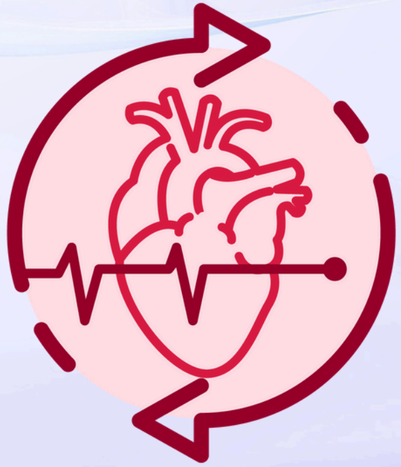
The Vibrant Longevity Summit

# The Heart of Longevity

## Innovations in Cardiovascular and Metabolic Care



Session 1

**Dr. Abid Husain MD, FACC, ABAARM**

Session 2

**Dr. Christopher Davis, MD**

Session 3

**Dr. Giovanni Campanile, M.D., FACC, ABIHM, FAARM**

Session 4

**Dr. Jack Wolfson, DO**

# The Heart of Longevity

Innovations in Cardiovascular and Metabolic Care

Session 1

**Dr. Abid Husain MD, FACC, ABAARM**

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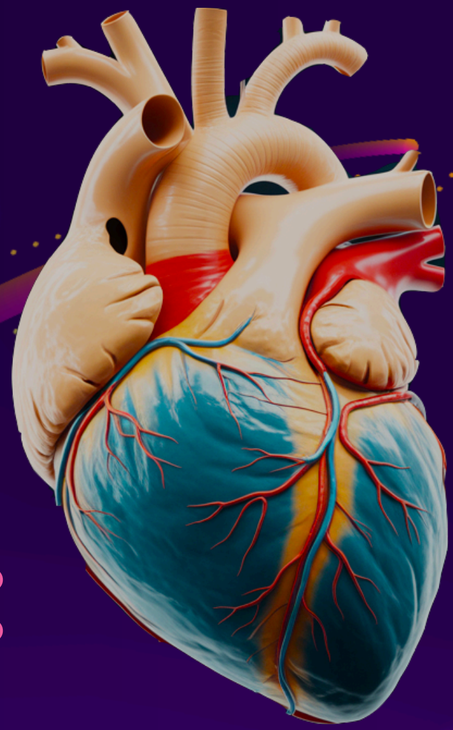
# Understanding Early Cardiovascular Decline:

## *The Role of Advanced Biomarkers*



## Meet Your Speaker

# Dr. Abid Husain

*MD, FACC, ABAARM*

Integrative, Preventative, & Cellular Cardiology

Longevity Medicine

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# Traditional vs Novel Biomarkers

The **positive predictive value (PPV)** of LDL-C alone for predicting cardiovascular events is generally **low.**

**The cost:**

- Missed high-risk patients
- Over treatment of low-risk patients
- Ignored treatment opportunities



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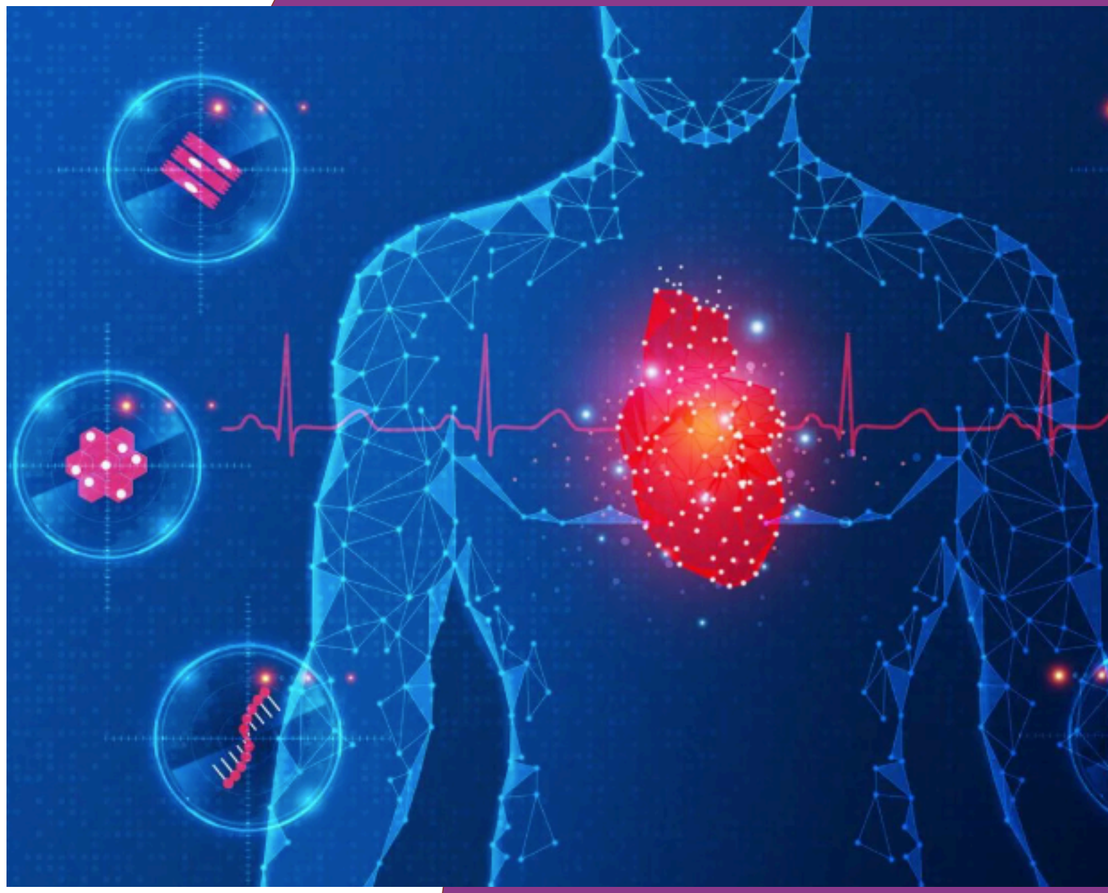
# Novel / Expanded Markers

*Lipid Markers*

- *Apolipoprotein B*
- *Small dense LDL*
- *Apolipoprotein (a)*

*Inflammatory Markers*

- *High sensitivity C-Reactive Protein*
- *Oxidized LDL*
- *Homocysteine*
- *ADMA/SDMA*





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# Expanded Lipid Markers



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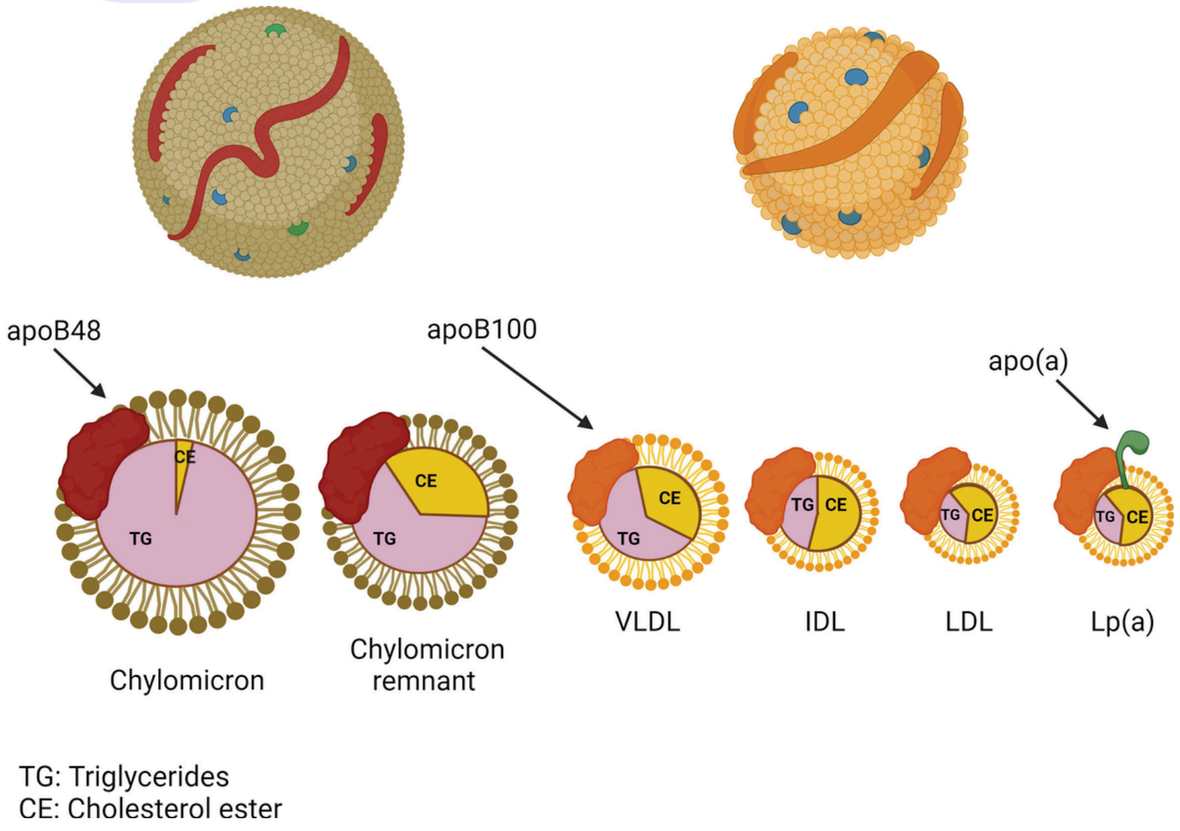


# LDL-C (mg/dl)

- Traditional and most commonly used
- Indirect methods to estimate the concentration of cholesterol within Low-Density Lipoprotein (LDL) particles in the blood
- Does not account for size or volume
- Does not account for small dense LDL

Diana De Oliveira-Gomes. Circulation. Apolipoprotein B: Bridging the Gap Between Evidence and Clinical Practice، Volume: ١٥٠، Issue: ١، Pages: ٦٢-٧٩، DOI: (١٠.١١٦١/CIRCULATIONAHA.١٢٤.٠٦٨٨٨٥)



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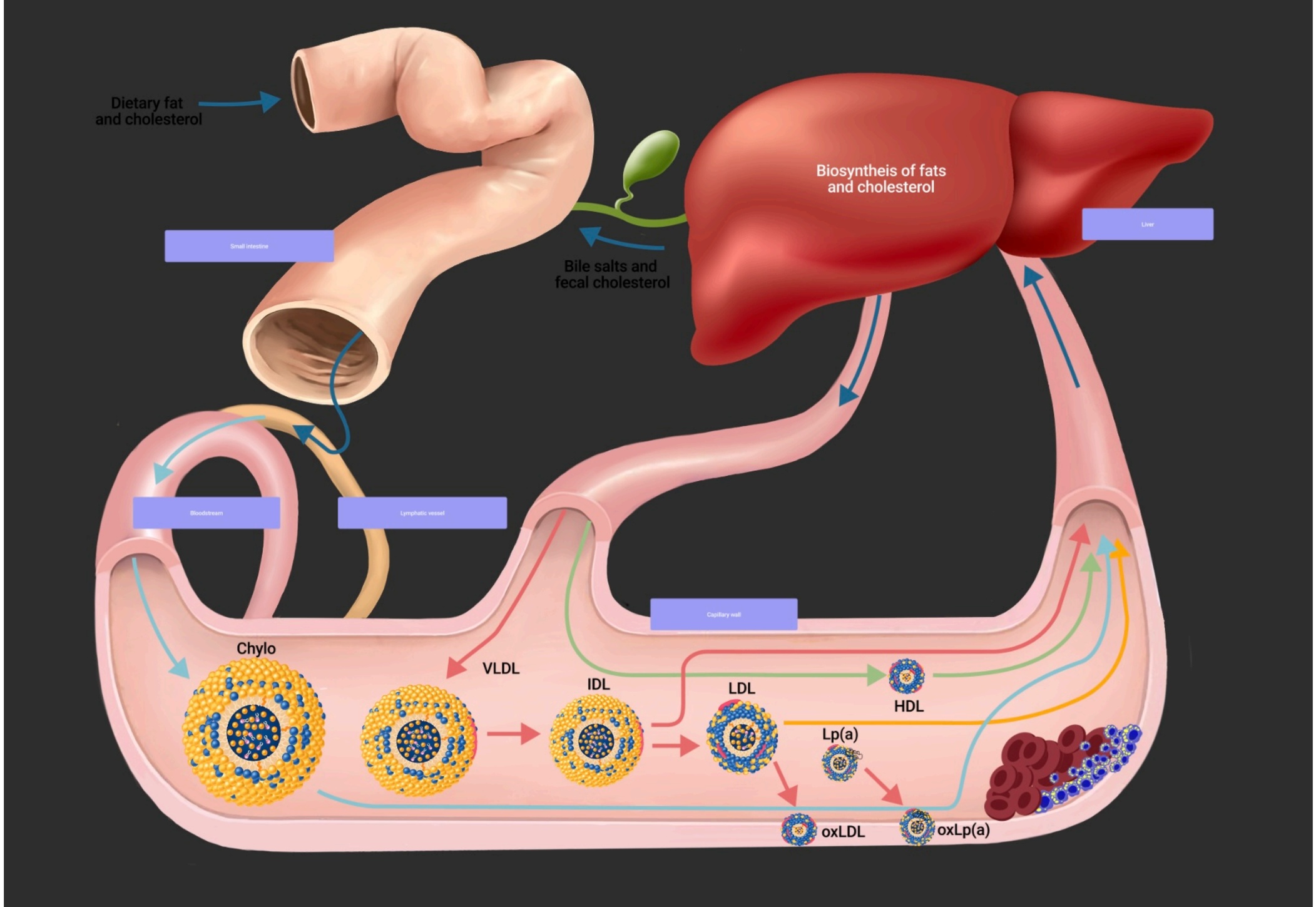
Dietary fat
and cholesterol
Small intestine
Bile salts and
fecal cholesterol
Biosyntheis of fats
and cholesterol
Liver
Bloodstream
Lymphatic vessel
Capillary wall
Chylo
VLDL
IDL
LDL
HDL
Lp(a)
oxLDL
oxLp(a)

# Apolipoprotein B

- Apolipoprotein B (ApoB) is the primary structural protein found on all potentially atherogenic lipoproteins, including LDL, VLDL, and IDL
- It facilitates the receptor-mediated uptake of LDL particles and contents by cells.
- ApoB-100, derived from the liver, is the predominant form circulating in plasma.
- ApoB provides a direct and accurate count of atherogenic particle numbers, even in a **non-fasted** state

Physiological Bases for the Superiority of Apolipoprotein B Over Low–Density Lipoprotein Cholesterol and Non–HighDensity Lipoprotein Cholesterol as a Marker of Cardiovascular Risk، Tamara Glavinovic ، MD؛ George Thanassoulis، J Am Heart Assoc. ٢٠٢٢؛١١:e٠٢٥٨٥٨. DOI: ١٠.١١٦١/JAHA.١٢٢.٠٢٥٨٥٨



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# ApoB vs LDL-P vs LDL-C

**1** **ApoB Measures ( mg/dL )**

ApoB quantifies all atherogenic particles via lipoprotein mass. This includes LDL, VLDL, IDL and cholomicron remnants in the blood.

**2** **LDL-P Measures ( nmol/L)**

Measures LDL particles. It may not capture the complete atherogenic burden from other cholesterol components but more accurate than LDL-C.

Closely correlated with ApoB

**3** **LDL-C ( mg/dL) : Most commonly used**

indirect methods to estimate the concentration of cholesterol within LDL

Quantifies the amount of cholesterol mass that is contained within LDL particles.

It does not measure the physical size or volume of the particles themselves, only the amount of cholesterol they carry.

Does not account for small dense LDL and can underestimate risk

**CAD Risk: ApoB & LDL-P correlates better with CAD risk than LDL-C. This is due to its direct measurement of particle numbers.**

Physiological Bases for the Superiority of Apolipoprotein B Over Low-Density Lipoprotein Cholesterol and Non–HighDensity Lipoprotein Cholesterol as a Marker of Cardiovascular Risk, Tamara Glavinovic , MD; George Thanassoulis, J Am Heart Assoc. 2022;11:e025858. DOI: 10.1161/JAHA.122.025858

# Small Dense LDL

- Large buoyant LDLs less atherogenic
- Small Dense LDLs pro-atherogenic
- Each LDL has one ApoB molecule making this a good proxy
- Can be measured directly or use LDL : Apo B ratio as proxy ( 1.2 )

Xiao, L., Zhang, K., Wang, F. *et al.* The LDL-C/ApoB ratio predicts cardiovascular and all-cause mortality in the general population. *Lipids Health Dis* **22**, 104 (2023). https://doi.org/10.1186/s12944-023-01869-1



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# Small Dense LDL

- More prone to oxidation
- Longer circulation time and harder for liver to clear
- More prone to binding to endothelial receptors
- Metabolic dysfunction and insulin resistance
- Reduced vascular flexibility

Ivanova EA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN. Small Dense Low-Density Lipoprotein as Biomarker for Atherosclerotic Diseases. Oxid Med Cell Longev. 2017;2017:1273042. doi: 10.1155/2017/1273042



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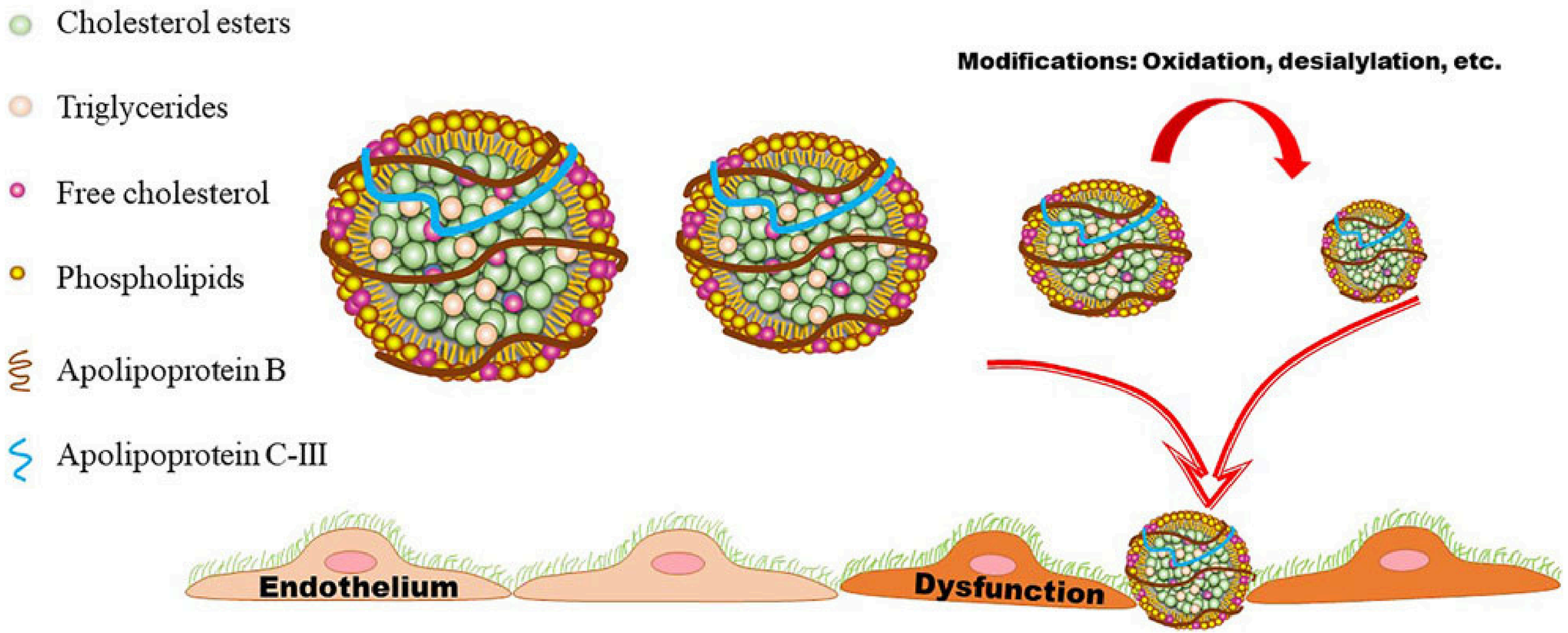
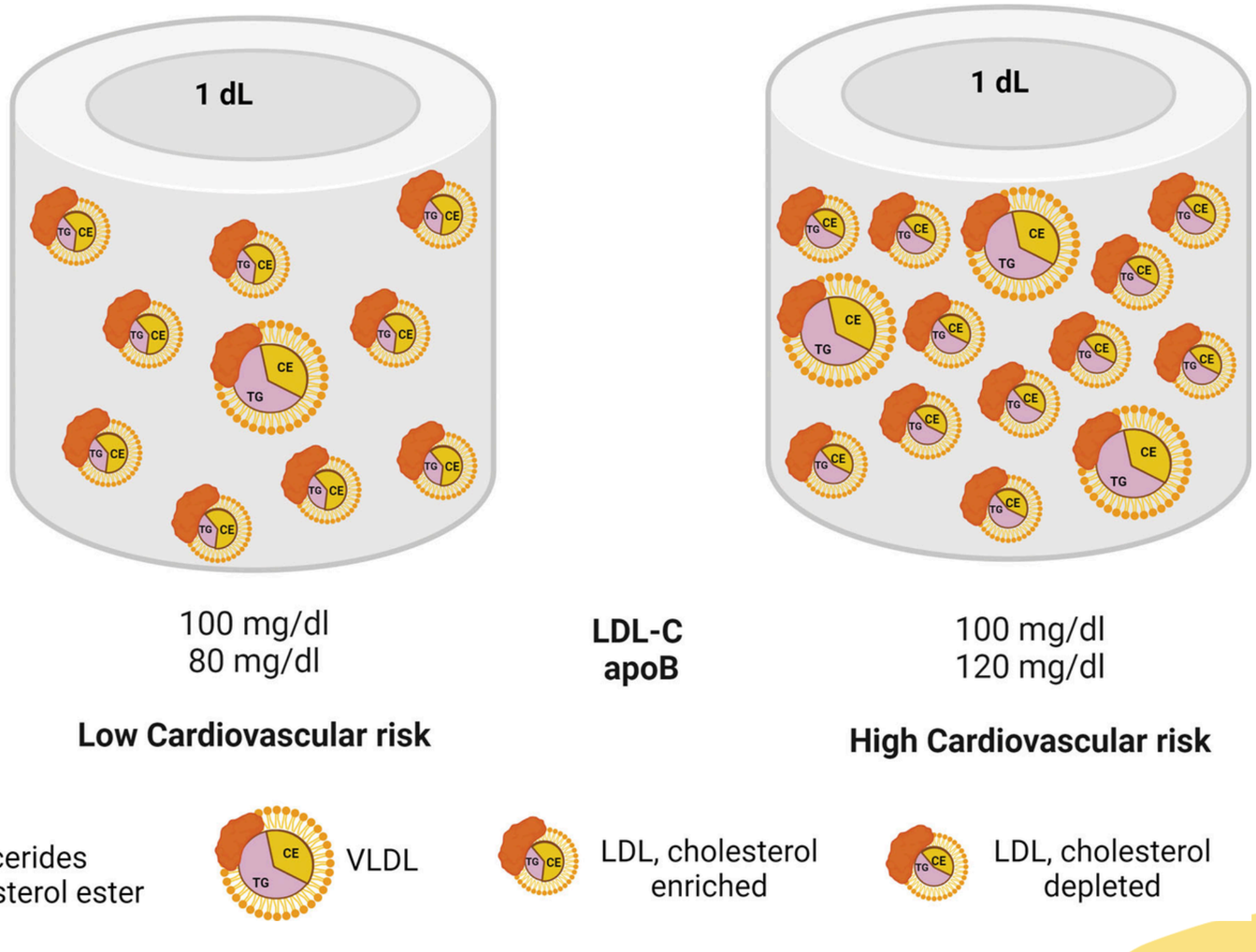
| | LDL I<br>Large LDL | LDL II<br>Intermediate LDL | LDL III<br>Small LDL | LDL IV<br>Very small LDL |
|---|---|---|---|---|
| **Diameter:** | 26.0–28.5 nm | 25.5–26.4 nm | 24.2–25.5 nm | 22.0–24.1 nm |
| **Density:** | 1.019–1.023 g/mL | 1.023–1.034 g/mL | 1.034–1.044 g/mL | 1.044–1.060 g/mL |




Qiao Y-N, Zou Y-L and Guo S-D (2022),Low-density lipoprotein particles in atherosclerosis.,Front. Physiol. 13:931931.,doi: 10.3389/fphys.2022.931931

# Putting it Together




Diana De Oliveira-Gomes. Circulation. Apolipoprotein B: Bridging the Gap Between Evidence and Clinical Practice، Volume: ١٥٠، Issue: ١، Pages: ٦٢-٧٩، DOI: (١٠.١١٦١/CIRCULATIONAHA.١٢٤.٠٦٨٨٨٥)



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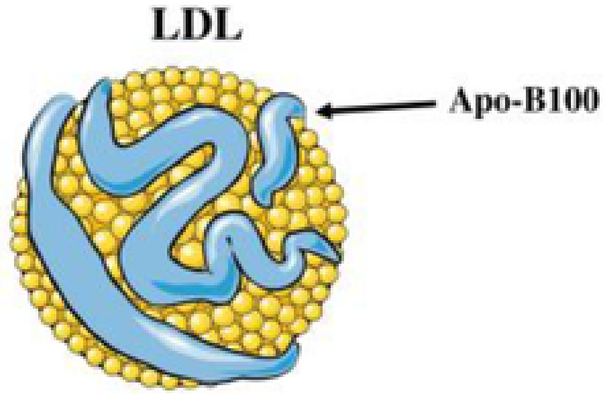
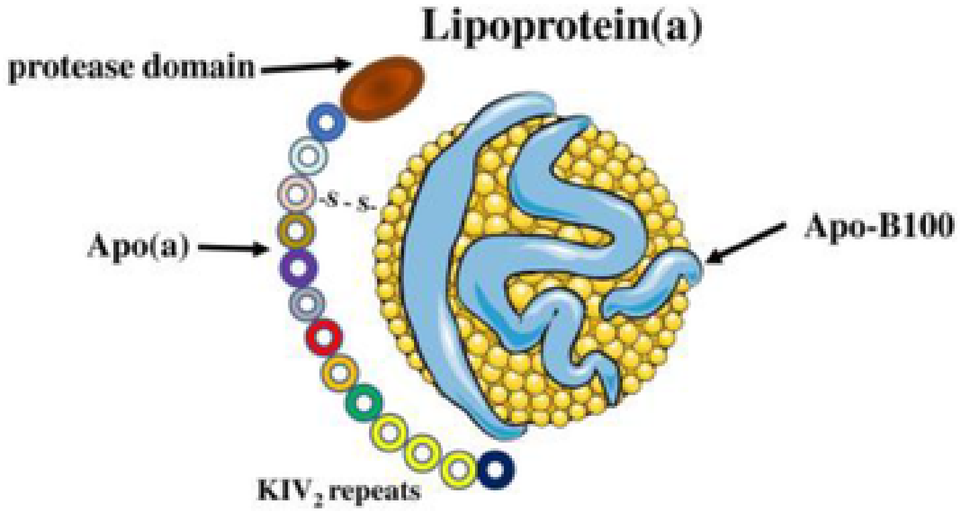
# Apolipoprotein (a) aka Lp (a)

- Large glycoprotein bound to LDL particle
- Genetically determined with little effect of diet, exercise or most medications
- Dual pathologic mechanism: atherogenic and prothrombotic



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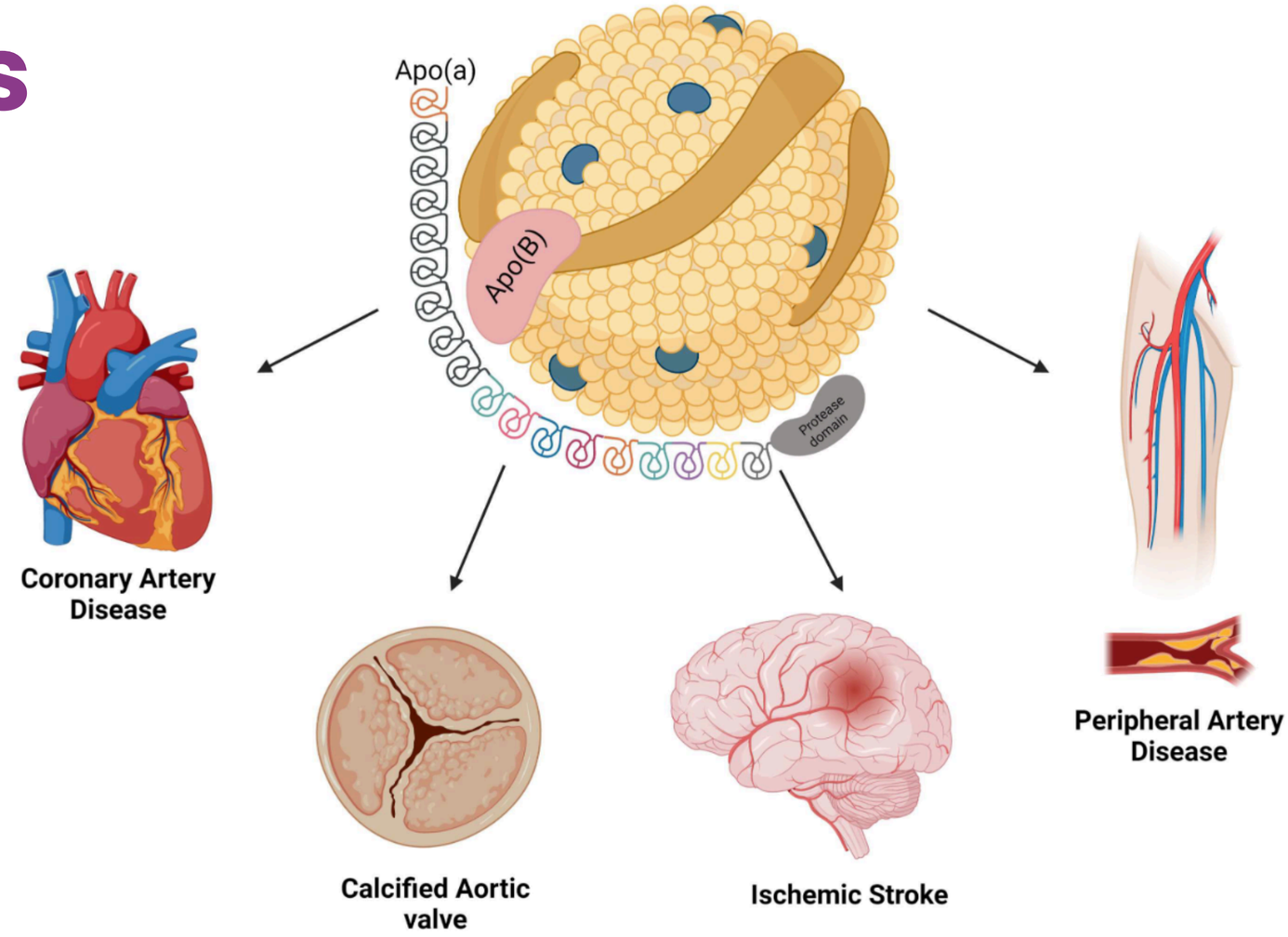
# Lp(a) associations

- Atherosclerosis
- Myocardial Infarction
- Aortic Stenosis
- Stroke
- Peripheral Artery Disease



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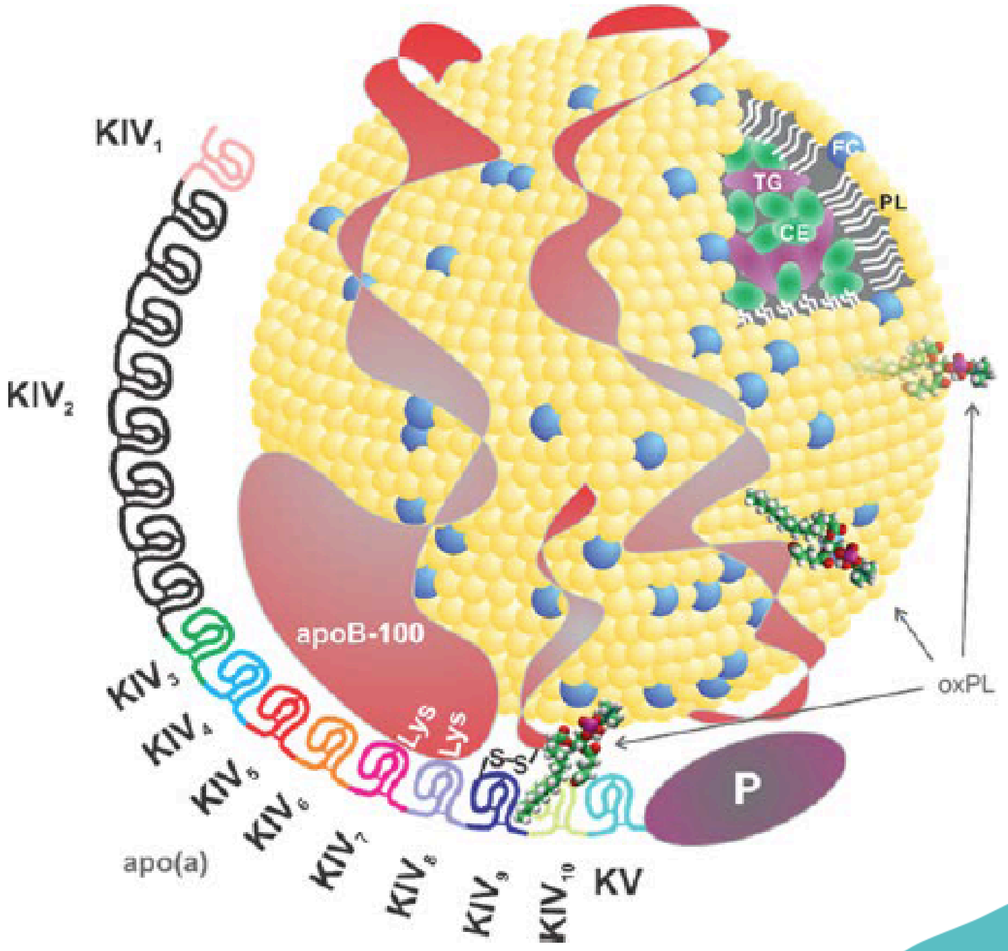
# Lp(a) Variability

Not everyone with elevated levels develop disease.

- Significant variability in associated SNPs
- Measurement challenges
  - inflammation and units
- Significant Kringle Repeats
- Outcomes data still pending



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# Inflammatory Markers



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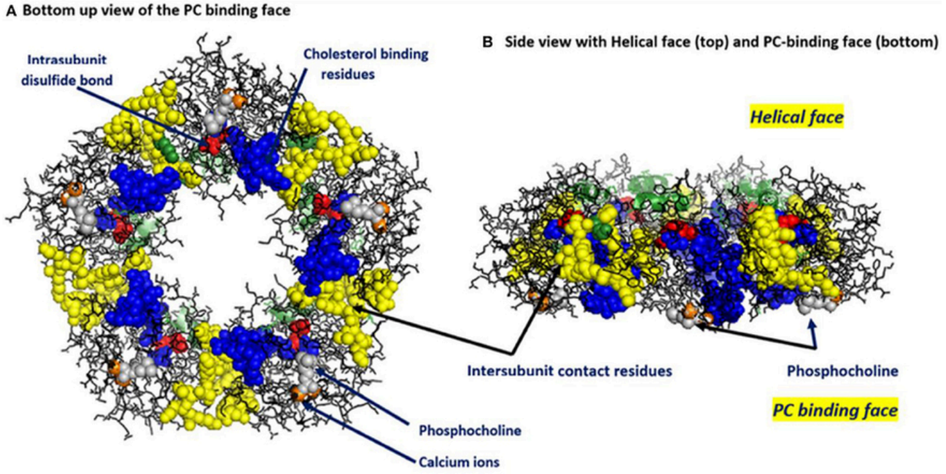
# High Sensitivity-C Reactive Protein

An acute phase reactant produced primarily by the liver in response to inflammatory cytokines, particularly IL-6.

- More sensitive than conventional CRP assay
- Detects low-grade *vascular* inflammation (0.1-10 mg/L range)
- Half-life: ~19 hours (stable biomarker)



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# hs-CRP: Evidence

- The most established and guideline-endorsed inflammatory biomarker for refining CVD risk
- Strong epidemiologic evidence: Landmark prospective studies like the **Physicians' Health Study** and **Women's Health Study** showed that hs-CRP predicts future myocardial infarction, stroke, and cardiovascular death even in people with normal LDL cholesterol.
- Independent risk factor: Elevated hs-CRP predicts risk independent of LDL-C, blood pressure, and smoking.

# hs-CRP: Support

Clinical guideline endorsement:

- **2019 ACC/AHA Guidelines**: hs-CRP is a **“risk-enhancing factor”** when borderline or intermediate risk is identified by pooled cohort equations.
- **ESC 2021**: acknowledges hs-CRP as a tool for reclassification in intermediate-risk individuals.



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# hs-CRP and Early Atherosclerosis

Reflects vascular inflammation & plaque instability complements lipid measures Subclinical Atherosclerosis

- MESA study: hs-CRP correlates with carotid intima-media thickness independent of LDL
- Each 1 mg/L increase associated with 0.01 mm CIMT increase



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# hs-CRP and Early Atherosclerosis

## Plaque Characterization

- Higher hs-CRP linked to vulnerable plaque features on intravascular ultrasound
- Associated with lipid-rich necrotic core and thin fibrous cap



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# hs-CRP and Early Atherosclerosis

## Clinical Prediction

- JUPITER trial: hs-CRP >2 mg/L predicted events in those with LDL <130 mg/dL
- Women's Health Study: hs-CRP superior to LDL in predicting future CV events



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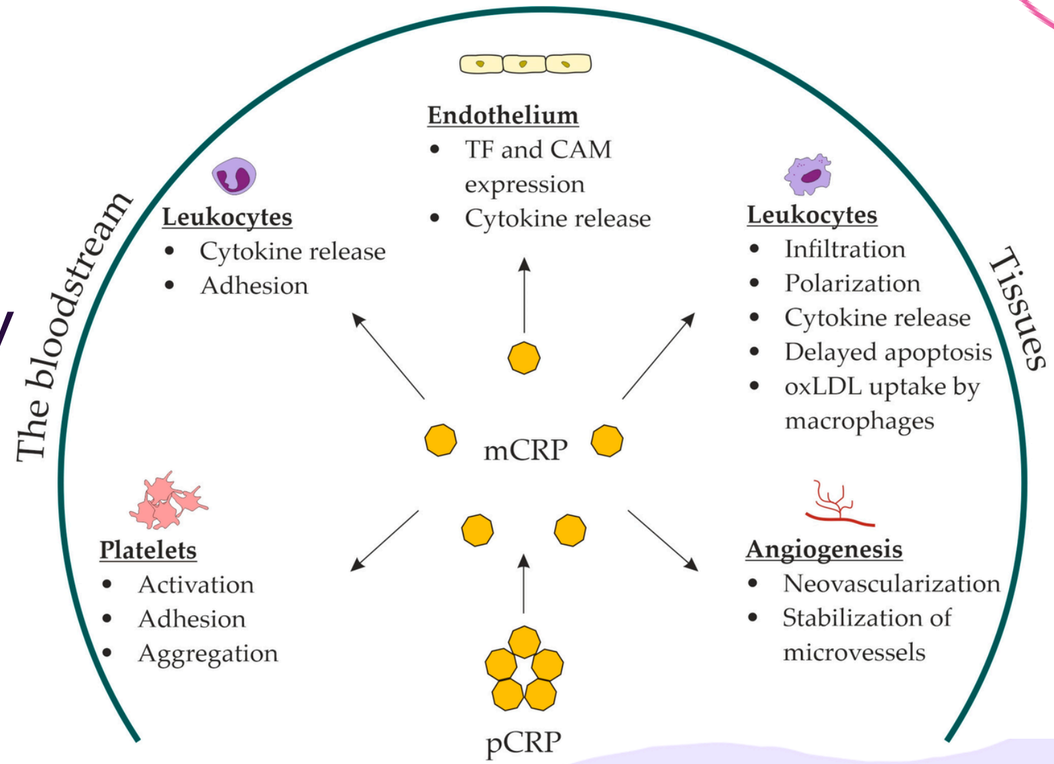
# CRP is Not just a marker

CRP identifies and propagates inflammation

- Increases endothelial vulnerability
- Amplifies immune and inflammatory activity
- Platelet activation
- Increases plaque vulnerability



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# CRP: Mechanisms

- Atherosclerotic plaques produce **IL-1β and TNF-α** → liver produces IL-6 → hepatocytes increase **CRP synthesis**
- **Downregulates eNOS expression** and activity in endothelial cells
- Induces **ICAM-1, VCAM-1, and E-selectin** expression in endothelial cells
- Stimulates **endothelin-1** (ET-1) release
- Binds to damaged cell membranes and activates the classical complement pathway, In the plaque shoulder region, this causes local inflammation and cell lysis — destabilizing fibrous caps



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# CRP: Mechanisms

- Stimulates macrophages and vascular smooth muscle cells to produce MMP-1, MMP-9
- Promotion of macrophage foam cell formation
- Impairs EPC survival, migration, and differentiation.
- Interacts with platelets in multiple ways to amplify thrombogenesis:
  - Induces conformational changes via membrane receptors
  - Increases fibrinogen binding via GPIIb/IIIa
  - Stimulates endothelial cells to release von Willebrand factor (vWF)
  - Amplifies platelet activation ($TXA_2$, P-selectin), integrin activation, and platelet–monocyte aggregate formation



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# hs-CRP: Limitations

- Non-specific: affected by infections, trauma
- Levels can vary day-to-day in the same person by 30–60%
- Chronic inflammatory diseases (baseline CRP already elevated; risk discrimination limited)



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# hs-CRP: Limitations

- Not causal in all contexts: multiple forms of CRP which may not be drivers of inflammation
- Overlap between low and high risk groups
  - Some patients with low hs-CRP still have major cardiovascular events.
  - Some with high hs-CRP never develop events (especially if elevation is due to non-vascular causes).

# Oxidized LDL

- LDL that has undergone oxidative modification (lipid peroxidation and ApoB protein oxidation) due to reactive oxygen species (ROS).

- It is not just “bad LDL” — it’s **the LDL form that directly triggers atherosclerosis**.



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# Oxidized LDL

- oxLDL is **taken up by macrophages** via scavenger receptors (CD36, SR-A1), leading to **foam cell formation** — the first visible sign of atherosclerosis.
- oxLDL is **pro-inflammatory**: It stimulates endothelial cells to express adhesion molecules (VCAM-1, ICAM-1) and promotes cytokine release (IL-1β, TNF-α).
- oxLDL is **immunogenic**: The immune system produces anti-oxLDL antibodies, which can form immune complexes and worsen vascular inflammation

# Oxidized LDL

- Serum vs plaque levels of oxLDL.
- Plaque oxLDL can be nearly 70 times higher than serum oxLDL
- Macrophage infiltration in plaque is strongly correlated with plaque oxLDL levels
- High levels of both serum and plaque oxLDL have been linked to plaque vulnerability and the risk of atherosclerotic rupture.



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# Oxidized LDL

- **Early atherogenesis signal** — often elevated **before** endothelial inflammation is systemically detectable
  - Before hs-CRP elevation
- **oxLDL is generated within the vessel wall even at the earliest stages** of plaque development, and accumulates in incipient lesions long before advanced plaque formation—suggesting it acts as an early marker of disease initiation.



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# Oxidized LDL

- short-term exposure (1–5 hours) to oxLDL instantly altered gene expression in pathways related to inflammation, extracellular matrix remodeling, redox balance, and lipid metabolism—indicating an early molecular “alarm” signal that precedes visible plaque formation

# Oxidized LDL:Limitations

- Assay standardization is poor; results can vary between labs.
- Levels can be transient — may not reflect chronic oxidative burden if measured at a single time point.
- Limited population-wide epidemiologic data compared to LDL-C, ApoB, or hs-CRP.
- Interpretation can be confounded in acute illness, since oxidative stress spikes during systemic inflammation.

# Combined Use of oxLDL + hs-CRP

- In a prospective cohort study (~425 ACS patients), **combined high oxLDL and high hs-CRP** yielded the **highest sensitivity and specificity (AUC ~0.89 vs. 0.83 for hs-CRP alone)** in predicting AMI or death over 3–5 years.
- Similar findings hold in stroke/TIA patients: **joint elevation of oxLDL and hs-CRP** was independently associated with higher risk of recurrent stroke, adverse vascular events, and poor functional outcomes.



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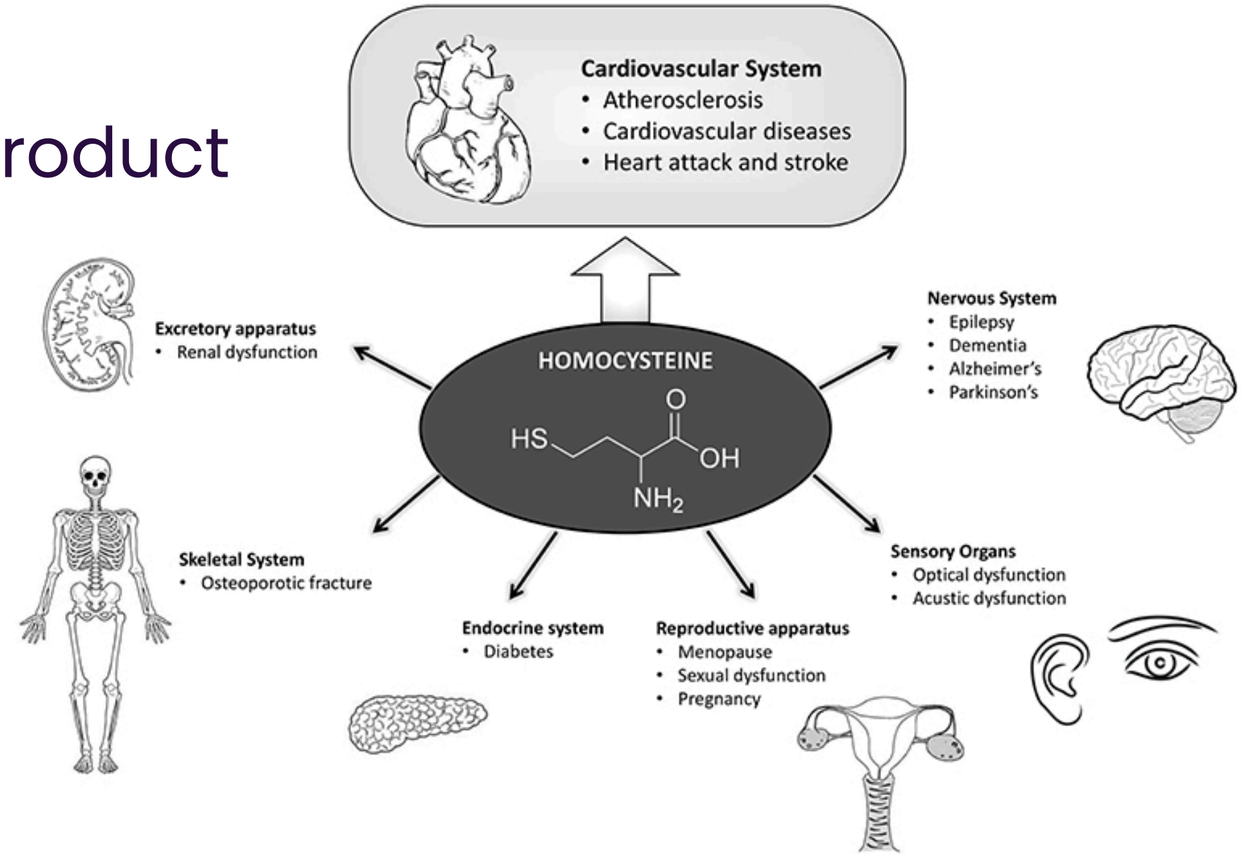
# Homocysteine

- Methionine metabolism byproduct
- Indicator of Methylation
- Has anti and pro-oxidant properties



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# Homocysteine: Vascular Mechanisms

Homocysteine is **directly toxic** to vascular tissue at high levels

- Endothelial dysfunction
  - Oxidative stress → NO depletion
  - eNOS uncoupling
- Pro-thrombotic state: ↑ platelet activation ↑ factor V activity, ↓ thrombomodulin
- VSMC proliferation: Stimulates smooth muscle migration into intima
- Matrix degradationIncreases: MMP activity → weakens plaque structure



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# Homocysteine: Impact of Levels

| Mechanism | Approx. Threshold | Impact |
|---|---|---|
| Endothelial dysfunction | ۱۰–۱۲ | ↓ NO، ↑ endothelin-۱ |
| Prothrombotic state | ⩾۱۵ | ↑ platelet activation، factor V activation |
| Elastin/collagen degradation | ⩾۱۵–۲۰ | ↑ aneurysm risk |
| Microvascular ischemia | ⩾۱۲ | Coronary microvascular angina |
| Oxidative stress overload | ⩾۱۵–۲۰ | Protein homocysteinylation، MMP activation |



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# Homocysteine: Impact of Levels

| Condition | Homocysteine Range | Reference(s) |
|---|---|---|
| Coronary Disease / CVD | ≥ 14 µmol/L (↑ risk); each +5 µmol/L → ~ +26% CAD risk | Stein et al. (1998), Toole et al. (2004), Ridker et al. (1999)JAMA Network |
| Ischemic Stroke | >15 µmol/L significantly ↑ risk; ~43% ↑ per +5 µmol/L | Meta-analysis and cohort studies MDPIAmerican Academy of NeurologyPMC |
| Heart Failure (CHF) | >10 µmol/L associated with incidence and severity | Framingham and other observational data FrontiersScienceDirect |
| Mortality (all-cause, CV) | ≥10 µmol/L inflection ~14.5–14.6 µmol/L | Recent cohort analyses BioMed CentralMDPI |



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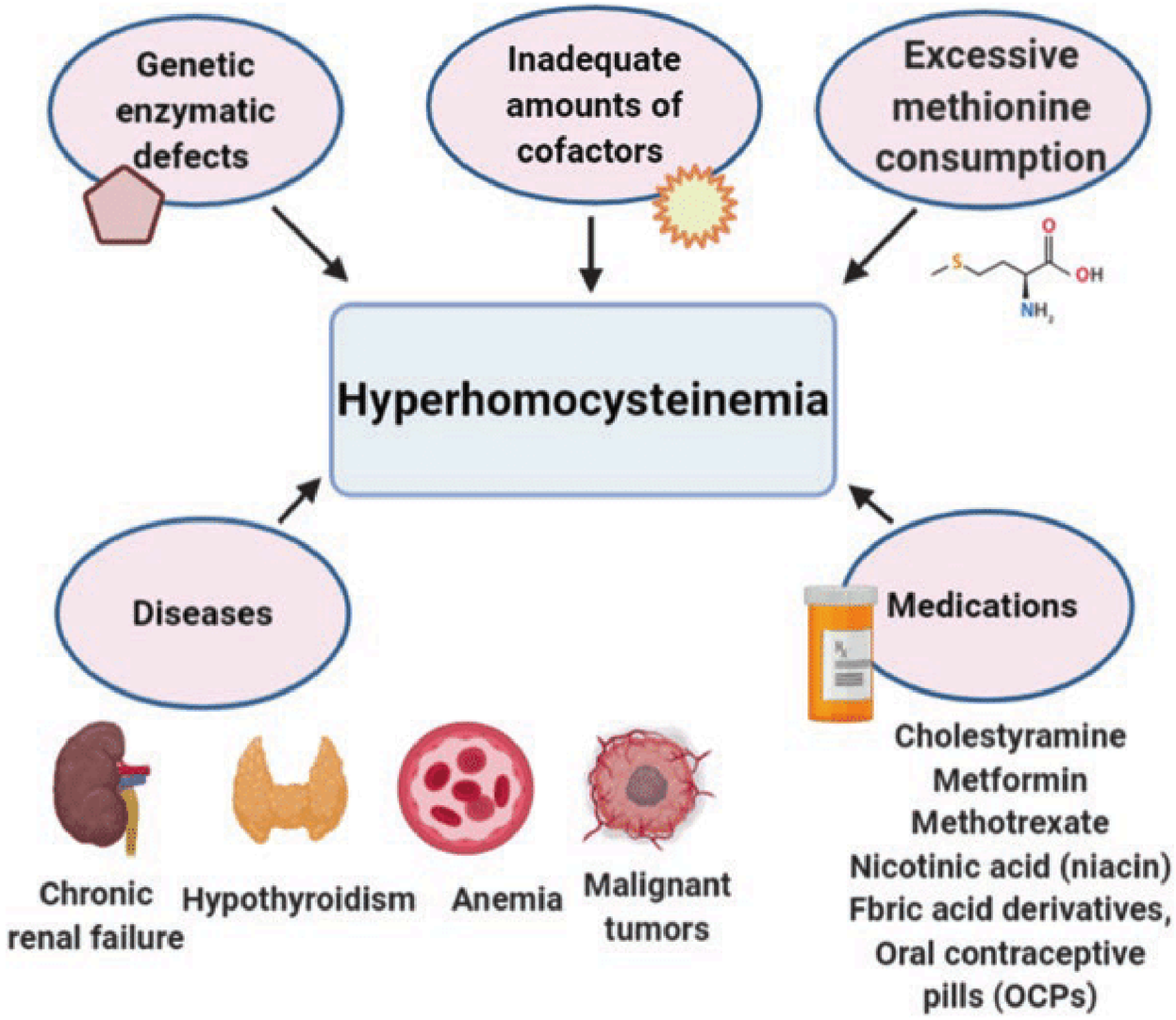
# Drivers of Homocysteine



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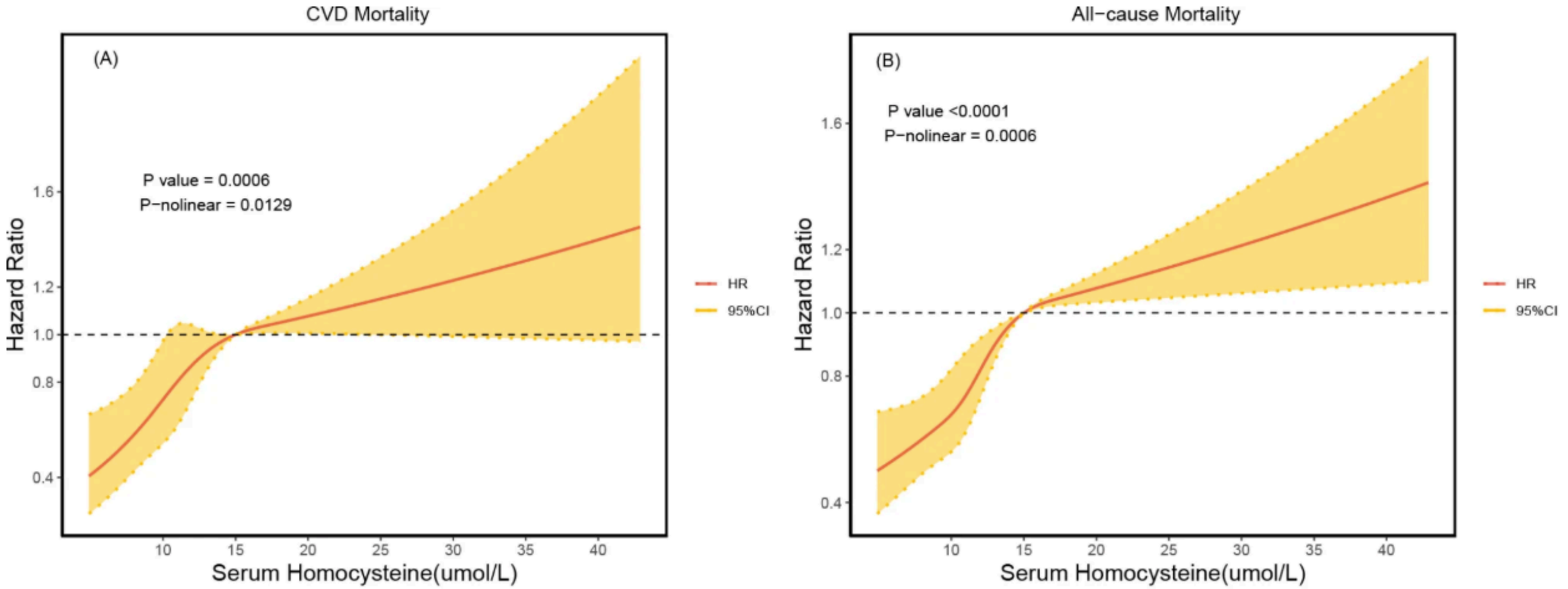
From: Association between homocysteine levels and mortality in CVD: a cohort study based on NHANES database

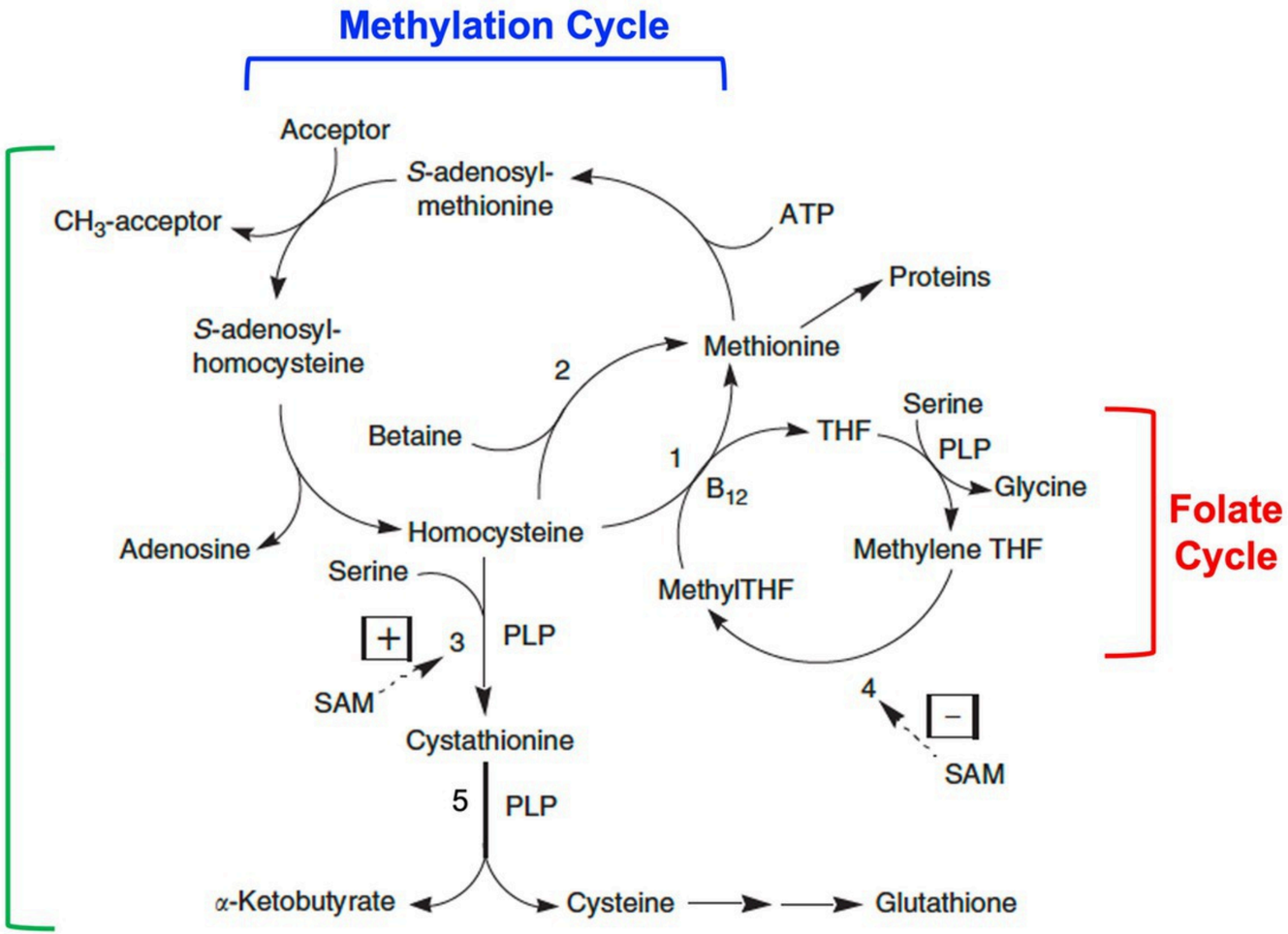



Dose–response relationships between Hcy and CVD mortality **(A)** and all-cause mortality **(B)**, Adjusted for age, sex, race/ethnicity, education, poverty income ratio, smoking status, history of hypertension or diabetes, eGFR, serum total cholesterol, serum uric acid, marital status, serum triglycerides, BMI, and serum vitamin B12

Liu, D., Fang, C., Wang, J. *et al.* Association between homocysteine levels and mortality in CVD: a cohort study based on NHANES database. *BMC Cardiovasc Disord* **24**, 652 (2024). https://doi.org/10.1186/s12872-024-04317-9

# Protective role of Homocysteine

*Under normal stress Homocysteine supports antioxidant defenses by fueling* ***glutathione (GSH)*** *synthesis via the transsulfuration pathway.*



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# Loss of Protective role

*Under extended oxidative and metabolic stress cause  Homocysteine buildup*

- *Changes occur to key enzymes*
- *Depletion of cofactors needed in Homocysteine metabolism*
- *Glutathione production blocked*




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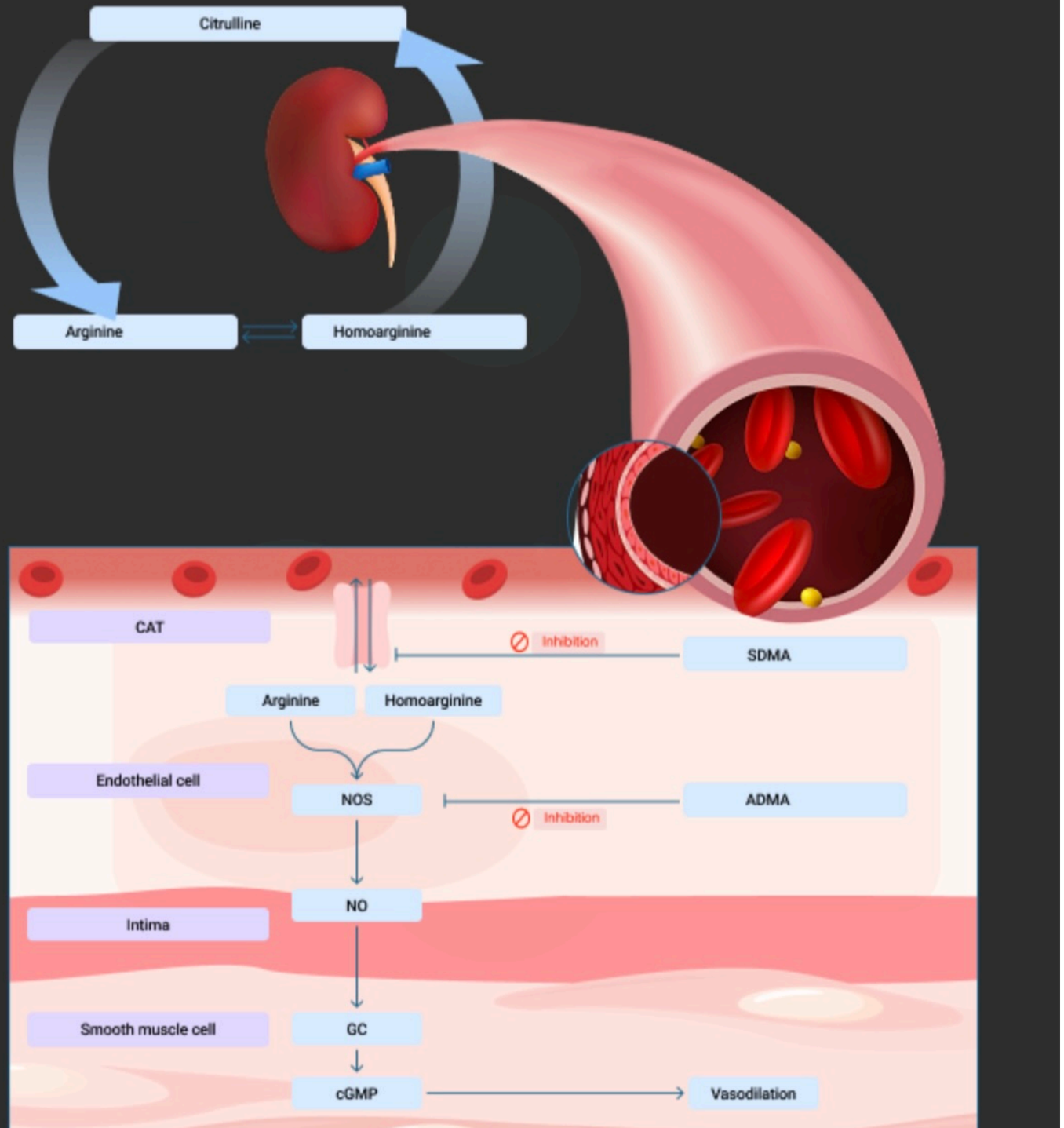
# Homocysteine: Limitations

- Elevated levels can result from genetic variants (MTHFR polymorphisms), B-vitamin deficiencies, renal dysfunction — not all are directly related to CVD risk.
- Lowering homocysteine with folate/B-vitamins doesn't consistently reduce cardiovascular events in clinical trials — suggesting it may be more a marker than a driver in some patients.
- Levels can fluctuate with diet, dehydration, and certain medications, so single-point measurement may not reflect chronic status




# Methylated Arginines

- **ADMA (asymmetric dimethylarginine):** Competitive inhibitor of eNOS.Causes reduced NO synthesis.Promotes eNOS uncoupling → ROS
- **SDMA (symmetric dimethylarginine):** Competes with L-arginine for cellular transport, marker of renal function.Limits intracellular arginine availability for NO production

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# Methylated Arginines

**Clinical Significance of ADMA**

- Elevated ADMA → **endothelial dysfunction, impaired flow-mediated dilation**.
- Predicts **cardiovascular events, stroke, renal outcomes**.
- Independent risk marker beyond LDL-C, CRP, HbA1c.

**Clinical Significance of SDMA**

- Strongly correlates with **renal function (eGFR, cystatin C)**.
- Elevated SDMA → **early renal impairment marker**.
- Adds prognostic value in **cardiovascular disease and mortality risk**.

# Methylated Arginines

**Increased production**: High methylation flux (SAM turnover), protein turnover.
Impaired clearance:

- ADMA → reduced DDAH activity (oxidative stress, hyperglycemia, homocysteine).
- SDMA → reduced renal clearance (early CKD, dehydration, high training load).

Other modulators:

- Genetics (DDAH/PRMT polymorphisms).
- Oral substrate competition (arginase activity, low citrulline).
- Diet/nutrients (folate, B12, creatine, betaine).

# Methylated Arginines: Therapeutic Implications

**ADMA-focused**

- **Support DDAH activity:** Reduce oxidative stress (statins, ARBs, antioxidants).
- **Lower methylation strain:** Folate, B12, B6, betaine, choline, creatine.
- **Substrate therapy:** L-arginine (6–15 g/day but poorly tolerated), L-citrulline (3–6 g/day; bypasses transport limits).
- **Endothelial support:** PDE5 inhibitors, statins, exercise.

**SDMA-focused**

- **Address renal stress:** Optimize BP, hydration, RAAS/SGLT2 modulation if indicated.
- **Bypass CAT competition:** L-citrulline preferred over arginine.
- **Nitrate-rich diet (beetroot, leafy greens):** Activates nitrate–nitrite–NO pathway, independent of eNOS.
- **Creatine supplementation:** Reduces SAM demand, indirectly lowering dimethylarginine burden

# Serial Monitoring

Different response timing

- hs-CRP: 2-4 weeks
- oxLDL: 1-3 months
- ApoB: 2-6 weeks
- Homocysteine: 2-4 weeks
- Lp(a): minimal change
- ADMA / SDMA: 4-8 weeks

# Summary: Clinical Takeaways

- *Early Warning*
- *Reveal Hidden Risk*
- *Risk Reclassification for Intermediate Ranges*
- *Each Marker Reflects a Different Pathological Pathway*



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# Therapeutic Targets

Expanding biomarkers speaks to the growing understanding of the complexity of  Atherosclerosis.

Targets for emerging therapies.

Will guide more nuanced and personalized treatment for atherosclerosis.



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# Thank You!

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# References


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# The Heart of Longevity

Innovations in Cardiovascular and Metabolic Care

Session 2

**Dr. Christopher Davis, MD**

The Vibrant Longevity Summit

# Addressing Residual Risk in Cardiovascular and Cardiometabolic Disease

## The Role of Environmental Toxins and Oxidative/Nitrative Stress

*Christopher Davis MD, FACC*

## Meet Your Speaker

# Christopher Davis, MD, FACC

**Founder Reveal Vitality and Longevity Institute**

Longevity Conference 2025

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# Learning Objectives

- Define and explain the concept of residual risk
- Briefly review nontraditional biomarkers
- Evaluate the role of environmental toxins as risk markers
- Describe the impact of oxidative and nitrative stress on endothelial and mitochondrial health
- Review biomarkers of oxidative and nitrative stress
- Discuss how genetic variants and gene-environment interactions affect risk
- Cases



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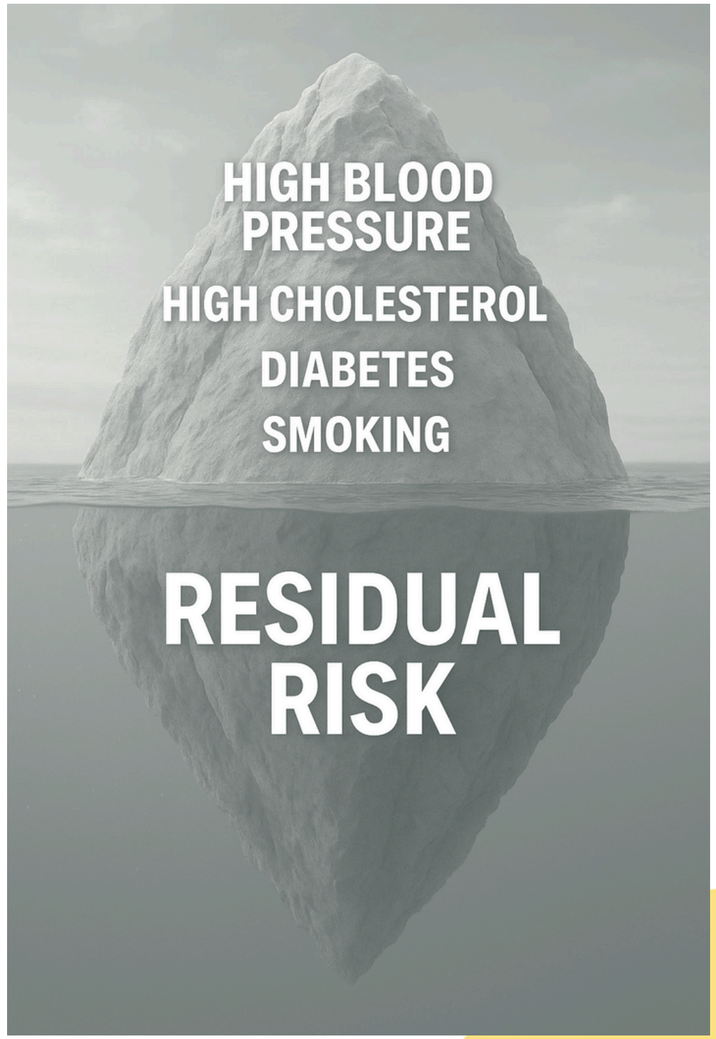
# Staggering Statistics

- 50% of heart attacks occur in individuals with normal LDL cholesterol levels. (Source: Sachdeva A. et al., Am Heart J. 2009)
- 80% of cardiovascular events in patients with Type 2 diabetes occur despite statin therapy and glucose control. (Source: American Diabetes Association; REACH Registry data)
- 1 in 3 adults who experience a major cardiovascular event have no standard modifiable risk factors such as hypertension, hyperlipidemia, or diabetes. (Source: Yusuf S. et al., Lancet. 2004 - INTERHEART Study)

# Definition of Residual Risk

- Residual risk: risk that remains after addressing traditional risk factors
- Exists despite normal cholesterol, blood pressure, and glucose levels
- Contributes to ongoing cardiovascular and metabolic disease burden



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# Nontraditional Risk Factors

- LDL particle size: small, dense LDL particles are more atherogenic
- LDL particle number (LDL-P) is a better predictor than LDL-C
- ApoB, Lp(a), oxidized LDL: advanced markers of lipid-related risk
- hsCRP,LpPLA2, myeloperoxidase: markers of vascular inflammation



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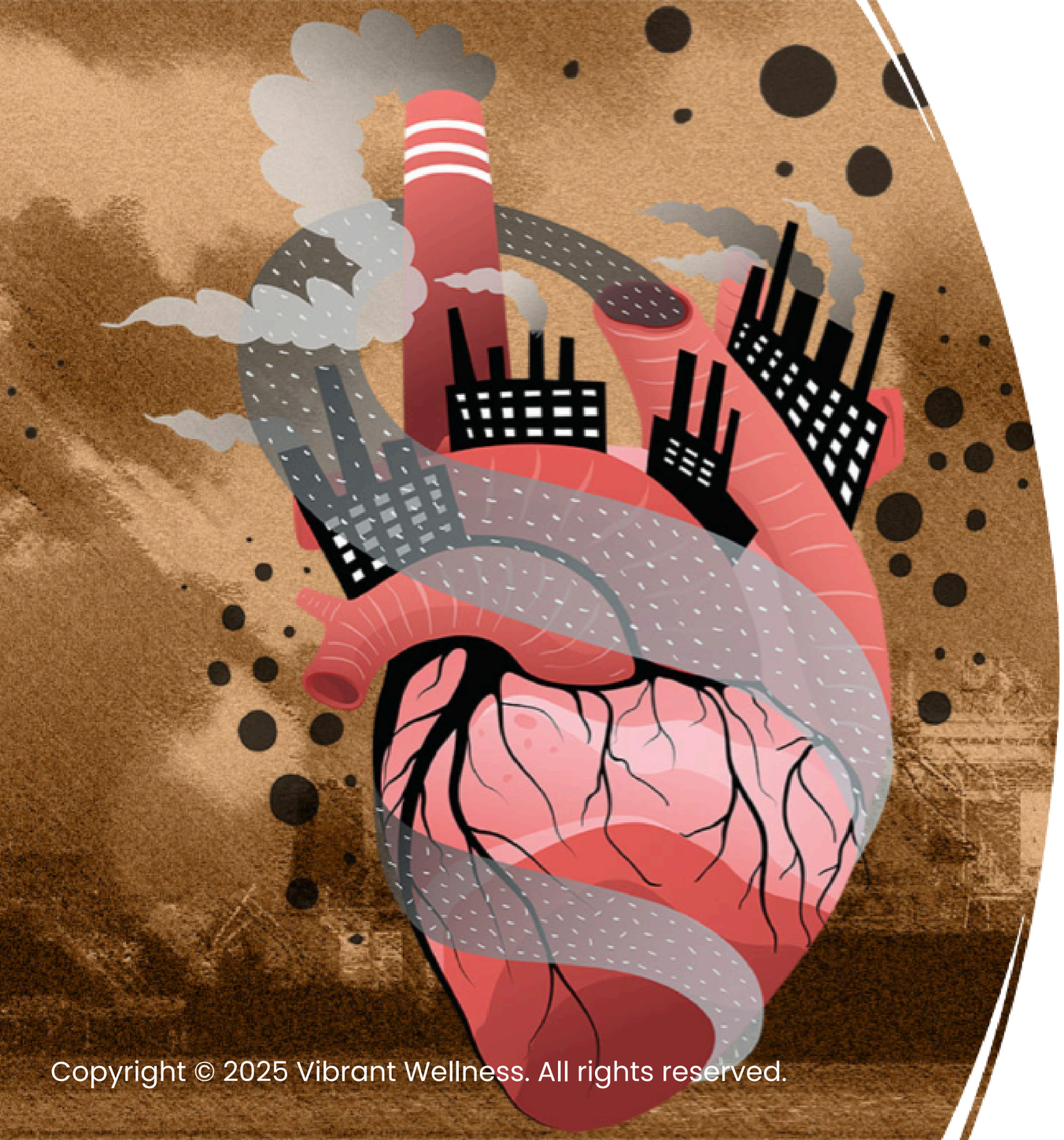
# Nontraditional Risk Facts

- High-sensitivity CRP (hsCRP) independently predicts cardiovascular events in people with normal LDL-C, and therapies like statins only partially reduce inflammation. (Source: Ridker PM et al., NEJM. 2008 - JUPITER Trial)
- Small dense LDL particles are 3 times more atherogenic than larger LDL particles and are often missed in standard cholesterol panels. (Source: Berneis K. and Krauss RM, Curr Opin Lipidol. 2002)
- Among patients undergoing intensive statin therapy, residual inflammatory risk (elevated hsCRP) and residual cholesterol risk (elevated ApoB) persist in over 30% of cases. (Source: Ridker PM, Eur Heart J. 2020)
- Patients with elevated Lp(a) have up to a 2- to 4-fold higher risk of coronary artery disease, regardless of LDL-C levels. (Source: Tsimikas S. et al., J Am Coll Cardiol. 2018)



# Environmental Toxins: An Underrecognized Nontraditional Risk Factor



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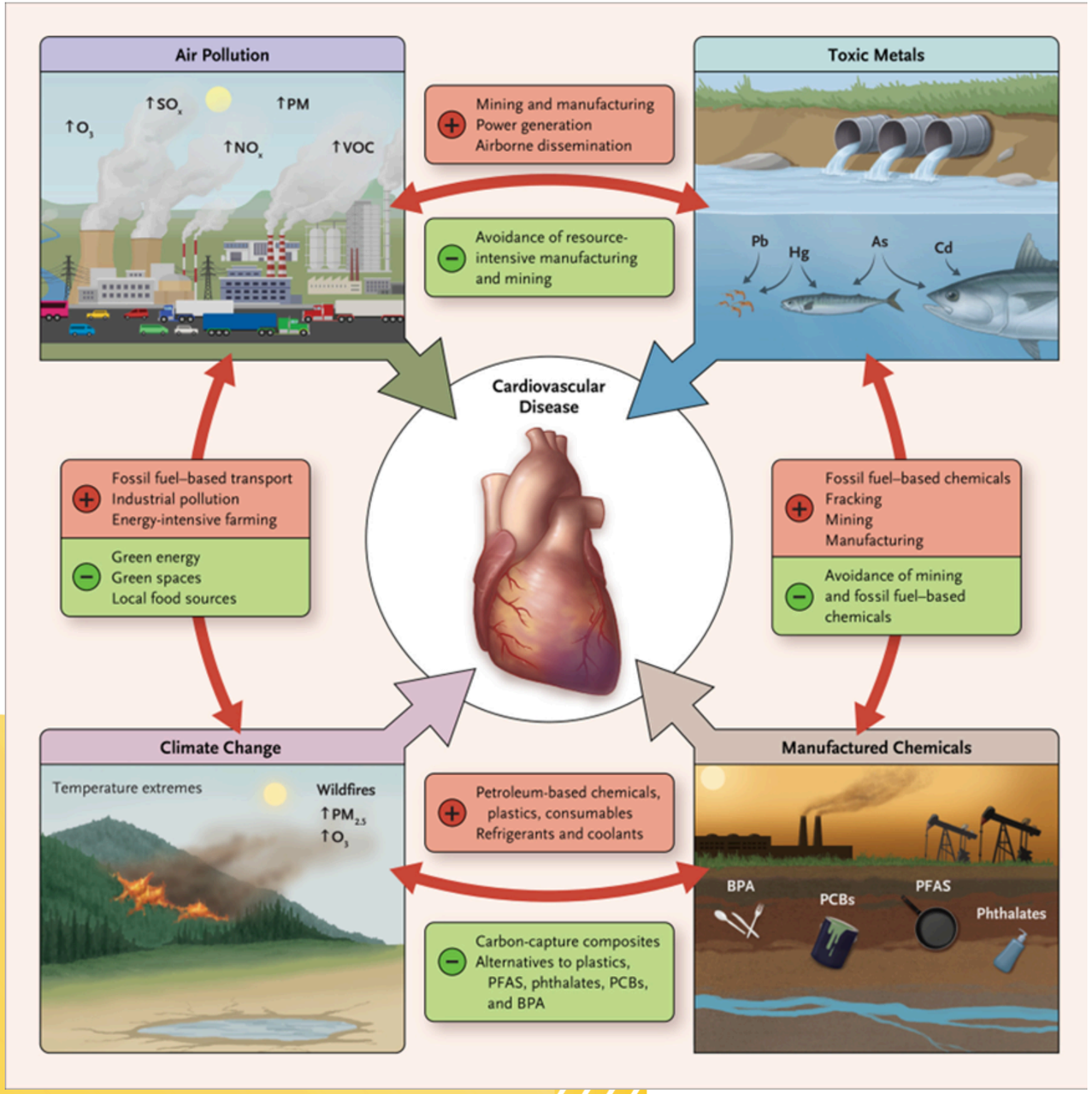
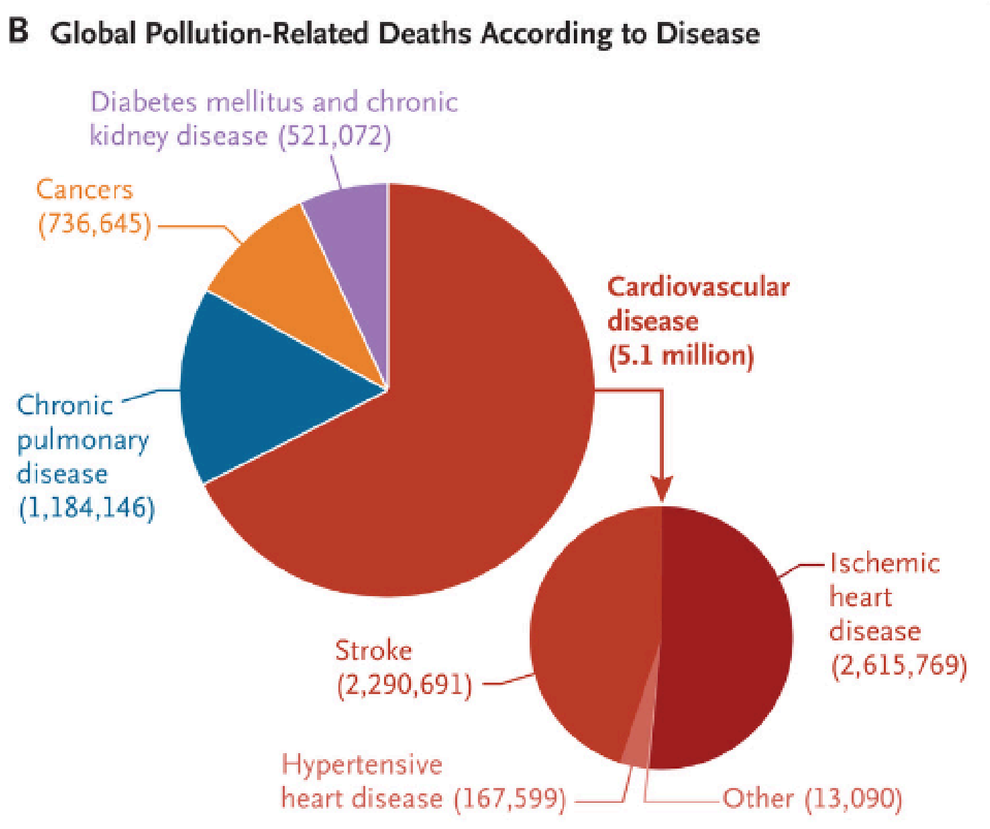
# Common Environmental Toxins






*N Engl J Med* 2021; 385:1881-1892

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# Lead as an Example...

A 2018 study published in *The Lancet Public Health* suggests that of the 2.3 million deaths every year in the United States, about 400,000 are attributable to lead exposure, of which 250,000 are from cardiovascular disease.

Even low-level lead exposure is linked to a **70% higher risk of dying from cardiovascular disease**

**Lanphear BP et al.** Low-Level Lead Exposure and Mortality in US Adults. *Lancet Public Health*. 2018;3(4):e177-e184.



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# Environmental Toxins and Lipoprotein Particle Alterations

| Toxin | Lipoprotein Impact | Mechanism |
|---|---|---|
| BPA | ↑ VLDL, ↑ sdLDL, ↓ HDL2 | SREBP activation, estrogen mimicry |
| Phthalates | ↑ sdLDL, ↓ HDL function | PPAR dysregulation, hepatic enzyme induction |
| Mercury | ↑ oxLDL, ↓ HDL | ROS generation, mitochondrial damage |
| Lead | ↑ LDL, ↓ ApoA1 | Oxidative stress, ER stress |
| PM2.5 | ↓ HDL2, ↑ inflammatory particles | Inflammation, impaired RCT |
| PCBs/Dioxins | ↑ cholesterol, ↓ LDLR | LXR/AhR pathway interference |

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# Mechanisms of Vascular Injury Associated with Environmental Toxins

- **Oxidative/Nitrative Stress**: Toxins like heavy metals and EDCs increase ROS/RNS, reducing nitric oxide (NO) and impairing endothelial function.
- **Pro-inflammatory Pathways**: Activation of NF-κB, TNF-α, IL-6, and CRP drives chronic vascular inflammation.
- **Immune Dysregulation**: Toxins alter macrophage phenotype toward pro-inflammatory M1 type.
- **Epigenetic Modifications**: Changes in DNA methylation and histone acetylation amplify inflammation.
- **Mitochondrial Dysfunction**: Energy deficits and ROS production further damage endothelial cells.



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# What is Oxidative  Stress?

An imbalance between production and accumulation of  reactive oxygen species (ROS) in cells and tissues and the ability of a biological system to detoxify these reactive products with antioxidants. Superoxide radicals ($O_2$•−), hydrogen peroxide ($H_2O_2$), hydroxyl radicals (•OH), and singlet oxygen ($^1O_2$) are commonly defined reactive oxygen species (ROS).



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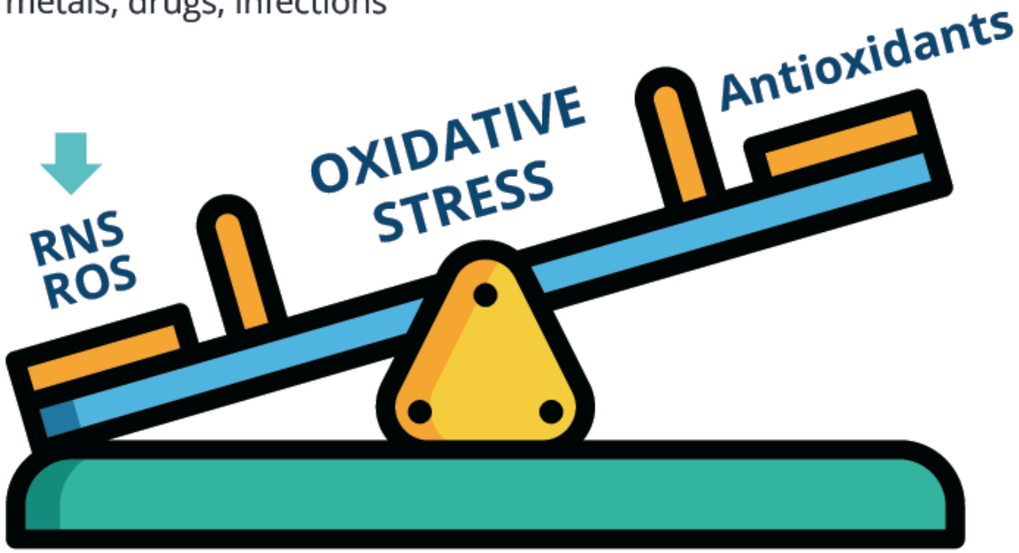
**Lifestyle**
Smoking, alcohol, poor diet, lack of exercise

**Environment**
Phthalates, pesticides, heavy metals, drugs, infections

- Catalase
- Gluthathione
- Superoxide dismutase
- Peroxidase
- Vitamins A, C, E




**Damage To:**

Mitochondrial DNA
Nuclear DNA

Lipid Peroxidation
Apoptosis

**Oxidative stress is beneficial at low levels and harmful at high levels.**

**Balance is crucial.**

VibrantWellness





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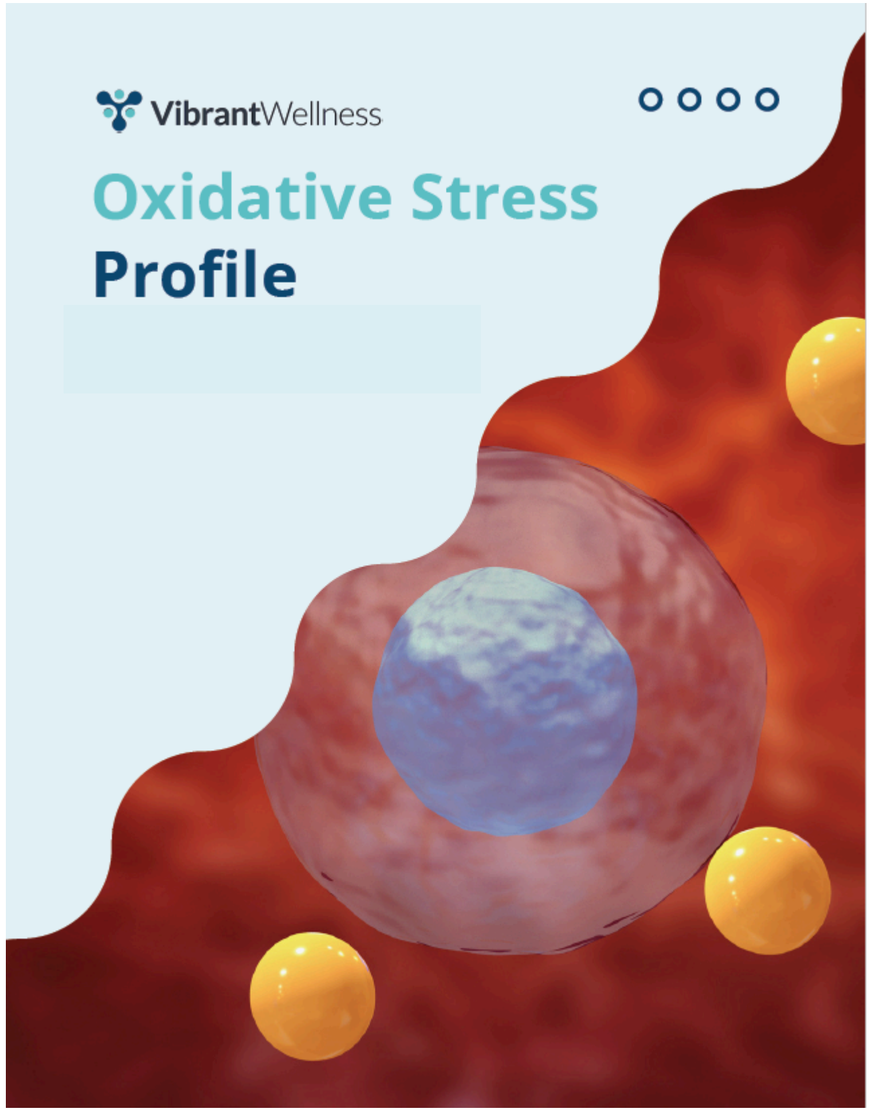


## Oxidative Damage Products Panel Markers

| | |
|---|---|
| **Lipid Peroxidation** | |
| Malondialdehyde | Glutathione 4-hydroxynonenal (GS-HNE) |
| 8-iso-prostaglandin F2α (8-iso-PGF2α) | 11-β-Prostaglandin F2α |
| 15(R)-Prostaglandin F2α | |
| **DNA Damage** | |
| 8-Hydroxy-2-deoxyguanosine (8-OHdG) | |
| 8-Hydroxyguanine | 8-Hydroxyguanosine |
| **Protein Oxidation** | |
| Dityrosine | 3-Bromotyrosine |
| 3-Chlorotyrosine | |
| **Nitrative Stress Biomarkers** | |
| 8-Nitroguanosine | 8-Nitroguanine |
| Nitrotyrosine | |
| **Advanced Glycation Products** | |
| Nε-(carboxymethyl) lysine (CML) | Nε-carboxyethyllysine (CEL) |



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antioxidants

MDPI

*Review*

# Lipid Oxidation Products and the Risk of Cardiovascular Diseases: Role of Lipoprotein Transport

**Markku Ahotupa** [1,2]

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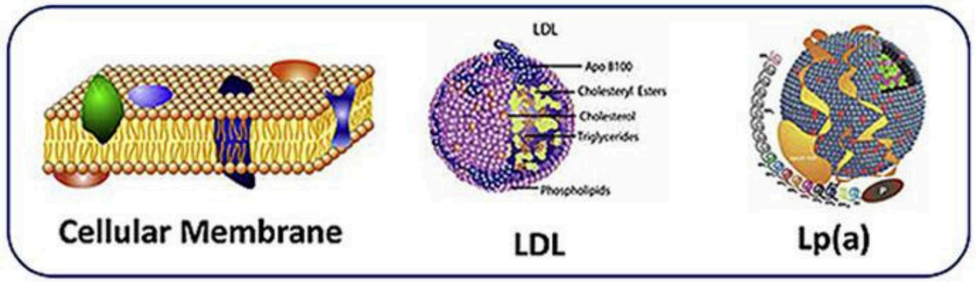
**Abstract:** Cholesterol has for decades ruled the history of atherosclerotic cardiovascular diseases (CVDs), and the present view of the etiology of the disease is based on the transport of cholesterol by plasma lipoproteins. The new knowledge of the lipoprotein-specific transport of lipid oxidation products (LOPs) has introduced another direction to the research of CVD, revealing strong associations between lipoprotein transport functions, atherogenic LOP, and CVD. The aim of this review is to present the evidence of the lipoprotein-specific transport of LOP and to evaluate the potential consequences of the proposed role of the LOP transport as a risk factor. The associations of cholesterol and lipoprotein LOP with the known risk factors of CVD are mostly parallel, and because of the common transport and cellular intake mechanisms it is difficult to ascertain the independent effects of either cholesterol or LOP. While cholesterol is known to have important physiological functions, LOPs are merely regarded as metabolic residues and able to initiate and boost atherogenic processes. It is therefore likely that with the increased knowledge of the lipoprotein-specific transport of LOP, the role of cholesterol as a risk factor of CVD will be challenged.

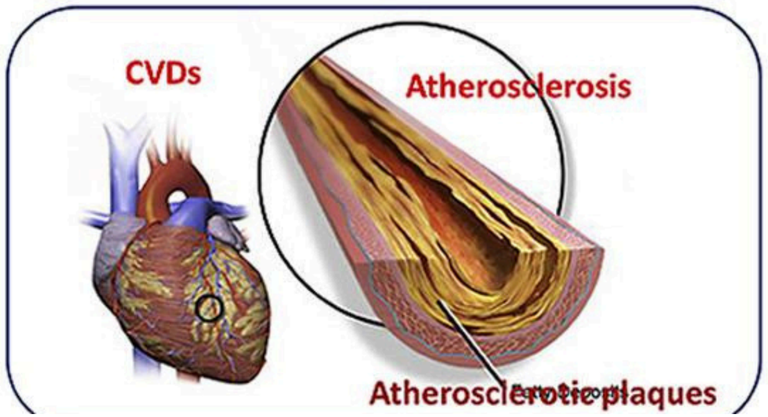
**Keywords:** atherosclerosis; cardiovascular diseases; cholesterol; high-density lipoprotein; lipid oxidation; lipoprotein functions; low-density lipoprotein; risk factors

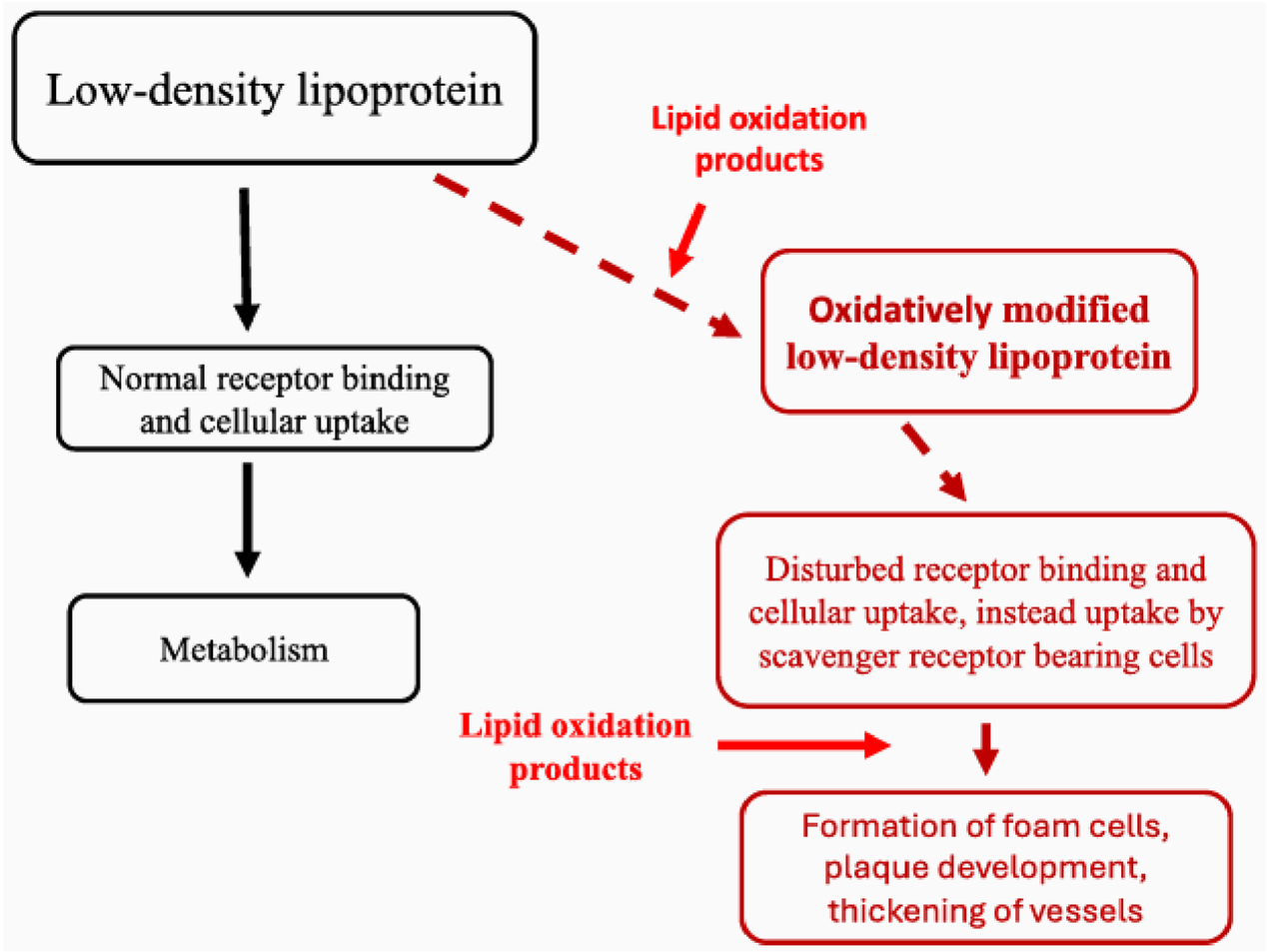



LPO

**Oxidized PL, CEs, 4-HNE,4-ONE, MDA**

**Inflammatory responses**
Monocytes, macrophages, and EC etc




Antioxidants 2024, 13, 512.



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# What is Nitrative Stress?

- **Nitrite ($NO_2^-$):** Normally non-reactive with DNA, but in the presence of reactive oxygen species (ROS) can form harmful nitrosating agents (e.g., $N_2O_3$) or nitrogen dioxide ($NO_2$). Contributes to lipid nitration and indirectly modifies proteins (e.g., forming nitrotyrosine or modifying cysteine).
- **Nitric Oxide (NO)*:* Produced enzymatically from L-arginine by nitric oxide synthase (eNOS for vascular health, nNOS for neurotransmission, iNOS during inflammation). Also formed non-enzymatically during stress, disease, or hypoxia. Has both antioxidant and pro-oxidant effects depending on tissue oxidative status.
- **Peroxynitrite ($ONOO^-$):** Generated from *NO and superoxide ($O_2\bullet^-$). Damages lipids, oxidizes amino acids like methionine and tyrosine, and induces DNA oxidation (e.g., 8-nitroguanine formation).
- **Nitrogen Dioxide ($NO_2$)*:* Not naturally produced in the body; arises from environmental sources (pollution, tobacco smoke, bacterial activity). Can form from nitrite decomposition or nitrite/nitrate exposed to ionizing radiation.



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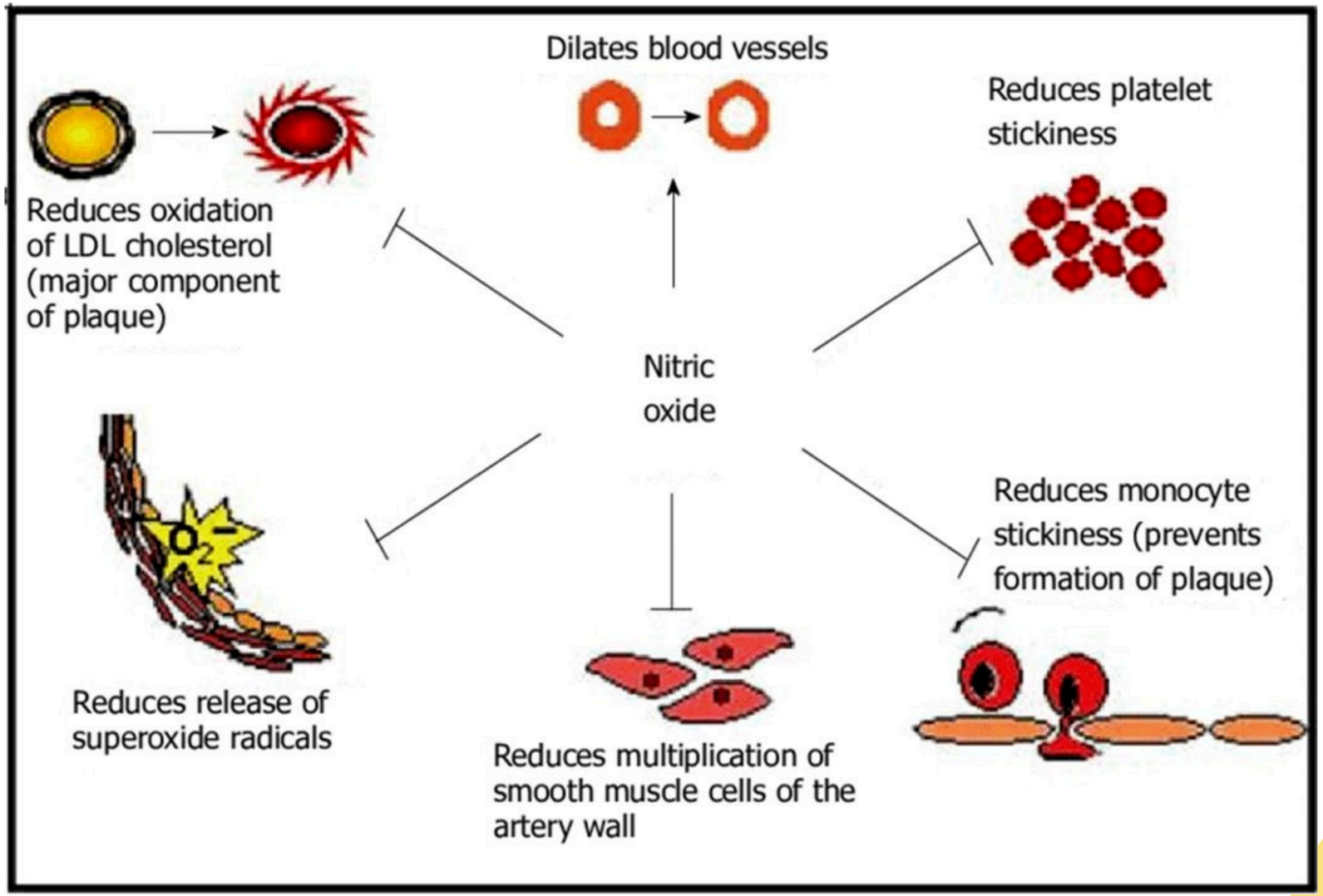
# Roles of Nitric Oxide in Vascular Disease



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# “The biochemistry of NO is intriguingly complex…”

Cell
Leading Edge

CellPress
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Review

## Nitric oxide signaling in health and disease

Jon O. Lundberg[1,*] and Eddie Weitzberg[1,*]
[1]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden
*Correspondence: jon.lundberg@ki.se (J.O.L.), eddie.weitzberg@ki.se (E.W.)
https://doi.org/10.1016/j.cell.2022.06.010

**SUMMARY**

The surprising discovery that the diatomic gas nitric oxide (NO) is generated by mammalian cells and serves to regulate a multitude of physiological processes has continued to fascinate biologists for almost four decades. Here, we discuss the basics of NO biology emphasizing recent advancements in the field including novel means of increasing NO bioactivity with therapeutic and nutritional implications.

*Cell*. 2022 Aug 4;185(16):2853-2878



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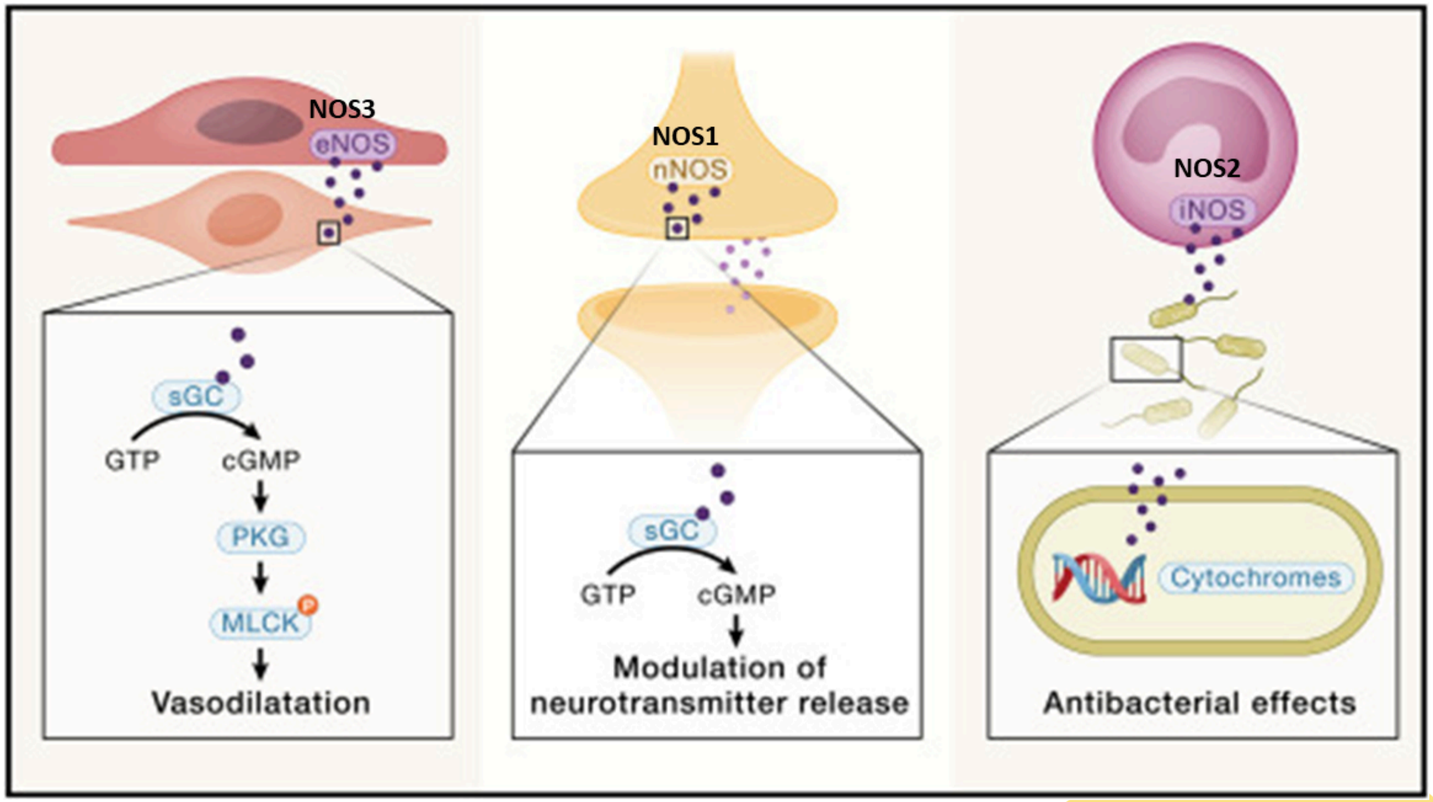
# Nitric Oxide Synthase(NOS) Isoforms

NOS exists in three isoforms, all of which generate NO and L-citrulline from L-arginine, molecular oxygen, and NADPH




*Cell*. 2022 Aug 4;185(16):2853-2878



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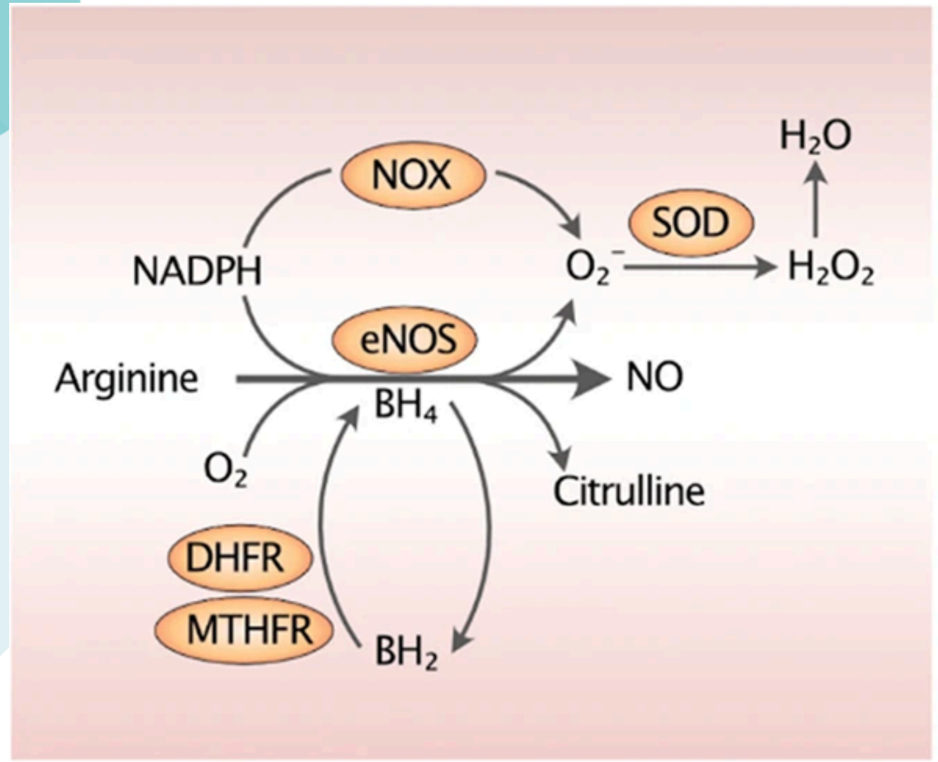
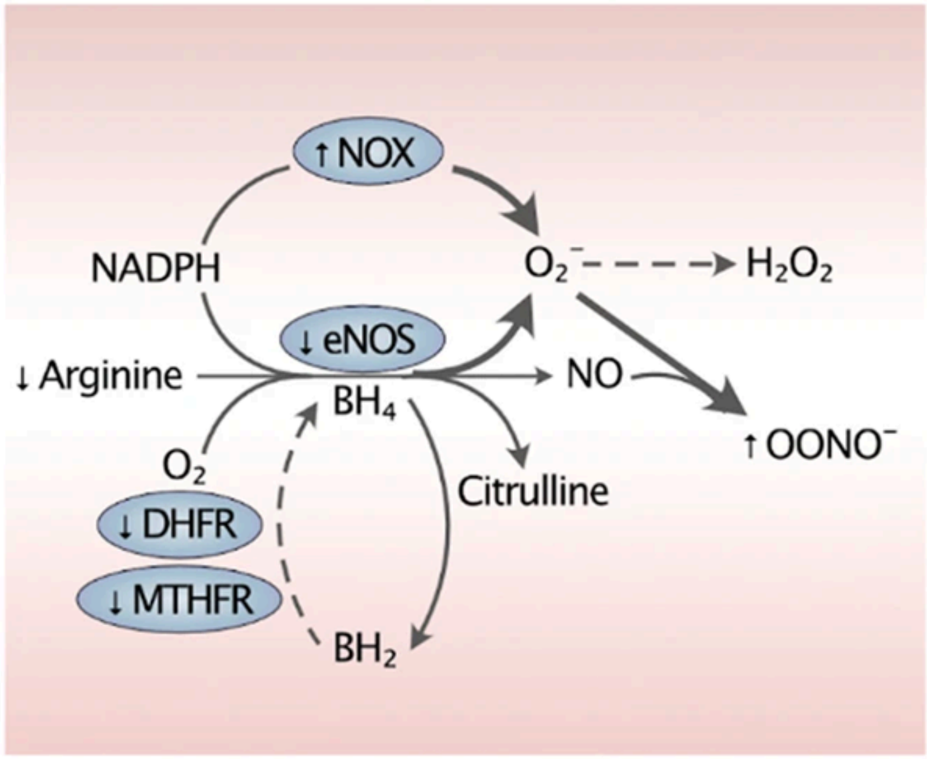
# What is eNOS Uncoupling?




When local concentrations of cofactors L-arginine and BH4 are depleted, or absent, nitric oxide synthase(NOS) formation of NO is diminished. Though NO production is halted, NOS still functions. Cofactor depleted NOS still transfers the electron to the oxygen forming **superoxide**. This function of NOS leads to uncoupling. The uncoupling of eNOS allocates superoxide to a local small concentration of NO, formed prior to cofactor depletion. *The reaction of NO with superoxide produces* ***PEROXINITRITE***



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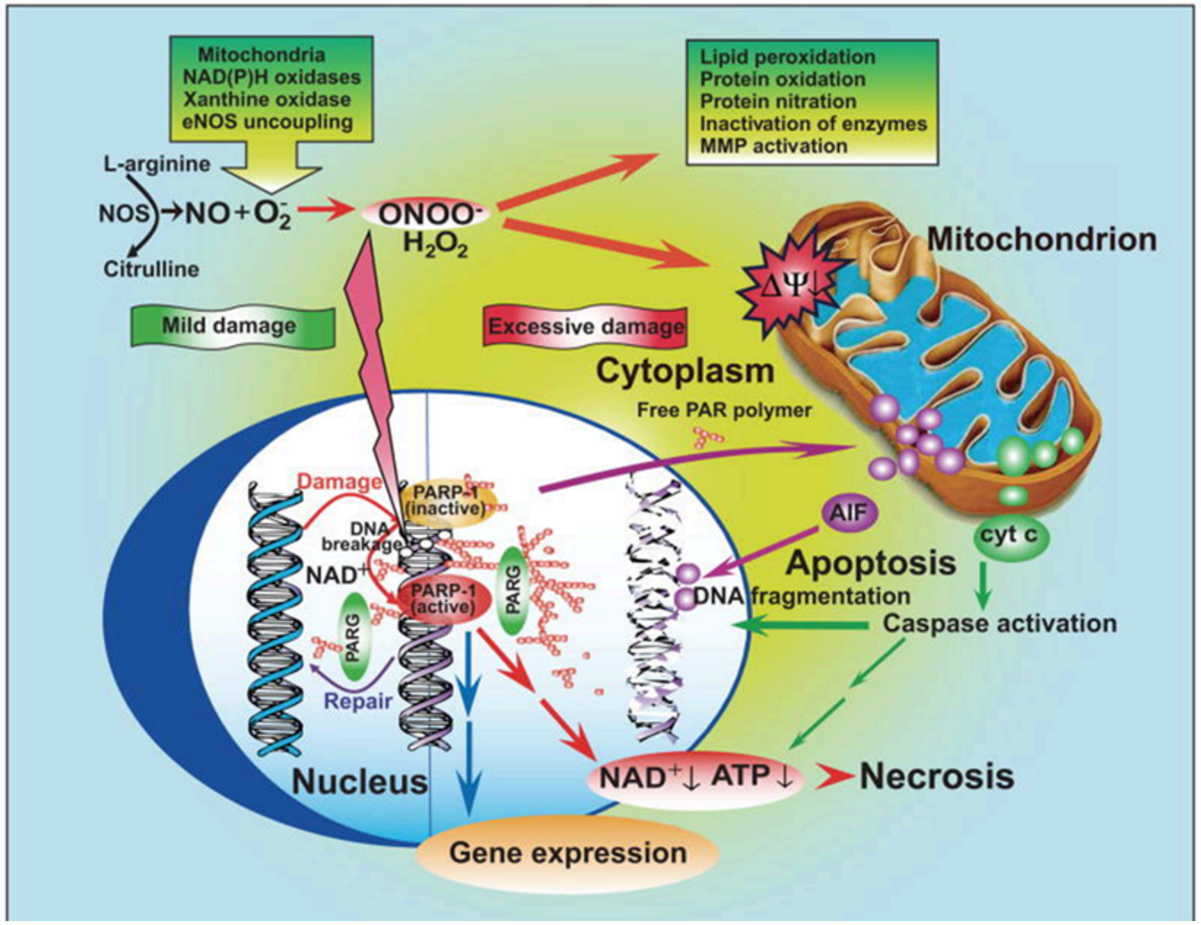
# Peroxynitrite as a Potent Oxidant

- Peroxynitrite ($ONOO^-$) is one of the most biologically reactive nitrogen-derived oxidants, and it plays a significant role in cardiovascular disease through mechanisms involving **oxidative and nitrative stress**.

- Nitric oxide ($NO\cdot$) reacts rapidly with superoxide ($O_2\cdot^-$) o**utcompeting superoxide dismutase (SOD)** ability to remove superoxide, leading to reduced bioavailable nitric oxide and increased oxidative/nitrative stress.



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# Pathophysiological Effects of Peroxynitrite in Cardiovascular Disease

**Endothelial Dysfunction**

- eNOS uncoupling**:** Peroxynitrite oxidizes tetrahydrobiopterin ($BH_4$), a cofactor for endothelial nitric oxide synthase (eNOS) leading to superoxide production instead of NO, amplifying oxidative stress.

**Lipid Oxidation**

- Peroxynitrite oxidizes LDL and HDL particles promoting foam cell formation and atherosclerotic plaque growth.

**Mitochondrial Dysfunction**

- Damages mitochondrial respiratory chain complexes leading to reduced ATP production and increased ROS/RNS.

**Prothrombotic Effects**

- Nitration of fibrinogen alters fibrin structure, increasing clot stability.
- Promotes platelet activation through oxidative/nitrative modification of membrane receptors.

**Inflammatory Signaling**

- Activates NF-κB and p38 MAPK pathways, upregulating adhesion molecules (VCAM-1, ICAM-1) and cytokines.
- Recruits monocytes and neutrophils to vascular endothelium.



Pacher, P., Beckman, J. S., & Liaudet, L. (2007). *Nitric oxide and peroxynitrite in health and disease*. **Physiological Reviews**, 87(1), 315–424.

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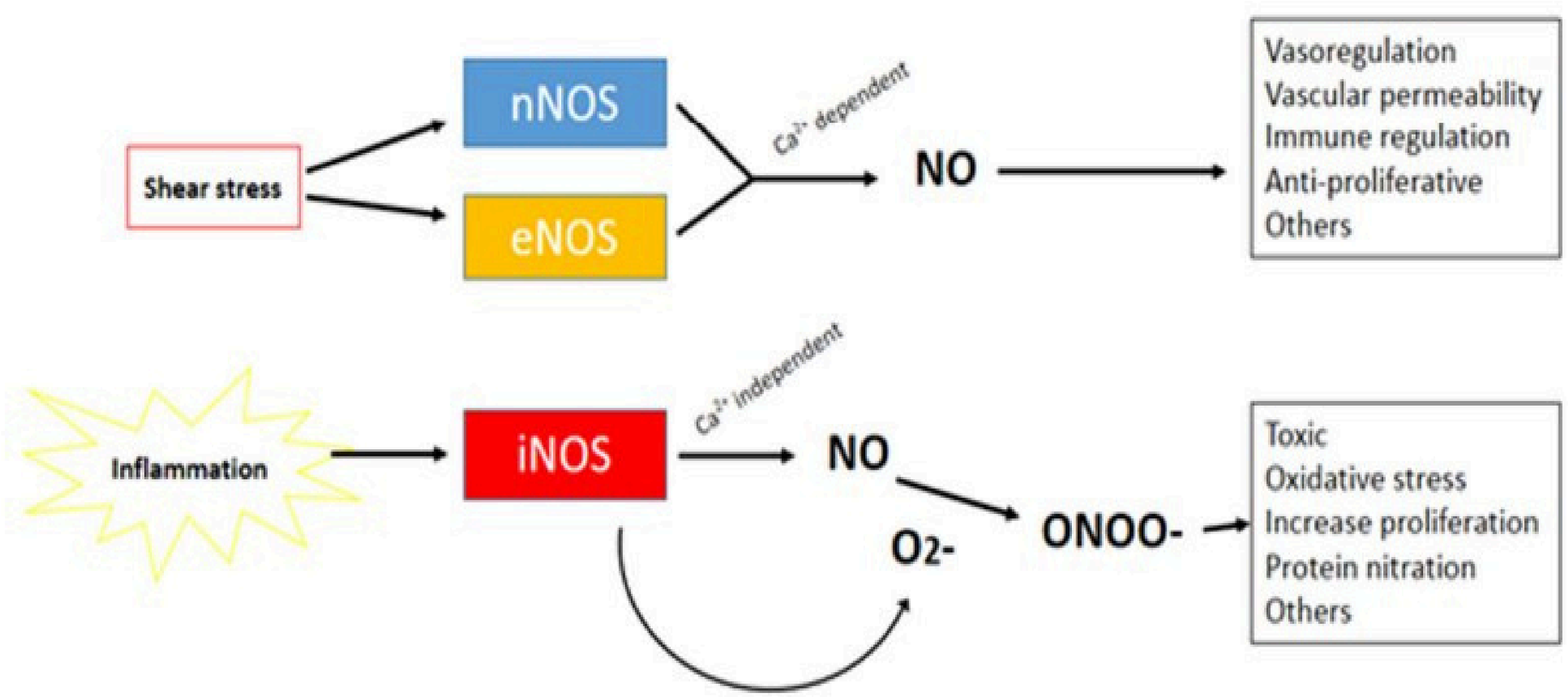
# iNOS Activation Stimulates Peroxynitrite Formation




*Biomedicine & Pharmacotherapy*. 93(2017). 370-375



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# Nitrative Stress Biomarkers

**8-Nitroguanosine** (RNA), **8-Nitroguanine** (DNA), and **Nitrotyrosine** (Proteins) are key biomarkers of damage from reactive nitrogen species (RNS).

- Each reflects a different molecular target of nitrative stress:
  - RNA damage → genetic variation and impaired protein synthesis.
  - DNA damage → mutagenesis and genomic instability.
  - Protein damage → enzyme inactivation, mitochondrial dysfunction, and inflammation.

- Common pathways:
  - **Peroxynitrite** formation from NO and superoxide.
  - Activation of oxidative/nitrative stress and pro-inflammatory signaling.

- Clinical impact:
  - Contributes to endothelial dysfunction, atherosclerosis, hypertension, insulin resistance, neurodegeneration, and other chronic cardiometabolic diseases.



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# Genetic Susceptibility to Oxidative/Nitrative Stress

**Oxidative Genetics Panel Markers**

| Gene | SNP ID |
|---|---|
| PRKAA2 | rs2796498 |
| PRKAA2 | rs10789038 |
| CAT | rs1001179 |
| CAT | rs7943316 |
| CAT | rs4756146 |
| COX-2 | rs20417 |
| CYB5R3 | rs916321 |
| CYP1A1 | rs1048943 |
| GLUL | rs10911021 |
| GPX1 | rs1050450 |
| GPX1 | rs1987628 |
| GPX2 | rs4902346 |
| GPX2 | rs2071566 |
| GPX4 | rs713041 |
| GSTM1 | rs366631 |
| GSTM5 | rs3754446 |
| GSTP1 | rs1695 |
| GSS | rs121909307 |
| GSR | rs8190955 |
| HMOX1 | rs2071746 |
| CYBA | rs4673 |
| CYBA | rs9932581 |
| SELENOP | rs3877899 |
| SOD1 | rs2234694 |
| SOD2 | rs4880 |
| SOD3 | rs1799895 |
| SOD3 | rs8192287 |
| TXNRD1 | rs7310505 |
| TXNRD2 | rs1548357 |
| TRXR2 | rs4485648 |
| XDH | rs206812 |
| XDH | rs2073316 |



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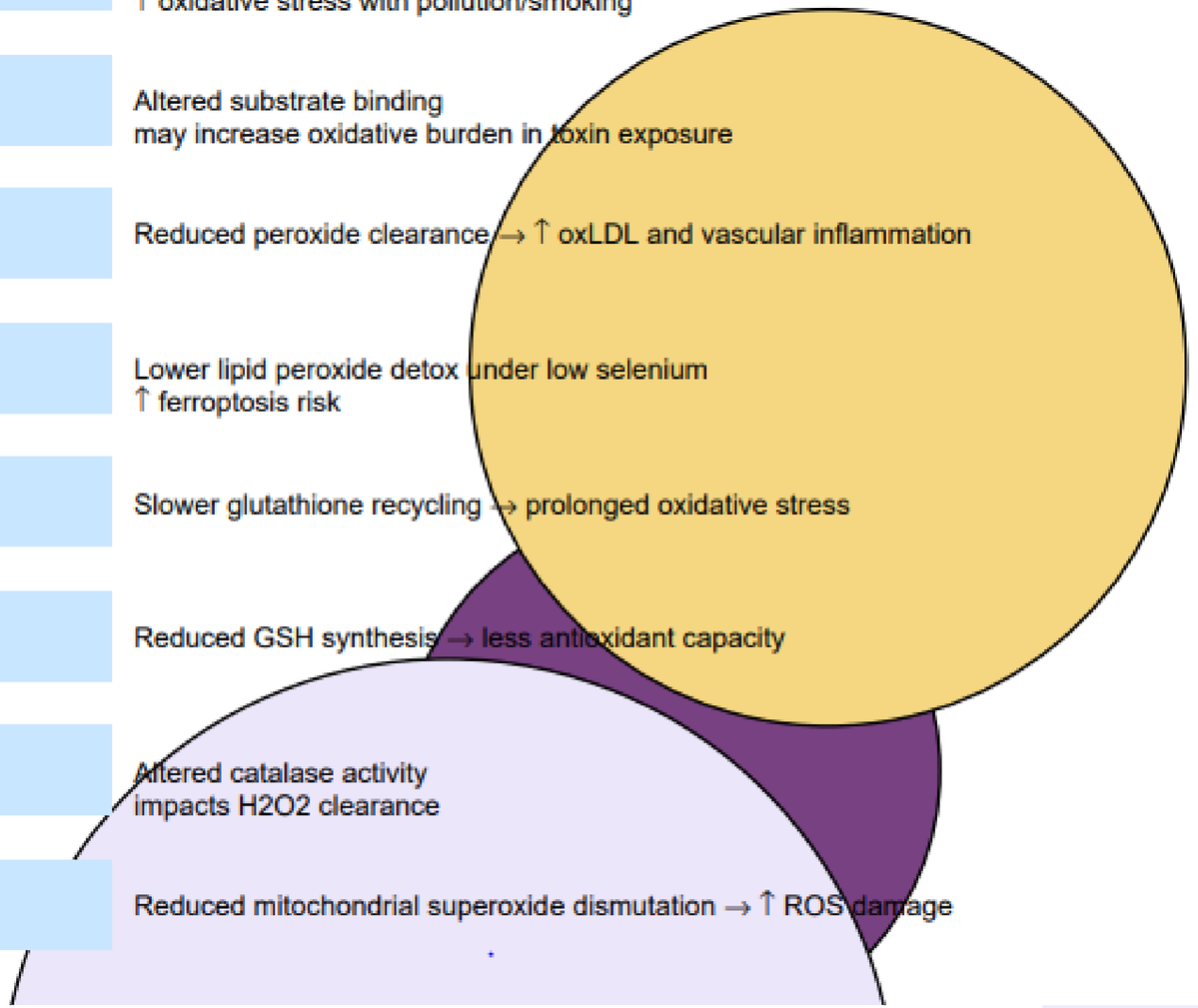
# Common Detox Gene Variants Influencing Cardiovascular Risk

| | |
|---|---|
| **GSTM1 (null)** | Loss of GST enzyme → impaired PAH/benzene detox<br>↑ oxidative stress with pollution/smoking |
| **GSTP1 Ile105Val** | Altered substrate binding<br>may increase oxidative burden in toxin exposure |
| **GPX1 rs1050450 (Pro198Leu)** | Reduced peroxide clearance → ↑ oxLDL and vascular inflammation |
| **GPX4 rs713041** | Lower lipid peroxide detox under low selenium<br>↑ ferroptosis risk |
| **GSR rs8190955** | Slower glutathione recycling → prolonged oxidative stress |
| **GSS rs121909307** | Reduced GSH synthesis → less antioxidant capacity |
| **CAT rs1001179** | Altered catalase activity<br>impacts $H_2O_2$ clearance |
| **SOD2 rs4880 (Ala16Val)** | Reduced mitochondrial superoxide dismutation → ↑ ROS damage |





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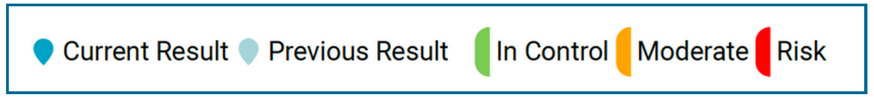
# Gene–Environment Interactions

- Epigenetic changes from toxin exposure affect gene expression
- Methylation and histone modification of inflammatory and metabolic genes
- Nutrigenomic interventions that support detoxification pathways

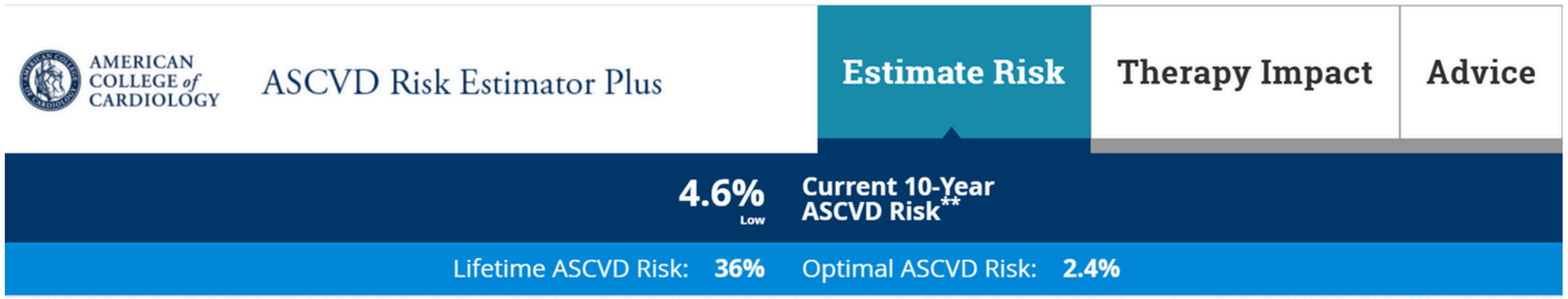
# Case 1- Assessing Residual Risk

51 yo male with history of anxiety presents with atypical LLQ pain. No other cardiac risk factors. Exercises regularly. Seen by cardiologist a year ago and told everything looked “good”.




**Cardiac Health Panel**

| Lipids | Current | Previous | Result | Reference |
|---|---|---|---|---|
| Cholesterol, Total (mg/dL) | 186 | | 0 199 240 | ≤199.0 |
| LDL Calculation (mg/dL) | 128 | | 0 99 129 | ≤99.0 |
| HDL Direct (mg/dL) | 36 | | 0 44 65 | ≥66.0 |
| Cholesterol/HDL Ratio | 5.2 | | 0 3.5 4.9 | ≤3.5 |
| Triglyceride (mg/dL) | 113 | | 0 149 200 | ≤149.0 |



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# Advanced Lipid and Inflammation Markers

| LDL Direct | Current | Previous | Result | Reference |
|---|---|---|---|---|
| LDL Direct (mg/dL) | 131 | | 0 99 129 | ≤99.0 |
| **Apolipoproteins** | **Current** | **Previous** | **Result** | **Reference** |
| Apo A-1 (mg/dL) | 125 | | 0 139 | ≥140.0 |
| Apo B (mg/dL) | 116 | | 0 89 119 | ≤89.0 |
| Apo B: Apo A-1 | 0.93 | | 0 0.59 0.8 | ≤0.59 |
| **Inflammation** | **Current** | **Previous** | **Result** | **Reference** |
| PLAC (nmol/min/mL) | 226 | | 0 224 | ≤224.0 |
| Homocysteine (µmol/L) | 12.1 | | 0 9 14 | ≤9.0 |
| hs-CRP (mg/L) | 0.4 | | 0 0.9 3 | ≤0.9 |
| ox-LDL* (U/L) | 70.5 | | 0 60 70 | ≤60.0 |
| MPO* (pmol/L) | 154.0 | | 0 599 2999 | ≤599.9 |
| **LipoProtein Markers** | **Current** | **Previous** | **Result** | **Reference** |
| sdLDL* (mg/dL) | 63.1 | | 0 50 | ≤50.0 |
| Lp(a) (mg/dL) | 46 | | 0 29 | ≤29.0 |

## Cardiax

⊕⊕ Homozygous Mutant ⊕⊖ Heterozygous ⊖⊖ Homozygous Wild

| Test Name | Gene Name | Risk Association | Your Mutation | Your Risk | Reference |
|---|---|---|---|---|---|
| ApoE | APOE | Higher total and LDL cholesterol | ⊖⊖ε4/ε4 | Elevated | ε3/ε3, ε2/ε3, ε1/ε4, ε1/ε2 |
| rs10757278 | 9p21 | Myocardial infarction | ⊖⊖A/A | Normal | A/A |

## Glycemic Control

| Test Name | Current | Previous | Result | Reference |
|---|---|---|---|---|
| Glucose(Diabetes) (mg/dL) | 88 | | 61 69 100 126 | 70.0-100.0 |
| Hemoglobin A1c (%) | 5.4 | | 0 5.6 6.4 | ≤5.6 |
| Glycated Serum Protein (umol/L) | 249 | | 0 285 | ≤285.0 |
| Insulin (µU/mL) | 8.2 | | 0 2.5 24.9 | 2.6-24.9 |

## Oxidative Stress Biomarkers

| Lipid Peroxidation | Current | Previous | Result (75th / 95th) | Reference |
|---|---|---|---|---|
| 11-β-Prostaglandin F2α (ug/g) | 0.11 | | 0.11 0.4 | ≤0.4 |
| 15(R)-Prostaglandin F2α (ug/g) | <0.05 | | 0.07 0.22 | ≤0.22 |
| 8-iso-prostaglandin F2α (8-iso-PGF2α) (ug/g) | 0.10 | | 0.1 0.26 | ≤0.26 |
| Glutathione 4-hydroxynonenal (GS-HNE) (ug/g) | 0.23 | | 0.3 2.5 | ≤2.5 |
| Malondialdehyde (ug/g) | 60.15 | | 72.87 163.53 | ≤163.53 |

| Fatty Acids: Omega-3 & 6 | | Current | Previous | Result | Reference |
|---|---|---|---|---|---|
| AA (Arachidonic acid) | Cellular | 16.56 | | 0 5.49 19.0 | 5.5-19.01 (%) |
| AA/EPA | Cellular | 23.0 | | 0 2.4 10.9 | 2.5-10.9 |
| EPA | Cellular | 0.72 | | 0 0.14 2.26 | 0.15-2.26 (%) |
| LA (Linoleic acid) | Cellular | 7.67 | | 0 3.21 10.4 | 3.22-10.49 (%) |
| Omega-3 Index | Cellular | 5.00 | | 0 2.65 7.99 12.6 | 8.0-12.65 (%) |
| Total Omega-3 | Cellular | 2.81 | | 0 3.24 13.9 | 3.25-13.99 (%) |
| Total Omega-6 | Cellular | 26.75 | | 0 11.0 34.9 | 11.03-34.96 (%) |

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# Environmental Toxin Panel

## High (>95th percentile)

Heavy Metals | Environmental Toxins

| TEST NAME | CURRENT RESULT | PREVIOUS RESULT | CURRENT RESULT / PREVIOUS RESULT | REFERENCE |
|---|---|---|---|---|
| Barium* | 13.96 | | 0 2.33 5.59 | ≤5.59 ug/g |
| Lead* | 25.11 | | 0 0.52 1.16 | ≤1.16 ug/g |
| Mercury* | 26.64 | | 0 0.57 1.61 | ≤1.61 ug/g |
| Thallium* | 0.52 | | 0 0.24 0.43 | ≤0.43 ug/g |
| 2-Hydroxyisobutyric Acid (2HIB) | 4316.25 | | 0 795 1215 | ≤1215.72 ug/g |
| Bisphenol A (BPA)* | 17.61 | | 0 2.12 5.09 | ≤5.09 ug/g |
| Butylparaben* | 15.79 | | 0 0.25 4.39 | ≤4.39 ug/g |

* Indicates NHANES population data reference ranges.

## Moderate (75th-95th percentile)

Heavy Metals

| TEST NAME | CURRENT RESULT | PREVIOUS RESULT | CURRENT RESULT / PREVIOUS RESULT | REFERENCE |
|---|---|---|---|---|
| Aluminum | 23.29 | | 0 17.8 45.1 | ≤45.15 ug/g |
| Antimony* | 0.1 | | 0 0.07 0.16 | ≤0.16 ug/g |
| Arsenic* | 12.9 | | 0 11.9 52 | ≤52 ug/g |
| Cadmium* | 0.6 | | 0 0.29 0.8 | ≤0.8 ug/g |

## Moderate (75th-95th percentile)

Heavy Metals | Environmental Toxins

| TEST NAME | CURRENT RESULT | PREVIOUS RESULT | CURRENT RESULT / PREVIOUS RESULT | REFERENCE |
|---|---|---|---|---|
| Nickel | 8.25 | | 0 6.37 12.1 | ≤12.13 ug/g |
| Tellurium | 0.61 | | 0 0.42 0.89 | ≤0.89 ug/g |
| Tin* | 2.03 | | 0 1 3.72 | ≤3.72 ug/g |
| Glyphosate | 7.01 | | 0 1.65 7.6 | ≤7.6 ug/g |
| N-Acetyl (2,Hydroxypropyl) Cysteine (NAHP)* | 381.77 | | 0 101 403 | ≤403 ug/g |
| Tiglylglycine (TG) | 0.3 | | 0 0.09 3.24 | ≤3.24 ug/g |

* Indicates NHANES population data reference ranges.



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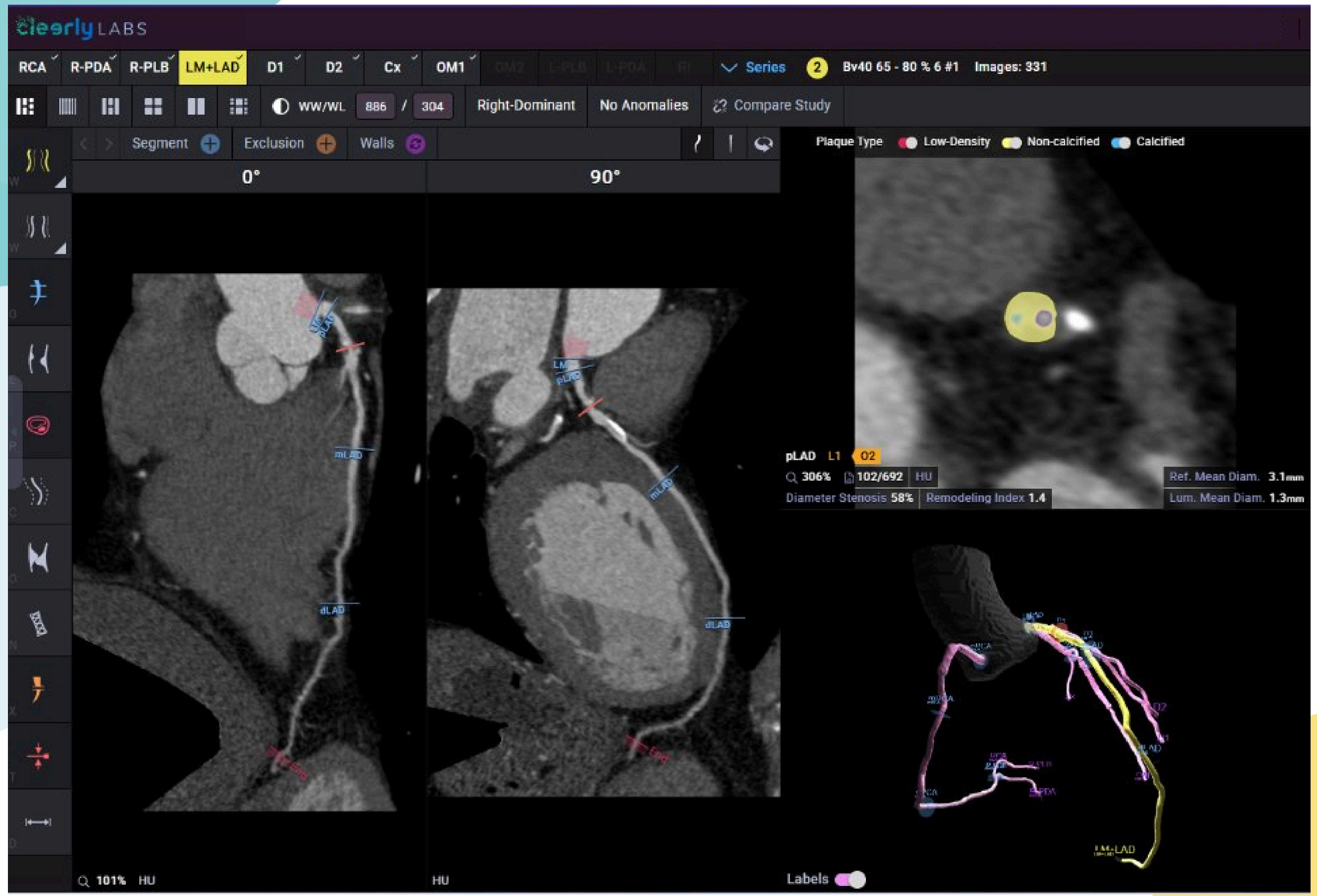
Cleerly LABS
RCA
R-PDA
R-PLB
LM+LAD
D1
D2
Cx
OM1
Series
2
Bv40 65 - 80 % 6 #1
Images: 331
WW/WL
886
304
Right-Dominant
No Anomalies
Compare Study
Segment
Exclusion
Walls
0°
90°
Plaque Type
Low-Density
Non-calcified
Calcified
pLAD
L1
O2
306%
102/692
HU
Diameter Stenosis 58%
Remodeling Index 1.4
Ref. Mean Diam. 3.1mm
Lum. Mean Diam. 1.3mm
101%
HU
HU
Labels

# Case 2- Addressing Residual Risk

66 yo male personal trainer presents for evaluation secondary to elevated coronary calcium score. He is very active and denies any cardiovascular symptoms.

## Cardiac Health Panel

| Lipids | Current | Previous | Result | Reference |
|---|---|---|---|---|
| Cholesterol, Total (mg/dL) | 250 | | 0 199 240 | ≤199.0 |
| LDL Calculation (mg/dL) | 167 | | 0 99 129 | ≤99.0 |
| HDL Direct (mg/dL) | 57 | | 0 44 65 | ≥66.0 |
| Cholesterol/HDL Ratio | 4.4 | | 0 3.5 4.9 | ≤3.5 |
| Triglyceride (mg/dL) | 126 | | 0 149 200 | ≤149.0 |

| LDL Direct | Current | Previous | Result | Reference |
|---|---|---|---|---|
| LDL Direct (mg/dL) | 171 | | 0 99 129 | ≤99.0 |

| Apolipoproteins | Current | Previous | Result | Reference |
|---|---|---|---|---|
| Apo A-1 (mg/dL) | 145 | | 0 139 | ≥140.0 |
| Apo B (mg/dL) | 137 | | 0 89 119 | ≤89.0 |
| Apo B: Apo A-1 | 0.94 | | 0 0.59 0.8 | ≤0.59 |

| Inflammation | Current | Previous | Result | Reference |
|---|---|---|---|---|
| PLAC (nmol/min/mL) | 220 | | 0 224 | ≤224.0 |
| Homocysteine (µmol/L) | 16 | | 0 9 14 | ≤9.0 |
| hs-CRP (mg/L) | 0.4 | | 0 0.9 3 | ≤0.9 |
| ox-LDL* (U/L) | 66.0 | | 0 60 70 | ≤60.0 |
| MPO* (pmol/L) | 361.0 | | 0 599 2999 | ≤599.9 |

| LipoProtein Markers | Current | Previous | Result | Reference |
|---|---|---|---|---|
| sdLDL* (mg/dL) | 93.1 | | 0 50 | ≤50.0 |
| Lp(a) (mg/dL) | <10 | | 0 29 | ≤29.0 |

## Oxidative Stress Biomarkers

| Lipid Peroxidation | Current | Previous | Result (75th 95th) | Reference |
|---|---|---|---|---|
| 11-β-Prostaglandin F2α (ug/g) | 0.11 | | 0.11 0.4 | ≤0.4 |
| 15(R)-Prostaglandin F2α (ug/g) | <0.05 | | 0.07 0.22 | ≤0.22 |
| 8-iso-prostaglandin F2α (8-iso-PGF2α) (ug/g) | 0.10 | | 0.1 0.26 | ≤0.26 |
| Glutathione 4-hydroxynonenal (GS-HNE) (ug/g) | >10 | | 0.3 2.5 | ≤2.5 |
| Malondialdehyde (ug/g) | 180.00 | | 72.87 163.53 | ≤163.53 |

## Glycemic Control

| Test Name | Current | Previous | Result | Reference |
|---|---|---|---|---|
| Glucose(Diabetes) (mg/dL) | 89 | | 61 69 100 126 | 70.0-100.0 |
| Hemoglobin A1c (%) | 5.1 | | 0 5.6 6.4 | ≤5.6 |
| Glycated Serum Protein (umol/L) | 248 | | 0 285 | ≤285.0 |
| Insulin (µU/mL) | 4.0 | | 0 2.5 24.9 | 2.6-24.9 |

| Fatty Acids: Omega-3 & 6 | | Current | Previous | Result | Reference |
|---|---|---|---|---|---|
| AA (Arachidonic acid) | Cellular | 18.48 | | 0 5.49 19.0 | 5.5-19.01 (%) |
| AA/EPA | Cellular | 17.1 | | 0 2.4 10.9 | 2.5-10.9 |
| EPA | Cellular | 1.08 | | 0 0.14 2.26 | 0.15-2.26 (%) |
| LA (Linoleic acid) | Cellular | 7.67 | | 0 3.21 10.4 | 3.22-10.49 (%) |
| Omega-3 Index | Cellular | 3.80 | | 0 2.65 7.99 12.6 | 8.0-12.65 (%) |
| Total Omega-3 | Cellular | 2.81 | | 0 3.24 13.9 | 3.25-13.99 (%) |
| Vitamin D, 25-OH | Serum | 51.0 | | 0 29.9 108 | 30.0-108.0 (ng/mL) |



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| | | |
|---|---|---|
| **DOB: 07/20/1957 AGE: 66**<br>Gender: M<br>Patient ID: 3648<br>Health ID: 8573016725098491 | Collected: 10/24/2023 / 13:19 EDT<br>Received: 10/24/2023 / 21:21 EDT<br>Reported: 10/29/2023 / 02:32 EDT | DAVIS, CHRISTOPHER |

| Test Name | In Range | Out Of Range | Reference Range | Lab |
|---|---|---|---|---|
| Male: 93-415 mcg/dL<br>Female: 19-237 mcg/dL | | | | |
| **FSH** | | **<0.7 L** | 1.6-8.0 mIU/mL | TP |
| **LH** | | **<0.2 L** | 1.6-15.2 mIU/mL | TP |
| PROGESTERONE | 0.5 | | <1.4 ng/mL | TP |
| PROLACTIN | 8.0 | | 2.0-18.0 ng/mL | TP |
| **ESTRADIOL** | | **73 H** | < OR = 39 pg/mL | TP |
| Reference range established on post-pubertal patient population. No pre-pubertal reference range established using this assay. For any patients for whom low Estradiol levels are anticipated (e.g. males, pre-pubertal children and hypogonadal/post-menopausal females), the Quest Diagnostics Nichols Institute Estradiol, Ultrasensitive, LCMSMS assay is recommended (order code 30289).<br><br>Please note: patients being treated with the drug fulvestrant (Faslodex(R)) have demonstrated significant interference in immunoassay methods for estradiol measurement. The cross reactivity could lead to falsely elevated estradiol test results leading to an inappropriate clinical assessment of estrogen status. Quest Diagnostics order code 30289-Estradiol, Ultrasensitive LC/MS/MS demonstrates negligible cross reactivity with fulvestrant. | | | | |
| **PSA, TOTAL** | | **4.34 H** | < OR = 4.00 ng/mL | TP |
| The total PSA value from this assay system is standardized against the WHO standard. The test result will be approximately 20% lower when compared to the equimolar-standardized total PSA (Beckman Coulter). Comparison of serial PSA results should be interpreted with this fact in mind.<br><br>This test was performed using the Siemens chemiluminescent method. Values obtained from different assay methods cannot be used interchangeably. PSA levels, regardless of value, should not be interpreted as absolute evidence of the presence or absence of disease. | | | | |
| **LEAD (VENOUS)** | | **7.4 H** | <3.5 mcg/dL | TP |
| Verified by repeat analysis. | | | | |

# Total Toxins Summary

VibrantWellness

Vibrant Wellness | 3521 Leonard Ct, Santa Clara, CA 95054
1(866) 364-0963 | support@vibrant-america.com | www.vibrant-wellness.com

| LAST NAME | | | | | |
|---|---|---|---|---|---|
| LENZA | MICHAEL | Male | 1957-07-20 | 240424657Z | 2024-05-08 00:00 (PDT) |

## High (>95th percentile)

Heavy Metals

| TEST NAME | CURRENT RESULT | PREVIOUS RESULT | CURRENT RESULT / PREVIOUS RESULT | REFERENCE |
|---|---|---|---|---|
| Lead* | 2.65 | | 0 0.52 1.16 | ≤1.16 ug/g |

* Indicates NHANES population data reference ranges.

## Moderate (75th-95th percentile)

Heavy Metals | Environmental Toxins

| TEST NAME | CURRENT RESULT | PREVIOUS RESULT | CURRENT RESULT / PREVIOUS RESULT | REFERENCE |
|---|---|---|---|---|
| Barium* | 2.37 | | 0 2.33 5.59 | ≤5.59 ug/g |
| Butylparaben* | 0.6 | | 0 0.25 4.39 | ≤4.39 ug/g |
| Dimethyl phosphate (DMP)* | 16.84 | | 0 9.1 33.6 | ≤33.6 ug/g |
| Dimethyldithiophosphate (DMDTP)* | 2.83 | | 0 0.67 6.12 | ≤6.12 ug/g |

* Indicates NHANES population data reference ranges.

## Urine Creatinine

| TEST NAME | CURRENT RESULT | PREVIOUS RESULT | CURRENT RESULT / PREVIOUS RESULT | REFERENCE |
|---|---|---|---|---|
| Urine Creatinine | 1.22 | | 0 0.24 2.16 | 0.25-2.16 mg/mL |



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# CCTA and Plaque Characterization

## Summary

**Atherosclerosis**: **Stage 3** (998.7 $mm^3$ Total Plaque: 3.9 $mm^3$ Low-Density - Non-Calcified, 573 $mm^3$ Non-Calcified, 421.8 $mm^3$ Calcified)

**Stenosis**: **1 Severe** (mLAD); **4 Moderate** (pRCA, mRCA, pLAD, D1); **1 Mild** (pCx); **4 Minimal** (dRCA, R-PLB, LM, pCx);

**Dominance**: **Right-Dominant**

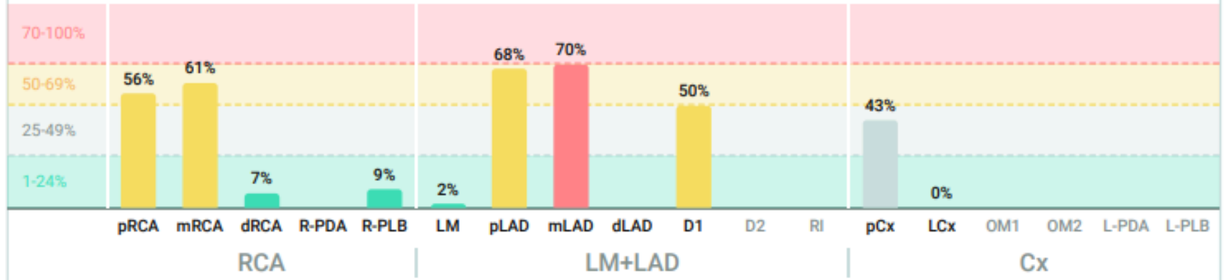
## Atherosclerosis | Stage 3

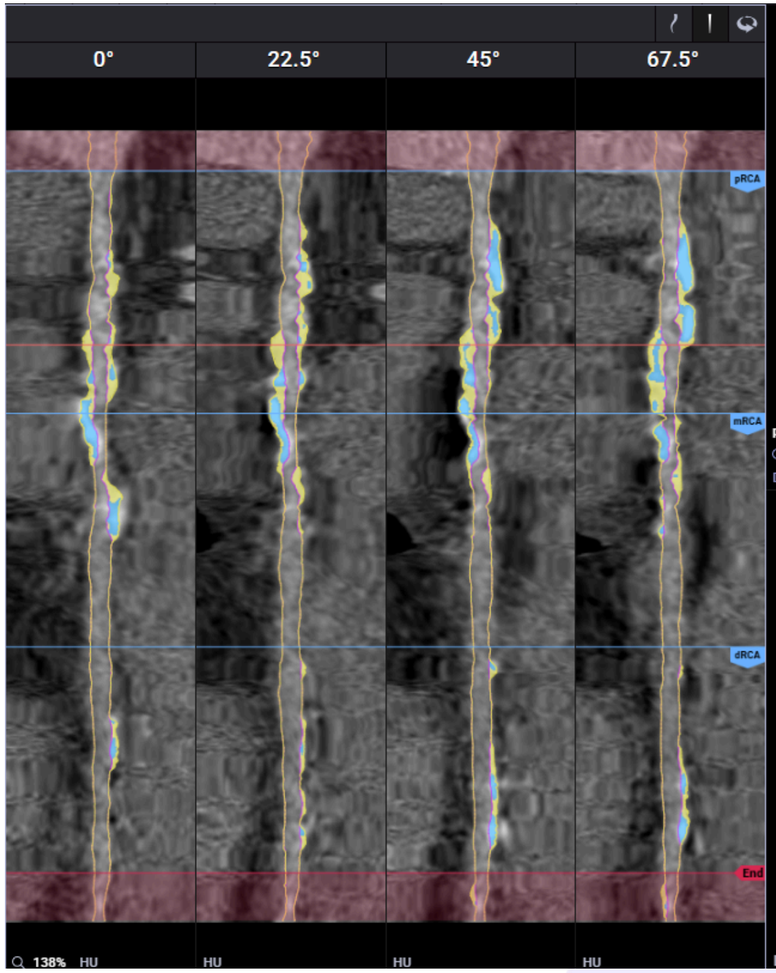
Min JK et al., Coronary CTA plaque volume severity stages according to invasive coronary angiography and FFR
Journal of Cardiovascular Computed Tomography

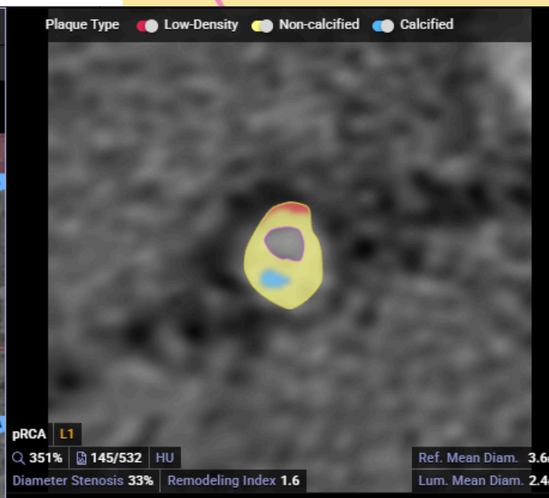
| Territory | Plaque Volume ($mm^3$) | | | | Percent Atheroma Volume | Plaque Stage | | |
|---|---|---|---|---|---|---|---|---|
| | TOTAL | Low-Density - Non-Calcified | Non-Calcified | Calcified | | Stage | $mm^3$ | PAV |
| RCA | 573.3 | 2.4 | 374.8 | 196.1 | 39.4% | 0 | 0 | 0% |
| LM+LAD | 336.1 | 1.5 | 157.6 | 177 | 34.3% | 1 | >0-250 | >0-5% |
| Cx | 89.3 | 0 | 40.6 | 48.7 | 20.4% | 2 | >250-750 | >5-15% |
| TOTAL | 998.7 | 3.9 | 573 | 421.8 | 34.7% | 3 | >750 | >15% |

## Stenosis

| Severe | Moderate | Mild | Minimal |
|---|---|---|---|
| ≥70% or ≥50% LM only: 1 | 50-69%: 4 | 25-49%: 1 | 1-24%: 4 |







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# Treatment Recommendations

- Started moderate dose statin
- Oral detoxification protocol, IR sauna
- IV phosphatidylcholine and chelation
- Nutraceuticals- nitric oxide supplement, glycocalyx supplement, B- complex, K2D3, and omega-3.
- Modified Mediterranean diet



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## Cardiac Health Panel

| Lipids | Current | Previous | Result | Reference |
|---|---|---|---|---|
| Cholesterol, Total (mg/dL) | 182 | | 0 199 240 | ≤199.0 |
| LDL Calculation (mg/dL) | 99 | | 0 99 129 | ≤99.0 |
| HDL Direct (mg/dL) | 64 | | 0 44 65 | ≥66.0 |
| Cholesterol/HDL Ratio | 2.8 | | 0 3.5 4.9 | ≤3.5 |
| Triglyceride (mg/dL) | 97 | | 0 149 200 | ≤149.0 |
| **LDL Direct** | **Current** | **Previous** | **Result** | **Reference** |
| LDL Direct (mg/dL) | 101 | | 0 99 129 | ≤99.0 |
| **Apolipoproteins** | **Current** | **Previous** | **Result** | **Reference** |
| Apo A-1 (mg/dL) | 165 | | 0 139 | ≥140.0 |
| Apo B (mg/dL) | 82 | | 0 89 119 | ≤89.0 |
| Apo B: Apo A-1 | 0.50 | | 0 0.59 0.8 | ≤0.59 |
| **Inflammation** | **Current** | **Previous** | **Result** | **Reference** |
| PLAC (nmol/min/mL) | 99 | | 0 224 | ≤224.0 |
| Homocysteine (µmol/L) | 12.0 | | 0 9 14 | ≤9.0 |
| hs-CRP (mg/L) | 1.5 | | 0 0.9 3 | ≤0.9 |
| ox-LDL* (U/L) | 51.0 | | 0 60 70 | ≤60.0 |
| MPO* (pmol/L) | 319 | | 0 599 2999 | ≤599.9 |
| **LipoProtein Markers** | **Current** | **Previous** | **Result** | **Reference** |
| sdLDL* (mg/dL) | 73.9 | | 0 50 | ≤50.0 |
| Lp(a) (mg/dL) | <10 | | 0 29 | ≤29.0 |

## Glycemic Control

| Test Name | Current | Previous | Result | Reference |
|---|---|---|---|---|
| Glucose(Diabetes) (mg/dL) | 98 | | 61 69 100 126 | 70.0-100.0 |
| Hemoglobin A1c (%) | 5.5 | | 0 5.6 6.4 | ≤5.6 |
| Glycated Serum Protein (umol/L) | 280 | | 0 285 | ≤285.0 |
| Insulin (µU/mL) | 6.0 | | 0 2.5 24.9 | 2.6-24.9 |

## Oxidative Stress Biomarkers

| Lipid Peroxidation | Current | Previous | Result (75th 95th) | Reference |
|---|---|---|---|---|
| 11-β-Prostaglandin F2α (ug/g) | 0.13 | | 0.11 0.4 | ≤0.4 |
| 15(R)-Prostaglandin F2α (ug/g) | 0.07 | | 0.07 0.22 | ≤0.22 |
| 8-iso-prostaglandin F2α (8-iso-PGF2α) (ug/g) | 0.13 | | 0.1 0.26 | ≤0.26 |
| Glutathione 4-hydroxynonenal (GS-HNE) (ug/g) | 0.21 | | 0.3 2.5 | ≤2.5 |
| Malondialdehyde (ug/g) | 61.98 | | 72.87 163.53 | ≤163.53 |



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# Case 3- Regressing Plaque Burden

## Cardiac Health Panel

| Lipids | Current | Previous | Result | Reference |
|---|---|---|---|---|
| Cholesterol, Total (mg/dL) | 234 | | 0 199 240 | ≤199.0 |
| LDL Calculation (mg/dL) | 152 | | 0 99 129 | ≤99.0 |
| HDL Direct (mg/dL) | 46 | | 0 44 65 | ≥66.0 |
| Cholesterol/HDL Ratio | 5.1 | | 0 3.5 4.9 | ≤3.5 |
| Triglyceride (mg/dL) | 225 | | 0 149 200 | ≤149.0 |
| **LDL Direct** | **Current** | **Previous** | **Result** | **Reference** |
| LDL Direct (mg/dL) | 154 | | 0 99 129 | ≤99.0 |
| **Apolipoproteins** | **Current** | **Previous** | **Result** | **Reference** |
| Apo A-1 (mg/dL) | 140 | | 0 139 | ≥140.0 |
| Apo B (mg/dL) | 129 | | 0 89 119 | ≤89.0 |
| Apo B: Apo A-1 | 0.92 | | 0 0.59 0.8 | ≤0.59 |
| **Inflammation** | **Current** | **Previous** | **Result** | **Reference** |
| PLAC (nmol/min/mL) | 230 | | 0 224 | ≤224.0 |
| Homocysteine (µmol/L) | 33.2 | | 0 9 14 | ≤9.0 |
| hs-CRP (mg/L) | 2.8 | | 0 0.9 3 | ≤0.9 |
| ox-LDL* (U/L) | 69.0 | | 0 60 70 | ≤60.0 |
| MPO* (pmol/L) | 589.0 | | 0 599 2999 | ≤599.9 |
| **LipoProtein Markers** | **Current** | **Previous** | **Result** | **Reference** |
| sdLDL* (mg/dL) | 73.1 | | 0 50 | ≤50.0 |
| Lp(a) (mg/dL) | <10 | | 0 29 | ≤29.0 |

## Glycemic Control

| Test Name | Current | Previous | Result | Reference |
|---|---|---|---|---|
| Glucose(Diabetes) (mg/dL) | 82 | | 61 69 100 126 | 70.0-100.0 |
| Hemoglobin A1c (%) | 5.3 | | 0 5.6 6.4 | ≤5.6 |
| Glycated Serum Protein (umol/L) | 238 | | 0 285 | ≤285.0 |
| Insulin (µU/mL) | 5.0 | | 0 2.5 24.9 | 2.6-24.9 |

## Oxidative Stress Biomarkers

| Lipid Peroxidation | Current | Previous | Result (75th 95th) | Reference |
|---|---|---|---|---|
| 11-β-Prostaglandin F2α (ug/g) | 0.20 | | 0.11 0.4 | ≤0.4 |
| 15(R)-Prostaglandin F2α (ug/g) | 0.09 | | 0.07 0.22 | ≤0.22 |
| 8-iso-prostaglandin F2α (8-iso-PGF2α) (ug/g) | 0.12 | | 0.1 0.26 | ≤0.26 |
| Glutathione 4-hydroxynonenal (GS-HNE) (ug/g) | 0.19 | | 0.3 2.5 | ≤2.5 |
| Malondialdehyde (ug/g) | 35.24 | | 72.87 163.53 | ≤163.53 |

| Fatty Acids: Omega-3 & 6 | | Current | Previous | Result | Reference |
|---|---|---|---|---|---|
| AA (Arachidonic acid) | Cellular | 16.76 | | 0 5.49 19.0 | 5.5-19.01 (%) |
| AA/EPA | Cellular | 20.0 | | 0 2.4 10.9 | 2.5-10.9 |
| EPA | Cellular | 0.84 | | 0 0.14 2.26 | 0.15-2.26 (%) |
| LA (Linoleic acid) | Cellular | 7.01 | | 0 3.21 10.4 | 3.22-10.49 (%) |
| Omega-3 Index | Cellular | 2.64 | | 0 2.65 7.99 12.6 | 8.0-12.65 (%) |
| Total Omega-3 | Cellular | 2.81 | | 0 3.24 13.9 | 3.25-13.99 (%) |
| Total Omega-6 | Cellular | 26.75 | | 0 11.0 34.9 | 11.03-34.96 (%) |



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# Environmental Toxin Panel

## High (>95th percentile)

Heavy Metals | Environmental Toxins

| TEST NAME | CURRENT RESULT | PREVIOUS RESULT | CURRENT RESULT / PREVIOUS RESULT | REFERENCE |
|---|---|---|---|---|
| Lead* | 1.68 | | 0 – 0.52 – 1.16 | ≤1.16 ug/g |
| 2-Hydroxyisobutyric Acid (2HIB) | 4797.15 | | 0 – 795 – 1215 | ≤1215.72 ug/g |
| 4-Nonylphenol | 7.63 | | 0 – 0.42 – 2.06 | ≤2.06 ug/g |
| Diethyldithiophosphate (DEDTP)* | 0.94 | | 0 – 0.17 – 0.3 | ≤0.3 ug/g |

* Indicates NHANES population data reference ranges.

## Moderate (75th-95th percentile)

Heavy Metals | Environmental Toxins

| TEST NAME | CURRENT RESULT | PREVIOUS RESULT | CURRENT RESULT / PREVIOUS RESULT | REFERENCE |
|---|---|---|---|---|
| Aluminum | 19.01 | | 0 – 17.8 – 45.1 | ≤45.15 ug/g |
| Antimony* | 0.11 | | 0 – 0.07 – 0.16 | ≤0.16 ug/g |
| Cesium* | 6.47 | | 0 – 6.37 – 10.3 | ≤10.3 ug/g |
| Mercury* | 1.23 | | 0 – 0.57 – 1.61 | ≤1.61 ug/g |
| Tellurium | 0.47 | | 0 – 0.42 – 0.89 | ≤0.89 ug/g |
| Thallium* | 0.26 | | 0 – 0.24 – 0.43 | ≤0.43 ug/g |
| Atrazine mercapturate* | 0.04 | | 0 – 0.02 – 0.05 | ≤0.05 ug/g |
| Bisphenol A (BPA)* | 4.14 | | | ≤5.09 ug/g |

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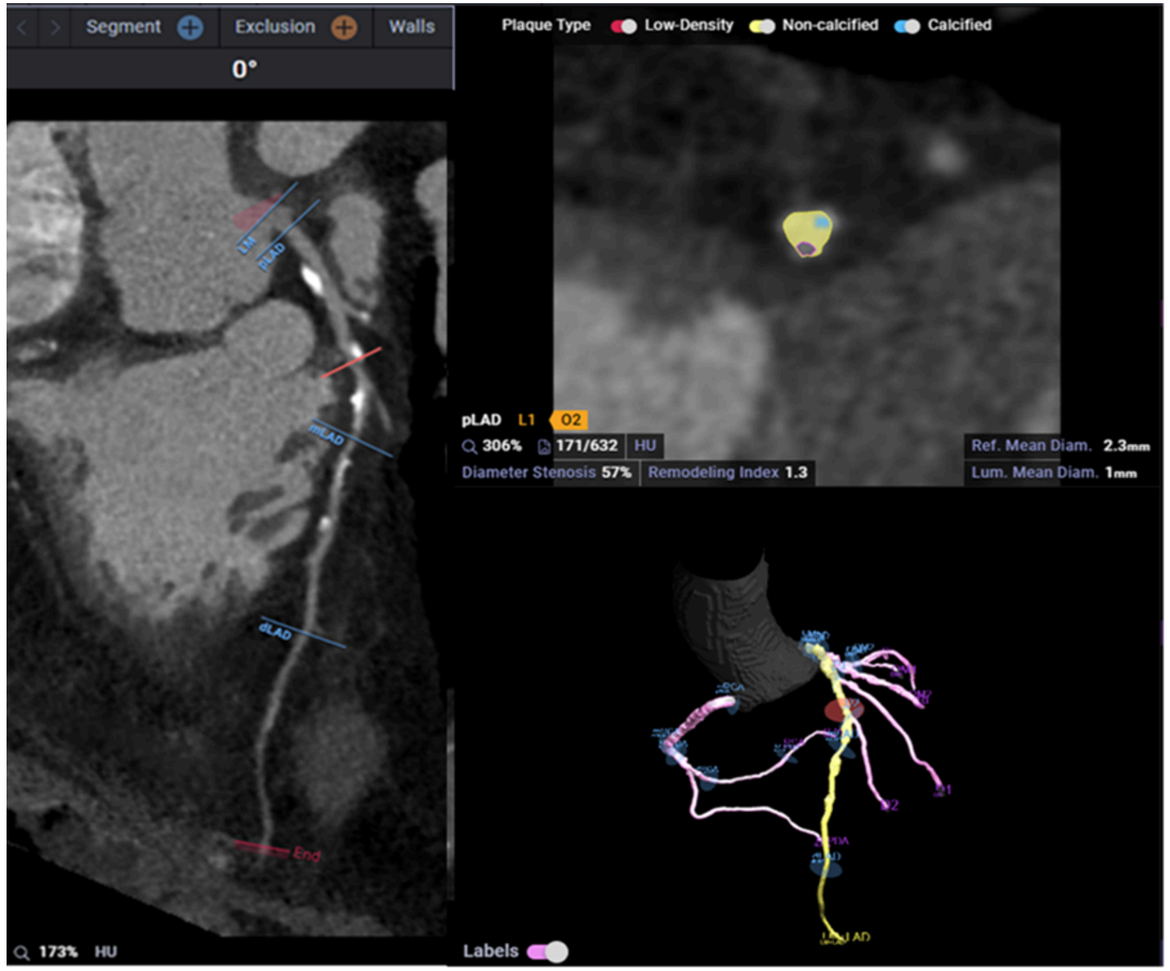
# CCTA and Plaque Characterization




cleerly

Coronary Imaging Service

| Patient | MRN | Cleerly ID | Study Date | Provider |
|---|---|---|---|---|
| | 939755 | 0DE39C25 | 7/7/2023 10:35 AM | DAVIS CHRISTOPHER |

## Summary

| | |
|---|---|
| Atherosclerosis | **Stage 3** (499.4 $mm^3$ Total Plaque: 0.2 $mm^3$ Low-Density - Non-Calcified, 345.7 $mm^3$ Non-Calcified, 153.5 $mm^3$ Calcified) |
| Stenosis | **2 Severe** (mRCA, RI); **2 Moderate** (pRCA, pLAD); **3 Mild** (R-PLB, mLAD, D1); **6 Minimal** (pRCA, mRCA, R-PDA, LM, mLAD, pCx); |
| Dominance | **Right-Dominant** |

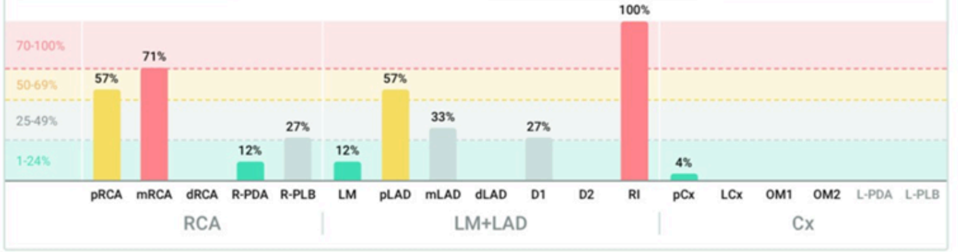
## Atherosclerosis | Stage 3

Min JK et al., Coronary CTA plaque volume severity stages according to invasive coronary angiography and FFR
Journal of Cardiovascular Computed Tomography

| Territory | Plaque Volume ($mm^3$) | | | | Percent Atheroma Volume | Plaque Stage | | |
|---|---|---|---|---|---|---|---|---|
| | TOTAL | Low-Density - Non-Calcified | Non-Calcified | Calcified | | Stage | $mm^3$ | PAV |
| RCA | 212.8 | 0.1 | 199.1 | 13.6 | 16.9% | 0 | 0 | 0% |
| LM+LAD | 281.1 | 0.1 | 141.1 | 139.9 | 23% | 1 | >0-250 | >0-5% |
| Cx | 5.5 | 0 | 5.5 | 0 | 1.7% | 2 | >250-750 | >5-15% |
| TOTAL | 499.4 | 0.2 | 345.7 | 153.5 | 17.8% | 3 | >750 | >15% |

## Stenosis

| Severe | Moderate | Mild | Minimal |
|---|---|---|---|
| ≥70% or ≥50% LM only: 2 | 50-69%: 2 | 25-49%: 3 | 1-24%: 6 |



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# Treatment Recommendations

- Started moderate dose statin
- Oral detoxification protocol, IR sauna
- IV phosphatidylcholine
- Nutraceuticals- nitric oxide supplement, glycocalyx supplement, B- complex, K2D3, and omega-3.
- Modified Mediterranean diet



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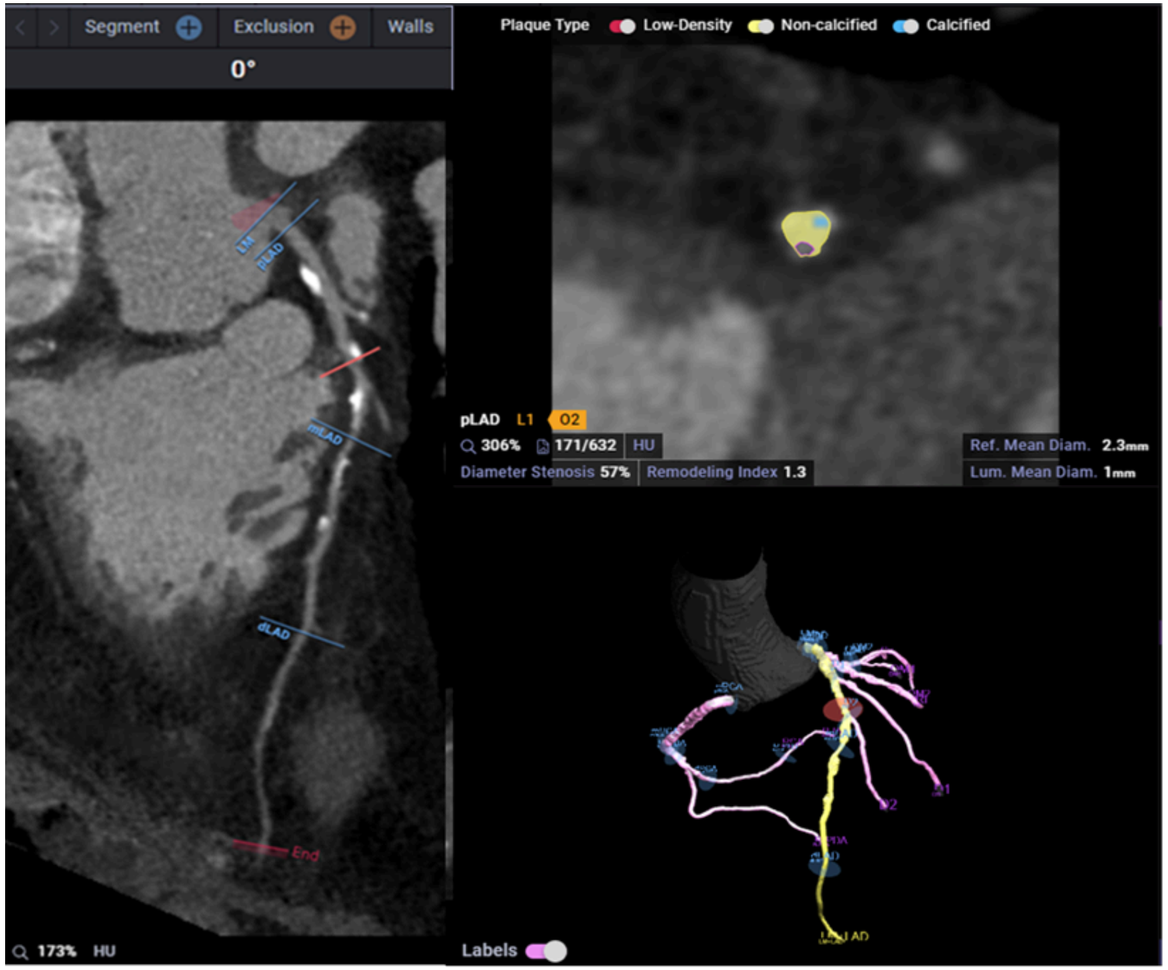
# CCTA Pre/Post

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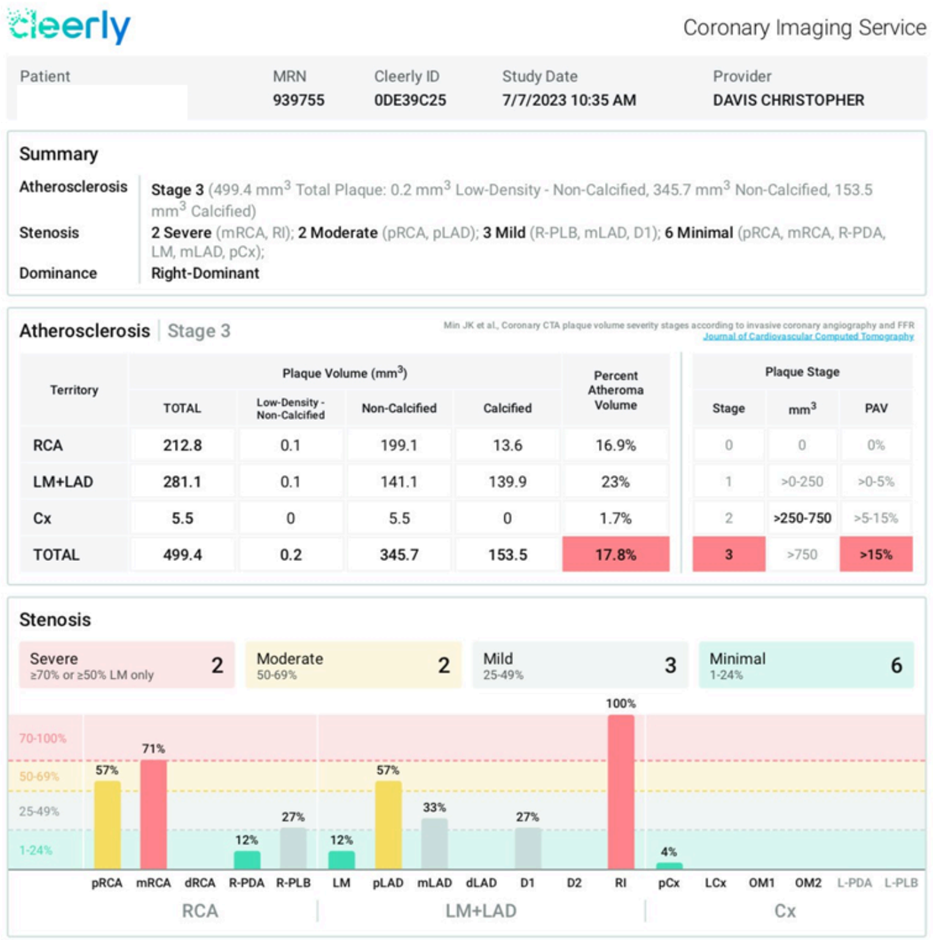
# Plaque Assessment Pre/Post Therapy



cleerly — Coronary Imaging Service

| Patient | MRN | Cleerly ID | Study Date | Provider |
|---|---|---|---|---|
| | 939755 | 0DE39C25 | 7/7/2023 10:35 AM | DAVIS CHRISTOPHER |

**Summary**

| | |
|---|---|
| Atherosclerosis | **Stage 3** (499.4 $mm^3$ Total Plaque: 0.2 $mm^3$ Low-Density - Non-Calcified, 345.7 $mm^3$ Non-Calcified, 153.5 $mm^3$ Calcified) |
| Stenosis | **2 Severe** (mRCA, RI); **2 Moderate** (pRCA, pLAD); **3 Mild** (R-PLB, mLAD, D1); **6 Minimal** (pRCA, mRCA, R-PDA, LM, mLAD, pCx); |
| Dominance | **Right-Dominant** |

**Atherosclerosis** | Stage 3

Min JK et al., Coronary CTA plaque volume severity stages according to invasive coronary angiography and FFR — Journal of Cardiovascular Computed Tomography

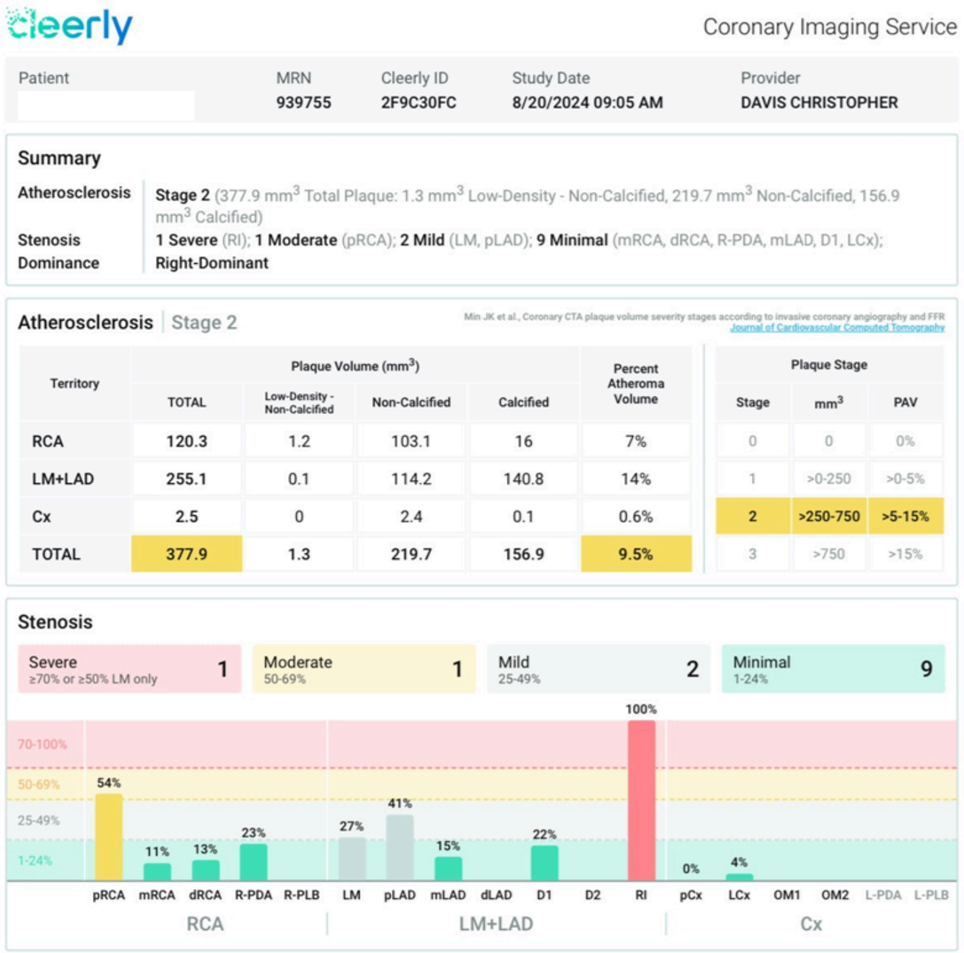
| Territory | Plaque Volume ($mm^3$) | | | | Percent Atheroma Volume | Plaque Stage | | |
|---|---|---|---|---|---|---|---|---|
| | TOTAL | Low-Density - Non-Calcified | Non-Calcified | Calcified | | Stage | $mm^3$ | PAV |
| RCA | 212.8 | 0.1 | 199.1 | 13.6 | 16.9% | 0 | 0 | 0% |
| LM+LAD | 281.1 | 0.1 | 141.1 | 139.9 | 23% | 1 | >0-250 | >0-5% |
| Cx | 5.5 | 0 | 5.5 | 0 | 1.7% | 2 | >250-750 | >5-15% |
| TOTAL | 499.4 | 0.2 | 345.7 | 153.5 | 17.8% | 3 | >750 | >15% |

**Stenosis**

| Severe ≥70% or ≥50% LM only | Moderate 50-69% | Mild 25-49% | Minimal 1-24% |
|---|---|---|---|
| 2 | 2 | 3 | 6 |



7/23



cleerly — Coronary Imaging Service

| Patient | MRN | Cleerly ID | Study Date | Provider |
|---|---|---|---|---|
| | 939755 | 2F9C30FC | 8/20/2024 09:05 AM | DAVIS CHRISTOPHER |

**Summary**

| | |
|---|---|
| Atherosclerosis | **Stage 2** (377.9 $mm^3$ Total Plaque: 1.3 $mm^3$ Low-Density - Non-Calcified, 219.7 $mm^3$ Non-Calcified, 156.9 $mm^3$ Calcified) |
| Stenosis | **1 Severe** (RI); **1 Moderate** (pRCA); **2 Mild** (LM, pLAD); **9 Minimal** (mRCA, dRCA, R-PDA, mLAD, D1, LCx); |
| Dominance | **Right-Dominant** |

**Atherosclerosis** | Stage 2

Min JK et al., Coronary CTA plaque volume severity stages according to invasive coronary angiography and FFR — Journal of Cardiovascular Computed Tomography

| Territory | Plaque Volume ($mm^3$) | | | | Percent Atheroma Volume | Plaque Stage | | |
|---|---|---|---|---|---|---|---|---|
| | TOTAL | Low-Density - Non-Calcified | Non-Calcified | Calcified | | Stage | $mm^3$ | PAV |
| RCA | 120.3 | 1.2 | 103.1 | 16 | 7% | 0 | 0 | 0% |
| LM+LAD | 255.1 | 0.1 | 114.2 | 140.8 | 14% | 1 | >0-250 | >0-5% |
| Cx | 2.5 | 0 | 2.4 | 0.1 | 0.6% | 2 | >250-750 | >5-15% |
| TOTAL | 377.9 | 1.3 | 219.7 | 156.9 | 9.5% | 3 | >750 | >15% |

**Stenosis**

| Severe ≥70% or ≥50% LM only | Moderate 50-69% | Mild 25-49% | Minimal 1-24% |
|---|---|---|---|
| 1 | 1 | 2 | 9 |



8/24



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# Case 4- Genetics and Residual Risk



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- 67 year old active male with history of CAD s/p PCI of obtuse marginal branch in 4/21 followed by another PCI of RCA in 11/21 secondary to rapid progression of disease. He presented for a second opinion in 5/23. He had just decided to pursue a carnivore diet as a means of addressing his CAD after doing some internet research. I recommended delaying the carnivore diet until after we got his labs back which would include an advanced lipid panel with inflammation markers and genetics. He wanted to proceed so we we decided to get followup labs in 6 weeks.
- Medications: Clopidogrel, Rosuvastatin, ASA, Niacin ER

**Cardiac Health Panel**

| Lipids | Current | Previous | Result | Reference |
|---|---|---|---|---|
| Cholesterol, Total (mg/dL) | 206 | | 0 199 240 | ≤199.0 |
| LDL Calculation (mg/dL) | 125 | | 0 99 129 | ≤99.0 |
| HDL Direct (mg/dL) | 62 | | 0 44 65 | ≥66.0 |
| Cholesterol/HDL Ratio | 3.3 | | 0 3.5 4.9 | ≤3.5 |
| Triglyceride (mg/dL) | 86 | | 0 149 200 | ≤149.0 |
| **Inflammation** | **Current** | **Previous** | **Result** | **Reference** |
| PLAC (nmol/min/mL) | 199 | | 0 224 | ≤224.0 |
| Homocysteine (µmol/L) | 9.0 | | 0 9 14 | ≤9.0 |
| hs-CRP (mg/L) | 0.3 | | 0 0.9 3 | ≤0.9 |
| ox-LDL* (U/L) | 63.0 | | 0 60 70 | ≤60.0 |
| MPO* (pmol/L) | 319 | | 0 599 2999 | ≤599.9 |

**Cardiax** — ⊕⊕ Homozygous Mutant ⊕⊖ Heterozygous ⊖⊖ Homozygous Wild

| Test Name | Gene Name | Risk Association | Your Mutation | Your Risk | Reference |
|---|---|---|---|---|---|
| ApoE | APOE | Higher total and LDL cholesterol | ⊖⊖ε3/ε4 | Elevated | ε3/ε3, ε2/ε3, ε1/ε4, ε1/ε2 |

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## Cardiac Health Panel

| Lipids | Current | Previous | Result | Reference |
|---|---|---|---|---|
| Cholesterol, Total (mg/dL) | 206 | | 0 199 240 | ≤199.0 |
| LDL Calculation (mg/dL) | 125 | | 0 99 129 | ≤99.0 |
| HDL Direct (mg/dL) | 62 | | 0 44 65 | ≥66.0 |
| Cholesterol/HDL Ratio | 3.3 | | 0 3.5 4.9 | ≤3.5 |
| Triglyceride (mg/dL) | 86 | | 0 149 200 | ≤149.0 |
| **Inflammation** | **Current** | **Previous** | **Result** | **Reference** |
| PLAC (nmol/min/mL) | 199 | | 0 224 | ≤224.0 |
| Homocysteine (µmol/L) | 9.0 | | 0 9 14 | ≤9.0 |
| hs-CRP (mg/L) | 0.3 | | 0 0.9 3 | ≤0.9 |
| ox-LDL* (U/L) | 63.0 | | 0 60 70 | ≤60.0 |
| MPO* (pmol/L) | 319 | | 0 599 2999 | ≤599.9 |

## Cardiax

⊕⊕ Homozygous Mutant ⊕⊖ Heterozygous ⊖⊖ Homozygous Wild

| Test Name | Gene Name | Risk Association | Your Mutation | Your Risk | Reference |
|---|---|---|---|---|---|
| ApoE | APOE | Higher total and LDL cholesterol | ⊖⊖ε3/ε4 | Elevated | ε3/ε3, ε2/ε3, ε1/ε4, ε1/ε2 |

5/4/2023

## Cardiac Health Panel

| Lipids | Current | Previous | Result | Reference |
|---|---|---|---|---|
| Cholesterol, Total (mg/dL) | 524 | | 0 199 240 | ≤199.0 |
| LDL Calculation (mg/dL) | 423 | | 0 99 129 | ≤99.0 |
| HDL Direct (mg/dL) | 63 | | 0 44 65 | ≥66.0 |
| Cholesterol/HDL Ratio | 8.3 | | 0 3.5 4.9 | ≤3.5 |
| Triglyceride (mg/dL) | 199 | | 0 149 200 | ≤149.0 |
| **LDL Direct** | **Current** | **Previous** | **Result** | **Reference** |
| LDL Direct (mg/dL) | 422 | | 0 99 129 | ≤99.0 |
| **Apolipoproteins** | **Current** | **Previous** | **Result** | **Reference** |
| Apo A-1 (mg/dL) | 155 | | 0 139 | ≥140.0 |
| Apo B (mg/dL) | >240 | | 0 89 119 | ≤89.0 |
| Apo B: Apo A-1 | >1.5 | | 0 0.59 0.8 | ≤0.59 |
| **Inflammation** | **Current** | **Previous** | **Result** | **Reference** |
| PLAC (nmol/min/mL) | 230 | | 0 224 | ≤224.0 |
| Homocysteine (µmol/L) | 16.2 | | 0 9 14 | ≤9.0 |
| hs-CRP (mg/L) | 2.8 | | 0 0.9 3 | ≤0.9 |
| ox-LDL* (U/L) | 115 | | 0 60 70 | ≤60.0 |
| MPO* (pmol/L) | 2980 | | 0 599 2999 | ≤599.9 |
| **LipoProtein Markers** | **Current** | **Previous** | **Result** | **Reference** |
| sdLDL* (mg/dL) | 105 | | 0 50 | ≤50.0 |
| Lp(a) (mg/dL) | <10 | | 0 29 | ≤29.0 |

## Oxidative Stress Biomarkers

| Lipid Peroxidation | Current | Previous | Result (75th 95th) | Reference |
|---|---|---|---|---|
| 11-β-Prostaglandin F2α (ug/g) | 0.41 | | 0.11 0.4 | ≤0.4 |
| 15(R)-Prostaglandin F2α (ug/g) | 0.23 | | 0.07 0.22 | ≤0.22 |
| 8-iso-prostaglandin F2α (8-iso-PGF2α) (ug/g) | 0.30 | | 0.1 0.26 | ≤0.26 |

6/28/2023



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# The Role of Nutrigenetics

## Saturated Fats and the ACE Gene

### Saturated Fats

Some modern diet trends tout saturated fats as good for you, while others disagree. Whether a diet high in saturated fats cause diabetes, obesity, and heart disease is largely dependant on your genes.

### APOE gene

In addition to the well-known link to Alzheimer's, the **APOE E4 allele** is also linked to an increased risk of heart disease. This increase in heart disease is varies greatly based on saturated fat consumption.

### ACE Gene

The angiotensin-converting enzyme (ACE) plays a role in maintaining blood pressure at a normal level. People with the ACE deletion/deletion genotype had an **increase** in blood pressure on a diet **higher in saturated fat**.

### Other Genes Affecting Saturated Fats

**APOA2 gene** increased risk of obesity, especially with high saturated fat consumption.
**TCF7L2 gene** is a gene that has been linked in numerous studies to an increased risk of type 2 diabetes.

Genetic Lifehacks
Learn. Experiment. Optimize.

Article: Saturated Fats

| Gene | RS ID | Effect Allele | Your Genotype | Notes About Effect Allele |
|---|---|---|---|---|
| ACE | rs4343 | G | GG | Increased risk of high blood pressure and heart disease with high saturated fat diet |
| APOA2 | rs5082 | G | AA | Increased risk of obesity with high saturated fat; overall |
| TCF7L2 | rs7903146 | T | TC | Increased risk of type 2 diabetes &metabolic syndrome with high saturated fat diet |

**ACE (angiotensin-converting enzyme) gene:**
Researchers looked at the interaction between ACE deletion and saturated fat intake. People with the ACE deletion/deletion genotype had an increase in blood pressure on a diet higher in saturated fat. There was also an increase in heart disease. In people without the ACE deletion/deletion variant, saturated fat consumption had no effect on the risk of heart disease.

**TCF7L2 Gene:**
TCF7L2 is a transcription factor gene that has been linked in numerous studies to an increased risk of type 2 diabetes. The variant causes a significant increase in triglycerides and total cholesterol when



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# Case 5 – Epigenetic Risk

**78  year old extremely active male with hx of erectile dysfunction, dyslipidemia, and HTN presented with recent anginal symptoms.**

EXAMINATION:
CCTA Calcium Scoring

CLINICAL INDICATION: Male, 79 years old. I25.10  ATHEROSCLEROTIC HEART DISEASE OF NATIVE CORONARY ARTERY WITHOUT ANGINA P Coronary artery disease screening.

TECHNIQUE: Breath-hold, gated, noncontrast CT scan of the heart was performed using a multi-slice CT scanner. Coronary artery calcium was quantified using Agatston method. Unless otherwise specified, incidental thyroid, adrenal, renal, and pulmonary nodules do not require dedicated imaging follow-up.

CONTRAST: None.

COMPARISON: None

FINDINGS:
Calcium score is as follows:
LM: 0
LAD: 11 lesions with a score of 1591



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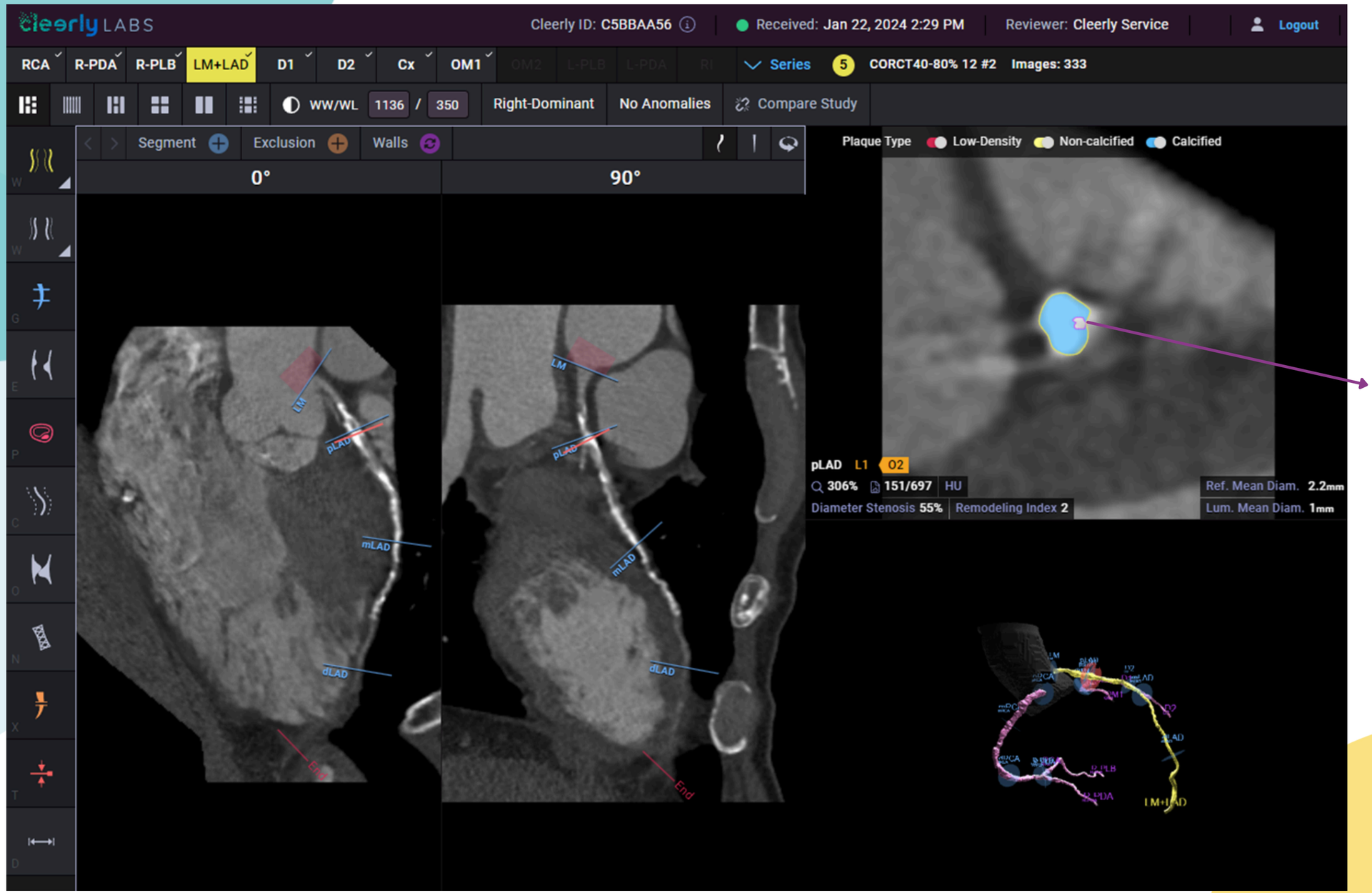

# IGL Toxin Panel (lymphocytes)

| | |
|---|---|
| Doctor \| Therapist | Dr. Christopher Davis, M.D., F.A.C.C. |
| Internal reference \| Reference-ID | 25721 |
| Number of parameters | 13 |
| Material | EDTA |

Blood Collection Time 09:15 a.m.

| Test name | Review | AM | MAD | Value 1 | Value 2 | Value 3 | Value 4 | SI units |
|---|---|---|---|---|---|---|---|---|
| iEC - intracellular Electrical Capacity - in Lymphocytes | | | | | | | | |
| 1 Aflatoxin B1 | very high | 536,12 nmol/l | 6,72 nmol/l | 537,46 | 526,71 | 532,09 | 548,21 | nmol/l |
| 2 Aluminium | tolerable | 3,63 nmol/l | 0,02 nmol/l | 3,63 | 3,63 | 3,59 | 3,67 | nmol/l |
| 3 Antimony | tolerable | 125,70 nmol/l | 1,26 nmol/l | 125,70 | 124,44 | 128,21 | 124,44 | nmol/l |
| 4 Benzoquinone | borderline | 248,02 nmol/l | 3,40 nmol/l | 247,40 | 254,82 | 244,93 | 244,93 | nmol/l |
| 5 Bisphenol A (BPA) | high | 396,59 nmol/l | 1,98 nmol/l | 396,59 | 396,59 | 392,62 | 400,56 | nmol/l |
| 6 Cadmium | tolerable | 56,00 nmol/l | 0,56 nmol/l | 56,00 | 55,44 | 55,44 | 57,12 | nmol/l |
| 7 Cetyltrimethylammoniumbromid (CTABr) | tolerable | 81,48 nmol/l | 0,31 nmol/l | 82,10 | 81,28 | 81,28 | 81,28 | nmol/l |
| 8 Chlorotoluene | very high | 590,42 nmol/l | 7,44 nmol/l | 594,88 | 600,83 | 582,98 | 582,98 | nmol/l |
| 9 Chrom-VI | tolerable | 39,07 nmol/l | 0,58 nmol/l | 38,88 | 39,27 | 40,05 | 38,10 | nmol/l |
| 10 Diesel-exhaust-gases | very high | 478,54 nmol/l | 4,18 nmol/l | 477,35 | 472,58 | 486,90 | 477,35 | nmol/l |
| 11 Formaldehyde | borderline | 233,92 nmol/l | 1,17 nmol/l | 233,92 | 236,26 | 233,92 | 231,58 | nmol/l |
| 12 Fumonisin B1 | tolerable | 145,52 nmol/l | 1,09 nmol/l | 144,80 | 147,70 | 144,80 | 144,80 | nmol/l |
| 13 Fungisterol A | very high | 549,65 nmol/l | 4,10 nmol/l | 546,92 | 546,92 | 546,92 | 557,86 | nmol/l |
| 14 Glyphosate / AMPA | tolerable | 0,11 nmol/l | 0,00 nmol/l | 0,11 | 0,11 | 0,11 | 0,11 | nmol/l |
| 15 Lead | borderline | 179,81 nmol/l | 1,57 nmol/l | 179,36 | 179,36 | 177,57 | 182,95 | nmol/l |
| 16 Lindane | very high | 511,67 nmol/l | 2,57 nmol/l | 514,24 | 509,10 | 509,10 | 514,24 | nmol/l |
| 17 Mercury inorganic | very high | 586,32 nmol/l | 4,36 nmol/l | 581,96 | 581,96 | 593,60 | 587,78 | nmol/l |

| Test name | Review | AM | MAD | Value 1 | Value 2 | Value 3 | Value 4 | SI units |
|---|---|---|---|---|---|---|---|---|
| iEC - intracellular Electrical Capacity - in Lymphocytes | | | | | | | | |
| 20 Nitrosamine | very high | 509,00 nmol/l | 4,46 nmol/l | 510,28 | 500,07 | 510,28 | 515,38 | nmol/l |
| 21 Organophosphate | tolerable | 9,89 nmol/l | 0,04 nmol/l | 9,96 | 9,86 | 9,86 | 9,86 | nmol/l |
| 22 Phthalates | high | 377,07 nmol/l | 3,75 nmol/l | 375,19 | 371,44 | 382,69 | 378,94 | nmol/l |
| 23 Polybrominated-biphenyls (PBB) | high | 385,35 nmol/l | 3,36 nmol/l | 384,39 | 384,39 | 380,55 | 392,08 | nmol/l |
| 24 Triclosan | high | 352,41 nmol/l | 4,44 nmol/l | 355,07 | 347,97 | 347,97 | 358,62 | nmol/l |



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# Epigenetic Impact Related to DNA Adducts

**DNA - Adducts**
Genomic DNA from leucozytes

| | | |
|---|---|---|
| Requisition # | | Wittbek, February 07th, 2024 |
| Order number | | |
| Patient name | | Labor input February 05th, 2024 |
| Date of birth | | Labor output February 06th, 2024 |
| Age of the patient | 80 Years | Blood Collection February 02nd, 2024 |
| Doctor I Therapist | Dr. Christopher Davis, M.D., F.A.C.C. | Blood Collection Time 09:15 a.m. |
| Internal reference I Reference-ID | 25721 | |
| Number of parameters | 13 | |
| Material | EDTA | |

| Match I Adduct found | Review | Result | | Gene identified | optimal reference value [SI units] | |
|---|---|---|---|---|---|---|
| Total DNA | high | 61,68 | µg/ml | | 30,0 - 60,0 | µg/ml |
| DNA - Adducts | | | | | | |
| #1 Dichlorodiphenyltrichloroethane (DDT) | | 20,00 | ng/ml | B9EIK3 | DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 26 | |
| #2 Pentachlorophenol (PCP) | | 14,40 | ng/ml | 11p15.4 | Sphingomyelin Phosphodiesterase 1 | |
| #3 Cyclohexanedimethanol (CHDM) | | 5,30 | ng/ml | 2q14.1 | Hematopoietin-1, Interleukin 1 Alpha | |
| #4 Polybrominated-biphenyl (PBB) | | 16,90 | ng/ml | 7p15.3 | Interleukin 6, B-Cell Stimulatory Factor 2 | |
| #5 Glyphosate/AMPA | | 17,00 | ng/ml | 17q22 | LpO, Lactoperoxidase | |
| DNA - associated Zinc (Zn) | low | 17,00 | ng/ml | | 21,0 - 74,0 | ng/ml |

| Comments adducts | Gene translations |
|---|---|
| #1 Insecticide | #1 In addition, this gene is a candidate tumor suppressor and is located in the critical region of loss of heterozygosity (LOH). |
| #2 Pesticide | #2 Diseases associated with SMPD1 include Niemann-Pick Disease, Type B and Niemann-Pick Disease, Type A. |
| #3 Basic material for the technical production of polyurethanes and polyesters. | #3 Diseases associated with IL1A include Irritant Dermatitis and Cholesteatoma Of Middle Ear. Among its related pathways are PEDF Induced Signaling and IL-1 signaling pathway. Gene Ontology (GO) annotations related to this gene include cytokine activity and interleukin-1 receptor binding. |
| #4 PBB are suspected to be toxic, carcinogenic and liver damaging. In addition, toxic properties with consequences such as memory and muscle weakness and immune defects are suspected. PBB is used as a flame retardants and as a plasticizer in plastics. | #4 Diseases associated with IL6 include Kaposi Sarcoma and Rheumatoid Arthritis, Systemic Juvenile. |
| #5 Herbicide | #5 Diseases associated with LPO include Dental Caries and Aplasia Of Lacrimal And Salivary Glands. |



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Genomic DNA from leucozytes

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*Int. J. Biol. Sci.* 2021, Vol. 17 4353

IVYSPRING INTERNATIONAL PUBLISHER

*International Journal of Biological Sciences*

2021; 17(15): 4353-4364. doi: 10.7150/ijbs.66537

Review

# IL-1β in atherosclerotic vascular calcification: From bench to bedside

Jialing Shen[1*], Ming Zhao[2*], Chunxiang Zhang[3,6✉], Xiaolei Sun[1,2,3,4,5,6,7,8✉]

Interleukin-1 beta (IL-1β) is considered a key inflammatory cytokine that plays a significant role in promoting vascular calcification, essentially contributing to the development of hardened arteries by stimulating the process of bone-like mineral deposition within the blood vessel walls; research indicates that high levels of IL-1β are associated with increased vascular calcification, making it a potential therapeutic target for cardiovascular diseases.



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Original Article

# Admixture Mapping of Coronary Artery Calcified Plaque in African Americans With Type 2 Diabetes Mellitus

Jasmin Divers, PhD; Nicholette D. Palmer, PhD; Lingyi Lu, MS; Thomas C. Register, PhD; J. Jeffrey Carr, MD; Pamela J. Hicks, BA; R. Caresse Hightower, BS; S. Carrie Smith, BS; Jianzhao Xu, BS; Amanda J. Cox, PhD; Keith A. Hruska, MD; Donald W. Bowden, PhD; Cora E. Lewis, MD; Gerardo Heiss, PhD; Michael A. Province, PhD; Ingrid B. Borecki, PhD; Kathleen F. Kerr, PhD; Y.-D. Ida Chen, PhD; Walter Palmas, MD; Jerome I. Rotter, MD; Christina L. Wassel, PhD; Alain G. Bertoni, MD; David M. Herrington, MD; Lynne E. Wagenknecht, DrPH; Carl D. Langefeld, PhD; Barry I. Freedman, MD

***Background***—The presence and severity of coronary artery calcified plaque (CAC) differs markedly between individuals of African and European descent, suggesting that admixture mapping may be informative for identifying genetic variants associated with subclinical cardiovascular disease.

***Methods and Results***—Admixture mapping of CAC was performed in 1040 unrelated African Americans with type 2 diabetes mellitus from the African American-Diabetes Heart Study, Multi-Ethnic Study of Atherosclerosis and Family Heart Study using the Illumina custom ancestry informative marker panel. All cohorts obtained computed tomography scanning of the coronary arteries using identical protocols. For each ancestry informative marker, the probability of inheriting 0, 1, and 2 copies of a European-derived allele was determined. Linkage analysis was performed by testing for association between each ancestry informative marker using these probabilities and CAC, accounting for global ancestry, age, sex, and study. Markers on 1p32.3 in the *GLIS1* gene (rs6663966, logarithm of odds [LOD]=3.7), 1q32.1 near CHIT1 (rs7530895, LOD=3.1), 4q21.2 near PRKG2 (rs1212373, LOD=3.0), and 11q25 in the *OPCML* gene (rs6590705, LOD=3.4) had statistically significant LOD scores, whereas markers on 8q22.2 (rs6994682, LOD=2.7), 9p21.2 (rs439314, LOD=2.7), and 13p32.1 (rs7492028, LOD=2.8) manifested suggestive evidence of linkage. These regions were uniformly characterized by higher levels of European ancestry associating with higher levels or odds of CAC. Findings were replicated in 1350 African Americans without diabetes mellitus and 2497 diabetic European Americans from Multi-Ethnic Study of Atherosclerosis and the Diabetes Heart Study.

***Conclusions***—Fine mapping these regions will likely identify novel genetic variants that contribute to CAC and clarify racial differences in susceptibility to subclinical cardiovascular disease. **(*Circ Cardiovasc Genet*. 2013;6:97-105.)**

**Key Words:** admixture mapping ■ ancestry ■ cardiovascular disease risk factors ■ type 2 diabetes mellitus

Despite similar or more detrimental cardiovascular disease (CVD) risk factor profiles, African Americans (AAs) have markedly lower levels of coronary artery calcified plaque (CAC) relative to European Americans (EAs).[1,2] This observation is consistent in persons with and without type 2 diabetes mellitus (T2DM)[3,4] and suggests that CVD risk factors have differential impacts on atherosclerosis based on ethnicity. The underlying cause(s) of ethnic differences in CAC are not well understood and likely reflect the interplay between multiple genetic and nonconventional CVD risk factors.[5] Wassel et al[6] reported positive association between CAC in AAs and proportion of European ancestry. We performed admixture mapping in 1040 AAs with T2DM to determine genomic regions contributing to ethnic differences in subclinical CVD. T2DM led to higher levels of CAC with the potential for improved power to better discriminate susceptible individuals. Regional admixture mapping (RAM), or mapping by admixture linkage disequilibrium (MALD), is a gene mapping tool used to



## Analyses in Other Study Samples

Results in additional samples are summarized in online-only Data Supplement Table VIa and VIb, including associated Manhattan plots. These plots show supportive evidence in identified regions, indicating that the association is not likely an uncontrolled artifact. Analyses in the MESA sample with AAs without diabetes identified numerous nearby SNPs with *P* values ranging between $10^{-3}$ and $10^{-4}$ in each region. The chromosome 8 region had an SNP whose *P* value was $2.5\times10^{-5}$ with additional supporting evidence around it. Results are shown in Figure 1A for *Log* (*CAC* + 1) and Figure 1B for presence of CAC.

We conducted association tests using available GWAS data on EAs in MESA and DHS. Figure 2A shows that the strongest results in MESA EAs were on chromosome 11 near the 11p15.4 peak, with several SNPs located near the sentinel marker with *P* values between $10^{-4}$ and $10^{-5}$. We also observed associations

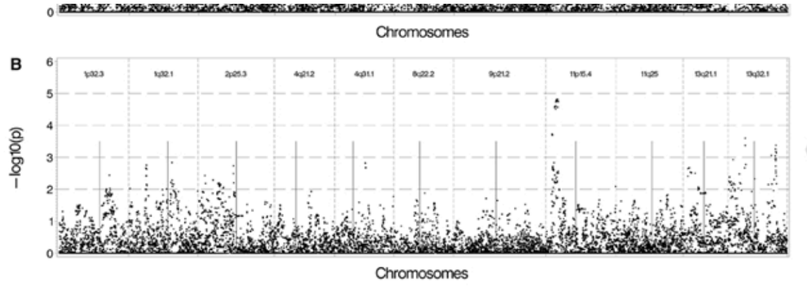


**Figure 2. A**, Genetic association results in European Americans (EAs) in Multi-Ethnic Study of Atherosclerosis (MESA) using Log (coronary artery calcified plaque [CAC]+1) as the outcome and genotyped and imputed SNPs found 500 kb upstream and downstream of the sentinel marker in each region. **B**, Genetic association results in EAs in MESA using presence of CAC as the outcome and genotyped and imputed SNPs found 500 kb upstream and downstream of the sentinel marker in each region.

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Genomic DNA from leucozytes

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IL-1 beta General Information: IL-1 beta Protein, Antibody, and Gene

**IL-1 beta General Information**

| APPROVED SYMBOL | APPROVED NAME |
|---|---|
| IL1B | interleukin 1 beta |
| **HGNC ID** | **SYNONYMS** |
| HGNC:5992 | IL-1B, IL1-BETA, IL1F2 |
| **LOCUS TYPE** | **CHROMOSOMAL LOCATION** |
| gene with protein product | 2q14.1 |
| **GENE FAMILY** | **HCOP** |
| Endogenous ligands Interleukins | Orthology Predictions for IL1B From HGNC |



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# Conclusions

- Residual risk in cardiovascular and cardiometabolic diseases arises from numerous factors, with a significant contributor being exposure to environmental toxins.
- Environmental toxins drive oxidative and nitrative stress and activate pro-inflammatory pathways.
- Residual risk is further shaped by each individual's unique genetic and epigenetic profile.
- A comprehensive personalized risk assessment is paramount if we are to impact the ever growing incidence of cardiovascular disease.

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# Thank You!

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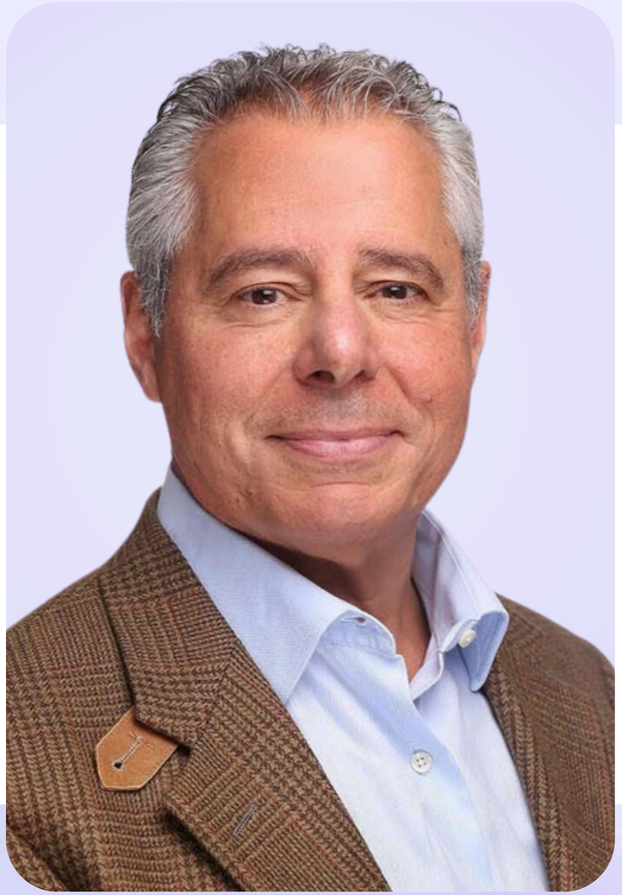
# The Heart of Longevity

Innovations in Cardiovascular and Metabolic Care



Session 3

**Dr. Giovanni Campanile, M.D., FACC, ABIHM, FAARM**

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# Protocols fot The Prevention and Reversal of Heart Disease

The use of Advance Cardiac Biomarkers and Advanced Cardiac Imaging

*Giovanni Campanile, MD, FACC*

## Meet Your Speaker

# *Giovanni Campanile, MD, FACC, ABIHM, FAARM*


Founder and Medical Director of CorAeon
The Functional Medicine & Cardiology Practice

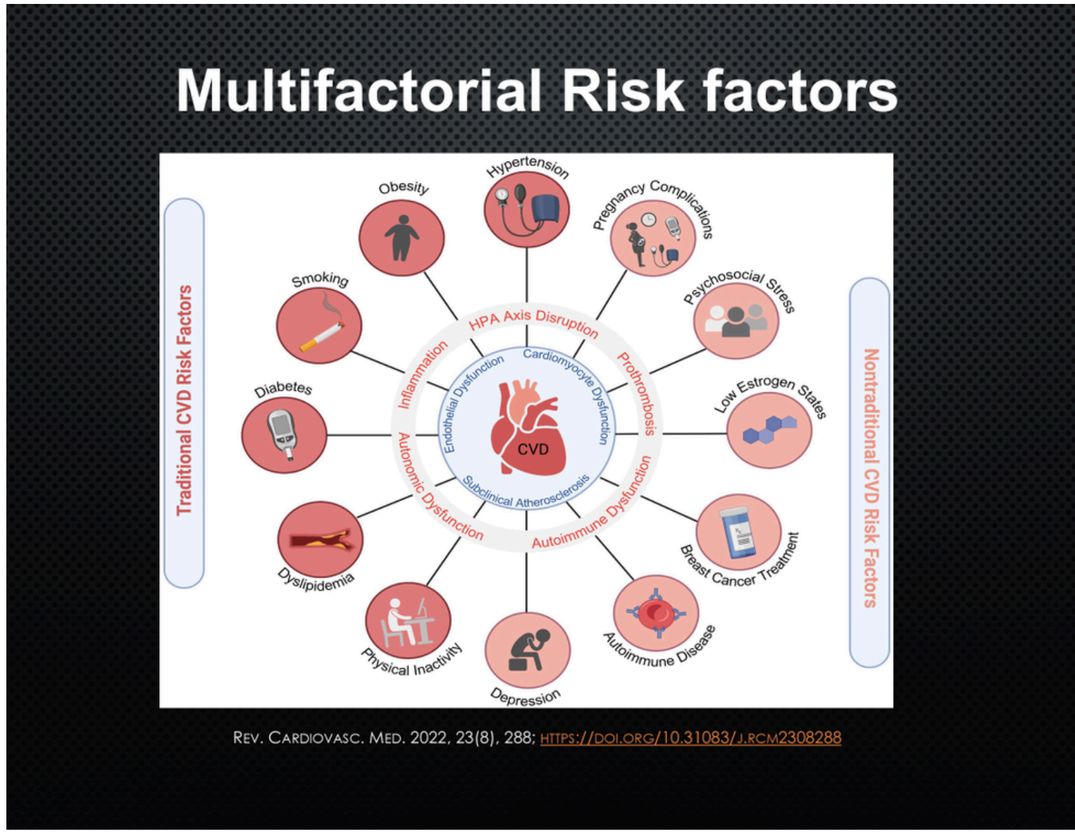

Longevity Conference 2025


Contact: campanile4@gmail.com
Cell: 201-638-8007

www.functionalheart.com
www.coraeon.com

# Learning Objectives

- Understand the Atypical Risk factors for Atherosclerotic Heart Disease
- Review the Pathophysiology of Coronary Artery Disease
- Review the influence of insulin and carbohydrate metabolism as it relates to heart disease
- How to assess and treat inflammation as it relates to heart disease
- The Prognostic Utility of Advanced Cardiac Biomarkers
- The use of advanced AI Cardiac Imaging
- The Importance of Diet and Omega 3 Fatty Acids
- The Holy Grail - Reversal of Heart Disease



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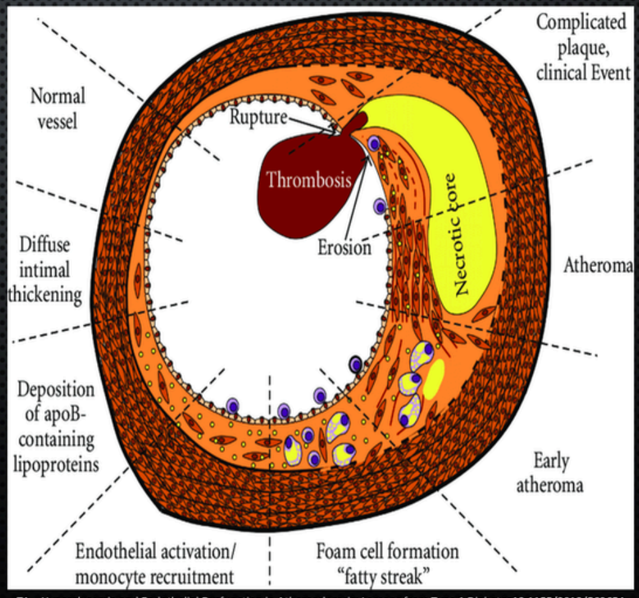
# The Clinical Problem

- Atherosclerosis begins early, sometimes in utero, and worsens silently over decades
- ASCVD is a Lifestyle Disease and is completely preventable
- We do not have great tools to evaluate subclinical ASCVD
- The first sign of ASCVD in many patients is cardiac sudden death
- Imaging technology that can identify early disease and track the progress of therapies

**"Atherosclerosis is a multifocal, smoldering, immunoinflammatory disease of medium-sized and large arteries fueled by lipids." [Falk, 2006]**




T1 - Hyperglycemia and Endothelial Dysfunction in Atherosclerosis: Lessons from Type 1 Diabetes10.1155/2012/569654 International journal of vascular medicine



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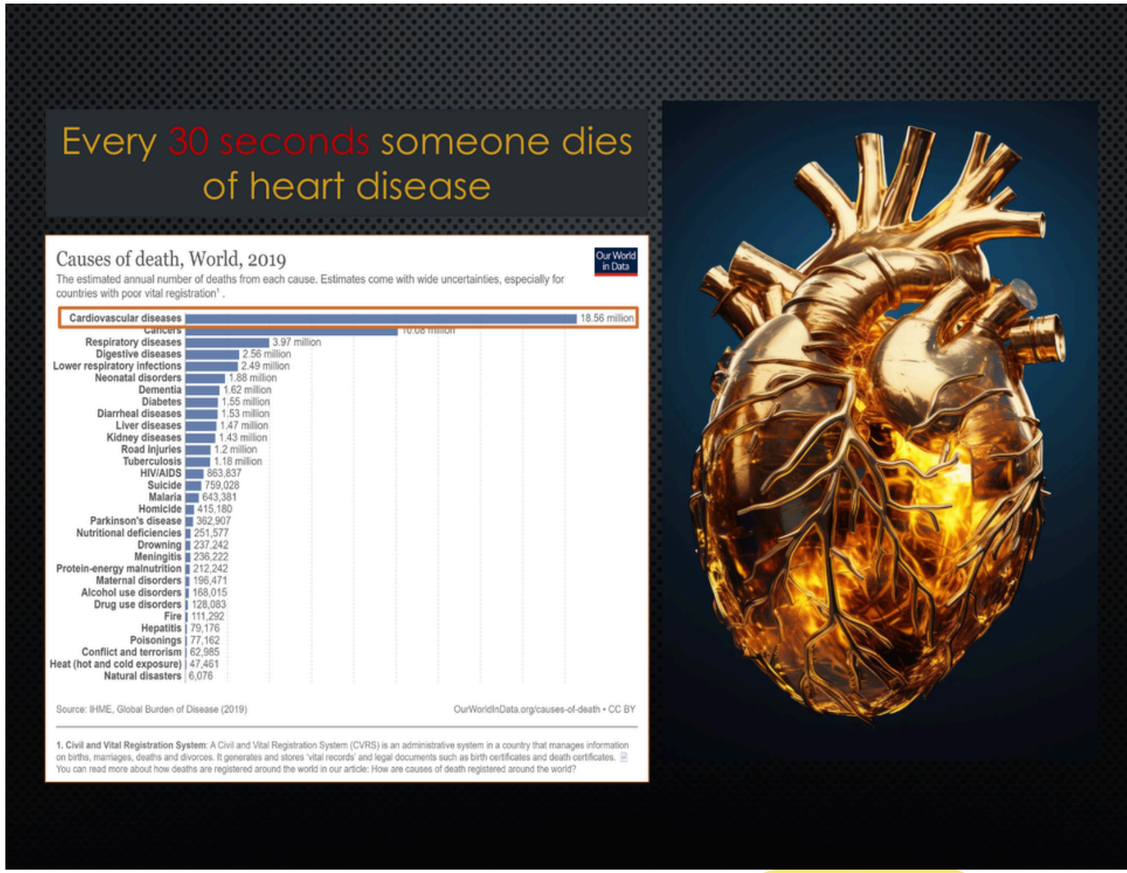
# The Clinical Problem

- INTERHEART STUDY - 90% of MI Risk was preventable
- In the Western World - ASCVD causes 20 mil deaths / year while cancer causes 10 mil deaths / year
- In surveys women fear breast cancer greater than ASCVD even though mortality from ASCVD is 10X greater
- Premenopausal Women are at lower risk, but are not risk free - YOUNG-MI Trial found that women were perceived to be at lower risk and less likely to be treated



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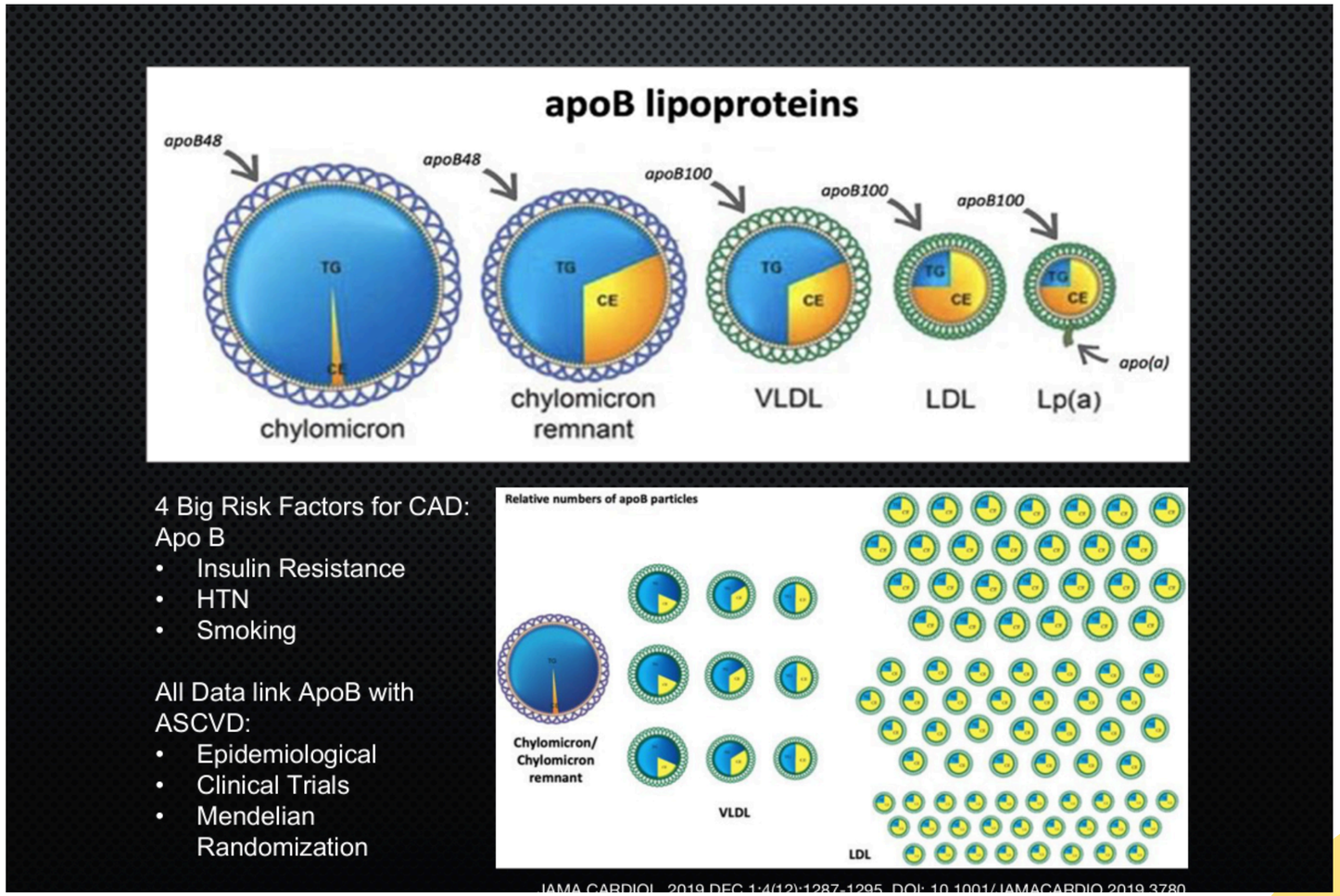
# APO B Lipoproteins



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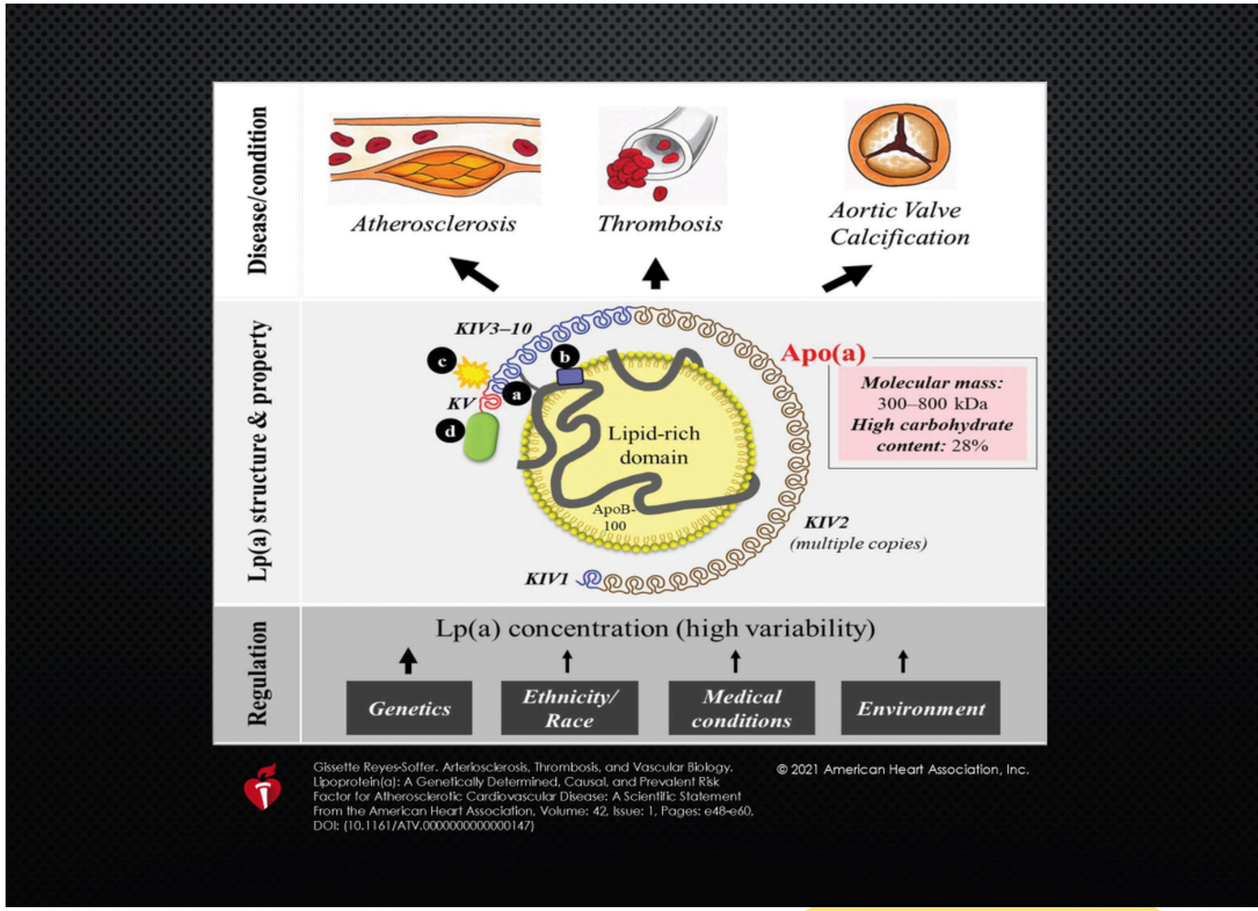
# Lipoprotein a – Lp(a)

- Lifestyle change does not help
- Target ApoB to 30-40 mg/dl
- PCSK9I – lower Lp(a) 30%
- Lipoprotein Apheresis
- Consider ASA
- Nattokinase
- Echocardiogram to assess for AS



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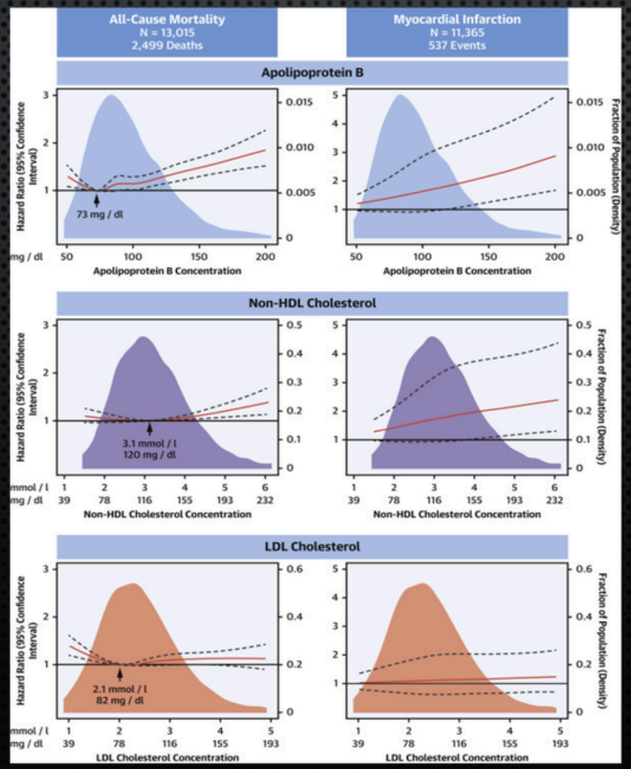
# Advanced Lipid Markers

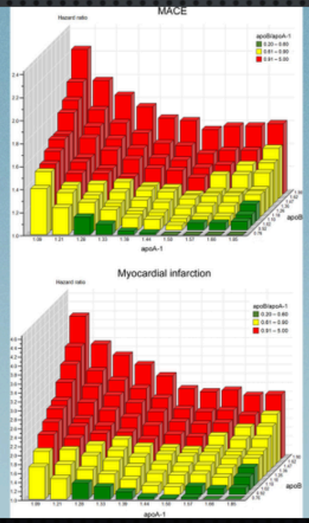
## ADVANCED LIPID PANEL




CLINICAL THERAPEUTICS/VOLUME 44, NUMBER 8, 2022ORIGINAL RESEARCH
APOLIPOPROTEIN B DISPLAYS SUPERIOR PREDICTIVE VALUE THAN OTHER LIPIDS FOR LONG-TERM PROGNOSIS IN CORONARY ATHEROSCLEROSIS PATIENTS

APO B - Biomarker & Causally related to ASCVD

May go back to a time when we energy deprived - good for us until 100 years ago




We do not really need any Apo B - most animals do not have it.
Children have ApoB <20mg/dl
Peter Libby B&WH
If ApoB <30 - no CAD



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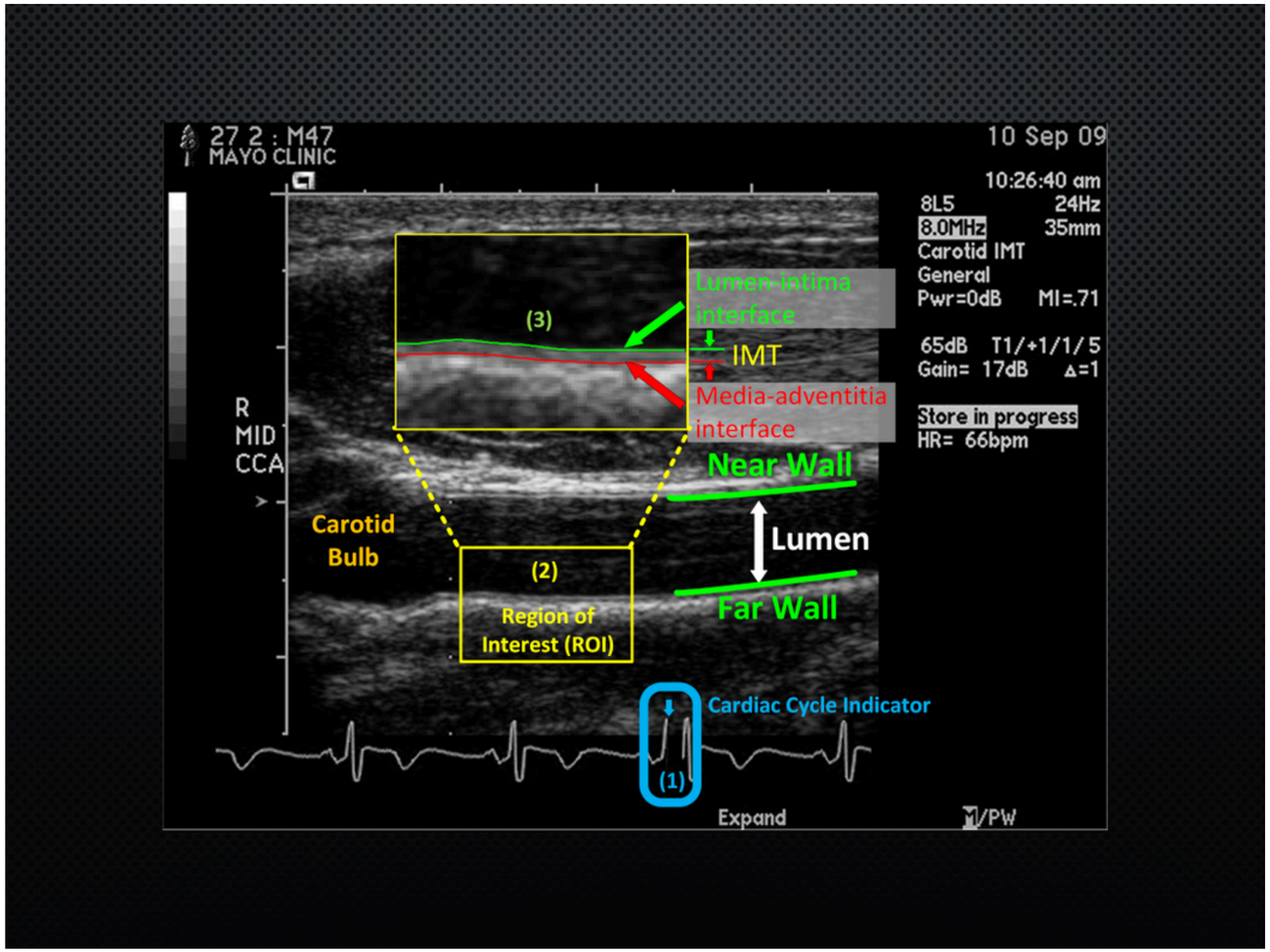
# CIMT



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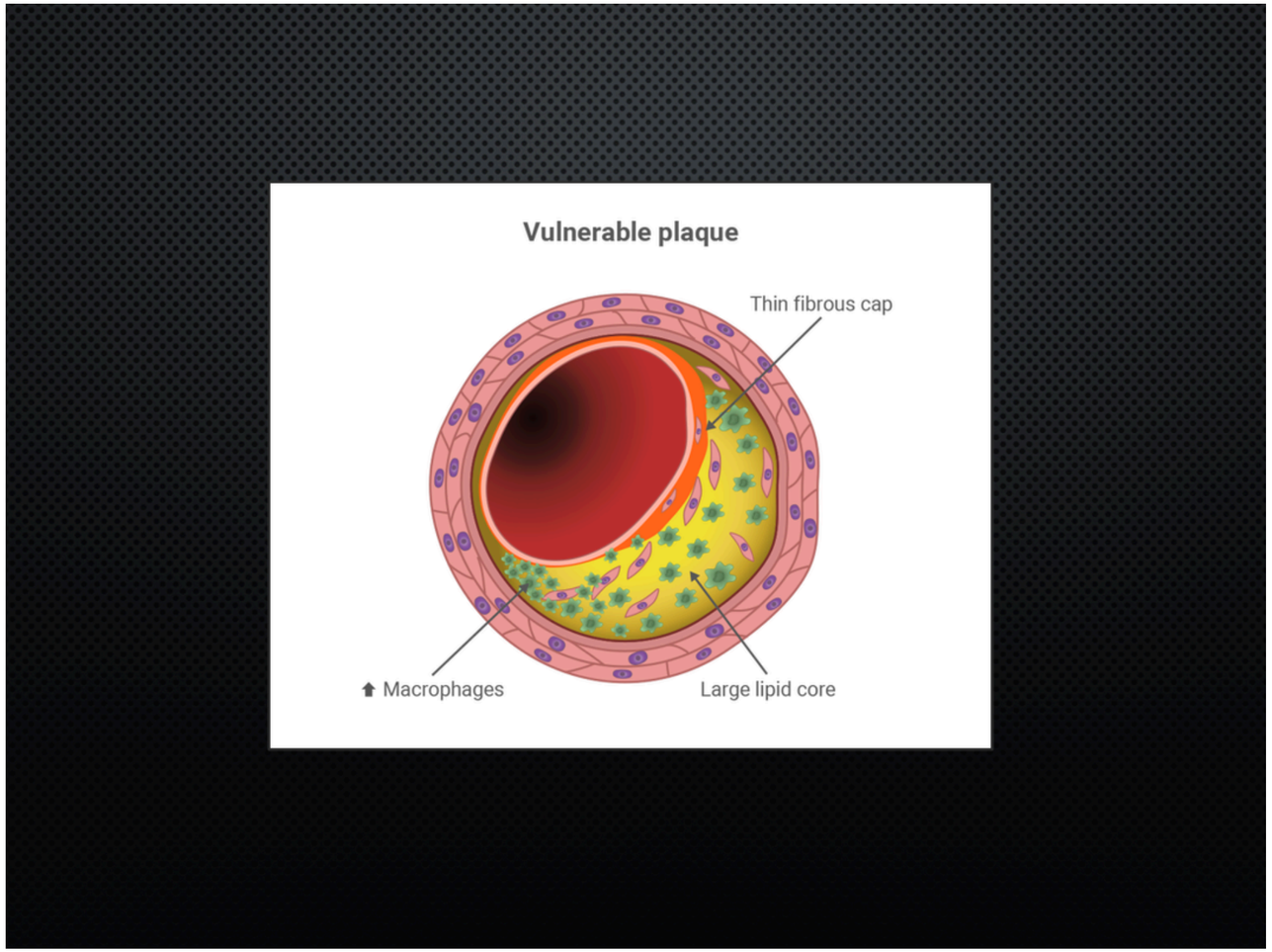
# VULNERABLE PLAQUE



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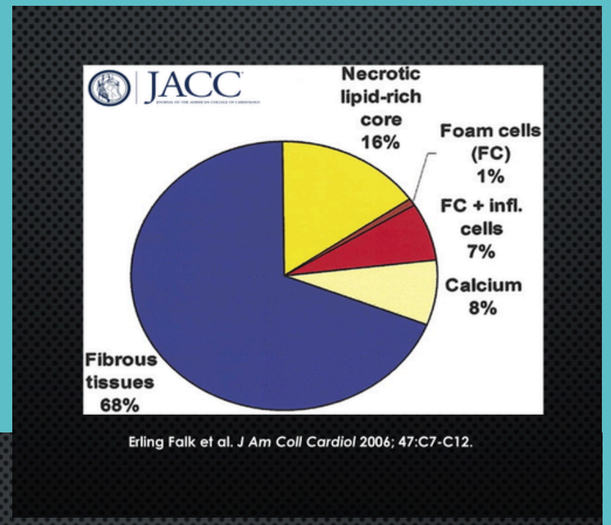
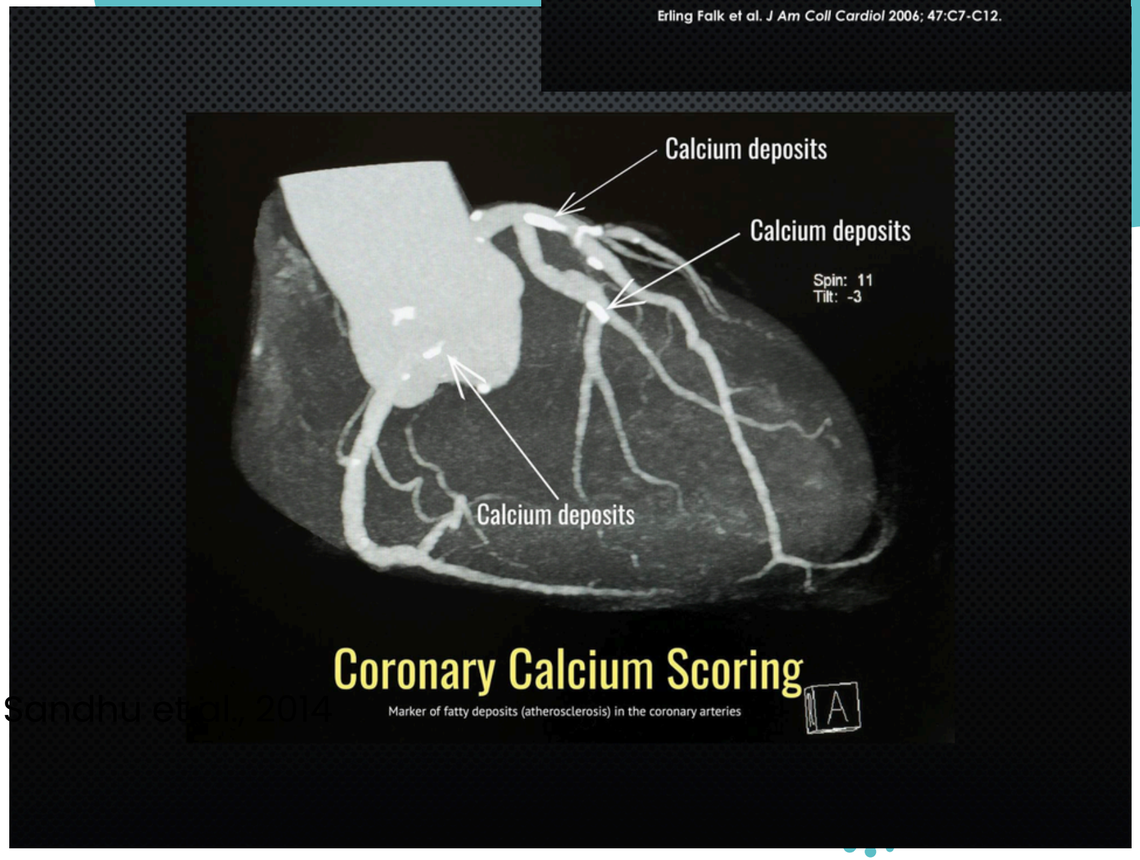
# Coronary Artery Calcium Score

- First developed by Arthur Agatston
- Linear relationship between degree of plaque and degree of calcium
- Low dose radiation screening test
- Helpful in young patients if abnormal and in older patients if score is low
- a zero score does not guarantee the absence of plaque



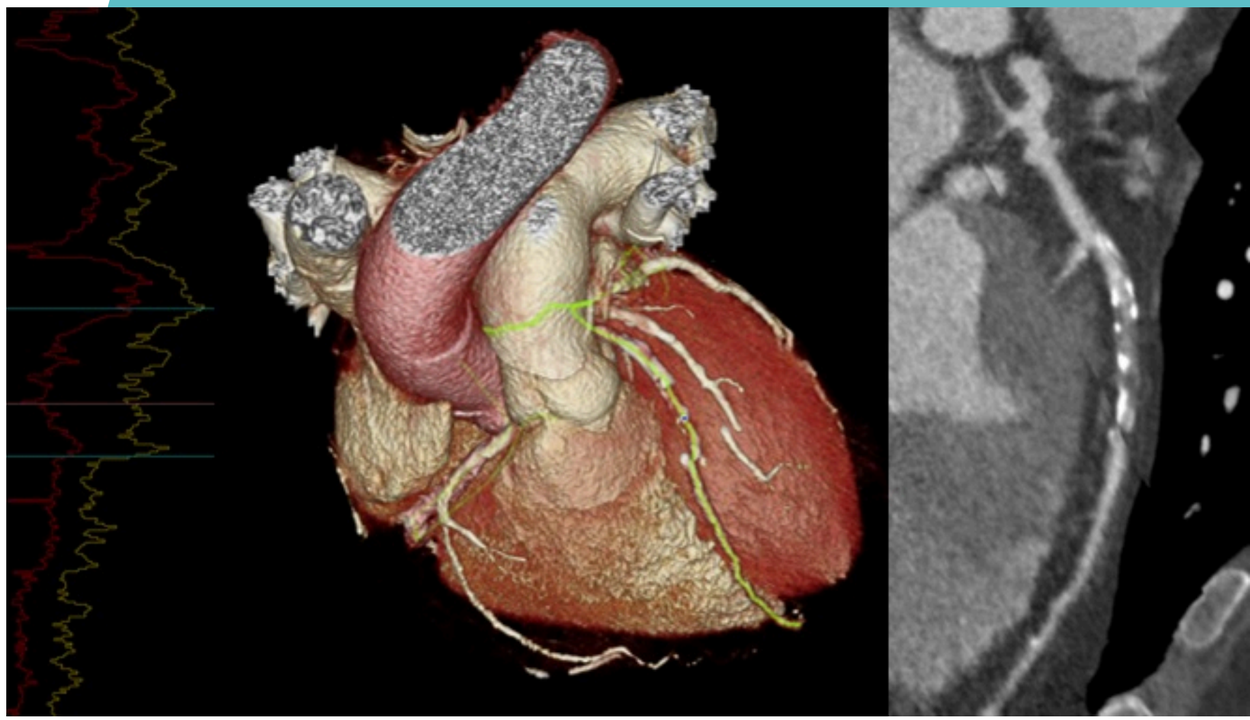

Erling Falk et al. *J Am Coll Cardiol* 2006; 47:C7-C12.




Sandhu et al. 2014

# Coronary CT Angiogram (CCTA)

- An angiogram that gives detail of the wall of the artery
- Can identify plaque on the inside of the endothelium before it starts to narrow the lumen
- 1-2 mSvt of Radiation
- NRC limits to 50mSVT / Year
- Living at sea level = 1mSvt/year
- Living in Denver = 4-5mSvt / Year
- Cost = $1400-$2500





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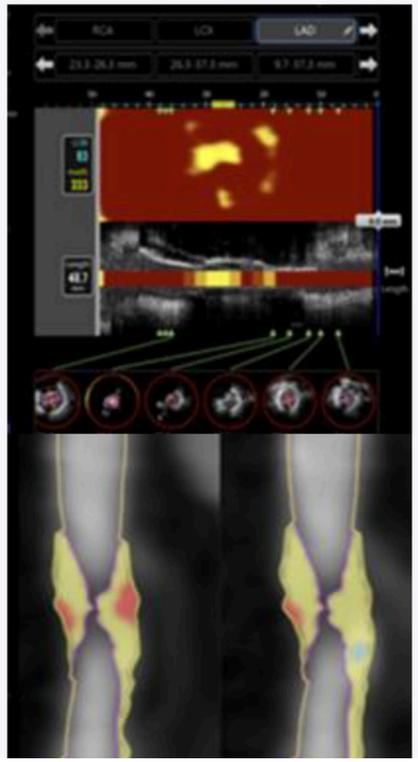
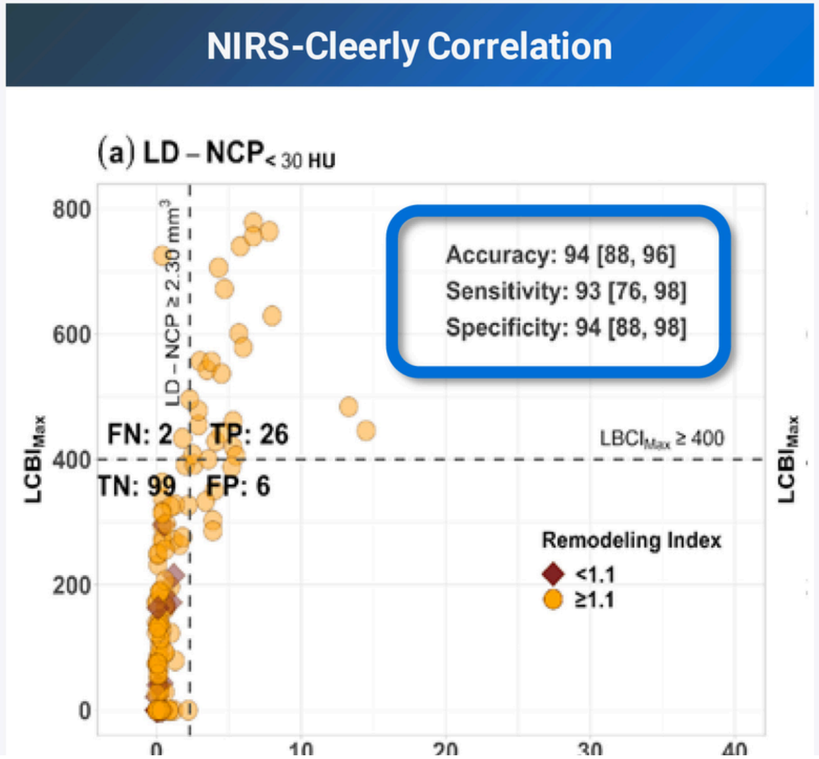
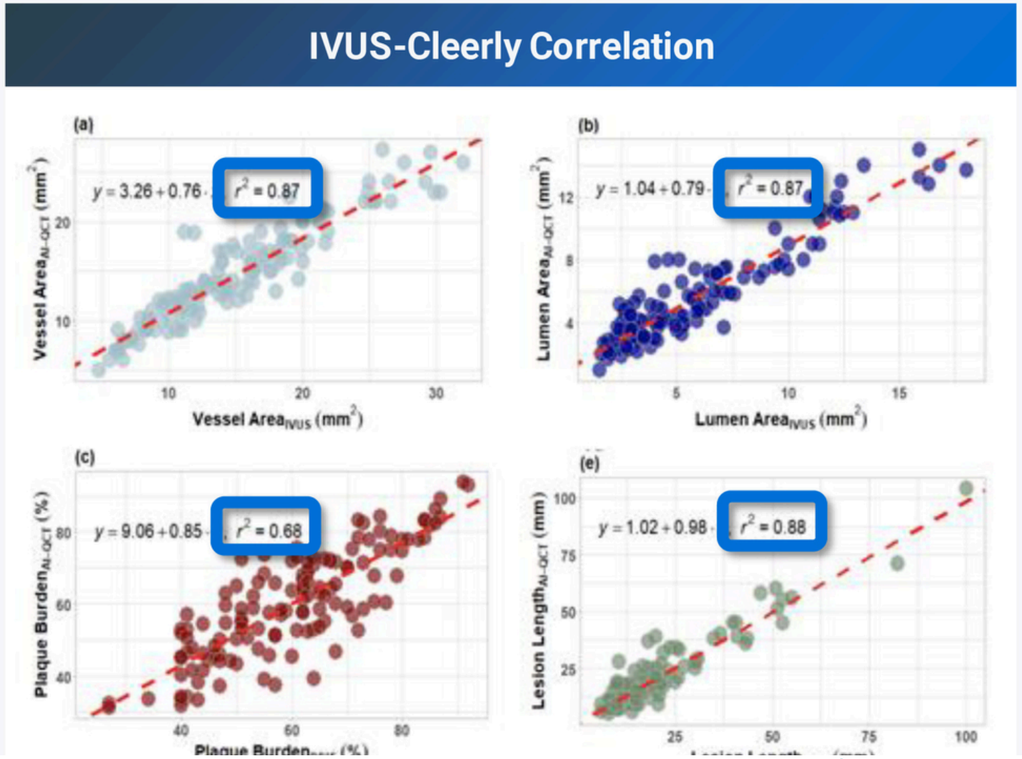
# CLEERLY – AI Enabled CCTA

- Correlates very well with “Gold Standards”
  Near Field InfraRed Spectroscopy and IVUS

- Ground Truth: NIRS-IVUS[14] (for lipid-rich plaque)





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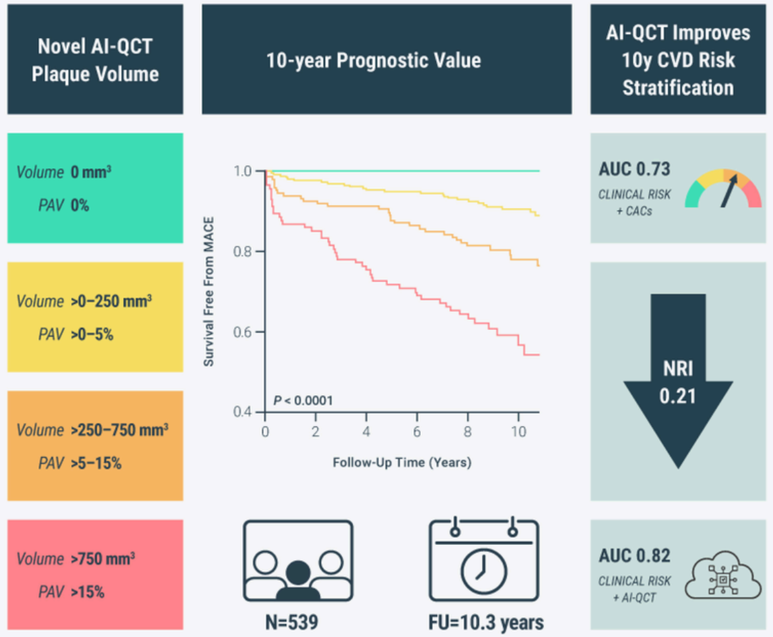
# CLEERLY – AI Enabled CCTA

## Improved CV Risk Assessment

### MACE Prediction:

- AI-QCT modestly outperformed prediction of long-term MACE events compared to:
  - Risk Score (ASCVD etc.)
  - Agatston Score
  - Stenosis presence
  - FFRCT[15]

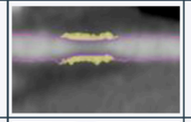
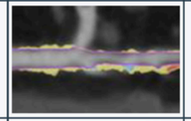
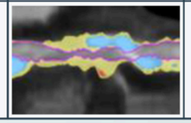



*Modified Figure from Nurmohamed et al JACC Cardiovasc Imag 2024

Source: [15] Nurmohamed, Nick S et al. AI-Guided Quantitative Plaque Staging Predicts Long-Term Cardiovascular Outcomes in Patients at Risk for Atherosclerotic CVD. JACC. Cardiovascular imaging vol. 17,3 (2024): 269280. doi:10.1016/j.jcmg.2023.05.020

# CLEERLY – AI Enabled CCTA

## Emphasize Atherosclerosis as the Primary Disease Target

| Plaque Description | | TPV ($mm^3$) | PAV (%) | Possible Examples* (GDMT = Guidelines Directed Medical Therapy) |
|---|---|---|---|---|
| No Plaque |  | 0 | 0 | Baseline GDMT. Consider de-escalation. |
| Mild Plaque |  | >0 to 250 | >0 to 5% | Statins. Ezetimibe. |
| Moderate Plaque |  | >250 to 750 | >5-15% | High Intensity Statins. Ezetimibe. Rivaroxaban. Aspirin. Inclisiran. Bempedoic Acid. Other. |
| Severe Plaque |  | >750 | >15% | High Intensity Statins. Ezetimibe. Rivaroxaban. Aspirin. PCSK-9 Inhibitor. Colchicine. Icosapent ethyl. Inclisiran. Bempedoic Acid. Others. |

**ACC Innovations in Prevention Working Group developed for patients with lipid disorders, diabetes, hypertension, obesity and tobacco use–personalize treatment based upon actual disease.*[23]

cleerly





## Treat

Evidence-based precision care helps drive treatment pathways that target actual disease over indirect markers.

**Treatment based upon:**

- **Amount** of disease
- **Type** of disease
- **Progression** of disease

ACC "Treat Disease" algorithms suggest repeat Cleerly analyses at 3-2-1 years for patients with mild, moderate and severe disease, respectively.



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# CLEERLY – AI Enabled CCTA




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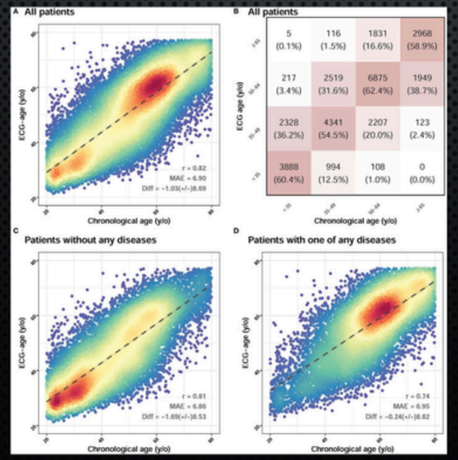
# AI-ECG

Front Cardiovasc Med. 2022; 9: 754909.

Electrocardiogram-Based Heart Age Estimation by a Deep Learning Model Provides More Information on the Incidence of Cardiovascular Disorders



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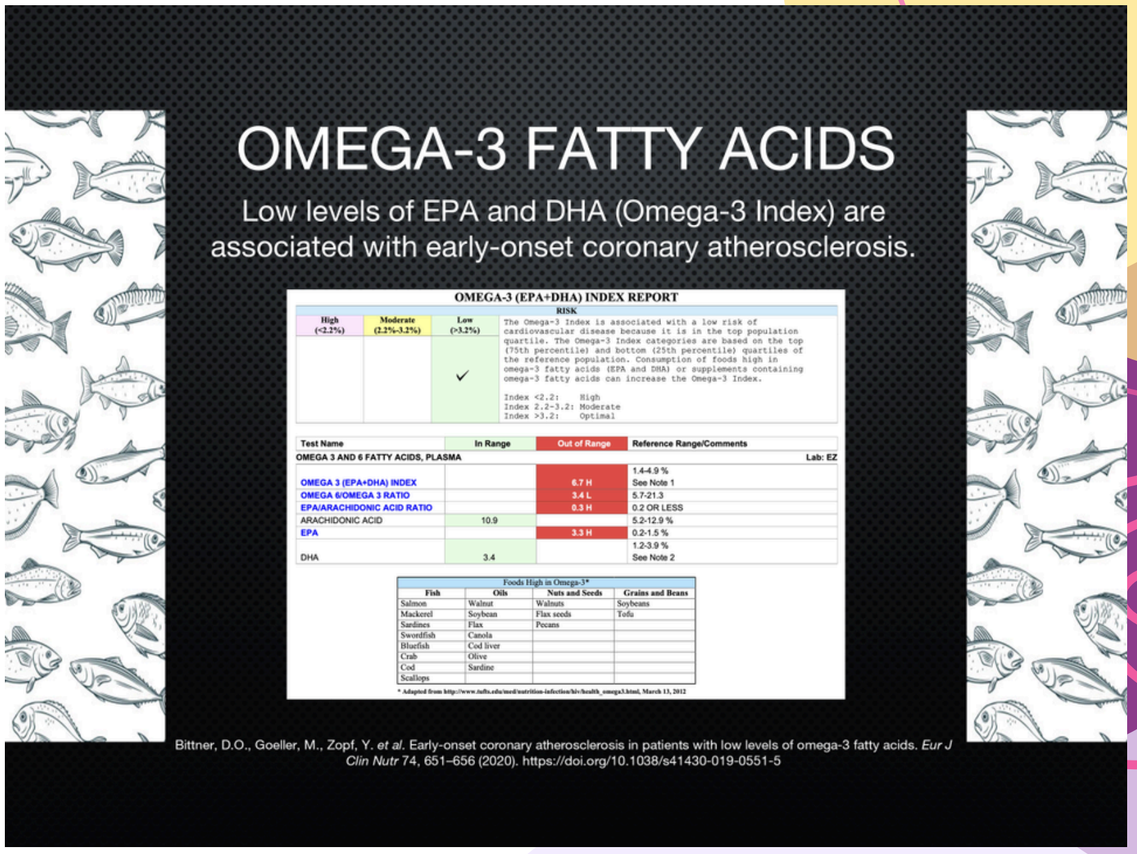
# Health Benefits of EPA & DHA

- **Reduces stickiness of Platelets - ASA effects without downside**
- **Anti-Inflammatory**
- **Improves cellular membrane flexibility and improves cellular metabolism**
- **REDUCE-IT Study - 25% reduction in CV events**
- **Evaporate Study - decreased coronary plaque by 17%**
- **Meta Analysis (Mayo Clinic Proceedings, Feb 2021) 40 studies**
  **Risk of fatal MI reduced by 35%**
- **Improves HRV**
- **SMASH Fish**



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# Exercise

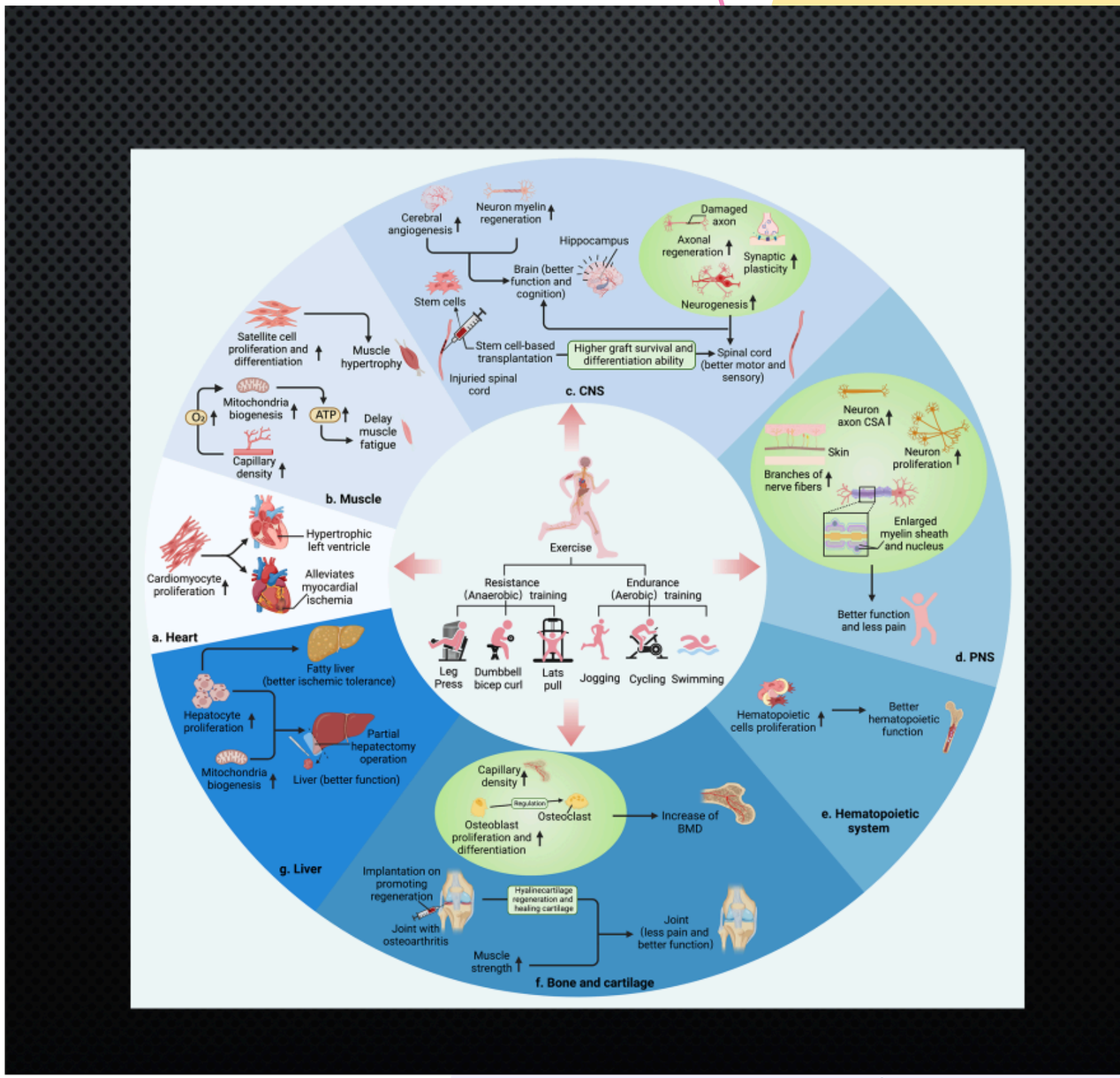
- **If Exercise were a drug it would  be a sensational geroprotective – prevents heart disease, dementia, osteoporosis, depression, diabetes, and obesity**

- **Too much exercise can be counterproductive – at about 50 min of high-intensity exercise the body's ability to deal with oxidative stress is exhausted and endothelial function is negatively affected – studies have shown that people who have run multiple marathons have higher CAC**

- **Cpenhagen City Heart Study – Tennis, Badminton, and soccer the best, followed by running, cycling, calisthenics, and swimming**

- **Enjoying, playing and social activities all promote Longevity**

- **150-300 minutes per week ; Zone 2, HIIT, Strength, Yoga, Tai Chi**

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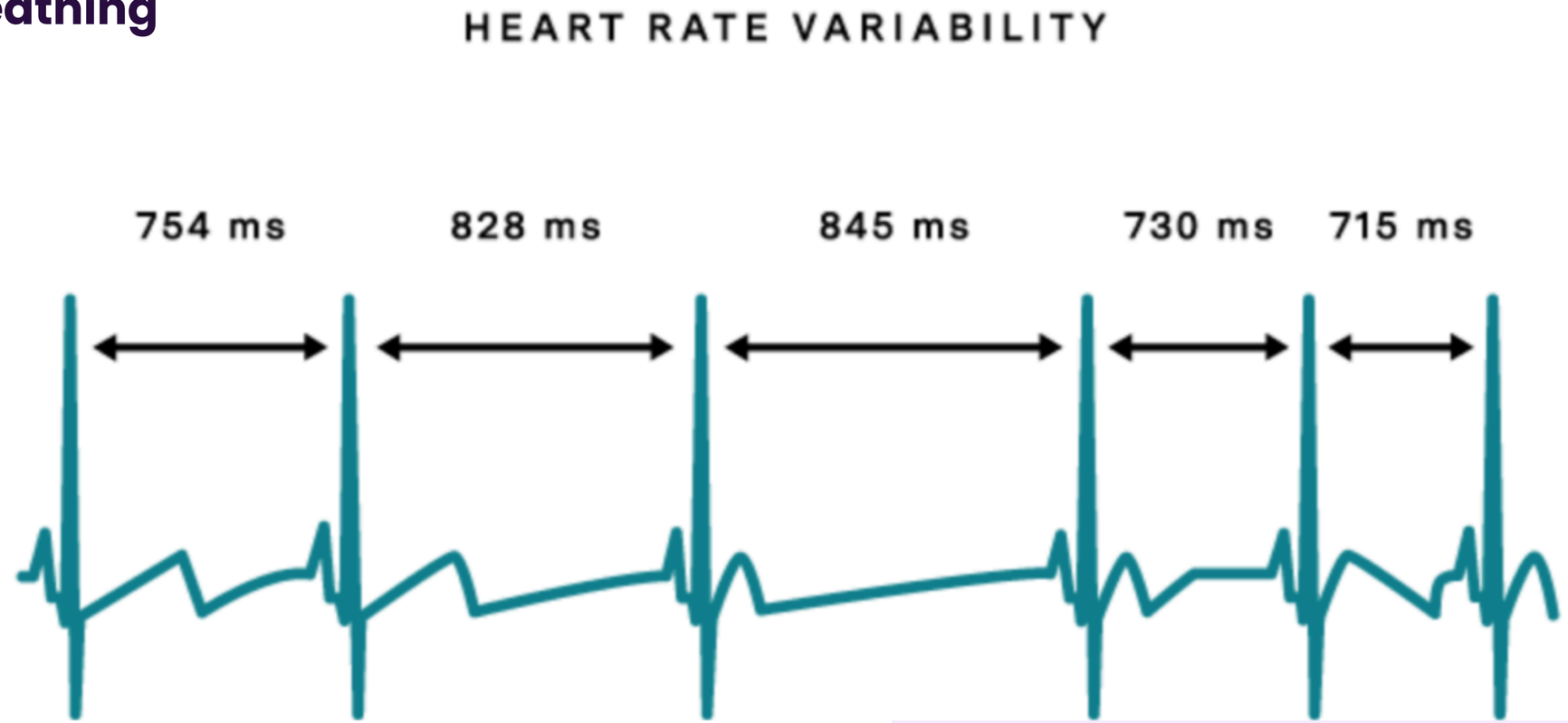
# Exercise – Heart Rate & HRV

- **HRV – more variable when you take slow deep breaths:**
  - **Pranayama Universal Breathing**
  - **Heart Math Biofeedback**
  - **Sauna**
  - **Yoga**
  - **Meditation**
  - **Healthy Diet**
  - **Connection with others**
  - **Regular exercise**



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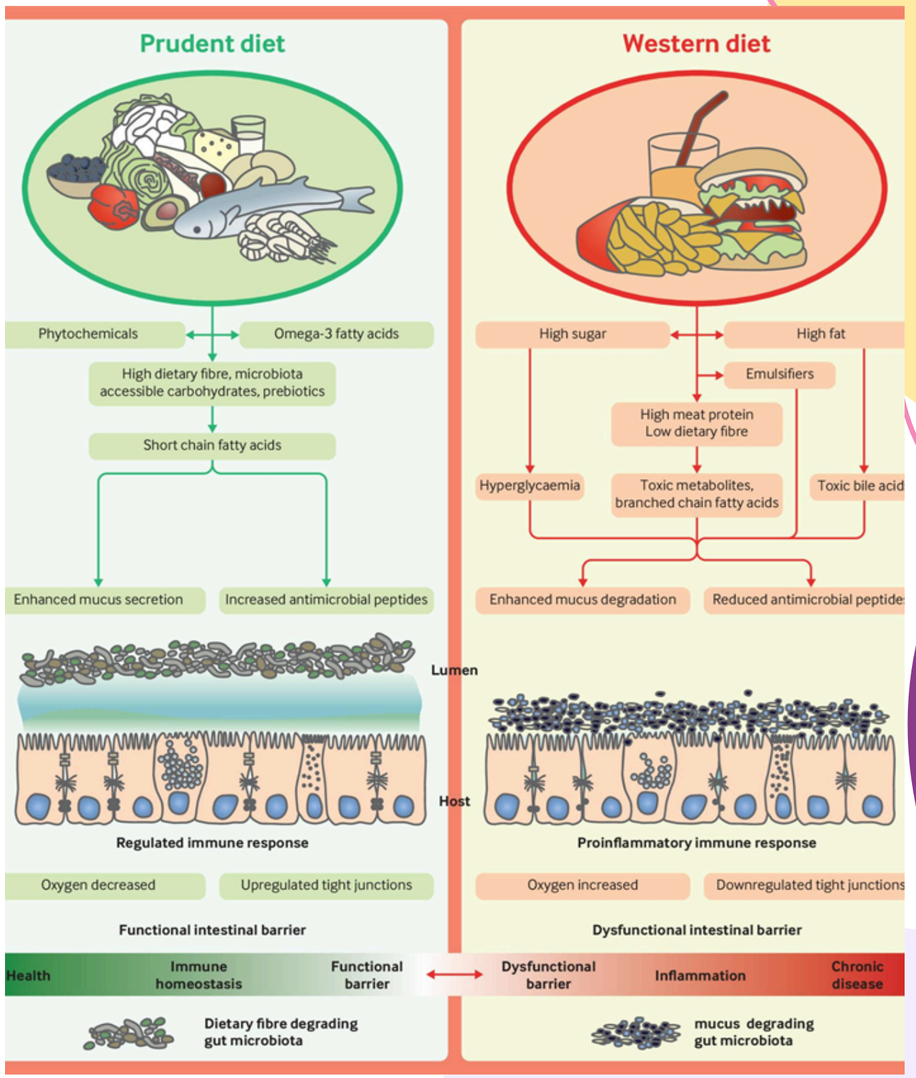
# Nutrition for CV Health

- The Mediterranean Diet has been rated by US News and World Report as the best overall diet for multiple years
- Low refined carbohydrates, low saturated fats, which prevent CVD, Diabetes, Dementia, Obesity, and Cancer
- PREDIMED - 30% reduction of CV events plus decreased diabetes, cognitive decline and obesity - high fat from olive oil and nuts were beneficial



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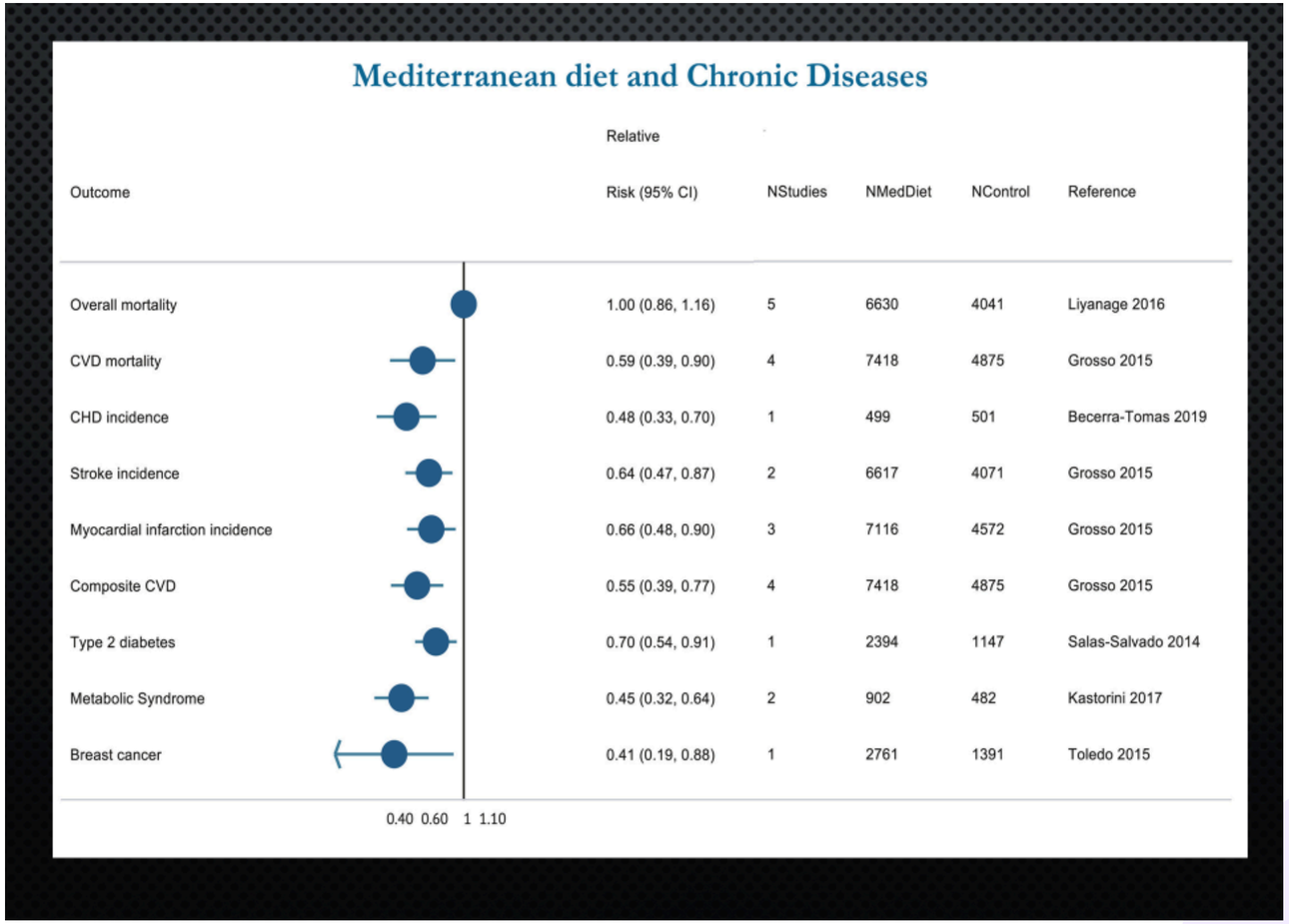
# Nutrition for CV Health



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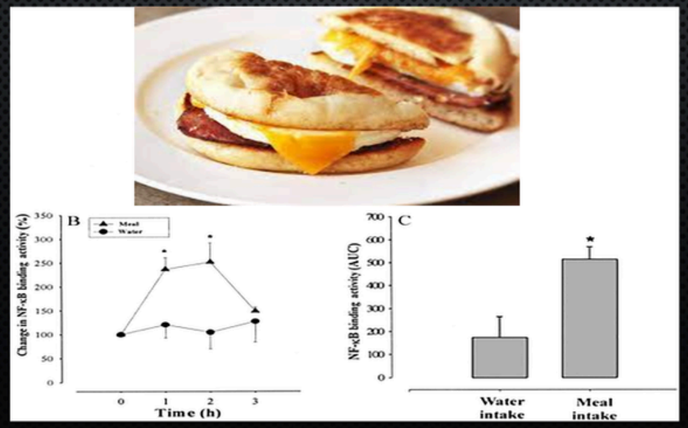
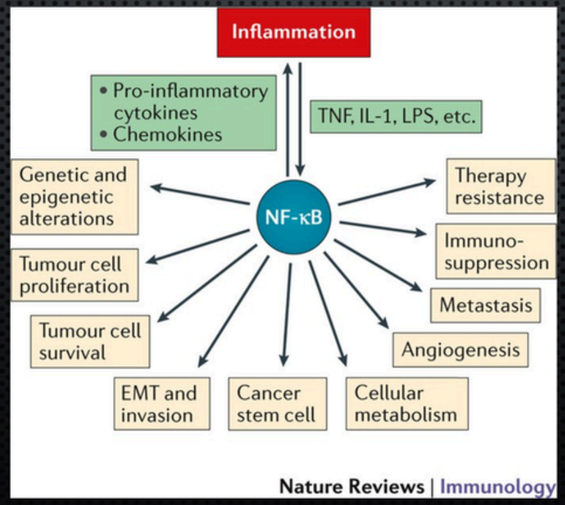
# Nutrition for CV Health

Am J Clin Nutr. 2004 Apr;79(4):682-90. doi: 10.1093/ajcn/79.4.682.
Increase in intranuclear nuclear factor kappaB and decrease in inhibitor kappaB in mononuclear cells after a mixed meal: evidence for a proinflammatory effect

Patients were given an egg-muffin and sausage-muffin and 2 hash browns, which contained 910kcal, 81g carbohydrate, 51g fat, and 32 g protein over 15 min.



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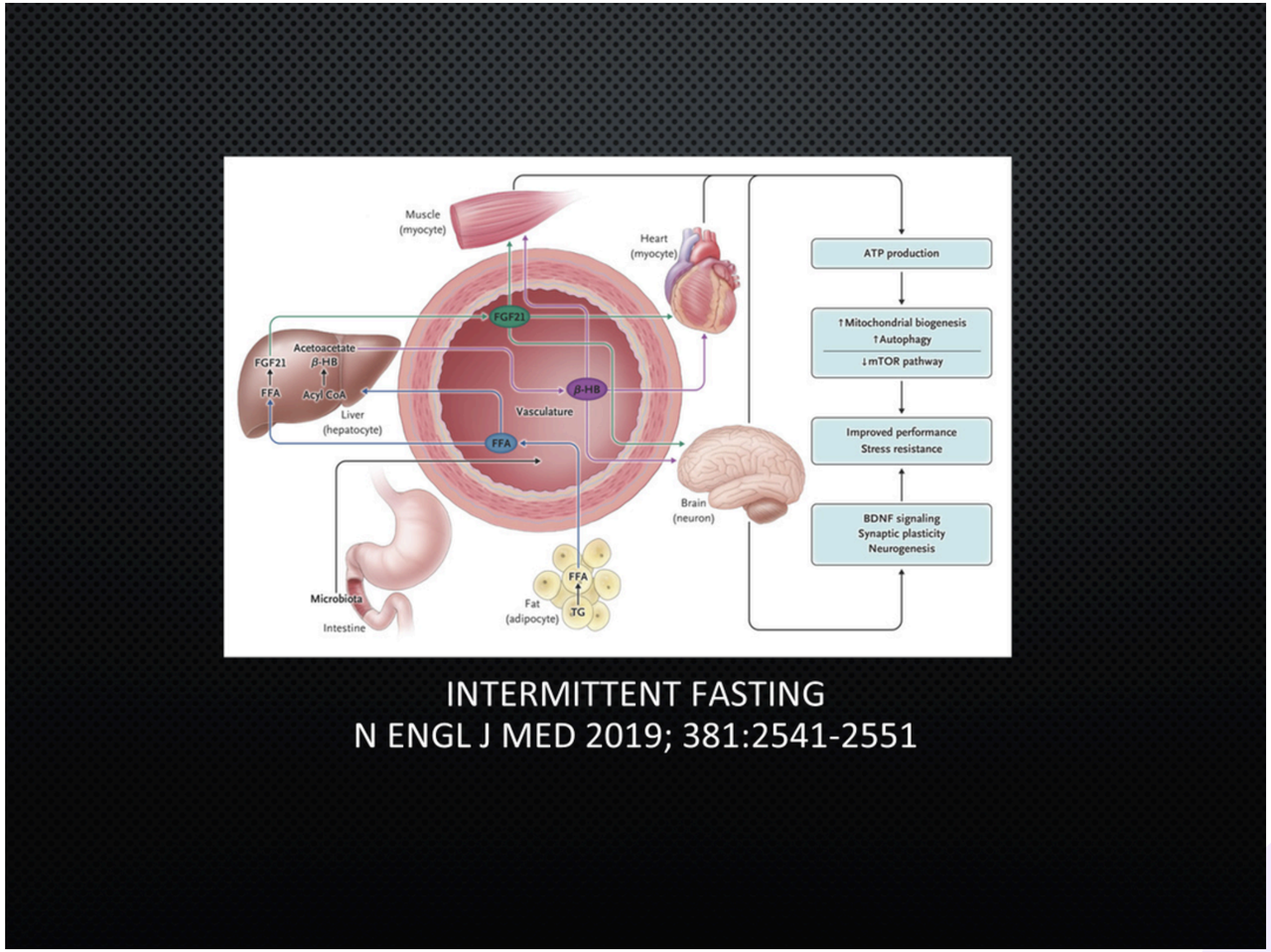
# Nutrition for CV Health



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# GLP-1 Agonists

- Semaglutide = GLP-1 Agonist (Glucagon-Like Peptide-1)
- Trizepetide = GIP ( Glucose-Dependent Insulinotropic Polypeptide) & GLP-1 agonist
- Approved for Weight Loss and Diabetes
- Do not cause hypoglycemia if glucose levels are normal
- Benefit on MACE is independent of A1C lowering (LEADER, SUSTAIN-6, REWIND)
- Significant reduction in CVA, kidney failure, CHF, HFpEF
- Risks: Mac Deg, Depression, Muscle Loss, Suicidal Ideation
- ADA & AHA/ACC Guidelines - GLP-1 Agonist recommended in Pts with DM2 and established ASCVD or high CV risk even if A1C is normal
- Possible Mechanisms
  - Improved Endothelial Function
  - Reduced Inflammation - decreased hsCRP
  - Plaque Stabilization
  - Reduces Blood Pressure
  - Reduces LDL & TG



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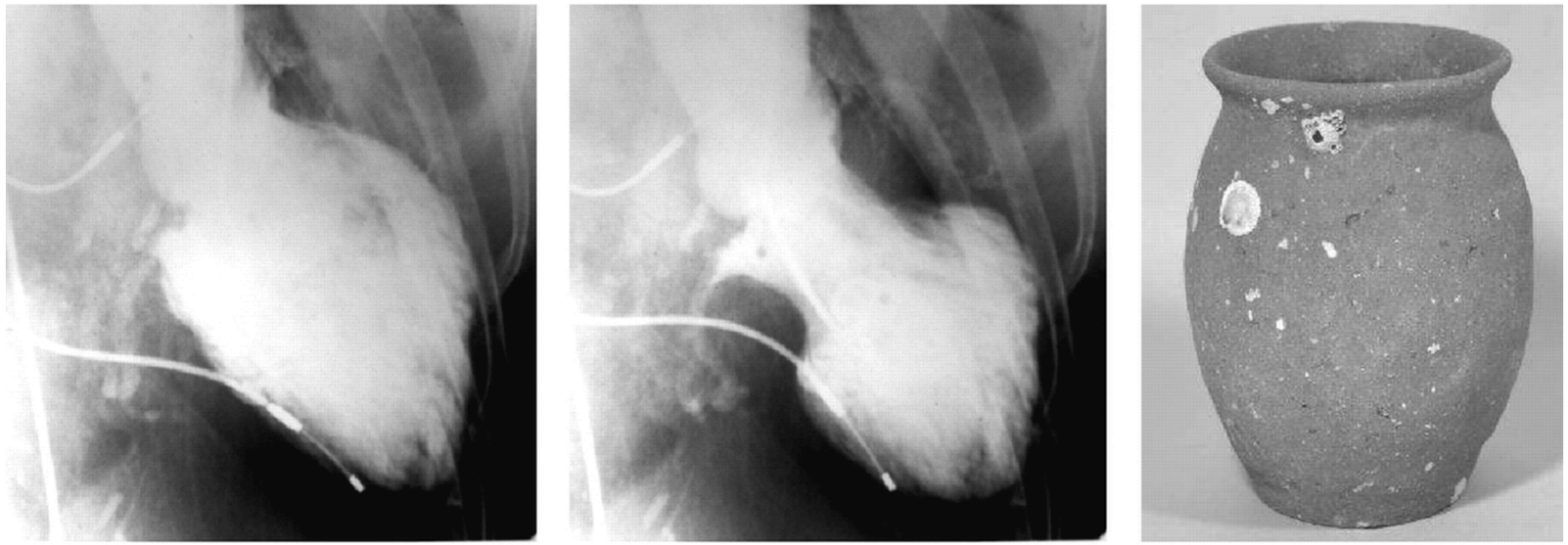
# Women & Heart Disease

- Women are more likely to have ischemia with non-obstructive coronary disease from coronary microvascular dysfunction or coronary vasospasm
- They're more likely to have SCAD (spontaneous coronary artery dissection)
- They're more likely to have stress (Takostubo) cardiomyopathy than men
- Lancet 2015 - Meta Analysis, statins benefit women both in primary and secondary prevention
- PALM Registry - Women are less likely to be offered a statin
- Female Specific Risk Factors foe ASCD
    - Menarche when early or late
    - Polycystic ovary syndrome
    - Infertility
    - Spontaneous pregnancy loss
    - Parity
    - Adverse pregnancy outcomes like preeclampsia
    - Lack of breastfeeding
    - Early menopause

# Takotsubo Cardiomyopathy
# Broken Heart Syndrome



A B C



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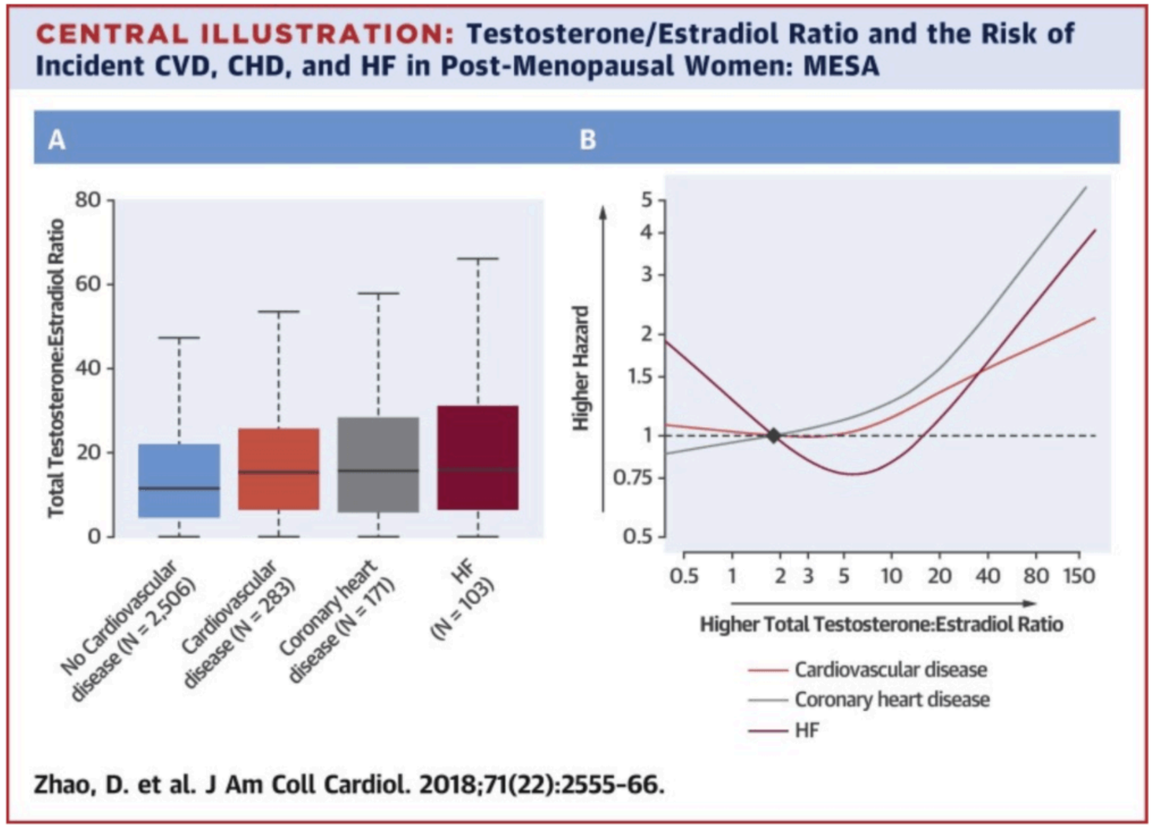
# MENOPAUSE & CVD

- More Visceral Fat
- Women with higher androgens had more CAC progression (PCOS - riskier Phenotype)
- More Insulin Resistance
- Atherogenic Dyslipidemia, increased LDL, TG and decreased HDL
- Endothelial Dysfunction
- Increased Blood Pressure



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# HRT & CVD

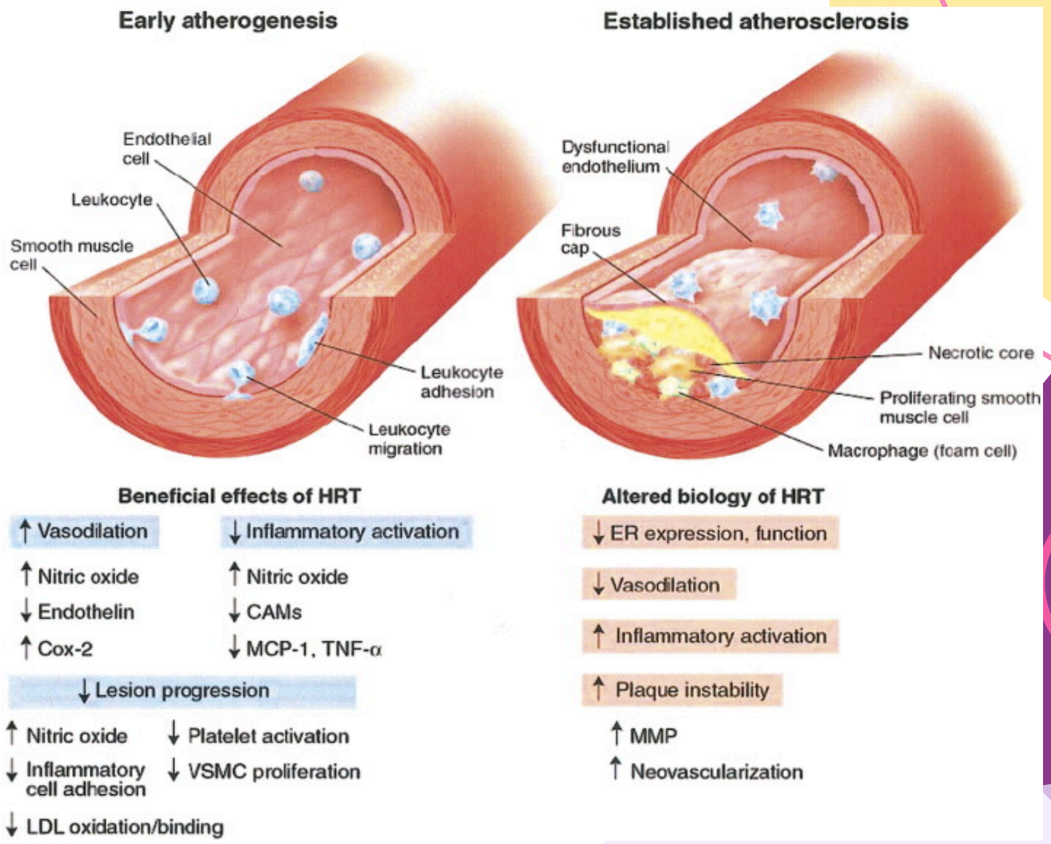
- **Risks of HRT**
  - Higher CRP
  - Can be prothrombotic - can increase prothrombin and decrease antithrombin III
  - Can increase TG
  - Can destabilize plaque during the first year of treatment

- **Benefits of HRT**
  - Lower LDL and increased HDL
  - Improved Endothelial Fx

**Avoid oral HRT :**

Hx CVD, Blood clots, high TG, Gallbladder Dz, Hx of Breast or Endometrial Cancer

Transdermal Estrogen may be les risky



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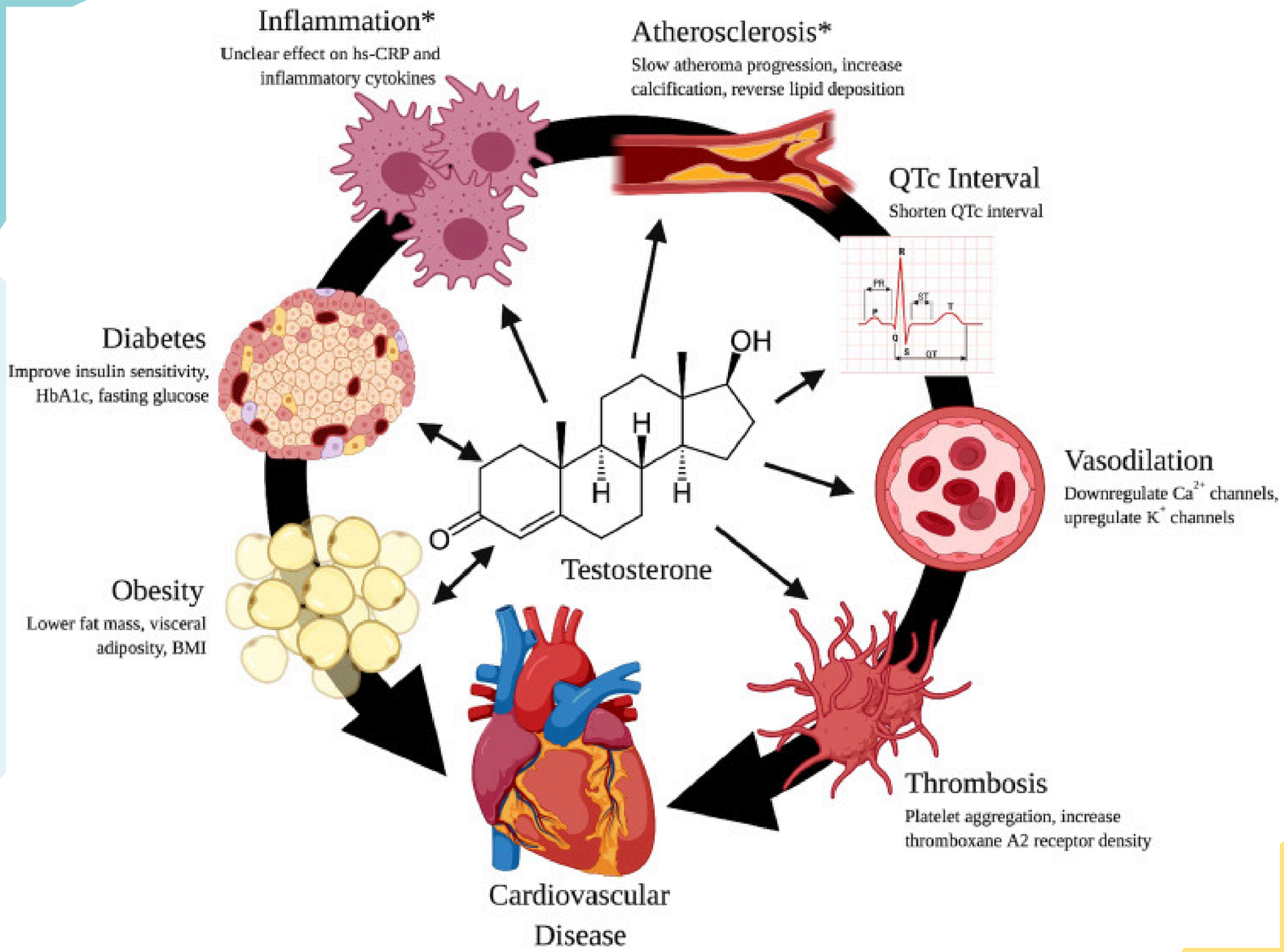




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- Traverse Trial - No increased CV risk
- Heart Disease is not a contraindication but an indication
- More Muscle Mass = Less Insulin Resistance
- Helps Promote Healing
- Improves Endothelial Function
- Helps Angiogenesis
- Helps Myocytes Regenerate after injury
- Helps Protein Deposition in Skeletal Musscle & Heart

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**Erythrocytosis:**

- Increased Epogen in Kidneys
- Increases Oxygen Carrying Capacity - Performance enhancer
- A Benefit if not Severe (HCT<55, HGB<19.5)
- Increases Platelet Inhibiting Factors - no increased blot clot risk
- Not Polycythemia - a bone marrow disease that does increase blood clot risk
- Also consider OSA, Smoking, Nicotine

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**DHT - Dihydrotestosterone**

- Male Pattern Baldness
- Excessive Body or Facial Hair
- Enlarged Prostate

**Treatment:**

- Saw Palmetto
- Pumpkin Seed Oil Extract
- Finasteride (Decreased Libido)

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## Most Importantly:

## Testosterone and Estrogen give motivation to do the Lifestyle changes necessary for a healthy heart

# Treatment of Lipids & ASCVD

- Lifestyle Change
- Statins - Cholesterol Sythesis Inhibition, Increased LDL Receptors, Increase LDL Clearence
- Aim for LDL <55 or ApoB <60 (40 if Lp(a) elevated)
- Add Ezetimibe early if needed (Watch LFTs)
- If CAC Above 300 or Lp(a) elevated - PCSK9i - lower LDL by 50%
- Bempedoic Acid - Prodrug, less myopathy, not as effective (lowers LDL 18%) - blocks ATP-citrate Lyase in the cholesterol synthesis pathway - upstream to HMG-CoA reductase (Statins)
- Statins & Bempedoic Acid block cholesterol synthesis which leads to up regulation of the LDL receptor on the surface of the liver
- Inclisiran - PCSK9i via small interfering RNA - prevents the tranlation of the PCSK9 molecule - the protein is never made ORION 10 & 11 - 50% reduction of LDL
- Supplements - Bergamot, Berberine, RYR
- Sytrinol - Leucine & Nicotinic Acid, Flavones and tocotrienols - affects SIRT/NAD+/AMPK - can reduce LDL by 27%



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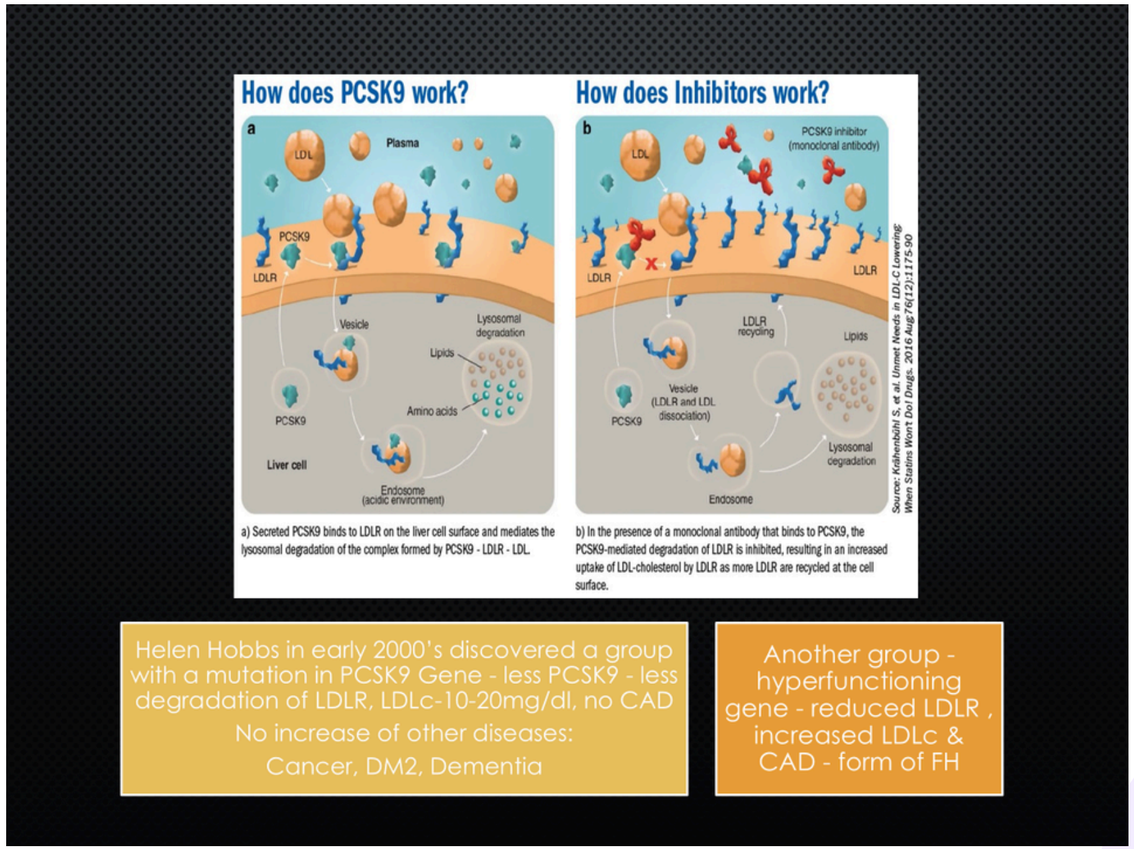
# PCSK9 Inhibitor
# (Proprotein Subtilisin/ Kexin Type 9)



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# Statins

**Cholesterol is essential for Life**
**Smith-Lemli-Optz Syndrome: Microencephaly, death**

**Cholesterol Pool Sizes**

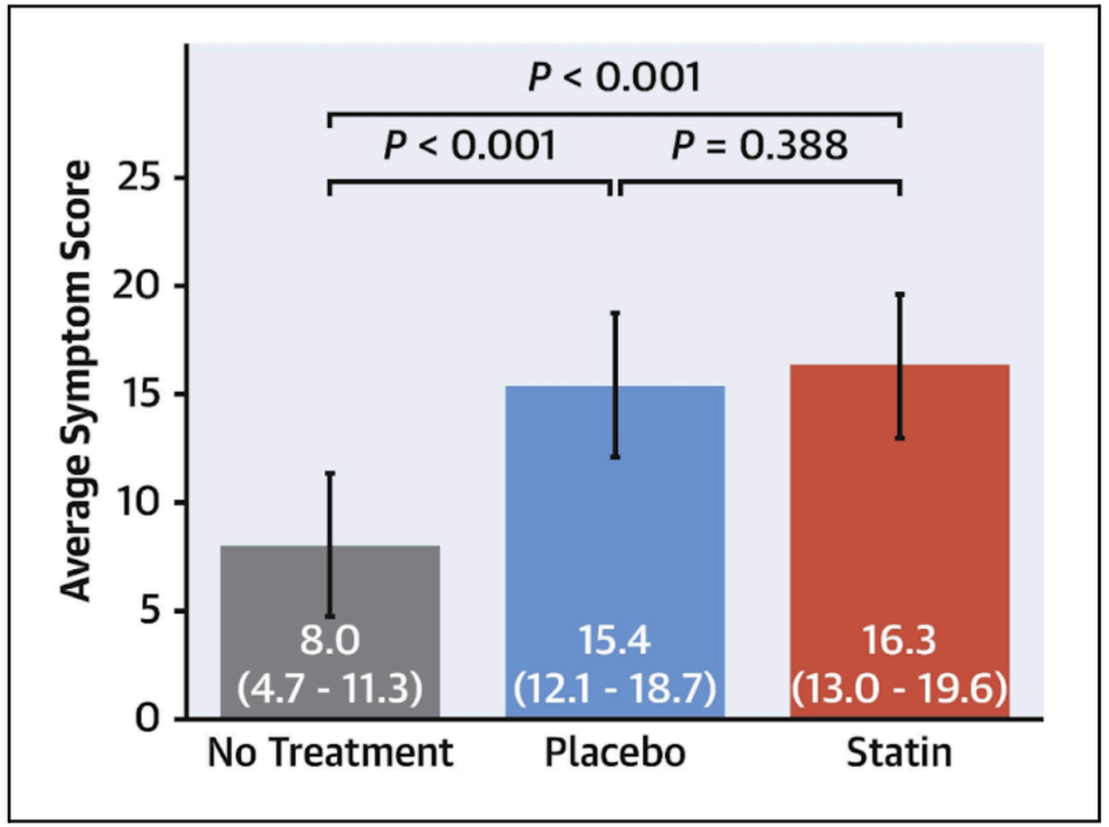
| 9.36 gms = 0.33 oz = ~ 2 tsp | mg/kg | g/70 kg |
|---|---|---|
| Liver | 27.0 | 1.89 |
| Red blood cells | 37.0 | 2.59 |
| Lipoproteins | 20.3 | 1.42 |
| Peripheral tissues | 133.7 | 9.36 |

Investigators concluded that neither the size nor turnover of these pools was significantly affected by blood lipid or lipoprotein levels nor by statin treatment, and thus whole-body cholesterol turnover did not correlate with the usual parameters of atherosclerotic risk

Statins - 7% Muscle aches
Increase in Transaminases
Ins resistance - 0.4% DM2
Follow HgbA1C, Insulin, CGM

No convincing data on negative Mitochondrial effects

Zone 2 testing (180-age)
No good data that CoQ10 helps



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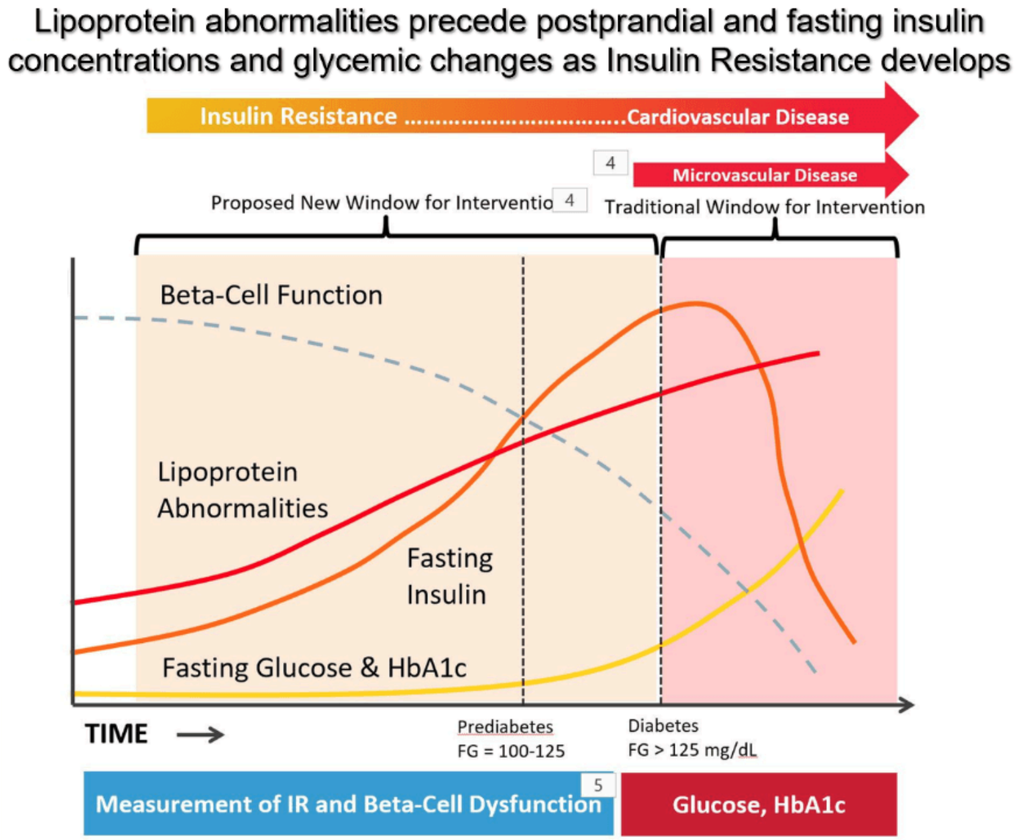
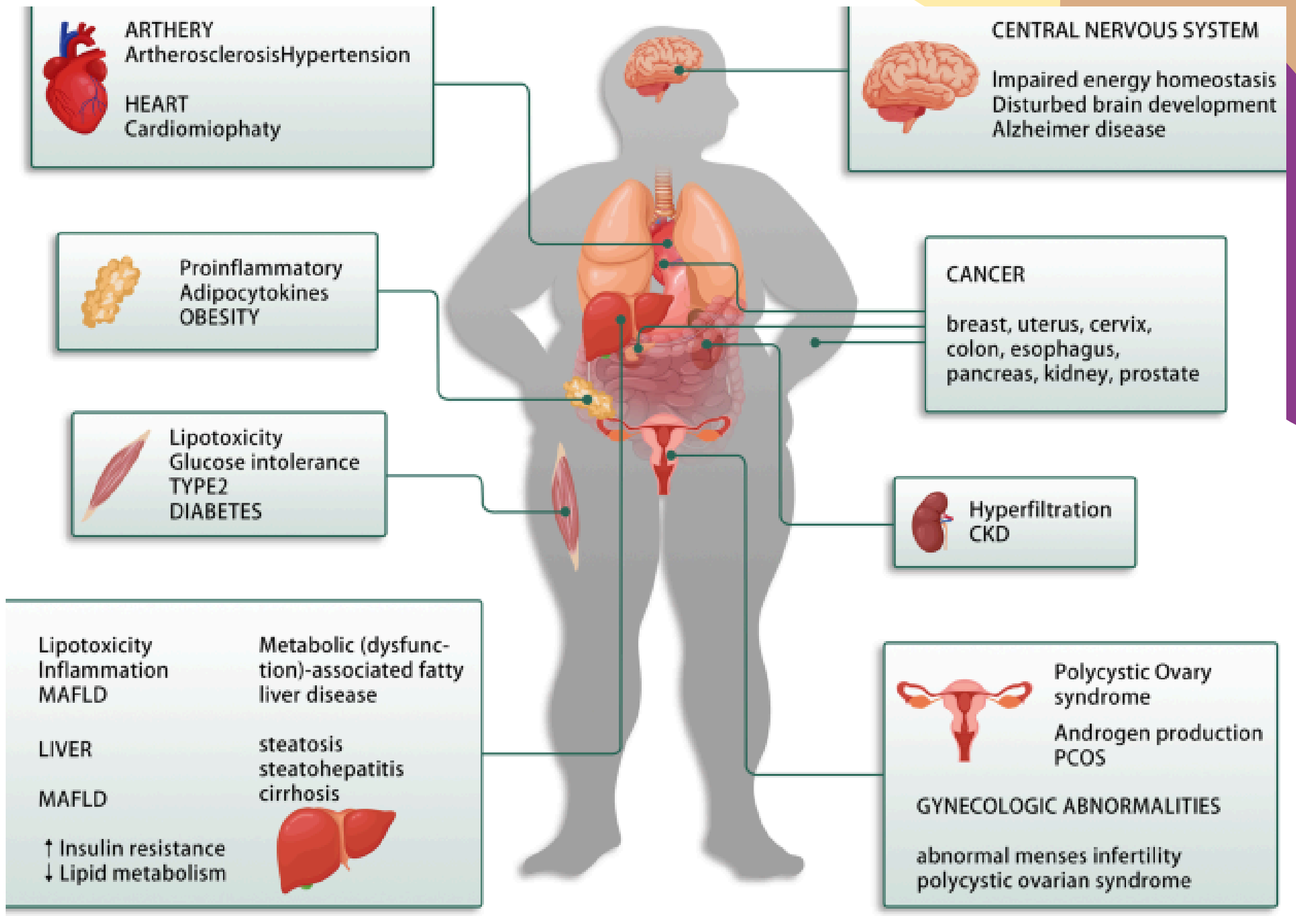
# Insulin Resistance & CVD



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# How to Reverse Insulin Resistance in 90 Days

- Whole, minimally processed carbohydrates - Green Leafy Vegetables, berries, fiber-rich vegetables
- Minimize refined carbohydrates
- Adequate Protein Intake
- Avoid seed oils that are in packaged foods
- Consume Fats - MUFA, PUFA and moderate amounts of SFA
- Avoid frequent eating and snacking
- Exercise - Zone 2, HIIT, Strength training
- Mediterranea Ketogenic Diet (Short Course) - Metabolic Flexibility
- Consider Exogenous Ketones
- TRE and not eating for 3 h before bedtime
- Sleep 7-9 hours nightly
- Lower Stress - Exercise, Meditation, Yoga, Biofeedback
- What to measure:
  Insulin
  TG/HDL - surrogate for insulin resistance
  Uric Acid - AMORIS Study - Low UA was indicative of Healthspan



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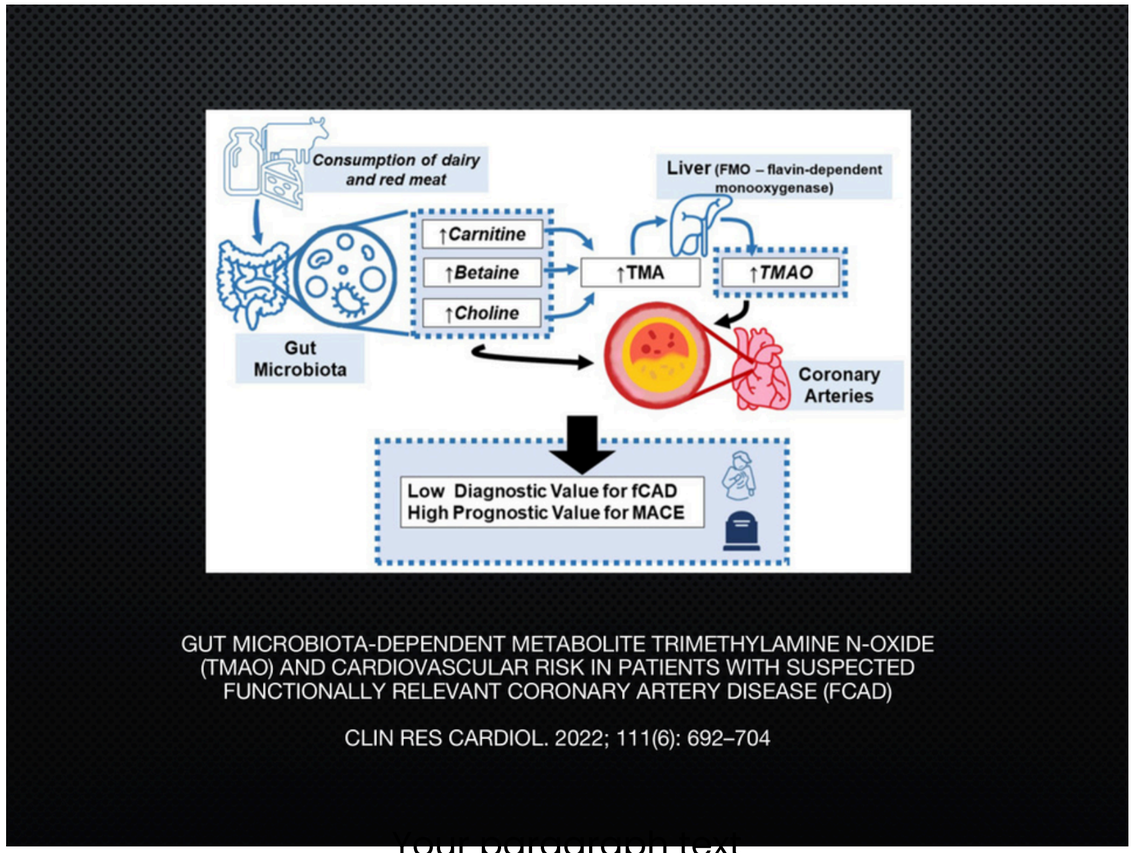
# TMAO




Your paragraph text

Clinical and Interpretive Problems

- TMAO can vary day to day
- Confounding factors: kidney Fx, age, sex, - when researchers adjust for eGFR, the association between TMAO and CVD weakens or disappears
- Not clear if TMAO is causal or merely an indicator of underlying metabolic dysfx
- Liver Enzyme FMO3 converts TMA into TMAO, and can vary significantly due to genetics, sex, and disease states



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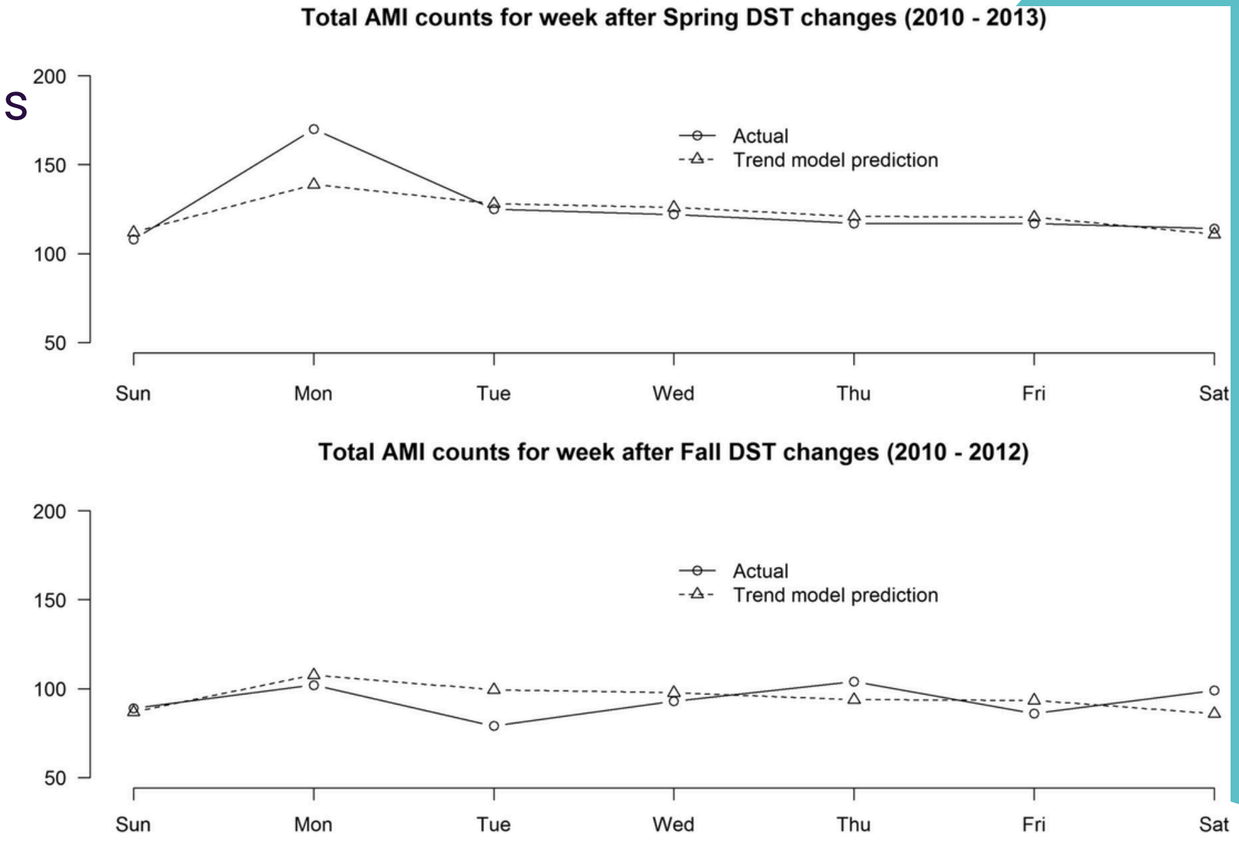
# Sleep and Cardiovascular Disease

- 24% increased risk of myocardial infarction the day after daylight savings in the spring
- In the Fall there is 21% reduction
- Short Sleep duration and incident coronary artery calcification - JAMA - higher adrenaline, higher spikes in cortisol, and blunting of GH, increased BP
- The common pathway for chronic disease with lack of sleep is an augmented sympathetic nervous system




Sandhu et al., 2014



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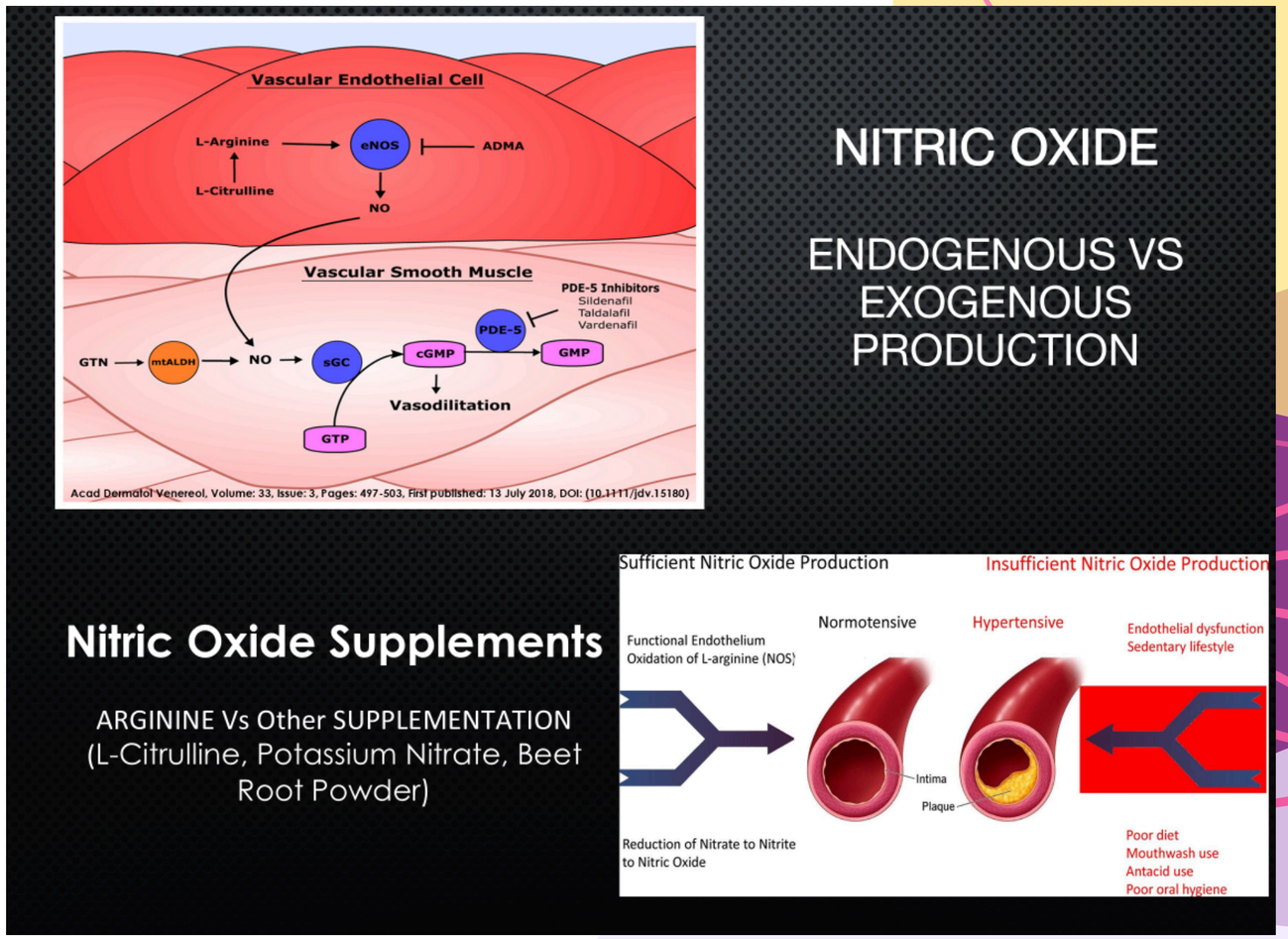
# ENDOTHELIAL FUNCTION

LifeStyle Modifications:
Regular Exercise
Mediterranean Diet
Maintain Optimal Body Composition
Stress Management
Quit Smoking and avoid secondhand smoke
Folic Acid
Maintain Normal BP
Optimize Lipids
Keep Uric Acid, Insulin and BS Low
Sunlight - NO Made in Skin

Oral production of NO - occurs through the enterosalivary nitrate pathway, where oral bacteria reduce dietary nitrate (from foods like green leafy vegetables) to nitrite, and then to NO in the mouth



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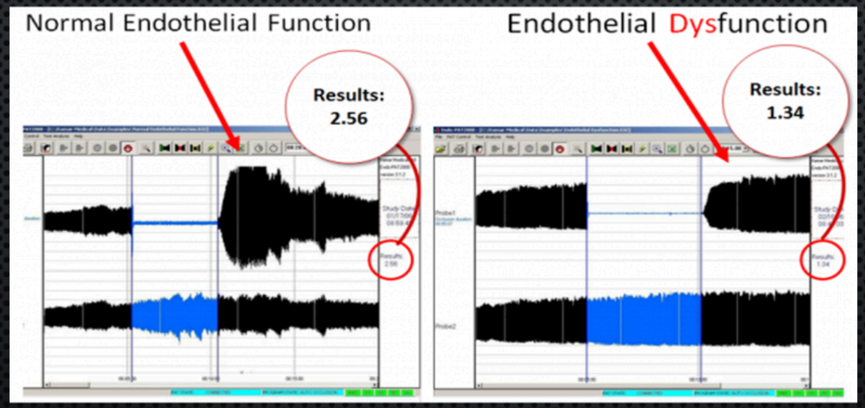
# ENDOTHELIAL FUNCTION




IN A STUDY OF 528 PATIENTS WITH HIGH RISK FOR CV EVENTS OVER 5 YEARS, THE ENDOPAT REACTIVE HYPEREMIA INDEX (RHI) WAS MEASURED BEFORE AND AFTER CORONARY ANGIOGRAM.4 THE RHI, BRAIN NATRIURETIC PEPTIDE (BNP), AND CV SCORE BY SYNTAX WERE INDEPENDENT RISK PREDICTORS FOR ALL FUTURE CV EVENTS SUCH AS MI, CV DEATH, UNSTABLE ANGINA, ISCHEMIC CVA, CORONARY ARTERY BYPASS GRAFT, CHF, AND PAD. WHEN RHI WAS ADDED TO FRS, BNP, AND SYNTAX, THE NET RECLASSIFICATION INDEX WAS SIGNIFICANTLY IMPROVED BY 27.5 %



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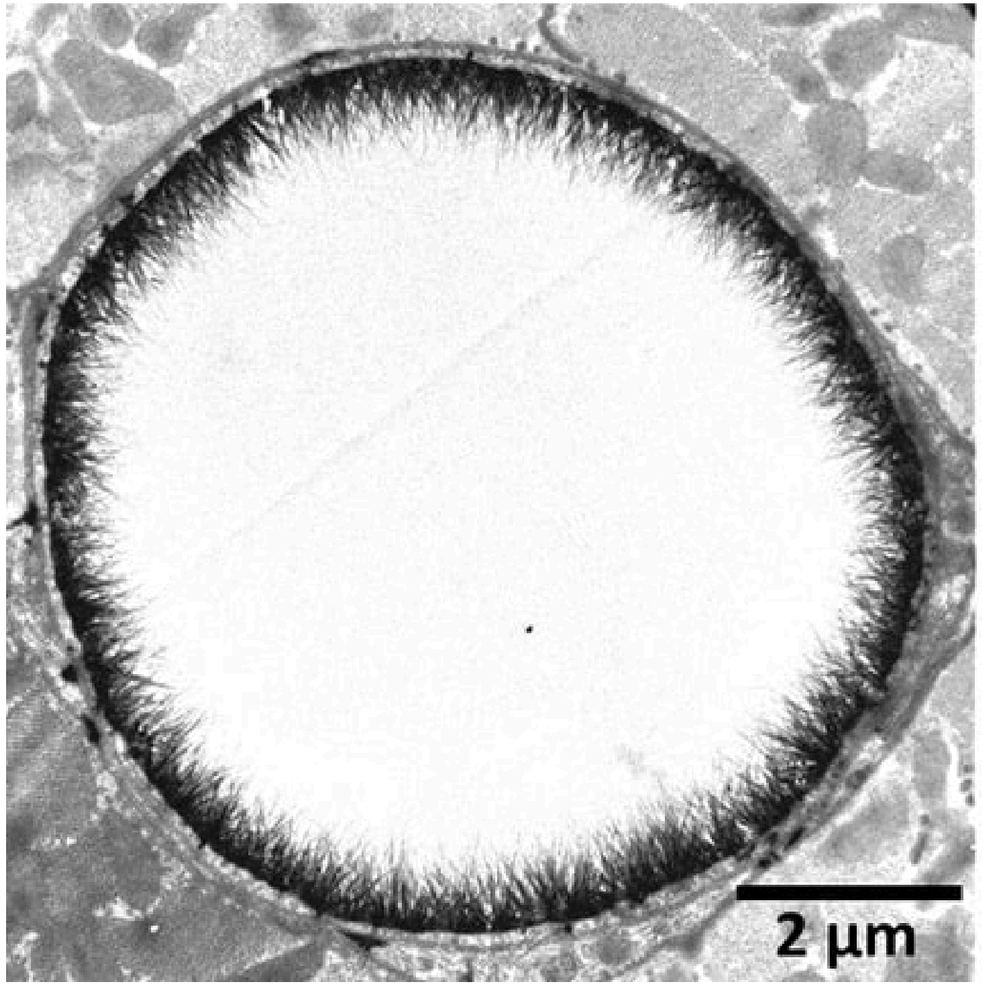
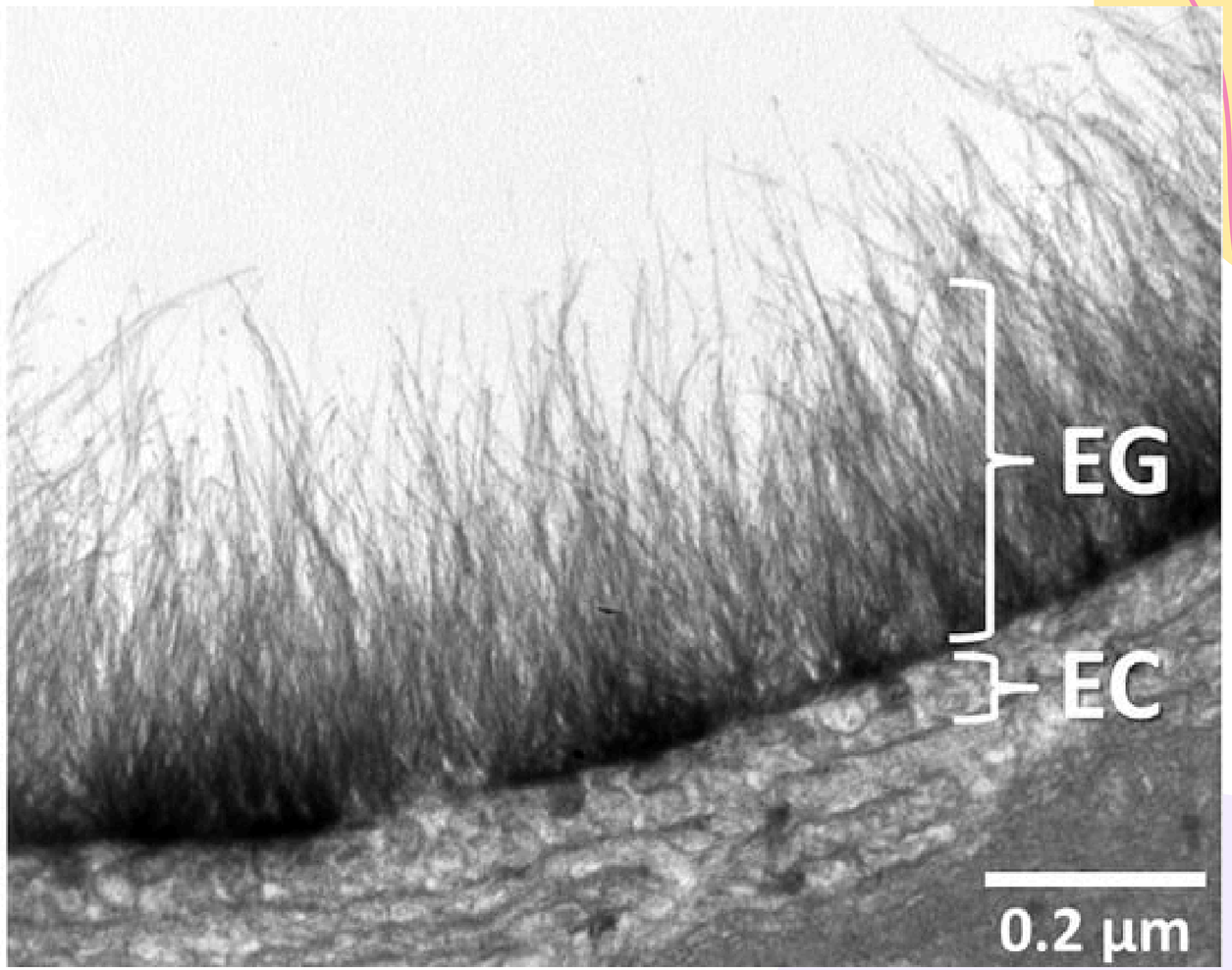
# GLYCOCALYX



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# GLYCOCALYX

Causes of Damage to the Glycocalyx

Systemic and local inflammation
Diabetes mellitus
Chronic and acute kidney disease
Stroke
Cancer
Sepsis
Ischemia-reperfusion
Atherosclerosis
High blood pressure
Viral infections
Traumatic brain injury
Trauma
Excess sodium
Hypovolemia



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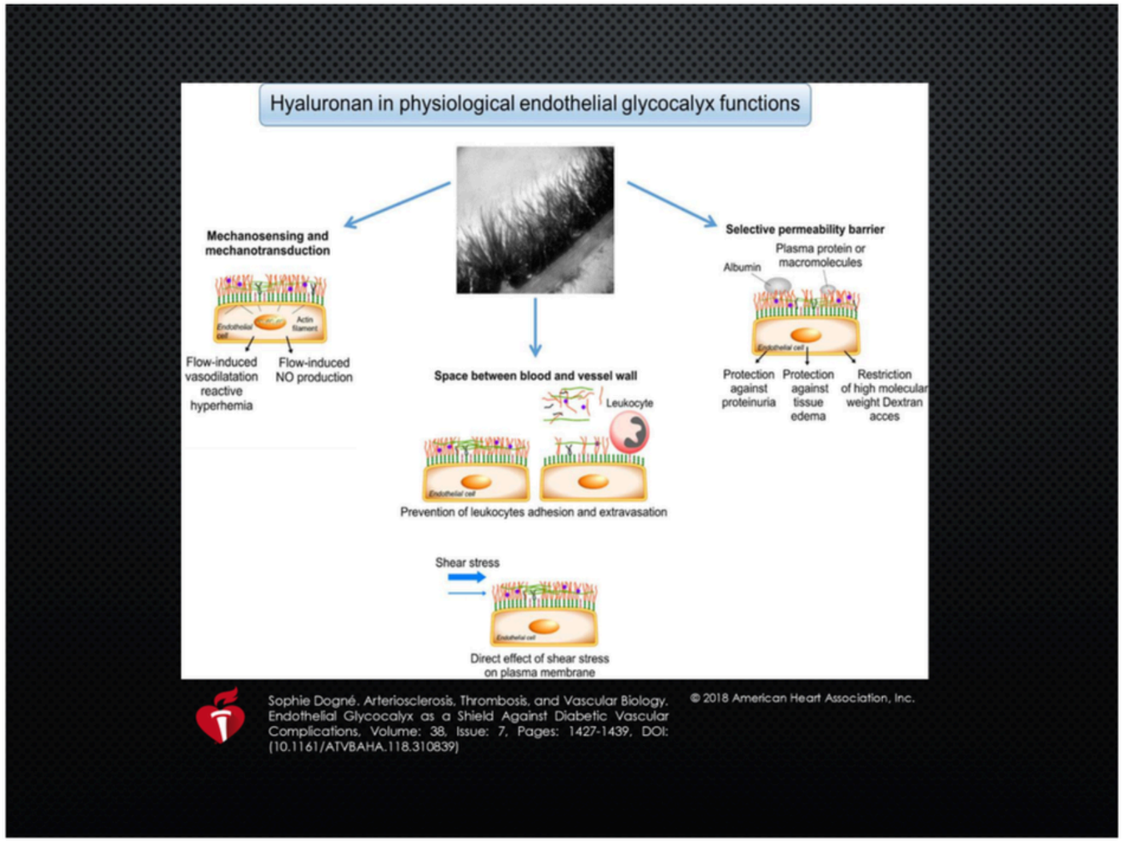
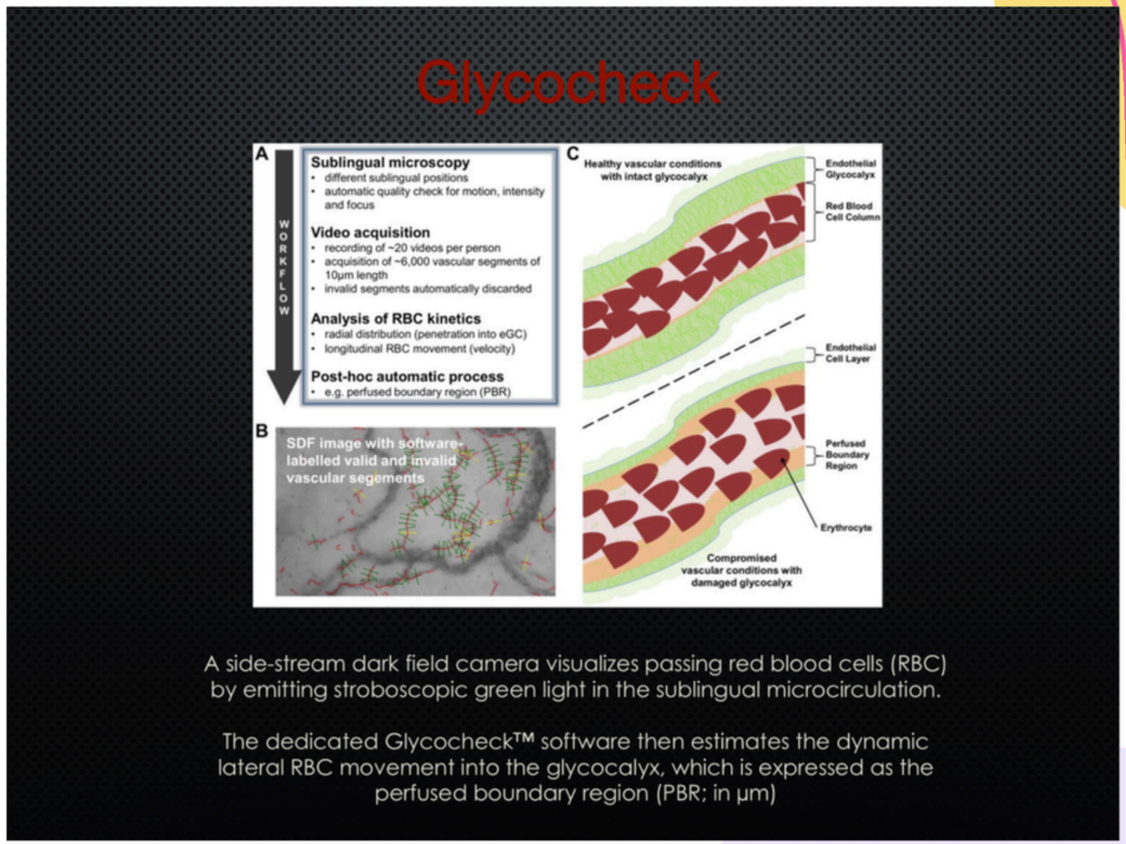
# GLYCOCALYX




A side-stream dark field camera visualizes passing red blood cells (RBC) by emitting stroboscopic green light in the sublingual microcirculation.

The dedicated Glycocheck™ software then estimates the dynamic lateral RBC movement into the glycocalyx, which is expressed as the perfused boundary region (PBR; in µm)

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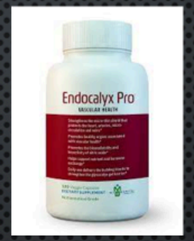
# GLYCOCALYX

- Healthy Diet - Polyphenols, Fiber and Nutrient-Dense Foods
- Regular physical exercise
- Quality Sleep
- Adequate hydration
- Minimize Processed foods and added Sugar
- Add Sulfur Rich Foods - Sulfur is structural component of the Glycocalyx - Meat, fish, and alliaceous (Onions, Garlic) and cruciferous Vegetables
- Omega 3 Fatty Acids
- Vitamin D
- Sulforophane
- Resveratrol
- Statins
- Manage DM, HTN, Inflammation

| Treatment | Reference |
|---|---|
| Hydrocortisone | Chappell et al. 2007, 2009b, 2010 [41, 43, 44] |
| Antithrombin | Chappell et al. 2009a, 2009b, 2010 [42–44] |
| Protein C | Marechal et al. 2008 [50] |
| Nitric oxide | Bruegger et al. 2008 [45] |
| Hyaluronic acid and chondroitin sulphate | Henry and Duling 1999 [13] |
| Sulodexide | Broekhuizen et al. 2010 [54] |
| Lidoflazine | Flameng et al. 1983 [55] |
| Albumin | Jacob et al. 2006, 2009 [46, 47] |
| Hydroxethyl starch | Rehm et al. 2004; Jacob et al. 2006 [8, 46] |
| N-acetylcysteine | Nieuwdorp et al. 2006 [9] |
| Metformin | Eskens et al. 2013 [51] |




Chondroitin Sulfate


Glucosamine Sulfate


RHAMNAN SULFATE



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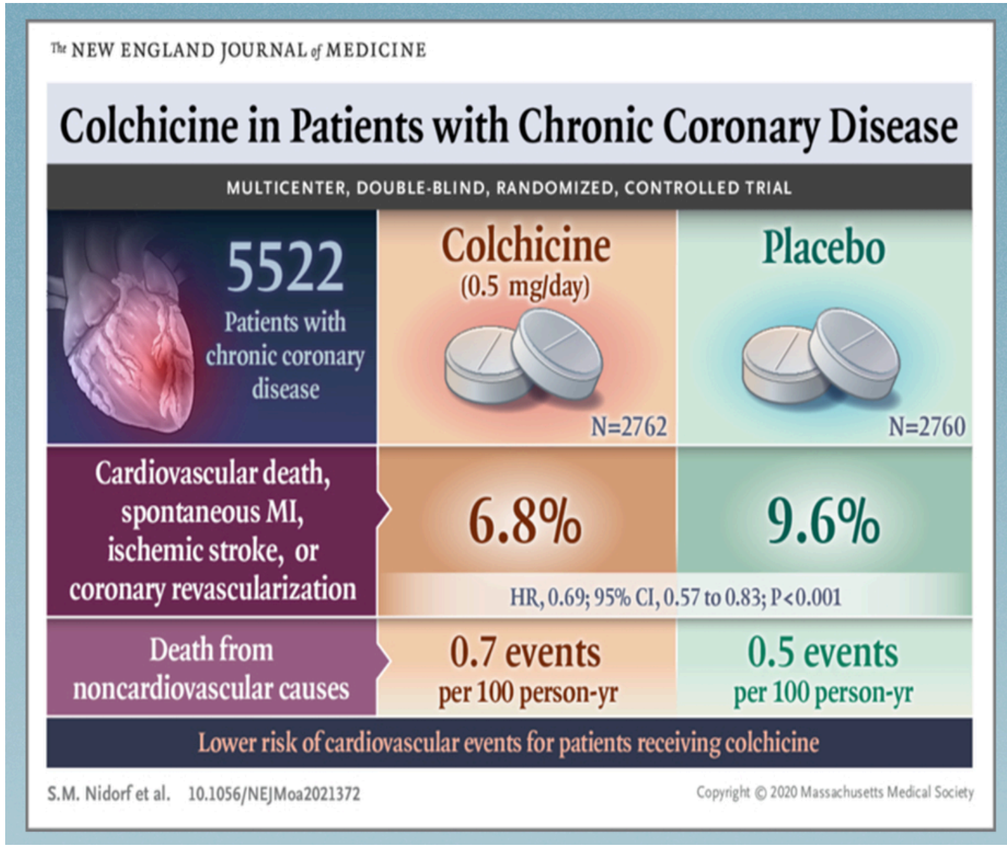
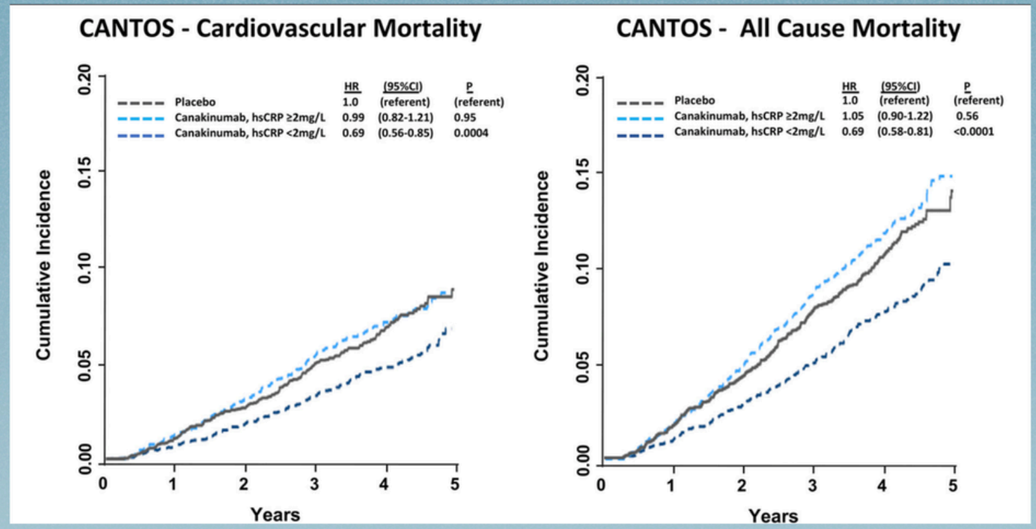
# INFLAMMATION



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# INFLAMMATION

- hs CRP
- LpPLA2 - produced inside artery walls
- MPO (Myeloperoxidase) - produced by white cells in response to inflammation
- Fibrinogen - A protein involved in blood clotting. High Levels=Increased CV Risk
- IL-6 (Interleukin 6) - A cytokine involved in the inflammatory response
- OxPL-ApoB - Found on Lipoproteins, highly pro-inflammatory
- GGT - High Levels = Low Glutathione - High Oxidative Stress

# INFLAMMATION

- Anti-Inflammatory Diet
- Regular Physical Exercise
- Maintain a Healthy Weight
- Stress Management
- Prioritize Sleep
- Quit Smoking
- Limit Alcohol
- Anti-Inflammatory Diet
  - Fruits & Vegetables
  - O3FA
  - Whole Grains
  - Lean Protein
  - Healthy Fats
  - Herbs & Spices: Turmeric, Garlic, Cinnamon, Ginger
  - Limit Added Sugars and Processed Foods



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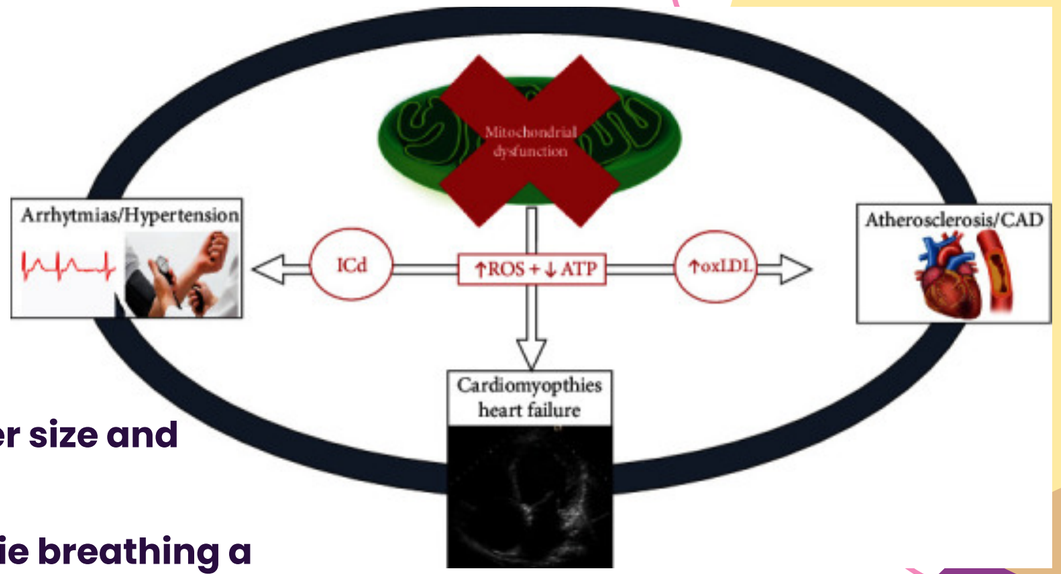
# MITOCHONDRIA




- L-Carnitine
- Polyphenols
- Vitamins C & E
- Co-enzyme Q10
- Alpha Lipoic Acid
- Omega 3 FA
- Mito-Q10( Modified CoQ10 - gets into Mitochondria due to its smaller size and positive charge - absorbed into mitochondria 1000 X better)
- NAD+ - NR, NMN
- Exercise - especially HIIT , Strength Training, EWOT - exercising whlie breathing a highe concentration of oxygen
- Calorie Restriction & Weight Loss
- CD36 Antagonists - CD36 receptor plays a role in the uptake of fatty acids by cells
- PPAR Ligands - a nuclear receptor related to lipid and glucose metabolism
- Beta Blockers
- ACE Inhibitors
- ARBs
- Statins
- Metformin
- Peptides - MOTS-c, SS-31
- Methylene Blue
- 1-MNA - precursor for NMN
- Sauna
- Cold Exposure
- Red Light Therapy
- HBOT
- Prioritize Quality Sleep
- Nutrition - Nutrient-Dense Foods, Healthy Fats, Quality Protein, consider a Ketogenic Diet, Intermittent or Time Restricted Eating, Support the Gut Microbiome

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# MITOCHONDRIA

**Cinical and functional markers**
**Physical symptoms can be key indicators, especially when they involve issues with high-energy demands like the brain, muscles, and heart.**

- **Muscular problems: Common symptoms include muscle weakness, fatigue, poor growth, muscle cramps, and exercise intolerance.**
- **Neurological issues: Patients may experience seizures, stroke-like episodes, migraines, developmental delay, dementia, and problems with movement coordination (ataxia).**
- **Ophthalmic and audiological symptoms: Visual problems like optic atrophy and retinopathy, drooping eyelids (ptosis), and hearing loss are frequently observed.**
- **Cardiovascular and renal problems: These can include heart muscle weakness (cardiomyopathy), irregular heartbeats (arrhythmia), and kidney disease.**
- **Metabolic and gastrointestinal issues: Patients may develop diabetes, liver disease, poor appetite, chronic vomiting, and bowel problems.**
- **Multisystem disorders: Often, a combination of several of these symptoms will appear, making diagnosis challenging.**

**Biochemical markers**
**Blood, urine, and cerebrospinal fluid tests can reveal metabolic irregularities associated with impaired mitochondrial function.**

- **Lactate and pyruvate: Elevated levels of lactate and pyruvate in the blood or cerebrospinal fluid indicate that cells are resorting to anaerobic metabolism for energy due to dysfunctional mitochondria.**
- **Lactate-to-pyruvate ratio: This ratio is a valuable metric for diagnosing mitochondrial respiratory chain dysfunction, particularly when lactate levels are high.**
- **Amino acids: Abnormal amino acid profiles, including elevated alanine, glycine, and others, can be found in blood and urine.**
- **Acylcarnitines: The balance of different acylcarnitines can be analyzed to evaluate the efficiency of fatty acid metabolism within the mitochondria.**
- **Cytokine stress markers: Elevated levels of growth differentiation factor 15 (GDF-15) and fibroblast growth factor 21 (FGF-21) have shown utility in diagnosing mitochondrial disorders, though they lack perfect specificity.**
- **Oxidative stress markers: Increased oxidative stress, a hallmark of mitochondrial dysfunction, can be measured by assessing levels of antioxidants like coenzyme Q10 and glutathione.**

**Genetic markers**
**Directly testing for genetic mutations is often considered the gold standard for diagnosis.**

- **Mitochondrial DNA (mtDNA) analysis: Screening the mitochondrial genome for pathogenic mutations, rearrangements, or deletions is crucial. These mutations can be tissue-specific, so testing in blood, urine sediment, or muscle may be necessary.**
- **Nuclear DNA (nDNA) panels: A large number of mitochondrial proteins are encoded by nuclear genes. Panels that sequence relevant nuclear genes can reveal a genetic basis for the dysfunction.**
- **Cell-free mtDNA: Elevated levels of mitochondrial DNA in the plasma, a sign of cellular damage, can serve as a marker in diseases like sepsis and acute respiratory distress syndrome.**

**Histological and imaging markers**
**Invasive and non-invasive methods can be used to visualize mitochondrial health in specific tissues.**

- **Muscle biopsy: Analysis of a muscle tissue sample may reveal "ragged red fibers"—an abnormal accumulation of mitochondria under the muscle cell membrane. Biochemical assays can also measure the activity of the mitochondrial respiratory chain complexes.**
- **Magnetic resonance (MR) spectroscopy: Non-invasive imaging can estimate lactic acid levels in the brain and provide information on high-energy phosphate metabolism in muscles.**
- **Positron emission tomography (PET): Specialized PET imaging can measure mitochondrial function and oxidative capacity in vivo**

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# MITOCHONDRIA

**Symptomatic and supportive treatments**

- **Managing symptoms**: Medications are often used to manage specific symptoms that arise from mitochondrial dysfunction. For example, anti-seizure medications can be used to treat seizures associated with the disorder.
- **Avoiding stressors**: It is critical for people with mitochondrial disease to avoid physiological stressors that can trigger a metabolic crisis or worsen symptoms, such as infections, dehydration, and prolonged fasting. During minor illnesses, supportive therapies like intravenous fluids and electrolytes may be required.
- **Avoiding specific drugs**: Certain medications can be toxic to mitochondria and should be avoided or used with caution. These include valproic acid, which is contraindicated in some mitochondrial disorders, and some anesthetics used during surgery.

**Supplements and cofactors**

A variety of vitamins and supplements are used, often in a "cocktail" approach, to support mitochondrial function, though evidence for their effectiveness can be limited and variable. Some of the most common include:

- **Coenzyme Q10 (CoQ10)**: This is a component of the electron transport chain and a powerful antioxidant. Supplementation is often recommended, particularly for those with a documented CoQ10 deficiency.
- **L-Carnitine**: This supplement helps transport fatty acids into the mitochondria for energy production. It is used when carnitine deficiency is documented in patients.
- **Creatine**: This compound acts as an energy buffer in tissues with high energy demand, like muscles and the brain.
- **Arginine and Citrulline**: As precursors to nitric oxide (NO), these amino acids can be used to treat or prevent stroke-like episodes, particularly in patients with MELAS syndrome.
- **B Vitamins**: Riboflavin (B2) and thiamine (B1) are cofactors in energy metabolism and are used in some cases.
- **Alpha-lipoic acid (ALA)**: An antioxidant and cofactor in energy metabolism, ALA can help reduce oxidative stress.
- **Folinic acid**: Supplementation is recommended for patients with cerebral folate deficiency, a condition sometimes associated with mitochondrial disease.

**Lifestyle interventions**

Lifestyle changes are a core part of managing mitochondrial dysfunction.

- **Exercise**: Regular, monitored exercise, especially endurance and resistance training, is one of the few proven methods for improving mitochondrial function. It promotes mitochondrial biogenesis (the creation of new mitochondria) and can increase a patient's strength and endurance.
- **Diet**: Nutritional management is critical. Some patients may benefit from specific dietary modifications, such as a high-fat, low-carbohydrate (ketogenic) diet, particularly for conditions like pyruvate dehydrogenase deficiency.

**Emerging and experimental treatments**

- **Mitochondrial Replacement Therapy (MRT)**: This is an in vitro fertilization (IVF) technique used to prevent mothers with mitochondrial disease from passing mutated mitochondrial DNA (mtDNA) to their children. It involves replacing the mother's mutated mitochondria with healthy ones from a donor egg. It is approved in some countries but remains controversial and is not yet available in the U.S. for clinical application.
- **Gene therapy**: Experimental approaches are exploring gene therapy to correct the underlying genetic defects. For example, research targeting Leber hereditary optic neuropathy (LHON) has shown positive results in some clinical trials.
- **Investigational medications**: Several drugs are in various stages of clinical trials to address different aspects of mitochondrial dysfunction, including promoting biogenesis and clearing damaged mitochondria.
- **Tissue-specific therapy**: A technique to replace damaged mitochondria with autologous (the patient's own) healthy mitochondria extracted from healthy tissue is being researched for localized issues, such as heart problems in newborns
- Peptids - MOTS-c - Exercise Mimetic, Humanin

# MITOCHONDRIA- PEPTIDES

**Key mitochondrial-derived peptides**

**MOTS-c (mitochondrial open reading frame of the 12S rRNA type-c)**
**Function: MOTS-c acts as an "exercise mimetic," primarily enhancing systemic insulin sensitivity and improving glucose metabolism in skeletal muscle. In response to metabolic stress, it can move from the mitochondria to the nucleus to regulate gene expression.**
**Research findings:**
**Animal studies show that administering MOTS-c can reverse age-dependent insulin resistance and improve physical performance.**
**It may help regulate energy balance and protect against diet-induced obesity, osteoporosis, and cardiovascular diseases.**
**MOTS-c expression increases in skeletal muscle after exercise.**
**Clinical status: While promising, MOTS-c has not yet been widely used in disease treatment, and effective methods for clinical application are still under development**
**.**
**Humanin (HN)**
**Function: HN was the first MDP discovered and is primarily known for its neuroprotective and cytoprotective properties. It helps cells survive stress by activating antioxidant defense systems, regulating apoptosis, and increasing ATP production.**
**Research findings:**
**Preclinical studies show potential for treating neurodegenerative disorders, such as Alzheimer's disease, and protecting against cardiovascular diseases.**
**It has shown anti-inflammatory effects and can improve insulin sensitivity in rodent models.**
**Clinical status: Researchers are developing modified versions, or analogues, of Humanin to enhance its stability and potency for potential therapeutic use.**

**Small Humanin-Like Peptides (SHLPs)**
**Function: The six SHLPs (SHLP1–6) are encoded in the same mitochondrial region as Humanin and have both distinct and overlapping functions.**
**Research findings:**
**SHLP2 and SHLP3 are known to be cytoprotective and can improve mitochondrial health and insulin sensitivity.**
**SHLP6 has been found to promote apoptosis in certain cancer cells.**
**The functions and mechanisms for all six peptides are still being actively researched.**

**Other peptides that target mitochondria**
**SS-31 (elamipretide)**
**Function: This mitochondrial-targeting peptide helps stabilize the inner mitochondrial membrane and protect against oxidative damage. It improves cellular energy production and reduces oxidative stress.**
**Research findings: Preclinical studies have shown neuroprotective, cardioprotective, and anti-aging benefits.**
**BPC 157**
**Function: Though not exclusively mitochondrial, this peptide has been shown to target several body systems, including the brain, immune system, and cardiovascular system. Some research points to its ability to affect mitochondrial function and cellular integrity**

# MITOCHONDRIA- METHYLENE BLUE

Methylene blue improves mitochondrial function by acting as an alternative electron carrier within the electron transport chain (ETC) and by providing antioxidant protection. This dual mechanism can enhance cellular energy production and mitigate oxidative stress, particularly at low doses.

Electron shuttling
Methylene blue (MB) has a unique redox property that allows it to cycle between an oxidized (blue) and a reduced (colorless) form.

- Bypasses damaged complexes: When portions of the ETC are impaired due to aging, disease, or injury, MB can accept electrons from one complex (specifically NADH from Complex I) and donate them to a later complex, such as cytochrome *c*.
- Improves electron flow: By "shuttling" electrons, MB effectively bypasses the bottleneck, allowing the ETC to maintain a more consistent flow of electrons and continue producing ATP, the cell's main energy currency.
- Increases efficiency: This action helps restore function in compromised mitochondria and boosts overall mitochondrial respiration and oxygen consumption.

Antioxidant effects
Mitochondria produce reactive oxygen species (ROS) as a natural byproduct of cellular respiration, which can cause oxidative stress and cellular damage.

- Scavenges free radicals: MB can directly scavenge and neutralize these harmful ROS.
- Reduces electron leakage: By improving the efficiency of electron transport, MB helps prevent the "leakage" of electrons that leads to excess ROS production in the first place.
- Upregulates antioxidant defenses: Research also suggests that MB can activate genes related to antioxidant defenses, further protecting the cell.

Promoting mitochondrial biogenesis
In addition to repairing existing damage, methylene blue has been shown to stimulate the growth of new mitochondria, a process known as mitochondrial biogenesis.

Dose-dependent effects
The effects of methylene blue are dose-dependent, meaning that low and high concentrations can have opposite effects.

- Low doses: Stimulate mitochondrial respiration and offer protective benefits. The typical effective low dose is well below toxic levels. <30mg/d
- High doses: Can produce toxic effects and inhibit mitochondrial function.

Potential therapeutic applications
Methylene blue's ability to improve mitochondrial function is being researched for several conditions where mitochondrial dysfunction is a key factor.

- Neurodegenerative diseases: Including Alzheimer's and Parkinson's disease. Its ability to cross the blood-brain barrier is particularly beneficial for treating brain health issues.
- Aging: Age-related mitochondrial decline contributes to a variety of diseases. MB's effect on biogenesis and oxidative stress shows potential for mitigating the aging process at a cellular level.
- Chronic fatigue syndrome (CFS): By boosting ATP production, MB may address the energy shortfalls associated with CFS.
- Stroke and brain injury: In animal models, MB has shown neuroprotective benefits and improved cognitive outcomes by protecting neurons from injury-induced mitochondrial damage
- Caution G6PD def, SSRI, SNRI, MOAIs, TCAs, Triptans (Migrains), Opioids, Bupropion (Wellbutrin), Lithium, CKD, Heinz Body Anemia



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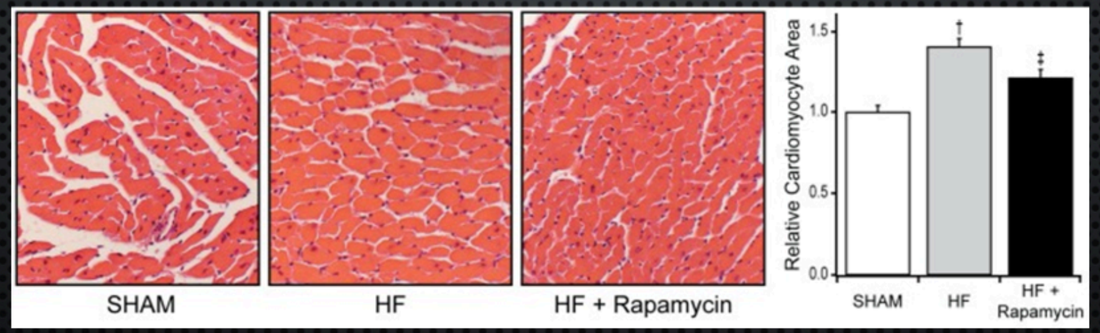
# Rapamycin

- Improves Cardiac Function
- Promotes Autophagy - inhibits mTOR - may protect heart cells from apoptosis (programmed cell death)
- Reduces inflammation and oxidative stress
- Lessens Atherosclerosis
- Mayo Clinic is recruiting seniors for a trial using low dose rapamycin for CAD
- At high doses can cause kidney dysfunction, glucose intolerance and immunosuppresion

Sirolimus (Rapamycin) is the product of the bacterium Streptomyces hygroscopicus originally found in a soil sample from Easter Island, also known as "Rapa Nui." Because of this history, sirolimus has been marketed as rapamycin and has been found to be an effective immunosuppressant as well as antiproliferative agent.




ANTI-REMODELING EFFECTS OF RAPAMYCIN IN EXPERIMENTAL HEART FAILURE EFFECT OF MTOR INHIBITION WITH RAPAMYCIN ON PATHOLOGIC REMODELING IN ESTABLISHED HF
PLOS ONE. 2013; 8(12)



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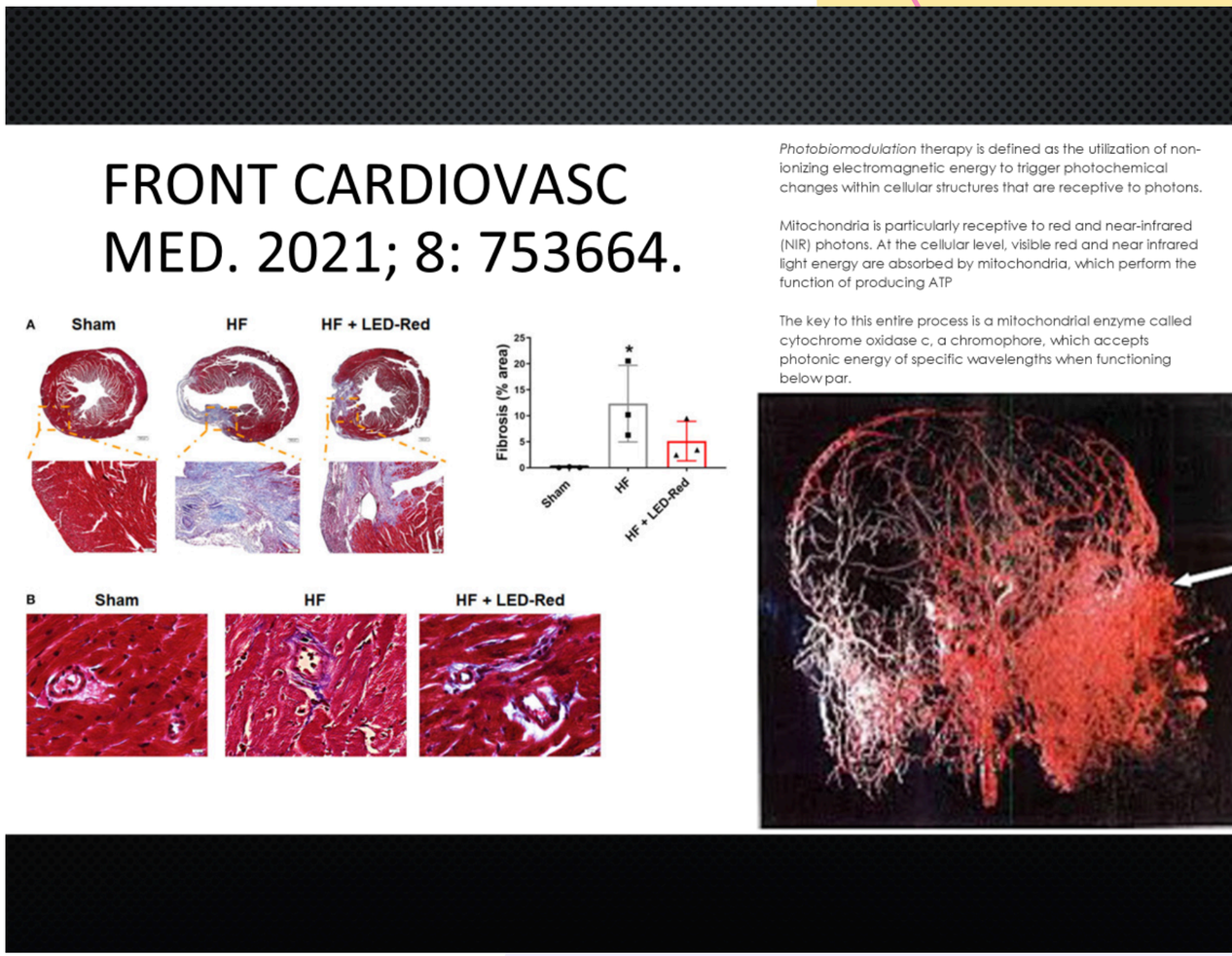
# PHOTOBIOMODULATION

- Boosts Mitochondrial Function and energy production - PBM works by stimulating photoreceptors within the mitochondria of cardiomyocytes which increase ATP production
- Reduces inflammation
- Promotes tissue repair and regeneration
- Decreases Oxidative Stress by reducing reactive oxygen species (ROS)
- Inhibits cardiac remodeling

Research

- Animal studies show that PBM can reduce infarct size
- PBM can improve outcomes for heart failure
- Mouse model of accelerated cardiac aging shows that PBM can mitigate CV remodeling, Improve Heart Function, and extend lifespan
- By normalizing lipid levels, PBM can reduce ASCVD



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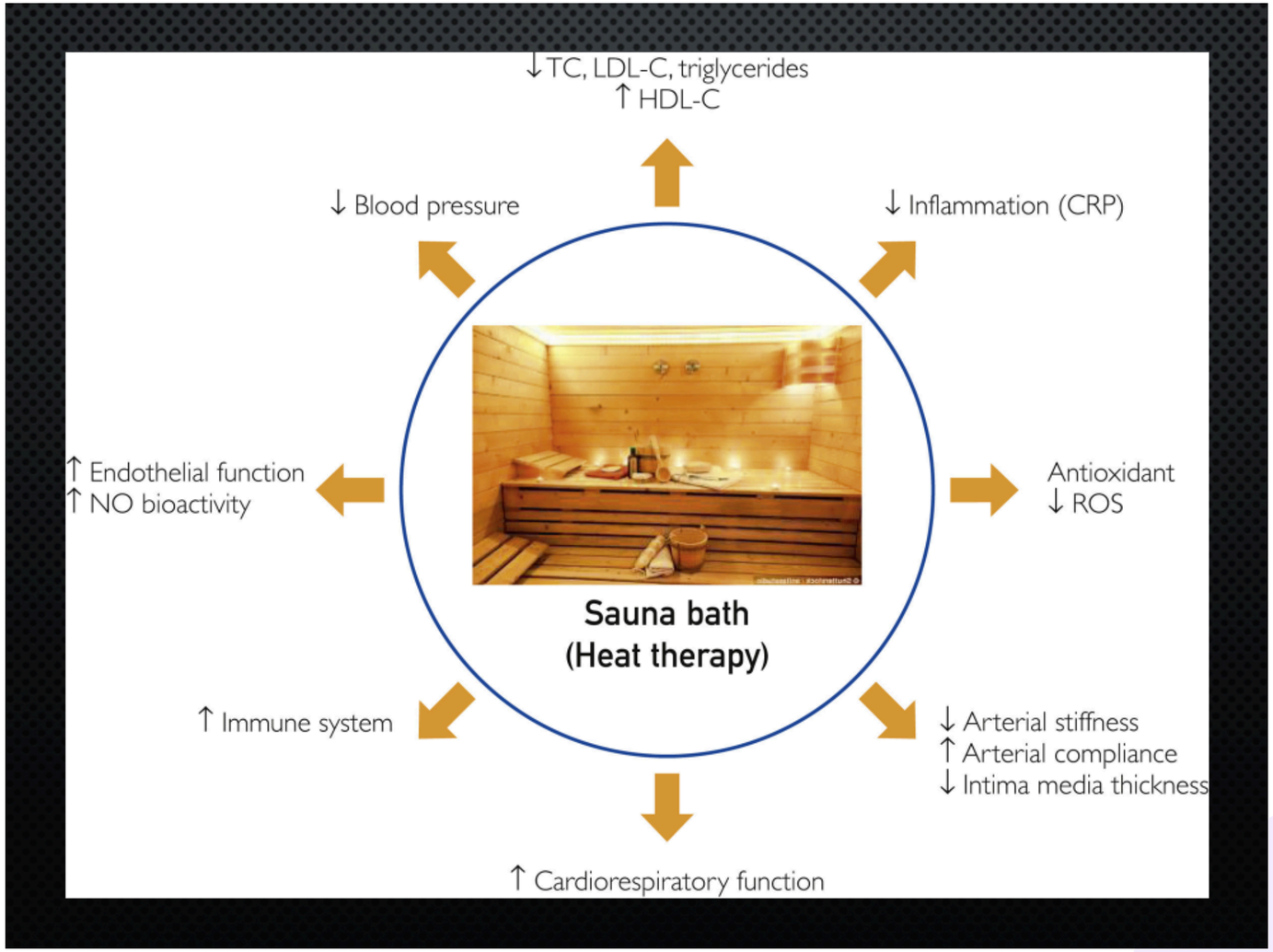
# SAUNA



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# CRYOTHERAPY




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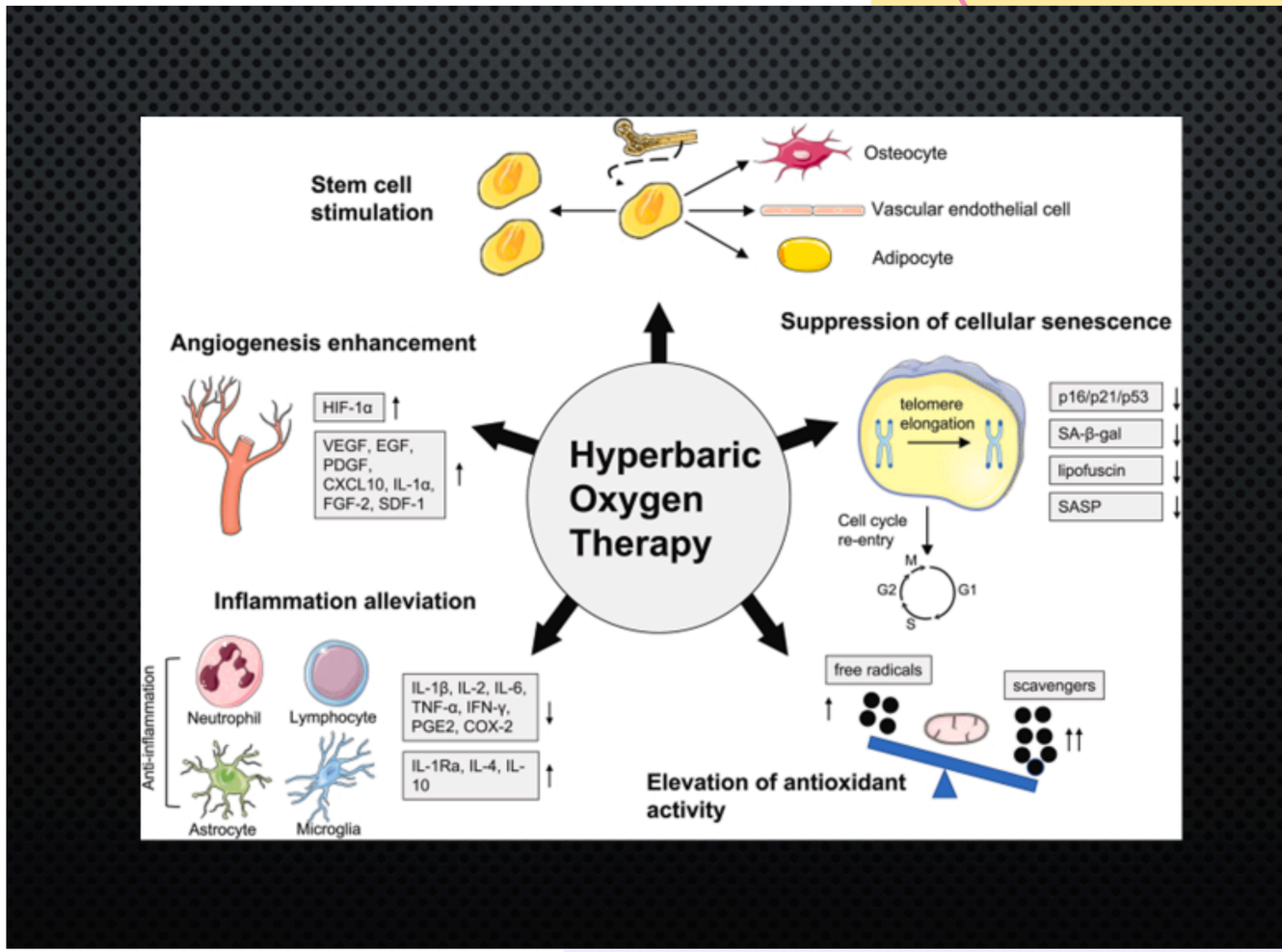
# HYPERBARIC OXYGEN THERAPY (HBOT)

- Improves Heart Function after a Heart Attack
- Helps Heart Failure
- Promotes Blood vessel Growth - Vascular Endothelial Growth Factor (VEGF)
- Reduces Inflammation and Oxidative Stress
- Not FDA Approved for CVD



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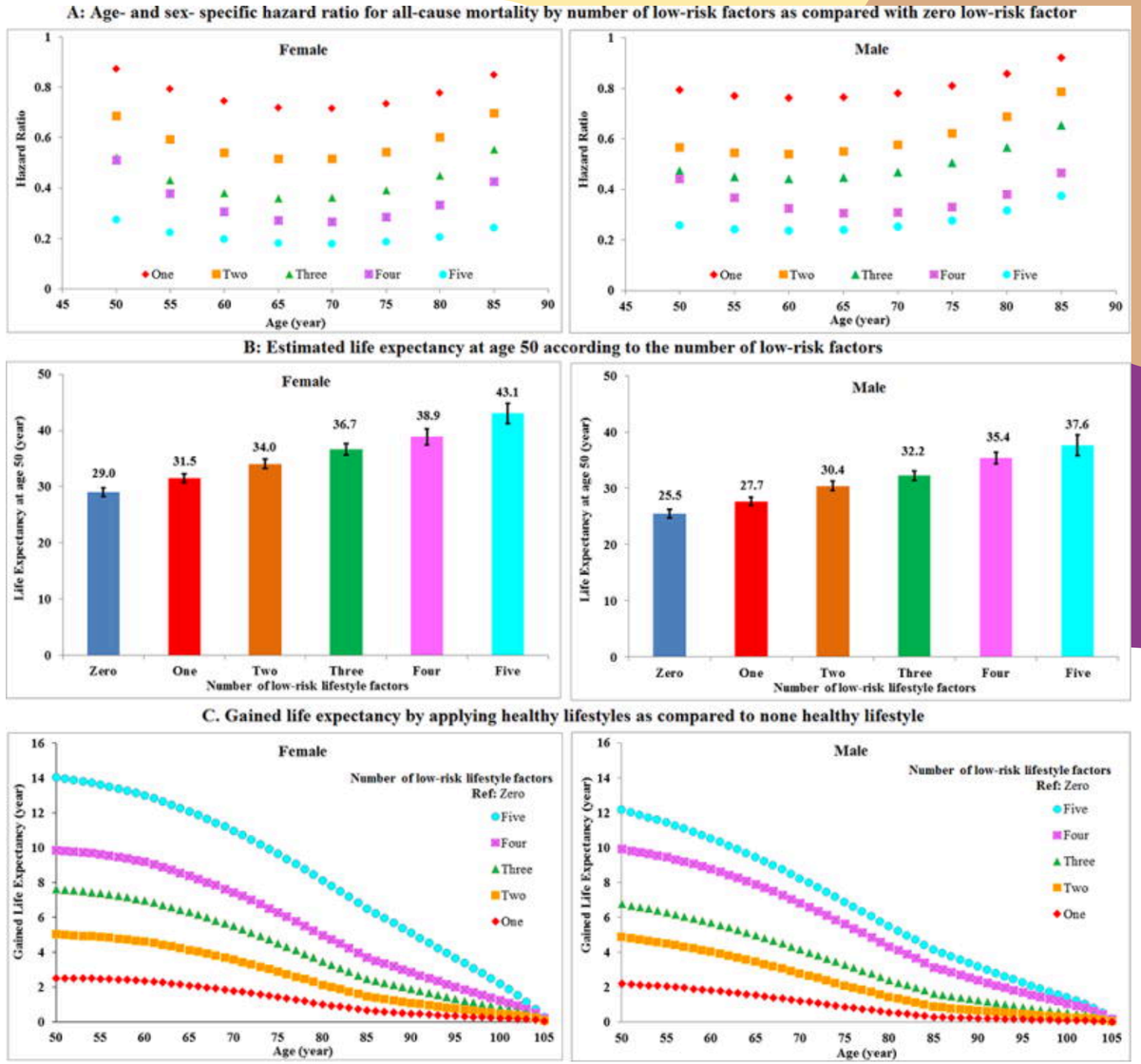
# Reducing Risk Factors

Circulation

. 2018 Jul 24;138(4):345-355.
doi: 10.1161/CIRCULATIONAHA.117.032047.
**Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population**

The projected life expectancy at age 50 years was on average 14.0 years (95% CI, 11.8-16.2) longer among female Americans with 5 low-risk factors compared with those with zero low-risk factors; for men, the difference was 12.2 years (95% CI, 10.1-14.2).

BMI
Cigarette Smoking
Alcohol Consumption
Physical Activity
Healthy Eating



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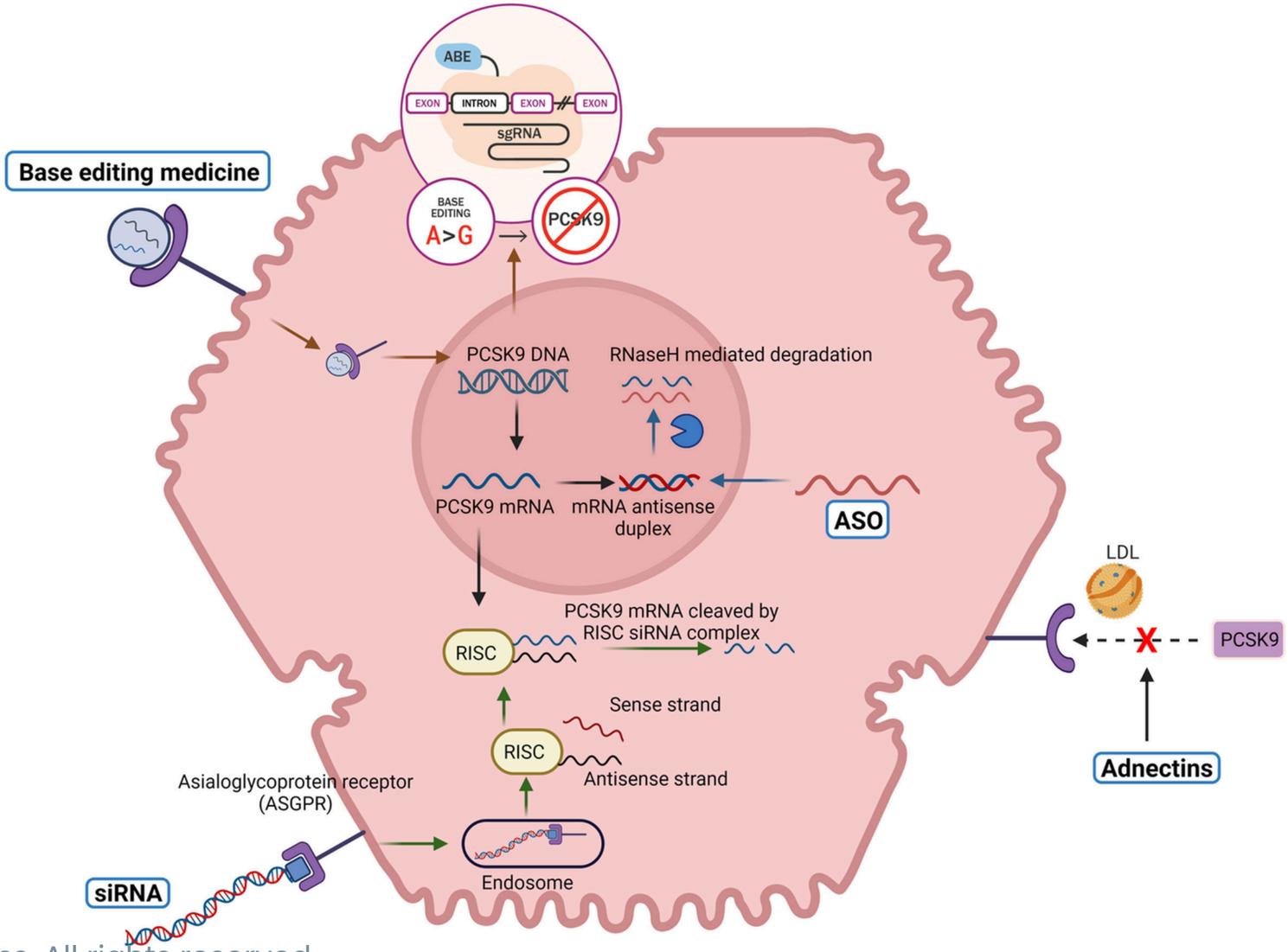
Curr Atheroscler Rep
. 2024 May;26(5):139-146.
doi: 10.1007/s11883-024-01198-3. Epub 2024 Mar 18.

# Gene Editing for the Treatment of Hypercholesterolemia



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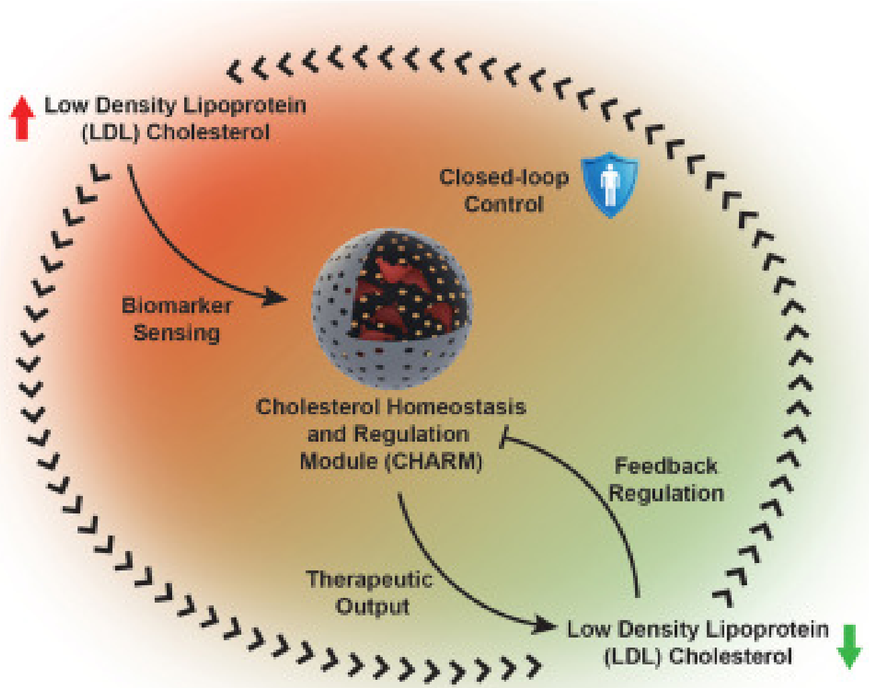
## A closed-loop cholesterol shunt controlling experimental dyslipidemia

Unal et al., 2025, Cell Metabolism 37, 1–10 October 7, 2025 © 2025

- A tiny implantable “genetic circuit” called CHARM that can sense and correct high cholesterol in real time
- The CHARM circuit is a piece of genetic engineering housed inside human cells. These cells are then placed inside a small, protective capsule that is implanted into the body.
- The sensor is a special protein which can detect high cholesterol
- The switch is a gene that is “turned on”
- The therapeutic protein, adnectin, works by neutralizing PCSK9
- The circuit creates a “closed-loop” system - it senses a problem (high cholesterol), solves it (producing a therapeutic protein) and then stops producing the protein once the problem is corrected



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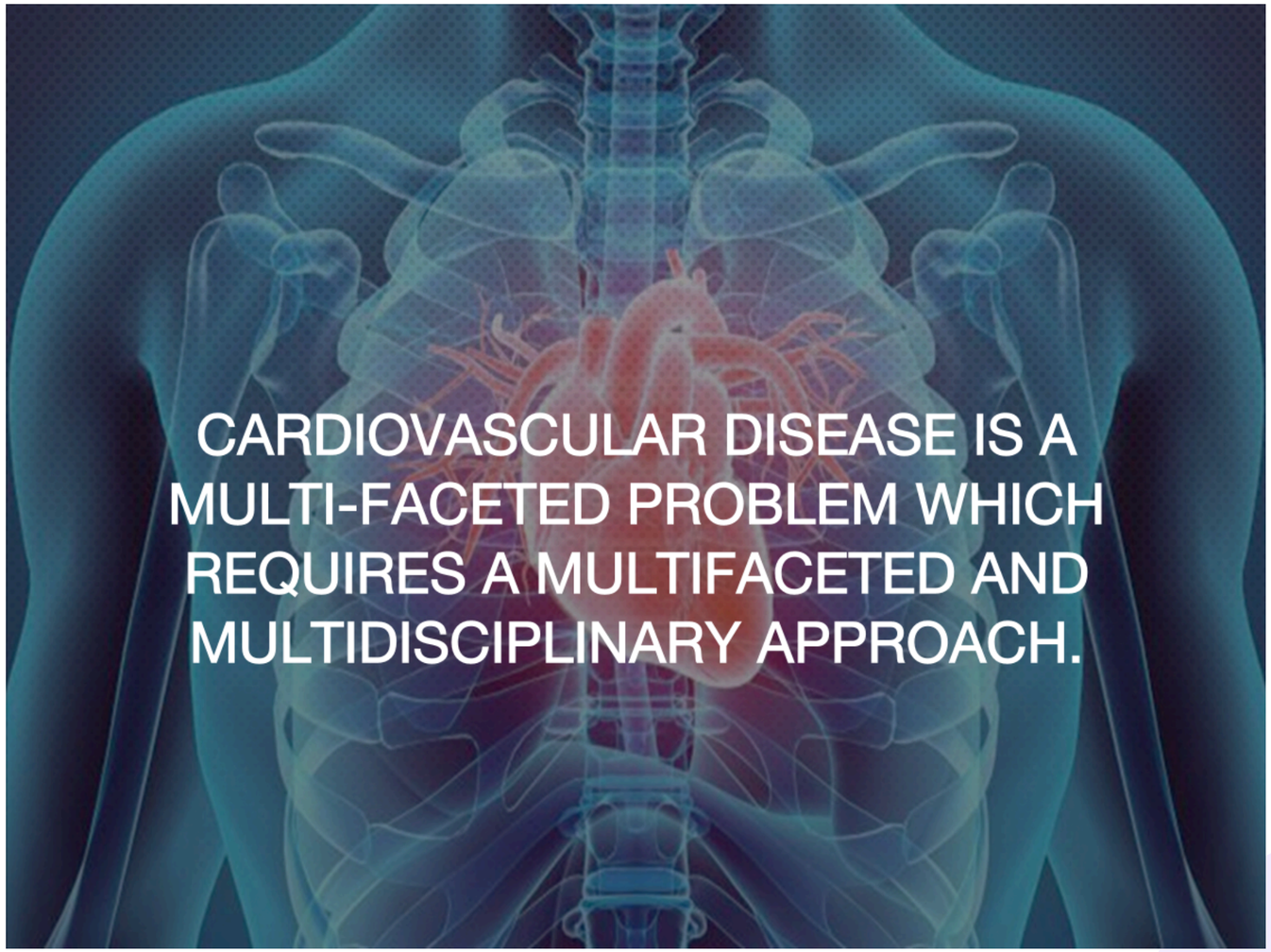


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# Thank You!

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**www.functionalheart.com**

# The Heart of Longevity

Innovations in Cardiovascular and Metabolic Care

Session 4

**Dr. Jack Wolfson, DO**

# All Disease is from Two Things



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# Too much bad stuff
# Not enough good stuff



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# Cardiologist Gone Rogue



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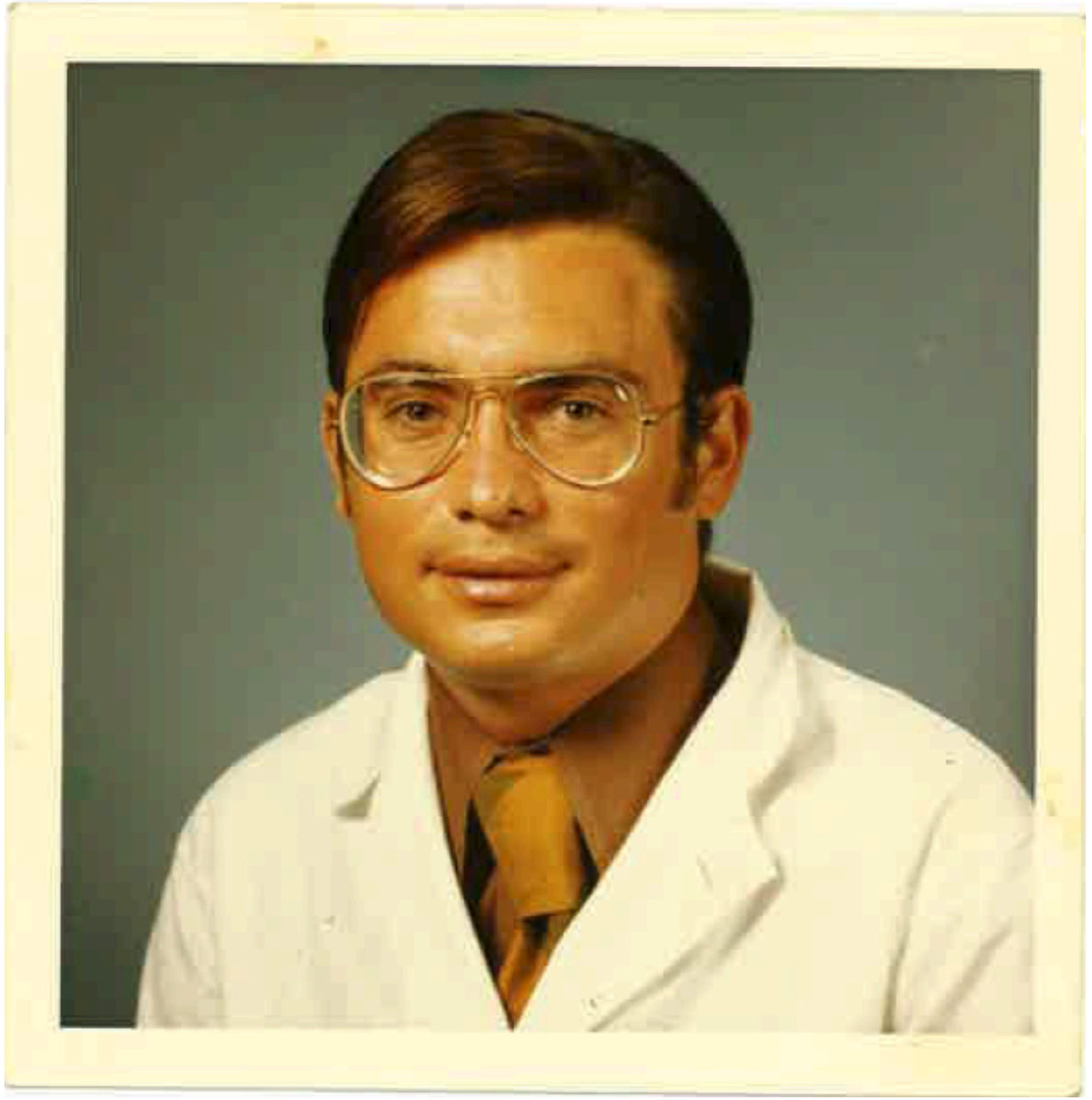



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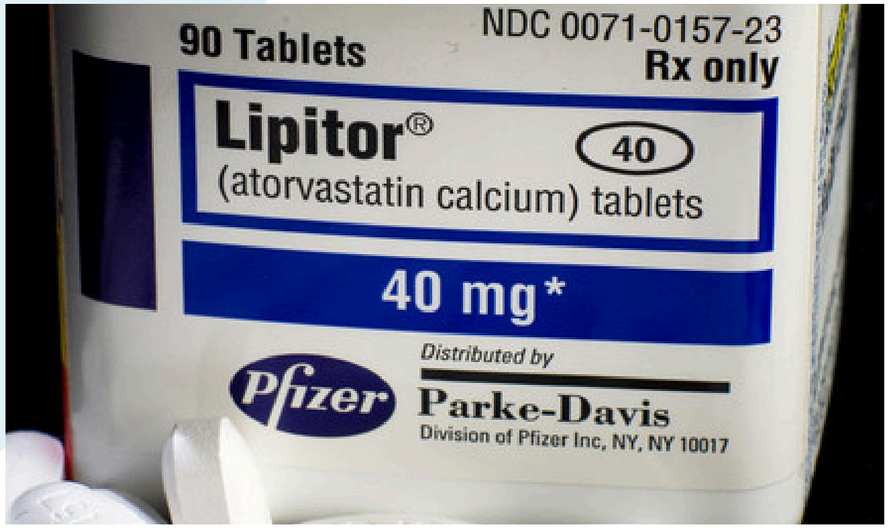





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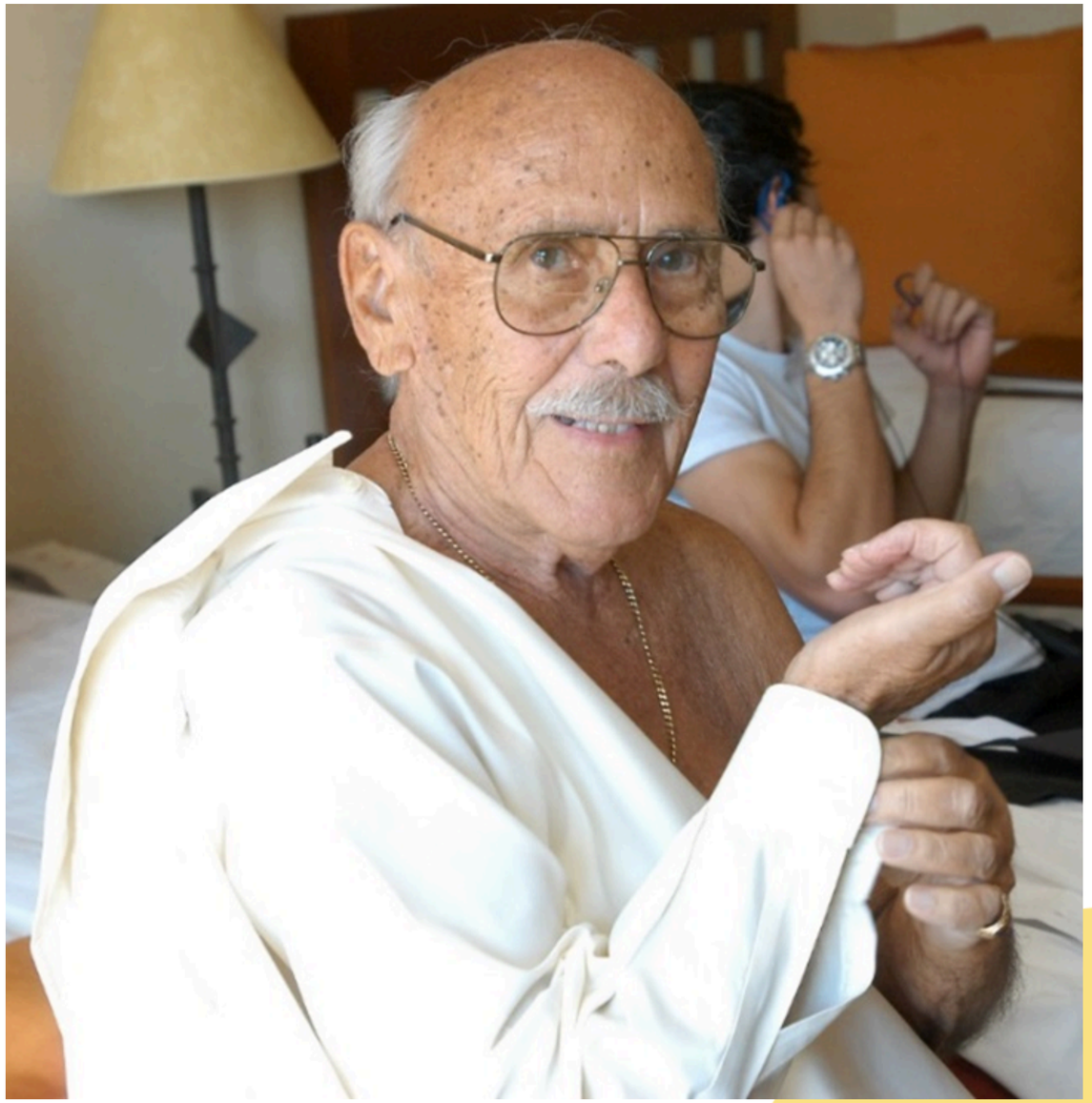



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# Becoming a DC



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# About Dr. Jack Wolfson

- Senior partner at large CV group
- Director of Cardiology, Medicine and Rehab
- Phoenix Top Doc
- Top 50 Functional Medicine Doctor
- 5X Top Holistic MD
- International Speaker and author
- Founder NaturalHeartDoctor.com




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# Cardiovascular Disease (CVD) in the 21st Century

- #1 Killer in the World
- Millions of heart attacks every year
- Millions suffer from AFIB, CHF, HTN
- Trillions in pharma and procedures



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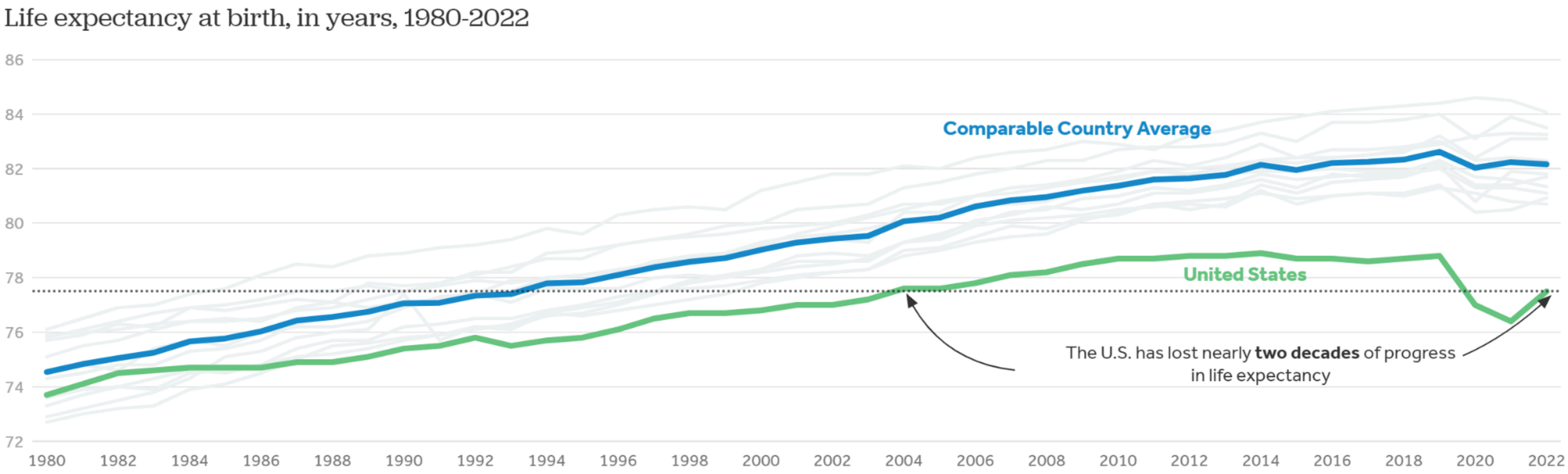
# Life Expectancy Up 3 Years in the Last 45




Notes: Comparable countries include Australia, Austria, Belgium, Canada, France, Germany, Japan, the Netherlands, Sweden, Switzerland, and the U.K. See Methods section of "How does U.S. life expectancy compare to other countries?"



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# Why THEY think CVD is so rampant?

- Genetics
- Consequence of getting old
- Bad luck
- Pharmaceutical deficiency

# I Don’t Prescribe Statin Drugs

# I Don’t Prescribe PCSK9 Inhibitors



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# BP Drugs: The goal is to get them off ASAP



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Hypertension
Volume 74, Issue 6, December 2019; Pages 1436-1447
https://doi.org/10.1161/HYPERTENSIONAHA.119.13827

American Heart Association.

CARDIOVASCULAR DISEASE RISK

# Cardiovascular Risk and Atherosclerosis Progression in Hypertensive Persons Treated to Blood Pressure Targets

Janine Gronewold, Rene Kropp, Nils Lehmann, Andreas Stang, Amir A. Mahabadi, Hagen Kälsch, Christian Weimar, Martin Dichgans, Thomas Budde, Susanne Moebus, Karl-Heinz Jöckel, Raimund Erbel, and Dirk M. Hermann



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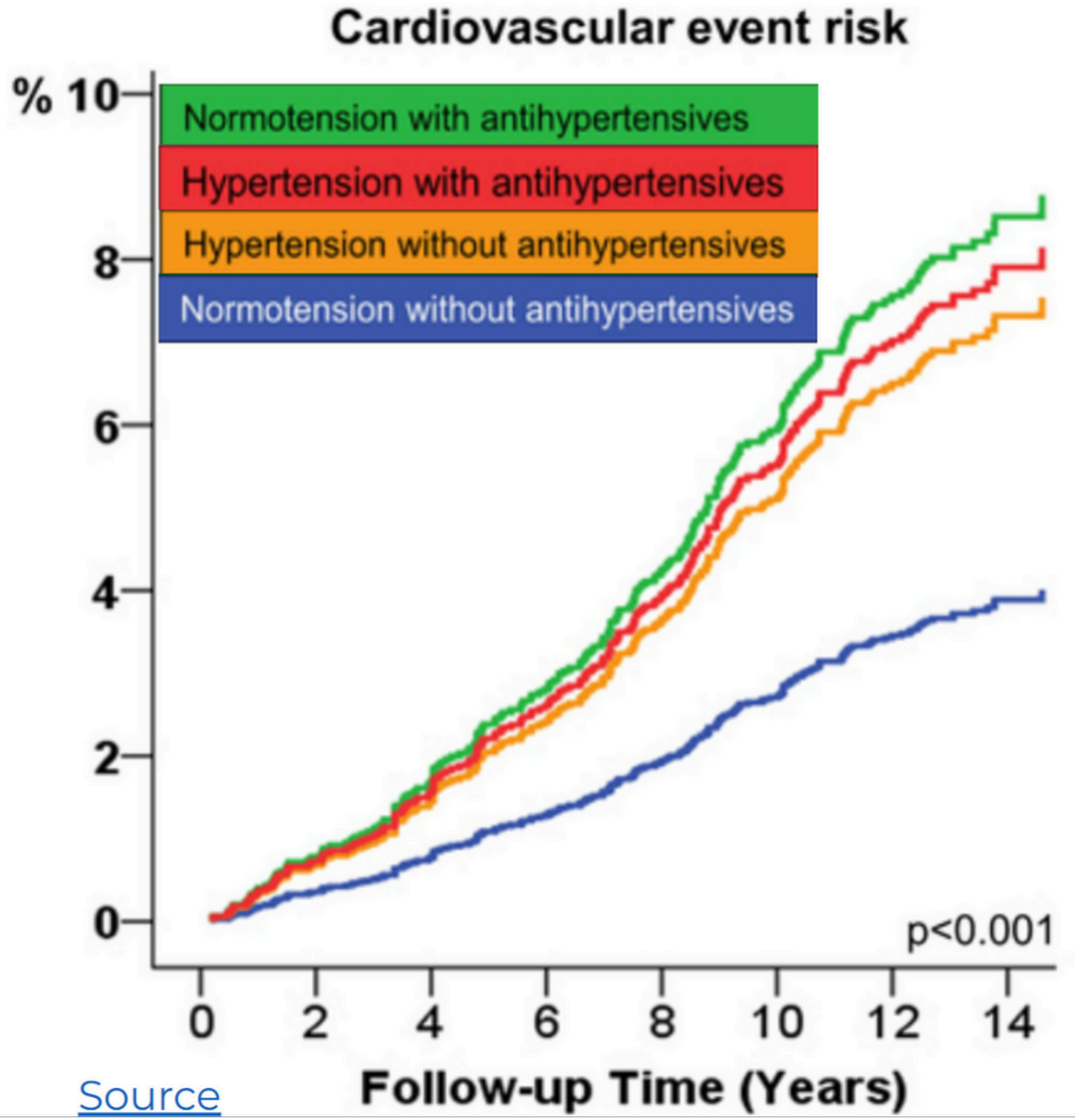


Source



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# I Never Order Nuclear Stress Tests



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# I Never Order Coronary Calcium Scans (or Cleerly)



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# I DO Order the Most Advanced Lab Tests in the World



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# Everyone Gets....

- Mold mycotoxin panel
- Envirotoxin panel
- Metals
- Intracellular nutrients
- Wheat Zoomer
- Advanced cardiovascular analysis
- Gut Zoomer



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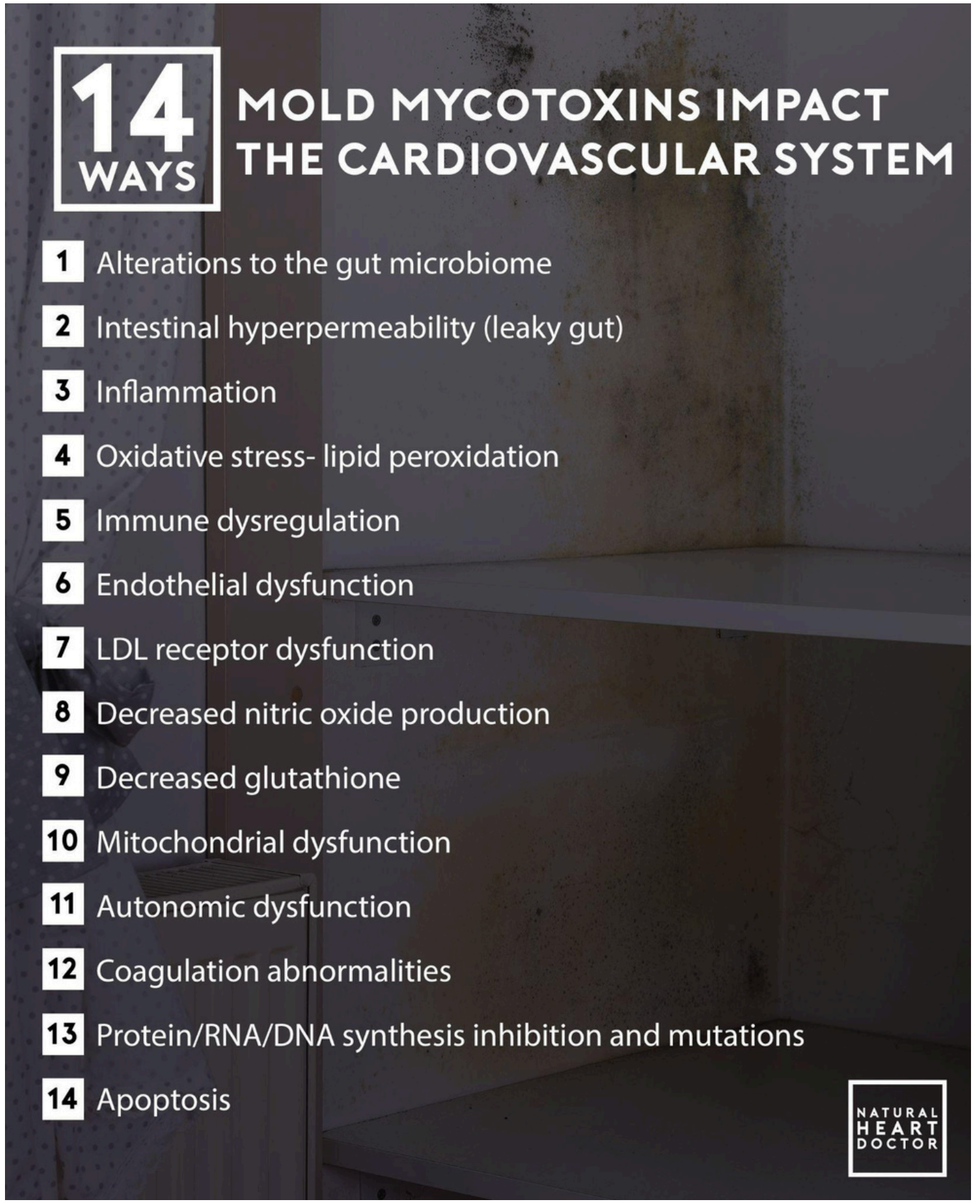




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The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPI

ORIGINAL ARTICLE

# Microplastics and Nanoplastics in Atheromas and Cardiovascular Events

**Authors**: Raffaele Marfella, M.D., Ph.D. , Francesco Prattichizzo, Ph.D., Celestino Sardu, M.D., Ph.D., Gianluca Fulgenzi, Ph.D., Laura Graciotti, Ph.D., Tatiana Spadoni, Ph.D., Nunzia D'Onofrio, Ph.D., +35 , and Giuseppe Paolisso, M.D. Author Info & Affiliations

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# Glyphosate linked to 265% increase in heart attack risk

PLoS One. 2025 Jan 24;20(1):e0317908. doi: 10.1371/journal.pone.0317908. eCollection 2025.

## BMI-mediated association between glyphosate exposure and increased risk of atherosclerotic heart disease: A large-scale cross-sectional study

Wendi Xu [1], Zhe Chen [2], Yuhong Jiang [3], Hongbo Zeng [4], Nan He [5], Ziyi Liu [6], Meirong Zhou [1]

Affiliations + expand

PMID: 39854502 PMCID: PMC11759382 DOI: 10.1371/journal.pone.0317908



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# The Heart Attack Path

Toxins Damage the Gut Microbiome

Leaky Gut/Intestinal Hyperpermeability

Inflammation
Oxidative Stress
Immune Activation

Endothelial Dysfunction

Autonomic Dysfunction

Plaque Formation
Coronary Artery Disease



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# Walk the Talk



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# Thank You!



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# The Heart of Longevity

## Innovations in Cardiovascular and Metabolic Care

Session 1

**Dr. Abid Husain MD, FACC, ABAARM**

Session 2

**Dr. Christopher Davis, MD**

Session 3

**Dr. Giovanni Campanile, M.D., FACC, ABIHM, FAARM**

Session 4

**Dr. Jack Wolfson, DO**