Chapter 2: Pharmacological cholesterol-lowering treatment in adults

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INTRODUCTION
Therapeutic lifestyle measures to reduce serum cholesterol levels have been broadly recommended by prior guidelines.\(^1,12\) Although clinically appealing, such measures typically reduce serum cholesterol to only a small extent, and have not been shown to improve clinical outcomes (Supplemental Tables 1–5 online). The Work Group therefore chose to focus the recommendations for treatment on pharmacological interventions. However, it is important to note that many of these measures may improve general health (independent of any effect on lipid levels).

The primary rationale for pharmacological cholesterol-lowering treatment is to reduce morbidity and mortality from atherosclerosis. Although limited clinical data support a link between treatment of dyslipidemia and better renal outcomes,\(^13\) more recent trials have not confirmed this hypothesis.\(^14\)

Although several different medications lower LDL-C, only regimens including a statin (including statin/ezetimibe) have been convincingly shown to reduce the risk of adverse cardiovascular events in CKD populations. Therefore, the recommended approach for pharmacological cholesterol-lowering treatment in CKD focuses on the use of statins (with or without ezetimibe) in people at risk of future cardiovascular events.

BACKGROUND
LDL-C is not suitable for identifying CKD patients who should receive pharmacological cholesterol-lowering treatment
LDL-C is strongly and independently associated with risk of atherosclerotic events in the general population;\(^15\) knowledge of this association facilitated the discovery that statins reduce coronary risk. Initially, statin use was limited to those with substantially elevated LDL-C (>4.5 mmol/l [>174 mg/dl]), but subsequent work indicated that the relative risk (RR) reduction associated with statin use is relatively constant across a broad range of baseline LDL-C levels, suggesting that absolute benefit from statin treatment is proportional to baseline coronary risk rather than baseline LDL-C.

Associations between LDL-C and coronary artery disease in dialysis patients. Observational data indicate that dialysis patients with the highest and lowest levels of LDL-C and TC are at the highest risk of adverse outcomes such as all-cause and cardiovascular mortality.\(^16-19\) This paradoxical association between cholesterol and outcomes appears to be due to effect modification by protein energy wasting, inflammation and malnutrition,\(^20,21\) which are all common in kidney failure and are themselves associated with a high risk of adverse outcomes. Put differently, patients with one of more of these three conditions are more likely to also have low cholesterol, which confounds the apparent association between cholesterol and the risk of cardiovascular death. Although cardiovascular risk is increased in dialysis patients with higher LDL-C and TC, elevated cholesterol seems unsuitable as the criterion for statin prescription in patients with kidney failure because it will fail to identify those with low cholesterol—who are also at high risk.

Associations between LDL-C and coronary artery disease in CKD patients with eGFR ≥15 ml/min/1.73 m\(^2\). As eGFR declines, the magnitude of the excess risk associated with increased LDL-C decreases. For instance, the hazard ratio [HR] (95% confidence interval [CI]) of incident myocardial infarction (MI) associated with LDL-C >4.9 mmol/l (>190 mg/dl) (as compared to 2.6–3.9 mmol/l [100–131 mg/dl]) is 3.01 (2.46–3.69), 2.30 (2.00–2.65) and 2.06 (1.59–2.67) for people with eGFR of ≥90, 60–89.9 and 15–59.9 ml/min/1.73 m\(^2\), respectively. Figure 1 shows the relation between LDL-C and the risk of hospitalization for MI for selected values of baseline eGFR.

The figure shows that the relation between LDL-C and the risk of MI appears linear at LDL-C above 2.6 mmol/l (100 mg/dl). The HR (95% CI) of MI associated with each 1 mmol/l (39 mg/dl) increase in LDL-C above 2.6 mmol/l (100 mg/dl) is 1.48 (1.43–1.54), 1.33 (1.27–1.40), 1.26 (1.18–1.35), 1.20 (1.09–1.30) and 1.13 (1.01–1.27) among people with eGFR of 90, 60, 45, 30 and 15 ml/min/1.73 m\(^2\), respectively. The weaker and potentially misleading association between LDL-C and coronary risk among those with lower levels of kidney function (a group who is at the highest absolute risk) argue against its use for identifying CKD patients who should receive pharmacological cholesterol-lowering treatment.

Which CKD patients should receive pharmacological cholesterol-lowering treatment?
To maximize the ratio of benefits to harms and costs, contemporary clinical practice emphasizes three potential determinants of the decision to prescribe lipid-lowering treatment in people with normal kidney function: baseline coronary risk; case-fatality rate following MI; and evidence that lipid-lowering treatment is beneficial.\(^23\)

Baseline coronary risk. The 10-year incidence risk of coronary death or non-fatal MI (numerically equivalent to the rate of such events per 1000 patient-years) is often used as
Figure 1 | Adjusted relation between LDL-C and HR of myocardial infarction by eGFR as a continuous variable. Data are adjusted hazard ratios for MI during a median follow-up period of 48 months. Data are from 836,060 participants in the Alberta Kidney Disease cohort and have been adjusted for age, sex, diabetes, hypertension, Aboriginal status, socioeconomic status, proteinuria categories, statin use, and the Charlson comorbidities (cancer, cerebrovascular disease, congestive heart failure, chronic pulmonary disease, dementia, metastatic solid tumor, MI, liver disease, hemiplegia/paraplegia, peptic ulcer disease, peripheral vascular disease, and rheumatic disease). eGFR, estimated glomerular filtration rate; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction. Reproduced from Tonelli M, Muntner P, Lloyd A, et al. Association between LDL-C and Risk of Myocardial Infarction in CKD. J Am Soc Nephrol 2013; 24: 979–986 with permission from American Society of Nephrology conveyed through Copyright Clearance Center, Inc; accessed http://jasn.asnjournals.org/content/24/6/979.long

Figure 2 | Future 10-year coronary risk based on various patient characteristics. Data are unadjusted rates from 1,268,029 participants in the Alberta Kidney Disease cohort. CKD refers to eGFR 15-59.9 ml/min/1.73 m² or with proteinuria. CABG, coronary artery bypass grafting; CHD, coronary heart disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; DM, diabetes mellitus; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack.
Table 3 | Rate of coronary death or non-fatal MI (by age and eGFR)

| Subgroup                        | Rate (95% CI) of coronary death or non-fatal MI (per 1000 patient-years) |
|---------------------------------|------------------------------------------------------------------------|
|                                 | Overall                                                                 |
|                                 | Male                                                                    |
|                                 | Female                                                                  |
| Age ≥40 years (eGFR G1-G4)      | 3.2 (2.9–3.6)                                                          | 17.3 (17.0–17.7) | 20.2 (19.6–20.8) | 14.9 (14.6–15.3) |
| eGFR G3a-G4                    | 4.7 (4.2–5.4)                                                          | 24.3 (23.4–25.2) | 19.9 (19.4–20.4) | 15.2 (14.5–16.0) |
| eGFR G1-G2                     | 4.6 (4.0–5.3)                                                          | 23.4 (22.6–24.2) | 19.3 (18.8–19.8) | 12.0 (11.4–12.6) |
| Age ≥50 years (eGFR G1-G4)      | 3.6 (2.5–5.3)                                                          | 16.9 (16.3–17.5) | 19.9 (19.4–20.4) | 12.9 (12.4–13.4) |
| eGFR G3a-G4                    | 1.2 (0.9–1.6)                                                          | 9.7 (9.0–10.5)   | 12.9 (12.4–13.4) | 7.5 (6.7–8.5)    |
| eGFR G1-G2                     | 1.6 (1.2–2.0)                                                          | 8.2 (7.5–9.0)    | 3.2 (2.9–3.6)    | 1.9 (1.6–2.3)    |
| Age 40-50 years (eGFR G1-G4)    | 14.9 (14.6–15.3)                                                       | 17.4 (16.9–17.9) | 19.3 (18.8–19.8) | 12.7 (12.3–13.1) |
| eGFR G3a-G4                    | 17.4 (16.9–17.9)                                                       | 23.4 (22.6–24.2) | 19.9 (19.4–20.4) | 16.4 (15.8–17.0) |
| eGFR G1-G2                     | 12.0 (11.4–12.6)                                                       | 15.2 (14.5–16.0) | 12.9 (12.4–13.4) | 6.7 (6.3, 7.2)   |

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction.

Data are unadjusted rates from 1,268,029 participants in the Alberta Kidney Disease cohort. People with diabetes, MI, and other cardiovascular disease were included. Data do not apply to people with kidney transplants.

the benchmark for assessing future coronary risk; the risk in patients with prior MI (in whom the rate of new MI is 20 per 1000 patient-years) is generally considered as sufficiently high to clearly warrant ongoing statin treatment. Most national guidelines for the general population also recommend universal or very liberal use of statin treatment among those with coronary risk that is lower than those with prior MI (but still substantially higher than average), such as those with diabetes or prior stroke. There is no consensus on the level of future coronary risk that is sufficient to justify statin treatment, but in the judgment of the Work Group on Lipid Treatment in CKD, the level of future coronary risk that is sufficient to justify statin treatment is generally considered as at least 10 per 1000 patient-years (both men and women) is consistently greater than 10 per 1000 patient-years, even in those without diabetes or prior MI. In contrast, the rate of coronary death or incident MI among CKD patients aged ≥50 years is low in those without diabetes or prior MI (Figure 2) – although it is higher than in otherwise comparable people without CKD. Further inspection of the absolute risks indicate that participants aged 40–50 years have average rates of CHD death or incident MI that are consistently less than 10 per 1000 patient-years.

**Case-fatality rate following myocardial infarction.** Multiple studies demonstrate that the risk of death following MI is increased among people with CKD, as compared to otherwise comparable people with normal kidney function. The absolute risk of death is especially high in patients treated with chronic dialysis.

Evidence that pharmacological cholesterol-lowering treatment is beneficial. The evidence supporting the clinical benefits of statin treatment in adults (alone or in combination with ezetimibe) differs substantially by severity of CKD. This evidence is presented in Supplemental Tables 6–18 online and summarized below.

Collectively, available evidence argues against the use of LDL-C to identify CKD patients who should receive cholesterol-lowering treatment and suggests focusing instead on two factors: the absolute risk of coronary events, and the evidence that such treatment is beneficial. This is the approach taken in the recommendations that follow. Prior studies convincingly demonstrate that treatments to prevent cardiovascular events are systematically underused in CKD populations despite their high baseline risk. This suggests that a concerted attempt will be required to identify and treat CKD patients that are likely to benefit from lipid-lowering therapy.

**How should the dose of pharmacological cholesterol-lowering treatment be determined in CKD patients?**

Guidelines for the general population recommend that (among patients receiving statin treatment), the dose of atorvastatin 80 mg/day reduced major cardiovascular events during a 4.9-year period of treatment.

Subgroup analysis of the TNT trial reported that atorvastatin 80 mg/day reduced major cardiovascular events...
to a greater extent than atorvastatin 10 mg/day, in 3107 patients with CKD defined by eGFR < 60 ml/min/1.73 m² and pre-existing coronary artery disease (HR 0.68; 95% CI 0.55–0.84). Serious adverse events and treatment discontinction were increased in the high dose statin group for both people with and without CKD; the RRs of these adverse events were numerically higher in people with CKD as compared to those without, but no significance testing was performed. However, TNT participants were pretreated with 10 mg of atorvastatin during the run-in phase, and therefore were preselected for atorvastatin tolerance. In addition, the mean eGFR among TNT participants with CKD was approximately 53 ml/min/1.73 m², and patients with heavy proteinuria were excluded. Therefore, whether these findings apply to the broader population of people with CKD is uncertain.

Given the potential for toxicity with higher doses of statins and the relative lack of safety data, the Work Group suggests that prescription of statins in people with eGFR < 60 ml/min/1.73 m² or RRT should be based on regimens and doses that have been shown to be beneficial in randomized trials done specifically in this population (Table 4). Patients with progressive renal dysfunction who are tolerating an alternative regimen do not necessarily need to be switched to a regimen described in Table 4, although dose reduction may be prudent in patients with severe kidney dysfunction who are receiving very aggressive regimens. Given less concern about drug toxicity in the setting of better kidney function, patients with eGFR ≥ 60 ml/min/1.73 m² (and no history of kidney transplantation) may be treated with any statin regimen that is approved for use in the general population. In the judgment of the Work Group, existing evidence does not support a specific on-treatment LDL-C target and thus adjusting the dose of statin regimens based on LDL-C levels is not required.

Safety data from large clinical trials suggest that the excess risk of adverse events associated with these regimens is similar among people with and without CKD. In the judgment of the Work Group, these considerations suggest that measurement of creatine kinase (CK) or liver enzyme assays is not required in asymptomatic patients.

Certain medications and grapefruit juice increase blood levels of statins (Supplemental Tables 19, 20 online). If such medications are required in patients who are otherwise good candidates for statin treatment, physicians may consider one of two strategies. For medications that will be required only for short periods (such as an antibiotic), the statin could be temporarily discontinued. For medications that will be required for more than a few days, a switch to an alternative statin or reducing the statin dose could be considered to reduce the risk of drug toxicity. Patients with CKD appear to be at increased risk of adverse events when statins and fibrates are used in combination (Supplemental Tables 21–28 online). For this reason, the Work Group recommends that fibrates not be used concomitantly with statins in patients with CKD. As mentioned earlier, given that evidence of clinical benefit is greater for statins than for fibrates, the Work Group recommends that statins be prescribed in preference to fibrates when clinicians are trying to choose between the two classes of medication.

Statins are contraindicated in pregnant or breast-feeding females; in people with active liver disease; and in people with transaminase levels that are three times or more the upper limit of normal. There is no evidence that the risk of liver dysfunction differs in people with CKD, as compared to those without. Regardless of CKD severity, the Work Group recommends that baseline levels of transaminases be measured before initiating statin treatment. Routine follow-up measurements of transaminases are not recommended, given the low frequency of abnormalities among people without abnormal values at baseline. Similarly, the Work Group does not recommend measurement of CK levels at baseline or during follow-up, unless the patient develops symptoms suggestive of myopathy.

2.1.1: In adults aged ≥ 50 years with eGFR < 60 ml/min/1.73 m² but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), we recommend treatment with a statin or statin/ezetimibe combination. (1A)

**Table 4 | Recommended doses (mg/d) of statins in adults with CKD**

| Statin            | eGFR G1-G2 | eGFR G3a-G5, including patients on dialysis or with a kidney transplant |
|-------------------|------------|------------------------------------------------------------------------|
| Lovastatin        | GP         | nd                                                                     |
| Fluvastatin       | GP         | 80°                                                                  |
| Atorvastatin      | GP         | 20°                                                                  |
| Rosuvastatin      | GP         | 10°                                                                  |
| Simvastatin/Ezetimibe | GP       | 20/10°                                                                |
| Pravastatin       | GP         | 40                                                                    |
| Simvastatin       | GP         | 40                                                                    |
| Pitavastatin      | GP         | 2°                                                                   |

All statins may not be available in all countries. Lower doses than those used in major trials of statins in CKD populations may be appropriate in Asian countries. Note that rosuvastatin 40 mg daily is not recommended for use in CKD 1-2 non-transplant patients, as it may increase the risk of adverse renal events. Cyclosporin inhibits the metabolism of certain statins resulting in higher blood levels. Data based on 1ALERT, 24D, 3AURORA, 4SHARP. Abbreviations: eGFR, estimated glomerular filtration rate; GP, general population; nd, not done or not studied.

**Rationale**

Data on the effects of statins and statin/ezetimibe combination in non-dialysis dependent adults with eGFR < 60 ml/min/1.73 m² are presented in Supplemental Tables 6–10, 15–17 online. The SHARP trial included 9270 participants with CKD (mean eGFR of 27 ml/min/1.73 m²) to receive simvastatin 20 mg plus ezetimibe 10 mg daily or placebo, and followed them for 5 years. Thirty-three percent of participants (n = 3023) were receiving dialysis at randomization and 23% (n = 2094) had diabetes. Statin plus ezetimibe therapy led to a significant 17% reduction in the relative hazard of the primary outcome of major atherosclerotic
events (coronary death, MI, non-hemorrhagic stroke, or any revascularization) compared with placebo (HR 0.83; 95% CI 0.74–0.94), driven by significant reductions in non-hemorrhagic stroke and coronary revascularization. Among the 6247 patients with CKD not treated by dialysis at randomization, treatment with simvastatin plus ezetimibe did not reduce the risk of progression to end-stage renal disease (ESRD) requiring RRT. The risk of serious adverse events was similar in participants assigned to treatment and to control.

These data are supported by post hoc analyses of randomized trials of statin vs. placebo that focus on the subset of participants with CKD at baseline. In general, these analyses suggest that statins reduce the RR of cardiovascular events to a similar extent among patients with and without CKD but that the absolute benefit of treatment is larger in the former due to their higher baseline risk.\(^34\) In addition, the risk of adverse events associated with statin treatment appeared similar in participants with and without CKD. However, most of the participants with CKD in these analyses had eGFR 45–59.9 ml/min/1.73 m\(^2\) and very few had eGFR <30 ml/min/1.73 m\(^2\).

Since the absolute risk in people who are non-dialysis-dependent with eGFR <60 ml/min/1.73 m\(^2\) aged ≥50 years is consistently greater than 10 per 1000 patient-years, in the judgment of the Work Group, knowledge of LDL-C is not required to gauge average coronary risk in this population. Although multivariable prediction instruments might yield more precise estimates of risk for individuals, the Work Group judged that the increased simplicity of an age-based approach was defensible for patients aged ≥50 years based on the data presented above and would enhance uptake of the guideline.

There is no evidence that ezetimibe monotherapy will improve clinically relevant outcomes in patients with or without CKD. Therefore, ezetimibe monotherapy is not recommended.

The combination of findings from SHARP, post hoc analyses of randomized trials from the general population (focusing on the subset with CKD), and the large body of evidence from the general population trials collectively provide a strong rationale for this recommendation. In the judgment of the Work Group, these data warrant a strong recommendation.

2.1.2: In adults aged ≥50 years with CKD and eGFR ≥60 ml/min/1.73 m\(^2\) (GFR categories G1-G2) we recommend treatment with a statin. (IB)

Rationale

The risk of future coronary events in patients aged ≥50 years with CKD is markedly increased, as compared to those without CKD, and the rate of coronary death or non-fatal MI in this population exceeds 10 per 1000 patient-years even in the absence of prior MI or diabetes (Table 3). Most patients with CKD and eGFR ≥60 ml/min/1.73 m\(^2\) have proteinuria and slightly reduced or normal eGFR; many such patients would have been included but not recognized in randomized trials of statins done in the general population, since many such trials did not assess proteinuria at baseline. On the other hand, this population was explicitly excluded from participation in SHARP, for which the primary inclusion criterion was elevated serum creatinine [Scr] (hence, reduced eGFR).

Existing data suggest that the relative benefit of statin treatment is not influenced by the presence of albuminuria: CARDS\(^35\) and the Cholesterol and Recurrent Events (CARE) trial\(^36\) both tested for an interaction between the presence of albuminuria and the effect of statin treatment on cardiovascular events. Both found no significant interaction (\(p = 0.7\) and \(p = 0.59\), respectively), suggesting that the benefit of statins is similar in people with and without albuminuria.

A randomized trial of pravastatin 40 mg daily vs. placebo in CKD patients with preserved GFR (i.e., eGFR categories G1-G2) but microalbuminuria found no significant risk reduction associated with pravastatin treatment on the risk of cardiovascular events (RR 0.87; 95% CI 0.49-1.57),\(^37\) although the number of events was small (\(n = 47\)). A post hoc analysis of CARE participants with slightly more events (\(n = 60\)) found a significant reduction in the risk of the primary outcome (CHD death or non-fatal MI) among the subset of CKD patients with eGFR categories G1-G2 (HR of pravastatin vs. placebo 0.48; 95% CI 0.28-0.83).

Given these data, the high cardiovascular risk among people with CKD and eGFR categories G1-G2, the large body of evidence supporting the efficacy of statins in the general population, and the lack of an \(a\) priori reason why statins would be less effective in the presence of proteinuria (i.e., the lack of justification for a new trial done specifically in people with CKD and eGFR categories G1-G2), the Work Group judged that a strong recommendation was appropriate.

2.2: In adults aged 18-49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest statin treatment in people with one or more of the following (2A):

- known coronary disease (myocardial infarction or coronary revascularization)
- diabetes mellitus
- prior ischemic stroke
- estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%

Rationale

As mentioned, the risk of coronary events is age-dependent in people with CKD, just as it is in the general population. Although the absolute rate of such events is lower among people with CKD who are less than 50 years of age, the coexistence of other risk factors increases the rate of coronary death or non-fatal MI substantially. In the subset of CKD patients aged <50 years with diabetes or prior vascular disease (MI, coronary revascularization, stroke or transient ischemic attack), the rate of coronary death or incident MI
2.3.1: In adults with dialysis-dependent CKD, we suggest the Framingham risk score, \(^{38}\) SCORE, \(^{39}\) PROCAM, \(^{40}\) estimated using any validated risk prediction tool such as the 10-year incidence of coronary death or non-fatal MI may be increased in CKD patients (although to a lesser extent than in the general population), increased LDL-C levels should be considered when estimating coronary risk in CKD patients aged <50 years. The 10-year incidence of coronary death or non-fatal MI may be estimated using any validated risk prediction tool such as the Framingham risk score, \(^{38}\) SCORE, \(^{39}\) PROCAM, \(^{40}\) ASSIGN, \(^{41}\) or the QRISK2. \(^{42}\) Overall, these instruments tend to overestimate future coronary risk and usually incorporate information on LDL-C. However, since most do not explicitly consider the presence of CKD, which would be expected to increase coronary risk for any given set of traditional cardiovascular risk factors, such overestimation should be less pronounced in CKD populations.

Patients whose 10-year risk of coronary death or non-fatal MI is <10% could choose to receive statin treatment if they placed relatively more value on a small absolute reduction in the risk of cardiovascular events, and relatively less value on minimizing the risks of polypharmacy and drug toxicity. On the other hand, patients valuing the potential benefits of statin treatment to a lesser extent than the potential harms might choose not to receive statin treatment even if their 10-year risk of coronary death or non-fatal MI is >10%.

2.3.1: In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination not be initiated. (2A)

RATIONALE

There are three large-scale RCTs of statin treatment that enrolled dialysis patients. Data from these trials are presented in Supplemental Tables 11–13, 17 online.

The 4D Study (Die Deutsche Diabetes Dialyse Studie)

The 4D, a multicenter, double blind, randomized trial assigned 1255 HD patients with type 2 diabetes to receive 20 mg of atorvastatin daily or placebo. \(^{43}\) After 4 weeks of treatment, atorvastatin reduced the median LDL-C level by 42%, and placebo by 1.3%. At least 1-mmol/l (39-mg/dl) difference in LDL-C level was maintained throughout the treatment period. During median follow-up of 4 years, 469 patients (37%) reached the primary endpoint (a composite of cardiac death, nonfatal MI, and fatal and nonfatal stroke): 226 assigned to atorvastatin and 243 assigned to placebo (RR 0.92; 95% CI 0.77–1.10; p = 0.37). Atorvastatin had no effect on the single components of the primary endpoint with the exception of fatal stroke, in which RR was 2.03 (95% CI 1.05–3.93; p = 0.04). The secondary endpoint of combined cardiac events (RR 0.82; 95% CI 0.68–0.99; p = 0.03) was significantly reduced, but not all combined cerebrovascular events (RR 1.12; 95% CI 0.81–1.55; p = 0.49) or total mortality (RR 0.93; 95% CI 0.79–1.08; p = 0.33).

AURORA Study (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Dialysis: an Assessment of Survival and Cardiovascular Events)

In this international double-blind randomized trial, 2776 HD patients were assigned to receive rosvastatin 10 mg daily or placebo, and followed for a median of 3.8 years. \(^{44}\) Despite the mean reduction in LDL-C of 43% in the intervention group, the combined primary endpoint of death from cardiovascular causes, nonfatal MI, or nonfatal stroke was not reduced (HR 0.96; 95% CI 0.84–1.11; p = 0.59). Rosuvastatin did not reduce the risk of individual components of the primary endpoint, nor of all-cause mortality (HR 0.96; 95% CI 0.86–1.07; p = 0.51).

SHARP (Study of Heart and Renal Protection)

This international double-blind randomized trial assigned 9270 participants ≥40 years old with CKD to receive simvastatin 20 mg plus ezetimibe 10 mg daily or placebo, and followed them for 4.9 years. \(^{14}\) Thirty-three percent of the patients (n = 3023) were receiving maintenance dialysis at randomization. The remaining 6247 CKD patients had a mean eGFR of 27 ml/min/1.73 m\(^2\). Mean reduction in LDL-C among the treatment group was 0.83 mmol/l (32 mg/dl), compared to placebo. Statin plus ezetimibe therapy was associated with a significant 17% RR reduction of the primary outcome of major atherosclerotic events (coronary death, MI, non-hemorrhagic stroke, or any revascularization) compared to placebo (HR 0.83; 95% CI 0.74–0.94). SHARP indicated that risk for the primary outcome of major atherosclerotic events other than death was reduced by simvastatin/ezetimibe among a wide range of patients with CKD. Combination treatment did not significantly reduce the risk of the primary outcome in the subgroup of over 3000 patients treated with dialysis at baseline.

A systematic review pooling data from all available randomized trials done in CKD populations reported significant heterogeneity between dialysis and non-dialysis patients for the benefit of statins on major cardiovascular events (HR for dialysis 0.96; 95% CI 0.88–1.03; HR for non-dialysis 0.76; 95% CI 0.72–0.79; p for heterogeneity <0.001). \(^{34}\) When findings from SHARP, 4D and AURORA are considered together, the clinical benefit of statins (alone or in combination with ezetimibe) in prevalent dialysis patients is uncertain. Another meta-analysis in essence confirmed the results, although the data were analyzed in a different manner. \(^{45}\) Even if statins truly do prevent cardiovascular events in prevalent dialysis patients, it is clear that the magnitude of any relative reduction in risk is substantially
smaller than in earlier stages of CKD.\textsuperscript{34} However, if this speculative benefit among dialysis patients is confirmed in future studies, the absolute benefit might be comparable to that in people with less severe CKD, due to the higher event rate among dialysis patients.\textsuperscript{46}

The smaller RR reduction noted in SHARP could be due to lower compliance to study drug in the subgroup of dialysis patients. Dialysis patients showed on average a 0.60 mmol/l (23 mg/dl) LDL-C reduction in comparison to the non-dialysis CKD group which outlined a 0.96 mmol/l (37 mg/dl) LDL-C decrease.

In summary, these data suggest that despite the exceedingly high cardiovascular risk in dialysis patients, it is uncertain whether statin regimens lead to clinical benefit in this population. Therefore, in the judgment of the Work Group, initiation of statin treatment is not recommended for most prevalent HD patients. However, patients might reasonably choose statin treatment if they are interested in a relatively small, uncertain reduction in cardiovascular events. Since very high LDL-C might increase the likelihood of benefit from statin in a dialysis patient,\textsuperscript{47} patients who meet this criterion may be more inclined to receive a statin, recognizing that the benefit remains uncertain. Other factors that might influence a patient’s decision to receive statin could include recent MI or greater life expectancy (both favoring treatment), and more severe comorbidity or higher current pill burden (both favoring non-treatment).

2.3.2: In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, we suggest that these agents be continued. (2C)

Rationale
SHARP, 4D and AURORA do not directly address the question of whether statins should be discontinued in patients initiating dialysis, who may be systematically different from prevalent dialysis patients. However, 2141 (34%) of SHARP patients without kidney failure at baseline commenced dialysis during the trial and were analyzed in the non-dialysis group – in which overall benefit was observed.\textsuperscript{14}

In the judgment of the Work Group, it is reasonable to continue statins in patients who are already receiving them at the time of dialysis initiation, recognizing that the magnitude of clinical benefit may be lower than in patients with non-dialysis-dependent CKD. Physicians should consider periodically reviewing the clinical status of dialysis patients and revisiting the decision to prescribe statins as required.

Given the lack of direct evidence that statin treatment is beneficial in dialysis patients, this recommendation is graded as weak. Discontinuation of statin or statin/ezetimibe may be warranted in patients who place a relatively low value on a small potential relative reduction in cardiovascular events, and a relatively high value on the risks of polypharmacy and drug toxicity.

2.4: In adult kidney transplant recipients, we suggest treatment with a statin. (2B)

Rationale
The risk of future coronary events in kidney transplant recipients is markedly elevated: data from the placebo arm of the ALERT trial suggest that the rate of cardiovascular death or non-fatal MI is approximately 21.5 per 1000 patient-years.\textsuperscript{48} Data on the rate of non-fatal MI by age are not available for kidney transplant recipients, but a population-based study from Australia and New Zealand suggests that the rate of cardiovascular death alone is approximately 5 per 1000 patient-years even among those aged 25–44 years.\textsuperscript{49}

Data on the effect of statins in adult kidney transplant recipients are presented in Supplemental Tables 29–31 online. ALERT examined the effect of statin therapy on cardiovascular risk reduction in 2102 patients aged 30–75 years with functioning kidney transplants who were followed for 5–6 years. Fluvastatin therapy (40–80 mg/day) led to a non-significant 17% reduction in the primary outcome of coronary death or non-fatal MI, compared to placebo (RR 0.83; 95% CI 0.64–1.06). However, fluvastatin led to a significant 35% relative reduction in the risk of cardiac death or definite non-fatal MI (HR 0.65; 95% CI 0.48–0.88),\textsuperscript{48} and an unblinded extension study found that randomization to fluvastatin was associated with a significant reduction in the original primary outcome after 6.7 years of follow-up. In the judgment of the Work Group, the apparent benefits observed in ALERT are consistent with the effects of statins in the general population, and suggest that statins are beneficial in patients with a functioning kidney transplant. However, the nominal lack of statistical significance in the primary analysis and the existence of a single randomized trial favor a weak recommendation.

The age at which statin treatment should begin in kidney transplant recipients is uncertain: the risk of coronary events is age-dependent, and ALERT did not enroll participants younger than 30 years. However, ESRD treated by kidney transplantation is a chronic disease, with cardiovascular risk expected to increase over time even in the presence of optimal graft function. In the judgment of the Work Group, these considerations warrant treatment in all adult kidney transplant recipients. However, younger patients (for example, those <30 years and without traditional cardiovascular risk factors) could choose not to receive statin treatment if they placed relatively less value on a small absolute reduction in the risk of cardiovascular events, and relatively more value on minimizing the risks of polypharmacy and drug toxicity.

Considerations for International Settings
In some Asian countries, doses of statins tend to be lower than those used in Western countries, due to concern about drug toxicity and clinical trial data indicating that such doses safely reduce LDL-C\textsuperscript{50,51} and improve clinical outcomes.\textsuperscript{52,53} Therefore, physicians practicing in such countries may choose to prescribe lower doses than recommended in Table 4.
**Suggested Audit Criteria**
- One year before and after the publication of this guideline, assess the proportion of non-dialysis-dependent adults aged ≥50 years with eGFR < 60 ml/min/1.73 m² that receive treatment with a statin or statin/ezetimibe combination.
- One year before and after the publication of this guideline, assess the proportion of adults aged ≥50 years with CKD and eGFR > 60 ml/min/1.73 m² that receive treatment with a statin.
- One year before and after the publication of this guideline, assess the proportion of adult kidney transplant recipients that receive treatment with a statin.
- One year before and after the publication of this guideline, assess the prevalence of statin use among non-dialysis-dependent adults aged 18–49 years with CKD and at least one of the following risk factors: known coronary disease (MI or coronary revascularization), diabetes mellitus, previous ischemic stroke, or predicted 10-year risk of CHD death/non-fatal MI >10%.

**KEY POINTS**
- Coronary risk is sufficiently high to justify prescription of statins in people aged ≥50 with non-dialysis-dependent CKD or a kidney transplant.
- Coronary risk in people aged <50 years with non-dialysis-dependent CKD is lower, but the presence of additional cardiovascular risk factors may increase risk to justify statin prescription. Given the evidence that treatment with statins improves vascular outcomes in this population, such treatment is suggested for patients aged <50 years with non-dialysis-dependent CKD and known vascular disease (prior MI, coronary revascularization or stroke), diabetes, or other risk factors that increase the 10-year risk of coronary death or non-fatal MI (as estimated using a validated risk calculator) to >10%.
- Patients with dialysis-dependent CKD should not be initiated on statin or statin/ezetimibe treatment, given the lack of evidence that such treatment is beneficial. However, statin or statin/ezetimibe treatment should not necessarily be discontinued among existing users when dialysis treatment is initiated.
- Physicians should be alert to the possibility of toxicity resulting from substances that increase blood levels of statins (e.g., grapefruit juice, certain medications).

**RESEARCH RECOMMENDATIONS**
- An extended observational study should be undertaken of the SHARP study cohort to determine whether the reduction in major atherosclerotic events resulting from 5 years of LDL-C lowering persists in the long-term, and whether LDL-C lowering significantly delays renal disease progression in people with non-dialysis-dependent CKD and eGFR < 60 ml/min/1.73 m².
- Given that the majority of early CKD is managed in primary care, audits of pharmacological cholesterol-lowering treatment should be undertaken in this setting.
- Data from the AURORA, 4D and SHARP studies (dialysis cohort) should be pooled to undertake individual patient data meta-analysis to more comprehensively assess the benefits and risks of cholesterol-lowering treatment in people with dialysis-dependent CKD.

**DISCLAIMER**
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**SUPPLEMENTARY MATERIAL**
*Supplemental Table 1*: Summary table of RCT examining the effect of exercise in CKD 5HD patients [continuous outcomes]
*Supplemental Table 2*: Summary table of RCT examining low vs. moderate protein diet in CKD patients without DM [categorical outcomes]
*Supplemental Table 3*: Summary table of RCT examining low vs. moderate protein diet in CKD patients without DM [continuous outcomes]
*Supplemental Table 4*: Summary table of RCT examining statin therapy vs. lifestyle modification in kidney transplant recipients without DM [categorical outcomes]
*Supplemental Table 5*: Summary table of RCT examining statin therapy vs. lifestyle modification in kidney transplant recipients without DM [continuous outcomes]
*Supplemental Table 6*: Summary table of RCT examining statin therapy vs. usual care in patients with CKD without DM [categorical outcomes]
*Supplemental Table 7*: Summary table of RCT examining statin therapy vs. usual care in patients with CKD without DM [continuous outcomes]
*Supplemental Table 8*: Summary table of RCTs of statins vs. placebo in patients with CKD with and without DM [categorical outcomes]
*Supplemental Table 9*: Summary table of RCTs of statins vs. placebo in patients with CKD in various stages of CKD with and without DM [categorical outcomes]
*Supplemental Table 10*: Evidence profile of RCTs examining the effect of statins vs. placebo in patients with CKD with and without DM
*Supplemental Table 11*: Summary table of RCTs of statins vs. placebo in dialysis patients with and without DM [categorical outcomes]
*Supplemental Table 12*: Summary table of RCTs of statins vs. placebo in dialysis patients with and without DM [continuous outcomes]
Supplemental Table 13: Evidence profile of RCTs examining the effect of statins vs. placebo in dialysis patients with and without DM

Supplemental Table 14: Summary table of RCT examining statin vs. placebo in patients with ADPKD [continuous outcomes]

Supplemental Table 15: Summary table of RCT examining simvastatin/ezetimibe combination vs. simvastatin/placebo in CKD patients without DM [categorical outcomes]

Supplemental Table 16: Summary table of RCT examining simvastatin/ezetimibe combination vs. simvastatin/placebo in CKD patients without DM [continuous outcomes]

Supplemental Table 17: Summary table of RCT of statin + ezetimibe vs. placebo in CKD patients [categorical outcomes]

Supplemental Table 18: Summary table of RCT examining the effect of dose of atorvastatin in CKD patients with DM [categorical outcomes]

Supplemental Table 19: Drug interactions

Supplemental Table 20: Effects of grapefruit juice on statin pharmacokinetics and recommendations

Supplemental Table 21: Patients on statin + fibrate therapy reporting any adverse event

Supplemental Table 22: Patients receiving statin + fibrate therapy reporting other individual adverse events

Supplemental Table 23: Patients on statin + fibrate therapy reporting treatment related adverse events

Supplemental Table 24: Patients on statin + fibrate therapy discontinuing due to adverse events

Supplemental Table 25: Patients on statin + fibrate therapy with increased ALT or AST

Supplemental Table 26: Patients on statin + fibrate therapy with increased CK

Supplemental Table 27: Patients receiving statin + fibrate therapy reporting rhabdomyolysis

Supplemental Table 28: Patients receiving statin + fibrate therapy reporting rhabdomyolysis

Supplemental Table 29: Summary table of RCTs of statin vs. placebo in kidney transplant patients [categorical outcomes]

Supplemental Table 30: Summary table of RCTs of statin vs. placebo in kidney transplant patients [continuous outcomes]

Supplemental Table 31: Evidence profile of RCTs examining the effect of statins vs. placebo in kidney transplant recipients

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/home/guidelines/lipids