Strategies for Improving Long-Term Survival in Patients with ESRD

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In 2003, more than 320,000 people in the United States were receiving dialysis for ESRD, with predicted increases to 650,000 by 2010 and 2 million by 2030. Mortality from cardiovascular disease (CVD) in patients with ESRD is 10 to 30 times higher than in the general population. The exact mechanism of accelerated CVD in patients with kidney disease is unknown. Treatment costs for ESRD are in excess of $14 billion annually (6.4% of Medicare budget). Strategies to improve long-term outcomes include aggressive risk factor modification, minimization of dialysis complications, and kidney transplantation. Because abnormalities of mineral metabolism contribute to mortality risk, phosphate binder therapy is fundamental. More expensive non-calcium-containing phosphate binders such as sevelamer have been recommended to reduce cardiovascular calcification. However, the lack of outcome data and the $2 to $3 billion annual cost make it difficult to justify widespread utilization of newer binders as first-line therapy. Conversely, kidney transplantation is known to improve survival in ESRD. Progression of atherosclerosis and CVD in patients with renal failure is largely due to loss of renal function per se, and provision of a functioning kidney through renal transplantation halts the progression of CVD and dramatically reduces mortality. Despite this fact, many patients lose Medicare funding for immunosuppressive therapy 3 yr posttransplantation. To achieve the goal of prevention of cardiovascular mortality in patients with ESRD, it clearly would be more prudent, efficacious, and cost-effective to use Medicare prescription drug dollars to provide full coverage for life-long immunosuppressive drug therapy after renal transplantation.


It has been predicted that in the near future, there will be an alarming increase in the incidence and prevalence of ESRD both in the United States and worldwide. In 2003, more than 320,000 people with kidney failure were being treated with dialysis in the United States, and the prevalence is predicted to increase to 650,000 by 2010 and 2 million by 2030 (1,2). Mortality associated with ESRD is primarily due to cardiovascular disease (CVD), which accounts for 50% of the deaths among dialysis patients. Upon starting dialysis, 40 to 75% of patients will already have manifestations of CVD (3–5).

In ESRD, there are two primary mechanisms for CVD, namely vascular remodeling and vascular calcification. Vascular calcification, a marker of atherosclerosis and arterial stiffness, is common among dialysis patients and seems to be a significant risk factor for cardiovascular mortality. The American Heart Association issued a statement in 2003 that recommended patients with chronic kidney disease be considered a “highest risk group” for subsequent cardiovascular disease events (1). Although traditional risk factors for CVD are prevalent in patients with ESRD, they cannot fully explain the high mortality rate that has been reported. Other risk factors, such as electrolyte disturbances, fluid imbalance, and chronic inflammation, must also be considered.

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atherosclerotic vascular disease. Vascular remodeling can occur as a result of increased tensile stress, leading to medial wall thickening of the artery with subsequent luminal narrowing in small-resistance arteries. This remodeling process may be mediated through endothelial cell production of growth-regulating and vasoactive factors. Coronary calcification seems to be more prevalent in patients with renal disease compared with age- and gender-matched control subjects (13–15). The calcification associated with ESRD can occur in either the intima or the media of the arterial wall. Schwarz et al. (15) has shown that coronary plaques in uremic patients are characterized by marked calcification, increased media thickness, and infiltration and activation of macrophages. The primary difference in the plaques between the renal and nonrenal patients was in the composition of the plaque, not the size. It was initially thought that vascular calcification occurred as a passive process that resulted from calcium-phosphorus crystal deposition as a result of increased calcium-phosphorus ion product and hyperparathyroidism. Recently, it was suggested that calcification is an active cell-mediated process whereby vascular smooth muscle cells assume a bone-forming phenotype (16,17). The exact mechanisms for vascular calcification and the relationship between arterial wall calcification and atherosclerosis are poorly understood. It is likely that the excess cardiovascular calcification that is observed in patients with ESRD is a multifactorial process. Figure 1 summarizes the plethora of factors that potentially are involved in the pathogenesis, including hyperparathyroidism, hyperphosphatemia, hypertension, abnormal glucose metabolism, treatment with vitamin D analogs, and abnormalities in lipid metabolism. It seems that alterations in mineral metabolism may contribute to the development of vascular calcification (18). Vascular calcification has been associated with increased mortality in patients with ESRD (19,20).

Matsuoka et al. (21) observed that the finding of coronary calcification has prognostic significance in dialysis patients. The 5-yr survival of patients with a coronary calcium score >200 was 30% lower than patients with a score <200 (21). For a more detailed discussion of the mechanisms of CVD, please refer to Dr. McCullough’s article in this supplement issue.

Risk Factors for CVD in ESRD

Patients with ESRD typically exhibit a number of risk factors that could translate into increased risk for mortality from CVD. It is difficult to determine whether these factors alone or in combination with other processes lead directly to acceleration of the atherogenic process. Further study will be necessary to elucidate these mechanisms. The National Kidney Foundation Task Force has provided recommendations regarding the epidemiology of CVD risk factors associated with ESRD. This statement recognized that the excess risk for CVD in these patients may be attributable in part to the higher prevalence of traditional risk factors and in part to hemodynamic and metabolic factors specifically related to ESRD. Therefore, risk factor identification and reduction should focus on both classes of risk factors (22).

Traditional Risk Factors. Traditional risk factors for CVD are those defined from the studies of the Framingham population, including older age, diabetes, male gender, family history of coronary disease, hypertension, history of smoking, physical inactivity, high LDL levels, low HDL levels, menopause, and psychosocial stress. Evaluation of patients who were on dialysis showed that white race, older age, male gender, diabetes, and smoking were independent risk factors for death from CVD. It is interesting that hypertension and higher serum cholesterol were not found to be significant risk factors for mortality in dialysis patients. This paradox may be an example of so-called “reverse epidemiology,” which is explained by the fact that the relationships of serum cholesterol to mortality and hypertension to mortality display a U-shaped curve (23–26). In this regard, the reverse epidemiology may be explained by the fact that malnutrition and cardiomyopathy lead to excess mortality in dialysis patients with the lowest cholesterol levels and BP. Nonetheless, on the basis of results of cross-sectional studies, mortality from CVD in dialysis patients is substantially higher than that predicted from analysis of traditional risk factors, suggesting that additional nontraditional risk factors must be involved (23,27,28).

Kidney Disease–Related Cardiovascular Risk Factors. Kidney disease–related risk factors include albuminuria, proteinuria, extracellular fluid volume overload, disorders of calcium and phosphorus metabolism, electrolyte imbalance, hypertriglyceridemia, hyperhomocysteinemia, chronic inflammation or infection, elevated lipoprotein (a), increased thrombogenic factors, malnutrition, anemia, increased oxidative stress, and other uremic toxins (3). As renal function declines, most patients will have abnormal serum phosphorus and calcium concentrations, decreasing vitamin D levels, and increased levels of parathyroid hormone (PTH). Abnormalities of phosphorus and calcium metabolism, particularly hyperphosphatemia, seem to contribute to cardiovascular calcification.
(9,14,18,29). Increased serum phosphorus concentrations (29,30) and elevated calcium-phosphorus ion product are independent predictors for death in patients with ESRD (29–31). Ganesh et al. (30) reported that patients with serum phosphorus >6.5 mg/dl had a relative risk of 1.41 for cardiac death and 1.20 for sudden death. A weak association between PTH levels between 496 and 9476 pg/ml and mortality was also reported. In a more recent analysis, after adjustment for case mix and laboratory values, serum phosphorus concentrations >5.0 mg/dl were associated with increased relative risk for death (32). Higher adjusted serum calcium concentrations were also associated with increased risk for death. Moderate to severe hyperparathyroidism (PTH concentrations >600 pg/ml) likewise were associated with increased relative risk for death. When examined collectively, the population-attributable mortality risk percentage for disorders of mineral metabolism was 17.5%, owing largely to the high prevalence of hyperphosphatemia (32). Unfortunately, these observational studies provide correlations but do not elucidate the mechanism or prove causality. Giachelli et al. (33) proposed that phosphorus may have a direct effect on vascular smooth muscle cells that predisposes these cells to behave like osteoblasts and deposit calcium in the arterial walls of patients with ESRD. For instance, when vascular smooth muscle cells are cultured in high-phosphate medium, there is upregulation of the transcription of osteocalcin, a bone-specific protein (34). Overall, these data suggest that disorders of mineral metabolism and, most important, hyperphosphatemia play an important role in the development of cardiovascular calcification in patients who have chronic kidney disease and are on maintenance dialysis.

Uremia is also a proinflammatory state associated with markers of chronic inflammation such as C-reactive protein and increased levels of proinflammatory cytokines, both of which correlate with increased mortality (35). These cytokines and inflammatory stimuli are thought to play a role in the progression of atherosclerotic disease (36). Oh et al. (37) found that coronary calcium scores in young patients who were on dialysis correlate significantly with elevated C-reactive protein levels. Vascular inflammation may trigger calcification in dialysis patients at the end of their dialysis session, when the plasma is maximally alkalized (38). Some authors have suggested that oxidative stress and chronic inflammation may be the primary mechanisms underlying the excess CVD reported in patients with ESRD (39,40).

**Dialysis-Related Risk Factors.** In addition to all of the risk factors mentioned above, there may be risk factors that are attributable to the dialysis procedure _per se_. These risk factors include hemodynamic stress caused by intra- and interdialytic changes in cardiac filling pressures and wide fluctuations in BP, bioincompatibility of dialyzer membranes, dialysate impurities, and rapid changes in serum electrolyte concentrations (41).

**Mortality Benefit Associated with Selected ESRD Interventions**

**Phosphate Binders**

Hyperphosphatemia has been identified as an independent risk factor for increased cardiovascular mortality in patients with ESRD (30,32). The multifaceted therapeutic approach to control of serum phosphorus includes dietary phosphorus restriction, adequate dialysis, and usually treatment with dietary phosphate binders. Phosphate binders that are currently used in clinical practice include calcium-based agents such as calcium acetate and calcium carbonate and the non–calcium-based agents sevelamer and lanthanum carbonate. Data from observational studies have suggested that coronary artery calcium scores and large-vessel calcification correlate with the daily dose of calcium-based phosphate binder (8,18). The Treat-to-Goal study demonstrated that dialysis patients who received sevelamer hydrochloride (Renagel, Genzyme, Cambridge, MA) had slower progression of coronary and aortic calcification than patients who received calcium-based phosphate binders (42). In a _post hoc_ analysis of this study, oral calcium loading was identified as the key factor associated with progressive coronary artery and aortic calcification (43). However, deficiencies in the design of this study make it difficult to assess the validity of the calcium loading hypothesis. Unfortunately, the study was not designed such that non–phosphate binder exposure to calcium was kept similar between the two groups. In this regard, patients in the sevelamer treatment group received supplemental calcium in at least three forms: (1) Nighttime supplementation of calcium carbonate on an empty stomach to treat hypocalcemia; (2) adjustment of dialysate calcium concentration during the study to maintain normal serum calcium concentrations; and (3) sevelamer-treated patients received larger doses of vitamin D analogues, which would be likely to enhance dietary calcium absorption. It is entirely possible that sevelamer-treated patients who were given calcium supplementation on an empty stomach were actually exposed to a greater oral calcium load than were patients who received calcium acetate as a phosphate binder. Another _post hoc_ analysis of this study reported no difference in the rates of progression of coronary and aortic calcification in patients who were treated with calcium acetate compared with those who were treated with calcium carbonate even though predicted oral calcium loading would have been significantly greater in patients who were treated with calcium carbonate (44). Overall, the results of this study and deficiencies in study design suggest that some mechanism other than calcium loading may be responsible for the finding that sevelamer-treated patients have slower progression of cardiovascular calcification.

Another important critique of the Treat-to-Goal study is the failure to achieve equivalent control of LDL and total cholesterol in the two treatment groups. Because sevelamer is a bile acid sequestrant, sevelamer-treated patients had significantly lower levels of total cholesterol and LDL cholesterol compared with patients who received calcium-based phosphate binders. Because LDL may play a significant role in the progression of coronary artery calcification, the investigators should have controlled LDL in both groups. In fact, previous studies in the general population have shown that administration of a HMG-CoA reductase inhibitor ameliorates or reverses coronary artery calcification (45,46). Preliminary results of a recent study also suggested that administration of colestevin (bile acid sequestrant) in combination with atorvastatin slowed the progression...
of aortic calcification in dialysis patients (47). These investigators speculated that the decrease in aortic calcification resulted from control of serum phosphorus and LDL cholesterol levels. Thus, dramatic reductions in cholesterol levels may provide an explanation for the reduced rate of cardiovascular calcification that was reported in the sevelamer-treated patients in the Treat-to-Goal study.

Kidney Transplantation

Patients with chronic renal failure have dramatically higher rates of cardiovascular morbidity and mortality than the general population (Figure 2). Cardiovascular mortality increases 10-fold in patients with ESRD, even after adjustments for the effects of age, gender, race, and the presence of diabetes (48). Ischemic heart disease and congestive heart failure each are present in approximately 50% of patients who start dialysis, and the case fatality rate of these diseases in patients with ESRD is extremely high. Moreover, patients who are on dialysis experience dramatically rapid progression of atherosclerosis (49). It was recognized recently that chronic renal insufficiency per se seems to be a risk factor for cardiovascular mortality (50). Shulman et al. (51) showed that in the general population, elevated serum creatinine is one of the strongest predictors of mortality. Furthermore, the level of renal function attained after renal transplantation is strongly associated with increased risk for cardiovascular death (52). A serum creatinine >1.5 mg/dl was found to be a significant risk factor for cardiovascular death. Moreover, cardiovascular death risk increased progressively with higher levels of serum creatinine.

Renal transplantation has been shown to confer a significant survival advantage over maintenance dialysis (Figure 3) (53). It is likely that most of the survival advantage is related to decreases in both progression of CVD and cardiovascular mortality after successful kidney transplantation (54). The CVD rates peaked during the first 3 mo after transplantation and thereafter progressively decreased with time posttransplantation (Figure 4). This improved survival was evident in both living and deceased donor transplants, even in patients with ESRD caused by diabetes. In contrast, the CVD rates in dialysis patients who were on the transplant waiting list increased sharply and progressively in association with waiting list vintage (Figure 4). This survival advantage conferred by successful renal transplantation is particularly striking in view of the fact that immunosuppressive medications have many potentially deleterious effects on standard cardiovascular risk factors. The immunosuppressive regimens can cause or worsen hypertension, hyperlipidemia, and diabetes. Furthermore, there are abnormalities of mineral metabolism after transplantation such as hypercalcemia as a result of residual hyperparathyroidism and increased gastrointestinal calcium absorption and hypophosphatemia as a result of PTH-induced phosphaturia. Thus, it is apparent that the predominant theme underlying the rapid progression of atherosclerosis and CVD in patients with renal failure is the loss of renal function per se and that provision of a functioning kidney through renal transplantation halts the progression of CVD and dramatically reduces cardiovascular mortality risk (54).

![Figure 2. Cardiovascular mortality in patients with ESRD. This figure displays the cardiovascular mortality in the general population compared with patients who have renal failure and are treated with either dialysis or renal transplantation. The data presented are stratified by age, gender, and race. NCHS, National Center for Health Statistics multiple cause of mortality data files International Classification of Diseases codes 402, 404, 410 to 414, and 425 to 429; USRDS, United States Renal Data System. Reprinted from reference (4), with permission.](image_url)

![Figure 3. Adjusted relative risk for death after cadaveric kidney transplantation. The transplant group was 23,275 recipients of a first cadaveric transplant. The reference group was 46,164 dialysis patients on the transplant waiting list (relative risk 1.0). Patients in both groups had equal length of follow-up since placement on the waiting list. Values were adjusted for age, gender, race, cause of ESRD, and time from first dialysis treatment to placement on the waiting list. The points at which the risk for death and the likelihood of survival were equal in the two groups are indicated. A log scale was used. Reprinted from reference (53), with permission.](image_url)
Pharmacoeconomic Considerations

The majority of interventions that are made in the health care setting increase the per-patient lifetime health care costs. If our overall goal in clinical practice were to minimize total health care costs, then providing no treatment would be the preferred alternative. Clearly, this is not our goal, and a more appropriate therapeutic goal should be maximization of the health gain received from any particular therapy. Because health care resources have become more limited in recent years, pharmacoeconomic assessment of therapeutic interventions has become common practice. The cost of therapy is clearly an important consideration in patients with ESRD. The annual direct costs for ESRD are $23 billion (55). Compared with maintenance dialysis, renal transplantation has been shown to reduce overall lifetime health care cost along with increasing patient benefit. The benefit of renal transplantation was first described in 1968, when it was shown to increase patient survival and quality of life (56). Studies since that time have validated these results and have shown increases in quality of life in addition to increased employment rate (53,57–59). Renal transplantation is more cost-effective even in patients who are nonadherent with medical therapy posttransplantation (60). However, dialysis is one of the most expensive health interventions for which reimbursement is provided. Although the initial cost of renal transplantation may be higher, after 2 to 3 postoperative years, it becomes a cost-saving intervention when compared with dialysis, even considering the cost of maintenance immunosuppression (61,62). Thus, it seems logical that an intervention that has been proved to reduce mortality and is cost-effective should be promoted to reduce the economic burden of dialysis while increasing patient quality of life.

Another important consideration in the cost of ESRD treatment is adjunctive therapy with phosphate binders. On the basis of results from the Calcium Acetate Renagel Evaluation study (63) and average wholesale prices, the doses that are necessary to treat hyperphosphatemia with PhosLo (Nabi Pharmaceuticals, Boca Raton, FL) and Renagel would result in projected annual costs per patient of $732 and $4283, respectively. In this regard, it should be noted that if concerns over calcium loading with calcium-based phosphate binders lead to the widespread adoption of sevelamer as the first-line phosphate binder, then the cost for treatment of the 300,000 patients who are on dialysis in the United States would increase by >$1.0 billion annually. Because doses of sevelamer two to three times higher than those used in the Calcium Acetate Renagel Evaluation study are now used routinely to treat hyperphosphatemia, the actual costs may well exceed $2 to $3 billion annually. Although the lipid-lowering properties of sevelamer may play a beneficial role in slowing the progression of cardiovascular calcification (42), cost-benefit analysis suggests that a combination of an HMG-CoA reductase inhibitor and a calcium-based phosphate binder might be a more cost-effective alternative (63).

The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines have recommended the use of non–calcium phosphate–binding agents for several common clinical situations (64). However, these treatment guidelines were developed without consideration of the economic impact. Given the enormous financial burden of caring for dialysis patients, it is imperative that before widespread implementation, costly new therapeutic agents must be shown to have similar efficacy in achieving K/DOQI guidelines for phosphorus and calcium-phosphorus ion product. The additional costs should also be justified by validation of the beneficial effects of the higher priced drugs on rates of hospitalization and mortality. To date, phosphate-binder therapy with sevelamer has not been shown to meet either of these criteria. Manns et al. (65) recommended that the hypothesized benefits of sevelamer on cardiovascular mortality be tested in well-designed, randomized intervention trials before embarking on national programs to expand Medicare coverage to cover the cost of sevelamer. It was estimated that sevelamer would have to show a 45% reduction in hospitalizations to offset its substantially increased cost. Moreover, because the actual doses of sevelamer that are necessary to
achieve control of serum phosphorus may be higher than those used in previously published studies, the true economic impact of widespread implementation of the K/DOQI Bone Metabolism guideline for phosphate binder therapy may well be greater than the current projected costs.

These cardiovascular mortality and economic data raise an important question: Is it wise to accept the unproved calcium-loading hypothesis regarding cardiovascular calcification and spend an additional $3 billion per year for newer phosphate binder therapy when we already have an ESRD therapy, in the form of renal transplantation, that has been proved to halt progression of CVD and significantly improve mortality? This is not a trivial issue. Although immunosuppressive therapy to maintain functioning renal allografts has been shown to reduce cardiovascular mortality in patients with ESRD, many patients lose their Medicare funding for immunosuppressive therapy a mere 3 yr after transplantation. With regard to our goal of prevention of cardiovascular mortality in patients with ESRD, it would clearly be more prudent, efficacious, and cost-effective to use the soon-to-be-available Medicare prescription drug dollars instead to provide coverage for life-long immunosuppressive drug therapy after renal transplantation.

Conclusion
The role of CVD as a cause of mortality in ESRD patients has received recent attention, and a focal point of the discussion is the process of vascular calcification. The precise mechanism of CVD in these patients remains unknown, but it is likely that a plethora of different factors contribute to the process. Thus, it is probably overly simplistic to implicate and target a single factor as the most important pathogenic mechanism in the development of cardiovascular calcification. Detection of risk factors for CVD (both traditional and kidney disease related) in the early stages of renal impairment may be necessary to have a significant impact on outcome. Additional studies with mortality end points are urgently needed to determine whether therapeutic measures aimed at prevention of cardiovascular calcification will translate into an improvement in long-term cardiovascular mortality. As our knowledge of the mechanisms of CVD in chronic kidney disease continues to expand, additional targets for intervention will be identified, and it is likely that a multifaceted therapeutic approach will be required to achieve a substantial reduction in cardiovascular mortality in dialysis patients.

Currently, only one therapy has been shown to reduce cardiovascular mortality in patients with ESRD. This therapy is renal transplantation. It is apparent from the available literature that with regard to prolonging life and reducing cardiovascular mortality, dialysis is not a good substitute for provision of a well-functioning kidney with transplantation. On the basis of efficacy and pharmaco economics analyses, serious consideration should be given to revision of the Medicare Modernization Act such that all kidney transplant recipients are eligible for life-long full prescription drug coverage for immunosuppressive medications.

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