Tip of the Iceberg: There is a REVOLUTION in Preventive Cardiology

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Disclosures

- Nothing to Disclose

Objectives

- **What is a vulnerable plaque** and how does that relate to cardiovascular risk?
- What can "modern" imaging tell us about cardiovascular risk
- What can we do ourselves to address cardiac risk
- What new targets are available to address cardiac risk

Adaptability

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Greensboro News & Record | Advice, Comics, TV, Hot Line | Wednesday, May 13, 1987

HEART ATTACK: 'At first it was hard for me to say the words in connection with myself'

By MARTHA LONG
Staff Writer

Some things about that evening are hazy, as if bandaged with a layer of gauze, and some are very clear. The clearest things don't deal with medical science, but with me.

Mental reconstruction brings a chuckle or two now, although a heart attack isn't an amusing occurrence by any stretch of the imagination. Human nature, however, often is.

I am not unacquainted with the practice of prayer, and that evening I said several silent ones. But in typical human fashion, my realization that control was not in my hands alternated with belief that it was. So in spite of the knowledge that, even with expert medical attention, my next breath was not guaranteed, I assumed my next column was. Surely this was something to write about, and I tried to think of a really good lead.

Actually, not one word came to me in spite of the fact that I was experiencing medical marvels first hand. And that brought on feelings of inferiority. I must have misspent the greater part of my life; I must have been in the wrong profession all this time.

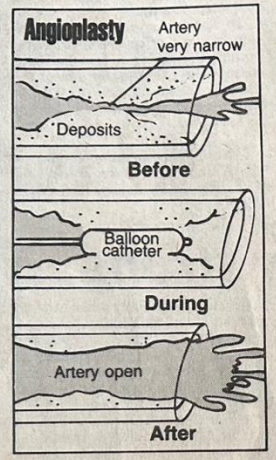
Time.

I was so aware of it — far beyond the minutes that ticked away on the wall clock above me. The clock and the people in the room were the only things there that didn't fit my image of something from outer space.

It was a little after 7 p.m. Saturday, Feb. 21, and the room was the cardiac catheterization lab at Moses Cone Hospital. Shortly before, the heart monitor by my hospital bed had sounded its alarm, and I had been whisked to the lab to undergo a non-surgical procedure known as angioplasty.

I would watch as Dr. Tom Stuckey, assisted by Dr. Bruce Brodie, carried out the procedure. When it was over, the blockage in the artery would go from 100 percent to 40 or 50 percent.

For a week or so before, I had noticed an occasional funny feeling in my chest. I was then a moderate smoker, so I decided to cut down on my smoking and, first chance I had, get a chest X-ray.



Margaret Baxter / News & Record

Next I noticed chest pain when I walked my dog, particularly at night. I wrapped a scarf over my mouth and nose to ward off the frigid air.

On Thursday evening when I walked Lady, the pain was sharper. Even though it eased off once I got inside and sat down, I decided to call my doctor.

Dr. Bill Stafford said it sounded like angina. If the pain returned, he would meet me at the hospital. If not, he would see me at his office the next morning. Friday morning he said my EKG looked normal to him, but he'd get a cardiologist to read it. I was given some medication and told to keep in touch.

I worked Friday, then went to a party. After I went to bed, however, I experienced typical angina discomfort for most of the night. Saturday morning, I still felt lousy, but delayed calling the doctor.

About 2 p.m., Dr. Stafford called to check on me. I needed to go to

Martha Long, who writes a soci[illegible] column for the News & Record

things they usually do under those circumstances. Dr. Stuckey said it would be wise to have an angiogram on Monday and to remain there until then. By the time I was moved to a room, I felt pretty good.

I had my dinner and got the 6 o'clock news. Soon, I'd settle down with the book I'd brought. Then suddenly I felt a sharp pain in my chest, and the monitor sounded. In seconds Dr. Stuckey and several nurses were there. I was having a heart attack, and something had to be done about the blocked artery. Angioplasty.

While the doctor was giving me the word and nurses were doing various things, I periodically glanced up at the TV as if to catch up with a show I don't usually watch. Crazy, yet I kept on doing it.

The only thing I was aware of was an image on the screen, but the diversion was my defense mechanism at work. I wasn't ready for this.

As if on a trapeze, a lot of emotional baggage swings trough your mind in such a crisis. Sometimes you want to cry and laugh at yourself at the same time. Like when you are brought face to face with reality and the foolishness of vanity.

You see, I really don't think of myself as being as old as I am, and I don't think much about age difference in the presence of younger adults. The shocker came when the doctor (I hope he'll laugh along with me) told me about the risks of the procedure. As I was handed the consent form and a pen, he assured me by saying, "If it were my mother ..."

His mother! He's young, but surely not that young! Besides, does he really think I look my age?

After the blow to my vanity had subsided, the reality of all my years hit me full force. I had indeed spent more years on this earth than awaited me, even under the best of circumstances. I not only wanted to stick around, but to push back the passage of time.

In the lab, hanging over my chest was a big camera. On the left side of me were several TV screens. I could look at them and see pictures see any blockages in an artery.

It is a strange sensation to watch the screen and see the catheter being guided into position.

Once the problem was located, that catheter was removed and replaced by the one with the balloon. It looked like clear plastic.

When the balloon was in the clogged artery, it was inflated and deflated to stretch the artery and flatten the deposits against the wall. The blood once again flowed through. The rest of my heart's anatomy looked good.

It had never occurred to me that my children had been informed of the situation, so I was happily surprised when, shortly after the angioplasty was completed, I turned my head toward the door and saw all three girls. After we exchanged hugs and kisses, they got a thorough rundown from the doctor of what had transpired.

While still in the lab, Dr. Stuckey ran the pictures by me again, pausing at some shots to explain particulars. Only one hour and 27 minutes had lapsed from the time the monitor sounded until the angioplasty was initiated. Quick action, of course, is a big plus.

Incidentally, there is the risk that the artery will narrow again, usually within six months, and the risk is greater for women than men.

Whether you're a man or woman, if it's your heart attack, you don't measure it psychologically on a scale of 1 to 10. A heart attack may come with or without pain, but not without fear. Rehabilitation is far from purely physical.

My own fear certainly didn't subside when the emergency was over, in spite of the sense of security the hospital offered. Before settling down to sleep at night, I wondered if I would wake up in the morning. My first thought when I did was, "Thanks be; I'm still here."

When I progressed physically to having a portable monitor around my neck, I had to progress emotionally to the fact that it was safe.

Toward the end of my stay, removing the monitor for a shower was an exercise in courage. But it was an exercise in courage compared to the

'Surely this was something to write about,' columnist Martha Long recalls thinking during treatment for a heart attack, 'and I tried to think of a really good lead'

Scared? You bet! The first couple of sessions at rehab, I tried to keep under wraps my panic about exercising. Of course, nobody fools program director Freddie Duehring, whose heart and soul are in cardiac rehabilitation. As for the rest of the group, I soon learned that we were all brothers at heart.

Fear, anxiety and depression seem to have an especially strong hold on heart-attack victims. I'm no stranger to the surgeon's knife or to serious illness, but they did not produce the same emotional trauma.

At first it was hard for me to say the words "heart attack" in connection with myself. They sounded so

buddy put it, I not only am n[illegible] smoking, I am not even cheating!

A heart attack will put you [illegible] touch with the reality of your m[illegible] tality. The fear isn't about one's r[illegible] gious faith or a lack of it, but rath[illegible] the desire to be part of this work[illegible]

Give me my walking shoes a[illegible] my diet. Hold the stress. Whoev[illegible] wrote that musical "Stop the Wor[illegible] I Want To Get Off?" was definite[illegible] not playing my song.

• • •

Miss Manners would never ap[illegible] prove, I'm sure, but this public[illegible] thank you is extended with no less[illegible] warmth and appreciation than a[illegible] personal note or word. Your[illegible] thoughtfulness was overwhelming[illegible] Your caring was a tremendous[illegible]

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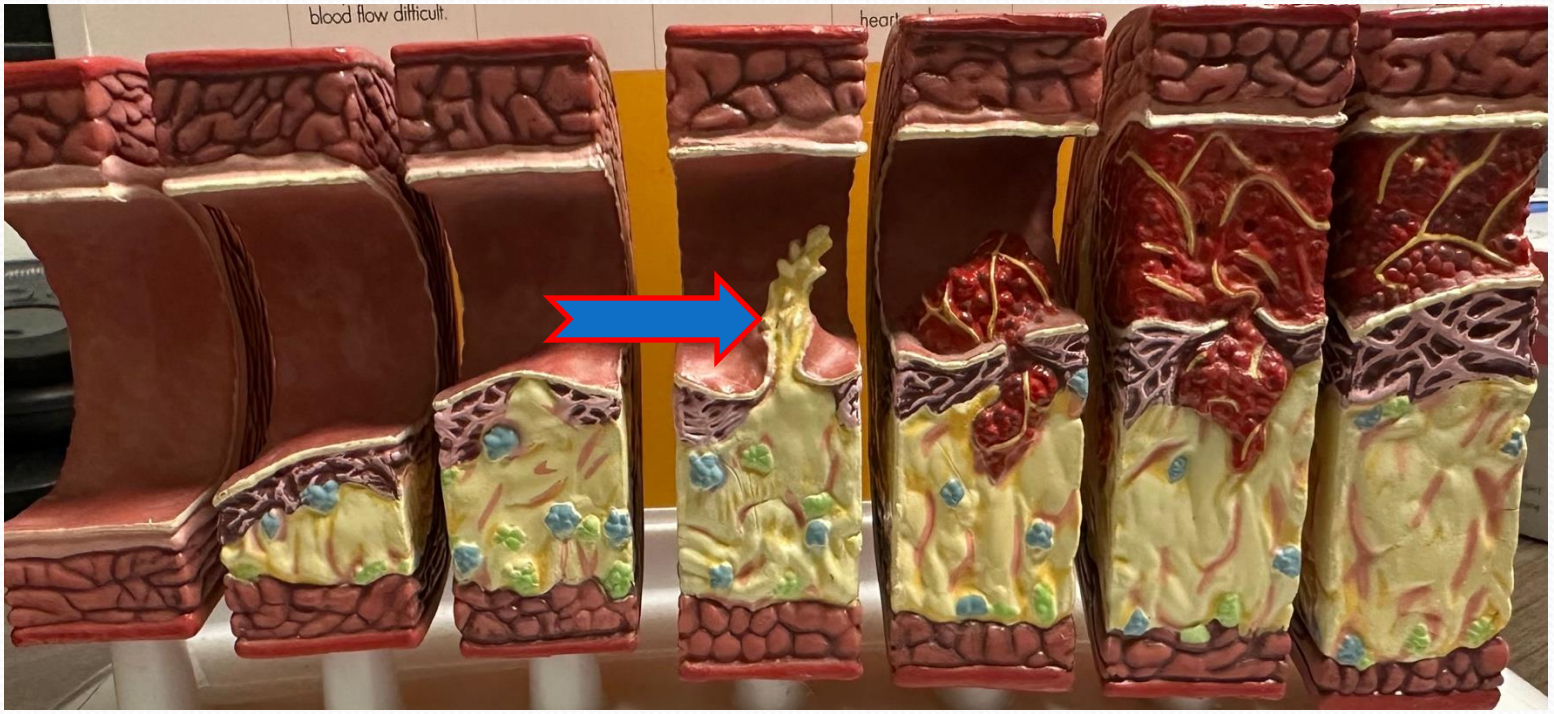
How does a Garden Variety Heart Attack Happen?
Plaque Rupture



Statins shrink the plaque and toughen up the surface lining. Aspirin reduces the potential for a clot

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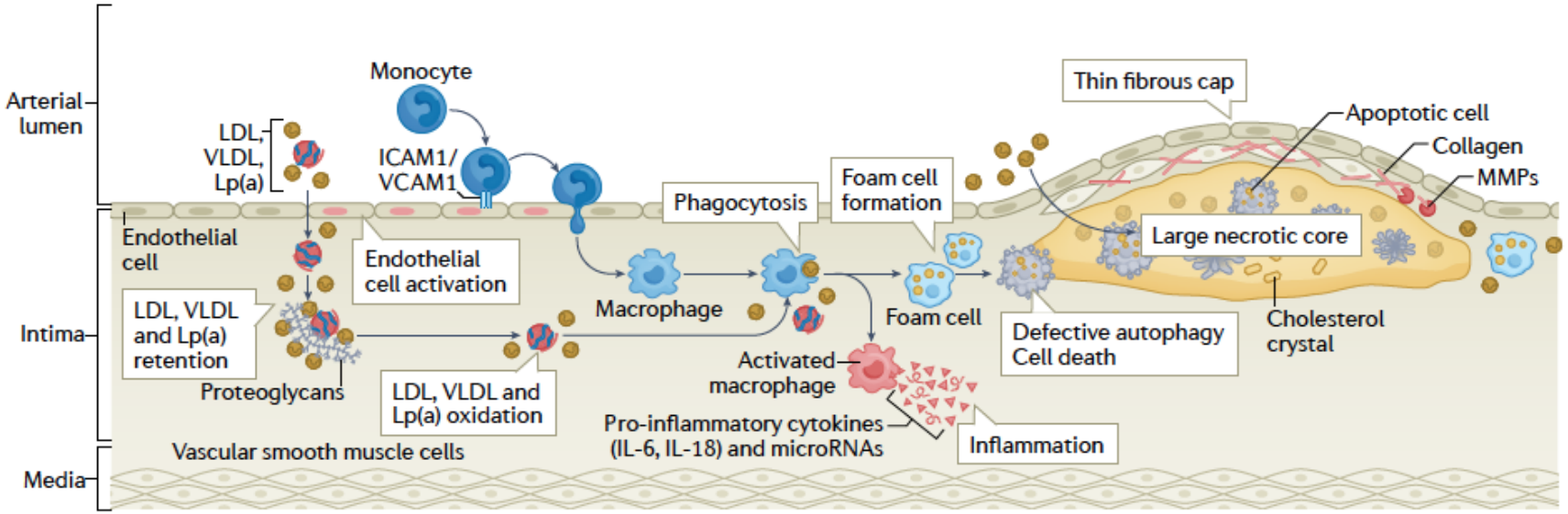
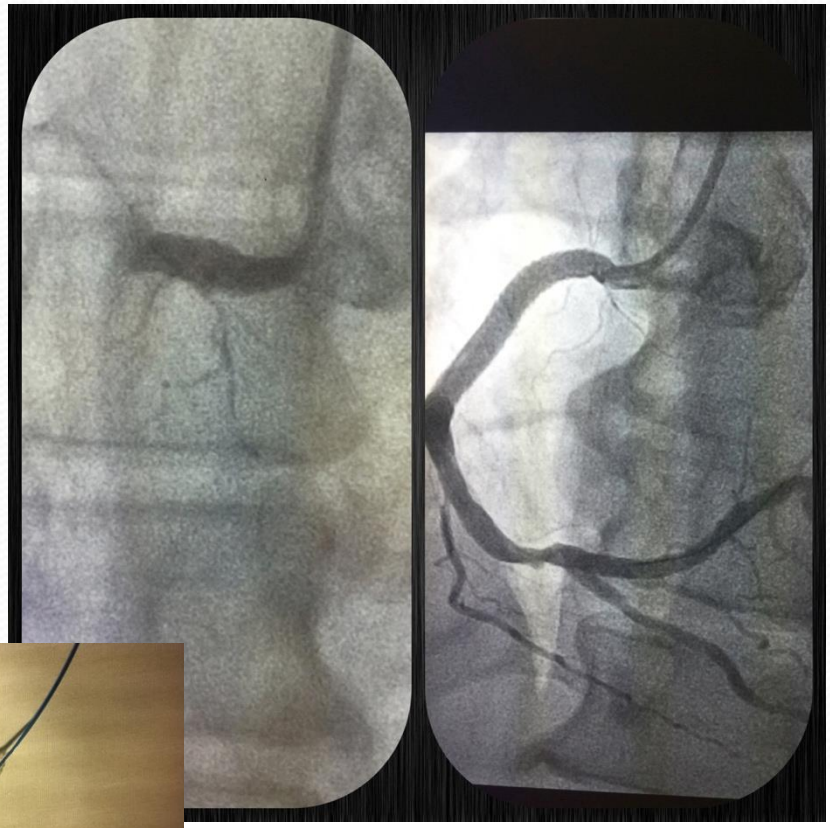
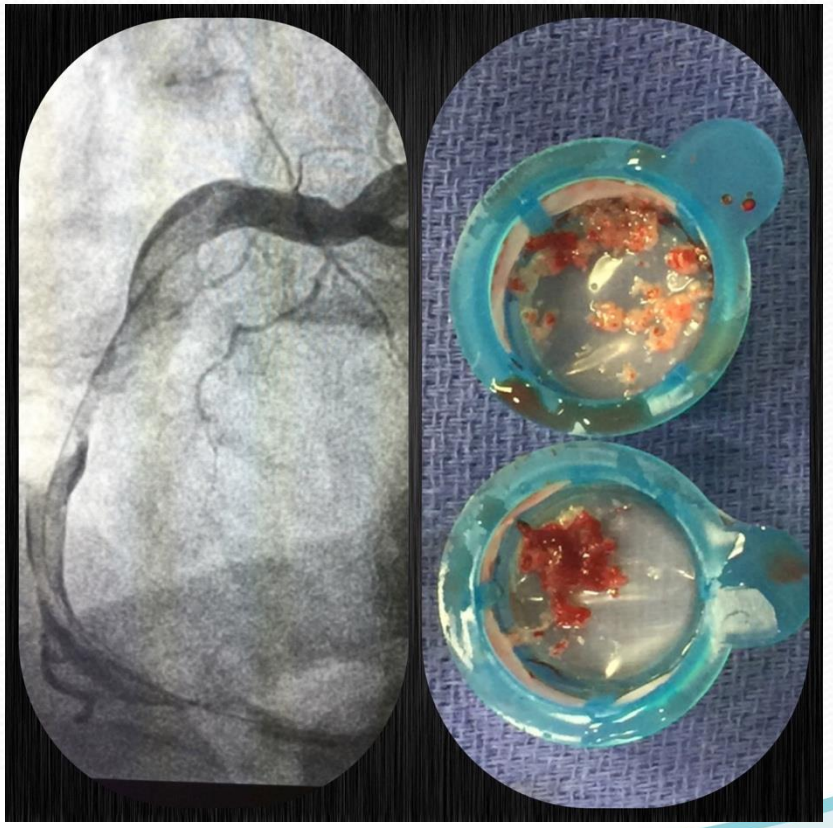
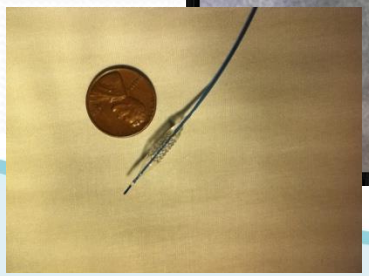

Arterial lumen
Intima
Media
LDL, VLDL, Lp(a)
Monocyte
ICAM1/ VCAM1
Endothelial cell
Endothelial cell activation
LDL, VLDL and Lp(a) retention
Proteoglycans
LDL, VLDL and Lp(a) oxidation
Vascular smooth muscle cells
Macrophage
Phagocytosis
Foam cell formation
Foam cell
Activated macrophage
Pro-inflammatory cytokines (IL-6, IL-18) and microRNAs
Inflammation
Thin fibrous cap
Apoptotic cell
Collagen
MMPs
Large necrotic core
Defective autophagy Cell death
Cholesterol crystal

Garden Variety Heart Attack







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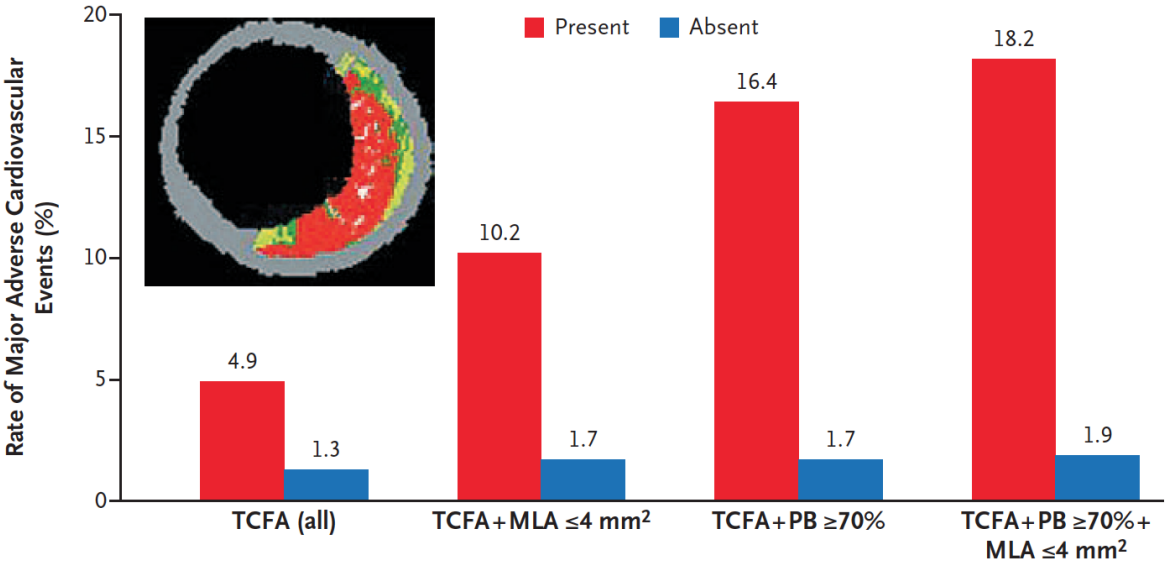

Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

Figure 2. Event Rates for Lesions That Were and Those That Were Not Thin-Cap Fibroatheromas, at a Median Follow-up of 3.4 Years.

Event rates associated with 595 nonculprit lesions that were characterized as thin-cap fibroatheromas (TCFA) and 2114 that were not by means of radiofrequency intravascular ultrasonographic imaging are shown according to minimal luminal area (MLA) and plaque burden (PB) as detected on gray-scale intravascular ultrasonography. The inset shows an example of a thin-cap fibroatheroma imaged by radiofrequency ultrasonography. Data on prevalence are for one or more such lesions per patient. Lesions in patients with indeterminate events were excluded. (For additional details, see Table 6 in the Supplementary Appendix.) CI denotes confidence interval.

Stone et al. N Engl J Med 2011;364:226-35

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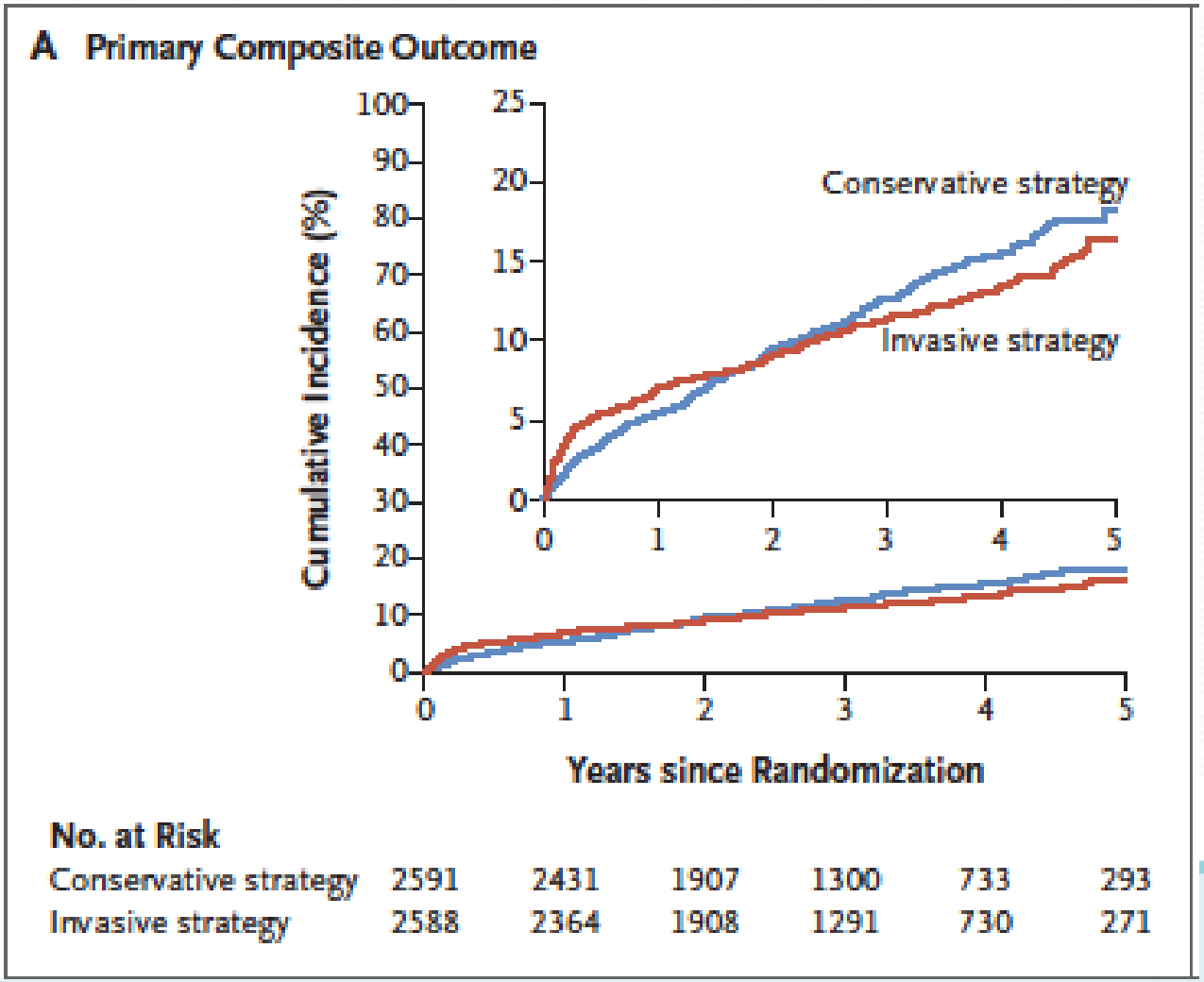
Ischemia Trial Results



Stone et al. N Engl J Med 2020;382:1395-407.

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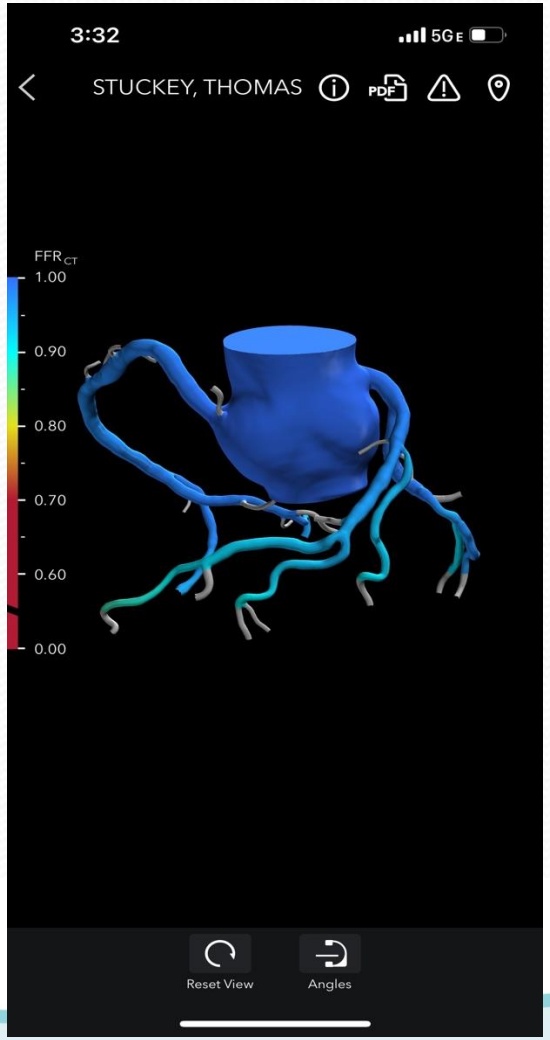
Outer Wall: 0.830cm³
In-Between: 0.466cm³
-100HU ~ 0HU:0.0740cm³
1HU ~ 50HU:0.0775cm³
51HU ~ 150HU:0.151cm³
151HU ~ 350HU:0.0912cm³
351HU ~ 1000HU:0.0598cm³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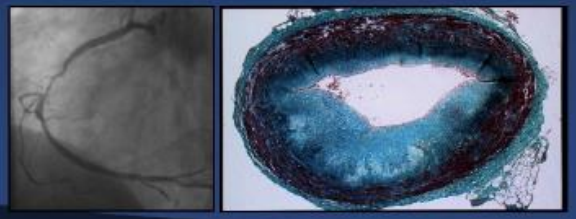
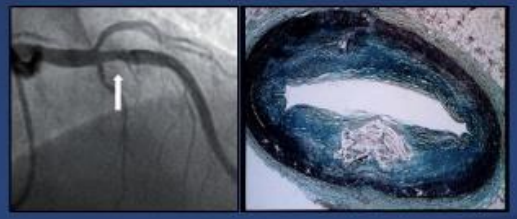
The Final Word

Ischemia, vulnerable plaque, prognosis and treatment

Symptoms of ischemia (angina, exertional dyspnea)	CV risk factors, inflammation, recent ACS
↓	↓
Ischemia ⟷	Vulnerable plaque
↓	↓
Treat to relieve symptoms (anti-anginal drugs, revasc)	Treat to prevent CV death, MI, ACS (APT, lipid lowering, revasc)





Mount Sinai Heart

Cardiovascular Research Foundation®

Slide. Gregg Stone

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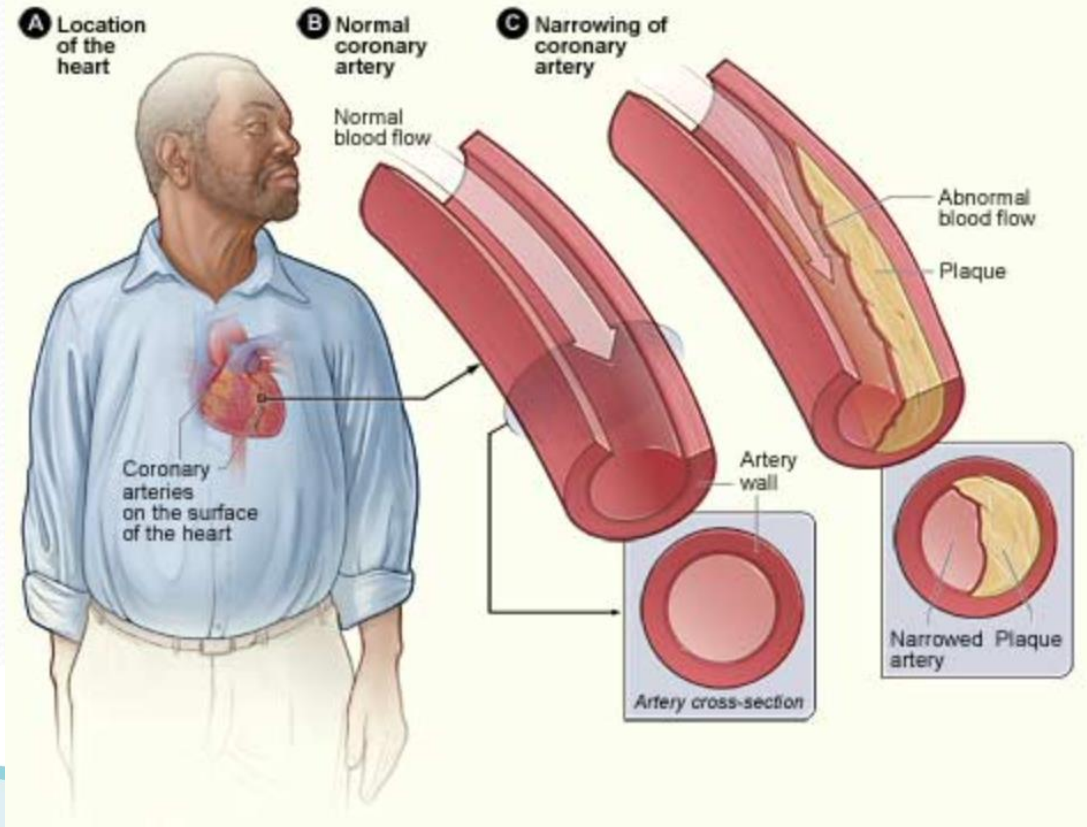
Would you want to know if you have Coronary Artery Disease?



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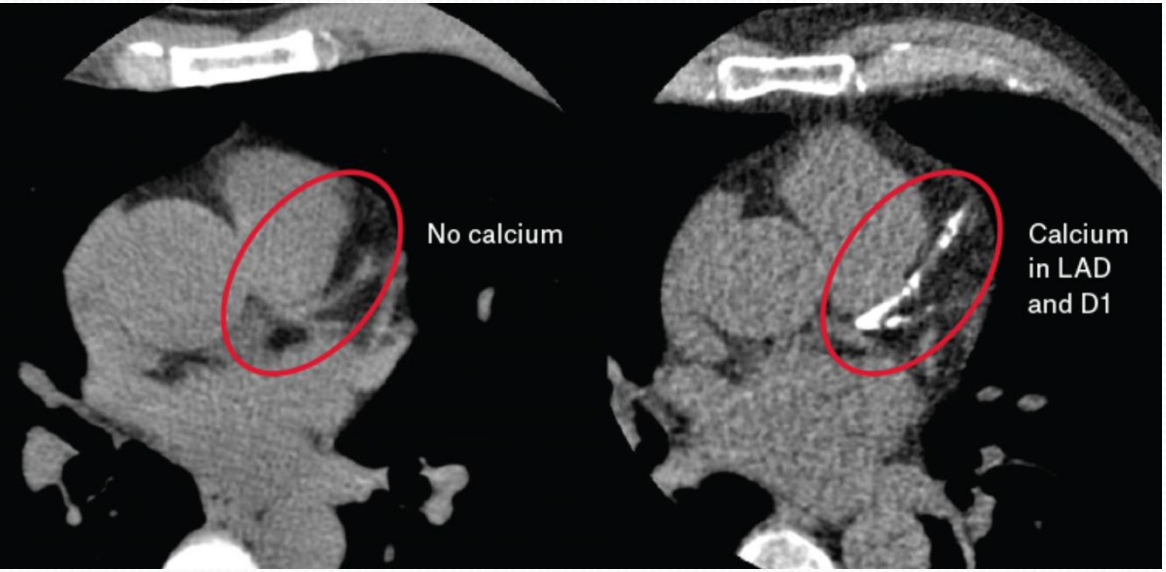
What is coronary artery **Calcium Score Scan (CAC)**?



- **Rapid CT scan of heart**
- **Does not require contrast**
- **No prep is required**
- **“Inexpensive”**
- **Low radiation dose**
- **Powerful prognostic data**

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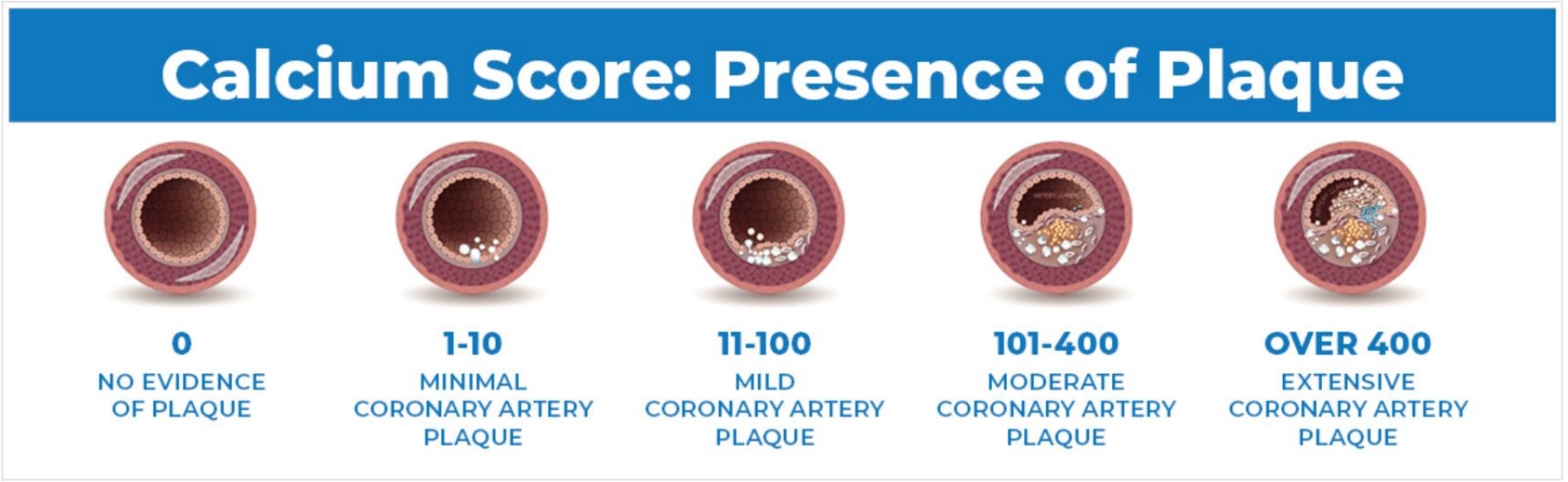
What are the clinical implications of the presence and absence of CAC?



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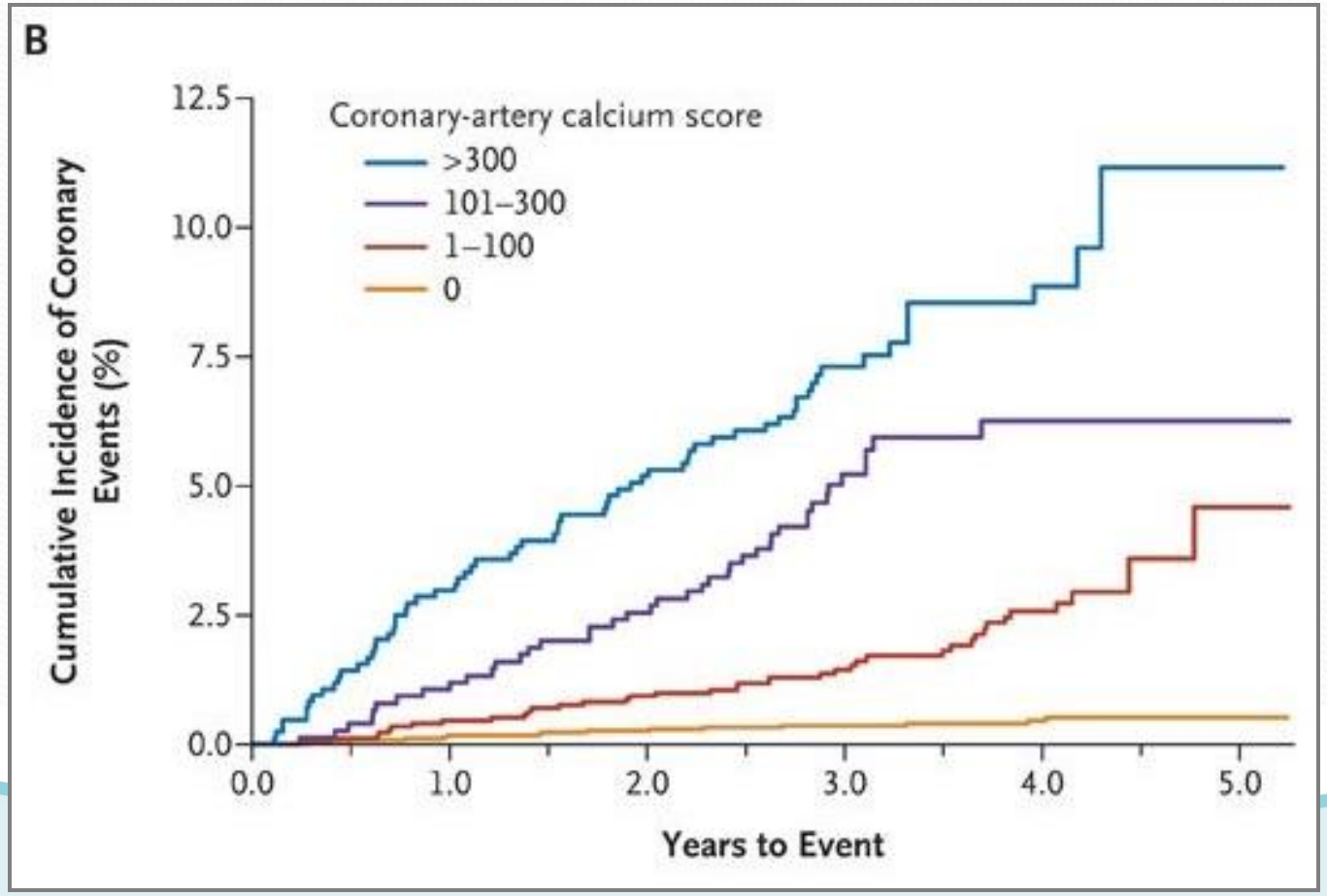
Elevated Calcium Score -> Elevated Risk

Multi-Ethnic Study of Atherosclerosis (MESA)



(Detrano, NEJM 2008)

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Plaque burden, not stenosis is the major predictor of CV risk

Impact of Plaque Burden Versus Stenosis on Ischemic Events in Patients With Coronary Atherosclerosis JACC 2020

Martin Bødtker Mortensen, Omar Dzaye, Flemming Hald Steffensen, Hans Erik Bøtker, Jonathon Leipsic, Bjarne Linde Nørgaard

23,279 patients from Western Denmark Heart Registry

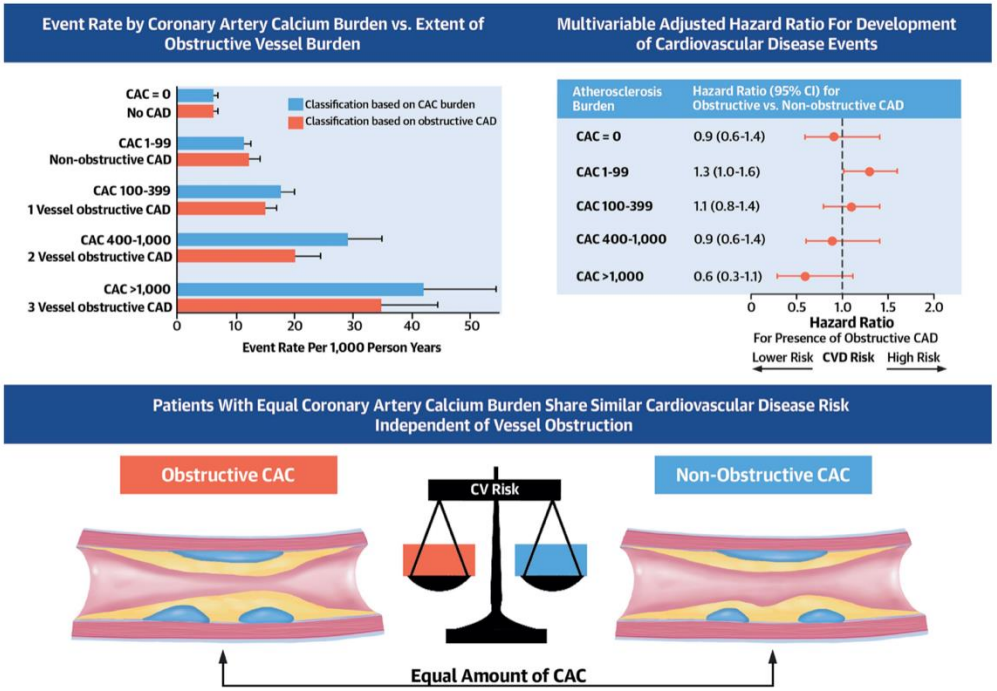

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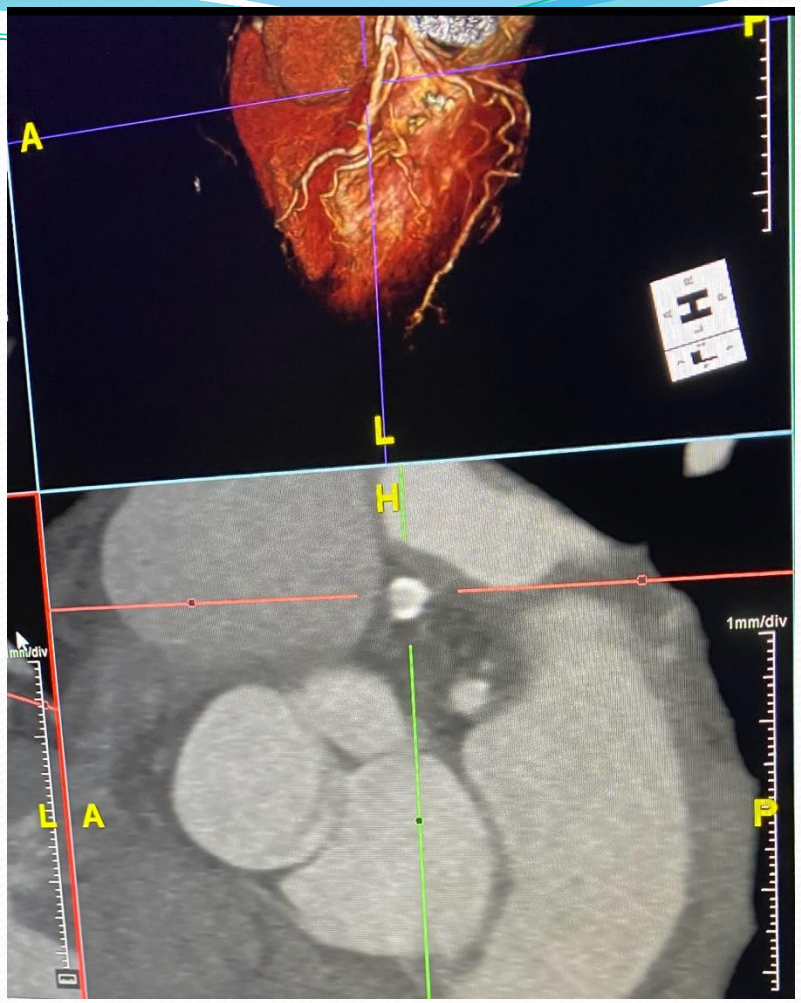
Table | Graph | Export Measur...

Artery	Lesion No	Score	Volume	Mean	Mas
Coronaries T	9	382	380		71.7
LM Total	0	0	0		0
LAD Total	4	116	120		20.9
LCX Total	1	160	129		29.6
RCA Total	4	106	131		21.2
Other Total	0	0	0		0
Total	9	382	380		71.7

Percentile Ranking: 74 (MESA)

Gender: Male Age: 67 Ethnicity: White

Patient size for mass score



Thomas Stuckey Calcium Score

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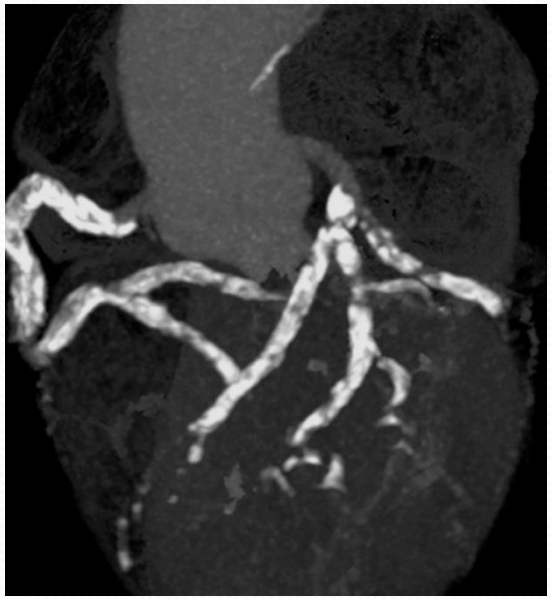
What to do if CAC is high?

Treat same as you would for other high-risk pts:

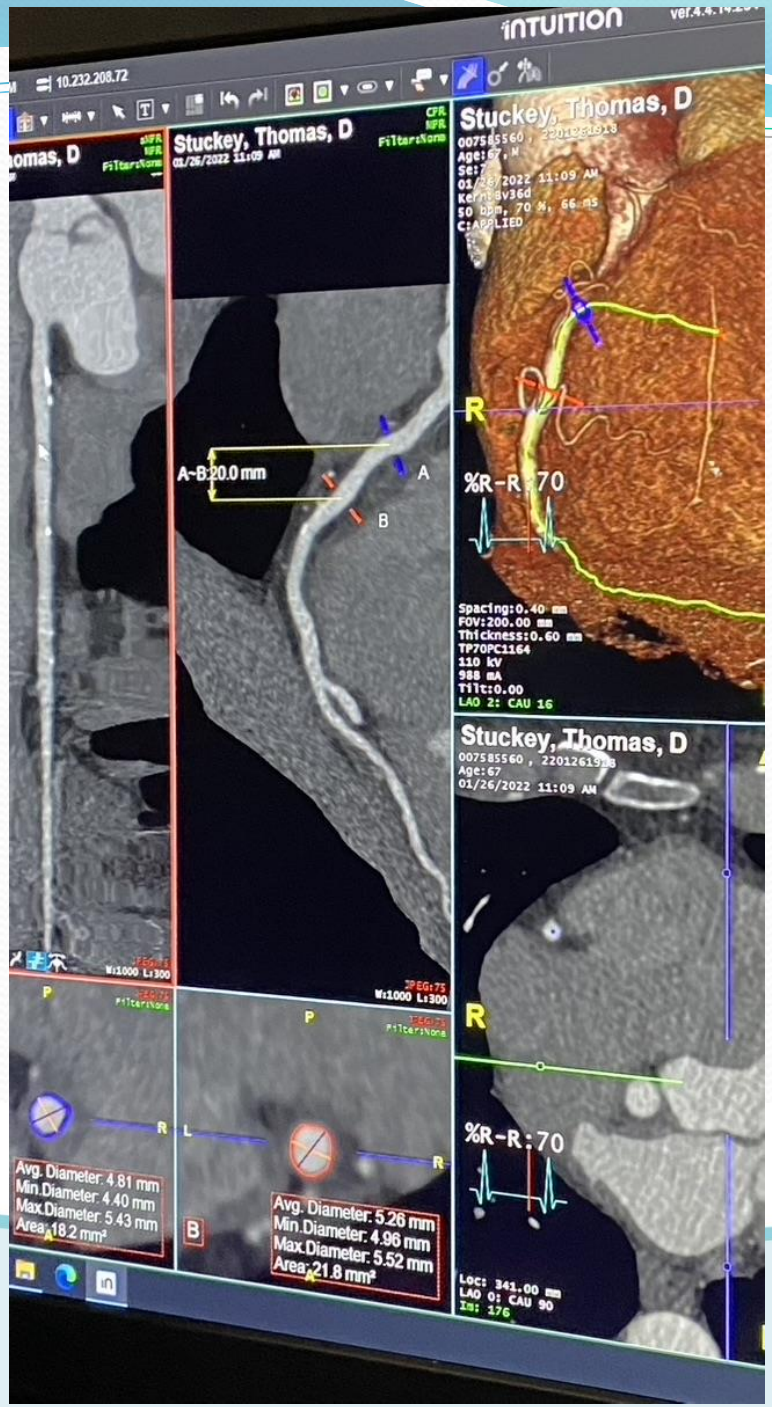
- ✓ Aggressive prevention: statin(add on lipid lowering agent) & aspirin
- ✓ Lifestyle changes

- ✓ Most will not need any other testing, especially if active lifestyle and no Sx



Testing for CAD and Vulnerable Plaque

- Calcium scoring
- Coronary CTA
- Noninvasive FFR
- CT Pet
- Nirs IVUS
- OCT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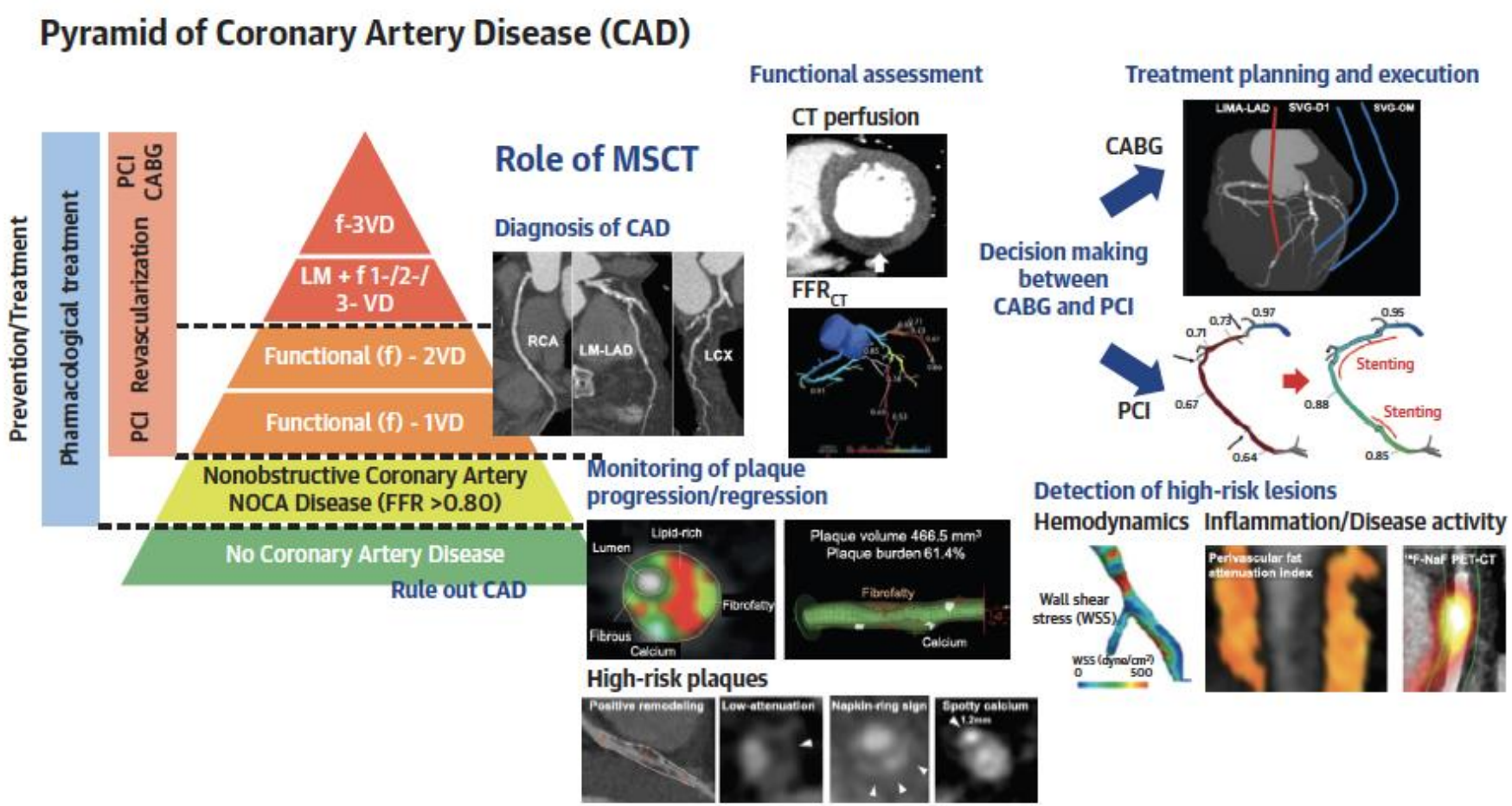
Area: 18.2 mm²
Avg. Diameter: 5.26 mm
Min.Diameter: 4.96 mm
Max.Diameter: 5.52 mm
Area: 21.8 mm²

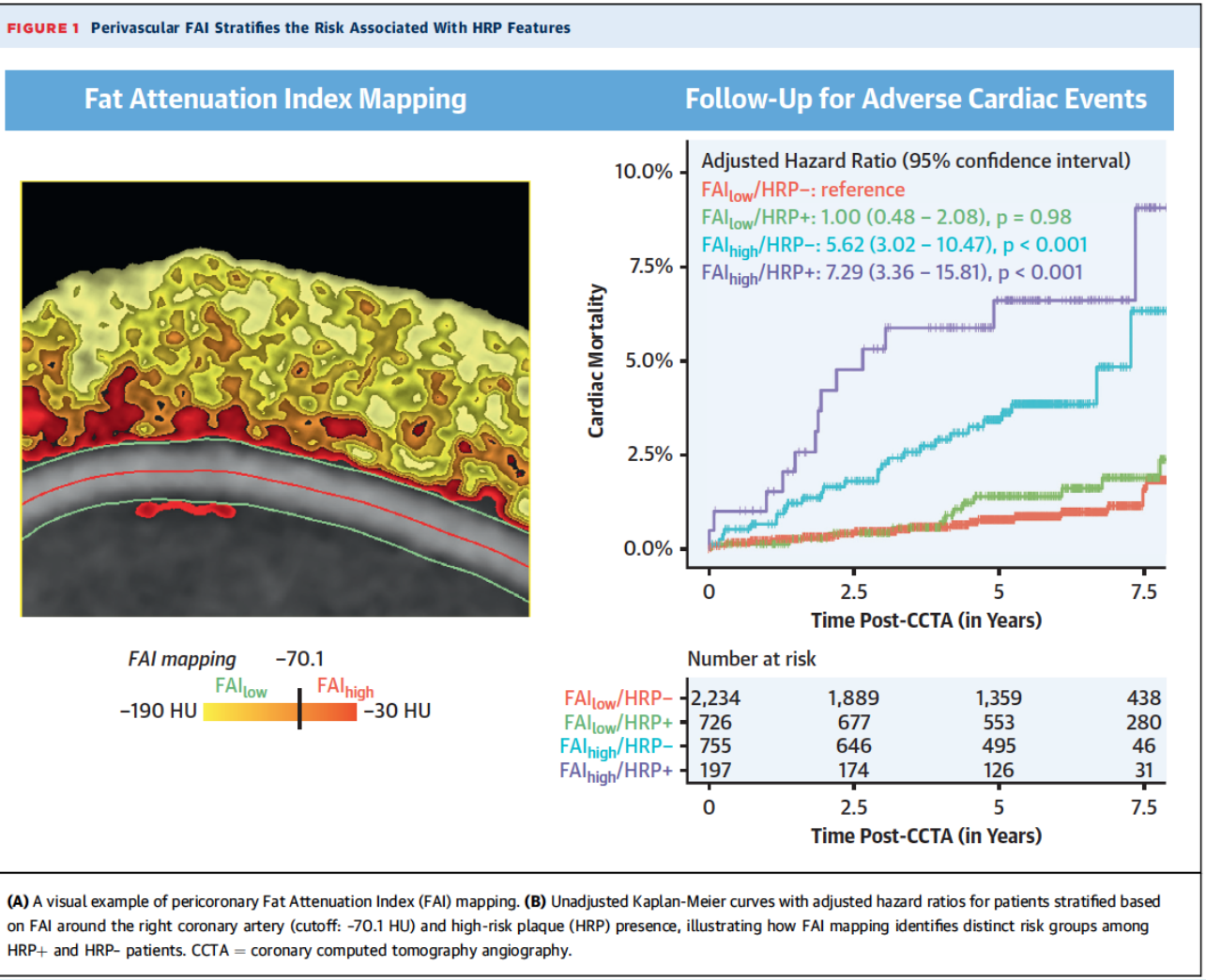
CENTRAL ILLUSTRATION The Pyramid of Coronary Artery Disease and the Diagnostic Role of Multislice Computed Tomography



Serruys, P.W. et al. J Am Coll Cardiol. 2021;78(7):713-736.

Perivascular Fat Attenuation Index Mapping

FIGURE 1 Perivascular FAI Stratifies the Risk Associated With HRP Features

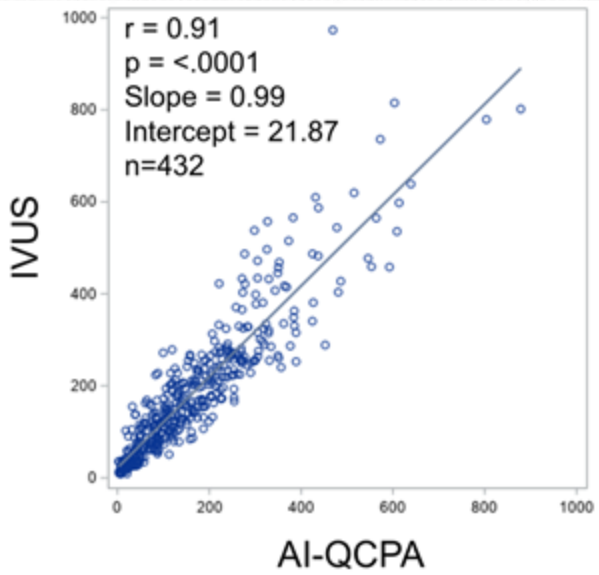


(A) A visual example of pericoronary Fat Attenuation Index (FAI) mapping. **(B)** Unadjusted Kaplan-Meier curves with adjusted hazard ratios for patients stratified based on FAI around the right coronary artery (cutoff: -70.1 HU) and high-risk plaque (HRP) presence, illustrating how FAI mapping identifies distinct risk groups among HRP+ and HRP- patients. CCTA = coronary computed tomography angiography.

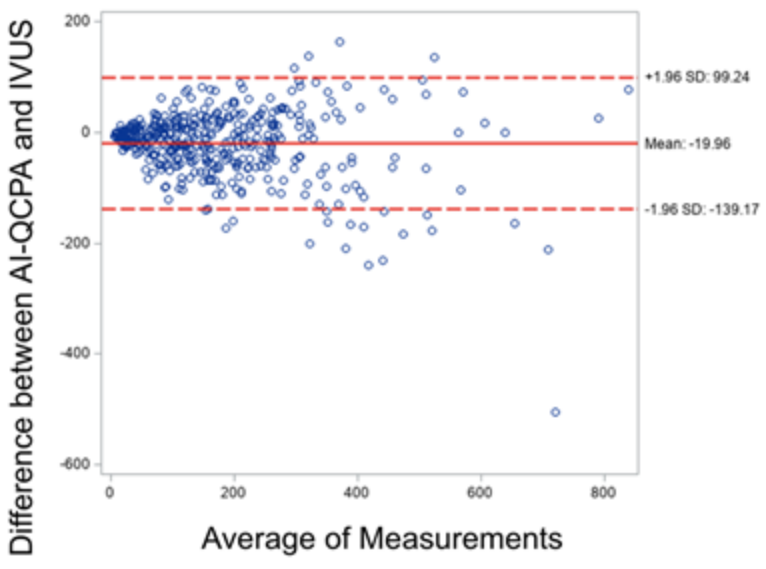
Oikonomou et al. J Am Coll Cardiol 2020;76:755-7

Total Plaque Volume Per Lesion

Scatterplot with Slope



Bland-Altman Analysis



Narula, Stuckey, et al EHJI 2023

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Plaque: Quantified and Characterized

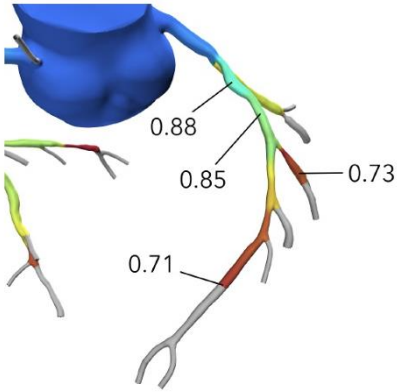
Case Example: Serial lesions with diffuse non-calcified and calcified plaque in proximal LAD.

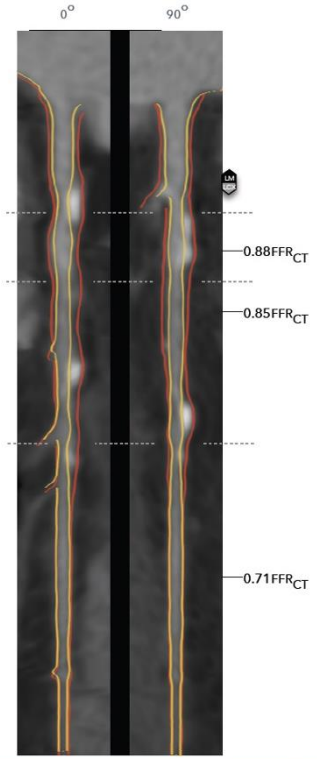
LAD Plaque overview

CORONARY SYSTEM (including branches)	TOTAL PLAQUE MM^3	CALCIFIED PLAQUE	NON-CALCIFIED PLAQUE	LOW ATTENUATION PLAQUE
Left Main	3	0	3	0
Left Anterior Descending	273	50	223	8
Total	276	50	226	8

Quantitative plaque is provided on vessels > 1.8 mm.

VESSEL BOUNDARY
- outer wall boundary
- lumen boundary





LAP (Low attenutation Plaque) and PR (positive remodeling)

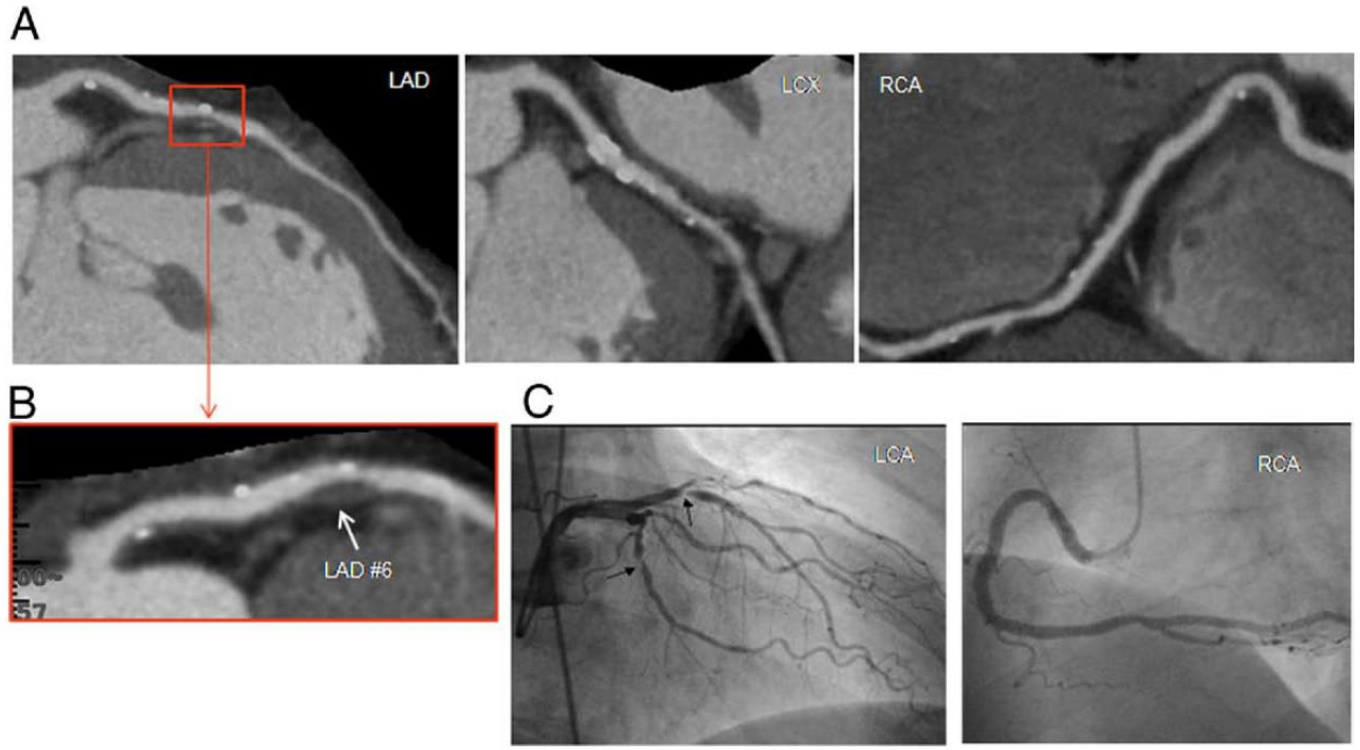


Figure 2 **Example of a Patient With ACS 6 Months After CT Angiography**

(A) Curved multiplanar reformation images of left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA). **(B)** Positive remodeling, low-attenuation plaque, and spotty calcification were detected in LAD #6 on coronary computed tomography (CT) angiography. **(C)** Acute coronary syndrome (ACS) occurred 6 months after CT angiography. LAD #6 was determined as the culprit lesion based on invasive coronary angiogram findings. Please note the location of the lesion proximal to the first septal branch, both in CT angiography before the event and coronary angiogram after the event when the patient was brought to the catheterization laboratory for percutaneous coronary intervention. LCA = left coronary artery.

Motoyama et al. J Am Coll Cardiol 2009;54:49-57

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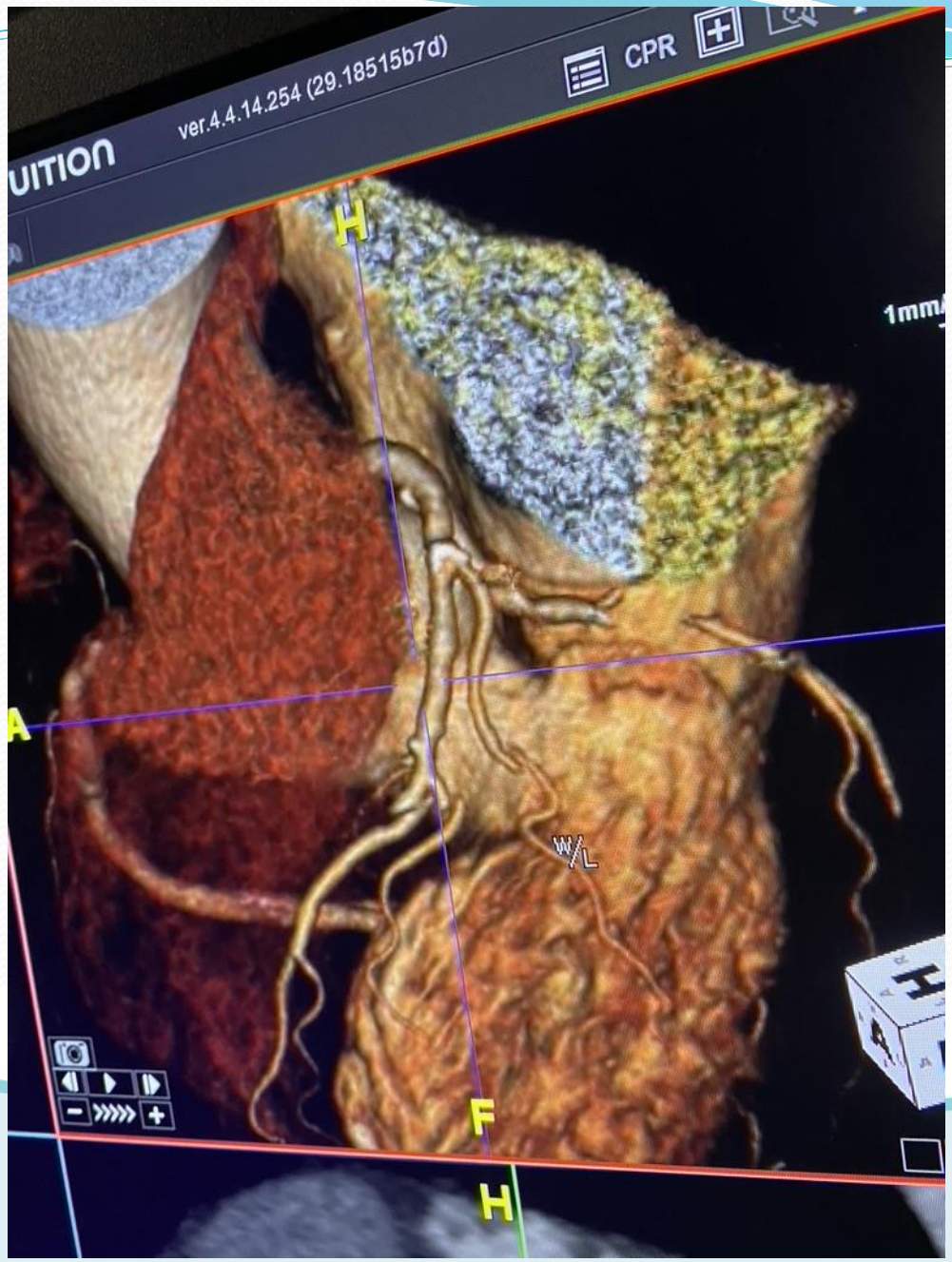

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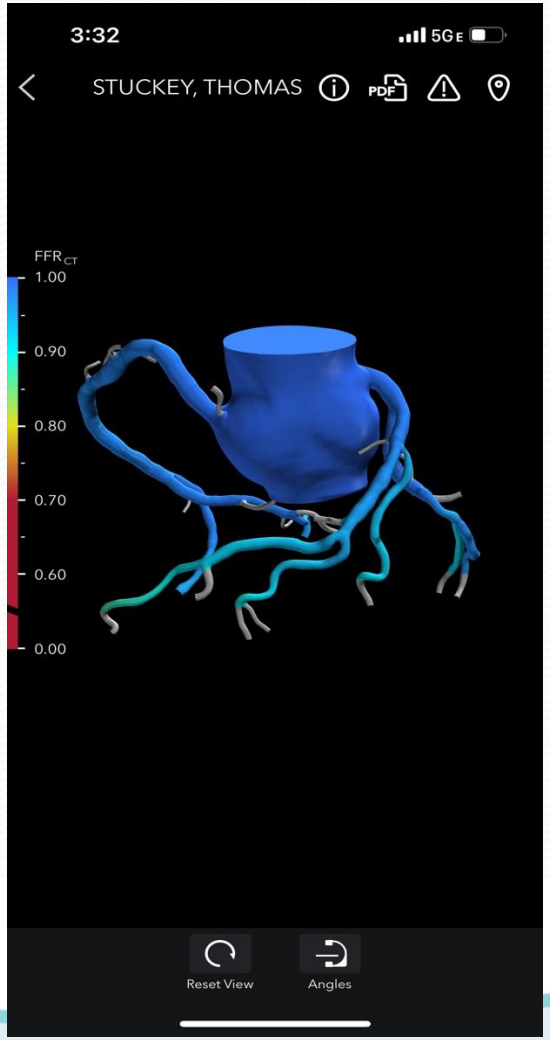
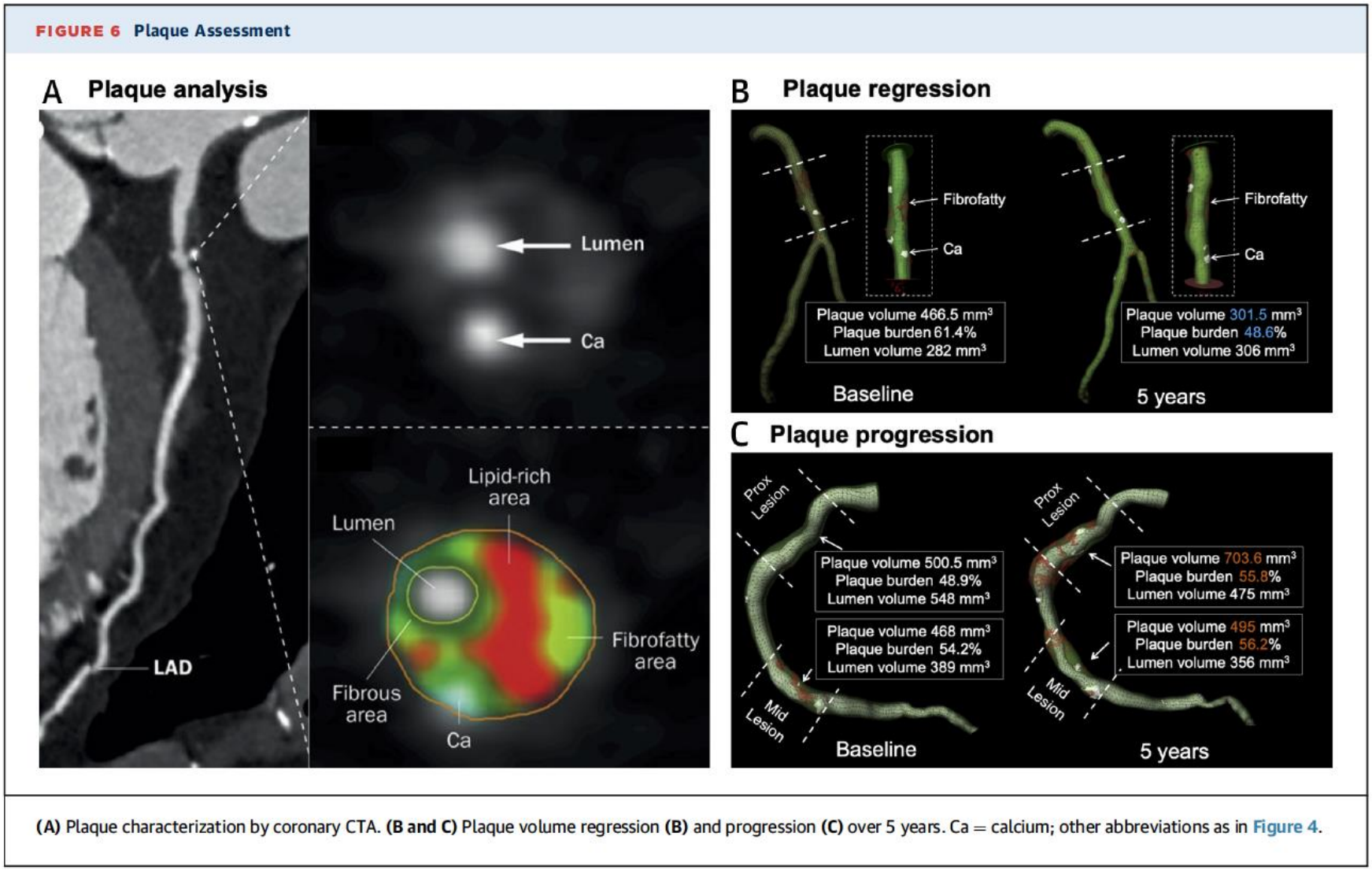


Lp(a) 120 nmol/l/LDL 68 - I am in a race for my own mortality

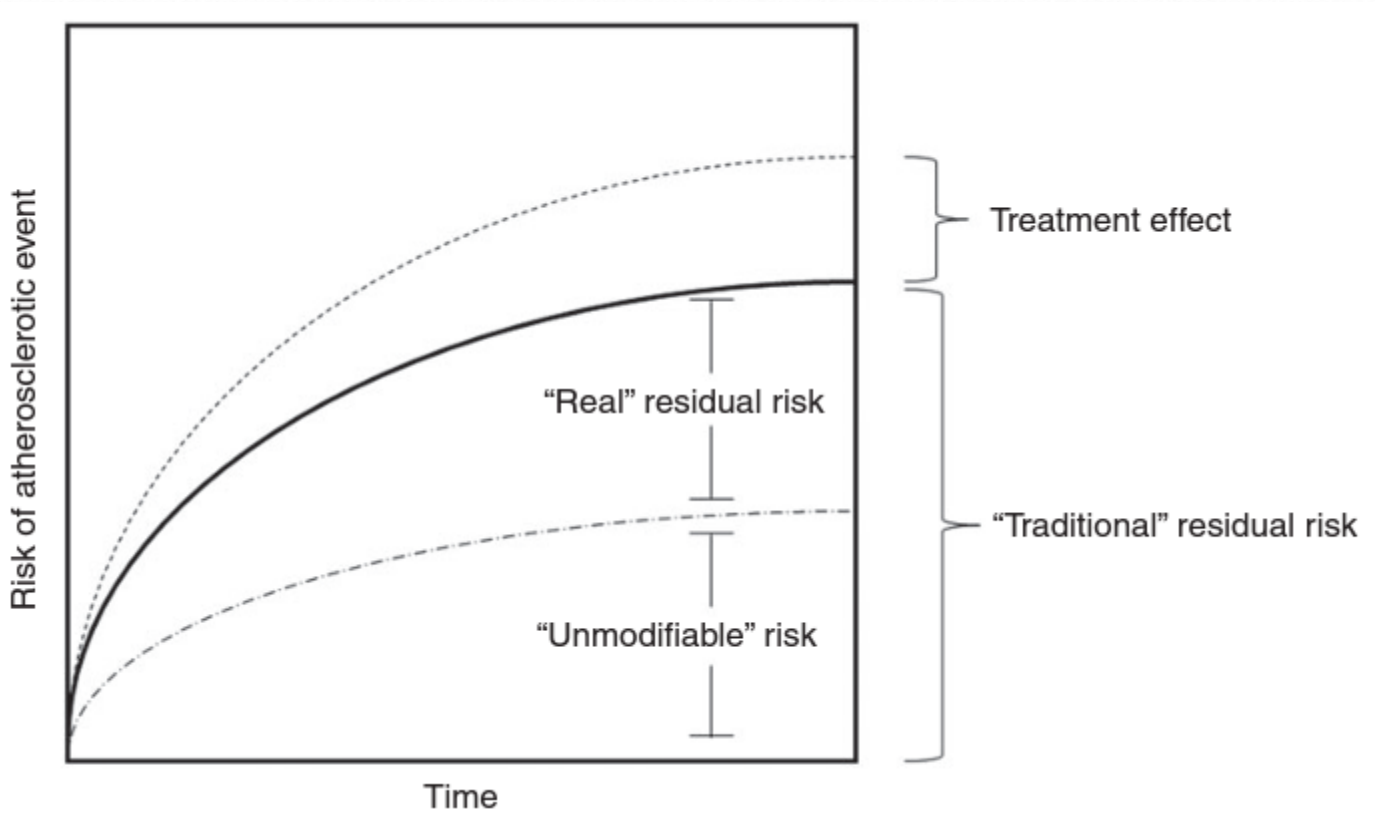


(A) Plaque characterization by coronary CTA. **(B and C)** Plaque volume regression **(B)** and progression **(C)** over 5 years. Ca = calcium; other abbreviations as in Figure 4.

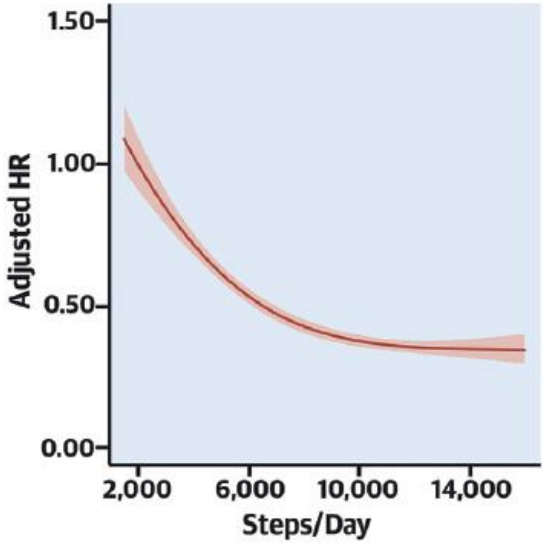
Serruys et al. J Am Coll Cardiol 2021;78:713-76

Addressing Risk

Addressing Residual Risk After Statin Treatment

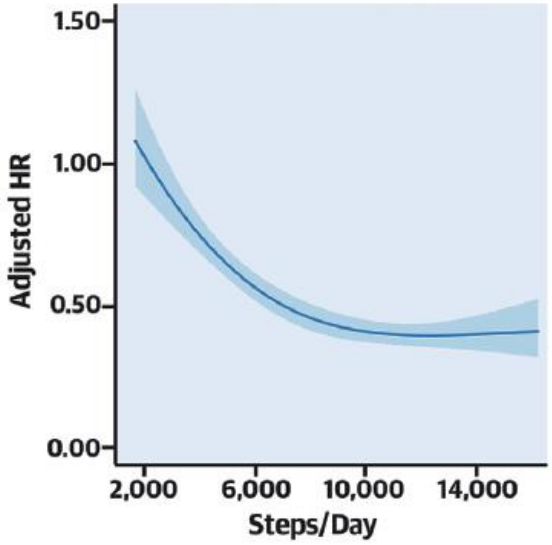


All-Cause Mortality



	Steps/day	Adjusted HR (95% CI)
Minimum dose	2,517	0.92 (0.84-0.99)
Optimum dose	8,763	0.40 (0.38-0.43)
Risk reduction at 16,000 steps	16,000	0.35 (0.30-0.40)

Incident CVD (Fatal and Nonfatal)



	Steps/day	Adjusted HR (95% CI)
Minimum dose	2,735	0.89 (0.79-0.99)
Optimum dose	7,126	0.49 (0.45-0.55)
Risk reduction at 16,000 steps	16,000	0.42 (0.33-0.53)

Step count targets were independent of:

Sex

Device wear location (wrist vs hip)

Additional health benefits with higher step cadence, irrespective of total step count

Stens NA, et al. J Am Coll Cardiol. 2023;82(15):1483-1494.

THE SIX PILLARS OF LIFESTYLE MEDICINE

The aim of lifestyle medicine is to redesign health delivery to rely on therapeutic lifestyle interventions as a primary modality to treat, prevent, manage, and reverse chronic cardiometabolic conditions.

CMHC Cardiometabolic Health Congress

AMERICAN COLLEGE OF Lifestyle Medicine

CONE HEALTH

Results of the Pritikin Program

- Meets the rigorous requirements necessary for Medicare approval
- Results documented in more than 100 published scientific studies

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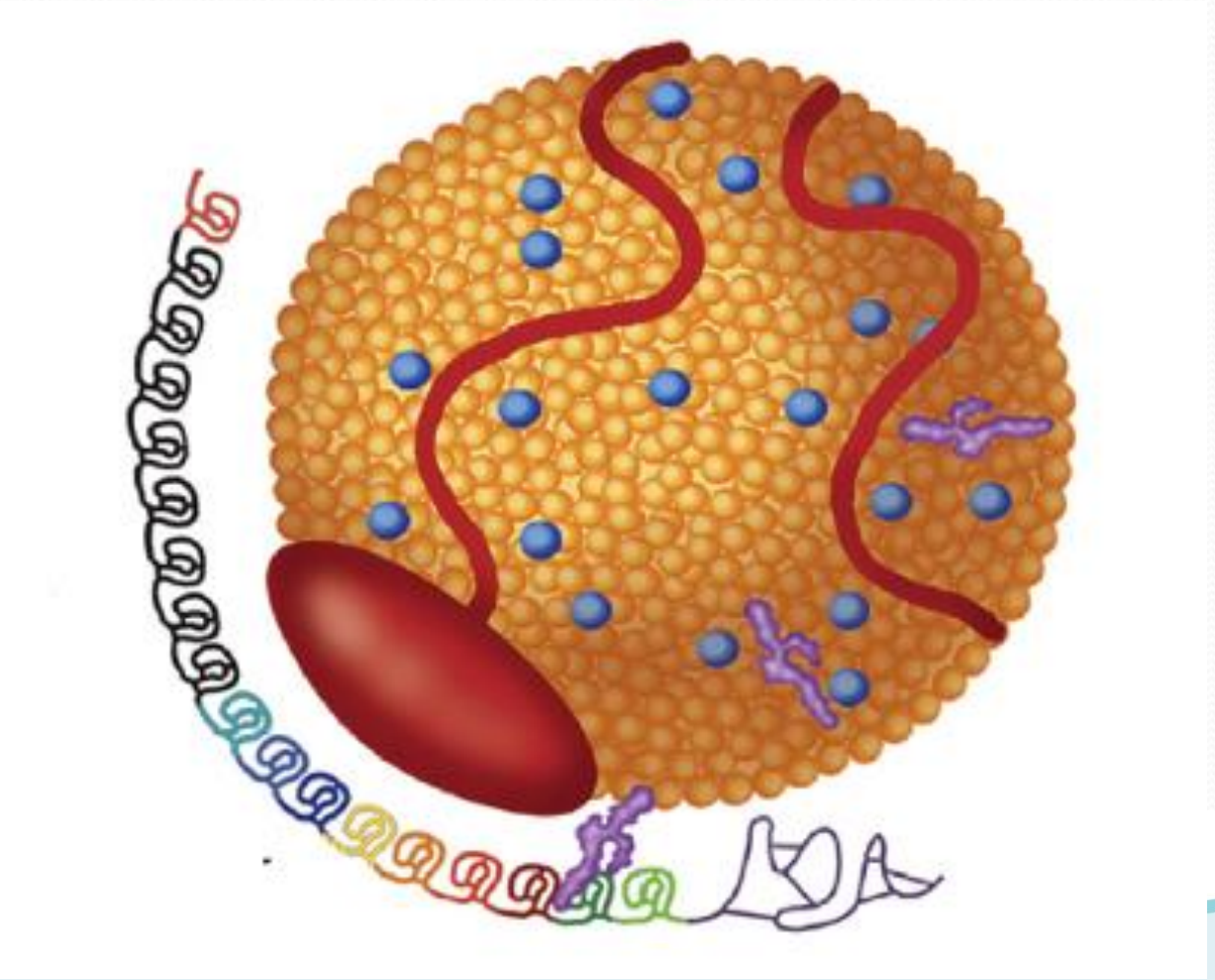
Addressing Cardiac Risk



The New England
Journal of Medicine

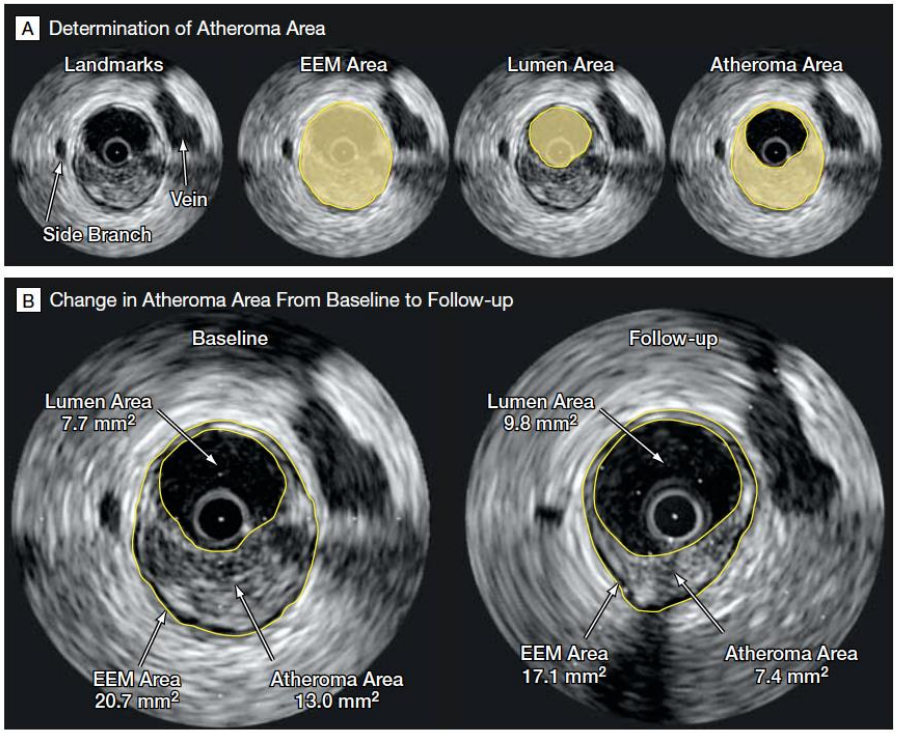
VOLUME 343 AUGUST 24, 2000 NUMBER 8

EFFECTS OF ESTROGEN REPLACEMENT ON THE PROGRESSION OF CORONARY-ARTERY ATHEROSCLEROSIS

DAVID M. HERRINGTON, M.D., M.H.S., DAVID M. REBOUSSIN, PH.D., K. BRIDGET BROSNIHAN, PH.D., PENNY C. SHARP, ED.D., SALLY A. SHUMAKER, PH.D., THOMAS E. SNYDER, M.D., CURT D. FURBERG, M.D., PH.D., GLEN J. KOWALCHUK, M.D., THOMAS D. STUCKEY, M.D., WILLIAM J. ROGERS, M.D., DAVID H. GIVENS, M.D., AND DAVID WATERS, M.D.

High Versus Low intensity Statin Impact

Figure 3. Intravascular Ultrasound Images at Baseline and Follow-up



A, Atheroma area is calculated by subtracting the lumen area from the area of the external elastic membrane (EEM). B, Patient randomized to 80 mg of atorvastatin. There is substantial reduction in atheroma area (from 13.0 to 7.4 mm²). A lesser increase in lumen area is noted (from 7.7 to 9.8 mm²). See video at http://jama.com/cgi/content/full/291/9/1071/DC1.

Nissen et al, JAMA, 2004

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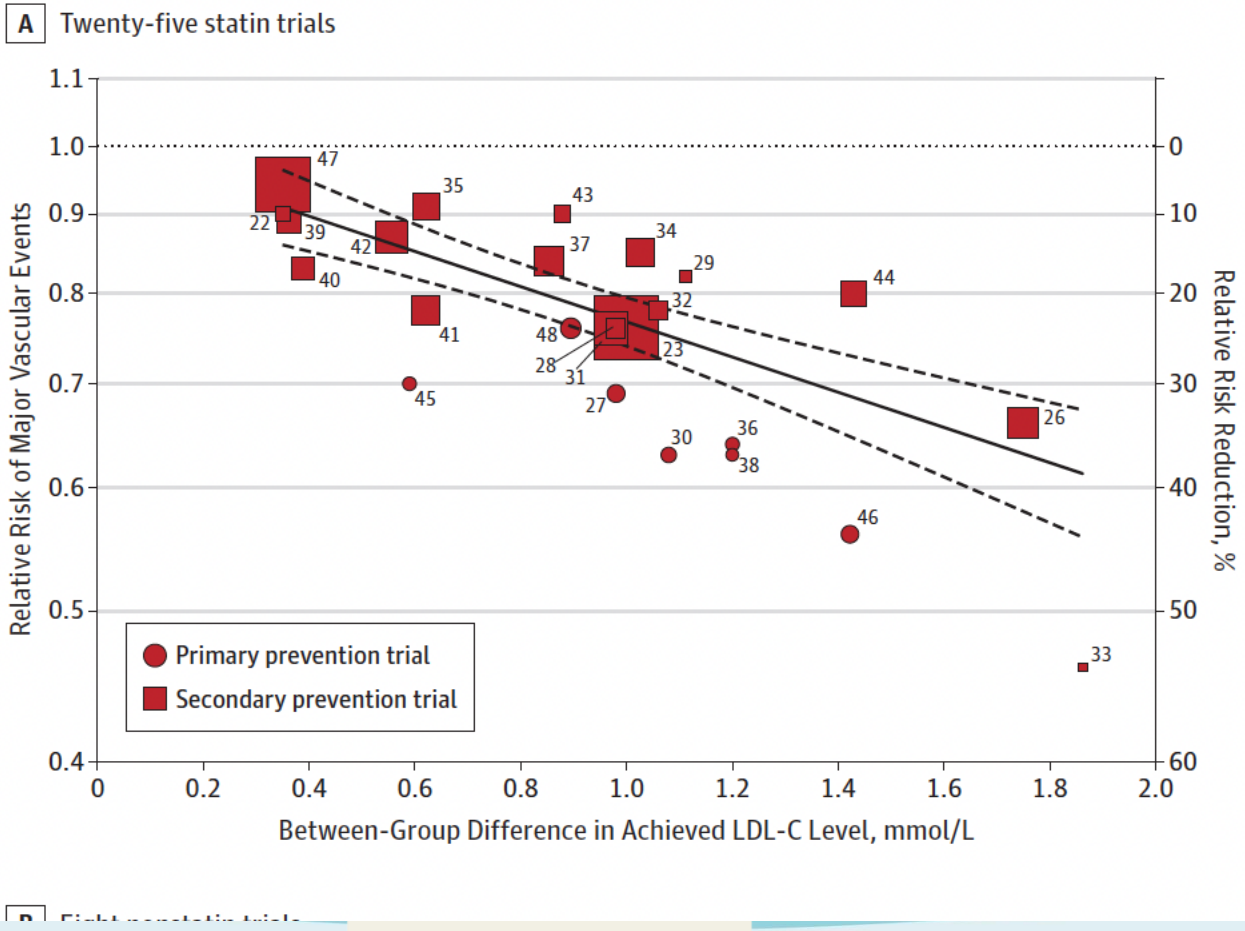
Figure 2. Association of Between-Group Difference in Achieved Low-Density Lipoprotein Cholesterol (LDL-C) Levels and Risk of Major Vascular Events



Silverman et al. JAMA.2016;316(12):1289-1297.

Disease Severity Staging + Standard Medical Management Recommendations

Overall considerations: Consider GLP1 treatment if BMI >27 | Lifestyle modification guidance especially in higher stages

Stages	TPV	LDL	Nomogram percentile >50th and/or risk enhancers[3]*	Rx
Mild	1-100	Goal: <100	Consider intensifying to moderate Rx	Statin ± ASA
Moderate	>100-250	Goal: <70	Consider intensifying to severe Rx	High intensity statin ± PCSK9I ± Bempedoic Acid ± Ezetimibe ± ASA If DM: Intensify therapy with GLP1 ± SGLT2I
Severe	>250-750	Goal: <55	Consider intensifying to extensive Rx	High intensity statin ± PCSK9I ± Bempedoic Acid ± Ezetimibe ASA Aggressive BP Rx If DM: Intensify therapy with GLP1 ± SGLT2I If elevated BMI: weight loss treatment If elevated CRP & LDL at target: consider anti-inflammatories
Extensive	>750	Goal: as low as can be achieved; at least <50		Same as severe ± Colchicine ± Icosapent Ethyl

*Risk enhancers include family history of premature ASCVD, primary hypercholesterolemia, metabolic syndrome, chronic kidney disease, chronic inflammatory conditions, history of premature menopause and history of pregnancy associated conditions that increase later ASCVD risk, high-risk race/ethnicity, lipids/biomarkers associated with increased ASCVD risk[3]

References:

1. Tzimas, George, et al. Age- and Sex-Specific Nomographic CT Quantitative Plaque Data From a Large International Cohort. JACC Cardiovascular Imaging (2023). DOI: https://doi.org/10.1016/j.jcmg.2023.05.011
2. Freeman, Andrew, et al. Integrating Coronary Atherosclerosis Burden and Progression with Coronary Artery Disease Risk Factors to Guide Therapeutic Decision Making. AJM (2022) DOI:https://doi.org/10.1016/j.amjmed.2022.10.021.
3. Arnette, Donna, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation (2019). DOI: 10.1161/CIR.0000000000000678.

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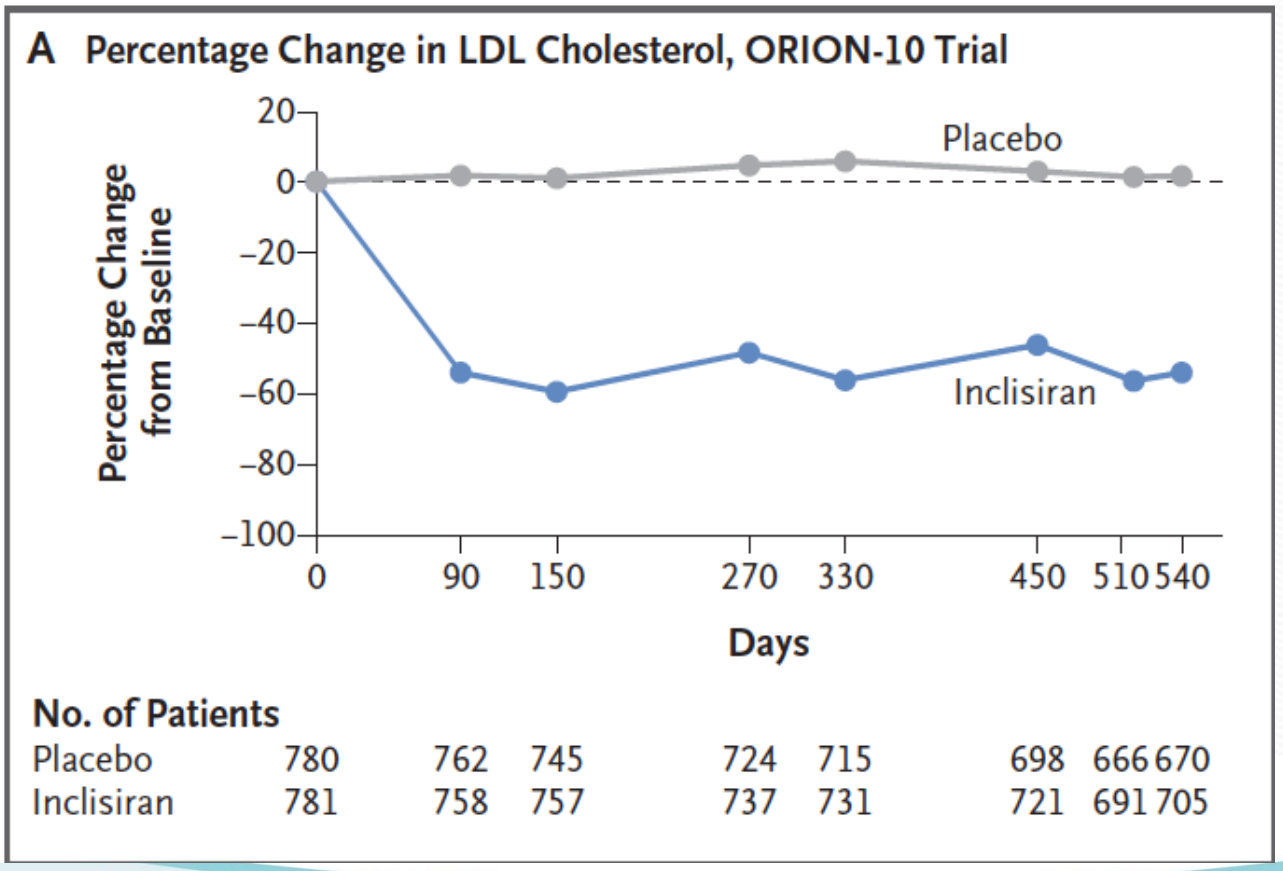
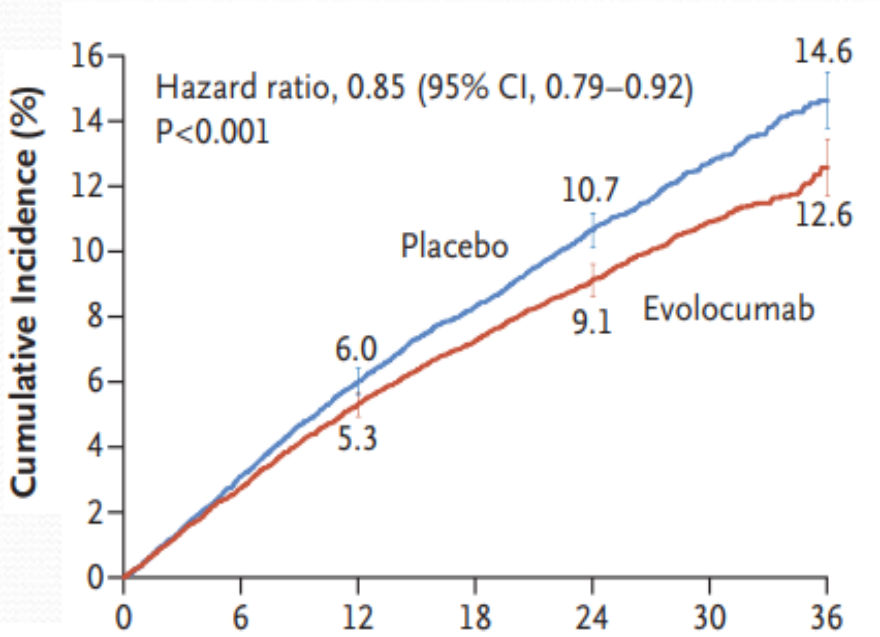
Pharmacologic Intervention with SiRna for LDL

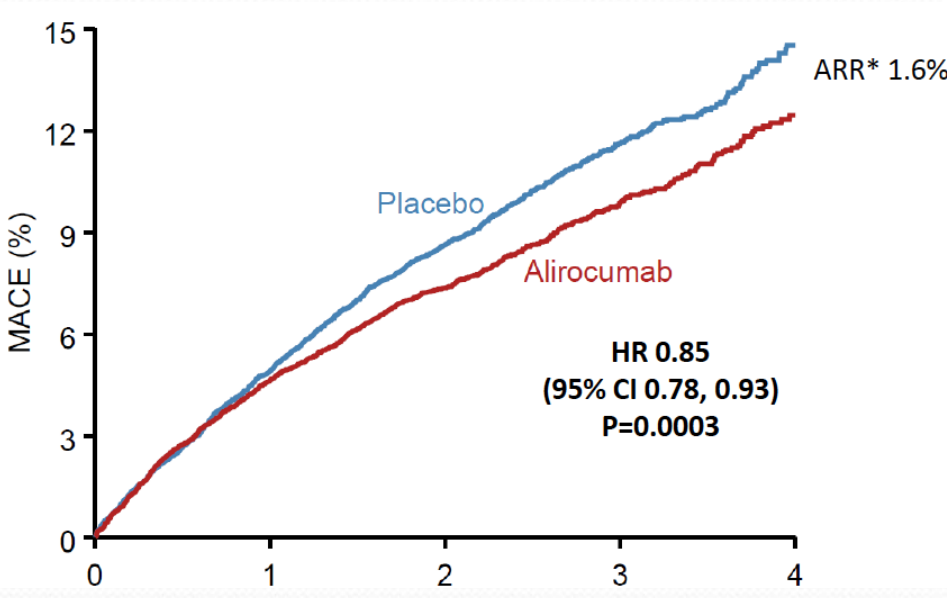
Inclisiran



Ray et al. N Eng J Med 2020;382:1507-19.

PCSK-9 Inhibitors and Outcomes





Sabatine MS et al. N Engl J Med 2018
Schwartz GG et al. N Engl J Med 2018

PACMAN-AMI/Evolve

JAMA | Original Investigation

Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction The PACMAN-AMI Randomized Clinical Trial

Lorenz Räber, MD, PhD; Yasushi Ueki, MD, PhD; Tatsuhiko Otsuka, MD; Sylvain Losdat, PhD; Jonas D. Häner, MD; Jacob Lonborg, MD; Gregor Fahrni, MD; Juan F. Iglesias, MD; Robert-Jan van Geuns, MD, PhD; Anna S. Ondracek, MSc; Maria D. Radu Juul Jensen, MD, PhD; Christian Zanchin, MD, PhD; Stefan Stortecky, MD; David Spirk, MD; George C. M. Siontis, MD, PhD; Lanja Saleh, PhD; Christian M. Matter, MD; Joost Daemen, MD, PhD; François Mach, MD; Dik Heg, PhD; Stephan Windecker, MD; Thomas Engstrøm, MD, PhD; Irene M. Lang, MD; Konstantinos C. Koskinas, MD, MSc; for the PACMAN-AMI collaborators

Raber et al. JAMA 2022;327(18):1771-1781

Patients with AMI (N-STEMI/STEMI) undergoing coronary angiography & successful PCI of the infarct vessel & 2 non-infarct related arteries with angiographic evidence of atherosclerosis (20-50% DS)

Alirocumab PACMANAMI

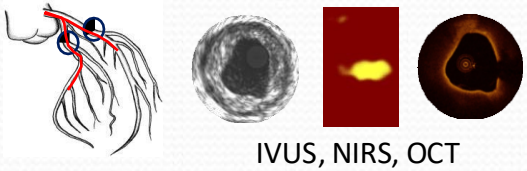
POC

No statin, LDL >125 mg/dL (>3.2 mmol/L)

On Statin, LDL >70 mg/dL (>1.8 mmol/L)

Enrollment of 300 Patients

Baseline



IVUS, NIRS, OCT

Baseline blood sampling

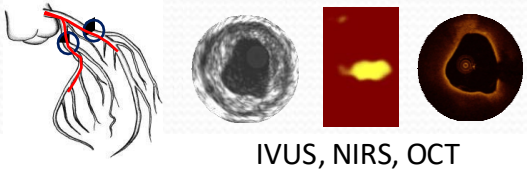
Alirocumab s.c. 150 mg / 2 weeks + Rosuvastatin 20 mg

R 1:1

Placebo s.c. / 2 weeks + Rosuvastatin 20 mg

Initiated <24 hrs after PCI

52 weeks



IVUS, NIRS, OCT

Blood sampling 4 weeks
3 visits, 4 phone calls
Blood sampling 52 weeks

Am Heart J 2021;238:33-44.

ENDPOINTS: Plaque burden, NIRS lipid, cap thickness

Raber et al. JAMA 2022; 327(18):1771-1781

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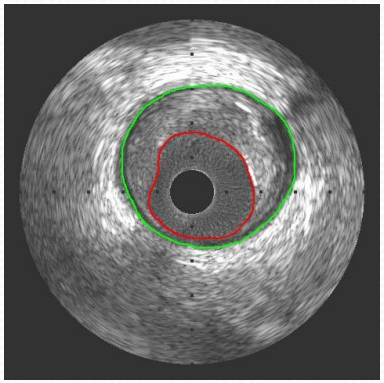
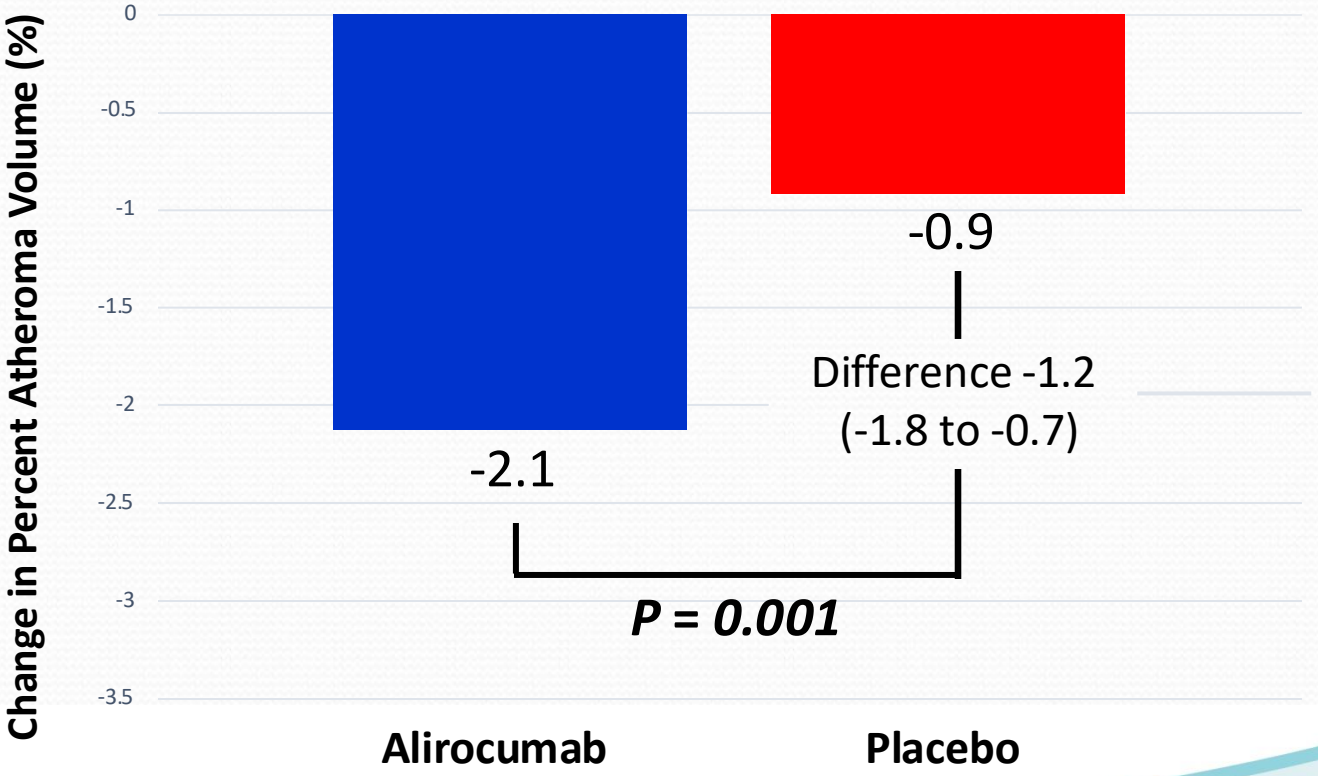
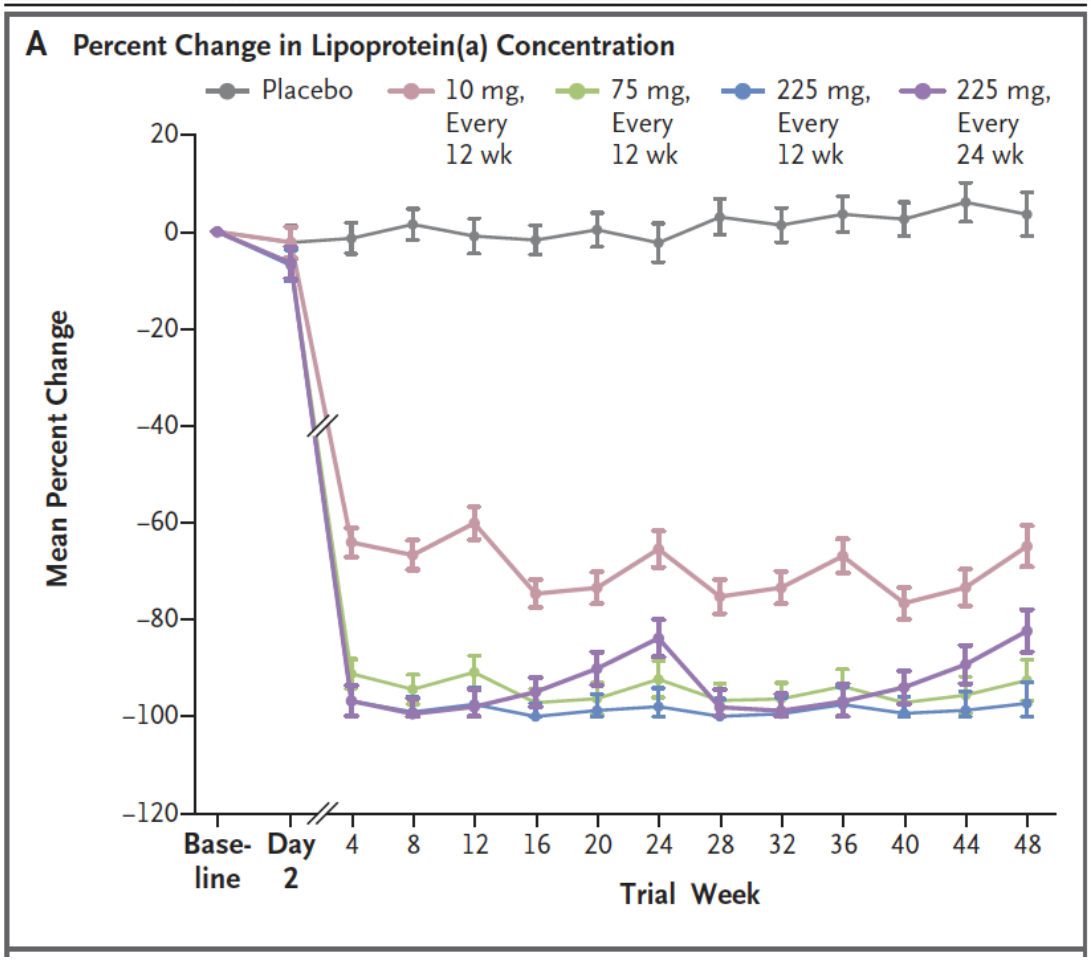
Primary EP:
Change in Percent Atheroma Volume (IVUS)





Ocean a Lp(a) Study (Olpasiran) - SiRNA



N Engl J Med 2022;387:1855-64.

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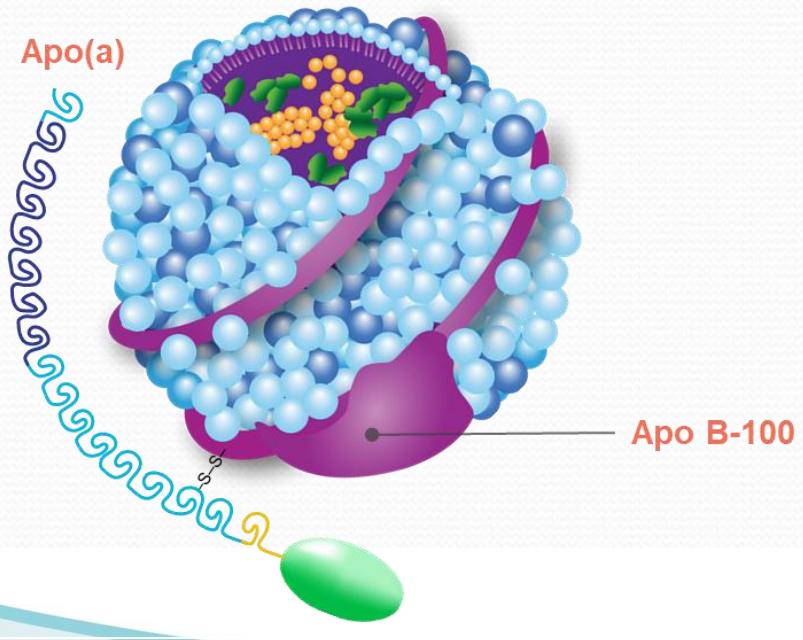
Lipoprotein A - A Sleeper



- More than 1.4 billion individuals worldwide
- More than 70 million Americans
- 70-90% of the level is under genetic control
- Lifestyle and diet have no impact on this risk

LP(a) Recommendation

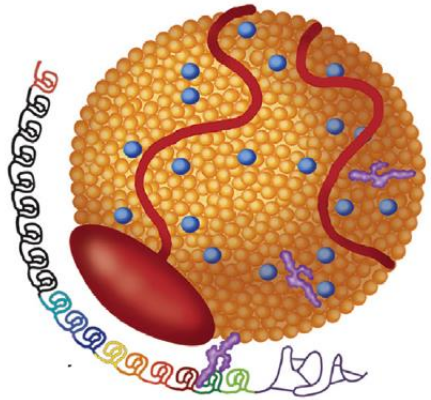
- "It is absolutely crucial that patients have their LP(a) level measured, particularly those with premature cardiovascular disease or strong family histories…..almost everybody should now have LP(a) measured, probably in their twenties, to know if they are at risk for ASCVD and can get proper guidance"

CENTRAL ILLUSTRATION Lipoprotein(a) Is Associated With Adverse Plaque Progression

191 Patients With Advanced Multivessel Coronary Artery Disease on Long-Term Guideline-Directed Preventive Therapies

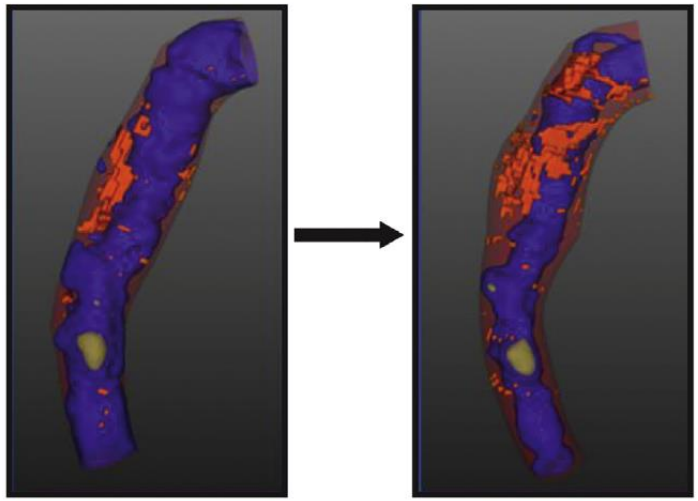
Lp(a) Measurement

Example patient Lp(a) concentration: 82.2 mg/dL



Repeat CCTA to Assess Plaque Progression

Low-attenuation plaque volume (orange regions) increased from 81.4 mm^3 to 132.9 mm^3



Elevated lipoprotein(a) is associated with accelerated progression of low-attenuation plaque, independent of traditional cardiovascular risk factors

Kaiser, Y. et al. J Am Coll Cardiol. 2022;79(3):223-233.

1.4 Billion Worldwide, More than 70 million Americans

Kaiser et al. J Am Coll Cardiol 2022;79:223-33

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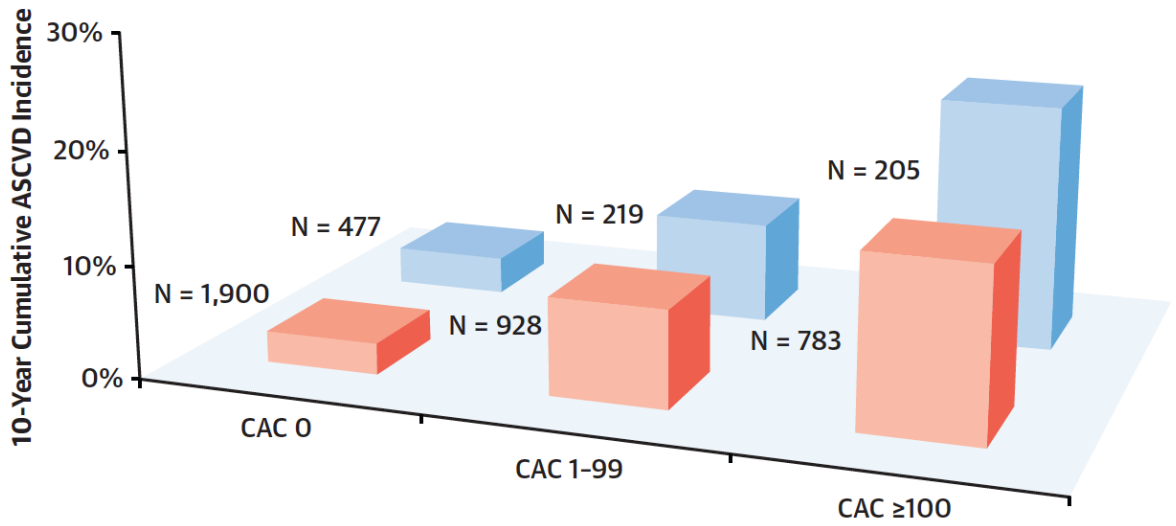
Multi-Ethnic Study of Atherosclerosis/Dallas Heart Study

FIGURE 1 10-Year ASCVD Incidence Across Lp(a) (Quintiles 1-4, Quintile 5) and CAC (0, 1-99, ≥100) Groups



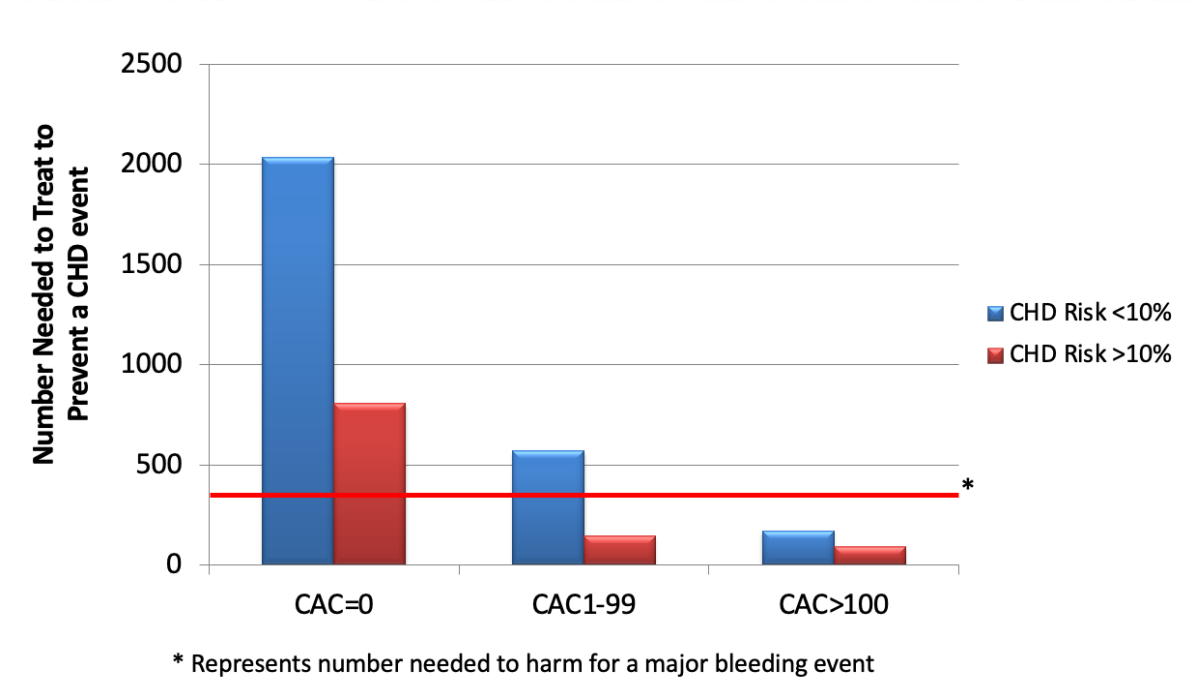
	CAC 0	CAC 1-99	CAC ≥100
Lp(a) Quintile 5	3.4% (1.7%-5.0%)	9.0% (5.0%-13.0%)	22.0% (15.9%-28.0%)
Lp(a) Quintiles 1-4	2.8% (2.0%-3.6%)	8.6% (6.7%-10.6%)	15.1% (12.5%-17.8%)

Lp(a) Quintile 5 Lp(a) Quintiles 1-4

The highest 10-year atherosclerotic cardiovascular disease (ASCVD) incidence among MESA (Multi-Ethnic Study of Atherosclerosis) participants was seen in the lipoprotein(a) [Lp(a)] quintile 5 with coronary artery calcium (CAC) ≥100 group, while the lowest 10-year ASCVD incidence was seen in the Lp(a) quintiles 1 to 4 with the CAC = 0 group. A higher 10-year ASCVD incidence was apparent in the Lp(a) quintile 5 group when compared with Lp(a) quintiles 1 to 4 group only among participants with CAC ≥100.

Mehta et al. J Am Coll Cardiol 2022;79:757-68

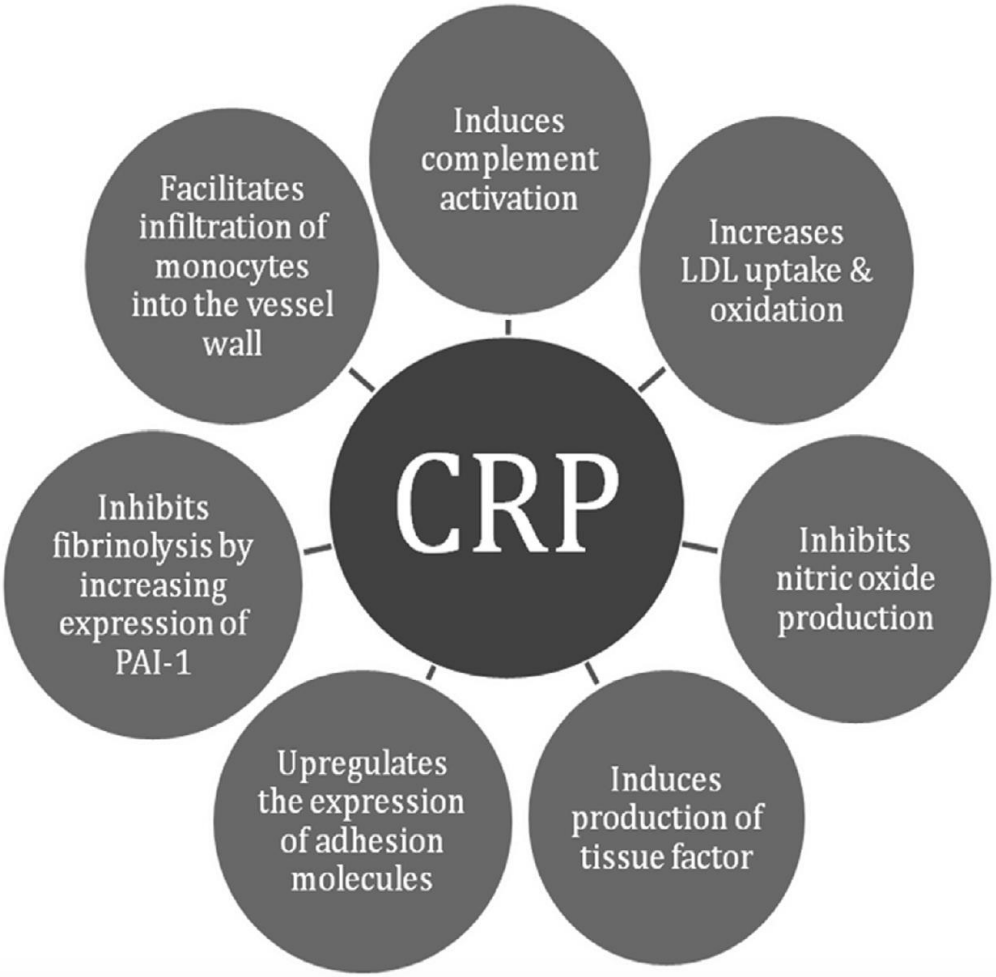
Risk/Benefits of ASA According to CAC



Miedema et al. ASA and CAC – Circ Quality 2014

CONE HEALTH

C-reactive protein, inflammation and coronary heart disease



Shrivastava et al. The Egyptian Heart Journal (2015) 67, 89–97

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Other Cardiac Risk Factor Targets

- Hypertension
- Obesity
- Triglyceride Rich Lipoproteins
- Smoking

Therapeutics

Before open label drug

Month after 1 dose of open label drug

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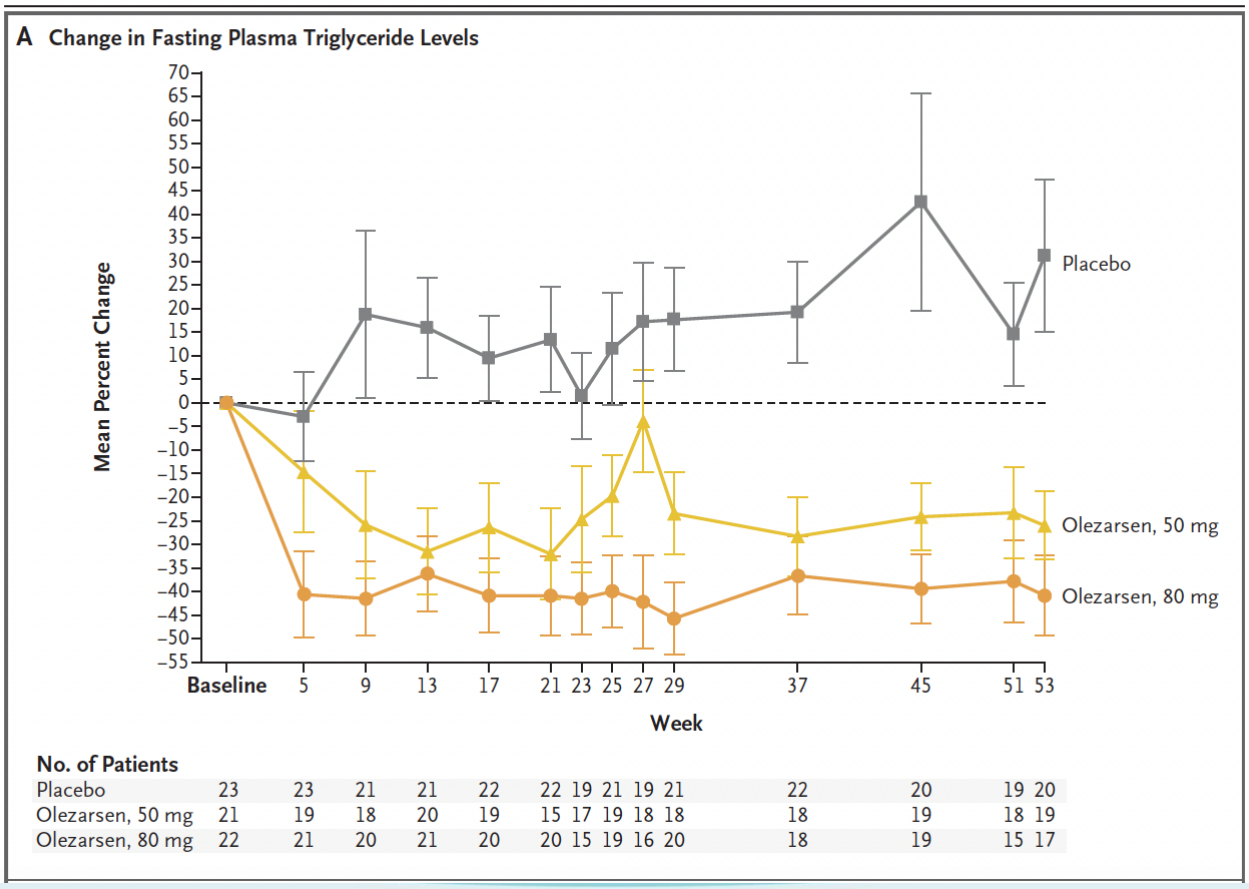
Olezarsen in Familial Chylomicronemia

The NEW ENGLAND JOURNAL of MEDICINE



Apo C III production reduction
N Engl J Med 2024;390:1781-92

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KARDIA-3 Cohort B

Randomized, double-blind study in high CV risk patients with uncontrolled hypertension

Study Population

N~60

Key Inclusion Criteria

- Adult patients 18+ years of age
- CKD (eGFR 30-44 ml/min/1.73m²)
- Automated office SBP (AOSBP) ≥140 & ≤170 mmHg
- 24-hour mean ASBP ≥ 130
- On stable doses of 2+antihypertensive agents; one must be a thiazide/thiazide-like diuretic or CCB or loop diuretic
- ACEi/ARB allowed at appropriate therapeutic doses

Key Exclusion Criteria

- Secondary HTN
- Proteinuria > 3g/d
- K ≥ 4.8 mEq/L at plasma screening
- Poorly controlled DM (eg., A1C>9)
- CV event within 3 months
- EF< 40%
- Clinically significant valvular heart disease
- NYHA class III or IV heart failure

Maintained on stable background antihypertensive regimen

1:1:1:1 RANDOMIZATION

- Zilebesiran 600 mg
- Zilebesiran 300 mg
- Zilebesiran 150 mg
- Placebo

6-month DBTP

Continue background antihypertensive medication regimen
aHTN intensifcation allowed only after M3

Outcomes and Endpoints

Primary Objective

- To evaluate the add-on effect of zilebesiran on SBP as assessed **by OBPM** at Month 3

Primary Endpoint

- Change from baseline at Month 3 in **seated office SBP**

Secondary Endpoint

- Change from baseline at Month 3 and Month 6 in 24 hour mean SBP and DBP, assessed by ABPM
- Change from baseline at Month 3 in seated office DBP
- Change from baseline at Month 6 in seated office SBP and DBP
- Change in serum AGT

No Stratification for Cohort B

Initiate Mar 2024

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Icosapent Ethyl On LAP Regression – Evaporate Trial

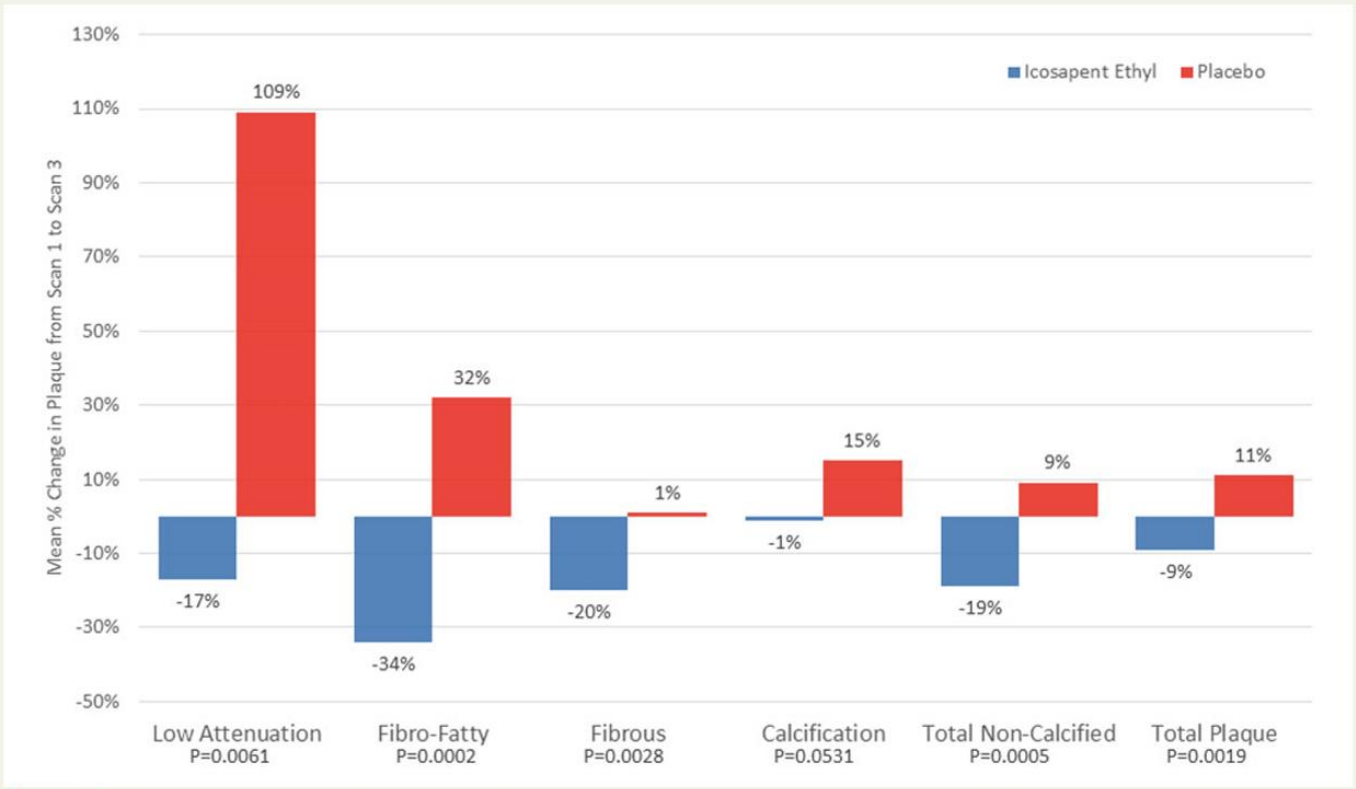

Figure 1 Mean plaque progression for each type of plaque composition measured on cardiovascular CT for the icosapent ethyl and placebo groups (icosapent ethyl group, $n = 31$ and placebo group, $n = 37$) after multivariable adjustment. Univariable analysis and multiple linear regression were used to examine the change in plaque levels between the cohorts. Multivariable models were adjusted by age, sex, diabetes status, hypertension, and baseline triglyceride levels. All statistical analyses report two-sided *P*-values for the outcomes. A *P*-value <0.048 was considered significant for the outcomes.

80 patients
Scanned at
18 months

Budoff et al. EHJ 2020;41:3925-3932

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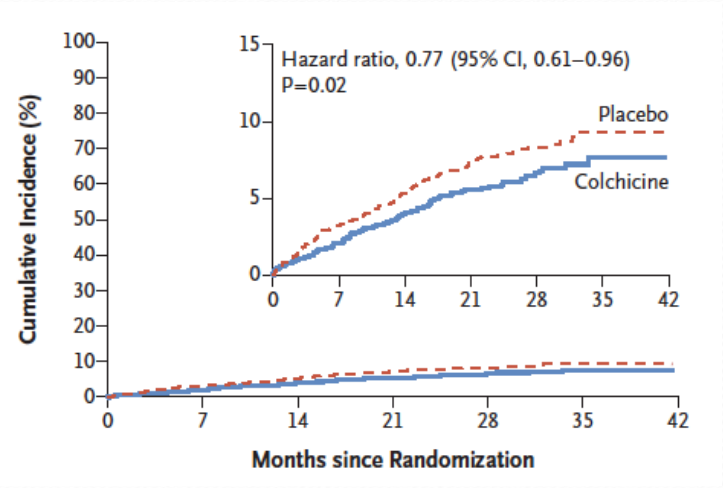
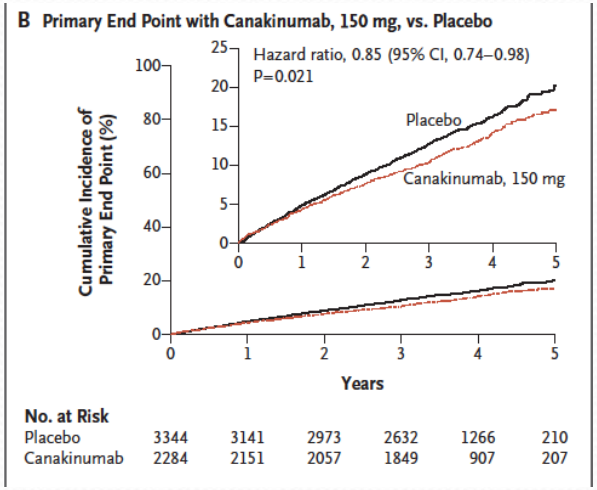
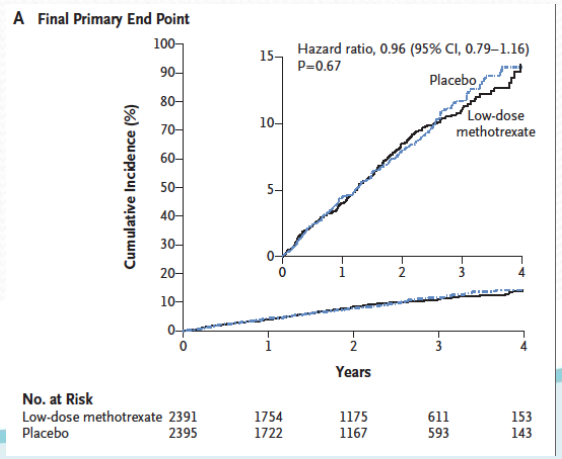
Colchicine, MTX, and Canakinumab





Ridker et al. NEJM 2017; 377:1119-1131.
Tardif et al. NEJM 2019; 381:2497-505
Ridker et al. NEJM 2019;380:752-762



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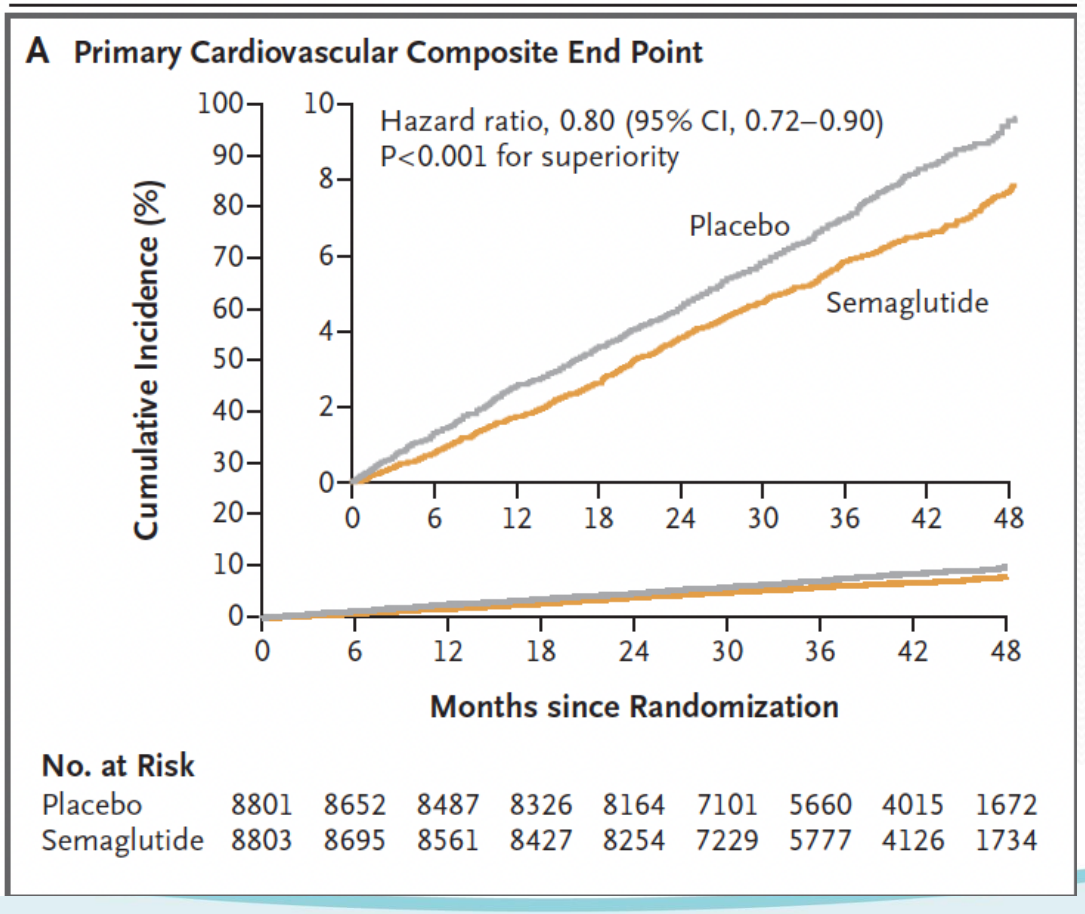
Semaglutide and Cardiovascular Mortality In Patients with Obesity and No Diabetes



Lincoff et all. N Engl J Med 2023;389:2221-32.

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Conclusions

- Vulnerable plaque results in unexpected ACS
- Life style changes are key to a healthy milieu, but multiple unidentified risk factors can elevate risk unexpectedly
- Imaging techniques for vulnerable plaque identification are improving rapidly, and can be obtained non invasively
- Targeted therapeutic options are developing rapidly
- A highly organized, strategic approach to preventive cardiovascular care is needed

THANK YOU

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