Asymmetric Dimethylarginine Enhances Cardiovascular Risk Prediction in Patients With Chronic Heart Failure

Christina Dückelmann, Friedrich Mittermayer, Dominik Georg Haider, Johann Altenberger, Jörg Eichinger, Michael Wolzt

Objective—The purpose of this study was to investigate whether elevated asymmetrical dimethylarginine (ADMA) concentrations are associated with increased cardiovascular risk in chronic heart failure (HF) patients.

Methods and Results—253 patients with symptomatic chronic HF and impaired left ventricular function (median age 70 years, 202 males) were followed for a median of 14.2 months (interquartile range 6.8 to 21.2). ADMA and N-terminal pro-brain natriuretic peptide (NT-proBNP) were assessed by high performance liquid chromatography and by an enzyme-linked immunosorbent assay, respectively. Subjects with ADMA concentrations in the highest tertile had a significantly higher adjusted hazard ratio (HR; 2.00; 95% confidence interval [CI] 1.01 to 3.97) for occurrence of an end point (cardiac decompensation, major adverse cardiovascular events or all-cause mortality) compared with patients in the lowest tertile (P = 0.046) during the first 6 months of follow-up. NT-proBNP also identified subjects at risk before adjustment for confounders at 6 and 12 months of follow-up. HR for patients with ADMA and NT-proBNP in the highest tertile was significantly increased (3.68, CI 1.67 to 8.14; at 6 months follow-up) compared with patients without ADMA and NT-proBNP in the highest tertile (P < 0.001).

Conclusions—Elevated ADMA plasma concentrations are associated with adverse cardiovascular outcome in patients with chronic HF. Quantification of ADMA with NT-proBNP improves risk stratification in this cohort. (Arterioscler Thromb Vasc Biol. 2007;27:2037-2042.)

Key Words: asymmetrical dimethylarginine • heart failure • natriuretic peptides • risk factor

Symptomatic heart failure (HF) has an estimated prevalence of 0.4% to 2% in the European population and increases with age.1,2 The prognosis of HF patients is poor despite improved diagnostic and therapeutic measures.1–4 Plasma concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) have been established as risk marker in clinical practice, and its diagnostic and predictive value has been confirmed in patients with HF.5,6 However, the prognostic accuracy of NT-proBNP is limited and the continuous search for novel markers as indicators of clinical outcome is needed. Among candidates that may improve identification of subjects at elevated cardiovascular risk are plasma concentrations of asymmetrical dimethylarginine (ADMA), which is formed by methylation of protein arginine residues. ADMA is an endogenous inhibitor of nitric oxide (NO) synthesis and elicits cardiovascular effects when administered to humans.7–9 Previous studies have demonstrated that ADMA may predict cardiovascular events in patients with coronary artery disease or peripheral artery disease.10–12 In patients with idiopathic pulmonary hypertension, mild to advanced chronic kidney disease or end-stage renal failure increased ADMA levels are associated with detrimental outcome.13–15 Although elevated ADMA plasma concentrations have been described in patients with HF,16–19 little is known about the prognostic significance of this finding.

We hypothesized that plasma ADMA concentrations may be associated with cardiovascular outcome in patients with HF and have studied the predictive value of this endogenous NO synthase inhibitor in a prospective cohort study.

Materials and Methods

Study Design

Between December 2004 and June 2006 all consecutive patients with diagnosis of chronic HF and reduced left ventricular function, who were admitted at the ward or referred to the outpatient HF clinic at the tertiary care hospital of the Salzburger Landeskliniken/Paracelsus Medical University, were invited to participate in a prospective cohort study. Inclusion criteria were written informed consent, left ventricular ejection fraction (EF) of ≤ 40%, age ≥ 18 years, and a scheduled visit for follow-up at the HF clinic. Exclusion criteria were acute cardiac decompensation within the previous 7 days, need for coronary revascularization, or acute coronary syndrome. The study protocol was approved by the independent Ethics Committee of the Medical University of Vienna (EC# 541/2004).

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2037
Patients
Two hundred and seventy-six White subjects with stable chronic HF and impaired left ventricular function (LVEF) as assessed from echocardiography or angiography were eligible for the study. At study entry, medical and surgical history, physical condition, and medication were recorded. Details of HF diagnosis and history of cardiac decompensation were evaluated by review of hospital records. HF was considered of ischemic origin when a history of myocardial infarction or wall motion abnormalities with corresponding angiographic findings was reported. Patients were prospectively followed-up until February 2007 through outpatient visits or telephone contact for the occurrence of a study end point.

Laboratory Monitoring
For determination of ADMA, its stereoisomer symmetric dimethylarginine (SDMA), L-arginine, and NT-proBNP, venous blood was taken at study entry. Plasma was separated after centrifugation and stored at −30°C until batch analysis. All samples were pseudo-anonymised before analysis to avoid bias. Quantification of arginines was performed by high-performance liquid chromatography (HPLC) as described previously.20,21 The coefficients of variation for inter- and intraassay variations are <3% for all analytes. The detection limit for (methyl-)arginines is 0.04 μmol/L. NT-proBNP concentrations were measured using a commercially available enzyme-linked immunosorbent assay from Biomedica Medizinprodukte (Vienna, Austria). The assay detection limit was 5 fmol/mL at 95% B/B0. The inter- and intraassay coefficients of variation were <4.5% and <6.5%, respectively. Glomerular filtration rate (GFR) was estimated from serum creatinine according to the Modification of Diet in Renal Disease Study equation.22

Study End Points
The composite clinical end point was defined as the occurrence of cardiac decompensation, major adverse cardiovascular events (MACE), or all-cause mortality. Decompensation was defined as progressive resting dyspnoea associated with clinical signs of pulmonary or peripheral congestion requiring hospitalization and treatment with an intravenous diuretic.23 MACE was defined as cardiac arrest, pulmonary embolism, acute coronary syndrome, or acute cerebrovascular event. Classification of end points was adjudicated from hospital records and reports.

Statistical Analysis
Continuous data are presented as medians (interquartile range). Categorical data are given as counts or percentages. For univariate comparison of continuous data Mann–Whitney U test was applied. Spearman rank correlation was used for assessment of associations between continuous variables. Categorical variables were compared using the χ²-test. Multivariate Cox regression analysis was applied to assess the independent effect of baseline ADMA and NT-proBNP on the composite end point and to adjust for potential confounders. Tertiles of continuous variables were included as confounders if these variables were associated with ADMA or NT-proBNP according to Spearman rank correlation coefficients. Categorical variables were entered into the model if they influenced ADMA or NT-proBNP according to univariate analysis. In addition, adjustment for age, sex, and LVEF, and LVEF were performed in all analyses. For the combination of ADMA and NT-proBNP subjects were grouped into 3 categories for the Cox regression analysis: 3, ADMA and NT-proBNP in the highest tertile; 2, ADMA or NT-proBNP in the highest tertile; 1, ADMA and NT-proBNP outside the highest tertile. Results of the Cox regression analysis are presented as hazard ratio (HR) with 95% confidence intervals (CI) and survival curves according to tertiles of ADMA. A 2-sided probability value <0.05 was considered as statistically significant. Calculations were performed with SPSS for Windows (Version 14.0, SPSS Inc).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results
Two hundred and fifty-three subjects were included in the study (92% of eligible patients during the observation period). Subject characteristics are summarized in Table 1. Concomitant medication is given in supplemental Table I (available online at http://atvb.ahajournals.org). There was no difference in the use of medication between patients grouped by ADMA tertiles. One hundred and eighty-six patients (74%) had a medical history of decompensation. The median age was 70 years (interquartile range [IQR], 61 to 77), 202 patients (80%) were male, and median duration of follow-up was 14.2 months (IQR, 6.8 to 21.2).

Follow-up was available from all subjects. During the first 6 months of follow-up, 55 clinical end points occurred including 36 cases of decompensation (66%), 3 major cardiovascular events (5%), and 16 deaths (29%). Within 12 months of follow-up, there were 76 clinical end points, including 44 cases of decompensation (58%), 8 major cardiovascular events (10%), and 24 deaths (32%). During total follow-up, 101 patients had a clinical end point, including 58 cases of decompensation (57%), 9 major cardiovascular events (9%), and 34 deaths (34%).

Cumulative event-free survival rates at 2, 4, and 6 months were 95%, 94%, and 83%, respectively, in patients with ADMA concentrations in the lowest tertile (≤0.51 μmol/L; Figure 1). In patients with ADMA in the highest tertile (>0.64 μmol/L) cumulative event-free survival rates were 91%, 81%, and 70% after 2, 4, and 6 months, respectively. Patients with ADMA concentrations in the highest tertile (>0.64 μmol/L) had a significantly higher HR for occurrence of a composite end point during a 6-month follow-up compared with patients in the lowest tertile (≤0.51 μmol/L) before (P<0.05) and after (P<0.05) adjustment for GFR, age, sex, LVEF, systolic blood pressure (SBP), and BMI (Table 2). However, this risk association was lost at later time.

### Table 1. Subject Characteristics

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<th>Glomerular filtration rate (ml/min)</th>
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<td>Body mass index (kg/m²)</td>
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<td>L-arginine (μmol/L)</td>
<td>113 (69–194)</td>
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<tr>
<td>ADMA† (μmol/L)</td>
<td>0.57 (0.48–0.68)</td>
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<tr>
<td>SDMA‡ (μmol/L)</td>
<td>0.68 (0.50–0.93)</td>
</tr>
<tr>
<td>NT-proBNP§ (pg/mL)</td>
<td>1910 (1232–3156)</td>
</tr>
</tbody>
</table>

Data are presented in absolute numbers or as median (interquartile ranges) as appropriate. NYHA indicates New York Heart Association.
†Asymmetric Dimethylarginine; ‡Symmetric dimethylarginine; §N-terminal pro-brain natriuretic peptide.
ADMA and Risk in Heart Failure

points, and there was no correlation between ADMA concentrations and outcome at a follow-up of 12 months or beyond.

Patients with NT-proBNP in the highest tertile (>2512 pg/mL) had a significantly higher HR for occurrence of a composite end point after 6 months, 12 months, and at total follow-up than patients with NT-proBNP in the lowest tertile (≤1534 pg/mL) (Figure 2). However, in multivariate analysis, this association between NT-proBNP and outcome after 6 months and 12 months was lost when data sets were adjusted for GFR (Table 2). Patients with NT-proBNP in the lowest tertile (≤1534 pg/mL) had cumulative event-free survivals of 95%, 92%, and 84% after 2, 4, and 6 months, respectively. Event-free survival of patients with NT-proBNP in the highest tertile (>2512 pg/mL) were 87%, 75%, and 63% after 2, 4, and 6 months, respectively.

The statistical combination of ADMA with NT-proBNP concentrations improved risk estimation. Event-free survival of patients with ADMA and NT-proBNP in the lowest tertile was 92%, 84%, and 73% after 5, 10, and 15 months, respectively (Figure 3). In contrast, event-free survival of subjects with ADMA and NT-proBNP in the highest tertile was 58%, 48% and 36% after 5, 10 and 15 months, respectively.

Patients with ADMA and NT-proBNP concentrations in the highest tertile (n=32) had a 4.5-fold higher risk (HR, 95% confidence interval, CI 2.1 to 9.7; P<0.001) for a clinical end point compared with subjects without ADMA (>0.64 μmol/L or NT-proBNP >2512 pg/mL after 6 months follow-up (Figure 3). After multiple adjustment HR for the composite end point in patients with ADMA and NT-proBNP in the highest tertile was 3.68 (CI 1.67 to 8.14) after 6 months compared with those patients without ADMA and NT-proBNP concentrations in the third tertile (P<0.001). At 12 months follow-up, HR for concentrations of ADMA and NT-proBNP in the highest tertile was 3.70 (CI 1.0 to 6.9, P<0.001), and 3.48 (CI 2.03 to 5.98) after total follow-up compared with patients without ADMA and NT-proBNP levels in the highest tertile, respectively.

Characteristics of patients grouped by clinical end point are presented in supplemental Table II. The prevalence of atrial fibrillation or history of myocardial infarction was more frequent in subjects who experienced an end point during the observation period.

There was no correlation between ADMA concentrations and death, decompensation, or MACE alone. ADMA concentrations were associated with L-arginine (P<0.001, r=0.225) and symmetric dimethylarginine (SDMA) (P<0.001, r=0.386). SDMA was associated with age (P=0.002, r=0.197), LVEF (P=0.007, r=−0.170), L-arginine (P=0.006, r=0.174), and GFR (P<0.001, r=−0.311). There was also no relationship between ADMA or NT-proBNP and atrial fibrillation, diabetes mellitus, smoking, hypertension, presence of angina, or history of myocardial infarction or cerebral ischemia and no association with outcome in groups of patients with different HF etiology. Age, GFR, SBP, and BMI were associated with occurrence of a clinical end point after multivariate adjustment.

Discussion

This study demonstrates that elevated plasma ADMA concentrations in patients with chronic HF are associated with occurrence of cardiac decompensation, MACE, or all-cause mortality in a prospective cohort study during a 6-month follow-up, with a 4.5-fold risk elevation when both ADMA and NT-proBNP plasma concentrations were increased. This predictive value remained fully intact after inclusion of other clinical parameters into a hazard model. The short-term association between ADMA and clinical end point was lost during prolonged observation.

The occurrence of end points was similar to that reported in other prospective cohort studies in HF patients. The population of patients with chronic HF is not homogeneous regarding prognosis, even within the same category of functional impairment. The clinical importance of predictive markers for risk stratification is indicated by the fact that most end points occurred in the subgroup of subjects with ADMA and NT-proBNP values in the highest tertile. Importantly, 48% of these patients remained event-free during 10 months, in contrast to 84% of subjects with ADMA and NT-proBNP in the lowest tertile during an equivalent observation period. In the present study, clinically relevant cardiovascular end points were comparatively infrequent in patients with impaired LVEF but low ADMA and NT-proBNP plasma concentrations. This supports the concept that ADMA might be useful as an additive marker to assess risk in this population. Interestingly, the relationship between ADMA and clinical end points was best during the first 6 months of the observation period, when most events occurred. This finding might be attributable to statistical reasons because the number of patients at risk decreased over time. Nevertheless, enhanced risk may be estimated by combination of ADMA with NT-proBNP also during prolonged follow-up.

It is unclear whether elevated ADMA in patients with HF may also directly impair vascular or cardiac function and thereby contribute to increased risk. Intravenous infusion of ADMA affects cardiovascular hemodynamics in healthy subjects, increases sodium reabsorption, and decreases vascu-
Elevated plasma concentration of ADMA is associated with concentric left ventricular hypertrophy and left ventricular dysfunction in hemodialysis patients. Augmented ADMA decomposition in transgenic mice is paralleled by reduced systolic blood pressure, systemic vascular resistance, and cardiac stroke volume. Metabolism of ADMA is mainly regulated by dimethylarginine dimethylaminohydrolases (DDAH) and to a smaller amount by urinary excretion in healthy humans. This is consistent with data that ADMA accumulation and reduced NO signaling is associated with DDAH activity in animal studies.

On the other hand, the number of MACE in this study was rather small and one would have expected that ADMA—through its effect on endothelial function—would promote MACE precipitation. It is not established whether biologically active intracellular ADMA concentrations are represented by assessment of circulating levels. In studies in healthy volunteers, plasma concentrations of ADMA which induced acute cardiovascular effects were considerably higher than in this cohort. However, ADMA concentrations seen in this study are in the range of those in patients at risk for acute coronary events. In our subjects with HF, ADMA was not related to renal function, which is an important determinant of circulating ADMA concentrations in renal failure. This indicates that reduced degradation by DDAH or increased ADMA production by protein arginine methyltransferases play an important role for ADMA regulation. It can be speculated whether modulation of DDAH activity or expression may represent a target for therapeutic interventions in cardiovascular disorders. No specific treatment to modulate ADMA concentrations is presently available. The fact that SDMA was not associated with the composite clinical end-point is consistent with the findings that SDMA does not inhibit NO synthase.

This study also confirms the valuable role of plasma NT-proBNP measurement in patients with heart failure, as previously demonstrated in clinically stable or acutely decompensated subjects. The additional information provided by ADMA was clearly demonstrable, and no correlation was detectable between ADMA and NT-proBNP in the subjects under study. Of note, the association between NT-proBNP and outcome was substantially reduced when differ-

### Table 2

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Multivariate analysis: adjustment for age, sex, glomerular filtration rate, left ventricular ejection fraction, systolic blood pressure, and body mass index.

Combination: Group 1, ADMA and NT-proBNP outside the highest tertile; Group 2, ADMA or NT-proBNP in the highest tertile; Group 3, ADMA and NT-proBNP in the highest tertile.
tertile 2: ADMA or NT-proBNP in the highest tertile, and tertile 3: ADMA and NT-proBNP in the highest tertile, respectively.

differences in renal function were accounted for in multivariate analyses. Although our result therefore indicates that ADMA and NT-proBNP represent independent risk markers in HF patients, their additive predictive value might be explained by their different origin of generation, as NT-proBNP is predominantly formed in the cardiac ventricles.

ADMA plasma levels in this study were in the range observed in healthy subjects, in patients with gestational diabetes or peripheral artery disease using HPLC analysis. The method of ADMA quantification is however not standardized, and methodologic differences complicate comparisons between different laboratories. In particular, results obtained using a novel enzymatic immunoassay may differ from HPLC results.

**Limitations**

Circulating ADMA concentrations were obtained from clinically stable patients only and did not take into account differences regarding history of decompensation or other potentially confounding factors. On the other hand, this unselected and heterogeneous cohort may enable better extrapolation of the current findings to other patients. The proportion of subjects with ischemic cardiomyopathy was also lower than expected from epidemiological studies. Biomarkers such as natriuretic peptides have been shown to indicate early a response to treatment. This clinical effect on ADMA is yet unknown. Several drugs which are commonly prescribed in HF may also reduce plasma ADMA concentrations, such as agents acting on the angiotensin system or insulin sensitizers.

In conclusion, this study shows that elevated ADMA plasma concentrations enhance cardiovascular risk prediction in patients with chronic HF. In particular, patients had a greater than 4-fold risk elevation for the occurrence of a clinical end point when both ADMA and NT-proBNP plasma concentrations were increased.

**Acknowledgments**

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**Disclosures**

None.

**References**


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