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See related article, “Podocyte-Specific Overexpression of the Antioxidant Metallothionein Reduces Diabetic Nephropathy,” on pages 2077–2085.

## Statin Use Prolongs Patient Survival after Renal Transplantation

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Kidney transplantation reduces mortality and cardiovascular deaths, more so than dialysis, although survival for both re-

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mains worse than in nonrenal disease populations. This may be for reasons of preexisting cardiovascular disease acquired during renal progression or dialysis; however, recent population data suggest even minor kidney dysfunction (which is almost universal in graft recipients) is associated with increased cardiovascular risk.<sup>1</sup>

The pathophysiology underlying increased cardiovascular risk is certainly complex, and it would be naive to assume that dyslipidemia is the only causal factor. Nevertheless, observational data suggest, even after renal transplantation, that cholesterol is a predictor of cardiovascular events.<sup>2</sup> This obviously raises the issue of whether statins should be administered to renal graft recipients with proven target organ damage for secondary prevention or even for primary prevention. Available evidence for statin treatment in renal patients is only relatively good for the early stages of chronic kidney disease because it is based only on *post hoc* analyses of subcohorts of patients who happened to have diminished estimated GFR and were included in the large statin trials.<sup>3</sup>

With respect to hemodialysis or transplant patients, matters are less clear. There is no large controlled prospective trial in a general hemodialysis population, and in the 4D study of patients who had type 2 diabetes and were on dialysis,<sup>4</sup> no significant effect of atorvastatin was seen on the composite cardiovascular end point. *Post hoc* analyses showed that adjudicated coronary death was reduced to the same extent as in nonrenal patients in the major statin trials (by 19% per 1-mmol lower LDL cholesterol); other cardiac causes—specifically sudden death—were much less affected, so the composite end point was not significantly reduced.

With respect to transplant patients, the only randomized, prospective, controlled trial, the Assessment of LEscol in Renal Transplantation (ALERT) study,<sup>5</sup> showed no significant difference in the primary composite end points (major adverse cardiac events defined as cardiac death, nonfatal myocardial infarction, and coronary intervention, despite 32% lowering of LDL cholesterol during a mean follow-up of 5.1 yr). Coronary intervention is usually regarded as a “soft” end point; it is of note, therefore, that fewer cardiac deaths or cases of nonfatal myocardial infarction from “harder” end points were observed (70 *versus* 104, a risk reduction of 35%;  $P = 0.005$ ). The ALERT trial also found no significant effect of statin treatment on graft loss<sup>6</sup> or graft function,<sup>7</sup> in line with findings that fluvastatin fails to prevent renal transplant vasculopathy,<sup>8</sup> and in contrast to the positive finding of a past retrospective single-center study of protection by statins against acute graft rejection in sirolimus-treated patients<sup>9</sup> and despite animal experiments suggesting benefit on chronic allograft nephropathy.<sup>10</sup> Although a relation between lipid concentrations and loss of kidney function was observed in patients with primary kidney disease,<sup>11</sup> in the setting of kidney transplantation, lipid concentrations do not seem to play a major role in the genesis of renal function loss.

*Post hoc* analyses of the ALERT study are also consistent with cardiovascular benefit. In this cohort of graft recipients, early initiation of lipid-lowering therapy had a more favorable effect on cardiac events than late intervention.<sup>12</sup> Interestingly, lowering of LDL cholesterol by 1 mmol/L reduced cardiac death or myocardial infarction by approximately 30%<sup>13</sup> in this admittedly small sample, even more intensely than the 19% that the collaborative cholesterol-lowering trialists found.<sup>14</sup> The surprising magnitude of the effect might have been influenced by co-medication with cyclosporine, which in a recent study reduced acute infarction size.<sup>15</sup>

Wiesbauer *et al.*<sup>16</sup> in this issue of *JASN* assessed a total of 2041 kidney graft recipients—all patients who underwent transplantation between 1990 and 2003. Of these registry patients, 302 used statins at baseline and 1739 did not. Because this is a nonrandomized, observational study, it is important to mention that the two groups differed with respect to parameters (all more unfavorable in the statin-treated patients regarding cardiovascular disease burden and risk factors, the number of HLA mismatches, and, importantly, age, which mainly accounted for the failure to see a significant effect with unadjusted data). Despite the worse cardiovascular risk profile, the 12-yr survival rate was numerically higher in statin users than in non-users (73 versus 64%; unadjusted  $P = 0.055$ ). Of the deaths that occurred after 90 d, cardiac causes accounted for 26%. Statin use was not associated with decreased overall mortality by univariate analysis, but statistical significance was achieved by accounting for confounding by multivariate analysis (hazard ratio 0.64 95% confidence interval 0.48 to 0.86;  $P < 0.003$ ). In general, one has to be cautious in interpreting study results for which the overall difference is NS, but the major cause for failure to achieve significance with the unadjusted data was the higher age in the statin users (in the Collaborative Transplant Study [CTS] a similar survival difference was also seen only after multivariate adjustment; G. Opelz, Department of Immunology, Heidelberg, personal communication, September 4, 2008). No significant effect was found with respect to long-term graft survival. This finding is in line with the past observation that pravastatin had no effect on acute rejection<sup>17</sup> and the long-term results of the effects of statins in the CTS.

There is, of course, information on the use of statins in recipients of other organ grafts, specifically cardiac grafts, which is also of potential interest with respect to pathophysiology and outcome in renal transplantation. After heart transplantation, statins reduced mortality in several studies.<sup>18,19</sup> In one 4-yr randomized trial of simvastatin, LDL cholesterol was lowered from 156 to 115 mg/dl, and survival was higher (88.6%) in statin users than in non-statin users (70.3%).<sup>20</sup>

Experimental studies provide fascinating novel insights into how statins may affect ischemic heart disease. More

conventional findings include the observations that in a murine model of cardiac transplantation, atorvastatin reduced coronary atherosclerosis, infiltration by inflammatory cells, and expression of TGF- $\beta$  and adhesion molecules.<sup>21</sup> Lipophilic statins also suppress cytotoxicity of natural killer cells.<sup>22</sup> In patients with coronary artery disease, statins improve impaired differentiation of endothelial progenitor cells into cardiomyogenic cells,<sup>23</sup> promote neovascularization,<sup>24</sup> and reduce oxidative stress through S-nitrosylation and activation of thioredoxin in endothelial cells.<sup>25</sup> This is of interest, because atorvastatin therapy also improves endothelial dysfunction after renal transplantation.<sup>26</sup> Furthermore, in the model of apolipoprotein E knockout mice with renal failure, statins reduced vascular calcification by decreasing oxidative stress and cholesterol independently,<sup>27</sup> which is of some interest in view of the high prevalence of coronary calcification in kidney graft recipients.

The good news in the article by Wiesbauer *et al.*<sup>16</sup> is statin use in this nonrandomized registry population had a beneficial effect, a welcome addition to the results of the presumably underpowered prospective ALERT study, in which the primary end point was negative but the *post hoc* analyses of subgroups yielded positive results.<sup>5</sup> The bad news is such observational data have important limitations. Here we mention two potential limitations: A center effect and survivor or comorbid effect.

First, only a few centers in Austria offer transplantation services. Posttransplantation surveillance may be in the hands of different specialties (internists or surgeons) having different treatment and LDL target policies, ranging from treatment of a few patients with low-dosage statins to all patients on a “polypill.” The outcome theoretically may not reflect statin treatment but the level of care. Second, patients develop end-stage renal failure at different rates of progression (rapid, slow), whether exposed or not exposed to a nephrologist (late referral), and with or without statin treatment before transplantation. One cannot quantify these factors, but what we know from the registry data is that statin users were significantly longer on dialysis than non-statin users, were older, and had a higher burden of cardiovascular disease. Impressively, despite more comorbidity and longer time on dialysis, mortality was lower. Nevertheless, hidden confounders (not accounted for by the multivariate model: Statin treatment before transplantation or discontinuation of treatment) might theoretically have an impact in the registry sample<sup>16</sup>; that is, any unknown effect including unquantifiable bias of indeterminate direction and origin may influence the result. Because of the lack of randomization, registry data do not definitely prove causality of statin treatment.

What practical conclusions can one draw from these findings? A major argument in favor of statins is that treatment is remarkably safe,<sup>4,5</sup> so treatment carries very little risk for damage. With respect to treatment recommenda-

tions, it is our view the very strong data of cardiac transplantation studies should also be taken into consideration: In view of such data, kidney graft recipients should not be denied the likely benefit of statin treatment, although the benefit still remains to be rigorously proved.

## DISCLOSURES

None.

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See related article, "Statin Use Is Associated with Prolonged Survival of Renal Transplant Recipients," on pages 2211–2218.

## Is the ER Stressed out in Diabetic Kidney Disease?

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Despite decades of concerted mechanistic research, the pathogenesis of progressive diabetic nephropathy remains uncertain. Although improved glycemic control and treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers ameliorate the progression of diabetic nephropathy to end-stage kidney disease, the mechanisms for such salutary effects have not been clearly identified and are likely myriad. Moreover, these interventions do not forestall progression of disease, at least in the majority of sufferers, but merely retard it. Thus, new insights into the mechanisms of this disease will be critical so that additional and more effective therapies can be discovered.

In this issue of *JASN*, Cohen and Schlöndorff and colleagues<sup>1</sup> provide such an insight by demonstrating the induction of a number of genes that are involved in endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) in tubulointerstitial cells of kidney biopsies from humans with progressive diabetic nephropathy compared with similar regions from normal individuals and those with early diabetic nephropathy or minimal-change disease. ER stress is caused by any physiologic, pathophysiologic, or pharmacologic stimulus that increases the demands on the ER to synthesize proteins or degrade improperly folded proteins. These stimuli trigger the UPR, which reduces the amount of nascent protein that enters the ER

lumen, increases ER capacity to fold protein through enhanced transcription of genes of ER chaperones and folding catalysts, and induces degradation of misfolded and aggregated proteins.<sup>2</sup> With massive ER stress, these prosurvival aspects of the UPR can be superseded by proapoptotic aspects, leading to programmed cell death.<sup>2</sup>

In their article in this issue, the investigators demonstrate increased expression of several genes for protective ER chaperone proteins as well as increased expression of a prosurvival gene for a basic leucine zipper-containing transcription factor X-box binding protein 1 (XBP1) in tubulointerstitial cells in two independent sets of patients with progressive diabetic nephropathy. In contrast, they found no induction or even suppression of genes for proapoptotic features of the UPR. Although there have been several previous reports of induction of UPR in podocytes and other kidney cells by high glucose, albumin, or other compounds found in diabetic plasma and glomerular filtrate,<sup>3–5</sup> the article by Cohen and Schlöndorff and colleagues<sup>1</sup> is the first to show induction of UPR genes in human diabetic nephropathy.

That ER stress is responsible for diabetic injury is not a new concept. A plethora of reports show that high glucose and free fatty acids in patients with diabetes can induce ER stress and UPR gene induction in pancreatic  $\beta$  cells (for recent reviews see references<sup>2,6–12</sup>). The  $\beta$  cell is particularly susceptible to ER stress because it makes nearly 1 million proinsulin molecules per minute<sup>2</sup> and any increase in this demand, such as with insulin resistance, can lead to accumulation of unfolded protein and cause  $\beta$  cell failure and frank type 2 diabetes.

In a similar vein, diabetes triggers ER stress and the UPR in proximal tubular cells as a result of exposure to high glucose, free fatty acids, and other features of the diabetic milieu. Because induction of the same genes was much less dramatic in minimal-change disease, it is likely that a combination of factors in addition to exposure to filtered proteins is responsible. The investigators found that a combination of elevated albumin and glucose levels induce some of the same UPR genes in cultured proximal tubular cell lines that were enhanced *in vivo*. The substantial augmentation of oxidative stress in diabetic tubuli is one likely responsible factor for these effects.<sup>13</sup> Oxidative stress clearly induces ER stress and *vice versa*.<sup>14</sup> Indeed, ER stress can induce oxidative stress in pancreatic  $\beta$  cells, and a similar process may contribute to enhanced oxidative stress in diabetic nephropathy.<sup>15</sup>

The finding of increased mRNA levels for genes involved in the protective responses of the UPR but not for proapoptotic genes suggests that the ER stress found in the tubulointerstitial cells in these patients with progressive diabetic nephropathy is adaptive and sustainable. Indeed, physiologic activation of the UPR often selectively enhances the prosurvival aspects of the response.<sup>16</sup> This pattern is consistent with adaptive *versus* terminal UPR activation and seems

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