Title: Antiplatelet Drugs and Coronary Stents

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At the conclusion of this PBLD, the participant will be able:

1. To understand the mechanisms of antiplatelet agents used to treat patients with cardiovascular disease.
2. To discuss the use of platelet function assays.
3. To develop a plan for perioperative management of patients with coronary artery stents; timing of surgical intervention, bridging therapy, and choice of anesthesia.
CASE

CASE PRESENTATION

The patient is a 75-year old male patient with coronary artery disease (CAD) who is being considered for the repair of abdominal aortic aneurysm. On the myocardial perfusion scan, there was evidence for reversible ischemia. Coronary angiography was, therefore, performed showing relevant coronary stenosis of the proximal LAD and the proximal RCA. In the cardiologist’s, coronary re-vascularization should be the priority. The vascular surgeon states that there is also an indication for surgery within the next two months because the aneurysm size increased by 0.5 cm to the diameter of 5.0 cm in the last six months.

Questions:

1) In your opinion, what would be the best option for this patient? What would you recommend if the patient refuses CABG surgery?
2) The cardiologist performed percutaneous coronary intervention, and placed coronary stents. Describe the differences between drug-eluting stents (DES) and bare-metal stents (BMS) in terms of antiplatelet therapy.
3) When would you perform anesthesia and surgery at earliest?
4) How would you manage platelet inhibitors, especially dual antiplatelet therapy in the perioperative period?
5) What is your anesthesia plan? Any consideration(s) for regional techniques, epidural or spinal anesthesia?
6) Is there any value in testing platelet function before anesthesia or surgery?

CASE CONTINUATION 1

Although you asked the cardiologist to implant a BMS stent, the patient got implanted with two DES in the LAD and the RCA. The patient is now treated with aspirin (80 mg/d) and clopidogrel (75 mg/d). You discussed with the vascular surgeon, and postponed the operation. But only 1 month later, the patient came in complaining of severe low back pain, and the emergent CT scan showed the aneurysm with a diameter of 6.5 cm. The surgeon says that the patient needs now urgent surgery within the next days due to potential rupture.

Questions:

1) When would you schedule this surgery? How do you manage platelet inhibitors?
2) Is a bridging therapy needed? What options are available for bridging? Is there any risk associated with a bridging therapy?

3) Do you perform additional laboratory analysis? What is the value of troponin and/or brain natriuretic peptide (BNP) assays in this setting?

4) What are your anesthesia plans?

5) What is the value of platelet function testing in this setting?

CASE CONTINUATION 2

You stopped clopidogrel immediately, but continued with aspirin until the day before surgery. Two days later, the operation was performed under general anesthesia. Preoperative troponin and BNP were normal. During surgery, the surgeon complains of increased bleeding. The surgeon wants you to do something.

Questions:

1) What do you answer to the surgeon? What do you want the surgeon to do?

2) What about half-lives of platelet inhibitors and their implication for therapy with platelet concentrates?

3) What is the value of monitoring platelet function in this situation? Which platelet monitoring do you choose?

4) Why do not some patients on antiplatelet therapy develop increased bleeding tendency?

5) What are the possibilities to improve platelet function pharmacologically?

6) Do you perform any special monitoring of cardiac function/ischemia after transfusion of platelets, or any other hemostatic intervention for possible stent thrombosis?

CASE CONTINUATION 3

The operation was successful, and the patient is doing well. There has been no sign of postoperative cardiac ischemia by troponin, ECG and echocardiogram. Clopidogrel and aspirin were resumed on the 3rd postoperative day. Cardiac controls after 1 and 2 months went uneventfully. After 6 months, the patient develops acute low back pain with paresis of the left leg due to the protruding disc, and needs urgent lumbar decompression. The neurosurgeon is afraid of increased bleeding during and after surgery.
Questions:

1) What do you answer to your neurosurgeon? When would you perform surgery? What type of anesthesia do you choose?

2) What is the value of monitoring in this setting now? Do you consider a bridging therapy?

3) What are your treatment options?
DISCUSSION

Antiplatelet therapy is the current standard for the prevention of cardiovascular ischemia and stent thrombosis. Owing to the increased use of coronary stents, patients treated with antiplatelet therapy have increasing implications for the anesthesiologists’ daily business under two main conditions:

- A relevant coronary artery disease requiring intervention is detected in patients scheduled for elective surgery.
- A patient scheduled for emergent or elective surgery is treated with dual antiplatelet therapy due to coronary angioplasty and stenting within days, weeks or months before surgery.

Coronary stents

In 1986, coronary stents were introduced in clinical practice to treat the complications from the balloon angioplasty. These stents are metallic scaffolds, deployed within a diseased coronary artery segment to maintain luminal patency and to reduce re-stenosis of the coronary vessel. Intracoronary stents have had consistently two main problems during their development: a percutaneous intervention transforms a stenotic lesion into an unstable area due to rupture of its endothelial lining. The latter leads to platelet activation and inflammation that initiate a thrombotic cascade, potentially resulting in acute stent occlusion. After the introduction of aspirin/ticlopidine combination and high-pressure post-dilation, acute and subacute bare metal stent (BMS) thrombosis was reduced from about 24% to 2%. However, in-stent restenosis remained to be a problem with a rate of 20 to 30%. In-stent restenosis is due to multiple factors including vascular smooth muscle cell proliferation, and releases of mitogens and cytokines from platelets, endothelial cells, and inflammatory cells. The proliferation and migration result in neointimal hyperplasia and in-stent restenosis. Drug-eluting stents (DES) were subsequently introduced into practice in April 2003, after animal and clinical studies reported a dramatic reduction in the incidence of in-stent restenosis compared to BMS. In DES, the metal backbone of the BMS is coated with polymer matrix, which serves as a carrier of a medication that is eluted for a certain period of time. Types of DES in clinical practice at this time include:

- Cypher Sirolimus - active component is sirolimus which is eluted almost completely by 30 days after placement.
- Paclitaxel eluting stent – has initial burst release of paclitaxel, followed by constant slow release for up to 90 days.
- Other drug eluting stents release everolimus and zotarolimus as an active ingredient but they are used less frequently.

The prolonged release of the drugs substantially reduces inflammation and smooth muscle cell proliferation within the stent and decreases the rate of in-stent restenosis from 20-30% to 4%-6% on one hand; however, it interferes with the normal endothelialization of the stent. That leads to a prolonged exposure of the stent framework to circulating platelets and other...
blood elements and a need for prolonged antiplatelet coverage after stent implantation to prevent stent thrombosis. Endothelialization takes place eventually in all stents, BMS or DES. Antiplatelet therapy is aimed to help control acute, inflammatory state following the stent placement. Dual antiplatelet therapy has been proven to be effective for most patients following percutaneous coronary intervention (PCI). Therefore, the administration of clopidogrel or prasugrel together with aspirin is recommended in patients with ACS, and in patients undergoing percutaneous coronary intervention (PCI) and stent placement. Intravenous anticoagulation is typically implemented after PCI until oral clopidogrel/aspirin loading is achieved. Anticoagulant therapy includes heparin and/or direct thrombin inhibitors such as bivalirudin. GPIIb/IIIa inhibitors such as abciximab, tirofiban, or eptifibatide are sometimes used during the acute phase as well. Dual oral antiplatelet therapy is continued typically for at least 1 month with BMS and 12 months with DES.

**Antiplatelet drugs**

Indications for antiplatelet medications include: stroke, acute myocardial infarction, acute coronary syndrome, angina, PCI, cardiac surgery, primary and secondary cardiovascular disease prevention, peripheral vascular disease and other thrombotic disorders.

1) **Aspirin** is the most commonly used antiplatelet drug in patients with atherosclerotic disease. After oral or rectal administration, it is rapidly absorbed from the gastrointestinal tract with peak levels occurring 30 to 40 min after ingestion. Aspirin is an irreversible cyclooxygenase type I (COX1) inhibitor. COX1 catalyzes the conversion of arachidonic acid to prostaglandin H2. Prostaglandin H2 is rapidly converted to several bioactive prostanoids including thromboxane A2 and prostaglandin I2. Thromboxane A2 generation is highly sensitive to inhibition by aspirin. The major adverse effect of aspirin is an increased risk for upper gastrointestinal bleeding.

2) **Clopidogrel** is a pro-drug and has no direct antiplatelet activity on its own. It is administered orally and has variable absorption. It is metabolized in the liver in a two-step process by CYP3A4/3A5 and CYP2B6/1A2/2C9/2C19 esterases to produce an active metabolite which inhibits platelet aggregation. Peak concentration of the active metabolite is observed in 1 to 2 hours. The active metabolite binds to the platelet P2Y12 receptor and irreversibly inhibits adenosine-5’-diphosphate (ADP)-induced platelet aggregation. The major side effect of clopidogrel is an increased risk of bleeding. Its use in the perioperative period has been associated with increased need for blood products and re-exploration for bleeding after cardiac surgery. Other less common side effects of clopidogrel include neutropenia, thrombocytopenia, thrombotic thrombocytopenic purpura, and rash.

3) **Prasugrel** is a thienopyridine derivative as clopidogrel. It also binds to the platelet P2Y12 receptor to irreversibly inhibit ADP-induced platelet aggregation. Compared to clopidogrel, it is 10 to 100 times more potent, and it significantly reduces the death from cardiovascular causes, nonfatal myocardial infarction or non-fatal stroke Prasugrel is a pro-drug and must be metabolized to an active metabolite to exhibit its antiplatelet effect, but its conversion is more rapid involving only one step (CYP3A4 dependent). Prasugrel’s faster onset of activity and improved clinical efficacy can be explained by 2.2 times higher levels of
active metabolites compared to clopidogrel. It is administered orally, rapidly absorbed, and metabolized to achieve the peak concentration in 0.5 hr. Again, the most significant adverse effect is major bleeding. When compared with clopidogrel, prasugrel caused a higher incidence of life threatening bleeding. The role of prasugrel in the perioperative treatment of the atherothrombotic disease remains to be determined since it is more potent than clopidogrel, and is associated with an increased risk for bleeding.

4) Ticagrelor is an orally administered, reversible P2Y<sub>12</sub> receptor antagonist that does not require metabolic activation for its clinical effects. It has one known active metabolite. Its onset and offset is much faster than clopidogrel. The effect peaks in 2 to 4 hrs after oral administration and its terminal half-life is approximately 7 hrs. When compared with clopidogrel, ticagrelor is more effective in platelet inhibition and reducing ischemic events without increased bleeding risk. Ticagrelor is regarded as reversible; however, platelet inhibition as assessed with VerifyNow<sup>®</sup> and light transmission aggregometry persisted up to 120 hrs after cessation and did not substantially differ from platelet inhibition induced by clopidogrel between 48 and 120 hrs after cessation of either drug.

5) Elinogrel is an investigational drug. It is direct-acting, competitive, reversible P2Y<sub>12</sub> receptor inhibitor with a novel structure (sulfonylurea). A major potential advantage of elinogrel is that it can be used in both intravenous and oral preparations. Phase I and II studies demonstrated the ability of elinogrel to rapidly inhibit ADP-induced platelet aggregation if i.v. administration. Platelet inhibitions during the acute and chronic therapy were stronger compared to clopidogrel, and the efficacy of elinogrel was sustained during the intravenous-to-oral transition and throughout the chronic administration. There was no increased rate of clinically relevant bleedings. Results from a recently finished phase III study should be published soon.

6.) Cangrelor is another investigational drug. It is a short acting, intravenous, reversible, competitive inhibitor of platelet aggregation that acts by directly inhibiting P2Y<sub>12</sub> receptor. Cangrelor rapidly achieves near complete inhibition of ADP-induced platelet aggregation – steady state is achieved at 30 min without loading dose. Return of platelet function is also very quick - within 60 min of discontinuation of the drug, because of its elimination half-life of less than 9 min. It is metabolized by sequential dephosphorylation in the plasma which makes it attractive for patients with liver or kidney failure. No active metabolites are produced. CHAMPION PLATFORM study and CHAMPION PCI trial, both comparing cangrelor with clopidogrel, were terminated early for the lack of efficacy end points. Cangrelor, though, is an attractive alternative in the perioperative settings. The BRIDGE trial is ongoing phase II clinical trial attempting to establish the best dosing of cangrelor for safe “bridging” of patients in the perioperative period. Major side effects are bleeding and transient increase in liver enzymes.

Reduced drug responsiveness
None of the antithrombotic drug currently available is a 100% effective in the prevention of adverse thrombotic events. The reasons for inadequate drug effect while on treatment may be several:
a. Patient noncompliance with the prescribed medication may be a significant cause for treatment failure (3% to 40%).
b. Patient inability to pay for or access the medication.
c. Inadequate education about the necessity of continuing the medication at the time of hospital discharge.
d. True resistance to antiplatelet medications.
e. Inappropriate use of stents or type of stents (BMS vs. DES).
f. Other pathophysiologica mechanisms (e.g., inflammation)

True resistance to aspirin, defined as inability of aspirin to inhibit COX-1-dependent TXA₂ production, is very low – 1% to 2%. But up to 30% of patients treated with aspirin may have inadequate response to aspirin treatment at doses of < 300 mg daily, and may be susceptible to treatment failure. Those patients are discovered by an in vitro test of platelet function and are described as having persisting “high platelet reactivity (HPR)”, “biochemical resistance” or “reduced responsiveness”. Clinical thrombosis is a very late sign of HPR if it is present, but is not a proof that HPR is the cause of the thrombosis.

Conditions associated with inflammatory response such as unstable angina, AMI, diabetes, and surgery are associated with HPR in aspirin-treated patients. Other mechanisms for HPR include genetic polymorphisms of the platelet glycoprotein receptor and COX-1 and COX-2 alleles, generation of aspirin-insensitive COX, and increased platelet turnover (e.g., after surgery). Higher dosages of aspirin may increase the number of aspirin responders as determined by response to in vitro tests of platelet function. The concomitant administration of nonselective reversible COX-1 inhibitors such as ibuprofen and naproxen may impair the efficacy of aspirin because of competition for the common docking site within the COX-1 channel. Analgesic drugs with minimal effects on COX should therefore be considered particularly in patients who have undergone a PCI with stent placement.

HPR or reduce responsiveness occurs with usual doses of clopidogrel more frequently than with aspirin and other P2Y₁₂ receptor inhibitors. Frequencies up to 56% depending on the assay or method used have been reported. Intrinsic factors that affect the interaction of the active metabolite with its receptor such as genetic alteration of CYP2C19 gene, P2Y₁₂ receptor polymorphism, or alterations of intracellular signaling mechanisms may be involved. Again, some non-responders can be converted to responders by increasing the loading or maintenance doses. Clopidogrel’s activation to active metabolite is dependent on metabolism by the CYP enzyme system. Its efficacy may be influenced by drugs that are also CYP3A substrates. For example, randomized clinical trials have demonstrated the ability of the proton pump inhibitors to reduce the antiplatelet effect of clopidogrel.

Some patients demonstrate HPR in response to treatment with both aspirin and clopidogrel. These patients are at very high risk for DES thrombosis and death. HPR to one class of antiplatelet drugs though, does not necessary confer to HPR to other classes. For example, use of prasugrel increased platelet inhibition in patients for whom HPR was demonstrated using clopidogrel. The degree of HPR may also differ depending on body mass index, stress, comorbidities and the timing of drug administration in relation to events such as PCI or surgery. Diabetic patients have been found to have consistently high level of HPR. In general, the perioperative period is associated with increased catecholamine levels which have been identified as a risk for increased HPR.
Platelet function monitoring

The gold standard for platelet function testing is the light transmittance aggregometry. It consists of measuring the transmission of light through platelet rich plasma after exposure to a platelet agonist using platelet poor plasma as a reference (of light transmittance). This laboratory method requires substantial sample preparation, special equipment, and trained personnel. However, rapid decisions have to be made in the perioperative period. Recently, there have been extensive efforts in developing point-of-care (POC) tests for rapid assessment of the effect of the antiplatelet drugs. POC platelet monitoring can be performed with systems as PFA-100® (good sensitivity for aspirin but not for P2Y12 receptor inhibitors); Multiplate® (whole blood impedance aggregometry that allows testing with different activators including TRAP, ADP, arachidonic acid, collagen, and ristocetin); Plateletworks® (results highly depend on time between sample collection and testing); VerifyNow® (easy to use and can be considered a bedside test, it has a narrow dynamic range and may not be able to discriminate between very strong or between very weak levels of P2Y12 receptor inhibition); Thromboelastography Platelet Mapping® (a modification of the original thromboelastography essay that enables a quantitative analysis of platelet function. Thromboelastography measures the physical properties of a forming clot by the use of an oscillating cup that holds a sample of whole blood. The contribution of P2Y12 to clot formation is measured by the addition of 10 µmol ADP). All these systems have specific advantages and limitations. In addition, these assays require proper equipment, trained personnel and regular quality control for valuable results.

Different observational clinical studies gave some evidence that patients undergoing cardiac surgery with the most impaired platelet function will bleed most. However, other studies could not show such association. Importantly, the in vitro platelet function testing cannot mimic the multiple and complex in vivo activation of platelets. Other studies used POC platelet function monitoring to assess bleeding risk in patient with recent cessation of antiplatelet therapy before regional or neuroaxial anesthesia. However, the value of platelet function monitoring in the perioperative period has still to be defined.

Continuation of drug therapy in the perioperative period

Patients with BMS and DES should continue their dual antiplatelet therapy until the stents have endothelialized completely. The question is: how long does it take for the endothelialization?

In patients with BMS, the American college of chest physicians, the American society of regional anesthesia (ASRA), and the American college of cardiology/American heart association (ACC/AHA) guidelines suggest at least 4 to 6 weeks of dual therapy to allow for endothelialization. Ideally, patients with BMS should continue dual antiplatelet therapy for one year.

For patients with DES the length of dual antiplatelet therapy is still investigated. The possibility for delayed endothelialization of DES was first brought up during the World Congress of Cardiology in 2006. In a meta-analysis of the first generation DES compared to BMS, the occurrence of the combined endpoint of total mortality and Q wave MI was 38% (sirolimus stents) and 16% (paclitaxel stents) higher in DES compared to BMS. Those
findings were repeated in the BASKET-LATE study (Basel Stent Cost-Effectiveness Trial–Late Thrombotic Events) which reported a significantly greater incidence of death and nonfatal MI in patients who had received DES than in those who received bare-metal stents after clopidogrel had been discontinued at 6 months. The 2007 AHA/ACC/SCAI/ACS/ADA science advisory report concluded that premature discontinuation of dual-antiplatelet therapy markedly increases the risk of catastrophic stent thrombosis and death or MI. The benefits and indications for treatment with dual antiplatelet therapy beyond one year are subject of ongoing studies. Still, for patients with clinical features associated with stent thrombosis such as renal insufficiency, diabetes, or procedural characteristics such as multiple stents, or bifurcating lesions, extended dual-antiplatelet therapy beyond 1 year may be reasonable.

To eliminate the premature discontinuation of aspirin and/or of P2Y_12 receptor inhibiting therapy, the following is recommended in the perioperative period:

a. Aspirin given for primary prevention should be stopped 5 days before any elective surgery.

b. Aspirin in high-risked patients (e.g., diabetes, documented cardiovascular disease, increased global risk) should be continued during the perioperative phase with exceptions of surgery in closed spaces or with potential catastrophic outcomes in case of bleeding (e.g., neurosurgery, spine surgery). In the latter cases, aspirin should be stopped 5 days before surgery.

c. Before implantation of a stent, the physician should discuss the need for dual-antiplatelet therapy. In patients not expected to comply with 12 months of therapy with P2Y_{12} receptor inhibitors, whether for economic or other reasons, strong consideration should be given to avoiding a DES.

d. In patients who are undergoing preparation for PCI and who are likely to require invasive or surgical procedures within the next 12 months, consideration should be given to implantation of a bare-metal stent or performance of balloon angioplasty with provisional stent implantation instead of the routine use of a DES.

e. A greater effort by healthcare professionals must be made before patient discharge to ensure that patients are properly and thoroughly educated about the reasons they are prescribed P2Y_{12} receptor inhibitors and the significant risks associated with prematurely discontinuing such therapy.

f. Patients should be specifically instructed before hospital discharge to contact their treating cardiologist before stopping any antiplatelet therapy, even if instructed to stop such therapy by another healthcare provider.

g. Healthcare providers who perform invasive or surgical procedures and who are concerned about peri-procedural and post-procedural bleeding must be made aware of the potentially catastrophic risks of premature discontinuation of therapy with P2Y_{12} receptor inhibitors. Such professionals who perform these procedures should contact the patient’s cardiologist if issues regarding the patient’s antiplatelet therapy are unclear, to discuss optimal patient management strategy.

h. Elective procedures for which there is significant risk of perioperative or postoperative bleeding should be deferred until patients have completed an appropriate course of
therapy with P2Y\textsubscript{12} receptor inhibitors (12 months after DES implantation if they are not at high risk of bleeding and a minimum of 1 month for BMS implantation).

i. For patients treated with DES who are to undergo subsequent procedures that mandate discontinuation of dual antiplatelet therapy, P2Y\textsubscript{12} receptor inhibitor should be stopped, but aspirin should be continued if at all possible and the P2Y\textsubscript{12} receptor inhibitor restarted as soon as possible after the procedure because of concerns about late stent thrombosis.

**Regional anesthesia**

Chronic pain patients treated with dual antiplatelet therapy are a clinical dilemma for pain physicians and anesthetists when non-invasive pain therapy fails, and a neuroaxial or regional blockade becomes one of the few options for these patients. Aspirin monotherapy is not considered as bleeding risk in patients scheduled for regional or neuroaxial interventions. A recent retrospective analysis showed that epidural analgesia could be safely performed in 306 vascular surgery patients receiving clopidogrel until the day before surgery. No neurological complications were reported. However, ASRA guidelines recommend the interval of 7 days after clopidogrel cessation before the intervention to reduce the potential risk of hematoma formation or hemorrhage after neuroaxial or deep regional block procedures. Superficial regional block procedures as axillary or femoral nerve blockade may be an exception to this rule. Using a proper platelet function analyzer, the specific interval for clopidogrel stopping can potentially be reduced when the platelet function is normalized even before the 7 days interval is completed. POC platelet function monitors are likely to help the anesthesiologist to establish more objective criteria for perioperative antiplatelet management but further studies of clinical and economic outcomes are necessary to justify their routine use.

**Bridging therapy**

The irreversible effect of clopidogrel on platelets requires its withdrawal at least 5 days before surgery to reduce the risk of perioperative hemorrhage. However, acute withdrawal in patients with recent stent implantation increases the risk of perioperative stent thrombosis massively. Bridging therapies are therefore required. In patients on dual antiplatelet therapy, the continuation of aspirin is recommended except in particular patients with neurosurgical procedures. To administer unfractionated or low-molecular weight heparin, before and after surgery in a manner that minimizes the bleeding risk is probably the most common strategy. The advantage of heparin is its short half-life time and the possibility to reverse its effects with protamine. However, neither unfractionated heparin nor low-molecular weight heparin can provide the direct antiplatelet effects equivalent to the use of clopidogrel and/or aspirin. The same is true for “bridging” attempts with warfarin or other antithrombin agents such as bilvarudin.

Further recent publications reported the administration of the short-acting i.v. glycoprotein IIb/IIIa receptor inhibitor tirofiban and eptifibatide up to few hours before surgery. These protocols are mostly based on the experiences with patients with acute coronary syndromes
and have been successfully used in case series and small studies. Due to a paucity of evidence supporting glycoprotein IIb/IIIa receptor inhibitors, additional studies are warranted. Most “bridging” strategies are associated with increased risk of perioperative bleeding. In summary, there are no sufficient data to recommend “bridging” therapy with specific drugs. Future research should address how to optimally manage perioperative patients treated with dual antiplatelet therapy and a high risk of thrombotic events.
FURTHER READING/REFERENCES


