Journal of Biochemical and Molecular Toxicology

WILEY

REVIEW

Optimizing Outcomes in Heart Transplantation: The Role of High-Intensity Statin Therapy

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Received: 6 August 2024 | **Revised:** 10 September 2024 | **Accepted:** 11 November 2024

Funding: The authors received no specific funding for this work.

Keywords: coronary allograft vasculopathy | graft rejection | heart transplantation | high-intensity statins | statin therapy

ABSTRACT

Heart transplantation is a vital procedure for patients with end-stage heart failure, but it faces significant challenges, including graft dysfunction, rejection, and cardiac allograft vasculopathy (CAV), which can compromise long-term graft success. Research suggests that statin therapy may offer significant benefits to heart transplant recipients, such as improved long-term survival and reduced rates of graft rejection and mortality. The aim of this review is to thoroughly examine the recent literature on this topic since 2005. Early use of high-dose statins appears to be particularly effective in preventing vasculopathy and improving outcomes, although a titrated approach may help to reduce side effects. High-dose statins may provide superior cardiovascular benefits, including lower rates of CVD, slower progression of CVD and improved long-term graft survival. Despite potential concerns about adverse effects, evidence suggests that high-intensity statins improve cholesterol levels without increasing serious adverse events after transplantation. The goal of statin therapy in heart transplant recipients is to balance the well-established benefits seen in the general population with the specific needs of this group, with the ultimate goal of improving both longevity and quality of life.

1 | Introduction

Since its discovery in 1967, heart transplantation (HT) has remained a life-saving treatment for patients with end-stage heart failure, increasing survival rates by more than a decade. However, there are far more heart transplant candidates than heart donors. This is further complicated by issues such as graft dysfunction and failure, immunosuppression-related complications and allograft rejection, such as cardiac allograft vasculopathy (CAV), acute cellular rejection (ACR), and antibody-mediated rejection (AMR), which limit graft viability [1]. Although the donor pool has expanded due to recent innovations [2], posttransplant care should be optimized to increase the survival of the transplanted organ. CAV is a unique form of

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coronary artery disease that affects the vasculature of the transplanted heart and is a leading cause of morbidity and mortality in heart transplant recipients. As such, the management and mitigation of CAV progression is a critical aspect of posttransplant care. Terminal malignancy is a significant cause of death late after heart transplantation.

Statins are inhibitors of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthesis pathway [3]. Statin therapy, widely used to manage hyperlipidemia and prevent atherosclerotic cardiovascular disease, has attracted attention for its potential benefits in heart transplant recipients, including reducing the incidence of CAV and improving long-term outcomes, regardless of lipid levels [4–9]. The International Society for Heart and Lung Transplantation Guidelines (2024) strongly recommend (Class I; Level of Evidence A) initiation of statins within 1–2 weeks of heart transplantation, regardless of cholesterol levels [10]. Statins are believed to reduce the incidence of cardiac allograft rejection and graft vasculopathy and increase the survival rates of heart transplant patients [11].

In 2011, the FDA issued a boxed warning for Zocor (simvastatin), introducing new restrictions and dosage limits to reduce the risk of muscle injury, liver damage, and rhabdomyolysis. Drug interactions, particularly with cyclosporine, have been identified as a major cause of statin-related adverse effects, leading to changes in the labeling of cyclosporine and statins, and a shift in managing posttransplant hyperlipidaemia. Tacrolimus has since replaced cyclosporine in most immunosuppressive regimens. However, discrepancies exist between drug information sources and guidelines regarding statin interactions with cyclosporine or tacrolimus, with limited data on tacrolimus [12]. While statin use in heart transplant patients is well-supported, long-term complications like myopathy and hepatotoxicity remain unclear. Further research is needed on dosing, preoperative use, and statin therapy in heart donors. This article reviews the current understanding of statin therapy in heart transplantation, focusing on its effects on CAV progression, outcomes, and safety.

2 | Statins and Heart Transplantation

2.1 | Potential Mechanisms of Action

There is a well-known association between dyslipidemia and the development of CAV, one of the main etiologies of allograft rejection [11]. Statins may increase the survival rate of heart transplants by decreasing serum cholesterol levels. According to animal studies, hypercholesterolemia might result in hyperplasia of allograft vessel intima and lipid deposition [13]. Statins can also increase the stability of atherosclerotic plaques in mouse models of heart transplants [14]. Their effect on the decreased atherosclerosis of the grafts and their improved endothelial function and decreased endothelial permeability has been revealed in heart transplant patients [15] (Figure 1).

In addition, statins may reduce allograft rejection by several mechanisms (see graphical abstract). Statins have pleiotropic properties, including increasing apoptosis, inhibiting angiogenesis, downregulating circulating cytokines, and reducing circulating monocytes [16]. One possible mechanism is the reduction in the synthesis of prenylated proteins, which ultimately leads to the inhibition of protein biosynthesis, resulting in a reduction in the proliferation, angiogenesis, and differentiation of tumor cells, as well as affecting the proliferation of vascular smooth muscle

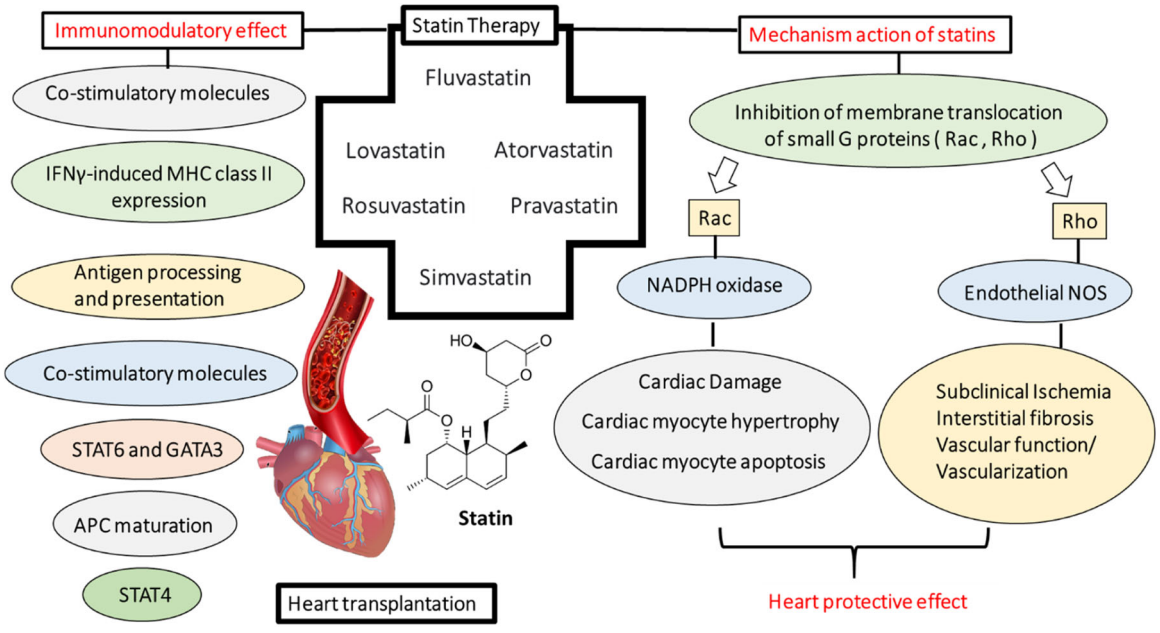

FIGURE 1 | Effect of different statins (fluvastatin, atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin) on the outcome of heart transplantation in patients with end-stage heart failure. Statin therapy has been shown to exert immunomodulatory effects by reducing co-stimulatory molecules, inhibiting IFNγ-induced MHC class II expression and increasing antigen-presenting cell (APC) maturation. These changes contribute to a reduction in antigen processing and presentation, influenced by decreased STAT4 and increased STAT6 and GATA3 activity. Together, these effects help to reduce graft rejection and CAV, ultimately improving long-term graft survival and patient outcomes.

cells and the production of nitric oxide [17]. However, they boost the expression of growth factor genes, which might increase the proliferation of smooth muscle cells [18].

Statins have been shown to have immunological effects in vitro, including regulation of DNA in cycling cells, inhibition of monocyte chemotaxis, regulation of natural killer cell cytotoxicity and inhibition of antibody-dependent cellular cytotoxicity. These effects may be due to changes in circulating lipids or other mechanisms. These inhibitors have been shown to reduce natural killer cell function and antibody-dependent cellular cytotoxicity, which can increase immunosuppression and lead to clinically reduced allograft rejection [19, 20]. Statins' immunomodulatory effects are also exerted via and enhancing the effects of immunosuppressive agents such as cyclosporine [21] associated with anti-inflammatory effects. However, they might increase the production of regulatory T cells, which is associated with an impaired antitumor response [22].

Statins have been shown to directly reduce the virulence and pathogenicity of several organisms, affect their signaling pathways and interact with several antimicrobial agents. They may provide protection against infections caused by several pathogens including *Staphylococcus aureus*, *Mycobacterium tuberculosis* and Candida species. However, further clinical trials are needed to validate the benefits of statins in preventing posttransplant infections [23]. These combined effects may ultimately reduce the incidence of cardiac allograft dysfunction in heart transplant recipients, as evidenced by a meta-analysis showing a 67% reduction in coronary vasculopathy and a 63% reduction in hemodynamically significant rejection episodes. They also have antitumor effects in heart transplant recipients, as confirmed by the same meta-analysis showing a 70% reduction in terminal cancer in these patients [16]. This anticancer effect is not dependent on the statin dose or cholesterol reduction level. Statins impact metalloproteinases, enzymes that aid in cell transformation [24]. They also block the production of dolichol, ubiquinol, farnesol, and geranylgeraniol, which are involved in angiogenesis, tumor cell growth, and differentiation [25, 26]. These mechanisms likely account for the lower cancer rates observed in heart transplant patients on statin therapy [27].

2.2 | Postoperative Statin Therapy in HT Patients

Statin therapy's impact on long-term survival, graft rejection, and inflammation in heart transplant patients has drawn significant clinical interest [16, 28]. A meta-analysis showed reduced all-cause mortality, fatal rejections, coronary vasculopathy, and terminal cancer in patients treated with statins [16]. Table 1 is a summary of findings regarding therapeutic effects of statins in patients with heart transplantation.

Studies suggest early initiation of high-dose statins may prevent vasculopathy better, though titrated doses can reduce adverse effects. In 2011, a pilot, randomized study by Potena and colleagues compared early maximal-dose fluvastatin (80 mg/day) with a titrated-dosing strategy (starting at 20 mg/day) in heart transplant patients. Both approaches were similarly effective in achieving LDL levels below 100 mg/dL at 12 months, but the maximal-dose group had faster LDL reduction and lower overall LDL levels. While the safety was comparable, the maximal-dose group showed potential advantages in preventing pathological changes in graft coronary arteries, with less intimal volume increase and a higher prevalence of negative remodeling [28]. A subgroup analysis from a study on the impact of everolimus on allograft vasculopathy found that patients on "high-dose" statins experienced a significantly smaller increase in maximal intimal thickness compared to those on "low-dose" statins [36]. Pravastatin and simvastatin have been linked to increased survival and reduced graft rejection [37], with simvastatin also reducing myocardial TNF-alpha expression, which affects inflammation and rejection [38]. However, atorvastatin can cause myopathy, particularly with cyclosporine [39]. Statins like pravastatin, fluvastatin, and low-dose simvastatin are safer with calcineurin inhibitors, especially cyclosporine, but their lipid-lowering effects are modest [40]. A study transitioning 30 heart transplant patients from cyclosporine to tacrolimus with atorvastatin showed improved cholesterol levels and was well-tolerated by most participants [32]. The FDA's 2011 regulations for simvastatin highlighted risks of muscle injury, liver damage, and rhabdomyolysis, especially in combination with cyclosporine, making tacrolimus the preferred calcineurin inhibitor in many regimens [12]. Tacrolimus is preferred over cyclosporine as a calcineurin inhibitor due to differences in their interactions with statins. Cyclosporine increases systemic exposure to statins, leading to a higher risk of complications. This occurs because cyclosporine inhibits cytochrome P450 3A4 (CYP3A4), which is involved in statin metabolism, and affects P-glycoprotein (PGP) and organic anion transporting polypeptide (OATP1B1), both of which transport statins [12, 41, 42]. In contrast, tacrolimus does not significantly affect these transporters or enhance statin exposure, thereby reducing the risk of statin-related side effects [12]. Studies show that while cyclosporine increases statin levels and the risk of adverse events, tacrolimus does not interfere with statin pharmacokinetics, making it a safer choice when combining statins with calcineurin inhibitors [41].

Data from the Heart Transplant Lipid Registry and other studies confirm statin therapy lowers the risk of death and rejection, independent of lipid levels [43]. Statins combined with angiotensin receptor blockers and steroid withdrawal also significantly improved survival [22, 34]. A long-term study with simvastatin showed increased survival and reduced coronary allograft vasculopathy [37]. Statin therapy has been associated with lower incidences of rhabdomyolysis, myositis, and transaminase elevation, while reducing low-density lipoprotein and cardiac allograft vasculopathy [35]. Data from the Heart Transplant Lipid Registry showed that statin therapy was the only factor independently associated with reduced death and fatal rejection [44]. Chronic renal failure (CRF) after heart transplantation, a common complication, increases mortality, but statin therapy has been linked to a lower risk of CRF, emphasizing the need for further studies [45].

3 | Immunomodulatory Effects of Statins

Statins, inhibitors of HMG-CoA reductase, are widely used as lipid-lowering agents but also possess significant immunomodulatory properties. These effects extend beyond cholesterol regulation and influence immune responses, particularly

TABLE 1 | The effect of statin therapy on heart transplantation outcomes.

References	Patient population	Statin therapy	Outcomes assessed	Primary results	Adverse effects	Conclusion
Ellimuttil et al.[8]	One hundred and forty-three adult heart transplant recipients (2013–2017)	Statin intensity (low/moderate/high)	CAV-free survival	No significant association between statin intensity and time to CAV	Not reported	High-intensity statin therapy may not provide additional long-term benefit
Golbus et al.[29]	Three hundred and forty-six adult heart transplant recipients (2006–2018)	Longitudinal statin intensity	Heart failure, myocardial infarction, revascularization, all-cause mortality, rejection	Low-intensity statins were used initially, but higher-intensity statins showed early post-HT benefits	No statin-related adverse events in high-intensity group	High-intensity statin therapy provided early benefits posttransplant but had no long-term adverse effects
Golbus et al.[30]	Three hundred and forty-seven adult heart transplant recipients (2006–2018)	Low vs. moderate/high-intensity statin	Coronary revascularization, heart failure, death, rejection, CAV	Mod/high-intensity statin therapy reduced rejection and CAV significantly (HR 0.47 for CAV)	Not reported	Mod/high-intensity statins significantly reduced CAV and rejection, independent of lipid levels
Heeney et al.[31]	Twenty-four adult heart transplant recipients (2005–2015)	High-intensity statin	Tolerability, LDL reduction, myalgias, hepatotoxicity, rhabdomyolysis	Statins reduced total cholesterol by 35 mg/dL ($p = 0.02$), LDL by 19 mg/dL ($p = 0.10$); no major adverse events	One case of myalgia (4%), no hepatotoxicity or rhabdomyolysis	High-intensity statins are safe and effective for refractory hyperlipidemia in HT patients on tacrolimus
Luo et al.[11]	One hundred and sixty-eight heart transplant patients at National Taiwan University Hospital (ages 6–74)	Statins (78 patients, 57.4%)	Cardiac allograft survival, freedom from cardiac death	Statin group had significantly better 5-year survival and freedom from cardiac death ($p < 0.01$).	Not explicitly stated	Statins improved cardiac allograft survival and freedom from cardiac death in heart transplant patients.
Frohlich et al.[27]	Two hundred and fifty-five heart transplant patients at University Hospital Zurich, survived first year posttransplant	Statins	Cancer risk, overall survival	Statin use associated with reduced cancer risk (HR 0.33) and improved cancer-free and overall survival ($p < 0.0001$)	Not explicitly stated	Statins significantly reduced cancer risk and improved survival after heart transplantation
Skalicka et al.[32]	Thirty heart transplant recipients with dyslipidemia, refractory to fluvastatin	Atorvastatin after conversion from fluvastatin	Lipid levels (cholesterol, LDL, triglycerides)	Statins (atorvastatin) significantly reduced cholesterol, LDL, and triglyceride levels ($p < 0.0001$)	No myotoxicity, liver toxicity, or new-onset diabetes observed	Conversion to atorvastatin was safe and effective in reducing lipid levels in heart transplant patients
Lubitz et al.[33]	Two hundred and eighteen heart	Statins	Chronic renal failure (CRF) risk, mortality	Statins associated with reduced CRF risk (HR	Not explicitly stated	Statins reduced CRF risk and were linked to

(Continues)

TABLE 1 | (Continued)

References	Patient population	Statin therapy	Outcomes assessed	Primary results	Adverse effects	Conclusion
	transplant recipients from 1986–2003			0.25, $p < 0.01$) and lower mortality in CRF patients (HR 8.5)		lower mortality in heart transplant recipients
Lubitz et al.[34]	Two hundred and twenty adult heart transplant recipients between 1986 and 2003, survived beyond 3 months	Statins, angiotensin receptor blockers	Long-term survival	Statin use associated with improved long-term survival (HR 0.53, 95% CI 0.40–0.70)	Not explicitly stated	Statins were linked to improved long-term survival in heart transplant recipients
Grigioni et al.[35]	One hundred and eighty-six heart transplant survivors treated with statins between 1985 and 2001	Pravastatin (48%), atorvastatin (37%), simvastatin (14%)	Cardiac allograft vasculopathy, mortality	Statin therapy significantly reduced the risk of cardiac allograft vasculopathy and mortality ($p < 0.001$)	Low rates of rhabdomyolysis (0.37%), myositis (0.74%), and transaminase elevation (0.37%) per year of treatment	Statins were effective in reducing cardiac allograft vasculopathy and mortality with manageable adverse effects

by inhibiting major histocompatibility complex class II (MHC-II) expression and thereby modulating T-cell activation. This occurs through the inhibition of the inducible promoter IV of the transactivator CIITA, especially in cells like endothelial cells and macrophages, without affecting constitutive MHC-II expression [46, 47]. Consequently, statins can suppress MHC-II-mediated immune responses, offering a new mechanism for immunosuppression in organ transplantation and other conditions [48].

In heart transplant patients, the immunomodulatory effects of statins have shown clinical benefits, such as reduced inflammation and graft rejection. Statins decrease TNF-alpha levels in myocardial tissue and lower circulating monocyte levels, thereby reducing allograft dysfunction and improving survival rates [38]. The immunosuppressive potential of statins also manifests in their ability to alter the monocyte population and regulate adhesion molecules, influencing immune responses posttransplantation [49].

Beyond transplantation, studies suggest that statins could benefit autoimmune diseases. For instance, statin therapy in systemic lupus erythematosus (SLE) patients resulted in improved endothelial function and increased flow-mediated dilation (FMD), with benefits observed both in patients with and without conventional cardiovascular risk factors. Additionally, atorvastatin showed a significant increase in resting brachial artery diameter compared to control groups, indicating vascular improvements [50]. These vascular effects align with the broader anti-inflammatory and immunomodulatory actions of statins, which have been associated with reduced disease activity in rheumatoid arthritis, improvements in proteinuria in vasculitis, and better vascular outcomes in systemic sclerosis [51].

Clinical trials have further demonstrated differential effects of various statins on immune markers. For example, atorvastatin led to downregulation of MHC-II antigens and CD38 activation on T cells, while simvastatin had opposite effects. Interestingly, simvastatin inhibited superantigen-mediated T-cell activation, which may contribute to its protective role in infections like staphylococcal bacteremia [52]. Statin therapy, particularly high-dose regimens, has also been shown to increase regulatory T cell (Treg) frequency and elevate anti-inflammatory cytokines like IL-10 and TGF-β, while reducing pro-inflammatory cytokines like IFN-gamma [53].

These findings underscore the potential for statins to serve as adjunct immunosuppressive therapy in both transplantation and autoimmune diseases. They not only help prevent graft rejection but may also reduce cancer risk in transplant recipients and benefit patients with chronic inflammatory conditions [27, 54]. The pleiotropic effects of statins, including their anti-inflammatory and immunosuppressive actions, make them promising candidates for broader therapeutic applications in immune-mediated diseases [51]. However, further prospective studies are needed to fully elucidate their long-term benefits and mechanisms in these contexts.

4 | Intensity of Statin Therapy in HT

The intensity of statin therapy, characterized by reduced low-density lipoprotein cholesterol (LDL-C), is crucial in posttransplant

care [55]. Intense statin therapy has been associated with improved outcomes in the general population, but its effects on heart transplantation patients have not been as thoroughly studied [56]. A growing body of evidence suggests that high-intensity statin therapy may confer superior benefits to moderate-intensity regimens, particularly in the early period following transplantation. In the general population, high-intensity statins are well-established in reducing the risk of cardiovascular events [16]. Translating this benefit to heart transplant patients requires understanding this group's unique safety and efficacy considerations. For instance, heart transplant recipients are on complex medication regimens, including immunosuppressive therapy, which could interact with statin metabolization and amplify potential side effects [57]. Comparisons of moderate-intensity and high-intensity statins generally demonstrate a favorable profile for intense statin therapy. Nevertheless, the existing literature on the use of high-intensity statins in heart transplant recipients is limited. Studies such as those by Heeney et al. [31] have begun to fill this gap by demonstrating the feasibility of administering high-intensity statins in heart transplant recipients receiving tacrolimus. The concern with high-intensity statins revolves around potential adverse events, such as myopathy and liver enzyme elevations, which could be exacerbated by concomitant medications used in immunosuppression.

Despite these concerns, evidence points toward a positive impact of high-intensity statins on cholesterol levels without a concomitant increase in serious adverse events, offering a promising outlook on their use posttransplantation. It is critical, however, to maintain vigilant monitoring for side effects, especially considering the potential for drug–drug interactions in this patient population. In heart transplant recipients, the reduction in LDL-C levels could translate to decreased rates of CAV, delay the progression of existing CAV, or possibly improve long-term graft survival. However, this correlation requires a more comprehensive investigation. Moreover, studies have indicated that factors such as the timing of statin initiation, the dose intensity, and the specific statin used can influence the time to adverse cardiovascular events following transplantation [58]. In support of this, some retrospective analyzes have suggested the benefits of higher statin intensity early after transplantation, emphasizing early and potent statin therapy might safeguard against the rapid development of CAV in the first few years posttransplant, a period when the risk is exceptionally high [28, 59]. Tacrolimus is a cornerstone immunosuppressant used in heart transplant recipients and is known for its effectiveness in preventing graft rejection. However, this medication can complicate the use of statins due to its impact on cytochrome P450 enzymes, which are involved in statin metabolism. The interaction between high-intensity statins and tacrolimus can lead to increased statin blood levels and a heightened risk for statin-related side effects. The safety and efficacy of high-intensity statins in this context have been evaluated in several studies, including Heeney et al. [31], which reported no significant increase in adverse events with high-intensity statins in patients receiving tacrolimus. There is a critical need for further research, particularly large-scale, randomized controlled trials, to validate the safety and efficacy of this approach. Addressing the gap in knowledge about statin intensity and its implications for CAV and other transplant-related outcomes is of utmost importance. Research should also explore patient-specific factors, such as genetic polymorphisms, that may affect statin metabolism and response in the transplant setting [29, 30].

5 | Preoperative Statin Therapy in HT Patients

Preoperative statin therapy has received significant attention in the field of cardiovascular medicine, especially regarding its impact on heart transplant recipients. Statins possess anti-inflammatory and immunomodulatory properties that can reduce primary graft dysfunction and mortality in heart transplant recipients (Figure 1). These are critical factors for transplant surgeries' short- and long-term success. Optimizing pretransplant care, including the potential benefits of statin therapy, cannot be underestimated as clinicians aim to enhance patient outcomes. Understanding the influence of preoperative statin use on heart transplantation outcomes is crucial, as it could affect preoperative protocols and long-term patient care strategies [4]. Table 2 is a summary of studies exploring preoperative benefits of statin therapy in heart transplantation patients.

Remnant cholesterol (RC) is the cholesterol in triglyceride-rich lipoproteins linked to atherosclerosis and CAV. High RC levels are a risk factor for cardiac events. Despite statin use, managing RC remains inconsistent, as statins may not effectively lower all lipid fractions [6, 62]. A study of 184 recipients found elevated RC levels were associated with CAV onset, and statin therapy did not consistently reduce RC levels [6]. This raises questions about statins' efficacy in managing RC and suggests the need for alternative treatments. While statins show potential in pre-transplant care, their effects vary, with some studies showing survival benefits and others minimal posttransplant impact. Limitations of the study include its retrospective design and potential selection bias. Prospective, randomized studies are needed to confirm these findings and refine statin use in heart transplant care.

6 | Statin Therapy in Pediatric HT Patients

Pediatric heart transplantation is a life-saving procedure for children with end-stage heart disease. While the surgery can dramatically improve survival and quality of life, it also introduces a new set of challenges, one of which is the prevention of CAV. Despite the positive results observed in adults, the impact of statin therapy on the pediatric heart transplant population remains uncertain and requires further investigation [7]. The use of statin therapy for pediatric heart transplant recipients has been inconsistent. This variability is partly due to the nuances of the pediatric population, such as differences in lipid metabolism compared to adults and the lack of clear guidelines specifically tailored for children [5]. Table 3 presents a summary of findings reported by studies investigating the effects of statin therapy on pediatric patients undergoing heart transplantation.

Pravastatin may help reduce the risk of coronary artery vasculopathy (CAV) in pediatric heart transplant recipients. A review showed that pravastatin significantly lowers CAV risk in these

TABLE 2 | List of studies investigating therapeutic effects of preoperative statin therapy in HT patients.

References	Population (*N*)	Statin group (%)	Control group (%)	Primary outcomes	Secondary outcomes	Conclusion
Baba et al.[4]	Thirty-eight heart transplant recipients	Atorvastatin group (not specified)	—	Preoperative statin therapy reduces 2-month postoperative complications (OR: 0.06, $p = 0.0128$)	Atorvastatin associated with lower CRP	Chronic statin use protective against postoperative complications
Peled et al.[60]	Two hundred and seventy-five HT recipients	167 (61%)	108 (39%)	Reduced risk of primary graft dysfunction (PGD) (21% vs. 60%, $p < 0.001$), in-hospital mortality (HR: 0.33, $p = 0.001$)	Reduced 1-year and 5-year mortality (HR: 0.33 and 0.39)	Statin use reduces PGD, in-hospital mortality, and long-term mortality
Krishnan et al.[61]	Two hundred and fifty-nine HT recipients	133 (51%)	126 (49%)	No significant difference in 30-day mortality (9% vs. 7%, $p = 0.58$)	No difference in posttransplant AF incidence (16% vs. 19%, $p = 0.59$)	Statin therapy did not impact short-term mortality or AF incidence post-HT

TABLE 3 | Summary of studies on the therapeutic effects of statins in pediatric heart transplantation patients, including study design, patient population, statin type, outcomes assessed, results, and safety.

Study	Patient population	Statin type	Statin use	Outcomes assessed	Results
Townsend et al.[5]	Three thousand four hundred and eighty-five pediatric HTRs (< 17 years)	General statin	Consecutive (17%), intermediate (19%), none (65%)	CAV incidence, graft loss	No association between statin use and graft survival or CAV incidence in both unmatched and matched analyzes
Greenway et al.[63]	Nine hundred and sixty-four pediatric HTRs (5–18 years)	General statin	Early statin use in 30%–35% ≥ 10 years	Rejection, PTLD, CAV, survival	Statin use was associated with earlier rejection (HR 1.42), no benefit in PTLD, CAV, or survival
Mahle et al.[64]	One hundred and twenty-nine pediatric HTRs	Pravastatin	Routine pravastatin therapy	CAV incidence, cholesterol levels	Pravastatin use reduced CAV incidence ($p = 0.03$) and total cholesterol (162 ± 29 to 137 ± 20 mg/dL, $p = 0.01$)
Seiplet et al.[65]	Fifty pediatric HTRs	Pravastatin	40% treated with pravastatin	Hyperlipidemia, cholesterol levels, safety	Significant reduction in TC (236 ± 51 to 174 ± 33 mg/dL) and LDL (151 ± 32 to 99 ± 21 mg/dL), $p < 0.0001$
Chin et al.[66]	Thirty-eight pediatric HTRs	Atorvastatin	Average dosage of 0.2 ± 0.1 mg/kg/day	Lipid profiles, safety	Twenty percent reduction in total cholesterol, 18% reduction in triglycerides, and 26% reduction in LDL

patients [64]. Besides lowering cholesterol, pravastatin might protect the coronary arteries, which is important for children. The drug's effect on total cholesterol in kids could also support heart health and graft longevity. However, more prospective studies are needed to confirm these benefits and understand how pravastatin works in children. The link between statin uses and CAV in pediatric heart transplant patients is not fully clear. While statins have shown varied effects on CAV in adults, their impact on children remains uncertain [5]. This uncertainty raises questions about whether adult statin protocols are suitable for children or if adjustments are needed. It is crucial to examine factors like genetic predispositions, pretransplant lipid levels, and age to tailor statin therapy for young patients [5]. Despite potential benefits, statin therapy has not shown clear improvements in rejection rates or survival for pediatric heart transplant recipients [63]. This highlights the complexity of post-transplant care and the need for comprehensive approaches. A prospective trial is needed to better understand statins' role and provide clearer guidance for pediatric heart transplant care.

7 | Statin Therapy in Heart Donors

Despite advancements in surgical techniques and postoperative care, myocardial injury during the perioperative period can significantly affect the short- and long-term outcomes of heart transplantation [67]. Reducing myocardial injury is thus a critical component of posttransplant care. One potential method for reducing myocardial injury is the pretreatment of organ donors with simvastatin [35]. Simvastatin is a lipid-lowering agent that belongs to the class of drugs known as statins, which have been noted for their ability to manage cholesterol levels and their pleiotropic effects that may protect against myocardial ischemic damage [37]. This treatment strategy has attracted attention due to its potential to improve transplant outcomes. The pretreatment of organ donors with simvastatin has been associated with a reduction in biomarkers of myocardial injury posttransplant. Additionally, it has been indicated that simultaneous treatment with tacrolimus may not significantly impact the baseline immunosuppressive effects in these patients [68]. A decrease in troponin levels and other markers following transplantation indicates less injury to the cardiac tissue, which can be critical for the survival of the graft and the recipient. Moreover, studies have shown that simvastatin treatment may lead to a decrease in inflammatory cytokines and growth factors that are involved in the body's rejection response. Another notable benefit of donor simvastatin treatment is the reduced need for rejection treatments that can lead to hemodynamic compromise. By modulating the immune response and potentially reducing the severity of cellular rejection, simvastatin may minimize the need for aggressive immunosuppressive therapies that can have serious side effects and impact patient morbidity and mortality. Concerns about the safety of administering medications to organ donors are paramount, given the potential implications for multiple recipients. However, evidence suggests that simvastatin treatment does not adversely affect noncardiac transplant function, making it a potentially safe and effective adjunct to the standard care of organ donors. The absence of adverse effects in recipients of noncardiac solid organ transplants from simvastatin-treated donors underscores the drug's general safety profile. Before the widespread adoption of this therapy, the potential risks and benefits must be carefully weighed in each case. However, given the documented safety and possible benefits, donor simvastatin treatment represents a promising strategy for improving heart transplant outcomes.

8 | Conclusion

Postoperative statin therapy improves survival and graft function in heart transplant recipients, likely due to its anti-inflammatory and immunomodulatory effects, independent of lipid control. Early statin use should become standard practice, with future research focusing on optimizing protocols for dosage and timing. Further investigation is needed to clarify the precise mechanisms behind these benefits, but routine statin therapy holds significant promise for enhancing patient outcomes and quality of life.

Author Contributions

Nima Ghavamikia: conceptualization, investigation, writing–original draft, writing–review and editing. **Hossein Saffarfar:** conceptualization, investigation, writing–original draft, writing–review and editing. **Babak Seifdavati:** writing–original draft. **Mohaddeseh Jamali:** writing–original draft. **Shadi Izadidehkordi:** writing–original draft. **Seyyed Abbas Pakmehr:** writing–original draft. **Mohammadreza Aghabali:** writing–original draft. **Negar Jahani:** writing–original draft. **Payam Ali-Khiavi:** writing–original draft. **Abtin Soleimanian:** writing–original draft. **Ahmed Hjazi:** writing–original draft. **Reza Shahhoseini:** conceptualization, writing–original draft, writing–review and editing and supervision. **Milad Vahedinezhad:** conceptualization, writing–original draft, writing–review and editing and supervision.

Acknowledgments

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no data sets were generated or analyzed during the current study.

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