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

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Aims
To obtain estimates of the efficacy and safety of pre-operative aspirin in patients undergoing coronary artery bypass grafting (CABG).

Methods and results
Eligible studies included randomized controlled trials (RCTs) and observational studies of patients undergoing CABG, comparing pre-operative aspirin with no aspirin/placebo, and reporting at least one of our primary outcomes. In eight RCTs (n = 805), pre-operative aspirin increased post-operative bleeding [Mean difference (MD), 104.9 mL; 95% confidence interval (CI), 19.2–190.6; P = 0.016] and reoperation [odds ratio (OR), 2.52; 95% CI, 1.18–5.38; P = 0.017], but not transfusion requirements (MD, 0.62 units; 95% CI, −0.06–1.30; P = 0.072). Subgroup analysis suggested that bleeding was increased with aspirin doses ≤325 mg/day, but not with lower doses. In 14 observational studies (n = 4485), pre-operative aspirin increased post-operative bleeding (MD, 113.6 mL; 95% CI, 45.2–182.0; P = 0.001) and transfusion requirements (MD, 0.34; 95% CI, 0.12–0.56 units; P = 0.002), but not reoperation (OR, 1.12; 95% CI, 0.69–1.83; P = 0.647). Neither analysis detected a significant effect on myocardial infarction or death.

Conclusion
Pre-operative aspirin increases post-operative bleeding, but this may be avoided by the use of aspirin doses <325 mg/day. Most of the RCTs are old and the meta-analysis was underpowered for efficacy outcomes. A large randomized trial is necessary to determine the safety and efficacy of pre-operative aspirin in the setting of contemporary cardiac surgical practice.

Keywords
Aspirin • Coronary bypass surgery • Haemorrhage • Myocardial infarction • Mortality

Introduction
Early post-operative aspirin increases graft patency,1 reduces ischaemic complications, and improves survival2 in patients undergoing coronary artery bypass grafting (CABG). However, the benefits of continuing aspirin treatment until the day of surgery (pre-operative aspirin) are unclear. Most patients awaiting coronary bypass surgery are already taking daily aspirin at doses ranging from 81 to 325 mg, and there is conflicting evidence whether or not aspirin should be stopped before surgery.3 Arguments for stopping aspirin include the potential for increased bleeding and transfusion requirements during and after surgery,4,6 and the lack of evidence from randomized trials showing benefit from continuing aspirin until the day of surgery.3 Several studies, however, suggest that pre-operative aspirin given at low doses does not increase bleeding,6,7 and improves both graft patency8 and survival.9,10

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Methods

We adopted the methods detailed in the QUOROM\textsuperscript{13} and MOOSE\textsuperscript{14} guidelines for meta-analyses of randomized and observational studies.

Study search

Two reviewers (J.C.J.S. and R.W.) independently searched MEDLINE (1950 to February 2007), EMBASE (1980 to February 2007), and the Cochrane Databases (to first quarter 2007) for potentially eligible studies. Additional searches were performed of the CINAHL database (1982 to February 2007), ACP Journal Club (1991 to 2007), and the Database of Abstracts of Reviews of Effects (to fourth quarter 2006). The search terms included acetylsalicylic acid, aspirin, ASA, coronary artery bypass, coronary artery bypass graft, graft occlusion, and graft patency. The reference lists of relevant papers were also searched.

Eligibility and data extraction

Studies were eligible for inclusion if they met all of the following criteria: (i) randomized controlled trials (RCTs) or observational cohort studies; (ii) involving adult patients (age ≥18 years); (iii) undergoing first-time CABG with or without combined procedures (e.g. valve replacement); (iv) performed ‘on pump’ (with cardiopulmonary bypass); (v) the presence of a group receiving aspirin prior to surgery compared to a control group (aspirin discontinued or placebo given); and (vi) reported at least one of our safety or efficacy endpoints (post-operative blood loss, packed red blood cell transfusion, reoperation, perioperative MI, or death). Studies or subgroups of patients in which the aspirin or control group received other anticoagulants or antiplatelet drugs were excluded in order to avoid the potential for confounding.

The corresponding authors of studies with missing data were contacted to request additional unpublished data if available.

Eligibility assessment and data extraction were performed independently in a blinded and standardized fashion by two reviewers (J.C.J.S. and R.W.). Extracted data included assessment of study quality, study design, patient demographics, baseline characteristics, aspirin dose, number of days free of aspirin prior to surgery (control group only), perioperative use of antifibrinolytic drugs, and safety and efficacy endpoints. Disagreements between reviewers were resolved by consensus.

Data analysis

We used kappa statistics to assess agreement between reviewers. A random-effects model based on an inverse variance method was used for combining the results from individual trials.\textsuperscript{15} We used the χ² test of homogeneity with statistical significance set at alpha = 0.10 to test for heterogeneity. We also used the I² statistic, a measure of percent of total variability due to heterogeneity among studies, to measure the inconsistencies between included studies. Data on bleeding and transfusions were summarized as the mean difference (MD) between treatment groups in the number of millilitres of post-operative mediastinal drainage of blood and units of packed red blood cells (PRBC) transfused, respectively. PRBC transfusions that were reported in millilitres were converted into number of units transfused using a conversion rate of 300 mL per unit.\textsuperscript{16} Reoperation, perioperative MI, and death were summarized by odds ratios (ORs) with 95% confidence intervals (CIs). A two-sided P-value of <0.05 was considered statistically significant.

Subgroup analysis was used to explore heterogeneity between study results. We hypothesized a priori that there would be heterogeneity between studies that used different aspirin doses and that patients treated with higher doses of aspirin would have increased post-operative bleeding.\textsuperscript{17} We also explored heterogeneity by date of publication and by quality of the studies based on the Jadad score for RCTs which looks at the specific aspects of randomization, blinding, and loss to follow-up.\textsuperscript{18} As there is no validated quality score for observational studies, we performed subgroup analysis only by aspirin dosage and date of publication.

When multiple treatment groups were evaluated in a single study, only those groups receiving aspirin were included in the meta-analysis. To compare these multiple aspirin groups to non-aspirin groups, the sample size of the control group was divided evenly by the number of aspirin groups as suggested by the Cochrane Collaboration.\textsuperscript{19} This method was employed for both the RCT and observational study analyses.

Treatment groups that discontinued aspirin less than seven days before surgery were analysed in the pre-operative aspirin group based on aspirin’s ability to irreversibly inhibit platelet function for the life of the platelet (5–10 days).

For binary outcomes such as death, MI, and reoperation, groups with zero events were assigned a value of 0.5 for the purposes of analysis.\textsuperscript{19}

Publication bias was assessed using funnel plots and the Egger’s test for asymmetry. A P-value of <0.1 was considered to represent significant asymmetry.\textsuperscript{20}

Results

Search results

We identified 4092 potential eligible citations (Figure 1). After review of titles, 3896 were rejected leaving 196 potentially eligible studies. The abstracts of these citations were reviewed and an additional 161 were rejected. Thirty-five studies consisting of 15 RCTs and 20 observational cohort studies were then retrieved in full text.

Four studies reported the total number of transfusions but did not report PRBC transfusions separately.\textsuperscript{10,21–23} and one study provided the number of patients who received transfusions without quantifying the amounts of blood transfused.\textsuperscript{24} Another five studies omitted standard deviations from their transfusion
The corresponding authors for these ten articles were contacted to request the missing data. One author was able to provide unpublished data thus allowing inclusion of the study in the meta-analysis. Five of the other nine studies were included in our analysis because they reported one of our other safety or efficacy outcomes.

Four potentially eligible studies were non-English and were translated from French, Japanese, Serbian, and Lithuanian. Three were included in the analysis and one was excluded due to lack of standard deviations in their data.

**Qualitative findings**

Assessment of the study selection agreement between the two reviewers resulted in a kappa score of 0.78 (95% CI, 0.73–0.83).

**Studies included**

Eight RCTs involving a combined total of 805 patients, and 14 observational studies involving a combined total of 4485 patients were included in the meta-analysis.

**Study design**

The designs of RCTs and observational studies included in our meta-analysis are summarized in Tables 1 and 2, respectively.

Aspirin dosages in the RCTs varied from 80 mg to 2600 mg daily. Nine out of 14 observational studies reported aspirin dosages and these varied from 85 to 2400 mg daily.

Most RCTs did not report whether or not patients received perioperative antifibrinolytic drugs such as tranexamic acid or aprotinin. One RCT reported that 25% of their aspirin group and none of their control group received aminocaproic acid peri-operatively, while another reported not using antifibrinolics at all. Seven out of 14 observational studies reported on antifibrinolytic use; in one study a fraction of patients received aprotinin, in one study all patients received aprotinin, in one study all patients received tranexamic acid, and in four studies no patients received antifibrinolytic therapy.

Post-operative antiplatelet regimens were reported in only three of eight RCTs. One study gave the pre-operative aspirin group 100 mg of aspirin daily after surgery and the pre-operative control group one placebo tablet daily after surgery. Two studies gave aspirin post-operatively to both pre-operative treatment groups at dosages of 150 and 325 mg daily.
### Table 1 Overview of RCTs evaluating pre-operative aspirin use in CABG

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Jadad Score</th>
<th>Blinded</th>
<th>n</th>
<th>Mean Age</th>
<th>Female (%)</th>
<th>Design</th>
<th>Post-operative Treatment</th>
<th>ASA Dose(s)</th>
<th>Antifibrinolytic Used</th>
<th>Endpoints Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuller et al.</td>
<td>1985</td>
<td>1/5</td>
<td>No</td>
<td>30</td>
<td>57</td>
<td>NR</td>
<td>Grp 1: No ASA for &gt;7 day (n = 9)</td>
<td>NR</td>
<td>325 – 2600 mg daily</td>
<td>NR</td>
<td>Bleeding, death</td>
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<td></td>
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<td></td>
<td></td>
<td>Grp 2: ASA 325 mg at 12 h pre-op (n = 11)</td>
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<td></td>
<td>Grp 3: ASA 650 mg every 6 h for 48 h pre-op (n = 10)</td>
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<tr>
<td>Karwande et al.</td>
<td>1987</td>
<td>1/5</td>
<td>No</td>
<td>36</td>
<td>63</td>
<td>29</td>
<td>Grp 1: No ASA (n = 10)</td>
<td>NR</td>
<td>80 mg daily</td>
<td>NR</td>
<td>Bleeding</td>
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<td></td>
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<td></td>
<td></td>
<td>Grp 2: ASA 80 mg night before surgery (n = 14)</td>
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<td></td>
<td></td>
<td>Grp 3: ASA 80 mg night before + Dipyridamole 75 mg night before and morning of surgery (n = 12)</td>
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<tr>
<td>Ferraris et al.</td>
<td>1988</td>
<td>2/5</td>
<td>No</td>
<td>34</td>
<td>62</td>
<td>12</td>
<td>Grp 1: ASA 325 mg day before surgery (n = 16)</td>
<td>NR</td>
<td>325 mg daily</td>
<td></td>
<td>Bleeding, transfusion, MI, death</td>
</tr>
<tr>
<td>Goldman et al.</td>
<td>1991</td>
<td>4/5</td>
<td>Yes</td>
<td>351</td>
<td>60</td>
<td>0</td>
<td>Grp 1: ASA 325 mg night before surgery (n = 176)</td>
<td>Both groups received ASA 325 mg 6 h post-op</td>
<td>325 mg daily</td>
<td></td>
<td>Bleeding</td>
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<td></td>
<td></td>
<td>Grp 2: Placebo (n = 18)</td>
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</tr>
<tr>
<td>Hockings et al.</td>
<td>1993</td>
<td>4/5</td>
<td>Yes</td>
<td>102</td>
<td>60</td>
<td>7</td>
<td>Grp 1: ASA 100 mg daily for 7 day pre-op (n = 50)</td>
<td>Grp 1: ASA 100 mg daily</td>
<td>100 mg daily</td>
<td>NR</td>
<td>Bleeding, transfusion</td>
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<td></td>
<td>Grp 2: Placebo (l = 52)</td>
<td>Grp 2: Placebo daily</td>
<td></td>
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<tr>
<td>Kallis et al.</td>
<td>1994</td>
<td>4/5</td>
<td>Yes</td>
<td>100</td>
<td>62</td>
<td>19</td>
<td>Grp 1: ASA 300 mg daily for 2 weeks pre-op (n = 50)</td>
<td>NR</td>
<td>300 mg daily</td>
<td>NR</td>
<td>MI, death</td>
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<td></td>
<td>Grp 2: Placebo (n = 50)</td>
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<tr>
<td>Matsuzaki et al.</td>
<td>1997</td>
<td>1/5</td>
<td>NR</td>
<td>62</td>
<td>63</td>
<td>34</td>
<td>Grp 1: ASA mean dose 262 ± 111 mg daily stopped 2 days before surgery (n = 11)</td>
<td>NR</td>
<td>250 ± 116 mg daily</td>
<td></td>
<td>Bleeding, transfusion, death</td>
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<td>(Japanese)</td>
<td></td>
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<td></td>
<td>Grp 2: ASA mean dose 239 ± 120 mg daily up to day of surgery (n = 11)</td>
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<td></td>
<td>Grp 3: ASA discontinued ≥7 day pre-op (n = 40)</td>
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<tr>
<td>Morawski et al.</td>
<td>2005</td>
<td>4/5</td>
<td>Yes</td>
<td>102</td>
<td>61</td>
<td>15</td>
<td>Grp 1: ASA 150 mg at 12 and 3 h before surgery (n = 51)</td>
<td>Both groups received ASA 150 mg daily</td>
<td>300 mg daily</td>
<td>No</td>
<td>Bleeding, transfusion, MI, death</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Grp 2: Placebo (n = 51)</td>
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</tbody>
</table>

Grp., Group; NR, not reported; ASA, acetylsalicylic acid (aspirin).

*Jadad score (1–5) with 5 being the highest quality.*

*Excluded from analysis.*
Baseline characteristics

The mean age of patients varied from 57 to 63 in the RCTs and 54 to 69 in the observational studies. The percentage of female patients varied from zero to 34 in the RCTs and zero to 32 in the observational studies. Most of the studies did not report the proportion of diabetic patients or the mean left ventricular function. The great majority of patients for all studies were undergoing elective surgery. The mean number of bypass grafts performed within the RCTs and observational studies varied from 2.1 to 3.6. The breakdown of the types of grafts used (for example: internal mammary, saphenous vein, radial artery) was generally not reported.

Quality

The RCTs were either very low quality \(^2\) with Jadad scores of one or two out of five, or of high quality with Jadad scores of four.\(^5\),\(^6\),\(^28\),\(^31\) Only four out of the eight RCTs were reported as blinded.\(^5\),\(^6\),\(^28\),\(^31\)

Randomized controlled trials

Safety outcomes

Pre-operative aspirin increased the volume of post-operative bleeding (MD, 104.9 mL; 95% CI, 19.2–190.6; \(P = 0.016\)) (Figure 2), but did not significantly increase transfusion requirements (MD, 0.62 units; 95% CI, –0.06–1.30; \(P = 0.072\)) (Figure 3). Rates of reoperation were significantly higher in the pre-operative aspirin groups (OR, 2.52; 95% CI, 1.18–5.38; \(P = 0.017\)) (Figure 4).

Moderate heterogeneity was present in the analyses of bleeding (\(P = 0.093; I^2 = 41.2\%\)) and was eliminated when studies were analysed separately according to aspirin dose (Figure 5). Studies using doses of aspirin \(\geq 325\) mg demonstrated a significant increase in bleeding (MD, 229.6 mL; 95% CI, 18.7–440.5; \(P = 0.033\), \(P\) heterogeneity = 0.220, \(I^2 = 32.1\%\)), whereas studies in which patients received \(< 325\) mg did not demonstrate a significant increase in bleeding (MD, 65.3 mL; 95% CI, –20.2–150.8; \(P = 0.134\), \(P\) heterogeneity = 0.173, \(I^2 = 37.3\%\)). Heterogeneity between subgroups was significant (\(P = 0.094\)). Heterogeneity remained evident when studies were analysed by year of publication or quality.

Heterogeneity was not statistically significant for the outcome of post-operative transfusion (\(P = 0.110; I^2 = 47.0\%\)).

Efficacy outcomes

No differences in the rates of perioperative MI (OR, 1.04; 95% CI 0.35–3.07; \(P = 0.948\)) or death (OR, 1.21; 95% CI 0.31–4.71; \(P = 0.780\)) were evident between the two groups (Figures 6 and 7).

Observational studies

Safety outcomes

Pre-operative aspirin was associated with a significant increase in the volume of post-operative bleeding (MD, 113.6 mL; 95% CI, 45.2–182.0; \(P = 0.001\)) (Figure 2) and transfusion requirements (MD, 0.34 units; 95% CI, 0.12–0.56; \(P = 0.002\)) (Figure 3). Rates of reoperation, on the other hand, were not significantly different between the two groups (OR, 1.12; 95% CI, 0.69–1.83, \(P = 0.647\)) (Figure 4). There was statistical heterogeneity for bleeding and transfusion outcomes. We were unable to explore the effect of aspirin dose on heterogeneity because many studies did not report aspirin dose. Heterogeneity was not eliminated when subgroup analysis was performed by date of publication.

Efficacy outcomes

Only one observational study reported perioperative MI rates.\(^23\) There was no significant reduction in mortality among the patients receiving pre-operative aspirin compared with no aspirin (OR, 0.59; 95% CI, 0.34–1.02; \(P = 0.06\)) (Figure 7).

Publication bias analysis

There was statistically significant asymmetry in the funnel plots for the outcomes of bleeding and mortality in the RCTs and for mortality in the observational studies. It is difficult to interpret this in the context of the mortality studies. Overall, there was no significant difference in mortality found likely due to lack of power.

Asymmetry among the RCTs for the safety outcome of bleeding was due to a disproportionate number of studies reporting an increase in bleeding with pre-operative aspirin use (Figure 8). This may represent the bias of authors to submit and journals to publish positive studies showing an effect of pre-operative aspirin on post-operative bleeding.

Discussion

The key finding of our meta-analysis is that pre-operative aspirin increases the risk of post-operative bleeding. Doses of aspirin less than \(325\) mg/day did not appear to increase bleeding. Many of the studies were old and our meta-analysis was underpowered for efficacy outcomes.

The benefit of aspirin for preventing ischaemic events is believed to be mediated primarily by its ability to inhibit platelet cyclooxygenase-1 (COX-1), thereby blocking thromboxane A\(_2\) production, a powerful platelet agonist and vasoconstrictor.\(^43\) Inhibition of platelet COX-1 is saturable at low aspirin doses. Higher aspirin doses have not been shown to be more effective than lower doses for inhibiting platelet COX-1, but instead increase the risk of bleeding which is consistent in our findings of an excess of bleeding with \(\geq 325\) mg/day doses of aspirin.

The success of CABG is highly dependent on maintaining blood flow in grafts that bypass diseased coronary arteries. Between 3 and 12% of saphenous vein grafts occlude within one month after surgery,\(^44\) and graft failure is associated with a mortality rate of 9%.\(^45\) Early graft failure is believed to be caused primarily by thrombotic mechanisms induced by endothelial injury resulting from handling and distension of the vein graft, leading to platelet and coagulation activation and thrombus formation.\(^44\) The use of a cardiopulmonary bypass circuit may also induce a systemic prothrombotic state by activating tissue factor, kallikrein, and complement.\(^46\) Early post-operative aspirin has been shown to improve post-operative graft patency\(^8\) and reduce the risk of complications associated with cardiopulmonary bypass and open heart surgery including MI, stroke, renal failure, and death.\(^2\) Keeping patients on aspirin prior to surgery may help attenuate the inflammatory response during the operative period and may also reduce
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>Mean age</th>
<th>Female (%)</th>
<th>Design</th>
<th>ASA Dose(s)</th>
<th>Antifibrinolytic used?</th>
<th>Endpoints reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson et al. (1978)</td>
<td>25</td>
<td>54</td>
<td>0</td>
<td>Prospective cohort with retrospective matched controls</td>
<td>600–2400 mg daily</td>
<td>NR</td>
<td>Bleeding, transfusion</td>
</tr>
<tr>
<td>Torosian et al. (1978)</td>
<td>98</td>
<td>54</td>
<td>11</td>
<td>Retrospective cohort of 100 consecutive patients, 98 included in analysis with 2 deaths excluded</td>
<td>600–2400 mg daily</td>
<td>NR</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Rawitscher et al. (1991)</td>
<td>100</td>
<td>61</td>
<td>24</td>
<td>Prospective cohort</td>
<td>85–325 mg daily</td>
<td>NR</td>
<td>Bleeding, transfusion, death</td>
</tr>
<tr>
<td>Reich et al. (1994)</td>
<td>197</td>
<td>68</td>
<td>32</td>
<td>Retrospective cohort</td>
<td>NR</td>
<td>No</td>
<td>Transfusion</td>
</tr>
<tr>
<td>Vuylsteke et al. (1997)</td>
<td>144</td>
<td>61</td>
<td>19</td>
<td>Prospective cohort</td>
<td>≤325 mg daily</td>
<td>No</td>
<td>Bleeding, transfusion</td>
</tr>
<tr>
<td>Jakics et al. (1999)</td>
<td>177</td>
<td>64</td>
<td>28</td>
<td>Retrospective cohort</td>
<td>325 mg daily</td>
<td>No</td>
<td>Bleeding, transfusion</td>
</tr>
<tr>
<td>Weightman et al. (2002)</td>
<td>797</td>
<td>62</td>
<td>17</td>
<td>Prospective cohort</td>
<td>NR</td>
<td>No</td>
<td>Transfusion, death</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Methodology</td>
<td>Follow-up</td>
<td>ASA Duration</td>
<td>Outcome</td>
<td>Treatment</td>
<td></td>
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</tr>
</tbody>
</table>
| Chavanon et al.  (2002) | French     | Retrospective cohort | NR        | Grp 1: ASA within 2 day of surgery ($n = 172$)  
Grp 2: ASA within 3–7 day of surgery ($n = 162$)  
Grp 3: No ASA for >7 day before surgery ($n = 78$) | NR | All groups received periop Aprotinin | Bleeding, transfusion |
| Ray et al. (2003)  |            | Retrospective cohort | NR        | Grp 1: No ASA for >7 day before surgery ($n = 497$)  
Grp 2: ASA within 7 day of surgery ($n = 105$)  
Grp 3: Clopidogrel within 7 day of surgery $^a$ ($n = 11$)  
Grp 4: ASA+Clopidogrel within 7 day of surgery $^a$ ($n = 46$) | NR | NR | Transfusion |
| Gerrah et al. (2003) |            | Prospective cohort | 100 mg daily | Grp 1: ASA up to surgery ($n = 10$)  
Grp 2: No ASA for >7 day before surgery ($n = 10$)  
Grp 3: ASA+Clopidogrel up to surgery ($n = 46$) | 100 mg daily | Grp 1: 20%  
Grp 2: 29% | Bleeding, transfusion, death |
| Gerrah et al. (2004) |            | Prospective cohort | 100 mg daily | Grp 1: ASA daily up to surgery ($n = 46$)  
Grp 2: No ASA for >7 day before surgery ($n = 48$)  
Grp 3: No ASA for >7 day before surgery ($n = 48$) | 100 mg daily | Grp 1: 100%  
Grp 2: NR | Bleeding, transfusion, MI |
| Gerrah et al. (2005) |            | Prospective cohort | 100 mg daily | Grp 1: ASA daily for 10d before surgery ($n = 14$)  
Grp 2: No ASA for >7 day before surgery ($n = 18$)  
Grp 3: No ASA for >7 day before surgery ($n = 18$) | 100 mg daily | NR | All patients received periop tranexamic acid | Death |
| Bybee et al. (2005) |            | Retrospective cohort | NR        | Grp 1: ASA daily for <5 day before surgery ($n = 1316$)  
Grp 2: No ASA for >5 day before surgery ($n = 320$)  
Grp 3: No ASA or heparin before surgery ($n = 28$) | 100 mg daily | NR | Bleeding |
| Veikutiene et al. (2005) | Lithuanian | Prospective cohort | NR        | Grp 1: ASA daily before surgery ($n = 25$)  
Grp 2: Heparin before surgery $^a$ ($n = 22$)  
Grp 3: No ASA or heparin before surgery ($n = 28$) | NR | NR | Bleeding |

Grp, Group; NR, not reported; ASA, acetylsalicylic acid (aspirin).  
$^a$Excluded from analysis.
Randomized controlled trials
(7 studies, n = 705)

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean difference (95% CI)</th>
<th>% weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuller (Grp 2) (1985)</td>
<td>170.00 (-177.44, 517.44)</td>
<td>5.1</td>
</tr>
<tr>
<td>Fuller (Grp 3) (1985)</td>
<td>514.00 (-78.96, 1107.95)</td>
<td>2.0</td>
</tr>
<tr>
<td>Kranz (1987)</td>
<td>45.00 (-197.17, 257.17)</td>
<td>10.9</td>
</tr>
<tr>
<td>Ferrans (1988)</td>
<td>597.00 (89.03, 1124.97)</td>
<td>2.4</td>
</tr>
<tr>
<td>Goldman (1991)</td>
<td>105.00 (-56.95, 266.95)</td>
<td>15.1</td>
</tr>
<tr>
<td>Hockings (1993)</td>
<td>204.00 (-75.68, 483.68)</td>
<td>7.3</td>
</tr>
<tr>
<td>Matsuoka (Grp 2) (1997)</td>
<td>43.00 (-81.14, 147.14)</td>
<td>22.1</td>
</tr>
<tr>
<td>Matsuoka (Grp 1) (1997)</td>
<td>-3.00 (-86.51, 80.51)</td>
<td>25.1</td>
</tr>
<tr>
<td>Morawecki (2005)</td>
<td>273.00 (45.86, 500.11)</td>
<td>9.9</td>
</tr>
<tr>
<td>Overall</td>
<td>104.04 (19.24, 190.65)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Increased with no ASA Increased with ASA

Overall effect: $p = 0.016$
Heterogeneity $\chi^2 = 13.60$ (df = 8), $P = 0.093$

$R^2 = 41.2\%$

Observational studies
(10 studies, n = 1053)

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean difference (95% CI)</th>
<th>% weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torosian (1978)</td>
<td>480.00 (153.91, 808.09)</td>
<td>3.4</td>
</tr>
<tr>
<td>Michelson (1978)</td>
<td>482.00 (139.36, 824.34)</td>
<td>3.2</td>
</tr>
<tr>
<td>Rawitscher (1991)</td>
<td>81.00 (29.85, 132.15)</td>
<td>14.1</td>
</tr>
<tr>
<td>Vuytselaie (1997)</td>
<td>31.00 (-70.53, 132.53)</td>
<td>11.5</td>
</tr>
<tr>
<td>Jäkli (1999)</td>
<td>230.00 (-59.61, 567.61)</td>
<td>3.4</td>
</tr>
<tr>
<td>Chavacon (Grp 1) (2002)</td>
<td>26.00 (-151.83, 123.83)</td>
<td>11.3</td>
</tr>
<tr>
<td>Chavacon (Grp 2) (2002)</td>
<td>11.00 (-85.16, 106.16)</td>
<td>11.8</td>
</tr>
<tr>
<td>Gerath (2003)</td>
<td>177.00 (15.06, 338.94)</td>
<td>8.2</td>
</tr>
<tr>
<td>Gerath (2004)</td>
<td>230.00 (140.85, 319.15)</td>
<td>12.2</td>
</tr>
<tr>
<td>Gerath (2005)</td>
<td>171.00 (40.26, 295.74)</td>
<td>10.2</td>
</tr>
<tr>
<td>Vakulina (2005)</td>
<td>-49.90 (-163.63, 63.83)</td>
<td>10.8</td>
</tr>
<tr>
<td>Overall</td>
<td>113.59 (45.16, 182.02)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Increased with no ASA Increased with ASA

Overall effect: $p = 0.001$
Heterogeneity $\chi^2 = 34.81$ (df = 10), $P < 0.01$

$R^2 = 71.3\%$

Figure 2 Analysis of RCTs and observational studies for safety endpoint: post-operative bleeding.
Figure 3 Analysis of RCTs and observational studies for safety endpoint: post-operative PRBC transfusion.
cardiovascular events while awaiting surgery. Pre-operative aspirin increases bleeding, but it remains to be established whether it may yet be associated with a net clinical benefit and whether this benefit can be achieved using low-dose aspirin, thereby avoiding the increase in bleeding associated with higher doses.

The strengths of our study are that we included all RCTs and observational studies that reported relevant clinical outcomes.
Figure 5 RCT subgroup analysis for bleeding by aspirin dose.

Figure 6 Analysis of RCTs for efficacy endpoint: myocardial infarction.
Figure 7 Analysis of RCTs and observational studies for efficacy endpoint: mortality.
thereby enabling us to obtain estimates of the effect of pre-operative aspirin on safety and efficacy outcomes. Methods for exploring heterogeneity were stated a priori which allowed us to better validate our results and to clarify the relationship between aspirin dosage and bleeding.

Our meta-analysis also has limitations. There was large variation in aspirin doses and quality of study reporting, and publication dates spanned a 25 year period. We classified patients who stopped taking aspirin less than 7 days before their surgery as having received pre-operative aspirin, thereby potentially diluting any impact of pre-operative aspirin on both safety and efficacy outcomes. Differences between treatment groups in the post-operative use of aspirin or other antiplatelet drugs may have confounded estimates of the safety and efficacy of pre-operative aspirin. Meta-analyses of observational studies also possess limitations due to the inherent biases that exist in non-randomized, unblinded studies. Finally, even when the results of the studies were combined, there was insufficient power to reliably determine the effect of pre-operative aspirin on efficacy outcomes.

There have been important changes over the past 25 years in the anaesthetic, surgical, and medical management of patients undergoing CABG surgery. One of the most notable is the routine intraoperative use of antifibrinolytics such as tranexamic acid. Multiple studies have shown that the use of antifibrinolytics significantly reduces post-operative bleeding in cardiac surgery. The studies that used perioperative antifibrinolytics for their patients found no significant increase in bleeding or reoperation. Updated perioperative strategies in cardiac surgery may reduce or even eliminate the bleeding risk of pre-operative aspirin that was found in this analysis which included many historical studies that may be considered outdated.

In 2005, Bybee and colleagues published a cohort study involving 1636 consecutive patients undergoing first-time isolated CABG. Patients were divided into those who had received aspirin within 5 days of surgery (n = 1316) and those who had no aspirin within 5 days of surgery (n = 320). There were some differences between the two treatment groups, most notably the greater proportion of patients having had an MI within 1–7 days of surgery in the aspirin group compared with the no aspirin group (41.2% vs. 17.0%, P < 0.01). This likely reflects a greater proportion of urgent patients in the aspirin group. All patients received intraoperative antifibrinolytic therapy with tranexamic acid.

Risk-adjusted in-hospital mortality was found to be lower in the aspirin group (OR 0.34, P < 0.01) with no significant difference in reoperation or transfusions.

The benefit of pre-operative aspirin is more likely to be evident in a contemporary study because they will include older and sicker patients. In the 10 year period between 1990 and 1999, the Society of Thoracic Surgeons CABG database reported a 10% decrease in elective cases and an 87% increase in urgent cases. There was also a 12% increase in female patients, and a 53% increase in diabetic patients. The 2004, ACC/AHA guidelines state that the benefits of continuing aspirin may outweigh the risks for those who have had recent acute coronary syndromes and require CABG.

The question as to the safety and efficacy of pre-operative aspirin in CABG patients is yet to be answered for our current patient population on low-dose aspirin and with the routine use of perioperative antifibrinolytics. Our group is currently conducting a pilot RCT comparing pre-operative aspirin use vs. placebo with a primary endpoint of graft patency and secondary endpoints of death, MI, transfusion, bleeding, and reoperation. A large, randomized study will be needed to determine the true safety and efficacy of this therapy in the setting of contemporary cardiac surgical practice.

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References


