The case for preoperative aspirin administration in patients undergoing elective CABG: is it open or closed?

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Aspirin is one of the most widely used and commonly prescribed medications in the world. It was first approved by the US Food and Drug Administration (FDA) in 1985 for the secondary prevention of cardiovascular events in patients following an acute myocardial infarction (MI) (1) and continues to be prescribed widely for patients with and those at heightened risk for atherosclerotic cardiovascular disease (ACVD)-related events.

Aspirin inhibits the synthesis of platelet thromboxane A_2 and reduces platelet assembly and aggregation at sites of vascular injury (2). Thromboxane A_2 is the end-product of an enzymatic conversion that begins with arachidonic acid being converted to prostaglandin H2 by cyclooxygenases (COX1 & COX2). Only COX1 is found within platelets. These prostaglandins are subsequently converted by specific synthases to down-stream prostaglandins, including prostaglandin I2, E2, D2, and F2α and thromboxane A_2 (3). Aspirin irreversibly inhibits the binding of arachidonic acid to COX1 and subsequently prevents the formation of thromboxane A_2. Since platelets cannot regenerate COX1, the resumption of platelet activity depends on bone marrow production of new platelets (4).

Aspirin has been studied extensively in the treatment of patients with acute coronary syndrome (ACS) (5,6), yielding a reduction in death and nonfatal MI. A large and widely cited meta-analysis of aspirin use for secondary prevention in patients with a history of MI, stroke, transient ischemic attack or other high risk conditions (unstable angina, stable angina, peripheral vascular disease) was conducted by the Antiplatelet Trialists' Collaborators. They identified a significant reduction of non-fatal MI (one third reduction) and vascular death (one sixth) among these high risk patients (7). Accordingly, aspirin has become a mainstay in

the treatment of patients with established ACVD.

What is the current position on preoperative aspirin administration?

Because patients with ACVD on aspirin therapy may at times require cardiac or non-cardiac surgery, decisions surrounding antiplatelet medications in the perioperative period have been emphasized in several contemporary management guidelines. These guidelines are summarized in *Table 1*. Considered collectively, a consistent message for preoperative aspirin administration among patients undergoing CABG is lacking. Does this represent true equipoise or a lack of randomized clinical trial-based evidence?

What is the evidence?

Myles and colleagues recently conducted a much-needed and thought-provoking study, "Stopping *vs*. Continuing Aspirin before Coronary Artery Surgery-(ATACAS)" (13)— a randomized trial of 27 patients scheduled for elective CABG, but who were considered to have increased risk for cardiovascular and other serious post-operative events based on either age >70 years, left ventricular impairment, concomitant valvular or aortic surgery, redo-cardiac surgery, chronic obstructive lung disease (COPD), renal impairment, obesity, pulmonary hypertension, or peripheral vascular disease. Aspirin taken within 4 days of surgery was an exclusion. Eligible patients were then randomized, employing a 2-by-2 factorial design, to aspirin versus placebo and tranexamic acid versus placebo. Patients received either 100 mg enteric-coated aspirin or placebo within 1 to 2 hours

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Table 1 Summary of guidelines

Society	Noncardiac pre-operative recommendations	Noncardiac postoperative recommendations	Cardiac surgical preoperative recommendations	Cardiac surgical postoperative recommendations
American College of Cardiology/American Heart Association (ACC/AHA)	Reasonable to continue aspirin if benefits outweigh risk (IIb); not beneficial in noncardiac elective surgery (III) (8)	Not addressed	Continue aspirin (Ia, level B) (9)	Given within 6 hours post-op and continued indefinitely (class I, level A) (9)
Society of Thoracic Surgery (STS)	Reasonable to continue aspirin except in patients with a high risk of bleeding (IIa) (4)	Not addressed	No recommendations given for stable patients	Given within 6–24 hours post-op (class I, level A) (4)
European Society of Cardiology (ESC)	Aspirin continuation may be considered on an individual basis (IIb); aspirin should be discontinued in those whom hemostasis would be difficult (10)	Not addressed	Continue aspirin (IC) (10)	Restarted within 24 hours, preferably 6 hours (IB) (11)
American College of Chest Physicians (ACCP)	Moderate to high risk patients: continue aspirin (IIC); low risk patients: stop aspirin 7–10 days prior (IIC) (12)	Not addressed	Continue aspirin (IIC) (12)	Not addressed

All guidelines referenced address patients without a coronary stent within 6 weeks.

of surgery. Patients received postoperative aspirin according to the practices at the participating hospitals. The median time to postoperative aspirin in the aspirin group was 18.5 hours (interquartile range, 12.3–22.9) and was 18.8 hours (interquartile range, 13.1–23.5) in the placebo group. The primary outcome was a composite of death and thrombotic events (including nonfatal MI). MI was defined as a rise of troponin or creatine kinase (CK)-MB plus as least one of the following: ischemic symptoms, development of pathological Q waves on a surface 12-lead electrocardiogram (ECG), or ST segment elevation or depression; or a significant rise in troponin I (>10 ng/mL), troponin T >4.0, or CK-MB >3 times the upper limit of normal in patients with no Q waves. Secondary outcomes included death, nonfatal MI, major hemorrhage (requiring surgical exploration), cardiac tamponade, and need for transfusion. Postoperative antiplatelet medication was managed according to local hospital practice.

Overall, there were no significant differences between study groups for either the primary or secondary outcome measures. A primary outcome occurred in 202 (19.3%) of aspirin-treated patients versus 215 (20.4%) in the placebo group [risk ratio: 0.94; 95% confidence interval (CI): 0.80–1.12; P=0.55]. Reoperation for hemorrhage occurred in 19 (1.8%) patients in the aspirin group and 22 (2.1%) patients in the placebo group (risk ratio: 0.87; 95% CI: 0.47–1.60; P=0.75). There was not a significant difference in blood product transfusion rates between groups. The investigators

concluded that administrating aspirin preoperatively did not increase the risk of bleeding nor decrease the risk of death or MI. The findings from the tranexamic acid arm of the study have not yet been published.

The ATACAS study represents the largest randomized clinical trial performed to date that was designed to answer a question encountered regularly in clinical practice. Accordingly, the investigators and participating sites should be acknowledged for their meaningful contribution; however, we believe that it is important for clinicians to better understand the patients and conditions, also common in daily patient care, not represented in the study, as well as several potential limitations that collectively lead us to conclude that there are opportunities for future research undertakings i.e., the case is open.

What was the primary take-home message?

The overall findings of ATACAS suggest that aspirin, administered within 1–2 hours of elective CABG, neither reduces the incidence of post-operative MI, stroke or death nor increases the risk of major bleeding or blood product transfusion, in stable patients.

Was the chosen primary endpoint optimal?

The primary safety and efficacy endpoints of ATACAS, considered collectively, represent many of the post-operative

events that impact patient outcomes, length of hospital stay, resource utilization and cost. The missing endpoint that many cardiologists and cardiac surgeons would find important is early (within the first 30 days) saphenous vein occlusion (14). Vein graft harvesting causes endothelial disruption (injury) and localized platelet activation. The primary endpoint of MI would likely capture some of these events, but many could have been missed due to "silent" graft occlusion—i.e., no ECG changes or cardiac enzyme elevations. While the study would have been more complex and costly if routine coronary angiography or cardiac computed tomography (CT) angiography was included, the early equivalent of incomplete revascularization is known to be associated with less favorable clinical outcomes (15).

Was the preparation and timing of aspirin administration prior to CABG optimal?

The investigators chose to use an enteric-coated aspirin preparation. In settings where a rapid onset of platelet inhibition is required, non-enteric coated aspirin represent the standard of care. A study evaluating the pharmacokinetics of enteric versus non-enteric coated aspirin given orally at a dose of 325 mg to healthy subjects showed that it took 30 minutes for maximum thromboxane A_2 inhibition with the non-enteric coated preparation compared to 240 minutes for the enteric coated preparation. The thromboxane activity decreased by only 20% within 30 minutes with the enteric coated tablet, which is not sufficient to prevent thromboxane-related platelet aggregation (16). Patients participating in the "Continuing *vs.* Stopping Aspirin" study were given a 100 mg enteric coated aspirin 1–2 hours prior to surgery. Based on the well-known pharmacokinetics of aspirin, there is a high likelihood that there was not sufficient time to reach Cmax and maximum platelet inhibition prior to the start of the surgery. Once surgery begins and the patient is placed on cardiopulmonary bypass, local concentrations and related pharmacodynamics effects i.e., at coronary sites of plaque of newly placed bypass conduits would be quite low.

At least one study evaluating the bioequivalence of different aspirin formulations found that enteric coated aspirin had a higher rate of incomplete thromboxane inhibition compared to dispersible aspirin and an even higher rate of attenuated effects among subjects of high body weight (17). In the study by Myles and colleagues, the mean weight in the aspirin group was 85 kg, which, extrapolating to the work of Cox cited above, corresponds

to a 20–30% probability of suboptimal (sub-threshold) platelet inhibition.

Was it wise to stop aspirin prior to CABG?

This study had a higher than expected rate of MI in both groups. The ATACAS investigators speculate that this was the end-result of closer monitoring and increased troponin surveillance i.e., higher detection rate. Could this actually be because aspirin was stopped in many patients at least 4 days prior to surgery, leading to a higher risk of complications? By stopping aspirin early, there could have also been patients who were excluded from participating in the study if they experienced a coronary event in the interim before CABG. This would have biased the outcomes. Perhaps there is a separate take-home message that applies to some high-risk patients- aspirin should not be stopped prior to CABG.

What is the optimal approach to aspirin administration in high-risk patients?

Where does this leave us in terms of treatment and management in the future? Most of the guidelines do not advocate stopping aspirin in ACS, which was not the focus of ATACAS. A previously conducted cohort study found that disruption of antiplatelet therapy portended worse outcomes-particularly in patients with ACS when compared to nonusers and patients remaining consistently on antiplatelet therapy (18). In ATACAS preoperative aspirin administration was not associated with a greater risk of major bleeding and blood product use. Does this support the hypothesis that aspirin given 1–2 hours before placing a patient on cardiopulmonary bypass does not achieve a platelet-inhibiting effect?

What are the best next steps?

It will be interesting to review the data from the tranexamic acid arm of ATACAS; however, given the lack of either a bleeding signal or reduction in clinical thrombotic and other major post-operative events it may be challenging to interpret and translate the findings with respect to preoperative aspirin use. Additional randomized clinical trials employing a strategy of non-enteric coated aspirin given ~4–6 hours prior to CABG may be instructive. Large-scale registries and pragmatic trials of patients undergoing CABG either on aspirin or not on aspirin may also provide

complementary and hypothesis-generating observations.

Aspirin is a mainstay in the management of patients with ACVD. The findings from ATACAS suggest that aspirin, given 1–2 hours before elective CABG is neither beneficial nor harmful. Clinicians must always use sound judgement in patient care, prescribing aspirin to patients who stand to benefit from its antithrombotic effects and those in whom the risk outweighs the benefit. Though not tested in ATACAS, we recommend continuing aspirin in patients with ACS up to the time of surgery. In addition, all patients undergoing CABG should receive aspirin post-operatively-typically within 6–12 hours of surgery unless hemostasis has not been successfully achieved. Although a century in the making, aspirin and its optimal use in clinical practice remains somewhat of a mystery—the case is far from closed.

Acknowledgements

Footnote

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