Medical audit

Current practice in the use of antiplatelet agents in the peri-operative period by UK vascular surgeons

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Background: There currently appears to be no firm consensus with regards to the use of antiplatelet agents during the peri-operative period in vascular surgical practice.

Methods: A nine-part questionnaire relating to peri-operative antiplatelet use was sent to 137 ordinary members of the Vascular Surgical Society of Great Britain and Ireland (VSS-GBI).

Results: Of the 137 questionnaires sent, 90 were returned (66%). For patients undergoing infra-inguinal bypass, carotid endarterectomy and varicose vein surgery, over 90% of vascular surgeons continue antiplatelet agents peri-operatively; however, in the case of aortic aneurysm repair, this figure is lower (77%). Three of the respondents stated that they would stop clopidogrel, but not aspirin, prior to surgery because of concerns over increased operative bleeding. In patients starting routine heparin prophylaxis against thrombosis, most surgeons opted to continue antiplatelet therapy (82%), although in patients requiring therapeutic heparin treatment, opinions were almost equally split. Most vascular surgeons (93%) would to start an alternative antiplatelet agent if a patient was intolerant of aspirin for gastrointestinal reasons.

Conclusions: Although the benefits of antiplatelet drugs in the long-term reduction of vascular events is established, evidence supporting their use in the peri-operative period is scarce. The general consensus of opinion from this survey suggests that most vascular surgeons do not stop antiplatelet drugs pre-operatively.

Key words: Antiplatelet – Vascular surgery – Questionnaire – Peri-operative

With a growing awareness in surgical practice that vascular disease is a systemic process, the multi-system benefits of antiplatelet agents have become better appreciated. Peripheral vascular disease is a marker of risk for cardiovascular mortality, and studies using aspirin in both cardiovascular and cerebrovascular disease have shown surprisingly consistent risk reductions in vascular events and death (~20%) that are seemingly independent of the population studied.¹ In arterial surgery, there is a particularly high incidence of cardiovascular mortality and morbidity, hence arousing interest in agents that provide

cardiovascular protection. Studies in aortic surgery have demonstrated that over 50% of postoperative deaths are attributable to coronary artery disease and a recent audit by the UK Vascular Anaesthetic Society found the peri-operative mortality for elective aneurysm repairs to be 7.3%.^{2,3}

Although evidence from meta-analyses confirms that long-term use of antiplatelet agents reduces the rate of myocardial infarction and ischaemic stroke in patients with symptomatic peripheral arterial disease (PAD), conclusive evidence is currently unavailable on the effect

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Regarding abdominal aortic aneurysms: *(please circle preferred answer)*

1. I usually prescribe antiplatelet agents to patients with an AAA without evidence of symptomatic peripheral vascular disease. YES / NO / UNSURE

2. I usually stop antiplatelet agents preoperatively. YES / NO / UNSURE
If yes – how many days preoperatively?

3. I usually re-start these agents as soon as the patient is able to eat and drink. YES / NO / UNSURE

Comments:

Regarding carotid endarterectomy

4. I usually stop antiplatelet agents preoperatively. YES / NO / UNSURE
If yes – how many days preoperatively?

If yes – I restart them within 24hrs of surgery. YES
- I restart them >24hrs post surgery. YES

Regarding infrainguinal bypass

5. I usually stop antiplatelet agents preoperatively. YES / NO / UNSURE
If yes – how many days preoperatively?

If yes to above and antiplatelet prophylaxis planned
- I restart them within 24hrs of surgery. YES
- I restart them >24hrs post surgery. YES

Other scenarios

6. I usually continue antiplatelet agents whilst the patient is on therapeutic heparin treatment. YES / NO / UNSURE

7. I usually continue antiplatelet agents whilst the patient is on subcutaneous heparin thrombosis prophylaxis. YES / NO / UNSURE

8. I usually stop antiplatelet agents preoperatively in a patient undergoing varicose vein surgery. YES / NO / UNSURE
If yes – how many days preoperatively?

9. In patients intolerant of aspirin for gastric reasons I usually:
Discontinue antiplatelet therapy. YES
Try an alternative antiplatelet agent. YES
Concomitantly prescribe a gastro-protective drug with aspirin. YES

Figure 1 Antiplatelet agent questionnaire.

of antiplatelet drugs in the peri-operative period in vascular surgery.^{1,4,5} In particular, it is unclear if the risk of bleeding outweighs the benefits produced by the inhibition of thrombosis. In addition, controversy exists over the management of patients who are intolerant of aspirin and in patients concurrently prescribed heparin. Our survey was designed to assess current antiplatelet use in the UK in these contentious areas.

Materials and Methods

A questionnaire (Fig. 1) was sent out to 137 ordinary members of the Vascular Surgical Society of Great Britain and Ireland (VSS-GBI). The names and addresses were

selected by highlighting every third ordinary member in sequence from the UK listed in the 2000 *VSS-GBI Handbook*. Ordinary members of the VSS-GBI who were selected, but who were clearly radiologists, were excluded.

The 9-part questionnaire was sent out with a stamped-addressed return envelope to the selected individuals. The first 5 questions related to antiplatelet agents in patients undergoing arterial procedures, questions 6 and 7 concerned the use of antiplatelet agents in patients on heparin, question 8 concerned varicose vein surgery and question 9 the management of patients intolerant of aspirin for gastrointestinal reasons. The questionnaire was intentionally limited to one side of A4 paper in an attempt to improve the response rate. The questions were intentionally phrased

Table 1 Discontinuation of antiplatelet agents pre-operatively

Operation	Discontinue	Continue	Unsure	n
Aortic aneurysm repair	22% (19)	77% (67)	1% (1)	87 (0*)
Carotid endarterectomy	8% (6)	91% (70)	1% (1)	77 (11*)
Infra-inguinal bypass	8% (7)	92% (80)	0% (0)	87 (1*)
Varicose vein surgery	7% (6)	92% (79)	1% (1)	86 (0*)

*Indicates the number of vascular surgeons not performing these procedures.

Table 2 Number of days pre-operatively that antiplatelet agents were discontinued

Operation	Mean (days)	Median (days)	Range (days)	n
Aortic aneurysm repair	7.3	7	2–14	19
Carotid endarterectomy	3.2	2.5	1–6	6
Infra-inguinal bypass	7.1	7	2–14	7
Varicose vein surgery	7.2	7	3–14	6

'usually' so that respondents did not feel that their answers had to hold in all eventualities. The questionnaires were sent out in September 2001 and the closing date for responses was 12 weeks later. The questionnaire responses were anonymous and, therefore, no reminders were sent.

Results

Of the 137 questionnaires sent, 90 were returned (66%). Two forms were returned uncompleted; the first was from a general surgeon who no longer performs vascular surgery and the second by a VSS-GBI member who is not a vascular surgeon. Of the other 88 respondents, 6 did not complete either one or two of the nine questions on the form. Ten of the 88 vascular surgeons omitted the question regarding carotid endarterectomy and one omitted the infra-inguinal bypass question, as they do not routinely perform these procedures.

Use of antiplatelet agents in the peri-operative period

The great majority of vascular surgeons do not stop antiplatelet agents prior to carotid endarterectomy and infra-inguinal bypass (Table 1). However, almost a quarter of vascular surgeons routinely stop antiplatelet agents prior to abdominal aortic aneurysm repair. Three of the respondents specifically stated that they would discontinue clopidogrel 5–7 days pre-operatively due to increased bleeding problems, although all of these particular surgeons indicated that they would not stop aspirin. There was a wide range in the number of pre-operative days that antiplatelet agents were stopped (Table 2) and then re-started (Table 3). In the case of aortic abdominal aneurysm (AAA) repair, 88% of surgeons who stop antiplatelet agents pre-operatively would re-start the drugs when the patient was able to eat or drink.

Antiplatelet agent prescription in patients being prescribed heparin

In patients receiving prophylactic heparin, most surgeons opted to continue antiplatelet therapy (82% *versus* 16%, and 2% unsure), although in patients on therapeutic heparin treatment opinions were almost equally split between those opting to stop or continue antiplatelet agents (51% *versus* 47%, respectively).

Antiplatelet agents in patients intolerant of aspirin for gastrointestinal reasons

Of the three options offered in the questionnaire (Fig. 1), 93% of surgeons stated that they would prefer to start an alternative antiplatelet agent in a patient intolerant of aspirin for gastrointestinal reasons, 16% would continue aspirin with addition of a gastroprotective drug and only 9% would discontinue antiplatelet therapy completely. Several surgeons selected more than one option to represent their usual practice, hence the total number of responses was greater than 100%.

Use of antiplatelet agents in patients with abdominal aortic aneurysms

Of the responding vascular surgeons, 39% routinely prescribe antiplatelet agents to patients with aortic aneurysms

Table 3 Days pre-operatively for re-starting antiplatelet agents

Operation	< 24 h	> 24 h	n
Carotid endarterectomy	67% (4)	33% (2)	6
Infra-inguinal bypass	57% (4)	43% (3)	7

In the case of aortic aneurysm repair, 88% of surgeons stated that they would re-start antiplatelet agents as soon as the patient was able to eat and drink.

without evidence of symptomatic peripheral arterial disease, 60% did not and only 1% were unsure.

Patterns of practice in those surgeons stopping antiplatelet agents pre-operatively

All surgeons that stopped antiplatelet agents pre-operatively for one or more of the arterial procedures stopped them for an aortic aneurysm repair. Only 6 of these 19 surgeons stopped antiplatelet agents consistently for all three of the arterial procedures surveyed. Three surgeons stated that they do not stop these agents for carotid endarterectomy, but do for the other two arterial procedures; similarly, one surgeon did not stop antiplatelet agents for infra-inguinal bypass, but did stop them for carotid endarterectomy and aortic aneurysm repair.

Discussion

Evidence from large trials evaluating the peri-operative risks and benefits of antiplatelet agents is scarce. We were unable to find any large trials in peripheral vascular surgery primarily designed to assess the peri-operative effects of antiplatelet agents. In deciding whether to continue antiplatelet agents in the peri-operative period, two fundamental questions need to be addressed: (i) what effect do antiplatelet agents have in reducing cardiovascular mortality and morbidity, in patients undergoing vascular surgery; and (ii) to what extent are additional bleeding complications caused by antiplatelet therapy in the peri-operative period? Interestingly, we found that the mean time for antiplatelet agents to be stopped pre-operatively for carotid endarterectomy was much shorter than for the other procedures (Table 2). This probably represents a heightened awareness among vascular surgeons of the potential disastrous consequences of thrombotic, rather than bleeding, complications for this particular procedure.

The number of studies in vascular surgery assessing antiplatelet agents and bleeding complications is small, and few have assessed it as the primary study design. In one large multicentre trial looking at the effect of aspirin plus dipyridamole *versus* placebo in 549 patients undergoing saphenous vein femoropopliteal bypass, no difference in patency rate was demonstrated between the two groups.⁶ There was, however, a reduction in myocardial infarction (MI) and stroke in patients randomised to the antiplatelet drugs and, in addition, the rate of re-operation for bleeding was almost double in the aspirin plus dipyridamole group although this did not reach statistical significance ($P = 0.13$). Likewise, there was no difference in the incidence of wound haematomas or gastrointestinal bleeding. The majority of data available on operative adverse bleeding events from antiplatelet drugs originates from cardiac surgery. In a large case-control study of 8641 consecutive

patients undergoing coronary artery bypass grafting, the odds ratio for a reduction of in-hospital mortality with pre-operative aspirin therapy was 0.73 ($P = 0.03$).⁷ In this study, no significant difference was seen in the quantity of chest tube drainage, transfusion requirement or need for re-exploration due to haemorrhage.

Several articles have been published reporting increased peri-operative bleeding with clopidogrel and the manufacturers have recommended caution with the use of clopidogrel in patients undergoing major surgery.⁸⁻¹⁰ In our survey, only three vascular surgeons (4%) stated that they would stop clopidogrel pre-operatively but not aspirin, due to concerns over operative bleeding. This may be because there is currently a lack of randomised trial data concerning clopidogrel in peripheral vascular surgery. However, in an observational study from Philadelphia, consisting of 403 consecutive patients undergoing coronary artery bypass grafting (CABG), those that received thienopyridines (ticlopidine or clopidogrel) within 3 days of surgery ($n = 76$) had a significantly increased requirement for surgical re-exploration due to excessive bleeding ($n = 327$; 10.5% *versus* 2.4%; $P = 0.001$).⁸ The thienopyridine-treated group also required a greater quantity of blood products (49% *versus* 35%; $P < 0.05$).⁸

The combination of heparin and antiplatelet agents is commonplace in cardiological practice for the prevention of thrombotic events in patients with acute coronary syndromes.¹¹ Following discussion with vascular colleagues, it became clear that a difference in opinion exists on the role of antiplatelet drugs in patients either commencing on heparin for thrombo-embolic prophylaxis or therapeutic reasons. Our survey identified that the majority of surgeons continue antiplatelet drugs in patients prescribed routine heparin for thrombo-embolic prophylaxis; however, opinions were almost equally split for patients requiring therapeutic heparin treatment. Evidence supporting the use of heparin in reducing peri-operative events in vascular surgery comes from a randomised multicentre study from the Joint Vascular Research Group, who found that intraoperative heparin significantly reduced the risk of fatal and non-fatal MI, yet blood loss was not significantly affected.¹²

Our survey has demonstrated that over a third of vascular surgeons would prescribe an antiplatelet agent to a patient with an aortic aneurysm without evidence of symptomatic peripheral arterial disease. Data from the UK Small Aneurysm Trial demonstrated that patients with aortic aneurysms and a reduced ankle brachial pressure index (ABPI) have an increased mortality, particularly for cardiovascular causes (66% of deaths).¹³ The overall death rate per 100 patients/year for each tertile of ABPI was 11.6 (ABPI < 0.87), 6.9 (ABPI 0.87–1.02) and 6.2 (ABPI > 1.02), and an ABPI < 0.87 was strongly associated with cardiovascular death, and the adjusted hazard ratio for each 0.2 unit

decrease in ABPI was 1.28 (95% CI, 1.11–1.38).¹³ A systematic review considering the balance between benefit and harm from aspirin treatment determined the threshold at which patient benefit exceeds harm to be 1.5% events per year in primary cardiovascular prevention.¹⁴ Most patients with PAD and an AAA exceed this rate and probably justify antiplatelet prophylaxis.

Although not related directly to the peri-operative period, we were eager to survey the management of patients with gastric intolerance of aspirin. When gastric intolerance occurs, the choices are to: (i) change to another agent, with clopidogrel currently being the agent of choice; (ii) start a gastroprotective drug; or (iii) discontinue antiplatelet therapy completely. Large studies such as CAPRIE have demonstrated that clopidogrel has a lower rate of gastrointestinal bleeding complications than aspirin. However, this trial did not include patients who were intolerant of aspirin or had a history of dyspepsia; therefore, this can only be used as indirect evidence that clopidogrel is a safer option in patients who are intolerant of aspirin.¹⁵ However, the majority of vascular surgeons in our survey favoured this option. The combined use of a gastroprotective drug with aspirin therapy is an alternative method of managing the patient intolerant of aspirin for gastrointestinal reasons, but the relative reduction in bleeding complications with this drug combination in patients intolerant of aspirin alone is presently unknown. Some concern must also be voiced over the long-term effect of gastric acid suppression with proton pump inhibitors and H₂ blockers.^{16,17} Discontinuing antiplatelet therapy completely cannot be recommended as it is preferable that these patients continue antiplatelet therapy for prophylaxis against secondary vascular events.

Conclusions

This survey has demonstrated that, in carotid and peripheral arterial surgery, the great majority of vascular surgeons continue antiplatelet agents peri-operatively; however, in the case of aortic aneurysm surgery, this consensus is less strong. The study has also demonstrated that the most popular management option in patients with gastrointestinal intolerance of aspirin is using alternative antiplatelet agent. With the growing acceptance of the benefits of antiplatelet agents in reducing the rate of myocardial infarction and stroke in vascular patients, it may become increasingly difficult to conduct large, placebo-controlled, peri-operative trials of antiplatelet agents. As a consequence, vascular surgeons will need to continue balancing the risks and benefits of antiplatelet drugs for individual patients undergoing vascular surgery, and extrapolate the results of data obtained in comparable clinical contexts. The controversy that exists may become

more complex in the future with the advent of newer and more effective antithrombotic agents as well as the use of existing agents in combination with aspirin.¹⁸

References

1. Anon. Collaborative meta-analysis of randomised trials of antiplatelet therapy for the prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324**: 71–86.
2. Johnston KW. Nonruptured abdominal aortic aneurysm: six-year follow-up results from the multicenter prospective Canadian aneurysm study. Canadian Society for Vascular Surgery Aneurysm Study Group. *J Vasc Surg* 1994; **20**: 163–70.
3. Bayly PJ, Matthews JN, Dobson PM, Price ML, Thomas DG. In-hospital mortality from abdominal aortic surgery in Great Britain and Ireland: Vascular Anaesthesia Society audit. *Br J Surg* 2001; **88**: 687–92.
4. Robless P, Mikhailidis DP, Stansby G. Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with peripheral vascular disease. *Br J Surg* 2001; **88**: 787–800.
5. Jackson M, Clagett P. Antithrombotic therapy in peripheral arterial occlusive disease. *Chest* 2001; **119** (Suppl 1): 283S–99S.
6. McCollum C, Alexander C, Kenchington G, Franks PJ, Greenhalgh RM. Antiplatelet drugs in femoropopliteal vein bypasses: a multicenter trial. *J Vasc Surg* 1991; **13**: 150–61.
7. Dacey LJ, Munoz JJ, Johnson ER, Leavitt BJ, Maloney CT, Morton JR *et al*. Effect of preoperative aspirin use on mortality in coronary artery bypass grafting patients. *Ann Thorac Surg* 2000; **70**: 1986–90.
8. Swarup V, Oh CJ, Richard EN, Fischman DL, Savage MP. Risk of post-operative hemorrhage associated with ticlopidine or clopidogrel use prior to coronary artery bypass grafting. *Circulation* 2000; **102** (Suppl 2): II-648.
9. Hongo R, Ley J, Yee R. Impact of preoperative clopidogrel in coronary artery bypass grafting. *Circulation* 2000; **102** (Suppl 2): II-555.
10. Yende S, Wunderink R. Effect of clopidogrel on bleeding after coronary artery bypass surgery. *Crit Care Med* 2001; **29**: 2271–5.
11. Fragmin during Instability in Coronary Artery Disease (FRISC) Study Group. Low-molecular-weight heparin during instability in coronary artery disease. *Lancet* 1996; **347**: 561–8.
12. Thompson JE, Mullee MA, Bell PR, Campbell WB, Chant AD, Darke SG *et al*. Intraoperative heparinisation, blood loss and myocardial infarction during aortic aneurysm surgery: a Joint Vascular Research Group Study. *Eur J Vasc Endovasc Surg* 1996; **12**: 86–90.
13. Powell JT, Brady AR, Thompson SG, Fowkes FGR, Greenhalgh RM. Are we ignoring the importance of ankle pressures in patients with abdominal aortic aneurysm? *Eur J Vasc Endovasc Surg* 2001; **21**: 65–9.
14. Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. *Heart* 2001; **85**: 265–71.
15. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; **348**: 1329–39.
16. Weinstein WM. Proton pump inhibitors and *H. pylori* infection: why the concern? *Curr Gastroenterol Report* 1999; **1**: 507–10.
17. Pohl T, Domschke W. Results of short- and long-term medical treatment of gastroesophageal reflux disease (GERD). *Langenbecks Arch Surg* 2000; **385**: 317–23.
18. The Clopidogrel in Unstable angina to prevent Recurrent Events investigators C. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345**: 494–502.