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Clinical research

Plasma levels of asymmetrical dimethylarginine and adverse cardiovascular events after percutaneous coronary intervention[1]

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KEYWORDS
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Aims We investigated the predictive value of plasma concentration of asymmetrical dimethylarginine (ADMA) on clinical outcome in patients undergoing percutaneous coronary intervention (PCI).

Methods and results One-hundred and fifty-three consecutive patients with stable angina and undergoing PCI were prospectively enrolled for clinical follow-up. Plasma ADMA levels were determined before procedure by high performance liquid chromatography. The major adverse cardiovascular events included cardiovascular death, myocardial infarction, and repeat revascularization of target vessels. Patients were grouped into tertiles according to their plasma ADMA levels. Over a follow-up period of 16 months (median), cardiovascular events occurred in 6 patients of tertile I (<0.50 μM), in 17 patients of tertile II (0.50–0.62 μM), and in 28 patients of tertile III (>0.62 μM), $P<0.001$. By multivariate analysis, tertiles of ADMA levels were independently associated with a higher risk of adverse cardiovascular events after PCI (relative risk: tertile II vs I: 3.0 [1.2–7.7], $P=0.022$; tertile III vs I: 5.3 [2.2–12.9], $P<0.001$). Moreover, plasma ADMA level in the highest tertile also appeared as a significant risk factor of subsequent death and non-fatal myocardial infarction after PCI (tertile III vs I, $P=0.04$).

Conclusion Pre-procedural plasma ADMA levels may independently predict subsequent adverse cardiovascular events in patients undergoing PCI. Measurement of plasma ADMA levels could provide a rationale for risk stratification of patients by measuring ADMA levels before intervention.

Introduction

Impaired bioavailability of endothelium-derived nitric oxide (NO) and endothelial dysfunction may play a potential role in the pathogenesis of restenosis after percutaneous coronary intervention (PCI).[1] In addition, they also have been suggested to be associated with long-term risk of cardiovascular events in patients with coronary artery disease (CAD), including those who have undergone coronary angioplasty.[2] However, the mechanism of derangement of L-arginine-NO pathway that leads to endothelial dysfunction in CAD patients remains elusive, and recently, asymmetrical dimethylarginine (ADMA) has been implicated as an important contributing factor. ADMA is characterized as a circulating endogenous inhibitor of NO synthase,[3,4] and may compete with L-arginine

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as the substrate for NO synthase. Moreover, it can increase oxidative stress by uncoupling of electron transport between NO synthase and L-arginine, and hence decrease both the production and availability of endothelium-derived NO.[5] Elevations of ADMA level have been observed in patients with various risk factors of CAD, including hypercholesterolaemia,[6] essential hypertension[7] and diabetes.[8] We have also reported that plasma ADMA level might be a novel risk factor of CAD.[9] In addition, two recent studies have shown that plasma ADMA level is both an independent risk factor of cardiovascular mortality in patients with end-stage renal disease and a predictor of acute coronary events in middle-aged men.[10,11] However, whether elevation of plasma ADMA level is associated with worse clinical course of patients undergoing PCI remains unknown. Hence, in this study, we aimed to study prospectively the association between plasma ADMA level and later adverse cardiovascular events in a cohort of patients with stable CAD and undergoing PCI.

Methods

Study patients

From July 1999 to Dec 2001, we prospectively enrolled patients with angina symptoms and positive exercise stress test who were referred to this institute for coronary angiography and PCI. In patients with multi-vessel CAD, only those who undergoing PCI in single vessel were included. Exclusion criteria included patients with renal dysfunction (serum creatinine >1.5 mg/dl), severe hepatic or thyroid disease, chronic or acute inflammation, and unstable hemodynamic conditions. Patients with myocardial infarction (MI) or unstable angina in the previous one month were also excluded.

Study protocol

All medications were withdrawn for 12 h. Cigarette smoking and beverages containing alcohol or caffeine were avoided for at least 12 h. After informed consent was obtained and 12 h overnight fasting, blood samples were collected before procedure for measurement of plasma ADMA, L-arginine and homocysteine levels. Symmetrical dimethylarginine (SDMA), the biologically inactive stereoisomer of ADMA, was also determined. Diagnostic coronary angiography, ventriculography and coronary angioplasty were performed with standard procedures. Coronary stents were implanted for suboptimal results, National Heart, Lung, and Blood Institute classification type C through F dissection, or any dissection inducing flow reduction after coronary angioplasty. Coronary angiograms were independently reviewed by two expert angiographers who were unaware of the patients' clinical and analytic data. Optimal views of the target lesions were analyzed off-line with the automated edge detection CASS II system (Pie-Medical, Maastricht, the Netherlands). Calibration was performed on a contrast-filled guiding catheter. Angiographic measurements of minimal lumen diameter (MLD) and reference diameter (average diameters of proximal and distal non-involved segments) were obtained at end-diastole. Acute gain was calculated as post-procedural MLD minus pre-procedural MLD. Success of coronary angioplasty was defined as final MLD after coronary angioplasty >50% of the reference diameter without major complications (MI, urgent bypass surgery or death). After the procedure, aspirin (100 mg) was indefinitely prescribed, whereas ticlopidine (250 mg twice daily) was continued for 4 weeks in patients undergoing stent implantation. Medications for treatment of angina pectoris (calcium channel blockers, beta-blockers and nitrates) were continued. All patients were then prospectively followed by office visit monthly or by telephone contact for the occurrence of first-ever major adverse cardiovascular events, which were defined as cardiovascular death, myocardial infarction, and repeat revascularization of target vessel. Follow-up angiography and repeat PCI if needed were performed only by clinical indications.

Determination of plasma L-arginine, ADMA, homocysteine, and high-sensitivity C-reactive protein concentrations

The blood samples were centrifuged at 3000 rpm for 10 min at 4 °C immediately after collection. The plasma samples were then kept frozen at −70 °C until analysis. Plasma homocysteine concentrations were measured by enzyme immunoassay (Axis Homocysteine EIA, Axis-Shield AS, Oslo, Norway), which has been shown to correlate well with high-performance liquid chromatography (HPLC) method with a correlation coefficient (r^2) of 0.94.[12] Determination of high-sensitivity C-reactive protein (CRP) levels was performed with use of latex enhanced immunophelometric assays on a BN II analyzer (Dade Behring, Marburg, Germany). The upper normal value of CRP is 0.5 mg/dl in our laboratory. Plasma L-arginine, ADMA and SDMA concentrations were determined by HPLC using precolumn derivatization with o-phthaldialdehyde (OPA) as described previously.[9] Briefly, plasma samples and standards were extracted on solid-phase extraction cartridges (Sep-Pak, Accell Plus CM, Waters, Milford, Massachusetts). HPLC was carried out on a liquid chromatography system (Model 470, Waters, Milford, Massachusetts). Samples and standards were incubated for exactly 3 minutes with the OPA reagent (5.4 mg/ml OPA in 0.4 M borate buffer, pH 10.0, containing 0.4% 2-mercaptoethanol) before automatic injection into the HPLC system. Samples were eluted from the column with 0.96% citric acid/methanol 68.5/31.5 (v/v), pH 6.8, at a flow rate of 1 ml/min. The OPA derivatives of L-arginine, ADMA, and SDMA were separated on a C_6H_5 column (Microsorb-MV™, Varian, Walnut Creek, California) and the fluorescence detector was set for an excitation wavelength of 340 nm and an emission wavelength of 455 nm. The recovery rate for ADMA was >90%, and the within-assay and between-assay variation coefficients were not more than 7% and 8%, respectively.

Statistical analysis

All parametric values were presented as mean±standard deviation. The study population was grouped into tertiles according to the plasma levels of ADMA. Parametric continuous data among tertiles were compared by Kruskal–Wallis analysis of variance or analysis of variance followed by multiple comparisons. Post-hoc comparison was performed by Bonferroni test. Categorical data were compared by means of Chi-square test or Fisher's exact test. Pearson correlation coefficients were calculated to examine possible correlations between continuous variables. Actuarial event-free survival curves were estimated by use of the Kaplan–Meier method and compared by log-rank test. Univariate and multivariate Cox proportional hazards regression analysis was performed to determine independent predictors of major adverse cardiovascular events and the composite endpoints of death and MI for all patients studied. All the variables presented in Table 1 were further tested by univariate regression analysis and those with a P value <0.2 were included into multivariate

Table 1 Clinical characteristics of study subjects

	Tertile I (*n*=51)	Tertile II (*n*=51)	Tertile III (*n*=51)	*P* values
Age (years)	72±7	70±11	71±6	0.47
Gender (M/F)	46/5	45/6	42/9	0.45
LVEF[a] (%)	61±14	63±14	61±17	0.80
Systemic hypertension	33 (64.7%)	34 (66.7%)	38 (74.5%)	0.53
Hypercholesterolaemia	23 (45.1%)	31 (60.8%)	22 (43.1%)	0.15
Current smoker	14 (27.5%)	25 (49.0%)	16 (31.4%)	0.05[b]
Diabetes mellitus	14 (27.5%)	15 (29.4%)	23 (45.1%)	0.12
Previous MI	19 (37.3%)	17 (33.3%)	10 (19.6%)	0.13
Previous CABG[c]	4 (7.8%)	1 (2.0%)	3 (5.9%)	0.40
Serum creatinine (mg/dl)	1.2±0.3	1.2±0.3	1.2±0.3	0.89
Total cholesterol (mg/dl)	184±31	194±40	186±27	0.26
HDL-cholesterol (mg/dl)	41±9	39±10	39±11	0.76
LDL-cholesterol (mg/dl)	114±24	118±29	118±23	0.74
Triglyceride (mg/dl)	130±64	177±110	160±97	0.10
Medications				
Aspirin	42 (82.3%)	36 (70.6%)	41 (80.4%)	0.59
Nitrate	28 (54.9%)	32 (62.7%)	25 (49.0%)	0.36
Calcium antagonists	23 (45.1%)	31 (60.8%)	25 (49.0%)	0.22
ACE[d]-inhibitors	16 (31.4%)	20 (39.2%)	24 (47.1%)	0.23
β-blockers	25 (49.0%)	13 (25.5%)	22 (43.1%)	0.20
Lipid-lowering agents	14 (27.5%)	18 (35.3%)	10 (19.6%)	0.23
Multi-vessels disease	32 (62.7%)	31 (60.8%)	31 (60.8%)	0.97
Stent	20 (39.2%)	13 (25.5%)	17 (33.3%)	0.33
Quantitative angiographic analysis				
Reference lumen diameter (mm)	2.91±0.49	2.83±0.47	2.88±0.37	0.64
MLD (mm)	0.72±0.46	0.71±0.40	0.73±0.43	0.98
Percent stenosis (%)	75.0±15.1	75.0±13.0	74.9±13.1	1.00
Final MLD (mm)	2.43±0.49	2.18±0.51	2.31±0.42	0.03[e]
Acute gain (mm)	1.72±0.73	1.47±0.53	1.59±0.55	0.12
L-arginine (μM)	79.3±20.4	85.5±26.2	86.7±16.2	0.18
ADMA (μM)	0.42±0.05	0.56±0.03	0.75±0.13	<0.001
SDMA (μM)	0.67±0.32	0.52±0.20	0.55±0.21	0.06
L-arginine/ADMA ratio	190.2±52.6	154.0±45.8	118.5±27.6	<0.001
Homocysteine (μM)	12.4±3.5	13.5±5.1	13.5±5.7	0.49
CRP (mg/dl) (median/range)	0.15 (0.01–3.80)	0.12 (0.03–3.25)	0.09 (0.01–3.53)	0.49
CRP > 0.5 mg/dl	11 (21.6%)	6 (11.8%)	9 (17.6%)	0.38

[a]LVEF=left ventricular ejection fraction.
[b]tertile II vs tertile I: *P*=0.04.
[c]CABG=coronary artery bypass surgery.
[d]ACE=angiotensin converting enzyme.
[e]tertile I vs tertile II: *P*=0.02, tertile III vs tertile II: *P*=0.02.

model. Plasma ADMA levels was tested either as continuous variable or by tertiles. To examine if the assumption of proportional hazards was met, we checked each covariates by plotting the survival curves on a log-minus-log scale, and found no violation to this assumption. The relative risk (RR) and 95% confidence intervals were calculated. A *P* value of less than 0.05 was considered to be statistically significant. The SPSS 10.0 (SPSS Inc., Chicago, Illinois) software package was used for statistical analysis.

Results

Patient characteristics

The study group consisted of 153 patients (133 males, 20 females, mean age: 71±8 years). PCI was performed successfully in all patients, and there were no in-hospital complications. In particular, 94 patients (61%) had multi-vessel disease, 27 (18%) had left ventricular dysfunction (ejection fraction <50%), and 50 (33%) underwent coronary stenting. Patients were grouped into tertiles according to the plasma ADMA levels: <0.50 μM (tertile I), 0.50–0.62 μM (tertile II), and >0.62 μM (tertile III). The baseline clinical and angiographic characteristics of the study groups are summarized in Table 1. Clinical and angiographic parameters showed no differences among the three groups, with the exception that there were slight more current smokers (*P*=0.05) and smaller MLD after procedure (*P*=0.03) in patients of tertile II.

Clinical follow-up

All patients received clinical follow-up, with a median duration of 16 months (range: 1.0–43.5 months). Table 2 shows total deaths and major adverse cardiovascular

Table 2 Adverse cardiovascular events during clinical follow-up

	Tertile I (*n*=51)	Tertile II (*n*=51)	Tertile III (*n*=51)	*P* values[a]
Death	1	2	5	0.22
Cardiovascular death	0	2	3	0.27
MI	0	2	4	0.18
Death and non-fatal MI	1	4	8	0.087
TVR	6	11	24	<0.001
MACE (Cardiovascular death, MI, and TVR)	6	17	28	<0.001

[a]By log-rank test.
MACE=major adverse cardiovascular events; TVR=target vessel revascularization.

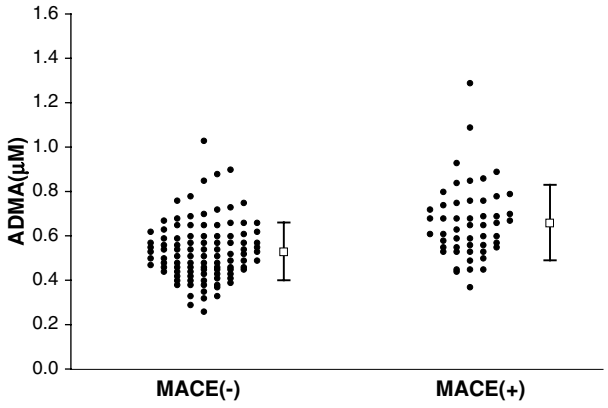

Fig. 1 Plasma levels of ADMA in patients with and without cardiovascular events. Each point represents one subject; bars indicate mean±SD.

events after PCI. During the follow-up period, 51 patients experienced major adverse cardiovascular events. In particular, there were 6 patients with MI, 4 who underwent coronary artery bypass surgery and 41 who underwent target vessel revascularization. Eight patients died, with 5 due to cardiovascular causes and the remaining 3 patients due to adenocarcinoma of the lung, lymphoma and acute pancreatitis, respectively.

Pre-procedural plasma ADMA levels and clinical events

The plasma concentrations of ADMA in patients with and without major adverse cardiovascular events during the follow-up period were 0.66±0.17 μM and 0.54±0.14 μM, respectively (Fig. 1). By grouping patients into tertiles of ADMA, only 6 cardiovascular events occurred in patients of tertile I, compared to 17 events in patients of tertile II and 28 events in patients of tertile III (P<0.001, Table 2). This difference was mainly caused by more cases undergoing target vessel revascularization during follow-up period in patients of tertile II and III (P<0.001, Table 2). By Kaplan–Meier analysis, event-free survival from major adverse cardiovascular events was significantly associated with ADMA tertile (P<0.001), with outcome being the worst in those patients with highest plasma ADMA levels (Fig. 2A). Moreover, when considering the composite endpoint of death and non-fatal MI, there was a trend toward worse outcome in patients with higher ADMA tertiles (P=0.087 by log-rank test, Fig. 2B). In univariate proportional hazards regression analysis, higher ADMA tertiles were associated with a risk of future major adverse cardiovascular events after PCI, while other variables, including plasma SDMA, homocysteine and CRP levels, were not (Table 3). The plasma ADMA levels did not correlate with plasma homocysteine levels, plasma CRP levels, total plasma cholesterol, HDL-cholesterol, LDL-cholesterol as well as triglyceride levels.

Multivariate analysis of risk factors for major adverse cardiovascular events

To identify the effect of plasma ADMA level and the classic cardiovascular risk factors as independent predictors of major adverse cardiovascular events, we performed a multivariate Cox regression analysis. As shown in Table 3, the only independent predictor of major cardiovascular events was tertile of plasma ADMA levels. In the highest and middle tertiles of ADMA, event risk were about 5.3 and 3.0 times that in the lowest tertile, respectively (tertile II vs I, P=0.022, tertile III vs I: P<0.001, Table 3). A marked risk gradient for adverse cardiovascular events was noted across the tertiles of plasma ADMA levels after adjustment for other covariates. In addition, by considering the plasma ADMA levels as a continuous variable, the relative risk would be increased by 36% when plasma ADMA levels increased by 0.1 μM (RR: 1.36, 95% confidence interval:

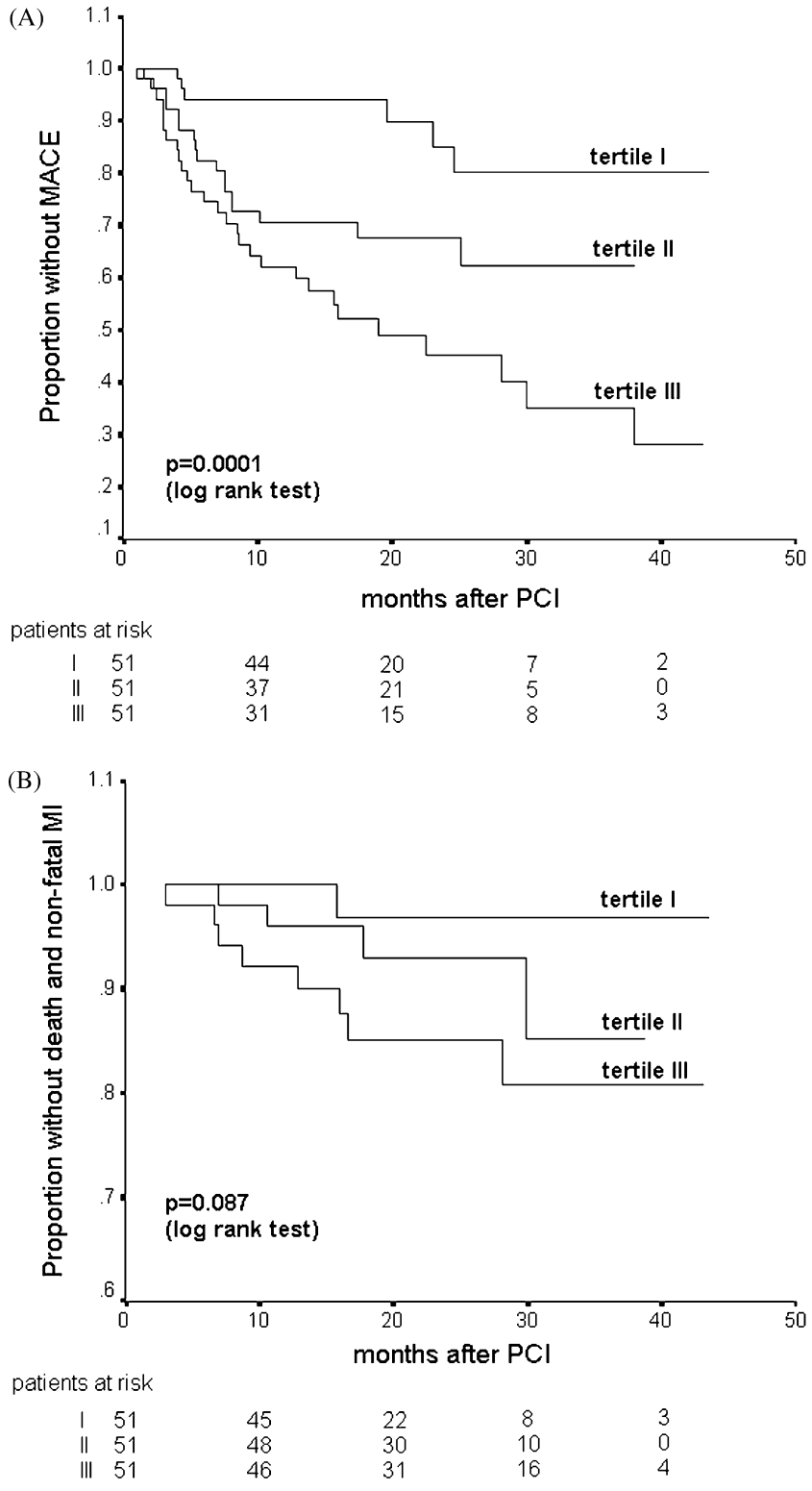

Fig. 2 Kaplan–Meier analyses demonstrating proportion of patients without major adverse cardiovascular events (MACE) (A) and death and non-fatal MI (B) during follow-up. Patients are divided into tertiles according to plasma ADMA levels.

1.18–1.57). As for the composite endpoint of death and non-fatal MI, in addition to the use of β-blocker and multi-vessel CAD, ADMA levels in the highest tertile appeared as a significant independent risk factor in the Cox regression model (P=0.04, Table 3). In contrast, classic risk factors, including diabetes, hypertension and current smoking, did not appear to be of predictive value for subsequent major adverse cardiovascular events.

Table 3 Cox regression analysis for major adverse cardiovascular events and death and non-fatal MI

	Major adverse cardiovascular events				Death or non-fatal MI			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variables	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Age (years)	1.00 (0.96–1.03)	0.77	–	–	0.98 (0.92–1.05)	0.57	–	–
Gender	1.02 (0.43–2.39)	0.97	–	–	0.59 (0.08–4.51)	0.61	–	–
Previous MI	1.06 (0.59–1.92)	0.85	–	–	0.73 (0.20–2.66)	0.63	–	–
Hypertension	1.07 (0.58–1.95)	0.84	–	–	1.53 (0.42–3.58)	0.52	–	–
Hypercholesterolaemia	1.19 (0.69–2.07)	0.54	–	–	0.39 (0.12–1.28)	0.12	0.28 (0.72–1.11)	0.07
Diabetes	1.37 (0.78–2.41)	0.27	–	–	1.76 (0.59–5.23)	0.31	–	–
Current smoker	0.98 (0.55–1.75)	0.95	–	–	1.63 (0.55–4.86)	0.38	–	–
Multi-vessel disease	1.11 (0.63–1.96)	0.71	–	–	2.59 (0.71–9.47)	0.15	5.72 (1.32–24.87)	0.02
Use of stent	1.06 (0.60–2.13)	0.68	–	–	0.55 (0.15–1.99)	0.36	–	–
Use of β-blocker	1.03 (0.59–1.82)	0.91	–	–	0.13 (0.02–1.02)	0.05	10.09 (0.01–0.77)	0.03
Use of ACE[a] inhibitor	1.83 (1.05–3.18)	0.03	1.67 (0.96–2.90)	0.07	2.51 (0.82–7.70)	0.11	10.90 (0.23–3.50)	0.88
LVEF[b] <0.40	0.80 (0.25–2.56)	0.70	–	–	2.75 (0.61–12.46)	0.19	3.09 (0.54–17.56)	0.20
Baseline RD[c] (mm)	1.14 (0.61–2.13)	0.68	–	–	1.65 (0.47–5.82)	0.43	–	–
Post-procedure MLD[d] (mm)	0.97 (0.55–1.72)	0.92	–	–	0.75 (0.24–2.42)	0.63	–	–
Homocysteine (μM)	1.00 (0.96–1.04)	0.88	–	–	1.01 (0.93–1.09)	0.86	–	–
CRP > 0.5 mg/dl	1.34 (0.69–2.61)	0.39	–	–	0.77 (0.17–3.47)	0.73	–	–
SDMA (μM)	0.36 (0.09–1.42)	0.15	0.49 (0.12–12.9)	0.34	0.13 (0.01–3.14)	0.21	–	–
ADMA tertiles								
Tertile II vs I	3.29 (1.30–8.36)	0.012	3.00 (1.17–7.67)	0.022	3.81 (0.43–34.12)	0.23	4.29 (0.45–41.23)	0.21
Tertile III vs I	5.87 (2.43–14.19)	<0.001	5.26(2.16–12.85)	<0.001	7.15 (0.81–57.29)	0.06	9.33 (1.09–79.72)	0.04

[a] ACE=angiotensin converting enzyme.
[b] LVEF=left ventricular ejection fraction.
[c] RD=reference diameter.
[d] MLD=minimal luminal diameter.

Discussion

Major findings

The results of this study showed that elevated plasma concentration of ADMA, an endogenous NO synthase inhibitor, is an independent predictor of worse cardiovascular outcome after PCI. In particular, patients with plasma ADMA levels <0.50 μM was identified as a subgroup with much better event-free survival. Our findings extended previous observations in middle-aged men in Finland and patients with end-stage renal disease,[10,11] and demonstrated the predictive value of measuring ADMA levels for cardiovascular events after coronary interventions.

Plasma ADMA in coronary artery disease

Endothelium-derived NO is synthesized from L-arginine by NO synthase and plays a pivotal role in normal cardiovascular homeostasis.[13] NO contributes to resting vascular tone and acetylcholine-induced vasorelaxation in normal and atherosclerotic coronary arteries.[14,15] In addition, NO also inhibits platelet adhesion and aggregation, inhibits leukocyte adhesion and suppresses smooth muscle cell proliferation and extracellular matrix formation.[16–19] Impaired NO bioavailability plays a central role in the initiation and progression of atherosclerosis, and may also be involved in the complex process of restenosis after arterial injury.[1] In animal studies, administration of L-arginine may reduce neo-initima formation and vascular remodeling after arterial injury by balloon angioplasty or stenting.[20,21] The beneficial effect of L-arginine may be abolished by administration of N^G-nitro-L-arginine methyl ester, a NO synthase inhibitor, indicating a NO-mediated mechanism.[21] Moreover, restoration of vascular NO production by adenovirus-mediated NO synthase gene transfer significantly reduced luminal narrowing after angioplasty in animals, suggesting that vascular NO deficiency may relate to restenosis after angioplasty.[22,23] On the other hand, through loss of NO-mediated inhibition of platelet aggregation and leukocyte adhesion, impaired NO bioavailability may also contribute to acute atherothrombotic events and subsequent adverse cardiovascular outcome after coronary intervention. Although the mechanism of derangement of NO production remains not fully clear, suppression of NO synthase by an endogenous inhibitor of NO synthase, ADMA, has been implicated as one of the possible mechanisms. ADMA is synthesized by methylation of arginine residues in protein and is released as the protein is hydrolyzed. ADMA may compete with L-arginine as the substrate for NO synthase and decrease the production of endothelium-derived NO. Moreover, it may also uncouple the electron transfer between NO synthase and L-arginine, increase oxidative stress, and further impair the availability of endothelium-derived NO.[5] Elevation of plasma ADMA levels has been related to various risk factors of atherosclerosis, including

hypercholesterolaemia,[6] essential hypertension,[7] hypertriglyceridemia,[24] insulin resistance[25] and diabetes.[8] Moreover, Miyazaki et al. reported that plasma ADMA concentrations correlated well with carotid intima-media thickness, an index of early atherosclerosis, in 116 individuals without symptoms of coronary artery disease or peripheral arterial occlusive disease.[26] We also reported that plasma ADMA levels might be useful in predicting significant CAD and correlated well with the extent and severity of coronary atherosclerosis.[9] These observations imply that plasma ADMA level is a potential risk factor of atherosclerosis and CAD. Intriguingly, this hypothesis was corroborated by two recent studies, which demonstrated that elevated ADMA level is associated with increased risks of cardiovascular events and mortality in middle-aged men in Finland and in patients with end-stage renal disease, respectively.[10,11] Since PCI, including balloon angioplasty and coronary stenting, has become one of the standard treatments of CAD, our study was the first one to show that pre-procedural ADMA levels may be an independent predictor of adverse cardiovascular events in patients treated with PCI. In addition, compared with patients with higher ADMA levels, only six adverse cardiovascular events occurred in the subset of patients with ADMA levels in the lowest tertile (<0.50 μM). Thus, pre-procedural measurement of ADMA levels may allow stratification of patients with respect to the risk for subsequent cardiovascular outcome after PCI. In patients with high plasma levels of ADMA and need to undergo PCI, promising therapeutic strategies, such as intracoronary brachytherapy and drug-eluting stent, may be beneficial. In addition, whether long-term supplement of L-arginine or NO donor may reduce the risk of adverse outcome after PCI in these patients may need further studies.

Pathophysiological mechanisms

The mechanisms by which ADMA increases the risk of cardiovascular events in our patients is not clear, but probably involves the impairment of bioavailability of endothelial NO and subsequently causing endothelial dysfunction. Vallance et al. showed that intra-arterial infusion of ADMA caused a dose-dependent fall in forearm blood flow.[4] Böger et al. demonstrated that, in young hypercholesterolemic patients, elevated plasma ADMA concentrations were associated with impaired endothelium-dependent vasodilatation.[6] Endothelial dysfunction has been shown to predict acute and long-term cardiovascular events in patients with CAD,[2,27,28] and is likely related to subsequent clinical complications after PCI. Böger et al. recently demonstrated that ADMA might be a pro-atherogenic molecule by stimulating the secretion of monocyte chemotactic protein-1, increasing endothelial superoxide radical formation, and potentiating monocyte adhesion, which may partly explain the worse cardiovascular outcome in patients with elevated plasma ADMA level.[29] Nevertheless, the exact mechanisms are still unknown and need further investigation.

Recent studies have demonstrated that elevated concentrations of ADMA may be involved in the pathogenesis of hyperhomocysteinemia-mediated endothelial dysfunction.[30,31] Other investigators also questioned about the association between ADMA and the risk of acute coronary events, and addressed the influence of plasma homocysteine levels.[32] Our study, however, did not show any association between homocysteine and ADMA or between homocysteine and adverse cardiovascular events after PCI. The results of studies investigating the association between homocysteine and restenosis or clinical outcome after coronary angioplasty/stenting remained conflicting,[33–35] and our results concerning about the relation among homocysteine, ADMA and outcome after PCI needed to be confirmed in larger cohort.

Limitations

First, our patient population was relatively older and small in size; further studies in larger and younger populations may be informative. Second, since our patients received follow-up coronary angiography by clinical indications, and which was done in less than one-half of patients (61 patients, 40%), potential bias related to incomplete angiographic follow-up could not be excluded, and whether ADMA influenced the process of restenosis after PCI is not known. Third, in our study, elevated plasma CRP levels were not related to adverse cardiac events after successful PCI. This result was in disagreement with previous studies, which have consistently showed that elevated plasma CRP levels are associated with short-term and long-term adverse outcome after either coronary angioplasty or stenting.[35–37] Older age, exclusion of acute coronary syndrome and relatively low CRP levels compared with previous studies, suggestive of a low risk population, may account for these disparate findings in our patients. The relation between ADMA and acute coronary syndrome needs further clarification.

Conclusions

Our study indicates that elevation of pre-procedural ADMA levels may be an independent predictor of subsequent major adverse cardiovascular events after PCI. Measurement of plasma ADMA levels could provide a rationale for risk stratification before intervention. Whether supplement with L-arginine may be beneficial to the subgroup of patients with elevated ADMA level warrant further investigation.

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