

# Prevention of the renarrowing of coronary arteries using drug-eluting stents in the perioperative period: an update

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**Abstract:** The management of patients scheduled for surgery with a coronary stent, and receiving 1 or more antiplatelet drugs, has many controversies. The premature discontinuation of antiplatelet drugs substantially increases the risk of stent thrombosis (ST), myocardial infarction, and cardiac death, and surgery under an altered platelet function could also lead to an increased risk of bleeding in the perioperative period. Because of the conflict in the recommendations, this article reviews the current antiplatelet protocols after positioning a coronary stent, the evidence of increased risk of ST associated with the withdrawal of antiplatelet drugs and increased bleeding risk associated with its maintenance, the different perioperative antiplatelet protocols when patients are scheduled for surgery or need an urgent operation, and the therapeutic options if excessive bleeding occurs.

**Keywords:** stent thrombosis, antiplatelet agents, aspirin, clopidogrel, surgical bleeding, perioperative management

## Introduction

Percutaneous coronary interventions (PCIs) and coronary stent placement are now frequently and increasingly used. Among coronary stents, drug-eluting stents (DESs) seem to have some advantages over bare-metal stents (BMSs), but they need more time for complete endothelialization.<sup>1-3</sup> As antiplatelet therapy is a key part of the management of all these patients, during the perioperative period, its management is one of the most important safety issues and, nowadays, has many controversies.<sup>4</sup>

First, the withdrawal of antiplatelet agents (APAs) seems to be associated with an increased risk of perioperative stent thrombosis (ST), myocardial infarction (MI), and death.<sup>5,6</sup> Second, surgery under an altered platelet function could lead to an increased risk of bleeding, outweighing the benefit of continuous antiaggregation in some procedures, mainly those performed in a closed space.<sup>7,8</sup>

Because of the conflict in the recommendations, this article reviews the protocols of administration of APAs after the performance of a PCI with a DES placement and their management in patients scheduled for elective surgery or need an emergency intervention.

## Antiplatelet agents

The most commonly used antiplatelet drugs are cyclooxygenase (COX) inhibitors, such as aspirin; adenosine diphosphate (ADP) receptor P2Y<sub>12</sub> antagonist, such as clopidogrel, ticlopidine, prasugrel; and integrin  $\alpha$ IIb $\beta$ 3 (glycoprotein IIb/IIIa [GPIIb/IIIa]) receptor antagonists.<sup>9,10</sup>

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## Aspirin

The prostanoid TXA<sub>2</sub> is the main inductor of platelet aggregation and vasoconstriction. That is, the vascular prostanoid PGI<sub>2</sub> is the main platelet aggregation inhibitor and induces an intense vasodilatation effect. The antiplatelet action of aspirin includes the selective blocking of the platelet TXA<sub>2</sub> synthesis by the irreversible acetylation of the enzyme COX-1, whereas COX-2-mediated PGI<sub>2</sub> production is largely insensitive to low-dose aspirin inhibition.<sup>11</sup> The main pharmacokinetic characteristics of aspirin are known for a long time. Aspirin, the regular uncoated tablet, is rapidly absorbed in the stomach and upper intestine, reaching peak plasma levels at 30–40 minutes after ingestion (oral bioavailability 40%–50%). Enteric-coated aspirin can take up to 3–4 hours to reach peak plasma levels after its administration<sup>12</sup> although the half-life of aspirin is close to 15–20 minutes because of its rapid clearance from the circulation. The mean life span of human platelets is approximately 8–10 days due to both platelet and megakaryocytes COX-1 inhibition by aspirin. However, as about 10%–12% of circulating platelets are replaced every 24 hours, complete recovery of platelet aggregation may occur in 50% of cases by day 3 and in 80% of cases by day 4.<sup>13</sup> The efficacy and safety of low-dose aspirin are well documented. Aspirin reduces the risks of stroke and composite outcome of stroke or death in patients with prior stroke or transient ischemic attack.<sup>14</sup> Low doses of aspirin decrease the risk of acute MI or death in patients with both unstable angina and chronic stable angina, reduce stroke or death in patients with transient cerebral ischemia,<sup>15–17</sup> prevent thrombotic complications in patients with polycythemia vera,<sup>18</sup> and reduce early occlusion after aortocoronary bypass surgery<sup>19</sup> and carotid endarterectomy.<sup>20</sup>

The balance between preventing vascular occlusion and causing excess bleeding with aspirin depends critically on the absolute thrombotic vs hemorrhagic risk of the patient.<sup>9</sup> The meta-analyses by Antithrombotic Trialists' Collaboration about the effects of antiplatelet therapy among patients at high risk of occlusive vascular disease<sup>17</sup> have shown that the benefits of aspirin far exceed the bleeding risks. However, it is known that some patients under aspirin therapy at usual doses (75–150 mg aspirin daily) still fail to have an optimal inhibition of thromboxane A<sub>2</sub> pathway. These patients with such "aspirin resistance" could remain at high thrombotic risk with important clinical implications. There is a lack of uniformly accepted definition,<sup>21</sup> and the exact prevalence is unknown but has been suggested to be between 5.5% and 60%.<sup>22</sup> This phenomenon is important because in patients with some comorbidities, such as diabetes mellitus,

hypertension, heart failure, inflammatory disorders, which may enhance aspirin resistance, the combination therapy, rather than aspirin-alone therapy, will be necessary to reach optimal antiplatelet inhibition.<sup>22</sup>

## ADP receptor antagonists

The ADP P2Y<sub>12</sub> receptor plays a central role in the formation and stabilization of thrombus and is also essential in the complete activation of GPIIb/IIIa. Clopidogrel, ticlopidine, and prasugrel act as APAs by irreversibly binding to the ADP P2Y<sub>12</sub> receptor on platelets, subsequently preventing ADP-associated platelet aggregation.<sup>23</sup>

## Clopidogrel

Clopidogrel is a parent drug. After oral administration, clopidogrel needs to be metabolized in the liver through a cytochrome P450 (CYP3A4) to active metabolite SR 26334.<sup>24</sup> Its plasma elimination half-life is approximately 8 hours. Clopidogrel produces detectable inhibition of platelet aggregation 2 hours after the administration of 400–600 mg oral doses, and as in the case of aspirin, platelet function returns to normal about 7 days after the last dose of clopidogrel. The benefits of clopidogrel for patients with an increased risk of recurrent ischemic events,<sup>17,25</sup> stroke,<sup>26</sup> and acute coronary syndromes (ACS)<sup>27</sup> have been established by large, well-conducted randomized clinical trials. As aspirin and clopidogrel have different and complementary mechanisms of action, the combination therapy (dual antiplatelet therapy [DAT]) is more effective in preventing ST and in those presenting with ACS, compared with antiplatelet monotherapy.<sup>28,29</sup> The American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) have published guidelines for the use of APAs in patients who undergo PCI.<sup>30,31</sup> A current antiplatelet protocol in patients with DESs is discussed in a separate section of this article. DAT has been associated with significantly increased risk for major bleeding in studies of more than 1 month duration compared with antiplatelet monotherapy.<sup>28</sup> Infrequent complications include intracranial hemorrhage (0.4%) and severe neutropenia (0.5%).<sup>26</sup>

## Prasugrel

Prasugrel is the most recently marketed oral thienopyridine derivative. The main advantages of prasugrel are that it has a faster onset of action (30 minutes) than clopidogrel, and it is a more potent P2Y<sub>12</sub> receptor antagonist, leading to higher effects of inhibition of platelet aggregation, lesser variability of response, and a lower incidence of drug resistance than

clopidogrel.<sup>32</sup> Prasugrel is indicated for the prevention of atherothrombotic events in patients with ACS undergoing PCI.<sup>33</sup> In the analysis of the recent TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel – Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) designed to compare clopidogrel with prasugrel in patients undergoing PCI, the benefit from the intensive platelet inhibitory effects associated with prasugrel was more pronounced in patients with high risk (patients with ST segment elevation MI (STEMI) and those with diabetes).<sup>34,35</sup> However, this reduction in thrombotic events was associated with a significant increase in the risk of bleeding, which overcame the benefit of prasugrel in certain groups.

### Integrin $\alpha$ IIb $\beta$ 3 (GPIIb/IIIa) receptor antagonists: abciximab, tirofiban, and eptifibatide

After recognizing that the interaction between fibrinogen and GPIIb/IIIa is the major final step in platelet aggregation, this GP became the target of novel antiplatelet drugs, ie, the GPIIb/IIIa antagonists, such as abciximab, tirofiban, and eptifibatide. These drugs can be used alone or in combination with clopidogrel.<sup>36</sup>

#### Abciximab

Abciximab is a chimeric Fab fragment of the murine antihuman GPIIb/IIIa. It blocks fibrinogen ligand binding to GPIIb/IIIa. After an intravenous (IV) bolus administration, its half-life is <30 minutes. Abciximab (0.25 mg/kg IV bolus dose and 0.125  $\mu$ g/kg/min infusion) produces a rapid inhibition of ADP-induced platelet aggregation with peak effects 2 hours after bolus administration. After stopping infusion, a gradual recovery of platelet function is observed and then returns to >50% of baseline in most patients within the first 24 hours, and nearly in all patients within the first 48 hours.<sup>37</sup> Abciximab is recommended as adjunct therapy in PCI. A meta-analysis of the 3 major clinical trials<sup>38–40</sup> on the use of abciximab in patients undergoing PCI showed that abciximab treatment reduced the incidence of ischemic events and all-cause mortality.<sup>41</sup> Bleeding and thrombocytopenia were the 2 most important adverse reactions associated with abciximab. Approximately 1%–2% of patients treated with abciximab have platelet counts <50,000/L, but in almost all cases, the thrombocytopenia was effectively controlled by stopping the drug administration.<sup>42</sup>

#### Tirofiban

Tirofiban is a specific nonpeptide antagonist of GPIIb/IIIa receptors derived from tyrosine. Bolus doses of 15  $\mu$ g/kg

followed by tirofiban infusions 0.15  $\mu$ g/kg/min produced both an inhibition of platelet aggregation induced by ADP nearly 100% and an increase of the bleeding time >30 minutes. Recovery of platelet function was achieved >50% within 4 hours after discontinuing drug infusion.<sup>43</sup> Tirofiban is effective in patients with unstable angina and non-Q-wave MI<sup>44</sup> and protects patients undergoing coronary angioplasty for ACS.<sup>45</sup>

#### Eptifibatide

Eptifibatide is a synthetic heptapeptide with high selectivity by GPIIb/IIIa receptor inhibition. Bolus dose of 180  $\mu$ g/kg of eptifibatide followed by 1  $\mu$ g/kg/min infusion decreases platelet-induced ATP aggregation >95% and increases bleeding time to 22 minutes when compared with control values of 7–8 minutes. After stopping eptifibatide infusion, platelet function recovers >50% of baseline aggregation within the first 4 hours.<sup>46</sup> Eptifibatide reduces the acute adverse outcome of patients undergoing PCI,<sup>47</sup> and it is also beneficial in patients with unstable angina.<sup>48</sup> However, a significant interindividual variation in the inhibitory responses to eptifibatide has been reported.<sup>47</sup>

### Monitoring antiplatelet effect

Tests of platelet function attempt to measure the point in the activation process reached by the platelets of an individual patient. Possible reasons for measuring platelet function in patients include screening, diagnosis, monitoring antiplatelet therapy, monitoring prohemostatic therapy, predicting thrombosis, predicting bleeding, and assessing stored platelets.<sup>49</sup> In the perioperative period, it would be helpful to identify patients who are at risk of bleeding because of platelet dysfunction related to the administration of any APA. However, none of these tests has been validated for routine clinical practice and for monitoring antiplatelet efficiency in perioperative period of coronary interventions; the reason could be a lack of standardization, poor correlation between various tests, and expensiveness of some of them.<sup>50</sup>

A wide variety of tests are available for the measurement of platelet function, and each has its advantages and disadvantages. The tests available for assessing platelet function can be summarized as follows (Table 1).<sup>49,51</sup>

- *Turbidimetric platelet aggregometry* could be considered the reference assay to diagnose platelet disorders. However, it needs a platelet-rich, high-volume plasma sample; the results are not completely standardized; the laboratory procedure is complex; and the test is time consuming.

**Table 1** Main platelet function test for monitoring aspirin/clopidogrel therapy

Platelet function test for monitoring aspirin	Serum thromboxane B2; urinary 11-dehydro thromboxane B2; platelet aggregometry (turbidimetric); platelet aggregometry (impedance); VerifyNow aspirin assay; Plateletworks; TEG platelet Mapping system; and platelet function analyzer – 100
Platelet function test for monitoring clopidogrel	VASP phosphorylation (flow cytometry); platelet aggregometry (turbidimetric); platelet aggregometry (impedance); VerifyNow P2Y12 assay; Plateletworks; and TEG platelet mapping system
Platelet function test for monitoring GP IIb/IIIa antagonists	Platelet aggregometry (turbidimetric); platelet aggregometry (impedance); VerifyNow TRAP assay; plateletwork; and platelet flow cytometry

**Abbreviations:** TEG, thrombelastograph; VASP, vasodilator-stimulated phosphoprotein; TRAP, thrombin receptor activating peptide.

- *Impedance aggregometry* is more physiological than the optical one, but it still requires a reasonably high sample volume, and this assay is also time consuming and expensive.
- The *platelet function analyzer* (PFA-100) explores the platelet adhesive capacity, measuring the closure time taken for a platelet plug to occlude an aperture in a membrane impregnated with collagen and epinephrine or ADP.<sup>52</sup> Although the test has advantages such as simplicity, rapid readout, low sample volume, no requirement for sample preparation, and that aspirin and clopidogrel have been shown to prolong this closure time, there is no evident correlation between these results and an increased perioperative bleeding.
- The *Plateletworks analyzer* measures the percentage of aggregation of whole blood before and after exposure to ADP. Its results are contradictory when compared with optical aggregometry: there is good correlation for clopidogrel<sup>53</sup> but limited usage for aspirin.<sup>54</sup> Then, it needs further studies.
- *Thromboelastography* is a whole blood coagulation monitor that can demonstrate the alteration of platelet aggregation. However, it is unable to detect the specific defects that occur with the administration of aspirin or clopidogrel.
- The *Ultegra rapid platelet function assay* system (known as VerifyNow<sup>®</sup>) is a whole blood, point-of-care assay that incorporates a single-use cartridge with some biochemical reagents that can detect platelet dysfunction.<sup>55</sup> It is a simple, true point-of-care device that does not need rapid pipetting and requires only a small sample volume. It has been proposed to monitor efficacy of aspirin and clopidogrel and to detect the aspirin-resistant population.
- *Phosphorylation of vasodilator-stimulated phosphoprotein* for the measurement of P2Y12 antagonism is commercially available as a flow cytometry kit. It is dependent on the target of clopidogrel (P2Y12), and it needs low sample volume and whole blood assays, but the sample preparation is not easy, and it requires a flow cytometer and an experienced technician.  
Unfortunately, none of these tests has good correlation with perioperative bleeding, so they could not predict the bleeding tendency in a patient under the effects of aspirin or clopidogrel. Further clinical investigations are necessary in this field.

## Drug-eluting stents

BMSs have been developed to reduce the rate of restenosis after angioplasty. However, the restenosis rate remains high, existing in >20% of cases, leading to ischemic coronary syndromes, or requiring revascularization in >10% of cases. Although the BMS virtually eliminates the elastic recoil and premature negative remodeling, the proliferation of the endothelium is even more important and uncontrolled than with angioplasty alone. This concept was the basis for the development of DESs. By preventing neointimal hyperplasia, the DES has reduced the need for revascularization under 10%.<sup>1,56,57</sup> In brief, a DES is a metal stent, stainless steel or cobalt–chromium alloy, coated with a polymer containing a drug with antiproliferative properties. There are drugs from the *limus* family (sirolimus or rapamycin, everolimus, pimecrolimus, zotarolimus, biolimus, tacrolimus), paclitaxel (Taxol<sup>®</sup>)<sup>58</sup> (Table 2).

During angioplasty, the atherosclerotic material and subendothelial tissue are exposed to the blood stream, initiating the process of thrombus formation and obstruction

**Table 2** Types of drug-eluting stent by composition

Stent	Manufacturer	Platform	Drug	Polymer
Cypher™	Cordis, J&J	Stainless steel, tubular	Sirolimus	Permanent
Taxus™	Boston Scientific	Stainless steel, tubular	Paclitaxel	Permanent
Endeavor™	Medtronic	Chrome-cobalt, multiple rings	Zotarolimus	Permanent
Xience V™	Abbott	Chrome-cobalt, multiple rings	Everolimus	Permanent
Promus™	Boston Scientific	Chrome-cobalt, multiple rings	Everolimus	Permanente
Costar™	Conor	Stainless steel, tubular	Paclitaxel	Biodegradable
Axxion™	Biosensors	Stainless steel, tubular	Paclitaxel	Permanent
Yukon™	Translumina	Stainless steel, tubular	Sirolimus	No polymer
Janus™	Sorin	Coating carbon, tubular	Tacrolimus	No polymer
Coroflex™	Braun	Chrome-cobalt, tubular	Paclitaxel	Permanent
Nobori™	Terumo	Stainless steel, multiple rings	Biolimus	Biodegradable

Adapted from Sierra et al<sup>97</sup> with permission.

of the coronary lumen. The metallic surface of the stent is an additional thrombogenic stimulus that persists until it is covered with endothelium. In the case of BMS, it is expected to be coated within 4–8 weeks, whereas in DES, the drug not only inhibits cell proliferation but also causes endothelial dysfunction and a local inflammatory reaction, impairing the normal healing process of an arterial injury; therefore, the thrombotic risk may persist even for years.<sup>59,60</sup>

## Current antiplatelet protocols in patients with DESs

APA is recommended in the treatment of patients who had undergone PCI. After the combination therapy using aspirin and clopidogrel was introduced, the incidence of ST was reduced to <1% of the patients,<sup>61</sup> and it became unusual after the first month in BMS. However, ST may occur months to years after the implantation of DES in association with premature cessation of APA. The 2007 update of the ACC/AHA/Society for Cardiovascular Angiography and Interventions (SCAI) 2005 guideline for the use of APA in patients who undergo PCI is summarized in Figure 1.<sup>62,63</sup>

### APA before or during PCI

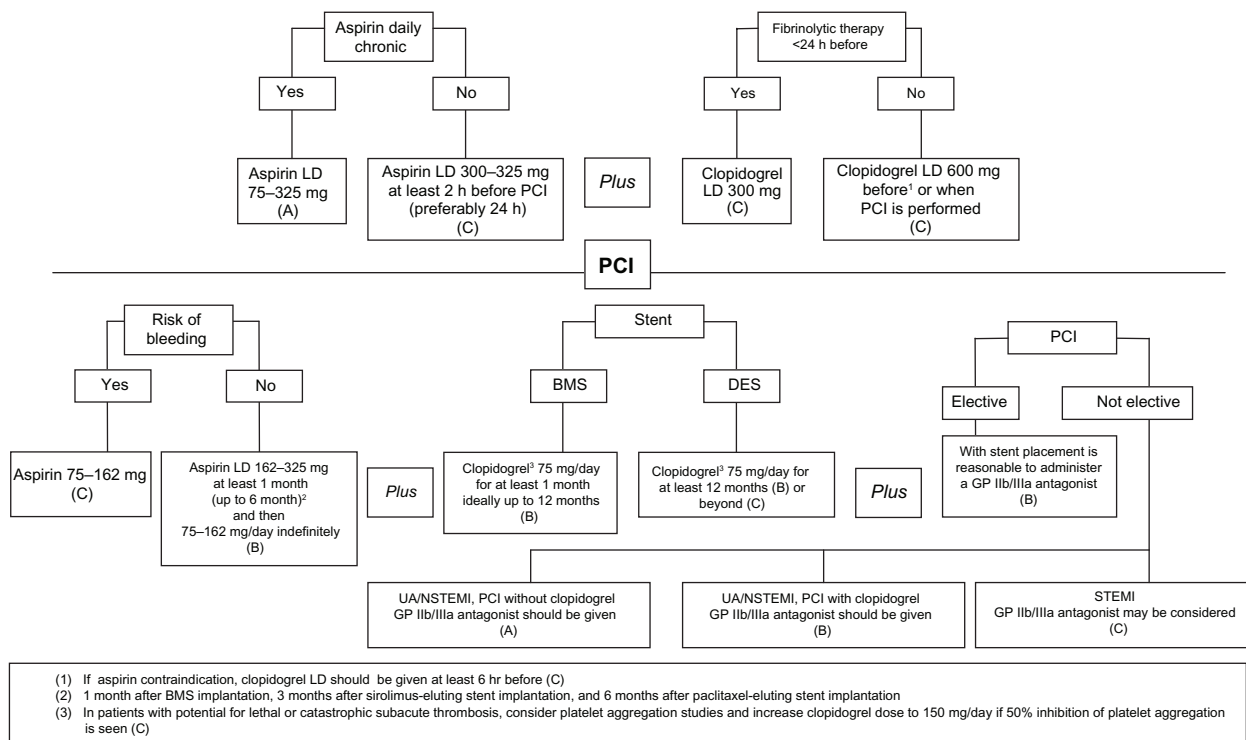
- Patients who were already receiving daily long-term aspirin therapy should be given 75–325 mg of aspirin before PCI (level of evidence: A).
- Patients who were not receiving daily long-term aspirin therapy should be given 300–325 mg of aspirin at least 2 hours (preferably 24 hours) before PCI (level of evidence: C).
- A clopidogrel loading dose (LD), usually of 600 mg, should be administered before or during PCI (level of evidence: C).

- In patients undergoing PCI after 12–24 hours of fibrinolytic therapy, a clopidogrel oral LD of 300 mg may be considered (level of evidence: C).
- If clopidogrel is given at the time of PCI, supplementation with GPIIb/IIIa receptor antagonists may be beneficial (level of evidence: B).
- In patients with absolute contraindication to aspirin, a single administration of clopidogrel both 300 and 600 mg LD at least 6 hours before PCI, supplemented with or without GPIIb/IIIa antagonists, at the time of PCI is recommended (level of evidence: C).

There is an agreement about the benefit of higher LD of clopidogrel in patients undergoing PCI. Several authors have analyzed the effects of different LDs (300 or 600 mg) on the inhibition of platelet aggregation, myonecrosis (troponin I release), and clinical outcomes in patients undergoing PCI. Greater dose of clopidogrel has shown an increase of antiplatelet effect and a significant decrease of major adverse cardiac events, in comparison with 300 mg LD, which supports a clinical benefit of higher dose of clopidogrel in patients subjected to PCI.<sup>64,65</sup>

### APA after PCI

- In patients subjected to PCI and with no allergies or increased risk of bleeding, aspirin 162–325 mg daily should be given for at least 1 month after BMS implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation. Afterward, a daily dose of 75–162 mg of aspirin should be maintained indefinitely (level of evidence: B).
- The use of low-dose aspirin is supported by data from post hoc analysis of the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study.<sup>66</sup> No differences in



**Figure 1** The 2007 update on the recommendations of the ACC/AHA/SCAI 2005–2007 last-updated guidelines on use of antiplatelet drugs in patients who undergo PCI.

**Note:** In parenthesis, the level of evidence is given.

**Abbreviations:** PCI, percutaneous coronary intervention; LD, loading dose; BMS, bare-metal stent; DES, drug-eluting stent; UA, unstable angina; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction.

the efficacy among the 3 aspirin dose groups (<100 mg, 101–199 mg, and  $\geq 200$  mg) in combination with clopidogrel have been found. However, an increase of major bleeding incidence has been reported with the highest dose of aspirin either alone or with the combination of clopidogrel.<sup>67</sup> Therefore, these data suggest an optimal daily dosage of aspirin between 75 and 100 mg to minimize bleeding risk (level of evidence: C).

- In post-PCI patients receiving a BMS, clopidogrel should be given for a minimum of 1 month, whereas it should be given only for a minimum of weeks for patients with an increased risk of bleeding (level of evidence: B).
- In all post-PCI patients with DES and without high risk of bleeding, clopidogrel 75 mg daily should be given for at least 12 months (level of evidence: B).

These recommendations are based on the antiplatelet regimens used in clinical trials conducted to achieve the approval of US Food and Drug Administration (low-risk lesions in low-risk patients). The anticipated times have been taken for the predicted metal stent struts adequate endothelialization time, which reduces the ST risk efficiently. The effect of continuous use of clopidogrel in patients receiving BMS or DES at 6 and 12 months was analyzed by an observational study including

3,165 patients. Clopidogrel did not modify the incidence of death or MI at 24 months in patients with BMS. However, the continuous use of clopidogrel was associated with lower rates of death or MI in patients with DES.<sup>68</sup> The American Heart Association Science Advisory (AHA) stresses the importance of 12 months DAT and provides reports about the potential hazards associated with premature discontinuation of these drugs, and thus, they recommend that the prolongation of clopidogrel therapy beyond 1 year may be considered in patients undergoing DES placement (level of evidence: C).

In a recent meta-analysis, a triple therapy (aspirin plus thienopyridine plus cilostazol) has been evaluated to know the effect of adding cilostazol to a dual antiplatelet regimen to prevent stent restenosis.<sup>69</sup> The 6-month restenosis rates are significantly lower with triple therapy vs DAT, which seems a promising way to reduce cardiac events in patients with coronary artery stent.

## Bleeding and thrombotic risk stratification in the perioperative period

The perioperative management of APA must be based on the optimal assessment of benefit – risk relationship. This

includes the stratification of the perioperative hemorrhagic risk associated with the continuation of APAs throughout surgery and the stratification of the thrombotic risk associated with the discontinuation of APA (Table 3).<sup>7,8,70–72</sup>

## Bleeding risk

The perioperative risk for hemorrhage depends on the type of APA, the monotherapy or combination therapy, and the surgical procedures. As a general rule, the risk of bleeding probably increases when the patient receives a dual therapy or when antiplatelet therapy is associated with an anticoagulant drug (heparin, low-molecular-weight heparin, fondaparinux, warfarin). When aspirin is given as monotherapy, the surgical bleeding and its related complications have been calculated to increase by a factor 1.5,<sup>73</sup> but it is controversial if this result could be extended to all surgical procedures.<sup>72</sup> Indeed, the evidence on the risk of bleeding in patients under the effect of APA is also controversial, and the results of several recent studies are not fully conclusive.<sup>74</sup>

Finally, the increased bleeding risk with aspirin does not mean necessarily an increase in mortality or morbidity, an increase in transfusion requirements,<sup>75</sup> or a worse result in the surgical procedure, with the exception of surgery in a closed space, and possibly transurethral prostatectomy. Moreover, the risk of surgical bleeding is also increased in these patients due to DAT. Burger et al<sup>73</sup> have demonstrated, through a meta-analysis of 41 studies involving 49,590 patients undergoing different types of noncardiac surgery, that the bleeding risk is multiplied by a factor 1.5 when aspirin treatment is continued. Yet, this is not accompanied by the increased risk of major bleeding complications, with the exception of cases in which minor bleeding may have catastrophic results, such as intracranial surgery. Also prostate surgery, transurethral resection, and radical surgery are generally considered high

risk for bleeding, but in the last few years, the improved resection techniques and laparoscopic approach have helped to reduce the risk of hemorrhage in these cases.<sup>76</sup>

There are no randomized controlled studies that evaluate the risk of bleeding when continuing treatment with clopidogrel in noncardiac surgery. In some case series, the continuation of clopidogrel in the perioperative period is not associated with excessive bleeding.<sup>77</sup> With regard to coronary bypass surgery, the CURE trial showed no major bleeding among patients who continued clopidogrel treatment up to 5 days before surgery vs patients who discontinued clopidogrel 5 days or more before surgery, without any difference in mortality.<sup>78</sup>

In conclusion, in noncardiac surgery, bleeding could be considered as a “minor” complication, and severe events are more frequently of cardiac origin.

## Thrombotic risk

ST is a severe complication that is associated with a high incidence of acute MI (22%–90%) and death (30%–45%).<sup>79–81</sup> The current procedure of DAT with aspirin and thienopyridine (usually clopidogrel) has reduced the incidence of ST to around 2% in the long term.<sup>82,83</sup> According to the time elapsed since the stent implantation, ST is considered “early” in the first 30 days, “late” from 30 days to 1 year, and “very late” after 1 year.<sup>84</sup> The first 30 days after stent placement is the period of higher risk of thrombosis, with an incidence of 60%–75% of cases with ST.<sup>82</sup> Although early ST is generally considered to be related to the procedure, late and very late events are less frequent, and discontinuation of antiplatelet therapy seems to be an important risk factor.<sup>84</sup>

Nevertheless, over the past few years, some observational studies found that late and very late DES thromboses occurred more frequently than reported in previous randomized controlled trials, with an increased risk of mortality.<sup>85</sup>

**Table 3** Proposed stratification of the hemorrhagic risk related with the continuation of antiplatelet agents through the perioperative period and the thrombotic risk associated with their discontinuation

Minor	Moderate	Major
<b>Hemorrhagic risk</b> Transfusion usually not needed; minor plastic/general/OS surgery; and biopsies, tooth extraction, surgery of the anterior segment of eye	Transfusion usually needed; cardiac surgery; major OS/visceral/ENT/urology or reconstructive surgery	Possible bleeding in an enclosed space; cranial surgery; spinal surgery; surgery of the posterior; segment of eye; and transurethral prostatectomy
<b>Thrombotic risk</b> >6 mo after AMI; CABG; percutaneous coronariography; BM; coronary surgery; and CVS (>12 mo if high-risk patient or associated complications)	>12 mo after DES; 6–36 wks after AMI; CABG; BMS; and CVS (6–12 mo if high-risk patient or associated complications)	<12 mo after DES; <6 wks after AMI; CABG; BMS; and CVS (<6 mo if high-risk patient or associated complications)

**Abbreviations:** OS, orthopedic surgery; ENT, ear-nose-throat surgery; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; BMS, bare metal stent; DES, drug-eluting stent; CVS, cerebrovascular stroke.

It appeared to be related to the premature discontinuation of antiplatelet therapy and with the higher use of DESs in off-label indication (around 60% of cases in real-world practice).<sup>86</sup> Thus, the safety of DES was questioned.

Recent studies with longer follow-up period allow us to summarize the current situation. In a recent Swedish observational study of 17,198 patients followed up for 1–4 years after stent placement, no significant differences in the risk of death or MI were found between both types of stent, in the case of either on-label or off-label use.<sup>87</sup> Lastly, Kirtane et al<sup>88</sup> have published an extensive meta-analysis of DES vs BMS in on-label and off-label uses. They conclude that the use of DES compared with BMS is associated with a significant reduction (46%–55%) in target vessel revascularization. These results seem to be consistent in demonstrating that DES use is safe for a broad range of lesions and patients at various risk levels.

However, there are different time patterns for the ST depending on the type of stent. Although early thrombosis is more frequent in BMS, the incidence of late and very late thromboses is higher in DESs.<sup>82,89</sup> Several studies have identified multiple factors that contribute to ST (Table 4).<sup>90</sup> Some scoring systems have been recently developed to estimate the risk for ST; one of them include 8 significant predictors, with a stratification of patients in low, medium, and high risk groups, and has been validated using 1-year data from 4,820 patients (Table 5).<sup>91</sup>

Finally, it is necessary to highlight that because of its relation with perioperative period, most authors agree that premature discontinuation of DAT was strongly associated with ST<sup>82,90,92</sup> with a higher risk if clopidogrel is discontinued during the first 6 months after stenting. At 12 months, the cessation of clopidogrel does not appear to be related with a higher risk of ST.<sup>93,94</sup>

## Management of APAs in the perioperative period

Around 5% of patients with a coronary stent are scheduled for noncardiac surgery within the first year after stent implantation.<sup>94</sup> Perioperative incidence of major adverse

cardiac events and mortality in noncardiac surgery in these patients can reach a rate of 2.5%–21.4% in the case of ST.<sup>95</sup> This increased risk is strongly associated with the time elapsed from stenting to surgery and the premature discontinuation of DAT. Thus, this risk could be reduced by delaying surgery until the prescribed antiplatelet regimen is completed.<sup>77,96</sup> Abrupt cessation of antiplatelet therapy may be followed by an increase of platelet reactivity or “rebound” effect in patients on chronic antiplatelet treatment. In addition, surgery itself creates a thrombogenic situation. The endocrine response to surgical stress may indirectly contribute to adverse cardiovascular events, such as increased vascular reactivity (vasospasm), platelet activation, increased clotting factors in plasma, and decreased fibrinolysis, in the perioperative period. Then, the risk of cardiac event in the perioperative period is not entirely prevented by continued DAT.

The decision to discontinue the antiplatelet therapy before surgery should be based on careful cardiovascular and thrombotic risk assessment of the patient and on the type of surgery and bleeding risk. In patients with coronary stent, it is essential to have specific information on the characteristics of coronary disease that has led to stent implantation, the date of procedure, the type of stent implanted, and the current antiplatelet regimen.<sup>97</sup>

The recommendations about the perioperative management of antiplatelet therapy in these patients are not fully agreed, but they can be summarized as follows (Figure 2):<sup>7,8,71,96–100</sup>

- Whenever possible, antiplatelet therapy should be maintained during the high-risk period for as long as it is currently recommended: low-dose aspirin (75–100 mg) indefinitely, and clopidogrel 75 mg at least during 12 months after DES placement. Therefore, if the surgery is likely to cause little or no risk of bleeding, it is recommended to continue the antiplatelet therapy. However, regarding elective procedures in which there is a significant risk of perioperative bleeding, surgery should be delayed until patients have completed the DAT.

**Table 4** Risk factors of stent thrombosis

Procedure-related factors	Stent malposition; stent underexpansion; stent length; persistent slow coronary blood flow; positive remodeling; and residual arterial dissection
Patient and lesion-related factors	Stenting in the setting of an acute coronary syndrome; premature antiplatelet therapy discontinuation; no response to aspirin and/or clopidogrel; low ejection fraction; diabetes mellitus; advanced age; stenting: bifurcated lesions, long lesions, small vessels, complex lesions; and in-stent restenosis
Characteristics of stent-related factors	Delayed endothelialization; type of drug, kinetics of drug release; material and designing; polymer versus nonpolymer; type of polymer; and hypersensitivity to polymer



**Table 5** Clinical risk score for prediction of stent thrombosis and risk stratification as developed by Baran et al<sup>91</sup>

Clinical factors	Hazard ratio	Weight
Thienopyridine discontinuation <6 mo	5.28	5
Insulin treated diabetes	4.74	5
Left main stenting	2.73	3
Smoking status	2.63	3
Lesion length >28 mm	2.35	2
Multiple stenting	2.25	2
Moderate to severe lesion calcification	2.25	2
Reference vessel diameter <3 mm	1.72	2
Total possible score		24
Risk stratification		
Low (ST rate%)		0–6 (0.8)
Moderate (ST rate%)		7–13 (3.6)
High (ST rate%)		14–24 (12.6)

**Abbreviation:** ST, stent thrombosis.

- In all cases, it is recommended that a low-dose aspirin (75–100 mg) is maintained throughout the perioperative period, unless the risk of bleeding clearly outweighs thrombotic risk. To reduce the potential risk of bleeding, aspirin dose >200 mg should be replaced by 75 or 100 mg.
- The treatment should be substituted by low-dose aspirin in the case of patients treated with clopidogrel as monotherapy, and where discontinuation is mandatory (unless contraindicated).
- If antiplatelet therapy must be discontinued, it should be stopped the shortest time possible: 2 days for aspirin and 5 days for clopidogrel. Thereafter, treatment should be restarted as soon as possible following surgery after ensuring hemostasis, between 6 and 48 hours during the postoperative period. Depending on the withdrawal time and to accelerate antiplatelet response, LD administration may be indicated as follows: aspirin 250 mg, clopidogrel 300 mg.

Protocols involving the use of short-acting substances, such as IV administration unfractionated heparin and the infusion of either epifibatid or tirofiban, have been proposed to act as a bridge when the discontinuation of clopidogrel and/or aspirin is mandatory. It should be started 3 days before surgery and stopped 4–8 hours before surgery.<sup>101,102</sup> However, currently there is not enough evidence to recommend their use.<sup>71</sup> Some authors defend that if aspirin is maintained, the short-term discontinuation of clopidogrel may be relatively safe without bridge therapy.<sup>103</sup>

## Management of the APAs in cases of emergency surgery

In the patients under the effect of any APA and undergoing emergency surgery, the key questions are the decision on

the need to prevent or to treat bleeding, minimizing the risks of ischemia and ST, and whether the hemorrhagic risk may endanger the vital or functional prognosis of the intervention. The following strategies could be considered to decrease the consequences of hemorrhage.

## Pharmacological treatment

The administration of desmopressin has been suggested to reduce excessive bleeding in patients scheduled for cardiac surgery under the effects of aspirin. However, consistent beneficial effects of this practice cannot be shown in large studies, and the drug cannot be recommended for current practice as an effective hemostatic agent in patients treated with aspirin.<sup>104</sup> The use of recombinant factor VII is controversial. It has been included “off-label” in some strategies or protocols to control a life-threatening hemorrhage because it could reverse the inhibitory effect of clopidogrel,<sup>105</sup> but there is not enough evidence to support its inclusion as a standard recommendation in urgent surgery for patients under the effect of an APA.

## Platelet transfusion

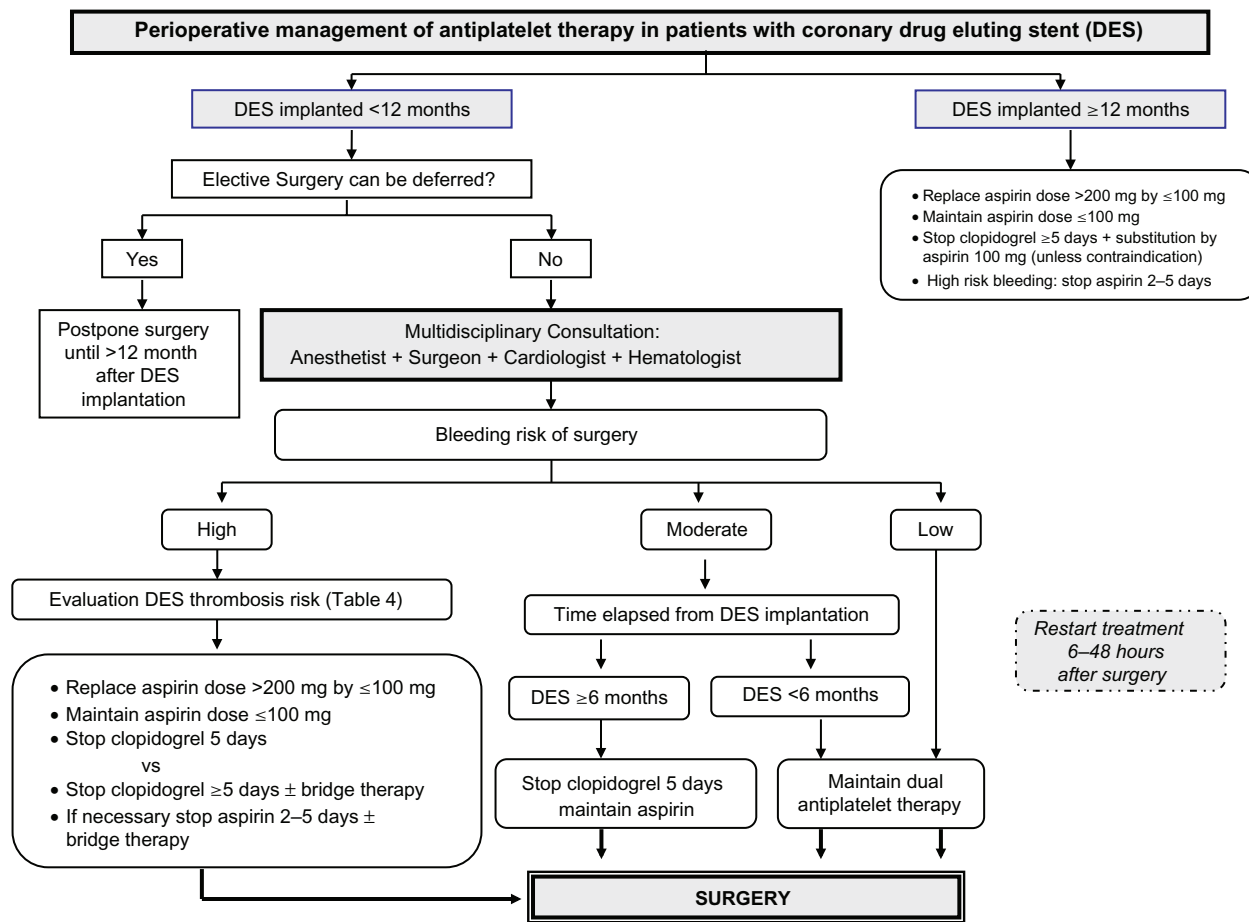
As there is no drug to directly antagonize the antiplatelet effect of aspirin or clopidogrel, sometimes, platelet transfusion (1 U/5–10 kg) may be needed to stop bleeding.<sup>106</sup> Regular prophylactic transfusion of platelets should be discouraged and evaluated carefully on a case-by-case basis, considering the expected benefit gained from it and the possible risks of platelet transfusion. In patients who have received clopidogrel, despite the low immediate hemostatic effect, the preoperative transfusion of platelets could be a good alternative to facilitate postoperative hemostasis, only if the patients undergo surgery with high bleeding risk.<sup>52,107</sup>

The dilemma of whether to transfuse platelets before the beginning of clinical bleeding or only with the aim of treating a clinically significant hemostatic alteration depends in most cases on the kind of surgery and if the inherent bleeding could have a bad vital or functional implication.

## Semiurgent surgery

What to do if surgery cannot be delayed and the patient is in a high-risk period for thrombosis? The management of APA should have minimizing the ST risk as priority, trying to expose the patient to the minimal bleeding risk. Several protocols have been proposed with a multidisciplinary approach, although none of them has been completely validated.<sup>9,106</sup>

- *Low bleeding risk:* The recommendation is to maintain dual therapy until the day before surgery.



**Figure 2** Perioperative management of antiplatelet therapy in patients with drug-eluting stents (DES).

- *Moderate bleeding risk:* Aspirin should be continued, and clopidogrel should be stopped 5 days before surgery. Some authors have proposed a bridging therapy, with the infusion of tirofiban and unfractionated heparin started 3 days before surgery and maintained until 6 hours before surgery, mainly if the patient has additional risk factors and very high thrombotic risk of DES,<sup>101</sup> or the infusion of tirofiban only started 4 days before surgery until 4 hours before surgery.<sup>108</sup>
- *High bleeding risk:* Aspirin and clopidogrel should be discontinued 5 days before surgery (considered to be the best option), or aspirin and clopidogrel should be stopped 10 days before surgery and a bridging therapy should be started as explained earlier.

## Conclusions

Surgery after coronary stent placement is associated with a moderate to high risk of major adverse cardiac events, mostly caused by in-stent thrombosis due to the prothrombotic and proinflammatory states, which lead to hypercoagulability associated with surgical intervention. The interruption

of antiplatelet therapy before surgery and/or through the perioperative period could have a rebound effect with an increase in the hypercoagulation and prothrombotic state and more risk for ST.

On the other hand, the maintenance of APA could increase the risk of bleeding in some interventions, with a wide range of implications: from no influence in the development of surgery and outcome to a vital risk associated with bleeding in closed spaces. So, the challenge for the surgical team is to use a therapy that can minimize both thrombotic and hemorrhagic risks to reach the better benefit for the patient.

Although there is no valid algorithm for all situations, current trend is to delay all surgery that is not life-threatening if the stent has high thrombotic risk and, if not possible, to give optimal protection to the patients with BMS or DES with the maintenance of at least an APA, or running an alternative protocol with anticoagulants and aspirin. In all other patients, aspirin should be maintained throughout the perioperative period if possible, balancing individual benefit/risk ratio of the withdrawal of APA.

## Disclosure

The authors report no conflicts of interest in this work.

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