Moderator’s View: Should we diagnose CKD using the ‘one-size fits all’ KDIGO 2012 guideline or do we need a more complex age-specific classification system?

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The KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease was published January 2013 [1]. Based on evidence provided by meta-analyses including >1.5 million subjects, this document proposed a new classification system for chronic kidney disease (CKD). This classification system is meant to be universal and is independent of age. Recently, Moynihan et al. [2] expressed strong concern in the BMJ series ‘Too much medicine’ about the harms of overdiagnosing CKD in low-risk elderly due to the use of a single eGFR threshold for all age groups. This leads to a brisk debate in the weeks thereafter showing very different views on this topic. We therefore invited two leading experts to debate the pros and cons of using age-specific cutoffs for diagnosing CKD.

Conte, Minutolo and De Nicola present data showing that the relationship between GFR and morphological changes in the elderly is inconsistent. Reduced kidney function in this age group is the result of a mixture of physiological senescence, subclinical vascular disease and initial kidney structural changes which are difficult to separate from each other, thereby rendering the histopathological kidney function association less suited for defining kidney disease. They therefore focus on how to use the association between kidney measures and hard clinical outcomes like end-stage renal disease (ESRD) and death for diagnosing and classifying CKD. They describe how relative and absolute risk changes with age and draw parallels to traditional risk factors like blood pressure, cholesterol and glucose, which also have lower relative risks but higher absolute risks in the elderly. Still, nobody recommends age-specific thresholds for these risk factors today. Conte et al. argue that there is no reason to treat CKD different from other risk factors and conclude that the current thresholds defining CKD should not be changed in the elderly.

Glassock has long advocated against the K/DOQI classification system for several reasons, but particularly its consequences for the elderly. In this elegant debate contribution he guides us through the potential problems with a definition using one threshold for all ages. He stresses the view that a decline in GFR is often a normal phenomenon associated with normal aging referring to cohorts with a substantial proportion of apparently healthy elderly having eGFR <60 mL/min/1.73 m². There are also studies describing histological signs of nephrosclerosis in the majority of kidney donors aged 70–77 years. Proteinuria is highlighted as an essential finding of clinical relevant kidney disease leading to the dilemma whether the large group of elderly with GFR stage 3A and normal albuminuria has kidney disease or not. He also highlighted the fact that a 25% increased mortality risk (compared with eGFR 80 mL/min) is found at eGFR levels ranging from 74 mL/min/1.73 m² in the youngest to 50 mL/min/1.73 m² in those 75+ years. Glassock strongly concludes that a reduced GFR has different implications in different age groups, and the KDIGO guidelines should therefore be revised to include thresholds defining CKD that are age dependent.

The current pro-con debate clearly shows that there is no universal agreement on CKD diagnosis and classification. However, national guidelines, hospitals and individual physicians need to decide on how to deal with this clinical problem. We would therefore like to add some general comments to broaden the previous discussion with the hope to facilitate the choice of how CKD should be diagnosed.

First, is the term CKD a useful concept at all? Most kidney disease diagnosis is based on histopathological classifications which are often immature, complex and confusing with overlapping clinical features. This has seriously hampered kidney research and cooperation with non-nephrologists. Although
initiating disease processes vary, most kidney diseases have similar pathophysiological mechanisms for further progression of the disease. Currently available treatment options are also surprisingly similar in different kidney diseases further supporting a common wide-ranging CKD definition. Furthermore, the INCIPe study demonstrated that a large proportion of CKD patients identified by the KDIGO 2012 criteria have relevant kidney disease; [3] one-third were found to have a specific chronic nephropathy (glomerulonephritis, diabetes nephropathy, polycystic kidney disease, ischemic nephropathy, etc.), one-third had undetermined chronic nephropathy (not matching any of the strictly pre-defined specific chronic nephropathies above, but had an abnormal renal ultrasound (parenchymal hyper echogenicity, reduced cortical thickness, resistive index >0.75), leaving only one-third with lone reduced eGFR or lone microalbuminuria.

Secondly, there is the philosophical question whether there can be something as normal ‘physiologic’ ageing. When bodily functions decline with increasing age, is this just normal physiology and therefore to be accepted, or is it pathophysiology needing intervention to improve quality and quantity of life? In medicine there is nowadays general consensus that changes in lifestyle are to be encouraged to optimize healthy ageing. Furthermore, specific interventions are instituted for various age-related medical problems, such as prescribing vitamin D and calcium for age-related osteoporosis, and lens implantations for age-related cataract. Why should kidneys be different? Is a loss of nephrons due to age-related nephrosclerosis less important than the loss of the same number of nephrons due to for instance IgA nephropathy? It is an old Roman proverb ’Senectus ipse morbus’, or in plain English ’Old age in itself is an illness’. When we accept this view there is no need to be reluctant to diagnose diseases or to acknowledge presence of risk factors in the elderly. The only dilemma is whether there are treatments available and if so, whether we are going to treat these conditions. Will benefits outweigh risks? This balance may be different in elderly. However, in our view it is not dependent on age per se, but on physical condition. In younger subjects with co-morbidities we sometimes also choose not to treat because the risk/benefit balance of intervention is anticipated not to be favourable. The debate is therefore actually not about age, but about frailty.

Thirdly, there is another important general question with decisive influence on the current debate: should nephrology remain a hospital-based sub-specialty exclusively providing life-supporting treatment of end-organ failure, or should we shift focus towards the early stages of kidney diseases to prevent its progression and complications? Renal replacement therapy is extremely expensive, patients have low quality of life and mortality is very high, so this is clearly not a fully satisfying option. On the contrary, KDOQI and KDIGO guidelines advocate opportunistic screening in risk groups using a wide CKD definition. Although we recognize that the current CKD diagnosis and classification system have weaknesses, and treatment options for early stages of CKD are limited, most nephrologists generally support the idea of focus on the early CKD stages.

Fourthly, implementation of clinical guidelines is always a crucial point. Most agree that eGFR and albuminuria are major kidney measures that need to be integrated in a diagnostic classification system. The KDIGO system now comprises 18 groups (plus the cause of the CKD), a number that is already difficult to manage for most physicians. Clearly using one threshold for all ages is a compromise with reduced accuracy in the youngest and oldest subjects. However, introducing an extra-dimension like age-specific threshold would, in our view, increase the complexity of the classification system substantially. Even if this could be a theoretical improvement of the system, we are afraid that it would make implementation in general practice impossible.

Fifthly, relatively few subjects diagnosed to have CKD with the KDIGO criteria will progress to ESRD while many more will suffer from cardiovascular events (CVD) [4]. This is sometimes put forward as an argument against the wide CKD concept claiming that these patients will receive appropriate care through established CVD screening and treatment programmes. However, the vascular process in CKD patients is different from mainstream CVD patients. CKD patients increasingly suffer from medial artery calcification (Monckeberg sclerosis) caused by ’osteoblast-like’ cell transformation of fibroblasts due to oxidative stress, uremia and hyperphosphatemia [5]. This process is insufficiently influenced by standard CVD prevention with statins, antihypertensive- and antithrombotic drugs [6]. CKD patients clearly need CKD-specific approaches and therefore need to be diagnosed as CKD patients. The large decisive randomized clinical trials are missing in nephrology so far, but there is emerging evidence that kidney specific treatments not part of the standard CVD prevention programme are useful: early phosphate restricted diet and medical treatment of other aspects of CKD bone-mineral disease; [7] reducing albuminuria using ACE inhibitors and salt restriction; [8] adequate diuretic treatment of salt and fluid retention in resistant hypertension; [9, 10] treatment of metabolic acidosis [11] and protein reduction [12] are considered as important treatment for CKD patients.

Sixthly, for more specific comments on the KDIGO guideline and the fixed CKD thresholds used, we must look into its evidence base. The working group was able to draw on a series of interesting articles based on data from the CKD Prognosis Consortium [13]. With 2 million participants worldwide and thousands of clinical outcomes the results themselves are widely generalizable and highly accurate. It is therefore more a question on how to interpret the data and how to work with preventive medicine in general. One such aspect, which is interpreted very differently in the accompanying debate contributions, is the declining relative risk associated with a certain level of reduced eGFR seen with increasing age. This is, however, a general effect also seen with other risk factors like hypertension [14], hypercholesterolemia [15] and smoking [16]. On the other hand, as Conte et al. pointed out in the pro-con debate, there is an increasing absolute risk with increasing age for that level of reduced eGFR. This brings forward the question what is more important for a patient, their relative risk to die or their absolute risk? It may well be the latter. Of note, this opposing relative-absolute risk phenomenon is a general effect also seen with other risk factors like hypertension and hypercholesterolemia, etc. As late as the 1970s, the prevailing medical practice was to...
ignore high blood pressures and hypercholesterolemia in the elderly, even though epidemiologic data demonstrated associations with clinical outcome in elderly patients also. During the last two decades many clinical trials showed that antihypertensive and lipid lowering drugs could improve outcome in the elderly, and today nobody advocates age-specific cutoffs for hypertension and hypercholesterolemia.

In summary, we find that the KDIGO 2012 guideline for diagnosis and classification of CKD has a strong evidence-based foundation, including the choice to use universal kidney function thresholds in all age groups. The reduced relative risks in the elderly are counteracted by the higher absolute risks for important clinical outcomes like acute kidney injury, ESRD and death. A large proportion of CKD patients have relevant kidney-specific diseases, and optimal cardiovascular prevention can only be offered to these high-risk patients if they are recognized as CKD patients. Lastly, a universal threshold for all ages will facilitate widespread implementation. Of course no classification system is perfect and good clinical judgment is especially important around the diagnostic thresholds. We agree that clinicians should consider co-morbid conditions and life expectancy of the patient and the trajectory of eGFR or urinary albumin results, and communicate to patients that stable mildly reduced renal function in the absence of other risk factors (eGFR 45–59 mL/min and no albuminuria) is a low-risk situation that usually can be observed with focus on cardiovascular prevention. However, this holds true for elderly as well as younger patients. In our opinion the KDIGO classification system should therefore be implemented without age-specific thresholds.

REFERENCES


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