

Statins and the kidney

Beneficial effects of statins on the kidney

B Afzali, D J A Goldsmith

Insights from GREACE

In healthy humans, a normal decline in renal function begins soon after maturity and constitutes a fairly constant decrease in glomerular filtration, which averages 8 ml/min lost glomerular filtration rate (GFR) (6%) for each decade after the age of 40.¹

Prevention of the development or progression of chronic renal failure is the holy grail of nephrology. Success will depend in part on the screening and detection of underlying renal disorders but systemic diseases, namely hypertension and diabetes mellitus, remain the "big players" in the causation of end-stage renal failure. Early detection of renal disease is very feasible in both settings using microalbuminuria as a marker of increased cardiovascular and renal risk. Although there are many effective interventions, organisational (health service resource allocation) and motivational (because alterations to patients' lifestyles are often required) challenges often need to be overcome first.

The association between raised blood pressure and adverse renal outcome in hypertension² and in diabetes³ has become universally accepted, with control of blood pressure now being the cornerstone of "nephroprotection".⁴ Angiotensin converting enzyme inhibitors and angiotensin receptor blockers have achieved pre-eminent status among antihypertensive drugs, with suggestions that their actions go further than can be explained by a reduction of blood pressure alone.⁵ However, several other important risk factors for the development of renal failure have been identified that, independently or in concert with blood pressure, can cause renal deterioration.⁶ These include sex, smoking, proteinuria, and dyslipidaemia.⁴

One of the paradoxes in renal medicine has been the enormous amount of experimental, mainly murine, evidence that dyslipidaemia leads to glomerulosclerosis (reviewed in detail in Oda and Keane⁷ and Buemi and colleagues⁸) in contrast to the dearth of epidemiological or trial based evidence that reversal of dyslipidaemia in humans is nephroprotective. Rare conditions, such as morbid

obesity, have been shown to be associated with focal glomerulosclerosis, but it is hard to generalise this information, except possibly in the USA.⁹ Nevertheless, because the similarities between atherosclerosis and glomerulosclerosis are compelling,¹⁰ it stands to reason that the beneficial effects of statins on cardiovascular disease may also be generalised to the kidney.

Several recent trials in hypertensive/dyslipidaemic cohorts, many of whom had mild to moderate chronic renal impairment, have now begun to address this apparent paradox, and the results of such a trial are reported by Athyros *et al* in this issue of the journal.¹¹

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The Greek atorvastatin and coronary-heart-disease evaluation (GREACE) trial examined the use of atorvastatin at doses aimed to achieve pronounced reductions in low density lipoprotein cholesterol in 1600 Greek patients with established coronary heart disease.¹² Eight hundred were allocated to atorvastatin (median dose, 24 mg), and 95% of these subjects achieved the lipid reduction goals (low density lipoprotein cholesterol falling by 45–50% and high density lipoprotein cholesterol rising by 7%). In comparison to "usual" care, the use of atorvastatin reduced total mortality (relative risk (RR), 0.57; confidence interval (CI), 0.39 to 0.78; $p = 0.0021$), coronary mortality (RR, 0.53; CI, 0.29 to 0.74; $p = 0.0017$), coronary morbidity (RR, 0.46; CI, 0.25 to 0.71; $p < 0.0001$), and stroke (RR, 0.53; CI, 0.30 to 0.82; $p = 0.034$). Renal function was examined in this study using Cockcroft-Gault derived creatinine clearance (CrCl) values.¹¹ The mean CrCl at entry was 77 ml/min. Patients on atorvastatin showed a 12% rise in CrCl, patients on other statins a 4.9%

rise in CrCl, and statin free patients a 5.2% fall in CrCl over 36 months of follow up. The effect on CrCl was evident from as early as six weeks, there was a clear dose-response relation, and those with the lowest CrCl at entry showed the greatest relative improvement with atorvastatin treatment. Other potentially important factors such as blood pressure, antihypertensives, sex, and smoking were well balanced across the two groups.

Similarly, the CARE study was a randomised trial of pravastatin versus placebo in 4159 subjects with hyperlipidaemia and a previous history of myocardial infarction.¹³ Patients were prospectively followed up for 60 months, with end-points being major adverse cardiovascular events. A change in renal function could be calculated in 3384 subjects, of whom 690 (20.4%) had modification in diet in renal disease GFR of < 60 ml/min/1.73 m². A stepwise inverse relation between pretreatment GFR and deceleration of renal dysfunction with pravastatin was demonstrated, and most benefit was seen in those with lower GFR at baseline (the pravastatin group who had a baseline GFR < 40 ml/min had a 2.5 ml/min/1.73 m² slower renal decline than the placebo group, compared with 1.3 ml/min/1.73 m² for the group with GFR > 40 ml/min). Proteinuria at baseline was also associated with a much greater protective effect of pravastatin use.¹⁴

One of the largest statin based cardiovascular disease prevention trials was the heart protection study.¹⁵ Adults aged 40–80 years with previous cardiovascular disease or diabetes were allocated either placebo or 40 mg simvastatin daily. All cause mortality was reduced in the treatment arm (1328 (12.9%) deaths among 10 269 allocated simvastatin v 1507 (14.7%) among 10 267 allocated placebo; $p = 0.0003$) as a result of a highly significant 18% (SE, 5%) proportional reduction in the coronary death rate (587 (5.7%) v 707 (6.9%); $p = 0.0005$).

The 5903 patients with diabetes in this trial were further studied and compared in more detail with the 14 573 non-diabetic subjects. Unadjusted serum creatinine concentrations increased for all patients, with or without diabetes, over a period of 4.6 years; however, allocation to simvastatin significantly reduced the rise in serum creatinine in both cohorts.¹⁶

Abbreviations: CI, confidence interval; CrCl, creatinine clearance; GFR, glomerular filtration rate; GREACE, Greek atorvastatin and coronary-heart-disease evaluation; RR, relative risk

When these data from large cohorts are combined with those from trials evaluating the use of statins in subjects with significant proteinuria and diverse renal pathologies/renal impairment a stronger picture emerges. Fried *et al* undertook a meta-analysis of 13 controlled trials in 404 subjects.¹⁷ Despite the small numbers of subjects in each trial, when the outcomes were pooled it was shown that the use of lipid lowering treatment (mainly, but not exclusively, statins) was associated with a protective effect on renal function loss. There was a lower rate of decline in GFR with treatment compared with controls (treated patient' renal function declined at a rate of 0.156 ml/min/month; 95% CI, 0.026 to 0.285 ml/min/month; $p = 0.008$). The study results were statistically homogeneous, and in a regression analysis, the effect of treatment on the GFR did not correlate with study quality, the percentage change in cholesterol, the type of lipid lowering agent, or the cause of renal disease.

Most of the subjects had either diabetes and/or nephrotic syndrome, and although the degree of renal impairment was similar, the rate of renal decline shown by these subjects was greater than that seen in hypertensive/dyslipidaemic populations without a primary renal pathology (typically, < 0.1 ml/min/month).

“It is now clearer than ever before that there are compelling reasons to use statins in patients with chronic renal failure to achieve both nephroprotection and cardioprotection”

Finally, it must be remembered that mild chronic renal failure and, separately but additively, microalbuminuria, are associated with a pronounced increase in susceptibility to cardio-

vascular disease.^{18, 19} Indeed, the risks conferred by chronic renal failure and proteinuria are comparable to left ventricular hypertrophy and diabetes, with patients at the same risk of future adverse cardiovascular events as those with a previous cardiovascular history. In other words, this is a form of “secondary” prevention (both renal and cardiovascular) because the “primary” event was the development of proteinuria or renal impairment.

Using this latest evidence from the GREACE trial, it is now clearer than ever before that there are compelling reasons to use statins in patients with chronic renal failure to achieve both nephroprotection and cardioprotection. On this basis, the question should now be asked of someone in chronic renal failure: why is this patient not yet on a statin?

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