의학석사 학위논문

# Impact of Perioperative Beta-Blocker Use on The Occurrence of Atrial Fibrillation After Cardiac Surgery
# - a Meta-Analysis -

# 심장수술환자에서 수술 전후 베타 차단제의 사용이 수술 후 심방세동 발생에 미치는 영향에 대한 메타분석 연구

2019 년 8 월

서울대학교 대학원
의과대학 임상의과학과
김 수 현

# ABSTRACT

**Objectives:** This meta-analysis was conducted to evaluate the impact of perioperative use of BB on POAF after cardiac surgery other than isolated CABG.

**Methods:** Five online databases were searched. Studies were included if they (1) enrolled patients who underwent cardiac surgery other than isolated CABG and (2) demonstrated the impact of perioperative use of BB on POAF based on the randomized controlled trial or adjusted analysis. The primary outcome was the occurrence rates of POAF after cardiac surgery. A meta-regression and Subgroup analysis were performed according to the proportion of patients with cardiac surgery other than isolated CABG and the timing of BB use, respectively.

**Results:** Thirteen articles (5 randomized and 8 non-randomized studies: n=24,101) were selected. Proportion of enrolled patients undergoing cardiac surgery other than isolated CABG ranged from 7% to 100%. The BBs were used in preoperative, postoperative and both periods in 5, 5 and 3 studies, respectively. The pooled analyses showed that the risk of POAF was significantly lower in patients with perioperative BB than those without (odds ratio, 95% confidence interval=0.67, 0.54-0.83). Further analyses demonstrated that the risk of POAF was lower in the BB group irrespective of the proportion of non-isolated CABG and the timing of administration. In-hospital mortality was reduced by 50% in BB group (OR, 95% CI=0.50, 0.32-

0.79). Perioperative stroke and LOS were not significantly different between BB and non-BB groups.

**Conclusions:** Perioperative use of BB is effective in preventing POAF even in patients undergoing cardiac surgery other than isolated CABG.

**Keywords: Cardiac Surgery, Atrial Fibrillation, Beta-Blocker**

**Student Number: 2011 - 21970**

# CONTENTS

# LIST OF TABLES AND FIGURES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AF | = atrial fibrillation |
| BB | = beta-blocker |
| CABG | = coronary artery bypass graft surgery |
| CI | = confidence interval |
| LOS | = length of stay |
| MD | = mean difference |
| MeSH | = medical subject heading |
| NRS | = non-randomized study |
| OR | = odds ratio |
| POAF | = postoperative atrial fibrillation |
| PRISMA | = Preferred Reporting Items for Systematic reviews and Meta-analyses |
| RCT | = randomized controlled trial |
| ROB | = risk of bias |
| ROBINS-I | = Risk Of Bias In Non-randomized Studies of Interventions |

# INTRODUCTION

Atrial fibrillation (AF) is one of the most common complications after cardiac surgery. Although it resolves spontaneously in most patients, postoperative AF (POAF) after cardiac surgery is associated with significant mortality and morbidity, including prolonged ventilator support, renal failure and stroke [1, 2]. Many studies have evaluated the effect of different pharmacologic and non-pharmacologic interventions to prevent POAF after cardiac surgery, and current European guidelines recommend perioperative use of beta-blockers (BB) in patients undergoing cardiac surgery to prevent POAF [3]. However, evidences for this recommendation are mostly from studies exclusively enrolling patients undergoing coronary artery bypass graft surgery (CABG) [4] and current American guidelines recommend the use of perioperative BB to prevent POAF only for patients undergoing CABG [5].

Therefore, this meta-analysis was conducted to evaluate the impact of perioperative use of BB on the occurrence of POAF after cardiac surgery other than isolated CABG.

# MATERIALS AND METHODS

## 1. Data Source & Literature Search

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [6]. Full-text articles evaluating the impact of perioperative use of BB on the incidence of POAF were searched for in the Medline, Embase, Cochrane Central Register of Controlled Trials, Web of Science and Scopus databases on September 21, 2018. No restrictions were placed on the language or publication year.

The following keywords and medical subject heading (MeSH) terms were searched in Medline: ("adrenergic beta-antagonists"[MeSH Terms] OR "phenoxypropanolamines"[MeSH Terms] OR beta antagonist[Title/Abstract] OR beta blocker[Title/Abstract] OR metoprolol[Title/Abstract] OR propranolol[Title/Abstract] OR esmolol[Title/Abstract] OR timolol[Title/Abstract] OR atenolol[Title/Abstract] OR bisoprolol[Title/Abstract] OR acebutolol[Title/Abstract] OR nadolol[Title/Abstract] OR nebivolol[Title/Abstract] OR labetalol[Title/Abstract] OR carvedilol[Title/Abstract]) AND ("cardiac surgical procedures"[MeSH Terms] OR "heart valve prosthesis implantation"[MeSH Terms] OR surgery[Title/Abstract] OR surgical[Title/Abstract]) AND ("arrhythmias, cardiac"[MeSH Terms] OR atrial fibrillation[Title/Abstract]) OR arrhythmia[Title/Abstract]) OR tachycardia[Title/Abstract]). The search strategies for other databases were adapted from this strategy.

## 2. Study Selection

Study selection was independently performed by two reviewers based on the selection criteria. Any disagreements between the reviewers were resolved through discussion. The study selection was conducted following two levels of screening: the titles and abstracts of the searched studies were screened at the first level and the full texts were reviewed at the second level.

Studies were included if they met the following criteria: (1) studies enrolled patients who underwent cardiac surgery but not exclusively CABG and (2) studies analyzed the impact of perioperative use of BB on the incidence of POAF. When duplicated publications with overlapping study populations were found, the most appropriate article for the present study was selected.

## 3. Data Extraction

The study characteristics and the patients' baseline data were extracted independently by two reviewers. Data regarding study outcomes were also independently extracted by two reviewers. Any disagreements between the two reviewers were resolved through discussion.

## 4. Assessment of Quality

The overall study quality was assessed independently by two reviewers using the Cochrane Risk of Bias Tool for randomized controlled trials (RCTs) and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-

I) for non-randomized studies (NRSs) [7]. In the ROBINS-I, seven domains of risk of bias (ROB) were assessed and the overall ROB was determined to be low, moderate, serious or critical based on the assessment of each domain. Any disagreements between the reviewers were resolved through discussion.

## 5. Statistical Analysis

The primary outcome was the incidence of POAF. Secondary outcomes included in-hospital mortality, postoperative stroke, length of stay (LOS) and complications related to the use of BB such as bradycardia, hypotension, permanent pacemaker insertion and reduction in BB dose.

Dichotomous outcomes were compared as odds ratios (ORs) with the 95% confidence interval (CI). For a continuous outcome, results were presented as mean difference (MD) with 95% CI. For studies that reported median and interquartile values, the mean values and standard deviations were estimated using a formula [8]. For studies reporting results through both multivariable regression and propensity-score matching analyses, propensity-score matching estimates were selected for the present analyses. Statistical heterogeneity between the studies was assessed with the $\chi^2$ test and the $I^2$ statistics. $I^2$ values of 25%, 50% and 75% have been suggested to be indicators of low, moderate and high heterogeneities, respectively [9]. A random-effects model with the DerSimonian and Laird method was used if substantial heterogeneity was found ($I^2$ >50%); otherwise, a fixed-effects model was applied using the Mantel–Haenszel and inverse variance methods for binary outcomes with count data and the other outcomes, respectively.

Pooled estimates from RCTs and NRSs, and overall pooled estimates were presented. The impact of the use of BB on the primary outcome according to the proportion of surgery other than isolated CABG was evaluated with a univariate meta-regression analysis. A subgroup analysis was performed for the primary outcome to identify the influences of timing of BB use (preoperative vs. intra- or postoperative vs. both pre- and postoperative use). Heterogeneity between subgroups was assessed using the Cochran’s Q test. For BB dose reduction in the BB group, the pooled proportion estimate was calculated using the Freeman-Tukey double arcsine transformation [10]. A funnel plot and Egger’s test for asymmetry were applied to assess the possibility of publication bias among the studies for the primary outcome and not for the secondary outcomes because of the small number of studies included [11].

All analyses were performed using R version 3.5.1 (meta package). Two-sided P values <.050 were considered statistically significant.

# RESULTS

## 1. Identification of Studies

The database searches found 10,206 articles. Among these, 10,179 publications were excluded, because it was clear from the title and abstract that they did not fulfill the selection criteria. Full manuscripts of the remaining 27 studies were reviewed. Nine publications were excluded because inclusion criteria were not met and a further three studies because of duplicated data. Another 2 studies were also excluded because only unadjusted results were demonstrated. Therefore, a total of 13 studies were included in this review (Figure 1) [12-24].

## 2. Study Characteristics and Patient Populations

Among the 13 studies with 25,496 patients, 5 studies demonstrated the results of RCTs (n = 1,395), and 8 presented the outcomes of NRSs (n = 24,101). Proportions of patients who underwent surgery other than isolated CABG ranged from 7% to 100%. The BB were used in the preoperative, intra- or postoperative, and both periods in 5, 5 and 3 studies, respectively. Types of BB evaluated were metoprolol, landilolol and mixed in 5, 2 and 1 studies, respectively. They were not described in the other 5 studies (Table 1). On an average, the patients were in their 60s and 70s, and 30% of the patients were female. The occurrence rates of POAF varied from 7.2% to 47.2% (Table 2).

## 3. Quality of the Included Studies

The ROB of RCTs was graded as low, high or unclear. For the random number generation, 3 studies [13, 18, 22] were rated as low, whereas the other 2 studies [12, 19] were rated unclear. For blinding of participants and personnel domain, 2 studies [12, 13] were rated as low while the other 3 studies were rated as high. The ROB of the 5 studies was considered low for the other 5 domains. All of the 8 NRSs were graded as having an overall moderate ROB because confounding variables were appropriately adjusted using multivariable models and matching in six [15-17, 20, 21, 24] and two [14, 23] studies, respectively. The other ROB items were graded as low (Table 3).

## 4. Primary Outcomes

### 4.1. Impact of the Use of Beta-Blockers on The Occurrence of POAF

Pooled analyses from all of the included studies revealed that perioperative use of BB was associated with a 33% reduction of the occurrence of POAF (OR [95% CI] = 0.67 [0.54, 0.83], $I^2$ = 76.8%, Figure 2). There was no significant difference between the OR from RCTs and that from NRSs (*P* = .414).

### 4.2. Impact of the Use of Beta-Blockers According to the Proportion of Patients with Non-Isolated CABG

The meta-regression analysis revealed that the impact of the use of BB was not significantly affected by the proportion of patients with non-isolated CABG (*P* for trend = .611, Figure 3).

### 4.3. Impact of the Use of Beta-Blockers According to the Timing of Administration

The ORs for the use BB vs. non-use of BB was 0.80, 0.66 and 0.50 when they were used in preoperative, intra- or postoperative, and both pre- and postoperative periods, respectively. The Cochran's Q test showed a marginally significant difference in the ORs according to the timing of administration (*P* = .088, Figure 4).

## 5. Secondary Outcomes

### 5.1. In-Hospital Mortality

The In-hospital mortality was reported in 6 studies (4 RCTs and 2 NRSs) [12-14, 19, 21, 22]. One [12] out of the 6 studies was excluded from subsequent pooled analyses because mortality rates were 0% in both groups, thus OR could not be calculated. In another study [23], a result comparing in-hospital mortality was presented only by univariate analysis and an adjusted OR was demonstrated for 90-day mortality. Pooled analysis of the former 5 studies with 4,115 patients demonstrated a significantly lower risk of in-hospital mortality in the BB group than in the non-BB group (OR [95% CI] = 0.50 [0.32, 0.79], $I^2$ = 15.6%, Figure 5). However, the pooled estimate was not statistically significant when it was drawn from 7,612 patients after including the OR of 90-day mortality from the latter study (OR [95% CI] = 0.65 [0.38, 1.12], $I^2$ = 51%, Figure 5).

## 5.2. Postoperative Stroke

The risk of postoperative stroke was drawn from 5 studies (3 RCTs and 2 NRSs with 6,344 patients [12-14, 22, 23]. The pooled analysis demonstrated that the risk of postoperative stroke was not significantly different between the BB and non-BB groups (OR [95% CI] = 0.89 [0.59, 1.35], $I^2$ = 0%, Figure 6).

## 5.3. Length of Hospital Stay

A pooled analysis from 6 studies [12-14, 19, 22, 23] with 6,492 patients showed that the LOS was not significantly different between the BB and non-BB groups (MD [95% CI] = -0.22 [-0.70, 0.26] days, Figure 7).

## 5.4. Events Associated with the Use of Beta-Blockers

Postoperative events associated with the use of BB such as bradycardia, hypotension and permanent pacemaker insertion were reported in two [13, 22], two [13, 22], and three [12, 13, 22] studies, respectively (Figure 8). The ORs for BB effect on bradycardia and hypotension were 6.06 (95% CI 1.27, 28.88) and 0.20 (95% CI 0.01, 4.32), respectively based on one study [13]. The pooled OR on permanent pacemaker insertion was 1.02 (95% CI 0.20, 5.07). A pooled analysis from 4 studies [13, 18, 19, 22] showed that BB dose reduction was needed in 31% of patients in the BB group (Figure 9).

## 6. Publication Bias

Funnel plots and Egger's test for asymmetry suggested a publication bias for the primary outcome (*P* = .037; Figure 10).

# DISCUSSION

The present meta-analysis demonstrated that perioperative use of BB resulted in a 33% reduction in the occurrence of POAF after cardiac surgery other than isolated CABG.

The incidence of POAF after cardiac surgery varies from 20% to 50%, depending on the definition, the methods of detection, and the specific types of surgery [3, 25-27]. The POAF usually develops within 2 to 4 postoperative days, with a peak incidence on the second postoperative day [28, 29]. Current European guidelines on the prevention of POAF after cardiac surgery issued perioperative administration of BB as a class I recommendation with a level of evidence A [3]. However, this recommendation was made based on a meta-analysis enrolling studies with mostly analyzed patients who underwent isolated CABG rather than other types of cardiac surgery [30]. This might be the reason that current American guidelines recommended the use of BB for prevention of POAF for CABG patients but not for overall cardiac surgery patients [5, 26]. A recently updated meta-analysis showed again the benefit of BB on the prevention of POAF after cardiac surgery [31]; the authors included 53 RCTs and demonstrated that the perioperative use of BB substantially reduced the occurrence of supraventricular arrhythmias by 56% (RR 0.44, 95% CI 0.36 to 0.53; $p <$ 0.001) after cardiac surgery. However, the analysis still enrolled studies mostly analyzing the benefit of the use of BB in isolated CABG patients; 45

out of the 53 studies were exclusively enrolled patients undergoing isolated CABG. The present meta-analysis was conducted because the evidence for the routine administration of perioperative BB to prevent POAF after cardiac surgery is still lacking for types of cardiac surgery other than isolated CABG. The pooled analysis demonstrated that the use of BB resulted in a 33% reduction of the risk of POAF after cardiac surgery. The meta-regression showed that the benefit of the use of BB was not significantly different among studies with different proportions of enrolled patients with non-isolated CABG. In the subgroup analysis, the timing of the use of BB showed no statistically significant differences regarding the protective effect on POAF. However, the OR was lowest when it was used at both pre- and postoperative periods than isolated preoperative or postoperative use only (ORs 0.50, 0.80 and 0.66, respectively, $p$ = 0.088). This could be explained by possible adverse effects associated with a rebound phenomenon caused by discontinuation of the BB after surgery in patients who took them before surgery. This result is in accordance with current recommendations which described that patients who are already taking BB should continue to take them before and after surgery [32].

Although most episodes of POAF are transient and self-limiting in nature, they are significantly associated with mortality and morbidities including a 2 to 4 times greater risk of stroke, heart failure, bleeding from anticoagulation, renal failure and prolonged ventilator care [1-3, 25-27, 29]. The results of the present study showing a 50% reduction of in-hospital mortality. However, this positive interpretation should be drawn carefully, because there was no statistical significance when the pooled estimates included the OR of 90-day mortality in one more study [20]. In addition, the reduction of POAF did not translate into improvement of clinical outcomes such as a reduced occurrence of postoperative stroke or length of hospital stay. This might be due to the fact that only a small number of studies were included in our analyses.

## Study Limitations

There are several limitations to be noticed in this study. First, the studies included were not all RCTs, and confounding factors could affect the results of our analysis, although only adjusted results were included in the present study. Second, protocols regarding the use of BB such as the types of drugs and timing of the use varied between studies. Finally, a publication bias could not be ruled out as the funnel plot and Egger's test indicated the possibility of unpublished small studies with negative results for the use of BB.

# CONCLUSIONS

The perioperative use of BB is effective in preventing POAF even in patients undergoing cardiac surgery other than isolated CABG.

# REFERENCES

1. Almassi GH, Pecsi SA, Collins JF, Shroyer AL, Zenati MA, Grover FL. Predictors and impact of postoperative atrial fibrillation on patients' outcomes: a report from the randomized on versus off bypass trial. J Thorac Cardiovasc Surg 2012;143:93-102.
2. Kaw R, Hernandez AV, Masood I, Gillinov M, Saliba W, Blackstone EH. Short- and long-term mortality associated with new-onset atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis. J Thorac Cardiovasc Surg 2011;141:1305-12.
3. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg. 2016;50:e1-e88.
4. Crystal E, Connolly SJ, Sleik K, Ginger TJ, Yusuf S. Interventions on prevention of postoperative atrial fibrillation in patients undergoing heart surgery: a metaanalysis. Circulation 2002;106:75–80.
5. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:e652-e735.
6. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. Int J Surg 2010;8:336-41.
7. Sterne JA, Hernán MA, Reeves BC, et al. Robins-I: A tool for assessing

risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.

8. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.
9. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
10. Freeman MF, Tukey JW. Transformations related to the angular and the square root. The Ann of Math Statist 1950;21:607-11.
11. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455-63.
12. Connolly Stuart J, Cybulsky Irene, Lamy André, Roberts Robin S, O'brien Bernard, Carroll Sandra, Crystal Eugene, Thorpe Kevin E, Gent Michael. Double-blind, placebo-controlled, randomized trial of prophylactic metoprolol for reduction of hospital length of stay after heart surgery: the beta-Blocker Length Of Stay (BLOS) study. Am Heart J 2003;145:226–32.
13. Auer J, Weber T, Berent R, et al. A comparison between oral antiarrhythmic drugs in the prevention of atrial fibrillation after cardiac surgery: The Pilot Study of Prevention of Postoperative Atrial Fibrillation (SPPAF), a randomized, placebocontrolled trial. Am Heart J 2004;147:636–43.
14. Coleman CI, Perkerson KA, Gillespie EL, et al. Impact of prophylactic

postoperative beta-blockade on post-cardiothoracic surgery length of stay and atrial fibrillation. Ann Pharmacother 2004;38:2012-6

15. Workman AJ, Pau D, Redpath CJ, et al. Post-operative atrial fibrillation is influenced by beta-blocker therapy but not by pre-operative atrial cellular electrophysiology. J Cardiovasc Electrophysiol 2006;17:1230-8.
16. Shirzad M, Karimi A, Tazik M, et al. Determinants of postoperative atrial fibrillation and associated resource utilization in cardiac surgery. Rev Esp Cardiol 2010;63:1054-60.
17. Silva RG, Lima GG, Guerra N, Bigolin AV, Petersen LC. Risk index proposal to predict atrial fibrillation after cardiac surgery. Rev Bras Cir Cardiovasc 2010;25:183-9.
18. Sakaguchi M, Sasaki Y, Hirai H, et al. Efficacy of landiolol hydrochloride for prevention of atrial fibrillation after heart valve surgery. Int Heart J 2012;53:359-63.
19. Skiba MA, Pick AW, Chaudhuri K, et al. Prophylaxis against atrial fibrillation after cardiac surgery: beneficial effect of perioperative metoprolol. Heart Lung Circ 2013;22:627-33
20. Cheng N, Gao C. Prophylactic effects of metoprolol on the prevention of atrial fibrillation after cardiac surgery are dose dependent. Heart Surg Forum. 2014;17:E54-E60.
21. Toppen W, Sareh S, Satou N, et al. Do preoperative beta-blockers improve postoperative outcomes in patients undergoing cardiac surgery? Challenging societal guidelines. Am Surg 2014;80:1018-21
22. Sezai A, Osaka S, Yaoita H, et al. Safety and efficacy of landiolol

hydrochloride for prevention of atrial fibrillation after cardiac surgery in patients with left ventricular dysfunction: Prevention of Atrial Fibrillation After Cardiac Surgery With Landiolol Hydrochloride for Left Ventricular Dysfunction (PLATON) trial. J Thorac Cardiovasc Surg 2015;150:957-64.

23. O'Neal JB, Billings FT, Liu X, et al. Effect of Preoperative Beta-Blocker Use on Outcomes Following Cardiac Surgery. Am J Cardiol 2017;120:1293-7.

24. Yokota J, Nishi H, Sekiya N, Yamada M, Takahashi T. Atrial fibrillation following aortic valve replacement: impact of perioperative use of intravenous β-blocker. Gen Thorac Cardiovasc Surg 2017;65:194-9.

25. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 2008;51:793-801.

26. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64:e1-e76.

27. Mathew JP, Parks R, Savino JS, et al. Atrial fibrillation following coronary artery bypass graft surgery: predictors, outcomes, and resource utilization. MultiCenter Study of Perioperative Ischemia Research Group. JAMA 1996;276:300-6.

28. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med

2002;347:1825-33.

29. Aranki SF, Shaw DP, Adams DH, et al. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. Circulation 1996;94:390-7.
30. Crystal E, Garfinkle M.S, Connolly SS, Ginger TT, Sleik K, Yusuf SS. Interventions for preventing postoperative atrial fibrillation in patients undergoing heart surgery, Cochrane Database Syst Rev 2004;4:CD003611.
31. Blessberger H, Kammler J, Domanovits H, et al. Perioperative beta-blockers for preventing surgery-related mortality and morbidity. Cochrane Database Syst Rev 2018;3:CD004476.
32. Sousa-Uva M, Head SJ, Milojevic M, et al. 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. Eur J Cardiothorac Surg. 2018;53:5-33.

**TABLE 1. Study Characteristics**

| Study | Operative Era | Country | Study type | Study population | | | Type of BB | Use of BB | Surgery other than iCABG (%) | | | Statistical methods |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Total | BB group | Control | | | Total | BB group | Control | |
| *Connolly et al.* | 1999 | Canada | RCT | 1000 | 500 | 500 | metoprolol | postop | 13 | 13 | 12 | RCT |
| *Auer et al.* | 2001-2002 | Austria | RCT | 127 | 62 | 65 | metoprolol | both | 43 | 35 | 49 | RCT |
| *Coleman et al.* | 1999-2003 | USA | NRS | 1660 | 830 | 830 | metoprolol | postop | 41 | 41 | 41 | Matching |
| *Workman et al.* | 1999-2005 | UK | NRS | 212 | 141 | 71 | not described | preop | 16 | - | - | MV |
| *Shirzad et al.* | 2002-2008 | Iran | NRS | 15431* | 12890 | 2541 | not described | preop | 7 | - | - | MV |
| *Silva et al.* | - | Brazil | NRS | 448 | 239 | 209 | not described | both | 25-33† | - | - | MV |
| *Sakaguchi et al.* | 2008-2010 | Japan | RCT | 60 | 30 | 30 | landilolol | postop | 100 | 100 | 100 | RCT |
| *Skiba et al.* | - | Australia | RCT | 148 | 75 | 73 | metoprolol | postop | 28 | 31 | 26 | RCT |
| *Cheng et al.* | 2009-2012 | China | NRS | 614 | 437 | 177 | metoprolol | both | 39 | 39 | 40 | MV |
| *Toppen et al.* | 2008-2013 | USA | NRS | 2120 | 1277 | 843 | not described | preop | 71 | 40 | 89 | MV |
| *Sezai et al.* | - | Japan | RCT | 60 | 30 | 30 | landilolol | postop | 23 | 23 | 23 | RCT |
| *O'Neal et al.* | 2009-2015 | USA | NRS | 3497 | 2294 | 1203 | not described | preop | 48‡ | 39‡ | 65‡ | PSM |
| *Yokota et al.* | 2010-2013 | Japan | NRS | 119 | 32 | 87 | mixed | preop | 100 | 100 | 100 | MV |

RCT = randomized controlled study, NRS = non-randomized study, BB = beta-blocker, iCABG = isolated coronary artery bypass graft surgery, PSM = propensity score matching, MV = multivariable analysis.

*History of beta-blocker use was identified in 15431 of 15580 total study patients.

†Possible proportion was estimated.

‡Data were drawn from overall study population (n = 4076, BB group vs control = 2648 vs 1428)

**TABLE 2. Patients Characteristics**

| Study | Age (year) | | Female (%) | | Hypertension (%) | | Diabetes (%) | | Dyslipidemia (%) | | CHF (%) | | POAF (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BB group | Control | BB group | Control | BB group | Control | BB group | Control | BB group | Control | BB group | Control | |
| *Connolly et al.* | 63±10 | 62±10 | 22 | 20 | - | - | - | - | - | - | | | 35.1 |
| *Auer et al.* | 68±9 | 63±12 | 40 | 42 | 66 | 55 | 34 | 19 | - | - | | | 47.2 |
| *Coleman et al.* | 66±13 | 66±11 | 28 | 28 | 65 | 65 | 28 | 26 | 57 | 58 | | | 26.0 |
| *Workman et al.* | 63±3 | | 26 | | 55 | | 12 | | 79 | | | | 25.0 |
| *Shirzad et al.* | 58±1 | | 27 | | 51 | | 31 | | 65 | | | | 7.2 |
| *Silva et al.* | 61±12 | | 36 | | - | - | 30 | | 40 | | | | 22.1 |
| *Sakaguchi et al.* | 69±9 | 69±10 | 50 | 43 | 70 | 63 | 30 | 23 | 30 | 23 | | | 36.7 |
| *Skiba et al.* | 68±2 | 63±1 | 25 | 18 | 57 | 60 | 19 | 29 | 60 | 59 | | | 34.5 |
| *Cheng et al.* | 63±8 | 63±8 | 47 | 38 | 59 | 63 | 43 | 38 | 23 | 22 | | | 26.4 |
| *Toppen et al.* | 64±14 | 59±16 | 32 | 37 | 78 | 49 | 31 | 20 | - | - | | | 16.2 |
| *Sezai et al.* | 65±10 | 68±9 | 13 | 20 | 77 | 63 | 53 | 43 | 40 | 57 | | | 25.0 |
| *O'Neal et al.* | 64±12* | 63±13* | 30* | 35* | 79* | 63* | 42* | 31* | 44* | 32* | | | 30.3 |
| *Yokota et al.* | 73±10 | | 47 | | 70 | | 20 | | 37 | | | | 39.5 |

BB = beta-blocker, CHF = congestive heart failure, POAF = postoperative atrial fibrillation.

*data from the entire group before matching

## Table 3. Quality Assessment of Included Studies

| Quality assessment by Cochran Risk of Bias Tool for randomized controlled trials | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other sources of bias | |
| *Connolly et al.* | unclear | low | low | low | low | low | low | |
| *Auer et al.* | low | low | low | low | low | low | low | |
| *Sakaguchi et al.* | low | low | high | low | low | low | low | |
| *Skiba et al.* | unclear | low | high | low | low | low | low | |
| *Sezai et al.* | low | low | high | low | low | low | low | |
| **Quality assessment by Risk Of Bias In Non-randomized Studies of Interventions for non-randomized studies** | | | | | | | | |
| Study | Bias due to confounding | Bias in selection of participants into the study | Bias in measurement of interventions | Bias due to departures from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result | Overall |
| *Coleman et al.* | moderate | low | low | low | low | low | low | moderate |
| *Workman et al.* | moderate | low | low | low | low | low | low | moderate |
| *Shirzad et al.* | moderate | low | low | low | low | low | low | moderate |
| *Silva et al.* | moderate | low | low | low | low | low | low | moderate |
| *Cheng et al.* | moderate | low | low | low | low | low | low | moderate |
| *Toppen et al.* | moderate | low | low | low | low | low | low | moderate |
| *O'Neal et al.* | moderate | low | low | low | low | low | low | moderate |
| *OYokota et al.* | moderate | low | low | low | low | low | low | moderate |

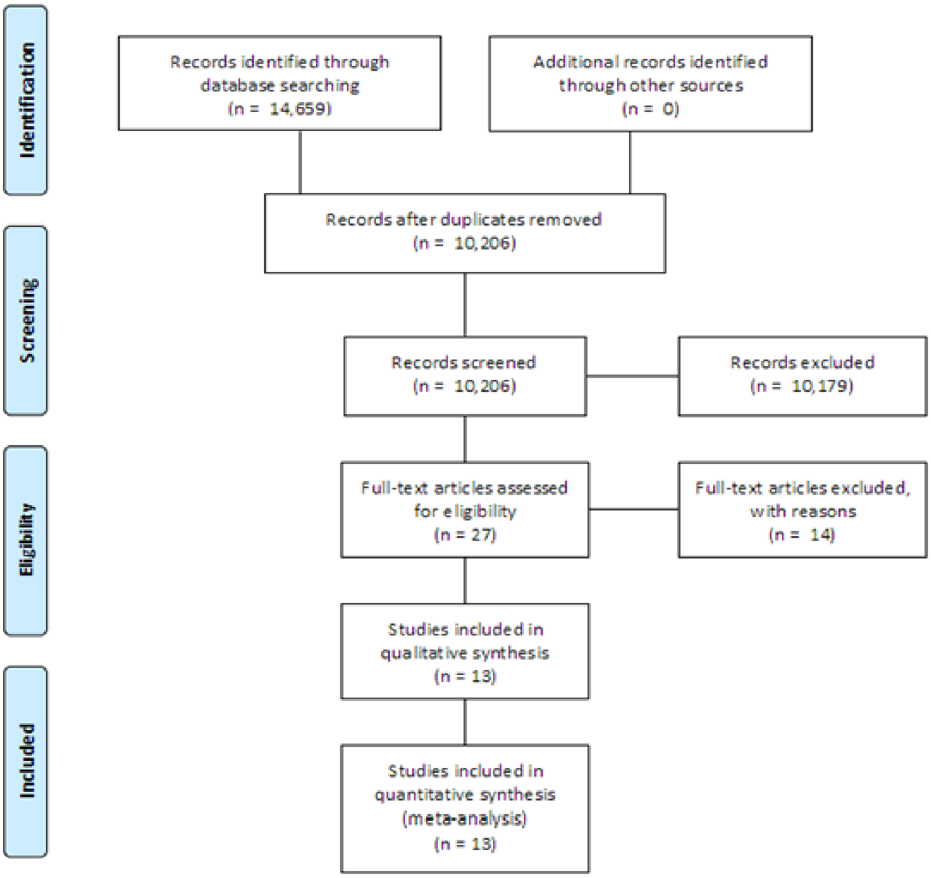



**FIGURE 1. Flow diagram based on Preferred Reporting Items for Systematic Reviews and Meta-analyses.**

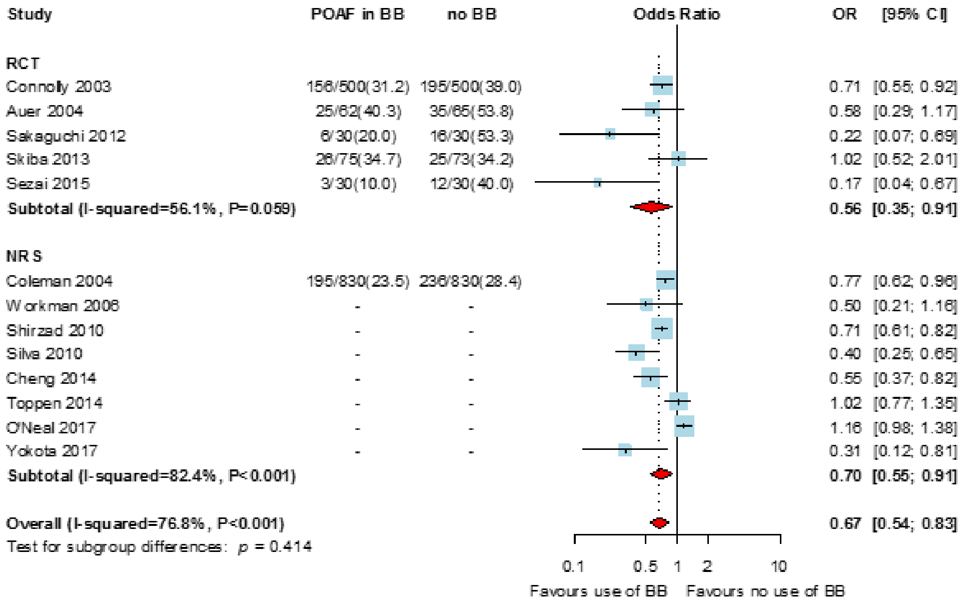



**FIGURE 2. Odd ratio (OR) of the occurrence rates of postoperative atrial fibrillation between patients with beta-blocker (BB) and those without BB (CI = confidence interval).**

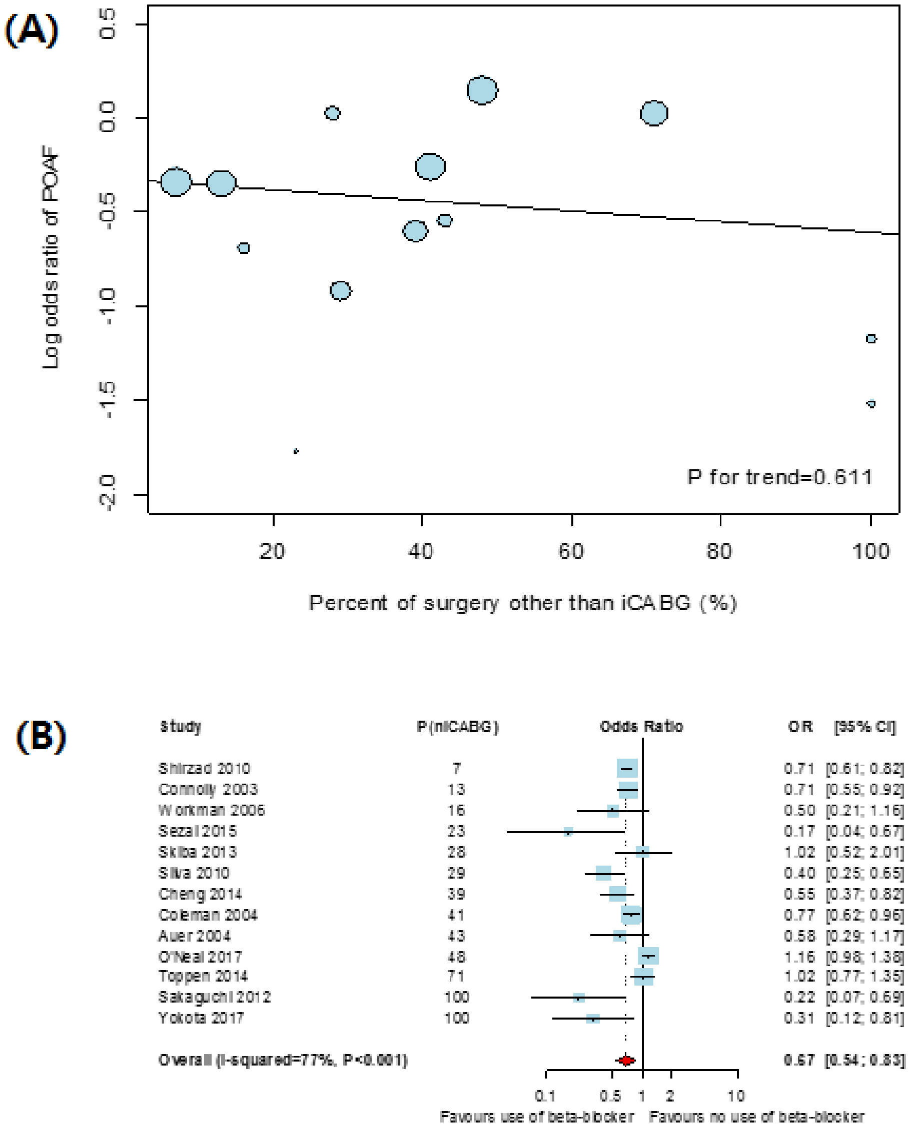



**FIGURE 3. (A) Meta-regression analysis and (B) a forest plot demonstrated that proportions of patients who underwent surgery other than isolated coronary artery bypass grafting (iCABG) was not significantly associated with the odds ratio (OR) of postoperative atrial fibrillation (POAF) between beta-blocker (BB) and non-BB groups (CI = confidence interval).**

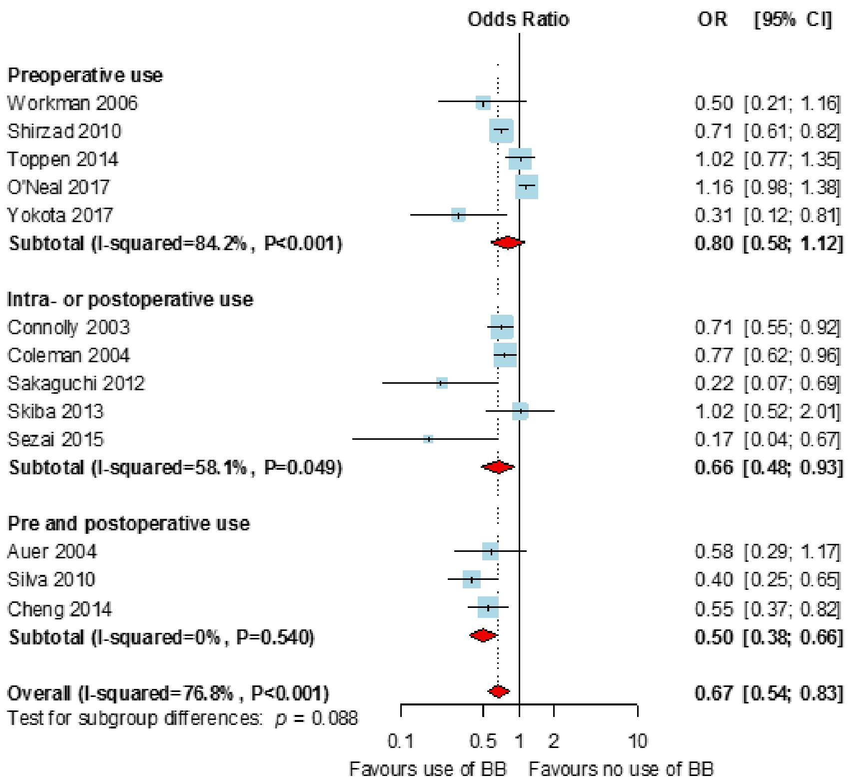
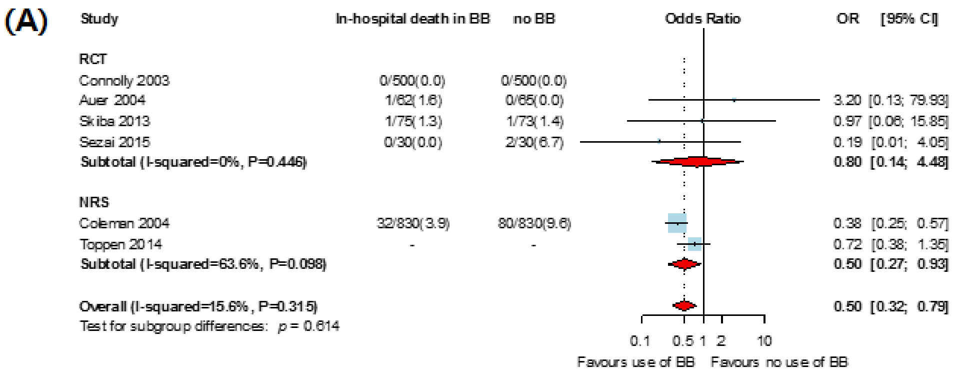



**FIGURE 4. Subgroup analysis of odds ratio (OR) according to the timing of administration of beta-blocker (BB) (CI = confidence interval).**



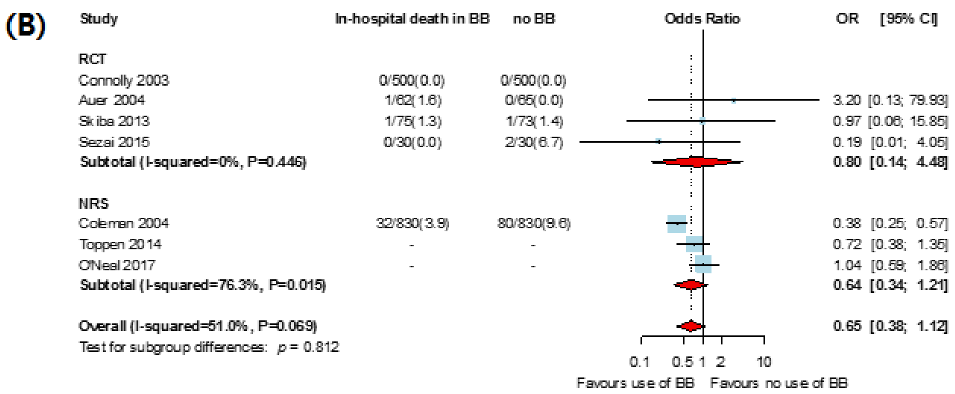




**FIGURE 5. (A) Pooled analysis of in-hospital mortality between patients with beta-blocker (BB) and those without BB showed a statistically significant difference. (B) However, the OR became insignificant when the result of 90-day mortality from one study (O'Neal et al.) was added (OR = odd ratio, CI = confidence interval).**

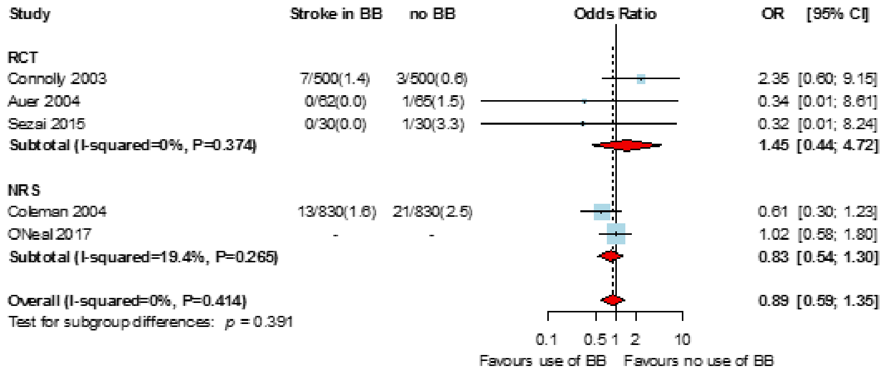



**FIGURE 6. Odds ratio (OR) of postoperative stroke in patients with beta-blocker (BB) and those without BB (CI = confidence interval).**

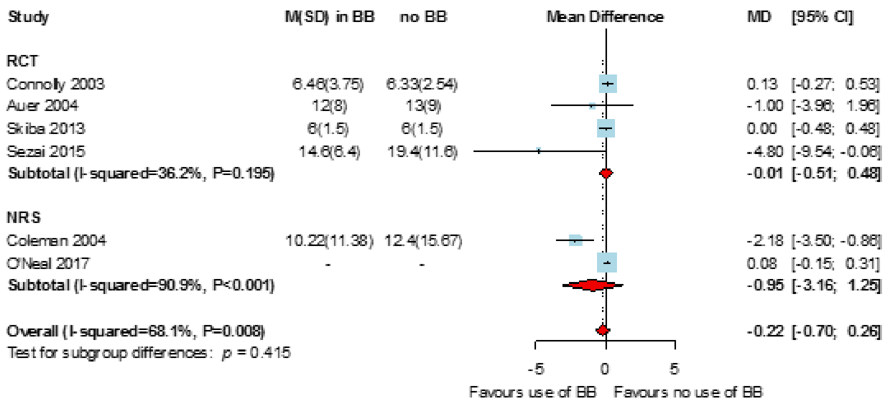



**FIGURE 7. Mean difference (MD) of length of hospital stay in patients with beta-blcocker (BB) and those without. (M = mean, SD = standard deviation, CI = confidence interval, RCT = randomized controlled trial, NRS = non-randomized study).**

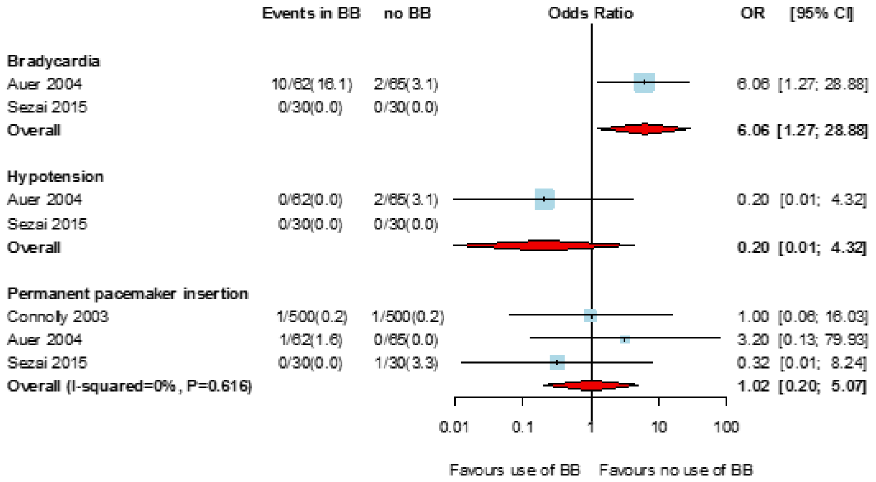



**FIGURE 8. Odds ratio (OR) regarding (A) bradycardia, (B) hypotension and (C) a need of permanent pacemaker insertion in patients with beta-blocker (BB) and those without BB. (CI = confidence interval).**

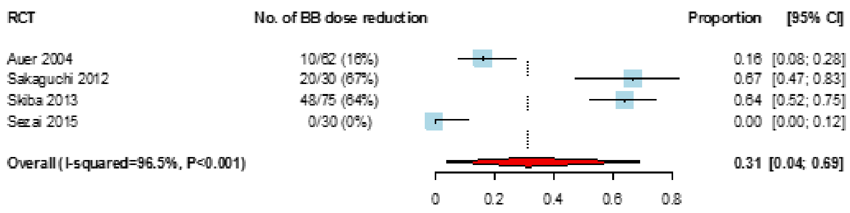



**FIGURE 9. Proportions of patients in whom beta-blocker (BB) dose reduction was needed. (CI = confidence interval, RCT = randomized controlled trial).**

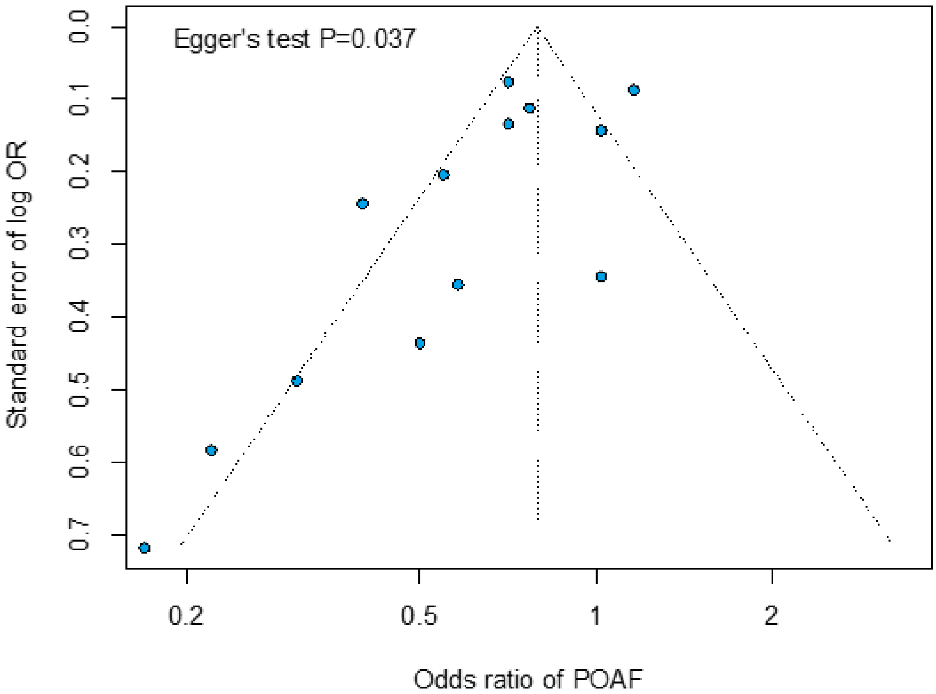



**FIGURE 10. Funnel plots and Egger's test for asymmetry.**

# 국문 초록

# 심장수술환자에서 수술 전후 베타 차단제의 사용이 수술 후 심방세동 발생에 미치는 영향에 대한 메타분석 연구

**김 수 현**

**의학과, 임상의과학과**

**서울대학교 대학원**

**서론**: 심방세동은 심장 수술 후 발생하는 가장 흔한 합병증 중 하나로 수술 후 질병 이환율과 사망률을 유의하게 증가시킨다. 본 연구는 수술 전후 베타 차단제 사용이 단독 관상동맥 우회로 수술 이외의 심장 수술 후 발생하는 심방세동에 미치는 영향에 대하여 메타분석을 시행하고, 그 임상적 의미를 도출하고자 한다.

**방법**: 5개의 주요 온라인 문헌 데이터베이스를 검색하여 다음 두 가지 기준에 적합한 연구들을 취합하였다. (1) 단독 관상동맥 우회로 수술 이외의 심장 수술을 시행한 환자군을 대상으로 한 연구인 동시에 (2) 무작위대조시험 혹은 보정분석을 바탕으로 수술 전후 베타 차단제의 사용이 수술 후 발생하는 심방세동에 미치는 영향을 분석한 연구인 경우 본

연구 대상에 포함하였다. 심장 수술 후 심방세동의 발생율을 분석의 일차 결과로 설정하였고, 단독 관상동맥 우회로 수술 외의 심장 수술 환자의 비율 및 베타 차단제의 사용 시점을 근거로 각각 메타회귀분석 및 하위집단 분석을 시행하였다.

**결과:** 5개의 무작위 대조 연구 및 8개의 비무작위 연구를 포함하여 총 13개의 문헌을 연구대상으로 선정하였다. 연구에 포함된 환자 중 단독 관상동맥 우회로 수술 외의 심장 수술을 받은 환자의 비율은 7% 에서 100%의 범주를 보였다. 베타 차단제는 5개의 연구에서 수술 전, 5개의 연구에서 수술 후 혹은 수술 중, 나머지 3개의 연구에서는 수술 전후 모든 시점에 사용되었다. 혼주 분석 결과, 수술 후 심방세동 발생의 위험도는 수술 전후 베타 차단제를 사용한 군이 그렇지 않은 군에 비하여 유의하게 낮았다 (odds ratio (OR), 95% confidence interval (CI) = 0.67, 0.54-0.83). 하위집단 분석 결과, 단독 관상동맥 우회로 수술 외의 심장 수술 환자의 비율 및 베타 차단제의 사용 시점은 수술 전후 베타 차단제의 사용이 수술 후 심방세동의 발생 위험도를 낮추는데 유의한 영향을 미치지 못하였다. 베타 차단제를 사용한 환자군에서 병원 내 사망률은 유의하게 50 % 감소하였다 (OR, 95% CI = 0.50, 0.32-0.79). 수술 전후 뇌졸중의 발생과 재원 기간은 베타 차단제를 사용한 군과 그렇지 않은 군 사이에 유의한 차이를 보이지 않았다.

**결론:** 수술 전후 베타 차단제의 사용은 심장 수술 후 발생하는 심방세동 예방에 유의한 효과를 보인다.

주요어: 심장수술, 심방세동, 베타 차단제

학번: 2011-21970