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Background

Despite improvements in kidney transplantation, complications including cardiovascular morbidity contribute to a reduced patient and graft survival. The amino acid homoarginine exerts a variety of beneficial effects that may be clinically relevant in kidney transplant recipients.

Aim

To assess the effect of homoarginine serum concentrations on cardiovascular events, renal outcomes and mortality in kidney transplant recipients.

Design & Patients

Assessment of Lescol in Renal Transplantation study (ALERT):

- multicenter randomized controlled trial
- kidney transplant recipients
- clinical data collected at baseline (randomization) and regular follow-up visits every 6 months
- patients followed until time of death, censoring or end of the study
- inclusion criteria for ALERT:
 - * age 30-75 years
 - * received a kidney transplant more than 6 months before
 - * serum cholesterol concentration between 4.0 and 9.0 mmol/L
 - * additional criterion for the present analysis:
 - available homoarginine measurement at baseline

Methods

- Homoarginine was measured by reverse-phase HPLC
- Homoarginine status divided into 4 categories (quartiles): $\leq 1.39 \mu\text{mol/L}$ (quartile 1), $>1.39 \leq 1.81 \mu\text{mol/L}$, $>1.81 \leq 2.33 \mu\text{mol/L}$, $>2.33 \mu\text{mol/L}$ (quartile 4);
- Cox regression analysis to calculate hazard ratios (HR) of baseline homoarginine status on clinical outcomes:
 - 1) major adverse cardiovascular events
 - 2) combined cerebrovascular events
 - 3) non-cardiovascular death
 - 4) all-cause mortality
 - 5) renal endpoint of graft loss or doubling of serum creatinine
- All analyses adjusted for age, sex, fluvastatin treatment, diabetes mellitus, CAD, Smoking, SBP, LDL-C, estimated GFR

Results

Table 1. Baseline characteristics and clinical parameters (at baseline) in kidney transplant recipients (N=1870) grouped by quartiles of homoarginine.

	Homoarginine categories			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Age years	48 (10)	50 (11)	50 (11)	50 (11)
Sex % male	52	61	72	77
Total time on RRT years	7.6 (5.1)	7.5 (5.2)	7.5 (4.8)	7.0 (4.5)
BMI kg/m^2	24.7 (4.2)	25.4 (4.4)	26.3 (4.4)	26.5 (4.2)
Syst blood pressure mmHg	144 (19)	144 (20)	145 (19)	145 (18)
Diabetes mellitus %*	26	20	17	15
CAD %	9	10	8	11
Laboratory parameters				
CRP mg/dl	4.3	4.2	3.2	3.4
LDL-C mmol/l	4.1 (1.1)	4.1 (1.0)	4.2 (1.0)	4.2 (1.0)
Creatinine $\mu\text{mol/l}$	155 (83)	145 (54)	143 (53)	140 (46)
Calcium mmol/l	2.4 (0.2)	2.4 (0.2)	2.4 (0.2)	2.4 (0.1)
Phosphate mg/dl	3.8 (0.8)	3.6 (0.7)	3.6 (0.7)	3.5 (0.6)
eGFR ml/min	45 (16)	48 (17)	50 (15)	51 (17)

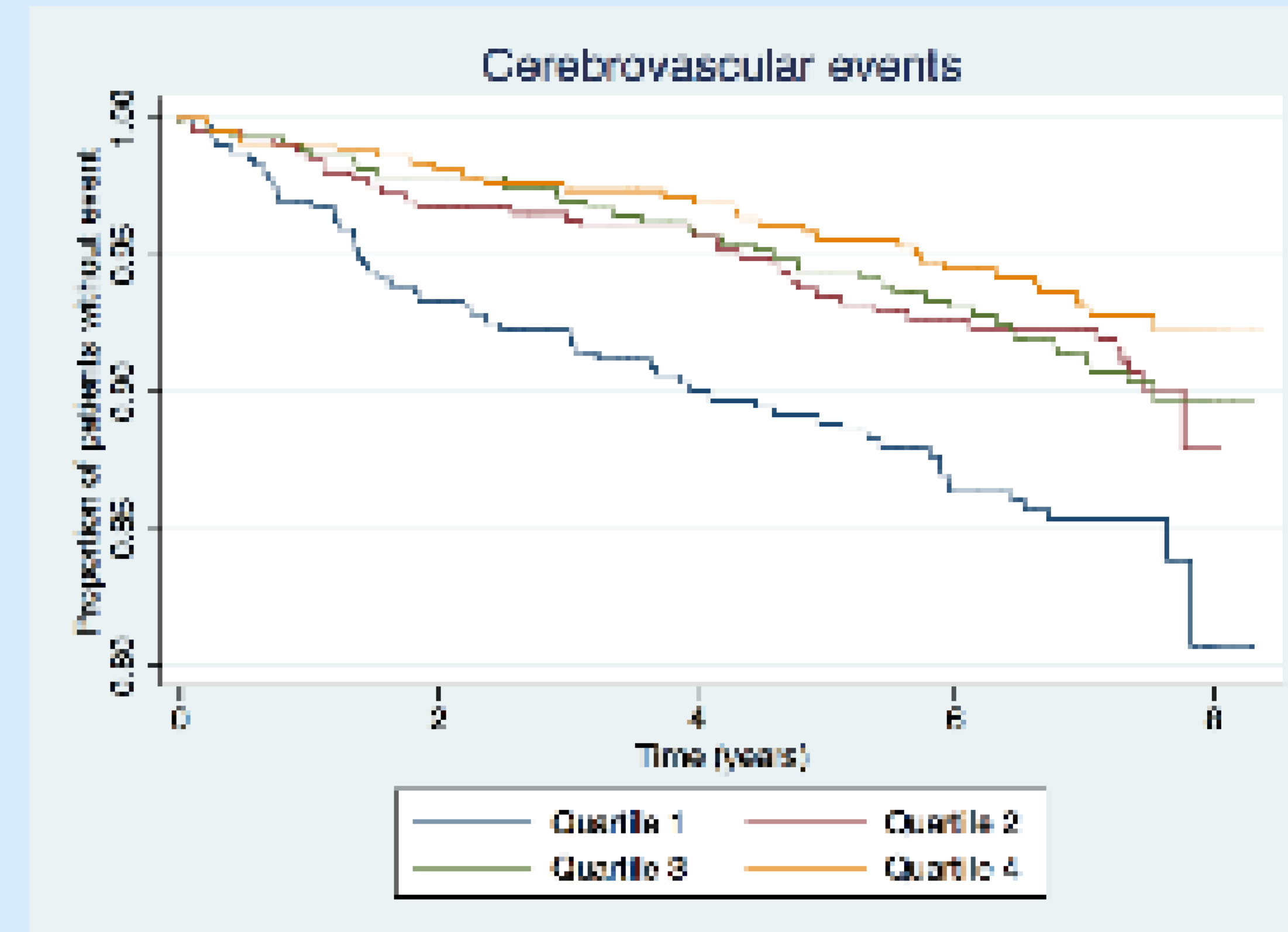


Figure 1: KM curves for the occurrence of cerebrovascular events according to quartiles of homoarginine levels at baseline

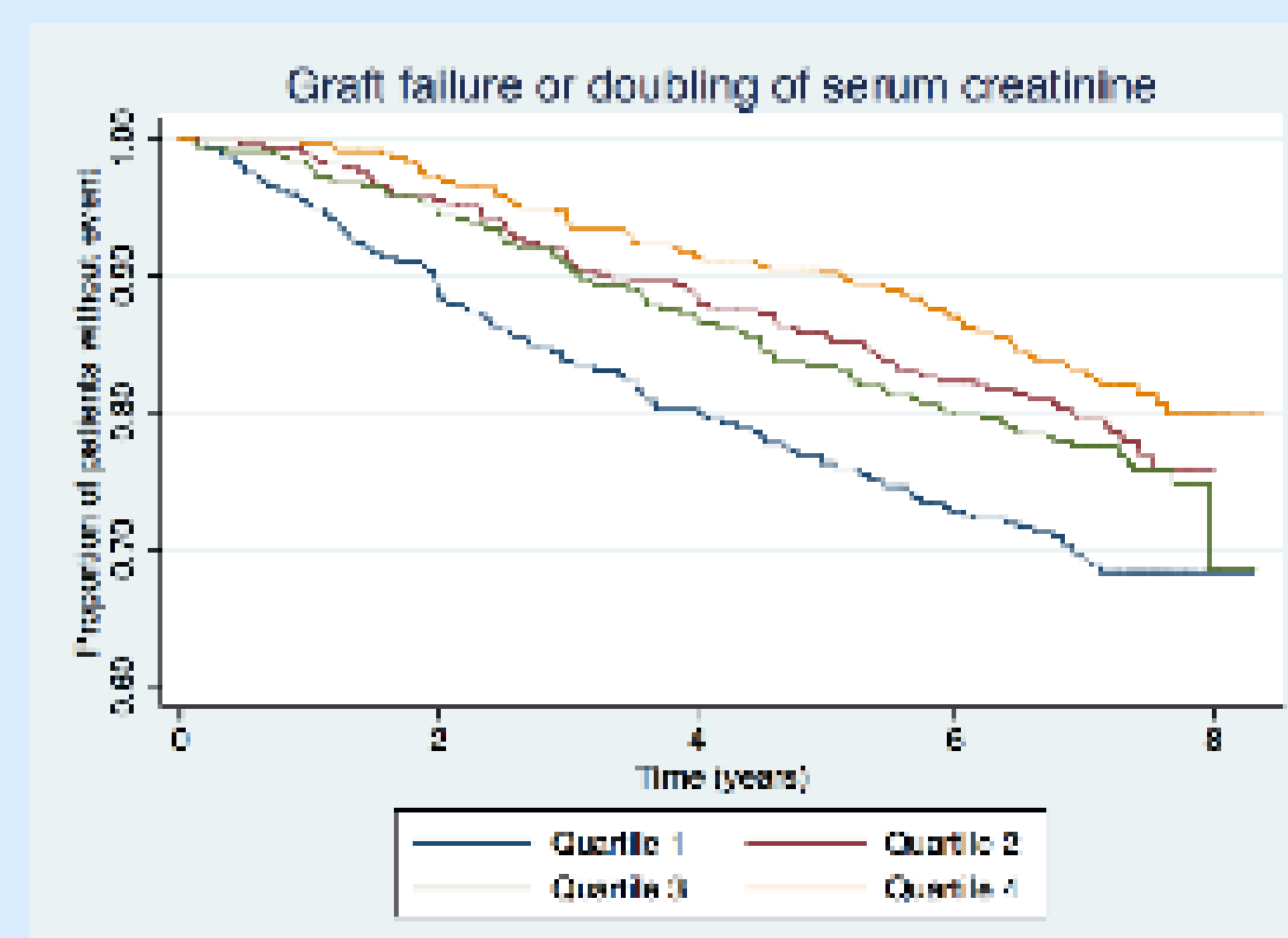


Figure 2: KM curves for the occurrence of the renal endpoint according to quartiles of homoarginine levels at baseline

Table 2. Adjusted Hazard ratios (95% CI) for cerebrovascular, cardiovascular and non-cardiovascular events, all-cause mortality and the renal endpoint according to homoarginine levels at baseline

Outcome	homoarginine quartiles			
	Q1 n=471	Q2 n=467	Q3 n=470	Q4 n=462
cerebrovascular events				
Adj. ² HR (95% CI)	2.38 (1.47-3.87)	1.31 (0.79-2.19)	1.29 (0.78-2.12)	1
cardiovascular events				
Adj. ² HR (95% CI)	0.91 (0.61-1.33)	0.91 (0.62-1.32)	1.00 (0.70-1.43)	1
non-cardiovasc. death				
Adj. ² HR (95% CI)	1.44 (0.89-2.33)	1.27 (0.80-2.01)	0.93 (0.58-1.50)	1
All-cause mortality				
Adj. ² HR (95% CI)	1.39 (0.98-1.96)	1.23 (0.88-1.72)	1.01 (0.72-1.42)	1
renal endpoint				
Adj. ² HR (95% CI)	1.58 (1.15-2.16)	1.06 (0.77-1.48)	1.46 (1.07-1.99)	1

Conclusions & implication

- Low homoarginine is strongly associated with cerebrovascular events, graft loss and progression of kidney failure in renal transplant recipients.
- Whether interventions with homoarginine supplementation improve clinical outcomes, requires further evaluation.

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