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ORIGINAL ARTICLE

Coronary event rates in liver transplant recipients reflect the increased prevalence of cardiovascular risk-factors

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Summary

Increased prevalence of cardiovascular risk-factors in liver transplant recipients compared with pretransplant and standard population data has been acknowledged. The impact of risk-profiles on cardiovascular event rates or death, however, has not yet been established. Here we evaluate the development of risk-factors during a prospective follow-up of 10 years in 302 patients and compare numbers of coronary events with data from the German Prospective Cardiovascular Münster (PROCAM)-Score population. Prevalence of overweight (17% vs. 27%), hypertension (70% vs. 80%), and diabetes (21% vs. 25%) increased from early to late after transplantation, while elevated serum cholesterol (64% vs. 37%) and triglycerides (40% vs. 21%) became less frequent. Cardiovascular risk-profiles favoring tacrolimus over ciclosporin A based immunosuppression early after transplantation converged over time. Increased risk-scores in liver transplant recipients matched with score standardized event rates in the PROCAM population (ratio: 1.11, 95% CI: 0.53–2.03), nine events were predicted for the transplant population and oppose 10 events observed. Thus, indicating a reflection of increased cardiovascular risk-profiles in corresponding numbers of cardiovascular events.

Introduction

Previously, we reported findings of an increased prevalence of cardiovascular risk-factors (CVRF) in adult liver transplant recipients at a median follow-up of 18 months after transplantation [1]. Also, Sheiner *et al.* [2] reported increased rates of hypertension (HTN) and diabetes in patients surviving more than 5 years post-liver transplantation (post-LT) compared with the general US population. Evidence for the clinical relevance of CVRF in LT recipients has first been drawn from observations that death secondary to cardiovascular or cerebrovascular disease is among the three most common causes for late hepatic graft loss [3]. Likewise, in the Birmingham liver transplant population the relative risk of ischemic heart disease and death from cardiovascular disease was 3.07 and 2.56, respectively, compared with registry data from England and Wales [4]. Contrarily, Fernández-Miranda *et al.* [5] found the prevalence of obesity, HTN, or hypercholesterolemia (HCHOL) at more than 5 years of follow-up to be no different from figures in the general Spanish population with a correspondingly low number of cardiovascular events. The authors, however, emphasized the young recipient age in their series.

In general, impaired lipid metabolism in post-transplant populations has been attributed mainly to steroid administration, while arterial HTN has been associated with calcineurin-inhibitor (CNI) treatment [6]. Both findings were more pronounced in ciclosporin A (CsA) based immunosuppressive regimens than in tacrolimus (Tac) treated patients [1,7,8]. The incidence of post-transplant diabetes mellitus (PTDM) reported in liver transplant recipients is inconsistent [2,9,10] and discrepant findings may reflect patient selection rather than post-transplant determinants [11].

Here we evaluate the prevalence of CVRF in a prospective 10-year longitudinal follow-up study of our adult liver transplant population, report cardiovascular events observed during this period, and compare those numbers with numbers of coronary events observed in the Prospective Cardiovascular Münster (PROCAM) Study [12].

Patients and methods

The study population of 302 adult survivors after orthotopic liver transplantation has been characterized earlier [1]. In brief, 399 LT were performed in 366 patients since 1988. By the end of 1993, all 302 adult patients alive with a minimum follow-up of 6 months post-LT and complete sets of data were evaluated for the presence of CVRF. All patients were prospectively followed for 10 years. Re-evaluation of CVRF took place in 2003. Cardiovascular events, patient death, and hepatic graft loss that occurred within the 10-year observation period were recorded. Parameters obtained were arterial blood-pressure, height, weight, medication, date of visit, and serum levels of total cholesterol, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, triglycerides, and glucose after a fasting period of at least 12 h.

Overweight (HBMI) was defined as BMI (weight/height^2) above 27.8 kg/m^2 in male or 27.3 kg/m^2 in female patients. Serum levels of total cholesterol exceeding 200 mg/dl or triglycerides exceeding 175 mg/dl were defined as HCHOL or hypertriglyceridemia (HTRI), respectively. A systolic blood-pressure over 139 mmHg, a diastolic blood-pressure over 89 mmHg, or antihypertensive treatment (except single diuretic therapy) was considered arterial HTN. A glucosemia of more than 120 mg/dl, or antidiabetic treatment were defined as hyperglycemia (HGLY). All data was obtained at the patient's last visit to our outpatient department before census. Changes in medication were left to the discretion of the physician in charge in the outpatient department (R.N.). None of the patients received statin treatment.

The PROCAM study recruited approximately 30 000 volunteers from 52 large companies and public services in the Münster and Northern Ruhr area [12]. Based on findings in 5389 middle-aged male (35–65 years) who entered the study before 1985, the PROCAM Score has been developed. Coefficients for the PROCAM scoring scheme are given in Table 1. The points assigned to each patient add up to the PROCAM score. Classes of PROCAM scores were built to give the estimated 10-year risk of acute coronary events. As socioeconomic factors are considered to have a major influence on CVRF development [13], the PROCAM risk score for acute coronary events, derived from a German standard population, has been chosen for comparison of our post-transplant results with general population data.

The score standardized event ratio (SER) and 95% CI have been calculated according to formulas given for calculation of standardized mortality ratios.

Table 1. Coefficients of the PROCAM scoring scheme: Details of the PROCAM scoring scheme have been published in [12]. Based on 325 acute coronary events occurring within 10 years of follow-up among 5389 men aged 35–65 years the point scoring scheme has been developed. The sum of points for each coefficient results in the PROCAM score, predicting the individual risk of coronary events.

Coefficient	PROCAM points
Age (years)	
35–39	0
40–44	6
45–49	11
50–54	16
55–59	21
60–65	26
LDL cholesterol (mg/dl)	
<100	0
100–129	5
130–159	10
160–189	14
≥190	20
HDL cholesterol (mg/dl)	
<35	11
35–44	8
45–54	5
≥55	0
Triglycerides (mg/dl)	
<100	0
100–149	2
150–199	3
≥200	4
Systolic blood pressure (mmHg)	
<120	0
120–129	2
130–139	3
140–159	5
≥160	8
Diabetes mellitus	
No	0
Yes	6
MI in family history	
No	0
Yes	4
Smoker	
No	0
Yes	8

LDL, low density lipoprotein; HDL, high density lipoprotein; MI, myocardial infarction.

In brief,

$$\mathrm{SER} = \frac{\Sigma E_{\mathrm{obs}}}{\Sigma(R_{\mathrm{PRO}} \times N)}, \quad (1)$$

where E_{obs} is the number of events observed in each class of the study population, R_{PRO} is the event rate given in the PROCAM population (per 1000) for each class, N is the number of individuals (in 1000) in each class of the study population, and

$$95\% \quad \mathrm{CI}_{\mathrm{low}} = \frac{[\Sigma E_{\mathrm{obs}} + 1 - (1.96 \times \sqrt{\Sigma E_{\mathrm{obs}}})]}{\Sigma(R_{\mathrm{PRO}} \times N)}, \quad (2)$$

and

$$95\% \quad \mathrm{CI}_{\mathrm{up}} = \frac{[\Sigma E_{\mathrm{obs}} + 2 + (1.96 \times \sqrt{\Sigma E_{\mathrm{obs}}})]}{\Sigma(R_{\mathrm{PRO}} \times N)}. \quad (3)$$

An SER of 1.0 implies that the rate of events in PROCAM classes is the same in the liver transplant population and the standard population, while an SER>1.0 or <1.0 implies that the rate is greater or lower for the liver transplant population compared with the standard population, respectively.

All other calculations were carried out using the SPSS software package (Version 10.0, SPSS Inc., Chicago, IL, USA). Data is expressed as median and range, or mean ± SE of mean. For statistical analysis Mann–Whitney *U*-test, *t*-test, and chi-square test were used as appropriate. *P*-value of <0.05 was considered statistically significant. Survival rates were calculated according to the Kaplan–Meier method.

Results

A total of 302 patients entered the study in 1993 (time-point T1). Patients that required liver re-transplantation ($n = 13$) or have been lost in follow-up ($n = 8$) were excluded from analysis altogether, while patients who died during follow-up ($n = 54$) or presented with incomplete sets of data in 2003 ($n = 28$) were included in the analysis of cardiovascular events. Causes of death and cardiovascular events observed in 281 patients are given in Tables 2 and 3, respectively. One hundred and ninety-nine liver transplant recipients were eligible for re-evaluation of CVRF in 2003 (time-point T2). Details of the study design and basic demographics are given in Fig. 1. The 1 and 10 year survival figures of all 366 consecutive adult patients who received LT between September 1988 and July 1993 were 90% and 73%, respectively.

In those 199 patients presenting with complete sets of data in 1993 and 2003, median follow-up equaled 18 months (6–59) with a median age of 48 years (19–68) at T1 and 122 months (116–172) at T2 (last in-person visit before census). Rates of steroid-free patients were 21.6% and 89.5%, respectively ($P < 0.001$).

Table 2. Causes of death in long-term follow-up after liver transplantation: Fifty-four patients of 302 adult survivors after liver transplantation (LT) entering the study in 1993 died during a 10-year follow-up. Cause and time (months after LT) of death are given. Fatalities because of cardiovascular disease are detailed in Table 3.

Cause of death	Months after LT
Recurrent disease	
HCC	38, 57, 74, 160
Alcoholism	23, 27, 59, 105
Hepatitis B	10, 12, 91
CCC	36, 36
Hepatitis C	93, 118
PBC	65
De novo malignancy	
Lung	53, 78, 84, 118, 139, 141
Oropharynx	90, 106
Skin	57, 85
Esophagus	36
Stomach	97
PTLD	51
Thyroid gland	92
Mamma	112
Infections	
Sepsis/MOF	106, 114, 119, 149, 166
PcP	37
Pneumonia	76
De novo hepatitis C	60
Cardiovascular	
MI	67, 120, 121
CI	122
Immunology	
Chronic rejection	95
Others	
GI-bleeding	57, 71
ICB	79
Pulmonary embolism	25
Acute pancreatitis	32
Hypoglycemia	73
Renal failure	129
Suicide	89
Dementia	106
Unknown	123

HCC, hepatocellular carcinoma; CCC, cholangiocellular carcinoma; PBC, primary biliary cirrhosis; PTLD, post-transplant lymphoproliferative disease; MOF, multi-organ failure; PcP, pneumocystis carinii pneumonia; MI, myocardial infarction; CI, cerebral infarction; GI, gastrointestinal tract; ICB, intracranial bleeding.

Immunosuppression

Seventy-five and 69 patients received CsA- or Tac-based immunosuppression at both time-points, respectively. During follow-up, 48 patients (39%) were switched from CsA-based immunosuppression to Tac. Additionally, two

Table 3. Cardiovascular events in long-term follow-up after liver transplantation. During a follow-up of 10 years, 26 cardiovascular events have been observed in 302 adult survivors after liver transplantation (LT) entering the study in 1993. Fatal and nonfatal events, time of occurrence after LT, and basic immunosuppression during follow-up are given. 'CsA' labels patients that received ciclosporin A in 1993 and did not change basic immunosuppression thereafter. 'Tac' patients have not been changed from a tacrolimus (Tac) based regimen. Patients that have been switched from ciclosporin A to Tac during follow-up are labeled 'CsA/Tac'. One patient has been taken from a Tac based regimen off CNI treatment altogether (Tac/no CNI). Where applicable, PROCAM scores predicting the individual risk of coronary events [12] have been given.

Cardiovascular event	Months after LT	Immunosuppression	PROCAM score
Fatal			
MI	67	Tac	51
MI	120	Tac	n.a.
MI	121	CsA	22
CI	122	CsA	n.a.
Nonfatal			
CHD	69	Tac	42
CHD	70	CsA	42
CHD	75	Tac	52
CHD	96	CsA/Tac	48
CHD	108	CsA/Tac	62
CHD	115	Tac	48
CHD	120	Tac	31
CHD	120	CsA	n.a.
CHD	124	CsA	n.a.
CHD	139	CsA	41
MI	36	CsA	n.a.
TIA	60	Tac	n.a.
CI	27	Tac	n.a.
CI	74	Tac	n.a.
CI	84	Tac	n.a.
CI	85	Tac	33
CI	120	Tac	n.a.
CI	134	CsA	n.a.
CI	135	CsA/Tac	n.a.
CI	152	CsA	62
AA	108	CsA/Tac	n.a.
pAOD	154	Tac/no CNI	42

MI, myocardial infarction; CI, cerebral infarction; CHD, coronary heart disease; TIA, transitoric ischemic attack; AA, aortic aneurysm; pAOD, peripheral arterial occlusive disease; n.a., not applicable.

patients received Tac in 1993 and have been converted to CsA thereafter (3%). In 2003, five patients were entirely off CNI treatment.

Gender and age distribution as well as length of follow-up did not differ between the CsA- and Tac-group of patients. The rate of steroid-free patients at T1 equaled 14.7% in patients under CsA treatment, and was significantly higher in Tac treated patients (34.8%, $P = 0.005$). At T2, more than 90% of all patients were off steroids

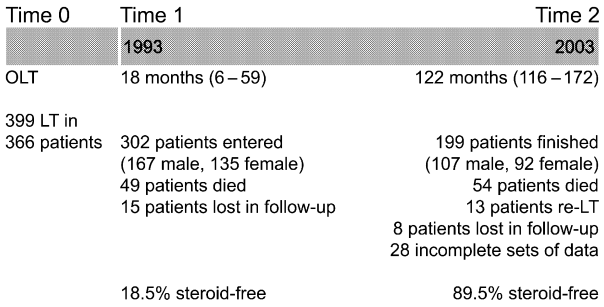

Figure 1 Study design and basic demographics: A total of 399 liver transplants have been performed in 366 adult patients before July 1993. Before census in 1993, 49 patients died and 15 have been lost in follow-up. Details are given in [1]. The remaining 302 patients entered the study in 1993 with a minimum follow-up of 6 months. In 2003, 199 patients finished with a median follow-up of 122 months. The rate of steroid-free patients equaled 89.5% in 2003. During the 10-year observation period, 54 patients died, 13 patients required re-transplantation, eight patients were lost in follow-up, and 28 patients presented with incomplete sets of data.

with no statistical differences between immunosuppression groups (CsA: 92%, Tac: 94%).

In the CsA-group, mean CsA dose has been decreased from 259 ± 10.8 mg/day at T1 to 162 ± 7.0 mg/day at T2 ($P < 0.001$). Dosage in the Tac-group demonstrated no major changes over 10 years (4.7 ± 0.24 mg/day vs. 5.4 ± 0.90 mg/day, $P = 0.452$). Numbers of observed cardiovascular events did not demonstrate preference for any of the immunosuppressive groups (Table 3).

Body mass index and overweight

Mean BMI increased from 24.9 ± 0.29 kg/m^2 at T1 to 25.6 ± 0.30 kg/m^2 at T2 in male patients ($P < 0.001$). According to BMI, 15.1% and 27.4% were considered overweight, respectively ($P < 0.001$). In female patients, BMI increased from 24.2 ± 0.39 kg/m^2 at T1 to 24.8 ± 0.51 kg/m^2 ($P = 0.029$). Also, the rate of overweight increased from 19.8% to 26.4% ($P < 0.001$).

At both time-points, a comparable prevalence of overweight was observed in CsA- and Tac-treated patients (T1: 17.3% vs. 17.8%, $P = 0.583$; T2: 25.3% vs. 28.4%, $P = 0.684$).

Arterial hypertension

In male patients, the prevalence of arterial HTN was 68.9% at T1. This number increased to 84.0% at T2 ($P < 0.001$). Corresponding figures in female patients were less pronounced (70.8% vs. 75.3%, $P = 0.164$). The number of patients with antihypertensive treatment increased to nearly 50% in 2003 from 31% in 1993 ($P < 0.001$). Also, the proportion of patients requiring

more than one antihypertensive drug to lower elevated blood-pressure increased within 10 years of follow-up (12% vs. 23%, $P < 0.001$).

In 1993, the prevalence of arterial HTN was significantly higher in the CsA-group compared with patients with Tac treatment (81.3% vs. 59.4%, $P = 0.004$). During the follow-up of 10 years, numbers converged in both groups (84.0% vs. 80.0%, $P = 0.538$).

Diabetes mellitus

Overall numbers of diabetics were higher in male patients. Over time, however, increasing prevalence of HGLY has been observed in both gender groups (male: 30.8% vs. 35.5%, $P < 0.001$; female: 8.7% vs. 13.0%, $P < 0.001$). In parallel, numbers of patients treated with antidiabetic drugs or requiring insulin injections significantly increased within 10 years (11% vs. 15%, $P < 0.001$). At both time-points, diabetic conditions were observed with comparable frequencies in CsA- or Tac-treated patients (T1: 18.7% vs. 24.6%, $P = 0.252$; T2: 21.3% vs. 27.5%, $P = 0.386$).

Impaired lipid metabolism

In strong contrast to HBMI, HTN and HGLY, the prevalence of impaired lipid metabolism, defined by either HTRI or HCHOL, decreased during the observation period with no obvious differences in male and female patients. In 1993, 63.8% of all patients presented with elevated cholesterol levels, and 40.4% demonstrated HTRI. Ten years thereafter, the prevalence of HCHOL and HTRI was 36.7% ($P < 0.001$) and 20.7% ($P < 0.001$), respectively. Also, the mean serum cholesterol levels decreased from 221.7 ± 5.43 and 229.1 ± 6.30 mg/dl to 185.6 ± 3.83 ($P < 0.001$) and 191.6 ± 4.80 mg/dl ($P < 0.001$) in male and female patients, respectively. Corresponding figures for triglyceride levels were 208.9 ± 18.95 and 165.0 ± 11.39 mg/dl in male and female patients in 1993. In 2003, mean triglyceride levels had decreased to 143.1 ± 8.47 ($P < 0.001$) and 113.0 ± 6.95 mg/dl ($P < 0.001$), respectively.

At T1, the prevalence of HCHOL (69.3% vs. 47.8%, $P = 0.007$) or HTRI (47.3% vs. 30.4%, $P = 0.029$) has been higher in patients with CsA-based immunosuppression than in Tac-based regimens. Ten years thereafter, prevalence of impaired lipid metabolism did not demonstrate statistical differences in both groups (HCHOL: 41.3% vs. 31.9%, $P = 0.24$; HTRI: 18.7% vs. 18.8%, $P = 0.979$).

PROCAM score

Data determining the smoking status in our patients must be considered unreliable. Patients had been required to quit smoking prior to transplantation and were constantly asked not to smoke thereafter. Also, data giving the family history of cardiovascular events may be incomplete. Therefore, calculated PROCAM scores may underestimate the actual cardiovascular risk in our transplant population.

The PROCAM score of all 75 middle-aged men (35–65 years) has been calculated at T1 with a median follow-up of 18 months (6–49). The median PROCAM score equaled 42 (10–64) in our study population and was significantly higher than in the PROCAM standard population ($P = 0.009$) [12]. Forty-nine of 75 patients have been followed for the entire period of 10 years. Twenty-four patients died and two underwent re-LT. Altogether, eight nonfatal and two fatal coronary events have been observed in this particular group of patients (13%). PROCAM scores of patients suffering a cardiovascular event are given in Table 3, if applicable. Comparing the distribution of observed risk-scores in transplant recipients experiencing cardiovascular disease (median 42, 22–62) and in patients without events (median 39, 10–64), a shift to higher PROCAM scores became apparent, however, failing to reach statistical significance ($P = 0.087$).

Thirty-two patients have been eligible for PROCAM score calculation at T1 and T2 (49 survivors minus 17 dropouts because of age limit of 65 years). Interestingly, the median PROCAM score in those patients did not increase over 10 years of follow-up [T1: 41.5 (10–62), T2: 39.5 (11–52), $P = 0.911$], although age has a major impact in terms of PROCAM points. Points assigned for LDL and HDL cholesterol as well as triglyceride levels significantly decreased, while points allocated for systolic blood pressure values or diabetes mellitus demonstrated only a small increase or no increase at all.

The percentage of observed coronary events in each PROCAM class of our study population and the estimated event rate from the PROCAM standard population is given in Fig. 2. With reference to PROCAM classes, the SER in our study population calculates with 1.11 (95% CI: 0.53–2.03), indicating an event rate in liver transplant recipients comparable with estimates from the PROCAM population (Table 4).

Discussion

High prevalence of CVRF in liver transplant populations has been widely acknowledged, although the evolution of CVRF over time and the risk of cardiovascular events compared with nontransplant populations remain unclear.

In our prospective observational study, we were able to demonstrate that irrespective of basic CNI medication the prevalence of overweight, arterial HTN and diabetes

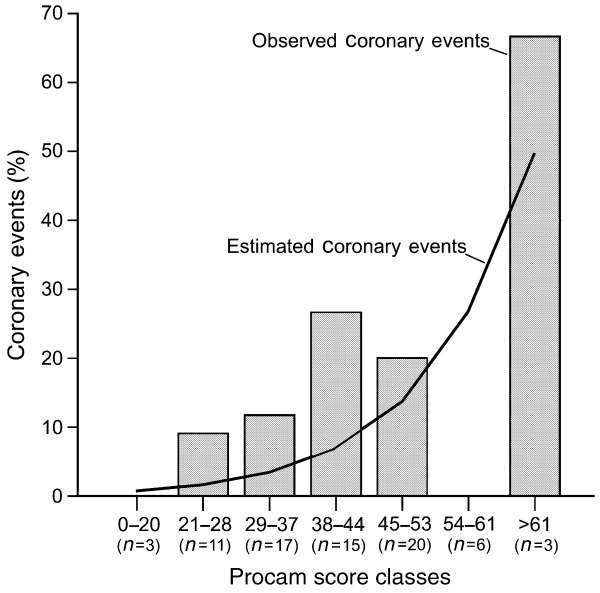

Figure 2 Estimated and observed coronary events: In 75 male patients after liver transplantation eligible for PROCAM score calculation [12] in 1993, 10 coronary events were observed within 10 years. The percentage of patients in each PROCAM class that suffered coronary events is given (gray bars). The curve depicts the estimated risk of coronary events from the PROCAM standard population (percent). (n: number of patients at risk in 1993).

mellitus increased within 10 years of follow-up, while the number of patients presenting with impaired lipid metabolism decreased over time. In parallel, the rate of steroid-free patients has been increased significantly. Overall, observed risk scores in our transplant population were higher than in the PROCAM standard population [12].

Comparison of long-term survivors after liver transplantation with data from the US general population demonstrated increased rates for arterial HTN and diabetes mellitus in liver transplant recipients, while obesity and HCHOL occurred as frequently as in the general population [2]. Equally, using the Framingham risk equation, Johnston *et al.* [4] found slightly increased cardiovascular risk-scores in the Birmingham transplant population compared with the Framingham standard population.

Prospectively observing the evolution of cardiovascular risk factors over a period of 10 years, the estimated risk for coronary heart disease events in our liver transplant population did not change significantly. Although we found an increasing prevalence and severity of overweight, arterial HTN and diabetes mellitus, the prevalence of impaired lipid metabolism decreased over time.

In keeping with our findings, Everhart *et al.* [14] described a major weight gain in liver transplant recipients during the first year after transplantation followed by minor increases in subsequent years. Also, the development of persistent arterial HTN has previously been described [15]. Another prospective trial, however, allowed for discontinuation of antihypertensive medication in a small number of patients after steroid withdrawal [16]. The prevalence of new-onset PTDM has previously been determined 7.2% at 1 year after liver transplantation [10], most likely caused by an impaired β-cell function [17]. In a Spanish transplant population, none of the patients without diabetes mellitus at 1 year post-transplantation developed PTDM in two consecutive years [9]. After steroid withdrawal, a decreased prevalence of HCHOL in liver transplant recipients has been demonstrated [16,18].

In strong contrast to our and other findings detailed above, Fernandez-Miranda *et al.* [5] reported a decreasing prevalence of arterial HTN and diabetes mellitus over 5 years of follow-up. In this study, however, significant numbers of patients with known arterial HTN or diabetes mellitus prior to liver transplantation were excluded from the respective analysis. Thus, results may represent patient selection rather than evolution of CVRF in the entire liver transplant population.

Comparison of various CNI-based immunosuppressive regimens revealed cardiovascular risk-profiles in favor of Tac [1,7,8,19–24]. Similarly, in 1993 we found a significantly higher prevalence of arterial HTN and impaired lipid metabolism, accompanied by a lower rate of steroid-

PROCAM score	Events in PROCAM population (1/1000) (R_{PRO})	Individuals in study population (1000) (N)	Events expected in study population ($R_{PRO} \times N$)	Events observed in study population (E_{obs})
00–20	5	0.003	0.015	0
21–28	15	0.011	0.165	1
29–37	23	0.017	0.391	1
38–44	66	0.015	0.990	3
45–53	148	0.020	2.960	4
54–61	281	0.006	1.686	0
>61	432	0.003	1.296	1
Σ			8.988	10

Table 4. Coronary events observed after liver transplantation and in the PROCAM Population: Coronary events in patients after liver transplantation ($n = 75$) eligible for PROCAM score calculation [12] have been recorded during a 10-year follow-up. Based on PROCAM score categories and numbers of events observed in the PROCAM population, numbers of events expected in our transplant population have been calculated and put into perspective with numbers of events observed.

free recipients, in patients under CsA treatment. In 2003, however, prevalence of CVRF in both groups converged. Also, the incidence of cardiovascular events did not demonstrate any difference between CNI-groups within 10 years of follow-up. Likewise, Textor *et al.* [25] demonstrated peak numbers of hypertensive patients under CsA-based regimens immediately following transplantation with decreasing numbers in subsequent months. Under Tac treatment, increasing proportions of hypertensive patients were observed. At 24 months, differences between both groups were almost compensated. Also, Fernandez *et al.* [26] demonstrated no differences between CsA and Tac with respect to glucose metabolism impairment on low maintenance doses. Divergent rates of HCHOL have been considered a sequel of diverse steroid treatment rather than differences in metabolic side-effects of CsA and Tac [27].

Based on the PROCAM risk score determination in 1993 and a prospective follow-up of 10 years in our liver transplant population, scores were higher than in the standard population, and the score standardized ratio for acute coronary events calculated with 1.11 (95% CI: 0.53–2.03), indicating an incidence of events reflecting increased scores. Recently, Neal *et al.* [28] described the 10-year risk of coronary heart disease predicted from the Framingham risk score 11.5% in their liver transplant population compared with 7.0% in a local English population. The incidence of myocardial infarction or stroke in liver transplant recipients, however, did not exceed numbers observed in gender and age matched local controls. Therefore, the authors wondered whether the increased prevalence of CVRF in liver transplant recipients actually translates into increased numbers of cardiovascular events. The median length of follow-up in this series was 54 months (6–90 months), which may explain the low incidence of cardiovascular events. Patients awaiting liver transplantation are well selected to prevent perioperative coronary incidents, and the prevalence of CVRF prior to LT is low [1,28]. Furthermore, atherosclerotic lesions may develop early, but will progress to clinical disease slowly over years [29]. In our observation, the majority of cardiovascular events occurred more than 90 months post-LT (Table 3). Johnston *et al.* [4] found a relative risk of 3.07 for ischemic cardiac events in their Birmingham liver transplant population compared with a gender and age matched local population.

In summary, male long-term survivors after liver transplantation presented with an increased prevalence of cardiovascular risk factors and corresponding numbers of coronary events. No significant change of observed risk scores has been detected over an observation period of 10 years. Over the same period of time, however, differences between CsA and Tac based immunosuppressive regimens converged.

As clinical disease develops over years, coronary event rates may even rise with longer observation periods. The impact of primary and secondary prevention efforts, including early steroid withdrawal, CNI-free immunosuppression, and statin intervention on cardiovascular disease rates needs to be evaluated. For the time being, close surveillance of liver transplant recipients is required. Current guidelines for the management of post-LT CVRF have recently been published [6].

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