

Original Article



The Effects of Preoperative Aspirin on Coronary Artery Bypass Surgery: a Systematic Meta-Analysis

Doyeon Hwang , MD^{1,*}, Joo Myung Lee , MD, MPH, PhD^{2,*}, Tae-Min Rhee , MD¹, Young-Chan Kim, MD¹, Jiesuck Park , MD¹, Jonghanne Park , MD, PhD¹, Chul Ahn, PhD³, Young Bin Song , MD, PhD², Joo-Yong Hahn , MD, PhD², Ki-Bong Kim, MD, PhD⁴, Young-Tak Lee, MD, PhD⁵, and Bon-Kwon Koo , MD, PhD^{1,6}



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Correspondence to

Bon-Kwon Koo, MD, PhD
Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, 101, Daehak-ro, Jongno-gu, Seoul 03080, Korea.
E-mail: bkkoo@snu.ac.kr

*Doyeon Hwang and Joo Myung Lee contributed equally to this work.

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ORCID iDs

Doyeon Hwang 
<https://orcid.org/0000-0002-0215-5319>
Joo Myung Lee 
<https://orcid.org/0000-0002-2178-4014>
Tae-Min Rhee 
<https://orcid.org/0000-0002-0504-0736>
Jiesuck Park 
<https://orcid.org/0000-0001-6924-7106>
Jonghanne Park 
<https://orcid.org/0000-0002-8860-8445>
Young Bin Song 
<https://orcid.org/0000-0003-3986-9152>
Joo-Yong Hahn 
<https://orcid.org/0000-0002-4412-377X>
Bon-Kwon Koo 
<https://orcid.org/0000-0002-8188-3348>

¹Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Korea
²Department of Internal Medicine and Cardiovascular Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
³Division of Biostatistics, Center for Devices and Radiological Health, Food and Drug Administration, Silver Spring, MD, USA
⁴Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul, Korea
⁵Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
⁶Institute of Aging, Seoul National University, Seoul, Korea

ABSTRACT

Background and Objectives: Aspirin plays an important role in the maintenance of graft patency and the prevention of thrombotic event after coronary artery bypass graft surgery (CABG). However, the use of preoperative aspirin is still under debate due to the risk of bleeding.

Methods: From PubMed, EMBASE, and Cochrane Central Register of Controlled Trials, data were extracted by 2 independent reviewers. Meta-analysis using random effect model was performed.

Results: We performed a systemic meta-analysis of 17 studies (12 randomized controlled studies and 5 non-randomized registries) which compared clinical outcomes of 9,101 patients who underwent CABG with or without preoperative aspirin administration. Preoperative aspirin increased chest tube drainage (weighted mean difference 177.4 mL, 95% confidence interval [CI], 41.3–313.4; p=0.011). However, the risk of re-operation for bleeding was not different between the preoperative aspirin group and the control group (3.2% vs. 2.4%; odds ratio [OR], 1.23; 95% CI, 0.94–1.60; p=0.102). There was no difference in the rates of all-cause mortality (1.6% vs. 1.5%; OR, 0.98; 95% CI, 0.64–1.49; p=0.920) and myocardial infarction (MI) (8.7% vs. 10.4%; OR, 0.83; 95% CI, 0.66–1.04; p=0.102) between patients with and without preoperative aspirin administration.

Conclusions: Although aspirin increased the amount of chest tube drainage, it was not associated with increased risk of re-operation for bleeding. In addition, the risks of early postoperative all-cause mortality and MI were not reduced by using preoperative aspirin.

Keywords: Coronary artery bypass surgery; Aspirin

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Hwang D, Lee JM, Rhee TM, Kim YC, Park J, Park J, Song YB, Hahn JY, Kim KB, Lee YT, Koo BK; Data curation: Hwang D, Lee JM, Rhee TM, Kim YC, Park J, Park J, Ahn C, Hahn JY, Koo BK; Formal analysis: Hwang D, Lee JM, Rhee TM, Kim YC, Park J, Park J, Lee YT, Koo BK; Investigation: Hwang D, Lee JM, Rhee TM, Kim YC, Park J, Park J, Ahn C, Song YB, Hahn JY, Kim KB, Koo BK; Methodology: Hwang D, Lee JM, Rhee TM, Kim YC, Park J, Koo BK; Supervision: Ahn C, Song YB, Hahn JY, Kim KB, Lee YT, Koo BK; Writing - original draft: Hwang D, Lee JM.

INTRODUCTION

Aspirin plays an important role in preventing cardiovascular events in patients with coronary artery disease, regardless of revascularization.^{1,2)} In patients who undergo coronary artery bypass graft surgery (CABG), the safety and efficacy of aspirin administration before and after surgery were investigated by several studies.³⁻⁸⁾ Preoperative aspirin was reported to reduce the incidence of myocardial infarction (MI),⁵⁾ and improve venous graft patency^{3,4)} and survival.^{6,7)} However, it also increases the risk of bleeding.^{5,9)} In this regard, there has been controversy in the preoperative administration of aspirin.

The current the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline for CABG recommends preoperative aspirin use as a class I recommendation,^{10,11)} and the the Society of Thoracic Surgeons (STS) guideline recommends discontinuation of aspirin before elective CABG in patients at high-risk of bleeding as a class IIa recommendation, due to increased postoperative bleeding risk.^{12,13)} Furthermore, 2 recent studies showed conflicting results for aspirin administration before CABG. The most recent meta-analysis presented significantly increased risks of postoperative bleeding and subsequent re-operation in patients with preoperative aspirin.⁵⁾ Conversely, a large-scale multicenter Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial showed that preoperative aspirin use resulted in neither a lower risk of death or MI nor a higher risk of bleeding compared with the placebo group.¹⁴⁾

We performed this updated meta-analysis to evaluate the safety and efficacy of preoperative administration of aspirin in patients with planned CABG.

METHODS

The Supplementary Materials describes study methods in detail (**Supplementary Data 1 and 2**).

Data sources and searches

PubMed, EMBASE, Cochrane Central Register of Controlled Trials, the United States National Institutes of Health registry of clinical trials, and relevant websites were searched for pertinent published or unpublished studies. The electronic search strategy was complemented by manual examination of references cited by included articles, recent reviews, editorials and meta-analyses. No restriction was imposed on language, study period or sample size.

Study selection

Studies that met each of the following criteria were considered eligible for meta-analysis: performed before November 21, 2017; safety and efficacy outcomes of patients after CABG including re-operation for bleeding, all-cause mortality or MI after CABG were clearly reported; the outcomes were compared between the preoperative aspirin administration group and the control group which did not use preoperative aspirin; aspirin was used within 4–5 days before CABG in the preoperative aspirin group and was held at least 4–5 days before CABG in the control group.^{9,15)} The studies with both elective and emergent CABG and those of randomized controlled trial (RCT) and non-randomized prospective observational study (non-RCT) design were included. Eligible non-RCTs were adjusted appropriately for baseline differences between groups with or without preoperative aspirin use (propensity score-

based matching or multivariate adjustment). Non-RCTs without multivariable- or propensity score-based adjustment and single-arm studies without comparison or control group were not included. Two investigators (YCK and JP) independently performed screening of titles and abstracts, identified duplicates, reviewed full articles, and determined their eligibility. Disagreements were resolved by discussion.

Data extraction and quality assessment

Summary data reported in the published manuscripts were analyzed. A standardized form was used to extract study characteristics, study design, number of study patients, dose, and regimen of aspirin administered before and after CABG, patient age, proportion of cardiovascular risk factors, characteristics of CABG, proportion of venous or arterial grafts, proportion of on-pump CABG, indications for CABG, and proportion of 3-vessel disease or left main disease. The rates of all-cause mortality, in-hospital mortality, MI, re-operation for bleeding and the amount of chest tube drainage and red blood cell (RBC) transfusion were collected, along with the definitions of outcomes used in the individual studies.

The quality of eligible studies was assessed using the Cochrane Collaboration's tool for assessing the risk of bias for RCTs, and the Newcastle-Ottawa Scale (NOS) and the Strengthening The Reporting of OBServational Studies in Epidemiology (STROBE) checklist for non-RCTs. We did not exclude individual studies from the analysis based on the thresholds of NOS or STROBE checklists.

Outcomes

The primary outcome was re-operation for bleeding. Secondary outcomes were all-cause mortality, MI, and the amount of bleeding described by chest tube drainage (mL) and RBC transfusion (unit). For purpose of this analysis, chest tube drainage was recorded at or close to 12 hours after surgery. Other clinical outcomes, including all-cause mortality and MI, were early postoperative events within 30 days from CABG or occurred in hospital. None of the included studies reported clinical events of patients awaiting CABG.

Statistical analysis

Among the primary and secondary outcomes, re-operation for bleeding, all-cause mortality and MI were analyzed using random effect model with generic inverse variance method. Odds ratio (OR) with 95% confidence interval (CI) is presented as summary statistic. Numerical variables, including chest tube drainage and RBC transfusion, are presented as weighted mean difference (WMD) between the preoperative aspirin group and the control group with 95% CI. We excluded data which were presented as median with interquartile range and which did not report standard deviation.

Statistical heterogeneity was quantified using the I^2 statistic. Publication bias¹⁶⁾ was assessed by funnel plot asymmetry and Egger's and Begg's tests. When visual asymmetry of funnel plot was suspected, the trim-and-fill method was used to calculate an adjusted OR. Subgroup analyses were performed according to the study design (RCT or non-RCT) and the use of cardiopulmonary bypass (CPB) support. As technique of CABG and peri-operative care has evolved throughout the century,¹⁷⁾ the impact of publication date on the overall pooled ORs for re-operation for bleeding were evaluated, using cumulative meta-analysis. Two-sided p values <0.05 were considered statistically significant. Statistical analysis was performed using STATA/SE 12.0 (StataCorp LP, College Station, TX, USA). The present study complied with the Preferred Reporting Items for Systematic Reviews and Meta-

Analyses guideline (**Supplementary Table 1**) and the Meta-analysis of Observational Studies in Epidemiology guideline.

RESULTS

Search results

From 5,767 candidate articles, 54 articles were extracted for full article review. Of these, 17 articles with 9,101 patients satisfied the inclusion criteria (**Figure 1**). Characteristics of excluded articles are summarized in **Supplementary Data 2**. The final 17 articles consisted of 12 RCTs and 5 non-RCTs. Among the final 17 articles, 15 articles reported the rate of re-operation for bleeding, 10 articles reported the rate of all-cause mortality and 9 articles reported the rate of MI. We assessed the amount of bleeding after CABG in the form of chest tube drainage (9 articles) and RBC transfusion (8 articles). The major characteristics of the 17 individual articles are summarized in **Table 1**.

Risk of bias of included studies

Among 12 RCTs, 6 RCTs did not report the method of random sequence generation and allocation concealment, and had unclear risk of bias.¹⁸⁻²³ Although 6 RCTs were not double-blind studies, all endpoints were objective findings (re-operation, all-cause mortality and MI) and the judgment of outcomes was not likely to be influenced by the blinding. Only 1 trial demonstrated high-risk of bias in incomplete outcome data (**Supplementary Table 2**).²² All non-RCTs satisfied at least 16 criteria in the reports of observational studies in epidemiology checklist; **Supplementary Table 3** presents the results of NOS.

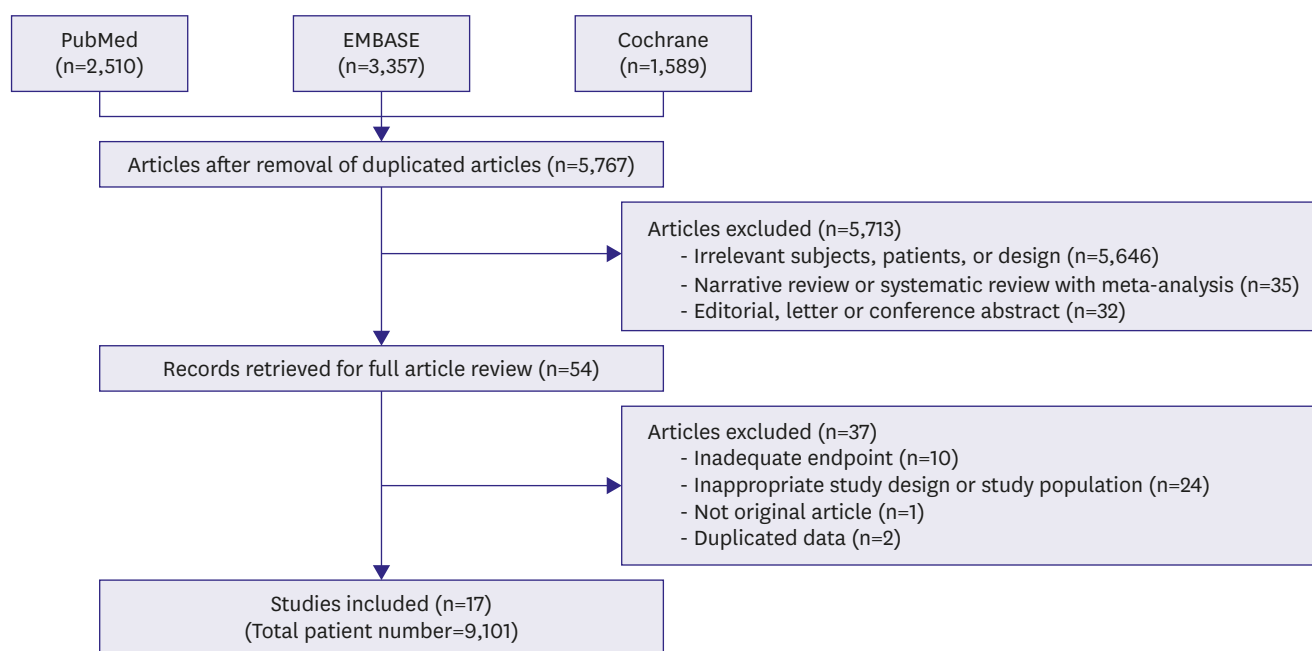


Figure 1. Flow chart of study selection process. The study flow chart following the guideline of PRISMA is presented. PRISMA = Preferred Reporting Items For Systematic Reviews And Meta-Analyses.

Table 1. Characteristics of included studies

Author (year)	Study design	Follow-up duration	No. of patients		Administration of aspirin	Postop antiplatelet	Other antiplatelet	Urgent or elective CABG
			Preop. aspirin	Control				
Fuller et al. (1985)	RCT	In hospital	21	9	Aspirin group: aspirin 650–2,600 mg beginning 48 hours pre-operatively. Control: no aspirin.	NA	NA	Elective
Ferraris et al. (1988)	RCT	In hospital	16	18	Aspirin group: aspirin 325 mg, once 1 day before surgery. Control: no aspirin.	NA	NA	Elective or urgent
Goldman et al. (1991)	RCT	In hospital	176	175	Aspirin group: aspirin 325 mg once 1 day before CABG. Control: placebo once before CABG.	Both groups received 325 mg of aspirin daily	NA	Elective
Hockings et al. (1993)	RCT	In hospital	50	52	Aspirin group: aspirin 100 mg, daily for 7 days. Control: placebo for 7 days before CABG.	Both groups received 100 mg of aspirin daily	No other antiplatelet therapy	Elective
Kallis et al. (1994)	RCT	In hospital	50	50	Aspirin group: aspirin 300 mg, daily for 2 weeks. Control: placebo for 2 weeks before CABG.	NA	No other antiplatelet therapy	Elective
Klein et al. (1998)	RCT	In hospital	40	38	Aspirin group: aspirin 100 mg, daily for 10 days+intraoperative aprotinin. Control: placebo for 10 days+intraoperative aprotinin.	NA	NA	Elective
Srinivasan et al. (2003)	Non-RCT	In hospital	170	170	Aspirin group: aspirin intake within 7 days until the day of surgery. Control group: aspirin was discontinued at least 7 days.	NA	No other antiplatelet therapy	Elective or urgent
Morawski et al. (2005)	RCT	In hospital	51	51	Aspirin group: aspirin 150 mg, 12 hours and 3 hours before surgery. Control: aspirin was discontinued at least 10 days, placebo	Both groups received 150 mg of aspirin daily	No other antiplatelet therapy	Elective or urgent
Bybee et al. (2005)	Non-RCT	In hospital	1,316	320	Aspirin group: aspirin exposure within 5 days. Control group: aspirin was discontinued at least 5 days.	NA	NA	Elective or urgent
Ghaffarinejad et al. (2007)	RCT	In hospital	100	100	Aspirin group: received aspirin preoperatively+intraoperative aprotinin. Control: aspirin was discontinued at least 7 days+intraoperative aprotinin.	Both groups received aspirin	No other antiplatelet therapy	Elective
Deja et al. (2012)	RCT	30 days	387	396	Aspirin group: aspirin 300 mg, the night before surgery. Control: placebo, aspirin was stopped for 7 days.	Both groups received 300 mg of aspirin daily	No other antiplatelet therapy	Elective
Mikkola et al. (2012)	Non-RCT	In hospital	153	153	Aspirin group: aspirin exposure within 3 days. Control: aspirin was discontinued at least 7 days.	Both groups received aspirin	No other antiplatelet therapy	Elective
Berg et al. (2013)	RCT	In hospital	12	8	Aspirin group: aspirin until the day before surgery. Control: aspirin withdrawal 7 days before.	NA	No other antiplatelet therapy	Elective
Huang et al. (2015)	Non-RCT	30 days	728	725	Aspirin group: aspirin exposure within 5 days. Control: aspirin was discontinued at least 5 days.	NA	No other antiplatelet therapy	Elective or urgent
Xiao et al. (2015)	Non-RCT	In hospital	709	709	Aspirin group: aspirin was continued preoperatively. Control: aspirin was discontinued at least 5 days.	Both groups received 100 mg of aspirin daily	No other antiplatelet therapy	Elective
Myles et al. (2016)	RCT	30 days	1,047	1,053	Aspirin group: aspirin once preoperatively. Control: placebo, no aspirin within 4 days.	NA	NA	Elective
Lee et al (2017)	RCT	In hospital	24	24	Aspirin group: aspirin 100mg was administered every morning until the operative day. Control: no aspirin within 4 days.	Both groups received 100 mg of aspirin and 75 mg of clopidogrel daily	Both groups received 100 mg of aspirin and 75 mg of clopidogrel daily	Elective

CABG = coronary artery bypass graft surgery; NA = not applicable; Preop. = preoperative; RCT = randomized controlled trial.

Comparison of re-operation for bleeding

The observed rates of re-operation for bleeding in pooled analysis were 3.2% and 2.4% for the preoperative aspirin group and the control group, respectively, and were not different between the 2 groups in pooled analysis (pooled OR, 1.23; 95% CI, 0.94–1.60; $p=0.102$) (Figure 2). The pooled analysis demonstrated no statistical heterogeneity ($I^2=0.0\%$). Although the visual estimation of funnel plot and Egger's test showed possibility of publication bias in the pooled analysis, trimmed and filled OR also showed similar results (trimmed and filled OR, 1.03; 95% CI, 0.80–1.33; $p=0.809$) (Supplementary Figure 1A). No individual study substantially affected the pooled OR of re-operation for bleeding (Supplementary Figure 2A). In addition, the potential effect of increased rates of re-operation for bleeding in the preoperative aspirin group was gradually decreased toward equivalent risk with the control group in the recent study period. (Supplementary Figure 3).

Preoperative administration of aspirin was significantly associated with increased amount of chest tube drainage (WMD 177.4 mL; 95% CI, 41.3–313.4; $p=0.011$; $I^2=94.0\%$) (Figure 3).

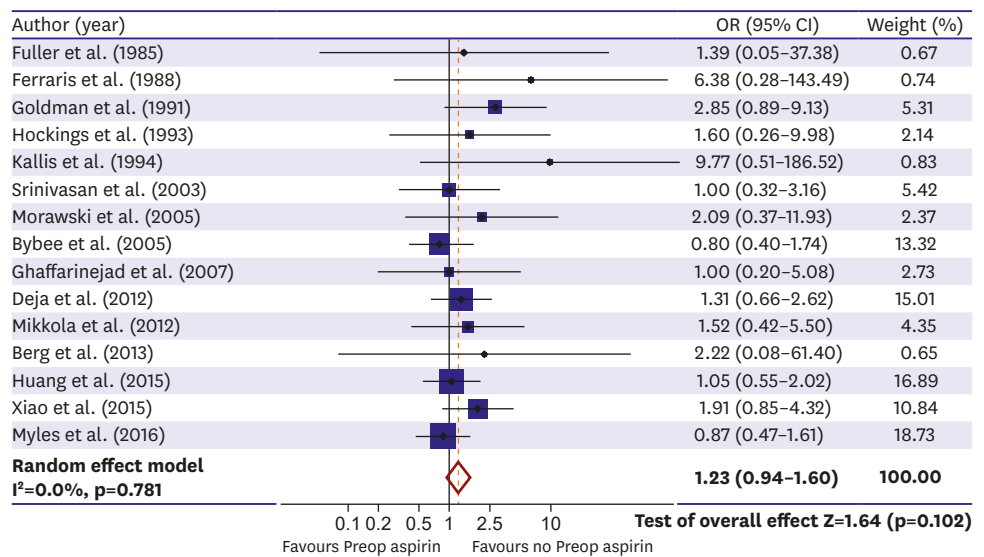


Figure 2. Forest plot comparing re-operation for bleeding with or without preoperative aspirin. ORs with 95% CIs are presented for individual studies and the pooled overall effect. CI = confidence interval; OR = odds ratio; Preop = preoperative.

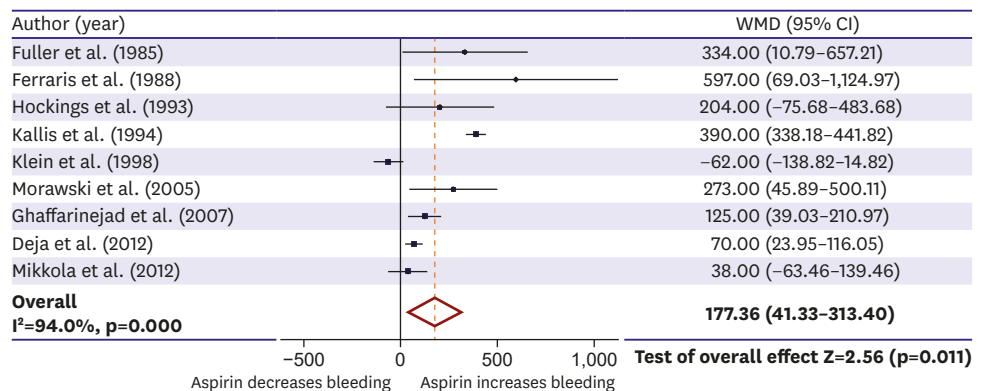


Figure 3. Forest plot comparing chest tube drain with or without preoperative aspirin. WMDs with 95% CIs are presented for individual studies and the pooled overall effect. CI = confidence interval; WMD = weighted mean difference.

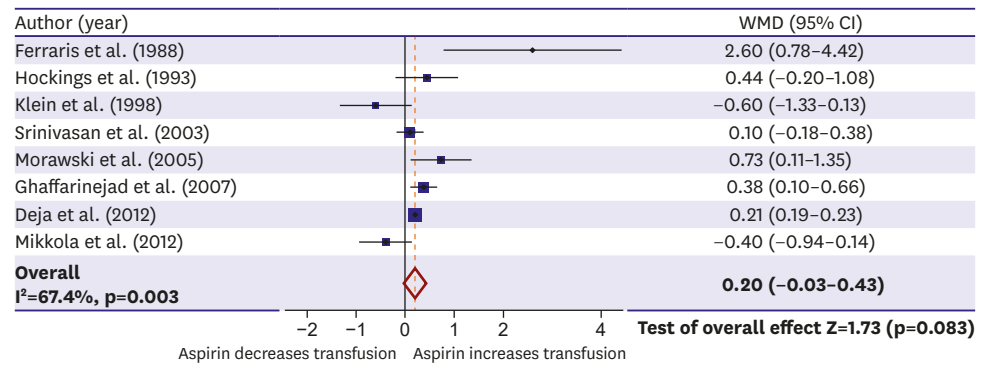


Figure 4. Forest plot comparing RBC transfusion with or without preoperative aspirin. WMDs with 95% CIs are presented for individual studies and the pooled overall effect. CI = confidence interval; RBC = red blood cell; WMD = weighted mean difference.

However, the amount of RBC transfusion was comparable between the preoperative aspirin group and the control group (WMD 0.20 units; 95% CI –0.03–0.43; p=0.083; I²=67.4%) (Figure 4).

Comparison of all-cause mortality and myocardial infarction

The observed rates of all-cause mortality were 1.6% and 1.5% for the preoperative aspirin group and the control group, respectively. Pooled analysis showed no significant difference in the rates of all-cause mortality without statistically significant heterogeneity (pooled OR 0.98; 95% CI, 0.64–1.49; p=0.920; I²=13.6%) (Figure 5). There was visual asymmetry of funnel plot but trimmed and filled OR also showed similar results (Supplementary Figure 1B). Also, there was no individual study effect on the pooled analysis (Supplementary Figure 2B).

The observed rates of MI in the pooled analysis were 8.7% and 10.4% in the preoperative aspirin group and the control group, respectively. The difference was not statistically significant and there was no significant heterogeneity (pooled OR, 0.83; 95% CI, 0.66–1.04; p=0.102; I²=0.0%) (Figure 6). The publication bias was not evident according to the symmetrical funnel plot supported by the Egger's and Begg's tests (Supplementary Figure 1C) and there was no evident individual study effect (Supplementary Figure 2C).

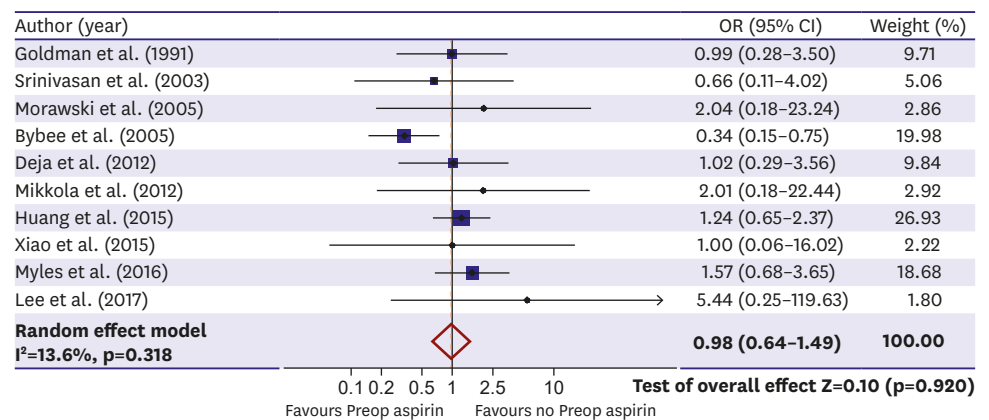


Figure 5. Forest plot comparing all-cause mortality with or without preoperative aspirin. ORs with 95% CIs are presented for individual studies and the pooled overall effects. CI = confidence interval; OR = odds ratio; Preop = preoperative.

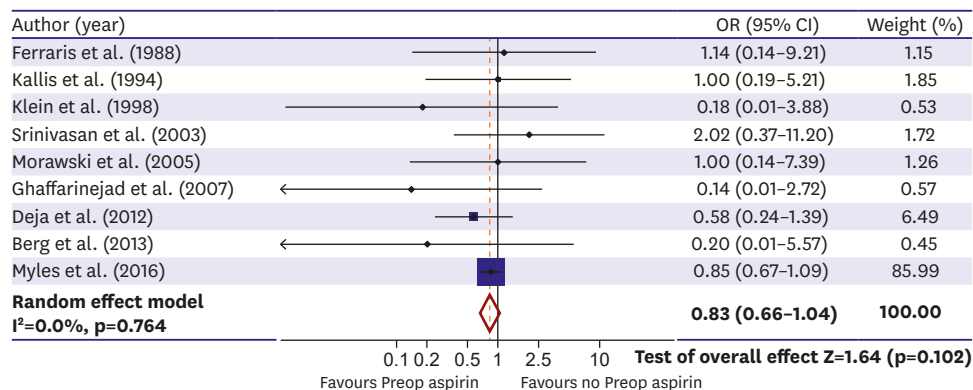


Figure 6. Forest plot comparing MI with or without preoperative aspirin. ORs with 95% CIs are presented for individual studies and the pooled overall effects.

CI = confidence interval; MI = myocardial infarction; OR = odds ratio; Preop = preoperative.

Subgroup analysis

Subgroup analysis was performed for the study design and support of CPB during surgery (Figure 7). As for the study design, there were no significant differences between the preoperative aspirin group and the control group for all study endpoints in both RCTs and non-RCTs. Also, the use of CPB during surgery did not affect the risks of re-operation for bleeding, early all-cause mortality and early MI in the preoperative aspirin group. Interaction p values were not significant in any of the subgroups.

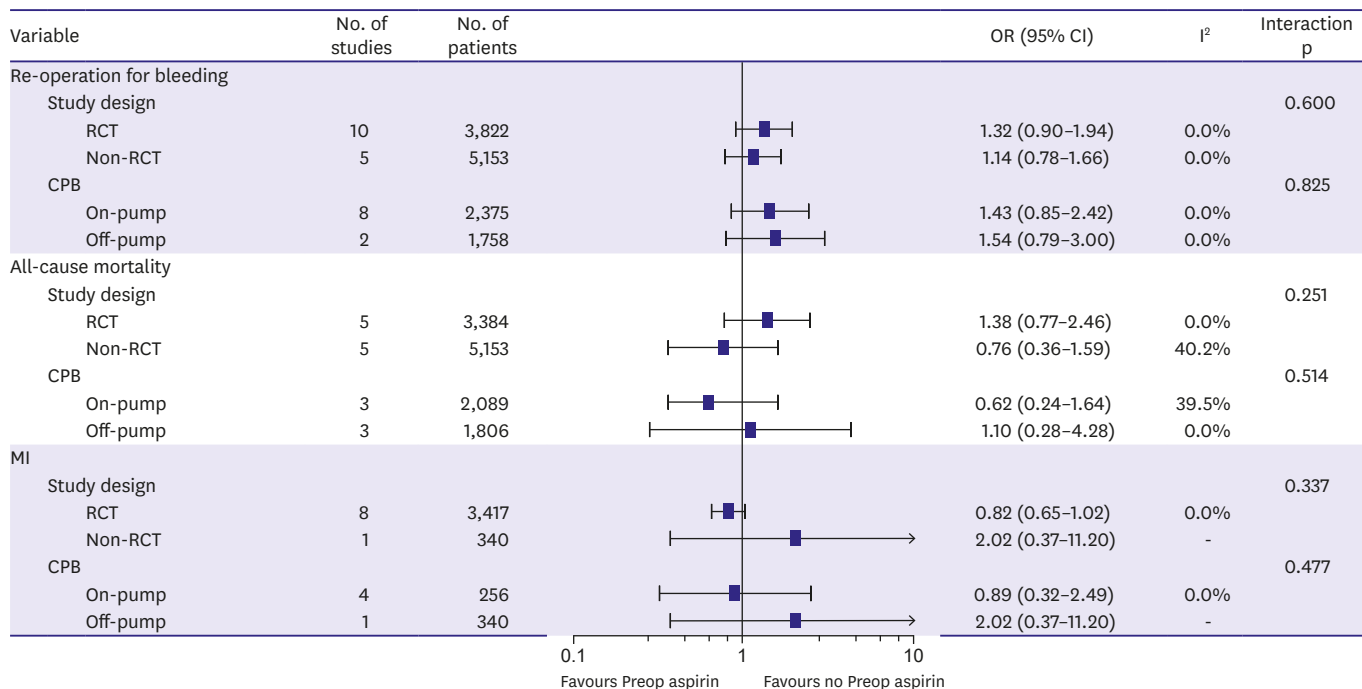


Figure 7. Subgroup analysis according to the study design and support of CPB during CABG. The study design and support of CPB did not affect the results of preoperative aspirin use for re-operation for bleeding, all-cause mortality and MI.

CABG = coronary artery bypass graft surgery; CI = confidence interval; CPB = cardiopulmonary bypass; MI = myocardial infarction; OR = odds ratio; Preop = preoperative; RCT = randomized controlled trial.

DISCUSSION

We performed an updated systematic review and meta-analysis that investigated the safety and efficacy of aspirin administration before CABG. The principal findings were: 1) although preoperative aspirin use before CABG significantly increased the amount of chest tube drainage, this was not associated with increased risk of re-operation for bleeding; 2) the rates of all-cause mortality and MI were comparable between patients with or without preoperative aspirin use; 3) there was a temporal trend of decreased rate of re-operation for bleeding in the preoperative aspirin group; and 4) the study design and support of CPB did not affect the results of preoperative aspirin use for re-operation for bleeding, all-cause mortality and MI.

Since the antiplatelet effect of aspirin was introduced about 50 years ago, the clinical impact of aspirin in coronary artery disease and its pathophysiologic mechanisms have been extensively studied.⁹⁾ In previous meta-analysis, Antiplatelet Trialists' Collaboration reviewed 145 randomized trials about long-term use of aspirin as secondary prevention.²⁴⁾ They included 70,000 high-risk patients and reported that long-term aspirin use was beneficial, not only in patients with acute coronary syndrome, but also in patients with history of MI, stroke, or transient ischemic attack. In addition, previous studies demonstrated the effects of aspirin on the reduction of acute complications after percutaneous revascularization¹⁾²⁵⁾ and maintaining graft patency after CABG.³⁾²⁰⁾ All these results demonstrated the benefits of aspirin as a secondary prevention of cardiovascular disease. In this regard, current guidelines from ACCF/AHA and STS for CABG recommend indefinite use of aspirin after CABG as a class I recommendation.¹⁰⁻¹³⁾

Conversely, there has been controversy on the preoperative administration of aspirin for CABG patients, as aspirin increases the risk of bleeding.²⁶⁾ Recent studies showed contradictory results regarding preoperative aspirin use. Hastings et al. performed a systematic meta-analysis of 13 RCTs which compared clinical outcomes of patients with or without preoperative aspirin use, and reported that preoperative aspirin significantly increased the risks of postoperative bleeding and subsequent re-operation. They also reported that the use of preoperative aspirin reduced the risk of MI without decreasing the risk of mortality.⁵⁾ The most recent large-scale multicenter ATACAS trial showed that preoperative aspirin use resulted in neither a lower risk of death or MI nor a higher risk of bleeding or re-operation, compared with the placebo group.¹⁴⁾ In addition, current guidelines were published in 2011 and 2012, and do not reflect the results of recent studies.¹⁰⁻¹³⁾

We performed an updated systematic meta-analysis, including 17 studies, with the largest population than previous ones, to evaluate the safety and efficacy of preoperative aspirin use in patients undergoing CABG. We mainly focused on the bleeding which mandated re-operation. Although the degree of bleeding, assessed by the amount of chest tube drainage, was increased in patients with preoperative aspirin use, re-operation for bleeding was comparable between patients with or without preoperative aspirin administration. Although 2 previous meta-analyses, which included only RCTs, showed significantly increased risk of re-operation for bleeding in the preoperative aspirin group,⁵⁾²⁷⁾ we did not observe additional risk of re-operation for bleeding in the preoperative aspirin group. Since the sample size of the current meta-analysis was the largest, the possibility of beta error might be minimal. The different results among the meta-analyses on the risk of re-operation for bleeding might be partially explained by the results of cumulative meta-analysis, which show progressive shifting of OR from greater toward equivalent risk in the recent study periods. This result may reflect the recent improvements in surgical techniques, including shorter operating times, more refined suturing, and a less invasive operative approach,

and anesthesia methods. All these factors might have contributed to reduce the overall risk of re-operation for bleeding, regardless of preoperative use of aspirin.¹⁷⁾

Regarding the efficacy of preoperative aspirin administration, we did not observe any consistent benefit of preoperative aspirin for all-cause mortality and MI during hospitalization compared with the control group. These results are in line with the most recent ATACAS trial.¹⁴⁾ However, as the risk of MI was decreased in the pooled analysis of RCTs with borderline significance and previous studies suggested improved outcomes in mortality and MI with the use of preoperative aspirin in long-term follow-up, we could not exclude the potential benefit of preoperative aspirin.⁵⁻⁷⁾ The long-term follow-up data of the ATACAS trial will provide additional insight.

There are some limitations of the current study. First, this meta-analysis included clinically and methodologically diverse studies, including the specific method and dose of preoperative aspirin administration. In several studies, higher dose of preoperative aspirin than currently recommended was used. Nonetheless, preoperative aspirin did not increase the risk of re-operation for bleeding in this study. To minimize any impact of preoperative aspirin on clinical outcomes in the control group, we classified the patients, who held aspirin at least 4–5 days before CABG, as the control group. Second, the differences between treatment groups in the postoperative use of aspirin or other antiplatelet drugs may have confounded estimates of the safety and efficacy of preoperative aspirin use. Third, we could not adjust for patient-level confounders and unmeasured confounders, such as baseline characters of patients, operator's experience, adequacy of medical treatment other than antiplatelet agents, and the volume of CABGs performed in each institution. However, to minimize the imbalance of measured or unmeasured confounders between the groups, we only included randomized controlled studies and non-randomized controlled studies which were adequately adjusted for baseline differences between the groups. In addition, subgroup analysis of randomized controlled studies, which could minimize the potential of unrecognized confounders, showed the consistent results with pooled analysis of randomized and non-randomized controlled studies. Fourth, as this study included study populations with predominantly elective surgery and generally low-risk of bleeding, our study could not provide information on the use of preoperative aspirin in a subgroup of patients with different bleeding risk or urgent CABG. Therefore, this study results could not be generalized to these high-risk of patients and individualized strategy of antiplatelet therapy is still needed to these patients. Further study is warranted to confirm the safety of preoperative aspirin use before CABG in patients with high-risk of bleeding or urgent CABG. Last, the wide range of publication dates, spanned about a 30-year period, could be another source of bias.

In conclusion, although aspirin increased the amount of chest tube drainage, it was not associated with increased risk of re-operation for bleeding. In addition, the risks of early postoperative all-cause mortality and MI were not reduced by using preoperative aspirin. Current meta-analysis did not find solid evidence for the discontinuation of aspirin in patients undergoing CABG.

SUPPLEMENTARY MATERIALS

Supplementary Data 1

Search strategy on PubMed, EMBASE and Cochrane Library

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Supplementary Data 2

Characteristics of the excluded studies

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Supplementary Table 1

Checklist of items to include when reporting a systematic review or meta-analysis (PRISMA guideline)

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Supplementary Table 2

The Cochrane collaboration's tool for assessing risk of bias of 12 randomized clinical trials in meta-analysis

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Supplementary Table 3

The Newcastle-Ottawa Scale for assessing the quality of 5 non-randomized studies in meta-analysis

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Supplementary Figure 1

Funnel plots for evaluating publication bias. Funnel plot asymmetry and Egger's and Begg's tests were assessed for re-operation for bleeding (A), all-cause mortality (B) and MI (C). When visual asymmetry of funnel plot was suspected, the trim-and-fill method was used to calculate an adjusted ORs with 95% CIs.

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Supplementary Figure 2

Individual study effect. The boxes and horizontal lines indicate ORs and 95% CIs for each study excluded. There was no evident individual study effect for re-operation for bleeding (A), all-cause mortality (B) and MI (C).

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Supplementary Figure 3

Cumulative meta-analysis of re-operation for bleeding. The potential effect of increased rates of re-operation for bleeding in the preoperative administration of aspirin group was gradually decreased toward equivalent risk with the control group in the recent study period.

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