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Insights into myocardial infarction after noncardiac surgery in patients with a prior coronary artery stent

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Physicians commonly encounter patients undergoing noncardiac surgery who have previously received a coronary artery stent.[1] Several large observational studies have demonstrated that patients who have a coronary artery stent within the six months before noncardiac surgery have an increased risk of perioperative myocardial infarction (MI).[2 3] MI is the most common major vascular complication after noncardiac surgery, and it substantially increases a patient's risk of 30-day mortality.[4 5]

Among patients with a coronary artery stent who undergo noncardiac surgery, uncertainty exists regarding the mechanism of MI and how to prevent this complication. Dr. Wasowicz and colleagues[6] report a study in the April issue of the British Journal of Anaesthesia that provides insights into these two important issues. These investigators have conducted one of the few prospective cohort studies evaluating patients who have a coronary artery stent and subsequently undergo noncardiac surgery.[6]

They performed perioperative platelet function testing using a Platelet Mapping Assay (PMA) to test their hypothesis that adequate platelet inhibition would reduce the incidence of the primary outcome of major adverse cardiac events (i.e. MI, congestive heart failure, in-stent thrombosis, coronary revascularization, or death) within 30 days after noncardiac surgery. Strengths of their study include: the systematic daily ECG and troponin measurements for five days after surgery; and blinding of outcome assessors to the PMA results. Their findings, of declining levels of platelet inhibition the longer anti-platelet drugs were held before surgery, support that PMA was measuring platelet inhibition.

Investigators at three Canadian hospitals included 209 patients who received a bare metal stent within two yrs, or a drug eluting stent within any time frame before noncardiac surgery. Eight patients were not tested and were therefore not included in the final analyses. Baseline therapy included dual antiplatelet therapy in 161 patients (80%); however, 66 patients (33%) stopped taking aspirin more than three days before surgery, and only 35 patients (17%) received clopidogrel within five days of surgery.

A major adverse cardiac event occurred in 40 patients (20%). Although the authors used a broad composite endpoint, most of the events were MI; 32 patients (16%) suffered a non-ST-segment elevation MI (NSTEMI), and four patients (2%) experienced an ST-segment elevation MI (STEMI). It is fortunate that MI dominated the primary outcomes (i.e. MI represented 90% of the primary outcomes), because the relationship between platelet inhibition and major adverse cardiac events may vary across the individual outcomes. Most MIs (21 of the 36 MIs, 58%) occurred within 24 h after surgery, and ECG localization suggested that 75% of the MIs occurred in the territory supplied by the stented coronary artery.

In contrast to the authors' hypothesis, multivariable logistic regression did not demonstrate an association between the percentage of platelet inhibition before surgery (evaluated as a continuous variable) and the primary outcome (i.e. odds ratio, 1.00; 95% CI, 0.99–1.02). Moreover, comparing patients who did and did not suffer a major adverse cardiac event, the authors demonstrated no difference in the median percentage of platelet inhibition based on aspirin and clopidogrel separately at three time points (i.e. just before surgery, in the post anaesthesia care unit, and the day after surgery), with one exception. The median percentage of clopidogrel platelet inhibition at 24±4 h after surgery was higher in patients who suffered the primary outcome compared with patients who did not suffer this outcome (56.9 *vs* 36.7, P=0.001).

Based on their finding that the majority of MIs were NSTEMIs, the authors suggest that this indicates a supply-demand mismatch mechanism; however, a diagnosis of NSTEMI is not pathognomonic of supply-demand mismatch. Intracoronary optical coherence tomography (OCT) is the most advanced intra-coronary imaging

modality to detect thrombosis in a coronary artery.[7] Dr. Ino and colleagues[7] performed intracoronary OCT in 49 patients who experienced an NSTEMI in the non-operative setting, and 32 patients (65%) demonstrated a coronary artery thrombus. Therefore even patients suffering an NSTEMI may have coronary artery thrombus as the mechanism.

Although ECG evidence of NSTEMI does not inform the mechanism of perioperative MI in patients with a coronary artery stent, other findings in the study by Dr. Wasowicz and colleagues appear to support their position that the majority of MIs were because of supply-demand mismatch.[6] First, there was substantially more intraoperative blood loss (853 mls *vs* 295 mls, *P*=0.0001) and a higher risk of receiving ≥2 units of blood (35 *vs* 12%, *p*=0.001) among patients who experienced the primary outcome, compared with patients who did not. Bleeding can lead to supply-demand mismatch MI, and many studies have reported an independent association between major bleeding and perioperative MI.[4 7 8] The authors should undertake analyses to determine if perioperative bleeding and blood loss were independently associated with perioperative MI. Second, their finding of no association between the percentage of platelet inhibition before surgery and the primary outcome argues against thrombus being a dominant mechanism, which suggests supply-demand mismatch as the more common mechanism of perioperative MI.

Although guidelines advocate for the continuation of antiplatelet therapy to prevent perioperative MI in patients with a coronary artery stent,[7] the authors' findings raise the possibility that this approach may cause more harm than good. The 20 patients who had their anti-platelet agents held for at least seven days before surgery did not experience an increase in the incidence of the primary outcome, compared with patients who did not have their anti-platelet agents held for at least seven days before surgery (15 *vs* 20%, respectively). Patients taking clopidogrel who suffered the primary outcome had a higher median percentage of platelet inhibition, the day after surgery, than patients who did not suffer the primary outcome. This may reflect that perioperative administration of clopidogrel increased patients' risk of bleeding and that this bleeding led to MIs. Although these findings question the recommendation to continue anti-platelet therapy in patients with a coronary artery stent, who are undergoing noncardiac surgery, caution is required because it is possible that the patients who were at higher risk of a perioperative MI had their anti-platelet agents continued.

Evidence from clinical trials suggests bleeding may be an important pathway causing MI and refutes the efficacy of anti-platelets to prevent perioperative MI. POISE-2 randomized 10 010 patients undergoing noncardiac surgery to perioperative aspirin or placebo. Aspirin did not prevent MI but increased the risk of major bleeding, and major bleeding was an independent predictor that patients would subsequently experience an MI.[8] CRASH-2 randomized 20 211 trauma patients with, or at risk of, significant haemorrhage to tranexamic acid (an anti-fibrinolytic agent) or placebo. Tranexamic acid reduced all-cause mortality and bleeding mortality, and despite its anti-fibrinolytic actions, tranexamic acid reduced the risk of MI (Relative Risk, 0.64; 95% CI, 0.42–0.97).[9] Moreover, in the CRASH-2 pre-specified subgroup of 13 273 patients who had traumatic bleeding and received tranexamic acid or placebo within three h of their injury, tranexamic acid reduced the risk of MI (Odds Ratio, 0.49; 95% CI, 0.30–0.81).[10]

Although evidence supports that some perioperative MIs in patients who have a coronary artery stent are as a result of thrombosis,[11] the study by Wasowicz and colleagues suggests that a substantial proportion of these MIs are because of supply-demand mismatch from perioperative bleeding. Moreover, the study by Wasowicz and colleagues highlights that patients undergoing noncardiac surgery who have a coronary artery stent are at substantial risk of bleeding; 17% of patients received ≥2 units of blood, 18% had a haemoglobin level <90 after surgery, and 12% of patients had >1000 ml of surgical blood loss.[6]

The perioperative setting presents a challenging situation with competing physiological mechanisms of MI. We need to develop strategies that decrease the risk of perioperative bleeding, and there is also a need for strategies to decrease the risk of coronary artery thrombosis. Considering the CRASH-2 data raises the question of whether tranexamic acid during, and at the end of, noncardiac surgery can reduce the risk of bleeding and supply-demand mismatch MI. If this resulted in true haemostasis at the end of surgery it than may be safe to restart anti-platelet therapy after noncardiac surgery and hopefully minimize the risk of coronary artery thrombosis. Large trials in perioperative medicine (e.g. beta-blockers, aspirin, clonidine, nitrous oxide)[8 12–14] have highlighted the risk in assuming basic science, physiology, observational studies, and small trials are adequate to inform optimal perioperative management. Until large trials evaluating interventions in patients undergoing noncardiac surgery who have a coronary artery stent are undertaken, physicians will remain uncertain regarding what management strategy they should use to safely prevent perioperative MI.

Declaration of interest

Dr P.J. Devereaux is part of a group that has a policy of not accepting honorariums or other payments from industry for their own personal financial gain. They do accept honorariums or other payments from industry to support research endeavors and for reimbursement of costs to participate in meetings such as scientific or advisory committee meetings. Based on study questions he originated and grants he wrote, he has received grants from Abbott Diagnostics, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Covidien, Octapharma, Philips Healthcare, Roche Diagnostics, and Stryker. He has also participated in an advisory boarding meeting for GlaxoSmithKline, an expert panel meeting for Astra Zeneca, and a consultancy meeting for Boehringer Ingelheim.

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Standardizing end points in perioperative trials: towards a core and extended outcome set

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Varied definitions and inconsistent reporting of outcomes across trials investigating similar clinical problems limit the value of this research.[1 2] Such variability also undermines systematic reviews and meta-analyses aiming to synthesize relevant primary research on a particular question.[3 4] Two key issues underpin this problem, namely which outcomes are selected and what criteria are used to define them. For example, even an apparently simple and binary outcome, such as postoperative mortality, may be reported at different time points (commonly in hospital, 28, 30, or 90 days) and using alternative criteria (e.g. 'all-cause mortality' or 'cardiovascular mortality') in different trials. Likewise, inconsistent definitions of organ injury or composite end points (e.g. morbidity or quality-of-life measures) threaten the validity of any pooled analyses.[5] The findings of medical research should