Chronic Kidney Disease (CKD): The New Silent Killer

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For the past several decades, the health care needs of Americans have shifted from predominantly acute episodic therapy to long-term treatment of chronic conditions in a more quality driven value based model. These chronic conditions affect nearly half the population of the United States, accounting for the majority of resources applied to healthcare. Both nationally and in our own network the most prominent outlier from a cost standpoint is CKD (see figure below).

Figure 1
LVH: Allowed Cost by Claim Volume (Data generated from a Populytics analysis).

CKD is clearly the outlier among the more prominent Chronic Diseases. The size of each bubble represents the $ cost per member per month. The Y axis is the number of claims related to each condition per year and the X axis is the total allowed payment for each condition for 1 year. The at-risk population includes hypertensives, diabetics, those with a cardiovascular disease or family history of CKD and ancestry (American Indians and Southwest Pacific origin).
The prevalence of CKD as defined in Table 2 by the National Kidney Foundation in their Statement Paper on CKD Kidney Disease Improving Global Outcomes (KDIGO) has been progressively increasing to 1 in 9 patients over the age of 18 in the last NHANES survey.

<table>
<thead>
<tr>
<th>Criteria for CKD (either of the following present for &gt;3 months)</th>
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<tbody>
<tr>
<td>Markers of kidney damage (one or more)</td>
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<tr>
<td>Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol])</td>
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<td>Urine sediment abnormalities</td>
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<td>Electrolyte and other abnormalities due to tubular disorders</td>
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<td>Abnormalities detected by histology</td>
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<td>Structural abnormalities detected by imaging</td>
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<td>History of kidney transplantation</td>
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<th>Decreased GFR</th>
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<td>GFR &lt;60 ml/min/1.73 m² (GFR categories G3a-G5)</td>
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Table 2
CKD is defined as abnormalities of Kidney Structure or function, present for > 3 months, with implications for health.

In 2012 KDIGO released a new classification (Table 3) which included the glomerular filtration rate (GFR) as well as albuminuria which has been shown to be complimentary to low estimated GFR with regard to both independently influencing prognosis as demonstrated in the heat map depicted in Table 3.
Table 3
Risk of chronic kidney disease progression, frequency of visits, and referral to nephrology according to estimated glomerular filtration rate (eGFR) and albuminuria. The GFR and albuminuria grid depict the risk of progression, morbidity, and mortality by color, from best to worst (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of visits (number of times per year). Green can reflect CKD with normal eGFR and albumin-to-creatinine ratio (ACR) only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements at 3 and deep red 4 times per year. These are general parameters only, based on expert opinion and must take into account underlying comorbid conditions and disease state, as well as the likelihood of impacting a change in management for any individual patient. “Refer” indicates nephrology services are recommended. *Referring clinicians may wish to discuss with their nephrology service, depending on local arrangements regarding treating or referring.

As CKD progresses it often leads to serious cardiovascular disease (CVD) events. A patient diagnosed with CKD Stage 3 has a 24.3 % chance of dying from a CVD event as compared to a 1.3 % chance of progressing on to end stage kidney disease (ESKD). The risk of a subsequent CV event is much higher among patients with ESKD than among individuals with normal renal...
function. After stratification for age, race, and gender, mortality from CVD is 10 to 20 times higher in patients undergoing dialysis than among the general population. 

This increased risk was clearly demonstrated to exist not only in advanced CKD with ESKD but also in lesser stages of CKD. The Valsartan in Acute Myocardial Infarction Trial (VALIANT), which examined the relationship between CKD and CV outcomes in patients who had experienced acute myocardial infarction. This randomized controlled trial demonstrated that even mild renal insufficiency is a major risk factor for adverse cardiovascular events. The increased risk demonstrated in the analysis was progressive, beginning with an estimated GFR of less than 81mL per minute per 1.73 m2 of body surface area. Each 10-unit decrease in GFR was associated with a 10% increase in the relative risk of death or in nonfatal CV complications. In addition, the incidence of CV events in the patients was far greater than the incidence of adverse renal events, confirming CKD as a potent, independent risk factor for CV events. Another study, supported by the National Institute of Diabetes and Digestive and Kidney Diseases, highlighted how important CKD is to public health. This study, which observed more than 1.1 million ambulatory adults from the Kaiser Permanente Renal Registry, revealed a graded association between estimated GFR and cardiovascular events (Figure 2), hospitalization, and risk of death.
Figure 2. Age-standardized rates of cardiovascular events (coronary heart disease, heart failure, ischemic stroke, or peripheral arterial disease), according to estimated glomerular filtration rates (GFR) among 1,120,295 ambulatory adults.

This indicates the importance of screening our high-risk patients for CKD, identifying the presence of this high risk chronic disease, and appropriately staging it. Once diagnosed, these patients should be treated for secondary prevention of CVD just as a diabetic is, even if they have never had a CV event. Furthermore, evidence supports the need for earlier intervention to reduce acidosis, anemia, and hyperparathyroidism. These abnormalities are now recognized when the GFR fall to less than 60 mL per minute per 1.73 m² of body-surface area. ii
The role of the Primary Care Physician is paramount in treating this increasing epidemic associated with the ever-increasing population of diabetics and hypertensives. Below is listed what should be done once the diagnosis of CKD is made and Figure 3 reviews a practical approach based on stage of CKD regarding detection and management.

What should be done:

- Recognize and test at-risk patients
- Diagnose CKD and add appropriate stage to the problem list
- Provide aggressive CVD secondary prevention measures
- Manage Blood Pressure and diabetes to goal
  - Use of ACE inhibitor or ARB (not together) especially if ACR is > 1000 mg / g creatinine
- Monitor eGFR and Albumin to Creatinine Ratio on regular basis
- Consider patient safety issues in CKD
  - Educate Patients not to use non-steroidal anti-inflammatory medications (and document this in the EMR)
  - Dose adjust medications that are excreted by the kidney appropriated as GFR reduces
  - Avoid IV contrast where possible
    - IF needed make sure hydrated adequately with normal saline
  - Avoid gadolinium if GFR is < 30
- Appropriate referral to a nephrologist when appropriate
  - Acute kidney injury (AKI) or abrupt sustained fall in GFR
  - GFR <60 ml/min/1.73m² with CV disease present
  - GFR <45ml/min/1.73m² without CV disease
  - Progression of CKD with a decline in eGFR of more than 5 / year
  - A consistent finding of significant albuminuria (ACR > 300 mg albumin / gr creatinine
  - Persistent unexplained proteinuria (after a negative urological evaluation)
  - Hypertension refractory to treatment with 3 or more antihypertensive agents
  - Secondary hyperparathyroidism, persistent anion gap acidosis, non-iron deficiency anemia
  - Persistent abnormalities of serum potassium
  - Recurrent extensive nephrolithiasis
  - Hereditary kidney disease
Figure 3: Summary of practical approach to the detection and management of CKD.

ACE-I . angiotensinconverting enzyme inhibitor; ACR . albumin-to-creatinine ratio; AKI . acute kidney injury; ARB . angiotensin receptor blocker; ASA . acetylsalicylic acid/aspirin; A stage . albuminuria category; CAD . coronary artery disease; CKD . chronic kidney disease; CKD-MBD . chronic kidney disease mineral and bone disorder; CVA . cerebrovascular accident; CVD . cardiovascular disease.; DM . diabetes mellitus; eGFR . estimated glomerular filtration rate; ESA . erythropoietin-stimulating agent; G stage . GFR category; Hb . hemoglobin; HTN . hypertension; iPTH . intact parathyroid hormone; NSAIDs . nonsteroidal anti-inflammatory drugs; 25-OH vit . 25-hydroxy vitamin D; PICC . peripherally inserted central catheter line; PT INR . prothrombin time international normalized ratio; RAAS . renin angiotensin aldosterone system.
CKD clearly is a silent killer that with early recognition, staging, and addressing the tremendous risk of CVD can be addressed. A finite number of these patients will progress and early referral to a nephrologist will make a large difference in helping to slow the progression of the CKD even further. This will further prolong the time to needing renal replacement therapy, as well as assisting in the transition to a preemptive renal transplant ideally; and if not, to dialysis. These measures will clearly improve the quality and value of care provided to this chronic disease.

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iii Keith DS, Nicols GA, Gullion CM, Brown JB, Smith DH; Longitudinal Follow-up and Outcomes Among a Population With Chronic Kidney Disease in a Large Managed Care Organization Arch Intern Med. 2004;164:659-663

