

Screening for CKD with eGFR: Doubts and Dangers

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The early identification of chronic kidney disease (CKD) is a legitimate enterprise if it provides meaningful opportunities for effective and safe interventions that reduce the risk of death, end-stage renal disease, or complications of renal dysfunction. The screening of *unselected* populations not already known to be at risk of CKD has the potential of harm and has not been shown to be cost-effective. The application of formulas for the estimation of GFR (eGFR) to the guidelines for staging of chronic kidney disease (Kidney Disease Outcomes Quality Initiative, K/DOQI) as universal screening tools is of dubious value and has inherent dangers. This conclusion is based both on the unreliability of current formulas for determining eGFR and flaws in the K/DOQI schema for staging of CKD. The failure to take into account the normal age- and gender- associated decline in GFR and the lack of a requirement for other evidence of kidney disease in CKD stage 3 leads to an erroneous categorization of large numbers of mostly elderly and female subjects as having an intermediate stage of a lethal disease. Criteria for CKD staging should take into account the percentile distribution of eGFR by age and gender. *Targeted* screening for CKD is likely to be more cost-effective than *universal* screening. Whether early identification and treatment of subjects with “reduced” levels of GFR within the normal range for their age/gender, but without any other manifestations of kidney disease, will reduce the subsequent risk of cardiovascular events or progression to end-stage-renal disease is currently unproven.

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A whirlwind of unjustified enthusiasm for the relatively newer methods of estimating glomerular filtration rate (eGFR) is blowing all over the world. This wind, a veritable Santa Ana (a hot wind that emerges from the Great Basin and pours into Los Angeles gusting at 100 km/h desiccating vegetation and causing bush fires), originates from the publication in 2002 of a classification system for the staging of chronic kidney disease (CKD) by the National Kidney Foundation and the Kidney Disease Outcomes Quality Initiative (K/DOQI), which made eGFR a defining component (1). The estimation of renal function, primarily creatinine clearance, from such measurements is not new, having been part of clinical nephrology for more than three decades (2). Recent refinements have allowed for estimation of GFR (in ml/min/1.73 m²) from serum creatinine concentrations using equations derived from careful studies of 1642 subjects all with proven kidney disease (3). This four-variable Modification of Diet in Renal Disease (MDRD) equation is currently the most widely used and best studied. The inclusion of age and gender, as two of the four variables used in this equation, was not to adjust for normal variation in GFR with aging and gender, but simply to function as “surrogates” for the unmeasured quantity of endogenous creatinine production, which does vary with age and by gender.

In patients with unequivocal kidney disease, the description of renal function as an estimate of GFR is undoubtedly more informative than the serum creatinine concentration alone. However, the application of such estimates to the epidemio-

logic evaluation of the overall CKD burden in the community-at-large (containing large numbers of healthy persons) and the utility of the derived values of eGFR as screening tools for the identification of individuals with CKD have not yet been prospectively validated. Routine reporting of eGFR calculated from a plasma creatinine concentration measured as part of clinical chemistry testing will, in our view, often be “automatically” translated into a K/DOQI-CKD stage and thereby function as a form of “covert” *universal* screening for CKD. The GFR estimating formulas were not originally developed with this purpose in mind.

The implications of widespread (global) use of an eGFR-based system of classification of a “disease” are enormous, not only for society but also for the individual. Although the NKF (Kidney Disease Outcomes Quality Initiative [KDOQI]) classification system is not wholly based on eGFR, it is the defining component (1). Proteinuria (both “micro-albuminuria” and “macro-albuminuria”) and other manifestation of “kidney damage” are also used to define CKD stage 1 and 2, but classifications of CKD stages 3, 4, and 5 are assessed by eGFR alone (1). Because these latter categories constitute at least 60% of the total putative CKD population, the use of eGFR has a crucial role in determining what is now called “CKD,” in this, the post-K/DOQI era. This commentary, intended as a Mistral (a cold northerly wind that blows down the Rhone valley and Southern France into the Mediterranean sea), will therefore focus on eGFR and its implications, particularly in relationship to screening for the detection of CKD in the population as a whole.

eGFR Is Unreliable in Defining CKD

The addition of eGFR to the evaluation of CKD was a conceptual advance, but the ramifications of using eGFR to diag-

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nose CKD in individuals not already known to have this condition needs to be carefully considered. We agree with Melamed, Bauer, and Hostetter that GFR is the accepted measure for renal function. Perfection in this measurement is not needed or feasible, but the values of GFR derived from estimating equations and their application to diagnosis must at least do no harm. The present definition of CKD stages 1 and 2 depends more on evidence of "kidney damage," principally abnormal albuminuria, than upon eGFR. Indeed, using serum creatinine concentration based equations for defining and separating CKD stage 1 and 2 is pointless because the equations deriving eGFR are unreliable when the eGFR is >60 ml/min/1.73 m² (4). Moreover, the selection of a GFR of 90 ml/min/1.73 m² as the lower limit of "normal" conflicts with population estimates of eGFR. Only a minority of the population (mostly younger men) have an eGFR >90 ml/min/1.73 m² (5). The MDRD formula significantly "underestimates" true GFR above 60 ml/min/1.73 m² (6), especially in obese subjects.

Questions have also been raised as to whether using "microalbuminuria" (elevated albumin excretion above the "normal" range but below the levels of usual detection by qualitative means) is a true reflection of "kidney disease" but is rather a marker of a generalized disturbance in endothelial function ("chronic vascular disease") (7). The major flaw of using eGFR to categorize CKD is most obvious for CKD stage 3. The NKF/K/DOQI staging system contains the unfortunate error of using an absolute threshold of eGFR ≥ 30 ml/min/1.73 m² (as assessed by the MDRD formula) for defining CKD stage 3, and does not require any corroborating evidence of "kidney damage" (such as abnormal albuminuria) (1). To use a binary approach to diagnosis is bound to cause trouble. GFR can be estimated but diagnosis cannot. Proper treatment requires precision in diagnosis. As we have pointed out elsewhere, these values of eGFR overlap extensively with the normal age- and gender-adjusted values for eGFR (8). The consequence of this flaw is very significant in that it categorizes a substantial fraction of otherwise normal, healthy older individuals (over age 65 yr) as having CKD stage 3 when they do not have any clinically relevant abnormality. This distortion is most marked in females and is the probable explanation for the excess of females with CKD stage 3 compared with an overabundance of males with newly treated end-stage renal disease (ESRD) (CKD stage 5) (9). This error will also lead to a categorization of a substantial number of normal living kidney donors as having CKD stage 3 after donation (10). The use of an absolute threshold for defining CKD also virtually guarantees that CKD will increase in prevalence as population demographics change with time. Thus, CKD prevalence will track with age and with eGFR. A simple adjustment of the threshold for defining CKD stage 3 by use of percentiles of eGFR for age and gender derived from healthy cohorts would eliminate this flaw and reduce the estimated prevalence of CKD in the community to more credible levels (5,8). The addition of abnormal albuminuria as a requirement for defining CKD stage 3 would reduce the estimates of prevalence of CKD even further (11). We postulate that if these adjustments were made in the definition of what constitutes "authentic" CKD, that the overall prevalence rate of stage 3

CKD in the population-at-large would be shown to have remained relatively constant over the past several decades (at least in the United States), as we have argued elsewhere (8). Another source of error, often neglected in population-wide surveys, is that a single serum creatinine concentration is unreliable in assessing chronicity of disease. The original definition of CKD included a time-component: namely, the persistence of a reduced GFR or "kidney damage" for at least 3 mo (1). This component was incorporated into the definition to exclude random variation of and/or the development of transient declines in eGFR. Such repeated measurements are not usually practical in population-wide surveys. The use of a single eGFR measurement to categorize CKD stage 3 can result in a "false positive" assignment to CKD stage 3 in as many as 30% of subjects (12).

It is worth reemphasizing that the MDRD formula was derived from a relatively small sample of subjects with a prior diagnosis of CKD, and with overt kidney damage. However, we still have only incomplete information as to whether the same formula can be applied to diverse populations with varying body habitus, ancestry, prevailing diet, or geography (6). Early findings suggest that modifications of the original MDRD formula will be required in these populations (13). Correction of eGFR to a standard body surface area (BSA), explicitly included in the MDRD formula, may also give rise to errors when the individual are very obese or very lean (14).

Widespread and uncritical use of the current K/DOQI advocated MDRD formula without modifications can, and likely will, lead to erroneous estimates of the population-wide prevalence of CKD. The issue of "calibration" of serum creatinine measurements to a single "global gold-standard" has been vigorously discussed elsewhere (15). Such calibration is needed to compare the individual results for eGFR with those published using the MDRD formula, particularly when the eGFR is >60 ml/min/1.73 m² (CKD stage 1 and 2), but it is less important for CKD stages 3, 4, and 5 or for serial measurements in individual patients.

We conclude that the use of eGFR alone for classifying CKD is not justified and should not be applied globally (8). We do believe that eGFR, as determined by the MDRD equation, is sufficiently accurate for ordinary clinical purposes, such as following the changes of renal function over time in an individual patient with overt kidney disease. However, we do not concur with *mandatory (obligated by regulation)* laboratory reporting of eGFR (as presently exist in the United Kingdom and in several states in the USA) as calculated by the current MDRD formula from a single serum creatinine concentration combined with subsequent automatic assignment of a CKD stage without due consideration of expected age- and gender-associated changes of eGFR and the presence of evidence of "kidney damage." The argument that such calculated values of eGFR may help physicians determine drug-dosing regimens (avoiding toxicity and optimizing the therapeutic levels when drugs eliminated by GFR are used) has some merit, but it is not yet agreed which formula is best for this purpose (16). Furthermore, using eGFR values adjusted to standard BSA area can introduce drug dosing errors in the very obese and very lean

(4). The relationship of BSA to total body water (TBW) is not constant over all ages, genders, and ancestry (17). The value for TBW may be an important parameter in determining drug dosage. Elderly subjects may have a reduction in TBW (17). If the absolute value for eGFR is a more important parameter for determining drug dosage, then adjustment for BSA may give rise to errors in the obese and the lean, independent of age (14,16). Absolute true GFR values will be underestimated in the obese and overestimated in the very lean. These errors can give rise to problems of drug dosing in the elderly as well. For example, imagine two individuals each 60 yr of age with identical serum creatinine levels of 1.35 mg/dl. One of the individuals weighs 100 kg and is 1.9 m tall (BSA = 2.28 m²) and the other weighs 70 kg and is 1.6 m tall (BSA = 1.73 m²). The calculated eGFRs (MDRD) for both of these individuals are identical at 57 ml/min/1.73 m², and they both therefore have stage 3 CKD, according to K/DOQI. However, the uncorrected GFR for the heavier individual is actually 75 ml/min and is 57 ml/min for the lighter individual. Which of the two values for eGFR is the more appropriate one for selecting a dose of a potentially toxic agent depending on GFR for its elimination?

eGFR Should Not Be Used in Isolation as a Means for Screening Populations for CKD

Screening for disease in apparently healthy individuals in the hope that early identification can lead to more successful intervention strategies is a very reasonable intention (18). However, such screening needs to address a very specific purposes, must identify the characteristics of the population to be screened with respect to the likely prevalence of disease, and the tools used for screening must be easily applied, relatively inexpensive, and have appropriate levels of sensitivity and specificity. An intervention based on early detection also must improve the long-term outcome of the disease (18). While it is true, as pointed out by Melamed, Bauer, and Hostetter, that the progression of CKD in the presence of definite disease, particularly in the presence of proteinuria, can be modified by interventions, such as the use of inhibitors of angiotensin II, the evidence that such approaches can alter the progression of stage 3 CKD in the absence of other definitive features of kidney damage has not yet been proven. Because of the infrequent "progression" to later stages of CKD in such circumstances, it is doubtful that such intervention will be formally tested.

Finally, the cost-effectiveness of screening needs to be estimated and both the benefits and harms clearly articulated (18). Current evidence suggests that CKD may meet criteria for justifying screening (18). What is less certain is what screening methods should be used and what populations should be screened. It is widely agreed that additional studies of the "benefits, risks and costs of screening for CKD, including randomized, controlled trials, are needed in the general (US) population before final recommendations can be made" (18). *Universal* screening for CKD based on eGFR alone cannot be recommended, but *targeted* screening based on the existence of hypertension, diabetes, or a family history of CKD and proteinuria may be effective (18,19). The programs described by Mel-

amed, Bauer, and Hostetter in their Editorial and the Kidney Early Evaluation Program (KEEP) of the National Kidney Foundation (20) are good examples of these efforts.

Thus, on the basis of the available evidence, we believe, as do others (19), that *universal* screening for CKD using eGFR in isolation would be expensive, unproductive, and potentially harmful. The number of individuals who need to be screened to identify a single individual in whom a reasonably useful intervention could be offered is likely to be extremely large. Both the "false positive" and "false negative" rates would be dauntingly high using the current classification CKD schema (21).

We have argued earlier that a high percentage of older individuals, many of whom are females, will have an eGFR less than 60 ml/min/1.73 m². Most of these individuals will not have overt proteinuria or other evidence of kidney damage, and the eGFR may fall within the expected range of normal for the age and gender of the individual. For example, in the most recent iteration of the sequential population-based examinations conducted in the United States (NHANES 1999–2004) (22), 76% of the participants with an eGFR of 30 to 59 ml/min/1.73 m² (CKD stage 3) did not have abnormal proteinuria and only 6% had overt macroalbuminuria. Almost 55% of the participants classified as CKD stage 3 were over 60 yr of age and 37% were over the age of 70 yr. Screening for CKD, based on eGFR alone, will identify a largely older population (mostly female), many of whom will not have any corroborative evidence of "kidney disease." Thus, it can be assumed that eGFR-based screening will generate a large number of "false positives," using current criteria, leading to unnecessary investigations, referrals, cost, and anxiety. In a long-term (25 yr follow-up) longitudinal study of men with a high risk of cardiovascular disease (the MRFIT study) (23), it was noted that an eGFR of <60 ml/min/1.73 m² in the absence of "dipstick positive" proteinuria had a positive predictive value of only 5.6% for the future development of treated ESRD. The addition of ≥1+ proteinuria to an eGFR of <60 ml/min/1.73 m² improved the positive predictive value to about 26%. The majority of patients who are destined to develop treated ESRD would not be detected by a screening program based on eGFR alone ("false negatives"). The combination of an eGFR and urinary protein (or albumin) excretion improves both the "false positive" and "false negative" rates, but still the positive predictive value is only 1 of 4 and the negative predictive value is about 8 of 10. These parameters, focused primarily on the outcome of treated ESRD, are insufficient to warrant an investment in universal eGFR screening.

Targeted screening is quite another matter. On this point, we agree with Melamed, Bauer, and Hostetter. Enrichment of the a priori probability of finding an individual with a progressive form of renal disease will enhance the positive predictive value and minimize the negative predictive value of the screening test. Thus, *targeted* eGFR-based or proteinuria screening of individuals with a history of diabetes, hypertension, or a family history of renal disease may prove to be of value (18,20,24). However, screening for proteinuria alone may be easier, cheaper, and more reliable in this subset of individuals (25). It is still unknown whether screening for microalbuminuria will

be better than screening for macroalbuminuria in terms of overall secondary prevention of progressive renal disease (26). Accurate, reliable, inexpensive, and rapid point-of-service methods or devices that measure low, but abnormal levels of albumin excretion are now available and studies are in progress to better define their value in the overall screening paradigm (27). Because *targeted* screening involves identification of individuals with at least two modifiable risk factors, diabetes and hypertension, one can logically ask whether the addition of another screening maneuver (*e.g.*, eGFR) will contribute materially to the prevention of disease, over and above the management of the already identified risk factors. We are not aware of any convincing evidence that treatment of subjects with a “low” eGFR (but one that is normal for age and gender) in the absence of proteinuria or hypertension has any effect on the rate of change of GFR.

The Benefit of eGFR Screening on Identifying Cardiovascular Risk Is Unproven

Proponents of eGFR screening postulate that discovery of a reduced eGFR, *i.e.*, CKD stage 3, also identifies subjects at increased risk for fatal and nonfatal cardiovascular (CV) events, even after adjustment for many comorbid factors, such as age, hypertension, diabetes, and obesity. Unfortunately, many of the epidemiologic studies suggesting that such an eGFR-related risk for CV events exists are unable to determine cause and effect, and many are also unable to adjust fully for the concomitant effect of proteinuria and the full range of comorbid factors known to contribute to CV risk. In the largest study (1,120,295 subjects) reported to date, Go *et al.* (28) reported that the hazard ratio (HR) for CV events in subjects with repeated serum creatinine measurement and an eGFR of 45 to 59 ml/min/1.73 m² (early CKD stage 3, often called CKD stage 3A) was 1.20 (confidence interval, 1.10 to 1.30) compared with subjects with eGFR >60 ml/min/1.73 m², after adjustment for most conventional risk factors, including proteinuria (but not including smoking race or activity level). While this HR is significantly different from 1.0, it is still small and could have been due to confounding (lack of adjustment for unmeasured risk factors). Importantly, the HR for all cause death did not differ from 1.0 when those subjects with an eGFR of 45 to 59 ml/min/1.73 m² were compared with the subjects with an eGFR >60 ml/min/1.73 m², after adjustment for comorbidity (28). In subjects with an eGFR <45 ml/min/1.73 m², a striking elevation of HR for both CV events and all-cause death was noted (28). Thus, well-established CKD, as heralded by a decline in eGFR levels well below the normal range, adjusted for both age and gender, is undoubtedly associated with an increased risk of CV events and death. Such events and early death, before the development of CKD stage 5, account for the low rates of treated ESRD (<0.5% per year of follow-up) in the older group of subjects (12). Older individuals who reach treated ESRD should be viewed as “survivors” of the risk of CV disease (CVD) that develops as CKD progresses to late stage 3 and stage 4, and are thus quite different from those individuals in earlier stages of CKD. Others have also observed that the impact of CKD (as currently defined) on the risk of death is markedly blunted

as subjects grow older; a phenomenon that may be explained by the high prevalence of a “reduced” eGFR in the elderly population, partly because of the normal decline of eGFR with aging (5).

Can the high risk of CV events in those with a reduced eGFR be used as a rationale for *universal* eGFR-based screening? We think not, although this proposal has not yet been tested in a prospective manner. The prevalence of an eGFR in the range where CV event rates increase greatly (HR >3.0), approximately <45 ml/min/1.73 m², is quite low (about 2%) in the general population (although it would be expected to be higher in populations enriched for diabetes and/or hypertension) (20). Thus, screening of 100 subjects for an “abnormal” eGFR would yield about 2 individuals at risk, and the great majority of these could already be identified by application of the conventional Framingham Risk Scoring. The anticipated marginal benefit of adding eGFR <45 ml/min/1.73 m² alone, in the absence of concomitant proteinuria, is, in our opinion, insufficient to warrant *universal* or even *targeted* screening for eGFR alone. The use of “statins” to mitigate the occurrence of fatal and nonfatal CV events in subjects with CKD (eGFR <60 ml/min/1.73 m²) has recently been examined in a large meta-analysis by Strippoli *et al.* (29). Although such therapy reduces lipid levels and CV endpoints in CKD, irregardless of stage, no benefits accrue for all-cause mortality. A role for “statins” in the primary prevention of CVD in CKD remains unproven. At the present time, a reduction in GFR alone cannot be used as an indication for “statin” therapy for prevention of CV events or for slowing the rate of progression of CKD (30). The indications for the use of “statins” in CKD are “the same as for people with normal kidney function” (30).

In sum, we do not doubt that progressive CKD is a contributor to the risk of CV events and premature death. This seems to be a well-established fact. However, we argue that the magnitude of the effect of a reduced eGFR alone on CVD, particularly in the range of 45 to 59 ml/min/1.73 m², which is within the normal range for many elderly subjects, has been greatly overemphasized. Because of the low frequency of eGFR <45 ml/min/1.73 m² in the general population, we doubt that screening for eGFR in this population will be of much value, over and above conventional risk-stratification approaches, such as the Framingham Risk Score. Adjustments of the weights given to the parameters included in this scoring system for patients with reduced eGFR may improve its performance as a predictor of CV risk (31). The poor performance of eGFR alone as a predictor of future progression of CKD stages 1 to 3 to treated ESRD (CKD stage 5D) further weakens support for *universal* eGFR-based screening, but the performance characteristics of such screening might be enhanced by a more targeted and multiphasic approach. A great deal more research is needed in this area to establish the proper role of eGFR screening with or without concomitant proteinuria (microalbuminuria or macroalbuminuria) screening. In our opinion, until the results of this research are available, public health authorities, national governments, scientific societies, and voluntary health agencies should resist the temptation to engage in or endorse massive, population-wide screening based on eGFR alone.

Conclusions

The development and evaluation of methods to reliably estimate GFR in diverse populations are incomplete. Much needs to be done to establish the role of this tool in assessment for the global burden of CKD and for its application in “staging” of presumed CKD. Current classification criteria for CKD are deficient in several respects and need to be changed. The current CKD classification is too imprecise to be the basis for a policy of universal screening for CKD by estimating GFR. An intensive evaluation of the overall efficiency and cost-effectiveness (in terms of the “hard” outcomes of prevention of premature death, of avoidance of fatal and nonfatal CV events and of reduction in the incidence of treated ESRD) is needed before large scale efforts using eGFR to identify subjects at risk for these outcomes can be justified.

It is time for the storm to abate and for a gentle wind of change, carrying hard-earned facts, to clear the air. The clinical tool of eGFR is here to stay, but the way it should be used in clinical practice needs to be better defined. Epidemiologists too should handle eGFR with care.

Disclosures

None

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