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AN EDUCATIONAL PUBLICATION FROM THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Reducing Cardiovascular Events in Patients with Chronic Kidney Disease

Originally presented by: Tonelli M, MD; Keane WF, MD; Baigent C, FFPH, FRCP; Shlipak M, MD; Tuttle KR, MD; Parving H-H, MD

Discussion of presentations and a satellite symposium at the 2011 World Congress of Nephrology

Vancouver, British Columbia April 8 – 12, 2011

Discussed by: GORDON MOE, MD, FRCP(C)

Chronic kidney disease (CKD) is a primary risk factor for the development of cardiovascular disease (CVD). Because of the close association between the two, therapies intended to prevent CKD progression also tend to improve CVD outcomes. Other therapies, such as lipid-lowering treatment, are directly beneficial in reducing CV risk, while having no direct effect on renal disease. Continuing progress in elucidating the nature of the relationship between CKD and CVD has led to an increasingly sophisticated approach to disease management. Updated treatment recommendations are currently being revised in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI), as well as in the Kidney Disease: Improving Global Outcomes (KDIGO) and Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-8) guidelines. This issue of *Cardiology Scientific Update* discusses recent advances in the understanding of the somewhat atypical nature of CVD in patients with CKD, considers potential guideline changes, and examines the evidence for currently recommended treatment practices.

Epidemiology

CKD is among the most pervasive diseases in the western world. Estimates of its prevalence in the United States (US) differ according to the statistical methods used; the National Health and Nutrition Examination Survey (NHANES) estimated a prevalence of 14.2% in the US population for 2003–2006.[1] This prevalence has increased by approximately 2% since the 1980s, most likely related to the increasing age of the population and risk factors such as diabetes and hypertension. Diabetes remains the most common cause of CKD and end-stage renal disease (ESRD).[1]

CKD severity is graded according to glomerular filtration rate (GFR). The current NKF-KDOQI system identifies 5 stages (Table 1).[2] GFR is usually estimated (eGFR) using formulae based on serum creatinine testing. Among these, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula is considered to be the most accurate for grading CKD, particularly at high eGFR levels.[3]

Mortality and morbidity are greatly increased in patients with CKD. In the US and Europe, a 20-year-old Caucasian patient with ESRD has a life expectancy of an additional 15 years, compared to 60 years for a person of the same age in the general population. A wide difference persists through life; at age 80, dialysis patients have a life expectancy 5 years less than the age-matched general population.[4]

Chronic Kidney Disease and Cardiovascular Disease

CKD is associated with increased incidence of CVD. In patients with ESRD, 42% of deaths are due to CVD, compared to 31% in the general population. The manifestations of CVD are also different in the CKD population; arrhythmias and cardiac arrest account for 61% of CVD mortality in ESRD, while acute myocardial infarction (MI), which accounts for more than half of CVD deaths in the general population, has an incidence of only 12% in ESRD.[5] Acute coronary syndrome is seen in 12%–25% of patients with CKD, but carries an unusually high mortality of about 60%. There is a graded and independent relationship between eGFR and CVD outcomes. The hazard ratio (HR) increases from 1 at eGFR >60 mL/min/1.73m^2 to more than 3 at eGFR <15 mL/min/1.73m^2 for any CV event.[6] An association also exists between increasing proteinuria and CVD. Ongoing research by the National Kidney Foundation demonstrates an additive, and sometimes synergistic, effect on CVD mortality between decreasing eGFR and increasing albuminuria.

The principal subclinical pathogenic mechanisms underlying CVD in CKD are left-ventricular hypertrophy, decreased lower extremity blood flow as measured by ankle brachial index, and vascular stiffness.[7,8] Each of these processes shows a direct relationship to increasing severity of CKD.

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

Table 1: Stages of Chronic Kidney Disease (CKD)			
Stage	Description	GFR (mL/min/ 1.73m^2)	Prevalence in US; n (1000), %
1	Kidney damage with normal GFR	≥90	5600, 2.8
2	Kidney damage with mildly decreased GFR	60–89	5700, 2.8
3	Moderately decreased GFR	30–59	7400, 3.7
4	Severely decreased GFR	15–29	300, 0.1
5	Kidney failure (ESRD)	<15 or dialysis	391, 0.2

GFR = glomerular filtration rate; ESRD = end-stage renal disease
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A hallmark of CKD is the atypical lipid profile commonly seen in these patients with CVD. Low-density lipoprotein cholesterol (LDL-C) shows little or no elevation, total cholesterol is lower than normal, high-density lipoprotein cholesterol (HDL-C) is decreased, and triglycerides are frequently elevated.[10] Unusual features are also observed in coronary artery histopathology. Plaque calcium is dramatically increased in the arterial media. Inflammatory markers such as C-reactive protein (CRP), macrophages (CD68), terminal complement complex (C5b-9), and hypoxia-inducible factor (HIF) are elevated, and also distributed within the vascular structure of the coronary arteries. Endothelial dysfunction is more diffuse, and plaque hemorrhage is increased in patients with CKD.[11]

Management of CVD in patients with CKD

Blood pressure control

Blood pressure (BP) control is important for both limiting progressive kidney damage and attenuating the underlying pathological processes that lead to CVD. The NKF-KDOQI guidelines recommend a target BP of <130/80 mm Hg in stage 1–4 CKD.[12] If hypertension is present, treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) is recommended, usually in combination with a diuretic. Sodium intake should be restricted to <2.3 g/day, as per the Dietary Approaches to Stop Hypertension (DASH) recommendations.[13]

There has been some debate as to whether the targets for BP control should be lower in patients with CKD. Previous studies have yielded mixed results; some have shown CVD benefits with a diastolic BP <80 mm Hg, while others have found no difference between these lower diastolic targets and a diastolic BP as high as 90 mm Hg. The recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[14] showed no overall CVD outcome benefit from lowering BP to a target of <120/70 mm Hg versus <140/90 mm Hg, although macroalbuminuria was lower. The risk of stroke was also reduced significantly (HR 0.59; 95% confidence interval [CI] 0.39–0.89; *P*=0.01), but at a cost of accelerated reduction of eGFR and increased hypotension. It is expected that both the JNC 8 and the new KDIGO guidelines, which replace those of the NKF-KDOQI, may liberalize the BP goal for CKD to <140/90 mm Hg, probably with exceptions for certain groups, such as patients with macroalbuminuria.

Lipid lowering

The use of LDL-lowering therapy to prevent CV events in CKD has been controversial; the unusual lipid profile seen in this patient population does not provide a clear direction for lipid control, and the relatively low proportion of cardiac events seen in CKD-related CVD also has cast doubt on the need for cholesterol therapy. The indeterminate results seen in the Die Deutsche Diabetes Dialyse Studie (4D)[15] and A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA)[16] were not helpful in clarifying this question. In 4D, 1255 subjects with type 2 diabetes receiving maintenance hemodialysis were randomized to atorvastatin (20 mg daily) or placebo over 4 weeks and followed for a median of 4 years. The primary endpoints (composite of death from cardiac causes, nonfatal MI, and stroke) were not significantly reduced in the atorvastatin group compared with controls (relative risk [RR] 0.92; 95% CI 0.77–1.10; P=0.37). Although a significant reduction in overall cardiac events was observed with atorvastatin (RR 0.82; P=0.03), there was no significant impact on total mortality (RR 0.93; P=0.33). Results also showed a slight increase in cerebrovascular events (RR 1.12; P=0.49). AURORA comprised 2776 patients, also undergoing maintenance hemodialysis, who were randomized to rosuvastatin (10 mg daily) or placebo. Treatment was given over 3 months and 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 (HR 0.96; 95% CI 0.84–1.11; P0.59), and no improvement in all-cause mortality (HR 0.96; P=0.51).

In order to elucidate the role of LDL-lowering therapy in CKD, the Study of Heart and Renal Protection (SHARP) study employed an intensive regimen with endpoints designed to identify the effects of the treatment on the atherosclerotic component of CKD-related CVD.[17] The criteria for enrollment to SHARP included patients aged ≥40 years with a history of CKD, either receiving dialysis or not on dialysis but with serum creatinine ≥1.7 mg/dL (150 μmol/L) in men, ≥1.5 mg/dL (130 μmol/L) in women. In addition, patients needed to have neither a clear indication nor a contraindication for LDL-lowering treatment. The primary CVD outcome was major atherosclerotic events (coronary death, MI, nonhemorrhagic stroke, or any revascularization). Secondary outcomes included major vascular events (cardiac death, MI, any stroke, any revascularization), and components of major atherosclerotic events. The study drug was a combination of ezetimibe 10 mg and simvastatin 20 mg daily (this fixed combination is not available in Canada). The combination was used to avoid the adverse effects that would be expected in a monotherapy statin dose large enough to produce a similar LDL reduction. Patients (N=9438) were randomized to ezetimibe/simvastatin (n=4193), placebo (n=4191), or simvastatin alone (n=1054, for safety analysis). Patients in the simvastatin-only arm were re-randomized to the study drug or placebo after 1 year to further evaluate the effectiveness and safety of combining ezetimibe with simvastatin. Follow-up was approximately 5 years. At baseline, the mean eGFR in

the nondialysis cohort was 27 mL/min/1.73m^2, albuminuria was present in 80% of patients, 27% of patients were on hemodialysis, and 5% were on peritoneal dialysis. Mean lipid levels for all participants were as follows: LDL 2.8 mmol/L, HDL 1.1 mmol/L, triglycerides 2.3 mmol/L, and total cholesterol 4.9 mmol/L.

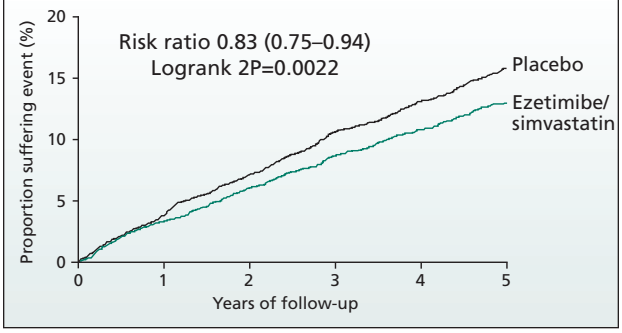
The primary results of SHARP, originally shown at the American Society of Nephrology's Kidney Week 2010, were presented at a 2011 WCN symposium entitled "Chronic Kidney Disease: Pathogenesis, Epidemiology, Prevention, Consequences." LDL cholesterol was reduced by 1.07 mmol/L at 1 year with the ezetimibe/simvastatin combination relative to the placebo group; simvastatin alone lowered LDL cholesterol by 0.74 mmol/L versus placebo. At 2.5 years, the LDL reduction due to ezetimibe/simvastatin was 0.85 mmol/L, a 32% reduction relative to placebo (*P*=0.0001). The investigators attributed the decline in effect to noncompliance in approximately one-third of patients by the study midpoint. Significant reductions were also observed in total cholesterol and in triglycerides.

The primary outcome of SHARP (Figure 1) was a 17% reduction (risk ratio 0.83; *P*=0.0022) in major atherosclerotic events. Significant risk ratio reductions, ranging from 12% to 28%, were seen in major vascular events, except for hemorrhagic stroke. The risk ratio for ischemic stroke was 0.79. There was no overall effect on mortality. Results for the primary endpoint were the same for dialysis and nondialysis patients. Investigators estimated that with full compliance, use of the ezetimibe/simvastatin combination would result in 30–40 fewer atherosclerotic events per 1000 patients treated for 5 years.

Further to the results of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS trial), concerns were raised about increased cancer incidence. However, there was no difference in cancer rates between the treatment and placebo groups in SHARP. No other significant safety issues were observed in this trial. Safety concerns have emerged in other statin studies. In the 4D trial, which investigated the use of atorvastatin in diabetic patients on dialysis, there was a doubling of the risk of fatal stroke compared with placebo (4% versus 2%; risk ratio=2.03, *P*=0.04).[15] Similarly, there was an increased number of fatal and nonfatal strokes in dialyzed diabetic patients on rosuvastatin in the AURORA trial.[16] It should be noted that these findings were associated with initiating statin therapy in this patient population, rather than patients who were already being treated with statins prior to starting dialysis. As outlined by Herrington et al,[18] ezetimibe/simvastatin significantly reduced nonhemorrhagic stroke (risk ratio 0.75; 95% CI 0.60–0.94; *P*=0.01) and a nonsignificant elevation in hemorrhagic stroke (risk ratio 1.21; 95% CI 0.78–1.86; *P*=0.4). This resulted in a net significant stroke reduction (risk ratio 0.81; *P*=0.04).

The current NKF-KDOQI guidelines recommend statin therapy for patients with diabetes, CKD, and LDL cholesterol ≥5.5 mmol/L, but specifically recommend against initiating statins in patients with diabetes who are on hemodialysis, unless there is a specific CV indication.[12] Potential updates to the guidelines in the light of these recent studies would be to use statins or statin/ezetimibe in combination in patients with diabetes and CKD, but not to initiate statin therapy in patients with diabetes who are undergoing dialysis.

Figure 1: Major Atherosclerotic Events in the SHARP Trial[17]



SHARP = Study of Heart and Renal Protection

Glycemic control

Glycemic control is central to the treatment of diabetes. At present, the target for hemoglobin A_{1C} is <7.0%, regardless of the presence of CKD.[12] Three major trials have investigated the impact of lowering this target to <6%–6.5%, but this resulted in increased severe hypoglycemia in each trial. The ACCORD trial was terminated 17 months early due to increased all-cause and CV mortality,[19] while the Action in Diabetes and Vascular Disease – Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial[20] and Veterans Affairs Diabetes Trial (VADT)[21] showed no CVD benefit. However, new onset of micro- and macroalbuminuria were reduced in ADVANCE and ACCORD.

The long-term United Kingdom Prospective Diabetes Study[22] (UKPDS; median follow-up 10 years, maximum 30 years) investigated a less intensified glycemic control regimen with a target A_{1C} range of 7.5%–8.5%. Mortality, nonfatal MI, and microvascular disease were all reduced with this less intensified glycemic control.

A recent unpublished systematic review of key outcomes, undertaken for the guideline NKF-KDOQ1 update, shows no improvement in all-cause mortality with intensive glycemic control. Nonfatal MI is the only CV outcome that shows slight improvement. There is a markedly increased risk of severe hypoglycemia. The totality of current evidence would suggest that A_{1C} control of 6.4%–7.0% in patients with established type 2 diabetes does not improve most clinical outcomes at 4–10 years of follow-up compared to treatment that achieved A_{1C} levels of 7.3%–8.4%. Intensive control does, however, result in greater harm in terms of increased severe hypoglycemia. Proposed revisions to the guidelines suggest a target A_{1C} >7.0% in patients with comorbidities, such as CVD, which limit life expectancy (this definition would include patients with CKD).

Therapeutic agents were not specifically recommended in the guidelines, although metformin should be avoided due to the risk of lactic acidosis. Dietary control of carbohydrates and avoidance of high protein intake are recommended.

Anemia

Anemia is commonly associated with CKD, and is a risk factor for CVD and premature mortality, as well as adversely affecting quality of life.[23] As a result of the large effect this type of treatment was known to have on hemoglobin levels, erythropoiesis-stimulating agents (ESAs) such as darbepoetin were included in the NKF-KDOQI guidelines before efficacy trials were available.

However, a placebo-controlled trial of darbepoetin in 4038 patients[24] demonstrated no CV benefit to patients with CKD, diabetes and anemia, despite increased hemoglobin levels, while there was a significant increase in the risk of fatal and nonfatal stroke (5% versus 2.6% in the placebo group; *P*=0.001), and an increase in cancer recurrence and mortality. Other non-placebo controlled trials that compared different hemoglobin target levels for ESA therapy also failed to demonstrate CVD or mortality benefits.[25,26] Thus, the KDIGO guidelines are not expected to recommend ESA therapy for CVD reduction in CKD.

Bone metabolism disorders

There are as yet insufficient data to support treatment of bone metabolism disorders in CKD, but there is observational evidence that serum phosphorus may be a therapeutic target for the reduction of CVD risk. This is not the case for parathyroid hormone.[27]

Integrated therapy

The Steno-2 study[28] compared an intensive, multifactorial approach to standard therapy in 160 Danish patients with type 2 diabetes and persistent microalbuminuria. The therapeutic targets were A_{1C} <6.5%, total cholesterol <4.5 mmol/L, and BP <130/80 mm Hg. Patients in the intensive therapy arm were treated with pharmacotherapy to achieve targets, together with behaviour modification. All received low-dose acetylsalicylic acid, as well as blockers of the renin-angiotensin system to treat their microalbuminuria. After 8 years of follow-up, patients in the intensive treatment arm achieved 50% reductions in relative risk of major CV events and relative reduction in mortality at 13 years.

Conclusion

Advances in the understanding of both quantitative and qualitative differences in CVD associated with concomitant CKD are helping to clarify the types of treatment that are most effective in reducing the elevated CV risk present in this large patient population. Appropriate therapies designed to help patients meet BP, lipid, and glycemic targets are likely to greatly improve cardiac outcomes in patients with CKD.

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Dr. Moe has no disclosures to announce in association with the contents of this issue.

SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from Merck to support the distribution of this issue of *Cardiology Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Division of Cardiology, St. Michael's Hospital, and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party. This publication may include discussion of products or product indications that have not been granted approval by Health Canada. This content is intended for medical, scientific, and educational purposes only.