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 deficiency9 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 rate5,6 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.
## 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.  
  - Consider a low fat, low cholesterol diet, and increase exercise.

- **Assess LDL-C levels.**
  - If not at an optimal level, consider lipid-lowering therapies described in the National Cholesterol Education Program/Adult Treatment Panel III (NCEP ATP III) Guidelines.  
  - Consider the addition or titration of statins or ezetimibe.

- **Assess insulin sensitivity.**
  - If not at an optimal level, consider insulin-sensitizing therapies described in the American Diabetes Association guidelines for the management of pre-diabetes/diabetes.  
  - Consider metformin for pre-diabetes/diabetes or CVD.

- **Assess blood pressure.**
  - If not at an optimal level, consider initiating, or titrating, antihypertensive therapy.  
  - Consider renin-angiotensin-aldosterone system (RAAS) inhibitors or diuretics.

- **Consider L-arginine or L-citrulline supplementation to enhance NO production, and to improve vasodilation and vascular tone.**  
  - Consider the use of L-arginine or L-citrulline supplements in patients with low ADMA levels.

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

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

- **Assess renal function.**
  - If SDMA levels are not optimal, consider further assessment and treatment considerations for kidney disease, as outlined in the National Kidney Foundation guidelines.  
  - Consider the use of renin-angiotensin-aldosterone system (RAAS) inhibitors or diuretics.

### References