SJHG Heartbeat

Number 128 **July/August 2008**

Should Cardiologists be Interested in CKD?

Patients with chronic kidney disease (CKD) are increasingly being recognized as high-risk for developing cardiovascular events or being associated with higher risk in those with known cardiovascular disease (CVD). The converse is also true, in that the presence of atherosclerotic CVD should now be recognized as an independent risk factor for the development and progression of kidney disease.

This intimate relationship between two broad disorders is separated less by clinical and therapeutic issues than by the cardiology and nephrology subspecialty departments responsible for them. The two disorders share risk factors and pathophysiology. Both reduced glomerular filtration rate (GFR) and a urinalysis, which provides a window into the systemic vasculature, appear to be surrogate markers for endothelial dysfunction and are independent risk factors for systemic atherosclerosis, thus posing similar risk for renal and CV disease.

Accordingly, physicians should be trying to focus more on early recognition of CKD, and more aggressive risk-factor management to prevent development or progression of CVD and CKD. This *Heartbeat* will clarify the association between CVD and CKD, outline parameters to identify this tough patient group, and offer clear insights into how to best manage the CV and renal risk in these CKD patients.

With the release of Joint National Committee report (JNC 7) in 2003, CKD made the hit parade of CV risk factors (Fig 1).[1]

Figure 1. CVD Risk Factors.

- Hypertension
- Cigarette smoking
- Obesity (BMI $\geq$ 30 kg/m^2)
- Physical inactivity
- Dyslipidemia
- Diabetes mellitus
- Microalbuminuria
- Estimated glomerular filtration rate (GFR) < 60mL/min/1.73m^2
- Age (older than 55 for men, 65 for women)
- Family history of premature CVD (men under age 55 or women under age 65)

Risk Equivalent

The incidence of CKD in the U.S. continues to increase, with over 10% of the population now having some form of it. These patients have markedly increased CV risk. Because of this risk, the National Kidney Foundation (NKF) has designated CKD a CHD risk equivalent. Data suggests that CKD is as powerful a risk factor as diabetes mellitus, another CHD risk equivalent disease.[2]

CKD might seem far removed from cardiology, but looking at the 'at-risk' group – those with hypertension, diabetes, heart failure or vascular disease, and those taking diuretics, angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs)—one sees they are the bulk of a general cardiology out-patient clinic. Furthermore, cardiologists and primary-care practitioners do risk assessment for CHD, which should include looking at GFR and

checking for urine microalbuminuria. So, cardiologists and primary-care practitioners are ideally placed to identify those at risk of developing CKD and to play an important role in the prevention or palliation of renal impairment; hoping that by so doing they can intervene to reduce associated CV morbidity.

Making this diagnosis is important so that we can more aggressively treat higher risk CV patients and refer them to nephrology, but interestingly, patients who know they have kidney disease are more compliant. Blood pressures are lower and are more likely to be controlled to goal. *Patients are more afraid of kidney failure then dying from heart disease.*

Link between CVD and CKD

Two recent reports demonstrate the vast pathophysiologic overlap between atherosclerotic CVD and CKD. The first showed a strong independent relationship between CVD and multiple measures of renal dysfunction among volunteer participants in a screening program for people with kidney-disease risk factors.[3] **Dr Daniel E Weiner** (Tufts–New England Medical Center, Boston, MA), a coauthor of the report highlighting the increased risk of renal dysfunction and CKD when there is known CVD — lauds both studies for calling attention to the links between the two disorders. **"When you think of one, you should probably think of the other".**

"In people with CVD, we should screen for kidney disease. And when we find it, we should treat it," Weiner said. "If you stay on top of it, you can manage the progression of kidney disease fairly well, and for a lot of people who live long enough, you can really make a difference by slowing it down." Screening consists merely of estimating GFR (now routinely given in NJ as part of our Basic Metobolic Profile blood test) and checking urine periodically for protein. Therapy would largely duplicate CV pharmacotherapy except, for example, "maybe you focus more on ACE inhibitors or angiotensin receptor blockers for blood pressure control," because those drugs can be renoprotective.

In the other analysis CVD itself is portrayed as a major independent risk factor for future renal functional decline and for CKD in a community-based population.[4] Based on the ongoing **Kidney Early Evaluation Program** (KEEP) of the **National Kidney Foundation**, the presence of CV disease was independently associated with its traditional risk markers but also with low hemoglobin levels, microalbuminuria (defined as > 30 mg/L) and CKD (estimated GFR < 60 mL/min per 1.73 m^2) - Figure 2. A combination of the kidney-related markers compounded the risk of CV disease and also predicted mortality.

Figure 2. Significant Risk Factors for CVD in KEEP

- Microalbuminuria, > 30 mg/L
- Estimated GFR, 30 – 59 mL/min/1.73 m^2
- Hb ≤ 12.8 g/dL.

Compared to an absence of both CKD and CVD, CKD without CV disease about doubled the age-adjusted mortality risk ($P = 0.05$), CVD without CKD tripled it ($P = 0.003$), and a presence of both disorders nearly quadrupled the risk, with a hazard ratio of 3.8 ($P < 0.001$). Given that more than one-fourth of those in the study who had all three kidney-related risk factors also had CV disease, these findings suggest that screening for CVD would be of high yield among patients with these risk markers but no CVD symptomatology.

Premature Death Rate

Chronic kidney disease - even in early stages - is responsible for a substantial proportion of deaths that occur before age 65, according to a prospective study in Taiwan recently published in Lancet.[5] They estimated that the national prevalence of CKD was 12%. Disease in stages 3-5 (glomerular filtration rate no greater than 59 mL/min/1.73 m), Figure 3, accounted for 60% of the total prevalence. National prevalence ranged from 5.2% among subjects ages 20-24, to 37% among subjects 65 years old and older. Even

slight proteinuria was associated with significantly increased mortality. Death occurred before age 65 in 39% of subjects with CKD.

Figure 3. Stages of Chronic Kidney Disease

Stage	Description	GFR ml/min/1.73m^2
1	Kidney damage with normal or increased GFR	$\geq$ 90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney Failure	< 15 or dialysis

"Chronic kidney disease can be ranked as one of the most preventable risk factors (for early mortality) worldwide," lead author Dr. Chi-Pang Wen and his colleagues' state. "The under diagnosis and under treatment of chronic kidney disease is universal, and the lack of awareness of the problem or the lost opportunities for prevention is a global one."

Their recommendation: "The general public, by knowing their glomerular filtration rate and testing their urine, can take the necessary first step to reduce associated risk factors and to attenuate the increasing rate of this disease."

Therapeutic Modalities

"When you think of one you should probably think of the other." This is important for identification and obviously then for treatment. Aggressive atherosclerosis prevention measures to be considered are:

- Lipid and inflammatory modification
  - ►LDL-C < 70mg/dL
  - ►HDL-C > 60mg/dL
  - ►TG < 150mg/dL
  - ►hsCRP < 1mg/L
  - ►Lp-PLA$_2$ (PLAC) < 160ng/ml
- Blood pressure control: < 120/80
- Glycemic control: HbA1C close to 6.0 %
- Smoking cessation
- Normalization of body weight with an appropriate diet and exercise program

All patients with CHD or Diabetes Mellitus and now CKD as a CHD risk equivalent should be on aspirin, statins, ACE inhibitors and beta-blockers if post MI or with a low LVEF < 40%, along with therapeutic lifestyle changes (TLC).

A II Blockade: All patients with known or high risk for CHD should have a blood pressure (BP) goal of < 130/80mmHg. Patients with known CKD should have goal BP of < 120/80mm/Hg. Focus more on angiotensin II blockade with ACE inhibitors or angiotensin receptor blockers (if ACE inhibitors aren't tolerated) as part of a probable multiple drug BP reduction program. This class is associated with cardio-renal protection by decreasing microalbuminuria, assisting in control of BP, and slowing progression of both CVD and CKD. *The ACE inhibitor/amlodipine combination (Lotrel) is particularly effective, giving a little more protection in terms of allowing your vessels to vasodilate (ACCOMPLISH). The idea is that you have healthier blood vessels in addition to lower blood pressures.*

Dyslipidemia in CKD: Patients with CKD frequently have mixed dyslipidemia and often require treatment with multiple lipid-lowering drugs. The most common pattern is an HDL-C triglyceride (TG) axis disorder (high TG/low HDL-C). As in diabetes mellitus or metabolic syndrome, statins are the cornerstone of therapy with a goal LDL-C of < 100mg/dL and a non-HDL-C (total cholesterol – HDL-C) goal of < 130mg/dL.[6] An apoB level should be < 90mg/dL. *In those with the highest risk (known vascular disease) and CKD; LDL-C, non-HDL-C and apoB should be < 70, 100 and 80 respectively.*

For most patients with CKD, differences in their pharmacokinetic properties give some statins (atorvastatin & fluvastatin) a safety advantage in patients with advanced CKD. Although most other lipid-lowering agents can be used safely with statins in combination therapy in patients with CKD, the fibrates are renally metabolized

and require both adjustments in dose and very careful monitoring due to the increased risk of rhabdomyolysis. *See Tables 1 & 2 below.*

Summary/Conclusions

- Mortality from CVD is 10-30 times higher in patients with kidney disease than in the general population. CKD is an independent risk factor for CVD and these patients should be considered in the highest-risk group for CVD events. Conversely CVD is independently associated with the development and progression of CKD.
- Routine evaluation of patients with or at high risk for CVD should include measurement of spot urine microalbumin and an estimation of GFR. Anemia, decreased GFR, and microalbuminuria are all independently associated with CVD and when all three were present CVD was common and survival was reduced.
- When caring for individuals with preexisting CV disease and multiple CVD risk factors, primary care physicians and cardiologists should be checking for the development and progression of CKD. Attention should be directed to the potential complications of kidney disease that may require consultation by a nephrologist. Diabetes and hypertension often do not prompt screening for CKD. These high-risk groups should be screened for CKD.
- Therapeutic measures that reduce CV risk factors in CKD patients and CKD risk in CVD patients leading to improved survival (aspirin, angiotensin II blockade and statins) should be instituted along with TLC, blood sugar and BP control.

Recent data[8] which supports my own clinical experience reveals that patients with CKD are less likely to receive appropriate CV treatments and are frequently under-treated. The authors comment: "The relative underuse of ACE inhibitors or ARBs in patients with diagnosed CKD is striking, because *these are exactly the ones who might benefit the most from these drugs*." They add: "We can only speculate that this underuse might be related to providers' fears of adverse events such as hyperkalemia or sudden increases in serum creatinine."

Table 1. Dosing Modifications for Lipid-Lowering Drugs in CKD

Agent	GFR 60–90 ml/min/1.73 m^2	GFR 15–59 ml/min/1.73 m^2	GFR <15 ml/min/1.73 m^2	Notes
Statins				
Atorvastatin	No	No	No	
Fluvastatin	No	Not defined	Not defined	↓dose to one-half at GFR <30 ml/min/1.73 m^2
Lovastatin	No	↓to 50%	↓to 50%	↓dose to one-half at GFR <30 ml/min/1.73 m^2
Pravastatin	No	No	No	Start at 10 mg/day for GFR <60 ml/min/1.73 m^2
Rosuvastatin	No	5–10 mg	5–10 mg	Start at 5 mg/day for GFR <30 ml/min/1.73 m^2, max dose 10 mg/day
Simvastatin	No	No	5 mg	Start at 5 mg if GFR <10 ml/min/1.73 m^2
Non- statins				
Nicotinic acid	No	No	↓to 50%	34% kidney excretion
Cholestyramine or Colesevelam	No	No	No	Not absorbed
Ezetimibe	No	No	No	
Fenofibrate	↓to 50%	↓to 25%	Avoid	May ↑serum creatinine
Gemfibrozil	No	No	No	NLA recommends a dose of 600 mg/day for GFR 15–59 ml/min/1.73 m^2 & avoiding use for GFR<15 ml/min/1.73 m^2
Omega FAs	No	No	No	

Adapted from the K/DOQI clinical practice guidelines.[7] FA = fatty acid; NLA = National Lipid Association.

Table 2. Proposed Treatment Algorithm for Lipid Management in Patients With CKD (Stage 3 to 5)

Lipid Disorder	Therapeutic Option (See Table 1 for Dose Adjustments)
Moderate to severe CKD, Stages 3 to 4 (GFR 15-59ml/min/1.73 m^2)	
Elevated LDL-C	1) Atorvastatin, add ezetimibe if not at LDL-C goal 2) Fluvastatin, add ezetimibe if not at LDL-C goal
Mixed dyslipidemia (↑TG and ↓HDL-C with or without ↑ LDL-C) - not at non-HDL goal (Non-HDL-C = TC – HDL-C)	1) Atorvastatin or fluvastatin + ezetimibe 2) Fluvastatin + gemfibrozil 600 mg/day + ezetimibe if not at non-HDL goal 3) Statin + omega-3 fatty acids, add ezetimibe if not at non-HDL goal 4) Statin + fenofibrate 48 mg/day, add ezetimibe if not at non-HDL goal
Very high triglycerides (triglyceride ≥500 mg/dl)	1) Gemfibrozil 600 mg/day 2) Omega-3 fatty acids 3–4 g/day 3) Fenofibrate 48 mg/day
CKD stage 5 (hemodialysis or GFR <15 ml/min/1.73 m^2)	Cardiovascular Disease and Subsequent Kidney Disease
Elevated LDL-C	Atorvastatin (10–80 mg/day) or fluvastatin 40 mg/day, add ezetimibe if not at LDL-C goal
Mixed dyslipidemia	Atorvastatin or fluvastatin 40 mg/day, add ezetimibe 10 mg/day or omega-3 fatty acids 3–4 g/day if not at non-HDL goal
Very high triglycerides	Omega-3 fatty acids 3–4 g/day or gemfibrozil 600 mg/day

Mario L Maiese DO, FACC, FACOI
Clinical Associate Professor of Medicine, UMDNJSOM Email: maiese1@comcast.net

Heartbeats online: www.sjhg.org

***Heartbeat* is a South Jersey Heart Group publication.**

---

[1] Chobanian AV et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* May 21 2003; 289: 2560-72.

[2] Foley RN, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 2005; 16:489-495.

[3] Elsayed EV, et al. Cardiovascular disease and subsequent kidney disease *Arch Intern Med*. June 11 2007; 167(11): 1130-1136.

[4] McCullough PA, et al for the KEEP Investigators. Independent components of chronic kidney disease as a cardiovascular risk state: Results From the Kidney Early Evaluation Program (KEEP). *Arch Intern Med* June 11 2007; 167: 1122-1129.

[5] Wen C-P, et al. Chronic kidney disease a common cause of premature death. *Lancet* June 26 2008; 371: 2173-2182.

[6] Harper CR, et al. Managing dyslipidemia in chronic kidney disease. *J Am Coll Cardiol* June 27 2008; 51:2375-2384.

[7] K/DOQI Clinical practice guidelines for managing dyslipidemia in chronic kidney disease. *Am J Kidney Dis* 2003;41(Suppl 3):S1-S237.

[8] Kidney disease patients receive fewer medications post MI. *Clin J Am Soc Nephrol* July 2008*;* Advance online publication.