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Statin Use for CAV Prevention in Pediatric Heart Transplant Recipients: Helpful or Harmful?

As highlighted by Dr. D'Addese in her review of aspirin use to prevent cardiac allograft vasculopathy (CAV) in the latest PHTS Newsletter, CAV remains the major Achilles heel to long-term graft survival after heart transplantation, with no proven strategies identified to prevent CAV development in children. With their greater patient numbers and resources for large-scale research, studies of adult heart transplant recipients (HTRs) remain a primary source of information from which we extrapolate management and treatment options for our pediatric HTRs. The adult data on statin use is compelling, with a recent meta-analysis of statin use in adult HTRs demonstrating decreased all-cause mortality, rejection, and CAV.[1] However, as we all well know, children are not just tiny adults, and so adult strategies for CAV prevention may or may not be truly applicable to our patient population. With this background in mind, we felt a contemporary evaluation of the PHTS registry could help us better understand the prevalence and efficacy of statin use in pediatric HTRs.[2]

Background

Statins (HMG-CoA reductase inhibitors), through their effective treatment of hyperlipidemia, are commonly utilized for primary and secondary prevention of traditional atherosclerotic cardiovascular disease in adults. They have been hypothesized to attenuate the ischemia-reperfusion injury inherent to cold storage of donor hearts as well as have immune modulatory effects, and early initiation in the first few months post-transplant have demonstrated the greatest benefit to adult HTRs.[3] The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of HTRs recommend consideration of statin therapy in all HTR (pediatric and adult).[4]

However, considerations unique to our pediatric population have limited uptake of statin usage, including concerns about safety during childhood growth and puberty, lack of Federal Drug Administration labelling for some statin medications in children, lack of liquid medication formulations, and conflicting data on the true efficacy of statins in the absence of the more metabolically driven risk factors for coronary atherosclerotic disease in adult HTRs. Moreover, the pediatric literature on statin use in pediatric HTRs is largely limited to single center series with mixed results, and the previous study of the PHTS database by Dr. Greenway and colleagues found no association between statin use in the first-year post-transplant and post-transplant survival or CAV development, and in fact raised concern for risk of earlier rejection.[5] The authors identified important limitations of their study, including the distinct possibility that the patients receiving statins represented a higher-risk cohort, with numerous unidentified confounding factors, leaving interpretation and extrapolation of the results to standard-risk pediatric HTRs challenging.

The last two decades have brought long-term safety and efficacy data on statin use in the pediatric familial hyperlipidemia population. Moreover, given the limited options to prevent or treat early CAV and extent graft survival in pediatric HTRs, statins continue to be commonly prescribed by many pediatric heart transplant practitioners. The goal of our recent study was thus to evaluate the contemporary prevalence and trends of statin use in pediatric HTRs and the association between statin use and CAV incidence as well as graft survival.

Study Design

Pediatric patients (<17 years at primary heart-only transplant) were identified from the PHTS database between January 2001 through December 2018, with three years of follow up data available. Our analysis specifically sought to evaluate the use of statins as a primary prevention therapy (i.e., prior to the development of endpoints such as CAV that would prompt treatment) and thus evaluated the use of statin therapy in the first 3 years post-transplant (Figure 1). As statins have a more established safety profile in children ≥10 years of age, a sub-analysis was undertaken for patients who were ≥10 years old at the time of transplant.

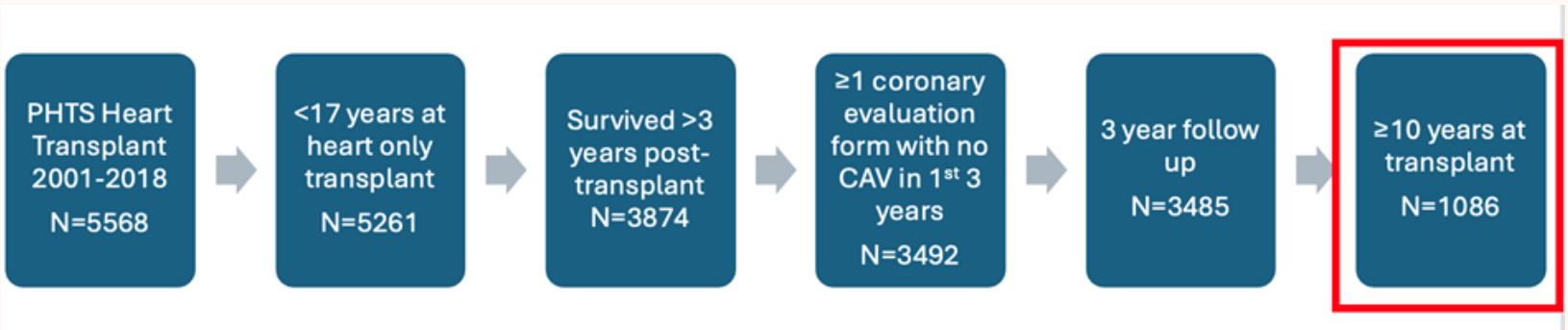


Figure 1. Study cohort flowchart.

Statin use was identified on the annual post-heart transplant follow up forms and classified as:

1. Consecutive (present on all 3 forms)
2. Intermediate (1-2 forms)
3. None (0 forms).

Statin utilization patterns were evaluated. The primary endpoints evaluated were graft survival and freedom from CAV diagnosis. A secondary analysis was performed looking at center practice variation, which compared patients not on statins at low (0-25%) statin use centers to those on statins at high (76-100%) statin use centers in an attempt to compare standard risk pediatric HTRs receiving, or not receiving, protocol-driven statin preventative therapy.

Key Results

Of the 3485 pediatric HTRs who met inclusion criteria, 17% received consecutive statin therapy, 19% intermediate use, and 65% no statin in the first 3-years post-transplant, while in the ≥10-year-old cohort (n=1086), 29% received consecutive statin therapy, 32% intermediate use, and 39% no statin (Figure 2). Patients not on statins represented a different patient population (younger, congenital heart disease, higher cardiopulmonary support). However, in the older cohort, the patients on consecutive vs intermediate vs no statin use were largely similar. Therefore, in conjunction with increased statin usage in this group, the outcome analyses focused on this group.

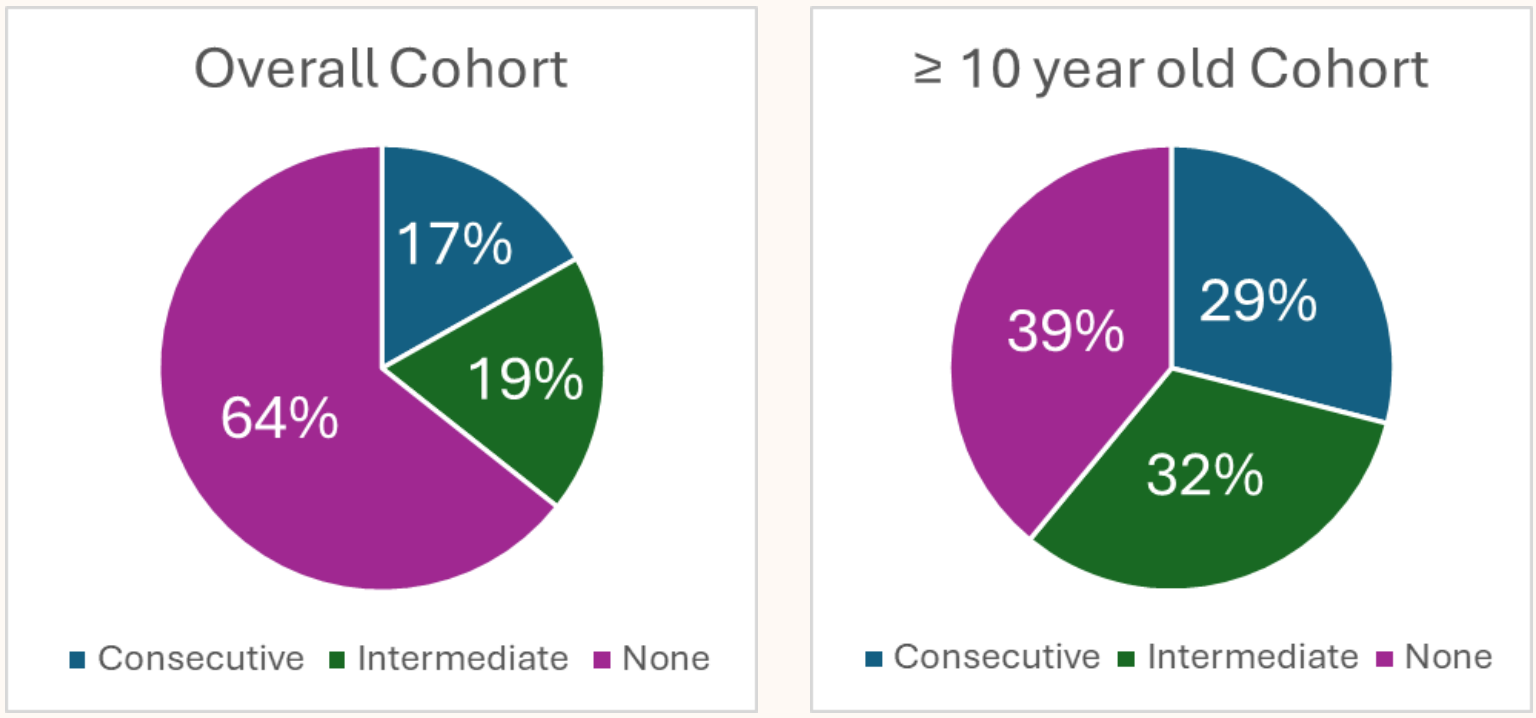


Figure 2. Statin usage in the first 3-years post-transplant in the overall and ≥10-year-old cohorts.

Statin use was highly variable across the 54 PHTS centers, with 20 sites having 0-25% of their patients in the overall cohort on statins, 23 sites 25-50% of patients, 8 sites 50-75% of patients, and 3 sites 75-100% of their patients on statins across the first three annual follow up visits (Figure 3).

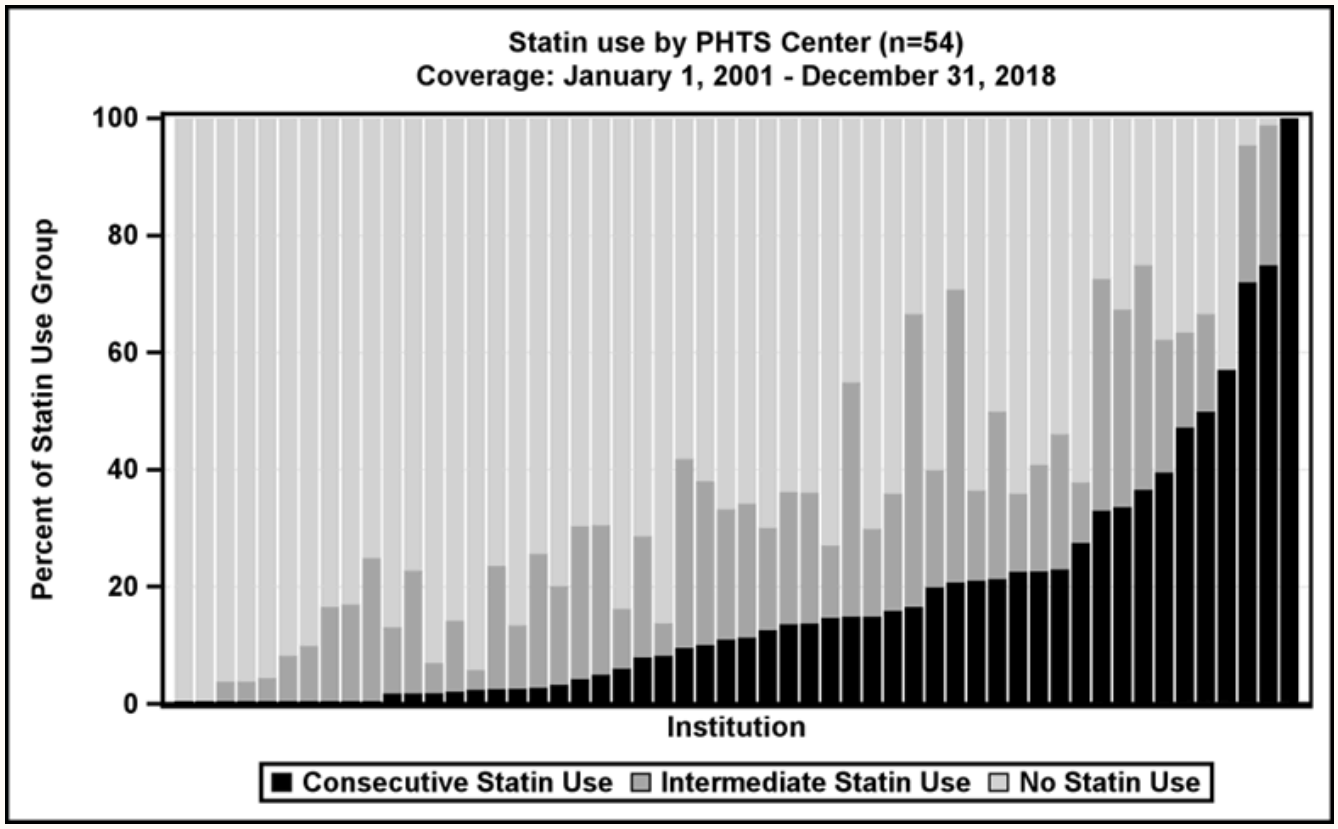


Figure 3. Statin use by PHTS center in the overall cohort.

Statin use:

- Increased with increasing patient age
- Was more likely to be initiated by the 1-year visit in ≥10-year-olds (42%) vs 3-years (8%) or 5-years (3%) post-transplant
- Overall and consecutive statin usage increased over time in the ≥10-year-olds, but not in the overall cohort
- Was not associated with improved graft survival or decreased incidence of CAV in multivariate or propensity score matched analysis, or in the comparison of center practice variation

Implications, Limitations and Future Directions

This contemporary PHTS study of statin use in children did not demonstrate statins to be protective in terms of graft survival or prevention of CAV. However, there are important limitations inherent to the registry data, which begin with the need to define early statin use at the 1-year post-transplant follow up form, which is beyond the timeframe of highest statin benefit post-transplant seen in the adult data. Statin medication type and dosing is not collected. CAV is diagnoses on coronary angiography, which is likely a late identifier of disease. Finaly, adolescents may age out of receiving care at PHTS centers, which limits long-term outcomes data. This study does seem to put to rest any clearly identified harm from statins in children, at least from a graft survival standpoint, and so we turn back to the adult data, which continues to compel us to further study the potential benefits of early statin use in children. A prospective study of early statin use in pediatric HTRs that utilizes imaging techniques that can provide early diagnosis of CAV, and that supports collection of long-term follow up data, is likely the only way we will be able to identify with certainty whether statins are truly helpful in our pediatric patients. Given the equipoise in the literature, the safety data on statin use from other pediatric populations, and the practice variation seen between PHTS centers, a prospective trial that evaluated statin and aspirin use for the prevention of CAV and improvement in long-term graft survival in pediatric HTRs is needed.

References

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