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Progress of Angiographic Cardiac Allograft Vasculopathy in Patients With Long-Term Transplantation: Longitudinal Evaluation of Its Association With Dyslipidemia Patterns

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Cardiac allograft vasculopathy (CAV) is a progressive disease with limited options for secondary prevention. Ways to manage lipid parameters and dyslipidemia patterns in care after transplantation remain unclear. In this longitudinal study, we included 32 patients with long-term heart transplantations (median interval after transplant 13.8 years) with angiographic manifest CAV. In 299 matched nonstented segments at 3 distinct time points ([TPs] 0 to 2, with median intervals of 2 years, respectively), progress of diameter stenosis (Δ%DS) defined CAV progress. Values above the median of maximal Δ%DS defined substantial CAV progress. Category of left ventricular ejection fraction was evaluated at TP0 and TP3 (2 years after TP2). Findings were correlated with dyslipidemia patterns at TP0, and lipid variations at follow-up (TP1 to TP3). Analyses included routine lipid assessment, and triglycerides/high-density lipoprotein-cholesterol ratio (TG/HDL-c) and atherogenic index of plasma (AIP). At TP1 and TP2, patients with increase of TG/HDL-c ≥0.1 (p = 0.02, respectively) and with increase of AIP (p = 0.01 and p = 0.049, respectively) presented a greater maximal Δ%DS. Dyslipidemia patterns at TP0 did not show a relevant association with CAV progress. At TP2, increase of TGs, TG/HDL-c, and AIP were associated with substantial CAV progress (odds ratio [OR] 5.0, p = 0.046, and OR 9.2, p = 0.01, OR 6.6, p = 0.02, respectively). At TP3, patients with CAV-related worsening of left ventricular ejection fraction category presented with a greater increase of TG/HDL-c (p = 0.03). Although findings at TP0 did not affect CAV progress, an increase of TG/HDL-c could define patients at greater risk of CAV progress and CAV-related deterioration of graft function.

Cardiac allograft vasculopathy (CAV) remains a major limitation to survival and graft function after successful heart transplantation (HTx).[1] Because CAV is typically characterized by its progressive nature,[2] regular angiographic follow-up is recommended after HTx.[3]

To classify CAV and the related risk of mortality and retransplantation, the International Society of Heart and Lung Transplantation (ISHLT) provides a nomenclature when maximal angiographic stenoses and left ventricular dysfunction represent primary parameters defining increasing severity.[3]

Quantitative coronary angiography (QCA) represents a valid quantification tool in non-transplanted and HTx patients to objectify coronary lesions in angiography.[4–6] By defining segments of interest, QCA can be performed in both stented and nonstented segments. Hence, it provides information regarding mean and maximal CAV progress in all patients with HTx, including those having previously undergone percutaneous coronary intervention and within ISHLT CAV categories.

Over the last decades, improvement regarding prevention of CAV development could be achieved through newer immunosuppressive therapies and an increased use of statins, indicating that the course

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of the disease can be altered using pharmacologic intervention. In adults, the use of statins for primary prevention is recommended regardless of cholesterol levels, with typically initially low doses owing to pharmacologic treatment interactions and risk for toxicity.[3]

The prevention of CAV progress remains a challenge with limited therapeutic options for secondary prevention.[3] A better understanding of potentially modifiable risk factors seems therefore most relevant to address progress to severe CAV grades and CAV-related deterioration of left ventricular ejection fraction (LVEF). In long-term transplanted patients, nonimmune risk factors, particularly dyslipidemia or insulin resistance syndrome (IRS), are postulated to represent major risk factors for CAV and are frequent co-morbidities.[7] However, relevant gaps of knowledge remain. First, studies have mainly been performed regarding the effect of dyslipidemia on CAV development, and the effect of dyslipidemia pattern on CAV progress is less studied. Here, dyslipidemia remains primarily an overall diagnosis, and the relevance of distinct dyslipidemia pattern is poorly understood. Moreover, the impact of variations of lipid parameters over time is largely understudied.[8] Whether variations of triglycerides to high-density lipoprotein (TG/HDL-c), an established surrogate of IRS, and the atherogenic index of plasma (AIP), both easily accessible biomarker diagnostic markers for cardiovascular events, could be associated with CAV progress, lacks studies.

On the basis of these considerations, we performed a longitudinal study in patients with long-term transplants with established angiographic CAV, with the aims to (1) objectify progress of nonstented lesion of CAV using longitudinal QCA measurements, (2) evaluate the association of CAV progress with baseline dyslipidemia pattern and variations of lipid values over time, and (3) correlate these parameters with CAV-related deterioration of LVEF at long-term follow-up.

Methods

We analyzed angiographic, echocardiographic, and laboratory examinations performed in adult patients with HTx presenting with angiographic manifestation of CAV between 2005 and 2019 at our European academic center. The study was approved by the local ethics committee. The investigation conforms with the principles of the Declaration of Helsinki.

Patients with HTx (1) who had undergone ≥3 coronary artery angiographies since the diagnosis of ISHLT CAV grade ≥1, and (2) with each coronary artery angiography having a respective interval of ≥1 year among examinations were included. Patients with CAV after de novo HTx, defined as post-transplant interval ≤1 year, and stented segments were excluded from analysis.

Time point 0 (TP0) defined the time point of first angiographic and laboratory analysis and was termed baseline. TP1 and TP2 defined the 2 following time points at which CAV progress was analyzed using QCA. If multiple angiograms were available, examinations with a 2-year interval were chosen for QCA analysis, representing a common interval of invasive post-transplant care.[3] TP3 was set at 2 years after TP2, if possible.

QCA analysis was performed off-line using standard biplane angiographic imaging. Coronary arteries were divided into 15 segments according to the American Heart Association definition. Side branches with a reference vessel diameter (RVD) of >1.5 mm were deemed large and included in QCA analysis. Vessel contours and reference diameter were defined using the automatic edge-detection program. Minimal luminal diameter, RVD, segment length, and %DS (calculated by [1 − minimal luminal diameter/RVD] × 100) were assessed per segment in each patient at each time point.[5,9] QCA analysis was performed using QangioXA version 7.3 (Medis Medical Imaging Systems, Leiden, The Netherlands).

Segments analyzed at TP0 were matched with equal segments at TP1 and TP2. The change of diameter stenosis (%DS) defined progress of CAV at each time point and was derived for each matched segment as Δ%DS = %DS (at TP1 or TP2) minus %DS at TP0.[5] Mean and maximal Δ%DS were assessed per patient. Using the maximal Δ%DS, patients were dichotomized as high versus low, according to the respective median value of the overall population at each time point.

LVEF was categorized as preserved (LVEF ≥50%), mildly reduced (LVEF <50% and ≥41%), or reduced (LVEF £40%) at TP0 and TP3 according to the findings in routinely performed echocardiography. A change to a lower LVEF category at TP3 than at TP0 defined deterioration of LVEF. Here, patients' data were adjudicated for verification of the most probable reason for the LVEF decrease and regarding the exclusion of other potential reasons besides CAV.

Data were obtained from the patients' medical records. Laboratory values were obtained at the time point of the angiography or included if obtained within 3 months before the examination. Examiners performing QCA analyses were blinded to baseline data. Statin intensity category was defined according to current recommendations.[10]

Low-density lipoprotein-cholesterol (LDL-c), HDL-c, TGs, and TG/HDL-c were included in this analysis, given these parameters have previously been associated with CAV.[7,11,12] TG/HDL-c was deemed a surrogate parameter of IRS as previously described.[13,14] We also added the parameters of total cholesterol, non-HDL-c, and AIP to our analysis. As previously established, AIP was defined as logarithmically transformed ratio of TG/HDL-c, and non-HDL was calculated following the equation: total cholesterol − HDL-c = non-HDL-c. Post-transplant lipoprotein (a) (Lp(a)) was also included in the baseline lipid analysis.

We used TG/HDL-c ≥3 and LDL-c ≥100 mg/100 ml as previously suggested, potentially relevant cut-off values regarding CAV.[11,15] Because no cut-off values for TGs, HDL-c, and total cholesterol have been associated with CAV, we used cut-off values defined as relevant for cardiovascular disease in patients without transplant: total cholesterol ≥200 mg/100 ml, non-HDL-c ≥130 mg/100 ml, TGs ≥150 mg/100 ml, low HDL-c as HDL-c <40 mg/100 ml in men and HDL-c <50 mg/100 ml in women.[16–20] A cutoff of Lp(a) ≥30 mg/100 ml was used, as previously described.[21] Large AIP was defined as AIP in at least the third tertile. Single dyslipidemia pattern was defined as 1 abnormal lipid parameter of total cholesterol, LDL-c, HDL-c, TGs, or non-HDL-c. Mixed dyslipidemia pattern was defined as ≥2 abnormal values of these lipid parameters.

Absolute increase or decrease was defined by the difference of the values at the respective time points compared with the values at TP0. Because relevant cutoffs have not specifically been defined in patients with HTx, a relevant variation was defined based on values associated with an increased risk for cardiovascular disease and/or mortality in patients without transplant[22–24]: LDL-c increase ≥10 mg/100 ml, total cholesterol increase ≥20 mg/100 ml, and HDL-c decrease ≥0.1 mmol/L (3.9 mg/100 ml). An increase of TGs ≥10 mg/100 ml and an increase of TG/HDL-c ≥0.1 1 were chosen as cutoffs for this study, given a greater risk of type 2 diabetes mellitus and an elevated risk of insulin resistance in patients without transplant were previously described, respectively.[25,26] Relevant cutoffs regarding the increase of non-HDL-c and AIP with atherosclerosis are not clear; therefore, cutoffs were defined as increase of non-HDL-c greater than or equal to median and increase of AIP greater than or equal to the third tertile at the respective time point.

The normal distribution of parameters was tested with the Shapiro-Wilk test. Continuous data are expressed as means with SD or medians with interquartile ranges (IQR). Unpaired continuous data were compared with the unpaired Student's *t* test or Mann-Whitney *U* test, as appropriate. For paired comparison of continuous variables, either paired *t* test or Wilcoxon signed ranks test were used, as appropriate. Categorical data are expressed as numbers and percentages and compared with the chi-square test or Fisher's exact test, as

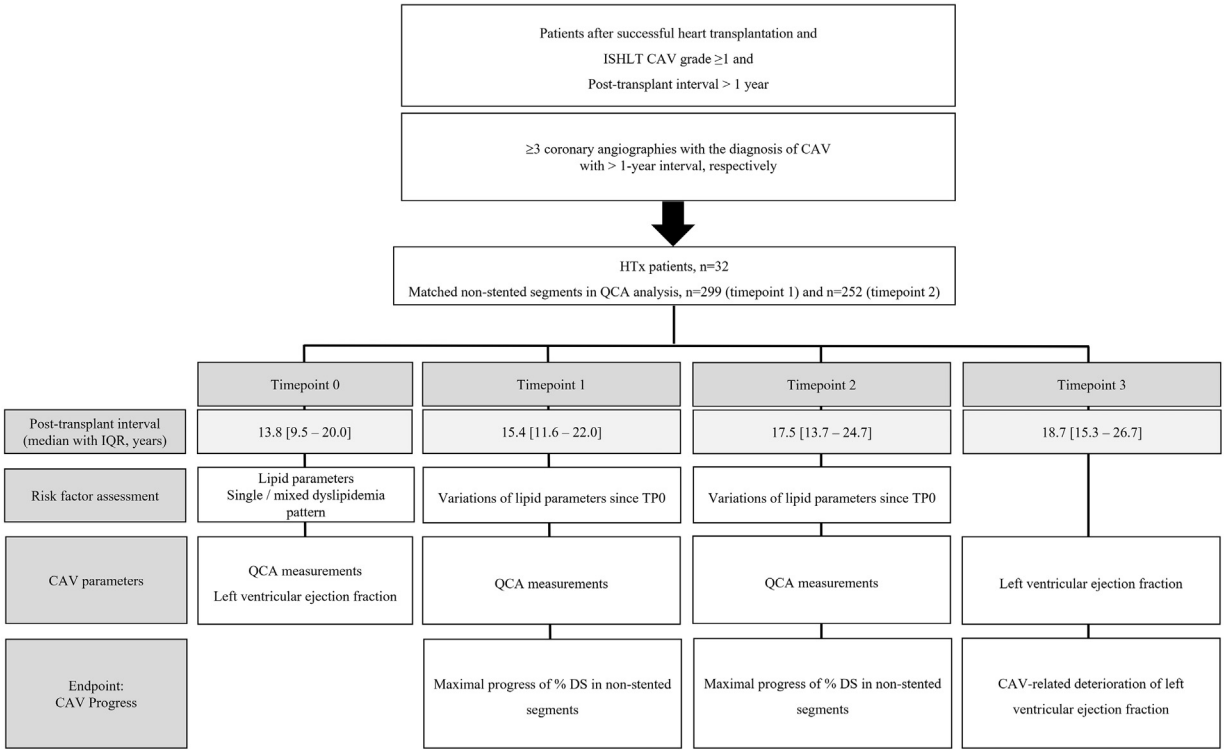

Figure 1. Study flow chart.

appropriate. Odds ratio (OR) with 95% confidence interval (CI) were assessed using binary logistic regression. Significant OR of variations were adjusted in multivariable analysis for (1) potential baseline confounders such as severity of CAV at baseline and baseline values of the respective parameter, and (2) for potential treatment confounders such as cortisone treatment and intensity of statin therapy. A p value <0.05 was considered significant. IBM® SPSS® statistics version 29 (Chicago, IL, USA) was used for analysis.

Results

The study flow chart is presented in Figure 1. In total, 299 matched nonstented segments (TP1) and 252 matched nonstented segments (TP2) were analyzed using QCA in 32 patients. Median age at HTx was 52.9 years (IQR 35.4 to 58.3); median post-transplant interval to angiography at TP0 was 13.8 years (IQR 9.5 to 20.0), and 75% of patients were male. The baseline characteristics are listed in Table 1. QCA measurements in addition to medication and treatment changes at TP2 are listed in Supplementary Tables 1 and 2.

Maximal Δ%DS according to the categories of dyslipidemia pattern at TP0 are presented in Figure 2. Patients with an Lp(a) ≥30 mg/100 ml after transplant had a greater maximal Δ%DS at TP2 (p = 0.02). There was a nonsignificant trend that patients with TG/HDL-c ≥3 and large AIP (third tertile or greater: 0.10) at TP0 had greater maximal Δ%DS at TP1 and TP2, whereas differences in the prevalence of no/single/mixed dyslipidemia patterns were not significant regarding maximal Δ%DS.

The maximal Δ%DS according to relevant lipid variations at TP1 and TP2 are presented in Figure 3.

At TP1, patients in whom an increase of TG/HDL-c ≥0.1 and an increase of AIP had developed presented with greater maximal Δ%DS than did patients without (p = 0.02 and p = 0.01, respectively). Similarly, patients in whom an increase of TG/HDL-c ≥0.1 and an increase of AIP at TP2 had developed presented with a greater maximal Δ%DS than did patients without these increases (p = 0.02 and p = 0.049, respectively). Comparison of maximal Δ%DS according to other categories of variations of lipid parameters showed no significant difference.

The median values of maximal Δ%DS at TP1 and TP2 compared with TP0 were 14.1% and 19.7%, respectively, and these values were used to define substantial CAV progress at the respective time points. The associations of baseline lipid parameters and variations over time regarding the dichotomized parameter of substantial CAV progress are listed in Table 2.

At TP1, there was a nonsignificant trend that baseline TG/HDL-c values ≥3 might be associated with substantial CAV progress (OR 5.4, p = 0.06). An increase of TGs ≥10 mg/100 ml showed a borderline association with substantial CAV progress (OR 4.4, p = 0.05). In addition, any increase of AIP and an increase of AIP ^{3}3 days tertile showed a trend toward an association with a substantial CAV progress at TP2 (OR 3.7, p = 0.08 and OR 4.3, p = 0.07, respectively). Other baseline lipid parameters and variations over time showed no significant association with this end point at TP1.

At TP2, increases of TGs, TG/HDL-c, and AIP were associated with substantial CAV progress (OR 5.0, p = 0.046, OR 9.2, p = 0.01, and OR 6.6, p = 0.02, respectively). Using the cut-off values of patients without transplant, an increase of TGs ≥10 mg/100 ml and of TG/HDL-c ≥0.1 were associated with a substantial CAV progress at TP2 (OR 5.5, p = 0.04 and OR 9.2, p = 0.01, respectively). In addition, an increase of AIP ≥3 days tertile was associated with a substantial CAV progress at TP2 (OR 5.6, p = 0.04). Other baseline lipid parameters and variations over time showed no significant association with a substantial CAV progress at this time point.

After adjustment for values of TG/HDL-c and CAV severity at TP0, the association of an increase of TG/HDL-c with substantial CAV progress at TP2 remained significant (OR 5.9, 1.0 to 34.6, p = 0.049), and after adjustment for potential treatment confounders such as cortisone therapy and statin intensity category at TP2 (OR 5.9, 1.1 to 33.3, p = 0.04).

After adjustment for values of AIP and severity of CAV at TP0, there was a borderline association of increase of AIP with substantial

Table 1
Characteristics of the overall population at timepoint 0

Parameters	
Age at HTx, years	52.9 [35.4 – 58.3]
Male sex, n (%)	24 (75.0)
Post-transplant interval, years	13.8 [9.5 – 20.0]
CAV severity*	
Non-severe CAV, n (%)	21 (65.5)
Severe CAV, n (%)	11 (34.4)
Reason for HTx	
Ischemic cardiomyopathy, n (%)	7 (21.9)
Dilative cardiomyopathy, n (%)	20 (62.5)
Others, n (%)	5 (15.6)
Comorbidities	
Dyslipidemia, n (%)	18 (56.3)
Arterial hypertension, n (%)	23 (71.9)
Obesity†, n (%)	8 (25.0)
Diabetes mellitus, n (%)	7 (21.9)
History of rejection, n (%)	3 (9.4)
Lipid values	
Total cholesterol, mg/dl	168 (152 – 178)
LDL-c, mg/dl	88 (75 – 111)
HDL-c, mg/dl	61 (48 – 74)
Triglycerides, mg/dl	107 (66 – 160)
Non-HDL-c, mg/dl	104 (88 -138)
TG/HDL-c	1.6 (0.9 – 3.3)
Atherogenic index of plasma	0 (-0,36 – 0.17)
Renal function	
Estimated glomerular filtration rate, ml/min	45.3 (31.9 - 60.0)
KDIGO categories	
60 ml/min, n (%)	9 (7)
45-59 ml/min, n (%)	8 (6.3)
30-44 ml/min, n (%)	10 (7.8)
<30 ml/min, n (%)	5 (3.9)
Study intervals	
Interval TP1-TP0, years	2.0 [1.6 - 2.3]
Interval TP2-TP1, years	2.0 [1.5 – 3.0]
Interval TP3-TP2, years	2.3 [1.6 – 3.1]

* Nonsevere CAV was defined as ISHLT CAV 1 and severe CAV as ISHLT CAV ≥2 (including patients with a history of previous PCI).
† Obesity was defined as body mass index ≥30 kg/m^2.
Data are shown as median [IQR] or n (%).
CAV = cardiac allograft vasculopathy; HTx = heart transplantation; ISHLT = International Society of Heart and Lung Transplantation; KDIGO = Kidney Disease: Improving Global Outcomes.

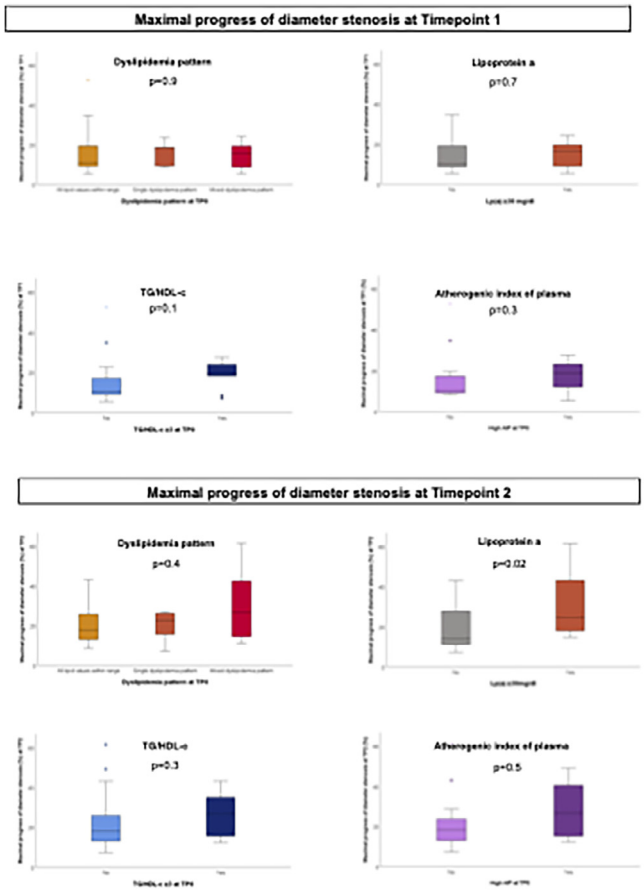

Figure 2. Maximal progress of diameter stenosis in matched nonstented segments according to categories of dyslipidemia pattern at TP0. TP1, matched nonstented segments: 299. TP2, matched nonstented segments: 252. Multiple dyslipidemia pattern was defined as ≥2 abnormal values of total cholesterol, LDL-c, HDL-c, triglycerides, and/or non-HDL-c. Large AIP is defined as AIP of at least the third tertile.

CAV progress at TP2 (OR 5.2, 0.9 to 31.0, p = 0.07). After adjustment for cortisone therapy and statin intensity at TP2, the association of increase of AIP with substantial CAV progress at TP2 remained significant (OR 6.4, 1.3 to 32.6, p = 0.03).

After adjustment for values of TGs and severity of CAV at TP0, the association of increase of TGs with substantial CAV progress at TP2 was not significant. A trend toward an association (OR 4.8, 0.9 to 26.3, p = 0.07) after adjustment for cortisone therapy and statin intensity could be documented.

All patients presented with normal LVEF at TP0. CAV-related reduction in LVEF was diagnosed in 23.3% of patients at TP3.

Patients with CAV-related decrease in LVEF at TP3 had a significantly greater decrease of HDL-c (p = 0.046) and a significantly greater increase of TG/HDL-c (p = 0.03) between TP0 and TP3 (Figure 4). Other variations showed no significant differences between patients with and those without LVEF decrease. There were no significant differences in values of total cholesterol, LDL-c, HDL-c, non-HDL-c, TGs, TG/HDL-c, and AIP at TP0 and TP3 between patients with and those without LVEF decrease at TP3.

Discussion

This longitudinal study in 32 patients with long-term HTx with angiographic manifest CAV revealed that (1) variations of TG/HDL-c, a marker of IRS, TGs, and AIP were associated with substantial CAV progress in matched nonstented segments; (2) the association of a TG/HDL-c increase with substantial CAV progress was independent of baseline TG/HDL-c values and CAV severity, and independent of potential treatment confounders, such as cortisone therapy and statin intensity category; and (3) CAV-related decrease in LVEF at long-term follow-up was associated with greater increase of TG/HDL-c.

Our results highlight the progressive nature of prognostically relevant angiographic CAV in nonstented segments over time and thereby underline the clinical relevance of secondary prevention. In our cohort, lipid values at TP0 did not affect CAV progress, indicating that absolute values of lipids are effectively treated with lipid-lowering medication. Our findings accord with previous results showing an association of IRS and its surrogate, the TG/HDL-c ratio, with CAV development and severity.[12,13] We add important information by showing that AIP could also represent a tool for further risk stratification in patients with HTx with CAV.

There is a particularly large prevalence of IRS reported in patients with HTx compared with the population without transplant, which seems to be related to side effects of immunosuppressive[27,28] and potentially of statin therapy.[29] From patients without transplant, it is known that the pathologic changes in the coronary arteries induced by insulin resistance are multifactorial. Importantly, these are also typical changes reported in CAV. First, insulin signaling plays a relevant role in the activation of nitric oxide, a potent vasodilator and antiatherogenic agent.[30] Second, compensatory hyperinsulinemia can accelerate atherosclerotic processes by multiple mechanisms that are also related to CAV, including vascular smooth muscle cell

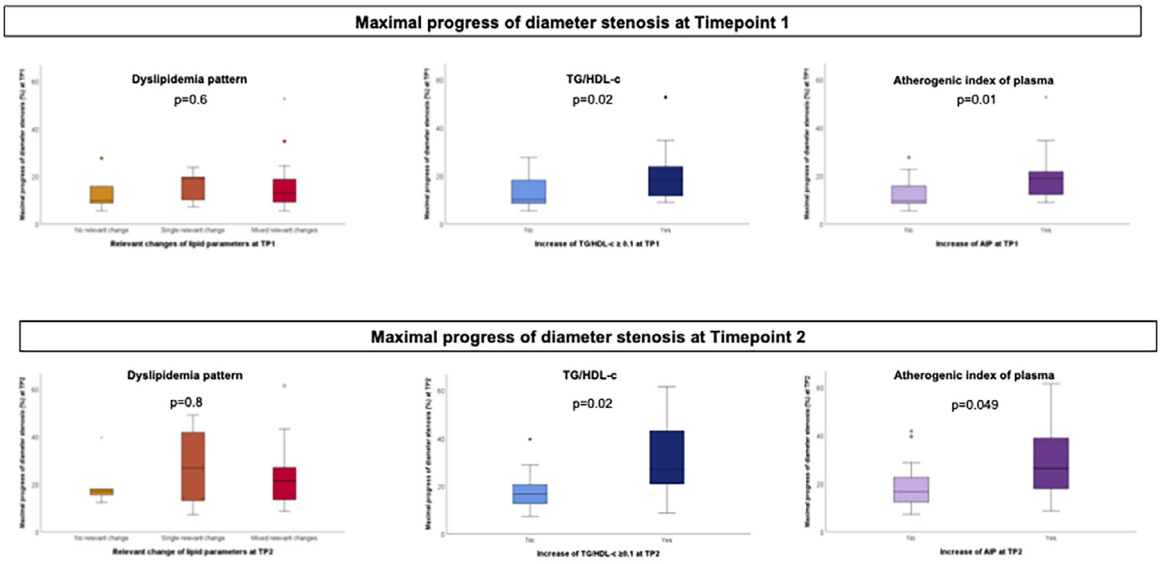

Figure 3. Maximal progress of diameter stenosis in matched nonstented segments according to relevant variations of lipid parameters. TP1, matched nonstented segments: 299. TP2, matched nonstented segments: 252. Mixed changes were defined as ≥2 predefined changes of total cholesterol, LDL-c, HDL-c, triglycerides, and/or non-HDL-c.

Table 2
Associations of lipid parameters at TP0 and variations of lipid parameters with substantial CAV progress

	High CAV progress*			
	Timepoint 1		Timepoint 2	
Parameter	OR (95% CI)	p-value	OR (95% CI)	p-value
Absolute values at timepoint 0 (continuous)				
Total cholesterol	1.0 (1.0 – 1.0)	0.3	1.0 (1.0 – 1.0)	0.8
LDL-c	1.0 (1.0 – 1.0)	0.5	1.0 (1.0 – 1.0)	0.7
HDL-c	1.0 (0.9 – 1.0)	0.1	1.0 (1.0 – 1.0)	0.3
Triglycerides	1.0 (1.0 – 1.0)	0.9	1.0 (1.0 – 1.0)	0.9
TG/HDL-c ratio	1.1 (0.8 – 1.6)	0.7	1.1 (0.8 – 1.6)	0.5
Non-HDL-c	1.0 (1.0 – 1.0)	0.4	1.0 (1.0 – 1.0)	0.7
Atherogenic index of plasma	1.7 (0.2 – 17.0)	0.6	0.9 (0.1 – 7.7)	0.9
Abnormal baseline values at timepoint 0 (dichotomized)				
Total cholesterol ≥200 mg/dl	0.7 (0.1 – 4.7)	0.7	1.5 (0.2 – 10.7)	0.7
LDL-c ≥100 mg/dl	0.8 (0.2 – 3.3)	0.7	2.3 (0.5 – 10.5)	0.3
Low HDL-c†	3.2 (0.5 – 19.6)	0.2	1.4 (0.3 – 7.8)	0.7
Triglycerides ≥150 mg/dl	1.0 (0.2 – 4.5)	1.0	1.0 (0.2 – 4.5)	1.0
Non-HDL-c ≥130 mg/dl	1.9 (0.3 – 11.5)	0.5	1.8 (0.4 – 9.7)	0.5
Mixed pattern‡	1.6 (0.2 – 11.3)	0.6	1.6 (0.2 – 11.3)	0.6
TG/HDL-c ratio ≥3	5.4 (0.9 – 32.3)	0.06	2.6 (0.5 – 13.0)	0.3
Atherogenic index of plasma ≥0.24	5.6 (0.5 – 58.0)	0.2	1.5 (0.2 – 10.7)	0.7
Variation since timepoint 0 (dichotomized)				
Increase of total cholesterol	1.2 (0.3 – 5.1)	0.8	1.9 (0.3 – 8.9)	0.4
Increase of LDL-c	0.8 (0.2 – 3.1)	0.7	0.6 (0.1 – 2.8)	0.6
Decrease of HDL-c	0.7 (0.2 – 2.8)	0.6	1.2 (0.3 – 5.1)	0.8
Increase of triglycerides	3.3 (0.8 – 14.1)	0.1	5.0 (1.0 – 24.3)	**0.046**
Increase of non-HDL-c	1.1 (0.2 – 4.8)	0.9	1.3 (0.3 – 6.6)	0.7
Increase of TG/HDL-c	2.5 (0.6 – 10.6)	0.2	6.3 (1.2 – 32.2)	**0.03**
Increase of atherogenic index of plasma	3.7 (0.9 -15.8)	0.08	6.6 (1.4 – 31.1)	**0.02**
Predefined variation since timepoint 0 (dichotomized)				
Increase of total cholesterol ≥20 mg/dl	0.3 (0.04 – 1.5)	0.1	3.8 (0.6 – 23.9)	0.2
Increase of LDL-c ≥10 mg/dl	0.5 (0.1 – 2.3)	0.4	1.2 (0.3 – 5.0)	0.8
Decrease of HDL-c ≥3.9 mg/dl	0.3 (0.05 – 1.3)	0.1	1.2 (0.3 – 5.4)	0.8
Increase of triglycerides ≥10 mg/dl	4.4 (1.0 – 19.9)	0.05	5.5 (1.1 – 28.4)	**0.04**
Increase of non-HDL-c ≥ median	0.9 (0.2 – 3.6)	0.8	1.7 (0.4 – 7.3)	0.5
Mixed changes§	0.8 (0.2 – 3.1)	0.7	1.7 (0.4 – 6.7)	0.5
Increase of TG/HDL-c ≥0.1	2.6 (0.6 – 11.6)	0.2	9.2 (1.6 – 51.4)	**0.01**
Increase of atherogenic index of plasma ≥3d tertile	4.3 (0.9 – 21.3)	0.07	5.6 (1.1 – 27.5)	**0.04**

* Substantial CAV progress was defined as maximal (%DS at TP1 or TP2 −%DS at TP0) of each patient of at least median value of the overall population at the respective time point.

† Low HDL-c was defined as HDL-c <40 mg/100 ml in men and HDL-c <50 mg/100 ml in women.

‡ ≥2 abnormal values of total cholesterol, LDL-c, HDL-c, triglycerides, and/or non-HDL-c.

§ ≥2 predefined changes of total cholesterol, LDL-c, HDL-c, triglycerides, and/or non-HDL-c.

HDL-c = high-density lipoprotein; LDL-c = low-density lipoprotein; TG/HDL-c = triglycerides/HDL-c ratio.

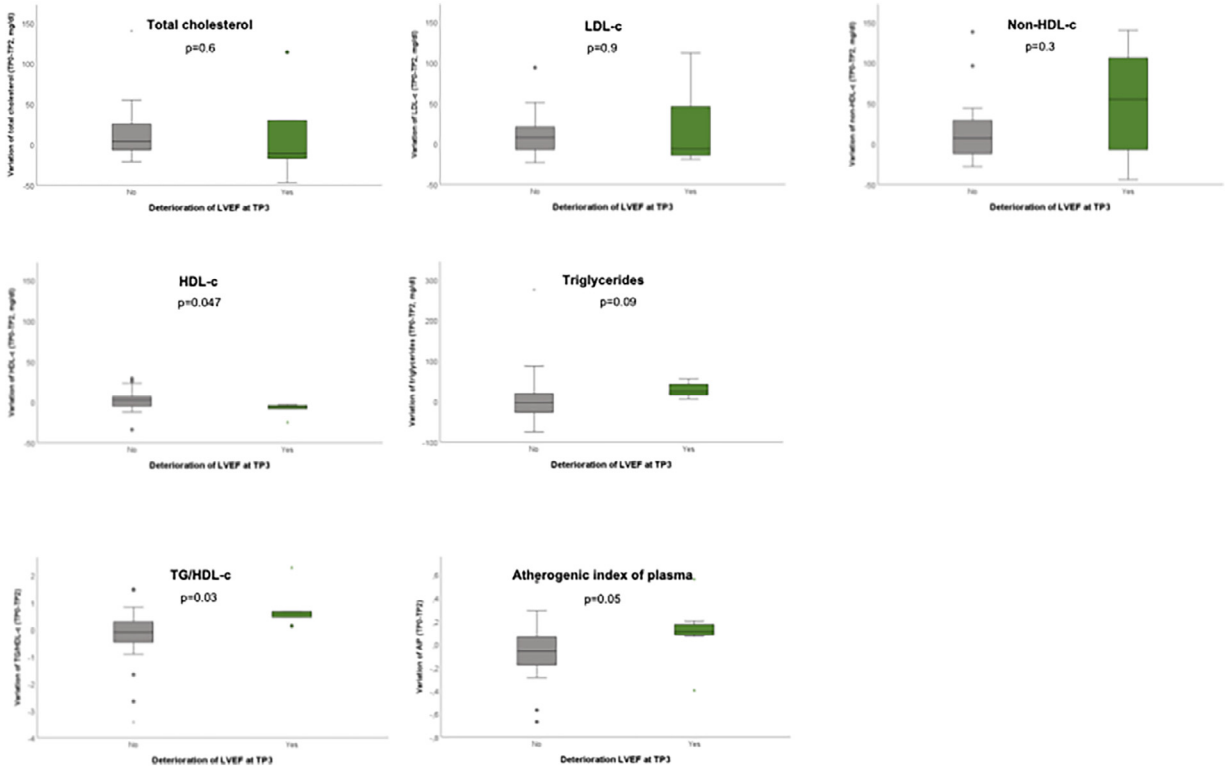

Figure 4. Variation of lipid values at TP2 according to CAV-related deterioration of LVEF at TP3.

growth and proliferation.[31] Finally, insulin resistance is associated with cardiometabolic abnormalities, each of which represents risk factors for atherosclerosis and CAV.[27] In particular, insulin resistance is typically characterized by elevated circulating levels of TGs in combination with low HDL-c.[32] Also combining these 2 parameters, AIP is a valid tool to determine the fractionated esterification rate of HDL-c and has been described as an important tool for CV risk stratification beyond the routine lipid profile and when other atherogenic parameters appear normal.[33]

So far, the association of TG/HDL-c and TGs with CAV has mainly been evaluated on the basis of baseline values.[13] Our results underline the importance of assessing not only baseline lipid parameters but also their variations over time for a better definition of patients with HTx at greater risk of CAV progress. In a large study including >10,000 participants without transplant, an increase of TG/HDL-c ≥0.1 points was related to a 51% increased risk of insulin resistance.[26] Using this cut-off value for an increase of TG/HDL-c, patients in our study also had a relevant association regarding this end point of greater CAV progress, suggesting that this cutoff could also apply to patients with HTx. Further studies are needed to define an optimal threshold of TG/HDL-c reduction before or after the development of CAV.

Increased insulin resistance is predictive of a decrease in LVEF in patients without transplant.[34] Here, chronic inflammation and impaired coronary artery flow reserve have been postulated as potential pathomechanisms.[35,36] In addition, there could be an impact of the interaction of insulin resistance and aldosterone, which contributes to left ventricular dysfunction by prohypertrophic and myocardial fibrosis effects, independently of blood pressure.[37,38] Recently, data have emerged suggesting high-intensity interval training in patients with HTx as a potential additional nonpharmacologic treatment option for CAV prevention.[39] This is of particular interest because physical exercise also represents a primary treatment option of insulin resistance.[40]

Lp(a) is emerging as a risk factor for CAV.[21,41] Our results accord with a previous study showing that a cutoff of Lp(a) ≥30 mg/100 ml defined patients with HTx as at risk for a progress to more severe grades of CAV.[21] Here, similarly to their effect on IRS, immunosuppressive agents could have an indirect effect on nonimmune risk factors for CAV, given they also promote an increase in the levels of Lp(a).[42–44] There is recent evidence that there could be a relevance of intra-individual Lp(a) variability in patients without transplant.[45] Whether routine serial measurements of Lp(a) would add relevant information to define patients with HTx at greater risk of CAV is currently not known.

Prospective studies are needed to assess the extent to which variations of TG/HDL-c and AIP in patients with HTx could be used as biomarker for the definition of patients with HTx at risk of greater CAV progress, their interaction with Lp(a), and whether improving insulin resistance in patients with HTx could represent a beneficial approach regarding secondary CAV prevention and outcome after transplant.

In conclusion, variations of TG/HDL-c, a marker of IRS, and AIP are associated with greater progress of preexisting CAV and CAV-related deterioration of LVEF in our cohort of patients with long-term transplantation. This parameter could help define patients with HTx at greater risk of CAV progress and offer potential targets for secondary prevention evaluated in larger prospective studies.

Although statistical analyses were performed using many QCA measurements, the number of our patient cohort was relatively small, and results must be validated in larger prospective studies. However, this cohort size was comparable to other studies using QCA for the assessment of angiographic CAV in patients with HTx and provides insights into CAV progress in a cohort of patients with a very long follow-up after transplant who are largely underrepresented in CAV studies. This analysis provides the limitation of a cross-sectional study in which, to the best of our knowledge, the first available angiographic data with CAV were analyzed. However, this does not

represent the time point of first CAV diagnosis in all patients. Although CAV and atherosclerosis share some overlapping characteristics, larger prospective studies are needed to assess the extent to which the cut-off values of laboratory parameters defining risk factors in patients without transplant can be translated to patients with HTx with CAV. The individual dynamics of CAV progress are not yet fully understood, and the time points of our study are set pragmatically. This could lead to a potential underestimation of CAV progress in some patients. Potential era effects on our findings cannot be excluded. Although QCA is a well-established method, angiography can potentially underestimate the extent of CAV in comparison with intracoronary artery imaging. Although QCA has been shown to have a good inter- and intra-observer reproducibility and was performed by 2 experienced cardiologists at a large academic center, it was not validated at a core laboratory. In addition, because this study did not include findings of intracoronary artery imaging, the primary underlying pathology leading to CAV progress, such as intimal hyperplasia, atherosclerotic plaques, and/or pathological remodeling, is not known and could potentially differ among patients. Studies including serial intracoronary artery imaging are needed to further quantify the direct effect of IRS in comparison with other risk factors on CAV progress. The extent to which metabolic abnormalities are related to the early progression of CAV during the first year after transplant needs to be further addressed in specific studies. The impact of dietary changes on CAV progress needs to be evaluated in future prospective studies.

Declaration of competing interest

Dr. Hausleiter reports grants and personal fees from Abbott Vascular and grants and personal fees from Edwards Lifesciences, outside the submitted work. Dr. Reichart is cofounder of XTransplant GmbH. Dr. Mehilli reports lecture fees from Daiichi Sankyo, SIS Medical, Biotronik, Astra Zeneca, and Bristol Myers Squibb, outside the submitted work. Dr. Massberg reports grants from the German Federal Ministry of Education and Research/German Center for Cardiovascular Research, grants from the German Research Foundation, grants from Boston Sientific, and grants from Foundation Leduq Transatlantic Network of Excellence, outside the submitted work. The remaining authors have no competing interest to declare.

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Supplementary materials

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