The management of ischemic heart disease in patients with chronic kidney disease (CKD) is a special challenge for clinicians. The recent heightened awareness of CKD as an important risk factor for cardiovascular death is a welcome development; the eventual outcome will be clinical trials targeting CKD patients for prevention and treatment of coronary heart disease and its devastating complications. The reader is urged to consult National Kidney Foundation (NKF) task forces dealing with cardiovascular disease in chronic renal failure (1,2) and, most recently, lipid management (3). At the present time, however, clinicians are often faced with a nettlesome dilemma in their approach to renal patients with ischemic heart disease; most of the evidence-based practice guidelines are based on clinical trials performed in patients without CKD. Patients with renal disease have typically been excluded from major cardiovascular treatment trials in the past; although there is no shortage of recent reviews on cardiovascular disease in renal disease (4–10), there is most certainly a paucity of good clinical trial data in CKD patients. The application of imperfect data to clinical practice, however, is nothing new for clinicians, as this is common in medical practice.

It is not my intention to offer a general review on cardiovascular disease and renal disease, but rather to present my (admittedly idiosyncratic) approach to clinical management of coronary heart disease in renal patients distilled partly from the literature and personal experience. This paper will focus on cardiac disease in dialysis patients, but I will also attempt to frame special cardiac management issues pertaining to nondialysis CKD patients.

Background

Epidemiology and the Burden of Cardiovascular Disease in ESRD Patients

Patients receiving renal replacement therapy on dialysis are at extraordinarily high risk for death. The death rate for all US dialysis patients in 1998–2000 was 236/1000 patient-years (11). Cardiac disease is the major cause of death in dialysis patients, accounting for about 45% of all-cause mortality (12). Approximately 20% of cardiac deaths are attributed to acute myocardial infarction (AMI) (12). The burden of coronary heart disease in end-stage renal disease (ESRD) patients is projected to increase, as the greatest increase in treated ESRD has occurred in patients with the highest risk for cardiovascular disease, older patients and those with diabetic nephropathy. There were an estimated 315,000 US dialysis patients in 2002 (11), with a projected number of 520,000 US dialysis patients in 2010 (12).

The number of patients with non–dialysis-dependent renal failure is considerably larger. In 1988–1994, there were an estimated 10.9 million US patients having chronic renal insufficiency with serum creatinine > 1.5 mg/dl (13). These projections raise an interesting “paradox of the missing dialysis patients”— why is the “feeder” population of CKD more than 30 times larger than the dialysis population? It appears that the risk of death for (nondialysis) CKD patients is considerably greater than developing ESRD (11). A plausible explanation is that excess cardiovascular death (including coronary heart disease) in the CKD population prevents most CKD patients from developing ESRD; even “mild” renal insufficiency is associated with increased cardiovascular mortality (14,15). Logically, the greatest potential survival benefit from cardiac intervention in patients with renal disease would be derived from targeting patients for CHD prevention and treatment before the development of severe CKD.

Chronic renal failure is a condition characterized by generalized vasculopathy (16). A variety of risk factors (many of them important in CKD patients before the development of ESRD) contributing to accelerated cardiovascular morbidity and mortality in renal patients include hypertension, dyslipidemia, hyperglycemia, smoking, physical inactivity, enhanced thrombogenicity, hyperparathyroidism, hyperhomocysteinemia, increased sympathetic tone (including sleep apnea), and ele-
vated levels of ADMA (asymmetric dimethyl arginine). The development of left ventricular hypertrophy may be promoted by anemia and vascular noncompliance. Aortic stiffness (assessed by aortic pulse wave velocity) is an independent predictor of cardiovascular and all-cause death in dialysis patients (17). Premature coronary artery calcification has been detected in young dialysis patients, and the metabolic milieu of ESRD, including elevated calcium-phosphate product (18), and the synergistic effect of hyperparathyroidism, and inflammation (as reflected by levels of C-reactive protein) (19) may be implicated. Vascular endothelial dysfunction likely contributes to the expression of atherosclerotic disease, and even a single hemodialysis run may adversely affect endothelial function (20). Hyperglycemia may markedly reduce coronary vasodilator function (21) (by promoting the formation of advanced glycation end-products, which oppose nitric oxide-mediated endothelial-dependent relaxation) (22). The composition of coronary plaques in patients with ESRD may be qualitatively different, with increased media thickness and marked calcification of the affected coronary arteries (23,24). The pathophysiologic significance of coronary artery calcification in ESRD patients, therefore, may be different from the nornrenal population.

It is nearly impossible to accurately apportion the absolute contribution of “obstructive” coronary artery disease to cardiovascular morbidity and mortality in ESRD patients. This may strike some readers as pedantic, but it does have implications for the potential magnitude of therapeutic benefit that can be derived from coronary revascularization. Sudden cardiac death may be implicated in 60% of all cardiac deaths in dialysis patients. In the United States Renal Data System (USRDS) database, “cardiac arrest, cause unknown” accounts for 47% of all cardiac deaths, and another 13% are attributed to arrhythmia (25). Besides obstructive coronary artery disease (CAD), factors contributing to the peculiar vulnerability of ESRD patients to sudden death include left ventricular hypertrophy, electrolyte shifts in hemodialysis patients, and abnormalities in myocardial ultrastructure and function, including endothelial function, interstitial fibrosis, decreased perfusion reserve, and diminished ischemia tolerance (26–29). The nonphysiologic nature of conventional hemodialysis schedules (usually administered thrice weekly in the United States on Monday, Wednesday, Friday or Tuesday, Thursday, Saturday) may also contribute to increased cardiac death; this hypothesis is based on a study by Bleyer et al. (30), who found that significantly higher cardiac mortality occurs on Mondays (and to a lesser extent, Tuesday, the other dialysis day after the long interdialytic weekend). It is plausible that long-duration daily hemodialysis might lead to improved survival in ESRD patients, particularly if maintenance of “physiologic loading conditions” is accompanied by the amelioration of left ventricular hypertrophy and avoidance of significant electrolyte abnormalities (interdialytic hyperkalemia and intradialytic hypokalemia).

**Acute Myocardial Infarction**

Acute myocardial infarction in dialysis patients is a catastrophic event associated with dismal long-term survival (31–33). We have previously reported a 1-yr 59% mortality and 2-yr 73% mortality in 34,189 dialysis patients hospitalized with AMI in the US from 1977 to 1995 (31) (Figure 1). Even more striking is the poor outcome of patients treated in the “era of reperfusion,” with 1-yr and 2-yr mortalities of 62% and 74% in 1990–95, and 2-yr mortality of 78% in 1991–97 (34). Renal transplant recipients fare better, with a 2-yr mortality of 34% after hospitalization for AMI in 1977–96 (35).

We have speculated that the poor outcome of these patients may be due to a combination of underdiagnosis and undertreatment (i.e., therapeutic nihilism) (36) — “To the guy with a hammer, everything looks like a nail.” If a dialysis patient arrives on a Monday morning in the outpatient dialysis unit 5 kg above dry weight and complaining of dyspnea and angina, what procedure is most likely to occur first: an electrocardiogram (ECG) or the scheduled dialysis run? Circulatory congestion attributable to the ingestion of pepperoni pizzas and myocardial ischemia due to AMI might cause the same symptoms, and a nephrologist could easily choose dialysis as the first procedure under these clinical circumstances, with potentially devastating results if the patient’s primary problem is actually AMI and not pepperoni pizza. Ongoing preliminary work at the Cardiovascular Special Studies Center of USRDS and a recent publication by Berger et al. (36a) suggest both underrecognition of AMI due to “atypical clinical presentations” and undertreatment.

Poor survival after AMI is a general phenomenon in patients with CKD, and it is not restricted to dialysis patients. There is an increasing gradient of mortality risk observed with more severe renal dysfunction in AMI (37–39). In-hospital mortality is correlated with renal function, and there is a strikingly greater risk of death in patients with estimated creatinine clearance (CrCl) < 60 ml/min. (Figure 2) One-year AMI
mortality in elderly (≥65 yr) patients enrolled in the Cooperative Cardiovascular Project (CCP) in 1994–95 was 24% in patients with serum creatinine <1.5 mg/dl, 46% for Cr = 1.5 to 2.4 mg/dl, and 66% for Cr = 2.5 to 3.9 mg/dl (38). Similar findings were reported by Walsh et al. (40). In a recent pooled analysis from the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO II-b, GUSTO-III) studies, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrillen Therapy (PURSUIT), and Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON-A) acute coronary syndrome trials, both ST-segment elevation and non-ST-segment elevation MI with CrCl < 70 ml/min were associated with increased 1-mo and 6-mo mortality (41).

One astounding finding in patients with CKD and AMI is that the likelihood of receiving therapies proven to reduce mortality in clinical trials on AMI treatment is inversely related to the severity of renal failure (36a,37–39,42). This applies to the use of aspirin, β-blockers, and reperfusion therapy. In the study by Wright et al. (37), the use of angiotensin-converting enzyme (ACE) inhibitors at hospital discharge was also inversely related to the degree of renal impairment. Importantly, in these observational studies, the use of all these standard therapies were associated with decreased mortality. In the McCullough et al. study (42) from Henry Ford Hospital, the age-adjusted relative risk reduction of in-hospital mortality for patients receiving aspirin and β-blockers ranged from 64% to 80% across all renal function groups (compared with no treatment with either agent). In the Wright et al. study at the Mayo Clinic, the use of aspirin and β-blocker therapy at discharge and initial treatment with reperfusion therapy were independently associated with a 30% reduction in post-discharge deaths. In the Shlipak et al. study (38) of Medicare beneficiaries in the CCP database, aspirin was associated with a 48% to 60% range of reduction in 1-mo mortality across renal function categories, β-blockers were associated with a 38 to 42% reduction in 1-mo mortality, and ACE inhibitors were associated with a 48% to 59% reduction in 1-mo mortality. We have reported preliminary findings on the apparent under-utilization of thrombolytic therapy in dialysis patients. Using claims data from USRDS, we identified 33,277 dialysis patients hospitalized for AMI in 1991–97 who did not receive coronary reperfusion therapy and suffered a 2-yr mortality rate of 78%, compared with 176 patients receiving intravenous thrombolytic therapy with a 2-yr mortality rate of 60%. In a comorbidity-adjusted Cox model, thrombolytic therapy was associated with a 28% reduction in all-cause death risk (34). The poor outcome of CKD patients with AMI would appear to be partially attributable to therapeutic nihilism (and for dialysis patients, perhaps fueled by fear of potential complications such as hemorrhage and the unavailability of clinical trial outcome data due to the exclusion of ESRD patients from all AMI trials). For patients with AMI, no treatment is equivalent to bad treatment.

The use of glycoprotein IIb/IIIa receptor antagonists as adjunctive therapy in acute coronary syndromes and percutaneous coronary intervention (PCI) in CKD is more controversial but supported by recent data. In the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial of tirofiban in acute coronary syndrome (ACS) (patients excluded for Cr ≥ 2.5 mg/dl), tirofiban was effective in reducing ischemic ACS complications, and there was no synergistic relationship between use of tirofiban and degree of renal impairment for the development of hemorrhagic complications (43). Using observational data from the Michigan Cardiovascular Outcomes and Reporting Program, Freeman et al. (44) reported an increase in major bleeding and reduced in-hospital mortality in patients with ACS and renal failure receiving glycoprotein (GP) IIb/IIIa antagonists. In the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial (epifibatide), the beneficial effect of the agent and attributable hemorrhagic complications were not different in patients with CrCl < 60 ml/min (mean, 48 ml/min). Jeremias et al. (45) reported no increased risk of complications with abciximab in patients undergoing PCI with Cr ≥ 2.0 mg/dl (findings concordant with a recent publication by Best et al. [45a]). In contrast, Frilling et al. (46), using the Ludwigshafen IIb/IIIa-Antagonist Registry, reported a fivefold risk of any bleeding associated with abciximab in 44 patients with impaired renal function (Cr ≥ 1.3 mg/dl), but the absolute number of episodes was only 6.8%. There are a paucity of data on the use of glycoprotein IIb/IIIa antagonists in dialysis patients, although anecdotally, abciximab is probably the most widely used of these agents in dialysis patients undergoing PCI. Current US product labeling of available GP IIb/IIIa antagonists includes a reduced dose of epifibatide in chronic renal failure (with no additional recommendation for Cr ≥ 4.0 mg/dl), 50% reduction in tirofiban dose in dialysis patients, and no dose adjustment for abciximab. It should be stressed that there are currently few published data on the safety and efficacy of these agents in dialysis patients. Prudence dictates careful clinical observation of all dialysis patients after PCI (including ready
availability of blood products), regardless of the particular therapeutic strategy employed.

Anticoagulation practice in dialysis patients with PCI and/or ACS will be limited by elimination kinetics of the drugs (including uncertainty in dialysis patients) and the ability to monitor therapy. During PCI, the monitoring of activated clotting time allows for dose-adjustment with unfractionated heparin. Low-molecular weight heparin has generally been avoided in ESRD patients, partly due to safety issues (with very prolonged half-life) and, until recently, inability to rapidly monitor therapeutic effect. One useful anticoagulant agent in ESRD patients undergoing PCI is bivalirudin (Angiomax), a direct thrombin inhibitor, which is predominantly renally excreted, and (FDA-approved) appropriate adjustments for all degrees of renal impairment, including dialysis-dependence, are provided by the manufacturer (47).

Other untested adjunctive therapies for ACS in ESRD patients appear promising. The use of clopidogrel reduces the risk of recurrent cardiovascular events (with an increased risk of bleeding) in the “general population” (48). At my institution, we have generalized the results of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial (48) and applied them to ESRD patients (a practice consistent with the application of other therapies not specifically tested in ESRD patients but proven in the general population). In the setting of PCI with coronary stenting, the combination of 81 to 325 mg/d aspirin (lifelong) and clopidogrel (30 d or longer if used for other indications) is standard therapy, including for ESRD patients.

Patients with ESRD due to diabetic nephropathy have a 34% increased risk of death after AMI (compared with non-DM) (31). In diabetic patients with AMI, insulin glucose infusion reduces long-term mortality (49,50). It has been proposed that some of the cardioprotective benefit of insulin may derive from myocardial effects independent of metabolic modulation (51). Future trials in diabetic CKD patients would be appropriate.

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Tables 1 to 3 summarize our general approach to the management of AMI in dialysis patients. In chronic hemodialysis patients, the optimal timing for resumption of routine dialysis is controversial. In our own program, we have arbitrarily delayed routine dialysis in the first 24 h after AMI (unless forced by metabolic derangements), a practice supported by preliminary data from Kong et al. (52), who reported that 20% of 45 dialysis patients with AMI suffered unexpected ventricular fibrillation during hemodialysis, with five lethal outcomes.

**Medical Management of Chronic CAD in Dialysis Patients**

Table 4 summarizes our general approach to the medical management of ischemic heart disease in dialysis patients. Most approaches to treatment represent generalization of established therapies in non-ESRD, with a few modifications. The maintenance of relative euvolemia is a key aspect of the management of these patients (53). Hemodynamic target dry weight may be a moving target in chronic dialysis patients (particularly diabetic patients), who may lose muscle mass over time—the same weight might denote inadequate fluid removal 2 yr later with declining lean body mass. In our practice, we rely on echocardiography for assessment of hemodynamic dry weight and occasionally elective right heart catheterization followed by right heart monitoring during dialysis/ultrafiltration to help determine true hemodynamic dry weight. Anemia may exacerbate angina; adherence to Dialysis Outcomes Quality Initiative (DOQI) anemia treatment guidelines is assumed in these patients. Hemodialysis can trigger angina, and alterations in dialysis prescription, including prolongation of treatment time to permit decreased ultrafiltration rate may be helpful in amelioration of dialysis-associated myocardial ischemia (54). Some nephrologists will sometimes omit anti-anginal therapy before dialysis if it is perceived that the agents are exacerbating unstable intradialytic hemodynamics, but this practice is more empiric than evidence-based. Inability to perform dialysis without hemodynamic instability or angina, however, should prompt further cardiac investigations for as-

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**Table 1. Acute myocardial infarction (AMI) in dialysis patients: diagnostic pitfalls**

- Atypical presentations delay diagnosis.
- Symptoms of volume overload and those of AMI may be identical. Would a hemodialysis patient with chest pain or dyspnea receive an immediate ECG?
- Left ventricular (LV) hypertrophy with ST-segment changes, prevalent among dialysis patients, makes ECG diagnosis of acute MI more difficult.
- Specificity of cardiac biomarkers may be problematic when they are present at low levels. Cardiac troponins should be used for AMI diagnosis.
- Current troponin I assay has higher specificity for AMI diagnosis, but troponin T is better for future prediction of all-cause death in outpatient, asymptomatic hemodialysis patients.
- Cardiac biomarker-based diagnosis of AMI requires time-appropriate rise and fall of the biomarker.

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<tr>
<th>Cardiac biomarker-based diagnosis of AMI requires time-appropriate rise and fall of the biomarker</th>
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**Table 2. Treatment of AMI in dialysis patients**

- Antiplatelet agents (aspirin), clopidogrel.
- Anticoagulants, bivalirudin for percutaneous coronary intervention (PCI).
- Glycoprotein IIb/IIIa antagonists (tirofiban, abciximab)?
- Coronary reperfusion (STEMI)
  - Primary PCI (hemorrhagic risk potentially lower than that of thrombolytic therapy)
  - Thrombolytics
- β-blockers.
- Angiotensin-converting enzyme (ACE) inhibitors.
- Nitroglycerin
- Statins

| a Modified from reference 76a. |

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Table 3. Pitfalls in the treatment of AMI in dialysis patients

<table>
<thead>
<tr>
<th>Therapeutic nihilism</th>
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<td>● Exclusion of end-stage renal disease (ESRD) patients</td>
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<tr>
<td>from clinical trials.</td>
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<td>● Relative contraindications to thrombolytic therapy are</td>
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<td>always present.</td>
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<td>Volume status</td>
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<td>● Echocardiography</td>
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<td>● Right heart catheterization in patients undergoing</td>
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<td>PTCA/STENT for peri-procedure dialysis management.</td>
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<tr>
<td>● Iso-osmolar radiocontrast media used for angiography.</td>
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<tr>
<td>Dialysis</td>
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<td>● Defer routine dialysis in first 24 h?</td>
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<tr>
<td>● Acute dialysis may be forced by other therapies (for</td>
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<tr>
<td>example, hypervolemia secondary to angiography).</td>
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<td>● Modification of dialysis runs in low-output states.</td>
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* Modified from reference 76a.

Table 4. Medical management of chronic CAD in dialysis patients

| Antiplatelet agents (aspirin ± clopidogrel).              |
| β-blockers.                                              |
| ACE inhibitors (angiotensin receptor blockers in ACE-     |
|   intolerant patients).                                   |
| Long acting nitrates for angina.                         |
| Calcium channel blockers (predominantly amlodipine) as    |
|   adjunctive therapy for angina/hypertension.            |
| Statins.                                                 |
| Adherence to DOQI guidelines for anemia management.      |
| Maintenance of hemodynamic dry weight (assessed by a     |
|   variety of methods, including echocardiography).       |
| Alterations in dialysis prescription (e.g., prolongation |
|   of treatment time to permit decreased ultrafiltration |
|   rate) for amelioration of dialysis-associated myocardial |
|   ischemia.                                              |
| Intradialytic hemodynamic instability/inability to tolerate |
|   medical therapy may be an indication for nonmedical   |
|   treatment.                                              |

The treatment of dyslipidemia in chronic renal failure was the subject of a recent DOQI task force, and the reader is urged to consult this comprehensive document (3). Previous treatment trials in dialysis patients have essentially been large case series and pilot studies. Statin therapy (e.g., simvastatin in placebo-controlled randomized trial) is safe and efficacious for treatment of hypercholesterolemia in dialysis patients (55,56). It is reasonable to treat dialysis patients (or for that matter CKD patients) as CHD-equivalent (like diabetes) and treat to a goal of LDL-cholesterol < 100 mg/dl. It is a bit more uncertain for the frequent occurrence in chronic hemodialysis patients of “low HDL-cholesterol, normal LDL-cholesterol, and increased triglycerides (the typical type 2 DM profile). In these patients, we will use statins for overt CHD, but it is less clear if they should be used for all dialysis patients. It is plausible that these high-risk patients might all benefit from statin therapy. Hopefully, the 4-D (Die Deutsche Diabetes Dialyse Studie) trial on the use of atorvastatin in type 2 diabetic patients will resolve this issue in dialysis patients. On the basis of current enrollment and event rates, preliminary data may be available in 2004. In my own practice, I sometimes employ combination therapy with statins (frequently atorvastatin) and sustained-release niacin (Niaspan) in patients with elevated LDL-cholesterol, decreased HDL-cholesterol, and increased triglycerides who do not respond adequately to monotherapy with a statin. Hepatic enzymes are monitored frequently in these patients on combination therapy. Combination therapy with ezetimibe, an inhibitor of intestinal brush border absorption of cholesterol, and statins is another approach to reducing LDL-cholesterol. The Study of Heart and Renal Protection (SHARP) trial, which began enrollment in June 2003 will test the efficacy of ezetimibe and simvastatin for the reduction of cardiovascular events in patients with varying degrees of CKD, including ESRD.

The cornerstone of medical therapy for CHD (and cardiomyopathy) might be β-blockers. Dialysis patients with dilated cardiomyopathy benefit from β-blocker therapy (57–59). The publication of a randomized, placebo-controlled trial of carvedilol in 114 Neapolitan dialysis patients with a dilated cardiomyopathy and NYHA class 2 and 3 chronic heart failure (CHF) by Cice et al. (57) was a remarkable accomplishment, as few clinical trials have been conducted on cardiac disease in dialysis patients. The authors reported a sustained objective improvement in LV systolic function (documented by serial echocardiography) at 1 yr, with improvement (P < 0.05) of mean LV ejection fraction from 26 ± 8% to 35 ± 11% versus no change with placebo. Nearly 30% of class 3 CHF patients receiving carvedilol shifted to class 2 compared with no significant improvement after placebo. Cice et al. have recently reported that the 2-yr mortality rate in the placebo group was 73% versus 52% in the carvedilol group (P < 0.01), with a 49% reduction in all-cause death risk with carvedilol and a 56% reduction in all-cause hospitalization risk (58). It has been proposed that prophylactic β-blocker therapy might reduce the cardiovascular mortality of dialysis patients (particularly diabetic patients) (59a). Given the safety of these agents and comparatively modest cost, this would be a worthy subject for a large-scale randomized clinical trial.

Clinical trials on antioxidant therapy in the general population have been profoundly disappointing to antioxidant vitamin enthusiasts. In dialysis patients, the issue is less clear, as two randomized clinical trials suggest that cardiovascular events in dialysis patients can be reduced by antioxidant therapy: Vitamin E Secondary Prevention with Antioxidants of Cardiovascular Disease in End-Stage Renal Disease (SPACE trial) (60) and acetylcysteine (61). The degree of oxidative stress is greater in the dialysis population; for this reason, there may be a special niche for antioxidant therapy. Future clinical trials
testing the effects of anti-oxidant therapy in dialysis patients are warranted.

**Cardiac Arrest**

Sudden cardiac death may be implicated in 60% of all cardiac deaths in dialysis patients, making it potentially the single largest cause of death in dialysis patients. Strategies to reduce the risk of succumbing to this lethal event should concentrate on reducing the likelihood of cardiac arrest and increasing the probability of surviving cardiac arrest (62). The risk of cardiac arrest increases over time after dialysis initiation (vintage effect), with an event rate of 110 events/1000 patient-years at 2 yr, rising to 208 events/1000 patient-years 5 yr after initiation in patients with diabetic ESRD (11). Identification of high-risk patients by assessment of LV function, ischemic burden, and biomarkers (particularly cardiac troponin T) might facilitate targeted intervention in high-risk patients. Treatment with agents known to improve cardiac survival in the general population (e.g., aspirin, β-blockers, ACE inhibitors, statins, etc.) might also reduce the risk of sudden cardiac death in ESRD patients.

The maintenance of physiologic loading conditions and avoidance of large electrolyte shifts are specific strategies applicable to dialysis patients. Karnik et al. (63) reported a cardiac arrest rate of 7 per 100,000 hemodialysis sessions (with Monday the most likely day for cardiac arrests). Cardiac arrest was nearly twice as likely in patients dialyzed against a 0 or 1.0 mEq/L potassium dialysate on the day of cardiac arrest. Becker et al. (64) reported on cardiac arrest outside hospitals in Seattle and King County from 1990 to 1996 using Emergency Medical Services (EMS) data. There were 47 cardiac arrests in dialysis centers, with an annual incidence of 0.746.

Linda Becker has kindly shared with me the dialysis-specific resuscitation data (47 patients), which did not appear in her paper. There were 41 witnessed events, and bystander CPR was administered to 41 patients. In 29 patients (62%), the cardiac rhythm was ventricular fibrillation (VF) or ventricular tachycardia (VT). The overall survival to hospital discharge was 30%; of the patients with VT/VF, it was an impressive 38%. It must be acknowledged that Seattle/King County is widely regarded for its outstanding EMS system; these survival data reflect swift EMS response times and expert crews. These data also make a compelling case for the availability of defibrillators in all dialysis units. The logical conclusion is that automatic external defibrillators (AED), which are widely used (and intended for nonmedical operators), including in all US commercial jet aircraft, some casinos, and many public facilities, should be available in all dialysis centers. The mortality rate is about 10% per min in the first 5 min after cardiac arrest (including with CPR), and survival is uncommon after 10 min—this is the reason why AED are critical, as EMS response times will always be problematic.

Unfortunately, most cardiac arrests occur at home. We have recently presented preliminary data on the apparent striking underutilization of implantable cardioverter defibrillators (ICD) in cardiac arrest survivors on dialysis (65). The 1-yr mortality of 3380 dialysis patients discharged alive from hospital without ICD was 60% compared with 40% in 167 dialysis patients receiving ICD within 30 d of cardiac arrest. In a Cox model, there was a 47% reduction in mortality risk associated with ICD therapy. I believe that a randomized, prospective trial on the efficacy of ICD for the reduction of mortality in dialysis patients would be appropriate.

**Diagnosis of CAD in ESRD Patients**

The identification of coronary artery disease in ESRD patients has typically focused on high-risk (predominantly diabetic) renal transplant candidates, despite the fact that a minority of ESRD patients is actually deemed to be transplant candidates. Current practice guidelines address screening for CAD in high-risk renal transplant candidates (66) and wait-listed patients (67), but they do not address the patients at highest risk for cardiac death: dialysis patients not being considered for transplantation. We have previously reported that there is an early hazard of AMI associated with dialysis initiation, as 29% of MI in dialysis patients occur within 1 yr and 52% within 2 yr of initiation of dialysis (31). I would argue that some type of assessment of global cardiac risk would be appropriate after dialysis initiation, provided that testing can guide clinical management (and this is the usual Gordian knot of clinical practice, as the evidence supporting intervention is frequently weak or not existent).

The key issue in diagnosis/testing for CAD in ESRD patients is how the clinician will use the resultant information. The ability to accurately predict coronary anatomy on a noninvasive test is not equivalent to the predictive value of the test for prognostication of future cardiac events. When renal transplant candidates are screened for CAD by noninvasive stress imaging tests, one clinical goal is risk stratification for future adverse cardiac events. The second goal is to actually predict coronary anatomy, if prophylactic coronary revascularization is solely based on angiographic findings (68). If restenosis is an issue after PCI, the sensitivity of the stress-imaging test to predict coronary anatomy is important, because there may be no other clinical surrogates to identify occult restenosis.

Exercise stress electrocardiography is problematic in many ESRD patients. Non-cardiac exercise limitations (e.g., peripheral vascular disease [PVD]) and the high prevalence of left ventricular hypertrophy and uninterpretable stress electrocardiographic findings, make stress imaging preferable. Some ESRD patients without PVD are able to successfully undertake treadmill exercise for stress imaging, but the majority will require pharmacologic stress (69).

The accuracy of pharmacologic stress nuclear imaging in renal transplant candidates (compared with angiography) has been disappointing in the few published series (70–72) that actually compared stress nuclear imaging to coronary angiography (rather than prediction of future clinical events) in the entire study population. Marwick et al. reported 37% sensitivity and 73% specificity for detection of CAD defined as 50% or more stenosis and 29% sensitivity for 70% or more stenosis for dipyridamole SPECT (single-photon emission computed tomography) thallium imaging. In Vandenberg’s series (72), the sensitivity and specificity of pharmacologic stress thallium
imaging in diabetic renal or pancreas transplant candidates compared with a 75% coronary stenosis were 62% and 76%, respectively. Boudreau et al. (71) reported better accuracy, with 86% sensitivity and 72% specificity for detection of coronary stenoses of more than 70% reduction in cross-sectional area by dipyridamole planar thallium imaging. Using a novel stress protocol of combined dipyridamole-exercise thallium imaging in chronic hemodialysis patients (only 14% with DM), Dahan et al. (73) have reported the highest level of diagnostic accuracy for stress nuclear imaging in ESRD patients, with a sensitivity of 92% and specificity of 89% compared with coronary artery diameter stenosis ≥70%. There are few publications on dobutamine stress echocardiography in ESRD patients employing coronary angiography in the entire study cohort. We prospectively screened 50 renal transplant candidates (39 DM) and performed dobutamine stress echocardiography and subsequent quantitative coronary angiography (QCA) on the entire cohort (74). The sensitivity and specificity of the stress echo alone (not including other data such as induction of angina) were 75% and 71%, respectively, for QCA stenosis >70% and 75% and 76%, respectively, for visually estimated stenosis >75% (the latter definition used in Manske’s study on prophylactic coronary revascularization) (68). There are few data comparing stress echo to stress nuclear imaging in ESRD patients. We have presented preliminary data (75) on the concordance of adenosine stress nuclear scintigraphy, dobutamine stress nuclear scintigraphy, and dobutamine stress echocardiography in the same 33 ESRD patients. The adenosine and dobutamine stress nuclear studies were 91% concordant (κ = 0.76); adenosine stress nuclear and dobutamine echo concordance was 72% (κ = 0.43). Angiography was performed in the 16 patients who had at least one positive test; compared with stenosis >70%, the sensitivity of stress echo was 100% versus 58% for adenosine stress nuclear imaging, and 75% specificity for echo and 87% specificity for adenosine nuclear imaging.

The utility of stress myocardial imaging studies for the prediction of MI and cardiac death in ESRD patients evaluated for kidney or kidney-pancreas transplantation was recently assessed in a meta-analysis published by Rabbat et al. (76). Although their work was limited by the relative paucity of suitable primary data, forcing the combining of eight stress nuclear and four echocardiographic studies to obtain an adequate sample size (and thus precluding a head-to-head echo/nuclear comparison), it is my belief as a reviewer of this paper that the authors accomplished the meta-analysis equivalent of creating a silk purse from a sow’s ear. When compared with negative tests, positive tests (which include fixed defects indicative of previous MI, but not inducible ischemia) had a significantly increased relative risk (RR) of future MI (RR, 2.73; 95% CI, 1.25 to 5.97) and cardiac death (RR, 2.92; 95% CI, 1.66 to 5.12). In diabetic patients, there were comparable relative risks. Importantly, a fixed defect was not predictive of MI, but it was strongly predictive of cardiac death (RR, 4.74; 95% CI, 2.26 to 7.94). Unfortunately, the meta-analysis did not include the important effect of LV ejection fraction as an independent predictor of survival. From a management perspective, it would be easy for me to deal with a normal stress imaging study (provided we also know that there is a normal LV ejection fraction and no significant valve disease). Patients with reversible defects (i.e., inducible ischemia) would normally receive coronary angiography. In the general population, current practice guidelines factor in the “risk area” in clinical management (i.e., small segments have a good prognosis and may not need further evaluation). In the ESRD population (particularly diabetic patients undergoing nuclear imaging), the poor sensitivity of the testing for detection of inducible ischemia (compared with angiography) may alter the approach to ESRD patients. In our own practice, we would usually perform coronary angiography for any reversible defect or significant reduction of LV ejection fraction (<40%) in evaluating ESRD patients.

What do we do with fixed defects? If the imaging test were accurate at predicting anatomy (and we knew the LV ejection fraction), we could dispense with performing coronary angiography. The problem is that all of the non-invasive modalities generally employed are imperfect at best, and very operator-dependent. One interpretation of the paper by Rabbat et al. is that these patients with old scars from previous MI perhaps had an arrhythmogenic nidus for sudden cardiac death. The exclusion of other ischemic (non-infarcted) coronary artery vascular territories is important in this setting; for this reason, our approach is to perform angiography in these patients.

Figure 3 summarizes our current management algorithm for cardiac evaluation of renal transplant candidates. We rely on dobutamine stress echocardiography for noninvasive stress imaging in ESRD patients. In ESRD patients who are not transplant candidates, a similar approach is employed for symptomatic patients (dyspnea, angina, refractory CHF, hemodynamic instability during dialysis, etc) and patients with impaired LV systolic performance. Patient with unexplained impaired LV systolic performance (both in the ESRD and general populations) deserve coronary angiography to rule out CAD as a cause of cardiomyopathy.
There is no reliable method to predict LV ejection fraction by physical exam, and the information is prognostically important, and cardiomyopathy is common in ESRD patients (77), and there are proven treatments for cardiomyopathy; it is therefore recommended that all ESRD patients be evaluated for LV systolic function after dialysis initiation (with stable volume status at e.g. 60 to 90 d after initiation), at the time of renal transplant evaluation and at some arbitrary repeat frequency on dialysis (e.g., every 12 to 24 mo). The most cost-effective test is an echocardiogram, because valvular disease (e.g., aortic stenosis) and echocardiographic measures related to volume status and cardiac function can be assessed at the same time. Right atrial pressure can be estimated by the size and degree of inspiratory collapse of the inferior vena cava (78) and is routinely measured in all dialysis patients in our cardiac ultrasound laboratory. Transplant waitlisted patients present a special problem, and recent guidelines suggest frequent (annual) surveillance stress imaging in high-risk patients (67). Note that our current algorithm employs surveillance stress imaging 12 to 16 wk after PCI because of the high rate of restenosis. We hope to be able to abandon this practice after coated stents are demonstrated to be efficacious in ESRD patients.

Other Diagnostic Testing (Noninvasive Imaging). Noninvasive imaging for detection of CAD is a rapidly evolving field. Cardiac magnetic resonance imaging has the potential for assessment of function, regional perfusion, metabolism, and even coronary anatomy, including the composition of plaques (and computerized tomography offers similar capabilities). It is likely to play a key role in CAD assessment in the near future in referral centers.

Coronary artery calcification in ESRD patients has attracted increasingly more attention because of its greatly increased prevalence in younger ESRD patients (18), its association with metabolic abnormalities and markers of chronic inflammation (19,79,80), and the demonstration that sevelamer attenuates the progression of coronary artery calcification (compared with calcium-based phosphate binders) (81). One persistent question regarding imaging of coronary calcification (by electron beam computerized tomography or other methods) is the inability to distinguish between intimal (e.g., atherosclerotic) and medial calcification, as these entities may represent different diseases. In the general population, the evolving (and still controversial) role of screening for coronary calcification is partly risk stratification for future cardiovascular events, and it is partly an index of atherosclerotic coronary artery disease burden. If non-atherosclerotic disease is an important component of ESRD patient coronary artery calcification, it puts a different spin on testing (and potential treatments). Conceptually, imaging of calcification might be equivalent to assessing aortic pulse wave velocity, with vascular noncompliance related to calcification—very important prognostically, but mechanistically different than obstructive CAD. At the present time, assessment of coronary artery calcification in ESRD patients is a promising technique that requires prospective validation of the utility of testing for prediction of cardiovascular events (or angiographically defined obstructive CAD).

Coronary Angiography

Contrast nephropathy is a potentially serious complication of diagnostic coronary angiography and PCI in patients with CKD. Gruberg et al. (82) reported a 14.9% in-hospital mortality rate and 37% 1-yr mortality rate in patients with baseline Cr ≥ 1.8 mg/dl and ≥ 25% increase in serum creatinine (or need for dialysis) within 48 h after PCI, compared with a 4.9% in-hospital mortality rate and 19% 1-yr mortality rate in patients without this degree of acute renal dysfunction. The need for acute dialysis after PCI is associated with a marked increase in in-hospital mortality (82–84). There are a multiplicity of risk factors for contrast nephropathy, including baseline renal dysfunction, peripheral vascular disease, diabetes, CHF, cardiogenic shock, volume depletion, chronic liver disease, and contrast volume (84–86). Freeman et al. (84) suggest a role for the “maximum radiographic contrast dose (MRCD)” to avoid severe contrast nephropathy requiring acute dialysis; MRCD is calculated as 5 ml × weight (kg)/serum creatinine (mg/dl) (84) (although one wonders whether estimated GFR would provide a better predictive model than serum creatinine). The actual cause of mortality in patients suffering contrast nephropathy after coronary intervention is uncertain.

Contrast nephropathy has not been systematically investigated in dialysis patients, probably because of the perception that “they can’t develop worsening renal failure.” Residual renal function is important in dialysis patients (and correlates with survival), particularly in maintenance of euvoolemia. The loss of residual renal function might compromise the ability to perform successful chronic ambulatory peritoneal dialysis. For this reason, we do not deny dialysis patients strategies (excluding hydration) to reduce contrast nephropathy.

In the cardiac catheterization laboratory, we routinely use ioxixanol for all coronary angiographic and PCI procedures in patients with all stages of CKD, because it is an iso-osmolar radiocontrast agent (minimizing volume stress in dialysis patients) and because it is less nephrotoxic (87). All patients at risk for contrast nephropathy (including dialysis patients with residual renal function) receive acetylsalicycete for attenuation of risk (88–91) at a dose of 600 mg orally (two doses the day before and two on the same day following angiography). For emergent procedures, a single dose of 1000 mg has been employed (92). Fasting nondialysis patients without overt CHF are usually hydrated 6 to 12 h before the procedure with one half normal saline at approximately 75 to 100 cc/h (and post procedure), although a recent randomized trial comparing half-isotonic (0.45% sodium chloride plus 5% glucose) with isotonic (0.9% saline) infusion indicated that isotonic saline infusion is actually more efficacious for prevention of contrast nephropathy (93) (and should prompt reexamination of standard hydration regimens employed before angiography). Diabetic outpatients may pose special problems if adequate preprocedure hydration is desired. In patients with questionable volume status and/or LV dysfunction, right heart catheterization is performed first and the patient can safely receive hydration rapidly with hemodynamic monitoring (to a target pulmonary capillary wedge pressure of 14 to 18 mmHg). We do not administer any further hydration if the pulmonary cap-
illary wedge pressure is \( \geq 19 \) mmHg. In the past, we employed a regimen of forced osmotic diuresis with right heart monitoring similar to the methodology of the Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE) study (minus the dopamine), which may have a modest benefit (94), but we abandoned this approach, primarily because it is laborious. Similarly, the administration of fenoldopam appeared promising (and was utilized in our laboratory) on the basis of the pilot study data (86), but recent preliminary multicenter trial data presented in April 2003 at the American College of Cardiology sessions did not report a favorable effect of fenoldopam on reducing contrast nephropathy.

All measures to reduce the volume of contrast administered are appropriate. All patients should undergo complete echocardiographic examinations (including with echo contrast if LV imaging is not ideal) before elective PCI cases, some operators will “stage” the procedure to reduce the acute contrast load. In dialysis patients, the risk of hemorrhage is greater during PCI, and it is our practice to ideally have patients with preprocedure hemoglobin values of 12 g/dl. Severely anemic patients are transfused preprocedure on a dialysis run (to avoid hyperkalemia from the blood transfusion). All dialysis patients (with the exception of patients opposed to transfusion) undergoing PCI should have a current “type and screen” to facilitate cross-matching of blood for unexpected emergency transfusion.

Biomarkers

Cardiac and inflammatory biomarkers may provide an additional method of risk stratification and identification of ESRD patients who are candidates for cardiac evaluation (and perhaps certain therapies). In a prospective study of 663 dialysis patients, Stenvinkel et al. (95) reported the prognostic value of different levels of C-reactive protein (CRP) for prediction of all-cause mortality. (It is frustrating that the appropriate therapeutic consequences for elevated CRP are not yet established.) Plasma brain natriuretic peptide (BNP), a cardiac biomarker elevated in conditions associated with increased cardiac filling pressures, might be helpful in following volume status over time and for identifying dialysis patients with LV systolic dysfunction and LVH (96,97). In my opinion, the best prognostic biomarker is cardiac troponin T. Our group recently published a prospective study of the predictive value of cardiac troponin T (cTnT) and cardiac troponin I (cTnI) for subsequent all-cause death in 733 asymptomatic patients undergoing routine outpatient hemodialysis (98). Figure 4 shows Kaplan-Meier survival curves by baseline troponin cutoffs for cTnT and cTnI. Dialysis patients without detectible cTnT (<0.01 μg/L) have a benign prognosis with a 2-yr mortality rate of 8.4%. In contrast, baseline cTnT levels of \( \geq 0.10 \) μg/L were predictive of a 47% 2-yr mortality rate (with intermediate values associated with graded risk). The presence of detectible cardiac troponin T may reflect left ventricular mass (99) (and perhaps cardiomyopathy) and severity of underlying CAD (100). As concisely stated by Hamm et al. (101) in their editorial accompanying our paper, “The data could imply that this marker (cTnT) should enter routine clinical risk assessment in end-stage renal patients independent of any symptoms or history of coronary artery disease. At the moment, though, it is frustrating that the appropriate therapeutic consequences are not yet established.”

Our study on the predictive value of cardiac troponins...
should help to clarify the persistently vexing clinical problem of the interpretation of modest elevations in cardiac troponins occurring in hospitalized dialysis patients. This finding has previously been ascribed to false positive elevations in cardiac troponins, as earlier publications have questioned the specificity of these biomarkers for the diagnosis of acute coronary syndrome in dialysis patients. One frequently overlooked requirement for the diagnosis of AMI is that there should be a time-appropriate rise and fall of the cardiac biomarker. These elevations are not spurious; the biomarker is elevated and is a powerful predictor of mortality. Paradoxically, the same patient’s test (which is predictive of mortality in the outpatient setting) might be dismissed as a false positive in a hospital setting. The potential dual role of cardiac troponin testing in dialysis patients must be acknowledged to avoid incorrect clinical decisions—defining acute coronary syndromes and the prediction of mortality (complementary but discrete tasks). Despite these issues, cardiac troponin T does reliably predict short-term prognosis in patients with ACS in patients with renal dysfunction (102).

**Coronary Revascularization**

The optimal method of coronary revascularization in dialysis patients is controversial. PCI has a superior in-hospital or even 30 d post-procedure survival (the typical outcomes judged by quality assurance entities) compared with coronary artery bypass (CAB) surgery. If one judges success by short-term outcome, PCI is advantageous, particularly as patients can typically be discharged from hospital within 24 h of the procedure. There are currently two major problematic issues with PCI in dialysis patients: higher repeat revascularization rates and long-term mortality compared with CAB.

The accurate interpretation of studies on procedural outcome in dialysis patients is a potentially treacherous problem if nonfatal end points commonly employed in nonrenal patients are used in survival analysis. In the nonrenal population, the risk of all-cause death in the first year after PCI is low compared with the risk of restenosis, making a comparison of restenosis risk a reasonable primary end point for a trial of PTCA versus coronary stents. If a large number of patients die, however, in the first 6 mo, repeat revascularization would be a meaningless end point, because the best outcome (i.e., lowest repeat revascularization rate) would occur in the group with the highest death rate! In preliminary work at the Cardiovascular Special Studies Center of USRDS, we compared the repeat revascularization and death rates in 8724 dialysis receiving CAB surgery, 5470 patients receiving percutaneous transluminal coronary angioplasty (PTCA) alone, and 7118 with coronary stents in the US from 1995 to 1999 identified in the USRDS database (103). Only 21% of patients receiving stents underwent repeat coronary revascularization of any type (CAB, PTCA, or stent), with a repeat revascularization rate of 218/1000 patient-years. The death rate, however, was a staggering 360/1000 patient-years (in the ESRD population, all-cause mortality mirrors cardiac mortality). Figures 5A and 5B (showing diabetic patients with revascularization procedures performed in 1995–97) demonstrate the importance of using a composite end point (including death) in the evaluation of procedural outcome in these patients.

The follow-up of dialysis patients (including those waitlisted for transplant) after PCI poses a special clinical problem. Dialysis patients not infrequently have angina or dyspnea, and the nephrologist’s burden is to determine whether the symptoms (if there are any) after an initially successful procedure are related to subsequent episodes of recurrent myocardial ischemia (either from restenosis or new obstructive CAD unrelated to the index PCI). The typical dialysis patient is preload-sensitive; due to the high prevalence of left ventricular hypertrophy (≥75%) and frequent occurrence of abnormal diastolic function. Most US hemodialysis patients are exposed to 1 d of increased volume stress after the long interdialytic weekend. The accurate determination of the etiology of anginal

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**Figure 5.** (A) Probability of repeat coronary revascularization after an index coronary revascularization procedure in dialysis patients with diabetic end-stage renal disease (ESRD). (B) Probability of repeat coronary revascularization or death after an index coronary revascularization procedure in dialysis patients with diabetic ESRD. Data from Ma JZ, et al. The likelihood of repeated coronary revascularization procedures (CRP) after first CRP in dialysis patients. *J Am Soc Nephrol* 10: 249A, 1999.
symptoms in a dialysis patient by subjective criteria is virtually impossible—volume overload (i.e., circulatory congestion) and obstructive coronary artery disease (including restenosis after PTCA or stent) can produce identical symptoms: dyspnea or angina. If eating a pepperoni pizza, Virginia ham, or five bags of potato chips on a Sunday night and in-stent restenosis produce the same symptoms (dyspnea/angina), it is plausible that a nephrologist might choose the wrong therapy when confronted by a dialysis patient with anginal symptoms. Alternatively, some patients truly have “silent ischemia”. For this reason, the subsequent occurrence of anginal symptoms after PCI cannot be used as a reliable surrogate for restenosis. In the nonrenal population, excess death risk is not attributed to the occurrence of restenosis. In ESRD patients, the issue is less clear, as the rate of the competing death event is considerably higher than the repeat revascularization rate. Finally, there have been no large prospective angiographic series in which the entire cohort of stent patients is restudied at time intervals after PCI to determine the true restenosis rate and rate of new disease progression. Recurrent episodes of myocardial ischemia may be either silent or equally probable, its clinical recognition obscured by volume status (including the effects of proscribed pepperoni pizza). Accordingly, in our own ESRD program at Hennepin County Medical Center, all dialysis patients undergoing PCI with PTCA or stents have dobutamine stress echocardiography performed at time intervals chosen to detect occult restenosis (usually 12 to 16 wk after procedure).

As I write this section of this paper, my institution awaits the first shipment of sirolimus-coated coronary stents. Although the drug-coated stent trials did not enroll ESRD patients, the early reports from the Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions (RAVEL) trial have been extraordinary, with a 26.6% restenosis rate at 6 mo for 118 patients receiving uncoated stents compared with 0% in the 120 patients receiving sirolimus-coated stents for native coronary lesions (104). Preliminary data suggest that the benefit is sustained for at least 1 yr (105). Sousa et al. (106) have reported an in-stent restenosis of 0% and target-vessel revascularization of 10% at 2 yr in 30 patients. Sirolimus-coated stents also appear promising for the treatment of in-stent restenosis (107).

There are two key issues relating to drug-coated stents in ESRD patients. First, will the vanishingly low restenosis rates reported in lower-risk patients carry over to dialysis patients? If they do, it would mean fewer repeat revascularization procedures (and we would abandon our surveillance strategy of stress imaging at 12 to 16 wk post-PCI for diagnosis of “occult” restenosis). The second issue is whether the long-term survival rate will be improved by coated stents.

Coronary brachytherapy has already been established as an adjunct to PCI in the setting of in-stent restenosis. There are currently no data pertaining to ESRD patients, but Gruberg et al. (108) retrospectively compared 118 chronic renal failure (CRF) patients (mean Cr, 2.0 mg/dl) with 481 nonrenal patients receiving intracoronary radiation and 14 CRF patients receiving placebo for treatment of in-stent restenosis. The re-restenosis rate in CRF patients was 22.6% after radiation versus 53.8% after placebo. The re-restenosis rate was comparable in CRF and nonrenal patients after radiation, but the 6-mo cardiac mortality was higher in the CRF group (6.8% versus 1.5%).

Patients receiving brachytherapy currently receive longer minimum postprocedure treatment with clopidogrel (1 mo post-stent and 6 mo post-brachytherapy; aspirin therapy is life-long after both). Clopidogrel may pose special problems in a dialysis patient if they also happen to be waitlisted for cadaveric renal transplant. Current guidelines suggest stopping clopidogrel (but not aspirin) 1 wk before elective (usually noncardiac) surgery, due to the excessive intraoperative bleeding that can occur in patients treated with clopidogrel. As cadaveric renal transplants cannot be planned 7 d in advance, it is recommended that this issue be addressed before the ESRD patient is committed to clopidogrel therapy.

Chronic renal failure is a predictor of adverse outcome after PCI. Azar et al. (109) in a retrospective case-control study compared the outcome of 34 dialysis patients receiving coronary stents in 40 lesions to nonrenal controls with 80 lesions matched for treatment site, diabetic status, lesion length, and reference vessel diameter. Aspirin, ticlopidine, and heparin were used in most patients. Angiographic success was achieved in 91% of ESRD patients and 97% of controls. At 9-mo follow-up, target lesion revascularization was 35% in the ESRD group (18% mortality) versus 16% in the controls (2% mortality). Adverse outcomes in patients with CKD are not limited to dialysis-dependent renal failure (110–114). Rubenstein et al. (109) compared the immediate and long-term outcomes of 362 renal failure patients (Cr > 1.5 mg/dl; median Cr, 1.9 mg/dl) with 2972 patients with normal renal function undergoing PCI in 1994–97. The in-hospital mortality was 10.8% for the renal patients and 1.1% in the controls matched for age and gender (P < .0001). Blood transfusion occurred in 43% of renal patients versus 14% of controls. The renal group included 27 dialysis patients with an in-hospital mortality of 11.1%. The 1-yr actuarial survival was 75% for the renal group and 97% for the matched controls (P < 0.00001). The event-free survival for death, AMI, or repeat coronary revascularization was 55% for the renal group and 78% for matched controls (P < 0.00001). As shown in Figure 6, the long-term survival of the dialysis subset was similar to the other renal failure patients. Figure 7 (111) shows the increased mortality after successful PCI at the Mayo Clinic related to severity of renal failure (as judged by estimated creatinine clearance).

There appears to be a relative survival advantage associated with CAB versus PCI (PTCA or stent) in dialysis patients, and this is consistent with earlier publications focused predominantly on the more favorable outcome of dialysis patients after CAB compared with PTCA (115–119). Using USRDS data, we compared the survival of dialysis patients receiving their first coronary revascularization procedure in 1995–98: 4836 dialysis patients with PTCA, 4280 stent patients, and 6668 CAB patients (120). The 2-yr all-cause survival was 48% in both PCI groups and 56% after CAB. In a Cox proportional hazards model, the risk of all-cause death was 20% lower for CAB versus PTCA (P < 0.0001) and 6% lower for stent compared
with PTCA (P = 0.03). Although the in-hospital mortality is lower for PCI (4.1% for stent, 6.4% for PTCA, and 8.6% for CAB), the survival curves for CAB and PCI cross at 6 mo. As shown in Figure 8, the long-term survival is more favorable after CAB compared with PCI in dialysis patients. These data are concordant with other clinical trials performed in nonrenal patients, most notably the diabetic subset of the bypass angio-
plasty revascularization investigation (BARI) trial. In dialysis patients, however, the survival advantage with surgery is not restricted to diabetic patients.

In a subsequent preliminary analysis (121), we have reported that the survival benefit of surgery is attributable to the utilization of internal mammary grafts (in clinical practice, this would predominantly reflect grafting of the left internal mammary artery to the left anterior descending [LAD] coronary artery). In patients who received surgery without internal mammary grafts, there was no relative survival advantage compared with PCI. There are two implications to this observation: the benefit of surgery is derived by patients who need revascular-
ization of the LAD vascular territory and who have suitable target vessels (i.e., not severe diffuse disease).

I believe it is possible to derive a pragmatic approach to dialysis patient selection for coronary revascularization, based on the small clinical series and observational studies from administrative databases. Patients who do not need revascular-
ization of the LAD vascular territory are appropriate candidates for PCI (if anatomically suitable). Stents are preferable to PTCA (predominantly for the lower restenosis risk) (122). CAB should be considered in these patients for repeated epi-
sodes of restenosis not responsive to other available strategies (e.g., brachytherapy, coated stents, etc). The use of repeated PCI may be attractive in patients who are not clearly surgical candidates, particularly because the performance of repeat PCI does not have adverse survival consequences (123). Patients with obstructive disease in the LAD (who are anatomically appropriate candidates for LIMA grafts to the LAD) should be considered for surgery as the preferred option, particularly if there is multivessel CAD requiring revascularization. It is prudent (when possible) to avoid placement of left arm arte-
riovenous fistula in patients with functioning LIMA grafts, as hemodynamic interference (i.e., “steal” and myocardial ischemia) of upper extremity arteriovenous fistula with ipsilateral
internal mammary grafts has been reported in dialysis patients (124). It is unknown if the survival advantage associated with LIMA grafts is altered by the concurrent presence of ipsilateral arteriovenous fistula in these patients. Single-vessel LAD disease management presents a special problem, as some surgeons dislike redo coronary revascularization procedures (and valve surgery) in patients with a patent LIMA graft (because of the possible risk of injuring the graft with sternotomy). The rate of progression of coronary artery disease, including multivessel disease, may potentially be more rapid in ESRD patients (125); a case can be made for a delaying strategy of PCI initially and surgery if/when the patient develops multivessel disease with LAD involvement. Hopefully, all measures to retard the progression of CAD are employed in these patients. The presence of mild aortic stenosis (not sufficiently severe to warrant valve replacement) might push the clinician to choose PCI as a waiting strategy until valve replacement is indicated, as the rate of progression of valvular aortic stenosis is likely to be greater in ESRD patients. Dialysis patients are clearly a high-risk surgical subset for in-hospital morbidity and mortality (126). Patients with non–dialysis-dependent renal failure are also at higher risk for morbidity and mortality after CAB compared with nonrenal patients (127,128), but the postoperative recovery (127) and morbidity (including acute renal failure) may be reduced by the use of off-pump coronary artery bypass (129). At my own institution, off-pump CAB is also preferred, including in dialysis patients. The clinician must make an honest appraisal of their own institutional experience, framed in the context of expected surgical outcomes from available databases.

There are few data on the comparative outcome of medical therapy versus revascularization for the treatment of ischemic heart disease in ESRD patients. Manske et al. (68) studied the outcome of 26 angina-free diabetic renal transplant candidates (with preserved left ventricular systolic function, no left main disease, and at least one coronary artery stenosis in the proximal two thirds of the vessel with a visually estimated stenosis of >75% and a translesional pressure gradient of 15 mmHg) who were randomized to either medical therapy with nifedipine and aspirin or prophylactic coronary revascularization with PTCA (if judged technically feasible) or CAB. Ten of thirteen medically treated versus two (both PTCA) of 13 revascularized patients had a prespecified cardiac end point (unstable angina, MI, or cardiac death) at a median time of 8.4 mo after randomization (P = 0.002), and the trial was prematurely terminated. In retrospect, the medical treatment arm employed questionable therapy, as β-blocker therapy was not used. The revascularization arm of the study treated the eight PTCA and five CAB patients as receiving equivalent therapies, which is also problematic. Noninvasive evaluation was not used in this clinical trial.

**Conclusion**

I have attempted to present my perspective on the management of a special population at extraordinarily high risk for CHD and its complications, patients with CKD. The goal of those entrusted with promoting the health and welfare of these patients should be aggressive efforts to diagnose, treat, and most importantly, prevent CHD in these patients. As a population at particularly high risk for CHD, our efforts should be rewarded with measurable improvements in cardiovascular outcomes in these patients.

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