Optimal Management of Chronic Kidney Disease—Priority #1: Reduction of Cardiovascular Risk

By Murray Berall, MD, FRCPC
Nephrologist
Humber River Regional Hospital
Weston, Ontario

Cardiovascular disease (CVD) consistently ranks at or near the top of the list of leading causes of death in Canada and elsewhere in the developed world.[1-3] For the general population in Canada, the most recent statistics show that 27.6% of all deaths were attributable to heart disease or stroke.[1] In certain higher-risk populations, the risk of CV death is considerably higher. People with chronic kidney disease (CKD) have a risk of dying from CV causes that is significantly higher than it is for the general population. The risk of a CKD patient developing a CV event or CV mortality far exceeds their risk of dying from or developing kidney-related complications. As such, managing CV risk should be the primary concern for healthcare practitioners who treat patients with CKD.

This review includes a general overview of CKD (*e.g.,* epidemiology, diagnosis, monitoring) and a discussion of the association between CKD and CVD. The review also includes some specific insight and guidance on the management of CV risk factors, with a focus on dyslipidemia, informed by recent findings from lipid-lowering trials in the CKD population.

Epidemiology of CKD

CKD is a major public-health problem in Canada. Recent statistics indicate that 2.6 million Canadians have or are at risk for kidney disease.[4] The incidence and prevalence of CKD are also expected to rise in the years to come, considering Canada's aging population (the prevalence of CKD increases dramatically with age[5]), the increase in type 2 diabetes[6] (one of the leading causes of CKD[7]), as well as the improving expected survival of people with CKD (in part due to improvements in survival rates for CVD[8]).

A population of patients with CKD can be subdivided into stages, based on severity of the disease (Table 1).[4] U.S. data have shown that the proportion of patients is approximately equal in stages 1 to 3, while those with the most severe disease (stages 4 and 5) make up a very small minority (approximately 2% of the total).[9] In Canada, the same appears to hold true, but it is worth noting that the prevalence of end-stage renal disease has been steadily increasing over the past two decades. Data from the

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TABLE 1.
The Five Stages of Chronic Kidney Disease[4]

	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Remaining kidney function	> 90%	60 to 89%	30 to 59%	15 to 29%	< 15%
Symptoms	None	None	Early symptoms may include fatigue, poor appetite and itching	Stage 3 symptoms may get worse	Symptoms may include poor sleep, difficulty breathing, itchiness, and frequent vomiting
Estimated glomerular filtration rate (eGFR)	90 mL/min or more	60 to 89 mL/min	30 to 59 mL/min	15 to 29 mL/min	Less than 15 mL/min

TABLE 2.
Individuals at High Risk of Chronic Kidney Disease[11]

- Hypertension
- Diabetes mellitus
- Heart failure
- Atherosclerotic coronary, cerebral or peripheral vascular disease
- Unexplained anemia
- Family history of end stage renal disease (ESRD)
- First Nation's peoples

Canadian Organ Replacement Registry (CORR) show that approximately 38,000 Canadians were living with kidney failure in 2009, which was more than triple the prevalence in 1990 (11,000).[10] The number of people requiring dialysis grew from 5,900 in 1990 to 22,300 in 2009, while the number on the transplant list grew from 1,600 to 3,000.

CKD: Screening and Diagnosis

Given the fact that risk reduction in CKD is important and achievable, early identification of the disease is an important goal for optimizing outcomes. However, screening at the general-population level is not feasible. Instead, the Canadian Society of Nephrology (CSN) recommends screening only among high-risk groups (*e.g.,* elderly people, those with hypertension and/or diabetes; Table 2).[11]

While there are a number of tools that can identify or quantify renal problems, the CSN endorses the use of the estimated glomerular filtration rate (eGFR) as a tool for early diagnosis and staging of kidney disease. The eGFR is a calculation based on serum creatinine level, adjusted for age, sex and race. There are a number of on-line eGFR calculators available, including one hosted by the U.S. National Kidney Foundation (*www.kidney.org*). An eGFR of less than 60 mL/min/1.73 m^2 is considered diagnostic of CKD.

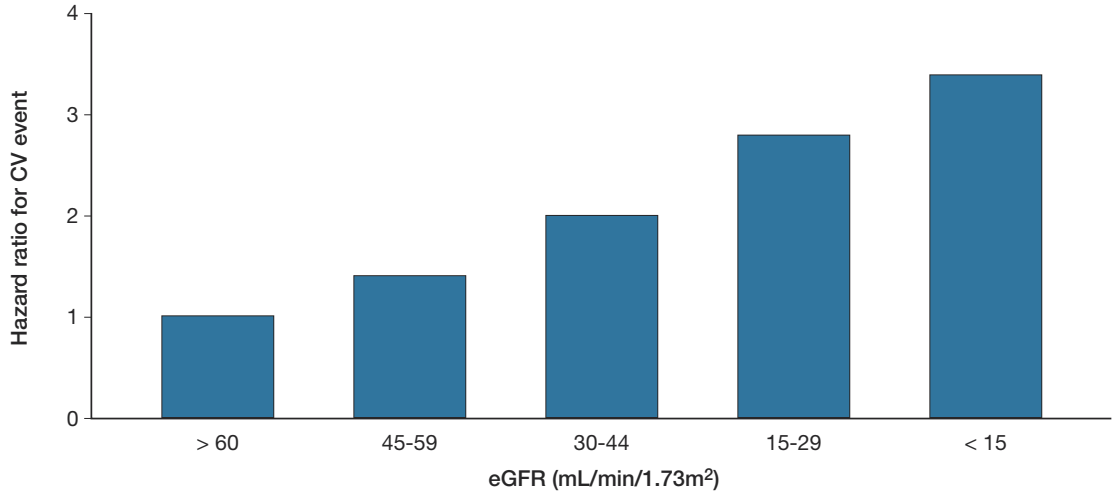
Association Between CKD and CVD

The association of CKD with CVD and vice-versa is strong, as illustrated by the high proportion of CKD patients who have a comorbid diagnosis of a CV condition. Statistics have shown that approximately three quarters of patients with CKD have left ventricular hypertrophy, 30% to 63% have overt heart failure, 75% to 85% have coronary artery disease, and 12% to 25% have experienced an acute coronary syndrome.[12]

Cardiovascular mortality rates in CKD are far higher than those in the general population. While the risk is high-

FIGURE 1.

Relationship Between eGFR and CVD Outcomes[15]



Adjusted for baseline age, sex, income, education, coronary disease, chronic heart failure, stroke or transient ischemic attack, peripheral artery disease, diabetes, hypertension, dyslipidemia, cancer, hypoalbuminemia, dementia, liver disease, proteinuria, prior hospitalizations and subsequent dialysis requirement.

est for those with end-stage renal disease (up to 30 times higher than the general population[13]), there is a graded relationship between degree of renal dysfunction and risk of CV death.[14,15] Even those with more modest renal dysfunction are at significantly increased risk of CV death compared to those without CKD (Figure 1).[15]

Monitoring CV Risk in CKD. In order to determine CV risk, multiple expert panels have recommended the use of the Framingham Risk Score (FRS) calculation. Based on several easily obtainable variables, the FRS provides an estimated 10-year risk of CVD.[16] However, the FRS has substantial limitations. It does not take into account many important risk factors, including CKD. In addition, many unique variables (*e.g.,* vascular calcification from calcium, phosphate, hyperparathyroidism, adipokines, oxidative stressors, etc.[26]) exist in the uremic milieu that are not accounted for by the FRS. The FRS does not, therefore, provide an accurate estimate of CV risk in patients with CKD, nor does any other standardized tool currently in use.

As such, clinicians need to have an alternate plan in place to estimate CVD risk in CKD patients. As discussed above, there is a graded relationship between eGFR and CV risk. At eGFR levels above 60 mL/min, a patient's CV risk reflects the traditional Framingham risk factors. For every value below 60, CVD risk rises and becomes less dependent on Framingham parameters.

This correlation of eGFR with CV risk is strengthened by the addition of proteinuria information. A Canadian study published in 2011 examined the associations among proteinuria, eGFR, and adverse CV events.[17] The data were drawn from province-wide laboratory data from Alberta between 2002 and 2007. After a median follow-up of 35 months, the investigators concluded that the risk of major CV events increased with higher levels of proteinuria at any given level of eGFR and that their data supported the use of proteinuria measurement with eGFR for definition and risk stratification in CKD. The measurement of both eGFR and proteinuria is also important for the monitoring of the CKD itself, with the two variables giving a much more accurate picture of risk than either variable followed independently. Patients with stage-2 CKD (as measured by eGFR) with proteinuria,

for example, have a greater chance of developing progressive kidney disease than those with stage-3 disease and no proteinuria.

In addition to the markers of kidney dysfunction, specific anatomic/physiologic risk factors have also been identified as being associated with increased CVD risk in CKD. Researchers from the MultiEthnic Study of Atherosclerosis (MESA)[15] reported that vascular calcification, arterial wall thickness, left ventricular hypertrophy, decreased lower-extremity blood flow and vascular stiffness were significant predictors of CVD risk.

Managing Dyslipidemia in CKD

While certain elements of cardiovascular risk reduction are similar in CKD and the general population (*e.g.,* smoking cessation, maintenance of a healthy body weight), there are many considerations that are specific to CKD. The following section discusses some of the particular considerations specific to dyslipidemia.

Given the fact that risk reduction in CKD is important and achievable, early identification of the disease is an important goal for optimizing outcomes.

Dyslipidemia. The lipid profile in CKD can vary dramatically from that of the general population. In advanced CKD, for example, levels of LDL-C tend to be low (due to impaired lipoprotein lipase activity and some degree of malnutrition). However, intermediate-density lipoprotein cholesterol (IDL-C), which is even more atherogenic than LDL, is often high. One should consider, therefore, that a normal LDL-C measurement does not necessarily preclude dyslipidemia or CV risk in a patient with CKD.

Historically, the exclusion of patients with CKD from most major lipid-lowering trials, coupled with the equivocal and/or conflicting findings of those few trials that did include patients with CKD, has confounded attempts to make evidence-based recommendations for management. Further confounding the issue were the different CKD etiologies (*e.g.,* diabetes vs. glomerulonephritis) and disease stages in those trials, which made it difficult to extrapolate data to CKD in general. The following section details the results of some of those trials with negative or equivocal results.

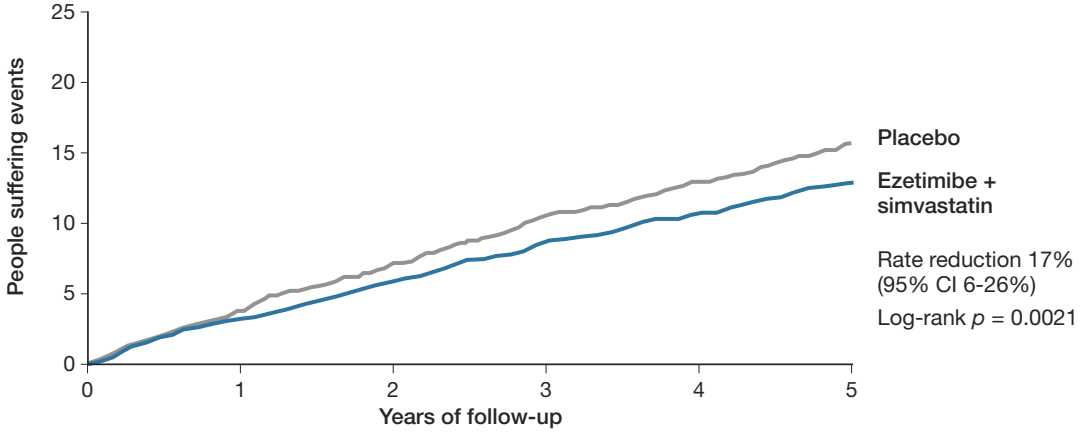
ALERT. The Assessment of Lescol in Renal Transplantation (ALERT) study was a randomized, controlled trial designed to investigate the effects of fluvastatin 40 mg or 80 mg daily in renal transplant recipients.[18] While the statin treatment was found to lower LDL-C by 32% compared to placebo over the trial's five- to six-year period, the investigators did not observe a significant effect on the incidence of renal outcomes (renal graft loss, doubling of serum creatinine, or decline in GFR). Furthermore, there was no significant clinical benefit observed in any patient subgroup.

4D. In the Deutsche Diabetes Dialyse Studie (4D), researchers prospectively randomized 1,255 subjects with type 2 diabetes and end-stage renal disease (all patients were on dialysis) to receive either atorvastatin 20 mg or placebo.[19] There was no significant difference between the groups for the primary combined endpoint of CV death, nonfatal MI, and stroke over four years (statin treatment was associated with a nonsignificant 8% reduction in this endpoint). The study did, however, show a significant increased risk of fatal stroke and a significant decreased risk of all cardiac events combined for atorvastatin relative to placebo.

AURORA. This trial, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), evaluated the effect of rosuvastatin in 2,776 patients undergoing hemodialysis.[20] For the primary endpoint of time to a major CV event (non-fatal myocardial infarction, non-fatal stroke or CV death), there was no significant difference between patients treated with rosuvastatin 10 mg daily and those treated with placebo. This was despite the fact that, over the trial's mean follow-up of 3.2 years, there were significant reductions in

FIGURE 2.

Incidence of Major Atherosclerotic Events in SHARP: Ezetimibe + Simvastatin vs. Placebo[23]



Number at risk						
Placebo	4620	4204	3849	3469	2566	1269
Ezetimibe + simvastatin	4650	4271	3939	3546	2655	1265

LDL-C and C-reactive protein (CRP) for rosuvastatin compared to placebo.

TNT. The Treating to New Targets (TNT) study was a major CV trial that enrolled 10,000 subjects with clinically evident coronary heart disease and elevated LDL-C.[21] These patients were randomized to receive a low (10 mg daily) or high (80 mg daily) dose of atorvastatin. In one of the trial's secondary analyses, atorvastatin therapy was found to be associated with a dose-dependent, significant improvement in eGFR from baseline levels.

Expert recommendations. Despite the relative absence of compelling data to guide them, the CSN did make recommendations based on the best possible evidence. In their 2008 recommendations, the CSN endorsed a target LDL-C level of 2.0 mmol/L or lower for patients with CKD in stage 3 or stage 4.[22] This is in line with the current Canadian recommendations for other high-risk groups (in the 2009 Canadian recommendations, the goal is an LDL-C of less than 2.0 mmol/L or a 50% reduction in LDL-C[16]). These guidelines also advise taking a fasting lipid profile no sooner than six weeks after initiation or change of lipid-lowering therapy and every six to 12 months if the results might influence therapeutic decisions. The findings of the recent SHARP study, discussed next, have helped to validate the 2008 CSN recommendation.[23]

SHARP. The SHARP trial was designed to evaluate the effect of lipid-lowering therapy on CV events in 9,270 people with CKD.[23] To be eligible for the study, subjects had to be at least 40 years old and either be on dialysis or have elevated creatinine (blood creatinine ≥ 150 µmol/L in men or ≥ 130 µmol/L in women). Subjects with a definite history of CVD at baseline were excluded.

The primary outcome of the trial was a major atherosclerotic event (defined as myocardial infarction, coronary death, ischemic stroke, or any revascularization procedure).

Subjects were randomized to placebo, ezetimibe 10 mg plus simvastatin 20 mg daily, or simvastatin 20 mg daily. Patients in the latter group were subsequently re-randomized at one year to ezetimibe 10 mg plus simvastatin 20 mg daily or placebo.

The investigators reported that, after the first year, the combination led to an additional 1.07 mmol/L reduction in LDL-C relative to simvastatin alone (mean baseline LDL-C was 2.8 mmol/L). The authors estimated that ezetimibe contributed approximately one third of the lipid-lowering benefit associated with combination therapy.

At the end of the trial (mean follow-up 4.9 years), there was a significant 17% reduction in the primary endpoint observed for the ezetimibe + simvastatin combination compared to placebo ($p = 0.0021$; Figure 2).

The proportional reduction in major atherosclerotic events produced by a given reduction in LDL-C held steady regardless of age, gender, presence of diabetes, history of vascular disease, and baseline lipid profile.

Despite the relative absence of compelling data to guide them, the CSN did make recommendations based on the best possible evidence. (…) The findings of the recent SHARP study have helped to validate the 2008 CSN recommendations.

This observation mirrors that of lipid-lowering trials in non-CKD populations and helps to validate the CSN (and others') recommendations to target an LDL-C of less than 2.0 mmol/L.

In SHARP, combination ezetimibe + simvastatin treatment was also associated with statistically significant reductions in nonhemorrhagic stroke (25% reduction, $p = 0.01$) and arterial revascularization procedure (21% reduction, $p = 0.0036$).

There were no significant between-group differences for the secondary endpoints of progression to ERSD or mortality; nor were there any significant between-group differences in cancer or any other safety endpoints (*e.g.,* myopathy, hepatitis, and gallstones).

Discussion. The observation that the primary endpoint benefits were observed in all subgroups of the trial makes the results relevant to most real-world CKD patients.

The question remains, however, regarding why SHARP had a positive result while AURORA and 4D did not. There are several possible explanations. Compared to those earlier studies, SHARP was a larger trial with a more specific endpoint. It also included a substantial proportion of subjects with less advanced CKD at baseline. In SHARP, of the total cohort of more than 9,000 patients, only about 3,000 were on dialysis. The average eGFR was 27, and approximately 80% of patients had proteinuria; 36% of the cohort were in stage 3 CKD. Researchers have speculated that the CV pathology in earlier-stage CKD is more similar to the general population than is the pathology of later-stage CKD. In light of this speculation, the finding of greater benefits from lipid lowering in SHARP compared to the AURORA and 4D trials, which examined only stage 5 CKD patients, makes intuitive sense.

Before SHARP, decisions about the use of statins in CKD were, out of necessity, made with limited evidential support. Some nephrologists used statins routinely, while others were extrapolating the results of the AURORA and 4D trials to all of CKD and opting to recommend cessation of statin treatment for their patients with CKD. Following the favorable efficacy and safety findings of the SHARP study, however, one should expect a more consistent approach to the use of statins (and ezetimibe) in CKD.

With respect to dosing, clinical trials in CKD have evaluated low statin doses. This is due to the potential for an increased risk of statin-related myopathy with decreasing eGFR. As such, in clinical practice, evidence-based medicine suggests that a low statin dose is a prudent strategy for patients with CKD. Concomitant use of ezetimibe may help to compensate for the limited lipid-lowering effects of these low doses. Adding ezetimibe has previously been shown to pro-

Summary: Take-home Messages

- Screening for CKD is recommended for high-risk patient groups (*e.g.*, elderly people, those with hypertension and/or diabetes).
- Estimated glomerular filtration rate (eGFR) is the recommended tool for early diagnosis and staging of kidney disease.
- Quantifying proteinuria/albuminuria provides valuable additional prognostic information compared to eGFR alone.
- The Framingham Risk Score is not an optimal tool to estimate CV risk in patients with CKD.
- Patients with CKD should be considered to be at elevated risk of CVD, with lower eGFR scores correlating to higher CV risk.
- Optimal risk-reduction interventions should be provided where appropriate, *e.g.*:
  - Dyslipidemia: treat to a target of < 2.0 mmol/L (or 50% reduction from baseline) using a low-dose statin; add ezetimibe for additional lipid lowering.
  - Hypertension: treat to a target blood pressure of < 130/80 mmHg, with ACE inhibitors or ARBs recommended as the preferred primary treatment agents.

vide an incremental benefit similar to doubling the statin dose three times (*e.g.*, titrating from 10 mg to 80 mg daily).

While it is true that the SHARP study did not show a significant reduction in overall mortality, the significant reduction in morbidity should still provide sufficient rationale for implementing lipid-lowering therapy in patients with CKD. Reduction in morbidity is associated with a lower use of healthcare resources and has the potential to improve patient quality of life, issues of major importance in the CKD population.

Management of Other CVD Risk Factors

Proteinuria. Specifically targeting proteinuria as a means of reducing CV risk has not yet been proven to be an effective strategy in CKD. However, proteinuria is associated with CV and renal risk, and recently completed studies suggest that statins reduce proteinuria.

The PLANET studies assessed the effects of atorvastatin 80 mg/day or rosuvastatin 10 or 40 mg/day on urinary protein excretion and renal function in patients with elevated LDL-C and moderate proteinuria.[24] PLANET I enrolled 325 subjects with diabetes, while PLANET II included 220 subjects without diabetes. The primary endpoint of both studies was the change in urinary protein:creatinine ratio from baseline to week 52 or to the last on-treatment observation.

In PLANET I, atorvastatin led to a 15% reduction in proteinuria on top of that achieved with ACE inhibitor or ARB therapy, while rosuvastatin had no significant effect on proteinuria. Patients in the rosuvastatin group also had a significantly greater loss of kidney function over the 52 weeks of the trial than those in the atorvastatin group.

In PLANET II, atorvastatin reduced proteinuria by more than 20% at weeks 26 and 52, while rosuvastatin had no such effect. Kidney function declined significantly only in the rosuvastatin 40 mg/day group.

The divergent effects of atorvastatin and rosuvastatin on proteinuria and eGFR did not reflect differences in

lipid lowering, which were comparable in all treatment groups.

Hypertension. There is a lack of conclusive data suggesting an ideal blood pressure target in CKD patients. However, the 2011 Canadian Hypertension Education Program continues to recommend a target blood pressure of less than 130/80 mmHg (though this is currently under debate for 2012, with an anticipated change to less than 140/90 in CKD patients), with ACE inhibitors or ARBs recommended as the preferred treatment agents.[25]

Conclusion

CKD is a major public-health concern in Canada. As the population ages and the prevalence of type 2 diabetes grows, the overall incidence and prevalence of CKD can also be expected to increase.

CVD is by far the most frequent cause of death among patients with CKD, with the risk substantially exceeding that of the general population. Management of patients with CKD should therefore include optimal strategies for CV risk reduction.

Recent evidence suggests that treatment of dyslipidemia in CKD should be similar to that of other high-risk groups: targeting an LDL-C of less than 2.0 mmol/L (or a 50% reduction). Proteinuria is associated with CV and renal risk, and there may be a role for pharmacotherapy aimed at reducing proteinuria (*i.e.,* statins), although the effect of this strategy in CKD remains to be proven. Similarly, although data are inconclusive regarding an ideal blood-pressure target in CKD, recommendations have been made for controlling hypertension in these patients.

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