JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 3, NO. 2, 2010

ISSN 1936-8798/10/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2009.11.017

STATE-OF-THE-ART PAPER

Perioperative Management of Patients With Drug-Eluting Stents

Ali O. Abualsaud, MD,* Mark J. Eisenberg, MD, MPH†

Montreal, Quebec, Canada

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.

From the *Division of Cardiology, Royal Victoria Hospital/McGill University Health Centre, Montreal, Quebec, Canada; and the †Divisions 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.

Manuscript received August 27, 2009; revised manuscript received November 17, 2009, accepted November 30, 2009.

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",

"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.

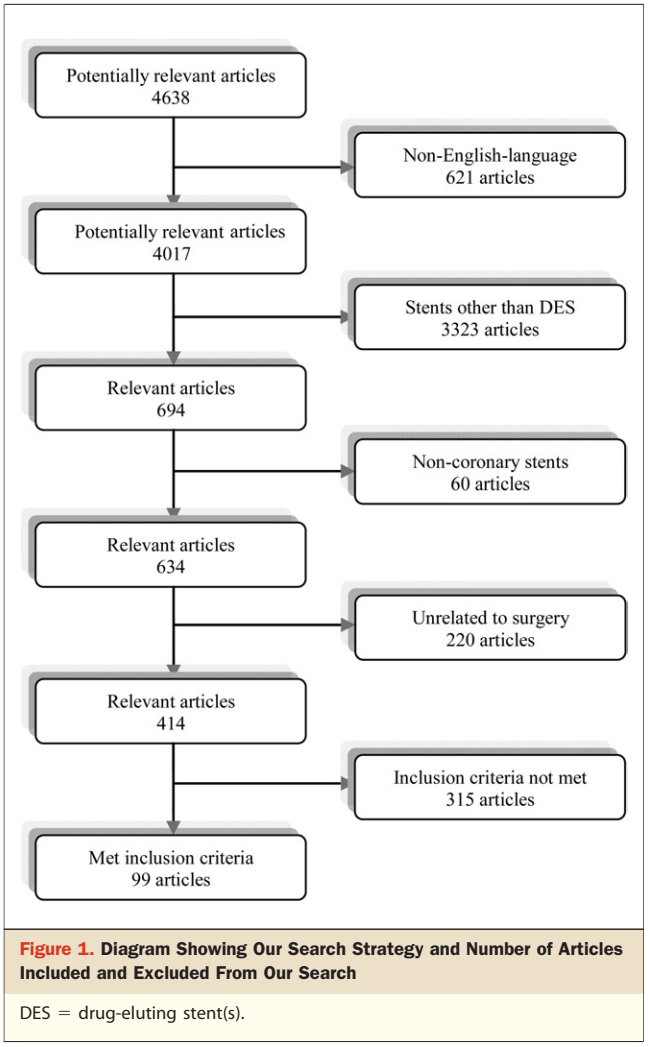

Figure 1. Diagram Showing Our Search Strategy and Number of Articles Included and Excluded From Our Search

DES = drug-eluting stent(s).

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
GP = glycoprotein
LMWH = low molecular weight heparin
MACE = major adverse cardiac events
PCI = percutaneous coronary intervention
ST = stent thrombosis
STEMI = ST-segment elevation myocardial infarction
UFH = unfractionated heparin
VLST = very late stent thrombosis

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

Table 1. Risk Factors of Stent Thrombosis in Patients With DES

Patient factors
ACS
Reduced left ventricular ejection fraction
MACE within 30 days of PCI
Diabetes mellitus
Renal insufficiency
Gene polymorphism
Hypercoagulable states (e.g., malignancy, surgery, diabetes)
Procedural factors
Residual dissection
Incomplete stent apposition
Stent underexpansion
"Crush" technique
Side branch occlusion
Coronary anatomy
Vessel size
Type C lesion
Left main coronary artery stent
Increased lesion length
Thrombus
Bifurcation
In-stent restenosis
Plaque characteristics
Multivessel disease
Total occlusion
Bypass graft
Stent factors
Stent surface
Hypersensitivity to polymer
Drugs
Antithrombotic and anticoagulation therapy
Cessation of antiplatelets
Antiplatelet resistance
Inhibition of platelet aggregation

Data adapted from references 4,8,14,16,22–28.
ACS = acute coronary syndromes; DES = drug-eluting stent(s); MACE = major adverse cardiac events; PCI = percutaneous coronary intervention.

risk secondary to catecholamine release, increased platelet aggregability, and decreased fibrinolysis leading to a hypercoagulable 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).

Antiplatelet 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

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 3, NO. 2, 2010
FEBRUARY 2010:131–42

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

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

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).

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 <5 days 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 3. Hemorrhagic Risk in Noncardiac Surgery

Surgical Hemorrhagic Risk	Blood Transfusion Requirement	Type of Surgery
Low	Usually not required	Peripheral, plastic, and general surgery, biopsies; minor orthopedic, otolaryngology, and general surgery; endoscopy; eye anterior chamber; dental extraction and surgery
Intermediate	Frequently required	Visceral surgery; cardiovascular surgery; major orthopedic, otolaryngology, urologic reconstructive surgery
High	Possible bleeding in a closed space	Intracranial neurosurgery; spinal canal surgery; eye posterior chamber surgery

Data adapted from Chassot et al. (83).

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,

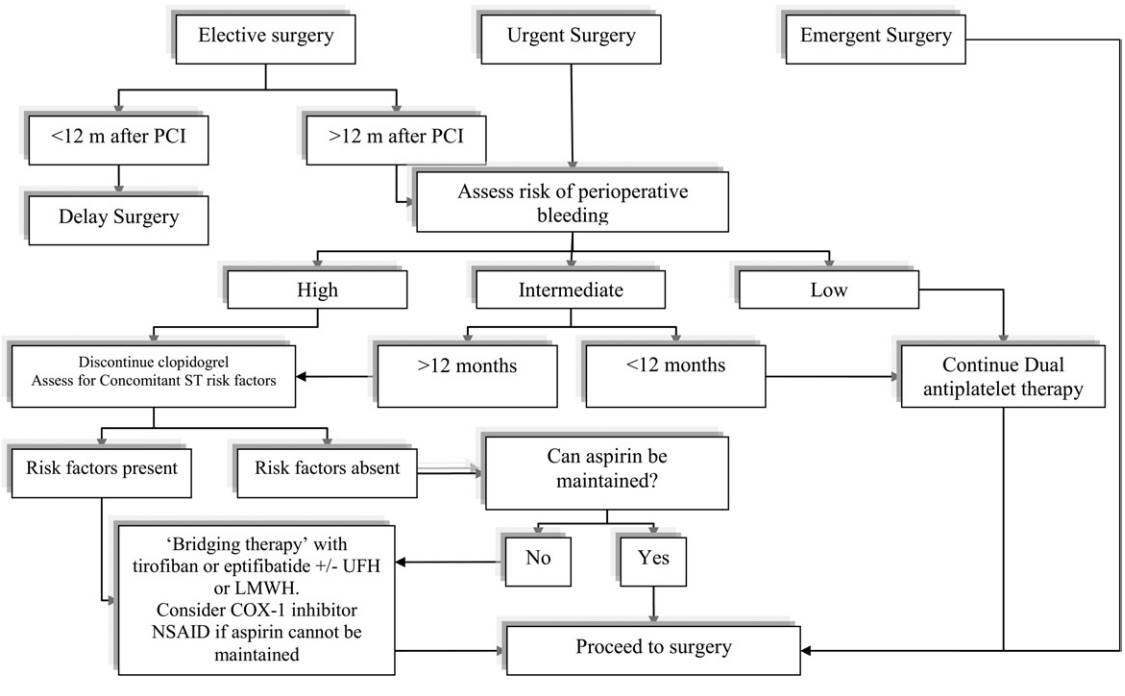

Figure 2. Algorithm of Perioperative Management of Patients With DES

COX = cyclooxygenase; DES = drug-eluting stent(s); LMWH = low molecular weight heparin; NSAID = nonsteroidal anti-inflammatory drug; PCI = percutaneous coronary intervention; ST = stent thrombosis; UFH = unfractionated heparin.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 3, NO. 2, 2010
FEBRUARY 2010:131–42

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".

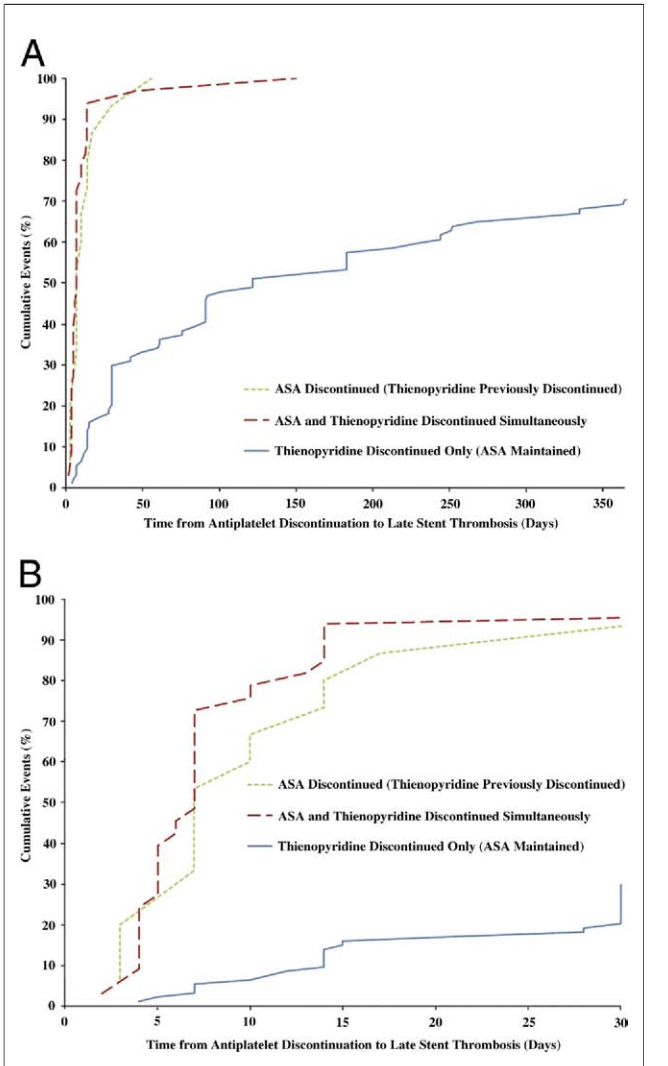

Figure 3. Cumulative Proportion of Late Stent Thrombosis Cases Among Patients Who Discontinued Antiplatelet Therapy

(A) Within 1 year of discontinuing antiplatelet therapy. **(B)** Within 30 days of discontinuing antiplatelet therapy. Data adapted from Eisenberg et al. (18). ASA = acetylsalicylic acid.

"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 eptifibatide (Integrilin, Millennium Pharmaceuticals, Boston, Massachusetts) and ti-

rofiban (Aggrastat, Merck and Co., Inc., West Point, Pennsylvania) are competitive reversible binders to GP IIb/IIIa receptors and dissociate rapidly with less affinity than abciximab (99). Their half-life is quite short, and platelet function is completely restored 2 to 4 h after stopping the infusion, making them potentially suitable for perioperative use.

Although GP IIb/IIIa inhibitors have not been studied in the perioperative setting, their use as a "bridge" when thienopyridines are stopped before surgery could be considered. Ideally, "bridging" should be started within 2 to 4 days after stopping oral antiplatelets. This means patients would have to be admitted to hospital several days before surgery. Even though this strategy is not practical in most cases, it might be worthwhile in patients at extremely high risk of DES thrombosis. Moreover, if a patient is already admitted to undergo urgent surgery, this strategy might be considered. Therefore, in patients with DES with an increased risk of perioperative bleeding and a significant risk of ST who are undergoing surgery, bridging therapy with aspirin and a GP IIb/IIIa inhibitor with or without heparin could be considered. This strategy entails stopping thienopyridines 5 days before surgery and admitting the patient to the hospital several days before surgery to begin tirofiban or eptifibatide and UFH infusions. Both are then stopped 6 h before surgery (87). Importantly, the bleeding risk with GP IIb/IIIa inhibitors also has to be considered. This strategy is mostly of theoretical interest at the present time. We know of no large studies examining this strategy. The only study we could find was a recent report of 7 patients considered to be at a high risk of both ST and surgical bleeding. In these patients, it was demonstrated that bridging with eptifibatide was associated with a good post-operative outcome without increased perioperative hemorrhage (100).

Discontinue both aspirin and thienopyridines and consider other alternatives. If the risk of surgical bleeding is potentially catastrophic or fatal, such as in intracranial, medullary, and posterior chamber surgeries, aspirin cessation might be necessary. In these cases aspirin and thienopyridines should be discontinued 5 days before surgery. Given the increased risk of ST with cessation of antiplatelet agents, intensive perioperative monitoring and early interventions are of paramount importance. Moreover, dual antiplatelet therapy should be reintroduced once the risk of hemorrhage is diminished.

In patients with concomitant risk factors of ST, "bridging therapy" with a GP IIb/IIIa inhibitor with or without heparin could be considered. According to recommendations of the French Society of Anesthesiology and Intensive Care, if withdrawal of antiplatelet agents is necessary, substitution of another nonsteroidal anti-inflammatory drug such as flurbiprofen (50 mg × 2, withdrawn 24 h before surgery) or LMWH (85 to 100 IU aXa/kg for 12 h) might be indicated (90).

The use of nonselective cyclooxygenase-1 inhibitor nonsteroidal anti-inflammatory drugs as an alternative to aspirin such as flurbiprofen, sulfinpyrazone, 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 eptifibatide 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.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 3, NO. 2, 2010
FEBRUARY 2010:131–42

Management of Post-Operative ST

Because ST most often presents as an STEMI, the most appropriate management is early reperfusion therapy. Post-operative 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 $P2Y_{12}$ 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 InhibitioN 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 $P2Y_{12}$ receptor antagonist. Unlike clopidogrel, ticlopidine, and prasugrel, ticagrelor is a nonthienopyridine adenosine triphosphate analog that binds directly and reversibly to $P2Y_{12}$ 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 $P2Y_{12}$ receptor antagonist 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 ThienopyriDines 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.

PRT060128 (Portola, San Francisco, California) is an investigational, direct-acting, reversible $P2Y_{12}$ receptor antagonist that can be administered orally or intravenously (109). Various other novel antiplatelet agents, such as the protease-activated receptor-1 antagonist E5555, thrombin receptor antagonists such as SCH-530348, and new thromboxane inhibitors such as the NCX-4016 are all undergoing investigations (109). Therefore, perioperative management of patients with DES is likely to evolve with the release of newer antiplatelet agents.

Conclusions

Perioperative management of patients with DES is a critical issue. Maintenance of dual antiplatelet therapy remains the mainstay of ST prevention. In cases with high risk for bleeding, maintaining short-term single antiplatelet therapy with aspirin is associated with low risk of ST. If aspirin must be discontinued, various management strategies could be considered, although there are few evidence-based data in this regard. Furthermore, intensive post-operative monitoring and prompt intervention are of paramount importance should ST occur. With additional prospective trials and registry formation, further information could be obtained to aid in the release of official guidelines. Moreover, the release of novel reversible antiplatelet agents would likely change current strategies, making perioperative management of patients with DES a less-complicated task.

Reprint requests and correspondence: Dr. Mark J. Eisenberg, Divisions of Cardiology and Clinical Epidemiology, Jewish General Hospital/McGill University, 3755 Cote Ste-Catherine Road Suite A-118, Montreal, Quebec H3T 1E2, Canada. E-mail: mark.eisenberg@mcgill.ca.

REFERENCES

1. King SB III, Smith SC Jr., Hirshfeld JW Jr., et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2008;51:172–209.
2. Grines CL, Bonow RO, Casey DE Jr., et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. J Am Coll Cardiol 2007;49:734–9.
3. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1598–660.
4. Hodgson JM, Stone GW, Lincoff AM, et al. Late stent thrombosis: considerations and practical advice for the use of drug-eluting stents: a report from the Society for Cardiovascular Angiography and Interventions Drug-eluting Stent Task Force. Catheter Cardiovasc Interv 2007;69:327–33.
5. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implementation. JAMA 2007;297:159–68.
6. Rodriguez AE, Mieres J, Fernandez-Pereira C, et al. Coronary stent thrombosis in the current drug-eluting stent era: insights from the ERACI III trial. J Am Coll Cardiol 2006;47:205–7.
7. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. J Am Coll Cardiol 2005;45:2088–92.
8. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.
9. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:1519–21.
10. Update to FDA Statement on Drug-Eluting Stents. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/medsun/news/printer.cfm?id=575. Accessed January 5, 2010.
11. Babapulle MN, Joseph L, Belisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. Lancet 2004;364:583–91.
12. Hasdai D, Garratt KN, Holmes DR Jr., Berger PB, Schwartz RS, Bell MR. Coronary angioplasty and intracoronary thrombolysis are of limited efficacy in resolving early intracoronary stent thrombosis. J Am Coll Cardiol 1996;28:361–7.
13. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994;331:496–501.
14. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. Circulation 2001;103:1967–71.
15. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.
16. Kuchulakanti PK, Chu WW, Torguson R, et al. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. Circulation 2006;113:1108–13.
17. Windecker S, Meier B. Late coronary stent thrombosis. Circulation 2007;116:1952–65.
18. Eisenberg MJ, Richard PR, Libersan D, Filion KB. Safety of short-term discontinuation of antiplatelet therapy in patients with drug-eluting stents. Circulation 2009;119:1634–42.
19. Gurbel PA, DiChiara J, Tantry US. Antiplatelet therapy after implantation of drug-eluting stents: duration, resistance, alternatives, and management of surgical patients. Am J Cardiol 2007;100:18M–25M.
20. Patrono C, Bachmann F, Baigent C, et al. Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European society of cardiology. Eur Heart J 2004;25:166–81.
21. Tsimikas S. Drug-eluting stents and late adverse clinical outcomes lessons learned, lessons awaited. J Am Coll Cardiol 2006;47:2112–5.
22. Schuhlen H, Kastrati A, Dirschinger J, et al. Intracoronary stenting and risk for major adverse cardiac events during the first month. Circulation 1998;98:104–11.
23. Luscher TF, Steffel J, Eberli FR, et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. Circulation 2007;115:1051–8.
24. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.
25. Colombo A, Corbett SJ. Drug-eluting stent thrombosis: increasingly recognized but too frequently overemphasized. J Am Coll Cardiol 2006;48:203–5.
26. Park DW, Park SW, Park KH, et al. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. Am J Cardiol 2006;98:352–6.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 3, NO. 2, 2010
FEBRUARY 2010:131–42

27. Moreno R, Fernandez C, Hernandez R, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. J Am Coll Cardiol 2005;45:954–9.
28. Ortolani P, Ardissino D, Cavallini C, et al. Effect of sirolimus-eluting stent in diabetic patients with small coronary arteries (a SES-SMART substudy). Am J Cardiol 2005;96:1393–8.
29. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. J Am Coll Cardiol 2006;47:175–81.
30. Auer J, Berent R, Weber T, Eber B. Risk of noncardiac surgery in the months following placement of a drug-eluting coronary stent. J Am Coll Cardiol 2004;43:713; author reply 4–5.
31. Satler LF. Recommendations regarding stent selection in relation to the timing of noncardiac surgery postpercutaneous coronary intervention. Catheter Cardiovasc Interv 2004;63:146–7.
32. Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol 2000;35:1288–94.
33. Murphy JT, Fahy BG. Thrombosis of sirolimus-eluting coronary stent in the postanesthesia care unit. Anesth Analg 2005;101:971–3.
34. Artang R, Dieter RS. Analysis of 36 reported cases of late thrombosis in drug-eluting stents placed in coronary arteries. Am J Cardiol 2007;99:1039–43.
35. Schouten O, Bax JJ, Damen J, Poldermans D. Coronary artery stent placement immediately before noncardiac surgery: a potential risk? Anesthesiology 2007;106:1067–9.
36. Samama CM, Thiry D, Elalamy I, et al. Perioperative activation of hemostasis in vascular surgery patients. Anesthesiology 2001;94: 74–8.
37. Rosenfeld BA, Beattie C, Christopherson R, et al. The effects of different anesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. Perioperative Ischemia Randomized Anesthesia Trial Study Group. Anesthesiology 1993;79:435–43.
38. Blake GJ, Ridker PM. Inflammatory bio-markers and cardiovascular risk prediction. J Intern Med 2002;252:283–94.
39. Priebe HJ. Triggers of perioperative myocardial ischaemia and infarction. Br J Anaesth 2004;93:9–20.
40. Burger W, Chemnitius JM, Kneissl GD, Rucker G. Low-dose aspirin for secondary cardiovascular prevention—cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation—review and meta-analysis. J Intern Med 2005;257:399–414.
41. Collet JP, Montalescot G, Blanchet B, et al. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. Circulation 2004;110:2361–7.
42. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. J Am Coll Cardiol 2005;45:456–9.
43. Head DE, Sebranek JJ, Zahed C, Coursin DB, Prielipp RC. A tale of two stents: perioperative management of patients with drug-eluting coronary stents. J Clin Anesth 2007;19:386–96.
44. Nasser M, Kapeliovich M, Markiewicz W. Late thrombosis of sirolimus-eluting stents following noncardiac surgery. Catheter Cardiovasc Interv 2005;65:516–9.
45. Brown MJ, Long TR, Brown DR, Wass CT. Acute coronary syndrome and myocardial infarction after orthopedic surgery in a patient with a recently placed drug-eluting stent. J Clin Anesth 2006;18:537–40.
46. Vicenzi MN, Meislitzer T, Heitzinger B, Halaj M, Fleisher LA, Metzler H. Coronary artery stenting and non-cardiac surgery–a prospective outcome study. Br J Anaesth 2006;96:686–93.
47. Wilson SH, Fasseas P, Orford JL, et al. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. J Am Coll Cardiol 2003;42:234–40.
48. Sharma AK, Ajani AE, Hamwi SM, et al. Major noncardiac surgery following coronary stenting: when is it safe to operate? Catheter Cardiovasc Interv 2004;63:141–5.
49. Reddy PR, Vaitkus PT. Risks of noncardiac surgery after coronary stenting. Am J Cardiol 2005;95:755–7.
50. Schouten O, van Domburg RT, Bax JJ, et al. Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. J Am Coll Cardiol 2007;49:122–4.
51. Brotman DJ, Bakhru M, Saber W, et al. Discontinuation of antiplatelet therapy prior to low-risk noncardiac surgery in patients with drug-eluting stents: a retrospective cohort study. J Hosp Med 2007; 2:378–84.
52. de Souza DG, Baum VC, Ballert NM. Late thrombosis of a drug-eluting stent presenting in the perioperative period. Anesthesiology 2007;106:1057–9.
53. Rabbitts JA, Nuttall GA, Brown MJ, et al. Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. Anesthesiology 2008;109:596–604.
54. Rhee SJ, Yun KH, Lee SR, et al. Drug-eluting stent thrombosis during perioperative period. Int Heart J 2008;49:135–42.
55. Kim HL, Park KW, Kwak JJ, et al. Stent-related cardiac events after non-cardiac surgery: drug-eluting stent vs. bare metal stent. Int J Cardiol 2008;123:353–4.
56. Godet G, Le Manach Y, Lesache F, Perbet S, Coriat P. Drug-eluting stent thrombosis in patients undergoing non-cardiac surgery: is it always a problem? Br J Anaesth 2008;100:472–7.
57. Assali A, Vaknin-Assa H, Lev E, et al. The risk of cardiac complications following noncardiac surgery in patients with drug eluting stents implanted at least six months before surgery. Catheter Cardiovasc Interv 2009;74:837–43.
58. Compton PA, Zankar AA, Adesanya AO, Banerjee S, Brilakis ES. Risk of noncardiac surgery after coronary drug-eluting stent implantation. Am J Cardiol 2006;98:1212–3.
59. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation 2000;102: 624–9.
60. von Mach MA, Eich A, Weilemann LS, Münzel T. Subacute coronary stent thrombosis in a patient developing clopidogrel associated thrombotic thrombocytopenic purpura. Heart 2005;91:e14.
61. Antman EM, Hand M, Armstrong PW, et al.; Canadian Cardiovascular Society, American Academy of Family Physicians, American College of Cardiology, American Heart Association. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2008;51:210–47.
62. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–33.
63. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334:1084–9.
64. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411–20.
65. Leon MB, Baim DS, Popma JJ, et al.; Stent Anticoagulation Restenosis Study Investigators. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. N Engl J Med 1998;339:1665–71.
66. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. The CHARISMA trial. N Engl J Med 2006;354:1706–17.
67. Akowuah E, Shrivastava V, Jamnadas B, et al. Comparison of two strategies for the management of antiplatelet therapy during urgent surgery. Ann Thorac Surg 2005;80:149–52.
68. Murphy MF, Brozovic B, Murphy W, Ouwehand W, Waters AH; British Committee for Standards in Haematology, Working Party of the Blood Transfusion Task Force. Guidelines for platelet transfusions. Transfus Med 1992;2:311–8.
69. Sun JC, Crowther MA, Warkentin TE, Lamy A, Teoh KH. Should aspirin be discontinued before coronary artery bypass surgery? Circulation 2005;112:e85–90.

70. Srinivasan AK, Grayson AD, Pullan DM, Fabri BM, Dihmis WC. Effect of preoperative aspirin use in off-pump coronary artery bypass operations. Ann Thorac Surgery 2003;76:41–5.
71. Ferraris VA, Ferraris SP, Moliterno DJ, et al. The Society of Thoracic Surgeons practice guideline series: aspirin and other antiplatelet agents during operative coronary revascularization (executive summary). Ann Thorac Surg 2005;79:1454–61.
72. Purkayastha S, Athanasiou T, Malinovski V, et al. Does clopidogrel affect outcome after coronary artery bypass grafting? A meta-analysis. Heart 2006;92:531–2.
73. Ascione R, Ghosh A, Rogers CA, Cohen A, Monk C, Angelini GD. In-hospital patients exposed to clopidogrel before coronary artery bypass graft surgery: a word of caution. Ann Thorac Surg 2005;79:1210–6.
74. Yende S, Wunderink RG. Effect of clopidogrel on bleeding after coronary artery bypass surgery. Crit Care Med 2001;29:2271–5.
75. Chu MW, Wilson SR, Novick RJ, Stitt LW, Quantz MA. Does clopidogrel increase blood loss following coronary artery bypass surgery? Ann Thorac Surg 2004;78:1536–41.
76. Leong JY, Baker RA, Shah PJ, Cherian VK, Knight JL. Clopidogrel and bleeding after coronary artery bypass graft surgery. Ann Thorac Surg 2005;80:928–33.
77. Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation 2004;110:1202–8.
78. Payne DA, Hayes PD, Jones CI, Belham P, Naylor AR, Goodall AH. Combined therapy with clopidogrel and aspirin significantly increases the bleeding time through a synergistic antiplatelet action. J Vasc Surg 2002;35:1204–9.
79. Chapman TW, Bowley DM, Lambert AW, Walker AJ, Ashley SA, Wilkins DC. Haemorrhage associated with combined clopidogrel and aspirin therapy. Eur J Vasc Endovasc Surg 2001;22:478–9.
80. Ernst A, Eberhardt R, Wahidi M, Becker HD, Herth FJ. Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. Chest 2006;129:734–7.
81. Moore M, Power M. Perioperative hemorrhage and combined clopidogrel and aspirin therapy. Anesthesiology 2004;101:792–4.
82. Qureshi AI, Saad M, Zaidat OO, et al. Intracerebral hemorrhages associated with neurointerventional procedures using a combination of antithrombotic agents including abciximab. Stroke 2002;33:1916–9.
83. Chassot PG, Delabays A, Spahn DR. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. Br J Anaesth 2007;99:316–28.
84. Howard-Alpe GM, de Bono J, Hudsmith L, Orr WP, Foex P, Sear JW. Coronary artery stents and non-cardiac surgery. Br J Anaesth 2007;98:560–74.
85. Dalal AR, D'Souza S, Shulman MS. Article de synthese court: Les tuteurs coronariens actifs et l'anesthesie [Brief review: coronary drug-eluting stents and anesthesia]. Can J Anaesth 2006;53:1230–43.
86. May AE, Geisler T, Gawaz M. Individualized antithrombotic therapy in high risk patients after coronary stenting. A double-edged sword between thrombosis and bleeding. Thromb Haemost 2008;99:487–93.
87. Broad L, Lee T, Conroy M, et al. Successful management of patients with a drug-eluting coronary stent presenting for elective, non-cardiac surgery. Br J Anaesth 2007;98:19–22.
88. Brilakis ES, Banerjee S, Berger PB. Perioperative management of patients with coronary stents. J Am Coll Cardiol 2007;49:2145–50.
89. Newsome LT, Weller RS, Gerancher JC, Kutcher MA, Royster RL. Coronary artery stents: II. Perioperative considerations and management. Anesth Analg 2008;107:570–90.
90. Albaladejo P, Marret E, Piriou V, Samama CM. Perioperative management of antiplatelet agents in patients with coronary stents: recommendations of a French Task Force. Br J Anaesth 2006;97:580–2.
91. The Scottish Intercollegiate Guidelines Network (SIGN). Management of stable angina. A National Clinical Guideline. February 2007. Available at: http://www.sign.ac.uk/pdf/sign96.pdf. Accessed January 5, 2010.
92. Elzayat E, Habib E, Elhilali M. Holmium laser enucleation of the prostate in patients on anticoagulant therapy or with bleeding disorders. J Urol 2006;175:1428–32.
93. Sandhu JS, Ng CK, Gonzalez RR, Kaplan SA, Te AE. Photoselective laser vaporization prostatectomy in men receiving anticoagulants. J Endourol 2005;19:1196–8.
94. Vicenzi MN, Ribitsch D, Luha O, Klein W, Metzler H. Coronary artery stenting before noncardiac surgery: more threat than safety? Anesthesiology 2001;94:367–8.
95. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994;331:489–95.
96. Dent H, Lekic Z, Vicenzi M. Unfractionated heparin and coronary artery stenting. Br J Anaesth 2006;97:582; author reply 582.
97. Frishman WH, Burns B, Atac B, Alturk N, Altajar B, Lerrick K. Novel antiplatelet therapies for treatment of patients with ischemic heart disease: inhibitors of the platelet glycoprotein IIb/IIIa integrin receptor. Am Heart J 1995;130:877–92.
98. Faulds D, Sorkin EM. Abciximab (c7E3 Fab). A review of its pharmacology and therapeutic potential in ischaemic heart disease. Drugs 1994;48:583–98.
99. Kleiman NS. Pharmacokinetics and pharmacodynamics of glycoprotein IIb-IIIa inhibitors. Am Heart J 1999;138:263–75.
100. Bigalke B, Seizer P, Geisler T, Lindemann S, Gawaz M, May AE. Perioperative antiplatelet therapy in patients at risk for coronary stent thrombosis undergoing noncardiac surgery. Clin Res Cardiol 2009;98:335–9.
101. Patrono C, Coller B, FitzGerald GA, Hirsh J, Roth G. Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:234S–64S.
102. Contreras M. Final statement from the consensus conference on platelet transfusion. Transfusion 1998;38:796–7.
103. Hay A, Olsen KR, Nicholson DH. Bleeding complications in thrombocytopenic patients undergoing ophthalmic surgery. Am J Ophtalmol 1990;109:482–3.
104. Jarvis B, Simpson K. Clopidogrel: a review of its use in the prevention of atherothrombosis. Drugs 2000;60:347–77.
105. Miller RD. Transfusion therapy. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, editors. Miller's Anesthesia. 7th edition. Philadelphia, PA: Churchill Livingstone, 2009;55:1760.
106. Samama CM, Djoudi R, Lecompte T, Nathan-Denizot N, Schved JF. Perioperative platelet transfusion: recommendations of the Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSaPS) 2003. Can J Anaesth 2005;52:30–7.
107. Eto K, Goto S, Shimazaki T, et al. Two distinct mechanisms are involved in stent thrombosis under flow conditions. Platelets 2001;12:228–35.
108. FDA Approves Effient to Reduce the Risk of Heart Attack in Angioplasty Patients. 2009. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm171497.htm. Accessed January 5, 2010.
109. Angiolillo DJ, Capranzano P. Pharmacology of emerging novel platelet inhibitors. Am Heart J 2008;156:S10–5.
110. Weerakkody GJ, Jakubowski JA, Brandt JT, et al. Comparison of speed of onset of platelet inhibition after loading doses of clopidogrel versus prasugrel in healthy volunteers and correlation with responder status. Am J Cardiol 2007;100:331–6.
111. Weerakkody GJ, Jakubowski JA, Brandt JT, Payne CD, Naganuma H, Winters KJ. Greater inhibition of platelet aggregation and reduced response variability with prasugrel versus clopidogrel: an integrated analysis. J Cardiovasc Pharmacol Ther 2007;12:205–12.
112. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.
113. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 3, NO. 2, 2010
FEBRUARY 2010:131–42

Aggregation-Thrombolysis in Myocardial Infarction 44 trial. Circulation 2007;116:2923–32.
114. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J 2006;27:1038–47.
115. Cannon CP, Husted S, Harrington RA, et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. J Am Coll Cardiol 2007;50:1844–51.
116. Storey RF, Husted S, Harrington RA, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. J Am Coll Cardiol 2007;50:1852–6.
117. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.
118. Zeidner JF, Frishman WH, Lerner RG. Investigational antiplatelet drugs for the treatment and prevention of coronary artery disease. Cardiol Rev 2008;16:250–9.
119. Cangrelor: Product Overview. The Medicines Company. Available at: http://www.themedicinescompany.com/products_cangrelor.shtml. 2009. Accessed January 5, 2010.

Key Words: antiplatelet therapy ■ drug-eluting stent ■ noncardiac surgery ■ perioperative ■ stent thrombosis.