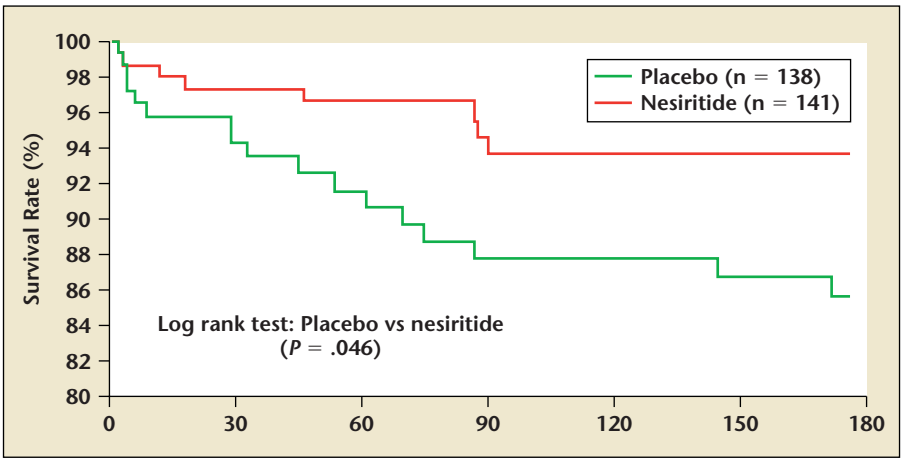

Figure 1. *Kaplan-Meier survival curves to day 180 by treatment group. Reprinted with permission from Mentzer RM et al.*[4]

to the ICU or until ICU discharge (whichever came first). Nearly 50% of the patients studied had diabetes, with a mean serum creatinine of 1.1 mg/dL and GFR of 80 mL/min/1.73 m^2. Cardiopulmonary bypass has been associated with perturbation of renal function.

Nesiritide was associated with a smaller rise in serum creatinine compared to placebo (0.15 mg/dL vs 0.34 g/dL; $P < .001$), a smaller decrease in GFR (−10.8 mL/min/1.73 m^2 vs −17.2 mL/min/1.73 m^2; $P = .001$), and greater urine output (2926 mL vs 2350 mL; $P < .001$). In addition, nesiritide-treated patients had a trend toward a lower 30-day mortality and a significantly lower 180-day mortality (6.6% vs 14.7%; $P = .046$) (Figure 1).

The results of the NAPA trial show a positive effect on mortality and a protective effect on renal function, in contradistinction to what has been described in the previously mentioned meta-analysis. Perturbation of renal function has been associated with worse outcomes in patients with a variety of cardiovascular conditions, including heart failure. The results of this trial should provide considerable comfort to those concerned about the potential effects that nesiritide may have on renal function and mortality. This trial suggests a renal-preserving effect of nesiritide in patients with left ventricular systolic dysfunction undergoing coronary artery bypass surgery with cardiopulmonary bypass. Larger, sufficiently powered clinical trials are planned to further clarify the impact of nesiritide on mortality and renal function in patients with ADHF. ■

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Kidney Disease

Estimated Glomerular Filtration Rate: Why Is It Important?

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[*Rev Cardiovasc Med.* 2007;8(1):46-49]

Assessing Kidney Function—Measured and Estimated Glomerular Filtration Rate

Stevens LA, Coresh J, Greene T, Levey AS

N Engl J Med. 2006;354(23):2473-2483

With the demographic shift in Western societies toward a population that is older, more obese, and prone to type 2 diabetes and hypertension, there is increasing interest in the effects of chronic kidney disease (CKD) on the cardiovascular system. The numbers of individuals in the United States who meet a definition of CKD based on a reduced estimated glomerular filtration rate (eGFR) or evidence of kidney damage as shown by imaging studies or biomarkers are expected to increase sharply over the next several decades. Since approximately half of all deaths in those with CKD are attributed to cardiovascular causes, there is rationale to explore CKD as a "cardiovascular risk state." This article will review a recent summary of the state of the art, with respect to eGFR as a surrogate for renal function and renal parenchymal mass.[1]

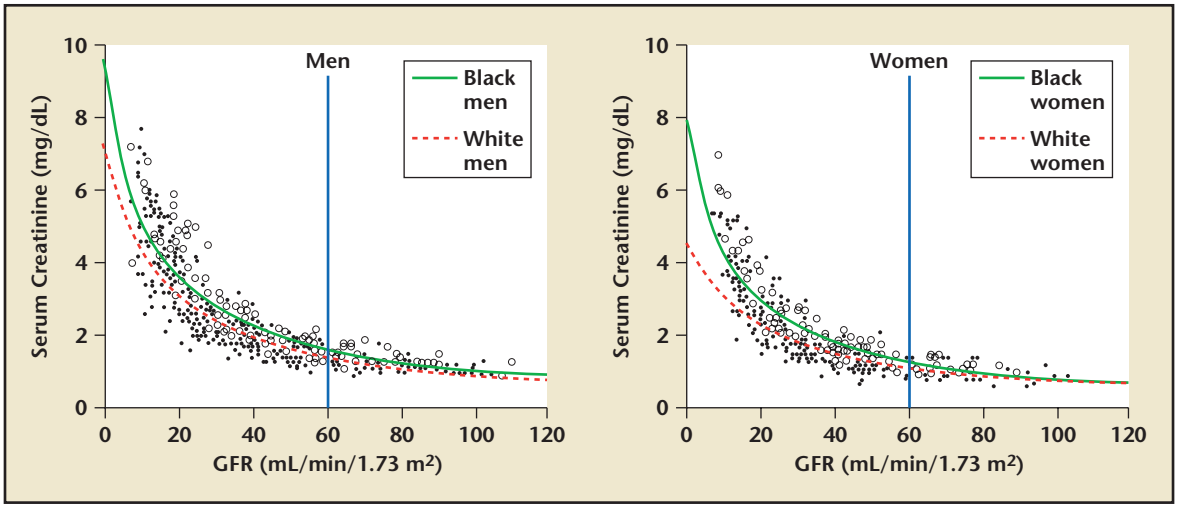
Glomerular Filtration Rate

The eGFR is accepted as the best overall measure of kidney filtration function. It does not measure renal hemodynamic, metabolic, or endocrine function; however, it does correlate with essential normal function of the kidneys because eGFR is a surrogate for renal parenchymal mass. Normal values, which are related to age, sex, and body size, are approximately 130 mL/min/1.73 m^2 in young men and 120 mL/min/1.73 m^2 in young women.[1] Mean values decline with age because of a drop in functioning nephrons. Creatinine is derived from skeletal muscle creatine and has a molecular weight of less than 1 kilodalton, making it freely filtered by the glomerulus. Creatinine is also secreted by the renal tubules, with greater amounts of creatinine eliminated by this route in patients with CKD. Thus, glomerular filtration and tubular secretion are the 2 components of creatinine clearance. Many studies support the similarity of creatinine clearance to eGFR and its reciprocal relationship with the serum creatinine level (Figure 1).[1] Thus, the blood creatinine level depends on skeletal muscle mass and reflects 2 processes occurring in the kidney, making it a poor reflection of renal filtration function. There has been a worldwide move to the use of estimating equations for eGFR and reporting this value alongside the serum creatinine value in the clinical laboratory report. The 4-variable Modification of Diet in Renal Disease equation for eGFR is the preferred method because it does not rely on body weight or other laboratory values that are not uniformly collected. The equation is: $186.3 \times (\text{serum creatinine} - 1.154) \times (\text{age} - .203)$; calculated values are multiplied by .742 for women and by 1.21 for African Americans.[1]

Cystatin C: A Potential Replacement for Creatinine and eGFR

A recently approved blood test reflecting renal filtration function is cystatin C. Cystatin C is a nonglycosylated, low-molecular mass (13 kilodaltons) protein produced by all nucleated cells. Its low molecular mass and its high isoelectric point allow it to be freely filtered by the glomerular membrane and 100% reabsorbed by the proximal tubule. The serum concentration of cystatin C

Figure 1. *Relationship between serum creatinine and estimated glomerular filtration rate (GFR). Reprinted with permission from Stevens LA et al.[1]*



correlates with eGFR and, in combination with a stable production rate, provides a sensitive marker of renal filtration function. Serum levels of cystatin C are relatively independent of weight and height, muscle mass, and age or sex, making it less variable than creatinine.[2] Furthermore, measurements can be made and interpreted from a single random sample with reference intervals in women and men being 0.54 mg/L to 1.21 mg/L (median 0.85 mg/L, range 0.42-1.39 mg/L). Levels of this protein are affected by corticosteroids and thyroid function, and thus more research is needed before this test can replace serum creatinine and the eGFR value in the clinical laboratory.

CKD as a Cardiovascular Risk State

The potential explanations for how the CKD state can cause, accelerate, or worsen atherosclerosis and myocardial disease have been of considerable interest in clinical and research communities.[3] The 4 basic explanations are: 1) uncontrolled confounding, or the impact of multiple risk factors/comorbidities that occur in CKD patients, especially older age; 2) therapeutic nihilism, meaning CKD patients receive lesser degrees of cardioprotective therapies; 3) excess treatment toxicities, intolerances, or risks such that therapy cannot be used or offers a less favorable benefit-to-risk ratio; and 4) a unique vascular pathobiology that occurs in the CKD state.[4] As eGFR decreases below 60 mL/min/1.73 m^2, a complex set of biologic processes are initiated in the best treated patient and are reflected by a constellation of clinical factors, notably hypertension (Figure 2).[1] A reduction in renal clearance of a variety of nitrogenous products could be injurious to the vascular system in many ways.[5] This could be in part due to activation of a variety of neurohormonal, inflammatory, and oxidative pathways that work to accelerate the atherosclerosis process, causing vascular injury throughout the body.[6] The presence of urine microalbuminuria (MA) or gross proteinuria represents, to some degree, this ongoing process at the level of the glomerulus. Neurohormonal activation is clearly implicated in myocardial injury and the development of heart failure as one form of cardiovascular disease (CVD) in those with CKD.[7] An alternative line of thinking would suggest that a reduction in eGFR is a surrogate for a reduction in renal parenchymal mass. With this reduction in renal tissue, there is a relative deficiency in renally produced protective substances, including erythropoietin and perhaps a variety of other proteins. Thus the anemia and its related risks reflect to some degree this axis of cardiorenal function. It is therefore important to realize that eGFR, MA, and anemia all represent important measurable components of CVD risk in patients undergoing screening for CKD.[8] Studies suggest that when all 3 markers of CKD are present, one fourth of individuals will have already incurred a cardiovascular event (myocardial infarction or stroke).[9] Because of these epidemiologic observations, conventional cardiovascular risk reduction in patients with CKD has gained great support.[10] Thus, in all cardiovascular patients, the eGFR, presence of MA, and hemoglobin should be documented and understood in terms of prognosis and management. The review by Stevens and colleagues[1] has given a solid foundation for eGFR as the cornerstone of these 3 measures of renal function and health in our patients. ■

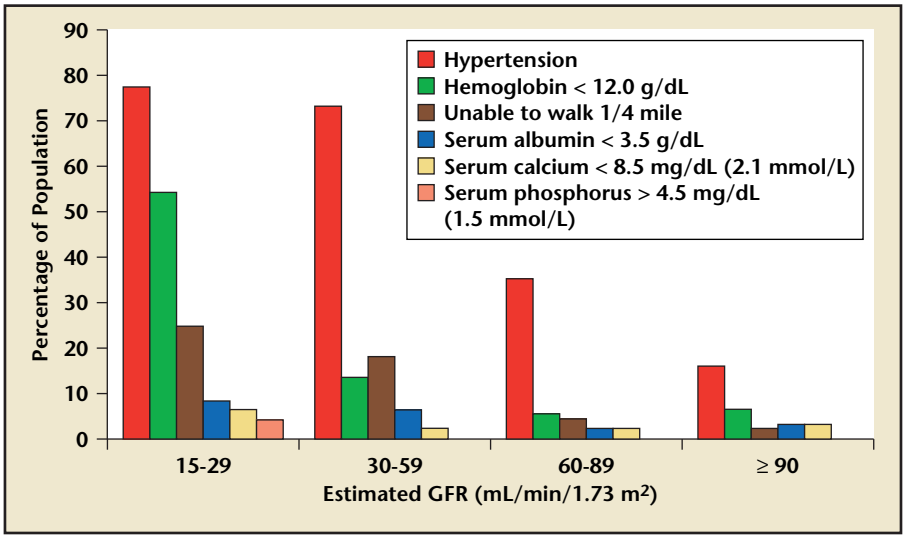


Figure 2. *Clinical and metabolic factors stratified by estimated glomerular filtration rate (GFR) level. Reprinted with permission from Stevens LA et al.[1] Copyright © 2006 Massachusetts Medical Society. All rights reserved.*

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Atrial Septal Defects

A Retrospective of Atrial Septal Defect Closure Devices

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[*Rev Cardiovasc Med.* 2007;8(1):49-52]

Device Closure Rates of Simple Atrial Septal Defects Optimized by the STARFlex Device

Nugent AW, Britt A, Gauvreau K, et al.

J Am Coll Cardiol. 2006;48(3):538-544

Percutaneous closure of atrial septal defects (ASDs) has been a goal for 30 years.[1] Nugent and colleagues[2] present an historical retrospective of the effectiveness of a particular ASD occluder design championed by the group at Boston Children's Hospital and led by James Lock, MD.

The original model, the Clamshell (C.R. Bard Inc., Murray Hill, NJ), was known as the "double-umbrella" device. It consisted of 2 opposing squares of knitted Dacron® (Invista, Wichita, KS) stretched open by 4 metallic (stainless steel) arms with a single joint in the middle of each outstretched arm. The device was delivered through a sheath positioned across the secundum defect. The left atrial (LA) side was opened first, with care to keep all the "legs" of the device on the LA side of the septum, then the device was pulled into the septum, and the right side was allowed to spring open. A narrow metallic connector was present between the 2 umbrellas. This model was used from 1989 to 1991.

Because of concern regarding arm fractures that were observed in the follow-up period, the device was redesigned using a newer and thicker metal alloy with 2 joints in each arm. The new device was named the CardioSEAL® occluder (NMT Medical Inc., Boston, MA) (Figure 1A). It still had a narrow metallic connector between the 2 discs that potentially allowed movement within the ASD orifice. The CardioSEAL was used from 1997 to 1999, when it was replaced by a self-centering device, the STARFlex® (NMT Medical Inc., Boston, MA). This device had strings between the tips of the disc squares that forced the umbrellas to remain centered within the ASD when deployed (Figure 1B), and it utilized nitinol metal.

Devices were all measured according to the "stretched" diameter of the ASD. This standard measurement is determined by placing a sizing balloon across the atrial septum and noting the maximal balloon diameter that does not demonstrate any residual Doppler color-flow around the balloon when viewed on a transesophageal echocardiogram (TEE) or an intracardiac echocardiogram (Figure 2). Intracardiac echo/Doppler has been increasingly used to deploy these devices, but in the authors' series, all patients had the device deployed while under general anesthesia with TEE guidance. The TEE is

Figure 1. *The evolution of the "umbrella" ASD occluder.* **(A)** *The CardioSEAL device with 2 arm joints.* **(B)** *The STARFlex device with self-centering mechanism. ASD, atrial septal defect.*