UC San Diego

UC San Diego Previously Published Works

Title

Burden of atherogenic lipids and association with cardiac allograft vasculopathy in heart transplant recipients,

Permalink

https://escholarship.org/uc/item/1339f2nh

Authors

Birs, Antoinette S
Kao, Andrew S
Silver, Elizabeth
et al.

Publication Date

2024-11-01

DOI

10.1016/j.jacl.2024.10.005

Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NoDerivatives License, available at https://creativecommons.org/licenses/by-nd/4.0/

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Journal of Clinical Lipidology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Clinical Lipidology

journal homepage: www.elsevier.com/locate/jacl

Original Research

Burden of atherogenic lipids and association with cardiac allograft vasculopathy in heart transplant recipients☆,☆☆

Antoinette S. Birs, MD [a,*], Andrew S. Kao, MD [b], Elizabeth Silver, MD [a], Eric D. Adler, MD [a], Pam R. Taub, MD [a], Michael J. Wilkinson, MD [a]

[a] Division of Cardiovascular Medicine, Department of Medicine, University of California, San Diego, La Jolla, CA, USA
[b] Univerity of California San Diego School of Medicine, La Jolla, CA, USA

ARTICLE INFO

Key Words:
Dyslipidemia
Heart transplant
Cardiac allograft vasculopathy
Cardiovascular disease prevention
Atherosclerosis, Statins

ABSTRACT

Background: Cardiac Allograft Vasculopathy (CAV) is a leading cause of morbidity and mortality after heart transplantation. There are limited contemporary studies examining post-transplant lipid management and cardiometabolic health.

Objective: We study the burden of cardiometabolic derangements post transplantation and its impact on CAV in a modern cohort of heart transplant recipients.

Methods: All heart transplant (HTx) recipients between January 2019 and December 2020, with two lipid assessments and angiographic surveillance were included. Logistic regression was used to assess association of lipid levels with cardiovascular outcomes and CAV.

Results: Among 87 HTx recipients, atherogenic lipids were significantly elevated after Htx. Median LDL-C increased from a baseline level of 69.5 mg/dL to 86.5 mg/dL, $p = 0.002$, non-HDL-C 91.5 mg/dL to 118 mg/dL, $p < 0.001$, triglycerides 94.5 mg/dL to 133 mg/dL, $p < 0.001$, and remnant cholesterol 19 mg/dL to 27 mg/dL, $p < 0.001$. Increases in non-HDL-C, triglycerides, and remnant cholesterol were significantly associated with increased risk of CAV (Stanford Grade 4 and intimal thickness). Increases in triglycerides and remnant-C were associated with increased risk of composite major adverse cardiovascular events.

Conclusion: We demonstrate a significant increase in atherogenic lipids two years following transplantation with low use (20 %) of high-intensity statin. Increase in atherogenic lipids was associated with increased risk of CAV and increase in triglycerides and remnant cholesterol with increased MACE. Future studies examining cardiometabolic consequences of heart transplantation and optimal treatment strategies to reduce risk of CAV and MACE are needed.

Introduction

Heart transplantation is a lifesaving measure prolonging and improving the quality of life for patients with end stage heart failure. Significant advancements in transplant medicine have increased the expected lifespan from several years to well over a decade for most transplant recipients. Due to long-term exposure to immunosuppression and limited preventive strategies, cardiometabolic complications after solid organ transplantation (SOT) persist. Greater attention to the optimization of cardiometabolic risk in this population to promote graft

☆ Brief Title: Atherogenic Lipids and Cardiac Allograft Vasculopathy following Heart Transplantation ☆☆ Condensed Abstract: Given the high incidence of cardiac allograft vasculopathy after heart transplant, treatment of post-transplant cardiometabolic complications, including dyslipidemia, is a critical aspect of post-transplant care. Despite statin therapy, in a cohort of 87 heart transplant recipients at a single academic center, we observed significant increases in LDL-C, non-HDL-C, triglycerides, and remnant cholesterol over 2 years. Increases in atherogenic lipids were associated with risk of developing Stanford 4 or greater severity CAV. Lipid-lowering therapy should be intensified after heart transplant to mitigate cardiometabolic risk in this population.Abbreviations (< 10): Acute Cellular Rejection, ACR; Cardiac Allograft Vasculopathy, CAV; Heart Transplant, HTx; Intravascular Ultrasound, IVUS; Maximal Intimal Thickness, MIT; Left Main, LM; Proximal Left Anterior Descending, pLAD; Mid Left Anterior Descending, mLAD

* Corresponding author at: Division of Cardiovascular Medicine, Department of Medicine, University of California, 9394 Medical Center Drive, La Jolla, San Diego, CA, USA.

E-mail addresses: abirs@health.ucsd.edu (A.S. Birs), mjwilkinson@health.ucsd.edu (M.J. Wilkinson).

https://doi.org/10.1016/j.jacl.2024.10.005
Received 18 July 2024; Accepted 9 October 2024
1933-2874/© 2024 National Lipid Association. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

longevity and decrease MACE is needed.

Dyslipidemia, hypertension, and new onset diabetes after transplant (NODAT) are common post-transplant conditions affecting nearly 90 % of HTx recipients by 5 years. Many of these conditions result from the obligatory use of immunosuppressive medications, namely corticosteroids and calcineurin inhibitors, which are associated with development of hyperglycemia, insulin resistance, and beta cell injury. A highly aggressive form of diabetes, NODAT, is a commonly reported problem following transplantation.[1-3] While statin therapy is associated with a significant reduction in all-cause mortality and incidence of cardiac allograft vasculopathy (CAV), the use of high-intensity statins is often avoided due to drug-drug interactions as well as historical concerns regarding the development of myositis and rhabdomyolysis.[4-7] In clinical practice, statin intensity may be even lower than the statin intensity prescribed during the pre-transplant period. While coronary artery disease and cardiac events are mitigated by heart transplantation, a decrease in intensity of lipid lowering therapy and concurrent amplification of atherogenesis is particularly worrisome for patients with a history of diabetes, cerebrovascular disease or obesity, in whom atherosclerotic disease may persist within the peripheral vasculature (neurovascular and renovascular beds). Long term exposure to a deranged cardiometabolic state can worsen pre-existing extra-cardiac disease, intensify donor derived coronary atherosclerotic disease, and trigger de-novo atherosclerotic disease within the transplanted heart.

Cardiac allograft vasculopathy, a progressive obliteration of coronary vasculature and a major cause of long-term morbidity, causes death and graft failure in one out of 3 transplant recipients by 10 years. While the pathophysiology of CAV is predominately immune mediated, through unknown mechanisms, aggressive lipid lowering has been associated with reduction in CAV severity and progression[6,8-9]. The presence of intimal thickening and angiographically visible disease has strong prognostic capabilities, however other factors may also play significant role in morbidity free survival. In a case-control prospective study of 54 heart transplant patients with the same degree of severe intimal proliferation, those with hyperlipidemia were more likely to suffer CV outcomes than those without hyperlipidemia[10].

As there is an increased long-term survivorship of transplant patients, cardiometabolic complications resulting from transplant therapies and effects on long term morbidity-free survival and CAV are of major concern. There is poor consensus on how to approach prevention of CAV and MACE in this population, and ideal targets or thresholds for atherogenic lipid levels are unknown. As part of addressing this knowledge-gap, we assessed the burden of cardiometabolic derangements and its impact on CAV in a modern transplant population.

Methods

Study description

This is a single-center, retrospective study of consecutive heart transplant recipients having undergone transplantation between January 1, 2019, through December 31, 2020. Patients were included if they met all the following criteria: aged 18 years or older, alive greater than one year after transplant, and had lipid assessments by standard lipid panel and completed surveillance angiograms (including at least one with intravascular ultrasound (IVUS)) for assessing CAV (Fig. 1).

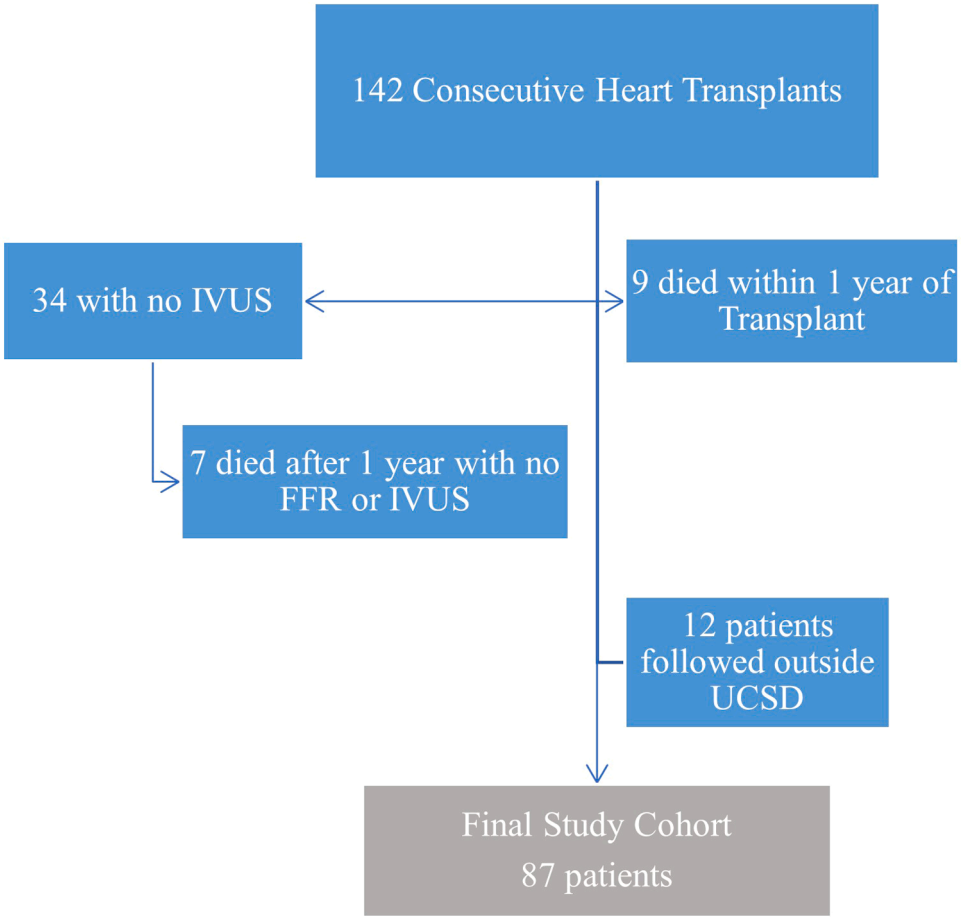

Fig. 1. Patient Flow Diagram. Patients who received heart transplant between 2019 and 2020 were identified ($n = 142$) and screened for exclusion criteria. Those alive > 1 year with baseline and post-transplant lipid studies, and surveillance for cardiac allograft vasculopathy. Patients following at other institutions post-transplant were not included. A total of 87 patients were included.

Baseline data

Baseline demographic data on donors and recipients was obtained from the United Network of Organ Sharing (UNOS) database and review of electronic medical record. Echocardiographic, angiographic and medication data were collected from annual visit evaluations. Laboratory results were collected from the electronic medical record. Baseline lipids and laboratory studies were the closest available results performed prior to transplantation. Lipid evaluations performed at UC San Diego laboratories used standard assays. LDL-C was calculated using the Friedwald equation. Non-HDL cholesterol was calculated from the formula total cholesterol (TC) minus high density lipoprotein cholesterol (HDL-C). Remnant cholesterol was calculated from the formula TC minus low density lipoprotein cholesterol (LDL-C) minus HDL-C. We categorized patients in lower and higher cardiovascular (CV) risk profiles based on pre-transplant comorbidities. Patients with ischemic cardiomyopathy, history of diabetes, and/or pre-HTx A1C $\geq$ 6.5 % were considered to have high CV risk, all other patients were considered to have a low CV risk and these patients typically had history of congenital, genetic, or post-partum cardiomyopathy and no history of diabetes or A1C $>$ 6.5 %.

Per protocol, all patients are initiated on a calcineurin inhibitor, mycophenolate and steroids post-transplant unless adverse side effects prompt modification. All patients with a diagnosis of CAV would be initiated on MTOR inhibitor. All transplant patients were initiated on pravastatin 40 mg and aspirin 81 mg prior to discharge as part of routine post-transplant care unless contraindicated. Initiation of lipid lowering therapies was tracked and the first date of prescription was recorded. Up-titration and addition of lipid lowering therapy was at the discretion of the treating clinician. This study was approved by the institutional review board of University of California, San Diego. All authors agree with and confirm that this study adheres to the principles of the World Medical Association Statement on Organ and Tissue Donation, the Declaration of Helsinki, and the Declaration of Istanbul as stated in the ISHLT statement on transplant ethics.

Intravascular Ultrasound (IVUS)

Coronary angiography included standard view of the right and left system. All studies were performed annually starting at 1 year post transplant. Per protocol, coronary angiogram and IVUS is performed annually for five years unless declined by the patient or relative contraindication was identified. The most common relative contraindications were renal, neurologic, and vascular access concerns. IVUS imaging was performed from the distal LAD to left main ostium at an automatic pullback rate of 1 mm/*sec*. CAV by IVUS was graded according to the Stanford classification and the International Society for Heart and Lung Transplantation classification for coronary angiography (F.G.S. Goar, Circulation, 1992; Mehra ISHLT working group, 2010). For discrete lesions, intimal thickness (IT, mm), minimal lumen area (MLA, mm^2), and lesion location were recorded.

Follow-up and clinical outcomes

Patients were followed from time of transplant until date of death or loss to follow-up. Allograft pathology data were recorded and graded according to the ISHLT classifications (acute cellular rejection classification: grade 0R to 3R; pathological antibody-mediated rejection classification: grade 0–3). Progression to severe CAV was graded by Stanford (grade 4) at second year post-transplant, ISHLT class 1 or maximal intimal thickness (MIT) $>$ 1.0 mm. The rate of the composite endpoint of cardiovascular death, percutaneous coronary intervention or peripheral artery intervention or diagnosis (major adverse cardiovascular events, MACE) was quantified during the study period.

Statistical analysis

Categorical variables are presented as counts and percentages and were compared by the chi-square test, Kruskal-Wallis, or Fischer exact test. Continuous variables are presented as mean +/- SD or median (IQR) and were compared using 2-sample Student's *t*-tests or the Wilcoxon rank sum test as appropriate. Statistical significance was set as a $P < 0.05$. Statistical analysis was performed with R software. Logistic regression was used for association between mg/dL lipid levels and measures of CAV and MACE, adjusted for donor age, sirolimus use and occurrence of clinically significant rejection (2R or pAMR2). While several confounding variables have been reported in the literature, in efforts to maintain a parsimonious model, we selected three variables with strong clinical associations to CAV development.

Results

Of 142 heart transplants performed within the designated study period, 87 patients were included, and 55 patients were excluded in the final analysis. 9 patients did not survive 1 year following transplant, 7 died after 1 year however had no angiogram, 12 patients had no angiogram within our system, and 27 patients did not meet the IVUS angiogram requirement (Fig. 1). At time of transplant, participants were a median age of 59 years old (IQR: 48–64), 75 % were men and 40.2 % were White (Table 1). While 70 % had a history of non-ischemic cardiomyopathy, there was a moderate prevalence of ASCVD risk factors amongst the recipients, 29 % of patients had diabetes, 39 % had prior tobacco use and 10 % had prior cerebrovascular accident (CVA) or transient ischemic attack (TIA) with a median BMI of 25.4 kg/m^2. Donors were a median 33 years old (IQR: 26–42), 79 % were male with median BMI of 26.1 kg/m^2, 55 % were white non-Hispanic. Coronary angiography was available for 50.6 % of donors, with only 2.3 % of performed angiograms deemed abnormal. Hypertension was the most common comorbidity, affecting 20 % of donors.

Lipids

Overall, median atherogenic lipid values two years following transplant were higher when compared to pre-transplant levels (LDL-C: 69.5 vs 86.5 mg/dL, $p = 0.002$, non-HDL-C: 91.5 vs 118 mg/dL, $p < 0.001$, triglycerides: 94.5 vs 133 mg/dL, $p < 0.001$, and remnant cholesterol 19 vs 27 mg/dL, $p < 0.001$) (Table 2). Throughout the study a total of 82 patients had both a post-transplant year 1 and year 2 LDL-C value. Of these 82 patients, 22 % of patients had a mean LDL-C $<$ 70 mg/dL throughout the study period. The percentage of patients with LDL-C of 70 mg/dL or lower at baseline was 50.6 % with only 20.7 % of patients maintaining an LDL $<$ 70 mg/dL by year two, p value $<$ 0.001. As shown in the central illustration, all components of the lipid panel from year 2 studies rose when compared to pre-transplant baseline values.

Most patients in our cohort had non-ischemic cardiomyopathy (69/87) and over 1/3 (37/87) had no CV risk factors as defined as history of dialysis, diabetes, TIA or stroke or tobacco use. Of 87 recipients, 49 % were considered higher cardiovascular risk and were significantly more likely to be male. Among transplant recipients, a history of ischemic cardiomyopathy and the use of mTOR inhibitors were both significantly associated with $a > 25$ % increase in LDL-C post-transplantation. The history of ischemic cardiomyopathy was associated with an odds ratio (OR) of 10.17 ($p = 0.01$), while the use of mTOR inhibitors was associated with an OR of 6.36 ($p = 0.04$).

Lipid-Lowering drug therapy

Drug therapy varied amongst patients prior to transplant, 39 % of patients were on no statin therapy, 6 % on low-, 31 % on moderate- and 24 % were on high-intensity statin (Fig. 2). Atorvastatin 40 mg was the most common high intensity statin (12/21) with Atorvastatin 80 mg to

Table 1
Baseline Characteristics of Heart Transplant Recipients and Donors, $n = 87$.

Recipient	Total ($n = 87$)
Age - median [IQR]	59.0 [48.0, 64.0]
Male - n (%)	65 (74.7)
BMI, kg/m^2- median [IQR]	25.4 [21.9, 29.3]
Race – n (%)	
White, non-Hispanic	35 (40.2)
Black	13 (14.9)
Hispanic	32 (36.8)
Asian	7 (8.0)
Blood type – n (%)	
A	32 (36.8)
AB	5 (5.7)
B	12 (13.8)
O	38 (43.7)
Etiology – n (%)	
Ischemic	18 (20.7)
Non-Ischemic	69 (70.3)
Creatinine- median [IQR]	1.2 [0.9, 1.5]
Multi-organ Listing- n (%)	16 (18.4)
Prior LVAD- n (%)	17 (19.5)
PRA – median [IQR]	0 [0.0, 4.5]
CV Risk Factors	
Prior CVA/TIA -n (%)	9 (10.3)
Diabetes -n (%)	25 (28.7)
Dialysis -n (%)	5 (5.7)
Cigarette Use -n (%)	34 (39.1)
Never	53 (60.9)
Use > 1 year pre-transplant	27 (31.0)
Use within 1 year pre-transplant	7 (8.0)
Donor	Total ($n = 87$)
Age - median [IQR]	33.0 [26.0, 42.5]
Male – n (%)	69 (79.3)
BMI, kg/m^2- median [IQR]	26. 1 [22.9, 30.1]
Race – n (%)	
White, non-Hispanic	48 (55.2)
Black	5 (5.7)
Hispanic	29 (33.3)
Asian	2 (2.3)
Other	3 (3.4)
Cause of Death – n (%)	
Anoxia	38 (43.7)
Head Trauma	35 (40.2)
CVA	12 (13.8)
Other	2 (2.3)
Coronary Angiography – n (%)	
Performed, Normal	42 (48.3)
Performed, Abnormal	2 (2.3)
Not performed	43 (49.4)
CV Risk Factors	
Tobacco use – n (%)	10 (11.5)
Hypertension – n (%)	18 (20.7)
Diabetes – n (%)	2 (2.3)
CDC High Risk Donor – n (%)	33 (37.9)
Creatinine- median [IQR]	1.1 [0.7, 1.4]
Post-Operative Characteristics	Total ($n = 87$)
Immunosuppressive Therapy	
Sirolimus at 1 Year	44 (50.6)
Post Transplant Viremia requiring treatment	
CMV	33 (37.9)
Hepatitis C	11 (12.6)
Rejection events	
AMR or ACR requiring treatment	20 (23.0)
Positive DSA	22 (25.3)

Values are median [IQR] or n (%).
ACR = Acute cellular rejection; AMR = Antibody mediated rejection; BMI = Body Mass Index; CMV = Cytomegalovirus; CVA = Cerebrovascular accident; DSA = Donor specific antibody; IQR = Interquartile range; LDL = Low density lipoprotein; LVAD = Left ventricular assist device; PRA = Panel-reactive antibody; TIA = Transient ischemic attack.

follow (7/21). At time of discharge, 85/87 patients were prescribed moderate intensity statin therapy with pravastatin 40 mg. Two years following transplant, <20 % of patients were on high intensity statin (Table 3). Rosuvastatin 20–40 mg was the most commonly prescribed high intensity statin (14/17). Pravastatin 40 mg was the most prescribed moderate intensity (38/68). Two patients were on low-intensity statins. Icosapent ethyl was the most used non-statin lipid lowering therapy with 10 patients prescribed by year 2. Three patients were prescribed a PCSK9 inhibitor monoclonal antibody.

Table 2
Two Year Lipid Trends Post Heart Transplant, $n = 87$.

	Baseline pre-transplant, median [IQR]	Year Two, median post-transplant [IQR]	P value*
LDL-C (mg/dL)	69.5 [52.3, 99.8]	86.5 [72.3, 111.5]	0.002
HDL-C (mg/dL)	38.0 [31.3, 46.0]	49.0 [42, 61.8]	<0.001
Non-HDL-C (mg/dL)	91.5 [72.0, 123.0]	118.0 [99.5, 139.8]	<0.001
Total Cholesterol (mg/dL)	130.0 [107.0, 170.8]	170.0 [148.5, 200.0]	<0.001
Triglycerides (mg/dL)	94.5 [71.5, 142.5]	133.0 [108.5, 203.5]	<0.001
Remnant-C (mg/dL)	19.0 [14.3, 29.0]	27.0 [21.5, 40.8]	<0.001

Values are median [IQR]; p-value based on Wilcoxon signed rank test with continuity correction.
HDL-C = High density lipoprotein cholesterol; LDL-C = Low density lipoprotein cholesterol; Non-HDL-C = non-high-density lipoprotein cholesterol; Remnant-C = Remnant cholesterol.

Cardiac Allograft Vasculopathy

Of 87 patients, 81 had IVUS data in year 1, and 73 in year 2 post-transplant. Significant intimal thickening considered to be MIT > 1.0 mm, was present in 21 % (17/81) of patients at year 1, and 28.7 % (21/73) of patients at year 2, this is reflected by the increasing prevalence of Stanford 4 disease over time (Fig. 3). When stratified by Stanford classification, patients with higher severity of CAV also had higher non-HDL-cholesterol levels than those with lower grades (Fig. 4A), $p = 0.03$. Most patients had no evidence of angiographic disease, 84 %, and 62 % of patients at years 1 and 2, respectively.

Outcomes

In a median follow up time of 1523 days [IQR 1326, 1678], 4.17 years, 7 total events (death, PCI, or diagnosis of PAD) occurred. One patient suffered CV death, 4.6 % of patients (4/87) received PCI, and 2.3 % (2/87) underwent treatment or referral for peripheral arterial disease. There were no ST elevation myocardial infarctions (STEMI) or non-STEMIs. Three patients were censored for non-CV death, two of which were cancer related and one multi-organ failure with failure to thrive. Maximal Intimal Thickness > 1.0 mm was present in 24 patients by an average 603 days post-transplant. Less than half, 34 out of 73 patients, had severe CAV by IVUS and 29 patients had angiographic evidence of disease (ISHLT classification 1 or higher) by year two. In unadjusted logistic regression analysis, for every unit of increase of LDL-C, non-HDL-C, TC, triglyceride, and remnant-C there was a statistically significant increased likelihood of developing Stanford grade 4, ISHLT class > 1 disease (remnant cholesterol was not significant), or MIT > 1.0 mm, Table 4A. In logistic regression modeling adjusted for donor age, sirolimus use and significant rejection, only atherogenic lipids particles, non-HDL-C, triglycerides, and remnant cholesterol remained statistically significant, Table 4B. Increasing triglycerides, and remnant cholesterol levels were associated with the composite outcome of death, PCI or symptomatic PAD, p-value 0.02.

Discussion

Over the past half century, advancements in transplant medicine

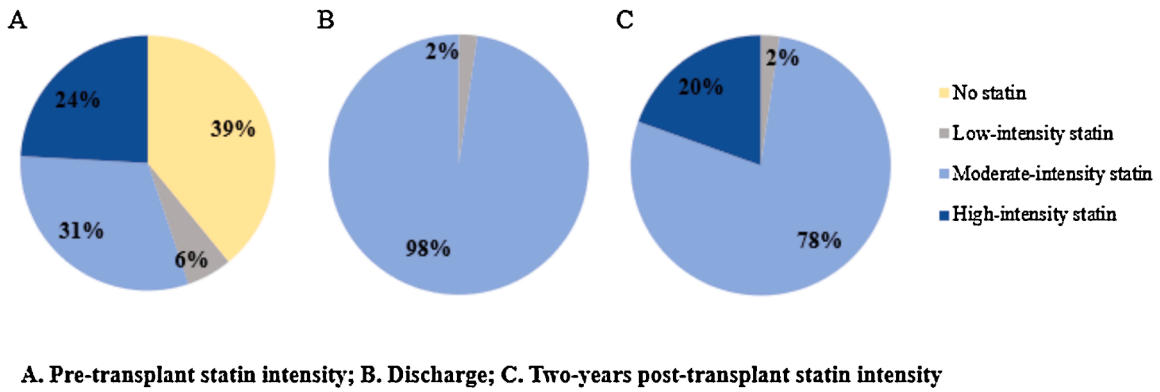

Fig. 2. Statin Intensity Pre and Post Heart Transplantation. This figure illustrates statin intensity trends ranging from pre-transplant to two years post-transplant. Pie graph A demonstrates baseline statin use, graph B demonstrates post-transplant discharge statin, and graph C demonstrates statin intensity two years post-transplant. Pre-transplant there is a higher rate of high intensity statin use with 24 % of patients on high intensity. Post transplant discharge most patients are on moderate intensity and by year two, 20 % of patients are on high intensity statin.

Table 3
Lipid Lowering Therapies in Heart Transplant recipients, $n = 87$.

Statin Therapies	Two Years Post transplant, n (%)
High Intensity	17 (19.5 %)
- Rosuvastatin 20–40 mg	14
- Atorvastatin 40 mg	3
Moderate Intensity	68 (78.2 %)
- Pravastatin 40 mg	38
- Rosuvastatin 10 mg	15
- Rosuvastatin 5 mg	12
- Atorvastatin 20 mg	3
Other	2 (2.3 %)
Rosuvastatin 2.5 mg	2
Non-Statin Therapies	16 (18.4 %)
Ezetimibe	3
Icosapent Ethyl	10
PCSK9 inhibitor	3
Evolocumab 140 mg	1
Alirocumab 75 mg	2

Values are n (%).
PCSK9i = Proprotein convertase subtilisin/kexin type 9 inhibitor.

have markedly increased the average lifespan of heart transplant recipients. While a heavy focus remains on one-year survival, comorbidities resulting from obligatory transplant medications are of rising concern. Increased long-term survivorship and higher incidence of comorbid conditions among transplant recipients exacerbate cardiometabolic consequences, posing a threat to long-term graft function and morbidity-free survival[3,9,11-13]. We report a significant rise in lipid levels post-transplantation and the association between increasing atherogenic lipid levels and the risk of cardiac allograft vasculopathy (CAV).

Firstly, we observed a significant increase in all components of the lipid panel over two years of standard immunosuppressive therapy. Specifically, the median LDL-C level post-transplant rose 23 % from baseline levels, and remnant cholesterol increased 60 %, exposing patients to higher risk of MACE due to atherogenic lipoproteins beyond LDL-C[14]. The International Society for Heart and Lung Transplantation (ISHLT) guidelines support the use of statins post-transplant to promote graft longevity, treat dyslipidemia, and prevent cardiac allograft vasculopathy.[15-19] While statins remain a cornerstone of post-transplant prevention and prophylaxis, there are no specific lipid or triglyceride targets in transplant population, nor are there specific guidelines describing the optimal management strategy for prevention and treatment of disease in those with ischemic cardiomyopathy, or high-risk comorbidities (diabetes, prior stroke). Furthermore, the addition or transition to Sirolimus or other mTOR inhibitors, which are known to mitigate CAV progression, has been associated with worsening dyslipidemia. This was corroborated by our study, which found that patients prescribed mTOR inhibitors had a 6.36-fold increased risk of experiencing an increase in LDL-C following transplantation[8,20-21].

The use of high-intensity statins after heart transplant is often limited due to concerns of myositis and rhabdomyolysis from drug interactions

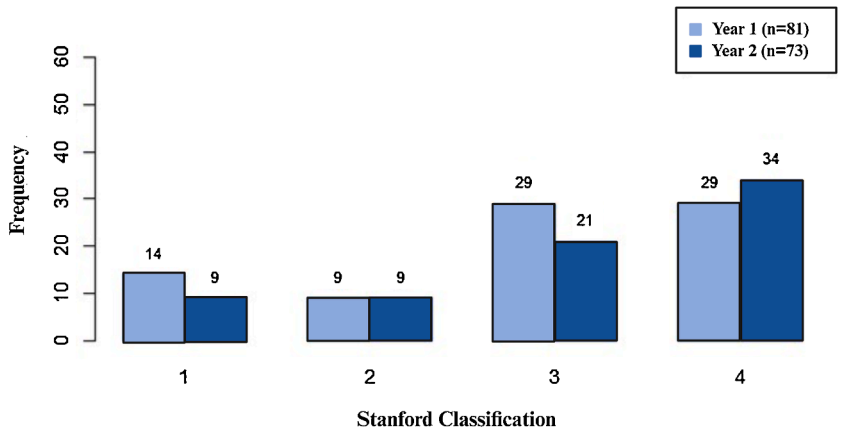

Fig. 3. Cardiac Allograft Vasculopathy Severity, Stanford Classification at Year 1 and Year 2. High grades of cardiac allograft vasculopathy were present in year 1 surveillance imaging with intravascular ultrasound (IVUS), 36 % of patients had severe disease. By year two, those with severe disease rose to 47 % and fewer patients had grade 1 (minimal) or grade 3 (moderate) disease.

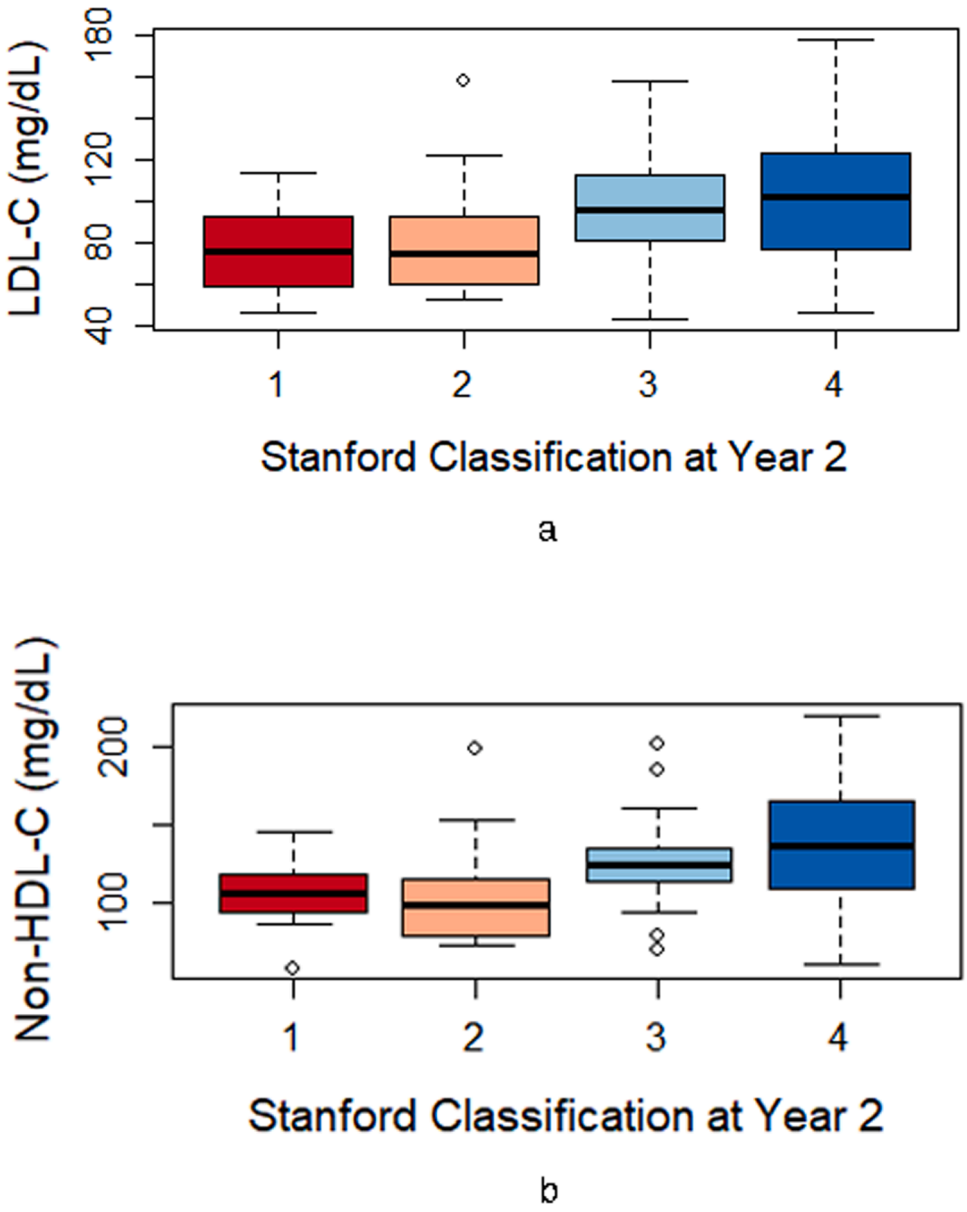

Fig. 4. (A) Boxplot of CAV classification and Lipid Values, Two Years Post-Transplant. Mean LDL-C value of patient with minimal, mild, moderate and severe CAV. Patients with higher severity of CAV have a trend towards higher LDL-C, p value 0.10 by Kruskal-Wallis. (B) Boxplot of CAV classification and Lipid Values, Two Years Post-Transplant. Patients with higher CAV severity have higher non-HDL-C values, p value 0.03 by Kruskal-Wallis.

Table 4A
Unadjusted Logistic Regression model for cardiac allograft vasculopathy and composite MACE by lipid level.

	LDL-C (mg/dL)		Non-HDL (mg/dL)		Total Cholesterol (mg/dL)		Triglycerides (mg/dL)		Remnant Cholesterol (mg/dL)	
	Odds Ratio	p	Odds Ratio	p	Odds Ratio	p	Odds Ratio	p	Odds Ratio	p
Primary Outcome										
Stanford Grade 4	1.020	**0.03**	1.022	**<0.01**	1.014	0.05	1.008	**0.02**	1.038	**0.02**
ISHLT Class > 1	1.018	0.05	1.018	**0.02**	1.014	0.05	1.006	0.06	1.028	0.07
MIT > 1.0 mm	1.013	0.15	1.019	**0.02**	1.016	**0.04**	1.010	**< 0.01**	1.050	**< 0.01**
Secondary Outcome										
Composite Mace[b]	1.004	0.77	1.015	0.17	1.005	0.65	1.011	**0.02**	1.053	**0.02**

occurring between statin and immunosuppressants, which share CYP metabolism pathways[7,22-24]. As a result, statin intensity may be even lower than the statin intensity prescribed during the pre-transplant period. Reflecting national and guideline practices, fewer patients in our cohort were on high intensity statin following transplant compared to statin intensity pre-transplant, and even fewer were on triglyceride lowering agents in our cohort. While the trials shaping much of today's statin practices were conducted in the 1990s and early 2000s and included combinations of older and less commonly used medications, no clinical trials have evaluated a modern cohort of transplant recipients[7,19,25-27]. Notably, in recent, large meta-analysis, myopathy events were not significantly different in patients with statin use[4].

Table 4B
Adjusted Logistic Regression model for cardiac allograft vasculopathy and composite MACE by lipid level.

	LDL-C (mg/dL)		Non-HDL (mg/dL)		Total Cholesterol (mg/dL)		Triglycerides (mg/dL)		Remnant Cholesterol (mg/dL)	
	Odds Ratio	P	Odds Ratio	p	Odds Ratio	p	Odds Ratio	p	Odds Ratio	p
Primary Outcome										
Stanford Grade 4	1.016	0.08	1.018	**0.02**	1.011	0.13	1.008	**0.03**	1.038	**0.03**
ISHLT Class > 1	1.015	0.12	1.015	0.06	1.012	0.12	1.005	0.12	1.024	0.13
MIT > 1.0 mm	1.010	0.30	1.016	**0.04**	1.014	0.08	1.010	**< 0.01**	1.051	**< 0.01**
Secondary Outcome										
Composite Mace[b]	1.003	0.81	1.014	0.22	1.004	0.72	1.010	**0.02**	1.052	**0.02**

ISHLT = International society of heart and lung transplantation; LDL-C = Low density lipoprotein cholesterol; MIT = Maximal intimal thickness.
Adjust for Donor age, Sirolimus use by year 2, History of 2R or pAMR2 Rejection.
[a]Primary Outcome: Severe Cardiac Allograft Vasculopathy; Stanford Grade 4, Maximal Intimal Thickness > 1.0 mm, ISHLT Class > 1.
[b]Secondary Outcome: Composite of cardiovascular death, percutaneous coronary intervention, or symptomatic peripheral arterial disease.

Ultimately, 20 % of patients transitioned to high intensity statin over two years following transplant. As transplant guidelines have no recommendations in regard to statin titration, most up-titrations occurred at provider's discretion, primarily in patients with secondary prevention indications, such as prior stroke, or ischemic heart disease. In efforts to find safe and effective methods of lipid-lowering for CAV in transplant patients, Broch et al. conducted the first randomized controlled trial examining the use of a monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9, evolocumab. The study demonstrated a mean LDL-C reduction of 1.1mmol/L (42.54 mg/dL) in patients treated with evolocumab[28]. Although no significant change in maximal intimal thickness was observed, longer follow-up is planned to assess for potential changes over time and future studies prospectively testing the impact of non-statin lipid-lowering therapies on cardiometabolic risk and CAV in heart transplant recipients are needed.

Intimal thickening is a valuable prognostic tool for predicting adverse outcomes in transplant patients. However, the threshold for what is considered significant continues to evolve due to changes in comorbidities, preservation strategy and viral exposure.[29-30] These factors can impact immune signaling, alter coronary endothelium and change inflammatory pathways, affecting baseline intimal thickening. Mehra et al. challenge the notion of intimal thickening as a sole prognostic indicator, demonstrating that in patients with comparable intimal thickness, adverse events were influenced more by other comorbid conditions. Their study found that hyperlipidemia was a significant predictive factor for adverse cardiac events[10]. Similarly, our data also ties elevated lipid levels with adverse events. For most components of the lipid panel, unit increase in lipids was associated with increasing presence of IVUS and angiographic disease in adjusted and unadjusted models. Overall, the incidence of subclinical IVUS disease by our definition was high. We used a conservative MIT cutoff of 1.0 mm for significant subclinical disease based on previous published data and high baseline presence of IT on year 1 studies (72 % Stanford 3 or higher disease)[10,31].

Indeed, while any vasculopathy noted within a coronary artery of a transplanted heart may be categorized under the umbrella term "CAV", lesions may be distinct entities sensitive to various treatment strategies. For instance, lesions may primarily be neoatherosclerotic plaque, donor derived atherosclerotic plaque or immune mediated concentric intimal thickening[17,32-34]. These three etiologies may overlap or exist independently with varying responses to stenting, aggressive lipid control or use of mTOR inhibition. In a recent study by Watanabe et al., patients with donor atherosclerosis experience worsening CAV progression post-transplant compared to those without donor atherosclerosis[32]. These inherent and pathophysiologic differences may account for the observed variability in prognosis and graft longevity associated with CAV[17].

Implementing primary prevention strategies is of high importance to extend event-free survival, mitigate the adverse effects of atherogenic lipids and enhance overall outcomes post-transplantation. Lipid management should be a key feature of post-transplant care which revolves around healthcare maintenance, and optimization of comorbidities. Use of non-statin therapies such as PCSK9 inhibitor monoclonal antibodies, inclisiran, ezetimibe and bempedoic acid may be used to address LDL and residual risk in this population. Future studies directed towards clinical trials to systematically study and identify prevention strategies for SOT patients is of paramount importance.

Study limitations

This study had several limitations. First, this is a single center retrospective study which limits generalizability, and our findings may be limited by our modest population size. Use of mTOR inhibitors has been demonstrated to attenuate CAV and plaque progression as well as increase atherogenic lipids. Use of mTOR inhibitor was high in our cohort which may not reflect the prescribing protocols of all centers. Additionally, we were unable to adjust for differences in donor derived CAD which may confound the assessment of CAV. CAV is a chronic condition and complications from CAV typically occur after 5 years following transplantation. Mean follow-up time was roughly 4 years. While IVUS is a highly sensitive measure of CAV often detecting early and subclinical disease longer-term follow-up is warranted to establish CAV risk in this population. Additionally, IVUS and angiograms were graded by one of two operators and were not independently reviewed by a core laboratory. As a retrospective, real-world study, lipids were also not measured in a standardized way across all patients, and we relied on the availability of lipid values obtained as a part of routine medical care. Our data also cannot allow us to determine reasons for the patterns of lipid-lowering therapy use we observed (e.g. concerns around costs of therapy or potential side-effect risks, drug-drug interaction risks, or actual side-effects experienced by patients pre- or post-transplant with lipid-lowering therapies). Current guideline recommendations leave statin titration open for varying practices; therefore, our center's protocol may not be representative of other centers. A multi-center study evaluating lipid lowering strategies, and assessment of adverse events related to statin use is necessary to better define tolerance in this population. Establishment of LDL targets for transplant recipients who have primary and secondary prevention indications should be systematically studied in a prospective or randomized control study to establish the impact of lipid control on CV events and CAV. Lastly, while inflammatory markers are not routinely measured in the transplanted patient at our center, there is evidence to suggest that an inflammatory milieu may contribute to the development of CAV, and should be investigated[35].

Conclusion

In a modern cohort of transplant recipients, there is a significant increase in the atherogenic lipids following heart transplantation, along with low use of high-intensity statins. Higher levels of atherogenic lipids, especially non-HDL-C, are associated with incident angiographic and IVUS determined CAV. While dyslipidemia and adverse cardiometabolic effects following transplant have been previously

recognized, our experience, in the current era of immunosuppression and increasing patient survival, adds to the growing body of evidence supporting the critical need to address the cardiometabolic consequences, including dyslipidemia, following transplant to protect graft longevity and morbidity free survival. Future studies focusing on emerging non-statin lipid lowering therapies are necessary in this population in which concerns for drug-drug interactions with immunosuppressing therapies often limits use of statin therapy.

Ethical statement

This study was approved by the institutional review board of University of California, San Diego. All authors agree with and confirm that this study adheres to the principles of the World Medical Association Statement on Organ and Tissue Donation, the Declaration of Helsinki, and the Declaration of Istanbul as stated in the ISHLT statement on transplant ethics.

CRediT authorship contribution statement

Antoinette S. Birs: . **Andrew S. Kao:** Writing – review & editing, Writing – original draft, Validation, Data curation. **Elizabeth Silver:** Writing – review & editing, Validation, Data curation. **Eric D. Adler:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Pam R. Taub:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Michael J. Wilkinson:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

MW: Dr. Wilkinson is a consultant to Amarin, Regeneron, Kaneka, and The Kinetix Group; reports advisory board fees from Novartis and NewAmsterdam and speaker fees from Regeneron; has received grant support from Amgen (investigator-initiated study) and support through an institutional consulting agreement with Novartis paid to his institution for advising on research; and has contracted research grants to his institution with Amgen, Novartis, Ionis, and Mineralys, and Lilly.

PT: Dr. Pam R. Taub is a consultant for Amgen, Novartis, Esperion, Boehringer Ingelheim, Lilly, Novo Nordisk, Medtronic and Edwards and is a shareholder in Epirium Bio.

EA: Chief Medical Officer and Head of Research: Lexeo Therapeutics. Shareholder: Rocket Pharmaceuticals. Scientific Founder: Papillion Therapeutics. Founder, Scientific Board and Shareholder: Corstasis Therapeutics.

The other authors have nothing to disclose. Use of AI and AI-assisted Technologies Statement: AI was not used for any aspect of this manuscript preparation or writing.

References

1. Hansen MK, Mortensen MB, Warnakula Olesen KK, Thrane PG, Maeng M. Non-HDL cholesterol and residual risk of cardiovascular events in patients with ischemic heart disease and well-controlled LDL cholesterol: a cohort study. *Lancet Reg Health - Europe*. 2024;36, 100774.
2. Jindal RM, Sidner RA, Milgrom ML. Post-transplant diabetes mellitus. The role of immunosuppression. *Drug Saf*. 1997;16:242–257.
3. Cuomo G, Cioffi G, Di Lorenzo A, et al. Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors Use for Atherogenic Dyslipidemia in Solid Organ Transplant Patients. *J Clin Med*. 2022;11.
4. Vallakati A, Reddy S, Dunlap ME, Taylor DO. Impact of Statin Use After Heart Transplantation. *Circulation*. 2016;9, e003265.
5. Stojanovic I, Vrtovec B, Radovancevic B, et al. Survival, graft atherosclerosis, and rejection incidence in heart transplant recipients treated with statins: 5-year follow-up. *J Heart Lung Transplant*. 2005;24:1235–1238.
6. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of Pravastatin on Outcomes after Cardiac Transplantation. *New Eng J Med*. 1995;333:621–627.
7. Page 2nd RL, Miller GG, Lindenfeld J. Drug therapy in the heart transplant recipient: part IV: drug-drug interactions. *Circulation*. 2005;111:230–239.
8. Topilsky Y, Hasin T, Raichlin E, et al. Sirolimus as primary immunosuppression attenuates allograft vasculopathy with improved late survival and decreased cardiac events after cardiac transplantation. *Circulation*. 2012;125:708–720.
9. Khush KK, Hsich E, Potena L, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-eighth adult heart transplantation report - 2021; Focus on recipient characteristics. *J Heart Lung Transplant*. 2021;40:1035–1049.
10. Mehra MR, Ventura HO, Uber PA, Scott RL, Park MH. Is all intimal proliferation created equal in cardiac allograft vasculopathy? The quantity–quality paradox. *J Heart Lung Tranplant*. 2003;22:118–123.
11. Lund LH, Edwards LB, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Heart Transplantation Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J Heart Lung Transplant*. 2016;35:1158–1169.
12. Israni AK, Snyder JJ, Skeans MA, et al. Predicting coronary heart disease after kidney transplantation: Patient Outcomes in Renal Transplantation (PORT) Study. *Am J Transplant*. 2010;10:338–353.
13. Parekh J, Corley DA, Feng S. Diabetes, hypertension and hyperlipidemia: prevalence over time and impact on long-term survival after liver transplantation. *Am J Transplant*. 2012;12:2181–2187.
14. Olga C, Xavier P, Isaac S, et al. Remnant Cholesterol, Not LDL Cholesterol, Is Associated With Incident Cardiovascular Disease. *J Am Coll Cardiol*. 2020;76:2712–2724.
15. Frohlich GM, Rufibach K, Enseleit F, et al. Statins and the risk of cancer after heart transplantation. *Circulation*. 2012;126:440–447.
16. See Jr VY, DeNofrio D, Goldberg L, et al. Effect of atorvastatin on postcardiac transplant increase in low-density lipoprotein cholesterol reduces development of intimal hyperplasia and progression of endothelial dysfunction. *Am J Cardiol*. 2003;92:11–15.
17. Schmauss D, Weis M. Cardiac allograft vasculopathy: recent developments. *Circulation*. 2008;117:2131–2141.
18. Magnani G, Carinci V, Magelli C, Potena L, Reggiani LB, Branzi A. Role of statins in the management of dyslipidemia after cardiac transplant: randomized controlled trial comparing the efficacy and the safety of atorvastatin with pravastatin. *J Heart Lung Tranplant*. 2000;19:710–715.
19. Kobashigawa JA, Moriguchi JD, Laks H, et al. Ten-Year Follow-Up of a Randomized Trial of Pravastatin in Heart Transplant Patients. *J Heart Lung Tranplant*. 2005;24:1736–1740.
20. Asleh R, Briasoulis A, Kremers WK, et al. Long-Term Sirolimus for Primary Immunosuppression in Heart Transplant Recipients. *J Am Coll Cardiol*. 2018;71:636–650.
21. Masetti M, Potena L, Nardozza M, et al. Differential effect of everolimus on progression of early and late cardiac allograft vasculopathy in current clinical practice. *Am J Transplant*. 2013;13:1217–1226.
22. Norman DJ, Illingworth DR, Munson J, Hosenpud J. Myolysis and acute renal failure in a heart-transplant recipient receiving lovastatin. *N Engl J Med*. 1988;318:46–47.
23. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J*. 2019;41:111–188.
24. Wiggins BS, Saseen JJ, Page RL, et al. Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins and Select Agents Used in Patients With Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2016;134:e468–e495.
25. Campana C, Iacona I, Regazzi MB, et al. Efficacy and pharmacokinetics of simvastatin in heart transplant recipients. *Ann Pharmacother*. 1995;29:235–239.
26. Park JW, Siekmeier R, Lattke P, et al. Pharmacokinetics and pharmacodynamics of fluvastatin in heart transplant recipients taking cyclosporine A. *J Cardiovasc Pharmacol Ther*. 2001;6:351–361.
27. Ichimaru N, Takahara S, Kokado Y, et al. Changes in lipid metabolism and effect of simvastatin in renal transplant recipients induced by cyclosporine or tacrolimus. *Atherosclerosis*. 2001;158:417–423.
28. Broch K, Lemström K, Gustafsson F, et al. Randomized Trial of Cholesterol Lowering With Evolocumab for Cardiac Allograft Vasculopathy in Heart Transplant Recipients. *J Am Coll Cardiol HF*. 2024. https://doi.org/10.1016/j.jchf.2024.04.026. null0 (0).
29. Kadosh BS, Birs AS, Flattery E, et al. Cardiac allograft vasculopathy in heart transplant recipients from hepatitis C viremic donors. *Clin Transplant*. 2024;38.e15294.
30. Birs AS, Bui QM, Gernhofer Y, et al. Cardiac allograft vasculopathy outcomes among donation after circulatory death heart transplant recipients. *JHLT Open*. 2024;4.
31. Sperry BW, Qarajeh R, Omer MA, et al. Influence of Donor Transmitted and Rapidly Progressive Coronary Vascular Disease on Long-Term Outcomes After Heart Transplantation: A Contemporary Intravascular Ultrasound Analysis. *J Card Fail*. 2021;27:464–472.
32. Watanabe T, Seguchi O, Yanase M, et al. Donor-Transmitted Atherosclerosis Associated With Worsening Cardiac Allograft Vasculopathy After Heart

Transplantation: Serial Volumetric Intravascular Ultrasound Analysis. *Transplantation*. 2017;101:1310–1319.

33. Couto-Mallón D, Almenar-Bonet L, Barge-Caballero E, et al. Prevalence, Characteristics, and Prognostic Relevance of Donor-Transmitted Coronary Artery Disease in Heart Transplant Recipients. *J Am Coll Cardiol*. 2023;82:753–767.

34. König A, Sohn H-Y, Rieber J, Schiele TM, Kilian E, Klauss V. Coronary Plaque Classification Using Intravascular Ultrasound—Radiofrequency Analysis in a Heart Transplant Patient With Severe Atherosclerosis. *J Heart Lung Transplantat*. 2007;26:960–961.