

Organ transplantation and drug eluting stents: Perioperative challenges

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Abstract

Patients listed for organ transplant frequently have severe coronary artery disease (CAD), which may be treated with drug eluting stents (DES). Everolimus and zotarolimus eluting stents are commonly used. Newer generation

biolimus and novolimus eluting biodegradable stents are becoming increasingly popular. Patients undergoing transplant surgery soon after the placement of DES are at increased risk of stent thrombosis (ST) in the perioperative period. Dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ inhibitor such as clopidogrel, prasugrel and ticagrelor is instated post stenting to decrease the incident of ST. Cangrelor has recently been approved by Food and Drug Administration and can be used as a bridging antiplatelet drug. The risk of ischemia *vs* bleeding must be considered when discontinuing or continuing DAPT for surgery. Though living donor transplant surgery is an elective procedure and can be optimally timed, cadaveric organ availability is unpredictable, therefore, discontinuation of antiplatelet medication cannot be optimally timed. The type of stent and timing of transplant surgery can be of utmost importance. Many platelet function point of care tests such as Light Transmittance Aggregrometry, Thromboelastography Platelet Mapping, VerifyNow, Multiple Electrode Aggregrometry are used to assess bleeding risk and guide perioperative platelet transfusion. Response to allogenic platelet transfusion to control severe intraoperative bleeding may differ with the antiplatelet drug. In stent thrombosis is an emergency where management with either a drug eluting balloon or a DES has shown superior outcomes. Post-transplant complications often involved stenosis of an important vessel that may need revascularization. DES are now used for endovascular interventions for transplant orthotropic heart CAD, hepatic artery stenosis post liver transplantation, transplant renal artery stenosis following kidney transplantation, *etc*. Several antiproliferative drugs used in the DES are inhibitors of mammalian target of rapamycin. Thus they are used for post-transplant immunosuppression to prevent acute rejection in recipients with heart, liver, lung and kidney transplantation. This article describes in detail the various perioperative challenges encountered in organ transplantation surgery and patients with drug eluting stents.

Key words: Drug eluting stents; Cangrelor; Stent thro-

mbosis; Organ transplant; Antiplatelet medication; Platelet function assays; Mammalian target of rapamycin inhibitors; Post-transplant immunosuppression; Post-transplant endovascular inhibition; Ticagrelor; Thromboelastograms platelet mapping; Novolimus; Biolimus A9

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Core tip: Patients undergoing transplant surgery soon after the placement of drug eluting stents (DES) are at increased risk of stent thrombosis (ST) in the perioperative period. Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor is instated post stenting to decrease the incident of ST. Cadaveric organ availability is unpredictable, therefore, discontinuation of antiplatelet medication cannot be optimally timed. Many platelet function point of care tests are used to assess bleeding risk and guide perioperative platelet transfusion. Response to allogenic platelet transfusion to control severe intraoperative bleeding may differ with the antiplatelet drug. DES are now used for endovascular interventions for post-transplant orthotopic heart coronary artery disease, hepatic artery stenosis post liver transplantation, *etc.* Antiproliferative drugs used in DES are also used for post-transplant immunosuppression.

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INTRODUCTION

Percutaneous coronary intervention (PCI) is presently the most frequent revascularization procedure used for treating coronary artery disease (CAD). It surpasses coronary artery bypass grafting. Balloon angioplasty and coronary stenting are the most common percutaneous coronary interventions.

Angioplasty is complicated by vessel spasm, recoil, and abrupt closure. Coronary stenting with bare metal stents (BMS) may prevent these complications, however, they are associated with restenosis rates of 25%-30%^[1]. Studies on stent thrombosis (ST) with BMS show that clinical consequences of angiographic ST includes a 64.4% incidence of death or myocardial infarction at the time of ST and a six-month mortality of 8.9%^[2]. For clinically defined ST events, the associated six-month mortality is as high as 20.8%. Due to such high risk of death following ST, it must be prevented at all costs. The angiographic outcome yielded by primary percutaneous intervention (PPCI) by drug eluting balloons (DEB)-only in selected patients was comparable to those stented by BMS alone and when DEB insertion was followed by stenting with BMS. If the patient has potential contraindications to DES, then DEB-only is a good alternative^[3].

When the stented coronary artery is narrowed due

to the development of neo-intimal hyperplasia within the stent, it is termed as restenosis. An inflammatory reaction, both acute and chronic, results when there is arterial trauma and a foreign body response. Smooth muscle migration and proliferation result in scar tissue formation within the stent, thus narrowing the vessel lumen. This process generally begins to occur in first six to eight weeks after stenting, but can be seen beyond one year after stent placement.

DES was introduced to reduce the rate of restenosis. The antiproliferative drug eluted inhibits smooth muscle and endothelial cell proliferation^[4], thus delaying the inflammatory response. The layering of endothelial cells over the stent is slower paced than with BMS. When the stent is endothelialized, it becomes incorporated into the artery. Complete healing of first generation DES may take upto two years^[5]. The drug is held and released by a biocompatible polymer coating^[6]. However, endothelialization of the stent may also be delayed. This increases the risk of subacute ST. Risk of after DES implantation is related to stent length, stenting across branch ostia, disruption of adjacent vulnerable plaques, and plaque prolapse^[7]. Failure to form a complete neo-intimal layer over stent struts or impaired healing makes the stent more susceptible to thrombosis^[8]. Premature interruption of DAPT, renal failure, cardiac compromise with low ejection fraction (EF), bifurcation stenting and diabetes contribute to the risk of thrombotic events in DES^[9].

DES

The type of stent can have significant implications on the perioperative management of a transplant recipient (Table 1).

First generation DES

Coronary first generation drug eluting stents were coated with antiproliferative drugs sirolimus and paclitaxel. First generation stents used were Paclitaxel eluting TAXUS (Boston Scientific, Natick, MA) stent (PES) and sirolimus eluting CYPHER (Cordis, Miami, FL) stent (SES). Paclitaxel, which is derived from a Pacific Yew Tree (*Taxus brevifolia*), is a cytotoxic anti-neoplastic drug which causes cell-cycle arrest in the G2/M phase transition^[10,11]. PES, have a bimodal release that is completed in approximately two weeks^[12]. Sirolimus is a macrolide antibiotic with potent antifungal, immunosuppressive, and anti-mitotic activities, and is produced by the fungus *Streptomyces hygroscopicus*^[11]. Sirolimus is cytostatic, and produces cell-cycle arrest in the G1/S phase transition. Sirolimus eluting stents (SES) slowly elute over a time frame of four to six weeks.

Second generation stents

Everolimus and zotarolimus are drugs used in second generation durable polymer stents. Second generation stents commonly used are zotarolimus eluting stent

Table 1 Types of stents

Generation of DES	Drug eluted	Some commercially available products	Features
First generation	Sirolimus, Paclitaxel	TAXUS, CYPHER	High Incidence of stent thrombosis, subacute as well as late thrombosis
Second generation	Zotarolimus, Everolimus	ENDEAVOR, XIENCE V	Safer and more efficacious as compared to first generation stents
Third generation	Novolimus, Biolimus A9	SYNERGY, BIOMATRIX, NOBORI, DESyne	Newer generation biodegradable stents which have shown superior outcomes

DES: Drug eluting stents.

(ZES) ENDEAVOR (Medtronic Inc. NJ) and everolimus eluting stent (EES), XIENCE V (Guidant Corporation, IN). Everolimus is a derived from sirolimus. Everolimus has a shorter half-life, and a greater bioavailability. It also has different blood metabolite patterns, as compared to sirolimus^[13].

Third generation stents

Newer generation biodegradable drug-eluting stents are designed to manage the longer side effects of residual durable polymer which persist after the drug has been completely eluted. The biodegradable polymer is applied to the abluminal side or outside surface only. Thus the inner or luminal side is free from the drug. After 3-4 mo of implantation, this stent loses most of its coating, acquiring a profile which is similar to that of a BMS^[14,15]. Novolimus and Biolimus A9 have been used in the third generation biodegradable stents. Biolimus A9 is a highly lipophilic analogue of sirolimus. The uptake by the coronary vessel wall is much better, thus the risk of systemic immunosuppression and toxicity is reduced^[16]. Novolimus is an active metabolite of sirolimus. It provides efficacy at lower dose (85 mcg of novolimus vs 140 mcg of sirolimus) and a lower polymer load^[17]. Recent ones introduced are the SYNERGY, BioMatrix, Nobori and DESyne stents^[18]. The NOBORI is a biodegradable biolimus eluting stent. Third generation stents with bioresorbable scaffolds such as the Abbott's BVS®, an everolimus-eluting device with a poly-L-lactic acid (PLLA)-base, is now seeing increasing clinical use. Elixir's DESolve®, a PLLA-based novolimus-eluting device is another device used clinically. Biotronik's DREAMS®, a metallic magnesium-based paclitaxel-eluting device, is a third device that has been deployed^[19]. The drug attaches directly, without polymer to the textured stent surfaces, in stents such as the BioFreedom stents and Yukon Choice stents^[18]. Coatings which are non-pharmacological, such as carbon, silicon carbide and titanium-nitride-oxide provide better outcomes than BMS. Gene eluting stents such as the Genous stent, function by promoting the attachment of endothelial progenitor cells^[18].

A meta-analysis of 51 trials that included a total of 52158 randomized patients concluded that all DES have demonstrated superior efficacy when compared with BMS^[20]. First generation stents have a high incidence of stent thrombosis, both subacute as well as late thrombosis^[9]. Among DES, second-generation devices are

substantially safer and more efficacious when compared with first-generation devices^[20]. These second generation stents are now being used to revascularize blocked left main coronary artery and are clearly superior to CABG. RESOLUTE all-comers (Randomized Comparison of a Zotarolimus-Eluting Stent with an Everolimus-Eluting Stent for Percutaneous Coronary Intervention) trial showed that ZES was noninferior to EES at 12-mo for the primary end point of target lesion failure^[21]. The NOBLE (Coronary Artery Bypass Grafting vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis) and EXCEL (Evaluation of XIENCE Everolimus Eluting Stent vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trials were conducted to compare PCI vs CABG. The EXCEL trial concluded that there was an equipoise for long-term mortality between CABG and PCI in subjects with unprotected left main coronary artery (ULMCA) disease up to an intermediate anatomical complexity. The anatomical and clinical characteristics impacted the decision making between CABG and PCI, and also in prediction of the long term mortality^[22]. Clinical characteristics which shifted long-term mortality predictions in favor of PCI was COPD, male gender and old age. Reduced left ventricular ejection fraction, lower creatinine clearance, younger age and female gender favored CABG^[22]. Thus PCI of the ULMCA with drug-eluting stents is safe and effective when performed in high volume centers with expertise^[23]. The SYNERGY bioresorbable polymer everolimus-eluting stent was noninferior to the PROMUS Element Plus everolimus-eluting stent with respect to 1-year target lesion failure^[24]. In a large meta-analysis, bioresorbable polymer based biolimus eluting stents (BP-DES) were associated with superior clinical outcomes compared with BMS and first generation DES and similar rates of death/MI, MI and target vessel revascularization (TVR) compared with second generation durable polymer DES. However, there were higher rates of ST compared with cobalt chromium EES^[25]. The novolimus eluting coronary stent DeSyne was found to be superior to ZES at a five year follow up^[26].

Various strategies have been employed to reduce the adverse effects associated with the drug eluting stents. A novel curcumin loaded nanoparticles (Cur-NP) preparation administered intravenously after stent implantation recovered endothelium function by accelerating endothelial cells restoration^[27].

Combretastatin CA4 inhibits the SMC cycle more

effectively than paclitaxel and sirolimus. It may be a newer antiproliferative drug which can be used for drug-eluting stents^[28]. Another drug called MiR-21 modulates the post stenting inflammatory response. This may have a therapeutic potential to clinical efficacy of stenting^[29].

ANTIPLATELET MEDICATION

Antiplatelet medications prevent thrombus formation till the stent is completely endothelialized. Intraluminal thrombus formation may lead to vascular occlusion, transient ischemia, or infarction^[27]. Antiplatelet drugs interfere with platelet adhesion, release and/or aggregation^[30].

Aspirin

Aspirin binds to enzyme cyclo-oxygenase preventing conversion of arachidonic acid to thromboxane, thus interfering with platelet action. Aspirin alone has little or no effect on angiographic or clinical restenosis. Lower doses of aspirin, 75-100 mg, are used in combination with other antiplatelet agents. Higher dose of aspirin is associated with increased risk of bleeding when used along with clopidogrel without any added benefit^[31].

Aspirin irreversibly inhibits platelets. Therefore, its action lasts until a significant number of platelets have been synthesized. By day 3, complete recovery of platelet aggregation may occur in 50% of cases. By day 4, complete recovery occurs in approximately 80% of cases^[32]. Reduced aspirin responsiveness can be measured by impedance platelet aggregometry^[33]. Some of the potential causes of reduced aspirin responsiveness include non-compliant intake, genetic polymorphisms of COX-1, increased platelet turnover and drug interactions^[34].

Clopidogrel

Clopidogrel has an active metabolite which irreversibly inhibits the acts on the ADP P2Y₁₂ receptor. The P2Y₁₂ receptor plays a vital role in the formation of a thrombus since it amplifies and completes the ADP response to thromboxane, thrombin and collagen^[35], and completes the activation of GP IIb/IIIa and GP I a/IIa for further stabilization of platelet aggregates^[36,37]. At steady state, the average inhibition level observed with a dose of 75 mg of clopidogrel per day is between 40%-60%. The prevalence of reduced clopidogrel response in patients is evaluated between 5% and 44%^[38] and is termed as high on treatment platelet reactivity (HTPR). Some of the causes of clopidogrel HTPR include genetic polymorphisms of the P2Y₁₂ receptor and of CYP3As, accrued release of adenosine phosphate, and up-regulation of other platelet activation pathways^[35].

Ticagrelor

It is a direct-acting, oral, newer reversible P2Y₁₂ receptor antagonist, and has a faster onset, and is more predictable and potent than clopidogrel. It binds allosterically to the

platelet ADP P2Y₁₂ receptor, thus, the binding does not cause a conformational change in the P2Y₁₂ receptor. It has a short offset time. It does need metabolic activation. It has a superior safety profile as compared to clopidogrel or prasugrel as seen in the PLATO (Platelet Inhibition and Patient Outcomes) study^[39]. It has been proven superior than clopidogrel in patients with chronic kidney disease. However, it should be avoided in patients with moderate-to-severe hepatic impairment and high bleeding risk^[40]. Complications include lung injury and dyspnea due to endogenous adenosine release^[41].

Prasugrel

Prasugrel is an oral irreversible inhibitor of the P2Y₁₂ receptor. Current European Society of Cardiology guidelines recommend prasugrel or ticagrelor over clopidogrel in patients with acute coronary syndromes (ACS) after PCI^[42]. If clopidogrel is used as a first line antiplatelet agent, then a platelet function assay should be performed, and a switch to prasugrel or ticagrelor is recommended for those with HTPR^[43]. The advantage of prasugrel is that it has a 5%-6% or low percentage of non-responders^[43].

Cangrelor

Cangrelor is an intravenous short-acting (half-life 3-6 min) P2Y₁₂ inhibitor, which is directly reversible. It does not require metabolic conversion. Intravenous cangrelor can produce rapid platelet aggregation with almost full recovery of platelet activity within 60-90 min of withdrawal^[44]. When cangrelor is administered intravenously to patients with CAD, the risk of MACE and stent thrombosis is reduced. There are however, increased events of minor bleeding^[44]. Additionally, cangrelor plays an important role in cases where cardiologist is not comfortable preloading a patient with antiplatelet therapy before an angiography, when it is uncertain that the patient may need urgent surgery. It has been recently approved by the FDA in June 2015^[45].

It is useful as a "bridging therapy" in patients with stents or acute coronary syndrome who need surgery, since they are increased risk for stent thrombosis when oral P2Y₁₂ therapy is temporarily stopped^[46].

The optimal duration of dual antiplatelet therapy has been a topic of debate. Most trials which compare antiplatelet strategies after PCI in a population state that the risk of bleeding and ischemia are average. Unfortunately, the information to recommend choices based on individual patient risks is scarce, especially beyond 1 year of DES placement and DAPT. There are many common risk factors associated with individual patient risks of ischemia and bleeding^[47].

A trial compared 6 wk of clopidogrel, aspirin and oral anticoagulation medications with 6 mo of clopidogrel therapy. However, there were no superior outcomes with the 6 wk triple therapy^[48]. Another study determined when permanent DAPT is discontinued before 30 d post cobalt chromium everolimus-eluting stent implantation, there was a strong association with ST. If the DAPT was discontinued after 90 d, it was safer^[49]. A large multicenter

study determined that the safety and efficacy of a 6-mo DAPT post implantation of new-generation DES was noninferior to that of a 12-mo DAPT^[50].

There is a lot of debate regarding short term dual antiplatelet therapy vs extended dual antiplatelet therapy. A study concluded that extended DAPT is associated with 8 fewer myocardial infarctions per 1000 treated patients per year. But unfortunately, there were 6 more major bleeding events than shorter-duration DAPT. Thus the duration of the DAPT should ideally be optimized taking into account the patient's values and preferences^[51]. A meta-analysis concluded that among selected patients undergoing DES implantation, a short duration (3-6 mo) of DAPT appears as the safest strategy. An extended duration (24-36 mo) of DAPT reduces thrombotic complications but with an excess in major bleeding complications^[52-54]. The duration of DAPT is challenging to adjust in those patients with an increased bleeding or thrombotic risk. These patients need a personalized DAPT duration, which is tailored to patients's, not stent's, characteristics^[55].

Two large studies, the Patient Related Outcomes With Endeavor vs Cypher Stenting Trial (PROTECT), and PROTECT US, determined that at a median follow-up of 4.1 years, major bleeding occurred in 2.8% subjects and ischemic events in 6.3%^[47]. There was no difference in mortality or stroke^[56].

The SECURITY trial which studied 6 mo vs 12 mo dual antiplatelet therapy following second generation DES implantation concluded that in a low-risk population, the 6 mo of DAPT following second-generation DES implantation was acceptable for the incidence of death, MI and stroke^[57]. The OPTIMIZE trial results stated that in patients with stable coronary artery disease or low-risk ACS treated with zotarolimus-eluting stents, 3 mo of DAPT was noninferior to 12 mo for NACCE, (NACCE; a composite of all-cause death, myocardial infarction (MI), stroke, or major bleeding) without significantly increasing the risk of stent thrombosis^[58].

The 2014 ACC/AHA current guidelines^[59] recommend 12 mo of DAPT post DES implantation. As the result of several randomized clinical trials showing the safety of a shorter duration of DAPT, the European Heart Society altered their recommendations to 6-12 mo of DAPT post DES implantation^[42].

PERIOPERATIVE MANAGEMENT

Transplant organ recipients usually have end stage organ disease and other comorbidities, and can be assigned the American Society of Anesthesiologists Grade 4 status. Furthermore, all transplant surgery can be classified as high risk. Thus, potential transplant recipients with drug eluting stents require extensive workup and evaluation. It is essential that the transplant anesthesiologist, surgeon and cardiologist be a part of the multidisciplinary team to help determine the optimal management for surgery in these patients. Such patients also need to be

screened carefully by the Transplant Center's Selection Committee prior to UNOS listing as a potential organ recipient. Major considerations would be whether the recipient would tolerate such a high risk associated with the transplant surgery and whether the organ is being optimally allocated (Table 2).

Living donor transplant surgery is an elective procedure and can be optimally timed so that the risk of intraoperative bleeding and ischemia is minimized in a drug eluting stent recipient. On the other hand, cadaveric organ availability is unpredictable, therefore, the discontinuation of antiplatelet therapy cannot be optimally planned. Discontinuation of anti-platelet medication for transplant surgery can pose a significant challenge for perioperative management. Patients undergoing transplant surgery soon after the placement of coronary stents are at increased risk of ST in the perioperative period. The risk of perioperative ischemia is higher if the stent were originally inserted for ACS rather than stable coronary artery disease (SCAD). When antiplatelet therapy is discontinued due to risk of bleeding, the risk of ST is clearly elevated, especially during surgery, which is generally a hypercoagulable state due to increased fibrin formation. If the antiplatelet therapy is continued, there may be bleeding, which in turn leads to hypotension. Hypotension may slow the blood through the stent resulting in ST. Thus risk of ST will be elevated in the perioperative period regardless of whether the antiplatelet therapy is continued or not. If the patient is on top of the Transplant Center's recipient list, one may discontinue oral antiplatelet medication and use a bridging therapy till a cadaveric organ is obtained. However, such a strategy may have inherent risks and would need meticulous monitoring.

ACC/AHA guidelines state in patients undergoing urgent noncardiac surgery during the first 4 to 6 wk after BMS or DES implantation, dual antiplatelet therapy should be continued unless the relative risk of bleeding outweighs the benefit of the prevention of stent thrombosis. In patients who have received coronary stents and must undergo surgical procedures that mandate the discontinuation of P2Y₁₂ platelet receptor-inhibitor therapy, it is recommended that aspirin be continued if possible and the P2Y₁₂ platelet receptor-inhibitor be restarted as soon as possible after surgery. Perioperative management of antiplatelet therapy should be formulated by a team of the surgeon, anesthesiologist, cardiologist, and patient, who should weigh the relative risk of bleeding with that of stent thrombosis^[59].

Aspirin is usually continued throughout the surgical procedure. The 2014 European Society of Cardiology and European Association for Cardiothoracic Surgery guidelines on myocardial revascularization support the 5 d clopidogrel withdrawal period before CABG. These guidelines also add that platelet function testing should be used to guide antiplatelet therapy interruption rather than a specified arbitrary time period^[42]. Recent studies state that patients on aspirin and clopidogrel < 5 d before CABG who had preoperative ADP-induced platelet aggregation \geq

Table 2 Antiplatelet drugs

Drug	Mechanism of action	Duration of action	Platelet responsiveness	Features
Aspirin	Aspirin binds to enzyme cyclo-oxygenase preventing conversion of arachidonic acid to thromboxane	Effect of aspirin lasts until a significant pool of new platelets is synthesized	Reduced aspirin responsiveness can be measured by impedance platelet aggregometry	Aspirin alone has little or no effect on angiographic or clinical restenosis
Clopidogrel	Irreversibly inhibits the ADP P2Y12 receptor	At steady state, the average inhibition level observed with a dose of 75 mg of clopidogrel per day is between 40%-60%	The prevalence of reduced clopidogrel response in patients is evaluated between 5% and 44% and is termed as HTPR	Some of the causes of clopidogrel HTPR include genetic polymorphisms of the P2Y12 receptor and of CYP3As, accrued release of adenosine phosphate, and up-regulation of other platelet activation pathways
Ticagrelor	Direct-acting, oral, newer reversible P2Y12 receptor antagonist	It binds allosterically to the platelet ADP P2Y12 receptor, thus, the binding does not cause a conformational change in the P2Y12 receptor. It has a short offset time	More predictable and potent than clopidogrel	Should be avoided in patients with moderate-to-severe hepatic impairment and high bleeding risk. Complications include lung injury and dyspnea due to endogenous adenosine release
Prasugrel	Oral irreversible inhibitor of the P2Y12 receptor	Effect of prasugrel lasts until a significant pool of new platelets is synthesized	Better inhibition for those with high HTPR	A 5%-6% or low percentage of non-responders
Cangrelor	Intravenous directly reversible P2Y12 inhibitor	Half-life 3-6 min	Rapid platelet aggregation with almost full recovery of platelet activity within 60-90 min of withdrawal	Useful to preload with antiplatelet therapy before the angiography should the patient's anatomy require urgent surgery

HTPR: High on treatment platelet reactivity.

50% have bleeding risk similar to those receiving aspirin monotherapy, thus a 5 d clopidogrel discontinuation period may not always be necessary^[60]. Guidelines also recommend the discontinuation of ticagrelor 5 d prior to surgery and recommencing therapy as soon as it is safe to do so. Since prasugrel has more prolonged and effective platelet inhibition than clopidogrel, it should be stopped 7 d prior to surgery^[42].

The risk of stent thrombosis is associated with stent type and time from stenting to surgery. It will be highest if BMS or DES is inserted within 30 d of the transplant surgery. The risk is high when the surgery is carried out < 1 mo after BMS and < 6 mo after DES, is intermediate if performed between 1-6 mo after BMS and 6-12 mo after DES, and low if performed > 6 mo after BMS and > 12 mo after DES^[61].

A study involving over 12000 patients with previous coronary stenting who underwent over 17000 surgical procedures stated that cardiac death occurred in 2.5%, myocardial infarction in 1.5%, and serious bleeding event in 6.4%. Surgery increased 1.58 × the risk of cardiac death during follow-up. Older generation stents were associated with higher risk of adverse events as compared to BMS > 12 mo before surgery. Newer DES showed similar safety as BMS > 12 mo and between 6 and 12 mo. They also trended to be safer between 0 and 6 mo^[61].

European Guidelines state that most surgical procedures can be performed on DAPT or ASA alone with acceptable rates of bleeding^[42]. The timing of surgery mattered most during the first 6 mo after PCI, with

respect to MACE events. There was no association of the stent type (BMS vs DES) with MACE after surgery. The guidelines further state that whenever possible, the elective non cardiac surgery should be postponed till the completion of the full course of DAPT ideally, 6 mo in SCAD and 1 year in acute coronary artery syndrome (ACS) patients, and that surgery be performed without discontinuation of aspirin^[42]. Shorter duration of DAPT may be justifiable if surgery cannot be delayed. In very high risk patients, 5 d prior to surgery, patient maybe switched from clopidogrel to a reversible antiplatelet agent with a short half-life such as IV tirofiban or eptifibatide, and stop the infusion 4 h prior to surgery^[42]. The substitution of DAPT with LMWH or UFH is ineffective. In surgical procedures with low-to-moderate bleeding risk, surgeons should be encouraged to operate while maintaining DAPT^[42].

Various Platelet Function Assays for P2Y12 Receptor Antagonisms are Light Transmittance Aggregometry, (LTA), vasodilator stimulated phosphoprotein (VASP), VerifyNow, TEG Plateletmapping and Multiple Electrode Aggregometry (MEA)^[62]. The LTA uses plasma and optically measures platelet aggregation, and is considered the gold standard. The VASP uses whole blood and flow cytometry to specifically measure P2Y12 activity, as it is the only assay which is not affected by the ADP's effect on the P2Y1 receptor, and thus is specific for P2Y12 inhibition. The VerifyNow P2Y12 assay uses whole blood, and optically measures platelet aggregation. Advantages of VerifyNow is that it is readily available in clinical settings and is a point of care assay^[62]. The Assessment

of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) trial is a very large observational platelet function study. It stated that upto 50% of 30-d post-PCI ST could be attributed to HTPR, which was defined as a P2Y12 reaction unit value of > 208 with VerifyNow® test^[63]. Point of care platelet function testing can also be done with TEG Plateletmapping (TEG-PM). It measures the degree of platelet inhibition resulting from aspirin or ADP receptor antagonists and correlates well with light transmission aggregometry^[64]. TEG-PM can measure the percentage adenosine 5'-diphosphate platelet receptor inhibition (ADP-PRI) by clopidogrel prior to urgent transplant surgery. An ADP PRI of 30% or more can be classified as high bleeding risk. Another study was conducted to predicted risk of bleeding and adverse outcomes by TEM-PM in patients taking clopidogrel within 7 d of non-cardiac surgery. Interestingly, there was no correlation between duration of clopidogrel omission and percentage ADP-PRI^[65].

Excessive bleeding can be treated by allogenic platelet transfusions (PT) in patients on P2Y12 receptor inhibitors. Though the American Association of Blood Banks 2015 clinical practice guidelines suggests prophylactic platelet transfusion for patients having major elective nonneuraxial surgery with a platelet count less than 50×10^9 cells/L, there is no recommendation for platelet transfusions for patients on dual antiplatelet therapy^[66]. In the APTITUDE-Coronary Artery Bypass Graft (APTITUDE- CABG) study, VASP reactivity index, was assessed before and after *in vivo* PT administered for excessive bleeding in patients undergoing cardiac surgery while on a maintenance dose of aspirin and clopidogrel ($n = 45$), prasugrel ($n = 6$), or ticagrelor ($n = 3$). When compared with baseline, there was a significant relative increase of 23.1% in platelet activation after PT transfusion. PT restores platelet reactivity in patients with ACS/PCI and in patients undergoing cardiac surgery on P2Y12 RI while bleeding with a less effect with increasing potency of P2Y12 inhibition^[67]. A recent study stated that clopidogrel had no effect on donor PLT function. Prasugrel has mild effect on donor platelet function. Ticagrelor completely abolished ADP mediated PLT activation in all assays tested. The observed effects were due to Ticagrelor and not elevated adenosine concentrations in the patient's plasma. A modified multiple electrode aggregometry (MEA) assay can be used to determine whether the patient would be likely to benefit from platelet (PLT) transfusions^[68].

The BRIDGE trial was a pharmacodynamic study evaluating platelet reactivity of cangrelor vs placebo in ACS and/or patients with a stent who were at increased risk of thrombotic events because of discontinuation of an oral P2Y12 inhibitor before cardiac surgery^[46]. The primary efficacy end point [percentage of patients with all samples during the infusion achieving platelet reactivity unit (PRU) < 240 as determined by VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] was met in 98.8% of cangrelor- treated patients compared to 19.0%

of placebo-treated patients. After discontinuation of cangrelor, platelet reactivity was similar for both cangrelor and placebo groups^[55]. Cangrelor has been approved by the FDA in June 2015^[45]. When cangrelor occupies the P2 Y12 receptor, the active metabolite of clopidogrel is unable to bind to it. However, this reaction is avoided when clopidogrel is given at the end of the cangrelor infusion. Earlier administration increases the recovery of platelet function. Antiplatelet effects of prasugrel were apparent when prasugrel was administered 0.5 h before cangrelor was stopped^[69,70].

In the Drug Eluting Stent Event Registry of Thrombosis (DESERT)^[71], the largest case- control registry of late/very late thrombosis after DES, 75% of ST events occurred after 1 year, similar to the 60% rate observed in a study^[71]. Furthermore, the clinical presentation of late/very late ST events in DESERT was mainly ST-segment-elevation myocardial infarction (67%). More than half of all ST-related MIs were Q-wave MIs, and subsequent mortality was increased 8-fold after an ST-related MI, the greatest hazard of any MI type^[71].

In stent restenosis can be managed with BMS, brachytherapy, rotational atherectomy and cutting balloons, DEB and DES. A meta-analysis concludes that for treatment of any type of coronary in-stent restenosis (ISR), PCI with everolimus-eluting stents is optimal, because of the best angiographic and clinical outcomes. Use of drug coated balloons (DCB) is also favored, because of its ability to provide favorable results without adding a new stent layer^[73]. Additionally, when DES are implanted to treat BMS restenosis, at 6 mo, struts coverage is more complete when compared with DES implanted in atherosclerotic lesions^[74]. In patients with DES-ISR, EES were superior, both clinically, as well as angiographically, when compared with DEB^[75].

POST TRANSPLANT IMMUNOSUPPRESSION

The drugs sirolimus, everolimus, biolimus and novolimus are inhibitors of the mammalian target of rapamycin (mTOR). After organ organ transplantation, the mTORs are used along with calcineurin inhibitors (CNIs) to provide immunosuppression. They are also used as proliferation signal inhibitors coated on DES. Their use in cancer therapy bears the same mechanism. Everolimus antagonizes the negative effects of CNIs kidney cell and neuronal metabolism and stimulates mitochondrial oxidation, thus reducing the vascular inflammation^[13]. In transplantation, everolimus has been used post-transplant in heart, liver, lung and kidney transplant recipients to prevent acute rejection. In kidney transplant patients, everolimus may minimize or remove calcineurin inhibitors^[76]. Interestingly, renal transplant patients with DES had a low rate of ST, probably related to the immunosuppressants given to prevent kidney rejection^[77]. Everolimus has also been approved by the FDA for use in liver transplantation (LT), and is safe for use with tacrolimus within the first month

after LT^[78].

POST TRANSPLANT ENDOVASCULAR INTERVENTION WITH DES

DES has been successfully used to stent stenotic lesions post-transplant surgery. Transplant coronary artery disease (TCAD) is a major cause of morbidity and mortality after the first year after orthotopic heart transplantation (OHT). OHT patients with ISR have poor long-term prognosis^[79]. EES used on OHT patients with TCAD is associated with a low incidence of target vessel revascularization (TVR) and target lesion revascularization (TLR)^[80]. Unfortunately, long-term mortality remains high in orthotopic heart transplantation (OHT) recipients after PCI with either DES or BMS^[81].

Transplant renal artery stenosis (TRAS) following kidney transplantation has an incidence rate ranging from 6% to 23%. Endovascular intervention with DES improves blood pressure control and allograft function^[82]. ISR occurs in as many as 13% of patients after PTA and stent insertion. A case report describes three such patients, of which, in two patients, the transplant renal artery remained patent after insertion of PES, and one patient required balloon angioplasty 7 mo after the DES was inserted^[83]. BMS have been used to treat lung transplant related pulmonary artery stenosis^[84]. DES have been placed into the pulmonary veins as a bridge to heart lung transplantation in a patient with extensive and recurrent congenital pulmonary vein stenosis^[85]. DES have been safely used and may prevent ISR in patients who undergo intracoronary bone marrow mononuclear cell transplantation post coronary stenting^[86]. Orthotopic liver transplantation (OLT) is commonly complicated by hepatic artery stenosis (HAS). It can lead to hepatic artery thrombosis, with subsequent liver failure in 30% of the patients. Though traditionally this was managed with either surgical revascularization or retransplantation, use of DES has resulted in high technical success and provided for excellent patency. Avoidance of hepatic artery thrombosis is possible in > 95% of patients with endovascular treatment and close follow-up^[87]. Paclitaxel eluting balloon has been employed successfully to treat biliary anastomotic strictures after liver transplantation^[88]. Stents have also been used to manage stenosis in the hepatic veins and/or inferior vena cava above hepatic venous anastomosis to relieve an outflow venous block following living donor liver transplantation^[89].

CONCLUSION

Though several perioperative challenges encountered in organ transplantation surgery and patients with drug eluting stents, these can be optimally managed with proper planning and teamwork, ensuring patient safety.

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