Open Access

OBM Transplantation

Review

Update in the Use of Percutaneous Coronary Intervention for Cardiac Allograft Vasculopathy After Heart Transplantation

Richard Cheng [1], Jon Kobashigawa [1, 2, *]

1. Cedars-Sinai Smidt Heart Institute, Los Angeles, California, USA; E-Mails: Richard.Cheng2@cshs.org; Kobashigawaj@cshs.org
2. 127 S. San Vicente Blvd, Third Floor Cardiology A3107, Los Angeles, CA 90048, USA

* **Correspondence:** Jon Kobashigawa; E-Mail: Kobashigawaj@cshs.org

Academic Editor: Yasuhiko Sugawara

Special Issue: Perspectives on Heart Transplantation

OBM Transplantation
2019, volume 3, issue 2
doi:10.21926/obm.transplant.1902061

Received: January 23, 2019
Accepted: April 01, 2019
Published: April 09, 2019

Abstract

Cardiac allograft vasculopathy (CAV) limits long-term survival after heart transplantation. CAV with discrete or tubular lesions can be treated with percutaneous coronary intervention (PCI) with high procedural success. Revascularization with balloon angioplasty, bare-metal stents, and first-generation drug-eluting stents has been associated with high and unacceptable restenosis rates. However, second-generation drug-eluting stents are associated with favorable stent and lesion patency. Stent and lesion patency now closely resemble the expected rates in their use in non-transplant CAD. A PCI strategy with routine follow-up surveillance angiography is associated with favorable survival, and should be considered established therapy especially in patients who are ineligible for re-transplantation. Drug-coated balloons may offer an alternative revascularization option and require a shorter duration of dual anti-platelet therapy. Randomized data is needed to determine who to treat, when to treat, and with what to treat CAV after heart transplantation, and the optimal duration of dual anti-platelet therapy.

Keywords
CAV; cardiac transplantation; PCI; DES; revascularization; CAD

1. Perspectives on Heart Transplantation

Orthotopic heart transplantation (OHT) remains the therapy of choice for select patients with end-stage heart failure. While median graft survival is well beyond a decade, factors such as malignancy, chronic graft dysfunction, and cardiac allograft vasculopathy (CAV) continue to limit long-term survival. CAV is also known as transplant coronary artery disease (CAD) and shares little with native CAD in morphology or pathophysiology. CAV unlike CAD is a diffuse disease involving not only the epicardial vessels, but also the microvasculature. It is characterized by concentric intimal hyperplasia with minimal calcification, and while it can have discrete or tubular lesions, it is often associated with distal arteriopathy, resulting in both proximal and distal segments being equally affected. There is usually poor or no collateral supply and an absence of compensatory arterial remodeling. Most importantly the process is primarily immunologically driven and often rapidly progressive [1-3].

CAV is diagnosed angiographically and described, according to the International Society for Heart and Lung Transplantation (ISHLT) CAV grading scale (Table 1), after resting vasospasm is excluded, as mild, moderate or severe based on severity and distribution of stenoses, as well as presence of allograft dysfunction [3]. Ischemia-reperfusion, immunologic, and infectious insults promote chronic endothelial cell injury and inflammation leading to a form of coronary vasculitis with diffuse concentric fibrous intimal thickening [3]. As angiographic diagnosis lags behind disease, adjunct intravascular ultrasonography (IVUS) can be used to assess for early intimal thickening. The rapid progression of ≥0.5 mm intimal thickening in the first year after transplantation is associated with downstream mortality, non-fatal major adverse cardiac events, and development of angiographic CAV [4]. More recently evidence has emerged for the use of optical coherence tomography to detect layered fibrotic plaque and bright spots, which are strongly associated with downstream CAV progression. These intravascular findings may represent the presence of organized and repeated mural arterial thrombosis and chronic vascular rejection [5, 6]. Further studies are needed to investigate the use of intravascular imaging in the identification and tailoring of therapies to patients at highest risk of CAV.

CAV can exhibit morphological subtypes of discrete or tubular lesions (type A), which angiographic appear similar to non-transplant CAD, diffuse concentric narrowing (type B), with sharp tapering (type B1) or gradual tapering (type B2), and irregularly narrowed vessels with occluded branches and distal obliteration (type C) as illustrated in Figure 1 [1]. The latter types of CAV are associated with worse prognosis [3, 7]. CAV typically has poor or no collateral supply, and when occluded is equally likely to be occluded in a proximal segment as a distal segment [1]. The compensatory arterial remodeling seen in non-transplant CAD (Glagov's phenomenon) is impaired in CAV by a fibrous infiltration of the media and adventitia [2].

Table 1 International Society for Heart and Lung Transplantation recommended nomenclature for cardiac allograft vasculopathy.

ISHLT CAV Grade	Definition
CAV 0 (Not significant)	No detectable angiographic lesion
CAV 1 (Mild)	Angiographic left main (LM) <50%, or primary vessel with maximum lesion of <70%, or any branch stenosis < 70% (including diffuse narrowing) without allograft dysfunction
CAV 2 (Moderate)	Angiographic LM <50%; a single primary vessel ≥70%, or isolated branch stenosis ≥70% in branches of 2 systems, without allograft dysfunction
CAV 3	Angiographic LM ≥50%, or two or more primary vessels ≥70% stenosis, or isolated branch stenosis ≥70% in all 3 systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF ≤45% usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific; see text for definitions)

Definitions

a). A "Primary Vessel" denotes the proximal and Middle 33% of the left anterior descending artery, the left circumflex, the ramus and the dominant or co-dominant right coronary artery with the posterior descending and posterolateral branches.

b). A "Secondary Branch Vessel" includes the distal 33% of the primary vessels or any segment within a large septal perforator, diagonals and obtuse marginal branches or any portion of a non-dominant right coronary artery.

c). Restrictive cardiac allograft physiology is defined as symptomatic heart failure with echocardiographic E to A velocity ratio >2 (>1.5 in children), shortened isovolumetric relaxation time (<60 msec), shortened deceleration time (<150 msec), or restrictive hemodynamic values (Right Atrial Pressure >12mmHg, Pulmonary Capillary Wedge Pressure >25 mmHg, Cardiac Index <2 l/min/m2)

Adapted from Mehra, et al [3].

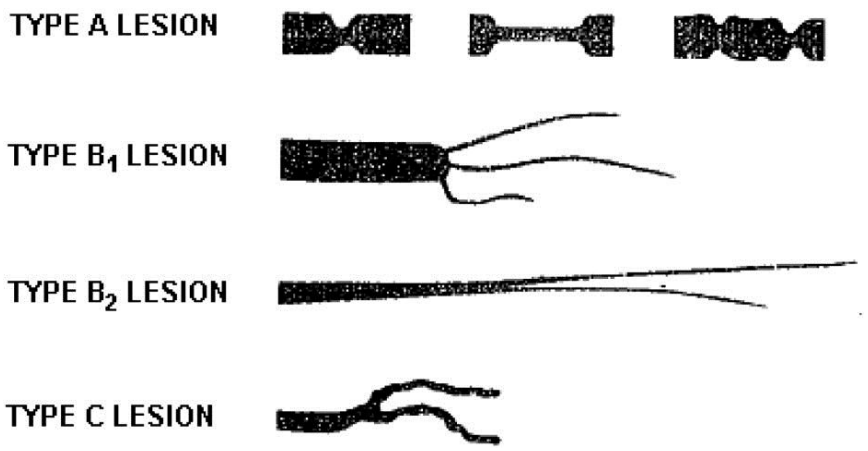


Figure 1 Stanford classification of anatomic abnormalities in transplant coronary vascular disease [1].

The treatment of CAV is not adequate and therefore centers on primary prevention and traditional risk factor modification including treatment of diabetes, hypertension and hyperlipidemia. Statin therapy by their lipid-lowering and pleotropic effects decreases development of CAV and overall mortality [8]. Treatment of immune factors might also slow the development of CAV and include management of HLA antibodies, and prevention and treatment of CMV infections and allograft rejection. The use of certain antiproliferative immunosuppression drugs such as mycophenolate mofetil and proliferation signal inhibitors (PSI) such as sirolimus and everolimus have been reported to reduce first-year intimal thickening in *de novo* heart transplants [9-11]. In addition, early intensification of immunosuppression known as induction therapy with anti-thymocyte globulin [12], and maintenance of an increased level of immunosuppression are associated with reduced first-year intimal thickening [13]. After development of CAV, PSI drugs have been shown to slow the progression of this disease [14, 15]. The only definitive treatment is re-transplantation especially in the presence of distal arteriopathy (types B and C morphologies) for which no revascularization options are available [7].

Type A focal or tubular CAV is amenable to revascularization with percutaneous coronary intervention (PCI) [1]. While there is no randomized data for the use of PCI for CAV after heart transplantation, there has been a large clinical experience at multiple centers supporting its feasibility. Various studies have demonstrated clinical benefit in stent and lesion patency as well as overall allograft survival [16-20]. As an aside, experience with surgical revascularization for CAV is poor with perioperative mortality approximating 30% due to the diffuse nature of this disease. Thus, coronary artery bypass surgery has been largely abandoned for CAV [7].

2. Early Experience with Percutaneous Coronary Intervention: Balloon Angioplasty and Bare Metal Stents

Early experience with balloon angioplasty demonstrated feasibility of percutaneous revascularization, with angiographic success approximating 90% in reducing lesion stenosis to ≤50%. However, restenosis occurred in 55% of lesions at 8 months in a multicenter registry. Patients with distal arteriopathy had significantly lower survival and increased need for repeat revascularization, and overall survival was only 61% at 19 months [7]. Despite increased experience with angioplasty, restenosis rates remained high occurring in 53%-72% of lesions at 8-12 months [21, 22], worse than the expected restenosis rates in the use of angioplasty in native CAD which approximates 30% at 1-yr. With the advent of bare metal stents (BMS), PCI in CAV saw reduced restenosis rates [21, 23]. Early experience with BMS resulted in angiographic restenosis of 44% at 4.6 months [23]. with more contemporary cohorts demonstrating 1-yr angiographic restenosis rates of 22%-49% [18, 19, 21, 22, 24]. Clopidogrel and statin use were found to be higher in patients without restenosis,[22] an association replicated in a mixed balloon angioplasty and BMS cohort [25]. Higher doses of immunosuppression were also associated with less restenosis [21]. However, as compared with clinically-driven target lesion revascularization (TLR) in native CAD [26], lesion failure remained high in CAV despite the use of BMS. However, it is important to note that restenosis rates in CAV cohorts may appear higher due to frequent use of annual surveillance angiography. These annual studies are performed as the donor heart is denervated and there are no anginal symptoms of CAV post-transplantation. In native CAD, patients having had PCI undergo angiographic follow-up only when clinically indicated, thus

restenosis rates can be 3 times lower than those found in transplant patients with PCI who undergo routine annual surveillance angiography [26].

3. Controversy in Remote Lesion Progression in Patients with in-Stent Restenosis

Despite improved angiographic results, there continues to be controversy on the impact of PCI on clinical outcomes. In fact, some investigators have concern about harm from PCI. To that point, one study of 25 patients who received BMS for treatment of CAV found that those who developed in-stent restenosis had increased late lumen loss in non-stented reference lesions as compared with patients without in-stent restenosis. This led to the concern that stenting may incite inflammation of non-stented lesions, and may in fact be detrimental [27].

4. First-Generation Drug-Eluting Stents: Paclitaxel- and Sirolimus-Eluting Stents

Drug-eluting stents (DES) are stents with polymer coated metallic scaffolds, and initial iterations eluted paclitaxel and sirolimus to prevent intimal growth and reduce restenosis rates. As a PSI, sirolimus-eluting stents seemed a natural fit for percutaneous revascularization for CAV. Afterall, systemic PSI attenuates CAV development. Early and contemporary experience with the use of first-generation DES were indeed generally associated with less in-stent restenosis than with the use of BMS [19, 28], with recent cohorts demonstrating angiographic 1-yr in-stent restenosis rates of 12.5-16% [18, 20]. However, restenosis rates still remained higher when contrasted to the use of first-generation DES in native CAD. In fact, some cohorts have demonstrated no differences in long-term lesion patency between DES and BMS, suggesting a catch-up phenomenon [24, 28]. The initial experience with the use of first-generation DES for CAV has therefore tempered the excitement for percutaneous revascularization for CAV after heart transplantation.

5. Second-Generation Drug-Eluting Stents

Second generation everolimus or zotarolimus-eluting DES have consistently demonstrated improved clinical and angiographic outcomes as compared with first generation DES [10, 29]. Our center's early experience with the use of everolimus-eluting stents in 21 heart transplant patients and 34 CAV lesions was associated with binary restenosis and TLR of 5% and 6%, respectively, at one year, lower rates than previously reported with the use of first-generation DES.[30] Our updated experience of 48 patients and 113 lesions demonstrate 1 and 3-yr in-stent restenosis rates approximating 3% and 10%, respectively [17]. comparable to the use of everolimus-eluting DES in native CAD with 1 and 3-yr target lesion failure rates of 4% and 9% [29]. It is not clear why first-generation DES did not share the same success as second-generation DES but differences in eluted drug, polymer, and thickness and material of metallic scaffold may be to blame. With device iterations in drug, polymer, and stent-design, the gap in stent patency rates between CAV and native CAD has narrowed significantly. PCI is now not only feasible with high procedural success, but is also increasingly associated with reliable mid-to-long term angiographic outcomes. In a cohort with severe CAV with index PCI at 9.4 years after transplantation, a revascularization strategy utilizing second-generation DES was associated with, remarkably, 1, 3, and 5-yr survival of 93.2±3.3%, 82.4±5.1%, and 68.0±7.4%, which are comparable to the general heart transplant

population [16]. With advent of "third" generation drug-eluting stents with biodegradable polymers and novel polymer-free designs, stent and lesion patency may finally be equivalent to that of their use in native CAD. As a field we have come a long way indeed.

6. Future Directions: Intracoronary Physiology and Intravascular Ultrasound

While IVUS is well studied in the transplanted heart to assess intimal thickening as a predictor of clinical and angiographic outcomes, its use is not established in guiding PCI for CAV after heart transplantation. In fact, its utility in native CAD has been under intense debate until recently. Two large trials randomizing patients to IVUS-guided PCI versus conventional PCI demonstrated IVUS guidance resulted in 50% reductions in MACE driven by reductions in TLR and stent thrombosis [31, 32]. Our center has found a similar relationship in the use of IVUS in PCI for CAV after heart transplantation.[33] Further investigations are warranted.

7. Future Directions: Drug-Coated Balloons and Need for Randomized Data

Several questions remain unanswered regarding the optimal modality for revascularization. Second-generation DES are associated with acceptable rates of lesion patency. Will there be a role for drug-eluting stents with biodegradable polymers and novel polymer-free designs? Will there be a role for drug-coated balloons either to replace the use of DES in the treatment of CAV or to be used to treat intermediate severity lesions which are risk to progress? What is the optimal duration of dual anti-platelet therapy after development of CAV, and can it be used to stabilize non-stented lesions? Currently, drug-coated balloons seem to be a natural fit for revascularization of CAV after heart transplantation due to the diffuse nature of CAV and the frequent involvement of smaller distal vessels. Until recently, drug-coated balloons have only been found to be efficacious for treatment of in-stent restenosis, being as good at preventing TLR as compared with re-stenting with a DES [34], but data is emerging for their use in *de novo* lesions as well. Sirolimus drug-coated balloons are also being developed. With ongoing advances in intracoronary physiology, intravascular imaging, and percutaneous treatment modalities, randomized data is needed to determine the who to treat, when to treat, and with what to treat CAV after heart transplantation, and the optimal duration of dual anti-platelet therapy.

8. Summary

While re-transplantation remains the definitive treatment for severe and rapidly progressive CAV, for patients with focal or tubular lesions, PCI is associated with high procedural success. The use of second-generation DES is associated with favorable stent and lesion patency and now closely resemble the expected rates in their use in native CAD. A PCI strategy with routine follow-up surveillance angiography is associated with favorable survival, and should be considered established therapy especially in patients who are ineligible for re-transplantation. Drug-coated balloons may offer an alternative revascularization option and require a shorter duration of dual anti-platelet therapy.

Acknowledgments

The authors have no specific acknowledges for this work.

Author Contributions

R.C. performed the literature search. Both R.C. and J.K. contributed to the writing of the draft and final versions of the manuscript. J.K. supervised the project and approved the final version.

Funding

The authors received no specific funding for this work.

Competing Interests

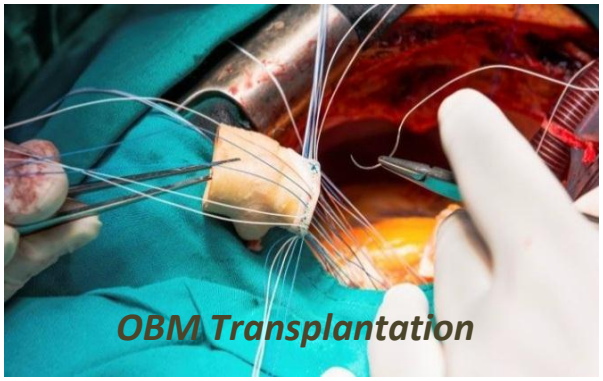
The authors have declared that no competing interests exist.

References

1. Gao SZ, Alderman EL, Schroeder JS, Silverman JF, Hunt SA. Accelerated coronary vascular disease in the heart transplant patient: coronary arteriographic findings. J Am Coll Cardiol. 1988; 12: 334-340.
2. Kobashigawa J, Wener L, Johnson J, Currier JW, Yeatman L, Cassem J, et al. Longitudinal study of vascular remodeling in coronary arteries after heart transplantation. J Heart Lung Transplant. 2000; 19: 546-550.
3. Mehra MR, Crespo-Leiro MG, Dipchand A, Ensminger SM, Hiemann NE, Kobashigawa JA, et al. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. J Heart Lung Transplant. 2010; 29: 717-727.
4. Kobashigawa JA, Tobis JM, Starling RC, Tuzcu EM, Smith AL, Valantine HA, et al. Multicenter intravascular ultrasound validation study among heart transplant recipients: outcomes after five years. J Am Coll Cardiol. 2005; 45: 1532-1537.
5. Baran DA. shedding light on cardiac allograft vasculopathy: OCT to predict progression of disease. JACC Cardiovasc Imaging. 2017; 10: 785-786.
6. Clemmensen TS, Holm NR, Eiskjaer H, Logstrup BB, Christiansen EH, Dijkstra J, et al. Layered fibrotic plaques are the predominant component in cardiac allograft vasculopathy: systematic findings and risk stratification by OCT. JACC Cardiovasc Imaging. 2017; 10: 773-784.
7. Halle AA, 3rd, DiSciascio G, Massin EK, Wilson RF, Johnson MR, Sullivan HJ, et al. Coronary angioplasty, atherectomy and bypass surgery in cardiac transplant recipients. J Am Coll Cardiol. 1995; 26: 120-128.
8. Kobashigawa JA, Moriguchi JD, Laks H, Wener L, Hage A, Hamilton MA, et al. Ten-year follow-up of a randomized trial of pravastatin in heart transplant patients. J Heart Lung Transplant. 2005; 24: 1736-1740.
9. Kobashigawa JA, Tobis JM, Mentzer RM, Valantine HA, Bourge RC, Mehra MR, et al. Mycophenolate mofetil reduces intimal thickness by intravascular ultrasound after heart transplant: reanalysis of the multicenter trial. Am J Transplant. 2006; 6: 993-997.
10. Eisen HJ, Kobashigawa J, Starling RC, Pauly DF, Kfoury A, Ross H, et al. Everolimus versus mycophenolate mofetil in heart transplantation: a randomized, multicenter trial. Am J Transplant. 2013; 13: 1203-1216.

11. Kobashigawa JA, Pauly DF, Starling RC, Eisen H, Ross H, Wang SS, et al. Cardiac allograft vasculopathy by intravascular ultrasound in heart transplant patients: substudy from the Everolimus versus mycophenolate mofetil randomized, multicenter trial. JACC Heart failure. 2013; 1: 389-399.
12. Azarbal B, Cheng R, Vanichsarn C, Patel JK, Czer LS, Chang DH, et al. Induction therapy with antithymocyte globulin in patients undergoing cardiac transplantation is associated with decreased coronary plaque progression as assessed by intravascular ultrasound. Circ Heart Fail. 2016; 9: e002252.
13. Cheng R, Azarbal B, Yung A, Chang DH, Patel JK, Kobashigawa JA. Elevated immune monitoring early after cardiac transplantation is associated with increased plaque progression by intravascular ultrasound. Clin Transplant. 2015; 29: 103-109.
14. Mancini D, Pinney S, Burkhoff D, LaManca J, Itescu S, Burke E, et al. Use of rapamycin slows progression of cardiac transplantation vasculopathy. Circulation. 2003; 108: 48-53.
15. Raichlin E, Bae JH, Khalpey Z, Edwards BS, Kremers WK, Clavell AL, et al. Conversion to sirolimus as primary immunosuppression attenuates the progression of allograft vasculopathy after cardiac transplantation. Circulation. 2007; 116: 2726-2733.
16. Cheng R, Kransdorf E, Chang D, Patel J, Kobashigawa J, Azarbal B. TCT-401 a strategy of percutaneous coronary intervention with drug-eluting stents for the treatment of cardiac allograft vasculopathy may normalize survival. J Am Coll Cardiol. 2018; 72: B162.
17. Cheng R, Vanichsarn C, Patel JK, Currier J, Chang DH, Kittleson MM, et al. Long-term clinical and angiographic outcomes of percutanenous coronary intervention with everolimus-eluting stents for the treatment of cardiac allograft vasculopathy. Catheter Cardiovasc. 2017; 90: 48-55.
18. Colombo P, Bruschi G, Sacco A, Oreglia J, De Marco F, Colombo T, et al. Percutaneous coronary interventions in cardiac allograft vasculopathy: a single-center experience. Transplant Proc. 2010; 42: 1286-1290.
19. Gupta A, Mancini D, Kirtane AJ, Kaple RK, Apfelbaum MA, Kodali SK, et al. Value of drug-eluting stents in cardiac transplant recipients. J Am Coll Cardiol. 2009; 103: 659-662.
20. Lee MS, Tarantini G, Xhaxho J, Yang T, Ehdaie A, Bhatia R, et al. Sirolimus- versus paclitaxel-eluting stents for the treatment of cardiac allograft vasculopathy. JACC Cardiovasc Interv. 2010; 3: 378-382.
21. Benza RL, Zoghbi GJ, Tallaj J, Brown R, Kirklin JK, Hubbard M, et al. Palliation of allograft vasculopathy with transluminal angioplasty: a decade of experience. J Am Coll Cardiol. 2004; 43: 1973-1981.
22. Simpson L, Lee EK, Hott BJ, Vega DJ, Book WM. Long-term results of angioplasty vs stenting in cardiac transplant recipients with allograft vasculopathy. J Heart Lung Transplant. 2005; 24: 1211-1217.
23. Wong PM, Piamsomboon C, Mathur A, Chastain HD, 2nd, Singh DJ, Liu MW, et al. Efficacy of coronary stenting in the management of cardiac allograft vasculopathy. J Am Coll Cardiol 1998; 82: 239-241.
24. Reddy PR, Gulati A, Steen L, Sinacore J, Leya F, Heroux A. Outcomes of bare metal versus drug-eluting stents in allograft vasculopathy. J Heart Lung Transplant. 2008; 27: 1222-1228.

25. Wellnhofer E, Hiemann NE, Hug J, Dreysse S, Knosalla C, Graf K, et al. A decade of percutaneous coronary interventions in cardiac transplant recipients: a monocentric study in 160 patients. J Heart Lung Transplant. 2008; 27: 17-25.
26. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007; 115: 2344-2351.
27. Jonas M, Fang JC, Wang JC, Giri S, Elian D, Har-Zahav Y, et al. In-stent restenosis and remote coronary lesion progression are coupled in cardiac transplant vasculopathy but not in native coronary artery disease. J Am Coll Cardiol. 2006; 48: 453-461.
28. Nfor T, Ansaarie I, Gupta A, Bajwa T, Allaqaband S. Comparing long-term outcomes between drug-eluting and bare-metal stents in the treatment of cardiac allograft vasculopathy. Catheter Cardiovasc Interv. 2009; 74: 543-549.
29. Dangas GD, Serruys PW, Kereiakes DJ, Hermiller J, Rizvi A, Newman W, et al. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions). JACC Cardiovasc Interv. 2013; 6: 914-922.
30. Azarbal B, Arbit B, Ramaraj R, Kittleson M, Young A, Czer L, et al. Clinical and angiographic outcomes with everolimus eluting stents for the treatment of cardiac allograft vasculopathy. J Interv Cardiol. 2014; 27: 73-79.
31. Zhang J, Gao X, Kan J, Ge Z, Han L, Lu S, et al. Intravascular Ultrasound Versus Angiography-Guided Drug-Eluting Stent Implantation: The ULTIMATE Trial. J Am Coll Cardiol. 2018; 72: 3126-3137.
32. Hong SJ, Kim BK, Shin DH, Nam CM, Kim JS, Ko YG, et al. Effect of Intravascular Ultrasound-Guided vs Angiography-Guided Everolimus-Eluting Stent Implantation: The IVUS-XPL Randomized Clinical Trial. Jama. 2015; 314: 2155-2163.
33. Cheng R, Geft D, Krandrof E, Patel J, Kobashigawa J, Azarbal B. TCT-634 percutaneous coronary intervention with drug-eluting stents for the treatment of cardiac allograft vasculopathy and the impact of intravascular ultrasound and stent characteristics on lesion patency: 4-year outcomes. J Am Coll Cardiol. 2018; 72: B253.
34. Lee JM, Park J, Kang J, Jeon KH, Jung JH, Lee SE, et al. Comparison among drug-eluting balloon, drug-eluting stent, and plain balloon angioplasty for the treatment of in-stent restenosis: a network meta-analysis of 11 randomized, controlled trials. JACC Cardiovasc Interv. 2015; 8: 382-394.



Enjoy *OBM Transplantation* by:

1. Submitting a manuscript
2. Joining in volunteer reviewer bank
3. Joining Editorial Board
4. Guest editing a special issue

For more details, please visit:
http://www.lidsen.com/journals/transplantation