Optimal Cardiovascular Therapy for Patients with ESRD over the Next Several Years

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This review points out the high morbidity and mortality associated with cardiovascular disease in patients with ESRD. Although there have been few randomized controlled trials that have examined this clinical problem in the population of patients with ESRD, there is a growing appreciation of the presentations and consequences of cardiovascular disease in this cohort. The etiology of this disease is multifactorial and the consequences include sudden death, coronary artery disease, and heart failure. The sudden death associated with ESRD has been linked to a progressive cardiac fibrosis that also accompanies left ventricular hypertrophy. Ischemic coronary disease is also common in this population.

With regard to new therapy, efforts to control extracellular fluid volume and thereby control blood pressure are important. Two randomized trials have not shown the benefit of lowering low-density lipoprotein cholesterol concentrations in patients with ESRD, but such a strategy is thought to be beneficial in patients with chronic kidney disease. Efforts to optimally control calcium and phosphate concentrations are also beneficial, because vessel calcification remains a major problem for ESRD patients. The increase in vessel calcification leads to an increase in arterial stiffness and an increase in pulse wave velocity, which, in turn, increases cardiovascular morbidity and mortality.

Additional recommendations are provided in this review including the use of erythrocyte stimulating agents, the cautious use of beta blockers with patients with a low ejection fraction systolic failure, and drugs that block the renin-angiotensin-alderosterone system.

Clin J Am Soc Nephrol 4: S106–S109, 2009. doi: 10.2215/CJN.04640709

The increased frequency of cardiovascular death among patients with chronic kidney disease (CKD) has been emphasized in many recent publications (1). This increase in cardiovascular morbidity and mortality is true for subcategories of cardiovascular disease including congestive heart failure, stroke, myocardial infarction, and composite death rates from cardiovascular causes (1). One problem that has limited progress in this field has been the fact that there has been a paucity of well designed randomized controlled trials that address the issue of which drugs or combinations of drugs are most effective in either reducing or slowing the growth of cardiovascular morbidity and mortality in ESRD and CKD patients. In fact, patients with CKD and ESRD have been routinely excluded from large trials of cardiovascular morbidity and mortality. This has resulted in a dearth of literature that speaks to evidence-based or best practice therapy in cardiovascular disease in patients with ESRD.

Etiology and Presentations

The etiology of cardiovascular disease in ESRD is multifactorial. As shown in Figure 1, there are several modifiable, nonmodifiable, and specific uremia-related factors that contribute to cardiovascular morbidity and mortality. As shown in the figure, all of these factors sum to increase arterial stiffness and increase blood pressure (BP); as a result, increase left ventricular stress. Arterial stiffness leads to an increase in pulse wave velocity, an independent risk factor for cardiovascular morbidity and mortality. The factors shown in Figure 1 are relevant for the development and progression of atherosclerosis patients with ESRD and for the development of vascular stiffness. The aggregate of these derangements in physiology that occur in advanced CKD and ESRD is that the morphology of the left ventricle changes over time. For example, after years of exposure to high BP and an increased afterload, in conjunction with anemia, hyperparathyroidism, and high levels of circulating angiotensin II levels, the development of concentric left ventricular hypertrophy may occur. This form of ventricular abnormality is characterized by a thickened left ventricular myocyte, a preserved left ventricular ejection fraction and left ventricular volume, but a reduction in left ventricular distensibility leading to a "stiff" ventricle. In contrast, in patients whose physiology is dominated by volume overload who have an increase in cardiac output, eccentric left ventricular hypotrophy may develop. This abnormality is characterized by an expanded left ventricular cavity and an elongated myocardial myocyte. Patients with eccentric left ventricular anatomy often have a decrease in ejection fraction and an expanded left ventricular volume (systolic dysfunction). In one study of these phenotypes in patients with ESRD, the prevalence of these abnormalities was equal (2). Abnormal diastolic or systolic function leads to a susceptibility to volume overload and pulmonary edema and an increased risk of sudden death (3,4).

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ISSN: 1555-9041/401–0106

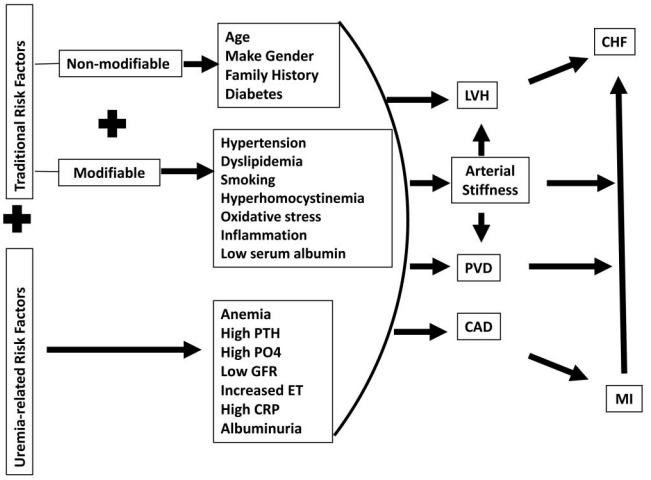

Figure 1. Factors in cardiovascular disease for ESRD patients. From Qunibi W, Hillis LD, Henrich WL: Coronary artery disease in end-stage renal disease patients. In: *Principles and Practice of Dialysis* 4th ed., edited by Henrich WL, Philadelphia, Wolters Kluwer Health/Lippincott, Williams & Wilkins (http://lww.com), 2009, pp. 335–356.

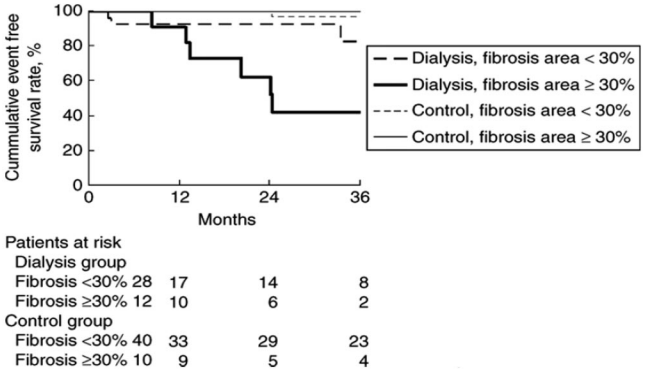

Figure 2. Cardiac fibrosis associated with increased mortality in ESRD patients. Reprinted by permission from Macmillan Publishers Ltd: *Kidney Int* (Aoki J, Ikari Y, Nakajima H, Mori M, Sugimoto T, Hatori M, Tanimoto S, Amiya E, Hara K: Clinical and pathologic characteristics of dilated cardiomyopathy in hemodialysis patients. *Kidney Int* 67: 333–340, 2005) (reference 7), copyright 2005.

As emphasized by others in this symposium, it is becoming abundantly clear that one of the major causes of death in ESRD patients is sudden death. There are several reasons why this may occur in a person with left ventricular hypertrophy: abnormalities in the coronary microcirculation are known to occur in left ventricular hypertrophy such that there is a myocyte/capillary mismatch; there is impaired coronary reserve; there is reduced aortic compliance and increased activity of the sympathetic nervous system; there is an increase in the activity of the renin-angiotensin system; and, because the patient is on dialysis, sudden changes in potassium, calcium, or magnesium concentrations may also play some role. In recent years it has been increasingly recognized that a common left ventricular abnormality is an increase in intermyocytic fibrosis in the left ventricle, a development that is associated with the risk of sudden death (5). Detecting myocardial fibrosis has been difficult to accomplish in patients, but new studies on such patients using acoustic densitometry and a measurement called "integrated back scatter signal" show promise with regard to being able to detect accurately the burden of increased myocardial fibrosis *in vivo* (6). Moreover, there are pathologic correlates for these *in vivo* findings, as shown in a recent study in which endomyocardial biopsies were performed in patients with ESRD and heart failure not due to ESRD (7). In this study, the prevalence of fibrosis was linked to the likelihood of cardiac death (see Figure 2).

It would be logical to ask which factor or factors are most likely responsible for this development of fibrosis in heart muscle. Recent work suggests that some adrenal steroids may be profibrotic (8) or that the mammalian target of rapamycin pathway may be involved in uremic fibrosis (9). These studies therefore provide evidence that opposing the effects of adrenal steroids or blocking the mammalian target of rapamycin pathway may lead to some mitigation of the fibrosis. Such observations in the laboratory offer hope that there will soon be new therapies to prevent or delay the insidious development of cardiac fibrosis in ESRD patients in the not too distant future.

Therapeutic Strategies

The question that is posed by all of these studies is what is likely to be effective in improving cardiovascular morbidity and mortality in the next several years? Numerous recent studies have extolled the virtues of short daily or nocturnal dialysis programs to control volume and BP (see reference 10 for a summary of this topic). Depending on the results of current ongoing National Institutes of Health trials on short daily and nocturnal dialysis, this may soon become more common as patients opt for this therapy. It is also important to point out that improving the uremic milieu is effective in improving systolic function. One recent study suggested that patients with very poor systolic function could achieve excellent systolic function after a successful renal transplant (11). In this study, the most successful results were seen in patients who had been on dialysis for less than 17 mo. This in turn implies that the longer a patient stays on dialysis, the more irreversible or intractable the systolic dysfunction becomes and a less dramatic improvement may occur after transplant. Another recent study by Agarwal *et al.* (12) suggests that there is great benefit on BP and overall heart performance if patients have dry weight reduced by as little as 1 kg. This paper suggests that this can be done safely under careful circumstances. With regard to pharmacologic interventions, there is now evidence that the use of angiotensin converting enzyme inhibitor therapy is beneficial in reducing cardiovascular events in ESRD patients (13).

A benefit of lowering LDL cholesterol concentrations in patients with ESRD has not been shown to date. The 4D study (14) failed to show a benefit of lowering LDL cholesterol in diabetic patients with ESRD. Similarly, a new trial published only recently in nondiabetic patients produced a similar result (15). These two very well done studies raise the question of whether

Table 1 . Summary of findings of several investigators at this conference

- Maintain euvolemia (increased use of extra sessions, nocturnal or quotidian dialysis)
- Excellent BP control (predialysis systolic BP < 130/80), using ACEI/ARB as first line agents where needed
- Monitor for LVH/LVMI with an echocardiogram or MRI (no contrast) Q 12 to 24 months
- Manage calcium/phosphorus to a low predialysis phosphorus, if possible, and a PTH of less than 500 pg/ml (or 1.5 to 2 times normal); replete Vitamin D where possible; controversy over Ca-containing vs. non-Ca-containing Phosphate binders at present
- Hematocrit to guidelines
- Avoid catheters
- Improved nutrition
- LDL cholesterol to <100 mg/dl, <70 in patients with documented coronary artery disease
- Cautious use of beta blockers for low ejection fraction systolic failure
- Passive resistance exercise where feasible
- Stay tuned for evidence of benefit of aldosterone blocking agents on myocardial fibrosis/sudden death

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; PTH, parathyroid hormone.

statin therapy should be recommended in patients with ESRD at the present time. One last factor to consider is the issue of the calcium-phosphorus product, where a great deal of work has pointed out that the calcification of blood vessels is more complicated than simple manipulation of the calcium and phosphorus concentrations. In this regard, the demonstration of bone-forming genes in blood vessels, which are detected before calcification occurs, suggest that such genes have an effect to promote vessel calcification (16). The reason that this is such a major consideration is that vessel calcification leads to an increase in pulse pressure and an increase in vessel stiffness, which, in turn, exacerbates abnormalities in left ventricular function and increases left ventricular overload. Several studies have demonstrated that the increase in vessel stiffness is associated with an increase in pulse wave velocity (17), and that pulse wave velocity increases as renal function declines (18). The vascular calcification score in the thoracic aorta correlates well with the pulse wave velocity (19).

Summary

Conclusions from this review suggest that vessel calcifications are very common in ESRD and having such calcifications and vessel stiffness confers a poor prognosis. Although there certainly are calcifications that occur in the media of the vessel in ESRD patients, even if the lumen is patent, the overall stiffness of the vessel may be important for survival.

With regard to management of patients with ESRD and cardiovascular risks going forward, Table 1 summarizes the findings of several investigators at this conference. Implicit in this discussion and these recommendations is the value of an early assessment of left ventricular function to provide a baseline value and inform more precise therapy. One priority is to maintain euvolemia in patients with ESRD through the use of extra dialysis sessions and nocturnal or daily dialysis. A second focus has to be on excellent BP during the interdialytic period using drugs that block the renin-angiotensin system as first line agents. We recommend an echocardiogram at the beginning of dialysis, to be repeated every 12 to 24 mo. Should new technology confirm that acoustic densitometry is useful at detecting myocardial fibrosis, then that would be a useful additional test to obtain. Most practitioners now aim to manage the calcium-phosphorus product to as low of a predialysis phosphate concentration as possible and a parathyroid hormone concentration of less than 500 pg/ml. In addition to managing hematocrit to guidelines, a new emphasis from this conference and from recent literature is to avoid, as much as possible, temporary dialysis catheters. In patients with prior myocardial infarction and evidence of peripheral vascular disease, managing the LDL cholesterol to less than 100 mg/dl is recommended. Also beneficial is the cautious use of beta blockers in patients with low ejection fraction systolic failure (20,21). Using drugs that block the aldosterone system in preventing increased myocardial fibrosis awaits further investigation but is a promising therapy of the future.

Acknowledgments

The author thanks Ms. Tina Luther for expert secretarial assistance.

Disclosures

None.

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