Elevated ADMA levels may identify:
- Endothelial dysfunction
- Pre-diabetes/diabetes
- Subclinical cardiovascular disease

Elevated SDMA levels 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. ADMA (asymmetric dimethylarginine) and SDMA (symmetric dimethylarginine), its structural isomer, are metabolites of L-arginine, an amino acid that is catalyzed to L-citrulline and NO by nitric oxide synthase (NOS).

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 identifies subclinical cardiovascular disease. Conversely, SDMA is primarily excreted in the urine and identifies reduced renal function.

Clinical Use
ADMA/SDMA may be measured in individuals with multiple risk factors for the development of cardiovascular disease.

Clinical Significance
Cardiovascular Significance:
- Elevated ADMA levels are associated with the presence of hypertension\(^1\), insulin resistance\(^1\), and hyperlipidemia\(^2\).
- Elevated ADMA levels are associated with subclinical atherosclerosis:
  - Elevated ADMA concentrations correlate with internal carotid artery bulb intimal media thickness\(^3\), a hemodynamically unstable region vulnerable to nitric oxide deficiency\(^4\) and plaque formation.
  - Elevated ADMA in young adults has been associated with increased CT coronary isomer calcification\(^6\).
- Individuals with established coronary artery disease and elevated ADMA levels have more than twice the risk for adverse events (MI, stroke) than those with normal ADMA levels\(^6\).

Renal Significance:
- Elevated SDMA levels positively correlate with reduced renal function as measured by eGFR\(^7\).

Sample Type
The ADMA/SDMA test should be performed on a serum sample, 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, also known as NCD (National Coverage Determination) or LCD (Local Coverage Determination) have been established or posted by CMS (Medicare & Medicaid). Guidelines should be reviewed for coverage and limitation. Limited information has been provided by the majority of the larger carriers (Aetna, United Healthcare, Cigna, Blues).

Understanding Medical Necessity
The following ICD-10 codes for ADMA/SDMA are listed as a convenience for the ordering physician. The ordering physician should report the diagnosis code that best describes the reason for performing the test.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnosis Code</th>
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<tbody>
<tr>
<td>Type 2 Diabetes Mellitus with Hyperglycemia</td>
<td>E11.65</td>
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<tr>
<td>Type 2 Diabetes Mellitus without Complications</td>
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<tr>
<td>Other Specified Diabetes Mellitus without Complications</td>
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<tr>
<td>Pure Hypercholesterolemia, Unspecified</td>
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<td>Familial Hypercholesterolemia</td>
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<td>Metabolic Syndrome</td>
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<td>Essential (primary) Hypertension</td>
<td>I10</td>
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<td>Atherosclerotic Heart Disease of Native Coronary Artery without Angina Pectoris</td>
<td>I25.10</td>
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<td>Atherosclerotic Heart Disease of Native Coronary Artery with Unstable Angina Pectoris</td>
<td>I25.110</td>
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<td>Impaired Fasting Glucose</td>
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<tr>
<td>Impaired Glucose Tolerance Test (oral)</td>
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<tr>
<td>Abnormal Finding of Blood Chemistry, Unspecified</td>
<td>R79.9</td>
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</table>
### Treatment Considerations

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

- **Assess LDL-C levels.**
  - If not at goal, consider lipid-lowering therapy, ideally with a statin-based regimen if not contraindicated.

- **Assess blood pressure.**
  - If not at goal, consider initiating, or titrating, antihypertensive therapy.
    - **Note:** An elevated blood pressure may contribute to endothelial dysfunction and the development of coronary artery disease and subsequent renal disease.
  - Consider L-Arginine or L-Citrulline supplementation to improve vasodilation and vascular tone.
    - **Note:** L-Arginine and L-Citrulline enhance the production of nitric oxide which has anti-inflammatory, anti-thrombotic, anti-hypertensive, and anti-oxidant effects.

- **Assess risk for pre-diabetes/diabetes.**
  - If abnormal fasting glucose or oral glucose tolerance test, consider PPAR agonists, metformin, or DPP-IV inhibitors if not contraindicated.

- **Assess the presence of CAD with imaging techniques such as CIMT or coronary artery calcium scoring.**
  - Consider aspirin therapy if not contraindicated.
  - Consider clopidogrel if history of CAD (i.e. myocardial infarction or revascularization) and/or cerebrovascular disease (i.e. TIA or stroke).

### References