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Statin therapy is not associated with improved outcomes after heart transplantation in children and adolescents

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HMG-CoA reductase inhibitors;
PTLD

BACKGROUND: Although used routinely, the pleiotropic benefits of statins remain understudied in children after heart transplantation. We hypothesized that statin therapy would reduce the incidence of rejection, cardiac allograft vasculopathy (CAV) and post-transplant lymphoproliferative disease (PTLD).

METHODS: This study was a retrospective review of 964 pediatric (ages 5 to 18 years) heart transplant recipients in the multicenter Pediatric Heart Transplant Study registry from 2001 to 2012. Patients were excluded if they were undergoing re-transplantation, survived <1 year post-transplant, or had missing data regarding statin use. The effects of statins beyond the first year were estimated by Kaplan-Meier and Cox regression multivariable analysis for freedom from PTLD, rejection requiring treatment, any severity of CAV, and survival.

RESULTS: Statin use was variable among participating centers with only 30% to 35% of patients ≥ 10 years of age started on a statin at <1 year post-transplant. After the first year post-transplant, statin-treated children (average age at transplant 13.24 $\pm$ 3.29 years) had significantly earlier rejection (HR 1.42, 95% CI 1.11 to 1.82, $p = 0.006$) compared with untreated children (transplanted at 12 $\pm$ 3.64 years) after adjusting for conventional risk factors for rejection. Freedom from PTLD, CAV and overall survival up to 5 years post-transplant were not affected by statin use, although the number of events was small.

CONCLUSIONS: Statin therapy did not confer a survival benefit and was not associated with delayed onset of PTLD or CAV. Early (<1 year post-transplant) statin therapy was associated with increased later frequency of rejection. These findings suggest that a prospective trial evaluating statin therapy in pediatric heart transplant recipients is warranted.

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Drugs used to lower serum cholesterol levels by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase are collectively known as "statins," and were first demonstrated to be beneficial post-heart transplantation

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in adults. Early statin therapy lowered cholesterol as expected but also decreased the frequency of rejection with hemodynamic compromise, decreased the frequency of cardiac allograft vasculopathy (CAV), and improved survival.[1] These benefits were maintained at 10-year follow-up and the pravastatin-treated group showed significantly greater freedom from angiographic CAV and death compared with a control group.[2] Although the statin-treated group had a lower cholesterol, cholesterol itself was not a risk factor for CAV, raising the possibility of additional transplant-related benefits from the use of statins.[1,2] The initial observations of lipid abnormalities post-transplant and the efficacy of statins, both pravastatin and atorvastatin, for the treatment of hypercholesterolemia have since been extended to the pediatric heart transplant population.[3–7]

In addition to positive effects on lipid levels, pravastatin was also associated with a lower incidence of angiographic CAV in children after heart transplant.[8]

Statins may also have other beneficial effects related to immunomodulation, many of which remain poorly understood.[9,10] Improved cancer-free survival has been found in adults, including heart transplant recipients, among whom statin therapy reduced the hazard of occurrence of any malignancy (predominantly skin but including a variety of cancers) by 67%.[11,12] However, the impact of statin use on the development of malignancy has not been explored in pediatric recipients where post-transplant lymphoproliferative disease (PTLD) remains a serious problem.[13,14]

Although appreciation of the effects of statins has increased and these drugs are widely prescribed, their use in pediatric heart transplant recipients remains insufficiently studied. This retrospective study was designed to review the potential effects of statin therapy on outcomes post-transplant. Using the Pediatric Heart Transplant Study (PHTS) database, statin therapy was assessed in a population of children and adolescents having undergone heart transplantation. We hypothesized that statin therapy would be associated with a lower incidence of rejection, CAV and PTLD in pediatric recipients treated within the first year post-transplant.

Methods

Patient population

The PHTS registry prospectively collects pre- and post-transplant data from participating centers. The collection of annual follow-up data on transplant recipients was initiated on July 1, 1996. The available study population consisted of all children (age $\leq$18 years at listing) from 36 institutions in North America and the UK (see Appendix). Each center obtained approval from its respective institutional human investigational committee before data collection began. From this population we retrospectively reviewed recipients transplanted during childhood or adolescence (ages 5 to 18 years at time of transplantation) throughout the study period from 2001 to 2012. By 2001, a relatively large ($\sim$16%) and stable number of patients were receiving statins and this time period allows for at least 1 year of follow-up data. The statin group included patients who received a statin within the first year post-transplant. The non-statin group included patients who had not received a statin before an event. The occurrence of rejection was defined as any biopsy-proven or clinically identified rejection event (acute cellular or antibody-mediated rejection) that required treatment. The presence of CAV was defined as any degree of CAV documented by angiography, intravascular ultrasound or dobutamine stress echocardiography. Patients undergoing re-transplantation, whose survival was $<$1 year post-transplant, or for whom data regarding statin use were not available were excluded from the analysis.

Data analysis

We collected baseline patient characteristics from annual follow-up forms, which are reported as mean $\pm$ standard deviation. Descriptive statistics were used to present differences between those patients treated with statins and those who did not receive statin therapy. Freedom from rejection, PTLD and CAV were assessed by the Kaplan–Meier method and differences analyzed by log-rank test. Multivariable Cox proportional hazards models were used to determine risk factors for rejection and statin use and included recipient and donor demographics. Hazard ratios (HRs) were expressed with 95% confidence intervals (CIs), with $p \leq 0.05$ considered statistically significant. All statistical analyses were performed using SAS software (version 9, SAS Institute, Cary, NC).

Results

From the total study population of 4,017 patients we identified 964 primary heart transplant patients who were between 5 and 18 years of age, transplanted between 2001 and 2012, survived to the first year post-transplant, and had at least 1 year of follow-up data available (Figure 1). Of these patients, 317 received a statin within the first year after transplantation. There were missing data for statin use in 56 patients, but exclusion of these patients did not affect our results. Early statin therapy was relatively uncommon in children $<$5 years of age, with only 102 patients prescribed a statin in the first year after transplant. Demographic characteristics between statin-treated and untreated patients were similar with respect to diagnosis, gender and ethnicity, as well as the presence of pre-transplant morbidities and the absence of hepatic dysfunction (Table 1). Patients receiving a statin were slightly older and more likely to have panel-reactive antibodies (PRA) of $>$10% and had a statistically shorter ischemic time compared with patients who did not receive a statin. Patients receiving a statin were more likely to have received induction therapy and to have received steroids, either pre-transplant or at 30 days post-transplant, but there were no significant differences between the use of maintenance immunosuppressive drugs.

Statins were utilized more frequently in patients $>$10 years of age ($p < 0.0001$; Figure 2). In patients 5 to 9 years of age, 20% were being treated with a statin by 1 year post-transplant and 30% were receiving a statin by 2 years post-transplant. Statin use was similar in patients 10 to 14 and 15 to 18 years of age. In patients $\geq$10 years of age, 30% to 35% were receiving a statin by 1 year post-transplant and

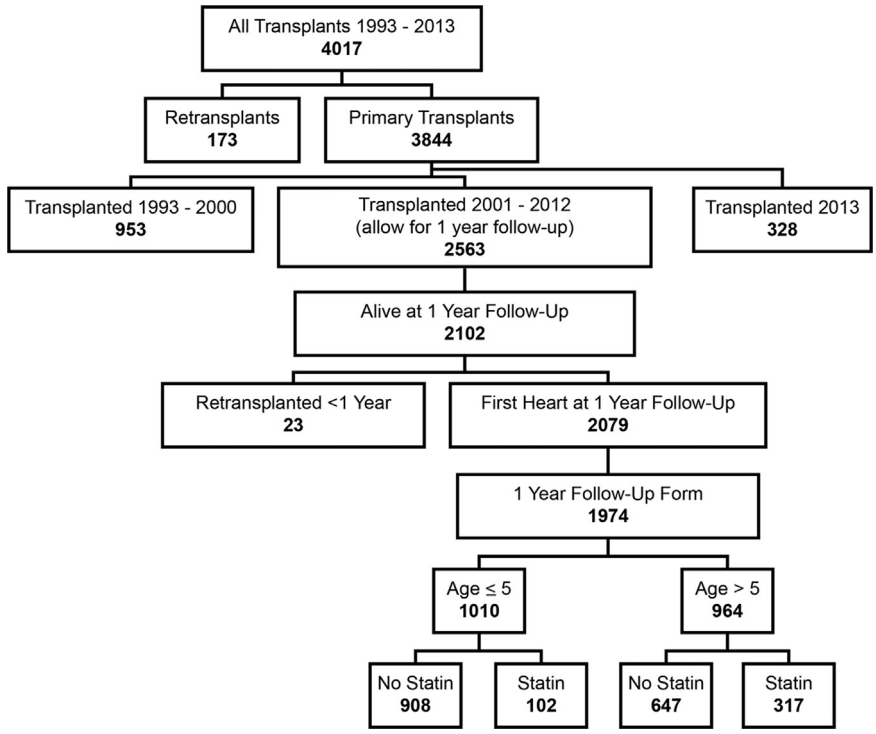

Figure 1 Selection of PHTS patients for study inclusion. In the final analysis there were 317 patients in the statin-treated group and 647 in the untreated group.

~50% were on a statin by 2 years post-transplant. The relatively low percentage of children receiving early statin therapy was reflected in practice variability across the participating centers (Table 2). For all age groups, the number of children receiving a statin increased with increasing time post-transplant although 25% to 35% of children >10 years post-transplant were still not on a statin. Factors predictive of statin use by multivariable analysis included use of induction therapy and larger donor (Table 3). Other statistically significant factors included cytomegalovirus (CMV) status, use of steroids, lower ejection fraction, longer ischemic time and donor-recipient gender mismatch. Rejection in the first year was not associated with early statin use ($p = 0.46$).

Table 1 Study Patient Demographics by Statin Use

Variables	Statin ($n = 317$)	No statin ($n = 647$)	p-value
Cardiomyopathy[a]	193 (60.88%)	372 (57.50%)	0.32
Age at transplant	13.24 ± 3.29	12.00 ± 3.64	<0.0001
Gender (male)[a]	180 (56.78%)	373 (57.65%)	0.80
Race (white)[a]	211 (66.56%)	439 (67.85%)	0.69
Status at transplant (1A)	235 (74.13%)	507 (78.36%)	0.29
Donor-specific crossmatch	24 (7.57%)	54 (8.35%)	0.40
History of diabetes[a]	1 (0.32%)	3 (0.46%)	0.74
History of hypertension[a]	9 (2.84%)	12 (1.85%)	0.33
History of malignancy[a]	12 (3.79%)	14 (2.16%)	0.14
PRA >10%	58 (18.30%)	82 (12.67%)	0.02
AST	72.54 ± 118.87	75.03 ± 179.32	0.85
ALT	58.17 ± 150.33	53.32 ± 141.13	0.67
Ischemic time (min)	201.3 ± 61.77	210.7 ± 62.61	0.03
Induction therapy	246 (78.59%)	425 (66.20%)	<0.0001
Cyclosporine	110 (37.04%)	203 (35.30%)	0.61
Tacrolimus	227 (85.02%)	476 (86.86%)	0.47
Sirolimus	13 (5.35%)	24 (5.16%)	0.91
Pre-operative steroids	87 (27.71%)	130 (20.12%)	0.008
Intra-operative steroids	295 (97.36%)	611 (96.68%)	0.57
Maintenance steroids	194 (79.84%)	324 (68.07%)	0.0009

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PRA, panel-reactive antibodies.
[a]Data collected at listing.

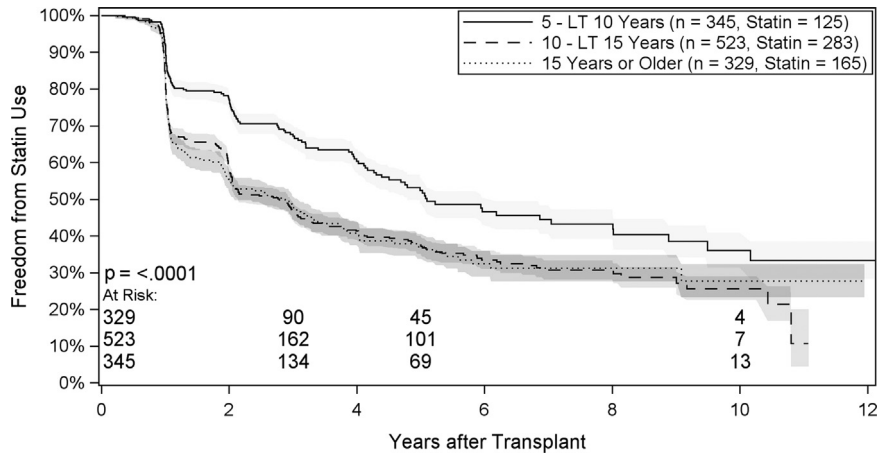

Figure 2 Time to first statin use stratified by age at transplant. Numbers above the horizontal axis refer to the number of patients in each group at 3, 5 and 10 years post-transplant (LT, less than).

In children who received early statin therapy there was no significant difference in overall survival up to 10 years post-transplant compared with children who were not treated with a statin ($p = 0.34$; Figure 3). However, there was a significantly higher incidence of rejection in the statin-treated group of children after 1 year of follow-up ($p = 0.0008$; Figure 4).

To identify a selection bias for statin use in high-risk recipients, we examined whether a history of early rejection could explain the higher mortality among the statin users. In the non-rejectors at 1 year, overall survival post-transplant was unaffected by statin use ($p = 0.24$), with no significant differences detected between the groups up to 10 years post-transplant. A similar result was seen for patients with a history of early rejection who demonstrated equivalent survival regardless of statin use ($p = 0.87$). However, patients receiving a statin had a significantly increased risk for rejection requiring treatment >1 year post-transplant if they had experienced early rejection ($p = 0.0046$; Figure 5). Similarly, in the subgroup without early rejection, there was also a trend toward an increased risk of late rejection in the statin group ($p = 0.0596$; Figure 6). The earlier time to rejection beyond 1 year was also seen when the analysis was restricted to patients ≥ 10 years of age ($p = 0.01$; data not shown), suggesting that our result is not an effect of age. Risk factors for a first episode of rejection after 1 year post-transplant by multivariable analysis showed that statin use, early rejection, Hispanic origin, history of malignancy at listing, history of cardiopulmonary resuscitation (CPR) and pre-operative steroids were all associated with increased risk of rejection in this cohort, whereas white race was a protective factor (Table 4). It is important to note that early statin use and early rejection were independent risk factors for later rejection and that the interaction between first year rejection and statin use in the first year was not significant.

Similar to overall survival, statin use post-transplant did not have a significant association with the incidence of PTLD ($p = 0.64$; Figure 7). The incidence of any degree of CAV was likewise not associated with statin use ($p = 0.48$; Figure 8). Comparable results were also seen when events were restricted to moderate-severe CAV, with a similar frequency of events seen in both statin-treated and untreated children ($p = 0.22$; data not shown).

Table 2 Variable Statin Use Post-transplant by the 36 Participating PHTS Centers

Percent of patients on a statin at 1 year	Number of hospitals
0%	7
>0% to 10%	2
>10% to 25%	8
>25% to 50%	9
>50%	10

PHTS, Pediatric Heart Transplant Study.

Discussion

In this large, retrospective and registry-based study we did not find statin therapy to be associated with improved survival in patients transplanted in childhood or adolescence. Furthermore, statin therapy was associated with an increased risk of rejection. In the original study by Kobashigawa et al, there was a beneficial effect of early statin therapy on cardiac rejection with hemodynamic compromise, but there was no difference in the incidence of mild or moderate episodes of cardiac rejection between the statin-treated and untreated groups.[1] That study only addressed survival during the first year after cardiac

Table 3 Significant Results From a Multivariable Hazard Analysis for Statin Use at 1-Year Follow-up

Variables	HR (95% CI)	*p*-value
CMV	1.36 (1.08 to 1.71)	0.009
Male recipient:female donor	0.65 (0.48 to 0.89)	0.006
Induction therapy	1.76 (1.33 to 2.33)	<0.0001
Maintenance steroids	1.62 (1.18 to 2.21)	0.003
Donor body surface area	1.97 (1.45 to 2.68)	<0.0001
Estimated ejection fraction	0.98 (0.97 to 0.996)	0.02
Ischemic time (min)	0.998 (0.996 to 0.999)	0.01
Rejection in first year	—	0.46

CMV, cytomegalovirus.

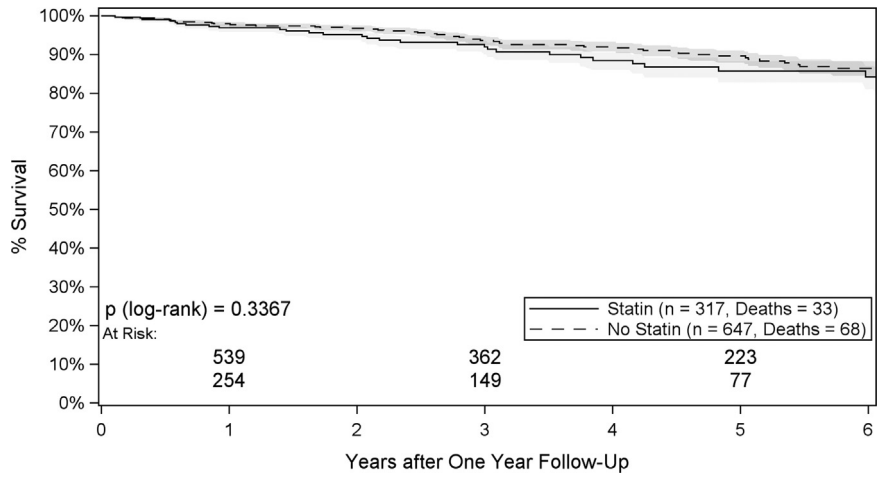

Figure 3 Survival after 1-year follow-up stratified by statin use.

transplantation, although subsequent studies suggested that long-term benefit is also derived from statin therapy.[2,15,16] Furthermore, the benefits obtained from the relatively high doses of pravastatin (40 mg/day) studied[1] seemed to be obtained using lower doses of pravastatin (20 mg/day) or simvastatin (10 mg/day) with respect to 1-year survival and incidence of rejection.[17] In a multicenter, observational cohort study using data from the Heart Transplant Lipid Registry, 1,186 adult patients were studied and it was found that statin-treated patients had a lower frequency of death (4% vs 13.7%, $p < 0.0001$, HR 0.29, 95% CI 0.13 to 0.67) and fatal rejection (2.4% vs 7.2%, $p = 0.0001$, HR 0.27, 95% CI 0.09 to 0.78).[18] These effects were independent of lipid values and the statin-associated survival advantage appeared early and persisted up to 2.5 years after transplantation.[18]

Although none of the studies that followed the original Kobashigawa et al trial[1] were randomized, and therefore may be influenced by selection bias, the cumulative data in adult heart transplant patients suggest that statin therapy has a beneficial effect on survival and protects against rejection, particularly hemodynamically significant rejection. Similarly, in adult kidney transplant patients, use of pravastatin was associated with decreased frequency of rejection when used with cyclosporine.[19] Data are more limited in pediatrics, but one single-center, retrospective study indicated that there were significantly fewer rejection episodes in the first year post-transplant in those patients who received atorvastatin.[20]

In contrast to these findings we did not find statin therapy to be associated with improved survival in patients transplanted in childhood or adolescence. Furthermore, statin therapy was associated with an increased risk of rejection in our study cohort, which increased with time post-transplant. Unfortunately, given the nature of the registry data, detailed data were not available for events during the first year post-transplant that may have led to the initiation of a statin within that first year. Given that statins were initiated early in relatively few patients (20% to 40%, as shown in Figure 2), statin therapy itself may indicate a high-risk subgroup identified early by clinicians. This may be one possible explanation as statin users tended to have human leukocyte antigen sensitization and were of slightly older age, both recognized as risk factors for CAV.[21] However, in a stratified analysis based on early rejection as a potential risk factor for later rejection as well as for a selection bias for patients being initiated on a statin in the first year, statin use remained associated with later rejection. Furthermore, in

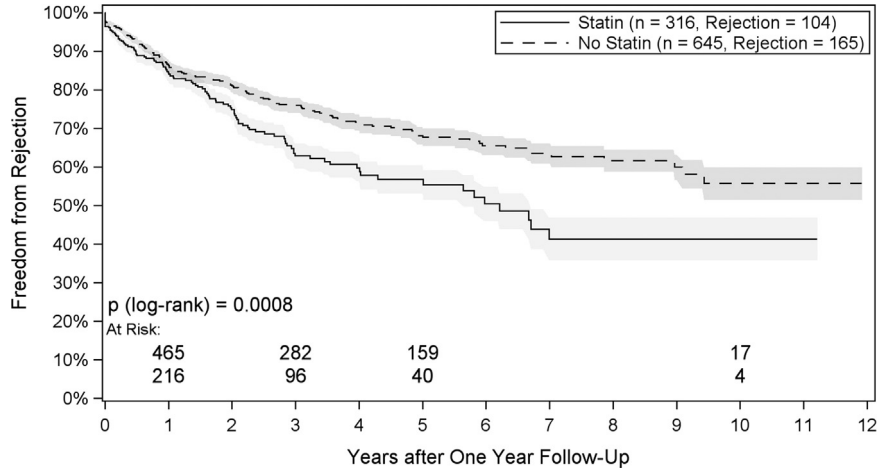

Figure 4 Rejection after 1-year follow-up stratified by statin use.

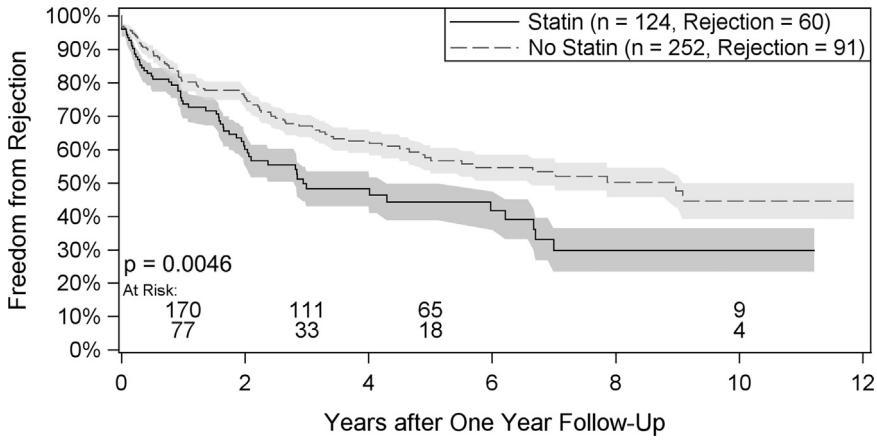

Figure 5 Rejection after 1-year follow-up stratified by statin use for patients with an episode of rejection within the first year post-transplant.

the multivariable analysis, rejection history and statin use were independent risk factors for rejection beyond the first year.

In addition to their beneficial effects on cholesterol levels, pravastatin and atorvastatin have also been associated with a lower incidence of CAV in pediatric heart transplant recipients.[8,20] In our cohort, statin therapy was not associated with a decreased incidence of CAV and results of the analysis were similar whether we looked at moderate-severe CAV or any degree of CAV. This may be partly due to hypercholesterolemia with atherosclerosis being a much more common co-factor for the development of CAV in adults than in children, or that the incidence of pediatric CAV is too low, as compared with adults, to allow our study design to discern a difference.

There are also reports of statin use associated with a decreased incidence of malignancy and improved cancer-free survival in adult heart transplant recipients.[11,12] In a single-center study that included 132 pediatric and adult heart transplant recipients transplanted between 2007 and 2012, those patients treated empirically with a statin (flucastatin, atorvastatin or rosuvastatin) had improved 5-year overall survival compared with untreated recipients (94.6% vs 74.1%, $p < 0.05$).[18] In the same study, in univariate analyses, there were no significant differences in the incidence of cancer or rejection.

In one retrospective study of 255 adult heart transplant recipients, the incidence of malignancy was reduced in patients receiving a statin (34% vs 13%, $p < 0.003$), and statin use was associated with improved cancer-free and superior overall survival ($p < 0.0001$).[12] The statin effects observed in that study were independent of immunosuppressive therapy, statin dose and cholesterol levels. However, a protective effect of statin therapy on the incidence of PTLD was not seen in our study. The discordance of our data with the adult-derived data is perhaps understandable given the known differences in the rates and types of malignancy in children and adults post-transplant. The adult studies demonstrated statins to be efficacious in the prevention of malignancies, such as breast or prostate cancer, where mechanisms are very different from the mostly virally driven processes seen in PTLD, which is the predominant malignancy in pediatric recipients. Furthermore, young children are more predisposed to PTLD because they tend not to have been exposed to Epstein–Barr virus before initiation of immunosuppression, and younger recipients are also less likely to be treated with a statin.

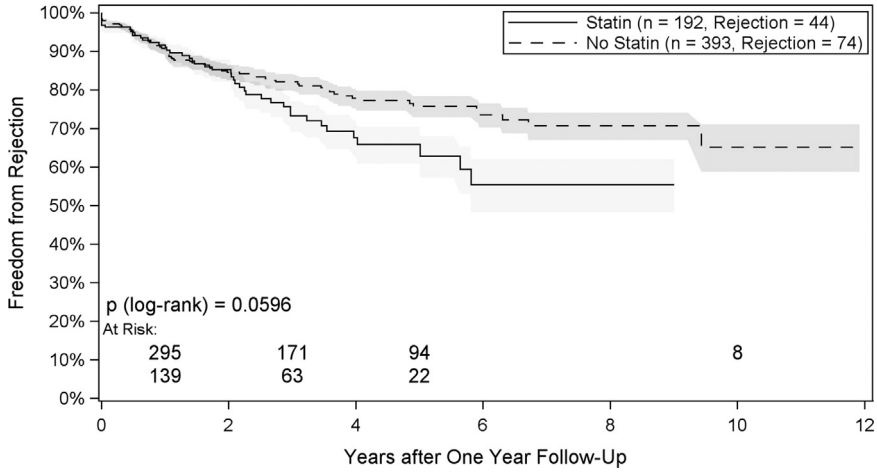

Figure 6 Rejection after 1-year follow-up stratified by statin use for patients without an episode of rejection within the first year post-transplant.

Table 4 Statistically Significant Covariates From Multivariable Hazard Analysis for Rejection After 1 Year of Follow-up

Variables	HR (95% CI)	*p*-value
Statin use at 1-year follow-up	1.42 (1.11 to 1.82)	0.006
Recipient white race	0.63 (0.49 to 0.81)	0.0003
Hispanic ethnicity	1.79 (1.32 to 2.43)	0.0002
History of malignancy	2.10 (1.19 to 3.69)	0.01
Age at transplant (squared)	1.003 (1.001 to 1.004)	0.0006
Steroids (pre-operative)	1.34 (1.02 to 1.77)	0.04
CPR	1.35 (1.04 to 1.75)	0.02
Rejection in first year	2.09 (1.64 to 2.67)	<0.0001
First-year rejection × statin at 1 year[a]	—	0.47

CPR, cardiopulmonary resuscitation.
[a]Interaction between first-year rejection and statin use in the first year.

These findings were built upon on a previous study from the PHTS that addressed the prevalence of hyperlipidemia and the effect of statin therapy on lipid abnormalities post-transplant.[3] Lipid abnormalities in patients after heart transplantation have been well described, and statin use is accepted therapy for hypercholesterolemia in pediatric heart transplant patients.[4,5,7,17] However, in the current study we found that statins were initially prescribed in a relatively small proportion of patients, but this number increased with time post-transplant. Statin use was similar in patients of ages 10 to 14 and 15 to 18 years, suggesting that most practitioners see these groups as equivalent with regard to safety of statin prescription. There was a great deal of variability among PHTS centers with regard to timing of statin initiation, suggesting that statin use is an area of considerable practice variation in pediatrics despite the published adult literature supporting its use.

Limitations

Although our study is the largest pediatric study to address the effect of statins post-transplant in children, its findings are unexpected and counter the reasonably substantial and consistent adult literature. A limitation of our analysis is the retrospective nature and the relatively few events documented in our cohort. The power to assess longer term outcomes (>5 years) was also limited due to decreased data availability over time. It is possible that statins exert different effects in adults than in children, which could explain the potentially harmful results of statin therapy we observed. Related to this is the possibility that different doses or timing schedules are required for children in order for statins to be effective. Another limitation is that the statin group was defined as those placed on statin therapy by 1 year post-transplant (because earlier data were not available)—where some could have been treated very early, similar to adult studies, with others beginning statin treatment very late into the first year. Furthermore, no adjustment was made for patients coming off statins or put on statins later post-transplant. The dose and effects of later statin therapy were also not assessed in this study.

Variability of practice among centers and the lack of data regarding dosing schedules and duration of treatment may also limit the generalizability of our conclusions. A survey of the participating PHTS centers (19 of 36 responding) revealed that 14 of those 19 have an institutional policy for statin use: 13 of 19 relate using statins at an older age and 18 of 19 do not relate statin use to biopsy schedule.

Heterogeneity of practice is also likely reflected in peri-transplant steroid use (as shown in Table 1). We were not able to incorporate this variability into our analysis, but it remains as a potential confounder. Other than a potential selection bias, however, which is inherent in all retrospective multivariate analyses, the limitations specified do not explain the finding of a higher risk for rejection in the statin-treated group.

In conclusion, our study has shown that early statin therapy after heart transplantation in children and adolescents does not confer a survival advantage or decrease the frequency of PTLD or CAV events. Instead, early statin therapy appears to be associated with an increased risk of rejection later, after the first year. Additional studies are needed to better define which patients are to be placed on statins, and the biologic as well as clinical effects of statins in children, especially those who do not possess the same metabolic or cardiovascular profile as their adult counterparts. The fact that statins are prescribed and signals of a

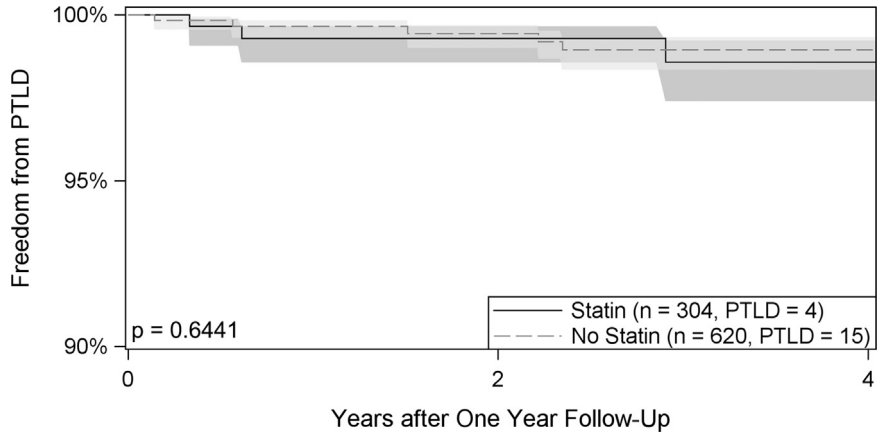

Figure 7 Incidence of PTLD after 1-year follow-up stratified by statin use.

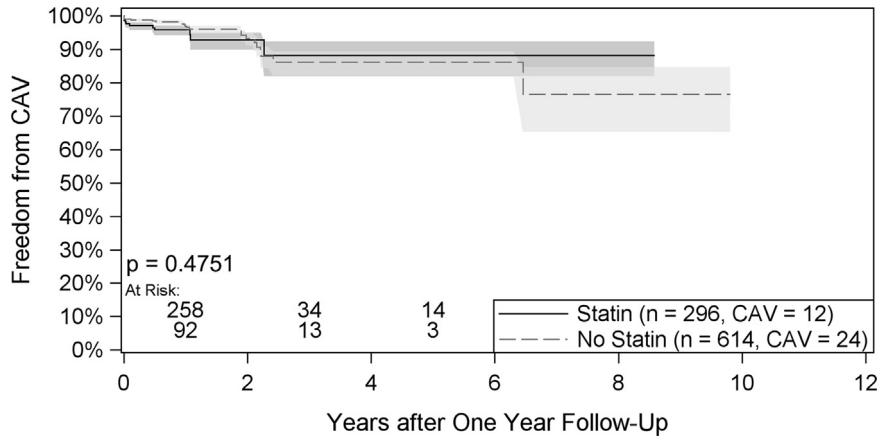

Figure 8 Incidence of any degree of CAV after 1-year follow-up stratified by statin use.

potential adverse effect are observed highlights the need for a prospective interventional trial of statins in pediatric heart recipients.

Disclosure statement

The authors have no conflicts of interest to disclose.

Appendix

PHTS participating institutions: Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; Arkansas Children's Hospital, Little Rock, AR; Cardinal Glennon Children's Medical Center, St. Louis, MO; Children's of Alabama, Birmingham, AL; Children's Healthcare of Atlanta, Atlanta, GA; Children's Hospital, Boston, MA; The Children's Hospital at Montefiore, New York, NY; The Children's Hospital of Philadelphia, Philadelphia, PA; Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA; Children's Hospital of Wisconsin, Milwaukee, WI; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Cleveland Clinic Children's, Cleveland, OH; Columbia University-Morgan Stanley Children's Hospital of New York Presbyterian, New York, NY; Duke Children's Hospital, Durham, NC; Freeman Hospital, Newcastle upon Tyne, UK; Hospital for Sick Children, Toronto, ON, Canada; Joe DiMaggio Children's Hospital, Hollywood, FL; Johns Hopkins Hospital, Baltimore, MD; Loma Linda University Medical Center, Loma Linda, CA; Medical University of South Carolina, Charleston, SC; Monroe Carell Jr. Children's Hospital at Vanderbilt University, Nashville, TN; Nationwide Children's Hospital, Columbus, OH; Phoenix Children's Hospital, Phoenix, AZ; Primary Children's Hospital, Salt Lake City, UT; Riley Hospital for Children, Indianapolis, IN; Seattle Children's, Seattle, WA; St. Louis Children's Hospital, St. Louis, MO; Texas Children's Hospital, Houston, TX; University of Alberta, Edmonton, AB, Canada; University of Florida, Shands Hospital, Gainesville, FL; University of Iowa Children's Hospital, Iowa City, IA; University of Miami, Jackson Memorial Hospital, Miami, FL; University of Michigan, CS Mott Children's Hospital, Ann Arbor, MI; University of Minnesota, Amplatz Children's Hospital, Minneapolis, MN; University of North Carolina, Chapel Hill, NC; University of South Florida–All Children's Hospital, St. Petersburg, FL; and University of Texas, Children's Medical Center, Dallas, TX.

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