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Perioperative management of coronary artery stents in South Africa

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Patients who receive a drug-eluting coronary artery stent (DES) will be placed on dual antiplatelet therapy (DAPT) for a period of six months to a year to prevent platelet activation and thrombosis of the stent. Non-cardiac surgery should be delayed until the patient has completed DAPT. If surgery has to be performed before the stipulated time required for DAPT, a multidisciplinary approach should be taken, involving a cardiologist, surgeon and anaesthetist. Stopping DAPT and risking stent failure must be weighed up against the risks of expected surgical bleeding. All patients who are scheduled for surgery within the stipulated period, should be managed perioperatively in a high dependency unit and in a hospital where 24-hour catheterisation laboratory (cath lab) services are available.

Keywords: angioplasty, coronary stents, platelets, DAPT, non-cardiac surgery

Angioplasty and stenting

The procedure of angioplasty and stenting is not a benign process. The angioplasty balloon is expanded to a pressure of 8 atmospheres (atm) which is equivalent to 6 000 mmHg. When fibrosis is present in the coronary artery, balloon pressures can exceed 18 atm in an attempt to fracture the plaque. The pressures generated are far greater than normal physiological pressures, and as a consequence, fissuring and tearing of the endothelium occur. A breach in the endothelium is a potent activator of the clotting systems. (See Role of platelets in clotting). In addition to the breach in the endothelium, placement of stents in the coronary artery causes turbulence because of the foreign body which protrudes into the lumen of the artery. The turbulent flow causes shear stresses that activate platelets via von Willebrand Factor (vWF). vWF is present in the plasma and on normal endothelium in a coiled form, which protects the GP1b receptor on vWF and prevents platelets from binding to vWF. Exposure of vWF to shear stresses leads to the uncoiling of the molecule and exposes the GP1b receptors, which then bind to GP1b binding sites on the platelet. This leads to platelet adherence and activation. Initially, the activated platelets flatten and begin to form a pavement across the luminal obstruction. Activation of these platelets results in release of platelet granules containing calcium and ADP and further platelet adhesion and aggregation occurs at the apex of the obstruction and begins to propagate distally (Figure 1.)[1] Activation of platelets leads to a conformational change in the shape of the platelet resulting in filopodial extensions which express GPIIb/IIIa fibrinogen receptors, which bind to other platelets using circulating soluble fibrinogen. This acts to strengthen the platelet plug. Thrombosis ensues because the activated platelets initiate the clotting cascade by converting prothrombin to thrombin, which in turn converts soluble fibrinogen to insoluble fibrin, which strengthens the clot. After stenting, platelet adhesion can rapidly progress to thrombosis and stent failure in a few hours. Acute management of stent placement involves blocking the shear stress-induced platelet activation by loading the patient with high doses of the $P2Y_{12}$ blocking thienopyridines (clopidogrel or prasugrel). Subsequently, the patient is placed on dual antiplatelet therapy (DAPT), adding low-dose aspirin (< 100 mg/d) to a daily dose of a thienopyridine. Because of costs, a generic clopidogrel is commonly used (Costs R250/month compared to ±R1 000/month for the ethical clopidogrel, prasugrel or ticagrelor medications). Clopidogrel is a prodrug which relies on activation in the liver using CYP450 enzymes. 1–35% of individuals may lack the specific enzyme (CYP 2C19) and as a consequence are nonresponders. Nonresponse depends on ethnicity; up to 10% of people of African descent and up to 35% of Asians are nonresponders. Prasugrel is more effectively converted into its active form during absorption via intestinal CYP3A. This results in a more predictable and effective platelet inhibition and is used as a second-line drug in the event of clopidogrel nonresponse.[2] The attending cardiologist will maintain the patient on DAPT for a period of time following stent placement, depending on stent type and the coronary artery stented (See section: Algorithms for perioperative management of patients with coronary stents).

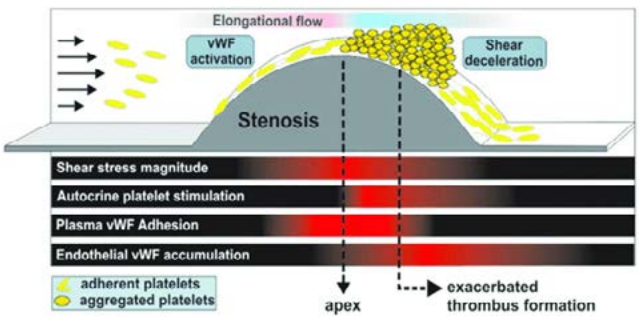

Figure 1: Platelet activation and aggregation due to shear stresses[1]

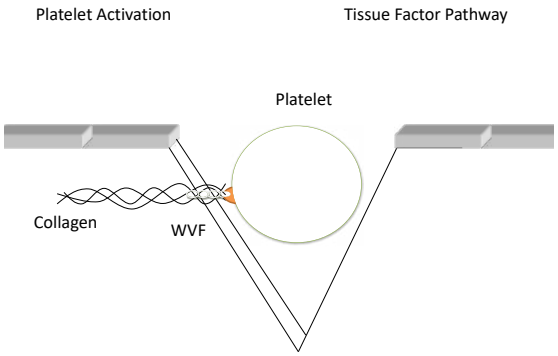

Figure 2: Platelets adhere to the subendothelium via GP1b receptors on the platelet, which bind to exposed collagen and vWF. Further binding to collagen via collagen α1β1 and PGVI receptors initiates a conformational change in the platelet. It flattens onto the surface of the subendothelium, forming a pavement layer of platelets that covers the breach.

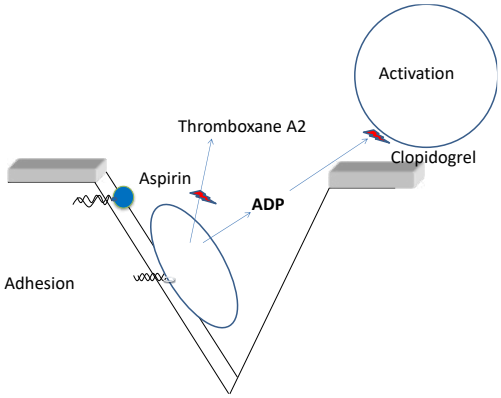

Figure 3: The conformational change releases platelet granules, which contain thromboxane A2 and ADP as well as α granules which contain fibrinogen, Factor V and an adherent molecule p-selectin. Thromboxane A2 activates the thromboxane – prostanoid receptor (TP) on the platelet surface and activates the platelet. ADP binds to $P2Y_1$ and $P2Y_{12}$ receptors on platelets, releasing dense granules, which enhance the aggregation adhesion of other platelets.

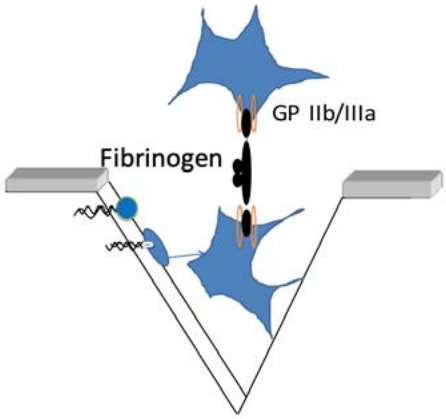

Figure 4: ADP, acting on the platelet receptors, causes further conformational change in the activated platelet, everting the platelet membrane and creating long filopodial extensions, which greatly enhance the surface area. In this process, GPIIb/IIIa receptors are exposed, facilitating adherence of other platelets via binding with soluble fibrin.

Role of platelets in clotting

When angioplasty is performed, the endothelium is torn and this sets off the coagulation process in an attempt to close the breach and start the process of healing the tear. Two interacting mechanisms are initiated resulting in the formation of localised clot to close the breach. Platelets adhere to the subendothelium and are activated, leading to the attraction and adherence of other circulating platelets to form a platelet plug. Simultaneously, tissue factor (TF) is released from the subendothelium to initiate the tissue factor pathway, which ultimately results in the thrombin burst. This accelerates the clotting mechanism via a powerful feedback loop that maintains the clotting cascade and ultimately results in the production of a clot that is strengthened by the incorporation of insoluble fibrin produced from circulating fibrinogen.

Pharmacological note 1

Low-dose aspirin blocks the production of thromboxane A and the thienopyridines such as clopidogrel and prasugrel cause a permanent block of the platelet $P2Y_{12}$ receptor. DAPT refers to both aspirin and a thienopyridine and prevents platelet activation and aggregation. Full replacement of platelet numbers is required to restore the platelet component of clotting and this takes 7–10 days and depends on normal bone marrow function. The GPIIb/IIIa receptor blockers such as eptifibatide (Integrillin®) and tirofiban HCl (Aggrastat®) form a competitive block with fibrinogen and prevent platelet cross-linking. The half-lives of these agents are relatively short, ~ 2 hours. They are delivered by intravenous infusion. They are useful in managing patients perioperatively, where short-acting but powerful platelet inhibition is required. An example of this is in bridging therapy between stopping the thienopyridine and surgery in high-risk cases.

Pharmacological note 2

Tranexamic acid can be used as a clot stabiliser as it is incorporated into the fibrin network in place of plasmin and acts to impede clot lysis.

In the event of emergency surgery when DAPT has not been stopped, approximately 10% of patients will have severe bleeding (characterised as fatal bleeding, transfusion of more than four units or haemodynamic instability). This figure can approach 20% in cardiac surgery. The effects of DAPT can be minimised by immaculate surgical technique, use of tranexamic acid to stabilise clot, provision of fibrinogen to facilitate platelet cross-linking (cryoprecipitate), clotting factors (FFP) and platelet transfusion. (On a personal observation: it has been noted that patients on DAPT who undergo emergency cardiac surgery may not have severe bleeding as characterised above, but tend to bleed for longer postoperatively and receive greater numbers of red blood cell [RBC] units overall than patients who are not receiving DAPT).

Algorithms for perioperative management of patients with coronary stents

The majority of the approximately 20 000 stents that are placed annually in South Africa are drug-eluting stents (DES). Bare metal stents (BMS) are occasionally deployed, but because of the high re-stenosis rate (30%), most cardiologists choose to use DES. Re-stenosis in BMS occurs because of intimal ingrowth as a consequence of the foreign body in the lumen of the coronary artery. DES were developed to combat this effect. DES are coated in a drug-eluting polymer which acts to prevent intimal ingrowth. The drug elution peaks at six weeks and lasts up to nine months, depending on the type of stent. DAPT is recommended for six weeks following BMS and six months to one year following DES. Elective surgery should be delayed until DAPT has been stopped according to these broad recommendations. There have been multiple trials assessing the risk of major adverse cardiac

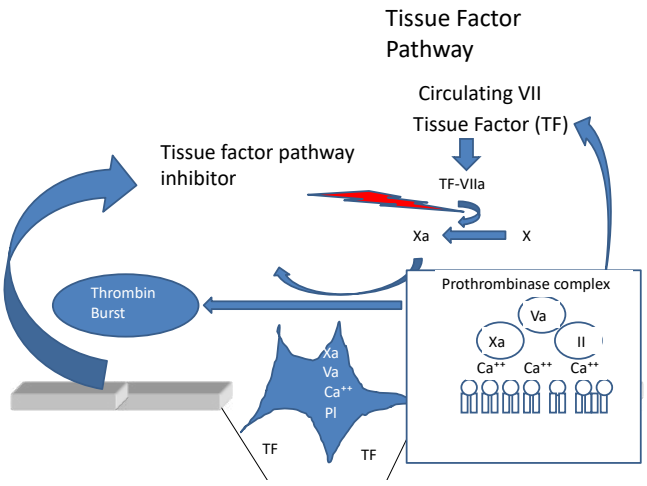

Figure 5: Simultaneously with platelet activation, tissue factor (TF) is released from the exposed subendothelium and initiates the TF pathway. TF combines with and activates circulating Factor VII. The TF-VIIa complex activates Factor X and Xa combines with activated Factor V, calcium and the negative phospholipid layer on the activated platelet to form the prothrombinase complex, which converts prothrombin to thrombin. Thrombin releases TF pathway inhibitor from normal adjacent endothelium and this acts to stop the TF-VIIa activation of X.

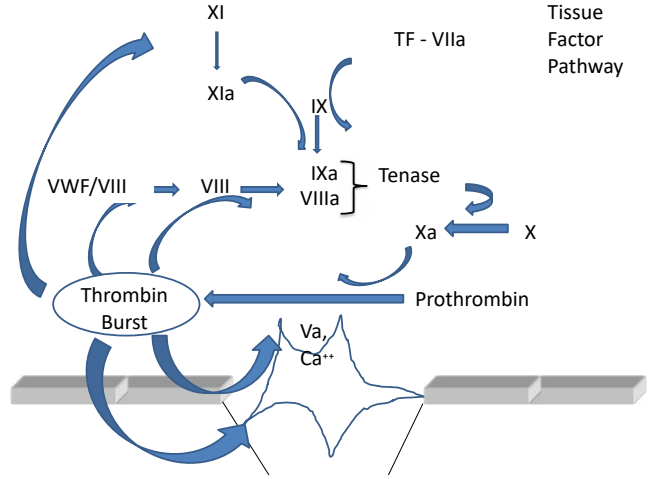

Figure 6: Thrombin acts to cause a positive feedback loop which increases the production of thrombin. Thrombin acts on the PAR1 and PAR4 receptors on platelets to activate and aggregate platelets. It activates Factor XI, which activates Factor IX. It also acts on circulating vWF-Factor VIII complexes to separate Factor VIII. The activated VIIIa and IXa form a tenase which activates Factor X.

events (MACE) following BMS and DAPT on patients who have had DAPT stopped and are presented for surgery. High risk for MACE is present if non-cardiac surgery is performed in the first six months following BMS (in one study of 200 000 patients who received stents, 3.5% were readmitted for non-cardiac surgery during the first six months. Surgery was complicated by myocardial infarction (MI) in 4.7% of cases, and 21% of perioperative MIs were fatal).[3] The highest MACE risk is present in the first four to six weeks after BMS. In a study of approximately 42 000 patients who had surgery up to two years after stenting, published in JAMA, it was found that the incidence of MACE was 11.6%in the first six weeks; 6.4% six weeks to six months; 4.2% six to 12 months; 3.5% 12 to 24 months. The rates appear to stabilise after six months.[4]

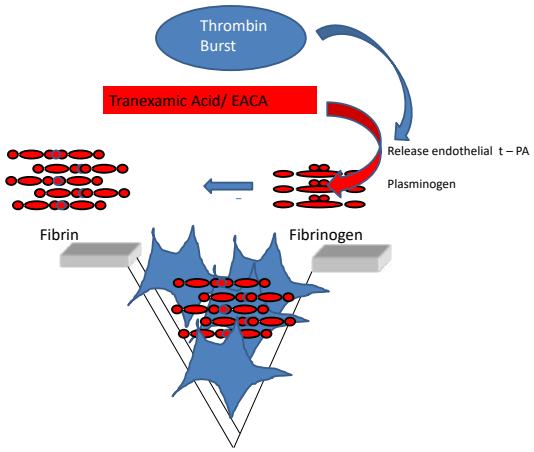

Figure 7: The thrombin burst serves as a positive feedback loop to enhance clot formation. It also acts on soluble fibrinogen to become insoluble fibrin and enable cross-linking between molecules. This adds greatly to clot stability. At the same time, thrombin releases endothelial tissue plasminogen activator (t-PA), which acts on plasminogen to convert it to plasmin. This is incorporated into the fibrin network and because it is an enzyme used to break down fibrin, it moderates the clot extension beyond the endothelial breach.

The 2016 ACC/AHA guideline-focused update on duration of dual antiplatelet therapy in patients with coronary artery disease recommends the following:

1. Elective non-cardiac surgery should be delayed 30 days after BMS implantation and optimally six months after DES implantation. Based on more recent data, we have not distinguished BMS and DES based on DAPT duration, and most of our experts do not prefer use of BMS to reduce DAPT duration to 30 days. Generally, we prefer six months delay for non-cardiac surgery that can be deferred after either BMS or DES.
2. Elective non-cardiac surgery after DES implantation, in patients for whom $P2Y_{12}$ inhibitor therapy will need to be discontinued, may be considered after three months if the risk of further delay of surgery is greater than the expected risks of stent thrombosis.[5]

Ideally, DAPT should be discontinued in consultation with the cardiologist who placed the stent. If the elective surgery cannot be delayed safely, the cardiologist will stop DAPT and continue with low-dose aspirin. If the cardiologist deems that the stent is a low-risk stent and that the patient is in the window between six months and a year, they will stop the DAPT and not use any bridging therapy. Ideally this should be done at least 5–7 days preoperatively to allow for normal platelet replacement from megakaryocytes in the bone marrow. In high-risk surgery such as retinal surgery and neurosurgery, aspirin will be stopped as well. If the stent is a high-risk stent, such as a left main or left anterior descending coronary artery stent, and if the patient is in the window four weeks to six months after DES placement, bridging therapy may be used. DAPT is stopped at seven days preoperatively and the patient is admitted to a high dependency unit four days preoperatively and a GP IIb/IIIa blocker delivered by intravenous infusion until the day of surgery, when it is stopped six hours preoperatively. DAPT is restarted as soon as the risk of

bleeding has passed and is given in the form of a full loading dose of the thienopyridine and low-dose aspirin. For example, if clopidogrel is used, 300–600 mg are delivered po and then 75 mg daily. The patient should have surgery in a hospital where 24-hour catheterisation laboratory (cath lab) services are available. The patient should be managed in a high dependency unit, perioperatively and a high index of suspicion for development of cardiac ischaemia due to stent closure should be maintained at all times until full DAPT anticoagulation is resumed. The high-risk period for thrombosis is 24–48 hours postoperatively, when circulating fibrinogen levels peak as a response to surgery.

Conclusion

MACE following cessation of DAPT in patients who have received DES is highest during the first four to six weeks after placement of the DES. The incidence drops from six weeks to six months and then remains stable after six months for the life of the stent. If a patient is on DAPT for DES and needs surgery, cessation of DAPT should be carried out in a combined multidisciplinary approach with the cardiologist, surgeon and anaesthetist.

Suggested further reading

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Appendix 1: Brigham and Women's Hospital guidelines for management of patients undergoing surgery with history of coronary artery