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Original Article

Higher levels of SDMA and not ADMA are associated with poorer survival of trial patients with systemic ANCA-associated vasculitis

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Abstract

Objective: Endothelial dysfunction, increased cardiovascular events (CVE), and accelerated atherosclerosis have been described in patients with small vessel vasculitis and collagen vascular disease. Identifying predictors of cardiovascular risk will help to optimize short- and long-term care of patients with vasculitis. The present study investigates the predictive role of the endogenous nitric oxide synthase (NOS) inhibitor asymmetric dimethylarginine (ADMA) and its stereoisomer symmetric dimethylarginine (SDMA) for cardiovascular risk, all-cause mortality, and renal function in patients with anti-neutrophil-cytoplasmic antibodies-associated small vessel vasculitis (AASV) subjected to standardized treatment regimens in four European Vasculitis Study Group trials representing all stages of renal disease.
Methods: Sera from 89 patients with AASV were available for measuring SDMA, ADMA, and arginine using liquid chromatography/mass spectrometry at the time of active disease and remission. Clinical data on disease activity, remission, relapse rate, and 5-year follow-up data for CVE and renal outcome were collected.
Results: SDMA and ADMA levels were not predictive of CVE at 5 years of follow-up. The overall CVE rate was low in the present cohort of AASV (8%). However, SDMA, and not ADMA, levels were significantly associated with poorer survival (death/ESRD) independent of entry glomerular filtration rate.
Conclusion: This novel outcome in a well-defined group of patients with AASV might indicate a different mechanism of endothelial response in AASV as compared with atherosclerosis. This should be further explored in a larger cohort of AASV patients with a higher CVE rate and/or a longer follow-up. Moreover, these findings should be correlated to other markers of vascular damage.
Keywords: ADMA, SDMA, vasculitis, cardiovascular events, renal outcome, biomarker

Introduction

Endothelial dysfunction, increased cardiovascular events (CVE), and accelerated atherosclerosis have been described in patients with systemic autoimmune diseases such as large and small vessel vasculitis and collagen vascular disease (1, 2). Inflammation during active disease might promote vascular dysfunction and accelerate long-term risk of atherosclerosis. In remission, other risk factors including hypertension, diabetes, chronic kidney disease (CKD), proteinuria, and chronic steroid use could also play an important role (3). Understanding predictors of cardiovascular risk and disease could therefore be of help to identify novel cardiovascular risk factors and optimize short- and long-term care of patients with vasculitis.

Discovered over 40 years ago, asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) were described as end-products of protein catabolism without a functional role. In 1992, Vallance et al. (4) described ADMA as an inhibitor of nitric oxide synthase (NOS). Preclinical studies revealed that the epidemiological associations of ADMA with endothelial dysfunction, vasoconstriction, elevation of blood pressure, and aggravation of atherosclerosis were causative in nature (5). ADMA is an independent marker for mortality in ambulatory patients with peripheral vascular disease and predicts cardiovascular risk and death in the community (6, 7). The stereoisomer of ADMA, SDMA, which does not directly inhibit NOS, was initially thought only to be related to renal function. Subsequent studies revealed that SDMA interferes with l-arginine uptake and that it has a pathogenic role through pro-inflammatory action and reduced endothelial nitric oxide availability (8-10). In some studies, SDMA outperformed ADMA in predicting CVE (Dallas Heart study) (11). Moreover, SDMA has been associated with total non-cardiac mortality in patients with stable coronary heart disease and stroke (12, 13).

On this background, we hypothesized that ADMA and SDMA levels might be predictive of the cardiovascular risk, all-cause mortality, and renal function of patients with anti-neutrophil-cytoplasmic antibodies (ANCA)-associated small vessel vasculitis (AASV) subjected to well-defined treatment regimens in four European Vasculitis Study Group (EUVAS) trials.

Methods

Study population

The study population was derived from four therapeutic trials performed by the EUVAS. Depending on serum availability, 32 patients of the "NORAM" study, 20 patients of the "CYCLOPS" study, 23 patients of the "CYCAZAREM" study, and 14 patients of the "MEPEX" study were included (14-17). Trial characteristics are summarized in Table 1.

These studies were multicenter, randomized, controlled trials. Patients and the investigators who assessed trial outcomes were not blinded to treatment assignment. Inclusion criteria were newly diagnosed granulomatosis with polyangiitis (Wegener's) (GPA), microscopic polyangiitis (MPA), or renal-limited vasculitis (RLV), based on renal involvement attributable to active vasculitis, a biopsy demonstrating necrotizing glomerulonephritis, confirmatory non-renal histology, or ANCA positivity (18). Exclusion criteria were coexistence of other multisystem autoimmune diseases, hepatitis B or C, or HIV infection; previous cancer; pregnancy; or age younger than 18 or older than 80 years. The "NORAM" study did not include patients with more than slight renal involvement at entry, whereas the "MEPEX" study included only patients with serum creatinine levels > 500 µmol/L (5.8 mg/dL) or imminent renal failure requiring dialysis.

Trials were conducted according to the Declaration of Helsinki. Informed consent was obtained from each participant, and each participating center reviewed the trial protocol and granted ethical approval.

Drug regimens

Drug regimens were well-defined and consisted of an induction treatment with cyclophosphamide (CYCAZAREM, CYCLOPS, MEPEX, and control arm of NORAM) with or without plasma-exchange (MEPEX) or low-dose methotrexate (trial arm of NORAM), plus glucocorticoids (Table 1). Maintenance treatment comprised azathioprine, cyclophosphamide, or methotrexate. Prophylaxis against corticosteroid-induced gastritis, fungal infection, and *Pneumocystis jirovecii* pneumonia was recommended but not mandatory.

Evaluations and clinical and laboratory data

Study assessments were performed at the beginning of the study, monthly until remission, 3 months thereafter, and at the time of relapse. Assessment included a complete blood count, C-reactive protein, myeloperoxidase (MPO)-ANCA, proteinase 3 (PR3)-ANCA, and serum creatinine. The glomerular filtration rate, applying the Modification of Diet in Renal Study (MDRD) formula, was measured at the time of entry, at the time of remission, and at the end of the study. Disease activity was measured in terms of the Birmingham Vasculitis Activity Score (BVAS) and the Disease Extension Index (DEI) (19, 20). Cumulative damage from any cause since the onset of disease was scored using the Vasculitis Damage Index (VDI) (21).

A 5-year follow-up of all trial patients was performed, collecting information about events such as development of diabetes, coronary heart disease, stroke, deep vein thrombosis, and need for revascularization (22-25). Coronary heart disease, stroke, and revascularization are summarized as CVE. Start of dialysis (end-stage renal disease, ESRD) and follow-up days alive were also documented.

Plasma concentrations of SDMA and ADMA and arginine were measured applying liquid chromatography/mass spectrometry method described elsewhere (26). Storage at -18°C up to 15 years does not change measurements over time documented by annual controls.

Statistical analysis

Random assignments to treatment arms were computer-generated and performed centrally by permuted blocks of 4, stratified by country and disease. Data were collected in record books, entered into a central computerized database, and validated against the record books before analysis. Patients' characteristics and risk factors were summarized as counts and percentages for categorical variables and as mean±standard deviation or median (25^{th} to 75^{th} percentiles) for continuous variables as appropriate. Patients were classified into low and

Table 1. Trial characteristics

EUVAs Trial Name	Number of pts included in present study	Investigation whether	Drug Regimen	Results
NORAM	32	MTX can replace CYC in early treatment of AASV	randomized, MTX vs oral CYC+Predni	MTX can replace CYC for initial treatment of early AASV, but less effective for pts with extensive disease and pulmonary involvement, also more relapse with MTX
CYCLOPS	20	pulse CYC vs daily oral CYC is better for induction of remission	randomized, pulse IV CYC vs daily oral CYC+Predni	Pulse CYC induced remission as oral with fewer cases of leukopenia and at reduced cumulative dose of CYC
CYCAZAREM	23	exposure to CYC in pts with generalized vasculitis can be reduced by substitution of AZA	randomized, AZA after achievement of remission or continuation of CYC+Predni	In pts with generalized vasculitis withdrawal of CYC and substitution with AZA did not increase rate of relapse
MEPEX	14	addition of PE is more effective than IV methylpred in achievement of renal recovery in pts with serum creatinine >5.8mg/dL	randomized, IV methylpred or PE in addition to oral CYC+Predni	PE increased the rate of renal recovery in AASV. Pt survival and severe adverse event rates were similar in both groups.

MTX: methotrexate; CYC: cyclophosphamide; methylpred: methylprednisolone; predni: prednisolone; PE: plasma exchange; pts: patients

high SDMA groups according to the median value of SDMA in remission. Group differences of risk factors between low and high SDMA groups were tested by chi-square for categorical variables and by t-test or Wilcoxon test for continuous variables. The associations of these factors with vascular events after 5 years were evaluated in logistic regression, measured by odds ratios (ORs) for the likelihood of vascular events after 5 years. Multivariable logistic regression analyses were also performed to adjust for the potential confounding effects of other risk factors including age, sex, and glomerular filtration rate (GFR) at entry. The associations between these factors and GFR after the 5-year visit were assessed in linear regression. Kaplan-Meier survival probabilities were calculated with time to event for death. Survival differences between SDMA groups were evaluated using the log-rank test. A multivariable Cox regression analysis was performed to evaluate the association of SDMA levels with composite endpoint of death and renal failure up to 5 years at time point of active disease and in remission, adjusting for confounding variables such as cardiovascular disease; entry C-reactive protein (CRP), entry DEI, and entry BVAS; age; and sex. A p less than 0.05 was considered to be statistically significant. All data analyses were performed using SAS version 9.4 (Cary; NC, USA).

Table 2. Patients characteristic and basic clinical data

		SDMA <=0.971	SDMA > 0.971	
	All N=89	N=44	N=45	p
Age (years)	57.5±14.7	49.5±14.0	65.4±10.6	<0.001
Male gender, n (%)	50 (56.2)	22 (50)	28 (62.2)	0.245
Cardiovascular Disease, n (%)	8 (10.5)	1 (2.6)	7 (18.4)	0.025
CRP mg/dl	125.9±286.5	187.2±394.8	66.0±66.5	0.046
BVAS	16.6±7.7	15.8±7.7	17.4±7.7	0.320
DEI	5.8±2.3	6.0±2.2	5.6±2.5	0.392
CKD stage, n (%)				<0.001
1 & 2	36 (40.5)	34 (77.3)	2 (4.4)	
3	17 (19.1)	7 (15.9)	10 (22.2)	
4 &5	36 (40.5)	3 (6.8)	33 (73.3)	
Vascular event 5 yr, n (%)	7 (7.9)	2 (4.6)	5 (11.1)	0.250
Relapse, n (%)	45 (50.6)	32 (72.7)	13 (28.9)	<0.001
follow_up_days_alive_RF (days)	1895.1±1158.6	2166.2±975.4	1629.9±1268.7	0.028
censored_alive_ESRF, n (%)	81 (91.0)	43 (97.7)	38 (84.4)	0.029

CRP: c-reactive protein; BVAS: Birmingham vascular activity score; DEI: disease extent index; CKD: chronic kidney disease; RF: renal failure; ESRF: end stage renal failure

Results

Clinical characteristics

Sera from 89 patients who participated in the four EUVAS trials (NORAM, CYCLOPS, CYCAZAREM, and MEPEX) were available for measuring SDMA, ADMA, and arginine levels. The clinical characteristics of these patients are summarized in Table 2. According to average age, sex, organ manifestations, and relapse rate, this cohort reflects the entire spectrum of patients with AASV including patients with various stages of kidney disease (14-17).

By stratifying all 89 participants at the median of SDMA in remission (0.971 µmol/L), higher SDMA levels (>0.971 µmol/L) were found in older patients and those with more advanced CKD, defined by estimated GFR (eGFR) <30 mL/min. Also, those with higher SDMA levels did not live longer (1630 vs. 2166 follow-up days alive). Higher relapse rates were observed in patients (primarily NORAM patients) with SDMA levels <0.971.

Dimethylarginine levels in patients with active vasculitis and remission

Dimethylarginines and arginine levels were compared between patients with active vasculitis (n=89) and those in remission (n=89) (Figure 1). Only the SDMA levels in patients in remission declined significantly after treatment compared with the levels in patients with active vasculitis (p<0.001). This was not true for ADMA and arginine. SDMA levels in remission were also significantly higher in patients who were MPO-ANCA-positive than in those who were PR3-ANCA-positive (mean of SDMA level 1.44 vs. 0.98 µmol/L, p=0.026).

Dimethylarginines and renal function

SDMA and ADMA levels were statistically higher in advanced CKD (eGFR <30 mL/min) for active disease and in remission. This finding was more

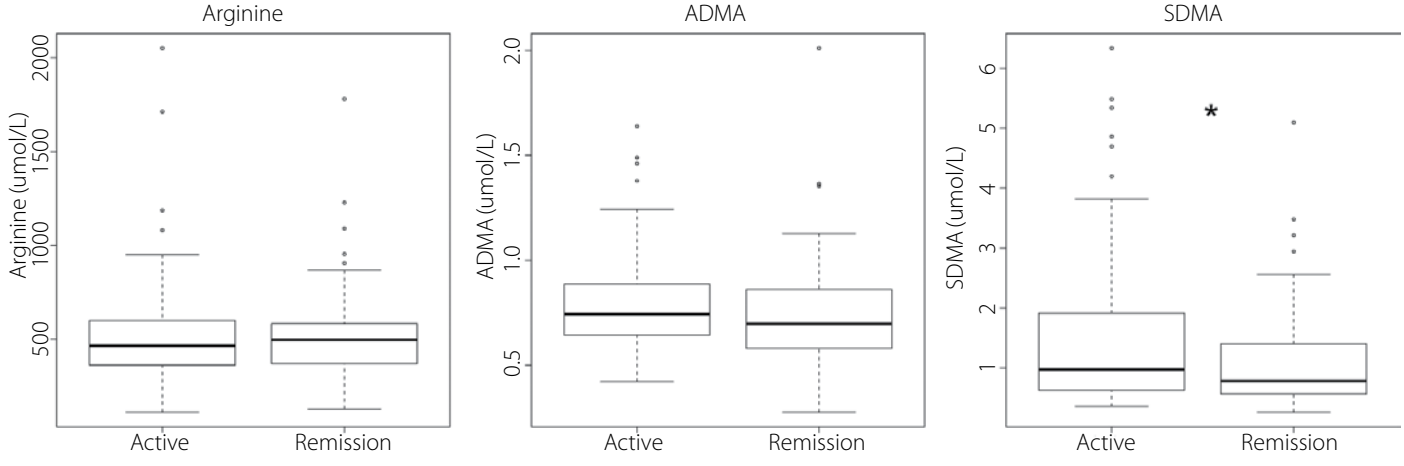

Figure 1. Arginine, ADMA, and SDMA levels were measured in patients at the time of active vasculitis and in remission; only the SDMA levels were significantly higher in patients with active vasculitis (p<0.001)

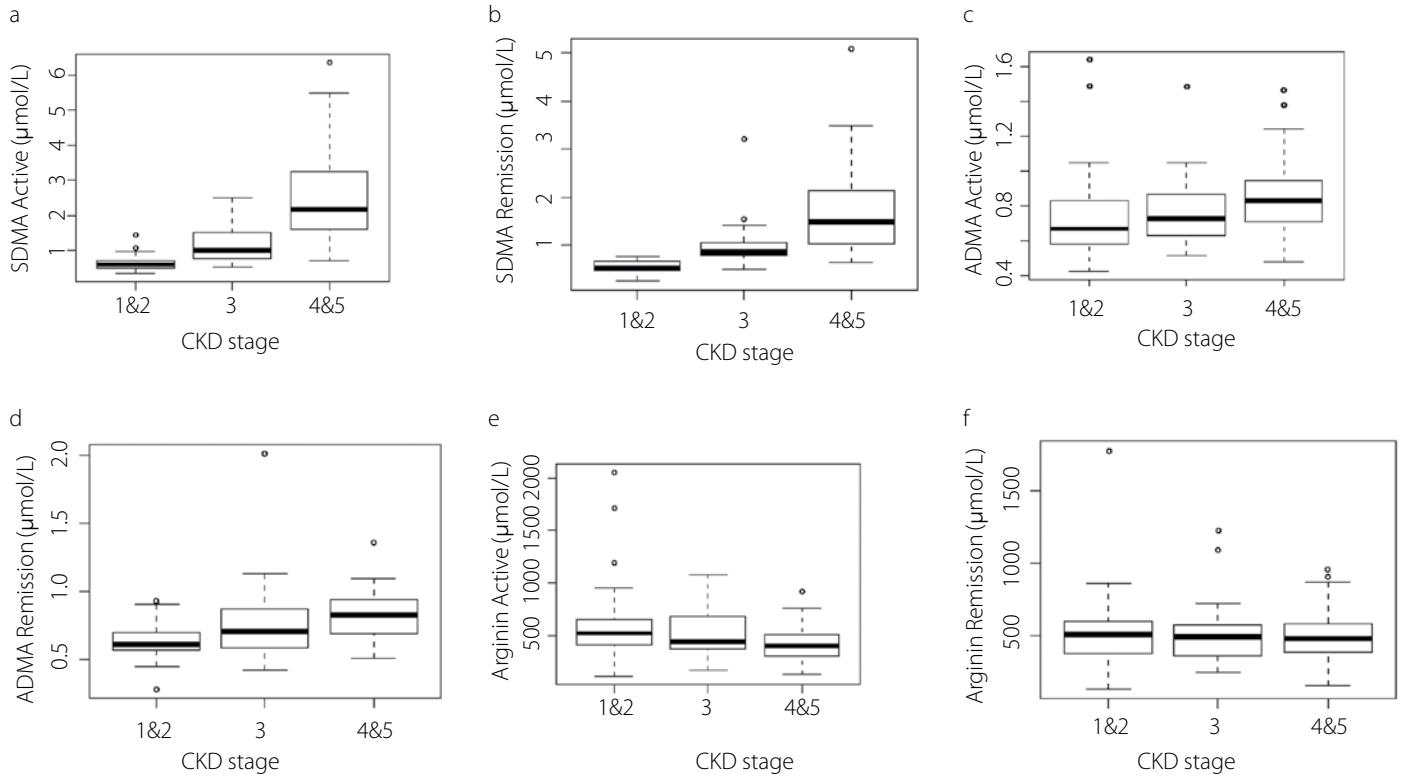

Figure 2. a-f. For SDMA and ADMA, all levels were statistically higher in advanced CKD for active disease and in remission, nevertheless this finding was more pronounced for SDMA levels (SDMA active and in remission p<0.001) (a, b); than for ADMA active (p=0.046, remission p<0.001) (c, d); arginine levels were statistically lower in advanced CKD for patients with active vasculitis but not for those in remission (e,f)

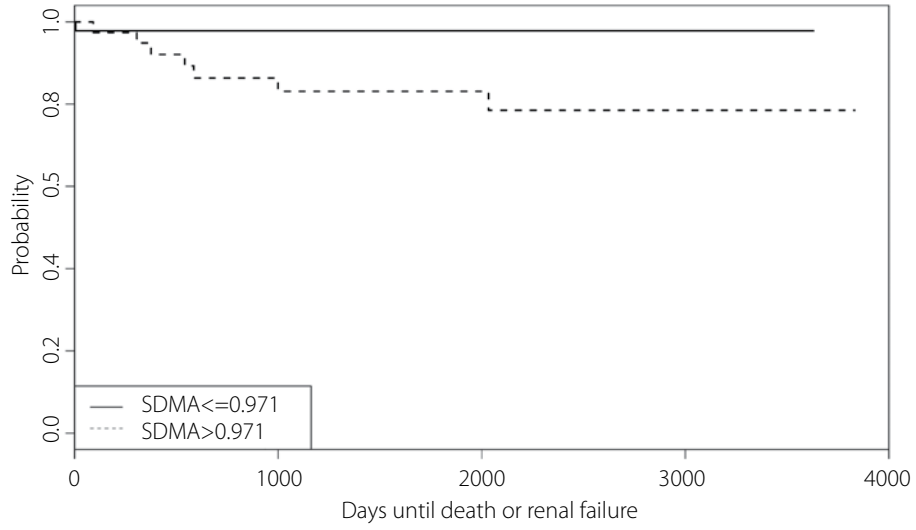

Figure 3. Kaplan-Meier survival probabilities were calculated with time to event for death or renal failure and stratified according to means SDMA level (µmol/L); patients with higher SDMA levels had a lower survival probability that was statistically significant (p=0.04, HR, 0.119, 95% CI, 0.015-0.969)

pronounced for SDMA levels (SDMA active and in remission, both p<0.001 (Figure 2a, b) than for ADMA (active p=0.046 and in remission, p<0.001 (Figure 2c, d). Arginine levels were statistically lower in advanced CKD for patients with active vasculitis but not for those in remission (Figure 2e, f). In a multivariable analysis adjusting for age, sex, cardiovascular disease, and BVAS score none of the three markers, neither at the time of active disease nor at remission, were predictive of eGFR at the 5-year visit.

Dimethylarginines and vascular events

ADMA, SDMA, and arginine were tested as predictors for vascular events after 5 years. Univariate analysis showed only a trend for higher SDMA levels of patients with active vasculitis being predictive for vascular events (p=0.086, OR 1.5, 95% CI, 0.944-2.390). However, this trend was not confirmed by a multivariable analysis adjusting for age, sex, and entry GFR regardless whether samples were derived from patients with active disease or in remission. As ratios of L-arginine/ADMA have been used to indirectly assess the nitric oxide production, we also tested ratios such as arginine/ADMA and ADMA/SDMA as potential predictors for vascular outcome, but this did not yield any new findings. In addition, we performed an analysis stratified for the different immunosuppressive trial regimens. We did not observe any significant differences of dimethylarginine levels in the four different trial cohorts. In a separate analysis, the vascular event rate was numerically higher for MPO-positive patients, but the difference was not statistically significant (p=0.06, OR 5.4, 95% CI, 0.92-31.81).

Dimethylarginines and long-term outcome

In a Cox regression analysis, SDMA levels at time of active disease and SDMA and ADMA levels at time of remission were found to be significantly associated with long-term survival (SDMA active p=0.015, SMDA remission p<0.001, ADMA remission p=0.003). In a subsequent multivariate analysis adjusting for entry eGFR, age, sex, cardiovascular disease, and entry BVAS score, only the SDMA level in patients in remission remained a significant predictor for long-term outcome (p=0.017, HR, 4.3, (95%

CI, 1.30-14.24)). Kaplan-Meier survival probabilities with time to event for death or renal failure as composite outcome and with patients stratified according to the median of SDMA levels at time of remission were performed. Higher SDMA levels were associated with a lower survival probability (p=0.04, HR, 0.119, 95% CI, 0.015-0.969) (Figure 3).

Discussion

The present study investigates the predictive role of the endogenous NOS inhibitor ADMA and its stereoisomer SDMA for cardiovascular risk, all-cause mortality, and renal function in trial patients with AASV treated in a standardized fashion according to their disease stage. We identified elevated SDMA levels at the time of remission and not ADMA as a predictor of poorer overall survival and renal outcome. In addition, SDMA levels did discriminate between active state and remission of vasculitis. But both markers failed to predict cardiovascular outcome in these patients with systemic AASV.

Compared with a healthy general populations and other cohorts with cardiovascular and renal disease, mean SDMA and ADMA levels during active disease as well as in remission were elevated in our cohort (27-29). This finding is in line with clinical studies showing higher levels of SDMA in patients with chronic inflammatory processes (9). After treatment, SDMA levels decreased in our cohort, suggesting that less inflammation could be related to lower SDMA levels. This was not true for ADMA as its levels remained elevated. Interestingly, other investigators have found that in patients with acute inflammation, ADMA was lower in the state of acute inflammation and increased after the inflammation resolved (30, 31). This indicates that, in contrast to our teleological reasoning, ADMA might act as a brake on overwhelming iNOS activity. A decrease in ADMA levels in the state of acute inflammation may actually serve to stimulate NO synthesis to fight the underlying cause. The fact that we did not observe a decrease of ADMA levels might reflect a specific endothelial response in vasculitis.

In our cohort, ADMA, SDMA, arginine, or their ratios did not independently predict CVE after 5 years, regardless whether samples were from patients with active disease or in remission. However, the overall CVE rate at 5 years was low in the present cohort (8%) but similar to others. Terrier et al. (31) found a 9.5% CVE rate after 5 years in 42 patients with AASV (26% after 10 y). In a retrospective matched-pair cohort study of 113 patients with AASV, more CVE occurred in the AASV group (23 of 113) than in the CKD group (16 of 113) (2).

Several pathways can interfere with the main ADMA degrading enzyme, i.e., DDAAH (32). This might help explain why ADMA levels were not predictive of CVE in the present study. If baseline ADMA levels are already elevated, additional stimuli, such as active vasculitis, might not be powerful enough to change ADMA levels substantially.

ADMA and SDMA were also studied as markers of cardiovascular risk in two other autoimmune diseases, systemic lupus erythematosus and Behçet disease, but only retrospectively (33, 34). Increased levels of ADMA were found in 107 patients with SLE with a history of previous CVE and correlated significantly with measures of disease activity (35). Unfortunately, SDMA levels were not measured in these studies, and the prospective role of these novel markers were not tested.

The composite endpoint of death or renal failure up to 5 years was analyzed in our cohort. Elevated SDMA levels at time of remission indicated a significant lower overall survival probability. Importantly, this result remained significant after adjusting for entry serum creatinine, indicating that SDMA might have a role independent of renal function, as seen in other studies. For example, SDMA has been found to independently predict total and not cardiac mortality in a large (n=3523) multi-ethnic cohort representative of the general population, in patients after renal transplantation, and after stroke (11, 13, 35). It is discussed that SDMA might be a more sensitive and early indicator of renal function or even a mediator for other processes such as atherosclerosis (10). This idea of being a marker above and beyond renal function is supported by a study by Bode-Boeger in which SDMA correlated with glomerular filtration rate but was also able to describe extent of coronary artery disease independently (8). Whether an association of SDMA with poor outcome, as in the present study, or CVD as in other studies, is due to its direct pro-inflammatory action and reduced endothelial nitric oxide availability and/or to its relationship to renal function is not known (8, 9).

The present study may have limitations, as the rather large vasculitis patient cohort is composed of smaller subgroups representing the different renal disease stages studied in the EUVAS therapeutic trials and as the numbers of patients in each subgroup were determined by the availability of serum samples and do not reflect the proportion of AASV patients with different disease stages seen in the clinic. However, the cohort represents the entire spectrum of patients with AASV including those with and without renal manifestation and relapse. The evaluation of the impact on the CVE rate was limited by the fact that other cardiac risk factors such as hyperlipidemia and its treatment were not recorded and therefore could not be accounted for such as done with the Framingham disease risk score. Negative results might be due to lower power or small sample size but it could also be a true finding. Further evaluation with a larger study would be needed to validate our findings. Because of the relatively large amount of NORAM patients with no or slight renal involvement, but a very high relapse rate, low SDMA values are significantly correlated to relapse.

In summary, SDMA and ADMA levels were not predictive of CVE at a 5-year follow-up. However, the overall CVE rate was low in the present cohort of AASV. Interestingly, SDMA levels and not ADMA levels were significantly associated with poorer survival (death/ESRD) independent of entry glomerular filtration rate. This novel finding in a well-defined group of AASV patients indicates a different mechanism of endothelial response in AASV. This should be further explored in a larger cohort of AASV patients with a higher CVE rate and/or a longer follow-up. Moreover, these findings should be correlated to other markers of vascular damage.

Ethics Committee Approval: Trials were conducted according to the Declaration of Helsinki. Informed consent was obtained from each participant and each participating center reviewed the trial protocol and granted ethical approval.

Informed Consent: Each patient received an informed consent.

Peer-review: Externally peer-reviewed.

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