Comparative Risk of Statin Exposure on Adverse Cardiovascular Outcomes in Heart Transplant Recipients

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Background

- Long-term survival for heart transplant (HTx) recipients remains affected by post-transplant dyslipidemia leading to the development of a form of rapidly progressive atherosclerosis, known as cardiac allograft vasculopathy (CAV).
- Most recipients require immunosuppressive therapy to prevent acute allograft rejection, although agents such as calcineurin inhibitors (CNIs) and corticosteroids may precipitate metabolic dysfunction leading to the rise in LDL cholesterol after HTx.
- Current guidelines recommend lower intensity or dosing of statins to reduce the risk of interactions with CNIs.
- As a result, available evidence for LDL-lowering efficacy and cardiovascular outcomes in HTx recipients is restricted mainly to low- or moderate-intensity statins.
- There is a need to investigate alternative antilipemic therapies or combinations with immunosuppressants for CAV prevention in HTx recipients.

Purpose

- Briefly, this retrospective cohort study using the large global federated electronic medical record database (TriNetX) aims to add to the current literature regarding the perioperative management of HTx recipients, specifically in relation to the safety and efficacy of statin exposure in preventing cardiac allograft vasculopathy and adverse cardiovascular events.

Methods

- A TriNetX query was conducted using electronic health record (EHR) data within the US Collaborative Network.
- Patients aged 18 to 75 years with ICD or CPT codes for diagnosis, procedure, or evaluation related to HTx between 1/1/2015 and 12/31/2024 were separated into cohorts based on post-transplant treatment with or without statins.
- All patients were prescribed immunosuppressive therapy.
- Cohorts underwent propensity score matching (PSM) by baseline demographics (age at transplant, race, sex), comorbidities (T2DM, HTN, HLD, PVD, nicotine dependence), and characteristics (BMI, systolic BP, HbA1c, serum creatinine, and LDL-C).
- Primary outcome was combined 5-Point MACE.
- Secondary outcomes included all-cause mortality, cardiovascular disease, ischemic heart disease, cerebrovascular disease, heart failure, invasive cardiac procedures, and myalgia.

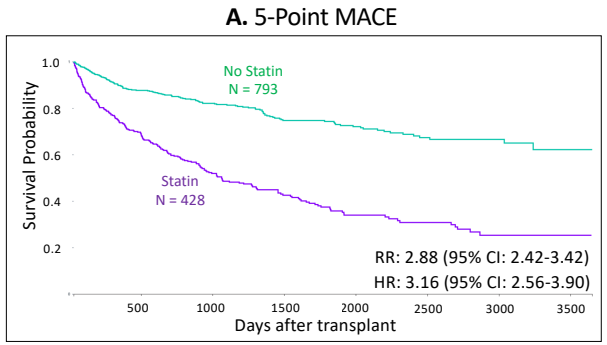
Results

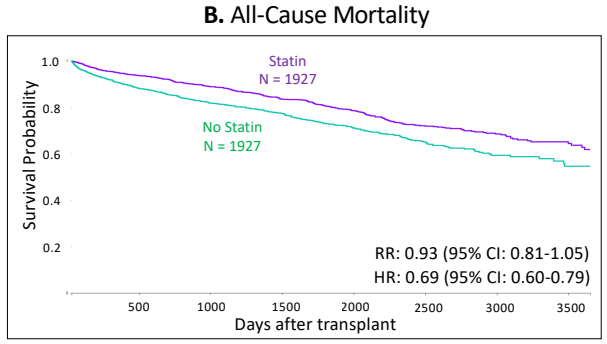
Demographics	No Statin (N=1,927)	Statin (N=1,927)
Age at HTx, years (mean +/- SD)	47.3 +/- 16.6	47.2 +/- 16.5
White (n, %)	1,208 (62.7)	1,225 (63.6)
Male (n, %)	1,202 (62.4)	1,230 (62.8)
BMI, kg/m^2 (mean +/- SD)	26.9 +/- 6.0	27.5 +/- 5.6 *
Hypertension (n, %)	1,092 (56.7)	1,050 (54.5)
Systolic BP, mmHg (mean +/- SD)	122.1 +/- 23.7	117.6 +/- 23.5 *
Hyperlipidemia (n, %)	775 (40.2)	774 (40.2)
LDL Cholesterol, mg/dL (mean +/- SD)	86.0 +/- 37.5	82.7 +/- 35.7 *
Type 2 Diabetes (n, %)	627 (32.5)	582 (30.2)
Hemoglobin A1c, %, (mean +/- SD)	5.9 +/- 1.4	6.0 +/- 1.2
Nicotine Dependence (n, %)	415 (21.5)	396 (20.6)
Peripheral Vascular Disease (n, %)	106 (5.5)	103 (5.3)
Creatinine, mg/dL (mean +/- SD)	1.8 +/- 1.9	1.6 +/- 1.5 *

Table 1. After PSM, baseline characteristics, vitals, and lab data prior to HTx. *p < 0.05

Demographics cont.	No Statin (N=1,927)	Statin (N=1,927)
Immunosuppressants (n, %)		
Tacrolimus	989 (51.3)	966 (50.1)
Mycophenolate mofetil	815 (42.3)	807 (41.9)
Cyclosporine	139 (7.2)	157 (8.1)
Sirolimus	142 (7.4)	162 (8.4)
Azathioprine	145 (7.5)	132 (6.9)
Antilipemic (n, %)		
Omega-3 fatty acid	75 (3.9)	80 (4.2)
Ezetimibe	69 (3.6)	71 (3.7)
Fenofibrate	37 (1.9)	28 (1.5)
Icosapent ethyl	10 (0.5)	11 (0.6)
Evolocumab	19 (1.0)	10 (0.5)

Table 2. After PSM, co-prescribed immunosuppressant and antilipemic medications in the post-transplant period. *p<0.05





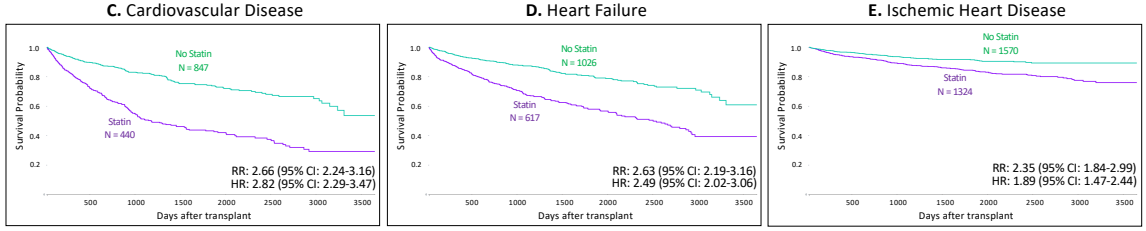


Figure 1. Kaplan Meyer curves showing reported rates of major adverse cardiac event (MACE) and all-cause mortality in HTx recipients based on statin exposure. Outcomes were analyzed from 30 days to 10 years after transplant. Patients with prior outcomes were excluded from analysis.

Results

- After PSM, patients in the statin cohort displayed generally healthier baseline cardiometabolic profiles, based on lower systolic blood pressure, LDL cholesterol, and creatinine.
- Cohorts were prescribed immunosuppressants and other antilipemic agents at equal proportion.
- The primary outcome of 5-Point MACE was significantly higher in the statin cohort, with early distinction in the first year.
- The statin cohort also experienced higher rates of cardiovascular disease, ischemic heart disease and heart failure.
- Statin exposure was associated with significantly higher risk of post-transplant invasive cardiac procedures, RR = 5.19 (95% CI: 4.30-6.27).
- Myalgia was also more common with statin exposure, RR = 2.00 (95% CI: 1.53-2.62)

Conclusions

- Statins alone may be insufficient to achieve optimal cardiovascular prevention in this unique population.
- Statin exposure after HTx was associated with a higher relative risk of MACE, but no significant difference in all-cause mortality.
- By excluding patients with prior outcomes from analysis, these findings highlight the higher rates of new onset CVD or first incidence of MACE but do not account for benefits of continuing statins in the context of pre-existing CVD.
- While graft failure was not specifically compared, the rate of interactions between statins and immunosuppressants associated with poorer outcomes appears insignificant, as cohorts were equally prescribed CNIs.
- Future studies may consider direct comparison of statins and other alternative or adjunct therapies, such as PCSK9 inhibitors, for post-transplant cardiovascular protection.

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