Asymmetric dimethylarginine is an independent risk factor for coronary heart disease: Results from the multicenter Coronary Artery Risk Determination investigating the Influence of ADMA Concentration (CARDIAC) study

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Background Asymmetric dimethylarginine (ADMA) plasma levels have been shown to be elevated in diseases related to endothelial dysfunction such as hypertension, hyperlipidemia, diabetes mellitus, and others. It has been shown that ADMA predicts cardiovascular mortality in patients who have coronary heart disease (CHD). However, the question whether ADMA is an independent risk factor for CHD still remains unresolved.

Methods The CARDIAC study is a multicenter case-control study, designed to detect differences in ADMA plasma levels between patients with CHD and controls from the general population. We included in our analysis 131 cases and 131 controls, matched for age, sex, and body mass index.

Results We found that cases had higher ADMA plasma levels than controls (0.70 μmol/L [0.59-0.87 μmol/L] vs 0.60 μmol/L [0.54-0.69 μmol/L], $P < .001$). To evaluate the predictive power of ADMA regarding CHD, we calculated 2 multivariate logistic regression models including laboratory parameters and traditional risk factors. The odds ratio for ADMA in the multivariate model including the laboratory characteristics was 2.59 (1.61-4.17; $P < .001$); the odds ratio for the multivariate model including other risk factors was 6.04 (2.56-14.25; $P < .001$) for the third tertile (>0.72 μmol/L) versus the first (<0.58 μmol/L).

Conclusions We conclude from the results of our study that ADMA is an independent risk factor for CHD. (Am Heart J 2006;152:493.e1-493.e8.)

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Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of all 3 isoforms of nitric oxide (NO) synthase.[1] Asymmetric dimethylarginine originates from degradation of methylated proteins in the course of physiologic protein turnover.[2,3] Circulating ADMA is metabolized by the specific enzyme dimethylarginine dimethylaminohydrolase, into L-citrulline and dimethylamine.[4] A minor part of circulating ADMA is excreted via the kidneys. When administered to healthy volunteers, ADMA produces the expected effects corresponding to NO synthase inhibition such as elevation of blood pressure, vasoconstriction, increased renovascular resistance, reduced forearm blood flow, reduced heart rate, and reduced cardiac output.[5-7]

In the last few years, ADMA has emerged as a novel cardiovascular risk factor. It has been shown that ADMA plasma levels are elevated in hypertension,[8] hypercholesterolemia,[9] type 2 diabetes mellitus,[10]

Table I. Patients characteristics of the overall study population, cases, and controls

		All N = 262	Cases n = 131	Controls n = 131	P
ADMA	μmol/L	0.63 (0.56-0.77)	0.70 (0.59-0.87)	0.60 (0.54-0.69)	<.001
Sex (male/female)*	n	204/58	102/29	102/29	1
Age*	years	55.9 ± 9.1	55.9 ± 9.1	55.9 ± 9.1	.995
BMI*	kg/m^2	26.4 ± 3.1	26.4 ± 3.3	26.3 ± 3.0	.815
sys RR	mm Hg	130 (120-140)	135 (120-140)	130 (120-140)	.669
dia RR	mm Hg	80 (80-90)	80 (71-90)	80 (80-90)	.113
Cholesterol	mmol/L	5.76 ± 1.23	5.83 ± 1.33	5.64 ± 1.02	.291
LDL	mmol/L	3.73 ± 1.11	3.74 ± 1.18	3.73 ± 0.99	.976
HDL	mmol/L	1.16 (0.96-1.44)	1.14 (0.94-1.44)	1.17 (1.01-1.44)	.377
Triglycerides	mmol/L	1.70 (1.16-2.31)	1.84 (1.35-2.43)	1.38 (0.92-1.91)	<.001
Creatinine	μmol/L	80.43 ± 18.21	81.38 ± 15.43	79.62 ± 20.31	.492
hs-CRP	mg/L	1.58 (0.69-3.91)	1.87 (0.77-4.29)	1.00 (0.45-3.12)	.008
Smoker	n (%)	70 (26.7)	50 (38.2)	20 (15.3)	<.001
Adiposity	n (%)	30 (11.5)	16 (12.2)	14 (10.7)	.698
Hypercholesterolemia	n (%)	130 (49.6)	99 (75.6)	31 (23.7)	<.001
Hypertension	n (%)	200 (76.3)	126 (96.2)	74 (56.5)	<.001
Diabetes mellitus	n (%)	40 (15.3)	33 (25.2)	7 (5.3)	<.001
No. of risk factors					
0	n (%)	34 (13.0)	1 (0.8)	33 (25.6)	
1	n (%)	76 (29.0)	15 (11.6)	61 (47.3)	
2	n (%)	74 (28.2)	49 (38.0)	25 (19.4)	
3	n (%)	59 (22.5)	51 (39.5)	8 (6.2)	
4	n (%)	13 (5.0)	11 (8.5)	2 (1.6)	
5	n (%)	2 (0.8)	2 (1.6)	0	<.001
Lipid-lowering agents	n (%)	84 (32.1)	75 (57.3)	9 (6.9)	<.001
Aspirin	n (%)	127 (48.5)	113 (86.3)	14 (10.7)	<.001
β-Blockers	n (%)	96 (36.6)	81 (61.8)	15 (11.5)	<.001
ACE inhibitors	n (%)	87 (33.2)	80 (61.1)	7 (5.3)	<.001
Calcium antagonists	n (%)	34 (13.0)	22 (16.8)	12 (9.2)	.066
Nitrates	n (%)	81 (31.0)	77 (58.8)	4 (3.1)	<.001
No. of drugs used	n	1.94 ± 1.80	3.42 ± 1.16	0.45 ± 0.86	<.001

Data are given as mean ± SD, if normal distributed, and median with 25th to 75th percentile if not normal distributed. Statistical significance for differences between groups has been calculated by Student *t* test or Mann-Whitney *U* test, dependent on the distribution of the data. Proportions are given as number of subjects and percentage. Statistical significance of differences in proportions has been calculated by the χ^2 test. *ACE*, Angiotensin-converting enzyme. *sys RR*, Systolic blood pressure; *dia RR*, diastolic blood pressure.
*Matching variables.

hyperhomocysteinemia,[11] and end-stage renal failure.[12] These diseases are linked to an impairment of the NO-pathway and endothelial dysfunction (for review, see reference[13]). Importantly, ADMA was found to be an independent cardiovascular risk factor.[14-16]

Valkonen et al[17] showed that the risk for acute coronary events is 3.9-fold increased in the highest quartile of ADMA plasma levels compared with other quartiles in a prospective case-control study including middle-aged, nonsmoking men. In a prospective trial including 225 hemodialysis patients, patients with an ADMA plasma concentration in the highest quartile had a 3-fold higher risk of death from any cause than patients with ADMA levels below the median.[14] Asymmetric dimethylarginine and age were the strongest predictors of cardiovascular events and total mortality during a mean of 33.4 months of follow-up. Most recently, Schnabel et al[16] published a study including 1874 patients with coronary heart disease (CHD). They could show that those patients with a baseline ADMA plasma concentration in the highest tertile had a 2.48-fold risk for future cardiovascular events in comparison to the patients in the lowest tertile during a mean follow-up of 2.6 years. Furthermore, in a multivariate model, ADMA was the strongest risk predictor besides B-type natriuretic peptide.

Coronary heart disease (CHD) is one of the most important causes of death in the western world. Established cardiovascular risk factors such as hypertension, hypercholesterolemia, diabetes mellitus, and smoking do not account for the total risk in epidemiologic studies. Therefore, there is need for additional factors predicting the risk for cardiovascular events relating to physiologic and pathophysiologic mechanisms. The NO pathway plays a crucial role for an adequate function of the vasculature.[18] Therefore, an impairment of the NO pathway is accompanied by endothelial dysfunction, an important early step in the development of cardiovascular diseases. As outlined above, ADMA has been shown to interact with the NO pathway, and its plasma levels are elevated in numerous diseases related to endothelial dysfunction.