Cardiovascular disease relates to intestinal uptake of *p*-cresol in patients with chronic kidney disease

Ruben Poesen, Liesbeth Viaene, Bert Bammens, Kathleen Claes, Pieter Evenepoel, Björn Meijers

Division of Nephrology, Department of Microbiology and Immunology, University Hospitals Leuven, Leuven, Belgium

INTRODUCTION AND OBJECTIVES

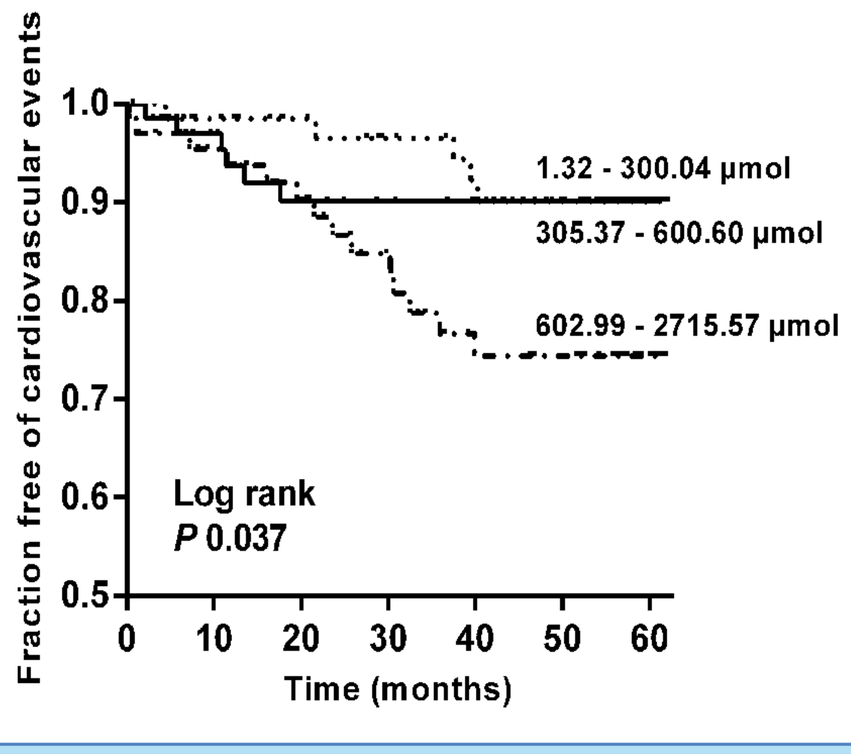
Serum *p*-cresyl sulfate associates with cardiovascular disease in patients at different stages of chronic kidney disease (CKD). *p*-Cresyl sulfate concentrations are determined by intestinal uptake of *p*-cresol, human metabolism to *p*-cresyl sulfate and renal clearance. Whether intestinal uptake of *p*-cresol itself is associated with cardiovascular disease in patients with renal dysfunction has not been studied to date.

METHODS

We performed a prospective study in patients with CKD stage 1 - 5 (clinicaltrials.gov NCT00441623). Intestinal uptake of *p*-cresol, under steady state conditions, was estimated from 24h urinary excretion of *p*-cresyl sulfate. Primary endpoint was time to first cardiovascular event, i.e., cardiac death, myocardial infarction/ischemia, ventricular arythmia, cardiovascular surgery, cerebrovascular accident or symptomatic peripheral arterial disease. Statistical analysis was done using Kaplan Meier estimates and Cox proportional hazard analyses.

RESULTS

In a cohort of 200 patients, median 24h urinary excretion of *p*-cresyl sulfate was 457.47 µmol (IQR 252.68 - 697.17). After a median follow-up of 52 months, 25 patients reached the primary endpoint (tertile 1/2/3: 5/6/14 events, see Figure). Higher urinary excretion of *p*-cresyl sulfate was related with cardiovascular events (univariate hazard ratio per 100 µM increase: 1.112, *P* 0.0015). In multivariate analysis, urinary excretion of *p*-cresyl sulfate remained a predictor of cardiovascular events, independent of markers of renal function (HR 1.120, *P* 0.0022) and in different models with other cardiovascular risk factors (Framingham, cardiovascular history, presence of diabetes mellitus and biochemical parameters) (see Table).



Model	24h urinary excretion of *p*-cresyl sulfate	
	Hazard ratio per 100 µmol increase (95% confidence interval)	*P*
1. Unadjusted	1.112 (1.041 – 1.187)	0.002
2. Prior cardiovascular disease and diabetes mellitus	1.083 (1.005 – 1.167)	0.04
3. eGFR and 24h proteinuria (Ln)	1.120 (1.042 – 1.205)	0.002
4. Creatinine and age	1.120 (1.040 – 1.206)	0.003
5. Albumine and body mass index	1.078 (1.014 – 1.146)	0.02
6. Systolic blood pressure and parathormone (Ln)	1.106 (1.038 – 1.179)	0.002
7. Hemoglobin and C-reactive protein (Ln)	1.112 (1.041 – 1.187)	0.002

CONCLUSIONS

Intestinal uptake of *p*-cresol associates with cardiovascular disease, independent of renal function. Insights into mechanisms governing intestinal generation and absorption of *p*-cresol may lead to identification of novel therapeutic targets to reduce cardiovascular disease risk in patients with CKD.

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Ruben Poesen

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