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Cardioprotective role of statins in chronic kidney disease: do we have the answer?

Bengt C. Fellström[1]

The observational study by Szummer *et al.* shows that patients with advanced chronic kidney disease (CKD) are treated less with statins after myocardial infarction, even though statins benefit survival in CKD classes 1–4. The study's limitations are obvious, but such a population may be more representative. The results indicate that statins should be used more frequently after myocardial infarction in CKD classes lower than 5, a conclusion supported by the recently presented Study of Heart and Renal Protection (SHARP).

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The use of statins in the general population to reduce cardiovascular risk and patient mortality has been very well documented (Figure 1). However, most of these studies have systematically excluded patients with renal failure. In patients with chronic kidney disease (CKD) and, especially, end-stage renal disease, the mortality rate from cardiac disease and the burden of peripheral vascular disease are substantial compared with those in the nonrenal population. *Post hoc* analyses from statin studies in the general population, including primary- and secondary-prevention studies, have demonstrated that patients with moderately reduced renal function may benefit from the use of statins, leading to a reduction in cardiac or cardiovascular events.[1,2] Still, these *post hoc* reports with fairly small subgroups of patients are not powered to make these claims. In addition, studies such as the renal Treating to New Targets (TNT) trial compared different doses of statins, showing a greater risk reduction with a higher dose and an effect size that seemed larger than that seen in the group with glomerular filtration rate (GFR) greater than 65 ml/min.[3]

[1]*Department of Nephrology, Uppsala University, Uppsala, Sweden*

Correspondence: *Bengt C. Fellström, Department of Nephrology, Uppsala University, SE-75185 Uppsala, Sweden. E-mail: bengt.fellstrom@medsci.uu.se*

Similarly, there is a paucity of studies in the renal transplant population. Seven years ago, the first such study in renal transplant patients was published,[4] showing that the combined end point of cardiac death or nonfatal myocardial infarction (MI) was significantly reduced. Furthermore, the primary end point of major adverse cardiac events was also significantly reduced in the extended study with 2 more years of follow-up.[5] However, the primary end point of major adverse cardiac events was negative in both the Deutsche Diabetes Dialysis (4D) Study in diabetic patients on hemodialysis treatment[6] and the AURORA trial,[7] two large-scale randomized controlled trials in hemodialysis patients. In a *post hoc* analysis of the AURORA trial, diabetic patients appeared to do better on a statin with respect to cardiovascular end points.

Szummer *et al.*[8] (this issue) performed an observational study of data in the SWEDEHEART registry, including more than 42,000 patients admitted to Swedish cardiology intensive care units for MI from 2003 to 2006. The authors investigated statin use and its effects in relation to renal function following discharge of survivors. The use of statins at discharge was significantly lower in patients with renal failure than in those with normal renal function: 81% in CKD class 1 (GFR >90 ml/min), 29% in CKD 4 (GFR 15–30 ml/min), and 31% in CKD 5 (GFR <15 ml/min or patient on dialysis). The 1-year follow-up on mortality demonstrated a significant interaction between a reduction in mortality at 1 year (registry data) and a decreasing GFR ($P<0.0001$), interesting results since they demonstrate a larger effect size with better renal function. The overall reduction of mortality risk by statins was 37%. Even in CKD 4, there was a significant 1-year mortality risk reduction of 27%, whereas in CKD 5, there was no effect at all, but a trend toward increased risk.

Of course, this observational study has limitations, as treatment was not randomized, and the study lacks a control arm. The authors attempted to adjust for potentially important confounding factors by defining a propensity score with a large number of factors for statin and nonstatin treatment. Still, there were clear findings about effect dependence on renal function. A sensitivity analysis for missing data did not change the overall results. Furthermore, the outcome is limited to mortality based on death registries; no other cardiovascular end point, such as cardiac or cardiovascular morbidity or mortality, was captured in this study. In addition, there was no independent critical events committee to adjudicate the end points occurring in the study.

The advantage of such an observational study is that the cohort may be more representative of the real population than when patients are entered into a controlled, randomized study with exclusion and inclusion criteria. The findings of Szummer *et al.*[8] are interesting in that sense, notwithstanding the limitations of a non-randomized trial.

In a previous communication regarding the same registry, the authors also identified the likelihood that active interventional treatment of MI using percutaneous transluminal coronary angioplasty, stenting, or coronary artery bypass grafting was related to renal dysfunction at admittance, showing that the eligibility for active intervention decreased substantially with the degree of renal failure.[9] Intervention was given to only 15% of patients with advanced renal failure (CKD 5), as

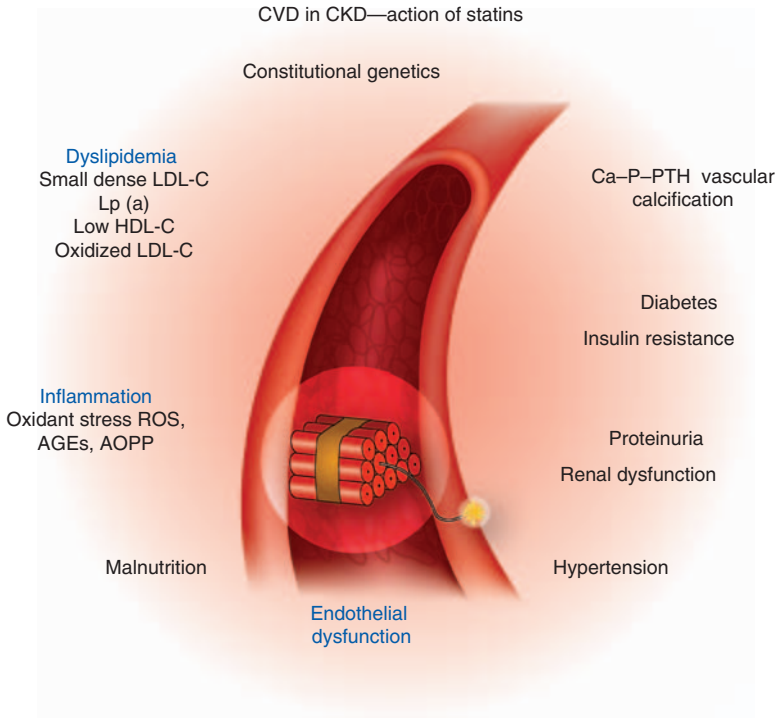

Figure 1 | Factors influencing the accelerated cardiovascular disease (CVD) in chronic kidney disease (CKD). Factors potentially targeted by statins are highlighted in blue (dyslipidemia, inflammation, and endothelial dysfunction). AGEs, advanced gylcosylation end products; AOPP, advanced oxidation protein products; Ca, calcium; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); P, phosphorus; PTH, parathyroid hormone; ROS, reactive oxidative species.

compared with 62% of those with normal renal function. However, the benefit declined with lower renal function.

The largest-ever statin trial in renal patients is the Study of Heart and Renal Protection (SHARP),[10] in which 9438 CKD patients were randomized—6382 predialysis patients and 3056 dialysis patients, of whom 2540 were on hemodialysis and 496 on peritoneal dialysis. They were treated with either 20 mg simvastatin plus 10 mg ezetimibe or placebo over 4.9 years of follow-up and showed a 16.5% overall risk reduction ($P<0.0022$) in the primary atherosclerotic end point (the primary end point was changed in 2009 before unblinding). In addition, the original end point of major adverse cardiac events was positive, with a 16.1% risk reduction ($P<0.0010$). It seems as if there may be a higher effect size in predialysis than in dialysis patients with CKD, about 20% versus about 10%, according to the presentation at the ASN, and data on the website of SHARP. But apparently no significant interaction was observed between the two subgroups ($P=0.25$), indicating that they should be treated as one cohort. In the dialysis cohort alone, the effect seems to be a non-significant risk reduction of about 10% in dialysis patients, which is in accordance with the two previous statin trials in dialysis patients (8% in the 4D Study and 4% in AURORA, not significant); the low-density lipoprotein reduction was of similar magnitude in the three studies, or even a bit higher in AURORA (1.1 mmol/l) and 4D (1.3 mmol/l) than in SHARP (0.85 mmol/l). Unfortunately, no publication is available at the moment from SHARP, and thus the medical community has to confine its opinion to what has been presented at the American Society of Nephrology and uploaded to the SHARP website (www.sharpinfo.org). No substudy has been presented yet to show whether division into subgroups by low-density lipoprotein level influences the outcome. A publication is under way, however.

In summary, the observational study by Szummer *et al.*[8] based on the SWEDEHEART registry demonstrates that renal patients are less likely to receive statin treatment upon discharge from the hospital after an acute MI and that this is strongly related to the degree of renal dysfunction, despite the fact that an effect on survival at 1 year seems to be present in CKD 1–4 (GFR >15 ml/min), as well as a less obvious effect in CKD 5. The limitations of such an observational, unrandomized design need to be recognized, but it should also be appreciated that in such studies the patients may be more representative of a real patient population. The results indicate that statins should be used more frequently than they are after MI, at least in CKD classes lower than 5. This view gains support from the recent SHARP trial, the largest-ever randomized primary-prevention statin trial in renal patients.

DISCLOSURE
The author declared no competing interests.

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