Thrombosis of a drug-eluting stent (DES) is a catastrophic complication. The risk of stent thrombosis (ST) is increased in the perioperative setting and is strongly associated with the cessation of antiplatelet therapy. This article reviews the perioperative management of patients with DES with a clinical focus on the perioperative use of antiplatelet therapy. Cessation of dual antiplatelet therapy is the single most significant predictor of perioperative ST. Available data on perioperative management of patients with DES are limited, and recommendations are therefore limited. To avoid ST with DES, aspirin and thienopyridines should ideally 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 outcome. However, if the bleeding risk outweighs the risk of ST, other potential strategies include treatment with aspirin alone, “bridging therapy” with aspirin and a glycoprotein IIb/IIIa inhibitor and/or heparin, and “bridging therapy” without aspirin. Novel antiplatelet therapies are promising and potentially valuable in the perioperative management of patients with DES. Maintaining dual antiplatelet therapy is the mainstay of perioperative ST prevention. However, short-term discontinuation of thienopyridines might be associated with relatively low risk if aspirin therapy is maintained perioperatively. (J Am Coll Cardiol Intv 2010;3:131–42) © 2010 by the American College of Cardiology Foundation

Multiple reports of perioperative stent thrombosis (ST) in patients with drug-eluting stents (DES) have been published. Stent thrombosis is a catastrophic complication, and the perioperative management of such patients is a major clinical issue. This risk of ST is lowered primarily with the use of dual antiplatelet therapy (1). The common practice of cessation of dual antiplatelet therapy to avoid excessive perioperative bleeding should be minimized, because it puts patients at a higher risk of perioperative ST (2). American and European guidelines recommend dual antiplatelet therapy with aspirin and a thienopyridine in patients with DES for at least 12 months after percutaneous coronary intervention (PCI) to prevent ST (1-4). This review focuses on the perioperative use of antiplatelet agents in patients with DES undergoing noncardiac surgery and strategies to avoid ST.

Methods

Search strategy. A search was carried out in the PubMed database with the terms: “drug eluting”, “stent thrombosis”, “perioperative”, “antiplatelet”, and “surgery”. The search captured 4,638 articles; 4,017 were English-language articles. Of these articles, 694 included DES and 414 articles involved surgeries or perioperative settings. Ninety-nine articles remained after excluding unrelated articles (Fig. 1).

Our search included articles discussing pharmacological aspects and evidence-based uses of available and investigational antiplatelet therapies, particularly in a perioperative setting and their effect on bleeding risk. The search combined the following terms interchangeably: “perioperative”,

From the *Division of Cardiology, Royal Victoria Hospital/McGill University Health Centre, Montreal, Quebec, Canada; and the †Division of Cardiology and Clinical Epidemiology, Jewish General Hospital/McGill University, Montreal, Quebec, Canada. Dr. Eisenberg is a National Researcher of the Quebec Foundation of Health Research.

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“noncardiac surgery”, “non-cardiac surgery”, “antiplatelets”, “aspirin”, “thienopyridines”, “clopidogrel”, “ticlopidine”, “glycoprotein IIb/IIIa inhibitors”, “perioperative”, “bleeding”, “heparin”, “prasugrel”, “AZD6140”, “drug-eluting”, and “late stent thrombosis”. Furthermore, due to the large number of references with these terms, we searched the Medical Subject Headings service provided by PubMed with these terms to obtain the specific results that we sought. Finally, citations from those selected articles were examined for other relevant articles.

**Inclusion/exclusion criteria.** English-language articles discussing DES, ST, and antiplatelet therapy in the perioperative setting were included. Non–English-language articles, noncoronary stents, and cardiac surgery articles were excluded.

**ST in DES**

Despite the great success of DES, data demonstrating associated late and very late stent thrombosis (VLST) have raised many concerns regarding their safety (5–9). In response to concerns of ST, a Food and Drug Administration Circulatory System Advisory Panel Meeting concluded in December 2006 that DES were associated with a small yet significant risk of late stent thrombosis compared with bare-metal stents (BMS). However, the risk of death or myocardial infarction was only increased in off-label use, which corresponds to at least 60% of DES use (10). Subsequently the American Heart Association/American College of Cardiology (AHA/ACC)/Society for Cardiovascular Angiography and Interventions/American College of Surgeons/American Dental Association published an advisory on the risks of premature cessation of antiplatelet therapy and its significance in reducing the risk of ST and on the hazards of premature cessation (2).

Stent thrombosis is a sudden and potentially catastrophic complication of PCI. It usually manifests as ST-segment elevation myocardial infarction (STEMI), malignant arrhythmias, or death (7,11–13). Available data demonstrate a high mortality ranging between 9% and 45% with ST (5–9,14–18).

Stent thrombosis is a platelet-mediated process that occurs through progressive platelet activation and aggregation leading to thrombus formation (19,20). PCI causes endothelial and medial damage that heals by neointimal formation, usually within 2 to 6 weeks with BMS (21).

However, with DES, re-endothelialization and neointimal healing are delayed, keeping stent struts exposed, which causes platelet aggregation and thrombus formation (21).

Several risk factors for ST, including stent-related, procedure-related, and patient-related variables, have been described (Table 1) (4,8,14,16,22–28). Moreover, hypersensitivity to the stent polymer has been described (29). However, the single most important predictor of ST is the premature cessation of dual antiplatelet therapy (8,26,30–34).

**Noncardiac Surgery and ST**

The risk of perioperative ST has been well-established in patients undergoing noncardiac surgery early after PCI. It was demonstrated that patients undergoing noncardiac surgery had increased mortality within 6 weeks after PCI compared with patients undergoing surgery after 6 weeks (35). After major surgery, there is a rise in thrombogenic
risk secondary to catecholamine release, increased platelet aggregability, and decreased fibrinolysis leading to a hyper-coagulable state (36–39). In addition, acute withdrawal of antiplatelet therapy might trigger a rebound effect and increase the risk of ST (40–42). Therefore, due to such a high risk of mortality, prevention of thrombosis is crucial.

There are limited data concerning perioperative ST in patients with DES (Table 2) (9,30,33,43–58). However, in keeping with previous reports, available data suggest that the rate of major adverse cardiac events (MACE) with DES is higher in early surgery compared with late surgery, with no difference between sirolimus-eluting and paclitaxel-eluting stents. Furthermore, most cases of MACE were associated with the cessation of antiplatelet therapy (9,30,43,44,50–52).

### Antipatelel Therapy for Patients With DES

Antiplatelet agents are crucial in ST prevention, which is a platelet-mediated process by acting on various steps of the thrombus formation process (20). However, when used perioperatively, antiplatelet agents are associated with an increased risk of surgical bleeding. Adding thienopyridines to aspirin (dual antiplatelet therapy) yields a synergistic effect and is the standard of care after DES implantation to avoid ST (14). Ticlopidine is similar to clopidogrel but is limited by side effects such as agranulocytosis and thrombotic thrombocytopenic purpura (59,60).

In the 2007 updated ACC/AHA guidelines on management of STEMI, the addition of thienopyridines to aspirin is recommended regardless of reperfusion therapy for at least 14 days and up to 1 year if there is no risk of bleeding (61). Dual antiplatelet therapy proved to be beneficial in reducing cardiac events in PCI (62–64). Furthermore, dual antiplatelet therapy was superior to either aspirin or thienopyridines alone in prevention of ST (13) and was also superior to the combination of aspirin and warfarin (65). In the 2007 focused update by the ACC/AHA/Society for Cardiovascular Angiography and Interventions on PCI, dual antiplatelet therapy is recommended for all patients receiving DES unless there is a high risk of bleeding (1).

The guidelines also add that in patients with clinical features associated with ST (i.e., renal insufficiency, diabetes, or procedural characteristics, such as multiple stents or treatment of a bifurcation lesion) extending dual antiplatelet therapy beyond 1 year might be reasonable (1).

The efficacy of dual antiplatelet therapy in reducing MACE after PCI over the first year was demonstrated by the PCI-CURE (Clopidogrel in Unstable angina to prevent Recurrent Ischemic Events) study and the CREDO (Clopidogrel for the Reduction of Events During Observation) study in patients undergoing PCI with BMS (62,64). In the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) study, a similar reduction of MACE was achieved in secondary prevention of patients without acute coronary syndromes and not undergoing PCI, with no significant benefit of clopidogrel beyond 1 year, in addition to a higher risk of bleeding (66).

### Perioperative bleeding with antiplatelet therapy

The single most important predictor of ST is the cessation of antiplatelet therapy (8,26,30,32,67,68). Nevertheless, balancing the risk of ST against the risk of bleeding associated with antiplatelet agents is critical. The effect of dual antiplatelet therapy in surgical bleeding has been mostly studied in cardiac surgery. Most data suggest that, at a low dose, taking aspirin perioperatively in bypass surgery is associated with a low risk of excessive bleeding (69–71). However, the addition of thienopyridines to aspirin results in a significant increase in bleeding, blood product transfusions, ventilation
requirements, length of hospital stay, and surgical re-exploration in patients kept on thienopyridines (72–76). In the CURE trial, it was concluded that there was a 1% increase of excessive bleeding in patients with clopidogrel held before coronary artery bypass graft surgery (77). For this reason, the ACC/AHA guidelines recommend that, in patients taking clopidogrel for whom coronary artery bypass graft surgery is planned, the drug should be withheld for at least 5 days unless the urgency for revascularization outweighs the risks of excess bleeding (61).

In noncardiac surgery, the data concerning the risk of surgical bleeding with dual antiplatelet therapy are limited and conflicting. In a meta-analysis by Burger et al. (40), including a total of 49,590 patients undergoing noncardiac surgery, it was concluded that aspirin continuation led to an increase in bleeding by a factor of 1.5. However, this increase did not lead to a higher level of the severity of bleeding complications or fatal bleeding except in intracranial surgery and possibly transurethral prostatectomy. Moreover, withdrawal of aspirin was associated with a higher incidence of cardiac, cerebral, and peripheral vascular events (40). In a study by Payne et al. (78), a 3.4-fold increase in bleeding time was observed after combining 75-mg clopidogrel and 150-mg aspirin in healthy volunteers. Therefore, it would be expected that dual antiplatelet therapy would increase surgical bleeding.

Several case reports describe significant and even fatal post-operative hemorrhage with dual antiplatelet therapy after vascular, orthopedic, and even endoscopic procedures (79–81). However, several studies demonstrate that, even though there was an increase in surgical bleeding and

**Table 2. Studies and Reports of MACE in Patients With DES Undergoing Noncardiac Surgery**

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Patients, n</th>
<th>Time After PCI</th>
<th>Stent Type</th>
<th>Type of Surgery</th>
<th>Antiplatelet Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbitts et al. (53)</td>
<td>520</td>
<td>203.5 days median</td>
<td>SES and PES</td>
<td>Various</td>
<td>Discontinued in 64.2%</td>
<td>MACE in 28 patients (5.4%); ST in 4 patients</td>
</tr>
<tr>
<td>Schouten et al. (50)</td>
<td>192</td>
<td>0–24 months</td>
<td>SES, PES, and BMS</td>
<td>Various</td>
<td>Early surgery (n = 30); Discontinued in 43.3%</td>
<td>Early surgery (n = 30) (MACE in 4 patients); Late surgery (n = 162); Discontinued in 47.8%</td>
</tr>
<tr>
<td>Rhee et al. (54)</td>
<td>141 (136 NCS)</td>
<td>7.6 ± 3.3 months</td>
<td>SES and PES</td>
<td>Various</td>
<td>Discontinued in all</td>
<td>All events were off antiplatelets</td>
</tr>
<tr>
<td>Kim et al. (55)</td>
<td>138</td>
<td>Not reported</td>
<td>DES and BMS</td>
<td>Not reported</td>
<td>Discontinued in all</td>
<td>ST in 7 cases (5%); mortality in 5 cases (71%)</td>
</tr>
<tr>
<td>Brotman et al. (51)</td>
<td>114</td>
<td>125–354 days</td>
<td>PES, SES, and BMS</td>
<td>Various</td>
<td>Discontinued in 77.2%</td>
<td>MACE in 3 pt (2.2%) on days 6, 264, and 367</td>
</tr>
<tr>
<td>Godet et al. (56)</td>
<td>96</td>
<td>1 week to 36 months</td>
<td>SES, PES, and BMS</td>
<td>Vascular, urology, orthopedic, abdominal</td>
<td>Aspirin discontinued in 24%, clopidogrel discontinued in 36%</td>
<td>MI in 12 patients (12.5%); ST in 1 BMS, ST in 1 DES</td>
</tr>
<tr>
<td>Assali et al. (57)</td>
<td>78</td>
<td>183–1,125 days</td>
<td>SES, PES and ZES</td>
<td>Various</td>
<td>Aspirin discontinued in 82%, clopidogrel discontinued in 58%</td>
<td>MACE in 6 patients (7.7%); mortality in 2 patients (33.3%)</td>
</tr>
<tr>
<td>Compton et al. (58)</td>
<td>38</td>
<td>260 days median</td>
<td>SES and PES</td>
<td>Various</td>
<td>Major surgery (aspirin continued in 78% and clopidogrel in 41%); Minor surgery (aspirin continued in 94% and clopidogrel in 39%)</td>
<td>No MACE</td>
</tr>
<tr>
<td>McFadden et al. (9)</td>
<td>4</td>
<td>331–442 days</td>
<td>2 SES 2 PES</td>
<td>Bladder Colon Endoscopy</td>
<td>Discontinued in all</td>
<td>ST in 4 patients, no mortality</td>
</tr>
<tr>
<td>Nasser et al. (44)</td>
<td>2</td>
<td>4 and 21 months</td>
<td>SES</td>
<td>Neck Hip</td>
<td>Discontinued in all</td>
<td>ST in 2 patients, mortality in 1 patient</td>
</tr>
<tr>
<td>Head et al. (43)</td>
<td>2</td>
<td>8 and 6 months</td>
<td>Transplant</td>
<td>Discontinued in 1 patient Held in 1 patient 1 day pre-operative, resumed 1 day post-operative</td>
<td>ST in 1 patient, bleeding in 2 patients, no mortality</td>
<td></td>
</tr>
<tr>
<td>Auer et al. (30)</td>
<td>1</td>
<td>12 weeks</td>
<td>PES and BMS</td>
<td>Knee</td>
<td>Discontinued</td>
<td>ST of DES with patent BMS</td>
</tr>
<tr>
<td>Murphy et al. (33)</td>
<td>1</td>
<td>2 weeks</td>
<td>SES</td>
<td>Abdominal</td>
<td>Held for 1 day</td>
<td>ST, no mortality</td>
</tr>
<tr>
<td>de Souza et al. (52)</td>
<td>1</td>
<td>29 months</td>
<td>PES</td>
<td>Urology</td>
<td>Discontinued</td>
<td>ST, no mortality</td>
</tr>
</tbody>
</table>

BMS = bare-metal stent(s); MACE = major adverse cardiac events; MI = myocardial infarction; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); ST = stent thrombosis; ZES = zotarolimus-eluting stent(s).
transfusion requirements, there was no change in mortality or surgical outcome (46–48,82). Therefore, the increased risk of perioperative hemorrhage with antiplatelet agents is not necessarily associated with increased morbidity, mortality, or surgical outcome. Furthermore, the cessation of antiplatelet therapy in the setting of DES increases the perioperative risk of ST and MACE. Therefore, the risk of withdrawing antiplatelet therapy in patients with DES might outweigh the risk of retaining them particularly in high-risk patients. Moreover, the routine cessation of antiplatelets perioperatively should not be practiced, and each patient must be managed on a case-by-case basis.

Strategies for Perioperative Management of DES

Because of the lack of prospective studies and guidelines, there are a wide variety of potential approaches to the perioperative management of DES and antiplatelet therapy (19,43,83–91). The perioperative management of patients with DES should be carried out on an individual case-by-case basis. The approach should be managed in a multidisciplinary manner by the patient’s cardiologist, surgeon, hematologist, and anesthetist. Many factors should be considered, particularly the surgical hemorrhagic risk (Table 3) and the thrombotic risk of the DES (Table 1). Subsequently, the estimated risk of ST should be weighed against the risk of bleeding (Fig. 2).

Aspirin and thienopyridines throughout surgery. As a general approach, all elective surgical procedures should be delayed by at least 6 months and ideally 12 months after DES placement. However, if surgery cannot be delayed due to urgency, maintaining dual antiplatelet therapy with aspirin and thienopyridines is of paramount importance as the risk of ST is significantly increased. This applies to most surgical procedures, except those in areas where bleeding is in a closed space and might be catastrophic, such as intracranial.
spinal medullary, and posterior chamber ophthalmic surgeries (40,82). Bleeding risk is also increased in transurethral prostate resection; however, the use of potassium-titanyl-phosphate laser is considered safe (92,93).

Patients undergoing surgical procedures 12 months after PCI are likely at a lower risk of perioperative ST and MACE compared with earlier surgery (2,5,64). However, given the increasing reports of VLST and significant delays in re-endothelialization with DES, the risk is still significant. Therefore, maintaining dual antiplatelet therapy should be a priority if the risk of perioperative bleeding is acceptable. In contrast, if concomitant risk factors are absent and the hemorrhagic risk is significant, withdrawing thienopyridines while maintaining aspirin would be reasonable (18).

The Scottish Intercollegiate Guidelines Network (SIGN) state that, if emergency or urgent noncardiac surgery is required, dual antiplatelet therapy should be continued whenever possible unless bleeding risk is unacceptable. In this case, antiplatelet therapy should be reintroduced as soon as possible post-operatively (91).

**Discontinue thienopyridines and maintain aspirin.** If the risk of perioperative bleeding is significantly high, whether due to surgical factors or patient-related factors, then thienopyridines may be discontinued 5 days before surgery, and aspirin should be maintained. However, because ST usually occurs quite soon post-operatively, clopidogrel should be restarted once the risk of bleeding has been diminished (ideally within the first 24 h) with a loading dose of 300 mg to 600 mg (30,32,33,94).

Maintaining single antiplatelet therapy with aspirin applies to patients without concomitant risk factors of ST undergoing surgery more than 12 months after PCI. In a recent study, it was concluded that short-term discontinuation of antiplatelet therapy is relatively safe if aspirin is maintained; however, the risk of ST was still present (Fig. 3) (18). Therefore, in the case of early surgery or the presence of ST risk factors, “bridging therapy” might be advisable.

**“Bridging therapy” with aspirin and heparin.** Heparin is commonly used as a substitute to aspirin or thienopyridines, because of its efficacy in the treatment of unstable angina and non-ST-segment elevation myocardial infarction. However, heparin is an antithrombin agent and not an antiplatelet. The use of antithrombotics such as unfractionated heparin (UFH) and low molecular weight heparin (LMWH) has been proposed in perioperative management of DES. However, these therapies have not been proven to be effective (87). Moreover, perioperative heparin use was still associated with high mortality (46). In addition, heparin and warfarin were not effective in preventing acute and subacute ST in the early days of BMS (95). The hypercoagulability after abrupt cessation of UFH has to be considered as well (96). Furthermore, given that ST is a platelet-mediated process, it is expected that antithrombotics (UFH and LMWH) are not ideal for “bridging”.

"Bridging therapy" with aspirin and a glycoprotein (GP) IIb/IIIa inhibitor. GP IIb/IIIa is a platelet integrin. Platelet activation transforms the integrin into a state of high-affinity to fibrinogen, which is the final common pathway of platelet aggregation and clot formation. GP IIb/IIIa inhibitors act by blocking fibrinogen-mediated cross-linking between platelets, thereby inhibiting platelet aggregation (97). Abciximab (ReoPro, Eli Lilly and Company, Indianapolis, Indiana) causes a prolonged irreversible antagonism of GP IIb/IIIa leading to platelet aggregation inhibition that lasts for at least 48 h and up to 7 days (98). Given its prolonged inhibition time, abciximab should not be used perioperatively. The synthetic peptides epitifibatide (Integrilin, Millennium Pharmaceuticals, Boston, Massachusetts) and ti-
The use of nonselective cyclooxygenase-1 inhibitor non-steroidal anti-inflammatory drugs as an alternative to aspirin such as flurbiprofen, sulfipyrazone, indobufen, or triflusal has been studied. The main advantage is their reversible antiplatelet effect and that platelet function is restored within 24 h after discontinuation. However, randomized clinical trials revealed conflicting results (101). Even though it is unknown how well they perform in the perioperative setting, their use as an alternative in high-risk surgery could be considered.

Patients undergoing surgical procedures after 12 months of PCI have a lower risk of perioperative ST and MACE compared with earlier surgery (35). However, given the increasing reports of VLST and significant delay in re-endothelialization with DES, the risk is still significant. Therefore, maintaining dual antiplatelet therapy should be of paramount importance if the risk of perioperative bleeding is acceptable. In contrast, if concomitant risk factors are absent and the hemorrhagic risk is significant, withdrawing thienopyridines while maintaining aspirin would be reasonable. However, in patients with risk factors of ST undergoing procedures with a significant hemorrhagic risk, “bridging” therapy could be considered.

Management of Perioperative Hemorrhage

Patients undergoing any type of surgery should have a platelet count of at least 50,000/µl to minimize the risk of hemorrhage (68,102). This hemorrhagic risk threshold is increased to 100,000/µl in patients undergoing neurosurgery or posterior chamber ophthalmic surgery (103). Hemostasis requires the presence of at least 50% of functional platelets. Because the effect of antiplatelet agents is not reversible, fresh platelets are the only way to re-establish normal coagulation. However, new platelets might be affected by residual drug in the circulation. Clopidogrel has a half-life of 8 h (104). Thus, in the case of major bleeding, hemostasis might be restored with fresh platelet concentrate transfusion after 16 to 24 h from the last intake without significant inhibition. The plasma half-life of tirofiban and epifibatide is close to 2 h, and 60% to 90% of normal platelet function is restored after 6 h from discontinuation (99). Fresh platelet transfusion is rarely required in this case.

Transfusion of 1 platelet concentrate usually increases serum platelet count by 5,000/µl to 10,000/µl 1 h after transfusion in a 70-kg adult (105). However, several risk factors play a role in the response to platelet transfusions (106). Other supportive measures include the replacement of lost blood by the transfusion of packed red cells or other blood products such as cryoprecipitate, fresh frozen plasma, recombinant factor VII, and desmopressin.
Management of Post-Operative ST

Because ST most often presents as an STEMI, the most appropriate management is early reperfusion therapy. Postoperative thrombolytic therapy is not possible, given the excessive risk of bleeding. Moreover, thrombolytic therapy is less effective when compared with primary PCI and might be even less effective in cases of ST, which is more platelet-mediated (107). Therefore, primary PCI is the treatment of choice for perioperative ST. Patients carrying a higher risk of ST, whether due to the cessation of dual antiplatelet therapy or the presence of concomitant risk factors, should be monitored closely post-operatively until dual antiplatelet therapy is fully restarted.

Novel Antiplatelets

Various novel antiplatelet agents are expected to be released in the near future. Available data demonstrate results that would most likely facilitate the perioperative management of DES and likely will change our current approach.

Prasugrel is a novel orally administered thienopyridine prodrug metabolized via cytochrome P450 in the liver. Prasugrel has been recently approved by the Food and Drug Administration for use with PCI (108). Similar to clopidogrel, prasugrel binds selectively and irreversibly to the platelet P2Y12 receptor (109). However, prasugrel has a much more rapid, potent, and consistent platelet inhibition, with a loading dose of 60 mg compared with the standard 300 mg of clopidogrel (110,111). The TRITON–TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitorN with Prasugrel–Thrombolysis In Myocardial Infarction 38) clinical trial compared clopidogrel use of 300-mg loading dose and 75-mg daily dose with prasugrel with a 60-mg loading dose and 10-mg daily dose in acute coronary syndromes (112). A significant reduction of ischemic events was demonstrated. The incidence of ST was decreased from 2.4% with clopidogrel to 1.1% with prasugrel. However, there was an increased risk of bleeding, including fatal bleeding. In The PRINCIPLE–TIMI 44 (Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis In Myocardial Infarction 44) trial, the use of prasugrel loading dose of 60 mg and maintenance daily dose of 10 mg achieved a greater level of platelet function inhibition compared with high-dose clopidogrel with 600-mg loading dose and 150-mg maintenance daily dose amongst patients undergoing PCI (113). However, frequency of bleeding tended to be more with prasugrel. Even though prasugrel seems to be effective in patients with acute coronary syndromes undergoing PCI, its perioperative use might be limited, given the increased risk of bleeding and its irreversible antiplatelet inhibition. Prasugrel would potentially be useful immediately after surgery due to rapid and potent platelet inhibition.

Ticagrelor (AZD6140) is also a novel oral adenosine diphosphate P2Y12 receptor antagonist. Unlike clopidogrel, ticlopidine, and prasugrel, ticagrelor is a nonthienopyridine adenosine triphosphate analog that binds directly and reversibly to P2Y12 without any metabolic activation. It was demonstrated that ticagrelor achieved a greater platelet aggregation inhibition compared with clopidogrel (114). Furthermore, peak inhibition was observed 2 to 4 h after a dose of ticagrelor. This was demonstrated as well in the phase 2 DISPERSE-2 (Dose confirmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non-ST-segment Elevation myocardial infarction) trial, showing greater mean levels of platelet inhibition than clopidogrel with no significant risk of bleeding (115,116). The recent phase 3 clinical PLATO (PLATelet inhibition and patient Outcomes) trial demonstrated a significant reduction in MACE with ticagrelor compared with clopidogrel (117). Moreover, ST was reduced to 2.9% with ticagrelor compared with 3.8% with clopidogrel. Furthermore, there was no significant difference in the rates of major bleeding. The main advantage of using ticagrelor perioperatively would be its reversibility, relatively short half-life (6 to 13 h), and its rapid onset of action (109). Patients with DES would discontinue ticagrelor only 1 day before surgery and it would be resumed soon after surgery, thus diminishing both the risk of perioperative hemorrhage and ST.

Cangrelor is also a novel reversible P2Y12 receptor agonist that is administered intravenously. Similar to ticagrelor, cangrelor does not require metabolic activation. Phase 2 studies demonstrate a rapid onset of action and a greater degree of platelet inhibition compared with clopidogrel. Furthermore, when compared with abciximab, incidence of adverse cardiac events was similar in both, and platelet aggregation returned to baseline more rapidly after stopping the infusion with cangrelor (109,118). The phase 3 CHAMPION (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) clinical trial has been discontinued due to failure to meet efficacy endpoints. However, the BRIDGE (Maintenance of Platelet inhibition With cangRelor After discontinuation of ThienopyrDiines in Patients Undergoing surGEry) trial is ongoing to show safety in “bridging” patients perioperatively (119). Given its rapid onset, reversibility, and a 3-min half-life, cangrelor would be a potential “bridging therapy” in the perioperative setting. However, similar to bridging with GP IIb/IIIa inhibitors, patients would require prior admission for initiation of intravenous infusion. In this case, cangrelor would be stopped minutes before procedure and resumed sooner than other antiplatelets post-operatively. Moreover, even maintaining cangrelor throughout surgery might be considered, given its clinical profile.
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Key Words: antiplatelet therapy ■ drug-eluting stent ■ noncardiac surgery ■ perioperative ■ stent thrombosis.