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Everolimus-Eluting Second-Generation Stents for Treatment of *De Novo* Lesions in Patients with Cardiac Allograft Vasculopathy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDE 1 **Łukasz Pyka**
ADE 1 **Michał Hawranek**
EFG 1 **Bożena Szyguła-Jurkiewicz**
BC 1 **Piotr Desperak**
BF 1 **Wioletta Szczurek**
EG 1 **Andrzej Lekston**
AEG 1 **Mariusz Gąsior**
BF 2 **Michał O. Zembala**
F 2 **Szymon Pawlak**
FG 2 **Marian Zembala**
AE 3,4 **Piotr Przybyłowski**

1 Third Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
2 Department of Cardiac, Vascular and Endovascular Surgery and Transplantology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
3 Silesian Center for Heart Diseases, Zabrze, Poland
4 First Department of General Surgery, Jagiellonian University, Medical College, Cracow, Poland

Corresponding Author: Łukasz Pyka, e-mail: l.t.pyka@gmail.com
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Background: Cardiac allograft vasculopathy is a major cause of cardiac allograft rejection. Percutaneous coronary intervention has become the main form of treatment of significant focal lesions. Despite the significance of the problem, data remain scarce. With a large population of transplant recipients undergoing coronary angiography at our center, we decided to analyze the implications of the use of everolimus-eluting second-generation stents by performing 6-month clinical and angiographic follow-up.





Material/Methods: From December 2012 and August 2019, 319 patients after heart transplantation undergoing coronary angiography at our institution were analyzed. Subsequently, 22 patients underwent *de novo* angioplasty with second-generation everolimus-eluting stents. The primary study endpoint was angiographic restenosis as evaluated by quantitative coronary angiography. Secondary outcomes included binary restenosis, target lesion revascularization, and cardiac death during the follow-up period (6 months).

Results: Patient comorbidities included hypertension (77.3%), type 2 diabetes mellitus (68.2%), dyslipidemia (68.2%), and obesity (31.8%). Primary success was obtained in all of the treated lesions. The analysis of quantitative coronary angiography after 6-month follow-up revealed low late lumen loss (0.22 ± 0.40). Significant restenosis was observed in 1 of the cases. There were no deaths in the 6-month observation period.

Conclusions: In the analyzed population, invasive strategy with second-generation everolimus-eluting stents for *de novo* lesions in cardiac allograft vasculopathy resulted in a low rate of binary restenosis, low late lumen loss, and no deaths during the 6-month follow-up.

MeSH Keywords: Coronary Artery Disease • Drug-Eluting Stents • Transplantation Tolerance

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Background

Cardiac allograft vasculopathy (CAV) remains one of the most important causes of cardiac allograft rejection. The pathologic characteristics of CAV show a broad spectrum of abnormalities that often differ from coronary disease of native arteries [1]. CAV is most commonly associated with diffuse concentric intimal thickening that starts in distal small vessels, involving both epicardial and intramyocardial coronary vessels of the allograft.

The pathogenesis of CAV is thought to be a consequence of immune and nonimmune processes, and treatment strategies need to address the complex etiology as well as the progressive nature of the disease [1]. Optimizing strategies for prevention, diagnosis, and treatment of CAV constitute a major challenge. Treatment modalities for advanced CAV are limited. They focus on modification of risk factors, use of statins, and intensification of immunosuppression in order to prevent the development of angiographically significant CAV.

The first-choice CAV treatment is immunosuppression. The proliferation signal inhibitors, such as everolimus and sirolimus, are potent agents that inhibit cellular proliferation, stimulated in response to alloantigens. Replantation is the only available state-of-the-art treatment for diffuse CAV, although it is associated with increased sensitization and higher mortality rates compared to the initial transplantation. It is also vastly limited by the shortage of donor organs. Due to technical challenges and poor outcomes, coronary artery bypass grafting is rarely performed [2]. Percutaneous coronary intervention (PCI) appears to be an attractive alternative for select patients with focal CAV, but its value in diffuse disease is not well established. Moreover, the use of balloon angioplasty and implantation of bare metal stents (BMS) provide insufficient results. The total number of restenoses is high, and occurrence of graft dysfunction has been reported [3]. Results of initial analyses assessing first-generation drug-eluting stents (DES) showed significantly less restenosis in comparison to BMS. However, stent patency remained significantly worse than what would be expected in PCI of native coronary arteries [4].

Studies assessing second-generation everolimus-eluting stents have generally provided improved results in comparison to the previously available technology. The occurrence of restenosis, target lesion failure, repeat revascularization, and major adverse cardiac events were significantly lower, while no impact on survival was observed [5,6]. These outcomes have not been unequivocally confirmed in studies on CAV patients. Data on the efficacy of second-generation DES in CAV remain limited.

With a large cohort of post-transplant patients at our disposal, we decided to analyze the impact of everolimus-eluting second-generation stents (EES) in heart transplant recipients

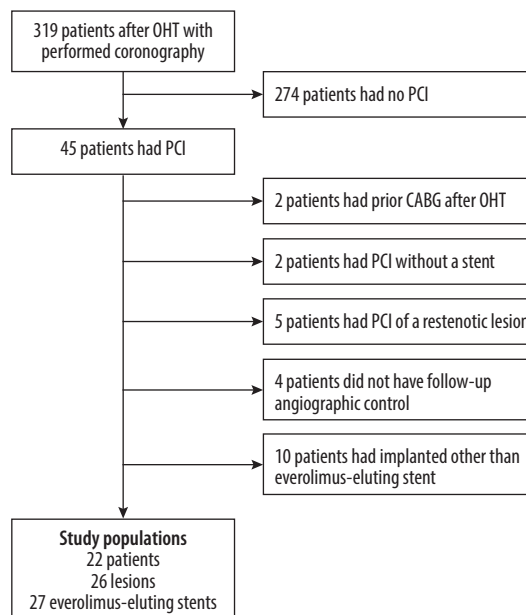


Figure 1. Study flow chart.

for the treatment of CAV on 6-month angiographic and clinical follow-up.

Material and Methods

From December 2012 and August 2019, 319 patients after heart transplantation undergoing coronary angiography at our institution were analyzed. In the study period, 45 patients underwent PCI. Patients who had balloon angioplasty of a restenotic lesion or in a previously treated vessel, who had other stents implanted than second-generation EES, patients post-CABG after heart transplantation, as well as those with no angiographic control, were excluded from further analysis, leaving 22 patients in the analyzed cohort. The study flow-chart is presented in Figure 1.

PCI procedures were performed according to the standard local practice. Patients were routinely administered unfractionated heparin with a target activated clotting time of 250–300 s. Intracoronary nitroglycerin (100–200 mg) was used for prevention of vasospasm. Initial and follow-up angiography was performed with the same projections. After the procedures, quantitative coronary analysis (QCA) was performed by 2 independent specialized physicians. QCA calibration was performed using the guiding catheter. The parameters assessed in the study included: minimal lumen diameter, reference vessel diameter, percent diameter stenosis, and late lumen loss.

Table 1. Baseline characteristics of the study population.

| Parameter | Study population N=22 | | Parameter | Study population N=22 | |
|-------------------------------------------|--------------------------|-----------|----------------------------------------------------------|--------------------------|-------------|
| Time from heart transplant to PCI (years) | 9.7±4.54 | | Previous PAD, n/N (%) | 3/22 | (13.6) |
| Age, years, median (Q1–Q3) | 58 | (50–66) | Chronic kidney disease, n/N (%) | 10/22 | (45.5) |
| Male sex, n/N (%) | 17/22 | (77.3) | Hyperthyroidism, n/N (%) | 5/22 | (22.7) |
| BMI, kg/m ² , median (Q1–Q3) | 28 | (24–32) | Hypothyroidism, n/N (%) | 2/22 | (9.1) |
| Weight, kg, median (Q1–Q3) | 175 | (164–178) | SBP, mmHg, median (Q1–Q3) | 123 | (117–130) |
| Height, m, median (Q1–Q3) | 85 | (71–91) | DBP, mmHg, median (Q1–Q3) | 80 | (74–84) |
| Cause of OHT | | | Creatinine, μmol/L, median (Q1–Q3) | 117 | (96–137) |
| Coronary artery disease, n/N (%) | 14/22 | (63.6) | Hemoglobin, mmol/L, median (Q1–Q3) | 8.6 | (7.7–9.3) |
| Dilated cardiomyopathy, n/N (%) | 7/22 | (31.8) | Hematocrit, %, median (Q1–Q3) | 41 | (37–44) |
| Others, n/N (%) | 1/22 | (4.5) | Red blood cells, 10 ⁹ /mL, median (Q1–Q3) | 4.6 | (4.4–5.2) |
| Cardiovascular risk factors | | | White blood cells, 10 ³ /mL, median (Q1–Q3) | 6.3 | (4.7–7.6) |
| Arterial hypertension, n/N (%) | 17/22 | (77.3) | Platelets, 10 ⁶ /mL, median (Q1–Q3) | 189 | (156–248) |
| Hypercholesterolemia, n/N (%) | 15/22 | (68.2) | Serum tacrolimus level, ng/mL, median (Q1–Q3) | 6.7 | (5.5–7.8) |
| Diabetes mellitus, n/N (%) | 15/22 | (68.2) | Serum mycophenolate mofetil level, ng/mL, median (Q1–Q3) | 1.64 | (1.29–1.76) |
| Obesity, n/N (%) | 7/22 | (31.8) | Serum everolimus level, ng/mL, median (Q1–Q3) | 5.7 | (5.3–6.7) |
| Previous PCI after OHT, n/N (%) | 11/22 | (50.0) | LVEF, %, median (Q1–Q3) | 54 | (53–55) |
| Previous stroke, n/N (%) | 2/22 | (9.1) | | | |

BMI – body mass index; CABG – coronary artery bypass grafting; DBP – diastolic blood pressure; LVEF – left ventricular ejection fraction; MI – myocardial infarction; OHT – orthotopic heart transplant; PAD – peripheral artery disease; PCI – percutaneous coronary intervention; Q1–Q3 – quartile 1 and 3; SBP – systolic blood pressure.

The primary endpoint of the study was the occurrence of angiographically significant restenosis evaluated by quantitative coronary angiography (QCA). Secondary outcomes included: binary restenosis, target lesion revascularization (TLR), and cardiac death after a 6-month follow-up period. The standard endpoint definitions were utilized for this study. Binary restenosis was defined as a late lumen loss of at least 50%. TLR was defined as planned or emergent PCI of the previously treated lesion, including a region of 5 mm before and after the implanted stent. All deaths were considered cardiac unless a definite non-cardiac cause could be established. Clinical, angiographic, procedural, and mortality data were obtained retrospectively using a web-based reporting system. Patients were observed for a period of 6 months after the initial procedure. Surveillance angiography and quantitative coronary analysis were routinely performed at 6 months after index hospitalization, as per standard protocol at our center. Additional information was obtained by telephone contact or from medical records, if necessary.

This study was approved by Ethics Committee of the Medical University of Silesia and was conducted according to the principles outlined in the Declaration of Helsinki. All patients provided written informed consent.

Results

We assessed 22 consecutive patients with International Society of Heart and Lung Transplantation moderate (left main <50%; a single main vessel ≥70% or branch stenosis ≥70% in 2 separate coronary systems) or severe CAV (left main ≥50% or ≥2 major vessels ≥70% stenosis, or side-branch stenosis ≥70% in all 3 coronary systems) [1]. In all of the patients, PCI of *de novo* lesions with second-generation everolimus-eluting stents was performed (Xience, Abbot Vascular, Santa Clara, CA, USA) between December 2012 and August 2019 at the Silesian Center for Heart Diseases.

Table 2. Procedural characteristics of study population.

| Parameter | Study population N=22 | Parameter | Study population N=22 |
|-------------------------------------------|--------------------------|----------------------------------------------|--------------------------|
| PCI ad hoc, n/N (%) | 20/22 (90.9) | Treated vessels | |
| Vascular access during PCI | | LAD, n/N (%) | 13/26 (50.0) |
| Radial, n/N (%) | 12/22 (54.5) | LCx, n/N (%) | 8/26 (30.8) |
| Femoral, n/N (%) | 10/22 (45.5) | RCA, n/N (%) | 5/26 (19.2) |
| Vascular access conversion, n/N (%) | 2/22 (9.1) | TIMI flow 3 after intervention, n/N (%) | 26/26(100.0) |
| No. of affected major vessels | | Total number of stents, n | 27 |
| 1, n/N (%) | 13/22 (59.1) | Device per patients, number, mean±SD | 1.11±0.35 |
| 2, n/N (%) | 8/22 (36.4) | Device length, mm, mean±SD | 20.7±6.7 |
| 3, n/N (%) | 1/22 (4.5) | Device diameter, mm, mean±SD | 2.91±0.62 |
| Total number of treated lesions, n | 26 | Deployment pressure, atmospheres, mean±SD | 14.1±2.6 |
| Lesions per patients, number, mean±SD | 1.12±0.50 | Complications during PCI | |
| Percent diameter stenosis,%, mean±SD | 79.2±10.3 | Acute occlusions, n/N (%) | 0/22 (0.0) |
| Bifurcation, % (n/N) | 7/26 (26.9) | Dissection, n/N (%) | 0/22 (0.0) |
| Predilatation, % (n/N) | 15/27 (53.6) | Slow/No-reflow, n/N (%) | 0/22 (0.0) |
| Postdilatation, % (n/N) | 10/27 (35.7) | GP IIb/IIIa inhibitor, n/N (%) | 1/22 (4.5) |

GP – glycoprotein; LAD – left anterior descending artery; LCx – left circumflex artery; LMCA – left main coronary artery; OHT – orthotopic heart transplant; PCI – percutaneous coronary intervention; RCA – right coronary artery; TIMI – thrombolysis in myocardial infarction.

The clinical characteristics are presented in Table 1. Patient comorbidities included hypertension (77.3%), type 2 diabetes mellitus (68.2%), dyslipidemia (68.2%), and obesity (31.8%). The etiology of heart failure prior to heart transplantation was primarily ischemic (63.6%). The median age of the study population was 58 (50–66) years and 77.3% of subjects were male. The mean time from heart transplantation to first coronary intervention was 9.7±4.54 years. All patients received optimal individualized immunosuppression. Standard immunosuppressive therapy included tacrolimus or cyclosporine and mycophenolate mofetil. In patients with diagnosed CAV, everolimus was used unless contraindicated. All of the patients were administered dual-antiplatelet therapy with aspirin continuously and clopidogrel for 6–12 months after the index procedure. Data on pharmacological treatment are presented in Table 2.

The majority of analyzed lesions were located in the left anterior descending coronary artery (50.0%), followed by the left circumflex (32.6%) and right coronary artery (19.2%). Primary success was obtained in all of the treated lesions. All patients had TIMI flow 3 after the intervention. Complete procedural characteristics are presented in Table 3. The analysis of

quantitative coronary angiography after 6-month follow-up revealed low late lumen loss (0.22±0.40). Significant restenosis was observed in 1 of the cases (Table 4). There were no deaths during the follow-up period.

Discussion

This observational, retrospective study shows that second-generation everolimus-eluting stents are safe, and their use was associated with low occurrence of restenosis, low late lumen loss, and no incidence of deaths during the 6-month follow-up in patients with CAV.

Major multicenter randomized studies have suggested that drug-eluting stents (DES) could significantly reduce the 6- to 9-month restenosis rate as well as major adverse events in patients with native coronary artery disease [7–11]. In contrast to results of studies of native coronary artery disease, some authors have found no differences between clinical and/or angiographic outcomes in heart transplant recipients after BMS and DES implantation. The study by Park et al., in a group of

Table 3. Pharmacotherapy on discharge.

| Parameter | Study population N=22 | |
|-----------------------------------|--------------------------|---------|
| Tacrolimus, n/N (%) | 18/22 | (81.8) |
| Cyclosporine, n/N (%) | 2/22 | (9.1) |
| Mycophenolate mofetil, n/N (%) | 9/22 | (40.9) |
| Sirolimus, n/N (%) | 3/22 | (13.6) |
| Everolimus, n/N (%) | 7/22 | (31.8) |
| Acetylsalicylic acid, n/N (%) | 22/22 | (100.0) |
| P2Y12 receptor inhibitor, n/N (%) | 22/22 | (100.0) |
| Alfa-blocker, n/N (%) | 3/22 | (13.6) |
| ACE inhibitor/ARB, n/N (%) | 14/22 | (63.6) |
| Calcium antagonist, n/N (%) | 11/22 | (50.0) |
| Statin, n/N (%) | 21/22 | (95.4) |
| Atorvastatin, n/N (%) | 14/22 | (63.6) |
| Rosuvastatin, n/N (%) | 7/22 | (31.8) |
| Allopurinol, n/N (%) | 7/22 | (31.8) |
| Insulin, n/N (%) | 3/22 | (13.6) |

ACE – angiotensin converting enzyme; ARB – angiotensin receptor blocker; CABG – coronary artery bypass grafting; PCI – percutaneous coronary intervention.

45 heart transplant recipients, demonstrated no significant reduction in TLR or clinical outcomes between BMS and DES [12], and they found that BMS use was sufficient for CAV lesions and that the lack of TLR reduction in the DES group might have been due to differences in CAV pathology or the use of immunosuppressive therapy. Unlike native coronary artery disease, CAV is characterized by extensive fibrosis and decreased number of smooth muscle and inflammatory cells within the in-stent intimal layer. Thus, stents coated with antiproliferative agents may not have had as much effect in CAV. Nonetheless, many other studies showed significantly different outcomes. Among others, in the analysis by Nfor et al., PCI with first-generation DES was associated with significantly lower in-stent restenosis rates compared to BMS (2.8% vs. 16.1%, $p=0.05$) in heart transplant recipients [13]. Mortality rates during 1-year follow-up did not differ (23% vs. 28%, $p=ns$). These findings were relatively consistent in other studies, which was confirmed by Dasari et al. in a systematic review of studies comparing DES with BMS, which showed a significant decrease of restenosis with drug-eluting stents in CAV, with no significant impact on mortality [14]. In light of the available data, it seems certain that DES implantation is currently superior to BMS and balloon angioplasty in CAV-related percutaneous coronary interventions.

Table 4. Quantitative coronary analysis.

| Parameter | Study population N=22/n=26 |
|-------------------------------|-------------------------------|
| Index hospitalization | |
| Lesion length, mm, mean±SD | 19.3±7.3 |
| MLD, mm, mean±SD | 2.52±0.48 |
| RVD before stent, mm, mean±SD | 2.88±0.59 |
| RVD after stent, mm, mean±SD | 2.58±0.48 |
| %MLD, %, mean±SD | 6.3±4.0 |
| %MLA, %, mean±SD | 11.7±7.2 |
| Follow-up | |
| MLD, mm, mean±SD | 2.30±0.67 |
| %MLD, %, mean±SD | 15.8±20.0 |
| %MLA, %, mean±SD | 25.0±22.5 |
| Late Lumen Loss, mean±SD | 0.22±0.40 |
| Binary restenosis | 1 (4.5%) |

MLA – minimal lumen area; MLD – minimal lumen diameter; RVD – reference vessel diameter.

Our analysis shows that the implantation of second-generation everolimus-eluting stents can provide superior results, which is in line with other available data. Previous studies reported that the use of sirolimus- or paclitaxel-coated stents in patients with CAV resulted in a relatively high restenosis rate of 12.5–22.6% (at 12-month follow-up) in comparison to 4.1% (at 6-month follow-up) in our analysis [15–17]. The late lumen loss and incidence of binary restenosis in our study were comparable to data reported by Cheng et al. (0.24±0.80 and 6.1%, respectively) [18]. The authors, similarly to our study, analyzed outcomes of PCI with EES in patients with CAV during a longer follow-up of 2.5±1.5 years. Azarbal et al. also analyzed clinical and angiographic outcomes of 21 heart transplant recipients who underwent PCI with EES during 12±5 months of follow-up [19] and observed no deaths during follow-up. The target lesion revascularization rate was 5.9%, again confirming the potentially better outcomes with EES.

The available data on EES are derived from relatively small studies performed on relatively heterogenous patient subsets. The results, however, are generally similar and very encouraging, which is confirmed in our analysis. Although there are no data from randomized trials or even from large registries to clearly support this notion, it seems that second-generation EES currently remains the best option for CAV patients.

Study limitations

This single-center observational study is retrospective, non-randomized, and limited to CAV patients requiring revascularization. Although we used well-established quantitative angiographic methods, angiography is known to underestimate the extent of CAV, especially in comparison to intravascular ultrasound or optical coherence tomography. Intravascular imaging data were not acquired in our patient population. Therefore, we cannot confirm or exclude a potential role of different mechanisms of remodeling and lumen loss, in addition to intimal hyperplasia both at the non-PCI sites of coronary arteries and within the implanted stents [20].

Comparisons of our results with other studies have numerous confounding factors, such as local treatment variances. Clinical outcomes might differ due to local treatment preferences,

differences in immunosuppression regimens, difference in approach to the prevention and therapy of rejection, and differences in clinical approach to the modification of risk factors. It is clear that without a prospective, randomized study, whether or not PCI can significantly impact mortality will remain an open question. Such a study would be a prerequisite to evaluate the potential benefit of everolimus-eluting stents in comparison to other interventional modalities.

Conclusions

In the analyzed population of cardiac allograft vasculopathy patients undergoing percutaneous coronary intervention using second-generation EES, we observed a low restenosis rate, a low rate of late lumen loss, and no incidence of deaths during the 6-month follow-up.

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