroke, and incidence of MI in both carvedilol and metoprolol groups.

### Risk of bias assessment

SSA, AA, and MZ evaluated the methodological quality of the research by employing the critical appraisal tools for cohort studies developed by the Joanna Briggs Institute (JBI)[10] and the Cochrane risk of bias assessment tool for randomized trials.[12] Inconsistencies were addressed with the assistance of a third reviewer (MH).

### Data synthesis and statistical analysis

Statistical analyses were performed with Stata Corp. (2017) Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC. Point estimates and 95% confidence intervals (CIs) for the prevalence of mortality, bradycardia, electrical cardioversion, stroke, and MI in two groups were calculated. The pooled risk ratios (RRs) with a 95% confidence interval (CI) will be assessed using random or fixed-effect models. The random-effects model was selected because of considerable methodological heterogeneity among studies. The between-study heterogeneity was assessed by Cochran's Q test and the $I^2$ statistic. Publication bias was evaluated statistically by using Egger's test and the trim and fill method ($p<0.05$ was considered indicative of statistically significant publication bias).[13,14] The funnel plot was not used for publication bias assessment because there were fewer than ten studies in each analysis.[15]

## Results

### Study selection

Figure 1 displays the flow diagram of the study selection. We identified 7503 papers through databases (PubMed, EMBASE, Web of Science, Scopus, Cochrane) and screened 5440 papers after removing duplicates. First, we ruled out 5331 papers by title and abstract since their subject or outcome were irrelevant to our study. We assessed 109 studies by full-text review. Five articles were selected. Overall, five studies (four randomized trials[16-19] and one retrospective cohort[8]) fulfilled the inclusion criteria.

### Study characteristics

The proportion of female individuals ranges from 25.4 to

40.0%. The mean age of the study population ranges from 59±10 years to 63±9 years. The mean follow-up duration was between 3 (days) and 9 (days). All of the included trials started treatment before surgery except Jalalian *et al*.,[19] who started treatment on the first post-op day. Most studies used serial ECG for detection of POAF,[8,17-19] while Acikel *et al*. used days ECG monitoring.[16] Other characteristics of the included studies are summarized in Table 1.

## Quality of included studies

The risk of bias assessment of the studies is summarized in Tables 2 and 3. All of the studies were considered low-risk of bias in the final assessment.[16]

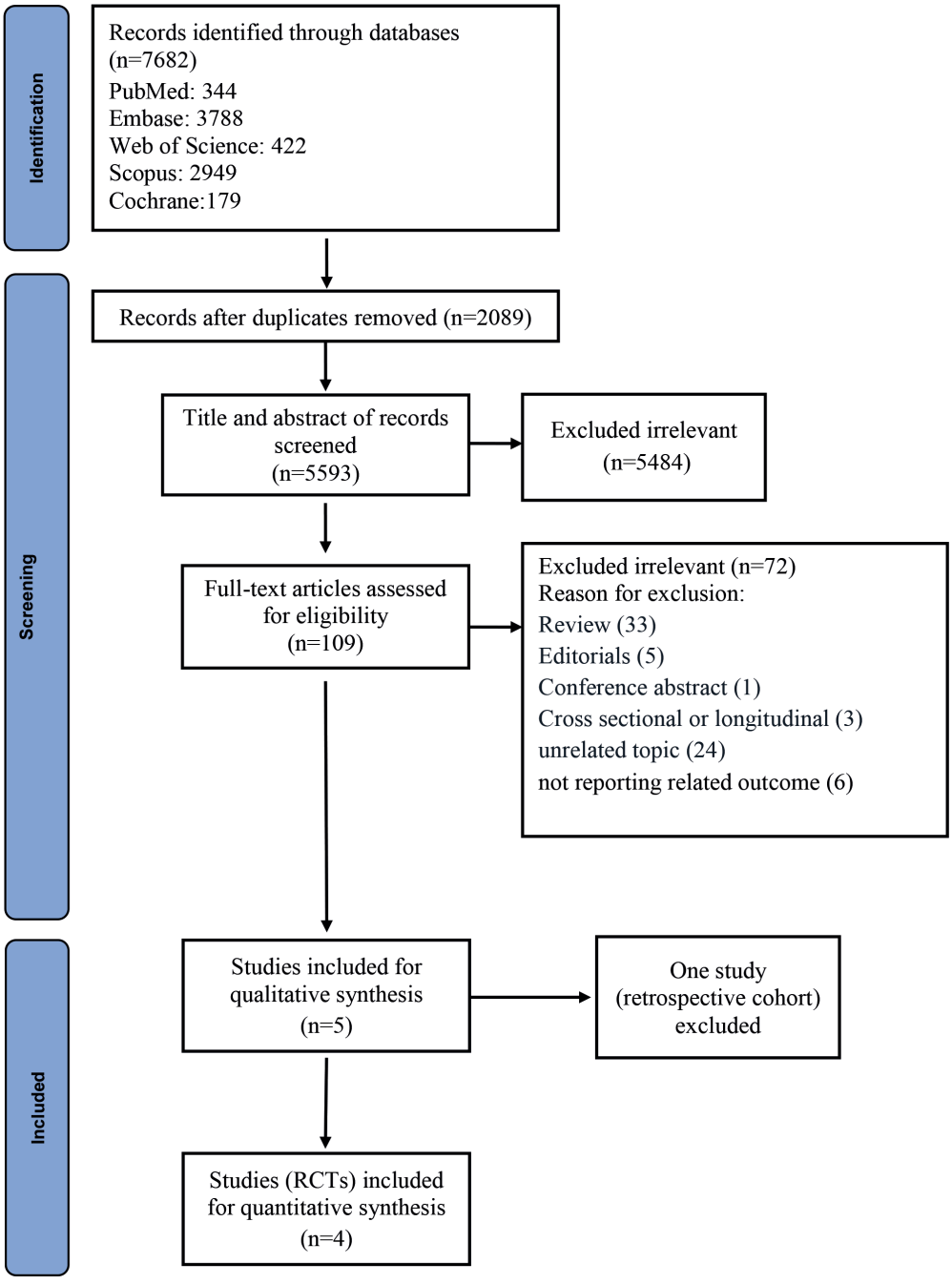


**Figure 1.** Flowchart of the study.

**Table 1.** Study characteristics.

| First author, publication year | Study design | Study population | Study arms | Female (%) | Country | Post-op follow-up | Treatment start timeline (days) | BB therapy duration | AF detection method |
|---|---|---|---|---|---|---|---|---|---|
| Haghjoo, 2007 | Clinical trial | 120 | 2 (carvedilol *vs* metoprolol tartrate) | 57 (47.5) | Iran | 5 | 10 days before surgery | 15 days (10 days before surgery till 5 days after surgery) | Serial ECG |
| Acikel, 2008 | Clinical trial | 110 | 2 (carvedilol *vs* metoprolol tartrate) | 31 (28.2) | Turkey | 3 | 3 days before surgery | 6 days (3 days before surgery till 3 days after surgery) | ECG monitoring |
| Jalalian, 2014 | Clinical trial | 150 | 2 (carvedilol *vs* metoprolol tartrate) | 55 (36.6) | Iran | 5 | First postoperative day | 5 days (first postoperative day till 5 days after surgery) | NR |
| Ozaydin, 2012 | Clinical trial | 311 | 3 (carvedilol *vs* metoprolol succinate *vs* N-acetyl cysteine + carvedilol) | 80 (25.7) | Turkey | 9.6 in Metoprolol group 8.6 in Carvedilol group | 7 days before surgery | 7 days before surgery till 9.6 days after surgery for met; and 7 days before surgery till 8.6 days after surgery for car | Holter monitoring and serial ECG |
| Stones, 2022 | Retrospective cohort | 134 | NA | 39 (29.1) | USA | 3 | First postoperative day | NR | Serial ECG |

BB, beta-blockers; AF, atrial fibrillation; ECG, electrocardiogram; NR, not reported; NA, not applicable.

**Table 2.** Risk of bias assessment of studies.

| First author, publication year | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and researchers (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|---|---|---|---|---|---|---|---|
| Haghjoo, 2007 | Unclear risk | Unclear risk | Low risk | Low risk | High risk | Low risk | Low risk |
| Acikel, 2008 | Unclear risk | Unclear risk | High risk | Low risk | High risk | Low risk | Low risk |
| Jalalian, 2014 | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk |
| Ozaydin, 2012 | Low risk | Low risk | Low risk | Low risk | Unclear risk | Low risk | Low risk |

**Table 3.** Risk of bias assessment of cohort study.

| First author, publication year | Stones, 2022 |
|---|---|
| Were the two groups similar and recruited from the same population? | Low risk of bias |
| Were the exposures measured similarly to assign people to both exposed and unexposed groups? | Low risk of bias |
| Was the exposure measured in a valid and reliable way? | Low risk of bias |
| Were confounding factors identified? | Low risk of bias |
| Were strategies to deal with confounding factors stated? | Low risk of bias |
| Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? | Low risk of bias |
| Were the outcomes measured in a valid and reliable way? | Low risk of bias |
| Was the follow-up time reported and sufficient to be long enough for outcomes to occur? | High risk of bias |
| Was appropriate statistical analysis used? | Low risk of bias |

## POAF

Our meta-analysis reveals a significant reduction in the risk of POAF with Carvedilol compared to metoprolol (RR: 0.628, 95% CI 0.473 to 0.834). Figure 2 demonstrates the POAF risk ratio in different studies as well as the overall estimate. The results of the study indicated that carvedilol exhibited an additional 13% decrease in preventing POAF in comparison to metoprolol (RD: 0.13, 95% CI -0.2 to -0.06, p<0.0001). Figure 3 presents the POAF risk difference across various studies, along with the overall estimate. The overall estimates for mortality, stroke, MI, bradycardia, and electrical cardioversion in the carvedilol group as compared to the metoprolol group were 0.3% *versus* 0.7%, 0.0% *versus* 0.3%, 0.3% *versus* 0.3%, 2.9% *versus* 3.3%,

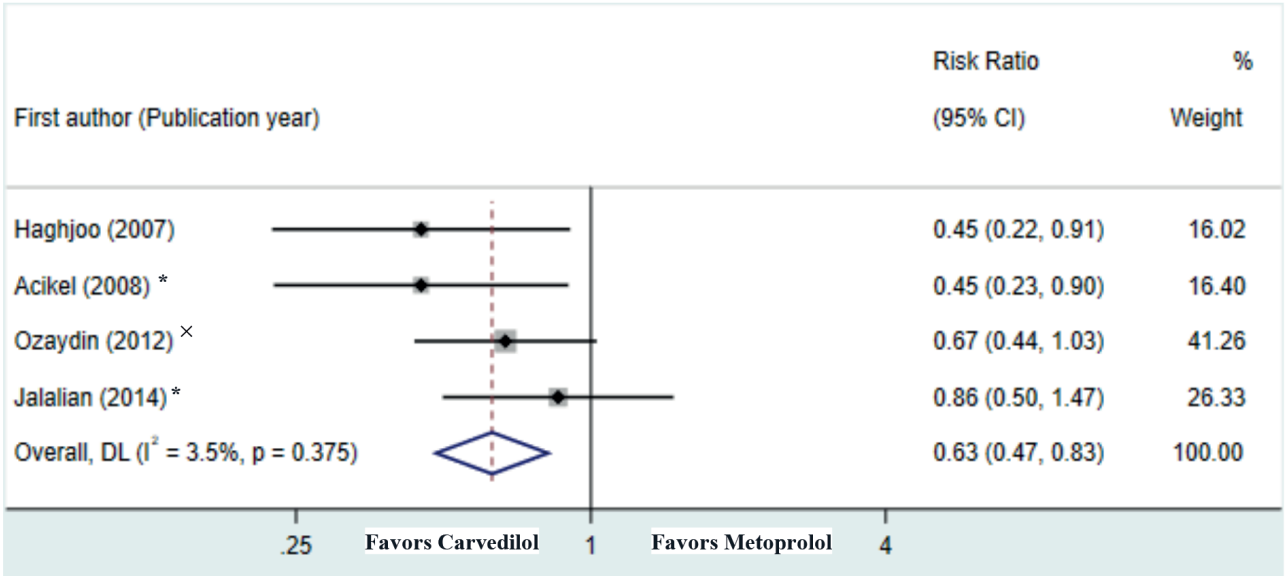


**Figure 2.** Pooled risk ratio for postoperative atrial fibrillation between metoprolol and carvedilol. The square box represents the point estimate for an individual trial, while the diamond indicates the overall estimate of the combined effect (relative risk) across multiple trials. *Metoprolol tartarate; ×metoprolol succinate.

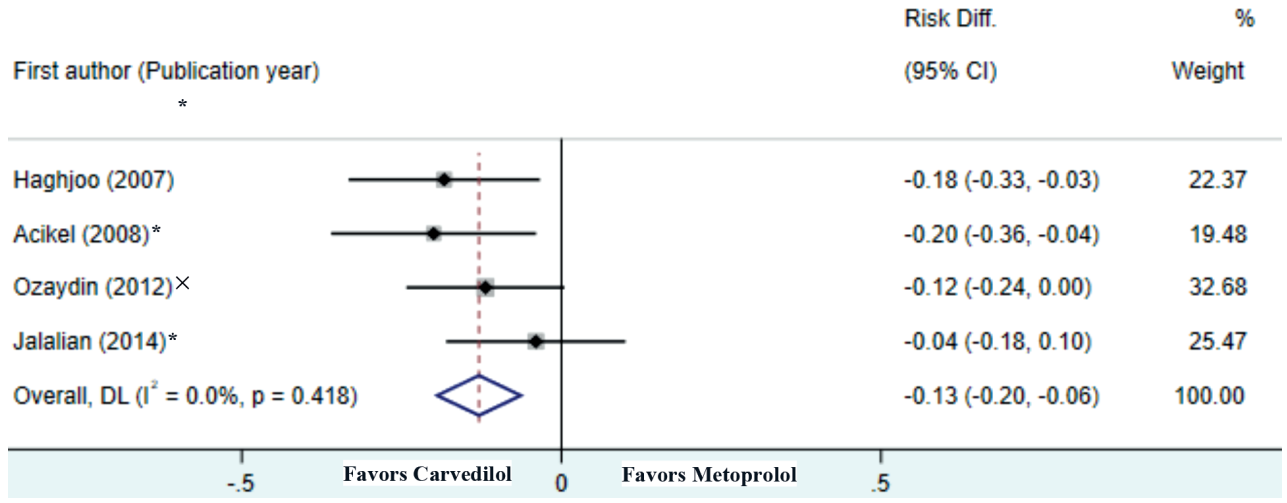


**Figure 3.** Pooled risk difference for postoperative atrial fibrillation) between metoprolol and carvedilol. The square box represents the point estimate for an individual trial, while the diamond indicates the overall estimate of the combined effect (risk difference) across multiple trials. *Metoprolol tartarate; ×metoprolol succinate.

and 2.5% *versus* 2.6%, respectively. Overall estimates of mortality, stroke, MI, and electrical cardioversion in the carvedilol and metoprolol groups are demonstrated in Figures 4-6.

### Publication bias

There was not considerable publication bias according to the Egger test (p=0.320). Also, the trim and fill method indicated ignorable publication bias among studies (*Appendix B*).

## Discussion

The most common postoperative complication of CABG is known to be POAF, with an incidence rate of 20 to 40%.[20,21] The POAF predisposes patients to embolic events (e.g., stroke) and MI. On the other hand, the anticoagulant administration to prevent the aforementioned complication increases the risk of bleeding. Furthermore, POAF is associated with higher mortality rate, hospital stay, and cost.[20,22] It is suggested that inflammation and oxidative stress might play a part in.[23,24] Carvedilol is a beta blocker with antioxidant properties.[25] We conducted this meta-analysis to compare the efficacy of perioperative carvedilol and metoprolol administration for prevention of POAF after CABG. We found that patients who received carvedilol were significantly less likely to experience POAF when compared to those receiving metoprolol (RR [95%CI]: 0.628 [0.473, 0.834]). Additionally, carvedilol reduced the risk of POAF 13% more than metoprolol (RD [95%CI]: 0.13 [-0.2, -0.06], p<0.0001). In a meta-analysis conducted by Di Nicolantonio *et al.*, in comparison to metoprolol, carvedilol demonstrated significantly lower odds of POAF.[26]

We found that carvedilol was associated with a lower risk of POAF in patients undergoing CABG when compared with metoprolol. This mitigated risk might be attributable to its antioxidant and anti-inflammatory attributes in part, considering the role of inflammation and oxidative stress in POAF pathogenesis.[16,18,27] Inflammatory markers (e.g., C-reactive protein) are reported to be elevated in patients who encounter POAF after CABG, while carvedilol is suggested to reduce CRP as well.[23,24,28]

Many other factors are known to play a role in the pathogenesis of POAF, i.e., myocardial remodeling, sympathetic/parasympathetic activation, atrial pressure alterations, and operative trauma.[29-32] Carvedilol has shown stronger sympatholytic characteristics than other beta-blocking agents.[17] Carvedilol stimulates the production of nitric oxide, which could alleviate

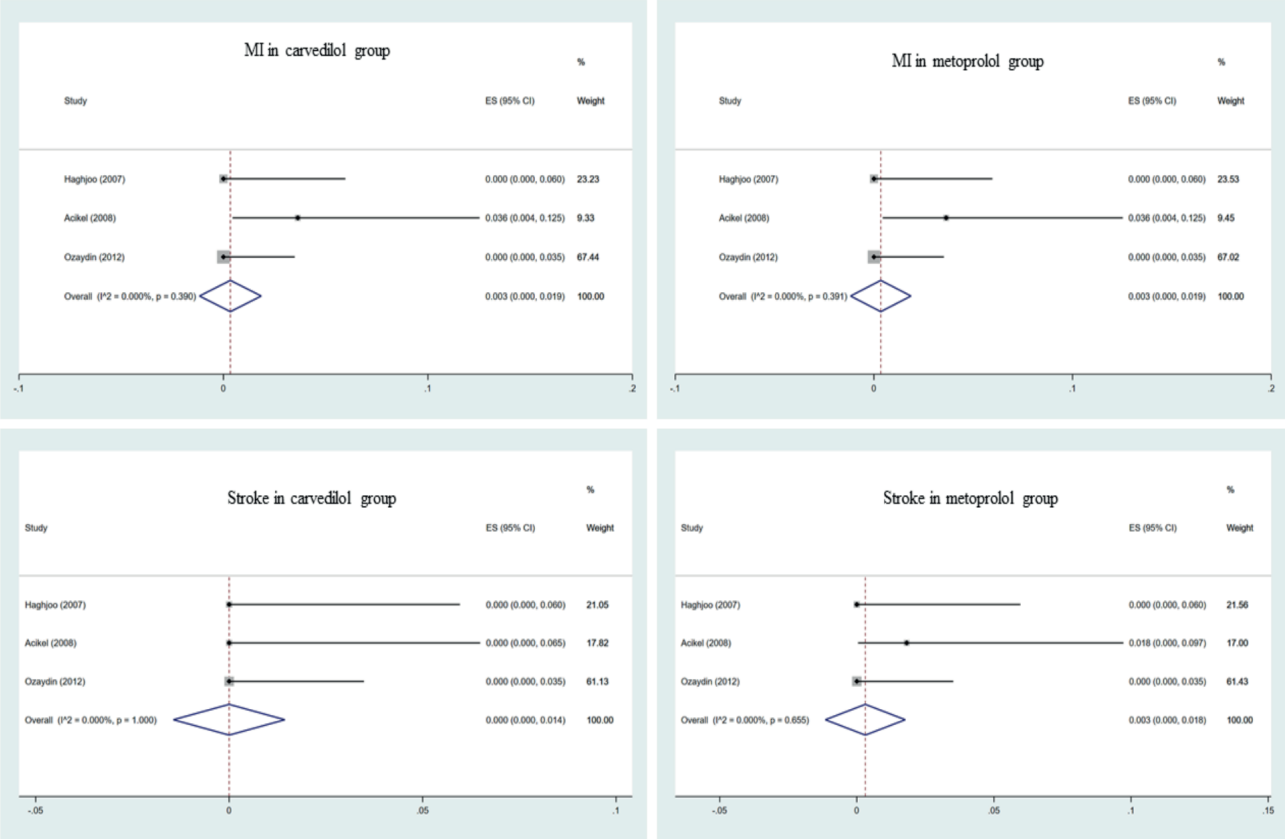


**Figure 4.** Overall estimate of stroke and myocardial infarction in metoprolol group. The square box represents the point estimate for an individual trial, while the diamond indicates the overall estimate of the combined effect (risk difference) across multiple trials. MI, myocardial infarction.

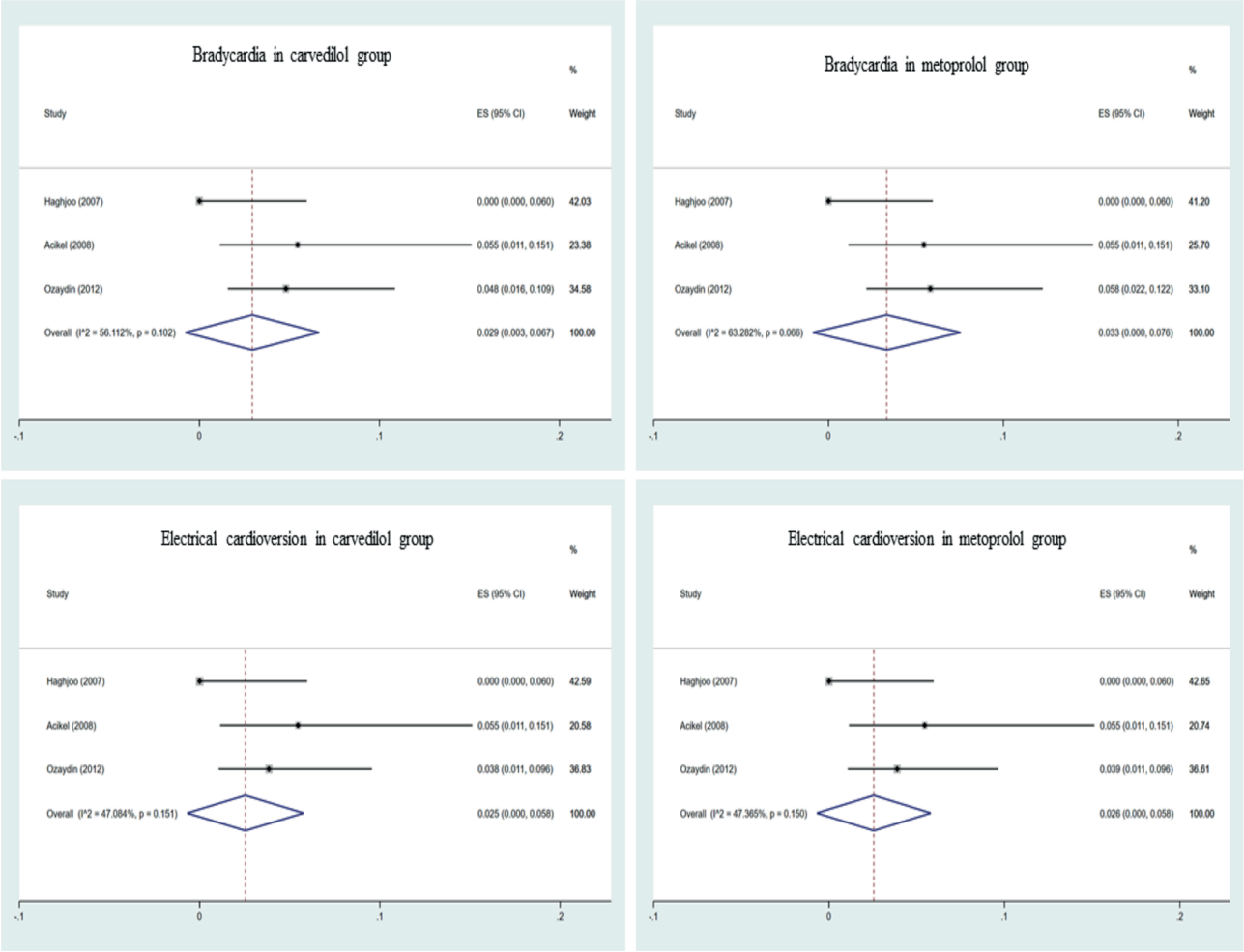


**Figure 5.** Overall estimate of bradycardia and electrical cardioversion in metoprolol group. The square box represents the point estimate for an individual trial, while the diamond indicates the overall estimate of the combined effect (risk difference) across multiple trials.

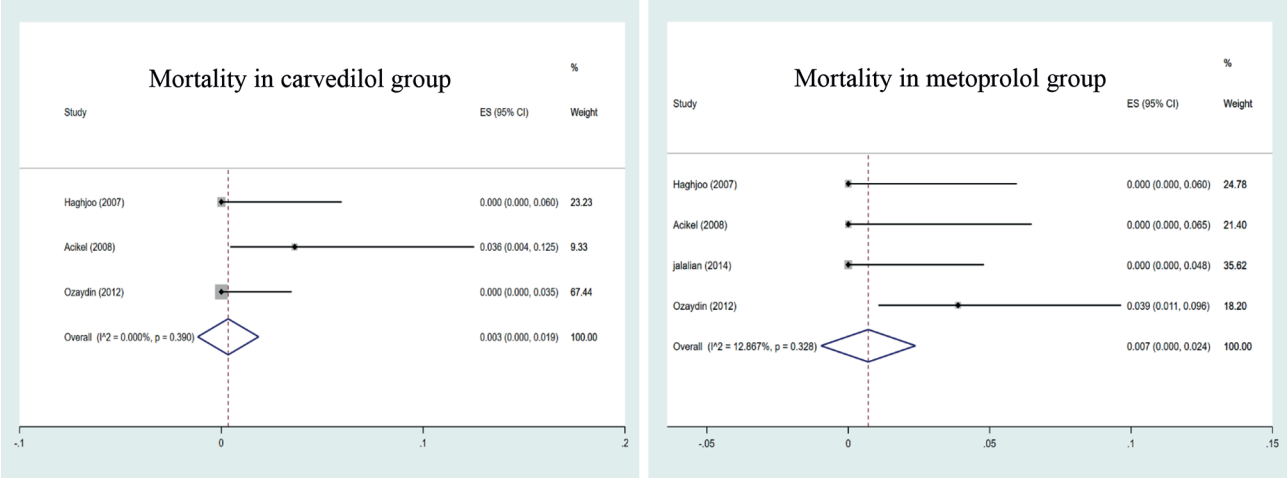


**Figure 6.** Overall estimate of mortality in carvedilol and metoprolol groups. The square box represents the point estimate for an individual trial, while the diamond indicates the overall estimate of the combined effect (risk difference) across multiple trials.

sympathetic activity both at the presynaptic level by norepinephrine release inhibition and the postsynaptic level by blocking catecholamines.[17,33,34] Hence, the reduced risk of POAF with carvedilol might be explained in part by the sympatholytic properties of this beta-blocking agent.

The overall pooled mortality rate was 0.3% [95%CI: 0.00%, 0.019%] in the carvedilol arm, while it was 0.7% [95%CI: 0.0%, 0.024] in the metoprolol arm. While the statistical comparison of the mortality rate was not feasible in this study, the postoperative mortality rate of patients receiving Carvedilol was nearly half that of metoprolol. Carvedilol was associated with reduced mortality compared to metoprolol in chronic heart failure (CHF) patients, according to a large clinical trial.[35]

The pooled incidence of stroke was 0.0% in patients receiving carvedilol and 0.3% in ones receiving metoprolol. Carvedilol is suggested to be associated with a lower rate of death by stroke in CHF patients compared to metoprolol (RR 0.37, CI 0.19-0.71, p=0.0027).[36] Carvedilol has demonstrated neuroprotective attributes in focal cerebral ischemia and might mitigate ischemic damage to brain tissue.[37] The pooled rate of MI, and the need for electrical cardioversion were simultaneously very low and similar in both groups. Overall, carvedilol significantly reduces the recurrence rate of MI; nonetheless, the comparison of carvedilol and metoprolol in terms of secondary prevention of MI in patients undergoing CABG remains to be assessed.[38]

Our study found a pooled bradycardia incidence of 2.9% in the carvedilol group and 3.3% in the metoprolol group. Significantly, Shin *et al*. reported a higher incidence of emergent bradycardia in patients who received metoprolol compared to carvedilol, as indicated by their fully adjusted proportional hazards regression analysis.[39] Also recent studies have shown a higher risk of bradycardia in patients receiving metoprolol than carvedilol.[40,41] In conclusion, it appears that carvedilol may be a considerably safer choice than metoprolol for preventing POAF.

## Limitations

The mortality rate, MI, bradycardia, and the need for electrical cardioversion were extremely low, preventing comparison of these outcomes between study groups using risk ratios (OR or RR).

## Conclusions

Carvedilol demonstrates superiority over metoprolol in reducing the incidence of POAF in patients undergoing CABG. The mortality rate, MI, bradycardia, and the need for electrical cardioversion were very low in patients receiving carvedilol and metoprolol. Large-scale, double-blind, randomized controlled trials with adequate follow-ups specifically designed to evaluate and compare metoprolol versus carvedilol outcomes are needed.

## Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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*Online supplementary material:*
*Appendix A.*
*Aooendix B.*