Coronary Heart Disease in Chronic Renal Insufficiency: Some Management Considerations

STEPHEN G. ROSTAND
Nephrology Research and Training Center, Division of Nephrology, Department of Medicine, The University of Alabama at Birmingham, Birmingham, Alabama.

Cardiovascular diseases (CVD) are the leading causes of death in end-stage renal disease (ESRD) populations. In an era when CVD mortality in the United States has been declining in the general population, no such reduction in mortality has been noted for ESRD patients in whom mortality from heart disease of all causes has progressively increased and now represents approximately 50% of all deaths. Moreover, in ESRD populations, death rates from myocardial infarction and from all other cardiac causes, irrespective of age, exceed those for the population at large (1). In fact, rates of new myocardial infarction in patients with renal insufficiency but not yet at end stage are triple those of the general population (2). This has raised questions about whether patients with chronic renal failure have a unique susceptibility to CVD, whether rates of atherosclerosis are accelerated in renal failure, and whether ESRD is a vasculotoxic condition.

A partial explanation for these observations may come from the demographic characteristics of ESRD populations. Increased age is an important unmodifiable demographic factor associated with cardiovascular risk. During the past 15 yr, the median incident age of patients with ESRD in the United States has increased by more than a decade, from 53 yr in 1980 to 64 yr in 1995. Patients older than age 65 now represent nearly 68% of all new dialysis patients. Moreover, during the same time period, the greatest percentage increase in incidence of ESRD (nearly sevenfold) was seen in the those age 75 and older. As a result, there are nearly triple the number of those age 65 and older in dialysis populations than are in the general U.S. population (3). Because CVD is seen more commonly in older populations, it is not surprising that there is a high prevalence of preexisting comorbid cardiovascular conditions in new ESRD patients. Thus, for example, in 1997, 34.7% had a history of congestive heart failure, 25.1% had a history of coronary artery disease (CAD), 9.4% had a history of coronary myocardial infarction, and 15.6% had a history of coronary peripheral vascular disease, a surrogate marker for CAD (4). Such preexisting cardiovascular conditions have long been known to adversely affect ESRD survival.

Other important risks for fatal and nonfatal cardiovascular events are the diseases that cause ESRD. Of these, hypertension and diabetes mellitus, which cause 70% of all ESRD in the United States, are strongly associated with the development of CVD, particularly CAD, whose attendant ischemia not only can produce acute coronary syndromes but also can contribute significantly to other cardiac disorders. For example, it is know to be the underlying basis for 70% of congestive heart failure (5). Though seen less often as causes of renal failure, systemic lupus erythematosus, vasculitides, and atherosclerotic renal disease, resulting either from direct effects on the vasculature or from the effects of steroid therapy, are strongly associated with the presence of CAD as is the nephrotic syndrome.

However, although age, hypertension, and diabetes are important risks for CVD in ESRD populations, present data reveal that increased rates of cardiovascular mortality are seen across all age groups (1). When the results of current studies are compared with ones done in an era when the median age of ESRD patients was less than 40 yr and when diabetics were largely excluded from dialysis and transplantation but also showed high cardiovascular mortality, one must conclude that demographics alone cannot explain the predilection for CAD events in ESRD.

CAD Risk Factors in Renal Failure and the Effects of Their Modification

ESRD is associated with many established and newly recognized risk factors for ischemic heart disease and its consequences (Figure 1). When these aggregated risks are coupled with the current ESRD demographics, cardiovascular morbidity and mortality are virtually assured. Thus, it seems reasonable that modifying these factors may serve effectively in primary and secondary prevention or reduction of cardiovascular events.

Dyslipoproteinemia

Lipoprotein abnormalities are the most often discussed established CAD risk factors seen in renal failure. Hypertriglyceridemia is most commonly observed in ESRD but has a weaker statistical association with CAD than other frequently
noted lipoprotein abnormalities (6), such as elevated total serum cholesterol, VLDL, LDL, Lp (a), and apolipoprotein CIII and reduced HDL and apolipoproteins AI, AII, and AIII. The extent of these changes depends on the duration and severity of renal insufficiency because these abnormalities become more apparent as renal deterioration advances (7). Moreover, their pathophysiologic significance may vary with race and gender (8,9).

Factors that contribute to uremia-associated dyslipoproteinemia include obesity, diabetes mellitus, uremic glucose intolerance, hyperparathyroidism (HPTH), reduced active vitamin D metabolites, early menopause (in the case of women), and possibly carnitine deficiency that impairs fatty acid metabolism.

There is consensus that treatment of dyslipidemia in non-ESRD populations can lead to stabilization and even regression of atherosclerotic plaque and to a reduction of fatal and nonfatal myocardial ischemic events over time periods ranging from 6 mo to 2 yr or more (10,11). Although there is little question that lipid-lowering agents can favorably modify lipoprotein concentrations in both non-ESRD and ESRD populations, unlike non-ESRD populations, there is no evidence to show reductions of cardiovascular events in renal failure (12). Perhaps the inability to see such benefits relates to the fact that it may take as long as 2 to 5 yr to see a decrease in cardiovascular events, barely enough time to see such improvements in ESRD patients whose 5-yr survival on dialysis is only 40 to 50% (4). Nevertheless, because lipoprotein abnormalities are observed early in the course of progressive renal deterioration, it seems more likely that intervention at a time well before the patient approaches ESRD may yield the best results. Fibrin acid derivatives, bile sequestrants, omega-3 polyunsaturated fatty acids, and nicotinic acid have been used to correct dyslipoproteinemia in ESRD, but the best tolerated are the statin drugs. Studies that tested the effects of L-carnitine supplementation showed that although blood carnitine levels could be restored, there were no significant effects on lipid profiles (13).

Hypertension
Hypertension is a well-established risk factor not only for myocardial ischemia, atherogenesis, and coronary artery calcification but also for the development of left ventricular hypertrophy (LVH). By contributing to LVH, hypertension represents an important risk for sudden cardiac death. Forces on arterial and aortic walls produced by increased BP alter vascular endothelial cell function by inciting arterial oxidative stress and inflammatory responses. These effects in turn initiate the atherosclerotic process and stimulate various growth-promoting peptides (14). The attendant endothelial dysfunction can lead to hypertrophy, hyperplasia, lipid incorporation, and calcification of the vascular smooth muscle and to associated reductions in vascular compliance and thus to tissue ischemia. The reduced elasticity of the aorta and peripheral arteries further contributes to increased cardiac work, LVH, and increased cardiovascular mortality in ESRD patients (15).

Because hypertension is a major hazard for CAD and stroke and because BP reduction can reduce the risk for myocardial infarction, it is disheartening that BP is not particularly well controlled in ESRD patients (16). This may be due to numerous factors, including medication cost, lack of patient compliance and education about their medications, selection of an inappropriate dry weight, excess interdialytic weight gain, sub-

Figure 1. Interrelationship of risk factors for heart disease, cardiac performance, and cardiovascular events in chronic renal insufficiency.
optimal therapy, and withholding antihypertensive medications before dialysis. Whatever the reasons, efforts to improve BP need to be intensified. In this regard, the use of ambulatory BP monitoring may be of great use because it allows a more comprehensive assessment of daily variations of BP than single measurements and therefore may be better in helping to determine the best antihypertensive strategies.

Many drugs are available for the task. Recently published data from the Heart Outcomes and Prevention Evaluation study (17) suggest that in high-risk patients, the use of an angiotensin-converting enzyme inhibitor (ACEI) significantly reduces death rates for stroke, myocardial infarction, and all cardiovascular causes, effects that could not be attributed simply to BP lowering. Thus, drugs of this class may be beneficial in ESRD patients, especially if hyperkalemia does not become a problem. The use of β-blockers may also have a beneficial effect in this group who either have or are at high risk for developing cardiovascular complications. In addition, there may be a theoretical benefit from using calcium channel blockers because they have been shown in animal studies to decrease intravascular and myocardial calcium content (18).

**Left Ventricular Hypertrophy**

LVH is an important risk factor for death after myocardial infarction; LVH and increased left ventricular mass index are the most common structural abnormalities of the heart seen in renal failure. LVH can be attributed in large part but not exclusively to the effects of hypertension. The high prevalence of LVH in ESRD populations may well account for their observed excess fatal coronary heart disease events, for in addition to increased coronary mass there is a reduced density of capillaries with respect to cardiomyocytes as well as an increase of the wall to lumen ratios of intramyocardial arterioles (19,20). Such changes can decrease myocardial tolerance to ischemia by creating an imbalance between oxygen supply and demand. This may contribute to the decreased coronary vasodilator reserve noted with LVH and may also explain the 25 to 30% prevalence of myocardial ischemia seen in ESRD patients who have no anatomically significant coronary event documented by angiography (9).

Secondary HPTH, elevated levels of endothelin, and other inhibitors of nitric oxide synthesis may also contribute to altered endothelial and cardiomyocyte growth and function. It seems reasonable that coronary vasodilators, e.g., nitrates, calcium channel blockers, and estrogens, or drugs that improve endothelial function such as lipid lowering agents and ACEI may be beneficial. ACEI may also produce regression of LVH. Although regression of LVH may be associated with lower cardiac mortality, such regression is infrequently seen in ESRD. If such a benefit is to be derived, as with therapy for dyslipoproteinemia, early intervention with antihypertensive agents may ultimately be most effective. At present, however, there is no evidence for such benefits in the ESRD population.

**Anemia**

Anemia contributes to myocardial ischemia by producing high cardiac output and increased cardiac work, reduced coronary artery filling times, reduced myocardial oxygen delivery, and reduced coronary artery dilator reserve. These effects are additive to those of LVH. It now is well established that treatment of uremic anemia with erythropoietin can improve cardiac performance (21). Although correction of hematocrit to concentrations above 30% has improved the well-being of most patients undergoing renal replacement therapy and may have decreased the number of anginal episodes, there are no studies to show that the number of other fatal and nonfatal cardiac events has been reduced.

**Diabetes Mellitus and Carbohydrate Intolerance**

Diabetes mellitus is the most common cause of renal failure in the United States and is associated not only with hypertension but also with hypertriglyceridemia and hypercholesterolemia—elevated LDL and depressed HDL cholesterol concentrations—with LVH and with hyperfibrinogenemia. Moreover, chronic renal failure, independent of diabetes mellitus, is also associated with insulin resistance and glucose intolerance. Both are associated with the accumulation of advanced glycation end products that may induce cellular activation and endothelial damage, ultimately contributing to or even accelerating atherogenesis (22).

There is considerable evidence that aggressive glucose control can significantly reduce microvascular and macrovascular complications of diabetes. Therefore, it is important not only to manage diabetes aggressively before the onset of renal disease but also to continue rigorous glycemic control after ESRD has developed. Because hypoglycemic reactions are more common in renal failure, there is a tendency for nephrologists and others who care for diabetics with ESRD to allow blood glucose concentrations to remain at levels that would be unacceptable in the absence of renal failure, thus sustaining the risk for vascular damage and atherosclerosis. Sustained rigorous glycemic control before the onset, as well as after the initiation, of renal replacement therapies may be important in reducing cardiovascular morbidity and mortality in diabetic patients as has been shown by Wu et al. (23). However, whether such benefits would be offset by excessive hypoglycemic complications needs to be investigated further.

**Altered Pituitary-Gonadal Axis**

It has long been observed that women who develop ESRD have abnormal menstrual cycles; they either cease menstruating or menstruate infrequently, and they often fail to ovulate. Thus, women with ESRD seem to have premature menopause and, as a result, may be at cardiovascular risk earlier than postmenopausal women in the non-ESRD population. Women with ESRD have symptoms of ischemic heart disease and significant anatomic CAD with a greater frequency than women without ESRD, but still their high rates of CAD and symptoms of myocardial ischemia are less than those of men (8). Nevertheless, these findings suggest that women with ESRD may have accelerated atherosclerosis and may benefit from estrogen replacement therapy. In this regard, the HERS Trial described a late benefit of estrogen replacement in postmenopausal women (24). Thus, it may be that estrogen replace-
ment therapy in women with renal failure may reduce coronary artery risk; however, Stehman-Breen et al. (25) observed that estrogen replacement therapy is prescribed less frequently in ESRD than in non-ESRD women. Recent studies have found that treatment of postmenopausal women with ESRD using estradiol could increase HDL cholesterol and apolipoprotein A1 (26,27). Although such improvements may confer protection, once again there are no large-scale studies showing coronary events to be decreased (26). Conjugated estrogen may also be beneficial because of its effects as a coronary vasodilator, but this effect may be countered by its stimulation of vascular smooth muscle calcification (28). Perhaps this might in part contribute to the early increase in cardiovascular events noted in the HERS study (24). Thus, the impact of estrogen replacement therapy on preventing cardiovascular events in ESRD remains to be determined.

**Hyperhomocysteinemia**

Hyperhomocysteinemia has emerged as an important risk factor for fatal and nonfatal coronary events (29). In patients with established CAD, it is also a strong predictor of mortality (30). Homocysteine has been shown to enhance neutrophil-endothelial interactions and impair endothelium-dependent vasodilatation. As in the general population, hyperhomocysteinemia is seen with high prevalence and has been found to be an independent predictor of CVD events in renal failure (31).

Homocysteine metabolism is critically dependent on vitamin B_{6}, vitamin B_{12}, and folic acid; thus, deficiencies in these vitamins could limit homocysteine metabolism and produce hyperhomocysteinemia. In renal failure, poor nutrition coupled with removal of water-soluble vitamins by dialysis may partially explain a tendency to deficiencies of these vitamins and the high prevalence of hyperhomocysteinemia. In non-ESRD populations, treatment with folic acid alone or in combination with vitamins B_{12} and B_{6} has been shown to lower homocysteine levels, but to date no clinical, randomized trials measuring the effects of lowering homocysteine levels on cardiovascular events have reported their results. In renal failure, most patients are prescribed multivitamins with enough folic acid to reduce homocysteine, at least in nonuremic subjects. Thus, current folic acid supplementation regimens may be inadequate in renal failure because hyperhomocysteinemia and excess cardiovascular events persist.

**Calcitropic Hormone and Calcium/Phosphorus Dysregulation**

HPTH, hypovitaminosis D, and hyperphosphatemia are nearly universally found in ESRD and develop progressively as renal function deteriorates. Although these alterations are most often considered in the context of renal osteodystrophy, there is a growing body of evidence to support the view that elevated parathyroid hormone (PTH), reduced production of active vitamin D metabolites, altered tissue responsiveness to these hormones, sustained hyperphosphatemia, and the aggressive use of calcium supplements and vitamin D analogs are important in the pathogenesis and maintenance of CVD in chronic renal failure (32). Both PTH and vitamin D increase the calcium concentration of vascular smooth muscle and cardiac myocytes, thereby altering myocardial oxidative metabolism and affecting BP, cardiac contractility, and force generation. This can cause the heart to be more critically dependent on oxygen and, thus, more susceptible to ischemia. Vitamin D depletion can produce vascular smooth muscle cell growth and proliferation, and hypovitaminosis D is associated with coronary artery calcification, a phenomenon that has recently been found to be exuberant in human uremic hearts when compared with nonuremic hearts (33,34). In this regard, in renal failure, HPTH is associated with reduced luminal diameter of small intramyocardial arteries. Vitamin D deficiency and HPTH can produce increased cardiac mass and are associated strongly with heart valve calcification, and HPTH is associated with myocardial fibrosis and calcification. In renal failure, HPTH has been shown to affect adversely lipoprotein metabolism and to produce insulin resistance and glucose intolerance. A role for vitamin D is less clear, but 1,25(OH2)D3 has been shown to correct glucose intolerance, insulin resistance, and hypertriglyceridemia in ESRD patients on dialysis (32).

One of the common consequences of altered calcium and phosphorus homeostasis resulting from these changes in calcitropic hormones is hyperphosphatemia and an elevated calcium × phosphate products that are often difficult to control and that are associated with calcification of soft tissues, including the aorta, coronary, and other medium sized arteries. It is therefore not surprising that one marker of this dysfunctional calcium/phosphorus regulation, hyperphosphatemia, is associated with a significantly increased risk of mortality in ESRD (35). Attempts to correct serum PTH concentrations to 100 to 300 pg/ml, hyperphosphatemia to less than 6.5 mg/dl, and keeping calcium × phosphate products in the range of 50 to 60 must begin early in the course of renal failure, well before the need for dialysis. There are numerous calcium supplements and vitamin D analogs as well as a novel non–aluminum-containing phosphate binder that are available for use. However, one must be careful not to suppress PTH excessively or to produce hypercalcemia or hypervitaminosis D for these can also contribute to metastatic vascular calcification; once established, such calcification is rarely reversed.

Taken together, these changes in PTH and vitamin D status and calcium/phosphorus control, either through direct or permissive effects on cardiac metabolism, glucose intolerance, hypertension, dyslipoproteinemia, vascular smooth muscle hypertrophy and arterial calcification, and LVH, contribute significantly to the sustained high rates of morbidity and mortality from cardiac dysfunction, atherosclerosis, and CVD seen in uremia. The ubiquity of this metabolic derangement, practically unique to renal failure, may also explain why the benefits of modifying more traditional risk factors have not been unequivocally seen in ESRD as they have in the non-ESRD population.

**Inflammation**

Increasingly, atherosclerosis and acute coronary events are being viewed more as a consequence of inflammation and less as simply the result of vascular lipid accumulation. The in-
flamation is thought to result from processes that induce vascular endothelial dysfunction, thus leading to the production of vasoactive substances, cytokines, thromboxanes, and growth factors and to the accumulation of macrophages and T lymphocytes in atherosclerotic lesions (36). One such marker of this process is the acute phase reactant C-reactive protein (CRP). Other inflammatory markers include serum amyloid A, inerleukin-6, and intercellular adhesion molecule-1. Several studies have shown a strong association between elevated CRP concentration and coronary artery risk, particularly in those with previous myocardial infarction and unstable angina. It is also a strong predictor of fatal myocardial infarction (37).

CRP has also been observed to be elevated in hemodialysis patients, in association with an atherogenic lipoprotein profile. It was also a strong predictor of death from cardiovascular events (38). Elevated concentrations of numerous cytokines that mediate inflammatory processes have been observed in hemodialysis patients. The reasons for this are uncertain but could relate to biocompatibility of the dialyzer membrane; less biocompatible, unmodified cellulosic membranes have greater cytokine-generating potential and have been associated with greater patient all-cause as well as coronary mortality (39). In addition, exposure of dialysis patients to numerous bacterial infections as well as chronic inflammatory reactions from internal, artificial, or in-dwelling vascular access devices may contribute. With respect to infection, it is believed that only chronic infections with herpes simplex virus-1 and Chlamydia have been associated with increases of coronary heart disease, at least in non-ESRD populations.

In transplant patients, inflammation produced by chronic rejection might contribute to CVD events. There is also an association with frequency of acute rejection episodes (40). Whether this is related to the high corticosteroid doses used to suppress rejection is uncertain. However, steroid use is much reduced since the advent of newer antirejection medications. These data suggest that in ESRD, chronic inflammation of diverse causes may contribute to the excess CVD mortality seen in this group. Although measurements of CRP and other acute phase reactants may be useful prognostic indicators in patients with acute coronary syndromes, additional studies will be needed to determine their value as markers for atherosclerosis risk.

**Dialysis as a Risk Factor**

Although hemodialysis itself is not widely believed to be a promoter of atherogenesis, its effects on inflammation might suggest such a role. However, the hemodynamic effects of hemodialysis do contribute to myocardial ischemia that often occurs during a dialysis session. The reasons for this include increased heart rate and decreased coronary filling time, leading to reduce coronary blood flow and to decreased tissue oxygen delivery resulting from a pH-mediated enhancement of oxygen affinity for hemoglobin (Bohr effect). When coupled with the high prevalence of LVH, anemia, reduced coronary vasodilator reserve, and underlying CAD, hemodialysis can simultaneously reduce myocardial oxygen delivery at a time when the increased heart rate is producing a greater myocardial oxygen requirement. This mismatch between oxygen supply and demand may account not only for the many clinically apparent cardiac events occurring during dialysis but also for episodes of silent ischemia that have been recorded during hemodialysis using ambulatory ECG monitoring (41,42).

There are other important factors that may also contribute to myocardial ischemia. For example, as noted above, the nature of the dialyzer membrane may have a significant impact on acute coronary events and their outcome. The use of low concentrations of dialysate calcium decreases cardiac contractility and may predispose patients to lower BP and to hypotensive episodes with attendant risks for ischemia and arrhythmia (43). The intermittent nature of hemodialysis has been associated with increased rates of sudden and cardiac deaths perhaps partly as a consequence of volume overload that produces increased myocardial wall stress, especially when coupled with the previously mentioned hemodynamic effects of dialysis. Moreover, inadequate dialysis is associated with higher mortality. As a result of the foregoing, there is increasing interest in dialysis sessions of longer duration and with shorter interdialytic intervals, and many centers are studying the benefits of nightly hemodialysis. However, currently there is no broad body of evidence to show that such changes in the hemodialysis prescription will reduce cardiovascular morbidity and mortality. It also remains to be seen whether avoidance of low dialysate calcium can also reduce cardiovascular events. However, unless hypercalcemia is a problem, there is no justification for the use of low-calcium dialysate.

Peritoneal dialysis is also associated with a high risk for cardiovascular mortality. The reasons for this are complex. In the past, diabetics and patients with severe CVD were more often referred for this modality, but that is not the case now. The use of acetate in the dialysate may affect lipoprotein profiles and thus be atherogenic. Similarly, the high prevalence of adynamic bone disease in this group could predispose them to a greater risk for vascular calcification with attendant cardiovascular complications.

In summary, identification and management of risk factors for CAD early in the course of renal insufficiency and early detection of the presence of CAD itself have the potential to reduce fatal and nonfatal cardiovascular events in ESRD patients. In an era when late referral for nephrologic care is common, thus, in part, contributing to the high rate of cardiovascular complication seen in ESRD, achieving a goal of early referral will be difficult and will require nephrologists to work with non-nephrologists to manage pre-ESRD patients and to educate them about the importance of early intervention and referral.

**Silent Ischemia, Occult CAD, and Nonatherosclerotic Coronary Disease: Risks for Cardiovascular Events in ESRD**

Although modification of the previously discussed risk factors may variably reduce cardiovascular events, these risk factors alone have not proved to be good predictors of future cardiovascular events. Therefore, because the presence of CAD
is a predictor of future cardiovascular events, it is also important to identify patients with underlying CAD to manage their renal failure and comorbid conditions effectively with the least risk for cardiovascular compromise. A review of the medical records of dialysis patients has been shown to be the best source of data for estimating the risk of future fatal and nonfatal cardiovascular events. Such reviews reveal that older, white men; diabetics; those with confirmed histories of angina, myocardial infarction, or peripheral vascular disease; and those with low predialysis systolic BP are at particularly high risk. However, although the majority of patients who enter ESRD programs do not have a history of CVD, angina, or peripheral vascular disease, a significant number have silent myocardial ischemia, with or without obvious CAD involving a major vessel, or have occult CAD. These patients may also be at increased risk for future cardiovascular events.

The significance of silent myocardial ischemia is difficult to assess, particularly in a patient who is younger than 50 yr and does not have a history of ischemic heart disease. In such patients, the presence of a positive myocardial perfusion scan may require confirmation by coronary arteriography. Positive stress-perfusion scans or ischemic ECG findings on ambulatory monitoring have been noted in approximately 2 to 3% of the non-ESRD population (44). However, silent ischemia is detected more often in those with histories of myocardial infarction or chronic stable angina and in those high-risk patients, described in the preceding paragraph, and carries a more ominous prognosis than in those with apparent low risk. In these patients, data suggest that future cardiovascular events depend more on severity and number of coronary vessels involved than on the presence of symptoms.

The prevalence of silent myocardial ischemia in ESRD patients is uncertain, but given the demographics and the clustering of risk factors in ESRD, one must suppose that it is more prevalent than in the non-ESRD population. Several small studies using ambulatory ECG monitoring during hemodialysis showed a prevalence of silent ischemia and occult CAD of approximately 33% (range, 15 to 100%) (45). Some data suggest that its occurrence may be associated with an increase in cardiovascular events, but the numbers of patients studied have been too small to draw a definitive conclusion.

Occult CAD is usually found when coronary artery calcification is seen or suspected by chest x-ray, ECG, echocardiogram, or computed tomography scan of the chest or when coronary angiography is done for evaluation for other cardiac disorders or for preoperative evaluation. In ESRD, this is seen most often in patients with peripheral vascular disease and in diabetics, in whom its presence is a major determinant of survival. In ESRD, it has been found in approximately one third of patients. Occult coronary disease can be discovered without resorting to coronary angiography. The use of noninvasive techniques such as electron beam computed tomography (EBCT) detects the presence of coronary artery calcification and thereby the presence of coronary atherosclerosis. Although it cannot determine the degree of coronary artery occlusion, the severity of calcification determined by EBCT does predict a population at high risk for silent myocardial ischemia (46). However, EBCT has not been found to be an accurate predictor of cardiovascular events in high-risk asymptomatic adults (47). Thus, when appropriate, the use of ECG stress testing using dipyridamole or adenosine coupled with myocardial perfusion scanning with thallium or sestamibi and possibly echocardiography will be the most specific and sensitive methods of determining the presence of silent myocardial ischemia and the further need for coronary angiography. The use of ambulatory ECG may be useful, but the high prevalence of LVH makes interpretation of the ECG alone difficult even if it is performed during the stress of hemodialysis.

There is also a subgroup of patients who may or may not have symptoms of myocardial ischemia associated with positive ECG or perfusion scans in the absence of significant narrowing of a major coronary artery. This has been noted in approximately 25 to 30% of patients (9). This circumstance is often triggered by hypertensive crises or by profound hypotension and tachycardia often occurring during dialysis. These patients are usually younger, more often African American, with histories of hypertension, and a high prevalence of LVH and more severe anemia. As noted previously, this is probably related to the loss of coronary vasodilator reserve, possibly related to alterations in the structure, function, and number of myocardial arterioles producing a greater susceptibility to myocardial ischemia and to cardiovascular mortality.

The foregoing raises questions about how extensively to evaluate the heart in ESRD patients given their propensity for cardiovascular events. This will depend on a careful assessment of potential risk. Certainly not every patient needs ECG stress testing, ambulatory ECG monitoring, or coronary angiography, including patients in whom occult CAD or silent ischemia has been revealed. In fact, coronary angiography, because of its own inherent risks, should be reserved for clinical situations in which an intervention such as coronary bypass grafting (CABG) or percutaneous coronary angioplasty (PTCA) is contemplated. Figure 2 presents an approach to evaluating asymptomatic CAD in renal failure.

One reason to identify dialysis patients who are likely to suffer cardiovascular events is to reduce their occurrence when patients are placed in high-risk situations. One important circumstance is surgery, to which ESRD patients are exposed often. It is widely known that patients with CAD have a high risk for intra- and perioperative cardiac events and death. Such patients are older and have signs of congestive heart failure and CAD. Their incidence of perioperative infarction is approximately 4 to 5% and between 2 and 20% during the 2 yr after surgery in the general population (48, 49). In ESRD, such data are unavailable, but one might expect that the results would at best be the same. Thus, in such high-risk patients, further assessment of myocardial perfusion and delineation of coronary anatomy may be helpful in deciding a medical management plan for the pre- and postsurgical period. Although the use of long-acting nitrates can decrease myocardial ischemic episodes, one might choose in addition to use β-blockers before and immediately after surgery, a strategy that has been shown to reduce immediate and long-term postoperative cardiovascular events (49). One might also consider, as prophyl-

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laxis, CABG or coronary angioplasty with stent placement before undertaking the needed surgery such as is often done in diabetics before renal transplantation. However, there have been no prospective, randomized studies in this setting to evaluate whether these invasive prophylactic measures, which have their own morbidity and mortality, actually reduce fatal and nonfatal cardiovascular events.

Symptomatic CAD

In ESRD patients, the management of stable and unstable angina is approximately the same as in the non-ESRD population (Figure 3) and consists of nitrates to improve coronary flow, β-blockers to decrease heart work and oxygen demand, and, if indicated, calcium-channel blockers to vasodilate coronary arteries and to reduce BP. Platelet inhibition with aspirin, ticlopidine, or glycoprotein IIa/IIIb antagonists is effective, with the last more likely to be used with unstable angina and as an adjunct to angioplasty with or without stent placement. The use of these antiplatelet drugs alone or together with unfractionated heparin can significantly reduce the number of myocardial infarctions or deaths (50). The use of unfractionated heparin and aspirin as antithrombin therapy is a standard practice. Low-molecular-weight heparins have also been variably effective in unstable angina. Thrombolytic therapy should be reserved for patients with acute myocardial infarction. Warfarin has been shown to be at least as effective as aspirin in preventing recurrence or death after an initial myocardial infarction. Antithrombin therapy, especially with warfarin, presents added risks for bleeding complications in hemodialysis patients, who often receive heparin during their dialysis session. In these patients, close attention to prothrombin time is essential; it may also be necessary to avoid or minimize the use of heparin during dialysis.

Failure of medical management may ultimately necessitate CABG or angioplasty to prevent a first myocardial infarction or a recurrence. CABG is frequently performed in ESRD patients with a reportedly “acceptable” perioperative mortality. However, a review of numerous small series reveal that the perioperative death risk varies between 1 and 25% (51). A recent large study in ESRD patients showed a perioperative mortality of approximately 12.5% or approximately threefold greater than in non-ESRD patients (51). Percutaneous coronary angioplasty is a less invasive alternative that has approximately half the periprocedure mortality as CABG but that is associated with higher recurrence of cardiovascular events and a greater need for repeat procedures because of restenosis. Despite a higher initial mortality rate, patients undergoing CABG have a longer overall survival than those with PTCA (51–53). However, it is uncertain what fraction of those who have PTCA had concomitant stent placement, because PTCA + stent is associated with a lower incidence of restenosis, less need for revascularization, and fewer episodes of angina (54).

Conclusion

As outlined in the limited space above, the increased cardiovascular morbidity and mortality seen in renal failure are the result of complex interactions among a myriad of demographic, disease-related, and treatment-related factors. Because this increased cardiovascular risk occurs well before the onset of ESRD, the present trend of late nephrologic referral and the failure to recognize these risks and to intervene early may contribute to the excess fatal and nonfatal cardiovascular

Figure 2. Scheme for evaluation and treatment of silent myocardial ischemia or suspected occult coronary artery disease in patients with renal failure. Solid lines represent a pathway for low-risk patients; broken lines represent a pathway for high-risk patients.
events in ESRD. On the basis of currently available data, it seems reasonable to conclude that if these events are to be prevented or reduced in the ESRD population, then early detection and management of cardiovascular risk and disease and early referral for specialty care, even before there is significant decline in renal function, may be necessary. Such interventions may limit the need for coronary angioplasty, which has a high failure rate, and CABG with its attendant high perioperative mortality rate when performed in ESRD patients.

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