

Percutaneous Coronary Interventions in the High-Risk Renal Patient: Strategies for Renal Protection and Vascular Protection

Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA*,
Aaron D. Berman, MD, FACC

*Divisions of Cardiology, Nutrition and Preventive Medicine, Department of Medicine,
William Beaumont Hospital, 4949 Coolidge, Royal Oak, MI 48073, USA*

The worldwide pandemic of obesity is threatening to erase considerable progress made in the primary and secondary prevention of coronary artery disease (CAD). Obesity has a direct and colinear relationship to the increasing prevalence of the metabolic syndrome and type 2 diabetes. Recent data suggest that chronic kidney disease (CKD) and CAD have the same conventional risk factors, including the metabolic syndrome, dyslipidemia, smoking, hypertension, and, very importantly, diabetes [1]. Approximately 50% of patients with diabetes develop CKD after 20 years of the disease [2]. With type 2 diabetes now occurring in early adulthood in large numbers of overweight and obese individuals, in future decades one can expect increasing numbers of individuals with CKD to develop CAD and require percutaneous coronary intervention (PCI). In the last 10 years sufficient data have accumulated for major guidelines committees to consider CKD a major, independent CAD risk factor [3].

Chronic kidney disease and cardiovascular risk

CKD is defined through a range of estimated glomerular filtration rate (eGFR) values by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) as depicted in Fig. 1 [4]. Most studies of cardiovascular

outcomes have found that a breakpoint for the development of contrast-induced nephropathy (CIN), later restenosis, recurrent myocardial infarction, diastolic/systolic congestive heart failure, and cardiovascular death occurs below an eGFR of 60 mL/min/1.73 m², which roughly corresponds to a serum creatinine level higher than 1.5 mg/dL in the general population [5–8]. Because creatinine level is a crude indicator of renal function and often underestimates renal dysfunction in women and elderly persons, calculated measures of eGFR or creatinine clearance by the Cockcroft-Gault equation or by the Modification of Diet in Renal Disease (MDRD) equations, now available on personal digital assistants, are the preferred methods of estimating renal function [4]. The four-variable MDRD equation for creatinine clearance is ideal for the catheterization laboratory because it does not rely on body weight [4]:

$$(186.3^* [\text{serum creatinine}^{-1.154}]^* [\text{age}^{-2.033}])$$

Calculated values are multiplied by 0.742 for women and by 1.21 for African Americans.

In addition, microalbuminuria at any level of eGFR is considered to represent CKD and has been thought to occur as the result of endothelial dysfunction in the glomeruli [9]. A simple definition for microalbuminuria is a random urine albumin/creatinine ratio (ACR) of 30/300 mg/g. An ACR higher than 300 mg/g is usually considered gross proteinuria. It is critical to understand that the risk of CIN is related in a curvilinear fashion to the eGFR as shown in Fig. 2 [10].

* Corresponding author.

E-mail address: pmc975@yahoo.com
(P.A. McCullough).

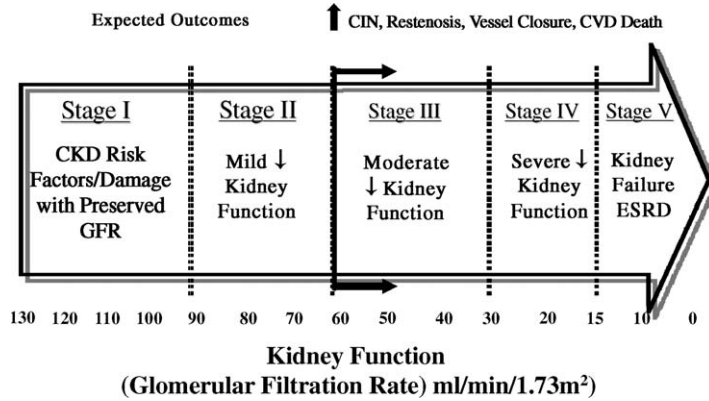


Fig. 1. The classification of chronic kidney disease (CKD) according to the National Kidney Foundation KDOQI. Increased rates of adverse events are generally seen below an estimated glomerular filtration rate of 60 mL/min/1.73 m². CIN, contrast-induced nephropathy; ESRD, end-stage renal disease; GFR, glomerular filtration rate. (Adapted from McCullough PA. Beyond serum creatinine: defining the patient with renal insufficiency and why? Rev Cardiovasc Med 2003;4(Suppl 1):S3.)

There are several leading explanations for why CKD is such a potent risk factor for adverse outcomes, including CIN, after cardiovascular events [11]:

1. Excess comorbidities in CKD patients, including older age and diabetes
2. Underused end-organ protective strategies in CKD patients, or therapeutic nihilism
3. Excess toxicities from conventional therapies used including radiocontrast material and antithrombotic agents
4. The unique pathobiology of the CKD state, which includes intrarenal vasoconstriction when exposed to iodinated contrast agents

Small rises in creatinine level following percutaneous coronary intervention are linked to poor outcomes

CIN, defined as a transient rise in creatinine level of more than 25% above the baseline, occurs in approximately 13% of nondiabetics and 20% of diabetics undergoing PCI (Fig. 2) [12]. Fortunately, rates of CIN leading to dialysis are low (0.5%–2.0%), but, when they occur, they are related to catastrophic outcomes including a 36% in-hospital mortality rate and a 2-year survival of only 19% [12]. Transient rises in creatinine level are directly related to longer ICU and hospital-ward stays (3 and 4 more

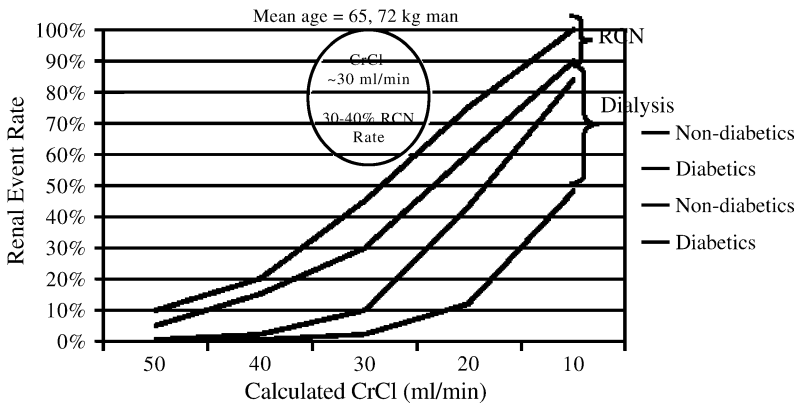


Fig. 2. Validated risk of acute renal failure requiring dialysis after diagnostic angiography and ad hoc angioplasty (assumes a mean contrast dose of 250 mL and a mean age of 65 years). CrCl, creatinine clearance; RCN, radio-contrast nephropathy. (From McCullough PA, Sandberg KR. Epidemiology of contrast-induced nephropathy. Rev Cardiovasc Med 2003;4(Suppl 5):S5; with permission.)

days, respectively) after bypass surgery [13]. Recently, it has been shown that even transient rises in creatinine level translate to differences in adjusted long-term outcomes after PCI (Fig. 3) [14]. This finding suggests that when renal function declines, atherosclerosis accelerates, and hence CAD progresses at a higher rate. An additional explanation is that even reversible CIN may be a marker of endothelial dysfunction and limited microvascular reserve, conferring a poor prognosis. This possibility raises the intriguing issue of whether renal protection might influence long-term CAD outcomes [11].

Rationale for renal protection for intervention patients

End-organ protection for CKD patients at risk (eGFR < 60 mL/min/1.73 m²) can be thought of in two realms: renal protection and vascular protection. Long-term cardiorenal protection involves two important concepts. The first is blood pressure control in CKD to an ideal systolic blood pressure lower than 120 mm Hg [3]. The second is use of an agent that blocks the renin-angiotensin system, such as an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB) as the base of therapy [15]. Both agents will cause a chronic rise in creatinine level greater than 25% above the baseline in approximately 10% to 15% of elderly cardiovascular

patients [16]. It has been shown, that despite the rise in creatinine level, ACE inhibitor/ARB agents show large benefits in reducing the number of new cases of end-stage renal disease (ESRD), congestive heart failure, or cardiovascular death [17–21]. It has been sufficiently shown that these benefits extend to nondiabetics and to African Americans with CKD [22,23]. Prevention measures done before PCI include hydration, measures to reduce the direct cellular toxicity of the contrast, and, importantly, measures to reduce the intrarenal vasoconstriction and oxidative stress that occur uniquely in CKD patients when exposed to iodinated contrast [10]. 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 creatinine level, one can expect a shorter hospital stay and improved long-term survival.

Pathophysiology of contrast-induced nephropathy

There are three core elements in the pathophysiology of CIN: (1) direct toxicity of iodinated contrast to nephrons, (2) microshowers of atheroemboli to the kidneys, and (3) contrast- and atheroemboli-induced intrarenal vasoconstriction [24]. Direct toxicity to nephrons with iodinated contrast has been demonstrated and seems to be related to the osmolality of the contrast [25]. Hence, low-ionic or nonionic and low-osmolar or iso-osmolar contrast agents have been shown to be less nephrotoxic in vitro. Microshowers of cholesterol emboli are thought to occur in about 50% of percutaneous interventions in which a guiding catheter is passed through the aorta [26]. Most of these showers are clinically silent. In approximately 1% of high-risk cases, however, an acute cholesterol emboli syndrome can develop manifested by acute renal failure, mesenteric ischemia, livedo reticularis, decreased microcirculation to the extremities, and in some cases, embolic stroke. Finally, intrarenal vasoconstriction as a pathologic vascular response to contrast media, and perhaps as an organ response to cholesterol emboli, is a final hypoxic/ischemic injury to the kidney during PCI caused by activation of the renal sympathetic nervous system and a reduction in renal blood flow [27]. The most important predictor of CIN is underlying renal dysfunction. The remnant nephron theory postulates that after sufficient chronic kidney damage has occurred and the eGFR is reduced to less than 60 mL/min/1.73 m², the

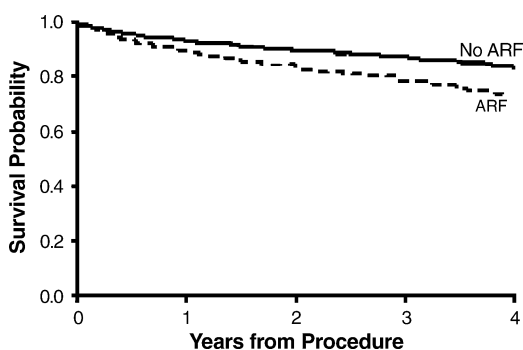


Fig. 3. Adjusted long-term outcomes in 7586 patients with and without acute renal failure after angioplasty ($P < 0.0001$). Acute renal failure is defined as a 0.5-mg/dL or greater rise in creatinine after PCI. ARF, acute renal failure; MI, myocardial infarction. (Adapted from Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002;105(19):2264; with permission.)

remaining nephrons must pick up the remaining filtration load, have increased oxygen demands, and are more susceptible to ischemic and oxidative injury.

Prevention of contrast-induced nephropathy

For patients with significant CKD (eg, a baseline eGFR < 60 mL/min/1.73 m²) a CIN prevention strategy should be employed. In general, at an eGFR of 30 mL/min/1.73 m², the expected rate of CIN is 30% to 40%, and the rate of acute renal failure requiring dialysis is approximately 2% to 8% (Fig. 2) [24]. There are four basic concepts in CIN prevention: (1) hydration, (2) choice and quantity of contrast, (3) pre-, intra-, and postprocedural end-organ protection with pharmacotherapy, and (4) postprocedural monitoring and expectant care.

Hydration with intravenous normal or ½ normal saline is reasonable starting 3 to 12 hours before the procedure at a rate of 1 to 2 mL/kg/h [28]. A simple intravenous rate to remember from clinical trials of hydration is 150 mL/h. Those at risk should receive at least 300 to 500 mL of intravenous hydration before contrast is administered. If there are any concerns regarding volume overload or heart failure, a right-heart catheterization is strongly recommended for management during and after the case. A urine output of 150 mL/h should be the target for hydration after the procedure. If patients have more than a 150-mL/h diuresis, extra losses should be replaced with more intravenous fluid. In general, this strategy calls for hydration orders of normal or ½ normal saline at 150 mL/h for at least 6 hours after the procedure. When adequate urine flow rates were achieved in a clinical trial setting, there was a 50% reduction in the rate of CIN observed [28].

As discussed previously, the lower the ionicity and osmolality of the contrast agent, the less renal toxicity is expected. This observation has now been confirmed in two large-scale, double-blind, randomized, controlled trials. In the Iohexol Cooperative Study (N = 1196), iohexol (Omnipaque; Amersham Health, Princeton, New Jersey) was found to be superior to the high-ionic contrast agent (diatrizoate meglumine [Hypaque-76]; Amersham Health) in patients with diabetes and baseline CKD [29]. In the recently completed Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media (NEPHRIC) study, iodixanol

(Visipaque; Amersham Health), a nonionic, iso-osmolar contrast agent, was proven to be superior to iohexol, with lower rates of CIN observed [30]. Iodixanol has also been demonstrated to be less thrombogenic than other contrast agents in the COURT trial with a 45% reduction in major adverse cardiac events compared with ioxaglate meglumine (Hexabrix; Mallinckrodt Inc., St. Louis, Missouri). Iodixanol is therefore the contrast agent of choice in patients at high renal risk undergoing intervention [31]. In general, it is desirable to limit contrast to less than 100 mL for any procedure [10]. If staged procedures are planned, it is desirable to have more than 10 days between the first and second contrast exposure if CIN has occurred on the first contrast exposure.

More than 35 randomized trials have tested various strategies for the prevention of CIN [10]. Most of these trials were small, underpowered, and did not find the preventive strategy under investigation to be better than placebo. A few lessons have been learned from these trials:

1. Diuretics in the form of loop diuretics or mannitol can worsen CIN if there is inadequate volume replacement for the diuresis that follows.
2. Low-dose or renal-dose levels of dopamine cannot be achieved despite its popularity in practice, given the counterbalancing forces of intrarenal vasodilation through the dopamine-1 receptor and the vasoconstricting forces of the dopamine-2, alpha, and beta receptors.
3. Renal-toxic agents including nonsteroidal anti-inflammatory agents, aminoglycosides, and cyclosporin should not be administered in the periprocedural period.

There are currently no approved agents for the prevention of CIN. The most popular strategy at this time is optimal hydration, use of iodixanol as the contrast agent of choice, and oral or intravenous administration of *N*-acetylcysteine, a cytoprotective agent against oxidative injury. A recent meta-analysis of *N*-acetylcysteine suggested benefit in the pooled analysis; however, a large definitive randomized trial of *N*-acetylcysteine in the prevention of CIN is needed (Fig. 4) [32]. Most operators believe, given the seriousness of CIN as a complication, the relative safety of the strategies used, and the evolution of clinical trials shaping current practice, that the combination of hydration and the use of iodixanol and *N*-acetylcysteine is a reasonable three-pronged

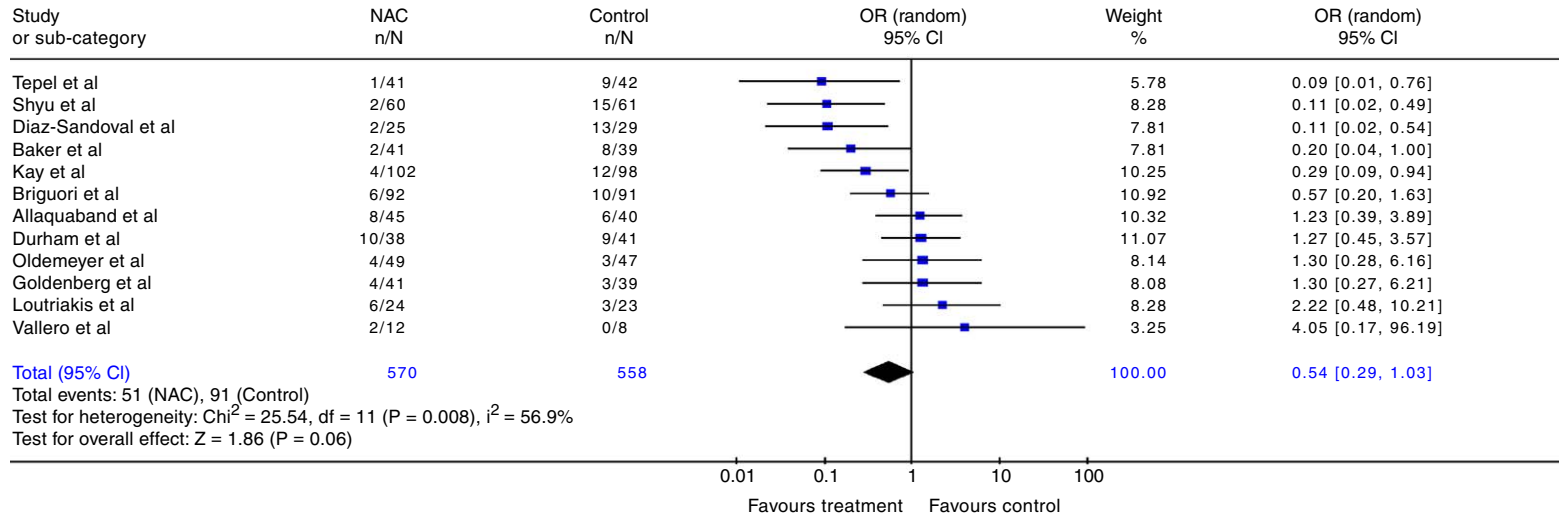


Fig. 4. Meta-analysis of the effects of *N*-acetylcysteine versus control for the risk of contrast media-induced neuropathy in subjects with baseline renal impairment, stratified by effect size. NAC, *N*-acetylcysteine; OR, odds ratio. (Adapted from Fishbane S, McCullough PA, Rudnick M. Systematic review of the role of *N*-acetylcysteine in the prevention of contrast media-induced nephropathy. *J Am Soc Nephrol* 2003;14:1553.)

approach to minimize CIN and the risk of acute renal failure requiring dialysis.

Postprocedural monitoring is an issue in the modern era of short hospital stays and outpatient procedures. In general, in high-risk patients in the hospital hydration should start 12 hours before the procedure and continue at least 6 hours afterwards. A serum creatinine level should be measured 24 hours after the procedure. For outpatients, particularly those with eGFRs below 60 mL/hour, either an overnight hospital stay or discharge to home with 48-hour follow-up and creatinine measurement is advised. It has been demonstrated that individuals who develop severe CIN have a rise in creatinine level of more than 0.5 mg/dL in the first 24 hours after the procedure [33]. Hence, discharge to home may be considered for those who have not had this degree of

creatinine elevation and who otherwise have had uneventful courses.

In summary, for CIN risk assessment and prevention, the items in **Box 1** are advised. It is important to discuss CIN risks in the consent process. For those with eGFR lower than 30 mL/min/1.73 m², the possibility of dialysis should be mentioned. For those with eGFR lower than 15 mL/min/1.73 m², nephrology consultation is advised with possible planning for dialysis after the procedure.

Coronary pathobiology in chronic kidney disease

As renal function declines, a host of abnormalities develop, including changes in coagulation, fibrinolysis, lipids, endothelial dysfunction, homocysteine, anemia, calcium–phosphorus balance, and many other factors that have been related to CVD [11]. The leading hypotheses explaining these changes include chronic hyperactivation of the renin–angiotensin system leading to adverse cardiac remodeling, accelerated atherosclerosis, and symptomatic events [11]. There are approximately 15 to 20 biologic hypotheses concerning renal dysfunction, uremia, and the acceleration of atherosclerosis [34]. At least six therapeutic approaches, including homocysteine reduction, modification of dyslipidemia with statins/ezetimibe, attenuation of vascular calcification with statins or sevelamer, use of cardiac and renal protective natriuretic peptides, and anemia correction with exogenous erythropoietin, have been investigated in prospective randomized treatment trials [34].

The decision to carry out coronary intervention in renal patients

Patients with CKD undergoing PCI also have worse short- and long-term clinical outcomes, including death, than patients with normal renal function. In the early days of PCI, the clinical outcomes with conventional balloon angioplasty alone in CKD patients were extremely poor: single-center case series evaluating small numbers of patients reported restenosis rates as high as 81%, three to four times higher than in CAD patients with normal renal function [35]. Based on these observations, coronary bypass and grafting (CABG) was considered the preferred mode of coronary revascularization for patients with CKD. The contemporary practice of deployment of intracoronary stents after balloon angioplasty has

Box 1. Renal protection checklist for patients at high risk undergoing percutaneous coronary intervention

1. Calculate eGFR (creatinine clearance): risk is increased if eGFR is less than 60 mL/min/1.73 m².
2. Check diabetic status: risk is fivefold higher in diabetic patients.
3. Discuss CIN risk in informed-consent process.
4. Discontinue nonsteroidal anti-inflammatory drugs and other renal-toxic drugs.
5. Arrange nephrology consult for eGFR less than 15 mL/min/1.73 m² for dialysis planning after PCI.
6. Hydration with normal saline or ½ normal saline or sodium bicarbonate, 150 mL/h 3 hours before and 6 hours after procedure [28,50,51].
7. Ensure urine flow rate greater than 150 mL/h after PCI.
8. Iodixanol is the preferred contrast agent.
9. Limit contrast volume to less than 100 mL.
10. Administer *N*-acetylcysteine, 600 mg in 30 cm³ of ginger ale: two doses orally, two times/d before PCI and two doses orally, two times/d after PCI.

improved the immediate procedural success rates with PCI, nearly obviating the need for emergent CABG, and has decreased restenosis rates [35].

The emergence of new technology has also improved the ability to treat complex coronary artery lesions. Because CKD patients frequently have complex lesions, the impact of these technologies on clinical outcomes of PCI was examined in a large cohort of CKD patients. The immediate and long-term outcomes of 362 CKD patients undergoing PCI were compared with outcomes of 2972 patients with normal renal function undergoing PCI. CKD patients were older and had a greater incidence of comorbidities [36]. Strikingly, the in-hospital mortality rate of the CKD patients was 10-fold higher than that of patients with normal renal function (10.8% versus 1.1%, $P < 0.0001$). Although the use of new interventional devices, including stents, improved immediate procedural success rates, CKD patients also had higher long-term mortality rates (27.7% versus 6.1%, $P < 0.0001$) than patients with normal renal function [36].

Similar results were found in a group of patients undergoing intracoronary radiation for the treatment of in-stent restenosis [37]. In-hospital and 6-month clinical and angiographic outcomes of 118 CKD patients were compared with outcomes of 481 patients with normal renal function. Intracoronary radiation significantly reduced the rates of recurrent in-stent restenosis in patients with CKD compared with CKD patients treated without intracoronary radiation (53.8% versus 22%, $P = 0.04$). Short- and long-term major adverse events, including death, were more frequent in patients with CKD than in those with normal renal function, however. Likewise, the overall 1-year mortality rates in CKD patients undergoing saphenous vein graft interventions are higher than in persons with normal renal function [38].

The effect of varying degrees of renal dysfunction on short- and long-term mortality was assessed in 5327 patients undergoing PCI [39]. In this study, patients with lower creatinine clearance rates and those receiving dialysis were more likely to have multivessel CAD, saphenous vein graft disease, and complex coronary artery lesions and were less likely to be completely revascularized at the end of the procedure. Patients with more severe degrees of renal dysfunction and those receiving dialysis also had higher rates of in-hospital death, periprocedural myocardial infarction, and need for urgent CABG than patients with normal renal function. Renal dysfunction

was an independent predictor of adverse outcomes during and after PCI, in a dose-dependent fashion: patients with CKD had higher rates of myocardial infarction and higher short- and long-term mortality rates than patients with normal renal function. In the multivariate analysis, the relative risk of death was highest for dialysis patients (8.91; 95% confidence interval, 5.3–15.0; $P < 0.001$). In the multivariate model, the risk of death during follow-up was highest for patients with ESRD, followed by patients with moderate renal dysfunction (creatinine clearance rate < 50 mL/min). Moderate or severe renal insufficiency was associated with a greater risk of death than diabetes.

Overall, these studies demonstrate that although new interventional techniques have improved the immediate procedural outcomes in patients with CKD undergoing PCI, these patients still have worse short- and long-term outcomes than patients with normal renal function. It is not clear from the available data whether these worse outcomes are caused by the renal dysfunction itself, the extent and severity of CAD, or a greater frequency of comorbidities than seen in patients with normal renal function. Although most of the studies compare outcomes of CKD patients with those in patients with normal renal function, the more pertinent question is whether, with a given degree of CAD and comorbidities, do patients with CKD undergoing coronary revascularization fare better or worse than CKD patients treated with medical therapy alone. In a retrospective study of 4758 high-risk patients admitted with acute coronary syndromes, surgical and percutaneous revascularization conferred better outcomes in CKD patients than medical therapy alone [40]. In this study, although patients with severe CKD were disproportionately treated with medical therapy alone, coronary revascularization was associated with better long-term survival, especially in patients treated with PCI (Fig. 5). In summary, the available studies to date indicate that, despite the associated high risk, efforts to revascularize patients with CKD seem to be justified.

Primary angioplasty for acute coronary syndromes

The specific situation of acute ST-segment elevation acute myocardial infarction (STEMI) as a subset of acute coronary syndrome (ACS), poses

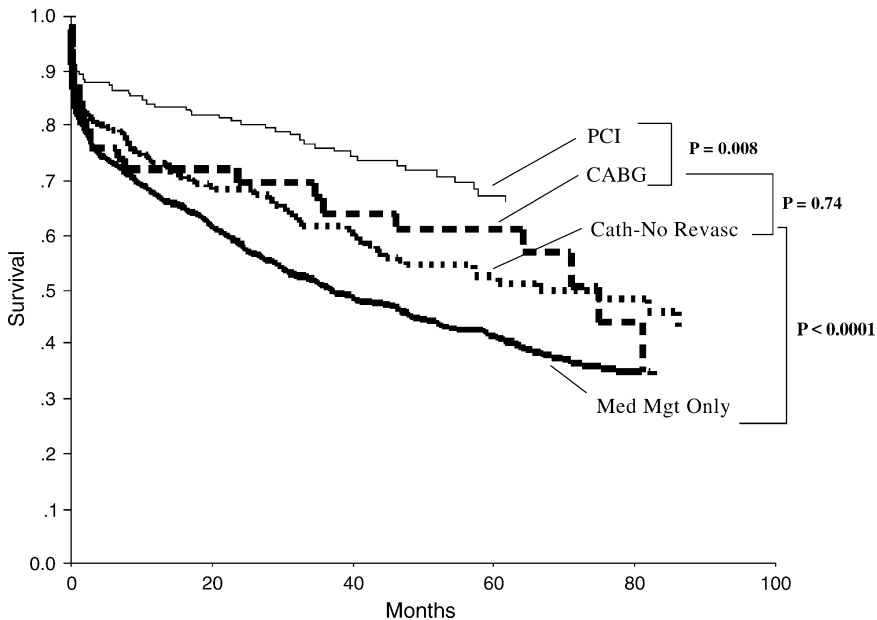


Fig. 5. Long-term survival in patients with severe chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/1.73 m²) by revascularization (Revasc) or management strategy used, adjusted for the propensity for revascularization, type of acute coronary syndrome, medical therapy received, and other significant baseline variables. CABG, coronary artery bypass grafting; Cath, catheterization; Med Mgt, medical management; PCI, percutaneous coronary intervention. (From Keeley EC, Kadakia R, Soman S, et al. Analysis of long-term survival after revascularization in patients with chronic kidney disease presenting with acute coronary syndromes. *Am J Cardiol* 2003;92:513; with permission.)

particular time-dependent issues. In STEMI, each hour that passes without reperfusion is associated with higher mortality and reduced benefit with reperfusion. CKD patients presenting with a myocardial infarction are less likely to receive aggressive therapy than those with normal renal function and are twice as likely to die in the hospital: the overall 1-year mortality rate of dialysis patients after a myocardial infarction is higher than 50% [41]. The prognostic importance of CKD in patients undergoing primary PCI for STEMI was analyzed using data from the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial (CADILLAC) [42]. Although a serum creatinine level higher than 2.0 mg/dL was an exclusion criterion, baseline laboratory values were frequently not available before enrollment because of the urgency of the procedure. Of the 1933 patients with baseline creatinine values available, 350 patients had a creatinine clearance rate of 60 mL/min or less. The clinical outcomes of these patients were compared with those of the 1583 patients with creatinine clearance rates higher than 60 mL/min. Consistent

with other reports, patients with CKD were older, had more comorbidities, and were more likely to have three-vessel coronary artery disease. Procedural success rates were lower in CKD patients than in patients with normal renal function (87.2% versus 92%, $P = 0.01$), and CKD patients had a more than ninefold greater mortality at 1 month and a fivefold increase in mortality at 1 year. A key finding from the CADILLAC trial was that CKD is independently related to severe ($>70\%$) restenosis (Fig. 6) and late occlusion of coronary vessels [42]. In addition, there was a graded relationship between eGFR and mortality during the follow-up period (Fig. 7). The mechanism of restenosis in patients with CKD is not understood, and outcomes in CKD patients with drug-eluting stents have not been reported. A recently presented prospective registry in CKD non-STEMI has basically confirmed the findings of the CADILLAC trial and suggests the processes that work to create poor outcomes in STEMI are operative in non-STEMI patients as well [43].

Early series of thrombolysis in ESRD reported unacceptably high complication and mortality

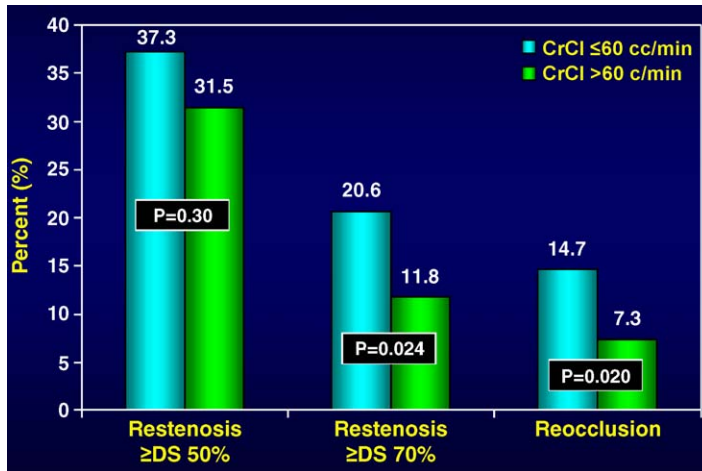


Fig. 6. Rates of restenosis after primary angioplasty for ST-segment elevation acute myocardial infarction in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial (N = 2082). CrCl, creatinine clearance; DS, diameter of stenosis. (From Sadeghi HM, Stone GW, Grines CL, et al. Impact of renal insufficiency in patients undergoing primary angioplasty for acute myocardial infarction. *Circulation* 2003;108(22):2274; with permission.)

rates [41]. In general, when available, primary angioplasty of the infarct-related vessel is the preferred approach in the ESRD patient with STEMI [41]. In a recent case series of 15 ESRD patients undergoing primary angioplasty for STEMI, however, there was a 40% incidence of cardiogenic shock on hospital admission [44]. The success rate for primary angioplasty was 80%, but the in-hospital mortality was 53%. Like all the

subtypes of ACS, there are no prospective, randomized trials of these specific approaches in ESRD.

Adjunctive medical therapy for vascular protection

Adjunctive medical therapy is key to vascular protection for CKD patients undergoing PCI. Because patients with CKD are the highest-risk

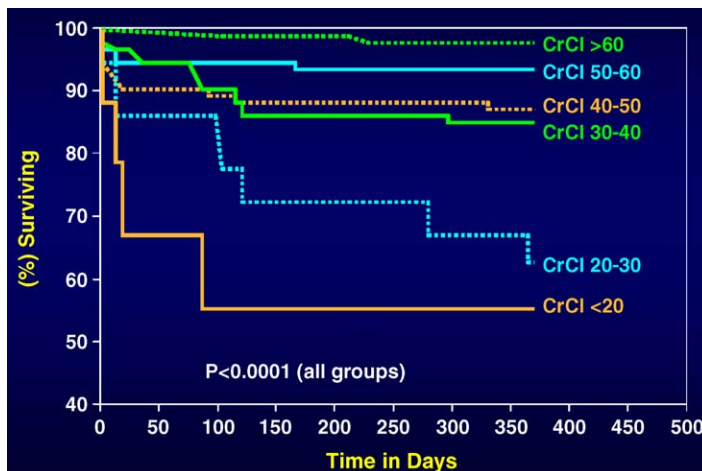


Fig. 7. All-cause mortality after primary angioplasty for ST-segment elevation acute myocardial infarction in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial (N = 2082). (From Sadeghi HM, Stone GW, Grines CL, et al. Impact of renal insufficiency in patients undergoing primary angioplasty for acute myocardial infarction. *Circulation* 2003;108(22):2272; with permission.)

subset treated by the interventionist, all the usual treatments, including aspirin, clopidogrel, ACE inhibitors or ARBs, beta blockers, and statins should be used [41]. Of interest, Khanal and coworkers [45] studied a PCI database (N = 29,409) in which pre- and postprocedure serum creatinine levels were measured. A total of 11,017 subjects (37.5%) were taking statins at baseline. Both groups (statin, no-statin) had baseline creatinine levels of 1.2 mg/dL. The rates of CIN and acute renal failure requiring dialysis were lower in the statin group. Although this study could have been confounded, the baseline characteristics were well matched, and renal protection may indeed be yet another indication for statin use.

A comprehensive discussion of intravenous antiplatelet and antithrombotic therapy is beyond the scope of this article. No large trials of abciximab have reported outcomes in patients in CKD. The small-molecule glycoprotein 2b/3a receptor antagonists (eptifibatide, tirofiban) must be given in a reduced dose when the creatinine clearance level falls below 45 mL/min [46]. Retrospective studies suggest that, even though the bleeding risk is higher, the benefit of these agents outweighs the risk in CKD [41]. Both unfractionated and fractionated heparin have, in part, renal-dependent clearance mechanisms and have been linked to higher bleeding rates in patients with CKD. There are no accepted dose-reduction protocols for unfractionated heparin in CKD patients. With low molecular weight heparins, anti-factor Xa clearance begins to be reduced at creatinine clearance rates of 50 to 80 mL/min. At creatinine clearance rates below 30 mL/min, the steady-state levels of anti-factor Xa activity are increased by 65% with repeated doses of low molecular weight heparin, and bleeding events can be expected without dose adjustment [47]. Although no recommendations have been published for intravenous use in the catheterization laboratory, a reasonable approach with enoxaparin is to administer 0.5 mg intravenously and then 1 mg/kg/d subcutaneously for ACS treatment in a patient not receiving dialysis and with a creatinine clearance rate below 30 mL/min [47–48]. A recent meta-analysis of bivalirudin suggests that this agent may be the ideal antithrombotic to use during PCI in patients with CKD [49]. In this study by Chew [49], 5035 patients went PCI. Twenty-six per cent of these patients had a creatinine clearance rate below 60 mL/min, and most of them received bivalirudin for PCI at a dose of 1.0-mg/kg intravenous bolus and a 2.5-mg/kg/

hour infusion for 4 hours. Bleeding rates were considerably lower than seen in patients treated with unfractionated heparin. The absolute ischemic and bleeding benefit of bivalirudin increased with declining degrees of renal function (normal function: 2.2%; mild dysfunction: 5.8%; moderate dysfunction: 7.7%; severe dysfunction: 14.4%; *P* trend < 0.001).

Although patients with CKD and ESRD are at higher risks for both thrombosis and bleeding, it seems that careful, adjunctive therapy selected for these patients makes a difference in long-term outcomes. Like the decision to revascularize, the decision to use adjunctive pharmacology comes at increased risks and relative benefits.

Summary

CKD is the most important factor in predicting adverse short- 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 CIN prophylaxis. The pathogenesis of CIN goes beyond serum creatinine and involves a unique vascular pathobiology in which interrelates renal and CVD outcomes are interrelated. Attempts at PCI in patients with CKD and ESRD are high-risk procedures, but the risks involved seem to be warranted given comparative outcomes in conservatively treated patients. The benefits of short- and long-term vascular protective therapies in CKD patients have been confirmed, and these therapies are an important component of PCI care.

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