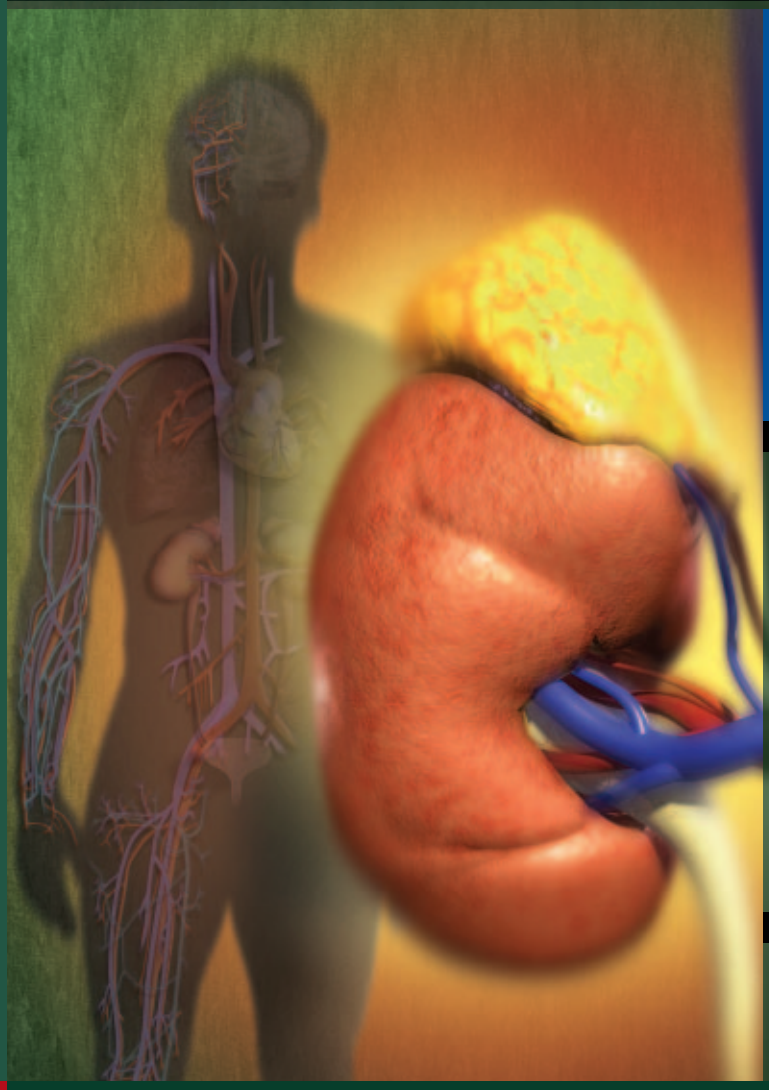
Implications of PRESERVING LONG-TERM RENAL FUNCTION After Renal Transplantation

PRESENTED BY:

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES OF
THE NATIONAL INSTITUTES OF HEALTH
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Renal Function as a Predictor of Graft and Patient Survival



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Target Audience

Transplant surgeons, transplant nephrologists, transplant nurses, transplant coordinators, pharmacists, and other healthcare professionals who are involved in the treatment and management of renal transplant recipients.

Educational Objectives

After completion of this educational monograph, the reader will be able to:

- Recognize the magnitude of the problem of chronic kidney disease in the general population
- State correlations between renal dysfunction, cardiovascular disease, and mortality in the general population
- Describe the associations between renal dysfunction and traditional and nontraditional cardiovascular disease risk factors
- Describe the prevalence of cardiovascular disease and cardiovascular mortality in patients with chronic kidney disease and in renal transplant recipients
- Associate the strong relationship between renal function and graft and patient survival in renal transplant recipients
- Recognize the role of accurate assessment of graft function and diagnosis of rejection and other conditions following renal transplantation in optimizing graft and patient survival
- Discuss possible links between immunosuppressive protocols and kidney failure and cardiovascular disease risk in renal transplant recipients
- Apply implications of current knowledge for the refinement of renal transplant recipient management strategies to reduce the burden of cardiovascular disease and to improve long-term graft and patient survival.

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Renal Function as a Predictor of Graft and Patient Survival

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Introduction

More than 200,000 kidney transplantations have been performed in the United States in the last 35 years, and over this time, graft survival has improved substantially.[1,2] Transplantation is now the preferred treatment approach for end-stage renal disease (ESRD) and confers a significant survival benefit over dialysis.[3-5] This benefit is largely a result of decreased cardiovascular (CV) death and is maintained in spite of the use of immunosuppressive therapy, which can increase hypertension, cause diabetes, worsen existing diabetes, and contribute to anemia.[5-9] Nonetheless, CV events and infection-related death remain the primary causes of mortality in transplant recipients and occur substantially more frequently in these patients than in the general population.[10-13]

Transplantation restores renal function, both excretory and endocrine, and preservation of the restored renal function ensures long-term graft survival. Long-term graft survival is, in turn, both dependent on and defined by a well-functioning kidney. It is tempting to hypothesize that patient survival advantages also accrue because of improved glomerular filtration rate (GFR) following successful kidney transplantation. However, mechanisms linking improved patient survival with improved GFR remain speculative.

Loss of renal function is an established risk factor for both CV and infection-related death,[14] which is concerning, as kidney transplant recipients rarely if ever have a normal GFR. In one analysis, 90% of kidney transplant recipients had chronic kidney disease (CKD) in the transplanted kidney (GFR <60 mL/min/1.73 m^2 or GFR ≥60 to 89 mL/min/1.73 m^2 plus evidence of kidney damage) and 75% had GFR levels <60 mL/min/1.73 m^2.[15] The prevalence of posttransplant CKD may be explained partially by early inflammatory events such as T-cell–mediated release of proinflammatory cytokines that occur during delayed graft function, which often leads to acute rejection.[16,17] However, the sustained incidence of CKD in kidney transplant recipients despite impressive reductions in the incidence of acute rejection episodes argues that dose-dependent nephrotoxicity, which can occur with calcineurin inhibitor-based immunosuppressive regimens, may negatively influence long-term graft survival. With the availability of nonnephrotoxic immunosuppressants, clinicians have new options for immunosuppressive protocols that may further improve graft and patient survival.

Table 1

Summary of Recipient, Donor, and Transplant Variables (%) for Deceased Transplants Associated with Elevated 1-Year Serum Creatinine

	1-Year Serum Creatinine (mg/dL)		
	≤1.5	>1.5	*P* Value
Recipient variables			
Male gender	49.4	71.8	<.0001
Black race	19.3	29.7	<.0001
Diabetes	22.1	18.4	<.0001
Previous transplant	13.9	15.8	<.0001
Donor variables			
Male gender	67.8	56.6	<.0001
Black race	9.2	10.3	<.0001
Age >50 years	9.3	28.3	<.0001
Transplant variables			
Cold ischemia time >24 hours	34.2	38.3	<.0001
Delayed graft function	16.2	26.9	<.0001
Clinical acute rejection	30.2	1.7	<.0001
Zero mismatch	12.1	9.1	<.0001

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The third in a series, this monograph will discuss the relationship between renal function during the first year posttransplantation, and long-term graft survival and mortality. This educational activity is based on presentations by Bruce Kaplan, MD, and Donald M. Hricik, MD, given in November 2003 at a roundtable discussion presented by the National Institute of Allergy and Infectious Diseases entitled "Implications of Preserving Long-Term Renal Function After Renal Transplantation" and is designed to increase awareness of the importance of preserving renal function in kidney transplant recipients.

Renal Function in Kidney Transplant Recipients

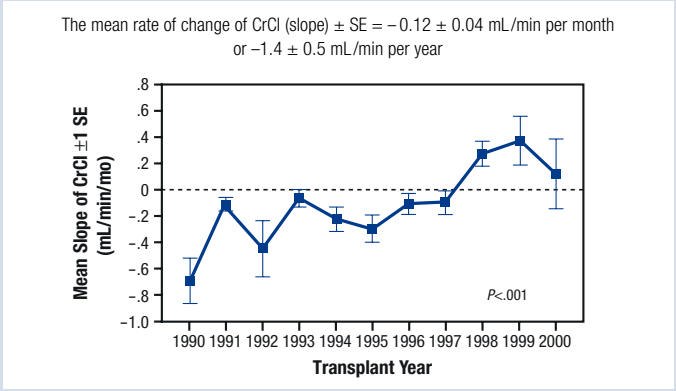
Renal function as measured by absolute serum creatinine values and change in GFR during the first year following kidney transplantation has improved over time. Although still far from normal levels, the 1-year serum creatinine values for deceased donor kidney recipients decreased steadily from 1.82 ± 0.82 to 1.67 ± 0.82 mg/dL during the decade from 1988 to 1998 (P<.001).[3] Individuals with poor 1-year renal function (serum creatinine levels >1.5 mg/dL) are significantly more likely to be male, African-American, or have had a previous transplant (P<.0001 for all values) (Table 1).[3]

The rate of decline in renal function over the first year posttransplantation also stabilized over the last decade of the 20th century. In an analysis of patients receiving deceased kidney transplants from 1990 to 2000, Gourishankar et al found that the mean rate of change in creatinine clearance was –1.4 ± 0.5 mL/min per year (P<.001) (Figure 1, page 2).[18] In fact, after 1997 the proportion of patients who showed improving renal function over time (positive slope) increased to more than 65% compared with less than 40% in earlier years. In this study, women were more apt to have a more rapid decline in creatinine clearance following transplantation as were those with higher 2-year diastolic blood pressure (DBP) and those who had any episode of acute rejection. The improved renal function was evident despite the fact that a significantly greater percentage of donors were over the age of 60 years after 1997 (12.6% versus 4.9%, respectively; P=.02). In addition, a significantly greater proportion of recipients had prior failed transplants (9.2% versus 2.7%, respectively; P=.002) than in 1997 or before.

The reasons for the changes in 1-year serum creatinine values are not entirely clear. However, the improvement has been measured during a period of increased reliance on older donors, typically an important risk factor for poorer outcomes.[19,20] Improved donor management to reduce cold ischemia time and the consequences of revascularization

Figure 1

The Mean Rate of Change of Creatinine Clearance (Slope) ±1 Standard Error (SE) from 1990 to 2000



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may have contributed. However, donor variables significantly associated with elevated 1-year serum creatinine levels were male gender, African-American ethnicity, and age >50 years ($P<.0001$ for all values).[3] Other variables including human leukocyte antigen (HLA) mismatching, incidence of decreased graft function (DGF), and incidences of acute rejection have also improved over time.[3] Better management of CV risk factors such as hypertension and dyslipidemia may also have contributed to better 1-year renal function among more recent kidney transplant recipients.

Despite these improvements, the percentage of kidney transplant recipients with significant renal dysfunction may be substantial. In a recent analysis of 459 patients who received kidney transplants at least 6 months prior to study enrollment (mean follow-up, 7.7 years), 90% exhibited CKD, as defined by the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation (Table 2).[15,21] Even more disturbing, at least 60% of patients were in CKD stage 3 with a GFR between 30 and 59 mL/min/1.73 m^2. Thus, any impact of CKD on graft or patient survival will affect a large majority of kidney transplant recipients.

Renal Function and Graft Loss

As mentioned earlier, long-term graft survival is both dependent on and defined by a well-functioning kidney. Thus, it is not surprising that the risk of graft loss correlates with the severity of renal dysfunction as measured by serum creatinine levels.

To clarify the role of renal function at 1 year for predicting long-term graft survival, Hariharan et al assessed data for more than 100,000 individuals who received deceased or living donor kidney transplants between 1988 and 1998.[3] The influence of a number of variables on graft survival was evaluated and a strong independent correlation between serum creatinine levels and graft loss was confirmed; the relative hazard for graft failure was 1.63 (95% confidence interval [CI], 1.61–1.65; $P<.0001$) with each incremental increase of 1.0 mg/dL of serum creatinine at 1 year, regardless of donor age or whether the donor was living or deceased. Figure 2 shows the relationship between serum creatinine levels and graft survival in deceased kidney recipients based on Kaplan-Meier estimations of these data.[3] Similar results were found for those from living donors.

An inverse relationship between acute rejection and 1-year graft survival also has been demonstrated. Overall mean graft survival rates after the first year increased by 4.2% per year for transplantations performed from 1988 to 1996.[2] However, a disproportionate percentage of this benefit occurred among individuals who had not experienced an acute rejection episode. Over this period, graft survival rates improved by 10.2% per year in patients who had no acute rejection episodes compared with 2.4% per year for those who did (Figure 3). These data suggest that the decrease in acute rejection rates achieved through the improved use of newer immunosuppressive regimens may account, in large part, for the increase in long-term graft survival.

On the other hand, Meier-Kriesche et al found that although overall early acute rejection rates (<6 months posttransplantation) decreased by 58% in the years between 1995 and 2000 for recipients of both living and deceased donor kidneys, this decrease did not translate into improvement in long-term graft survival.[22] In fact, when 2-year graft survival data were censored for patients who died with a functioning graft, relative risk of graft loss actually increased slightly for both deceased and living donor transplants (Figures 4 and 5). Recovery of renal function following an acute rejection was more indicative of long-term graft survival at 3 years and 6 years than acute rejection per se. Baseline serum creatinine levels were established at 6 months posttransplantation and compared with 1-year levels. Patients who had an early acute rejection episode and whose serum creatinine levels returned to within 95% of baseline levels at 1 year

Table 2

Classification of Patients According to Chronic Kidney Disease Stage

	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
N (%)	10 (2.2)	103 (22.4)	274 (59.7)	66 (14.4)	6 (1.3)
GFR (mL/min/1.73 m^2)*					
Mean ± SD	98.6 ± 11.5	71.9 ± 8.2	44.2 ± 8.4	24.0 ± 4.2	11.5 ± 2.9
Median	94.5	70.5	44.0	24.7	11.8
Serum creatinine (mg/dL)					
Mean ± SD	0.8 ± 0.1	1.1 ± 0.2	1.7 ± 0.4	2.8 ± 0.5	5.1 ± 1.3
Median	0.9	1.1	1.6	2.7	4.8
Range	0.7-1.0	0.7-1.5	1.0-2.7	1.9-3.8	3.9-6.7

*GFR, glomerular filtration rate, calculated using the abbreviated Modification of Diet in Renal Disease Study Equation, which is equal to 186 x (serum creatinine)$^{-1.154}$ x (age)$^{-.203}$ x (0.742 if female) x (1.210 if African-American).

SD, standard deviation.

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posttransplantation demonstrated similar long-term graft survival as those who never experienced acute rejection at all. In contrast, an incrementally greater risk of graft loss was associated with failure to restore 95% of baseline renal function in the same time frame (Table 3).[22] Thus, in this study, the increased risk of graft loss associated with the incidence of acute rejection was largely limited to the subset of patients who do not regain baseline renal function.

It is reasonable to hypothesize that the extent of graft injury resulting from acute rejection, as measured by recovery of renal function, may be a critical factor in long-term graft survival. Meier-Kriesche et al also have shown that, although the rate of acute rejection has decreased in recent years, fewer of those who did experience acute rejection were able to recover baseline renal function than those not experiencing acute rejection (Table 4).[22]

These data clearly indicate that the subpopulation of patients with acute rejection who do not regain adequate renal function are most vulnerable to graft loss and will require new approaches to management in order to improve long-term graft survival beyond current levels.

Renal Function and Mortality After Transplantation

The relationship of renal function to mortality has been well characterized in patients with CKD. However, fewer data are available from the transplant population. Wolfe et al showed that transplantation confers a 4-fold decrease in the annual death rate compared with patients on dialysis and an almost 2-fold decrease compared with those

Figure 2

Posttransplantation Renal Function in the First Year Predicts Long-term Deceased Kidney Transplant Survival

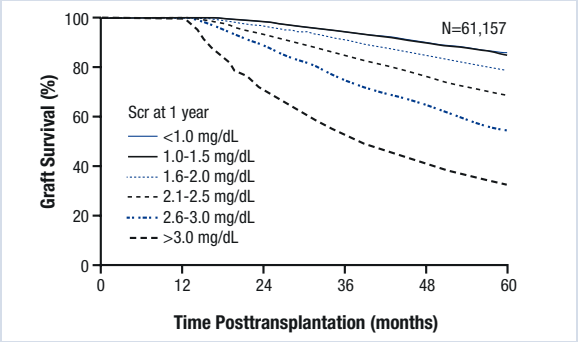

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Figure 3

Relative Hazard of Graft Failure After the First Year Posttransplantation, According to the Presence or Absence of Clinical Acute Rejection in the First Year

After censoring of data for patients who died with a functioning kidney, the reduction in the relative hazard per year was 2.4% for those with acute rejection and 10.2% for those without.

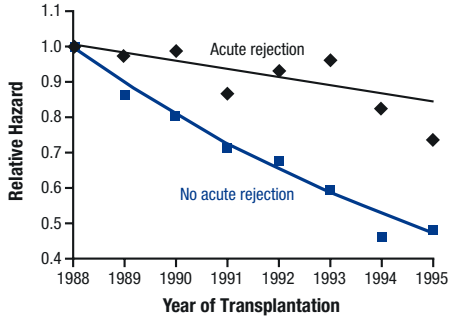

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Figure 4

Incidence of Acute Rejection Episodes During the First 6 Months Posttransplantation by Era

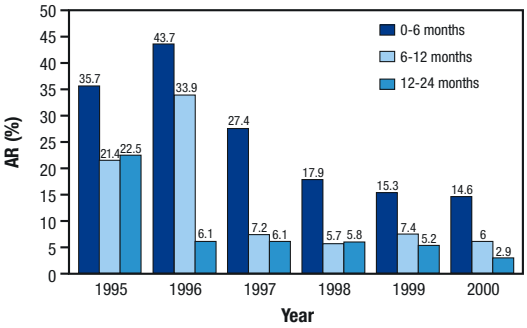

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Figure 5

Relative Risk of Death-Censored Graft Loss by Donor Type from 1995 to 2000

Model corrected for induction, antiproliferative, and inhibitor medication regimens at baseline, cold ischemia time, panel-reactive antibody level, human leukocyte antigen (HLA)-A, -B, and -DR mismatches, recipient and donor gender, ethnicity, age, presence of delayed graft function, primary diagnosis, and waiting time on dialysis.

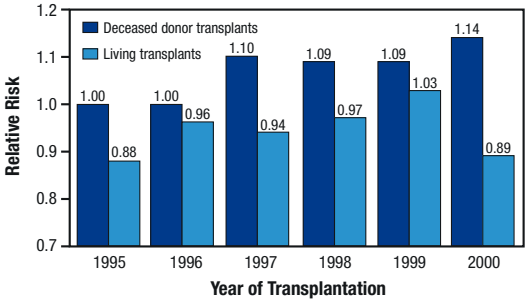

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Table 3

Multivariate Risk Estimates for Death-censored Graft Survival by Acute Rejection Status and Functional Return to Baseline*

Return to % Baseline Status Following Acute Rejection	Hazard†	95% Confidence Interval
95%	1.067	(0.882, 1.291)
85%-95%	1.223	(0.874, 1.713)
75%-85%	2.739	(2.024, 3.705)
<75%	5.130	(4.332, 6.076)

*Return to baseline function estimated by calculated creatinine clearance (Cockcroft-Gault).

†No acute rejection =1.000.

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Table 4

Rate of Return to Baseline Renal Function* After Acute Rejection by Era

Year of Transplantation	Return to Baseline	No Return to Baseline	Rate of Return
1995	292	245	54.4%
1996	561	259	68.4%
1997	86	149	36.6%
1998	99	139	41.6%
1999	116	144	44.6%
2000	69	101	40.6%
2001	14	22	38.9%

*Return to baseline function estimated by 1/serum creatinine.

Significant linear trend (P<.001) toward no return to baseline as tested by the Cochran-Armitage trend test.

Adapted with permission from Meier-Kriesche H-U, et al. *Am J Transplant*. 2004;4:378-383.

patients who were on the waiting list for transplantation.[5] The survival benefit is attributed to reduced rates of CV disease and infection-related death. Nonetheless, in an analysis of 58,900 adult patients who received a primary kidney transplant between 1988 and 1998, CV disease and infection-related death accounted for approximately 42% of deaths beyond 1 year posttransplantation (Table 5).[14] Further analysis of these data indicated that 1-year serum creatinine levels directly correlated with the risk of CV death independent of many known risk factors for cardiovascular disease (CVD) (Figure 6).[14] Kidney transplant recipients who had a serum creatinine level >2.5 mg/dL at 1 year post-transplantation had a 4-fold increase in risk of infection-related death compared with those whose serum creatinine levels were <1.2 mg/dL (Figure 7).[14]

Some data suggest that modification of immunosuppressive therapy may improve the risk of infection-related death. Immunosuppression appears to accelerate the age-related decline in immune function, making older recipients more vulnerable to all infections or more severe infections.[23] These patients generally require lower doses of immunosuppressants to prevent acute rejection episodes than do younger patients, suggesting that a dosage adjustment may reduce infection-related death without increasing acute rejection rates. In contrast to the elderly, African-American kidney transplant recipients may require higher doses of immunosuppressive agents to achieve acute rejection rates similar to those found in Caucasians.[24-27] Consistent with this observation, Meier-Kriesche et al found that after transplantation, African-Americans have a lower risk of infection-related death (relative risk [RR], 0.7) and a higher risk of acute rejection (RR, 1.3) than do Caucasians.[27] More aggressive immunosuppression may lead to improved long-term graft survival in the African-American kidney transplant population without increasing rates of infection-related death.

Mechanisms Linking Renal Function with Long-term Outcomes

Whereas the mechanisms linking renal function with graft and patient survival remain elusive, shared risk factors provide clues as to how these outcomes are related. Renal dysfunction is frequently correlated with many of the risk factors for CVD in the general population and those with CKD (Table 6). Prior to transplantation, patients with ESRD frequently have hypertension, diabetes, other comorbidities, and risk factors associated with increased CV risk. Although restored renal function following transplantation reduces CV risk substantially, the underlying comorbidities may contribute to declining function in the transplanted kidney. Unfortunately, there have been few interventional studies demonstrating that treatment of CV risk factors improves or preserves renal function in transplanted kidneys. However, as discussed below, the observational data suggest that renal function at 1 year may serve as a marker for CV complications and can indicate therapeutic targets.

Hypertension

The alarming prevalence of hypertension among kidney transplant recipients emphasizes the need for careful management of blood pressure in this population. In an analysis of 459 kidney transplant recipients, Karthikeyan et al found that the majority of patients who had received kidney transplants at least 6 months prior to study enrollment were hypertensive (systolic blood pressure [SBP]

Table 5

Cause of Death in Primary Renal Transplant Recipients Beyond 1 Year of Transplantation

Cause of Death	N	%
Cardiovascular	1,797	30.1
Infectious	698	11.7
Malignancy	603	10.1
Other	2,865	48.1
All	5,963	100

Adapted with permission from Meier-Kriesche H-U, et al. *Transplantation*. 2003;75:1291-1295.

≥140 mmHg, or DBP ≥90 mmHg, or BP <140/90 mmHg and on antihypertensive medication) regardless of their degree of renal function.[15] However, the mean SBP, and the incidence of both controlled and uncontrolled hypertension significantly increased with decreasing GFR (Table 7). The percentage of patients affected ranged from 60% of those with stage 1 CKD to 89% of those with stage 4 CKD and 100% of those with stage 5 CKD.

Consistent with these observations, in an analysis of nearly 30,000 patients Opelz et al revealed that, 1 year after transplantation, 75% had SBP >130 mmHg and that elevated SBP was independently and significantly associated with chronic graft failure (*P*<.0001) over 7 years of follow-up.[28] Furthermore, the association of SBP with long-term graft loss was significant, even in the absence of acute rejection (*P*<.0001). This observation argues against the hypothesis that elevated blood pressure results from kidney damage secondary to acute rejection, which is primarily responsible for increased rates of graft loss.

Other independent risk factors for 1-year graft loss included African-American recipient race, diabetic nephropathy, donor or recipient age >60 years, cold ischemia time >24 hours, one or more HLA mismatches, and >50% preformed antibodies (*P*<.05 for all values).[28] However, the relationship between race, hypertension, and graft survival may be complicated. Cosio et al found a correlation between hypertension and graft survival in African-Americans, but not Caucasians. However, there was no statistically significant difference between normotensive African-American and Caucasian recipients, with respect to allograft survival. There was an 8-fold greater allograft survival rate in hypertensive Caucasian recipients (24.6 ± 7 years) than in hypertensive African-American recipients (3.1 ± 0.7 years). Although the prevalence of hypertension was similar in the two groups, African-Americans had a significantly higher 6-month average mean arterial blood pressure than did Caucasians (105 ± 8 mmHg versus 102 ± 7 mmHg, respectively; *P*=.002) and a significantly shorter mean allograft half-life (7.7 ± 1.3 years versus 24 ± 3 years, respectively; *P*<.0001).[29]

Clearly, optimizing treatment of hypertension in the kidney transplant population warrants further investigation. Despite extensive clinical evidence that treating blood pressure saves lives, hypertension is poorly controlled in the general population, especially among African-Americans. The complex treatment regimens required for immunosuppression further complicate antihypertensive therapy in kidney transplant recipients. However, lower blood pressure may prolong graft survival as well as patient survival. Aggressive blood pressure control (in the general population) has been shown to slow the progression of renal deterioration in chronic renal disease.[30,31] Future studies are needed to establish whether similar antihypertensive methods will be as effective in the kidney transplant population.

Diabetes

Diabetes is the leading cause of ESRD,[32] and new-onset diabetes is a major complication following kidney transplantation.[33,34] Growing evidence indicates that impaired renal function, hypertension, impaired glucose tolerance, dyslipidemia, and obesity are inexorably linked. Metabolic syndrome, which frequently precedes the onset of diabetes, typically involves some combination of these symptoms. The relationship of impaired glucose tolerance and graft survival is evident in the observation that post-transplant diabetes is associated with decreased graft survival (RR, 1.63; 95% CI, 1.46-1.84; *P*<.0001) and increased mortality (RR, 1.87; 95% CI, 1.60-2.18; *P*<.0001).[33]

Figure 6

Cardiovascular Death by Serum Creatinine Level at 1 Year Posttransplantation

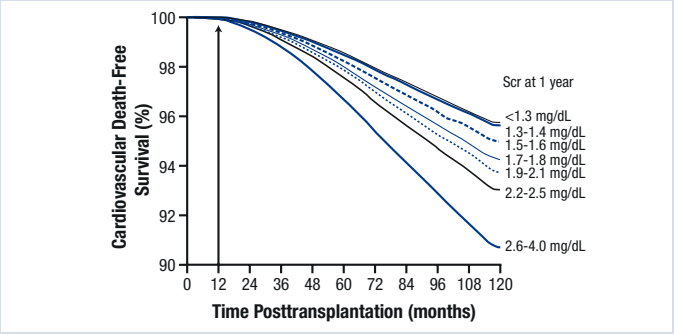

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Figure 7

Relative Risk of Infectious Death by Serum Creatinine Level at 1 Year Posttransplantation

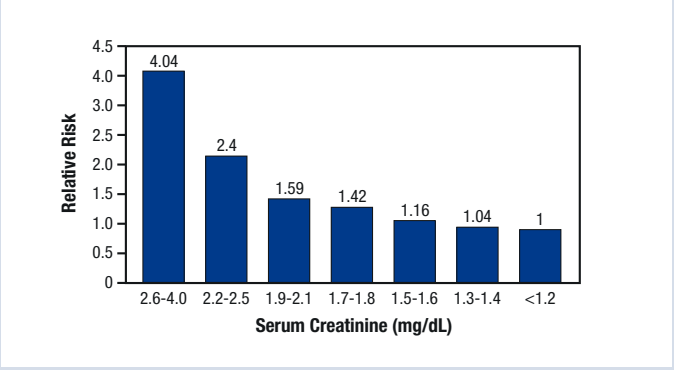

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Table 6

Risk Factors for Cardiovascular Disease in Patients with Chronic Kidney Disease

Traditional	Nontraditional
Hypertension	Anemia
Diabetes	Inflammation
Age	Reactive oxygen species
Smoking	Advanced glycation end products
↑ Low-density lipoprotein cholesterol	Hyperhomocysteinemia
↓ High-density lipoprotein cholesterol	Hyperparathyroidism

Simultaneous kidney-pancreas transplantation (SKPT) has provided a rare opportunity to evaluate the impact of intervention on long-term outcomes. In 18,549 patients with type 1 diabetes and renal failure who received a deceased donor kidney transplant, living donor kidney transplant, or an SKPT, restoration of some insulin production resulted in an 8-year patient survival rate similar to that of living donor kidney transplantation (72% for both) and superior to that of deceased kidney transplantation alone (55%).[35] These indirect data are consistent with the hypothesis that impaired glucose tolerance may contribute to reduced renal function in kidney transplant recipients.

Lipids

In their characterization of CV risk factors in kidney transplant recipients, Karthikeyan et al found that dyslipidemia was extremely prevalent; 30%, 74%, and 76% of recipients had suboptimal control of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and non–HDL-C, respectively.[15] However, the only lipid parameter to correlate with decreasing GFR was elevated serum triglyceride levels, suggesting that other factors may be more important to lipid levels posttransplantation (Table 8). Given the significance of abnormal lipid values to CV risk in the general population, it is alarming to find that only 41% of kidney transplant recipients in this study were on lipid-lowering therapy. In addition, optimal LDL-C control had not been achieved in the majority of the treated patients.

C-reactive Protein

With the growing appreciation of the inflammatory nature of CVD, C-reactive protein (CRP) has become established as a marker of CVD. Allograft rejection often involves an inflammatory process and thus may be associated with elevated CRP concentrations. In a small retrospective study, pretransplant CRP levels were predictive of mortality in kidney transplant recipients.[36] Among 115 patients, CV mortality was significantly associated with elevated CRP levels (RR, 1.19; $P<.05$). It is somewhat surprising that there was no correlation with rates of acute rejection or graft failure.

Anemia

Anemia defined as hemoglobin levels ≤13 g/dL for males and ≤12 g/dL for females is a common, early complication of CKD and is relatively common in patients following kidney transplantation.[37,38] The causes of anemia in kidney transplant recipients are varied and include bone marrow suppression resulting from immunosuppression, iron deficiency, and use of inhibitors of the renin-angiotensin-aldosterone system (RAAS).[38]

The time course of anemia in a mixed cohort study was similar to that of renal dysfunction early posttransplantation. Anemia was prevalent immediately following surgery and improved over the first 3 to 6 months.[37] However, a slow decline in serum hemoglobin levels began again between 6 and 12 months, which paralleled decreasing renal function in the transplanted kidney. By 2 years posttransplantation, almost 30% of patients had become anemic.

This observation was supported by a study by Vanrenterghem et al who surveyed 4263 kidney transplant recipients 6 months to 5 years posttransplantation.[39] At study entry, 38.6% of the patients were anemic. Twice as many patients with serum creatinine levels >2 mg/dL were anemic as those with serum creatinine levels ≤2 mg/dL. Use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients without posttransplant erythrocytosis and use of mycophenolate mofetil also were found to be independent risk factors for anemia occurring at some time between 6 months and 5 years posttransplantation.[39]

Applying a more stringent definition of anemia (hemoglobin <11 g/dL) to a similar population, Karthikeyan et al confirmed that anemia significantly correlated with increasing severity of CKD; anemia was present in 2.9% of kidney transplant recipients with stage 2 CKD posttransplantation and increased to 33% of those with stage 5 CKD ($P<.001$ for trend from stage 1 to stage 5) (Table 9).[15]

In kidney transplant recipients with existing CV risk factors, anemia may be a source of additional CV risk. Djamali et al found that iron deficiency

Table 7

Blood Pressure Control According to Chronic Kidney Disease Stage*

	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	*P* Value†
Systolic BP (mmHg)						
Mean ± SD	120 ± 16	131 ± 17	133 ± 16	139 ± 17	138 ± 19	.01
Diastolic BP (mmHg)						
Mean ± SD	77 ± 6	79 ± 8	78 ± 9	79 ± 9	80 ± 12	.42
Hypertension (%)††	60	83	87	89	100	.02
Uncontrolled hypertension (%)**	10	36	36	59	50	.002
Medication Use (%)						
ACEI	10	20	25	18	0	.87
ARB	0	1.0	4.4	1.5	0	.60
ß-Blocker	20	35	51	62	33	<.001
CCB	20	51	49	56	67	.16
α-Blocker	10	11	17	24	50	.004
Diuretic	0	15	19	44	83	<.001
Antihypertensives per Patient						
Mean ± SD	0.7 ± 0.8	1.3 ± 1.1	1.7 ± 1.1	2.2 ± 1.3	2.3 ± 0.5	<.001

* Stage 1, glomerular filtration rate (GFR) ≥90 mL/min/1.73 m^2; Stage 2, GFR 60-89 mL/min/1.73 m^2; Stage 3, GFR 30-59 mL/min/1.73 m^2; Stage 4, GFR 15-29 mL/min/1.73m^2; Stage 5, GFR <15mL/min/1.73 m^2.

† *P* values are for tests of trend.

†† Hypertension — More than one systolic BP value ≥140 mmHg or more than one diastolic BP value ≥90 mmHg or BP <140/90 mmHg and patient taking at least one antihypertensive medication.

** Uncontrolled hypertension — Hypertensive patients with more than one systolic BP value ≥140 mmHg or more than one diastolic BP values ≥90 mmHg. From stage 1 to stage 5.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BP, blood pressure; SD, standard deviation.

Adapted with permission from Karthikeyan V, et al. *Am J Transplant.* 2004;4:262-269.

posttransplantation was independently associated with risk of a CV event (RR, 1.6; *P*=.042) in patients at high risk because of type 1 diabetes.[40]

The implications of these observations in the long term are not clear, and whether treatment of anemia can improve graft survival and decrease mortality in kidney transplant recipients remains to be determined. In a population of patients with anemia (Hb <12 g/dL), 75% of whom had chronic renal dysfunction (serum creatinine ≥1.5 mg/dL), aggressive treatment with intravenous iron and subcutaneous erythropoietin was shown to improve left ventricular hypertrophy and congestive heart failure, and statistically increased ejection fraction.[41] Similar benefits may result with treatment after transplantation, although this has not been tested.

Advanced Glycation End Products

Advanced glycation end products (AGEs) are particularly attractive as a theoretical link between renal dysfunction and CVD. They form through a multistep, nonenzymatic process that, in the presence of hyperglycemia or other abnormal chemical conditions, results in irreversible binding of sugar to protein.[42] These glycated proteins, in turn, result in protein cross-linking that is responsible for the thickening of basement membranes and may contribute to diabetic nephropathy and vascular disease. AGEs bind to and activate macrophages, triggering production of free radicals and perpetuating a proinflammatory, pro-oxidant state.[43]

The relationship between the AGE, pentosidine, and renal function has been demonstrated in a study that monitored plasma pentosidine levels over time following kidney-pancreas and kidney-only transplantation.[44] Changes in plasma pentosidine levels were compared to glycohemoglobin levels in three groups: patients with diabetes who received a kidney-pancreas transplant, patients with diabetes who received a kidney only, and patients without diabetes who received a kidney only. Prior to transplantation, plasma pentosidine concentrations were elevated 20- to 35-fold in all three groups compared with normal volunteers. Following an initial significant decrease in all three groups after transplantation, plasma pentosidine concentrations did not change significantly after the fourth month posttransplantation and no significant differences among the groups were evident after 2 years of follow-up. Plasma pentosidine and glycohemoglobin levels were not correlated in any of the subgroups. Glycohemoglobin levels returned to the normal range within 3 months of kidney-pancreas transplantation, although this protocol did not confer any advantage over kidney transplantation alone in reducing pentosidine levels.[44] A second study of pentosidine plasma and tissue concentrations found that there were high concentrations of tissue pentosidine several months (and years) after successful transplantation of either kidney or kidney-pancreas, which suggests a role of AGEs in cardiovascular morbidity and questions the ability of the transplanted organ to reverse pre-existing vascular disease.[45]

Immunosuppression and Renal Function

To understand the role of immunosuppressive therapy in eventual graft loss, acute rejection and chronic allograft nephropathy need to be considered separately. Although the use of immunosuppressive regimens has greatly reduced early acute rejection rates, calcineurin inhibitors have long been associated with development of chronic allograft nephropathy (Table 10). There has been some controversy as to the implications for long-term outcomes. Two years after deceased kidney transplantation, evidence of chronic allograft nephropathy was present in 62% of kidney biopsies from patients taking tacrolimus and 72% from individuals taking cyclosporine.[46] However, Burke et al reported that the majority of cyclosporine-treated recipients of both living donor and deceased kidneys tolerated long-term cyclosporine therapy without evidence of progressive toxic nephropathy.[8]

Table 8

Lipid Parameters According to Lipid-lowering Therapy* and Chronic Kidney Disease Stage†

	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	*P* Value‡
All Patients (%)						
TC >200 mg/dL	67	54	59	56	67	.77
Non–HDL-C >130 mg/dL	100	86	96	93	100	.38
LDL-C >100 mg/dL	89	72	75	72	80	.82
HDL-C <40 mg/dL	44	27	30	35	17	.87
TG >150 mg/dL	44	48	57	67	67	.02
On lipid-lowering therapy (%)	40	30	44	42	50	.07

*Lipid-lowering therapy refers to treatment with a statin, fibrate, or niacin.

†Stage 1, GFR ≥90 mL/min/1.73 m^2; Stage 2, GFR 60-89 mL/min/1.73 m^2; Stage 3, GFR 30-59 mL/min/1.73 m^2; Stage 4, GFR 15-29 mL/min/1.73 m^2; Stage 5, GFR <15 mL/min/1.73 m^2.

‡*P* values are for tests of trend from stage 1 to stage 5.

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Adapted with permission from Karthikeyan V, et al. *Am J Transplant.* 2004;4:262-269.

Table 9

Hemoglobin According to Chronic Kidney Disease Stage*

	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	*P* Value†
Hemoglobin						
Mean ± SD (g/dL)	14.2 ± 1.6	14.0 ± 1.4	13.2 ± 1.5	11.8 ± 1.5	11.7 ± 1.1	<.001
On Epo (%)	0	0	4.4	21	67	<.001
Hemoglobin						
<11 g/dL (%)	0	2.9	6.6	27	33	<.001
<11 g/dL and on Epo (%)	0	0	22	33	50	.16

*Stage 1, GFR ≥90 mL/min/1.73 m^2; Stage 2, GFR 60-89 mL/min/1.73 m^2; Stage 3, GFR 30-59 mL/min/1.73 m^2; Stage 4, GFR 15-29 mL/min/1.73 m^2; Stage 5, GFR <15 mL/min/1.73 m^2.

†*P* values are for tests of trend from stage 1 to stage 5.

SD, standard deviation; Epo, erythropoietin.

Adapted with permission from Karthikeyan V, et al. *Am J Transplant.* 2004;4:262-269.

To assess the impact of calcineurin inhibitor treatment on long-term outcomes, 128 patients who received deceased first kidney transplants between 1986 and 1989 and who were treated initially with cyclosporine plus prednisone, but no azathioprine, were followed for at least 10 years. Outcomes were compared with 185 historical controls who received kidney transplants between 1979 and 1986 and were treated initially with azathioprine and prednisone, but no cyclosporine. The results clearly showed that the benefit of cyclosporine treatment on graft survival was limited to the first few years following transplantation. The rate of graft survival among patients receiving cyclosporine was superior to those on azathioprine up to 3 years. However, after 10 years of therapy with the respective study drugs, graft survival was reduced from 73% to 50% in those receiving cyclosporine and from 59% to 45% in those receiving azathioprine. Moreover, at 10 years posttransplantation, serum creatinine levels and mean blood pressure were significantly higher and hypercholesterolemia was more prevalent in the cyclosporine-treated patients than in azathioprine-treated patients. More patients receiving azathioprine experienced graft loss due to acute rejection than those taking cyclosporine (23.8% versus 10.9%, respectively; *P*=.046), whereas a significantly greater proportion of cyclosporine-treated patients had graft loss due to chronic nephropathy (40.6% versus 16.8%, respectively; *P*=.008). There was no significant difference in all-cause mortality or CV mortality between the treatment groups at 10 years.[47]

Using Risk Data to Improve Patient Outcomes

Clearly, renal function in the transplant population is strongly associated with graft survival and mortality. This association is undoubtedly a result of the interplay of risk factors for rejection, CVD, and infection as well as the treatment regimens used. Identifying patients early, in the first year posttransplantation, who are at high risk of late renal failure is critical to developing targeted care. Adjustments in immunosuppressive regimens and the use of antihypertensive medications may be important in ameliorating some of the risk for these patients.

In the interest of comparing treatment regimens in a timely fashion, renal function has been suggested as a surrogate endpoint for long-term graft survival and mortality in clinical trials. Despite their strong correlations, serum creatinine levels, creatinine clearance rates and GFR do not reach the predictive level required for a reliable surrogate endpoint for graft or patient survival. In part because the association between serum creatinine levels and graft failure or patient death runs on a continuum, there is no clear cutoff value above or below which an event (graft loss or death) will occur with a significant degree of certainty. As a result, the number of incorrect predictions is high.

Using prediction diagnostics, Kaplan et al found that using 1-year serum creatinine levels to predict graft loss at 2 years resulted in incorrect predictions 37% of the time.[48] Using 1-year serum creatinine levels as a measure of posttransplant renal function was no better for predicting death at 2 years, with wrong predictions occurring 46% of the time.[48] Furthermore, between 85% and 95% of the variables that explain graft loss cannot be identified among those in current databases (optimistic r^2 values in the range of 15%).[48] These findings suggest that important variables have yet to be identified or are not commonly included in large databases. However, these events may not be predictable in nature. Nonetheless, the absence of predictive value in no way detracts from the importance of renal dysfunction as a risk factor for subsequent graft loss and patient death.

Table 10

Immunosuppression Side Effect Profiles

	CsA	Tac	Srl	Ster	MMF
Hypertension	++	+	∅	++	∅
Hyperglycemia	+	++	∅	+++	∅
Renal dysfunction	++	++	∅	∅	∅
Hyperlipidemia	++	+	++	++	∅
Hyperkalemia	+++	+++	∅	∅	∅
Tremor	∅	+	∅	∅	∅
Hirsutism	+	∅	∅	∅	∅
Gingival hyperplasia	+	∅	∅	∅	∅
Hypophosphatemia	++	++	+	∅	∅
Osteoporosis	±	±	∅	+++	∅
Malignancy	+	+	?	∅	+

CsA, cyclosporine; Tac, tacrolimus; Srl, sirolimus; Ster, steroids; MMF, mycophenolate mofetil.

+++ = severe; ++ = moderate; + = mild; ± = opposite; ∅ = none; ? = unknown.

Adapted from Martin Zand, MD.

Summary

Long-term graft survival may expand the availability of much-needed donor kidneys for primary transplantation by reducing the need for second transplantations in addition to reducing morbidity and mortality for individual kidney transplant recipients. The short-term benefits of immunosuppression to reduce acute rejection have been the focus of intensive research. Unfortunately, this emphasis may have obscured the importance of preserving renal function for long-term graft and patient survival. Observational studies have clearly demonstrated that the markedly reduced incidence of early acute rejection seen in recent years has not translated into the expected increase in positive long-term outcomes. Instead, renal function in transplanted kidneys has been shown to be a major factor in determining long-term graft and patient survival. Management of a number of pre- and posttransplant factors associated with progression of renal dysfunction in transplanted kidneys, including the use of therapeutic regimens that preserve renal function, is likely to improve graft survival and mortality. The next monograph in this series will discuss these modifiable donor and recipient factors as targets for preservation of renal function.

Renal Function as a Predictor of Graft and Patient Survival

CE Post-Test and Evaluation

Release Date: September 2004 Expiration Date: September 30, 2005

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POST-TEST

1. After 1997, the proportion of patients who showed improving function over time (positive slope):
   a. decreased to 40% compared with more than 65% in earlier years.
   b. increased to 40% compared with less than 25% in earlier years.
   c. increased to more than 65% compared with less than 40% in earlier years.
   d. decreased to 65% compared with more than 75% in earlier years.
   e. has decreased to 65%, reflecting the decline in quality of deceased kidneys in recent years.

2. After censoring data for patients who died with a functioning graft, the relative hazard for graft loss was ___% per year for those who had acute rejection following transplantation between 1988 and 1996.
   a. increased by 10.2%
   b. increased by 2.4%
   c. reduced by 10.2%
   d. reduced by 2.4%
   e. none of the above

3. Patients whose serum creatinine returned to baseline after an early episode of acute rejection demonstrated:
   a. similar long-term graft survival as those who did not experience acute rejection.
   b. similar long-term graft survival as those who experienced acute rejection but whose serum creatinine did not return to baseline.
   c. long-term graft survival between that of patients who experienced acute rejection but whose serum creatinine did not return to baseline and those who did not have acute rejection.
   d. better long-term graft survival than those who did not experience acute rejection.
   e. worse long-term graft survival than those who did experience acute rejection but did not return to baseline.

4. Wolfe, et al. have shown that transplantation confers:
   a. a 4-fold decrease in annual death rate compared with patients on dialysis and a similar decrease compared to those dialysis patients who are healthy enough to be on the waiting list for transplantation.
   b. a 4-fold decrease in annual death rate compared with patients on dialysis and an almost 2-fold decrease compared to those dialysis patients who are healthy enough to be on the waiting list for transplantation.
   c. a 4-fold decrease in annual death rate compared to those dialysis patients who are healthy enough to be on the waiting list for transplantation and less than an 8-fold increase compared to the general population.
   d. a 2-fold decrease in annual death rate compared to those dialysis patients who are healthy enough to be on the waiting list for transplantation and less than an 8-fold increase compared to the general population.
   e. None of the above.

5. Meier-Kriesche H-U, et al. reported a 4-fold increase in_____compared with those whose serum creatinine was <1.2 mg/dL in the first posttransplant year.
   a. CV death in transplant recipients with serum creatinine >2.5 mg/dL
   b. graft loss in transplant recipients with serum creatinine >2.5 mg/dL
   c. infection in transplant recipients with serum creatinine >2.5 mg/dL
   d. all-cause mortality in transplant recipients with serum creatinine >2.5 mg/dL
   e. none of the above.

6. The findings of Meier-Kriesche H-U, et al. with regard to infectious death in renal transplant recipients suggest that the risk of infectious death in transplant recipients:
   a. is not associated with renal insufficiency.
   b. is independent of immunosuppressive therapy.
   c. may require different approaches to immunosuppression based on patient renal function.
   d. is associated with lower risk of cardiovascular disease.
   e. may require different approaches to the use of ACE inhibitors and ARBs based on renal function.

7. Which of the following are independent risk factors for late posttransplant anemia?
   a. impaired renal function.
   b. use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in patients without posttransplantation erythrocytosis.
   c. use of mycophenolate mofetil.
   d. all of the above.
   e. none of the above.

8. In a study by Cosio, et al. graft loss was associated with hypertension:
   a. in Caucasians but not African-Americans.
   b. in African-Americans but not Caucasians.
   c. in both Caucasians and African-Americans but correlated more strongly for Caucasians.
   d. in both Caucasians and African-Americans who had at least 1 other CV risk factor.
   e. none of the above.

9. Advanced glycation end products (AGEs) are particularly attractive as a theoretical link between renal insufficiency and CVD because the accumulation of AGEs leads to:
   a. crosslinking of proteins in basement membranes.
   b. activation of macrophages.
   c. release of proinflammatory and pro-oxidant factors.
   d. all of the above.
   e. none of the above.

10. Plasma levels of AGEs return to normal levels within 3 months of kidney transplantation.
    a. True
    b. False

11. Renal insufficiency is a strong risk factor for long-term graft loss and patient mortality in renal transplant recipients.
    a. True
    b. False

12. Renal insufficiency has strong predictive value for graft loss and patient mortality in renal transplant recipients.
    a. True
    b. False

(Post-test answer key on next page)

Renal Function as a Predictor of Graft and Patient Survival

Post-test Answer Key

1. A B C D E	3. A B C D E	5. A B C D E	7. A B C D E	9. A B C D E	11. A B
2. A B C D E	4. A B C D E	6. A B C D E	8. A B C D E	10. A B	12. A B

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The University of Minnesota would appreciate your comments regarding the quality of the information presented.

1. The program objectives were fully met.

   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree

2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.

   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree

3. The educational activity has enhanced my professional effectiveness and improved my ability to treat/manage patients.

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5. The information presented was *without* promotional or commercial bias. ❑ Agree ❑ Disagree

6. What changes will you make in your practice as a result of participating in this program?

   _____

   _____

   _____

7. Comments/suggestions regarding *this* material.

   _____

   _____

   _____

8. Recommendations for *future* presentations.

   _____

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