Supplemental data file to:

CALCINEURIN INHIBITOR BASED IMMUNOSUPPRESSIVE THERAPY, ORGAN DONOR AGE AND LONG TERM OUTCOME AFTER TRANSPLANTATION

AN ANALYSIS OF INTERACTIONS AND ASSOCIATIONS

by

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Target variables: Immunosuppressive regimen which was active on day 90 after tpl, donor age.

Inclusion: all patients who received a kidney transplant between Jan 1 1990 and Dec 31 2003 (N=2031) and had a functioning graft at day 90 (N=1829).

Description of statistical methods

Baseline characteristics

Continuous variables are described by mean and standard deviation and compared between groups by analysis of variance, or, in case of skew distributions, described by median, 25th and 75th percentiles and compared by Kruskal-Wallis-tests. Categorical variables are described by frequencies and percentages and compared by chi-square tests.

Survival analysis

Our study aimed at assessing the interaction of the associations of donor age and immunosuppressive therapy (IT) at day 90 after engraftment (including calcineurin inhibitors: CNI+, not including calcineurin inhibitors: CNI-) on actual graft survival (treating graft loss or death as event), functional graft survival (censoring patient death) and patient survival (censoring graft loss). For all types of survival analysis, we considered only the period from engraftment until graft loss (censoring for later death) or death with functioning graft. The distribution of these outcomes was illustrated by Kaplan-Meier curves, stratified for immunosuppressive therapy and categorized donor age (group I: 35 years or less, group II: 35-49 years, group III: 49-65 years, group IV: 65 years or more). In our study we were primarily interested in patients older than 65; therefore this relatively small number of patients constituted a separate group (group IV). The remaining patients were divided into three approximately equally-sized age groups.

Multivariable Cox proportional hazards regression was used to adjust the interaction effect of donor age and immunosuppressive therapy at day 90 after engraftment for the potentially confounding covariates year of engraftment, time on dialysis before engraftment, recipient age, presence of cardiac or vascular disease, serum cholesterol level, mean arterial blood pressure, and diabetes status as well as type of donor (cadaveric or living). All these covariates entered the analysis with their values measured at time of engraftment, since a confounder is required to be causally independent of the effect of interest. In a second analysis, we additionally included biopsy confirmed acute rejection, delayed graft function and log serum creatinine level at day 90 after engraftment. Since these variables are measured after engraftment, we cannot rule out that they are already affected by donor age and immunosuppressive therapy. Therefore, these variables are not considered as confounders but rather assumed to mediate the effect of our target variables on the outcome. For the analysis of functional graft survival, we additionally included sum HLA mismatches, panel reactive antibodies (categorized into 0-10, 10-30 and 30-100) in our model. Since we are studying the interaction of donor age and type of IT, results are presented by adjusted hazard ratio (AHR) estimates referring to the

comparison of patients with different donor age within each IT group, and also by hazards ratio referring to the comparison of CNI+ and CNI- patients within each donor age group.

Potential interactions of any variables with donor age or immunosuppressive therapy were checked for statistical significance. The assumption of proportional hazards was assessed by evaluating interactions of each variable with log of time for statistical significance. Significant interactions with log of time led to the inspection of scaled Schoenfeld residuals, partitioning of the time axis based on the course of the Schoenfeld residuals and the subsequent estimation of two piecewise constant hazard ratios for such variables. The non-linearity of the donor age effect was taken into account by first, creating four groups according to donor age as outlined above, and second, by depicting the hazard ratio of donor age on survival graphically using restricted cubic splines using the RCS macro available at www.meduniwien.ac.at/msi/biometrie.
Median follow-up time (25^{th}, 75^{th} percentiles) was computed using the Kaplan-Meier method with inverse status indicator.

Handling of missing data

Missing values are a problem commonly encountered in studies like ours. Particularly in the analysis of multivariable models one may end up with 30-40% complete observations even if each variable has no more than 5-10% missing values. Therefore, we applied multiple imputation to our data set, which is currently the state-of-the-art technique to deal with missing values. We used SAS/PROC MI to generate 20 completed data sets and SAS/PROC MIANALYZE to properly combine Cox regression results from each of the completed data sets (http://support.sas.com/rnd/app/da/new/dami.html). Generally, results obtained by multiple imputation can be biased if covariate values are not missing just randomly. Therefore, we assessed the sensitivity of our initial results on the assumption of randomly missing data by artificially doubling the amount of missing data in each covariate in two ways: first, purely at random and second, only in subjects with covariate values higher than the median. The results from both analyses were then compared.
All statistical analyses were done using the SAS System V9.1 (SAS Institute Inc., 2003, Cary, NC, USA). P-values lower than 0.05 were considered as indicating statistical significance. Kaplan-Meier curves were drawn using the R/survplot program of Frank Harrell's Design package (cran.r-project.org).

Baseline data

Considered Variables:

donorage10	Age of donor (decades)
age_tpl10	age of recipient (decades)
khk cmp	coronary heart disease+MCI, Heart insufficiency+others
vascid1 vascid2	cerebrovascular/peripheral vascular dis.
year_tpl	Year of first kidney transplantation
dialysezeit	years between first RRT and TPL
cholest10	Cholest / 10
bloodpressidneu	# Bloodpressure lowering drugs
acei_arb	ACEI/ARB (contained in bloodpressidneu)
diabetes	
map10	MAP / 10
bcar	biopsy confirmed acute rejection
dgf	
creat90	Creatinine reading at day 90 after TPL
mmsum	
pra_g	PRA: 0=0-10, 1=10-30, 2=30-100 (Dr.Oberbauers Classification)
cad	Cadaveric donor

Used in models:

donorage1	Donor age <36 (vs. Donor age 65+)
donorage2	Donor age 36-49 (vs. Donor age 65+)
donorage3	Donor age 50-64 (vs. Donor age 65+)
immg9O	IS=CA vs. IS=noCA
noCA_DA1	Bei IS=noCA: Donor age <36 vs. 65+
noCA_DA2	Bei IS=noCA: Donor age 36-49 vs. 65+
noCA_DA3	Bei IS=noCA: Donor age 5O-64 vs. 65+
CA_DA1	Bei IS=CA: Donor age <36 vs. 65+
CA_DA2	Bei IS=CA: Donor age 36-49 vs. 65+
CA_DA3	Bei IS=CA: Donor age 5O-64 vs. 65+

Patient characteristics ("Table 1")

Variable (at TPL)	Total	Total	IS=CNI- (day 90)	IS=CNI-	IS=CNI+ (day 90)	IS=CNI+	P
	N non-missing	Mean (SD) or N (%) or Median (P25, P75)	N non-missing	Mean (SD) or N (%) or Median (P25, P75)	N non-missing	Mean (SD) or N (%) or Median (P25, P75)	
Donor age	1761	43.0 (16.0)	234	42.8 (15.6)	1527	43.0 (16.0)	0.84
Recipient age	1829	48.2 (15.5)	242	45.3 (15.1)	1587	48.6 (15.5)	0.002
KHK	1125	271 (24.1%)	154	29 (18.8%)	971	242 (24.9%)	0.10
CMP	1125	169 (15.0%)	154	14 (9.1%)	971	155 (16.0%)	0.027
Vascid1	1062	127 (12.0%)	150	9 (6.0%)	912	118 (12.9%)	0.015
Vascid2	1062	206 (19.4%)	150	19 (12.7%)	912	187 (20.5%)	0.025
Year of first RRT	1829	1994 (1991, 1998)	242	1992 (1989, 1997)	1587	1995 (1991, 1998)	<0.001
Year of (first) TX	1829	1996 (1993, 2000)	242	1994 (1991, 1999)	1587	1997 (1993, 2000)	<0.001
Years on dialysis	1829	2.2 (1.9)	242	2.2 (2.1)	1587	2.2 (1.9)	0.74
Cholesterol at TX	1520	210.0 (72.5)	170	200.7 (89.1)	1350	211.2 (70.1)	0.077
Bloodpressidneu (# blood pressure lowering drugs)	1829	2 (1, 3)	242	0 (0, 3)	1587	2 (1,3)	<0.001
ACEI/ARB	1829	725	242	59	1587	666	<0.001

		(39.6%)		(24.4%)		(42.0%)	
Diabetes	1829	379 (20.7%)	242	40 (16.5%)	1587	339 (21.4%)	0.084
MAP (at TX)	1593	100.0 (93.3, 110.0)	177	101.7 (93.3, 110.0)	1416	100.0 (92.4, 110.0)	0.18
Hypertension (MAP>107 or >=1 bp med.)	1829	1516 (82.9%)	242	150 (62.0%)	1587	1366 (86.1%)	<0.001
PRA: 0-10 PRA: 10-30 PRA: 30-100	1756	1523 (86.7%) 152 (8.7%) 81 (4.6%)	230	199 (86.5%) 20 (8.7%) 11 (4.8%)	1526	1324 (86.6%) 132 (8.7%) 70 (4.6%)	0.99
MMSUM	1663	3 (2, 3)	170	3 (2, 3)	1493	3 (2, 3)	0.51
Cadaveric kidney donors	1812	1692 (93.4%)	238	225 (94.5%)	1574	1467 (93.2%)	0.44
Mediators:							
BCAR	1829	586 (32.0%)	242	81 (33.5%)	1587	505 (31.8%)	0.61
DGF	1718	372 (21.7%)	227	51 (22.5%)	1491	321 (21.5%)	0.75
Creatinine at day 90	1720	1.6 (1.3, 2.5)	205	1.8 (1.3, 2.8)	1515	1.6 (1.3, 2.4)	0.030

Correlations

All Pearson correlation coefficients whose absolute values are greater than 0.2:

NAME	_with_	corr_p	_grade_	
year_tpl	year_first	0.90182	*** Strong	***
bloodpressidneu	acei_arb	0.64907	*** Moderate	***
year_tpl	bloodpress	0.48585	*** Weak	***
year_firstrrt	bloodpress	0.42644	*** Weak	***
khk	vascid2	0.41522	*** Weak	***
year_tpl	acei_arb	0.39868	*** Weak	***
vascid2	diabetes	0.36589	*** Weak	***
year_firstrrt	acei_arb	0.36454	*** Weak	***
donorage10	dgf	0.33878	*** Weak	***
age_tpl10	khk	0.33516	*** Weak	***
age_tpl10	vascid2	0.29976		
khk	diabetes	0.28057		
donorage10	year_tpl	0.23182		
donorage10	year_first	0.20937		
age_tpl10	vascid1	0.20850		
khk	vascid1	0.20255		
khk	cmp	-0.23685		
year_firstrrt	cholest10	-0.24577		
year_tpl	cholest10	-0.28283		
year_firstrrt	dialysezei	-0.38391	*** Weak	***

Propensity analysis

Which variables are independent predictors of type of immunosuppresive regimen?
Multivariable logistic regression analysis, backward stepwise elimination, no interactions assumed

Odds ratios: >1 - > high value of variable favours CNI+
<1 - > high value of variable favours CNI-

Parameter	Odds Ratio	Lower 95% CL OR	Upper 95% CL OR	Pr > |t|
year_tpl	1.11681	1.07784	1.15720	<.0001
cholest10	1.02375	1.00213	1.04585	0.0313

How much of the variation in IS is explained by these variables (computed via the relimplr macro available at www.meduniwien.ac.at/msi/biometrie):

Proportion of Explained Variation (PEV)

PEV	Marginal	Partial	Variables
1	2.24%	2.86%	year_tpl
2	0.05%	0.67%	cholest10
Model	2.91%		

Association of variables with donor age

This analysis compares the distribution of all confounders between the 4 groups defined by donor age. Significant associations were found for: (cf. Appendix A for full results):

	All			Donor age											
				<36			36-49			50-64			65+		
	year_tpl			year_tpl			year_tpl			year_tpl			year_tpl		
	N	Mean	Std	N	Mean	Std	N	Mean	Std	N	Mean	Std	N	Mean	Std
year_tpl P=0	1761	1996	4.1	547	1995	4.1	552	1996	4.1	511	1997	3.9	151	1998	3.8
age_tpl P=0	1761	48.1	15.5	547	46.3	16.5	552	46.4	15.1	511	48.5	13.6	151	59.5	14.0
mmsum P=0	1606	2.4	1.3	492	2.3	1.2	498	2.4	1.3	476	2.4	1.3	140	3.0	1.5

	All		Donor age							
			<36		36-49		50-64		65+	
	N	ColPctN	N	ColPctN	N	ColPctN	N	ColPctN	N	ColPctN
Khk										
0	829	76.4	234	76.0	270	79.9	256	78.5	69	61.1
1	256	23.6	74	24.0	68	20.1	70	21.5	44	38.9
khk P=0.0005	1085	100.0	308	100.0	338	100.0	326	100.0	113	100.0
vascid2										
0	831	81.0	233	79.3	259	82.0	269	86.8	70	66.0
1	195	19.0	61	20.7	57	18.0	41	13.2	36	34.0
vascid2 P=0	1026	100.0	294	100.0	316	100.0	310	100.0	106	100.0
Diabetes										
0	1399	79.4	417	76.2	457	82.8	416	81.4	109	72.2
1	362	20.6	130	23.8	95	17.2	95	18.6	42	27.8
diabetes P=0.004	1761	100.0	547	100.0	552	100.0	511	100.0	151	100.0
dgf										
0	1319	78.5	492	93.9	433	82.5	318	65.3	76	52.4
1	362	21.5	32	6.1	92	17.5	169	34.7	69	47.6
dgf P=0	1681	100.0	524	100.0	525	100.0	487	100.0	145	100.0

	All				Donor age															
					<36				36-49				50-64				65+			
	creat90				creat90				creat90				creat90				creat90			
	N	Median	P25	P75	N	Median	P25	P75	N	Median	P25	P75	N	Median	P25	P75	N	Median	P25	P75
creat90 P=0	1657	1.6	1.3	2.5	499	1.5	1.2	2.2	524	1.6	1.2	2.5	491	1.7	1.4	2.8	143	1.9	1.4	3.4

Associations of variables with the interaction of donor age and CNI:

The following table shows the p-values for testing an interaction of CNI and donor age in the model
Variable ~ CNIGroup + DonorAgeGroup + CNIxDonorAge, using a general linear or a logistic model for continuous or categorical variables, respectively.

Obs	variable	pvalue
1		.
2	map10	0.10020
3	year_tpl	0.83647
4	dialysezeit	0.89662
5	cholest	0.02133
6	age_tpl	0.01141
7	MMSum	0.09564
8	pra_g	0.17232
9	khk	0.34927
10	cmp	0.45416
11	vascid1	0.60520
12	vascid2	0.79019
13	diabetes	0.69551
14	bcar1	0.33351
15	dgf	0.68446
16	cad	0.53177
17	logcreat90	0.00050

	All			Donor age											
				<36			36-49			50-64			65+		
	Cholest			cholest			cholest			cholest			cholest		
	N	Mean	Std	N	Mean	Std	N	Mean	Std	N	Mean	Std	N	Mean	Std
CNI- P=0.0796	1301	211.7	70.5	380	219.5	77.9	413	208.6	66.7	388	209.0	68.8	120	206.1	62.4
CNI+ P=0.2534	164	199.9	90.3	37	176.4	83.3	59	211.7	79.9	55	198.8	94.1	13	218.7	128.3

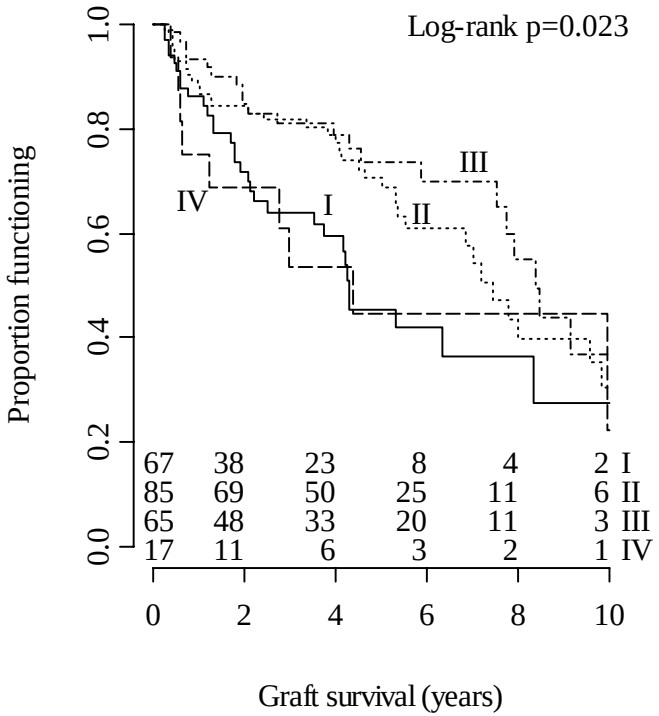
	All			Donor age											
				<36			36-49			50-64			65+		
	age_tpl			age_tpl			age_tpl			age_tpl			age_tpl		
	N	Mean	Std	N	Mean	Std	N	Mean	Std	N	Mean	Std	N	Mean	Std
CNI- P=0	1527	48.6	15.5	480	47.2	16.0	467	46.3	15.3	446	48.8	13.8	134	60.5	13.5
CNI+ P=0.0053	234	45.1	15.1	67	39.9	18.4	85	46.8	13.7	65	46.4	11.5	17	51.7	15.3

	All				Donor age															
					<36				36-49				50-64				65+			
	creat90				Creat90				creat90				creat90				creat90			
	N	Median	P25	P75	N	Median	P25	P75	N	Median	P25	P75	N	Median	P25	P75	N	Median	P25	P75
CNI- P=0	1458	1.6	1.3	2.5	449	1.5	1.2	2.0	452	1.6	1.2	2.5	429	1.7	1.4	2.7	128	1.9	1.5	3.4
CNI+ P=0.0331	199	1.8	1.3	2.9	50	2.1	1.3	4.3	72	1.6	1.1	2.3	62	2.0	1.5	3.2	15	1.9	1.2	2.9

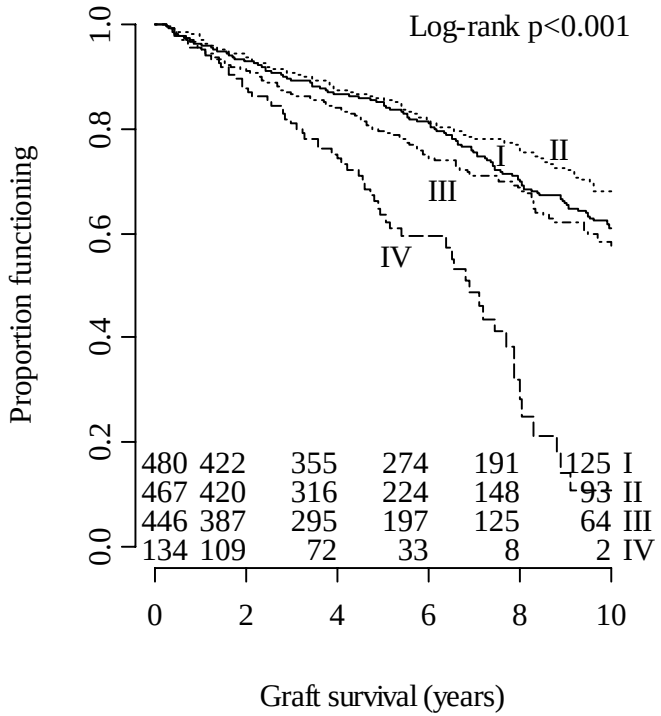
Actual graft survival (event=death or graft failure; N=1829, 587 events)

Kaplan-Meier-curves:

CNI-:

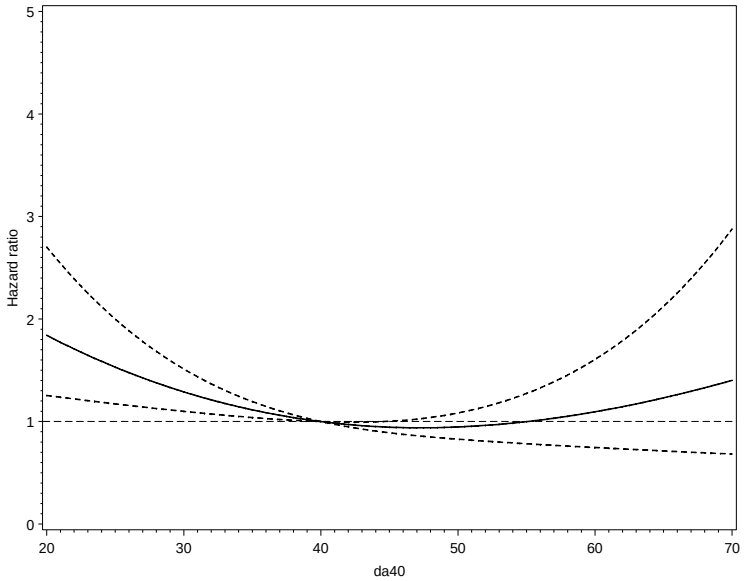


CNI+:

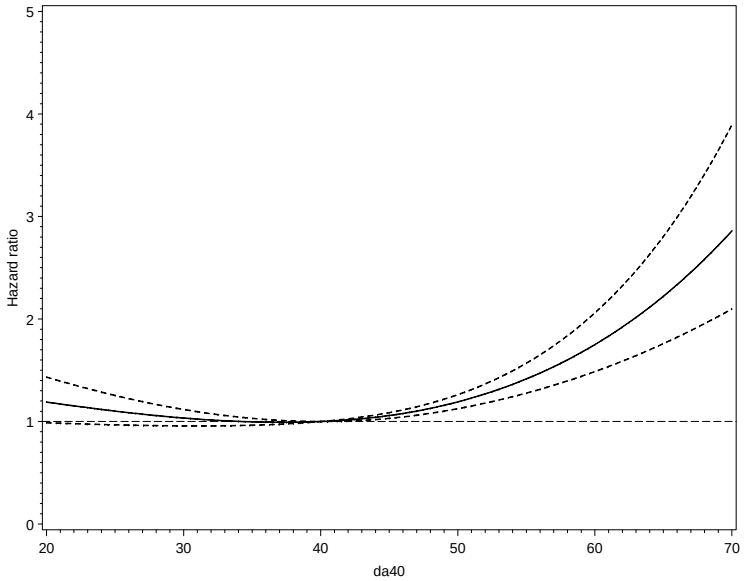


Crude hazard ratio estimates (reference: donor age=40 yrs):

CNI-:



CNI+:



Variable	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	Pr > Chi-Square
immg90	0.721	0.358	1.453	0.3601
noCA_DA1	1.051	0.501	2.203	0.8952
noCA_DA2	0.577	0.278	1.199	0.1405
noCA_DA3	0.476	0.219	1.034	0.0606
CA_DA1	0.373	0.276	0.504	<.0001
CA_DA2	0.310	0.226	0.425	<.0001
CA_DA3	0.431	0.318	0.585	<.0001

Adjusted hazard ratios

(all confounders, multiple imputation, 20 imputed data sets):

Actual graft survival (N=1829, >90 days of follow-up, 587 events):

Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
immg90	0.70209	0.33190	1.48520	0.3546
noCA_DA1	1.21513	0.54405	2.71396	0.6343
noCA_DA2	0.65645	0.30158	1.42888	0.2887
noCA_DA3	0.58771	0.25736	1.34211	0.2070
CA_DA1	0.43564	0.31704	0.59860	<.0001
CA_DA2	0.39837	0.28672	0.55350	<.0001
CA_DA3	0.53502	0.39108	0.73195	<.0001
age_tpl10	1.18691	1.11028	1.26883	<.0001
khk	1.11101	0.88355	1.39703	0.3667
cmp	1.19764	0.90867	1.57852	0.1992
vascid1	1.13361	0.83110	1.54623	0.4249
vascid2	1.28206	0.98747	1.66454	0.0620
year_tpl	0.94486	0.91902	0.97142	<.0001
dialysezeit	1.02637	0.98381	1.07078	0.2284
cholest10	0.99789	0.98521	1.01073	0.7456
map10	1.01199	0.99394	1.03037	0.1940
diabetes	1.43944	1.16663	1.77606	0.0007
cad	0.76449	0.53602	1.09034	0.1382

Using different parametrization to assess the effect of IS in various donor age groups (IS_DAx refers to the HR of CNI+ vs. CNI- in donor age group x):

Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
donorage1	1.21513	0.54405	2.71396	0.6343
donorage2	0.65645	0.30158	1.42888	0.2887
donorage3	0.58771	0.25736	1.34211	0.2070
IS_DA1	0.25171	0.16891	0.37510	<.0001
IS_DA2	0.42607	0.29124	0.62333	<.0001
IS_DA3	0.63915	0.40395	1.01130	0.0559
IS_DA4	0.70209	0.33190	1.48520	0.3546
age_tpl10	1.18691	1.11028	1.26883	<.0001
khk	1.11101	0.88355	1.39703	0.3667
cmp	1.19764	0.90867	1.57852	0.1992
vascid1	1.13361	0.83110	1.54623	0.4249
vascid2	1.28206	0.98747	1.66454	0.0620
year_tpl	0.94486	0.91902	0.97142	<.0001
dialysezeit	1.02637	0.98381	1.07078	0.2284
cholest10	0.99789	0.98521	1.01073	0.7456
map10	1.01199	0.99394	1.03037	0.1940
diabetes	1.43944	1.16663	1.77606	0.0007
cad	0.76449	0.53602	1.09034	0.1382

Analysis including mediators:

Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
immg90	0.70031	0.32771	1.49654	0.3575
noCA_DA1	1.29585	0.58331	2.87878	0.5243
noCA_DA2	0.71526	0.32019	1.59781	0.4134
noCA_DA3	0.57948	0.24981	1.34422	0.2035
CA_DA1	0.48087	0.34088	0.67833	<.0001
CA_DA2	0.42732	0.30394	0.60080	<.0001
CA_DA3	0.55800	0.40481	0.76916	0.0004
age_tpl10	1.19376	1.11531	1.27772	<.0001
khk	1.07208	0.84953	1.35292	0.5566
cmp	1.23459	0.93460	1.63086	0.1369
vascid1	1.15666	0.86924	1.53912	0.3162
vascid2	1.23724	0.96369	1.58845	0.0945
year_tpl	0.94354	0.91764	0.97017	<.0001
dialysezeit	1.02422	0.98166	1.06863	0.2690
cholest10	0.99779	0.98517	1.01057	0.7331
map10	1.01205	0.99347	1.03097	0.2047
diabetes	1.46093	1.18500	1.80111	0.0004
cad	0.75780	0.53318	1.07705	0.1221
bcar1	0.96746	0.80717	1.15959	0.7204
dgf	1.11297	0.89278	1.38746	0.3411
logcreat90	1.09452	0.98856	1.21185	0.0821

Analysis without multiple imputation (N=801, Events=181):

Crude effect, only data for which complete covariate information is available:

Variable	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	Pr > Chi-Square
immg90	0.315	0.092	1.072	0.0646
noCA_DA1	0.227	0.054	0.955	0.0430
noCA_DA2	0.307	0.086	1.094	0.0685
noCA_DA3	0.237	0.062	0.901	0.0347
CA_DA1	0.447	0.258	0.775	0.0041
CA_DA2	0.374	0.210	0.667	0.0009
CA_DA3	0.548	0.315	0.954	0.0335

Adjusted effect, only data with complete covariate information:

Variable	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	Pr > Chi-Square
immg90	0.312	0.088	1.106	0.0713
noCA_DA1	0.193	0.042	0.881	0.0337
noCA_DA2	0.320	0.089	1.159	0.0827
noCA_DA3	0.307	0.079	1.197	0.0890
CA_DA1	0.445	0.246	0.805	0.0074
CA_DA2	0.387	0.207	0.723	0.0029
CA_DA3	0.588	0.326	1.061	0.0780
age_tpl10	0.972	0.853	1.107	0.6674
khk	1.118	0.730	1.711	0.6077
cmp	1.047	0.565	1.939	0.8847
vascid1	0.900	0.518	1.564	0.7094
vascid2	1.475	0.937	2.322	0.0933
year_tpl	0.996	0.950	1.045	0.8687
dialysezeit	1.133	1.040	1.235	0.0042
cholest10	1.015	0.996	1.035	0.1303
map10	1.035	0.996	1.076	0.0776
Diabetes	1.747	1.203	2.537	0.0034
cad	0.678	0.398	1.156	0.1539

Conclusion: Restricting the analysis to patients with complete covariate information changes the crude effect substantially. Therefore, the observed change in the adjusted effect, which is of the same magnitude as that of the crude effect, is considered a consequence of the greatly reduced sample size (43.8%) and number of events (30.8%) and of a possible selection bias due to the restriction on complete cases.

Subgroup analysis (IS=CNI- or CNI+)

IS=CNI-:

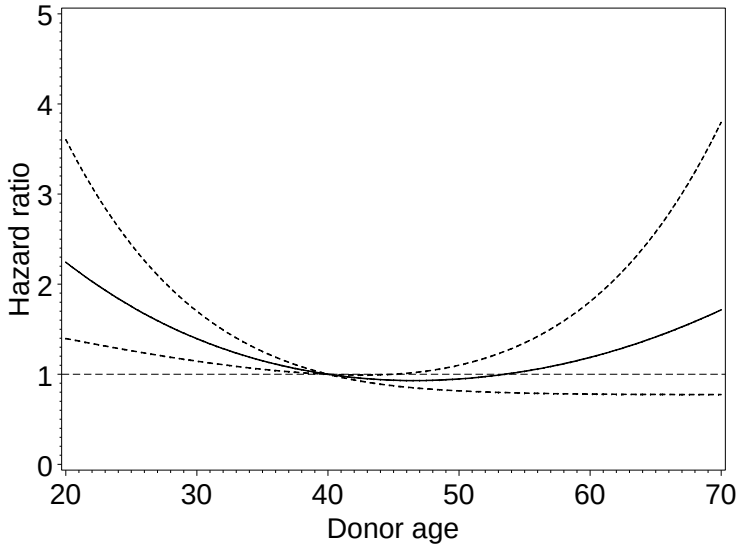
Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
donorage1	1.02871	0.42909	2.46627	0.9493
donorage2	0.59607	0.26022	1.36538	0.2210
donorage3	0.53258	0.22431	1.26450	0.1532
age_tpl10	1.15838	0.98667	1.35997	0.0725
khk	1.05341	0.44479	2.49483	0.9050
cmp	1.06154	0.42900	2.62672	0.8968
vascid1	1.79577	0.40763	7.91109	0.4357
vascid2	1.12597	0.45218	2.80376	0.7971
year_firstrrt	0.88818	0.83163	0.94857	0.0004
dialysezeit	0.87483	0.77052	0.99327	0.0390
cholest10	1.00146	0.97479	1.02885	0.9156
map10	1.02134	0.97913	1.06537	0.3262
diabetes	1.16724	0.65748	2.07222	0.5973
cad	0.75222	0.28395	1.99271	0.5667

IS=CNI+:

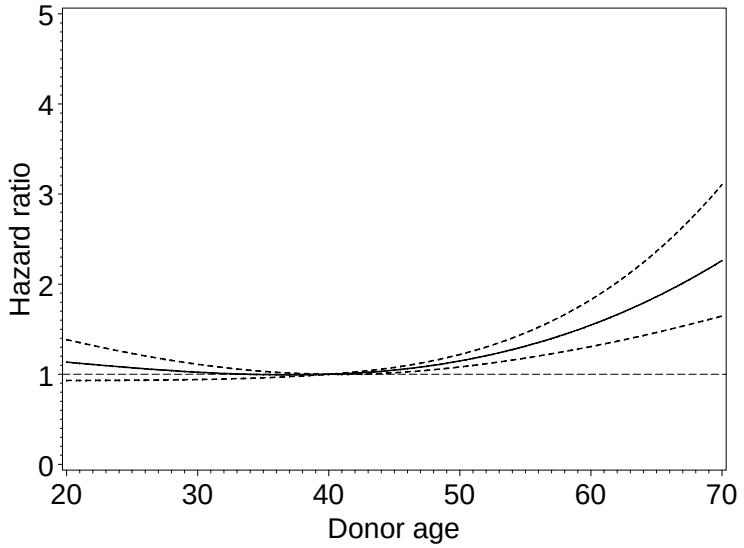
Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
donorage1	0.45825	0.33054	0.63529	<.0001
donorage2	0.41685	0.29986	0.57949	<.0001
donorage3	0.55540	0.40356	0.76436	0.0003
age_tpl10	1.20018	1.11299	1.29421	<.0001
khk	1.06092	0.81093	1.38796	0.6643
cmp	1.20605	0.85835	1.69459	0.2761
vascid1	1.13582	0.80790	1.59684	0.4592
vascid2	1.32344	0.99602	1.75849	0.0532
year_firstrrt	0.96504	0.93486	0.99619	0.0282
dialysezeit	0.99828	0.94263	1.05721	0.9530
cholest10	1.00012	0.98529	1.01517	0.9877
map10	1.01033	0.99054	1.03052	0.3085
diabetes	1.48447	1.18606	1.85795	0.0006
cad	0.77838	0.52897	1.14540	0.2037

Adjusted hazard ratio estimates:

CNI-:



CNI+:



Assessment of proportional hazards assumption: interaction of variables with log(time):

Interactions with log(_time_)

var1	raw_p	False Discovery Rate p-value
	.	.
immg90	0.13459	0.66755
noCA_DA1	0.57667	0.78997
noCA_DA2	0.39672	0.78997
noCA_DA3	0.89452	0.89452
CA_DA1	0.59434	0.78997
CA_DA2	0.60409	0.78997
CA_DA3	0.32232	0.78997
age_tpl	0.72791	0.88389
khk	0.19634	0.66755
cmp	0.89271	0.89452
vascid1	0.16488	0.66755
vascid2	0.40658	0.78997
year_tpl	0.48741	0.78997
dialysezeit	0.79850	0.89452
cholest	0.00008	0.00140
diabetes	0.07220	0.61369
map	0.49375	0.78997

Model with cholest*log(time):

Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
immg90	0.66811	0.32423	1.37668	0.2742
noCA_DA1	1.17063	0.54366	2.52064	0.6872
noCA_DA2	0.64567	0.30469	1.36826	0.2536
noCA_DA3	0.56110	0.25260	1.24638	0.1559
CA_DA1	0.42978	0.31292	0.59029	<.0001
CA_DA2	0.38580	0.27771	0.53595	<.0001
CA_DA3	0.53314	0.38916	0.73038	<.0001
age_tpl	1.01732	1.01034	1.02434	<.0001
khk	1.10855	0.87428	1.40558	0.3936
cmp	1.21822	0.90489	1.64005	0.1913
vascid1	1.16625	0.84510	1.60943	0.3455
vascid2	1.20470	0.90940	1.59589	0.1920
year_tpl	0.93909	0.91344	0.96545	<.0001
dialysezeit	1.02381	0.98139	1.06806	0.2757
cholest	0.99678	0.99484	0.99872	0.0012
cholest_time	1.00236	1.00117	1.00355	0.0001
diabetes	1.46395	1.18565	1.80758	0.0004
map	1.00106	0.99918	1.00294	0.2696

Conclusion: Adequate modeling of the effect of cholesterol has no impact on the findings on the interaction of Donorage and IS.

Model with HR for cholest divided into two parts: follow-up 0-3 years, and more than 3 years:

Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
immg90	0.67258	0.32644	1.38574	0.2822
noCA_DA1	1.18801	0.55193	2.55715	0.6596
noCA_DA2	0.64308	0.30339	1.36309	0.2494
noCA_DA3	0.56439	0.25396	1.25427	0.1603
CA_DA1	0.42875	0.31214	0.58894	<.0001
CA_DA2	0.38592	0.27783	0.53606	<.0001
CA_DA3	0.53071	0.38736	0.72710	<.0001
age_tpl	1.01719	1.01023	1.02419	<.0001
khk	1.10525	0.87189	1.40105	0.4070
cmp	1.21686	0.90314	1.63955	0.1950
vascid1	1.16870	0.84663	1.61328	0.3394
vascid2	1.20486	0.90913	1.59680	0.1924
year_tpl	0.94013	0.91443	0.96655	<.0001
dialysezeit	1.02379	0.98145	1.06796	0.2753
cholest_0_3	0.99750	0.99547	0.99952	0.0155
cholest_3_on	1.00101	0.99956	1.00247	0.1731
diabetes	1.46402	1.18575	1.80759	0.0004
map	1.00109	0.99922	1.00296	0.2519

Conclusion: modeling of the time-dependent effect of cholesterol by partitioning the time axis into two parts (</> 3 years after TPL) has no impact on the findings on the interaction of Donorage and IS.

Analysis of interactions:

Do any covariates modify the combined effects of IS and donor age? The corresponding interaction tests are carried out using one of 20 imputed data sets because of feasibility:

Obs	variable	with_variable	Pr > Chi-Square	DF	False Discovery Rate p-value
1	age_tpl	immg90 noC...	0.0246	7	0.0739
2	khk	immg90 noC...	0.1105	7	0.1657
4	vascid1	immg90 noC...	0.5839	7	0.5839
5	vascid2	immg90 noC...	0.4798	7	0.5397
6	year_tpl	immg90 noC...	0.0955	7	0.1657
7	dialysezeit	immg90 noC...	0.2089	7	0.2686
8	cholest	immg90 noC...	0.0216	7	0.0739
9	map	immg90 noC...	0.0353	7	0.0795
10	diabetes	immg90 noC...	0.0093	7	0.0739

To avoid spurious findings, the false discovery rate p-values (which correct for multiple testing) should be used. No significances are found. Nevertheless, subgroup analysis were carried out for non-diabetic and diabetic patients.

Non-diabetic (N=1399, 419 events):

Variable	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	Pr > Chi-Square
immg90	0.774	0.344	1.743	0.5365
noCA_DA1	1.289	0.543	3.063	0.5652
noCA_DA2	0.617	0.268	1.417	0.2548
noCA_DA3	0.640	0.268	1.531	0.3159
CA_DA1	0.358	0.247	0.519	<.0001
CA_DA2	0.274	0.186	0.402	<.0001
CA_DA3	0.437	0.304	0.628	<.0001
age_tpl	1.021	1.014	1.028	<.0001
khk	0.998	0.779	1.280	0.9903
cmp	1.362	1.050	1.768	0.0201
year_tpl	0.946	0.916	0.977	0.0007
vascid1	1.047	0.773	1.417	0.7673
vascid2	1.163	0.886	1.526	0.2757
cholest	1.000	0.998	1.001	0.6114
MAP	1.002	1.000	1.004	0.0233

Diabetic (N=362, 152 events):

Variable	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	Pr > Chi-Square
immg90	0.438	0.097	1.981	0.2838
noCA_DA1	0.894	0.189	4.236	0.8878
noCA_DA2	0.443	0.087	2.263	0.3281
noCA_DA3	0.134	0.018	0.994	0.0493
CA_DA1	0.545	0.294	1.010	0.0538
CA_DA2	0.757	0.400	1.432	0.3919
CA_DA3	0.752	0.404	1.403	0.3707
age_tpl	1.002	0.987	1.018	0.7560
khk	1.106	0.758	1.615	0.6017
cmp	1.600	1.009	2.539	0.0457
year_tpl	0.941	0.890	0.995	0.0330
vascid1	1.173	0.768	1.790	0.4609
vascid2	1.387	0.983	1.957	0.0628
cholest	1.001	0.998	1.003	0.5175
MAP	0.999	0.994	1.004	0.5953

The effects of IS and donor age on actual graft survival differ in their magnitude but not in their direction between diabetic and non-diabetic patients.

KHK and CMP show a higher effect in diabetic than in non-diabetic persons.

Detailed description of our approach to handle missing data

Missing values are a problem commonly encountered in studies like ours. Particularly in the analysis of multivariable models one may end up with 30-40% complete observations even if each variable has no more than 5-10% missing values. Therefore, we applied multiple imputation (Ref.) to our data set, which is currently the state-of-the-art technique to deal with missing values.

Multiple imputation is carried out in three steps. In step one, regression models are estimated from the non-missing observations which use each covariate in turn as the dependent variable and all other covariates as independent variables. In step two, multiple versions of the original data set are produced by replacing the missing values of covariates by values that follow the regression models of step 1. These so-called imputations vary between the different versions of the reconstructed data set because the regression models of step 1 cannot perfectly predict missing covariate values, and the imputation procedure reflects the model uncertainty properly by randomly drawing values from the predicted distribution instead of imputing the expected covariate value. In step 3, each imputed data set is analyzed by Cox regression and then the regression results are combined, properly taking into account the within-data set variation and the between-data set variation when computing confidence intervals for hazard ratios. The between-data set variation will be low if a covariate can be well predicted by other covariates, but high if the prediction model of a covariate lacks precision. For the former case, multiple imputation provides a powerful analysis. In the latter case, multiple imputation analysis will not be much better than an analysis of the complete observations, but still improves the estimation of parameters related to covariates with small amounts of missing data in terms of precision.

If for some covariates the amount of missing data exceeds a certain level (10% say), results obtained by multiple imputation can be biased if the assumption that covariate values are missing just randomly does not hold. Therefore, we assessed the sensitivity of our initial results on the assumption of randomly missing data by artificially doubling the amount of missing data in each covariate in two ways: first purely at random and second, only in subjects with covariate values higher than the median. The results from both analyses differed only marginally from our initial results (the detailed results are given in our supplemental data file), suggesting that any violation of the assumption of randomly missing data that could be present in our data would not affect our conclusions.

Assessing the sensitivity of our results on the assumption of randomly missing data

Outcome: actual graft survival (event=death or graft loss)

Multiple imputation analysis with artificially generated not-randomly missing values (doubling the amount of missing data in each covariate):

Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
immg90	0.72918	0.33908	1.56808	0.4187
noCA_DA1	1.28514	0.58274	2.83416	0.5341
noCA_DA2	0.69910	0.31837	1.53509	0.3723
noCA_DA3	0.56911	0.24642	1.31441	0.1869
CA_DA1	0.44200	0.31692	0.61646	<.0001
CA_DA2	0.40212	0.28625	0.56490	<.0001
CA_DA3	0.54993	0.39431	0.76698	0.0004
age_tpl10	1.20330	1.12693	1.28484	<.0001
khk	1.03339	0.80888	1.32022	0.7921
cmp	1.16129	0.84545	1.59511	0.3532
vascid1	1.36996	0.90534	2.07304	0.1344
vascid2	1.25250	0.93809	1.67227	0.1262
year_tpl	0.94744	0.92204	0.97354	<.0001
dialysezeit	1.02717	0.98471	1.07147	0.2133
cholest10	0.99743	0.98383	1.01121	0.7121
map10	1.01301	0.99406	1.03231	0.1791
diabetes	1.47187	1.19905	1.80678	0.0002
cad	0.76381	0.53587	1.08870	0.1362

Multiple imputation analysis with artificially generated randomly missing values (doubling the amount of missing data in each covariate):

Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
immg90	0.67938	0.32742	1.40966	0.2991
noCA_DA1	1.21996	0.57042	2.60914	0.6082
noCA_DA2	0.64279	0.30193	1.36846	0.2516
noCA_DA3	0.52923	0.23505	1.19157	0.1243
CA_DA1	0.45865	0.33157	0.63444	<.0001
CA_DA2	0.41108	0.29455	0.57371	<.0001
CA_DA3	0.53213	0.38574	0.73409	0.0001
age_tpl10	1.20489	1.12795	1.28708	<.0001
khk	1.09979	0.84251	1.43565	0.4798
cmp	1.04953	0.76867	1.43301	0.7583
vascid1	1.05862	0.76904	1.45725	0.7240
vascid2	1.14789	0.85418	1.54260	0.3551
year_tpl	0.94919	0.92357	0.97552	0.0002
dialysezeit	1.02502	0.98237	1.06952	0.2544
cholest10	0.99556	0.98208	1.00921	0.5206
map10	1.01098	0.99248	1.02982	0.2464
diabetes	1.48868	1.21270	1.82747	0.0001
cad	0.77712	0.54449	1.10914	0.1647

Comparison with original multiple imputation analysis:

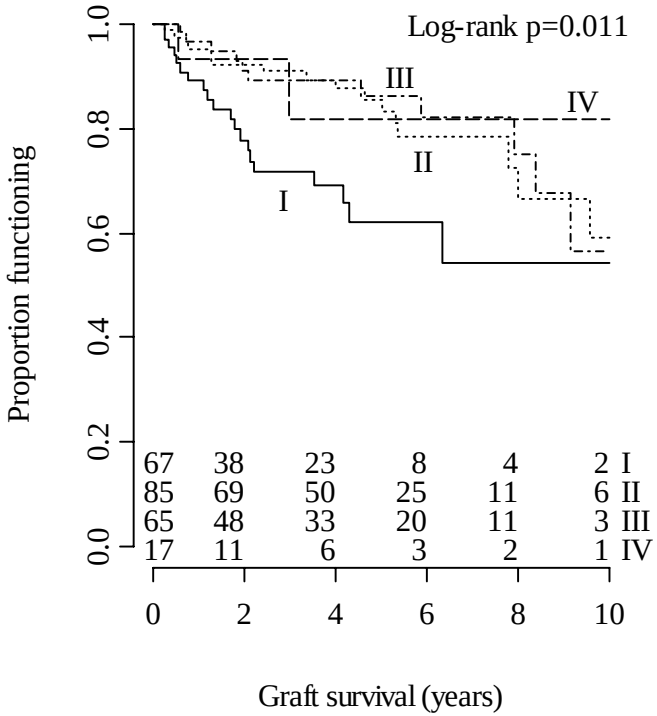
Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|	Not-randomly missing values Hazard Ratio	Randomly missing values Hazard Ratio
immg90	0.68519	0.32787	1.43193	0.3146	0.72918	0.67938
noCA_DA1	1.18106	0.53195	2.62227	0.6824	1.28514	1.21996
noCA_DA2	0.64164	0.29744	1.38416	0.2579	0.69910	0.64279
noCA_DA3	0.57432	0.25586	1.28919	0.1788	0.56911	0.52923
CA_DA1	0.43548	0.31670	0.59881	<.0001	0.44200	0.45865
CA_DA2	0.39972	0.28862	0.55359	<.0001	0.40212	0.41108
CA_DA3	0.53755	0.39286	0.73553	0.0001	0.54993	0.53213
age_tpl10	1.18773	1.11086	1.26992	<.0001	1.20330	1.20489
khk	1.06383	0.83769	1.35103	0.6104	1.03339	1.09979
cmp	1.19566	0.90393	1.58154	0.2090	1.16129	1.04953
vascid1	1.16924	0.87616	1.56036	0.2861	1.36996	1.05862
vascid2	1.28796	0.99769	1.66268	0.0521	1.25250	1.14789
year_tpl	0.94593	0.92054	0.97202	<.0001	0.94744	0.94919
dialysezeit	1.02614	0.98366	1.07047	0.2316	1.02717	1.02502
cholest10	0.99843	0.98658	1.01042	0.7958	0.99743	0.99556
map10	1.01260	0.99405	1.03149	0.1840	1.01301	1.01098
diabetes	1.44447	1.17431	1.77679	0.0005	1.47187	1.48868
cad	0.76119	0.53391	1.08522	0.1316	0.76381	0.77712

There is no parameter for which the estimate from the data set with artificially generated missing values lies outside the confidence interval for that parameter computed from the original data set. Moreover, the hazard ratio estimates are very close to the original estimates even in the case of not-randomly missing values. The highest deviation is observed for vascid1, for which the amount of missing values was 42%.

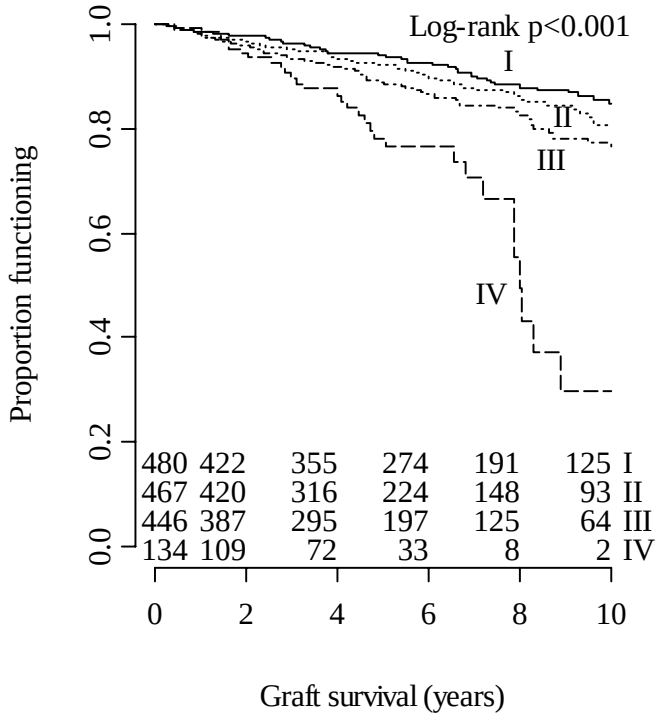
Functional graft survival (N=1829, 275 events):

Kaplan-Meier analysis

CNI-:

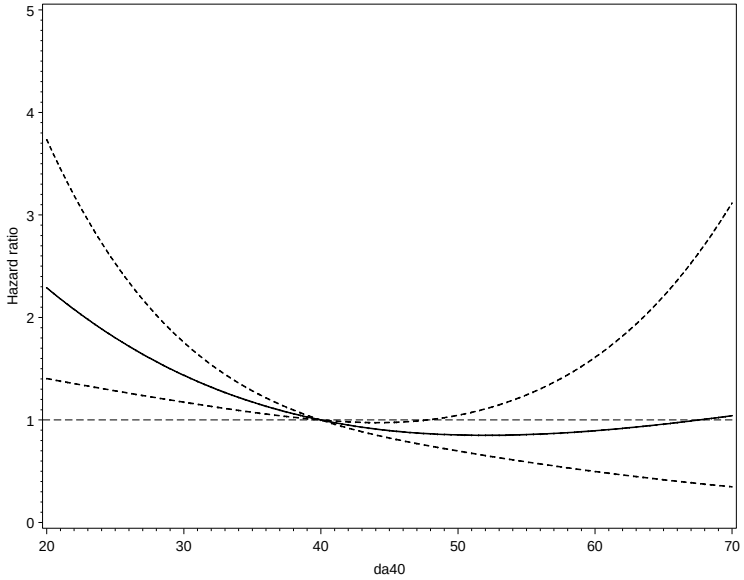


CNI+:

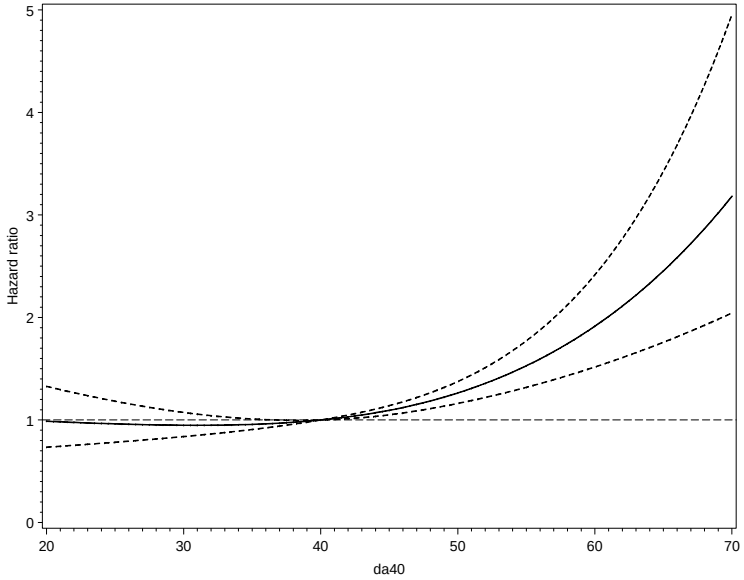


Crude hazard ratios

CNI-:



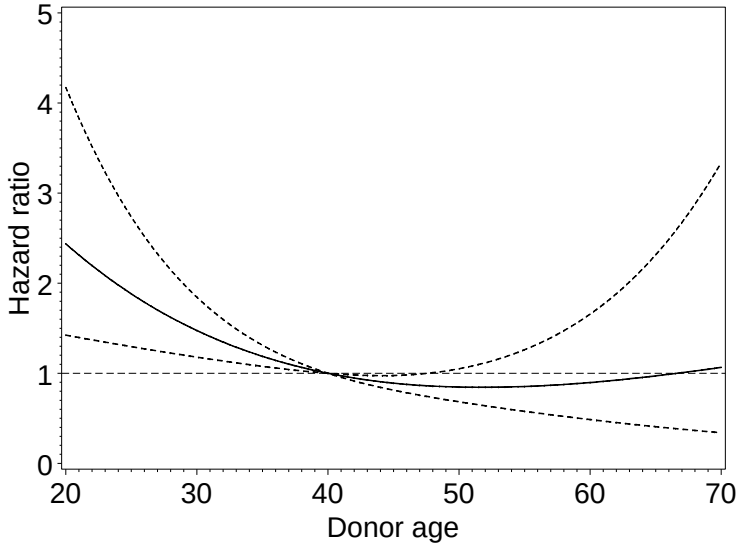
CNI+:



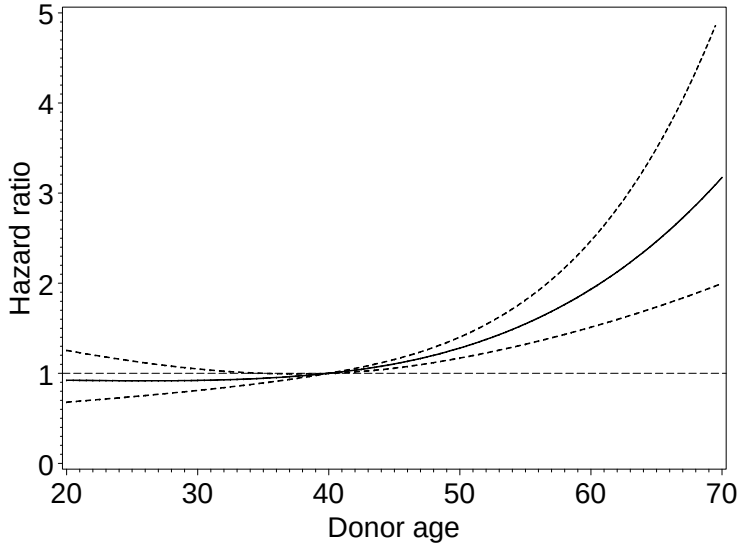
Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
immg90	1.68594	0.40100	7.0882	0.4759
noCA_DA1	2.88222	0.67372	12.3304	0.1535
noCA_DA2	1.19366	0.27271	5.2247	0.8142
noCA_DA3	1.05552	0.23249	4.7922	0.9442
CA_DA1	0.26098	0.16701	0.4078	<.0001
CA_DA2	0.33392	0.21452	0.5198	<.0001
CA_DA3	0.43637	0.28420	0.6700	0.0002

Adjusted:

CNI- (model only including PRA, Cholest, vascid1, vascid2):



CNI+:



Full model, excluding mediators (DGF, BCAR, Crea90):

Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
immg90	1.96121	0.45945	8.3717	0.3630
noCA_DA1	2.55125	0.58836	11.0628	0.2108
noCA_DA2	1.19185	0.26950	5.2709	0.8170
noCA_DA3	1.10716	0.24115	5.0831	0.8958
CA_DA1	0.21642	0.13490	0.3472	<.0001
CA_DA2	0.30443	0.19069	0.4860	<.0001
CA_DA3	0.41014	0.26242	0.6410	<.0001
age_tpl10	0.91483	0.83606	1.0010	0.0526
khk	1.11466	0.75798	1.6392	0.5709
cmp	1.14628	0.75221	1.7468	0.5153
vascid1	1.01794	0.57905	1.7895	0.9475
vascid2	1.02326	0.56312	1.8594	0.9334
year_tpl	0.93911	0.90015	0.9798	0.0039
dialysezeit	1.03174	0.97148	1.0957	0.3087
cholest10	0.99135	0.96998	1.0132	0.4217
map10	1.00949	0.98252	1.0372	0.4860
diabetes	1.53479	1.10026	2.1409	0.0119
cad	0.70532	0.42048	1.1831	0.1859
mmsum	1.03981	0.93414	1.1574	0.4724
pra_g	1.01405	0.79477	1.2938	0.9104

Model including mediators (but excluding pra and vascid to avoid overfit):

Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
immg90	1.93114	0.45173	8.2556	0.3746
noCA_DA1	2.61591	0.59968	11.4111	0.2007
noCA_DA2	1.27693	0.28761	5.6693	0.7479
noCA_DA3	1.10929	0.24076	5.1111	0.8941
CA_DA1	0.23825	0.14392	0.3944	<.0001
CA_DA2	0.32628	0.20178	0.5276	<.0001
CA_DA3	0.43112	0.27575	0.6740	0.0002
age_tpl10	0.90987	0.83134	0.9958	0.0403
khk	1.20094	0.84458	1.7077	0.3059
cmp	1.13308	0.76324	1.6821	0.5338
year_tpl	0.93747	0.90098	0.9754	0.0014
dialysezeit	1.02675	0.96877	1.0882	0.3734
cholest10	0.98893	0.97125	1.0069	0.2260
map10	1.01061	0.98685	1.0349	0.3840
diabetes	1.51738	1.11788	2.0596	0.0075
cad	0.71383	0.42556	1.1974	0.2014
mmsum	1.04787	0.94152	1.1662	0.3911
dgf	1.12384	0.81650	1.5469	0.4737
bcar1	1.01927	0.78511	1.3233	0.8860
logcreat90	1.04654	0.91067	1.2027	0.5212

Different parametrization

Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
donorage1	2.68180	0.60426	11.9023	0.1945
donorage2	1.22322	0.27225	5.4959	0.7927
donorage3	1.12500	0.24091	5.2535	0.8809
IS_DA1	0.16197	0.09430	0.2782	<.000
IS_DA2	0.49847	0.28685	0.8662	0.0135
IS_DA3	0.73789	0.38609	1.4102	0.3577
IS_DA4	1.92740	0.44610	8.3274	0.3795
age_tpl10	0.91541	0.83777	1.0003	0.0507
khk	1.03328	0.68435	1.5601	0.8751
cmp	1.15916	0.75879	1.7708	0.4918
vascid1	1.18146	0.71552	1.9508	0.5103
vascid2	1.07421	0.72268	1.5967	0.7218
year_tpl	0.93898	0.90257	0.9768	0.0018
dialysezeit	1.02895	0.96921	1.0924	0.3497
cholest10	0.98977	0.97207	1.0078	0.2639
map10	1.00968	0.98576	1.0342	0.4307
diabetes	1.52363	1.10851	2.0942	0.0095
cad	0.72774	0.43330	1.2223	0.2296
mmsum	1.03642	0.93550	1.1482	0.4935
pra_g	0.98966	0.77660	1.2612	0.9330

Assessing interactions with log(time)

Interactions with log(_time_)

var1	raw_p	False Discovery Rate p-value
	.	.
immg90	0.80969	0.97256
noCA_DA1	0.24155	0.97256
noCA_DA2	0.31315	0.97256
noCA_DA3	0.83475	0.97256
CA_DA1	0.78065	0.97256
CA_DA2	0.35711	0.97256
CA_DA3	0.96421	0.97256
age_tpl10	0.91200	0.97256
khk	0.97256	0.97256
cmp	0.83961	0.97256
vascid1	0.35761	0.97256
vascid2	0.80058	0.97256
year_tpl	0.52556	0.97256
dialysezeit	0.83934	0.97256
cholest10	0.44533	0.97256
map10	0.66232	0.97256
diabetes	0.21767	0.97256
cad	0.88663	0.97256
mmsum	0.56503	0.97256
pra_g	0.66494	0.97256

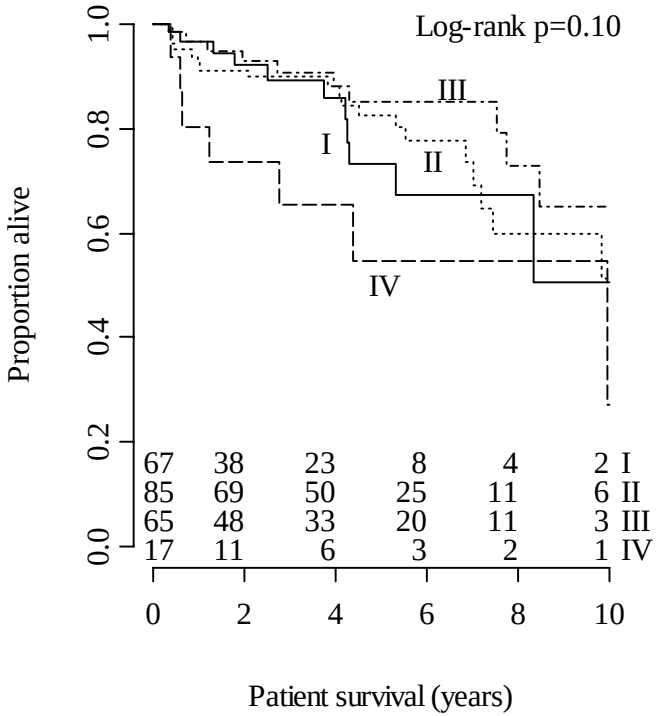
Interactions with Donorage-IS

variable	with_variable	Pr > Chi-Square	DF	False Discovery Rate p-value
age_tpl	immg90 noC...	0.1131	7	0.2941
khk	immg90 noC...	0.3506	7	0.4558
cmp	immg90 noC...	0.2066	7	0.3905
vascid1	immg90 noC...	0.3424	7	0.4558
vascid2	immg90 noC...	0.9714	7	0.9714
dialysezeit	immg90 noC...	0.2103	7	0.3905
year_tpl	immg90 noC...	0.0613	7	0.1991
cholest	immg90 noC...	0.0510	7	0.1991
map	immg90 noC...	0.7015	7	0.7599
diabetes	immg90 noC...	0.5699	7	0.6735
cad	immg90 noC...	0.2543	7	0.4133
mmsum	immg90 noC...	0.0108	7	0.1086
pra_g	immg90 noC...	0.0167	7	0.1086

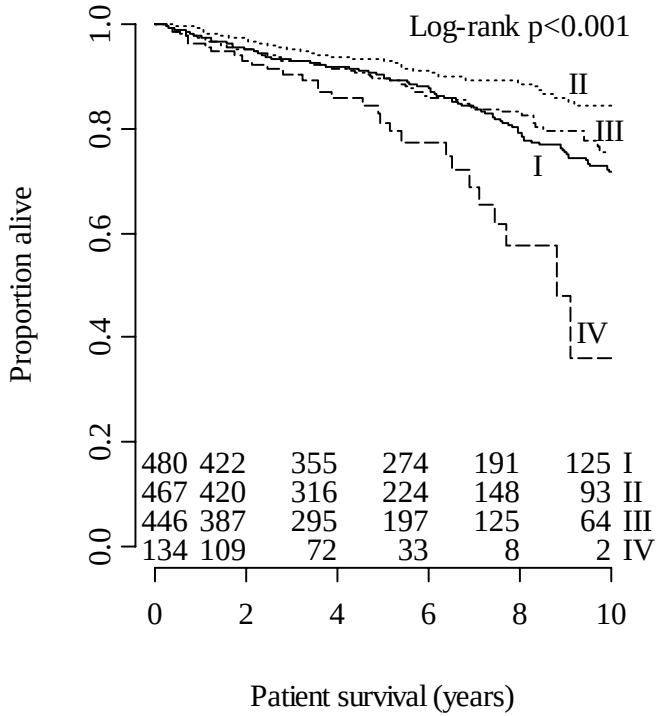
Patient survival (graft-loss-censored; N=1829, 312 events)

Kaplan-Meier analysis

CNI-:

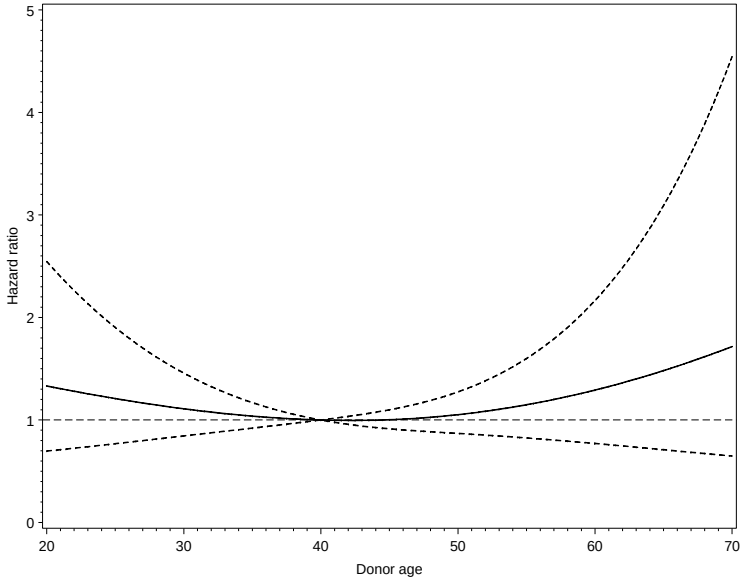


CNI+:

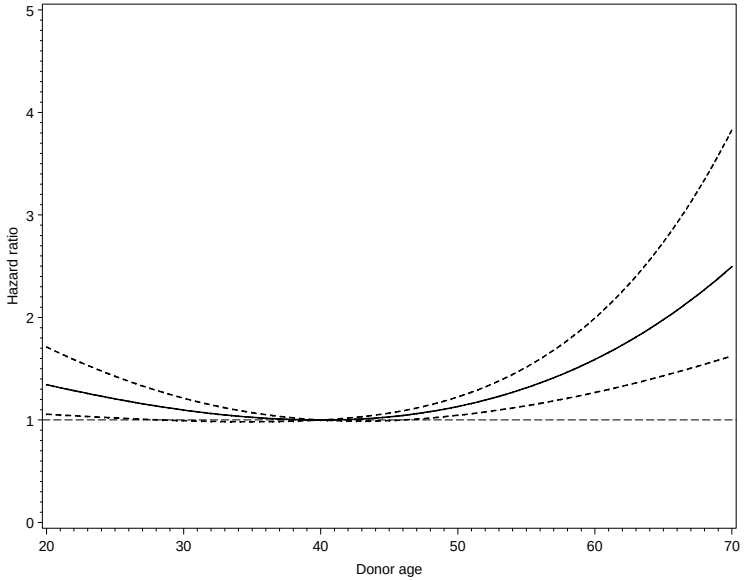


Crude hazard ratios

CNI-:



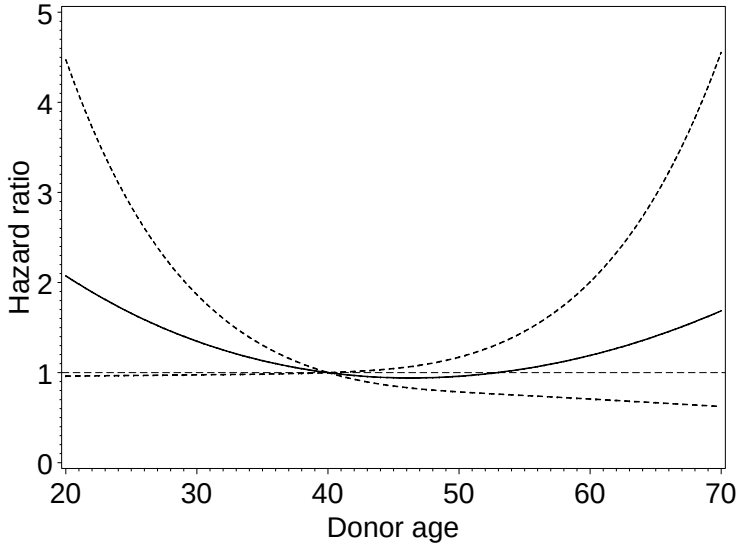
CNI+:



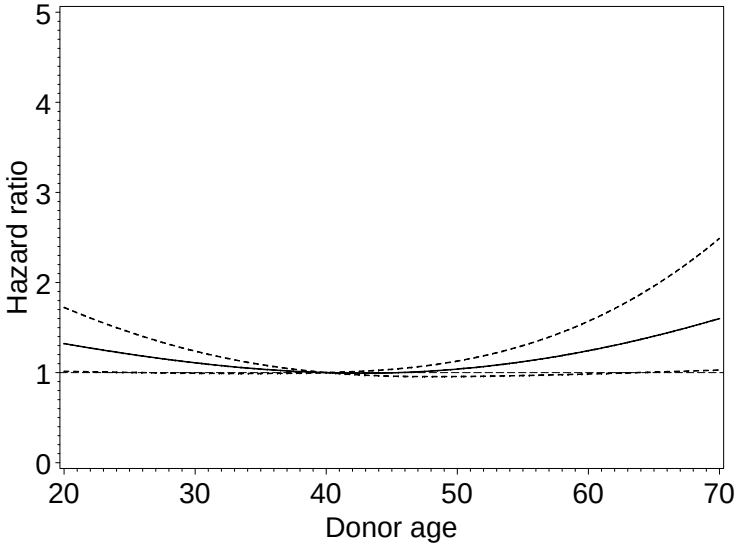
Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
immg90	0.48380	0.20984	1.11542	0.0884
noCA_DA1	0.46555	0.17658	1.22743	0.1222
noCA_DA2	0.40810	0.16844	0.98872	0.0471
noCA_DA3	0.32887	0.12650	0.85496	0.0225
CA_DA1	0.50100	0.33066	0.75909	0.0011
CA_DA2	0.30080	0.19174	0.47189	<.0001
CA_DA3	0.44047	0.28526	0.68012	0.0002

Adjusted hazard ratios

CNI- (model only including rec-age, heart/vascular disease, cholesterol):



CNI+:



Full model, excluding mediators (DGF, BCAR, Crea90):

Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
immg90	0.34690	0.14481	0.83104	0.0176
noCA_DA1	0.66214	0.24145	1.81581	0.4230
noCA_DA2	0.50892	0.20155	1.28503	0.1528
noCA_DA3	0.44997	0.16713	1.21149	0.1140
CA_DA1	0.78674	0.50638	1.22231	0.2859
CA_DA2	0.52662	0.32906	0.84279	0.0075
CA_DA3	0.71815	0.45929	1.12293	0.1466
age_tpl10	1.64906	1.48127	1.83585	<.0001
khk	1.02896	0.71756	1.47552	0.8755
cmp	1.17957	0.80738	1.72332	0.3911
vascid1	1.17557	0.78713	1.75569	0.4261
vascid2	1.39943	0.99913	1.96012	0.0506
year_tpl	0.95111	0.91517	0.98846	0.0108
dialysezeit	1.03278	0.97139	1.09805	0.3022
cholest10	1.00470	0.98803	1.02166	0.5822
map10	1.01592	0.98411	1.04876	0.3289
diabetes	1.45234	1.09916	1.91900	0.0087

Test for interaction of donorage-groups and IS: p=0.75

Model including mediators:

Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
immg90	0.32732	0.13582	0.78881	0.0128
noCA_DA1	0.65978	0.23644	1.84111	0.4268
noCA_DA2	0.55325	0.21545	1.42066	0.2184
noCA_DA3	0.41898	0.15335	1.14472	0.0898
CA_DA1	0.90707	0.56129	1.46585	0.6904
CA_DA2	0.57869	0.35608	0.94046	0.0273
CA_DA3	0.75199	0.47920	1.18006	0.2150
age_tpl10	1.65963	1.48869	1.85020	<.0001
khk	1.02383	0.70864	1.47919	0.8992
cmp	1.18815	0.81249	1.73751	0.3718
vascid1	1.17116	0.77944	1.75976	0.4435
vascid2	1.40731	1.00847	1.96387	0.0445
year_tpl	0.94746	0.91120	0.98516	0.0067
dialysezeit	1.03261	0.97120	1.09790	0.3050
cholest10	1.00571	0.98881	1.02290	0.5096
map10	1.01593	0.98423	1.04865	0.3269
diabetes	1.44816	1.09665	1.91234	0.0091
bcar	0.87559	0.34655	2.21222	0.7787
dgf	1.16123	0.85692	1.57359	0.3349
logcreat90	1.14115	0.99373	1.31044	0.0614

Test for interaction of donorage-groups and IS: p=0.61

Different parametrization:

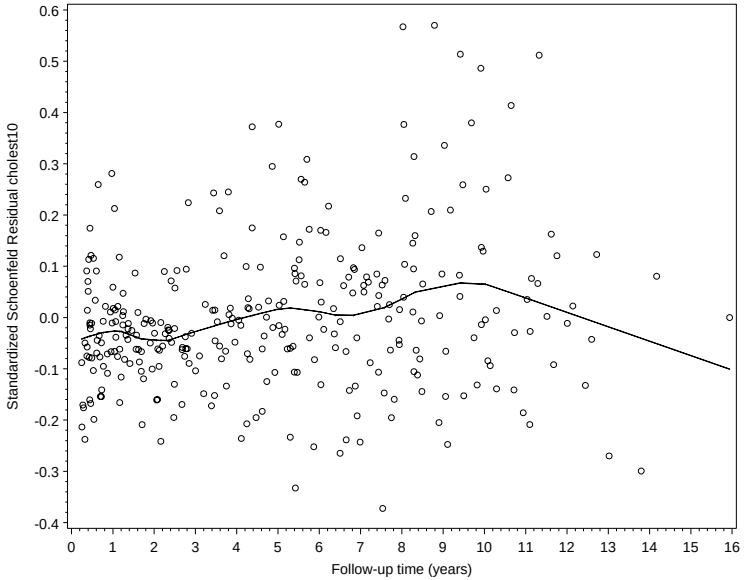
Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
donorage1	0.63510	0.23467	1.71884	0.3714
donorage2	0.48336	0.19399	1.20439	0.1186
donorage3	0.43676	0.16258	1.17334	0.1004
IS_DA1	0.41784	0.22117	0.78939	0.0072
IS_DA2	0.36331	0.21343	0.61847	0.0002
IS_DA3	0.54504	0.28323	1.04888	0.0692
IS_DA4	0.32683	0.13671	0.78135	0.0119
age_tpl10	1.64977	1.48283	1.83551	<.0001
khk	1.01920	0.73492	1.41345	0.9088
cmp	1.18168	0.81131	1.72113	0.3825
vascid1	1.16545	0.78938	1.72067	0.4384
vascid2	1.42422	1.02285	1.98310	0.0364
year_tpl	0.95359	0.91766	0.99093	0.0153
dialysezeit	1.03456	0.97315	1.09984	0.2765
cholest10	1.00731	0.98960	1.02534	0.4199
map10	1.01453	0.98403	1.04596	0.3532
diabetes	1.42963	1.08702	1.88021	0.0106

Tests for interactions with log(time):

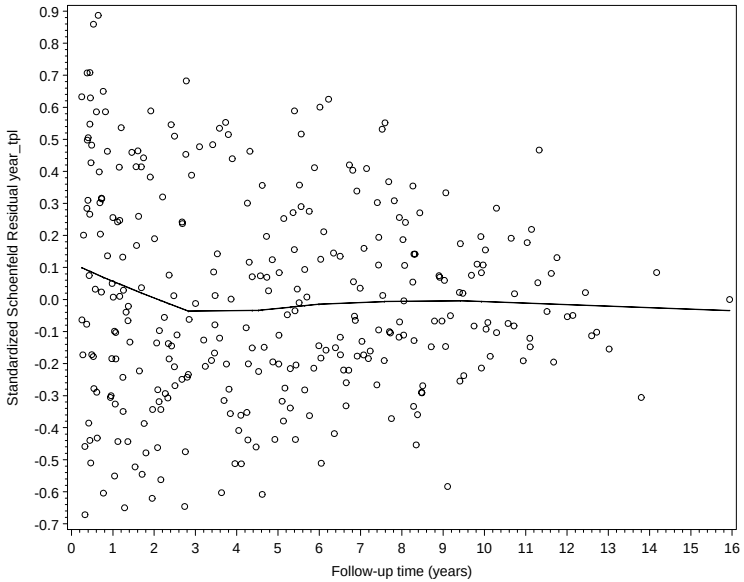
Interactions with log(_time_)

var1	raw_p	False Discover Rate p-value
	.	.
immg90	0.59811	0.84732
noCA_DA1	0.34117	0.65471
noCA_DA2	0.38512	0.65471
noCA_DA3	0.81311	0.87038
CA_DA1	0.33509	0.65471
CA_DA2	0.68559	0.87038
CA_DA3	0.18365	0.65471
age_tpl10	0.81919	0.87038
khk	0.52016	0.80389
cmp	0.25731	0.65471
vascid1	0.36091	0.65471
vascid2	0.11961	0.65471
year_tpl	0.00102	0.00869
dialysezeit	0.79814	0.87038
cholest10	0.00001	0.00018
map10	0.88924	0.88924
diabetes	0.36131	0.65471

Time-dependent effect of cholest: Plot of scaled Schoenfeld residuals



Time-dependent effect of year_tpl:



Adjusted hazard ratios, accounting for time-dependent effects:

Parameter	Hazard Ratio	Lower 95% CL HR	Upper 95% CL HR	Pr > |t|
immg90	0.35014	0.14672	0.83558	0.0181
noCA_DA1	0.71741	0.26129	1.96971	0.5191
noCA_DA2	0.55207	0.21966	1.38752	0.2063
noCA_DA3	0.47104	0.17464	1.27050	0.1370
CA_DA1	0.80893	0.51969	1.25917	0.3476
CA_DA2	0.54769	0.34182	0.87754	0.0123
CA_DA3	0.75755	0.48345	1.18705	0.2256
age_tpl10	1.65050	1.48220	1.83791	<.0001
khk	1.05500	0.73589	1.51249	0.7689
cmp	1.23387	0.84578	1.80005	0.2737
vascid1	1.17316	0.79100	1.73994	0.4243
vascid2	1.42151	1.01745	1.98603	0.0394
dialysezeit	1.03518	0.97382	1.10041	0.2674
y1tpl_to1	1.03479	0.96183	1.11330	0.3593
y1tpl_from1	0.91824	0.87880	0.95945	0.0001
cholest10_to3	0.96323	0.93431	0.99306	0.0162
cholest10_from3	1.02404	1.00402	1.04445	0.0184
map10	1.01582	0.98473	1.04789	0.3210
diabetes	1.43537	1.08739	1.89472	0.0107

Interactions with donor age and IS:

variable	with_variable	Pr > Chi-Square	DF	False Discovery Rate p-value
age_tpl10	immg90 noC...	0.8054	7	0.8949
khk	immg90 noC...	0.5958	7	0.7448
vascid1	immg90 noC...	0.9781	7	0.9781
vascid2	immg90 noC...	0.1072	7	0.4860
dialysezeit	immg90 noC...	0.1458	7	0.4860
year_tpl	immg90 noC...	0.2775	7	0.5297
cholest10_bis3	immg90 noC...	0.3433	7	0.5297
cholest10_ab3	immg90 noC...	0.2487	7	0.5297
map	immg90 noC...	0.3708	7	0.5297
diabetes	immg90 noC...	0.0858	7	0.4860

Slope of reciprocal creatinine

The MEANS Procedure

Analysis Variable : slope

IS	Donor Age	N Obs	Median	25th Pctl	75th Pctl
NoCA	<36	28	-0.0238425	-0.1220328	0
	36-49	52	-0.0184232	-0.0786198	0.0135047
	50-64	37	0	-0.0523631	0.0010501
	65+	13	-0.0221773	-0.1221851	0
CA	<36	431	-0.0046288	-0.0451980	0.0171564
	36-49	431	-0.0111572	-0.0508886	0.0060998
	50-64	409	-0.0133783	-0.0443007	0.0041974
	65+	115	-0.0132762	-0.0416521	0.0105803

CNI-

Kruskal-Wallis Test

Chi-Square	3.8878
DF	3
Pr > Chi-Square	0.2738

CNI+

Kruskal-Wallis Test

Chi-Square	8.0250
DF	3
Pr > Chi-Square	0.0455

Appendix A: Association of characterics with donor age

	year_tpl			
	N	**Median**	**P25**	**P75**
All	1761	1996	1993	2000
dagroup P(Kruskal-Wallis)=0				
1 (<36)	547	1994	1991	1998
2 (36-49)	552	1997	1993	2000
3 (50-64)	511	1997	1994	2000
4 (65+)	151	1999	1995	2001

	dialysezeit		
	N	**Mean**	**Std**
All	1761	2.2	1.9
dagroup P(ANOVA)=0.7898			
1 (<36)	547	2.1	1.9
2 (36-49)	552	2.2	2.0
3 (50-64)	511	2.2	1.9
4 (65+)	151	2.1	1.7

	cholest		
	N	**Mean**	**Std**
All	1465	210.4	73.0
dagroup P(ANOVA)=0.366			
1 (<36)	417	215.7	79.2
2 (36-49)	472	209.0	68.4
3 (50-64)	443	207.7	72.4
4 (65+)	133	207.3	70.8

	age_tpl		
	N	Mean	Std
All	1761	48.1	15.5
dagroup P(ANOVA)=0			
1 (<36)	547	46.3	16.5
2 (36-49)	552	46.4	15.1
3 (50-64)	511	48.5	13.6
4 (65+)	151	59.5	14.0

	map10		
	N	Mean	Std
All	1531	10.1	5.0
dagroup P(ANOVA)=0.9922			
1 (<36)	487	10.1	5.3
2 (36-49)	472	10.1	5.3
3 (50-64)	448	10.0	4.1
4 (65+)	124	10.1	5.2

	MMSum			
	N	Median	P25	P75
All	1606	3.0	2.0	3.0
dagroup P(Kruskal-Wallis)=0				
1 (<36)	492	2.0	2.0	3.0
2 (36-49)	498	2.0	2.0	3.0
3 (50-64)	476	2.0	2.0	3.0
4 (65+)	140	3.0	2.0	4.0

	pra_g					
	0		1		2	
	N	RowPctN	N	RowPctN	N	RowPctN
All	1486	86.7	150	8.8	78	4.6
dagroup P(Chi2)=0.2425						
1 (<36)	458	85.0	52	9.6	29	5.4
2 (36-49)	459	86.9	44	8.3	25	4.7
3 (50-64)	428	86.3	47	9.5	21	4.2
4 (65+)	141	93.4	7	4.6	3	2.0

	khk			
	0		1	
	N	RowPctN	N	RowPctN
All	829	76.4	256	23.6
dagroup P(Chi2)=0.0005				
1 (<36)	234	76.0	74	24.0
2 (36-49)	270	79.9	68	20.1
3 (50-64)	256	78.5	70	21.5
4 (65+)	69	61.1	44	38.9

	cmp			
	0		1	
	N	RowPctN	N	RowPctN
All	924	85.2	161	14.8

	cmp			
	0		1	
	N	RowPctN	N	RowPctN
dagroup P(Chi2)=0.776				
1 (<36)	264	85.7	44	14.3
2 (36-49)	292	86.4	46	13.6
3 (50-64)	273	83.7	53	16.3
4 (65+)	95	84.1	18	15.9

	vascid1			
	0		1	
	N	RowPctN	N	RowPctN
All	904	88.1	122	11.9
dagroup P(Chi2)=0.1711				
1 (<36)	257	87.4	37	12.6
2 (36-49)	284	89.9	32	10.1
3 (50-64)	276	89.0	34	11.0
4 (65+)	87	82.1	19	17.9

	vascid2			
	0		1	
	N	RowPctN	N	RowPctN
All	831	81.0	195	19.0
dagroup P(Chi2)=0				
1 (<36)	233	79.3	61	20.7

	vascid2			
	0		1	
	N	RowPctN	N	RowPctN
2 (36-49)	259	82.0	57	18.0
3 (50-64)	269	86.8	41	13.2
4 (65+)	70	66.0	36	34.0

	Diabetes			
	0		1	
	N	RowPctN	N	RowPctN
All	1399	79.4	362	20.6
dagroup P(Chi2)=0.004				
1 (<36)	417	76.2	130	23.8
2 (36-49)	457	82.8	95	17.2
3 (50-64)	416	81.4	95	18.6
4 (65+)	109	72.2	42	27.8

	cad			
	0		1	
	N	RowPctN	N	RowPctN
All	113	6.5	1631	93.5
dagroup P(Chi2)=0.9423				
1 (<36)	33	6.1	511	93.9
2 (36-49)	35	6.4	510	93.6

	cad			
	0		1	
	N	RowPct N	N	RowPct N
3 (50-64)	34	6.7	471	93.3
4 (65+)	11	7.3	139	92.7

	bcar1			
	0		1	
	N	RowPctN	N	RowPct N
All	1193	67.7	568	32.3
dagroup P(Chi2)=0.7394				
1 (<36)	369	67.5	178	32.5
2 (36-49)	366	66.3	186	33.7
3 (50-64)	355	69.5	156	30.5
4 (65+)	103	68.2	48	31.8

	dgf			
	0		1	
	N	RowPct N	N	RowPct N
All	1319	78.5	362	21.5
dagroup P(Chi2)=0				
1 (<36)	492	93.9	32	6.1
2 (36-49)	433	82.5	92	17.5
3 (50-64)	318	65.3	169	34.7
4 (65+)	76	52.4	69	47.6

	creat90			
	N	Median	P25	P75
All	1657	1.6	1.3	2.5
dagroup P(Kruskal-Wallis)=0				
1 (<36)	499	1.5	1.2	2.2
2 (36-49)	524	1.6	1.2	2.5
3 (50-64)	491	1.7	1.4	2.8
4 (65+)	143	1.9	1.4	3.4