AJKD

In the Literature

The Management of Dyslipidemia in CKD: New Analyses of an Expanding Dataset

Commentary on Upadhyay A, Earley A, Lamont JL, et al (Lipid-lowering therapy in persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med. 2012;157[4]:251-262) and Palmer SC, Craig JC, Navaneethan SD, et al (Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med. 2012;157[4]:263-275).

Abnormalities of lipid metabolism, which can lead to an altered serum lipid and lipoprotein profile (dyslipidemia), are common in patients with chronic kidney disease (CKD). Certain patterns of dyslipidemia, specifically an elevated low-density lipoprotein (LDL) cholesterol level, contribute to an increased risk of atherosclerotic vascular disease in the general population. It therefore seems likely that dyslipidemia contributes to the high risk of cardiovascular disease (CVD) in patients with CKD.[1-4] In addition, the association between dyslipidemia and CKD has led to the hypothesis that lipids may contribute to kidney disease progression.

In November 2000, the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (KDOQI) began developing a clinical practice guideline on the management of dyslipidemia in CKD. Researchers from Tufts Medical Center (working within the framework of the Agency for Healthcare Research and Quality Evidence-based Practice Center) conducted the evidence review for the KDOQI guideline work group, assessing more than 10,000 relevant abstracts and selecting 258 articles for detailed review and data extraction. However, at the time that the KDOQI Clinical Practice Guidelines for Managing Dyslipidemias in CKD were published in April 2003,[5] no randomized controlled trials (RCTs) of lipid-lowering treatment that specifically assessed clinical end points in patients with CKD had been published. Therefore, the KDOQI dyslipidemia guideline work group relied on studies relevant to the general population and extrapolated their results to patients with CKD. Specifically, the guideline suggested treating patients with CKD according to their levels of coronary heart disease risk and LDL cholesterol, as recommended by the National Cholesterol Education Program's Adult Treatment Panel III guideline.[6] The KDOQI guideline also recommended that most patients with CKD be considered at the "highest level" of coronary heart disease risk for treatment decisions.

Since then, several major RCTs involving patients with CKD have been completed. In the ALERT (Assessment of Lescol in Renal Transplantation) trial, fluvastatin failed to reduce the composite primary end point of major adverse cardiac events (MACEs) when compared to placebo in stable kidney transplant recipients.[7] However, secondary end points were less frequent in patients receiving active therapy and there was a significant difference in the frequency of the primary end point after an extended follow-up period.[8] In both 4D (Die Deutsche Diabetes Dialyse Studie), which assessed the impact of atorvastatin in diabetic dialysis patients,[9] and AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events), which assessed rosuvastatin in dialysis patients,[10] statin therapy failed to reduce MACEs despite the expected decreases in LDL cholesterol levels. However, in the much larger SHARP (Study of Heart and Renal Protection), the combination of simvastatin and ezetimibe reduced the primary end point (a composite of cardiovascular events resulting from atherosclerotic disease) in a population of patients with CKD, including 2,527 (27%) receiving hemodialysis and 496 (5%) receiving peritoneal dialysis.[11] Nevertheless, in a prespecified subgroup analysis, it appeared that the treatment effect of simvastatin/ezetimibe was greater in non–dialysis-dependent patients with CKD, who were more likely to adhere to the study treatment and demonstrated a larger decrease in LDL cholesterol level compared with patients on dialysis therapy.

As a result of these and other trials, there has been growing recognition that treating dyslipidemia with statins in order to reduce CVD risk is safe and effective in the early stages of CKD; however, there remains controversy over whether statins are beneficial in patients with CKD on hemodialysis therapy. Therefore, in 2011, Kidney Disease: Improving Global Outcomes (KDIGO) convened a work group to review the evidence and develop a clinical practice guideline. The same Tufts Medical Center Evidence-based Practice Center /that performed the evidence review for the KDOQI guideline conducted a literature update; a meta-analysis resulting from this review was recently published.[12] At the same time, Palmer et al[13] also

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Table 1. A Comparison of 2 Meta-analyses on Lipid-Lowering Therapies in CKD

	Upadhyay et al[12]	Palmer et al[13]
Selected Study Characteristics		
Last date searched	Nov 2011	Feb 2012
Group size selection	≥100 adults, ≥25 children	None
Minimum follow-up	≥6 mo	≥8 wk
Interventions studied	Lipid-lowering therapies excluding dietary supplements, phosphate binders, apheresis, stanols, or sterols	Statins
Included trials published as only abstracts	No	Yes
No. of trials analyzed	18	139
Major Results[a]		
All-cause mortality		
NDD-CKD	0.83 (0.70-0.98); moderate	0.81 (0.74-0.88); moderate-high
Dialysis	0.96 (0.90-1.02); moderate	0.96 (0.88-1.04); moderate-high
Transplantation	NA[b]	1.05 (0.84-1.31); low
Cardiovascular mortality		
NDD-CKD	1.00 (0.25-3.95); high	0.78 (0.68-0.89); moderate-high
Dialysis	1.00 (0.87-1.14); high	0.94 (0.82-1.07); moderate-high
Transplantation[b]	NA	0.68 (0.45-1.02); low
Major cardiac event		
NDD-CKD	0.77 (0.71-0.83); moderate	0.76 (0.73-0.80); moderate-high
Dialysis	0.96 (0.80-1.15); moderate	0.95 (0.87-1.03); moderate-high
Transplantation	NA[b]	0.84 (0.66-1.06); low
Myocardial infarction		
NDD-CKD	0.74 (0.65-0.83); moderate	0.55 (0.42-0.72); NA
Dialysis	0.72 (0.56-0.92); moderate	0.87 (0.71-1.07); NA
Transplantation	NA[b]	0.70 (0.48-1.01); NA
Stroke		
NDD-CKD	0.72 (0.48-1.07); very low	0.61 (0.38-0.98); NA
Dialysis	1.47 (1.09-2.00); very low	1.30 (0.79-2.11); NA
Transplantation	NA[b]	1.18 (0.62-2.24); NA

Abbreviations: CKD, chronic kidney disease; NA, not available; NDD-CKD, non–dialysis-dependent chronic kidney disease.
[a]Presented as relative risk (95% confidence interval); study quality.
[b]In the meta-analysis by Upadhyay et al,[12] transplant recipients were included in the "CKD not on dialysis" group.

published an independent meta-analysis of relevant statin treatment trials.

WHAT DO THESE IMPORTANT STUDIES SHOW?

These 2 meta-analyses were conducted using very different methods, but reached remarkably similar conclusions (Table 1). Both meta-analyses included studies of patients with all stages of CKD, as well as studies that recruited patients both receiving and not receiving dialysis or kidney transplantation for end-stage kidney disease. Although the meta-analysis of Palmer et al[13] examined only statin trials, this was the class of drug used in most of the studies in the meta-analysis by Upadhyay et al.[12] Both meta-analyses included studies with comparison groups that received placebo, no treatment, standard care, or alternative lipid-lowering therapy. Both included studies that specifically recruited CKD populations, as well as those that did not target patients with kidney disease, but reported results in subgroups of participants with decreased estimated glomerular filtration rates (<60 mL/min/1.73 m^2). The latter is an acknowledged weakness of the relevant trials and meta-analyses. Importantly, both meta-analyses assessed study quality, albeit using different methods.

Most of the trials included in the meta-analysis by Palmer et al[13] were excluded from the meta-analysis by Upadhyay et al[12] because they contained fewer than 100 participants per treatment group. SOLAR (Study of Lescol in Acute Rejection) was excluded from the meta-analysis by Upadhyay et al[12] because follow-up was only 3 months.[14] ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm) was not included in the meta-analysis by Upadhyay et al[12] because, at the time, it was published only as an abstract.[15] The IDEAL (Incremental

Decrease in End Points Through Aggressive Lipid Lowering) Study,[16] the HPS (Heart Protection Study),[17] and the UK-HARP-I (first United Kingdom Heart and Renal Protection) Study[18] were also not included in the meta-analysis by Upadhyay et al.[12]

Both meta-analyses found that, in patients with CKD who were not receiving dialysis and had not received a kidney transplant, lipid-lowering therapy reduced all-cause mortality, MACEs, and myocardial infarction (Table 1). The meta-analysis of Palmer et al[13] also found a reduction in cardiovascular mortality and strokes in patients with CKD who were not receiving renal replacement therapy, but the meta-analysis by Upadhyay et al[12] did not. Neither of the meta-analyses found a reduction in mortality or cardiac events in dialysis patients (Table 1). In addition, a metaregression analysis by Palmer et al[13] found that stage of CKD explained much of the variation in treatment effects between trials, which suggests that the effect of statins on cardiovascular events may be lessened in patients with more advanced stages of CKD. The treatment had no discernible effects on kidney disease progression in these trials. Finally, there was no apparent increase in adverse events in patients who were treated with lipid-lowering therapies in either meta-analysis.

There were some important limitations of these 2 meta-analyses, as noted by the authors. Including post hoc CKD subgroup analyses from trials that did not target patients with CKD could bias the results. There also was considerable heterogeneity in treatment effects between trials, which makes pooling the results potentially problematic. However, Palmer et al[13] showed that much of the heterogeneity could be explained by the stage of CKD. When trials were grouped according to CKD stage, no important heterogeneity in treatment effect was evident with respect to the major outcomes. Some of the difference in the 2 meta-analyses, although minor, could be explained by the less restrictive study inclusion criteria and therefore larger sample size in Palmer et al[13] compared to the meta-analysis by Upadhyay et al.[12] Finally, neither meta-analysis could rigorously examine the effects of medication nonadherence in explaining the differences between studies or subgroups within studies.

HOW DO THESE STUDIES COMPARE WITH PRIOR STUDIES?

Both these meta-analyses were preceded by systematic reviews carried out several years earlier by the same groups. However, in both instances, substantially more data were included in the more recent analyses. In general, the meta-analyses produced few surprises and results were consistent with those of the individual trials in CKD, particularly the largest of these, SHARP.[11] Thus, the fact that lipid-lowering reduced atherosclerotic CVD in patients with early stages of CKD is not surprising.

However, the question remains as to why statins are less effective at reducing cardiovascular events in hemodialysis patients. One explanation is that many of the CVD events in these patients are not directly related to atherosclerotic disease. Consistent with this hypothesis is the fact that the incidence of myocardial infarction was decreased in hemodialysis patients who were receiving active treatment in the meta-analysis by Upadhyay et al[12] (but not in the meta-analysis by Palmer et al[13]). Another explanation is that dialysis patients are less adherent to the study medication regimen and thus smaller decreases in LDL cholesterol levels are achieved in these patients compared with patients with CKD who were not receiving dialysis, as was the case in SHARP.[11] However, Palmer et al[13] found no difference in LDL cholesterol level reduction between CKD stages among pooled studies. In any case, these studies suggest that in order to improve outcomes in dialysis patients, more may need to be done than simply managing traditional CVD risk factors.

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

It is unlikely that new lipid-lowering RCTs will be carried out in patients with advanced CKD any time soon. Therefore, clinicians will need to base their decisions on the existing evidence, taking into account patient values and preferences. The KDIGO clinical practice guideline was initiated to review the current evidence and make recommendations to help health care professionals make the best possible therapeutic decision in the care of an individual patient with CKD. The guideline, in its final stages of development as this editorial was being drafted, is expected to be published by mid-2013. Based on the evidence, it is likely that treatment with a statin will be indicated in patients with early stages of CKD who are at increased risk of coronary heart disease. However, taking into consideration the data summarized in these 2 meta-analyses, the work group will find limited evidence supporting the use of lipid-lowering regimens in patients with CKD who are receiving dialysis.

In the absence of evidence, clinicians will need to base therapeutic decisions in dialysis patients on clinical judgment, taking into account patient views and preferences in this population. A similar situation applies to kidney transplant recipients, for whom the available evidence to support the use of lipid-lowering regimens is limited.

Finally, there is virtually no evidence to suggest that any lipid-lowering agents other than statins improve patient-level outcomes. The combination simvastatin/ezetimibe used in SHARP was safe and effective.[11] However, the lack of a treatment group receiving only ezetimibe makes it impossible to tell whether ezetimibe added benefit to that of the statin alone, although ezetimibe accounted for approximately one-third of the LDL cholesterol level decrease achieved in the combination therapy arm of the trial. Similarly, there are no RCTs in the general population showing that ezetimibe improves patient-level outcomes. Thus, it remains plausible but unproved that adding agents to a statin to lower LDL cholesterol level will increase benefit.

In summary, these meta-analyses provide a valuable tool to assess the strength of evidence for treating dyslipidemias in patients with CKD. The forthcoming KDIGO guideline on dyslipidemia will take this one step further and provide clinicians with recommendations for management based on this and other evidence. However, despite the remarkable progress in this field, there remain gaps in our knowledge, particularly with regard to managing dyslipidemia in patients receiving renal replacement therapy. Clearly, new therapeutic approaches and additional studies examining new preventative strategies beyond the use of statins are needed to reduce the incidence of CVD in all patients with CKD.

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