Ambulatory Blood Pressure Monitoring Trumps Estimated Glomerular Filtration Rate in Predicting Cardiovascular Risk in Low-Risk Populations

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See related article, pp 18–26

Identifying risk factors that predict cardiovascular morbidity and mortality has been the holy grail of epidemiologists. Identifying such risk factors can be used to target individuals in whom modifiable risk factor should be mitigated. Among the first studies to identify cardiovascular risk factors was the Framingham Heart Study. A cohort in the town of Framingham, MA, was followed for many years, and the risk of cardiovascular events was related to the presence of several risk factors such as age, sex, smoking, total cholesterol, high-density lipoprotein cholesterol, antihypertensive therapy, systolic blood pressure (BP), and diabetes mellitus. In 1961, after 6 years of follow-up, the term “factors of risk in the development of coronary heart disease” was used by Dr William Kannel.1 These factors of risk, now known as cardiovascular risk factors, have been validated by many studies; they are now the basis of guiding cardiovascular risk-reduction such as lowering cholesterol.2 For example, the current Adult Treatment Panel III guidelines use the Framingham risk calculator to direct cholesterol lowering therapy.3 However, these risk factors that relied on simple measures of cardiovascular risk were not found to be perfect in predicting outcomes.2 Although a number of investigations have tried to identify additional risk factors, the number of markers that can predict cardiovascular events and more importantly improve the Framingham risk score is few.4 Nonetheless, novel risk factors, such as the assessment of kidney damage, and better ways to measure BP merit further study.

In this article of Hypertension, a meta-analysis of individual data was conducted from several thousand participants from many countries to evaluate the usefulness of systolic ambulatory BP (ABP) and estimated glomerular filtration rate (eGFR) in predicting cardiovascular morbidity and mortality and all-cause mortality.5 The major results of the study are as follows. At the population level, the authors found that low glomerular filtration rate was predictive of cardiovascular mortality. In contrast, systolic ABP was predictive of both cardiovascular mortality and all-cause mortality. Neither eGFR nor ABP was predictive of noncardiovascular mortality. With respect to cardiovascular morbidity, whereas eGFR predicted only cardiovascular events and strokes, systolic ABP predicted cardiovascular events, cardiac events, coronary events, and stroke. Thus the authors appropriately conclude that 24-hour systolic ABP was of greater value in predicting cardiovascular morbidity and mortality, as well as all-cause mortality in contradistinction to low glomerular filtration rate. The authors conclude that eGFR is not of great value when 24-hour ABP monitoring is available in the general population. However, some cautionary remarks are in order.

First and foremost, the number of patients with chronic kidney disease (CKD), the risk factor of interest, was present in fewer than 12%. CKD can be defined when eGFR is <60 mL/min per 1.73 m² for ≤3 months. In this study, serum creatinine concentration (and therefore eGFR) was not measured at 3 months; thus the study failed to establish chronicity and potentially created a misclassification bias for the diagnosis of CKD. Because serum creatinine was measured only once, it allows for the calculation of spot eGFR. The percent of participants with spot eGFR between 45–60 mL/min per 1.73 m² was only 10.4%. Spot eGFR of 30–45 mL/min per 1.73 m² (stage 3B CKD) was present in only 1.1% of the participants and lower eGFRs were not noted in any participant. Such patients may have been deliberately excluded from the study because the authors dropped those participants who had serum creatinine concentration >3 SDs creatinine away from the mean of the center. Proteinuria, a marker of both kidney and cardiovascular disease, was not available in 44% of the participants. Because this study did not have a higher risk population, such as the elderly or those with diabetes mellitus, where a lower eGFR would be more prevalent, the study cannot adequately compare the value of ABP and eGFR in a higher risk population. Markers of kidney disease (eGFR or proteinuria) may well compare differently to systolic ABP in this higher risk group.

The next question that emerges is whether eGFR when added to the traditional Framingham risk marker would improve the prediction of cardiovascular risk. This can be better understood in the context of reclassifying the cardiovascular risk from moderate risk to low risk or from moderate risk to high risk. The Net Reclassification Index and Index of Discriminant Improvement are 2 newer statistics than can measure the added value of a new risk factor or biomarker over and above established ones.6 Although this was not measured in this study, we can infer from the study results that adding eGFR to the risk prediction may have added little to enhance risk prediction. For example, after accounting for 24-hour systolic ABP, the additional risk predicted by eGFR...
was <0.25% for cardiovascular mortality, the composite cardiovascular end-point or stroke. Does eGFR modify the relationship of systolic ABP on hard outcomes? From this study, the answer seems to be no. With the caveat that the power to detect interaction is limited, the multiplicative interaction term of eGFR × systolic ABP was not significant. Accordingly, systolic ABP is no more (or no less) damaging among people with lower eGFR. Would the interaction of proteinuria × systolic ABP be significant cannot be answered by this investigation, given the limited information on proteinuria.

Given that cardiovascular risk of systolic ABP is not modified by eGFR, why is it that randomized trials have failed to detect reduction in cardiovascular risk with lowering BP among patients with CKD? The 3 trials in question were African American Study of Kidney (AASK) Disease, Modification of Diet in Renal Disease, and Ramipril Efficacy in Nephropathy (REIN-2) trial. Compared with usual BP (=140/90 mm Hg), a lower BP target (=120/80) did not lower cardiovascular morbidity or mortality. These trials achieved a good BP difference between the aggressive BP and usual groups, and therefore cardiovascular benefits should have been noted. Although it is possible that these trials were underpowered to detect cardiovascular benefit, or BP is not causally related to cardiovascular outcomes, it is more likely that this may be so because therapy was directed using clinic BP. Clinic BP can fail to detect masked hypertension (and therefore cannot treat this condition). Clinic BP can misclassify white coat hypertension as true hypertension (and therefore needlessly treat this condition). In fact, AASK investigators have published a high burden of masked hypertension among participants. Although ABP monitoring may not be feasible for the routine management of hypertension, home BP monitoring is a more viable option for diagnosing and managing hypertension in CKD. The investigators promise us that the comparative value of home BP and eGFR to predict cardiovascular morbidity and mortality will be described in a future article. This is a laudatory goal and merits further study.

In conclusion, this individual level meta-analysis suggests that in the general population with a low prevalence of kidney disease, 24-hour ABP trumps eGFR for the prediction of cardiovascular morbidity and mortality. However, it is quite possible that for the prediction of cardiovascular morbidity and mortality, among high-risk patients with more substantial CKD, eGFR or proteinuria may trump 24-hour ABP. In my opinion, both ambulatory BP monitoring and markers of kidney damage (especially proteinuria) have a place in cardiovascular risk prediction.

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