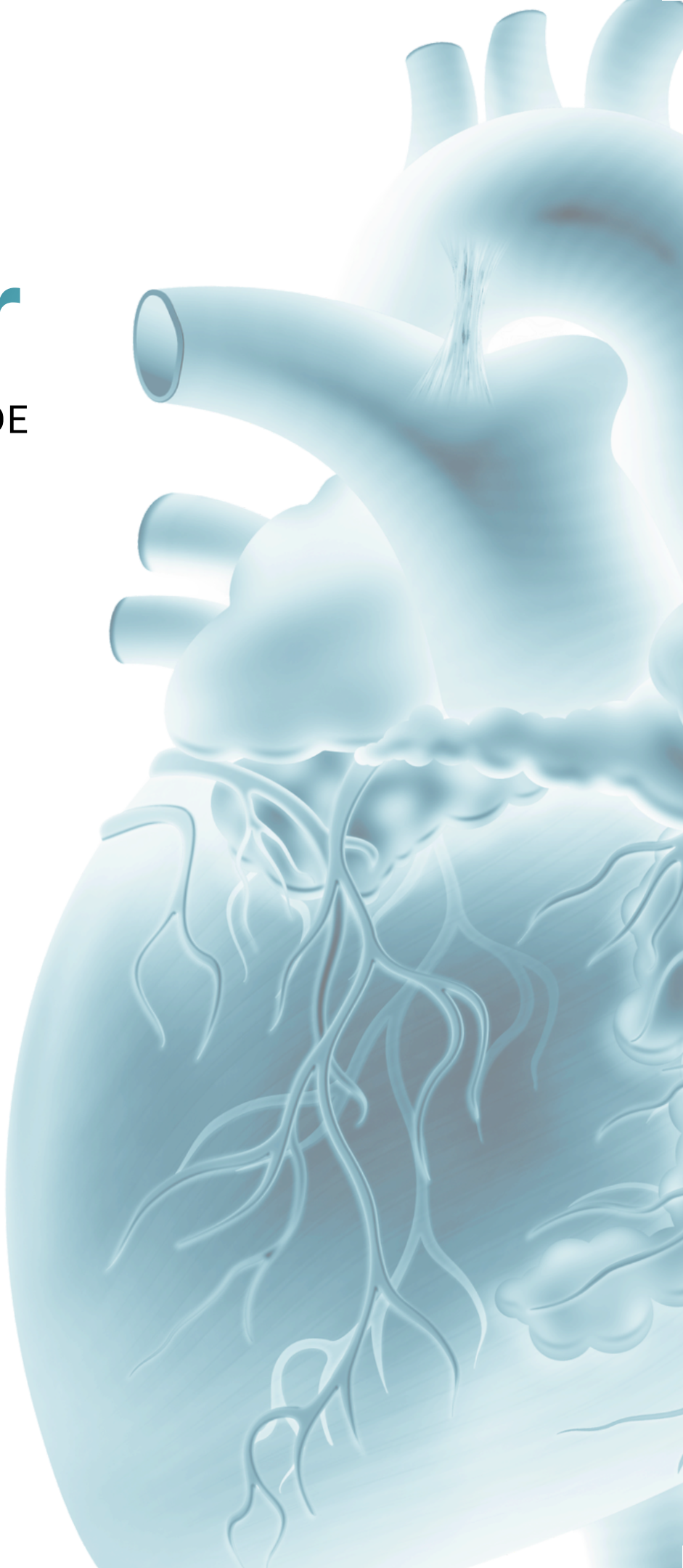
Cardio Zoomer

INTERPRETIVE GUIDE



VibrantWellness

Overview of Cardio Zoomer

The Cardio Zoomer delivers a comprehensive view of cardiovascular health by combining advanced biomarkers and genetics into one clear, actionable profile.

This test goes beyond standard cardiovascular panels by measuring a broader range of high-resolution biomarkers, giving providers deeper insight into underlying drivers of heart and vascular risk.

What The Panel Tracks:

Cholesterol & Lipid Health
Assesses cholesterol quality and particle risk

Blood Pressure & Circulation
Evaluates vessel function and blood flow

Inflammation & Recovery
Identifies inflammation impacting recovery and endurance

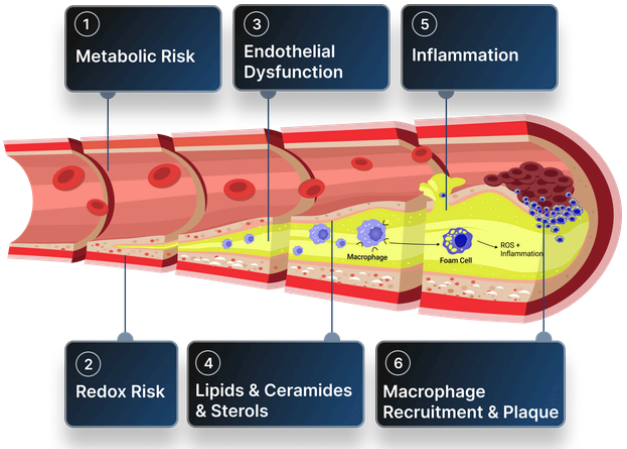
Metabolic Balance
Assesses glucose control and cardiometabolic stress

Clotting & Cardiac Stress
Evaluates clotting risk and heart workload

A more complete, connected view of heart health that helps providers take clearer, more confident action.

Table of Contents

Introduction



Cardiovascular disease (CVD) remains the leading cause of death globally, accounting for approximately 31% of all deaths.[1] CVD refers to the following [4] entities[2] :

- **Coronary artery disease (CAD):** Sometimes referred to as coronary heart disease (CHD), results from decreased myocardial perfusion that causes angina, myocardial infarction (MI), and/or heart failure. It accounts for one-third to one-half of the cases of CVD
- **Cerebrovascular disease:** Includes stroke and transient ischemic attack (TIA)
- **Peripheral artery disease (PAD):** A disorder in which narrowed arteries reduce blood flow to the limbs, often causing pain or cramping during activities such as walking.
- **Aortic atherosclerosis:** Includes thoracic and abdominal aneurysms

In the United States alone, heart disease is responsible for 1 in every 5 deaths.[3] Despite these alarming statistics, many individuals remain unaware of their risk, as traditional assessments often fail to detect underlying issues. The following conditions represent well-established cardiometabolic risk factors that drive endothelial dysfunction, atherosclerosis, and subsequent CVD.

CONDITION	PREVALENCE
Hyperglycemia	Estimates from the Center of Disease Control and Prevention (CDC) reports that over 38.4 million Americans have diabetes, which is 11.6% of the population, and about 97.6 million adults have prediabetes (38% of the adult population).[4]
Hypercholesterolemia	Approximately 10% of adults aged 20 or older have total cholesterol levels above 240 mg/dL. Slightly more than half of U.S. adults (54.5%, or 47 million people) who could benefit from cholesterol medicine are currently taking it.[5]
Hypertension	Approximately 76.4 million, 1 in 3, American adults have high blood pressure (hypertension), which is defined as an elevated pressure of 140 mmHg systolic or higher and/or 90 mmHg diastolic or higher. National Health and Nutrition Examination Survey (NHANES) data showed that 78 percent were aware of their condition and 68 percent were using anti-hypertensive medication; however, less than 64 percent of those receiving treatment had their condition controlled.[6]
Hypertriglyceridemia	About one-quarter of U.S. adults aged 20 and over had elevated triglyceride levels (≥150 mg/dL) during 2009–2012.

What is the Cardio Zoomer?

The Cardio Zoomer is an advanced assessment designed to clarify the complex interplay between cardiovascular, metabolic, and inflammatory systems. It moves beyond traditional lipid panels to deliver systems-level insights that help identify the root causes of cardiovascular risk, often before symptoms emerge.

Cardio Zoomer analyzes blood and urine samples across multiple panels that include the following markers:

METABOLIC RISK

Glucose Regulation

- Hba1c
- Glucose
- Glycated Serum Protein

Insulin Resistance

- C-Peptide
- Insulin
- HOMA-IR
- Adiponectin

Metabolic Factors

- TMAO
- L-Carnitine
- Ferritin
- Leptin

Renal Function

- Sodium
- Potassium
- Chloride
- Carbon Dioxide
- Glucose (Renal)
- BUN
- Creatinine
- eGFR
- eGFR (African American)
- BUN/Creatinine Ratio
- Serum Osmolality
- Uric Acid
- Cystatin C

Hepatic Function

- ALT
- AST
- GGT
- Bilirubin (Total)
- Protein (Total)
- Alkaline Phosphatase

Inflammation

- hsCRP
- Homocysteine
- IL-6
- TNF-α

Omega Fatty Acids

- EPA
- DPA
- DHA
- LA
- AA
- AA/EPA ratio
- Omega 6 Total
- Omega-3 Total
- Omega-3 Index

Clotting Risk

- NTproBNP
- Troponin - T
- Creatine Kinase

Scores

- Reynolds Risk Score
- Framingham Risk Score

LIPIDS AND RATIOS

Lipids

- Cholesterol (TC)
- Triglycerides (TG)
- HDL Direct
- Non-HDL-C
- LDL Direct
- sdLDL
- Lp(a)
- Apolipoprotein A-1
- Apolipoprotein B

Lipid Ratios

- TC/HDL-C
- TG/VLDL-C
- ApoB/ApoA-1
- HDL-C/TG

Endothelial Dysfunction

- ADMA
- SDMA
- Homoarginine
- Arginine
- Citrulline
- Arginine/ADMA
- Arginine/SDMA
- Homoarginine/ADMA
- Homoarginine/SDMA
- Choline

Macrophage Recruitment and Plaque

- MPO
- PLAC
- oxLDL

CERAMIDES AND RATIOS

Ceramides

- Cer(d18:1/16:0)
- Cer(d18:1/18:0)
- Cer(d18:1/24:1)

Ceramide Ratios

- Cer(d18:1/16:0)/Cer(d18:1/24:0)
- Cer(d18:1/18:0)/Cer(d18:1/24:0)
- Cer(d18:1/24:1)/Cer(d18:1/24:0)

STEROLS

Sterol Balance Score

Production Markers

- Desmosterol
- Lathosterol

Absorption Markers

- Beta-Sitosterol
- Campesterol

Redox Risk

- 8-OHdG
- F2-Isoprostane
- Malondialdehyde
- Nitrotyrosine
- 3-Chlorotyrosine
- Urine Creatinine

Which Patients Would Benefit From These Tests?

Conditions and symptoms that may benefit from Cardio Zoomer testing include individuals with:

- Coronary heart disease
- Arrhythmia
- Hypertension
- Hypercholesterolemia
- Dyslipidemia
- Obesity
- Prediabetes or diabetes
- Metabolic syndrome
- Chest discomfort or tightness
- Elevated high sensitivity-CRP (hs-CRP) / inflammation
- Shortness of breath on exertion
- Persistent fatigue / low stamina
- Poor circulation or cold extremities
- History of cerebrovascular disease
- Family history of coronary artery disease

Technology and Methodology

Vibrant uses protein microarray for leptin, sandwich ELISA for TNF-a, mass spectrometry for the oxidative stress markers, endothelial dysfunction markers, ceramides, and sterols, and the Roche Cobas platform for all the remainder of the Cardio Zoomer markers.

MICROARRAY
- Leptin

SANDWICH ELISA
- TNF-a

REAL TIME PCR
- All Variants (Cardio Genetics)

MASS SPEC (LC-MS/MS)
- 8-OHdG
- F2-Isoprostane
- Malondialdehyde
- Nitrotyrosine
- 3-Chlorotyrosine
- ADMA
- SDMA
- Homoarginine
- Arginine
- Citrulline
- TMAO
- L-Carnitine
- Cer(d18:1/16:0)
- Cer(d18:1/18:0)
- Cer(d18:1/24:1)
- Desmosterol
- Lathosterol
- Beta-Sitosterol
- Campesterol

ROCHE COBAS PLATFORM
- HbA1c
- Glucose
- Glycated serum protein
- C-peptide
- Insulin
- Adiponectin
- Ferritin
- ALT
- AST
- GGT
- Bilirubin (Total)
- Alk Phosphatase
- Sodium
- Potassium
- Chloride
- Carbon Dioxide
- BUN
- Creatinine
- Uric Acid
- ApoB
- LDL
- Lp(a)
- sdLDL
- HDL
- ApoA-1
- Triglycerides
- Cholesterol
- Non-HDL-C
- Cholesterol Balance Score
- hsCRP
- NTproBNP
- Homocysteine
- IL-6
- MPO
- PLAC
- oxLDL
- D-dimer
- Troponin-T
- Creatine Kinase

Cardio Zoomer Markers

Interpretation of Results

10 YEAR RISK SCORES

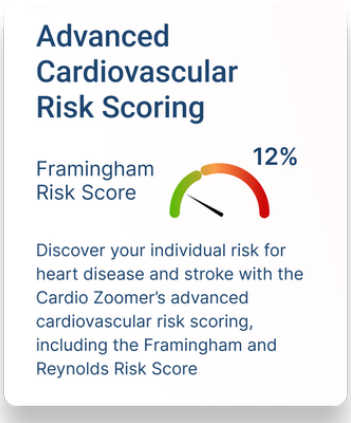
The Framingham Risk Score (FRS) and Reynolds Risk Score (RRS) are tools used to estimate an individual's 10-year risk of developing cardiovascular events.

Framingham Risk Score

Risk categories are typically defined as:

Low: (<10%) **Intermediate:** (10-20%) **High:** (>20%)

The Framingham Risk Score is a validated clinical tool used to estimate an individual's 10-year probability of developing CVD. The information required to estimate risk includes **age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure lowering medication use, diabetes status, and smoking status.**[8]



Reynolds Risk Score

Risk categories are generally defined as:

Low: (<5%) **Intermediate:** (5-10%) **High:** (>10%)

The Reynolds Risk Score **builds upon the traditional Framingham model** by adding two key predictors of cardiovascular events: hs-CRP, a marker of systemic vascular inflammation, and family history of premature heart disease.

These additions improve risk discrimination, especially for women and for individuals without established CVD whose traditional markers may not fully capture underlying risk.[9]

Risk-Enhancing Factors[10]

- Family history of premature Atherosclerotic Cardiovascular Disease (ASCVD)
  - Males, age <55 y/o
  - Females, age <65 y/o
- Primary hypercholesterolemia
  - LDL-C 160–189 mg/dL (4.1–4.8 mmol/L)
  - Non–HDL-C 190–219 mg/dL (4.9–5.6 mmol/L)
- Metabolic syndrome (MetS) – only 3 of the following criteria need to be met
  - Increased waist circumference (by ethnically appropriate cut off points)
  - Elevated triglycerides (>150 mg/dL, non-fasting)
  - Elevated blood pressure
  - Elevated glucose
  - Low HDL-C (<40 mg/dL in men; <50 mg/dL in women)

- Chronic kidney disease (CKD) (eGFR 15–59 mL/min/1.73 m2 with or without albuminuria; not treated with dialysis or kidney transplantation)
- Chronic inflammatory conditions, such as psoriasis, rheumatoid arthritis (RA), lupus, or HIV/AIDS
- History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia
- Lipids/biomarkers: associated with increased ASCVD risk
    - Persistently elevated primary hypertriglyceridemia (≥175 mg/dL, non-fasting);
    - If measured:
        - § Elevated hs-CRP (≥2.0 mg/L)
        - § Elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a).
        - § Elevated apoB (≥130 mg/dL): A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
        - Low ankle-brachial index (<0.9)

10-Year Risk Scores in Racial and Ethnic Groups

Cardiovascular risk calculators show variable accuracy across racial and ethnic groups. In South Asians, tools such as the Framingham and Reynolds scores often underestimate risk, partly due to earlier onset of cardiometabolic disease.[11] In African Americans, performance is more mixed—Framingham models have shown reasonable discrimination in some studies, and the Pooled Cohort Equations represent an improvement, though calibration issues persist.[12]

For Hispanic, other Asian, and Native American populations, evidence is limited, but available data suggest that traditional models may either overestimate or underestimate risk depending on the subgroup, highlighting the need for more population-specific validation and refinement.[13] [14]

Clinicians should consider the impact of racial and ethnic disparities when assessing cardiovascular disease risk, as social determinants of health, access to care, environmental exposures, and chronic stress can significantly influence outcomes. Risk assessment should be individualized and interpreted within the broader clinical and population health context rather than relying solely on standard risk calculators.

Risk calculators are most useful in primary prevention and are not intended for patients who have already had a heart attack, stroke, or heart failure event, as their risk is already considered high. Results should always be interpreted in the context of the patient's broader metabolic, genetic, and inflammatory profile, along with clinical judgment, rather than viewed in isolation.

Metabolic Risk

Glucose

Fasting glucose provides a direct measure of blood sugar after an overnight fast and reflects short-term glycemic control.

High glucose

- Mild elevations in the prediabetic range accelerate vascular aging, reduce arterial elasticity, and promote atherosclerosis through oxidative stress, endothelial dysfunction, and chronic inflammation. Insulin resistance, common in prediabetes, further contributes to these vascular changes.[15]
- Impaired fasting glucose (IFG) is defined by the American Diabetes Association (ADA) as 100–125 mg/dL (5.6–7.0 mmol/L) or a 2-hour oral glucose tolerance test (OGTT) of 140–199 mg/dL (7.8–11.1 mmol/L).
- The relationship between fasting glucose and CVD follows a J-shaped curve, with the lowest risk observed at 85–99 mg/dL. Glucose levels above 100 mg/dL progressively increased risk for ischemic heart disease, MI, thrombotic stroke, and cardiovascular mortality.[16]

Low glucose

- Hypoglycemia is often a side effect of insulin or oral hypoglycemic therapy. Severe or rapid drops in glucose can precipitate myocardial ischemia, arrhythmias, and increased cardiovascular stress.
- Hypoglycemia triggers catecholamine release (epinephrine, norepinephrine), causing vasoconstriction, platelet activation, increased myocardial oxygen demand, and endothelial stress.[17]
- Acute or recurrent hypoglycemia induces proinflammatory mediators and markers of vascular endothelial stress, especially in type 1 diabetes.[18]

Thus, monitoring glucose trends over time is essential for early identification of metabolic dysregulation and prevention of diabetes and CVD.

Glycated Serum Protein (GSP)

GSP reflects average blood glucose levels over a shorter duration, approximately 2 to 3 weeks, due to the shorter half-life of serum proteins compared with red blood cells. Unlike fasting glucose or HbA1c, GSP testing does not require fasting and can capture more acute fluctuations in glycemic control.

High GSP levels indicate recent hyperglycemia and are linked to increased oxidative stress, endothelial injury, and vascular inflammation, pathways that contribute to atherosclerosis and CVD.[19]

GSP measurement is particularly valuable in clinical scenarios where HbA1c may be unreliable, such as anemia, recent blood transfusion, or conditions affecting red blood cell turnover. It may also be advantageous in situations where maintaining a fasting state is impractical. Because of its sensitivity to short-term changes, GSP provides an additional tool for monitoring glycemic variability and cardiovascular risk, especially in patients with fluctuating glucose control or comorbid conditions that interfere with traditional glycemic markers.[15]

Hemoglobin A1c (HbA1c)

Normal: Below 5.7% **Prediabetes:** 5.7% to 6.4% **Diabetes:** 6.5% or higher

HbA1c **reflects average blood glucose levels over the past 2 to 3 months.** It provides insight into long-term glycemic control and is a well-established indicator of diabetes risk.

Maintaining HbA1c below 5.7% is generally considered optimal for cardiometabolic health however emerging evidence suggests that HbA1c functions as a continuous risk marker for cardiovascular outcomes. Analysis from the UK Biobank showed that cardiovascular risk nadirs at approximately HbA1c 5.0%, with risk increasing progressively above 5.4% for atherosclerotic CVD.[20] Studies indicate that individuals with HbA1c values between 5.5% and 6.5% represent a large segment of the population at elevated cardiovascular risk. Targeting early intervention within this range may offer substantial absolute risk reduction through lifestyle and metabolic optimization.[2]

Insulin

Insulin is a pancreatic hormone that regulates glucose uptake by allowing cells to utilize or store circulating glucose. When tissues such as the liver, adipose tissue, and skeletal muscle become less responsive to insulin stimulation, glucose uptake becomes impaired. In response, pancreatic β-cells increase insulin secretion, resulting in compensatory hyperinsulinemia.

Insulin resistance is largely an acquired condition driven by excess adiposity, though genetic predisposition contributes. Over time, it can progress to metabolic syndrome, metabolic dysfunction-associated steatotic liver disease (MASLD) which was previously called non-alcoholic fatty liver disease (NAFLD), or type 2 diabetes (T2D).

High fasting insulin often precedes dysglycemia and is strongly associated with cardiovascular risk, including atherosclerosis, hypertension, dyslipidemia, and pro-inflammatory states. **Lifestyle modification remains the cornerstone of management: calorie reduction and limiting high-glycemic carbohydrates help decrease insulin burden, while regular physical activity enhances insulin sensitivity and increases energy expenditure.[22]**

One of the key mechanisms behind the metabolic benefits of exercise is improved translocation of insulin-responsive glucose transporter type 4 (GLUT4). Muscle contractions stimulate GLUT4-containing vesicles to move to the cell membrane, increasing glucose uptake into skeletal muscle and adipose tissue. In a cohort of more than 87,000 women, engaging in vigorous exercise at least once per week was associated with a 33% lower risk of developing T2D, independent of BMI and other confounders, highlighting how physical activity directly improves insulin action and glucose regulation.[2]

C-peptide

C-peptide is a byproduct of proinsulin cleavage and serves as a stable, reliable marker of endogenous insulin production. Although insulin and C-peptide are secreted in equal amounts, their clearance differs: insulin is rapidly metabolized by the liver (~5 to 10 minutes), while C-peptide is cleared more slowly by the kidneys (30-35 minutes).[24] This slower clearance makes C-peptide a more stable indicator of pancreatic insulin output.

The primary indications for measuring C-peptide levels include evaluating fasting hypoglycemia associated with hyperinsulinism and assessing pancreatic insulin secretory reserve.[20]

Fasting hypoglycemia with hyperinsulinism: Helps determine whether insulin is endogenously produced by the pancreas or administered exogenously as an injection.

- **If C-peptide and insulin are elevated**, it indicates that the pancreas is the source of insulin.
- **If C-peptide is low or undetectable** and insulin in elevated, it likely reflects endogenous insulin since injected insulin does not contain C-peptide.[20]

Assessment of insulin secretory reserve: Provides insight into β-cell function and residual insulin production.

- **Low C-peptide** is associated with impaired β-cell function seen in type 1 diabetes, advanced T2D.25 This level of deficiency indicates limited insulin-producing capacity and if C-peptide levels are <0.6 ng/mL fasting, it may warrant insulin therapy.[20] [26]
- **Borderline low C-peptide** is associated with early T2D or partial recovery after interventions (lifestyle changes, medications, surgeries, or immunomodulatory treatments) that suggests restoration of insulin secretion capacity and may warrant further non-insulin therapies (metformin, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT2 inhibitors).
- **High C-peptide** has differential diagnoses including beta cell tumor (insulinoma), sulfonylurea therapy, insulin autoimmune syndrome (Hirata disease), or kidney disease affecting C-peptide clearance and may indicate insulin resistance in the context of hyperglycemia.[2]

Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)

HOMA-IR is a calculated index derived from fasting glucose and insulin levels, used to estimate the degree of insulin resistance. Insulin resistance is a central feature of metabolic syndrome and a key contributor to the development of T2D and CVD.

Lower HOMA-IR score suggests the cells are efficiently responding to insulin and can be observed in individuals with high insulin sensitivity (athletes, lean individuals)[27] however lower than normal HOMA-IR levels can be associated to inadequate insulin production[28] or low fasting glucose due to

- dietary (short-term very low-carbohydrate diets in adults with overweight, obesity, or T2D[29] malnutrition[30] or low caloric intake[31]) or
- physiological factors (weight loss[32] adrenal insufficiency-lack of cortisol has been shown to increase insulin sensitivity[33] or medications lowering insulin secretion).

Higher HOMA-IR score suggests a greater level of insulin resistance and increased cardiometabolic risk.

Paradoxically, long-term low carbohydrate diets in healthy adults were observed to have higher HOMA-IR values[34] HOMA-IR is particularly useful in early detection before overt hyperglycemia occurs, allowing for earlier intervention. **Improving insulin sensitivity through exercise, weight loss, and anti-inflammatory diets can significantly reduce cardiovascular risk.**[35]

Adiponectin

Adiponectin is an anti-inflammatory, insulin-sensitizing hormone secreted by adipose tissue.

Higher levels of adiponectin are associated with a lower risk of atherosclerosis, T2D, and CVD.

Low adiponectin levels are commonly seen in obesity, insulin resistance, and metabolic syndrome. Adiponectin enhances endothelial function and inhibits the progression of plaque in arterial walls. Increasing adiponectin through exercise, and consumption of monounsaturated fats may help improve metabolic health and reduce cardiovascular risk.[36]

Metabolic Factors

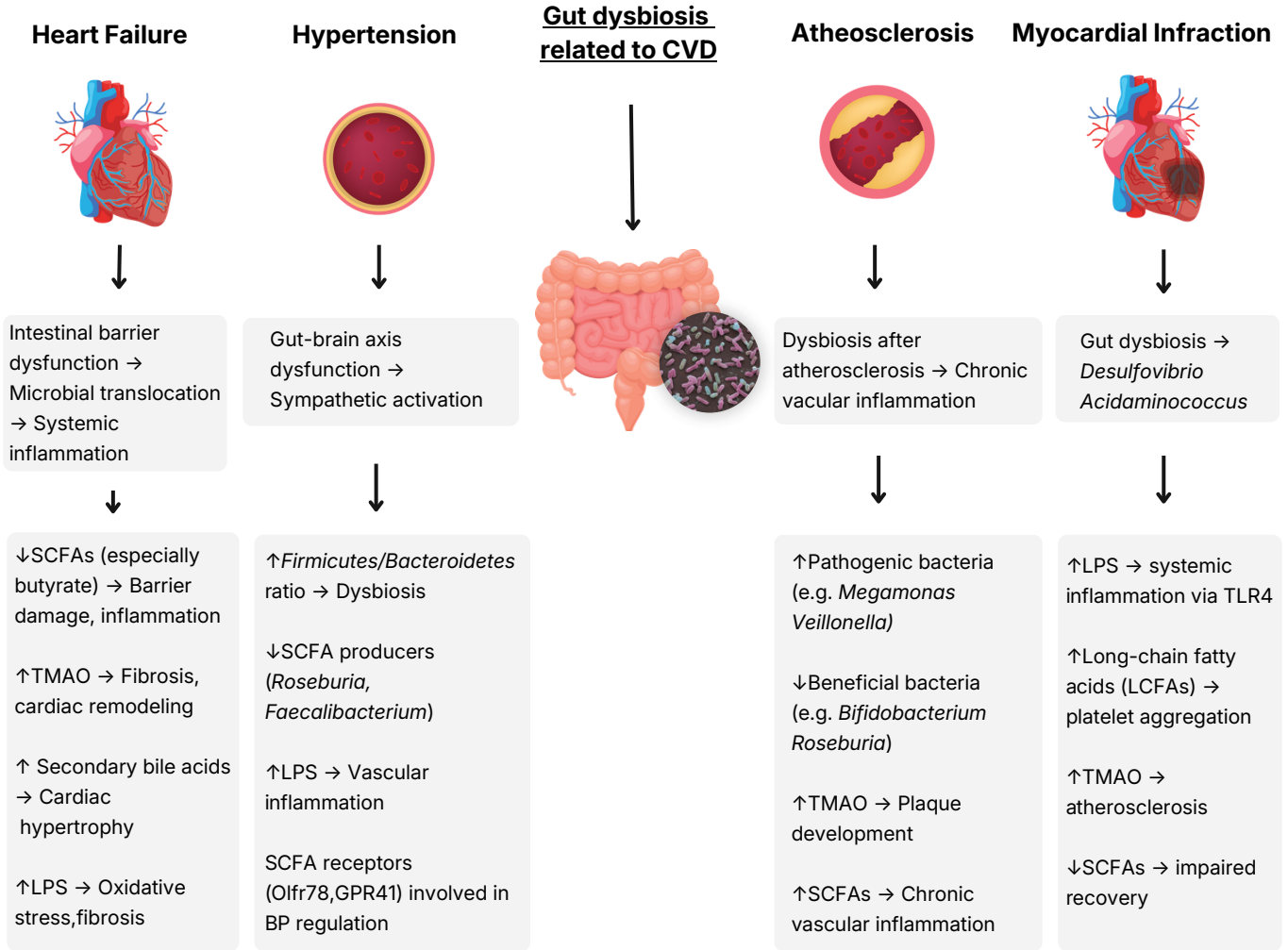


Figure 2. *Gut dysbiosis and cardiovascular diseases.*
Source: Muttiah B, Hanafiah A.Gut Microbiota and Cardiovascular Diseases: Unraveling the Role of Dysbiosis and Microbial Metabolites.Int J Mol Sci. 2025;26(9):4264. Published 2025 Apr 30. doi:10.3390/ijms26094264

Trimethylamine N-oxide (TMAO)

TMAO is a metabolite produced by gut microbiota from dietary substrates such as choline, phosphatidylcholine, L-carnitine, and betaine, commonly found in red meat, eggs, liver, fish, and poultry. Individual differences in gut microbiota composition strongly influence TMAO production, with certain bacterial species (e.g., Clostridia, Proteus, Shigella, Acinetobacter, Prevotella) converting these precursors into TMA, which is subsequently oxidized to TMAO in the liver.

High TMAO levels have been linked to increased cardiovascular risk, including atherosclerosis, MI, stroke, and endothelial dysfunction, likely through mechanisms involving impaired cholesterol transport, enhanced vascular inflammation, and prothrombotic signaling. TMAO levels may also reflect diet, gut dysbiosis, and gut barrier integrity, and high concentrations have been associated with renal toxicity and proinflammatory responses.[37]

Dietary and lifestyle interventions can modulate TMAO concentrations. Reducing intake of TMAO precursors, increasing fiber consumption, and supporting a healthy gut microbiome may help lower circulating TMAO and potentially reduce cardiovascular risk. Conversely, certain healthy foods such as saltwater fish may contribute to elevated plasma TMAO despite overall cardiovascular benefits, underscoring the importance of interpreting TMAO levels in the context of diet and individual microbial profiles.[38]

L-Carnitine

L-carnitine is essential for transporting long-chain fatty acids into mitochondria for β-oxidation, supporting ATP production and normal cardiac energetics. Adequate levels help maintain mitochondrial efficiency, limit oxidative stress, and support vascular function.[39]

Low L-carnitine may reflect insufficient intake, malabsorption, chronic illness, or increased metabolic demand. Clinically, low levels can impair myocardial energy production and contribute to fatigue, reduced exercise tolerance, and impaired cardiac recovery.[40]

High L-carnitine may result from diets rich in red meat, supplemental use, or metabolic imbalance. In individuals with gut dysbiosis, excess L-carnitine is converted into trimethylamine (TMA), which the liver oxidizes to TMAO, a metabolite associated with atherosclerosis progression and higher long-term cardiovascular risk.[41]

Despite the rise in TMAO, some research indicates that L-carnitine supplementation did not significantly affect other CVD markers like LDL cholesterol in certain healthy populations, suggesting the relationship is complex and may not be a simple cause-and-effect scenario.[42]

The dichotomy suggests the possibility that in patients recovering from an acute MI, L-carnitine may have ‘protective’ effects in the short-term but long-term risk-enhancing effects on atherosclerosis, particularly if administered via high-dose supplements. Thus, it may be beneficial for myocardial energy production and recovery, yet potentially pro-atherogenic when chronically elevated, especially in the context of unfavorable gut microbial metabolism. Given the pro-atherogenic pathway, the net clinical benefit of L-carnitine must be carefully weighed against its cardioprotective effects.[43]

Ferritin

Ferritin is an intracellular iron-storage protein that also rises as an acute-phase reactant in the presence of systemic inflammation.

High ferritin is associated with higher cardiovascular and metabolic risk due to its links with oxidative stress, insulin resistance, and chronic inflammation, all of which accelerate endothelial injury and atherogenesis.

However, ferritin elevation can result from iron overload or inflammatory processes, and distinguishing between these is critical for accurate assessment. Interpreting ferritin alongside inflammatory markers (e.g., hs-CRP) helps differentiate the two:[44]

- **High ferritin with normal hs-CRP** suggests true iron accumulation
- **High ferritin with elevated hs-CRP** is more likely driven by inflammation
- Additional markers, such as transferrin saturation and soluble transferrin receptor, can further clarify iron status.

Low ferritin may indicate iron deficiency, which can impair oxygen delivery and cardiac function, particularly in patients with heart failure.[45]

Leptin

Leptin is an adipokine secreted by adipose tissue that **regulates satiety, energy balance, and metabolic signaling.**

High leptin, commonly seen in obesity and insulin resistance, reflects leptin resistance and is associated with increased sympathetic activity, vascular inflammation, and a higher risk of hypertension and atherosclerosis.[46]

Leptin deficiency or resistance is associated with dysregulation of cytokine production, increased susceptibility to infections, autoimmune disorders, malnutrition, and inflammatory responses.[47]

Hepatic Function

Emerging evidence suggests a crucial bidirectional relationship between cardiovascular and liver health. MASLD is associated with various metabolic syndromes, including obesity, diabetes, and dyslipidemia, which are common risk factors for CVD.[48]

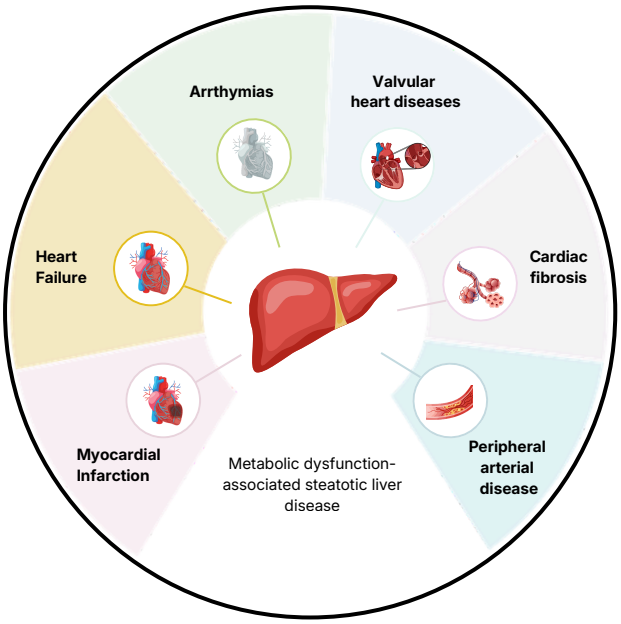


Figure 3. *Cardiovascular complications associated with metabolic dysfunction-associated steatotic liver disease. Image from https://pmc.ncbi.nlm.nih.gov/articles/PMC12304865/*

Alanine Aminotransferase (ALT) / Aspartate Aminotransferase (AST)

ALT and AST are liver enzymes, with ALT predominantly found in the liver, but both can be found in other tissues such as the kidneys, heart, and muscle cells.

Low ALT levels are generally not a concern but may be due to vitamin B6 deficiency, malnutrition, or CKD.[49]

High ALT levels indicates definite liver cell injury due to multiple factors.[50]

- **Physiological:** extreme physical exertion, diurnal variation – nadir at 4:00 hr and peak at 16:00 hr, sex – higher in makes than females due to hormones, ethnicity – higher in Mexican Americans, genetic SNP rs3826795, higher body fat mass index)
- **Pathological:** Metabolic dysfunction-associated fatty liver disease (MAFLD), Metabolic dysfunction-associated steatohepatitis (MASH), chronic hepatitis B or C, autoimmune hepatitis, alpha-1 antitrypsin deficiency, drug associated-, occupational exposure-, or herbal supplement-induced liver injury, hemochromatosis, Wilson disease, Celiac disease, ischemic hepatitis, Budd-Chiari syndrome, vascular disease, genetically related conditions affecting the liver.

Additionally, patients with higher ALT levels have a significantly greater risk of future cardiovascular events, even when traditional lipids are normal.[51]

Elevations in AST may be alcohol-related (in patients with alcohol use disorder, AST to ALT ratio is generally at least 2:1, steatohepatitis, cirrhosis, or non-hepatic (hemolysis, myopathy, thyroid disease, exercise).52

Other possible considerations for elevated ALT and AST are:

- Medications, including but not limited to NSAIDs, antibiotics, statins, anti-seizure drugs, acetaminophen, allopurinol, anti-tuberculosis drugs, statins, antifungals, antidepressants, antipsychotics, and antivirals.[48]

Clinical Pearl

In patients with elevated ALT and AST, evaluate intake of dietary supplements containing curcumin. Elevated ALT and AST can be seen in curcumin-induced liver injury.[53] In a 2025 clinicopathological series of 11 patients with turmeric supplement–associated hepatitis, most patients (91%) showed predominantly elevated transaminases, while only one patient had a primary elevation in alkaline phosphatase. Liver function tests returned to normal in all patients after stopping turmeric supplements, although some required additional corticosteroid treatment.[54]

GGT (Gamma-Glutamyl Transferase)

GGT is an enzyme central to glutathione metabolism and antioxidant defense, and elevated serum levels reflect increased oxidative stress and hepatic metabolic load. Its distribution is abundant in liver, kidney, pancreas, intestine, and prostate. It is more specific for biliary disease when compared to alkaline phosphatase because it is not present in bone.[48]

High GGT promotes endothelial dysfunction and atherosclerosis, and is associated with insulin resistance, hypertension, dyslipidemia, and subclinical vascular stress.[55] Notably, GGT often rises **before traditional cardiovascular risk markers** such as cholesterol, fasting glucose, or obesity, making it an early indicator of cardiometabolic risk.[56]

High GGT is associated with hepatitis, cirrhosis, NAFLD, cholestasis, alcoholic liver disease, and liver metastases, congestive heart failure, coronary artery disease, obstructive sleep apnea, systemic lupus erythematosus, diabetes, obesity, certain cancers (prostate, breast, lung, gastrointestinal), oxidative stress, infection (*Cytomegalovirus, Epstein-Barr)*.[57] High GGT, along with AST, suggests alcohol abuse however GGT should not be used alone since it is not very specific for alcohol.[48]

Low GGT is a associated with knee-joint degenerative disease, gastric cancer, anemia, renal cyst, cervical cancer, and preeclampsia.[58]

Cholestasis

Cholestasis is impaired bile flow, whether intrahepatic (e.g., primary biliary cholangitis, primary sclerosing cholangitis, drug-induced liver injury) or extrahepatic (e.g., gallstones, malignancy).

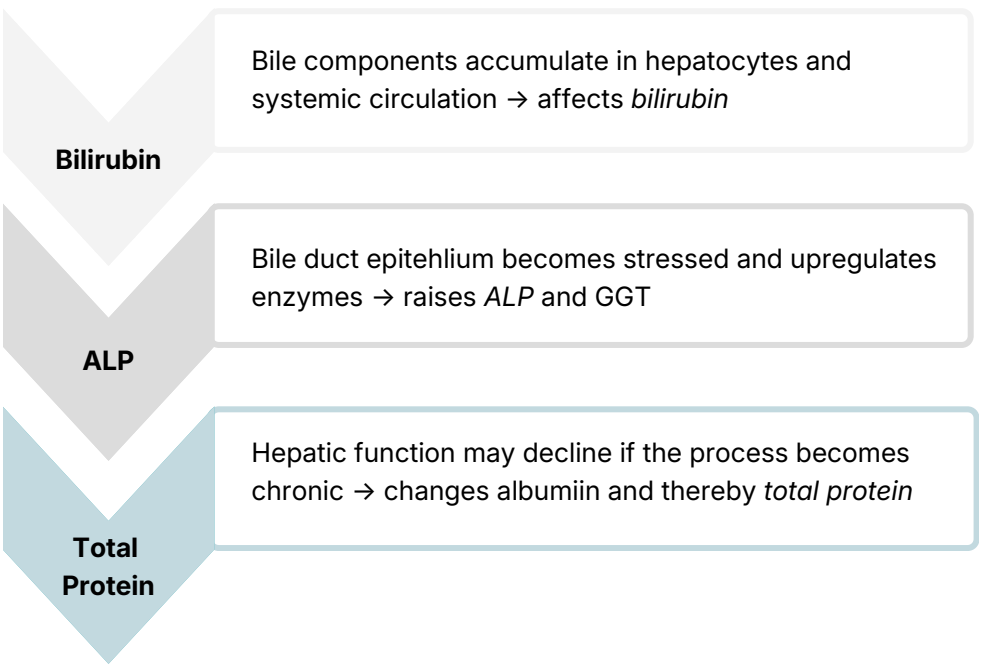


Figure 4. *Relationship of bilirubin, ALP, and total protein*

Bilirubin (Total)

Bilirubin is a potent antioxidant byproduct of heme metabolism. After bilirubin is produced from heme breakdown, it is water-insoluble, so the liver must conjugate it with glucuronic acid to make it water-soluble for safe excretion into bile. This conjugation step prevents bilirubin from accumulating in tissues and enables its elimination through the biliary tract and intestine.

Total bilirubin measures the combined amount of unconjugated and conjugated bilirubin.

High unconjugated bilirubin deposits itself into tissues, leading to jaundice, the yellow discoloration of skin and sclerae, whereas **high conjugated bilirubin** is indicative of cholestasis and liver/biliary pathology.

Alkaline Phosphatase (ALP)

ALP is an enzyme that helps break down proteins and aids chemical reactions in the body. It is present in all tissues, but highest in the liver, bile ducts, bones, intestines, and placenta.

High ALP in vascular tissue can contribute to CVD, particularly in conditions marked by oxidative stress such as CKD. Higher ALP activity also **promotes vascular calcification**, which allows calcium salts to accumulate in arterial walls, resulting in arterial stiffness and endothelial dysfunction, both central to atherosclerosis progression. ALP **promotes inflammatory cytokines** in vascular tissue, amplifying vascular smooth muscle cell calcification and inflammatory signaling, which together **worsen plaque formation** and may influence plaque instability.[59] Additionally, transient hyperphosphatasaemia is associated with concurrent infections in over 60% of cases, particularly gastrointestinal (GIT) infections.[48]

Low ALP is less common than having an elevated level but may indicate malnutrition, zinc or magnesium deficiency, hypothyroidism, and rare genetic conditions including hypophastasia, and Wilson disease.[60]

Total Protein

Total protein blood test measures the total amount of protein in blood, including albumin and globulins, to check liver and kidney health, nutritional status, and immune function, with albumin being the most abundant plasma protein, representing 50-60% of the plasma's total protein content. [61] [62]

Low total protein often reflects autoimmune diseases (e.g. celiac, Crohn's), infection, inflammation, increased metabolism, kidney disease, liver disease, malnutrition.[63]

High total protein is generally associated with amyloidosis, dehydration, hepatitis B, hepatitis C, HIV/AIDS, monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, infections or inflammation. A high protein diet doesn't cause high blood protein.[64]

Renal Function

I**n recent years, a growing body of evidence has revealed a close and bidirectional relationship between renal function and CVD. Impaired renal excretion can lead to the accumulation of metabolic waste, which may adversely affect cardiovascular function.** In addition, the kidneys and cardiovascular system jointly regulate blood pressure, fluid balance, and metabolic homeostasis. As such, renal dysfunction is not only a frequent comorbidity of CVD but may also act as a precipitating factor in its development.[65]

For example, **the Renin-Angiotensin-Aldosterone-System (RAAS) is a crucial mediator of cardiac, vascular, and renal physiology through regulating vascular tone and salt and water homeostasis.** In addition to the main physiological functions, the RAAS has a significant role in the pathophysiological conditions of hypertension, heart failure, other CVD, and renal diseases.[66]

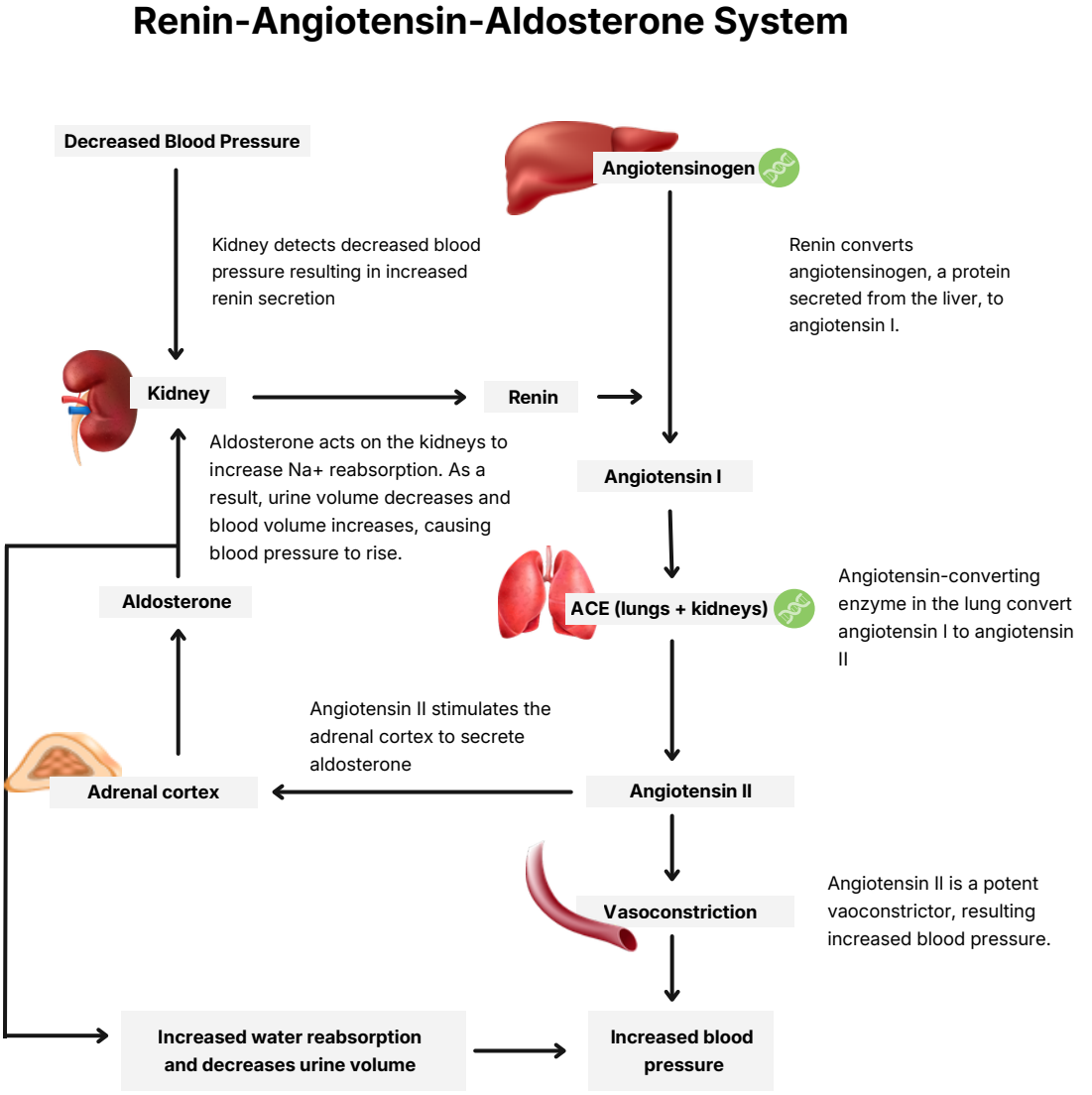


Figure 5. *This figure illustrates the Renin-Angiotensin-Aldosterone (RAAS), a key hormonal pathway that maintains blood pressure and fluid balance.*

Sodium

Sodium is an extracellular cation for nerve and muscle function and a vital electrolyte for fluid balance. While healthy kidneys normally manage excess sodium, **excess sodium intake** in those with CKD may have fluid retention, raised blood pressure, and strained kidneys, leading to swelling, heart issues, and faster disease progression, making sodium restriction a key treatment. Normal blood volume is maintained via the RAAS that adjusts sodium excretion to regulate extracellular fluid volume and arterial blood pressure.[67]

Generally, while reducing sodium intake may help maintain healthy blood pressure, some studies reported that a very low sodium intake (<2g/day) has been associated with an elevated risk of heart attack, stroke, and higher CVD mortality.[68] This may be due to scenarios where lowering salt too much may be harmful because it activates RAAS, triggering the production of hormones that could have harmful cardiovascular effects such as more vasoconstriction. Due to the controversy of ideal sodium intake, a cautious approach may be appropriate.

Potassium

Serum potassium is essential for maintaining normal electrical activity in the heart. Potassium helps set the resting membrane potential and controls the timing of repolarization, which allows heart muscle cells to reset between beats. When potassium levels fall below or rise above the normal range, electrical conduction becomes unstable, leading to a higher risk of life-threatening arrhythmias.

High potassium (hyperkalemia) is often caused by acute and chronic kidney disease but may also be associated with excessive dietary potassium in those with impaired kidney function, hemolysis, rhabdomyolysis, metabolic acidosis, sepsis, dehydration, and insulin deficiency, as seen in diabetic ketoacidosis.[69]

Dietary surveys consistently show that people in the United States consume less potassium than recommended, leading to a dietary potassium gap where there is a significant deficit between the recommended daily intake (3,400 mg and 2,600mg for males and females aged 19-50 years and older, respectively) is lower than the average intake of potassium consumption (3,016 mg and 2,320 mg for men and women aged 20 years and older, respectively.[70]

Low potassium (hypokalemia) increases the excitability of cardiac cells and interferes with normal repolarization which may lead to

- Higher risk of ventricular arrhythmias - When the heart becomes overly excitable, it can trigger rapid or chaotic rhythms that impair pumping and may lead to cardiac arrest.
- A prolonged QT interval which means the heart takes longer than normal to reset electrically between beats. This creates an unstable period where dangerous rhythms can be initiated.
- Increased sensitivity to digoxin, a cardiac medication that increases contractility and slows conduction. Hypokalemia allows digoxin to bind more strongly to heart cells, raising the risk of toxicity. Digoxin toxicity can trigger severe arrhythmias, including life-threatening ventricular rhythms.
- Possible worsening of hypertension since hypokalemia promotes vasoconstriction and impairs sodium excretion, both of which contribute to higher blood pressure.
- Common causes of hypokalemia are diuretic therapy (loop or thiazide), gastrointestinal losses, poor intake, hyperaldosteronism, and renal potassium-wasting conditions.
- Even mild hypokalemia can be linked to a 2.1-fold increased stroke risk and 32% increased mortality risk.[71]

Chloride

Serum chloride is a major extracellular anion essential for maintaining osmotic pressure, fluid balance, and renal function. In contrast to sodium, which primarily reflects water balance and vasopressin activity, chloride exerts broader effects on neurohormonal activation, acid–base regulation, renal tubular function, and diuretic responsiveness.[72]

Hyperchloremia often indicates metabolic acidosis (e.g., severe diarrhea and diabetic ketoacidosis [DKA]), whereas hypochloremia is commonly associated with metabolic alkalosis (caused by vomiting or diuretic use). These changes in chloride levels can reflect shifts in volume status, renal handling, or underlying metabolic disturbances, making it a useful marker in evaluating both cardiovascular and renal health.[73]

Low Chloride (hypochloremia), is frequently observed in heart failure (HF) patients treated with loop diuretics, and is independently associated with adverse outcomes, diuretic resistance, and arrhythmic risk.[68]

Notably, patients with low chloride levels often fall into two distinct profiles.

- Low chloride and low sodium, typically due to fluid overload and dilution.
- Low chloride with normal sodium, suggesting true depletion, often from diuretics, and is frequently accompanied by elevated bicarbonate and low potassium levels. This second group may be especially prone to diuretic resistance and arrhythmias, highlighting the importance of recognizing these biochemical patterns to guide treatment.[68]

High Chloride (hyperchloremia) often has iatrogenic causes such as chloride-rich intravenous fluids, which may provoke renal vasoconstriction through tubuloglomerular feedback and increase metabolic demands at the cellular level. Experimental data also implicate chloride dysregulation in myocardial electrical disturbances and an increased risk of sudden cardiac death.[68]

Carbon Dioxide (Bicarbonate / CO_2)

Carbon dioxide (measured as total CO_2, mostly in the form of bicarbonate ion) reflects the body's acid–base balance and is tightly regulated by the kidneys, lungs, and buffering systems. When blood pH deviates from normal, the kidneys and lungs collaboratively regulate acid–base balance by adjusting bicarbonate reabsorption/excretion and CO_2 elimination/retention to restore homeostasis.[74]

- **Low bicarbonate/CO_2** from metabolic disturbances, such as kidney disease, diarrhea, or ketoacidosis, impairs the acid–base buffer system and promotes endothelial dysfunction, activates RAAS, vascular calcification, and may increase long-term cardiovascular risk.[70] [75] [76]
- **High bicarbonate** typically reflects metabolic alkalosis due to vomiting, diuretic use, volume depletion, or mineralocorticoid excess. While high bicarbonate is less directly linked to cardiovascular events, alkalosis-driven electrolyte shifts may increase susceptibility to arrhythmias and exacerbate hypertension.[77]

Glucose (Renal/Glycosuria)

High urine glucose (glycosuria) occurs when glucose is excreted in the urine, usually because blood glucose exceeds the renal threshold or due to impaired tubular reabsorption. The most common cause is hyperglycemia from uncontrolled diabetes, which promotes oxidative stress, endothelial dysfunction, and inflammation, all of which increase CVD risk.[78] Other causes include renal tubular disorders (e.g., Fanconi syndrome), certain medications (like SGLT2 inhibitors), or acute stress hyperglycemia. Persistent glycosuria in diabetes reflects poor glycemic control, which is associated with higher rates of heart attack, stroke, and heart failure.

Low or absent glucose in the urine is typically normal and indicates proper renal glucose handling. Rarely, low glycosuria may occur in hypoglycemia, prolonged fasting, or congenital tubular defects that increase glucose reabsorption. In contrast to high glycosuria, low urinary glucose is generally not linked to cardiovascular risk, unless it reflects severe systemic hypoglycemia or restrictive glucose availability in metabolic disease.

BUN (Blood Urea Nitrogen)

BUN measures a waste product from protein breakdown, indicating kidney function

- **High BUN** levels are associated with increased CVD risk through both direct toxic effects and as a marker of impaired kidney function. Urea acts as a uremic toxin that promotes endothelial dysfunction, vascular smooth muscle cell apoptosis, oxidative stress, and systemic inflammation through gut barrier disruption, can modify proteins and contributes to atherosclerosis and vascular damage.[79] Regarding impaired kidney function, high BUN levels may suggest that your kidneys aren't working as they should and may be due to high protein-diet, dehydration, again (infants and children have lower BUN), medications (carbamazepine, methotrexate, tetracycline, burns, urinary tract blockage, stress, heart attack, upper GI bleeding. [80] [81]
- **Low BUN** is uncommon but may occur in low-protein diet, small body type, overhydration, or liver disease.[7]

Extreme levels (high and low) can also be associated to higher risk of ischemic stroke.[82]

Creatinine (Cr)

Creatinine is used to assess kidney function. The muscles use creatine to supply the muscles with energy and in this process, breaks down muscle tissue to release the waste product, creatinine, into the bloodstream. Typically, the kidneys can filter out creatinine, but in kidney dysfunction, this may lead to elevated creatinine levels.

- **High creatinine** levels indicate reduced kidney function (decreased eGFR). For every 5 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ decrease in eGFR below 60, there is a 14% higher risk of coronary heart disease, independent of traditional cardiovascular risk factors. Lower eGFR and higher albuminuria are independently associated with increased risk of cardiovascular mortality, heart failure, stroke, and coronary disease, with individuals with CKD more likely to die from cardiovascular events than progress to kidney failure. The mechanisms include both traditional shared risk factors (hypertension, diabetes, dyslipidemia) and kidney-specific factors such as chronic inflammation, protein-energy wasting, mineral and bone disorders, endothelial dysfunction, and accumulation of uremic toxins. High creatinine may be due to high protein intake, creatine supplementation, high intensity exercise, high muscle mass, medications.[83]
- **Low creatinine** is associated with high eGFR and can be considered beneficial but may reflect reduced muscle mass (from aging, malnutrition, or vegetarianism, or liver issues, sarcopenia. It is important to note that while low creatinine itself isn't a direct mechanism of cardiovascular risk, these associated conditions, such as sarcopenia (age-related muscle loss) and frailty, are increasingly recognized as significant risk factors for poor cardiovascular outcomes, including heart failure and mortality. [84] Low creatinine may be due to low protein intake, low muscle mass, pregnancy, muscle wasting, severe liver disease.[79]

BUN/Creatinine Ratio

The BUN/Creatinine ratio is used to assess kidney function, hydration status, and nitrogen balance. It helps differentiate pre-renal, renal, and post-renal causes of altered kidney markers when BUN and creatinine are interpreted together rather than in isolation.

- **High BUN/Creatinine ratio** signals poor kidney blood flow, often due to heart failure (HF) or dehydration, indicating increased cardiovascular risk and worse outcomes, reflecting neurohormonal activation, decreased cardiac output, and kidney congestion, making it a key prognostic marker for severe cardiac issues and mortality. Common causes include dehydration, hypovolemia, heart failure or reduced cardiac output, increased protein catabolism (high protein diet-GI bleed, corticosteroid use, reduce renal perfusion due to hypotension or vascular disease.[85] In cardiovascular populations, persistently high ratios are associated with worse prognosis, especially in acute and chronic heart failure.[86]
- **Low BUN/Creatinine ratio** indicates reduced urea production or disproportionate creatinine elevation. This may be due to liver dysfunction (impaired urea synthesis), low protein intake or malnutrition, overhydration, supernormal excretion of urea as in sickle cell anemia, increased creatinine production as in rhabdomyolysis, or more effective removal of urea than creatinine during dialysis.[87]

At all stages of renal insufficiency, creatinine is a much more reliable indicator of renal function than BUN because BUN is far more likely to be affected by dietary and physiologic conditions not related to renal function.[83]

eGFR (Estimated Glomerular Filtration Rate)

eGFR estimates kidney filtration capacity and is used to screen, diagnose, and stage CKD. It reflects how efficiently the kidneys filter waste products from the blood and maintain fluid, electrolyte, and hormonal balance.

- **Low eGFR** is an independent predictor of CVD, heart failure, and mortality due to its impact on endothelial function, inflammation, and vascular health. It indicates reduced kidney function caused by hypertension, diabetes, atherosclerotic or nephrotoxic damage, and is associated with increased risk of MI, stroke, heart failure, and cardiovascular mortality.[88]
- **Normal or high eGFR** is generally protective; falsely high values may occur in glomerular hyperfiltration from early diabetes, obesity, high-protein intake, or pregnancy, which may increase future cardiovascular risk.[89] [90] Persons with low muscle mass have higher eGFR based on creatinine alone than eGFR based on creatinine and cystatin C.[91]

eGFR (African American)

This marker is similar to eGFR but is adjusted for individuals of African American descent. Race-based eGFR coefficients have been widely re-evaluated; major nephrology organizations, such as the national Kidney Foundation (NKF) now recommend race-neutral reporting or the newer Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations that avoid race as a modifier because race-based adjustments can delay diagnosis and affect access to care. Clinicians should interpret eGFR in context, and when race-based values are reported, consider confirming with cystatin C or race-neutral eGFR equations.[92]

Serum Osmolality

Osmolality measures the solute concentration in the blood, influenced by sodium, glucose, and urea and reflects the body's water-electrolyte balance and the ability to maintain proper plasma concentration.

- **High osmolality** can result from dehydration, hyperglycemia, kidney dysfunction, or uremia, leading to vascular stress, endothelial dysfunction, and hypertension.[93]
- **Low osmolality** may occur with overhydration, hyponatremia, or syndrome of inappropriate antidiuretic hormone secretion (SIADH), potentially contributing to fluid overload and cardiac stress.[94]

Uric Acid

Uric acid is a waste product created when the body breaks down purines.

- **High uric acid (hyperuricemia)** is associated with endothelial dysfunction, inflammation, and oxidative stress, hypertension, diabetes mellitus, and dyslipidemia, which are well known to be related to risk factors for coronary artery disease (CAD). Causes include reduced renal excretion (CKD), high purine diet, or metabolic syndrome. Hyperuricemia is also the biochemical precursor to gout. Recent imaging technology has revealed that deposition of crystals can occur in the coronary arteries as well as the joints.[95] The Mediterranean, DASH and plant-based diets are naturally lower purine intake and have been associated with reduced uric acid levels and may be beneficial as an adjuvant therapy in the management of hyperuricemia.[96] [97]
- **Low uric acid** is less common but may be due to genetic disorders, Fanconi syndrome, diabetes, anti-gout drugs, pregnancy, malnutrition, and family history of hypouricemia.[98]

Cystatin C

Cystatin C is an alternative marker of kidney function that is less influenced by muscle mass. It has noted to identify cardiovascular risk better than creatinine-based estimates across multiple outcomes including incident CVD, CVD mortality, all-cause mortality, and heart failure due to its ability to detect subclinical kidney dysfunction, direct involvement in atherosclerotic processes, and stronger associations with inflammation and vascular pathology.[99] [100]

- **High cystatin C** indicates impaired filtration and is strongly linked to increased CVD risk due to CKD-related microvascular damage and may be due to lower eGFR, inflammation, diabetes, lower serum albumin.[101]
- **Low cystatin C** is rare and usually reflects high eGFR (hyperfiltration), which may occur with high-protein meals, pregnancy, early diabetes mellitus, polycystic kidney disease, sickle cell anemia, high altitude renal syndrome and obesity.[102]

Redox Risk

Oxidative stress occurs when the production of reactive oxygen species (ROS) exceeds the body's antioxidant and repair capacity, resulting in damage to lipids, proteins, DNA, and RNA. Nitrosative (or nitrative) stress is a related but distinct process caused by excess reactive nitrogen species (RNS), which promotes protein nitration, disrupts normal cellular signaling, and impairs mitochondrial function.

Redox risk reflects the overall balance of oxidative and nitrosative activity in relation to the body's antioxidant and redox-regulating capacity, and therefore represents the patient's functional risk for impaired cellular signaling, metabolic dysfunction, and reduced physiological resilience.

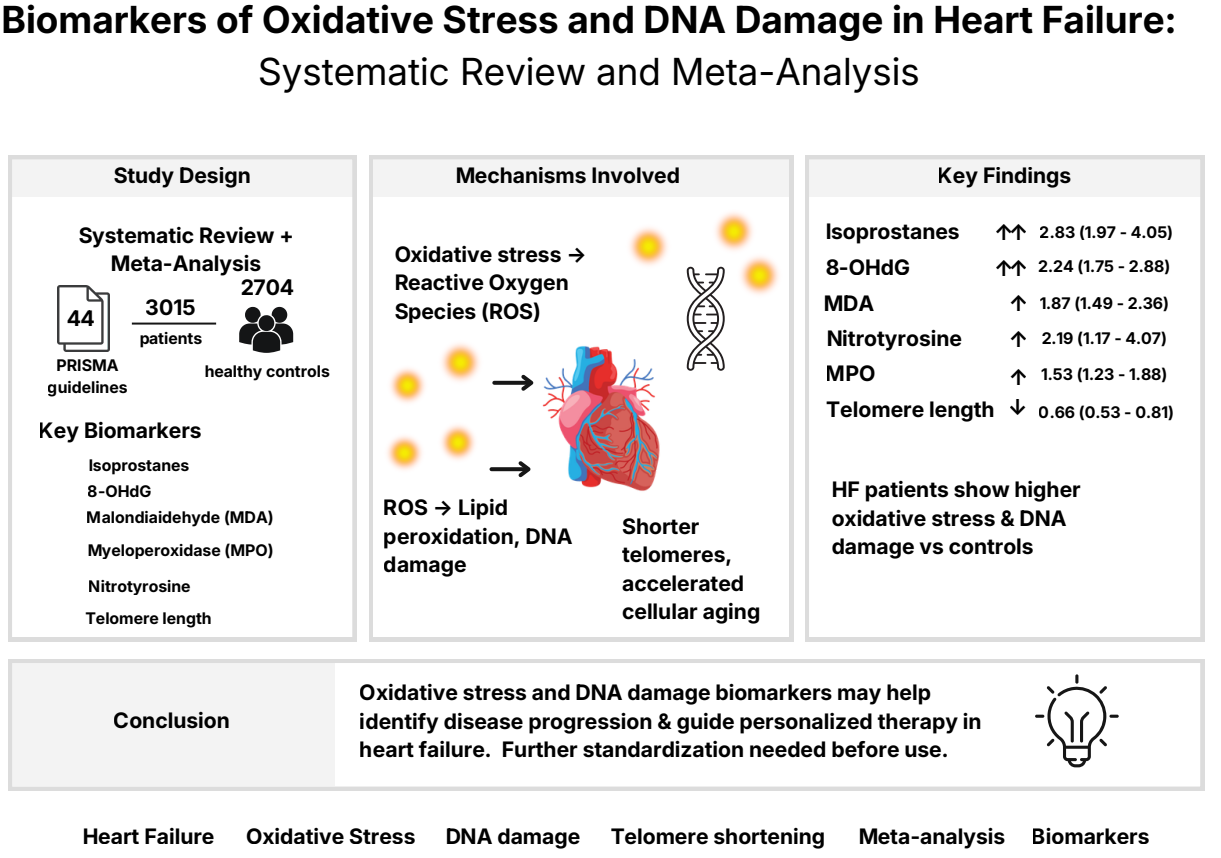


Figure 6. *Biomarkers of Oxidative Stress and DNA Damage in Heart Failure. Milani F, Porreca A, Rosano G, Vitiello L, Volterrani M, Russo P, Bonassi S. Oxidative Stress and DNA Damage Biomarkers in Heart Failure: A Systematic Review and Meta-Analysis. Antioxidants. 2025; 14(10):1249. https://doi.org/10.3390/antiox14101249*

8-OHdG (8-Hydroxy 2-Deoxyguanosine)

8-OHdG reflects oxidative damage to DNA. Measuring 8-OHdG provides insight into the body's oxidative burden and can guide the use of antioxidants or lifestyle changes aimed at reducing oxidative damage and supporting vascular integrity.[103]

High 8-OHdG indicates more reactive oxygen species (ROS) activity, mitochondrial dysfunction, and impaired antioxidant defenses, conditions that accelerate atherosclerosis, endothelial injury, plaque instability, and cardiometabolic disease. Causes include chronic inflammation, smoking, diabetes/insulin resistance, toxin exposure, and high oxidative burden.[104]

F2-Isoprostane

F2-Isoprostanes are one of the more stable products of lipid peroxidation, making it a reliable marker of oxidative stress.[105]

High F2-isoprostane signals oxidative injury to cell membranes, which drives endothelial dysfunction, LDL oxidation, vascular stiffness, and hypertension, key contributors to CVD. Causes include smoking, obesity, metabolic syndrome, chronic inflammation, and poor antioxidant capacity.[106]

Malondialdehyde

Malondialdehyde (MDA) is a byproduct of polyunsaturated fatty acid peroxidation and serves as a direct indicator of oxidative damage to cell membranes.

High MDA is associated with endothelial dysfunction, LDL oxidation, and accelerated atherosclerosis, making it a meaningful biomarker of redox-driven cardiovascular risk. Higher MDA concentrations have also been observed in individuals with hypertension, diabetes, and coronary artery disease, where oxidative stress contributes to plaque initiation and instability.[107] [101]

Nitrotyrosine

Nitrotyrosine forms when peroxynitrite (ONOO–) reacts with tyrosine residues, making it a marker of nitrosative stress and endothelial dysfunction.

High nitrotyrosine impairs nitric oxide (NO) signaling, reduce vasodilation, and promote vascular inflammation which can worsen hypertension, insulin resistance, and atherosclerosis. This may be due to chronic inflammation, high oxidative burden, diabetes, and mitochondrial dysfunction.[108]

3-Chlorotyrosine

3-Chlorotyrosine is produced when myeloperoxidase (MPO) reacts with tyrosine residues.

High chlorotyrosine reflects MPO-driven oxidative stress, which oxidizes LDL, damages endothelium, destabilizes plaques, and strongly increases cardiovascular event risk. Causes include neutrophilic inflammation, smoking, infections, chronic inflammatory disease, and active atherosclerotic plaque biology.[109]

Urine Creatinine

Urine creatinine is used to normalize oxidative-stress markers to account for urine concentration.
*See **Creatinine** under the Renal Function Panel for causes of high and low values.*

Omega Fatty Acids

EPA (Eicosapentaenoic Acid)

EPA is an omega-3 fatty acid primarily derived from marine animals such as fatty fish. Humans can convert the plant omega-3, alpha-linolenic acid (ALA), into EPA, but the conversion rate is low and variable (1-5% efficiency).[110] EPA is associated with anti-inflammatory and anti-thrombotic effects that help reduce triglycerides, stabilize plaques, and improve endothelial function, mechanisms strongly associated with lower CVD risk.[111] [112]

- **High EPA** typically reflects high omega-3 intake or supplementation and is generally cardioprotective.
- **Low EPA** indicates insufficient omega-3 intake, poor conversion from ALA, competitive suppression by excess omega-6 fatty acids, or high oxidative stress, contributing to a pro-inflammatory lipid environment and higher CVD risk.[106] [113]

DPA (Docosapentaenoic Acid)

DPA is an intermediary omega-3 fatty acid formed when ALA or EPA is metabolized and contributes to anti-inflammatory lipid mediators and supports vascular repair and endothelial health.[114]

- High DPA generally reflect adequate omega-3 status and are associated with reduced cardiovascular mortality. Because DPA can retroconvert to EPA, it may serve as an additional reservoir for cardioprotective omega-3 activity.[110]
- Low DPA often occurs with low intake of marine omega-3s, metabolic stress, or impaired elongation/desaturation pathways, contributing to a more pro-inflammatory lipid profile and increased CVD risk.[109] [110]

LA (Linoleic Acid)

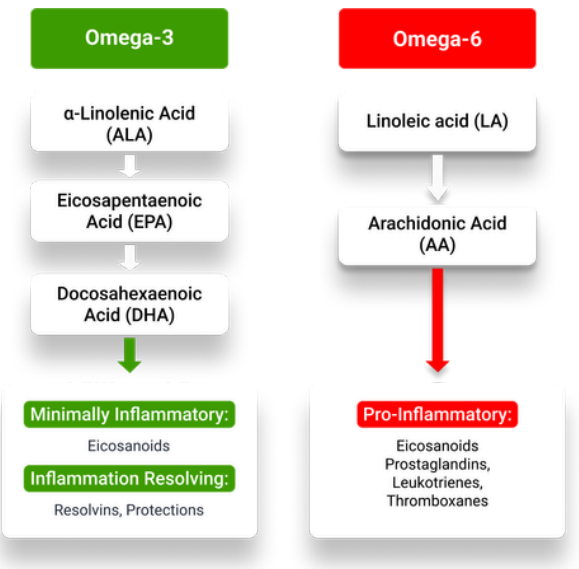
Linoleic acid (LA) is an essential omega-6 fatty acid critical for cell membrane structure, lipid metabolism, and inflammation modulation.

- **Within normal physiological ranges**, LA intake and circulating levels are consistently associated with reduced LDL-C, improved metabolic health, and lower CVD risk.[115] [116] LA itself does not promote inflammation, however, when LA intake is high relative to insufficient omega-3 status, eicosanoid pathways may shift toward greater arachidonic acid production. This imbalance in the omega-6:omega-3 ratio can contribute to a more pro-inflammatory setting, promoting oxidative stress, endothelial dysfunction, and lipid instability in high-risk patients.[117] [118]
- **High LA:** The primary cause of high linoleic acid levels is increased consumption of seed oils and other vegetable oils, which have become the predominant sources of dietary fat in Western diets, with the standard American diet containing 14 to 25 times more omega-6 fatty acids than omega-3 fatty acids, with the majority of omega-6 coming from LA.[119]
- **Low LA:** often reflects very low-fat diets, malabsorption,[120] or high oxidative stress.[121]

AA (Arachidonic Acid)

AA is a long-chain omega-6 fatty acid that serves as a precursor to both pro-inflammatory and pro-resolving eicosanoids. **Maintaining AA within an optimal range, rather than excessively suppressing it, is important for physiological immune function.[111]**

- **When AA is disproportionately elevated**, it may indicate a pro-inflammatory lipid environment that accelerates atherogenesis. Elevated AA can contribute to vascular inflammation, platelet activation, and endothelial injury, increasing cardiovascular risk, especially when EPA/DHA are low.[122]
- **Low AA** may result from low omega-6 intake, impaired elongation/desaturation, statin or anti-inflammatory medication use, or metabolic dysfunction; overly low levels impair membrane repair and eicosanoid balance and may reflect poor overall fatty acid status.[109]



AA/EPA

The AA/EPA ratio reflects the balance between pro-inflammatory (AA-derived) and anti-inflammatory (EPA-derived) eicosanoids.

- **High AA/EPA ratio** indicates dominance of arachidonic-acid pathways, promoting platelet activation, vasoconstriction, endothelial dysfunction, and atherosclerotic progression, clear contributors to cardiovascular risk. Causes include low omega-3 intake, high omega-6 intake, chronic inflammation, insulin resistance, and metabolic dysfunction.123 Strategies to reducing the omega-6/3 ratio include reductions in the intake of refined omega-6 seed oil, and increasing the intake of marine omega-3s, either through dietary means or supplementation.[124]
- **Low AA/EPA ratio** reflects higher EPA availability and a more anti-inflammatory lipid environment, generally associated with reduced CVD risk.[125] Very low ratios may occur with high-dose omega-3 supplementation.

Omega-6 Total

Total omega-6 reflects combined intake and metabolism of omega-6 fatty acids (mainly LA and AA). Within physiological ranges, adequate omega-6 intake, especially LA, is linked to lower LDL-C and reduced cardiovascular risk.[126]

*See **Linoleic Acid and Arachidonic Acid** for causes of high and low values.*

Omega-3 Total

Total omega-3 represents combined levels of ALA, EPA, DPA, and DHA.
Note: Vibrant currently does not measure ALA.

*See **EPA, DPA,** and **DHA** for causes of high and low values.*

Total omega-3 measurements in **plasma** or **serum** reflect more recent dietary intake and are influenced by acute consumption patterns. These measurements provide absolute concentrations but are less standardized and more variable than the omega-3 index.[127]

Note that Vibrant reports cellular fatty acids levels within red blood cells (RBC), which are generally considered more stable and reflective of longer-term nutrient status compared to serum and plasma measurements.

Omega-3 Index

Omega-3 Index (EPA + DHA % of RBC fatty acids)

The Omega-3 Index measures the percentage of EPA and DHA in the red blood cell membranes, expressed as a percentage of the total fatty acids in the RBCs, and serves as a long-term indicator of omega-3 status.

- Low omega-3 index (<4%) reflect poor long-term omega-3 status and are linked with higher inflammation, increased platelet reactivity, and membrane instability.[128]
- Omega-3 index ≥8% is associated with lower risk of sudden cardiac death, arrhythmias, heart failure, and overall CVD mortality. High index values typically result from consistent intake of fatty fish or omega-3 supplementation and are generally protective.

- Very high omega-3 index levels may occasionally occur with high-dose supplementation. Recent studies indicate these levels are not associated with excessive anticoagulation or a clinically significant increased risk of bleeding or clotting.[129]

The omega-3 index is best measured when assessing CVD risk, monitoring long-term omega-3 status, or guiding supplementation strategies. It is particularly useful because it correlates inversely with total mortality, cardiovascular events, stroke, and directly with complex brain functions.

Endothelial Dysfunction

NO is essential for blood vessel health because it signals the vascular smooth muscle to relax, causing vasodilation and improving blood flow and oxygen delivery to tissues. NO also helps protect the endothelium by inhibiting platelet aggregation, reducing vascular inflammation, and limiting abnormal smooth muscle proliferation, all of which lower the risk of hypertension and atherosclerosis.[130]

NO is produced by nitric oxide synthase (NOS) using **L-arginine** as the primary substrate, generating **L-citrulline** as a byproduct. Citrulline can then be recycled back to arginine to sustain NO production. **Homoarginine** can also serve as a weaker alternative substrate for NOS, and may enhance NO bioavailability.

ADMA directly inhibits the production of NO by blocking the endothelial NOS enzyme from converting the precursors into NO, whereas **SDMA** indirectly limits NO production by competing with arginine transport into cells, reducing substrate availability.[131]

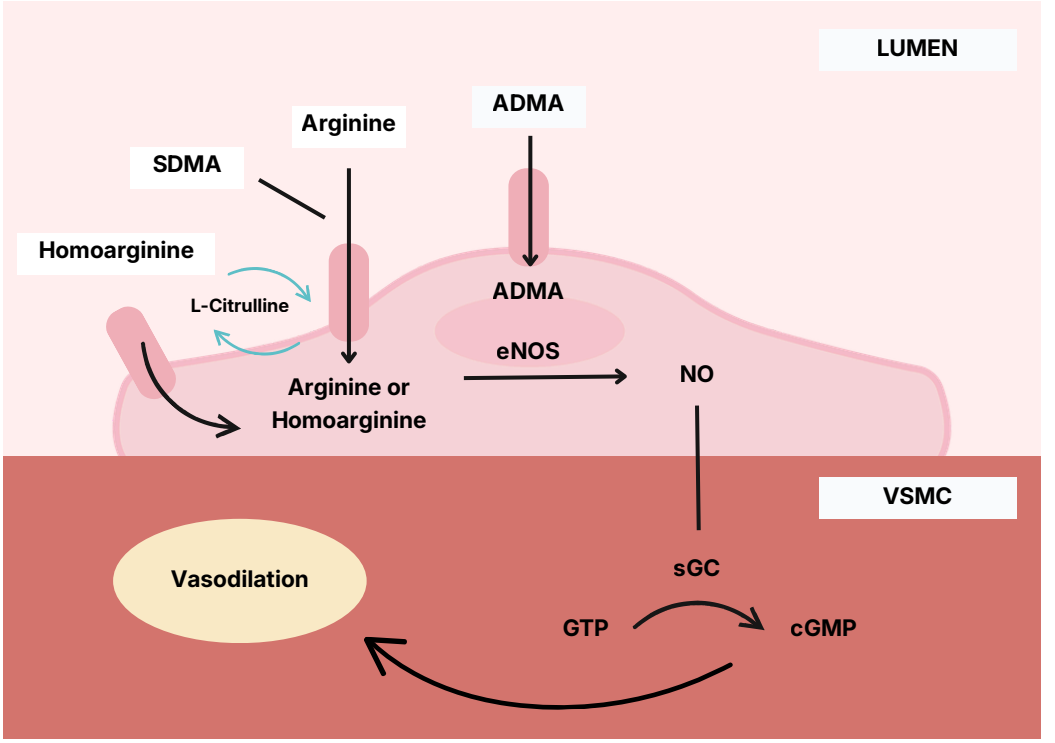


Figure 7. *Overview of Nitric Oxide (NO) Metabolites. Mortensen KM, Itenov TS, Stensballe J, et al. Changes in nitric oxide inhibitors and mortality in critically ill patients: a cohort study. Ann Intensive Care. 2024;14(1):133. Published 2024 Aug 27. doi:10.1186/s13613-024-01362-7*

Asymmetric Dimethylarginine (ADMA)

ADMA is a byproduct of protein breakdown via the enzyme Dimethylarginine Dimethylaminohydrolase (DDAH), thus when DDAH activity is low (due to oxidative stress or inflammation) ADMA can accumulate. Once arginine enters the cell, ADMA directly inhibits NOS enzymatic activity by competing with L-arginine at the enzyme's active site, which reduces NO production, promoting vasoconstriction, endothelial dysfunction, arterial stiffness, inflammation, and thrombosis.

High ADMA may arise from oxidative stress, renal dysfunction, inflammation, insulin resistance, and reduced ADMA metabolism. [132] [133] [134]

Symmetric Dimethylarginine (SDMA)

SDMA is a byproduct of protein breakdown excreted by the kidneys and competes with L-arginine for cationic amino acid transporters (CAT), thereby limiting substrate availability for NOS.

High SDMA is associated with impaired NO production, endothelial dysfunction, and elevated cardiovascular risk, especially in renal impairment. Causes include reduced renal clearance, inflammation, oxidative stress, and high protein breakdown.[130] [131] [132]

Homoarginine

Homoarginine is a structural analog of L-arginine that can also be used by NOS to produce NO.

- **High homoarginine** is generally considered protective.[135] Elevations typically occur with high protein intake or supplementation.
- **Low homoarginine** is linked to endothelial dysfunction, T2D, arterial stiffness, heart failure progression, and higher cardiovascular mortality. Causes include low dietary lysine, low protein intake, impaired metabolic synthesis, kidney disease, and chronic inflammation.

Arginine

Arginine is the most nitrogen-rich amino acid and is the primary substrate for NO synthesis, a molecule critical for vasodilation, inhibition of platelet aggregation, and overall endothelial health.[136] Adequate arginine levels support proper vascular tone and immune function. However, in conditions with elevated ADMA or SDMA, arginine utilization may be impaired.[137]

- **High arginine** is usually favorable and supports NO production but can rise with supplementation or reduced catabolism.
    - **Clinical pearl:** Elevated arginine does not necessarily increase NO production excessively. The primary concern with arginine excess relates to hemodynamic effects from NO-mediated vasodilation rather than nitrosative stress.[138] Studies of arginine supplementation at doses of 3-8 g/day have shown these levels to be safe without causing acute pharmacologic effects.[139]

- **Low arginine** reduces NO availability, promoting endothelial dysfunction, hypertension, and impaired vascular repair. Causes include stress from trauma, burn injury, small-bowel resection, and renal failure, inflammation, high arginase activity, metabolic syndrome, and inadequate dietary intake.[140] [141] [142] Several studies suggest that arginine supplementation in healthy subjects does not lead to a significant increase in NO production.[135]

Citrulline

Citrulline is the precursor to arginine. NOS also produces citrulline as a byproduct when converting arginine to NO, and this citrulline can be recycled back to arginine, creating a local substrate regeneration pathway. L-Citrulline has more availability than L-arginine as an NO precursor because of its high intestinal absorption.[143] [144]

L-citrulline's systemic effects positively impact hypertension, atherosclerosis, inflammation, insulin resistance, T2D, and CVD. Emerging evidence also suggests that L-citrulline itself can positively impact skeletal muscle and adipose tissue to improve metabolic syndrome[145] Watermelon has been noted to be a rich food source of citrulline.[142]

- **High citrulline** may be caused by citrullinemia type I and II, compromised renal function, other genetic conditions (lysinuric protein intolerance and dihydrolipoamide dehydrogenase deficiency)[146] [147]
- **Low citrulline** may be associated with reduced enterocyte mass since citrulline is mainly synthesized by small bowel enterocytes. This may be caused by short bowel syndrome, villous atrophy diseases (e.g. celiac, Crohn's), mucosal damage from chemotherapy and radiotherapy, intestinal mucositis, acute rejection in intestinal transplantation, critical illnesses and sepsis.[148] [149]

Arginine/ADMA

This ratio reflects the balance between NO substrate (arginine) and NO inhibitor (ADMA).

- **Low arginine/ADMA ratio** suggests impaired NO bioavailability, higher oxidative stress, and increased cardiovascular risk despite normal standalone biomarker values. However, even when arginine levels are adequate, elevated ADMA can suppress NO synthase activity, leading to endothelial dysfunction, vasoconstriction, and atherosclerotic progression. Thus, this ratio can be clinically useful for identifying patients who have the metabolic appearance of sufficient arginine yet remain NO-deficient due to elevated endogenous NOS inhibition. Specifically, cardiovascular patients with increased ADMA plasma levels could be the best target of arginine supplementation.[135]
- **High arginine/ADMA** ratio signifies favorable NO production capacity and is generally cardioprotective; elevations often reflect high arginine levels or low ADMA burden.

Arginine/SDMA

The arginine/SDMA ratio reflects the balance between arginine availability for NO production and SDMA-mediated reduction in arginine transport into endothelial cells.

- **Low arginine/SDMA ratio** suggests impaired intracellular arginine delivery and decreased NO generation, contributing to vascular stiffness, hypertension, and microvascular dysfunction. SDMA may not appear as potent as ADMA when evaluated alone, but in ratio form, it reveals functional transport limitations that increase cardiometabolic and renal-linked CVD risk. This ratio is valuable for detecting endothelial stress earlier than traditional lipid markers.
- **High arginine/SDMA ratio** indicates stronger NO potential and is generally beneficial, often due to higher arginine intake or low SDMA levels.

Homoarginine/ADMA

The homoarginine/ADMA ratio evaluates the counterbalance between homoarginine, a weak NO substrate associated with vascular protection, and ADMA, a strong NO inhibitor linked to atherosclerosis.

- **Low homoarginine/ADMA ratio** suggests impaired NO-dependent endothelial signaling and have been associated with increased cardiovascular and all-cause mortality. This ratio helps identify patients with dual-risk patterns, low vascular substrate and high NOS inhibition, which is more predictive than either marker alone. Clinically, it highlights individuals who may have accelerated vascular aging or plaque vulnerability despite otherwise normal lipid findings.
- **High homoarginine/ADMA ratio** reflects enhanced NO capacity and is generally cardioprotective.

Homoarginine/SDMA

The homoarginine/SDMA ratio reflects the interaction between vascular NO substrate (homoarginine) and disrupted arginine transport (SDMA).

- **Low homoarginine/SDMA ratio** indicates greater endothelial transport limitation, decreased NO generation, and heightened oxidative and inflammatory vascular stress. This pattern is associated with hypertension, kidney-linked endothelial dysfunction, and elevated cardiovascular risk. The ratio is particularly helpful in patients with renal involvement, because SDMA rises early in renal impairment and can amplify endothelial dysfunction even when other markers appear controlled.
- **High homoarginine/SDMA ratio** suggests favorable NO bioavailability and may indicate robust amino-acid metabolism and renal clearance.

Lipids and Ratios

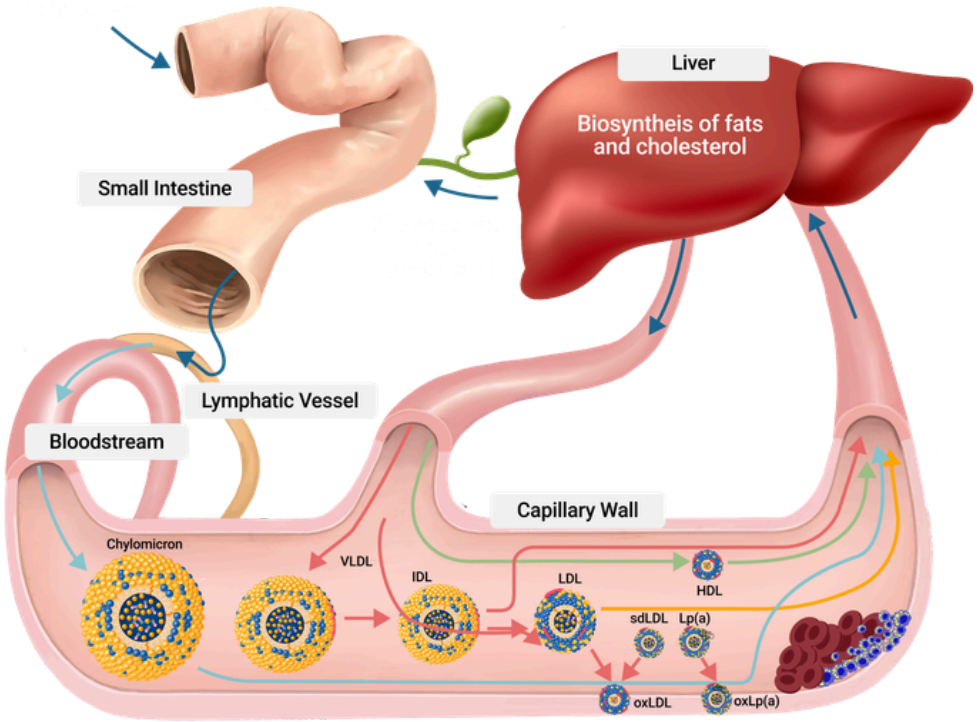


Figure 8. *Journey of dietary fats and cholesterol through digestion, absorption, and circulation. It highlights the formation of different lipoproteins (chylomicrons, CLDL, LDL, HDL, and Lp(a)) and their roles in cholesterol transport, and how oxidized LDL contributes to plaque formation and accumulation*

Cholesterol

Cholesterol can be introduced into the blood exogenously through the diet or endogenously. Approximately 30% of cholesterol comes from dietary sources and remaining 70% of body cholesterol being produced by the liver.[150] [151]

It is important to note that dietary cholesterol content alone does not significantly influence plasma cholesterol values.[152] It is only one of several dietary factors that can influence serum cholesterol levels. Others include saturated fatty acids, trans fatty acids, soluble fiber, and total caloric intake.[153]

Individual responses vary considerably, with some people being "hypo-responders" and others "hyper-responders" based on genetically determined intestinal cholesterol absorptive capacity. However, saturated and trans fats generally have larger and more predictable effects on blood cholesterol than dietary cholesterol itself.

When measuring total cholesterol, this marker represents the sum of all circulating cholesterol carried by lipoproteins, including LDL, VLDL, and HDL.

High total cholesterol levels are associated with increased cardiovascular risk primarily when driven by LDL-rich particles. ***Refer to causes of high LDL.***

Elevated total cholesterol's **predictive value is enhanced when considered alongside ratios or other lipid fractions**, as patients with normal TC may still harbor significant residual risk. **Persistent elevation** signals the need for comprehensive evaluation of lipid metabolism and potential lifestyle or pharmacologic interventions.

Triglycerides (TG)

Triglycerides are the most common type of fat in the body and reflect circulating lipids used for energy storage and transport via VLDL particles.

- **High TG** increases cardiovascular risk, especially when combined with low HDL or high sdLDL, by promoting endothelial dysfunction, and postprandial lipemia.
- Associated conditions with elevated triglyceride levels include diabetes mellitus, hypothyroidism, chronic renal failure, pancreatitis, bulimia, obesity, excessive alcohol intake, lipodystrophy, glycogen storage disease, ileal bypass surgery, pregnancy, systemic lupus erythematosus, monoclonal gammopathy, multiple myeloma, lymphoma, pregnancy, and certain drugs including estrogen, isotretinoin, β-blockers, glucocorticoids, bile acid–binding resins, thiazides, and protease inhibitors.[154]

High-Density Lipoprotein, Direct

HDL is known as "good cholesterol" because it facilitates reverse cholesterol transport, removing excess cholesterol from tissues and blood vessels, and has anti-inflammatory, antioxidant, and endothelial-protective effects.

Low HDL is associated with higher cardiovascular risk and occurs with insulin resistance, overweight, obesity, smoking, inflammation, metabolic syndrome, and genetic factors (familial hyperlipidemia, ApoA1 deficiency, Tangier disease) or medications (beta blockers, certain hormones such as high dose androgens and progestins, diuretics)[155] [156] [157]

Non-HDL-C

Non-HDL-C represents all atherogenic remnants such as LDL, VLDL, IDL, and Lp(a).
Note: Vibrant currently does not report VLDL and IDL separately; however, they are included in the measurement of non-HDL-C

High non-HDL-C reflects the full burden of the cholesterol transported in atherogenic lipoproteins, it is crucial to prediction of CVD risk and it is closely associated with plaque progression. Several meta-analyses found that non-HDL-c correlated more closely with cardiovascular risk than LDL-c, both at baseline and during therapy.[158]

It is particularly useful in hypertriglyceridemic patients, where LDL-C may underestimate total atherogenic particle load.[159]

- When serum triglycerides exceed ~300 mg/dL (3.36 mmol/L), the Friedewald formula for estimating LDL-C is LDL-C = TC – HDL-C – (TG ÷ 5) but becomes unreliable. This is because, at these triglyceride levels, VLDL particles carry proportionally more triglyceride and less cholesterol, so the fixed 'TG ÷ 5' factor no longer reflects true VLDL-cholesterol. As a result, the calculated LDL-C often substantially underestimates the actual atherogenic lipoprotein burden.
- However, when triglycerides are markedly elevated, typically >400–500 mg/dL,160 the cholesterol content of these particles becomes increasingly variable, and apoB may provide a more accurate measure of total atherogenic particle number than any cholesterol-based estimate.[157]

Low-Density Lipoprotein, Direct

LDL is commonly referred to as "bad cholesterol" due to its central role in the development of atherosclerosis. The liver usually processes two-thirds of the circulating LDL.[161] LDL transports cholesterol to tissues, and when present in excess, it can deposit cholesterol into arterial walls, leading to plaque formation.

However, measurement of LDL cholesterol levels alone is not sufficient to assess cardiovascular risk. Approximately 40% of persons with coronary heart disease have a total cholesterol level of less than 200 mg per deciliter (5.2 mmol per liter). Conversely, many persons with a moderate elevation in LDL cholesterol level never have a clinical cardiovascular event.[162]

LDL Direct is often considered superior to calculated LDL-C because LDL Direct measures LDL cholesterol **directly in the blood sample**, whereas calculated LDL-C (commonly using the Friedewald equation) calculates LDL from other lipid values (total cholesterol, HDL-C, and triglycerides), which introduces potential error.

The Friedewald formula assumes a fixed relationship between triglycerides and VLDL, which becomes inaccurate when **triglycerides are elevated (>400 mg/dL), very low LDL levels are present, or in non-fasting samples.**

Studies also show that calculated LDL-C frequently underestimates LDL levels in high-risk patients, potentially affecting cardiovascular risk classification and treatment decisions. Because of these limitations, direct LDL measurement can improve **patient classification and clinical decision-making** in lipid management.

Small Dense LDL (sdLDL)

Small Dense LDL (sdLDL) particles are a subfraction of LDL that are more atherogenic due to their smaller size, have increased susceptibility to oxidation, and a greater ability to penetrate the endothelium.

High sdLDL occurs with insulin resistance, high TG, metabolic syndrome, and diabetes. Even when total LDL-C is normal, high sdLDL may signal hidden risk.[163]

Lipoprotein (a) (Lp(a))

Lp(a) is an LDL-like particle with an added apolipoprotein(a) component, making it more atherogenic and prothrombotic. A 2024 study e**stimated Lp(a) to be six times more atherogenic than LDL on a per particle basis.**[164] Additionally, studies estimate that Lp(a) can be 70 to 90% or more **genetically** determined, thus, unlike other lipids, this genetic determination means Lp(a) levels remain stable throughout a person's lifetime after age five and are minimally affected by fasting status, diet, or environmental factors.[165]

Elevated Lp(a) is an independent risk factor for coronary artery disease, aortic stenosis, and stroke. Identifying elevated Lp(a) is critical for refining cardiovascular risk stratification, especially in individuals with a strong family history of heart disease.

Non-genetic influences that may cause

- Increases in Lp(a) can be observed in inflammatory states (including acute infections such as the influenza), pregnancy, hypothyroidism, growth hormone therapy, and kidney disease.
- Lowered Lp(a) levels have been observed during severe acute-phase illness, with postmenopausal hormone replacement therapy, in hyperthyroidism, and in liver disease. For this reason, testing during a clinically stable period is recommended to support more accurate interpretation.[166]

Lp(a) testing may also be useful to explain less-than-expected LDL-C reduction with statins, since statins do not lower Lp(a) levels, but when these are elevated, the cholesterol content of Lp(a) contributes significantly to calculated and directly measured LDL-C.[166] [167] [168] Thus, *overall* risk can still be meaningfully improved by addressing modifiable markers such as ApoB and LDL-C, which are responsive to diet and lifestyle interventions.

Apolipoprotein A-1 (ApoA1)

ApoA1 is the main protein component of HDL and plays a central role in reverse cholesterol transport and antioxidant defense.

Higher ApoA1 levels generally reflect efficient cholesterol clearance and are associated with reduced risk of atherosclerosis, commonly driven by strong HDL metabolism or exercise.[169]

Apolipoprotein B (ApoB)

ApoB is the primary protein component on all atherogenic lipoproteins (including LDL, VLDL, IDL, and Lp(a)).Each atherogenic particle carries one ApoB molecule, making ApoB a more accurate count of the number of cholesterol-containing particles than LDL-C alone.

Elevated ApoB levels are strongly associated with a higher risk of cardiovascular events, even when traditional lipid panels appear normal. Causes include insulin resistance, high TG, genetic dyslipidemia, or high refined-carbohydrate intake.[170]

Lipid Ratios

Total Cholesterol/ High Density Lipoprotein Cholesterol (TC/HDL-C)

This ratio reflects the balance of total cholesterol versus cardioprotective HDL.

High ratios predict increased cardiovascular risk by indicating higher atherogenic burden relative to HDL-mediated clearance.

This ratio often predicts cardiovascular events more reliably than total cholesterol alone because it incorporates both risk-promoting and protective components. It has also been noted that at any LDL-C level, individuals with an elevated TC/HDL-C ratio remained at substantially higher risk of developing CHD.[171]

Triglycerides/Very Low Density Liproprotein- Cholesterol (TG/VLDL-C)

Very low-density lipoprotein (VLDL) is produced by the liver to transport triglycerides (primary cargo) and cholesterol to tissues throughout the body. Considered a “bad” cholesterol, high VLDL-C contributes to plaque buildup, atherosclerosis, and cardiovascular risk. VLDL-C breaks down into LDL, making it a key component of lipid metabolism. The TG/VLDL-C ratio estimates how triglyceride-rich the VLDL particles are.

A **high** ratio either indicates that

- Triglycerides are higher relative to cholesterol within the VLDL-C particle, or
- A greater proportion of cholesterol relative to triglycerides within the VLDL-C particle

The ratio highlights qualitative changes in lipoproteins composition as the liver packages and clears triglycerides from the VLDL particles, and may be a marker of metabolic stress such as insulin resistance, fatty liver, or inflammation.[172] [173] **Interpreting it alongside other lipid and metabolic markers provides insight into hidden atherogenic risk before overt abnormalities develop.**

Apolipoprotein B / Apoliprotein A-1 (ApoB/ApoA-1)

The ApoB/ApoA-1 ratio compares the number of atherogenic particles (ApoB) to protective HDL particles (ApoA-1), providing a robust measure of atherogenic risk.

High ratios strongly predict cardiovascular events and reflect an imbalance favoring cholesterol deposition over removal. This ratio often outperforms traditional cholesterol ratios in predicting myocardial infarction and cardiovascular mortality.[174] It is particularly useful in patients with discordant lipid panels, where ApoB and ApoA-1 better capture residual risk.[175]

HDL-C/TG

The HDL-C/TG ratio integrates protective HDL and pro-atherogenic triglyceride levels into a single metric of metabolic health.

High HDL-C/TG suggests efficient TG metabolism, strong HDL function, and lower cardiovascular risk.

PARTICLE SIZE TESTING

Vibrant does not use NMR (nuclear magnetic resonance)-based lipoprotein particle size testing. Large prospective cohort studies, including the Multi-Ethnic Study of Atherosclerosis (MESA) and the Framingham Offspring Study, show that while LDL particle number (LDL-P) is associated with atherosclerotic cardiovascular disease (ASCVD) risk, LDL particle size adds little to no incremental risk prediction once LDL-C, non-HDL-C, and apolipoprotein B (ApoB) are known.

ApoB directly reflects the total number of atherogenic particles (including VLDL, IDL, LDL, and lipoprotein(a)) and is therefore a more biologically aligned and clinically actionable marker of particle burden.[176] [177]

For this reason, multiple cardiology societies now recommend ApoB in preference to particle size testing, citing its lower cost, high analytical reproducibility, standardized methods, and independence from proprietary technologies.[178] [179] Importantly, LDL size patterns themselves do not independently drive disease, and in routine clinical practice, NMR particle size results rarely change management when ApoB and standard lipid markers are already available.

Ceramides and Ratios

Ceramides are bioactive sphingolipids that play essential structural and regulatory roles in human cells. In addition to supporting cell membrane integrity, they function as signaling molecules that **regulate inflammation, programmed cell death, endothelial function, and lipid and glucose metabolism.**

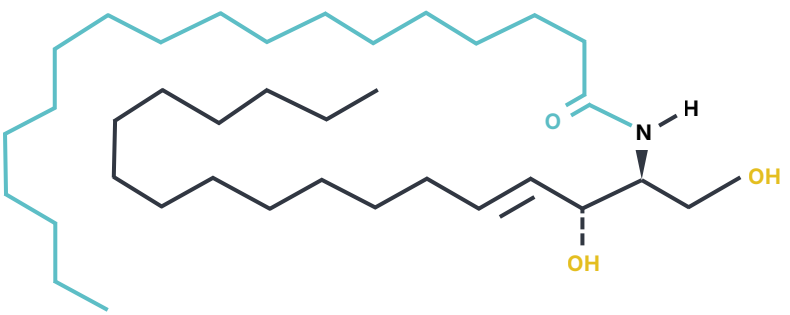
Note on topical ceramides: *Ceramides used in skincare and cosmetic products are applied to the skin to restore the epidermal barrier and retain moisture. Studies indicate that topical ceramides do not significantly enter systemic circulation and therefore do not impact blood ceramide levels or cardiovascular risk.*[180] [181]

Ceramides are composed of a sphingosine backbone and a fatty acid chain. For example, Figure 8 depicts Cer(d18:1/18:0), with a sphingosine backbone containing 18 carbons and one double bond (d18:1) and a fatty acid chain containing 18 carbons with no double bonds (18:0). Structural differences in chain length and saturation are clinically important because they determine biological activity and cardiovascular risk.

Cer (d18:1/d18:0)

sphingosine backbone (d18:1 = 18 carbons,1 double bond)

fatty acid chain (18:0 = 18 carbons,no double bonds)



Structural Formula	Shorthand notation	Relative Risk Level
Cer(d18:1/16:0)	Cer(16:0)	Strongest adverse risk signal
Cer(d18:1/18:0)	Cer(18:0)	Elevated Risk
Cer(d18:1/24:1)	Cer(24:1)	Intermediate risk
Cer(d18:1/24:0)	Cer(24:0)	Lowest Risk

Figure 8. Ceramide(d18:1/18:0) Structure

Elevated circulating ceramides primarily reflect endogenous production within the liver, adipose tissue, and vascular cells.

Higher ceramide concentrations, particularly the shorter chain ceramides, **Cer(16:0) and Cer(18:0), are the primary pro-inflammatory and lipotoxic species** that are consistently associated with inflammation, insulin resistance, obesity, endothelial dysfunction, atherosclerotic plaque progression, and future cardiovascular events, even in individuals with normal LDL-C, triglycerides, or ApoB, supporting the role of ceramides as independent and complementary risk markers.[182] [183] [184]

Studies have demonstrated that high-fat diets containing krill oil and DHA/EPA supplementation may lower liver Cer(16:0) and serum Cer(18:0), and Cer(24:0) while increasing liver Cer(24:0).[185]

Cer (d18:1/16:0)

Ceramide (d18:1/16:0), also known as C(16:0) ceramide, is one of the most pro-inflammatory and pro-atherogenic ceramide species.[185]

High Cer (16:0) is associated with increased risk of coronary artery disease, insulin resistance, and metabolic dysfunction. C(16:0) ceramide contributes to mitochondrial dysfunction and promotes vascular cell apoptosis, both of which accelerate plaque formation and instability.

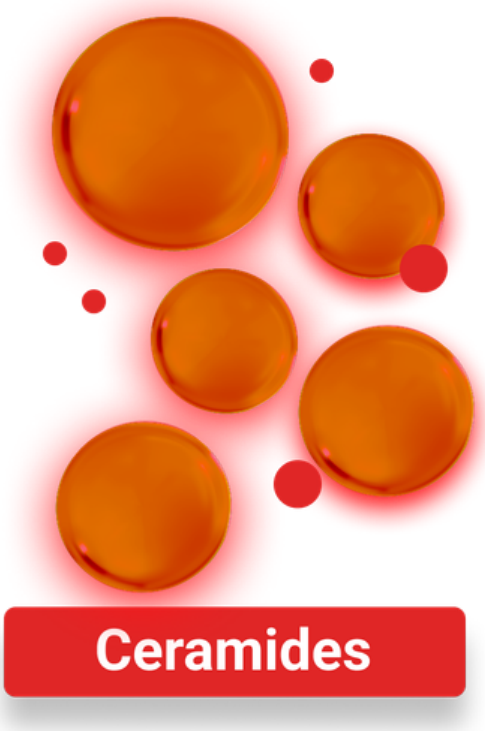
Low or normal values indicate reduced ceramide-driven vascular stress and typically reflect favorable metabolic health.

Cer (d18:1/18:0)

Ceramide (d18:1/18:0), or C(18:0) ceramide, is another saturated ceramide species associated with metabolic disease and cardiovascular risk.[185]

High Cer (18:0) is seen in obesity, T2D, and individuals with advanced atherosclerosis. Like C16:0, it contributes to inflammation and lipotoxicity, further impairing endothelial health.

Low or normal Cer (18:0) indicates minimal ceramide-mediated vascular injury.



Cer (d18:1/24:1)

Cer (d18:1/24:1), known as Cer(24:1), is a long-chain unsaturated ceramide with one double bond. Cer(24:1) is not beneficial, and is associated with major adverse cardiovascular events, but has a different mechanism due to its double bond compared to the saturated ceramides (16:0, 18:0).

The double bond is significant because while Cer (24:1) is still harmful when elevated, its relative risk signal is weaker and often reflects systemic metabolic stress rather than direct lipotoxicity. The double bond reduces membrane rigidity and toxicity which produces fewer apoptotic and inflammatory signals and allows it to engage in different, less damaging metabolic pathways.

Unsaturated very-long–chain ceramides such as Cer(24:1) are particularly associated with atherosclerotic plaque instability, vascular inflammation, and metabolic dysfunction.

Elevated Cer(21:1) levels may be caused by insulin resistance and metabolic syndrome, chronic inflammation, high saturated fat intake, NAFLD, poorly controlled diabetes, oxidative stress and mitochondrial dysfunction.[185]

Low Cer(21:1) levels may reflect impaired ceramide elongation, metabolic inflexibility, or high-risk cardiometabolic states, while higher levels are linked with better metabolic health.

Cer (d18:1/16:0) / Cer (d18:1/24:0)

A **high ratio** indicates a shift toward more atherogenic ceramides (C16:0) and away from the protective long-chain species (C24:0). This pattern is associated with insulin resistance, systemic inflammation, plaque vulnerability, and substantially elevated cardiovascular event risk.

Cer (d18:1/18:0) / Cer (d18:1/24:0)

A **high ratio** reflects increased vascular injury signaling due to greater abundance of C18:0 relative to C24:0. Elevated values correlate with high cardiometabolic stress, advanced metabolic syndrome, and higher risk for coronary events.

Cer (d18:1/24:1) / Cer (d18:1/24:0)

Cer(24:0) is generally the least harmful and often considered neutral, even cardioprotective in some studies.[185]

Why Cer(24:0) is considered “neutral”:

- It does not activate inflammatory or apoptotic pathways strongly.
- It competes with harmful ceramides (like 16:0) and can dilute their toxic influence.[185]
- Lower Cer 24:0 is a marker of liver dysfunction and predicts higher cardiometabolic risk because the body shifts toward more harmful ceramides (16:0, 18:0).

A **high ratio** indicates increased amounts of the pro-inflammatory Cer(24:1) relative to the more stable Cer (24:0) species. This shift suggests enhanced fatty acid desaturation, oxidative stress, and higher cardiovascular risk.

Cer(24:0) is included as a reference when standardizing ceramide risk levels, but it is not reported individually because due to its consideration as a relatively neutral or protective ceramide compared to the others, and serves primarily as a denominator for risk ratios, not as a risk marker on its own.

Sterols

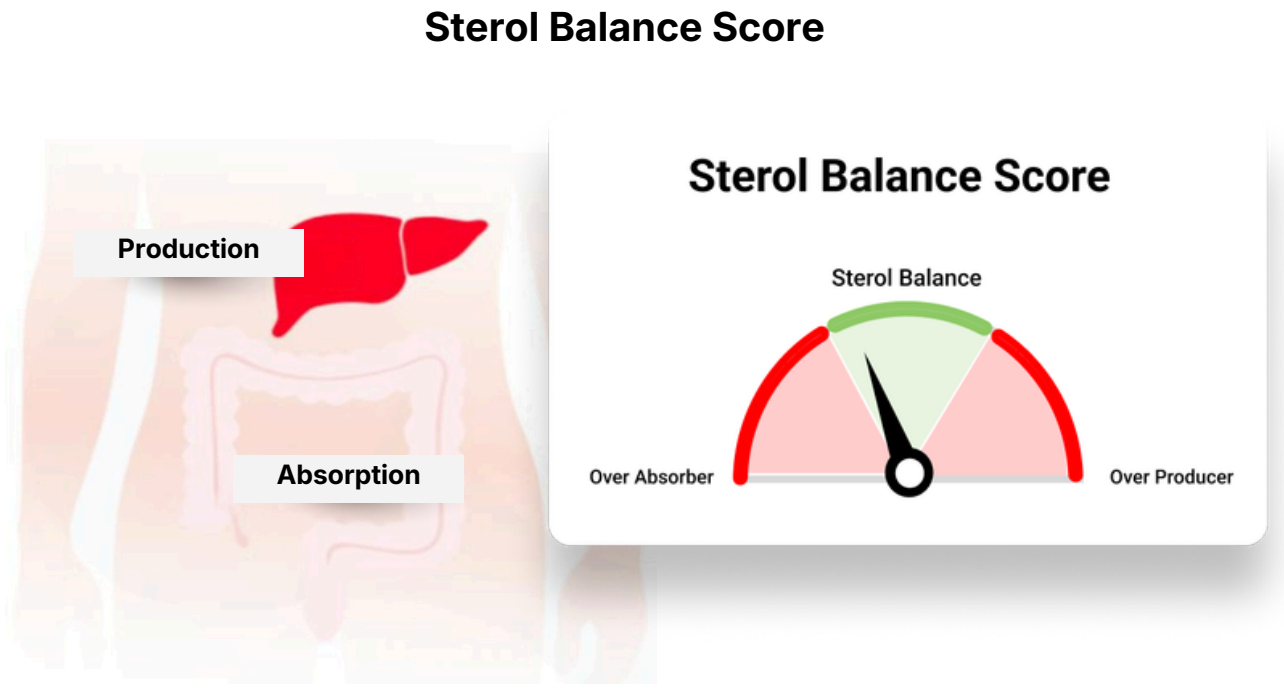


Figure 9. *The Sterol Balance Score reflects the interplay between endogenous cholesterol production in the liver and absorption from the intestine, helping identify whether a patient is predominantly an "over-producer" or "over-absorber" of cholesterol.*

Unlike individual sterol markers, which are interpreted independently, the sterol balance score reflects the **relative dominance of production versus absorption pathways.**

Elevated **desmosterol** and **lathosterol** indicate increased hepatic cholesterol synthesis or insufficient LDL receptors, while high **beta-sitosterol** and **campesterol** reflect greater intestinal sterol absorption.

Identifying the dominant pathway may help explain why some patients with dyslipidemia do not respond to traditional treatment approaches, thus support for more precise, personalized interventions is needed. By using the Sterol Balance Score alongside ApoB and LDL-C, clinicians can refine risk assessment and improve lipid management outcomes.

PRODUCTION MARKERS

Over-producers often respond better to synthesis-lowering therapies (e.g., statins, berberine) if it is due to hepatic synthesis or PCSK9 inhibitors to allow more LDL receptor availability.[186] [187]

Demosterol

Desmosterol is a key intermediate in endogenous cholesterol synthesis, and elevated levels reflect increased hepatic cholesterol production.

High desmosterol is associated with higher LDL particle formation and greater atherosclerotic risk, particularly in patients who are "over-producers" of cholesterol. Because of its link to synthesis, patients with elevated desmosterol often respond more favorably to therapies that suppress hepatic cholesterol production, such as statins or nutraceuticals like berberine.

Lathosterol

Lathosterol is another synthesis marker that reflects activity in hepatic cholesterol production.

High lathosterol correlates with increased VLDL and LDL output from the liver, reinforcing its role as a surrogate for endogenous cholesterol overproduction. Higher levels are linked to cardiometabolic risk and may indicate individuals who benefit most from synthesis-lowering interventions.

ABSORPTION MARKERS

Over-absorbers typically benefit more from absorption-targeted strategies (e.g., ezetimibe to block absorption and plant sterol modulation via dietary management).[188]

Beta-Sitosterol

Beta-sitosterol is a plant sterol absorbed through the intestine and serves as a clinical marker of cholesterol absorption efficiency.

High beta-sitosterol suggests that intestinal absorption is a major driver of dyslipidemia, which has been associated with greater atherosclerotic burden in "over-absorbers." In these cases, therapies that block absorption, such as ezetimibe or targeted dietary approaches, can be particularly effective.

Campesterol

Campesterol is another plant sterol used to assess intestinal cholesterol absorption, and elevated concentrations indicate enhanced uptake of sterols across enterocytes.

Higher campesterol levels are linked to increased chylomicron and LDL formation, contributing to elevated cardiovascular risk in individuals with absorption-dominant lipid patterns. Patients with elevated campesterol generally respond well to absorption-focused strategies rather than synthesis-focused therapies.

Inflammation

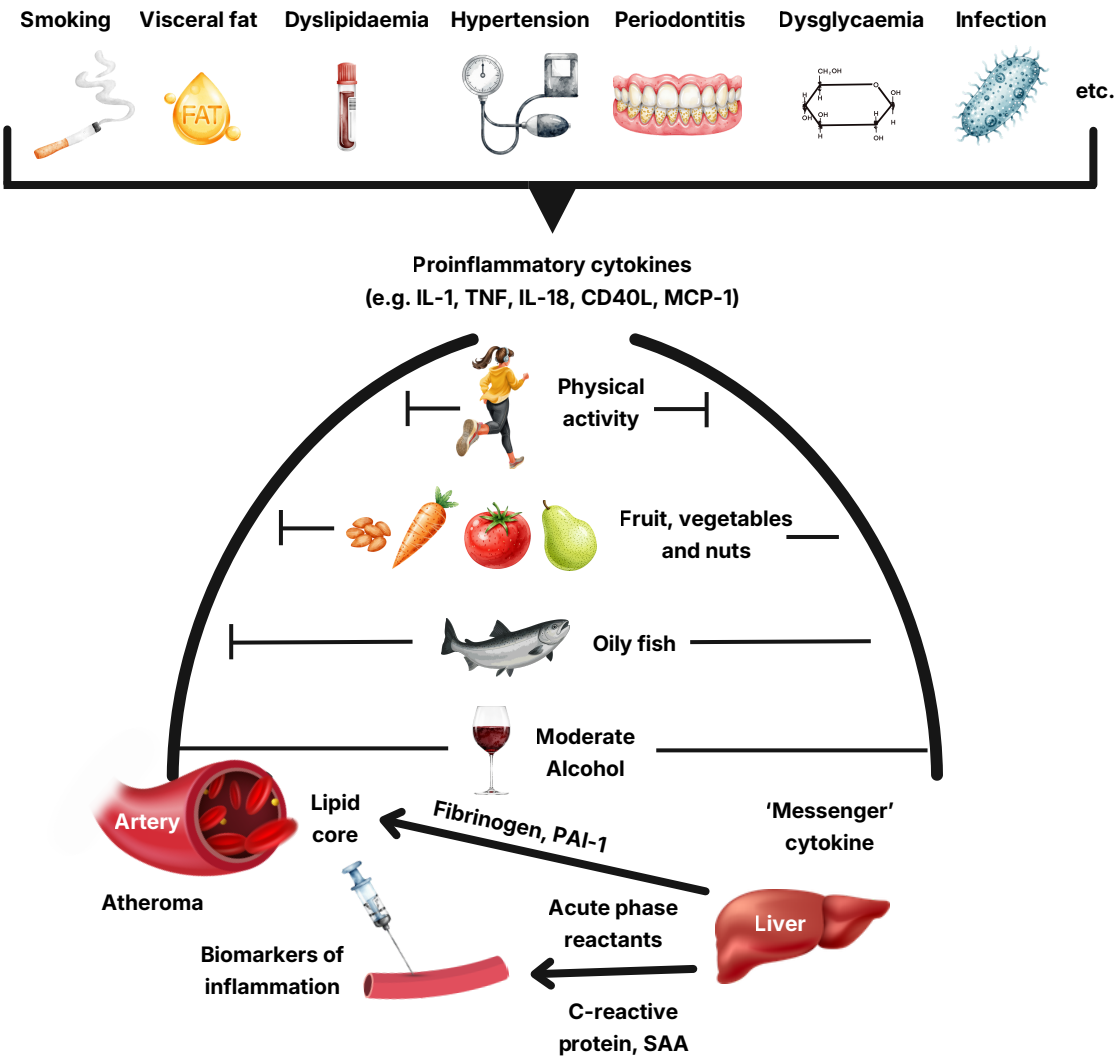


Figure 10. Risk Modifiers Influence Atherogenesis Through Effects on Inflammation as Reflected by Biomarkers of the Acute-Phase Response. Mensah GA, Arnold N, Prabhu SD, et al. Inflammation and cardiovascular disease: 2025 ACC scientific statement: a report of the American College of Cardiology. J Am Coll Cardiol. 2025. Published online ahead of print. doi:10.1016/j.jacc.2025.08.047

High-Sensitivity C-Reactive Protein (hs-CRP)

hs-CRP is an acute-phase reactant produced by the liver in response to IL-6 and other cytokines. It reflects low-grade systemic inflammation. Hs-CRP is a sensitive marker of inflammation and a well-validated predictor of cardiovascular risk. hs-CRP is useful both for risk stratification and for monitoring the effectiveness of anti-inflammatory and lifestyle interventions.

High hs-CRP is associated with endothelial dysfunction, atherosclerotic plaque formation, plaque instability, and increased risk of heart attack and stroke.

Levels >2 mg/L are generally considered risk-enhancing for ASCVD. Persistent elevations may indicate chronic metabolic, infectious, autoimmune, or lifestyle-related inflammatory processes.[189]

Mildly elevated hs-CRP (above 1.0 mg/L) can indicate heightened cardiovascular risk, particularly when combined with other risk factors.

Homocysteine (Hcy)

Homocysteine is a sulfur-containing amino acid formed during methionine metabolism that, when elevated, is linked to endothelial damage, oxidative stress, and thrombosis, and increased risk of atherosclerosis, stroke, and peripheral artery disease.

High Hcy promotes oxidative stress, impairs NO signaling, and damages the endothelium, contributing to atherogenesis and thrombosis. Elevations often reflect insufficient B-vitamin status (B6, B12, folate), renal impairment, genetic variants (e.g., MTHFR), hypothyroidism, or certain medications.[190]

Low Hcy is uncommon and typically not clinically significant.

Interleukin-6 (IL-6)

IL-6 is a pro-inflammatory cytokine released by immune cells, adipose tissue, and vascular endothelium.

High IL-6 indicates active inflammation and stimulates hepatic production of CRP. High IL-6 levels correlate with increased cardiovascular risk through promotion of endothelial dysfunction, plaque progression, and insulin resistance, and is strongly linked to atherosclerosis and plaque instability and increased risk of MI and stroke. Chronic elevations are seen in obesity, metabolic syndrome, autoimmune disease, chronic infections, and aging.[191]

Tumor Necrosis Factor- alpha (TNF-α)

TNF-α is a central inflammatory cytokine produced by macrophages and adipocytes. It drives endothelial activation, increases vascular oxidative stress, and contributes to insulin resistance.

High TNF-α is linked to advanced atherosclerosis, heart failure progression, and chronic cardiometabolic inflammation, oxidative stress, obesity, visceral adiposity, autoimmune disease, chronic infections, and chronic heart failure.[192]

Macrophage Recruitment and Plaque

MPO (Myeloperoxidase)

MPO is an oxidative enzyme released by activated neutrophils and macrophages in the vascular wall. It generates reactive oxygen species (ROS) that promote LDL oxidation, endothelial dysfunction, and nitric oxide (NO) depletion—key drivers of atherogenesis.

High MPO reflects active oxidative stress and inflammation, is associated with plaque instability, and increases risk of acute coronary syndromes.[193]

Because MPO is neutrophil-derived, acute infection or neutrophilia can temporarily elevate MPO, so results are best interpreted when the patient is clinically stable (or repeated after recovery if elevated).[194]

PLAC (Lipoprotein-Associated Phospholipase A2, Lp-PLA2)

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as PLAC, is produced by macrophages and carried primarily on LDL particles. It hydrolyzes oxidized phospholipids in LDL, generating lysophosphatidylcholine and oxidized fatty acids which are pro-inflammatory mediators that promote monocyte recruitment and plaque inflammation within the arterial wall.

High Lp-PLA2 activity reflects active lipid oxidation and vascular inflammation within atherosclerotic plaques and is associated with plaque instability and a higher risk of coronary events and stroke. It is considered a marker of vulnerable plaque rather than generalized systemic inflammation, and may be especially informative when LDL or oxidized LDL is also elevated.[195]

ox-LDL (Oxidized Low-Density Lipoprotein)

Oxidized LDL (oxLDL) forms when LDL particles undergo oxidative modification within the arterial wall, making them highly atherogenic. oxLDL promotes monocyte recruitment and is readily taken up by macrophages via scavenger receptors, driving foam cell formation and plaque development. It also contributes to endothelial dysfunction and vascular inflammation.[196]

High oxLDL reflects increased oxidative stress and atherogenesis, and is associated with plaque progression and instability. Additionally, low levels of oxLDL (8 µg/ml) has been observed to synergistically activate both macrophages and mast cells, amplifying endothelial dysfunction through released TNF-α and histamine.[197]

Cardiac Stress and Clotting Risk

NT-proBNP

N-terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) is a hormone released when the heart muscle is stretched or under stress. NT-proBNP also helps regulate blood pressure and fluid balance.[198] NT-proBNP is one of the strongest predictors of future cardiovascular events among commonly measured biomarkers[199] and is particularly valuable for identifying risk of heart failure, MI, stroke, and death.

High NT-proBNP is predictive of increased cardiovascular mortality, especially in older adults or those with hypertension and structural heart disease.[200] [202]

Troponin-T

Troponin-T proteins are released when heart muscle cells are injured or stressed making it a highly specific marker of cardiac muscle injury and is the gold standard biomarker for detecting myocardial damage.

In the general population, each standard deviation increase in high-sensitivity cardiac troponin is associated with a 13-18% increased risk of CVD.[200] Among patients with stable coronary artery disease, troponin levels help predict which patients are at highest risk for future events.[201]

High troponin-T can indicate myocardial injury and predict future cardiovascular events, including heart attacks, heart failure, and death. The predictive value increases with age and is particularly useful in people 65 years and older. [199] [200]

Creatine Kinase (CK)

Creatine Kinase is an enzyme released from muscle tissue, including cardiac muscle, and can rise in response to myocardial injury, inflammation, or trauma.

Persistently elevated CK in cardiovascular patients may also reflect statin-associated muscle injury or inflammatory myopathies that complicate lipid-lowering care. In cardiac risk assessment, CK is a supportive marker that helps contextualize muscle-related stress and potential cardiac involvement.

If not a heart attack, creatine kinase can elevate due to

- Skeletal muscle injury or recent exercise, especially from eccentric exercises[202]
- Metabolic muscle stress[203]
- Reduced renal clearance[204]
- Hypothyroidism[204]
- Muscle sensitivity to supplements or statin-like compounds. It has been noted that true statin-associated myopathy with CK >10× upper limit of normal occurs in <0.1% of patients.[203]

CK elevation alone does not diagnose myocardial injury. Troponin would be required for cardiac specificity.[204] The 2012 Universal Definition of Myocardial Infarction established troponin as the gold standard due to its superior sensitivity (99.2%) and specificity (92% vs 40% for Creatine Kinase-Myocardial Band).[205]

General Cardiovascular Care

Comprehensive dietary, nutraceutical, and lifestyle interventions are central to cardiovascular risk reduction in individuals with abnormal lipid values, obesity, and genetic susceptibility to CVD. Dyslipidemia and obesity are major contributors to atherosclerotic cardiovascular disease, and genetic factors can further increase risk, necessitating a multifaceted, evidence-based approach.[206] [207]

Dietary Considerations

Dietary patterns with the strongest evidence for cardiovascular benefit include the **Mediterranean, DASH, and plant-based diets**. [208] [209] [210] [211] [212] [213] [214] These diets emphasize:

- **Whole foods:** High intake of vegetables, fruits, whole grains, legumes, nuts, and lean proteins (such as fish, poultry, and low-fat dairy), while limiting red and processed meats, refined carbohydrates, and sugar-sweetened beverages.[10]
- **Low Saturated Fat:** Saturated fat should be reduced to less than 6–7% of total calories, trans fat to less than 1%, and dietary cholesterol to less than 200 mg/day, with a preference for monounsaturated and polyunsaturated fats.[208-211]
- **High Fiber:** Increased dietary fiber (10–25 g/day) and plant stanol/sterol intake (~2 g/day) are recommended for additional lipid-lowering effects.[211] [212]

- **Low Sodium:** Sodium intake should be limited to ≤2 g/day, especially in those with hypertension.[210-213] Studies have observed that decreasing salt intake from 10 g to 5 g can reduce blood pressure by approximately 5 to 10 mmHg.[215]
- **Adequate Potassium:** Increasing the intake of potassium with foods such as bananas, tomatoes, or coconuts reduces blood pressure by approximately between 5 and 10 mmHg.[216]

Potential barriers to adhering to a heart-healthy diet should be assessed, including food access and economic factors; these factors may be particularly relevant to persons from vulnerable populations, such as individuals residing in either inner-city or rural environments, those at socioeconomic disadvantage, and those of advanced age.[10]

Nutraceutical Considerations

Nutraceuticals with strong evidence to be beneficial include omega-3 fatty acids (EPA/DHA), which lower triglycerides and reduce CVD risk, particularly at higher doses. Polyphenols, carotenoids, and phytosterols found in plant-based foods also contribute to improved lipid profiles and reduced inflammation.[207 212 214 216] Other promising natural antihypertensive compounds can be found in Table 1.

Table 1. Natural Antihypertensive Compounds Catgorized by Antihypertensive Class[a]

ANTIHYPTERTENSIVE THERAPEUTIC CLASS	FOOD AND INGREDIENTS	NUTRIENTS AND SUPPLEMENTS
Angiotensin Converting Enzyme Inhibitors	Egg Yolk Fish (specfic): • Bonito • Dried salted fish • Fish sauce • Sardine muscle/protein • Tuna Garlic Gelatin Hawthorne berry Milk products (specfic) • Casein • Whey (hydrolyzed) Sea vegetables (kelp) Seaweed (wakame) Wheat germ (hydrolyzed) Zein (corn protein)	Melatonin Omega-3 fatty acids Pomegranate Pycnogenol Zinc
Angiotensin Receptor Blockers	Celery Fiber Garlic Monounsaturated Fatty Acids (MUFA)	Coenzyme Q10 Gamma linolenic acid Potassium Sodium intake restriction Taurine Vitamin C Vitamin B6 Zinc

Beta Blockers	Hawthorn berry	
Calcium Channel Blockers	Celery Fiber Garlic Hawthorn berry MUFA	Alpha lipoic acid Calcium Magnesium N-acetyl cysteine Oleic acid Omega-3 fatty acids: • Eicosapentanoic acid • Docosahexenoic acid Taurine Vitamin B6 Vitamin C Vitamin E
Central Alpha Agonists ***Reduce sympathetic nervous system activity***	Celery Fiber Garlic Protein	Coenzyme Q10 Gamma linolenic acid Potassium Sodium intake restriction Taurine Vitamin C Vitamin B6 Zinc
Direct Renin Inhibitors		Vitamin D
Direct Vasodilators	Celery Cooking oils with monounsaturated fats Fiber Garlic MUFA Soy	Alpha linolenic acid Arginine Calcium Falvonoids Magnesium Omega-3 fatty acids Potassium Taurine Vitamin C Vitamin E
Diuretics	Celery Hawthorn berry Protein	Calcium Coenzyme Q10 Fiber Gamma linolenic acid L-carnitine Magnesium Potassium Taurine Vitamin B6 Vitamin C Vitamin E

[a] Adapted from Mark Houston[217]

Lifestyle Considerations

The foundation for managing cardiovascular markers is through dietary changes and healthy lifestyle across a person's life span. **Studies have noted those with a genetic predisposition for increased coronary heart disease can reduce their risk by up to 50% through changes in lifestyle.**[218]

Maintaining a Healthy Weight and Weight Management

Maintaining a healthy weight provides substantial cardiovascular benefits across multiple physiologic domains, with improvements in lipid profiles, blood pressure, circulation and vascular function, inflammatory markers, and thrombotic factors that collectively reduce cardiovascular disease risk.

From a weight management perspective, losing 10 kg (22 lbs) can lead to a 10 to 20 mmHg decrease in systolic pressure and a 5 to 10 mmHg decrease in diastolic pressure.[216] This 10 mmHg reduction may increase the quality of life and extend life expectancy by up to approximately 5 years.[216]

Physical Activity

Adults should engage in at least 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity (or an equivalent combination of moderate and vigorous activity) to reduce ASCVD risk.[10] For adults unable to meet the minimum physical activity recommendations, engaging in some moderate- or vigorous-intensity physical activity, even if less than this recommended amount, can be beneficial to reduce ASCVD risk.[10] Practicing exercise such as walking, swimming, and dancing for 45 to 60 min improves cardiac inotropism (force or strength of heart muscle contraction) and chronotropism (rate of heartbeat) and reduces blood pressure by 10 to 20 mmHg.[216] Decreasing sedentary behavior in adults may be reasonable to reduce ASCVD risk10 In addition to the recommendation of exercise, neighborhood environment and access to facilities for physical activity should be assessed.[10]

Table 2. *Definitions and Examples of Different Intensities of Physical Activity*[a]

Intensity	METS	Examples
Sendentary Behavior[b]	1-1.5	Sitting, reclining or lying; watching television
Light	1.6 - 2.9	Walking slowly, cooking, light housework
Moderate	3.0 - 5.9	Brisk walking (2.4-4 mph), biking (5-9 mph), ballroom dancing, active yoga, recreational swimming

Vigorous	≥6	Jogging/running, biking (≥10 mph), single tennis,swimming laps

[a] Adapted from Arnett et al.[10]
[b] Sedentary behavior is defined as any waking behavior characterized by an energy expenditure ≤1.5 METs, but is not considered a component of sedentary behavior.

Sleep Management

Potential mechanisms for which poor sleep quality and sleep disorders such as insomnia, obstructive sleep apnea, restless leg syndrome may increase coronary heart disease risk include increased inflammation, oxidative stress, exacerbating autonomic nervous system dysfunction, inducing metabolic and endocrine disorders and contributing to abnormal coagulation function.[219]

Restorative sleep, defined by the National Sleep Foundation Scientific Advisory Council as being "wide awake, alert, and energetic throughout the day without the aid of stimulants" is a pillar of lifestyle medicine influenced by sleep duration, quality, and disorders.

Sleep duration follows a U-shaped curve with both short and long durations associated with cardiovascular risk.[220] Short sleep appears could reflect the lack of a sufficient opportunity for 7-8 hours of sleep (e.g., work schedules, caretaking responsibilities, lifestyle choices) or some factor interfering with sleep duration that results in short sleep (e.g., insomnia, chronic pain, restless leg syndrome).[221] Long sleep is more strongly predictive of cardiovascular risk, which may be due to comorbidities and other risk factors.[225]

Measured by average hours of sleep per night, **the American Heart Association states the ideal level is 7-9 hours daily for adults.** With adequate sleep, the body experiences a phenomenon known as nocturnal dipping where heart rate, cardiac output, and systemic blood pressure all decrease. This reduction in cardiovascular workload protects the cardiovascular system by mitigating endothelial stress, shifts the body into a state of parasympathetic dominance, which lowers inflammation and oxidative stress, and can improve glucose metabolism and cortisol levels.[222]

Considerations for better sleep include[223]

- Establishing a consistent sleep routine by going to bed and waking up around the same time everyday.
- Optimizing the environment by keeping the bedroom dark, quiet and cool (around 60-67F or 15-19C) to promote uninterrupted rest.
- Sleep hygiene – avoiding screens (phones, TVs, computers) at least one hour before bed, as blue light inhibits melatonin.
- Regulating circadian rhythm by getting bright, natural sunlight during the day.
- Avoiding sleep disruptors such as heavy meals, caffeine, nicotine, and alcohol before bed as they may interfere with the ability to fall and stay asleep.

Stress Management

Increased sympathetic tone, which drives the fight-or-flight response, may result in vascular hypertrophy that contributes to the development of hypertension.[224]

The American Heart Association's 2017 guidelines established levels less than 120/80 mm Hg as optimal, and hypertension defined as 130-139 mm Hg systolic pressure (top number) or 80-89 mm Hg diastolic pressure (bottom number).[225]

Emotional events can cause arrhythmia with acute emotional stress possibly provoking severe catecholamine release, leading to direct cardiac muscle cell injury due to calcium overload, microvascular vasoconstriction in the heart, and hypertension.[220] Workers exposed to high job strain, long hours, or low rewards have a 10%–40% higher excess risk of CVD than their unstressed counterparts.[226]

Evidence supports cognitive behavioral therapy (CBT), mindfulness-based stress reduction (MBSR), and yoga for stress management, cardiovascular risk reduction, and psychological health and quality of life though the quality and consistency of data vary.[227] [228] [229]

Smoking Cessation of Combustible and Electronic Cigarettes, and Vaping Devices

Approximately 7,357 chemicals of many different classes can be found either bound to or in free form in the aerosol or gas phase, with over 4,000 compounds linked to CVD, most studies suggest that carbon monoxide, reactive oxygen species, and nicotine are responsible for the pathogenesis of smoking-induced cardiovascular disorders.[230] Secondhand smoke exposure, even for a short time, can damage blood vessels and cause blood to become stickier, increasing a non-smoker's risk of developing heart disease by 25%–30%.[231]

By 10 to 15 years of abstinence, the risk of cardiovascular mortality has been noted to be comparable to that of never-smokers.[222]

Cardiovascular Health Education

Health literacy should be assessed every four to six years to maximize recommendation effectiveness.[10]

Retesting

General timeframes for retesting may depend on the responsiveness of the marker.

Inflammation Markers: 2–8 weeks
Lipids & ApoB: 6–12 weeks
Glucose, Insulin, Homocysteine: 8–12 weeks
Oxidative Stress, Ceramides, & Sterol Markers: 8–16 weeks

Note: There is no consensus established for the optimal retesting timeframe for these laboratory markers. Retesting should depend on the clinical situation, the care plan implemented, and the clinician's judgment.

Synergistic Tests

Cardio Genetics

While the Cardio Zoomer provides valuable insights on real-time functional biomarkers, its combined use with the Cardio Genetics Panel, which identifies inherited predispositions, offers a more complete picture of cardiovascular risk. that may increase a patient's lifetime risk, even before changes appear in routine labs, revealing how those genetic predispositions are currently expressed in the patient's physiology. When used together, providers can assess inherited risk and understand how it interacts with current metabolic, vascular, and inflammatory status, enabling a more informed and individualized approach to risk management and early intervention.

Hormone Zoomer

Hormone, stress, and cardiovascular systems are closely linked. Cortisol rhythm affects blood pressure, endothelial function, and lipid patterns; estrogen and androgen metabolism influence inflammation, oxidative stress, and vascular tone; and endocrine disruptors directly affect cardiometabolic aging. Pairing Cardio Zoomer with Hormone Zoomer connects "hormonal drivers" with "cardiovascular outcomes," helping clarify how daily stress, hormone metabolism, melatonin timing, and environmental load are influencing long-term cardiovascular stability.

Gut Zoomer

Cardiovascular patterns rarely exist in isolation. Gut-derived inflammation, microbial metabolites, SCFA balance, bile acid signaling, and barrier strength influence cholesterol behavior, oxidative stress, blood pressure trends, and metabolic load. Pairing Cardio Zoomer with Gut Zoomer links "vascular signals" to the "terrain" that shapes them—clarifying whether cardiometabolic strain is being amplified by dysbiosis, permeability, microbial imbalance, or gut–brain stress patterns.

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Results may be affected by pre-analytical variables related to specimen type, collection, handling, transport, and storage. Serum, EDTA whole blood, and plasma specimens may be impacted by factors such as hemolysis, lipemia, icterus, clotting, anticoagulant effects, insufficient sample volume, delayed shipment or improper storage conditions.

Risk and Limitations, continued

EDTA whole blood specimens may exhibit anticoagulant-related interference for certain analytes, while plasma and serum results may vary depending on clotting time, centrifugation parameters, and time to separation. Urine specimens may be impacted by factors such as improper collection technique, contamination, insufficient sample volume, delayed shipment, or improper storage conditions. Variability in urine concentration or dilution may also influence analyte measurements. Degradation or instability of certain analytes may occur if specimens are not collected or shipped according to recommended guidelines, potentially affecting result accuracy or leading to a Test Not Performed (TNP). In some TNP cases, repeat testing may be recommended when clinically appropriate, although repeat testing may still not yield a reportable result if the underlying limitations persist.

Results generated using laboratory testing methodologies are subject to inherent analytical limitations related to instrument performance, assay specifications of individual FDA-approved and laboratory-developed test (LDT) analytes included in the test panel, and methodological variability. As with all clinical laboratory testing, there is a small chance that the laboratory could report incorrect results.

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