EDITORIAL

Should all patients with chronic kidney disease take a statin? A commentary to a meta-analysis of randomized control trials

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Chronic renal failure (CRF) is associated with dyslipidemia.[1] In advanced stages of CRF a paradoxical reverse relation is seen between low cholesterol and high cardiovascular risk ("reverse epidemiology").[2] Because of the high cardiovascular risk in patients with chronic kidney disease (CKD), there has been considerable interest in treating this condition with statins. There has also been considerable concern, however, with respect to side effects[3], hepatotoxicity and particularly rhabdomyolysis; this concern had been heightened after the respective problems with cerivastatin.[4]

Unfortunately, the desirable one big trial in predialysis CKD as well as in dialyzed or kidney transplanted patients is not available which would resolve all issues. It was therefore of some interest to combine the available literature and perform a meta-analysis to estimate the relative risk reduction in the different stages of CKD: Thus in the absence of definite evidence the results can at least provide helpful suggestions for the management of dyslipidemia in these patients.

Currently available evidence: 50 randomized or quasi randomized and placebo controlled trials of statins comprising 30,087 patients were included in the metaanalysis of Strippoli.[5]

Reduction of lipids: Overall, statins significantly reduced total cholesterol by 42.3 mg/dl and low-density lipoprotein (LDL) cholesterol by 43.1 mg/dl.

Reduction of proteinuria and progression of nephropathy: Because of some positive animal experiments[6] it had been expected that statins not only reduce cardiovascular endpoints, but also interfere with proteinuria and with progression of nephropathy. Against this background, it is of note that in this meta-analysis in 6 small trials comprising 311 patients proteinuria was reduced by 0.73 g/24 h, while glomerular filtration was not reduced at all.

Reduction of cardiovascular endpoints: As to cardiovascular endpoints, fatal cardiovascular events were significantly lowered in CKD patients who were not yet on dialysis; the relative risk was 0.78 (0.73–0.84), whilst no significant effect was found on all-cause mortality (RR 0.92, 0.82–1.03).

Side effects: There was no significant evidence of more side effects compared to placebo.

There are several *problems* with this meta-analysis. With respect to the overall data included the metaanalysis was certainly underpowered. CKD is a high cardiovascular risk condition[7], but nevertheless the total number of subjects was undoubtedly not sufficient to detect a significant effect on overall mortality. The average duration of exposure to statins in these studies was 3 years, whilst real-life exposure to statins may be up to decades.

On the positive side the authors adhered to rigorous criteria – 2 authors independently reviewed the literature and extracted data on the following items: all cause mortality, fatal cardiovascular and cerebrovascular events as well as non-fatal cardiovascular and cerebrovascular events (myocardial infarction, stroke, sudden death, composite), endstage renal disease, doubling of serum creatinine, lipid concentrations, creatinine clearance and 24-hour urinary protein excretion. The relative risk was calculated for dichotomous data and continuous measurements were presented as weighted mean differences.

The authors' criteria led to the exclusion of 819 of the 869 articles, mainly because they were not randomized controlled trials leaving a meagre 50 randomized controlled trials or subsets of randomized controlled trials (54 comparisons). These trials concerned predialysis CKD patients (n = 26), hemodialysis or peritoneal dialysis patients (n = 11) and transplant recipients (n = 17).

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Actually, the greatest piece of evidence for CKD came from only few cohorts: the PPP trial (Pravastatin Pooling Project), the CARE trial (Cholesterol and Recurring Events), the LIPID trial (Long-Term Intervention with Pravastatin in Ischemic Disease) and the WOSCOPS trial (West of Scotland Coronary Prevention Project Study). In these studies all included patients who met the criteria of CKD were assessed, although specific randomisation for CKD was of course not performed. The evaluation is therefore a posthoc analysis with all its limitations.

In the studies on predialysis patients further heterogeneity comes in with respect to the primary kidney diseases: diabetic nephropathy (n = 6), hypertensive nephropathy (n = 2), polycystic kidney disease (n = 1) and other forms of nephrotic or non-nephrotic glomerulonephritis.

For hemodialysed patients only one study was available which included a the relatively specific group of patients namely type 2 diabetics (Die Deutsche Diabetes Dialyse Studie – 4D).

For patients with kidney transplants only the ALERT trial (Assessment of Lescol in Renal Transplantation) was available.

As expected, the data quality precluded strong statements for most questions.

As to the *lipid lowering efficacy* of statins: LDL cholesterol was lowered by an average of 43.1 mg/dl with significant heterogeneity between the different statins, no significant effect on high-density lipoprotein was seen, a significant reduction of triglycerides was found in all patient groups (–23.7 mg/dl) except the (diabetic) dialysis patients.

With respect to *renal endpoints*, 24 h urinary protein excretion in CKD patients decreased by an average of 0.73 g/24 h but no significant change of creatinine clearance was noted.

With respect to the *cardiovascular risk*, 43 trials with no statistically significant heterogeneity showed an approximately 20% reduction of cardiovascular mortality and also an approximately 20% decrease in the risk of non-fatal cardiovascular events. All-cause mortality was not significantly affected.

In allograft recipients no significant reduction of acute allograft rejection within 3 months post transplantation was noted (in contrast to some reports on cardiac transplantation).

The key findings can be summarized with the statement that:

1) statins cause well documented benefit concerning lipid lowering, reduction of cardiovascular events and reduction of proteinuria in CKD patients
2) major side effects were not seen, specifically no rhabdomyolysis (with the exception of the withdrawn agent, cerivastatin) and no hepatotoxicity, attesting to the safety of statins.
3) the cardiovascular benefit is broadly equivalent to that seen in non-renal patients included in cardiological studies.

One issue remains undecided, i.e. whether patients on hemodialysis should routinely be treated with statins. The opinions are divided and range from the suggestion to treat routinely [8] to the advise to treat at least dialysed patients with manifestations of coronary heart disease, leaving undecided the issue whether primary treatment of asymptomatic patients should be considered.[1] Statistical "purists" argue that because of the apparently "negative" outcome of the 4D study dialysed patients should not be treated with statins. It is of note, however, that – as described elsewhere – 10% less myocardial infarction was seen in the 4D study per 1 mmol/l lower LDL cholesterol, the same reduction as seen in previous trials in cardiological patients.[1] The sceptics will have to wait, however, until the results of the AURORA[9] and SHARP trials[10] are in.

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