Coronary artery disease in renal transplant recipients

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■ **BACKGROUND** Coronary artery disease is a major cause of death in transplant recipients.

■ **PURPOSE** To review current approaches for the detection, evaluation, and treatment of coronary artery disease in transplant recipients.

■ **SUMMARY** Renal transplantation promotes the development of coronary artery disease primarily because immunosuppressant medications accentuate known coronary risk factors such as hypertension, hypercholesterolemia, and hyperglycemia that accelerate the progression of coronary artery disease existing before transplantation. Physicians can monitor a patient's risk status by regular inquiries for symptoms and by simple clinical tools such as the Framingham Study Coronary Heart Disease Risk Prediction Chart in asymptomatic patients. Patients found to be at high risk for coronary artery disease can then undergo dobutamine echocardiography or other noninvasive tests, and patients with positive studies can subsequently undergo angiography. The cost-effectiveness of such an approach is presented. In recent studies at our institution, patients with coronary artery disease had decreased numbers of $CD2^+$ and $CD3^+$ circulating lymphocytes. In addition, in immunosuppressed transplant recipients with coronary artery disease, there was a decrease in $CD8^+$ lymphocytes, whereas in nonimmunosuppressed, nontransplant patients there was a decrease in $CD4^+$ lymphocytes.

■ **CONCLUSIONS** A systematic approach to screening patients for coronary artery disease before transplantation can identify those at highest risk and potentially save money and lives. Possible new avenues of research may focus on the role of the lymphocytes in coronary atherosclerosis.

■ INDEX TERMS: CORONARY DISEASE; KIDNEY TRANSPLANTATION; RISK FACTORS
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BETWEEN 1970 and 1990 approximately 100 000 renal transplantations were performed in the United States. At the current rate of approximately 10 000 to 11 000 per year, as many renal transplantations will be performed in the next 9 to 10 years as were performed in the previous 20 years. The mortality rates within the first year after renal transplantation have decreased to less than 2% for living-related and less than 7% for cadaver allograft recipients, and allograft success rates at 1 year now exceed 80% for cadaver grafts, 92% for mismatched living-related transplants, and 99% for human lymphocyte antigen (HLA)-identical siblings.

Coronary artery disease was the most common cause of death in renal allograft recipients who survived longer than 10 years in one study that reviewed 21 transplantation centers. Coronary artery disease accounted for 14% to 50% of deaths, malignant diseases 9% to 28%, infection 7% to 28%, and liver failure 8% to 28%.[1] These data have been reinforced by more recent studies. In a comparison of the causes of death in renal transplant recipients at the University of Minnesota in the 1970s and in the 1980s, deaths due to infection

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within 10 years after renal transplantation decreased, but cardiovascular deaths actually tended to increase.[2] The percentage of deaths due to cardiovascular causes increased, from 31.4% in the 1970s to 51.1% in the 1980s, and myocardial infarctions increased, from 15.1% to 19.9%. Death of the recipient due to cardiovascular disease remains one of the most common causes of allograft failure.

Also of concern is the trend for older patients to receive transplants and the fact that in the 1990s approximately 30% of the patients receiving transplants have insulin-dependent diabetes mellitus.

This article will review and update (1) general and transplantation-related risk factors for coronary artery disease; (2) clinical, noninvasive, and invasive approaches to diagnosing coronary artery disease; (3) an algorithm for cost-effective use of these techniques based on annual reassessment of the patient's coronary risk status; (4) approaches to treating coronary risk factors that are susceptible to modification; (5) results of treatment of established coronary occlusive lesions by invasive techniques; and (6) new insights into the etiology of coronary atherosclerosis reflected in alterations of lymphocyte subsets.

GENERAL AND TRANSPLANTATION-RELATED CORONARY RISK FACTORS

Perhaps the most useful way to group coronary risk factors is into those not susceptible to modification (increasing age, male sex, atherosclerotic disease in other vascular beds, and family history of premature coronary artery disease before age 55); those difficult to modify (smoking, excess weight, sedentary life-style, increased lipoprotein[a] level, and, in renal transplant recipients, dose of prednisone and cyclosporine); and those susceptible to intervention and modification (hypertension, hyperglycemia, increased low-density lipoprotein [LDL] cholesterol levels, decreased high-density lipoprotein [HDL] cholesterol levels, left ventricular hypertrophy, and erythrocytosis).

Coronary risk factors after transplantation are really the worsening of risk factors present before transplantation, predominantly by the effects of immunosuppressant medications, with the result that the degree of coronary artery disease existing before transplantation appears to have an accelerated course after transplantation. For example, in a series of 403 recipients of 464 renal allografts (96% from cadaver donors, 87% first transplants, and 21% in recipients with diabetes), ischemic heart disease developed during a follow-up of 46.1 ± 36.2 months after transplantation in 11% of patients who had no previous coronary disease.[3] This exceeded the *prevalence* of ischemic heart disease before transplantation (9.5%) and was more than three times the expected incidence (3.4%). Similar accelerated risks were seen for cerebrovascular disease (6% incidence after transplantation vs 3.7% prevalence before) and all vascular disease (15.8% incidence after vs 12.9% prevalence before). This study's shortcoming was that the identification of coronary artery disease was based on clinical and electrocardiographic findings and did not involve stress tests or coronary angiography.

Coronary artery disease before transplantation

In the same study, ischemic heart disease before transplantation imparted a relative risk of ischemic heart disease after transplantation of 5.41, which exceeded that of any other risk factor, including diabetes (relative risk 3.39).[3] Consequently, the first step in determining coronary artery disease risk after transplantation is to clearly define the state of the coronary vessels at the time of transplantation.

Although one typically assumes that coronary risk begins at 50% or 70% coronary occlusion, Proudfit et al[4] reported significant 10-year coronary mortality rates in individuals having less than 50% occlusion. In his study of 521 patients followed for longer than 10 years, of those who had 30% to 50% narrowing of at least one coronary artery, 16% died of coronary artery disease, and 33% either died of coronary artery disease, had a subsequent myocardial infarction, or had arteriographic evidence of progression of coronary disease.[4] However, these data represent patients studied approximately 20 years ago, and current downward trends in the risks of coronary events might well decrease such adverse outcomes if a similar study were done today.

Hyperglycemia

Patients with diabetic end-stage renal disease have a particularly high frequency of coronary artery disease at the time of evaluation for transplantation. In five studies of 303 patients with end-stage renal disease due to diabetic nephropathy, the prevalence of coronary occlusion of greater than 50% ranged from 38% to 55%,[5–9] and approximately 25% of patients had greater than 70% coronary occlusion.[7,9]

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In our series of 100 patients with end-stage diabetic nephropathy, coronary artery disease accelerated alarmingly after transplantation. Among the 25 patients with greater than 70% occlusion, progression to a new myocardial infarction occurred in 52% (13 of 25) at an average time of 21.3 months after angiography.[7] In fact, eight of 14 myocardial infarctions (one patient had two myocardial infarctions) occurred within 18 months of angiography. Even those with less than 70% coronary occlusion were not exempt: progression to a new myocardial infarction occurred in 11% (eight of 75) at an average time of 35.9 months after angiography. Only one of these myocardial infarctions occurred within 18 months of angiography. Within approximately 2 years after angiography, the frequency of new myocardial infarctions was a remarkable 31%[7]; other investigators have found frequencies of 22%[8] and 11%.[9]

In addition, there is an increased frequency of de novo diabetes after transplantation as a consequence of both prednisone and cyclosporine use. The frequency of steroid-associated diabetes after transplantation has been reported to range from 3.4% to 46.0%, depending on the criteria for diagnosis and the duration of follow-up.[10] However, the frequency appears to be increasing with the use of cyclosporine, a finding reflected in a study by Roth et al[11] in which diabetes mellitus developed after transplantation in 9.1% of 99 patients receiving azathioprine and methylprednisolone and in 18.6% of patients receiving cyclosporine and methylprednisolone. Some other clinical studies have also implicated cyclosporine in causing diabetes after transplantation,[12–15] but some have not.[16,17]

However, even in one prospective randomized study that concluded that diabetes after transplantation was no more frequent in patients who received cyclosporine than in those who did not (6.9% vs 6.4%), cyclosporine levels were higher in patients who developed diabetes even though the dose was lower, suggesting that other medications such as verapamil or diltiazem were used and contributed to the higher cyclosporine levels and susceptibility to diabetes.[16]

In another study, 10 of 19 patients treated with cyclosporine and prednisone had impaired tolerance to glucose given intravenously, compared with just one of 14 patients treated with azathioprine and prednisone.[18] Fasting C-peptide levels were also significantly higher in the cyclosporine-prednisone group. In cultured murine and human pancreatic islets, cyclosporine directly inhibits insulin release and leads to a concurrent increase in residual insulin content.[19]

Hypertension

Hypertension after transplantation is more pronounced with cyclosporine than with glucocorticoid treatment.[20] This condition requires careful evaluation for specific treatable causes, including rejection, renal transplant artery stenosis, recurrent disease, de novo glomerulonephritis, contribution of the native kidneys, excessive weight gain, and other causes not related to transplantation.[21]

Hyperlipidemia

At least three studies now show an association between hypercholesterolemia after transplantation and cardiovascular disease. In a series of 403 renal transplant recipients treated with prednisone and azathioprine and followed an average of 46.1 ± 36.2 months, the 70 patients with ischemic heart disease had significantly higher total cholesterol levels (275 ± 82 mg/dL) than the 365 patients with no ischemic disease (244 ± 62 mg/dL).[3]

In a series of 500 cyclosporine-treated patients there was a 36.7% frequency of hypercholesterolemia, which developed within 6 months after transplantation in 82%. Cardiovascular or cerebrovascular occlusive events were more common in the hyperlipidemic (15.4%) than in the nonhyperlipidemic patients (5.2%; $P < .001$).[22]

In a retrospective study that was conducted primarily during the cyclosporine era, Drueke et al[23] found that 25 kidney allograft recipients with cardiovascular disease had higher cholesterol and triglyceride levels than did 29 without such disease (6.5 ± 1.5 vs 5.6 ± 1.2 μmol/L, $P < .02$; and 2.0 ± 0.9 vs 1.2 ± 0.4 μmol/L, $P < .001$, respectively).

Hyperlipidemia after transplantation is multifactorial, and prednisone and cyclosporine are independent risk factors for it.[24] The pattern of hyperlipidemia changes from typical type IV (increased triglyceride and very-low-density lipoprotein [VLDL] cholesterol levels and decreased HDL-cholesterol levels) in dialysis patients to types IIA and IIB (increased total, LDL, VLDL, and HDL cholesterol levels) in renal transplant recipients.[25] However, in a matched series of 26 patients, the presumed beneficial increase in HDL cholesterol level was found to be due almost entirely to an increase in

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the HDL-3 subfraction, whereas it is the HDL-2 subfraction that probably confers protection from atherosclerosis.[26]

Most results have been derived from different populations at different times after transplantation. Therefore, the elevations in total cholesterol concentration range from 16% to 78% (mean approximately 27%).[25] When 66 renal transplant recipients treated with prednisone and azathioprine were compared with 490 treated with prednisone and cyclosporine, total cholesterol levels in excess of 300 mg/dL were found in 49% of the azathioprine group compared with 38% of the cyclosporine group, and triglyceride levels in excess of 500 mg/dL were noted in 9% of the azathioprine group compared with 15% of the cyclosporine group.[22]

A second pattern of dyslipidemia may also be seen later, when triglyceride levels dramatically increase (≥ 1000 mg/dL) and HDL cholesterol levels severely decline. This pattern may occur in association with grossly excessive weight gain and diabetes mellitus after transplantation, and it carries a risk for acute pancreatitis. Lipoprotein (a), believed to be an independent risk factor for coronary artery disease, has been shown to decrease from median levels of approximately 38 mg/dL during dialysis to 10 mg/dL after transplantation.[27]

Erythrocytosis

Erythrocytosis, a unique posttransplantation coronary risk factor, is generally defined as a hematocrit of greater than 51% in the absence of other causes. It typically occurs within the first 2 years and affects 4% to 17% of renal transplant recipients.[28] Patients at high risk for this complication are men, patients with diabetes, those with hematocrits greater than 30% at the time of transplantation, those with native kidneys remaining, and those with a well-functioning renal allograft.[29] The risk of thrombotic events in individuals with erythrocytosis is in the range of 18% to 24%.[30]

DIAGNOSING CORONARY ARTERY DISEASE

Clinical assessment

A generally sound clinical mechanism for evaluating coronary risk is an annual assessment by means of the Framingham Heart Study Coronary Heart Disease Risk Prediction Chart (*Table 1*).[31] (It should be emphasized that this chart is applicable only to asymptomatic patients.) Although it can be useful in determining whether an asymptomatic patient is at significant risk for coronary artery disease, it gives a high numerical score (9) to left ventricular hypertrophy (LVH) as determined by electrocardiography (ECG).[31] However, ECG has a poor sensitivity for diagnosing LVH. LVH detected by more sensitive techniques such as echocardiography has not been studied as a weighted factor in coronary risk assessment and cannot be legitimately substituted for the absence of LVH on ECG.

One can use this chart to compare a patient's 10-year risk of acquiring coronary artery disease with the average 10-year age-adjusted risk for the general population of men and women. When a patient's probability approaches 20% or represents a doubling of a low 10-year risk (< 10%) in the general population, it may be appropriate to proceed to a noninvasive study of the patient's coronary artery status. Additional information, such as the dose or duration of prednisone treatment and the presence or absence of erythrocytosis, may help to create an even better profile of patients at high risk for coronary artery disease after transplantation.

Pryor et al[32] have recently reinforced the importance of the medical history and physical findings in identifying patients at increased risk for coronary artery disease. In a group of 1030 consecutive outpatients referred for evaluation of cardiac symptoms, "compared with the treadmill exercise test, initial (clinical) evaluation was slightly better able to distinguish patients with or without any coronary disease and was similar in the ability to identify patients at increased risk for dying or with anatomically severe disease." Only 168 of these patients subsequently underwent catheterization. As pointed out in the editorial review of this study, the number of patients undergoing coronary angiography was small, there may have been ascertainment bias in the way these patients were selected for referral, and the frequency of coronary events was low.[33]

Recently, a 6-minute walk test was used to predict mortality and morbidity in patients with known left ventricular dysfunction with or without overt congestive heart failure.[34] These patients were identified in a prospective cohort study in the Studies of Left Ventricular Dysfunction (SOLVD) Registry Substudy.[35] In the stratified random sample of 898 patients who had either radiologic evidence of congestive heart failure or an ejection fraction of 0.45 or less, 833 patients took the test. During a follow-up of 242 days, 52 (6.2%) died, 78 (9.4%) were hospital-

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TABLE 1
FRAMINGHAM HEART STUDY CORONARY HEART DISEASE RISK PREDICTION CHART*

1. Find points for each risk factor

Age (if female), years

Age	Points	Age	Points
30	−12	41	1
31	−11	42–43	2
32	−9	44	3
33	−8	45–46	4
34	−6	47–48	5
35	−5	49–50	6
36	−4	51–52	7
37	−3	53–55	8
38	−2	56–60	9
39	−1	61–67	10
40	0	68–74	11

Age (if male), years

Age	Points	Age	Points
30	−2	48–49	9
31	−1	50–51	10
32–33	0	52–54	11
34	1	55–56	12
35–36	2	57–59	13
37–38	3	60–61	14
39	4	62–64	15
40–41	5	65–67	16
42–43	6	68–70	17
44–45	7	71–73	18
46–47	8	74	19

High-density lipoprotein (HDL) cholesterol, mg/dL

HDL	Points	HDL	Points
25–26	7	51–55	−1
27–29	6	56–60	−2
30–32	5	61–66	−3
33–35	4	67–73	−4
36–38	3	74–80	−5
39–42	2	81–87	−6
43–46	1	88–96	−7
47–50	0		

Total cholesterol, mg/dL

Cholesterol	Points	Cholesterol	Points
139–151	−3	220–239	2
152–166	−2	240–262	3
167–182	−1	263–288	4
183–199	0	289–315	5
200–219	1	316–330	6

Systolic blood pressure, mm Hg

Blood pressure	Points	Blood pressure	Points
98–104	−2	140–149	3
105–112	−1	150–160	4
113–120	0	161–172	5
121–129	1	173–185	6
130–139	2		

Other factors	Points: Yes	Points: No
Cigarette smoking	4	0
Diabetes		
Males	3	0
Females	6	0
Left ventricular hypertrophy by electrocardiography (ECG-LVH)	9	0

2. Add points for all risk factors

(Age) + (Total cholesterol) + (HDL) + (Smoking) + (Diabetes) + (ECG-LVH) = (Total)

3. Look up risk corresponding to point total

Points	Probability, % 5 years	10 years
≤1	<1	<2
2	1	2
3	1	2
4	1	2
5	1	3
6	1	3
7	1	4
8	2	4

Points	Probability, % 5 years	10 years
9	2	5
10	2	6
11	3	6
12	3	7
13	3	8
14	4	9
15	5	10
16	5	12

Points	Probability, % 5 years	10 years
17	6	13
18	7	14
19	8	16
20	8	18
21	9	19
22	11	21
23	12	23
24	13	25

Points	Probability, % 5 years	10 years
25	14	27
26	16	29
27	17	31
28	19	33
29	20	36
30	22	38
31	24	40
32	25	42

4. Compare with average 10-year risk

Age, years	Probability, % Women	Men
30–34	<1	3
35–39	<1	5
40–44	2	6

Age, years	Probability, % Women	Men
45–49	5	10
50–54	8	14
55–59	12	16

Age, years	Probability, % Women	Men
60–64	13	21
65–69	9	30
70–74	12	24

5. Comment

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ized for congestive heart failure, 114 (13.7%) either died or were hospitalized for congestive heart failure, and 252 (30.3%) were hospitalized for any reason.[34] The patients with the poorest performance (who walked ≤ 300 meters in 6 minutes) had a significantly greater chance of dying (10.23% vs 2.99%; $P = .01$), of being hospitalized (40.91% vs 19.90%; $P = .002$), and of being hospitalized for heart failure (22.16% vs 1.99%; $P < .0001$) than those with the best performance (who walked ≥ 450 meters).[34]

In this study, ejection fraction and distance walked were equally strong and independent predictors of death and of hospitalization for heart failure during follow-up. Also, remarkably, the 6-minute walk test predicted mortality and hospitalization rates better than either the ejection fraction or the New York Heart Association functional heart failure classification, especially levels II and III.[34]

Although this study did not focus on coronary artery disease (in fact, due to the selection algorithm these patients were less likely to have ischemic heart disease as a cause of left ventricular dysfunction), 51% of the patients did have ischemic heart disease. Unfortunately, the relationship of ischemic heart disease and the performance at either end of the spectrum was not reported. However, as a practical method for evaluating the overall cardiac risk for patients being evaluated for transplantation, this simple test deserves a trial. Also unfortunately, the authors did not provide a useable coronary risk-evaluation chart.[34]

Renal transplant recipients with diabetes have a high frequency of coronary artery disease at the time of transplantation and rapid progression afterwards. Manske et al[36] have identified both low-risk and high-risk subgroups in this population. Among 141 consecutive diabetic candidates for renal transplantation who underwent coronary arteriography, 14 of the 16 patients age 45 or older had coronary artery disease. Thus, the investigators concluded that patients 45 years old or older with end-stage renal disease due to diabetic nephropathy are at high risk and require coronary angiography.

Of the remaining 125 patients under age 45, 90 were used to determine clinical factors predictive of coronary artery disease, and the remaining 35 were used as a test set to validate these factors. Diabetic patients at low risk were under age 45, had diabetes less than 25 years, had a smoking history of less than 5 pack-years, and did not have ST-T wave changes on ECG. Coronary artery disease was absent in 22 of 23 patients with this profile, but was absent in only 14 of 47 without these criteria.[36]

TABLE 2
SENSITIVITY AND SPECIFICITY OF TESTS FOR CORONARY ARTERY DISEASE

Test	Sensitivity, %	Specificity, %
Exercise-based tests		
Electrocardiography[37]	65	85
Thallium 201		
Planar		
Patients without diabetes[37]	84	87
Patients with uremia and diabetes[9]	67	62
Single-photon emmission computed tomography	96	83
Echocardiography[40]	84	86
Resting stress tests		
Dipyridamole thallium 201		
Patients without diabetes[41]	79	76
Patients with uremia and diabetes[42]	37	73
Adenosine thallium 201[43]	83	75
Dipyridamole positron emission tomography rubidium 82 (patients without diabetes)[41]	95	82
Patients without left ventricular hypertrophy[44]	85	88
Patients with left ventricular hypertrophy[44]	55	60
Dipyridamole echocardiography[45]	60	93
Dobutamine echocardiography[46–48]	82	88

Noninvasive, exercise-based diagnostic testing

Exercise-based screening tests are a traditional way of assessing coronary artery disease. The sensitivity and specificity of these tests (*Table 2*) can help one select which to use, but other variables influence their utility.[37–40] These tests may have altered sensitivity and specificity in patients with diabetes, uremia, or LVH. For example, in patients without diabetes the exercise thallium test has a sensitivity of approximately 84% and a specificity of 87%,[37] whereas in uremic diabetic patients it has a sensitivity of only 67% and a specificity of 62%.[9]

The exercise thallium test also becomes less specific with LVH because of its tendency to show a "fixed relative decrease in lateral wall thallium 201 count density, frequently mimicking lateral wall infarction."[38] If the exercise level does not increase the heart rate to 85% or more of the maximum predicted heart rate, the identification of ischemia decreases from 56% to 35% with single-vessel disease, from 80% to 58% with two-vessel disease, and from 88% to 50% with three-vessel disease.[39]

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Because only approximately 10% of diabetic patients with end-stage renal disease can achieve 85% of the maximum predictive heart rate in an exercise test, they should be carefully screened to exclude those with severe neuromyopathy and poor general conditioning who could not complete the test satisfactorily. If there is a question about this, it may be worthwhile to prescreen both diabetic and nondiabetic patients with the 6-minute walk test (see above) to determine if they can complete exercise testing.[34]

Noninvasive, resting diagnostic testing

For those transplantation candidates and recipients unable to complete exercise testing, a variety of noninvasive, resting diagnostic tests are available.[41–48] However, some have already been shown to be less useful in the presence of diabetes, uremia, and LVH. For example, dipyridamole thallium stress testing has a sensitivity of 79% and specificity of 76% in nondiabetic patients,[41] but a sensitivity of only 37% and a specificity of 73% in patients with uremia and diabetes.[42] The sensitivity of dipyridamole positron-emission tomographic scanning in the absence of left ventricular hypertrophy (85%) decreases to 55% when LVH is present.[44]

Currently, one of the most attractive noninvasive resting tests for evaluating coronary artery disease is dobutamine echocardiography, with an overall sensitivity of approximately 82% and a specificity of approximately 88%.[46–48] In one major study of 70 men given 2.5 to 40 μg/kg/minute of dobutamine to evaluate the induction of any new wall-motion abnormality, this test had a sensitivity of 86%, a specificity of 95%, and an accuracy of 89%, compared with angiography at a cutoff point of 70% occlusion.[46] In another study of 103 patients (64 of them men) given 2.5 to 30 μg/kg/min of dobutamine, among the 55 patients who had normal echocardiograms at rest, the sensitivity of the test was 89%, the specificity was 85%, and the accuracy was 87% compared with angiography at a cutoff point of 50% occlusion.[47] However, in a recent prospective study of 217 patients without previous myocardial infarction, the sensitivity was 72% and the specificity was 83%.[48]

Recent preliminary data from our own series of 14 patients with end-stage renal disease and 14 controls matched for age, gender, and the presence of coronary artery disease suggest that when peak doses of dobutamine can be achieved, dobutamine echocardiography has the same sensitivity in both groups (86%) and virtually identical specificity (94% and 100%, respectively).[49] However, the inability of some patients to tolerate peak dobutamine doses lessens the utility of the test and realistically decreases its sensitivity. Nevertheless, the ability of dobutamine echocardiography to evaluate both resting left ventricular function and inducible ischemic changes as wall-motion abnormalities makes it an attractive diagnostic test.

Coronary arteriography: still the gold standard, but not as pure as once thought

Coronary arteriography, generally accepted as the standard of reference for coronary artery disease, remains essential for the performance of transluminal angioplasty, other nonsurgical methods of opening obstructed coronary arteries, and coronary artery bypass surgery itself. However, it may be subject to misinterpretation because of difficulties brought about by diffuse disease, the angle of viewing a vessel, and deceptive luminal size after percutaneous transluminal coronary angioplasty (PTCA).

Some of these drawbacks have been made apparent by intracoronary ultrasonography.[50] Because coronary arteriography is expensive and patients must be hospitalized for it, strenuous efforts are constantly being made to find a safe, accurate, and inexpensive noninvasive technique to detect coronary artery disease.

EVALUATING CORONARY ARTERY DISEASE IN RENAL TRANSPLANT RECIPIENTS

The key to detecting significant coronary artery disease in asymptomatic renal transplant recipients is repeated quantitative evaluation for known risk factors at least once a year. For this purpose, the Framingham Coronary Heart Disease Risk Prediction Chart is a valuable asset[31] (*Table 1*). However, patients who have extremely serious risk factors such as malignant hypertension, severe diabetes, or very high LDL cholesterol levels that place them in the top percentiles of the distributions may exceed the predicted risk.[31] In general, there are two major aspects of cardiac risk: abnormal resting left ventricular function and inducible ischemia. An algorithm for utilizing a combination of clinical criteria, noninvasive testing at rest, and, when indicated, coronary arteriography is shown in the *Figure*.

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The first step in using the algorithm is to decide before transplantation if the patient is at high risk (has angina, a previous myocardial infarction, a high-risk diabetic profile, or a high-risk nondiabetic profile) and warrants a noninvasive resting or exercise-based test for coronary artery disease, and possibly coronary arteriography.

If a high-risk patient is found to have coronary occlusive disease of greater than 70%, the findings are evaluated to decide whether (1) angioplasty or coronary artery bypass grafting surgery (CABG) is indicated before transplantation because of symptoms and the location and appearance of the occlusive lesions; (2) transplantation is too great a risk because of the diffuseness and severity of the disease and degree of left ventricular dysfunction; or (3) no interventional therapy is necessary before transplantation because of the lack of symptoms and the location and appearance of the occlusive lesions, but yearly reevaluation is necessary.

If a patient at high risk has less than 70% occlusive disease and no clinical evidence of ischemia, transplantation should be feasible with the understanding that reevaluations should be done with noninvasive testing at least yearly. Patients at low risk before transplantation also need clinical reevaluation at least yearly to determine if their risk has increased, at which point they enter the high-risk pattern of management.

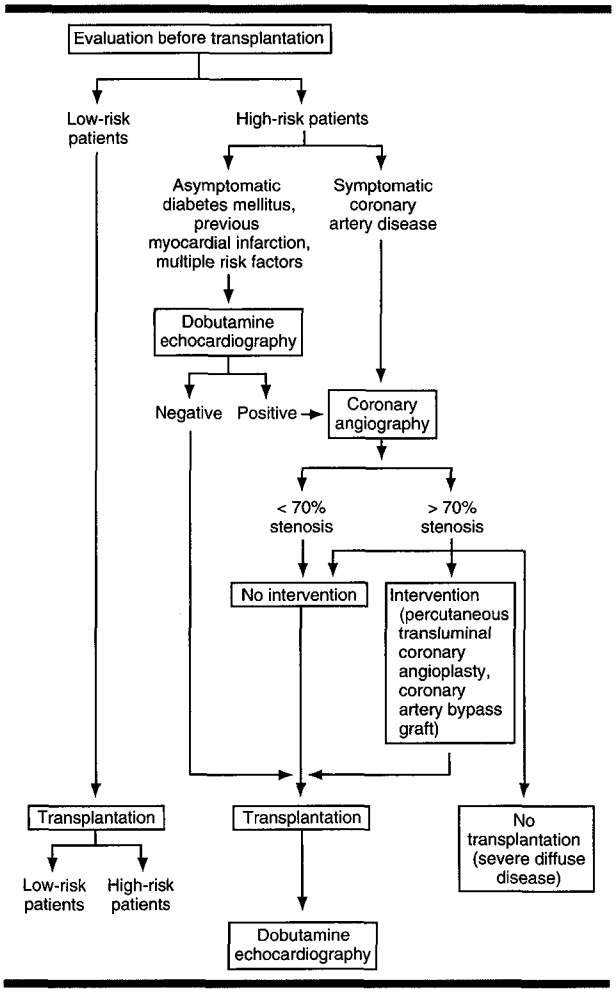

FIGURE. Algorithm for detecting and treating coronary artery disease in renal transplantation candidates and transplant recipients. The combination of clinical, noninvasive, and angiographic findings determine both current coronary artery status and future monitoring requirements.

Cost considerations

Suppose we use dobutamine echocardiography to screen 100 renal transplantation candidates who have diabetes and end-stage renal failure (and a 25% prevalence of significant coronary artery disease).[51] The validity of what follows depends on whether the high sensitivity and specificity of dobutamine echocardiography holds up in patients with diabetes and end-stage renal disease. If the sensitivity remains 82% and the specificity 88%, the test would correctly identify 21 of the 25 patients who have coronary artery disease (who would then undergo coronary angiography), and it would incorrectly identify 9 of the other 75 (who would also undergo coronary angiography). The total cost of 30 coronary angiograms ($120 000) and 100 dobutamine echocardiograms ($70 000) would be approximately $190 000.

Among such a population of 100 uremic diabetic patients, 11 might die of coronary artery disease within 21 months.[51] With a sensitivity of 82%, dobutamine echocardiography would miss four patients who have coronary artery disease; two might have an infarct and one might die within 21 months.[51] The other 10 patients with potentially fatal coronary artery disease would be identified by the screening program, undergo appropriate intervention, and then either be allowed to pursue renal transplantation or be denied transplantation if their coronary artery disease and myocardial disease were too severe. One patient might die despite detection and intervention.

For patients who are suitable candidates for intervention, CABG, and to a lesser degree, PTCA

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TABLE 3
COST COMPARISONS IN THE EVALUATION OF CORONARY ARTERY DISEASE IN RENAL TRANSPLANT RECIPIENTS WITH DIABETES

With screening	
Dobutamine echocardiography for 100 patients	$70 000
Coronary angiography for 30 patients identified as having coronary artery disease (21 correctly, 9 incorrectly)	$120 000
Transplantation for two patients who subsequently die (one despite screening and intervention, one of undetected coronary artery disease) within 21 months	$202 000
Hemodialysis for 21 months for three patients unacceptable by screening for transplantation	$172 200
Coronary artery bypass surgery for three patients	$114 000
Repeat dobutamine echocardiography and coronary angiography after 1 year for three patients with coronary artery disease not yet requiring intervention	$14 100
Total cost	$692 300
Without screening	
Transplantation for 11 patients with undetected coronary artery disease who are likely to die within 21 months after transplantation	$1 111 000
Value of 11 transplantable kidneys	—

may be preferable to medical therapy.[52] In a recent 2-year case-control follow-up study of 26 diabetic patients who were candidates for renal transplantation, the 13 patients who had either PTCA or CABG had significantly fewer myocardial infarctions and deaths than did the 13 medically treated patients: 15% vs 77%, and 8% vs 38%, respectively.[52] The only two myocardial infarctions in the treated group were in two of the eight treated with PTCA.

The cost of cadaveric renal transplantation for the 11 patients expected to die within 21 months would be approximately $1 111 000 (each cadaver transplant costs approximately $83 000 for the first year and $18 000 for the next 9 months).[53,54] This cost does not include the inestimable value of a cadaveric kidney that could have gone to another recipient.

The nine surviving patients with known coronary artery disease would be distributed in three groups: three would have bypass surgery before transplantation; three would have coronary artery disease not yet requiring bypass surgery; and three would have such severe cardiac disease that they would not be acceptable transplant candidates.

The expenses involved in this approach are shown in *Table 3*. There is a substantial cost savings of approximately $418 700 ($1 111 000—$692 300) brought about by screening a high-risk population for coronary artery disease before renal transplantation. Even more important, this approach can save lives and permit the prudent use of a scarce resource—transplantable cadaveric kidneys. This analysis, based on a 25% prevalence of coronary artery disease in uremic diabetic patients, would need to be recalculated for other levels of prevalence in different groups.

TREATING MODIFIABLE CORONARY RISK FACTORS

Hypertension

Even when hypertension in a renal transplant recipient is due to some secondary and otherwise treatable cause such as rejection or renal artery stenosis, one should consider what additional effects an antihypertensive medication has that could enhance or detract from its usefulness. Special attention should be given to the angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists.

ACE inhibitors can decrease proteinuria in diabetic nephropathy of a wide range of severity[55–57] and delay the progression of diabetic nephropathy.[58] They decrease the incidence of overt congestive heart failure and related hospitalizations in patients with asymptomatic left ventricular dysfunction.[59] In patients manifesting congestive heart failure after myocardial infarction, ACE inhibitors lessen the frequency of severe congestive heart failure and recurrent myocardial infarction and improve survival (presumably by inhibiting neurohumoral activation and attenuating ventricular remodeling).[60] They also improve survival after acute myocardial infarction.[61] They are capable of reducing coronary risk factors such as hypercholesterolemia (possibly as a consequence of decreasing heavy proteinuria in nephrotic patients) and erythrocytosis.[28]

In addition, in animals, ACE inhibitors can decrease glomerulosclerosis, vascular hypertrophy in numerous vascular beds including coronary arteries,[62] and interstitial fibrosis caused by cyclosporine, even when the glomerular filtration rate and tubulointerstitial changes are not improved.[63] Consequently, both experimental and clinical data indicate that ACE inhibitors are highly desirable to control hypertension and to achieve numerous secondary benefits if the drug is safe for the patient in question.

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The risks of ACE inhibitors include not only common difficulties such as cough and relatively rare problems such as angioneurotic edema, but also special problems in renal transplant recipients. If the presence of significant transplant renal artery stenosis has not been recognized, the use of an ACE inhibitor may lead to acute renal failure and possibly even loss of the allograft. Diffuse severe nephrosclerosis within the allograft, a condition in which hyaline changes in multiple preglomerular afferent arterioles may simulate the hemodynamic effects of main renal artery stenosis, may respond similarly to an ACE inhibitor with a decrease in glomerular filtration rate.

In fact, there are a variety of clinical situations associated with a decrease in afferent arteriolar blood flow (the use of cyclosporine, nonsteroidal anti-inflammatory medications, or amphotericin B; polycystic kidney disease with impaired renal function; cirrhosis with ascites; severe congestive heart failure; severe salt depletion or diuresis-induced volume contraction) in which the introduction of an ACE inhibitor could lead to worse renal function and possibly acute renal failure.

Decreases in the glomerular filtration rate (69.9 to 61.6 mL/min) have been reported in a clinical study of 23 hypertensive kidney transplant recipients given captopril (75 mg/day) and cyclosporine.[64] Obviously, if the glomerular filtration rate is already compromised, a further decrease could readily lead to worrisome levels of hyperkalemia. Episodes of acute renal failure requiring temporary hemodialysis have been reported when an ACE inhibitor has been used in conjunction with cyclosporine.[65,66] The use of an ACE inhibitor has been reported to cause anemia in renal transplant recipients receiving azathioprine.[67] Consequently, before introducing an ACE inhibitor to treat hypertension in renal transplant recipients, a thoughtful evaluation of the patient's clinical condition is absolutely necessary.

Calcium antagonists may be very useful in renal allograft recipients but also have areas of concern. In contrast to 75 mg/day of captopril, 30 mg/day of nifedipine tended to stabilize the glomerular filtration rate (70.6 to 70.0 mL/min) in cyclosporine-treated recipients.[64] The calcium antagonists may protect against the adverse hemodynamic effects of cyclosporine, presumably by blunting the afferent arteriolar vasoconstriction caused by cyclosporine.

Some calcium antagonists (verapamil, diltiazem, and nicardipine) increase cyclosporine levels through inhibition of the hepatic cytochrome P-450 3A4 and P-450 2D6 enzymes; others (nifedipine, isradipine) do not influence cyclosporine levels.[68] When a calcium antagonist is known to increase the cyclosporine level, advantage can be taken of this to reduce the dosage level of expensive cyclosporine. However, if one is not aware of this effect, or forgets to account for it when discontinuing a calcium antagonist, wide swings in the cyclosporine level and possible allograft dysfunction may occur.

Perhaps relevant to the concern about accelerated coronary artery disease in transplant recipients is the recent finding in a short-term study that diltiazem can retard allograft coronary atherosclerosis, which develops rapidly in cardiac transplant recipients.[69]

From these studies it would appear that an ACE inhibitor or a combination of an ACE inhibitor and a calcium antagonist could confer cardiac and renal benefits with minimal renal side effects.

Hyperlipidemia

Dietary treatment is recommended for patients without coronary artery disease and fewer than two risk factors when the LDL cholesterol level is 160 mg/dL or greater. For patients without coronary artery disease but with two or more risk factors, diet therapy is initiated at a lower level of LDL cholesterol, 130 mg/dL or greater. Patients with coronary artery disease should start diet treatment at LDL cholesterol levels greater than 100 mg/dL.

Drug treatment is recommended for patients without coronary artery disease and with fewer than two risk factors when the LDL cholesterol level is 190 mg/dL or greater. For patients without coronary artery disease but with two or more risk factors, drug treatment is instituted when the LDL cholesterol level is 160 mg/dL or greater. Patients with coronary artery disease should begin drug treatment at LDL cholesterol levels of 130 mg/dL or greater.[70]

Treatment of hypercholesterolemia after renal transplantation can be difficult. The American Heart Association step I diet (which allows an intake of saturated fat of 8% to 10% of total calories, 30% or less of calories from total fat, and less than 300 mg of cholesterol per day) caused an 8% decrease in total cholesterol ($P < .03$), but only a 6% reduction in LDL cholesterol, which was not significant.[71]

Because diet decreases excessive LDL cholesterol levels only minimally after transplantation, lipid-

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lowering medications are very often necessary. In a prospective, randomized, double-blind crossover study of 11 renal allograft recipients who were treated with prednisone and azathioprine (but not cyclosporine) and who had stable renal function for 8.4 ± 1.2 years, lovastatin brought about a 21% decrease in total cholesterol levels (307 ± 14 to 244 ± 13 mg/dL; $P < .05$), and a 28% decrease in LDL cholesterol levels (214 ± 12 to 155 ± 11 mg/dL; $P < .05$). In addition, HDL cholesterol levels increased by 8% and triglyceride levels decreased by 19%, but neither change was significant.[72]

Because rhabdomyolysis and acute renal failure increase in frequency when HMG-CoA reductase inhibitors are used in patients receiving cyclosporine, dosage adjustments and additional monitoring are necessary. Among 44 cardiac transplant recipients treated with cyclosporine and lovastatin in daily doses of just 10 to 20 mg, there was a significant decrease in total cholesterol (282 ± 54 to 208 ± 62 mg/dL; $P < .005$), LDL cholesterol (172 ± 55 to 128 ± 30 mg/dL; $P < .005$), and triglycerides (222 ± 94 to 173 ± 79 mg/dL; $P < .005$), but there was no significant change in HDL cholesterol (50 ± 13 to 47 ± 14 mg/dL).[73] In the presence of cyclosporine, HMG-CoA reductase inhibitor activity increased to approximately four to eight times predicted levels.[73]

Lovastatin in low dosages (10 to 20 mg per day) has also been used successfully in renal transplant recipients receiving cyclosporine.[74] In a study of 24 cyclosporine-treated recipients of renal allografts functioning for a mean of 4.1 years who had total cholesterol levels of 240 mg/dL or more, 10 mg of pravastatin given for 6 months (after 4 weeks of a step I National Cholesterol Education Program cholesterol-reduction diet, which did not significantly reduce cholesterol levels) effected significant decreases in total cholesterol (320.1 to 261.4 mg/dL; $P < .01$) and LDL cholesterol (202.1 to 118.7 mg/dL; $P < .01$) but no significant change in HDL cholesterol or triglycerides.[75] Of note, the cyclosporine dosage was relatively low (2 to 4 mg/kg/day) with a mean of 2.7 ± 1.3 mg/kg/day, and the agent used (pravastatin) was an HMG-CoA reductase inhibitor that, because of its water solubility, may have primarily entered hepatocytes and not muscle cells.[75]

In a study of 270 nontransplantation patients who had hypercholesterolemia and 50% or greater coronary stenosis, treatment with lovastatin (80 mg/day) and a cholesterol-lowering diet was associated with a 4.1% decrease in average percent diameter stenosis; placebo was associated with an increase of 0.9% ($P = .005$).[76]

When severe hypertriglyceridemia develops after renal transplantation, typically in association with a very low HDL cholesterol level, dietary therapy alone is likely to be inadequate.[77] Treatment in this situation is generally gemfibrozil (600 mg twice a day) or nicotinic acid, which may require dosages in the range of 2000 mg/day. Gemfibrozil, with its known side effects of liver impairment, gallstone formation, anemia, and rhabdomyolysis when used in combination therapy, can effectively reduce elevated triglyceride levels and offers an additional benefit by improving low HDL cholesterol levels. Nicotinic acid, which can cause hepatotoxicity particularly in the long-acting form and rhabdomyolysis in combination therapy, can also provoke uncontrolled hyperglycemia in cardiac transplant recipients receiving both cyclosporine and prednisone.

Bile acid sequestrants may actually tend to increase triglyceride levels and, theoretically, decrease cyclosporine absorption, although this has not been documented. The possibility of indirectly treating hyperlipidemias that are associated with heavy urinary protein excretion by means of ACE inhibitors should also be kept in mind. Similarly, a number of drugs commonly used to treat hypertension can affect blood lipid levels. Fortunately, ACE inhibitors and calcium antagonists are lipid-neutral.[78,79]

There have been interesting developments in the use of aspirin,[80] vitamin E as an antioxidant,[81] and moderate alcohol intake[82] as means of lowering the risk of myocardial infarction. Certainly, a comprehensive life-style modification as "an adjunct to, not a substitute for, conventional medical therapy" may also powerfully reduce risk.[83]

CORONARY ARTERY BYPASS GRAFTING AND TRANSLUMINAL ANGIOPLASTY

A review of the results of cardiac surgery in patients with end-stage renal disease from the 1970s to 1986 included 45 patients who underwent CABG, three of whom also had valve replacement surgery.[84] The patients were predominantly men (9:1), and most had two or three vessels bypassed (29% and 42%, respectively). The perioperative mortality rate was 4.2%. Survival at 4 years was 60%, comparable in that era to the survival of hemodialysis patients not undergoing cardiovascu-

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TABLE 4
RESULTS OF CORONARY ARTERY BYPASS GRAFTING (CABG) AND PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA) IN PATIENTS WITH RENAL FAILURE

Author	Year	Intervention	No.	Mean age, years	Hospital mortality, %	Overall mortality, %	Follow-up, months
Bolman[85]	1984	Transplantation	12	44	17	25	33.3 (8–93)
Albert[86]	1987	Dialysis	17	51	0	12	...
Rostand[87]	1988	Dialysis	20	52	20	45	31.0 (0–84)
		Transplantation	4	40	0	25	38.3 (6–74)
Opsahl[88*]	1988	Dialysis, CABG	39	62	3	31	34.9 ± 30.1
		Dialysis, no surgery	39		...	46	17.2 ± 15.2
Deutsch[89*]	1989	Dialysis	16	62	6	...	...
		CABG only	30	62	...	...	...
Kahn[90]	1990	Dialysis, PTCA, CABG[†]	17	60	12	41	20
Batiuk[91]	1991	Dialysis	25	57	20	30	28.6 (10–83)
De Meyer[92]	1991	Dialysis, CABG, PTCA[‡]	13	53	...[‡]	25	36
		Transplantation, CABG, PTCA	13	48	...[‡]	15	36
Manske[52*§]	1992	Dialysis, PTCA, CABG	13	40	0	8	24.3 (7–43)
		Dialysis, medical treatment	13	41	...	38	19.7 (8– 50)

*Case-matched control study
[†]PTCA was used with CABG in four patients and alone in the remaining patients
[‡]PTCA was used with CABG in two patients; in-hospital mortality was 11% of 18 with CABG
[§]All with insulin-dependent diabetes; 8 PTCA, 5 CABG

lar operations (56%), but lower than that in CABG patients with normal renal function (60% to 85%)[84] One series of 14 renal allograft recipients (including five diabetic patients) was reported in 1984.[85] Twelve patients underwent CABG: two (17%) died perioperatively, and one died nearly 4 years later of a perforated ulcer.[85]

Since those reports, eight other major though relatively small single-center reports of CABG or PTCA or both have appeared,[52,86–92] but some of them include patients operated on in the 1970s[87,88,91] (*Table 4*).

Several themes emerge from these studies. First, the perioperative mortality rate has decreased, from 20% to a range of 0% to 12% in studies restricted to the 1980s.[52,86,89,90,92] Second, perioperative morbidity is, nevertheless, greater in dialysis patients than in matched controls.[89] There was a need for longer mechanical ventilation, duration of hemodynamic support, length of stay in the intensive care unit, and length of hospital stay.[89] Intraoperative myocardial infarction was more frequent,[89] and increased postoperative bleeding has also been noted.[84,92]

Third, the overall mortality rate is lower in patients who undergo CABG than in medically treated patients, especially in those with insulin-dependent diabetes.[52,88] Fourth, relief of symptoms is achieved with a high degree of success.[86–88,90–92] Fifth, although symptomatic relief is readily achieved with PTCA, its benefits are transient and aggressive restenosis limits the long-term benefit.[90] According to Kahn and colleagues, coronary bypass surgery may be the preferred therapy for this unique patient group.[90] Sixth, "long-term" CABG follow-up ranges between means of only 20 to 38 months and still has mortality figures of 8% to 45% for dialysis patients and 15% to 25% for transplant patients. However, when case-control studies were done, the CABG patients fared better than patients who did not undergo surgery.[52,88]

NEW INSIGHTS: T LYMPHOCYTES IN CORONARY ATHEROSCLEROSIS

In the special circumstance of transplantation, coronary atherosclerosis appears to accelerate.[93] In cardiac transplantation, coronary atherosclerosis may be additionally promoted by incompatibility for HLA-A2,[94] by lymphocytotoxic B lymphocyte antibodies,[95] and by CMV infection.[96,97]

In general, the factors leading to the development of atherosclerotic plaques are complex but include three major components: (1) accumulation of

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TABLE 5
T-LYMPHOCYTE SUBSETS IN LONG-TERM RENAL TRANSPLANT RECIPIENTS WITH OR WITHOUT CORONARY ARTERY DISEASE*

Lymphocyte† subset	Coronary artery disease (n = 5)‡	No coronary artery disease (n = 24–29)	*P* value§
$CD2^+$	856 ± 310	1631 ± 788	.039
$CD3^+$	734 ± 373	1666 ± 727	.009
$CD4^+$	53 ± 21	53 ± 11	NS
$CD8^+$	254 ± 124	578 ± 322	.035
$CD8^+/CD11b3^+$	54 ± 34	106 ± 116	NS
$CD8^+/CD11b3-$	200 ± 103	471 ± 289	.05

*From Braun, reference 21
†Values represent mean absolute counts per mm^3 ± 1 standard deviation
‡Mean age 53.8 years (range 37–69 years)
§Nonpaired *t* test; *P* uncorrected for number of leukocyte markers tested

TABLE 6
T-LYMPHOCYTE SUBSETS IN MATCHED NONIMMUNOSUPPRESSED PATIENTS WITH OR WITHOUT CORONARY ARTERY DISEASE*

Lymphocyte subset†	Two- or three-vessel coronary artery disease (n = 11)	No coronary artery disease (n = 11)	*P* value‡
$CD2^+$	1218 ± 443	1795 ± 488	.009
$CD3^+$	1088 ± 427	1652 ± 458	.007
$CD4^+$	705 ± 256	1164 ± 401	.005
$CD8^+$	424 ± 214	426 ± 140	NS
$CD4^+/CD45RA^+$	310 ± 175	461 ± 276	NS
$CD4^+/CD29^+$	411 ± 181	570 ± 149	.036

*From Villa et al, reference 100
†Values represent mean absolute counts per mm^3 ± 1 standard deviation
‡Nonpaired *t* test; *P* uncorrected for number of leukocyte markers tested

lipids, predominantly cholesterol, (2) development of a fibrous cap of smooth muscle cells in connective tissue, and (3) infiltration of inflammatory cells. Macrophages and T lymphocytes together constitute approximately 40% of the cells in the fibrous cap region and up to 70% of cells in the core region of advanced plaques.[98] In studies of human aortic atherosclerotic plaques, T lymphocytes were actually more numerous than macrophages in the early fibrous lesions and nearly as numerous as macrophages in the complicated plaques.[99]

About the same time as these reports appeared, we were studying T-lymphocyte subsets in renal transplant recipients who had functioning grafts for at least 10 years. A unique T-lymphocyte pattern emerged when we compared five patients who had overt coronary artery disease with 27 who had no clinical coronary artery disease.[21] The patients with coronary artery disease had 55% fewer circulating T lymphocytes measured as $CD2^+$ or $CD3^+$ and fewer $CD8^+$ cells, both suppressor and cytotoxic (*Table 5*). These differences were not explainable by patient age, gender, or duration of the transplant.

Because of these intriguing findings, we then tested a population of individuals who had not undergone transplantation or immunosuppression, all of whom had already been studied with coronary arteriography. Twenty-two patients, consisting of 11 with and 11 without arteriographic evidence of coronary artery disease, all matched for age, sex, and contemporaneous angiographic study, had a similar investigation of their T-lymphocyte subsets.[100] The 11 patients with coronary artery disease had 34% fewer T lymphocytes measured as $CD2^+$ or $CD3^+$ cells (*Table 6*). However, these nonimmunosuppressed patients had significantly fewer $CD4^+$ cells, rather than fewer $CD8^+$ cells as seen in the immunosuppressed transplant recipients.

Therefore, both groups of patients with coronary artery disease had fewer $CD2^+$ and $CD3^+$ lymphocytes than patients without coronary artery disease, although this was more pronounced in the immunosuppressed renal transplant recipients. However, in the immunosuppressed renal transplant recipients, it was the $CD8^+$ subsets that were significantly lower in the presence of coronary disease, whereas in the nonimmunosuppressed patients who did not undergo transplantation it was primarily the $CD4^+$ subsets that were relatively reduced.

Possibly, long-term immunosuppression more effectively interfered with the $CD4^+$ T-lymphocyte populations in all of the long-term renal transplant recipients, thereby leaving the $CD8^+$ cells as markers of coronary atherosclerosis. On the other hand, in the more typical nonimmunosuppressed, nontransplantation population with coronary artery disease, the $CD4^+$ subsets and the helper-inducer $CD4^+/CD29^+$ cells were most notably affected. If these specific T-lymphocyte subsets are actively involved in the genesis of atherosclerotic plaques, the process might utilize either subset, depending on the immune status of the host.

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Therefore, any immune therapy directed at the traditional $CD4^+$ subsets seen only in nonimmunosuppressed patients with coronary atherosclerosis might be confounded by a shift to utilization of the $CD8^+$ subsets in the continuing development of atherosclerotic plaques. It was recently reported that atherectomy specimens from coronary arteries of nonimmunosuppressed patients contained substantial numbers of $CD4^+$ lymphocytes with variable interleukin-2R expression.[101] The presence of predominantly $CD4^+$ cells in such specimens would lend support to our finding that peripheral $CD4^+$ cells are relatively decreased and are actually physically involved in the development of coronary atherosclerotic lesions.

Although the precise mechanisms for involvement of T-lymphocyte subsets in coronary atherosclerosis are still being defined, the detection of low circulating levels of these subsets may ultimately be useful as a quantifiable marker of the activity of coronary artery disease when referenced to the appropriate control population. Furthermore, exploration of T-cell participation in atherosclerotic lesions may reveal entirely new therapeutic approaches to the treatment of coronary atherosclerosis.

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