Original Article

Pre-operative use of aspirin in patients undergoing coronary artery bypass grafting: a systematic review and updated meta-analysis

Karla Solo[1], Shahar Lavi[2], Tawfiq Choudhury[2], Janet Martin[1,3], Immaculate F. Nevis[4], Chun Shing Kwok[5], Rafail A. Kotronias[6], Natsumi Nishina[7], Sandro Sponga[8], Diana Ayan[2], Mamas A. Mamas[5], Rodrigo Bagur[1,2,5]

[1]Department of Epidemiology and Biostatistics, Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada; [2]London Health Sciences Centre, London, Ontario, Canada; [3]Department of Anesthesia & Perioperative Medicine, Centre for Medical Evidence, Decision Integrity & Clinical Impact (MEDICI), Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada; [4]Health Quality Ontario, Toronto, Ontario, Canada; [5]Keele Cardiovascular Research Group, Institute for Applied Clinical Science and Centre for Prognosis Research, Institute of Primary Care and Health Sciences, University of Keele, Stoke-on-Trent, UK; [6]Oxford University Clinical Academic Graduate School, Oxford University, Oxford, UK; [7]Faculty of International Communication, Gunma Prefectural Women's University, Tamamura, Gunma, Japan; [8]Cardiothoracic Department, University Hospital of Udine, Udine, Italy

Contributions: (I) Conception and design: K Solo, R Bagur, S Lavi, J Martin, MA Mamas, T Choudhury, CS Kwok, RA Kotronias, N Nishina, S Sponga, D Ayan; (II) Administrative support: R Bagur; (III) Provision of study materials or patients: K Solo, R Bagur; (IV) Collection and assembly of data: K Solo, R Bagur; (V) Data analysis and interpretation: K Solo, IF Nevis, R Bagur; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Rodrigo Bagur, MD, PhD, FAHA. University Hospital, London Health Sciences Centre, 339 Windermere Road, N6A 5A5, London, Ontario, Canada. Email: rodrigobagur@yahoo.com.

Background: Aspirin therapy improves saphenous vein graft (SVG) patency in patients undergoing coronary artery bypass graft (CABG), however, its use in the pre-operative period remains controversial. Therefore, we conducted a systematic review and meta-analysis of randomized-controlled trials (RCTs) to update the evidence about risk and benefits of pre-operative aspirin therapy in patients undergoing CABG.

Methods: Electronic databases (Medline, Embase, PubMed, Cochrane Library, and Scopus) were searched to identify RCTs evaluating the effect of aspirin versus placebo/control before CABG. Two investigators independently and in duplicate screened citations and extracted data and rated the risk of bias. The strength of evidence was appraised using the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach. Meta-analysis was performed using a random-effects model. The main outcomes of interest were 30-day mortality, peri-operative myocardial infarction (MI), chest tube drainage and SVG occlusion.

Results: A total of 13 RCTs involving 4,377 participants (2,266/2,111 pre-operative aspirin/control) met the inclusion criteria. Pre-operative aspirin reduced the risk of SVG occlusion [risk ratio (RR): 0.69, 95% confidence interval (CI): 0.49–0.97, P=0.03, I^2=16%], but no differences in mortality (RR: 1.41, 95% Cl: 0.73–2.74, I^2=0%) and MI (RR: 0.84, 95% CI: 0.69–1.03, I^2=0%) were found. However, pre-operative aspirin increased chest tube drainage (MD: 100.40 mL, 95% CI: 24.32–176.47 mL, P=0.01, I^2=84%) and surgical re-exploration (RR: 1.52, 95% CI: 1.02–2.27, P=0.04, I^2=8%), with no significant difference in RBC transfusion (RR: 1.06, 95% CI: 0.90–1.25, I^2=35%).

Conclusions: Based on trials where the rated body of evidence was of low to very-low quality, pre-operative aspirin improves SVG patency but increases chest tube drainage and need for surgical re-exploration.

Keywords: Coronary artery bypass; pre-operative; aspirin; continuous aspirin exposure; interrupted aspirin exposure

Submitted Mar 26, 2018. Accepted for publication May 25, 2018.
doi: 10.21037/jtd.2018.05.187
View this article at: http://dx.doi.org/10.21037/jtd.2018.05.187

Introduction

The use of acetylsalicylic acid (aspirin) is associated with a reduction in major adverse cardiovascular events (MACE) and improvement in saphenous vein graft (SVG) patency after coronary artery bypass graft (CABG) surgery (1-5). Despite these benefits, there are still concerns regarding the risk of bleeding when administered in the pre-operative period (1,3,5). The 2012 Society of Thoracic Surgeons guidelines suggest that it may be reasonable to discontinue aspirin for a few (2 to 3) days before CABG to reduce perioperative bleeding and blood transfusions (6). However, there are concerns that discontinuing aspirin in patients who are on chronic therapy prior to surgery may trigger a "rebound phenomenon" in platelet activity that potentially leads to an increased risk of MACE during surgery (7). In this regard, the 2015 American Heart Association Scientific (AHA) Statement recommends that aspirin should be administered pre-operatively and within 6 hours after CABG and be continued indefinitely to reduce SVG occlusion (8).

Randomized controlled trials (RCTs) and previous meta-analyses had been conducted to evaluate the management of aspirin use before CABG (9-15). However, most individual studies were underpowered or yielded conflicting results, which raises concern about the robustness of conclusions. Importantly, the Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial (16) has recently been published providing substantial weight to the current evidence base considering its large sample size. Therefore, an updated systematic review and meta-analysis of RCTs is required to assess clinical outcomes, balance the risks and benefits and thus, enhance decision-making process in this subset of patients. A secondary objective of this review is to explore differences between patients on aspirin with a temporary interruption of the treatment and patients without the interruption in the cohort of patients receiving pre-operative aspirin using an indirect comparison analysis.

Methods

Data sources and searches

A comprehensive literature search on Medline, Embase, PubMed, Cochrane Library and Scopus databases was conducted from conception to November 2016 and a weekly alert for electronic databases was set up until May 9, 2018. The search strategy combined Medical Subject Headings (MeSH) and keywords "aspirin or coronary artery bypass". The search was not restricted by year of publication or language, and duplicates were removed. When duplicate reports of the same study were identified, only the report with the most complete data and detailed methodology description was included. We also checked reference lists of included RCTs and previous reviews for cross-checking. *Table S1* of Supplement provides a list of excluded studies with reasons for exclusion.

Study selection

The titles and abstracts yielded by the search were screened independently and in duplicate by two independent investigators (K Solo and T Choudhury) against the inclusion criteria. Any discrepancies between reviewers were resolved by discussion after consulting a third investigator (R Bagur). This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines (17) (*Figure S1*).

Eligibility criteria

We included RCTs in which patients undergoing CABG were randomly assigned to pre-operative aspirin or placebo/control before surgery. Patients receiving any dose of aspirin up to the day (within 24 hours) of CABG surgery, regardless of the pre-operative date of initiation and previous duration of aspirin therapy, were considered as the intervention group. Patients receiving placebo or no aspirin before (within 24 hours) CABG surgery, regardless of pre-operative date of initiation and previous duration of aspirin administration, were considered as the control group. Eligible RCTs were required to meet the following criteria: (I) patients undergoing CABG were randomly allocated either to the intervention or the control group; (II) RCTs must not combine aspirin with any other antithrombotic agents in the intervention arm; (III) their primary outcomes

must be at least one of the following: mortality, myocardial infarction (MI), chest tube drainage or bleeding, or SVG occlusion; and (IV) extractable data for at least one of these outcomes must be available. When eligible RCTs have more than 2 intervention arms, of which 2 or 3 were eligible, we included all eligible arms.

Data extraction

The full reports of eligible studies were retrieved, and data were extracted independently and in duplicate (K Solo and T Choudhury). Publication details (location, year of publication, author), study and patient characteristics (sample size, length of follow-up, rate of loss to follow-up, aspirin status prior study, demographic and clinical data), procedural characteristics, intervention details (dose, frequency, duration, time of drug administration), and outcomes data were extracted, with differences resolved by discussion with third reviewer (R Bagur).

Quality assessment

Risk of bias was assessed using the Cochrane Risk of Bias tool (18), and the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) system (19) was used to appraise the overall quality of evidence. A summary of quality of evidence was constructed in an evidence profile using GRADEpro software (https://gradepro.org/).

Data synthesis and analyses

Primary outcomes of interest included mortality, peri-operative MI, chest tube drainage and SVG occlusion (per-graft analysis, accounting for clustering effects). Secondary outcomes included need for red blood cell (RBC) transfusions, number of RBC units transfused (one unit of packed-RBC was assumed to be 400 mL), need for surgical re-exploration and stroke.

We reported descriptive statistics as percentages for categorical variables and mean [standard deviation (SD)] or median [interquartile range (IQR) or range] for continuous variables. When outcome data were available only as median (IQR or range), mean (SD) were calculated (20,21). Intention-to-treat analysis was followed whenever possible. When a small proportion of studies did not report the uncertainty of point estimates (i.e., SD, IQR, or range), we imputed the missing SDs using single imputation. However, if a large proportion of the data was missing, we set the SD equal to zero (21). Using worst-best sensitivity analysis, we accounted for the missing data of patients who were excluded post randomization and were not analyzed using the original randomized treatment sizes. In best case analysis (scenario 1), we assumed that all excluded patients had the outcome event in the control group, and none in the intervention group, whereas, in worst-case analysis (scenario 2), all excluded patients had the outcome event in the intervention group, and none in the control group. For SVG occlusion endpoint, since grafts within an individual are correlated, we calculated effective sample size (ESS) (which is the new sample size after accounting for clustering effects) instead of the originally reported sample size to account for clustering effects (22). An intra-cluster correlation of 0.177, which was obtained from an external source (23), was used to calculate ESS. Review Manager, version 5.3 (Nordic Cochrane Center, The Cochrane Collaboration) was used to perform pairwise meta-analysis to obtain a pooled estimate of the mean difference (MD) or the risk ratio (RR) and its corresponding 95% confidence interval (CI) with a random-effects model to account for heterogeneity. A continuity correction was used when there were zero events in one of the study arms. When RCTs reported zero events in all study arms for a given endpoint, the correction was not used, but the study was still displayed in the graph for transparency purposes. Post-hoc sensitivity analyses were performed to explore potential differences between random-effects and fixed-effects models and to ascertain the potential influence of studies with high risk of bias on treatment effect.

In addition, we performed an indirect treatment comparison via placebo as a common comparator to explore the impact of prior aspirin use among patients who were randomized to aspirin. Continuously exposed aspirin group was defined as patients receiving aspirin throughout the preoperative period (before and after randomization), whereas interrupted group was defined as patients receiving aspirin who were already on aspirin but had to stop aspirin temporarily due to study protocol until randomization (*Figure 1*). We performed a meta-analysis involving RCTs of continuously exposed aspirin versus placebo to estimate the treatment effect: RR_{CP}. Another meta-analysis was performed comparing interrupted aspirin versus placebo to obtain RR_{IP}. An indirect estimate was then computed using the following formula and back transformed to obtain the estimated treatment effect of interrupted aspirin versus continuously exposed aspirin: RR_{IC} (24).

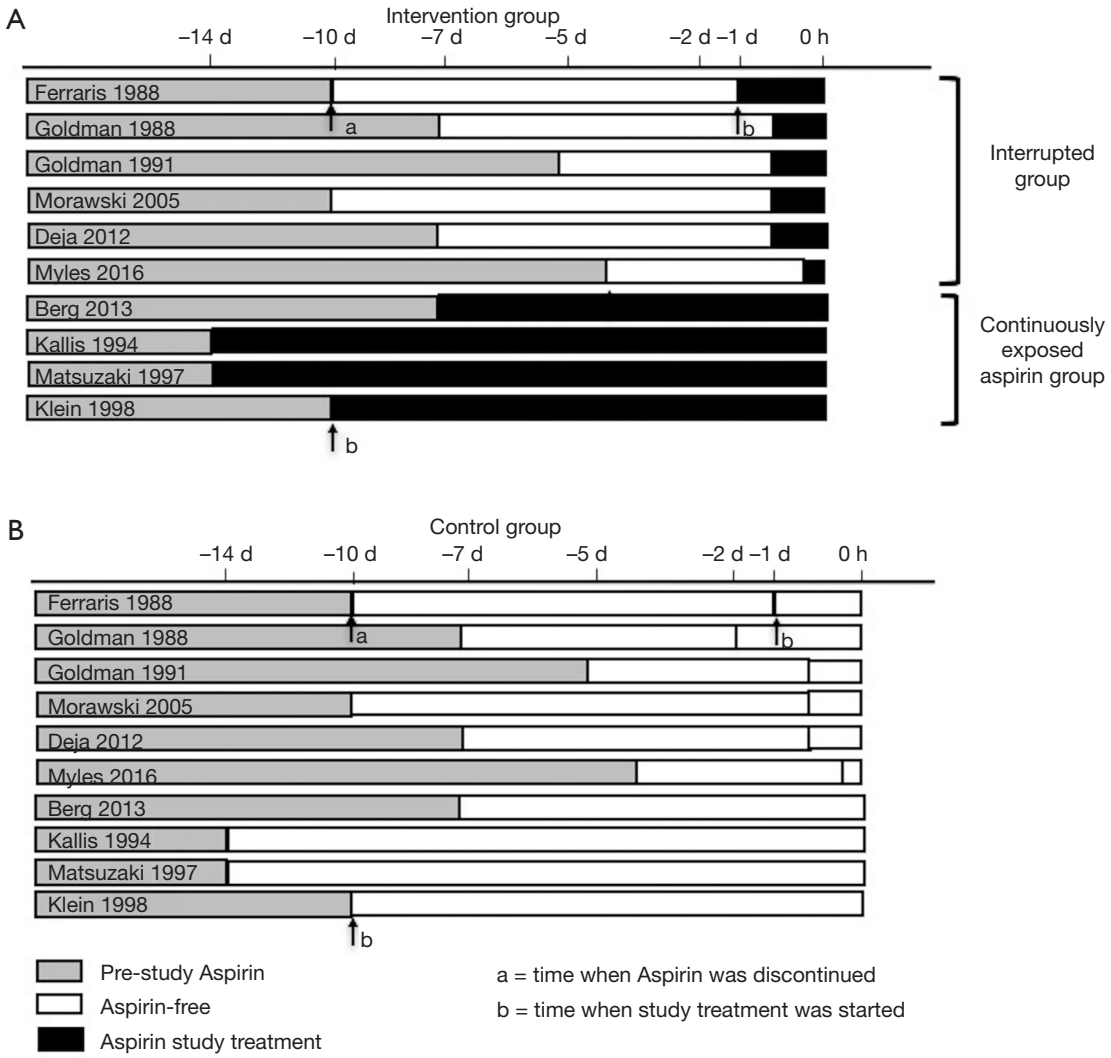

Figure 1 Flow chart of the study timeline for trials that clearly defined the pre-operative aspirin period in the intervention group (A) and control group (B). CABG occurred at 0 hour (reference frame) and events were measured in the CABG reference frame. In (A), trials that had an aspirin-free period before CABG (and restarted on the day of surgery, defined as within 24 hours of surgery) are considered as the interrupted group. Otherwise, they are considered as the continuously aspirin exposed group. Arrow a indicates when aspirin was stopped before randomization. Arrow b indicates when study drugs (aspirin or placebo) were administered. CABG, coronary artery bypass graft; ASA, aspirin; d, day; h, hour.

$$logRR_{IC}=logRR_{IP}-logRR_{CP}$$
$$var(logRR_{IC})=var(logRR_{IP})+var(logRR_{CP})$$

where *var* is the variance of treatment effect.

Post-hoc subgroup analysis was performed to determine whether the dose of aspirin influenced the relative treatment effect. For trials with multiple study arms of different doses, we combined doses of aspirin into a single arm leading to a low-dose (≤100 mg) and high-dose (>100 mg) groups. The Cochrane Q-statistic (I^2) was used to assess the consistency among studies, with I^2 <25% considered low, I^2 25–50% moderate, and I^2 >75% high statistical heterogeneity (25). Clinical heterogeneity was also evaluated and described narratively. Both Egger's test and funnel plot (when >10 studies) were used to examine potential publication bias. Two-sided P values of <0.05 were considered statistically significant.

Results

Study selection, trial and patient characteristics

Thirteen RCTs (1,16,26-36) including 4,377 participants met the inclusion criteria (*Figure S1*). One trial (28) was followed by another publication with longer follow-up information (2). Clinical characteristics and end-points were defined according to study author definitions (*Tables 1,2*). Overall, 2,266 participants were randomly assigned to pre-operative aspirin (within 24 h of surgery) and 2,111 to control (no aspirin within 24 h of surgery). Age ranged from 53 to 67 years and 85% were male (3,682/4,350) from studies that reported age (1,16,26-36) and sex (1,16,27-36). A total of 996 (29%) patients had diabetes mellitus, 2,937 (71%) hypertension, and 1,194 (32%) previous MI. The vast majority (99%) of participants underwent elective CABG surgery and one trial (27) did not report whether CABG was performed in an elective or urgent setting. On-pump CABG was performed in 95% (3,775/3,984) of patients. Participants received between 2 to 4 grafts per-patient. Three trials (16,33,35) were rated as low-risk of bias, six (1,26,28,30,31,34) as moderate, and four (27,29,32,36) as high (*Figure S2*).

Mortality

There was no significant difference in effect estimates for 30-day mortality (RR: 1.41, 95% Cl: 0.73–2.74; I^2=0%; *Figure 2A*). Although best case analysis did not alter the findings, worst-case analysis showed a significant increase in the incidence of mortality at 30 days with aspirin (*Figure S3A,B*). This worst-case scenario is consistent with potential bias due to missing data since the observed point estimate became significant. Sensitivity analysis comparing random-versus fixed-effects suggests no difference in effect estimates between the two models (*Table 3*). Overall rating of confidence in estimates was very low, due to imprecision, indirectness, risk of bias, missing data, and potential publication bias (*Table 4*).

Myocardial infarction

No significant difference in effect estimates was found for peri-operative MI (RR: 0.84, 95% CI: 0.69–1.03, P=0.09; I^2=0%; *Figure 2B*). Although worst case analysis did not alter the findings, best-case analysis suggested a significant reduction in rates of MI (*Figure S4A,B*). Again, this best-case scenario is consistent with potential bias due to missing data as the conclusion became significant. Sensitivity analysis comparing random- versus fixed-effects suggests no difference in effect estimates between the two models (*Table 3*). Post-hoc sensitivity analysis confined to trials with low-risk of bias (16,34,36) showed a similar non-significant effect estimates (RR: 0.86, 95% CI: 0.70–1.04; I^2=0%). Overall, our confidence in the estimate was very low, owing to indirectness, potential publication bias, and risk of bias due to inadequate randomization, blinding process, missing data, and potential selective reporting of the outcome (*Table 4*).

Chest tube drainage

Aspirin was associated with an increased chest tube drainage with a MD of 100.40 mL (95% CI: 24.32–176.47 mL, P=0.01, I^2=84%; with imputation for missing standard deviations, *Figure 2C*). Sensitivity analysis without imputation (MD: 73 mL, 95% CI: –5.04 to 152 mL, P=0.07; I^2=80%) significantly altered the effect size. A post-hoc sensitivity analysis suggests no difference between random-versus fixed-effects (*Table 3*). In summary, our confidence in estimates was very low, due to imprecision, indirectness, and risk of bias due to inadequate randomization, blinding methods, and missing data (*Table 4*). In addition, the asymmetric funnel plot indicated potential evidence for publication bias (P<0.001; *Figure S5*).

SVG occlusion

Aspirin was associated with significant treatment effect benefits against SVG occlusion (RR: 0.69, 95% CI: 0.49–0.97, P=0.03, I^2=16%) (*Figure 2D*). Worst- and best-case sensitivity analyses were not performed due to lack of information. Sensitivity analysis comparing random-versus fixed-effects suggests no differences in effect estimates between the two models (*Table 3*). Overall rating of confidence in estimates was low, owing to indirectness, potential publication bias, and risk of bias due to lack of information about allocation concealment, blinding, different follow-up periods, and high rate of incomplete data (*Table 4*).

Secondary outcomes

There was an increased risk of surgical re-exploration among patients assigned to pre-operative aspirin (RR: 1.52, 95% CI: 1.02–2.27; P=0.04, I^2=8%). No significant

Table 1 Characteristics of the included trials

First author (year), enrollment period, study type, and location	ASA status pre-random; clinical setting; length of F/U; loss of F/U rate	Antifibrinolytic; post anti-thrombotic use	Comparator, n	Baseline patient characteristics				
				Age (years)	Male, n (%)	DM, n (%)	HTN, n (%)	No. of grafts per pts
Fuller [1985], NR, single center, USA	NR; elective on-pump CABG; peri-operative; none (0%) were excluded	NR; NR	No ASA at least within 12-h pre-op (n=9)	59	–	–	–	3.4
			ASA 325 mg 12-h pre-op (n=11)	53	–	–	–	3.1
			ASA 650 mg every 6-h beginning 48 h pre-op & ending 6-h pre-op (n=10)	60	–	–	–	3.2
Ferraris [1988], 1986–1987, single center, USA	Stopped ASA ≥10 d pre-CABG; urgent & elective on-pump CABG; NR; unclear	Aminocaproic acid (n=4 in ASA group); NR	No ASA on the day of CABG (n=18)	61±9	16 [89]	–	–	3.2±0.6
			ASA 325 mg as a single dose on the day of CABG (n=16)	64±8	14 [88]	–	–	3.6±0.8
Goldman [1988], 1983–1986, multi-center, USA	Stopped ASA ≥7 d pre-study entry; elective on-pump CABG; 30 days; none (0%) were excluded	NR; started 6-h post-CABG	Placebo 48-h pre-op (n=153)	58±7	153 [100]	–	75 [49]	3.2
			ASA 325 mg OD 12-h pre-op (n=154)	58±8	154 [100]	–	73 [47]	
			ASA 325 mg TID 12-h pre-op (n=155)	59±7	155 [100]	–	65 [42]	
Goldman [1991], 1986–1988, multi-center, USA	Stopped ASA ≥5 d pre-CABG; first, elective on-pump CABG; 8 [4–58] days; 28% (n=138) were excluded	NR; ASA 325 mg 6-h after CABG in all pts	Placebo as a single dose 12-h pre-CABG (n=175)	60±7	175 [100]	–	88 [50]	–
			ASA 325 as a single dose 12-h pre-CABG (n=176)	60±8	176 [100]	–	99 [56]	–
Hockings [1993], 1986–1989, single center, Australia	NR; elective CABG; 6 months; 27% (n=38) were excluded	NR; ASA daily in ASA group	Placebo 7 d pre-op (n=52)	60±9	48 [92]	3 [5.8]	16 [31]	2.8±1.6‡
			ASA 100 mg daily 7 d pre-op (n=50)	60±9	47 [94]	3 [6.0]	25 [50]	2.6±1.6‡
Kallis [1994], NR, single center, UK	Stopped ASA ≥14 d pre-CABG; first, elective on-pump CABG; hospital discharge; none (0%) were excluded	NR; NR	Placebo OD 14 d pre-op until the day of CABG (n=50)	62	40 [80]	0 [0]	–	3.4
			Aspirin 300 mg OD 2 w pre-op until the day of CABG (n=50)	62	41 [82]	0 [0]	–	3.5
Matsuzaki [1997], 1994–1995, single center, Japan	Used ASA ≥14 d pre-CABG; elective on-pump CABG; 24 h post-CABG; 0% in total	Tranexamic acid (all pts); NR	No ASA 2 d pre-op (n=11)	64±5	8 [72]	–	–	2.1±0.9
			ASA 81–330 mg until the day of CABG (n=11)	62±11	7 [64]	–	–	2.4±1.1

Table 1 (*continued*)

Table 1 (*continued*)

First author (year), enrollment period, study type, and location	ASA status pre-random; clinical setting; length of F/U; loss of F/U rate	Antifibrinolytic; post anti-thrombotic use	Comparator, n	Baseline patient characteristics				
				Age (years)	Male, n (%)	DM, n (%)	HTN, n (%)	No. of grafts per pts
Klein [1998], NR; NR; Denmark	Pre-treated ASA; first elective CABG; hospital discharge; 6% were excluded	Aprotinin; NR	Aprotinin and placebo 10 days pre-op until surgery (n=38, n'=36)	62±7	34 [89]	–	–	2.13‡
			ASA 100 mg/d OD and aprotinin 10 d pre-op until surgery (n=40, n'=37)	64±6	33 [83]	–	–	2.30‡
Morawski [2005], NR, single center, Poland	Stopped ASA ≥10 d pre-CABG; urgent (n=18) & elective (n=84) on-pump CABG; 7 days; none (0%) were excluded	No; NR	Placebo (n=51)	61±8	42 [82]	10 [20]	29 [57]	2.9±0.8
			ASA 150 mg 12 hours and 3 hours before CABG (n=51)	61± 8	45 [88]	9 [18]	34 [67]	3.0±0.8
Ghaffarinejad [2007], 2005–2006, single center, Iran	NR; first, elective CABG; hospital discharge; 0% in total	Aprotinin; started ASA within 6 h post-op (all pts)	No ASA 7 d pre-op (n=100)	57±10	70 [70]	23 [23]	36 [36]	–
			ASA 80-160 mg pre-op (n=100)	57±9	67 [67]	34 [34]	40 [40]	–
Deja [2012], 2003–2006, single center, Poland	Stopped ASA ≥7 d pre-CABG; elective on-pump (81%) & off-pump CABG; 53.3 (42.1–63.3) months; 17 (2%) were excluded	40 *vs.* 35% with tranexamic acid & 18 *vs.* 23% with aprotinin in placebo *vs.* ASA, respectively; ASA 300 mg daily 6-h post-op in all pts	Placebo on the night before surgery (n=400, n'=396)	59 [54–66][a]	297 [75]	94 [24]	320 [81]	3 [2–3]
			ASA 300 mg as a single dose on the night before CABG (n=400, n'=387)	59 [53–66][a]	315 [81]	105 [27]	331 [86]	3 [2–3]
Berg [2013], 11 months, NR, Norway	NR; elective CABG; first post-operative day; none (0%) were excluded	NR; NR	No ASA 7 d before CABG (n=8, n'=7)	58 [20][b]	6 [86]	0 [0]	7 [100]	–
			ASA 160 mg daily until the day before surgery (n=12, n'=11)	65 [23][b]	9 [82]	0 [0]	7 [64]	–
Myles [2016], 2006–2013, multi-center, Australia	Stopped ASA ≥4 d pre-CABG; on-pump (97%) & off-pump elective CABG; 30 d; 27 pts were excluded after randomization	50 *vs.* 49.8% with tranexamic acid & 0.7 *vs.* 1.0% with aprotinin in control *vs.* ASA groups, respectively; ASA within 24-h in control (76%) *vs.* ASA (78.4%) groups	Placebo 1-2 h before CABG (n=1,068, n'=1,053)	66±10	858 [82]	368 [35]	845 [80]	3 [2–4]
			ASA 100 mg 1–2 h before CABG (n=1,059, n'=1,047)	67±10	872 [83]	347 [33]	847 [81]	3 [2–4]

Mean ± standard deviation. [a], median (Q1–Q3); [b], median (range); ‡, vein grafts. ASA, aspirin; CPB, cardiopulmonary bypass; d, days; DM, diabetes mellitus; HTN, hypertension; F/U, follow-up; h, hours; n', sample size analyzed; NR, not reported; OD, once daily; TID, three times a day; pre-op, pre-operative; pts, patients; USA, United States of America; w, weeks.

Table 2 Description of endpoints in the included trials

Study author	Death	MI	Blood loss	Surgical re-exploration	RBC transfusions	Cardiac re-intervention	Stroke	Graft occlusion
Fuller [1985]	Peri-operative death	NA	24-hour CT drainage	No definition	No definition	NA	NA	NA
Ferraris [1988]	Postoperative death	Post-operative MI	12-hour CT drainage	No definition	No definition	NA	NA	NA
Goldman [1988]	30-day mortality (non-extractable)	NA	35-hour median chest tube drainage	No definition	No definition	NA	NA	Median: 367 days (62 to 527 days). Assessed by angiography
Goldman [1991]	NA	Post-operative MI	35-hour CT drainage	No definition	No definition	NA	NA	At 8-day assessed using angiography. "A single vessel graft was defined patent"
Hockings [1993]	Postoperative death	NA	48-hour CT drainage	No definition	No definition	NA	NA	At 6-month, assessed by angiography
Kallis [1994]	Death at discharge	Peri-operative MI	Post-operative CT drainage	According to criteria published by Kirklin and Barrett-Boyes	Transfusion was given when hematocrit <28%	NA	NA	NA
Matsuzaki [1997]	Peri-operative death	NA	24-hour CT drainage	NA	No definition	NA	NA	NA
Klein [1998]	NA	Peri-operative definite MI (new Q-wave post-operative); determine both by the routine clinical diagnostics and cardiologist reviewing the data	24-hour CT drainage	NA	When hematocrit <18% during, and <21% after surgery	NA	NA	NA
Morawski [2005]	Early post-operative death	Peri-operative MI (new Q wave in ECG, CK-MB >50 U with ECG changes, or 4-fold increase in CK-MB level)	12-hour CT drainage	No definition	Transfusion was given if hemoglobin level <8.0 g/dL	NA	NA	NA
Ghaffarinejad [2007]	In-hospital death	Definite MI (new QS on ECG & wall-motion abnormality on echo with/with-out CK-MB >30 IU/L)	Post-operative CT drainage	No definition	No definition	NA	NA	NA
Deja [2012]	30-day all-cause death	Peri-operative MI	27–33-hour CT drainage	Re-explore chest if bleeding >200 mL/h in the first 4 hours post-op or 100 mL/hour thereafter	Transfuse RBC if hematocrit drops <25%	PCI only	NA	NA
Berg [2013]	Post-operative death	Post-operative acute MI	18-hour CT drainage	No definition	NA	NA	NA	NA
Myles [2016]	30-day all-cause death	30-day MI (according to the 3rd universal definition, type 5)	Total CT drainage	No definition	Transfused at days 1 and 2	NA	30-day stroke	NA

RBC, red blood cells; CT, chest tube; NA, not applicable or available; MI, myocardial infarction; CK, creatinine kinase.

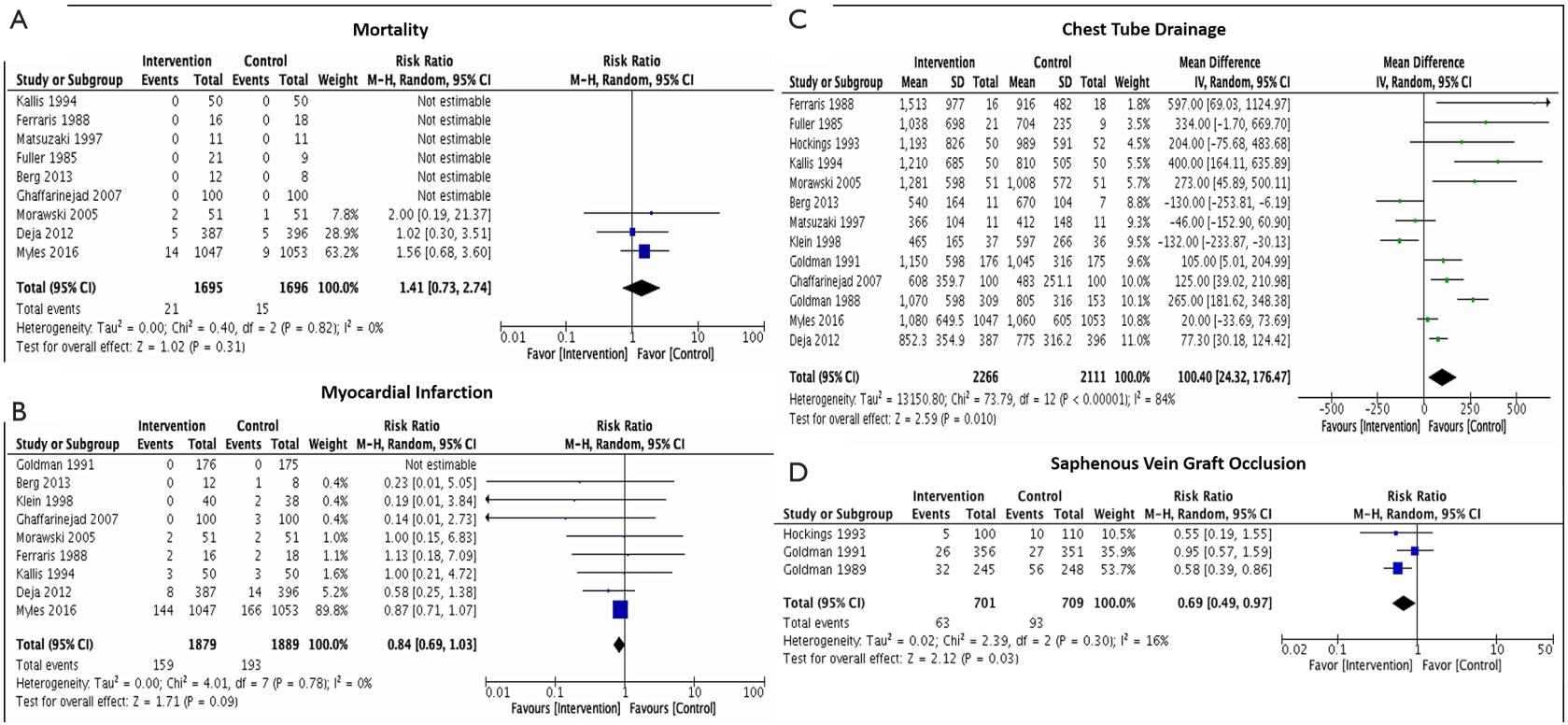

Figure 2 Forest plots of pooled treatment effect estimates of (A) mortality; (B) myocardial infarction; (C) chest tube drainage (in mL); and (D) saphenous vein graft occlusion in patients undergoing coronary artery bypass graft surgery. M-H, Mantel-Haenszel; CI, confidence interval.

Table 3 Sensitivity analysis for clinical outcomes comparing fixed-effects and random-effects models

Outcomes	Fixed-effect model		Random-effects model	
	RR (95% CI)	OR (95%CI)	RR (95% CI)*	OR (95% CI)
Mortality	1.41 (0.73–2.73)	1.42 (0.73–2.77)	1.41 (0.73–2.74)	1.42 (0.72–2.77)
Myocardial infarction	0.83 (0.68–1.01)	0.81 (0.64–1.01)	0.84 (0.69–1.03)	0.82 (0.65–1.02)
Chest tube drainage (mL)	MD: 68 [43–95]		MD: 100 [24–176]	
Vein graft occlusion (per graft)	0.68 (0.51–0.92)	0.65 (0.46–0.91)	0.69 (0.49–0.97)	0.65 (0.43–1.01)
Surgical re-exploration	1.63 (1.15–2.32)	1.63 (1.15–2.32)	1.52 (1.02–2.27)	1.58 (1.03–2.42)
RBC transfusions (units)	MD: 0.37 (0.14–0.59)		MD: 0.41 (−0.13 to 0.94)	
RBC transfusions (proportion)	1.06 (0.95–1.18)	1.08 (0.92–1.27)	1.06 (0.90–1.25)	1.09 (0.84–1.41)
Stroke	1.08 (0.53–2.17)	1.08 (0.53–2.19)	1.08 (0.53–2.18)	1.08 (0.53–2.20)

*, primary analysis. RBC, red-blood cells; RR, risk ratio; OR, odds ratio; CI, confidence interval; MD, mean difference.

Table 4 GRADE assessment for overall quality of evidence

No. of subjects (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk ratio (95%CI)	Absolute effect of aspirin per 1,000 patients treated per year (95% CI)
Mortality: 3,391 (9 RCTs)	Serious[a]	Not serious[b]	Serious[c]	Serious[d]	Strongly suspected[k]	⊕◯◯◯ (very low)	1.41 (0.73–2.74)	4 more events (2 fewer to 15 more)
Myocardial infarction: 3,768 (9 RCTs)	Serious[e]	Not serious[b]	Serious[c]	Serious[d]	Strongly suspected[k]	⊕◯◯◯ (very low)	0.84 (0.69–1.03)	16 fewer events (3 more to 32 fewer)
Postoperative chest tube drainage: 4,377 (13 RCTs)	Serious[f]	Serious[g]	Serious[c]	Serious[d]	Strongly suspected[h]	⊕◯◯◯ (very low)	–	–
Saphenous vein graft occlusion: 760 (3 RCTs)	Serious[i]	Not serious[b]	Serious[c]	Not serious[j]	Strongly suspected[k]	⊕⊕◯◯ (low)	0.69 (0.49–0.97)	NA*

*NA, not applicable because the unit of analysis was the vein graft and not the patient; [a], of ten studies, one study deliberately took patients from an assigned group to a separate group after randomization occurred; two studies did not provide an adequate description of randomization in sufficient detail; eight studies did not adequately report allocation concealment; and six studies neither blinded the personnel nor adequately described the method of blinding. Two studies had missing data; [b], I^2 value <75%; [c], most studies used higher doses of aspirin than are currently used in clinical practice (80–100 mg/day) and several studies stopped aspirin longer (>14 days) than the current practice, which may not directly relevant to the current clinical practice. In addition, saphenous vein graft occlusion may be a surrogate for myocardial infarction or death. Studies reporting the occlusion are relatively old with different follow-up times; [d], the confidence intervals are wide and/or cross the line of no effect; [e], of nine studies, three studies did not provide an adequate description of randomization in sufficient detail or did not perform appropriate randomization; seven studies did not adequately report allocation concealment; and three studies did not blind the personnel nor adequately described the method of blinding. Three studies had missing data; [f], of 13 studies, five studies did not provide an adequate description of randomization in sufficient detail or did not perform appropriate randomization; eleven studies did not adequately report allocation concealment; six studies neither blinded the personnel nor adequately described the method of blinding, and a high rate of loss to follow-up in one study; [g], I^2 value ≥75 %; [h], a funnel plot and Egger's test suggested significant evidence for publication bias (P<0.001); [i], of three studies, all studies did not provide adequately report allocation concealment, one study did not describe the method of blinding, and a high rate of loss follow-up to assess patency in two studies; [j], narrow 95% CI and clustering effect was considered; [k], one study was excluded from the review because the abstract was never published as a full study. CI, confidence interval.

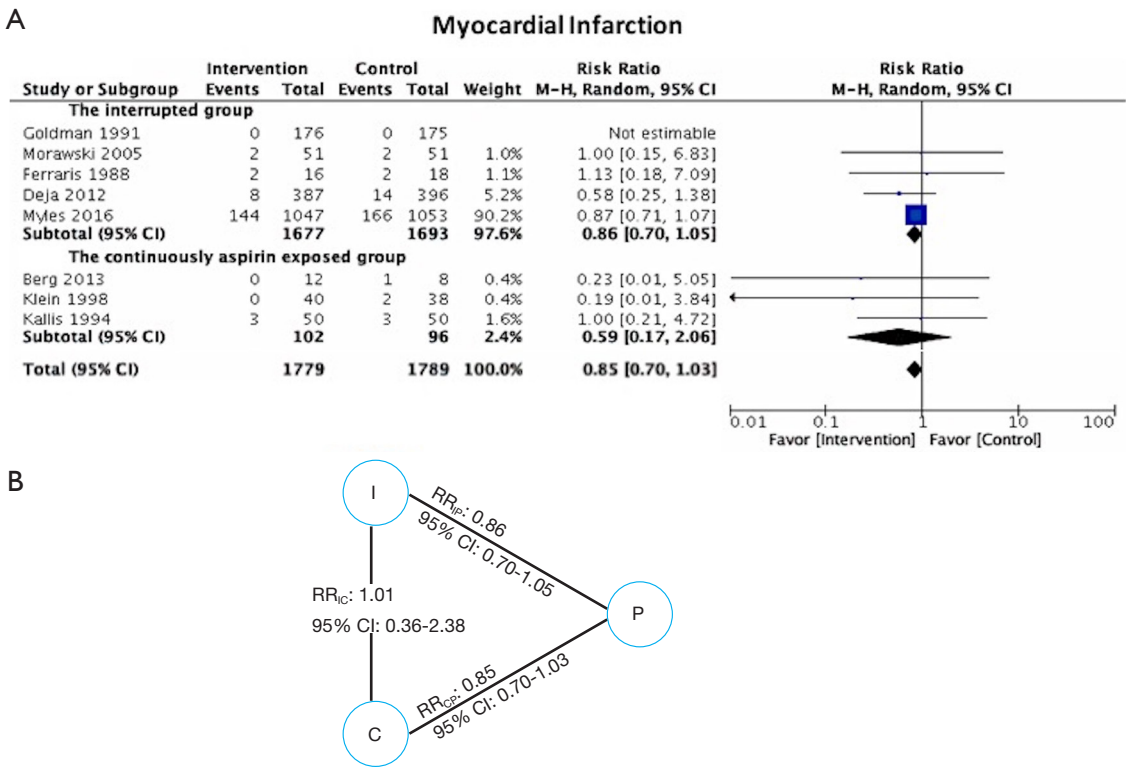

Figure 3 Direct and indirect comparisons. (A) Direct treatment comparisons for the interrupted group and the continuously aspirin exposed group; (B) indirect comparison between treatment strategies. M-H, Mantel-Haenszel; CI, confidence interval; I, aspirin with interruption; C, aspirin without interruption; P, placebo/control.

differences in effect estimates were found for patients receiving RBC transfusions (RR: 1.06, 95% CI: 0.90–1.25; I^2=35%), number of units of RBC transfused (MD: 0.41, 95% CI: −0.13 to 0.94; I^2=70%), and stroke (RR: 1.08, 95% CI: 0.53–2.18; I^2=0%) (*Figure S6*).

Indirect comparison

Eight trials reporting MI (16,27,28,30,32,33,35,36) clearly described aspirin exposure prior to the study enrollment. An indirect comparison analysis showed that there was no statistically significant difference in MI between patients who were continuously exposed to aspirin before CABG and those who were not (RR: 1.01, 95% CI: 0.36–2.38) (*Figure 3*).

Dose of aspirin

Subgroup analysis between low-dose (≤100 mg/day) and high-dose (>100 mg/day) of aspirin showed no significant difference in rates of mortality (interaction P=0.69, I^2=0%) and MI (interaction P=0.55, I^2=0%). However, a significant statistical interaction of dose was found for chest tube drainage (P=0.05, I^2=74.7%) and surgical re-exploration (P=0.04, I^2=76.3%) (*Figure 4*). Overall, the inconsistency of subgroup effect across outcomes reduced our confidence in the credibility of the results.

Discussion

The results of this meta-analysis of 13 RCTs including 4,377 patients undergoing CABG show that pre-operative aspirin reduced the risk of SVG occlusion, but no significant differences in mortality, peri-operative MI and stroke were found. Furthermore, subgroup analysis by dose showed that pre-operative aspirin may produce differential effects on chest tube drainage and surgical re-exploration, but not on mortality nor myocardial infarction. The strategy of

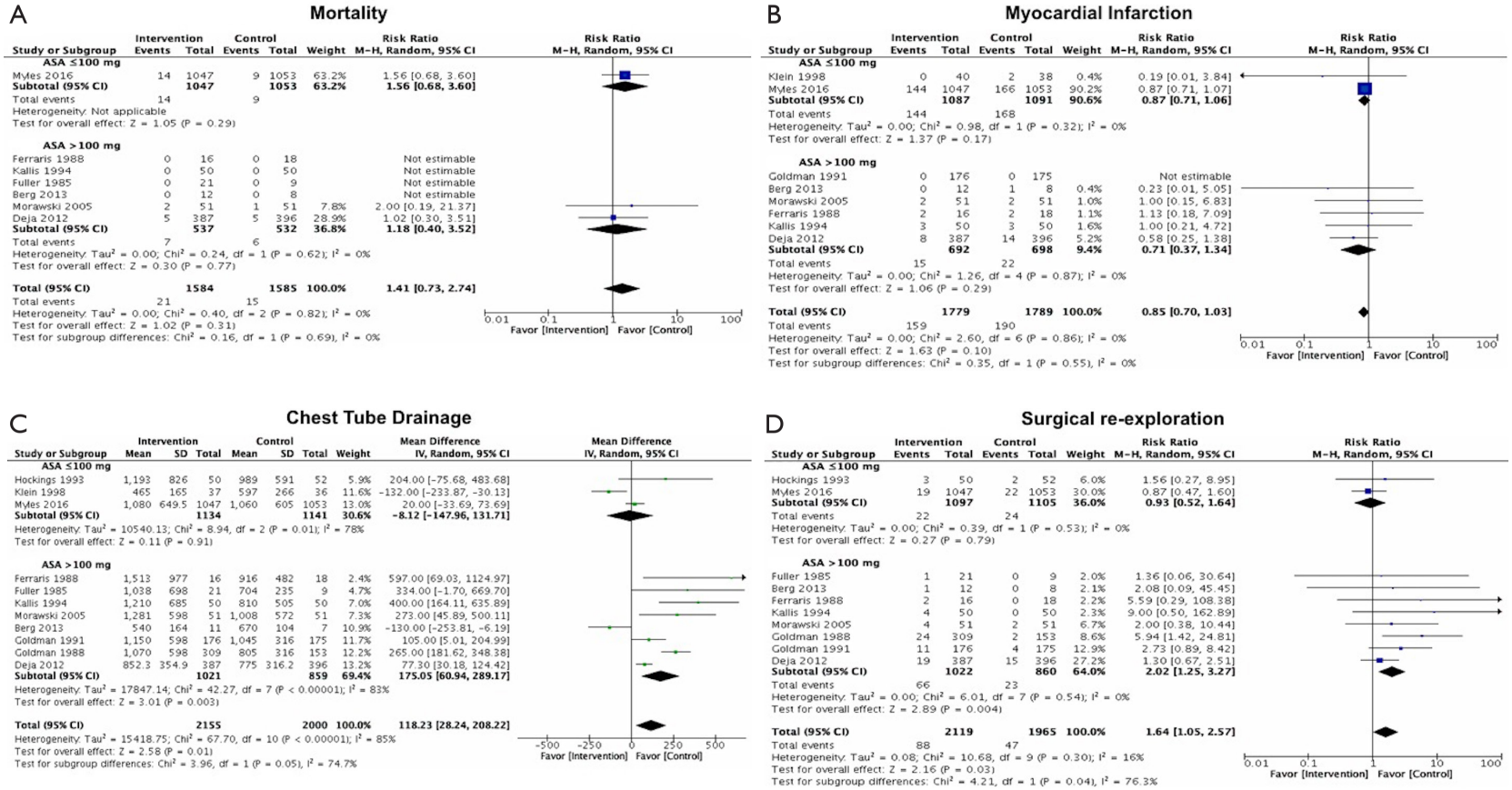

Figure 4 Subgroup analyses of the effect of aspirin on (A) mortality; (B) myocardial infarction; (C) chest tube drainage; and (D) need for surgical re-operation, by total daily dose of aspirin. M-H, Mantel-Haenszel; CI, confidence interval.

continuing aspirin before CABG surgery were also found to be no different from aspirin discontinuation in terms of myocardial infarction. Notably, the strength of the evidence was very low quality, mostly because of high risk of bias; imprecision; indirectness in the applicability of aspirin doses, surrogate outcomes, and timing of discontinuation or restarting; as well as potential for publication bias.

Pre-operative aspirin and outcomes: mortality

Our findings could not confirm or exclude a protective treatment effect of aspirin for mortality and are in line with previous meta-analyses (10,12). This is in contrast to some observational studies which suggested a positive effect on mortality with pre-operative aspirin use (3,5), and a prospective, longitudinal cohort study which suggested aspirin withdrawal before CABG as an independent predictor for mortality (4). The discrepancy may be due to the study design. Nonetheless, the findings of these observation studies and of our analysis remain limited in their interpretation. Even though RCT is considered high-quality evidence, our findings remain inclusive due to low statistical power. Moreover, although the observational data more likely reflect population and settings relevant in real-world clinical practice, they are prone to confounding bias. Well-designed pragmatic trials are therefore warranted to confirm the benefit of pre-operative aspirin on mortality.

Myocardial infarction

Unlike the results of our primary analysis and further sensitivity analysis of trials with low risk of bias, a previous meta-analysis (12) evaluating the effect of aspirin before CABG has suggested significant protective effects for aspirin against MI as compared with control [Peto (odds ratio): 0.79, 95% CI: 0.64–0.99; I^2=0%]. However, this meta-analysis included trials that assessed aspirin in combination with other antiplatelet therapy and trials that were not designed to measure clinical outcomes. Inclusion of such studies may have introduced significant variability in study protocols across trials and augment the treatment effect on MI, allowing for statistical significance to be reached. Moreover, the rationale of using Peto OR to estimate the relationship between interventions and outcome is unclear. According to a simulation study, Peto OR is appropriate to use when event rates are below 1% (37). However, the incidence rate of MI reported in that meta-analysis was between 9% and 11%. It is notable that the upper limit of the CI in the previous meta-analysis for MI was borderline significant, and therefore should be interpreted cautiously as the estimate may not be adequately robust to provide definitive conclusions for clinical practice.

However, our finding is in agreement with recent meta-analyses (14,15) that showed no significant benefit of pre-operative aspirin against MI, though the evidence is of very low quality. In the absence of high quality evidence of protective effect, clinicians should now consider other aspects (e.g., patient's value and preference, perceived risk, resources) when providing an optimal prophylactic management plan to the patients.

Chest tube drainage

Previous observational studies and meta-analysis (3,5,12) showed that the use of pre-operative aspirin was associated with an increased risk of blood loss, surgical re-exploration and RBC transfusions. These findings are consistent with our analysis, with the exception that the likelihood of RBC transfusions did not reach statistical significance in our study. Notably, the observed increased risk of blood loss was mostly found in trials allocating participants to higher doses of aspirin (>100 mg/day). However, the clinical significance of an increased risk of 100 mL blood loss is certainly questionable.

SVG patency

It is well-established that SVG occlusion has been the limiting factor of long-term outcome after CABG. Although the risk of occlusion increases with time, early occlusion occurs more commonly. Thus, providing early prophylaxis against the occlusion, especially, during pre-operative period conceptually has promising results. Our meta-analysis shows that pre-operative aspirin provides a significant benefit to SVG patency, which is a plausible finding given the anticipated antiplatelet effect of aspirin.

However, the available data is insufficient to recommend an optimal dose of aspirin, although a possible larger protective effect with a medium-dose (300–325 mg/day) in reducing graft occlusion compared to low-dose (50–150 mg/day) of aspirin was documented in an indirect comparison meta-analysis (38). Nonetheless, due to the observational nature of the study design, these data should be interpreted with caution.

Aspirin with or without temporary interruption before CABG in the intervention group

There was a variation in study protocols between studies in terms of stopping aspirin use prior to study enrollment among patients receiving pre-operative aspirin. Our indirect comparison analysis failed to show a significant difference in MI between aspirin with temporary interruption and without the interruption before CABG among patients receiving pre-operative aspirin. In contrast, EACTS guidelines (39) have recently recommended the continuation of aspirin throughout the pre-operative period in patients on aspirin who are undergoing CABG to reduce ischemic events. However, the recommendation was based on class IIa and level of evidence C. Certainly, the evidence is not robust enough to make a definite conclusion. Nonetheless, further research is warranted to confirm the benefit and risk of continuing aspirin in CABG patients on aspirin.

Clinical implication

Observational studies (40-42) investigating on the association of SVG occlusion and clinical outcomes have suggested that there may be an association between SVG occlusion and clinical outcomes. However, the current evidence fails to provide a sufficient connection between SVG patency and clinical outcomes. Despite a significant reduction in occlusion, these data fail to support the hypothesis that pre-operative aspirin protects patients undergoing CABG from mortality and MI. In the absence of high quality evidence of protective effect of pre-operative aspirin on patient-relevant outcomes and continuation of aspirin in patient on aspirin, clinicians should now consider patient's value and preference when providing an optimal prophylactic management plan to the patients.

Strengths and limitations

The strengths of our work include a comprehensive literature search, restriction to RCTs, duplicate evaluation of eligibility and data abstraction, risk of bias tool, and the use of GRADE system for quality of evidence assessment.

The present study has several limitations. The results of this analysis should be interpreted considering its limitations. The main limitation lies with the small number of studies, patients and events informing each outcome of interest. Most studies were short-term trials with duration up to 30 days post-CABG; therefore, the treatment effects beyond one month remain uncertain for relevant patient-important clinical outcomes and SVG patency. Moreover, the incidence of SVG occlusion was measured at very different time-points (8 to 527 days). Other limitations include the high loss-to-follow-up rate, which may overestimate the results due to the potential risk of selection bias, and the relatively old studies reporting the occlusion data, which may not reflect the recent clinical practice. Hence, the clinical interpretation of our finding remains limited by the potential bias due to missing data. Furthermore, our indirect comparison analysis may be underpowered to show a significant impact of wash-out period prior to randomization among patients receiving pre-operative aspirin. Additionally, our indirect treatment comparison is observational by nature, therefore, the result of our analysis may be at risk of confounding bias. Well-designed head-to-head comparative studies may therefore be needed to provide a definitive answer to the question of whether we should continue or stop aspirin before CABG. Moreover, since trials included in this meta-analysis primarily consisted of elective CABG patients, it limits our ability to generalize our findings to higher-risk patients such as individuals admitted with acute coronary syndrome and undergoing CABG during the index hospitalization, where the risk for ischemic events is significantly higher. Lastly, patient-level data were not available, precluding therefore, a more robust adjustment for any differences in clinical and surgical/procedural variables (i.e., on-pump versus off-pump or use of antifibrinolytics), or a combined clinical end point (i.e., composite outcome) that used for statistical convenience.

Conclusions

Our results suggest that pre-operative aspirin before CABG surgery is associated with lower risk of SVG occlusion, though no significant differences in clinical outcomes were found. Furthermore, aspirin dose may induce differential effects on chest tube drainage and surgical re-exploration; however, the effects of dose and aspirin interruption on mortality and MI are still unclear. These data are based on trials where the strength of evidence consists of low to very-low quality, therefore, well-designed RCTs are needed to provide a more reliable estimate for patient-important outcomes.

Acknowledgements

A special thanks to Dr. Per O. Vandvik, Department of

Medicine, Innlandet Hospital Trust, Gjøvik, Norway, for his constructive comments that greatly contributed to improving the manuscript.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Goldman S, Copeland J, Moritz T, et al. Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. Circulation 1988;77:1324-32.
2. Goldman S, Copeland J, Moritz T, et al. Saphenous vein graft patency 1 year after coronary artery bypass surgery and effects of antiplatelet therapy. Results of a Veterans Administration Cooperative Study. Circulation 1989;80:1190-7.
3. Dacey LJ, Munoz JJ, Johnson ER, et al. Effect of preoperative aspirin use on mortality in coronary artery bypass grafting patients. Ann Thorac Surg 2000;70:1986-90.
4. Mangano DT; Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 2002;347:1309-17.
5. Bybee KA, Powell BD, Valeti U, et al. Preoperative aspirin therapy is associated with improved postoperative outcomes in patients undergoing coronary artery bypass grafting. Circulation 2005;112:I286-92.
6. Ferraris VA, Saha SP, Oestreich JH, et al. 2012 update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations. Ann Thorac Surg 2012;94:1761-81.
7. Lordkipanidze M, Diodati JG, Pharand C. Possibility of a rebound phenomenon following antiplatelet therapy withdrawal: a look at the clinical and pharmacological evidence. Pharmacol Ther 2009;123:178-86.
8. Kulik A, Ruel M, Jneid H, et al. Secondary prevention after coronary artery bypass graft surgery: a scientific statement from the American Heart Association. Circulation 2015;131:927-64.
9. Alghamdi AA, Moussa F, Fremes SE. Does the use of preoperative aspirin increase the risk of bleeding in patients undergoing coronary artery bypass grafting surgery? Systematic review and meta-analysis. J Card Surg 2007;22:247-56.
10. Sun JC, Whitlock R, Cheng J, et al. The effect of pre-operative aspirin on bleeding, transfusion, myocardial infarction, and mortality in coronary artery bypass surgery: a systematic review of randomized and observational studies. Eur Heart J 2008;29:1057-71.
11. Ma X, Ma C, Yun Y, et al. Safety and efficacy outcomes of preoperative aspirin in patients undergoing coronary artery bypass grafting: a systematic review and meta-analysis. J Cardiovasc Pharmacol Ther 2014;19:97-113.
12. Hastings S, Myles P, McIlroy D. Aspirin and coronary artery surgery: a systematic review and meta-analysis. Br J Anaesth 2015;115:376-85.
13. Hastings S, Myles P, McIlroy D. Aspirin and coronary artery surgery: an updated meta-analysis. Br J Anaesth 2016;116:716-7.
14. Sa M, Soares AF, Miranda RGA, et al. Stopping versus continuing acetylsalicylic acid before coronary artery bypass surgery: A systematic review and meta-analysis of 14 randomized controlled trials with 4499 patients. Eur J Cardiothorac Surg 2017;52:838-47.
15. Aboul-Hassan SS, Stankowski T, Marczak J, et al. The use of preoperative aspirin in cardiac surgery: A systematic review and meta-analysis. J Card Surg 2017;32:758-74.
16. Myles PS, Smith JA, Forbes A, et al. Stopping vs. Continuing Aspirin before Coronary Artery Surgery. N Engl J Med 2016;374:728-37.
17. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264-9, W64.
18. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
19. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
20. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.
21. Higgins J, Green S. editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011. Available online: http://handbook.cochrane.org. Accessed 19 December 2016.
22. Killip S, Mahfoud Z, Pearce K. What is an intracluster correlation coefficient? Crucial concepts for primary care researchers. Ann Fam Med 2004;2:204-8.
23. Nazarian SM. Predictor of early saphenous vein graft

patency, platelet hyper-reactivity and aspirin-insensitive thromboxane generation in patients undergoing coronary artery bypass graft surgery. Johns Hopkins University, 2009.
24. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683-91.
25. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
26. Fuller JK, Copeland JG. Does short-term pre-operative aspirin in coronary bypass patients increase post-operative bleeding? Vasc Endovascular Surg 1985;19:174-8.
27. Ferraris VA, Ferraris SP, Lough FC, et al. Preoperative aspirin ingestion increases operative blood loss after coronary artery bypass grafting. Ann Thorac Surg 1988;45:71-4.
28. Goldman S, Copeland J, Moritz T, et al. Starting aspirin therapy after operation. Effects on early graft patency. Circulation 1991;84:520-6.
29. Hockings BE, Ireland MA, Gotch-Martin KF, et al. Placebo-controlled trial of enteric coated aspirin in coronary bypass graft patients. Effect on graft patency. Med J Aust 1993;159:376-8.
30. Kallis P, Tooze JA, Talbot S, et al. Pre-operative aspirin decreases platelet aggregation and increases post-operative blood loss--a prospective, randomised, placebo controlled, double-blind clinical trial in 100 patients with chronic stable angina. Eur J Cardiothorac Surg 1994;8:404-9.
31. Matsuzaki K, Okabe H, Kajihara N, et al. A prospective study of the timing of discontinuation of aspirin before coronary artery bypass grafting. Nihon Kyobu Geka Gakkai Zasshi 1997;45:1710-4.
32. Klein M, Keith P, Dauben H, et al. Aprotinin counterbalances an increased risk of peri-operative hemorrhage in CABG patients pre-treated with Aspirin. Eur J Cardiothorac Surg 1998;14:360-6.
33. Morawski W, Sanak M, Cisowski M, et al. Prediction of the excessive perioperative bleeding in patients undergoing coronary artery bypass grafting: role of aspirin and platelet glycoprotein IIIa polymorphism. J Thorac Cardiovasc Surg 2005;130:791-6.
34. Ghaffarinejad MH, Fazelifar AF, Shirvani SM, et al. The effect of preoperative aspirin use on postoperative bleeding and perioperative myocardial infarction in patients undergoing coronary artery bypass surgery. Cardiol J 2007;14:453-7.
35. Deja MA, Kargul T, Domaradzki W, et al. Effects of preoperative aspirin in coronary artery bypass grafting: a double-blind, placebo-controlled, randomized trial. J Thorac Cardiovasc Surg 2012;144:204-9.
36. Berg K, Langaas M, Ericsson M, et al. Acetylsalicylic acid treatment until surgery reduces oxidative stress and inflammation in patients undergoing coronary artery bypass grafting. Eur J Cardiothorac Surg 2013;43:1154-63.
37. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med 2007;26:53-77.
38. Lim E, Ali Z, Ali A, et al. Indirect comparison meta-analysis of aspirin therapy after coronary surgery. BMJ 2003;327:1309.
39. 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.
40. Alexander JH, Hafley G, Harrington RA, et al. Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. JAMA 2005;294:2446-54.
41. Lopes RD, Mehta RH, Hafley GE, et al. Relationship between vein graft failure and subsequent clinical outcomes after coronary artery bypass surgery. Circulation 2012;125:749-56.
42. Halabi AR, Alexander JH, Shaw LK, et al. Relation of early saphenous vein graft failure to outcomes following coronary artery bypass surgery. Am J Cardiol 2005;96:1254-9.

Cite this article as: Solo K, Lavi S, Choudhury T, Martin J, Nevis IF, Kwok CS, Kotronias RA, Nishina N, Sponga S, Ayan D, Mamas MA, Bagur R. Pre-operative use of aspirin in patients undergoing coronary artery bypass grafting: a systematic review and updated meta-analysis. J Thorac Dis 2018;10(6):3444-3459. doi: 10.21037/jtd.2018.05.187

Supplementary

Table S1 Excluded studies

Excluded studies	Reasons for exclusion
Mayer 1981	Wrong intervention (ASA in combination with dipyridamole)
Dale 1981	Wrong intervention (ASA in combination with warfarin)
Chesebro 1982	Not RCT
Gallagher 1983	Not RCT
Meister 1984	Wrong timing of study drug administration (after CABG)
Rajah 1985	Wrong timing of study drug administration (after CABG)
Boelaert 1986	Wrong timing of study drug administration (after CABG)
Chesebro 1986	Not RCT
Karwande 1987	Primary outcomes: platelet function, prostacyclin synthesis
Gershlick 1988	Wrong intervention (ASA in combination with dipyridamole)
Sanz 1990	Wrong timing of study drugs administration (after CABG)
Sethi 1990	Post-hoc analysis of previously published RCT
Goldman 1994	Wrong timing of study drugs administration (after CABG)
Akowuah 2005	Wrong intervention (ASA in combination with clopidogrel)
Cvetkovic 2012	Abstract not reporting data for meta-analysis purposes
Mirhosseini 2013	Wrong intervention, primarily assessed DVT
Heidari 2016	Wrong intervention (ASA in combination with clopidogrel)

RCT, randomized controlled trial; CABG, coronary artery bypass graft; DVT, deep venous thrombosis.

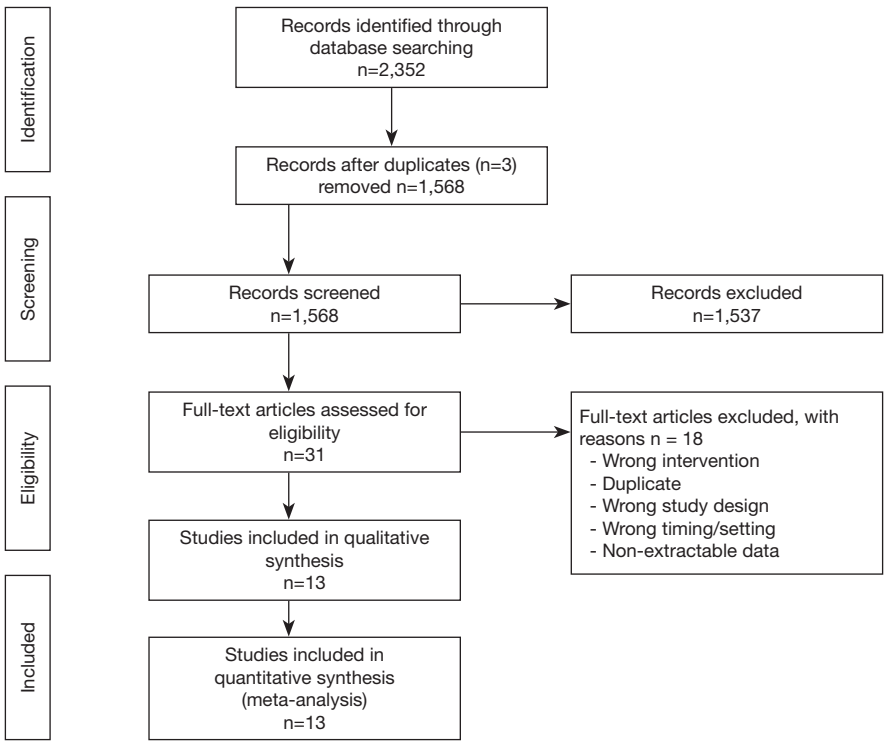

Figure S1 Flow diagram based on PRISMA. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

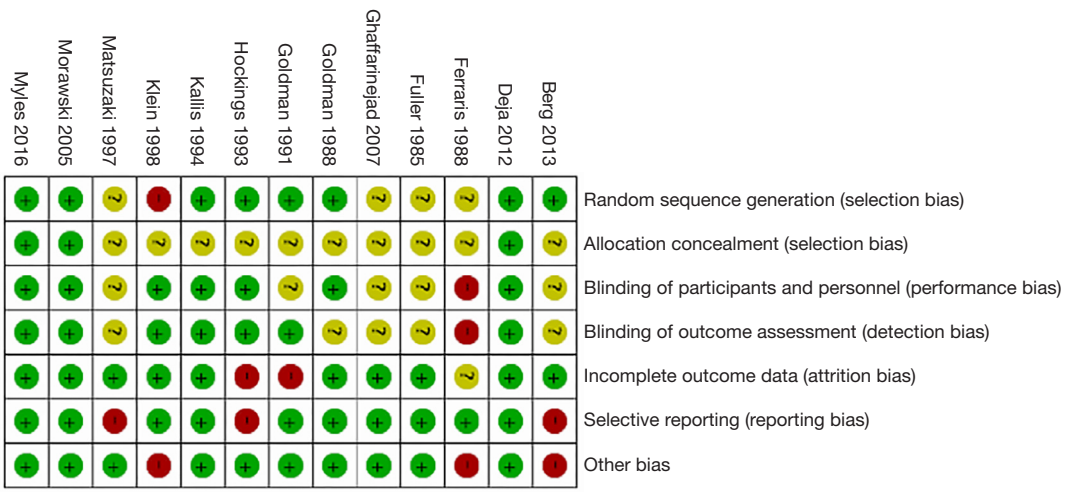

Figure S2 Risk of bias assessment. Critical appraisal of included trials assessing the seven domains (randomization, allocation concealment, blinding, completion of outcome data, selective outcome reporting, and other sources of bias). Green circle indicates low risk of bias, red circle indicates high risk of bias, and yellow circle indicates unclear reporting or uncertain risk of bias.

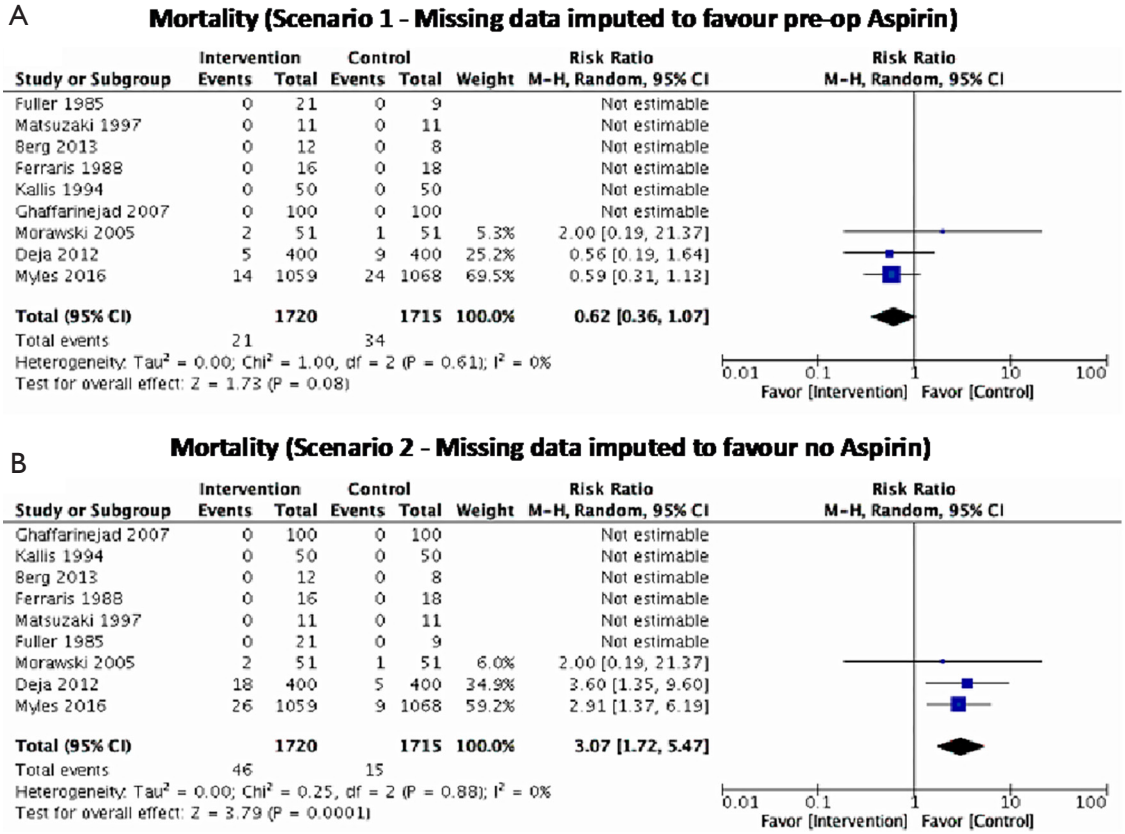

Figure S3 Worst-best sensitivity analysis. (A) Forest plots of pooled treatment effect estimates of mortality after adjusting for missing data within all control participants with missing data were assumed to have the events, and none in the aspirin group; (B) all aspirin participants with missing data were assumed to have the events, and none in the control group.

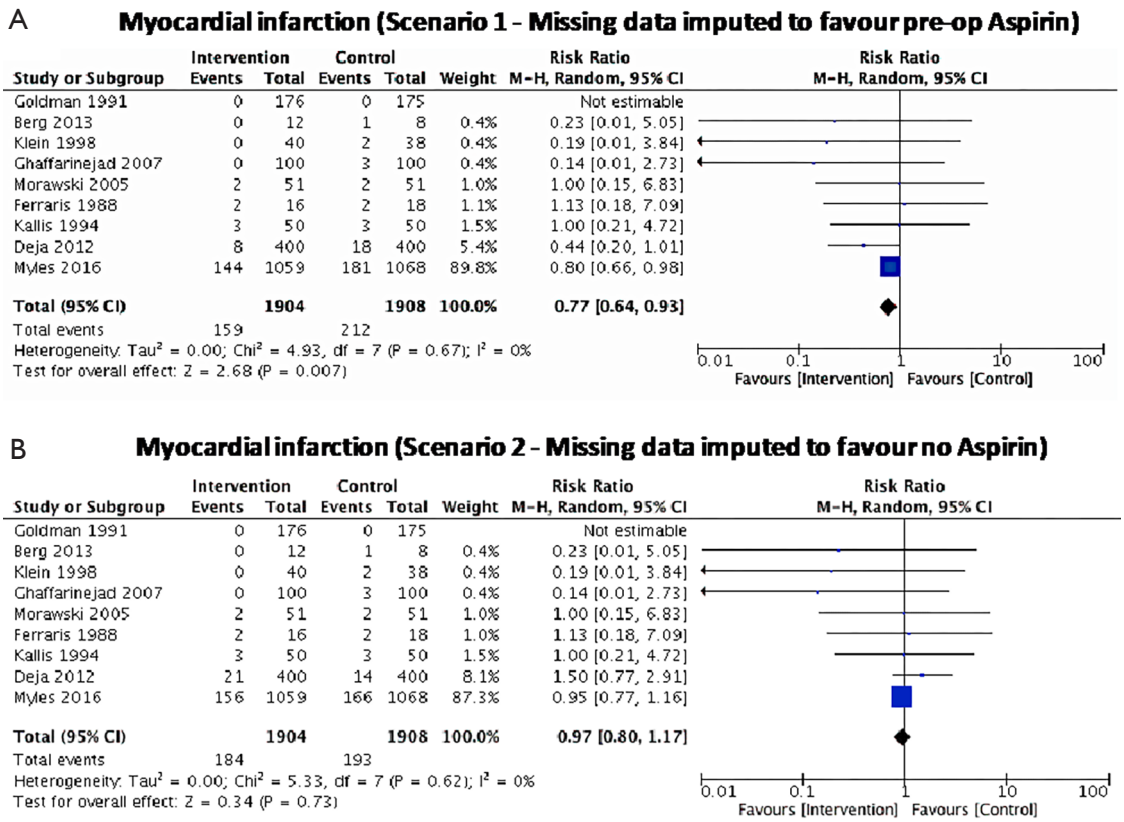

Figure S4 Worst-best sensitivity analysis. (A) Forest plot of pooled treatment effect estimates of proportion of myocardial infarction after adjusting for missing data within, all control participants with missing data were assumed to have the events, and none in the aspirin group; (B) all aspirin participants with missing data were assumed to have the events, and none in the control group). M-H, Mantel-Haenszel; CI, confidence interval.

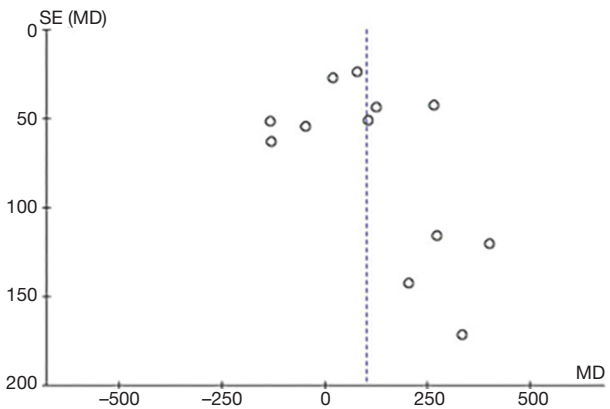

Figure S5 Funnel plot evaluating potential publication bias for the risk of post-operative bleeding. Egger's test suggested significant evidence for publication bias (P<0.001). MD, mean difference.

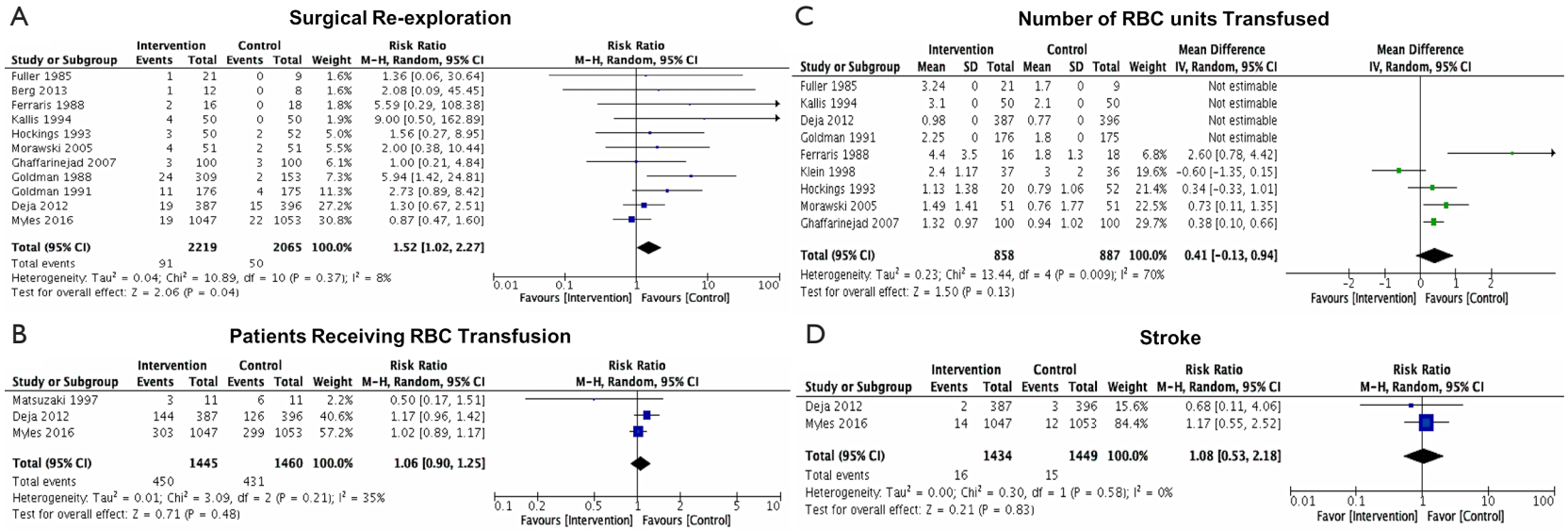

Figure S6 Forest plots of pooled treatment effect estimates of (A) surgical re-exploration; (B) need for RBC transfusion; (C) number of RBC units transfused; and (D) stroke in patients undergoing coronary artery bypass graft surgery. Imputation was not done for RBC transfusion due to large proportion of missing standard deviations. RBC, red blood cells; M-H, Mantel-Haenszel; CI, confidence interval.