Reflections in Hypertension

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Target Blood Pressure in Patients With End-Stage Renal Disease: Evidence-Based Medicine or the Emperor's New Clothes?

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One area of hypertension where it is generally acknowledged that we are not doing a very good job is chronic kidney disease (CKD). As highlighted by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7),[1] the dramatic decline in death rates from coronary heart disease and stroke that we have witnessed in the past 30 years has not been paralleled by any decline of end-stage renal disease (ESRD), which, in contrast, has been showing a relentless increase.[1] Many of these incident cases of ESRD have been attributed to poorly controlled hypertension, and the others mostly to diabetes. Renal disease and diabetes are the two conditions where JNC 7[1] and other guidelines such as the National Kidney Foundation (NKF)[2,3] have proposed lower thresholds for treatment (130/80 mm Hg vs. 140/90 mm Hg) than in other hypertensive patients, so one would think that the relationship between blood pressure (BP) and clinical outcomes should be particularly tight in these conditions.

The only intervention study that has looked at both of these groups is the Hypertension Optimal Treatment (HOT) study,[4] which was designed to see whether reducing BP to levels lower than in previous trials would produce a greater reduction of events (as predicted by epidemiologic studies). A second reason for the study was to test the J-curve hypothesis,[5] which stated that a more aggressive reduction of BP would result in a paradoxical increase of events than more moderate reductions. The study recruited 18,790 hypertensive patients and randomized them to three groups with different target diastolic BPs: <90 mm Hg, <85 mm Hg, and <80 mm Hg. The main conclusion of HOT was somewhere between these two extremes: there was no convincing evidence of additional benefit at the lowest levels of pressure, but also no evidence of harm. One reason why the results were less conclusive than hoped was that there was less separation of the three target levels of BP than was expected. In diabetic patients, however, there was strong evidence that the lower the pressure, the lower the risk. These findings give strong support for the adoption of the lower target BP in diabetes.

A much less publicized analysis of the HOT data looked at patients with CKD.[6] Out of a total of 18,597 patients in whom serum creatinine values were available at baseline, 2821 had an estimated glomerular filtration rate (GFR) of <60 mL/min. These patients had an event rate during the 3.8 years of follow-up that was approximately twice as high as the rate in patients with normal renal function (GFR >60 mL/min), consistent with other studies showing that impaired renal function is an independent risk factor for cardiovascular disease.[7] The other finding of note

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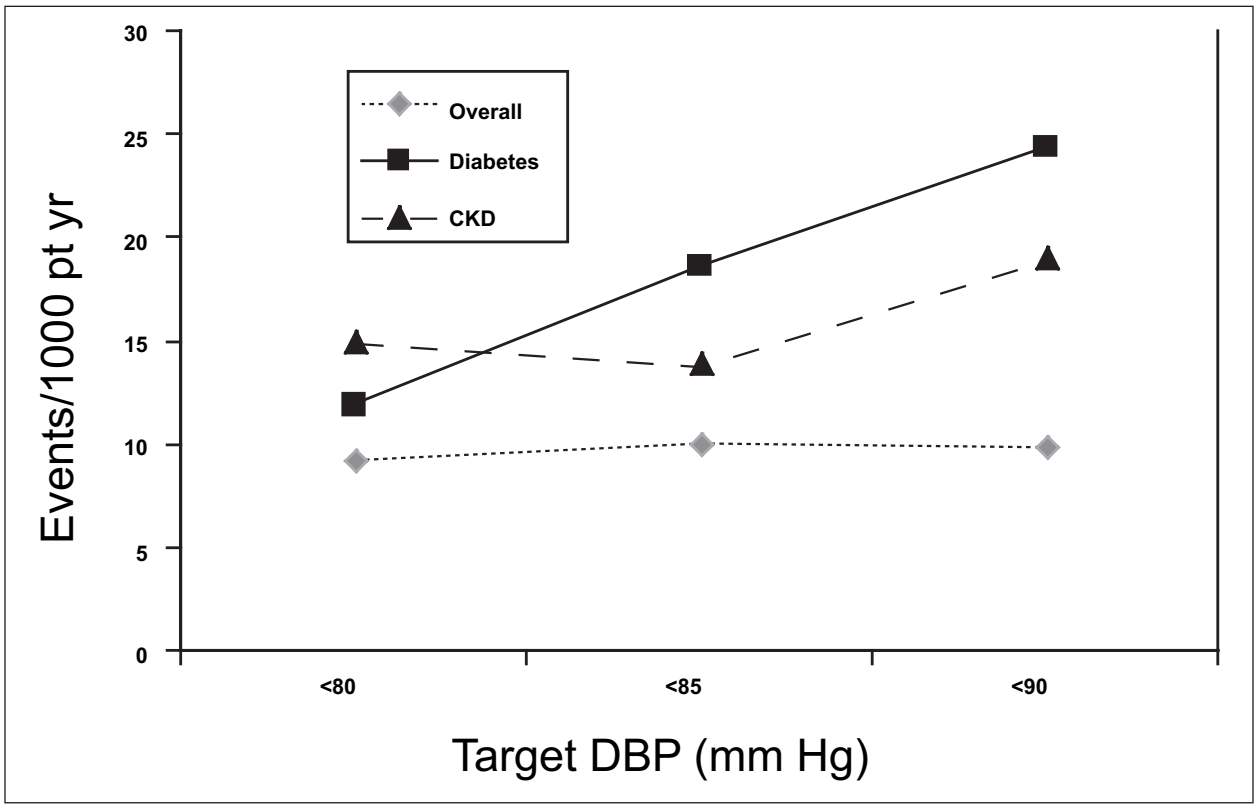

Figure 1. Data from the Hypertension Optimal Treatment (HOT) study showing the effects of three different target levels of diastolic blood pressure (DBP) on cardiovascular events in three different groups: the overall sample, patients with diabetes, and patients with chronic kidney disease (CKD). Data adapted from Lancet. *1998;351:1755–1762*[4] *and* J Am Soc Nephrol. *2001;12:218–225.*[6]

was that aggressive reduction of BP, in marked contrast to patients with diabetes, provided no additional benefit in reducing this risk, as shown in Figure 1. Two other randomized controlled trials of patients with CKD—Renoprotection in Patients with Nondiabetic Renal Disease (REIN-2)[8] and the African American Study of Kidney Disease (AASK)[9]—also found that more aggressive BP reduction conferred no additional benefit. More recently, a secondary analysis of the AASK data reported that in one of the three drug groups (amlodipine), there was a reduction of one of the secondary end points in the lower blood pressure group.[10] The significance of this is unclear. A third trial, the Modification of Diet and Renal Disease (MDRD),[11] did find that randomization to a lower target BP (120/75 mm Hg vs. 140/90 mm Hg) was associated with a reduced likelihood of progression to renal failure and overall cardiovascular events, however. It is not clear why these studies have given discrepant results: the MDRD was the longest (6 years as opposed to 3 years for REIN-2 and 4 years for AASK), and it was only after 2 years that the protective effect became apparent. The cumulative probability curves of events for the two groups diverged after 2 years, but showed no further separation between 3 and 6 years.

BP AND MORTALITY IN ESRD

If it is correct that BP is such an important risk factor for the development of ESRD, it would be reasonable to suppose that it is also closely related to the incidence of cardiovascular events in patients with ESRD, since the vast majority of these patients are hypertensive, and cardiovascular disease is the leading cause of death. The US Renal Data System statistics[12] indicate that 45% of all deaths in patients on hemodialysis are from cardiovascular disease. Unfortunately, there have been no clinical trials investigating the consequences of treating hypertension in this population. There have, however, been at least 20 observational studies relating BP and mortality in patients on hemodialysis, which have recently been reviewed by Agarwal,[13] who concluded that "analysis of incident cohorts reveals a clear link between elevated BP and mortality." This makes it sound as though these studies support the recommendations of JNC 7 and the NKF, but examination of them shows that this is, unfortunately, not the case.

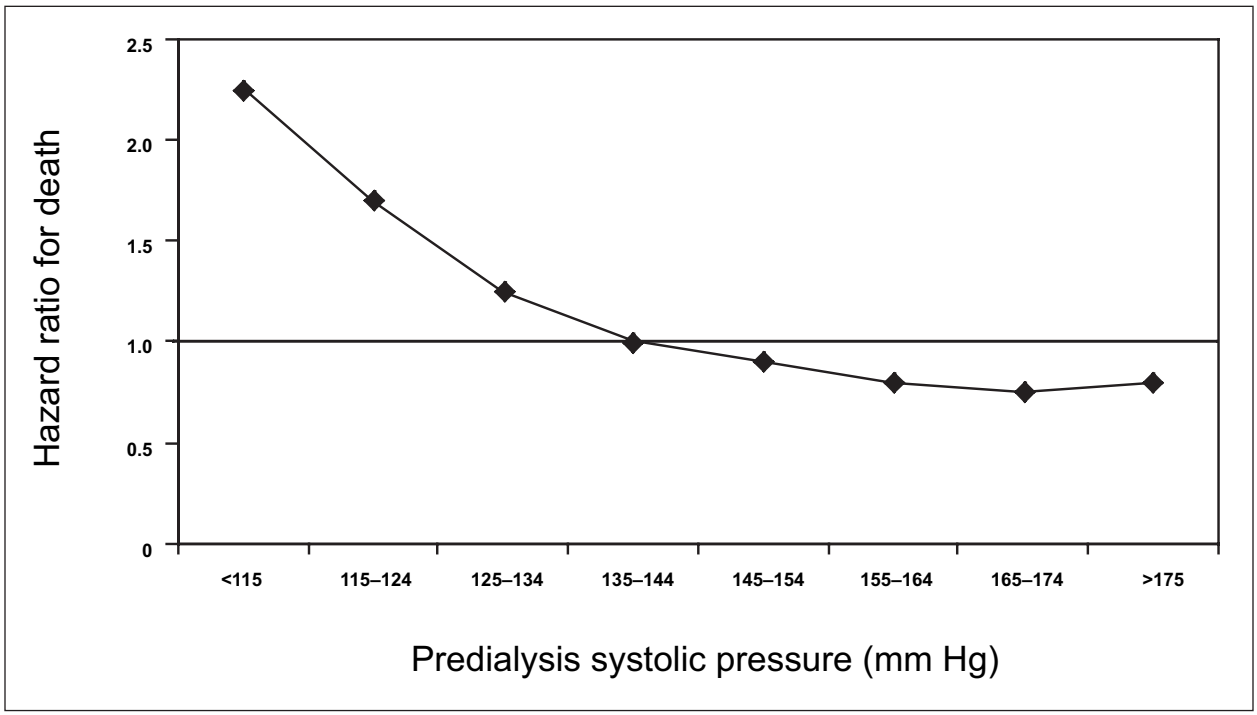

Figure 2. Relationship between predialysis systolic pressure and death in patients on hemodialysis. Adapted with permission from JAMA. *2002;287:1548–1555.*[14]

This series of observational studies has shown that the usual relationship between systolic BP and risk is rarely found, and the actual relationship may be inverse (higher pressures being associated with lower risk),[14–16] absent,[17,18] or U-shaped (both extremes of BP related to increased risk).[19,20] Although a limited number of these studies did conclude that patients with uncontrolled hypertension were at higher risk,[21,22] not one of the studies has shown the usual graded and curvilinear relationship between increased systolic BP and risk that is so clearly seen in other populations. A potential complicating factor here is that BP is measured somewhat differently in hemodialysis patients than in regular hypertensives, and most of the available data are obtained from readings taken at the time of dialysis, either just before (predialysis) or just after (postdialysis). The former readings tend to be the higher of the two. Let us look at some examples. Zager et al.[20] examined data from 5433 patients on hemodialysis in a commercial US operation (Dialysis Clinic, Inc.), and reported a U-shaped relationship between postdialysis BP and mortality. Thus, a systolic BP <130 mm Hg was actually related to an increased death rate, and at the other end of the scale it was only when systolic BP exceeded 170 mm Hg that there was any suggestion of increased mortality. For predialysis BP, the relationship was generally similar, except that a high systolic BP was not associated with increased mortality. Foley et al.[23] used the US Renal Data System to analyze the outcomes of 11,142 patients on hemodialysis, 63% of whom died over an average follow-up period of 3.8 years. They looked at both predialysis and postdialysis BP, and systolic and diastolic BP separately. The strongest predictors of mortality were a low predialysis and postdialysis diastolic BP, with relatively little impact of systolic BP. They therefore proposed that a high pulse pressure may be the best predictor, driven largely by the effects of a low diastolic BP. Similar findings were reported in a Japanese population by Iseki et al.,[24] who found that a low diastolic BP was related to poor survival, and that the level of systolic BP had no effect. In the largest study to date,[14] 37,069 patients on hemodialysis were followed for 1 year. Both predialysis and postdialysis systolic BP showed an inverse relation with mortality (Figure 2). Thus, in contradiction to the NKF recommendations, risk for both measures of BP in patients was higher in patients with systolic BP 125–134 mm Hg than 135–144 mm Hg. This was still true after adjusting for other variables known to affect mortality. In a multivariate model, both systolic and pulse pressure were significant predictors of risk, but a subgroup analysis showed that pulse pressure was a significant independent predictor only in patients with systolic BP <140 mm Hg. For any given level of systolic BP, a low diastolic BP was related to increased risk. This paper represents another example of obfuscation in this field: the

main conclusion of the abstract was "Pulse pressure is associated with risk of death in a large, nationally representative sample of patients undergoing maintenance hemodialysis," and the inverse relationship with systolic pressure was downplayed.

The most recent publication in this field, by Stidley et al.,[25] also used data from the Dialysis Clinic, Inc., and studied 16,959 patients from the time of starting hemodialysis. They confirmed the earlier finding of Zager et al.[20] from the same database that a low systolic BP (<120 mm Hg) was associated with increased mortality during the first 2 years of dialysis. And for those patients who survived the first 3 years of dialysis, a high baseline systolic BP (>150 mm Hg) was associated with increased mortality. If the BP measurements after starting dialysis were included, however, there was an inverse relation between predialysis BP and mortality, such that patients with a predialysis systolic BP between 120 and 129 mm Hg had a nearly two-fold higher mortality rate from cardiovascular disease than those with a systolic BP of 140–149 mm Hg. The relationships with postdialysis BP were less clear cut, but again, very low levels of systolic and diastolic BP were associated with increased mortality. A combined analysis of data from the United States, Europe, and Japan of 16,720 patients found that in univariate and multivariate analyses, a diagnosis of hypertension was associated with a 25% improvement of survival.[16]

Taken together, it is hard to see how these disparate findings can provide any support for the NKF recommendations that patients on hemodialysis should have a postdialysis BP <130/80 mm Hg. As described above, some of the observational studies actually found that BPs lower than this were associated with increased mortality. The situation is further complicated by the different findings for systolic and diastolic pressure. That a low diastolic pressure should be related to increased risk in these patients is not so surprising, since hemodialysis patients tend to be elderly, and studies in elderly hypertensives without impaired renal function have also found that at any level of systolic pressure, the cardiovascular risk is higher when diastolic BP is low.[26] And, in non-CKD patients with systolic hypertension, there is currently a controversy as to whether pulse pressure should be adopted as the main predictor of risk. Pulse pressure tends to be quite high in patients on hemodialysis, and the usually quoted reason for this is increased arterial stiffness, which has been clearly demonstrated with techniques such as measurements of pulse wave velocity and applanation tonometry.[27] In patients on hemodialysis, another factor may be the presence of an arteriovenous fistula. Unlike the situation with BP, there does seem to be a monotonic and positive relationship between arterial stiffness and mortality in hemodialysis patients.[27]

WHY SHOULD THE BP–MORTALITY RELATIONSHIP BE DIFFERENT IN ESRD PATIENTS?

In patients without CKD, there is universal agreement that a higher systolic pressure is associated with increased cardiovascular risk. This has been established in two types of studies; first, observational epidemiologic studies, reviewed by MacMahon et al.,[28] which showed a log-linear relationship between the lowest levels of BP and risk, steeper for strokes than for coronary events. And second, a considerable number of intervention studies have shown that lowering BP reverses the risk,[29] although in the case of coronary heart disease there has been some suggestion that the benefits may be less than expected from the epidemiologic studies. The only debate has been whether the relationship flattens out or reverses itself (the J-curve) at the lower end of the BP range.

In patients with moderate degrees of CKD, there is good evidence from epidemiologic studies that hypertension accelerates the decline of renal function,[30] and that it adds to cardiovascular risk,[7] but as described above, intervention studies have so far mostly failed to show that aggressive reduction of BP reverses this risk. In patients on hemodialysis, the picture becomes even more murky. The observational studies provide no consistent evidence that the relationship between BP and risk is the same as in patients with normal renal function, and there is not a single randomized intervention trial investigating the effects of BP reduction in hemodialysis patients.

The commonest explanation for the inverse or U-shaped relationship in dialysis patients is that there are two populations of patients. In one, who are conceived as being "high risk," it is argued that the low BP that is related to increased risk is a consequence of severe cardiovascular disease such as congestive heart failure. Thus, in the Foley et al. 1996 study,[15] increased BP was associated with left ventricular hypertrophy and congestive heart failure. Both are very common in patients on dialysis; left ventricular hypertrophy occurring in approximately 75% and heart failure in 40%.[7] In 2002, Foley et al.[23] suggested "reverse causality" to explain the U-curve, by which hypertension leads to congestive heart failure, which impairs cardiac function and hence results in a fall of BP.

This argument thus supposes that these patients comprise the first arm of the "U." The results of Stidley et al.,[25] quoted above, gave limited support for this: they found that a low baseline BP predicted early mortality (within 2 years of starting dialysis), whereas a high SBP predicted late mortality. The same database showed, however, that if BP levels measured during the course of hemodialysis were used, there was a general inverse relation between BP and mortality.

About 40% of hemodialysis patients have advanced coronary disease, and it has also been proposed that a high perfusion pressure is needed to keep the myocardium perfused. This idea is a resurrection of the original J-curve hypothesis,[5] which was not specifically applied to CKD patients, and postulated that when BP was lowered to very low levels, the risk was higher than at moderate levels, on the grounds that coronary artery perfusion occurred in diastole, and might be impaired if the pressure was too low. These findings, together with the concern that antihypertensive drug trials had shown rather disappointing reductions of coronary events, led to the establishment of the HOT trial described above. But HOT offered no support for this idea, because patients with known coronary heart disease who were randomized to the lowest target BP did better, not worse, than those without it.[31] Essentially the same result was found in the Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT),[32] in which patients with coronary disease documented by angiography, most of whom had BPs in the normal range at the start of the study, had lower rates of recurrent cardiac events if their BP was lowered further.

Another issue that has been raised[19] is the potential confounding effect of antihypertensive drugs. One study[33] reported that treated hypertensive patients on hemodialysis had half the risk of dying as the normotensive untreated patients, raising the possibility that antihypertensive drugs have some protective effect independent of their effects on BP. There is little evidence to support this view, however,[13] and in patients on home dialysis, of whom only 5% required antihypertensive drugs, the same U-shaped relationship between BP and mortality was observed as in several other studies.[34]

The measurement of BP in dialysis patients needs to be considered as a possible cause of these paradoxical findings. It has been questioned to what extent the measurements made at the time of dialysis, which were used in most of these studies, are representative of the BP level between dialyses.[35] Three prognostic studies have also used ambulatory BP monitoring to explore the relationship between BP and cardiovascular morbidity and mortality in hemodialysis patients.[36–38] The studies were small, and although all showed an association between ambulatory BP and outcome, none reported a relationship between outcome and predialysis measurements. The exact components of ambulatory BP that have been predictive of outcome have varied, although one observation has emerged consistently: loss of the normal nocturnal decline in BP carries a poor prognosis

A more plausible explanation, which has not gained much attention, is that in patients with advanced renal failure, the effects of hypertension are simply swamped by other toxic factors that are not operative in patients without ESRD. An analysis of 8600 patients in the Intermountain Heart Collaborative Study[39] who had their renal function assessed at the time of coronary angiography and followed for 3 years confirmed that impaired renal function increased the risk of myocardial infarction and death in these patients, and emphasized the fact that there was an excess risk that could not be accounted for by the traditional risk factors, including hypertension. Furthermore, the relationship between GFR and events was not linear—it was only in patients whose GFR was less than 57 mL/min where there was much increase in risk, and in this group the relative risk was 2.78. After adjusting for other variables (including the severity of disease on angiography) the risk was 2.08, whereas in the other subgroups with higher GFR it was not different from 1 (Figure 3). Other data support this idea. Thus, the annual death rate in the US Renal Data Service report was 23%,[11] while in another high-risk group (the HOPE placebo group[40]) annual rate of death, MI, and stroke was only 3.5%. Patients with advanced renal failure were excluded from HOPE. There are several potential candidates that could account for the excess mortality. These include disordered calcium and phosphorus metabolism, anemia, hyperhomocysteinemia, and inflammation.[39] All have been shown to be associated with increased risk, but only in patients with advanced ESRD.

CONCLUSIONS

Although both hypertension and cardiovascular disease are very common in patients with ESRD, and hypertension accelerates its development, it seems clear that the usual relationship between BP and risk is lost once patients get to the stage of going on dialysis. Possible explanations for this include the presence of high-risk, low-BP groups, inadequate BP measurements, and the swamping of

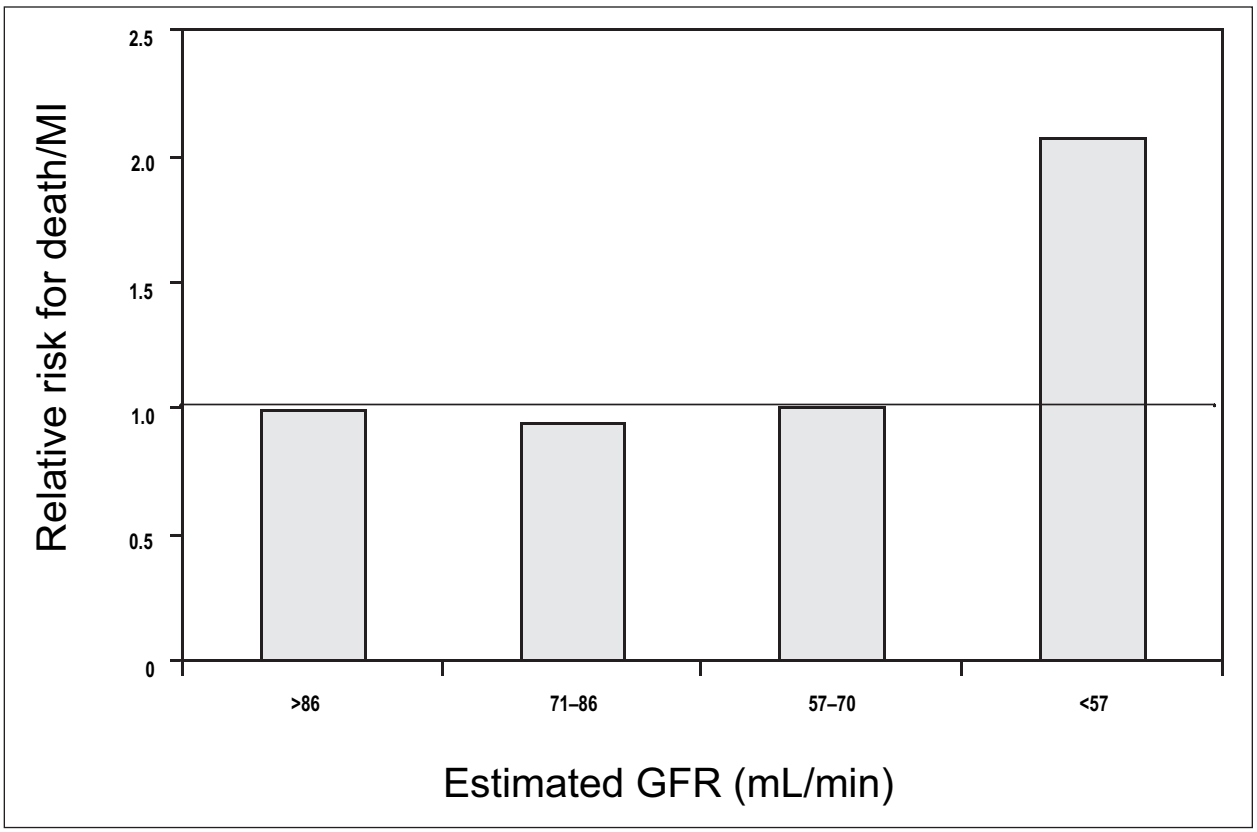

Figure 3. Relationship between estimated glomerular filtration rate (GFR) and the risk of death or myocardial infarction (MI). Referent level (relative risk 1.0) is GFR >86 mL/min. Data derived from Kidney Int. *2002;62:1776–1783.*[39]

the relationship by toxic factors present in patients with ESRD. Whether the BP–mortality relationship is U-shaped, inverse, positive, or simply flat is far from clear, but the statement that patients on hemodialysis should have their BP aggressively lowered seems unwarranted and even potentially harmful. In this era, when evidence-based medicine is supposed to hold sway, it seems that there are still instances where the Emperor has no clothes.

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