

# The Effect of Variable CYP3A5 Expression on Cyclosporine Dosing, Blood Pressure and Long-Term Graft Survival in Renal Transplant Patients

Silke Kain<sup>1</sup>, Heiko Zürcher<sup>1,3</sup>, Peter Martus<sup>4</sup>, Gerd Offermann<sup>2</sup>, Joachim Beige<sup>2</sup>, Reinhold Kreutz<sup>1,2</sup>

<sup>1</sup>Department of Clinical Pharmacology, <sup>2</sup>Department of Medicine Nephrology, <sup>4</sup>Department of Medical Informatics, Biometry and Epidemiology, Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin; <sup>3</sup>DRK-Klinikum Westend, Department of Cardiology, Berlin; <sup>5</sup>Department of Medicine Nephrology, Klinikum St. Georg, Leipzig, Germany

## Introduction:

The cytochrome-P450 3A5 (CYP3A5) iso-enzyme is expressed in the liver, intestine and kidney of individuals carrying the CYP3A5\*1 allele but not in carriers of the CYP3A5\*3 allele. Recently, the CYP3A5\*1 allele has been implicated in drug metabolism of cyclosporine and in blood pressure regulation (Figure 1). The role of CYP3A5\*1 allele for long-term dose requirements of cyclosporine, blood pressure and renal graft survival in renal transplant patients is unclear.

## Methods:

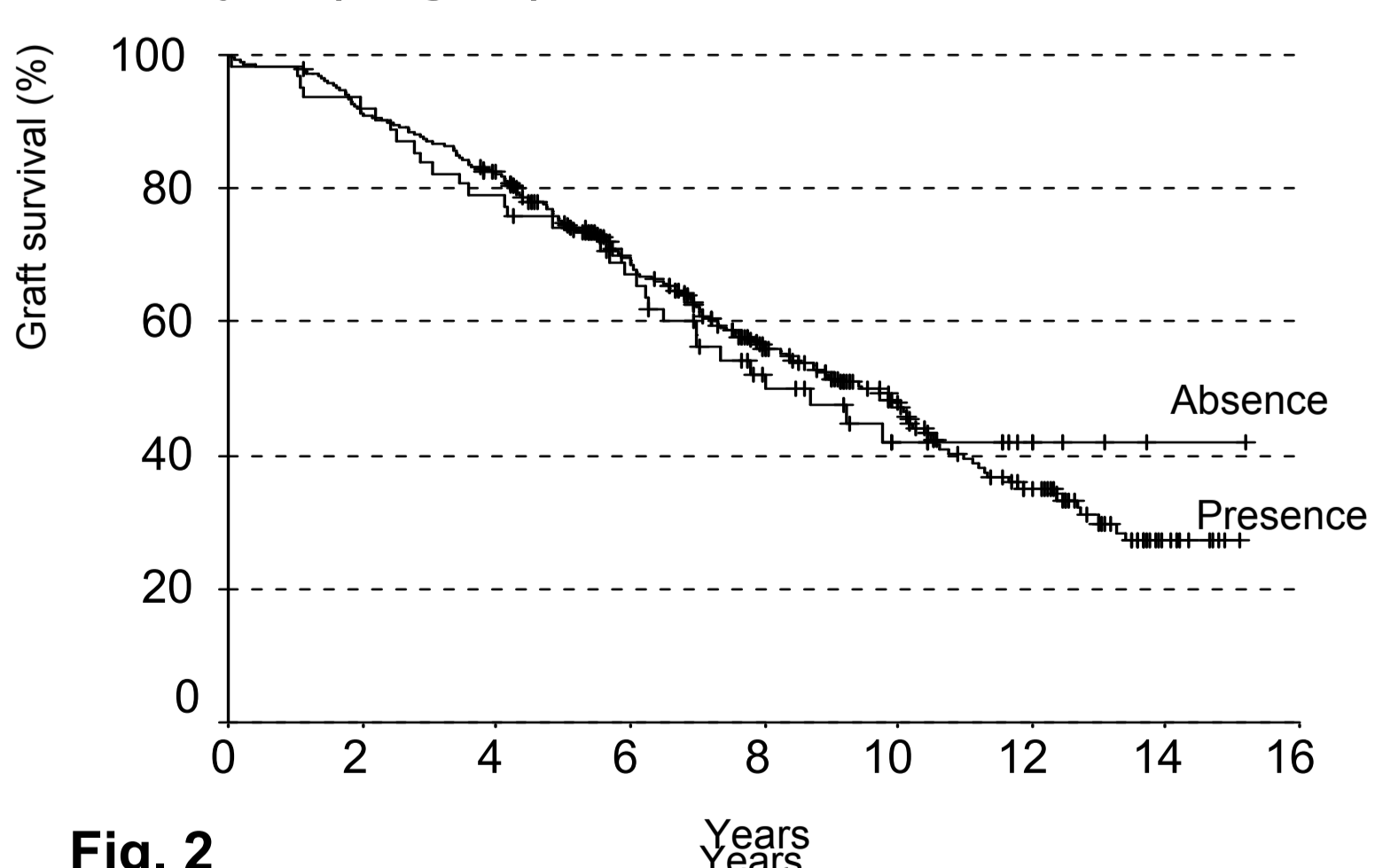
We studied 399 Caucasian patients (Table 1) from our single-centre registry who had stable graft function for more than 10 weeks after transplantation and were treated with a cyclosporine-based immunosuppressive regimen. The genotypes for CYP3A5\*1/\*3 were determined by a TaqMan PCR method. Cyclosporine dose requirements, blood pressure, antihypertensive medication, acute rejection, and serum creatinine, as well as graft survival were analyzed in relation to the presence or absence of the CYP3A5\*1 allele in recipients and donor kidneys. From 1984, patients were treated with the standard formulation of cyclosporine (Sandimmun®) and were switched after 1995 to the microemulsion formulation (Neoral®). Standard maintenance cyclosporine-based immunosuppressive therapy was performed by a triple regimen consisting of cyclosporine, 5 mg/day prednisolone, and 50 mg/day azathioprine or 1000 to 2000 mg/day mycophenolate mofetil. Patients that have been treated with other immunosuppressive compounds or were switched to other compounds were not included in our study.

**Table 1.** Characteristics of renal transplant recipients and donor kidneys in all patients and according to the presence or absence of the CYP3A5\*1 allele

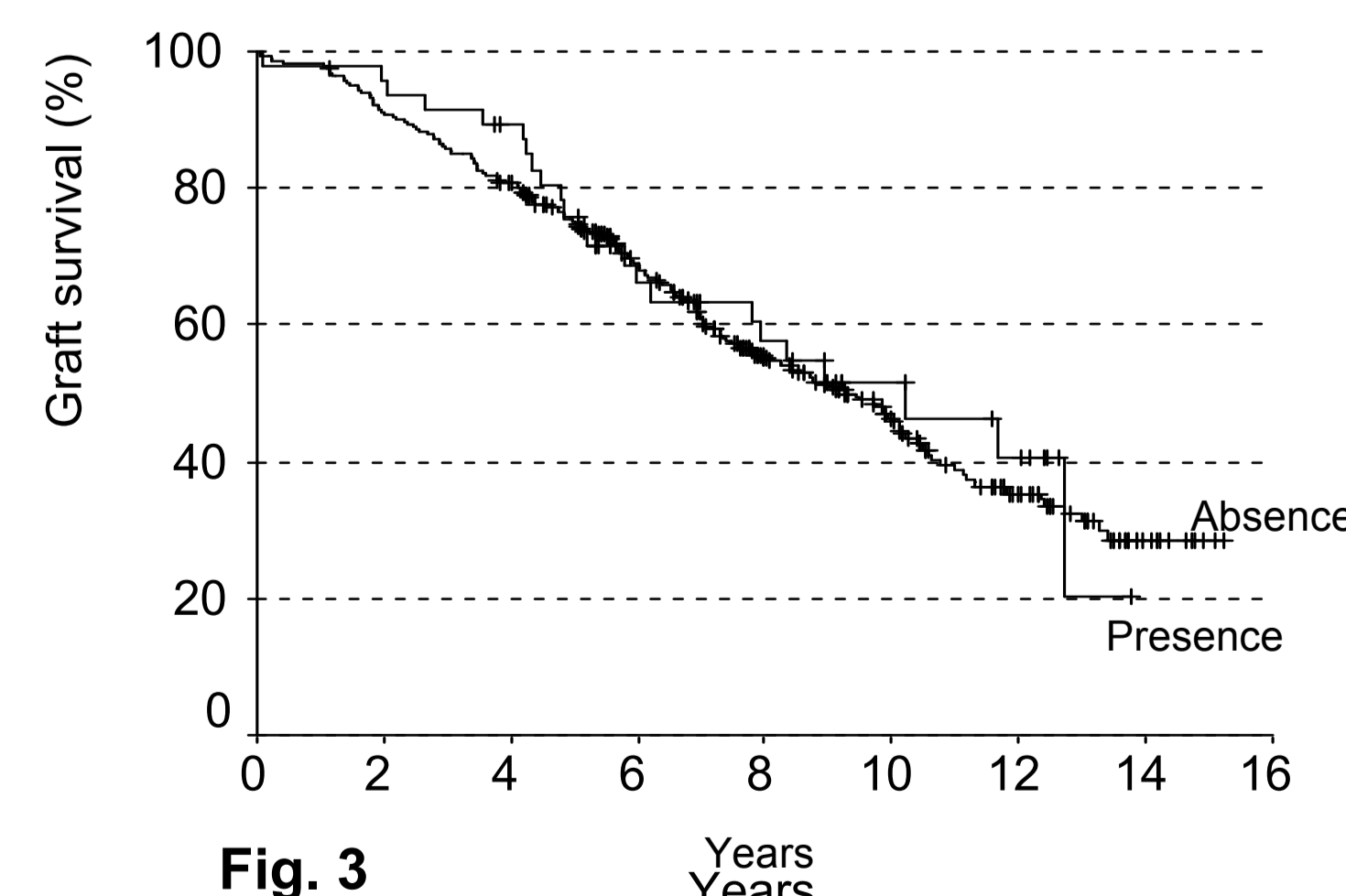
	CYP3A5*1 status		
	All	Absence	Presence
No. patients	399	337	62
Recipient age (years)	44.1 ± 12.4	44.5 ± 12.8	42.1 ± 13.4
Female (%)	39	39	40
Diabetic nephropathy (n)	31 (7.8%)	24 (7.1%)	7 (11.2%)
HLA mismatch points	6.3 ± 4.9	6.3 ± 4.9	6.4 ± 4.7
Cold ischemic time (hrs)	19.8 ± 7.9	19.8 ± 7.8	19.8 ± 8.2
Cadaveric donor (n)	379 (95%)	320 (95%)	59 (95%)
Number of 1 <sup>st</sup> Tx	333 (83%)	285 (85%)	48 (77%)
Kidney donor age (years)	41.0 ± 16.3	41.6 ± 15.9	37.7 ± 18.2
Female donor (%)	36	36	37
Hypertension before Tx (%)	50%	51%	48%
Hypertension 1 year after Tx (%)	58%	58%	57%

## Results:

The CYP3A5\*1 allele was found in 15.5% of the recipients and in 11.8% of the donor kidneys. The recipient CYP3A5\*1 allele had no effect on cyclosporine dose and blood concentrations at trough with and without dose-adjustment (Table 2). Blood pressure, number of antihypertensive compounds used for treatment, acute rejection and serum creatinine in recipient and donor kidneys showed also no difference according to the presence or absence of the CYP3A5\*1 allele (Table 3). Graft survival evaluated by Kaplan-Meier curves and Cox regression analysis were also not affected by the CYP3A5\*1 allele either in recipients (Fig.1) or donor kidneys (Fig.2).



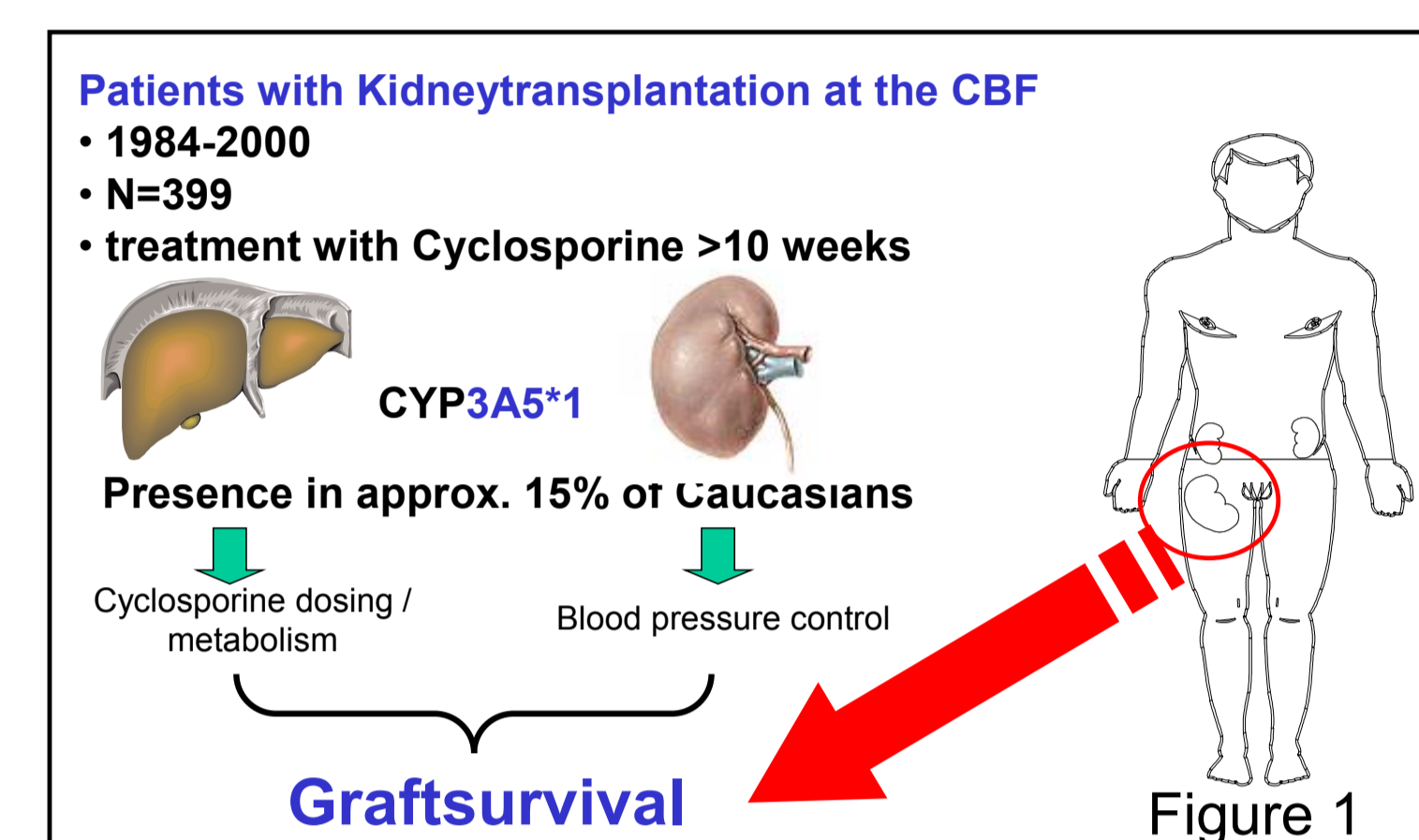
**Fig. 2**



**Fig. 3**

## Conclusions:

Our study demonstrates, that the presence of the CYP 3A5\*1 allele has no effect either on trough concentrations of cyclosporine or blood pressure control and renal outcome in renal transplantation. Therefore, it appears questionable whether pharmacogenetic testing for CYP3A5\*1 will have clinical impact on cyclosporine dosing and graft survival in Caucasian renal transplant patients.



**Table 2.** Cyclosporine dosing in all renal transplant recipients and according to the presence or absence of the CYP3A5\*1 allele

	CYP3A5*1 status		
	All	Absence	Presence
No. patients	399	337	62
Cyclosporine dose (mg/day)	263 ± 92.0	264 ± 94.8	260 ± 75.8
Cyclosporine dose per weight (mg/day)	3.89 ± 1.92	3.90 ± 2.00	3.83 ± 1.41
<b>Cyclosporine test method Tdx (n)</b>	159	133	26
Cyclosporine trough concentration (ng/mL)	211 ± 55.0	206 ± 48.6	230 ± 66.6
Dose-adjusted Cyclosporine trough concentration (ng/mL)	60.5 ± 23.9	59.7 ± 24.8	64.9 ± 18.4
<b>Cyclosporine test method Imx (n)</b>	240	204	36
Cyclosporine trough concentration (ng/mL)	147 ± 38.0	147 ± 37.2	147 ± 42.7
Dose-adjusted Cyclosporine trough concentration (ng/mL)	43.6 ± 17.4	43.9 ± 17.8	41.6 ± 15.5

**Table 3.** Blood pressure, antihypertensive medication, acute rejection, and serum creatinine according to the presence or absence of the CYP3A5\*1 allele in recipients and donor kidneys

	CYP3A5*1 status		
	All	Absence	Presence
<b>Recipients</b>			
No. patients	399	337	62
Systolic blood pressure (mmHg)	143 ± 15	144 ± 15	142 ± 16
Diastolic blood pressure (mmHg)	86 ± 9	86 ± 9	87 ± 11
Antihypertensive drugs (n)	1.39 ± 1.00	1.39 ± 1.06	1.40 ± 1.01
2 or more acute rejections (%)	10%	11%	10%
Serum creatinine 1 year after Tx (μmol/l)	164.9 ± 66.2	165.9 ± 65.8	159.5 ± 68.2
<b>Donor kidneys</b>			
No. patients	399	352	47
Systolic blood pressure (mmHg)	143 ± 15	142 ± 15	145 ± 15
Diastolic blood pressure (mmHg)	86 ± 9	86 ± 9	86 ± 9
Antihypertensive drugs (n)	1.39 ± 1.10	1.38 ± 1.0	1.49 ± 1.10
2 or more acute rejections (%)	8%	8%	6%
Serum creatinine 1 year after Tx (μmol/l)	164.7 ± 66.1	164.5 ± 66.1	167.9 ± 66.9