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ARTICLE

Prognostic Importance of Intimal Thickness as Measured by Intracoronary Ultrasound After Cardiac Transplantation

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ABSTRACT: *Background* Although intracoronary ultrasound (ICUS) has been validated for the early detection of transplant coronary artery disease (TxCAD), the prognostic importance of findings detected by this new imaging technique is unknown. *Methods and Results* This study examined the relation of clinical outcome in 145 heart transplant recipients (mean age, 45.1±11.1 years) with the amount of intimal thickness measured by ICUS during routine annual coronary angiography 1 to 10 years (mean, 3.1±2.2 years) after transplantation. From published autopsy data, a mean intimal thickness of >0.3 mm was considered significant. During a mean follow-up time of 48.2±10.2 months, 23 deaths (12 cardiac) occurred, and 6 patients required retransplantation. Angiographic TxCAD developed in 22 of 125 patients (17.6%) in the subgroup with normal angiograms at the time of ICUS and a follow-up annual angiographic study. In the total population and the subgroup, mean intimal

thicknesses of >0.3 and ≤0.3 mm, respectively, were associated with significantly inferior 4-year actuarial overall survival (73% versus 96%, *P*=.005; 72% versus 92%, *P*=.05), cardiac survival (79% versus 96%, *P*=.005; 80% versus 98%, *P*=.04), and freedom from cardiac death and retransplantation (74% versus 98%, *P*<.0001; 70% versus 96%, *P*=.001). In addition, ICUS predicted freedom from development of subsequent angiographic TxCAD in the subgroup that was initially normal (26% versus 72%, *P*=.02). A mean intimal thickness by ICUS of >0.3 mm was associated with inferior clinical outcome regardless of the presence of angiographic TxCAD and predicted the development of subsequent angiographic TxCAD. Despite significantly longer duration after transplantation, higher rejection incidence, and lower average daily cyclosporine dose, none of these covariates were independent risk factors for outcome. *Conclusions* These findings confirm the prognostic importance of mean intimal thickening of >0.3 mm in heart transplant recipients and suggest that these patients should be candidates for early interventional strategies.

Key Words: transplantation ■ ultrasonics ■ coronary disease ■ prognosis

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Accelerated coronary artery disease in the cardiac allograft (TxCAD) has become the leading cause of death beyond the first year after cardiac transplantation.[1] [2] [3] By 5 years after transplantation, up to 50% of recipients have angiographically evident TxCAD.[4] [5] [6] Coronary arteriography has been shown to be of value in predicting survival after cardiac transplantation.[7] [8]

However, it is well recognized that because of the predominantly concentric and longitudinal distribution of this disease,[9] visual assessment of coronary angiograms is a relatively insensitive method for its detection.[10] [11] Intracoronary ultrasound imaging (ICUS), on the other hand, has the ability to image the blood vessel in cross section and allows exact delineation of vessel wall morphology and quantification of intimal thickness.[12] [13] The diagnostic value, reproducibility, and safety of this new imaging modality have been established by our group[14] [15] [16] and others.[17] [18] However, the clinical application of ICUS has been poorly defined because the prognostic significance of coronary artery intimal thickening as measured by this method has not previously been reported for the transplanted or native heart.

Therefore, the primary objective of this study was to determine whether intimal thickness as measured by ICUS was of prognostic importance in predicting subsequent clinical outcome, including overall mortality, cardiac mortality, need for retransplantation, and development of angiographically visible TxCAD. A secondary objective was to assess whether ICUS provides prognostic information in the absence of angiographically visible TxCAD.

METHODS

Patients

The study population consisted of 145 adult heart transplant recipients (26 women, 119 men) with a mean age at transplantation of 45.1±11.1 years who consented to undergo ICUS during routine annual coronary angiography 1 to 10 years (mean, 3.1±2.2 years) after transplantation.

All patients were managed with standard immunosuppressive regimens, including prophylactic anti-lymphocyte antibody therapy during the early postoperative period and maintenance with prednisone, azathioprine, and cyclosporine. Episodes of moderate rejection according to the classification of the International Society for Heart and Lung Transplantation[19] were treated with increased doses of corticosteroids and, in refractory cases, rabbit anti-thymocyte globulin or OKT3.

Pretransplant and posttransplant clinical characteristics recorded for each patient included age at study, sex, and pretransplant diagnosis. Linearized rejection and infection rates were calculated for the first year after transplantation. Rejection episodes were counted as one event from onset to resolution as defined histologically. Infectious episodes were defined as episodes requiring hospitalization or intravenous antibiotic treatment. Actuarial rates of rejection and infection for the entire posttransplant course were determined.

The study protocol was approved by the Committee for the Protection of Human Subjects in Research at Stanford (Calif) University Medical Center, and written informed consent was obtained from all subjects before inclusion in the study.

Coronary Angiography

Coronary angiography was performed by the percutaneous femoral approach with standard angiographic techniques. After sublingual nitroglycerin premedication, multiple projections of the right and left coronary arteries were obtained. Arteriograms were assessed visually by two independent experienced angiographers who were not aware of the clinical or ICUS data. Quantitative techniques were not used, but serial cinefilms were compared side by side with reproductions of identical views on serial studies. Any luminal

stenosis or diffuse distal pruning was considered significant for the purpose of this study. Coronary angiography was repeated at annual intervals after transplantation unless clinically indicated to be needed more frequently.

Intracoronary Ultrasound Imaging

The procedure for ICUS image acquisition and analysis at this institution has been described previously in detail.[15] In brief, ICUS imaging was performed with a 5F or 4.3F 30-MHz ultrasound transducer (CVIS Inc). After completion of the coronary angiography and administration of 0.4 mg sublingual nitroglycerin, an 8F high-flow coronary guiding catheter with a 0.082-in internal diameter was positioned in the ostium of the left main coronary artery. The imaging system was then introduced into the left anterior descending coronary artery over a 0.014-in guide wire, and the ultrasound catheter was advanced to the midportion of the vessel, avoiding vessel segments <2 mm. Up to four distinct locations (mean, 3.2±1.0), separated by at least 1 cm, were selected for ultrasound measurements. These selected sites had a circular lumen, and vessel bifurcations and side branches were avoided. Ultrasound gain settings were adjusted for optimal visualization of the vessel-lumen interface. The studies were recorded on 0.5-in super VHS videotape for subsequent off-line analysis. Images were subsequently digitized onto a 512×512×8-bit matrix in 34-frame sequences obtained at 30 frames per second by an image processing computer (Dextra Medical Inc). The largest vessel lumen at end diastole was used for analysis. The lumen-vessel interface and, in the presence of intimal thickening, the external border of the intimal layer (intima-media interface) were traced by planimetry; this allowed calculation of mean intimal thickness. Measurements from all sites were averaged for each study. Intimal thickening of >0.3 mm was considered

significant on the basis of prior work from this laboratory[20] and autopsy observations in 164 unselected subjects 21 to 35 years old.[21] The range of intimal thickness in the coronary arteries of the latter population was 0.028 to 0.301 mm.[21]

Clinical Events

Clinical events recorded included death, retransplantation or listing for retransplantation, and development of TxCAD as assessed on subsequent annual follow-up angiograms. Causes of death and reasons for retransplantation were recorded. Cardiac death was defined as (1) sudden death from circulatory failure occurring within 1 hour of the onset of symptoms in the absence of rejection in a patient who had been clinically well, (2) death in the setting of an acute myocardial infarction, (3) death from congestive heart failure in the absence of rejection, or (4) death occurring within 3 months of retransplantation for TxCAD. Pathological findings at autopsy and on explanted hearts were reviewed when available. For the purpose of comparison, patients were categorized into groups on the basis of ICUS findings (intimal thickness of ≤0.3 versus >0.3 mm) and angiographic findings (any luminal stenosis or diffuse pruning of distal vessels versus normal angiogram). An intimal thickness of >0.3 mm was selected as the threshold for abnormality in this study on the basis of published autopsy data.[21] The presence of any angiographic disease was selected as the angiographic threshold for abnormality on the basis of the following rationale: recognized underestimation of TxCAD by angiography[10] [11] and previously reported prognostic impact of angiographically “minor” TxCAD lesions.[8] To test the hypothesis that intimal thickness in the presence of a normal angiogram predicts the outcome and development of subsequent angiographic disease, the subgroup of patients with normal angiograms at ICUS study was analyzed separately.

Patients were followed from the time of the ICUS studies performed between July 1990 and August 1993 until April 1995 or death for a mean follow-up of 48.2±10.3 months. No patient was lost to follow-up.

Statistical Analysis

Results are presented as mean±SEM or relative risk (95% CI) for actuarial and as mean±SD for all clinical data. The relation of ICUS and coronary angiography findings at baseline with outcome variables was examined by Kaplan-Meier[22] procedures to contrast absolute survival differences and by a log-rank (Mantel-Haenszel) test to assess for equality of survival curves.[23] Cox proportional-hazards methods were used to calculate relative risks (95% CI) for selected outcome variables with sufficient numbers of events.[24] The outcome variables tested were overall survival, cardiac survival, cardiac survival and/or freedom from retransplantation for cardiac causes, and freedom from development of subsequent angiographic TxCAD, the latter in the subgroup of patients with normal angiograms at the time of ICUS. Differences between groups in characteristics at baseline were assessed with χ^2 tests for categorical variables and two-tailed *t* tests for continuous variables. Linearized rejection and infection rates were quantified in 3-month intervals as episodes per 100 patient-days to account for the differences in numbers of patients in the groups. Comparisons were then performed between groups by use of a *z* statistic for rates and proportions. A value of $P \leq .05$ was considered statistically significant.

To address the question of the difference in duration after transplantation in patients with intimal thickness of ≥0.3 versus <0.3 mm, three different approaches were used. First, a time-shift correction of the outcome data was performed. The probability of freedom from angiographic TxCAD on follow-up in the group with

intimal thickening of ≤0.3 mm was time-shifted for duration after transplantation by multiplying each of the data points by the ratio of the mean duration after transplantation in the two groups (3.9/2.8). The difference in the event-free probability between the two groups was then compared by a log-rank (Mantel-Haenszel) test.

Second, the relative risk for overall mortality and development of angiographically visible TxCAD was calculated with the duration after transplantation as a covariate in the Cox proportional-hazards analysis. Both the total group and the subset of 126 patients who had normal coronary arteriograms at baseline were analyzed in this fashion.

The third analysis performed used the Cox proportional-hazards model to determine the relative risk of developing angiographic CAD in two subsets of patients whose ICUS studies were performed 1 and 2 years after transplantation. For each group separately, the relative risk in patients with intimal thickness of ≤0.3 versus >0.3 mm was compared. Because the numbers of patients and events were small in each group, the relative risk for subsequent angiographic disease in patients with intimal thickening measured 1 or 2 years after transplantation was determined.

To address the issue of how pertinent clinical factors, including infection, may be related to TxCAD and potentially affect survival, we compared the following end points in patients with intimal thickening of >0.3 versus ≤0.3 mm: (1) linearized infection rates during the initial year after transplantation with Student's *t* test; (2) actuarial infection rates and death from infection with the Cox-Mantel test; and (3) levels of immunosuppression that predispose to infection—such as total pulsed and maintenance corticosteroid doses, cyclosporine dose, and rejection incidence—with ANOVA. Statistical significance was defined as $P \leq .05$.

RESULTS

Baseline Clinical, Angiographic, and ICUS Characteristics

Table 1 gives the baseline characteristics of the study patients. Patients with an intimal thickness of >0.3 mm (n=47) were studied significantly later after transplantation compared with patients with an intimal thickness of ≤0.3 mm (n=98; 3.9±2.4 versus 2.8±2.0 years, *P*=.004) and had a higher rejection incidence during the initial 3 months after transplantation. Otherwise, there were no significant differences in clinical characteristics at baseline between the groups. Angiographic evidence of TxCAD was present in 19 patients (13%) at the time of ICUS.

Prognostic Impact of ICUS and Angiography

Intimal thickness as measured by ICUS but not angiographic evidence of TxCAD, duration after transplantation, or rejection incidence significantly predicted overall survival. Both methods were significant predictors of the other outcome variables, which included cardiac survival and freedom from cardiac death and/or retransplantation.

In the total population, intimal thickness of >0.3 versus ≤0.3 mm and the presence of any angiographic disease versus no angiographic disease were associated with overall actuarial 4-year survival rates of 73±7% versus 96±2% (*P*=.005) and 72±12% versus 92±3% (*P*=.05), cardiac survival rates of 79±5% versus 96% (*P*=.005) and 80±10% versus 98±1% (*P*=.04), and freedom from cardiac death and retransplantation of 74±7% versus 98% (*P*<.0001) and 70±11% versus 96±2% (*P*<.0001), respectively (Fig 1).

In the subgroup of patients with normal angiograms at the time of ICUS (n=126), an intimal thickness of >0.3 mm was associated with

decreased overall actuarial 4-year survival (72±8% versus 96±3%, *P*=.03), cardiac survival (89±5% versus 98%, *P*=.01), and freedom from cardiac death and retransplantation (80±7% versus 98%, *P*=.002). In addition, intimal thickness of >0.3 versus ≤0.3 mm in this subgroup predicted freedom from development of subsequent TxCAD (26±14% versus 72±11%, *P*=.02), as Fig 2 shows.

Because of the significant difference in duration after transplantation between patients with intimal thickening of >0.3 versus ≤0.3 mm, the probability of freedom from angiographically visible TxCAD was time-shifted for the group with intimal thickness of ≤0.3 mm. With this time-shift correction, the probability of freedom from angiographic TxCAD in patients with intimal thickness of ≤0.3 mm remained significantly higher (26±16% versus 73±12%, *P*<.0001) over the 4-year follow-up (Fig 3).

Table 2 gives the relative risks (95% CI) of death from any cause in the total population. An intimal thickness of >0.3 versus ≤0.3 mm but not the presence of angiographically visible TxCAD or duration after transplantation was associated with a significantly higher relative risk of death from any cause.

Table 3 gives the relative risks of death from any cause and of development of TxCAD in the subset of patients with normal angiograms at the time of ICUS. An intimal thickness of >0.3 versus ≤0.3 mm but not duration after transplantation predicted death and the development of angiographic disease.

To further address the issue of variable duration after transplantation at the time of ICUS study, the risk for subsequent development of angiographically visible TxCAD was determined in subsets of patients whose ICUS studies were performed at 1 and 2 years after transplantation. For each group separately, we examined the risk of mortality and subsequent angiographic disease

associated with intimal thickening of >0.3 mm. The relative risk of angiographic TxCAD associated with intimal thickening of >0.3 mm measured 1 year after transplantation was 2.8 (95% CI, 1.4 to 7.8) and thus similar to that of the whole group. However, this relative risk was not statistically significant (*P*<.09) owing to sample size (total n=48, events=4). Similarly, the relative risk associated with intimal thickening measured 2 years after transplantation was 2.5 (95% CI, 1.3 to 7.9) and was not statistically significant (*P*<.1) because of the small sample (total n=17, events=3). However, when patients studied 1 and 2 years after transplantation were combined (total n=65, events=7), the relative risk of subsequent angiographically visible TxCAD associated with intimal thickening of >0.3 mm was 4.9 (95% CI, 1.0 to 24.5; *P*<.05). Likewise, the relative risk for mortality of intimal thickening of >0.3 mm 1 or 2 years after transplantation was 4.6 (95% CI, 1.3 to 15.5; *P*<.05).

To address the issue of how infection might be related to TxCAD, we performed an analysis to determine whether a significant relation existed between intimal thickening and rejection incidence; actuarial infection rates; and levels of immunosuppression that predispose to infection, such as total pulsed corticosteroid dose or maintenance daily doses of corticosteroids, cyclosporine, and azathioprine. Linearized infection rates during the first year after transplant were similar in the two groups. Actuarial combined infection (viral, bacterial, and fungal) showed a trend toward higher rates (event-free probability at 5 years after transplantation, 14%) in patients with intimal thickening of >0.3 mm; however, the differences were not statistically significant compared with patients with intimal thickening of ≤0.3 mm (event-free probability at 5 years after transplantation, 18%). Likewise, the differences in individual infection rates (viral, bacterial, or fungal) were not statistically significant between the two

groups. Actuarial death rates from infection did not differ in patients with intimal thickness of >0.3 compared with ≤0.3 mm (event-free probability at 5 years after transplant, 80±9.6% versus 83±9.5%).

Fig 4 compares the actuarial rejection rates in patients with intimal thickening of >0.3 versus ≤0.3 mm. The probabilities of freedom from rejection were lower and linearized rejection rates (Table 1) were higher in patients with intimal thickening of >0.3 mm. This was paralleled by higher total pulsed corticosteroid dose (used for treatment of acute rejection) in patients with intimal thickening of >0.3 mm (8050±250 versus 5400±600 mg, $P \leq .05$); however, the average daily maintenance corticosteroid dose was similar in the two groups (0.20±0.01 versus 21±0.02 mg/kg). This was also true for maintenance doses assessed at 3-month intervals. In contrast, average daily maintenance cyclosporine dose was lower in patients with intimal thickening of >0.3 mm (3.33±0.24 versus 4.21±0.21 mg/kg, $P < .05$), and the difference was statistically significant beginning 18 months after transplantation (Fig 4).

Clinical Events

During a follow-up period of 48.2±10.3 months, 23 deaths (16%) occurred. Table 4 lists the causes of death: TxCAD was the leading cause of death (54%), followed by malignancies (23%) and infection (18%). In patients with intimal thickening of >0.3 mm, TxCAD accounted for 84% of deaths, whereas none of the deaths in the group with intimal thickening of <0.3 mm were due to TxCAD. Of the total study population (n=145), 6 patients (4%) required retransplantation. Reasons for retransplantation were TxCAD in 4 patients (67%), all of whom had intimal thickness of >0.3 mm, and unexplained allograft failure in 2 patients (33%) who also had intimal thickness of >0.3 mm. Examination of these 2 explanted hearts revealed diffuse intimal proliferation in all major epicardial vessels. In

the 2 patients with intimal thickening ≤0.3 mm, the cause of death was acute rejection, confirmed at autopsy. In the remaining patients, malignancy and infection accounted for 5 and 4 deaths, respectively. A repeated coronary angiogram obtained after a mean follow-up time of 48.2±10.3 months in 125 of 126 patients (99%) with normal angiograms at the time of ICUS revealed new TxCAD in 22 patients (17.6%).

DISCUSSION

This study, for the first time, provides evidence of the prognostic importance of ICUS measurement of intimal thickness. An intimal thickness of >0.3 mm was associated with significantly inferior survival and increased cardiac events, regardless of the presence of angiographic disease. Furthermore, ICUS predicted the development of subsequent angiographic TxCAD in this population after cardiac transplantation. Although patients with an intimal thickness of >0.3 mm had higher rejection incidence and lower cyclosporine average daily dose and were of longer duration after transplantation, none of these three confounding variables were significant predictors of outcome as determined from the Cox proportional-hazards analysis. The findings of higher rejection incidence and longer duration after transplantation in patients with intimal thickening are consistent with previous reports.[25]

In earlier work, Uretsky et al[8] reported a significant increased relative risk for cardiac events and cardiac mortality in patients with any angiographic evidence of TxCAD during follow-up. In a study from our institution,[7] the presence of angiographic luminal stenosis of ≥40% was associated with a 2-year survival rate of only 50%. Survival was directly related to disease severity, with the poorest outcome in patients with ≥70% stenosis or three-vessel involvement.

TxCAD is characterized pathologically as diffuse concentric and longitudinal fibrous intimal thickening; focal intimal plaques indistinguishable from nontransplant atherosclerosis also occur.[9] Accordingly, by angiography, the disease appears predominantly as diffuse, concentric narrowing of epicardial coronary arteries with pruning of distal vessels and lack of collateral vessels.[10] This explains the relatively low sensitivity of visual assessment of coronary arteriograms for TxCAD; angiography relies on the assumption that the adjacent vessel caliber is normal and therefore underestimates disease severity, as demonstrated by pathology-angiography correlation studies.[11] ICUS has been shown to be more sensitive than qualitative angiography in detecting TxCAD[15 17 18] and is considered to be the method of choice to detect early changes of TxCAD. We hypothesized that ICUS might provide prognostic information beyond that obtained from coronary angiography and might predict outcome in the absence of angiographically visible TxCAD.

In the present study, both ICUS and angiography significantly predicted cardiac survival and freedom from cardiac death and retransplantation, but only ICUS findings correlated significantly with overall survival. This is in accordance with the angiographic results obtained by Uretsky et al,[8] who defined TxCAD in a manner similar to that used in the present analysis. In our earlier report demonstrating a correlation of angiographic TxCAD with overall survival,[7] patients were included in the study if they had ≥40% angiographic coronary luminal stenosis. The angiographic definition for significant TxCAD in the present study (eg, any evidence of the disease) was chosen to allow comparison with ICUS findings. An ICUS intimal thickness of >0.3 mm was considered significant on the basis of pathological observations[21] and prior studies from this

laboratory.[20] The reasons for the association of intimal thickness with overall mortality can be explained by the high prevalence of death from TxCAD in patients with intimal thickness of >0.3 mm (Table 4). At the 4-year follow-up, the primary cause of death was TxCAD; in the subset of patients with intimal thickness of >0.3 mm, it accounted for 80% of deaths. It is interesting to note that infection, including cytomegalovirus, did not predict TxCAD or outcome in this study, despite previous observations.[25] This difference from prior studies probably is due to changes in treatment and prophylaxis for cytomegalovirus. Also of note is the fact that despite a higher rejection incidence during the initial 3 months after transplantation, rejection did not independently predict risk of outcome. The relative contribution of rejection per se versus the high doses of corticosteroids used for its treatment warrants further investigation. Likewise, the observations that rejection incidence was higher and cyclosporine doses were lower in patients with intimal thickening of >0.3 mm suggest that inadequate suppression of the alloimmune response might play an important role in the pathophysiology of TxCAD.

ICUS findings predicted clinical outcome even in patients with normal angiograms at the time of ICUS. The excellent 4-year survival of patients with an intimal thickness of ≤0.3 mm in this subgroup and the ability of coronary artery intimal thickness measured 1 or 2 years after transplantation to predict the risk of subsequent angiographic TxCAD suggest that ICUS may have important practical applications. For example, routine annual coronary angiography could be delayed safely in patients with an intimal thickness of ≤0.3 mm. In contrast, patients with intimal thickening of >0.3 mm 1 or 2 years after transplantation are at risk for subsequent angiographic disease and warrant closer follow-up to

assess disease progression. This approach to monitoring disease should be coupled with aggressive risk factor reduction. Thus, patients with intimal thickening of >0.3 mm are prime candidates for intervention strategies to slow the progression of TxCAD. From our observations, this management should include treatment of dyslipidemia, including hypertriglyceridemia and obesity. It should be pointed out that even in patients with intimal thickening of <0.3 mm, a small proportion subsequently developed angiographic disease. This emphasizes that further studies are required to fully characterize the limitations of ICUS and to determine the characteristics of patients whose disease progresses at a rapid rate.

Study Limitations

Several limitations apply to this study. First, the population represented a selected group of long-term survivors rather than a consecutive series of transplant patients. We are currently embarked on a progression study that will measure intimal thickening at baseline, and serially thereafter, to clearly define the rate of progression and the prognostic implications of this index of TxCAD. Second, the range of times after transplantation when the ICUS study was performed in the study population was wide. Because ICUS was introduced into clinical use only in the late 1980s, results in a large consecutive series of patients studied at baseline and serially after transplantation will not be available for several years. We have addressed this limitation using three different approaches, all of which support the prognostic importance of ICUS measurements of intimal thickening in heart transplant patients. Third, as a consequence of study design, the data from this study provide no information regarding onset or rate of progression of intimal thickening. This limitation is important because it relates to

potential bias in the selection of patients who have survived long enough to have ICUS. Clearly, prospective evaluation of all patients, beginning with baseline studies during the early posttransplant period and continuing with serial annual follow-up, is required to accurately describe the time course of intimal thickening in heart transplant recipients. However, given the experimental nature of this procedure and the associated cost, it is extremely difficult to obtain a consecutive series of patients. In an attempt to address this issue within the current cohort of patients, we obtained data from the subset of patients who were studied at 1 year (n=38) and subsequently at annual intervals during the follow-up period of 4 years. Patients whose rate of progression between 1 and 2 years was >0.2 mm had a greater probability of angiographic disease in the subsequent year (data not presented; they are part of a prospective study). Fourth, only the proximal two thirds of the left anterior descending artery was examined in this study, and the reported measurements of intimal thickness represent the disease process in only a limited number of coronary sites in each patient. However, given the predominantly diffuse nature of TxCAD,[26] measurements from one artery probably reflect the overall extent of the disease. Finally, we did not correlate ICUS findings with results of quantitative coronary angiography. This was not the purpose of this study, and we have previously shown that this method correlates closely with ICUS measurements.[14] The prognostic importance of quantitative coronary angiography findings after transplantation remains to be defined.

Conclusions

Intimal thickness as measured by ICUS is of prognostic importance in patients after cardiac transplantation, as demonstrated for the first time by these results. Even in the absence of angiographically visible

TxCAD, ICUS predicted clinical events and the development of subsequent angiographic TxCAD. These data suggest that in patients with intimal thickness of >0.3 mm, early intervention strategies are warranted to slow the progression of TxCAD. Because we previously reported hypertriglyceridemia and obesity to be independent risk factors for coronary artery intimal thickening in the transplanted heart, it would be important to target these abnormalities. In patients with an intimal thickness of ≤0.3 mm, routine annual coronary angiography may be safely delayed because this finding was associated with an excellent cardiac prognosis and slow progression of TxCAD over a 3-year follow-up period.

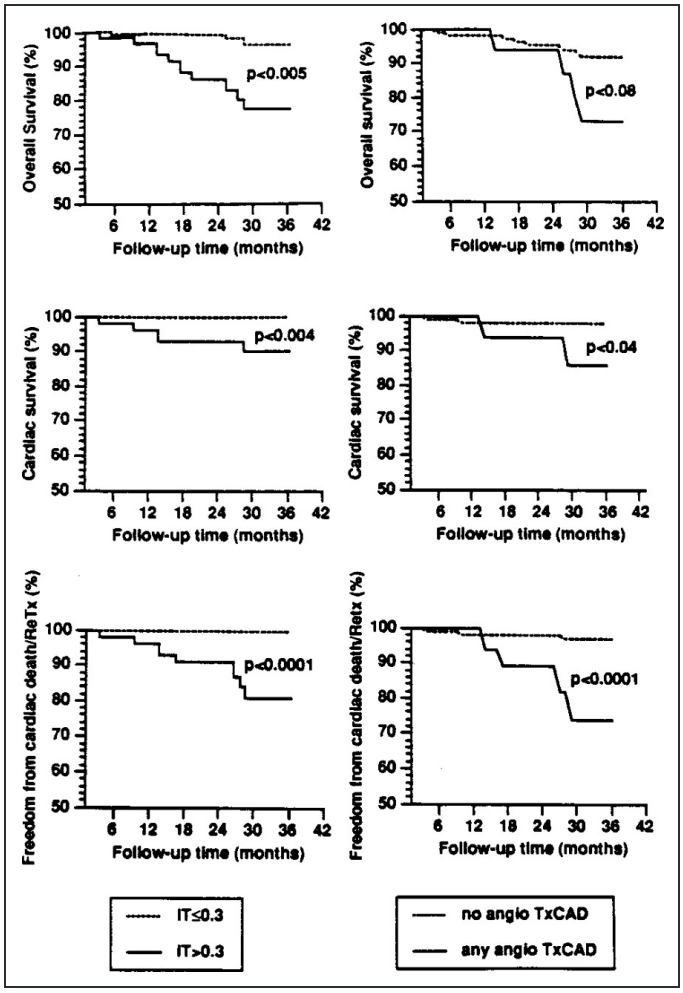

Figure 1. Plots showing overall survival, cardiac survival, and freedom from cardiac death and retransplantation in the total population according to intimal thickness (IT; >0.3 vs ≤0.3 mm) and any angiographic luminal stenosis or distal pruning vs no disease. TxCAD indicates transplant coronary artery disease; ReTx, retransplantation.

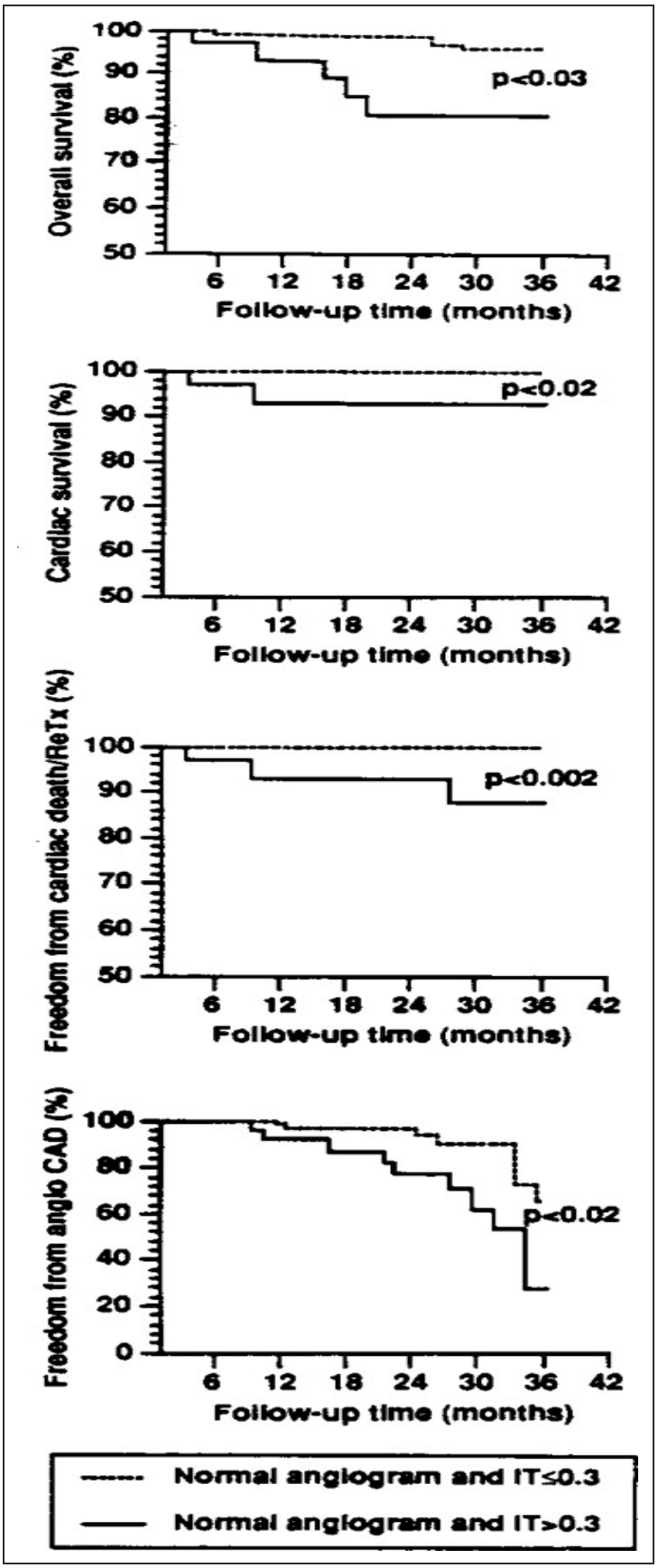
Overall survival (%)
100
90
80
70
60
50
p<0.03
6 12 18 24 30 36 42
Follow-up time (months)
Cardiac survival (%)
p<0.02
Freedom from cardiac death/ReTx (%)
p<0.002
Freedom from anglo CAD (%)
0
20
40
p<0.02
Normal angiogram and IT≤0.3
Normal angiogram and IT>0.3

Figure 2. Plots showing overall survival, cardiac survival, freedom from cardiac death and retransplantation (ReTx), and freedom from development of subsequent angiographic coronary artery disease (angio CAD) in the subgroup with a normal angiogram at the time of intracoronary ultrasound according to intimal thickness (IT; >0.3 vs ≤0.3 mm).

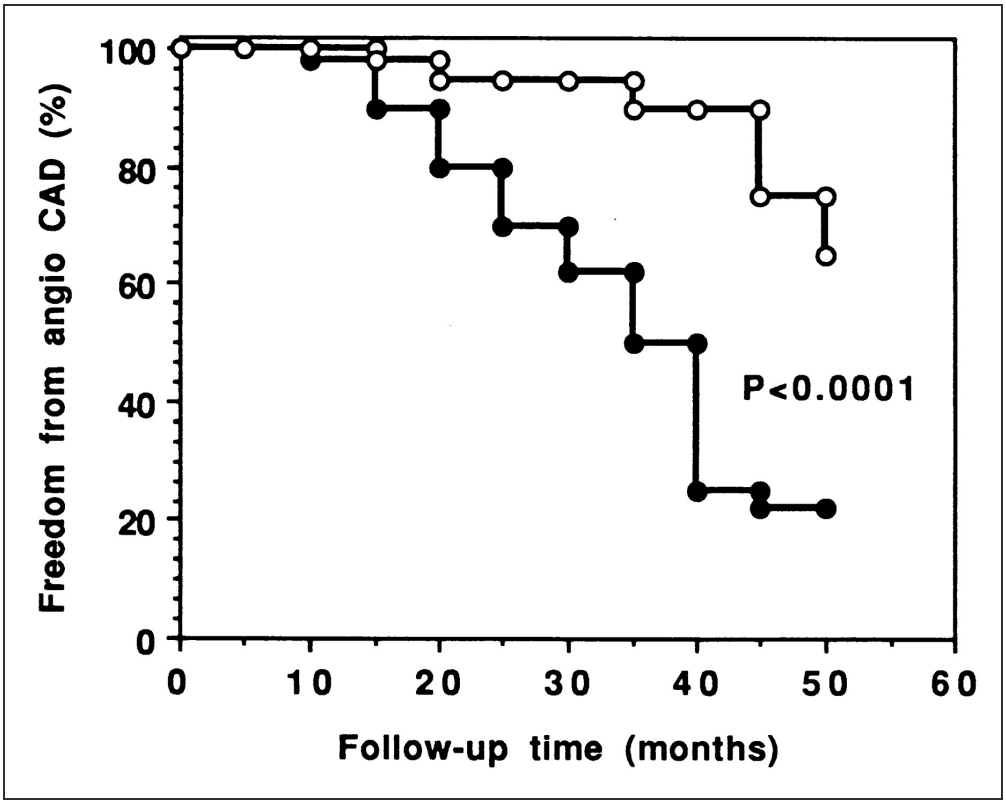

Figure 3. Plot showing freedom from development of subsequent angiographic coronary artery disease (angio CAD) in the subgroup of patients with normal angiograms at the time of intracoronary ultrasound according to intimal thickness of >0.3 vs ≤0.3 mm. In this analysis, the curve for the patient with intimal thickness of ≤0.3 mm has been time-shifted by multiplying each data point by the ratio of a mean duration after transplantation in the two groups, ie, 3.9/2.8 years. ○ indicates normal angiogram and intimal thickness ≤0.3 mm; •, normal angiogram and intimal thickness >0.3 mm.

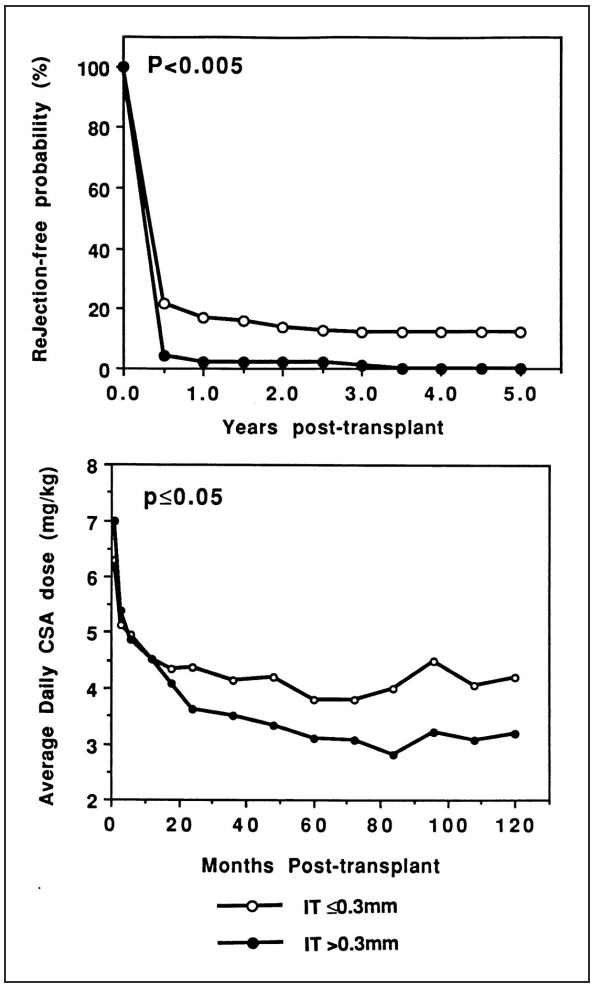

Figure 4. Plots showing actuarial rejection rates in patients with intimal thickness (IT) of ≤0.3 vs >0.3 mm (top) and average daily cyclosporine (CSA) doses in patients with intimal thickness of ≤0.3 vs >0.3 mm (bottom).

Table 1. Baseline Clinical, ICUS, and Angiographic Characteristics (Table view)

	All Patients (n=145)	IT >0.3 mm (n=47)	IT ≤0.3 mm (n=98)
Clinical characteristics			
Age at transplantation, y	45.1±11.1	45.2±9.6	45.0±11.8
Female sex, n (%)	26 (18)	6 (13)	20 (20)
Pretransplant diagnosis, %			
Coronary artery disease, n (%)	73 (50)	22 (47)	51 (52)
Dilated cardiomyopathy, n (%)	68 (47)	25 (53)	43 (44)
Other, n (%)	4 (3)	0 (0)	4 (4)

	All Patients (n=145)	IT >0.3 mm (n=47)	IT ≤0.3 mm (n=98)
Linearized rejection rates			
<3 months	1.30±0.10	1.59±0.19[3]	1.17 ±0.11
3-<6 months	0.47±0.06	0.44±0.10	0.48 ±0.07
6-<12 months	0.41±0.08	0.37±0.13	0.43 ±0.10
Linearized infection rates			
<3 months	0.85±0.08	0.82±0.14	0.86±0.10
3-<6 months	0.22±0.04	0.16±0.06	0.25±0.05
6-<12 months	0.20±0.05	0.14±0.06	0.22±0.04
Age at study, y	48.6±10.6	49.6±9.1	48.1±11.3
Years after transplantation	3.1±2.2	3.9±2.4[2]	2.8±2.0
ICUS characteristics			
Number of sites studied	3.2±1.0	3.1±1.0	3.2±1.0
Mean intimal thickness, mm	0.24 ±0.20	0.47±0.17[1]	0.13±0.10
Angiographic characteristics			
Any evidence of TxCAD, n (%)	19 (13)	17 (36)[1]	2 (2)

ICUS indicates intracoronary ultrasound; IT, intimal thickness as measured by ICUS; and TxCAD, transplant coronary artery disease. Data are expressed as mean±SD when appropriate.

[1] *P*<.0001.

[2] *P*=.004.

[3] *P*=.05.

Table 2. Relative Risks of Overall Mortality Associated With ICUS, Angiographic Findings, and Duration After Transplant in the Total Population (Table view)

Overall Mortality	Relative Risk	95% CI	*P*
ICUS: intimal thickness >0.3 vs ≤0.3 mm	4.7	1.3-14.7	.01
Angio: any vs no TxCAD	2.8	0.8-8.8	.09
Duration after transplant at ICUS study	1.07	0.9-8.1	.5

Abbreviations as in Table 1.

Table 3. Relative Risks of Overall Mortality and Developing Angiographic TxCAD Associated With ICUS Findings in the Subgroup With Normal Angiograms at the Time of ICUS (Table view)

	Relative Risk	95% CI	*P*

	Relative Risk	95% CI	*P*
Overall mortality			
ICUS: intimal thickness >0.3 vs ≤0.3 mm	4.0	0.8-14.1	.04
Duration posttransplant at ICUS study	1.1	0.8-9.3	.56
Development of angiographic TxCAD			
ICUS: intimal thickness >0.3 vs ≤0.3 mm	3.0	1.2-8.1	.02
Duration after transplant at ICUS study	0.97	0.7-8.5	.8

Abbreviations as in Table 1.

Table 4. Causes of Death (Table view)

	All Patients (n=23, 16%)	IT >0.3 mm (n=13, 28%)	IT ≤0.3 mm (n=10, 10%)
TxCAD	10 (54.5)	10 (84)	0 (0)
Infection	4 (18)	2 (8)	3 (30)
Rejection	0 (0)	0 (0)	2 (20)
Malignancy (lymphoid and nonlymphoid)	5 (23)	1 (8)	4 (40)
Unknown	1 (4.5)	0 (0)	1 (10)

IT indicates intimal thickening; TxCAD, transplant coronary artery disease. Data are expressed as number of patients (%). Cardiac deaths include deaths resulting from complications of retransplantation for TxCAD, occurring within 3 months of the procedure.

ARTICLE INFORMATION

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Sections

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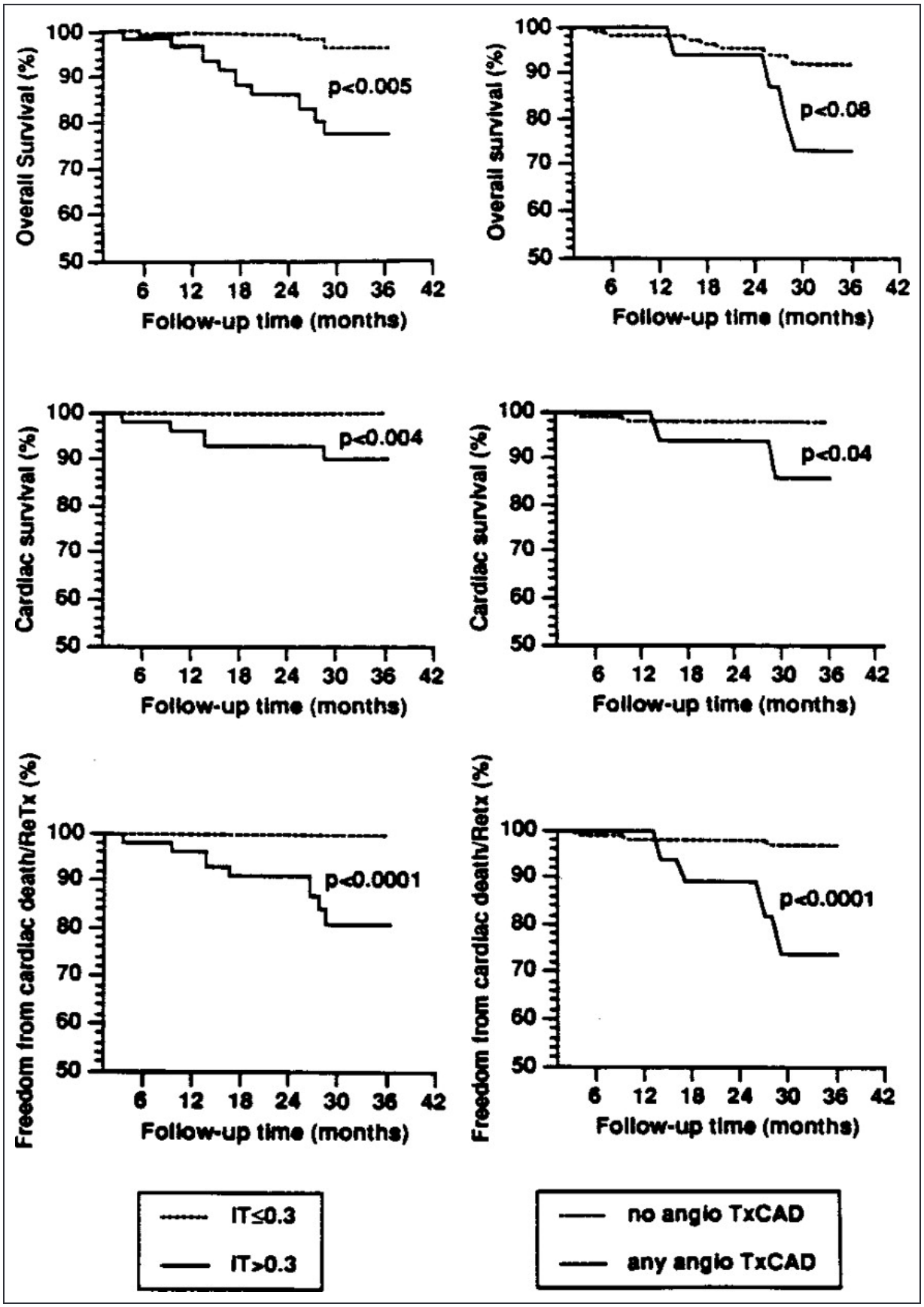
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100
90
80
70
60
50
p<0.005
6 12 18 24 30 36 42
Follow-up time (months)
Overall survival (%)
p<0.08
Cardiac survival (%)
p<0.004
Cardiac survival (%)
p<0.04
Freedom from cardiac death/ReTx (%)
p<0.0001
Freedom from cardiac death/Retx (%)
p<0.0001
IT≤0.3
IT>0.3
no angio TxCAD
any angio TxCAD

Figure 1. Plots showing overall survival, cardiac survival, and freedom from cardiac death and retransplantation in the total population according to intimal thickness (IT; >0.3 vs ≤0.3 mm) and any angiographic luminal stenosis or distal pruning vs no disease. TxCAD indicates transplant coronary artery disease; ReTx, retransplantation.

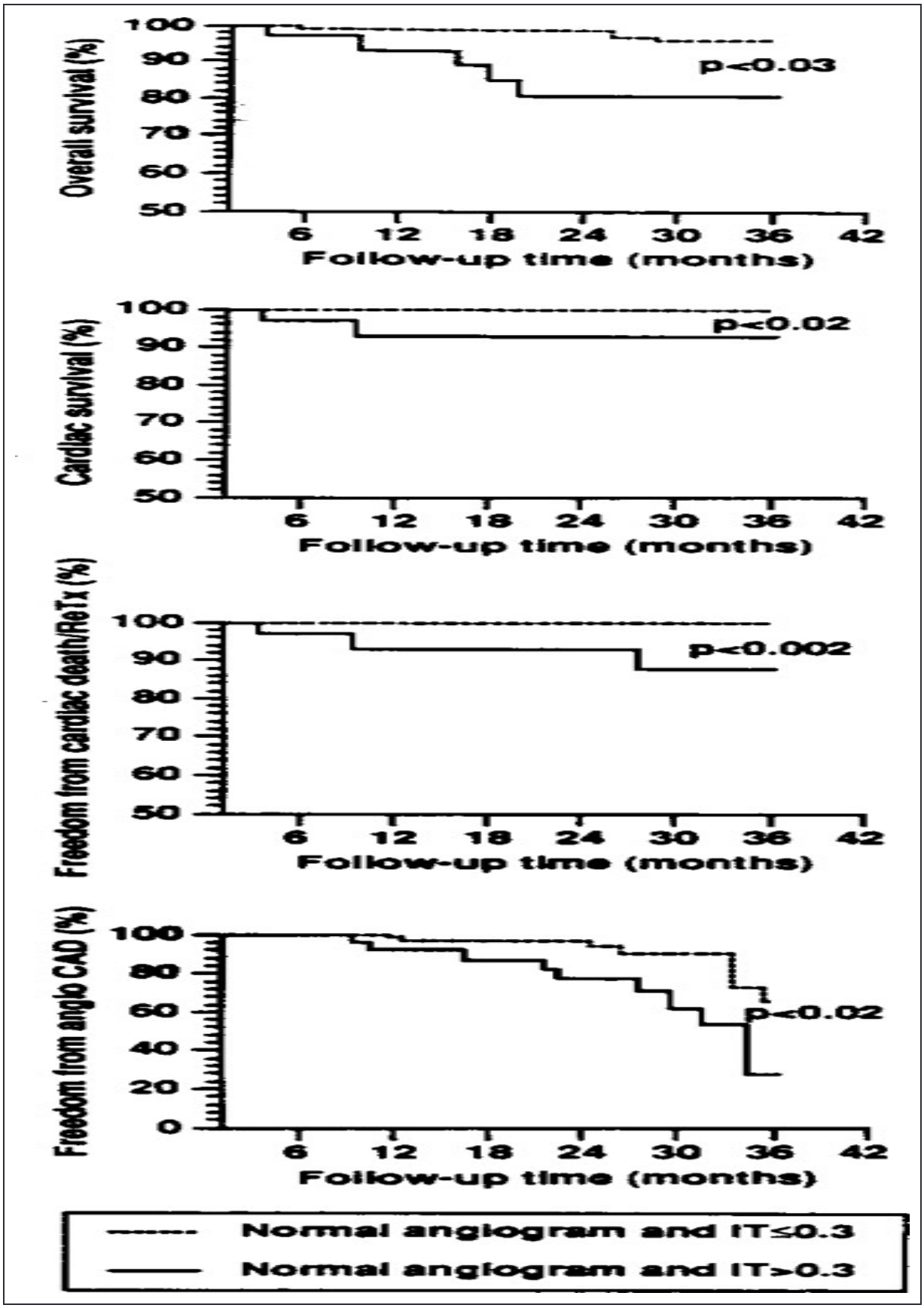
Overall survival (%)
100
90
80
70
60
50
p<0.03
6
12
18
24
30
36
42
Follow-up time (months)
Cardiac survival (%)
100
90
80
70
60
50
p<0.02
6
12
18
24
30
36
42
Follow-up time (months)
Freedom from cardiac death/ReTx (%)
100
90
80
70
60
50
p<0.002
6
12
18
24
30
36
42
Follow-up time (months)
Freedom from angio CAD (%)
100
80
60
40
20
0
p<0.02
6
12
18
24
30
36
42
Follow-up time (months)
Normal angiogram and IT≤0.3
Normal angiogram and IT>0.3

Figure 2. Plots showing overall survival, cardiac survival, freedom from cardiac death and retransplantation (ReTx), and freedom from development of subsequent angiographic coronary artery disease (angio CAD) in the subgroup with a normal angiogram at the time of intracoronary ultrasound according to intimal thickness (IT; >0.3 vs ≤0.3 mm).

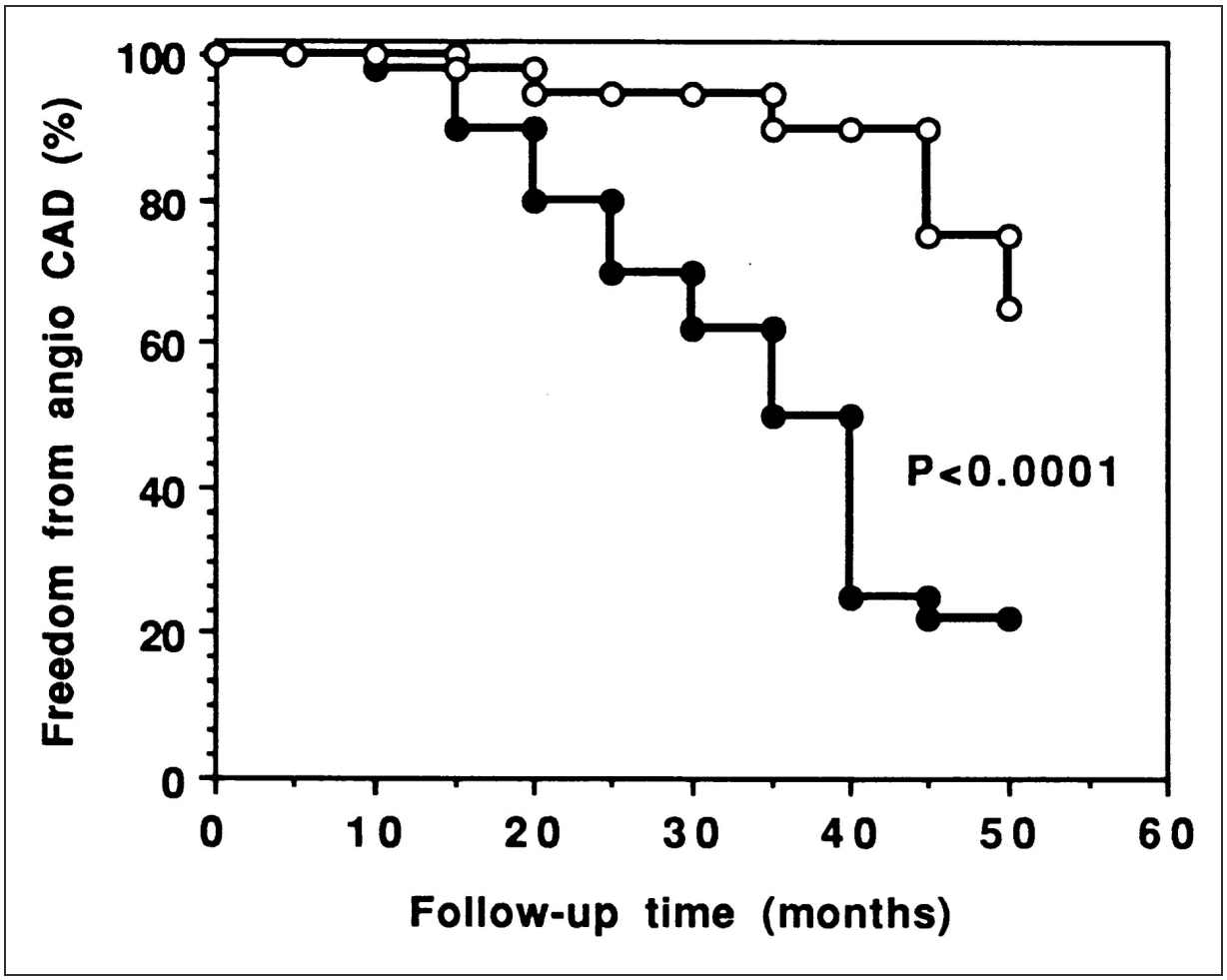

Figure 3. Plot showing freedom from development of subsequent angiographic coronary artery disease (angio CAD) in the subgroup of patients with normal angiograms at the time of intracoronary ultrasound according to intimal thickness of >0.3 vs ≤0.3 mm. In this analysis, the curve for the patient with intimal thickness of ≤0.3 mm has been time-shifted by multiplying each data point by the ratio of a mean duration after transplantation in the two groups, ie, 3.9/2.8 years. ○ indicates normal angiogram and intimal thickness ≤0.3 mm; •, normal angiogram and intimal thickness >0.3 mm.

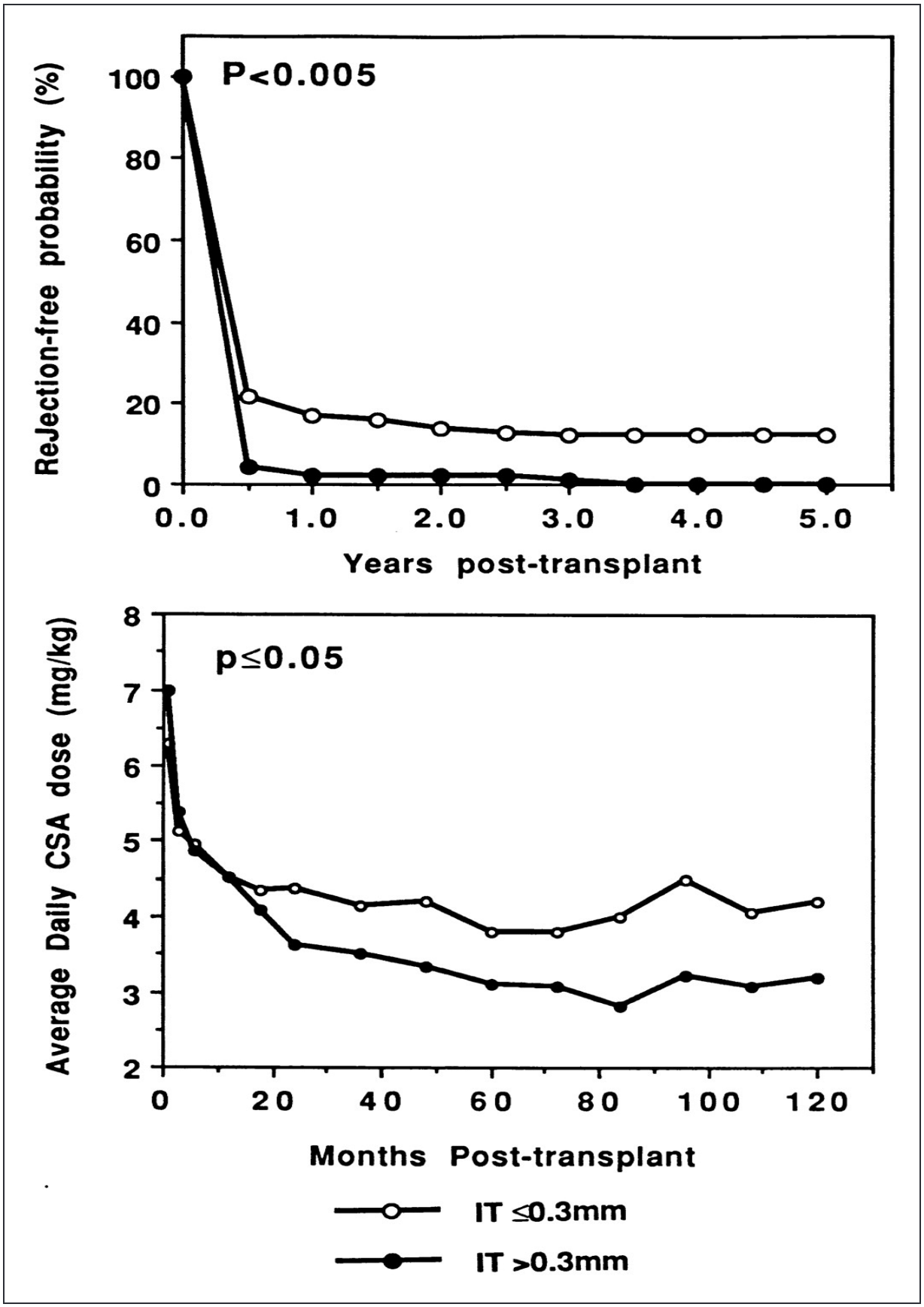
P<0.005
ReJection-free probability (%)
100
80
60
40
20
0
0.0
1.0
2.0
3.0
4.0
5.0
Years post-transplant
p≤0.05
Average Daily CSA dose (mg/kg)
8
7
6
5
4
3
2
0
20
40
60
80
100
120
Months Post-transplant
IT ≤0.3mm
IT >0.3mm

Figure 4. Plots showing actuarial rejection rates in patients with intimal thickness (IT) of ≤0.3 vs >0.3 mm (top) and average daily cyclosporine (CSA) doses in patients with intimal thickness of ≤0.3 vs >0.3 mm (bottom).

Table 1. Baseline Clinical, ICUS, and Angiographic Characteristics

	All Patients (n=145)	IT >0.3 mm (n=47)	IT ≤0.3 mm (n=98)
Clinical characteristics			
Age at transplantation, y	45.1±11.1	45.2±9.6	45.0±11.8
Female sex, n (%)	26 (18)	6 (13)	20 (20)
Pretransplant diagnosis, %			
Coronary artery disease, n (%)	73 (50)	22 (47)	51 (52)
Dilated cardiomyopathy, n (%)	68 (47)	25 (53)	43 (44)
Other, n (%)	4 (3)	0 (0)	4 (4)
Linearized rejection rates			
<3 months	1.30±0.10	1.59±0.19[3]	1.17 ±0.11
3-<6 months	0.47±0.06	0.44±0.10	0.48 ±0.07
6-<12 months	0.41±0.08	0.37±0.13	0.43 ±0.10
Linearized infection rates			
<3 months	0.85±0.08	0.82±0.14	0.86±0.10
3-<6 months	0.22±0.04	0.16±0.06	0.25±0.05
6-<12 months	0.20±0.05	0.14±0.06	0.22±0.04
Age at study, y	48.6±10.6	49.6±9.1	48.1±11.3
Years after transplantation	3.1±2.2	3.9±2.4[2]	2.8±2.0
ICUS characteristics			
Number of sites studied	3.2±1.0	3.1±1.0	3.2±1.0
Mean intimal thickness, mm	0.24 ±0.20	0.47±0.17[1]	0.13±0.10
Angiographic characteristics			
Any evidence of TxCAD, n (%)	19 (13)	17 (36)[1]	2 (2)

ICUS indicates intracoronary ultrasound; IT, intimal thickness as measured by ICUS; and TxCAD, transplant coronary artery disease. Data are expressed as mean±SD when appropriate.

[1] *P*<.0001.

[2] *P*=.004.

[3] *P*=.05.

Table 2. Relative Risks of Overall Mortality Associated With ICUS, Angiographic Findings, and Duration After Transplant in the Total Population

Overall Mortality	Relative Risk	95% CI	*P*
ICUS: intimal thickness >0.3 vs ≤0.3 mm	4.7	1.3-14.7	.01
Angio: any vs no TxCAD	2.8	0.8-8.8	.09
Duration after transplant at ICUS study	1.07	0.9-8.1	.5

Abbreviations as in Table 1.

Table 3. Relative Risks of Overall Mortality and Developing Angiographic TxCAD Associated With ICUS Findings in the Subgroup With Normal Angiograms at the Time of ICUS

	Relative Risk	95% CI	*P*
Overall mortality			
ICUS: intimal thickness >0.3 vs ≤0.3 mm	4.0	0.8-14.1	.04
Duration posttransplant at ICUS study	1.1	0.8-9.3	.56
Development of angiographic TxCAD			
ICUS: intimal thickness >0.3 vs ≤0.3 mm	3.0	1.2-8.1	.02
Duration after transplant at ICUS study	0.97	0.7-8.5	.8

Abbreviations as in Table 1.

Table 4. Causes of Death

	All Patients (n=23, 16%)	IT >0.3 mm (n=13, 28%)	IT ≤0.3 mm (n=10, 10%)
TxCAD	10 (54.5)	10 (84)	0 (0)
Infection	4 (18)	2 (8)	3 (30)
Rejection	0 (0)	0 (0)	2 (20)
Malignancy (lymphoid and nonlymphoid)	5 (23)	1 (8)	4 (40)
Unknown	1 (4.5)	0 (0)	1 (10)

IT indicates intimal thickening; TxCAD, transplant coronary artery disease. Data are expressed as number of patients (%). Cardiac deaths include deaths resulting from complications of retransplantation for TxCAD, occurring within 3 months of the procedure.