Antithrombotic therapy in patients at risk for coronary stent thrombosis undergoing non-cardiac surgery

Zuzana Moťovská, Petr Widimský

The Cardiocentre, 3rd Department of Internal Medicine – Cardiology, University Hospital Královské Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic

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Percutaneous coronary interventions have become the most commonly performed coronary revascularization procedures. At the same time, the probability has been increased that patients with intracoronary stents will have to undergo surgery. We can project that, in the Czech Republic, one thousand patients undergo non-cardiac surgery within six months of stent implantation annually. Two serious consequences emerge from this situation: (i) stent thrombosis in relation to discontinuation of antiplatelet therapy, and (ii) major bleeding in relation to continuation of antiplatelet therapy. The best solution to overcome the risks resulting from surgery performed in patients after stent implantation is to postpone the procedure until after re-endothelialization of the vessel surface has been completed. Because only approximately 5–10% of surgeries are performed as an urgent procedure, this could be a significant way to increase the safety of non-cardiac surgical procedures following stent implantation. Expert recommendations advise that 3 months after bare-metal stent PCI and 12 months after drug-eluting stent PCI, patients can be sent for non-cardiac surgery while continuing aspirin therapy. Difficult decisions regarding antiplatelet management arise when a patient still on dual antiplatelet therapy with aspirin and thienopyridine (usually clopidogrel) has to undergo surgery which cannot be postponed. A universal recommendation for this situation is unrealistic. Discussion among the attending cardiologist (cardiovascular risk), surgeon (the risk of bleeding), and the anesthesiologist (functional reserve, backup preparation) about this situation is recommended in order to achieve reasonable expert consensus.
Key words: Antiplatelet therapy – Intracoronary stents – Non-cardiac surgery

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Perkutánní koronární intervence se staly nejčastěji prováděnými výkony koronární revaskularizace. Tím se zvýšila pravděpodobnost, že nemocní s implantovaným intrakoronárním stentem budou podstupovat operační výkon. Podle dostupných statistických údajů lze předpokládat, že v České republice podstoupí ročně nekardiální operaci do šesti měsíců od implantace intrakoronárního stentu tisíc nemocných. Tato situace má dva závažné důsledky: (i) trombózu stentu v souvislosti s vysazením protidestičkové léčby a (ii) závažné krvácení v souvislosti s pokračováním protidestičkové léčby. Nejlepším způsobem, jak překonat rizika plynoucí z operací nemocných po implantaci stentu je odložit chirurgický výkon na dobu, kdy dojde k opětovné endotelializaci cévního povrchu. Protože se jako urgentní provádí přibližně pouze 5–10 % chirurgických výkonů, mohl by tento postup představovat významnou možnost zvýšení bezpečnosti nekardiálních chirurgických výkonů po implantaci intrakoronárního stentu. Podle doporučení skupin expertů lze pacienty odeslat na nekardiální výkony při pokračující léčbě kyselinou acetylsalicylovou tři měsíce po implantaci kovového stentu a 12 měsíců po implantaci lékového stentu. Rozhodování z hlediska protidestičkové léčby je obtížné v případech, kdy je nemocnému stále ještě podávána duální antiagregační léčba s kyselinou acetylsalicylovou a thienopyridinem (obvykle clopidogrelem) a musí podstoupit urgentní chirurgický výkon. Obecně platné doporučení pro tyto situace neexistuje. Doporučuje se, aby situaci společně prodiskutovali ošetřující kardiolog (kardiovaskulární riziko), chirurg (riziko krvácení) a anesteziolog (funkční rezerva, připravenost k řešení komplikací v průběhu operačního výkonu), a dospěli tak k optimálnímu postupu.
Klíčová slova: Antitrombotická léčba – Intrakoronární stenty – Nekardiologický výkon

Adresa: Assoc. Prof. Zuzana Moťovská, M.D., Ph.D., The Cardiocentre, 3rd Department of Internal Medicine – Cardiology, University Hospital Královské Vinohrady and Third Faculty of Medicine, Charles University, Ruská 87, 100 00 Prague 10, Czech Republic, e-mail: zuzana.motovska@iex.cz

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Introduction

Dual oral antiplatelet therapy, aspirin plus thienopyridine, has permitted a rapid increase in the use of intracoronary stents. Percutaneous coronary interventions (PCIs) have become the most commonly performed coronary revascularization procedures, accounting for approximately 60% of all revascularizations.[1,2] At the same time, the probability has increased that patients with (recently implanted) intracoronary stents will have to undergo (urgent) surgery. Two serious consequences emerge from this situation:

(i) ***stent thrombosis in relation to discontinuation of antiplatelet therapy***,

(ii) ***major bleeding in relation to continuation of antiplatelet therapy.***

Epidemiological data

There is an increasing trend in the number of coronary interventions.[3,4] In Europe, a total of 800,000 stenting procedures were reported in 2005, resulting in a 4% increase compared with 2004.[3] The number of PCIs in 2010 is projected to be about 1.5 million, with a stenting rate of almost 100%.[5] In addition, the number of surgical procedures is steadily increasing.[4] Today, over 40 million surgical procedures are performed annually in Europe.[6] The same trends are also present in the Czech Republic with approximately 2,000 PCIs involving stent implantation and approximately 70,000 surgeries (with every seventh being emergency surgery) per million inhabitants reported in 2007.[7,8]

To et al.[9] recently published the first systematic assessment of the incidence of non-cardiac surgery in a group of eleven thousand patients following PCI. Non-cardiac surgery was required frequently after PCI. During a 5-year follow-up, 26% (1 in 4 patients) underwent at least one non-cardiac surgical procedure; the 6-month occurrence of surgery was 5.1%, whereas, at 12 months, the cumulative rate was 8.6%. The annual incidence of surgery did not change significantly during the 5 years of follow-up. Based on these numbers we can project that, in the Czech Republic, one thousand patients undergo non-cardiac surgery within six months of stent implantation annually.

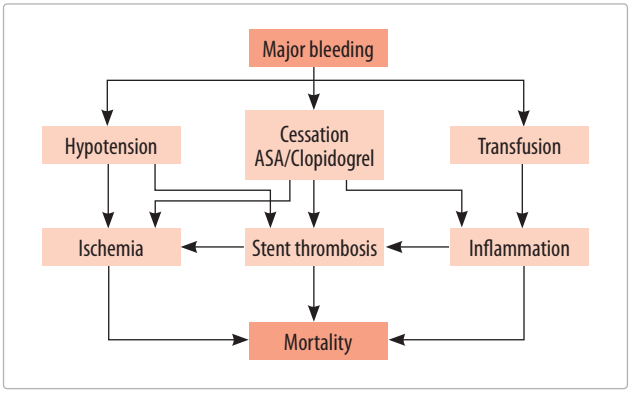

Figure 1 **Major bleeding and mortality after percutaneous coronary intervention**

Surgery promotes thrombosis

The stress response to surgery includes sympathetic activation and may trigger adverse cardiovascular outcomes.[10,11] Release of neuroendocrine hormones (epinephrine, norepinephrine, cortisol, and renin) promotes: (i) shear stress on arterial plaques, (ii) enhanced platelet activation, and (iii) vascular reactivity leading to vasospasm. Furthermore, the surgical patient is in a hypercoagulable state due to an increase in plasma clotting factors while fibrinolysis is decreased.[12,13] This alteration of hemostasis, which occurs during the perioperative period, may also increase the risk of intracoronary stents thrombosis.

Antiplatelet therapy and surgery – prevention of thrombosis versus bleeding risk

Secondary prevention with low-dose ***aspirin*** reduces the risk of stroke and myocardial infarction by about one third, and, most importantly, the risk of cardiovascular death by about one sixth.[14] Spontaneous aspirin discontinuation after 1 year of therapy occurs in up to 18% of patients with established coronary artery disease.[15] A systematic review in over 50,000 patients at risk of, or with coronary artery disease, demonstrated that aspirin withdrawal was associated with a three-fold increase in the risk of major adverse cardiac events (OR = 3.14, 95% CI 1.8–5.6, $p = 0.0001$).[16] A highly significant increase in the risk of adverse events occurred, on an average of 10 days, after discontinuing aspirin. Discontinuation of aspirin therapy in patients treated with either bare-metal or drug-eluting stents was identified as a strong independent predictor of stent thrombosis (OR = 1.91 95% CI 1.01–3.88, $p = 0.0487$).[17]

Surgery is a prothrombotic condition. However, perioperative continuation of antiplatelet agents increases the hazard of procedural bleeding. Burger et al.[18] published a systematic review focusing on cardiovascular risks after perioperative withdrawal of aspirin vs. bleeding risks associated with its continuation. They found that aspirin withdrawal resulted in an up to 10.2% of acute cardiovascular syndromes. Whereas aspirin increased the rate of perioperative bleeding complications by a factor of 1.5, and it did not lead to increased severity of bleeding complications (exceptions: intracranial surgery and transurethral prostatectomy).

Addition of a platelet $P2Y_{12}$ receptor antagonist to aspirin after stent implantation is essential for prevention of stent thrombosis until re-endothelialization of the vessel surface is complete. Analysis of a Dutch stent thrombosis registry[17] (21,009 patients and a total of 31,065 bare-metal or drug-eluting stents) showed that discontinuation of antiplatelet therapy with ***clopidogrel*** was a strong independent predictor of stent thrombosis. Cessation of clopidogrel in the first 30 days after PCI increased the hazard ratio for stent

thrombosis to 36.5 (95% CI 8.0–167.8), and the absence of clopidogrel therapy between 30 days and 6 months was also linked to a significantly increased risk of stent thrombosis (HR 4.6, 95% CI 1.4–15.3). Patients with stent thrombosis had discontinued clopidogrel for a median of five days.[17]

Premature discontinuation of clopidogrel after stent placement, due to a non-cardiac surgery, can have fatal consequences. Schouten et al.[19] analyzed a total of 192 patients who underwent surgery within two years after bare-metal or drug-eluting stent implantation. Discontinuation of clopidogrel antiplatelet therapy before the recommended time (bare-metal stents one month, sirolimus-eluting stents three months, paclitaxel-eluting stents six months) was strongly related to adverse outcomes. Incidence of major adverse cardiac events was 30.7% in the discontinuation group versus 0% in the patients who continued antiplatelet therapy per guidelines ($p = 0.026$). All postoperative major adverse cardiac events were fatal! No difference was observed with respect to the type of stent.

A clear relationship was documented between perioperative bleeding and administration of dual antiplatelet therapy including thienopyridine, shortly before or at the time of coronary bypass surgery.[20,21] Less data are available about clopidogrel continuation during non-cardiac surgery and the risk of bleeding. Van Kuijk et al.[22] presented data concerning the risk of bleeding in 550 patients undergoing non-cardiac surgery after intracoronary stent implantation (376 with a drug-eluting stent and 174 with a bare-metal stent). A strong relationship was found between perioperative use of dual antiplatelet therapy and the risk of bleeding. Every fourth patient on dual antiplatelet therapy suffered a major bleeding complication. The risk of severe bleeding in patients receiving dual antiplatelet therapy was five times higher than in patients on aspirin alone (21% vs. 4%, $p < 0.001$). Unfortunately, we did not find any data about the risk of bleeding associated with non-cardiac surgery in patients on clopidogrel monotherapy. Clopidogrel monotherapy is associated with less risk of bleeding than aspirin monotherapy when evaluated in high-risk cardiovascular patients not undergoing surgery.[23] Badreldin et al.[24] reviewed the effect of preoperative clopidogrel as mono- (n = 48) and combination therapy with aspirin (n = 277) on bleeding-related complications in patients undergoing coronary artery bypass grafting. No significant difference was reported with clopidogrel monotherapy compared to its use in combination with aspirin. The comparison of bleeding risk between clopidogrel and aspirin monotherapy was not presented.

Timing is everything

The combination of antiplatelet therapy cessation and clotting activation during surgery has been implicated in the pathogenesis of stent thrombosis in the perioperative period, especially in incompletely endothelialized stents. The best solution to overcome the risks resulting from surgery performed in patients after stent implantation is to postpone the operation until after re-endothelialization of the vessel surface has been completed. Because only approximately 5–10% of surgeries are performed as an urgent procedure, this could be a significant way to increase the safety of non-cardiac surgical procedures following stent implantation.[8,25,26]

The time required to establish complete bare-metal stent endothelialization in humans is unknown but probably requires at least three months.[27] Nuttal et al.[25] published a retrospective analysis of 899 patients who underwent non-cardiac surgery within 1 year of bare-metal stent PCI at Mayo Clinic. To the best of our knowledge, this is the largest study published to date, addressing perioperative adverse cardiac events in non-cardiac surgical patients after recent bare-metal stent implantation. The analyses assessing the association of time between PCI and surgery with major adverse cardiac events and bleeding are summarized in *Table 1*. Shorter time intervals between PCI and surgery were related to an increased likelihood of cardiac events. The adjusted odds ratio for major adverse cardiac events was 3.2 for surgery performed 0–30 days after bare-metal stent implantation. This value decreased significantly (OR = 1.4) for surgery performed 31–90 days after PCI ($p = 0.006$). The incidence of major adverse cardiac events was lowest when a surgery was performed at least 90 days following bare-metal stent implantation.[25]

Drug-eluting stents take longer to endothelialize because of the cytotoxic drugs used to reduce vascular smooth muscle cell growth after coronary intervention.[28] Unfortunately, the period with the highest risk of stent thrombosis is prolonged. Schulz et al.[29] studied the effect of dual antiplatelet therapy duration on the incidence of drug-eluting stent thrombosis in a cohort of 6,816 consecutive patients during a four-year observational period. The protective effect of clopidogrel, relative to stent thrombosis, was mostly confined to the first 6 months after drug-eluting stent implantation with no substantial benefit thereafter.[29] Two large recent studies documented that the risk of major postoperative adverse cardiac events is inversely related to the time interval following drug-eluting stent placement.[22,26] Although stabilization of the risks of adverse cardiac events, after 6 months was demonstrated, an overall reduction in the incidence of cardiac events was only seen when non-cardiac surgery was performed more than 1 year after drug-eluting stent placement *(Table 1)*. Non-cardiac surgery within 1 year of PCI was associated with an 80% increase in the rate of major adverse cardiac events compared with surgery postponed for at least 1 year (18% vs. 10%, $p = 0.015$).[22] The multivariate hazard ratio for adverse cardiac events was 2.0 (95% CI 1.1–3.5) for surgery within one year of stent placement compared to longer time-intervals. Additionally, the risk of bleeding decreased with increasing time intervals between PCI and surgery.[22,26]

Elective versus emergency surgery

Emergency surgery per se is usually associated with hemodynamic instability, blood loss, and activation of

Table 1 **Univariate analysis of characteristics associated with cardiac events or bleeding events in patients with bare-metal and drug-eluting stent undergoing non-cardiac surgery**

	Major adverse cardiac events				Bleeding events			
	Bare-metal stent[25]		Drug-eluting stent[22,26]		Bare-metal stent[25]		Drug-eluting stent	
	%	*p* value	%	*p* value	%	*p* value	%	*p* value
Days from stent to surgery		0.003		< 0.001		0.046	NA	
≤ 30	10.5		35		6.9			
31–90	3.8		13		4.6			
91–180	3.0		15		4.2			
181–270	2.6				2.6			
271–365	2.7		* 6		3.6			
> 365			9					
Emergent surgery		0.003		0.006		0.016		
Yes	11.7		17.9		9.7			
No	4.4		4.7		4.1			
Surgical risk		0.136	NA			< 0.001		
Low	2.2				1.6			
Intermediate	5.8				2.2			
High	6.2				10.2			

* 181–365

hemostasis. There is no time for careful backup preparation. Studies with patients who underwent non-cardiac surgery following bare-metal and drug-eluting stent implantation have documented that emergency surgery was independently associated with both major adverse cardiac events and bleeding complications *(Table 1)*.[22,25,26] In retrospective analyses of patients with stents, the need for emergency surgery was the strongest variable associated with major cardiovascular events.[25,26] The rate of major adverse cardiac events was 17.9% for patients undergoing emergency procedures after drug-eluting stents and 11.7% with bare-metal stents versus 4.7% in patients undergoing non-emergency surgery after drug-eluting stent and 4.4% after bare-metal stent PCI, respectively.[25,26] Monitoring of myocardial ischemia in these patients is necessary, especially since perioperative ischemia is often underdiagnosed.[30]

Treatment of perioperative stent thrombosis

Stent thrombosis is mostly associated with total occlusion of the coronary artery and manifests as an ST-segment elevation acute myocardial infarction, and must be treated with immediate reperfusion.[31,32] Primary PCI should be performed as the reperfusion of choice in the perioperative period. Unfortunately, PCI also carries an increased risk of bleeding when performed shortly after surgery because antithrombin (heparin, bivalirudin) and antiplatelet agents (including glycoprotein IIb/IIIa antagonists) need to be administered during the procedure. If major bleeding complicates the PCI procedure in patients with stent thrombosis early after surgery, a vicious circle is established, often with fatal outcomes *(Figure 1)*.[33,34]

Recommendations

The risk of mortality due to stent thrombosis and major bleeding *(Table 2)* in patients undergoing non-cardiac surgery following PCI with stents indicates that the best option for dealing with these situations is to prevent them. The European and American Expert Opinion Guidelines address the problem of non-cardiac surgery in patients following stent implantation.[35–37]

Before stent placement

Many patients with coronary disease who require non-cardiac surgery do not benefit from preoperative revascularization.[38,39] The Coronary Artery Revascularization Prophylaxis (CARP) trial[38] enrolled 510 stable patients with angiographic coronary artery disease (one third had 3-vessel disease, left-main disease was excluded) undergoing major vascular surgery (abdominal aortic aneurysm repair, lower extremity revascularization). Patients were randomized to revascularization (PCI in 59%) versus no revascularization before surgery. No benefit was observed in terms of postoperative acute myocardial infarction and survival in revascularized patients compared to patients without preoperative revascularization. Therefore, if a

Table 2 **Reported mortality on perioperative stent thrombosis**

	N	Patients with stent thrombosis (N)	Mortality
Schouten et al.[19]	192	4	100%
Brichon et al.[44]	32	3	33%

patient with coronary disease is known to require surgery, the first question to ask is whether the patient really needs revascularization prior to surgery. If PCI has to be performed (patients with an acute coronary syndrome, an early positive stress test indicating severe ischemia, or life-threatening coronary anatomy), use of drug-eluting stents should be avoided.

After stent placement

1. Timing of the operation. Guidelines recommend delaying non-cardiac surgery for at least six weeks and optimally up to three months after bare metal stent implantation *(Table 1)*.[35,36] After drug-eluting stent implantation, elective surgery should not take place until after at least 12 months of continuous dual antiplatelet therapy.[35,36] The need for surgery in relation to its timing and the specific pathology should be balanced against the risk of stent thrombosis and careful "case-by-case" consideration is advisable.
2. Antiplatelet therapy. Expert recommendations advise that 3 months after bare-metal stent PCI and 12 months after drug-eluting stent PCI, patients can be sent for a non-cardiac surgery, with continuation of aspirin therapy.[35,36] Aspirin should only be discontinued if the risk of bleeding outweighs the potential cardiac benefits. Discontinuation of aspirin should be considered in those in whom hemostasis (neurosurgery, ophthalmosurgery, transurethral prostatectomy) is difficult to control during the operative procedure.

Difficult decisions regarding antiplatelet management arise when a patient still on dual antiplatelet therapy with aspirin and thienopyridine (usually clopidogrel) has to undergo surgery which cannot be postponed. A universal recommendation for this situation is unrealistic. *Discussion between the treating cardiologist (cardiovascular risk), surgeon (bleeding risk) and the anesthesiologist (functional reserve, backup preparation)* about this situation is recommended in order to achieve reasonable expert consensus.[35,36,40] Aspirin should be continued if possible. Neither observational nor randomized study data are available regarding continuation of monotherapy with clopidogrel in this situation. If discontinuation of clopidogrel therapy is necessary, thienopyridine should be resumed after 24 h (or the next morning) after surgery, if there is adequate hemostasis. In patients who require temporary interruption of aspirin or clopidogrel, or both, before surgery, it is recommended that this treatment be stopped at least five days and, preferably ten days, prior to the procedure.[35] Heparin therapy, either unfractionated heparin or low molecular weight heparin, via subcutaneous injection, has been proposed during the period of time when thienopyridine is stopped, but efficacy has not been proven.[41,42] Heparin therapy is unlikely to protect against stent thrombosis since it has no antiplatelet properties.

Continuation of dual antiplatelet therapy is justified if the risk of stent thrombosis outweighs the risk of procedure-associated bleeding. In this situation, perioperative caregivers should be on guard for ischemic events and be prepared for surgical bleeding. In recently published observational analyses, the incidence of surgical bleeding complications is low despite the high rate of dual antiplatelet therapy.[9,26] The increased incidence of operations performed on patients using combined antiplatelet therapy[9] has enhanced the knowledge and ability of surgeons and anesthesiologists to manage it without serious complications.[43] For patients receiving antiplatelet therapy, i.e. aspirin, clopidogrel, or both, with excessive or life-threatening perioperative bleeding, transfusion of platelets and administration of other prohemostatic agents is recommended.

Conclusion

Non-cardiac surgery in patients following intracoronary stent implantation involves a risk of stent thrombosis, especially if surgery has to be performed within the period when dual antiplatelet therapy is necessary. Awareness, prevention, and early treatment of perioperative complications in these patients are best achieved by collaboration between surgeons, anesthesiologists, and cardiologists. In the future, reversible and parenteral $P2Y_{12}$ receptor antagonists (ticagrelor, cangrelor) may prove to be of value perioperatively.

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