Who might benefit from early aspirin after coronary artery surgery?

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Abstract

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was whether early administration of aspirin might optimize vein graft patency. More than 250 papers were found using the reported search, of which 4 new papers in addition to the previous 7 represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. Early postoperative aspirin administered within 6 h following coronary artery bypass grafting (CABG) has been shown to be optimal for prevention of vein graft occlusion. Early aspirin has significant benefit in reducing vein graft occlusion, mortality, myocardial infarction, stroke, renal failure and bowel infarction. The efficacy of early postoperative aspirin on vein graft patency diminishes the later it is administered. It has optimal benefit at 6 h, some benefit at 24 h and no benefit after 48 h post CABG. ACC/AHA, EACTS and ACCP have issued guidelines recommending administration of early aspirin or an alternative (clopidogrel, ticlopidine and indobufen) at 6 h or soon after bleeding has settled as the standard of care for optimization of vein graft patency. The ACCP guideline has also suggested that optimal prevention of cardiovascular complication should have higher value than prevention of postoperative bleeding. Several randomized, controlled studies, including a meta-analysis, have shown that early administration of aspirin following CABG is not associated with increased blood loss or transfusion requirement. Postoperative bleeding has been identified as a significant reason for non administration of early aspirin in a prospective study. It is essential to define/quantify the postoperative blood loss that precludes administration of early aspirin. This will enhance prompt administration in some cases and guide judgement, especially in patients with high-risk factors for vein graft thrombosis. Administration at 6 h is the optimal time to give aspirin as long as bleeding has settled.

Keywords: Bleeding • Early aspirin • Vein graft • Occlusion • Prevention • Optimal time

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

THREE-PART QUESTION

In [patients undergoing coronary artery bypass grafting] is [early administration of aspirin] better for [graft patency, without increased blood loss].

CLINICAL SCENARIO

You are the cardiothoracic registrar on call and the intensive care nurse asked if she should administer 300 mg aspirin to a 75-year old gentleman who is 6 h postoperative for coronary artery bypass grafting (CABG) with five vein grafts, even though his chest drain output had been 70–80 ml/h in the past 4 h. She said that, although she is aware of the strong evidence to suggest that early aspirin would protect his vein grafts from early occlusion, she is not sure if this would make his bleeding worse. Do you think it is safe to give the aspirin? You resolve to check the literature yourself.

SEARCH STRATEGY

Medline 1950 to November 2013 using the OVID interface ([exp Coronary Artery Bypass OR coronary artery bypass.mp OR vascular graft.mp] AND [exp aspirin OR aspirin.mp] AND [exp graft occlusion, vascular OR graft occlusion.mp OR vascular patency.mp] AND [maximally sensitive randomized control trial filter]). The search was limited to English language articles and the reference lists of each publication were also searched.

SEARCH OUTCOME

More than 250 papers were found using the reported search. From these, 11 papers were identified that provided the best evidence to answer the question. This updates a previous BET search by Musleh and Dunning (2003) on the same subject [2–12]. These papers are presented in Table 1.
<table>
<thead>
<tr>
<th>Author, date, journal and country, Study type (level of evidence)</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comment</th>
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<tr>
<td>Fremes et al. (1993), Eur J Cardiothoracic Surg, Canada [3] Meta-analysis (level 1a)</td>
<td>17 randomized studies with 4504 patients comparing effect of early postoperative aspirin ± dipyridamole on vein graft patency</td>
<td>Graft patency</td>
<td>Aspirin ± dipyridamole versus placebo: (OR: 0.6, 95% CI: 0.51–0.71, P &lt; 0.0001)</td>
<td>Early aspirin does not cause significant postoperative bleeding, but enhances early vein graft patency</td>
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<td>Result are reported as OR, ± 95% CI</td>
<td>Survival</td>
<td>Consistent aspirin use versus inconsistent aspirin use: RR: 0.58; 95% CI: 0.47, 0.70; P &lt;0.001</td>
<td>Preoperative aspirin is associated with postoperative bleeding, reoperation and transfusion</td>
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<td>Blood loss, transfusion requirement and reoperation</td>
<td>Preoperative aspirin + postoperative aspirin versus postoperative aspirin only = preoperative aspirin causes significant bleeding, transfusion requirement, reoperation, but no additional benefit on graft patency</td>
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<td>Gavaghan et al. (1991), Circulation, Australia [2] Prospective double-blind placebo-controlled randomized study (level 1a)</td>
<td>237 patients from a single centre were randomized following CABG: aspirin 127 vs placebo 110 given within 1 h post CABG and then daily. Aspirin was stopped 7 days before CABG</td>
<td>Early graft patency</td>
<td>Aspirin group 98.4% vs placebo group 93.8% (P = 0.004 using the ratio estimate technique)</td>
<td>The study clearly shows benefit of early aspirin (administered within 1 h post CABG) in enhancing both early and late vein graft patency rate</td>
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<td>Late graft patency</td>
<td>≥1 occluded distal anastomosis: (4 vs 14.3%, P = 0.003) in aspirin and placebo, respectively</td>
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<td>Late graft occlusion</td>
<td>At 1 year after CABG: aspirin 94.3% vs placebo 88.4%, P = 0.01. ≥1 occluded distal anastomosis: aspirin 11.9% vs placebo 29.5%, P = 0.001</td>
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<td>Goldman et al. (1991), Circulation, USA [4] Multicentre double-blind placebo-controlled randomized trial (Level 1a)</td>
<td>489 male elective patients Stopped aspirin 5 days before CABG Randomized to aspirin or placebo 12 h preoperatively then all had aspirin 6 h postoperative and daily</td>
<td>Early graft patency Blood loss</td>
<td>Aspirin group 7.4; 1.5% vs placebo group 7.8; 1.3%, (P = 0.871, 95% CI: −3.6 to 4.2%)</td>
<td>The results showed that preoperative aspirin has no significant benefit for vein graft patency, but is associated with more bleeding, transfusion requirement and reoperation</td>
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<td>Y-graft occlusion rate, aspirin group 0.0% (0 of 22) vs placebo group 7.0; 3.6% (3 of 44), P = 0.06; 6 h chest tube drainage: aspirin group 500 ml (lower 5%, 155 ml; upper 5%, 1899 ml) vs placebo group 448 ml (lower 5%, 115 ml; upper 5%, 1576 ml), P = 0.01; 36 h chest tube drainage: aspirin group 1150 ml (lower 5%, 499 ml; upper 5%, 3182 ml) vs placebo group 1045 ml (lower 5%, 331 ml; upper 5%, 2736 ml), P = 0.148</td>
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<td>Significant benefit of early aspirin was noted in vein graft with flow rate ≤ 20 ml/min and grafted artery diameter ≤1.5 mm</td>
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<td>Eagle et al. (2004), Circulation, USA [3] Systematic review and guideline (level 1a)</td>
<td>Aspirin is the drug of choice for prophylaxis against early saphenous vein graft closure. It is the standard of care and should be continued indefinitely given its benefit in preventing subsequent clinical events. (level of evidence: A)</td>
<td>Blood transfusions: aspirin group 900 ml vs placebo 725 ml, ( P = 0.006 )</td>
<td>The benefit of postoperative aspirin on SVG patency is lost when started &gt;48 h after surgery. Dosing regimens ranging from 100 to 325 mg daily appear to be efficacious. As the graft recipient coronary artery luminal diameter increases, SVG patency rates improve and the advantage of aspirin over placebo is reduced. Aspirin, given early after CABG (within 48 h) has been shown to reduce significantly subsequent mortality, MI, stroke, renal failure and bowel infarction</td>
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<td>Dunning et al. (2008), Eur J Cardiothoracic Surg, Europe [4] Systematic review (level 1a)</td>
<td>Recommendation: aspirin should be given postoperatively to all patients without contraindications after CABG to improve long-term vein graft patency</td>
<td>Platelet transfusion: aspirin group 42 + 3% vs placebo group 33 + 3%, ( P = 0.043 )</td>
<td>The superiority of clopidogrel over aspirin for optimizing graft patency after coronary artery bypass grafting has not yet been established and, thus, aspirin should be regarded as the drug of first choice</td>
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<td>Aspirin group 6.3 ± 1.6% vs placebo 2.4 ± 1.0%, ( P = 0.036 )</td>
<td>In patients having cardiac surgery for ACS, clopidogrel should be considered for 9–12 months in addition to aspirin (Grade B recommendation based on subanalyses of level 1b studies)</td>
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<td>Fail-safe mechanisms should exist to ensure</td>
<td>Clopidogrel (75 mg) is an acceptable alternative to aspirin for the optimization of vein graft patency after CABG (Grade B recommendation based on individual level 1b studies)</td>
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<td>Prompt postoperative initiation of aspirin therapy</td>
<td>The benefit of postoperative aspirin on SVG patency is lost when started &gt;48 h after surgery. Dosing regimens ranging from 100 to 325 mg daily appear to be efficacious. As the graft recipient coronary artery luminal diameter increases, SVG patency rates improve and the advantage of aspirin over placebo is reduced. Aspirin, given early after CABG (within 48 h) has been shown to reduce significantly subsequent mortality, MI, stroke, renal failure and bowel infarction</td>
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<td>Prospective controlled trials have demonstrated a graft patency benefit when aspirin was started 1, 7 or 24 h</td>
<td>Clopidogrel may further improve the patency of SVG when given in addition to aspirin, but this will be at the expense of an increase in bleeding complications (Grade B recommendation based on individual level 1a studies)</td>
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Table 1:  (Continued)

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<td>Stein et al. (2004), Heart, USA [10] Systematic review conference (level 1a)</td>
<td>Systematic review/conference</td>
<td>For all patients with coronary artery disease, we recommend aspirin, 75–162 mg/day, indefinitely (Grade 1A)</td>
<td>For patients with coronary artery disease undergoing CABG who are allergic to aspirin, we recommend clopidogrel, 300 mg, as a loading dose 6 h after operation followed by 75 mg/day p.o. (Grade 1C+)</td>
<td>Underlying values and preferences: This recommendation places a relatively high value on avoiding cardiovascular complications and a relatively low value on avoiding bleeding complications For patients undergoing CABG who have no other indication for VKA, we suggest clinicians not administer VKAs (Grade 2B) For patients undergoing CABG in whom oral anticoagulants are indicated, such as those with heart valve replacement, we suggest clinicians administer VKA in addition to aspirin (Grade 2C)</td>
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<td>Sanz et al. (1990), Thromb Res, Spain [8] Prospective double-blind placebo-controlled, randomized trial (level 1a)</td>
<td>927 consecutive patients randomized to either placebo Aspirin 50 mg or aspirin 50 mg tds and dipyridamole 75 mg tds First dose was given 7 h after operation All patients received preoperative dipyridamole 100 mg qds for 2 days and one dose 1 h after surgery All patients had angiography at 10 days surgery</td>
<td>Occluded distal anastomoses Patients with at least one occlusion Blood loss</td>
<td>Aspirin 14% asp + dipyrid 13%. Placebo 18%. ( P = 0.058 ) for aspirin</td>
<td>185 lost to follow-up (27 deaths) Randomization method not described Data not fully described in this paper Control group was no treatment rather than aspirin given 24 h after operation</td>
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<td>Chesebro et al. (1984), N Engl J Med, USA [12] Prospective double-blind placebo-controlled, randomized trial (level 1a)</td>
<td>202 patients randomized to receive aspirin 325 mg 7 h after surgery and dipyridamole 100 mg qds 2 days preoperatively and postoperatively 205 patients received placebo Angiography performed at 1 year</td>
<td>Patients with at least 1 occlusion at 1 year Occluded grafts at 1 year Blood loss</td>
<td>Aspirin 22%, placebo 47% Aspirin 11%, placebo 25% No data given</td>
<td>4 deaths Mean number of grafts in all patients was 2 Control group was no treatment rather than aspirin given 24 h after operation</td>
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<td>Sharma et al. (1983), Circulation, USA [9]</td>
<td>179 patients randomized to aspirin 975 mg/day, or aspirin</td>
<td>Graft patency at 1 year</td>
<td>Aspirin 78%, aspirin-dipyridamole 83%. Placebo 80%, ( P = NS )</td>
<td>80% angiograph rate</td>
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RESULTS

Gavaghan et al. in a double-blind placebo-controlled randomized study showed the highest efficacy of early postoperative aspirin (administered within 1 h of CAGB) in reducing the incidence of early and late vein graft occlusion. They also showed significant relative benefit of early aspirin for graft to vessel of calibre <1.25 mm or flow rate <20 ml/min and endarterectomy. However, this study also demonstrated that early aspirin is not associated with postoperative bleeding or increased transfusion [6].

Fremes et al. [5] in a meta-analysis of 17 randomized, controlled trials involving 4504 patients showed optimal benefit of early aspirin at 6 h. The study also demonstrated no evidence to suggest that postoperative early aspirin causes significant blood loss.

Sharma et al. in a prospective randomized double-blind trial demonstrated no benefit of early aspirin on vein graft patency after 48 h. This was true even in the patients at high-risk for graft occlusion, i.e. those who had small recipient coronary arteries and poor graft flows; patency rates were not improved by the antiplatelet agents after 48 h [9].

Paz et al. in a randomized trial of 927 patients with 1874 vein grafts identified predictors of early vein graft occlusion as female sex, obesity, history of congestive heart failure, rest angina, the vascularized artery, quality of distal bed, diameter of the graft artery, lack of antiaggregants and non-sequential graft technique [14].

Goldman et al. in a multicentred randomized trial of 489 patients showed that aspirin administered 12 h before CAGB caused significant blood loss, transfusion and reoperation.
also demonstrated that early postoperative aspirin reduces vein graft occlusion and is not associated with postoperative bleeding, unlike preoperative aspirin [7].

Eagle et al. in ACC/AHA practice guidelines suggest that aspirin is the drug of choice against early saphenous vein graft closure. Aspirin significantly reduces vein graft closure in the first postoperative year. They recommend that a mechanism should exist to ensure prompt initiation of aspirin. Prospective controlled trials have shown graft patency benefit when aspirin is administered within 1, 7 and 24 h, but no benefit after 48 h. Early aspirin has been shown to reduce significantly subsequent MI, bowel ischaemic, stroke, renal failure and mortality.

In true aspirin allergies, clopidogrel, ticlopidine and indobufen have been suggested as alternatives. However, warfarin did not demonstrate a consistent benefit for vein graft patency. Eagle et al. recommend that administration of aspirin within 48 h post surgery should be the standard of care. This systematic review also noted that the value of early aspirin on graft patency diminishes with increase in size of the grafted coronary artery [3].

Dunning et al. in EACTS guidelines on antiplatelet and anticoagulation therapy recommend that aspirin should be given within 24 h post CABG for optimization of vein graft patency. There was maximal benefit of aspirin the sooner it was given in the postoperative period. Giving aspirin 6 h postoperatively or when bleeding had settled was recommended as the optimal strategy. This was based on their ICVTS paper on the subject that provided the evidence. There was no demonstrable benefit of aspirin given after 48 h and none of the studies indicated a significant increase in postoperative bleeding as a result of early aspirin [4].

Stein et al. in the seventh ACCP conference on antithrombotic and thrombolytic therapy recommend aspirin, 75–162 mg/day, starting 6 h after operation over preoperative aspirin (Grade 1A). In patients in whom postoperative bleeding prevents the administration of aspirin at 6 h after CABG, they recommend starting aspirin as soon as possible thereafter (Grade 1C). For patients undergoing CABG, they recommend against addition of dipyridamole to aspirin therapy (Grade 1A). For patients with coronary artery disease undergoing CABG who are allergic to aspirin, the recommendation was clopidogrel, 300 mg, as a loading dose 6 h after operation followed by 75 mg/day p.o. (Grade 1C+). In patients who undergo CABG for non-ST-segment-elevation acute coronary syndrome, the conference recommended clopidogrel, 75 mg/day for 9–12 months following the procedure in addition to treatment with aspirin (Grade 1A). This recommendation places a relatively higher value on avoiding cardiovascular complications and a relatively low value on avoiding bleeding complications [10].

Gukop et al. in a prospective study showed that postoperative bleeding accounted for a significant non administration of early aspirin at 6 h as recommended by standard protocols. There was no demonstrable increased blood loss, transfusion or reoperation rate associated with early aspirin in this study [11].

**CLINICAL BOTTOM LINE**

There is significant evidence supporting postoperative aspirin within 6 h following CABG for optimization of vein graft patency [3,4,15]. Where aspirin is contraindicated, alternatives such as clopidogrel, ticlopidine and indobufen have been suggested by ACC/AHA. ACCP and EACTS guidelines.

ACC/AHA, ACCP and EACTS guidelines recommend administration of early aspirin or an alternative as the standard of care for optimization of vein graft patency [3,4,10]. Available evidence suggested an optimal dose of 325 mg of aspirin at 6 h or soon after bleeding settles, with a range of 75–325 mg daily subsequently [3,4,16]. The efficacy of postoperative aspirin for vein graft patency diminishes the later it is administered and there is no benefit when administered after 48 h [9].

Several randomized, controlled studies, including a meta-analysis, have shown that administration of postoperative aspirin following CABG is not associated with increased blood loss or transfusion requirement [5–7].

A prospective study identified postoperative bleeding as a significant reason for non administration of early aspirin. However, most of those bleeding were below the threshold for reexploration [11].

It is essential to define/quantify a bleeding threshold that precludes administration of early aspirin to avoid non essential delayed administration and guide judgement, especially in patients with higher risk factors for vein graft occlusion. Early aspirin has significant benefit in reducing vein graft occlusion, mortality, myocardial infarction stroke, renal failure and bowel infarction [3]. The efficacy of early aspirin is better the sooner it is administered.

Administration at 6 h is the optimal time to give aspirin as long as bleeding has settled.

**Conflict of interest:** none declared.

**REFERENCES**


