Statins and the Risk of Cancer After Heart Transplantation

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Background—Although newer immunosuppressive agents, such as mTOR (mammalian target of rapamycin) inhibitors, have lowered the occurrence of malignancies after transplantation, cancer is still a leading cause of death late after heart transplantation. Statins may have an impact on clinical outcomes beyond their lipid-lowering effects. The aim of the present study was to delineate whether statin therapy has an impact on cancer risk and total mortality after heart transplantation.

Methods and Results—A total of 255 patients who underwent heart transplantation at the University Hospital Zurich between 1985 and 2007 and survived the first year were included in the present study. The primary outcome measure was the occurrence of any malignancy; the secondary end point was 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% versus 13%; 95% confidence interval, 0.25–0.43 versus 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 that analyzed the time to tumor formation with or without statin therapy, adjusted for age, male sex, type of cardiomyopathy, and immunosuppressive therapy (including switch to mTOR inhibitors or tacrolimus), demonstrated a superior survival in the statin group. Statins reduced the hazard of occurrence of any malignancy by 67% (hazard ratio, 0.33; 95% confidence interval, 0.21–0.51; P<0.0001).

Conclusions—Although it is not possible to adjust for all potential confounders because of 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 need to be confirmed in a prospective trial. (Circulation. 2012;126:440-447.)

Key Words: cancer ■ cholesterol ■ heart transplantation ■ statins ■ transplantation ■ malignancy

N ewer immunosuppressive regimens such as mTOR (mammalian target of rapamycin) inhibitors or tacrolimus have steadily reduced the incidence not only of acute rejection but also of posttransplantation malignancy1–3; however, malignancy is still an important cause of long-term mortality in transplant recipients.4 The incidence of malignancy has been estimated at 20% after 10 years of chronic immunosuppression,5 and the relative risk may increase 100-fold for specific cancers compared with the general population.6 Heart transplant patients are at particular risk of developing posttransplantation malignancies, which is increased up to 4-fold compared with renal transplant recipients.6–11 Indeed, cancer is now a leading cause of death late after heart transplantation.12

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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.13,14 Intriguingly, in nontransplant patients, statin intake is associated with a decreased risk of malignancies such as lymphoma,15 breast,16 ovarian,17 colorectal,18,18a and lung and pancreatic cancer.19,20 Although elevated plasma cholesterol levels have been associated with the development of skin, colon, or prostate cancer,21–24 it is a matter of ongoing debate whether the potential benefit of statins in cancer may be explained by their cholesterol-lowering or potential pleiotropic, particularly immunomodulatory, effects.25,26

To the best of our knowledge, no data exist on the impact of statin use or cholesterol levels on cancer risk in immunosuppressed patients. Hence, the aim of the present 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 who underwent heart transplantation at the University Hospital Zurich between 1985 and

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2007 and survived the first year after transplantation. Statin therapy was initiated, usually 3 to 12 months after transplantation in patients who received transplants after 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. More detailed information about immunosuppressive therapy, including a switch to mTOR inhibitors or tacrolimus, lipid status, and episodes of rejection was recorded. Rejection was defined according to International Society for Heart and Lung Transplantation criteria, based on findings in the regular endomyocardial biopsy samples (greater than grade 1B rejection occurred in 205 patients [81%], and greater than grade 2 rejection occurred in 167 [66%], shown separately). 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 before transplantation in all patients according to the guidelines of the International Society for Heart and Lung Transplantation.

**Study End Points**
The primary outcome measure was the time from heart transplantation to the occurrence of any malignancy, defined as the detection of any malignant tumor. For this end point, the competing event death of nonmalignant cause was considered.

Secondary end points were overall survival and time to tumor occurrence, for which we additionally distinguished between skin versus nonskin malignancies. Non-skin malignancies included lymphoma; multiple myeloma; tumors of bladder, lung, gastrointestinal system, or kidneys; and tumors of unknown origin. Furthermore, we investigated whether high cholesterol was an independent risk factor for the occurrence of a malignancy or of the competing end point of death of a nonmalignant cause.

**Study Groups**
The outcome of patients receiving statin therapy was compared with patients without statins. Each day on statin treatment was recorded, and patients were divided into subgroups who received statins for >50% of the follow-up compared with patients given statins for <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 given statins). Furthermore, patients were assigned to 1 of 2 groups based on their mean fasting total cholesterol of all cholesterol measurements after 3 months after heart transplantation, ie, in a high-cholesterol group (total cholesterol ≥5.5 mmol/L) or a low-cholesterol group (total cholesterol <5.5 mmol/L), because lipid levels change in response to immunosuppressive therapy after heart transplantation.

**Statistical Analysis**
Statistical analysis was performed with “R” software and Stata 11.2 (StataCorp). Survival analysis was performed with the R package survival version (survival analysis, including penalized likelihood; R package version 2.34-1). Cumulative incidence curves were computed with the software package cmprsk (R package version 2.1.7). Nominal variables are presented as absolute (n) and relative frequency (%). To assess differences in nominal variables between groups, we used either χ² or Fisher exact test, as appropriate. Continuous variables are presented as median (interquartile range [25th to 75th percentile]). To assess differences between groups, the Mann-Whitney U test was used. To assess time-to-event end points and competing events, we computed cumulative incidence curves and provided estimates of the cumulative incidences at 8, 10, and 12 years, including 95% confidence intervals (CIs). Cumulative incidence curves were compared between groups according to the method of Bob Gray (cmprsk, R package version 2.1.7). For the primary outcome measure “freedom from malignancy,” the competing events “occurrence of skin malignancy,” “nonskin malignancy,” “death of nonmalignant cause,” and “censored” (denoted “event-free survival”) were distinguished.

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

To assess whether the relative risk reduction of the statin therapy was independent of cholesterol levels and of interactions between statin therapy and cholesterol values, a Cox regression model with cholesterol (cholesterol as nominal covariate, ≥5.5 mmol/L versus <5.5 mmol/L) and the statin groups was constructed. Kaplan-Meier estimates and log-rank tests for overall survival and median follow-up were computed with an inverted Kaplan-Meier estimate. CIs for median time to event were computed by the method of Brookmeyer and Crowley. A significance level of α=0.05 was adopted throughout the study, and all CIs were computed with 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 in the study (Table 1). The median follow-up for event-free survival from cancer was 12.6 years (25th to 75th percentile, 11.0–14.0 years; Table 1). During follow-up, 94 patients (37%) died, 29 of whom died of a malignancy (11% of the entire study group).

The groups did not differ with regard to age, sex, mean cholesterol values, rejections per patient per year, and cytomegalovirus risk (Table 2). Cumulative incidences of occurrence of neoplasia were 21% (95% CI, 0.16%–0.26%) at 8 years of follow-up, 27% (95% CI, 0.21%–0.32%) at 10 years, and 30% (95% CI, 0.25%–0.36%) at 12 years. Cumulative incidences of skin malignancies were 11% (95% CI, 0.07%–0.15%) at 8 years’ follow-up, 15% (95% CI, 0.11%–0.20%) at 10 years, and 17% (95% CI, 0.12%–0.21%) at 12 years. Cumulative incidences of the competing end point “death of nonmalignant cause” were 12% (95% CI, 0.08%–0.16%) at 8 years’ follow-up, 13% (95% CI, 0.09%–0.17%) at 10 years, and 16% (95% CI, 0.12%–0.21%) at 12 years.

**Impact of Statin Therapy on Malignancy Formation and Mortality**
Of the 151 patients undergoing statin therapy, 83 (55%) received low-dose (equivalent to simvastatin 10–30 mg) and 61 (40%) a high dose statin therapy (equivalent to 40–80 mg simvastatin). For 7 patients, detailed information on statin dose was lacking. Statin intake was recorded on a daily basis in the statin study population: Patients were undergoing statin therapy for a median of 64% (25th to 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 undergoing 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 than the nonstatin group at 8 years after transplantation (13% versus 34%; 95% CI, 0.07–0.18 versus 0.25–0.43), at 10 years after transplantation (18% versus 39%; 95% CI, 0.12–0.24 versus 0.30–0.49), and at 12 years of follow-up (22% versus 42%; 95% CI, 0.15–0.28 versus 0.33–0.52; \( P < 0.003 \)). Figure 1.

Nonmalignant cause of death was a competing end point: Statin use was associated with a reduction of risk of dying of a nonmalignant cause compared with the nonstatin group at 8 years after transplantation (7% versus 19%; 95% CI, 0.03–0.11 versus 0.12–0.27), at 10 years after transplantation (9% versus 19%; 95% CI, 0.04–0.13 versus 0.12–0.27), and at 12 years of follow-up (11% versus 24%; 95% CI, 0.06–0.16 versus 0.16–0.32; \( P = 0.02 \); Figure 1). Similarly, statin use

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics (n=255)</th>
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<tbody>
<tr>
<td>Male</td>
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<tr>
<td>Age at time of transplantation, y</td>
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<tr>
<td>Ischemic cardiomyopathy</td>
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<tr>
<td>Nonischemic cardiomyopathy</td>
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<tr>
<td>CMV high-risk constellation (recipient negative/donor positive)</td>
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<tr>
<td>Immunosuppressive therapy</td>
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<tr>
<td>Calcineurin inhibitors</td>
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<tr>
<td>Everolimus</td>
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<td>Azathioprine</td>
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<tr>
<td>Prednisone</td>
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<tr>
<td>Mycophenolic acid</td>
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<tr>
<td>Switch to tacrolimus</td>
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<td>Switch to mTOR inhibitors</td>
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<tr>
<td>Follow-up for freedom from cancer, y</td>
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</tbody>
</table>

Tumors, n (% of all tumors)
- Skin: 61 (56)
- Lymphoma: 18 (17)
- Unknown: 9 (9)
- Intestine: 7 (6)
- Brain: 6 (6)
- Bladder: 3 (3)
- Breast: 2 (2)
- Kidney: 2 (2)

Follow-up for overall survival, y: 13.7 (12.8–14.8)

Cause of death, n (% of all patients): 94 (37)
- Cancer, n (% of deaths): 29 (31)
- Cardiovascular, n (% of deaths): 49 (52)
- Infection, n (% of deaths): 9 (10)
- Other, n (% of deaths): 7 (7)

Rejections with ISHLT grade >1B, per year: 0.3 (0.1–0.6)

Rejections with ISHLT grade >2, per year: 0.1 (0–0.3)

CMV indicates cytomegalovirus; mTOR, mammalian target of rapamycin; and ISHT, International Society for Heart and Lung Transplantation.

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

<table>
<thead>
<tr>
<th>Table 2. Characteristics of Patients Receiving Statin Therapy Compared With Those Without Statins</th>
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<tr>
<td>Statin Therapy (n=151)</td>
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<tr>
<td>No Statin (n=104)</td>
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<tr>
<td>Male, n (%)</td>
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<tr>
<td>Age at time of transplantation, y</td>
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<tr>
<td>Follow-up for freedom from cancer, mo</td>
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<tr>
<td>Statin, n (%)</td>
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<tr>
<td>Simvastatin</td>
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<tr>
<td>Fluvastatin</td>
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<td>Atorvastatin</td>
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<tr>
<td>Pravastatin</td>
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<td>Statin-related myopathy (all patients received high-dose statin therapy)</td>
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<tr>
<td>Permanent discontinuation of statin therapy</td>
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<td>Immunosuppressive therapy, n (%)</td>
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<td>Calcineurin inhibitors</td>
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<tr>
<td>Azathioprine</td>
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<tr>
<td>Mycophenolic acid</td>
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<tr>
<td>Baseline cholesterol values, mmol/L</td>
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<tr>
<td>Reason for transplantation, n (%)</td>
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<tr>
<td>Ischemic cardiomyopathy</td>
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<td>Nonischemic cardiomyopathy</td>
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<td>Rejections with ISHLT grade &gt;1B, per year</td>
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<td>Rejections with ISHLT grade &gt;2, per year</td>
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<tr>
<td>CMV high-risk constellation, n (%)</td>
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<td>Tumors, n (% of all tumors within study group)</td>
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<tr>
<td>Skin</td>
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<tr>
<td>Lymphoma</td>
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<tr>
<td>Unknown</td>
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<td>Intestine</td>
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<td>Brain</td>
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<td>Bladder</td>
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<td>Breast</td>
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<tr>
<td>Kidney</td>
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<tr>
<td>Cause of death, n (% of all patients)</td>
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</tbody>
</table>

ISHT indicates International Society for Heart and Lung Transplantation; CMV, cytomegalovirus.

Categorical variables are presented as number of patients (%). Continuous variables are presented as median (25th–75th percentiles).
was associated with a reduced risk of developing nonskin malignancies 8 years after transplantation (4% versus 18%; 95% CI, 0.01–0.07 versus 0.11–0.26) and 10 years after transplantation (5% versus 20%; 95% CI, 0.02–0.09 versus 0.12–0.28) and at 12 years of follow-up (7% versus 22%; 95% CI, 0.03–0.11 versus 0.14–0.30; \(P = 0.04\); Figure 2), although there was no difference for occurrence of skin malignancies between the statin and nonstatin groups (\(P = 0.2\); Figure 2).

Patients receiving statins for >50% of the follow-up time had a lower risk of malignancy occurrence than those who received a statin for <50% of follow-up time (\(P = 0.02\)). This benefit persisted at 8 years (16% versus 25%; 95% CI, 0.08–0.23 versus 0.18–0.32), 10 years (21% versus 31%; 95% CI, 0.13–0.29 versus 0.23–0.38), and 12 years of follow-up (25% versus 34%; 95% CI, 0.16–0.34 versus 0.26–0.41; Figure 3).

Moreover, patients undergoing statin treatment ≥50% of the follow-up time were less likely to die of a nonmalignant cause of death than patients receiving statins <50% of the follow-up time (\(P = 0.007\); Figure 3). Importantly, this benefit persisted 8 years (7% versus 15%; 95% CI, 0.02–0.13 versus 0.09–0.20), 10 years (7% versus 17%; 95% CI, 0.02–0.13 versus 0.11–0.22), and 12 years after transplantation (8% versus 21%; 95% CI, 0.03–0.14 versus 0.15–0.27).

A Cox regression model that analyzed the time to tumor formation with or without statin therapy, adjusted for age, male sex, type of cardiomyopathy and immunosuppressive therapy, demonstrated a lower hazard for tumor formation in the statin group. (Table 3). Overall survival was improved in patients undergoing statin therapy versus 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 3 months after heart transplantation, were available (median number of cholesterol values, 5.5; minimum, 3; maximum 13). In a Cox regression model that analyzed event-free survival among patients with or without statin therapy and with cholesterol levels (≥5.5 versus <5.5, mmol/L) as covariates, the benefit of statin therapy (\(P = 0.0009\); hazard ratio, 0.43; 95% CI, 0.26–0.71) was independent of plasma cholesterol levels (\(P = 0.76\); hazard ratio, 1.09; 95% CI, 0.26–1.92). No significant interactions between statin therapy and cholesterol values on the development of tumors were detected (\(P = 0.72\); however, there was an increased risk for nonmalignant cause of death in the high-cholesterol group (\(P = 0.0003\)). In the high-cholesterol group, patients undergoing statin therapy had improved survival compared with those patients without statin therapy (\(P = 0.0003\)).

**Discussion**

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

Over the past 3 decades, the development of tumors in transplant recipients was steadily decreased by the introduction of newer immunosuppressive drugs, such as mTOR inhibitors or tacrolimus. However, although the 1-year survival rate improved dramatically since the early era of organ transplantation because of more targeted immunosuppression and optimized strategies to prevent severe acute organ rejection, overall long-term survival did not further improve over the past 20 years. 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. 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 beyond those conferred by the use of modern immunosuppressive therapy, mTOR inhibitors in particular.

These findings are in line with results from recent case-control studies in nonimmunosuppressed patients that indicated that statin use is associated with a reduction of the risk of colon, lung, and pancreatic cancer. In addition, a potential for statins as adjuvant therapy has been suggested, because statins reduce proliferation and increase apoptosis in women with high-grade breast cancer. Similarly, statins induce apoptosis of ovarian cancer cells and synergize with doxorubicin.

Moreover, the reduction of cancer risk in heart transplant recipients receiving statins was paralleled by a substantial reduction in total mortality. This confirms and extends findings of previous studies by Kobashigawa et al that pravastatin improves survival after heart transplantation particularly because of a reduction in graft atherosclerosis. Although the survival benefit associated with the use of statins had been confirmed by other groups and with other statins, data on cancer risk had not been reported to date. Because 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 each of which is associated with cell transformation, cell proliferation, and angiogenesis. Moreover, statins induce apoptosis via activation of caspase and mitochondrial pathways and modulate cell migration by downregulating chemokine secretion and receptor expression in a geranylgeranylation-dependent mechanism. In addition, statins suppress several adhesion molecules in organ tissue and leukocytes, such as intercellular adhesion molecule-1 or vascular cell adhesion molecule-1, and regulate metalloproteinases and several cytokines that are permissive for tumor growth. Because inhibition of metalloproteinases might prevent cell transformation, statins may reduce tumor formation as well as graft rejection.

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 >5.5 mmol/L), patients undergoing statin therapy were at a lower risk of malignancy formation than patients without statin treatment.

### 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</th>
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<tbody>
<tr>
<td>Statin therapy</td>
<td>0.33</td>
<td>0.21–0.51</td>
</tr>
<tr>
<td>Nonischemic 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 sex</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>
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<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</td>
<td>1.4</td>
<td>0.52–5.61</td>
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</table>

CI indicates confidence interval; mTOR, mammalian target of rapamycin.
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\textsuperscript{51} were able to 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\textsuperscript{52–54} and could represent another link between cholesterol and tumor growth. Although an inverse association of cholesterol levels and cancer risk had been reported previously,\textsuperscript{55–57} more recent evidence suggest that this observation may be a result of reverse causation.\textsuperscript{57} Therefore, a potential role of cholesterol in the development of malignancies remains elusive.

Role of Newer Immunosuppressive Agents in Malignancy Formation

Transplant-related malignancies arise from a complex interplay of immunologic and nonimmunologic risk factors.\textsuperscript{4} It remains a matter of debate, however, whether the type of immunosuppressive regimen, total dosage and duration of treatment, or the degree of immunosuppression is relevant to determining cancer risk. Previous publications demonstrated that the risk of posttransplantation malignancies is linked with azathioprine, but not with newer agents such as mycophenolate mofetil and sirolimus.\textsuperscript{4} Preliminary long-term data support the use of these newer agents, such as mTOR inhibitors or tacrolimus, with potential antitumor properties and lower cancer risk in transplant recipients.\textsuperscript{12}

Study Limitations

It is not possible to adjust for all the differences in therapy over a 2-decade follow-up period, especially during the recent era in which statins were used more frequently than in the previous era, when more intense immunosuppression was more likely to cause malignancy. Although retrospective analyses are subject to bias and confounding, randomized clinical trials addressing the role of statins in cancer in immunosuppressed patients are lacking, mainly because of the long follow-up periods needed. In particular, 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 the present study population. Only 18% of patients were switched to mTOR inhibitors or tacrolimus over time. Thus, cancer risk can be reduced further in the future with the use of newer immunosuppressive drugs.

The sample size of the present study must 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 posttransplantation follow-up schedule according to a standardized protocol in our heart transplantation clinic and had frequent checkups, at least on a half-yearly basis, which ensured careful patient monitoring and early detection of malignancies. Although the impact of immunosuppression on malignancy formation remains challenging, and different options such as 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{58–60} the number of severe rejections is increasingly considered to be a valuable approach to reflect the grade of immunosuppression, because the dosing of the immunosuppressive drugs varies not only by body weight but also depending on individual liver metabolization.\textsuperscript{61,62}

In view of the potential viral origin of cancer in transplant recipients, it is noteworthy that the cytomegalovirus high-risk constellation (donor positive, recipient negative) was similar in the statin and the control group.

In addition, the primary outcome measure of the present study, ie, the occurrence of malignancy, might be influenced by the occurrence of nonmalignant events, in particular cardiac death. Indeed, such events are known as competing risk events, and the Kaplan-Meier estimation procedure is not directly applicable under these conditions.\textsuperscript{63} As a consequence, the cumulative incidence function for the event of interest was calculated by appropriately accounting for the presence of competing risk events.

Conclusions

In spite of limitations in the ability to adjust for all potential confounders over a follow-up period of up to 25 years, when
factors related to the era of transplantation (such as overall intensity of immunosuppression and use of azathioprine) 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 results of statins are specific for heart transplant recipients who are at particularly high risk of cancer and can be extrapolated to all patients undergoing long-term immunosuppressive therapy (particularly with tacrolimus and mTOR inhibitors) must be confirmed in long-term randomized clinical trials.

Disclosures

Dr Lüscher receives research grants and honoraria from Pfizer. The other authors report no conflicts. Dr Ruschitzka receives research grants and speaker honoraria from Pfizer and MSD.

References


**CLINICAL PERSPECTIVE**

Although newer immunosuppressive agents have lowered the incidence of malignancies after transplantation, cancer remains a leading cause of death late after heart transplantation. Because statins are immunomodulatory drugs and reduce the incidence of rejection and improve survival after cardiac transplantation, the present study investigated whether statin therapy impacts cancer risk as well as cancer-free and total mortality in heart transplant recipients. During follow-up, a malignancy was diagnosed in 108 patients (42%). Interestingly, the cumulative incidence of any malignancy was reduced in patients receiving a statin 8 years after transplantation (34% versus 13%, P = 0.003), and the benefit persisted at the 10-year and 12-year follow-up. In addition, statin use was associated with improved cancer-free and overall survival (both P < 0.0001). Statins reduced the hazard of occurrence of any malignancy by 67% (hazard ratio, 0.33; P < 0.0001). A Cox regression model that analyzed the time to tumor formation with or without statin therapy, adjusted for age, male sex, type of cardiomyopathy, and immunosuppressive therapy (including switching to mTOR [mammalian target of rapamycin] inhibitors or tacrolimus), demonstrated a decreased hazard for tumor formation in the statin group. Thus, in spite of limitations in adjusting for all potential confounders over a follow-up period of up to 25 years, during which factors related to the era of transplantation (such as 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 transplant recipients. Whether these benefits of statins are specific for heart transplant recipients who are at particularly high risk of cancer or can be extrapolated to all patients undergoing long-term immunosuppressive therapy (particularly with tacrolimus and mTOR inhibitors) needs to be confirmed in long-term randomized clinical trials.
Statins and the Risk of Cancer After Heart Transplantation
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