Supplemental data to article

Mycophenolate Mofetil use is associated with prolonged graft survival after kidney transplantation

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Webtable 1

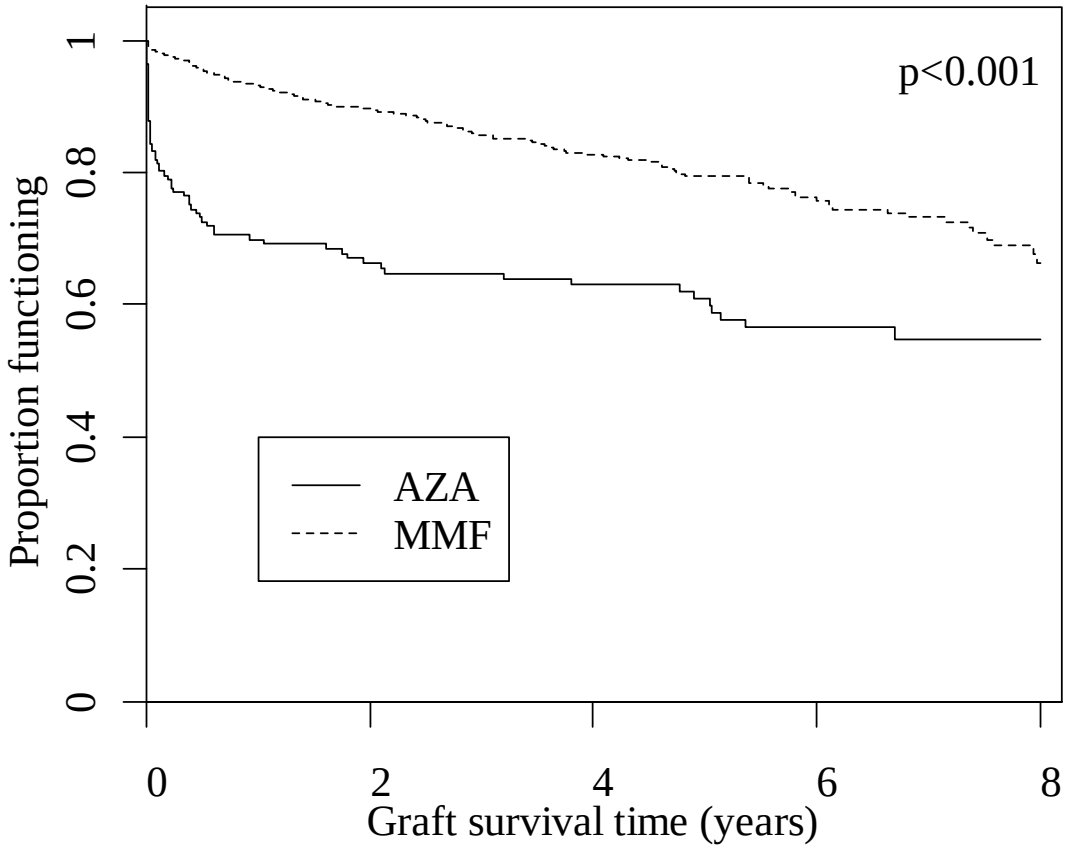
List of all variables in the database used for analysis.

Variable category	Variables
Patient demographics	Sex
	Date of birth
	Code of the referral dialysis center
	Diagnosis of native renal disease
	Date of first renal replacement therapy
	Date last seen
	Date of death
	Cause of death
Renal histology	Biopsy reading of native kidney disease
	Donor kidney biopsy (obtained before engraftment)
	Follow up biopsies
Transplantation	Date of transplantation(s)
	Date of graft failure(s)
	Donor source (cadaveric, living related/unrelated) and EUROTRANSPLANT-country
	Donor age
	Donor sex
	HLA MMs in A, B, DR
	Cold ischemic time
	Panel reactive antibodies max, latest
	CMV serology donor & recipient
	DGF/dialysis
	BCAR/CAN
	Treatment of rejection (steroid pulse/polyclonals)
Medication (annually)	Immunosuppressive induction therapy
	Maintenance immunosuppression
	Antihypertensive drugs and category (calcium channel blocker, beta /alfa blocker, ACEI/ARB, diuretics, vasodilators, else)
	Statins
	Erythropoietin(s)
	Oral antidiabetics
	Insulin
Comorbidities (annually)	Diabetes (0-2)

Variable category	Variables
	0…type 1, 1…type 2, 2…else
	Malignancy (0-3)
	0…no, 1…solid TU (and location), 2…PTLD, 3…else
	Liver (0-3)
	0…no, 1…alcohol, 2 viral, 3…else
	Lung (0,1)
	0…no, 1…COPD
	Heart (0-3)
	0 … no, 1…CHD, 2…CMP, 3…else
	Vascular (0-3)
	0…no, 1…cerebral, 2…peripheral, 3…else
	Blood pressure (syst/diast)
	HBV/HCV/CMV serology
	Body weight
Laboratory (annually)	Creatinine, BUN, sodium, potassium, phosphate, glucose, HbA1c, ASAT, ALAT, total protein, albumin, CRP, cholesterol, iPTH, haemoglobin, hematocrit, proteinuria, microalbuminuria

Webfigure 1

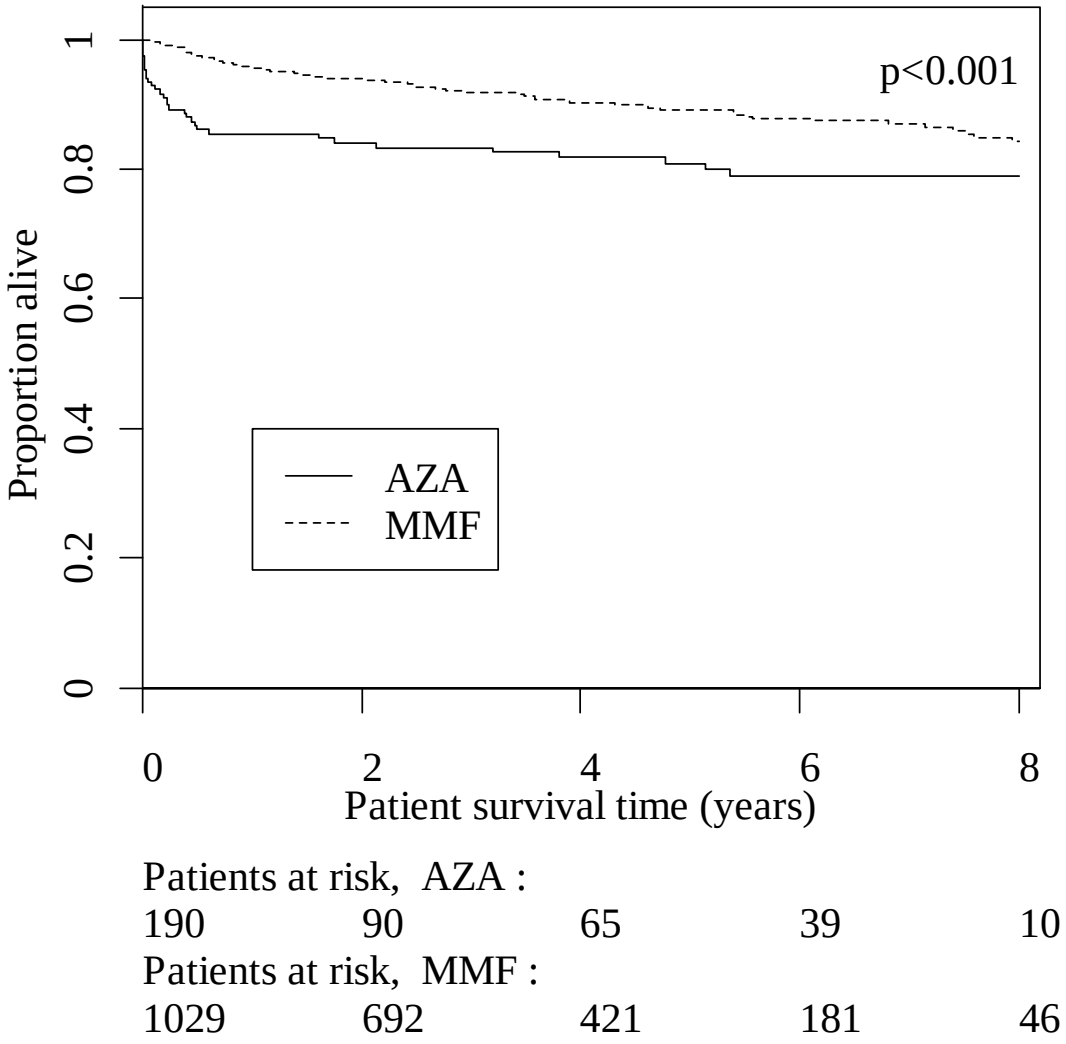
Kaplan-Meier plot of actual graft survival counting graft loss and death as event. The numbers below the x-axis refer to the subjects at risk at each time point. The p-value was derived from a log-rank test.



Patients at risk, AZA :				
190	90	65	39	10
Patients at risk, MMF :				
1029	692	421	181	46

Webfigure 2

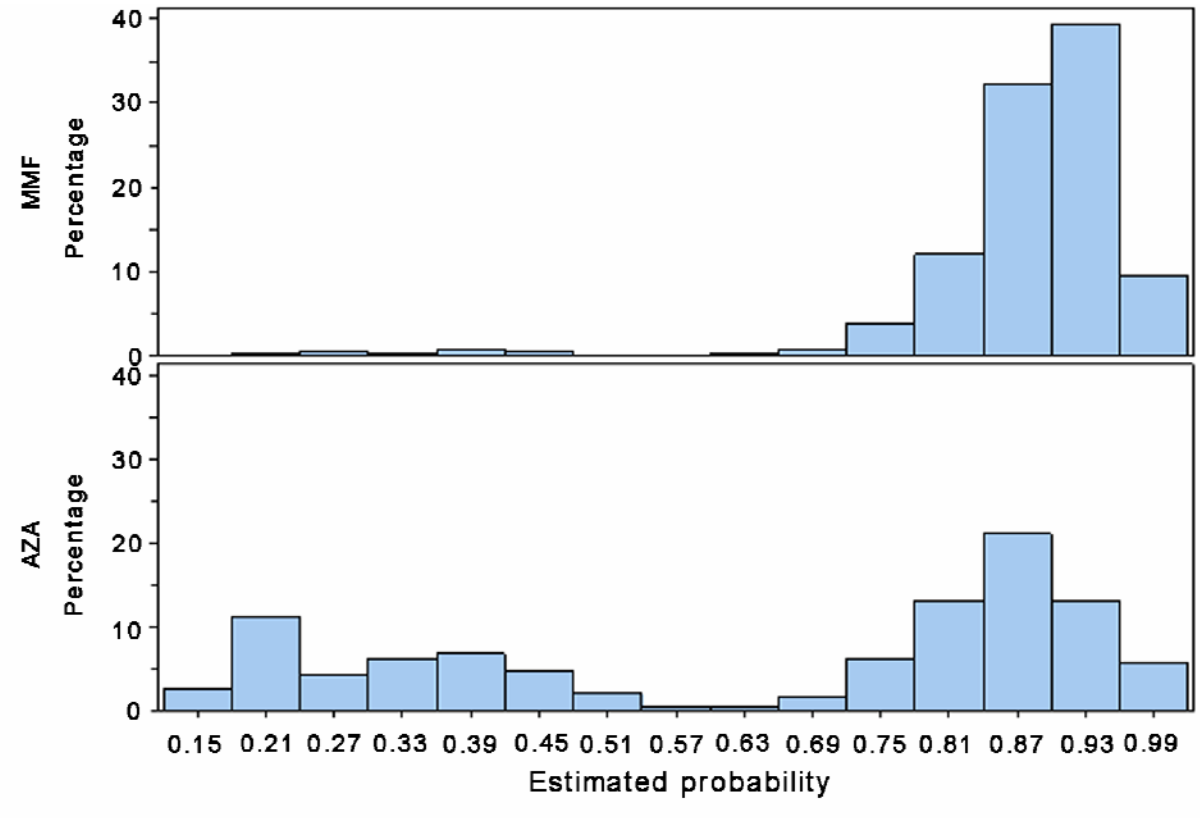
Kaplan – Meier plot of patient survival. The numbers below the x-axis show the patients at risk at two years intervals. The p-value was derived from a log-rank test.



Webfigure 3

Functional graft survival

Distribution of propensity score for functional graft survival of the groups MMF and AZA.



Webtable 2

Parameters used for propensity score model for functional graft survival

Parameter	Odds Ratio	95% confidence interval		p-value
Cardiomyopathy	1.09	0.42	2.87	0.839
MAP	1.01	1.00	1.02	0.021
Cholesterol	1.00	1.00	1.01	0.048
Time of dialysis	1.12	1.02	1.23	0.022
Sum of HLA mismatch	1.03	0.90	1.19	0.654
Coronary heart desease	0.64	0.33	1.25	0.177
CNI usage	0.06	0.03	0.09	< 0.001
Steroid usage	11.62	7.02	19.25	< 0.001

Webtable 3

Summary of the results derived from the five different analytical strategies analyzing the hazard of functional graft loss in the AZA vs MMF patients adjusted for several covariables.

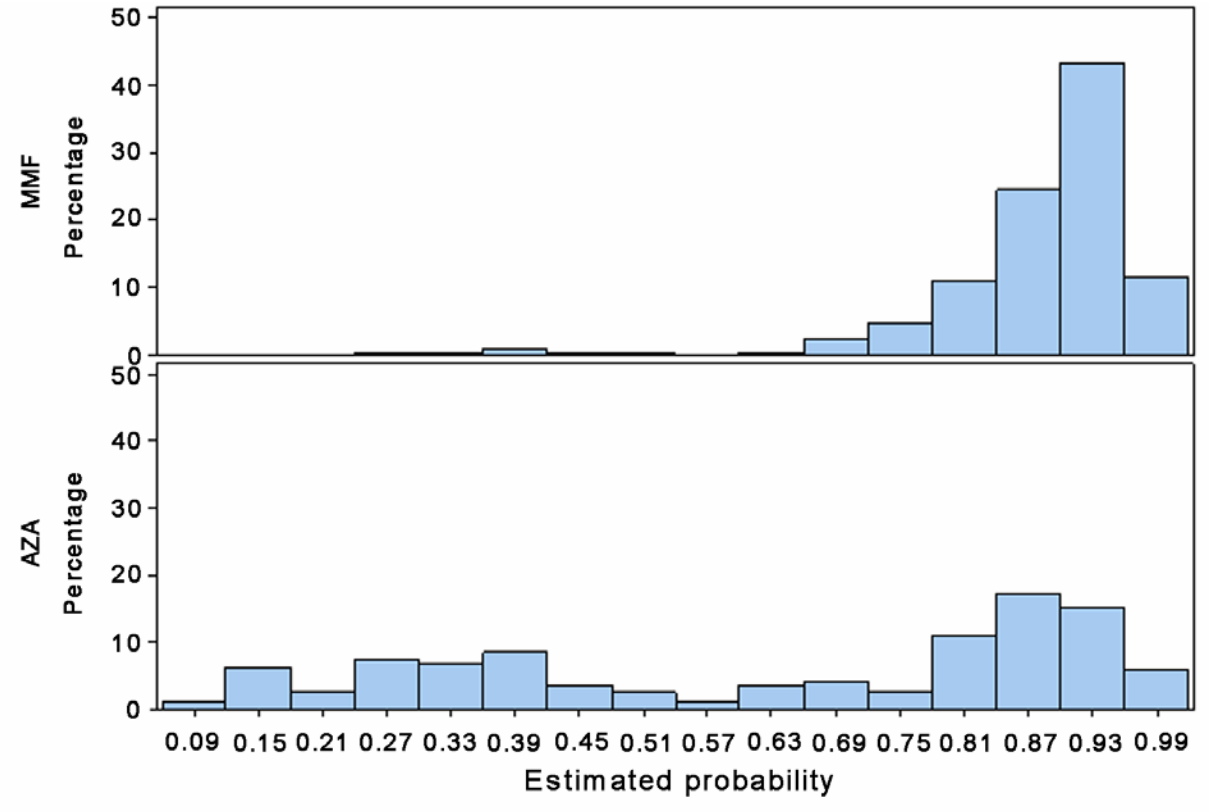
Parameter	Hazard Ratio	95% confidence interval		p-value
Complete case only (N=815, 62 events)				
AZA vs. MMF	2.15	1.16	4.02	0.016
Sum of HLA mismatch	1.21	1.00	1.45	0.046
Time on dialysis	1.14	1.00	1.29	0.042
MAP	1.01	1.00	1.02	0.002
CNI use	2.43	0.98	6.01	0.056
Steroid use	0.45	0.19	1.11	0.084
Multiple imputation (N=1219, 116 events)				
AZA vs. MMF	2.01	1.24	3.26	0.005
Sum of HLA mismatch	1.24	1.07	1.45	0.006
Time on dialysis	1.14	1.05	1.23	0.001
Cardiomyopathy	1.85	0.83	4.16	0.122
MAP	1.01	1.00	1.02	0.042
Cholesterol	0.99	0.99	1.00	0.002
Coronary heart disease	1.44	0.86	2.39	0.162
CNI use	1.66	0.96	2.86	0.070
Steroid use	0.59	0.35	1.01	0.054
Multiple imputation analysis, follow-up>1 year (N=948, 63 events)				
AZA vs. MMF	1.25	0.60	2.64	0.552
Sum of HLA mismatch	1.17	0.97	1.42	0.099
Time on dialysis	1.13	0.99	1.29	0.070
Cardiomyopathy	1.36	0.42	4.36	0.577
MAP	1.01	1.00	1.02	0.018
Cholesterol	1.00	0.99	1.00	0.087
Coronary heart disease	1.41	0.71	2.81	0.325
CNI use	0.56	0.23	1.38	0.206
Steroid use	1.26	0.51	3.07	0.619

Parameter	Hazard Ratio	95% confidence interval		p-value
Inverse probability of received treatment weighting (MSM)				
AZA vs. MMF	1.97	0.70	5.51	0.197
Propensity score model				
AZA vs. MMF	1.47	0.89	2.42	0.132
propensity	0.12	0.05	0.30	<0.001

Webfigure 4

Actual graft survival

Distribution of propensity score for actual graft survival of the groups MMF and AZA.



Webtable 4

Parameters used for propensity score model for actual graft survival

Parameter	Odds Ratio	95% confidence interval		p-value
Number of bloodpressure medications	1.17	1.04	1.31	0.008
Peripheral vascular disease	1.03	0.53	1.98	0.931
Coronary heart desease	0.73	0.36	1.50	0.375
Cardiomyopathy	1.23	0.52	2.92	0.623
MAP	1.01	1.00	1.02	0.078
Cholesterol	1.00	1.00	1.01	0.321
Recipient age	1.02	1.00	1.03	0.016
Year of transplantation	1.08	0.99	1.17	0.077
Time of dialysis	1.12	1.02	1.24	0.018
CIT	0.97	0.94	1.00	0.053
Donor age	0.99	0.98	1.00	0.130
Sum of HLA mismatch	0.95	0.83	1.09	0.451
Hemoglobin	1.00	0.85	1.18	0.989
CNI usage	0.06	0.04	0.10	< 0.001
Steroid usage	11.29	6.59	19.33	< 0.001

Webtable 5

Summary of the results derived from the five different analytical strategies analyzing the hazard of actual graft loss in the AZA vs. MMF patients adjusted for several covariables.

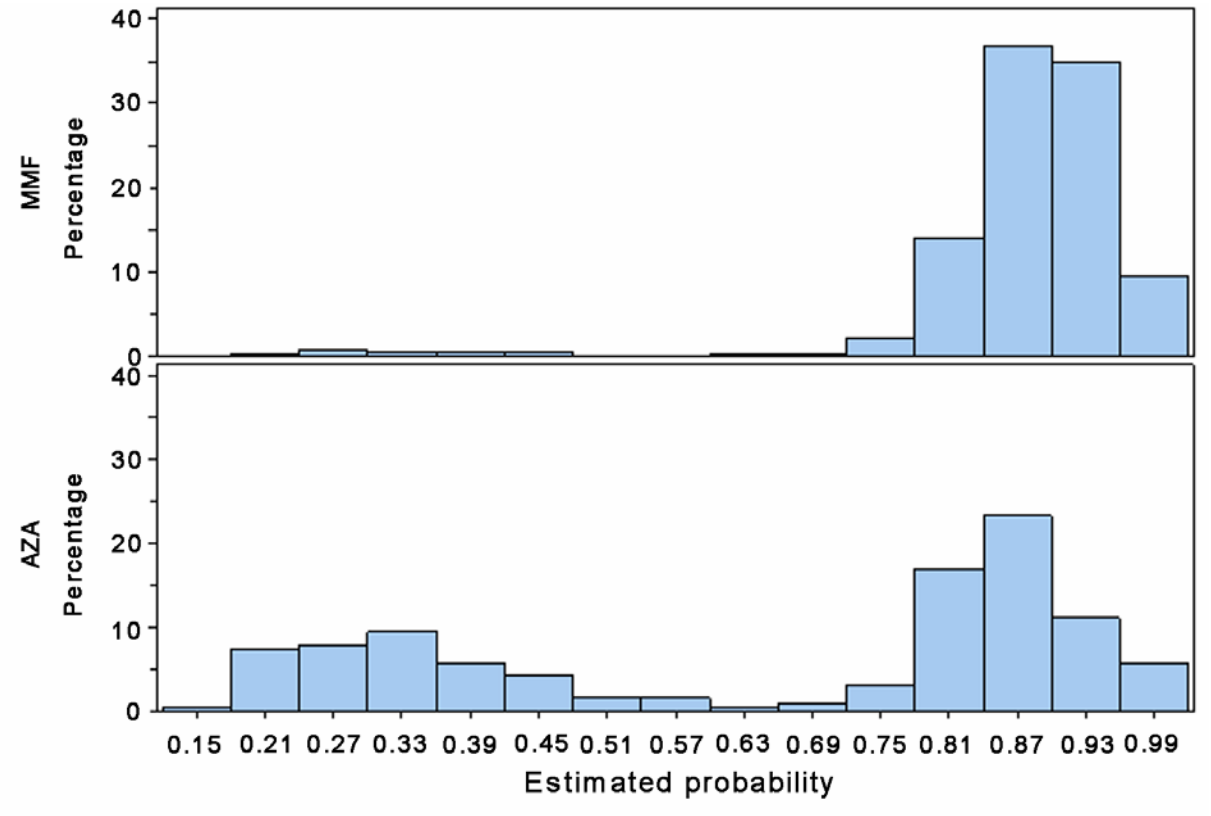
Parameter	Hazard Ratio	95% confidence interval		p-value
Complete case only (N=549, 102 events)				
AZA vs. MMF	2.04	1.22	3.39	0.006
sum of HLA mismatch	1.28	1.10	1.48	0.002
CIT	1.03	1.00	1.05	0.042
Number of bloodpressure medications	0.84	0.74	0.96	0.009
Peripheral vascular disease	1.51	0.97	2.34	0.067
Coronary heart disease	1.71	1.12	2.61	0.013
Hb	0.83	0.70	0.99	0.037
CNI use	2.46	1.36	4.45	0.003
Steroid use	0.54	0.30	0.97	0.039
Multiple imputation (N=1219, 247 events)				
AZA vs. MMF	2.21	1.61	3.03	<0.001
Donor age	1.01	1.00	1.02	0.047
Recipient age	1.01	1.00	1.02	0.011
Sum of HLA mismatch	1.13	1.02	1.26	0.026
CIT	1.02	1.00	1.05	0.082
Time on dialysis	1.08	1.01	1.16	0.020
Hb	0.87	0.78	0.97	0.010
MAP	1.00	1.00	1.01	0.152
Cholesterol	0.99	0.99	1.00	<0.001
Cardiomyopathy	1.61	0.96	2.70	0.067
Number of bloodpressure medications	0.90	0.83	0.98	0.015
Peripheral vascular disease	1.50	1.06	2.14	0.025

Parameter	Hazard Ratio	95% confidence interval		p-value
Coronary heart disease	1.72	1.06	2.79	0.029
Year of transplantation	1.12	1.04	1.20	0.002
CNI use	2.89	1.90	4.39	<0.001
Steroid use	0.41	0.27	0.62	<0.001
Multiple imputation analysis, follow-up>1 year (N=948, 129 events)				
AZA vs. MMF	1.06	0.62	1.83	0.829
Donor age	1.02	1.00	1.03	0.016
Recipient age	1.01	1.00	1.03	0.095
Sum of HLA mismatch	1.11	0.96	1.27	0.152
CIT	1.02	0.99	1.05	0.121
Time on dialysis	1.07	0.97	1.18	0.195
Hb	0.99	0.85	1.15	0.876
MAP	1.00	1.00	1.01	0.303
Cholesterol	1.00	0.99	1.00	0.090
Cardiomyopathy	1.18	0.60	2.30	0.626
Number of bloodpressure medications	1.00	0.89	1.13	0.991
Peripheral vascular disease	1.48	0.85	2.55	0.156
Coronary heart disease	1.36	0.71	2.59	0.345
Year of transplantation	1.00	0.87	1.13	0.945
CNI use	0.94	0.49	1.80	0.851
Steroid use	1.01	0.53	1.93	0.969
Inverse probability of received treatment weighting (MSM)				
AZA vs. MMF	1.73	0.81	3.69	0.158
Propensity score model				
AZA vs. MMF	1.50	1.09	2.07	0.013
propensity	0.05	0.02	0.09	<0.001

Webfigure 5

Patient survival

Distribution of propensity score for patient survival of the groups MMF and AZA.



Webtable 6

Parameters used for propensity score model patient survival

Parameter	Odds Ratio	95% confidence interval		p-value
Peripheral vascular disease	0.94	0.38	2.35	0.884
Cholesterol	1.00	1.00	1.01	0.175
Recipient age	1.01	1.00	1.02	0.036
Number of bloodpressure medications	1.17	1.05	1.31	0.006
Year of transplantation	1.09	1.01	1.17	0.020
CNI usage	0.07	0.04	0.11	< 0.001
Steroid usage	10.73	6.44	17.88	< 0.001

Webtable 7

Summary of the results derived from the five different analytical strategies analyzing the hazard of mortality in the AZA vs. MMF patients adjusted for several covariables.

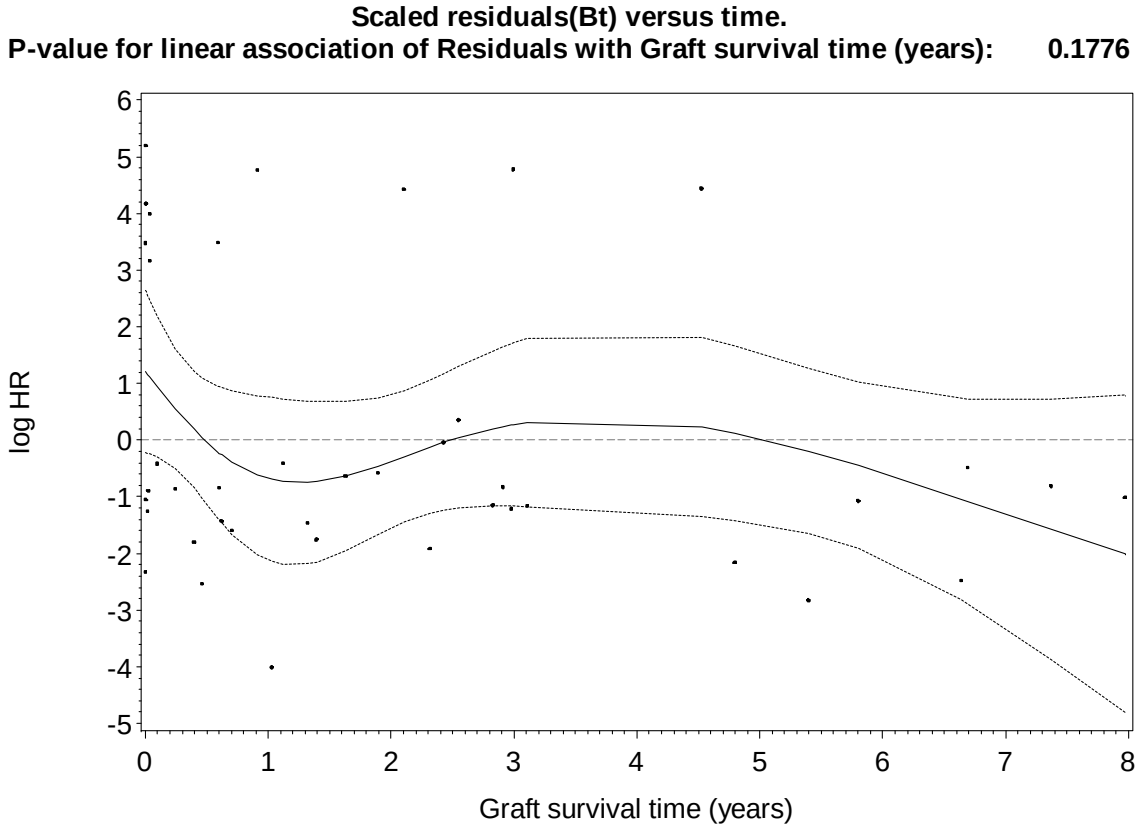
Parameter	Hazard Ratio	95% confidence interval		p-value
Complete case only (N=597, 65 events)				
AZA vs. MMF	1.74	0.94	3.24	0.079
Recipient age	1.04	1.02	1.06	<0.001
CIT	1.03	1.00	1.06	0.058
Peripheral vascular disease	1.95	1.18	3.22	0.009
Number of bloodpressure medications	0.80	0.67	0.94	0.008
CNI use	1.12	0.60	2.10	0.718
Steroid use	1.00	0.54	1.84	0.988
Multiple imputation (N=1219, 131 events)				
AZA vs. MMF	1.51	0.96	2.36	0.076
Recipient age	1.04	1.03	1.05	<0.001
Cholesterol	1.00	0.99	1.00	0.093
Peripheral vascular disease	1.79	1.16	2.76	0.009
Number of bloodpressure medications	0.84	0.75	0.94	0.003
Year of transplantation	0.96	0.89	1.04	0.348
CNI use	1.48	0.91	2.40	0.112
Steroid use	0.82	0.50	1.34	0.429

Parameter	Hazard Ratio	95% confidence interval		p-value
Multiple imputation analysis, follow-up>1 year (N=948, 66 events)				
AZA vs. MMF	0.93	0.43	2.01	0.852
Peripheral vascular disease	1.77	0.75	4.21	0.176
Cholesterol	1.00	0.99	1.01	0.950
Recipient age	1.05	1.02	1.07	<0.001
Number of bloodpressure medications	0.90	0.76	1.06	0.223
Year of transplantation	0.90	0.77	1.06	0.214
CNI use	1.37	0.59	3.20	0.461
Steroid use	0.85	0.36	2.03	0.715
Inverse probability of received treatment weighting (MSM)				
AZA vs. MMF	1.78	0.61	5.16	0.289
Propensity score model				
AZA vs. MMF	1.26	0.77	2.06	0.364
propensity	0.17	0.06	0.47	<0.001

Schoenfeld residual plots

Webfigure 6

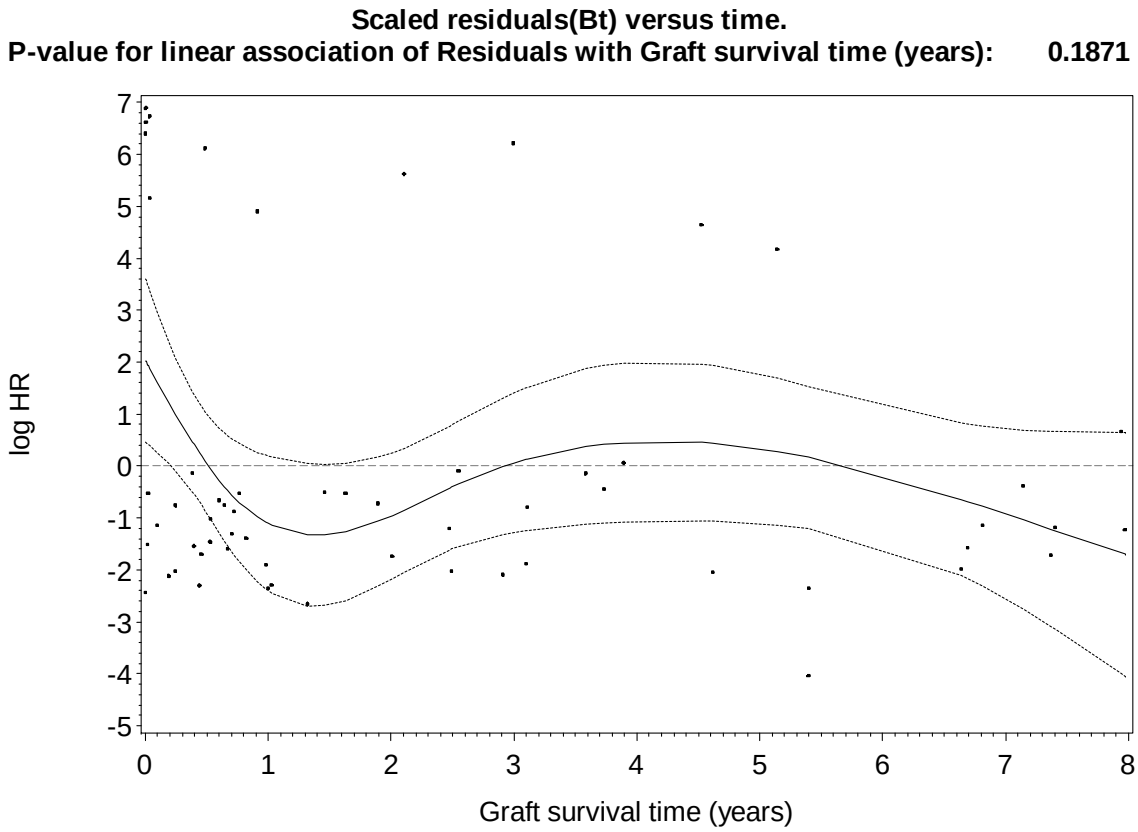
Functional graft survival (CCO analysis)



No change in the adjusted hazard ratio during time was detected.

Webfigure 7

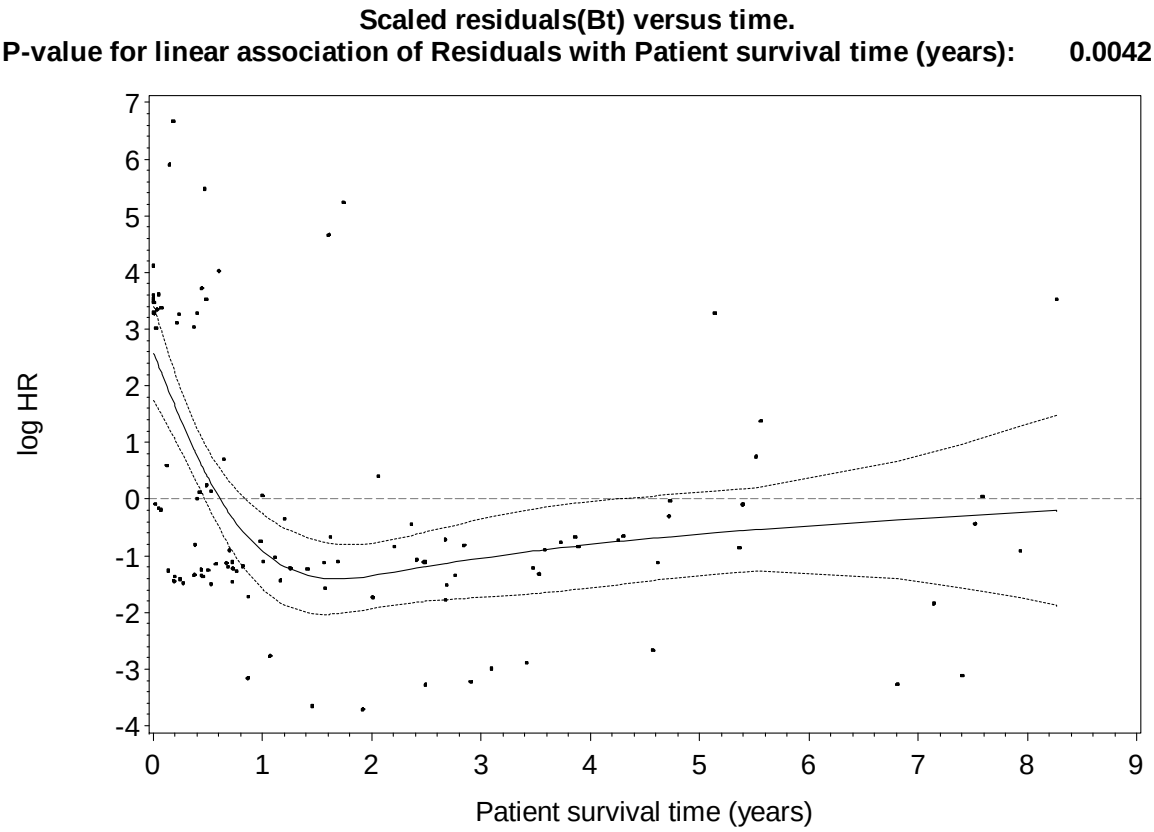
Actual graft survival (CCO analysis)



AZA is correlated with an increase at the very beginning of follow-up (see also patient survival), but not later on.

Webfigure 8

Patient survival (CCO analysis)



The adjusted hazard ratio of AZA during the first 6 months is >1, and reverted afterwards. After about 4 years, there is no difference between AZA and MMF.

This was also revealed by doing a separate analysis with follow-up > 1year (see forest plot).