

Antiplatelet therapy and coronary stents in perioperative medicine – the two sides of the coin

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New trends in interventional cardiology, e.g. the increasing practice of coronary intervention with stent implantation and the prolonged use of dual antiplatelet therapy – usually a combination of clopidogrel and aspirin – has also increased the number of patients presenting for non-cardiac surgery. The two most commonly used stent types, bare-metal stents (BMSs) and drug-eluting stents (DESs), mandate different lengths of dual antiplatelet drug therapy to avoid stent thrombosis. Perioperative caregivers face a knife-edge dilemma between perioperative stent thrombosis, due to preoperative discontinuation of antiplatelet drugs, or surgical bleeding, by continuation of therapy. Pre- and intraoperatively, the risk factors for thrombosis have to be balanced against the risk factors for surgical bleeding. As long as prospective trials are not available,

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the recommendations and guidelines of task forces and experts are based on retrospective studies and case reports. The perioperative management, decision trees and the importance of close interdisciplinary collaboration between cardiologists, surgeons and anaesthetists will be described.

Key words: percutaneous coronary intervention; coronary stents; dual antiplatelet drug therapy; non-cardiac surgery; perioperative stent thrombosis; regional anaesthesia and platelet function assays.

Anaesthetists are confronted with the problem of coronary stents and dual antiplatelet drug therapy under two conditions:

1. A coronary risk patient scheduled for non-cardiac surgery undergoes preoperative evaluation and a cardiological consultation, resulting in preoperative angiography and coronary stent implantation.
2. A patient with recent coronary artery stenting undergoing dual antiplatelet drug therapy presents for elective or emergency non-cardiac surgery.

Because of changes in current practice in interventional cardiology both scenarios are occurring more and more frequently. Ten years ago percutaneous transluminal coronary angioplasty (PTCA) without stent implantation was the standard procedure. The disadvantage of PTCA alone was:

- the risk of total coronary occlusion if PTCA failed and
- a restenosis rate of 30% or more.

The development of coronary stents compensated for most of these disadvantages. Today, up to 90% of all percutaneous coronary intervention (PCI) includes implantation of at least one coronary stent.¹ Stent implantation mandates dual antiplatelet drug therapy, i.e. the combination of a cyclooxygenase (Cox) 1-inhibitor with an adenosine diphosphate (ADP) receptor antagonist (thienopyridin), usually acetylsalicylic acid (ASA) and clopidogrel (plavix[®]). The duration of this regimen depends on the type of stent used. Currently, in drug-eluting stents (DESs), 6–12 months of dual antiplatelet therapy is recommended and there is a high probability that such a patient will require non-cardiac surgery during this time period. Discontinuation of antiplatelet drugs increases the risk of perioperative stent thrombosis, continuation increases the risk of surgical bleeding.

The technique of stent implantation is applied not only in the coronary vascular system, but also in the aorta and the carotid artery as well as in other peripheral arteries. This chapter will not address stenting in other vessel areas because the risk is only moderate after discontinuation of antiplatelet therapy and because available data is scarce.

CORONARY STENTS

In the last decade, coronary stent (Figure 1) implantation has become the interventional treatment of choice in patients with coronary artery disease (CAD).² Stents may reduce mortality in chronic CAD and re-infarction rate in acute coronary syndrome, although recent data suggest that in patients with stable coronary artery



Figure 1. A drug-eluting stent (Paclitaxel) with the balloon not inflated, inflated and inflated in a curved position to demonstrate the flexibility of the stent.

disease PCI did not reduce the risk of death, myocardial infarction or other major cardiovascular events when added to optimal medical therapy.³ Long-term outcome is limited by restenosis, which occurs due to excessive neointima formation.^{4,5} A clinically relevant restenosis rate occurs in 10–30% of patients treated with bare-metal stents (BMSs), depending on the individual risk profile of the patient (e.g. it is more frequent in diabetic patients) and stent type. The DES was developed to minimise the process of restenosis and re-interventions in the coronary system (clinical restenosis rate 5–10%). To date, DES use has not resulted in a reduction in mortality. In addition to technical problems with the implantation of this stent type, the emerging problem of early and late stent thrombosis has resulted in major concerns.^{6,7}

DRUG-ELUTING STENTS AND RECENT CONCERNS

The most frequently used DESs from the first generation were coated with either sirolimus (CYPHER-stent) or paclitaxel (TAXUS-stent). Sirolimus (rapamycin) is a macrolide antibiotic with potent immunosuppressive and antimetabolic properties, while paclitaxel is a potent anti-tumor drug.

Recently, concerns about an increased risk for late stent thrombosis have initiated a broad debate worldwide among cardiologists.^{8–10} Stent thrombosis is a serious adverse event, commonly associated with acute myocardial infarction and even sudden cardiac death. Numerous meta-analyses, registry reports and press releases have contributed to uncertainty. Different investigators looked at the same data using different analytical approaches.^{11–15} In these trials, DESs were either associated with an increased risk of morbidity/mortality or no significant differences were found. Approved indications for a DES include the treatment of discrete, previously untreated lesions. However, currently more than 60% of DES use is off-label in patients with complex conditions (such as multi-vessel disease or acute myocardial infarction) and bifurcating lesions, as well as in patients with diabetes and renal dysfunction, and this off-label use may be associated with an increased risk of both early and late stent thrombosis. The conclusion of recent expert discussions was that the ‘on-label’ use of a DES is safe and

efficient in terms of a highly significant reduction in target vessel revascularisation, while 'off-label use' is accompanied by higher event rates when a BMS is used, with early evidence that DESs show better results in certain 'off-label' indications.

DUAL ANTIPLATELET DRUG THERAPY AFTER CORONARY STENTING

Stent implantation *per se* is a thrombogenic procedure and initiates complex interactions between the surface of a stent and blood components, including the activation of platelets, the complement system and coagulation factors. Obviously, platelets play a pivotal role in this process. Several cardiological trials have demonstrated that the combination of ASA with a thienopyridine is superior to single drug therapy.^{16,17} Therefore, the combination of ASA and clopidogrel is the currently accepted and recommended drug regimen. ASA antagonises the production of thromboxane A₂ (TXA₂) by inhibition of Cox-1. The thienopyridines clopidogrel and ticlopidine inhibit irreversibly the binding of ADP at the P2Y₁₂-receptor (Figure 2).

Ticlopidine was replaced by clopidogrel because of less serious adverse events (gastrointestinal symptoms, neutropenia and thrombocytopenic purpura). Inhibition by ASA and thienopyridines is irreversible; the effect can only be antagonised by the

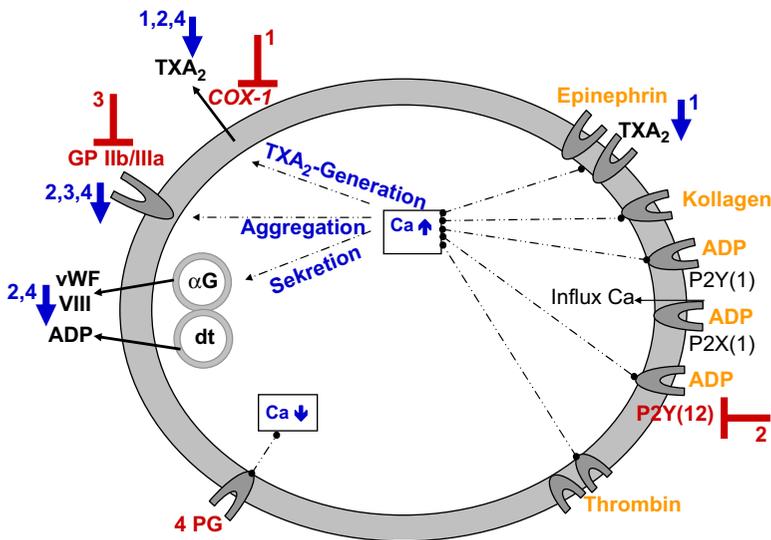


Figure 2. Modification of platelet function by antiplatelet drugs. An increase in the intracellular calcium concentration (Ca) upon binding of agonists (yellow) leads to their membrane-bound receptors subsequently leads to platelet activation, with the generation of thromboxane (TXA₂) from phospholipids via cyclooxygenase I (COX-1) and aggregation, with the expression of activated fibrinogen receptors (GP IIb/IIIa), secretion of various factors such as von Willebrand factor (vWF), coagulation factor VIII from α-granules (αG) and adenosine diphosphate (ADP) from dense granules (dG). Sites of action of antiplatelet drugs (red) and monitoring of their inhibiting effects (blue) are indicated as follows: 1, COX-1 inhibitor; 2, ADP receptor antagonists (blockade of P2Y₁₂, but not P2Y₁ and P2X₂); 3, GP IIb/IIIa inhibitors; 4, antiaggregatory prostaglandins. Agonists of similar signal transduction pathways may be used for monitoring specific platelet inhibitors e.g. epinephrine, collagen, or arachidonic acid for the COX-1 inhibitor and ADP for ADP receptor antagonists.

formation of a new platelet population or by platelet transfusion. Normal recovery of platelet function in healthy volunteers ranges from 3–7 days.

Guidelines

The European Society of Cardiology (ESC) guidelines recommend that after implantation of a BMS, clopidogrel must be continued for 3–4 weeks (level of evidence IA) and ASA lifelong. After a DES, clopidogrel should be administered in addition to ASA for 12 months (level of evidence IC).¹⁸ The American College of Cardiology (ACC)/American Heart Association (AHA) also recommend that, at the very least, patients should be treated with clopidogrel 75 mg and ASA 325 mg for 1 month after BMS implantation, for 3 months after sirolimus DES implantation, for 6 months after paclitaxel DES implantation and, ideally, for up to 12 months if they are not at a high risk for bleeding.¹⁹ The new AHA/ACC/ACS Science Advisory changed these recommendations, stating that the original recommendations were based on the antiplatelet regimen of trials conducted to obtain FDA approval (which meant low risk lesions in low risk patients). As DESs are now being used in high risk lesions and reports indicate that DESs may be associated with delayed endothelialisation, local hypersensitivity reactions and late stent thrombosis, the advisory panel recommends 12 months of dual antiplatelet therapy after placement of a DES in patients who are not at high risk of bleeding.²⁰

THE PERIOPERATIVE DILEMMA

From around the year 2000, retrospective studies and case reports began to be published warning of the high risk of severe complications, including myocardial infarction and cardiac death, in patients with recent coronary stenting and premature discontinuation of antiplatelet drug therapy.^{21–27} So far, no prospective randomised trials are available; and the only prospective observation study published demonstrated that – independent of the type of stent – patients with a recent coronary stent implantation of <35 days had the highest complication rate.²⁸ In addition to the time interval between stenting and non-cardiac surgery, several other factors increased the perioperative risk of stent thrombosis (Table I). Recent cardiological data confirm the concern that in the perioperative setting the risk of stent thrombosis in DES is also substantially increased. Interestingly, McFadden et al's study²⁴ demonstrated a DES thrombosis, but an open BMS, while another study reported a postoperative stent thrombosis 29 months after DES implantation.²⁹

Because of the lack of large prospective randomised trials, perioperative management is primarily based on the recommendations and guidelines of Task Forces and experts. The 2002 ACC/AHA Guideline updates on perioperative cardiovascular evaluation for non-cardiac surgery were based on few data and do not particularly address the specific problem of DESs. These guidelines, however, will be updated this year.

The ESC Guidelines for percutaneous coronary intervention state that, in patients in whom prolonged administration of clopidogrel is known to be unlikely – e.g. those in whom major extracardiac surgery is planned soon – DESs should be used with caution. In these patients BMSs are probably the safer choice.¹⁸

The new AHA/ACC/SCA Science Advisory addresses, in particular, the problem of premature discontinuation of dual antiplatelet therapy with a relevant statement on the perioperative setting²⁰:

Table 1. Risk of bleeding vs. risk of thrombosis.

Risk of bleeding complications	Perioperative risk of thrombosis
Time of discontinuation of antiplatelet agents	Time of discontinuation of antiplatelet agents
Type of surgery	Stent associated
- Urological surgery	- Type (DES, BMS)
- Parenchymatous organ surgery (liver; lung, etc)	- Time of implantation
- Intracranial and spinal surgery	- Number, location and length of stents
- Abdominal aortic aneurysm	Other variables
- Surgery of the retina	- Diabetes mellitus
	- Renal insufficiency
	- Low ejection fraction
	- Tumor

1. In patients who are likely to require surgical procedures within the next 12 months → Bare Metal Stents should be inserted.
2. Awareness by healthcare providers of the potentially catastrophic risk of premature discontinuation.
3. Elective procedures should be deferred until completion of thienopyridine therapy (12 months after DES).
4. If procedures mandate discontinuation, aspirin should be continued, if at all possible.

Recent review articles have tried to guide the treatment of patients awaiting non-cardiac surgery who have received a coronary stent.^{30–37}

Because of the increased risk with recent stenting, some experts have raised the question of whether PTCA without stenting could be an alternative practice. In a contemporary review of cardiovascular medicine, Auerbach et al suggested that PTCA may be the preferred choice in a patient who is known to need non-cardiac surgery within the next weeks, with the option of placing a stent for better long-term efficacy after recovering from the non-cardiac procedure.³⁸ The authors, however, cited only one retrospective study reporting a low incidence of adverse cardiac events in 350 patients who had undergone non-cardiac surgery within 2 months of successful balloon angioplasty between 1988 and 2001.³⁹ In contrast, Posner et al found no difference between 142 patients with recent PTCA (≤ 90 days before non-cardiac surgery) matched to patients with CAD. Only those patients revascularised by PTCA > 90 days before non-cardiac surgery seemed to have a lower risk of poor outcome than non-revascularised patients.⁴⁰ The use of PTCA without stenting is seen as controversial among cardiologists.

PERIOPERATIVE RISK OF BLEEDING

One of the first large, prospective, randomised trials demonstrating the beneficial effect of the antiplatelet agent clopidogrel, in addition to ASA, on outcome (the CURE Trial) showed that there were significantly more patients with major bleeding in the clopidogrel group than in the placebo group (3.7% vs. 2.7%; relative risk = 1.38;

$p < 0.01$) but there were not significantly more patients with episodes of life-threatening bleeding (2.1% vs. 1.8%; $p < 0.13$) or haemorrhagic strokes.¹⁶

In the subsequent years, most of the data were published from patients undergoing coronary artery bypass graft surgery. Depending on the interval between discontinuation of clopidogrel and the time of cardiac surgery, relevant variables such as transfusion requirements, intubation time and hospital stay were significantly increased. Mortality was highest when clopidogrel was given in the 2 days before surgery.^{41–44}

Data from large prospective trials of bleeding complications and their influence on outcome in non-cardiac surgery are not available. In the only prospective outcome study, by Vicenzi et al²⁸, 44.7% suffered complications after surgery, but most of them were of a cardiac nature and were not bleeding complications. From all of the available cardiac and non-cardiac surgery studies it may be concluded that, depending on the time of discontinuation of clopidogrel (and ASA), the bleeding risk may be increased, but in non-cardiac surgery the risk of stent thrombosis may be more pronounced and more relevant compared to bleeding.

PLATELET FUNCTION MONITORING

The widespread adoption of antiplatelet agents into everyday clinical practice makes platelet function monitoring desirable.^{35,45} Bleeding history is the recommended first level test in the preoperative evaluation of patients. Mucosal bleeding is the leading symptom of inherited and acquired platelet defects. Clinical bleeding symptoms, however, are rare in patients undergoing dual antiplatelet therapy without provocation such as surgery or tooth extraction. There is still no generally accepted method for the quantitative analysis of platelet function during dual antiplatelet therapy. *Platelet count* is not indicative of platelet function. *In vivo bleeding time* is poorly standardised, is temperature and drug dependent (catecholamines), can be influenced by vascular disorders, lacks specificity and sensitivity and is not predictive of bleeding.⁴⁶ *Conventional thrombelastography or thrombelastometry* cannot detect platelet inhibition by dual antiplatelet therapy, even when using test modifications such as the addition of a platelet inhibitor *ex vivo* (cytochalasin D, abciximab), which reflects the time-dependent contribution of platelets to overall clot formation.^{35,47}

Several modern platelet function analysers that are on the verge of clinical implementation analyse the platelets' response to agonists. COX-I inhibition induced by ASA can be detected by *platelet aggregometry* using arachidonic acid, epinephrine, or collagen. P2Y₁₂ receptor blockade induced by clopidogrel can be analysed by using ADP as an agonist. Optical and impedance platelet aggregometry assess platelet reactivity by measuring changes in luminescence or impedance upon platelet agonist stimulation. The need for time-consuming sample preparation in a non-physiological test milieu of platelet-rich plasma, as well as poor standardisation, limit the widespread clinical application of optical aggregometry.⁴⁸ Nevertheless, optical aggregometry still remains the accepted 'gold standard' for the detection of platelet function.⁴⁹ Multi-channel aggregometry compensates for the problem of long test duration. Impedance aggregometry⁵⁰ avoids several of the methodological problems of optical aggregometry⁵¹, with the Multiplate (Dynabyte) being the last generation impedance aggregometer. Impedance aggregometry has been used successfully in the diagnosis of antiplatelet drugs.⁵²

The Platelet Function Analyzer PFA-100 (Dade Behring) measures platelet adhesion and aggregation in citrated whole blood, in response to the agonists epinephrine and

collagen or ADP and collagen, at high shear rates. This method rapidly identifies ASA effects and platelet disorders prior to surgery.⁵³ A major limitation of the PFA-100 is its insensitivity to the biological effect of clopidogrel.⁵⁴

Flow cytometric assays for adhesive protein expression and receptor activation involved in adhesion (e.g. glycoprotein (GP) Ib), aggregation (e.g. GP IIb/IIIa), and secretion (e.g. P-selectin), as well as intracellular signal transduction (e.g. VASP®) with and without agonist stimulation, have been developed.^{49,55} None of these methods has, as yet, entered routine clinical practice but they are valuable tools in scientific platelet research.

In conclusion, the relationship between platelet function abnormalities and abnormal clinical bleeding or thrombosis still remains unclear. Further major limitations of these functional tests are the lack of validation and biological controls, cost, long observation times and difficulties in interpretation of the complex reaction tracings. Nevertheless, it can be assumed that clinical adoption of novel platelet function monitoring will facilitate the treatment of patients undergoing dual antiplatelet therapy.

REGIONAL ANAESTHESIA

Individual reports and case series showing the catastrophic consequences of, fortunately rare, spinal haematomas document the limited safety of punctures during antiplatelet therapy.^{56–58} It can be assumed that the clotting capacity under ASA and clopidogrel is insufficient to seal the artificial injury of small spinal blood vessels. Current trends in the anaesthesiological management of patients on ASA and clopidogrel with planned regional anaesthesia, are heterogenous.^{59,60} National guidelines consider dual antiplatelet therapy to be a contraindication for performing neuraxial anaesthesia.^{56–58} However, patients at risk of thrombosis, in particular, may benefit from regional anaesthetic procedures and invasive pain management.^{61,62} Basically, clopidogrel must be discontinued prior to elective neuraxial blockade or catheter insertion (the intervals extrapolated from pharmacological data are presented in Table 2) and drug interruption should be kept as short as possible after intervention.^{56–58} Blockades causing haemorrhagic complications that are easily treatable (e.g. peripheral nerve blocks), may be performed as atraumatically as possible in these patients without drug discontinuation if their standardised bleeding history is normal. General anaesthesia should be considered as an alternative to regional anaesthesia. Individual risk/benefit assessments, detailed patient briefing and very close monitoring after the blockade must be ensured and documented before any elective or emergency blockade. The coagulation status may be improved by counteracting the effects of ASA and clopidogrel with prophylactic platelet transfusion prior to spinal anaesthesia.⁶³ It must be taken into account that reversal of antithrombotic drugs and surgery *per se* increase

Table 2. Recommended drug-free intervals prior to regional anaesthesia.

Active substance	Before intervention	After intervention
Clopidogrel	7 days	No interval
Ticlopidin	10 days	No interval
Acetylsalicylic acid (ASA)	72 hours	No interval

Source: modified from Kozek-Langenecker et al.⁵⁸

the patient's risk of thrombosis.⁶⁴ Crystalloids/colloids with negligible side effects on haemostasis should be the preferred option for perioperative fluid management.⁶⁵

PERIOPERATIVE STRATEGIES AND DECISION TREES

The cardiologist, the surgeon and the anaesthetist have to balance the overall perioperative risk of stent thrombosis vs. surgical bleeding (see [Table 1](#)). The anaesthetist plays a central role in this management triangle. The cardiologist is likely to underline the risk of stent thrombosis and the surgeon that of relevant surgical bleeding. Based on the available data, treatment of the patient can be guided at an acceptable risk level following the decision tree outlined in [Figure 3](#)

- Elective surgery should be postponed until the end of mandated clopidogrel therapy.
- In emergency cases all perioperative care givers should be aware of the increased risk of intra- and postoperative bleeding.
- In semi-elective or urgent cases, management should be tailored to the thrombosis/bleeding tolerance, thus:
 - In high bleeding/low thrombosis risk scenarios it has to be accepted that the surgeon will insist on discontinuation of clopidogrel and ASA.
 - In high thrombosis/low bleeding risk scenarios it may be recommended that dual antiplatelet drug therapy continues until the day or the day before non-cardiac surgery.
 - In most of the intermediate cases ASA, at least, should be continued!

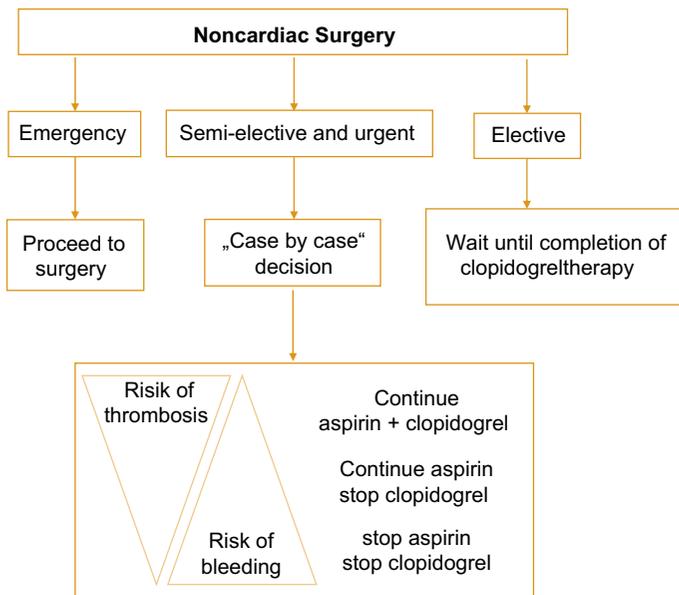


Figure 3. Preoperative decision tree for a patient with recent stent implantation undergoing dual antiplatelet therapy.

Dual antiplatelet therapy should be started postoperatively as soon as possible. It is a surgical decision that balances the total risk of bleeding and thrombosis. There seems to be a higher risk of stent thrombosis compared to surgical bleeding.

Management of surgical bleeding

Neither ASA nor clopidogrel can be antagonised pharmacologically. Platelet transfusion may be required. There are few reports on the efficacy of desmopressine and antifibrinolytics.

Management of stent thrombosis

In both non-surgical and surgical patients acute stent thrombosis presents as severe symptomatic myocardial infarction. Mortality is high, up to 20%, in both settings. After haemodynamic stabilisation, the patient should be rapidly transferred to an interventional cardiological unit with the option of re-PTCA and re-opening of the occluded stent.

SUMMARY

Dual antiplatelet drug therapy – usually a combination of clopidogrel and ASA – is mandatory for patients after PCTA and coronary stent implantation. All perioperative care givers should be aware of the thin divide between stent thrombosis and surgical bleeding. In the preoperative decision process, the risk factors increasing thrombosis, in particular the time and type of stenting, should be weighed against the risk factors for bleeding, in particular the type of surgery and time of discontinuation of one or both of the antiplatelet drugs.

Regional anaesthesia can be performed following national and international guidelines and recommendations.

Anaesthetists have to become more familiar with the pharmacological properties and profiles of antiplatelet drugs, as well as with new platelet function assays.

Finally, the surgical patient with a coronary stent undergoing dual antiplatelet drug therapy will have the greatest benefit if an interdisciplinary approach results in a close collaboration between the surgeon, the cardiologist and the anaesthetist.

Practice points

- The awareness of all perioperative care givers, cardiologists and other specialists of the problems and risks of recent coronary stenting and dual antiplatelet therapy seems to be the most important step in improving perioperative outcome. In almost no other field of perioperative medicine is the collaboration between the cardiologist, surgeon and anaesthetist so essential!
- The dynamic development of new stent technologies and new antiplatelet drugs makes the definition of well established, valid statements and recommendations for appropriate perioperative management difficult.

Research agenda

- New stents need to be designed that will offer benefits compared to the traditional bare metal stent (BMS) and drug eluting stent (DES) without the current risks of early and late stent thrombosis.
- New antiplatelet drugs need to be developed to allow a tailored therapy and facilitate the management of patients who are scheduled for emergency, semi-elective or elective surgery.
- Finally, new platelet function assays are currently under laboratory investigation or are being clinically tested. These may overcome some of the limitations and shortcomings of the older available assays, particularly their inability to reflect the in vivo situation.

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