Predictors and Evolution of Renal Function during 9 Years Following Heart Transplantation

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Abstract. Over a 9-yr period, heart transplantation was performed in 200 patients at Sahlgrenska University Hospital. Of these 200 patients, 151 were followed for 1 to 9 yr with regard to renal function, hemodynamics, cyclosporin A concentrations, and complications. Patients with a preoperative serum creatinine >130 μmol/L received inotropic drugs to test for reversibility of renal dysfunction. The end point was graft failure. The average preoperative GFR of 66 ± 17 ml/min per 1.73 m² declined to 52 ± 19, 44 ± 16, and 37 ± 17 at 1, 5, and 9 yr after heart transplantation, respectively. Altogether, the average GFR declined by 44%. There was no significant correlation between the preoperative GFR and postoperative renal function or survival. Recipient age was a predictor of renal function during the entire follow-up. Severe renal dysfunction (GFR <20 ml/min per 1.73 m²) developed in 20% of the patients, which was predicted by the recipient age at transplantation together with the GFR 1 yr after transplantation. A nomogram that shows the risk of developing severe renal dysfunction after heart transplantation is presented. Cyclosporin A concentrations and treatment with statins, calcium channel blockers, or angiotensin-converting enzyme inhibitors did not correlate with the evolution of renal function. Patients with a preoperative depressed renal function who improved on inotropic treatment seemed to have a poorer outcome compared with the other study patients.

Materials and Methods
During a 9-yr period (January 1988 through December 1996), 200 consecutive patients had their first Htx performed at Sahlgrenska University Hospital in Göteborg, Sweden. Patients 15 yr of age or older surviving at least the 1 yr follow-up were included in the study. Re-Htx and mortality were end points. Altogether, 49 patients were excluded from the study: 11 patients were under 15 yr of age and had no follow-up at our center, 31 patients died within 12 mo after Htx (none of them from renal dysfunction), four patients had a re-Htx within 6 mo of the first Htx, and three patients had a combined heart and kidney transplantation performed. The remaining 151 patients were included in the study and followed through December 1997.

All patients underwent a pre-Htx evaluation, including determination of renal function with GFR assessed by the plasma disappearance rate of chromium-51 edetic acid after a single injection. The values were corrected to a body surface area of 1.73 m². In addition to GFR, serum creatinine was determined. To be accepted for Htx at our center, the GFR value generally had to be at least 40 ml/min per 1.73 m². If any signs or history indicative of primary kidney disease or renal artery stenosis were present, further investigations had to be performed to exclude this. Right heart catheterization was performed by the internal jugular vein approach, using a Swan-Ganz pulmonary artery catheter (Baxter Health Care Corp., Edwards Division, Santa Ana, CA). Pressures and cardiac output were measured at rest, the latter by the thermodilution technique. Echocardiographic determination of left ventricular ejection fraction (EF) was performed in M-mode according to the cubic formula, and coronary angiography was also performed.

If a patient had a preoperative GFR value <40 ml/min per 1.73 m² or a serum creatinine >130 μmol/L, an inotropic drug was infused to...
test for a possible reversibility in renal impairment secondary to improved hemodynamics. Amrinone (Incor®, Sanofi Winthrop, Sanofi SA, Paris, France) was used for this test during 3 to 7 d of infusion (10 μg/kg per min). The hemodynamics were monitored with a Swan-Ganz® catheter in the pulmonary artery position. Renal function, according to serum creatinine, and hemodynamic parameters were followed daily. When the lowest serum creatinine value was achieved, GFR was determined. If GFR was ≥40 ml/min per 1.73 m², the patient could be accepted for Htx.

The correlation between pre- and post-Htx GFR and several pre-Htx variables was calculated using age at Htx, gender, etiology of heart failure, treated diabetes, blood lipids, GFR, cardiac index, EF, and type of immunosuppression induction therapy. The correlation between post-Htx GFR and the following post-Htx variables was also calculated: EF and CsA concentration at every follow-up, blood lipid values, the number of patients with treatment for hyperlipidemia, hypertension and diabetes, respectively, hemodynamic variables, and angiographic findings of graft coronary artery disease (graft-CAD) at the first and last year follow-up, respectively; treatment with statins and calcium channel blockers or angiotensin-converting enzyme (ACE) inhibitors during at least 50% of the first year, or at least 50% of the entire follow-up time, respectively; the number of treated cellular rejections and the occurrence of vascular inflammation in the endomyocardial biopsies during the first year post-Htx; need for postoperative short-term dialysis (early dialysis), development of severe renal dysfunction (GFR <20 ml/min per 1.73 m²), need for permanent dialysis (late dialysis), and cytomegalovirus infection.

The amount of contrast medium used at coronary angiography was approximately 50 ml of an iohexol solution (Omnipaque®, Nycomed Amersham, Oslo, Norway). Patients with a serum creatinine of ≥150 μmol/L were pretreated with 2 L of 5% glucose infusion during 12 h before the angiography, followed by 1 L of additional oral liquid afterward. Serum creatinine was measured again 1 d after angiography. Measurements of albuminuria and ultrasonography of the kidneys were not regularly performed. Patients on dialysis were excluded from measurements of renal function, but they were included in the group of patients who reached a filtration rate ≥40 ml/min per 1.73 m².

Hypertension was defined as diastolic BP repeatedly exceeding 90 mmHg. Diabetes was defined as a fasting blood glucose level repeatedly of 6.7 mmol/L or above. A cholesterol level of 6 mmol/L or higher was considered abnormal. Graft-CAD was defined as a reduction in lumen diameter of 50% or more in at least one coronary artery at coronary angiography. Rejection was defined as abnormal endomyocardial biopsy findings that required treatment, usually infusion of 1 g of methylprednisolone (Solu Medrol®, Pharmacia & Upjohn, Kalamazoo, MI) every day for 3 d. Cytomegalovirus infection was defined as positive laboratory findings (by antibody count or PCR). Before 1993, antithymocyte globulin (ATG) induction therapy was sometimes chosen because of a pre-Htx low GFR, and it was given to all patients from 1993 on. The CsA immunosuppression induction therapy included preoperative infusion of 4 to 8 mg/kg CsA (Sandimmun®, Sandoz Pharma, Basel, Switzerland), and the dose was dependent on renal function, 4 mg/kg oral azathioprine (Imurel®), Glaxo Wellcome, Greenford, United Kingdom) preoperatively, and perioperative injection of 500 mg of methylprednisolone. The ATG induction therapy included perioperative infusion of 2 mg/kg ATG (Thymoglobulin®, Pasteur-Merieux, Lyon, France), azathioprine as above, one preoperative and one perioperative injection of 500 mg of methylprednisolone. Postoperatively, ATG infusion was continued for at least 3 d where applicable; otherwise, the immunosuppression therapy was identical for all patients and included CsA twice a day. The doses were adjusted to a concentration of 300 to 400 ng/ml during the first month, 300 ng/ml up to 3 mo, and 200 ng/ml thereafter. Regular Sandimmun® was changed to Sandimmun Neoral® in 1995, but the routine for measuring GFR, in relation to this medication, was unchanged. Azathioprine was administered in a dose of 2 mg/kg daily and adjusted depending on the white blood cell count, and prednisolone (Prednisolon®, Pharmacia & Upjohn) was administered in a dose of 0.2 mg/kg daily during the first 3 wk followed by 0.1 mg/kg daily. The CsA concentration in whole blood was measured by the Cyclo-Trac® method (Incstar Corp., Stillwater, MN) and from 1995 on by the equivalent EMIT® method (Behring Diagnostica, San Jose, CA). Both methods measure the cyclosporine parent compound. The study was approved by the ethics committee at the Göteborg University.

Statistical Analyses

To test for statistical significance of differences, the Mann–Whitney U test and Wilcoxon signed rank test were used for unpaired and paired observations, respectively. The correlations between pre- and post-Htx variables versus post-Htx GFR values at different years were analyzed using the Spearman correlation test for continuous variables and the Mann–Whitney U test for dichotomous variables. The Spearman partial correlation rank statistic was used for corrected P values.

In evaluating the influence of induction therapy on renal function, a correction of the preoperative GFR value was performed by including GFR in a multivariate analysis. The effect of statins, calcium channel blockers, and ACE inhibitors on renal function, and the probability of developing severe renal dysfunction (GFR <20 ml/min per 1.73 m²) were evaluated according to the Poisson model (9), where the risk level included deviations. Graft survival was calculated according to the Kaplan–Meier method, and the log-rank test was used to test for statistical significance of correlation with pre-Htx GFR values. All P values are two-tailed. A P value of <0.05 was considered statistically significant, except in repeated measurements, where the significance limit was set to P < 0.01.

Results

Among 151 patients included in the study, 122 were male and 29 were female. Mean age was 44 ± 13 yr (range, 15 to 63). The patients were accepted for Htx due to severe heart failure and reduced renal function with an average GFR value of 66 ± 17 ml/min per 1.73 m² and an average serum creatinine of 108 ± 23 μmol/L. Pre- and post-Htx variables are presented in Table 1. The correlation between pre-Htx GFR and pre-Htx serum creatinine was r = −0.42 (P < 0.001). The mean follow-up time was 4.9 ± 2.6 yr based on the number of yearly follow-up investigations performed and 5.5 ± 2.5 yr concerning survival. Only 1.4% of 10,995 collected patient data was missing. The renal function, measured as GFR, decreased significantly through 2 yr following Htx. The differences compared with the previous year remained thereafter, although were not significant (Figure 1). However, some of the mean values at, for instance, years 6 to 9 were significantly lower compared with year 4 (P = 0.002, P = 0.062, P < 0.000, and P = 0.006, respectively). The average serum creatinine values pre-Htx, one-half year post-Htx, and yearly through 9 yr post-Htx were 108, 121, 133, 148, 149, 147, 153, 164, 151, 160, and 157 μmol/L (the value in μmol/L divided by 88 is approximately equal to mg/dl), respectively. The GFR
in patients who reached an end point at any time during follow-up did not differ significantly ($P > 0.05$) from that in the patients without an end point at each year. Pre-Htx and 1, 3, 5, and 7 yr post-Htx the GFR values among patients with an end point were 63 ± 20, 45 ± 17, 45 ± 11, 40 ± 13, and 40 ± 4 ml/min per 1.73 m$^2$, respectively, compared with 67 ± 16, 53 ± 19, 46 ± 16, 45 ± 16, and 45 ± 16 ml/min per 1.73 m$^2$, respectively, in those without an end point. Among the study patients, 20% developed severe renal dysfunction (GFR < 20 ml/min per 1.73 m$^2$) during follow-up, including six patients who needed permanent dialysis (see Figure 3).

**Reversibility Test of Renal Dysfunction before Htx**

To test for improvement in renal function through treatment with an inotropic drug in patients with renal impairment as defined in Materials and Methods, 10 of the study patients were treated with amrinon for an average of 4.9 ± 1.8 d. Cardiac index increased from 1.4 ± 0.4 to 2.5 ± 0.4 L/min per m$^2$ ($P = 0.006$) during the infusion period. The average serum creatinine of 151 ± 34 before the infusion decreased to 109 ± 14 μmol/L ($P = 0.0009$). The average GFR value after the infusion was 65 ± 14 ml/min per 1.73 m$^2$, and all patients could be accepted for Htx. Post-Htx, the GFR values in these 10 patients at 1, 3, 5, and 7 yr were 46, 48, 40, and 36 ml/min per 1.73 m$^2$ versus 52, 46, 45, and 47 ml/min per 1.73 m$^2$ in the other 141 study patients, respectively. However, among these 10 patients, four (40%) needed early dialysis and another two patients (20%) needed late dialysis, compared with nine (6%) and four (3%) among the other patients, respectively. No difference was found in graft survival, 8 (80%) in these 10 patients and 113 (80%) in the remaining study patients during the entire follow-up, respectively.

**Immunosuppression Induction Therapy and Renal Function**

Among the 151 study patients, 49 had CsA and 102 had ATG as immunosuppression induction therapy. Since some patients had received ATG because of a preoperative low GFR, we analyzed the difference between the immunosuppression induction therapy and the GFR values during the first year after

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**Table 1. Pre- and post-Htx data for study patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-Htx</th>
<th>1 Year Post-Htx</th>
<th>9 Years Post-Htx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>151</td>
<td>151</td>
<td>13</td>
</tr>
<tr>
<td><strong>Age, yr</strong></td>
<td>44 ± 13</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>122 (81)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>IHD, n (%)</strong></td>
<td>56 (37)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>DCMP, n (%)</strong></td>
<td>84 (56)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Other etiology, n (%)</strong></td>
<td>11 (7)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Diabetes mellitus, n (%)</strong></td>
<td>9 (6)$^b$</td>
<td>19 (13)</td>
<td>22 (15)$^*$</td>
</tr>
<tr>
<td><strong>Cholesterol, mmol/L</strong></td>
<td>5.0 ± 1.8$^c$</td>
<td>6.4 ± 1.4</td>
<td>5.8 ± 1.4$^c$</td>
</tr>
<tr>
<td><strong>Triglycerides, mmol/L</strong></td>
<td>1.5 ± 0.8$^c$</td>
<td>2.3 ± 1.1</td>
<td>2.3 ± 1.3$^*$</td>
</tr>
<tr>
<td><strong>Lipid-lowering drug, n (%)</strong></td>
<td>NA</td>
<td>54 (36)</td>
<td>95 (63)$^c$</td>
</tr>
<tr>
<td><strong>Antihypertensive drug, n (%)</strong></td>
<td>0</td>
<td>97 (64)</td>
<td>117 (77)$^c$</td>
</tr>
<tr>
<td><strong>GFR, ml/min per 1.73 m$^2$</strong></td>
<td>66 ± 17$^c$</td>
<td>52 ± 19</td>
<td>37 ± 17$^b$</td>
</tr>
<tr>
<td><strong>Creatinine, μmol/L</strong></td>
<td>108 ± 23$^c$</td>
<td>113 ± 37</td>
<td>157 ± 46$^b$</td>
</tr>
<tr>
<td><strong>Cardiac index, L/min per m$^2$</strong></td>
<td>1.8 ± 0.5$^c$</td>
<td>3.0 ± 0.7</td>
<td>3.0 ± 0.8$^*$</td>
</tr>
<tr>
<td><strong>SVR index, Wood Units</strong></td>
<td>36 ± 9</td>
<td>37 ± 10$^*$</td>
<td>NA</td>
</tr>
<tr>
<td><strong>EF, %</strong></td>
<td>21 ± 10$^c$</td>
<td>68 ± 10</td>
<td>68 ± 10</td>
</tr>
<tr>
<td><strong>Induction CsA/ATG, %</strong></td>
<td>32/68</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>CsA, μg/L</strong></td>
<td>NA</td>
<td>253 ± 98</td>
<td>167 ± 39</td>
</tr>
<tr>
<td><strong>Graft-CAD, n (%)</strong></td>
<td>NA</td>
<td>8 (5)</td>
<td>28 (19)$^*$</td>
</tr>
<tr>
<td><strong>Rejections, n/patient</strong></td>
<td>NA</td>
<td>2.3 ± 2.2</td>
<td>75 (50)$^*$</td>
</tr>
<tr>
<td><strong>CMV infection, n (%)</strong></td>
<td>NA</td>
<td>NA</td>
<td>28 (19)$^*$</td>
</tr>
<tr>
<td><strong>Early dialysis, n (%)</strong></td>
<td>NA</td>
<td>13 (9)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Late dialysis, n (%)</strong></td>
<td>NA</td>
<td>1 (1)</td>
<td>6 (4)$^*$</td>
</tr>
<tr>
<td><strong>Retransplantation, n (%)</strong></td>
<td>NA</td>
<td>NA</td>
<td>2 (1)$^*$</td>
</tr>
<tr>
<td><strong>Mortality, n (%)</strong></td>
<td>NA</td>
<td>25 (17)$^*$</td>
<td>NA</td>
</tr>
</tbody>
</table>

$^a$ Htx, heart transplantation; IHD, ischemic heart disease; DCMP, dilated cardiomyopathy; SVR, systemic vascular resistance; EF, ejection fraction; CsA/ATG, immunosuppression induction therapy with cyclosporin A or anti-thymocyte globulin; Graft-CAD, development of coronary artery disease after Htx; CMV, cytomegalovirus; Early dialysis, postoperative need for transient dialysis; Late dialysis, need for permanent dialysis; NA, not applicable. Asterisk in column “9 years post-Htx” means at the last follow-up.

$^b$ $P < 0.01$ versus 1 yr post-Htx.

$^c$ $P < 0.001$ versus 1 yr post-Htx.
correction for the pre-Htx GFR values. This showed that ATG induction therapy reduced the postoperative GFR value at 6 mo and 1 yr more than CsA induction ($P < 0.0002$ at both times). After this, no significant difference was found.

**Pre- and Post-Htx Variables Associated with Post-Htx Renal Function**

In a univariate analysis, there was no significant correlation between recipient age and preoperative GFR ($P = 0.16$), but there were significant negative correlations between recipient age at Htx and the GFR values at every year of follow-up (Table 2). The number of treated cellular rejections and patients with ischemic heart disease (IHD) as etiology of heart failure had a significant negative correlation with post-Htx GFR values during 6 mo to 2 yr and 3 to 7 yr post-Htx, respectively (Table 2). Post-Htx, there was a significant correlation between GFR at 1 yr and GFR up to the 7-yr follow-up (Table 2). There was no significant correlation between pre-Htx GFR and post-Htx GFR (except for the first half year) or survival. The use of statins for hypercholesterolemia and calcium channel blockers or ACE inhibitors for hypertension did not influence the evolution of renal function, either in the short term or in the long term. There was no significant correlation between CsA concentration and GFR at any time. A significant negative correlation between GFR and serum creatinine was found during the entire follow-up (correlation coefficient between $-0.68$ and $-0.82$, $P < 0.001$ at all years).

In the univariate analysis, the recipient age at Htx had a significant correlation with post-Htx renal function during the entire follow-up (Table 2). However, after correction for IHD, the recipient’s age lost its statistical significance, but high age and heart failure from IHD were most often found in the same patients. Among post-Htx variables, the significant predictive value of GFR-1 did not change after correction for the number of cellular rejections.

According to the Poisson model, the estimated hazard function for developing severe renal dysfunction (GFR < 20 ml/min per 1.73 m$^2$) was \( \text{exp}(-0.888 + [0.060 \times \text{recipient age at Htx}] - [0.449 \times \text{time since Htx}] - [0.129 \times \text{GFR at 1 yr post-Htx}] + [0.016 \times \text{GFR at 1 yr post-Htx} \times \text{time since Htx}]) \). The significances were $P = 0.004$, $P < 0.001$, and $P = 0.010$ for age, GFR at 1 yr post-Htx, and interaction, respectively. According to this analysis, the recipient age at the time of transplantation combined with the GFR level at 1 yr post-Htx predicted the risk of developing severe renal dysfunction during the entire follow-up. A nomogram that shows the time

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**Table 2. Univariate and multivariate analysis of pre- and post-Htx variables versus post-Htx GFR at various years**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Uncorrected $P$ Values</th>
<th>Corrected $P$ Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>$n$</td>
<td>151</td>
<td>124</td>
</tr>
<tr>
<td>Age at Htx</td>
<td>0.0009</td>
<td>0.009</td>
</tr>
<tr>
<td>IHD etiology</td>
<td>0.19</td>
<td>0.01</td>
</tr>
<tr>
<td>GFR-1</td>
<td>NA</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cellular rejection</td>
<td>0.01</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*a Uncorrected $P$ values according to univariate analysis are shown. Age was corrected for IHD, and GFR-1 was corrected for cellular rejection, and vice versa. GFR-1, GFR at year 1 post-Htx. Other abbreviations as in Table 1.*

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**Figure 1.** The evolution of GFR in 151 heart transplanted patients included in the study. The number of patients evaluated was 151, 151, 151, 134, 121, 102, 82, 66, 51, 33, and 13 at pre-Htx and post-Htx years 1/2 through 9, respectively. $P$ values versus the following measurement.
point post-Htx when a patient has a 50% probability of developing severe renal dysfunction, according to our results, is presented in Figure 2.

Discussion

Renal function is reduced among patients with severe heart failure. This is considered to be secondary to a low cardiac output and hormonal imbalance. There is also a correlation between renal function and survival in patients with heart failure (10). In a reversibility test, we attempted to optimize the renal function through improved hemodynamics by using inotropic drugs. The renal function improved considerably with this treatment and, except for a higher need for post-Htx dialysis, the outcome seemed similar among the 10 patients compared to the other study patients. Although few patients were included in the test, the result indicates that this might be an adequate method of identifying a renal reserve before Htx. However, since it is most probable that every patient with heart failure would improve in renal function from inotropic stimulation, the acceptance limit for the obtained renal function should perhaps be higher than for those who do not need to undergo a reversibility test.

After Htx, the hemodynamics were normalized (Table 1), and the sympathetic activity has previously been described to normalize after Htx (11). Despite these improvements, we found a 44% decline in renal function during 9 yr after Htx compared with the preoperative value (Figure 1). This decline is almost 10 times as great as expected in a healthy population (12). There was an initial marked decline in renal function followed by a slow decline throughout the follow-up. This finding is in contrast to the results of previous studies with shorter follow-up periods (2–5). Many factors are in all probability involved in the evolution of renal function following Htx: the transplantation procedure itself, the need for postoperative short-term dialysis, CsA treatment, development of hypertension and hypercholesterolemia, repeated coronary angiographies, and perhaps also immunologic factors.

CsA is considered to be the main cause of renal dysfunction post-Htx. It has been described in many studies as a dose-dependent nephrotoxic agent (3,7,13,14). After correction for the pre-Htx GFR level, we were surprised to find that ATG immunosuppression induction therapy seemed to affect the post-Htx renal function during the first postoperative year more than CsA. This may be just by chance, but induction therapy without cytolytic agents has earlier been described to improve renal function (15).

CsA is considered to constrict the afferent arterioles (7), to induce an elevation of the endothelin-1 level (16), and to stimulate the renin-angiotensin-aldosterone system (17). However, during the follow-up in our study, there was no significant correlation between CsA concentration and GFR at any time, or with the development of severe renal dysfunction (GFR <20 ml/min per 1.73 m²). The average CsA concentration in our study declined by 19% (not presented in Results) from 6 mo to 4 yr post-Htx. This is a smaller decline than the approximately 36% reduction shown by Greenberg et al. (2). If the nephrotoxicity of CsA is dose-dependent, a smaller decline in CsA concentration through the years should cause a more pronounced nephrotoxic effect. The average serum creatinine in the Greenberg study increased by 11% from year 1 to year 4, the same as in our study. Although the decline in CsA concentrations in the Greenberg study was almost twice as great as in ours, the decline in renal function was identical. This does not support a dose-dependent nephrotoxicity. There may instead be a nephrotoxic effect of CsA even below the treatment level. This is partly supported by the findings in a study by Waser et al. (18), who showed that the renal function did not improve from a reduction in CsA concentration. Hartmann et al. (19) and Goral et al. (20) found a constant GFR post-Htx despite CsA treatment. However, temporary with-

![Figure 2. Nomogram showing the time point post-Htx when a patient has a 50% probability of developing severe renal dysfunction (GFR <20 ml/min per 1.73 m²), according to the Poisson model on the study results. For instance, a patient 40 yr old at the time of Htx with a GFR value of 30 ml/min per 1.73 m² at 1 yr post-Htx has a 50% probability of developing severe renal dysfunction 7 yr after Htx.](image-url)
drawal of CsA treatment has been shown to improve renal function (13).

Circulating antibodies and immunologic proteins could theoretically deposit in the kidneys and accelerate fibrosis. There was a significant negative correlation between the number of rejections and GFR during the first 3 postoperative years. However, the renal function was not significantly influenced by the occurrence of vascular inflammation in endomyocardial biopsies. It has recently been shown that heart transplant recipients with both normal and impaired renal function have an elevated serum \( \beta_2 \)-microglobulin level compared with non-transplanted control subjects, which was considered to reflect an increased immunoactivity (21). The albumin excretion rate has also been shown to increase through the years following Htx, indicating a progressive glomerular and tubular dysfunction (19).

Different ways of reducing the progressive renal dysfunction post-Htx have been proposed. An interesting idea was presented in a study by Furlanut et al. (6), where the patients received CsA three times a day instead of twice a day, but no difference in renal function was found. Treatment with low doses of calcium channel blockers has been described to protect the kidneys from CsA toxicity (22). Preliminary results from the Norwegian ADA study on kidney transplanted patients show that nifedipine protects the kidneys in hypertensive renal transplant recipients from CsA nephrotoxicity significantly better than lisinopril (23). In our study, neither calcium channel blockers, ACE inhibitors, nor statins had a significant influence on renal function. Denys et al. found that hydration is sufficient to protect the kidneys from the toxicity of contrast medium used at coronary angiography (24). This routine was used in our patients.

The described incidence of end-stage renal dysfunction post-Htx varies from 3 to 8% (2,7,25). In the Stanford material, they found an incidence of 3.3%, and nine selected Htx patients had a renal transplantation with a 3 yr survival of 89% (25). During 9 yr, six patients in our study eventually required late dialysis (4%). However, as many as 20% of our patients (including those with dialysis) experienced a severe reduction in renal function, GFR <20 ml/min per 1.73 m\(^2\), and were consequently at high risk for dialysis.

Clinically useful predictors of renal function following Htx have not previously been described. Due to the long-term follow-up with a fairly large number of patients in our study, we were able to identify the recipient age at the time of Htx as a predictor of the renal function following Htx. An even more useful predictor was the combination of recipient age at the time of Htx and the GFR value at 1 yr post-Htx. A nomogram, according to the Poisson model based on our results, shows the time point post-Htx when a specific patient has a 50% probability of developing severe renal dysfunction, GFR <20 ml/min per 1.73 m\(^2\) (Figure 2). This may be used early in the follow-up post-Htx to identify those patients at risk of developing renal dysfunction requiring dialysis or kidney transplantation. Although not shown by this study, possible preventive measures to delay this development should be instituted at an early stage, including treatment for hypertension with calcium channel blockers (22–23), prevention of rejections and development of atherosclerosis by treatment with statins and omega-3-fatty acids (19), reduction of the number of coronary angiographies, and screening for suspicion of renal artery stenosis. Risk factors for development of renal dysfunction in nontransplanted patients should also be considered, including intensive treatment of diabetes mellitus and prevention of smoking (26).

**Conclusion**

The average GFR declined by 44% during 9 yr after Htx compared with the preoperative value. There was a continuous decrease in renal function during 9 yr following Htx. Post-Htx renal function and survival were independent of the preoperative level. Recipient age was a strong predictor of post-Htx renal function throughout the entire follow-up. The recipient
age at the time of Htx and the GFR value at 1 yr post-Htx are included in a nomogram that predicts the risk of developing severe renal dysfunction.

CsA induction therapy seemed to be less nephrotoxic than ATG during the first post-Htx year, and there was no significant correlation between post-Htx GFR and CsA concentration at any time. Treatment with statins, calcium channel blockers, or ACE inhibitors did not have a protective effect on renal function post-Htx.

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