The incidence and prevalence of chronic kidney disease (CKD) is increasing in the U.S. (1,2). Although some patients with CKD will ultimately develop renal failure, most patients with CKD will die of cardiovascular disease before dialysis becomes necessary (3). Patients with CKD have major proatherogenic lipid abnormalities that are treatable with readily available therapies. The severe derangements seen in lipoprotein metabolism in patients with CKD typically result in high triglycerides and low high-density lipoprotein (HDL) cholesterol. Because of the prevalence of triglyceride disorders in patients with CKD, after treating patients to a low-density lipoprotein goal, non-HDL should be calculated and used as the secondary goal of treatment. A review of the evidence from subgroup analysis of several landmark lipid-lowering trials supports treating dyslipidemia in mild to moderate CKD patients with HMG-CoA reductase inhibitors. The evidence to support treating dyslipidemia in hemodialysis patients, however, has been mixed, with several outcome trials pending. Patients with CKD frequently have mixed dyslipidemia and often require treatment with multiple lipid-lowering drugs. Although statins are the cornerstone of therapy for most patients with CKD, differences in their pharmacokinetic properties give some statins a safety advantage in patients with advanced CKD. Although most other lipid-lowering agents can be used safely with statins in combination therapy in patients with CKD, the fibrates are renally metabolized and require both adjustments in dose and very careful monitoring due to the increased risk of rhabdomyolysis. After reviewing the safety and dose alterations required in managing dyslipidemia in patients with CKD, a practical treatment algorithm is proposed. (J Am Coll Cardiol 2008;51:2375–84) © 2008 by the American College of Cardiology Foundation

The prevalence of stage 5 CKD (kidney failure or hemodialysis) is 0.1% of the U.S. population, and the prevalence of mild to severe disease (CKD stages 1 to 4) is 11% of the U.S. population (5).

Epidemiology of Cardiovascular Disease in Patients With CKD

Hemodialysis patients (stage 5 CKD) have extremely high morbidity and mortality from CVD. Based on data from the U.S. Renal Data System Coordinating Center Case-Mix Adequacy Study, the prevalence of clinical coronary heart disease (CHD) in hemodialysis patients is 40%, and CVD mortality is 10 to 30 times higher than in the general population.
characteristics of dyslipidemia in CKD

CKD causes profound dysregulation of lipoprotein metabolism, resulting in multiple lipoprotein abnormalities (Table 3) (12). Dyslipidemia develops during the early stages of CKD, and significant changes in apolipoproteins usually precede changes in plasma lipid levels (13,14). Depressed high-density lipoprotein (HDL) levels and increased triglyceride-rich lipoproteins are the major lipid abnormalities.

Reductions in plasma concentrations of apoprotein (Apo)A-I and ApoA-II are thought to play a large role in the low HDL cholesterol (HDL-C) levels. ApoA-I and ApoA-II are mandatory components of the HDL particle. Patients with CKD have been shown to have reduced genetic expression of these apoproteins at sites of HDL production (15). Another factor contributing to low HDL-C levels is the profound inflammation present in these patients. Chronic inflammation results in decreased albumin levels. Albumin serves as a carrier of free cholesterol from the peripheral tissues to HDL, and a reduction in albumin may contribute to reduced HDL-C levels (12).

The increased plasma triglyceride levels can be explained in part by significant increases in plasma ApoC-III levels. Apoprotein C-III is a potent inhibitor of the enzyme lipoprotein lipase, which is responsible for the degradation of triglyceride-rich particles (16). Numerous other factors contribute to the increased triglycerides observed in patients with CKD, and a comprehensive description is beyond the scope of this review.

Evidence Concerning Treatment in Hemodialysis Patients (CKD Stage 5)

Although hemodialysis patients have excessive risk of morbidity and mortality from CVD, the evidence concerning treatment of hemodialysis patients with lipid-modulating drugs is equivocal. There is observational evidence suggesting a benefit from treating dyslipidemia in patients on hemodialysis. In the U.S. Renal Data System Dialysis Morbidity and Mortality Study, 3,700 patients on hemodialysis were followed for 2 years. Statin users had a 32%
relative risk reduction in total mortality, whereas fibrate users had no reduction in cardiovascular or total mortality (17). In another observational study, the Dialysis Outcomes Practice Patterns Study, 9,800 hemodialysis patients were followed for 5 years, and statin users had a 31% (p = 0.0001) relative risk reduction in total mortality compared with nonusers (18).

The 4D trial (Die Deutsche Diabetes Dialyse Studie) is the only prospective randomized controlled clinical trial with statins in a hemodialysis population (Table 4) (19). A total of 1,200 type II diabetics on hemodialysis participated in this study and were randomized to atorvastatin 20 mg/day or placebo for 4 years. In stark contrast to the observational data, atorvastatin 20 mg/day had a nonsignificant 8% relative risk reduction (95% CI 0.77 to 1.10; p = 0.37) on the combined primary end point of cardiac death, nonfatal myocardial infarction (MI), or stroke. Furthermore, atorvastatin increased the risk of fatal stroke (RR 2.03; 95% CI 1.05 to 3.93; p = 0.04). In both the treatment and the control groups, 21% of the cardiac deaths were due to MI, whereas 59% were attributed to sudden cardiac death (19). This suggests that dysrhythmia may be an important cause of cardiovascular deaths in hemodialysis patients, and that this cause of death may not be modifiable with a statin. Another explanation for these negative results is that the 4D study population had atherosclerosis that was so advanced, patients were beyond obtaining benefit from drug therapy. These patients had been on dialysis for at least 2 years, 50% were smokers, and 50% had a prior history of MI.

The OPACH (Omega-3 Fatty Acids as Secondary Prevention Against Cardiovascular Events in Patients Who Undergo Chronic Hemodialysis) study was a recent randomized, double-blind, placebo controlled trial in 206 chronic hemodialysis patients (20). Participants were randomized to 1.7 g/day of omega-3 fatty acids administered as 2 capsules of omega-3 acid ethyl esters (eicosapentaenoic acid 45% and docosahexaenoic acid 37.5%) or an olive oil placebo. Although no significant reduction was seen in the combined primary end point of cardiovascular events or death (62 events in the omega-3 group and 59 in the control group), there was a 70% (95% CI 0.10 to 0.92; p = 0.036) relative risk reduction in MI. In addition, the incidence of adverse events was not significantly greater than placebo. This trial was limited by the small number of participants and the small changes in lipoproteins seen during the trial.

There are 2 large randomized trials underway that may help to answer the question concerning the use of statins in hemodialysis patients. The AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: an Assessment of Survival and Cardiovascular Events) trial is a randomized placebo controlled trial with 2,700 hemodialysis patients using rosuvastatin 10 mg/day (21). In another ongoing trial, the SHARP (Study of Heart and Renal Protection) trial, there will be an arm of the study with 3,000 hemodialysis patients randomized to simvastatin 20 mg/day or simvastatin 20 mg/day plus ezetimibe (22).

### Table 3

<table>
<thead>
<tr>
<th>Protein</th>
<th>Change</th>
<th>Effect on Plasma Lipids or LP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoA-I</td>
<td>↓</td>
<td>↓ HDL</td>
</tr>
<tr>
<td>LCAT</td>
<td>↓</td>
<td>↓ HDL-C, HDL-2/HDL-3</td>
</tr>
<tr>
<td>CETP</td>
<td>↑</td>
<td>↑ HDL-C</td>
</tr>
<tr>
<td>ACAT</td>
<td>↑</td>
<td>↑ VLDL-C, ↓ HDL-C</td>
</tr>
<tr>
<td>LPL</td>
<td>↑</td>
<td>↑ Trig (↓ delipidation of VLDL and CM)</td>
</tr>
<tr>
<td>VLDL receptor</td>
<td>↓</td>
<td>↓ VLDL, Trig</td>
</tr>
<tr>
<td>Hepatic lipase</td>
<td>↑</td>
<td>↑ IDL, CM remnants, HDL-TG, Trig, LDL-TG</td>
</tr>
<tr>
<td>LRP</td>
<td>↑</td>
<td>↑ IDL, CM remnants</td>
</tr>
<tr>
<td>ApoCII/CIII ratio</td>
<td>↓</td>
<td>↑ Trig (↑ LPL activity)</td>
</tr>
<tr>
<td>Pre-β HDL</td>
<td>↑</td>
<td>↑ Trig (↑ LPL activity)</td>
</tr>
</tbody>
</table>

Adapted from Vaziri (4).

- **↓** = decreases; **↑** = increases; **ACAT** = acyl-CoA (cholesterol acyl) transferase; **Apo = apoprotein; CETP** = cholesteryl ester transferase protein; **CM** = chylomicron; **DGAT** = acyl-CoA diacylglycerol acyl transferase; **HDL = high-density lipoprotein; HDL-C = high-density lipoprotein cholesterol; HDL-TG = high-density lipoprotein triglyceride; **IDL = intermediate-density lipoprotein; LCAT** = lecithin cholesterol acyl transferase; **LDL-TG = low-density lipoprotein triglyceride; LPL = lipoprotein lipase; LRP = low-density lipoprotein receptor-related protein; **Trig = triglyceride; VLDL = very-low-density lipoprotein; VLDL-C = very-low-density lipoprotein cholesterol; VLDL-TG = very-low-density lipoprotein triglyceride.**

### Evidence Concerning Treatment in Patients With Mild to Moderate CKD (CKD Stages 1 to 4)

In patients with earlier stages of CKD there are data derived from the subgroup analysis of several landmark secondary prevention trials (Table 4). The Heart Protection Study enrolled 20,000 British men and women age 40 to 80 years who were at increased risk of death from CVD due to diabetes, coronary heart disease (CVD), or other atherosclerotic disease (23). This 5-year study evaluated the benefit of lowering cholesterol with simvastatin 40 mg/day. The primary outcomes were total mortality and fatal and nonfatal vascular events. This large study population included a subgroup of 1,329 patients with CKD 3 with creatinine ranging from 1.3 to 2.3 mg/dl. There was a relative risk reduction of 28% (95% CI 0.72 to 0.85; p = 0.05). The event rate was 39.2% in the control group and 28.2% in the simvastatin arm, yielding an absolute risk reduction (ARR) of 11% and a number needed to treat of 9. This ARR is remarkable compared with the ARR of 5.4% for the entire Heart Protection Study population.

In the CARE (Cholesterol and Recurrent Events) study, over 4,000 patients with previous MI and plasma total cholesterol <240 mg/dl were randomized to pravastatin 40 mg/day or placebo and followed for approximately 5 years (Table 4). A subgroup of 1,700 patients with creatinine clearance <75 ml/min was evaluated. These patients with mild CKD had a 28% (95% CI 0.55 to 0.95; p = 0.02) relative risk reduction and a 4% ARR in the primary end point (death from coronary disease or symptomatic nonfatal myocardial infarction) when treated with pravastatin 40 mg/day (24).

The only published prospective randomized clinical trial evaluating statin therapy in patients with mild CKD is the
PREVEND IT (Prevention of Renal and Vascular End Stage Disease Intervention Trial) (Table 4) (25). In this primary prevention trial with a 2 × 2 factorial design, 864 patients with microalbuminuria were randomized to fosinopril 20 mg/day or matching placebo and to pravastatin 40 mg/day resulted in a nonsignificant 17% reduction (0.87 [95% CI 0.49 to 1.57]; p = 0.95) in the primary end point of cardiovascular mortality and hospitalization for cardiovascular morbidity. This study was powered to demonstrate a statistically significant 35% risk reduction (0.64–1.06) (p < 0.05) (25).

In the nonstatin, VA-HIT (Veterans’ Affairs High-Density Lipoprotein Intervention Trial), over 2,500 men with CHD were enrolled and randomized to gemfibrozil 1,200 mg/day or placebo. In this study, a subgroup of 1,000 men with a creatinine clearance <75 ml/min was identified. In post hoc analysis, these patients with mild to moderate CKD were found to have a 27% relative risk reduction (0.73 [95% CI 0.56 to 0.96]; p = 0.02) and a 6.3% ARR in fatal and nonfatal MI (28) (Table 4).

Of clinical trials in progress, the SHARP trial is an ongoing study with a subgroup of 6,000 patients with mild to moderate CKD (creatinine >1.5 mg/dl). Patients in this trial with clinical end points will be randomized to simvastatin 20 mg/day or simvastatin 20 mg/day plus ezetimibe 10 mg/day. There will be an additional arm in this study that includes 3,000 hemodialysis patients (22).

### Safety Issues in CKD Patients

#### Safety of statin therapy

Although all statins have been used safely in patients with CKD (stage 1 and 2), there are differences in statin pharmacokinetic properties that might confer safety advantages to some statins (stage 3 to 5). Statin adverse events are often dose related and related to increased blood concentrations of the drug. Statins that are more dependent on renal excretion are more likely to need dose adjustments (Table 5). Atorvastatin has <2% renal excretion and does not require a dose adjustment for GFR <30 ml/min/1.73 m² (29). Also, statins that are metabolized by
the cytochrome P450-3A4 system (CYP-3A4) are more likely to result in adverse events due to drug–drug interactions. Although fluvastatin and atorvastatin have minimal excretion in the kidney, fluvastatin does not use the CYP-3A4 route for metabolism (Table 5) and has no active circulating metabolites (30,31). In addition, fluvastatin pharmacokinetics are unchanged in patients on hemodialysis or on chronic ambulatory peritoneal dialysis (30,31).

Finally, the discovery that statins cause transient mild tubular proteinuria in some patients has caused some to question their effect on the natural progression of CKD (32). The completion of some of the major clinical trials already mentioned (e.g., the SHARP trial) should help to answer this question. However, the collective evidence from post hoc analysis of large clinical trials with cardiovascular end points suggests that statins may preserve renal function and reduce proteinuria over time. The Pravastatin Pooling Project was a post hoc subgroup analysis of data from 3 randomized controlled trials comparing pravastatin 40 mg/day to placebo in over 18,000 patients with a prior MI (33). Pravastatin reduced the adjusted rate of kidney function loss by 8% (0.08 ml/min/1.73 m²/year; 95% CI 0.01 to 0.15) and the relative risk of acute renal failure by 60% (95% CI 0.41 to 0.86; p = 0.005). In a recent meta-analysis, 22 placebo-controlled trials were identified that studied the renal benefits of statins. Statins reduced the rate of decline in GFR by 1.23 ml/min/1.73 m²/year compared with placebo. This review, however, was limited by significant between-trial heterogeneity (34).

The proposed renal-protective mechanism is based on in vitro observations that statins impede the normal reabsorption of albumin in the proximal tubule. Mevalonate, a metabolite in the cholesterol synthetic pathway, is reduced in patients on statins and is necessary for the normal reabsorption of albumin in the proximal renal tubule (35). In vitro studies indicate that protein reabsorption in proximal tubular cells is proinflammatory and contributes to tubulointerstitial disease; therefore, the blocking of protein reabsorption in tubular cells may be renoprotective over time. In summary, although statins may increase tubular proteinuria initially, they may reduce inflammation, slow fibrosis, and result in less proteinuria in the long term (36).

**Safety of fibrac acid derivatives**. Fibrac acid derivatives, also known as fibrates, are peroxisome proliferator activated receptor-α (PPAR-α) agonists and are metabolized in the kidney and predominantly eliminated via the renal route (37,38). A characteristic of this class of drugs is their propensity to cause a moderate reversible increase in serum creatinine. Fenofibrate and gemfibrozil are the fibrates available in the U.S. Gemfibrozil is less likely to cause this increase, but is more likely to cause rhabdomyolysis when combined with a statin, due to a pharmacokinetic interaction (39). Specifically, gemfibrozil raises statin blood concentrations by impairing the glucuronidation of statins, whereas fenofibrate’s effect on the glucuronidation of statins is minimal (Table 6) (40). In the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study, over 9,700 type II diabetics not taking a statin at baseline were randomized to micronized fenofibrate 200 mg/day or placebo and followed for 5 years (41). Plasma creatinine was closely monitored. During the study, plasma creatinine remained an average of 0.11 to 0.14 mg/dl higher in the fenofibrate group, which had a median concentration of 1.03 at study completion, compared with 0.90 mg/dl in the placebo group (p < 0.001). Finally, in a subgroup of 661 patients that were studied 8 weeks after ceasing study medication, the plasma creatinine returned from 1.03 to 0.89 mg/dl, suggesting no long-term renal sequelae.

Some have proposed that the fibrate-induced increase in serum creatinine is due to the reduced production of vasodilatory prostaglandins. Other investigators have suggested that PPAR-α agonists increase creatinine production without a reduction in GFR (42). In small retrospective studies, gemfibrozil appeared less likely to increase serum creatinine; however, more recent studies have suggested that gemfibrozil can also cause an increase in creatinine, but to a smaller degree than fenofibrate (43). More importantly, pharmacokinetic studies with gemfibrozil and patients with CKD indicate that the excretion of gemfibrozil is reduced to a lesser extent than fenofibrate (43). Fenoibrate is nondialysable and studies in patients with moderate CKD (GFR <50 ml/min/1.73 m²) demonstrated a reduced rate of fenofibrate excretion and accumulation of the drug with persistent usage (38).

Because of these pharmacokinetic characteristics, the NKF and the National Lipid Association (NLA) have issued recommendations for the cautious use of fibrates in patients with CKD (29). The NKF recommends that

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**Table 5 Clinical Pharmacokinetics of Statins**

<table>
<thead>
<tr>
<th>Rosuva</th>
<th>Atorva</th>
<th>Simva</th>
<th>Lova</th>
<th>Prava</th>
<th>Fluva</th>
</tr>
</thead>
<tbody>
<tr>
<td>T 1/2, h</td>
<td>20.8</td>
<td>15–30</td>
<td>2–3</td>
<td>2.9</td>
<td>1.3–2.8</td>
</tr>
<tr>
<td>Urinary excretion, %</td>
<td>10</td>
<td>&lt;2</td>
<td>13</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>CYP-3A4 metabolism</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CYP metabolism</td>
<td>2CY9</td>
<td>3A4</td>
<td>3A4</td>
<td>3A4</td>
<td>sulfation</td>
</tr>
</tbody>
</table>

Adapted from Blum (31).

---

**Table 6 Statin/Fibrate Pharmacokinetic Interactions**

<table>
<thead>
<tr>
<th>Gemfibrozil</th>
<th>Fenoibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>↑ Cmax by 1.8-fold</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>↑ Cmax by 2-fold</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>↑ Cmax by 2-fold</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>↑ Cmax by 2-fold</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>No effect</td>
</tr>
<tr>
<td>Cericvarstain</td>
<td>↑ Cmax by 2.8-fold</td>
</tr>
</tbody>
</table>

Adapted from Jacobson and Zimmerman (47).

- ↓ decreases; ↑ increases; Cmax = maximum concentration.
patients with GFR 60 to 90 ml/min/1.73 m² should reduce fenofibrate dosing by 50%, those with GFR 15 to 59 ml/min/1.73 m² should reduce dosing by 75%, and those on hemodialysis or with GFR <15 ml/min/1.73 m² should completely avoid use of fenofibrate. According to the NKF guidelines, gemfibrozil is designated as the fibrate of choice in patients with CKD and no dose adjustments are required for reduction in GFR (29).

The recent NLA guidelines for fenofibrate use are similar to the NKF guidelines, though they differ in their recommendations for gemfibrozil use. The recommended dose of gemfibrozil in CKD patients with GFR <60 ml/min/1.73 m² is 600 mg/day (50% reduction), and it is recommended to avoid all fibrates for GFR <15 ml/min/1.73 m². In addition, the NLA recommends measuring serum creatinine before starting fibrate therapy (39).

Finally, there are concerns about the tendency of fenofibrate to also increase already elevated homocysteine levels in patients with CKD (44). Elevated homocysteine levels are thought to be a risk factor for vascular disease and hypercoagulability. In the FIELD study, plasma homocysteine was an average of 3.7 μmol/l higher in the fenofibrate group; however, plasma homocysteine levels were at pre-study baseline within 8 weeks of stopping the fenofibrate (41). Other fenofibrate studies have demonstrated similar increases, whereas studies with other fibrates have not consistently demonstrated increases in homocysteine levels (45). The clinical relevance of fenofibrate-induced elevations in homocysteine is uncertain; however, the FIELD study with fenofibrate and the Coronary Drug Project (46) with clofibrate both demonstrated small but significant increases in venous thromboembolic disease in fibrate-treated patients.

Safety of statin-fibrate combinations. An additional safety consideration in patients with CKD is the safety of a statin when combined with a fibric acid derivative. Patients with CKD frequently have mixed dyslipidemia, and high-risk patients may need treatment with a statin and a fibric acid derivative. As discussed in the preceding, there are distinct pharmacokinetic differences between fibrates when combined with statins (Table 6). Gemfibrozil increases the plasma levels of all of the statins with the exception of fluvastatin, and thus increases the predisposition for rhabdomyolysis (47). This effect is not seen with fenofibrate and is not related to cytochrome P450 metabolism, but is due to the inhibition of the glucuronidation pathway involved in the metabolism of statins (47). Although gemfibrozil is the NKF fibrate of choice, fenofibrate is the preferred fibrate option when combining with a statin. However, both the statins and fenofibrate are independently associated with an increased risk of myopathy, and therefore there is increased risk of myopathy and rhabdomyolysis when these drugs are combined. For optimal safety in fibrate-statin combination treatment, the NLA recommends not using the maximum dose of a statin in combination with a fibrate (39).

Safety of other lipid-lowering drugs. The bile acid sequestrants, including colesevelam and cholestyramine, are generally safe to use in the setting of CKD, because they are not systemically absorbed; however, they can increase triglyceride levels and are contraindicated in patients with elevated triglycerides (48). In a recent study, 36 hemodialysis patients were treated with colesevelam 1.5 g before meals for 6 months. Investigators noted a 20% reduction in non–HDL-C (p < 0.0001) and a 63% reduction in median C-reactive protein values (p = 0.0259) (49).

There are limited data on the efficacy and safety of nicotinic acid in CKD. Pharmacokinetic studies indicate that 34% of the drug is excreted in the kidneys. According to the NKF guidelines, for those with GFR <15 ml/min/1.73 m², the dose should be reduced by 50%; otherwise no dosing changes are recommended (29).

There are small studies with ezetimibe indicating that it is safe and well tolerated in moderate to severe CKD and that no modified dosing for reduced GFR is required. In the UK-HARP II (United Kingdom Heart and Renal Protection II) study, 203 patients with varying degrees of renal failure were studied for 6 months (50). Participants included 152 pre-dialysis patients with creatinine levels >1.7 mg/dl, 18 patients on peritoneal dialysis, and 33 patients on hemodialysis. The control group received 20 mg/day simvastatin, and the treatment arm was treated with 20 mg simvastatin plus 10 mg/day ezetimibe. The treatment arm receiving 10 mg/day ezetimibe had a 21% greater reduction in LDL (p = 0.0001) than the monotherapy group, yet no adverse events were experienced with the addition of ezetimibe.

Lipid Management in CKD Patients Stages 3 to 4 (GFR 15 to 50 ml/min/1.73 m²)

The NKF and National Cholesterol Education Program Adult Treatment Panel (ATP) III offer similar guidelines for the management of dyslipidemia in patients with CKD; however, significant differences exist (29,51). In the NKF recommendations, CKD is regarded as a CHD risk equivalent and an annual lipid panel is recommended. As with any dyslipidemic patient, a comprehensive search for secondary causes of dyslipidemia should be conducted, including a search for endocrine disorders such as hypothyroidism and diabetes and medications such as corticosteroids, protease inhibitors, beta-blockers, diuretics, and estrogen.

Elevated LDL-C. Although patients with CKD frequently have multiple abnormalities in their lipid profile, LDL-C reduction is the primary goal of therapy. The NKF recommends LDL-C <100 mg/dl for patients with CKD. Currently the NKF does not recommend a more aggressive LDL goal for patients with CKD and symptomatic atherosclerotic disease (30). Based on the amended ATP III guidelines, it might be prudent to treat to an LDL goal of <70 mg/dl in patients with CKD with atherosclerotic disease.
As in the general population, statins are the cornerstone of therapy for dyslipidemia. Treatment with a statin in conjunction with therapeutic lifestyle changes is usually required to obtain these goals. All statins can be used safely in patients with CKD; however, differences in the pharmacokinetic properties give some statins a safety advantage in patients with advanced CKD (GFR < 30 ml/min/1.73 m²). Because the excretion of atorvastatin in the kidneys is negligible, no dose adjustment for reduced GFR or hemodialysis is required (Table 7). If combination therapy with a gemfibrozil is likely, then fluvastatin may be the safest choice. Other statins require dose adjustments as CKD becomes more advanced (30) (Table 7).

In patients not at their LDL goal on atorvastatin or fluvastatin, ezetimibe or bile acid sequestrants can be added safely (Table 8). Bile acid sequestrants’ safety may be limited by their tendency to increase triglycerides, which frequently are elevated in CKD. In addition, bile acid sequestrants may be limited by their tendency to bind to other medications and reduce their absorption (48).

**Mixed dyslipidemia.** Most patients with CKD have triglyceride as well as HDL abnormalities along with elevated LDL (mixed dyslipidemia). After LDL goal attainment, non-HDL should be the primary goal in the management of patients with CKD with mixed dyslipidemia. Non-HDL is the only lipid measurement that correlates positively with cardiovascular mortality in hemodialysis patients (52). Very-low-density lipoprotein and intermediate-density lipoprotein are both known to be elevated in patients with CKD with mixed dyslipidemia, and therefore non-HDL may be a better marker of atherogenic cholesterol levels. Based on NKF recommendations, patients with CKD should be

---

**Table 7**

<table>
<thead>
<tr>
<th>Agent</th>
<th>GFR 60–90 ml/min/1.73 m²</th>
<th>GFR 15–59 ml/min/1.73 m²</th>
<th>GFR &lt;15 ml/min/1.73 m²</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>↓ dose to one-half at GFR &lt; 30 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>No</td>
<td>Not defined</td>
<td>Not defined</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>No</td>
<td>↓ to 50%</td>
<td>↓ to 50%</td>
<td>↓ dose to one-half at GFR &lt; 30 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Start at 10 mg/day for GFR &lt; 60 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>No</td>
<td>5–10 mg</td>
<td>5–10 mg</td>
<td>Start at 5 mg/day for GFR &lt; 30 ml/min/1.73 m², max dose 10 mg/day</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>No</td>
<td>No</td>
<td>5 mg</td>
<td>Start at 5 mg if GFR &lt; 10 ml/min/1.73 m²</td>
</tr>
<tr>
<td><strong>Nonstatins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>No</td>
<td>No</td>
<td>↓ to 50%</td>
<td>34% kidney excretion</td>
</tr>
<tr>
<td>Cholestryramine</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Not absorbed</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Not absorbed</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>May ↑ serum creatinine</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>↓ to 50%</td>
<td>↓ to 25%</td>
<td>Avoid</td>
<td></td>
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<tr>
<td>Gemfibrozil</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NLA recommends a dose of 600 mg/day for GFR 15–59 ml/min/1.73 m² and avoiding use for GFR &lt; 15 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Omega-3 FAs</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from the K/DOQI clinical practice guidelines (29).

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**Table 8**

<table>
<thead>
<tr>
<th>Lipid Disorder</th>
<th>Therapeutic Option (See Table 7 for Dose Adjustments)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate to severe CKD, stages 3 to 4 (GFR 15–59 ml/min/1.73 m²)</strong></td>
<td>1) Atorvastatin, add ezetimibe if not at LDL-C goal&lt;br&gt;2) Fluvastatin, add ezetimibe if not at LDL-C goal</td>
</tr>
<tr>
<td><strong>Mixed dyslipidemia</strong> (not at non-HDL† goal)</td>
<td>1) Atorvastatin or fluvastatin + ezetimibe&lt;br&gt;2) Fluvastatin + gemfibrozil 600 mg/day + ezetimibe if not at non-HDL goal&lt;br&gt;3) Statin + omega-3 fatty acids, add ezetimibe if not at non-HDL goal&lt;br&gt;4) Statin + fenofibrate 48 mg/day, add ezetimibe if not at non-HDL goal</td>
</tr>
<tr>
<td>Very high triglycerides (triglyceride ≥ 500 mg/dl)</td>
<td>1) Gemfibrozil 600 mg/day&lt;br&gt;2) Omega-3 fatty acids 3–4 g/day&lt;br&gt;3) Fenofibrate 48 mg/day</td>
</tr>
<tr>
<td><strong>CKD stage 5 (hemodialysis or GFR &lt; 15 ml/min/1.73 m²)</strong></td>
<td>Atorvastatin (10–80 mg/day) or fluvastatin 40 mg/day, add ezetimibe if not at LDL-C goal&lt;br&gt;Atorvastatin or fluvastatin 40 mg/day, add ezetimibe 10 mg/day or omega-3 fatty acids 3–4 g/day if not at non-HDL goal</td>
</tr>
<tr>
<td><strong>Very high triglycerides</strong></td>
<td>Omega-3 fatty acids 3–4 g/day or gemfibrozil 600 mg/day</td>
</tr>
</tbody>
</table>

*Mixed dyslipidemia = elevated triglycerides and low HDL with or without elevated LDL; †Non-HDL = total cholesterol − HDL cholesterol; CKD = chronic kidney disease; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL-C = low-density lipoprotein cholesterol.
treated to an LDL-C <100 mg/dl and a non–HDL-C <130 mg/dl (30).

Patients with mixed dyslipidemia frequently require combination therapy with a statin plus additional lipid-lowering drugs that could include ezetimibe, a fibrate, niacin, or omega-3 fatty acids. Although ezetimibe has a negligible effect on HDL and triglycerides, the addition of ezetimibe to a statin results in a significant additional reduction in non–HDL-C, which is the secondary therapeutic goal in mixed dyslipidemia (Table 8). The combination of ezetimibe and a statin is relatively safe and well tolerated in patients with CKD (50).

The omega-3 fatty acids may also be used in combination with a statin. Although published data on this combination in patients with CKD is limited, omega-3 fatty acids do not have significant interactions with statins and do not require dose reductions for impaired renal function (53).

Although fibrates can be used to treat mixed dyslipidemia, they need to be used carefully, because they are predominantly metabolized by the kidneys. According to the NKF guidelines, gemfibrozil is the fibrate of choice in patients with CKD (29). There is still controversy concerning the safety of fenofibrate in patients with CKD, because of its propensity for increasing serum creatinine and homocysteine to a greater degree than gemfibrozil. Due to the increased risk of rhabdomyolysis with fibrate and statin therapy in patients with CKD, the combination requires more vigilant monitoring, and patients need to report muscle symptoms immediately. Combined with a statin, fenofibrate clearly has advantages due to its lack of pharmacokinetic interactions with statins and lower propensity for rhabdomyolysis (47). When gemfibrozil is selected for combination treatment with a statin, consideration should be given to changing the statin to fluvastatin, for which there is no pharmacokinetic interaction and fewer cases of rhabdomyolysis have been reported compared with other statins. Because of fluvastatin’s lower efficacy in LDL reduction, the addition of a third drug, ezetimibe, may be necessary (Table 8). Because CKD alone is a risk factor for rhabdomyolysis, the combination of a statin with any fibrate still needs to be weighed carefully from a risk-benefit perspective.

Niacin is also an option for the treatment of mixed dyslipidemia. Niacin has been shown to increase HDL-C, and reduce both lipoprotein (a) and triglycerides, which are elevated in patients with CKD, but its use is limited due to poor tolerability (50). The NKF clinical practice guidelines recommend reducing niacin dosing by 50% for GFR <60 ml/min/1.73 m² (39). Finally, if fenofibrate must be used, the dose should not exceed 48 mg/day and creatinine levels should be monitored carefully (39).

Another option for very high triglycerides is to treat with omega-3 fatty acids derived from fish oil. The main active ingredients in fish oil are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Four grams of omega-3 fatty acids per day, in the form of fish oil capsules, have been shown to reduce triglycerides 35% to 45% (54). The omega-3 fatty acids are safe in patients with CKD and have minimal drug interactions. Until recently, a major limitation was that over-the-counter preparations had only 200 to 300 mg omega-3 fatty acids per capsule, requiring the consumption of 12 to 16 capsules/day. The only available prescription-brand omega-3 fatty acid contains almost 900 mg omega-3 fatty acids, requiring only 4 capsules/day (54).

**Lipid Management in Hemodialysis Patients (CKD Stage 5; GFR <15 ml/min/1.73 m²)**

The options for hemodialysis CKD stage 5 patients are more limited than patients with CKD stages 1 through 4. For patients with elevated LDL-C, choosing statins with limited renal excretion, such as atorvastatin or fluvastatin, may be more important (Table 8). In mixed dyslipidemia, omega-3 fatty acids may have a more prominent role, because the NLA recommends avoiding fibrate use in patients with a GFR <15 ml/min/1.73 m² (39). In patients with very high triglycerides, clinicians can treat with 3 to 4 g/day omega-3 fatty acids, or if a fibrate must be used then gemfibrozil can be given at a reduced dose of 600 mg/day.

**Conclusions**

The incidence of CKD in the U.S. continues to increase, and now over 10% of the U.S. population has some form of CKD. These patients have markedly increased risk of cardiovascular events and death. Because patients with CKD are at high risk, the NKF has designated CKD a CHD risk equivalent, and studies suggest that CKD is as powerful a risk factor as diabetes mellitus (8). Although many factors other than lipids may contribute to the high cardiovascular event rates observed in patients with CKD, it is likely that dyslipidemia plays a major role. Early epidemiologic studies suggesting that high cholesterol was an advantage for hemodialysis patients were most likely confounded. The severe derangements seen in lipoprotein metabolism in patients with CKD typically results in high triglycerides and low HDL-C.
Statins are the cornerstone of therapy for most patients with CKD, except those with triglycerides >500 mg/dl, in which case gemfibrozil or an omega-3 fatty acid supplement from fish oil could be considered. Because of the high prevalence of triglyceride disorders in patients with CKD, non-HDL should be calculated for patients with CKD and used as the secondary goal of treatment.

Evidence from subgroup analysis of several landmark lipid trials supports treating dyslipidemia in mild to moderate patients with CKD, and this group represents the majority of patients with CKD. Currently there is no evidence to support treating hemodialysis patients; however, 2 large trials using statins with hemodialysis patients are underway. Because statins are relatively safe and the evidence for lowering cholesterol to reduce CVD is overwhelmingly positive in nonhemodialysis patients, it is reasonable to continue treating these patients until future trials are completed.

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