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Atherosclerotic Renal Artery Stenosis
Flaws in Estimated Glomerular Filtration Rate and the Problem of Progressive Kidney Injury

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Oclusive disease of the renal arteries poses a major problem. Most cases result from atherosclerotic disease, and the prevalence of incidental renal artery disease detected during imaging studies for symptomatic coronary, aortic, and peripheral vascular disease ranges from 14% to >35%, increasing with age. Although many (perhaps most) of these lesions produce only minor hemodynamic effects, it has long been recognized that when some “critical” level of occlusion is breached, poststenotic renal blood flow and glomerular filtration rate (GFR) fall, especially after lowering systemic arterial pressure. In some cases, kidney function can recover after restoring blood flow with either endovascular or surgical revascularization. Several prospective, randomized trials have examined whether the loss of renal function due to atherosclerotic renal artery stenosis can be managed best by medical therapy alone or would further benefit from renal revascularization. The study reported by Madder and colleagues in this issue of Circulation: Cardiovascular Interventions directly challenges whether conventional criteria for estimating GFR and directional trends in such trials are valid. This matter is important for physicians serious about considering renovascular disease.

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Atherosclerotic renal artery stenosis (ARAS) is primarily a disease of older persons, with mean ages for most series >70 years. Patient series subjected to renal artery procedures routinely have reduced kidney function, usually expressed as reduced GFR. Despite remarkable improvements for many hypertensive and cardiovascular end points, such as stroke and myocardial infarction, attributable in part to effective medical intervention, the prevalence of end-stage renal disease (CKD) has continued to increase over the past several decades. These observations raise the possibility that occlusive ARAS may be partly responsible for progressive renal injury.

How best to evaluate and characterize kidney function in these trials has been controversial. Previous observational reports of renal revascularization used a variety of methods mainly based on changes in serum creatinine levels ranging from 20% to 50% between pretreatment and follow-up values. Most often, these levels were obtained simply from review of clinical records, with little information regarding alterations in medications, clinical conditions, or standardized laboratory methodology for creatinine measurement. Because serum creatinine is recognized to be a function of muscle mass, ethnicity, sex, and metabolic turnover, it is difficult to interpret individual creatinine measurements. Over the past decade, a major theme developing within the field of nephrology has been to express more precisely actual kidney function using standardized measurements, hence the introduction of estimated GFR (eGFR) and the classification of chronic kidney disease (CKD) by stages.

Staging CKD by means of eGFR has provided an epidemiological bonanza for investigators. Original data were derived from measurement of a standardized clearance marker, specifically iothalamate, in patients enrolled in the Modification of Diet in Renal Diseases (MDRD) trial. Correlation with a standardized assay for serum creatinine allowed derivation of an equation relating age, ethnicity, sex, and several other variables to measured GFR. This equation was later simplified to one based on 4 variables that closely predict iothalamate GFR for patients with established kidney disease. Perhaps most importantly, application of eGFR to wider populations has identified epidemiological associations between overall mortality and other disease risk as a function of reduced GFR. As a result, numerous studies have confirmed graded increased in risk of cardiovascular mortality with progressively more advanced stages of CKD in general populations. Although it has long been recognized that patients with end-stage renal disease (defined as CKD stage 5 with eGFR <15 mL/min per 1.73 m2) have high rates of cardiovascular events and accelerated mortality, application of eGFR measurements have established (1) much higher prevalence of earlier CKD (stages 2, 3, and 4) than previously appreciated and (2) a progressive rise in metabolic abnormalities such as anemia, parathyroid dysfunction, and vascular calcification with earlier stages of disease. Recognition of the high prevalence of reduced GFR, particularly in older patients, and the benefits of adjusting medication dosing accordingly has led to widespread reporting of eGFR in many laboratories, which is a legal requirement in some states. Progressive changes in measured and eGFR were applied to examine outcomes in several forms of systemic disease included in the MDRD trial, the African-American Study of Kidney Disease trial, and others. A major limitation of this approach has been the recognition that rates of progression...
vary widely among different diseases and even among different individuals with the same kidney disorder.

Despite many positive attributes, universal application of eGFR remains controversial. In particular, it still remains subject to the dynamic variables that affect serum creatinine levels, including volume status, specific drug effects, and dietary changes. Because the MDRD equation was derived on the basis of data from patients with clinical kidney disease, its validity at higher levels of GFR was not examined when it was first used. Numerous subsequent studies indicate that divergence between eGFR and measured GFR broadens substantially in normal ranges of kidney function. For that reason, recent efforts have focused on improving estimates through populations that include larger numbers of normal subjects, such as kidney donors. As a result, several equations have been applied to different data sets, including MDRD, the Cockcroft-Gault, and the CKD Epidemiology Collaboration (CKD-EPI) equations. All of these equations fundamentally depend on measurement of serum creatinine levels. All diverge under some circumstances from measured GFR, thereby limiting their utility. Some authors expressed concern that eGFR by any of these systems can seriously misclassify up to 38%, or 10 million, persons in the United States.

It is within this context that Madder et al4 examined several formulations of eGFR for assessing renal function serially in patients with ARAS. They evaluated 541 measured values using near-simultaneous iothalamate GFR in 254 patients comparing the MDRD, CKD-EPI, 1/S-creatinine, and Cockcroft-Gault equations. The specific purpose was to define trends that could detect a 20% change in measured GFR as an outcome for trials of renal artery revascularization. Patients were treated in a variety of ways, including medical therapy alone and revascularization. No effort was made to analyze specific treatment effects for this cohort. Serum creatinine level was measured within 14 days of iothalamate GFR, with most (76%) measured on the same day and 89% within 3 days. The authors indicate that antihypertensive drugs and diuretics were not changed during this interval. Iothalamate GFR was measured by plasma disappearance using values obtained at 5, 10, and 15 minutes after administration. Group mean values were similar with all these methods (range, 48.8 to 53.2 mL/min per 1.73 m2), and overall correlations were mean values were similar with all these methods (range, 48.8 to 53.2 mL/min per 1.73 m2), and overall correlations were generally strong, with R2 ranging from 0.76 to 0.83. The actual direction of change (whether GFR was increasing or decreasing over time) was discordant in 28% to 40% of cases. The authors correctly argue that this level of disagreement fatally undermines the validity of using eGFR in a trial targeted at defining changes of 20%.

The study by Madder et al4 provides a welcome wake-up call to those interested in the effect of vascular disease on renal function. These results argue persuasively that measurements of eGFR are unlikely to provide meaningful outcome data for trials targeting such modest differences over time. Several additional factors warrant attention for those serious about evaluating renal injury related to ARAS. First, reproducibility of measured GFR over time is remarkably imprecise for a variety of reasons. Not only do clearance methods pivotally depend on tracer absorption, blood levels, and urine collections (when used), but also actual levels of filtration can be affected by volume status, dietary intake, and changes in drug therapy. Second, most conditions for which GFR represents a meaningful index of disease progression are symmetrical, meaning that a systemic process affecting both kidneys is in place such as diabetic nephropathy; glomerular diseases, such as IgA nephropathy; and autosomal-dominant polycystic kidney disease. By contrast, ARAS is nearly always intrinsically asymmetrical. Most individuals have 2 kidneys, and vascular disease rarely affects both to an equal degree. Hence, one can lose viable function in an affected kidney entirely and then have no further loss of function because the other is unaffected. A therapeutic intervention that appears to halt the progressive loss of GFR in ARAS simply may have eliminated the function of 1 kidney altogether (eg, total infarction of a kidney beyond a stenosis),13 with stable function in the contralateral kidney. Third, as a corollary of asymmetrical disease, the contralateral kidney is capable of adaptive change, albeit to varying degrees. As a result, it can develop overt hypertrophy with a compensatory rise in single-kidney GFR analogous to that observed after unilateral nephrectomy. This process may counteract changes in the stenotic kidney and obscure changes in GFR measurements that reflect filtration by both kidneys combined. Previous studies suggest that after kidney function is restored within the stenotic kidney, adaptive functional changes in the unaffected kidney regress to some degree. Hence, relying simply on measurement of GFR (by any method) seriously obscures much of the disease process for an asymmetrical disease. Any measurement of GFR as a primary outcome for such a disorder can have only limited value for patients other than those with a solitary functioning kidney or vascular occlusion affecting the entire renal mass.

What outcome measures should intervention trials for renovascular disease use? This question has been a painful thorn in the side of those planning such trials for >1 decade. Studies of Medicare recipients followed after identification of ARAS suggest that this group is at higher risk for many cardiovascular disorders than those without ARAS. Progressive renal impairment is only 1 of these and presents a much lower hazard than risk of stroke, new coronary disease, congestive heart failure, and death. From a clinician’s perspective, overall outcome measures that include cardiovascular events, renal dysfunction, hospitalization for circulatory congestion, and so forth that are believed to be related to ARAS offer practical value and are the basis for the largest trial undertaken in the United States to date: the CORAL (Cardiovascular Outcomes for Renal Atherosclerotic Le-
Effects have been observed in experimental models of ARAS, measures that may stimulate renal repair mechanisms. Such precise identification of patients who truly may benefit from and its potential for adverse outcomes may allow more.

Rather than focus on combined GFR, we believe that studies directed at identifying the pathways and limits of renal adaptation to reduced blood flow within the affected kidney hold the greatest promise. Results from studies of currently available antihypertensive drug therapy and statins indicate that many patients can achieve satisfactory blood pressure control with stable renal function, sometimes for many years.1 Carefully performed protocols examining individual renal function during constant sodium intake and renin-angiotensin system blockade indicate that even advanced ARAS sufficient to reduce blood flow, compartmental volumes, and single-kidney GFR levels can be associated with adaptation and preservation of intrarenal oxygenation.17 Hence, these patients have reduced oxygen consumption within the poststenotic kidney as a result of reduced glomerular filtration and energy-requiring solute transport. At some point, however, compensatory adaptation becomes overwhelmed, leading to rarefaction of kidney microvessels and activation of multiple inflammatory pathways that lead to tissue injury.18 It is likely that some vectors of inflammatory injury spill over beyond the kidney and have widespread effects elsewhere within the body. Recognizing this transition and its potential for adverse outcomes may allow more precise identification of patients who truly may benefit from renal revascularization, possibly combined with adjunctive measures that may stimulate renal repair mechanisms. Such effects have been observed in experimental models of ARAS using circulating endothelial progenitor cells, for example.19 Future trials may depend on (1) treating more targeted populations likely to have far greater change in kidney function and (2) evaluating outcome measures that reflect true recovery of parenchymal injury using single-kidney function and hard cardiovascular end points. This group of patients will be the one most likely to benefit from the costs and hazards of renal revascularization.

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