Elevation of asymmetric dimethylarginine in patients with unstable angina and recurrent cardiovascular events

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Aims We investigated the role of asymmetric dimethylarginine (ADMA) for clinical outcome of patients with unstable angina.

Methods and results Forty-five patients with stable angina, 36 patients with unstable angina, and 40 healthy controls were included in this study. Coronary artery disease (CAD) patients were prospectively followed for 1 year. ADMA levels were measured at baseline and after 6 weeks using a validated ELISA. Baseline ADMA concentration in controls was significantly lower than in patients with CAD (0.59 ± 0.23 vs. 0.76 ± 0.17 μmol/L; P < 0.001). Patients with unstable angina had significantly higher baseline ADMA levels than patients with stable angina (0.82 ± 0.18 vs. 0.73 ± 0.15 μmol/L; P = 0.01). There was a significant reduction of ADMA levels at 6 weeks after percutaneous coronary intervention (PCI) in patients with unstable angina who experienced no recurrent cardiovascular event (from 0.81 ± 0.14 to 0.73 ± 0.19 μmol/L; P < 0.05). In contrast, patients with unstable angina who had an event showed no significant decrease in ADMA at 6 weeks. Actuarial survival analysis showed a significantly higher event rate in patients with persistently elevated ADMA plasma concentrations.

Conclusion ADMA is significantly elevated in patients with unstable angina. A reduced ADMA level at 6 weeks after PCI may indicate a decreased risk of recurrent cardiovascular events.

KEYWORDS
Asymmetric dimethylarginine; Nitric oxide; Coronary artery disease

Introduction
Asymmetric dimethylarginine (ADMA) is an endogenous competitive inhibitor of the nitric oxide synthases (NOS). ADMA is produced by methylation of arginine residues in intracellular proteins via protein arginine N-methyltransferases (PRMT). The major pathway of elimination for ADMA is its degradation by dimethylarginine dimethylaminohydrolases (DDAH), whereas only a small amount is eliminated by renal excretion.

Elevation of circulating ADMA levels leads to an increased resting vascular tone and enhances several pro-atherogenic mechanisms including platelet aggregation and adherence of monocytes, proliferation of vascular smooth muscle cell, as well as extracellular matrix formation.

ADMA plasma levels are elevated in patients with cardiovascular risk factors like hypertension, diabetes, hypercholesterolaemia, and hyperhomocysteinaemia. Plasma ADMA levels are also related to cardiovascular complications such as peripheral artery disease, stroke, and congestive heart failure. Additionally, several studies have shown that ADMA is a cardiovascular risk marker in patients with cardiovascular disease, and prospective clinical studies have revealed that it is an independent risk factor of cardiovascular events in patients with end-stage renal failure and in other patient groups. In a recent study, Lu et al. showed that in patients with stable coronary artery disease (CAD), ADMA is an independent cardiovascular risk factor as well.

The role of ADMA in unstable angina has not been investigated so far. Therefore, we prospectively studied plasma ADMA levels in a cohort of patients with unstable and stable angina undergoing percutaneous coronary intervention (PCI).

Methods
Patients and study design
We enrolled 81 patients with either acute coronary syndrome or stable angina undergoing PCI from an ongoing prospective study...
who were referred to the Department of Cardiology and Angiology during a period of 2 years. During the study period, 1099 patients underwent PCI, and after evaluation of inclusion and exclusion criteria, 351 consecutive patients were enrolled in the ongoing study. The purpose of this ongoing study was to investigate whether a macrolide vs. placebo influences different inflammatory markers as well as other cardiovascular risk markers in patients with stable and unstable angina and whether the therapy has an impact on the recurrence of cardiovascular events during the 1 year follow-up period (unpublished results). From this population, the patients who were in the placebo group were consecutively included in our sub-study. Only two patients were lost to follow-up.

The predefined primary aim was to detect a statistically significant difference of ADMA between patients with stable and unstable angina. In a previous study of our working group, the mean of ADMA for patients with CAD was 0.62 μmol/L with a standard deviation of 0.21 μmol/L. We committed the clinical significant difference with (delta) 30%. So the effect size is 0.3 × (0.62)/0.21 = 0.89. To get an alpha P < 0.05 and a power ≥ 0.9, at least 28 patients are necessary. To have sure enough subjects per group, we decided to enrol at least 36 per group. Enrolment was stopped when for one group, the minimal pre-defined patient number of 36 was achieved. Because there were consecutively more patients with stable angina, there were 45 patients in the end, whereas in the group with unstable angina, only 36 patients were included. The pre-defined secondary aim of our study was to detect whether the change of the ADMA level during follow-up is related to the outcome of our study population.

According to justification of sample size, 81 consecutive patients of the ongoing study were included in our study. In this population, no patient was lost to follow-up. All data of these patients were available.

Inclusion criteria for stable angina were exercise-induced chest pain with ≥1 mm ST-segment depression in at least two contiguous standard leads or ≥2 mm ST-segment depression in at least two contiguous precordial leads in combination with symptoms according to the Canadian Cardiovascular Society classification.

Inclusion criteria for acute coronary syndrome were chest pain consistent with myocardial ischaemia lasting for at least 5 min at rest within 24 h of admission (Braunwald class IIb), elevation of troponin I or creatine kinase two times upper limit of normal and one of the following findings: electrocardiographic evidence of ischaemia, new wall motion abnormalities, or evidence of previous CAD.

Patients with acute coronary syndrome within 3 weeks prior to intervention, recanalization of chronic total occlusions, underlying malignancies, an age <18 years and women in childbearing age were excluded from our study.

Forty healthy subjects matched by age and gender were also included in this study. They have been recruited from the general population via the local newspaper. They were included in the study if they were between 25 and 85 years old and had no clinical or diagnostic evidence for CAD or other ischaemic vascular disease. Subjects suffering from any concomitant acute or chronic severe disease, or from severe renal failure (creatinine clearance <30 mL/min) were not included.

The study was approved by the local Ethics Committee, and all patients and control subjects gave written informed consent prior to enrolment.

At the time of PCI, all patients were in a fasting state. In all patients, diagnostic angiography, ventriculography, angioplasty, and stent placement were performed according to contemporary standards by femoral approach. Before intervention, all patients received weight adjusted intravenous heparin with a target activated clotting time >300 s in the absence of glycoprotein IIb/IIIa receptor blockers and 200–300 s in combination with glycoprotein IIb/IIIa receptor blockers. Administration of glycoprotein IIb/IIIa receptor blockers was left to operators decision.

Blood samples of all patients were collected for measurement of ADMA plasma levels, hs-CRP concentrations, and routine biochemical laboratory immediately after PCI. Blood from the control group was drawn after an overnight fasting period of at least 12 h.

Following angioplasty, all patients received aspirin 100 mg daily indefinitely and ticlopidine 250 mg b.i.d. or clopidogrel 75 mg q.d. for 6 weeks. Furthermore, standard medications for CAD, hypertension, and hypercholesterolaemia were continued or instituted as appropriate according to current guidelines.

Follow-up

All patients were followed for 1 year with follow-up visits at 6 weeks, 6 months, and 12 months. All adverse events defined as myocardial infarction, coronary vessel restenosis or symptomatic stenosis requiring revascularization, stroke, and death from any other cause were documented. During follow-up, repeated angiography was only performed when clinically indicated.

Biochemical analyses

After collecting, all blood samples for ADMA determination were centrifuged for 10 min at 2000 g at 4 °C and stored at −80 °C until analysis. All biochemical laboratory parameters were obtained immediately by the routine laboratory. In patients, CRP levels were measured using the high sensitivity method (ELISA, EUROIMMUN, Lübeck, Germany). Plasma ADMA levels were determined baseline and 6 weeks after PCI using a GC-MS valided ELISA method (ADMA®-ELISA, DLD Diagnostika GmbH, Hamburg, Germany) according to the manufacturer’s guidelines.

In healthy controls, ADMA and hs-CRP levels were measured once in a fasting state.

Statistical analysis

All data are expressed as mean ± SD or as median and interquartile range (IR). Categorical variables were compared by χ² test or exact Fisher’s test if appropriate. ADMA plasma levels were normally distributed, whereas hs-CRP levels were not normally distributed. Therefore, for comparison between baseline and 6 week ADMA concentration in one group, matched-pairs Student’s t-test (two-sided) was used, whereas for comparison of ADMA plasma levels between different groups Student’s t-test (two-sided) and ANOVA followed by Duncan’s correction was applied, respectively.

For the hs-CRP levels, the median and the IR is given. The hs-CRP levels of different groups were compared by the Mann–Whitney U test, whereas for comparison of CRP levels in one group between baseline and after 6 weeks, the Wilcoxon test was applied. Correlations were assessed by Spearman’s test.

Event survival curves at 1 year in patients with initially unstable angina with decreased vs. persistently elevated ADMA levels were obtained by the Kaplan–Meier method with a log-rank test. A value of P < 0.05 (two-tailed) was considered to be statistically significant. All calculations were performed with SPSS version 11.5.

Results

Baseline and follow-up data

Of 81 patients with CAD, 45 (55.6%) had stable and 36 (44.4%) had unstable angina. Patients’ and controls’ characteristics are shown in Table 1. Baseline demographic characteristics (gender, age, BMI) of the control group were not significantly different when compared with the patients. There were no significant differences regarding baseline clinical characteristics between the groups of patients with stable and unstable angina. PCI procedure was performed successfully in all patients and no procedure-related adverse events occurred during hospitalization. An adverse event during follow-up occurred in 18 patients.
Table 1  Clinical characteristics of patients with stable and unstable angina

<table>
<thead>
<tr>
<th></th>
<th>Stable angina (n = 45)</th>
<th>Unstable angina (n = 36)</th>
<th>Control group (n = 40)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.3 ± 8.7</td>
<td>66.7 ± 9.6</td>
<td>63.1 ± 7.9</td>
<td>0.10 (0.09)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>39/6</td>
<td>29/7</td>
<td>32/8</td>
<td>0.46 (0.62)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.9 ± 3.2</td>
<td>26.5 ± 3.9</td>
<td>26.4 ± 3.0</td>
<td>0.07 (0.07)</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>34 (75.5%)</td>
<td>30 (83.3%)</td>
<td>1 (2.5%)</td>
<td>0.40 (&lt;0.001)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (13.3%)</td>
<td>5 (13.9%)</td>
<td>—</td>
<td>0.38 (0.02)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>35 (77.8%)</td>
<td>31 (86.1%)</td>
<td>9 (22.5%)</td>
<td>0.34 (&lt;0.001)</td>
</tr>
<tr>
<td>Current nicotine abuse</td>
<td>9 (20.0%)</td>
<td>11 (31.4%)</td>
<td>4 (10%)</td>
<td>0.28 (&lt;0.001)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>113.6 ± 28.2</td>
<td>107.5 ± 18.9</td>
<td>103.9 ± 19.2</td>
<td>0.27 (0.24)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>214.1 ± 46.4</td>
<td>206.1 ± 52.0</td>
<td>206.8 ± 24.6</td>
<td>0.47 (0.64)</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>133.5 ± 39.6</td>
<td>127.3 ± 47.4</td>
<td>143.6 ± 25.5</td>
<td>0.53 (0.20)</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>45.3 ± 12.0</td>
<td>46.6 ± 11.3</td>
<td>45.4 ± 10.9</td>
<td>0.62 (0.87)</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>158.4 ± 104.9</td>
<td>158.6 ± 104.5</td>
<td>126.4 ± 55.5</td>
<td>0.99 (0.21)</td>
</tr>
<tr>
<td>Serum creatinine (mol/L)</td>
<td>0.98 ± 0.38</td>
<td>1.03 ± 0.53</td>
<td>1.01 ± 0.26</td>
<td>0.64 (0.84)</td>
</tr>
<tr>
<td>Multi-vessel disease</td>
<td>34 (75.6%)</td>
<td>28 (77.8%)</td>
<td>—</td>
<td>0.82 (&lt;0.001)</td>
</tr>
<tr>
<td>Stent</td>
<td>49 (15.6%)</td>
<td>33 (94.3%)</td>
<td>—</td>
<td>0.93 (&lt;0.001)</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitors</td>
<td>14 (31.1%)</td>
<td>16 (44.4%)</td>
<td>—</td>
<td>0.16 (&lt;0.001)</td>
</tr>
<tr>
<td>Amount of dye (mL)</td>
<td>196.6 ± 52.0</td>
<td>201.6 ± 76.0</td>
<td>—</td>
<td>0.86 (&lt;0.001)</td>
</tr>
<tr>
<td>Duration of PCI (min)</td>
<td>56.0 ± 21.7</td>
<td>58.7 ± 23.3</td>
<td>—</td>
<td>0.76 (&lt;0.001)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>27 (62.2%)</td>
<td>22 (61.1%)</td>
<td>—</td>
<td>1.0 (&lt;0.001)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>5 (11.1%)</td>
<td>3 (8.3%)</td>
<td>—</td>
<td>0.73 (&lt;0.001)</td>
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<tr>
<td>Therapy initiated at baseline</td>
<td></td>
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</tr>
<tr>
<td>ASA</td>
<td>45 (100%)</td>
<td>34 (94.4%)</td>
<td>3 (7.5%)</td>
<td>0.11 (&lt;0.001)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>35 (77.8%)</td>
<td>32 (91.4%)</td>
<td>1 (2.5%)</td>
<td>0.21 (&lt;0.001)</td>
</tr>
<tr>
<td>ACE inhibitor/AT1 blocker</td>
<td>35 (33.3%)</td>
<td>17 (50%)</td>
<td>1 (2.5%)</td>
<td>0.17 (&lt;0.001)</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitor</td>
<td>32 (71.1%)</td>
<td>25 (73.5%)</td>
<td>4 (10.0%)</td>
<td>0.94 (&lt;0.001)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>22 (73.3%)</td>
<td>21 (61.8%)</td>
<td>—</td>
<td>0.46 (&lt;0.001)</td>
</tr>
<tr>
<td>Data are mean ± SD; P-values resulted from the comparison between stable and unstable angina by unpaired Student’s t-test or χ² test if appropriate. P-values in parentheses are derived from comparison between control, stable and unstable angina by ANOVA or χ² test as appropriate. ASA, acetylsalicylic acid; ACE, angiotensin converting enzyme; AT1, angiotensin II type receptor.</td>
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</table>

with initially stable angina (40%) and in 15 patients with initially unstable angina (41.6%). Adverse events included CAD progression with symptomatic stenosis or restenosis requiring revascularization (n = 28), two myocardial infarctions, two strokes, and one death because of combined renal and heart failure.

**ADMA concentrations**

The healthy control group showed a lower mean ADMA plasma concentration (0.59 ± 0.23 μmol/L) when compared with all patients with stable and unstable CAD combined (at baseline 0.76 ± 0.17 μmol/L; P < 0.001 and at 6 week follow-up 0.74 ± 0.18 μmol/L; P < 0.001), respectively. In addition, the hs-CRP level was significantly lower in the healthy control group (0.88, IR: 0.56–1.50 vs. 7.29 mg/L, IR: 3.96–15.94 mg/dL; P = 0.001). In patients with stable angina, mean plasma ADMA concentration was 0.73 ± 0.15 μmol/L, whereas patients with unstable angina had an ADMA concentration of 0.82 ± 0.18 μmol/L at baseline (P = 0.01, Figure 1). For comparison, hs-CRP levels were 7.30 mg/L for patients with stable angina and 7.22 mg/L for patients with unstable angina at baseline (P = 0.70).

After 6 weeks, plasma concentration of ADMA in patients with stable angina remained unchanged when compared with baseline (0.73 ± 0.15 vs. 0.72 ± 0.14 μmol/L; paired P = 0.76), likewise in patients with unstable angina, no significant change of individual ADMA levels was observed after 6 weeks (0.82 ± 0.18 vs. 0.76 ± 0.22 μmol/L; paired P = 0.09; Figure 2). Hs-CRP levels decreased slightly, but not significantly in both groups 6 weeks after PCI (initially stable angina: 5.03 mg/L, IR: 1.98–11.49 mg/dL, P = 0.24; initially unstable: 4.63 mg/L, IR: 2.58–21.59 mg/dL, P = 0.16).

At baseline as well as after 6 weeks plasma, ADMA concentrations did not correlate with hs-CRP levels (baseline: r = −0.07, P = 0.63; 6 weeks: r = −0.07, P = 0.56).
ADMA concentration in patients with or without events during follow-up

The median elapsed time between the PCI and the occurrence of the vascular event was 197 days (IR: 103–243 days) in patients with stable angina and 152 days (IR: 78–292 days) in patients with unstable angina. Patients with unstable angina at baseline who did not experience an event during follow-up had a reduction of plasma ADMA concentration after 6 weeks (0.73 ± 0.19 vs. 0.81 ± 0.14 μmol/L at baseline; paired P = 0.04). In these patients also, hs-CRP levels decreased significantly from 6.60 (IR: 3.46–16.13 mg/dL) to 4.23 mg/L (IR: 1.53–6.81 mg/dL) (P = 0.03).

In contrast, it was an interesting preliminary observation to see that in patients with unstable angina experiencing an event within 1 year, elevated plasma ADMA levels remained elevated at 6 weeks (0.84 ± 0.23 vs. 0.81 ± 0.26 μmol/L, paired P = 0.63). Hs-CRP levels also remained unchanged in this subgroup (8.74 mg/L, IR: 5.96–22.73 mg/dL at baseline and 9.80 mg/L, IR: 2.74–27.02 mg/dL at 6 weeks; P = 0.87).

These initial observations led us to perform an actuarial survival analysis which showed a significantly higher event rate in initially unstable patients with persistently elevated ADMA plasma concentrations when compared with initially unstable patients with decreased ADMA plasma concentrations (log-rank P = 0.017, Figure 3).

A similar survival analysis did show a tendency that patients with persistently elevated hs-CRP levels also have a higher event rate as compared to patients with decreased hs-CRP, but this was not statistically significant (log-rank P = 0.20).

In patients with stable angina with or without event at follow-up, ADMA concentrations remained stable after 6 weeks when compared with baseline.

Discussion

This is the first prospective study to compare plasma ADMA concentrations in CAD patients with stable or unstable angina.

One important finding is that plasma ADMA levels are elevated in patients with CAD when compared with healthy controls. Furthermore, in patients with cardiovascular disease unstable angina is associated with a significantly higher elevation of ADMA plasma concentration when compared with stable angina. Finally, ADMA concentration fell significantly at 6 weeks after PCI in patients who had presented with acute coronary syndrome, if the acute coronary syndrome had resolved. In contrast, in patients who experienced another acute event during follow-up, ADMA concentration remained elevated at 6 weeks after PCI. Interestingly, in patients with unstable angina who experienced no event during follow-up plasma ADMA concentration reached levels comparable to those in patients with stable angina.

Both patient groups did not differ significantly concerning potentially influencing factors on ADMA concentration, such as the presence of hypercholesterolaemia, renal function, hypertension, or diabetes mellitus. Furthermore, administration of anticoagulant drugs as well as performance of the procedure was similar in patients with stable and unstable angina. In addition, drug treatment at 6 weeks was not significantly different in both patient groups, suggesting that differences of plasma ADMA levels were unrelated to drug effects or risk factor profiles.

In vitro as well as in vivo evidence suggests a putative role of oxidative stress in CAD, especially in unstable angina. For example, in clinical studies McMurry et al. demonstrated increased biochemical indicators of oxidative stress in patients with unstable angina compared with stable angina, and Aukrust et al. suggested elevated oxidative stress comitant with inflammatory markers in acute coronary syndrome as a possible pathomechanism, respectively. Inflammatory reaction and/or oxidative stress may induce endothelial dysfunction, which may aggravate coronary perfusion impairment in acute coronary syndrome and promote platelet activation. Valgimigli et al. proposed that oxidative stress may lead to plaque denudation and, via endothelial cell apoptosis, to plaque activation and...
therefore play a role in the progression of CAD and acute coronary syndrome.

Oxidative stress can also lead to elevation of ADMA by several mechanisms: ADMA generation is increased via a redox-regulated enhancement of the gene expression of PRMT2,3 eventually leading to an elevation of plasma ADMA concentration.23–25 Enzymatic degradation of ADMA is also impaired via redox-induced down-regulation of DDAH activity. About 80% of ADMA is selectively metabolized by DDAH to citrulline and dimethylamine, both of which do not interfere with NOS activity.26 There is evidence that DDAH is particularly sensitive to oxidative stress27,28 due to the presence of a reactive cysteine residue in the active site of the enzyme which is nitrrosylated by oxidative stress leading to an inhibition of DDAH activity.29

In contrast to stable angina pectoris, acute coronary syndrome is a condition characterized by elevated oxidative stress and cytokine production. Therefore, elevation of ADMA in unstable angina may reflect a novel underlying pathomechanism involved in this clinical syndrome. Persistent elevation of ADMA during follow-up may reflect persistent oxidative stress, and endothelial dysfunction resulting from this may explain the relationship with acute events during follow-up.

Interestingly, hs-CRP levels also remained elevated in initially unstable patients who experienced a further cardiovascular event during 1 year follow-up. We did not find a correlation between ADMA concentrations and CRP levels in our study population. A correlation between these two markers has been shown only once by Zoccali et al.30 in patients with end-stage renal disease.

Our study is limited by the relatively small sample size. The small sample size could be the reason why hs-CRP is not predictive in our study. However, the purpose of our study was to compare ADMA concentrations and CRP levels in our study population. A correlation between these two markers has been shown only once by Zoccali et al.30 in patients with end-stage renal disease.

Interestingly, there is evidence that ADMA itself may uncouple endothelial NOS (eNOS), such that molecular oxygen becomes the substrate for electron transfer rather than L-arginine. Under these conditions, eNOS produces superoxide anion instead of NO leading to elevated oxidative stress and reduced NO bioavailability inducing endothelial dysfunction,5,23,26

From our present data, it still remains unknown whether oxidative stress causes an elevation of plasma ADMA concentration or whether increased plasma ADMA concentration leads to an elevation of oxidative stress via uncoupling of eNOS. Therefore, further investigations are necessary to elucidate the pathomechanisms behind the elevation of ADMA in acute coronary syndrome.

One interesting issue would be to study the ADMA plasma concentration in combination with the coronary endothelial function during the PCI in acute coronary syndrome.

In a recent study, George et al.31 investigated the effects of supplementation with oral L-arginine on lymphocyte activation and antibody levels directed against oxidized LDL in patients with acute coronary syndrome undergoing percutaneous intervention. In that study, a significant rise in activated peripheral T lymphocytes by 43% and an increase in anti-oxLDL antibody titre by four-fold were observed at 1 month after PCI with stent implantation. L-Arginine treatment for 1 month induced a small decline in activated T-cells and significantly attenuated the rise in anti-oxLDL titer (by two-fold).

In contrast, in another study performed in patients with stable angina pectoris who were treated according to current guidelines L-arginine supplementation had no effect on endothelium-dependent vasodilation, markers of oxidative stress, or exercise capacity.32

The ability of L-arginine to induce biological effects in certain patient groups in vivo (the so-called ‘L-arginine paradox’) has been explained with the presence of elevated levels of the competitive inhibitor of NO synthase, ADMA, in these patients.33–34 Our study shows that patients with unstable coronary syndrome, in contrast to patients with stable angina pectoris, show high ADMA levels and may thus profit from L-arginine supplementation.

In conclusion, our study shows that CAD patients with stable or unstable coronary syndrome can be differentiated by measuring ADMA concentration. Even more, a persistent elevation of ADMA concentration is indicative of patients at high risk of experiencing an acute coronary event during follow-up.

Acknowledgements

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References


