The Risk of CVD:
How Are Patients With CKD Affected?

Patients with chronic kidney disease (CKD) are considered to be at the highest risk for cardiovascular disease (CVD). How should these patients be treated?

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CVD is the leading cause of death for patients with renal disease, as it is for the general population. However, the mortality rate due to CVD for patients with CKD is 10 to 30 times higher than for those who have normal kidney function. The American Heart Association recently published a statement recognizing that the presence of kidney disease is a risk factor for CVD.[1]

Recently, several authors have attempted to estimate the proportion of the population with subnormal renal function as a means to determine the "load" of chronic kidney disease (CKD) in the population. This information can help health-care planners estimate the number of patients who will need care for both CKD and end-stage renal disease (ESRD). The National Kidney Foundation developed a classification system for the levels of CKD to establish a consistency in its nomenclature (Table 1).[2]

The association of CVD and CKD has been controversial, since different epidemiologic studies have generated mixed results. Fundamentally, the diverse results of these studies are based on the similarity of the traditional risk factors for both CVD and CKD. However, some researchers were able to demonstrate that, despite this confounding effect, their popula-

Table 1

Classification of chronic kidney disease

Stage	Description	GFR (mL/sec/1.73m^2)	U.S. prevalence
1	Kidney damage with normal or increased GFR	> 1.5	3.3%
2	Kidney damage with mildly decreased GFR	1.0-1.49	3.0%
3	Moderately decreased GFR	0.5-0.99	4.3%
4	Severely decreased GFR	0.25-0.49	0.2%
5	Kidney failure	< 0.25 or dialysis	0.1%

GFR: Glomerular filtration rate

Table 2

Traditional vs. non-traditional CKD risk factors

Traditional risk factors

Older age
Male sex
Hypertension
Higher LDL-C levels
Lower HDL-C levels
Diabetes
Smoking tobacco
Physical inactivity
Menopause
Family history of premature CV events
Left ventricular hypertrophy

Non-traditional risk factors

Albuminuria
Homocysteinemia
Lipoprotein(a) and apolipoprotein(a) isoforms
Lipoprotein remnants
Anemia
Abnormal Ca/P metabolism
Extracellular fluid overload
Electrolyte imbalance
Oxidative stress
Inflammation (C-reactive protein)
Malnutrition
Thrombogenic factors
Sleep disturbances
Altered nitric oxide/endothelin balance

CKD: Chronic kidney disease
LDL-C: Low-density lipoprotein cholesterol
HDL-C: High-density lipoprotein cholesterol
CV: Cardiovascular
Ca: Calcium
P: Phosphate

tions of patients with CKD had greater rates of CVD when these similar risk factors were accounted for. More recently, newer "non-traditional" risk factors for CVD in CKD have been suggested (Table 2), but the magnitude of their role in CVD remains to be determined.

What do studies show?

In one study attempting to estimate the proportion of the population with CKD, serum creatinine (SC) levels were measured in the 6,233 adults enrolled in the Framingham Heart Study (mean age: 54 years). This resulted in 8.7% of men and 8.0% of women being classified as having renal insufficiency overall, with the prevalence increasing as a function of age.[3] When assessing the role of CKD on CVD, mild chronic renal insufficiency was defined as SC=136 µmol/L to 265 µmol/L for men, and SC=120 µmol/L to 265 µmol/L for women. Nineteen per cent of these subjects had prevalent CVD. During the 15-year followup, mild renal insufficiency in women was not associated with an increased risk of CVD events (hazard risk (HR)=1.04) or all-cause mortality (HR=1.08). However, in men, there was an increase in all-cause mortality (HR=1.42), but there was no association with CVD events (HR=1.17).[4]

In the Cardiovascular Health Study, which followed 5,888 adults over 65, 15.9% of men and 7.6% of women were found to have an elevated SC level (> 1.5 mg/dL for men, and > 1.3mg/dL for women). The prevalence of cardiac disease was 64% in persons with renal disease, compared to 43% in those without it. The odds ratio for the development of CVD given the presence of CKD was 2.34. The odds ratio was revised to 1.43, but remained statistically significant after controlling for the confounding effect of CVD risk factors.[5] This study was cross-sectional, as opposed to the Framingham study that followed patients for 15 years. This difference in design might account for the variation in results.

In another study, the risk of stroke was assessed in a 14-year followup of 7,690 men aged 40 to 59. It appeared the risk of stroke

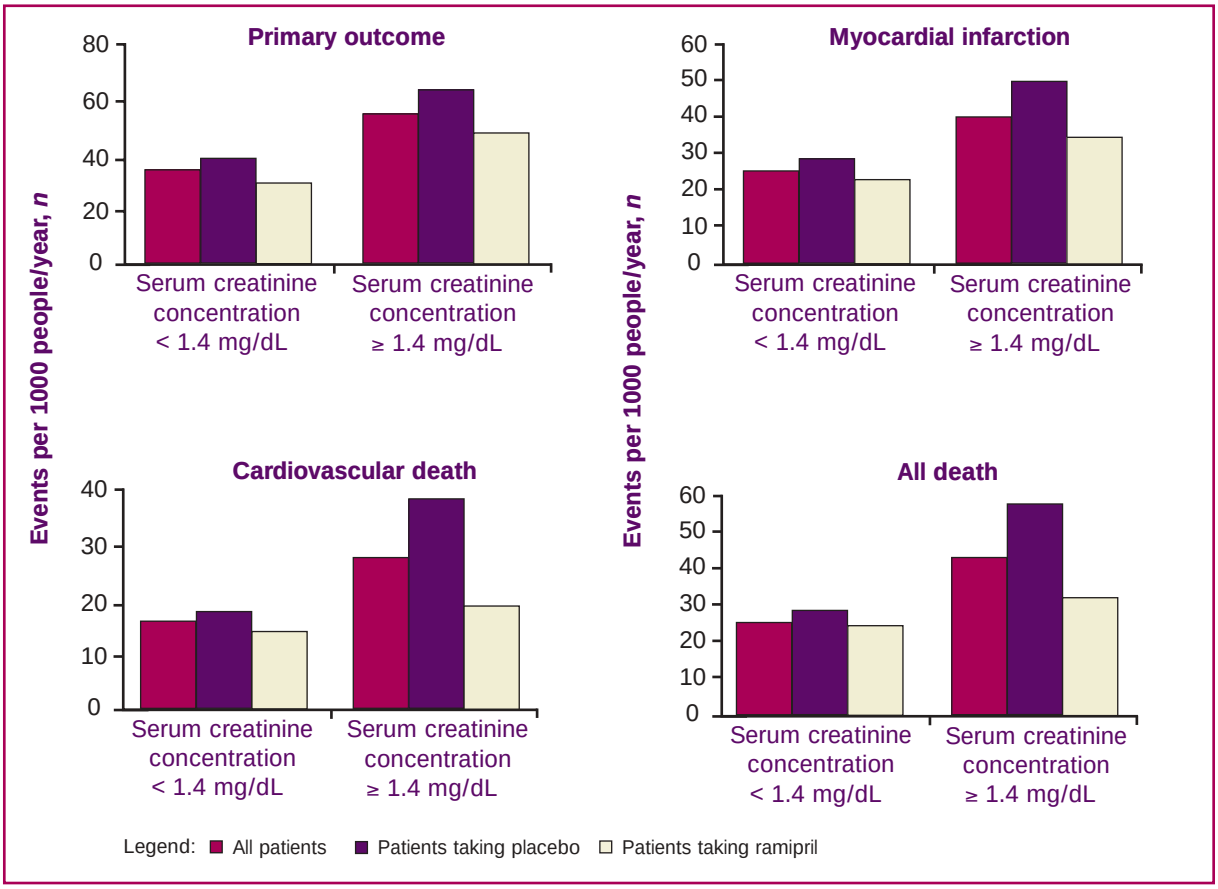

Figure 1. Outcomes for patients with a serum creatinine level < 1.4 mg/dL (< 124 µmol/L) or ≥ 1.4 md/dL (124 µmol/L) in the Heart Outcomes Prevention Evaluation (HOPE) trial.

increased significantly at SC levels > 116 µmol/L (relative risk (RR)=1.6). The risk of major ischemic heart disease increased with SC levels > 130 µmol/L (above the 97.5th percentile), but was attenuated when adjusted for other risk factors. All-cause and cardiovascular mortality also increased with SC levels >130 µmol/L.[6]

The presence of renal dysfunction has an important and significant impact on the outcome for persons who have a coronary angiogram or myocardial infarction (MI). The four-year survival is significantly worse for dialysis patients (HR=4.05) and patients with CKD (HR=7.32) after coronary angiography.[7] After correcting for clinical risk factors, the hazard ratios remained between 2 and 3. Subsequent to MI, there was an increase in risk of atrial and ventricular arrhythmias, heart

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block, asystole, hemodynamic problems (such as heart failure and acute mitral regurgitation), and increased mortality correlated to reduced renal function.[8,9]

Antihypertensive therapy

Usually, patients with kidney disease are excluded from studies assessing the effects of antihypertensive therapy on morbidity and mortality. There is, therefore, no data to confirm that lowering blood pressure will reduce CVD events in this high-risk population. In a subgroup analysis of the Heart Outcomes Prevention Evaluation (HOPE) study, a retrospective assessment was done based on the initial SC level.[10] The increased risk of event could be seen when the patients were divided into quartiles based on their SC levels. Patients in all groups benefited from treatment with ramipril, which reduced the risk of cardiovascular events and death in patients with SC > 1.4 mg/dL (124 µmol/L) (Figure 1). However, treated CKD patients still had a risk of cardiovascular event that was higher than that of the placebo-treated patients who had normal kidney function. Thus, kidney function appears to be a serious risk factor for event although treatment with ramipril is beneficial for the patient.

Lipid-lowering therapy

Patients with CKD are usually not eligible to be enrolled in studies assessing the effect of lipid-lowering therapy on morbidity and mortality from CVD. Subgroup analyses from a few of the large studies of lipid-lowering therapy have recently been published, and suggest that patients with CKD can benefit from this approach.

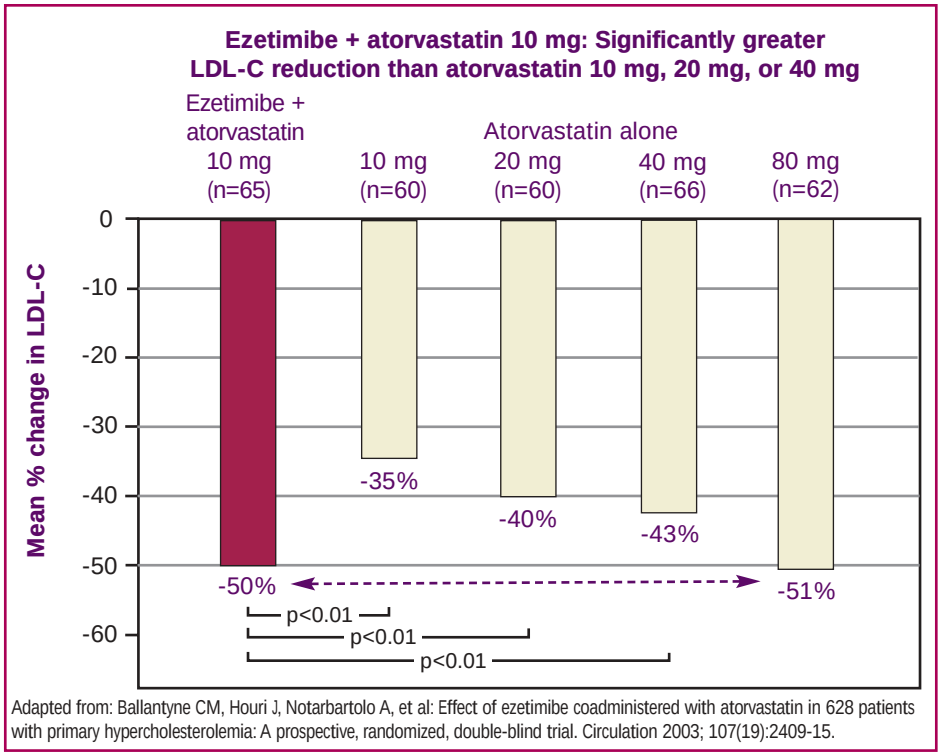
The Cholesterol And Recurrent Events (CARE) trial recruited patients who had already had an MI, and randomized them to placebo or pravastatin therapy; they were followed for an average of five years. Chronic renal insufficiency in this trial was defined as a calculated creatinine clearance < 75 mL/min. Using this definition, 1,711 subjects were identified. Their average age was 61.3, 78.4% were male, and 13.6% had diabetes. A significant 28% relative risk reduction of the primary end point (coronary artery disease death or non-fatal MI) was seen and it was of a similar extent to that seen in patients with normal

Table 3

Adjusted RR for the effect of pravastatin in patients with a prior MI

Event	RR	95% CI	P
Fatal CAD or non-fatal MI	0.72	0.54-0.94	0.02
CAD event	0.73	0.60-0.89	0.002
CVA	0.62	0.39-1.00	0.049
Revascularization	0.67	0.52-0.86	0.002
Total mortality	0.80	0.67-1.07	—

RR: Relative risk
MI: Myocardial infarction
CAD: Coronary artery disease
CI: Cardiac index
P: Probability
CVA:Cardiovascular accident



Adapted from: Ballantyne CM, Houri J, Notarbartolo A, et al: Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: A prospective, randomized, double-blind trial. Circulation 2003; 107(19):2409-15.

Figure 2: Ezetrol plus statin.

renal function (Table 3). A significant reduction in major coronary events, stroke and coronary revascularization was also found, although there was no reduction in mortality.[11] Although patients with CKD had a higher rate of CVD events, they were still able to benefit from treatment with pravastatin.

The Veterans' Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) was a study with men who had low high-density lipoprotein (HDL) and elevated triglyceride (TG) levels. In the subgroup analysis, CKD was also defined as a calculated creatinine clearance < 75 mL/minute. This resulted in 905 men being identified, among whom the mean age was 67.5, and 30% had diabetes. Gemfibrozil was effective in reducing the number of coronary events in this group of men with CKD (35% relative risk reduction). However, there was no effect on fatal and non-fatal stroke, revascularization, or mortality.[12] Since low HDL and elevated TG levels are common in renal insufficiency, this may offer an acceptable means of treatment if adverse events are low. However, fibrates are not recommended in patients with significantly reduced renal or liver function due to significant muscle toxicity. The utility of gemfibrozil and other fibrates is likely to be low in patients with renal disease.

In the Heart Protection Study (HPS), the use of simvastatin and vitamin E was studied in a 2x2 factorial design. Patients with known chronic renal failure or SC level > 200 µmol/L were excluded. A post-hoc analysis examined the results for participants with an elevated SC level (men with creatinine > 130 µmol/L, and women > 110 µmol/L). The results showed a benefit from simvastatin, but no benefit from vitamin E; this was in keeping with the results for patients with normal renal function. There was no evidence of any effect of vitamin allocation on the size of the benefit seen with simvastatin.[13]

Future treatments

Although mortality is inversely related to serum cholesterol levels in patients with ESRD, it is still believed that lipid abnormalities are important in cardiovascular morbidity and mortality in patients with CKD. The increased mortality associated with low serum cholesterol levels (and low serum albumin concentrations) is probably an expression of mortality being associated with malnutrition. However, there are several lipid abnormalities in CKD including the presence of small, dense low-density lipoproteins (LDLIII). There is a strong association between plasma TG and LDLIII concentrations. HDL levels are usually low in patients with CKD, thus increasing the risk of CVD.[14] The TG rich, apoB-containing lipoproteins correlate with the rate of progression of the CKD. Current research is conflicting as to whether statin treatment can slow the deterioration of renal disease, since it may have a limited effect on the dyslipidemia in CKD.

An alternative treatment that may be useful is cholesterol absorption inhibition. Currently, the only marketed drug of this class is ezetimibe. Ezetimibe works on the brush border of the small intestine, and limits the absorption of cholesterol in bile acids, as well as from ingested food and sloughed cells.[15] This results in a lowering of serum cholesterol, LDL cholesterol, TG, and C-reactive protein levels to an extent similar to low-dose statin therapy. When ezetimibe is added to statin therapy, the combination lowers serum total and LDL cholesterol levels to an extent similar to that of high-dose statin therapy (Figure 2). However, this combination is likely to have a lower risk of liver and muscle adverse effects than high-dose statin therapy.

Take-home message

- Patients with CKD represent about 8% to 9% of the population, and they are considered at the highest risk for CVD.
- Mortality rates due to CVD for patients with CKD is 10 to 30 times higher than individuals with normal kidney function.
- The prevalence of cardiac disease is 64% in persons with renal disease, compared to 43% in those without it.
- Gemfibrozil has a 35% relative risk reduction of coronary events for patients with CKD, but does not have an effect on fatal/non-fatal stroke, revascularization, or mortality.
- For lipid-lowering and antihypertensive therapy, patients with CKD benefit from ramipril and pravastatin treatment, but they still have a higher incidence of cardiovascular events than individuals with normal kidney function.
- Ezetimibe is currently the only marketed drug for cholesterol absorption inhibition. Ezetimibe combined with statin therapy lowers serum total and LDL-C levels to an extent similar to that of high-dose statin therapy.

Looking ahead...

Approximately 8% to 9% of the population has reduced renal function. These persons are at increased risk of CVD, and death from cardiovascular events. Subgroup analysis data suggests treatment with an angiotensin-converting enzyme inhibitor or lipid-lowering therapy will reduce this morbidity and mortality. However, there is no information for individuals with more serious renal disease, or for those who are on

dialysis or have a renal transplant. Studies are currently underway to determine whether or not statin-based, lipid-lowering therapies for persons with mild-to-severe renal disease (Study of Heart and Renal Protection [SHARP] trial) or for persons on dialysis (A Study to Evaluate the Use of Rosuvastatin in Subjects On Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events [AURORA] trial) will be beneficial and without serious adverse events. Canadian centres are enrolling patients to participate in these trials.

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Net Readings

1. Kidney Disease Outcomes Quality Initiatives
   www.kidney.org/professionals/kdoqi/index.cfm
2. *Circulation* Journal Article on CVD in CKD
   http://circ.ahajournals.org/cgi/content/full/108/17/2154