Dyslipidemia is common after heart transplantation (HT) and is attributed to immunotherapy, as well as dietary factors and genetic predisposition.1-3 Statins are well established in the treatment of dyslipidemia after HT and have been shown to reduce the incidence of cardiac allograft vasculopathy (CAV) and improve survival.1-4-7 The proposed mechanisms of action for the observed benefits of statins after HT are a result of a combination of their lipid-lowering properties and pleotropic effects, including favourable immunomodulatory effects and improvement in endothelial function.8

A wealth of data in atherosclerotic coronary disease supports the cardiovascular benefits of low-density-lipoprotein cholesterol (LDL-C) reduction, and current guidelines include recommendations for LDL-C target levels of < 1.8 mmol/L or < 1.4 mmol/L, depending on cardiovascular risk.9,10 Although guideline-directed therapy for HT recipients includes the initiation of a statin, ideal LDL-C target levels after HT have not been established. Furthermore, the relationship between LDL-C and the development of CAV after transplant has not been well explored, and there are currently no recommended LDL-C target levels specific to the HT population. The objectives of this study are to characterize lipid profiles early after HT and to evaluate the relationship between serum LDL-C values early post-transplant, and to evaluate the relationship between early LDL-C and the development of CAV.

Methods

Study design

We conducted a retrospective review of consecutive adults (age ≥ 18 years) who underwent HT at the University of Ottawa Heart Institute (Ottawa, Ontario, Canada) and Toronto General Hospital (Toronto, Ontario, Canada) between January 1, 2010 and December 31, 2018. The study was approved by the local research ethics boards and was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

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See page 1460 for disclosure information.
between LDL-C and CAV was assessed using Cox proportional hazards and logistic regression models adjusted a priori for clinically important covariates, including recipient and donor age, recipient sex, ischemic time, and pre-HT diabetes.

**Results:** A total of 386 patients followed for a median (range) of 4.4 (2.8-6.8) years were included. LDL-C at baseline (2.11 ± 0.86 mmol/L) and 1 year after HT (2.20 ± 0.88 mmol/L) was similar (P = 0.21), but it was lower at the end of follow-up (1.89 ± 0.74 mmol/L, P < 0.01). Of 309 patients who underwent angiography, 54% had CAV. The risk of CAV did not vary according to baseline, 1-year, or change from baseline to 1-year LDL-C. The odds of CAV at 1 year were equally likely across LDL-C values (adjusted odds ratio 1.00, 95% confidence interval: 0.61-1.63 for baseline, and adjusted odds ratio 1.25, 95% confidence interval: 0.74-2.10 for 1-year LDL-C).

**Conclusions:** No association was identified between early LDL-C and the development of CAV. Our findings do not support targeting a specific LDL-C for patients who do not otherwise meet criteria for guideline-recommended LDL-C target levels. Randomized studies are warranted to determine if lipid-lowering to a specific LDL-C target level modifies the risk of CAV.

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**Reporting of Observational Studies in Epidemiology** statement.11

**Study population**

All patients with ≥ 1 LDL-C measurement who survived the first year after HT were included. Patients were excluded from analysis if they were not followed locally, died in the first year after HT, underwent revascularization or had evidence of donor coronary disease at the time of HT, or had no recorded lipid values.

**Data collection**

The following variables were collected from electronic medical records at both institutions: baseline recipient demographics (age at HT, sex, transplant indication, height and weight, prior ventricular assist device, cytomegalovirus status, sensitization, total ischemic time); recipient comorbidities pre-HT (diabetes, hypertension, hyperlipidemia, serum creatinine); and donor demographics (age, sex, cytomegalovirus status). The use of lipid-lowering therapy including statins, ezetimibe, and other agents was extracted at baseline (defined as within 3 months of HT), 1 year, and last available follow-up after HT. There was no loss to follow-up.

**Lipid parameters**

Lipid values, including total cholesterol, LDL-C, high-density-lipoprotein cholesterol (HDL-C), non-HDL-C, and triglyceride levels were collected at baseline, 1 year, and last available follow-up after HT. In 6 patients for whom LDL-C could not be determined due to hypertriglyceridemia, a previously published modified formula for calculating LDL-C was used.15 LDL-C was evaluated as a continuous variable and as a categorical variable, according to 4 LDL-C groups based on cutoffs used in guideline-directed therapy of hyperlipidemia: < 1.5 mmol/L; < 1.8 mmol/L; < 2.0 mmol/L; and < 2.5 mmol/L.8,9,13,14 The change in LDL-C from baseline to 1 year after HT was assessed by categorizing patients into 4 groups (low to low, low to high, high to high, and high to low) according to these 4 LDL-C thresholds and defining “low” and “high” as below and above the threshold, respectively.

**Outcome measures**

The primary outcome was the incidence of angiographic CAV grades 1-3 (CAV1-3), per the International Society for Heart and Lung Transplantation (ISHLT) definition, during the study period.15 Secondary outcomes included the incidence of the following: (i) CAV1-3 at 1 year post-HT; (ii) maximal intimal thickness (MIT) ≥ 0.5 mm measured on intravascular ultrasound (IVUS) at 1 year post-HT; and (iii) a composite outcome of CAV grade 2-3 (CAV2-3), myocardial infarction, coronary revascularization, retransplantation, and/or cardiovascular mortality. MIT ≥ 0.5 mm was used because baseline angiography in the first few months after HT is not routine at either centre, and increased MIT values at 1 year after HT have been shown to be prognostic.16,17

**Statistical analysis**

Continuous variables were summarized using median and interquartile range due to nonparametric distribution, except...
for normally distributed lipid values, which were summarized using means and standard deviations. Dichotomous variables were summarized using frequencies. Between-group differences were evaluated using Wilcoxon rank-sum tests for continuous variables and \( \chi^2 \) and Fisher’s exact tests for dichotomous variables. To assess the impact of LDL-C on CAV1-3, the Cox proportional hazards model was used. The model was adjusted a priori for institution and the following clinically important covariates: donor age, ischemic time, recipient age, recipient sex, ischemic cardiomyopathy, pre-HT diabetes, pre-HT hypertension, and treated cytomegalovirus infection and rejection (ISHLT grade \( \geq 2R \) cellular rejection or pathologic antibody-mediated rejection (pAMR)). Logistic regression was used to evaluate the association between LDL-C and CAV1-3 at 1 year and MIT \( \geq 0.5 \) mm on IVUS. The association between HDL-C level and total cholesterol level as continuous variables and CAV1-3 at 1 year was conducted as a sensitivity analysis. Cox proportional hazards analysis was used to evaluate the association between LDL-C and the composite outcome after controlling for the effects of donor age and recipient sex. Only patients with complete data were included in the multivariable analyses. The data analysis was generated using SAS version 9.4 (SAS Institute Inc., Cary, NC) and GraphPad Prism, version 8 (San Diego, CA).

Results

A total of 461 patients received a HT during the study period, of which 386 patients with complete follow-up of a median (range) of 4.4 (2.8-6.8) years were included for further analysis (Fig. 1). Most of the 75 patients excluded from further analysis died in the first year after HT (n = 44) or were not followed locally (n = 21). Baseline characteristics for the excluded patients are provided in Supplemental Table S1.

The study cohort median age (range) was 54 (44-61) years; 75% were male; and 25% had ischemic cardiomyopathy as their transplant indication (Table 1). At the time of HT, 143 patients (37%) had hyperlipidemia, 108 (28%) had hypertension, and 73 (19%) had diabetes. After HT, all patients received induction immunosuppression, and most were on standard maintenance therapy with steroids (100%), calcineurin inhibitor (99%), and mycophenolic acid (99%). The use of sirolimus increased from 3% at baseline to 34% at the end of follow-up.

Most patients (94%) were initiated on statin therapy immediately after HT during the index hospitalization. The initial statin for the majority was pravastatin (n = 265; 69%), but atorvastatin (n = 72; 19%), rosuvastatin (n = 26; 7%), and simvastatin (n = 4; 1%) were also prescribed. At baseline, there were 2 patients (0.5%) on ezetimibe; no other lipid-lowering agents were used. At 2 years after HT, most patients remained on pravastatin (n = 188; 58%), atorvastatin (n = 88; 27%) or rosuvastatin (n = 33; 10%). The use of other lipid-lowering agents increased, with 30 patients (9%) on ezetimibe and 6 (2%) on fenofibrate 2 years after HT.

Lipid trends after HT

Serum lipids were measured at a median (range) of 18 (0-40), 367 (347-388), and 1665 (1057-2490) days after HT at baseline, 1 year, and last available test, respectively (Fig. 2). Mean total cholesterol at baseline was 4.17 ± 1.20 mmol/L, with an increase to 4.36 ± 1.14 mmol/L at 1 year (P = 0.02), and a subsequent decrease to 3.98 ± 0.99 mmol/L at the end of follow-up (P = 0.03). There was no significant difference in mean LDL-C at baseline (2.11 ± 0.86 mmol/L), compared with 1 year after HT (2.20 ± 0.88 mmol/L), but LDL-C was significantly lower at the end of study follow-up (1.89 ± 0.74 mmol/L), compared with baseline (P < 0.01).

HDL-C level at baseline was 1.31 ± 0.49 mmol/L and was unchanged at 1 year (1.33 ± 0.41 mmol/L, P = 0.64) and at the end of study follow-up (1.36 ± 0.62 mmol/L, P = 0.30). Non-HDL-C level at baseline was 2.95 ± 1.13 mmol/L and did not change significantly over time: 2.98 ± 1.08 mmol/L.

Figure 1. Study population flowchart. CAV0, cardiac allograft vasculopathy grade 0; CAV1-3, CAV grades 1-3; HT, heart transplantation; ISHLT, International Society for Heart and Lung Transplantation.
Other medications

Maintenance immunosuppression
- Ischemic
- Non-ischemic
- Prior ventricular assist device
- Pre-HT diabetes mellitus
- Pre-HT hypertension
- Pre-HT hyperlipidemia
- Primary graft dysfunction
- Prophylactic CMV

Risk of CAV according to LDL-C

A total of 309 patients (80%) had a coronary angiogram during the study period and were included in the multivariable analyses. Of these patients, 166 (54%) developed CAV (CAV1 = 155; CAV2 = 8; CAV3 = 3) over a median (range) follow-up time of 4.2 (2.7-6.6) years. Pre-HT cardiovascular risk factors of diabetes, hypertension and hyperlipidemia were more common in patients with CAV, compared with the incidence among those without CAV (Table 1). Donors were significantly older for recipients who developed CAV, compared with donors for those who did not develop CAV (median (range) donor age: 43 (31-51) vs 26 (21-36) years, respectively, \( P < 0.01 \). There was no difference in de novo use of proliferation signal inhibitors (5 patients with CAV vs 7 patients with no CAV, \( P = 0.56 \)) or other medications, including statins, between patients with vs without CAV. There were no differences between groups in terms of rates of ISHLT grade \( \geq 2R \) cellular rejection (69 patients with CAV vs 65 patients without CAV, \( P = 0.49 \)) or pathologic antibody-mediated rejection \( \geq pAMR1 \) (44 patients with CAV vs 30 patients without CAV, \( P = 0.26 \)).

The risk of CAV did not vary according to any of the prespecified LDL-C thresholds at baseline or at 1 year, with analyses adjusted for donor age, ischemic time, recipient age, recipient sex, ischemic cardiomyopathy, pre-HT diabetes, pre-HT hypertension, treated cytomegalovirus infection, and rejection (Fig. 4; Supplemental Table S2). There was also no significant relationship between the change in LDL-C from baseline to 1 year and the risk of CAV (Fig. 4; Supplemental Table S3).

Association between LDL-C and CAV at 1 year

There were 239 patients who underwent coronary angiography at 1 year after HT, of whom 102 (43%) had angiographic CAV1-3. There was no significant association between LDL-C and CAV at 1 year post-transplant—adjusted odds ratio (OR) 1.00, 95% confidence interval (CI): 0.61, 1.63 for baseline LDL-C, and adjusted OR 1.25, 95% CI: 0.74, 2.10 for 1-year LDL-C. There was also no association between baseline and 1-year HDL-C levels, or between baseline and 1-year total cholesterol level and CAV at 1 year (Supplemental Table S4).

One-year IVUS was performed in 176 patients: 97 (55%) had an MIT \( \geq 0.5 \) mm, and 79 (45%) had an MIT < 0.5 mm. When adjusted for confounders, baseline and 1-year LDL-C were not associated with an MIT \( \geq 0.5 \) mm on 1-year coronary angiography (OR 1.00, 95% CI: 0.62, 1.63 and OR 1.25, 95% CI: 0.74, 2.10, respectively).
Risk of the composite outcome according to LDL-C

There were 26 patients (8%) who experienced one or more events included in the composite outcome. First outcome events included in the analysis were: CAV2 (n = 8), CAV3 (n = 3), myocardial infarction (n = 2), coronary revascularization (n = 3), cardiovascular death (n = 10). There was no relationship between the composite outcome and baseline and 1-year LDL-C cutoffs on analyses adjusted for donor age and recipient sex (Table 2).

Discussion

In this multicentre study of 386 patients, baseline LDL-C values remained unchanged at 1 year after HT but decreased significantly by 4.6 (range: 2.9-6.8) years after HT. We did not identify an association between baseline, 1-year, or change from baseline to 1-year LDL-C cutoffs on analyses adjusted for donor age and recipient sex (Table 2).

Figure 2. Shown are baseline, 1-year, and last available (A) total cholesterol levels; (B) low-density lipoprotein cholesterol (LDL-C) levels; (C) triglyceride levels; and (D) high-density lipoprotein cholesterol (HDL-C) levels, for all included patients. Bars represent mean values, error bars represent standard deviations, and dots represent individual patients. *P < 0.05 compared to baseline.

Although there is robust evidence supporting the use of statins after HT, data are lacking to indicate that their benefits are attributable directly to their lipid-lowering effects, particularly early after HT. Our findings are corroborated by prior studies that have failed to demonstrate a clear relationship between LDL-C and CAV.4,5,7,18 In a seminal randomized controlled trial of early post-HT initiation of pravastatin, by Kobashigawa et al., there was no observed correlation between higher cholesterol levels and CAV development. A single-centre observational study of 194 patients reported less CAV with an LDL-C < 2.6 mmol/L, whereas more aggressive lowering of LDL-C to < 1.8 mmol/L was associated with worse outcomes. 19 Similarly, Asleh et al. found no association between LDL-C and the incidence of CAV in 227 patients treated with sirolimus-based immunosuppression but did raise the possibility of an association between higher LDL-C and greater risk of CAV in 96 patients treated with calcineurin inhibitor.20 Their findings also suggest that proliferation signal inhibitors such as sirolimus have a greater impact in reducing the risk of CAV irrespective of LDL-C. In contrast, a large multicentre observational analysis by Loupy et al. recently suggested an association between a 1-year LDL-C cutoff of ≥ 1.0 g/L (2.6 mmol/L) and risk of CAV progression. 21 We evaluated LDL-C at 1 year post-HT as a continuous variable, to better characterize its association with angiographic CAV as well as earlier signs of CAV, using IVUS data. Differences in statistical methods used, cohort baseline LDL-C values, and cohort CAV assessments in our study vs that of Loupy et al. may account for these discordant observations.
Figure 3. Cardiac allograft vasculopathy (CAV)-free survival according to low-density lipoprotein cholesterol (LDL-C) level (A) 1.5 mmol/L; (B) 1.8 mmol/L; (C) 2.0 mmol/L; and (D) 2.5 mmol/L at (left column) baseline and (right column) 1 year after transplant. Hazard ratio (HR) and 95% confidence interval (CI) are shown.
The mean LDL-C of 2.11 ± 0.86 mmol/L at baseline in our cohort was lower than those in other published cohorts.8,22-24 Some but not all studies with higher LDL-C values (means of 2.6 and 3.1 mmol/L) have reported a greater risk of CAV.19,20 The lower, early LDL-C values in our cohort are a possible explanation for the lack of observed association between LDL-C and CAV, compared to findings for other study populations.19,20 An IVUS study of 93 HT patients suggested an association between larger increases in LDL-C within the first year of transplant and CAV severity at 1 year.25 How can this finding be reconciled with that from the IVUS of our larger cohort of 176 patients? It is possible that there is no relationship between the 2, or that selection bias in the IVUS cohort accounts for the difference in findings. Alternatively, the small nonsignificant change in LDL-C from baseline to 1 year after HT observed in our cohort could account for the corresponding lack of association with CAV. Even with lower mean LDL-C values, a sizeable 54% of our study cohort developed CAV, which would not be expected if lower LDL-C values at baseline were protective against CAV development.

To the best of our knowledge, only one randomized study of 52 patients has evaluated LDL-C targeted statin therapy after HT.22 Potena et al. compared statin dose titration to target an LDL-C < 2.6 mmol/L vs maximal statin dose therapy early after HT.22 Angiographic CAV was not evaluated, and there was no difference in the development of early CAV as defined by an increase in MIT of ≥ 0.5 mm on IVUS at 1 year between the 2 patient groups.22 The authors reported higher average LDL-C in the small number of 4 patients with an increase in MIT ≥ 0.5 mm from baseline. At 1 year post-HT, there was no difference in LDL-C between the statin titration and maximal-dose groups. In our study, we did not find an association between 1-year LDL-C or change from baseline and either angiographic CAV1-3 or an IVUS MIT ≥ 0.5 mm at 1 year post-transplant. Randomized studies supporting or refuting the need for an LDL-C target after HT are needed.

**Non–lipid-lowering effects of statin therapy**

The immunomodulatory and endothelial effects of statin therapy are likely the primary reasons for their

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**Table 2. Risk of composite outcome of moderate–severe cardiac allograft vasculopathy grades 2-3, myocardial infarction, coronary revascularization, retransplantation, and cardiovascular death according to baseline and 1-year LDL-C**

| LDL-C, mmol/L | Unadjusted HR (95% CI) | P | Adjusted HR (95% CI)* | P |
|---------------|------------------------|---|-----------------------|---|
| Baseline                  |                        |   |                       |   |
| ≥ 1.8          | 0.48 (0.22, 1.03)       | 0.06 | 0.54 (0.25, 1.19)     | 0.13 |
| ≥ 2.0          | 0.50 (0.23, 1.09)       | 0.08 | 0.57 (0.26, 1.26)     | 0.16 |
| ≥ 2.5          | 0.49 (0.19, 1.31)       | 0.16 | 0.57 (0.21, 1.55)     | 0.27 |
| 1-year         |                        |   |                       |   |
| ≥ 1.8          | 1.21 (0.48, 3.06)       | 0.68 | 1.37 (0.54, 3.50)     | 0.50 |
| ≥ 2.0          | 1.05 (0.46, 2.39)       | 0.91 | 1.24 (0.54, 2.87)     | 0.61 |
| ≥ 2.5          | 1.33 (0.59, 2.98)       | 0.49 | 1.63 (0.72, 3.72)     | 0.24 |

CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

* Adjusted for the following variables: donor age, recipient sex.

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**Figure 4.** The risk of cardiac allograft vasculopathy (CAV) according to changes in low-density lipoprotein cholesterol (LDL-C) level groups of (A) 1.5 mmol/L; (B) 1.8 mmol/L; (C) 2.0 mmol/L; and (D) 2.5 mmol/L, from baseline to 1 year after heart transplantation.
well-established benefits after HT. The pathogenesis of CAV involves endothelial injury and dysfunction, smooth muscle cell proliferation, and ultimately, fibrosis and negative remodelling of coronary arteries. Statin therapy has been shown to inhibit proliferation of smooth muscle cells. Furthermore, improved endothelial function and increased coronary luminal area have been observed among patients after 1 year on statin therapy post-HT. Virtual histology IVUS and optical coherence tomography studies have also shown distinct differences in early fibrotic vs late necrotic and calcific plaque composition, suggesting differing pathologic mechanisms in CAV at various stages after HT.

Based on predominant inflammatory and immune-mediated coronary intimal thickening in early CAV, we postulate that the immunomodulatory effects of statin therapy may protect against CAV early after HT, and their lipid-lowering effects may impact CAV progression later after HT.

**Clinical implications of our study findings**

Statins are recommended in all HT patients, but despite their wide utilization, hyperlipidemia remains common, with an 88% incidence rate at 5 years post-HT reported in the ISHLT registry. The results from our study have important clinical implications given that ideal LDL-C target levels post-HT have not been established. Our findings do not support targeting a specific LDL-C for patients who do not otherwise meet criteria for non-HT guideline-recommended LDL-C targets. This conclusion is of clinical relevance, as achieving a low LDL-C with high-intensity statin therapy increases the risk of adverse effects, such as myositis, due to simultaneous calcineurin-inhibitor use, which increases serum statin levels. Additionally, there are currently at least 4 ongoing randomized clinical trials examining the use of potent LDL-C–lowering proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors (ClinicalTrials.gov identifiers: NCT03537742, NCT03734211, NCT03944577, and NCT04193306). Although this new class of cholesterol-lowering medications have demonstrated short-term safety and efficacy in reducing LDL-C in small case series of HT patients, their high costs may limit their wide application. Furthermore, these studies are being conducted in the early post-transplant population, and the importance of LDL-C reduction may differ depending on time from transplant.

**Limitations**

There are limitations to our study, including its retrospective design, the relatively small sample size, and the possibility of type 2 error accounting for our findings. Our adjusted analyses consider a suitable number of covariates that may confound the association between CAV and LDL-C, including donor age, ischemic time, recipient age and sex, ischemic cardiomyopathy, and pre-HT diabetes, but residual confounding exists. We evaluated the first available LDL-C as baseline values, but pre-HT LDL-C were not routinely available, as patients did not routinely have this bloodwork performed at our institutions pre-HT. It is possible that the lack of association between LDL-C and CAV early after HT was due to type 2 error. We provide medium-term rather than long-term follow up; however, our objectives were to evaluate the association between LDL-C and CAV early after HT, instead of late post-transplant when traditional cardiovascular risk factors are at play. Similarly, we examined the impact of early LDL-C, and the relevance of LDL-C later post-transplant remains unknown. Importantly, the frequency of coronary angiography and IVUS is not standardized within the 2 centers, thereby limiting the number of patients available for CAV analysis. Lastly, the small number of patients in our cohort with moderate–severe CAV limits evaluation of the relationship between LDL-C and significant angiographic CAV.

**Conclusions**

In this contemporary cohort of HT recipients at 2 large transplant centers with nearly universal use of statin therapy, there was no association between early LDL-C and the risk of CAV. Although LDL-C values were relatively low at baseline in this population, neither an increase nor decrease in LDL-C in the first year after HT was associated with CAV development. Our findings suggest that an aggressive LDL-C–lowering strategy early after HT may not be associated with a lower risk of CAV. However, further research, including randomized controlled trials, is warranted to determine if lipid-lowering to a specific LDL-C target level can decrease the development and progression of CAV after HT.

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**Disclosures**

The authors have no conflicts of interest to disclose.

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Supplementary Material
To access the supplementary material accompanying this article, visit CJC Open at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2021.07.011.