General Principles of GFR Interpretation in the Elderly

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In the United States, chronic kidney disease (CKD)—defined by reduced GFR <60 mL/min per 1.73 m² or presence of kidney damage—is very common in the elderly population. The prevalence of CKD is estimated to be 46.8 percent in those older than 70 years (1). However, the significance of reduced GFR in the elderly has been debated, and some suggest that reduced GFR is secondary to (expected) age-related changes in kidney function and is not evidence of true kidney disease. Regardless of the label, elderly patients with reduced levels of GFR are at higher risk for adverse outcomes and complications, and they require modification of drug dosages. Issues related to the accuracy and interpretation of GFR estimates in the kidney are discussed here.

Accuracy of eGFR in estimating mGFR in elderly

Measured GFR is considered the gold standard for evaluation of kidney function; however, it is difficult to perform in routine practice, and estimated GFR (eGFR) is more commonly used. The estimating equations are developed from serum levels of endogenous filtration markers, such as creatinine or cystatin C, in combination with other variables that act as surrogates for unmeasured non-GFR determinants of the filtration markers. The most commonly used eGFR equations are the Modification of Diet in Renal Disease (MDRD) study equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (1, 2). The MDRD study equation is widely used, but it underestimates GFR at higher levels, thereby overestimating the prevalence of CKD. The CKD-EPI creatinine equation improves on these limitations for adults of all ages, and the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines on the evaluation and management of CKD recommends reporting eGFR from creatinine (3–5).

Creatinine-based eGFR is not always sufficiently accurate for all clinical decision making. For example, it and other filtration markers should not be used in the newborn and young child. Most importantly, the levels of filtration markers are determined by factors other than GFR. For creatinine, its main non-GFR determinants are muscle mass and protein intake, both of which may be abnormal in the elderly and vary within an individual with changes in health status. For example, in a previously healthy 80-year-old man, a decline in GFR may be masked by weight loss and decreased oral intake. KDIGO recommends the use of a confirmatory test with measured GFR using an exogenous marker, a measured creatinine clearance, or eGFR based on cystatin C in such patients for whom accurate levels of GFR would change management (3–5).

Recent studies have shown that equations based on the combination of creatinine and cystatin C provide more accurate estimates of GFR estimation in elderly patients than either alone (6–8), and this has been demonstrated in at least two elderly populations (mean age 80 years) (9, 10). One of these studies compared the CKD-EPI equations with other equations also developed using standardized assays for creatinine and cystatin C and showed that the CKD-EPI creatinine, cystatin C, and combined creatinine-cystatin C equations were better than or equivalent to other equations, supporting the KDIGO recommendation to use CKD-EPI equations in the elderly population (9).

Use of GFR estimates in the elderly population

Estimates of GFR are commonly used in practice to detect CKD, evaluate the progression of kidney disease, predict a patient’s prognosis, and determine the level of kidney function for drug dosing.

Detection of CKD

The use of more accurate equations leads to more accurate detection and staging of CKD. A large meta-analysis of diverse populations from the Chronic Kidney Disease-Prognosis Consortium (CKD-PCC) found that the CKD-EPI creatinine equation more accurately classified individuals into the correct GFR stages than did the MDRD study equation in the general population and in the subgroup with ages ≥65 years (11). Similarly, another meta-analysis of similar cohorts showed that the CKD-EPI creatinine–cystatin C and cystatin C equations reclassified patients with CKD more accurately than did the CKD-EPI creatinine equation in the general population and in the subgroup with ages ≥65 years (12).

Assessment of progression

Change in GFR is the primary way in which progression of kidney disease is evaluated. Despite concerns that changes in GFR may not be sufficiently accurate in the elderly, given possible changes in non-GFR determinants, two large meta-analyses showed that declines in eGFR had strong and consistent associations with subsequent kidney failure and mortality, and these associations were consistent across different ages and with other clinical characteristics (13, 14).

Prediction of prognosis

Lower eGFR levels are associated with risk for adverse events such as cardiovascular disease (CVD), mortality, and ESRD. Data from CKD-PC showed that risk for all outcomes increased at levels below 75 mL/min/1.73 m² (15). In a subsequent publication, CKD-PC showed a significant positive interaction between age and GFR for all-cause mortality and CVD mortality, suggesting that lower eGFR had stronger adverse effects at younger ages and weaker effects at older ages (16). Nevertheless, GFR <60 mL/min/1.73 m² remains a significant risk factor for mortality and ESRD in older age. Of note, the absolute risk for mortality and CVD mortality with low eGFR was much higher at older age than in younger age categories, and in the elderly population consideration of both absolute and relative risks is critical to understanding risk factors.

Risk for other comorbid conditions

Several studies have demonstrated that lower GFR in old adults is associated with risk for bloodstream infection (17), global cognitive performance (18, 19), and frailty and diminished physical function in the elderly (20–22). These are strongly related to patient safety because they increase the risk of falls, disability, and worsening comorbidities and are important determinants of quality of life and longevity.

Dose adjustment of medication

Older adults are at a higher risk for the development of advanced diseases and comorbidities and, as such, frequently require multiple medications. KDIGO recommends that prescribers use the most accurate method for GFR estimation when drug dosing. The Cockcroft and Gault equation is inaccurate in the era of standardized creatinine assays and is no longer recommended for use (23, 24). Many still use that equation with the misconception that the use of weight overcomes the limitation of creatinine generation, but it does not; in fact, the sharp decline in eGFR with age (i.e., the “140-age” term) that occurs with the Cockcroft and Gault equation leads to a large underestimation of GFR in the very old.

Conclusions

The GFR is fundamental to understanding the nature and severity of kidney disease. There is now solid evidence that eGFR is accurate in the elderly and is appropriate to use to detect and stage CKD, to determine the prognosis and complications of CKD, and to determine the dosing of medications. Cystatin-C-based equations are the first equations that should be confirmed by clearance measurements of cystatin-C-based estimates of mGFR in appropriate clinical circumstances.

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References


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Hypertension remains a growing problem in our aging population. Recent data from the National Health and Nutrition Examination Survey (NHANES) estimate that almost one-third of the adult population meets the criteria for hypertension (1). Furthermore, the prevalence increases with age: 65 percent of individuals over the age of 60 are hypertensive. Approximately three-quarters of the population with diagnoses of hypertension require some form of pharmacologic therapy, and the percentage is as high as 82 percent among individuals over the age of 60.

The Framingham Heart Study helped to elucidate the expected trajectory of blood pressure in normotensive and hypertensive individuals with aging. Initially, both systolic (SBP) and diastolic blood pressure (DBP) increase linearly with age. However, SBP and DBP diverge around the fifth to sixth decade, when DBP begins to decline whereas SBP continues to increase (2). Subsequent studies have shown the predominance of isolated systolic hypertension in individuals over the age of 50, have described it as a major predictor of cardiovascular events, and have suggested its importance as a modifiable target (3, 4).

**Effects of treatment of hypertension on mortality and on cardiovascular and stroke outcomes**

In 2000, a meta-analysis (5) of eight key randomized controlled trials (RCTs), including the Systolic Hypertension in the Elderly Program (SHEP) (6) and the Systolic Hypertension in Europe (Syst-Eur) trial (7), examined total mortality and cardiovascular outcomes in relation to SBP and also evaluated the benefit of an-htihypertensive therapy on these outcomes. The authors defined systolic hypertension as a value of 160 mm Hg or greater and diastolic hypertension with a DBP of less than 95 mm Hg, excluding some trial participants with isolated diastolic hypertension. In a pooled analysis, higher SBP was associated with higher total mortality (hazard ratio [HR] 1.26; 95% confidence interval [CI] 1.13–1.40; per 10 mm Hg) and stroke risk (HR 1.22; 95% CI 1.04–1.40; per 10 mm Hg). By contrast, higher DBP was associated with a lower risk of all-cause mortality.

With regard to treatment, the target SBP varied by trial but was generally below 150 mm Hg (8). The results showed decreased total and cardiovascular mor-tality and reduced nonfatal cardiovascular events, particularly stroke, among the treated patients. A more recent Cochrane Database review included 15 trials with 24,055 patients, with the notable addition of the Hypertension in the Very Elderly Trials (HYVET), and came to a similar conclusion. They estimated a modest reduction in total mortality (relative risk 0.90, 95% CI 0.86–0.95) and reduction in cardiovascular mortality and morbidity (relative risk 0.72, 95% CI 0.68–0.77) with treatment of hypertension (9). However, it should be noted that achieved SBP was not less than 140 mm Hg in any of these trials and was often greater than 150 mm Hg. Nevertheless, the SHEP and HYVET trials, which did attain mean SBPs between 140 and 150 mm Hg, also reported favorable outcomes.

The Cochrane review included a subgroup analysis of treatment in very elderly patients (80 years or older), which showed no significant benefit in terms of all-cause mortality, including cardiovascular, coronary heart disease, or cerebrovascular disease mortality. Although clinical trial results provide solid evidence that controlling SBP below 150 to 160 mm Hg improves mortality in the elderly, the optimal target blood pressure is still unclear. Two relatively recent randomized trials have studied strict blood pressure control (SBP less than 140 mm Hg) versus moderate control (SBP 140 to 160 mm Hg) among older individuals and have shown no difference in outcomes, including cardiovascular and cerebrovascular events (10, 11). In addition, a secondary analysis of the International Verapamil-Trandolapril study (INVEST), which compared the efficacy of a calcium antagonist versus a noncalcium antagonist hypertension treatment strategy (12), examined the relationship between blood pressure and adverse outcomes in elderly patients with coronary artery disease (13). The target blood pressure for both arms of the trial was less than 140/90 mm Hg (and less than 130/85 mm Hg in patients with diabetes or renal impairment). In a secondary analysis, outcomes were examined according to achieved blood pressure after the participants were divided into four age categories ranging from less than 60 years to 80 years or older. At baseline, the older participants had higher SBP and the highest prevalence of myocardial infarction (MI), stroke, heart failure, chronic kidney disease, and other comorbid conditions and risk factors for cardiovascular events and death. During the trial, the very old had the highest incidence of adverse outcomes, including death, nonfatal MI, nonfatal stroke, all stroke, and the primary outcome, which combined death, nonfatal MI, and nonfatal stroke. The hazard ratios for the association of SBP during the trial with the combined outcome were “J-shaped” or “U-shaped” for all age groups, but the “optimal” SBP (i.e., the SBP at which the hazard ratio was at its nadir) was higher among older individuals. Whereas risk was lowest at SBPs of 110 to 120 mm Hg among patients under age 70, the lowest risk was at SBPs of 140 to 145 mm Hg for patients 70 and older.

In consideration of these data, members of the Eighth Joint National Committee (JNC 8) recommended more lenient blood pressure goals for individuals aged 60 years and older than in the previous guidelines, setting a target below 150/90 mm Hg (14). Although this target is in agreement with European guidelines (15), there is an interesting difference in that the European guidelines recommend beginning treatment when SBP is above 160 mm Hg to match the population included in the trials showing benefit. Of note, not all members of the JNC 8 panel agreed with raising the target blood pressure to below 150/90 mm Hg in the over-60 age group. The dissenting panel members recently presented a minority view (16) in which they argued that increasing the target will likely lead to a reduction in the intensity of antihypertensive treatment in this group, reversing the decades-long trend of better blood pressure control. They also point out that because older individuals are at higher risk of cardiovascular events than younger persons, this recommendation for less aggressive treatment applies to the group at the highest absolute risk of adverse events who stand to benefit the most.

The impact of frailty and comorbidity

These disagreements among experts reflect a lack of definitive RCT evidence to determine the optimum SBP for maximal cardiovascular event-free survival among older individuals. It must also be recognized that the elderly population is heterogeneous and includes individuals who are completely independent and robust in addition to those who are frail or even disabled. Therefore, setting blood pressure targets according to age alone may not be prudent. Some who support higher