The Unique Character of Cardiovascular Disease in Chronic Kidney Disease and Its Implications for Treatment with Lipid-Lowering Drugs

Joseph Nogueira and Matthew Weir

Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland

Although the risk for cardiovascular disease (CVD) is high in individuals with chronic kidney disease (CKD), there are very limited data to guide the use of lipid-lowering drugs (LLDs) in this population because the major trials of LLDs in the general population have included very few individuals with CKD. The pathophysiologic and epidemiologic differences of CVD in the CKD population suggest that the study findings derived in the general population may not be directly applicable to those with CKD, and the few trials that have been directed at patients with kidney disease have not shown clear clinical benefits of LLDs. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) Work Group has provided consensus-based guidelines for managing dyslipidemias in individuals with CKD and after renal transplantation. Since the publication of these statements, further data have emerged and multiple studies are ongoing to define better the role of LLDs in patients with CKD. In this article, the data that are pertinent to the CKD population are reviewed, and updated recommendations for use of LLD in the CKD population are provided.


During the past several decades, the advent and refinement of maintenance dialysis and kidney transplantation have essentially eliminated kidney failure per se as a cause of death in developed countries. However, as patients survive many years after the development of renal failure, comorbidities develop, progress, and ultimately cause death in these individuals. Cardiovascular disease (CVD) has ranked prominent among these comorbidities, accounting for nearly half of the deaths (1). All along the continuum of chronic kidney disease (CKD)—from microalbuminuria to ESRD—a higher risk for CVD has been observed (see Epidemiology of CVD in CKD). In fact, individuals with early CKD are more likely to die of CVD than to develop ESRD (2,3). Then, among those who survive to ESRD, the all-cause CVD mortality in patients with ESRD is many-fold higher than in the general population (4). Unfortunately, the reasons for the association of CKD with CVD are not clearly understood, and the role of various clinical interventions in stemming the CVD epidemic are not well defined. Complicating the issue is the potential variation in the pathophysiology and clinical behavior of CVD through the stages of CKD.

3-Hydroxy-3-methylglutaryl CoA reductase inhibitors (statins) and other lipid-lowering drugs (LLD) have been clearly demonstrated to lessen the morbidity and mortality of CVD in the general population; therefore, there is hope that the use of these drugs may likewise help patients with CKD (In addition, it has been theorized that dyslipidemia may contribute to the progression of CKD, such that LLD may prove to slow CKD progression.) Nevertheless, given differences in epidemiology and pathophysiology of CVD in CKD, there are reasons to question whether the cardiovascular benefits of LLD that are observed in the general population will also be realized in the CKD population. It is widely acknowledged that the current medical literature provides insufficient data to guide the use of LLD in the CKD population, in large part because renal insufficiency has been an exclusion criterion for most of the randomized, controlled studies that have addressed this issue. Although consensus-based guidelines on the treatment of dyslipidemias in individuals with CKD and with kidney transplants have been published by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) Work Groups, the nephrology and cardiology communities recognize the urgent need for high-quality clinical studies on this issue, and this has fueled the publication of subgroup analyses of previous large studies in the general population and the launching of large-scale clinical trials in the CKD population, as summarized in Table 1. To provide the reader with a better appreciation of the important issues that are germane to management of dyslipidemia in CKD, this article (1) briefly summarizes the literature on the benefits of LLD in the general population, (2) demonstrates the limited involvement of individuals with CKD in the studies in the general population, (3) discusses the epidemiologic and pathophysiologic reasons that the data that are derived from and the guidelines that are directed at the non-CKD population may not be applicable to the CKD population, (4) reviews the emerging literature on the management of dyslipidemia in patients with CKD (with em-
phasis on studies that have been published since the K/DOQI guidelines were put forth), (5) discusses issues of safety of LLD in the CKD population, and (6) provides updated recommendations for management pending the completion of important ongoing trials.

**Risk of Hyperlipidemia and the Benefits of LLD in the General Population**

Although a thorough review of the literature on the cardiovascular risk of hyperlipidemia and on the benefits of LLD in the general population is well beyond the scope of this article, suffice it to say that the data are extensive and compelling. There clearly is a direct correlation of increasing levels of total and LDL cholesterol with increasing risk for coronary artery disease (CAD) and coronary mortality (5,6). Treatment with LDL has shown clear benefit in primary prevention in individuals with hypercholesterolemia (7–13). In addition, secondary prevention studies of LLD have demonstrated anatomic benefit (14–20) and improvement in clinical outcomes (cardiovascular events and/or mortality) in individuals with a wide range of cholesterol levels (21–29), and multiple meta-analyses have confirmed these benefits (13,30–33). Studies have also shown clear benefit of statins when initiated in those with acute coronary syndromes (34–37). The Heart Protection Study (HPS), a landmark study that randomly assigned >20,000 individuals, demonstrated clear benefits of a statin in patients with and without diabetes in primary and secondary prevention roles irrespective of initial LDL cholesterol (38). In addition, the Cholesterol Treatment Trialists (CTT) Collaboration recently published a prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins, and it showed that therapy resulted in statistically significant reductions in the 5-yr incidence of all-cause mortality by 12%, coronary heart disease (CHD) mortality by 19%, and major vascular events by 21% per mmol/L (39 mg/dl) reduction of LDL cholesterol (39). The study’s findings also suggested that the absolute benefit of statin therapy does not depend on the initial lipid profile but rather is related primarily to the individual’s absolute risk for cardiovascular events and to the absolute reduction of LDL cholesterol achieved.

On the basis of the vast body of literature available in the general population, the National Cholesterol Education Program (NCEP) has periodically provided rigorously derived, consensus-based, and widely accepted recommendations on the treatment of hyperlipidemia, and the most recent full report was published in 2001 as the NCEP Adult Treatment Panel III (NCEP ATP-III) guidelines (40). This report outlined a method of assessing an individual’s risk for coronary heart disease, and then it proposed specific lifestyle and pharmacologic treatment guidelines based primarily on the CHD risk profile and the fasting LDL cholesterol level. Since the writing of the NCEP AT-III guidelines, several important studies, such as the HPS, have been published. To incorporate the findings of the subsequent trials, the NCEP issued a report in 2004 addressing the implications of these trials for the NCEP AT-III guidelines (41). Although the recommended thresholds for drug treatment and the LDL goals for the various groups did not change, they decided to footnote the algorithm to indicate that an LDL cholesterol goal of <70 mg/dl in very high-risk patients and <100 mg/dl in moderately high-risk individuals (two or more risk factors and a 10-yr risk of 10 to 20%) are reasonable therapeutic options on the basis of available clinical trial evidence. They also suggested that when LDL-lowering drug therapy is used in high- or moderately high-risk individuals, the intensity of therapy should be sufficient to achieve at least a 30 to 40% reduction in LDL cholesterol levels.

**Limited Data from Trials in the General Population on Effects of Lipid Lowering in Patients with Renal Insufficiency**

In contrast to the plethora of data to guide treatment with LLD in the general population, there is an unfortunate dearth of data in individuals with CKD because individuals with renal insufficiency have been systematically excluded from most of the large trials. As examples, exclusion criteria were serum creatinine ≥1.3 mg/dl for the Helsinki Heart Study (10), serum creatinine >1.75 mg/dl for West of Scotland Coronary Prevention Study (WOSCOPS) (12,42), serum creatinine ≥2 mg/dl for Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (43), “renal disease” for the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study (25), and creatinine ≥1.5 mg/dl or nephrotic syndrome for Bezafibrate Infarction Prevention (BIP) study (22). The HPS (38) excluded individuals with “severe renal disease or evidence of substantially impaired renal function,” such that only 375 individuals with serum creatinines from 110 to 200 μmol/L (1.25 to 2.28 mg/dl) for women and from 130 to 200 μmol/L (1.48 to 2.28 mg/dl) for men were included. Although the study found a modest benefit in the subgroup of individuals without diabetes and with renal insufficiency (see Table 1), the subgroup of individuals with diabetes and with renal insufficiency in the HPS study had a 95% confidence interval (CI) of the primary event rate ratio that crossed the line of unity, indicating a lack of statistically significant benefit. Also detailed in Table 1, subgroup analyses of the likewise massive Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) showed a lower rate of the primary end point of nonfatal myocardial infarction (MI) and fatal CHD in those patients with relatively mild renal dysfunction (11).

The Pravastatin Pooling Project (44) is the largest available data set involving statin treatment in individuals with CKD. It used a database that combined patient-level results from three randomized trials of pravastatin versus placebo in the general population: WOSCOPS (12), Cholesterol and Recurrent Events (CARE) study (26), and LIPID study (25). In the database, 4491 (22.8%) of 19,700 patients had “moderate” CKD, as defined by an estimated GFR of 30 to 60 ml/min per 1.73 m² body surface area. The primary outcome was time to MI, coronary death, or percutaneous/surgical coronary revascularization. Moderate CKD was independently associated with an increased risk for the primary outcome, with an adjusted hazard ratio (HR) of 1.26 (95% CI 1.07 to 1.49) compared with those with normal
Table 1. Randomized controlled trials of lipid-lowering drugs in individuals with chronic kidney disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Studied</th>
<th>Excluded if Known CAD?</th>
<th>Intervention and Duration</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subgroup analyses of studies involving the general population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin Pooling Project (44) (pooled data from WOSCOPS, CARE, and LIPID)</td>
<td>4491 subjects with eGFR 30 to 60 ml/min, LDL &gt;155 mg/dl in WOSCOPS, “average” in CARE, total cholesterol 155 to 270 mg/dl in LIPID</td>
<td>No</td>
<td>Pravastatin versus placebo for approximately 5 yr</td>
<td>Time to MI, coronary death, or percutaneous/surgical revascularization</td>
<td>Pravastatin reduced primary outcome (HR 0.77), similar to general population</td>
<td>Suggests benefit in secondary prevention setting in patients with relatively mild CKD</td>
</tr>
<tr>
<td>Heart Protection Study (38)</td>
<td>375 adults aged 40 to 80 yr with diabetes, coronary disease, noncoronary occlusive arterial disease without diabetes or treated hypertension; with nonfasting total cholesterol ≥135 mg/dl and with serum creatinine 1.25 to 2.28 mg/dl for women and 1.48 to 2.28 mg/dl for men</td>
<td>No</td>
<td>40 mg/d simvastatin versus placebo for 5 yr</td>
<td>First major vascular event (major coronary event, stroke, or revascularization)</td>
<td>Statistically significant reduction in primary outcome in patients with diabetes (HR 0.79; 95% CI 0.59 to 0.86; P = 0.0002) but not in patients without diabetes (HR 0.77; 95% CI 0.58 to 0.93) with this degree of renal insufficiency</td>
<td>Supports benefit of treatment with statins with relatively mild CKD, at least in those without diabetes</td>
</tr>
<tr>
<td>ASCOT-LLA (11,223)</td>
<td>6517 hypertensive adults aged 40 to 79 yr with at least three other cardiovascular risk factors and nonfasting total cholesterol ≥251 mg/dl and with undefined “renal dysfunction” but serum creatinine ≤2.26 mg/dl</td>
<td>No, as long as no previous MI or currently treated angina</td>
<td>Atorvastatin 10 mg or placebo along with two antihypertensive regimens in ≥2 factorial design), with planned follow-up of 5 yr stopped short at an average of 3.3 yr</td>
<td>Nonfatal MI and fatal CHD</td>
<td>Lower risk for primary outcome in atorvastatin (HR 0.61; 95% CI 0.44 to 0.83; P = 0.0025)</td>
<td>Further supports a role for statins in relatively mild CKD, even with average or lower-than-average cholesterol levels; unfortunately, the lack of a definition of “renal dysfunction” makes it unclear whom the findings should be applied</td>
</tr>
<tr>
<td><strong>Completed trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALERT (186)</td>
<td>2102 renal transplant recipients with total cholesterol level 154 to 346 mg/dl</td>
<td>No, as long as no MI in preceding 6 mo</td>
<td>Fluvastatin versus placebo, mean follow-up period of 5.1 yr</td>
<td>Occurrence of a major adverse cardiovascular event, defined as cardiac death, nonfatal MI, or coronary intervention procedure</td>
<td>No significant risk reduction in primary end point (RR 0.83; 95% CI 0.64 to 1.06); fewer cardiac deaths and nonfatal MI in statin group, but no differences on other secondary end points</td>
<td>Because observed cardiac event rate was lower than predicted, the trial had insufficient power to detect a significant reduction in primary end point</td>
</tr>
<tr>
<td>4-D (188)</td>
<td>1255 HD patients with type 2 diabetes and LDL 80 to 190 mg/dl and triglyceride &lt;1000 mg/dl</td>
<td>No, as long as no vascular intervention, CHF, or MI in preceding 3 mo</td>
<td>Atorvastatin 20 mg/d versus placebo, mean follow-up period of 4 yr</td>
<td>Composite of death from cardiac causes, nonfatal MI, and stroke</td>
<td>No significant difference in primary end point (RR 0.92; 95% CI 0.77 to 1.10; P = 0.37); increased risk for fatal stroke in statin group (RR 2.03; P = 0.04)</td>
<td>Perhaps a higher dose of statin or earlier treatment could have produced benefit; no safety problems, except increased risk for fatal stroke</td>
</tr>
<tr>
<td>PRIVE-NET (189)</td>
<td>864 individuals aged 25 to 75 yr in the Netherlands with microalbuminuria and creatinine clearance &gt;60% of normal age-adjusted value</td>
<td>No, total cholesterol &lt;5 mmol/L if previous MI, otherwise total cholesterol &lt;8 mmol/L</td>
<td>2 × 2 factorial of simvastatin 20 mg/d versus placebo and pravastatin 40 mg/d or placebo for 4 yr</td>
<td>Cardiovascular mortality or hospitalization for cardiovascular morbidity</td>
<td>No significant reduction in primary end point (HR 0.87; 95% CI 0.49 to 1.57; P = 0.649); simvastatin produced a trend in decreasing cardiovascular events (HR 0.6; 95% CI 0.33 to 1.1; P = 0.098)</td>
<td>This study was unable to show a benefit of statin at early end of CKD spectrum</td>
</tr>
<tr>
<td>UK-HARP-1 (190)</td>
<td>448 patients with CKD (on dialysis with scCr ≥2.7 mg/dl, 73 on dialysis, 133 with functioning transplant)</td>
<td>No</td>
<td>2 × 2 factorial of simvastatin 20 mg/d versus placebo and atorvastatin 20 mg/d versus placebo for 1 yr</td>
<td>Biochemical (lipid-lowering) efficacy and safety parameters</td>
<td>Statin treatment produced a sustained reduction of approximately one quarter in LDL cholesterol levels with no evidence of toxicity</td>
<td>Provides further support for the safety of statins in individuals with CKD, because the treatment group did not have an increased risk for abnormal liver enzymes, elevated CK, or serious myopathy</td>
</tr>
</tbody>
</table>

*(table continues)*
Table 1. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Studied</th>
<th>Excluded if Known CAD?</th>
<th>Intervention and Duration</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHARP</td>
<td>Goal is 9000 patients with CKD, predialysis SCr ≤1.7 mg/dl in men or ≤1.5 mg/dl in women or on dialysis</td>
<td>Yes, if history of MI or coronary revascularization procedure</td>
<td>Ezetimibe 10 mg/ simvastatin 20 mg combination daily (or simvastatin 20 mg/di versus placebo for at least 4 yr</td>
<td>Time to first major vascular event, defined as nonfatal MI or cardiac death, stroke, or revascularization</td>
<td>Ongoing; recruitment completed in summer 2006</td>
<td>Should clarify indications for LLD in CKD</td>
</tr>
<tr>
<td>AURORA</td>
<td>Goal is 3000 HD patients 80 to 80 yr of age</td>
<td>No</td>
<td>Rosuvastatin versus placebo</td>
<td>Total mortality and cardiovascular events?</td>
<td>Ongoing</td>
<td>Should clarify indications for statins in HD patients</td>
</tr>
</tbody>
</table>

*ALERT, Assessment of Lescol in Renal Transplant; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CARE, Cholesterol and Recurrent Events; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CK, creatinine kinases; CKD, chronic kidney disease; eGFR, estimated GFR; HD, hemodialysis; HR, hazard ratio; LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease; LLD, lipid-lowering drugs; MI, myocardial infarction; PREVEND-IT, Prevention of Renal and Vascular End-Stage Disease Intervention Trial; SHARP, Study of Heart and Renal Protection; SCr, serum creatinine; UK-HARP-1, First UK Heart and Renal Protection study; WOSCOPS, West of Scotland Coronary Prevention Study.

renal function. Pravastatin significantly reduced the incidence of the primary outcome in the patients with moderate CKD (HR 0.77; 95% CI 0.68 to 0.86), and this was similar to the effect of pravastatin on the primary outcome in patients with normal kidney function. The total mortality rate in those with moderate CKD also was lower in those who were treated with pravastatin (adjusted HR 0.86; 95% CI 0.74 to 1.00; P = 0.045). The authors concluded that pravastatin reduces cardiovascular event rates in people who have moderate CKD and are at high risk for CHD or have known CAD. It should be noted that CARE and LIPID patients all had CHD, such that the majority of patients in the Pravastatin Pooling Project—3310 (73.7%) of 4491—had known coronary disease. A benefit was demonstrated in primary and secondary outcomes in patients with known coronary disease at baseline, and statistical tests for interaction revealed no significant differential effect in patients with and without symptomatic coronary disease at baseline. Although the authors did not demonstrate a statistically lower relative risk (RR) for study outcomes in the subgroup of patients with this degree of CKD and without coronary disease (HR for primary outcome 0.82; 95% CI 0.52 to 1.31; NS), they did conclude that the statistical homogeneity among the groups with and without coronary disease at baseline (P > 0.5 for interactions) suggests that pravastatin benefits these patients irrespective of the presence or absence of known coronary disease at baseline. Although the Pravastatin Pooling Project strongly suggests that patients with GFR between 30 and 60 ml/min per 1.73 m² and known CHD will benefit from statins, the lack of statistically better outcomes in those without known coronary disease renders less forceful its conclusions of benefit in primary prevention. Also, it provides no guidance for treatment of individuals with more advanced renal failure.

Unique Epidemiology and Pathophysiology of Cardiovascular Disease in CKD

**Epidemiology of CVD in CKD**

The epidemiology of CVD in individuals with CKD is significantly different from that in the general population, and this may alter the risk–benefit ratio of LLD. On the basis of several cross-sectional studies, it seems that “traditional” cardiac risk factors are common in individuals with CKD but that the Framingham risk formula is inadequate in explaining the CVD risk in this population (45–47), suggesting that other, “nontraditional” risks are at play (48,49). There is a higher risk for CVD not just in dialysis patients but also in individuals with earlier stages of kidney dysfunction (50–54), including microalbuminuria (55–66). It has also been shown that much of the CAD in this population is asymptomatic (67,68). Furthermore, it is not entirely clear whether this association between CKD and CVD is an epiphenomenon or whether there is a cause–effect relationship. That is, is the increase in CVD risk due to renal insufficiency itself or rather to the disorders that lead to renal insufficiency (e.g., hypertension, diabetes)? Whatever the case, on the basis of the strong associations of CVD with CKD, the NKF issued a report in 1998 emphasizing the high risk for CVD in CKD and recommending that patients with CKD be considered in the highest risk group for subsequent CVD events (69). In 2003, The American Heart Association issued a Scientific Statement that echoed these recommendations and labeled the presence of CKD, whether manifested by proteinuria or reduced GFR, as an independent risk factor for CVD outcomes (70).

Without doubt, the cardiovascular mortality of hemodialysis patients is extremely high relative to the general population. Foley et al. (4) demonstrated in the late 1990s that this risk is several-fold higher for older individuals, and they showed an extremely chilling risk of approximately 500-fold greater for patients in their 20s. At first glance, these data would seem to make it obvious that such patients should be treated with statins. However, it should be noted that the definition of CVD mortality for this study incorporated deaths that would be caused by disorders in which dyslipidemia may not be a major pathogenic factor and on which the effect of LLD would be dubious, such as those caused by cardiomyopathy, cardiac arrest, pulmonary edema, and arrhythmias (1). For example, left ventricular hypertrophy is extremely common in patients...
with CKD (71–73) as well as ESRD (74–78), is a very strong predictor of mortality in this setting (76,78–80), and is probably largely unrelated to dyslipidemia.

Further complicating our understanding of CVD in CKD is that the epidemiologic associations of cholesterol level with mortality may be different in this setting. In contrast to the graded positive association in the general population, the relationship between total cholesterol levels and all-cause mortality among approximately 12,000 hemodialysis patients (81) demonstrated a somewhat U-shaped association, as shown in Figure 1. It shows that patients with very low cholesterol levels have a marked increase in morality and that the risk is fairly flat across the range of normal and moderately high cholesterol levels. It is not until very high levels of cholesterol that the mortality seems to increase. Of course, low cholesterol levels may be a marker of malnutrition, inflammation, and other chronic illnesses in this population rather than an independent risk factor, and clearly this may explain the high mortality at very low cholesterol levels. However, the lack of a graded increase in CVD risk in the normal and high-normal range (as is seen in the general population) argues for a less robust and less direct relationship between increasing cholesterol and mortality in the dialysis population. It should also be noted that three subsequent reports have documented a positive association with CVD outcomes. First, Tschope et al. (82) prospectively followed all consecutive patients who had diabetes and were newly admitted to 28 German dialysis centers between January 1985 and October 1987, and they found that patients who had diabetes and subsequently died from MI had significantly higher median total and LDL cholesterol levels than survivors. Second, Nishizawa et al. (83) showed that higher non-HDL cholesterol was a significant and independent predictor of cardiovascular mortality in hemodialysis in a cohort of 525 Japanese hemodialysis patients. Third, Block et al. (84) recently reported that total cholesterol was directly related to the risk for hospitalization for CVD in a large hemodialysis database. In sum, elevated cholesterol levels seem to be predictive of cardiovascular morbidity and mortality in the CKD population, but the relationship seems to be less direct than in the general population, especially in hemodialysis patients, in whom low cholesterol levels seem to identify a group at high risk for mortality.

As part of the discussion of the epidemiology of CVD in CKD, it should be noted that mortality as a result of atherosclerotic heart disease and acute MI have fallen 25 and 21%, respectively, since 1991 in prevalent patients with ESRD (85). However, it would be difficult to argue that the use of statins in this population deserves credit for this decline given that some studies have suggested that only a minority of patients with CKD are receiving LLD. For example, Seliger et al. (86) reported that among a cohort of 3716 patients who started dialysis in 1996, only 362 (9.7%) were being prescribed statins as of day 60 after starting dialysis. Tonelli et al. (87) reported in a prospective, cross-sectional study of consecutive patients who were seen by nephrologists in four Canadian centers for follow-up of progressive chronic renal insufficiency (all with creatinine clearances of ≤75 ml/min and with a mean creatinine clearance of 30.3 ± 18 ml/min) that only 35.6% of those with CVD and known hyperlipidemia were administered statins. Levin et al. (52) also reported that among a cohort of 313 patients with mild to moderate CKD (mean creatinine clearance 36 ml/min) and with a 46% incidence of CVD, only 13.5% were treated with an LLD; furthermore, only 25 (17.7%) of 143 in this cohort with known CVD were receiving such drugs. It is not clear whether these low rates of treatment with LLD are the result of therapeutic nihilism, concern for risk of adverse effects, problems in health care delivery, or others, but this does indicate that during the late 1990s, nephrologists and patients “voted with their feet” against widespread use of these agents in this high-risk population.

Pathophysiology of CVD in CKD

The character of CVD in CKD is distinct in large part because of differences in pathophysiology of cardiac and vascular disease in this setting. The list of potential pathophysiologic contributors to the CVD epidemic in CKD, especially in dialysis patients, is legion. Table 2 lists many of these, and a few are discussed in some detail. Clearly, these differences in pathophysiology may alter the effects of dyslipidemia and the risks/benefits of LLD in the CKD populations.

Alterations in Lipid Profiles in CKD. As detailed in Table 3, patients with CKD tend to have a different lipoprotein pattern than in the general population, and peritoneal dialysis patients tend to have an especially atherogenic lipid profile (88–90). How these alterations in lipid profiles affect the CVD risk and the response to LLD has not been adequately elucidated, but some of the observations and theoretical implications are discussed.

Hypertriglyceridemia is more common in patients with CKD, and this disturbance may be an important contributor to CVD in this population. Studies in the general population have suggested that an elevated triglyceride level is an independent risk factor for CVD (91,92). The cardiovascular risk of triglycerides may be the result of atherogenic “remnant lipoproteins,” which are made up primarily of VLDL cholesterol in patients.

Figure 1. The relative risk (RR) for death for groups of hemodialysis patients with different nonfasting serum cholesterol concentrations. The significance of differences in RR between other groups and the reference group (200 to 250 mg/dl) is shown over the bar. When no significance is shown, the probability value is $P > 0.05$. Reprinted from Lowrie and Lew (81), with permission.
with high triglyceride levels. This moiety is not routinely measured in lipid panels, but it can be estimated by calculating non-HDL cholesterol levels by subtracting HDL from total cholesterol (93). At least one report has suggested that non-HDL cholesterol may actually be a better predictor of mortality than LDL cholesterol (94). Some authors (including the K/DOQI work group) posit that the risk contribution of these atherogenic remnant proteins in patients with high triglyceride levels may be incorporated by considering non-HDL cholesterol in treatment algorithms (93).

Intermediate-density lipoprotein (IDL) cholesterol is another of the remnant lipoproteins that may be included in the non-HDL cholesterol fraction, and it has been reported to be an important atherogenic lipid component in the general population (95,96). It has been correlated with increased aortic pulse wave velocity in hemodialysis patients (97). Serum IDL cholesterol levels have been reported to be higher in patients with renal failure (98,99). Statins seem to lower IDL cholesterol in the general population (100,101) and in dialysis patients (102,103). Whether reductions in IDL cholesterol are associated with reductions in mortality is not known, but some have suggested that IDL cholesterol may be an important lipid component to target in individuals with renal failure (103).

Also, lipoprotein(a), a modified form of LDL, is a highly atherogenic lipoprotein particle that may be a relatively important player in CVD pathogenesis in the CKD population. It structurally resembles plasminogen and interferes with fibrinolysis, and it binds to macrophages and promotes foam cell formation and the deposition of cholesterol in atherosclerotic plaques (104,105). An elevated level predicted vascular events (106) and was found to be an independent risk factor for CVD in hemodialysis patients (107). The levels of lipoprotein(a) are especially high in peritoneal dialysis patients (89) and seem to decrease after kidney transplantation (90).

The increased levels of oxidative stress and inflammation that are seen in CKD may cause oxidative conversion from the native LDL to the more atherogenic oxidized LDL molecule (108). Statins seem to have antioxidant properties and anti-inflammatory effects (109), and they may ameliorate atherosclerotic processes by preventing oxidation of LDL cholesterol (110).

Multifaceted Vascular Disease. To understand vascular pathology, one must appreciate the contributions of both of the two important types or arterial disease: atherosclerosis (thickening of the intimal layer of arteries with lipid-rich deposits and plaques) and arteriosclerosis (diffuse thickening and loss of elasticity of arterial walls). Both seem to be problematic in patients with CKD, and there may be important differences in the pathophysiology of these processes as compared with the general population.

Atherosclerosis seems to be more common in individuals with CKD (111) and ESRD (112–116). The atherosclerotic lesions in ESRD have a distinct morphology, with a more calcified appearance (as opposed to fibroatheromatous) and relatively increased medial thickness (as opposed to intimal) as compared with the general population (117). It has been hypothesized that calcification in the setting of CKD may contribute to the atherosclerotic process, but to what degree this calcification may have an impact on the stability of the plaques is not clear (118,119). As is the case in the general population,

### Table 2. Potential contributors to development of CVD in individuals with CKDa

<table>
<thead>
<tr>
<th>Common to General Population</th>
<th>Unique to or Relatively Much More Important to the CKD Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>High LDL cholesterol</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Vascular calcification</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Uremic cellular metabolic derangements</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>LDL oxidation</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>Hypertriglyceridemia</td>
</tr>
<tr>
<td>Familial/inherited predisposition</td>
<td>High IDL cholesterol</td>
</tr>
<tr>
<td>Postmenopausal hormone changes</td>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td></td>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td></td>
<td>Hyperuricemia</td>
</tr>
<tr>
<td></td>
<td>Carnitine deficiency</td>
</tr>
<tr>
<td></td>
<td>Leptin</td>
</tr>
<tr>
<td></td>
<td>Recurrent intradialytic hypotension</td>
</tr>
</tbody>
</table>

### Table 3. Alterations in lipid profiles in CKD and ESRD

<table>
<thead>
<tr>
<th>Generally Increased Levels</th>
<th>Generally Decreased Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>Total cholesterol</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td>LDL cholesterol</td>
</tr>
<tr>
<td>Apoprotein B</td>
<td>HDL cholesterol</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>Apoprotein A1</td>
</tr>
<tr>
<td>IDL cholesterol</td>
<td></td>
</tr>
</tbody>
</table>

aCVD, cardiovascular disease; IDL, intermediate-density lipoprotein.
dyslipidemia probably plays a critical role in the atherosclerotic process in CKD (120).

Arteriosclerosis also seems to be an extremely important component of CVD that affects patients with CKD. Large artery distensibility is reduced in individuals with CKD (121) and ESRD (122), and the arterial stiffness seems to predict cardiovascular and all-cause mortality in patients with ESRD (123–126). Vascular calcification (VC), especially in the arterial media, is probably a major contributor to arteriosclerosis in CKD (127–130). Numerous autopsy and radiologic studies in the past several decades have demonstrated high rates of calcification of peripheral and central arteries (131–140), and coronary artery calcification is even common and progressive in young adult hemodialysis patients (141). VC is probably primarily due to abnormal mineral metabolism that is seen in renal failure (141–145), perhaps through a complex process involving osseous metaplasia of the vascular wall components (118,119,146). Associations of calcium/phosphorus/parathyroid hormone dysregulation with CVD and concerns that coronary artery calcification may beget coronary artery occlusive disease (147–150) argue for an important role of VC in the CVD epidemic in ESRD (84,151).

Precisely how VC interacts with lipids in the pathogenesis of vascular disease in CKD is unclear, but this issue is critical in understanding the effects of LLD in this population. A positive relationship between VC and serum total and LDL cholesterol and triglyceride levels was shown in the general population (149,152,153). A small Japanese study found that rapid progression of coronary artery calcification was associated with high triglyceride and low HDL cholesterol concentrations in long-term hemodialysis patients (154). Another study likewise found an association of low HDL cholesterol with VC (155). Two studies reported lower total cholesterol levels in dialysis patients with VC (141,156). Another study of 44 peritoneal dialysis patients did not note an association with lipid parameters (157).

**Endothelial Dysfunction.** Finally, endothelial dysfunction may also importantly contribute to the development of CVD in patients with renal insufficiency (158). Impaired endothelial vasodilation seems to be related to oxidative stress (159) and reduced levels of nitric oxide (160), likely as a result if accumulation in renal failure of an inhibitor of nitric oxide synthase, asymmetrical dimethylarginine (161–166). In addition, reduced levels of circulating endothelial progenitor cells and increased numbers of mature endothelial cells have been noted in renal failure and have been hypothesized to reflect ongoing endothelial injury and perhaps poor repair function (167–173).

In sum, we speculate that the pathophysiology of CVD in CKD involves many pathways that are interrelated and contribute in complex ways to the epidemic of CVD in this population. Although the discussion of this issue could continue for many more pages, the bottom line is that there are a similar number of lipids that are raised in renal insufficiency and those seen in the general population. The complex differences render very questionable the extrapolation of data on benefits of lipid lowering that are derived in nonuremic individuals to individuals with CKD. Also, the pleiotropic effects of statins on cell signaling, inflammation, cellular proliferation, atherosclerotic plaque stabilization, and endothelial dysfunction (174–179) may be different than those seen in the general population and may be important in modulating the effects of statins in the CKD population.

**Studies of LLD in the CKD Population**

In the 1990s, several small, short-term trials in ESRD patients had suggested that statins can safely be used to achieve changes in the lipoprotein profiles that would be expected to be beneficial (102,103,180–184). None of these studies was able to evaluate adequately the effect of treatment on important “hard” clinical end points, such as total or cardiovascular mortality (185).

In this effort to assess mortality effects of statins in this population, Seliger et al. (86) used a large national database, the US Renal Data System Dialysis Morbidity and Mortality Study Wave 2, to assess the association between statin use and mortality in incident dialysis patients. They found that statin use was associated with a 32% lower risk for total mortality (95% CI 0.54 to 0.87) and that this effect was independent of other parameters that are known to have an impact on mortality, including diabetes, age, previous CVD, and smoking. They also found a similarly reduced risk for cardiovascular-specific mortality (RR 0.64; 95% CI 0.45 to 0.91). Although this study suffered from the limitations that are inherent in a retrospective database review, the mortality effects of statins were noted to be similar to those that were observed in large, randomized, controlled trials in the general population; were independent of other effects of other known risk factors; and were thus interpreted to suggest that statins may be effective in improving survival in dialysis patients.

**Assessment of Lescol in Renal Transplant Study**

The Assessment of Lescol in Renal Transplant (ALERT) study (186) was a multicenter, randomized, double-blind, placebo-controlled trial that involved 2102 renal transplant recipients with total cholesterol levels of 154 to 346 mg/dl and compared treatment of fluvastatin with placebo. Patients were not excluded when they had known coronary heart disease as long as they had not had an MI in the preceding 6 mo. Of course, the patients were on transplant immunosuppressive drugs. The primary end point was the occurrence of a major adverse cardiac event, defined as cardiac death, nonfatal MI, or coronary intervention procedure. After a mean follow-up of 5.1 yr, fluvastatin lowered LDL cholesterol concentrations by 32%. Risk reduction with fluvastatin for the primary end point was not significant, with a risk ratio of 0.83 (95% CI 0.64 to 1.06; P = 0.139). There were fewer combined cardiac deaths or nonfatal MI in the fluvastatin group than in the placebo group (70 versus 104; risk ratio 0.65; 95% CI 0.48 to 0.88; P = 0.005). Coronary intervention procedures and other secondary end points did not differ significantly between groups. Also, no effect on renal allograft survival or renal function could be demonstrated in secondary analysis of the data (187). The authors of the study commented that because the observed cardiac event rate was lower than predicted at the outset, the trial had insufficient power to detect a significant reduction in the chosen primary
end point. Relevant to the CKD population, the mean creatinine clearance in the ALERT trial was 60 ml/min, and approximately half of the patients (n = 1017) in the ALERT study had significant renal insufficiency at inclusion (serum creatinine at least 1.57 mg/dl). Although the study could not show a clear benefit of statins in this population, it is important to note that it did not identify any substantial safety concerns in this population either.

Die Deutsche Diabetes Dialyse Studie (4-D) Study
The 4-D study (188) was a multicenter, randomized, double-blind, prospective study of 1255 patients who had type 2 diabetes, were receiving maintenance hemodialysis, and were randomly assigned to receive 20 mg/d atorvastatin or matching placebo. The primary end point was a composite of death from cardiac causes, nonfatal MI, and stroke. Secondary end points included death from all causes and all cardiac and cerebrovascular events combined. During a median follow-up period of 4 yr, 469 (37%) patients reached the primary end point, 226 of whom were assigned to atorvastatin and 243 to placebo (RR 0.92; 95% CI 0.77 to 1.10; P = 0.37). Atorvastatin had no significant effect on the individual components of the primary end point, except that the RR of fatal stroke among those who received the drug was 2.03 (95% CI 1.05 to 3.93; P = 0.04).

Atorvastatin reduced the rate of all combined cardiac events (RR 0.82; 95% CI 0.68 to 0.99; P = 0.03) but not all cerebrovascular events combined (RR 1.12; 95% CI 0.81 to 1.55; P = 0.49) or total mortality (RR 0.93; 95% CI 0.79 to 1.08; P = 0.33). Importantly, no cases of rhabdomyolysis or severe liver disease were detected, further alleviating safety concerns of statins in this population. The finding in this adequately powered study of lack of benefit in this population at extremely high cardiovascular risk demonstrates the danger in applying literature of the general population to those with ESRD, in whom so many other pathogenic pathways to CVD coexist with dyslipidemia. Nevertheless, the compelling literature in the general population to support treatment of patients with diabetes with statins and given the marginally significant reduction of all cardiac events (a secondary outcome) in patients who were on statin in this trial, the negative results from this single trial are not sufficiently robust to establish nontreatment of such patients as the only acceptable standard of care. Furthermore, it is certainly very plausible that treatment of patients with diabetes with statins earlier in the course of CKD would be beneficial. Finally, it also should be noted that a 20-mg dose of atorvastatin was used without dosage escalation and that a previous study suggested that an 80-mg dose of the drug is more effective than a 10-mg dose in patients with stable CAD (24), such that it is possible that benefit could have been realized had a larger dosage of statin been used.

Prevention of Renal and Vascular End-Stage Disease Intervention Trial
Prevention of Renal and Vascular End-Stage Disease Intervention Trial (PREVEND IT) involved individuals at the other (early) end of the kidney disease spectrum and likewise was unable to demonstrate a benefit of statins (189). It was a single-center (in the Netherlands), double-blind, randomized, placebo-controlled trial with a 2 × 2 factorial design involving fosinopril or placebo and pravastatin 40 mg or placebo. Patients were 28 to 75 yr of age and were found to have microalbuminuria on screening, and they were excluded when the creatinine clearance was <60% of the normal age-adjusted value. A total of 864 patients were randomly assigned, the mean follow-up was 46 mo, and the primary end point was cardiovascular mortality and hospitalization for cardiovascular morbidity.

Although fosinopril produced a significant reduction in albuminuria and was associated with a trend in decreasing cardiovascular events (HR 0.60; 95% CI 0.33 to 1.10; P = 0.098), 4 yr of treatment with pravastatin did not result in a significant reduction in urinary albumin excretion or cardiovascular events (HR 0.87; 95% CI 0.49 to 1.57; P = 0.649).

United Kingdom Heart and Renal Protection Studies
Two pilot studies have been completed in preparation for the Study of Heart and Renal Protection (SHARP), a large-scale, randomized trial of LDL in CKD to be discussed in the next section. The main aims of these studies were to establish the biochemical efficacy and to gain more information about the safety of cholesterol-lowering drugs in patients with CKD. In the first UK Heart and Renal Protection study (UK-HARP-I) (190), 448 patients with CKD were randomly assigned to simvastatin 20 mg/d or to placebo (along with aspirin 100 mg/d versus placebo in a 2 × 2 factorial design) for 1 yr. At the start, 242 patients were predialysis, 73 were receiving maintenance dialysis, and 133 had a functioning transplant. Simvastatin lowered LDL cholesterol by 26%, similar to the lipid-lowering effect in patients without CKD. The simvastatin-allocated group did not have a significantly increased risk for abnormal liver transaminases, elevated creatinine kinase, or serious myopathy. Then, because a more substantial lowering of cholesterol was expected to be needed to produce a demonstrable reduction in cardiac events, the second HARP pilot study (UK-HARP-II) was designed to assess the tolerability, safety, and biochemical efficacy of ezetimibe in combination with simvastatin (20 mg/d). Among the 203 patients who had CKD and were randomly assigned to ezetimibe/simvastatin versus simvastatin, proportional reductions in LDL cholesterol similar to those achieved in the general population were observed, and the combination was well tolerated (191).

Study of Heart and Renal Protection (SHARP)
SHARP is an investigator-initiated, industry-sponsored trial designed to compare ezetimibe/simvastatin versus placebo in approximately 9000 patients with CKD around the world, approximately 6000 of whom were intended to be predialysis and 3000 of whom were to be undergoing dialysis (192). Patients with previous MI or coronary revascularization and those with a functioning kidney transplant are excluded. With a plan to continue the treatment for at least 4 yr, the primary aim of the study is to assess the effects of LDL cholesterol lowering on the time to a first “major vascular event,” defined as nonfatal MI or cardiac death, nonfatal or fatal stroke, or revascularization. Secondary aims will include assessments of the effects of the
combination drug on progression to ESRD, various causes of death, major cardiac events, stroke, and hospitalization for angina. Of course, subgroup analyses will be conducted as well. The study commenced in 2003, and the recruitment phase was completed in the summer 2006. The landmark study is the largest nephrology trial ever undertaken, and it has the power to establish whether the drugs will protect patients with CKD from a first major vascular event. Its highly anticipated results should greatly clarify the indications for LLD in patients with CKD.

A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) Study
The AURORA study is a placebo-controlled, double-blind study of rosvustatin versus placebo in approximately 3000 hemodialysis patients from age 50 to 80 yr, irrespective of previous CVD and irrespective of baseline lipid levels. The primary study end point is the time to a major cardiovascular event (first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke). Secondary end points include all-cause mortality, major cardiovascular event-free survival time, time to cardiovascular death, time to noncardiovascular death, cardiovascular interventions, tolerability of treatment, and health economic costs per life-year saved. Study medication will be given until 620 patients have experienced a major cardiovascular event. By early 2005, more than 2750 patients had been randomly assigned (193,194). When published, the results of this study should help to clarify the role of statins in hemodialysis patients.

Safety of LLD in the CKD Population
A discussion of LLD in CKD would not be complete without mention of the safety considerations of such medications that are especially pertinent to this population. Reduced renal clearance of drugs and metabolites, uremic effects on protein binding and volume of distribution, dialysis-related removal of drugs, and impact of renal failure and drug–drug interactions on hepatic metabolism are factors that could theoretically alter the potential for toxicity of LLD in this population. However, accumulating evidence has been very reassuring on the risk of statins in the setting of CKD, and most classes of LLD can be used with appropriate precautions in this setting. The following discussion focuses on safety issues that are especially relevant to the CKD population.

Fibric acid derivatives may cause myositis and rhabdomyolysis, and it has been suggested that adjusting the dosage of these medications on the basis of renal function and exercising caution with potentially interactive combinations (e.g., with statins) may minimize risk for toxicity (195,196). Of note, three cases of reversible acute renal allograft dysfunction have been reported in patients who were treated with fenofibrate (197). Bile acid sequestrants have been reported to interfere with cyclosporine absorption, but this problem can be overcome if the drugs are administered at different times of the day. The effect of bile acid sequestrants on the absorption of other immunosuppressives is not known. It should also be remembered that bile acid sequestrants may increase triglyceride levels and therefore should be avoided in patients with marked hypertriglyceridemia, which is relatively common in dialysis patients (195,196). Nicotinic acid is partially (approximately one third) renally cleared, and it is recommended that the dosage be decreased to 50% in patients with GFR <15 ml/min (195). We are not aware of any data that would indicate special safety concerns regarding the use of nicotinic acid in patients who have CKD or are on immunosuppressive drugs.

The issue of statin-induced myositis and rhabdomyolysis has been a significant concern in this population, and the scores of fatalities as a result of rhabdomyolysis that were attributed to cerivastatin (Baycol, Bayer Corporation, Leverkusen, Germany), which ultimately caused its removal from the market in 2001, have weighed heavily in the risk–benefit debate of this class of drugs. Statin-induced rhabdomyolysis in patients with renal failure is the subject of a relatively recent review by Sica and Gehr (198), and the reader is referred to this article for a more thorough treatise on the subject. High levels of statins have been implicated as the major factor that predisposes to myotoxicity; therefore, an understanding of the clearance and metabolism of the drugs is important. Except for pravastatin, all statins are extensively metabolized by the cytochrome P450 (CYP) enzymes. Most of the statins, including atorvastatin, lovastatin, and simvastatin, are metabolized primarily by the CYP3A4 isoenzyme, and they are therefore susceptible to interactions with the myriad of drugs that have an impact on this enzyme. Among the important drug interactions are cyclosporin A, tacrolimus, azole antifungals, macrolide antibiotics, fibrates, nicotinic acid derivatives, protease inhibitors, and warfarin. Fluvastatin, however, is metabolized by the CYP2C9 pathway, and far fewer commonly prescribed drugs inhibit this pathway. Therefore, the potential for drug–drug interactions theoretically should be less with fluvastatin and pravastatin. The statins are primarily removed by hepatic metabolism, and the proportion of renal clearance is low except for pravastatin at 20 to 60% (199) and lovastatin at 30% renal excretion (198). All of the marketed statins are highly protein bound (>90%), except pravastatin, which is estimated to be 50% bound; therefore, removal with hemodialysis treatments should be minimal. Atorvastatin has a negligible renal excretion rate of <2%, pharmacokinetic studies have showed no effect of renal dysfunction (although only three patients with stage 5 CKD were studied) (200), and the package insert states that dosage adjustments are not necessary in patients with renal insufficiency. As discussed by Sica and Gehr (198), the limited pharmacokinetic studies have not indicated that dosage adjustments of other statins are necessary in renal failure, but the manufacturers have generally recommended lower starting dosages and cautious titration in patients with renal failure. Such recommendations seem prudent given evidence that the state of renal insufficiency has been associated with downregulation of the CYP enzyme system and hepatic metabolism of the drug (201–203), given the potential alterations in protein binding of these highly protein-bound drugs as a result of uremic toxins, and given the high rate of polypharmacy in this population. As discussed previously, the UK-HARP studies did not indicate higher rates of
rhabdomyolysis in patients who had CKD and were treated with simvastatin or ezetimibe/simvastatin (190,192). Likewise, the ALERT study did not show higher rates of muscle toxicity in kidney transplant recipients who were on immunosuppressive drugs (187), and no cases of rhabdomyolysis were seen during treatment with atorvastatin in the 4-D study (188). In practice, we believe that it is advisable to measure baseline creatinine kinase (CK) levels before starting statin therapy, and then patients should be instructed to report muscle symptoms and be queried about muscle symptoms on follow-up. Although routine monitoring of CK levels is probably not indicated, repeat CK measurements should be obtained and compared with baseline levels if symptoms develop. The reader is referred to the American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute Clinical Advisory on Statins for specific recommendations for managing abnormalities (204).

Although elevated levels of hepatic transaminases occur in 0.5 to 2.0% of patients who are treated with statins in the general population, it remains controversial whether statins cause significant hepatotoxicity (93,204). Several randomized, controlled trials have reported no significant difference in the incidence of persistently elevated aminotransferases between those who were treated with statins and those who were treated with placebo (9,21,38), and statins were noted not to worsen liver injury in patients with chronic transaminase elevations as a result of hepatitis B or C (93,204). Hepatotoxicity of statins could be dosage and/or level related; therefore, the issues of drug clearance and drug–drug interactions may also be applicable in this regard. To our knowledge, however, no study has demonstrated higher risk for statin-related hepatotoxicity in the CKD population; and the UK-HARP studies, the ALERT study, and the 4-D study did not indicate evidence of statin-related hepatotoxicity. Although many experts argue that routine monitoring of transaminases may be unnecessary, it is probably reasonable to check the levels initially, at 12 wk after starting therapy, and then periodically thereafter, as recommended by the US Food and Drug Administration and the American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute Clinical Advisory on Statins (204).

Cyclosporine and possibly tacrolimus increase levels of most statins, likely by competing for hepatic CYP enzymes that metabolize the drugs. As discussed previously, pravastatin does not rely on the CYP system for metabolism, and lovastatin is metabolized by a different isozyme (CYP2C9 rather than CYP34A) than what is affected by the calcineurin inhibitors (CNI). Despite the theoretical lack of interactions, cyclosporine has been associated with a 3.5-fold increase in fluvasatin area under the curve (AUC) in heart transplant patients (205), and cyclosporine produced a five-fold increase in pravastatin AUC in kidney transplant patients (206). Because of these findings of increased levels of non–CYP34A-metabolized statins in patients who are on cyclosporine, different mechanisms of interactions are likely at play, and emerging evidence suggests that cyclosporine-mediated inhibition of transport proteins may be involved (207). Organic anion-transporting polypeptide 1B1 (OATP1B1) is a liver-specific uptake transporter of various substrates, which include pravastatin and cerivastatin (207–209). Studies have demonstrated that elevations of cerivastatin when used in combination with cyclosporine are largely due to cyclosporine-induced inhibition of hepatic uptake by this OATP1B1 transporter (209,210), and a similar inhibition of OATP1B1 by gemfibrozil may be an important mechanism of its interaction with this statin (211,212). Also, P-glycoprotein transporter is an energy-dependent multidrug efflux pump that serves to protect against toxic compound accumulation by transporting such substances, which include statins, into the intestinal lumen, bile, and urine. Cyclosporine but not tacrolimus has been shown to be a potent inhibitor of P-glycoprotein (213,214), and its transport activity seems to be reduced in rats with chronic renal failure (215). Clearly, this inhibition of hepatic uptake and enteric efflux of statins in cyclosporine-treated patients could increase risk for toxic accumulation.

Nevertheless, the available evidence suggests that statins can be used safely with CNI if the statin dosage is reduced and if treatment with other potentially interacting agents is avoided or monitored carefully (195). The reader is referred to the K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Kidney Transplant Patients (195) for a more detailed discussion of the safety of LDL in the kidney transplant population. Although fluvastatin was safely used in kidney transplant patients in the ALERT study, no comparative trials of statins in this population have been done to our knowledge. Therefore, firm conclusions on the relative safety of the various statins in this setting cannot be made with confidence.

Limited evidence is accumulating that ezetimibe can be used safely in patients with CKD and in renal transplant recipients. As discussed previously, the UK-HARP-II study team reported that the ezetimibe/simvastatin combination was safe in patients with CKD (192). A noncontrolled study of 40 stable kidney transplant recipients, most of whom were on CNI, found the drug to be effective and safe as monotherapy or in combination with a statin (216). Three subsequent small studies likewise demonstrated effective lipid lowering without significant toxicity in renal transplant patients (217–219). Cyclosporine administration yielded a 3.4-fold greater AUC of ezetimibe in renal transplant patients (220), and there is a case report of supratherapeutic LDL cholesterol reduction in a cyclosporine-treated heart transplant patient who was on ezetimibe 10 mg/d (221). Therefore, a starting dosage of 5 mg/d, cautious dose titration, and close monitoring for adverse effects have been recommended (221) and are probably prudent when ezetimibe is co-administered with a CNI.

**Treatment Guidelines**

The NKF K/DOQI Clinical Practice Guidelines for Managing Dyslipidemia in Chronic Kidney Disease (93) were published in 2003, and this treatise addressed this topic in a rigorous, evidence-based manner and provided consensus recommendations of the work group. This document provided a detailed discussion of and recommendations for the screening, evaluation, and treatment of dyslipidemias in patients with CKD and dialysis patients. In addition to suggesting that remediable,
secondary causes of dyslipidemias (e.g., medications, nephrotic syndrome, hypothyroidism) be addressed as appropriate, K/DOQI Work Group in general deferred to NCEP AT-III guidelines, stating, “In the absence of data from randomized trials conducted in patients with CKD, it is reasonable to assume that the interventions recommended by the NCEP ATP-III will similarly reduce atherosclerotic CVD in patients with CKD.” The work group concluded that the evidence in the literature suggests that the expected 10-yr CHD risk is at least 20% in patients with CKD (69,222), thereby justifying the contention that CKD be considered a “CHD risk equivalent” and supporting NCEP ATP-III’s most aggressive lipid-lowering goals for these patients. The work group suggested that these NCEP ATP-III guidelines be applied directly to patients with stages 1 through 4 CKD, and it provided specific guidelines only for stage 5 CKD (see the next paragraph). The work group acknowledged the lack of sufficient data to support strong recommendations in this population, and it called for randomized trials to assess whether treatment of dyslipidemias will reduce the incidence of CVD.

The following are specific recommendations for treatment of dyslipidemias in adults with stage 5 CKD:

- For adults with stage 5 CKD and fasting triglycerides ≥500 mg/dl (≥5.65 mmol/L) that cannot be corrected by removing an underlying cause, treatment with therapeutic lifestyle changes and a triglyceride-lowering agent should be considered (Grade C recommendation)
- For adults with stage 5 CKD and LDL ≥100 mg/dl (≥2.59 mmol/L), treatment should be considered to reduce LDL to <100 mg/dl (<2.59 mmol/L) (Grade B recommendation)
- For adults with stage 5 CKD and LDL <100 mg/dl (<2.59 mmol/L), fasting triglycerides ≥200 mg/dl (≥2.26 mmol/L), and non-HDL cholesterol (total cholesterol minus HDL) ≥130 mg/dl (≥3.36 mmol/L), treatment should be considered to reduce non-HDL cholesterol to <130 mg/dl (<3.36 mmol/L) (Grade C recommendation)

Detailed rationales for each recommendation are provided in the text of the document. As discussed, specific recommendations targeting non-HDL cholesterol were provided in large part to address the probable contribution of “remnant lipoproteins” (VLDL and IDL) in patients with hypertriglyceridemia and ESRD. The article suggested that a statin be used first in the absence of contraindications, and it encouraged starting with a low dosage and carefully titrating while monitoring for toxicity. It suggested that second-line agents could include bile acid sequestrants (if triglyceride level <400 mg/dl), niacin, or possibly sevelamer hydrochloride.

Shortly after the publication of the ALERT study, the NKF K/DOQI convened a work group to draft guidelines for managing dyslipidemia in kidney transplant patients, and the group published their clinical practice guidelines in 2004 (195). The work group concluded that the incidence of CVD is very high in kidney transplant patients and that the available evidence suggests that the 10-yr cumulative risk for CHD is at least 20%. They stated that kidney transplant patients should be considered to have a “risk equivalent” for CHD in the NCEP ATP-III schema for management. Although they admitted that additional studies are needed in patients with CKD and kidney transplant patients, the work group adopted an approach that closely paralleled that of the NCEP ATP-III; but, as with the NKF K/DOQI guidelines for patients with CKD, it also addressed the issue of severe hypertriglyceridemia and remnant lipoproteins as measured with non-HDL cholesterol. The group offered exactly the same guidelines for transplant patients as those listed for patients with stage 5 CKD. The group stated that the existing data support the conclusion that statins can be safely used in combination with CNI (cyclosporine and tacrolimus) if the dosage is reduced and other agents that are metabolized by the CYP system (e.g., macrolide antibiotics, azole antifungal agents, calcium channel blockers, fribates, nicotinic acid) are avoided. The group recommended avoiding ezetimibe in kidney transplant patients until safety data were available. As discussed, subsequent data have indicated that cyclosporine may increase AUC of ezetimibe but that cautious use of ezetimibe in renal transplant is probably effective and safe.

In general, we believe that the current literature supports the recommendations of K/DOQI in regard to individuals with CKD as well as renal transplant recipients. We offer the following caveats on the basis of our review of the current literature:

- On the basis of the findings from the Pravastatin Pooling Project, we believe that it is advisable to treat aggressively individuals who have an estimated GFR of 30 to 60 ml/min per 1.73 m² and have known CHD and probably those without known coronary disease.
- We acknowledge the scarcity of literature in individuals without known CHD and in those with more advanced CKD, but we believe that it is reasonable to apply the currently accepted and footnoted (41) NCEP ATP-III schema for treatment on the basis of LDL cholesterol levels and LDL cholesterol goals to those who have not yet reached ESRD while using the K/DOQI recommendations for individuals with stage 5 CKD or for those with a functioning kidney transplant. Nevertheless, given the data from the HPS and the CTT Collaboration (discussed previously), we believe that there is a strong argument to abandon a threshold-based algorithm for treating hyperlipidemia. Rather, it may be advisable to treat those with high risk for atherosclerotic cardiac events regardless of initial LDL level and to treat with a potent dosage of a statin alone or in combination with a second-line drug to achieve a marked (at least 30 to 40%) reduction in LDL, at least to NCEP ATP-III LDL goal levels. Whether a lower goal LDL of <70 mg/dl may be indicated in patients with CKD is not clear, but we believe that it is a reasonable therapeutic option in patients with CKD. The increase in mortality in hemodialysis patients at lower cholesterol levels demands caution with such aggressive cholesterol lowering in this population.
- Acknowledging the high risk for CVD in CKD while understanding that only a fraction of this risk is attributable to CHD, we believe that it is reasonable but not mandatory to consider a reduced GFR, proteinuria, and perhaps mi-
croalbuminuria to be a “CHD risk equivalent” in the NCEP ATP-III schema.

- The recent 4-D Study indicates that the routine treatment of hemodialysis patients with diabetes may not be warranted, but it does rule out a benefit of higher dosages or earlier treatment.
- Ezetimibe is a reasonable choice for a second-line LLD in the CKD population and probably in kidney transplant recipients.

Conclusion

We believe that the literature supports a seemingly obvious conclusion that as the severity and duration of uremia increase, the epidemiology, pathophysiology, and response to treatment of CVD changes gradually from what is experienced in the general population to what is unique to the uremic milieu. It becomes much less clear whether LLD are of benefit as CKD advances, especially in dialysis patients, in whom the myriad competing pathogenic mechanisms of CVD may abrogate any benefit that LLD may provide. Clearly, there is great potential for benefit of statins and other LLD in this population, but the need for further study is urgent. Important large-scale studies are under way to clarify the best treatment strategy.

Disclosures

Both authors are investigators in the SHARP Study, which is supported by an unrestricted grant from Merck Schering-Plough.

References

cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 91: 2528–2540, 1995


43. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288: 2981–2997, 2002

44. Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA,


