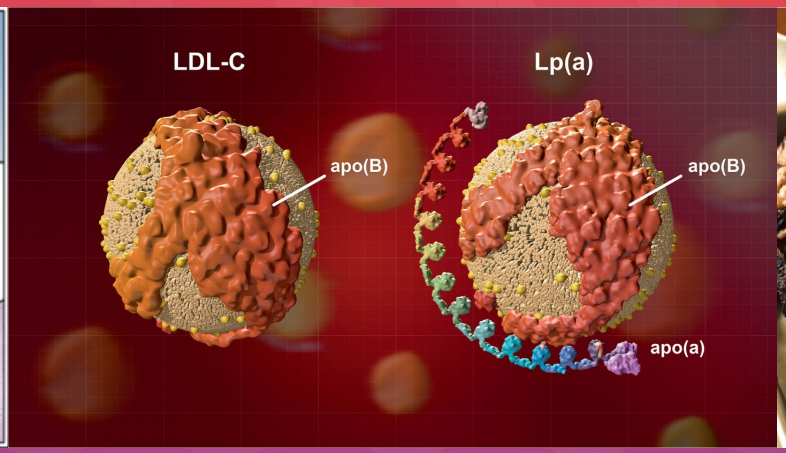
ROPER ST. FRANCIS HEALTHCARE

Clinical Lipid Review



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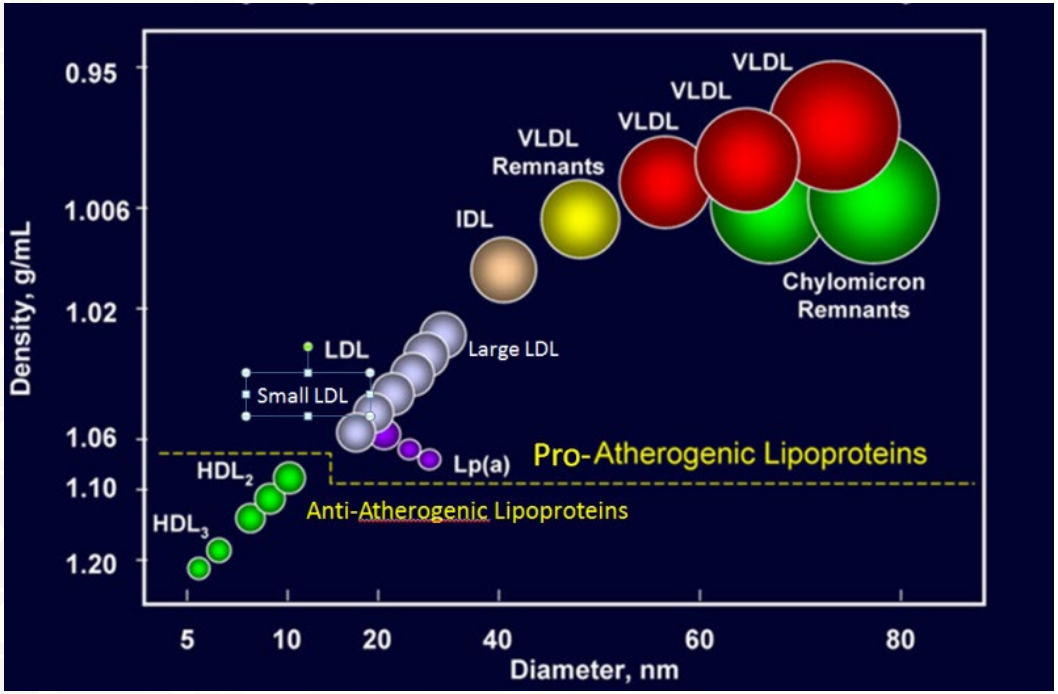
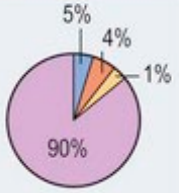
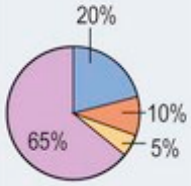
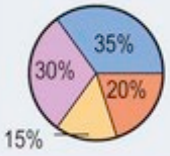
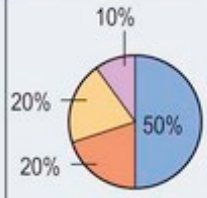
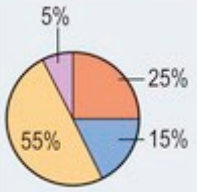
00/00/2022

Objectives

- Have a well informed approach to a standard lipid panel and understand the nuances to keep in mind while interpreting
- Understand the indications for advanced lipid biomarkers and how they change management
- Know when to get a coronary calcium score and how to manage abnormal results

Standard Lipid Panel



Composition of lipoproteins					
triglyceride cholesterol phospholipid protein	chylomicrons	VLDL	IDL	LDL	HDL
					
apolipoproteins	C, B-48, E, A	B-100, C, E	B-100, E	B-100	A, C, E

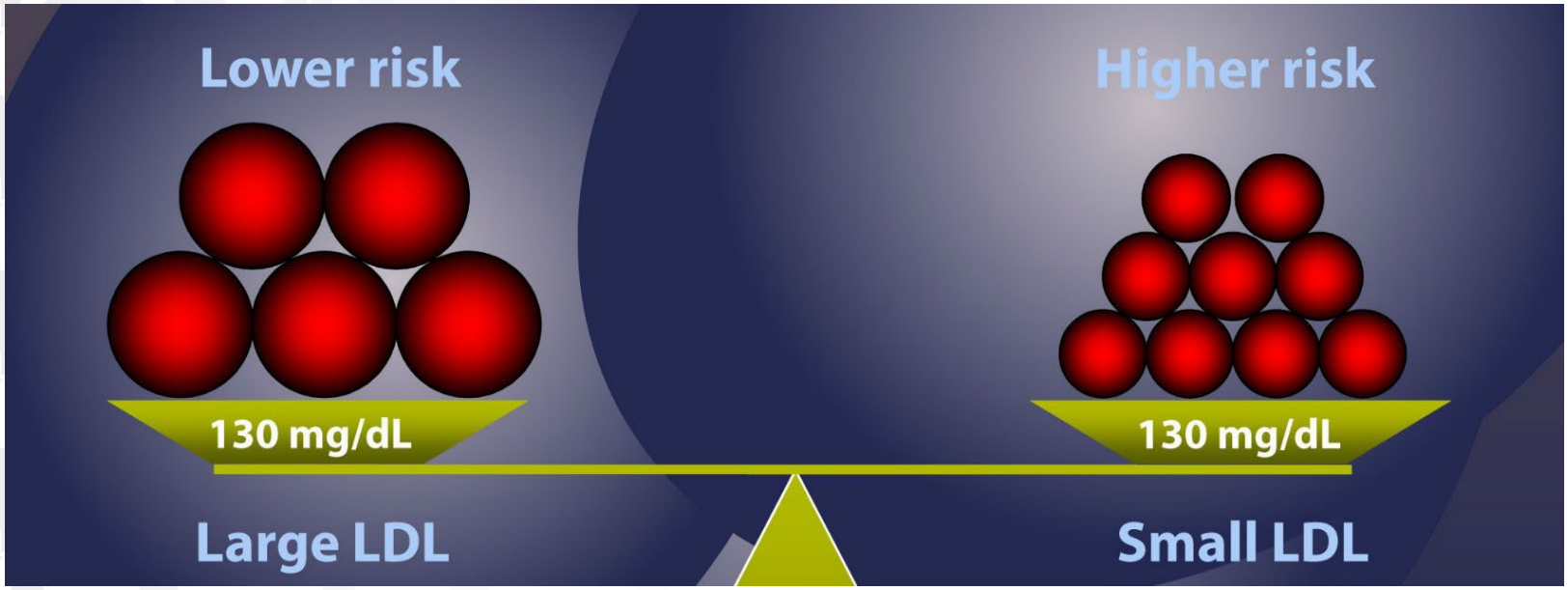
Lipoprotein Measurement

LDL-C: concentration of cholesterol in LDL particles

Non-HDL-C: concentration of cholesterol in apolipoprotein B containing particles

Apolipoprotein B: concentration of all potentially atherogenic particles

“My doctor said my LDL was normal.”



Atherogenic Dyslipidemia and Adiposopathy

Metabolic syndrome:

The NCEP ATP III definition*

In order to make a diagnosis of the metabolic syndrome a patient must present with **three or more** of the following five risk factors:

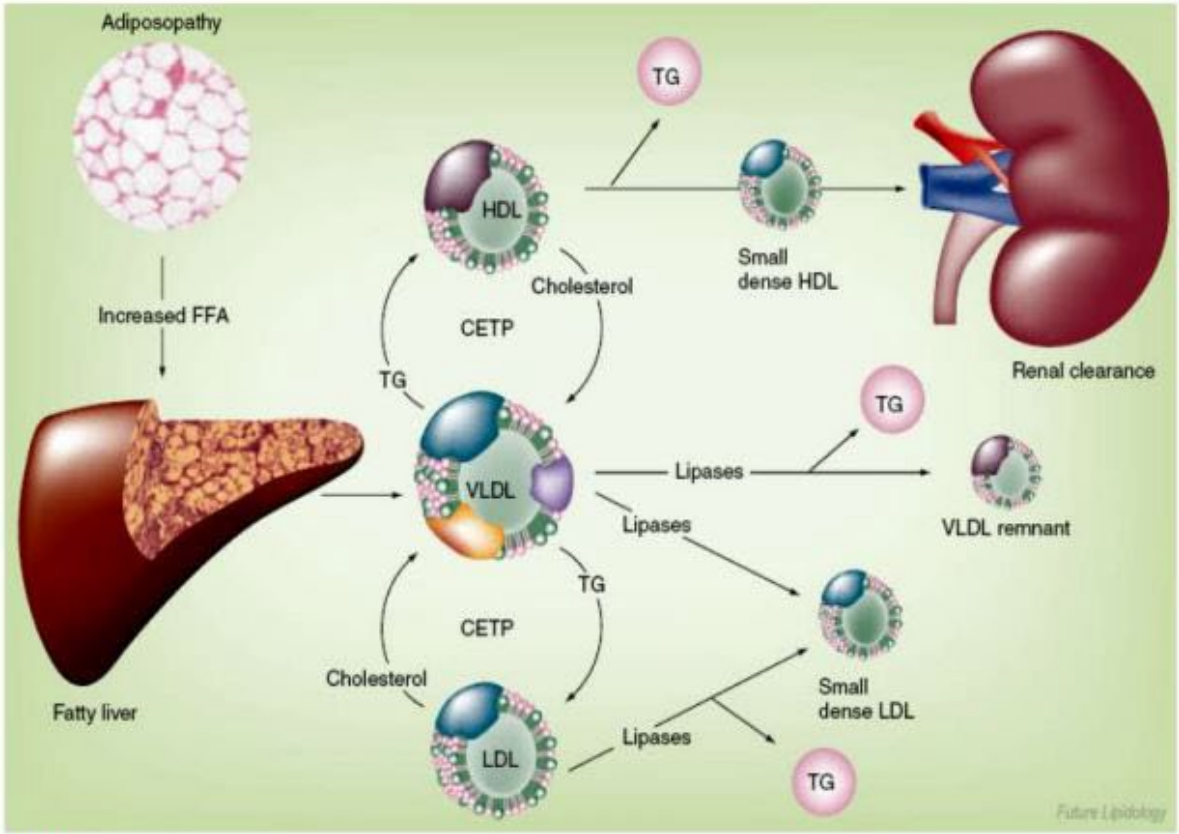
(Low density lipoprotein cholesterol is NOT a diagnostic component of MetSyn; TG level for MetSyn is >=175 mg/dL according to the 2018 ACC/AHA guidelines).

Risk Factor	Defining Level
Abdominal obesity Men Women	Waist circumference >102 cm (>40 in) >88 cm (>35 in)
Triglycerides	≥150 mg/dL (1.7 mmol/L)
HDL cholesterol Men Women	 <40 mg/dL (1.04 mmol/L) <50 mg/dL (1.30 mmol/L)
Blood pressure	≥130/ ≥85 mmHg
Fasting glucose	≥100 mg/dL (5.6 mmol/L)

*2001, updated 2005

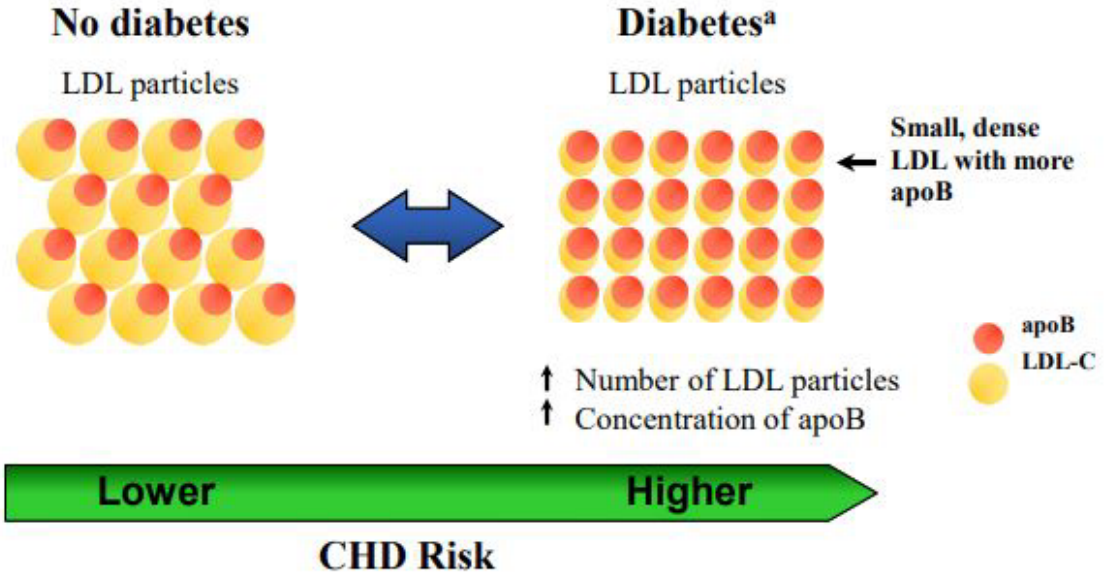
Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106;3143.

Mechanisms of Adiposopathic Dyslipidemia



Bays H, Ballantyne C. *Future Lipidology*. 2006;1:389-420.
Bays H, et al. *Expert Rev Cardiovasc Ther*. 2005;3:789-820.

LDL-C levels in people with diabetes can be misleading; Patients may have more LDL particles at a given LDL-C level



[a]Study conducted in patients with T2DM treated with insulin.
apoB=apolipoprotein B; CHD=coronary heart disease; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; T2DM=type 2 diabetes mellitus.

1. Selby JV et al. *Circulation*. 1993;88:381–387.
2. Feingold K et al. *Arterioscler Thromb*. 1992;12:1496–1502.
3. Sniderman AD et al. *Diabetes Care*. 2002;25:579–582.
4. Austin MA et al. *JAMA*. 1988;260:1917–1921.

Lipid Panel Considerations

- It is acceptable to ***screen*** with a nonfasting lipid
  - When LDL-C or TG screening results are abnormal the clinician should consider obtaining fasting lipids

- Non-HDL-C is measured reliably in either the fasting or the nonfasting state and can effectively guide ASCVD prevention

- LDL-C can be estimated from HDL-C and TG measurements
  - *LDL-C>100 mg/dL and TG ≤ 150 mg/dL* → reasonable to use the ***Friedewald formula***

    - *TG 150-400 mg/dL* → Friedewald formula for LDL-C estimation is less accurate
      - ***Martin/Hopkins method*** is recommended for LDL-C estimation throughout the range of LDL-C levels and up to TG levels of 399 mg/dL.

      - For *TG levels >400 mg/dL* LDL-C estimating equations are currently not recommended and newer methods are being evaluated.

Lipid Reporting Key Points

Table 3: Example of a Lipid Measurement Laboratory Report			
Patient Name			
Fasting Yes ( ) No ( )			
Measurement	**Desirable Values***	**Results**	**High Alert Values* (Refer to Lipid Specialist)**
Total cholesterol	<200 mg/dL		
HDL-C	>40 mg/dL for men >50 mg/dL for women		≤ 20 mg/dL
Non-HDL-C	<130 mg/dL <100 mg/dL for ASCVD* or high risk pts		≥220 mg/dL Consider inherited hyperlipidemia
LDL-C	<100 mg/dL <70 mg/dL for ASCVD or high risk pts		<50 untreated ≥190 mg/dL Consider Familial Hypercholesterolemia
TG	<150 mg/dL fasting <175 mg/dL nonfasting[1]		500-999 mg/dL – severe ≥1000 mg/dL – critical value
*Desirable and Alert values derived various sources.[4,22,23]			

Lipid Reporting Key Points

- LDL-C ≥ 190 mg/dL → High risk for FH
  - Need for aggressive LDL-C lowering
  - Further lab investigation for family members
- TG ≥ 500 mg/dL → Severe hypertriglyceridemia
  - See ACC/AHA 2021 Hypertrigylceridemia document
- Very low HDL-C→ LCAT Deficiency
  - Mutation—accumulation of unesterified cholesterol in cornea, kidneys, erythrocytes→ corneal opacities, CKD, hemolytic anemia
- Very low or undetected LDL-C→ Hypobetalipoproteinemia
  - Increased ASCVD risk; fatty liver, fibrosis, cirrhosis, fat malabsorption

Other Considerations

- Measurement Interval
  - 4-12 weeks after lipid treatment interventions from either lifestyle changes or medication
  - 3-12 months when stable, more often for confounding variables
    - Immunotherapy, HIV therapy
  - On injectable therapy
    - Document the time between injection and lab draw in your reporting
- Acutely Ill Patients
  - Acute MI can lower atherogenic lipid levels
    - Within 12 hours of an acute illness or four to eight weeks following the illness is a potential strategy
    - Regardless high risk patients are started on high intensity

Rule Out Secondary Causes of Hyperlipidemia

- Excessive alcohol intake
- Pancreatitis
- Non-lipid medication side effects:
  - retinoids, diuretics, beta-blockers, estrogen, tamoxifen, HIV infection and its treatments, atypical anti-psychotic medications, androgens, and corticosteroids
- Hepatic disease, nephrotic syndrome, uncontrolled diabetes, hypothyroidism, hyperthyroidism, primary biliary cholangitis, and HIV infection

Residual Atherogenic Risk

- What is it?
  - Patient that is high risk for clinical ASCVD that has markers for risk that can potentially be further reduced with further statin intensification or addition of non-statin therapies
- How do you assess and manage it?
  - Measurement of non-HDL-C, Apo-B and LDL-P have been described
- Triglyceride Rich Lipoproteins
  - Lipoproteins that contain both Apo-B and cholesterol
  - Explains the patient that remains at risk but LDL is at goal
    - Particularly seen in patients with TG elevation
    - Shown to have equivalent atherogenicity as LDL-C but interventional trials are lacking

Non-HDL-C

- [Non-HDLC] = [TC] – [HDL-C]
- Does not require TG measurement
  - Accurately determined in samples from fasting or nonfasting individuals
- Is a measurement of cholesterol carried by atherogenic apolipoprotein B-containing lipoproteins
    - LDL
    - Intermediate density lipoprotein (IDL)
    - Very low density lipoprotein (VLDL)
    - VLDL remnants, chylomicron particles, chylomicron remnants, and Lp(a)

Non-HDL-C

- Can be calculated from a standard lipid panel
- Surrogate, not a direct measurement
- After reduction of LDL to < 70, NLA recommends then reducing non-HDL-C to < 100 to address residual atherogenic risk secondary to elevated levels of triglyceride rich lipoproteins
- Several meta-analyses support both the superiority of non-HDL-C and apoB over LDL-C for both ASCVD risk assessment and for on treatment risk assessment

Non-HDL-C Recommendations

- ACC/AHA Risk Assessment Working Group
  - As no RCT's were identified that titrated drug therapy to specific non-HDL-C goals, no recommendation for or against the use of non-HDL-C goals was made
- National Lipid Associated Patient-Centered Dyslipidemia Management Recommendations
  - Non-HDL-C and LDL-C are the primary targets of therapy
    - When a patient is treated to his/her non-HDL-C goal, the LDL-C goal will almost always be attained, but the converse is less likely to be true, i.e., many patients treated to LDL-C goal will not have attained their non-HDL-C goal
- 2018 AHA Cholesterol Guideline
  - In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C ≥70 mg/dL or a non-HDL-C level of ≥100 mg/dL, it is reasonable to add a PCSK9 inhibitor following a clinician-patient discussion

Apolipoprotein B

- Present in all atherogenic particles, such as LDL, IDL, VLDL, and Lp(a)
- Less affected by TG and can be accurately measured in samples from fasting and nonfasting individuals
- Is currently classified as a risk enhancer for patients at intermediate risk for ASCVD, according to the 2018 AHA/ACC Multi-Society Cholesterol Guideline
- Not yet formally standardized
- 2018 AHA/ACC Multi-Society Cholesterol Guideline states that measurement of apoB can be considered if the presence of risk-enhancing factors would alter management, and a relative indication for measurement of apoB is present for TG > 200 mg/dL

ESC on Apolipoprotein B

- Considering the potential inaccuracy of LDL-C in dyslipidaemia, among patients with DM or high TG levels, and in patients with very low LDL-C levels, ***measurement of both ApoB and non-HDL-C is recommended as part of routine lipid analysis for risk evaluation in patients with elevated plasma TG***
  - With a preference over non-HDL-C in "people with high TG levels, DM, obesity, or very low LDL-C levels"

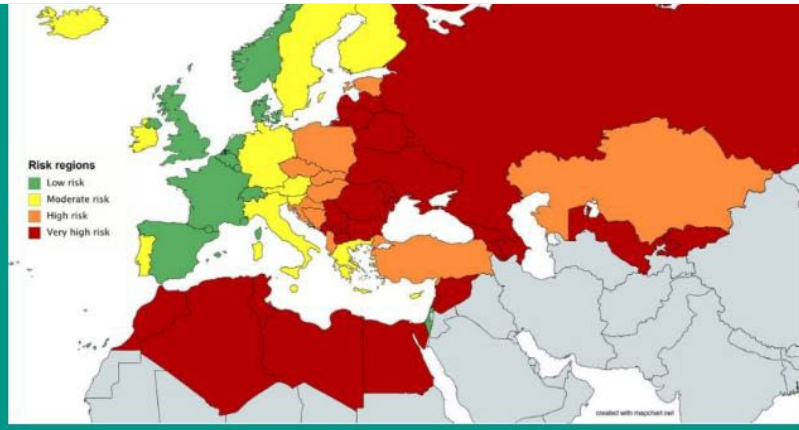
- Goals for lowering have been made my inference and not studied in RCTs
  - Very High < 65 High < 80 and Moderate < 100

Other ESC Goals

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on wholegrain products, vegetables, fruit, and fish.
Physical activity	3.5–7 h moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m^2, and waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg.[a]
LDL-C	**Very-high risk in primary or secondary prevention:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-lowering therapy. Current LDL-lowering treatment: an increased treatment intensity is required. **High risk:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL). **Moderate risk:** A goal of <2.6 mmol/L (<100 mg/dL). **Low risk:** A goal of <3.0 mmol/L (<116 mg/dL).
Non-HDL-C	Non-HDL-C secondary goals are <2.2, 2.6, and 3.4 mmol/L (<85, 100, and 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively.
ApoB	ApoB secondary goals are <65, 80, and 100 mg/dL for very-high-, high-, and moderate-risk people, respectively.
Triglycerides	No goal, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<53 mmol/mol).

ESC Risk Assessment

Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.



Risk of geographic region: Low risk | Moderate risk | High risk | Very high risk

Gender: Male | Female

Age: 40 - 69 years

Current smoking

Systolic blood pressure: 100 - 200 mmHg

mmol/L | mg/dL

Total cholesterol: 3 - 9 mmol/L

HDL-cholesterol: 0.7 - 2.5 mmol/L

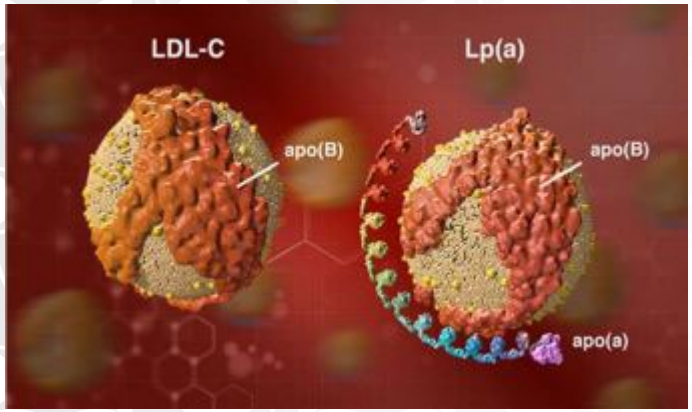
LDL-cholesterol: 0.1 - 9 mmol/L

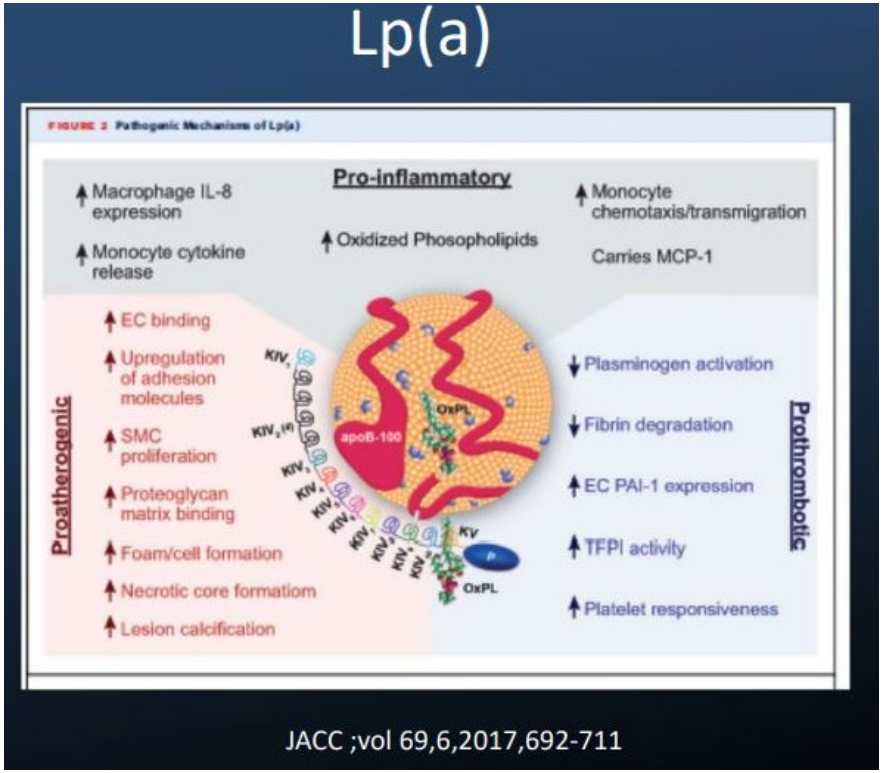
NLA Apo B Goals

- ApoB < 80 mg/dL for high-risk patients and < 90 mg/dL in primary prevention
- Did not specify a level of apoB to begin statin therapy in primary prevention and no specific recommendation was made for very high-risk patients other than the presumption that lower was better
- ApoB >110 mg/dl corresponds approximately to an LDL-C of 140-150 mg/dL in the United Kingdom (UK) Biobank or Framingham Study data

Lipoprotein (a)

- LDL particle that contains Apo-B-100 and apolipoprotein A
- Independent risk factor for ASCVD
- Typically genetically determined
  - Elevations can also be seen with:
    - Low estrogen levels, sever hypothyroidism, CKD, nephrotic range proteinuria
- Not standardized
  - Variability in measurement





Lipoprotein (a)

- Epidemiological, meta-analyses, mendelian randomization, and genome-wide association studies demonstrate that genetically elevated Lp (a) leads to higher risk for cardiovascular disease events, particularly acute myocardial infarction
- When do I measure it?
- ACC/AHA
  - No recommendations made
  - If Lp(a) testing are available to the clinician, a level of ≥ 50 mg/dL can be considered a risk-enhancing factor
- EAS/ESC Guidelines, NLA, and UK
  - At least once in an individual's lifetime
  - Premature ASCVD (age <55y M, 60y F)
  - Family member with premature ASCVD, esp if traditional risk factors absent
  - Genetic hypercholesterolemia
  - Family history of elevated Lp(a)
  - Recurrent ASCVD despite optimal lipid-lowering therapy
  - Progressive aortic valve stenosis
  - Risk reclassification for intermediate risk patients

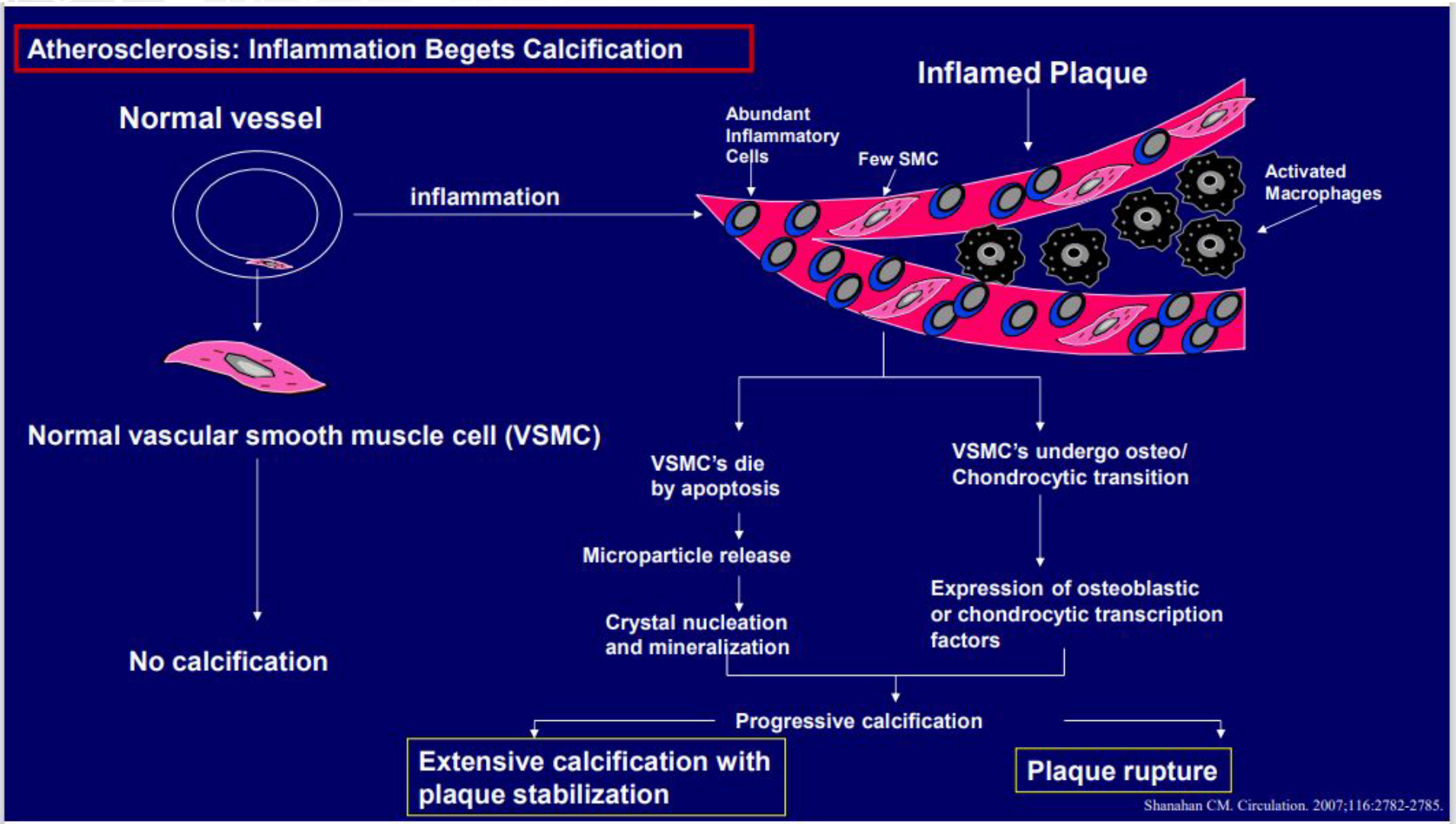
Virani SS et al 2022, in press; Baigent C et al. 2019 ESC/EAS guidelines for management of dyslipidaemias; Wilson DP et al J Clin Lipidol 2019.

Lp(a) Treatment Considerations

Class IIa Recommendation by NLA

- Primary prevention
  - Reasonable to intensify therapies to achieve greater ASCVD risk reduction
- Secondary Prevention
  - Use in addition to LDL and non-HD when considering non-statin therapies
  - FOURIER Trial
    - Addition of evolocumab to the treatment regimen of high risk patients already on high or moderate intensity statin with or without eztemibe showed that the greatest treatment benefit was obtained in those with baseline Lp(a) at or above a clinical threshold of 50 mg/dL as compared with those below the threshold
    - Lp(a) levels were reduced by 27%, however, not clear that reduction contributed independently to the treatment benefit
  - ODYSSEY OUTCOMES
    - Alirocumab use in high/very high risk patients confers the greatest absolute reduction in patients within the highest Lp(a) tertile (> 60 mg/dL)
- Niacin (Class III) has been shown to lower levels but no ASCD reduction
- Hormone replacement therapy in menopausal women (III)

Coronary Artery Calcium Scoring



CACS Indication

- Asymptomatic
- In primary prevention when risk is uncertain or if statin therapy is problematic, it can be helpful to measure CAC to refine risk assessment
- Risk is best refined in your intermediate risk patients
  - Everything goes back to calculating your 10 year ASCVD risk

- A CACS predicts ASCVD events in a graded fashion and is independent of other risk factors
  - 0 — Lowers risk, consider no statin unless DM, family hx of premature CAD, smoker
  - 1-99 — Favor statin, especially after age 55
  - 100 and greater — Statin initiation is indicated

Score of 0

- In asymptomatic patients, it correlates with a 0.1-0.2% annual risk of non-fatal MI, or CHD death over 10 years
- At 5 years of follow up:
  - 54% of patients still had a CACS of 0
  - 23% had CACS 1-9
  - 19% had CACS 10-50
  - 4% had CACS > 50
- In symptomatic patients with CACS 0 referred for evaluation of myocardial ischemia, 16% have inducible ischemia by PET scanning

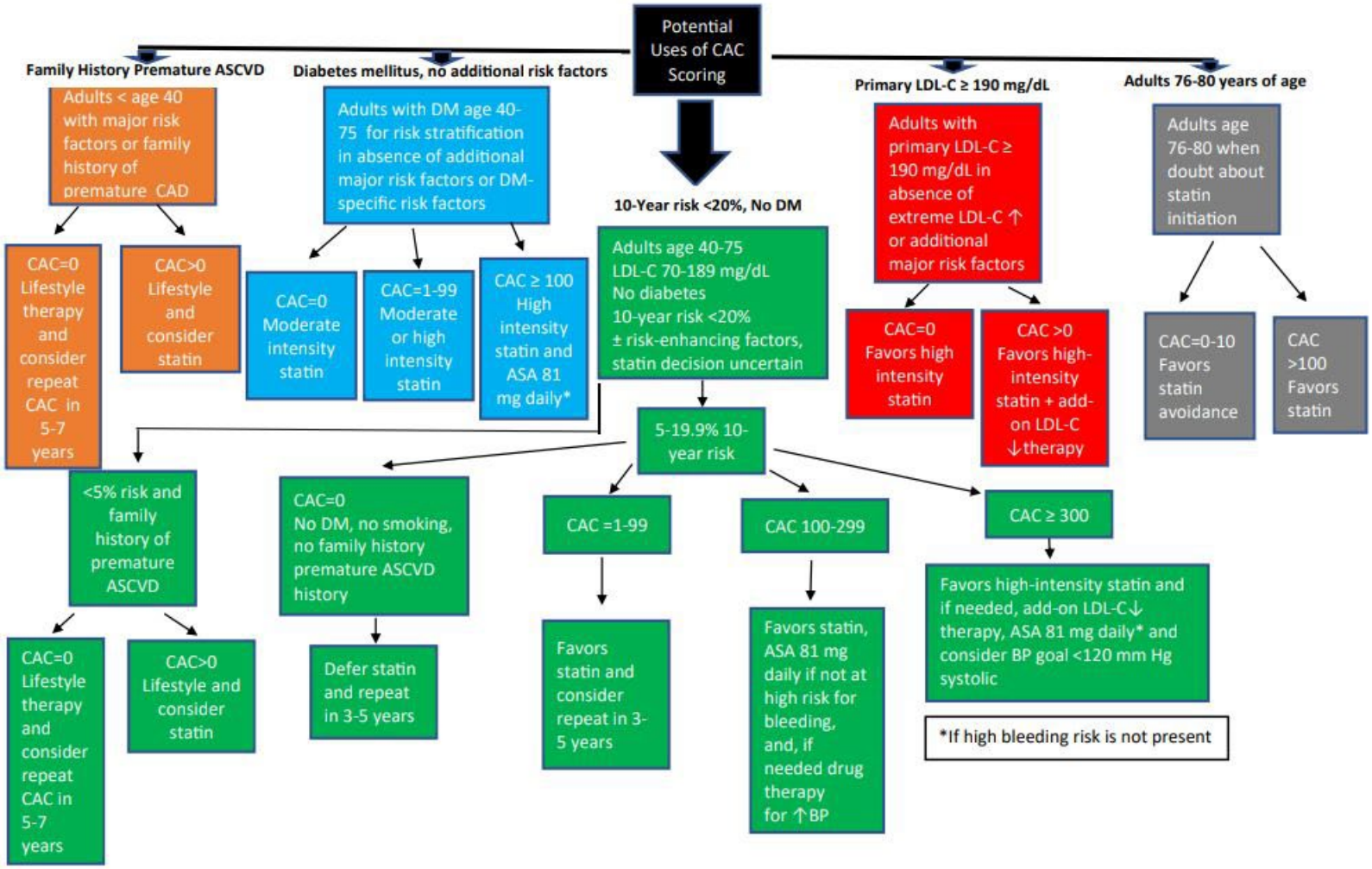
Mieres JH at al. Circulation 2005;111:682-696.
Blaha M et al. J Am Coll Cardiol Img 2009;2:692-700.
Gopal A et al. Int J Cardiol 2006;117:227-231.

CACS ≥ 100

- 5534 Multi-Ethnic Study of Atherosclerosis participants on no lipid-altering drugs were classified based upon CACS and baseline lipids, with a median follow-up of 7.6 years
- 256 hard CHD events occurred
  - Those with any coronary calcium accounted for 79% of the events
  - 50% of events occurred in the 21% of subjects with CACS ≥100 units
- When taking follow-up duration into account, the absolute event rate for those with CACS ≥100 was 16.9 per 1000 patient-years
  - 1.69% per year or ~18% over 10 years

Martin SS et al. Circulation 2014;129:77-86

CACS Treatment Algorithm



Who should get further testing?

- 3 coronary involvement confers high risk than single coronary involvement.
- When left main contributes to > 25% of the total score, this confers higher risk than just what the total score does.
- "More diffuse regional distribution of CAC or high left main CAC involvement should generally be viewed as an additional factor favoring more aggressive preventive pharmacotherapy. ***It should not routinely trigger downstream stress testing in those asymptomatic individuals who report a normal functional capacity***"
- "The presence of advanced left main coronary calcification should only prompt further workup (stress testing, cardiac catheterization) in the presence of ***concomitant clinically relevant cardiovascular symptoms***."

Who should get further testing?

- "There are no data to support the benefit of coronary angiography in asymptomatic individuals with high CAC scores, including those demonstrated to have an ischemic response to exercise testing."

- ISCHEMIA Trial
  - 5179 subjects with stable CAD showed no benefit on cardiovascular outcomes of an initial invasive strategy and medical therapy versus an initial conservative strategy of medical therapy alone and coronary angiography if medical therapy fails.

Incidental Coronary Calcification

- Should be reported as mild, moderate, or heavy/severe
- Mild– get a dedicated CACS
- Moderate or severe– correlates to a score ≥ 100 and indicates benefit from statin

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Questions?