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PROTOCOL FOR A PERIOPERATIVE APPROACH TO PATIENTS WITH CORONARY STENTS UNDERGOING NON-CARDIAC SURGERY

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Abstract

Patients undergoing angioplasty and stent insertion require double prophylactic anti-aggregation or monotherapy. This is a challenging procedure with a high risk of morbidity and coronary mortality. The aim of this protocol is to provide guidelines for a presurgical approach to patients with a coronary stent who will be undergoing non-coronary surgery. This protocol highlights potential complications that may occur, namely those related with the cardiac stent and the evaluation of cardiac risk, and notes the thrombotic and hemorrhagic risks associated with the surgical procedure and the decision algorithms for both elective surgery and urgent surgery involving the suspension and re-introduction of antiplatelet therapy. Our main goal is to outline an optimized approach to these cases in order to improve cardiac outcomes and to minimize the risk of complications.

INTRODUCTION

Percutaneous coronary interventions (PCI) are frequent, and include balloon angioplasties and stent insertion. Most patients undergo angioplasty with stent insertion, since the results of this procedure are more effective in preserving vascular permeability.[1] It is estimated that nearly 5-10% of patients undergo non-cardiac surgery in the first year after the insertion of their coronary stent. This percentage can rise up to 25% within the first 5 years.[1]

A stent is a solid scaffold that prevents vessel closure due to elastic recoil or vessel contracture.[2] Currently, there are two types of stents: the Bare Metal Stent (BMS) and the Drug Eluted Stent (DES), which includes the Bioresorbable Stent (BRS).[2,3,4]

- **BMS *(Bare Metal Stent):*** these stents are made of steel, cobalt chromium or platinum chromium without a pharmacological coating. The BMS ensures full endothelial coverage in averagely 12 weeks, which lowers the risk of stent thrombosis (ST). However, these stents are associated with a higher risk of restenosis due to neointimal proliferation (20% to 30%).[3] Currently, BMS insertion is recommended in particular contexts:
  1) In patients that do not comply with antiplatelet therapy;
  2) When there is a high bleeding risk;
  3) If surgical treatment and suspension of antiplatelet therapy are necessary within the first 6 weeks after the PCI.[3,4]

- **DES *(Drug Eluting Stent):*** The DES consists of a metallic structure with a polymer coating loaded with an antiproliferative agent. This drug is released in a gradual and controlled manned (i.e elution), which allows for its local diffusion in the vascular tissue, preventing excessive vascular growth (neointimal hyperplasia) and vascular occlusion. Second and third generation DES have a thin cobalt or platinum chromium structure coated with polymers that reduce local inflammation and reduce interference in the reendothelialization process.[3,4]

- **BRS *(Bioabsorbable DES):*** The BRS (Bioabsorbable DES) consists of a metallic or polylactic acid alloy coated by polymers. Once the drug is eluted, both the polymer and the structure are re-absorbed throughout time, until the stent is fully absorbed.[3,4]

All DES(s) are loaded with two classes of antiproliferative drugs:[3,4]

1 - Sirolimus and respective derivatives with cytostatic properties (Everolimus, Zotarolimus, Myolimus e Biolimus).

2 - Paclitaxel – An antineoplastic drug that stabilizes the microtubules prior to cell division, suspending the mitotic cell cycle. Currently, it is rarely used.

Stent-related complications

- **Stent Restenosis** – Due to neointimal thickening. Peak incidence at 4-12 weeks after insertion, but it may occur up until 8-9 months after insertion. Suspected when there are reoccurring symptoms.[2,3]

- **Stent thrombosis (ST)** – Sudden occlusion where the stent is inserted resulting from the formation of a platelet-rich thrombus. This can occur at any moment after the insertion of the stent, for an indeterminate number of years (table 1). Although ST is a rare complication, it is associated with a high mortality rate.[2,3] The diagnosis criteria for ST are outlined in table 2.

Table 1 Timing of Stent Thrombosis

Acute	24h after insertion
Subacute	Between 1 and 30 days
Late	Between 30 days and 12 months
Very late	> 1 year

Table 2 Diagnosis of Stent Thrombosis

Definitive diagnosis	Angiographic evidence of ST and chest pain with re-occurring alterations in the ECG or the ultrasound, or elevation of biomarkers. Autopsy validation.
Likely	Unexplained death within 30 days after PCI Infarction in the area where the stent was placed
Possible	Unexplained death > 30 days after PCI

PREOPERATIVE EVALUATION

Patients with heart disease who undergo non-cardiac surgery must be evaluated with particular care. Evaluation must de done in a systematic manner and according to current guidelines, as well as in collaboration with cardiology and surgery departments.

Regarding patients who have previously undergone a PCI, pre-anesthetic evaluation must focus on the following factors:

1 - Existence of any of the following conditions, and, if so, evaluate how well they are controlled:
  - Diabetes Mellitus
  - Heart failure
  - Kidney disease
  - Previous myocardial infarction (MI)
  - Previous stent thrombosis
2 - Patient's drinking/smoking/toxicophilic habits, with a special focus on:
  - Cocaine use
  - Tobacco use
3 - Ambulatory care:
  - Type and duration of antiplatelet therapy
4 - PCI data:
  - Stent types
  - Number
  - Data and clinical indications for the PCI
  - Stents' anatomical location
5 - Previous anesthetic/surgical history and previous hospitalizations;
6 - Existence of any predictive factors of MACE (Major Adverse Cardiovascular Events – table 3).[2,3]
7 - Evaluation of thrombotic and bleeding risks (table 4 and 5).[5]

Table 3 Predictive factors of MACE in patients with coronary stents – Cardiovascular high-risk patients

Clinical • Revised cardiac risk index >2 • Emergent/urgent surgery • Any stent < 4-6 weeks after SCA (especially if biomarkers +) • DES <8-12 weeks and SIHD • Premature discontinuation of platelet anti-aggregation • HTPR (High on-Treatment Platelet Reactivity) • Major perioperative bleeding
Related to the procedure • Incomplete revascularization after PCI • Persistent myocardial ischemia after PCI • Ostial, calcified, long and short lesions

DECISION ALGORITHMS

Currently, there are no specific or consensual recommendations regarding the perioperative care of patients on platelet anti-aggregation drugs. This approach must be multidisciplinary and seek consensus between the different medical specialties, namely cardiology, interventional cardiology, hematology, surgery and anesthesiology.

ELECTIVE SURGERY

The management of antiplatelet therapy in elective procedures is one the most important and controversial issues regarding patients with coronary stents. In patients on DAPT (Dual Antiplatelet Therapy) medication, surgery and invasive procedures are the most frequent cause of temporary suspension of antiplatelet therapy, which increases the risk of MACEs during perioperative care.[6] The alternative is to prolong DAPT, but this would increase the risk of severe perioperative bleeding, which can also increase the risk of cardiac events.[7]

Table 4

High risk	• BMS < 6 weeks after elective PCI or <6 months after PCI due to SCA • DES < 8 weeks due to stable ischemic disease < 6 months after SCA, or complex ICP associated with high thrombotic risk • 1st generation BRS < 12 months • <2 weeks after balloon angioplasty • Multiple clinical risk factors for ST • Previous ST (particularly if on antithrombotic therapy)
Intermediate risk	• BMS > 6 weeks and <6 months due to stable ischemic disease • DES > 8 weeks < 6 months due to stable ischemic disease • DES or BMS >6 or < 12 months after SCA or complex PCI associated with high thrombotic risk • 1st generation BRS - 1 to 3 years • Some risk factors (except previous ST)
Low risk	• BMS or DES > 6 months due to stable ischemic disease • DES or BMS due to SCA or complex PCI >12 months • Some risk factors

Most guidelines only provide recommendations for the first 12 months. As a result, many doctors indiscriminately suspend DAPT and adopt procedures with a lower bleeding risk.

Regarding perioperative care, current guidelines advise as follows:[1,4,8]

- BMS - Minimum 4 to 6 weeks of DAPT;
- DES - Minimum of 3 to 6 months of DAPT;
- Continuation of ASA (acetylsalicylic acid) monotherapy in most cases of stable ischemic disease, except when contraindicated due to bleeding risk;
- In post-ACS (Acute Coronary Syndrome) patients or in cases of high ischemic and thrombotic risks, the guidelines recommend DAPT for a period of 12 months (minimum 6 months);
- BRSs - Require 1 year or more depending on thrombotic risk;
- For balloon angioplasties, the guidelines recommend delaying surgery in the first 14 days after the procedure.

SUSPENSION OF ANTIPLATELET THERAPY

Due to the lack of randomized and well-designed studies that evaluate the risk-benefit ratio of perioperative antiplatelet therapy, decisions regarding this issue are made according to the balance between thrombotic and bleeding risks associated with each patient and each surgical procedure.

Table 5

Procedures that do not require suspension of platelet anti-aggregants	• Dental procedures, including dental extraction • Cataract surgery • Gastric endoscopies, colonoscopies, with or without biopsy • Minor dermatologic procedures
Low surgical bleeding risk	Types of surgery that allow adequate hemostasis: • Peripheral plastic surgery • Minor orthopedic surgery • Pacemaker or ICD implantation • Herniorrhaphy • Surgical procedures for varicose veins
High surgical bleeding risk	Surgeries and procedures associated with a high bleeding risk or in which bleeding is associated with a serious lesion in patients on anticoagulants/ anti-aggregants: • Urological surgery – transurethral resection of the prostate, nephrectomy, renal biopsy • Colonoscopic polypectomy, especially with sessile polyps with more than 1-2 cm • Surgeries to highly vascularized organs, such as kidneys, spleen and liver. • Intestinal resection surgery with possible bleeding on intestinal anastomosis • Major orthopedic surgery • Tumor ressection surgery • Heart surgery • Neurosurgery and medullary procedures • Surgery on posterior chamber of the eyeball • Neuroaxis anesthesia

The suspension of DAPT (namely of the 2 drugs) is associated with an increase of perioperative ST as well as other ischemic myocardial events:[1,3]

1st - Many patients might not have complete stent endothelialization;

2nd - The sudden discontinuation of ASA or thienopyridines may generate a rebound phenomenon (platelets that are regenerated display higher responsiveness and aggregation to thrombotic stimuli);

3rd - Some patients show variable degrees of chronic HTPR (High on-treatment platelet reactivity), which becomes evident once the DAPT is suspended.

The discontinuation of DAPT consists of the suspension of the administration of adenosine antagonists while

Table 6 **Recommendations on whether to proceed with surgery. ACC/AHA: American college of cardiology/American Heart Association; ESC/EACTS European Society of Cardiology/ European Association For Cardio-Thoracic Surgery.**

ACC/AHA (2016)			ESC/EACTS (2017)		
Stent type	Time range (months) ICP-CNC	Action	Any stent	Time range (months) ICP-CNC	Action
BMS	<1	Delay	Any condition	<1	Delay
	≥ 1	Proceed	No SCA/low risk	1-6	Consider
				≥ 6	Proceed
DES	≥ 3	Delay	SCA/high risk	1-6	Consider
	3-6	Consider		≥ 6	Proceed
	≥ 6	Proceed			

the ASA therapy is maintained – since most elective procedures can be safely performed on ASA.[1,3]

Certain procedures require the suspension of both drugs (e.g surgery in closed spaces), since any sort of hemorrhage can lead to serious complications.[1]

In practice, if one or both drugs are to be discontinued, it is recommended that clopidogrel, ticagrelor and the ASA are suspended 5 days before the surgery, and that prasugrel is suspended 7 days before.[1,4,5,9] Regarding ticagrelor, the most recent ESC/EACT guidelines recommend that the drug be suspended 3 days before the surgery – although the data presented are extrapolated from cardiac surgery.[1] Table 7 summarizes the current recommendations regarding DAPT suspension.

"BRIDGE" THERAPY

This strategy is aimed at patients at high thrombotic risk that will be undergoing "non-delayable" surgery associated with a high bleeding risk. In these cases, DAPT must be suspended. Antiplatelet drugs are preferable, since the formed thrombi are platelet-rich. Although heparin has been claimed to be an effective bridging agent, it has minimal benefits and can induce a prothrombotic state. Therefore, bridging therapy performed with anticoagulants, such as unfractionated heparin, low-molecular-weight heparin or direct thrombin inhibitors is not recommended in cases where DAPT has been suspended during preoperative care.[1]

Currently, it is recommended that bridging therapy is performed with GIIb/IIIa inhibitors, such as Tirofiban and Eptifibatide, or $P2Y_{12}$ antagonists such as Cangrelor (table 8).

The $P2Y_{12}$ should be suspended 5 to 7 days before the procedure. The patient is then admitted to the hospital and is administered a continuous intravenous infusion (no bolus) of Tirofiban or Eptifibatide before the procedure. These drugs must be suspended 4-6h and 4-8h before the procedure, respectively. The infusion is restarted in postoperative care until DAPT may be reintroduced. Cangrelor is an alternative as it has a very short half-life – a 0.75 μg/kg/min may be prolonged until a short time after the surgery/procedure.

Although bridging therapy may be relatively safe, ST may still occur. Furthermore, bridging therapy leads to a higher bleeding risk.[1,10]

RE-INTRODUCTION OF ANTIPLATELET THERAPY

It is essential that DAPT is re-initiated, preferably within the first 24h after suspension.[5] The re-introduction of the $P2Y_{12}$ requires a loading dose, but the ASA can be re-administered at a normal maintenance dosage. Table 9

Table 7 **Perioperative management of dual anti-aggregation.[4]**

	Low thrombotic risk	Intermediate thrombotic risk	High thrombotic risk
Low bleeding risk	Maintain AAS Suspend iP2Y12	Mantain AAS Mantain iP2Y12	Mantain AAS Mantain iP2Y12
High bleeding risk	Mantain AAS Suspend iP2Y12	Mantain AAS Suspend iP2Y12	Mantain AAS Suspend iP2Y12 *Consider bridging*
Bleeding risk for closed spaces	Suspend AAS Suspend iP2Y12	Suspend AAS Suspend iP2Y12	Suspend AAS Suspend iP2Y12 *Consider bridging*

Table 8 **Recommendations for bridging with GPIIbIIIa inhibitors.**

	Drug	Loading dose	Maintenance dose	Half-life	Platelet function recovery	Suspension of infusion before surgery
GPIIbIIIa Inhibitors	Eptifibatide	180 μg/ kg	2 μg/ kg/min	2.5h	2-4h	4-6h
	Tirofiban	0.4 μg/ kg	0.1 μg/ kg/min	2h	2-4h	4-6h
	Abciximab	0,25 mg/kg	0,125mg/kg/min	10-15m	12h	12h
Inhibitor Receptor P2Y12	Cangrelor	30 μg/kg	2-4μg/kg/min	3-6m	30-60m	1-6h

Table 9 **Recommendations for management of perioperative anti-aggregants.**

	Drug	Suspension time	Re-introduction dose	
			Loading	Maintenance
P2Y12Platelet receptor inhibitors	Clopidogrel	5 days	300-600mg	75mg/day
	Prasugrel	7 days	60mg	10mg/day
	Ticagrelor	3 to 5 days	180mg	90mg/2xday
COX-1 Inhibitor	Aspirine	3 to 5 days	325mg	75-325mg/day

displays the relevant recommendations regarding the suspension and re-introduction of platelet anti-aggregation drugs.

URGENT SURGERY

For patients that need surgical treatment during DAPT, it is important to evaluate the risk-benefit of prolonging DAPT, such as in elective surgery.[6,7] In cases where there is no time do suspend DAPT due to the urgency of the surgical procedure, and where there is a higher bleeding risk, it is important to correct platelet dysfunction.[1]

Therapy with platelet anti-aggregation drugs is one of the most frequent causes of acquired platelet dysfunction. The incidence of thrombocytopenia associated with these agents is approximately 2 to 13%.[11] Given the high bleeding risk associated, it is important that the following measures are considered:

- **Platelet transfusion:** Platelet prophylactic transfusion is not currently recommended given the lack of relevant studies on this procedure. Furthermore, the guidelines indicate that prophylactic transfusion carries a high bleeding risk.[11] In patients on dual antiplatelet aggregation therapy and with an intracranial hemorrhage, platelet transfusion requires an individualized clinical decision based on several clinical factors, including the degree of bleeding and the patient's level of consciousness. For surgeries that involve the central nervous system, the platelets are usually prophylactically transfused if the count is lower than 80 x 109 to 100 x 109 cells/L, although this is an arguable range.[11]
- **Antifibrinolytic agents** (tranexamic acid or aminocaproic acid) in order to reduce the bleeding risk.
  - ✓ Tranexamic acid should be administered at a dose of 10mg/kg via intravenous infusion, followed by a dose of 1mg/kg per hour ;
  - ✓ ε-aminocaproic acid (10x less potent than tranexamic acid) should be administered at a dose of 150mg/kg via intravenous infusion, followed by a dose of 15mg/kg per hour.

MONITORING PLATELET FUNCTION

Despite the heterogeneity in the response to platelet anti-aggregation drugs, laboratory tests aimed at evaluating the effect of antiaggregant drugs on platelet function have not been indicated as routine tests, as a solid correlation between their results and the clinical outcome in non-cardiac surgery has not yet been demonstrated.

The evaluation of coagulation tests (PT, aPTT) and the quantitative assessment of platelets do not allow for the proper ascertainment of platelet function.[1,4]

LIMITATIONS IN THE CURRENT GUIDELINES

Most guidelines are based on low-quality data and on the opinions of experts, which frequently leads to a variation in recommendations. Furthermore, the current guidelines only refer to the first 12 months after the patients undergo PCI.

The most recent guidelines by the American college of cardiology/American Heart Association (ACC/AHA), the European Society of Cardiology/ European Society of Anaesthesiology (ESC/ESA) and the European Association For Cardio-Thoracic Surgery (EACTS) already make recommendations regarding the surgical procedure and perioperative management of platelet anti-aggregation in patients with a stable ischemic cardiac disease (SIHD – defined as stable angina or MI>12 months without subsequent ischemia vs patients undergoing PCI due to ACS). The guidelines still lack a comprehensive description of specific risk factors and surgical risks.

The chart in Annex I outlines a proposed approach to cases of patients with cardiac stents who will be undergoing non-cardiac surgery.

CONCLUSION

In recent years, several clinical studies have been conducted in order to compare different pharmacological approaches and the duration of platelet antiaggregant therapy after an acute myocardial infarction or an elective coronary angioplasty. Different strategies have been evaluated that also consider the different characteristics of patients, drugs, different drug combinations and the duration of dual anti-aggregation. As mentioned above, it seems clear that there is no consensus or general guidelines that work as an effective substitute for good judgment and an accurate clinical evaluation of each particular case.

There are tools that, although not meant for patients with cardiac stents, may be useful for evaluating thrombotic and bleeding risk, such as the CHADS-VASC (thrombotic risk) and HAS-BLED (bleeding risk) risk scores.

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ANNEX 1

APPROACH TO CASES OF PATIENTS WITH CARDIAC STENT WHO WILL BE UNDERGOING NON-CARDIAC SURGERY