SUPPLEMENTARY DIGITAL CONTENT

Table S1, SDC. Modelling inputs for Cox regression and generalised estimating equation in the analysis of CNI nephrotoxicity after univariate analysis, backwards elimination, and sensitivity analysis of trial forced-input of CNI type (i.e. CSA versus TAC).

Recipient age and recipient sex
Recipient weight
Total HLA mismatch score
Total ischemia time, cold and warm ischemic times of kidney transplant
Donor age and donor sex
Induction therapy

Delayed graft function (defined by the need for hemodialysis post-transplant)
Pre-transplant donor specific antibody (any DSA above 500 MFI)
De novo donor specific antibody
Panel reactive antibody status
Retransplantation
Early acute cellular rejection
Early vascular rejection
Early humoral rejection
Antilymphocyte treatment
Late rejection

Tacrolimus versus cyclosporine therapy
Azathioprine versus MMF therapy
Prednisolone dose
Post-transplant hypertension

Table S2, SDC. Demographic characteristics and clinical outcomes of the CNI study patients versus those excluded. Mean ± SD (%). Any donor hyalinosis, pancreas transplant failure or recurrence of diabetes mellitus, or insufficient follow up biopsies formed *a priori* criteria for exclusion.

Group	**Included**	**Excluded**	**P<**
Parameter			
Number (patients)	200	143	
Kidney biopsy (n)	8.1±4.1	4.9±3.6	<0.001
Biopsy follow up (years)	7.4±4.4	2.7±4.0	<0.001
Donor hyalinosis (n, %)	0 (0%)	27 (26.9%)	<0.001
Male donor sex (n, %)	124 (62.0%)	84 (59%)	NS
Donor age (years)	26.8±9.9	27.5±9.9	NS
Recipient weight (kg)	68.7±13.3	68.8±14.1	NS
Recipient age (years)	38.0±6.8	38.7±7.4	NS
Recipient sex (n, % male)	107 (53.5%)	83 (58.5%)	NS
Recipient weight (kg)	68.7±13.3	68.8±14.1	NS
Total HLA mismatch score	4.6±1.2	4.5±1.3	NS
Total ischemia time (hours)	11.6±3.0	11.1±3.0	NS
Early pancreas thrombosis	0%	33 (23.2%)	<0.001
Death with function	37 (18.5%)	31 (21.8%)	NS

Table S3a, SDC. Calcineurin inhibitor doses and blood concentrations. Mean ± SD (number of samples in brackets to form the estimate)

Group	**Cyclosporine**	**Tacrolimus**
Parameter		
Number (patients)	57	143
CNI dose (mg/day)		
1 month (439/124)	522±159	9.3±3.6
3 months (49/136)	408±112	8.3±3.4
1 year(56/122)	355±90	6.2±2.9
3 years (53/115)	286±81	5.0±2.3
5 years (47/58)	278±83	4.2±2.0
7 years (14/14)	288±76	4.6±1.9
10 years (28/14)	216±73	3.8±2.0
CNI dose (mg/kg/day)		
1 month	8.2±2.1	0.14±0.050
3 months	6.4±1.6	0.12±0.051
1 year	5.4±1.5	0.090±0.041
3 years	4.3±1.3	0.071±0.033
5 years	4.2±1.3	0.063±0.035
7 years	4.3±1.2	0.070±0.031
10 years	3.2±1.2	0.054±0.028
Trough C0 CNI levels (ng/ml)		
1 month	329±109	11.1±9.2
3 months	233±100	10.1±3.4
1 year	224±97	8.8±3.1
3 years	199±115	7.6±2.3
5 years	180±98	6.6±2.1
7 years	178±213	5.0±2.5
10 years	119±73	7.4±2.5

Table S3b, SDC. Prednisolone doses by time after transplantation according to CNI used at transplantation. Mean ± SD.

Group	Cyclosporine	Tacrolimus	P value
Prednisolone dose (mg/kg/day)			
3 months	23.6±3.7	20.1±4.5	0.001
1 year	10.3±2.3	9.6±2.1	0.05
3 years	9.6±1.7	8.9±1.9	0.05
5 years	9.4±1.9	9.0±5.4	0.05
7 years	9.0±1.9	8.7±2.1	NS
10 years	8.5±2.3	7.6±2.5	NS

Table S4, SDC. The occurrence of CNI nephrotoxicity, defined by histology, according to CNI type and other factors. Univariate and multivariate Cox regression analysis (if applicable), after backwards elimination. For striped fibrosis, the risk factor recipient hypertension was forced in (to demonstrate its lack of relevance), and MMF/AZA were forced were out of the final model (because of high colinearity with TAC/CSA treatment assignment where adjustment was likely to be incomplete with a possible result). 95%CI is the 95 percentile confidence intervals.

Mild arteriolar hyalinosis (ah1)

	Hazard ratio	95%CI	P value
Cyclosporine (vs. tacrolimus)	1.70	1.21-2.39	0.002
Donor age (years)	1.01	0.99-1.03	0.09 (NS)

Moderate arteriolar hyalinosis (ah2)

	Hazard ratio	95%CI	P value
Cyclosporine (vs. tacrolimus)	1.14	0.740-1.74	0.561

Striped fibrosis

	Hazard ratio	95%CI	P value
Cyclosporine (vs. tacrolimus)	9.35	4.93-17.54	0.001
Donor age (years)	1.04	1.01-1.06	0.010
Recipient hypertension	1.01	0.56-1.82	NS (0.96)

Tubular calcification

	Hazard ratio	95%CI	P value
Cyclosporine (vs. tacrolimus)	3.78	2.19-6.51	0.001
Acute rejection	1.76	1.03-3.03	0.041

Table S5a, SDC. CNI nephrotoxicity and early CNI dose: Sensitivity analysis for drug exposure in the early months after transplantation. Univariate Cox regression analysis for histological markers of nephrotoxicity according to the averaged CSA and TAC doses used from 1 to 3 months post-transplantation.

Mild arteriolar hyalinosis (ah1)

	Hazard ratio	95%CI	P value
Cyclosporine (mg/kg/day)	0.961	0.82-1.125	0.617
Tacrolimus (mg/kg/day)	20.970	0.396-1109.9	0.133

Moderate arteriolar hyalinosis (ah2)

	Hazard ratio	95%CI	P value
Cyclosporine (mg/kg/day)	1.050	0.865-1.274	0.624
Tacrolimus (mg/kg/day)	0.585	0.002-214.1	0.859

Striped fibrosis

	Hazard ratio	95%CI	P value
Cyclosporine (mg/kg/day)	1.167	0.967-1.409	0.108
Tacrolimus (mg/kg/day)	0.064	0-793.789	0.567

Tubular calcification

	Hazard ratio	95%CI	P value
Cyclosporine (mg/kg/day)	1.053	0.874-1.268	0.588
Tacrolimus (mg/kg/day)	3.689	0.003-5342.9	0.725

Table 5b. Multivariate Cox regression analysis for averaged CSA dose from 1 to 3 months post-transplantation where MMF vs AZA is included into model.

Striped fibrosis

	Hazard ratio	95%CI	P value
Cyclosporine (mg/kg/day)	1.27	1.041-1.524	0.017
MMF use (versus AZA)	0.120	0.036-0.401	<0.001

Table S6, SDC. CNI nephrotoxicity and CNI dose: Sensitivity analysis for full exposure duration. Cox regression analysis for selected histological markers of nephrotoxicity according to the averaged CSA and TAC doses for all available measurements after-transplantation.

Mild arteriolar hyalinosis (ah1)

	Hazard ratio	95%CI	P value
Cyclosporine (mg/kg/day)	1.089	0.812-1.460	0.569
Tacrolimus (mg/kg/day)	4.534	0.064-321.8	0.487

Moderate arteriolar hyalinosis (ah2)

	Hazard ratio	95%CI	P value
Cyclosporine (mg/kg/day)	1.074	0.763-1.513	0.681
Tacrolimus (mg/kg/day)	0.099	0-49.816	0.466

Striped fibrosis

	Hazard ratio	95%CI	P value
Cyclosporine (mg/kg/day)	1.277	0.0894-1.823	0.179
Tacrolimus (mg/kg/day)	0.680	0-40,880.5	0.945

Tubular calcification

	Hazard ratio	95%CI	P value
Cyclosporine (mg/kg/day)	1.415	1.02-1.964	0.038
Tacrolimus (mg/kg/day)	33.514	0.007-130,229	0.423

Table S7, SDC. Nephrotoxicity and CNI blood levels. Cox regression analysis for histological markers of nephrotoxicity to average CSA and TAC concentrations taken from 1 month to 10 years after transplantation. Levels obtained from CSA microemulsion and oil suspension were combined.

Mild arteriolar hyalinosis (ah1)

	Hazard ratio	95%CI	P value
Mean CSA levels (ng/ml)	1.000	0.996-1.004	0.897
Mean TAC levels (ng/ml)	1.010	0.992-1.029	0.285

Moderate arteriolar hyalinosis (ah2)

	Hazard ratio	95%CI	P value
Mean CSA levels (ng/ml)	0.995	0.990-1.129	0.062
Mean TAC levels (ng/ml)	0.994	0.972-1.015	0.557

Striped fibrosis

	Hazard ratio	95%CI	P value
Mean CSA levels (ng/ml)	1.003	0.998-1.008	0.257
Mean TAC levels (ng/ml)	1.023	1.004-1.043	0.021

Tubular calcification

	Hazard ratio	95%CI	P value
Mean CSA levels (ng/ml)	1.001	0.996-1.006	0.618
Mean TAC levels (ng/ml)	1.023	1.005-1.042	0.011

Table S8, SDC. Univariate Cox regression analysis for relationships of histological markers of nephrotoxicity to average or maximal CSA and TAC levels from 3 months to 5 years after transplantation.

Mild arteriolar hyalinosis (ah1)

	Hazard ratio	95%CI	P value
Mean CSA levels (ng/ml)	1.000	0.996-1.003	0.818
Maximal CSA levels (ng/ml)	1.001	0.999-1.003	0.422
Mean TAC levels (ng/ml)	0.990	0.923-1.061	0.770
Maximal TAC levels (ng/ml)	1.011	0.954-1.071	0.716

Moderate arteriolar hyalinosis (ah2)

	Hazard ratio	95%CI	P value
Mean CSA levels (ng/ml)	0.994	0.989-0.999	0.015
Maximal CSA levels (ng/ml)	0.998	0.995-1.000	0.071
Mean TAC levels (ng/ml)	1.006	0.914-1.106	0.906
Maximal TAC levels (ng/ml)	1.013	0.931-1.102	0.768

Striped fibrosis

	Hazard ratio	95%CI	P value
Mean CSA levels (ng/ml)	1.001	0.997-1.005	0.642
Maximal CSA levels (ng/ml)	1.002	1.000-1.005	0.108
Mean TAC levels (ng/ml)	1.060	0.917-1.225	0.432
Maximal TAC levels (ng/ml)	1.056	0.932-1.196	0.393

Tubular calcification

	Hazard ratio	95%CI	P value
Mean CSA levels (ng/ml)	1.000	0.996-1.005	0.878
Maximal CSA levels (ng/ml)	1.002	0.999-1.004	0.162
Mean TAC levels (ng/ml)	1.111	0.984-1.256	0.090
Maximal TAC levels (ng/ml)	1.091	0.982-1.212	0.106

Table S9a, SDC. Predictors of Banff arteriolar hyalinosis score, adjusted for time after transplantation, using a linear generalised estimating equation from 1622 evaluable biopsies in 200 patients.

Banff arteriolar hyalinosis score (ah)

	Coefficient	SE	P value
Time (years)	0.107	0.008	<0.001
Tubular calcification (yes/no)	0.155	0.084	0.067
Glomerular congestion (yes/no)	0.107	0.051	0.037
Tubular atrophy (Banff ct score)	0.167	0.035	<0.001
Arterial thickening (Banff cv score)	0.181	0.044	<0.001

Table S9b, SDC. Predictors of the development of severe arteriolar hyalinosis (Banff ah score at 2 or greater) using a binomial generalised estimating equation, adjusted for time after transplantation. The risk factor of interstitial infiltration was included in this model to demonstrate the lack of relationship of arteriolar hyalinosis with T cell infiltration.

Severe arteriolar hyalinosis (Banff ah score 2 or greater)

	Odds ratio	95% CI	P value
Time (years)	1.320	1.243-1.403	<0.001
Tubular atrophy (Banff ct score)	1.778	1.348-2.346	<0.001
Arterial thickening (Banff cv score)	1.485	1.004-2.198	0.048
Interstitial infiltrate (i score)	0.911	0.695-1.192	NS (0.495)

Table S10, SDC. Predictors of chronic interstitial fibrosis (Banff chronic interstitial fibrosis score was the dependent variable) using linear generalised estimating equation analysis from 1622 evaluable biopsies in 200 patients. Factors evaluated included CSA versus TAC therapy, CNI nephrotoxicity using the Banff arteriolar hyalinosis score as the surrogate marker, were adjusted for time after transplantation and multiple measurements.

Interstitial fibrosis score (Banff score)

	Coefficient	SE	P value
Time (years post transplant)	0.070	0.009	<0.001
Acute interstitial infiltrate (i score)	0.120	0.031	<0.001
Arteriolar hyalinosis (ah score)	0.201	0.034	<0.001
Cyclosporine (vs TAC) therapy	0.349	0.048	<0.001

SDC Table 11. Predictors of renal function assessed by isotopic 99^{m}Tc DTPA glomerular filtration rate (GFR) using linear generalised estimating equation. Important factors influencing measured GFR included glomerular bold flow in arteries and arterioles (Banff cv and ah scores, respectively), the number of functioning glomeruli, and non-atrophic tubules to receive the glomerular ultrafiltrate. Minus coefficient denotes adverse effect.

Glomerular filtration rate (mls/min)

	Coefficient	SE	P value
Arterial thickening (Banff cv score)	-4.409	1.260	<0.001
Arteriolar hyalinosis (ah score)	-4.271	1.189	<0.001
Glomerulosclerosis (%)	-1.496	0.705	0.034
Tubular atrophy (Banff ct score)	-0.117	0.041	0.004

Table S12, SDC. Sensitivity analyses by Cox regression for elimination incorporating all subjects from the screened dataset including diabetic subjects and those with donor hyalinosis (i.e. excluded subjects). Tested risk factor include donor hyalinosis and CNI type. The purpose was to test the effect of post-transplant diabetes mellitus (n=319 screened subjects). The diabetic efect only influenced striped fibrosis and tubular calcification, and we could not demonstrate an additive effect on the progression of arteriolar hyalinosis.

Mild arteriolar hyalinosis (ah1)

	Hazard ratio	95%CI	P value
Donor hyalinosis (Y/N)	2.607	1.706-3.983	0.001
Diabetes mellitus	0.895	0.578-1.387	0.621
Cyclosporine (vs. TAC)	1.58	1.233-2.126	0.001

Moderate arteriolar hyalinosis (ah2)

	Hazard ratio	95%CI	P value
Donor hyalinosis (Y/N)	1.465	0.846-2.537	0.173
Diabetes mellitus	1.183	0.692-2.021	0.328
Cyclosporine (vs. TAC)	1.197	0.835-1.718	0.328

Striped fibrosis

	Hazard ratio	95%CI	P value
Donor hyalinosis (Y/N)	1.01	0.99-1.03	0.108
Diabetes mellitus	0.98	0.97-1.000	0.048
Cyclosporine (vs. tacrolimus)	1.58	1.12-2.23	0.010

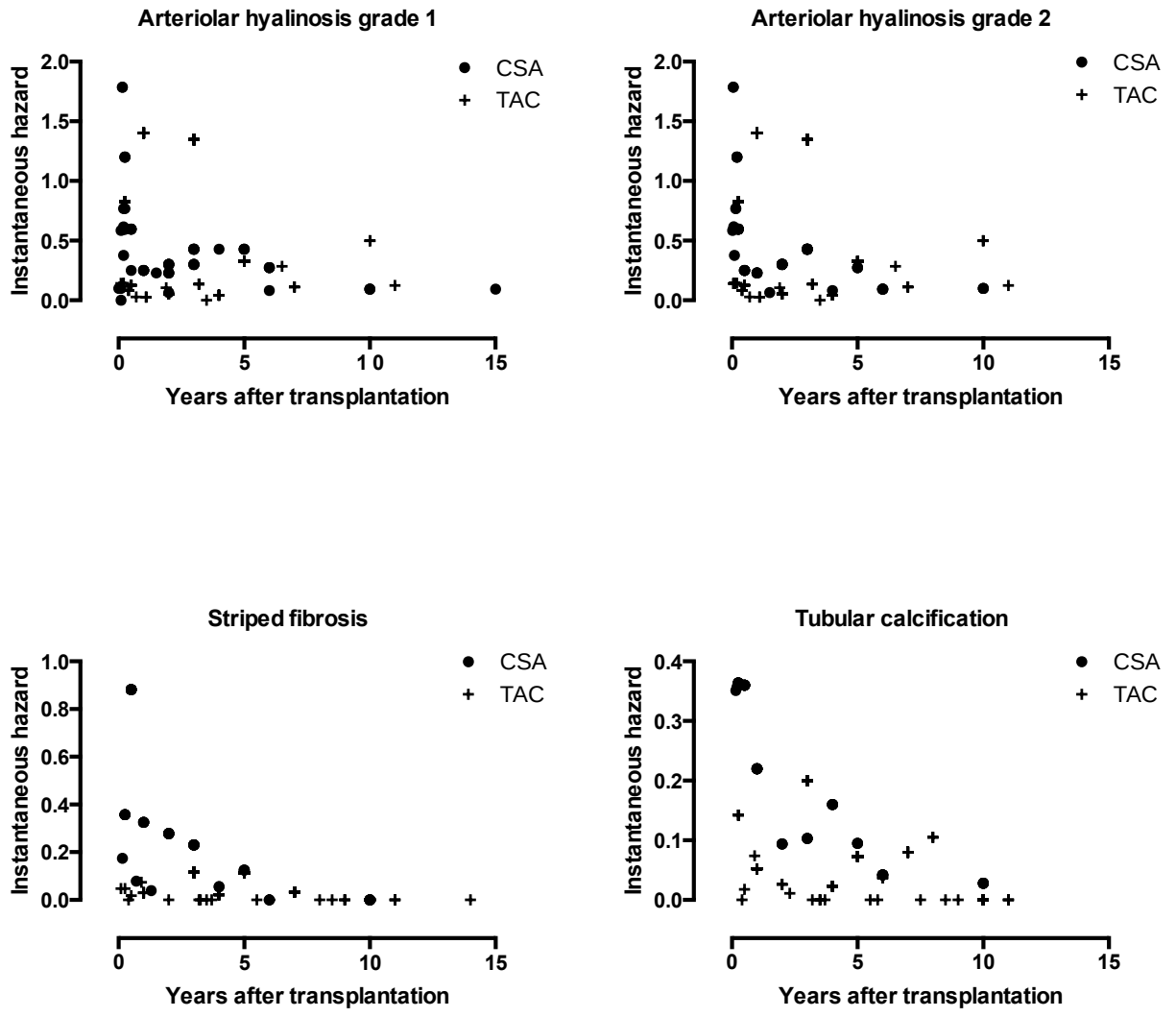
Tubular calcification

	Hazard ratio	95%CI	P value
Donor hyalinosis (Y/N)	0.589	0.284-1.223	0.156
Diabetes mellitus	1.801	1.052-3.085	0.032
Cyclosporine (vs TAC)	4.455	2.989-6.639	0.001

Table S13, SDC. Morphological study of arteriolar hyalinosis categorised by their individual Banff ah scores. Relative flow calculated from Poiseuilles's formula and expressed to values from normal arterioles without hyalinosis (pressure and viscosity omited from calculation). Displacement is the area occupied by the arteriole. Mean±SD or Number (%). Key a P<0.05, b<0.01, C<0.001 vs. ah 0.

Group	**Normal**	**Mild**	**Moderate**	**Severe**
Banff ah score	0	1	2	3
Arterioles (n)	38	12	25	25
Months post-transplant	3.2±4.9	68.6±46.2[a]	96.0±77.2[b]	112.0±36.9[b]
Displacement (um^2)	1021±711	878±752	707±391[b]	836±625[b]
Circumference (um)	110±40	102±28	95±30	100±39
Vascular wall (um^2)	953±506	658±554	553±293	731±555
Vessel thickness (um)	5.8±3.5	5.4±2.7	5.9±4.2	5.7±4.4
Lumenal area (um^2)	268±224	220±219	153±131[b]	104±84[c]
Lumenal eccentricity	0.69±0.13	0.70±0.14	0.70±0.18	0.72±0.14
Flow (% normal)	100±170	74±169	39±59[a]	20±34[b]
Flow reduction	0±170	26±169	61±59[a]	80±34 [b]

Figure S1, SDC. Instantaneous hazard ratios for markers of CNI nephrotoxicity according to CNI and time after transplantation. Note the high hazard early after transplantation, especially with CSA therapy.



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