The number of patients receiving antiplatelet therapy, including combination aspirin plus a P2Y12 inhibitor, is increasing. Also increasing is the number of surgical procedures done around the world, with approximately 250 million people undergoing major surgery each year (1). A growing proportion (>40%) of these are elderly, and many receive anti-platelet therapy. In patients at risk for coronary artery disease undergoing surgery, myocardial infarction (MI) is the most common (6%) cardiovascular complication and this has a mortality rate of 15% to 25% (2). The cost of perioperative cardiac events is estimated at $20 billion annually in the United States alone (2).

In this issue of the journal Korte et al. (3) publish a timely and commendable consensus paper on the perioperative management of antiplatelet therapy. Despite the relevance for a large number of patients, the authors faced a substantial challenge: The evidence base needed to provide strong perioperative recommendations is weak and thus the approach taken by the authors to establish a consensus statement from a group of diverse and highly experienced specialists, representing a range of relevant clinical societies, is well-justified. But the consensus paper should not obscure the fact that large scale clinical studies are needed to improve the evidence-base.

For patients undergoing surgery there are two opposing risks, thrombosis and bleeding complications, for which partial or near-complete platelet inhibition during and after surgery needs scrutiny. A recent small trial illustrates this dilemma, with aspirin reducing perioperative cardiac events but along with a tendency to increase bleeding complications (4). Korte et al. (3) rightly differentiate their recommendations according to the extent of potential benefit achievable. The group with the lowest expected benefit are patients receiving antiplatelet therapy for primary prevention, an intermediate group are those treated for secondary prevention, and a third group with potentially greatest benefit for anti-platelet therapy are those with coronary stents in situ. The data available on risk reduction in each of these groups of patients are mainly based on extrapolations from the general risk of cardiovascular events outside the specific setting of surgery.

Surgery is associated with platelet activation, due to many factors such as tissue release of platelet-activating factors, reduction in flow (including localised blood stasis), perioperatively applied hypothermia and sepsis (2, 5). The sympathetic hyperactivity associated with surgery promotes hypercoagulability by up-regulating coagulation and platelets and down-regulating fibrinolysis (6). There is also an increase in coronary shear stress, which may trigger plaque fissuring and acute coronary thrombosis (7), and a rise in circulating platelet release products immediately after surgery (8). Thus, the extrapolation of risk from non-surgical settings may substantially underestimate the potential benefit associated with anti-platelet therapy perioperatively. We know that acute withdrawal of chronic aspirin therapy results in a prothrombotic state (9, 10) potentially placing the perioperative patient at very high risk. Biondi-Zoccai et al. (11) did a meta-analysis of 50,279 patients at risk for coronary artery disease and found aspirin non-adherence/withdrawal in a non-surgical setting was associated with a three-fold increase in the risk of death and MI (11). The situation may be more pronounced perioperatively, with acute withdrawal of antiplatelet therapy being associated with a five- to 10-fold increased cardiac death rate (12). Thus the risks of withdrawing patients from antiplatelet drugs before surgery are likely to be greater than continuing them.

What is the evidence for increased bleeding complications during surgical interventions in patients on anti-platelet therapy? Again it is surprising how little information is available on this important issue. Most data comes from the cardiac surgical literature. A recent meta-analysis on the perioperative use of aspirin concluded with the finding that statistical power based on the limited data available is not sufficient for efficacy outcome assessment (13). Burger et al. (14) did a systematic review and meta-analysis of the surgical and interventional literature to determine the risks of low-dose aspirin withdrawal versus the bleeding risks associated with aspirin continuation (14). Aspirin withdrawal preceded 10% of cardiovascular complications (MI, stroke, peripheral arterial occlusion, cardiac death). Although aspirin increased the incidence of bleeding by 50%, it did not increase the severity or perioperative morbidity/mortality, except in intracranial surgery and, possibly, transurethral prostatectomy. The authors recommended discontinuing aspirin only if the risk of bleeding complications exceeds the cardiovascular risks of aspirin withdrawal.

Approximately 5% of patients undergo non-cardiac surgery within the first year...
after stenting (14). Surgery appears to increase the risk of stent thrombosis, MI, and death, particularly when patients undergo surgery early after stent implantation (14, 16). This seems to be related to withdrawal of anti-platelet therapy in many cases. However, most studies are too small to relate bleeding outcome to the added anti-ischaemic benefit (14). Furthermore, additional studies are needed for each of the different newly developed P2Y12 inhibitors, since their anti-platelet potency and bleeding risk differs substantially from clopidogrel (17).

The term and in particular the definition of aspirin resistance has been controversially discussed and up to 42% of patients undergoing coronary artery bypass grafting have been described not to have adequate platelet inhibition with aspirin treatment (18, 19). In addition, it has been postulated that coronary bypass grafting would result in an early post-operative window, in which patients are aspirin resistant (20). However, if collagen-induced TxA2-release is used as a measure of aspirin response, Cornelsen et al. (21) could not identify aspirin non-responders peri- or postoperatively. Santilli et al. (22) provide evidence that functional platelet assays reflect aspirin’s biochemical effect only with large variability in comparison to a constant aspirin effect seen with the direct biochemical pathway measure of serum thromboxane B2. These data imply that aspirin delivers constant antiplatelet effects pre- and post-operatively both in regards to the prevention of cardiovascular events as well as in regards to the risk of bleeding complications. In contrast to aspirin, the perioperative use of clopidogrel may result in variable protection and bleeding risk for individual patients (23). The recently introduced new P2Y12 inhibitors may not have the same problem of inter-patient variability, but are associated with more bleeding complications and thus their use in the perioperative setting may be restricted (24).

Many new antiplatelet drugs are currently under development, which will hopefully result in a better armamentarium of anti-platelet drugs, including short-acting reagents (such as the P2Y12 inhibitor ganczegrel), which promise to provide an anti-ischemic protection during surgery and uncompromised platelet function and thus less bleeding problems postoperatively.

Evidence-based practice relies upon expert interpretation of clinical research. Korte et al. (3) have reviewed the literature and provide useful consensus guidelines. Perhaps more importantly, they identify a need for definitive clinical trials. POISE-II (www.clinicaltrials.gov, identifier NCT01082874), a large trial investigating the effectiveness of aspirin in 10,000 patients with coronary artery disease undergoing non-cardiac surgery is currently underway, aims to provide valuable data to guide our decision-making with regards to aspirin therapy in the perioperative setting. Thus, based on this large scale trial and hopefully on consequent studies with other antiplatelet drugs and surgical settings, there is hope that in the near future perioperative antiplatelet therapy will be based on clinical evidence rather than having to rely on consensus.

Conflict of interest
Dr. Myles is a co-investigator for the POISE-II and ATACAS trials, investigator-initiated trials investigating the safety and effectiveness of aspirin in non-cardiac and coronary artery surgery, respectively.

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