Ischemic heart disease after renal transplantation

Principal discussant: Bertram L. Kasiske

Hennepin County Medical Center, Minneapolis, Minnesota, USA

CASE PRESENTATION

A 33-year-old man received a haplo-identical kidney transplant from his brother in 1979. He had had proteinuria for 16 years prior to transplantation, and his renal disease was attributed to chronic glomerulonephritis. He had developed hypertension 10 years before transplantation. He started maintenance hemodialysis 6 months before transplantation, and after initiating hemodialysis he underwent bilateral nephrectomy and splenectomy. In that same month he was hospitalized with chest pain, and a myocardial infarction was ruled out. He had no clinical signs and symptoms of ischemic heart disease (IHD); however, he had smoked 1/2 packs of cigarettes daily for approximately 7 years. He was not obese and his physical examination was unremarkable. An electrocardiogram and chest radiograph were normal.

After transplantation he was treated with azathioprine and corticosteroids. He had no acute rejection. Approximately 3 months after transplantation he sustained an anteroseptal myocardial infarction, documented by cardiac enzyme elevation and electrocardiographic changes. He continued to have chest pain, underwent coronary angiography, and had a 3-vessel coronary bypass operation 7 months posttransplant. He did well until he developed angina pectoris 8 years after transplantation. Angiography disclosed occlusions of all 3 bypass grafts and diffuse underlying coronary artery disease. He had a 2-vessel coronary artery bypass operation and remained symptom free until 18 years posttransplant, when he again developed chest pain. At that time percutaneous angioplasty of a single coronary artery relieved his symptoms.

Throughout his post-transplant course, he had elevated low-density lipoprotein (LDL) cholesterol (>130 mg/dL). He was prescribed 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, but he took these irregularly, complaining that they caused bloating and nausea. Fast- ing triglycerides were generally <200 mg/dL, and the high-density lipoprotein (HDL) cholesterol was low (<35 mg/dL) on several occasions. Lipoprotein(a) also was elevated (>30 mg/dL). He began taking an aspirin, 325 mg daily, after his first myocardial infarction, and he continued taking aspirin throughout his posttransplant course. He continued to smoke 1/2 packs of cigarettes per day; his fasting blood glucose was always normal. His blood pressure was well controlled with antihypertensive medications that included beta-blockers and converting enzyme inhibitors.

Twenty years after transplantation he had an acute rise in serum creatinine, but an allograft biopsy showed only mild chronic allograft nephropathy, and his immunosuppressive regimen (azathioprine and prednisone) was not changed. He developed intermittent atrial fibrillation, which was treated with repeated cardioversion and warfarin. Ultimately, he developed severe congestive cardiomyopathy, and his name was placed on the waiting list for a heart transplant shortly before he died. 21 years after renal transplantation. Just before he died, his serum creatinine was 1.8 mg/dL, his creatinine clearance was 53 mL/min, and he had 506 mg/day of protein in his urine.

DISCUSSION

Dr. Bertram L. Kasiske (Director of Nephrology, Hennepin County Medical Center, Minneapolis, Minnesota, USA): This patient illustrates a typical clinical course of post-transplant ischemic heart disease (IHD). The only screening for IHD in the pre-transplant evaluation was a history, physical examination, chest radiograph, and electrocardiogram, all of which were unremarkable. Nevertheless, it is likely that the myocardial infarction three months after transplantation resulted from coronary artery disease already present at the time of transplantation. Throughout the post-transplant course, the patient had recurrent coronary artery disease. Despite the progressive nature of this patient’s coronary artery disease and the less-than-optimal management of risk factors, aggressive and timely intervention was successful in pre-
serving his life with a functioning transplant for more than 20 years.

The past quarter-century has been a remarkable period for the development of effective immunosuppressive medications in renal transplantation. Current immunosuppression protocols have dramatically reduced the rate of early acute rejection and have substantially improved one-year graft survival rates. Indeed, death with a functioning allograft now competes with rejection as the most common cause of “renal allograft failure,” especially in the late post-transplant period. While the goal of transplantation is to have every patient die with a functioning kidney transplant, deaths after renal transplantation still occur much sooner than those of age- and gender-matched patients without renal failure [1]. Deaths due to infection and malignancies contribute to this increased mortality rate. However, the leading cause of death after renal transplantation is cardiovascular disease. Thus, further improvement in long-term renal allograft survival will depend in large part on our ability to reduce deaths from IHD. Although atherosclerotic cardiovascular disease (CVD) also causes morbidity and mortality from cerebral vascular disease and peripheral vascular disease, the management of risk factors for IHD will most likely reduce the risk for other atherosclerotic CVD complications as well.

The last 25 years also have been a remarkable period for the development of effective strategies for reducing the morbidity and mortality of IHD. Large, randomized, controlled trials in the general population have helped define the roles of risk-factor intervention with antihypertensive medications, lipid-lowering agents, aspirin prophylaxis, and other measures in reducing IHD. Of course, these trials have excluded patients with renal disease, and it is unlikely that adequately powered, randomized, controlled trials will ever be conducted to confirm the effectiveness in renal transplant recipients of each of the interventions already tested in large multicenter trials in the general population. Therefore, clinicians must decide what evidence can be used to assess which of the therapies effective in the general population should be applied to renal transplant recipients.

A reasonable approach might be to first establish that the relationship between a particular risk factor and IHD is similar in the renal transplant population to that in the general population. The relationship might not be the same if, for example, other pathogenetic factors unique to renal transplant recipients superseded other traditional risk factors in the development of atherosclerotic IHD. Therefore, one must establish that traditional, modifiable risk factors are independently associated with IHD events in renal transplant recipients, just as they are in the general population. Similarly, it is also important to determine that therapies proven to modify these risk factors (and to reduce the risk of IHD in the general population) are equally safe and effective in renal transplant recipients. Having established the link between the risk factor and IHD, and having defined therapy that safely modifies the risk factor, we must make a “leap of faith” that the reduction in IHD in the general population also occurs in renal transplant recipients.

**Screening for ischemic heart disease**

Pre-transplant IHD is an important risk factor for post-transplant IHD [2, 3]. In a study at the University of Minnesota, asymptomatic diabetic patients who had significant coronary artery disease (one or more lesions with >70% occlusion) were randomly allocated to medical management or revascularization prior to transplantation. Those who underwent revascularization with either angioplasty or bypass surgery had significantly fewer IHD events after transplant surgery [2]. This study suggested that some high-risk, asymptomatic patients would benefit from screening and pre-emptive treatment of IHD. Most transplant centers do not use coronary angiography to screen all high-risk transplant candidates. Angiography is not only invasive and costly, but it also can accelerate the patient’s need to initiate dialysis [4]. Most centers therefore rely on noninvasive cardiac stress testing to identify asymptomatic patients who need angiography.

The American Society of Transplantation (AST) recommends that patients at high-risk, that is, diabetics, older individuals defined as more than 40 to 45 years of age, and individuals with two or more cardiac risk factors, undergo a cardiac stress test as part of the pre-transplant evaluation [5]. The role of post-transplant screening for IHD is poorly defined.

**Risk factors for ischemic heart disease**

**Hypertension.** The evidence that the pharmacologic treatment of hypertension effectively reduces both stroke and IHD in the general population is incontrovertible. In a meta-analysis published in 1990, Collins and coworkers combined the results from 14 randomized trials that compared the use of diuretics and/or beta-blockers to placebo. Over a mean treatment duration of 5 years, they found a 35% to 40% reduction in stroke and a 20% to 25% reduction in coronary heart disease [6]. Evidence from randomized trials such as these led to the development of guidelines that recommend treatment of hypertension, with blood pressure thresholds tailored to overall IHD risk, using diuretics and beta-blockers as first-line agents [7]. More recently, interest has shifted to determining whether newer antihypertensive agents are as good or better at reducing IHD than diuretics and beta-blockers. A recent meta-analysis of trials comparing the effect of angiotensin-converting enzyme (ACE) inhibitors with placebo reported a 30% reduction in stroke and a 20% reduction in coronary heart disease despite only a 3 mm Hg reduction in systolic blood pressure [8].
Although this analysis was heavily dependent on a single large trial [9], it suggested that ACE inhibitors have protective effects that extend beyond blood pressure reduction, at least in patients selected on the basis of prior IHD or diabetes. In contrast, the data from randomized trials suggest, but do not conclusively prove, that calcium antagonists increase the risk of IHD compared to diuretics, beta-blockers, and ACE inhibitors [8, 10]. Altogether, these recent trials have (1) supported recommendations that diuretics and beta-blockers be used as first-line therapy, (2) suggested a beneficial role for ACE inhibitors in patients with diabetes or prior IHD, and (3) suggested that calcium antagonists probably should not be used as first-line therapy. Ongoing trials comparing antihypertensive agents should help clarify these issues.

Hypertension is common after renal transplantation. The use of calcineurin inhibitors, cyclosporine A (CsA), and tacrolimus; the use of corticosteroids; the presence of native kidneys; and renal allograft dysfunction (including renal artery stenosis) all likely contribute to the high prevalence of post-transplant hypertension. In patients treated with azathioprine and prednisone, the prevalence of hypertension is 50% to 70% [11]. The prevalence in patients treated with CsA is 65% to 85% [11].

Few studies have examined the relationship between blood pressure and IHD after renal transplantation. However, in 29,751 transplant recipients in the Collaborative Transplant Study, hypertension was associated with both decreased graft and patient survival [12]. Unfortunately, no statistical adjustment was made for renal dysfunction, and it is certainly plausible that the observed associations were due to the fact that graft dysfunction causes hypertension. In a study that included statistical adjustment for graft function, blood pressure was an independent predictor of graft survival in 277 renal transplant recipients [13]. In another study, hypertension was associated with graft failure among African Americans but not among whites [14]. However, none of these studies examined the relationship between blood pressure and IHD per se.

In a recent retrospective, uncontrolled, cross-sectional study of 287 patients, hypertension was more prevalent in transplant recipients with coronary artery disease than in those without CAD [15]. We examined the relationship between blood pressure during the first year after renal transplantation and the subsequent development of new IHD in a retrospective study of 1124 transplant recipients [16]. Although the qualitative relationship between blood pressure and IHD in transplant recipients was similar to that predicted by the Framingham Heart Study equations [17] (Table 1), the effect of blood pressure was not statistically independent of other risk factors [16]. Of course, a true effect of blood pressure on coronary artery disease might have been obscured by aggressive treatment of hypertension, other associated risk factors such as acute rejection, insufficient sample size, or a relatively short follow-up. Thus, although few studies have documented the relationship between blood pressure and IHD in renal transplant recipients, the data offer no reason for us to believe that the effect of hypertension on IHD is different in transplant patients compared to the general population.

The American Society of Transplantation recommends routine screening for hypertension and maintenance of blood pressure <140/90 mm Hg (but lower if possible) after renal transplantation [11]. The National Kidney Foundation Task Force on IHD recommends a therapeutic blood pressure target of <130/85 mm Hg, and <125/75 mm Hg in patients with proteinuria [18]. Antihypertensive medications generally are safe and effective in renal transplant recipients, and there are no medications for which there are absolute contraindications. However, some adverse effects of medications are more common in renal transplant recipients. Diuretics can raise the serum creatinine level in transplant patients. The ACE inhibitors also occasionally raise serum creatinine, but more often ACE inhibitors cause mild hyperkalemia, and they can contribute to anemia. Calcium channel blockers probably should be used with caution, at least as monotherapy [16]. Some calcium channel blockers increase blood levels of cyclosporine. Given the prevalence of IHD, beta-blockers and ACE inhibitors are particularly attractive for renal transplant recipients. In the end, more than half of transplant recipients need combination therapy to adequately control blood pressure.

Hyperlipidemia. Randomized controlled trials in the general population have provided convincing evidence that reducing LDL cholesterol effectively decreases the risk of IHD and lengthens survival. A meta-analysis of 5 randomized trials compared the effects of HMG-CoA reductase inhibitors to placebo in 30,817 patients [19]. Two of the trials included in the meta-analysis were primary prevention trials, while three studied patients with known coronary artery disease. Over a mean duration of 5.4 years of follow-up, treatment was associated with a 31% (95% confidence interval 26%–36%) reduction in the risk of coronary events and a 21% (14%–28%) reduction in all-cause mortality [19]. The reduction in risk was similar in men and women, and in those 65 and older versus those younger than 65 years. Several secondary prevention trials also have shown that nicotinic acid, alone or in combination with clofibrate or colestipol, reduced coronary artery disease. Fibrates, for example, gemfibrozil and bezafibrate, also have reduced coronary artery disease in secondary prevention trials. Because fibrates are more effective in reducing triglycerides and raising HDL than in reducing LDL, these latter trials have advanced the debate over the role of therapies targeting triglycerides and/or low HDL. Ongoing trials are studying whether reducing triglycerides and raising HDL reduces IHD in patients with normal or only modestly elevated LDL, a
Table 1. Relative risk for ischemic heart disease in subjects of the Framingham Heart Study versus patients more than one year after renal transplantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Framingham Men</th>
<th>Transplant Men</th>
<th>Framingham Women</th>
<th>Transplant Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.05</td>
<td>1.06</td>
<td>1.40</td>
<td>1.10</td>
</tr>
<tr>
<td>Age, years²</td>
<td>0.997</td>
<td>0.999</td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td>Cholesterol mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;160</td>
<td>0.52</td>
<td>0.00</td>
<td>0.77</td>
<td>0.00</td>
</tr>
<tr>
<td>160–199</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>200–239</td>
<td>1.19</td>
<td>2.39</td>
<td>1.23</td>
<td>2.07</td>
</tr>
<tr>
<td>240–279</td>
<td>1.66</td>
<td>2.02</td>
<td>1.28</td>
<td>2.44</td>
</tr>
<tr>
<td>≥280</td>
<td>1.93</td>
<td>2.25</td>
<td>1.71</td>
<td>1.84</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>1.64</td>
<td>1.02</td>
<td>2.32</td>
<td>9.16</td>
</tr>
<tr>
<td>35–44</td>
<td>1.28</td>
<td>1.37</td>
<td>1.46</td>
<td>1.48</td>
</tr>
<tr>
<td>45–49</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.37</td>
</tr>
<tr>
<td>50–59</td>
<td>0.95</td>
<td>1.32</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>≥60</td>
<td>0.61</td>
<td>1.07</td>
<td>0.65</td>
<td>0.99</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120 and &lt;80</td>
<td>1.00</td>
<td>0.25</td>
<td>0.59</td>
<td>0.56</td>
</tr>
<tr>
<td>120–129 or 80–84</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>130–139 or 85–89</td>
<td>1.33</td>
<td>1.05</td>
<td>0.93</td>
<td>1.26</td>
</tr>
<tr>
<td>140–159 or 90–99</td>
<td>1.68</td>
<td>1.19</td>
<td>1.30</td>
<td>1.63</td>
</tr>
<tr>
<td>≥160 or ≥100</td>
<td>1.86</td>
<td>1.47</td>
<td>1.59</td>
<td>0.31</td>
</tr>
<tr>
<td>Diabetes yes/no</td>
<td>1.53</td>
<td>2.78</td>
<td>1.82</td>
<td>5.40</td>
</tr>
<tr>
<td>Cigarette use yes/no</td>
<td>1.69</td>
<td>1.95</td>
<td>1.34</td>
<td>1.82</td>
</tr>
</tbody>
</table>

*Shown are relative risks. A relative risk greater or less than 1.00 indicates a higher or lower risk for ischemic heart disease, respectively. For example, among Framingham Heart Study men, the risk is 5% higher for each one year increase in age. Reference risks for cholesterol, HDL, and blood pressure are indicated by 1.00. Included in the model (but not in the table) were variables testing the effects of missing values (each P > 0.2). Abbreviation is HDL, high-density lipoprotein cholesterol. *P < 0.05, P values for Framingham co-efficients are not indicated [17].

Reprinted with permission from The American Society of Nephrology [16].

lipoprotein profile that is particularly common among diabetics. In the meantime, current guidelines emphasize the importance of reducing LDL, and HMG-CoA reductase inhibitors are clearly the most effective agents for reducing LDL cholesterol [20].

Hyperlipidemia is commonly defined using criteria set out by the National Cholesterol Education Program (NCEP) [20]. Low-risk total cholesterol and LDL cholesterol are <200 mg/dL and <130 mg/dL, respectively. High-risk total cholesterol and LDL are ≥240 mg/dL and ≥160 mg/dL. Low HDL is ≤40 mg/dL, and high fasting triglycerides are ≥200 mg/dL. In the National Kidney Foundation (NKF) Task Force on Coronary Vascular Disease (CVD), the prevalence of hyperlipidemia after renal transplantation was estimated by combining the results of studies reporting the proportion of patients with elevated lipoproteins [21]. In 5 studies, 63% of 549 patients had total cholesterol >240 mg/dL [22–26]. The LDL cholesterol was >130 mg/dL in 60% of 769 patients [22, 27, 28]. In contrast, nearly 90% of 777 patients had an HDL cholesterol <35 mg/dL [22, 23, 28, 29]. Triglycerides were >200 mg/dL in 36% of 1309 patients [22, 23, 25, 29–31]. Lipoprotein(a) was >30 mg/dL in 23% of 468 patients [26, 27, 32–34]. Thus hyperlipidemia, especially increased LDL, is common after renal transplantation.

Although few studies have rigorously examined the relationship between hyperlipidemia and IHD after renal transplantation, several observational studies have found correlations between hyperlipidemia and IHD after transplantation [3, 35–38]. We recently examined the relationship between lipid levels measured during the first year after transplantation and the subsequent development of new IHD in a retrospective study of 1124 transplant recipients [16]. The relationship between total cholesterol, HDL cholesterol, and IHD was similar in our transplant population compared with that predicted by the Framingham Heart Study equations (Table 1) [16]. Moreover, cholesterol (and triglycerides) continued to be independent predictors of IHD even after multiple risk factors, including acute rejection, were taken into account (Table 2). Thus, the best current evidence strongly suggests that hyperlipidemia is associated with IHD in renal transplant recipients.

The AST Guidelines recommend screening for hyperlipidemia at least once during the first six months and again at one year after transplantation with fasting total cholesterol, LDL, HDL, and triglyceride measurements [11]. Thereafter, annual screening for total cholesterol should be carried out in individuals with previously normal lipid levels and a low risk profile for CVD. Individuals with borderline or previously high lipid levels should have a complete fasting lipid profile obtained annually [11]. The NKF Task Force on CVD recently suggested that the NCEP Adult Treatment Panel II Guidelines be used for the management of hyperlipidemia in patients with chronic renal disease, including renal transplant.
recipients [21]. However, the NKF recommends that patients with chronic renal disease be considered in the highest risk category of the classification and treatment of hyperlipidemia. This approach would mean that transplant recipients should be managed as if they already had confirmed IHD (Fig. 1). Thus, patients with LDL >100 mg/dL should be started on a cholesterol reduction, Step II American Heart Association diet, with goal LDL <100 mg/dL [20]. This diet calls for a saturated fat intake <7% of total calories and cholesterol <200 mg/day.

Patients with LDL >130 mg/dL should be treated with both Step II diet and a lipid-lowering drug, with goal LDL <100 mg/dL (Fig. 1) [20]. The drug of choice is an HMG-CoA reductase inhibitor. However, the dose of the HMG-CoA reductase inhibitor should be reduced by 50% in patients who also are taking a calcineurin inhibitor, as blood levels of HMG-CoA reductase inhibitors are increased in patients receiving calcineurin inhibitors. It is reasonable and most cost-effective to tailor the selection of an HMG-CoA reductase inhibitor to the degree of LDL elevation. Cheaper, less-potent agents are suitable for patients with LDL 130–160 mg/dL, because many of these patients will reach target LDL <100 mg/dL. However, more expensive, more potent agents sometimes are indicated as initial therapy for patients with LDL >160 mg/dL (Fig. 1). Comparative studies in the general population have reported the relative potency of different HMG-CoA reductase inhibitors. In general, the least potent agents are fluvastatin and pravastatin, and the most potent is atorvastatin. Few, if any, HMG-CoA dose-response comparison studies are available in renal transplant recipients, treated with or without calcineurin inhibitors.

The management of patients who continue to have LDL >100 mg/dL despite treatment with a potent HMG-CoA reductase inhibitor is problematic (Fig. 1). Let me stress that treatment should not be abandoned, and patients should be encouraged to continue treatment, even if the target LDL is not reached. Physicians should remind their patients that the higher the initial LDL cholesterol, the greater the benefit of therapy. Additional management options can include changing the immunosuppressive drug and/or adding a second lipid-lowering agent. Each of these options carries some risk, so clinicians must weigh the relative risk and benefit. In general, the higher the LDL and the greater the risk for IHD, the more reasonable it becomes to change the immunosuppressive (if possible) or to add a second lipid-lowering agent. For patients treated with CsA, one should consider substituting tacrolimus for CsA. In randomized trials comparing tacrolimus to CsA, total and LDL cholesterol were significantly lower in tacrolimus-treated patients. Moreover, a recent trial randomly allocated CsA-treated patients with hyperlipidemia to either continue CsA or switch to tacrolimus. Those who were switched to tacrolimus had a 25% reduction in LDL cholesterol compared to those who remained on CsA [39]. Clinicians also should consider substituting or discontinuing rapamycin in patients who have marked hyperlipidemia. A more difficult decision is whether to discontinue low-dose prednisone. Discontinuing prednisone is associated with an increased risk of acute rejection (10% to 15%). In addition, although discontinuing prednisone can reduce total and LDL cholesterol somewhat, it also can reduce HDL. My own approach is to discontinue CsA in stable transplant recipients.

Few studies have examined the safety and efficacy of combination therapy with lipid-lowering agents in renal transplant patients. Bile acid sequestrants can be used effectively in combination with HMG-CoA reductase inhibitors, but bile acid sequestrants generally should be avoided in patients with high triglyceride levels. Concerns about reduced bioavailability of CsA have led to the recommendation that bile acid sequestrants not be

---

### Table 2. Risk factors for ischemic heart disease events occurring more than one year after renal transplantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk</th>
<th>95% C.I.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD: type 1 diabetes (0.18)</td>
<td>3.03</td>
<td>1.75–5.24</td>
<td>0.000</td>
</tr>
<tr>
<td>ESRD: type 1 diabetes in women (0.07)</td>
<td>2.79</td>
<td>1.26–6.17</td>
<td>0.012</td>
</tr>
<tr>
<td>ESRD: type 2 diabetes (0.07)</td>
<td>3.35</td>
<td>0.99–11.3</td>
<td>0.052</td>
</tr>
<tr>
<td>Diabetes not causing renal disease (0.04)</td>
<td>2.54</td>
<td>1.15–5.60</td>
<td>0.021</td>
</tr>
<tr>
<td>Age (1.00, mean = 41.8 y)</td>
<td>1.06</td>
<td>1.04–1.08</td>
<td>0.000</td>
</tr>
<tr>
<td>Age in women (0.44, mean = 41.5 y)</td>
<td>0.99</td>
<td>0.97–0.99</td>
<td>0.000</td>
</tr>
<tr>
<td>Smoking at the time of transplantation (0.25)</td>
<td>1.85</td>
<td>1.23–2.76</td>
<td>0.003</td>
</tr>
<tr>
<td>Underwent transplantation 1986–1992 (0.35)</td>
<td>0.60</td>
<td>0.39–0.92</td>
<td>0.019</td>
</tr>
<tr>
<td>Underwent transplantation after 1992 (0.26)</td>
<td>0.27</td>
<td>0.11–0.63</td>
<td>0.002</td>
</tr>
<tr>
<td>Two or more first-year rejections (0.16)</td>
<td>1.62</td>
<td>1.04–2.53</td>
<td>0.034</td>
</tr>
<tr>
<td>Bilateral nephrectomy (0.29)</td>
<td>0.45</td>
<td>0.26–0.77</td>
<td>0.004</td>
</tr>
<tr>
<td>Bilateral nephrectomy for PKD (0.04)</td>
<td>3.45</td>
<td>1.50–7.95</td>
<td>0.004</td>
</tr>
<tr>
<td>Serum albumin &lt;4.0 g/dL (0.54)</td>
<td>1.71</td>
<td>1.10–2.65</td>
<td>0.017</td>
</tr>
<tr>
<td>Proteinuria (0.17)</td>
<td>1.69</td>
<td>1.08–2.64</td>
<td>0.022</td>
</tr>
<tr>
<td>Cholesterol &gt;200 mg/dL (0.77)</td>
<td>2.18</td>
<td>1.01–4.72</td>
<td>0.048</td>
</tr>
<tr>
<td>Triglycerides &gt;350 mg/dL (0.07)</td>
<td>1.90</td>
<td>1.04–3.47</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Cox proportional hazards models (N = 1124 transplants and 123 IHD events) with and without stratifying for renal disease from type 1 diabetes, which violates the proportional hazards assumption. Shown are relative risks, 95% confidence intervals, P values, and (in parentheses) the proportion of patients having the characteristic indicated by that variable. A relative risk greater or less than 1.00 indicates a higher or lower risk for ischemic heart disease, respectively. Included in the models, but not in the table, were variables testing the effects of missing values (each with P > 0.5). Abbreviations are ESRD, end-stage renal disease; PKD, polycystic kidney disease. (Reprinted with permission from The American Society of Nephrology [16]).
administered at the same time as CsA. Fibric acid analogs can be used in combination with HMG-CoA reductase inhibitors, but the risk of myositis significantly rises with this combination, especially in CsA-treated patients. Nicotinic acid might be another option.

**Cigarette smoking.** Of course, no randomized controlled trials have yet proved that cigarette smoking causes IHD; such trials would be unethical. Nevertheless, numerous large, observational studies have shown cigarette smoking to be a major independent risk factor for IHD. In the Framingham Heart Study, for example, cigarette smoking increased the risk of coronary heart disease by 69% in men and 34% in women (Table 1) [17].

Cigarette smoking appears to be as prevalent among renal transplant recipients as it is in the general population [40]. In retrospective, observational studies, cigarette smoking has been linked to IHD [35, 37, 40], early mortality [40–42], and graft failure [43]. We found that the risk associated with cigarette smoking in renal transplant recipients with IHD appeared to be greater than the risk predicted by the Framingham Heart Study. Indeed, cigarette smoking increased the risk of a major IHD event by almost twofold both in men and women (Table 1) [16]. Intervention is often effective, so smoking cessation should be vigorously pursued in renal transplant recipients. Guidelines have been developed for smoking cessation [44, 45].

**Glucose intolerance.** Epidemiologic studies strongly suggest that diabetes greatly increases the risk of IHD in the general population. In the Framingham Heart Study, for example, diabetes increased the risk of coronary heart disease by 53% in men and 82% in women (Table 1) [17]. Although it is generally accepted that diabetes increases the risk of IHD, whether intensive glycemic control reduces the risk of IHD, whether intensive glycemic control reduces the risk of IHD has been more difficult to demonstrate. The Diabetes Control and Complications Trial revealed a (not statistically significant) tendency for IHD events to be reduced in the intensive glucose control group [46]. In the United Kingdom Prospective Diabetes Study, intensive glycemic control significantly reduced coronary heart disease events [47].

Thus, current evidence suggests that intensive glycemic control reduces the incidence of IHD in the general population.

A growing number of renal transplant candidates have renal disease caused by diabetes. In addition, some patients who do not already have diabetes develop diabetes after transplantation. Corticosteroids as well as calcineur-
rin inhibitors contribute to the high incidence of post-transplant glucose intolerance. The incidence of new diabetes requiring insulin is probably about 5% in the first year after renal transplantation. The incidence of glucose intolerance not requiring treatment with insulin has not been well defined.

Several observational studies demonstrated that diabetes is a risk factor for IHD after renal transplantation. The risk of IHD from diabetes is severalfold higher than the risk from diabetes predicted by the Framingham Heart Study equations (Table 1) [16]. It is likely that the factors important in the pathogenesis of diabetic nephropathy also are important in the pathogenesis of IHD. Whether new-onset, post-transplant diabetes is also associated with an increased risk of IHD has not been examined in large, epidemiologic studies. However, post-transplant diabetes is associated with decreased graft survival [48, 49].

Whether intensive glycemic control after renal transplantation will help prevent IHD is far from clear. Blood glucose control is likely to be more difficult to achieve safely in patients who have long-standing diabetes and end-organ damage. Autonomic neuropathy causing delayed gastric emptying and inability to sense hypoglycemia, for example, can make insulin dosing difficult. Pancreas or islet cell transplantation provides optimal glycemic control and might be a solution for some patients. Attempts should be made to prevent new-onset glucose intolerance by minimizing the use of corticosteroids and calcineurin inhibitors when possible.

**Exercise and weight reduction.** Diet and lack of regular exercise have been linked to IHD in observational studies in the general population. However, no randomized controlled trials have conclusively demonstrated that a weight-reduction diet or regular exercise program ameliorates IHD. In meta-analyses of randomized trials from the general population, single and multiple lifestyle interventions had modest effects on risk factors, and little effect on overall or cardiovascular mortality [50, 51]. Guidelines developed by the National Heart, Lung, and Blood Institute recommend weight loss to improve lipid profiles, blood pressure, and glycemic control in patients with type II diabetes [52]. A low-fat, low-calorie diet is recommended along with exercise [52].

Obesity is common after transplantation, in large part because of the use of corticosteroids. Sporadic evidence also suggests that regular exercise is rare among renal transplant recipients. In a retrospective study of 427 renal transplant recipients, body mass index >25 kg/m² was an independent risk factor for cardiovascular disease [37]. Otherwise, few data show that obesity or a sedentary lifestyle is an independent risk factor for IHD after renal transplantation. In addition, few data suggest that diet or regular exercise is effective in achieving long-term weight reduction and mitigating IHD after renal transplantation. Despite a lack of evidence to support their efficacy in renal transplant recipients, a weight reduction diet in obese patients and regular exercise in everyone should be encouraged given the potential for benefit and low risk.

**Homocysteine.** Several observational studies in the general population have linked elevated plasma homocysteine levels to IHD [53, 54]. Results of ongoing randomized, controlled trials to determine whether lowering homocysteine reduces the incidence of IHD have not yet been reported, however. Thus, it is not known whether homocysteine plays a pathogenetic role in IHD. The prevalence of hyperhomocysteinemia is high in renal transplant recipients compared to the general population. Moreover, renal transplant patients with IHD have higher homocysteine levels than do transplant patients without IHD [55, 56]. Although treatment with folic acid effectively reduces high homocysteine levels in renal transplant recipients [57, 58], whether this approach reduces IHD will remain uncertain until randomized trials are completed.

**Antioxidant vitamins.** Studies in the general population have frequently reported an association between various indicators of oxidized lipoproteins and IHD [59]. However, several adequately powered, randomized, placebo-controlled trials in the general population have failed to demonstrate that anti-oxidant vitamins reduce IHD. Evidence exists for an increased prevalence of small, dense LDL in renal transplant recipients that are more prone to oxidative modification than are larger, less dense LDL [24]. Evidence also suggests that oxidized lipoproteins are more common in renal transplant recipients than in the general population [24]. However, given the negative results of randomized trials in the general population and the lack of any intervention trials in renal transplant recipients, treatment with anti-oxidant vitamins does not appear to be warranted.

**Aspirin prophylaxis.** Studies have shown that low-dose aspirin is effective in preventing recurrent cardiovascular events in patients with IHD and/or cerebral vascular disease [60]. A number of guidelines recommend prophylactic aspirin in patients with IHD [60–63]. A low dose of aspirin, for example, 65–85 mg, appears to be as effective as higher doses [60, 64]. Some studies indicate that aspirin also is effective in patients without known CVD [60], but the evidence supporting the use of aspirin in such patients is not as strong. The U.S. Preventive Services Task Force concluded that there was evidence neither for nor against the use of aspirin for primary prevention [65]. The American Diabetes Association recommended aspirin in patients with diabetes who have other risk factors for CVD [62]. Because platelets from renal transplant patients tend to have increased aggregability, it seems reasonable to recommend daily, low-dose aspirin (65–85 mg/day) for renal transplant pa-
patients with IHD [66, 67]. Perhaps we should treat other high-risk patients as well; the risk is great enough to suggest that all renal transplant patients receive aspirin prophylaxis unless it is contra-indicated. My own approach is to use low-dose aspirin in all renal transplant recipients, unless it is contraindicated.

**Infections and inflammation.** Recent evidence suggests that IHD is a systemic disease characterized by inflammation. Systemic inflammatory markers such as C-reactive protein and fibrinogen have been correlated with IHD events. One of the reasons that aspirin has been effective in reducing IHD in patients with pre-existing cardiovascular disease might be its anti-inflammatory properties. However, few randomized controlled trials testing the efficacy of antimicrobial therapies in reducing infection and systemic inflammation in IHD have been completed to date [68]. In renal transplant recipients, IHD has been associated with low serum albumin, which might also be a marker of systemic inflammation [16]. Until additional randomized controlled trials are completed, it will be difficult to translate this and other observations supporting the role of infection and systemic inflammation in IHD into useful intervention strategies.

**Summary**

Dramatic improvements in renal allograft survival over the last 10 years have shifted the focus of post-transplant management from short-term considerations to reduction of deaths due to IHD (and other causes) over the long term. A growing body of evidence suggests that the high incidence of IHD after renal transplantation is in large part due to the high prevalence of traditional risk factors such as hypertension and hyperlipidemia. It is neither feasible nor necessary to demonstrate that treating risk factors like elevated blood pressure and LDL cholesterol is justified in reducing morbidity and mortality from IHD. Recent data suggest that the incidence of IHD is declining in some centers [16], likely because of the use of new medications that effectively reduce factors for IHD. Further emphasis on managing these risk factors, along with additional studies to identify new prevention strategies, are needed if progress in reducing this major cause of death in transplant patients is to continue.

**QUESTIONS AND ANSWERS**

**Dr. Nicolaos E. Madias (Executive Academic Dean, Tufts University School of Medicine, Boston, Massachusetts, USA):** Endothelial dysfunction caused by immunosuppressive agents might be one of the nontraditional risk factors that contribute to IHD after renal transplantation. As you know, ACE inhibitors and HMG-CoA reductase inhibitors defend the structural and functional integrity of the vasculature via mechanisms that extend beyond their antihypertensive and cholesterol-lowering properties. Furthermore, both of these families of drugs are renoprotective. Could you please comment on the merits of adopting a relatively liberal policy for using these medications in renal transplant recipients?

**Dr. Kasiske:** That is a very good point. A lot of data from studies in the general population indicate that ACE inhibitors and HMG-CoA reductase inhibitors have beneficial effects on endothelial function. We like these drugs for these and other reasons, not just because they reduce blood pressure and LDL cholesterol. In addition, up to one-fourth of our transplant population eventually develops persistent proteinuria, for example, over 500 mg/24 h, and some of these patients become nephrotic. Data suggest that we can reduce proteinuria using ACE inhibitors in renal transplant recipients. On the other hand, I know that some transplant centers are reluctant to use ACE inhibitors, because of the fear of provoking an increase in serum creatinine. We don’t feel that way, but we do watch serum creatinine closely after starting an ACE inhibitor. We also reduce the dose of HMG-CoA reductase inhibitors by about 50% in patients who are receiving cyclosporine A or tacrolimus because of the well-known interaction between these agents.

**Dr. Kasiske:** Left ventricular hypertrophy (LVH) is an independent risk factor for CVD. Do you have information on the magnitude of its role in renal transplant recipients and recommendations for its diagnosis and management? Also, could you comment on the recently reported association between coronary artery calcification, as detected by electron beam computed tomography, and the increased elemental calcium intake in young adult patients treated with dialysis [69]? It could represent yet another nontraditional risk factor for IHD in ESRD patients and renal transplant recipients.

**Dr. Kasiske:** Unfortunately, we do not have good data on LVH in our transplant population. We know that LVH often improves after transplantation, and there are a number of reasons for this. Before the introduction of erythropoietin, anemia was common in hemodialysis patients. Correcting anemia with transplantation no doubt decreased the incidence and severity of LVH in at least some studies from that era. Volume overload also can masquerade as LVH, and volume status can improve after transplantation. Whether other “uremic” factors can be improved with transplantation, and thereby cause a regression of LVH, is still debated. As you pointed out, electron beam tomography studies show a high incidence of coronary artery calcification in hemodialysis patients [69]. Of course, maintaining normal calcium and phosphorus levels in hemodialysis patients is always a challenge. In contrast, stable renal transplant recipients usually have normal calcium and phosphorus levels. Whether the incidence of coronary artery calcification after transplantation declines is unknown. Of course, the
clinical significance of coronary calcifications is also not known. They could contribute to the pathogenesis of coronary lesions or they could be an epiphenomenon of little functional significance.

**Dr. Hamid Rabb (Hennepin County Medical Center, University of Minnesota School of Medicine, Minneapolis, Minnesota):** Recent evidence has implicated inflammation in the pathogenesis of atherosclerotic CVD. In fact, data indicate that T-cells themselves could be major mediators of ischemic reperfusion injury and potentiate myocardial infarction. Activation of T-cells directed at the allograft, as we see in our transplant patients, could prime T-cells to promiscuously damage the myocardium. Is there any known link between T-cells and IHD after transplantation?

**Dr. Kasiske:** I am not aware of any studies addressing this directly, but it is a very interesting hypothesis. Indeed, the general hypothesis that systemic inflammation plays an important role in the pathogenesis of atherosclerotic CVD is a fascinating one. Unfortunately, almost all the data supporting it are circumstantial. However, I believe that it is a very plausible hypothesis, and perhaps mechanisms like those you are suggesting could be important. We have noted that low serum albumin after transplantation is associated with subsequent IHD events. It is possible that hypoalbuminemia acts as a marker of systemic inflammation, similar to elevations in C-reactive protein. On the other hand, we failed to find a statistically significant association between CMV infections and IHD in our transplant population. Nevertheless, the idea that a chronic inflammatory state, for example, from infections or subclinical rejection, primes T-cell involvement is a very good one.

**Dr. Mark Rosenberg (University of Minnesota School of Medicine):** As you know, we do not do a good job of controlling risk factors in our dialysis patients. Dialysis and transplant patients have a very high risk of CVD, and we might even be doing things to make that worse, such as calcium supplementation. How much of the burden of posttransplant CVD is present at the time of transplantation? Isn’t one of the best things we can do to prevent posttransplant CVD preventing pre-transplant CVD?

**Dr. Kasiske:** Certainly CVD is present in a large number of patients at the time of transplantation. However, in the Kaplan-Meier curve showing the accumulation of IHD events after transplantation [3], it is apparent that the risk for new events is still accruing even 15 to 20 years after transplantation. It is unlikely that these late events are due to pre-transplant IHD. It is more plausible that CVD is acquired both before and after transplantation. Your point is valid, and certainly risk factor management before transplantation in the dialysis population is important. However, the factors that cause a very high incidence of CVD in the dialysis population are still unclear. Perhaps systemic inflammation plays an important role, for example, inflammation from the dialysis membrane, infections, or other factors. Whether a high calcium-phosphorus product is important, and whether we might help reduce the incidence of CVD by avoiding calcium-containing phosphate binders are both important questions without answers at this time.

**Dr. Madias:** How much information do we have regarding the incidence of CVD in relatively comparable populations of dialysis and transplant patients? Do we have any good data on CVD in waiting list patients?

**Dr. Kasiske:** Robert Wolfe and coworkers compared the overall mortality of transplant recipients with those still on the waiting list [70]. Mortality was higher for patients on the transplant waiting list compared to transplant recipients. Of course, the assumption was made that everyone who was on the waiting list was a transplant candidate. Unfortunately, no data corroborate this assumption, and it is likely that an unknown proportion of waiting list patients were “on hold.” Nevertheless, the difference in mortality between waiting list and transplant patients was very large, and it is therefore unlikely to be artifactual. Although not addressed in this study, it is likely that much of the difference in mortality between these two populations is due to a difference in CVD events. At the American Society of Nephrology meeting in Toronto, October 13–16, 2000, we presented a preliminary analysis demonstrating that the incidence of CVD is indeed higher among patients on the waiting list compared to transplant recipients. It is remarkable that despite the very high prevalence of CVD risk factors after transplantation, transplant recipients still seem to have a lower incidence of CVD relative to comparable dialysis patients. That really suggests to me that there is something going on in the dialysis population that is very bad with respect to CVD.

**Dr. Charles A. Herzog (Cardiology Division, Hennepin County Medical Center, University of Minnesota School of Medicine, and Director of the Cardiovascular Special Studies Center, United States Renal Data System, Minneapolis):** Dr. Manske’s study is the only randomized, controlled trial examining the effects of pre-transplant screening and prophylactic intervention on outcomes [2]. The study suggested that revascularization of asymptomatic diabetic patients with significant coronary artery stenosis reduced the number of cardiac events compared to medical management. If this result is true, it provides a strong argument for screening as part of the pre-transplant evaluation. Unfortunately, the number of patients in the study was very small. In addition, optimal medical management has changed since the time of the study; if the study were done today, a beta-blocker might be selected instead of a calcium antagonist, for example. It is also unfortunate that revascularization included both bypass surgery and angioplasty, procedures that might
have very different success rates in this population. Where should we go from here?

**Dr. Kasiske:** I believe that a large-scale, randomized, controlled trial is warranted to examine outcomes after screening versus no screening in a population of high-risk patients. Screening could be done with a noninvasive stress test followed by angiography and revascularization as indicated by defined criteria. Appropriate inclusion and exclusion criteria could be specified to avoid including patients in whom such screening is necessary. Such a study also would need to address the issue of re-screening while patients are on the waiting list. Of course, the study would have to be designed in such a way that costs were not prohibitive.

**Dr. Michael Aaronson** (Nephrology Fellow, University of Minnesota Division of Nephrology): The patient in the case had an elevated lipoprotein(a), an inflammation marker. Given the current paradigm of inflammation as a possible risk factor for IHD, if a transplant patient has a normal serum creatinine, is it unreasonable to prescribe an anti-inflammatory medication in an attempt to decrease IHD? Also, if this patient had nephrotic-range proteinuria, would it have been reasonable to use nonsteroidal anti-inflammatory drugs to reduce the proteinuria?

**Dr. Kasiske:** These are both very good questions. Is the reduction in IHD from prophylactic aspirin seen in randomized trials in the general population due not only to the antiplatelet effect of aspirin but also to an anti-inflammatory effect? If there were a higher inflammatory state after renal transplantation, for whatever reasons, would anti-inflammatory medications be beneficial? Unfortunately, no clinical trial data answer this question. Obviously, the problem with using nonsteroidal anti-inflammatory medications is the potential for adverse effects, for example, an increase in serum creatinine, interstitial nephritis, gastrointestinal bleeding. Currently, we recommend the use of low-dose, prophylactic aspirin, for example, approximately 80 mg/day, in transplant recipients at risk for CVD. When we have patients with persistent proteinuria (>1 g/24 h), we first try using an ACE inhibitor to control the proteinuria, and we generally avoid using nonsteroidal anti-inflammatory agents in this setting.

**Dr. Madias:** Could you please expand on the most plausible reasons for the declining incidence of IHD observed in some centers? Also, could you comment on the role of screening for IHD after transplantation?

**Dr. Kasiske:** It is very heartening to see that the incidence of IHD has been declining in our transplant population. It would be nice to know why this is so, but we can only speculate. Of course, the incidence has been falling in the general population, and the reduction has been attributed to both better risk factor management and better screening and treatment of IHD in the general population. Perhaps our transplant recipients are more conscious of risk factors and are adopting healthier lifestyles. In addition, we have better antihypertensive medications and better lipid-lowering agents, and we have been using these aggressively in our transplant population. The other thing that appears to have changed over the years, at least in our institution, is the level of awareness of IHD and the aggressiveness of screening and intervention. We have been doing a lot more screening for IHD, and we have been doing a lot more intervention with bypass surgery, angioplasty, and stent placement. All of these could contribute to the reduced incidence of IHD events. In terms of screening after transplantation, that is also something we have discussed a lot lately. Should screening go beyond just the pre-transplant workup? Certainly patients with known IHD periodically receive a noninvasive cardiac stress test. Perhaps we should also be screening all high-risk patients after transplantation.

**Dr. Horacio Esteban Adrogue** (Medicine and Pediatrics Resident, University of Minnesota School of Medicine): What, if any, role do elevated levels of homocysteine play in the renal transplant patient as an independent risk factor for IHD? Are high levels considered as high a risk factor as in dialysis patients? How is this managed?

**Dr. Kasiske:** We know that homocysteine correlates with IHD after transplantation. We also know that one can lower homocysteine levels with a combination of vitamins B₉, B₁₂, and folate. Unfortunately, we are still waiting for the results of randomized trials that demonstrate lowering homocysteine reduces IHD events. One could argue that taking vitamins is innocuous, so that we should be doing this even without good data from clinical trials. On the other hand, transplant patients already take multiple medications, and adding more pills would increase the risk of noncompliance. I would hate to see a transplant patient miss doses of immunosuppressive medications because we complicated the drug regimen by adding a number of medications of unproven benefit.

**Dr. Madias:** Should the recommendations that you made, at least the relevant ones, be amended for pediatric transplantation?

**Dr. Kasiske:** I do not know. Cardiovascular risk factors have only recently received the attention of pediatric nephrologists. With improved outcomes after renal transplantation in the pediatric age group, more of these patients are surviving into adulthood. It is plausible that we will see more IHD in young adults who have had a transplant for an extended period. So I think there is a growing need for risk factor management in the pediatric age group. Unfortunately there are not a lot of data in this area.

**Dr. Aaronson:** Is the rate of IHD different in patients who have received a kidney transplant versus a kidney/
pancreas transplant? Is the kidney/pancreas transplant cardioprotective?

Dr. Kasiske: The problem that we have with understanding the benefits of pancreas transplantation is that there have never been any randomized controlled trials. Any arguments about the effects of pancreas transplantation on microvascular or macrovascular disease are highly speculative. Pancreas transplant recipients are highly selected patients. I do not think you can adequately adjust for this fact statistically by using multivariate analysis. I think the question is impossible to answer in the absence of clinical trials. Unfortunately, the obstacles to conducting such a trial might be insurmountable.

Dr. Madias: You mentioned some data indicating an inverse relationship between blood pressure in renal transplant recipients and graft survival. Did this relationship feature a threshold value below which no benefit on survival could be discerned? Also, were any classes of antihypertensive medications associated with increased benefit?

Dr. Kasiske: The Collaborative Transplant Study registry appears to show a simple linear relationship between blood pressure and graft failure [71]. There is no J-shaped curve, and one cannot see a threshold effect of blood pressure on patient or graft survival. Few data on the relative merits of different antihypertensive agents in renal transplant recipients are available, and certainly no data from large, randomized controlled trials that have measured outcomes in this population. In our recent observational study of risk factors for IHD, we found that patients who were taking dihydropyridine calcium antagonists one year after transplantation were at increased risk for subsequent IHD events [16]. No other antihypertensive medication was associated with IHD. This was a retrospective analysis, and there could be several reasons for this association. For example, the patients who were already at high risk for IHD might have been more likely to be treated with dihydropyridine calcium antagonists. Nevertheless, the fact that other studies in the general population have raised concerns about calcium antagonists and IHD makes this result disconcerting.

Dr. Shakeel Anjum (Nephrology Fellow, University of Minnesota Division of Nephrology): Considering that renal transplant patients are at high risk to begin with, and that they will be on immunosuppression after transplantation, would it be reasonable to give everyone a statin after transplantation?

Dr. Kasiske: The prevalence of hyperlipidemia and the risk for IHD are so high that one can make an argument that every patient should be started on an HMG-CoA reductase inhibitor as part of the initial immunosuppression protocol, or at least at the time of hospital discharge after transplantation. The agent then could be stopped if the recipient subsequently had low levels of low-density lipoprotein cholesterol. The advantage of this approach would be to avoid the common problem of undertreatment. I think that would be a reasonable approach, one worth considering.

Dr. Madias: If I recall correctly, in your analysis, bilateral nephrectomy for PKD increased the risk for IHD, but the same procedure for non-PKD patients was associated with decreased risk. Could you please comment on this issue?

Dr. Kasiske: Having a bilateral nephrectomy before transplantation, a practice that was more common 20 years ago, was associated with less IHD. This might result from better blood pressure control. However, when we looked for interactions in the analysis, we found that patients who had polycystic kidney disease and underwent bilateral nephrectomy had an increased risk of IHD. I suspect that many of those polycystic kidney disease patients had bilateral nephrectomy because they had very large kidneys. Polycystic kidney disease by itself was not a risk factor for IHD; it was only a risk factor among patients who had bilateral nephrectomy. In analyses such as this, the possibility always exists that one or more of the several risk factors were statistically significant only by chance. However, there is an independent study that also reported that patients with polycystic kidney disease have an increased risk of IHD after transplantation [72]. This makes it more likely that ours was not a chance finding.

Dr. Rosenberg: How much can we reduce the CVD burden by selecting immunosuppressive agents with minimal adverse effects on CVD risk factors? I was struck by a recent article looking at cyclosporine A versus tacrolimus that showed that both blood pressure and lipids were decreased with tacrolimus [73]. The other issue is whether steroid avoidance can decrease cardiovascular risk factors.

Dr. Kasiske: Unfortunately, most of the studies examining the effects of changes in immunosuppression on CVD risk have only followed patients over a relatively short period and have only measured one or two cardiovascular risk factors. While it might not be feasible to conduct trials to examine the incidence of CVD events for all different combinations of immunosuppression, it is nevertheless important to at least examine the effects of changes in immunosuppression on all of the well-established CVD risk factors over a sufficiently long period by intention-to-treat analysis. For example, it might be easy to show that after prednisone withdrawal, the serum cholesterol goes down and blood pressure improves. However, what you also have to factor into the CVD risk equation is the percentage of patients who have an acute rejection. In those patients, graft dysfunction or the higher doses of steroids required to treat rejection can adversely affect CVD risk. Perhaps the best approach is to randomize patients to different immu-
nosuppression strategies, measure all the known CVD risk factors over a follow-up period of at least several months, and then calculate the expected CVD risk based on validated equations such as the Framingham Heart Study equations. This approach might be a reasonable surrogate for cardiovascular events when it is not possible to follow enough patients over a long enough period to examine the effects of immunosuppression on actual CVD events.

Dr. Madias: Also, you have to factor in the difference in the incidence of new diabetes.

Dr. Kasikse: I agree. In addition to their effects on dyslipidemia and blood pressure, several immunosuppressive agents, such as corticosteroids, cyclosporine A, and sirolimus, contribute to the high incidence of post-transplant diabetes.

Dr. Robert Berkseth (Hennepin County Medical Center, University of Minnesota): Have you or anyone else examined the impact of renal replacement therapy prior to renal transplantation on subsequent transplant outcome, that is, hemodialysis versus peritoneal dialysis, adequacy of dialysis received, and possible incompatibility of membranes used for dialysis? Membranes and adequacy of dialysis have improved in recent years. Has the risk of CVD also improved?

Dr. Kasikse: I am not aware of any large observational studies or randomized controlled trials that have adequately addressed these important issues. What we need is large, multicenter, randomized controlled trials examining the effects of different dialysis prescriptions on CVD events. Unlike the transplant population, in which at least some data suggest that traditional risk factors correlate with CVD, in the dialysis population we have virtually no data suggesting that examining these surrogate end points is enough to assess the effects of therapies on CVD risk. Therefore, the studies would need to look at CVD events. Similarly, no data have addressed whether different dialysis therapies affect the incidence of CVD after transplantation.

Dr. Adrogue: Why did this patient have a splenectomy?

Dr. Kasikse: Two decades ago, before the cyclosporine A era, splenectomy often was performed to reduce the chances of acute rejection. This practice was abandoned many years ago.

Reprint requests to Dr. B. Kasikse, Director of Nephrology, Hennepin County Medical Center, 701 Park Avenue, Minneapolis, MN 55415-1829, USA.

E-mail:kasis001@umn.edu

REFERENCES


