Statin Intensity and Risk for Cardiovascular Events After Heart Transplantation

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Abstract.

Aims: Statins improve survival and reduce rejection and cardiac allograft vasculopathy (CAV) after HT. The impact of different statin intensities on clinical outcomes has never been assessed. We set out to determine the impact of statin exposure on cardiovascular outcomes after heart transplant (HT).

Methods: We performed a retrospective study of 346 adult patients who underwent HT from 2006 to 2018. Statin intensity was determined longitudinally post-HT based on ACC/AHA guidelines. The primary outcome was the time to the first primary event defined as the composite of heart failure hospitalization, myocardial infarction, revascularization, and all-cause mortality. Secondary outcomes included time to significant rejection and time to moderate-severe CAV. Adverse events were evaluated for subjects on high-intensity statin therapy. A Cox proportional hazards model was used to evaluate the relationship between clinical variables, statin intensity, and outcomes.

Results: Most subjects were treated with low-intensity statin therapy though this declined from 89.9% of the population at 1-month post-HT to 42.8% at 5-years post-HT. History of ischemic cardiomyopathy, significant acute rejection, older donor age, and lesser statin intensity (p=<0.001) were associated with reduced time to the primary outcome in a multivariable Cox model. Greater intensity of statin therapy was most beneficial early after HT. There were no statin-related adverse events for the 14 subjects on high-intensity statin therapy.

Conclusion: Greater statin intensity was associated with a reduction in adverse cardiovascular outcomes after HT.

Key Words: Statins, HMG CoA reductase inhibitors, heart transplantation, cardiac allograft vasculopathy

Introduction.

Treatment with HMG CoA reductase inhibitors (statins) is recommended early after heart transplant (HT)(1), as data support improved survival and reduced rejection and cardiac allograft vasculopathy (CAV) in statin-treated HT recipients.(2-8) While statins lower low-density lipoprotein cholesterol (LDL-C), there is evidence for additional non-LDL-C-lowering effects in cell culture and animal studies.(9) This is supported indirectly in clinical trials,(10, 11) with statins having potentially dose-dependent effects on inflammatory biomarkers.(12)

Despite evidence for statins' beneficial effects, both through LDL-C lowering and through non-LDL-C-lowering mechanisms, their use has been limited in some populations by dose-dependent drug-drug interactions, most notably with cyclosporine in transplant recipients.(13) As a result, studies in this population have only evaluated the efficacy of low- or moderate-intensity statin therapy, most often in comparison to no statin.(2, 3, 5, 6, 14) Current transplant guidelines recommend treatment with a lesser intensity statin than that used traditionally for management of hyperlipidemia or coronary artery disease.(1) Limited data, however, now support the safety of high-intensity statin therapy in patients treated with tacrolimus-based immunosuppression, the current standard of care after HT.(15, 16)

We performed a retrospective chart review of HT recipients to determine the impact of statin intensity, assessed longitudinally, on clinical outcomes. We secondarily evaluated the impact of statin intensity on rejection and CAV. We hypothesized that greater intensity of statin therapy would be associated with prolonged time to our primary composite endpoint of heart failure (HF) hospitalization, revascularization, myocardial infarction (MI), or death and that the impact of statin therapy on clinical outcomes would be greatest early after HT.

Methods.

Study design and patient selection.

We retrospectively identified patients older than 18 who underwent a first HT at the University of Michigan between January 2006 and March 2018. Patients who died within 30 days of HT or who were

managed by Pediatric Cardiology were excluded. Last follow-up was June 2018. Information was collected through chart review on patient demographics; comorbid conditions; medications; post-transplant coronary angiograms, echocardiograms, and positron emission tomography (PET) scans; rejection history; and all lipid levels post-HT. The PET imaging protocol has previously been published.(17) The study was approved by the University of Michigan Institutional Review Board and is in compliance with the *Declaration of Helsinki*. Informed consent was waived given the retrospective nature of this work.

Determination of statin intensity.

The prescribed statin and dose were extracted from the medical record at 1-month, 3-months, 6-months, 1-year, and 5-years post-HT. At each time point, subjects were categorized as being on no statin or on low-, moderate-, or high-intensity statin therapy as defined by the 2013 ACC/AHA Guidelines (Supplemental Table 1).(18) Time-points in which subjects were on no statin were assigned scores of 0 while time-points in which subjects were on low-, moderate-, or high-intensity statin therapy were assigned scores of 1, 2, or 3, respectively.

Given the established safety of low- and moderate-intensity statin therapy in transplant recipients,(2-8) we evaluated for elevations in serum aspartate transferase, alanine transferase, or creatinine kinase levels and for myalgias or rhabdomyolysis during high-intensity statin therapy. The clinical context surrounding statin discontinuation and all dose adjustments was reviewed.

Post-transplant protocols.

At our center, initial immunosuppression (a calcineurin inhibitor, mycophenolate mofetil and prednisone) and statin therapy (pravastatin 20 mg daily) are protocol driven. Subsequent drug therapy and evaluation for transplant vasculopathy with either noninvasive testing or coronary angiography with intravascular ultrasound (recommended annually regardless of perceived risk) is at the discretion of the treating transplant cardiologist.

Clinical events.

Outcomes were adjudicated by two cardiologists after chart review. HF hospitalization was defined as signs/symptoms of HF with at least one of the following criterion on or during admission in the absence of another etiology: abnormal hemodynamics, requirement for intravenous (IV) diuresis, or fall in ejection fraction. Hemodynamically significant HF during index admission for HT was considered early graft failure. Admission for IV diuresis in the first 90 days after HT not associated with rejection was considered post-operative diastolic dysfunction and not a HF hospitalization. MIs were defined as ST-elevation MIs (STEMIs) or type I non-STEMIs (NSTEMIs).

Rejection was defined according to the 2004 revised ISHLT criteria.(19) Significant rejection was defined as 2R or 3R cellular rejection, any antibody-mediated rejection, or hemodynamically significant, biopsy-negative rejection. Angiographic CAV was defined according to ISHLT nomenclature.(20) Moderate-severe CAV was defined as ISHLT CAV2 or CAV3 which requires at least one obstructive lesion in the proximal or middle third of either the left anterior descending, left circumflex, or right coronary artery or ISHLT CAV1 with allograft dysfunction or restrictive physiology.

Primary and secondary outcomes.

The primary outcome was the time to the first primary event defined as the composite of HF hospitalization, MI, revascularization, or all-cause mortality. We included HF hospitalizations as a primary event as progressive CAV contributes to myocardial dysfunction that increases risk for HF. Secondary outcomes included time to (1) significant rejection, (2) moderate-severe CAV by ISHLT criteria, or (3) clinical CAV, defined as the composite of myocardial flow reserve (MFR) < 2 on rest-stress rubidium-82 PET imaging, coronary revascularization, MI, or moderate-severe CAV on coronary angiography as above.

Statistical analysis.

Data were evaluated for normality and summarized as mean ± standard deviation or median [25th, 75th percentile] for continuous variables and count (%) for categorical variables, as appropriate. Kendall's

tau-b correlation coefficient was used to assess the association between statin intensity and LDL-C longitudinally. Univariable models identified candidate variables for the stepwise multivariable Cox regression model. Cox proportional hazards models were constructed for our primary and secondary outcomes including clinical variables as fixed covariates and first significant rejection episode and statin intensity as time-dependent covariates. For models violating the proportional hazards assumption, an interaction term with time was added to account for non-proportional hazards. For all multivariable analyses, a two-sided p-value < 0.05 was considered significant. All statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.5.1 (R Foundation for Statistical Computing).

Results.

Patient characteristics.

From January 2006 until March 2018, 356 adult patients underwent a first HT at the University of Michigan. Ten (10) patients were excluded: 6 died within 30 days of HT secondary to early graft failure and 4 were managed by Pediatric Cardiology. A total of 346 subjects were included in the final analysis. Most were male (78%) and white (81%) with a median age of 55.0 [46.0, 62.0] years at the time of HT. Twenty (20) subjects underwent dual heart/kidney transplant. Immunosuppression at 1-year included tacrolimus for 91.6%, mycophenolate mofetil for 74.3%, prednisone for 69.7%, and a proliferation signal inhibitor for 2.9%. Average LDL- C pre-HT was 81.5 mg/dL ± 31.9. Subjects with higher LDL-C levels were treated with greater intensity statin therapy (Kendall Tau = 0.152; p<.0001), presumably due to a perceived higher risk of post-HT adverse cardiovascular outcomes. Clinical characteristics by statin intensity 1-month post-HT are displayed in Table 1.

Statin therapy.

The majority of subjects were treated with pravastatin. At 1-month post-transplant, 97.3% of subjects were treated with pravastatin, declining to 73.0% at 5-years post-transplant (Supplemental Figure 1). The remaining subjects were treated with atorvastatin, rosuvastatin, or simvastatin. Initially, most

subjects were treated with low-intensity statin therapy though this declined from 89.9% of the population at 1-month post-transplant to 42.8% at 5-years post-HT (Figure 1; Table 1). At 5-years, 40.0% were treated with moderate-intensity statin therapy. Few subjects were treated with high-intensity statin therapy, with a maximum of 5.6% of subjects at 5-years post-HT. Changes in statin dose and intensity were frequent over subjects' clinical courses with the majority of subjects experiencing an increase in statin intensity over time. Fifty (50) subjects (14.8%) experienced a change in statin intensity between 1-month and 3-months, 44 subjects (13.4%) a change between 3-months and 6-months, 44 subjects (14.1%) a change between 6-months and 1-year, and 56 subjects (31.1%) a change between 1-year and 5-years.

Primary outcome.

One-hundred and six (106) of 346 subjects experienced at least one of the primary events. The first event was HF hospitalization for 56 subjects (52.8%), revascularization or MI for 7 subjects (6.6%), and death for 43 subjects (40.6%). In an unadjusted Cox regression model, significant acute rejection (as defined in the text), older donor age, and lesser statin intensity were associated with reduced time to the primary composite outcome (Table 2). Since statin intensity failed the proportional-hazards assumption, an adjusted model was created in which an interaction term was added between statin intensity and time. In the final semi-parametric model, history of ischemic cardiomyopathy, significant acute rejection, older donor age, and lesser statin intensity were all associated with reduced time to the primary composite outcome (Table 3). Greater intensity statin therapy was most beneficial early after HT.

Rejection.

Eighty-nine (89) of 346 subjects experienced a significant rejection episode. No clinical covariates were associated with time to rejection in univariable or multivariable Cox regression models (Supplemental Table 2).

CAV.

One-hundred and seventy-five subjects (175) underwent at least one coronary angiogram post-transplant of which 18 had evidence of ISHLT CAV2 or CAV3. Moderate-severe CAV was first documented on coronary angiography 4.36 [1.91, 5.52] years post-HT. Older donor age was associated with reduced time to moderate-severe CAV in univariable and multivariable analyses (HR 1.05; 95% CI 1.01-1.09; Supplemental Table 3).

Finally, we evaluated time to clinical CAV; 233 subjects had an assessment for CAV by either angiography or PET imaging. Seventy-six (76) of 233 subjects experienced the composite outcome, which was driven by an MFR < 2 in 58 subjects (76.3%), angiographic CAV in 14 subjects (18.4%), and revascularization or MI in 4 subjects (5.3%). Of the 58 subjects without a coronary angiogram, 27 had CAV diagnosed on PET imaging. Median time to event was 4.75 [2.81, 7.14] years post-HT. Older donor age was associated with reduced time to moderate-severe CAV in univariable and multivariable analyses (HR 1.02; 95% CI 1.01-1.04; Supplemental Table 4).

Adverse events.

Fourteen (14) subjects were treated with high-intensity statin therapy: 4 subjects were on high-intensity rosuvastatin and 10 on high-intensity atorvastatin. Thirteen subjects were concomitantly receiving tacrolimus and 1 subject was treated with cyclosporine (with atorvastatin). No subject experienced myalgias, myositis, rhabdomyolysis, or hepatotoxicity attributable to high-intensity statin therapy. Ten (10) subjects remained on high-intensity therapy once initiated, and 4 subjects underwent a dose reduction during clinical follow-up. In 3 cases, the rationale for the dose change was not documented, though there were no concomitant laboratory abnormalities. In one subject, the statin dose was decreased after a cytomegalovirus infection lead to an elevation in serum transaminase levels.

Discussion.

Current guidelines support initiation of statin therapy early after HT though at doses "lower than those recommended for [treatment of] hyperlipidemia" due to concern for pharmacological interactions

with calcineurin inhibitors.(1, 13) While the interaction between statins and cyclosporine is well documented, there is a paucity of data on the interaction between statins and tacrolimus,(13) and limited data suggest that tacrolimus and statins may be safe in combination.(15, 16) Furthermore, no studies have explored the incremental efficacy of treatment with moderate- or high-intensity statin therapy compared to low-intensity statin therapy, and the importance of treatment timing is unknown.

In this retrospective evaluation of the impact of longitudinal statin exposure after HT, greater statin intensity significantly prolonged time to our primary composite endpoint of HF hospitalization, revascularization, MI, or death. Greater statin intensity was most protective early after HT. Importantly, while only 14 patients were treated with high-intensity statin therapy, no adverse events were observed in this cohort treated predominantly with tacrolimus-based immunosuppression.

Prior studies have shown that statin therapy reduces cardiovascular events and mortality following HT. In the landmark study by Kobashigawa et al, 97 subjects were randomized to pravastatin 40 mg daily or to no statin.(6) At one year, subjects on pravastatin had significantly less hemodynamically significant rejection, better survival, and a lower incidence of CAV, the benefits of which were sustained at 10 years.(14) Similar results were seen on 1-year and 8-year follow-up of 72 subjects randomized to simvastatin 20 mg daily versus dietary therapy.(2, 5) Only one study compared two different statins prospectively though it evaluated low-intensity simvastatin versus low-intensity pravastatin.(3) While these and other studies established the benefit of statin therapy post-HT, they most often compared low- or moderate-intensity statin therapy to no statin, and none evaluated the safety and efficacy of high-intensity statin therapy.(4-6, 8)

This study adds to the literature in that we evaluated the comparative effectiveness of statin exposure (intensity and duration over time) on clinical outcomes. To fully understand the benefits of statin therapy post-HT, more comprehensive mechanistic evaluations of CAV are necessary, including assessments of coronary vascular dysfunction, a precursor to anatomic changes to the coronary vasculature.(21-24) Additionally, further studies are necessary to determine the extent to which statins act through LDL-C-lowering or through immunomodulatory mechanisms.(6, 25-27) In a recent study, pre-

operative treatment of cardiac donors with simvastatin significantly reduced recipient plasma inflammatory cytokine levels post-operatively, altered myocardial gene transcript signatures, and reduced treated episodes of hemodynamically significant rejection.(28) This suggests that very early statin therapy may have long-lasting effects on graft function, allorecognition, and immune responses that are consistent with the beneficial effects we observed after early treatment with a greater intensity statin.

Despite promising results, our study should be interpreted in the context of its limitations. First, the study was a single-center, observational study. Thus, there could be unmeasured differences between subjects who received more versus less intensive statin therapy. We believe, however, that subjects receiving a more intense statin may be those with greater perceived risk for clinical events. Thus, the benefits we observed with treatment occurred despite these individuals' potentially higher risk. Second, while statin intensity was evaluated at 5 time points to determine statin exposure, subjects may have undergone additional dose changes not captured in our chart review. This would affect all subjects equally, however, resulting in non-differential bias that would be unlikely to significantly impact the results. Third, only 233 subjects underwent evaluations for CAV by either PET imaging or coronary angiography, and angiography cannot evaluate for microvascular CAV. Thus, our ability to detect differences in time to moderate-severe CAV was limited. The additional subjects underwent alternative assessments for CAV including dobutamine stress echocardiograms or single photon emission computed tomography perfusion imaging. Since these modalities are less quantitative and thus less frequently used at our center for assessment of CAV, we did not include the results of these tests in our analyses. Next, we did not include LDL-C in our Cox regression model as statin intensity and LDL-C were confounded in exploratory analyses (i.e. patients with the highest lipid levels were treated with a greater intensity statin). Additionally, we did not account for other medications in our analyses aside from immunosuppressant therapy. This includes other lipid-lowering therapies as they were used rarely in our cohort, presumably because they are not recommended by HT guidelines and have potentially lesser effects on endothelial function and vascular inflammation.(29, 30) By not accounting for additional medications, we recognize that other drug interactions with statins could have been present; however, their impact on statin levels is highly variable

and cannot be reliably predicted.(13) Finally, consistent with past and current guidelines, very few subjects were treated with high-intensity statin therapy. Thus, the results were driven overwhelmingly by subjects on low- or moderate-intensity statin therapy. Future studies will be necessary to determine the safety and efficacy of high-intensity statin therapy on clinical outcomes, CAV, and rejection.

In conclusion, in a single-center study of subjects after HT, greater statin intensity prolonged time to HF hospitalization, revascularization, MI, or death. Greater statin intensity conferred the largest benefit early after HT. While few subjects were treated with high-intensity statin therapy, we observed no adverse events in this cohort. Future studies are needed to explore the safety and incremental efficacy of high-intensity statin therapy after HT.

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Conflict of Interest: V. L. Murthy has received consulting fees and stock options from Ionetix, Inc., owns stock in General Electric and Cardinal Health, has a research grant from Siemens Medical Imaging, and has provided expert witness testimony on behalf of Jubilant Draximage.

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Legends.

Figure 1: Statin intensity by time. The majority of subjects were treated with low-intensity statin therapy after heart transplant, though this declined over time in favor of treatment with moderate-intensity statin therapy. Few subjects were treated with high-intensity statin therapy.

Table 1: Baseline characteristics for 346 subjects by statin intensity 1-month after heart transplantation.

	Low Intensity (n=311)		Moderate or High Intensity (n=20)		No Statin (n=15)	
	Median (IQR)	Count (%)	Median (IQR)	Count (%)	Median (IQR)	Count (%)
Demographics						
Patient age at transplant, years	54.0 (46.0-61.0)		60.5 (42.8-63.3)		60.0 (41.0-63.5)	
Male gender		239 (76.8)		19 (95.0)		13 (86.7)
Race						
White		254 (81.7)		15 (75.0)		12 (80.0)
Black		52 (16.7)		4 (20.0)		1 (6.7)
Other		5 (1.6)		1 (5.0)		2 (13.3)
Comorbid conditions at time of transplant						
Body mass index, kg/m^2	27.8 (23.5-30.2)		26.9 (24.5-29.6)		23.7 (22.2-29.3)	
Diabetes mellitus		108 (34.7)		4 (20.0)		4 (26.7)
Hypertension		185 (59.5)		12 (60.0)		5 (33.3)
eGFR < 60 ml/min/1.73 m^2)		132 (42.6)		9 (45.0)		7 (50.0)
Transplant characteristics						
Ischemic cardiomyopathy		96 (30.9)		10 (50.0)		5 (33.3)
Organ						
Heart		293 (94.2)		20 (100)		13 (86.7)
Heart/Kidney		18 (5.8)		0 (0.0)		2 (13.3)

Donor age, years	32.0 (23.0-43.0)		40.0 (29.5-43.3)		44.0 (33.5-51.0)	
CMV status						
Donor (+)/Recipient (+)		96 (30.9)		5 (25.0)		3 (20.0)
Donor (-)/Recipient (-)		63 (20.3)		7 (35.0)		3 (20.0)
Donor (+)/Recipient (-)		72 (23.2)		7 (35.0)		6 (40.0)
Donor (-)/Recipient (+)		80 (25.7)		1 (5.0)		3 (20.0)
Ischemic time, minutes	160.0 (125.5-191.0)		154.0 (117.5-186.5)		151 (114.0-205.0)	

Twenty (20) subjects were treated at 1-month post-transplant with moderate or high- intensity statin therapy of which 19 were treated with a moderate-intensity statin and 1 a high-intensity statin. Key: CMV = cytomegalovirus; eGFR = estimated glomerular filtration rate; IQR = interquartile range; kg = kilogram.

Table 2: Univariable Cox model for time to heart failure hospitalization, revascularization, myocardial infarction, or death (n=346).

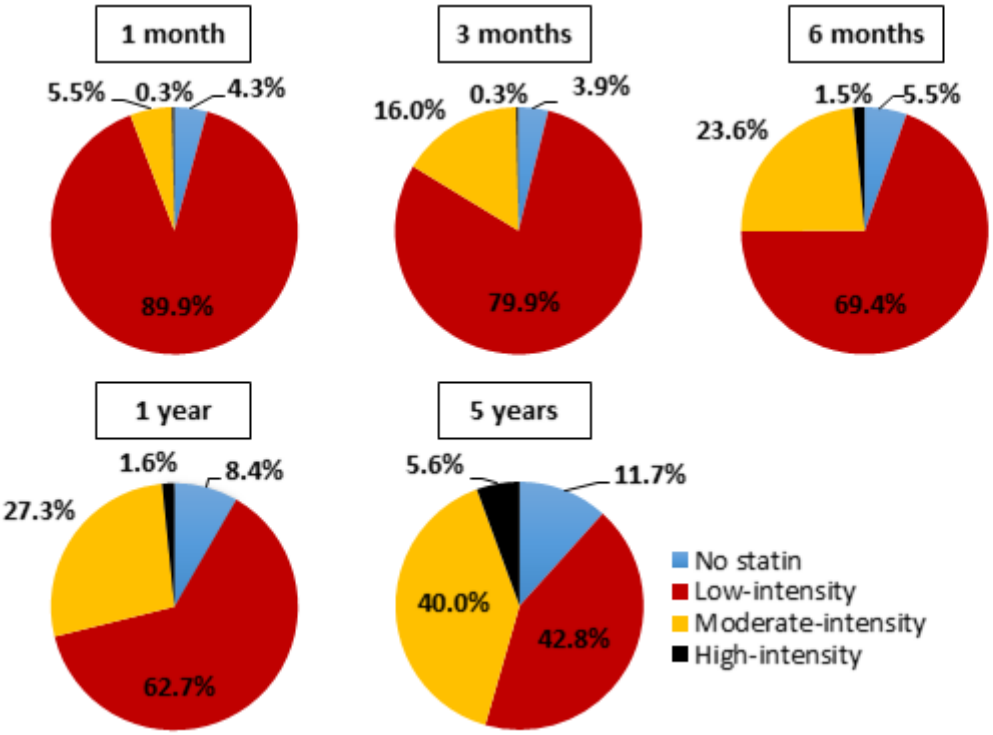
	Hazard Ratio	95% Confidence Interval	P-Value
Demographics			
Patient age at transplant, years	1.006	0.990 - 1.022	0.490
Male gender	1.175	0.729 - 1.896	0.500
Race (ref = white)			
Black	1.101	0.669 - 1.812	0.705
Other	0.455	0.063 - 3.272	0.434
Body mass index, kg/m^2	1.031	0.990 - 1.074	0.139
Transplant characteristics			
Ischemic cardiomyopathy	1.346	0.911 - 1.988	0.136
Donor age, years	1.020	1.004 - 1.036	0.013
CMV status [ref = *Donor (+)/Recipient (+)]*			
Donor (-)/Recipient (-)	1.065	0.609 - 1.864	0.824
Donor (+)/Recipient (-)	1.060	0.618 - 1.819	0.832
Donor (-)/Recipient (+)	1.376	0.825 - 2.296	0.221
CMV infection	1.359	0.744 - 2.483	0.318
Ischemic time, minutes	1.002	0.997 - 1.007	0.393
History acute rejection	2.150	1.447 - 3.194	<.001
Statin intensity	0.659	0.479 - 0.905	0.010

Key: CMV = cytomegalovirus; kg = kilogram; ref = reference.

Table 3: Multivariable Cox proportional hazards model for time to heart failure hospitalization, revascularization, myocardial infarction, or death.

	Hazard Ratio	95% Confidence Interval	P-Value
Ischemic cardiomyopathy	1.5063	1.0135 - 2.2388	0.0427
Donor Age	1.0188	1.0032 - 1.0347	0.0184
History acute rejection	2.3160	1.5527 - 3.4545	<0.0001
Statin intensity	0.3552	0.2069 - 0.6099	0.0002
Time * Statin intensity	1.0004	1.0001 – 1.0007	0.0105

History of ischemic cardiomyopathy, acute rejection, older donor age, and lesser statin intensity were associated with reduced time to the primary outcome in a multivariable model. As evidenced by the interaction between time and statin intensity, greater intensity of statin therapy was most beneficial early after transplant.



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