Asymmetric dimethylarginine predicts appropriate implantable cardioverter–defibrillator intervention in patients with left ventricular dysfunction


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Aims
More precise characterization of risk factors for occurring ventricular arrhythmia in patients (pts) with primary prevention implantable cardioverter–defibrillator (ICD) therapy is critical. We sought to investigate whether biomarkers of nitric oxide metabolism can predict the occurrence of ventricular tachyarrhythmias and might be used as risk markers in these pts.

Methods and results
Plasma levels of L-arginine (Arg), asymmetric dimethylarginine (ADMA), symmetrical dimethylarginine (SDMA), monomethyl L-arginine, and nitrite/nitrate were examined in 106 consecutive pts (mean age 65 years, 97 male, mean LV-EF 24 ± 6%), with ischaemic (n = 82) or non-ischaemic cardiomyopathy (n = 24) who underwent ICD implantation for primary prevention of SCD. Appropriate ICD intervention was assessed during a mean follow-up of 344 days, and occurred in 18 of 106 (17%) pts. Asymmetric dimethylarginine plasma levels were significantly higher in pts with appropriate ICD intervention compared with those without any ICD intervention (0.564 ± 0.083 μmol/L vs. 0.513 ± 0.088 μmol/L; P = 0.027). The Arg/ADMA ratio was found lower in pts with appropriate ICD intervention than in those without ICD intervention (144.71 ± 32.50 vs. 175.29 ± 41.29; P = 0.002). Univariate Cox regression showed that ADMA (P = 0.028) and the Arg/ADMA ratio (P = 0.003) were associated with a higher incidence of appropriate ICD intervention. In a multivariable Cox regression analysis, an ADMA concentration above the 50th centile was independently associated with appropriate ICD intervention, revealing a hazard ratio (HR) of 4.21 (CI 95%: 1.14–15.63; P = 0.028, Table 4). An Arg/ADMA ratio below the 25th centile had a HR of 3.83 (1.360–10.87; P = 0.011).

Conclusion
Asymmetric dimethylarginine and the Arg/ADMA ratio seem to be new biomarkers for the prediction of ventricular tachycardia/ventricular fibrillation episodes and of appropriate ICD intervention in pts with left ventricular ejection fraction dysfunction (LV-EF ≤ 35%), suggesting a value for risk stratification in these pts.

Keywords
ADMA • Arg/ADMA ratio • ICD intervention • Risk marker for SCD
Introduction

Patients (pts) with structural heart disease and reduced left ventricular function have an increased risk of sudden arrhythmic death (SCD). Implantation cardioverter–defibrillator (ICD) is the most effective approach to prevent SCD in pts with a left ventricular ejection fraction (LV-EF ≤ 35%).1– 4 Risk stratification is most important to avoid an unnecessary and expensive ICD implantation. Invasive and non-invasive parameters and methods, such as programmed ventricular stimulation,5 and electrocardiogram parameters using T-wave alternans,6 QRS-duration,7 and others have been tested but failed to significantly increase the positive predictive accuracy of these risk markers. Although reduced LV-EF (≤ 35%) remained the most important risk factor for SCD prediction until today, there is hence need for a more reliable risk analysis in pts with structural heart disease.

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase (NOS).8–10 Methylated arginines, such as ADMA, are risk factors for the development of endothelial dysfunction and atherosclerosis. Several cardiovascular diseases were found to be associated with elevated plasma levels of ADMA, i.e. diabetes,11 coronary artery disease (CAD),9,12 and congestive heart failure — as well as diabetic dyslipidemia.13–17 There is increasing evidence that ADMA may predict cardiovascular mortality. Pertinent studies showed that ADMA predicts mortality in pts with severe organ dysfunction on intensive care units,18 in pts with end-stage renal disease,19 as well as in pts with coronary syndromes.20,21 Recently, evidence suggested that increased levels of ADMA can predict all-cause mortality in a large community-based study group.22

Increased ADMA leads to endothelial dysfunction which will also play an important role in the development and progression of heart failure.23–25 Thus, elevated levels of ADMA seem to be a precursor of endothelial dysfunction which will deteriorate ventricular function and can promote the occurrence of life-threatening ventricular arrhythmias. The aim of the present study was to investigate whether ADMA and parameters of NO metabolism are able to predict a higher likelihood of ventricular tachyarrhythmic events in pts with LV-EF ≤ 35% who underwent ICD implantation.

Materials and methods

Study design

Between May 2008 and February 2009, 123 pts who received an ICD/cardioc synchronization therapy-defibrillator (CRT-D) device for primary prevention of sudden cardiac death (SCD) were consecutively included in the study. Implantation cardioverter–defibrillator implantation was applied according to actual ACC/AHA/ESC-guidelines for prevention of SCD,26 in pts with ischaemic cardiomyopathy (ICM) or non-ischaemic cardiomyopathy (NICM) with LV-EF ≤ 35%. Exclusion criteria were ICD implantation due to secondary prevention of SCD, renal failure with an estimated glomerular filtration rate (eGFR) < 30 mL/min and chronic liver disease. The study protocol complies with the Declaration of Helsinki, and was approved in May 2008 by the Ethic Committee of the University Hospital Magdeburg, Germany.

Patients

One hundred and twenty-three consecutive pts were included into the study after giving written informed consent. At study entry medical history, physical status, laboratory tests and baseline medication were recorded. Venous blood samples of all biomarkers were taken at that time, or one day before ICD implantation. Left ventricular ejection fraction was assessed by cardiac catheterization.

Ten pts were excluded because of declined follow-up within 180 days, four pts were excluded because of eGFR ≤ 30 mL/min, and three pts died early during the initial phase of follow-up. Hence, 106 pts, mean age 65.5 years (range 38–83 years), 97 males, 9 females were followed for a mean time of 344 ± 86 days. Follow-up visits were scheduled for every four months.

Follow-up/electrogram-analysis

At follow-up visits, during each non-scheduled hospitalization, or at the end of follow-up stored electrograms of the ICD were evaluated and potential arrhythmic episodes and ICD interventions were assessed in our device clinic by the attending staff. Implantation cardioverter–defibrillator intervention was defined as either correct antitachycardia pacing (ATP), or correct delivery of ICD shocks. Both intervention modes were interpreted as appropriate ICD intervention and defined as the end point of the study. Implantation cardioverter–defibrillator intervention, either ATP or shock delivery which followed atrial fibrillation, supraventricular ventricular tachycardia (SVT) or incorrect sensing was designated as inappropriate ICD intervention. Furthermore, a clinical evaluation with record of medication use and, if necessary, exclusion of factors triggering ventricular arrhythmias, such as electrolyte disturbances, was conducted on each follow-up visit.

Asservation of blood samples for biomarkers

Seven millilitre blood was drawn from a cubital vein using an 18-gauge needle (BD Diagnostic Systems, Franklin Lakes, New Jersey, USA) and a K3E-vacutainer® tube (BD Diagnostic Systems) for EDTA-plasma samples. EDTA-tubes were immediately centrifuged for 10 min at 2800 rpm. The supernatant was filled into 1.5 mL sample-tubes (Eppendorf, Hamburg, Germany) pseudonymized, and stored at −20°C until analysis in March 2009. Plasma ADMA, symmetric dimethylarginine (SDMA), monomethylarginine (MMA), and L-arginine (Arg) were determined by means of a recently described liquid chromatography-tandem mass spectrometric method.27 Plasma nitrite and nitrate levels were determined by iso- trope dilution gaschromatographic-mass spectrometric method according to the method of Tsikas.28 All blood samples were analysed by personnel blinded to the pts’ data. In addition to methylated arginines, N-terminal pro brain natriuretic peptide (NT-proBNP), and high-sensitive C-reactive protein (hs-CRP) were assessed from serum-samples. N-terminal pro brain natriuretic peptide was only available for 94 pts and hs-CRP for 104 pts. Basic laboratory-testing was performed in all pts including creatinine, urea, and GFR (eGFR), similar to the study of Levey et al.29
Statistical analysis

Continuous variables are presented as a mean ± standard deviation, and categorical variables are presented as number of pts (%). Pearson correlation was used to determine the relationship between methylated arginins and other continuous variables, such as NT-proBNP, eGFR, and the LV-EF. The study population was divided into two groups; one who experienced appropriate ICD intervention and one who did not. Welch test was used for comparison of blood markers between these groups.

Univariate Cox regression analysis was performed to assess the unadjusted hazard ratio (HR) with the corresponding 95% confidence intervals (CI 95%) for biomarkers studied. Log-rank test was used for comparison of time to event curves. Multivariate Cox regression was applied to determine whether ADMA, the Arg/ADMA ratio, and NT-proBNP remain predictors of appropriate ICD intervention in a multivariate model, adjusted for confounding variables such as age, eGFR, New York Heart Association (NYHA) functional class, CAD, diabetes, and LV-EF.

All statistical calculations were done two sided, with a P-value below 0.05 considered as statistical significant. Statistics were performed using SPSS® software, version 17.0 (SPSS Inc., an IBM company, Chicago, IL, USA), or SAS® software, version 9.2.0 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics of the study population as well as a comparison between pts who experienced appropriate ICD interventions with those who did not, are depicted in Table 1.
ICD intervention ($P = 0.365$). Furthermore, age, NYHA-functional class, and the left ventricular end-diastolic diameter (LVEDD) did not differ between these two groups (Table 1).

**Implantation cardioverter–defibrillator intervention**

Patients had mainly implanted ICD and CRT-D devices from the companies Boston scientific and St. Jude Medical. In the majority of the ICD pts two tachycardia zones were programmed, a 'ventricular tachycardia (VT)' zone of 180–220 bpm, and a 'VF' zone $>220$ bpm. Ventricular tachycardia falling into the 'VT' zone was first treated with ATP and if unsuccessfully terminated with shock delivery, whereas tachycardia falling into the 'ventricular fibrillation (VF)' zone was immediately treated with shock delivery only. Eighteen (16.9%) pts experienced one or more appropriate ICD-interventions, two pts (1.8%) had appropriate and inappropriate, and three pts (2.8%) had exclusively inappropriate ICD interventions.

Ventricular tachycardia was initially treated with appropriate ATP in 13 pts. Antitachycardia pacing alone was successful in seven pts, six pts needed ATP, and shocks to terminate VT/VF. Of the 11 pts (10.3%) with appropriate ICD shocks, six had ATP prior to shock delivery and five experienced only shocks. Six pts (5.6%) had more than one, but not more than 11 ICD shocks. The average time from ICD implantation until the first occurrence of an arrhythmic was 120.8 days (range 2–382 days). Two pts suffered from appropriate ICD intervention ($P = 1.2$ shock energy was 32.4 $+\pm$ shocks per patient were 2.4 shocks (range 1–11 shocks). Mean during the very first week of the follow-up period.

Of the pts who received ICD shocks the mean number of shocks per patient were 2.4 shocks (range 1–11 shocks). Mean shock energy was 32.4 $\pm$ 3.7 J. Besides appropriately treated VT/VF, non-sustained VT was more frequent in pts with appropriate ICD intervention ($14.5 \pm 25.2$) compared with those without ICD intervention ($1.2 \pm 3.0$; $P = 0.045$). Of note, the incidence of ICD intervention between pts with ischaemic (ICM, 15%), and NICM was not significantly different (29%; $P = 0.161$, Table 1).

**Biomarkers**

Levels of ADMA significantly differed between pts with ischaemic ($n = 89$, $0.528 \pm 0.091 \mu mol/L$) and NICM ($n = 17$, $0.484 \pm 0.066 \mu mol/L$; $P = 0.025$). However, the Arg/ADMA ratio was not significantly different ($P = 0.681$).

Correlations between biomarkers and several clinical parameters are shown in Table 2. Asymmetric dimethylarginine ($r = 0.222$; $P = 0.022$), SDMA ($r = 0.380$; $P < 0.001$), and levels of the Arg/ADMA ratio ($r = -0.228$; $P = 0.019$) were influenced by the age of the pts. All three types of methylated arginines showed a negative correlation with eGFR and the strongest correlation was observed for SDMA ($r = -0.600$; $P < 0.001$).

The correlation between biomarkers and LV-EF was moderate. N-terminal pro brain natriuretic peptide showed the strongest correlation with impaired LV-EF ($r = -0.338$; $P = 0.001$). Asymmetric dimethylarginine ($r = -0.222$; $P = 0.024$) and the Arg/ADMA ratio ($r = 0.212$; $P = 0.036$) correlated only weakly with the LV-EF. Other clinical parameters, such as the body mass index (BMI), LVEDD and medical intervention, did not show any significant correlation with measured biomarker levels.

**Asymmetric dimethylarginine in patients with appropriate implantation cardioverter–defibrillator intervention**

Differences in the mean biomarker levels between pts with and without appropriate ICD intervention are depicted in Table 3. Patients with appropriate ICD intervention had higher plasma-values of ADMA than pts without ICD intervention ($0.564 \pm 0.083 \mu mol/L$ vs. $0.512 \pm 0.088 \mu mol/L$; $P = 0.027$, Figure 1), and pts with ICD intervention had also a lower systemic level of the Arg/ADMA ratio ($144.70 \pm 32.50$ vs. $175.29 \pm 41.29$; $P = 0.002$, Figure 2). The Arg level was significantly different between the two groups, as well ($79.84 \pm 13.32 \mu mol/L$ vs. $89.19 \pm 22.86 \mu mol/L$; $P = 0.023$). For MMA, SDMA, and nitrite/nitrate no differences between pts with and without ICD intervention were found (Table 3).

Univariate Cox regression showed that ADMA ($P = 0.028$) and the Arg/ADMA ratio ($P = 0.003$) were associated with a higher incidence of appropriate ICD intervention. When the study group was divided into quartils, pts above the 50th centile were much more likely to undergo appropriate ICD intervention.

**Table 2 Pearson correlation ($r$) of systemic levels of methylarginines and several clinical parameters**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Age</th>
<th>eGFR</th>
<th>LV-EF</th>
<th>NYHA-class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r$</td>
<td>$P$</td>
<td>$r$</td>
<td>$P$</td>
</tr>
<tr>
<td>ADMA</td>
<td>0.222</td>
<td>0.022</td>
<td>-0.311</td>
<td>0.001</td>
</tr>
<tr>
<td>Arg</td>
<td>-0.063</td>
<td>0.524</td>
<td>0.022</td>
<td>0.821</td>
</tr>
<tr>
<td>Arg/ADMA</td>
<td>-0.228</td>
<td>0.019</td>
<td>0.230</td>
<td>0.018</td>
</tr>
<tr>
<td>MMA</td>
<td>0.179</td>
<td>0.067</td>
<td>-0.357</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Arg/MMA</td>
<td>-0.209</td>
<td>0.031</td>
<td>-0.357</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>SDMA</td>
<td>0.380</td>
<td>$&lt;0.001$</td>
<td>-0.600</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.109</td>
<td>0.297</td>
<td>-0.360</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>0.069</td>
<td>0.487</td>
<td>-0.080</td>
<td>0.420</td>
</tr>
</tbody>
</table>

ADMA, asymmetrical dimethylarginine; SDMA, symmetrical dimethylarginine; MMA, monomethyl Arg; NT-proBNP, N-terminal pro brain natriuretic peptide; hs-CRP, high-sensitive C-reactive protein; other abbreviations as in Table 1.
Asymmetric dimethylarginine in patients with inappropriate implantation cardioverter–defibrillator intervention

No statistical difference of the mean value of ADMA was found between pts with (n = 5) and without inappropriate ICD intervention (0.529 ± 0.054 μmol/L vs. 0.512 ± 0.089 μmol/L; \( P = 0.748 \)). Patients with inappropriate ICD intervention showed a tendency to higher values of the Arg/ADMA ratio than those with appropriate ICD interventions (175.96 ± 26.25 vs. 142.65 ± 33.23; \( P = 0.052 \)).

N-terminal pro brain natriuretic peptide in patients with appropriate implantation cardioverter–defibrillator intervention

Mann-Whitney U test revealed a significant difference between pts with and without appropriate ICD intervention (mean rank: 64.7 vs. 43.7; \( P < 0.001 \)). In a univariate Cox regression analysis, NT-proBNP per se was not associated with a higher risk for appropriate ICD intervention (\( P = 0.251 \)). However, a NT-proBNP concentration above the 50th centile (1013.50 pg/mL), revealed a HR of 4.587 (CI 95% 1.328–15.873; \( P = 0.016 \)) and NT-proBNP remained independently predictive for appropriate ICD intervention in a forced entry multivariate Cox regression model (\( P = 0.014 \), Table 4).

Discussion

To our knowledge this is the first study showing an association of elevated ADMA plasma levels and decreased Arg/ADMA ratios with a higher incidence of appropriate ICD interventions, representing higher occurrence of life-threatening ventricular tachyarrhythmias in pts with structural heart disease and low LV-EF (≤35%). Importantly, this coherency was independent from clinical variables such as, NYHA-functional class, eGFR, age, and LV-EF.

Asymmetric dimethylarginine and MMA are inhibitors of the NOS, with almost the same potential to inhibit these enzymes. The substrate of NOS is Arg which is transferred into NO and L-citrulline. Since Arg and ADMA bind competitively at the NOS, the ratio of Arg and the two inhibitors ADMA and MMA reflects substrate inhibitor ratios. It also indicates NO-bioavailability which is linked with endothelial dysfunction that is reversible by Arg. Asymmetric dimethylarginine reduces flow-mediated endothelium-dependent vasodilatation in healthy subjects as well as in hypercholesterolemic pts. Endothelial dysfunction plays an important role in the development of heart failure and may predict mortality in heart failure pts. Zoccali et al. found a link between ADMA, left ventricular hypertrophy and left ventricular dysfunction. Accordingly, high ADMA levels increase ventricular after-load and may induce left ventricular hypertrophy. Furthermore, ADMA induced endothelial dysfunction seems to reduce myocardial perfusion and NO in low concentrations, was found to inhibit left ventricular remodelling. Consistently, endothelial nitric oxide synthase deficient mice showed increased

Table 3 Biomarkers in patients with and without appropriate implantation cardioverter–defibrillator intervention

<table>
<thead>
<tr>
<th></th>
<th>No ICD intervention ( (n = 88) )</th>
<th>ICD intervention ( (n = 18) )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMA (μmol/L)</td>
<td>0.513 ± 0.088</td>
<td>0.563 ± 0.083</td>
<td>0.027</td>
</tr>
<tr>
<td>SDMA (μmol/L)</td>
<td>0.692 ± 0.192</td>
<td>0.731 ± 0.181</td>
<td>0.420</td>
</tr>
<tr>
<td>MMA (μmol/L)</td>
<td>0.124 ± 0.034</td>
<td>0.126 ± 0.022</td>
<td>0.792</td>
</tr>
<tr>
<td>Arg (μmol/L)</td>
<td>89.19 ± 22.86</td>
<td>79.84 ± 13.32</td>
<td>0.023</td>
</tr>
<tr>
<td>Arg/ADMA (μmol/L)</td>
<td>175.28 ± 41.29</td>
<td>144.71 ± 32.50</td>
<td>0.002</td>
</tr>
<tr>
<td>Arg/MMA (μmol/L)</td>
<td>753.43 ± 225.26</td>
<td>648.02 ± 125.74</td>
<td>0.012</td>
</tr>
<tr>
<td>nitrate (μmol/L)</td>
<td>0.599 ± 0.223</td>
<td>0.573 ± 0.195</td>
<td>0.617</td>
</tr>
<tr>
<td>Nitrate (μmol/L)</td>
<td>59.41 ± 39.99</td>
<td>62.48 ± 27.50</td>
<td>0.694</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>1645.18 ± 2618.45</td>
<td>2331.35 ± 1810.62</td>
<td>0.020</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>5.24 ± 9.41</td>
<td>4.68 ± 5.10</td>
<td>0.723</td>
</tr>
</tbody>
</table>

Values are given as mean ± standard deviation. Abbreviations as in Table 2.

Figure 1 Boxplot plasma value of asymmetric dimethylarginine (μmol/L). Patients with appropriate implantation cardioverter–defibrillator intervention (antitachycardia pacing/shock, \( n = 18 \)) had higher mean values of asymmetric dimethylarginine (μmol/L) than patients without implantation cardioverter–defibrillator intervention (\( n = 88 \); \( \# P < 0.05 \)). Boxes represent the 25th to 75th centile. The median is displayed by the line in a box.

during the follow-up (log rank \( P = 0.017, \) Figure 3). Asymmetric dimethylarginine above the 50th centile (0.509 μmol/L) was associated with a HR of 3.56 (CI 95%: 1.17–10.86; \( P = 0.025 \)). An Arg/ADMA ratio below 25th centile (141.188) had a HR of 4.85 (CI 95%: 1.91–12.34; \( P = 0.001 \)). In a multivariable Cox regression analysis in which age, BMI, CAD, diabetes, NYHA-functional class, LV-EF, eGFR, and one biomarker was included, concentration of ADMA above the 50th centile was independently associated with ICD interventions, revealing a HR of 4.67 (1.18–18.52; \( P = 0.028 \), Table 4). An Arg/ADMA ratio below the 25th centile was independently associated with ICD interventions as well, and had a HR of 3.83 (1.36–10.87; \( P = 0.011 \)).
Ventricular remodelling after myocardial infarction and chronic NOS-inhibition can induce myocardial fibrosis. Impairment of left ventricular function provides electrophysiologic conditions which favour the onset of life-threatening ventricular arrhythmias. In our study ADMA and the Arg/ADMA ratio were independent predictors of appropriate ICD intervention, suggesting that reduced NO-bioavailability may play a critical role in arrhythmogenesis.

**Determinants of methylarginines**

Symmetric dimethylarginine is primarily eliminated through the kidney. This is consistent with our data showing a strong correlation with eGFR. Asymmetric dimethylarginine and MMA are mainly degraded by the enzyme isotypes dimethylarginine dimethylaminohydrolases which are mainly expressed in the kidney and liver. Consequently, elimination decreases in pts with impaired eGFR.

We cannot prove that ADMA and a decreased Arg/ADMA ratio can be considered as surrogates of a higher risk for life-threatening ventricular arrhythmias or may even trigger VT/VF. However, it is conceivable that high levels of ADMA and a decreased Arg/ADMA ratio may promote ventricular arrhythmias by means of endothelial dysfunction and progression of heart failure with ventricular remodelling. Further insight into the exact molecular mechanism of how...
ADMA and Arg are related to the occurrence of VT/VF is mandatory.

**Study limitations**

In order to rule out that ICD implantation itself altered biomarker levels in our patient cohort before they entered the follow-up period, we analysed blood samples of five pts immediately before, and during ICD implantation with DFT testing by VF induction. No changes of ADMA, SDMA, MMA, Arg, nitrite, and nitrate were measured. Therefore, we assume that ICD implantation per se is not a confounder of our study.

Our study has a prospective design with consecutively enrolled pts that had a primary preventive indication for ICD implantation. The number of included pts is relatively small, and the incidence of pts that had a primary preventive indication for ICD implantation. Blood samples were not drawn at a fasting status in all pts and we cannot exclude alterations in ADMA or nitrate levels due to food or drug intake. This may have limited particularly the results of nitrate and nitrate determinations.

It cannot be concluded from our results whether our findings are exclusively related to pts with ischaemic cardiomyopathy or also to non-ischaemic cardiomyopathy, since the group of non-ischaemic pts was too small to perform any meaningful statistical comparisons between the two groups. The applicability of our findings to non-ICD pts, in order to predict a risk of sudden death, may not be allowed.

Taking these limitations into account, we could observe an association of elevated ADMA levels and a decreased Arg/ADMA ratio with ventricular arrhythmias. Therefore, our data suggest an additional value of these two biomarkers for risk stratification in pts with structural heart disease and LV-EF ≤ 35%.

**Conclusion**

Our study demonstrates that ICD pts with decreased left ventricular function are more likely to experience VT/VF episodes and appropriate ICD intervention when they have elevated ADMA levels and a decreased Arg/ADMA ratio. Our findings suggest that ADMA and the Arg/ADMA ratio may be used as additional risk markers in pts that are candidates for primary prevention ICD implantation. Further large prospective studies are warranted to assign the accuracy of ADMA and the Arg/ADMA ratio for risk stratification in these pts.

**Conflict of interest:** There are no conflicts of interests to disclose.

**References**


