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Reduction of Cardiac Allograft Vasculopathy by PCI: Quantification and Correlation With Outcome After Heart Transplantation

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ABSTRACT

Background: Percutaneous coronary intervention (PCI) might improve outcome at severe stages of cardiac allograft vasculopathy (CAV) among patients after heart transplantation (HTx). Yet, risk stratification of HTx patients after PCI remains challenging.

Aims: To assess whether the International Society for Heart and Lung Transplantation (ISHLT) CAV classification remains prognostic after PCI and whether risk-stratification models of non-transplanted patients extend to HTx patients with CAV.

Methods: At 2 European academic centers, 203 patients were stratified in cohort 1 (ISHLT CAV1, without PCI, n = 126) or cohort 2 (ISHLT CAV2 and 3, with PCI). At first diagnosis of CAV or first PCI, respectively, ISHLT CAV grades, SYNTAX scores I and II (SXS-I, SXS-II) were used to quantify baseline and residual CAV (rISHLT, rSXS-I, rSXS-II). RSXS-I > 0 defined incomplete revascularization (IR).

Results: SXS-II predicted mortality in cohort 1 ($P = 0.004$), whereas SXS-I ($P = 0.009$) and SXS-II ($P = 0.002$) predicted mortality in cohort 2. Post-PCI, IR ($P = 0.004$), high rISHLT ($P = 0.02$) and highest tertile of rSXS-II ($P = 0.006$) were associated with higher 5-year mortality. In bivariable Cox analysis, baseline SXS-II, IR and rSXS-II remained predictors of 5-year mortality post-PCI. There was a strong inverse relationship between baseline and rSXS-I (r = -0.55; $P < 0.001$ and r = -0.50; $P = 0.003$, respectively) regarding the interval to first reintervention.

Conclusion: People with ISHLT CAV classification could apply for risk stratification after PCI. SYNTAX scores could be complemental for risk stratification and individualization of invasive follow-up of HTx patients with CAV. (*J Cardiac Fail 2024;30:1222–1230*)

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Introduction

After successful heart transplantation (HTx), angiographic lesions commonly develop in the coronary vessels of transplanted hearts.[1] Their new onset and/or progression define cardiac allograft vasculopathy (CAV), a post-transplant pathology that represents a major limitation to survival.[2,3] Intracoronary imaging has highlighted the relevance of intimal hyperplasia (CAV^{IH}) and pathological remodeling in the development of angiographically manifest CAV.[4,5] Yet CAV also presents overlapping features with typical atherosclerosis of non-transplanted patients, such as the association with established cardiovascular risk factors and the presence of atherosclerotic plaques.[6,7]

The International Society for Heart and Lung Transplantation (ISHLT) provided a grading tool of 4 grades that correlates CAV severity with mortality and retransplantation.[3,8] Accordingly, moderate to severe stages of CAV (high-grade CAV, ISHLT CAV grades 2−3) are associated with mortality and worse graft survival.[9,10] However, the use of ISHLT grading has not been validated in HTx patients having undergone percutaneous coronary intervention (PCI), which leaves these patients without a consensus for evaluating the prognostic relevance of residual coronary pathology. Besides, the role of invasive therapy of severe stages of CAV has long been debated. Specifically, its therapeutic yield, the optimal amount of CAV reduction to achieve and the selection of appropriate candidates for PCI need further clarification. While risk-stratification tools, such as the SYNTAX (SYNergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) scores (SXS-I and -II), have been elaborated to optimize the selection of invasive treatment strategies in nontransplanted patients, their validity in HTx patients is largely understudied.[11-18]

The aim of this study was to (1) assess whether baseline SXS-I and SXS-II are predictive of mortality in HTx patients at differing stages of CAV, and it was evaluated in patients with low-grade CAV that did not warrant PCI or with high-grade CAV treated with PCI; (2) evaluate whether residual CAV after PCI, as defined by the ISHLT CAV classification and SYNTAX scores, correlates with mortality in HTx patients; and (3) define what baseline and/or residual CAV burdens are related to reintervention in HTx patients with high-grade CAV treated with PCI.

Methods

Study Population

We analyzed clinical data and coronary angiograms performed between 07/2000 and 12/2019 in adult HTx patients at 2 European academic centers. Standard techniques for PCI were used. The type of stent and choice of antiplatelet therapy after stenting were at the discretion of the operators. The study was approved by the local institutional review boards of the participating centers. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Key inclusion and exclusion criteria

Adult patients having undergone HTx and presenting with CAV were divided into 2 cohorts. Cohort 1 was a nonprocedural cohort that included HTx patients presenting with low-grade CAV without PCI who had remained stable until the last available angiography. Cohort 2 included HTx patients with high-grade CAV who had undergone PCI. Patients with ISHLT CAV 0 were excluded from this study. Patients with high-grade CAV having undergone post-transplant coronary artery bypass grafting (n = 5) and patients not amenable to PCI (n = 5) were also excluded from the study.

Timepoints

Timepoint 0 (TP0) was defined as the date of the first angiographic diagnosis of CAV in cohort 1 and of the first PCI as CAV treatment in cohort 2. At the respective timepoint 0, all angiograms of the included patients were retrospectively reviewed for complete representation and classification of coronary anatomy. Clinical endpoints were assessed at 5 years after the respective timepoint 0.[10]

Clinical Endpoints

The primary outcome was overall mortality at 5 years in both cohorts. In cohort 2, a secondary endpoint of first reintervention was assessed at 5 years. In deceased patients, source documents were adjudicated for verification of the event and analysis of the cause of death.

Assessment and definitions of baseline and pre-procedural CAV in cohort 1 and cohort 2

Angiograms were graded according to the established ISHLT nomenclature.[3] Baseline ISHLT CAV grade 1 (mild)

was termed "low-grade CAV," and ISHLT CAV grades 2 (moderate) and 3 (severe) were termed "high-grade CAV." The SXS-I and SXS-II were calculated using the official calculator.[19] The evaluation of SXS-I included 3 general variables (coronary arteries dominance, total number of lesions and vessel segments involved per lesion, presence of diffuse/small-vessel disease in addition to focal stenosis) and 8 characteristics of each lesion with ≥ 50% luminal obstruction in a vessel ≥ 1.5 mm (length, involvement of bifurcation or trifurcation, aortic ostial localization, chronic occlusion, tortuosity, calcification, and thrombus formation). The SXS-II combined the angiographic score SXS-I with clinical factors (age, gender, creatinine clearance, left ventricular ejection fraction, left main coronary artery disease, chronic obstructive pulmonary disease, peripheral vascular disease). In cohort 2, baseline scores represented pre-interventional scores.

Post-procedural assessment of residual CAV in cohort 2

After the PCI procedure, the residual ISHLT CAV grade was assessed based on the ISHLT CAV classification.[3] Residual ISHLT CAV grades 0 and 1 (no and mild residual angiographic lesions, respectively) were termed "low-grade residual CAV"; and residual ISHLT CAV grades 2 and 3 (moderate and severe residual angiographic lesions, respectively) "high-grade residual CAV." The residual SXS-I and II were assessed post-PCI.[15,16,20] A residual SXS-I = 0 was termed "complete revascularization," and a residual SXS-I > 0 "incomplete revascularization."[15]

Clinical parameters assessment

History of moderate/severe rejection was defined as an acute cellular rejection ≥ grade 2R after endomyocardial biopsy, according to the ISHLT grading system.[21,22] Estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI formula. Renal function was then categorized according to the Kidney Disease Improving Global Outcomes classification: kidney function was defined as normal in case of eGFR ≥ 90 mL/min/1.73 m^2; mildly reduced for eGFR between 60 and 89 mL/min/1.73 m^2; moderately reduced, between 30 and 59 mL/min/1.73 m^2; and severely reduced for eGFR ≤ 30 mL/min/1.73 m^2.

Statistics

Normality of variables was tested with the Shapiro-Wilk test. Continuous variables were expressed as mean (± standard deviation [SD]) or median with interquartile range (IQR). The ^{2} test or the Fisher exact test was applied to compare unpaired categorical variables, as appropriate. For paired comparison of continuous variables, either the paired *t* test or the Wilcoxon test were used, as appropriate. Patients in cohort 1 were dichotomized as baseline SXS-I = 0 or SXS-I > 0 and stratified according to tertiles of baseline SXS-II for survival analysis. Patients of cohort 2 were stratified according to tertiles of pre-procedural, baseline SXS-I and SXS-II, as well as to post-procedural parameters of residual CAV (residual ISHLT grades, incomplete vs complete revascularization, tertiles of residual SXS-II). Proportionality assumptions were tested for Cox models for each variable by testing the variables' interactions with time. For survival analysis, we applied Kaplan-Meier estimator analysis with a log-rank test. Hazard ratios (HR) with 95% confidence interval (95% CI) for independent predictors of endpoints were calculated with a Cox proportional hazard model. Variables showing a *P* value < 0.1 in the univariable Cox proportional hazard analysis were included in the subsequent bivariable model. Associations between the continuous variables of baseline and residual SXS-I and SXS-II and the interval between first PCI to first reintervention were evaluated using bivariate correlation. A *P* value < 0.05 was considered significant. IBM SPSS statistics (Armonk, NY), version 29, was used for analysis.

Results

Patients and baseline characteristics

The study's flow chart is shown in Fig. 1. Overall, 203 patients were included in the analysis (81.8% were male; median age at HTx was 51.4 years [41.8−58.0]); 32% had undergone HTx for ischemic and 51.7% for dilated cardiomyopathy. Median follow-up after TP0 was 57.6 months. One patient was lost to follow-up at 2.77 years after TP0 in cohort 2. Overall, 138 patients (68.0%) had a documented death within 5 years after TP0 or a follow-up time of 5 years after TP0. Immunosuppressive treatment included calcineurin inhibitor in 80.3% and mTOR inhibitors in 33.5% of patients. At TP0, statin therapy was documented in 69% of patients.

Baseline characteristics according to cohort

Characteristics of each cohort are shown in Table 1. In the global population, 126 patients (62.1%) presented with low-grade CAV without history of PCI (cohort 1), and 77 patients (37.9%) had undergone PCI for high-grade CAV (cohort 2). Patients in cohort 2 had longer intervals between TP0 and HTx (*P* = 0.001) and higher prevalences of diabetes mellitus, dyslipidemia and active smoking (*P* = 0.04, *P* = 0.05 and *P* = 0.05, respectively). Median SXS-I and SXS-II were higher in cohort 2 (all *P* < 0.001), and there was a higher prevalence of diffuse narrowing in cohort 2 (*P* = 0.006).

Pre- vs post-procedural characteristics of cohort 2

Pre- vs post-procedural characteristics of cohort 2 are shown in Supplementary Table 1. Post-procedural scores were lower than pre-procedural scores, indicating an overall procedural success regarding the reduction of CAV burden (all *P* <0.001). Low-grade residual CAV (residual

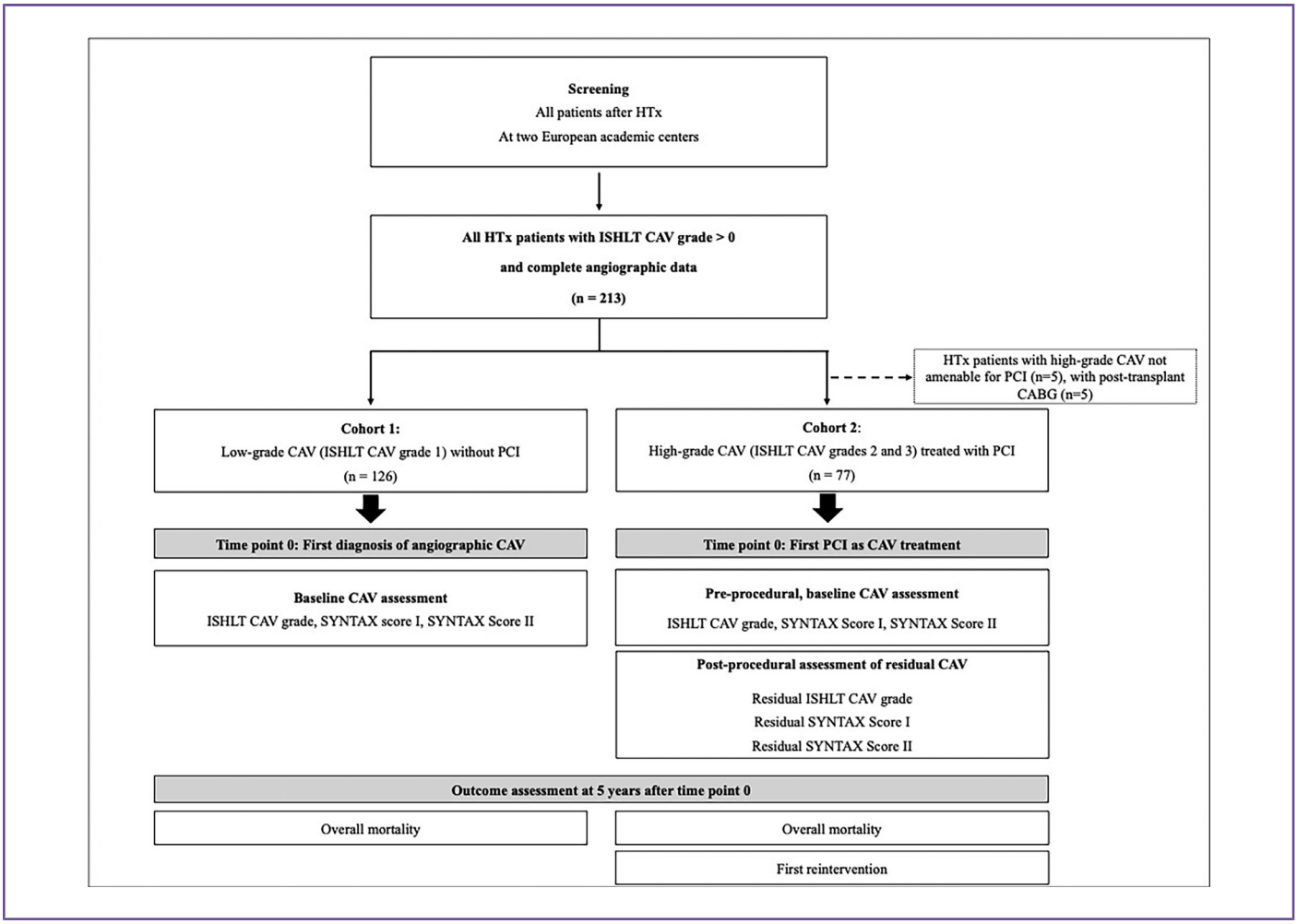

Fig. 1. Study flow chart. Patients were assigned to only 1 cohort. CABG, coronary artery bypass graft; CAV, cardiac allograft vasculopathy; HTx, heart transplantation; ISHLT, International Society for Heart and Lung Transplantation.

ISHLT CAV grades ≤1) was achieved in 80.5% of patients, and complete revascularization (residual SXS-I = 0) in 64.9%.

Mortality analysis

Mortality at 5 years after the respective timepoint 0 was comparable between cohort 1 and 2 (19.8% vs 19.5%; $P = 0.4$), as was re-transplantation (0.8% vs 0%; $P = 0.4$).

Prognostic value of baseline CAV characteristics in cohort 1

At 5-year follow-up, Kaplan-Meier analysis (Supplementary Fig. 1) showed that survival was similar for the patients with SXS-I = 0 and SXS-I > 0 (19.8% vs 20%; $P = 0.6$) and that patients in the highest tertile of the SXS-II had the highest mortality rates (31.8% vs 8.1% and 17.8%; $P = 0.02$). Univariable Cox analysis (Supplementary Table 2) confirmed the highest tertile of SXS-II as predictive for mortality at 5 years (HR 2.5 [1.4−4.8]; $P = 0.004$), while SXS-I was not associated with outcome.

Prognostic value of baseline CAV and post-procedural characteristics in cohort 2

In Kaplan-Meier analysis at 5-years (Fig. 2, A, B), mortality was highest in patients in the highest tertile of baseline SXS-I and SXS-II compared to patients in the respective lowest and intermediate tertiles (37% vs 8% and 12%; $P = 0.02$ and 41.4% vs 0 and 11.5%; $P = 0.002$, respectively). Mortality rates were also higher in patients with vs without diffuse coronary narrowing (38.5% vs 9.8%; $P = 0.005$), with high-grade residual CAV compared to low-grade residual ISHLT CAV grades 0 and 1 (40% vs 5.3% and 19.0%; $P = 0.02$; Fig. 3, A), with incomplete vs complete revascularization (40.7% vs 8%; $P < 0.001$) (Fig. 3, B), as well as in the highest tertile of residual SXS-II compared to the lowest and intermediate tertiles (36.7% vs 4% and 13.6%; $P = 0.008$; Fig. 3, C).

In univariable Cox analysis (Table 2), the highest tertiles of baseline SXS-I (HR 4.2 [1.4−12.2]; $P = 0.009$) and SXS-II (HR 7.1 [2.0−24.5] $P = 0.002$), as well as the presence of diffuse narrowing (HR 4.0 [1.4−11.8]; $P = 0.01$) were associated with 5-year mortality after first PCI. Post-PCI high-

Table 1 Baseline characteristics according to cohorts at the respective timepoint 0*

Clinical Characteristics	Cohort 1 n = 126	Cohort 2 n = 77	*P* value
Male sex, n (%)	104 (82.5)	62 (80.5)	0.7
Age at heart transplantation, years	51.4 [43.5–58.9]	51.2 [40.3–57.0]	0.4
Post-transplant interval, years	7.9 [2.8–13.3]	10.9 [6.2–15.2]	**0.001**
Arterial hypertension, n (%)	101 (80.2)	65 (84.4)	0.6
Diabetes mellitus, n (%)	34 (27.0)	32 (41.6)	**0.04**
Dyslipidemia, n (%)	93 (73.8)	66 (85.7)	**0.05**
Active smoker, n (%)	26 (20.6)	28 (36.4)	**0.05**
eGFR, mL/min/1.73 m^2	54 (38–61)	47 [38–61]	0.3
Renal function according to KDIGO classification			0.2
Normal, n (%)	5 (4.0)	4 (5.2)	
Mildly decreased, n (%)	44 (34.9)	18 (23.4)	
Moderately decreased, n (%)	57 (45.2)	47 (61.0)	
Severely decreased, n (%)	18 (14.3)	8 (10.4)	
Unknown eGFR at timepoint 0	2 (1.6)	0 (0)	
History of moderate/severe rejection, n (%)	6 (4.8)	9 (11.7)	0.1
Baseline angiographic parameters†			
Diffuse narrowing, n (%)	21 (16.7)	26 (33.8)	**0.006**
Baseline ISHLT CAV grade			
1, n (%)	126 (100.0)	0 (0)	
2, n (%)	0 (0)	55 (71.4)	
3, n (%)	0 (0)	22 (28.6)	
Baseline SYNTAX score I	0 [0–2.0]	9.0 [5.0–16.0]	< **0.001**
Baseline SYNTAX score II	26.8 [22.7–31.6]	32.8 [26.0–37.7]	< **0.001**

Data are shown as median (interquartile range, IQR) or n (%).

EGFR, estimated glomerular filtration rate; ISHLT, International Society for Heart and Lung Transplantation; KDIGO, Kidney Disease Improving Global Outcomes; PCI, percutaneous coronary intervention.

*Timepoint 0 represents the first angiographic diagnosis of CAV in cohort 1 and the first percutaneous intervention as CAV treatment in cohort 2.

†Baseline angiographic scores were assessed at the first angiographic diagnosis of CAV in cohort 1 and represent the pre-procedural findings at the timepoint of first percutaneous coronary intervention in cohort 2.

grade residual CAV (HR 3.6 [1.3–10.2]; $P = 0.02$), incomplete revascularization (HR 5.4 [1.7–17.0]; $P = 0.004$) and the highest tertile of residual SXS-II (HR 5.1 [1.6–15.9]; $P = 0.006$) were also associated with higher risk of 5-year mortality.

In bivariable Cox analysis (Supplementary Table 3), baseline SXS-II, incomplete revascularization, residual SXS-II remained predictors of 5-year mortality. There was a trend for a higher 5-year mortality with higher baseline SXS-I.

Reintervention in cohort 2

At least 1 reintervention had been performed in 42.9% of patients at 5 years after the first PCI treatment for CAV.

In Kaplan-Meier analysis at 5 years, reintervention remained more frequent in case of high-grade residual CAV after first PCI compared to residual ISHLT grades 0 and 1 (66.7% vs 26.3% and 41.9%; $P = 0.006$ (Fig. 4 A), after incomplete revascularization (59.3% vs 34%; $P = 0.008$; Fig. 4, B) and in the presence of diffuse narrowing (57.7% vs 35.3%; $P = 0.002$; Fig. 4, C). Univariable Cox analysis (Table 2) showed that diffuse narrowing (HR 2.8 [1.4–5.7]; $P = 0.004$), incomplete revascularization (HR 2.4 [1.2–4.8]; $P = 0.01$) and high-grade residual CAV (HR 3.0 [1.4–6.4]; $P = 0.004$) were predictive of reintervention at 5 years. In bivariable Cox analysis (Supplementary Table 3), the presence of diffuse narrowing and high-grade residual CAV remained predictors for this endpoint.

Effect of continuous scores on first PCI to first reintervention interval

A subgroup analysis was performed in patients of cohort 2 with reintervention within 5 years of the first PCI (n = 33). The median interval between first PCI and first reintervention was 14 months [8–35.5]. Spearman correlation analysis showed a strong inverse relationship between this interval and higher baseline SXS-I and SXS-II (r = -0.55; $P < 0.001$ and r = -0.47; $P = 0.006$, respectively), as well as residual SXS-I and residual SXS-II (r = -0.50; $P = 0.003$ and r = -0.45; $P = 0.003$, respectively). In Cox regression analysis, residual SXS I was associated with the endpoint of first reintervention at 5 years after TP0 (HR 1.09 [1.05–1.13]; $P < 0.001$).

Discussion

In this bicentric study that included a large population of HTx patients with CAV in 2 European countries, we identified several novel findings: (1) In addition to the ISHLT CAV classification, the SYNTAX-scores are valid predictors of mortality in HTx patients with CAV, with both scoring tools also applying to patients having undergone PCI; (2) using the SXS-II to combine the baseline assessment of focal CAV stenoses with relevant clinical factors and comorbidities is predictive of 5-year mortality in all HTx patients with CAV; (3) higher reduction of CAV burden, as assessed by ISHLT CAV classification, is associated with a higher survival rate at 5 years after first PCI; (4) anatomical characteristics, including baseline and residual SXS-I, as well as the presence of diffuse narrowing, might help to select individual post-procedural follow-up, as they are strongly associated with more frequent and earlier reinterventions.

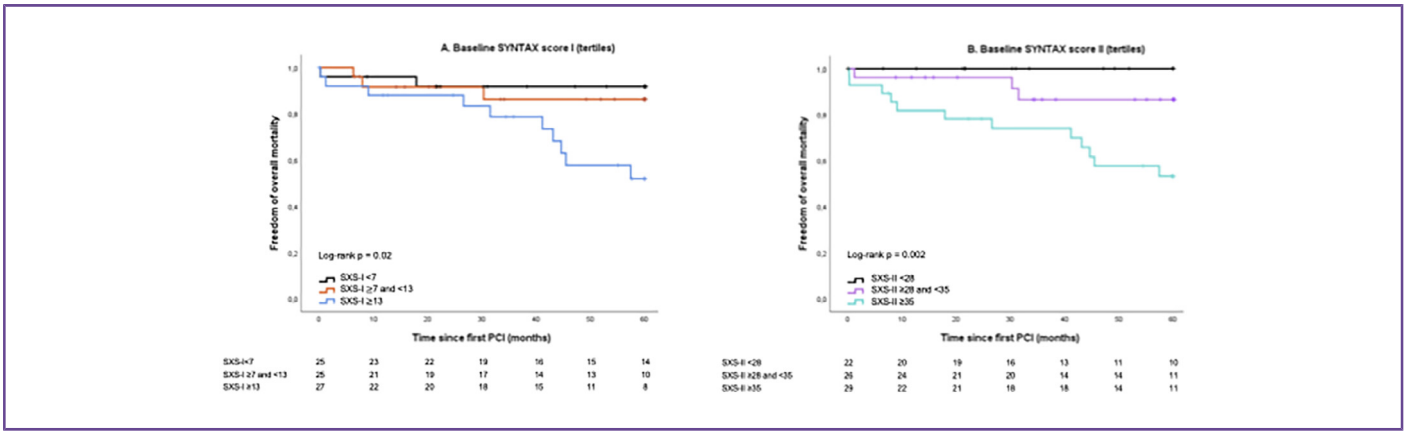

Fig. 2. Kaplan-Meier curves of baseline scores for the endpoint of mortality at 5 years after first PCI (cohort 2). A, Freedom from mortality according to the tertiles of baseline SYNTAX Score I. B, Freedom from mortality according to the tertiles of baseline SYNTAX Score II. *P* values of log-rank tests are shown. SXS, SYNTAX score; PCI, percutaneous coronary intervention.

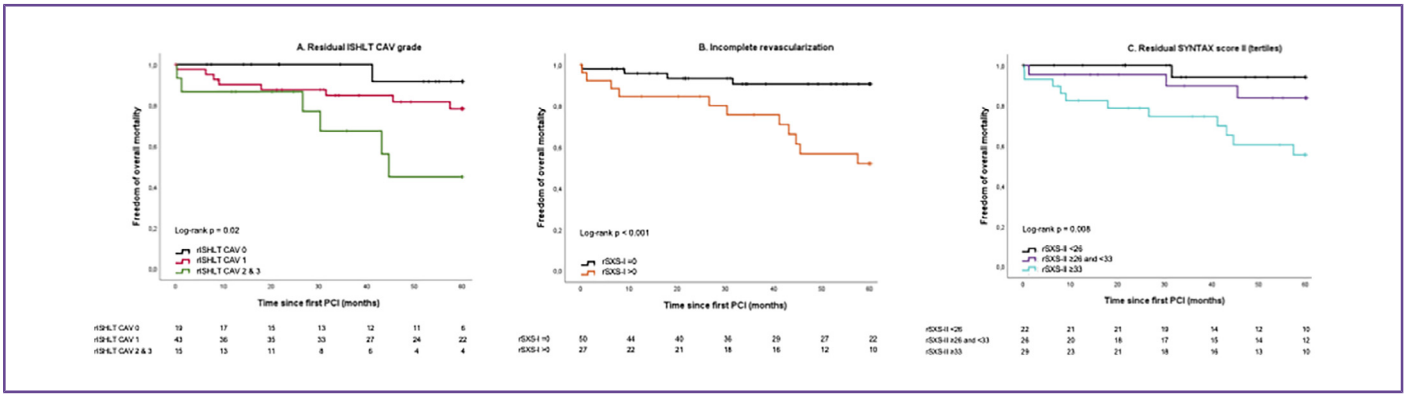

Fig. 3. Kaplan-Meier curves of post-procedural scores for the endpoint of mortality at 5 years after first PCI (cohort 2). A, Freedom from mortality according to residual ISHLT CAV grades. B, Freedom from mortality according to dichotomization in complete vs incomplete revascularization (residual SYNTAX score I = 0 vs residual SYNTAX score I > 0). C, Freedom from mortality according to the tertiles of residual SYNTAX score II. *P* values of log-rank tests are shown. CAV, cardiac allograft vasculopathy; ISHLT, International Society for Heart and Lung Transplantation; PCI, percutaneous coronary intervention; rISHLT grade, residual CAV grade according to ISHLT nomenclature; SXS, SYNTAX score; rSXS, residual SYNTAX score.

Table 2 Univariable Cox analysis of predictors of mortality and reintervention at 5 years after first PCI in cohort 2

	Mortality at 5 years after first PCI		Reintervention at 5 years after first PCI	
Parameters Baseline CAV	HR (95% CI)	*P* value	HR (95% CI)	*P* value
SYNTAX score I (highest tertile)	4.2 (1.4–12.2)	**0.009**	1.8 (0.9–3.5)	0.2
SYNTAX score II (highest tertile)	7.1 (2.0–24.5)	**0.002**	1.6 (0.8–3.2)	0.2
Presence of diffuse narrowing	4.0 (1.4–11.8)	**0.01**	2.8 (1.4–5.7)	**0.004**
Residual CAV				
High-grade residual CAV1*	3.6 (1.3–10.2)	**0.02**	3.0 (1.4–6.4)	**0.004**
Incomplete revascularization†	5.4 (1.7–17.0)	**0.004**	2.4 (1.2–4.8)	**0.01**
Residual SYNTAX score II (highest tertile)	5.1 (1.6–15.9)	**0.006**	1.2 (0.6–2.4)	0.6

CAV, cardiac allograft vasculopathy; HR (95% CI), hazard ratio (95% confidence interval); KDIGO, Kidney Disease Improving Global Outcomes.
*Residual ISHLT CAV grades 0 and 1 were termed "low-grade residual CAV" and residual ISHLT CAV grades 2 and 3 were termed "high-grade residual CAV".
†Incomplete revascularization was defined as residual SYNTAX score I > 0.

Characterization of coronary lesions in HTx patients amenable to PCI is challenging. The classical scores used in patients with native hearts have not been validated in HTx patients, despite their potential yield in this population. According to our study, SXS-I and SXS-II are valid predictors of mortality in HTx patients, before or after PCI, and their use can be considered in this setting. In the cohort with high-grade CAV treated with PCI, the

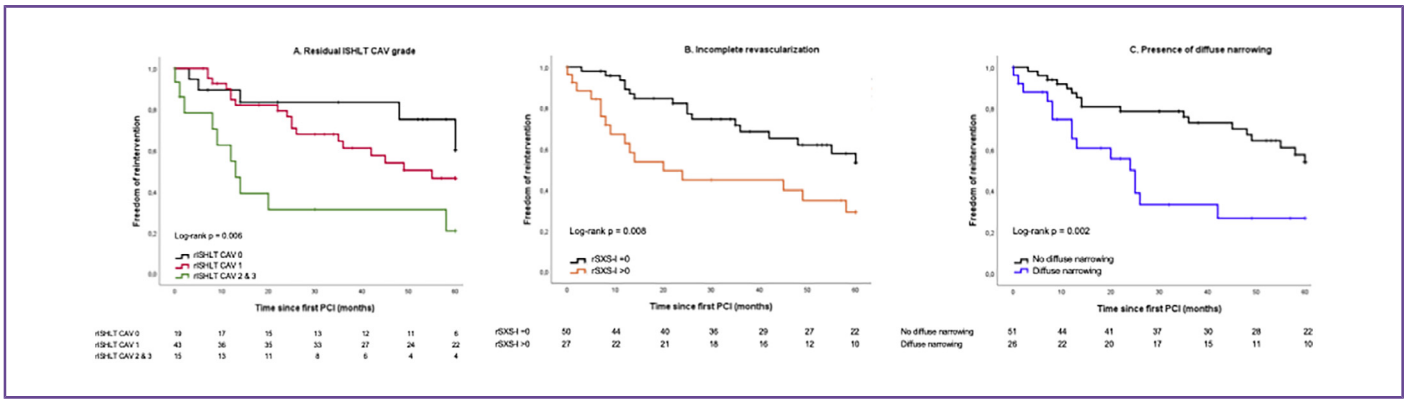

Fig. 4. Kaplan-Meier curves for the endpoint of reintervention at 5 years after first PCI (cohort 2). A, Freedom from reintervention according to residual ISHLT CAV grades. B, Freedom from reintervention according to dichotomization in complete vs incomplete revascularization (residual SYNTAX score I = 0 vs residual SYNTAX score I > 0). C, Freedom from reintervention according to dichotomization in presence of diffuse narrowing vs no presence of diffuse narrowing. *P* values of log-rank tests are shown. CAV, cardiac allograft vasculopathy; ISHLT, International Society for Heart and Lung Transplantation; PCI, percutaneous coronary intervention; rISHLT, residual CAV grade according to ISHLT nomenclature.

highest tertile of baseline SXS-I predicted higher mortality rates. Of note, in the respective tertiles of baseline SXS-I, the HTx patients in our study had similar survival rates compared to the reported major adverse cardiovascular and cerebrovascular events (MACCEs) rate reported in non-transplanted patients at 5 years, while presenting with lower absolute values of SXS-I.[23] This highlights the ability of SYNTAX score tertiles to discriminate patients at risk after HTx, as seen in non-transplanted patients. A potential explanation of the lower absolute SXS values correlating with similar survival compared to MACCEs at 5 years could be differences in the progress of the disease. CAV can develop as a rapidly progressive disease, ultimately leading to MACCEs, due to immunologic and nonimmunologic risk factors. Regarding nonimmunologic risk factors, HTx patients are exposed to higher rates of cardiovascular risk factors, potentially through the side effects of immunosuppression.[7,24-26]

Additionally, the ISHLT classification does not address comorbidities beyond CAV. Renal failure is particularly common in HTx patients and has a high impact on post-transplant mortality; this is not addressed.[2] The SXS-II includes this relevant aspect into risk stratification, as well as additional prognostically relevant factors after HTx, such as age and gender.[2] The SXS-II could, therefore, further improve risk stratification of HTx patients with CAV.

Invasive therapy in severe stages of CAV has long been under debate. Early studies had been conducted mostly in HTx patients having undergone balloon angioplasty alone or the implantation of bare metal stents. Results from those studies indicated that PCI had limited value, with particularly high rates of in-stent restenosis, reintervention and no relevant survival benefit.[27-30] Therefore, invasive therapy has long been deemed a symptomatic treatment without long-term benefit.[27] As opposed to that, recent studies have showed that with the advances in stent design and accompanying medical therapy, PCI correlated with improved survival in HTx patients for up to 5 years.[10,31] However, there are still many gaps in knowledge regarding the optimal amount of CAV reduction and the appropriate selection of patients who would benefit most from PCI. In our study, we assessed the prognostic impact of CAV reduction by PCI using the ISHLT classification and SYNTAX scores for the definition of post-procedural residual CAV burden. Here, residual ISHLT CAV grades predicted 5-year mortality rates, suggesting that the ISHLT classification could also apply to HTx patients treated with PCI. As shown in nontransplanted patients, the residual SXS-I, a surrogate of completeness of revascularization of focal stenosis, was also a strong predictor of 5-year mortality.[15] Both residual scores indicate that PCI could not only represent a symptomatic therapeutic option, but could also potentially improve survival in HTx patients with high-grade CAV. The association of low mortality rates with CAV reduction seen in our results confirms and extends findings that showed a prognostic benefit for patients with high-grade CAV treated with PCI as compared to patients not amenable to an invasive reduction of high-grade CAV.[10]

In our study, there was a strong association between SXS-I before and after PCI, and the interval between first PCI and first reintervention. Diffuse narrowing is not included in SXS-I in the absence of focal stenosis, but was a strong predictor of reintervention in our study, thereby extending previous results.[32] Overall, the combination of SXS-I and diffuse narrowing could identify HTx patients at high risk for reintervention.

The ISHLT classification was developed specifically to assess baseline CAV, and its validity has been confirmed recently for the contemporary era with improved immunosuppressive regimens,[8] but its use after PCI has not been validated so far. The observed validity of ISHLT classification after PCI in our study is, therefore, of paramount

importance, and it adds an important tool for the individualization of invasive CAV treatment. Although it is recommended in the revascularization guidelines,[33,34] several concerns have been raised about the use of the SYNTAX score in nontransplanted patients.[35] Whether these concerns are also relevant in HTx patients remains unclear. First, there are well-known limitations to the definition of lesion severity based solely on angiographic findings. The frequent use of intracoronary imaging might offer the opportunity to optimize SYNTAX score calculation in this cohort. Another issue is the consideration of lesions in small arteries in the SYNTAX score, despite the lack of benefit of revascularization in those arteries. However, these lesions are relevant in transplanted patients and are included in ISHLT CAV grade 1, which presents lower survival rates than in patients with ISHLT CAV grade 0.[10] Finally, adequate training to assess SYNTAX scores is recommended to reduce inter- and intra-observer variability. SYNTAX-based scores could be complemental to the ISHLT CAV classification regarding the selection of PCI candidates and the frequency of individual follow-up strategies after PCI. They could also offer additional quantification options of CAV progress within ISHLT CAV grades and particularly after PCI, thereby improving the definition of patients benefiting closer monitoring and intensified secondary prevention.

Limitations

Despite the important prognostic role of ISHLT classification and SYNTAX scores in HTx patients in our study, a limitation to both is their inability to differentiate between the presence of intimal hyperplasia vs atherosclerotic plaques as primary pathology in CAV. Also, whether achieving and maintaining low-grade residual CAV in the modern era of PCI could approximate survival in the outcomes of patients with baseline low-grade CAV needs to be addressed in large prospective studies. This study is not designed to assess the effects of other parameters regarding outcome or progress of CAV such as immunosuppressive regimens. Finally, it is unknown whether residual ISHLT and SYNTAX scores also apply to HTx patients with multiple reinterventions for CAV.

Analyses were performed in 2 large academic European centers, but the application of SYNTAX scores in the cohort of HTx patients needs further external validation in larger cohorts.

Conclusion

The established risk scores for coronary artery disease assessment in non-transplanted patients, SYNTAX scores I and II, apply in HTx patients and can be used at baseline and after PCI in this population. In addition, ISHLT CAV classification is still applicable after PCI. Reductions in both ISHLT CAV grade and SYNTAX scores after PCI are associated with higher survival rates at 5 years after first PCI. Use of SYNTAX scores could also help to individualize invasive follow-up due to the strong association with rate and time to reintervention.

Lay Summary

Risk stratification of heart transplanted (HTx) patients with cardiac allograft vasculopathy (CAV) undergoing percutaneous coronary intervention (PCI) remains challenging.

In patients presenting with ISHLT CAV grades 2 and 3 undergoing first PCI, incomplete revascularization (residual SYNTAX Score-I $>$ 0), high residual ISHLT CAV grade and the highest tertile of residual SYNTAX score-II were predictors of higher 5-year mortality. High residual ISHLT CAV grade predicted reintervention at 5 years and SYNTAX score-I showed an inverse relationship with the interval to first reintervention. People with ISHLT CAV classification could apply for risk stratification after PCI, and SYNTAX scores could add complemental information in HTx patients with CAV

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2024.07.011.

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