From Finland to Fatland: Beneficial Effects of Statins for Patients with Chronic Kidney Disease

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After maturity, healthy humans exhibit an age-dependent physiologic decline in renal function, amounting to an average of 0.75 ml/min lost GFR per year after the age of 40 (1). In the situation of chronic renal failure (CRF), accelerated renal decline supravenes irrespective of the underlying cause, indicating a final common pathway after the initial insult (Figure 1). In CRF caused by diabetes, for example, variable losses of 2 to 20 ml/min per yr have been reported (2–4).

The prevention of development of chronic renal impairment (CRI) is the aim of nephrologists. Sometimes this goal cannot be achieved easily partly because renal pathology is occasionally familial, such as in Alport’s syndrome or adult polycystic kidney disease (ADPKD), for which there is no specific therapy and no evidence of improved outcome through screening. Conversely, the systemic disorders, namely hypertension and diabetes, which remain the most common causes of end-stage renal failure, often present at a point when microalbuminuria, an early marker of renal disease and of increased cardiovascular risk, has already developed. Therefore, the emphasis is very much on early intervention to decelerate the rate of decline once CRF is established. Many factors (5) are now known to influence the progression of renal decline. Some, such as gender, are not open to adjustment, whereas others, including smoking, proteinuria, and hypertension (5,6), may be modified. Undoubtedly, the best evidence comes from the association between elevated BP and adverse renal outcome in both diabetic (7) and nondiabetic (8,9) patients. Successful reduction in BP improves renal outcome and is now the cornerstone of nephroprotection (6), with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers achieving primus inter pares status given that their actions seem to go further than can be explained by reduction of BP alone (10).

Animal models have clearly demonstrated that dyslipidemia is causally associated with glomerular injury and leads to the development of glomerulosclerosis. Elegant murine experiments that fulfill Koch’s postulates (11–16) support this assertion but, although highly interesting, fall outside the remits of this review. In summary, spontaneously hyperlipidemic rats and rats fed high-cholesterol diets are at increased risk of developing glomerulosclerosis, whereas lipid-lowering therapy and lipid-knockout mice are protected.

In humans, however, isolated hyperlipidemia, for example in conditions of familial hypercholesterolemia, does not seem to cause glomerulosclerosis, and there is no epidemiologic or trial-based evidence that reversal of dyslipidemia is nephroprotective in humans. In many ways, this is suggestive of interspecies differences in the susceptibility of the kidney to hyperlipidemia. With established CRF, an association between hyperlipidemia and progression of CRF has been documented in small series in the past (17), with data from conditions such as morbid obesity (rare except in the fatlands of North America) suggesting an association with focal glomerulosclerosis (18).

Post hoc analyses of several recent trials in hypertensive/dyslipidemic cohorts, many of whom had mild CRI, have helped to elucidate much of this paradox. In interpreting these post hoc analyses, it is important to exercise considerable caution as significant inaccuracies may accrue and there is increased risk of type I errors. It is the purpose of this review to examine the present state of evidence linking dyslipidemia and its treatment to renal functional decline. In addition, we explore other ways in which cardiovascular benefit may accrue to patients who have chronic kidney disease and are on statin therapy.

Functions of Statins (3-Hydroxy-3-Methylglutaryl CoA Reductase Inhibitors)

The mevalonate pathway (Figure 2) is important not only for cholesterol synthesis but also for cell-signaling processes. Statins, as inhibitors of the rate-limiting enzyme 3-hydroxy-3-methylglutaryl CoA (HMG CoA) reductase, have become one of the most successful pharmacologic interventions of the past decade for primary and secondary prevention of cardiovascular disease (CVD). The evidence that these drugs are effective and valuable is overwhelming (reviewed in detail in reference 19), leading to their almost universal use among cardiologists. Not only are the benefits of statins related to their cholesterol-lowering function, but also secondary effects (20) on cell signaling, anti-inflammation (21,22), cell proliferation, plaque stabilization (23), and improvement of endothelial function (24) all are thought to occur by inhibition of the mevalonate pathway.
Observational Associations between Dyslipidemia and Decline of Renal Function

Post hoc analyses of several large trials have recently evaluated the role of dyslipidemia on renal outcome over time. The first trial was from Finland—the Helsinki Heart Study—in which 2702 dyslipidemic (non-HDL cholesterol [non–HDL-C] >5.2 mmol/L) white men with normal renal function (creatinine <115 μmol/L) were recruited (25). However, in the end, 30 subjects with plasma creatinine between 116 and 135 μmol/L were included. A total of 4081 men were randomized to gemfibrozil (1200 mg/d) or placebo, and all were given dietary counseling to lower cholesterol. The patients were followed up for 5 yr and monitored for the occurrence of any cardiovascular event. The decline in renal function was estimated over time. During the study period, there was a monotonic increase in the mean serum creatinine levels in both gemfibrozil and placebo groups, averaging 3% (an increase of ~5 to 6 μmol/L). Hypertension accelerated renal functional decline significantly (~8 μmol/L for systolic BP >160 mmHg compared with ~5 μmol/L for systolic BP <140 mmHg). Participants with an elevated LDL to HDL ratio (>4.4) had a 20% faster decline than those with a ratio of <0.2. Both the contribution of the lipoprotein ratio and the protective effect of increased HDL-C alone remained significant after multiple regression analyses. As expected, hypertension and unfavorable lipoprotein ratios interacted as risk factors for deterioration of renal function.

The second major trial that shed light on the relation between dyslipidemia and renal dysfunction was The Physicians’ Health trial, in which 4483 healthy men were recruited and followed prospectively between 1982 and 1996. The primary end points were elevated serum creatinine, defined as >1.5 mg/dl (133 μmol/L), and reduced estimated creatinine clearance (CrCl), defined as <55 ml/min. Cholesterol parameters included total cholesterol (<200, 200 to 239, and >240 mg/

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terol, high non-HDL-C, and the ratio of total cholesterol to HDL. A multivariate regression analysis model adjusting for age and other confounding variables (smoking, BP, and body mass index) was used to calculate the odds ratio. After 14 yr, 134 (3.0%) men had elevated creatinine and 244 (5.4%) had reduced CrCl. The relative risk (RR) for elevated creatinine was 1.68 for total cholesterol >240 mg/dl, 2.12 for HDL <40 mg/dl, 2.22 for the highest quartile of total cholesterol/HDL ratio (>6.8), and 2.03 for the highest quartile of non–HDL-C (>196.1 mg/dl). Therefore, elevated total cholesterol, high non–HDL-C, a high ratio of total cholesterol to HDL, and low HDL in particular were significantly associated with an increased risk of developing renal dysfunction in men with an initial creatinine of <133 μmol/L (26).

The third trial to shed light on this area was a prospective trial of 574 patients who were aged 40 to 60 yr and had recent-onset type 2 diabetes but without overt nephropathy and were followed for 2 to 9 yr. Multiple stepwise regression analysis showed that total cholesterol, mean BP, and hemoglobin A1c (HbA1c) were the only independent predictors of the decrease in renal function and the increase in albuminuria. A high-risk population was defined as having a combination of total cholesterol, mean BP, and HbA1c higher than the 50th percentile. These high-risk patients had an odds ratio of 43 (95% confidence interval, 25 to 106) for microalbuminuria and 15 (95% confidence interval, 9 to 25) for clinical events related to arteriosclerosis compared with the rest of the group (27).

Although these trials and others have examined the interaction between dyslipidemia and change in renal function, some of the effects reported have been fairly modest. Clearly, post hoc analyses such as these are also limited by the problem of unmeasured confounding by other risk factors that are closely correlated to dyslipidemia. For example, in a post hoc analysis of the Atherosclerosis Risk in Communities study (28), in a population of 12,728 hyperlipidemic subjects with initially normal serum creatinines, hypertriglyceridemia and low HDL-C were found to be associated with a temporal increase in creatinine, an association that was considerably attenuated after adjustment for measures of insulin resistance. This may be indicative of a role for other aspects of the “metabolic syndrome” that might explain the apparent association between high HDL/low triglyceride and the risk of renal insufficiency.

Role of Statins in the Treatment of Dyslipidemia in Patients with Normal or Mildly Impaired Renal Function

The majority of clinical trials investigating the potential benefits of statins had cardiovascular outcomes as primary end points in patients with normal/mildly impaired renal function. Post hoc analyses of subsets have demonstrated beneficial effects of statins on the renal function of these cohorts. As there is a dearth of such studies using cholesterol lowering as the intervention and renal function as the primary outcome, we have to rely on these post hoc analyses as the best available evidence. These, although valuable, are not able to replace a trial with evolution of renal function with time as the primary end point. Furthermore, most of these studies attempt to exclude patients with chronic kidney diseases on the basis of plasma creatinine. This is an unsophisticated approach, and, as a result, many subjects are included with significantly reduced CrCl. This serendipity is to be welcomed.

The Cholesterol and Recurrent Events trial is one of these studies. The patient population was 4159 hyperlipidemic subjects with history of myocardial infarction, primary end points were major adverse cardiac event, the intervention was pravastatin to reduce serum cholesterol, and follow-up was for 60 mo (29). A post hoc subgroup analysis was performed on data from patients who had a GFR (MDRD-GFR) of <60 ml/min per 1.73 m² body surface area at baseline (n = 690). Multivariate regression was used to calculate rate of decline in MDRD-GFR for individuals who received pravastatin or placebo, controlling for prospectively determined covariates that might influence rates of renal function loss. Among all individuals with MDRD-GFR <60 ml/min per 1.73 m², the decline in GFR among the pravastatin group was not significantly different from that in the placebo group (0.1 ml/min per 1.73 m²/yr slower; P = 0.49). However, there was a significant negative correlation between GFR before treatment and pravastatin use, with more benefit accruing in patients with lower GFR at baseline (P = 0.04; rate of change of GFR in the pravastatin group was 0.6 ml/min per 1.73 m²/yr slower than placebo [P = 0.07] in those with baseline GFR <50 ml/min and 2.5 ml/min per 1.73 m²/yr slower [P = 0.0001] in those with a GFR <40 ml/min per 1.73 m² at baseline). Proteinuria at baseline was also associated with a much greater protective effect of pravastatin (P = 0.006) (30).

The second trial whose findings we can use in this way was the Heart Protection Study (31). The population was adults who were aged 40 to 80 yr and had previous CVD or diabetes. The intervention was 40 mg simvastatin daily or placebo. The primary end point was all-cause mortality, which was significantly reduced (1,328 [12.9%] deaths among 10,269 allocated simvastatin versus 1,507 [14.7%] among 10,267 allocated placebo; P = 0.0003) as a result of a highly significant 18% reduction in the coronary death rate (P = 0.0005). Considerable reductions of approximately one quarter in the first event rate for nonfatal myocardial infarction or coronary death (P < 0.0001), for nonfatal or fatal stroke (P < 0.0001), and for coronary or noncoronary revascularization (P < 0.0001) were observed. The 5,903 diabetic patients in this large trial were further studied and compared in more detail to the 14,573 nondiabetic subjects. Unadjusted serum creatinine concentrations increased for all patients, with or without diabetes, over a period of 4.6 yr. However, allocation to simvastatin significantly attenuated this rise in serum creatinine in diabetic and nondiabetic subjects (32).

The third trial was a large secondary CVD prevention trial (Greek Atorvastatin and Coronary-heart-disease Evaluation). The population was 1600 Greek patients with established coronary heart disease (33). The intervention involved 800 subjects who were allocated to atorvastatin (median dose, 24 mg). The end points were mortality and hard cardiovascular morbidity events. A total of 95% of these subjects achieved the lipid-reduction goals (LDL cholesterol [LDL-C] falling by 45 to
50% and HDL-C rising by 7%). The use of atorvastatin reduced, in comparison with “usual” care, total mortality (RR, 0.57; *P* = 0.0021), coronary mortality (RR, 0.53; *P* = 0.0017), coronary morbidity (RR, 0.46; *P* < 0.0001), and stroke (RR, 0.53; *P* = 0.034). Renal function was examined (once again using a post hoc analysis) in this study using Cockcroft-Gault–derived CrCl values (34). The mean CrCl at entry was 77 ml/min. Patients on atorvastatin showed a 12% rise in CrCl, patients on other statins showed a 4.9% rise in CrCl, and statin-free patients showed a 5.2% fall in CrCl during a 36-mo follow-up. The effect on CrCl was evident from as early as 6 wk, there was a clear dose-response relationship, and those with the lowest CrCl at entry showed the greatest improvement with atorvastatin therapy. Other potentially important factors, such as BP, antihypertensives, gender, and smoking, were matched between the two groups. Data concerning renal function from the recently reported Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm trial (35) are not yet generally available but will be of great interest as they will add significantly to the evidence base in this area.

**Statin Trials in Patients with Chronic Renal Disease**

Studying “nephrologic” rather than “hypertensive” patient cohorts should be a fertile testing ground on which to test the hypothesis that statins are nephroprotective. The rate of renal functional decline is usually higher, which reduces the number of subjects necessary to follow. However, there is also the risk that the cholesterol/statin effect may be swamped by other factors’ having an even greater impact on renal function (e.g., immunologic).

Many trials have examined renal function and proteinuria as end points after treatment with statins in patients with CRI. Fried et al. (36) undertook a meta-analysis of 13 controlled trials in 404 subjects. Despite the small numbers of subjects in each trial, when the outcomes were pooled, it was shown that the use of lipid-lowering therapy (mainly but not exclusively statins) was associated with a protective effect on loss of renal function amounting to 1.9 ml/min per yr, an effect the magnitude of which was related to length of treatment. However, these results should be interpreted with considerable caution as the largest of the studies included in this meta-analysis, which accounted for nearly one third of the total meta-analysis cohort, was actually a study of the nonstatin drug probucol, which has different biologic properties from the statins. In addition, the majority of subjects had diabetes and/or nephrotic syndrome, and although the degree of renal dysfunction was similar, the rate of renal decline observed was greater than that seen in hypertensive/ dyslipidemic populations without a primary renal pathology. Among a cohort of 30 children with “early” IgA nephropathy, similar beneficial effects have been observed on proteinuria, hematuria, and serum creatinine after fluvastatin therapy for 12 mo (37).

A prospective, controlled, open-label study using atorvastatin versus no lipid therapy on the progression of CRI and proteinuria in 56 patients who had preexisting renal disease and were already treated with ACE/angiotensin II receptor blocker therapy was undertaken by Bianchi et al. (38). By the end of 1 yr of therapy with atorvastatin, 24-h urinary protein losses had fallen from 2.2 to 1.2 g (*P* < 0.01), and renal function was stable (CrCl, 51 and 50 ml/min respectively; NS). This compares with no change in 24-h protein loss (2.0 *versus* 1.8 g) and a fall in CrCl (50 to 44 ml/min; *P* < 0.01) in the lipid-placebo group.

**Effect of Statins on Renal Allograft Function**

The picture of chronic decline of renal allograft function is more complex. Many factors in the context of “chronic allograft nephropathy” may be relevant to renal outcome, and these may in certain cases outweigh any putative benefit from statin use. A recent small study of fluvastatin use demonstrated a reduction in the decline of renal transplant function (using patients as their own controls) (39). These findings are in contrast to those of the Assessment of Lescol in Renal Transplantation (ALERT) trial, which also investigated the use of fluvastatin to reduce CV disease in renal transplant recipients (40)—a multicenter, randomized, double-blind, placebo-controlled trial in 2102 renal transplant recipients with total cholesterol 4.0 to 9.0 mmol/L was conducted, with patients randomly assigned 1:1 to fluvastatin or placebo and followed up for 5 to 6 yr. Primary outcomes were cardiovascular, whereas graft loss and doubling of serum creatinine were secondary end points. Use of fluvastatin was found to have no impact on primary or secondary outcomes, but these events were found to have low frequency in the study as a whole and the observations may have been a problem of insufficient power.

Likewise, renal transplant subjects showed improvement in brachial artery endothelial function but not in the prognostically more important parameter of large artery stiffness (elastic incremental modulus of the common carotid artery) after 36 mo of fluvastatin therapy (41). One explanation for these disappointing outcomes may be that fluvastatin is a weaker statin than the more modern members of this drug family, achieving ~20% reduction in LDL-C, not the 40 to 60% reduction seen with atorvastatin and rosuvastatin.

There is scant information on the effects of statin therapy on BP in renal transplant recipients. One case-controlled study recruited 113 stable recipients who had graft survival for >1 yr and had started on a statin (<1 yr posttransplantation) without subsequent alteration in type or dose and without change in dose or type of antihypertensives during the study period. The statin-treated group was compared with a control subject who were matched 1:1 by age, gender, donor source, year of transplant, and time since transplantation and met identical criteria but were not given a statin. Baseline, 6-mo, and 12-mo outpatient BP were reviewed and compared along with other possible BP predictors. A multivariate analysis was performed controlling for other influences on BP change. The systolic, diastolic, and mean arterial BP decreased by 7 mmHg (*P* = 0.005), 3 mmHg (*P* = 0.05), and 4 mmHg (*P* = 0.007), respectively, at 12 mo of follow-up in the statin group, whereas no BP change was seen in the control arm. At 12 mo, the systolic, diastolic, and mean arterial BP were lower in the statin group compared with the control group (*P* = 0.05, 0.03, and 0.02, respectively). These changes in BP were independent of
changes in serum lipid levels (42) and may represent the benefit of improved arterial endothelial function.

Effects on Renal Hemodynamics and Endothelial Function in Renal Failure

Vascular stiffness has emerged as one of the cardinal predictors of mortality in hemodialysis (HD) (43) and renal transplant patients (44). The reasons for increased stiffness in patients with renal failure are diverse (45) and include both functional and structural alterations, some of which are also seen in old age and diabetes. ACE inhibitors have been shown to cause amelioration of vascular stiffening (aortic pulse wave velocity [PWV]) and prolong survival on HD (46).

The effects of statins on vessel stiffening in renal failure have been examined recently. In a study by Kosch et al. (41), 26 patients who had undergone renal transplantation were assigned randomly 1:1 either to 40 mg/d fluvastatin or to placebo and then followed up for 3 yr. At baseline and after 6, 12, and 36 mo of treatment, carotid and brachial artery distensibility, endothelium-dependent flow-mediated vasodilation (FMD), and nitroglycerine-induced vasodilation of the brachial artery were measured by an echo-tracking device. A significant decrease in total and low-density cholesterol was observed after 6, 12, and 36 mo in patients who were treated with fluvastatin but not in the placebo group. Flow-mediated vasodilation increased with fluvastatin from 4.6 ± 2% to 12.4 ± 2% after 12 mo; this improvement was sustained with 13.4 ± 3% after 36 mo. Endothelium-independent nitroglycerine-induced vasodilation was similar in both groups at baseline and during therapy. Neither carotid nor brachial artery distensibility coefficients were altered by either treatment.

In another study, Ichihara et al. (47) examined large artery stiffness (aortic PWV) in individuals who had type 2 diabetes and were on HD (the acme of cardiovascular risk). Twenty-two patients who had normal serum lipid levels and received fluvastatin (20 mg/d) or a placebo were followed up for 6 mo. Serum lipid levels, serum levels of C-reactive protein (CRP), and measures of arterial stiffness (arterial PWV and ankle brachial indexes) were determined before and 3 and 6 mo after taking the medication. After 6 mo, the PWV and the serum oxidized LDL-C level increased significantly (from 1969 ± 140 to 2326 ± 190 cm/s and 70.4 ± 13.8 to 91.8 ± 15.5 U/L, respectively) in the placebo-treated patients. However, the fluvastatin group had a significantly reduced PWV (from 1991 ± 162 to 1709 ± 134 cm/s), oxidized LDL-C serum levels (from 89.0 ± 9.6 to 73.0 ± 5.8 U/L) and CRP (from 0.97 ± 0.32 to 0.26 ± 0.16 mg/dl) compared with those in the placebo group.

In patients with ADPKD (48), a recently reported double-blind crossover study using lipid-lowering therapy showed potent effects on renal hemodynamics. Ten normocholesterolemic ADPKD subjects were treated in random order for 4 wk with 40 mg of simvastatin or placebo daily. The primary end points were renal blood flow, GFR, and endothelial function (using inulin/para-amino hippurate to determine effective renal plasma flow and GFR and forearm vascular reactivity to acetylcholine, L-monomethylarginine, and nitroprusside by venous occlusion plethysmography). The plasma cholesterol fell from 4.2 to 3.2 mmol/L on simvastatin. Treatment with simvastatin was associated with an increase in GFR from 124 ± 4 to 132 ± 6 ml/min. Effective renal plasma flow increased from 494 ± 30 to 619 ± 67 ml/min. Simvastatin also significantly improved acetylcarnine-induced forearm vasodilation (as statins have been shown to do in the coronary arterial bed, too). One explanation for these findings would be enhanced nitric oxide production in patients on simvastatin, but these acute functional effects need to be separated from the other more chronic benefits of statin use on structural/morphologic parameters in the glomerulus.

Sixty normotensive patients with type 2 diabetes (38 men and 22 women; mean age, 56.5 yr), microalbuminuria (20 to 200 µg/min) and dyslipidemia (total cholesterol >200 mg/dl, LDL-C >160 mg/dl, HDL-C <35 mg/dl, and triglyceride >150 mg/dl) were enrolled in a double-blind study for 6 mo, receiving either cerivastatin (0.15 mg/d) or placebo (49). Plasma and urinary endothelin-1 concentrations were measured by RIA. Cervastatin reduced systolic BP slightly but not significantly. Plasma levels of total cholesterol, LDL-C, and triglycerides were significantly reduced after 6 mo of cervastatin treatment. A concomitant significant decrease in urinary albumin excretion (P < 0.01), and urinary and plasma endothelin-1 concentrations (P < 0.01) were found during this period, suggesting that modifications of endothelial function by statins may be important in modulating glomerular proteinuria.

Effects on Inflammation and Cardiovascular Mortality in Renal Failure

There is now growing evidence for an anti-inflammatory role of statins in vivo. Chang et al. (50) evaluated the effects of simvastatin on markers for inflammation, oxidative stress, and coagulation in HD patients. Sixty-two maintenance HD patients (mean age, 61) with serum cholesterol levels of 200 mg/dl or greater were randomly assigned to the treatment group and administered simvastatin, 20 mg/d, for 8 wk or to the control group. Cholesterol, albumin, high-sensitivity CRP (hs-CRP), malondialdehyde (MDA; an index of lipid peroxidation), and D-dimer (a marker of intravascular coagulation) were measured at baseline and again at 8 wk. In the control group, total cholesterol, serum albumin, hs-CRP, MDA, and D-dimer levels did not change. In the treatment group, simvastatin administration for 8 wk significantly reduced total cholesterol levels from 232 ± 25 to 165 ± 39 mg/dl and hs-CRP levels from a median of 0.23 mg/dl (range, 0.05 to 1.63 mg/dl) to 0.12 mg/dl (range, <0.006 to 1.45 mg/dl), whereas it increased serum albumin levels from 3.4 ± 0.3 to 3.6 ± 0.4 g/dl. Administration of simvastatin did not affect MDA and D-dimer levels. These results suggest that in addition to the lipid-lowering effect, simvastatin had an anti-inflammatory effect in HD patients. These findings are of importance as inflammation underpins not only atherosclerosis (51) but also one of the great issues that reduces survival on dialysis—the malign triad of malnutrition, inflammation, and mortality (52).
secure but may reflect decreased isoprenylation of Rac-1, a mediator of the IL-6 signal transduction pathway (53).

Conclusions and Future Trials
Statin use for dyslipidemia with concomitant significant reductions in LDL-C levels seems to slow renal functional decline, especially in concert with BP and antiproteinuria measures, at least as far as the post hoc analyses of large intervention trials go. Not only is there abundant experimental evidence that a combination of nephroprotective measures is highly effective (54) from a wide variety of animal models, but also now rapidly emerging evidence from diverse clinical sources support this assertion in humans.

The reasons to favor the use of statins in chronic renal disease include beneficial effects on renal hemodynamics, endothelial function (upregulating nitric oxide synthesis), and monocyte recruitment. Reduction of proliferation of mesangial (and vascular smooth muscle) cells and mesangial matrix accumulation induced by platelet-derived growth factor and insulin-like growth factor has also been demonstrated. Statins also have the ability to inhibit production of chemokines such as monocyte-chemotactic factor-1 and macrophage colony-stimulating factor and to promote apoptosis.

Many of these effects have cardiovascular benefits at the same time. Even if there were no good evidence for a beneficial renal outcome by using statins in patients with mild to moderate CRF, it is clearly known that mild CRF and separately but additively microalbuminuria are associated with a marked increase in susceptibility to CVD (55,56). Indeed, CRF and proteinuria, in the same manner as left ventricular hypertrophy and diabetes, confer the same risk of CVD as a positive history of previous events. In other words, the “primary” event is development of proteinuria or renal impairment, and all interventions subsequent to that are a form of “secondary” renal and cardiovascular prevention. Although studies have demonstrated, albeit in small study populations, that statins can effectively improve lipid profiles, as well as improve other measures such as markers of inflammation and surrogate markers of subclinical vascular disease, no completed randomized, clinical trial has examined the effect of statins on primary cardiovascular outcomes such as cardiac ischemic events, stroke, or cardiovascular-related mortality in patients with ESRD or with more than mild renal insufficiency.

Are all statins the same? The answer is probably yes. Negative studies may be explained by lack of potency in reducing LDL-C and/or raising HDL-C, but the desired effect can be achieved only when cholesterol reduction is significant. The increasing use of modern potent cholesterol-lowering drugs in trials (achieving 50% reductions in LDL-C) may be a valid explanation for the relatively recent large increase in evidence supporting the benefits of lipid lowering on renal function.

With regard to statin-related adverse effects, studies in CRF (29), in dialysis patients (57) and in renal transplant recipients (40), all are suggestive of good side-effect profiles. However, accurate estimates of the risk of adverse events (especially myopathy) are not available in patients with ESRD or moderate to severe CRI, because the existing clinical trials with statins in these patients have been small. A study by Tonelli et al. (29) excluded subjects with moderate to severe CRI or with more than mild proteinuria, whereas Harris et al. (57) had <90 patients on a statin.

Unanswered questions, though, include at what level should we start a statin (as so many renal patients have reduced cholesterol values as a result of malnutrition), and to what extent should we bear down on LDL-C as the primary target, or should we titrate to another target, e.g., CRP or IL-6 levels? Certainly, both lipid-lowering effects and pleiotropic/anti-inflammatory effects seem valuable, as shown by de Zeeuw’s group (58), which examined the relationship between CRP and GFR in 7317 nondiabetic subjects with mild CRI. Their findings indicate that elevated CRP is positively associated with cardiovascular and renal risk factors, namely age, body mass index, BP, serum cholesterol level, smoking, plasma glucose level, and elevated urinary albumin excretion. They also described an association between inflammation, as described by CRP, and renal hyperfiltration. Future trials should attempt to address these issues.

Despite the powerful advocacy for these drugs discussed above, there is a distinct lack of large, multicenter, placebo-controlled trials to assess the hard end points of cardiovascular events and mortality (59) as well as the effects of lipid lowering on the decline in renal function. The call for such trials is because there is some confusion, through co-localization of risk factors and reverse epidemiology (60), about the benefits of statins, particularly in the dialysis population (61). The pharmacoeconomic arguments for statin use (nephro- and cardioprotection) also need to be carefully interpreted. To this end, large-scale, prospective, randomized trials, such as the SHARP trial, are currently under way, or others, such as the 4-D trial, are now closed. The data from these studies are of the greatest clinical importance.

In the meantime, with our current understanding, statins need to be considered for use in the cardiovascular field in concert with BP reduction and aspirin and in the nephrologic field alongside BP reduction and antiproteinuric measures. There is an interesting and profitable comparison to be made between ACE inhibitors and statins. Both have direct effects on their primary targets—BP and lipids, respectively—but both have additional evidence for pleiotropy (benefits not entirely explicable by reference to the primary target). Both seem to benefit renal function and CVD in the renal population with its greatly increased risk of de novo or further CVD and progression to ESRD. We maintain that both are pivotal renoprotective maneuvers, with multiple clinical benefits to patients with chronic kidney disease.

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