

Cardiovascular Risk Factors in Cardiac Transplant Recipients

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Abstract

Over the last four decades, cardiac transplantation has become the preferred therapy for select patients with end-stage heart disease. Improvements in immunosuppression, donor procurement, surgical techniques, and post-transplant care have resulted in a substantial decrease in acute allograft rejection, which had previously significantly limited the survival of transplant recipients. Although current immunosuppressive therapies provide excellent protection from acute rejection, it is essential to understand the long-term consequences of these therapies, as well as the impact of conventional risk factors for heart disease. Risk factors for poor outcome post-transplantation can be divided into donor-specific characteristics, recipient-specific characteristics, and those risk factors that depend on interactions between the donor and recipient. Donor-specific risk factors for poor prognosis after heart transplantation include older donor age and longer ischemic time. Recipient-specific risk factors for poor outcome post-transplantation include increased recipient age, African American race, ischemic etiology of cardiomyopathy, hypertension, hypercholesterolemia, diabetes, renal insufficiency, the use of specific immunosuppressive regimens, elevated body mass index, tobacco use, obesity, and early post-transplant complications. Certain risk factors are specific to donor-recipient interactions, including the number of human leukocyte antigen mismatches, the presence of donor-specific antibodies post-transplantation, and cytomegalovirus mismatch status. A better understanding of these risk factors will allow providers to individualize therapy and optimize patient outcomes. (Trends in Transplant. 2008;2:135-47)

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Key words

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Introduction

Over the last four decades, cardiac transplantation has become the preferred therapy for select patients with end-stage heart disease. Improvements in immunosuppression, donor procurement, surgical techniques, and post-transplant care have resulted in a substantial decrease in acute allograft rejection, which had previously significantly limited survival of transplant recipients. According to the registry of the International Society for Heart and Lung Transplantation (ISHLT), the median survival of patients post-transplantation is currently 10 years, and up to 13 years for those surviving the first post-transplant year (Fig. 1)¹. In contrast, the major impediments to long-term allograft survival are the development of cardiac allograft vasculopathy (CAV) and malignancy. After five years, CAV and late graft failure (likely due to allograft vasculopathy) together account for 30% of deaths, followed by malignancies (22%) and non-cytomegalovirus (CMV) infections (10%)¹.

Although current immunosuppressive therapies provide excellent protection from acute rejection, it is essential to understand the long-term consequences of these therapies, as well as the impact of conventional risk factors for heart disease. Risk factors for poor outcome post-transplantation can be divided into donor-specific characteristics, recipient-specific characteristics, and those risk factors that depend on interactions between the donor and recipient (Table 1). The purpose of this review is to examine the current evidence for the role of these risk factors in the long-term prognosis of heart transplant recipients.

Donor-specific risk factors

Donor-specific risk factors for poor prognosis after heart transplantation include older donor age and longer ischemic time.

Donor age

The role of older donor age on the prognosis of heart transplant recipients is controversial. In the most recent report of the ISHLT registry, older donor age was a risk factor for one-year, five-year and ten-year mortality post-transplantation¹. In a multi-institutional analysis of over 7,000 cardiac transplant recipients over a period of 10 years, older donor age was a risk factor for fatal CAV². In another large, single-center study, older donor age was also associated with decreased survival³. However, programs that actively use older donor grafts have not seen a significant difference in overall survival, or the development of CAV when compared to recipients with younger allografts⁴. In these programs, highly selective donor and recipient matching may have resulted in the reported acceptable outcomes.

The main issue, however, is whether the difference in survival between older and younger recipients is clinically significant. In a recent analysis of the United Network for Organ Sharing (UNOS) database, heart transplant recipients 60 years and older had more infections (26 vs. 23%; $p < 0.001$), but had lower rates of rejection (34 vs. 43%; $p < 0.001$) as compared with recipients under 60 years of age. In addition, survival at five years was 75% for recipients under age 60 and 69% for patients age 60 or older. While this difference was statistically significant, it does not appear to be clinically significant⁵. Thus, in its listing criteria for heart transplantation, the ISHLT recommends that patients should be considered for cardiac transplantation if they are less than or equal to 70 years of age. Patients over 70 years of age who meet specific criteria may be considered for cardiac transplantation. For these patients, use of an alternate-type program (i.e. use of organs from older donors) should be pursued⁶.

Ischemic time

Data from the registry of the ISHLT indicate that the risk of primary graft failure and

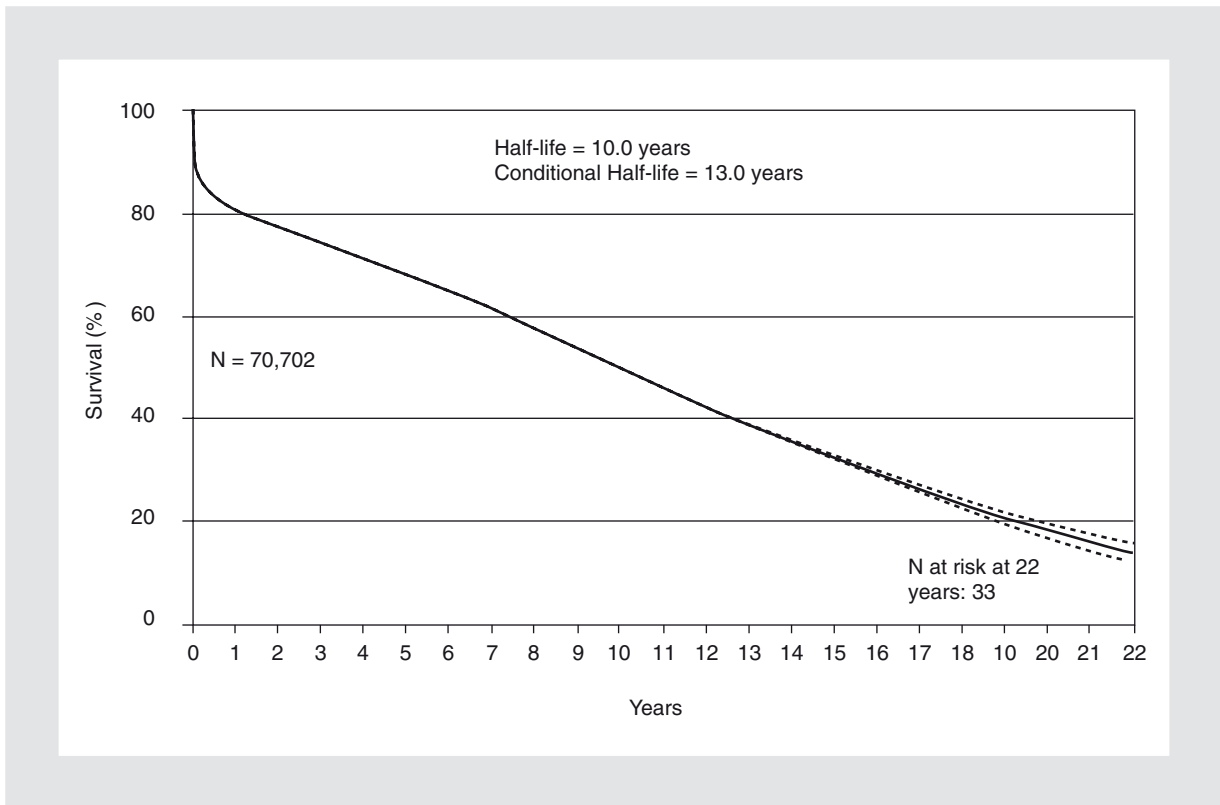


Figure 1. Kaplan-Meier survival data for adult and pediatric heart transplants performed between January 1982 and June 2005. Conditional half-life = time to 50% survival for those recipients surviving the first year post-transplantation. The transplant half-life (the time at which 50% of those transplanted remain alive, i.e. median survival) for the entire cohort of adult and pediatric heart recipients is currently 10 years, with a half-life of 13 years for those surviving the first year (reproduced with permission from Taylor, et al.¹).

Table 1. Risk factors for poor outcome post heart transplantation, divided into those that are donor-specific, recipient-specific, and those that rely on an interaction between donor and recipient factors

Donor-specific	Recipient-specific	Donor-recipient interactions
Increased donor age	Increased recipient age	HLA mismatches
Longer ischemic time	African American race	Anti-HLA antibodies
	Ischemic cardiomyopathy	CMV mismatch status
	Hypertension	
	Hypercholesterolemia	
	Diabetes mellitus	
	Renal insufficiency	
	Immunosuppressive agents	
	Tobacco use	
	Obesity	
	Early complications	

HLA: human leukocyte antigen; CMV: cytomegalovirus.

one-year mortality rises as ischemic time increases¹. Based on this, the maximum recommended ischemic time for the donor heart is six hours, and an ischemic time of over four hours is considered prolonged. However, several studies demonstrate varied effects of longer ischemic times on outcomes after heart transplantation⁷⁻¹⁰.

One study determined that donor ischemic time had no impact on overall survival, although longer ischemic time was associated with worse outcomes for donors over 50 years of age⁸. Another study demonstrated that even in young donors, longer ischemic time was associated with a need for longer postoperative inotropic support, and lower early ejection fraction, but no difference in right ventricular function at six months or survival at 12 months⁹. In further support of this, a recent retrospective review demonstrated that ischemic time over 300 minutes was not associated with increased 30-day mortality, but was associated with longer intensive care unit stay, increased incidence of primary graft failure, need for mechanical support, and complications such as acute renal failure¹⁰. Thus, the advantage of increasing the available donor pool by accepting donors with longer ischemic time must be weighed against the short-term increase in perioperative mortality and resource utilization in these patients.

Recipient-specific risk factors

Recipient-specific risk factors for poor outcome post-transplantation include increased recipient age, African American race, ischemic etiology of cardiomyopathy, hypertension, hypercholesterolemia, diabetes, renal insufficiency, the use of specific immunosuppressive regimens, tobacco use, obesity, and early complications post-transplantation.

Recipient age

Interestingly, the risk curve for recipient age on five-year mortality is U-shaped, with the

younger and older age groups having greater risk of five-year conditional mortality than the age group between 50 and 55 years (Fig. 2)¹. This is likely because younger recipients are more likely to have acute rejection, while older recipients suffer from greater comorbidities, including pulmonary and renal disease, as well higher risk for malignancy over time¹.

Race

There is evidence that racial disparity exists, with worse outcomes in African American transplant recipients in some studies, while others show no effect of race on post-transplant outcomes^{3,11,12}. In an analysis of over 7,000 cardiac transplant recipients, African American race was associated with an increased incidence of fatal allograft vasculopathy in a multivariate analysis². This was supported in a study of pediatric heart transplant recipients, where African American recipients had a lower five-year survival rate (51 vs. 69%) with a 1.7-fold increased risk of graft failure at five years¹³. These findings held true even after adjusting for indices of economic disparity, suggesting that immunologic variables may also play a role in this process, and in fact there was a greater number of HLA mismatches observed for African American heart transplant recipients.

Notably, a study of heart transplant recipients at Rush Medical Center demonstrated that compared with Caucasian recipients, African American recipients had more treated rejection episodes, more post-transplant hospitalizations, but no difference in five-year survival¹⁴. Race may also affect metabolism of immunosuppressive medications. It has been reported that African Americans have a lower trough level for tacrolimus compared to Caucasians and therefore require higher doses of these medications¹⁵. Thus, while immunologic factors might confer a worse prognosis to African American heart transplant recipients, it appears that specialized, comprehensive care may eliminate the racial disparity in outcomes after heart transplantation.

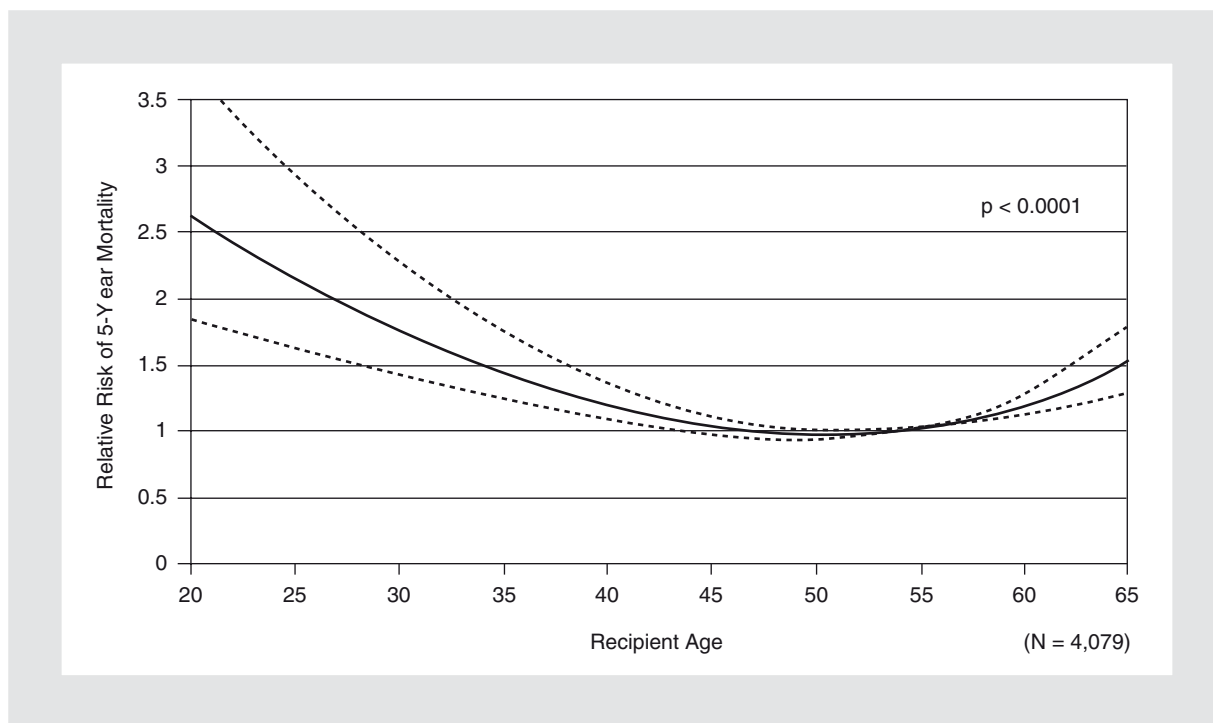


Figure 2. Effect of recipient age on the risk of five-year mortality (conditional on survival to one year) for recipients of heart transplants performed between January 1999 and June 2001. $n = 4,079$. The risk curve for recipient age is U-shaped, with the younger and older age groups having greater risk of five-year conditional mortality than the age group between 50 and 55 years. Dashed lines = 95% confidence limits (reproduced with permission from Taylor, et al.¹).

Etiology of cardiomyopathy

Ischemic pretransplant etiology is risk factor for poor outcomes post-transplantation. In the ISHLT registry, ischemic cardiomyopathy conferred a 13% increase in 10-year mortality and a 25% increase in 15-year mortality, although no effect was observed on one- and five-year survival¹. This is likely because ischemic cardiomyopathy is a risk for fatal allograft vasculopathy, a late complication of heart transplantation. This is supported by the findings of a retrospective study in over 7,000 heart transplant recipients, where ischemic cardiomyopathy was a risk factor for fatal CAV². Underlying this association, another study demonstrated that patients with ischemic cardiomyopathy pretransplantation are more likely to have other risk factors for poor outcomes, including hypertension and dyslipidemia, which could result in CAV¹⁶. Finally, atherosclerotic vascular disease would lead to more complications of stroke, vascular aneurysm rupture, and ischemia to vital organs.

Hypertension

There is a clear link between hypertension and conventional coronary atherosclerosis. Hypertension is also a common problem following cardiac transplantation, related in part to the use of corticosteroids, associated weight gain, and the use of calcineurin inhibitors, and in one study, has been associated with the development of CAV¹⁷. Furthermore, some studies indicate that treatment of hypertension may be beneficial in preventing the development or progression of CAV.

Patients randomized to diltiazem had a reduced incidence of angiographic CAV and death at five years¹⁸. Similarly, in 32 cardiac transplant recipients, intimal thickness at one year measured by intravascular ultrasound (IVUS) was significantly greater in the untreated control group than in those who received calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, or both¹⁹. In

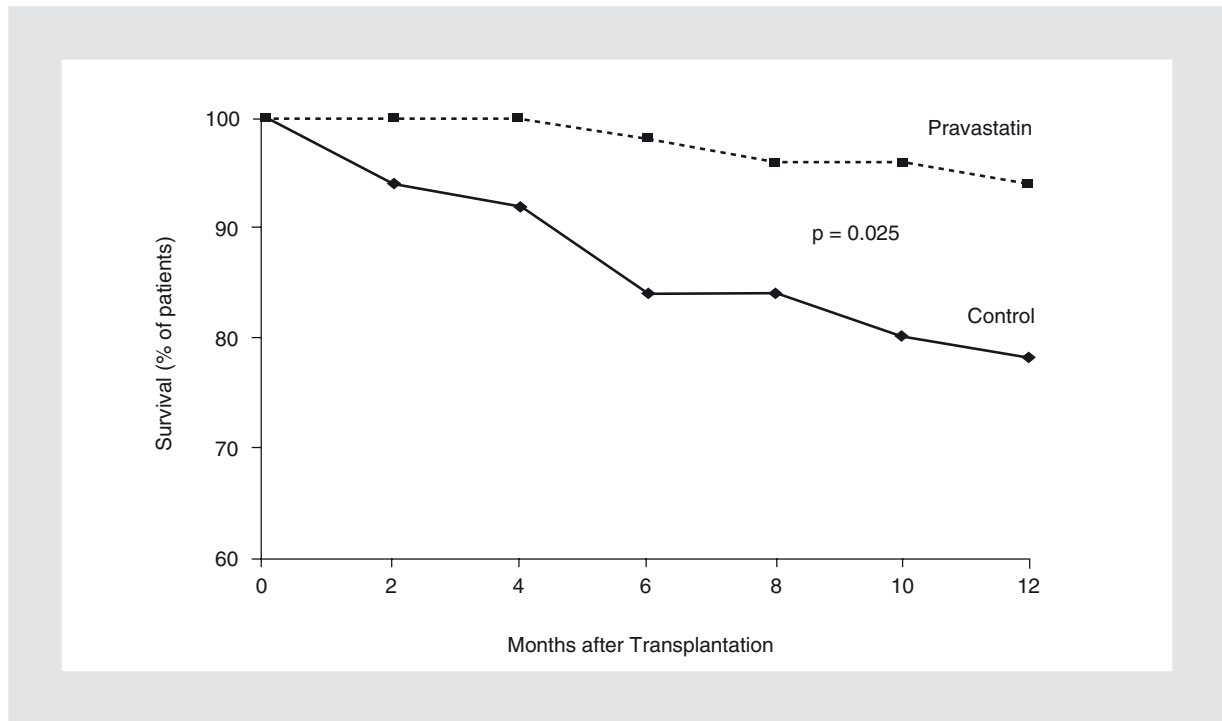


Figure 3. Survival during the first year after cardiac transplantation. One-year survival was significantly greater in the pravastatin group than in the control group (94 vs. 78%; $p = 0.025$) (reproduced with permission from Kobashigawa, et al.²³).

a more recent study, the combined use of these agents was more effective than either drug alone at reducing IVUS indices of CAV²⁰, and there is further evidence that use of ACE inhibitors or angiotensin receptor blockers results in improved outcomes¹². These results suggest that control of hypertension should be paramount in heart transplant recipients.

Hypercholesterolemia

In heart transplant recipients, hyperlipidemia at six months post-transplantation predicts the development of CAV at three years in one study²¹, and in another study, low-density lipoprotein elevation at one year post-transplantation was the only predictor for the development or progression of CAV by IVUS²². In addition, in a multicenter, retrospective analysis of heart transplant recipients, high total cholesterol was associated with an over four-fold increased incidence of nonfatal major cardiovascular events¹².

Notably, treatment initiated within two weeks of transplantation with hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors is associated not only with decreased development of coronary intimal thickening, but also a lower frequency of hemodynamically compromising rejection episodes and improved survival (Fig. 3)²³. These agents likely have an immunosuppressive effect in addition to their lipid-lowering activity. As hyperlipidemia is so common following transplantation, these findings suggest that all cardiac transplant recipients should receive HMG CoA reductase inhibitors.

Diabetes mellitus

Given that diabetes mellitus is a major cardiovascular risk factor leading to the development of end-stage heart disease, diabetes is common in patients pretransplantation. Furthermore, the use of steroids and tacrolimus post-transplantation may cause or worsen diabetes; up to 32% of heart transplant recipients are

diabetic by five years post-transplantation¹. However, the role of diabetes in post-transplant outcomes is not clear. Some studies show increased risk for infections, decreased survival and more CAV in diabetics, while other studies show no differences in outcome between diabetic and nondiabetic heart transplant recipients²⁴⁻²⁶.

In an analysis from the UNOS database of over 20,000 first-time heart transplant recipients, post-transplant survival among patients with uncomplicated diabetes was not significantly different than that among nondiabetics²⁷. However, when stratified by disease severity and pre-transplant diabetic complications, recipients with more severe diabetes had significantly worse survival and increased risk of CAV²⁷. In addition, in an analysis of the ISHLT registry, diabetes was associated with a 1.87-fold increased risk of one-year mortality and a 1.52-fold increased risk of five-year mortality¹. In a recent multicenter study, the presence of post-transplant diabetes was associated with an increased risk of nonfatal major adverse cardiac events¹² and, in another study, decreased survival³. Thus, similar to non-transplant patients, glucose control should be of paramount importance to possibly prevent post-transplant complications.

Renal insufficiency

Chronic renal failure after heart transplantation has been shown to predict left ventricular dysfunction, mortality, and nonfatal major adverse cardiac events post-transplantation^{12,28}, with the greatest risk observed in patients requiring dialysis¹². Pretransplant renal dysfunction may also predict the development of chronic renal impairment after heart transplantation, although this association is less clear^{29,30}. Other risk factors for the development of renal dysfunction after heart transplantation include older age, hyperlipidemia, and pretransplant diagnosis of ischemic cardiomyopathy^{28,31,32}, which are all themselves risk factors for poor

outcomes, suggesting a confounding effect. The worse outcome of patients with renal dysfunction emphasizes the importance of close follow-up and consideration of calcineurin inhibitor-free protocols³³⁻³⁵ or renal transplantation³⁶, as indicated, in these patients.

Immunosuppressive agents

The choice of immunosuppressive agent may affect heart transplant outcomes. Among calcineurin inhibitors, tacrolimus causes less hypertension, hyperlipidemia, and renal dysfunction than cyclosporine, with no difference in rejection, infection, or CAV^{37,38}. Mycophenolate mofetil (MMF), an inhibitor of the *de novo* pathway for purine biosynthesis, reduces rejection, allograft vasculopathy, and mortality compared with azathioprine³⁹⁻⁴¹.

Sirolimus, a member of the newest class of immunosuppressive agents, the proliferation signal inhibitors, also known as target of rapamycin (TOR) inhibitors, has also been shown to be superior to azathioprine, with a reduction in allograft rejection and the development of CAV⁴². However, in this randomized trial, no differences in one-year mortality were noted and sirolimus use was associated with a higher incidence of renal dysfunction and hypertension.

Similar promising results have been noted with everolimus, a related proliferation signal inhibitor. In a randomized, double-blind clinical trial comparing everolimus with azathioprine, patients receiving everolimus had a significant reduction in the primary efficacy endpoint, a composite of death, graft loss or retransplantation, loss to follow-up, biopsy proven acute rejection of ISHLT grade 3A or greater, or rejection with hemodynamic compromise. Furthermore, the progression of CAV, measured by IVUS at baseline (4-6 weeks after transplantation) and repeated at 12 months after transplantation, was significantly less in patients receiving everolimus. However, patients

receiving everolimus had a higher rate of bacterial infections and renal dysfunction⁴³.

The immunosuppressive regimens containing tacrolimus in combination with an anti-proliferative agent may offer the best long-term outcome. In a multicenter study, 343 *de novo* cardiac transplant recipients were randomized to receive one of three commonly used immunosuppressive regimens: tacrolimus plus sirolimus, tacrolimus plus MMF, or cyclosporine plus MMF, all in combination with corticosteroids⁴⁴. In the two tacrolimus groups compared to the cyclosporine group, there was a significantly lower frequency of any treated rejection in the first year after transplantation (Fig. 4). In addition, the tacrolimus plus MMF group compared to the other two groups had a significantly lower median level of serum creatinine and triglycerides. Rates of post-transplant diabetes were not significantly different among all three groups. From these data, tacrolimus plus MMF appears to offer more advantages than either tacrolimus plus sirolimus or cyclosporine plus MMF, including lower rates of rejections requiring treatment and a lower side-effect profile.

Tobacco use

Tobacco use is a risk factor for poor outcomes after heart transplantation in a number of studies. Many studies have focused on smoking pretransplantation, and shown an increase in the development of CAV¹⁷, fatal CAV², and increased mortality⁴⁵. However, even more importantly, ongoing smoking has also been shown to adversely affect outcomes. This is relevant, since studies indicate that approximately 33% of smokers resume cigarette use after transplantation⁴⁶⁻⁴⁸.

In one elegant study, 380 patients heart transplant recipients had urine cotinine levels covertly assessed (with ethical approval)⁴⁹. Of the 380 patients, 104 (27.4%) tested positive

for active smoking at some point post-transplantation, and 57 (15.0%) tested positive repeatedly. Smokers suffered significantly more deaths due to CAV (21.2 vs. 12.3%; $p < 0.05$), and due to malignancy (16.3 vs. 5.8%; $p < 0.001$). In a univariate analysis, smoking after heart transplantation shortened median survival from 16.28 years to 11.89 years (Fig. 5). After correcting for the effects of pretransplant smoking in time-dependent multivariate analysis, post-transplant smoking remained the most significant determinant of overall mortality ($p < 0.00001$). The authors concluded that tobacco smoking after cardiac transplantation significantly impacts survival by accelerating the development of graft vasculopathy and malignancy. These findings highlight the importance of ongoing smoking cessation counseling after transplant.

Obesity

Pretransplant obesity, as defined as body mass index (BMI), is associated with increased risk of death post-transplantation, both at 30 days and up to five years^{50,51}. In one study, the 30-day mortality was dramatically higher in obese patients (12 vs. 7.4%)⁵¹. These obese patients (BMI > 30 kg/m²) also demonstrated nearly twice the five-year mortality of patients with a BMI < 27 kg/m² (53 vs. 27%), with a shorter time to high-grade acute rejection as well as an increased annual high-grade rejection frequency when compared with normal-weight recipients ($p = 0.001$)⁵¹. In a multicenter study of 4,515 cardiac transplant patients, preoperative obesity ($> 140\%$ of ideal body weight) was associated with increased four-year mortality in males and a trend toward increased mortality in females⁵⁰. Obesity is also a risk factor for the development of CAV⁵² and post-transplant infections⁵⁰.

Finally, one study indicated that post-transplant obesity also confers worse outcomes, and patients having a BMI ≥ 33 kg/m² at any

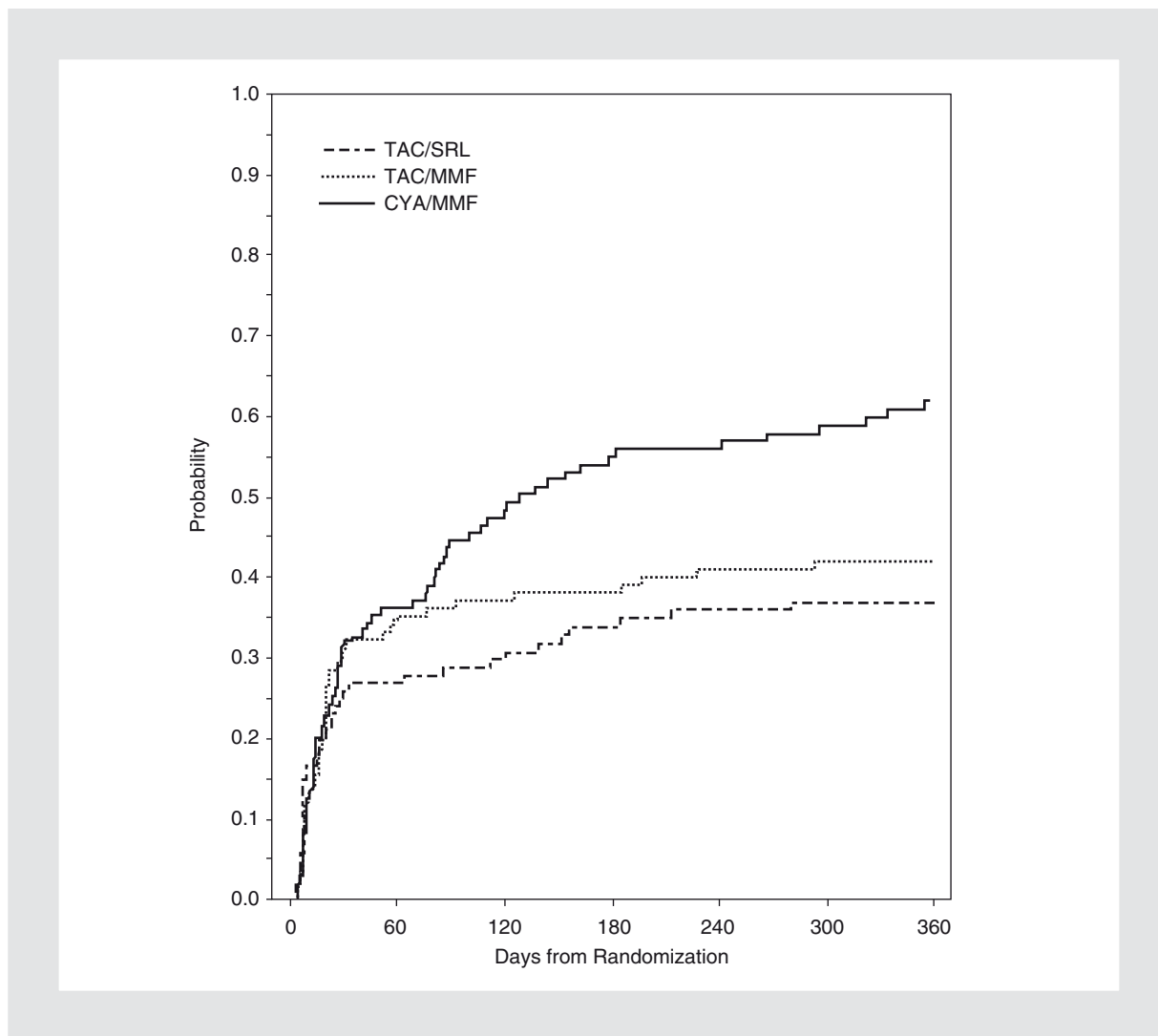


Figure 4. One-year incidence of any treated rejection was significantly lower in the tacrolimus groups (CYA/MMF = 59.6%, TAC/MMF = 42.1%, TAC/SRL = 35.1%, $p < 0.001$) (reproduced with permission from Kobashigawa, et al.⁴⁴). TAC: tacrolimus; SRL: sirolimus; MMF: mycophenolate mofetil; CYA: cyclosporin A.

time after transplantation had a trend towards increased risk of death¹². These studies form the basis for the ISHLT listing guidelines, which note that for obese patients, it is reasonable to recommend weight loss to achieve a BMI of $< 30 \text{ kg/m}^2$ or percentage ideal body weight $< 140\%$ of target before listing for cardiac transplantation⁶.

Early post-transplant course

The two major factors of early rejection and early infection impact the long-term survival of heart transplant recipients. Treated

rejection episodes, both early (prior to hospital discharge) and later (after discharge but during the first post-transplant year), were independently associated with a 48% increase in five-year mortality in an analysis by the ISHLT registry¹. The presence of treated infection episodes prior to hospital discharge was independently associated with a 37% increase in five-year mortality.

Supporting this observation, in a single-center study, 415 patients undergoing transplantation over a 15-year period were examined to determine factors associated with long-term

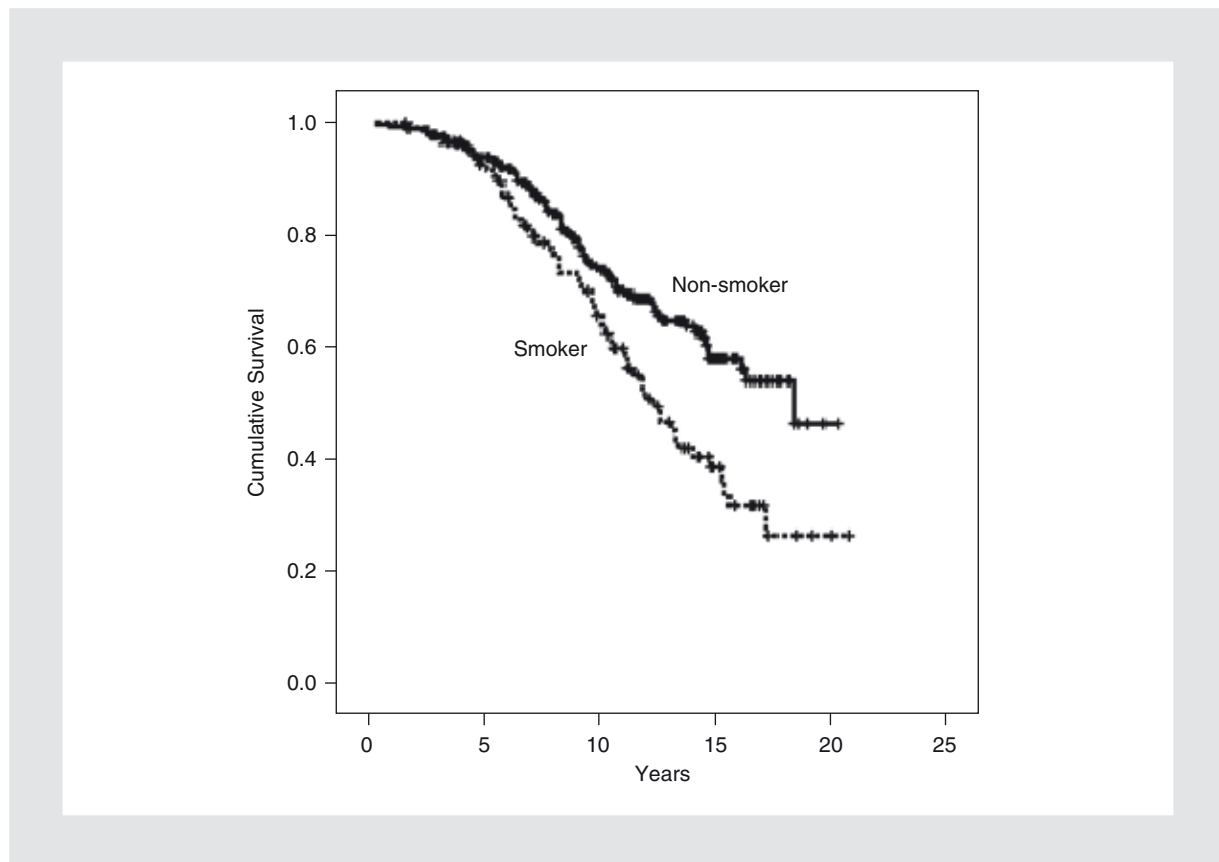


Figure 5. Kaplan-Meier curves demonstrating the impact of post-transplant smoking on survival. Cumulative survival in those with a single positive cotinine measurement was significantly poorer than that for nonsmokers post-transplantation (log-rank, $p = 0.0013$). Smoking post-transplantation significantly shortened median survival from 16.28 years (95% CI: 15.2-21.6) to 11.89 years (95% CI: 10.4-14.1) in univariate analysis (reproduced with permission from Botha, et al.⁴⁹).

survival³. The 158 patients who survived more than 10 years were compared with the 116 patients who died between two and six years. Long-term survivors had significantly fewer rejection episodes and viral, bacterial, fungal and total infections than did short-term survivors. In a multivariate analysis, fewer bacterial infections and rejection episodes were associated with longer survival. Thus, better control of infection and rejection during the first year after heart transplantation may improve survival, and closer monitoring of these patients for long-term complications may be warranted.

Donor-recipient interactions

Certain risk factors are specific to donor-recipient interactions, including the number of HLA mismatches, the presence of donor-

specific antibodies post-transplantation, and CMV mismatch status.

Number of human leukocyte antigen mismatches

The benefit of matching donor organs and recipients for HLA polymorphism has been well established in kidney transplantation, and sharing of kidneys based on good histocompatibility matching is now standard practice. However, because of poor preservation and short ischemic time tolerated by explanted hearts, HLA matching is rarely done in cardiac transplantation, and the extent of HLA mismatches has been associated with decreased survival post-transplantation. In the ISHLT registry, greater HLA matching (2-6 vs. 0-1 antigen matches) was associated with a 22%

reduction in five-year mortality¹. At 10 years, more mismatches at the HLA-DR and HLA-B loci were associated with worse survival, while at 15 years, more mismatches at the HLA-A locus were associated with worse survival¹.

These results are borne out in retrospective studies, which have also demonstrated a relationship between greater HLA mismatch and worse survival⁵³⁻⁵⁵, and other studies report correlation between greater HLA mismatch at the DR locus and rejection⁵⁶⁻⁵⁸. Retrospective analysis also suggests a correlation between the extent of HLA-DR mismatch and the subsequent development of CAV⁵⁹⁻⁶¹. While it is currently not feasible to perform HLA matching in heart transplant recipients, it is now standard practice at many centers to avoid HLA against which the recipient exhibits preformed cytotoxic antibodies⁶², since the development of HLA antibodies post-transplantation is also associated with worse outcomes, as discussed in the following section.

Development of anti-human leukocyte antigen antibodies

As would be expected, the development of HLA antibodies post-transplantation is associated with poor outcomes. This was demonstrated in a retrospective analysis of over 8,000 heart transplant recipients from the UNOS registry data⁶³. In this study, patients were divided into groups based on the percentage of panel reactive antibodies: 0, 1-10, 11-25, and over 25%. Increased levels of panel reactive antibodies were associated with increased rejection at one year, and decreased 30-day and one-year survival. This is supported by other studies^{64,65}, which have also demonstrated that the development of post-transplant HLA class II antibodies is associated with CAV⁶⁶.

More compelling that the development of nonspecific HLA antibodies demonstrated

by the panel reactive antibody screen would be the development of donor-specific HLA antibodies. In fact, in one study, the presence of donor-specific HLA antibodies, as determined with single HLA class I or class II beads, was associated with more frequent occurrence of acute rejection, development of CAV, and decreased survival⁶⁷. Recipients having antibodies only to HLA not in the transplant and those without any HLA antibodies had similar outcomes, suggesting that antibodies against antigens not present on the donor organ did not harm the graft. Thus, the results indicate that testing for donor-specific HLA antibodies may help in the management of heart transplant patients.

Interaction of donor and recipient cytomegalovirus status

Cytomegalovirus infection is a risk factor for poor outcome after heart transplantation. Evidence of prior CMV infection is a risk factor for CAV; evidence of prior CMV infection is more common in heart transplant recipients with CAV than in those without CAV⁶⁸.

Conclusion

In summary, there are multiple risk factors that can impact the long-term survival of heart transplant recipients, related to the donor, recipient, and donor-recipient interactions. Many of these risk factors are modifiable. For risk factors that are not modifiable, it nevertheless appears that careful monitoring and identification of risk factors may allow for prevention of future complications. Thus, an understanding of the risk factors in cardiac transplantation will allow for better prevention and earlier detection of post-transplant complications.

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