Noncardiac surgery following percutaneous coronary intervention

Percutaneous coronary intervention with implantation of a stent has become the most widely accepted coronary revascularization procedure. It effectively relieves ischemic symptoms, as well as improves survival in a selected group of high-risk patients. Yet, dilemmas arise when patients have to undergo noncardiac surgery after stent implantation. On the one hand, premature discontinuation of antiplatelet therapy has been found to be an important predictor of stent thrombosis. On the other hand, continuation of antiplatelet therapy might increase the risk of bleeding complications during the perioperative period. The issue is further complicated by the impact of timing of the noncardiac surgery on clinical outcomes. This article reviews the perioperative management of patients with coronary stent implantation, with special emphasis on the optimal timing of noncardiac surgery and perioperative use of antiplatelet therapy. Optimization of surgical risk by various pharmacological and nonpharmacological measures before noncardiac surgery are also discussed.

KEYWORDS: bleeding ■ noncardiac surgery ■ percutaneous coronary intervention ■ stent ■ thrombosis

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Since its inception more than 20 years ago, percutaneous coronary intervention (PCI) has undergone major advancements in both device refinement and variety. Operators' experience and knowledge on how to optimize outcomes and reduce complications have also improved tremendously. To date, PCI with stent implantation is the most widely accepted mode of coronary revascularization, and annual worldwide PCI usage exceeds 2 million. Yet, stent thrombosis remains a major hazard, limiting the success of PCI. With the utilization of high-pressure deployment techniques, coupled with intensive antiplatelet therapy after stent implantation, the incidence of stent thrombosis is approximately 1% following elective PCI, and 3–5% following urgent PCI for acute myocardial infarction [1,2]. Among others, premature discontinuation of antiplatelet therapy has been identified as an important factor leading to stent thrombosis [2].

Dilemmas arise when patients have to undergo noncardiac surgery after stent implantation. From the cardiologist's perspective, antiplatelet therapy is crucial in preventing stent thrombosis, and should not be discontinued without a good reason; however, from the surgeon's perspective, antiplatelet therapy would increase the risk of bleeding complications, leading to disastrous adverse events [3]. We will discuss this surprisingly ubiquitous circumstance with a real-life case that was encountered recently.

Mr P is a 54-year-old Chinese male with cardiovascular risk factors of diabetes mellitus and hypertension. He presented with a non-ST-segment elevation myocardial infarction in May 2010. PCI to the occluded mid-left circumflex artery, with implantation of two drug-eluting stents, was successfully performed (Figure 1). There was another significant stenosis at the proximal-to-mid left anterior descending artery (LAD).

As part of the workup for mild renal impairment 2 days after PCI, an ultrasound was performed, and showed a renal cell carcinoma in the right kidney. The management plan from the urologist was to perform a nephrectomy in late July 2010, 6 weeks after PCI, to the residual lesion in the LAD. In early June, the patient was readmitted for PCI to the LAD lesion. In consideration of the upcoming surgical procedure, the plan was to perform revascularization solely through balloon angioplasty without stent implantation. However, this initial plan had to be altered during the procedure, owing to suboptimal angiographic results. An endothelial progenitor cell-capture stent (Genous™, Bioengineered R stent™) was implanted successfully. Intravascular ultrasound interrogation was performed to optimize the stent expansion and apposition.

For the radical nephrectomy, the perioperative antiplatelet and antithrombin regimens were as follows: aspirin was continued

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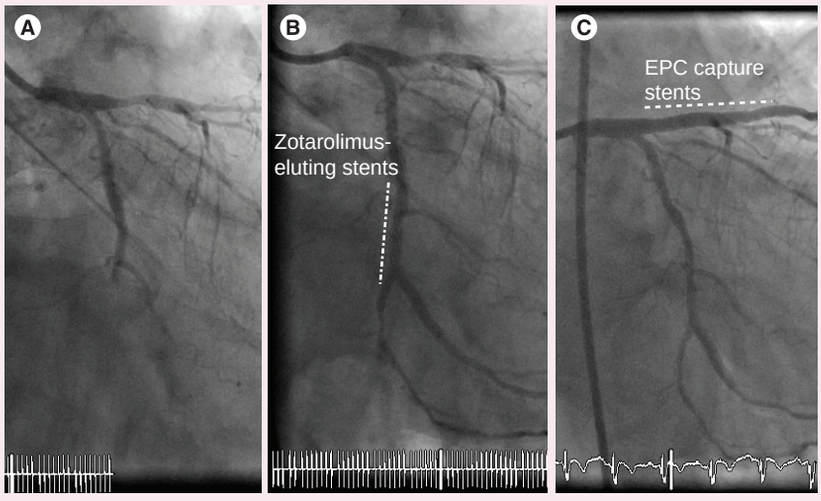

Figure 1. Angiographic findings of Mr P, who presented with a non-ST-elevation myocardial infarction. (A) Baseline angiography showing occluded mid-left circumflex artery (culprit for myocardial infarction) and significant proximal left anterior descending artery lesion. **(B)** A drug-eluting stent was implanted to the left circumflex artery. **(C)** An EPC-capture stent (Genous™ stent) was implanted to the left anterior descending artery following suboptimal angiographic results after balloon angioplasty.
EPC: Endothelial progenitor cell.

throughout the perioperative period and clopidogrel was stopped 7 days prior to surgery. A total of 3 days before surgery, we commenced continuous intravenous infusions of eptifibatide (to prevent platelet activation and adhesion) and unfractionated heparin (to prevent thrombin generation) until 8 h before surgery (per pharmacodynamic data from the eptifibatide product information sheet, stopping 4–6 h preoperatively would suffice if renal function was normal). The right nephrectomy was performed successfully, without ischemic complications or excessive bleeding. A clopidogrel 600-mg loading dose, followed by 75 mg daily, commenced the day after surgery. The patient recovered uneventfully, and was discharged 5 days after surgery. Serial hemoglobin and platelet measurements remained stable throughout the perioperative period.

Stent implantation, antiplatelet therapy & stent thrombosis

■ Contemporary PCI & antiplatelet regimen

From a histological perspective, stent placement into the coronary artery denudes the endothelium over the arterial wall. The stent struts are directly exposed to coronary circulation during the immediate period after implantation. The process of re-endothelialization of the stent strut takes place imminently after stent implantation; however, the time required to complete the process differs greatly between bare-metal stents and drug-eluting stents. After implanting bare-metal stents, approximately 4 weeks is needed for re-endothelialization of the stent struts to be completed. This is the rationale behind recommending 4 weeks of dual antiplatelet therapy after bare-metal stent implantation, although there are data suggesting that a shorter duration of 2 weeks may be safe [4]. After drug-eluting stent implantation, healing of the endothelium over the stent struts has been shown to be impaired secondary to antimetabolites impregnated in the stent strut coating. This results in a significantly longer time required for re-endothelialization [5]. Indeed, some investigators have postulated that re-endothelialization of the stent strut would never be complete with drug-eluting stents. In line with this, the risk of late (>1 year) stent thrombosis following drug-eluting stent implantation is higher than after bare-metal stent implantation [6], and this remains the case for up to 4 years after drug-eluting stent implantation [7].

■ Premature discontinuation of antiplatelet therapy

Bare-metal stents and more recently, drug-eluting stents, have gained increasing importance in the treatment of coronary artery disease, owing to its significant reduction in risk of restenosis compared with balloon angioplasty. Each year, several million coronary stents are implanted throughout the world. Penetration of drug-eluting stent varies in different countries, and can be as high as over 80% in some centers. However, occurrence of stent thrombosis, associated with a high incidence of fatal and nonfatal myocardial infarction, remains a major limitation for both bare-metal stents and drug-eluting stents. Large-scale registry studies and meta-analyses have found that, among other factors, premature discontinuation of antiplatelet therapy is the single most important predictor of stent thrombosis [2]. Recent guidelines recommend uninterrupted dual antiplatelet therapy with aspirin and thienopyridine for 4 weeks after bare-metal stent implantation, and 12 months after drug-eluting stent implantation [8].

Despite efforts to ensure prolonged dual antiplatelet therapy after coronary stent implantation, premature drug discontinuation continues to occur nonetheless. Previous studies found that that between 6.7 and 13.6% of patients discontinued their antiplatelet therapy after coronary stent implantation [9,10]. Patients who ceased antiplatelet therapy within 30 days after

drug-eluting stent implantation for acute myocardial infarction were found to have a higher mortality over the subsequent 11 months [10].

■ Thrombotic risk of noncardiac surgery following PCI

The perioperative management of patients with implanted coronary stents encompasses the delicate balance between an increased propensity for perioperative stent thrombosis and myocardial infarction with the discontinuation of antiplatelet treatment, and increased bleeding risk with continued antiplatelet therapy (Table 1) [11–23]. The majority of the PCI procedures performed in the current era involve the implantation of metallic stents, the benefit of which is a lowered risk of restenosis, and reduces the need for repeat revascularization compared with balloon angioplasty. These strengths are even more evident when drug-eluting stents are used.

There are a number of reports evaluating the risk and timing of stent thrombosis in patients undergoing noncardiac surgery after coronary stent implantation (Table 2). The reported risks of perioperative mortality varied widely, from 2.5 to 21.4%. There are a number of possible reasons for this discrepancy, including small sample sizes (n < 100) in most of these series, different durations between PCI and the noncardiac surgery, and the different nature of surgeries studied. Overall, studies have revealed that with bare-metal stent implantation, the risks of stent thrombosis and adverse events are significantly reduced when surgery is delayed for at least 6 weeks [16–23].

Reporting from the Mayo Clinic database, Wilson *et al.* analyzed the largest series of 207 patients, who underwent noncardiac surgery within 60 days after PCI with bare-metal stent implantation [17]. The antithrombotic regimen used was neither a standardized nor up-to-date regimen, with 21% of the patients being prescribed warfarin after stent implantation. They reported a total of eight deaths (4% mortality) during the perioperative period, all of whom had surgeries performed within the first 6 weeks after PCI. Overall, no association was found between the antiplatelet regimen before noncardiac surgery and the incidence of bleeding complications, hence suggesting it might be safe to continue with the prescribed antiplatelet regimen.

A small but prospective study demonstrated a remarkably high adverse event rate of 44.7%, and mortality rate of 5% amongst the cohort of 103 patients, all of which had undergone noncardiac surgery within 1 year after coronary stent implantation [20]. Adverse events were cardiac complications and bleeding only. More importantly, the results of the study demonstrated a statistically significant correlation between a shorter time span between stent implantation and surgery, and a higher risk of adverse events. Patients who underwent surgery fewer than 35 days after PCI had a 2.1-fold increased risk of complications compared with those who were operated on more than 90 days later.

A more recent study was conducted by Schouten *et al.*, and reviewed a total of 192 patients [21]. Patients were divided into either the early-surgery group (surgery performed when clopidogrel was

Table 1. Manipulation of antiplatelet therapy based on risk of surgical bleeding and risk of stent thrombosis.

Risk of stent thrombosis	Risk of surgical bleeding		
	High	***Moderate***	***Low***
High	Stop all oral antiplatelet agents Consider short-acting iv. antiplatelet agents Proceed with surgery Restart oral antiplatelet agents after surgery	Continue at least one oral antiplatelet agent if possible Consider short-acting iv. antiplatelet agents Proceed with surgery Restart oral antiplatelet agents after surgery	Continue all oral antiplatelet agents Proceed with surgery
Moderate	Stop all oral antiplatelet agents Proceed with surgery Restart oral antiplatelet agents after surgery	Continue one oral antiplatelet agent if possible Proceed with surgery Restart oral antiplatelet agents after surgery	Continue all oral antiplatelet agents Proceed with surgery
Low	Stop all oral antiplatelet agents Proceed with surgery Restart oral antiplatelet agents after surgery	Stop all oral antiplatelet agents Proceed with surgery Restart oral antiplatelet agents after surgery	Continue one oral antiplatelet agent if possible Proceed with surgery Restart oral antiplatelet agents after surgery

iv.: Intravenous.

Table 2. Coronary stent thrombosis and noncardiac surgery.

	Study	Type	Time period	Patients (n)	Time from PCI to surgery	Mortality rate (%) (95% CI)	Ref.
BMS	Kaluza *et al.* (2000)	Retr, NR	1996–1998	40	<42 days	21.4 (10.2–35.0)	[16]
	Wilson *et al.* (2003)	Retr, NR	1990–2000	207	<60 days	3.4 (1.2–6.3)	[17]
	Sharma *et al.* (2004)	Retr, NR	1995–2000	47	90 days	18.4 (8.6–30.4)	[18]
	Reddy *et al.* (2005)	Retr, NR	1999–2004	56		8.6 (2.3–17.5)	[19]
	Leibowitz *et al.* (2006)	Retr, NR	1995–2002	94	<90 days	14.6 (8.1–22.4)	[20]
Drug-eluting stents	Compton *et al.* (2006)	Retr, NR	2003–2006	38		2.5 (0.0–7.9)	[22]
	Rhee *et al.* (2008)	Retr, NR	2002–2006	141	<12 months	3.6	[11]
	Assali *et al.* (2009)	Retr, NR	2002–2006	78	>6 months	5.1	[12]
	Godet *et al.* (2008)	Retr, NR		96		2.1	[13]
Both drug-eluting stents and BMS	Schouten *et al.* (2007)	Retr, NR	1999–2005	192	<2 years	3.1 (1.0–6.1)	[21]
	Kim *et al.* (2008)	Retr, NR	2003–2006	239		Bare-metal stent: 0.0 Drug-eluting stent: 0.7	[14]
	Cruden *et al.* (2010)	Retr, NR	2003–2007	1953		Bare-metal stent: 0.6 Drug-eluting stent: 0.7	[15]

BMS: Bare-metal stent; NR: Nonrandomized; PCI: Percutaneous coronary intervention; Retr: Retrospective.
Adapted with permission from [3].

still required) or the late-surgery group (when clopidogrel was completed). Within the first 30 postoperative days, major adverse cardiac events occurred in four out of 30 patients (13.3%) in the early-surgery group, while only one major adverse cardiac event (0.6%) occurred in the remaining 162 patients from the late-surgery group. All five major adverse cardiac events were fatal. These studies, thereby, reflect the importance of prolonging the time span between PCI and surgery in order to avoid these undesirable, and often fatal, consequences.

Compared with bare-metal stents, less data reporting the risk of perioperative stent thrombosis after drug-eluting stent implantation are available. There are a number of anecdotal reports on late stent thrombosis associated with noncardiac surgery. In the Dallas Veterans Affairs Medical Center, 38 patients underwent 41 major and 18 minor noncardiac surgeries at 9–10 weeks after successful drug-eluting stent implantation (57% sirolimus-eluting stents and 43% paclitaxel-eluting stents) [23]. Antiplatelet therapy was continued during the perioperative period in 41% of the patients. No major adverse cardiac events or death occurred during or after the surgery, even when antiplatelet therapy was not discontinued. Despite the limitations of the small sample size, these findings suggest a low risk of major cardiac complications in patients undergoing noncardiac surgery after sirolimus- and paclitaxel-eluting stent implantation, even with the continuation of antiplatelet therapy.

Owing to the lack of good quality data, the perioperative management of patients with a drug-eluting stent should be carried out on a case-by-case basis, ideally with input from the cardiologist, surgeon and anesthetist. Factors that need to be considered include, not only the relative risk of bleeding and stent thrombosis, but also the potential clinical sequelae if these adverse events occur. Stent thrombosis in the left main coronary artery carries a grave prognosis, but may result in a nonfatal, less severe infarction if it occurs in an obtuse marginal branch instead.

Risk of surgical bleeding following PCI

Antiplatelet agents are perceived by many surgeons to cause excessive perioperative bleeding. A survey in a single institution demonstrated that 55.3% of patients had aspirin withheld before operation, and 100% of patients had clopidogrel withheld [24]. Another study revealed that 62% of urologists withdrew all antiplatelet agents for patients preoperatively, regardless of the nature of the procedure [25]. The surgery-specific risk and severity of perioperative bleeding for patients having antiplatelet agents remain understudied.

Transurethral prostatectomy and transrectal prostate biopsy were some of the few exceptions. Early reports suggested an increased risk of bleeding, and even mortality, in transurethral prostatectomy patients continuing on aspirin [26,27]. Subsequently, a randomized controlled trial carried out by Nielsen *et al.* demonstrated that, despite increased perioperative blood loss found with aspirin continuation in transurethral prostatectomy patients, there was no increase in transfusion rate or mortality [28]. Further studies, including a prospective study [29] and a randomized controlled trial [30] showed that there was no

significant difference in the incidence of hematuria, hemaspermia or rectal bleeding in patients who underwent transrectal prostate biopsy on aspirin therapy compared with those in whom aspirin was withheld. Reports on the newer laser prostatectomy showed no increased transfusion requirement, even when the patients continued with either clopidogrel or aspirin [31]. A meta-analysis revealed that, in patients on low-dose aspirin undergoing noncardiac surgery, the amount of bleeding increased by a factor of 1.5 [32]. However, this increase was not associated with any severe bleeding complications. This analysis included procedures such as epidural injection, cutaneous surgeries, dental extraction, needle biopsies, peritoneal dialysis catheter, endoscopic procedures, cataract surgery, hip fracture fixation and replacement, tonsillectomy, prostatectomy, carotid endarterectomy and peripheral artery bypass. A recently published randomized controlled trial compared the bleeding risk of patients undergoing noncardiac surgery with and without aspirin continuation [33]. Among the 220 patients enrolled, there was no difference in bleeding complication between the two groups. Moreover, the group in which aspirin was discontinued demonstrated a significantly higher incidence of major adverse cardiac events (9.0 vs 1.8%; p = 0.02).

Risk stratification before noncardiac surgery

Preoperative assessment is usually performed to give medical clearance for surgery, as well as provide necessary clinical information for informed judgments to be made by anesthesiologists and surgeons. Noncardiac surgical procedures can often be categorized into low, intermediate and high risk, which are associated with less than 1, 1–5 and more than 5% risk of cardiac complications (**Box 1**). Patients undergoing low-risk surgery do not often require any further preoperative cardiac testing. The Lee Index, which was revised from the Goldman index, is regarded by most clinicians as the most relevant cardiac risk-prediction index for noncardiac surgery. It identified six factors of prognostic importance in predicting major cardiac complications, consisting of type of high-risk surgery, existing ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus requiring insulin therapy and renal insufficiency (indicated by preoperative serum creatinine >2.0 mg/dl) [34].

In the revised American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, it is recommended that noninvasive functional assessment be undertaken in the presence of one or more of the six factors from the Lee Cardiac Risk Index, if it was likely to modify the patient's management.

Recently, the benefits of preoperative stress testing have been questioned, as a result of the Dutch Echocardiographic Cardiac Risk Evaluation (DECREASE)-2 study results, revealing that there were similar rates of perioperative death or myocardial infarction amongst patients who were tested by either dipyridamole myocardial perfusion scintigraphy or dobutamine stress echocardiography, and those who were not tested at all [35]. However, it is important to note the stringent definition of myocardial infarction utilized in the study, which was classified as the presence of both elevated cardiac enzymes and Q waves. This would naturally result in an underestimation of myocardial infarction occurrence, in the context of perioperative myocardial infarction commonly being clinically silent and without ST-segment elevation.

Coronary angiography is often not regarded as an ideal diagnostic option in the perioperative circumstance. Despite its significant prognostic value, the invasiveness of the procedure, and the debatable benefit of preoperative revascularization makes its associated risks greater than its benefits. Multidetector cardiac computed tomography is a promising alternative, with its high positive-predictive value of 95% for the detection of lesions in the left main trunk, and an almost 100% negative-predictive value [36]. However, more studies must be carried out to reaffirm its role as preoperative risk stratification.

Strategies for risk optimization: PCI-related issues

■ Deferring PCI after noncardiac surgery in a low-risk group

It is not an uncommon practice that surgeons or anesthetists request an evaluation of cardiac condition before major noncardiac surgery, especially in patients with history of coronary revascularization or multiple cardiovascular risk factors. For patients with significant coronary artery stenosis documented, the value of prophylactic revascularization is highly controversial, and should be considered on a case-by-case basis. The concept of a beneficial effect of prophylactic coronary revascularization before major noncardiac surgery is based on the assumption that perioperative myocardial infarction arises at the location in coronary arteries of significant stenosis. However, the validity of this assumption and hence, benefit of prophylactic revascularization, are questionable, as it has been found that most

Box 1. Risk stratification for noncardiac surgical procedures.

High risk
- Emergency operations
- Vascular, especially aortic
- Prolonged surgeries associated with drastic fluid shifts and/or blood loss

Intermediate risk
- Carotid endarterectomy
- Head and neck
- Intraperitoneal
- Pulmonary
- Orthopedic
- Prostate

Low risk
- Endoscopic procedures
- Superficial procedures
- Cataract
- Gynecology and breast
- Dental

myocardial infarctions develop from previously nonsignificant coronary stenoses. To date, there is no effective way of identifying these nonsignificant but vulnerable plaques, which could lead to perioperative myocardial infarction.

For clinically stable patients without indication for early PCI, the intention of reducing the risk of perioperative ischemic by prophylactic revascularization is not supported by recent clinical studies (see later). Moreover, the need for dual antiplatelet therapy following stent implantation might cause an inadvertent delay to surgery, which might be detrimental in some conditions, such as malignant disease.

The Coronary Artery Revascularization Prophylaxis (CARP) trial was the first randomized study that addressed the strategy of prophylactic coronary revascularization in patients with clinically stable coronary artery disease, who were scheduled for major vascular surgery [37]. Most of the patients in the CARP trial had low-risk coronary anatomy, such as single- or two-vessel disease, with a preserved cardiac function. The investigators found that prophylactic revascularization was safe, but failed to improve either perioperative or long-term clinical outcomes. More recently, the DECREASE V pilot study studied the role of prophylactic coronary revascularization in high-risk patients with preoperative extensive stress-induced ischemia [38]. Coronary angiography showed two-vessel disease in 24%, three-vessel disease in 67% and left main coronary artery disease in 8% of the patients. Once again, prophylactic revascularization before major noncardiac surgery failed to improve 30-day, as well as 1-year, clinical outcomes.

The latest ACC/AHA guideline suggests that PCI before noncardiac surgery is only indicated in high-risk clinical conditions, such as acute coronary syndrome, or high-risk angiographic features, such as left main disease, proximal LAD disease or multivessel coronary artery disease [39]. PCI to non-left main coronary artery stenoses in stable low-risk patients before noncardiac surgery is not warranted, and should be deferred.

■ Selection of appropriate revascularization strategies

Patients in whom coronary revascularization is indicated before noncardiac surgery constitute a unique group, where the mode of revascularization may be different from other patients. Among the various modes of percutaneous revascularization (e.g., balloon angioplasty, bare-metal stent and drug-eluting stent implantation), the main difference lies in the risk of restenosis and need for repeat revascularization. Current evidence does not support a clear survival benefit of one mode over another.

Although balloon angioplasty carries a higher risk of restenosis compared with stent implantation; the absence of mandatory postprocedural dual antiplatelet therapy may be a merit over the other two options for patients undergoing subsequent noncardiac surgery. In a series of 350 patients who underwent noncardiac surgery within 2 months of successful balloon angioplasty, the incidence of perioperative death or myocardial infarction was 0.9%. The repeat target vessel revascularization rate was 2.9% [40]. Therefore, balloon angioplasty appears to be a safe option in patients who require PCI before noncardiac surgery.

The optimal timing of the surgery is probably within the first 2–3 months after balloon angioplasty, as restenosis (if it were to happen) would not occur at this time and, therefore, the risk of perioperative myocardial ischemia is lower. Depending on the clinical and angiographic conditions, patients can undergo noninvasive stress tests and stent implantation after recovery from surgery. The recently emerged drug-eluting balloon is a novel device that may have good therapeutic potential in patients before noncardiac surgery [41]. It obviates the need for mandatory prolonged dual antiplatelet therapy and, possibly, could have a lower restenosis rate than conventional balloon angioplasty.

When optimal angiographic results cannot be achieved with balloon angioplasty, such as early recoil or flow-limiting dissection, stent implantation may become a necessary measure. Between

bare-metal stents and drug-eluting stents, the former is preferable before noncardiac surgery, as the duration of dual antiplatelet therapy required is shorter. Drug-eluting stent implantation is indicated when the risk of restenosis is very high, and noncardiac surgery can be safely postponed for at least 12 months until completion of the dual antiplatelet therapy. Intravascular ultrasound guidance to improve the efficacy of stent implantation, such as optimizing stent expansion and apposition, as well as precluding edge dissection, could be particularly important in this group of patients.

The endothelial progenitor cell-capture stent (Genous™ stent, OrbusNeich, FL, USA) is a stent coated with murine monoclonal antihuman CD34 antibodies, designed to attract circulating endothelial progenitor cells to rapidly establish a functional endothelial layer and promote healing. Therefore, there is a valid theoretical reason to postulate that an endothelial progenitor cell-capture stent could be an alternative to a bare-metal stent in a patient undergoing noncardiac surgery following PCI. The endothelial progenitor cell-capture stent has been shown to be safe in the clinical setting, including patients with ST-segment elevation myocardial infarction [42,43]. Although angiographic studies showed that the restenosis rate does not match that of drug-eluting stent, the theoretical lowered risk of stent thrombosis may be appealing to patients undergoing noncardiac surgery. A recent study reports a series of 22 patients on whom biological stents were used before lifesaving and undeferrable major noncardiac surgery could be performed. Despite a mean duration of antiplatelet therapy of only 12.5 days, no perioperative cardiac complications were reported [44].

Finally, coronary artery bypass surgery remains a reasonable option, especially in patients with complex multivessel coronary artery disease [45]. The main advantages of coronary artery bypass grafting, compared with PCI before noncardiac surgery, is that there is no need for dual antiplatelet therapy, as well as having a higher chance of achieving complete revascularization. However, patients' reluctance to undergo two major surgeries within a short period could be a major limitation for coronary artery bypass surgery as a revascularization option.

■ Optimal timing of noncardiac surgery following PCI

It has been repeatedly shown that a short duration between PCI and noncardiac surgery is a critical factor leading to high-risk perioperative major adverse events, especially thrombosis and myocardial infarction. This is mainly related to the increased risk of stent thrombosis before complete endothelialization of the exposed stent struts – contributed by the prothrombotic status of the surgery – with or without discontinuation of antiplatelet therapy. After bare-metal stent implantation, a delay of surgery for approximately 6 weeks after PCI is recommended. This is based on many, albeit retrospective, data suggesting that almost all major adverse events associated with noncardiac surgery occur when the surgery was performed up to 6 weeks after PCI. This is also the approximate time required for the antiplatelet effect of clopidogrel to diminish (~7 days) after completion of dual antiplatelet therapy (4 weeks).

For drug-eluting stents, the relevant data on optimal duration between PCI and noncardiac surgery is very limited. If surgery is performed within 1 month after PCI, the risk of perioperative stent thrombosis is similar between bare-metal stents and drug-eluting stents. Differences arise when the surgery is performed over 1 month post-PCI, in consideration of the longer time required for stent strut endothelialization after drug-eluting stent implantation. The timing and completeness of endothelialization of the stent strut of drug-eluting stents have been studied extensively over the past few years. Based on current evidence, mainly on first-generation drug-eluting stents, the time needed for endothelialization is believed to be substantially longer than bare-metal stents. Therefore, it is appropriate to predict that the risk of stent thrombosis might be higher for drug-eluting stents in surgeries performed 1 month post-PCI.

Another issue that needs to be considered in this context is the safety of deferring surgery. Surgery for benign conditions, such as benign prostate hypertrophy or hemorrhoids, can be delayed safely for a few months or even 1 year. On the other hand, there is a high risk associated with deferring surgery for malignant diseases owing to the possibility of metastasis, which would severely impact prognosis. For surgeries deemed urgent, a further reduction of risk using pharmacological measures is important.

Strategies for risk optimization: pharmacological issues

■ Bridging intravenous Gp IIbIIIa inhibitor

Under ideal situations, noncardiac surgery should be deferred until completion of dual antiplatelet therapy after coronary stent implantation. However, often this may not be feasible in patients with recently implanted drug-eluting

stents, as the nature of the underlying surgical emergency may preclude this waiting period of up to 12 months. The risk of stent thrombosis is particularly high if clopidogrel is discontinued beforehand. A pilot study explored the potential role of perioperative administration of tirofiban, a short-acting Gp IIbIIIa inhibitor, in patients who had undergone drug-eluting stent implantation, requiring urgent noncardiac surgery [46]. A total of 30 patients with a recently implanted drug-eluting stent, and subsequently scheduled to undergo noncardiac surgery, were recruited. Clopidogrel was withdrawn 5 days before surgery. A bridging Gp IIbIIIa inhibitor (tirofiban) was started, and continued until 4 h before surgery. Oral clopidogrel was resumed immediately after surgery. There were no cases of major adverse cardiac events or surgical re-exploration owing to bleeding complications. Although limited by the small sample size, this result suggests that, in patients with a recently implanted drug-eluting stent needing urgent noncardiac surgery, a 'bridging strategy' using intravenous Gp IIbIIIa inhibitor is a safe and feasible option. In view of the shorter duration of the antiplatelet effect, eptifibatide and tirofiban (rather than abciximab) may be the preferable bridging Gp IIbIIIa inhibitor before noncardiac surgery.

■ Prasugrel

Prasugrel is a member of the thienopyridine class of ADP receptor inhibitors. It reduces platelet aggregation by irreversibly binding to P2Y12 receptors. Compared with clopidogrel, prasurgrel provides more rapid and consistent inhibition of ADP-induced platelet aggregation. Its rapid onset of action allows metabolite concentration to peak within 30 min [47], enabling the achievement of an immediate antiplatelet effect, which is particularly important during urgent PCI.

To date, no studies have specifically assessed the risks and benefits of prasugrel in patients undergoing noncardiac surgery. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction (TRITON TIMI)-38 trial, which compared prasurgrel with clopidogrel in patients with acute coronary syndrome, the more potent prasugrel was found to be associated with higher bleeding risk in patients undergoing coronary artery bypass grafting [48].

Conclusion

Thrombosis of a coronary stent is a catastrophic complication. The risk of stent thrombosis is increased in the perioperative setting, and is strongly associated with the discontinuation of antiplatelet therapy. This article reviewed the perioperative management of patients with coronary stent implantation, with special emphasis on the optimal timing of noncardiac surgery and perioperative use of antiplatelet therapy. Discontinuation of dual antiplatelet therapy is the single most significant predictor of perioperative stent thrombosis. Available data on perioperative management of patients with drug-eluting stents are limited, and recommendations are predominantly based on the management of patients with bare-metal stents. To minimize the risk of perioperative stent thrombosis, aspirin and clopidogrel ideally should be continued throughout surgery. In spite of the increased risk of bleeding, this strategy is acceptable in many types of invasive surgical procedures, with no change in clinical outcomes. However, if the bleeding risk outweighs the risk of stent thrombosis, other potential strategies, including treatment with aspirin, with or without bridging therapy, using a short-acting Gp IIbIIIa inhibitor, should be considered. With the available evidence, continuing antiplatelet therapy is recommended for patients undergoing noncardiac surgery. For nonurgent surgery, deferring surgery until the completion of dual antiplatelet therapy (6 weeks after bare-metal stent and 12 months

Executive summary

- Perioperative management of patients with implanted stents requires a delicate balance between an increased thrombosis and myocardial infarction risk, with the discontinuation of antiplatelet therapy, and increased bleeding risk with continued antiplatelet therapy.
- For bare-metal stents, the risks of stent thrombosis and adverse events are significantly lower when surgery is delayed for at least 6 weeks following stent implantation.
- The limited scientific data available reveal that continuation of antiplatelet therapy was not associated with an increase in risk of severe bleeding complications. In fact, patients with discontinued treatment demonstrated a significantly higher incidence of adverse events.
- Prophylactic revascularization is not found to reduce the risk of perioperative ischemia and, hence, should be deferred until after surgery, unless indicated (e.g., with acute coronary syndrome or with high-risk angiographic features).
- Pharmacological options for risk optimization, such as the bridging Gp IIbIIIa inhibitor, can be considered when antiplatelet therapy is withdrawn preoperatively.

after drug-eluting stent implantation) would significantly reduce the risk of perioperative major adverse events.

Future perspective

There is exciting ongoing scientific research, which may lead to profound changes in the area of noncardiac surgery following PCI. Clinical studies on biodegradable stents have already started. It is conceivable that implantation of a biodegradable stent, which obviates the need for mandatory prolonged dual antiplatelet therapy, would become an attractive option for patients who have scheduled noncardiac surgery. Prasugrel, with its better efficacy than clopidogrel, is likely to become the first-line thienopyridine for patients undergoing percutaneous coronary intervention. Its potential side effect of increased bleeding complications in patients undergoing noncardiac surgery needs to be closely monitored. It is not an uncommon practice for surgeons requesting discontinuation of dual antiplatelet therapy before surgical operations, although scientific data have repeatedly confirmed the safety of continuing antiplatelet therapy during the perioperative period for most surgical procedures. A more intensive education program for physicians and surgeons on this aspect is warranted.

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