# Are acetylated dimethylarginines independent cardiovascular risk factors in CKD patients?

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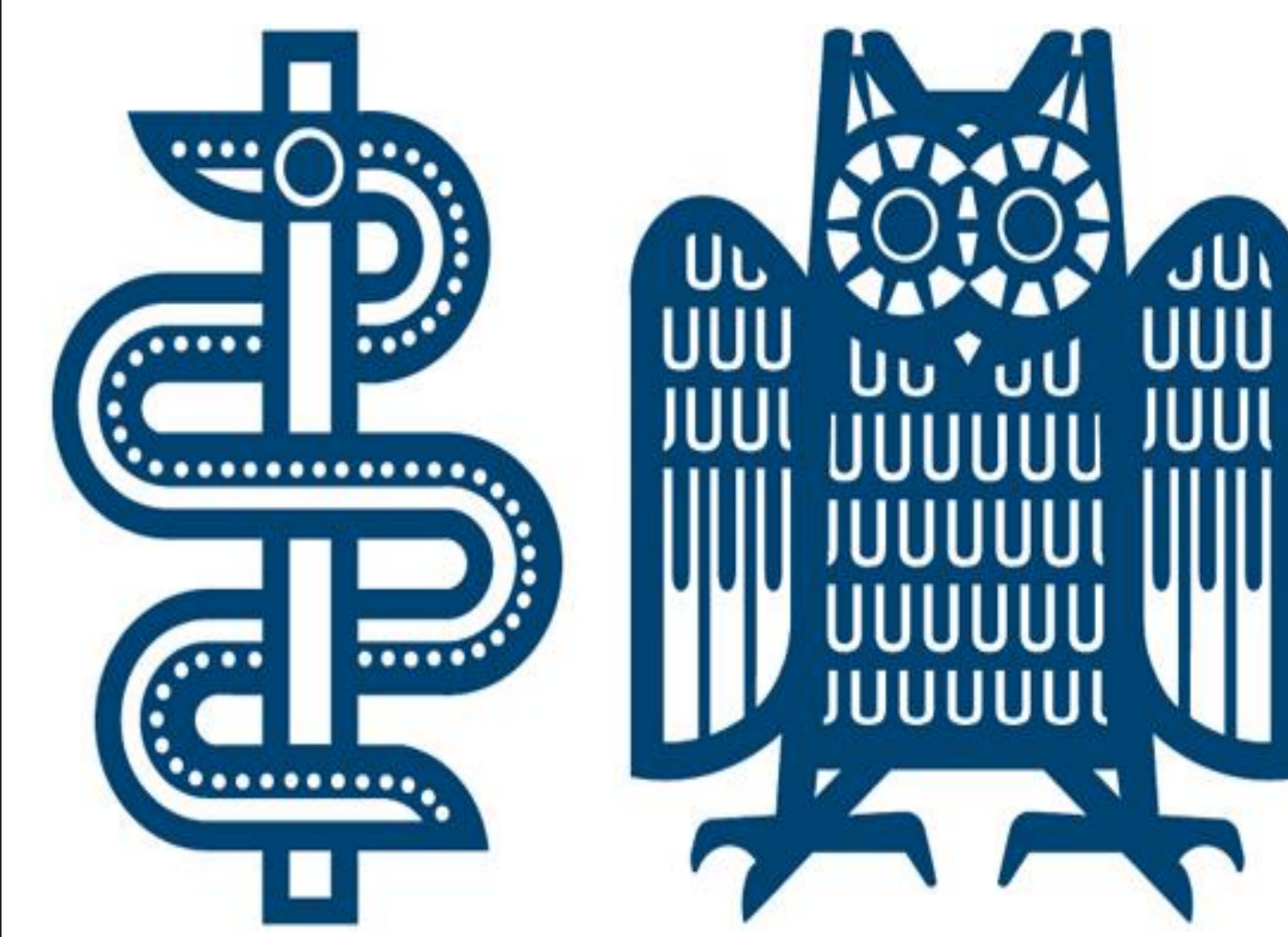
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Background

➢ Patients suffering from chronic kidney disease (CKD) have a substantial burden of cardiovascular disease, whose underlying pathophysiological mechanism cannot fully be explained by traditional risk factors.

➢ Therefore, non-traditional cardiovascular risk factors have to be taken into account.

➢ As such potential non-traditional risk factors, asymmetric dimethylarginine (ADMA) & symmetric dimethylarginine (SDMA) have been a focus of cardiorenal research for several years.

➢ It has recently been revealed that ADMA & SDMA become acetylated during their degradation. In murine models the acetylated ADMA (Ac-ADMA) & the acetylated SDMA (Ac-SDMA) were significantly associated with kidney function.

Hypothesis

➢ (a) a similar accumulation of Ac-ADMA & Ac-SDMA occurs in humans.

➢ (b) Ac-ADMA & Ac-SDMA are prominent predictors of incident cardiovascular events than ADMA & SDMA.

Methods

➢ Blood samples of 528 CKD patients KDIGO stage G2 to G4 who participated in our CARE FOR HOMe study were analyzed. ADMA, SDMA & acetylated metabolites were measured by liquid chromatography – tandem mass spectrometry. All patients were followed annually with standardized interviews during a follow up period of 4.6 ± 2.0 years.

Results

➢ All four metabolites accumulated in patients with more advanced CKD.

➢ ADMA: r = 0.340

➢ SDMA: r = 0.816

➢ Ac-ADMA: r = 0.594

➢ Ac-SDMA: r = 0.668

➢ During follow up, 144 patients suffered from a cardiovascular event.

➢ In univariate Cox-regression analyses, high plasma levels of all four metabolites were significantly associated with incident cardiovascular events.

➢ However, after adjustment for confounders including eGFR & traditional cardiovascular risk factors, only high plasma SDMA remained significantly associated with incident cardiovascular events.

Results
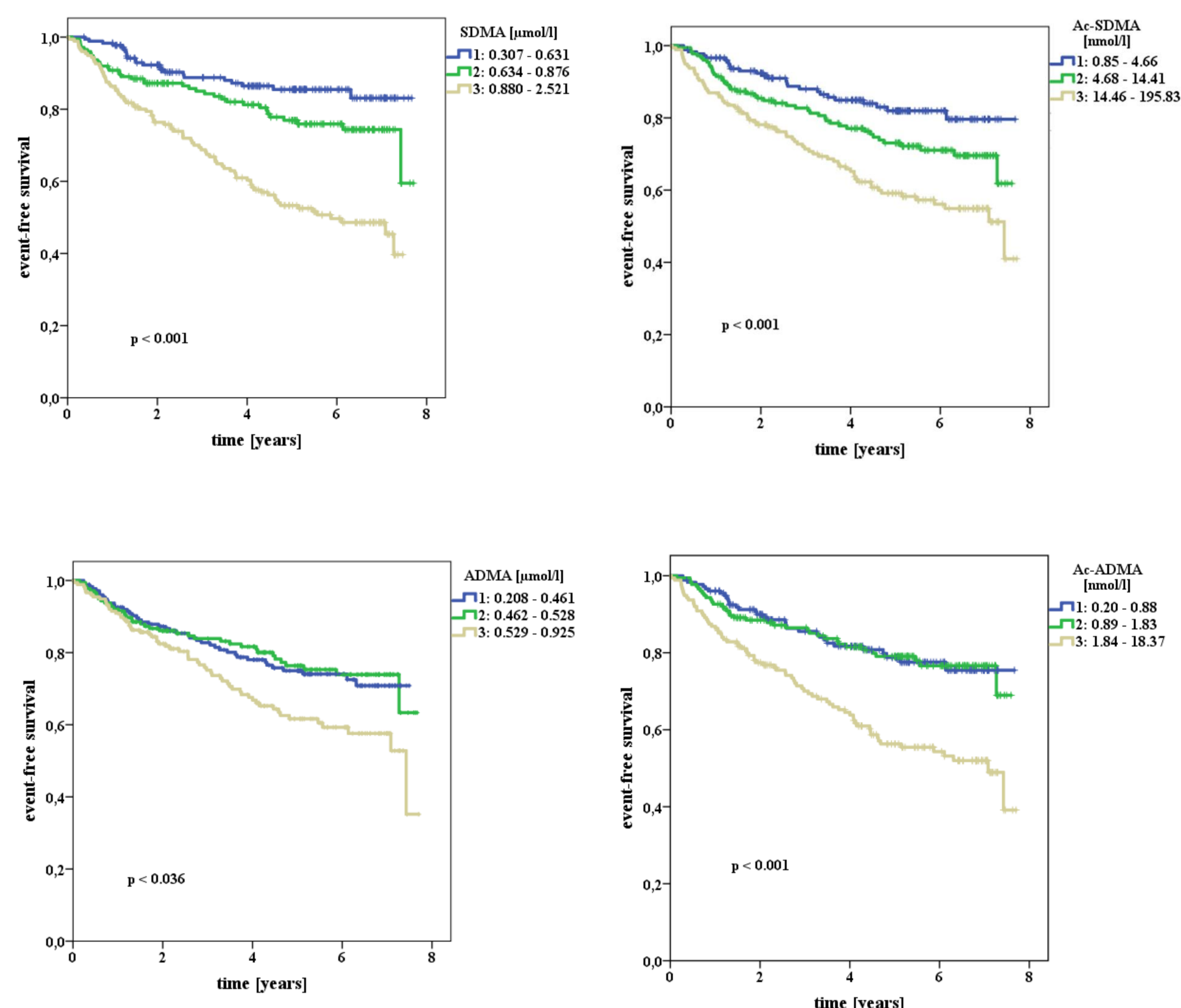
Figure 1: Kaplan Meier analyses for cardiovascular events: high plasma levels of ADMA, SDMA, Ac-ADMA and Ac-SDMA were all associated with lower event free survival.

ADMA	Modell 1 HR (95 % KI)	p	Modell 2 HR (95 % KI)	p	Modell 3 HR (95 % KI)	p	Modell 4 HR (95 % KI)	p
2. Tertile	0.929 (0.602 - 1.433)	0.738	0.857 (0.555 - 1.322)	0.484	0.737 (0.476 - 1.141)	0.171	0.818 (0.526 - 1.272)	0.372
3. Tertile	1.597 (1.082 - 2.357)	**0.019**	1.151 (0.771 - 1.719)	0.490	0.946 (0.630 - 1.420)	0.789	0.904 (0.595 - 1.374)	0.636
SDMA								
2. Tertile	1.687 (1.005 - 2.832)	**0.048**	1.381 (0.792 - 2.408)	0.255	1.151 (0.661 - 2.003)	0.620	1.421 (0.801 - 2.521)	0.229
3. Tertile	3.955 (2.491 - 6.278)	**<0.001**	2.465 (1.268 - 4.793)	**0.008**	1.807 (0.944 - 3.463)	0.074	2.384 (1.246 - 4.560)	**0.009**
Ac-ADMA								
2. Tertile	1.023 (0.638 - 1.642)	0.924	0.736 (0.447 - 1.214)	0.231	0.625 (0.376 - 1.040)	0.070	0.680 (0.411 - 1.125)	0.133
3. Tertile	2.429 (1.612 - 3.660)	**<0.001**	1.270 (0.768 - 2.102)	0.351	1.015 (0.610 - 1.690)	0.954	1.108 (0.662 - 1.853)	0.697
Ac-SDMA								
2. Tertile	1.675 (1.041 - 2.695)	**0.033**	1.295 (0.791 - 2.121)	0.304	1.121 (0.682 - 1.844)	0.652	1.157 (0.702 - 1.908)	0.566
3. Tertile	2.798 (1.795 - 4.360)	**<0.001**	1.325 (0.754 - 2.329)	0.327	1.095 (0.624 - 1.923)	0.751	1.308 (0.745 - 2.296)	0.349

Figure 2: Cox regression analysis for cardiovascular events. Model 1 is the univariate analyses. Model 2 is adjusted for estimated glomerular filtration rate (eGFR). Model 3 is adjusted for eGFR, age and sex. Model 4 is adjusted for eGFR, age, sex, diabetes mellitus, current smoking, total cholesterol, prevalent cardiovascular disease, body mass index (BMI) and systolic blood pressure (BP sys). HR: hazard ratio, 95 % CI = 95 % confidence interval, ADMA = asymmetric dimethylarginine, SDMA = symmetric dimethylarginine, Ac-ADMA = acetylated ADMA, Ac-SDMA = acetylated SDMA. α Reference is the first tertile.

Conclusion

➢ In the future, we need further investigations to analyze the underlying acetylation's mechanism & we have to clarify the role of SDMA in cardiorenal pathophysiology.

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