Chapter nine
Cardiovascular special studies

Remove my heart of stone. Replace my heart of stone. Inspire cardio-vascular prophylaxis.

Geoffrey Hill, “The Triumph of Love”
In this chapter we present a series of analyses predominantly relating to ischemic heart disease and its complications in ESRD patients. We look again at the epidemiology of acute myocardial infarction in dialysis patients, a major research interest of the Cardiovascular SSC, but this year use the perspective of hemoglobin level and AMI. We also turn our attention to cardiovascular disease in recipients of transplants from cadaveric and living related donors. In past ADRs we have focused on the dialysis population, looking at trends relating to cardiovascular events and diagnostic testing for ischemic heart disease. While the absolute magnitude of cardiovascular risk is considerably lower for transplant recipients, there is a common thread of cardiovascular disease in all ESRD patients, with one important clinical difference. Renal transplant candidates at high cardiovascular risk are typically screened for ischemic heart disease before being deemed eligible for renal transplantation; the converse is true for dialysis patients at the initiation of renal replacement therapy (although one could argue that the same logic should apply to the dialysis population, with its higher risk of cardiovascular morbidity and mortality). Not surprisingly, the immediate post-transplant period is associated with a higher risk of potentially lethal complications of ischemic heart disease. The diagnosis and treatment of this disease is thus an important part of pre-transplant evaluation in high-risk (e.g. older and diabetic) renal transplant candidates, particularly since it is the single largest cause of death following successful transplantation. It must be stressed that, although ESRD has traditionally been the focus of the USRDS, there is a large reservoir of cardiovascular disease in CKD patients before the initiation of renal replacement therapy. We focus here on cardiovascular disease in ESRD patients, but these data cannot be fully understood without recognizing the genesis of the disease in the entire CKD population. In Figures 9.2-7 we present a snapshot of the epidemiology of AMI in dialysis patients and its association with hemoglobin levels. Adverse outcomes after AMI have been linked to lower hematocrit levels in the general Medicare population (Wu et al.), but this has not been examined in dialysis patients. (In dialysis patients with a history of heart disease, “normalization” of hemoglobin levels has been linked to increased mortality (Besarab et al.). The proportion of patients with higher hemoglobin levels increased from 1991 to 2001, but prevalent dialysis patients with AMI continue to have lower...
hemoglobin levels before the event than non-AMI patients. There is a striking increase in mortality after AMI for patients with hemoglobin levels less than 10 g/dl. These data must be interpreted with caution, as they are observational and do not prove causality. It is plausible, for example, that the “sicker” patients (e.g., those with increased inflammation and “malnutrition”) could be relatively resistant to erythropoietin therapy, which may explain the association of lower hemoglobin levels and increased mortality after AMI. These data also suggest that in AMI patients there is no survival advantage associated with hemoglobin values above 11–12 g/dl. Figures 9.8–17 present cardiovascular event rates after transplantation. The proportion of patients with comorbid cardiovascular disease at the time of transplant increased between 1995 and 2001 in both cadaveric and living-related donor (LRD) transplant recipients. There is an early hazard of cardiovascular events in the immediate post-transplant period, with AMI and cardiac arrest having the greatest relative proportional hazard in the first month after transplant compared to successive months. In all instances, the early post-transplant cardiovascular event rate is lower for LRD patients compared to patients with cadaveric grafts, although the number of coronary revascularization procedures is small in both groups and not different over three years. These data apply to the entire transplant population; it is likely that event rates for diabetic patients are higher. Figures 9.18–26 contrast patterns of cardiac procedure use in cadaveric and LRD transplant patients. As expected, diagnostic procedures are clustered in the year before LRD transplants, reflecting the “controlled” timing of the transplant. Forty-two percent of patients receiving cadaveric transplants in 1995 were tested for ischemic heart disease (stress test or coronary angiogram), compared to 48 percent in 1999; rates for LRD patients rose from 36 to 40 percent. The absolute rate of coronary revascularization is low in both groups; in 1999 only 5.5 percent of cadaveric donor patients and 6.8 percent of LRD patients had received coronary revascularization in the three years prior to their transplants. Ischemic heart disease continues to be a problem after transplantation. Even in the first year post-transplant, diagnostic testing for ischemic heart disease is performed in only one-tenth of all transplant patients, while only one-quarter of all cadaveric graft recipients have echocardiograms in this period. Despite the known metabolic complications associated with immunosuppression, it also appears that lipid testing has been underutilized. Though the percentage of transplant recipients receiving a lipid test in the first year after transplant nearly doubled from 1996 to 1999, it reached a level of only 30 percent.
Hemoglobin & geographic variations in mortality after AMI

Dialysis patients with AMI have an increasingly large burden of comorbid cardiovascular disease. In 2001, 87 percent had comorbid ASHD, 86 percent had CHF, 92 percent had other cardiac conditions, 59 percent had CVA/TIA, and 84 percent had PVD (Figure 9.3). From 1991 to 2001, the proportion of patients with diabetic ESRD increased from 37 to 51 percent, and that of patients age 65 and older grew from 59 to 64 percent (Figure 9.2).

Reflecting the impact of EPO and changing target hemoglobin values, the proportion of non-AMI patients with hemoglobins of 11–13 g/dl grew from 6.6 percent in 1991 to 76.5 percent in 2001 (Figure 9.4). In 2001, however, only 58 percent of patients with AMI had a hemoglobin of 11–13 g/dl before their “index AMI.” This association does not prove causality, as lower hemoglobin levels may reflect EPO resistance and the underlying global severity of illness. These results do, however, point to the need for further analyses, which should include EPO dose.

With the exception of areas in Idaho, Oregon, the south central states, and the Ohio Valley, patients who suffer an AMI generally have lower mean hemoglobins than those who do not (Figure 9.5). Geographic patterns of one-year mortality rates for prevalent patients with an AMI are noticeably different when comparing rates in 1991–1993 to those in 1998–2000 (Figure 9.6). In the latter period, fewer states had mortality rates of greater than or equal to 116 per 100 patient years at risk, and the average rate in the upper quintile decreased from 150 to 127 (15 percent) between the two periods.

Rates of mortality after AMI have decreased since 1995 for all hemoglobin levels (Figure 9.7). There is, however, a significant mortality hazard after AMI associated with levels less than 10 g/dl (1,172 deaths/1,000 patient years in 2000 versus 953 for hemoglobins of 11–12 g/dl). When compared to mortality rates of patients with hemoglobins of 11–12 g/dl,
there is also a small increased rate for those with levels of 12 g/dl and above, but this may be a statistical artifact of mortality rates derived in a prevalent population with changing mean hemoglobin values over time.

Figures 9.2-3 point prevalent Medicare dialysis patients with AMI in the prevalent year; comorbidities identified from Medicare claims. Figure 9.4 point prevalent Medicare dialysis patients with at least one monthly EPO claim with a hemoglobin of 3.33–16.67 g/dl. For non-AMI patients, mean hemoglobin is calculated from January to the month of the earliest of transplant, loss-to-followup, death, or December of the year; for AMI patients, mean hemoglobin is calculated in the month of the AMI and the previous two months. Figure 9.5 point prevalent Medicare dialysis patients, 2001, by HSA, unadjusted. Mean hemoglobin calculated with same method used in Figure 9.4. Figure 9.6 per 100 patient years at risk, period prevalent Medicare dialysis patients admitted to hospital for AMI before December 31, 1993 (1991–1993 cohort) or December 31, 2000 (1998–2000 cohort), by state, unadjusted. Figure 9.7 point prevalent Medicare dialysis patients hospitalized for AMI; adjusted for age, gender, race, primary diagnosis, & dialysis time before AMI. Mean hemoglobin calculated in the month of the AMI & the previous two months.
Cardiovascular event rates after renal transplantation

From the standpoint of cardiovascular risk, the major change in transplant patient demographics between 1995 and 2001 has been the proportional increase in older patients (Figure 9.8). The percentage of cadaveric donor transplant patients older than 50 has risen from 40 to 51 percent, while that of patients older than 65 has grown from 9 to 15 percent. In patients receiving transplants from living-related donors (LRD), growth has been from 28 to 45 percent and from 6 to 15 percent, respectively.

The proportion of transplant patients with comorbid cardiovascular disease has also risen (Figure 9.9). In patients receiving cadaveric grafts, the percentage with comorbid ASHD and CHF grew from about 40 percent in 1995 to 50 percent in 2001. In LRD patients, the percentage with ASHD increased from 36 to 43 percent, and with CHF from 33 to 40 percent.

With the exception of coronary revascularization, rates for cardiovascular, all-cause, and combined events are higher for patients with cadaveric transplants (Figures 9.10–17). The post-transplant period is associated with an increased hazard for all events, particularly AMI and cardiac arrest in the first 30 days post-transplant, and CHF in the first 60 days. In the 30 days following a transplant, the estimated probability of AMI is 1.2 and 0.8 percent in cadaveric and LRD transplants, respectively; for cardiac arrest, 1.1 and 0.7 percent; and for CHF, 5.2 and 4.7 percent. For AMI, and particularly for cardiac arrest, a finer level of temporal detail would be helpful to clinicians, as it might stimulate further investigations on the appropriate use of cardiac monitoring and anti-ischemic/anti-arrhythmic therapies (e.g. beta-blockers) after transplantation.

The rate of CVA/TIA after transplantation is comparable to that of AMI, yet during renal transplant evaluation less attention is typically paid to the cerebrovascular disease burden. This may in part reflect the relative efficacy of therapies to treat cardiac ischemia and cerebrovascular ischemia, and in part the relative “aggressiveness” of cardiologists compared to neurologists. Further research in the diagnosis and treatment of cerebrovascular disease would benefit all ESRD patients.

Figures 9.8–9 first transplant patients with Medicare as primary payor, comorbidities identified from both the Medical Evidence form & Medicare claims. Figures 9.10–17 first transplant patients with Medicare as primary payor, 1995–1999 combined; adjusted for age, gender, race, primary diagnosis, & prior dialysis time. Monthly event rates during the first six months after transplant, & mean monthly event rates during each six-month interval following month six of transplant.
9.10 · Event rates & event-free probabilities: acute myocardial infarction

9.11 · Event rates & event-free probabilities: congestive heart failure

9.12 · Event rates & event-free probabilities: cardiac arrest

9.13 · Event rates & event-free probabilities: CVA/TIA

9.14 · Event rates & event-free probabilities: coronary revascularization

9.15 · Event rates & event-free probabilities: peripheral vascular disease

9.16 · Event rates & event-free probabilities: all-cause death

9.17 · Event rates & event-free probabilities: any cardiovascular event or death
Diagnosis & treatment of cardiac disease in renal transplant recipients

Because the average wait-list time exceeds three years, screening of cadaveric renal transplant candidates for ischemic heart disease poses special problems. As there may be a progression of atherosclerotic heart disease, the “warranty” of a “negative” stress test or coronary angiogram often expires as patients age on the list.

In the first and second years prior to a living-related donor (LRD) transplant, stress testing or coronary angiography is performed in 38 and 16 percent of patients; in recipients of cadaveric organs, percentages are 29 and 25 (Figure 9.20). Coronary revascularization use is low, with only about 2 percent of cadaveric recipients receiving the procedure in any of the three years prior to transplant. Rates are comparable for LRD patients, though slightly higher (5 percent) in the year before transplant.

In the year following transplantation, testing for ischemic heart disease is performed in 12 percent of cadaveric donor patients, and 10 percent of LRD patients; for coronary angiography, rates are 3.9 and 2.4; and for coronary revascularization, 1.3 and 1.2 (Figures 9.19–20 and 9.22). The potential morbidity (i.e. contrast nephropathy and graft loss) of coronary angiography and revascularization in renal transplant patients merits further attention. Fewer than one-third of patients receive lipid testing in the first year post-transplant (Figure 9.23).

There is significant use of diagnostic testing in wait-listed patients (Figure 9.26).

Figures 9.18–24 first transplant patients with Medicare as primary payer. Unadjusted first testing rates estimated using the Kaplan-Meier method. Figure 9.25 first transplant patients with Medicare as primary payer, 1995–1999 combined. Percent of patients receiving testing or treatment in the three years pre- or post-transplant. Figure 9.26 ESRD patients wait-listed for the first time, 1995–1999 combined.
HEMOGLOBIN & GEOGRAPHIC VARIATIONS IN SURVIVAL AFTER AMI

Figure 9.2 In the prevalent dialysis population with AMI, the proportion of older patients and patients with diabetic nephropathy increased from 1991 to 2001. Figure 9.3 A high proportion of AMI patients have comorbid cardiovascular disease. Figure 9.4 Lower hemoglobin values occur disproportionately in patients with AMI: 58 percent have hemoglobins of 11-13 g/dl, compared to 77 percent in patients without AMI. Figure 9.5 Patients who suffer an acute MI generally have lower mean hemoglobins than those who do not. Figure 9.7 The mortality rate after AMI is highest for patients with hemoglobin values less than 10 g/dl, and lowest for those with levels of 11-12 g/dl.

CARDIOVASCULAR EVENT RATES AFTER RENAL TRANSPLANTATION

Figure 9.8 Among the transplant population, the proportion of older patients and patients with comorbid cardiovascular disease increased from 1995 to 2001. Figure 9.9 Compared to recipients of transplants from cadaveric donors, patients receiving transplants from living-related donors have lower cardiovascular event rates. Figures 9.10-17 The highest cardiovascular event rates in transplant patients occur in the 30 days following the transplant, with lower long-term cardiovascular event-free survival for cadaveric graft recipients. The cardiovascular events of AMI, cardiac arrest, coronary revascularization, and CVA/TIA are relatively uncommon—the probability of each event in the first year post-transplant is less than 4 percent—compared to congestive heart failure and peripheral vascular disease, for which probabilities range from 10 to 17 percent.

DIAGNOSIS & TREATMENT OF CARDIAC DISEASE IN RENAL TRANSPLANT PATIENTS

Figures 9.18-24 Diagnostic testing for ischemic heart disease occurs most frequently in the one year before a living-related donor transplant. Figure 9.25 In the three years preceding their transplants, 48 percent of patients receiving a cadaveric graft in 1999 were screened for coronary artery disease with a stress test or coronary angiography, compared to 40 percent of patients receiving a living-related donor transplant. Coronary angiography is rarely used as the sole diagnostic test for coronary artery disease before a transplant. In three years following their transplants, about 22 percent of cadaveric graft recipients and 20 percent of LRD graft patients in 1999 underwent stress testing or coronary angiography. Rates of coronary revascularization in renal transplant recipients are low: 6-7 percent in the three years before a transplant, and 3 percent in the three years post-transplant. About 10 and 12 percent of recipients from living-related and cadaveric donors, respectively, are tested for coronary artery disease in the first year after transplant. Figure 9.26 By the end of their third year on the transplant waiting list, one-third of patients have received an echocardiogram, and one-quarter have received a stress test or coronary angiography.