Management of Antiplatelet Therapy in Patients With Coronary Artery Disease Requiring Cardiac and Noncardiac Surgery

Davide Capodanno, MD, PhD; Dominick J. Angiolillo, MD, PhD

Approximately 5% to 15% of patients undergoing coronary stent implantation are estimated to undergo a surgical procedure within 2 years. In the largest (N=126,773) cohort study to date describing the incidence and timing of noncardiac surgery after coronary stent placement, 12% of patients who received bare metal stents (BMSs) and 47% of patients who received drug-eluting stents (DESs) had early surgery, defined as surgical procedures occurring within 6 weeks in patients treated with BMSs or within 12 months in those treated with DESs. Although the majority were minor procedures, major surgical procedures were more likely to occur within 12 months of stent placement in comparison with 12 to 24 months. Interestingly, a decline in surgical procedures was noted after publication of the American College of Cardiology/American Heart Association Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery in 2007 (preguidelines 25% versus postguidelines 13%, P<0.001). Stented patients undergoing surgery are likely to discontinue dual-antiplatelet therapy (DAPT), composed of aspirin and a P2Y12 receptor antagonist (mostly clopidogrel, but may also include prasugrel or ticagrelor), thereby being exposed to a withdrawal of protection with subsequent risk for stent thrombosis or other ischemic events. In a survey of 1358 consecutive patients treated with DESs and discharged on aspirin and clopidogrel, surgery was identified as the second cause of early discontinuation within 1 year (21%) and the first cause of late discontinuation thereafter (49%).

Defining the fine balance between ischemic and bleeding risk remains a challenge in stented patients undergoing surgery treated with antiplatelet therapy. Understanding whether an antiplatelet drug should or should not be discontinued and tailoring treatment strategies based on the type of intervention are key to balancing the safety and efficacy profiles of antiplatelet medications in this particular scenario. Importantly, such a healthcare problem is relevant not only to the interventional cardiology community, but also to general cardiologists, surgeons, anesthesiologists, and primary care physicians. This article provides an overview of the currently available evidence on the perioperative management of antiplatelet therapy in patients with coronary artery disease (CAD), especially those treated with stents, undergoing surgery. In particular, a description of thrombus and bleeding profiles that characterize CAD patients undergoing surgery, considerations for the use of antithrombotic agents, and a review of current recommendations and future perspectives are provided.

Ischemic and Bleeding Risk in CAD Patients Requiring Surgery

Ischemic Risk

Antiplatelet therapy is a mainstay in the management of patients with CAD. This includes not only patients who have undergone stent implantation, but also those with an acute coronary syndrome (ACS) who are medically treated, in whom the clustering of adverse thrombotic events has been described in the early period after interruption of oral antiplatelet agents. The risk of a recurrent ischemic event for patients discontinuing or not adhering to aspirin treatment has been suggested to increase 3-fold, with similar estimates of risk in patients with an ACS, on secondary prevention for CAD and those undergoing coronary artery bypass grafting (CABG), and higher risk in patients treated with DESs. Importantly, stent thrombosis is a serious complication that is known to commonly present with death or a large nonfatal myocardial infarction, usually with ST elevation.

Rebound platelet reactivity after discontinuation of antiplatelet therapy has been advocated to lead the increased thrombotic risk in stented patients undergoing surgery. However, this hypothesis was not supported by 2 specifically designed randomized studies that used multiple time points, assays, agonists, and agonist concentrations. Differences in response profiles to aspirin after clopidogrel withdrawal have been suggested as a mechanism for differences in individual propensity to develop thrombotic complications. An alternative explanation for the reported clustering of ischemic events after discontinuation of clopidogrel is the recovery of platelet reactivity to pretreatment levels, and therefore more appropriately considered as “withdrawal of protection.” This may assume clinical relevance in specific settings such as surgery, which is inherently associated with an increased thrombotic and inflammatory environment, including increased cytokines, neuroendocrine inflammatory mediator release,

From the Ferrarotto Hospital, University of Catania, Catania, Italy (D.C.); and University of Florida College of Medicine-Jacksonville, Jacksonville, FL (D.C., D.J.A.).

Correspondence to Dominick J. Angiolillo, MD, PhD, University of Florida College of Medicine-Jacksonville, 655 West 8th St, Jacksonville, FL 32209.

E-mail dominick.angiolillo@jax.ufl.edu (Circulation. 2013;128:2785-2798.)

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platelet adhesiveness, persistently high platelet counts, and decreased or impaired fibrinolysis.\textsuperscript{20-22} Adding to the withdrawal of protection with DAPT discontinuation, in case of early surgery following percutaneous coronary intervention (PCI), these factors characterize a unique prothrombotic state that typically occurs in the vulnerable period in which stents are not fully endothelialized.

The first alarming report of adverse perioperative outcomes in BMS patients was published in 2000,\textsuperscript{23} followed by several additional reports of severe cardiac complications and death when surgical operations were performed within 3 to 7 weeks from BMS implantation.\textsuperscript{24-27} These studies, in general, are inherently biased in that patients who require surgery more rapidly are likely to be sicker. However, because BMS thrombosis is more frequent in the first 2 weeks after stent placement and rare more than 4 weeks after, when endothelialization of the stent has generally occurred, current guidelines recommend delaying surgery 4 to 6 weeks after BMS placement to allow proper thienopyridine use to reduce the risk of coronary stent thrombosis.\textsuperscript{28} This recommendation is presently given a IIa class with level of evidence B, reflecting the limited and sometimes conflicting evidence mostly coming from non-randomized studies. In a recent large-cohort registry from Wijeysundera et al,\textsuperscript{29} the incidence of 30-day ischemic events in patients with BMSs was 2.6\% when the interval between stent insertion and major elective cardiac surgery was 45 to 180 days and 6.7\% when the interval was <45 days.

Data on the risk of surgery after DES placement generally relates to small series with mixed results.\textsuperscript{30-36} DES thrombosis may occur late and has been reported up to 5.5 years after implantation, but particularly in the context of discontinuation of antiplatelet agents before noncardiac surgery.\textsuperscript{30-37} Although the risk of death, myocardial infarction, or stent thrombosis decreases significantly for the increasing interval between PCI and surgery, the intermediate-term risk extending at least 2 to 3 years remains \textapprox 1\%.\textsuperscript{38} In the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry, among 206 patients who received \geq 1 DESs and underwent major noncardiac surgery at a median of 6 months after PCI, the risk of cardiac death, myocardial infarction, or stent thrombosis was increased 27-fold in the week following noncardiac surgery in comparison with any other week after stent implantation, but data on how aspirin and clopidogrel were managed were not collected in such a way that it could be determined which patients were on antiplatelet therapy during the surgical procedure and those who were not.\textsuperscript{1} Wijeysundera et al\textsuperscript{39} reported a high (20\%) 30-day incidence of adverse ischemic events in 905 patients with DESs when the interval between stent insertion and surgery was <45 days, whereas the event rate was only 1.2\% once the interval exceeded 180 days. In aggregate, these findings support the understanding that early surgery and antiplatelet therapy discontinuation are risk factors for cardiac events at the time of noncardiac surgery after DES implantation, although some relative risk persists at longer term. It should be noted that the available studies are generally poorly informative on whether the risk of thrombotic events in the surgical period is mainly linked to discontinuation of thienopyridines, or both aspirin and thienopyridines. Consistently, current guidelines recommend withholding elective noncardiac surgery for at least 12 months after DES implantation in patients in whom thienopyridine therapy, or aspirin and thienopyridine therapy, will need to be discontinued perioperatively.\textsuperscript{28,39}

**Bleeding Risk**

When facing the problem of perioperative bleeding, it should be important to distinguish bleedings related to the surgical procedure itself from those that occur in patients on antithrombotic therapy, especially when anticoagulant and antiplatelet drugs are administered in proximity to surgery. In fact, certain procedures are not typically associated with postoperative bleeding in patients not on antithrombotic medications but may be if antithrombotics are given in proximity to the procedure. Interestingly, when surgeons are not aware if aspirin was used or not, they often cannot distinguish, based on the type of bleeding, patients on aspirin from those who have discontinued.\textsuperscript{40} The American College of Chest Physicians guidelines for the perioperative management of antithrombotic therapy have identified a group of surgeries and procedures that appear to be associated with a high risk for bleeding in the context of perioperative anticoagulant and antiplatelet drug use.\textsuperscript{41} An alternative approach coming from a joint national consensus defined the interventions at greater risk of bleeding within an array of different surgeries or invasive procedures (Table 1).\textsuperscript{42} CABG differs from other major surgeries in that it includes specific risk factors for bleeding, including full heparinization therapy, platelet dysfunction from the pump, and altered fibrinolysis.\textsuperscript{43}

Antiplatelet agents that irreversibly inhibit platelet function, thereby requiring 7 to 10 days for an entire platelet pool to be replaced regardless of their half-lives,\textsuperscript{44,45} are aspirin, ticlopidine, clopidogrel, and prasugrel. Most of the studies of aspirin use in the preoperative setting are not randomized; and, consequently, the maintenance of aspirin therapy may be a marker of increased comorbidity and, hence, also a marker of increased bleeding risk. Two randomized clinical trials conducted on the comparative effectiveness and safety of low-dose aspirin versus placebo in patients undergoing noncardiac surgery were prematurely stopped and are therefore underpowered for assessing bleeding and ischemic end points.\textsuperscript{46,47} Taking these limitations into account, both trials showed no significant differences between patients on aspirin and those on placebo in terms of bleeding events within 30 days from surgery,\textsuperscript{46,47} and one suggested the potential for a significant risk reduction in postoperative major adverse cardiac events.\textsuperscript{46} In a meta-analysis of 49,590 patients, the frequency of bleeding complications while on aspirin in patients undergoing noncardiac surgery varied between 0 (skin lesion excision, cataract surgery) and 75\% (transrectal prostate biopsy).\textsuperscript{48} Aspirin was found to be associated with a 1.5-fold increased risk of bleeding complications, but it did not increase the level of the severity of bleeding complications and acted only quantitatively on hemorrhages, with the exception of intracranial surgery and transurethral prostatectomy. As far as CABG is concerned, a meta-analysis of randomized and observational studies comparing preoperative aspirin with no aspirin/placebo showed that aspirin is likely to increase postoperative bleeding, but this may be avoided by the use of doses <325.
However, the importance of aspirin therapy on graft patency should also be noted, particularly during the first postoperative year.50,51

The first major evidence on the impact of P2Y12-inhibiting therapy on surgical bleeding derives from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial comparing clopidogrel versus placebo, on top of aspirin, in ACS patients.52 In CURE, a total of 2072 patients (16.5% of study population) underwent CABG at any time after randomization. Among these, the risk of CURE major bleeding occurred in 9.6% and 7.5% in the clopidogrel and placebo arms, respectively (relative risk, 1.27; 95% confidence interval [CI], 0.96–1.69; \(P=0.095\)).53 However, the bleeding hazards varied markedly according to whether clopidogrel was stopped for \(\leq 5\) days before surgery in comparison with \(>5\) days before surgery. Whereas no excess in any bleeding was observed for those stopping the drug for \(>5\) days before surgery (clopidogrel 4.4% versus placebo 5.3%), a 53% relative increase in major bleeding was seen for those who continued the drug within 5 days of surgery (clopidogrel 9.6% versus placebo 6.3%). Other studies, mainly retrospective in nature, reported on the perioperative continuation of clopidogrel, suggesting increased rates of bleeding with perioperative or periprocedural clopidogrel continuation in noncardiac surgery.24,26,54 In a study of 4330 patients undergoing CABG, those on clopidogrel plus aspirin within 5 and 2 days before surgery, respectively, were found to experience higher blood loss and reoperation for bleeding.55 This finding seems consistent irrespective of whether surgery is performed on- or off-pump56,57 and is likely to be sensitive to the loading dose administered.58 A systematic review of post hoc analyses from 3 prospective randomized studies and 17 observational studies yielded mixed results.59 In fact, contrary to the findings from the meta-analysis of randomized trials, the combination of observational studies showed that recent exposure to clopidogrel before CABG is associated with increased risk of postoperative death, reoperations for bleeding, blood loss, and need of blood transfusions. Another meta-analysis of 34 studies (29 observational) questioned that, although mortality is increased in clopidogrel-treated versus non-clopidogrel-treated patients at the time of CABG (odds ratio, 1.6; 95% CI, 1.30–1.96; \(P<0.00001\)), this is mainly influenced by the ACS status and case urgency, implying that ACS patients requiring urgent CABG should proceed with

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surgery without delay for a clopidogrel-free period, as also noted elsewhere. 

Prasugrel is a third-generation thienopyridine with more potent antiplatelet effects than clopidogrel, which was extensively evaluated in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) trial in the setting of ACS patients undergoing PCI. Because this was a trial intended for PCI, there were only 368 patients (2.7%) who underwent CABG during the study period, which however provided very informative results. Among patients undergoing CABG, the rate of TIMI major bleeding was greater with prasugrel than with clopidogrel (13.4% versus 3.2%, P < 0.001). The difference in CABG-related TIMI major or minor bleeding between prasugrel and clopidogrel was remarkable when the time from the last dose of the study drug was ≤3 days pre-CABG (26.7% versus 5.0%, P < 0.001), but also when the drug was discontinued within 4 to 7 days (11.3% versus 3.4%, P < 0.001). Consistently, a significantly higher mean 12-hour chest tube blood loss was observed with prasugrel in comparison with clopidogrel, without significant differences in red blood cell transfusion. These findings led to the package insert recommendation that, when possible, prasugrel should be discontinued at least 7 days before any surgery, including CABG. The pharmacodynamic basis for this recommendation has been recently reinforced by 2 pharmacodynamic studies.

Antiplatelet agents that reversibly inhibit platelet function are dipyridamole, cilostazol, nonsteroidal anti-inflammatory drugs and ticagrelor. These agents have self-limiting effects depending on their half-lives (ie, ≈10 hours for dipyridamole and cilostazol, 2–20 hours for different nonsteroidal anti-inflammatory drugs, and 8–12 hours for ticagrelor and its metabolites). Ticagrelor is a novel generation P2Y₁₂ receptor inhibitor, a first in class cyclopenyltriazolopyrimidine, with more potent antiplatelet effects than clopidogrel, but faster speed of offset, comparable residual platelet inhibition at 24 hours and 3 days after the last dose, and return to baseline platelet reactivity at day 5 similar to clopidogrel on day 7. In the Platelet Inhibition and Patient Outcomes (PLATO) trial, comparing ticagrelor versus clopidogrel in ACS patients treated with an invasive or noninvasive strategy, 1899 (10.2% of study population) patients underwent CABG at any time during randomization, and 6.8% had CABG within 7 days after discontinuation of study treatment. TIMI major bleeding occurred in 59.3% versus 57.6% (hazard ratio, 1.03; 95% CI, 0.89–1.19; P = 0.68) and TIMI minor bleeding in 21.1% versus 21.6% (hazard ratio, 0.97; 95% CI, 0.77–1.24; P = 0.82) in the ticagrelor and clopidogrel groups, respectively. None of the various bleeding definition rates, including fatal CABG-related bleeding, differed between the ticagrelor group and the clopidogrel group. Importantly, there was no difference in major/fatal/life-threatening CABG-related bleeding and blood loss between ticagrelor and clopidogrel, with respect to time from last intake of study drug before CABG, including when the drug was stopped 1 day before surgery. A further analysis investigating differences in specific causes of post-CABG deaths in the PLATO trial showed that the mortality reduction with ticagrelor versus clopidogrel was associated with fewer deaths from cardiovascular, bleeding, and infection complications. The Food and Drug Administration–approved package insert of ticagrelor recommends to discontinue ticagrelor at least 5 days before any surgery, including CABG, while the European Medicines Agency package insert recommends discontinuation for at least 7 days.

Although current guidelines recommend delaying elective CABG for ≥5 days after the last dose of clopidogrel and ticagrelor and 7 days after the last dose of prasugrel, if possible, concerns exist because this delay comes at the expense of increased risk of ischemic events while awaiting surgery. Indeed, an increase in residual antiplatelet effect was shown to be associated with a significant reduction of mortality in patients treated with prasugrel (adjusted odds ratio, 0.26; 95% CI, 0.08–0.85; P = 0.025) and ticagrelor (hazard ratio, 0.49; 95% CI, 0.32–0.77; P < 0.01) in comparison with clopidogrel in subanalyses of the TRITON TIMI 38 and PLATO trials. The survival benefit with these drugs was noted primarily in the first 30 days, suggesting that surgery-related perioperative outcomes are decreased by residual and continued antiplatelet therapy. Adding to similar findings described with clopidogrel and abciximab in patients undergoing CABG, these analyses coming from more contemporary trials investigating potent antiplatelet agents corroborate the understanding that platelet P2Y₁₂ inhibition does ultimately have a benefit in patients who undergo CABG, including less mortality, although at the price of an increase in bleeding and transfusion.

Practical Recommendations and Future Directions

Avoiding Unnecessary Revascularization or Stent Placement

Unrestricted use of noninvasive stress testing and coronary angiography may be a driver of unnecessary prophylactic revascularizations in patients with CAD referred to noncoronary surgery. Based on guidelines, noninvasive stress testing should be restricted to patients with ≥3 clinical risk factors (including history of ischemic heart disease, history of compensated or previous heart failure, history of cerebrovascular disease, diabetes mellitus, and renal insufficiency) and poor functional capacity who require vascular surgery. These patients may also benefit from β-blocker and statin use in the perioperative period.

Adding to the overemphasis on preoperative diagnostic assessment in patients with risk factors for CAD, the actual need for effective prophylactic coronary revascularization in patients with established stable CAD undergoing surgery is also debatable. In the Coronary Artery Revascularization Prophylaxis (CARP) trial, 510 patients with stable CAD at increased risk for perioperative cardiac complications were randomly assigned to undergo either revascularization (percutaneous or surgical) or no revascularization, before elective major vascular surgery. Preoperative coronary revascularization was not found to decrease the incidence of postoperative myocardial infarction (8.4% versus 8.4%, P = 0.99) or long-term mortality (22% versus 23%, P = 0.92) in comparison with no revascularization. Consistently, in a subsequent small randomized study targeting patients undergoing vascular
surgery with extensive CAD assessed by dobutamine echocardiography or stress nuclear imaging, revascularization did not improve the composite of all-cause death or myocardial infarction at 30 days in comparison with no revascularization (43% versus 33%, P=0.30). In addition, no benefit of revascularization was observed at 1 year (49% versus 44%, P=0.48).

The results of these 2 studies therefore suggest that, at least in patients with stable CAD, the adoption of a systematic prophylactic coronary revascularization strategy is not indicated. However, this statement may not be applicable to patients with ACS or those with severe ischemia on noninvasive testing at a blood pressure and heart rate that could be overcome in the perioperative period. Although there are no adequate clinical trials on which to base firm recommendations, American College of Cardiology/American Heart Association guidelines suggest that, in patients with active cardiac conditions such as acute (≤7 days) or recent (>7 days but ≤1 month) myocardial infarction with evidence of important ischemic risk by clinical symptoms or noninvasive study, it is reasonable to wait 4 to 6 weeks before performing elective surgery. If PCI is necessary, a careful balance between the urgency of noncardiac surgery and the risk of bleeding need to be considered. After an ACS, a strategy of plain old balloon angioplasty only without stent implantation may be safer than stent placement if a good angiography result is achieved. However, in patients revascularized by balloon angioplasty, surgery should not be postponed beyond 6 to 8 weeks to prevent restenosis. On the other side, delaying surgery for at least a week after balloon angioplasty allows for healing of the vessel injury and decreases the risk of acute or subacute closure.

In both stable and ACS patients, current American College of Cardiology/American Heart Association guidelines underline that, in case of low risk of bleeding or if the noncardiac surgery can be postponed 12 months or more, PCI with DES and prolonged DAPT may be considered. If the noncardiac surgery cannot be postponed and is likely to be performed within 1 to 12 months, then placement of a BMS and 4 to 6 weeks of DAPT is considered appropriate. However, at least in the stable CAD setting, these recommendations do not take into account emerging data that suggest a lower risk of late stent thrombosis with second-generation DES, with no need for prolonged DAPT.

Optimal Duration of DAPT and Stent Selection

Although practice guidelines advocate for prolonged use of DAPT after DES implantation and thus ideally postponing noncardiac surgery for 12 months, the optimal duration of DAPT remains unknown. This in turn is the basis for the conundrums surrounding optimal timing of surgery. Although an overview on the impact of DAPT duration goes beyond the scope of this article, observational studies have thus far yielded conflicting findings; some studies have suggested that shorter durations of treatment after DES implant (eg, 6 months) may be adequate for the prevention of thrombotic recurrences, whereas others have suggested that this should be even more prolonged (>12 months). However, in randomized clinical trials there appears to be some evidence of a more favorable risk-benefit ratio linked to shorter duration, likely attributed to the increased bleeding risk that occurs with longer duration of DAPT.

Several trials will further address this topic (Figure 1). The ongoing Dual Anti Platelet Study (DAPT, NCT00977938) is randomly assigning ≥20000 patients treated with BMS or DES free from events at 12 months to placebo versus additional 18 months of thienopyridine (clopidogrel or prasugrel) treatment. The Safety and efficacy of Six-month dual antiplatelet therapy after drug-eluting stenting (ISAR-SAFE, NCT00661206) will compare the efficacy of the 6- and 12-month DAPT strategies in reducing the rate of death, myocardial infarction, stroke, and major bleeding at 15 months in 6000 6-month event-free patients. These trials, in particular, will shed more light on the benefit of prolonging DAPT beyond 6 or 12 months, in addition to the evolving data on the bleeding risk with long-term P2Y12-inhibiting therapy. Indeed, these studies will provide insights on patients who may require surgery during participation in the trial, and how outcomes may be affected by stent type, as well.

Waiting for definitive large-scale trials, when a stent is needed in candidates for surgery, a BMS should be preferred over a DES, if possible, owing to its quicker endothelialization with shorter need for DAPT. Different approaches have been recently devoted to address the limitations of both BMS

Figure 1. Randomized clinical trials on the duration of dual antiplatelet therapy after stent implantation. Solid lines identify available or ongoing comparisons between different regimes of dual-antiplatelet therapy duration. Dotted lines identify theoretical comparisons that have not yet been the object of specific investigation. Studies whose results are available at the date of publication of this article are shown in black. Ongoing studies or studies whose results are not available are shown in gray. ARCTIC indicates Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and a Interruption Versus Continuation of Double Antiplatelet Therapy, One Year After Stenting; DAPT, The Dual Antiplatelet Therapy Study; DES-LATE, Duration of Dual Antiplatelet Therapy After Implantation of Drug-Eluting Stents; EXCELLENT, Efficacy of Xience/Promus versus Cypher in Reducing Late Loss After stenting; ISARSAFE, Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; ITALIC, Is There A Life for Drug-eluting Stents After Discontinuation of Clopidogrel; OPTIDUAL, Optimal Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus-Eluting Stent in the Real World Clinical Practice; PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia; RESET, Real Safety and Efficacy of 3-month dual antiplatelet therapy following Endeavor zotarolimus-eluting stent implantation; SCORE, Study of Optimal Clopidogrel Duration in Patients Receiving Drug Eluting Stents.
and DES by developing new stents with ideal features such as decreased thrombogenicity and no need for long-term DAPT.\textsuperscript{95,96} These include DES with biodegradable polymer, which theoretically may offer the early antirestenotic benefits of a standard DES and the long-term safety benefits of a BMS once the polymer has biodegraded, or DES that are polymer free. The absence of foreign materials contributes to the avoidance of the adverse effects of their presence at long term, is associated with improved healing, and, in particular, may reduce the requirements for long-term DAPT. Fully biodegradable scaffolds offer theoretical advantages over conventional stents, including potential reductions in adverse events such as late ST.\textsuperscript{95,96} However, the scaffold still persists up to 2 years, underscoring that long-term studies in large populations are indeed warranted to best define the safety of biodegradable technologies.\textsuperscript{95,96} Having a shorter DAPT duration after stent implantation may be beneficial in case a patient needs to interrupt or discontinue the medication before surgery. In this regard, second-generation DESs have been associated with a very favorable safety profile in terms of low rates of stent thrombosis, and the possibility of shorter regimens of DAPT has been advocated. In the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) trial, 6-month DAPT did not increase the risk of target vessel failure at 12 months after implantation of DES in comparison with 12-month DAPT in stratified analyses of patients receiving everolimus- or sirolimus-eluting stents.\textsuperscript{90} In the Real Safety and Efficacy of 3-month dual-antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation (RESET) trial, a strategy of 3-month DAPT following Endeavor zotarolimus-eluting stent implantation was found to be noninferior in comparison with 12-month DAPT following the other DES implantation for the primary composite end point of cardiovascular death, myocardial infarction, stent thrombosis, target vessel revascularization, or bleeding at 12 months (4.7% versus 4.7%; \( P \) for noninferiority=0.01).\textsuperscript{92} A prespecified analysis of the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia (PRODIGY) trial supported the understanding that optimal duration of DAPT may be stent-specific, with zotarolimus-eluting stents associated with lower need for prolonged antiplatelet therapy in comparison with BMSs, paclitaxel-eluting stents, or everolimus-eluting stents, whereas patients receiving paclitaxel-eluting stents may experience a significantly higher rate of stent thrombosis with a short DAPT regimen.\textsuperscript{91,92} The second-generation Xience Prime and Xience V everolimus-eluting stents have recently gained European CE Mark approval for use with DAPT for at least 3 months, and the Resolute Integrity zotarolimus-eluting stent for 1 month, which represents the shortest duration of DAPT for any major DES in Europe.\textsuperscript{98,99}

**Managing Perioperative Withdrawal of Antiplatelet Agents**

In patients treated with stents who are to undergo subsequent procedures that mandate discontinuation of P2Y\textsubscript{12} receptor inhibitors, guidelines recommend that aspirin should be continued if at all possible and the thienopyridine restarted as soon as possible after the procedure.\textsuperscript{28} A systematic review of 161 cases of late stent thrombosis and very late stent thrombosis reported from 84 articles suggested that, if aspirin therapy is maintained, short-term discontinuation of a thienopyridine might be relatively safe in patients treated with DES.\textsuperscript{100} Aspirin should only be discontinued if the known bleeding risks are similar or more severe than the observed cardiovascular risks of aspirin withdrawal. In patients who require early (<6 months) noncardiac surgery within placement of a DES, the American College of Chest Physicians guidelines suggest continuing DAPT around the time of surgery instead of stopping, depending on the bleeding risk intrinsic to each kind of intervention.\textsuperscript{41} This latter recommendation does not apply to CABG.

Clearly, in the absence of patient- and procedure-specific recommendations from practice guidelines, clinical judgment is key. Considerations on perioperative withdrawal of antiplatelet agents should include a precise upfront definition of the individual thrombotic profile of patients referred to surgery. In aggregate, the available information seems to identify patients at high risk of perioperative thrombotic events as those who have received a BMS within 1 month or a DES within 6 months, and those who have received a DES >12 months but remain at risk of stent thrombosis or life-threatening complications for unfavorable anatomic or procedural characteristics (ie, long stented segments, multiple stenting, overlapping stents, small vessels, bifurcation lesions, left main, last remaining vessel), or those with unfavorable clinical characteristics (ie, recent ACS, history of stent thrombosis, left ventricular ejection fraction, chronic kidney disease, diabetes mellitus). The need for keeping such high-risk patients on aspirin alone, clopidogrel alone, or both during the surgical period, should be individualized based on the surgical context (Table 1).

**Bridging Therapy**

The trade-off of using oral P2Y\textsubscript{12} receptor inhibitors (clopidogrel, prasugrel, or ticagrelor) in patients with ACS is the increased risk of bleeding complications in those requiring surgery if they have been exposed to oral P2Y\textsubscript{12} inhibition within the preceding 5 to 7 days. On the other hand, patients may develop recurrent complications during the waiting period of P2Y\textsubscript{12} inhibitors discontinuation before surgery, underscoring the need for strategies aimed at transient platelet inhibition to safely bridge patients to their surgical procedure with minimum risk of ischemic or bleeding events. Therefore, the ideal bridging agent should be effective in achieving platelet inhibition similar to that of the oral P2Y\textsubscript{12} receptor inhibitor, with a rapid onset of action and also rapid offset (short duration of action). Evidence on the efficacy and safety of short-acting antithrombotic drugs such as unfractionated heparin, low-molecular-weight heparin or short-acting glycoprotein IIb/IIIa antagonists (eg, tirofiban, eptifibatide) in the perioperative setting are sparse. However, it is important to emphasize that, if bridging is necessary, antiplatelet agents should be preferred over anticoagulants, because platelet accumulation at sites of vascular injury is well known as the primary event in arterial thrombosis.\textsuperscript{101} Importantly, unfractionated heparin makes platelets more reactive to activation by other agonists such as adenosine diphosphate and binds to the glycoprotein IIb/IIIa receptor on the platelet, resulting in a prothrombotic effect.\textsuperscript{102} Therefore, bridging with heparin can actually be potentially
harful. Although low-molecular-weight heparin does not stimulate platelets like unfractionated heparin, this does not have platelet inhibitory effects, which remain key for bridging.

On this background, the only approved agents with fast-acting and potent platelet inhibitory effects with relatively short duration of action are the small-molecule intravenous glycoprotein IIb/IIIa antagonists (eg, tirofiban, eptifibatide). A bridging strategy with perioperative administration of tirofiban was found to be feasible and reasonably safe in a small study of patients with a recently implanted DES and high-risk characteristics for stent thrombosis undergoing major or eye surgery,\textsuperscript{103} and later confirmed in slightly larger studies of patients undergoing major surgery.\textsuperscript{104} Another pilot study of 67 patients who underwent noncardiac or cardiac surgery after DES implantation suggested that, despite preoperative bridging with a glycoprotein IIb/IIIa inhibitor, postoperative stent thrombosis can still occur in patients requiring antiplatelet medication interruption.\textsuperscript{105} Notably, in these studies, aspirin was mostly continued throughout the perioperative period. In light of these mixed results, more studies are needed to assess the role of bridging therapy with glycoprotein IIb/IIIa inhibitors in patients who require P2Y\textsubscript{12} receptor antagonists.

Cangrelor is a nonthienopyridine adenosine triphosphate analogue that reversibly binds to the P2Y\textsubscript{12} receptor, and, unlike clopidogrel, prasugrel, and ticagrelor, it is administered intravenously with a rapid onset and offset of effect. In comparison with glycoprotein IIb/IIIa inhibitors, cangrelor features more desirable characteristics because of its faster offset and specificity to the P2Y\textsubscript{12} receptor (Table 2). In addition, differently from glycoprotein IIb/IIIa inhibitors, dose-finding studies designed to achieve a “thienopyridine-like” platelet inhibitory effect were specifically conducted for cangrelor to reduce the risk of bleeding with prolonged infusion. These pharmacological properties make cangrelor the ideal drug to be considered for bridging patients to surgery. This hypothesis has been recently tested in the phase II prospective, randomized, double-blind Maintenance of Platelet inhibition With cangrelor After discontinuation of Thienopyridines in Patients Undergoing surgery (BRIDGE) trial, in which 210 patients with an ACS or treated with a coronary stent and receiving a thienopyridine awaiting CABG surgery were randomly assigned to receive either cangrelor (0.75 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\)) or placebo for at least 48 hours.\textsuperscript{106} The study drug was discontinued 1 to 6 hours before CABG surgery. Aspirin therapy was maintained throughout perioperative period. Cangrelor consistently achieved and maintained platelet inhibition assessed by the VerifyNow P2Y\textsubscript{12} assay at levels known to be associated with a low risk of thrombotic events in comparison with placebo (platelet reaction units <240; 98.8% versus 19.0%; relative risk, 5.2; 95% CI, 3.3–8.1; \(P<0.001\)). Importantly, bridging with a prolonged infusion of cangrelor did not increase major bleeding before surgery, although minor bleedings, largely attributed to ecchymosis at the site of venous puncture, were more commonly documented with cangrelor.\textsuperscript{106} The BRIDGE trial therefore supports the hypothesis that bridging with intravenous cangrelor may be a successful strategy to provide adequate platelet P2Y\textsubscript{12} inhibition after thienopyridine discontinuation in patients referred to cardiac surgery. Although this approach has the potential to also be valid in noncardiac surgery, this possibility has still to be proven, given that different noncardiac operations have variable bleeding risk. Cangrelor is not still approved for clinical use, but filing with regulatory agencies is pending, also based on the results of a recent large-scale trial, showing the drug to be effective in reducing the rate of ischemic events during PCI, with no significant increase in severe bleeding.\textsuperscript{107}

Proposed bridging strategies with small-molecule glycoprotein IIb/IIIa antagonists or cangrelor are schematized in Figure 2. In brief, after discontinuation of the P2Y\textsubscript{12} inhibitor as per guidelines recommendations (7 days before surgery for prasugrel, 5 days before surgery for clopidogrel or ticagrelor), bridging with tirofiban or eptifibatide should be initiated ≈72 hours before surgery and continued up to 4 to 6 hours from surgery.\textsuperscript{103,104} In the absence of studies targeting specific levels of platelet inhibition, the maintenance-dosing regimen (0.1 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\) for tirofiban, 2.0 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\) for eptifibatide) should be that recommended according to the package insert of each molecule.\textsuperscript{108,109} A loading dose is not warranted given that bridging does not occur in an acute setting requiring immediate effects as in the ACS/PCI setting. In patients with renal impairment (creatinine clearance <50 mL/min), a dose reduction is warranted (0.05 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\) for tirofiban, 1.0 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\) for eptifibatide) and earlier suspension (8–12 hours) should be considered. In addition, the timing of surgery should be carefully defined to avoid extending glycoprotein IIb/IIIa antagonist infusion, given that the drugs are being used at the dosing regimen recommended for ACS/PCI settings that are known to be associated with an increased risk of bleeding that can be enhanced with prolonged infusion. Cangrelor is still not approved for clinical use, but may become a treatment option in the future. The dosing regimen and bridging scheme should reflect how cangrelor was tested in the BRIDGE trial,\textsuperscript{106} in which a tailored dose to achieve “thienopyridine-like” platelet inhibition (0.75 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\)) was

<table>
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<th>Table 2. Key Pharmacokinetic and Pharmacodynamic Characteristics of Cangrelor and Small-Molecule Glycoprotein IIb/IIIa Antagonists</th>
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<tr>
<td><strong>Onset of action</strong></td>
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<tr>
<td><strong>Potent platelet inhibition</strong></td>
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<tr>
<td><strong>Plasma half-life</strong></td>
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<tr>
<td><strong>Offset of action</strong></td>
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<tr>
<td><strong>P2Y\textsubscript{12}-specific (natural bridge)</strong></td>
</tr>
<tr>
<td><strong>“Targeted” Inhibition (thienopyridine-like)</strong></td>
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identified. In particular, this dose was one-fifth of that used in the PCI trial\(^{110}\) and without a loading bolus. No renal adjustments are required, because renal function does not affect the clearance of cangrelor. In addition, there is a larger window of opportunity to initiate treatment, which should be within 72 hours from \(\text{P}_2\text{Y}_{12}\) inhibitor discontinuation, and to extend treatment, which was tested up to 7 days. Discontinuation of cangrelor infusion can occur 1 to 6 hours before surgery. After noncardiac surgery, irrespective of bridging strategy, clopidogrel should be resumed with a loading dose as soon as oral administration is possible. Prasugrel and ticagrelor administration should be discouraged in the early period after surgery, given their increased potential for bleeding complications. If oral administration of clopidogrel is not possible, postsurgery bridging with an intravenous agent should be considered. Initiation of \(\text{P}_2\text{Y}_{12}\)-inhibiting therapy in patients undergoing CABG is at the discretion of the treating physician, given that coronary segments at risk of thrombotic complications will have been bypassed. However, it is recommended that oral \(\text{P}_2\text{Y}_{12}\)-inhibiting therapy be started in patients who presented with an ACS according to practice guidelines.\(^{111,112}\) Low-dose aspirin (\(<100\) mg/d) should be administered continuously throughout the perioperative period, with the exception of specific interventions (eg, neurosurgical) in which this may be contraindicated.

Indeed, the main limitation of bridging with intravenous antiplatelet therapies (glycoprotein IIb/IIIa inhibitors or cangrelor) is the need for several days of hospitalization to allow drug infusion. This is therefore accompanied by added costs during a time frame in which, for the most part, patients are simply waiting to undergo surgery and no other treatments are being provided. Therefore, alternative routes of administration of antiplatelet therapies are warranted. Transdermal delivery represents a potential strategy that is currently under investigation. Transdermal delivery has several benefits over intravenous delivery including patient preference because it is noninvasive, it has ease of administration, and it reduces the in-hospital length-of-stay. The development of transdermal tirofiban is ongoing.\(^{113}\)

**Platelet Function Measurement**

There is a broad variability in the individual response to different antiplatelet agents. In particular, numerous studies have shown that patients are at an increased risk of ischemic or bleeding complications depending on the level of platelet inhibition individually achieved. Platelet function assays have emerged as useful tools for their potential to identify patients at a higher risk of ischemic and bleeding complications.\(^{114,115}\) Tailoring antiplatelet treatment by increasing clopidogrel dosing or switching to alternative antiplatelet regimens

**Figure 2.** Proposed bridging protocols for patients on dual-antiplatelet therapy with aspirin plus a \(\text{P}_2\text{Y}_{12}\) receptor inhibitor referred to cardiac or noncardiac surgery. A, Bridging strategy with small-molecule glycoprotein IIb/IIIa inhibitors (GPI). B, Bridging strategy with cangrelor (cangrelor is an investigational product still not approved for clinical use).
in low responders according to platelet function assays has not proven to impact clinical outcomes.\textsuperscript{116,117} However, there is ongoing interest in platelet function measurement–based strategies that may theoretically reduce bleeding and waiting time in clopidogrel-treated patients undergoing CABG surgery. The thromboelastography platelet-mapping assay has been suggested to have a potential role in deciding the timing of off-pump CABG in patients who need continued clopidogrel therapy.\textsuperscript{119,120} In The Timing Based on Platelet Function Strategy to Reduce Clopidogrel-Associated Bleeding Relationship to CABG (TARGET-CABG) study, 180 patients on aspirin with or without clopidogrel therapy underwent thromboelastography before planned on-pump CABG to assess clopidogrel responsiveness and guide the timing of surgery.\textsuperscript{121} This strategy resulted in an overall 46% shortening of the guideline-recommended waiting period for clopidogrel-treated patients and was associated with the same amount of bleeding observed in clopidogrel-naïve patients. The US Society of Thoracic Surgeons has recently recognized the high negative predictive value of preoperative point-of-care testing in identifying patients with residual platelet reactivity and assigned specific classes of recommendation for platelet function testing as a tool for assessing bleeding risk, limiting blood transfusion, and optimizing antiplatelet therapy of patients undergoing cardiac surgery\textsuperscript{122} (Table 3). However, there is little guidance on the best test to be used and the optimal cut-off value to be considered.

### Platelet Transfusion

Blood transfusions are required as an emergency therapy in 1.8% to 8.0% of patients who bleed.\textsuperscript{123} Red blood cell transfusion has been found to increase platelet activation and aggregation in healthy volunteers, a mechanism that may partly explain the risk of recurrent ischemic events or mortality after transfusion in anemic patients with ACS.\textsuperscript{124} In case of hemorrhage that continues despite the usual hemostatic techniques, however, platelet transfusion may be considered as a strategy to reverse bleeding, even if platelet count is normal. In a small study on healthy volunteers, the earliest measured time when supplemented platelets were not inhibited by circulating active metabolite of prasugrel was 6 hours after the administration of a 60-mg loading dose.\textsuperscript{125} Accordingly, the package insert of prasugrel recommends platelet transfusion, when necessary, within 6 hours from the loading dose or 4 hours from the maintenance dose.\textsuperscript{126} Less effect on platelet aggregability may be anticipated in patients treated with a reversible P2Y\textsubscript{12} inhibitor such as ticagrelor in comparison with those on clopidogrel or prasugrel.\textsuperscript{127,128} No data exist with ticagrelor regarding a hemostatic benefit of platelet transfusion,\textsuperscript{129} but a study in healthy volunteers is ongoing (NCT01744288).

A strategy of reversal to normal hemostasis by platelet transfusion in patients on clopidogrel immediately before noncardiac surgery has been investigated in a small cohort.\textsuperscript{130} The authors did not find a significant increase in the incidence of perioperative major adverse cardiac events, but larger studies are needed to validate the safety and efficacy of this approach. Other approaches to promote hemostasis in the setting of emergent CABG surgery might include the use of aprotinin, aminocaproic acid, or tranexamic acid. Aprotinin was temporarily withdrawn worldwide in 2007 after studies suggested that its use increased the risk of death or complications, including renal failure requiring dialysis and myocardial infarction.\textsuperscript{131,132} In February 2012, the European Medicines Agency scientific committee reverted its previous standpoint regarding aprotinin, highlighting that the benefits of the drug may outweigh the risks in a restricted range of indications.\textsuperscript{133}

### Intracoronary Imaging

Although stent thrombosis is widely recognized as a multifactorial phenomenon, pathological studies have identified strut uncoverage as the primary substrate responsible for this event.\textsuperscript{134–136} A potential role for intracoronary imaging has been postulated as a tool to assess for adequate stent strut coverage by neointimal tissue growth. Optical coherence tomography is a high-resolution intravascular imaging modality based on infrared light emission, which, because of its resolution in the range of 10 to 15 μm, has emerged as a sensitive tool to assess the presence of stent strut coverage.\textsuperscript{137,138} For this reason, optical coherence tomography has the potential to provide evidence to guide the duration of antiplatelet treatment in stented patients who need to prematurely discontinue DAPT.\textsuperscript{139} This hypothesis, however, has not yet been prospectively tested.

#### Table 3. Recommendation for Platelet Function Monitoring in the Perioperative Period of Patients Undergoing Cardiac Surgery

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level of Evidence</th>
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<tbody>
<tr>
<td>Because of their high negative predictive value, preoperative point-of-care testing to assess bleeding risk may be useful in identifying patients with high residual platelet reactivity after usual doses of antiplatelet drugs, and who can undergo operation without elevated bleeding risk</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Point-of-care testing to assess perioperative platelet function may be useful in limiting blood transfusion</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>For patients on dual-antiplatelet therapy, it is reasonable to make decisions about surgical delay based on tests of platelet inhibition rather than arbitrary use of a specified period of surgical delay</td>
<td>Iib</td>
<td>B</td>
</tr>
<tr>
<td>Once postoperative bleeding risk is decreased, testing of response to antiplatelet drugs, either with genetic testing or with point-of-care platelet function testing, early after cardiac procedures might be considered to optimize antiplatelet drug effect and minimize thrombotic risk to vein grafts</td>
<td>Iib</td>
<td>B</td>
</tr>
<tr>
<td>For patients with high platelet reactivity after usual doses of clopidogrel, it may be helpful to switch to another P2Y\textsubscript{12} inhibitor (eg, prasugrel or ticagrelor)</td>
<td>Iib</td>
<td>C</td>
</tr>
</tbody>
</table>

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Implementation of Consensus Documents

The limitations and blind spots of the current guidelines of perioperative antithrombotic management include lack of recommendations on antithrombotic strategies to be applied differently based on patient- and procedure-related bleeding and thrombotic risk. In addition, clinical practice guidelines do not highlight precise operational guidance on the management of patients at high thrombotic risk for surgery not be postponed, and they lack clear specification on the mode of recovery of antiplatelet therapy after surgery. In general, recommendations are more specific on bridging of anticoagulant therapy (eg, heparin bridging in patients receiving warfarin) in patients with mechanical valves or atrial fibrillation, possibly as a result of increased awareness about the occurrence and consequences of thrombotic events. In particular, the American College of Chest Physicians guidelines advocate that bridging anticoagulation in patients on vitamin K antagonists for mechanical valves, atrial fibrillation, or venous thromboembolism should be considered based on the individual patient thromboembolic and procedural bleeding risk by balancing expected benefits and harms.41 In fact, bridging anticoagulation with heparin may be harmful, especially in therapeutic-dose regimens and in patients not at high thromboembolic risk undergoing high–bleed-risk procedures.140 In contrast, despite the magnitude of the problem both in terms of the number of patients affected and the potential clinical implications, few recommendations are available on bridging antiplatelet therapy in ACS/PCI patients requiring surgery. Therefore, the importance of a joint effort among all those responsible for the management of patients undergoing cardiac and noncardiac surgery to better define antiplatelet-bridging regimens should be emphasized. Sufficient time should be spent to make the patient informed of all positive and negative consequences related to the discontinuation of antiplatelet therapy in the perioperative period. Collaborative efforts in education and communication should be devoted across different subspecialties, including cardiologists, surgeons, and family doctors dealing with primary care. Working groups at the hospital, regional, and national level should be created to deal with the problem based on the local situation. Consensus documents endorsed by cardiology and surgery societies with Web-app dissemination are a viable way to fill the gaps on the issue of perioperative DAPT management, based on a multidisciplinary definition of the ischemic and bleeding risk linked to different operations.42 Indeed, implementing national registries to understand practice patterns and outcomes of specific bridging protocols may provide a better understanding of how these affect patient outcomes and identify areas that warrant improvement in patient care.

Conclusions

The American College of Cardiology/American Heart Association and American College of Chest Physicians guidelines emphasize the importance of adopting preventive strategies aimed at reducing the risk of premature DAPT discontinuation in stented patients undergoing surgery.26,41 This can be accomplished by avoiding DES implantation whenever possible, especially in patients who are likely to require invasive or surgical procedures within the next 12 months, and by delaying elective procedures for which there is significant risk of perioperative or postoperative bleeding. Strategies aimed at bridging patients on DAPT to their surgical procedure may benefit from the introduction into clinical practice of short-acting intravenous antiplatelet agents with a fast offset of action such as cangrelor. Clinical guidelines also recommend a greater effort by healthcare professionals before patient discharge to ensure proper education about the significant risks associated with prematurely discontinuing DAPT therapy. Similarly, healthcare providers who perform invasive or surgical procedures and who are concerned about periprocedural and postprocedural bleeding must be made aware of the potentially catastrophic risks of premature discontinuation of antiplatelet therapy. When issues regarding DAPT therapy arise, particularly in stented patients, cardiology consultation is indicated.

Disclosures

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