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EDITORIAL

Diabetic Kidney Disease: An ACEI (or an ARB) in the Hole

In this issue of *Advances of Chronic Kidney Disease*, the co-guest editors, Kevin Ho and Amy Jayne McKnight, deliver a state-of-the art review of diabetic kidney disease (DKD). The contributing authors have carefully reflected on various facets of this critically important condition, which constitutes the predominant diagnosis of ESRD within the United States. Their composition and melding of basic and clinical sciences related to DKD is outstanding and prescient. By contrast, I will wax toward the present.

For the first time ever, the U.S. Renal Data System (USRDS) reported a decline of 1303 patients entering the renal replacement therapy arena between 2010 (n = 116,946) and 2011 (n = 115,643), a cause celebré in the kidney world.[1] This indicates that fewer patients with DKD began renal replacement therapy. This observation may reflect an improvement in care, a difficult metric for this population. However, fewer diabetic patients with high degrees of comorbidity may have been offered the "nondialysis" approach,[2] despite advanced CKD, given that the risk of death may outcompete the risk of ESRD.[3,4]

Of note, the USRDS also reported that the single most important therapy, anti-renin-angiotensin aldosterone (RAAS) therapy, for DKD may be underutilized.[1] Per the USRDS 2013, in the Medicare population with heart failure, only 44.2% of ESRD patients on hemodialysis are prescribed an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB; Fig 1). This is juxtaposed against a 57.3% point prevalent usage rate in patients without CKD and 52.0% in those with CKD. In advanced CKD, defined as Stages 4 to 5, there is but a 42.4% usage rate (Fig 2). Rather than using anti-RAAS therapy, beta-blockers and other drugs are prescribed in a vulnerable population in which acute myocardial infarction and heart failure rates are worsening. The medication usage data in CKD patients with or without heart failure are nearly identical.

The USRDS data are baffling but clearly demonstrate an underutilization of anti-RAAS therapy. Moreover, the usage of anti-RAAS treatment decreases as CKD advances. Although this appears absurd, it is true. Prescriptions for patients with CKD are generally lower than would be anticipated, and it is a short extrapolation to realize that this would also include diabetics. Paradoxically, the population that would benefit most from anti-RAAS therapy is the one denied the treatment. Consequently, we have withdrawn from the most important weapon in our therapeutic armamentarium, running counter to all that we have been taught, and have self-generated a therapeutic "hole" that we must now refill.

The reasons for this are likely few, and none of them are good. First, there may be reticence to use these drugs until the bitter end for fear of accelerating the progression rate of kidney decline. Onuigbo and colleagues have described this phenomenon in great detail,[5] although it has been acknowledged since the advent of ACEI therapy that a decline in glomerular filtration rate (GFR) may occur. If there is a sudden decline in GFR, then bilateral renal artery stenosis may be present, but usually it is not. CKD of any etiology and of sufficient degree may induce an abrupt decline of GFR, and this is precisely what Onuigbo identified, a particularly vulnerable subset of CKD patients who developed acute kidney injury after anti-RAAS therapy initiation. However, this is the minority of patients treated by anti-RAAS therapy. This is also true of the DKD population. Some degree of serum creatinine elevation must be anticipated and tolerated. Note that Hou and colleagues demonstrated the successful use of benazepril in patients with serum creatinines of 3 to 5 mg/dL.[6] In fact, if the serum creatinine does not escalate, then the practitioner should consider these options: (1) determine if there is drug resistance attributable to drug nonadherence by the patient, (2) increase the

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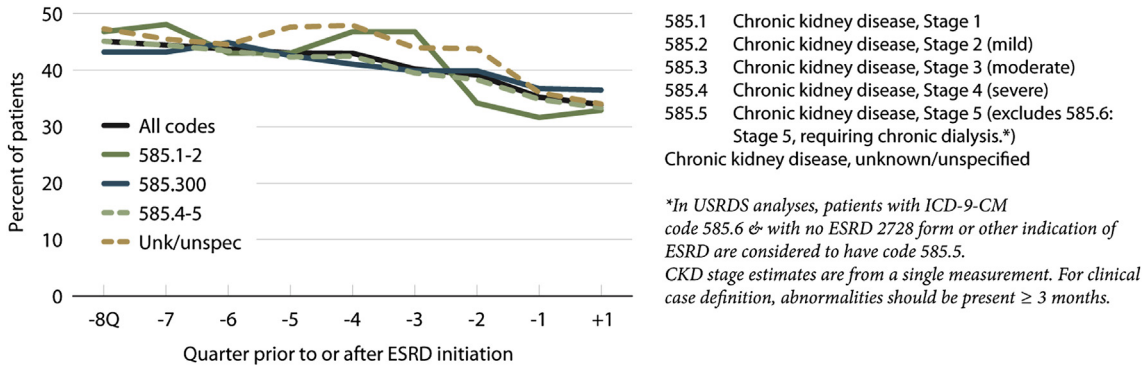

Figure 1. Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/direct renin inhibitor use in Medicare Part D enrollees in the transition to ESRD, 2011. Individuals with International Classification of Diseases, 9th Revision, Clinical Modification code 585.6 were excluded from analysis. The data reported here have been supplied by the U.S. Renal Data System. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government. (Figure 5.17, U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.) Reprinted with permission from Ref.[1]

dose, and (3) determine if another factor increased the GFR as the anti-RAAS therapy decreased it.

Option 1

Nonadherence is always an option. Patients do not like to take medications for disorders that do not physically hurt, such as hypertension,[7] and we are no different. However, pain powerfully provokes pill-taking, and DKD does not hurt. Multiple studies attest to the general inability to follow a scheduled drug regimen, and the percentage of adherence is inversely correlated with the number of drugs. Drug regimen simplification is an absolute requirement for all patients. Unfortunately, drug concentration measurements for nearly all commonly used medications in the CKD realm are absent unless the patient is also part of the transplantation, anticoagulation, anti-infective, cardiology, or seizure world. In brief, at each encounter, practitioners must themselves adhere to assessing drug adherence through conscientious medication reconciliation—National Patient Safety Goal No. 8 and Meaningful Use Core Measure 14—at each patient encounter.[8]

Option 2

Increasing the dose of RAAS blockade is often ignored unless the blood pressure is inadequately controlled. Then, the ACEI or ARB is increased, which may not adequately reduce the blood pressure, especially if the dosage is already more than half the maximum daily dose. A different class of antihypertensive should be considered,

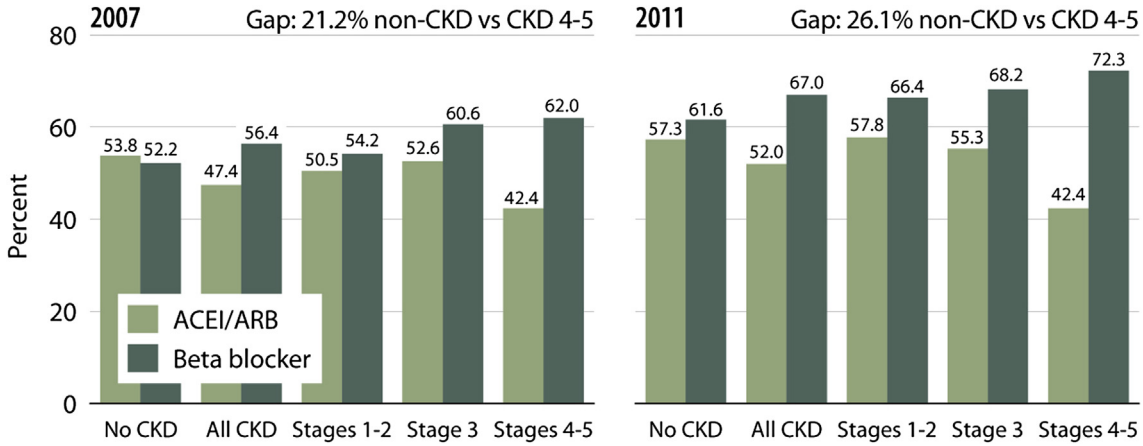

Figure 2. Gap in ACEI/ARB therapy for congestive heart failure between non-CKD and CKD populations, by CKD stage. Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker. The data reported here have been supplied by the U.S. Renal Data System. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government. (Table 4.b, U.S. Renal Data System, USRDS 2012 and 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2012 and 2013.) Reprinted with permission from Ref.[1]

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and one with therapeutic complementarity is best, ie, a diuretic that potentiates the anti-RAAS effect(s). However, given data from the Action to Control Cardiovascular Risk in Diabetes trial,[9,10] practitioners have likely relaxed their ambitions to tightly control diabetic patients' blood pressures. After all, the difference of achieving a systolic blood pressure of 130 mmHg vs 140 mmHg is an additional medication that a patient must take and the cost of that antihypertensive agent. However, the cost of this additional, generic blood pressure-lowering agent might only represent an additional $50 to $100 (U.S.) annually, but what is the advantage?

The benefit of blood pressure-lowering is not easily discernible between 130 and 140 mmHg at the glomerular level vis-à-vis proteinuria or at the kidney survival level. However, although intensive blood pressure-lowering is not efficacious in diabetes (140 vs 120 mmHg) for serious cardiovascular events, the continued application of anti-RAAS therapy may still be advantageous. Notably, a reanalysis of the Action to Control Cardiovascular Risk in Diabetes–Blood Pressure trial suggests that a lower blood pressure may yield better cardiovascular outcomes.[11] Stroke is a common complication in diabetes, and computed tomography scanning often reveals it as a silent manifestation of diabetic vasculopathy. Therefore, the index stroke event is often a "missed" event, and disturbingly, we often do not inform patients of this significant finding because no "clinical event" transpired. In the Secondary Prevention of Small Subcortical Strokes trial,[12] even diffuse white matter abnormalities represented prior cerebrovascular events. Because ACEI inhibition is approved as a measure for secondary stroke prevention, ongoing anti-RAAS blood pressure-lowering may be protective for stroke, but the blood pressure need only be reduced to 140 mmHg. Proteinuria is a tremendous risk factor for progression of CKD, even more so than blood pressure, and its presence is central to the Kidney Disease: Improving Global Outcomes CGA (Cause, GFR category, Albuminuria) Classification system.[13] Anti-RAAS therapy is potentially salutary by reducing albuminuria, and thereby interstitial inflammation, the most important predictor of a kidney's longevity. Importantly, the recently released JNC 8 guidelines advise caution in the use of anti-RAAS therapy in the elderly due to the risk of increasing the serum creatinine and hyperkalemia. Stringent adherence to this guideline may leave those with proteinuria and those who could tolerate anti-RAAS therapy at risk.[14] In summary, maintaining anti-RAAS therapy for its secondary stroke prevention and antiproteinuric effects must always remain a consideration in DKD.

Option 3

If the DKD patient's serum creatinine does not escalate after institution of anti-RAAS treatment, suspect that something is amiss. The patient may have been volume contracted, absolutely or relatively, and is no longer. Did the blood pressure increase concomitantly with the lack of fall in GFR? If so, then suspect clinically inapparent volume overload and consider diuretic therapy. Salt ingestion would be a common culprit and is discoverable by a simple 24-hour urine measurement of sodium. In addition, consider whether the patient had been taking a nonsteroidal anti-inflammatory drug (NSAID). The plethora of over-the-counter NSAIDs is staggering, and as I discovered during one of my supermarket drug-pricing excursions, NSAIDs are much more expensive over-the-counter, on a milligram-to-milligram cost basis, than their prescribed counterparts. A monitored, short-term NSAID prescription is likely superior to one that is unrestrained and unknown to the provider. In conclusion, if one has not therapeutically increased the serum creatinine, one must consider the above, rectify them, and increase anti-RAAS therapy.

Taken collectively, there are few reasons not to maximize anti-RAAS therapy, especially given the fact that these agents are beneficial in heart failure, a common accompanying feature of sick, hypertensive DKD patients. Possibly, reticence stems from the fear of inducing hyperkalemia, and this is actually referred to as a "misfear."[15,16] Avoidance of anti-RAAS therapy to avoid hyperkalemia is not well supported by literature. It exists, but it is far less common than believed. In addition, hyperkalemia at the level of 5.0 meq/L has hurt no one. If the threshold definition of hyperkalemia was set at 5.5 meq/L, then we and our patients will all be better for it. Enslavement by a threshold of 5.0 meq/L undoubtedly has had negative consequences because providers have denied the patient valuable therapy while reinforcing the false notion that such a potassium level is dangerous. The primarily potassium-based membrane potential is essentially a Nernst potential and is essentially the logarithm of the ratio of extracellular-to-intracellular potassium concentrations. Consequently, elevations of the baseline serum potassium from per se 4.5 meq/L by 0.5 and 1.0 meq/L only increase the membrane threshold potential by 3% and 6%, respectively, a clinically inert event, in the absence of an extremely low, serum ionized calcium concentration. Lastly, in addition, patients who have advanced CKD characteristically undergo multiple venipunctures, and this represents a problem: vein destruction in potential arteriovenous fistula candidates. The phlebotomist, intent on obtaining a specimen, may provoke pseudohyperkalemia from "ischemic" blood drawing because of overly vigorous fist-clenching and a too tightly applied tourniquet, as delineated by Don and colleagues.[17]

An anti-RAAS agent when used alone generally will not lead to hyperkalemia. In nondiabetic patients, this is borne out by the results of the African American Studies in Kidney Disease study, in which ramipril represented the ACEI arm of the original 3-arm study: ACEI

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ramipril, beta blocker metoprolol, and the dihydropyridine calcium channel blocker amlodipine.[18] At GFR levels greater than 40 mL/minute per 1.73 m^2, the frequency of hyperkalemia was only 1.6%, and it increased as GFR declined. Concomitant diuretic therapy generally attenuated hyperkalemia when the serum potassium level exceeded 5.5 meq/L.

Potassium elevations typically do not occur in the absence anti-RAAS therapy until the GFR is nearly 15 mL/minute per 1.73 m^2.[19] When hyperkalemia occurs in a diabetic individual, the diagnosis of type 4 renal tubular acidosis or hyperkalemic, hyperchloremic acidosis from hyporeninemic hypoaldosteronism is frequently invoked. This disorder is common to nephrologists, but it is actually not that frequent in general medical practice. However, more often than appreciated, another supervening circumstance has occurred—one that precipitates hyperkalemia that in turn impairs ammonium excretion.[20] Examples would include subclinical volume depletion in an individual with mild CKD who then experiences impaired ammoniagenesis from the lowered GFR; undisclosed obstructive uropathy from any of many causes, with consequent impairments of aldosterone bioactivity and potassium secretion; decreased effective circulatory volume from decompensated heart failure; or the coadministration of an agent that aggravates hyperkalemia, such as trimethoprim-containing compounds, an NSAID, heparin, or a calcineurin inhibitor in an allograft recipient. In brief, hyperkalemia in DKD is usually neither attributable to type 4 renal tubular acidosis nor the isolated administration of an anti-RAAS drug, and supplementary causes of hyperkalemia should be sought out.

In addition, at what level must hyperkalemia be treated? This is a debatable point to most; however, there are many patients that tolerate levels of 5.5 meq/L or greater without incident, and a threshold treatment level of 5.5 meq/L is reasonable. Dietary potassium restriction is the healthiest maneuver for the patient. The exclusion of red meat and its attendant higher levels of potassium and phosphate may also retard the progression of CKD. If hypobicarbonatemia and acidemia are present, then the administration of a loop agent in the salt-overloaded, edematous patient is preferred. Potassium levels are lowered, and serum bicarbonate levels are restored in parallel.

Bicarbonate or citrate administration in mildly hypobicarbonatemic individuals with CKD has successfully attenuated the progression of CKD and reduced hospitalization and mortality rates, without precipitating heart failure.[21,22] The bicarbonate strategy works similarly in DKD patients and in those with true distal renal tubular acidosis, but alkali treatment is underutilized because of an inappropriate fear of causing a volume-overloaded situation. The onset of edema in bicarbonate-treated patients is more of a nuisance in a minority of patients and is readily dispatched by loop diuretic therapy. Recall that Dr. Oliver Wrong carefully recorded the relative paucity of sodium bicarbonate-induced hypervolemia decades ago; he was right. Bicarbonate therapy may also increase as DKD patients begin more intensive antiproteinuric therapy with the combination therapy of ACEI (and presumably, ARB) plus spironolactone. Hyperkalemia, defined by serum potassium concentrations greater than 5.5 meq/L, does occur more frequently with this drug combination, as observed by Mehdi and colleagues in their trial comparing ACEI plus ARB therapy against ACEI plus spironolactone.[23] Lastly, a large-scale, multisite, clinical trial that examines the clinical efficacy of bicarbonate therapy in CKD patients is ongoing (ClinicalTrials.gov identifier: NCT01452412).

Hyperkalemia therapy via administration of sodium polystyrene sulfonate (SPS), with or without sorbitol, is ill advised. The time from administration to efficacy is on the order of 4 or more hours, if there is efficacy at all for this exchange resin with its relatively low K_m for potassium and which is more effective in vitro than in vivo.[24-27] The safety of SPS has also been called into question. In response, the sorbitol concentration in SPS-sorbitol combinations has been reduced, and this may have reduced the effectiveness of the compound because potassium loss may be more sorbitol-induced than a result of potassium resin binding. Newer potassium-lowering agents have been recently designed, and these bioengineered compounds may supplant SPS in the near future: patiromer, a polymeric potassium-binding compound,[28] and a microporous, zirconium silicate potassium-binding resin (ClinicalTrials.gov identifier: NCT01737697).

In conclusion, the hole in anti-RAAS therapy can enlarge no more. Given the magnitude and level of evidence that anti-RAAS therapy retards the progression of DKD and non-DKD,[29] we cannot afford to turn away from these treatments. If hyperkalemia occurs, then causes other than anti-RAAS therapy should be sought out. Thresholds of toleration of elevations of serum creatinine and potassium concentrations must be reset to higher levels. Treatment of hyperkalemia, when it occurs, must also be executed more judiciously as anti-RAAS therapy is continued.

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