CHOLESTEROL AND IT'S RELATIONSHIP TO CHRONIC DISEASES

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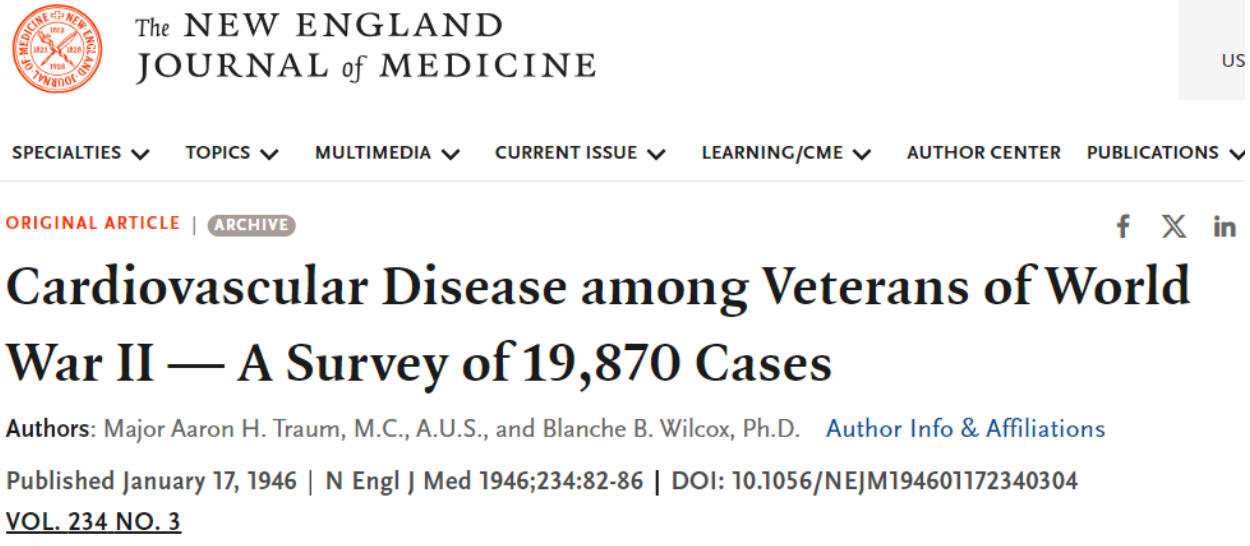
- No disclosures

OUTLINE

- Early screening for cholesterol
- How cholesterol impacts CVD and DM
- Lifestyle changes and lowering cholesterol
- Genetics

SCREENING

- Cholesterol screening is an integral part of **primary and secondary prevention of ASCVD.**
- It can detect a **vulnerable population** that may be **asymptomatic** but with a high risk of ASCVD due to genetic predispositions.
- Additionally, it can detect cholesterol elevations secondary to other diseases, such as diabetes, chronic kidney disease, and HIV infection, or due to drug usage, such as oral contraceptive drugs and others
- Furthermore, abnormally high levels of cholesterol components might indicate **familial hypercholesterolemia**



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SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

ORIGINAL ARTICLE | ARCHIVE

Cardiovascular Disease among Veterans of World War II — A Survey of 19,870 Cases

Authors: Major Aaron H. Traum, M.C., A.U.S., and Blanche B. Wilcox, Ph.D. Author Info & Affiliations

Published January 17, 1946 | N Engl J Med 1946;234:82-86 | DOI: 10.1056/NEJM194601172340304
VOL. 234 NO. 3

The most interesting feature in this group was the large number of young men affected and the high incidence of coronary-artery occlusion. Of the 991 patients with coronary arteriosclerotic heart disease, 491 (49.5 per cent) were under forty years of age,389 were between thirty and thirty-nine, and 235 were under thirty-five. Three hundred and fifty-seven patients (36 per cent) were diagnosed as having coronary-artery occlusion or myocardial infarction. Of these, 236 were under forty years of age and 177 were in the fourth decade, with 137 under thirty-five.

- The **Bogalusa Heart Study**, for example, demonstrated a strong correlation between childhood risk factors and the extent of atherosclerosis observed in young adults.

- Autopsy studies, such as the **Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study**, have shown that atherosclerotic changes can be found in the arteries of adolescents and young adults

PREVALENCE

- In the United States, approximately **20 percent of children** (age 6 to 19 years) have abnormal levels of one or more lipid value.
- The prevalence of adverse lipid levels increases with age, with 15 percent of children aged 6 to 11 years and **25 percent of adolescents aged 12 to 19 years having at least one adverse level**
- The prevalence of specific abnormalities are as follows (note that a child may have more than one abnormality)
- ●Elevated total cholesterol (TC; ≥200 mg/dL [5.2 mmol/L]) – 7.1 percent
- ●Elevated low-density lipoprotein cholesterol (LDL-C; ≥130 mg/dL [3.4 mmol/L]) – 6.4 percent
- ●Elevated non-high-density lipoprotein cholesterol (non-HDL-C) levels (≥145 mg/dL [3.8 mmol/L]) – 6.4 percent
- ●Elevated triglyceride (≥130 mg/dL [1.5 mmol/L]) – 10.2 percent
- ●Low HDL-C (<40 mg/dL [1.0 mmol/L]) – 12.1 percent

GUIDELINES FOR EARLY SCREENING:

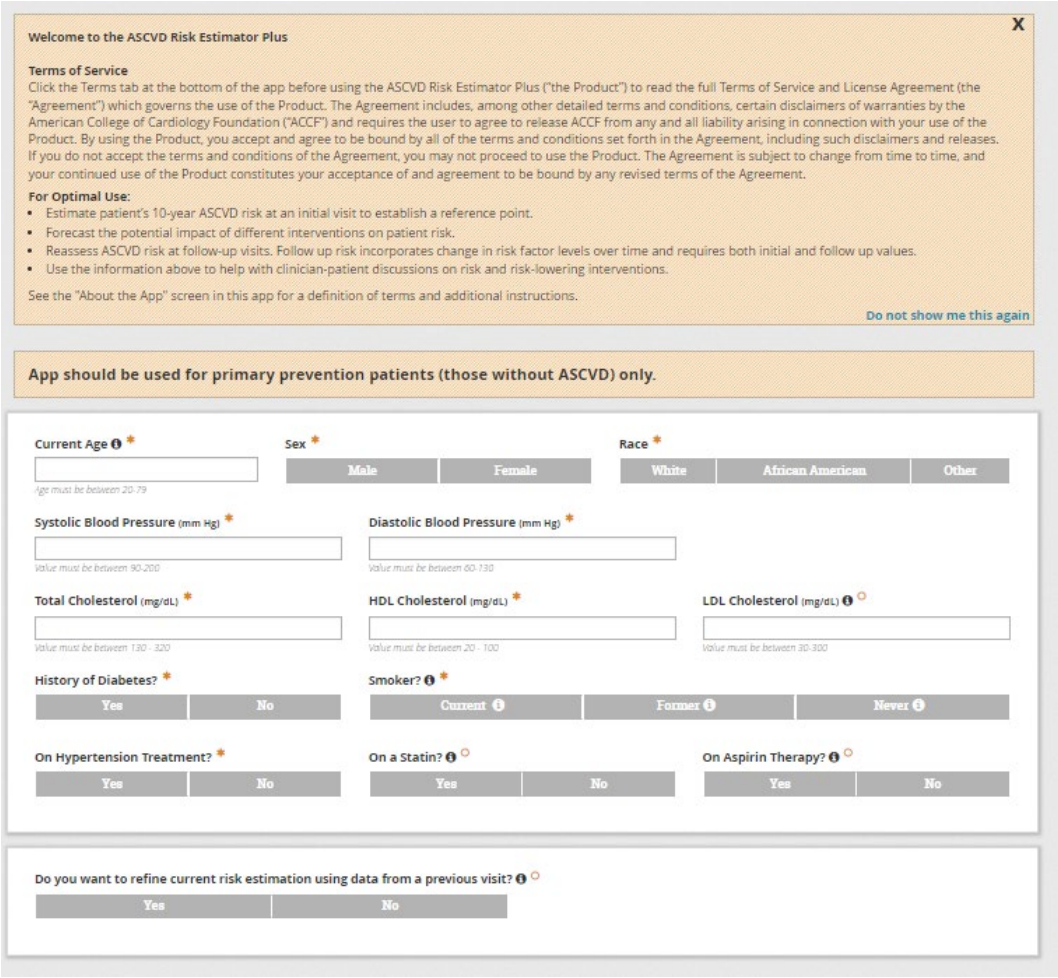
- **General Recommendations:**
  - **Healthy Adults:** The American College of Cardiology and the American Heart Association recommend **that healthy adults start getting their cholesterol checked every 4 to 6 years starting at age 20.**

  - **At-Risk Adults:** People with risk factors such as diabetes, high blood pressure, smoking, or a family history of heart disease should start screening earlier and may need to be tested more frequently.

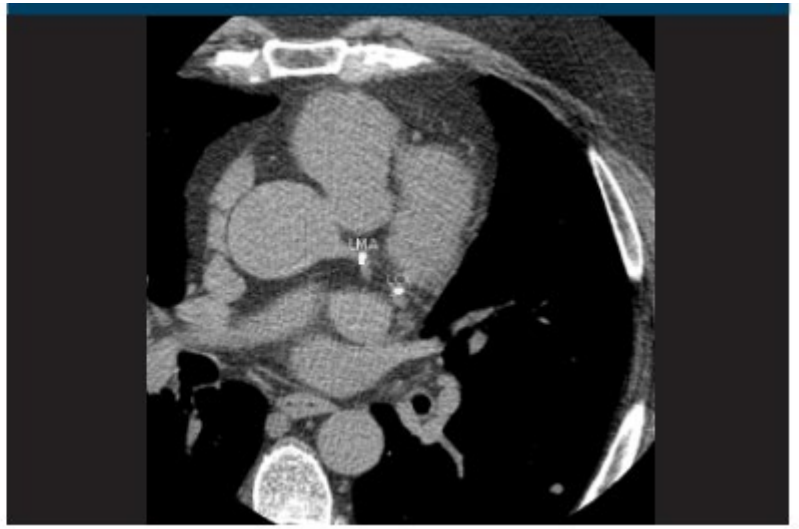
1. **Children and Adolescents:**
   - **Children:** Children should have their cholesterol checked at least once between ages 9 and 11.
   - **Adolescents:** Adolescents should have their cholesterol checked between ages 17 and 21. Those with obesity or diabetes may need more frequent screening

2. **Testing Process:**
   - **Lipid Panel**.
   - **Advanced lipid panel**

ACC AND MESA CALCULATORS



https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/



1. Gender	Male ○	Female ○			
2. Age (45-85 years)		Years			
3. Coronary Artery Calcification		Agatston			
4. Race/Ethnicity	Choose One				
5. Diabetes	Yes ○	No ○			
6. Currently Smoke	Yes ○	No ○			
7. Family History of Heart Attack (History in parents, siblings, or children)	Yes ○	No ○			
8. Total Cholesterol		mg/dL	or		mmol/L
9. HDL Cholesterol		mg/dL	or		mmol/L
10. Systolic Blood Pressure		mmHg	or		kPa
11. Lipid Lowering Medication	Yes ○	No ○			
12. Hypertension Medication	Yes ○	No ○			

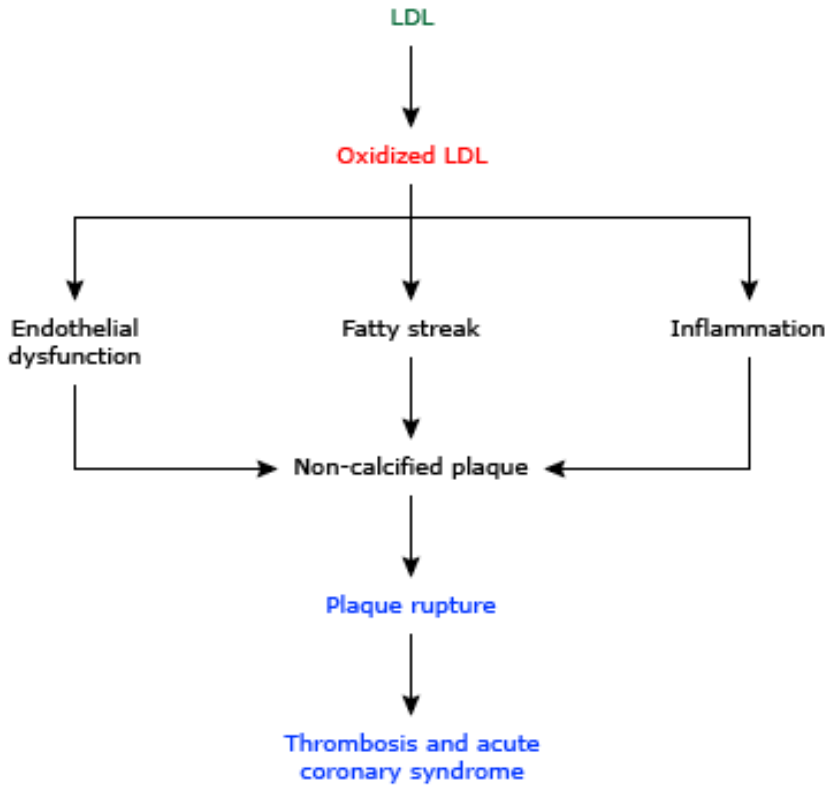
Calculate 10-year CHD risk

Using the Coronary Artery Calcium Score		
10 Year risk of a CHD Event	Coronary Age	Difference from Chronologic Age

Without Considering the Coronary Artery Calcium Score		
10 Year risk of a CHD Event	Coronary Age	Difference from Chronologic Age

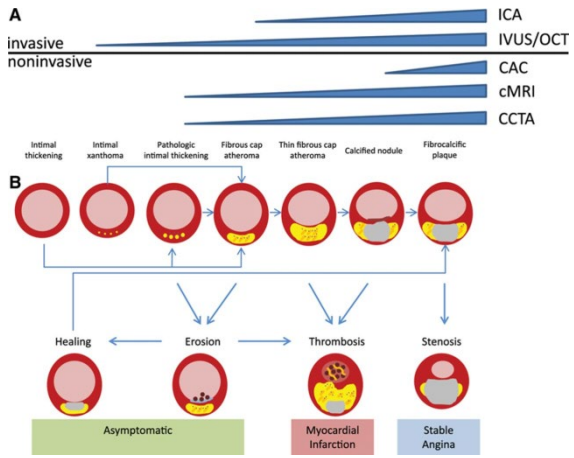
Start Over

https://internal.mesa-nhlbi.org/about/procedures/tools/mesa-score-risk-calculator



CHOLESTEROL AND HEART DISEASE

1. **LDL Cholesterol and Endothelial Dysfunction**:
    1. Low-density lipoprotein (LDL) cholesterol, often referred to as "bad" cholesterol, is a key player in atherosclerosis. When LDL particles circulate in the bloodstream, they can penetrate the endothelial layer of arteries, especially at sites of endothelial dysfunction
    2. Endothelial dysfunction can be triggered by factors such as hypertension, smoking, diabetes, and high cholesterol levels
2. **Oxidation and Inflammation**:
    1. Once inside the arterial wall, LDL particles undergo oxidation, becoming oxidized LDL (oxLDL). This oxidative modification is crucial as it makes LDL more atherogenic
    2. OxLDL triggers an inflammatory response, attracting monocytes to the site. These monocytes differentiate into macrophages, which engulf oxLDL, transforming into foam cells
3. **Formation of Fatty Streaks**:
    1. Foam cells accumulate within the arterial wall, forming fatty streaks, which are the earliest visible signs of atherosclerosis
    2. The continued accumulation of foam cells and other inflammatory cells leads to the formation of a lipid-rich necrotic core within the arterial plaque
4. **Plaque Progression and Complications**:
    1. Over time, the plaque grows and can become calcified, further narrowing the arterial lumen and reducing blood flow
    2. Plaques can also become unstable and rupture, leading to the formation of a thrombus and acute cardiovascular events such as myocardial infarction or stroke



PLAQUE REGRESSION

1. **Lipid-Lowering Therapies**:
    1. Statins, PCSK9 inhibitors, and other lipid-lowering agents have been shown to reduce plaque volume by lowering LDL cholesterol levels
    2. High-intensity statin therapy, in particular, has been associated with significant reductions in plaque volume as measured by intravascular ultrasound (IVUS)
2. **Anti-Inflammatory Effects**:
    1. Reducing inflammation within the arterial wall is another mechanism by which plaque regression can occur. Therapies targeting inflammatory pathways, such as canakinumab, have shown promise in reducing plaque burden
3. **Lifestyle Modifications**:
    1. Diet, exercise, and smoking cessation are critical components of plaque regression. These lifestyle changes can improve lipid profiles and reduce systemic inflammation

Clinical Evidence

- **Imaging Studies**:
    - Advanced imaging techniques, such as IVUS and coronary computed tomography angiography (CCTA), have been used to assess changes in plaque volume and composition. These studies have demonstrated that plaque regression is possible with appropriate medical therapy
- **Clinical Trials**:
    - Meta-analyses of clinical trials have shown that even a 1% reduction in percent atheroma volume (PAV) is associated with a 25% reduction in the odds of major adverse cardiovascular events (MACE)

- https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2022/01/10/23/23/coronary-atherosclerotic-plaque-regression

CHOLESTEROL AND DIABETES

- 37 million US adults have DM and type 2 accounting for 90-95%
- 8th leading cause of death and number 1 cause of kidney failure, lower limb amputation and adult blindness
- Diabetes commonly associated with **diabetic dyslipidemia** increasing risk of CVD
  - lower HDL-C
  - Increase triglycerides
  - Increase LDL-C
- High or borderline high total cholesterol is present in **70% of adults with diagnosed diabetes and 77% with undiagnosed diabetes**
  - 95% have evidence of CHD or two or more risk factors for CHD

GLP1 AGONISTS

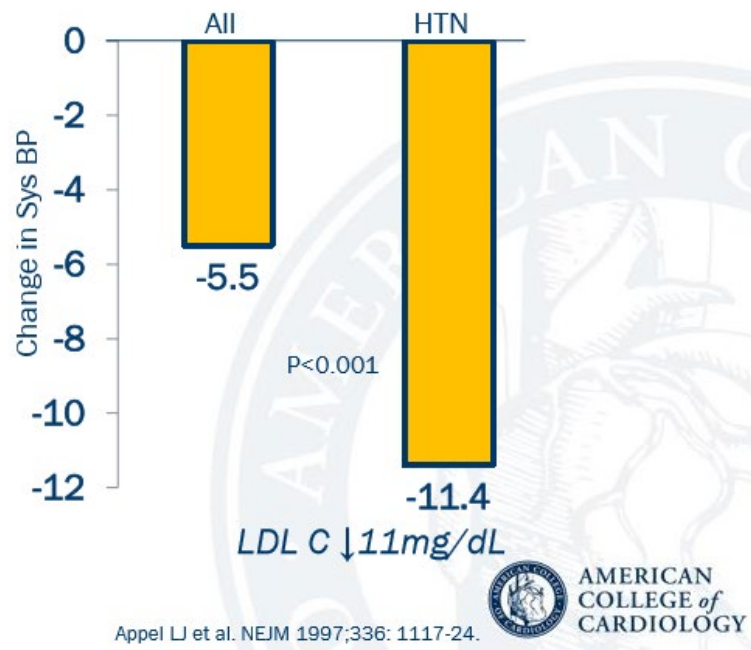
- GLP-1 receptor agonists (GLP-1RAs) have shown significant promise in the treatment of heart disease, particularly for patients with type 2 diabetes and obesity.
- **Cardiovascular Benefits: GLP-1RAs**, such as semaglutide and liraglutide, have been shown to reduce the risk of major adverse cardiovascular events (MACE), including cardiovascular death, heart attack, and stroke
- Mechanism of Action: These medications work by **enhancing glucose-dependent insulin secretion, suppressing glucagon secretion, and slowing gastric emptying**. They also have direct effects on the cardiovascular system, including **improving endothelial function and reducing inflammation**
- Clinical Trials: Recent clinical trials have demonstrated the efficacy of GLP-1RAs in reducing cardiovascular risk. For example, the **FDA approved semaglutide (Wegovy) for reducing cardiovascular events in adults with cardiovascular disease and obesity or overweight**.
- Safety Profile: gastrointestinal side effects such as nausea and vomiting. Warning for the risk of thyroid C-cell tumors, so they should not be used in patients with a history of medullary thyroid carcinoma.
- https://www.acc.org/latest-in-cardiology/articles/2024/04/15/11/19/glp1ras-in-clinical-practice

LIFESTYLE CHANGES AND LOWERING CHOLESTEROL

- DASH
- MEDITERRANEAN
- Exercise
- Stress
- Sleep
- Smoking
- Acohol

DASH Diet Study and BP Lowering

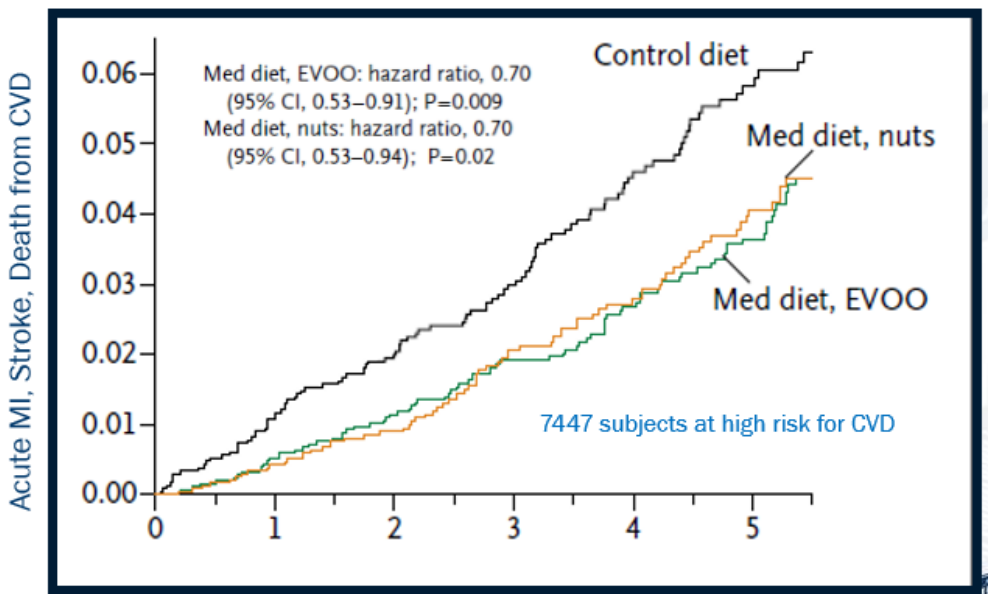
- Randomized trial of 459 adults, 8 weeks
  - ↑Fruits and Vegetables
  - ↑ low fat dairy, lower saturated and total fat
  - Low sodium, high potassium



Appel LJ et al. NEJM 1997;336: 1117-24.

AMERICAN COLLEGE of CARDIOLOGY

Mediterranean Diet and Primary Prevention of CVD: PREDIMED



EVOO: 1 L per week
Nuts: 30g/week walnuts, hazelnuts, almonds

Estruch R et al. NEJM 2013;368: 1279-1290

AMERICAN COLLEGE of CARDIOLOGY

DIETARY CHANGES

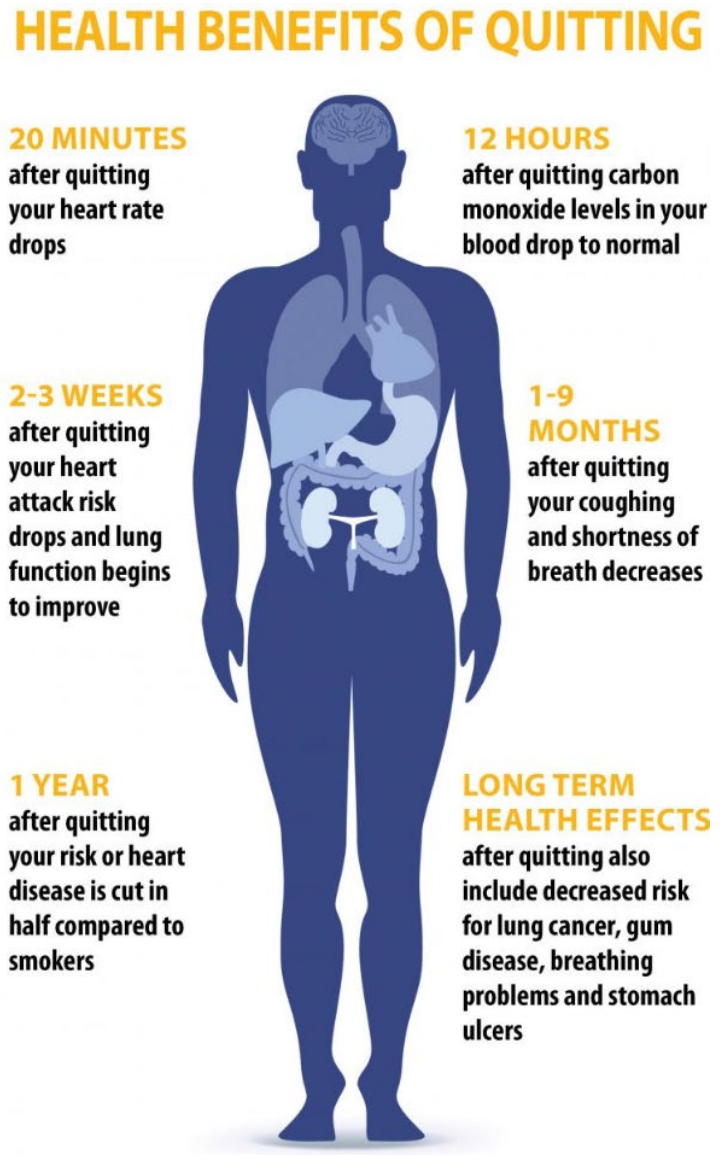
1. **Increase Soluble Fiber Intake**:
    1. Foods rich in soluble fiber, such as oats, beans, lentils, fruits, and vegetables, can help reduce LDL cholesterol levels by binding to cholesterol in the digestive system and removing it from the body.
2. **Choose Healthy Fats**:
    1. Replace saturated fats (found in red meat, butter, and full-fat dairy products) with unsaturated fats (found in olive oil, avocados, nuts, and fatty fish). Unsaturated fats can help lower LDL cholesterol and raise HDL cholesterol.
3. **Limit Dietary Cholesterol**:
    1. Reduce the intake of high-cholesterol foods, such as organ meats, shellfish, and egg yolks. While dietary cholesterol has less impact on blood cholesterol than saturated and trans fats, it is still beneficial to limit its intake.
4. **Avoid Trans Fats**:
    1. Trans fats, found in many processed and fried foods, can significantly raise LDL cholesterol and lower HDL cholesterol. Encourage patients to read food labels and avoid products containing partially hydrogenated oils.

PHYSICAL ACTIVITY

1. **Regular Exercise**:
    1. Encourage patients to engage in at least 150 minutes of moderate-intensity aerobic exercise (such as brisk walking, cycling, or swimming) per week. Regular physical activity can help raise HDL cholesterol and lower LDL cholesterol.
2. **Incorporate Strength Training**:
    1. Strength training exercises, such as weightlifting or resistance band exercises, should be performed at least twice a week. These activities can help improve overall cardiovascular health and support weight management.

WEIGHT MANAGEMENT
SMOKING CESSATION

1. **Achieve and Maintain a Healthy Weight**:
    1. Losing excess weight can help lower LDL cholesterol and triglycerides while raising HDL cholesterol. Even a modest weight loss of 5-10% of body weight can have significant benefits.
2. **Quit Smoking**:
    1. Smoking cessation is crucial for improving HDL cholesterol levels and overall cardiovascular health. Provide resources and support for patients to quit smoking, such as counseling, nicotine replacement therapy, or medications.



Alcohol Consumption

- Moderate Alcohol Intake:
- If patients choose to drink alcohol, advise them to do so in moderation. For men, this means up to two drinks per day, and for women, up to one drink per day. Excessive alcohol consumption can raise triglyceride levels and contribute to other health issues.

Stress Management

- Reduce Stress:
- Chronic stress can negatively impact cholesterol levels and overall heart health. Encourage patients to practice stress-reducing techniques such as mindfulness, meditation, yoga, or deep breathing exercises.

GENETICS

- FH
- Lipoprotein a – Lp(a)

FAMILIAL HYPERCHOLESTEROLEMIA (FH)

1. **LDLR Gene**:
    1. The LDLR gene provides instructions for **making low-density lipoprotein (LDL) receptors**, which are responsible for **removing LDL** cholesterol from the bloodstream. Mutations in the LDLR gene can lead to a **reduced number or function of these receptors**, resulting **in elevated LDL** cholesterol levels

2. **APOB Gene**:
    1. The APOB gene encodes **apolipoprotein B, a primary protein component of LDL particles**. Mutations in the APOB gene **can impair the ability of LDL particles to bind** to LDL receptors, leading to increased LDL cholesterol levels

3. **PCSK9 Gene**:
    1. The PCSK9 gene encodes **a protein that regulates the number of LDL receptors** on the surface of liver cells**. Gain-of-function mutations** in the PCSK9 gene can lead to **increased degradation of LDL receptors**, resulting in **higher LDL cholesterol levels**

OTHER GENETIC FACTORS

1. **ABCA1 Gene**:
    1. The ABCA1 gene is involved in **the transport of cholesterol out of cells** and into high-density lipoprotein (HDL) particles. Mutations in this gene can **affect HDL cholesterol levels** and overall cholesterol homeostasis

2. **CETP Gene**:
    1. The **CETP gene encodes cholesteryl ester transfer protein**, which facilitates the transfer of cholesterol esters from HDL to other lipoproteins. Variants in the CETP gene can influence **HDL and LDL cholesterol levels**

CLINICAL IMPLICATIONS

- **Genetic Testing**:
  - Genetic testing can help identify individuals with familial hypercholesterolemia and other genetic conditions affecting cholesterol metabolism. This can guide personalized treatment strategies and family screening.
- **Risk Assessment**:
  - Understanding the genetic basis of hypercholesterolemia can aid in **assessing cardiovascular risk and implementing early intervention** strategies to prevent atherosclerosis and related complications

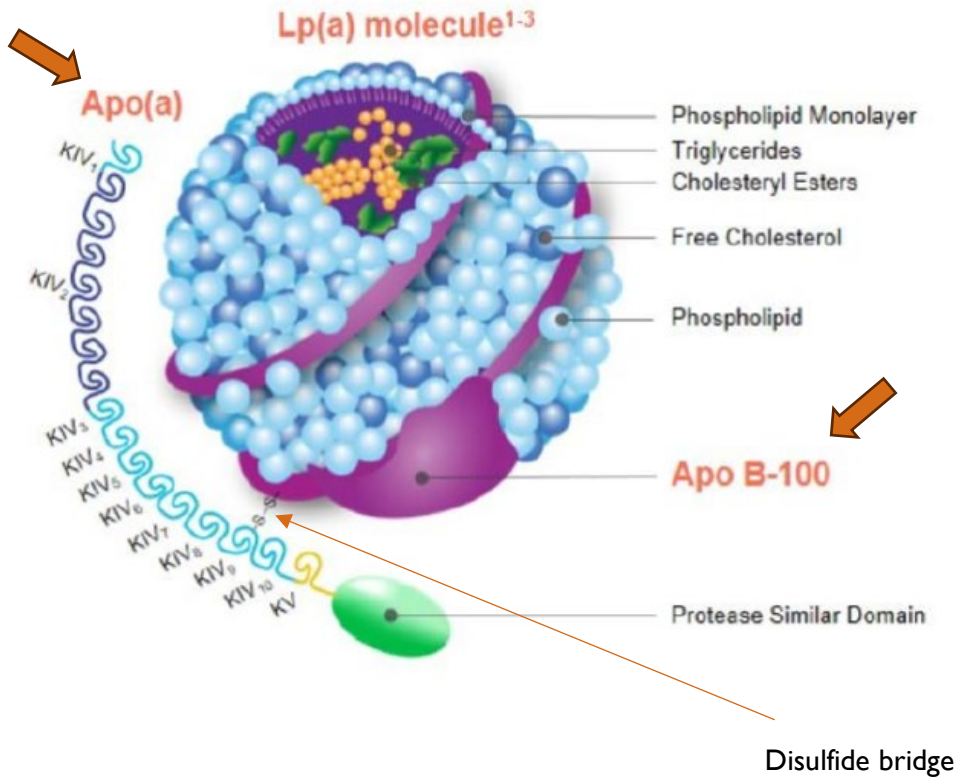
Lipoprotein a – Lp(a)

- Lipoprotein(a), or Lp(a), is a type of lipoprotein that is genetically inherited and is considered an independent risk factor for cardiovascular diseases, including **atherosclerosis and calcific aortic valve stenosis**

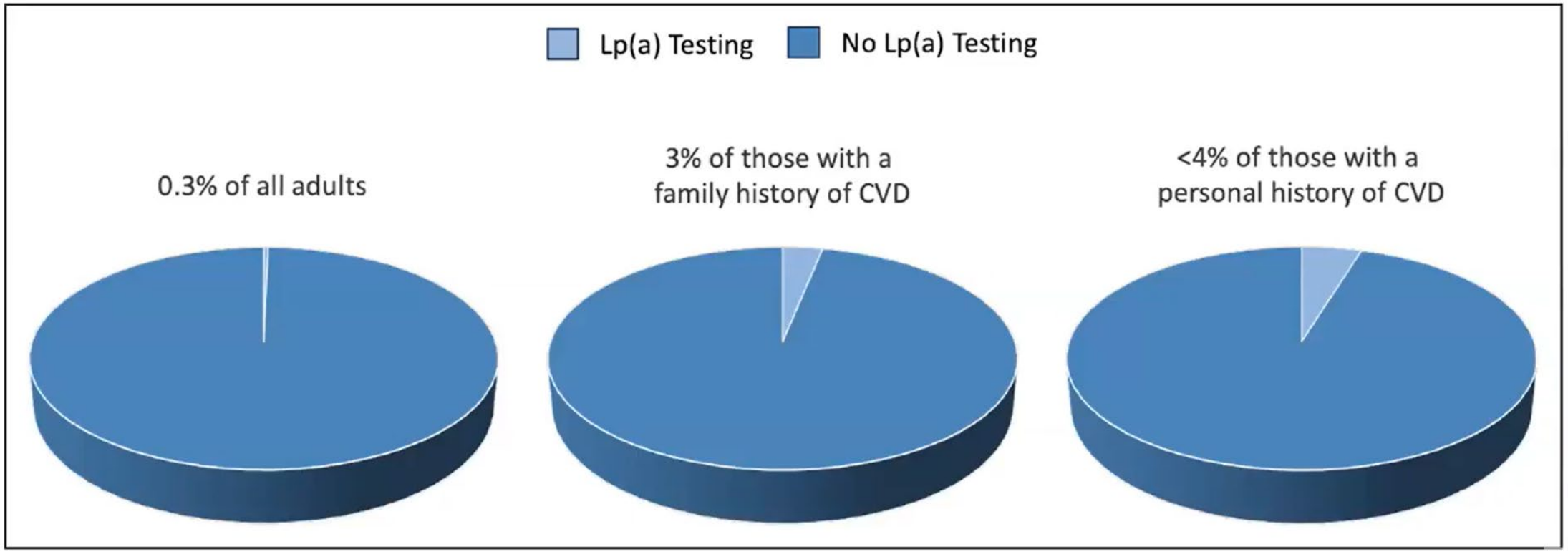
Lipoprotein(a) (Lp[a]) is a **low-density lipoprotein**–like molecule

with an **apolipoprotein (b)** moiety that is covalently

attached to apolipoprotein (a) (Apo[a]),



LIPOPROTEIN A - LOW TESTING RATES



Bhatia et al JAHA 2023

A Focused Update to the 2019 NLA Scientific Statement on Use of Lipoprotein(a) in Clinical Practice

Candidates for Lp(a) Screening

1. The adult population
2. The pediatric population (specifically, high-risk children and youth)
   - Clinically suspected or genetically confirmed familial hypercholesterolemia
   - First-degree relatives with a history of premature ASCVD
   - Ischemic stroke or unknown cause
   - First-degree relatives with elevated Lp(a)

Recommendations to Consider Offering to Patients

1. Lifestyle modification
2. Statins
3. Ezetimibe
4. PCSK9-directed therapies
5. Aspirin
6. Lipoprotein apheresis

Measure Lp(a) at least Once in all Adults and Selected High-risk Children

Action Items to Consider if High Risk:

- More intensive risk factor management, including LDL-C (Lp(a) is a risk-enhancing factor)
- Cascade screening
- Lifestyle modifications
- Therapies such as statin, PCSK9 inhibitor, asprin; apheresis if severe

QUESTIONS

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