Should We Measure Asymmetric Dimethylarginine in Patients with Coronary Artery Disease?

In this issue of Clinical Chemistry, Meinitzer et al. (1) present data from the Ludwigshafen Risk and Cardiovascular Health Study in which they assess asymmetric dimethylarginine (ADMA) as a cardiovascular biomarker in 3238 patients. Coronary angiography identified 2543 patients with coronary artery disease as well as 695 persons without significant disease. Study participants were followed for more than 5 years. The major finding of the study was that plasma ADMA was an independent predictor of total and cardiovascular mortality.

What Is ADMA?

ADMA is a naturally occurring amino acid that has the interesting property of competitively inhibiting the activity of nitric oxide synthase (NOS). ADMA is produced by methylation of arginine residues in intracellular proteins via protein arginine N-methyltransferases (PRMT). When these proteins are hydrolyzed, ADMA is released. ADMA is excreted in the urine, and, not surprisingly, plasma ADMA is increased in patients with end-stage renal disease (2). Parenthetically, patients with renal disease have an increased risk of cardiovascular morbidity and mortality, and in these patients plasma ADMA concentrations carry prognostic information (3). The primary route of ADMA clearance, however, is by enzymatic degradation (Fig. 1). Dimethylamine dimethylaminohydrolase (DDAH) converts ADMA to citrulline and dimethylamine. By regulating plasma and tissue concentrations of ADMA, DDAH protects NOS activity. Compelling evidence for the critical role of DDAH as an NOS regulator was demonstrated by studies of the transgenic DDAH mouse. These animals manifest increased DDAH activity, decreased plasma ADMA concentrations, increased plasma and urinary nitrogen oxides, and decreased vascular resistance, presumably attributable to increased NO (4).

Why Is ADMA important?

ADMA is an endogenous inhibitor of NO synthesis. In the blood vessel, NO relaxes vascular smooth muscle to increase blood flow and suppresses processes involved in vascular disease, including leukocyte adhesion, platelet aggregation, and vascular smooth muscle cell proliferation (5). NO is important in vascular regeneration, mediating angiogenesis (6) and the number of circulating endothelial progenitor cells. Therefore it seems logical that the endogenous NOS inhibitor ADMA would be associated with vascular disease.

An increase in circulating ADMA is often observed in patients with hypercholesterolemia, insulin resistance, diabetes mellitus, hypertension, and chronic renal disease (5, 7). These conditions are associated with vascular oxidative stress, which is known to impair DDAH activity (8). In humans, administration of ADMA causes an increase in vascular resistance (9), a reduction in vascular compliance, an attenuation of cerebral blood flow (10), an increase in sodium retention, and a decrease in cardiac output (9). Furthermore, in humans, plasma ADMA correlates with abnormal thickening of the carotid artery (11). These abnormal changes in vascular function and structure are harbingers of adverse cardiovascular events, as suggested by studies relating plasma ADMA to mortality in selected patient populations (3, 12).

Smaller previous studies in very selected patient populations had already suggested a role of ADMA in coronary artery disease. In a case-control study, nonsmoking middle-aged men in the highest quartile for ADMA (>0.62 μmol/L) had a 4-fold increased risk of acute coronary events (12). Lenzen et al. (13) found that an increase in the ADMA plasma concentration of 1 μmol/L increased risk of coronary heart disease 2.35-fold, a finding that was confirmed by Schnabel et al. (14), who studied 1874 patients with coronary artery disease. Patients with ADMA concentrations in the highest tertile at entry had a hazard ratio 2.5-fold higher than those in the lowest third. In a study of patients with unstable angina undergoing percutaneous coronary intervention (15), those in whom the serum concentration of ADMA was persistently increased 6 weeks after the intervention had higher cardiovascular event rates.

The study by Meinitzer et al. (1) extends the previous studies. The size of the study is impressive: 3238 patients underwent coronary angiography and were followed for more than 5 years, with no patients lost to follow-up. Because there were few exclusion criteria, the findings are relevant to the typical population of a cardiovascular practice. Plasma ADMA concentrations correlated with age, female sex, diabetes mellitus, current smoking, and C-reactive protein. Most importantly, ADMA predicted future cardiovascular events in patients with coronary artery disease. The predictive power of ADMA was independent of traditional cardiovascular risk factors, and patients in the highest quartile of plasma ADMA concentrations were at twice the risk of total and cardiovascular mortality.

Some other findings were notable in the current study. Although the relationship between ADMA and several cardiovascular risk factors (age, hyperlipidemia, diabetes mellitus, and menopause) was confirmed in this study, the authors found no correlation between ADMA and hypertension. This relationship has also been elusive in previous studies, possibly because blood pressure is maintained by many mechanisms. Smokers had higher ADMA concentrations than nonsmokers. Another interesting result was the confirmation of the association between homocysteine and glomerular filtration rate (r =
Impaired renal function is a recently acknowledged cardiovascular risk factor. Thus the association of homocysteine with cardiovascular disease may be just a reflection of increased risk in patients with renal insufficiency and might explain the failure of folate and B12 vitamins to decrease the incidence of cardiovascular events, despite reducing homocysteine, in recent clinical trials. A limitation of this study is that the study population was a rather homogenous group of middle-aged to elderly Caucasian individuals. Thus the findings of this study will need to be confirmed in a more demographically diverse population.

**Can We Lower ADMA Concentrations?**

A logical strategy to reverse the competitive inhibition of NOS by ADMA would be to employ supplemental L-arginine. However, studies of supplemental L-arginine in patients with coronary artery disease are small, and the results have been mixed. Agents that improve insulin resistance reduce plasma ADMA in humans (16). Drugs that block the angiotensin system are also useful in this regard. In the current study, patients receiving statin therapy had lower plasma ADMA concentrations. However, this effect of statins was observed in only 1 of 5 previous clinical trials (17). The results of the present study suggest that it might be worthwhile to readdress this issue, especially because new, specific drugs that increase DDAH expression and lower ADMA, like the farnesoid X receptor agonist GW 4064, are still in the early stage of development (18).

**Should We Measure ADMA in Every Patient with Coronary Artery Disease?**

Vallance (19) first advanced the idea that ADMA accumulation may be a cardiovascular risk factor in end-stage renal disease. In the last 15 years the relationship between ADMA and adverse cardiovascular outcomes has been thoroughly investigated in more than 500 publications. The accumulating evidence supports the view that ADMA is not only a marker but possibly a mediator of endothelial dysfunction, atherogenesis, and cardiovascular morbidity. The study by Meinitzer et al. represents another brick in the wall, if not the keystone. It is not yet time to accept ADMA as a cardiovascular risk marker to be used widely, but the study by Meinitzer and colleagues advances the proposition.

This work was supported by a grant to Dr. Kielstein from the Deutsche Forschungsgemeinschaft (Ki 8591/-1) as well as grants to Dr. Cooke from the National Heart, Lung and Blood Institute (R01 HL-63685; RO1 HL-75774; R01 HL-75774).
CA098303 and P01 AG18784; and PO1AI50153); Philip Morris U S A Inc.; the Tobacco Related Disease Research Program (11RT-0147); and Ajinomoto Inc.

Conflict of interest: Dr. Kielstein owns and hosts the website www.adma.com. Dr. Cooke is the inventor of patents, owned by Stanford University, for diagnostic and therapeutic applications of the NOS pathway from which he receives royalties.

References


Jan T. Kielstein
John P. Cooke*

Division of Cardiovascular Medicine
Stanford University Medical Center
Stanford, CA

* Address correspondence to this author at: Division of Cardiovascular Medicine, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94035 U S A. Fax 650-725-1599; e-mail john.cooke@stanford.edu.

DOI: 10.1373/clinchem.2006.078881