Beyond Serum Creatinine: Defining the Patient with Renal Insufficiency and Why?

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Chronic kidney disease is the most important factor in predicting adverse short- and long-term outcomes after percutaneous coronary intervention. Most studies of cardiovascular outcomes have found that a break point for the development of radiocontrast nephropathy (RCN), later restenosis, recurrent myocardial infarction, congestive heart failure, and cardiovascular death, occurs below an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m², which roughly corresponds to a serum creatinine (Cr) of > 1.5 mg/dL in the general population. Renal dysfunction is accurately recognized by calculating the eGFR from the age, serum creatinine, gender, race, and weight, and not from the serum creatinine alone. The pathogenesis of RCN goes beyond serum Cr and involves a unique vascular pathobiology that interrelates both the renal and cardiovascular disease outcomes. [Rev Cardiovasc Med. *2003;4(suppl 1):S2–S6*]

Key words: Cardiovascular disease • Chronic kidney disease • Angioplasty • Atherosclerosis • Acute renal failure • Radiocontrast nephropathy • Microalbuminuria • Dialysis

The Cardiorenal Intersection

The modern-day, first-world epidemics of obesity and hypertension are the central drivers of an epidemic of combined chronic kidney disease (CKD) and cardiovascular disease (CVD).[1] Among those who have had diabetes for 25 years or more, the prevalence of diabetic nephropathy in type 1 and type 2 diabetes is 57% and 48%, respectively.[2] Approximately half of all cases of end-stage renal disease (ESRD) result from diabetic nephropathy, and most of these cases are driven by obesity-related type II diabetes and hypertension. With the graying of America and with cardiovascular care shifting towards the elderly, there is an imperative

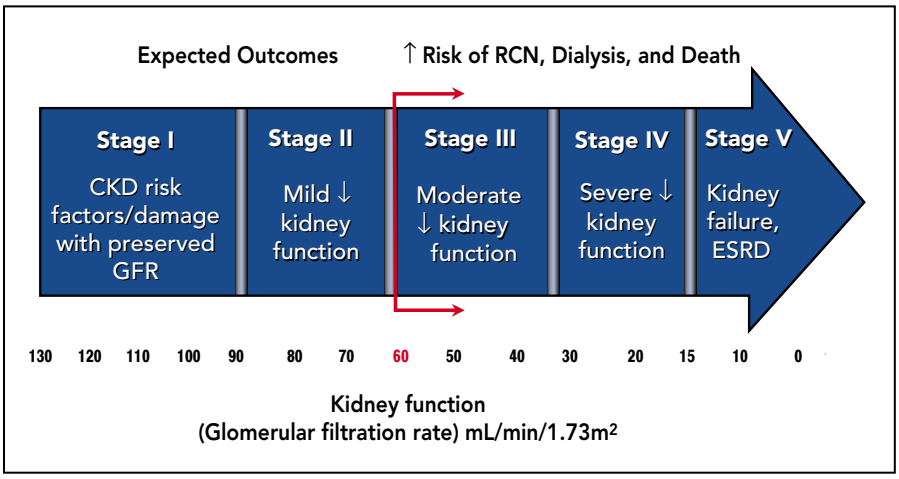


Figure 1. *The stages of chronic kidney disease (CKD) showing the classification of CKD according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI). Increased rates of adverse events are generally seen below an estimated glomerular filtration rate of 60 mL/min/1.73 m². RCN, radiocontrast nephropathy; GFR, glomerular filtration rate; ESRD, end-stage renal disease. Adapted from National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification.*[3]

to understand why decreasing levels of renal function act as a major adverse prognostic factor after percutaneous coronary intervention (PCI). Acute renal failure, as the most proximal renal event, is predictable; as such, it highlights an opportunity for the preventive measures that are outlined in other sections of this publication.

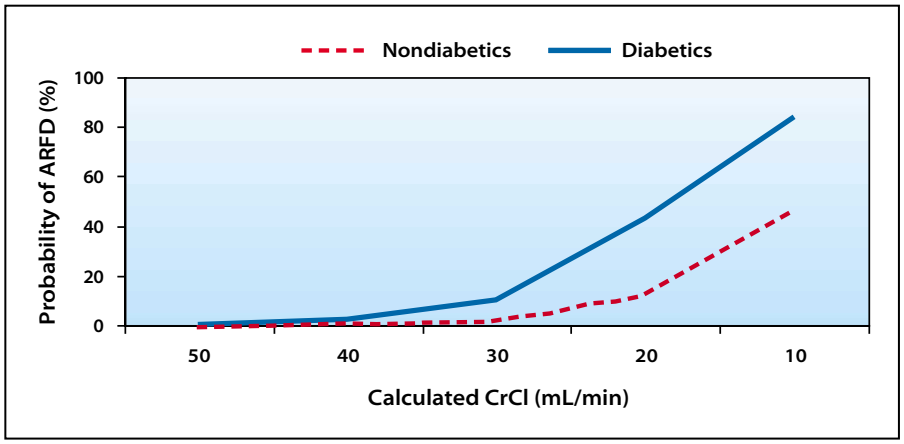
Chronic Kidney Disease and Renal Risk

CKD is defined by means of a range of estimated glomerular filtration rate (eGFR) values by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI), as depicted in Figure 1.[3] Most studies of cardiovascular outcomes have found that a break point for the development of radiocontrast nephropathy (RCN), later restenosis, recurrent myocardial infarction (MI), congestive heart failure (CHF), and cardiovascular death, occurs below an eGFR of 60 mL/min/1.73m², which roughly corresponds to a serum creatinine (Cr) of > 1.5 mg/dL in the general population.[4-7] Because Cr is a crude indicator of renal function and often underestimates renal dysfunction in women and the elderly, calculated measures of eGFR by the Cockroft-Gault equation or by the Modification of Diet in Renal Disease (MDRD) equations are the preferred methods of estimating renal function.[3] These equations are now available in software applications for personal digital assistants (PDAs) at Web sites http://pbrain.hypermart.net/medrules.html for the MedRules clinical prediction program and http://www.stanford.edu/~pmcheng/medmath/ for the MedMath medical calculator.

In addition, microalbuminuria at any level of eGFR is considered to represent CKD; it has been thought to occur as the result of hyperfiltration in the kidneys stemming from diabetes- and hypertension-related changes in the glomeruli.[8] Several definitions of microalbuminuria have been developed.[8] A simple definition of microalbuminuria is the measurement of 30–300 mg/L on a single, voided, casual specimen. A measurement greater than 300 mg/L is usually considered gross proteinuria.

It is critical to understand that the risk of RCN is related in a curvilinear fashion to the eGFR expressed in creatinine clearance, as shown in Figure 2.[9] Several leading explanations have been given for why CKD is such a potent risk factor for adverse outcomes after cardiovascular events, including RCN: 1) excessive comorbidities in CKD patients, including older age and diabetes; 2) underutilized end-organ protective strategies in CKD patients, or therapeutic nihilism; 3) excessive toxicities from conventional therapies,

Figure 2. *Validated risk of acute renal failure requiring dialysis (ARFD) after diagnostic angiography and ad-hoc angioplasty. This assumes a mean contrast dose of 250 mL and a mean age of 65. CrCl, creatinine clearance. Adapted, with permission, from McCullough et al.*[9]



including radiocontrast material and antithrombotics; and 4) the unique pathobiology of the CKD state, which includes intrarenal vasoconstriction when exposed to iodinated contrast agents.[10]

Small Rises in Creatinine Are Linked to Poor Long-Term Outcomes

In a study of 1826 consecutive patients undergoing PCI, we demonstrated that the overall risk of RCN, defined as a transient rise in Cr > 25% above the baseline, occurred in approximately 13% of nondiabetics and 20% of diabetics (Figure 3).[11] We also found that, fortunately, rates of RCN leading to dialysis are rare (0.4–2.0%); however, when they do occur, they are related to catastrophic outcomes, including a 36% in-hospital mortality rate and a 2-year survival of only 19%.[11] Transient rises in Cr are directly related to longer intensive care unit and hospital ward stays (3 and 4 more days, respectively) after bypass surgery.[12] Recently, it was shown that even transient rises in Cr translate to differences in adjusted long-term outcomes after PCI (Figure 4).[13]

What is going on in this population? The leading theory is that when renal function declines, the associated abnormal vascular pathobiology accelerates; hence, the progression of CVD events occurs at a higher rate. This raises the intriguing issue of end-organ protection.[10]

Rationale for Renal End-Organ Protection in Cardiovascular Procedures

End-organ protection for CKD patients at risk (ie, eGFR < 60 mL/min/1.73 m^2) can be thought of as three separate spheres: 1) long-term cardiorenal protection, 2) removal of renal toxins, and 3) preventive measures carried out before PCI.

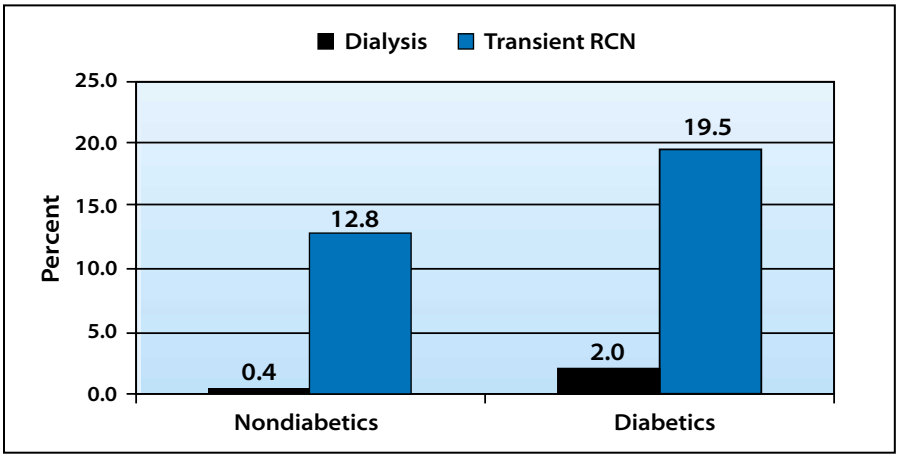
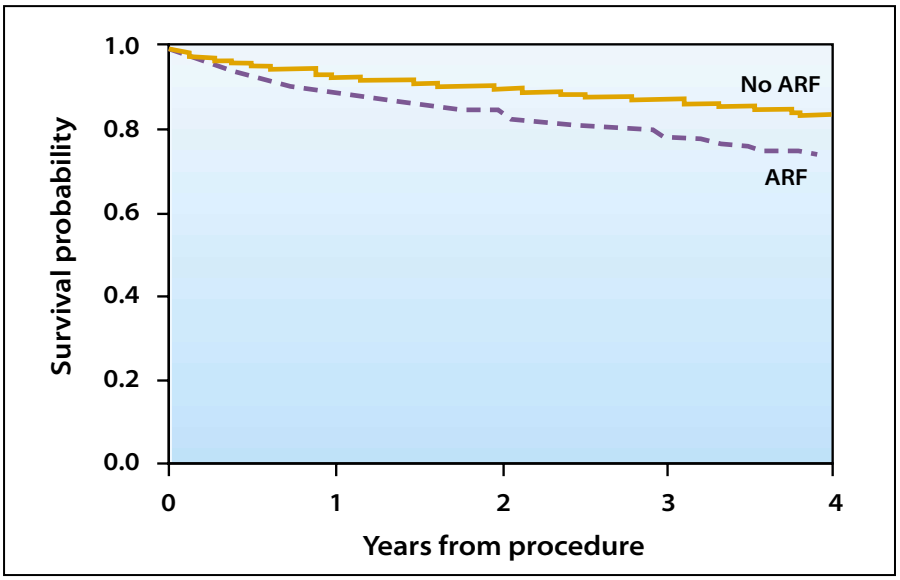


Figure 3. *Rates of transient radiocontrast nephropathy (RCN), defined as a rise in serum creatinine > 25% above baseline, and rates of acute renal failure requiring dialysis in 1826 consecutive patients undergoing angiography and percutaneous coronary intervention. Adapted from McCullough et al.*[11]

Long-term cardiorenal protection involves two important concepts: 1) blood-pressure control in CKD to a target of ~ 125/75 mm Hg,[14] and 2) the use of an agent that blocks the renin-angiotensin system (RAS), such as an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), as the base of therapy. Importantly, both agents will cause a chronic rise in Cr > 25% above the baseline in cardiovascular patients.[16] It has been shown, however, that despite the rise in Cr there are large benefits to be gained with the use of ACEI/ARB agents with respect to a reduction in new cases of end-stage renal disease (ESRD), CHF, or cardiovascular death.[17-23] It has also been sufficiently shown that these benefits extend to nondiabetics and to African

Figure 4. *Adjusted, long-term outcomes showing probability of survival from death or myocardial infarction in 7586 patients with and without acute renal failure (ARF) after angioplasty (P < 0.0001). ARF is defined as a ≥ 0.5 mg/dL rise in serum creatinine after percutaneous coronary intervention. Adapted, with permission, from Rihal et al.*[13]



Americans with CKD.[22,23]

Removal of renal toxins largely refers to the discontinuation of nonsteroidal anti-inflammatory agents, aminoglycosides, and cyclosporine. All of these agents complicate cardiovascular procedures and increase the risk of RCN.

Based on the totality of evidence to date, if a patient can be carried through a cardiovascular procedure (PCI or bypass surgery) without a rise in Cr, we can expect a shorter length of stay and improved long-term survival.

Preventive measures to take before PCI include hydration, reduction of the direct cellular toxicity of the contrast, and, importantly, reduction of the intrarenal vasoconstriction that occurs uniquely in CKD patients who are exposed to iodinated contrast.[9] Based on the totality of evidence to date, if a patient can be carried through a cardiovascular procedure (PCI or bypass surgery) without a rise in Cr, we can expect a shorter length of stay and improved long-term survival.

Unique Vascular Pathobiology in Chronic Kidney Disease

As renal function declines, a host of abnormalities, beyond a rise in serum creatinine, develops. These abnormalities include changes in coagulation, fibrinolysis, lipids, endothelial dysfunction, homocysteine, anemia, calcium/phosphorus balance, and many other factors that have been related to CVD.[10] The principal hypotheses for why these changes occur include chronic hyperactivation of the RAS that leads to adverse cardiac remodeling, accelerated atherosclerosis, and symptomatic events.[10] There is a growing body of evidence that suggests that erythropoietin deficiency and anemia are related to adverse ventricular remodeling and cardiac failure.[24] Hyperhomocystinemia is an obvious therapeutic target for future trials in acute coronary syndromes, given its predictable elevation in CKD, its known association with adverse outcomes, and its reduction with high doses of folic acid.[25] Lastly, advanced atherosclerosis related to abnormal vascular calcification driven by an elevated calcium-phosphorous product (CPP) is an attractive hypothesis in ESRD, where recent studies suggest that not only is CPP related to coronary calcification, but that the lowering of the CPP may reduce or stabilize the coronary calcification process.[26] Importantly, the most acute short-term result of this vascular pathobiology is paradoxical intrarenal vasoconstriction and ischemic renal injury resulting from exposure to iodinated contrast.[9] This phenomenon is now a major therapeutic target for prevention of RCN.

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Conclusions

Chronic kidney disease is the most important factor in predicting adverse short-term and long-term outcomes after PCI. Hence, the rationale for renal end-organ protection is based on chronic renal protection, avoidance of additive renal insults, and a comprehensive RCN prophylaxis. The pathogenesis of RCN goes beyond serum Cr and involves a unique vascular pathobiology that interrelates both the

Main Points

- Renal dysfunction is accurately recognized by calculating the estimated glomerular filtration rate (eGFR) from the age, serum creatinine, gender, race, and weight, and not from the serum creatinine alone.
- Even transient rises in creatinine that do not necessitate dialysis translate to differences in adjusted long-term outcomes after percutaneous coronary intervention, resulting in reduced probability of long-term survival from death or myocardial infarction.
- Radiocontrast nephropathy and other major adverse cardiac events after angioplasty begin to occur at eGFR rates < 60 mL/min/1.73 m^2.
- Beyond serum creatinine, the pathogenesis of chronic kidney disease comprises a unique vascular pathobiologic state that confers the highest cardiac-event rates of any group taken to the catheterization laboratory and has as a central feature, pathologic intrarenal vasoconstriction, which occurs in response to iodinated contrast.

renal and CVD outcomes. Through intense and systematic study of these unique mechanisms, new diagnostic and therapeutic targets will be discovered that will enhance the cardiac care of patients with CKD and hopefully will reduce the elevated risks and adverse outcomes associated with RCN. ■

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