Kidney-Heart Interactions: Epidemiology, Pathogenesis, and Treatment

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Heart disease accounts for approximately half of the deaths of patients with ESRD (1–3). In the past 5 yr, there has been increasing recognition of both coronary artery disease (CAD) and left ventricular hypertrophy (LVH) in ESRD patients, as these are the two typical presentations of heart disease in ESRD patients. It is also clear that many patients with chronic kidney disease (CKD) and a GFR of <60 ml/min are at risk for heart disease; many of these patients succumb to heart disease before reaching dialysis (4–6). This review includes a brief overview of the problem, a discussion of CAD and LVH, and an examination of the benefits of reducing BP and proteinuria on both the heart and the kidney and concludes with a brief section on treatment options for individuals with this disorder.

Overview of the Problem of Cardiovascular Disease in Patients with Kidney Disease

A growing awareness of heart disease in individuals with kidney disease as a major public health concern has increased sharply because of the revelation that there are millions of Americans with reduced kidney function (2). This fact, coupled with the understanding that many individuals with CKD do not reach dialysis because they die of heart disease (6), has expanded the concern about heart disease in both patients with CKD and patients with ESRD. Of interest is that whereas many superb prospective, randomized clinical trials have defined the scope of the appropriate therapy for heart disease in patients with normal kidney function, relatively few trials have addressed the issue in patients with kidney disease. Thus, the literature on cardiovascular disease (CVD) has focused on individuals without kidney disease, and guidelines regarding the management of heart disease in patients with ESRD in CKD, therefore, are largely opinion based (7).

The two clinical presentations of heart disease in patients with kidney disease are atherosclerotic vascular disease (particularly CAD) and LVH. Atherosclerosis has been known to be a particular problem in patients with ESRD for >25 yr since Lindner *et al.* (8) hypothesized that there was accelerated atherogenesis in patients with ESRD. In the Lindner study, 60% of a cohort who underwent dialysis for 6.5 yr died and 14 of these deaths were attributed to complications of atherosclerosis. Subsequent postmortem and angiographic studies confirmed that the prevalence of atherosclerosis is increased dramatically in patients who are on dialysis when compared with age-matched individuals without kidney impairment (9–13). Of note, this increase in atherosclerosis and, in particular, CAD is progressive over a range of reduced GFR. This has been shown by Anavekar *et al.* (5) and by Beddhu *et al.* (14). The major increase in risk for heart disease and death occurs at a GFR of <50 to 60 ml/min (5,14) (Figure 1). A major problem with the issue of coronary disease is that in many patients, there is a high burden of coronary disease despite that the patient is asymptomatic. In a recent study by deFilippi *et al.* (15), 44% of a large cohort of asymptomatic hemodialysis patients had significant coronary disease. This was confirmed recently by Ohtake *et al.* (16), who showed that coronary disease (defined as >50% stenosis in the coronary artery) was present in as many as 53% of a cohort of asymptomatic dialysis patients.

A second presentation of heart disease in this patient population is LVH. It is particularly important to understand this disorder in dialysis patients because as many as 80% of an incident dialysis population will have LVH as they begin dialysis (17). Individuals with LVH have both eccentric and concentric hypertrophy (18,19). Eccentric hypertrophy results from volume overload leading to cardiac myocyte dropout; LVH is characterized by a myocyte to arteriolar capillary mismatch. Concentric hypertrophy typically is the result of hypertension and increased afterload and is exacerbated by anemia, hyperparathyroidism, and high angiotensin II concentrations. Eccentric and concentric hypertrophy are relatively equivalent in prevalence in dialysis patients.

The dominant LV physiology that accompanies heart disease in patients who are on dialysis is that of diastolic dysfunction (17,19). This physiology results in a sharp increase in LV diastolic pressure with modest increments in LV volume; the implication of the physiology is that patients have a lower threshold to pulmonary edema under these circumstances (Figure 2). Conversely, patients who undergo ultrafiltration on dialysis can experience a sharp fall in LV diastolic pressure under circumstances of a modest volume reduction, thereby risking sudden hypotension and hemodynamic instability. Patients with LVH also often have a reduction in systolic function,

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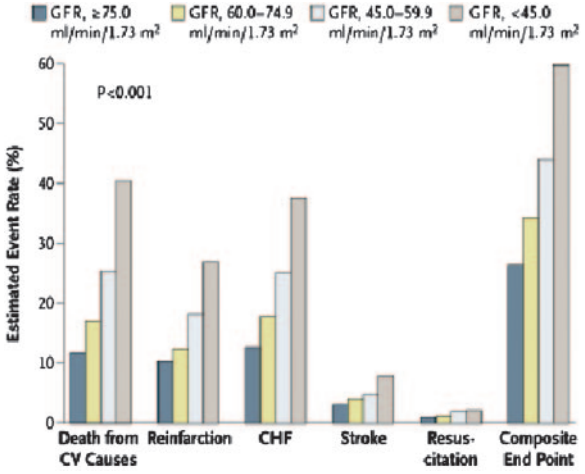

Figure 1. Kaplan-Meier estimates of the rates of death at 3 yr from cardiovascular (CV) causes, reinfarction, congestive heart failure (CHF), stroke, resuscitation after cardiac arrest, and the composite end point, according to the estimated GFR at baseline. From reference (5).

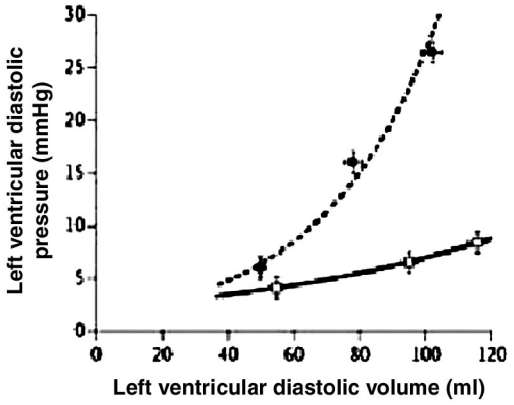

Figure 2. Diastolic pressure-volume relation in patients with diastolic heart failure and in control subjects. From reference (19). ---, Diastolic heart failure; —, control.

and the presence of this abnormality also exposes patients to the risk for sudden CV death (20).

Cardiac arrhythmias and cardiac deaths are common in dialysis patients of all ages but are particularly problematic in patients who are older than 65 yr (21). There are many potential reasons for the problem of sudden death: Abnormalities in the coronary microcirculation; impaired coronary reserve; reduced aortic compliance; increased activity of the sympathetic nervous system; the increased plasma concentration of angiotensin II; and sudden changes in the concentrations of potassium, calcium, and magnesium (which occur normally during dialysis) all can contribute to this problem. Another recent contributor to the problem of sudden death in this patient population may be related to the degree of fibrosis in the hearts of individuals on dialysis (22). In a recent study by Aoki *et al.* (22), myocardial biopsies revealed abnormal cardiac myocyte anatomy and an interposition of dense fibrosis in the hearts of individuals who were on dialysis. Individuals with a higher fibrosis score had a shorter survival than individuals with a lower fibrosis score, suggesting that the presence of dense fibrosis denotes intrinsic myocardial damage and lowers the threshold for arrhythmias.

In the aggregate, then, both CAD and LVH contribute to CV mortality in the dialysis population that dramatically exceeds that of the general population. This has been demonstrated in several recent publications and represents the major challenge for physicians who treat such patients. Figure 3 depicts this increase in CV mortality that occurs in this patient group graphically.

Causes of Coronary Disease and LVH in CKD/ESRD

A comprehensive discussion of all of the causes of heart disease in patients with CKD and ESRD is beyond the scope of this communication. This section provides a brief overview of several current issues that are relevant to the problem.

It is known that patients with kidney disease have a high prevalence of other disorders that independently are associated with poor CV outcomes. For example, the high prevalence of diabetes in any CKD/ESRD cohort, the presence of hypertension in virtually all of the patients, the presence of LVH by electrocardiogram or echocardiography in the great majority of patients, that most patients have reduced physical activity and low exercise tolerance, that many patients have a lower-than-ideal HDL cholesterol concentration, that there is high oxidant stress in this group of individuals, and that many individuals have a high concentration of inflammatory biomarkers all contribute to the high prevalence of heart disease in this group. It should be acknowledged that patients in this group do have a lower prevalence of some traditional CV risk factors. For example, this group of patients is less typically obese, uses tobacco less frequently, and has less hypercholesterolemia (lower LDL levels) than the general population. Figure 4 is a schematic depiction of how many of the factors that contribute to heart

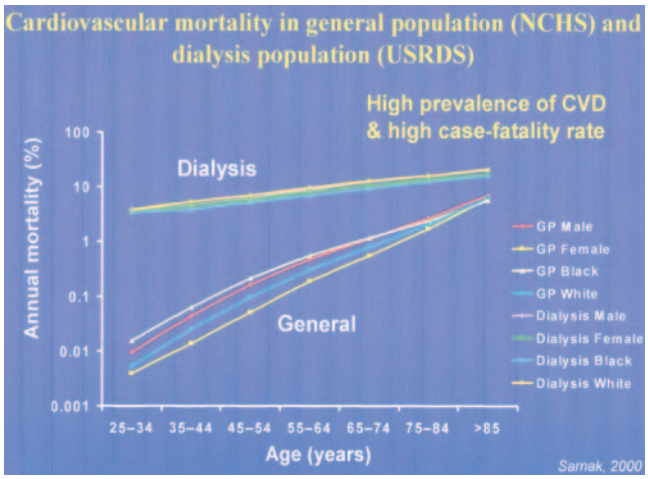

Figure 3. Cardiovascular mortality in general population (NCHS) and dialysis population (USRDS). Sarnak 2000 KI 58: 1758, 2000

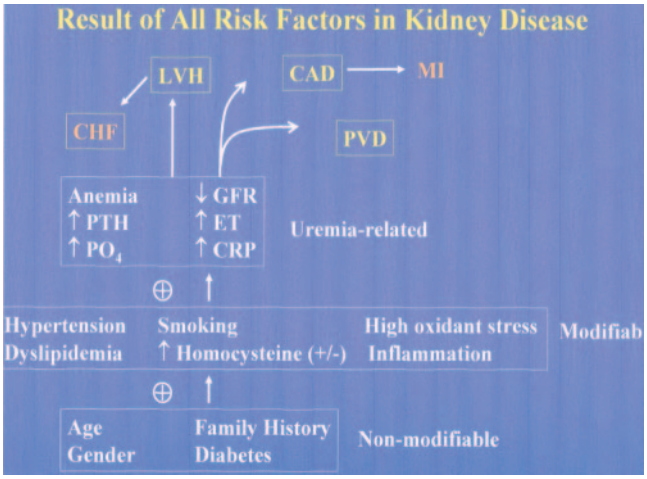

Figure 4. Risk factors that contribute to heart disease in patients with kidney disease.

disease in patients with kidney disease could result ultimately in LVH and CAD in patients with CKD and ESRD. A number of modifiable risk factors cited above are present in this patient group. Several uremia-related factors may also contribute to the problem; for example, anemia contributes to LVH, and a high calcium/phosphorus product will reduce aortic compliance that leads to an increased pulse wave velocity and an additional burden on the left ventricle. Vasoactive peptide concentrations (*e.g.*, with endothelin and angiotensin II) are elevated and act as potent vasoconstrictors that exacerbate coronary vasoconstriction. The net result of all of these factors is an increased prevalence of coronary disease and LVH in this patient group.

With regard to coronary disease in patients with ESRD, it is increasingly apparent that increased oxidant stress and inflammation are present, and this is reviewed in the following section. A number of nontraditional factors for coronary disease have also been identified in patients with CKD/ESRD. Hyperhomocysteinemia is associated with poorer survival in patients with coronary disease in the dialysis population (23). Recent studies on the ability of folic acid to lower the CV event rate by lowering homocysteine concentrations in patients with ESRD have been disappointing (24). For example, a recent study that used high-dose folic acid in 510 patients and had a mean follow-up of 24 mo did not detect any effect of folic acid on event-free survival (24). New prospective studies on this subject are under way and should reveal some insight into the best management of this problem.

Another area of growing interest and focus has been the heightened recognition that arterial calcification in coronary vessels is very common in patients with CKD and ESRD (25,26). There is currently a debate over whether the calcification in coronary vessels that is detected by electron beam tomography (EBCT) in patients with CKD/ESRD denotes intraluminal narrowing of these vessels. Much of the calcification in these coronary vessels of patients with uremia resides in the media of the vessel, which does not result in intraluminal narrowing of the vessel. A recent study suggested that the calcification score of vessels obtained did not correlate with the severity of vessel stenosis by coronary angiography (27). However, another recent study suggested that the calcium score that is obtained by EBCT is reliable in defining the number of coronary vessels involved in an ESRD population (28).

It is clear that the process of calcification in the coronary bed and other vascular beds is complicated; one new recently proposed factor that may have a major role to play in this calcification scheme is a substance called fetuin-A, which inhibits the mineralization of vascular smooth muscle cells both *in vitro* and *in vivo* (29). Even if the calcification of coronary vessels is not linked directly to intraluminal narrowing in patients with CKD and ESRD, the increased vascular stiffness in the aorta increases pulse pressure, which, in turn, results in increased afterload and the burden of cardiac work (30). An increase in pulse wave velocity occurs as renal function decreases, suggesting that there is a continuum of an increased burden on the heart as renal function declines (30). In summary, vessel calcifications are common in patients with CKD and ESRD, particularly in the coronary vascular bed. Having coronary vessel calcifications on EBCT denotes a poorer prognosis than not having them, but there is still controversy over the degree of coronary luminal narrowing that can be ascribed to these calcifications in this patient group.

Another subject of recent interest and study with regard to the cause of coronary disease has been the role of oxidant stress. In this regard, the accumulation of asymmetric dimethyl arginine has been shown to be a potent inhibitor of nitric oxide synthesis in endothelial cells (31). More problematic is the issue of whether antioxidant therapy can reduce CV events in patients with ESRD. In this regard, a recent study in which 134 patients who were on hemodialysis were followed for 14 mo received the potent antioxidant N-acetylcysteine (NAC; 600 mg twice daily) or a placebo. The primary end point in the study was a composite of myocardial infarction, CV death, coronary angioplasty, coronary artery bypass grafting, ischemic stroke, peripheral vascular disease, or peripheral vascular disease with amputations. The result of the study was mixed; 28% of the individuals in the NAC group reached one of the end points *versus* 47% of the individuals in the control group ($P < 0.03$) (32). However, for individual end points such as cardiac death, ischemic stroke, and peripheral vascular disease, there was no difference in the groups.

Finally, there is increasing interest as to whether biomarkers can predict individuals who are at particular risk for CV death in the setting of CKD or ESRD. deFilippi *et al.* (15) suggested that a combination of high C-reactive protein cardiac troponin-T levels not only predicts CV death in patients with ESRD but also identifies the subpopulation of patients with ESRD and multivessel coronary disease (15) (Figure 5). Similarly, the use of N-terminal pro brain natriuretic peptide levels may have some utility in predicting outcome in patients with ESRD as well (33). As more pathophysiologic factors of importance are identified for LVH and coronary disease and more biomarkers are linked to these processes, it is likely that there will be an array of screening tests that will identify a particular patient's particular risk for a CV death.

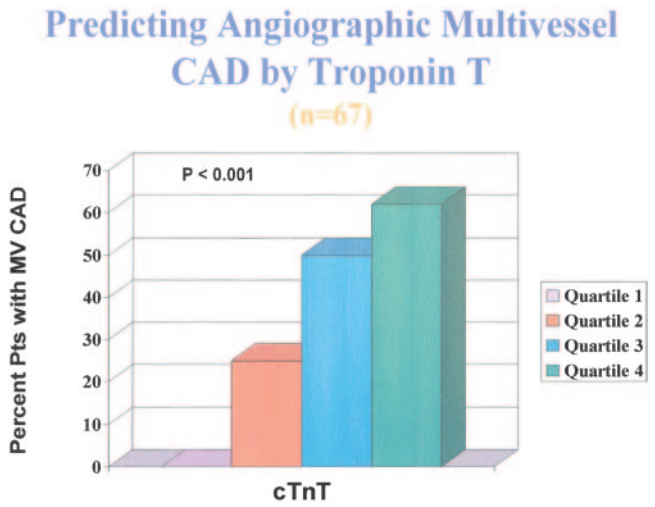

Figure 5. Predicting angiographic multivessel coronary artery disease (CAD) by troponin T ($n = 67$). From reference (15).

Can Both Heart and Renal Disease Be Affected Favorably by Lowering of BP, Inhibition of the Renin Angiotensin System, and Lowering of Urinary Protein Excretion?

Given that the prevalence of impaired kidney function continues to increase (34) in the context of higher BP and proteinuria (35,36), the question arises as to whether therapies that are directed at these abnormalities yield both a cardiac and a renal protective effect. This cardio–renal relationship is particularly evident in individuals with diabetes (37–39), a population of patients that accounts for the greatest proportion of the CKD/ESRD group (40). This section reviews the possibilities that interventions aimed at lowering BP *via* the inhibition of the renin-angiotensin system (RAS) and lowering protein excretion may be beneficial to both heart and kidney function.

Is Lowering BP Equally Cardio- and Renoprotective?

A large number of studies have repeatedly confirmed that treatment of increased BP decreases both cardiac and particularly cerebrovascular events in patients with diabetes (41–44) as well as those without diabetes (45,46). Such an effect of lowering BP is also one of the primary findings of a large meta-analysis that was performed by the Blood Pressure Lowering Treatment Trialist Collaboration that concluded, "Any commonly used regimen reduces the risk of total CV events and larger reductions in BP produce larger reductions in risk" (47). A similar protection afforded by decreasing BP on the progression of renal disease emerged from the analysis performed by Bakris *et al.* (48), who found a significant ($P < 0.05$) relationship between the achieved mean arterial pressure in 10 trials that were performed in patients with diabetes and the rate of decline in GFR in the same trials. The trials that demonstrated CV protection in individuals with diabetes were performed predominantly or almost exclusively in patients who had little or no underlying renal disease. Because the presence of renal disease *per se*, as noted above, imparts an added risk, it is unclear whether the results of those trials can be readily extrapolated to patients with impaired renal function. Furthermore, although target BP have been lowered progressively, it is not clear which component of the BP is important and whether the optimal BP is the same for the heart as it is for the kidney. In this regard, most CV trials have scant renal end points, and, conversely, renal trials are frequently devoid of CV outcome data. Recent trials in patients with overt diabetic nephropathy (49,50) monitored both renal and CV events, allowing perhaps for the first time the assessment of the effect of BP reduction on the CV and renal systems in the same patient population.

An analysis of the effect of achieved BP in the Irbesartan Diabetic Nephropathy Trial (IDNT) (51) sheds some light on the question at hand. This trial is a double blind, randomized, placebo-controlled trial performed in 209 clinics worldwide in patients with overt diabetic nephropathy (urinary protein >900 mg/24 h) and a serum creatinine concentration up to 3.0 mg/dl. Of the 1715 patients enrolled in the trial, 1590 had at least a 6-mo follow-up. In this group of patients, over a mean follow-up period of 2.6 yr, an average of eight BP were available per patient. As is depicted in Figure 6, the relative risk (RR) for reaching a renal end point (doubling of serum creatinine or ESRD, grouped by 10-mmHg increments) reveals that the risk progressively decreases as achieved systolic BP (SBP) decreases from 180 to 120 mmHg. The group below 120 mmHg did not have a risk substantially different from that of the 121- to 130-mmHg cohort. A 20-mmHg decrement in SBP was associated with a 47% risk reduction for developing a renal end point. Furthermore, achieved SBP is an independent risk factor for adverse renal outcomes, independent of the baseline SBP (51). These effects of SBP to slow progression of renal disease were also described in a trial of individuals without diabetes (52) but were not observed in the African American Study of Kidney Disease and Hypertension (AASK) trial of black individuals

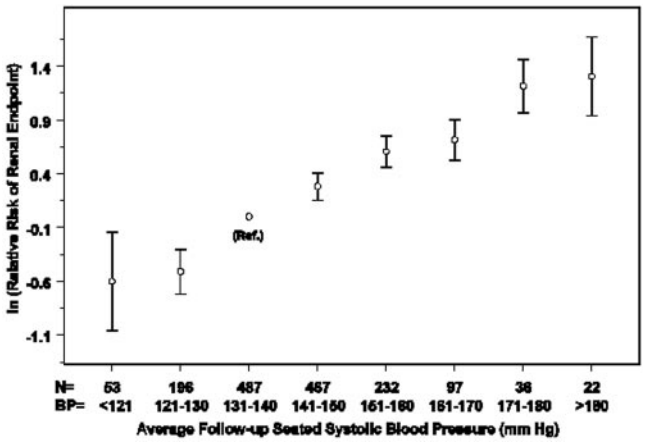

Figure 6. Natural log of the relative risk (RR) of reaching a renal end point by level of achieved follow-up systolic BP (SBP). The number of patients who were at risk for reaching a renal end point (doubling of baseline serum creatinine or ESRD, defined as serum creatinine ≥6.0 mg/dl or renal replacement therapy) is tabulated for each level of achieved follow-up systolic BP. From reference (51).

(53). The IDNT revealed no significant relation between diastolic BP (DBP) and renal outcomes (51).

An analysis of achieved BP and all-cause mortality/composite CV mortality in this same patient population provides a somewhat different picture (Figure 7). As is evident from the examination of Figure 7, the risk for both all-cause mortality (Figure 7A) and CV mortality (Figure 7B) rose in the subgroup of patients whose SBP was <120 mmHg by a RR of 3.05 and 4.06, respectively (both $P < 0.001$). There were only 53 patients in this subgroup, and an examination as to how these patients differed from the other 1537 patients revealed that they had a much higher prestudy history of heart disease and congestive heart failure (54). It is of note that when the effect of different levels of SBP are analyzed in only those patients with an SBP >120 mmHg, there is a highly significant protection for lowering SBP to this level for all-cause mortality, CV mortality, and congestive heart failure but not for risk for myocardial infarction or stroke (54).

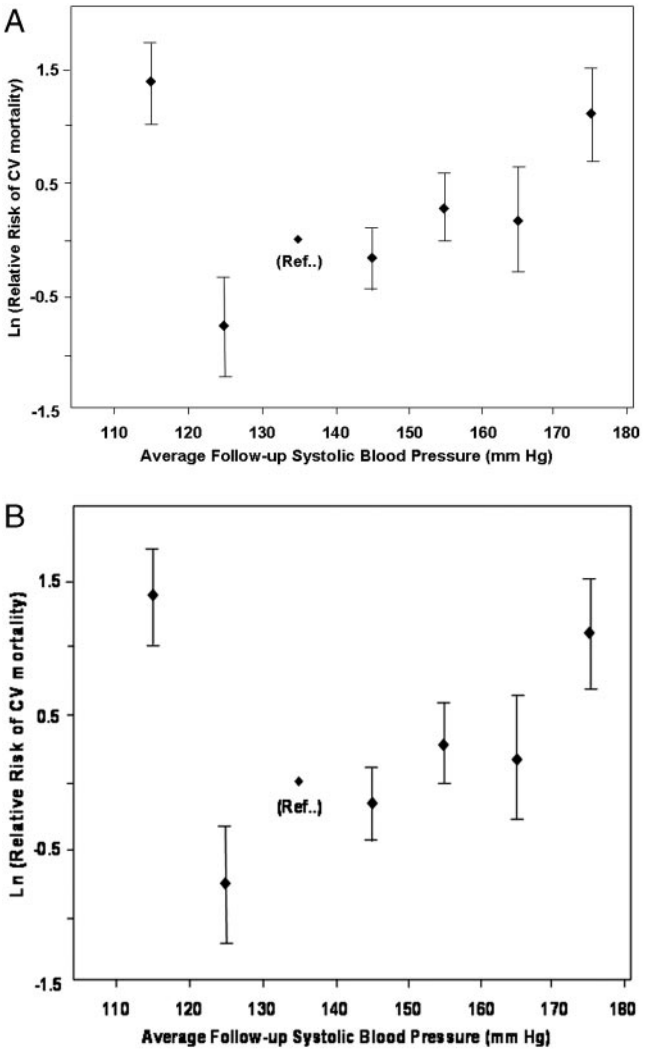

Figure 7. (A) Natural log of the RR of all-cause mortality by level of achieved follow-up SBP. The number of patients who are at risk for death by any cause is tabulated for each level of achieved follow-up SBP. From reference (51). (B) Natural log of the RR of cardiovascular mortality by level of achieved follow-up SBP. The number of patients who are at risk for death by any cause is tabulated for each level of achieved follow-up SBP. From reference (54).

In contrast to the neutral effect of changes in DBP on renal outcomes, decrements in DBP were associated with an opposing effect on the rate of myocardial infarction and strokes. Thus, whereas the former, as depicted in Figure 8, increased markedly at a DBP <85 mmHg per 10 mmHg (RR 1.61; 95% confidence interval 1.26 to 2.02; $P < 0.001$), the risk for strokes decreased (RR 0.65; 95% confidence interval 0.48 to 0.88; $P < 0.005$) (54).

The increased risk for acute coronary events again raises the old controversy of whether there is a J-point effect. Its existence has been championed by some (55) but questioned by others (56). Cruickshank (55) argued that at a DBP <85 mmHg, there may be a J-point effect in patients with underlying ischemic disease, as the coronary circulation is particularly sensitive to a decrease in DBP. The population studied in IDNT of elderly patients with type 2 diabetes and overt nephropathy is very likely to be enriched by such patients. Furthermore, it is of interest to note that the INVEST trial that studied patients with hypertension and CAD (57) also found a distinct association of lower DBP with myocardial infarctions (58). Likewise, a meta-analysis of seven large, randomized trials also revealed a J point at a DBP of 84 mmHg on all-cause mortality (59). Because decreasing DBP is associated with increasing pulse pressure, the possibility that an increment in pulse pressure may be culpable for these findings has been suggested. The findings in the Framingham cohort that revealed that an increase in CV events occurred in patients with a low DBP and an SBP >140 mmHg (60) supports such a contention. Although the effect of low DBP and increased pulse pressure are difficult to dissociate, it is of interest that in both INVEST and IDNT, the decrement of low DBP was not associated with an increase in strokes, suggesting that there is no overall vasculotoxic effect of an

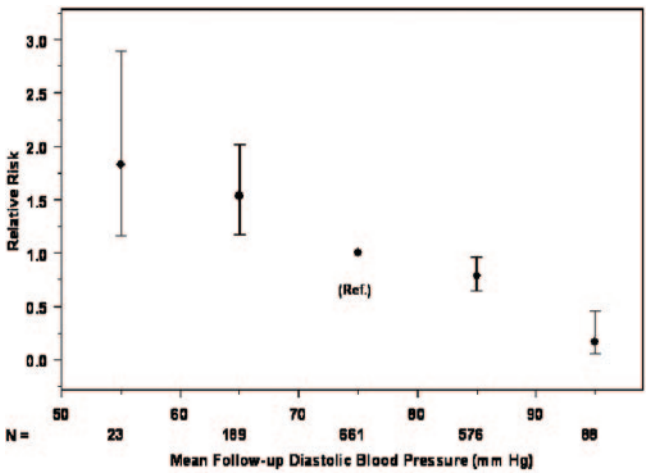

Figure 8. RR of myocardial infarction by level of achieved diastolic BP. The number of patients who are at risk for death for each level of BP is tabulated at the bottom. From reference (54).

increased pulse pressure and that the consequences of a low DBP are specific to the coronary circulation.

In summary, therefore, as pertains to BP, it seems that the progressive lowering of SBP to 120 mmHg is associated with improved renal protection and a decrement in mortality and CV events. However, at an SBP <120 mmHg, there is continued renal protection but an increase in all-cause mortality, CV mortality, and congestive heart failure in patients who have more severe underlying cardiac disease. When examined in populations that are enriched with patients with CAD, a J-curve effect is observed at a DBP <85 mmHg for acute myocardial infarction but not for renal progression. The effect of low DBP cannot be readily dissociated from the increase in pulse pressure; the failure to observe an increment in cerebrovascular events suggests an independent effect that most likely is mediated by impairment in coronary artery perfusion.

Does Inhibition of RAS Protect Both Heart and Kidney?

Numerous studies that were published in the 1980s and 1990s consistently showed that the inhibition of angiotensin-converting enzyme (ACE) reduces the risk for death and CV events after myocardial infarction (61–65) and increases survival in patients with decreased LV function (66–68). Such cardioprotective effects, particularly in hospitalizations related to congestive heart failure, were observed in both the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) (50) and IDNT (69) studies, which use angiotensin receptor blockers (ARB). In fact, these two classes of drugs (ACE inhibitors and ARB) seem to provide a comparable beneficial effect on CV outcomes both in patients with heart failure (70,71) and in patients with postmyocardial infarction (72,73). Likewise, on the background of a large body of experimental data suggesting a salutary effect of aldosterone on progressive cardiac fibrosis (74), the use of aldosterone inhibitors such as with spironolactone (75) or eplerenone (76) have been found to decrease significantly mortality in patients with advanced heart failure.

The renoprotective effect of RAS inhibition on the progression of renal disease has also been documented amply in individuals both with (77) and without diabetes (78). In fact, RAS inhibition may retard the progression of diabetic renal disease at every stage. Specifically, ACE inhibitors but not calcium channel blockers decrease the risk for conversion from normoalbuminuria to microalbuminuria (79). Similarly, both ACE inhibitors (80) and ARB (81) significantly decrease the rate of progression from microalbuminuria to overt proteinuria, but the two classes do not seem to differ in the rate at which renal function is lost in these patients (82). Finally, in patients with overt proteinuria, two independent studies have demonstrated a positive effect of ARB on the rate of loss of GFR (49,50). Whether such protection is also afforded by ACE inhibitors is not entirely known, as the results in small series have yielded variable results (83). Because the large trials did not have an ACE inhibitor component, this question may well remain unanswered. In analogy with the observation described above in cardiac protection, there is increasing interest in the possibility that aldosterone, independent of the RAS inhibition, could be implicated in the progression of renal disease. This has support in studies performed in experimental animals (84,85), but there are studies that suggest an antiproteinuric effect associated with aldosterone inhibition (86,87). Thus Bianchi *et al.* (87) observed in an uncontrolled pilot study a reversible decrease in protein excretion when 42 patients with CKD received 25 mg of Aldactone for 8 wk. These observations clearly call for the study of the effect of such agents on the progression of kidney disease with more established clinical end points.

The question that arises is whether there is an interaction between lowering BP and assignment to a RAS inhibitor. This interaction was examined in recent reports for both reduction in the rate of loss of renal function (51) and the risk for congestive heart failure (54). For the former, the analysis is depicted in Figure 9. It is of note that at any quartile of achieved SBP, the patients who were placed on the ARB had better renal outcomes than those who were assigned to the alternative treatment arms. In fact, assignment to the ARB resulted in a 33% risk reduction ($P < 0.001$) of reaching a renal end point beyond that achieved by lowering the SBP. The effects of lowering SBP and treatment with the ARB were completely independent and additive (51). A similar independent effect was observed for lowering SBP and assignment to the ARB in the decrement of congestive heart failure hospitalizations. Thus, while being on the ARB lowered the risk for heart failure by 29% and lowering SBP by 20 mmHg did so by 25%, the combination of both lowered the risk by 53% (54).

In summary, inhibition of the RAS with either an ACE inhibitor or an ARB provides both cardiac and renal protection. The protection is most marked for congestive heart failure. Inhibition of aldosterone provides survival advantage in patients with low LV ejection fraction and may also have antiproteinuric effects. The heart failure and renoprotective effects of RAS inhibition is independent and additive to the benefit obtained from lowering BP.

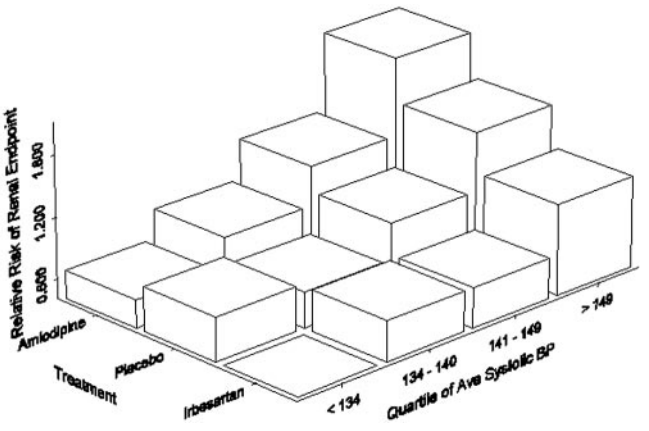

Figure 9. Simultaneous impact of quartile of achieved SBP and treatment modality on the RR of reaching a renal end point. Reprinted from reference (51), with permission.

Is Lowering Protein Excretion Equally Reno- and Cardioprotective?

Almost every multifactorial analysis of risk factors that predict the progression of kidney disease consistently points to the baseline level of proteinuria as an important predictor of such an event. This was observed in a study in individuals with type 1 diabetes (88), in the Gruppo Italiano di Studi Epidemiologici in Nefrologia study that also involves individuals without diabetes (89), and in the aforementioned RENAAL (90) and IDNT trials (91). Likewise, baseline proteinuria also has been found to be a predictor of CV events in these last two trials (92,93), as well as in other studies, such as Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) (94), Heart Outcomes Prevention Evaluation (HOPE) (95) and Framingham (96). Thus, there is little question that proteinuria is a marker or even a surrogate for enhanced renal and cardiac risk. What remains to be proved is whether lowering protein excretion *per se* reduces the risk. This was examined in a subanalysis of the aforementioned trials. Specifically, in RENAAL, a >30% reduction in protein excretion at 6 mo was associated with a significantly decreased risk for reaching a renal end point than those who did not do so (92). In fact, the analysis suggests that much of the renoprotective effect of the ARB antagonist that was used was mediated by lowering protein excretion. The reduction in protein excretion was also associated with a decrement in CV events such that halving of the protein excretion resulted in halving of the CV risk (92). In regard to renal protection, very similar data emerged from the analysis of IDNT (91), as a 50% reduction in proteinuria at 12 mo was associated with an approximate 50% reduction in reaching a renal end point. Although further data on this issue would be welcome, it seems that lowering protein excretion clearly is beneficial in protecting the kidney and probably the heart as well.

In summary, in answering the initially posed question as to whether what is good for the kidney is good for the heart, it is clear that lowering BP protects the kidney, but there may be levels of SBP and DBP below which some increase in risk emerges. A BP of 120/85 mmHg seems to be a "rational" target as of now. Inhibiting the RAS clearly is beneficial to both organs, but the protection that is afforded by aldosterone inhibition remains to been defined convincingly for the kidney. Finally, lowering urinary protein seems to slow the progression of kidney disease and also may be cardioprotective, but this latter observation will require further confirmatory data.

Treatment Options for LVH and CAD

As stated at the outset, relatively few studies have examined prospectively in randomized trials one therapeutic strategy for overt heart disease *versus* another in patients with CKD or ESRD. With regard to the management of LVH, two studies have probed the potential benefit of a β blocker in this setting (97,98). In the first of these studies, the β blocker carvedilol was used in ESRD patients with classes II and III New York Heart Association heart failure. During a 12-mo period, there was some improvement in the carvedilol group as compared with the placebo-treated group (97). In a follow-up of this patient group over several years, there was superior survival and fewer hospitalizations in the β blocker–treated group as compared with placebo (98). Taken together, these studies suggest that there may be a beneficial role for β blockers in the setting of advanced heart failure in dialysis patients. It should be stressed that in these trials, the use of a β blocker was not accomplished easily, as fully 21% of individuals who were exposed to the carvedilol therapy were forced to drop out of the study.

With regard to the management of CAD, there is an ongoing debate of the relative advantage of coronary artery bypass grafting *versus* percutaneous interventions. Several years ago, one study suggested that coronary artery bypass grafts were associated with an improved survival compared with percutaneous procedures (99). There are several reasons for why such a result might have been obtained, including that many patients with more complicated medical problems (and who therefore possess a very high risk for death in the periprocedure period) are excluded from coronary artery bypass grafting surgery. In addition, percutaneous procedures have improved in recent years. The clinical and angiographic restenosis rate in patients who undergo percutaneous interventions has been reduced dramatically recently (100). This field is moving rapidly as reports of improved patency with drug-eluting stents in this group of patients is now being reported. For example, in one such report of 10 consecutive patients who were on dialysis, 10 of 10 patients had a very good result that was durable for >1 yr without any deaths, recurrent myocardial infarction, or the need for target lesion revascularization (100).

Our current strategy in the population of patients with CKD and ESRD is to use a combination of low-dose aspirin and β blockers in patients with known coronary disease. The potential benefit of β blockers in all patients with stage 4/5 CKD and ESRD must await a randomized, prospective study. As mentioned above, there is no consensus on whether antioxidants are beneficial, and new studies are planned to answer this question. A recent study of the cholesterol-lowering agent atorvastatin in 1255 dialysis patients yielded mixed results over an average follow-up period of 4 yr (101). On the one hand, cardiac events were somewhat reduced in the atorvastatin-treated patients, but the RR of fatal stroke was increased in this group. This mixed result led to no significant effect on the composite end point of the study. These findings will require additional analysis and study, but our practice is to use statins to reduce LDL cholesterol concentrations in concordance with current guidelines (7). For patients with diabetes, tight glucose control is important, as is evident from the discussion on BP and protein excretion; the antihypertensive agent of choice in the patient population is a drug that interrupts the RAS axis, either an ACE inhibitor or an ARB. Extracellular fluid volume control *via* longer dialysis sessions or extra dialysis sessions is currently also becoming more usual. Whether nocturnal dialysis or quotidian dialysis will be effective and affordable in treating patients in the United States is under active study at present. Strict management of calcium and phosphorus is currently accomplished through a combination of phosphate binders, including non–calcium-containing phosphate binders. Guidelines for the management of the hematocrit and dyslipidemia now suggest that the hematocrit should be in the middle to upper 30s as a

minimum and the LDL cholesterol should be lowered to <100 mg/dl in dialysis patients and <70 mg/dl in patients with known coronary disease.

References

1. US Renal Data System: *USRDS 2004 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2004
2. Excerpts from the United States Renal Data System's 2000 Annual Report: Atlas of End-Stage Renal Disease in the United States. *Am J Kidney Dis* 36[Suppl 2]: S1–S137, 2000
3. Tyroler HA: Nutrition and coronary heart disease epidemiology. *Adv Exp Med Biol* 369: 7–19, 1995
4. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296–1305, 2004
5. Anavekar NS, McMurray JJV, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA: Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 351: 1285–1295, 2004
6. Keith DS, Nichols GA, Guillion CM, Brown JB, Smith DH: Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 164: 659–663, 2004
7. Cardiovascular Disease in Dialysis Patients Work Group. Clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 45[Suppl 4]: S7–S153, 2005
8. Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 290: 697–701, 1974
9. Ansari A, Kaupke CJ, Vaziri ND, Miller R, Barbari A: Cardiac pathology in patients with end-stage renal disease maintained on hemodialysis. *Int J Artif Organs* 16: 31–36, 1993
10. Rostand S, Kirk KA, Rutsky EA: The epidemiology of coronary artery disease in patients on maintenance hemodialysis: Implications for management. *Contrib Nephrol* 52: 34–41, 1986
11. Weinrauch L, D'Elia JA, Healy RW, Gleason RE, Christleib AR, Leland OS Jr: Asymptomatic coronary artery disease: Angiographic assessment of diabetics evaluated for renal transplantation. *Circulation* 58: 1184–1189, 1978
12. Weinrauch L, D'elia JA, Healy RW, Gleason RE, Takacs FJ, Libertino JA, Leland OS: Asymptomatic coronary artery disease: Angiography in diabetic patients before renal transplantation. *Ann Intern Med* 88: 346–348, 1978
13. Bennett W, Kloster F, Rosch J, Barry J, Porter GA: Natural history of asymptomatic coronary arteriographic lesions in diabetic patients with end-stage renal disease. *Am J Med* 65: 779–784, 1978
14. Beddhu S, Allen-Brady K, Cheung AK, Horne BD, Bair T, Muhlestein JB, Anderson JL: Impact of renal failure on the risk of myocardial infarction and death. *Kidney Int* 62: 1776–1783, 2002
15. deFilippi C, Wasserman S, Rosanio S, Tiblier E, Sperger H, Tocchi M, Christenson R, Uretsky B, Smiley M, Gold J, Muniz H, Badalamenti J, Herzog C, Henrich W: Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. *JAMA* 290: 353–359, 2003
16. Ohtake T, Kobayashi S, Moriya H, Negishi K, Okamoto K, Maesato K, Saito S: High prevalence of occult coronary artery stenosis in patients with chronic kidney disease at the initiation of renal replacement therapy: An angiographic examination. *J Am Soc Nephrol* 16: 1141–1148, 2005
17. Herzog CA, Ma JZ, Collins AJ: Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med* 339: 799–805, 1998
18. Ritz E, Wiecek A, Gnasso A, Augustin J: Is atherogenesis accelerated in uremia? *Contrib Nephrol* 52: 1–9, 1986
19. Zile MR, Baicu CF, Gaasch WH: Diastolic heart failure—Abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 350: 1953–1959, 2004
20. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giacone G, Cataliotti A, Seminara G, Stancanelli B, Malatino LS: Prognostic value of echocardiographic indicators of left ventricular systolic function in asymptomatic dialysis patients. *J Am Soc Nephrol* 15: 1029–1037, 2004
21. Meier P, Vogt P, Blanc E: Ventricular arrhythmias and sudden cardiac death in end-stage renal disease patients on chronic hemodialysis. *Nephron* 87: 199–214, 2001
22. Aoki J, Nakajima H, Mori M: Clinical and pathologic characteristics of dilated cardiomyopathy in hemodialysis patients. *Kidney Int* 67: 333–341, 2005
23. Mallamaci F, Zoccali C, Tripepi G, Fermo I, Benedetto FA, Cataliotti A, Bellanuova I, Malatino LS, Soldarini A; CREED Investigators: Hyperhomocysteinemia predicts cardiovascular outcomes in hemodialysis patients. *Kidney Int* 61: 609–614, 2002
24. Wrone EM, Hornberger JM, Zehnder JL, McCann LM, Coplon NS, Fortmann SP: Randomized trial of folic acid for prevention of cardiovascular events in end-stage renal disease. *J Am Soc Nephrol* 15: 420–426, 2004
25. Moe SM, O'Neill KD, Duan D, Ahmed S, Chen NX, Leapman SB, Fineberg N, Kopecky K: Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. *Kidney Int* 61: 638–647, 2002
26. Chertow GM, Burke SK, Raggi P; Treat to Goal Working Group: Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 62: 245–252, 2002
27. Sharples EJ, Pereira D, Summers S, Cunningham J, Rubens M, Goldsmith D, Yaqoob MM: Coronary artery calcification measured with electron-beam computerized tomography correlates poorly with coronary artery angiography in dialysis patients. *Am J Kidney Dis* 43: 313–319, 2004
28. Haydar AA, Hujairi NMA, Covic AA: Coronary artery calcification is related to coronary atherosclerosis in chronic renal disease patients: A study comparing EBCT-generated coronary artery calcium scores and coronary angiography. *Nephrol Dial Transplant* 19: 2307–2312, 2004
29. Moe SM, Reslerova M, Ketteler M, O'neill K, Duan D, Koczman J, Westenfeld R, Jahnen-Dechent W, Chen NX: Role of calcification inhibitors in the pathogenesis of vascular calcification in chronic kidney disease (CKD). *Kidney Int* 67: 2295–2304, 2005
30. Covic A, Gusbeth-Tatomer P, Goldsmith DJ: Arterial stiff-

ness in renal patients: An update. *Am J Kidney Dis* 45: 965–977, 2005
31. Zocalli C, Mallamaci F, Tripepi G: Novel cardiovascular risk factors in end-stage renal disease. *J Am Soc Nephrol* 15: S77, 2004
32. Tepel M, van der Giet M, Statz M, Jankowski J, Zidek W: The antioxidant acetylcysteine reduces cardiovascular events in patients with end-stage renal failure; a randomized, controlled trial. *Circulation* 107: 992–995, 2003
33. Longitano JP, Light P, Tiblier E, *et al.*: Correlation of N-verminal pro brain natriuretic peptide (NT-pronBNP) with depressed left ventricular function and mortality in chronic hemodialysis patients: Results of a two-year outcomes study [Abstract]. *J Am Soc Nephrol* 12: 223A, 2001
34. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS: Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 41: 1–12, 2003
35. Whelton PK, Perneger TV, He J, Klag MJ: The role of blood pressure as a risk factor for renal disease: A review of the epidemiologic evidence. *J Hum Hypertens* 10: 683–689, 1996
36. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, de Zeeuw D, Shahinfar S, Toto R, Levey AS: Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: A patient-level meta-analysis. *Ann Intern Med* 139: 244–252, 2003
37. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor, F, Marks JS: The continuing increase of diabetes in the US. *Diabetes Care* 24: 412, 2001
38. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339: 229–234, 1998
39. Perneger TV, Brancati FL, Whelton, PK, Klag MJ: End-stage renal disease attributable to diabetes mellitus. *Ann Intern Med* 121: 912–918, 1994
40. US Renal Data System: *USRDS Annual Data Report: Atlas of End-Stage Renal Disease in the United States*, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2003
41. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 317: 703–713, 1998
42. Schrier RW, Estacio RO, Esler A, Mehler P: Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int* 61: 1086–1097, 2002
43. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 351: 1755–1762, 1998
44. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 355: 253–259, 2000
45. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmaki K, Dahlof B, de Faire U, Morlin C, Karlberg BE, Wester PO, Bjorck JE: Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: The Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 353: 611–616, 1999
46. Tuomilehto J, Rastenyte D, Birkenhager WH, Thijs L, Antikainen R, Bulpitt CJ, Fletcher AE, Forette F, Goldhaber A, Palatini P, Sarti C, Fagard R: Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med* 340: 677–684, 1999
47. Turnbull F: Effects of different blood-pressure-lowering regimens on major cardiovascular events: Results of prospectively-designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 362: 1527–1535, 2003
48. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, Tuttle K, Douglas J, Hsueh W, Sowers J: Preserving renal function in adults with hypertension and diabetes: A consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 36: 646–661, 2000
49. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345: 851–860, 2001
50. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S; RENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861–869, 2001
51. Pohl M, Blumenthal S, Cordonnier D, De Alvaro F, DeFerrari G, Eisner G, Esmatjes E, Gilbert R, Hunsicker L, Lopes de Faria J, Mangili R, Moore J, Reisin E, Ritz E, Schernthaner G, Spitalewitz S, Tindall H, Rodby R, Lewis E; for the Collaborative Study Group: Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the Irbesartan Diabetic Nephropathy Trial (IDNT): Clinical implications and limitations. *J Am Soc Nephrol* 16: 3027–3037, 2005
52. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G: The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 330: 877–884, 1994
53. Wright JT, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG; for the African American Study of Kidney Disease and Hypertension Study Group: Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease. *JAMA* 288: 2421–2431, 2002
54. Berl T, Hunsicker L, Lewis J Pfeffer M, Porush J, Rouleau JL, Drury P, Esmaties E, Hricik D, Pohl M, Raz I, Vanhille P, Wiegman T, Wolfe B, Locatelli F, Goldhaber S, Lewis E: Impact of achieved blood pressure on cardiovascular out-

comes in the irbesartan diabetic nephropathy trial. *J Am Soc Nephrol* 16: 2170–2179, 2005
55. Cruickshank JM: Antihypertensive treatment and the J-curve. *Cardiovasc Drugs Ther* 14: 373–379, 2000
56. Hansson L: Antihypertensive treatment: Does the J-curve exist? *Cardiovasc Drugs Ther* 14: 367–372, 2000
57. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, Mancia G, Cangiano JL, Garcia-Barreto D, Keltai M, Erdine S, Bristol HA, Kolb HR, Bakris GL, Cohen JD, Parmley WW: A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): A randomized controlled trial. *JAMA* 290: 2805–2816, 2003
58. Messerli F, Kupfer S, Pepine: J curve in hypertension and coronary artery disease. *Am J Cardiol* 95: 160, 2005
59. Boutitie F, Gueyffier F, Pocock S, Fagard R, Pierre Boissel; for the INDANA project steering committee: J-shaped relationship between blood pressure and mortality in hypertensive patients: New insights from a meta-analysis of individual-patient data. *Ann Intern Med* 136: 438–448, 2002
60. Kannel WB, Wilson PW, Nam BH, D'Agostino RB, Li J: A likely explanation for the J-curve of blood pressure cardiovascular risk. *Am J Cardiol* 94: 380–384, 2004
61. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, *et al.*: Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 3: 327: 669–677, 1992
62. GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. *Lancet* 343: 1115–1122, 1994
63. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet* 345: 669–685, 1995
64. Ambrosioni E, Borghi C, Magnani B: The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. *N Engl J Med* 332: 80–85, 1995
65. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet* 342: 821–828, 1993
66. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 316: 1429–1435, 1987
67. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 325: 293–302, 1991
68. Garg R, Yusuf S: Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA* 273: 1450–1456, 1995
69. Berl T, Hunsicker LG, Lewis JB, Pfeffer MA, Porush JG, Rouleau JL, Drury PL, Esmatjes E, Hricik D, Parikh CR, Raz I, Vanhille P, Wiegmann TB, Wolfe BM, Locatelli F, Goldhaber SZ, Lewis EJ: Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. *Ann Intern Med* 138: 542–549, 2003
70. McKelvie RS, Yusuf S, Pericak D, Avezum A, Burns RJ, Probstfield J, Tsuyuki RT, White M, Rouleau J, Latini R, Maggioni A, Young J, Pogue J: Comparison of candesartan, enalapril, and their combination in congestive heart failure: Randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation* 100: 1056–1064, 1999
71. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klinger GH, Neaton J, Sharma D, Thiyagarajan B: Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—The Losartan Heart Failure Survival Study ELITE II. *Lancet* 355: 1582–1587, 2000
72. Dickstein K, Kjekshus J: Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: The OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet* 360: 752–760, 2002
73. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM; Valsartan in Acute Myocardial Infarction Trial Investigators: Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 349: 1893–1906, 2003
74. Weber K: Aldosterone in congestive heart failure. *N Engl J Med* 348: 1689, 2001
75. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 341: 709–717, 1999
76. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M: Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 348: 1309–1321, 2003
77. Parving HH, Rossing P, Hommel E, Smidt UM: Angiotensin-converting enzyme inhibition in diabetic nephropathy: Ten years' experience. *Am J Kidney Dis* 26: 99–107, 1995
78. Maschio G, Alberti D, Janin G; the Angiotensin-Converting Enzyme Inhibition in Progressive Renal Insufficiency Study Group: Effect of the angiotensin-converting enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 334: 939–945, 1996
79. Ruggenenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, Rubis N, Gherardi G, Arnoldi F, Ganeva M, Ene-Iordache B, Gaspari F, Perna A, Bossi A, Trevisan R, Dodesini AR, Remuzzi G; Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators: Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 351: 1941–1951, 2004
80. Kshirsagar AV, Joy MS, Hogan SL, Falk RJ, Colindres RE: Effect of ACE inhibitors in diabetic and nondiabetic

chronic renal disease: A systematic overview of randomized placebo-controlled trials. *Am J Kidney Dis* 35: 695–707, 2000
81. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 345: 870–878, 2001
82. Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, Mustonen J: Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 351: 1952–1961, 2004
83. Parving HH, Hovind P, Rossing K, Andersen S: Evolving strategies for renoprotection: Diabetic nephropathy. *Curr Opin Nephrol Hypertens* 10: 515–522, 2001
84. Quan ZY, Walser M, Hill GS: Adrenalectomy ameliorates ablative nephropathy in the rat independently of corticosterone maintenance level. *Kidney Int* 41: 326–333, 1992
85. Greene EL, Kren S, Hostetter TH: Role of aldosterone in the remnant kidney model in the rat. *J Clin Invest* 98: 1063–1068, 1996
86. Rachmani R, Slavachevsky I, Amit M, Levi Z, Kedar Y, Berla M, Ravid M: The effect of spironolactone, cilazapril and their combination on albuminuria in patients with hypertension and diabetic nephropathy is independent of blood pressure reduction: A randomized controlled study. *Diabet Med* 21: 471–475, 2004
87. Bianchi S, Bigazzi R, Campese VM: Antagonists of aldosterone and proteinuria in patients with CKD: An uncontrolled pilot study. *Am J Kidney Dis* 46: 45–51, 2005
88. Breyer JA, Bain RP, Evans JK, Nahman NS Jr, Lewis EJ, Cooper M, McGill J, Berl T: Predictors of the progression of renal insufficiency in patients with insulin-dependent diabetes and overt diabetic nephropathy. The Collaborative Study Group. *Kidney Int* 50: 1651–1658, 1996
89. Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G: Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. "Gruppo Italiano di Studi Epidemiologici in Nefrologia" (GISEN). *Kidney Int* 53: 1209–1216, 1998
90. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM: Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL. *Kidney Int* 65: 2309–2320, 2004
91. Atkins RC, Briganti EM, Lewis JB, Hunsicker LG, Braden G, Champion de Crespigny PJ, DeFerrari G, Drury P, Locatelli F, Wiegmann TB, Lewis EJ: Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. *Am J Kidney Dis* 45: 281–287, 2005
92. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM: Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation* 110: 921–927, 2004
93. Anavekar NS, Gans DJ, Berl T, Rohde RD, Cooper W, Bhaumik A, Hunsicker LG, Rouleau JL, Lewis JB, Rosendorff C, Porush JG, Drury PL, Esmatjes E, Raz I, Vanhille P, Locatelli F, Goldhaber S, Lewis EJ, Pfeffer MA: Predictors of cardiovascular events in patients with type 2 diabetic nephropathy and hypertension: A case for albuminuria. *Kidney Int Suppl* S50–S55, 2004
94. Wachtell K, Ibsen H, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlof B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristianson K, Lederballe-Pedersen O, Nieminen MS, Okin PM, Omvik P, Oparil S, Wedel H, Snapinn SM, Aurup P: Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: The LIFE study. *Ann Intern Med* 139: 901–906, 2003
95. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S; HOPE Study Investigators: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 286: 421–426, 2001
96. Kannel WB, Stampfer MJ, Castelli WP, Verter J: The prognostic significance of proteinuria: The Framingham study. *Am Heart J* 108: 1347–1352, 1984
97. Cice G, Ferrara L, DiBenedetto A, Russo PE, Marinelli G, Pavese F, Iacono A: Dilated cardiomyopathy in dialysis patients—Beneficial effects of carvedilol: A double-blind, placebo-controlled trial. *J Am Coll Cardiol* 37: 407–411 2001
98. Cice G, Ferrara L, D'Andrea A, D'Isa S, Di Benedetto A, Cittadini A, Russo PE, Golino P, Calabro R: Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: A prospective, placebo-controlled trial. *J Am Coll Cardiol* 41: 1438–1444, 2003
99. Szczech LA, Reddan DN, Owen WF, Califf R, Racz M, Jones RH, Hannan EL: Differential survival after coronary revascularization procedures among patients with renal insufficiency. *Kidney Int* 60: 292–299, 2001
100. Pinkau T, Mann JFE, Ndrepepa G, Mehilli J, Hadamitzky M, Braun S, Kastrati A, Schomig A: Coronary revascularization in patients with renal insufficiency: Restenosis rate and cardiovascular outcomes. *Am J Kidney Dis* 44: 627–635, 2004
101. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, Ritz E; German Diabetes and Dialysis Study Investigators: Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 353: 238–248, 2005; published erratum appears in *N Engl J Med* 353: 1640, 2005

This In-Depth Review by Berl and Henrich should provide background for the paper by Khan *et al*. in *JASN* (pages 244–253), which relates mortality from heart failure (systolic) to kidney function.