Supplemental Information

1. *Description of statistical analysis*

Marginal structural model analysis

Marginal structural modeling consists of two main steps. In the first step, a logistic regression model is estimates which estimates the probability of treatment onset for each patient in each time window (we used 3-month intervals in our study). In a second step, these probabilities are inverted and used as observation weights (inverse probability of received treatment weights) in a Cox regression modeling framework. The robust sandwich variance estimate (Lin and Wei, JASA 1992) must be used to assess significance of the treatment effect on survival. This simple implementation could lead to weights which could suffer from substantial variation leading to inflated variance. Therefore, use of stabilized weights was proposed. In this approach, for each patient two weights are computed: one including variables measured at baseline and one excluding them. The stabilized weights correspond to the ratio of these weights. To account for the use of baseline variables in computation of the denominator, baseline variables have to be included in the final Cox regression step. We used stabilized weights in our study. In the analysis of outcomes which could suffer from informative drop-out, e.g. death in the analysis of functional graft survival, the weights are further modified by first employing logistic regression in the same way as described but this time using drop-out as outcome to obtain weights corresponding to drop-out, and then multiplying the original (treatment onset) weights by the drop-out weights. This procedure exactly follows the suggestions of Robins et al (Epidemiology 2000, 550-560), Bodnar et al. (Am J Epidemiol 2004, 926-934) and Hernan et al (Epidemiology 2000, 561-570).

In the logistic regression step, we included all potential confounders measured at baseline, and all time-dependent confounders, as well as a cubic spline function of time. Continuous variables entered the analysis using cubic splines with four knots placed at the 10th, 40th, 60th and 90th percentiles. To account for patients that were already on a statin at baseline, the model involved separate parameters for each variable to compute treatment probabilities at baseline. (In a second analysis, we omitted these patients.) The logistic regression model first involved all candidate confounders. To avoid overfit, we reduced the model by variables that were neither associated with treatment onset nor with drop-out on a significance level of 20%. Since multiple imputation was applied, we performed the whole procedure on each imputed data set and combined the results.

2. *Characteristics of all 1,829 patients with graft survival of at least 90 days*

Variable	No. of pts. (Statin/No Statin)	Statins	No Statins	p-value
Mean recipient age (SD)	1829 (316/1513)	53.9 (11.5)	47 (15.9)	<.001
Mean donor age (SD)	1761 (298/1463)	46.5 (15.2)	42.2 (16)	<.001
Donor female gender (%)	1769 (299/1470)	129 (43.1%)	580 (39.5%)	0.236
Recipient female gender (%)	1769 (299/1470)	134 (44.8%)	576 (39.2%)	0.070
Cadaveric organ donor (%)	1829 (316/1513)	291 (92.1%)	1369 (90.5%)	0.370
Median time on dialysis, years (IQR)	1829 (316/1513)	2.3 (1.2, 3.3)	1.6 (0.8, 3)	<.001
Mean body weight, kg (SD)	1285 (267/1018)	74.5 (15.3)	69.5 (16.5)	<.001
Median HbA1c level, % (IQR)	1108 (242/866)	6.2 (5.7, 7)	6.1 (5.6, 6.6)	0.007
Mean panel reactive antibodies, % (SD)	1756 (312/1444)	3.8 (10.7)	5 (13.5)	0.134
Mean sum of HLA mismatches (SD)	1665 (309/1356)	2.6 (1.4)	2.4 (1.5)	0.011
Median cold ischemia time, hours (IQR)	1602 (271/1331)	13 (9, 20)	19 (12, 24)	<.001
Median no. of blood pressure drugs (IQR)	1829 (316/1513)	3 (2, 4)	2 (0, 3)	<.001
Mean systolic blood pressure, mmHg (SD)	1215 (254/961)	137.3 (15.3)	140.1 (39.6)	0.283
Mean diastolic blood pressure, mmHg (SD)	1215 (254/961)	79.6 (8.8)	82.7 (24.5)	0.049
Mean cholesterol level, mg/dl (SD)	1520 (308/1212)	211.2 (49.6)	213.7 (74.6)	0.567

Variable	No. of pts. (Statin/No Statin)	Statins	No Statins	p-value
Coronary heart disease (%)	1108 (254/854)	76 (29.9%)	191 (22.4%)	0.013
Other heart disease (%)	1108 (254/854)	45 (17.7%)	124 (14.5%)	0.214
Vascular disease (%)	1044 (246/798)	74 (30.1%)	212 (26.6%)	0.280
Biopsy confirmed acute rejection (%)	1801 (316/1485)	113 (35.8%)	484 (32.6%)	0.278
Chronic allograft nephropathy (%)	1829 (316/1513)	48 (15.2%)	212 (14%)	0.586

3. Hazard function (risk for graft loss or death per year)
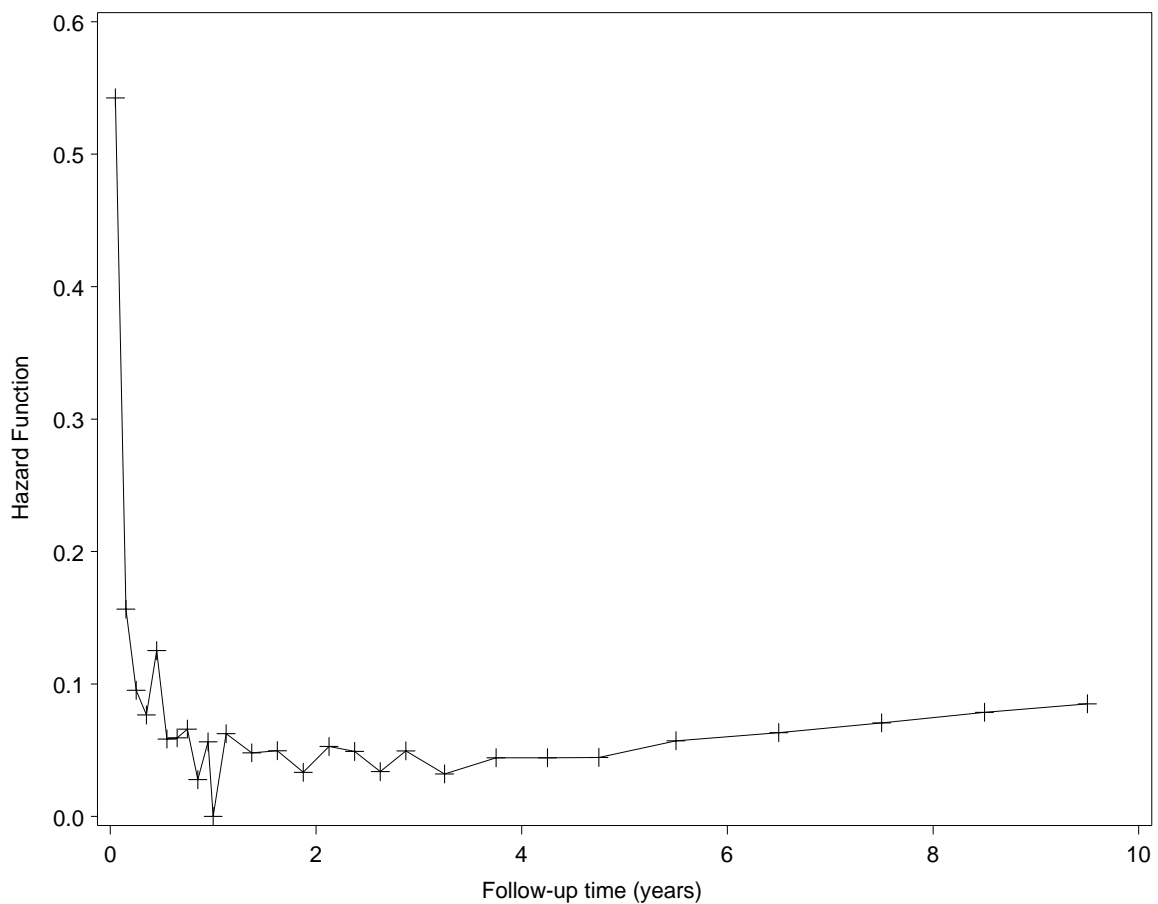
The plot shows a markedly increased risk for graft loss or death during the first few month after transplantation, and a constant hazard thereafter.

4. Complete Case Only analysis

Because of randomly missing data in many variables, the number of patients eligible for complete-case analysis is substantially reduced:

Patients	N	No. events	No. deaths	No. graft losses
Complete cases	1108	236	104	132
Full analysis	2041	588	303	285

The study population of 2041 patients can be seen as "the population" for which the HR estimates for patient survival, actual graft survival and functional graft survival are "population parameters". By definition, a 95% confidence interval for the HR computed from 1108 randomly selected patients covers its population value with 95% probability. Non-random selection would be indicated if the confidence interval excludes the inferred population value.

Since statin use is available for all patients, a full data analysis can be performed to compute the crude hazard ratio of statin use.

Comparison of crude hazard ratio estimates and results from MSM analysis, using complete-case-only (CCO) analysis (1108 patients) and multiple imputation analysis (2041 patients):

Outcome	Crude hazard ratio (95% confidence limits)	MSM: CCO hazard ratio (95% confidence limits)	MSM: multiple imputation hazard ratio (95% confidence limits)
Patient survival	0.77 (0.59, 1.0)	0.89 (0.57, 1.41)	0.69 (0.50, 0.95)
Actual graft survival	0.77 (0.63, 0.93)	0.84 (0.63, 1.14)	0.73 (0.58, 0.92)
Functional graft survival	0.76 (0.58, 1.0)	0.79 (0.50, 1.27)	0.84 (0.61, 1.17)

Results from MSM/multiple imputation are closer to crude estimates than to their MSM/CCO counterparts. For analysis of actual and functional graft survival, differences between CCO and multiple imputation results are less dramatic. The confidence intervals of the MSM/CCO hazard ratio cover the MSM/multiple imputation estimates (which are considered population values in this comparison), suggesting random selection.

However, the reduced number of patients leads to an inflation of confidence intervals. Since statin use is completely documented, a complete-cases-only analysis seems a waste of resources in the present study and bears the danger of overfitting the models due to a prohibitively high ratio of covariates and events. Therefore, such an analysis was not

further pursued. Instead, the multiple imputation approach was subjected to an analysis of sensitivity of the randomly missing data assumption (section 5).

5. Analysis of sensitivity of multiple imputation approach (comparison of results from multiple imputation after randomly deleting data and non-randomly deleting data)

To assess the sensitivity of the multiple imputation approach on the assumption of randomly missing data, we used the following procedure:

First, two new data sets were generated by doubling the amount of missing data in the variables coronary heart disease, cardiomyopathy, cerebrovascular disease, peripheral arterial disease, cholesterol, hemoglobin and mean arterial pressure (MAP). In the first set, missing values were generated randomly. In the second data set, only data above the median value of cholesterol level, hemoglobin level or MAP or with presence of heart disease or vascular disease were deleted.

Variable with missing values introduced…	… randomly		… non-randomly	
	Total N	% or Mean (SD)	Total N	% or Mean (SD)
Coronary heart disease (%)	779	26%	753	42%
Cardiomyopathy (%)	779	16%	753	26%
Cerebrovascular disease (%)	671	12%	654	22%
Peripheral arterial disease (%)	671	19%	654	36%
Mean cholesterol level (SD)	1269	206 (74)	1323	220 (75)
Mean hemoglobin level (SD)	1444	10.8 (2.7)	1469	11.1 (2.8)
Mean arterial pressure (SD)	1452	101 (51)	1483	105 (49)

Results from MSM after multiple imputation:

	Missing data generated	
	randomly	non-randomly
Outcome	Hazard ratio (95% confidence limits)	Hazard ratio (95% confidence limits)
Patient survival	0.65 (0.47, 0.89)	0.67 (0.49, 0.93)
Actual graft survival	0.71 (0.57, 0.90)	0.72 (0.57, 0.91)
Functional graft survival	0.83 (0.60, 1.16)	0.80 (0.57, 1.11)

6. *Analysis repeated without cholesterol*

Outcome	Parameter	Hazard ratio	Lower 95% limit HR	Upper 95% limit HR	Pr > |t|
Patient survival	Statin use	0.68	0.50	0.92	0.014
Actual graft survival	Statin use	0.72	0.58	0.90	0.003
Functional graft survival	Statin use	0.80	0.58	1.10	0.169

MSM analysis was repeated with each confounder left out in turn from the analysis (-*variable* indicates the variable that has been left out from analysis):

outcome	Hazard ratio	Lower 95% limit HR	Upper 95% limit HR	Pr > |t|
Patient survival -Cholesterol	0.68	0.50	0.93	0.014
Patient survival -blood pressure drugs	0.64	0.47	0.88	0.005
Patient survival -age at tpl	0.77	0.56	1.05	0.093
Patient survival -year of tpl	0.66	0.48	0.90	0.008
Patient survival -diabetes	0.70	0.51	0.97	0.030
Patient survival -cardio/vascular diseases	0.69	0.51	0.94	0.017
Patient survival -immunosuppression	0.69	0.50	0.94	0.020
Patient survival -hb	0.68	0.50	0.92	0.014
Patient survival -MAP	0.69	0.51	0.95	0.023

outcome	Hazard ratio	Lower 95% limit HR	Upper 95% limit HR	Pr > |t|
Actual graft survival -Cholesterol	0.72	0.58	0.90	0.003
Actual graft survival -blood pressure drugs	0.75	0.60	0.93	0.008
Actual graft survival -age at tpl	0.78	0.63	0.98	0.031

outcome	Hazard ratio	Lower 95% limit HR	Upper 95% limit HR	Pr > |t|
Actual graft survival -year of tpl	0.70	0.56	0.87	0.001
Actual graft survival -diabetes	0.74	0.59	0.93	0.010
Actual graft survival -cardio/vascular diseases	0.73	0.59	0.92	0.006
Actual graft survival -immunosuppression	0.73	0.58	0.92	0.007
Actual graft survival -hb	0.72	0.57	0.90	0.004
Actual graft survival -MAP	0.74	0.59	0.93	0.009

outcome	Hazard ratio	Lower 95% limit HR	Upper 95% limit HR	Pr > |t|
Functional graft survival -Cholesterol	0.80	0.58	1.10	0.169
Functional graft survival -blood pressure drugs	0.91	0.66	1.25	0.566
Functional graft survival -age at tpl	0.81	0.58	1.13	0.218
Functional graft survival -year of tpl	0.78	0.57	1.07	0.124
Functional graft survival -diabetes	0.83	0.60	1.15	0.266
Functional graft survival -cardio/vascular diseases	0.82	0.59	1.13	0.226
Functional graft survival -immunosuppression	0.82	0.59	1.14	0.232
Functional graft survival -hb	0.81	0.58	1.12	0.199
Functional graft survival -MAP	0.83	0.60	1.16	0.274

7. MSM analysis without statin users at baseline

Outcome	Parameter	Hazard ratio	Lower 95% limit HR	Upper 95% limit HR	Pr > |t|
Patient survival	Statin use	0.60	0.40	0.90	0.014
Actual graft survival	Statin use	0.64	0.48	0.86	0.003
Functional graft survival	Statin use	0.75	0.49	1.15	0.191

If only patients who were started with statins during follow-up were included in the analysis, effects were slightly more pronounced than in the initial analysis.

8. Clinical expertise models (HLA mismatches, CIT, Induction therapy, donor age forced into model)

outcome	Hazard ratio	Lower 95% limit HR	Upper 95% limit HR	Pr > |t|
Patient survival	0.650	0.474	0.892	0.008
Actual graft survival	0.740	0.589	0.929	0.010
Functional graft survival	0.809	0.586	1.117	0.198

Although donor age and induction therapy were significant predictors of functional graft survival and graft survival, their inclusion did not materially change our initial results.

9. Interaction analysis

Patient survival

var1	var2	raw_p	False Discovery Rate p-value
StatinUse	No blood pressure drugs	0.56381	0.72674
StatinUse	IS: others vs. S+MMF+CSA	0.31617	0.70260
StatinUse	IS: S+AZA+CSA vs. S+MMF+CSA	0.98909	0.98909
StatinUse	IS: S-free vs. S+MMF+CSA	0.40596	0.70335

var1	var2	raw_p	False Discovery Rate p-value
StatinUse	diabetes	0.40042	0.70335
StatinUse	CHD	0.52772	0.72674
StatinUse	cardiomyopathy	0.74358	0.78272
StatinUse	peripheral vascular disease	0.03293	0.21954
StatinUse	cerebral vascular disease	0.42201	0.70335
StatinUse	total cholesterol	0.10227	0.37154
StatinUse	LDL cholesterol	0.58139	0.72674
StatinUse	Hemoglobin HR of StatinUse at HB=11.1 (25th percentile) 0.81 (0.60, 1.07) HR of StatinUse at HB=13.6 (75th percentile) 0.45 (0.30, 0.66)	0.00012	0.00243
StatinUse	MAP HR of StatinUse at MAP=87.7 (25th percentile) 0.78 (0.58, 1.04) HR of StatinUse at MAP=103.3 (75th percentile) 0.62 (0.45, 0.86)	0.00179	0.01787
StatinUse	time on dialysis	0.73755	0.78272
StatinUse	age_at transplantation	0.22832	0.65235
StatinUse	year of transplantation	0.48113	0.72674
StatinUse	induction therapy	0.11146	0.37154
StatinUse	cold ischemia time	0.06513	0.32563
StatinUse	sum of HLA mismatches	0.73794	0.78272
StatinUse	donor age	0.30223	0.70260

Actual graft survival

var1	var2	raw_p	False Discovery Rate p-value
StatinUse	No of blood pressure drugs	0.80501	0.89445
StatinUse	IS: others vs. S+MMF+CSA	0.49655	0.75918

var1	var2	raw_p	False Discovery Rate p-value
StatinUse	IS: S+AZA+CSA vs. S+MMF+CSA	0.64530	0.75918
StatinUse	IS: S-free vs. S+MMF+CSA	0.50597	0.75918
StatinUse	diabetes	0.61149	0.75918
StatinUse	CHD	0.49985	0.75918
StatinUse	cardiomyopathy	0.98335	0.98335
StatinUse	peripheral vascular disease	0.05967	0.26339
StatinUse	cerebral vascular disease	0.62737	0.75918
StatinUse	total cholesterol	0.03725	0.24833
StatinUse	LDL cholesterol	0.41138	0.75918
StatinUse	hemoglobin	0.00356	0.03563
StatinUse	MAP	0.00237	0.03563
StatinUse	time on dialysis	0.54857	0.75918
StatinUse	age at transplantation	0.45724	0.75918
StatinUse	year of transplantation	0.46066	0.75918
StatinUse	induction therapy	0.62691	0.75918
StatinUse	cold ischemia time	0.06585	0.26339
StatinUse	sum of HLA mismatches	0.87815	0.92436
StatinUse	donor age	0.40654	0.75918

Functional graft survival

var1	var2	raw_p	False Discovery Rate p-value
StatinUse	No of blood pressure drugs	0.79527	0.98906
StatinUse	IS: others vs. S+MMF+CSA	0.06016	0.82389
StatinUse	IS: S+AZA+CSA vs. S+MMF+CSA	0.49057	0.97214
StatinUse	IS: S-free vs. S+MMF+CSA	0.89884	0.98906
StatinUse	diabetes	0.65572	0.98906
StatinUse	CHD	0.53468	0.97214
StatinUse	cardiomyopathy	0.51339	0.97214
StatinUse	peripheral vascular disease	0.78205	0.98906

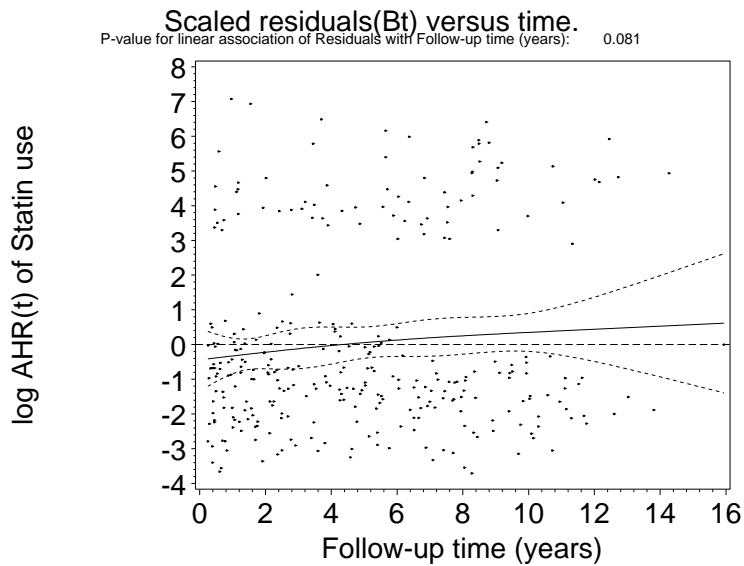| var1	var2	raw_p	False Discovery Rate p-value
StatinUse	cerebral vascular disease	0.97402	0.98906
StatinUse	total cholesterol	0.17417	0.97214
StatinUse	LDL cholesterol	0.48925	0.97214
StatinUse	hemoglobin	0.25805	0.97214
StatinUse	MAP	0.08239	0.82389
StatinUse	time on dialysis	0.23293	0.97214
StatinUse	age at transplantation	0.52998	0.97214
StatinUse	year of transplantation	0.98906	0.98906
StatinUse	induction therapy	0.60288	0.98906
StatinUse	cold ischemia time	0.44808	0.97214
StatinUse	sum of HLA mismatches	0.93232	0.98906
StatinUse	donor age	0.95469	0.98906

10. Assessment of proportional hazards assumption of statin use

The proportional hazards assumption in multivariable Cox regression was assessed by computing scaled Schoenfeld residuals and correlating them with time and rank of time. Because of the multiple testing situation involved, the significance level for testing the correlation was set to 1%.

Patient survival

Variable	Corr with time	Corr with ranked time	P-value Corr with time	P-value Corr with ranked time
Statin use	0.10	0.10	0.081	0.078
Coronary heart disease	0.01	0.02	0.824	0.770
Other heart disease	0.05	0.04	0.419	0.510
Year of engraftment	-0.13	-0.15	0.019	0.009
Diabetes	0.01	0.01	0.854	0.920
Cholesterol level	0.03	0.03	0.556	0.607

Variable	Corr with time	Corr with ranked time	P-value Corr with time	P-value Corr with ranked time
Peripheral vascular disease	-0.02	-0.03	0.696	0.642
MAP	0.06	0.06	0.259	0.258
Hb	-0.08	-0.07	0.174	0.221
Age at transplantation	0.02	0.02	0.712	0.768

Scaled residuals(Bt) versus time.
P-value for linear association of Residuals with Follow-up time (years):   0.081
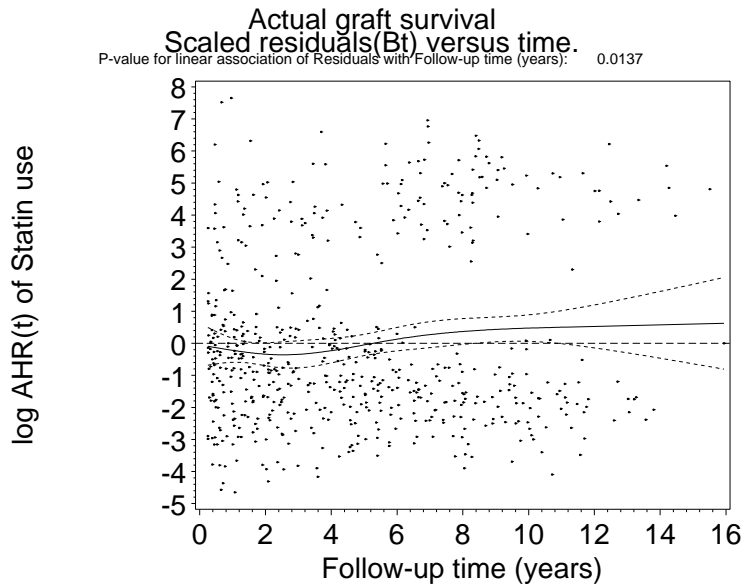
Comment: The plot shows a more pronounced effect during the first years, and later no effect of statin treatment. (exploratory finding because of non-significance of violation of ph assumption)
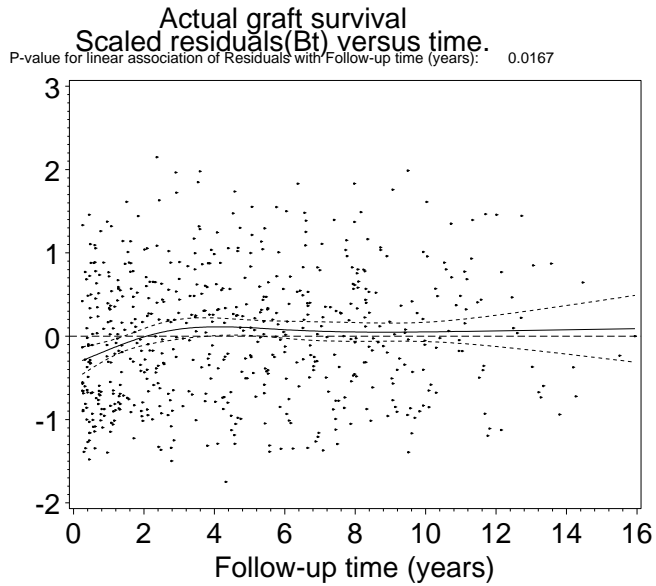
Actual graft survival

Variable	Corr with time	Corr with ranked time	P-value Corr with time	P-value Corr with ranked time
Statin use	0.10093	0.09386	0.0137	0.0219
Diabetes	-0.00669	-0.01051	0.8705	0.7978
MAP	-0.00344	-0.00113	0.9333	0.9780
Other heart disease	0.07285	0.05749	0.0756	0.1610
No blood pressure drugs	0.09797	0.11878	0.0167	0.0037
Year of engraftment	-0.03830	-0.03567	0.3506	0.3846
Coronary heart disease	-0.00443	-0.00138	0.9141	0.9732
IS: others vs. S+MMF+CSA	-0.04690	-0.03808	0.2529	0.3534
IS: S+AZA+CSA vs. S+MMF+CSA	-0.01034	0.00017	0.8011	0.9967
IS: S-free vs. S+MMF+CSA	-0.01490	-0.00952	0.7166	0.8167
Cholesterol level	0.02074	0.00949	0.6133	0.8171
Peripheral vascular disease	-0.01022	-0.01585	0.8034	0.6994
Age at transplantation	0.01198	0.02956	0.7705	0.4714
Hemoglobin level	-0.09844	-0.10288	0.0162	0.0120

Scaled Schoenfeld residuals were plotted against time for the variables: statin use, number of bloodpressure lowering drugs and hb (hemoglobin).Schoenfeld residuals of Statin use:

Actual graft survival
Scaled residuals(Bt) versus time.
P-value for linear association of Residuals with Follow-up time (years): 0.0137

Comment: the plot shows a more pronounced effect during the first four years, and a reverse effect after 7 years of follow-up (exploratory finding because of non-significance of violation of ph assumption)

Schoenfeld residuals of number of bloodpressure lowering drugs:

Actual graft survival
Scaled residuals(Bt) versus time.
P-value for linear association of Residuals with Follow-up time (years): 0.0167

Comment: the plot shows a protective effect of the number of blood pressure drugs during the first two years, and the reverse afterwards. Adjusting for this time-dependency by including an interaction with log(time) did not change the hazard ratio of statin use.
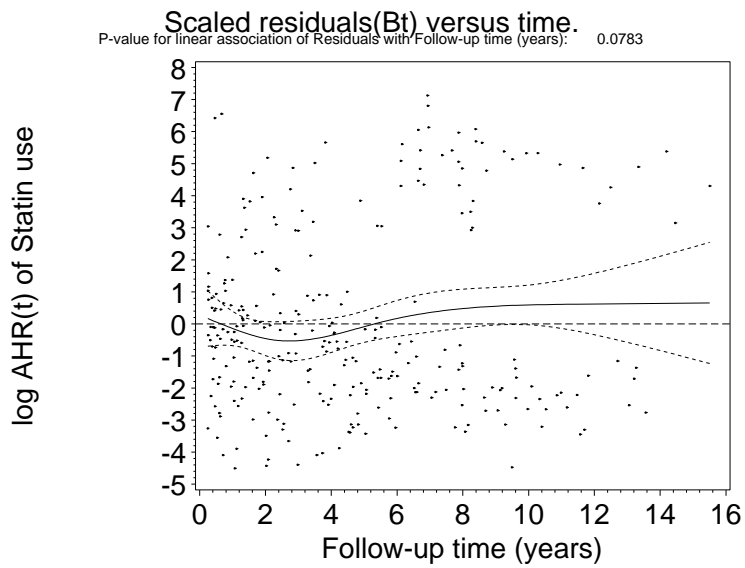
Schoenfeld residuals of hb:

Actual graft survival
Scaled residuals(Bt) versus time.
P-value for linear association of Residuals with Follow-up time (years):   0.0162

Comment: Higher hb levels are associated with better outcome only after about four years.

Functional graft survival

Correlation of scaled Schoenfeld residuals with time and with rank of time:

	Variable	Corr with time	Corr with ranked time	P-value Corr with time	P-value Corr with ranked time
1	Statin use	0.10466	0.08981	0.0783	0.1311
2	Age at tpl	-0.01987	0.02501	0.7389	0.6748
3	Diabetes	-0.03000	-0.02810	0.6147	0.6372
4	Peripheral arterial disease	0.01785	0.00781	0.7645	0.8957
5	Coronary heart disease	-0.00422	-0.00207	0.9435	0.9723
6	Cardiomyopathy	0.10959	0.07890	0.0651	0.1849
7	Year of tpl	0.06878	0.09196	0.2480	0.1221
8	Cholesterol level	0.01265	-0.01320	0.8319	0.8247
9	No of blood pressure drugs	0.08910	0.12973	0.1342	0.0288
10	IS: others vs. S+MMF+CSA	-0.07149	-0.06446	0.2297	0.2790
11	IS: S+AZA+CSA vs. S+MMF+CSA	-0.03570	-0.00250	0.5490	0.9666
12	IS: S-free vs. S+MMF+CSA	-0.06116	-0.05420	0.3044	0.3628
13	Hb	-0.12783	-0.15620	0.0313	0.0084

Scaled Schoenfeld residual plot for Statin use:

Scaled residuals(Bt) versus time.
P-value for linear association of Residuals with Follow-up time (years): 0.0783

The protective effect of Statin use appears to be most pronounced in a period of 1-5 years after transplantation. Later, there is equal or even higher (though non-significantly) risk of graft failure for Statin users compared to non-users.

11. *Cardiovascular death outcome*

Among the 2041 patients, 223 died with confirmed cardiovascular causes. 35 of these 223 deaths occurred before day 90. Extended Kaplan-Meier plot stratified for (time-dependent) statin use:
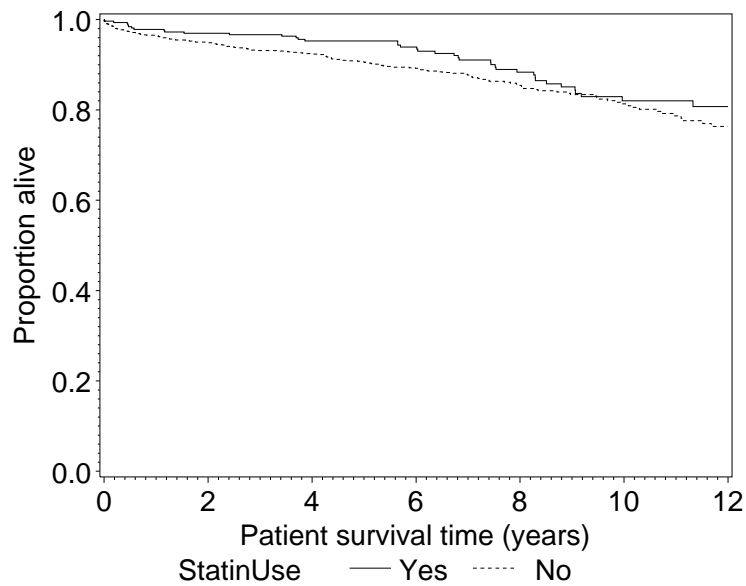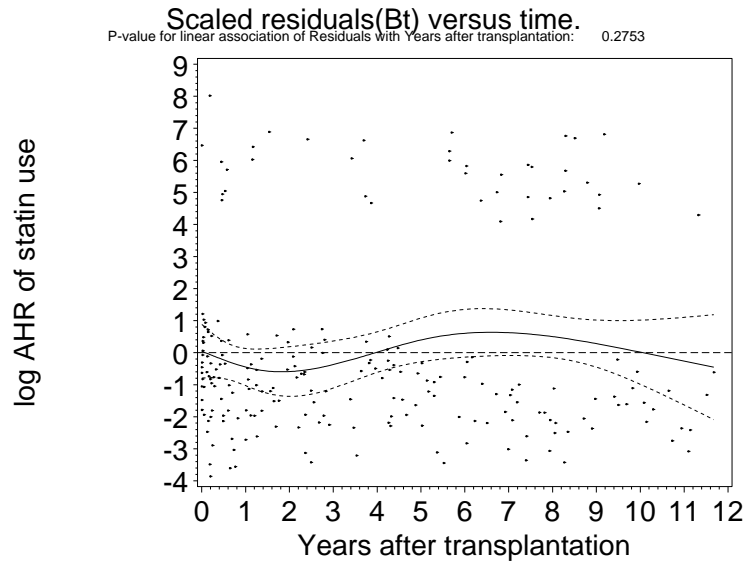

The confounder adjusted hazard ratios (MSM analysis and multivariable Cox regression; counting only cardiovascular causes; 223 events of 2041 patients) were:

Type of analysis	Hazard ratio	Lower 95% limit HR	Upper 95% limit HR	Pr > |t|
MSM analysis (adjusting for informative censoring due to death of other causes and graft loss)	0.591	0.344	1.014	0.067
Cox regression analysis (not adjusting for informative censoring)	0.802	0.565	1.139	0.217

The results from MSM analysis are very similar to those from all-cause mortality. Cox regression analysis, which does not account for informative censoring (death from other than cardiovascular causes) yields a higher hazard ratio.

Scaled Schoenfeld residuals of statin use versus time:

Scaled residuals(Bt) versus time.

P-value for linear association of Residuals with Years after transplantation: 0.2753

The Schoenfeld residuals plot and the extended Kaplan-Meier curves (section 13) show a more pronounced effect during the first years after transplantation, and a reverse situation thereafter. Summarizing the whole follow-up period into one hazard ratio results in a value of about 0.85 (counting cardiovascular deaths from day 90 as events) or 0.77 (counting all cardiovascular deaths as events).

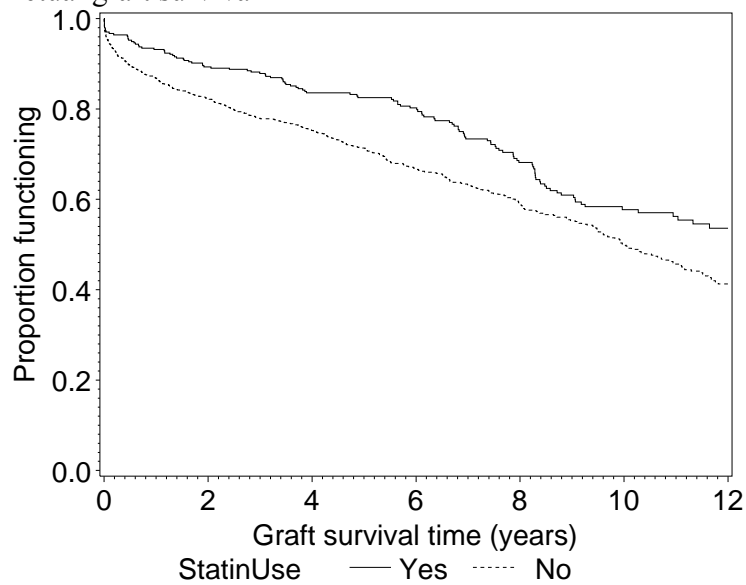## 12. *Analysis including events between days 0 and 90*

Kaplan-Meier analysis
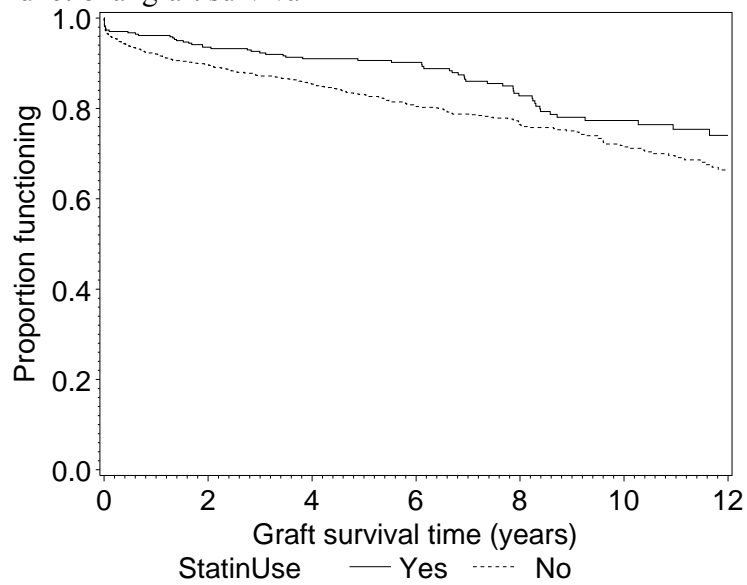
Extended (time-dependent group) Kaplan-Meier curves
Patient survival
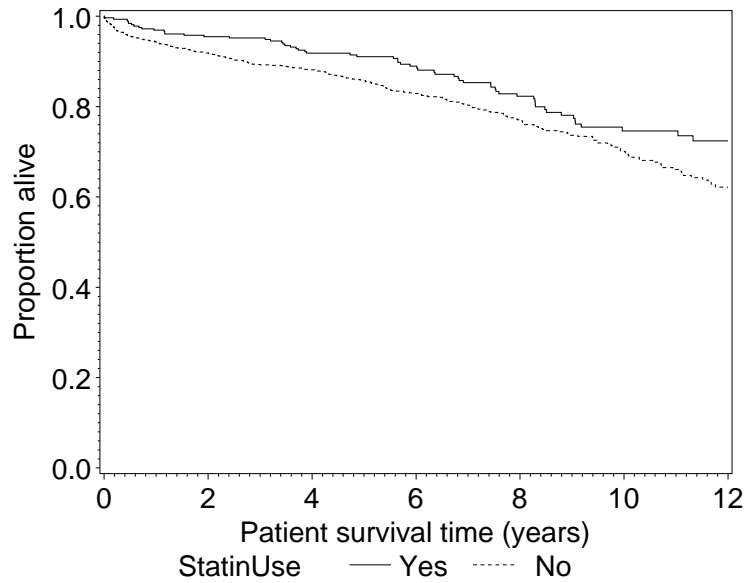
Actual graft survival

Functional graft survival

Results from marginal structural models

outcome	Hazard ratio	Lower 95% limit HR	Upper 95% limit HR	Pr > |t|
Patient survival	0.66	0.49	0.90	0.009
Actual graft survival	0.75	0.61	0.93	0.008
Functional graft survival	0.88	0.65	1.20	0.420

13. *Analysis of time to (biopsy confirmed) acute rejection*

Results from Kaplan-Meier analysis and Cox regression. Dependent variable: BCAR up to one year after transplantation.

STRATA: ...... StatinUse=No ——— StatinUse=Yes
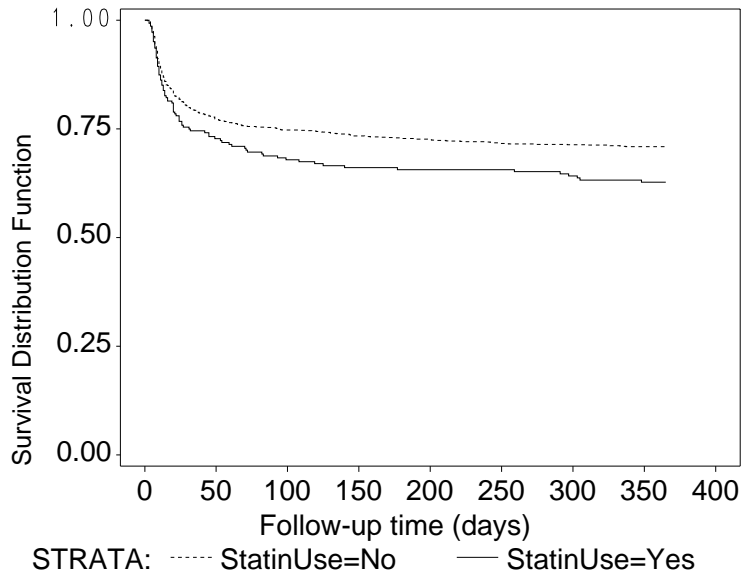
Crude hazard ratio:

Variable	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	Pr > Chi-Square
Statin use	1.33	1.06	1.66	0.0138

Multivariable Cox model:

Variable (measured at TPL)	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	Pr > Chi-Square
Statin use	0.91	0.70	1.17	0.4551
Cholesterol level	1.01	1.00	1.01	0.0038
$(Cholesterol/100)^2$	0.85	0.75	0.95	0.0039
No of blood pressure drugs	1.07	1.00	1.13	0.0440
Coronary heart disear	1.02	0.89	1.18	0.7604
Cardiomyopathy	1.08	0.93	1.26	0.3068
Cerebrovascular disease	1.06	0.89	1.25	0.5208
Peripheral arterial disease	1.11	0.96	1.29	0.1711
Time on dialysis	1.04	1.00	1.09	0.0452
diabetes	1.29	1.04	1.61	0.0235
Age at tpl	1.00	0.99	1.00	0.1633
Year of tpl	1.08	1.05	1.11	<.0001
HB	0.92	0.67	1.27	0.6160
MAP	1.00	1.00	1.01	0.0074
IS: others vs. S+MMF+CSA	1.24	0.97	1.60	0.0899
IS: S+AZA+CSA vs. S+MMF+CSA	2.30	1.69	3.14	<.0001
IS: S-free vs. S+MMF+CSA	1.25	0.75	2.08	0.3915
$(HB/10)^2$	0.81	0.17	3.89	0.7974
$(MAP/100)^2$	0.93	0.86	1.00	0.0457

Proportion of patients with biopsy-confirmed chronic allograft injury (formally CAN):

	Nr. of pts. (Statin/No Statin)	Statins	No Statins	p-value
Biopsy confirmed acute rejection (%)	2007 (302/1705)	105 (34.8%)	536 (31.4%)	0.25
Chronic allograft injury (%)	2041 (302/1739)	42 (13.9%)	219 (12.6%)	0.53

14. Analysis of actual graft survival

Actual graft survival

In this analysis, graft failure and death with a functioning graft occurring after the 90th day of engraftment were counted as endpoints. Actual graft survival after twelve years was 56% in the statin group and 45% in the non-statin group (unadjusted p-value: 0.007). In the univariate analysis, statin treatment was associated with improved actual graft survival compared to untreated patients (HR 0.77, 95% CI 0.63-0.93, p-value 0.006) (see Figure), which was confirmed in the multivariable model (HR 0.68, 95% CI 0.55-0.84, p-value <0.001) (see Table), as well as by MSM analysis (HR 0.73, 95% CI 0.58-0.92, p-value 0.007) . There was no interaction between statin treatment and any of the covariates of the multivariable model.

Kaplan-Meier curves of actual graft survival (endpoints: graft failure and death with functioning graft) according to statin use treated as time-dependent variable. Figures on the bottom indicate patients at risk at different times of follow-up.
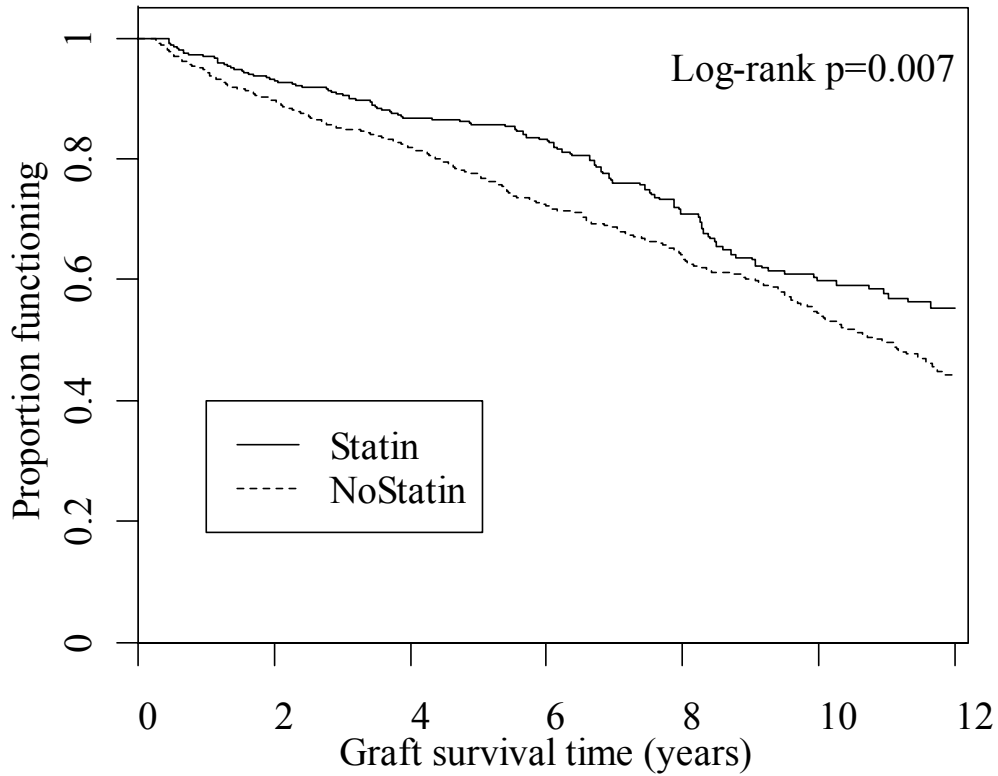
Multivariable Cox's proportional hazards model assessing the confounder-adjusted association of statin treatment on actual graft survival (graft failure and death with functioning graft counted as endpoints). [*] Standard immunosuppression was steroids + MMF + CNI

	HR	95% CI	p-value
Statin treatment	0.68	0.55 – 0.84	<0.001
Age (per decade)	1.26	1.18 – 1.34	<0.001
Year of transplantation	0.96	0.93 – 0.99	0.014
Diabetes mellitus	1.24	1.00 – 1.54	0.049
Coronary heart disease	1.24	0.97 – 1.60	0.088
Peripheral arterial disease	1.33	1.03 – 1.73	0.030
Cardiomyopathy	1.21	0.91 – 1.59	0.185
Mean arterial pressure (per 10 mmHg)	1.02	1.00 – 1.04	0.037
No. of blood pressure drugs	1.08	1.02 – 1.15	0.009
Cholesterol (per 50 mg/dl)	0.89	0.82 – 0.96	0.003
Hemoglobin (g/dl)	0.83	0.80 – 0.86	<0.001
Immunsuppression (S + AZA + CNI vs. standard)[*]	1.20	0.90 – 1.61	0.214
Immunsuppression (steroid-free vs. standard)[*]	1.05	0.74 – 1.48	0.790
Immunsuppression (else vs. standard)[*]	1.56	1.20 – 2.02	<0.001

15. Onset of statin treatment after transplantation

ProportionOnStatin
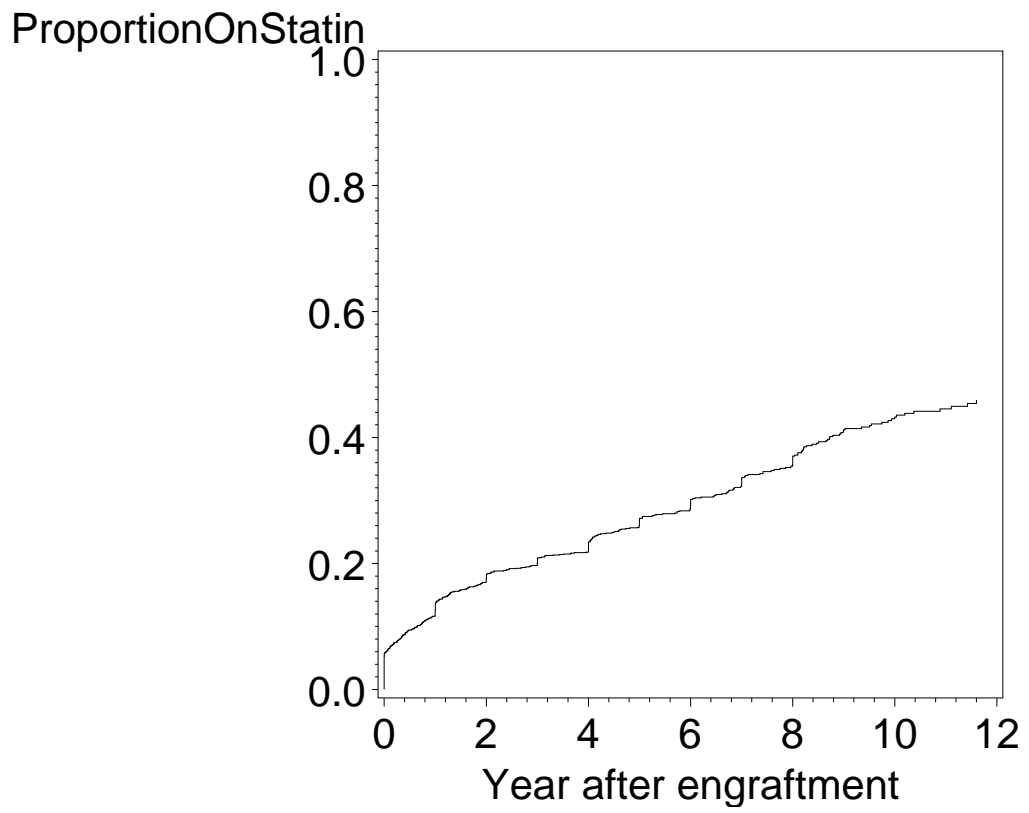
16. Multivariable Cox analysis assessing the effect of statin treatment on patient survival and functional graft survival

Multivariable Cox's proportional hazards model assessing the confounder-adjusted association of statin treatment on patient survival (death of any cause counted as endpoint).

	HR	95% CI	p-value
Statin treatment	0.64	0.48 – 0.86	0.003
Age (per decade)	1.71	1.54 – 1.9	<.001
Year of transplantation	0.96	0.92 – 1.00	0.029
Diabetes mellitus	1.33	1.01 – 1.76	0.041
Coronary heart disease	1.31	0.96 – 1.79	0.083
Peripheral arterial disease	1.45	1.05 – 2.00	0.026
Cardiomyopathy	1.15	0.78 – 1.69	0.464
Mean arterial pressure (per 10 mm/Hg)	1.01	1.00 – 1.01	0.002
Cholesterol (per 50 mg/dl)	0.91	0.81 – 1.02	0.112
Hemoglobin (g/dl)	0.87	0.83 – 0.92	<.001

Multivariable Cox's proportional hazards model assessing the confounder-adjusted association of statin treatment on functional graft survival (graft failure counted as endpoints, death censored). [*] Standard immunosuppression was steroids + MMF + CNI

	HR	95% CI	p-value
Statin treatment	0.76	0.55 – 1.04	0.086
Age (per decade)	0.99	0.91 – 1.08	0.907
Year of transplantation	0.95	0.91 – 0.99	0.014
Diabetes mellitus	1.18	0.85 – 1.63	0.330
Coronary heart disease	1.15	0.77 – 1.72	0.494
Peripheral arterial disease	1.17	0.78 – 1.75	0.439
Cardiomyopathy	1.23	0.87 – 1.73	0.239
No. of blood pressure medications	1.21	1.12 – 1.32	<0.001
Cholesterol (per 50 mg/dl)	0.87	0.78 – 0.97	0.010
Hemoglogin (g/dl)	0.80	0.76 – 0.84	<0.001
Immunsuppression (S + AZA + CNI vs. standard)[*]	1.37	0.87 – 2.14	0.171
Immunsuppression (steroid-free vs. standard)[*]	1.15	0.67 – 1.97	0.620
Immunsuppression (else vs. standard)[*]	2.13	1.43 – 3.16	<0.001