Organ transplantation and drug eluting stents: Perioperative challenges

Aparna Dalal

Aparna Dalal, Department of Anesthesiology, Icahn School of Medicine, New York, NY 10029, United States

Author contributions: Dalal A authored the paper.

Conflict-of-interest statement: The author has not received any financial support for this review article, nor has any conflicts of interest to disclose.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Correspondence to: Aparna Dalal, MD, Assistant Professor, Department of Anesthesiology, Icahn School of Medicine, Mount Sinai 1428 Madison Avenue, New York, NY 10029, United States. dalalanesthesia@gmail.com
Telephone: +1-212-2722545
Fax:+1-646-6853610

Received: March 16, 2016
Peer-review started: March 18, 2016
First decision: May 19, 2016
Revised: July 28, 2016
Accepted: September 13, 2016
Article in press: September 15, 2016
Published online: December 24, 2016

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 orthotopic 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

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

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 agent used. 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.

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%\(^\text{[1]}\). 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%\(^\text{[6]}\). 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\(^\text{[2]}\).

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\(^\text{[4]}\), 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 up to two years\(^\text{[7]}\). The drug is held and released by a biocompatible polymer coating\(^\text{[9]}\). 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\(^\text{[10]}\). Failure to form a complete neo-intimal layer over stent struts or impaired healing makes the stent more susceptible to thrombosis\(^\text{[8]}\). 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\(^\text{[10]}\).

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 G1/S phase transition\(^\text{[11]}\). 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\(^\text{[12]}\). PES, have a bimodal release that is completed in approximately two weeks\(^\text{[13]}\). Sirolimus is a macrolide antibiotic with potent antifungal, immunosuppressive, and anti-mitotic activities, and is produced by the fungus Streptomyces hygroscopicus\(^\text{[11]}\). 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
Thrombosis

BMS

52158 randomized patients concluded that all DES have different cells. Gene eluting stents such as the Genous stent, function titanium-nitride-oxide provide better outcomes than BMS. Pharmacological, such as carbon, silicon carbide and drug attaches directly, without polymer to the textured DREAMS clinical use. Elixir’s DESolve a poly-L-lactic acid (PLLA)-base, is now seeing increasing as the Abbott’s BVS. Third generation stents with biodegradable scaffolds such as the SYNERGY, BioMatrix, Nobori and DESyne stents and a lower polymer load lower dose (85 mcg of novolimus is an active metabolite of sirolimus. The uptake by the coronary vessel wall is much better, thus the risk of systemic immunosuppression and toxicity is reduced. 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. Recent ones introduced are the SYNERGY, BioMatrix, Nobori and DESyne stents. The Nobori is a biodegradable biolimus eluting stent. Third generation stents with biodegradable 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. The drug attaches directly, without polymer to the textured stent surfaces, in stents such as the BioFreedom stents and Yukon Choice stents. 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.

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. First generation stents have a high incidence of stent thrombosis, both subacute as well as late thrombosis. Among DES, second-generation devices are substantially safer and more efficacious when compared with first-generation devices. 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. 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 a 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. 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. Thus PCI of the ULMCA with drug-eluting stents is safe and effective when performed in high volume centers with expertise. The SYNERGY bioabsorbable polymer everolimus-eluting stent was noninferior to the PROMUS Element Plus everolimus-eluting stent with respect to 1-year target lesion failure. In a large meta-analysis, bioabsorbable 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. The novolimus eluting coronary stent DeSyne was found to be superior to ZES at a five year follow up.

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.

Combretastatin CA4 inhibits the SMC cycle more

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

ANTIPATELET MEDICATION

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

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.

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. Reduced aspirin responsiveness can be measured by impedance platelet aggregometry. Some of the potential causes of reduced aspirin responsiveness include non-compliant intake, genetic polymorphisms of COX-1, increased platelet turnover and drug interactions.

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, and completes the activation of GP IIb/IIIa and GP I a/II a for further stabilization of platelet aggregates. 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 high on treatment platelet reactivity (HTPR). Some of the causes of clopidogrel HTPR include genetic polymorphisms of the P2Y12 receptor and of CYP3A, accrued release of adenosine phosphate, and up-regulation of other platelet activation pathways.

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. 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. Complications include lung injury and dyspnea due to endogenous adenosine release.

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. 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. The advantage of prasugrel is that it has a 5%-6% or low percentage of non-responders.

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. 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. 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.

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.

The optimal duration of dual antiplatelet therapy has been a topic of debate. Most trials which compare anti-platelet 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.

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. 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. 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-analyses 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 that show 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[40]. Recent studies state that patients on aspirin and clopidogrel < 5 d before CABG who had preoperative ADP-induced platelet aggregation ≥
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[62].

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 tended 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 epti-fibatide, and stop the infusion 4 h prior to surgery. 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 Antagonists 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

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.
of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) trial is a very large observational platelet function study. It stated that 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[53]. 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 × 10⁹ cells/L, there is no recommendation for platelet transfusions for patients on dual antiplatelet therapy[66]. In the APTITUDE-Coronary Artery Bypass Graft (APTTITUDE- 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[69]. The primary efficacy end point [percentage of patients with all samples during the infusion 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[55]. 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[72]. 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[73]. 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

Dalal A. Organ transplantation and drug eluting stents
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.

REFERENCES

1. Presbitero P, Boccuzzi G. Restenosis treatment in the drug-eluting stent era. Ital Heart J 2005; 6: 514-521 [PMID: 16008157]
2. Cutlip DE, Baim DS, Ho KK, Popma JJ, Lansky AJ, Cohen DJ, Carrozza JP, Chauhan MS, Rodriguez O, Kuntz RE. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. Circulation 2001; 103: 1967-1971 [PMID: 11306525 DOI: 10.1161/CIRCULATIONAHA.103.151967]
3. Nijhoff F, Agostoni P, Belkacemi A, Nathoo HM, Voskuil M, Samim M, Doevendans PA, Stella PR. Primary percutaneous coronary intervention by drug-eluting balloon angioplasty: the nonrandomized fourth arm of the DEB-AMI (drug-eluting balloon in ST-segment elevation myocardial infarction) trial. Catheter Cardiovasc Interv 2015; 86 Suppl 1: S34-S44 [PMID: 26119971 DOI: 10.1002/ccd.26060]
4. Liuozzo JP, Ambrose JA, Coppola JT. Sirolimus- and taxol-eluting stents differ towards intimal hyperplasia and re-endothelialization. J Invasive Cardiol 2005; 17: 497-502 [PMID: 16145242]
5. Silber S, Albertsson P, Avilés FF, Camici PG, Colombo A, Hamm C, Jørgensen E, Marco J, Nordrehaug JE, Ruzyllo W, Urban P, Stone GW, Wijns W. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Eur Heart J 2008; 26: 804-847 [PMID: 18576984 DOI: 10.1093/eurheartj/ehi138]
6. Stone GW, Ellis SG, Cannon C, Harrington RA, Mauri L, Harrington PA, O’Shaughnessy CS, DeMaio S, Hall P, Popma JJ, Koglin J, Russell ME. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. JAMA 2005; 294: 1215-1223 [PMID: 16160130 DOI: 10.1001/jama.294.10.1215]
7. Moreno R, Fernández C, Hernández R, Alfonso F, Angiolillo DJ, Sabaté E, Escaned J, Bahúleos C, Fernández-Orozco A, Macaya C. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. J Am Coll Cardiol 2005; 45: 954-959 [PMID: 15766835 DOI: 10.1016/j.jacc.2004.11.065]
8. Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. Circulation 2011; 108: 1701-1706 [PMID: 14504181 DOI: 10.1161/01.CIR.0000311155.05840.80]
9. Iakovou I, Schmidt T, Bonizzi E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Covaja V, Briguori C, Gerecis U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005; 293: 2126-2130 [PMID: 15870416 DOI: 10.1001/jama.293.17.2126]
10. Rogers CD. Drug-eluting stents: clinical perspectives on drug and design differences. Rev Cardiovasc Med 2005; 6 Suppl 1: S3-12 [PMID: 15665795]
11. Smith ED, Rothman MT. Antiproliferative coatings for the treatment of coronary heart disease: what are the targets and which are the tools? J Interv Cardiol 2003; 16: 475-483 [PMID: 14632944 DOI: 10.1046/j.1540-8183.2003.01058.x]
12. Moliterno DJ. Healing Achilles—sirolimus versus paclitaxel. N Engl J Med 2005; 353: 724-727 [PMID: 16105991 DOI: 10.1056/NEJMoa058140]
13. Klawitter J, Nashan B, Christians U. Everolimus and sirolimus in transplantation-related but different. Expert Opin Drug Saf 2015; 14: 1055-1070 [PMID: 25912929 DOI: 10.1517/14744338.2015.1040388]
14. Longo G, La Manna A, Capodanno D, Tamburino C. The Ultimaster® coronary stent system: state of the art. Minerva Cardioangiol 2015; 63: 193-203 [PMID: 25900560]
15. Bozak F, Gonzalez-Rodriguez D, Sternberger Z, Belliz P, Biewley T, Chomaz JM, Barakat AI. Optimization of Drug Delivery by Drug-Eluting Stents. PLoS One 2015; 10: e0131082 [PMID: 26083626 DOI: 10.1371/journal.pone.0130182]
16. Piccolo R, Nicolino A, Danzi GB. The Nobori biolimus-eluting stent: update of available evidence. Expert Rev Med Devices 2014; 11: 275-282 [PMID: 24579987 DOI: 10.1586/17434440.2014.894458]
17. Costa JR, Abizaid A, Feres F, Costa R, Seixas AC, Maia F, Abizaid A, Tanajura LF, Staciu R, Siqueira D, Meredith L, Bhat V, Yan J, Ormiston J, Sousa AG, Fitzgerald P, Sousa JE. EXCELLA First-in-
Dalal A. Organ transplantation and drug eluting stents

Man (FIM) study: safety and efficacy of novelolimus-eluting stent in de novo coronary lesions. EuroIntervention 2008; 4: 53-58 [PMID: 19112779 DOI: 10.4244/EIJV4A10]

O’Brien B, Zafar H, Ibrahim A, Zafar J, Sharif F. Coronary Stent Materials and Coatings 2015: A Technology and Performance Update. Ann Biomed Eng 2016; 44: 523-535 [PMID: 26139297 DOI: 10.1007/s10439-015-1380-x]

Charpentier E, Barma A, Guilleneau L, Ljuldi JM. Fully bioreabsorbable drug-eluting coronary scaffolds: A review. Arch Cardiovasc Dis 2015; 108: 385-397 [PMID: 26113479 DOI: 10.1016/j.acvdis.2015.03.009]

Palmerini T, Benedetto U, Biondi-Zoccai G, della Riva D, Bacchi-Reggiani L, Smits PC, Vlaughann JS, Jensen LO, Christiansen EH, Berenese K, Valgimigli M, Orlandi C, Petrou M, Rapezzi C, Stone GW. Long-Term Safety of Drug-Eluting and Bare-Metal Stents: Evidence From a Comprehensive Network Meta-Analysis. J Am Coll Cardiol 2015; 66: 2496-2507 [PMID: 26065988 DOI: 10.1016/j.jacc.2015.04.017]

Iqbal J, Serremys PW, Silber S, Kelbara H, Richardt G, Morel MA, Negoita M, Buszman PE, Windecker S. Comparison of zotarolimus- and everolimus-eluting coronary stents: final 5-year report of the RESOLUTE all-comers trial. Circ Cardiovasc Interv 2015; 8: e002230 [PMID: 26047995 DOI: 10.1161/CIRCINTERVENTIONS.114.002230]

Campos CM, van Klaveren D, Farooq V, Simonton CA, Kappetein AP, Sabik JF, Steyerberg EW, Stone GW, Serremys PW. Long-term forecasting and comparison of mortality in the Evaluation of the Xience VeroElution Stent Eluting stent versus coronary artery bypass surgery for effectiveness of left main revascularization (EXCEL) trial: prospective validation of the SYNTAX Score. Eur J Heart 2015; 36: 1231-1241 [PMID: 25583761 DOI: 10.1093/europace/euh518]

Alam M, Shahzad SA, Akhtar A, Huang HD, Rogers PA, Ramanathan KB, Kleiman NS, Jneid H. Long-term clinical outcomes after percutaneous coronary intervention for unprotected left main coronary artery in heart transplant patients with cardiac allograft vasculopathy. Int J Cardiol 2012; 156: 101-104 [PMID: 22265522 DOI: 10.1016/j.ijcard.2012.11.115]

Kerekas DJ, Meredith ET, Windecker S, Lee Jobe R, Mehta SR, Sarembokk IJ, Feldman RL, Stein B, Dubois C, Grady T, Saio S, Kimura T, Christen T, Allocco DJ, Dawkins KD. Efficacy and forecasting and comparison of mortality in the Evaluation of the RESOLUTE all-comers trial. J Am Coll Cardiol 2015; 65: 2918-2015 [PMID: 1682-1687 DOI: 10.1161/01.01.ej.2015.02.119]

Hankey GJ, Eikelboom JW. Aspirin resistance. Lancet 2003; 367: 606-617 [PMID: 16488805 DOI: 10.1016/S0140-6736(06)68840-0]

Gachet C. The platelet P2 receptors as molecular targets for old and new antiplatelet drugs. Pharmacol Ther 2005; 108: 180-192 [PMID: 15955565 DOI: 10.1016/j.pharmthera.2005.03.009]

Boyaenaems JM, van Giezen H, Savi P, Herbert JM. P2Y receptor antagonists in thrombosis. Curr Opin Investig Drugs 2005; 6: 275-282 [PMID: 15816504]

Tanzri B, D’Ascenzo F, Garcia Rodriguez L, de Vries T, Morrison L, Reggiani L, Smits PC, Vlachojannis GJ, Jensen LO, Christiansen EH, Aradi D, Price MJ, Jeong YH, Angiolillo DJ, Stone GW, Curzen N, Ten Berg J, Kirtane A, Siller-Matula JM, Marucci R, Kundu A, Ahn CS, Sibbing D, Gurbel PA. Consensus on the use of on-treatment platelet reactivity to adenosine diphosphate receptors on blood platelets: potential new targets for antiplatelet therapy. Acta Biochim Pol 2005; 52: 411-415 [PMID: 15912207]

Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Smeets PC, Curzen N, Geisler T, Ten Berg J, Kirtane A, Siller-Matula JM, Mahla E, Becker RC, Bhil DL, Wikman R, Rao SV, Alexopoulos DA, Marucci R, Cury J, Trenk D, Sibbing D, Gurbel PA. Consensus on the update and definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013; 62: 2261-2273 [PMID: 24076493 DOI: 10.1016/j.jacc.2013.07.101]

Patrono C, Bachmann F, Baigent C, Bode C, De Caterina R, Charbonnier B, Fitzgerald D, Hirsh J, Husted S, Kvasnicka J, Montalescot G, Garcia Rodriguez L, Verheugt F, Vermuyen J, Wallentin L, Priori SG, Alonso Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Fernandez Burgos E, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth OA, Morais J, Deckers J, Ferreira R, Mazzotta G, Stieg PG, Teixeira V, Wilcox R. Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European society of cardiology. Eur Heart J 2004; 25: 166-181 [PMID: 14720534 DOI: 10.1016/j. ejhj.2003.10.013]

Palmerini T, Benedetto U, Biondi-Zoccai G, della Riva D, Mariani A, Sabatè M, Smits PC, Kaisers C, D’Ascanio F, Frati G, Mancone M, Genereux P, Stone GW. Clinical outcomes with biodegradable polymer-coated, everolimus-eluting coronary stent: the EVOLVE II Randomized Trial. Circ Cardiovasc Interv 2015; 8: pii: e002372 [PMID: 25855680 DOI: 10.1161/CIRCINTERVENTIONS.114.002372]

Spira D, Größinger G, Domschke N, Bantleon R, Schmehl J, Wiskirchen J, Wiessinger B. Cell Cycle Regulation of Smooth Muscle Cells—Searching for Inhibitors of Neointima Formation: Is Combretastatin A4 an Alternative to Sirolimus and Paclitaxel? J Vasc Interv Radiol 2016; 27: 1388-1395 [PMID: 26169455 DOI: 10.1016/j.jvir.2015.05.025]

McDonald RA, Halliday CA, Miller AM, Diver LA, Dakin RS, Montgomery J, McBride MW, Kennedy S, McClure JD, Robertson KE, Douglas G, Channon KM, Oldroyd KG, Baker AH. Reducing In-Stent Restenosis: Therapeutic Manipulation of miRNA in Vascular Remodeling and Inflammation. J Am Coll Cardiol 2015; 65: 2314-2327 [PMID: 26022821 DOI: 10.1016/j.jacc.2015.03.549]

Teng R. Ticagrelor: Pharmacokinetic, Pharmacodynamic and Pharmacogenetic Profile: An Update. Clin Pharmacokinet 2015; 54: 1125-1138 [PMID: 26063309 DOI: 10.2165/0020062-01-0290-2]

N Engl J Med 628 December 24, 2016 | Volume 6 | Issue 4 |
Dalal A. Organ transplantation and drug eluting stents

L, Valgimigli M, Wijns W, Witkowski A; European Society of Cardiology for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kohli P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Simes PA, Tamargo JL, Tendeira M, Torbicki A, Wijns W, Windecker S; EACTS Clinical Guidelines Committee, Sousa Uva M, Achenbach S, Pepeur J, Ansyuwu A, Badimon L, Bauersachs J, Baumbach A, Beygui F, Bonaros N, De Carlo M, Deaton C, Dobrev D, Dunning J, Eekhout E, Gielen S, Hasdai D, Kirchhof P, Luckraz H, Mahrholdt H, Montalescot G, Paparella D, Rastan AJ, Sammartin M, Sergeant P, Silber S, Tamargo J, ten Berg J, Thiele H, van Gerven R3, Wagner HO, Wassmann S, Wendler O, Zamorano JL. 2014 ESC/ EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur J Cardiotherorac Surg 2014; 46: 517-592 [PMID: 25173601 DOI: 10.1093/ejcts/ezu366]

Montalescot G, Sideris G, Cohen R, Meuleman C, Bal dit Sollier C, Barthélémy O, Henry P, Pin L, Beygui F, Collet JP, Marshall D, Luo J, Petitjean H, Drouet L. Prasugrel compared with high-dose clopidogrel in acute coronary syndrome. The randomised, double-blind ACAPULCO study. Thromb Haemost 2010; 103: 213-223 [PMID: 20062936 DOI: 10.1160/TIH09-07-0482]

Tang Y, Zhang YC, Chen Y, Xiang Y. Efficacy and safety of canagrelor for patients with coronary artery disease: a meta-analysis of four randomized trials. Int J Clin Exp Med 2015; 8: 800-808 [PMID: 25785060]

FDA. FDA approves new antiplatelet drug used during heart surgery procedure. [accessed 2015 Jun 25]. Available from: URL: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm452172.htm

Angiolillo DJ, Firstenberg MS, Price MJ, Tummala PE, Hutyra M, Welsby IJ, Voeltz MD, Chandna H, Ramaiah C, Brtko M, Cannon AR, Oliphant CS, Yeh RW, Camenzind E, Steg PG, Wijns W, Mills J, Ariotti S, Costa F, Valgimigli M. Coronary stent selection and optimal course of dual antiplatelet therapy in patients at high bleeding or thrombotic risk: navigating between limited evidence and clinical concerns. Curr Opin Cardiol 2015; 30: 325-332 [PMID: 26049377 DOI: 10.1097/HOC.0000000000000185]

Feleras S, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, King SB, Negoita L, Liu M, de Paula JE, Mangione JA, Meireles GX, Castello HJ, Nicolela EL, Perin MA, Devito FS, Labrunie A, Salvadori D, Gusmão M, Stacca R, Costa JR, de Castro JP, Abizaid AS, Bhati DL. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. J Am Coll Cardiol 2013; 62: 2510-2522 [PMID: 24177257 DOI: 10.1016/j.jacc.2013.02.183]

Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 130: 2215-2245 [PMID: 25085962 DOI: 10.1161/CIR.0000000000000105]

Picner D, Mazur P, Hymczak H, Stolitaki J, Litwinowicz R, Drwila R, Undas A. Preoperative platelet aggregation predicts perioperative blood loss and rethoracotomy for bleeding in patients receiving dual antiplatelet treatment prior to coronary surgery. Thromb Res 2015; 136: 519-525 [PMID: 26003782 DOI: 10.1016/j.thromres.2015.04.037]

Quiroga S, Llorente E, Alfonso F, Trueba L, Gómez Menchero A, Bousquet J, Carrión X, Sánchez Recalde A, Alfonso F, Pérez de Prado A, López Palop R, Sanchis J, Diarte de Miguel JA, Jiménez Navarro M, Muñoz L, Ramírez Moreno A, Tizón Marcos H. Dual Antiplatelet Therapy for 6 Months vs 12 Months After New-generation Drug-eluting Stent Implantation: Matched Analysis of ESTROFA-DAPT and ESTROFA-2. Rev Esp Cardiol (Engl Ed) 2015; 68: 838-845 [PMID: 26072146 DOI: 10.1016/j.rec.2015.01.008]

Spencer FA, Prasad M, Vandvik PO, Chetan D, Zhou Q, Guyatt G. Longer- Versus Shorter-Duration Dual-Antiplatelet Therapy After Drug-Eluting Stent Placement: A Systematic Review and Meta-analysis. Am J Cardiol Med 2015; 163: 118-126 [PMID: 26005909 DOI: 10.7326/M15-0083]

Verdoya M, Schaffer A, Barbieri L, Montalescot G, Collet JP, Colombo A, Suryapranata H, De Luca G. Optimal Duration of Dual Antiplatelet Therapy After DES Implantation: A Meta-Analysis of 11 Randomized Trials. Angiology 2016; 67: 224-238 [PMID: 26690931 DOI: 10.1016/j.angio.2015.03.009]

Becker RC, Helmy T. Are at least 12 months of dual antiplatelet therapy needed for all patients with drug-eluting stents? Not all patients with drug-eluting stents need at least 12 months of dual antiplatelet therapy. Circulation 2015; 131: 2010-2019, discussion 2019 [PMID: 26034083 DOI: 10.1161/CIRCULATIONAHA.114.013281]

Breuer SJ. Are at least 12 months of dual antiplatelet therapy needed for all patients with drug-eluting stents? All patients with drug-eluting stents need at least 12 months of dual antiplatelet therapy. Circulation 2015; 131: 2001-2009, discussion 2009 [PMID: 26034082 DOI: 10.1161/CIRCULATIONAHA.114.013279]

Ariotti S, Costa F, Valgimigli M. Coronary stent selection and optimal course of dual antiplatelet therapy in patients at high bleeding or thrombotic risk: navigating between limited evidence and clinical concerns. Curr Opin Cardiol 2015; 30: 325-332 [PMID: 26049377 DOI: 10.1097/HOC.0000000000000185]

Abo-Salem E, Alsidawi S, Jamal H, Effat M, Helmy T. Optimal Duration of Dual Antiplatelet Therapy after Drug-Eluting Stents: Meta-Analysis of Randomized Trials. Cardiovasc Ther 2015; 33: 253-263 [PMID: 26010419 DOI: 10.1111/1755-5922.12137]

Colombo A, Chieffo A, Frasher A, Garbo R, Masotti-Centol M, Salvatella N, Otoe Dominguez JF, Siffianon L, Tarantini G, Presbiore P, Menozzi A, Pacci E, Mauri J, Cesana DM, Giustino G, Sardella G. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol 2014; 64: 2086-2097 [PMID: 25236346 DOI: 10.1016/j.jacc.2014.09.008]

Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, King SB, Negoita L, Liu M, de Paula JE, Mangione JA, Meireles GX, Castello HJ, Nicolela EL, Perin MA, Devito FS, Labrunie A, Salvadori D, Gusmão M, Stacca R, Costa JR, de Castro JP, Abizaid AS, Bhati DL. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. J Am Coll Cardiol 2013; 61: 2510-2522 [PMID: 24177257 DOI: 10.1016/j.jacc.2013.02.183]
Dalal A. Organ transplantation and drug eluting stents

Variability: Review of the Literature and Practical Considerations. J Pharm Pract 2016; 29: 26-34 [PMID: 26594741 DOI: 10.1177/0897900115615000]

Dohi T, Machara A, Witzumibicher B, Rinaldi MJ, Mazzaferrini EL, Duffy PL, Weiser G, Neumann FJ, Henry TD, Cox DA, Stucker TD, Brodie BR, Litherland C, Briner SJ, Kirtane AJ, Mintz GS, Stone GW. Etiology, Frequency, and Clinical Outcomes of Myocardial Infarction After Successful Drug-Eluting Stent Implantation: Two-Year Follow-Up From the ADAPT-DES Study. Circ Cardiovasc Interv 2015; 8: e002447 [PMID: 26543737 DOI: 10.1161/CIRCINTERVENTIONS.114.02447]

Agarwal S, Coakley M, Reddy K, Riddell A, Mallett S. Quantifying the effect of antplatelet therapy: a comparison of the platelet function analyzer (PFA-100) and modified thromboelastography (mTEG) with light transmission platelet aggregometry. Anesthesiology 2006; 105: 675-683 [PMID: 17006604 DOI: 10.1097/00000542-200610000-00011]

Kavisivathanan R, Abbassi-Ghadi N, Kumar S, Mackenize H, Thompson K, James K, Mallett SV. Risk of bleeding and adverse outcomes predicted by thromboelastography platelet mapping in patients taking clopidogrel within 7 days of non-cardiac surgery. Br J Surg 2014; 101: 1383-1390 [PMID: 25088505 DOI: 10.1002/bjs.9592]

Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinnmouth AT, Capocelli KE, Cipolle MD, Cohn CS, Fung MK, Grossman BJ, Mintz PD, O’Malley BA, Sosok-Pizzani DA, Shander A, Stack GE, Weber KE, Weinstein R, Weld B, Ghitman G, Wong EC, Tobian AA. Platelet transduction: a clinical practice guideline from the AABP. Ann Intern Med 2015; 162: 205-213 [PMID: 25383671 DOI: 10.7326/M14-1589]

O’Connor SA, Amour J, Mercadier A, Martin R, Kermes M, Aftab J, Brugier D, Silvain J, Barthélémy O, Leprince P, Montalescot G, Collet JP. Efficacy of ex vivo autologous and in vivo platelet transfusion in the reversal of P2Y12 inhibition by clopidogrel, prasugrel, and ticagrelor: the APPTITUDE study. Circ Cardiovasc Interv 2015; 8: e002786 [PMID: 26553698 DOI: 10.1161/CIRCINTERVENTIONS.115.002786]

Scharbert G, Wetzel L, Schrottmaier WC, Kral JB, Weber T, Assinger A. Comparison of patient intake of ticagrelor, prasugrel, and clopidogrel in restoring platelet function by donor platelets. Transfusion 2015; 55: 1320-1326 [PMID: 25641006 DOI: 10.1111/trf.12977]

Lhemuisser T, Baker NC, Waksman R. Overview of the 2014 Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee meeting regarding cangrelor. J Interv Cardiol 2015; 28: 415-419 [PMID: 26381736 DOI: 10.1111/jic.12229]

Waksman R, Kirtane AJ, Torguson R, Cohen DJ, Ryan T, Rääber A, Pomar F, Melgares R, Rivero F, Jiménez-Quevedo P, Gonzalo N, Fernández C, Macaya C. A Prospective Randomized Trial of Drug-Eluting Balloons Versus Everolimus-Eluting Stents in Patients With In-Stent Restenosis of Drug-Eluting Stents: The RIBS IV Randomized Clinical Trial. J Am Coll Cardiol 2015; 66: 23-33 [PMID: 26139004 DOI: 10.1016/j.jacc.2015.04.063]

Gabardi S, Barolleti SA. Everolimus: a proliferation signal inhibitor with clinical applications in organ transplantation, oncology, and cardiology. Pharmacotherapy 2010; 30: 1044-1056 [PMID: 20874042 DOI: 10.1592/phco.30.10.1044]

Mota FM, Araujo J, Arruda JA, Júnior HT, Pestana JO, de Sousa JM, Lima VC. Clinical outcome of renal transplant patients after coronary stenting. Ann Bras Cardiol 2007; 88: 521-524 [PMID: 17589625 DOI: 10.1590/S0004-27302007000500004]

Rodríguez-Perálvarez M, Pérez-Medrano I, Guerero-Misas M, González V, Poyato A, Barrera P, Ferrin G, Pozo JC, Sánchez-Frias M, Ciria R, Briceño J, Montero JL, De la Mata M. Everolimus is safe within the first month after liver transplantation. Transpl Immunol 2015; 33: 146-151 [PMID: 26392195 DOI: 10.1016/j.trijim.2015.09.002]

Lee MS, Cheng RK, Kandzari DE, Kirtane AJ. Long-term outcomes of heart transplantation recipients with transplant coronary artery disease who develop in-stent restenosis after percutaneous coronary intervention. Am J Cardiol 2012; 109: 1729-1732 [PMID: 22463319 DOI: 10.1016/j.amjcard.2012.02.014]

Azarbal B, Arbi T, Ramanuj R, Kittleson M, Young A, Czer L, Rafei M, Currier J, Makkar R, Kobashigawa J. Clinical and angiographic outcomes with everolimus eluting stents for the treatment of cardiac allograft vasculopathy. J Interv Cardiol 2014; 27: 73-79 [PMID: 24118198 DOI: 10.1111/jic.12071]

Lee MS, Yang T, Kandzari D, Malmud E, Liao H, Kirtane A. Long-term clinical outcomes in patients treated with drug-eluting compared to bare-metal stents for the treatment of transplant coronary artery disease. Catheter Cardiovasc Interv 2012; 80: 533-538 [PMID: 21953766 DOI: 10.1002/ccd.23379]

Abate MT, Kaur J, Suh H, Darras F, Mani A, Nord EP. The use of drug-eluting stents in the management of transplant renal artery stenosis. Am J Transplant 2011; 11: 2235-2241 [PMID: 21827621 DOI: 10.1111/j.1600-6143.2011.03652.x]

Dousi H, Shabir S, Lipkin G, Riley P. Drug-eluting stent insertion in the treatment of in-stent renal artery restenosis in three renal transplant recipients. J Vasc Interv Radiol 2008; 19: 1757-1760 [PMID: 18952465 DOI: 2014; 2014]

Anaya-Ayala JE, Loebe M, Davies MG. Endovascular management of early lung transplant-related anastomotic pulmonary artery stenosis. J Vasc Interv Radiol 2015; 26: 878-882 [PMID: 25851200 DOI: 10.1016/j.jvir.2015.02.017]

Dragulescu A, Ghez O, Quilici J, Fraisse A. Paclitaxel drug-eluting stent placement for pulmonary vein stenosis as a bridge to heart-lung transplantation. Pediatr Cardiol 2009; 30: 1169-1171 [PMID: 19705189 DOI: 10.1007/s00226-009-9511-5]

Villa A, Arnold R, Sánchez PL, Gimeno F, Ramos B, Cantero T, Fernández ME, Sanz R, Gutiérrez O, Mota P, García-Brade J, San Román JA, Fernández-Avilés F. Comparison of neonatal hyperplasia with drug-eluting stents versus bare metal stents in patients undergoing intracoronary bone-marrow mononuclear cell transplantation following acute myocardial infarction. Am J Cardiol 2009; 103: 1651-1656 [PMID: 19539071 DOI: 10.1016/j.amjcard.2009.02.011]

Le L, Terral W, Zea N, Bazan HA, Smith TA, Loss GE, Bluth E, Sternbergh WC. Primary stent placement for hepatic artery stenosis after liver transplantation. J Vasc Surg 2015; 62: 704-709 [PMID: 26054583 DOI: 2015.04.004]

Hüsing A, Reinecke H, Cinvicini VR, Beckebaum S, Wilms C, Schmidt HH, Kabinar I. Paclitaxel-eluting balloon dilation of biliary
Dalal A. Organ transplantation and drug eluting stents

anastomotic stricture after liver transplantation. *World J Gastroenterol* 2015; 21: 977-981 [PMID: 25624733 DOI: 10.3748/wjg.v21.i3.977]

Fujimori M, Yamakado K, Takaki H, Nakatsuka A, Uraki J, Yamanaka T, Hasegawa T, Sugino Y, Nakajima K, Matsushita N, Mizuno S, Sakuma H, Isaji S. Long-Term Results of Stent Placement in Patients with Outflow Block After Living-Donor-Liver Transplantation. *Cardiovasc Intervent Radiol* 2016; 39: 566-574 [PMID: 26464222 DOI: 10.1007/s00270-015-1210-4]

- Reviewer: De Ponti R, Falconi M, Petix NR
- Editor: Qiu S
- Editor: A
- Editor: Lu YJ

P- Reviewer: De Ponti R, Falconi M, Petix NR
S- Editor: Qiu S
L- Editor: A
E- Editor: Lu YJ
