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Opinion Paper

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Age, stage and biomarkers for the definition of CKD: a construction in progress

Abstract: The international recommendations of the Kidney Disease: Improving Global Outcomes (KDIGO) to define chronic kidney disease (CKD) and classify patients in CKD stages are discussed in an opinion paper published in this issue of the journal. In this counterpoint, we will review some questions and criticisms raised by the authors to provide further contribution on the issue. In particular, we would like to discuss the age issue in the definition of CKD, the validity of the KDIGO staging, the validity of creatinine-based equations for the estimation of the glomerular filtration rate (GFR), as well as the clinical value of cystatin C and the epidemiological rather than clinical nature of the arguments proposed to justify recommendations in the KDIGO guidelines.

Keywords: chronic kidney disease; clinical practice guidelines; creatinine; cystatin C; KDIGO; stardardization.

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Introduction

Over the last two decades clinical practice guidelines have been increasingly perceived as an effective instrument to increase the quality of care both in acute and chronic conditions. The methodology for developing and testing the validity of guidelines has been well framed by the Enhancing the Quality and Transparency of Health Research [1], a cogent international initiative aimed at improving the reliability and value of clinical research and to produce effective recommendations that may ultimately improve health outcomes.

Guidelines have gained momentum in nephrology [2] and documents dealing with renal diseases or renal diseases complications have been produced by disparate organizations including scientific societies, independent foundations and governmental health funding agencies including technology assessment agencies such as the Agence Nationale d'Accreditation et d'Evaluation en Sante (ANAES) in France, the Agency for Health Care Policy and Research (AHCPR) in the USA or the National Institute for Health and Clinical Excellence (NICE) in UK. Public policy makers and health authorities now pose guidelines as a centerpiece in programs aimed at improving healthcare.

The Kidney Disease Global Outcomes Improvement (KDIGO) is undoubtedly the most successful initiative as for the production and dissemination of nephrology guidelines [3]. KDIGO was established in 2003 as an independent, non-profit foundation governed by an international Board and is managed by the National Kidney Foundation, an American foundation with vast experience in the field. This initiative is perceived as the most authoritative source of guidelines in nephrology worldwide.

Chronic kidney disease (CKD) is a major public health problem and as such it demands well-concerted screening and detection policies and wide-ranging intervention plans [4]. In 2002, the Kidney Disease Outcome Quality Improvement (KDOQI) group (an American working group funded by the National Kidney Foundation) issued a guidelines where CKD was defined and classified [5]. These guidelines produced uniform definitions of CKD and a new staging system for the classification of CKD severity. The staging system was accompanied by specific recommendations on the interventions needed – from prevention to treatment – to fight the CKD epidemic, stage by stage. Of note, these guidelines for the first time directly faced fundamental issues related to measurement of kidney function that had been almost ignored by the nephrology and the medical community at large. This document had a profound influence on the very conception of CKD and stimulated considerable research, stirred controversy and open discussion. Importantly, these guidelines fulfilled the scope of influencing public policy

and improving laboratory practice. After 10 years [6], the new knowledge on CKD which was generated by the revolutionary stimulus of the KDOQI guidelines made compelling an update of the same guidelines in the context of today's nephrology and public health realm. This new guideline was conceived as a far-reaching document with worldwide implications and as such it was produced under the aegis of KDIGO rather than by the National Kidney Foundation.

This long premise is important to understand the authoritativeness and the reach of the CKD-KDIGO guidelines and to appreciate the brave dedication of two investigators, Delanaye and Cavalier, in making a long series of objections to recommendations by these guidelines in a paper published in this issue of the journal [7]. Fully respecting Delanaye and Cavalier arguments and with the provision that fresh research on CKD staging remains of central importance, we believe that their arguments do not undermine the validity of the KDIGO guidelines. This counterpoint is the expression of a spontaneous "defense team" of the KDIGO guidelines by two independent clinical nephrologists and a laboratory professional who, eventually, is the Editor in Chief of the Journal.

Below we compactly identify the most critical objections made by Delanaye and Cavalier and provide our view on these objections.

The age issue in the definition of CKD

This is a long-standing debate with prominent renal investigators militating in the same side of Delanaye and Cavalier [8–11]. The essence of the debate is if it makes sense or not labeling as "diseased" healthy older subjects with a <60 mL/min/1.73 m².

Whenever a condition is defined on the basis of a threshold identified across a continuous variable, like it is the case for blood pressure (BP) or serum glucose, problems arise. There is no perfect threshold but still thresholds are useful for diagnosis and treatment [12] and facilitate education and communication with patients. The issue of age and CKD diagnosis is reminiscent of the strong debate on whether systolic hypertension in the elderly should be considered as a disease and if it should be treated [13]. Now hypertension guidelines recommend treatment of systolic hypertension also in individuals older than 80 years and set the BP goal in elderly individuals the same as in younger patients, i.e., <140/90 mm Hg or below, if tolerated [14]. That reduced estimated glomerular filtration rate (eGFR) portends an excess risk for adverse cardiovascular and renal outcomes in the old is now well demonstrated. In the CKD-Epi consortium meta-analysis (Supplemental data published in the WEB appendix of [15]), individuals >65 years with a GFR <59 mL/min/1.73 m² and >45 mL/min/1.73 m² and no albuminuria had a 44% excess risk for cardiovascular death as compared to those in the reference category (GFR <104 mL/min/1.73 m² and >90 mL/min/1.73 m²) and such a risk excess rose considerably at progressively higher levels of albuminuria. In this meta-analysis there was no effect modification by age on the cardiovascular risk associated with reduced eGFR or albuminuria [15]. In individuals ≥75 years and a GFR <59 mL/min/1.73 m² and >45 mL/min/1.73 m² the risk for end stage kidney disease (ESKD) is similar to that in individuals in the age range 18–54 years with the same GFR, i.e., four times (400%!) higher than that in individuals of the same age-categories and a GFR=80 mL/min/1.73 m² [16]. Age-dependent thresholds invoked by the opponents to current approach are difficult (when not impossible) to set because health risks relationships are quite variable across different clinical outcomes such as the risk of cardiovascular complications and ESKD and, more important, very difficult to implement in clinical practice. Thus, based on knowledge gathered so far, we believe that the indication of a single threshold <60 mL/min/1.73 m² for all ages makes sense. Said that, we also believe that, no matter whether a given GFR threshold is age-dependent or not, doctors should appropriately consider patient-specific factors, like background comorbidities, quality of life, benefits and costs to eventually individualize treatment.

Validity of the KDIGO staging (problems with stages G1 and 2 and with splitting G3 into G3a and G3b)

Delanaye and Cavalier make a remark on the precision demanded to quantitative estimates of the GFR for them be useful in clinical practice and then go to assert that, given the unsatisfactory precision of eGFR estimates (interquartile range about 10 mL/min/1.73 m²), it is hard to distinguish stage G3a and b. They also object there is no interest in knowing whether a given patient is at G1 or G2 stage.

Starting from the second objection, cystatin C based studies [17] have found gradients in prognosis at eGFR levels above 60, which supports the decision of the KDIGO

committee of separating the G1 and G2 categories for staging. Importantly, in the absence of other markers, neither of these categories constitute CKD. In this context we consider the remark about G1 and G2 stages just as a nuance. In general, categories of the kind are created for raising clinical attention by physicians rather than for diagnosis and treatment, like it is the case of the "pre-hypertension" category in the JNC-VII [18].

As to the identification of sub-stages a and b within stage 3, we believe that this rests on solid epidemiologic evidence. Indeed a meaningful risk difference exists among these two sub-stages for a variety of complications including cardiovascular disease, progression to end stage kidney disease, infection, impaired cognitive and physical function, and threats to patient safety (for review see position statement by Levey [4]). Again making treasure of the CKD-Epi consortium meta-analysis [14] (Table 2, ibidem), as compared to the reference category (GFR 90 mL/min/1.73 m^2–104 mL/min/1.73 m^2) individuals with stage 3a CKD and no albuminuria had 28% excess risk for death while the risk excess in those with stage 3b was 97%. The corresponding excess risk for cardiovascular death in these two GFR sub-categories was 52% and 240% and the risk for these outcomes rose in parallel at progressively higher levels of albuminuria. The issue of precision should not scotomize such relevant risk differences. Blood pressure is a much variable parameter and several measurements are required in order to make precise estimates. Yet this does not detract from the fact that in a clinical and public health perspective staging hypertension is much useful. Individuals with a eGFR <60 mL/min/1.73 m^2 require increased medical attention and therefore in these patients creatinine is measured repeatedly. Thus, as it case of BP, sub-staging may require repeated measurements. Even though the issue of GFR and albuminuria monitoring is dealt with in detail in the KDIGO guidelines, the need of repeated testing for sub-categorization (stages 3a and b) would have deserved better specification in the same guidelines.

Validity of creatinine-based equations for the estimation of the GFR

Delanaye and Cavalier object that actual serum creatinine may be a sufficiently informative measure of the GFR and that GFR measures calculated on the basis of creatinine and age, ethnicity and sex may be redundant. To us the superiority of GFR estimates over crude creatinine is out of question. Even the first MDRD equation [19] provided GFR estimates that were more accurate than creatinine clearance from 24-h urine collections and the CKD-Epi equation improved accuracy in the range of values >60 mL/min/1.73 m^2. As to crude creatinine measurements, it is well established that these measurements fail to capture important underlying GFR changes in a wide range of values, the "creatinine blind range" [20]. This blind range is generated by the marked biological between subjects variability of serum creatinine. Creatinine has very low within-subject biological variability and substantial between-subjects variability. Consequently, subjects can have creatinine values inappropriately elevated for their body built and metabolic characteristics (underlying reduced GFR) but these values may well remain within the population-based reference range. Of course such values remain unflagged by laboratories and escape the attention of clinicians. Therefore we maintain that crude creatinine is a less than ideal measure for the detection and screening of mild and moderate degrees of kidney impairment. The proposal by Pottel et al. [21] to consider only serum creatinine and to adapt the results to different normal reference values in different populations and contexts is too complex and as such inherently inapt to epidemiological and clinical needs.

Omission of GFR equations other than the MDRD and CKD-Epi

Delanaye and Cavalier lament that the KDIGO guidelines are largely influenced by studies by the CKD-Epi consortium and that the same guidelines omit discussion of other equations like the Mayo Clinic equation, the Lund Malmoe and the Berlin Initiative study equations. We believe that formulating recommendations based on the best available clinical studies – i.e., studies selected for rigorous methodology, large dimension and robust external validation – is the very strength of clinical guidelines. In this respect the MDRD and the CKD-Epi equations have been tested and adapted for diverse populations and settings. We concede that there are still important conditions where these equations still need further study. Yet there is no question that none of the other equations had the thorough external validation (a critical methodological issue) of the MDRD and the CKD-Epi equations. The CKD-Epi consortium is a formidable initiative including, American, Asian and European cohorts and a large number of investigators of diverse countries. We only applaud to this initiative which we perceive as rich, open and truly successful.

Confirmatory testing with cystatin C and other clearance measurements in specific circumstances when eGFR based on serum creatinine is less accurate

Delanaye and Cavalier note that, even though a standardized calibrator exists, for cystatin C we still lack a standardization method as good as that we have for creatinine (IDMS). It should be highlighted that several hundred measurands of clinical interest still lack metrological traceability to SI units because primary and secondary reference measurement procedures are unavailable, but can be accommodated in one on other of several calibration hierarchies of lower metrological order [22]. This is the case of cystatin C as the availability of an international reference preparation (ERM-DA471/IFCC) provides an effective tool for harmonizing results obtained with different methods and by different clinical laboratories. In addition, the authors remark that the recommendation of applying the eGFR-cys or the eGFR cys-creatinine equations for CKD confirmation is loosely grounded.

It is adamant that few biomarkers have been so extensively used and tested as creatinine has been. However time-honored, creatinine is not the perfect GFR biomarker. Research on novel biomarkers of renal function is a flourishing area. We agree that cystatin-C based GFR equations still represent a growing clinical research area rather than a mature research topic. We also believe that Delanaye and Cavalier would subscribe that cystatin-C is the most promising among emerging GFR biomarkers. The reclassification power (net reclassification index 19.4%) of the combined cystatin and creatinine equation is absolutely not trivial [23]. The study where this observation was made was large and externally validated. Findings in this study still need to be replicated in other settings in order to make strong recommendations about the application of cystatin-C equations for CKD diagnosis confirmation. Said that, we believe that the recent KDIGO guidelines fairly recognize the lack of definitive evidence related with this issue. The recommendation is indeed graded as 2B, i.e., it is a simple suggestion based on evidence of moderate quality. By now a problem with this biomarker is cost (an issue also relevant for the enzymatic method of measurement of creatinine). If ongoing and future research will confirm observations gathered so far and will allow an upgrading of the strength of the recommendation about cystatin-C, larger application of the method will facilitate cost reduction and hopefully cost-effectiveness, a phenomenon which occurred with other biomarkers [24]. Guidelines should not only distill the best evidence but also identify areas of uncertainty and present emergent evidence which may be the basis for future strong recommendations. By now, and correctly so, the proposal of applying cystatin-C GFR estimates remains just a suggestion.

Epidemiological rather than clinical nature of the arguments proposed to justify recommendations in the KDIGO guidelines

In the closing paragraph of his paper, Delanaye and Cavalier note that arguments used to justify the cut-off value of 60 mL/min/1.73 m², the superiority of the CKD-EPI creatinine equation over the MDRD equation, or the application of cystatin C instead of creatinine-based equations are epidemiological rather than clinical in nature. For example, it is because eGFR <60 mL/min/1.73 m² predicts higher mortality that we set a threshold for a CKD stage at this GFR value. They then contends that "…. in clinical practice, disease prediction for future population is not the primary role of the GFR estimation equation ….". We disagree on this consideration. Arguments based on risk prediction or risk association are both epidemiological and clinical. Prediction is at the heart of prognosis, i.e., a fundamental element whereupon clinical medicine is founded. Furthermore, CKD is also a strong risk factor for disparate adverse outcomes, from ESKD to myocardial infarction and stroke. CKD is a common and dangerous cardiovascular risk equivalent [25] and as such it is a relevant epidemiological issue configuring a true public health priority. Thus arguments based on risk represent a valid methodological rationale for setting diagnostic and prognostic thresholds in the process of guidelines building.

Even though dissenting with most remarks by Delanaye and Cavalier, we believe that they should be commended for going into the folds of this important KDIGO guidelines and for exposing areas where evidence is still weak and where important dissent exists. Guidelines are an evolutionary enterprise and, quoting our opponents, they "are not carved in stone". We absolutely concur with the view that continuous monitoring of the flow of clinical science, capturing new data and significant findings with clinical implication and attention to arguments refuting today's knowledge is fundamental to maintain guidelines as a live, worthwhile enterprise.

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