Commentary

To stop or continue aspirin before aortocoronary bypass operations—do we have enough evidence to adequately guide us?

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Aspirin is a cornerstone in secondary prevention of myocardial infarction (MI) and reduces mortality and ischemic events after coronary artery bypass grafting (CABG) (1,2). In patients with coronary artery disease, discontinuation of aspirin has been associated with an overall threefold increased risk of major adverse ischemic events and a ninetyfold increased risk in patients after coronary artery stenting (3).

Aspirin exerts its antiplatelet effect by irreversible acetylation of the serine residue (Ser 529) in cyclooxygenase (COX)-1 that prevents binding of arachidonic acid to the catalytic site (Tyr 385), thereby inhibits the synthesis of prostaglandin (PG) H_2. Subsequently, generation of thromboxane (Tx) A_2 and TxA_2-induced platelet aggregation are inhibited for the lifespan of the platelet (4). In addition, aspirin influences clot integrity by altering clot permeability and also exerts dose dependent effects on platelets that are independent of its effect on COX-1 (5). Since aspirin irreversibly inhibits platelet COX-1, it takes 8–10 days to achieve pretreatment levels of platelet aggregation after cessation of aspirin therapy (4). However, aspirin-induced platelet inhibition carries an increased risk of surgery-related bleeding and transfusion requirements particularly in cardiac surgery due to potentially untoward effects of cardiopulmonary bypass which triggers dilution, fibrinolysis and platelet dysfunction (6-9).

Today, there is ample evidence of a graded association between bleeding and transfusion requirements and both increased morbidity and mortality, after cardiac and non-cardiac surgery (10,11). Hemodynamic compromise, the need to discontinue antiplatelet drugs and the inherent risks of transfusion comprise the pivotal underlying mechanisms (12).

A large observational multicenter trial including 5,065 patients demonstrated that mortality was 1.3% among patients who received up to 650 mg aspirin within 48 hours after CABG as compared with 4.0% among those, who did not receive aspirin (P<0.001). Additionally, aspirin therapy was associated with a substantial decrease in non-fatal ischemic events, reducing the relative risk of MI, stroke, renal failure and bowel infarction by 48% to 74%. Importantly, early postoperative aspirin was not associated with an increased risk of bleeding (2).

Current professional guidelines consistently recommend administering aspirin to stable non-bleeding patients within 6–24 hours after CABG (13-15). However, driven by the concern of increased CABG-related bleeding, its well-known untoward effects on outcome and the lack of large clinical trials showing uniform anti-ischemic benefit of aspirin, the same professional guidelines issue disparate recommendations regarding preoperative discontinuation *vs.* perioperative continuation of aspirin and aspirin dose in patients with stable coronary artery disease (13-16).

The analysis of Cleveland Clinic database demonstrated that among 1,519 propensity matched patients undergoing isolated non-emergent CABG, those on aspirin within 5 days preoperatively had a similar incidence of ischemic events as compared to those patients who had discontinued aspirin ≥6 days preoperatively (1.8% *vs.* 1.7%). However, late discontinuation was associated with higher intraoperative (23% *vs.* 20%; P=0.03) and postoperative transfusion requirements (30% *vs.* 26%; P=0.009) but similar re-

thoracotomy rates (3.4% *vs.* 2.4%; P=0.10). Patients routinely were administered tranexamic acid (7).

In contrast, a recent meta-analysis by Hastings *et al.* included 13 randomized trials including 2,399 patients undergoing first-time isolated CABG and assigned to preoperative aspirin *vs.* placebo, demonstrated anti-ischemic benefits of aspirin at the cost of increased bleeding. While aspirin within 7 days before surgery reduced the odds of MI by 44%, it had no overall effect on mortality but increased postoperative chest tube drainage and volume of red blood cell transfusion and nearly doubled re-thoracotomy rate. Preoperative aspirin dose varied from 80 to 2,600 mg daily, antifibrinolytic use was inconsistent and postoperative aspirin regiments varied and were inconsistently reported (9).

The recently published aspirin and tranexamic acid for coronary artery surgery (ATACAS) study is a double blind randomized multicenter trial with the aim to determine whether preoperative aspirin would reduce the incidence of death or thrombotic complications in patients scheduled for on-pump or off-pump CABG with or without concomitant valve replacement (17). This study also assessed effects of tranexamic acid. In the accompanying publication by Sun *et al.*, the results of the ASA trial are reported. Patients were eligible if they had not taken aspirin within 5 days before CABG. Warfarin and $P2Y^{12}$ receptor inhibitors had to be stopped 7 days preoperatively. Intra- and postoperative transfusion was based on prespecified transfusion triggers and an algorithm defined management of excessive bleeding after cardiopulmonary bypass. Postoperative aspirin was administered in accordance with institutional guidelines. A 2-by-2 factorial design was used to randomize patients to aspirin (n=1,047; 100 mg one to two hours preoperatively) or placebo (n=1,053) and tranexamic acid or placebo.

In the current analysis, preoperative aspirin did neither reduce the composite of death and thrombotic events (nonfatal MI, stroke, pulmonary embolism, renal failure or bowel infarction) as compared to placebo (19.3% *vs.* 20.4%; P=0.55) nor did it increase major bleeding necessitating re-thoracotomy (1.8% *vs.* 2.1%; P=0.75). Transfusion rates did not differ between aspirin and placebo groups. Patients had a low frequency of prior MI. The lack of an adverse effect of aspirin on bleeding may be attributed to an overall low risk patient population (mean EuroSCORE 4.1±2.9 *vs.* 4.2±8), low single dose aspirin and use of tranexamic acid in half of the patients. The lack of efficacy of aspirin therapy may also have been influenced by the intrinsic thrombogenicity of the population with a low frequency of patients with prior MI. Tranexamic acid competitively inhibits the lysine binding sites on plasminogen and fibrinogen, thereby preventing cleavage of fibrinogen and platelet dysfunction. Evidence from a large meta-analysis including 10,488 patients underlines efficacy of tranexamic acid in reducing bleeding in cardiac and non-cardiac surgery (18).

Updates of professional guidelines committee will determine the weight given to the disparate findings of the Hastings meta-analysis and the ATACAS study. Perhaps they will find harmony in their interpretation in low-risk patients without prior MI- preoperative aspirin therapy may not be helpful. However, in patients with proven heightened thrombogenicity (i.e., those with prior MI), preoperative aspirin may be recommended.

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Footnote

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