Coronary stents and non-cardiac surgery: to bridge or not to bridge?

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Patients with coronary stents need antiplatelet therapy to reduce the risk of stent thrombosis. The standard therapy is lifelong low-dose aspirin with supplementary P2Y$_{12}$-inhibitor treatment during the first months. In patients who have suffered from an acute coronary syndrome (ACS), the P2Y$_{12}$-inhibitor is usually given for 12 months (1–3). In these patients, the new and stronger P2Y$_{12}$-inhibitors ticagrelor or prasugrel are preferred over clopidogrel, unless the patient is at high risk of bleeding (1–3). In stable coronary patients undergoing elective stenting, clopidogrel is used (3), and the recommended treatment duration depends on the type of stent: bare metal stents 1–3 months, first-generation drug-eluting stents (DES) 12 months and second-generation DES usually six months (3). Earlier cessation of dual antiplatelet therapy (DAPT) carries a high risk for stent thrombosis (4, 5).

A need for elective or acute surgery for cardiac or non-cardiac disease is not uncommon in patients with recent stent implantation (6–8). This clearly puts the clinician in a difficult dilemma as an operation is associated with bleeding: should surgery be performed during dual or mono antiplatelet therapy or maybe even without any antiplatelet therapy at all? As the risk of stent thrombosis is highest in the weeks after stent implantation, postponing the operation is an attractive option. Surgery in patients on low-dose aspirin is associated with increased risk of bleeding (9), and bleeding rates are higher when surgery is performed on DAPT (10). Bleeding is a particular problem in some surgical scenarios such as spinal and brain surgery, but also in less extensive procedures such as percutaneous organ biopsies, where neither compression nor direct surgical haemostasis can be performed, are major challenges.

In these situations, the surgeon may prefer to stop all antithrombotic medication, whereas individualised perioperative management of antiplatelet therapy guided by platelet function testing might be possible in selected patients undergoing elective surgery (11). Difficult dilemmas should be discussed at a multidisciplinary team conference with participation of a cardiologist, a surgeon, an anaesthesiologist and sometimes also other experts (12).

As mentioned, postponing surgery in patients on dual antiplatelets is advised if at all possible. Indeed, DES are most often used and the duration of DAPT is usually for 6–12 months, although with newer generation DES, it might be possible to shorten the time interval to three months (3). In life-threatening acute conditions, surgery may have to be performed on ongoing/uninterrupted DAPT. In other cases (e.g. operations for malignancies), surgery cannot be postponed for several months and given that these cases are particularly challenging they would need to be discussed in the multidisciplinary team.

The management of antithrombotic therapy in patients with coronary stents undergoing surgery is thus a major challenge and should be based on a balanced decision weighing the risk of peri- and postoperative bleeding against the risk of stent thrombosis. If surgery on DAPT is considered too risky and the presumed risk of stent thrombosis is low, the operation is performed on low-dose aspirin after stopping the P2Y$_{12}$ inhibitor prior to surgery: 3–5 days for ticagrelor and 5 days for clopidogrel and prasugrel (1–3, 12).

A difficult clinical dilemma arises if surgery has to be performed without any antiplatelet therapy at all, in particular in the first month(s) after coronary stenting, and especially if the P2Y$_{12}$ inhibitor has to be stopped within the first days or weeks after stenting (13). The latter situation is not uncommon and the risk of adverse cardiac events is very high and might be further enhanced by the proinflammatory and prothrombotic state associated with surgery (14, 15). Patients with recent ACS, diabetes, low ejection fraction, renal failure and patients who have been undergoing extensive stenting for three vessel disease or left main disease are at particularly high risk (16, 17). In such situations, particular attention is needed and it is recommended that these patients are admitted to a hospital with 24/7 PCI facilities (12). In cases where the risk of stent thrombosis is assumed to be very high, initiation of parenteral antithrombotic bridging therapy should be considered (12, 18).

Options for bridging therapy

Parental anticoagulants and antiplatelet drugs have been used as bridging therapy in patients with a very high risk for stent thrombosis that need surgery where P2Y$_{12}$ inhibitors and maybe also aspirin has to be interrupted. An important and powerful class of antiplatelet drugs is the intravenous glycoprotein IIb/IIIa inhibitors (19). Abciximab is an irreversible platelet inhibitor and not an option in this context, whereas the reversible-binding shorter-acting molecules eptifibatide and tirofiban are potential candidates for bridging therapy in patients with a very high risk of stent thrombosis that need surgery where treatment with P2Y$_{12}$ inhibitors and maybe also aspirin has to be interrupted. Both drugs are given as intravenous infusions and have been evaluated for efficacy and safety in...
these patients (20, 21). Management strategies including dosing schemes have been developed and this bridging strategy has been recommended in patients with a high risk of stent thrombosis undergoing surgery with high bleeding risk (20, 21). However, a recent meta-analysis of these and similar studies did not provide strong support for preoperative bridging with a glycoprotein IIb/IIIa inhibitor in patients undergoing surgery after coronary stenting since this strategy did not eliminate the risk of perioperative stent thrombosis. Also, peri- and postoperative bleeding was not negligible, and more studies investigating this bridging strategy are clearly needed (22).

For patients with normal renal function, the plasma half-lives of tirofiban and eptifibatide are 2.0 and 2.5 hours (h), respectively (19). The new intravenous P2Y12 inhibitor, cangrelor, has a plasma half-life of 3–6 minutes and is a rapid, potent, and reversible platelet inhibitor with a rapid offset of action. The effect of cangrelor was evaluated in a prospective, double-blind trial, including 210 patients with ACS or treated with a coronary stent and receiving a thienopyridine awaiting coronary artery bypass grafting (CABG) surgery (23). P2Y12 inhibitor treatment was stopped and patients were given either cangrelor or placebo for at least 48 h, which was discontinued 1–6 h before CABG. The primary efficacy endpoint of the study was platelet aggregation assessed daily with the VerifyNow assay. The main safety end point was excessive CABG surgery-related bleeding. A significantly greater proportion of patients treated with cangrelor had low levels of platelet aggregation throughout the entire treatment period compared with placebo. Excessive CABG surgery-related bleeding occurred in 11.8% (12 of 102) vs 10.4% (10 of 96) in the cangrelor and placebo groups, respectively (p=0.763). Minor bleeding episodes were numerically higher with cangrelor, but there were no significant differences in major bleeding prior to CABG surgery. Bridging therapy with cangrelor thus seems an attractive possibility; however, cangrelor is not yet available, and the drug should also be tested in the setting of non-cardiac surgery.

Another possibility is to bridge with an anticoagulant. Although platelets are the primary players in stent thrombosis, coagulation is also activated. Low molecular weight heparins (LMWH) are widely used in clinical practice (24) and are recommended for bridging in some patients on warfarin when surgery is needed (12). However, in stented patients who need bridging, the European Society of Cardiology (ESC) Guidelines on non-cardiac surgery discouraged the use of low-molecular-weight heparin (LMWH), as this approach might be associated with more bleeding (12).

In the present issue of Thrombosis and Haemostasis, an important study by Capodanno et al. (25) strongly supports this statement. In a retrospective analysis of patients with coronary stent(s) on any antiplatelet therapy undergoing non-cardiac surgery, they studied 515 patients of whom LMWH bridging was used in 251 (49%). The primary efficacy endpoint, the 30-day incidence of major adverse cardiac or cerebrovascular events occurred more frequently in patients who received LMWH (7.2% vs 1.1%, p=0.001). This was mainly driven by a higher rate of myocardial infarction (4.8% vs 0%, p<0.001). The primary safety endpoint, a 30-day composite of Bleeding Academic Research Consortium (BARC) score ≥2 bleedings, occurred more frequently in patients bridged with LMWH (21.9% vs 11.7%, p=0.002).

Importantly, their study was not randomised and confounding by indication will likely be at play; however, the main study findings remained significant across different methods of statistical adjustment and propensity matching. Acknowledging the limitations of the retrospective design and the possibility of unknown confounders, the study shows that bridging with LMWH in patient with coronary stents undergoing surgery has been common practice and reinforces that this strategy is detrimental and possibly harmful, resulting in worse ischaemic outcomes and a significantly increased risk of bleeding.

Obviously, more studies in this field are highly warranted. The field is currently one of the most difficult dilemmas in clinical cardiology and subject to much debate (26–28). Decisions are also made more challenging with the availability of the non-vitamin K oral anticoagulants (NOACs) (29). Decisions will often be prone to criticism and it is therefore advised that difficult cases are discussed with colleagues, preferably in a multidisciplinary team.

Conflicts of interest
SDK has received speaker honoraria from Aspen, AstraZeneca, and The Medicines Company and has participated in advisory board meetings for AstraZeneca. ELG has received speaker honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, and Pfizer and has participated in advisory board meetings for AstraZeneca, Bayer, and Bristol-Myers Squibb. MM has received speaker honoraria from AstraZeneca.

References
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