Statins and the Risk of Cancer after Heart Transplantation

Running title: Fröhlich et al.; Statins and cancer after heart transplantation

Georg Marcus Fröhlich, MD1; Kaspar Rufibach, PhD2; Frank Enseleit, MD1; Mathias Wolfrum, MD1; Michelle von Babo, BSc1; Michelle Frank, MD1; Reto Berli, MD1; Mathias Hermann, MD1; Johannes Holzmeister, MD1; Georg Noll, MD1; Thomas F. Lüscher, MD1; Frank Ruschitzka, MD1

1Cardiovascular Center, Cardiology, University Hospital Zurich; 2Division of Biostatistics, Institute for Social and Preventive Medicine, University of Zurich, Zurich, Switzerland

Correspondence:
Georg Marcus Fröhlich, MD
Cardiovascular Center Cardiology
Heart Failure/Transplantation Clinic
University Hospital Zurich
Rämistrasse 100
CH-8091 Zurich, Switzerland
Tel: +41 44 255 1111
Fax: +41 44 255 4401
E-mail: GeorgMarcus.Froehlich@usz.ch

Journal Subject Codes: [11] Other heart failure; [112] Lipids; [27] Other Treatment
Abstract:

**Background** - While newer immunosuppressive agents, like mTOR inhibitors, have lowered the occurrence of malignancies after transplantation, cancer is still the leading cause of death late after heart transplantation. Statins may impact on clinical outcomes beyond their lipid-lowering effects. The aim of the present study was to delineate whether statin therapy impacts on cancer risk and total mortality after heart transplantation.

**Methods and Results** - 255 patients who underwent heart transplantation at the University Hospital Zurich between 1985 and 2007 and survived the first year were included. The primary outcome measure was the occurrence of any malignancy, the secondary endpoint overall survival. During follow-up, a malignancy was diagnosed in 108 patients (42%). The cumulative incidence of tumors 8 years after transplantation was reduced in patients receiving a statin (34% vs. 13%, 95% CI 0.25-0.43 vs. 0.07-0.18, p<0.003). Statin use was associated with improved cancer-free and overall survival (both p<0.0001). A Cox-regression model analyzing the time to tumor formation with or without statin therapy, adjusted for age, male gender, type of cardiomyopathy and immunosuppressive therapy (including switch to mTOR inhibitors or tacrolimus) demonstrates a superior survival in the statin group. Statins reduced the hazard of occurrence of any malignancy by 67% (HR 0.33, 95% CI 0.21-0.51, p<0.0001).

**Conclusions** - Although it is not possible to adjust for all potential confounders due to the very long follow-up period, this registry suggests, that statin use is associated with improved cancer-free and overall survival after cardiac transplantation. These data will have to be confirmed in a prospective trial.

**Key words:** cholesterol; heart transplantation; statins; transplantation; malignancy
Introduction

Newer immunosuppressive regimens like mTOR inhibitors or tacrolimus have not only steadily reduced the incidence of acute rejection, but also of post-transplant malignancy\textsuperscript{1-3}. However, malignancy still is an important cause of long-term mortality in transplant recipients\textsuperscript{4}. The incidence of malignancy has been estimated at 20\% after 10 years of chronic immunosuppression\textsuperscript{5}, and the relative risk may increase 100-fold for specific cancers in comparison to the general population\textsuperscript{6}. Heart transplant patients are at particular risk of developing posttransplant malignancies that is increased up to four-fold compared to renal transplant recipients.\textsuperscript{6-11} Indeed, cancer is now a leading cause of death late after heart transplantation\textsuperscript{12}.

Importantly, HMG-CoA-reductase-inhibitors (statins) initiated after heart transplantation exert beneficial effects on the incidence of cardiac allograft rejection, transplant vasculopathy and survival rates.\textsuperscript{13,14} Intriguingly, in non-transplant patients, statin intake is associated with a decreased risk of malignancies such as lymphoma\textsuperscript{15}, breast\textsuperscript{16}, ovarian\textsuperscript{17}, colorectal\textsuperscript{18}, lung and pancreatic cancer\textsuperscript{19,20}. While elevated plasma cholesterol levels have been associated with the development of skin, colon or prostate cancer\textsuperscript{21-24}, it is matter of a still ongoing debate whether the potential benefit of statins in cancer may be explained by its cholesterol-lowering or potential pleiotropic, particularly immunomodulatory effects.\textsuperscript{25,26}

To the best of our knowledge, up to date no data exist on the impact of statin use or cholesterol levels on cancer risk in immunosuppressed patients. Hence, the aim of this study was to evaluate the influence of statin therapy and cholesterol levels beyond the role of immunosuppression on the development of malignancies and total mortality.
Methods

Study design and patient sample

We evaluated all patients 18 years of age or older, who underwent heart transplantation at the University Hospital Zurich between 1985 and 2007 and survived the first year after transplantation. Statin therapy was initiated usually three to twelve months after transplantation in patients transplanted after year 1995. Statin therapy was recorded on a daily basis from heart transplantation until the occurrence of malignancy or the end of the follow-up period. Follow-up was performed until December 2010.

All patients who received a statin were assigned to the statin group. Further, detailed information of immunosuppressive therapy including switch to mTOR inhibitors or tacrolimus, lipid status as well as episodes of rejections were recorded. Rejection was defined according to International Society for Heart and Lung Transplantation (ISHLT) criteria, based on findings in the regular endomyocardial biopsies (> ISHLT IB - occurred in n=205, 81% - and ISHLT > II - occurred in n=167, 66% - are shown separately) \(^{27}\). Only biopsy proven rejections > 1 month after the previous biopsy were counted as a de novo rejection.

Immunosuppressive therapy followed a standardized protocol in all patients and was recorded after 12 months, when levels of immunosuppressive drugs were in a steady state. Presence of malignancy was ruled out prior to transplantation in all patients according to the guidelines of the ISHLT.\(^ {27-29}\)

Study endpoints

The primary outcome measure was the time from HTX to the occurrence of any malignancy, defined as the detection of any malignant tumor. For this endpoint, the competing event “death from non-malignant cause” was considered.
Secondary endpoints were overall survival and time to tumor occurrence for which we additionally distinguished between skin vs. non-skin malignancies. “Non-skin” malignancies included lymphoma, multiple myeloma, tumors of bladder, lung, gastrointestinal system, kidneys and of unknown origin. Further, we investigated whether high cholesterol is an independent risk factor for the occurrence of a malignancy or of the competing endpoint of death from a non-malignant cause.

Study groups

The outcome of patients receiving statin therapy was compared to patients without statins. Each day on statin treatment was recorded and patients were divided into subgroups who received statins for more than 50% of the follow-up compared to with patients with less than 50% of follow-up. Patients were divided into a low-dose group (equivalent simvastatin dose of 10-30 mg) and a high-dose group (equivalent simvastatin dose of 40-80 mg). The decision to put patients on a “high-dose” statin therapy was based on cholesterol values > 5.5 mmol/l (n=24, 16% of patients on statin).

Furthermore, patients were assigned to two groups based on their mean fasting total cholesterol (TC) of all cholesterol measurements after three months after HTX, i.e. in a „high-cholesterol group“ (TC ≥ 5.5 mmol/l) and a „low-cholesterol group“ (TC < 5.5 mmol/l), as lipid levels change due to immunosuppressive therapy after HTX.

Statistical analyses

Statistical analysis was performed using “R” Software and Stata 11.2 (StataCorp, College Station, TX). The survival analysis was performed using the R-package survival Cumulative incidence curves are computed using the package “cmprsk”. Nominal variables are presented as absolute (n) and relative frequency (%). To assess differences in nominal variables between
groups we used either Chi² or Fisher's exact test, whichever was appropriate. Continuous variables are presented as median and interquartile range (25-75 percentile) within brackets. To assess differences between groups, the Mann-Whitney U-test was used. To assess time-to-event endpoints with competing events, we computed cumulative incidence curves and provide estimates of the cumulative incidences at 8, 10, and 12 years including 95% confidence intervals. Cumulative incidence curves were compared between groups according to the method of Gray.35 For the primary outcome measure “freedom from malignancy”, the competing events “occurrence of skin malignancy”, “non-skin malignancy”, “death from non-malignant cause”, and “censored” (denoted “event-free survival”) were distinguished.

Cox regression models were used to analyze the independent influence of the covariates “statin-group” on malignancy formation, where we adjusted these models for age, sex, underlying heart disease, conventional immunosuppression and change to mTOR inhibitors or tacrolimus (mTOR and tacrolimus as time-dependent co-variates).

To assess whether the relative risk reduction of the statin therapy is independent of cholesterol levels and of interactions between statin therapy and cholesterol values, a Cox regression model with cholesterol (cholesterol as nominal co-variate ≥5.5 mmol/l vs. <5.5 mmol/l) and the “statin-groups” was determined. Kaplan-Meier estimates and log-rank tests for overall survival and median follow-up were computed using inverted Kaplan-Meier estimate. Confidence intervals for median time to event were computed using the method by Brookmeyer and Crowley.36 A significance level of α = 0.05 was adopted throughout the study and all confidence intervals are computed using a confidence level of 95%.

Ethics committee approval

The study was approved by the ethics committee of the University of Zurich, Zurich Switzerland.
Results

Patient characteristics

All 255 patients who underwent heart transplantation at the University Hospital Zurich between 1985 and 2007 and survived the first year were included (Table 1). The median follow-up for event-free survival from cancer was 12.6 years (25th-75th percentile 11.0 – 14.0 years, Table 1). During follow-up 94 patients (37%) died, of whom 29 patients (11%) died due to a malignancy. The groups did not differ with regard to age, gender, mean cholesterol values, rejections per patient per year and CMV risk (Table 2).

Cumulative incidences of occurrence of neoplasia were 21% (95% CI 0.16 – 0.26%) at eight years follow-up, 27% (95% CI 0.21 – 0.32%) at ten years and 30% (95% CI 0.25 – 0.36%) at twelve years. Cumulative incidences of skin malignancies were 11% (95% CI 0.07 – 0.15%) at eight years follow-up, 15% (95% CI 0.11 – 0.20%) at ten years and 17% (95% CI 0.12 – 0.21%) at twelve years. Cumulative incidences of the competing endpoint “death from non-malignant cause” were 12% (95% CI 0.08 – 0.16%) at eight years follow-up, 13% (95% CI 0.09 – 0.17%) at ten years and 16% (95% CI 0.12 – 0.21%) at twelve years.

Impact of statin therapy on malignancy formation and mortality

Of the 151 patients on statin therapy, 83 patients (57%) received low-dose (equivalent to simvastatin 10-30 mg) and 61 (42%) a high dose statin therapy (equivalent to 40-80 mg simvastatin). In seven patients detailed information on statin dose was lacking. Statin intake was recorded on a daily basis in the statin study population: Patients were on statin therapy for a median of 64% (25th-75th percentile: 42 – 93%) of the follow-up time (time to occurrence of cancer). During follow-up, a malignancy was diagnosed in 108 patients (42%). Patients on statin therapy were more likely to survive without occurrence of malignancies (p < 0.003, Figure 1).
Patients in the statin group were at a lower risk of malignancy formation compared to the non-statin group (13% vs. 34%, CI 0.07 – 0.18 vs. 0.25 – 0.43) at eight years after transplantation, (18% vs. 39%, CI 0.12 – 0.24 vs. 0.30 – 0.49) 10 years after transplantation and (22% vs. 42%, CI 0.15 – 0.28 vs. 0.33 – 0.52; p<0.003. Figure 1) 12 years of follow-up.

“Non-malignant cause of death” is a competing endpoint: statin use was associated with a reduction of risk to die from a non-malignant cause compared to the non-statin group, (7% vs. 19%, CI 0.03 – 0.11 vs. 0.12 – 0.27) eight years after transplantation, (9% vs. 19%, CI 0.04 – 0.13 vs. 0.12 – 0.27) 10 years after transplantation and (11% vs. 24%, CI 0.06 – 0.16 vs. 0.16 – 0.32; p = 0.02; Figure 1) twelve years of follow-up.

Similarly, statin use was associated with a reduced risk of developing non-skin malignancies (4% vs. 18%, CI 0.01 – 0.07 vs. CI 0.11 – 0.26) eight years after transplantation, 10 years after transplantation (5% vs. 20%, CI 0.02 – 0.09 vs. CI 0.12 – 0.28) and twelve years of follow-up (7% vs. 22%, CI 0.03 – 0.11 vs. CI 0.14 – 0.30; p=0.04; Figure 2), while there was no difference for occurrence of skin malignancies between the statin and the non-statin group (p=0.2, Figure 2).

Patients receiving statins for more than 50% of the follow-up time had a lower risk of malignancy occurrence compared to patients who received a statin for less than 50% of follow-up time (p=0.02). This benefit persisted at eight years (16% vs. 25%; CI 0.08 – 0.23 vs. 0.18 – 0.32), ten years (21% vs. 31%; CI 0.13 – 0.29 vs. 0.23 – 0.38) and twelve years of follow-up (25% vs. 34%, CI 0.16 – 0.34 vs. 0.26 – 0.41; Figure 3).

Moreover, patients on statin treatment ≥ 50% of the follow-up time were less likely to die from a non-malignant cause of death compared to patients receiving statins less than 50% of the follow-up time (p-value: 0.007; Figure 3). Importantly, this benefit persisted eight years (7% vs. 0.32; p = 0.02; Figure 1) twelve years of follow-up.
15%; CI 0.02 – 0.13 vs. 0.09 – 0.20), 10 years (7% vs. 17%, CI 0.02 – 0.13 vs. 0.11 – 0.22) and
12 years after transplantation (8% vs. 21%, CI 0.03 – 0.14 vs. 0.15 – 0.27).

A Cox-regression model analyzing the time to tumor formation with or without statin
therapy, adjusted for age, male gender, type of cardiomyopathy and immunosuppressive therapy
demonstrates a lower hazard for tumor in the statin group. (Table 3).

Overall survival was improved in patients on statin therapy vs. the control group
(p<0.0001; Figure 4). Statin dose was not associated with malignancy occurrence (p=0.44).

Impact of cholesterol levels on malignancy formation and mortality

In 239 of 255 patients serial cholesterol measurements, obtained at least three months after HTX,
were available (median number of 5.5 cholesterol values (min. 3 – max. 13). In a Cox-regression
model analyzing the event free survival in patients with or without statin therapy and cholesterol
levels (≥5.5 μmol/l vs. <5.5 mmol/l) as co-variates, the benefit of statin therapy (p= 0.0009, HR
0.43, 95% CI 0.26-0.71) was independent of plasma cholesterol levels (p = 0.76, HR 1.09, 95%
CI 0.26-1.92). No significant interactions between statin therapy and cholesterol values on the
development of tumors were detected (p=0.72). But, there was an increased risk for “non-
malignant cause of death” in the high cholesterol group (p=0.0003). In the high cholesterol
group, patients on statin therapy had an improved survival as compared to those patients without
statin (p=0.0003).

Discussion

We here demonstrate that statin use is associated with a substantial reduction of cancer risk and
all-cause mortality in heart transplantation recipients. With a follow-up of up to 25 years it is not
possible to adjust away all the differences in therapy and especially during the recent era when
statins were used compared to the previous era in which there was more intense
immunosuppression with agents more likely to cause malignancy.

Over the last three decades the development of tumors in transplant recipients steadily
decreased by the introduction of newer immunosuppressive drugs, like mTOR inhibitors or
tacrolimus.³,¹² However, while the one year survival rate improved dramatically since the early
era of organ transplantation due to more targeted immunosuppression and optimized strategies to
prevent severe acute organ rejections, overall long term survival did not further improve over the
last 20 years¹². Long-term outcome after cardiac transplantation is still limited by graft
atherosclerosis and particularly by the risk of developing cancer, which remains a leading cause
of death after 15 years, modern immunosuppressive therapies notwithstanding.⁶,⁹,¹¹,¹² Hence, the
observed 67% hazard reduction to develop cancer associated with the use of statins in the present
study is of particular clinical relevance. Importantly, the benefits of statins were observed on top
of the use of modern immunosuppressive therapy – mTOR inhibitors, in particular.

These findings are in line with results from recent case-control studies in non-
immunosuppressed patients indicating that statin use is associated with a reduction of the risk of
colon¹⁸, lung¹⁹ and pancreatic cancer²⁰. In addition, a potential for statins as adjuvant therapy has
been suggested, as statins reduce proliferation and increase apoptosis in women with high grade
breast cancer¹⁶. Similarly, statins induce apoptosis of ovarian cancer cells and synergize with
doxorubicin¹⁷.

Moreover, the reduction of cancer risk in heart transplant recipients receiving statins was
paralleled by a substantial reduction of total mortality. This confirms and extends findings of
previous studies of Kobashigawa et al. that pravastatin improves survival after heart
transplantation particularly due to a reduction in graft atherosclerosis¹⁴. While the survival
benefit associated with the use of statins had been subsequently been confirmed by other groups and other statins, data on cancer risk had not been reported\textsuperscript{37-39}. Since the benefits of statins on mortality and cancer risk in the present study were independent of cholesterol lowering, potential mechanisms associated with the inhibition of the mevalonate HMG-Coenzyme A reductase pathway beyond cholesterol lowering alone should be considered. Indeed, statins downregulate the synthesis of dolichol, ubiquinol farnesol and geranylgeraniol\textsuperscript{40,41}, all of which are associated with cell transformation\textsuperscript{42}, cell proliferation\textsuperscript{43} and angiogenesis\textsuperscript{44}. Moreover, statins induce apoptosis via activation of caspase and mitochondrial pathways\textsuperscript{45} and modulate cell migration by down-regulating chemokine secretion and receptor expression in a geranylgeranylation dependent mechanism.\textsuperscript{40,46,47} In addition, statins suppress several adhesion molecules in organ tissue and leukocytes such as ICAM-1 or VCAM-1\textsuperscript{48} regulate metalloproteinases and several cytokines that are permissive for tumor growth.\textsuperscript{49} As inhibition of metalloproteinases might prevent cell transformation\textsuperscript{50} and statins may reduce tumor formation as well as graft rejection.\textsuperscript{51,52}

Interestingly, the beneficial effects of statins in the present study were not only independent of the immunosuppressive therapy but also of statin dose and cholesterol levels. Even in the “high-cholesterol” subgroup (defined as a mean cholesterol value of more than 5.5 mmol/l), patients on statin therapy were at a lower risk of malignancy formation compared to patients without statin treatment.

**Is there a link between cholesterol levels and cancer development?**

In patients after solid organ transplantation, data on the relation of cholesterol and statins on clinical outcome are sparse. In the present study, no significant association of elevated cholesterol values and cancer risk was detected. However, cholesterol is a major component of
the cell membrane and plays an important role in vesicular trafficking and cellular pathways. In line with this concept, Zhuang et al. could demonstrate a decreased apoptosis rate in cholesterol enriched prostate cancer cells. Moreover, cholesterol levels influence the activity of metalloproteinases that are actively involved in tumor promotion and could represent another link between cholesterol and tumor growth. While an inverse association of cholesterol levels and cancer risk had been reported previously more recent evidence suggest that this observation may be due to reverse causation. Therefore, a potential role of cholesterol in the development of malignancies remains still elusive.

The role of newer immunosuppressive agents in malignancy formation

Transplant-related malignancies arise from a complex interplay of immunologic and non-immunologic risk factors. It still remains a matter of debate, however, whether the type of immunosuppressive regimen, total dosage and duration of treatment or the degree of immunosuppression, are relevant to determining cancer risk. Previous publications demonstrated, that the risk of posttransplant malignancies is linked with azathioprine, but not with newer agents such as mycophenolate mofetil and sirolimus. Preliminary long-term data support the use of these newer agents, like mTOR inhibitors or tacrolimus, with potential antitumor properties and lower cancer risk in transplant recipients.

Limitations

It has to be acknowledged that it is not possible to adjust away all the differences in therapy over a two decades follow-up and especially during the recent era when statins were more frequently used compared to the previous era in which more intense immunosuppression was more likely to cause malignancy. While retrospective analyses are subject to bias and confounding, randomized clinical trials addressing the role of statins in cancer in immunosuppressed patients are still
lacking, which is mainly due to the long follow-up periods needed. Especially, the difference in azathioprine use between the study groups could be an important confounder. However, in a Cox regression model, azathioprine was not an independent risk factor for cancer in our study population. Only 18% of patients were switched to mTOR inhibitors or tacrolimus over time. Thus, cancer risk can be further reduced in the future with the use of newer immunosuppressive drugs.

The sample size of the present study has to be weighed against the high event rate of tumor occurrence and the long follow-up period of up to 25 years with a median follow-up for overall survival of 14.4 years. Importantly, all patients included in the study underwent a rigid post-transplant follow-up schedule according to a standardized protocol in our heart transplantation clinic and had frequent check-ups at least on a half-yearly basis, which assured a careful patient monitoring and early detection of malignancies. While the impact of immunosuppression on malignancy formation remains challenging and different options like the CD4, CD8, CD16 or CD20 cell count, the cumulative dose of the immunosuppressive agents or the number of biopsy proven rejections have been proposed\textsuperscript{60-62}, the number of severe rejections is increasingly considered to be a valuable approach to reflect the grade of immunosuppression, as the dosing of the immunosuppressive drugs varies not only by body-weight but is also depending on individual liver metabolism.\textsuperscript{63,64}

In view of the potential viral aetiology of cancer in transplant recipients, it is noteworthy that cytomegalovirus high-risk constellation (donor (D) +, recipient (R) −) was similar in the statin and the control group.

In addition, the primary outcome measure of this study, i.e. the occurrence of malignancy, might be influenced, by the occurrence of non-malignant events, cardiac death in particular.
Indeed, such events are known as competing risk events and the Kaplan–Meier estimation procedure is not directly applicable under these conditions.\(^6\) As a consequence the cumulative incidence function for the event of interest was calculated by appropriately accounting for the presence of competing risk events.

**Conclusion**

Thus, in spite of limitations in adjusting for all potential confounders over a follow-up period of up to 25 years, when factors related to the era of transplantation like overall intensity of immunosuppression, and use of azathioprine might have changed, the results of the present study suggest, that statin use is associated with a substantial reduction of cancer risk and all-cause mortality in heart transplantation recipients.

Whether these benefits of statins are specific for heart transplant recipients who are at particularly high risk of cancer and can be extrapolated to all patients on long-term immunosuppressive therapy (particularly tacrolimus and mTOR inhibitors) needs to be confirmed in long-term randomized clinical trials.

**Conflict of Interest Disclosures:** Thomas F. Lüscher: receives research grants and honoraria from Pfizer.

**References:**


27. Billingham ME, Cary NR, Hammond ME, Kemnitz J, Marboe C, McCallister HA, Snovar DC, Winters GL, Zerbe A. A working formulation for the standardization of nomenclature in the


Table 1. Patient characteristics. Categorical variables are presented as number of patients (%). Continuous variables are presented as median with 25th – 75th percentiles in brackets. The median follow-up for overall and event free survival is shown with 95% confidence intervals in brackets.

<table>
<thead>
<tr>
<th></th>
<th>n = 255</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>225 (88)</td>
</tr>
<tr>
<td>Age at time of transplantation (years)</td>
<td>51 (44 – 57)</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy (n, %)</td>
<td>106 (45)</td>
</tr>
<tr>
<td>Non-ischemic cardiomyopathy (n, %)</td>
<td>129 (55)</td>
</tr>
<tr>
<td>CMV high risk constellation (recipient negative/donor positive) (n, %)</td>
<td>73 (31)</td>
</tr>
<tr>
<td>Immunosuppressive therapy (n, %)</td>
<td></td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>247 (98)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>24 (10)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>179 (71)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>232 (93)</td>
</tr>
<tr>
<td>Mycophenolic acid</td>
<td>155 (62)</td>
</tr>
<tr>
<td>Switch to tacrolimus (n, %)</td>
<td>18 (7)</td>
</tr>
<tr>
<td>Switch to mTOR inhibitors (n, %)</td>
<td>28 (11)</td>
</tr>
<tr>
<td>Follow-up for freedom from cancer (years)</td>
<td>12.6 (11.0 – 14.0)</td>
</tr>
<tr>
<td>Tumors (n, % of all tumors)</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>61 (56)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>18 (17)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Intestine</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Brain</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Bladder</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Breast</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Kidney</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Follow-up for overall survival (years)</td>
<td>13.7 (12.8 – 14.8)</td>
</tr>
<tr>
<td>Cause of death (n, % of all patients)</td>
<td></td>
</tr>
<tr>
<td>Cancer (n, % of deaths)</td>
<td>94 (37)</td>
</tr>
<tr>
<td>Cardiovascular (n, % of deaths)</td>
<td>29 (31)</td>
</tr>
<tr>
<td>Infection (n, % of deaths)</td>
<td>49 (52)</td>
</tr>
<tr>
<td>Other (n, % of deaths)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Rejections ISHT &gt;IB (per year)</td>
<td>0.3 (0.1-0.6)</td>
</tr>
<tr>
<td>Rejections &gt; ISHT 2 (per year)</td>
<td>0.1 (0-0.3)</td>
</tr>
</tbody>
</table>
Table 2. Characteristics of patients receiving statin therapy compared to those without statins. Categorical variables are presented as number of patients (%). Continuous variables are presented as median with 25th - 75th percentiles in brackets.

<table>
<thead>
<tr>
<th></th>
<th>Statin therapy (n=151)</th>
<th>No statin (n=104)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>134 (89)</td>
<td>91 (88)</td>
<td>0.84</td>
</tr>
<tr>
<td>Age at time of transplantation (years)</td>
<td>52 (45–57)</td>
<td>50 (41-56)</td>
<td>0.70</td>
</tr>
<tr>
<td>Follow-up for freedom from cancer (months)</td>
<td>125 (72-184)</td>
<td>75 (40-127)</td>
<td>0.55</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>35 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>6 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>28 (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>82 (54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin related myopathy (all patients received high dose statin therapy)</td>
<td>5 (3)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Discontinuation of statin therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppressive therapy (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>147 (97)</td>
<td>100 (99)</td>
<td>0.65</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>96 (64)</td>
<td>83 (83)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mycophenolic acid</td>
<td>110 (74)</td>
<td>45 (45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline cholesterol values (mmol/l)</td>
<td>5.8 (4.9–6.1)</td>
<td>5.5 (5.0 – 6.7)</td>
<td>0.50</td>
</tr>
<tr>
<td>Cause of transplantation (n, %)</td>
<td></td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>69 (49)</td>
<td>37 (39)</td>
<td></td>
</tr>
<tr>
<td>Non-ischemic cardiomyopathy</td>
<td>71 (51)</td>
<td>58 (61)</td>
<td></td>
</tr>
<tr>
<td>Rejections ISHLT &gt; 1B (per year)</td>
<td>0.3 (0.1-0.6)</td>
<td>0.2 (0–0.6)</td>
<td>0.17</td>
</tr>
<tr>
<td>Rejections ISHLT &gt; 2 (per year)</td>
<td>0.1 (0-0.3)</td>
<td>0.1 (0-0.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>CMV high risk constellation (n,%))</td>
<td>37 (26)</td>
<td>36 (38)</td>
<td>0.08</td>
</tr>
<tr>
<td>Tumors (n, % of all tumors within study group)</td>
<td>54 (36)</td>
<td>54 (52)</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>32 (59)</td>
<td>29 (54)</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>7 (13)</td>
<td>11 (20)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (11)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>Intestine</td>
<td>2 (4)</td>
<td>5 (9)</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>3 (6)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>0</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>2 (4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cause of death (n, % of all patients)</td>
<td>37 (15)</td>
<td>57 (22)</td>
<td></td>
</tr>
<tr>
<td>Cancer (n, % of deaths)</td>
<td>10 (4)</td>
<td>19 (8)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular (n, % of deaths)</td>
<td>19 (8)</td>
<td>30 (12)</td>
<td></td>
</tr>
<tr>
<td>Infection (n, % of deaths)</td>
<td>4 (2)</td>
<td>5 (2)</td>
<td></td>
</tr>
<tr>
<td>Other (n, % of deaths)</td>
<td>4 (2)</td>
<td>3 (1)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Hazard ratios and confidence intervals of a Cox regression model investigating the time to tumor formation.

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin therapy</td>
<td>0.33</td>
<td>0.21 – 0.51</td>
</tr>
<tr>
<td>Non-ischemic cardiomyopathy</td>
<td>0.74</td>
<td>0.48 – 1.14</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.06</td>
<td>1.04 – 1.10</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.22</td>
<td>0.45 – 3.3</td>
</tr>
<tr>
<td>Calcineurin-inhibitor therapy</td>
<td>1.15</td>
<td>0.11 – 12.4</td>
</tr>
<tr>
<td>Azathioprine therapy</td>
<td>1.45</td>
<td>0.87 – 2.4</td>
</tr>
<tr>
<td>Mycophenolate therapy</td>
<td>0.81</td>
<td>0.47 – 1.37</td>
</tr>
<tr>
<td>Switch to mTOR inhibitor (per year)</td>
<td>1.7</td>
<td>0.34 – 5.7</td>
</tr>
<tr>
<td>Switch to Tacrolimus (per year)</td>
<td>1.4</td>
<td>0.52 – 5.61</td>
</tr>
</tbody>
</table>

Figure Legends:

Figure 1. Cumulative incidence curves comparing tumor occurrence (p < 0.003) and death from malignant vs. non-malignant origin (p = 0.02) in patients receiving statin therapy compared to patients without.

Figure 2. Cumulative incidence of “skin” (p=0.2) vs. “non-skin” malignancies (p=0.04) in patients with statin - vs. no statin.

Figure 3. Cumulative incidence curves comparing tumor occurrence (p=0.02) and death from malignant vs. non-malignant origin (p=0.007) in patients receiving statin therapy > 50% vs. < 50% of follow-up time. (TTC: time to cancer).

Figure 4. Overall survival of patients receiving statin therapy compared to patients without such treatment (Log-rank p<0.0001).
Cumulative probability of event

- --- <50% of TTC on Statin: death from non-malignant cause
- - - >= 50% of TTC on Statin: death from non-malignant cause
- - - - <50% of TTC on Statin: occurrence of neoplasia
- - - - - >= 50% of TTC on Statin: occurrence of neoplasia

Time since transplantation (years)
Statins and the Risk of Cancer after Heart Transplantation
Georg Marcus Fröhlich, Kaspar Rufibach, Frank Enseleit, Mathias Wolfrum, Michelle von Babo, Michelle Frank, Reto Berli, Mathias Hermann, Johannes Holzmeister, Georg Noll, Thomas F. Lüscher and Frank Ruschitzka

Circulation. published online July 3, 2012;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2012/06/28/CIRCULATIONAHA.111.081059

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/