ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 2074–2081
Published online 24 June 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12784

ORIGINAL RESEARCH ARTICLE

Statin intensity and risk for cardiovascular events after heart transplantation

Jessica R. Golbus[1]*, Sarah Adie[2], Matheos Yosef[3], Venkatesh L. Murthy[1], Keith D. Aaronson[1] and Matthew C. Konerman[1]

[1]*Department of Medicine, Division of Cardiology, University of Michigan, Ann Arbor, MI, USA;* [2]*University of Michigan Health System, Ann Arbor, MI, USA;* [3]*Michigan Institute of Clinical and Health Research, University of Michigan, Ann Arbor, MI, USA*

Abstract

Aims Statins improve survival and reduce rejection and cardiac allograft vasculopathy after heart transplantation (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 HT.

Methods and results We performed a retrospective study of 346 adult patients who underwent HT from 2006 to 2018. Statin intensity was determined longitudinally after HT based on American College of Cardiology/American Heart Association (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 cardiac allograft vasculopathy. 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. Most subjects were treated with low-intensity statin therapy although this declined from 89.9% of the population at 1month after HT to 42.8% at 5years after HT. History of ischaemic cardiomyopathy, significant acute rejection, older donor age, and lesser statin intensity ($p \leq 0.001$) 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.

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

Keywords Statins; HMG CoA reductase inhibitors; Heart transplantation; Cardiac allograft vasculopathy

Received: 24 January 2020; Revised: 26 March 2020; Accepted: 27 April 2020
**Correspondence to: Jessica Golbus, University of Michigan Health System, 2381 CVC SPC 5853 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5853 USA. Tel: 734-936-8214; Fax: 734-615-3326. Email: jgolbus@med.umich.edu*

Introduction

Treatment with HMG CoA reductase inhibitors (statins) is recommended early after heart transplantation (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-intensity or moderate-intensity statin therapy, most often in comparison with no statin.[2,3,5,6,14] Current transplant guidelines recommend treatment with a lesser intensity statin than that used traditionally for management of hyperlipidaemia 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]

© 2020 The Authors. ESC Heart Failure published by John Wiley & Sons Ltd on behalf of the European Society of Cardiology
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

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; co-morbid conditions; medications; post-transplant coronary angiograms, echocardiograms, and positron emission tomography (PET) scans; rejection history; and all lipid levels after 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 1month, 3months, 6 months, 1year, and 5years after HT. At each time point, subjects were categorized as being on no statin or on low-intensity, moderate-intensity, or high-intensity statin therapy as defined by the 2013 ACC/AHA Guidelines (Supporting Information, *Table S1*).[18] Timepoints in which subjects were on no statin were assigned scores of 0 while timepoints in which subjects were on low-intensity, moderate-intensity, or high-intensity statin therapy were assigned scores of 1, 2, or 3, respectively.

Given the established safety of low-intensity 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 treatment with high-intensity statin therapy. The clinical context surrounding statin discontinuation and all dose adjustments were reviewed.

Post-transplant protocols

At our centre, initial immunosuppression (a calcineurin inhibitor, mycophenolate mofetil, and prednisone) and statin therapy (pravastatin 20mg 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) are 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 aetiology: abnormal haemodynamics, requirement for intravenous diuresis, or decline in ejection fraction. Haemodynamically significant HF during index admission for HT was considered early graft failure. Admission for intravenous 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 or type I non-ST-elevation MIs.

Rejection was defined according to the 2004 revised International Society for Heart and Lung Transplantation (ISHLT) criteria.[19] Significant rejection was defined as 2R or 3R cellular rejection, any antibody-mediated rejection, or haemodynamically 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 (i) significant rejection, (ii) moderate–severe CAV by ISHLT criteria, or (iii) clinical CAV, defined as the composite of myocardial flow reserve <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 patients were excluded: six died within 30days of HT secondary to early graft failure, and four 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 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 81.5mg/dL ± 31.9. Subjects with higher LDL-C levels were treated with greater intensity statin therapy (Kendall tau-b = 0.152; $P < 0.0001$), presumably due to a perceived higher risk of adverse cardiovascular outcomes after HT. Clinical characteristics by statin intensity 1month after HT are displayed in *Table 1*.

Statin therapy

The majority of subjects were treated with pravastatin. At 1month post-transplant, 97.3% of subjects were treated with pravastatin, declining to 73.0% at 5years post-transplant (Supporting Information, *Figure S1*). The remaining subjects were treated with atorvastatin, rosuvastatin, or simvastatin. Initially, most subjects were treated with low-intensity statin therapy although this declined from 89.9% of the population at 1month after HT to 42.8% at 5years after HT

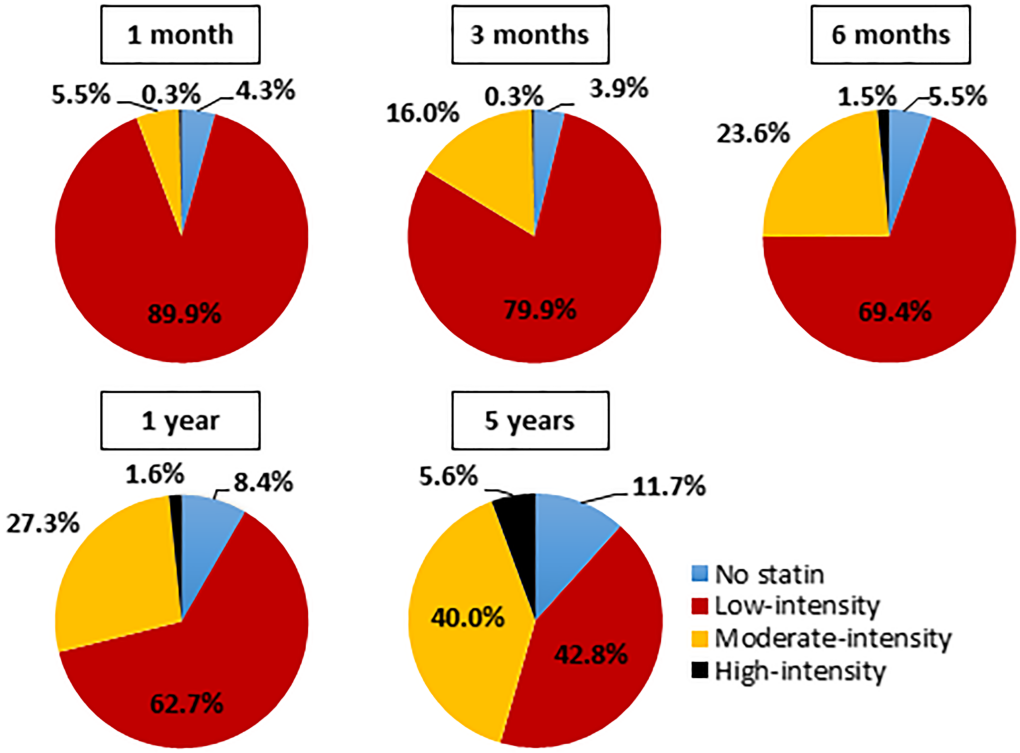
Table 1 Baseline characteristics for 346 subjects by statin intensity 1-month after heart transplantation

	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)
Co-morbid 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						
Ischaemic 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)
Ischaemic time, min	160.0 (125.5–191.0)		154.0 (117.5–186.5)		151 (114.0–205.0)	

Twenty subjects were treated at 1-month post-transplant with moderate-intensity or high-intensity statin therapy of which 19 were treated with a moderate-intensity statin and 1 a high-intensity statin. CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

DOI: 10.1002/ehf2.12784

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



(*Figure 1*; *Table 1*). At 5years, 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 5years after 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 subjects (14.8%) experienced a change in statin intensity between 1month and 3months, 44 subjects (13.4%) a change between 3 months and 6months, 44 subjects (14.1%) a change between 6months and 1year, and 56 subjects (31.1%) a change between 1year and 5years.

Primary outcome

One hundred six (106) of the 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 ischaemic 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.

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			
Ischaemic 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
Ischaemic time, min	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

CMV, cytomegalovirus; 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
Ischaemic 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 ischaemic 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.

Rejection

Eighty-nine (89) of the 346 subjects experienced a significant rejection episode. No clinical covariates were associated with time to rejection in univariable or multivariable Cox regression models (Supporting Information, *Table S2*).

Cardiac allograft vasculopathy

One hundred seventy-five (175) subjects 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 after 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; Supporting Information, *Table S3*).

Finally, we evaluated time to clinical CAV; 233 subjects had an assessment for CAV by either angiography or PET imaging. Seventy-six (76) of the 233 subjects experienced the composite outcome, which was driven by a myocardial flow reserve <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 after 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; Supporting Information, *Table S4*).

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 (13) 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 three cases, the rationale for the dose change was not documented, although 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 although 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-intensity or high-intensity statin therapy compared with 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 40mg daily or to no statin.[6] At 1year, subjects on pravastatin had significantly less haemodynamically 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 1year and 8years follow-up of 72 subjects randomized to simvastatin 20mg daily versus dietary therapy.[2,5] Only one study compared two different statins prospectively although it evaluated low-intensity simvastatin to low-intensity pravastatin.[3] While these and other studies established the benefit of statin therapy after HT, they most often compared low-intensity 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 after 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 haemodynamically 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-centre, 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. Because these modalities are less quantitative and thus less frequently used at our centre 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-intensity 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-centre 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.

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.

Funding

This work was supported by the Frankel Cardiovascular Center at the University of Michigan (J. R. G.); the National Institutes of Health (T32-HL007853, J. R. G.); the National Heart, Lung, Blood Institute at the National Institutes of Health (1R01HL136685 to V. L. M.); and the National Institute on Aging at the National Institutes of Health (1R01AG059729 to V. L. M.).

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Statin treatment by time. The majority of subjects were treated pravastatin after heart transplant though this declined with time since transplant in favour of atorvastatin, rosuvastatin, and simvastatin.

Table S1. Statin Intensity as Defined by ACC/AHA Guidelines.[1] Table abbreviated to include only statins prescribed for this cohort. Key: mg = milligrams

Table S2. Univariable Cox proportional hazards model for time to significant rejection. No clinical covariates were significantly associated with time to rejection (n=346). Key: CMV = cytomegalovirus; kg = kilogram; ref = reference.

Table S3. Univariable Cox proportional hazards model for time to moderate-severe CAV. Only older donor age was associated with reduced time to moderate-severe CAV on coronary angiography (n = 175). Key: CAV = cardiac allograft vasculopathy; CMV = cytomegalovirus; kg = kilogram; ref = reference.

Table S4. Univariable Cox proportional hazards model for time to clinical CAV. Clinical CAV was defined as the composite of PET-derived MFR <2, revascularization, myocardial infarction, or ISHLT CAV2 or CAV3 on coronary angiography. Older donor age was associated with reduced time to clinical CAV (n=233). Key: CAV = cardiac allograft vasculopathy; CMV = cytomegalovirus; kg = kilogram; MFR = myocardial flow reserve; PET = positron emission tomography; ref = reference.

References

1. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S, Fedson S, Fisher P, Gonzales-Stawinski G, Martinelli L, McGiffin D, Smith J, Taylor D, Meiser B, Webber S, Baran D, Carboni M, Dengler T, Feldman D, Frigerio M, Kfoury A, Kim D, Kobashigawa J, Shullo M, Stehlik J, Teuteberg J, Uber P, Zuckermann A, Hunt S, Burch M, Bhat G, Canter C, Chinnock R, Crespo-Leiro M, Delgado R, Dobbels F, Grady K, Kao W, Lamour J, Parry G, Patel J, Pini D, Towbin J, Wolfel G, Delgado D, Eisen H, Goldberg L, Hosenpud J, Johnson M, Keogh A, Lewis C, O'Connell J, Rogers J, Ross H, Russell S, Vanhaecke J. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010; **29**: 914–956.
2. Wenke K, Meiser B, Thiery J, Nagel D, von Scheidt W, Steinbeck G, Seidel D, Reichart B. Simvastatin reduces graft vessel disease and mortality after heart transplantation: a four-year randomized trial. *Circulation* 1997; **96**: 1398–1402.
3. Mehra MR, Uber PA, Vivekananthan K, Solis S, Scott RL, Park MH, Milani RV, Lavie CJ. Comparative beneficial effects of simvastatin and pravastatin on cardiac allograft rejection and survival. *J Am Coll Cardiol* 2002; **40**: 1609–1614.
4. Stojanovic I, Vrtovec B, Radovancevic B, Radovancevic R, Yazdanbakhsh AP, Thomas CD, Frazier OH. 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.
5. Wenke K, Meiser B, Thiery J, Nagel D, von Scheidt W, Krobot K, Steinbeck G, Seidel D, Reichart B. Simvastatin initiated early after heart transplantation: 8-year prospective experience. *Circulation* 2003; **107**: 93–97.
6. Kobashigawa JA, Katznelson S, Laks H, Johnson JA, Yeatman L, Wang XM, Chia D, Terasaki PI, Sabad A, Cogert GA. Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med* 1995; **333**: 621–627.
7. Patel DN, Pagani FD, Koelling TM, Dyke DB, Baliga RR, Cody RJ, Lake KD, Aaronson KD. Safety and efficacy of atorvastatin in heart transplant recipients. *J Heart Lung Transplant* 2002; **21**: 204–210.
8. See VY Jr, DeNofrio D, Goldberg L, Chang G, Sasseen B, Kolansky DM, Pickering F, Kao A, Loh E, Wilensky RL. 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.
9. Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins on the cardiovascular system. *Circ Res* 2017; **120**: 229–243.
10. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; **359**: 2195–2207.
11. Kinlay S, Schwartz GG, Olsson AG, Rifai N, Leslie SJ, Sasiela WJ, Szarek M, Libby P, Ganz P, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study Investigators. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. *Circulation* 2003; **108**: 1560–1566.
12. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, Ramsey KE, Palmisano J, Bilheimer DW, Pfeffer MA, Califf RM, Braunwald E. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004; **292**: 1307–1316.
13. Wiggins BS, Saseen JJ, Page RL, Reed BN, Sneed K, Kostis JB, Lanfear D, Virani S, Morris PB, American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology, Council on Hypertension, Council on Quality of Care and Outcomes Research, Council on Functional Genomics and Translational Biology. 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.
14. Kobashigawa JA, Moriguchi JD, Laks H, Wener L, Hage A, Hamilton MA, Cogert G, Marquez A, Vassilakis ME, Patel J, Yeatman L. Ten-year follow-up of a randomized trial of pravastatin in heart transplant patients. *J Heart Lung Transplant* 2005; **24**: 1736–1740.
15. Lemahieu WP, Hermann M, Asberg A, Verbeke K, Holdaas H, Vanrenterghem Y, Maes BD. Combined therapy with atorvastatin and calcineurin inhibitors: no interactions with tacrolimus. *Am J Transplant* 2005; **5**: 2236–2243.
16. Simonson SG, Raza A, Martin PD, Mitchell PD, Jarcho JA, Brown CD, Windass AS, Schneck DW. Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine. *Clin Pharmacol Ther* 2004; **76**: 167–177.
17. Konerman MC, Lazarus JJ, Weinberg RL, Shah RV, Ghannam M, Hummel SL, Corbett JR, Ficaro EP, Aaronson KD, Colvin MM, Koelling TM, Murthy VL. Reduced myocardial flow reserve by positron emission tomography predicts cardiovascular events after cardiac transplantation. *Circ Heart Fail* 2018; **11**: e004473.
18. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Tomaselli GF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; **129**: S1–S45.

19. Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, Andersen CB, Angelini A, Berry GJ, Burke MM, Demetris AJ, Hammond E, Itescu S, Marboe CC, McManus B, Reed EF, Reinsmoen NL, Rodriguez ER, Rose AG, Rose M, Suciu-Focia N, Zeevi A, Billingham ME. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant* 2005; **24**: 1710–1720.
20. Mehra MR, Crespo-Leiro MG, Dipchand A, Ensminger SM, Hiemann NE, Kobashigawa JA, Madsen J, Parameshwar J, Starling RC, Uber PA. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. *J Heart Lung Transplant* 2010; **29**: 717–727.
21. Hollenberg SM, Klein LW, Parrillo JE, Scherer M, Burns D, Tamburro P, Oberoi M, Johnson MR, Costanzo MR. Coronary endothelial dysfunction after heart transplantation predicts allograft vasculopathy and cardiac death. *Circulation* 2001; **104**: 3091–3096.
22. Lee JH, Okada K, Khush K, Kobayashi Y, Sinha S, Luikart H, Valantine H, Yeung AC, Honda Y, Fearon WF. Coronary endothelial dysfunction and the index of microcirculatory resistance as a marker of subsequent development of cardiac allograft vasculopathy. *Circulation* 2017; **135**: 1093–1095.
23. Loopez-Fernandez S, Manito-Lorite N, Gómez-Hospital JA, Roca J, Fontanillas C, Melgares-Moreno R, Azpitarte-Almagro J, Cequier-Fillat A. Cardiogenic shock and coronary endothelial dysfunction predict cardiac allograft vasculopathy after heart transplantation. *Clin Transplant* 2014; **28**: 1393–1401.
24. Colvin-Adams M, Harcourt N, Duprez D. Endothelial dysfunction and cardiac allograft vasculopathy. *J Cardiovasc Transl Res* 2013; **6**: 263–277.
25. Hiemann NE, Wellnhofer E, Knosalla C, Lehmkuhl HB, Stein J, Hetzer R, Meyer R. Prognostic impact of microvasculopathy on survival after heart transplantation: evidence from 9713 endomyocardial biopsies. *Circulation* 2007; **116**: 1274–1282.
26. Weis M, Pehlivanli S, Meiser BM, von Scheidt W. Simvastatin treatment is associated with improvement in coronary endothelial function and decreased cytokine activation in patients after heart transplantation. *J Am Coll Cardiol* 2001; **38**: 814–818.
27. Yi T, Rao DA, Tang PC, Wang Y, Cuchara LA, Bothwell AL, Colangelo CM, Tellides G, Pober JS, Lorber MI. Amelioration of human allograft arterial injury by atorvastatin or simvastatin correlates with reduction of interferon-gamma production by infiltrating T cells. *Transplantation* 2008; **86**: 719–727.
28. Nykanen AI, Holmstrom EJ, Tuuminen R, Krebs R, Dhaygude K, Kankainen M, Jokinen JJ, Lommi J, Helantera I, Raisanen-Sokolowski A, Syrjala SO, Lemstrom KB. Donor simvastatin treatment in heart transplantation. *Circulation* 2019; **140**: 627–640.
29. Liu PY, Liu YW, Lin LJ, Chen JH, Liao JK. Evidence for statin pleiotropy in humans: differential effects of statins and ezetimibe on rho-associated coiled-coil containing protein kinase activity, endothelial function, and inflammation. *Circulation* 2009; **119**: 131–138.
30. Landmesser U, Bahlmann F, Mueller M, Spiekermann S, Kirchhoff N, Schulz S, Manes C, Fischer D, de Groot K, Fliser D, Fauler G, Marz W, Drexler H. Simvastatin versus ezetimibe: pleiotropic and lipid-lowering effects on endothelial function in humans. *Circulation* 2005; **111**: 2356–2363.