ADMA/SDMA

CPT Code **82542***
Test Code **906897**
Sample Type **Serum**
Tube Type **SST**

Elevated levels of ADMA may identify:

- Endothelial dysfunction
- Pre-diabetes/diabetes
- Subclinical cardiovascular disease

Elevated levels of ADMA may identify:

- Reduced renal function and progressive kidney failure

Description

One of the earliest manifestations of endothelial dysfunction is nitric oxide (NO) deficiency, which promotes atherosclerosis. Asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA), its structural isomer, are metabolites of L-arginine, an amino acid that is catalyzed to L-citrulline and NO by nitric oxide synthase (NOS).[1,2]

Both ADMA and SDMA have distinct pathophysiologies and manifestations. ADMA is a competitive inhibitor of NOS thereby reducing NO production and promoting endothelial dysfunction. SDMA also interferes with NO production, but does so indirectly by reducing the cellular availability of arginine. ADMA is primarily cleared through enzymatic degradation in the bloodstream and its presence identifies subclinical cardiovascular disease (CVD).[1-4] Conversely, SDMA is primarily excreted in the urine and identifies reduced renal function.[5,6]

Clinical Use

ADMA/SDMA may be measured in individuals with multiple risk factors for the development of CVD.

Clinical Significance

Cardiovascular Significance:

- Higher levels of ADMA are associated with a 1.40x increased risk of CVD and coronary heart disease, as well as a 1.60x increased risk of stroke, in a general population.[2]
- Elevated ADMA levels are associated with the presence of hypertension,[7] insulin resistance,[7] and hyperlipidemia.[8]
- Elevated ADMA levels are associated with subclinical atherosclerosis:
  - Increased ADMA concentrations correlate with internal carotid artery bulb intimal media thickness,[3] a hemodynamically unstable region vulnerable to NO deficiency[9] and plaque formation.
  - Elevated ADMA in young adults is associated with increased coronary artery calcification.[4]
- Individuals with established coronary artery disease and elevated ADMA levels have more than twice the risk for adverse events (myocardial infarction, stroke) than those with normal ADMA levels.[10]

Renal Significance:

- Elevated SDMA levels positively correlate with reduced renal function, as measured by estimated glomerular filtration rate[5,6] and cystatin C.[11,12]

Specimen Type

The ADMA/SDMA test should be performed on a serum specimen, and fasting is recommended, but not required.

Testing Frequency

The frequency of testing is determined by an individual's medical history, but may be monitored in individuals with hyperlipidemia, hypertension, pre-diabetes/diabetes, or those who are at moderate to high risk for developing cardiovascular disease.

Commercial Insurance or Medicare Coverage

Coverage guidelines have not been established or posted by CMS (Medicare & Medicaid). We have reviewed the larger carriers (Aetna, UnitedHealthcare, Cigna, Blues) and information is limited or has not been posted.

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RELATIVE RISK

ADMA (ng/mL)

<100 Low	100-123 Moderate	>123 High

REFERENCE RANGE

SDMA (ng/mL)

73 - 135 Low	>135 High

TEST ADMA		TEST SDMA	Interpretation
Low		Low	• Normal endothelial function
Med	High	Low	• Endothelial dysfunction and possible presence of pre-diabetes/diabetes or CVD
Low		High	• Reduced renal function
Med	High	High	• Endothelial dysfunction and possible presence of pre-diabetes/diabetes or CVD • Reduced renal function

Treatment Considerations†

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ **Assess lifestyle habits.**
- Consider diet, exercise, and weight reduction efforts, if appropriate.[13]

✓ **Assess LDL-C levels.**
- If not at an optimal level,[8] consider lipid-lowering therapies described in the National Cholesterol Education Program/Adult Treatment Panel III (NCEP ATP III) Guidelines.[14]

✓ **Assess insulin sensitivity.**
- If not at an optimal level,[7] consider insulin-sensitizing therapies described in the American Diabetes Association guidelines for the management of pre-diabetes/diabetes.[15]

✓ **Assess blood pressure.**
- If not at an optimal level, consider initiating, or titrating, antihyper-tensive therapy.[1,16]
- Consider L-arginine or L-citrulline supplementation to enhance NO production, and to improve vasodilation and vascular tone.[1,17]

✓ **Assess the presence of coronary artery disease (CAD) with imaging techniques, such as carotid intima-media thickness (CIMT)[3] testing or coronary artery calcium (CAC)[4] scoring.**

✓ **Assess clotting risk.**
- Consider antiplatelet therapy if history of CAD (i.e., myocardial infarction or revascularization) and/or cerebrovascular disease (i.e., transient ischemic attack or stroke).[1]

✓ **Assess renal function.**
- If SDMA levels are not optimal,[5,6,11,12] consider further assessment and treatment considerations for kidney disease, as outlined in the National Kidney Foundation guidelines.[18]

** The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.*

† The treatment considerations are provided for informational purposes only and are not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, and assessment of the patient.

References

1. Sibal L, Agarwal SC, Home PD, Boger RH. The Role of Asymmetric Dimethylarginine (ADMA) in Endothelial Dysfunction and Cardiovascular Disease. *Curr Cardiol Rev.* 2010; 6 (2): 82-90. 2. Willeit P, Freitag DF, Laukkanen JA, et al. Asymmetric dimethylarginine and cardiovascular risk: systematic review and meta-analysis of 22 prospective studies. *J Am Heart Assoc.* 2015; 4 (6): e001833. 3. Maas R, Xanthakis V, Polak JF, et al. Association of the endogenous nitric oxide synthase inhibitor ADMA with carotid artery intimal media thickness in the Framingham Heart Study offspring cohort. *Stroke.* 2009; 40: 2715-2719. 4. Iribarren C, Husson G, Sydow K, Wang B, Sidney S, Cooke JP.. Asymmetric dimethyl-arginine and coronary artery calcification in young adults entering middle age: the CARDIA Study. *Eur J Cardiovasc Prev Rehabil.* 2007; 14: 222-229. 5. Kielstein JT, Boger RH, Bode-Boger SM, et al. Marked increase of asymmetric dimethylarginine in patients with incipient primary chronic renal disease. *J Am Soc Nephrol.* 2002; 13: 170-176. 6. Kielstein JT, Salperter SR, Bode-Boeger SM, Cooke JP, Fliser D. Symmetric dimethylarginine (SDMA) as endogenous marker of renal function – a meta-analysis. *Nephrol Dial Transplant.* 2006; (21): 2446-2451. 7. Stühlinger MC, Abbasi F, Chu JW, et al. Relationship between insulin resistance and an endogenous nitric oxide synthase inhibitor. *JAMA.* 2002; 287: 1420-1426. 8. Böger RH, Bode-Boger Sm, Szuba A, et al. Asymmetric dimethylarginine (ADMA): A novel risk factor for endothelial dysfunction its role in hypercholesterolemia. *Circulation.* 1998; 98: 1842-1847. 9. Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. *JAMA.* 1999; 282: 2035-2042. 10. Schnabel R, Blankenberg S, Lubos E, et al. Asymmetric dimethylarginine and the risk of cardiovascular events and death in patients with coronary artery disease: Results from the AtheroGene study. Circ Res. 2005; 97: e53-e59. 11. El-Khoury JM, Bunch DR, Hu B, Payto D, Reineks EZ, Wang S. Comparison of symmetric dimethylarginine with creatinine, cystatin C and their eGFR equations as markers of kidney function. *Clin Biochem.* 2016; (49): 1140-1143. 12. Wilcken DEL, Wang J, Sim AS, Green K, Wilcken B. Asymmetric dimethylarginine in homocystinuria due to cystathionine β-synthase deficiency: Relevance of renal function. *J Inherit Metab Dis.* 2006; 29: 30-37. 13. Tanahashi K, Akazawa N, Miyaki A, et al. Plasma ADMA concentrations associate with aerobic fitness in postmenopausal women. *Life Sci.* 2014;108(1):30-3. 14. Third report of the National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). National Institutes of Health. September 2002. *NIH Publication No.* 02-5215. 15. American Diabetes Association: Cardiovascular Disease and Risk Management: Standards of Medicare Care in Diabetes—2018. *Diabetes Care.* 2018;41(Supplement 1):S86-S104. 16. Chen JW, Hsu NW, Wu TC, Lin SJ, Chang MS. Long-term angiotensin-converting enzyme inhibition reduces plasma asymmetric dimethylarginine and improves endothelial nitric oxide bioavailability and coronary microvascular function in patients with syndrome X. *Am J Cardiol.* 2002;90(9):974-82. 17. Schwedhelm E, Maas R, Freese R, et al. Pharmacokinetic and pharmacodynamic properties of oral L-citrulline and L-arginine: impact on nitric oxide metabolism. *Br J Clin Pharmacol.* 2008;65(1):51-9. 18. National Kidney Foundation: KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl.* 2013; 3 (1): 1-150.

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