

Coronary Stent Placement Prior to Non-cardiac Surgery

a report by

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Percutaneous coronary angioplasty with stenting is commonly used for treatment of symptomatic coronary artery disease (CAD). The introduction of stents has reduced the incidence of restenosis, one of the major drawbacks of coronary angioplasty, and proved to be an alternative treatment for bypass surgery. Recently, drug-eluting stents were introduced as a means to lower restenosis rates even further. Since then drug-eluting stents have been implanted in nearly six million patients worldwide.¹ To prevent early in-stent thrombosis all patients receiving a coronary stent are prescribed dual antiplatelet therapy for a certain period, depending on the type of stent used. However, there is an increased concern of late thrombosis in coronary stents, in particular in drug-eluting stents, which might be attributable to interruption of antiplatelet therapy.²

It is estimated that approximately 5% of patients who undergo coronary stenting require some form of non-cardiac surgery within one year after stenting.³ Since non-cardiac surgery is known to induce hypercoagulability, this causes increased concern over the effects of previous coronary stenting on post-operative cardiac outcome, in particular in-stent thrombosis. On the other hand, patients with multiple cardiac risk factors are at high risk of post-operative adverse cardiac events and might even benefit from pre-operative prophylactic revascularisation.

The topic of coronary stenting and non-cardiac surgery can be divided in two issues: prophylactic coronary revascularisation and patients treated in the

past with angioplasty and stent placement scheduled for non-cardiac surgery. Peri-operative antiplatelet therapy is a major issue in both groups as antiplatelet therapy is crucial in the early phase after stent placement to prevent in-stent thrombosis; in addition, during long-term follow-up thrombotic events can occur with fatal outcome. This editorial will provide an update on the evidence for prophylactic coronary revascularisation in surgical patients, considerations with respect to the type, location and number of stents in patients undergoing non-cardiac surgery, and peri-operative antiplatelet therapy in surgical patients with a history of coronary stenting.

Prophylactic Coronary Revascularisation

Patients with multiple cardiac risk factors scheduled for major surgery are at increased risk of peri-operative cardiac complications. According to the guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA), it is highly recommended to refer these patients for non-invasive cardiac stress testing prior to surgery.⁴ The guidelines also recommend coronary angiography for patients with high-risk non-invasive test results, and myocardial revascularisation in patients with prognostic high-risk anatomy in whom long-term outcome is likely to be improved.

This recommendation was supported by the Coronary Artery Surgery Study, which showed a reduced incidence of non-fatal myocardial infarctions (MI) after previous bypass surgery among vascular surgery patients compared with

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3. Vicenzi MN, Meislitzer T, Heitzinger B et al., "Coronary artery stenting and non-cardiac surgery – a prospective outcome study", *Br J Anaesth* (2006);96(6): pp. 686–693.
4. Eagle KA, Berger PB, Calkins H et al., "ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery – Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery)", *Anesth Analg* (2002);94(5): pp. 1052–1064.

those treated medically: 8.5% versus 0.6%, respectively ($p=0.001$).⁵ More recently, data from the Bypass Angioplasty Revascularization Investigation trial showed that bypass surgery and percutaneous coronary intervention had similar low rates of post-operative cardiac events in non-cardiac surgery.⁶ However, these studies were not designed to assign the optimal strategy in severely ill patients with extensive CAD immediately prior to major non-cardiac surgery. In addition, these studies could not address the concern of delaying the non-cardiac surgical procedure because of testing, revascularisation and initiation of antiplatelet therapy since the time between revascularisation and non-cardiac surgery in these studies was, respectively, 4.1 and 2.4 years.

The randomised Coronary Artery Revascularization Prophylaxis (CARP) trial was the first study that addressed the strategy of prophylactic revascularisation compared with optimal medical therapy in patients with clinically stable CAD who were scheduled for major non-cardiac vascular surgery.⁷ This trial showed that prophylactic revascularisation was safe but did not improve peri-operative or long-term outcome. The long-term (median follow-up 2.7 years) mortality was 22% in patients allocated to prophylactic coronary revascularisation, compared with 23% in the medical only strategy ($p=0.92$). Also the incidence of peri-operative non-fatal MI was similar – respectively 12% and 14%, $p=0.37$. However, it must be noted that the majority of patients in the CARP trial had only one- or two-vessel disease. The recently conducted DECREASE V randomised pilot study in which the majority of patients had three-vessel disease also showed no peri-operative and long-term (follow-up one year) benefit of prophylactic coronary revascularisation.⁸ The findings of both CARP and DECREASE V support the current guidelines of the ACC/AHA on peri-operative management in high-risk patients to reserve revascularisation only for cardiac unstable patients. After successful non-cardiac surgery these patients should be regularly screened for the presence of ischaemic complaints and aggressive anti-ischaemic therapy, both medical and invasive, should be

considered. In DECREASE V a trend was observed for a ‘catch up’ of late cardiac events in patients treated medically. In these patients at high risk scheduled for major non-cardiac vascular surgery, prophylactic revascularisation might be switched to late revascularisation, preventing the delay of surgery.

Patients with a History of Coronary Stenting Undergoing Non-cardiac Surgery

Angioplasty with stenting is commonly used for treatment of symptomatic CAD. The introduction of stents has reduced the incidence of restenosis, one of the major drawbacks of coronary angioplasty, and proved to be an alternative treatment for bypass surgery. This strategy may be attractive compared with bypass surgery in patients scheduled for general surgery as the delay of the index surgical procedure is prevented. However, initially stent placement causes complete denudation of the arterial endothelial surface and stent struts may damage the media or penetrate into the lipid core, inducing inflammatory and coagulation activity. These factors temporarily increase the risk of in-stent thrombosis until a neo intima has been formed. Fortunately, the introduction of dual antiplatelet therapy (aspirin and clopidogrel) has overcome this complication and reduced the rate of in-stent thrombosis to less than 1%.

However, recent stent placement might be potentially harmful for patients undergoing non-cardiac surgery. Surgery increases the thrombosis risk due to a peri-operative stress response including sympathetic activation promoting shear stress on arterial plaques, enhanced vascular reactivity conducive to vasospasm, reduced fibrinolytic activity, platelet activation and hypercoagulability. In addition, while the surgical patient is in a hypercoagulable state dual antiplatelet therapy is often interrupted because of the fear of excessive bleeding complications during surgery. It should be noted in this respect that currently it is advised to give patients dual antiplatelet therapy at least one month after bare metal stenting, three months after sirolimus-eluting stenting, and six months after paclitaxel-eluting stenting.⁹

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8. Poldermans D, Schouten O, Vidakovic R et al., “The Effect of Preventive Coronary Revascularization on Postoperative Outcome in Patients Undergoing Major Vascular Surgery with Extensive Stress-induced Myocardial Ischemia During Preoperative Testing”, *Circulation* (2006);114(18): pp. II–523.

In a patient requiring coronary stenting because of an acute coronary syndrome who is known to require non-cardiac surgery in the near future, the type of coronary revascularisation requires special attention. If it is anticipated that non-cardiac surgery can be postponed at least six months, drug-eluting stent placement with at least six months of dual antiplatelet therapy might be the treatment of choice. On the other hand if non-cardiac surgery cannot be delayed that long, but for example only by two months, bare metal stenting should be considered. Bare metal stenting requires less prolonged dual antiplatelet therapy because of earlier endothelialisation and thus results in less chance of in-stent thrombosis. In case of anticipated semi-emergent non-cardiac surgery one might even consider the less effective method of coronary angioplasty only. Coronary stenting might then be considered after the non-cardiac surgical procedure if deemed necessary.

Peri-operative Antiplatelet Therapy in Patients with a History of Coronary Stenting

It is important to find the optimal balance between risks and benefits of antiplatelet therapy in the peri-operative period. The balance for patients with a history of coronary stenting undergoing non-cardiac surgery is that of bleeding because of continuous antiplatelet agent use on one hand and that of prevention of MI due to in-stent thrombosis on the

other. Unfortunately the existing evidence for making such a balanced decision is limited.

A meta-analysis of 49,590 patients by Burger et al revealed that although patients continuing aspirin in the peri-operative period had a higher risk of surgical bleeding, the severity of bleeding was not worse than in patients who discontinued antiplatelet therapy in the peri-operative period.¹⁰ In fact, recently several series of major non-cardiac vascular surgery showed the safety of continuing aspirin therapy in the peri-operative period. The evidence for other antiplatelet agents such as thienopyridines (including clopidogrel) is less well established. In their review Merritt et al found conflicting results. Some trials reported an increased risk of major bleeding and peri-operative mortality in patients receiving continuous clopidogrel therapy whereas in other reports no such increased risk was observed.¹¹

Studies with a short median interval between coronary stenting and non-cardiac surgery report higher cardiac complication rates compared with reports with longer median time intervals.^{3,12–19} Importantly, when studies with a longer median interval between PCI and non-cardiac surgery are evaluated in more detail, patients with early surgery experienced more cardiac events than those with late surgery. Discontinuation of antiplatelet therapy seems to be an important factor in this respect. In those studies that report on peri-operative discontinuation of antiplatelet therapy there was a clear trend towards a higher incidence of peri-

9. Smith SC Jr., Feldman TE, Hirshfeld JW Jr. et al., "ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention-Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention)", *J Am Coll Cardiol* (2006);47(1): pp. 216–235.
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operative events after stopping antiplatelet therapy. In one of the first reports on this issue Kaluza et al found that six out of eight patients who died in the peri-operative period were without antiplatelet therapy.¹² The same trend was found by Sharma et al: 86% of patients who discontinued antiplatelet therapy died peri-operatively versus only 5% in the group of patients who continued antiplatelet therapy.¹³ Recently this was confirmed in a study of 192 patients at Erasmus MC. In particular in patients with early non-cardiac surgery there was a marked difference in major adverse cardiac events (30% versus 0% respectively for patients who stopped and continued antiplatelet therapy).¹⁹

It seems that in patients undergoing non-cardiac surgery early after coronary stenting, antiplatelet therapy should be continued, although it must be noted that the evidence for this is limited and there are no randomised trials in this respect. Whether the balance of risks and benefits is also in favour of continuing antiplatelet therapy in patients who have undergone coronary stenting long before non-cardiac surgery remains to be determined.

However, as found by Ferrari et al, even after a long period following stenting, stopping antiplatelet therapy is a significant risk factor for adverse cardiac events.²⁰ ■

20. Ferrari E, Benhamou M, Cerboni P, Marcel B, "Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis", *J Am Coll Cardiol* (2005);45(3): pp. 456-459.
