

Coronary Artery Disease and Peripheral Vascular Disease in Chronic Kidney Disease: An Epidemiological Perspective

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Since Lindner's sentinel observation in 1974 highlighting the substantial burden of cardiac disease among patients receiving chronic dialysis, it has become increasingly apparent that accelerated atherosclerosis is an inevitable consequence of progressive loss in kidney function, resulting in significant morbidity and mortality [1–3]. Although there is consensus that chronic kidney disease (CKD) represents a state of accelerated atherosclerosis, and there is accumulating epidemiologic evidence linking worsening kidney function with increased cardiovascular event rates, direct evidence demonstrating a causal relationship has been lacking [4–12]. The critical nature of these relationships has resulted in the establishment of national task forces with support from national agencies to assist in describing the extent of the problem, to define better the contribution of known risk factors and potential novel risk factors to disease occurrence, and finally to develop therapeutic strategies for prevention [3].

This article describes the epidemiology of coronary artery disease (CAD) and peripheral vascular disease (PVD) among patients who have CKD. Special emphasis is given to studies that have described the natural history of these vascular conditions at different stages of CKD in accordance with current recommendations from the National Kidney Disease Outcomes Quality Initiative [13].

Assessing the burden of disease

Coronary artery disease

During the last decade, population-based and center-specific studies have provided estimates of the prevalence of CAD and PVD, but much of these data is limited to patients who have advanced kidney failure requiring renal replacement therapy [14–16]. In general, defining the prevalence of a condition requires accurate, reliable, and validated methods of disease ascertainment. Moreover, for comparison of disease prevalence among groups and throughout calendar periods, a standardized approach offers the best strategy for recognizing changing trends. Unfortunately, definitions used to define the presence of these conditions have varied widely, and the lack of a standardized approach in CAD and PVD ascertainment may have resulted in some variation.

The prevalence of clinical CAD among patients with newly diagnosed end-stage renal disease (ESRD) is between 38% and 40% [16]. In an analysis of 4025 patients from the Dialysis and Mortality and Morbidity Study (DMMS) Wave 2, Stack and colleagues [16] found that clinical CAD was present in 38% of patients who have new ESRD. In this study, CAD was defined as being present if patients had a history of coronary disease, myocardial infarction, or angina, prior angiography for CAD, abnormal angiogram or angioplasty, or coronary artery bypass grafting. Myocardial infarction was present in 14% and suspected in an additional 3%. Nineteen percent patients had a history of angina pectoris, and an additional 4% had suspected angina. Data from

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the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study found CAD present in 41.6% and myocardial infarction present in 18% [17]. Despite the lack of a standardized definition of CAD between these two separately administered studies, the similarity in prevalence rates is remarkable. Moreover, these values are also similar in magnitude to estimates derived from the Canadian Organ Replacement Registry (CORR) [18] and the Australian and New Zealand Organ Replacement Registries (ANZDATA) [15]. In general, rates are higher in older persons, diabetics, and those with coexisting cardiovascular conditions. An increasing prevalence of CAD at ESRD onset may be expected if current trends in ESRD incidence and prevalence prevail, but comprehensive analysis of longitudinal trends has not been performed. A preliminary comparison of CAD prevalence in the subjects enrolled in the Case Mix Severity Study (who had new ESRD at the study inception in 1986 and 1987) and those enrolled in DMMS Wave 2 found strikingly similar CAD rates (40% versus 38%), suggesting that burden of CAD has remained relatively stable at dialysis inception despite an aging dialysis population.

Despite the high prevalence of clinical CAD, the true estimate of CAD in this high-risk population, although undetermined, is probably substantially larger than estimates obtained from registry data or chart review. The average patient who reaches ESRD in the United States has a 42% probability of having diabetes, a 30% probability of having hypertension, and has an average age of 61 years, characteristics that are associated with silent coronary ischemia [19]. As a result, underestimation rather than overestimation of CAD prevalence using registry data is highly likely, and the true prevalence of CAD is almost certainly higher than estimates reported from these data. Indeed, a recent retrospective cohort by Gradaus and colleagues [20] found a strikingly high prevalence of angiographic CAD among 26 patients receiving maintenance dialysis. Of the entire cohort ($n = 26$), 65% had angiographic CAD, and 34% had at least two-vessel involvement. Even more alarming, 50% of the cohort demonstrated significant progression in disease, defined as the development of a hemodynamically significant stenosis of more than 50%. The availability of novel coronary screening methods such as electron beam CT may push this estimate even higher. Preliminary observations demonstrate a direct relationship between calcium scores and the

prevalence of atherosclerotic vascular disease [21]. Whether these scores are related to angiographically significant disease remains undetermined, however.

Peripheral vascular disease

PVD is increasingly recognized as an important contributor to adverse outcomes in patients who have advanced CKD [22–24]. Unfortunately, unlike CAD, epidemiologic studies describing the natural history of PVD are limited. Precise estimates of disease prevalence, again, are influenced by the underlying definition of PVD, which varies according to its clinical presentation. Defining patients who have PVD as those who had a prior diagnosis of PVD, amputation, intermittent claudication, or absent peripheral pulses, we have shown that 21% of newly diagnosed ESRD patients in the United States have clinical significant PVD using data from the DMMS Wave 2 study [16]. Among established hemodialysis patients, O'Hare and colleagues [22] reported similar prevalence (24%) using the same case-based definition. As before, a concern with these clinical definitions is the potential for the underestimation of true disease prevalence. Leskinen and colleagues [23] recently demonstrated that the prevalence of PVD might be as high as 30.6% among patients receiving maintenance dialysis when the ankle-brachial or toe brachial index measurements are included along with the standard clinical definitions as PVD indicators [23]. These estimates demonstrate the nontrivial magnitude of clinical PVD among patients who have advanced CKD and highlight the need for greater awareness, diagnostic strategies, and effective interventions.

Risk factors for coronary artery disease in patients who have chronic kidney disease receiving dialysis

Traditional Framingham-type risk factors do not explain the high prevalence of CAD among new dialysis patients (Table 1) [25–27]. These traditional factors typically include age, male gender, hypertension, diabetes, high total and low-density lipoprotein cholesterol, tobacco use, physical inactivity, and a family history of premature cardiovascular disease. Several studies have demonstrated that risk prediction equations derived from the Framingham study underestimate the burden of CAD disease in patients who have

Table 1
Traditional and nontraditional risk factors for coronary artery disease in chronic kidney disease

Traditional risk factors	Nontraditional (novel) risk factors
Nonmodifiable	Hyperhomocysteinemia
Advancing age	Elevated lipoprotein (a)
Male gender	Elevated fibrinogen
Modifiable	Low apolipoprotein A
Hypertension	Elevated inflammatory mediators
Diabetes mellitus	C-reactive protein
Elevated total serum cholesterol	Interleukin 6
Elevated low-density lipoprotein cholesterol	Oxidative stress
Low high-density lipoprotein cholesterol	Abnormal calcium/phosphate homeostasis
Tobacco use	Elevated calcium-phosphate product
Physical inactivity	Hyperphosphatemia
Family history of premature coronary disease	Malnutrition
	Albuminuria
	Dialysis modality

CKD [25–27]. These revelations have led to the development of several theories that may explain the large burden of CAD in these patients. First, traditional risk factors may not exert the same impact on coronary risk in the setting of CKD as they do in persons who have normal kidney function. Second, the presence of CKD may contribute additional atherogenic toxins or mediators that augment CAD risk above that imposed by traditional risk factors. These hypotheses currently are being explored by several investigators using data from large, community-based cohorts and from secondary analysis of large, randomized clinical trials [4,6,8,10].

Although many would agree that most of the Framingham risk factors increase the risk of CAD in the setting of CKD, conclusive evidence demonstrating these relationships is lacking. Cross-sectional analysis of data from the DMMS Wave 2 found strong associations between age, diabetes, and tobacco use with clinical CAD at ESRD initiation but failed to find any relationship between hypertension and serum cholesterol [16]. Similar findings were reported by the hemodialysis study group, raising the possibility that the patterns of association of known coronary disease risk factors with CAD may not be the same in CKD as in the general population [25]. At present, there is no conclusive explanation for these

findings, but confounding and effect modification of these relationships by other concurrent comorbid conditions present in advanced kidney failure is a strong possibility. More definitive studies using prospectively assembled cohorts to explain these associations are lacking. One particular study that has extended our understanding of these complex relationships in patients receiving dialysis is that by Parfrey and colleagues [28]. In addition to advancing age, diabetes, and diastolic blood pressure, these investigators found that echocardiographic abnormalities were strong independent predictors of de nova ischemic heart disease in a longitudinal cohort of 432 hemodialysis patients.

Of potential concern in many of the published studies is the lack of a significant association between serum cholesterol and hypertension and the clinical coronary disease outcomes [16,28]. More surprisingly, several published studies have demonstrated a reverse association between these well-established factors and coronary disease events, prompting a reassessment of the clinical importance of these factors in the setting of CKD [29,30]. An excellent illustration of these associations is that of serum cholesterol and mortality. Lowrie and colleagues [30] found that serum cholesterol levels varied inversely with mortality risk in a cohort of 12,000 hemodialysis patients. A step-wise increase in relative risk of death was seen for serum cholesterol levels lower than 200 mg/dL. These findings have prompted the search for alternative explanations, such as competitive risk from malnutrition, confounding, and effect modification by coexisting medical conditions, that might help explain these so-called “paradoxical relationships.”

Risk factors for coronary artery disease in the nondialysis chronic kidney disease population

Teasing out the independent contributions of established coronary risk factors and CAD in patients who reach ESRD is a difficult task. Unlike the general population that has normal kidney function, patients with ESRD represent highly selected populations, experience high rates of comorbid events, and undergo dialysis therapies that vary in technique and survival [14,31,32]. This constellation of factors makes it difficult, if not impossible, to elucidate the true association of known traditional risk factors with clinical CAD using standard epidemiologic approaches. More recently, studies have focused on patient groups

who have CKD but are not yet receiving dialysis, (potentially more homogeneous populations) to explore these relationships further.

Association of renal impairment with cardiovascular outcomes: a quantitative measure of traditional risk factor burden?

On of the most robust and consistent observations from several of the recently published studies is the strong, graded, independent association of elevated serum creatinine level or lower glomerular filtration rate with increased cardiovascular mortality [4–12]. These associations are arguably most evident in populations at high risk for cardiovascular events and are least evident in populations who have the least risk. In several of these studies, the associations of elevated serum creatinine levels with cardiovascular outcomes are independent of established traditional risk factors, suggesting that the observed relationships may be mediated entirely by novel or nontraditional factors. This conceptual framework may be flawed, however. Although worsening kidney function no doubt involves potential nontraditional risk factors, it may also involve components of traditional risk factors (severity or duration) that are not completely accounted for in the current definitions. For example, an elevated serum creatinine level may be more likely to indicate cumulative exposures of traditional risk factors such as hypertension and tobacco use and as a result provide a more quantitative measurement of these exposures than do single measurements. Accordingly, the strong association of elevated serum creatinine level and cardiovascular outcome may represent an indirect estimate of the cumulative effect of these traditional exposures on cardiovascular outcomes.

Contribution of traditional Framingham risk factors

Studies to date have not evaluated the simultaneous relative contributions of the so-called “traditional Framingham risk factors” and the nontraditional risk factors associated with clinical CAD in the setting of CKD. Defining and quantifying the contribution of each individual risk factor with vascular disease outcomes is a prerequisite for developing targeted interventional strategies and guiding public policy. For example, the claim that traditional risk factors impart the greatest risk in the CKD setting would be strengthened if it were shown (1) that the

prevalence of these factors increases with progressive decline in kidney function, (2) that each factor contributes independently to increased cardiovascular risk, and (3) that the magnitude of cardiovascular risk is greatest for those with the worst kidney function. Analysis of cross-sectional data at the population level has revealed that hypertension, impaired glucose tolerance, and tobacco use increase with declining kidney function, supporting the notion that these factors may contribute to the excess burden of CAD [33–35]. For example, Ejerblad and colleagues [33] have recently demonstrated a strong association between tobacco use and the likelihood of CKD in a population-based, case-control study involving 1924 subjects. The odds of CKD, defined as a serum creatinine level higher than 3.4 mg/dL on at least two consecutive occasions, was increased in subjects who had smoked more than 20 cigarettes/d for at least 40 years’ duration or who had a 20 pack-year history, as compared with controls. It is unclear, however, whether the same association exists between other traditional risk factors (such as hypercholesterolemia and its associated conditions, physical inactivity and obesity) and the likelihood of CKD. Second, although an increasing prevalence of traditional risk factors with declining kidney function suggests an augmentation of overall cardiovascular risk, it is by no means conclusive. The evidence would be stronger if independent associations were demonstrated between each traditional risk factor and coronary disease in patients who have reduced kidney function. Finally, definitive evidence linking traditional risk factors with CAD would require prospectively designed studies that illustrate an independent association of each factor with CAD and show that the associated risks increase in magnitude with worsening kidney function.

Contribution of nontraditional risk factors

The enormous burden of CAD among patients who have CKD is a perplexing observation that has led many to believe that nontraditional factors, accumulating in the setting of declining kidney function, exert a sizable impact [2,36]. Several inflammatory, thrombotic, and metabolic cardiovascular risk factors have been implicated as important contributors to the excess CAD burden in the CKD setting [37–43]. To date, however, no single study has demonstrated beyond doubt that any one or any combination of

these risk factors is causally involved in the acceleration of coronary disease in the CKD setting. Nonetheless, emerging data from several cross-sectional and prospective cohorts, regional or national in scope, have provided supportive evidence linking nontraditional factors with vascular disease in CKD.

Muntner and colleagues [37] have recently reported on the relationship of several inflammatory and novel cardiovascular risk factors with CKD (defined as a glomerular filtration rate of less than 60 mL/min/1.73m² based on the modified Modification of Diet in Renal Disease Study Formula equation) using data from the third National Health and Nutrition Examination Survey. As renal function decreased, levels of homocysteine, lipoprotein (a), fibrinogen, and C-reactive protein increased, while levels of apolipoprotein (a) decreased. Their findings are in agreement with several other smaller-center cohorts that have shown abnormally increased levels of these nontraditional factors in persons with CKD [38–40]. Similarly, Shlipak and colleagues [41] found strong independent correlations between several inflammatory and procoagulant markers and decline in renal function using baseline data from the Cardiovascular Health Study. In this study, higher levels of C-reactive protein, fibrinogen, interleukin-6, factor VII-c, factor VIII-c, plasmin–antiplasmin complex, and D-dimer were significantly associated with worsening kidney disease among individuals aged 65 years and older. These findings have been reproduced by other investigators and add to a growing body of literature demonstrating the presence of increased inflammation, oxidant stress, and impaired hemostatic function in persons who have CKD [42,43].

Although the cross-sectional data are interesting and suggestive, they are no substitute for prospectively designed epidemiologic studies. In fact, few published studies have investigated associations of nontraditional factors with coronary events in longitudinal cohorts. By far the most widely studied nontraditional factor is homocysteine, a sulfur-containing amino acid with putative thrombotic properties [44–51]. The increased thrombotic risk conferred by increased homocysteine levels in persons with homozygous genetic traits is undisputed, and pooled analysis of observational cohorts in the general population has suggested elevated homocysteine levels also confer increased cardiovascular risk [45–47]. Despite these observations, a reduction in coronary events with homocysteine lowering has not

been confirmed in clinical trials, although the results from several large-scale, randomized clinical trials are awaited [48]. Homocysteine levels increase in a dose-dependent fashion with declining kidney function, however. Furthermore, prospective studies of persons with CKD of varying degrees have identified an elevated homocysteine level as an independent risk factor for future coronary events [49–52]. Some have interpreted these findings as suggesting a more pathogenic role for homocysteine among persons who have reduced kidney function as compared with those who have normal kidney function. Whether this hypothesis can be confirmed in randomized clinical trials remains to be seen. The currently funded NIH FAVORIT trial in transplant recipients is a first step in answering this question (www.clinicaltrials.gov/ct/show/NCT00064753).

Risk factors for peripheral vascular disease in the general population

The epidemiology of PVD in CKD patients has received far less attention than that of CAD, and consequently the ability to develop risk factor profiles is reduced. Nevertheless, given the pathophysiologic similarities between PVD and CAD, it is likely that factors operating in one disease process are also important in the other. Risk factor profiles generated from longitudinal cohorts in the general population suggest that many, if not all, of the traditional coronary risk factors are also risk factors for development of PVD [53–56]. A recent review by Belch and colleagues [53] acknowledges the importance of several of these factors including advancing age, male gender, diabetes, hypertension, smoking, and hyperlipidemia. The relative importance of several novel risk factors such as lipoprotein (a), von Willebrand's factor, tissue plasminogen activator, and fibrin D-dimer has been demonstrated by investigators from the Edinburgh Artery Study [54,55]. Ridker and colleagues [56,57] demonstrated the independent predictive values of C-reactive protein and apolipoprotein-B 100 in the Physicians' Health Study, a prospective, randomized trial of aspirin and beta-carotene in the primary prevention of cardiovascular disease and cancer.

Risk factors for peripheral vascular disease in the chronic kidney disease population

Whether factors that predict PVD development in the general population are also predictive

in patients who have CKD is not fully understood. O'Hare and colleagues [58] found that advancing age, diabetes, and elevated systolic blood pressure were significantly associated with the risk for future amputations, as was a prior history of PVD in an analysis of 8633 patients receiving maintenance dialysis. Moreover, she demonstrated a gradient of risk with increasing serum phosphorus concentration, suggesting a further role for abnormal mineral metabolism in vascular disease development or progression. Taken together, population studies of CAD and PVD in patients receiving dialysis suggest that these vascular conditions have a similar natural history, with contributions from both traditional and nontraditional coronary risk factors.

To our knowledge, the contribution of novel cardiovascular risk factors to PVD development has not been evaluated in patients who have CKD but are not undergoing dialysis; however, a further study from the O'Hare group has provided useful insights [59]. Using data from the Heart and Estrogen/Progestin Replacement Study, they demonstrated a strong, graded, independent association of reduced kidney function with the risk of lower extremity vascular disease among postmenopausal women who have established CAD. The similarities between this study and those that have evaluated associations of reduced kidney function with other cardiovascular disease outcomes highlight the tremendous impact of reduced kidney

function on vascular outcomes, irrespective of location.

Outcomes of coronary artery disease and peripheral vascular disease in persons who have chronic kidney disease

Peripheral vascular disease

The impact of PVD on morbidity and mortality has been well described in persons who have ESRD and are receiving maintenance dialysis and, to a lesser degree, in persons who have varying levels of CLKD not requiring dialysis [60–63]. Multivariable analyses of incident dialysis cohorts from the United States Renal Data System (USRDS) have repeatedly demonstrated the independent predictive value of PVD on all-cause mortality [14,31,32]. Patients who present for dialysis because of new ESRD and who have a diagnosis of PVD from medical records experience a 66% higher crude mortality risk compared with those without PVD [31]. Moreover, with adjustment for established mortality predictors, PVD still carries a 37% higher adjusted mortality risk (Fig. 1). A more focused study by Eggers and colleagues [60] based on Medicare data from the USRDS database has permitted a quantitative assessment of the outcomes after lower extremity amputations in this high-risk population. In an analysis of 24,886 patients who experienced

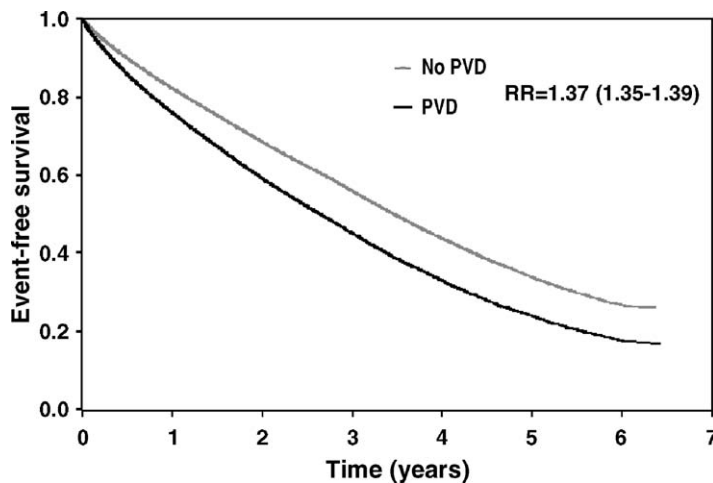


Fig. 1. Adjusted survival curves for new patients who had end-stage renal disease with and without peripheral vascular disease (PVD) in the United States who began dialysis between 5/1995 and 12/2000 and were followed until 2001. Relative risk (RR) is adjusted for age, gender, and race. (Adapted from Stack AG, Molony DA, Rahman SN, et al. Impact of dialysis modality on survival of new ESRD patients with congestive heart failure in the United States. *Kidney Int* 2003;64:1071–9.)

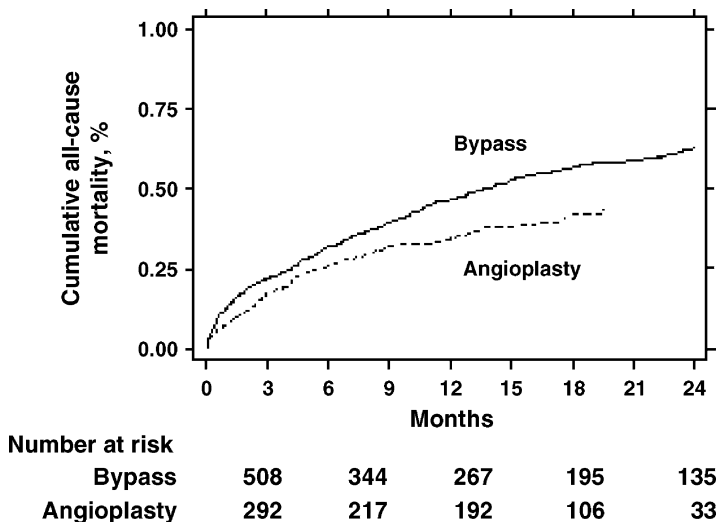


Fig. 2. Cumulative mortality of patients who have peripheral vascular disease after undergoing initial surgical bypass or percutaneous transluminal angioplasty (From Jaar BG, Astor BC, Berns JS, et al. Predictors of amputation and survival following lower extremity revascularization in hemodialysis patients. *Kidney Int* 2004;65:617; with permission.)

35,898 first amputations between 1991 and 1994, the overall survival at 2 years was 32.7%, compared with a survival of 63.2% for the entire ESRD dialysis population. For patients who experienced a toe-level amputation, the survival rates at 30 days, 90 days, and 2 years were 95.2%, 85.4%, and 44.8% respectively. For those with a below-knee amputation, survival rates were 89.6%, 75.2%, and 31.7%, respectively. For

patients who underwent an above-knee amputation, rates were lowest, at 76.3%, 52.7%, and 15.2%, respectively. The mortality risks were 37% higher for patients who underwent a below-knee procedure and more than twofold higher for those who underwent an above-knee amputation compared with those who had a toe-level procedure.

Although the prognostic impact of peripheral arterial disease (PAD) on mortality is well

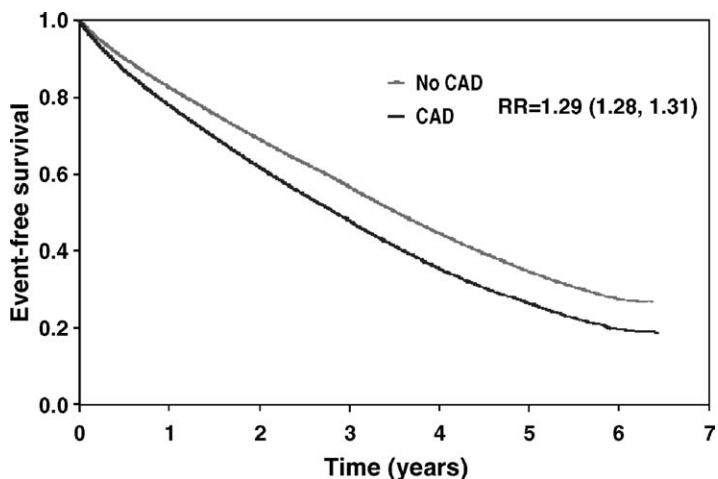
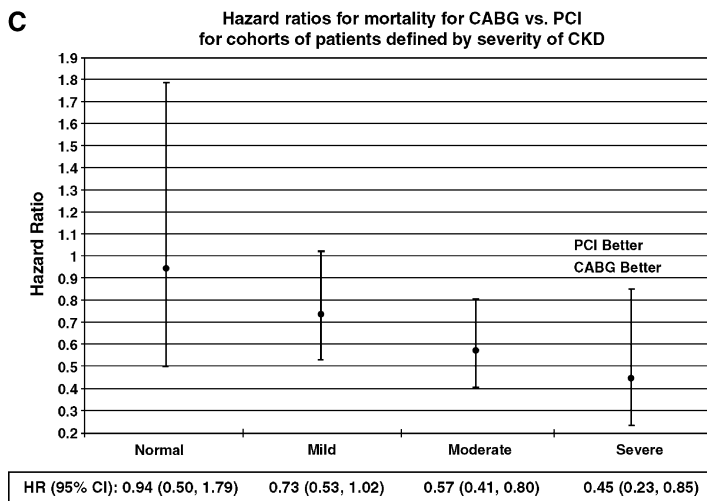
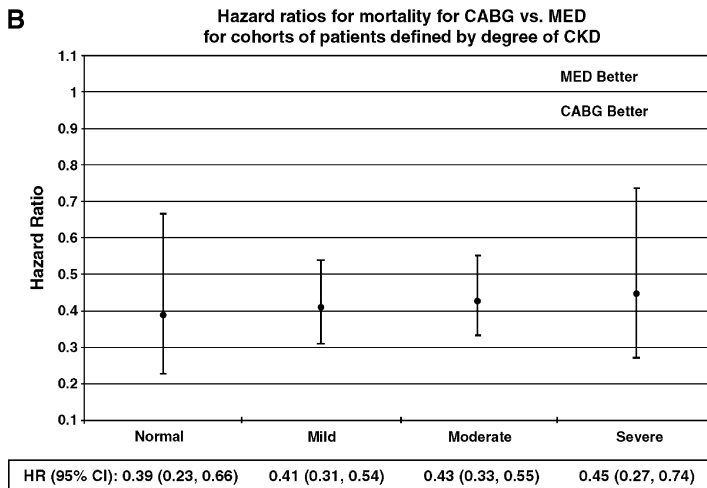
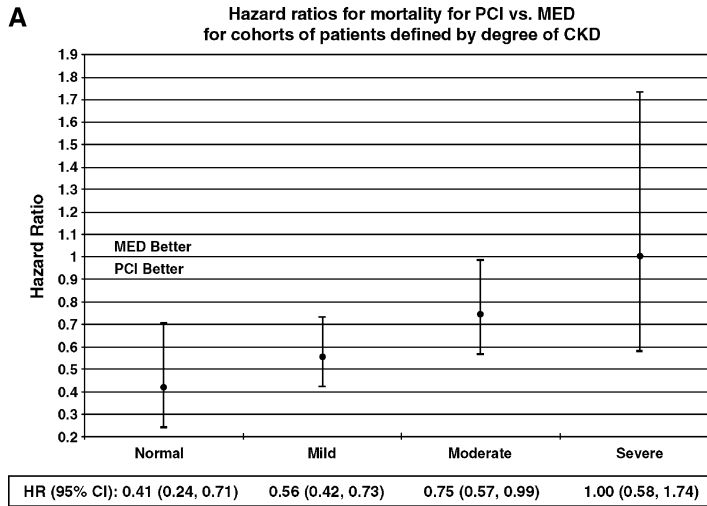


Fig. 3. Adjusted survival curves for new patients who have end-stage renal disease with and without coronary artery disease (CAD) in the United States who began dialysis between 5/1995 and 12/2000 and were followed until 2001. Relative risk (RR) is adjusted for age, gender, and race. (Adapted from Stack AG, Molony DA, Rahman SN, et al. Impact of dialysis modality on survival of new ESRD patients with congestive heart failure in the United States. *Kidney Int* 2003;64:1071-9.)



established, the relative benefits of different therapeutic interventions in these patients are less well studied. For example, one key question might be whether in patients who have severe lower extremity PAD outcomes after arterial bypass procedures are better than after angioplasty. Unfortunately, clinical trial data comparing these therapies in patients who have ESRD are not available, even in the general non-ESRD population. The recent work of Jaar and colleagues [64], however, has provided useful insights into the outcomes of patients who have ESRD and who have PAD requiring revascularization intervention. In a comparative analysis of 508 bypass surgeries and 292 angioplasties from the USRDS database, they found that the mortality risks of patients who underwent a first lower extremity bypass were more than fourfold higher than those of patients who underwent angioplasty, a difference that persisted after adjusting for case mix (Fig. 2). As the authors acknowledge, unmeasured baseline differences between the groups, such as severity of angiographic disease or duration of disease, could have accounted for these results given the observational, nonrandomized study design. The clinical benefits of other pharmacologic and nonpharmacologic measures for PAD management are yet to be tested in this population. The high prevalence of traditional cardiovascular risk factors in this population almost certainly contributes to the development and progression of PAD, suggesting that targeted efforts should be directed to the optimal management of these factors in patients who have ESRD, as in the general population. Furthermore, the accumulating body of evidence linking hyperphosphatemia, elevated calcium-phosphate product, and hyperparathyroidism with increased vascular disease burden and vascular-related mortality cannot be ignored; the mortality benefits of specific therapies to control these derangements need further evaluation [65–67]. Given the high prevalence of PAD, with its attendant morbidity

and mortality, in this population, it is perplexing that clinical trials are sparse.

Coronary artery disease

The optimal strategies for the management of CAD in patients who have CKD are yet to be defined. The clinical evidence favoring one or more treatment strategies has been gleaned thus far from analysis of observational cohorts with additional supportive evidence coming from secondary analysis of existing clinical trials. It has not been demonstrated that pharmacologic treatments or interventional cardiovascular procedures with proven efficacy in the general population are also effective in CKD cohorts, and such extrapolation must be viewed with caution. For many established therapies with established efficacy in the general population, it is unclear whether the therapeutic effect on outcomes is modified by the presence of renal impairment and, if so, to what degree.

Most clinical trials to date evaluating treatments for acute coronary syndromes (ACS) have excluded patients who have renal impairment at study entry [68–74]. Accordingly, it is unclear whether treatment strategies used in the management of ST segment elevation myocardial infarction (STEMI) or non-STEMI ACS are equally effective in CKD cohorts. Several major trials have demonstrated the clinical efficacy of thrombolytic agents, such as streptokinase and alteplase, and of platelet glycoprotein IIb/IIIa inhibitors, including abciximab, eptifibatide, and tirofiban, in the management of ACS in the general population. Unfortunately, in most studies subgroup analyses to evaluate therapeutic potential in persons with reduced renal function were not performed. Recent post hoc analyses of two large, randomized clinical trials, however, did not demonstrate any interaction between the level of renal impairment and glycoprotein IIb/IIIa inhibitors with respect to the primary end point, suggesting

Fig. 4. (A) Hazard ratios for mortality for medical (MED) management versus percutaneous coronary artery intervention (PCI) for cohorts of patients defined by severity of chronic kidney disease (CKD) (adjusted). (B) Hazard ratios for mortality for medical management (MED) versus coronary artery bypass grafting (CABG) for cohorts of patients defined by severity of chronic kidney disease (CKD) (adjusted). (C) Hazard ratios for mortality for coronary artery bypass grafting (CABG) versus percutaneous coronary artery intervention (PCI) for cohorts of patients defined by severity of chronic kidney disease (CKD) (adjusted). (From Reddan DN, Szczech LA, Tuttle RH, et al. Chronic kidney disease, mortality, and treatment strategies among patients who have clinically significant coronary artery disease. *J Am Soc Nephrol* 2003;14:2378; with permission.)

that the efficacy of these agents in patients who have CKD is equivalent to that of the general population [74,75]. An additional consideration in the use of these agents in persons who have ACS and renal impairment is whether the increased risk of bleeding is offset by therapeutic benefit in reducing ACS complications. What is clear from existing studies is that patients who present with ACS and who have coexisting renal impairment at baseline experience significantly higher mortality rates than those without renal impairment [76].

Whether the therapeutic benefits of aspirin, beta-adrenergic blockers, and statins in preventing cardiovascular events in the general population extend to patients who have CKD has not been firmly established [77–79]. Although results are conflicting, prospective cohorts and secondary analyses of clinical trials suggest that the clinical benefit of these agents in reducing cardiovascular events among patients who have ACS or prior CAD may be similar to that seen in the general population [78–80]. The limited availability of clinical trial data on secondary prevention of coronary events in advanced CKD patients has led to increased mining of large registries to assess cardioprotective associations. From these efforts, three points are worth noting. First, the use of known cardioprotective medications among new dialysis patients is abysmally low and warrants investigation. Second, calcium-channel blockers and 3-hydroxy-3-methyl-glutaryl coenzyme-A inhibitors seem to offer cardioprotection in new dialysis patients who have pre-existing cardiovascular disease [81,82]. Third, analysis of cohort data to evaluate an association between the use of cardioprotective medication and cardiovascular outcomes may be flawed, because the indication for medication use is likely to confound observed associations [83].

A diagnosis of CAD at dialysis initiation predicts significantly reduced patient survival (Fig. 3). During the past decade, controversy has existed as to the optimal revascularization strategy for patients who have CKD [84–89]. A recent study by Herzog and colleagues [90] in more than 15,784 dialysis patients found significantly better overall survival among those who were treated with coronary artery bypass surgery (CABG) as compared with percutaneous transluminal angioplasty (PTCA) or stent placement. Overall all-cause mortality was 20% lower, and cardiovascular mortality was 28% lower among patients in the CABG group versus those treated with PTCA. The mortality risks of stent placement

were also better than for PTCA; however, this benefit was mainly confined to nondiabetics. These findings have confirmed and have extended the observations of several other groups in demonstrating the benefit of CABG over PTCA and stent placement, at least in observational studies [84–89]. The question of confounding by selection bias will always remain, because patients who undergo CABG are likely to have more severe disease and to have higher overall cardiovascular risk than those treated with PTCA.

An equally interesting question is whether the advantage of CABG observed in ESRD cohorts extends to those with less severe renal impairment. The recent observations of Reddan and colleagues [91] from the Duke Cardiovascular Database have provided useful insights in this area. Comparisons of CABG with percutaneous coronary intervention or medical therapy alone yielded significant benefits in favor of CABG (Fig. 4). This benefit was observed in almost all stages of CKD, with one exception. Patients who have angiographic CAD who were classified as having normal kidney function had similar survival with either CABG or medical therapy. Furthermore, those who underwent percutaneous coronary intervention experienced significantly better survival than those who received medical therapy alone, except for those who had severe CKD. Again, although the potential for selection bias and indication bias exists in mortality comparisons of this nature, some messages are clear. First, the survival advantage of CABG over PTCA is consistent from several studies. Second, the impact of percutaneous coronary interventions and medical therapies on outcomes varies by level of renal function and highlights the need for randomized comparisons of these therapies.

Summary

The enormous burden of CAD and PVD in patients who have CKD contributes substantially to increased morbidity and mortality. The increased risk of vascular disease observed in CKD patients is likely to be multifactorial, with contributions from traditional and nontraditional cardiovascular factors. Given the overwhelming evidence on the known benefits of cardioprotective medications, their underuse remains puzzling in a population at enormous risk. During the past 5 years, the research community and national interest groups have made significant progress in

organizing a concerted approach to improve the management of patients who have CKD and vascular disease. Much work remains to be done. The development of national guidelines in the management of these patients at high risk for future cardiovascular events will be a welcome step. The evaluation of multitargeted interventions for reduction of cardiovascular risk through randomized clinical trials is desperately needed. Finally, the low use of known cardioprotective strategies in this high-risk group is a serious issue and warrants immediate attention at local and national levels.

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