Impact of Statin Use After Heart Transplantation
A Meta-Analysis

Ajay Vallakati, MD, MPH; Siddharth Reddy, MD; Mark E. Dunlap, MD; David O. Taylor, MD

Background—Although various studies revealed the beneficial effects of statins in post–cardiac transplant patients, these were relatively small and low-powered studies. We performed a meta-analysis of published studies to evaluate the role of statins in post–cardiac transplant patients, specifically examining the effects on hemodynamically significant/fatal graft rejection, coronary vasculopathy, terminal cancer, and overall survival.

Methods and Results—We searched PubMed, Cochrane CENTRAL, and Web of Science databases using the search terms “cardiac transplant” or “heart transplant,” and “statin” for a literature search. A random-effects model with Mantel–Haenszel method was used to pool the data. We identified 10 studies, 4 randomized controlled trials, and 6 nonrandomized studies, which compared outcomes in heart transplant recipients undergoing statin therapy to statin-naïve patients. A pooled analysis of 9 studies reporting mortality revealed that the use of statins was associated with significant reduction in all-cause mortality (odds ratio, 0.26; 95% confidence interval, 0.20–0.35; \( P<0.0001 \)). Statins also decreased the odds of hemodynamically significant/fatal rejection (odds ratio, 0.37; 95% confidence interval, 0.21–0.65; \( P=0.0005 \)), incidence of coronary vasculopathy (odds ratio, 0.33; 95% confidence interval, 0.16–0.68; \( P=0.003 \)), and terminal cancer (odds ratio, 0.30; 95% confidence interval, 0.15–0.63; \( P=0.002 \)).

Conclusions—The evidence from a pooled analysis suggests that statins improve survival in heart transplant recipients. Statins may prevent fatal rejection episodes, decrease terminal cancer risk, and reduce the incidence of coronary vasculopathy. Additional prospective studies are needed to further investigate and explain this association. (Circ Heart Fail. 2016;9:e003265. DOI: 10.1161/CIRCHEARTFAILURE.116.003265.)

Key Words: allograft ■ graft rejection ■ hydroxymethylglutaryl-CoA reductase inhibitors

Heart transplantation is a life-saving treatment option for carefully selected end-stage heart failure patients.1,2 Post-transplant care consists primarily of immunosuppression and treatment of hypertension. Statin therapy immediately after cardiac transplant has become an integral part of post–cardiac transplant care.3 The molecular mechanisms responsible for the beneficial effects of statins extend beyond cholesterol-lowering action. Pleiotropic properties of statins include promotion of apoptosis, inhibition of angiogenesis, downregulation of circulating cytokines, and reduction of circulating monocytes.1,4–7 These pleiotropic properties may contribute to reduction in the incidence of cardiac allograft dysfunction in heart transplant recipients.2,8–11 Terminal malignancy is an important cause of death late after heart transplantation.9 Statins, through inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase enzyme, decrease the production of farnesyl pyrophosphate, geranylgeranyl pyrophosphate, and other molecules involved in tumor cell proliferation, angiogenesis, and cell differentiation.12,13 This molecular mechanism suggests that statins might decrease the incidence of cancer in heart transplant recipients.9 However, statins also enhance the production of regulatory T cells, which impairs antitumor immune response and consequently promote the development of cancer.14 The effect of statin therapy on the incidence of cancer is not entirely clear.

See Clinical Perspective

Various observational and randomized controlled studies demonstrated the beneficial effects of statins in post–cardiac transplant patients.1,4,8,9 However, these were relatively small and low powered. We performed a meta-analysis of published studies to evaluate the role of statins in heart transplant recipients, specifically examining the effects of these agents on hemodynamic significant or fatal graft rejection, coronary vasculopathy, terminal cancer, and overall survival.

Methods

Study Design

Meta-analysis was conducted as per the PRISMA statement (Preferred Reporting Items for Systematic Reviews and
A checklist of each of the PRISMA criteria and how they were handled in our study is contained in Table I in the Data Supplement. The methodological quality of the studies was assessed using the Downs and Black checklist.16

Data Sources
We searched PubMed, Cochran CENTRAL, and Web of Science databases from their inception to June 1, 2015. We used the following terms “cardiac transplant” or “heart transplant” and “statin” for a literature search. Reference lists from relevant articles were reviewed to identify additional studies. Studies in languages other than English were not included.

Study Selection
Clinical trials were included in the meta-analysis if the following criteria were met: (1) studies that reported any of the following clinical outcomes in both treatment arms: mortality, hemodynamically significant or fatal rejection, coronary vasculopathy, terminal malignancy, and myopathy; (2) minimum follow-up period of at least 1 year; and (3) studies involving predominantly adult subjects (age >18 years). Case reports, editorials, case series, and review articles were not included. Studies with <5 patients in either treatment arm were not included.

Data Extraction
The titles and abstracts were screened for relevance by 2 independent reviewers (A.V. and S.R.). Differences between reviewers were discussed until consensus was reached. The manuscripts of selected titles/abstracts were assessed for inclusion, and the authors were contacted if further information was required. Using the selection criteria enlisted above, the 2 reviewers independently identified the papers to be included and excluded, and data from the included papers were extracted using predefined extraction flow sheets. Any differences in data extraction were discussed until agreement between both reviewers was reached. If a study compared different statins with statin-naive cohort, the data of all statins was combined into a single group for pooled analysis.

Data Analysis
Statistical analysis was performed with Review Manager (RevMan) software, version 5.2 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2012). A random-effects model with Mantel–Haenszel method was used to calculate pooled odds ratio and 95% confidence interval (CI). We assessed 5 outcomes: (1) mortality, (2) hemodynamically significant or fatal rejection, (3) coronary vasculopathy, (4) terminal malignancy, and (5) myopathy. Transplant vasculopathy, progression of coronary artery disease on intravascular ultrasound or death attributed to coronary artery disease, was defined as coronary vasculopathy. Death secondary to malignancy was designated as terminal cancer. Elevation of creatine phosphokinase above the upper limit of normal or rhabdomyolysis was defined as myopathy. Heterogeneity between studies was assessed using Cochran Q test and I² statistic, which

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**Figure 1.** PRISMA flow sheet (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).
denotes the percentage of total variation across studies that are a result of heterogeneity rather than chance. Heterogeneity was considered significant if the P value for the heterogeneity test was <0.05. Publication bias was assessed by visual inspection of funnel plots and Egger regression test. The influence of individual studies was examined by removing each study at a time to assess the degree to which the meta-analysis estimate depended on a particular study (exclusion sensitivity analysis).

Results
Study Outlines and Characteristics
We identified 10 studies1,2,4,8–11,17–20 (Figure 1), 4 randomized controlled trials and 6 nonrandomized studies, which...
compared outcomes in heart transplant recipients undergoing statin therapy to the outcomes in statin-naive patients. Ten-year follow-up of landmark study by Kobashigawa et al was published in 2005, and the data from the first study was included in meta-analysis. The pooled analysis included a total of 2295 heart transplant patients, of which 1635 received statin therapy and 660 did not receive statins. Details of the studies are reported in Table. The duration of follow-up in the included studies ranged from 12 months to 12 years. The quality of the included studies evaluated by the Downs and Black assessment method is presented in Table II in the Data Supplement.

**Total Mortality**

The pooled analysis of 9 studies reporting mortality in heart transplant recipients revealed that the use of statins was associated with significant reduction in all-cause mortality (odds ratio [OR], 0.26; 95% CI, 0.20–0.35; P<0.0001; Figure 2). There was no significant heterogeneity across the studies (P=0.84; I²=0%). There was no appreciable publication bias on inspection of the funnel plot (Figure I in the Data Supplement) or with the regression test of Egger (P=0.39). Sensitivity analysis did not reveal any significant change in effect size with the exclusion of any particular study. We further explored the robustness of our findings by changing the meta-analysis method from a random- to fixed-effects model. There was no change in summary effect size with fixed-effects model (OR, 0.26; 95% CI, 0.20–0.35; P<0.0001). Additionally, there was no change in significant findings resulting from a pooled analysis of randomized controlled trials (OR, 0.29; 95% CI, 0.10–0.82; P=0.02) versus observational studies (OR, 0.26; 95% CI, 0.20–0.35; P<0.0001).

**Hemodynamically Significant/Fatal Rejection**

Eight studies reported the effect of statins on hemodynamically significant/fatal rejection in heart transplant recipients. No significant heterogeneity was noted across the studies (P=0.27; I²=20%). Pooled analysis revealed that statins decreased the odds of hemodynamically significant/fatal rejection (OR, 0.37; 95% CI, 0.21–0.65; P=0.0005; Figure 3). No publication bias was detected by visual inspection of funnel plot (Figure II in the Data Supplement) or Egger regression test (P=0.54). Exclusion sensitivity analysis or switching to fixed-effects model did not change the summary effects size.

**Coronary Vasculopathy**

Four studies reported the impact of statins on coronary vasculopathy in heart transplant recipients. The average duration of follow-up in these 4 studies was 2.75 years. There was no significant heterogeneity across the studies (P=0.97; I²=20%). The use of statins resulted in reduction of the incidence of coronary vasculopathy (OR, 0.33; 95% CI, 0.16–0.68; P=0.003; Figure 4). There was no appreciable publication bias on visual inspection of the funnel plot (Figure III in the Data Supplement) or with the Egger regression test (P=0.45). There was no change in summary effect size with omitting 1 study at a time or fixed-effects model (OR, 0.32; 95% CI, 0.16–0.66; P=0.002).
Terminal Cancer

Four studies reported terminal cancer outcomes in heart transplant recipients undergoing statin therapy and statin-naive patients. The mean duration of follow-up in these 4 trials was 8.9 years. No heterogeneity was noted across the studies (P=0.68, I²=0%). Statins decreased the incidence of terminal cancer (OR, 0.30; 95% CI, 0.15–0.63; P=0.002; Figure 5). No publication bias was detected by visual inspection of funnel plot (Figure IV in the Data Supplement) or Egger regression test (P=0.84). Sensitivity analysis or switching to fixed-effects model did not change the summary effects size.

Myopathy

The pooled analysis of 5 studies reporting myopathy in heart transplant recipients revealed that the use of statins was not associated with increased risk of myopathy (OR, 1.70; 95% CI, 0.68–4.24; P=0.25; Figure 6). There was no significant heterogeneity across the studies (P=0.38; I²=0%). Publication bias could not be assessed as there were no events reported in the either arm in 3 studies. There was no change in summary effect size with omitting 1 study at a time or fixed-effects model. The outcomes from studies by Fröhlich et al (5/151) and Grigioni et al (6/186) were not included in the pooled analysis because these 2 studies reported the rates of myopathy only in heart transplant recipients undergoing statin therapy.

Discussion

There are 2 main findings of this study. First, statins provide substantial survival benefit and reduce hemodynamically significant rejection episodes in heart transplant recipients. Second, the use of statins is associated with lower incidence of coronary vasculopathy and terminal cancer.

To our knowledge, this is the largest meta-analysis involving a total of 2295 patients and evaluating the impact of statins in heart transplant recipients. A previous meta-analysis reported significant survival benefit with statin therapy in heart transplant recipients (relative risk 0.31; 95% CI, 0.13–0.7; P=0.006). The sample size of this pooled analysis of 3 studies involving only 246 patients was relatively small. Furthermore, only 2 (mortality and rejection) outcomes were studied in this pooled analysis.

Current guidelines strongly recommend (Class I; Level of Evidence A) initiation of statins within 1 to 2 days of heart transplantation, irrespective of lipid profile. Statins may improve survival in heart transplant recipients because of reductions of cholesterol levels. In porcine heart transplant models, diet-induced hypercholesterolemia resulted in accelerated allograft vessel intimal hyperplasia and increased lipid deposition. In heart transplant patients, statins not only reduce cholesterol levels but also decrease the incidence of graft atherosclerosis. Alternatively, cholesterol-independent effects of statins also play a major role in inhibiting allograft coronary artery vasculopathy, which occurs via mechanisms other than atherosclerosis. In murine heart transplant models, statins have been shown to promote atherosclerotic plaque stabilization. Statins downregulate nitric oxide synthase II gene expression that influences endothelial nitric oxide production. In heart transplant recipients, statin also improve coronary endothelial function. Through inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, statins decrease the synthesis of mevalonate and other prenylated proteins, farnesyl pyrophosphate and geranyl pyrophosphate, which mediate intracellular signal transduction. This leads to inhibition of protein biosynthesis, which in turn attenuates the proliferation of vascular smooth muscle tissue. Statins also downregulate the expression of growth factor genes, which are important for production of smooth muscle cells.

Our study showed that statins decreased the incidence of coronary vasculopathy and hemodynamically significant rejection episodes by 67% and 63%, respectively. Different hypotheses have been proposed to explain the potential immunomodulatory role of statins. Statins promote suppression of natural killer cell activity. Statins dramatically reduce lipoprotein levels, which results in higher concentration of unbound fraction of immunosuppressive drug, cyclosporine. This, in turn, augments the immunosuppressive actions of cyclosporine, which include attenuation of T-cell activity, reduction of monocyte chemotaxis, and downregulation of major histocompatibility complex-II gene expression.
Our study revealed that the use of statins in heart transplant recipients resulted in 70% reduction in terminal cancer. This is consistent with findings by Fröhlich et al showing that statin therapy is associated with 67% decrease in incidence of cancer. This benefit was not related to the dose of statin or intensity of cholesterol reduction. Statins influence metalloproteinases, enzymes that promote cell transformation. Additionally, statins inhibit the production of dolichol, ubiquinol, farnesol and geranylgeraniol, all of which are involved in angiogenesis, tumor cell proliferation, and differentiation. These molecular mechanisms probably explain the reduction in incidence of cancer in heart transplant patients on statin therapy.

Limitations
Our pooled analysis has several limitations. Because of the small sample size of relevant studies, we included the data from randomized controlled trials and nonrandomized studies. Inclusion of observational studies is associated with a potential bias, as the distribution of unmeasured confounding factors may not be similar between 2 comparison groups. Systematic reviews may have publication bias because of probability of publication of only positive studies or omission of pertinent studies from analysis. However, comprehensive literature search of multiple databases was performed, and publication bias was evaluated by Begg test and Egger regression test. The role of individual studies was examined by omitting 1 study at a time to evaluate the extent to which pooled analysis effect size depend on any single study (exclusion sensitivity analysis). Of note, the randomized controlled trials included in the pooled analysis were published more than 10 years ago, and medical care has changed during this time period. It is possible that the magnitude of benefit of statin therapy in the present era may not be exactly similar to that observed in the pooled analysis. However, care for these patients remains similar enough to conclude that benefit likely persists in the present day. Additionally, the majority of patients used in the clinical trials were those considered as moderate- or low-intensity statins. It is conceivable that the use of high-intensity statins might provide additional benefit.

Conclusions
Evidence from the pooled analysis suggests that statins improve survival in heart transplant recipients. Additionally, statins may prevent fatal rejection episodes, decrease terminal cancer risk, and reduce the incidence of coronary vasculopathy. Further prospective studies are needed to further investigate and explain this association.

Disclosures
None.

References

**CLINICAL PERSPECTIVE**

Current guidelines strongly recommend initiation of statins within 1 to 2 days of heart transplantation irrespective of lipid profile. Various observational and randomized controlled studies demonstrated the beneficial effects of statins in post–cardiac transplant patients. However, these were relatively small and low-powered. The authors performed a meta-analysis of published studies to evaluate the role of statins in heart transplant recipients, specifically examining the effects of these agents on hemodynamic significant or fatal graft rejection, coronary vasculopathy, terminal cancer, and overall survival. A pooled analysis of 9 studies revealed that the statins decreased the odds of coronary vasculopathy, hemodynamically significant rejection episodes, and terminal cancer by 67%, 63%, and 70%, respectively. Statins also reduced the total mortality by 73%. The molecular mechanisms responsible for the favorable effects of statins probably extend beyond cholesterol-lowering action. The magnitude of the benefits demonstrated by this pooled analysis is substantial, and the consistency of this favorable effect across several outcome measures is noteworthy. The findings support the current clinical practice of initiation of statins immediately after heart transplantation. The randomized controlled trials included in the pooled analysis were published more than 10 years ago, and medical care has changed during this time period. It is possible that the magnitude of benefit of statin therapy in the present era may not be exactly similar to that observed in the pooled analysis. However, care for these patients remains similar enough to conclude that benefit likely persists in the present day.
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SUPPLEMENTAL TABLE 1: PRISMA CHECKLIST

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<th>Item No</th>
<th>Checklist item</th>
<th>Reported on Page No</th>
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<td>TITLE</td>
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<tr>
<td>Title</td>
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<tr>
<td>ABSTRACT</td>
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<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
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<tr>
<td>INTRODUCTION</td>
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<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>3</td>
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<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
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<tr>
<td>METHODS</td>
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<td>Protocol and registration</td>
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<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
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<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
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</tr>
<tr>
<td>Information sources</td>
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<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
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<tr>
<td>Search</td>
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<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
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<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td>4</td>
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<td>Table 1: Items for Reporting on Meta-analyses (TAM) Checklist</td>
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<tr>
<td><strong>Data collection process</strong></td>
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<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
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<tr>
<td><strong>Data items</strong></td>
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<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
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<tr>
<td><strong>Risk of bias in individual studies</strong></td>
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<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
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<td><strong>Summary measures</strong></td>
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<tr>
<td><strong>Synthesis of results</strong></td>
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<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.</td>
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## SUPPLEMENTAL TABLE 2: Downs and Black quality scale

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<th>Overall score</th>
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SUPPLEMENTAL FIGURES

SUPPLEMENTAL FIGURE 1: Funnel plot of risk of total mortality
SUPPLEMENTAL FIGURE 2: Funnel plot of risk of hemodynamically significant/ fatal rejections
SUPPLEMENTAL FIGURE 3: Funnel plot of risk of coronary vasculopathy
SUPPLEMENTAL FIGURE 4: Funnel plot of risk of terminal cancer
SUPPLEMENTAL REFERENCES:


