Heart Disease from a 22nd Century Perspective: How Can We Predict the Future Now?

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“An ounce of prevention is worth a pound of cure.”

Benjamin Franklin

“Traditional” Risk Factors

What we already know

- Age
- Smoking
- Dyslipidemia (High LDL, Low HDL)
- Family History
- DMII
- Obesity

The Future of Risk Factors

What we will know

- hsCRP
- LpPLA2
- Advanced Lipid Panels (**Lp(a)**, Apolipoprotein B, etc), ADMA
- CAC/CCTA (with FFR)
- Mental health (stress) awareness

So who actually has heart attacks?

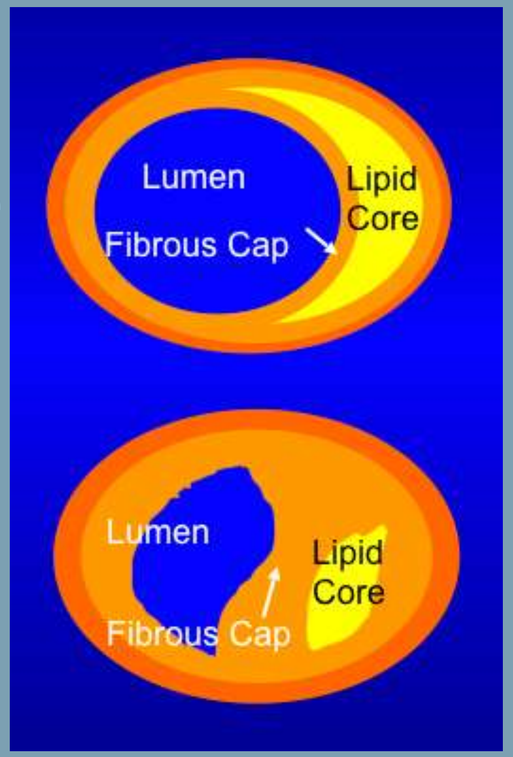
Significant CAD v. mild CAD

It is not necessarily the percentage that matters

- Significant CAD from a common sense standpoint (general population can understand) is BAD
- <50% occlusions causing MI
- Plaque composition and inflammation are key determinants

Vulnerable v. Stable Atherosclerotic Plaques

Vulnerable Plaque



- Thin fibrous cap
- Inflammatory cell infiltrates:

proteolytic activity

- Lipid-rich plaque

Stable Plaque

- Thick fibrous cap
- Smooth muscle cells: more extracellular matrix
- Lipid-poor plaque

CAC v. CCTA

Which would YOU choose?

- Risk analysis v. overall analysis
- ONLY analyzes calcium
- Which is the biggest threat- calcium or lipid-rich plaque?

“A CAC Score of 0 Is Not a Clean Bill of Heart Health”

But how old ARE you?!

- Danish (Western Denmark Hart Study) study evaluated 23,759 symptomatic patients
- Among patients with obstructive CAD on CCTA, the prevalence of a ZERO CAC score fell with increasing age
  - meaning, the younger we are, the more likely we are to potentially have CAD with a normal CAC
    - **<u>Prevalence of zero calcium score with obstructive CAD confirmed with CCTA:</u>**
      - 58% of people younger than 40
      - 34% of those aged 40-49
      - 18 of those ages 50-59
      - 9% aged 60-60 and 5% aged 70 and older
  - Concluded “Thus, a strategy that uses a CAC score of 0 to rule out obstructive CAD in all symptomatic patients will likely miss a sizable proportion of younger patients with obstructive CAD”

JAMA Cardiology

Source Reference: Bødtker Mortensen M, et al "Association of age with the diagnostic value of coronary artery calcium score for ruling out coronary stenosis in symptomatic patients" JAMA Cardiol 202

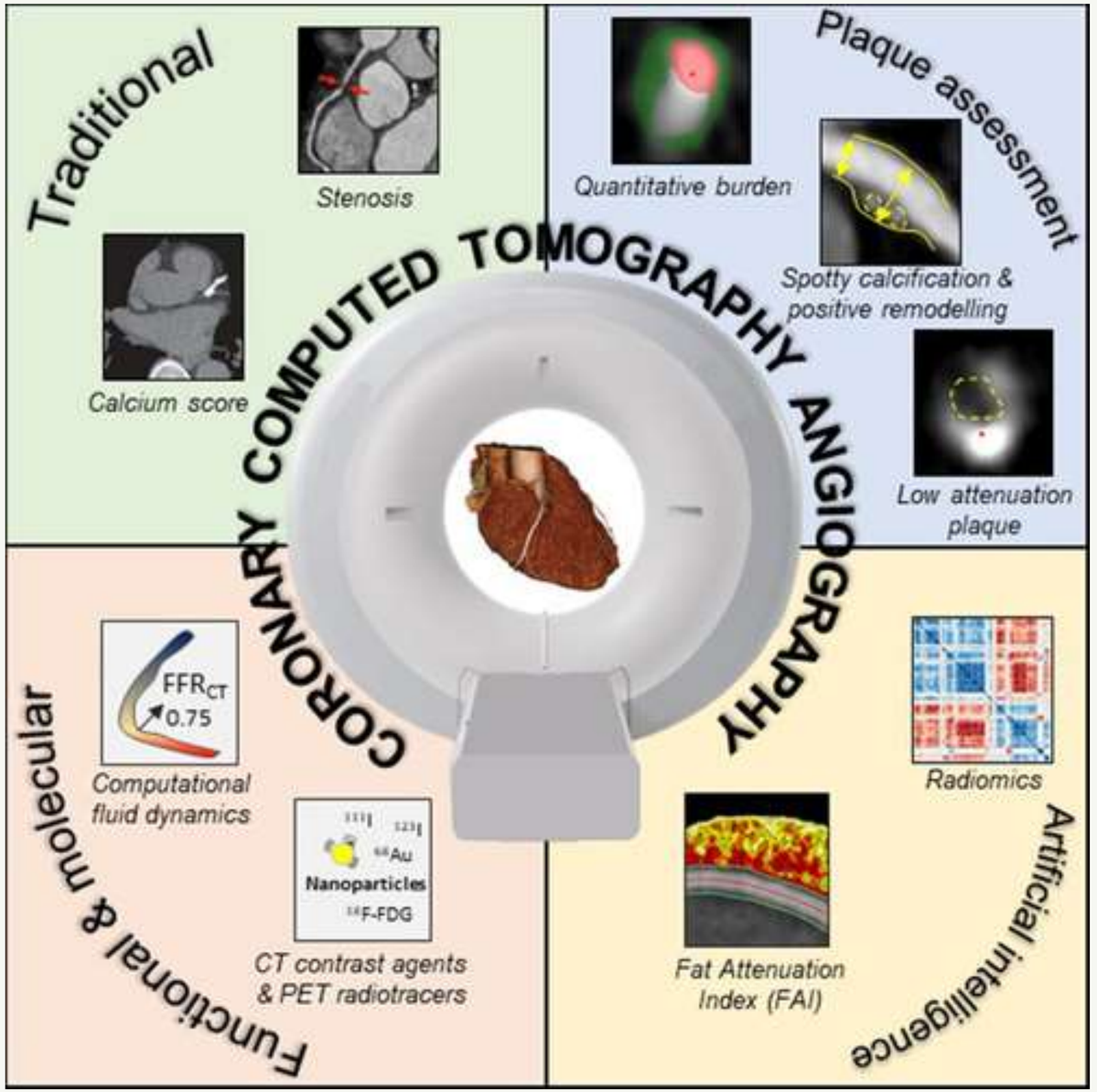
But there’s more…

- “Prevalence of Subclinical Coronary Artery Atherosclerosis in the General Population
  - Circulation, Sept 2021
  - 30,154 random individuals 50-69 years
    - without known CAD
    - 50.6% women!
    - ANY CCTA-detected atherosclerosis was found in 42.1%
    - High CAC scores convey a significant probability of “substantial stenosis” and 0 CAC does *not* exclude atherosclerosis

20 Sep 2021https://doi.org/10.1161/CIRCULATIONAHA.121.055340Circulation. 20

CCTA additions

because why have less when you can have more?



https://www.ahajournals.org/doi/10.1161/ATVBAHA.119.312899

Conclusion

- CAC more helpful in older population
- CAC for risk factor stratification, not for the dx of obstructive CAD causing symptoms
- CCTA should be considered in younger population with concern of CAD/ multiple risk factors

Example 1

- Patient D.J. - 42 years old with unrelenting fatigue—-yes, fatigue!
- CAC with PCP was zero
- Labs revealed LDL of 131. No family hx of coronary disease. No HTN. Non-smoker.
- Based upon index of suspicion, CCTA ordered

Findings:

The study quality: Diagnostic.

Coronary circulation is right dominant.

Left main coronary artery:
The left main coronary artery is of average length and large caliber.
No plaques in the left main.
The left main bifurcates in to the LAD and left circumflex coronary artery.

Left anterior descending coronary artery:
The LAD is a long artery of large caliber. It gives origin to diagonal and septal perforator branches.
Lipid density eccentric noncalcified plaque in the ostium of the LAD causing 10-20% obstruction.
Appearance of a ruptured plaque in the mid LAD causing critical obstruction and appears at least subtotally occluded. No plaques noted in the distal LAD/diagonal branches.

Left circumflex coronary artery:
The left circumflex is a large caliber artery of average length. It gives origin to obtuse marginal branches.
No plaques noted in the proximal circumflex.
The large caliber first obtuse marginal branch contains noncalcified plaque in the ostium and appears at least subtotally occluded.

Right coronary artery:
The RCA is a long artery of large caliber. It gives origin to the conus artery, acute marginal branches, the posterior descending artery and posterolateral ventricular branch.
No plaques in these branches.

Take home point #1

Prevention!

2021 ESC Prevention Guidelines- Changes…

- Major risk factors essentially remain the same
- Psychosocial stressors and air pollution are now recognized as being associated with ASCVD
  - Stress-management is reiterated multiple times
- CKD is an independent risk factor for ASCVD
- “Lower is better”
  - Proportional decrease in risk with LDL reduction
    - DMII with Established CAD patients goal LDL < 55mg/dL
- Big focus on new DMII medications SGLT-2 and GLP-1’s as first line (improve CV outcomes +/- weight loss)

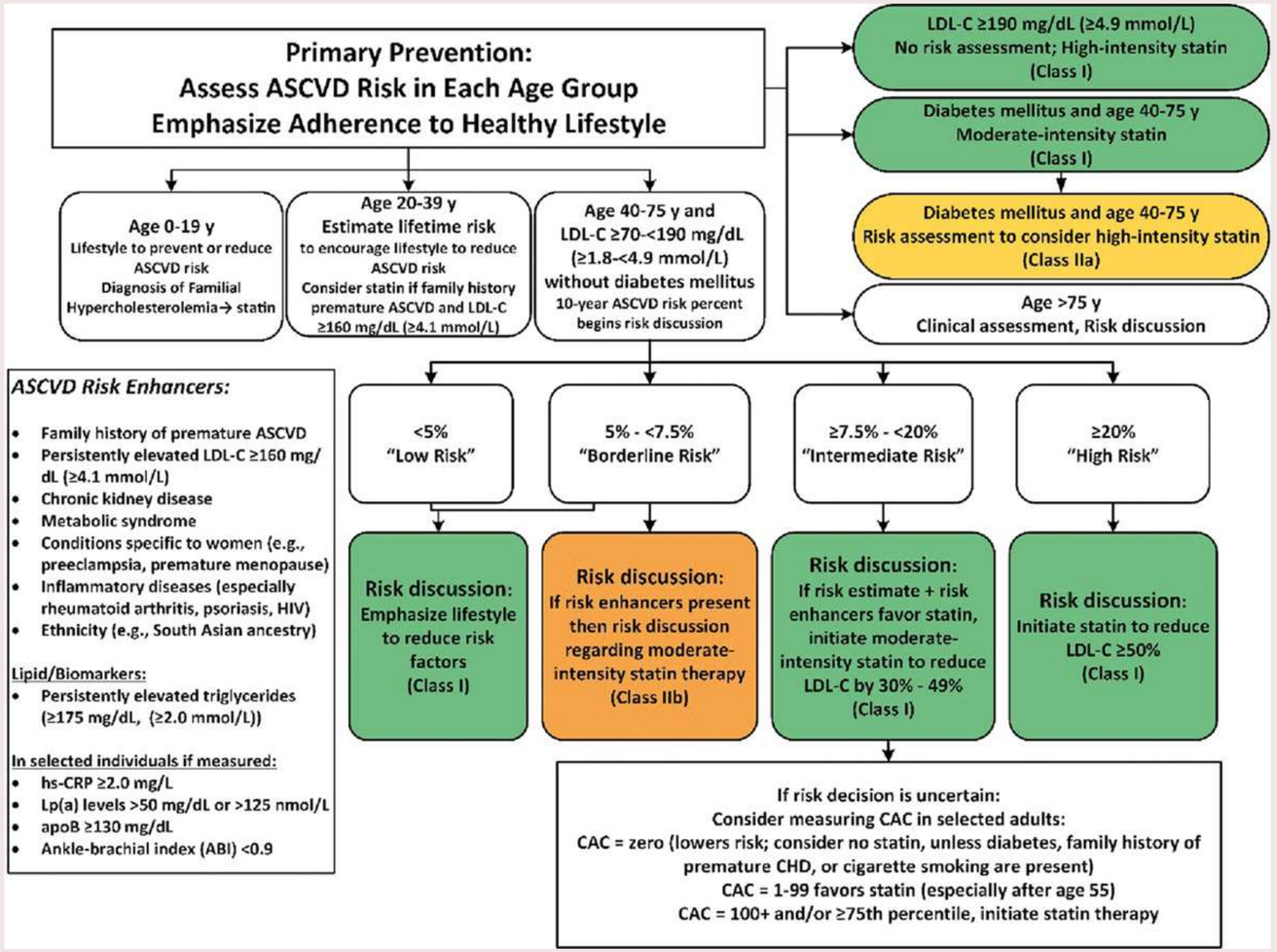
Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, H

Advancing the data…

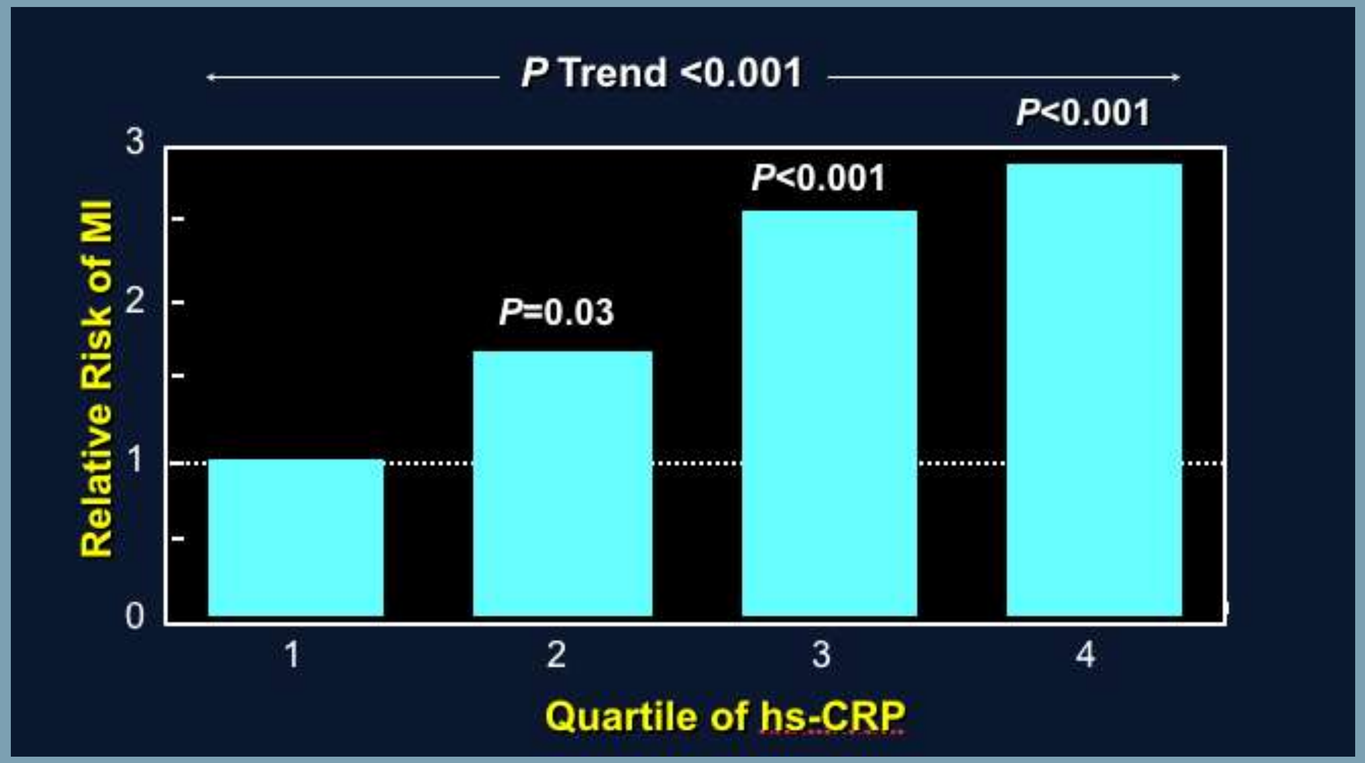
CRP v. hsCRP

- CRP is an acute-phase protein produced by the liver in response to cytokine production during tissue injury, inflammation or infection
- Standard CRP- determine levels which are increased up to 1,000 fold in response to infection or tissue destruction but can not adequately assess the normal range
- hsCRP- detect levels of CRP within the normal range, levels proven to predict future CV events

ACC/AHA Primary Prevention Guidelines 2019



hs-CRP risk of MI in “healthy” Men



Ridker et al, *N Engl J Med.* 1997;336:973–979.

What is the major problem?

Inflammation!

- **<u>Inflammation</u>**
  - endothelial dysfunction
  - Obesity
  - DMII
  - Smoking

Effects of Weight Loss on CRP in obese “healthy” women

O-O-O- Ozempic!

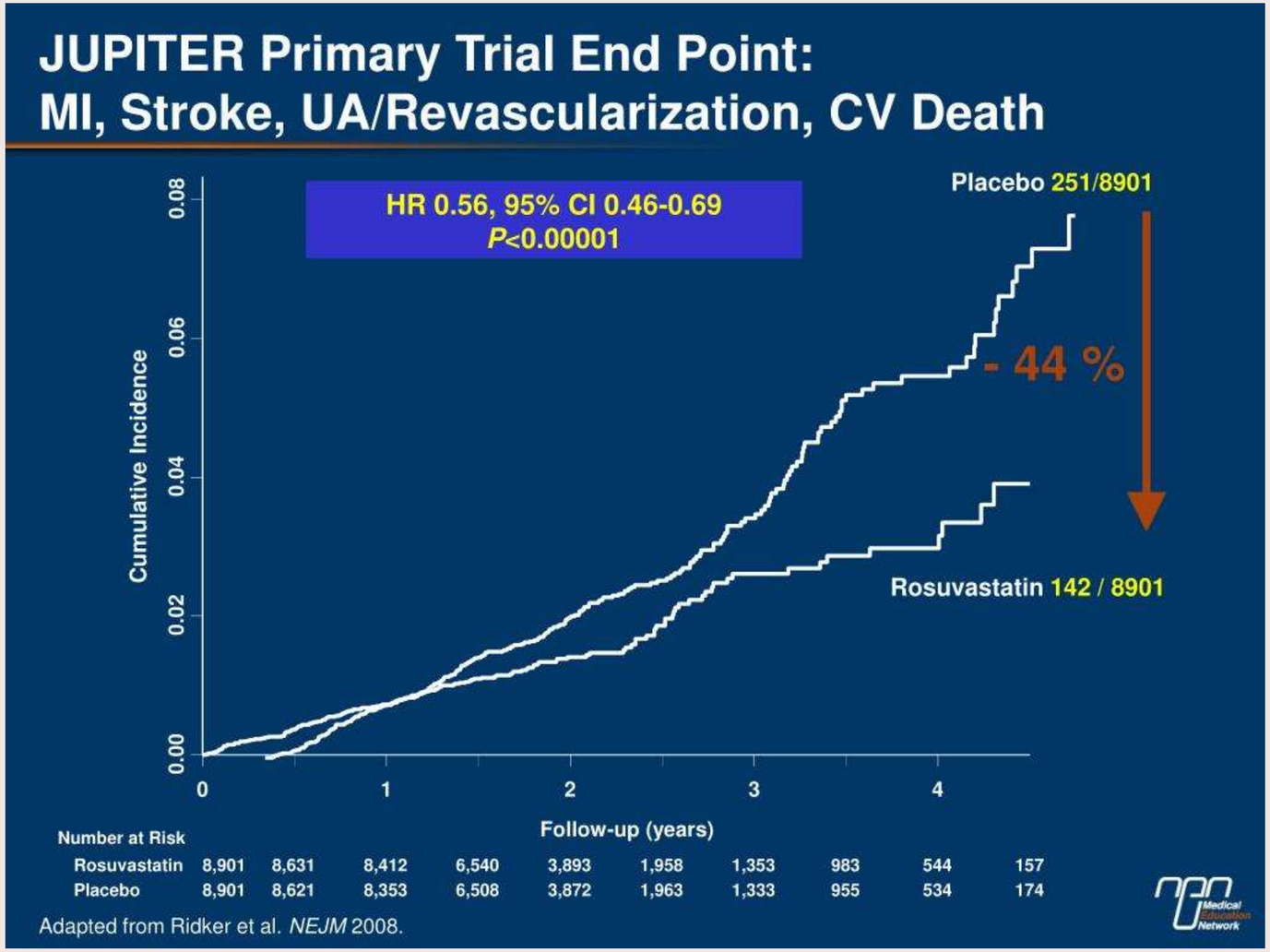
- 83 women (mean BMI 33.8) placed on very low fat diet for 12 weeks
- CRP reduced by 26%
- Average weight loss 7.9 kg
- Change in CRP assoc with change in TC, but not LDL, HDL or glucose; highly correlated with triglycerides

Heilbronn LK et al. *Arterioscler Thromb Vasc Biol* 2001;21:968-970.

Remember—Jupiter Trial?

- Patients with low to normal LDL who were considered increased CV risk due to elevated CRP who did not require statin treatment based on guideline therapy
- 44% reduction in primary endpoint for 20mg Rosuvastatin v. placebo
- 20% reduction in total mortality

Jupiter Trial



LpPLA-2

- "PLAC test"
  - lipoprotein-associated phospholipase A2
    - An enzyme that breaks down oxidized low-density lipoprotein in the vascular wall.
    - High levels are thought to promote atherosclerotic plaque burden

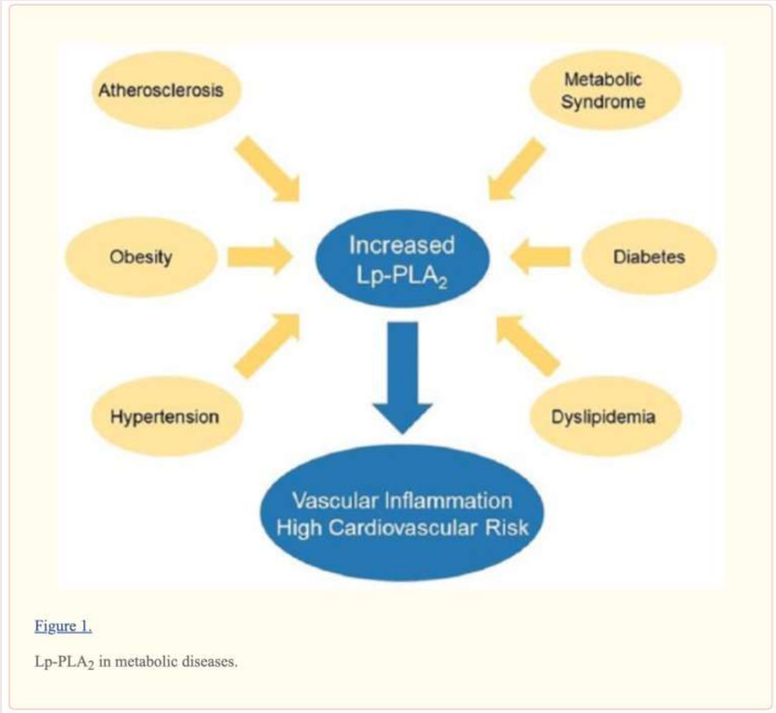
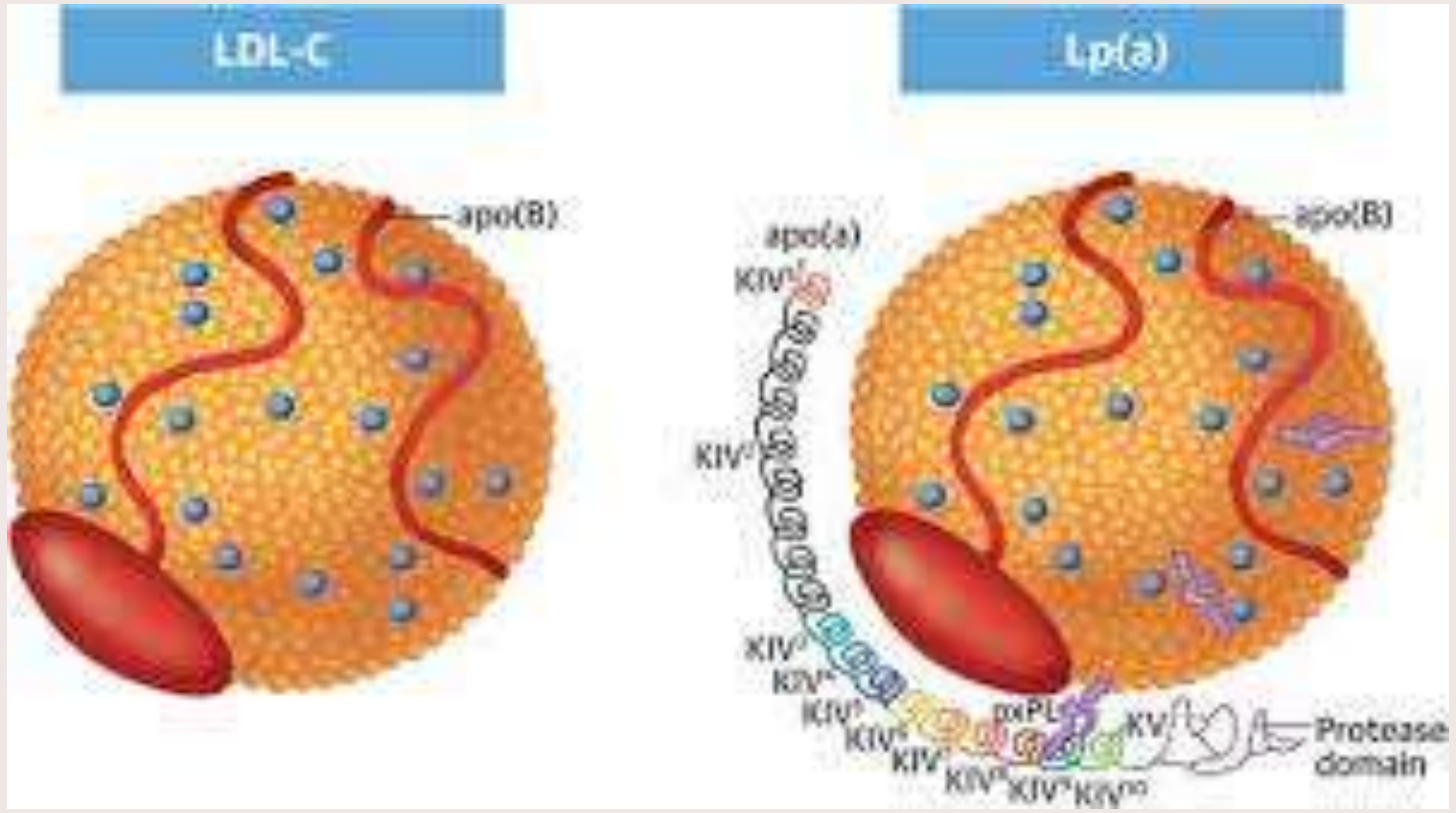


Figure 1.

Lp-PLA_2 in metabolic diseases.

Lipoprotein (a)

- Very atherogenic
- Increased risk of myocardial infarction
- people born with elevated lp(a) have 2-4x increased risk of CAD
- independent risk factor for CAD
- Mostly genetic



- INTERHEART trial- Lp(a) > 50 mg/dL assoc with increased risk of MI (p<0.001)

Lipoprotein (a)

continued…

- Association of Lipoprotein(a) wWith Atherosclerotic Plaque Progression
  - JACC, 01/2022k
  - 191 patients (80% male..grrrr..) with advanced stable CAD
  - median Lp(a) 100 mg/dL
  - no difference in CAD or plaque burden at baseline
  - Patients with high Lp(a) showed accelerated progression of low-attenuation plaque (necrotic core) compared with low Lp(a) patients
  - Conclusion: This may explain (the above) the association between Lp(a) and the high residual risk of myocardial infarction, providing support for Lp(a) as a treatment target in atherosclerosis

J Am Coll Cardiol. 2022 Jan, 79 (3) 223–233

Apolipoprotein B

- B= bad!
- A measure of non-HDL particles per volume
- ApoB plays a central role in carrying cholesterol and trigs *from* liver *to* utilization and storage sites
- VLDL, IDL and LDL each carry one Apo(B) therefore, apo(B) and these lipid values typically correlate (therefore, may have low LDL-C but elevated ApoB
- Cardiovascular risk is assoc more with the number and size of particles, not the concentration of cholesterol in these particles

ADMA

- asymmetric N, N-dimethyl-L-arginine
- competitive inhibitor of NOS (NO synthase) thereby reducing NO production and promoting endothelial dysfunction
- decrease with exercise, therefore more aerobic activity= better endothelial function

Advanced Lipid Profiles

Patient Example

06/2021- 44 yo woman without any medical issues

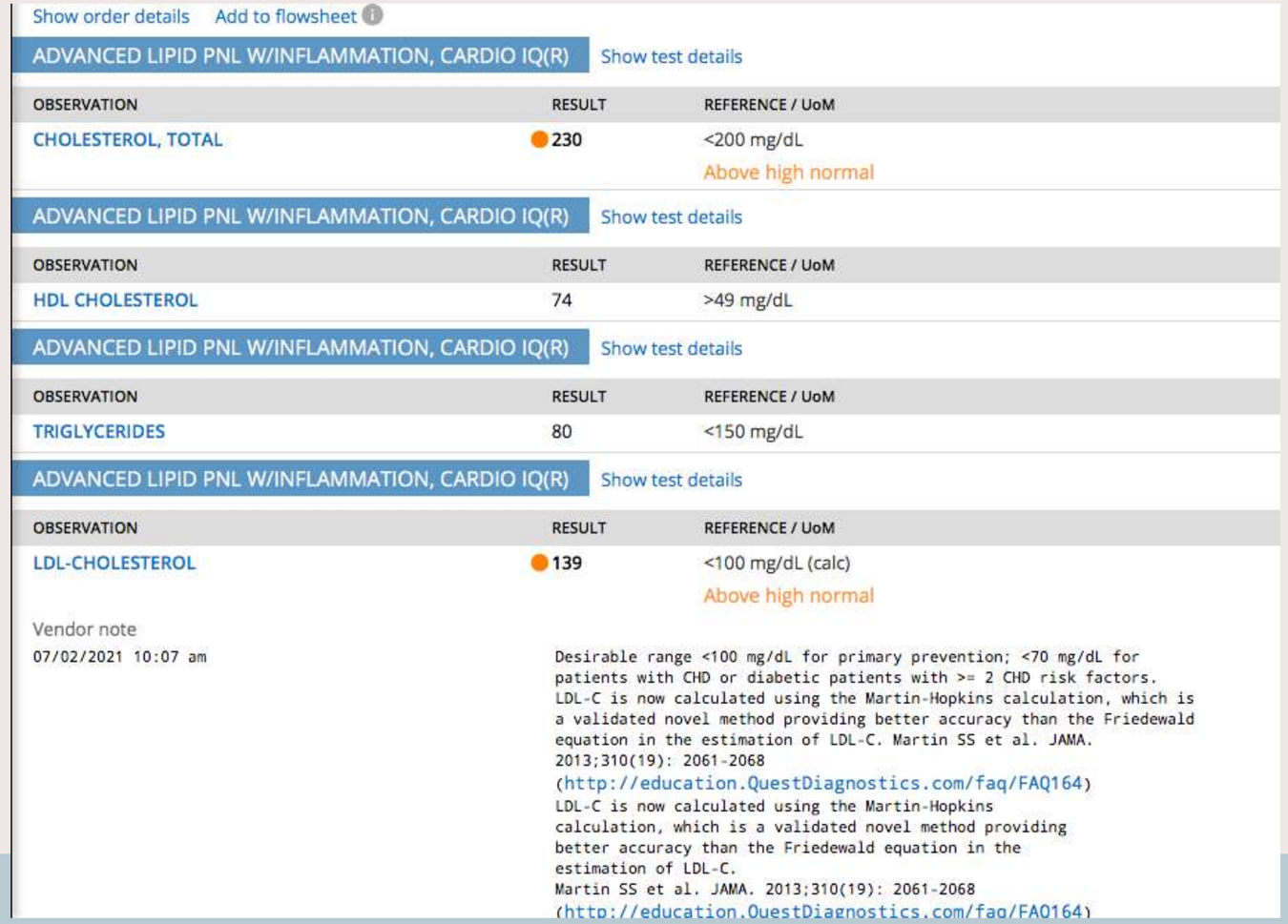
No Family Hx heart disease

Non-smoker

BMI- 25.4

“hx of high lp(a)”

What would you do next?



Show order details Add to flowsheet

ADVANCED LIPID PNL W/INFLAMMATION, CARDIO IQ(R) Show test details

OBSERVATION	RESULT	REFERENCE / UoM
CHOLESTEROL, TOTAL	230	<200 mg/dL
		Above high normal

ADVANCED LIPID PNL W/INFLAMMATION, CARDIO IQ(R) Show test details

OBSERVATION	RESULT	REFERENCE / UoM
HDL CHOLESTEROL	74	>49 mg/dL

ADVANCED LIPID PNL W/INFLAMMATION, CARDIO IQ(R) Show test details

OBSERVATION	RESULT	REFERENCE / UoM
TRIGLYCERIDES	80	<150 mg/dL

ADVANCED LIPID PNL W/INFLAMMATION, CARDIO IQ(R) Show test details

OBSERVATION	RESULT	REFERENCE / UoM
LDL-CHOLESTEROL	139	<100 mg/dL (calc)
		Above high normal

Vendor note
07/02/2021 10:07 am

Desirable range <100 mg/dL for primary prevention; <70 mg/dL for patients with CHD or diabetic patients with >= 2 CHD risk factors.
LDL-C is now calculated using the Martin-Hopkins calculation, which is a validated novel method providing better accuracy than the Friedewald equation in the estimation of LDL-C. Martin SS et al. JAMA. 2013;310(19): 2061-2068
(http://education.QuestDiagnostics.com/faq/FAQ164)
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Martin SS et al. JAMA. 2013;310(19): 2061-2068
(http://education.QuestDiagnostics.com/faq/FAQ164)

06/2021

OBSERVATION	RESULT	REFERENCE / UoM	DATE/STATUS	PHR	SIGNED
LDL PARTICLE NUMBER	1791	<1138 nmol/L Above high normal	07/02/2021 10:04 am	OFF	
Vendor note 07/02/2021 10:07 am	Relative Risk: Optimal <1138; Moderate 1138-1409; High >1409. Reference Range: <1138 nmol/L.				
LDL SMALL	230	<142 nmol/L Above high normal	07/02/2021 10:04 am	OFF	
Vendor note 07/02/2021 10:07 am	Relative Risk: Optimal <142; Moderate 142-219; High >219. Reference Range: <142 nmol/L.				
LDL MEDIUM	282	<215 nmol/L Above high normal	07/02/2021 10:04 am	OFF	
Vendor note 07/02/2021 10:07 am	Relative Risk: Optimal <215; Moderate 215-301; High >301. Reference Range: <215 nmol/L.				
HDL LARGE	11664	>6729 nmol/L	07/02/2021 10:04 am	OFF	
Vendor note 07/02/2021 10:07 am	Relative Risk: Optimal >6729; Moderate 6729-5353; High <5353. Reference Range: >6729 nmol/L.				
LDL PATTERN	A	A Pattern	07/02/2021 10:04 am	OFF	
Vendor note 07/02/2021 10:07 am	Relative Risk: Optimal Pattern A; High Pattern B. Reference Range: Pattern A.				
LDL PEAK SIZE	226.1	>222.9 Angstrom	07/02/2021 10:04 am	OFF	
Vendor note 07/02/2021 10:07 am	Relative Risk: Optimal >222.9; Moderate 222.9-217.4; High <217.4. Reference Range: >222.9 Angstrom. Adult cardiovascular event risk category cut points (optimal, moderate, high) are based on an adult U.S. reference population plus two large cohort study populations. Association between lipoprotein subfractions and cardiovascular events is based on Musunuru et al. ATVB.2009;29:1975. For additional information, please refer to http://education.QuestDiagnostics.com/faq/FAQ134 (This link is being provided for informational/educational purposes only.) This test is performed by an Ion Mobility method. This test was developed and its performance characteristics determined by The Cleveland HeartLab, Inc. It has not been cleared or approved by the U.S. FDA. The Cleveland HeartLab is regulated under Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research.				

ADVANCED LIPID PNL W/INFLAMMATION, CARDIO IQ(R) Show test details

OBSERVATION	RESULT	REFERENCE / UoM	DATE/STATUS	PHR	SIGNED
APOLIPOPROTEIN B	110	<90 mg/dL Above high normal	07/02/2021 10:04 am	OFF	

Vendor note
07/02/2021 10:07 am

Risk: Optimal <90 mg/dL; Moderate 90-119 mg/dL; High >= 120 mg/dL;
Cardiovascular event risk category cut points (optimal, moderate,
high) are based on National Lipid Association recommendations-
Jacobson TA et al. J of Clin Lipid. 2015; 9: 129-169 and Jellinger PS
et al. Endocr Pract. 2017;23(Suppl 2):1-87.

ADVANCED LIPID PNL W/INFLAMMATION, CARDIO IQ(R) Show test details

OBSERVATION	RESULT	REFERENCE / UoM	DATE/STATUS	PHR	SIGNED
LIPOPROTEIN (a)	307	<75 nmol/L Above high normal	07/02/2021 10:04 am	OFF	

Vendor note
07/02/2021 10:07 am

Risk: Optimal <75 nmol/L; Moderate 75-125 nmol/L; High >125 nmol/L.
Cardiovascular event risk category cut points (optimal, moderate,
high) are based on Tsimika S. JACC 2017;69:692-711.

ADVANCED LIPID PNL W/INFLAMMATION, CARDIO IQ(R) Show test details

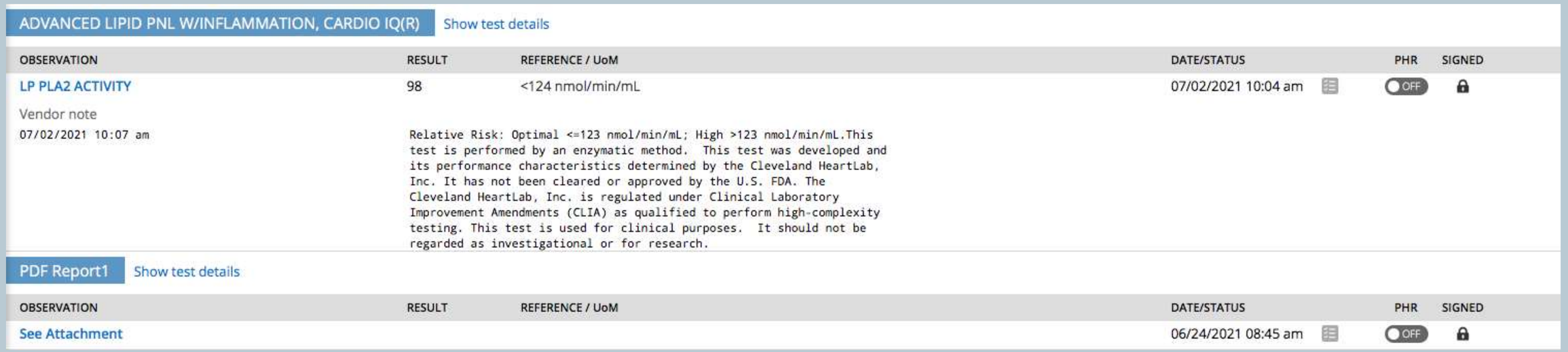
OBSERVATION	RESULT	REFERENCE / UoM	DATE/STATUS	PHR	SIGNED
HS CRP	0.6	<1.0 mg/L	07/02/2021 10:04 am	OFF	

Vendor note
07/02/2021 10:07 am

The AHA/CDC Guidelines recommend hs-CRP ranges for identifying
Relative Cardiovascular Risk in patients ages >17 years: <1.0 mg/L
Lower Relative Cardiovascular Risk; 1.0-3.0 mg/L Average Relative
Cardiovascular Risk; 3.1-10.0 mg/L Higher Relative Cardiovascular
Risk. For patients with higher cardiovascular risk, consider retesting
in 1-2 weeks to exclude a benign transient elevation secondary to
infection or inflammation from the baseline CRP value. Persistent
elevations of >10.0 mg/L upon retesting may be associated with
infection and inflammation. The AHA/CDC recommendations are based on
Pearson TA et al. Circulation. 2003;107:499-511.

For ages >17 Years:

hs-CRP mg/L	Risk According to AHA/CDC Guidelines
<1.0	Lower relative cardiovascular risk.
1.0-3.0	Average relative cardiovascular risk.
3.1-10.0	Higher relative cardiovascular risk. Consider retesting in 1 to 2 weeks to exclude a benign transient elevation in the baseline CRP value secondary



ADVANCED LIPID PNL W/INFLAMMATION, CARDIO IQ(R) Show test details

OBSERVATION	RESULT	REFERENCE / UoM	DATE/STATUS	PHR	SIGNED
LP PLA2 ACTIVITY	98	<124 nmol/min/mL	07/02/2021 10:04 am	OFF	

Vendor note

07/02/2021 10:07 am

Relative Risk: Optimal <=123 nmol/min/mL; High >123 nmol/min/mL.This test is performed by an enzymatic method. This test was developed and its performance characteristics determined by the Cleveland HeartLab, Inc. It has not been cleared or approved by the U.S. FDA. The Cleveland HeartLab, Inc. is regulated under Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research.

PDF Report1 Show test details

OBSERVATION	RESULT	REFERENCE / UoM	DATE/STATUS	PHR	SIGNED
See Attachment			06/24/2021 08:45 am	OFF	

Now what would you do? Anything different?

CCTA 09/2021

Findings:

The study quality: Diagnostic.

Coronary circulation is right dominant.

Left main coronary artery:
The left main coronary artery is short and large caliber.
Small eccentric noncalcified plaque in the distal left main causing less than 10% obstruction.
The left main bifurcates in to the LAD and left circumflex coronary artery.

Left anterior descending coronary artery:
The LAD is a long artery of large caliber. It gives origin to diagonal and septal perforator branches.
No plaques in these branches.

Left circumflex coronary artery:
The left circumflex is a large caliber artery of average length. It gives origin to obtuse marginal and posterolateral ventricular branches.
No plaques in these branches.

Right coronary artery:
The RCA is a long artery of moderate caliber. It gives origin to the conus artery, acute marginal branches and the PDA.
Noncalcified plaque at the ostium of the RCA causing obstruction in the range of 30-40%. No additional plaques noted in the rest of the RCA/PDA.

Now what would you do?

Treatment Strategies

Is not just statins, ya know.

- Medications—which meds work on what?
  - Statins
  - PCSK9 inhibitors
  - Bempedoic Acid (Nexlitol/ Nexlizet)- a new fav
  - Inclisiran
- Appropriate diabetes management
- Low-dose Colchicine- new!
- **Preventive measures**
  - weight loss, reduction of inflammation and focus on mental health
  - promote a heart-healthy diet (mediterranean or vegan)

Take Home Points

- The more information the better
- Communicate and explain to patient she importance of decreasing inflammation. Sometimes, the visualization of CAD on CCTA is all it takes
- Don’t be afraid of new tests and diagnostic studies to help prevent heart disease
- Educate Educate Educate! WEIGHT LOSS- Obesity is NOT healthy!
- Use tools to help patients visualize and understand
- Take the time to explain the benefits of exercise, diet and pharmacotherapy

In 20 years from now, will you wish that you had done something sooner?

“Prepare and prevent, don’t repair and repent”.

Author unknown