

# Scientific Update™

## Understanding the Relationship Between Hypercholesterolemia and CKD – How is Kidney Disease Impacted by Dyslipidemia?

Presentations and discussion from the 2011 Canadian Cardiovascular Congress

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Chronic kidney disease (CKD) is a major public health problem and one of the most prevalent chronic diseases in the Western world. Patients with CKD are also at increased risk for cardiovascular disease (CVD). However, CVD in patients with CKD likely involves additional disease mechanisms. For example, the relationship between serum total cholesterol and mortality differ between patients with CKD and the general population. This may explain, in part, why treatments known to reduce vascular events in the general population have not been shown to improve clinical outcomes in patients with CKD. Indeed, the complexity of the interaction between dyslipidemia and CVD in CKD likely explains, to a certain degree, the lack of consistent benefit from statin therapy in previous randomized controlled trials examining the use of statins in patients with CKD. The interplay among CKD, CVD, and dyslipidemia as well as the results of recently published trials will be the focus of review in this issue of *Cardiology Scientific Update*.

Chronic kidney disease (CKD) is an established public health concern, and is among the most prevalent diseases in the industrialized countries.<sup>1</sup> Estimates of the prevalence of CKD vary depending on the statistical method used. Compared to the Modification of Diet in Renal Disease (MDRD) equation, the new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimating glomerular filtration rate (GFR) identifies, in populations younger than 60 years, a greater number of patients with GFRs >60 mL/min/1.73 m<sup>2</sup>, and has greater sensitivity to detect CKD.<sup>2</sup> In the United States, the National Health and Nutrition Examination Survey (NHANES) estimated a prevalence of CKD of 14.2% for the years 2003-2006.<sup>3</sup> More-

over, the prevalence of both albuminuria and decreased GFR (by MDRD re-expressed to standard serum creatinine) has increased substantially from 1988-1994 to 1999-2004.<sup>4</sup> Mortality also increases exponentially as GFR declines. Among 1 120 295 adults within a large, integrated system of healthcare delivery, the adjusted hazard ratio (HR) for death is 1.2 with an estimated GFR (eGFR) of 45-59 mL/min/1.73 m<sup>2</sup> (95% confidence interval [CI], 1.1 to 1.2), 1.8 with an eGFR of 30-44 mL/min/1.73 m<sup>2</sup> (95% CI, 1.7 to 1.9), 3.2 with an eGFR of 15-29 mL/min/1.73 m<sup>2</sup> (95% CI, 3.1 to 3.4), and 5.9 with an eGFR <15 mL/min/1.73 m<sup>2</sup> (95% CI, 5.4 to 6.5).<sup>5</sup> Cardiovascular mortality also increases significantly among patients on dialysis when compared to the general population (Figure 1).<sup>6</sup>

### The Interaction Between CKD and Cardiovascular Disease (CVD)

Patients with CKD are at particularly high risk for the development of CVD and mortality outcomes.<sup>7,8</sup> In patients with end-stage renal disease (ESRD), 42% of deaths are due to CVD compared to 31% in the general population. The clinical presentation of CVD is also significantly different in the CKD patient population when compared to the general population; arrhythmias and cardiac arrest combined account for nearly two-thirds of CVD mortality in patients with ESRD, while myocardial infarction (MI), which is responsible for more than half of CVD deaths in the general population, accounts for approximately 10% in patients with ESRD.<sup>9</sup> It is noteworthy that close to one-half of the deaths of patients on dialysis are not considered to be cardiovascular-related. One of the implications of these findings is that the traditional risk factors associated with CVD and corresponding strategies proven effective in managing these risk factors in the general population – including hypertension, glycemia, dyslipidemia, and smoking – may not necessarily be applicable to patients with CKD.

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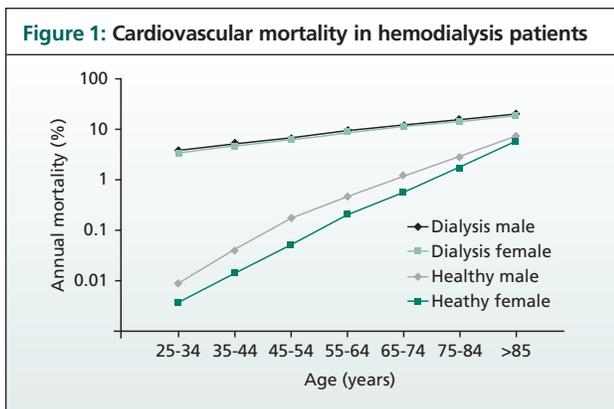
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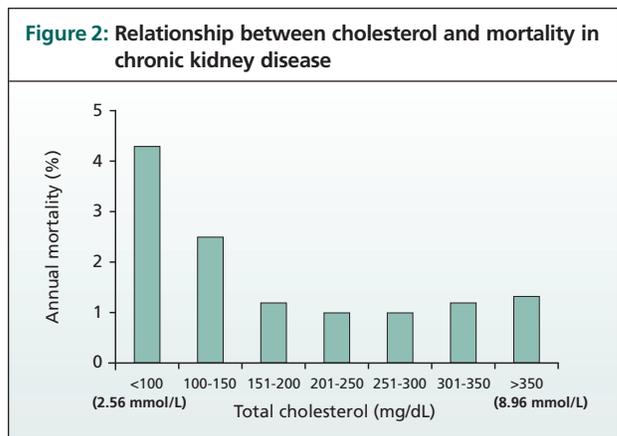
The structural and functional changes of the components of the CV system in patients with CKD may also be very different from those of the general population. Left ventricular hypertrophy and decreased lower extremity blood flow are common findings.<sup>10,11</sup> Likewise, the traditional and nontraditional risk factors for CVD in patients with CKD may also be different, and are related in part to the uremia.<sup>12</sup> In the case of CKD, many risk factors and metabolic alterations observed in the uremic milieu may contribute to the excessive risk of CVD.

### Is Dyslipidemia a Risk Factor for CVD in Patients With CKD?

#### Pattern of dyslipidemia in CKD

Both the lipid profile and the relationship between cholesterol and mortality differ in patients with CKD compared with the general population. There is typically little or no elevation in low-density lipoprotein cholesterol (LDL-C), total cholesterol is lower than normal, high-density lipoprotein cholesterol (HDL-C) is decreased, while triglycerides are elevated.<sup>13</sup> Reports from the UK Renal Registry<sup>14</sup> have demonstrated that the highest risk for mortality is actually seen in patients with the lowest total cholesterol, confirming earlier findings from 12 000 hemodialysis patients (Figure 2).<sup>15</sup> Indeed, in patients on dialysis, even the highest cholesterol levels are not associated with increased mortality risk. However, it is noteworthy that there presently exist very little data on LDL-C or other lipid fractions. There has also been limited information to date on CV outcomes in CKD populations not on dialysis.

Parsons et al<sup>16</sup> evaluated the prevalence and severity of CKD in a cohort of participants in a cardiac rehabilitation (CR) program and the effect of the program on various markers of CKD severity. All of the lipid fractions evaluated on admission and at discharge were within desirable ranges, and only HDL-C was found to be significantly different in CKD (n=369) and non-CKD (n=335) subjects. Those who were found to have CKD had significantly lower HDL-C levels than those who had no evidence of CKD (1.25 mmol/L versus 1.41 mmol/L;  $P=0.005$ ). The CR program resulted in a small (0.05 mmol/L) increase in



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HDL-C in the subjects with CKD, while that of non-CKD individuals decreased by 0.10 mmol/L.

#### Lipid lowering in CKD

Until recently, there has been a great deal of controversy regarding the institution of antihyperlipidemic therapy in CKD patients to prevent vascular events. Given the unusual lipid profile seen in this patient population, the benefits and optimal strategies for lipid control are unclear, particularly in light of the relatively low proportion of atherothrombotic events seen in CKD-related CV outcomes. Furthermore, some agents (eg, select fibric acid derivatives and nicotinic acids) are renally excreted and are either contraindicated or require dose adjustments in patients with low GFR. Further doubt was cast on the benefits of lipid-lowering therapy in CKD with the recent publication of indeterminate or negative results of 3 randomized, placebo-controlled trials.

**ALERT.** The Assessment of LEscol in Renal Transplantation (ALERT) trial randomized 2102 renal transplant recipients with total cholesterol 4.0-9.0 mmol/L to fluvastatin (n=1050) or placebo (n=1052).<sup>17,18</sup> After a mean follow-up of 5.1 years, fluvastatin was associated with a 32% reduction in LDL-C. Fluvastatin therapy did not significantly reduce the primary outcome of occurrence of a major adverse cardiac event, defined as cardiac death, nonfatal MI, or coronary intervention procedure (risk ratio [RR] 0.83 [95% CI, 0.64 to 1.06],  $P=0.139$ ), although there were fewer cardiac deaths and nonfatal MIs (70 versus 104, RR 0.65 [95% CI, 0.48 to 0.88],  $P=0.005$ ) in the fluvastatin group. There were no significant differences between treatment groups with respect to the need for coronary intervention procedures or other secondary endpoints.

**4D.** In *Die Deutsche Diabetes Dialyse Studie (4D)*,<sup>19</sup> 1255 subjects with type 2 diabetes undergoing maintenance hemodialysis received either atorvastatin (20 mg daily) or placebo over 4 weeks and followed for a median of 4 years. The primary endpoint (composite of death from cardiac causes, nonfatal MI, and stroke) were not significantly reduced in the atorvastatin group compared with controls (RR 0.92; 95% CI, 0.77 to 1.10;  $P=0.37$ ).

Although the atorvastatin group experienced a significant reduction in the rate of all cardiac events combined (RR 0.82; 95% CI, 0.68 to 0.99;  $P=0.03$ ), there was no such effect on total mortality (RR 0.93; 95% CI, 0.79 to 1.08;  $P=0.33$ ). Furthermore, there appeared to be a trend for a slight increase in cerebrovascular events (RR 1.12; 95% CI, 0.81 to 1.55;  $P=0.49$ ).

**AURORA.** A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA)<sup>20</sup> evaluated 2776 patients, also undergoing maintenance hemodialysis, randomized to rosuvastatin or placebo. Follow-up visits were scheduled to occur 3 months after randomization and at 6-month intervals. The average follow-up time was 3.8 years. There was no significant reduction in the primary endpoint (composite of death from CV causes, nonfatal MI, and nonfatal stroke) associated with rosuvastatin therapy (hazard ratio [HR] 0.96; 95% CI, 0.84 to 1.11;  $P=0.59$ ), and no improvement in all-cause mortality (HR 0.96;  $P=0.51$ ).

It is unclear why ALERT, 4D, and AURORA did not yield convincingly positive results with statin therapy. Possible reasons include lack of power, the exclusion of highest-risk patients, nonprecision of CV endpoints, relatively high drop-out rates, or simply the ineffectiveness of statins in patients with CKD because these patients are less responsive to statins or have a different type of CVD.

### SHARP

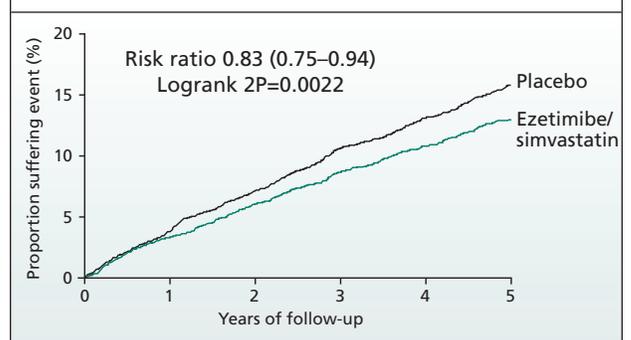
The recently published Study of Heart and Renal Protection (SHARP) study<sup>21</sup> was designed with the following considerations forming the rationale for the trial:

- Risk of vascular events is high among patients with CKD
- Lack of a clear association between cholesterol level and the risk of vascular disease
- The pattern of vascular disease is atypical, with a large proportion being non-atherosclerotic events
- Previous trials of LDL-C therapy in CKD are inconclusive

The SHARP study chose endpoints specifically designed to identify the effects of the treatment on the atherosclerotic component of CKD-related CVD.<sup>21</sup> A total of 9438 patients at 18 hospitals took part in the study. Inclusion criteria included age  $\geq 40$  years, a history of CKD, and either on dialysis or at least 2 measurements of serum or plasma creatinine  $\geq 1.7$  mg/dL (150  $\mu\text{mol/L}$ ) in men and  $\geq 1.5$  mg/dL (130  $\mu\text{mol/L}$ ) in women. Individuals with a history of MI or revascularization were excluded. A key criterion was the lack of a clear indication or contraindication for LDL-lowering treatment. The primary outcomes were major atherosclerotic events (coronary death, MI, non-hemorrhagic stroke, or any revascularization).

The study drug was a combination of the statin simvastatin 20 mg and ezetimibe 10 mg (this fixed-dose combination is not available in Canada). Patients were randomized to ezetimibe/simvastatin ( $n=4193$ ), placebo ( $n=4191$ ), or simvastatin alone ( $n=1054$  for safety analysis). Simvastatin patients were re-randomized to the study drug or placebo after 1 year. Median follow-up was 4.9 years. At baseline, the mean age was

**Figure 3: SHARP trial: Primary endpoint – major atherosclerotic events**



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62 years, 63% were men, 15% had vascular disease, and 23% had diabetes. The mean eGFR in the non-dialysis cohort was 27 mL/min/1.73m<sup>2</sup>, albuminuria was present in 80% of patients, 27% of patients were on hemodialysis, and 5% were on peritoneal dialysis. Lipid levels were as follows: LDL-C 2.8 mmol/L, HDL-C 1.1 mmol/L, triglycerides 2.3 mmol/L, and total cholesterol 4.9 mmol/L.

The primary results of SHARP have now been published.<sup>22</sup> Relative to placebo, the ezetimibe/simvastatin combination lowered LDL-C by an average of 0.85 mmol/L. LDL-C reduction with simvastatin alone was 0.74 mmol/L. Ezetimibe/simvastatin reduced major atherosclerotic events by 17% compared with placebo (11.3% versus 13.4%; RR 0.83; 95% CI, 0.74 to 0.94;  $P=0.0021$ ) (Figure 3). Nonsignificant reductions were observed in nonfatal MI (2.9% versus 3.4%; RR 0.84; 95% CI, 0.66 to 1.05;  $P=0.12$ ) and major coronary events (4.6% versus 5.0%; RR 0.92; 95% CI, 0.76 to 1.11;  $P=0.37$ ). Ezetimibe/simvastatin was also associated with significant reductions in nonhemorrhagic stroke (2.8% versus 3.8%; RR 0.75; 95% CI, 0.60 to 0.94;  $P=0.01$ ) and the need for arterial revascularizations (6.1% versus 7.6%; RR 0.79; 95% CI, 0.68 to 0.93;  $P=0.0036$ ). Results for the primary endpoint were similar for dialysis and non-dialysis patients.

In terms of safety, ezetimibe/simvastatin was not associated with an increased incidence of cancer (9.4% versus 9.5%;  $P=0.89$ ) or cancer-related death (2.8% versus 2.5%;  $P=0.26$ ) compared with placebo over the study period. In addition, there was slightly more nonvascular-associated mortality in the ezetimibe/simvastatin group than with placebo (14.4% versus 13.2%;  $P=0.13$ ). Investigators estimated that with full compliance, use of the ezetimibe/simvastatin combination would result in 40 fewer atherosclerotic events per 1000 CKD patients treated for 5 years, and 30 fewer events over the same time period per 1000 patients with slightly less severe kidney disease.

### Upcoming trials

The Lipid lowering and Onset of Renal Disease (LORD) trial<sup>23</sup> is a randomized, double-blind, placebo-controlled trial investigating the effect of atorvastatin on the progression of

kidney disease. Organizers recruited 88 subjects with Stages 2–4 CKD. The primary outcome measure is kidney function measured by eGFR calculated by both MDRD and Cockcroft and Gault equations. The 3-year LORD trial began in 2008. In a *post hoc* analysis,<sup>24</sup> Fassett et al determined that atorvastatin significantly reduced mean neutrophil gelatinase-associated lipocalin (NGAL; a biomarker of kidney injury) levels compared with placebo (-7.4 ng/mL/year versus +4.6 ng/mL/year;  $P=0.049$ ); however, NGAL did not predict CKD progression. There was no significant effect on levels of cystatin C (a biomarker of kidney function) with atorvastatin therapy.

## Conclusion

Clinicians recognize that CKD patients have “traditional” atherosclerotic disease, and that these patients respond to therapies known to be effective in general populations. These CKD patients, however, have complex vascular disease with additional pathogenic mechanisms compared to those operative in CVD patients without CKD. To improve clinical outcome in patients with CKD, one needs to better understand and address these additional mechanisms. Although the study design of SHARP does not permit one to conclude that the combination of ezetimibe and simvastatin offers incremental protection over simvastatin monotherapy, the results of this large-scale trial point to the safety and effectiveness of this combination in the reduction of major atherosclerotic events in patients with CKD.

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