Aspirin and coronary artery surgery: a systematic review and meta-analysis

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Abstract

Background: Aspirin administration before cardiac surgery represents a balance between preventing perioperative thrombotic events and promoting surgical bleeding. Clear evidence to guide the preoperative use of aspirin in patients undergoing cardiac surgery is lacking.

This systematic review and meta-analysis was performed to evaluate the efficacy and safety of preoperative aspirin, in patients undergoing coronary artery surgery.

Methods: We conducted a systematic review and meta-analysis of randomized trials involving patients undergoing coronary artery surgery assigned to preoperative aspirin therapy or no aspirin/placebo. The MEDLINE and EMBASE databases and Cochrane Central Register of Controlled Trials were searched up to March 2014 without language restrictions. Two reviewers performed independent quality review and data extraction. Efficacy outcomes of myocardial infarction (MI) and mortality, and safety outcomes of blood loss, red cell transfusion, and surgical re-exploration were compared.

Results: In 13 trials (n=2399), preoperative aspirin therapy reduced the risk of MI (OR, 0.56; 95% CI, 0.33–0.96; P=0.03), without a reduction in mortality (OR, 1.16; 95% CI, 0.42–3.22; P=0.77). Preoperative aspirin increased postoperative chest tube drainage (mean difference 168 ml; 95% CI, 39–297 ml; P=0.01), red cell transfusion (mean difference 141 ml; 95% CI, 55–226; P=0.001) and need for surgical re-exploration (OR, 1.85, 95% CI, 1.15–2.96; P=0.01). Studies were of low methodological quality, with significant heterogeneity identified.

Conclusions: In patients undergoing coronary artery surgery, preoperative aspirin reduces perioperative MI, but at a cost of increased bleeding, blood transfusion, and surgical re-exploration.

Key words: aspirin; blood transfusion; coronary artery bypass; myocardial infarction

Aspirin (acetylsalicylic acid) plays a key role in secondary prevention of myocardial infarction (MI) in patients with known coronary artery disease. High-level evidence supports this practice, and for reducing the short and long-term risk of thrombotic complications after coronary artery bypass graft (CABG) surgery, in part via maintenance of saphenous vein graft patency. However, in addition to beneficial effects, aspirin may also increase bleeding risks associated with cardiac surgery, including the need for blood transfusion and surgical re-exploration. Traditional practice has typically involved withholding aspirin for up to 7–10 days before cardiac surgery where possible, to limit this risk. Several observational studies have found evidence of increased perioperative bleeding in association with preoperative aspirin use, while previous pooled analyses of randomized and observational data support increased blood loss, transfusion and surgical re-exploration in patients receiving...
preoperative aspirin, with no apparent reduction in perioperative MI. Nevertheless, the total number of MIs reported in these studies was small, limiting the strength of any conclusions that could be drawn regarding the net effect of continuing aspirin up until the day of CABG surgery. 

In contrast, several observational studies suggest improved outcomes, including reduced mortality when aspirin was continued up until surgery or commenced within 48 h after surgery. While these studies suggest a protective effect of perioperative aspirin, they found no evidence of a significant increase in risk of bleeding or associated complications. Reflecting this, recent guidelines recommend maintaining aspirin until the day of surgery, suggesting a shift in priorities from primary concern over perioperative bleeding, to a heightened awareness of potential risks associated with perioperative thrombosis. However, other guidelines recommend stopping aspirin before elective CABG surgery in low risk patients (Class IIa), or stopping aspirin in the presence of increased bleeding risk, highlighting the limited and conflicting evidence on which current guidelines are based.

The net effect of competing anti-thrombotic and pro-bleeding actions of preoperative aspirin in patients undergoing cardiac surgery remains unknown. We therefore undertook a systematic review and meta-analysis of randomized trials, seeking to address both the efficacy and safety of continued preoperative aspirin therapy, in adult patients undergoing CABG surgery. Specifically we sought to determine whether preoperative aspirin reduced the risk of MI or death, potentially outweighing increased bleeding, red cell transfusion and surgical re-exploration.

### Methods

#### Search strategy

We performed a systematic review and meta-analysis according to PRISMA (www.prisma-statement.org) recommendations including a detailed and structured search for all randomized controlled trials comparing aspirin with control (placebo or no treatment) in adults undergoing first time coronary artery (on-pump or off-pump) surgery with or without concomitant valve surgery. We searched Medline and EMBASE databases, together with the Cochrane Central Register of Controlled Trials using the following medical subject headings and text words in varying combinations: aspirin, acetylsalicylic acid, ASA, CABG, coronary artery bypass, perioperative, and surgery. Searches were restricted using the filters of human and randomized controlled trial. A detailed description of the MEDLINE search strategy is presented in appendix A in the Supplement material. The search period extended from January 1946 to March 2014 and was applied without language restrictions. Two authors (SH and PSM) independently identified titles and abstracts of potentially eligible studies. Disagreement was resolved by consensus. Reference lists of relevant clinical studies and review articles were explored for additional studies (Fig. 1).

#### Eligibility and inclusion

Study inclusion required fulfilment of all of the following criteria: (i) randomized controlled trial; (ii) patients >18 years of age; (iii) CABG surgery, with or without concomitant valve or other procedures; (iv) with or without cardiopulmonary bypass; (v) an intervention of aspirin vs a comparison group receiving either no aspirin or placebo. All doses of aspirin were included. Studies or groups of patients within studies taking other antiplatelet medication, or anticoagulants other than heparin, were excluded.

#### Outcomes

Pre-specified efficacy outcomes were MI and operative mortality; safety outcomes included blood loss (measured by chest tube drainage), volume of red cell transfusion, and rates of surgical re-exploration. For the purposes of this analysis, chest tube drainage was recorded at or close to 12 h after surgery because later drainage likely contains an increasing proportion of serous exudate (i.e. not blood loss). Red cell transfusion was converted from units to millilitres, with one unit assumed to be 300 ml.

#### Data extraction

Patients were assigned to the treatment group if aspirin had been taken within seven days before surgery. Patients were assigned to the control group if they were given a matched placebo or were not administered aspirin within seven days of surgery. Data were extracted from included studies on the above efficacy and safety outcomes. Definitions of MI and timing of mortality varied between studies and all study-specific definitions were accepted. However, reports of ‘no major complications’ were not taken to represent zero events for our outcomes of interest and an explicit description of the absence of each specific adverse event was required in order to be included in the analysis as a count of zero.

Baseline characteristics of study groups, dose of aspirin, timing of preoperative aspirin cessation in control groups, and use of antibrinolytic agents were recorded for all included studies. Individual authors of included studies were contacted requesting additional unpublished study data.

#### Assessment of risk of bias

Risk of bias was assessed using the Cochrane risk of bias tool (Table 1).

#### Statistical analysis

Analyses were conducted using Review-Manager software (RevMan, version 5.2.3 for Windows; The Cochrane Collaboration, Oxford, UK; 2013). In view of the anticipated low incidence of MI and mortality, we used the Peto method to calculate odds ratio (OR) and 95% confidence interval (CI) with a fixed effect model. We used a random effects model when evidence of statistical heterogeneity was present ($I^2>40\%$ or heterogeneity $\chi^2$ test $P<0.05$). Single cells showing zero events automatically had 0.5 added to that cell to maintain its contribution to the analysis. Studies reporting no events for a given endpoint in either the control or treatment arm were excluded from analysis for that endpoint.
Numerical variables (blood loss, red cell transfusion) are presented as weighted mean difference with 95% CI. Reporting of blood loss varied across studies, some reporting median and others reporting range values. Such data were converted to mean (sd) according to previous recommendations. In studies where no range data were reported, sd was imputed, based on the sd of pooled study data (Supplementary Table 1). Evidence of reporting bias was assessed graphically using funnel plots (Supplementary Fig. 10).

All aspirin dose regimens were pooled for the primary analysis. However, recognizing that the risk and benefit may vary differently with dose, sensitivity analyses included assessment for evidence of a dose-response effect of aspirin, using a daily dose of 160 mg to stratify high-dose and low-dose regimens. This dose selection represented a pragmatic decision based on a combination of dosing regimens used in the existing studies and current practice. Additional sensitivity analyses included sequential exclusion of individual studies, stratification by study date to identify evidence of a significant temporal trend and exploration for evidence of interaction between concomitant antifibrinolytic use and aspirin administration, as it remains unknown whether the use of these agents may alter aspirin related bleeding risk and anti-thrombotic risk differently.

Results

Characteristics of included studies

A total of 13 randomized trials comprising 2399 coronary artery surgery patients were included in the analysis (Table 1). All studies included patients undergoing first time isolated CABG surgery with no additional cardiac procedures. Two studies included
patients undergoing urgent revascularization and two studies included groups of patients undergoing off-pump surgery. In view of the small total number of patients undergoing off-pump surgery together with the absence of individual patient-level data for these subgroups, specific sub-group analyses for patients undergoing on-pump and off-pump surgery was not undertaken.

Two studies reported volume of chest tube drainage at 12 h, one at 18 h, two at 24 h, one each at 35 h and 36 h, and one at 48 h. Two studies reported the volume of drainage at the time of chest drain removal, while the remaining studies reported chest tube drainage for an undefined postoperative period. Two studies utilized a transfusion algorithm, while only two studies specified the duration after surgery for which transfusion was assessed. Two studies reported criteria to determine the need for surgical re-exploration and only two studies specified a time period over which mortality was measured.

Five studies provided an explicit definition of MI. One study failed to ascribe mortality events to individual treatment arms so was excluded from the analysis of that outcome.

### Study design

Design features of included studies are summarized in Table 1. Aspirin dosage varied from 80 mg to 2600 mg daily. Antifibrinolytic use was inconsistent; eight studies did not comment on its use, while one study reported omitting antifibrinolytics. One study reported epsilon-aminocaproic acid use in 25% of patients in the aspirin group where it appeared to represent an

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<th>Postoperative aspirin use</th>
<th>Anti-fibrinolytic</th>
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<td></td>
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outcome, being used in patients where postoperative bleeding appeared excessive.21 Two studies included aprotinin in both control and aspirin groups25 27 and one study used a combination of aprotinin and tranexamic acid in similar proportions across both the placebo and aspirin groups.28

Postoperative aspirin regimens varied substantially between studies and were inconsistently reported. Six studies reported that aspirin was continued in the postoperative period;4 22 23 27 28 30 while three studies reported commencement of aspirin within 6 hours after surgery.1 22 27

Baseline characteristics
The mean age of patients varied from 57 to 63 years, the proportion of female patients ranging from 0 to 34%. Cardiac risk factors were inconsistently described in most studies, and preoperative ventricular function was quantified in less than half the studies. The mean number of bypass grafts ranged from 2.1 to 3.6 with variable conduit selection.

Methodological quality and evidence of bias
The overall quality of the included studies was low (Table 2). Only eight of the 13 trials were blinded.1 22–26 28 30 Several aspects of internal study validity were unable to be determined across the range of included studies. The method of randomization was described in only five of the 13 trials.19–21 23 30 Adequate blinding of both participants and outcome assessors was inconsistent.

Efficacy outcomes
Myocardial infarction
Eight studies (n=1437) reported incidence of MI using a variety of definitions.21 24–30 The incidence of MI was reduced in patients taking aspirin, 2.8% vs 5.6% (OR, 0.56; 95% CI: 0.33–0.96; P=0.03) with no significant heterogeneity (I^2=0%) (Fig. 2). Sequential exclusion of each study did not materially alter these results. The magnitude of reduction in odds of MI was greater in the low-dose aspirin subgroup (OR, 0.37; 95% CI: 0.14–0.96; P=0.04) compared with patients receiving doses greater than 160 mg (OR, 0.72; 95% CI, 0.57–1.42; P=0.88) although this difference was not significant (P=0.26) ( Supplementary Fig. 1). In studies published after year 2000, patients receiving preoperative aspirin had reduced odds for MI compared with control (OR, 0.53; 95% CI 0.28–0.99) while the effect was attenuated and became non-significant in studies published before year 2000 (OR, 0.74; 95% CI 0.24–2.30). However, the difference between early and late groups was not significant (P=0.61) (Supplementary Fig. 2).

Mortality
Only three studies (n=1005) reported operative mortality with a total of 15 deaths across studies.26 28 30 No difference in mortality was observed between aspirin and control groups (OR, 1.16; 95% CI, 0.42–3.22; P=0.77), with no significant heterogeneity detected (I^2=0, heterogeneity χ^2 test P=0.88) (Supplementary Fig. 3). Sequential exclusion of individual studies did not materially alter this result. The small number of studies precluded a meaningful analysis of the effect of aspirin dose on this outcome. All studies reporting mortality were published after year 2000, precluding a sensitivity analysis based on this study characteristic. One study reported a post hoc analysis of survival out to 3 years after surgery, which identified improved survival in the aspirin group (hazard ratio, 0.58; 95% CI, 0.33–0.99).28

Safety outcomes
Bleeding (chest tube drainage)
Blood loss was reported in 12 of the 13 studies (n=2279),19–29 with significant statistical heterogeneity identified (I^2=93%). Preoperative aspirin administration increased blood loss (weighted mean difference 168 ml; 95% CI, 39–297 ml; P=0.01) (Fig. 3). Sequential exclusion of each study did not materially alter these results. Stratified by dose, the difference in chest tube drainage was greater in patients receiving a total daily aspirin dose >160 mg, compared with placebo (mean difference 277 ml; 95% CI, 114–440 ml; P=0.001) (Fig. 4), while chest tube drainage did not differ between aspirin and placebo for patients receiving a total daily aspirin dose <160 mg (mean difference –1 ml; 95% CI, –157–156 ml; P=0.99). The difference between subgroups was statistically significant (P=0.02) indicating a dose-dependent effect of aspirin on chest-tube drainage. However, despite stratification according to aspirin dose, heterogeneity persisted within subgroups. In studies published before year 2000, patients receiving aspirin compared

<table>
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<th>Sequence Generation (Randomization)</th>
<th>Allocation Concealment (Selection bias)</th>
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with patients receiving placebo, had a higher volume of chest tube drainage (mean difference 0.224 ml; 95% CI, 39–408; P=0.02) than in studies published after 2000 (mean difference 66 ml; 95% CI, –44–176; P=0.24). However, the difference between subgroups was not significant (P=0.15) and heterogeneity persisted despite stratification by year of publication (Supplementary Fig. 4).

**Transfusion**

Nine studies (n=1775) reported total volume of packed red cells transfused per patient. One study described the total number of transfusions but did not differentiate between red cell and other blood products, necessitating its exclusion from this component of the analysis. The sd for volume of red cell transfusion was not reported in one study. Compared with placebo, preoperative aspirin increased the volume of red cell transfusion (weighted mean difference 141 ml; 95% CI, 55–226 ml; P=0.001) with marked heterogeneity present (I²=64%) (Supplementary Fig. 5). Sequential exclusion of each study did not materially alter these results. Stratified by aspirin dose, volume of transfused red cells was not increased in patients receiving low-dose aspirin compared with placebo (44 ml; 95% CI, –118–207 ml; P=0.59). In contrast, volume of transfused red cells was increased in patients receiving high-dose aspirin (206 ml; 95% CI, 79–334 ml; P=0.002). However, the difference between these subgroups was not significant (P=0.12) (Supplementary Fig. 6) and heterogeneity persisted despite stratification by dose. Compared with placebo, the difference in volume of transfused red cells in patients receiving preoperative aspirin was smaller in studies published after year 2000 (96 ml; 95% CI, 33–159 ml; P=0.003) compared with studies published before year 2000 (197 ml; 95% CI 15–379 ml; P=0.03). However, this difference between subgroups was not significant (P=0.3) and heterogeneity persisted despite stratification (I²=64%) (Supplementary Fig. 7).

The proportion of patients receiving any blood transfusion was reported in only one study, precluding a pooled analysis of this outcome.

**Surgical re-exploration**

Nine studies (n=1722) reported surgical re-exploration. Compared with placebo, patients receiving preoperative aspirin had a higher rate of surgical re-exploration, 5.6% vs 3.0% (OR, 1.85; 95% CI, 1.15–2.96; P=0.01), with no statistical heterogeneity between studies identified (I²=0%) (Fig. 5). Sequential exclusion of each study did not materially alter these results. Stratified by aspirin dose, the odds of requiring surgical re-exploration was attenuated and became non-significant in patients receiving lower-dose aspirin compared with placebo (OR, 1.48; 95% CI, 0.49–4.54; P=0.49). However, the difference in odds for re-exploration between high-dose and low-dose aspirin groups was not significant (P=0.67) (Supplementary Fig. 8). Compared with placebo, the odds for requiring surgical re-exploration in patients
receiving preoperative aspirin was greater in studies published before year 2000 (OR, 3.04; 95% CI 1.31–7.04; P=0.01), than in those published after year 2000 (OR, 1.34; 95% CI, 0.74–2.43; P=0.34). However, this difference between subgroups was not significant (P=0.12) (Supplementary Fig. 9).

Variability in reporting of anti-fibrinolytic use, together with reported use in both arms of some studies, at times unequally, precluded our planned exploration for evidence of effect modification by co-administration of these agents (Table 3).

Funnel plots did not identify evidence of substantial residual confounding and formal testing did not support a dose-response effect for outcomes other than chest-tube drainage. Importantly, we found no difference in mortality or the potentially thrombotic complications of MI and stroke. While this highlights the inability to generalize data from the non-operative to the operative context, these results may not be applicable to patients undergoing cardiac surgery.

Perioperative MI is a major cause of morbidity and mortality after CABG surgery. Contributing factors may include perioperative anaemia, inadequate myocardial protection during cardiopulmonary bypass, incomplete revascularization, and thrombotic complications to either native coronary vessels or coronary grafts. The platelet inhibitory effects of aspirin may be expected to reduce thrombotic risks, while direct anti-inflammatory effects may further contribute to protective effects of aspirin. The current study demonstrates that preoperative aspirin results in a significant reduction in perioperative MI in patients undergoing cardiac surgery.

With the updated inclusion of additional randomized trials, the current study complements and extends previous analyses, highlighting the dual effect of aspirin to reduce perioperative MI, but at the expense of increased bleeding. The magnitude of bleeding appeared to be dose-related, with no increase in bleeding indices found when the analysis was restricted to patients receiving low-dose aspirin only, while the protective effect against MI appeared well maintained. However, such differences must be interpreted cautiously as they represent an exploratory analysis, and formal testing did not support a dose-response effect for outcomes other than chest-tube drainage. Importantly, we found no difference in mortality with preoperative aspirin. While this is consistent with the net effect of aspirin recently reported by
the POISE 2 trial in patients undergoing non-cardiac surgery,\(^36\) the total number of events in our analysis was low (n=15), meaning considerable uncertainty regarding mortality continues to exist for patients undergoing cardiac surgery.

Both the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists make a Class I, Level A recommendation that antifibrinolytic therapy should be routinely used as a blood conservation measure\(^17\) with potential to modify the pro-bleeding and antithrombotic effects of aspirin differently. However, antifibrinolytic use was sporadic and uncontrolled in the included studies. No study presented outcome data stratified by the use of these agents, thus precluding a sensitivity analysis seeking evidence of an important interaction between preoperative aspirin and antifibrinolytic use. Previous studies confirm the efficacy of antifibrinolytics to reduce both chest tube drainage and transfusion requirements in patients receiving preoperative aspirin who undergo cardiac surgery.\(^4\) While the same study suggested a tendency toward a reduced composite outcome of thrombotic complications in patients receiving antifibrinolytic therapy, the net outcome of anti-thrombotic and pro-bleeding effects of aspirin in the presence of concurrent antifibrinolytic therapy remains important, but as yet unanswered, question.

The current study has a number of limitations. Included studies predominantly consisted of patients undergoing primary elective coronary revascularization, a group generally considered to be at low-risk for bleeding, potentially limiting the generalizability of our findings. Study quality was generally low, despite our attempts to minimize the potential for unrecognized confounding and bias by including only randomized trials in the analysis. Although large between-study variation in preoperative aspirin dose may have contributed to observed heterogeneity, the same characteristic permitted an exploratory analysis for a potentially important dose-response effect with aspirin. Such an effect was evident for chest tube drainage and, although not confirmed for other clinically important outcomes, may represent a type II error as a result of limited numbers of adverse events. It is possible that the magnitude and balance of aspirin effects may vary with the time interval used to define aspirin exposure before surgery. However, there is limited existing data directly addressing this question and our decision to explicitly define aspirin exposure as anytime within 7 days before surgery, was based on both traditional practice and the expected time-course for platelet pool regeneration.\(^40\)\(^41\) Nevertheless, optimal timing for aspirin withdrawal before surgery remains uncertain. Early postoperative aspirin is widely regarded as an important step in preventing coronary graft complications. However, inconsistent reporting of postoperative aspirin use, precluded an independent assessment of the impact of this variable on perioperative outcomes in our analysis. Although year of publication did not significantly affect results, the time period of included studies spans multiple decades over which surgical, anaesthetic and transfusion practice has evolved, meaning direct applicability of our results to contemporary practice remains uncertain.

Despite these limitations, the current analysis represents the best available estimate for the net effect of preoperative aspirin in patients undergoing cardiac surgery. High quality, definitive evidence for the net balance of anti-thrombotic and pro-bleeding effects of contemporary doses of preoperative aspirin in patients undergoing cardiac surgery, together with potential modification of this effect by concomitant antifibrinolytic therapy is still required. It is hoped that such evidence may be provided by the ATACAS trial (ATACAS Trial; ACTRN No. ACTRN012605000557639), a multicentre randomized factorial trial of aspirin and tranexamic acid in 4600 patients undergoing cardiac surgery, which is currently in progress.

**Conclusions**

Continuation of aspirin therapy in patients undergoing coronary artery surgery reduces perioperative MI, but at a cost of increased bleeding, blood transfusion, and surgical re-exploration. It is unknown whether the net balance of these effects meaningfully varies with aspirin dose and whether antifibrinolytic therapy can protect against bleeding complications, while preserving the beneficial effect on risk of MI.

**Supplementary material**

Supplementary material is available at *British Journal of Anaesthesia* online.

**Authors’ contributions**

S. H. has seen the original study data, reviewed the analysis of the data, revised the final manuscript, and is the author responsible for archiving the study files. P. M. and D.M. have seen the original
study data and reviewed the analysis of the data. All of the authors read and approved the final manuscript.

**Declaration of interest**

P.M. is supported by an Australian National Health and Medical Research Council Practitioner Fellowship, Melbourne, Australia. P.M. is an editor of the British Journal of Anaesthesia, on the editorial board of Anaesthesia and Intensive Care, is on the editorial board (associate) of Anesthesiology, on the Editorial Board of Heart Lung and Circulation and an Editorial Consultant for The Lancet. D.M. is on the editorial board of Journal of Cardiothoracic and Vascular Anesthesia.

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