''I would have everie man write what he knowes and no more.''—Montaigne
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Editorial

Coronary stents and perioperative anti-platelet regimen: dilemma of bleeding and stent thrombosis

The incidence of coronary artery disease (CAD) in the Western population is high and increasing. Its treatment, by coronary revascularization, was revolutionized in 1977 by Grüntzig who performed the first percutaneous transluminal coronary balloon angioplasty in Zürich, Switzerland. Nine years later the first coronary stent was deployed in Lausanne, Switzerland, by Sigwart and colleagues.[1 2] Currently, over 90% of all percutaneous coronary interventions (PCIs) involve placement of stents.[3]

Any PCI causes trauma to the vessel wall, rendering the endoluminal surface thrombogenic[4] and thus, adjunctive anti-platelet medication is a crucial element in preventing local coronary thrombosis.[5] Current recommendations call for initial dual anti-platelet therapy with aspirin and clopidogrel.[5–7] Aspirin is generally maintained for life. Clopidogrel treatment is recommended for at least 3–12 months depending on the type of stent implanted (6 weeks for bare metal stents).[5 7–9] There is a tendency to maintain dual anti-platelet treatment for increasingly long periods as it clearly improves the combined 1yr outcome with respect to death, myocardial infarction and stroke.[3]

Anaesthetists thus are increasingly confronted with patients who have had a recent stent implantation and are on anti-platelet therapy. The key question in such patients is whether the anti-platelet therapy should be maintained throughout the perioperative period or stopped before operation. There are arguments for both strategies. Patients on aspirin and clopidogrel undergoing cardiac surgery have an increased blood loss, require more blood transfusions and have a higher incidence of re-exploration for bleeding.[10–12] Also in non-cardiac surgery, patients receiving dual anti-platelet therapy have a 25–40% increased risk of bleeding.[13–16]

However, stopping anti-platelet therapy is associated with significant morbidity and mortality. Withdrawal of aspirin in patients with CAD is associated with a 2- to 4-fold increase in the risk of death and myocardial infarction, even with replacement low molecular weight heparin,[17 18] compared with patients who remain on the drug. Moreover, cessation of anti-platelet therapy is the major independent predictor of stent occlusion,[19 20] and stent thrombosis resulting in myocardial infarction after aspirin cessation has been reported as late as 15 months after PCI with drug-eluting stents.[21] Combining these data with the increased platelet adhesiveness and decreased fibrinolysis found in the perioperative period, it is reasonable to hypothesize that patients who have undergone PCI and who have recently stopped aspirin are at a particular risk of thrombotic postoperative complications including stent thrombosis.[22]

The anaesthetist faces the dilemma of stopping the anti-platelet treatment before operation to avoid bleeding and risking postoperative stent thrombosis, or to maintain anti-platelet therapy perioperatively; thus risking major blood loss but limiting the risks of postoperative stent thrombosis. The study by Vicenzi and colleagues[23] reported in this issue of the *British Journal of Anaesthesia* includes an analysis of the impact of anti-platelet agents and heparin on outcome. The authors assessed 103 patients with coronary stent implantation undergoing non-cardiac surgery. In all the three participating centres institutional guidelines existed regarding the perioperative anti-platelet regimen. These guidelines required either maintaining the anti-platelet therapy perioperatively or stopping anti-platelet drugs for a maximum of 3 days and replacing these drugs with medium dose heparin coverage. The primary outcome of this study was combined adverse outcome (cardiac, bleeding, surgical, sepsis and other) during the first 3 months after operation. The authors report a 45% complication rate and 5% mortality.[23] Interestingly, all but two complications were cardiac and most of the complications occurred early after surgery. In keeping with earlier studies,[13 24] they found that complications are particularly frequent when surgery is performed early (<35 days) after stent implantation. Even though this time limit was chosen somewhat arbitrarily, the association between very recent stenting and complications is less clear than in previous studies. In the paper of

Vicenzi and colleagues, complications were more frequent in patients with a recently placed coronary stent but not to the extent that all[24] or even the majority of complications occurred in the initial 35 days.[13] Somewhat surprisingly, a multivariate analysis found that patients with and without complications did not differ in terms of perioperative anti-platelet regimen. However, few details are given with regard to the use of anti-platelet agents. The findings of this study should be interpreted with some caution. Patients were not randomized to one or another heparin regimen raising the possibility of allocation bias. No distinction is made between different types of coronary stent. It is well established that drug-eluting stents are more thrombogenic than bare metal stents and individual clinicians' knowledge of what stent was used could have influenced management.

What do we learn from this study? Firstly, it offers further confirmation that patients with coronary stents are at a high risk of postoperative complications. Secondly, it supports the use of anti-platelet agents in this population. It seems likely that these patients are on anti-platelet drugs with good reason. Thirdly, it suggests that bleeding in non-cardiac surgery is not a common or important complication when compared with the incidence of cardiac events.

We lack high level scientific evidence on the optimum perioperative anti-platelet regimen in patients with coronary stents. In such a situation, we would normally call for a prospective randomized trial comparing the outcome of different perioperative anti-platelet regimens. Operation with full anti-platelet therapy, stopping all anti-platelet drugs before operation, and stopping clopidogrel but maintaining aspirin are potential regimens. It can be argued that such a trial would be unethical considering all the known complications of stopping the anti-platelet treatment.[17–21] However, we regularly encounter patients the evening before operation in whom all anti-platelet drugs have been stopped 7–10 days previously by the surgeon or the primary physician. In the guidelines of the European Society of Cardiology for PCI,[5] the authors state '*In patients in whom prolonged administration of clopidogrel is known to be unlikely (i.e. major extracardiac surgery planned soon) drug-eluting stents should be used with caution. In these patients, bare metal stents are probably the safer choice.*' It appears that some cardiologists expect anti-platelet therapy to be stopped before operation anyway. Others might argue that not stopping clopidogrel might be unacceptable considering the increased bleeding risks[10 11 14–16] and the impossibility of using regional anaesthesia. This argument may not be robust. The difference in packed red blood cell transfusions in most studies is only 1–2 units,[10 12] and there are several papers describing series in which no difference was found in terms of bleeding between patients with and without dual anti-platelet therapy (aspirin plus clopidogrel).[24 25] There appears to be a strong case for a study in patients on dual anti-platelet treatment who have recently undergone PCI and now require non-cardiac surgery. This study should compare a combined aspirin and clopidogrel therapy with aspirin alone. Deliberately stopping all anti-platelet drugs in such patients appears to be associated with an unacceptably high incidence of major cardiac complications, and thus unethical. The baseline incidence of cardiac complications reported by Vicenzi and colleagues is so high (>40%) that, with a hypothesized difference between groups of only 10% as achieved in the CREDO trial,[3] a preliminary sample size analysis yielded group sizes of less than 500 patients in each arm. Such a study thus appears realistic on a European level.

What should we do in the meantime? Without high level scientific evidence, anaesthetists, surgeons and cardiologists should establish local treatment algorithms for the management of patients who have had previous PCI and are now to undergo surgery. Such algorithms may include the following:

- All patients should receive a thrombo-embolic prophylaxis with (low molecular weight) heparin. However, heparin alone is insufficient.
- An initial period of 6–12 weeks after PCI should be defined during which, regardless of the anti-platelet regimen, only life-saving operations should be performed.
- For operations that can be scheduled after this initial period, simply stopping all anti-platelet drugs 7–10 days before operation is unwise. The majority of patients with coronary stents may benefit from an unchanged anti-platelet treatment perioperatively.
- In selected patients undergoing operations, historically associated with major blood loss or certain neurosurgical procedures, a combined aspirin–clopidogrel treatment might be reduced for a short period to aspirin and (low molecular weight) heparin treatment only.

D. R. Spahn[1*]
S. J. Howell[3]
A. Delabays[2]
P.-G. Chassot[1]
[1]*Department of Anaesthesiology*
[2]*Department of Cardiology*
University Hospital Lausanne
Lausanne
Switzerland
[3]*Academic Unit of Anaesthesia*
University of Leeds
UK
[*]*E-mail: donat.spahn@chuv.ch*

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