ATHEROSCLEROSIS PROGRESSION & REGRESSION: AGENTS TO IMPACT PLAQUE BURDEN

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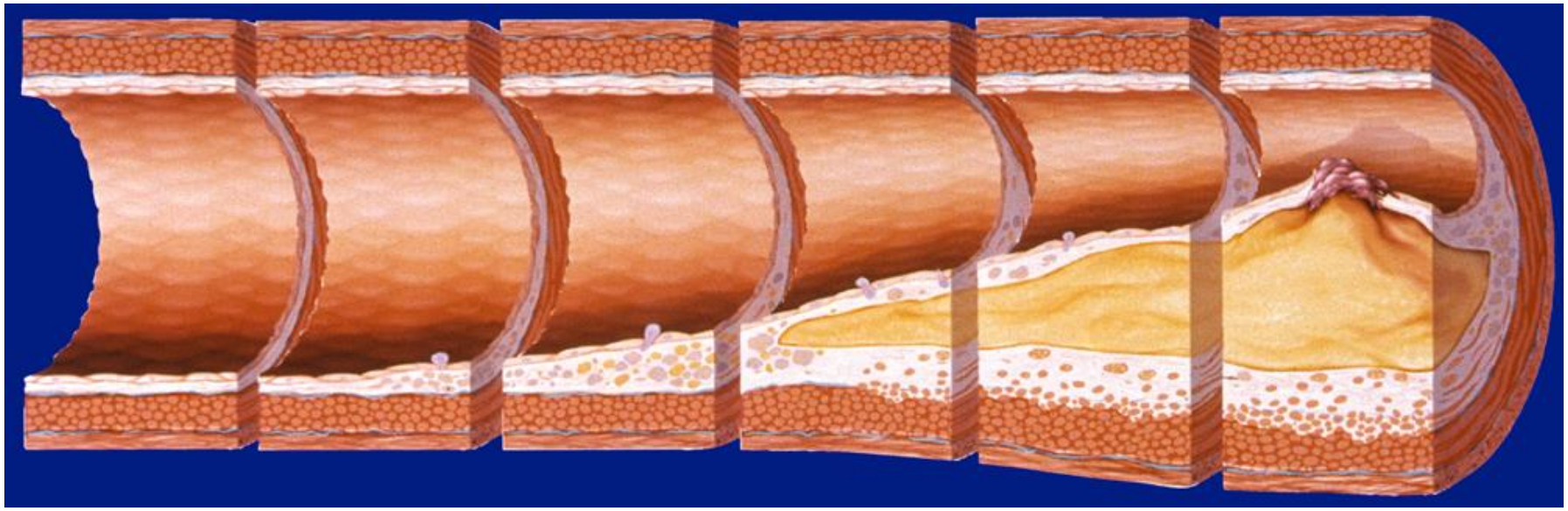
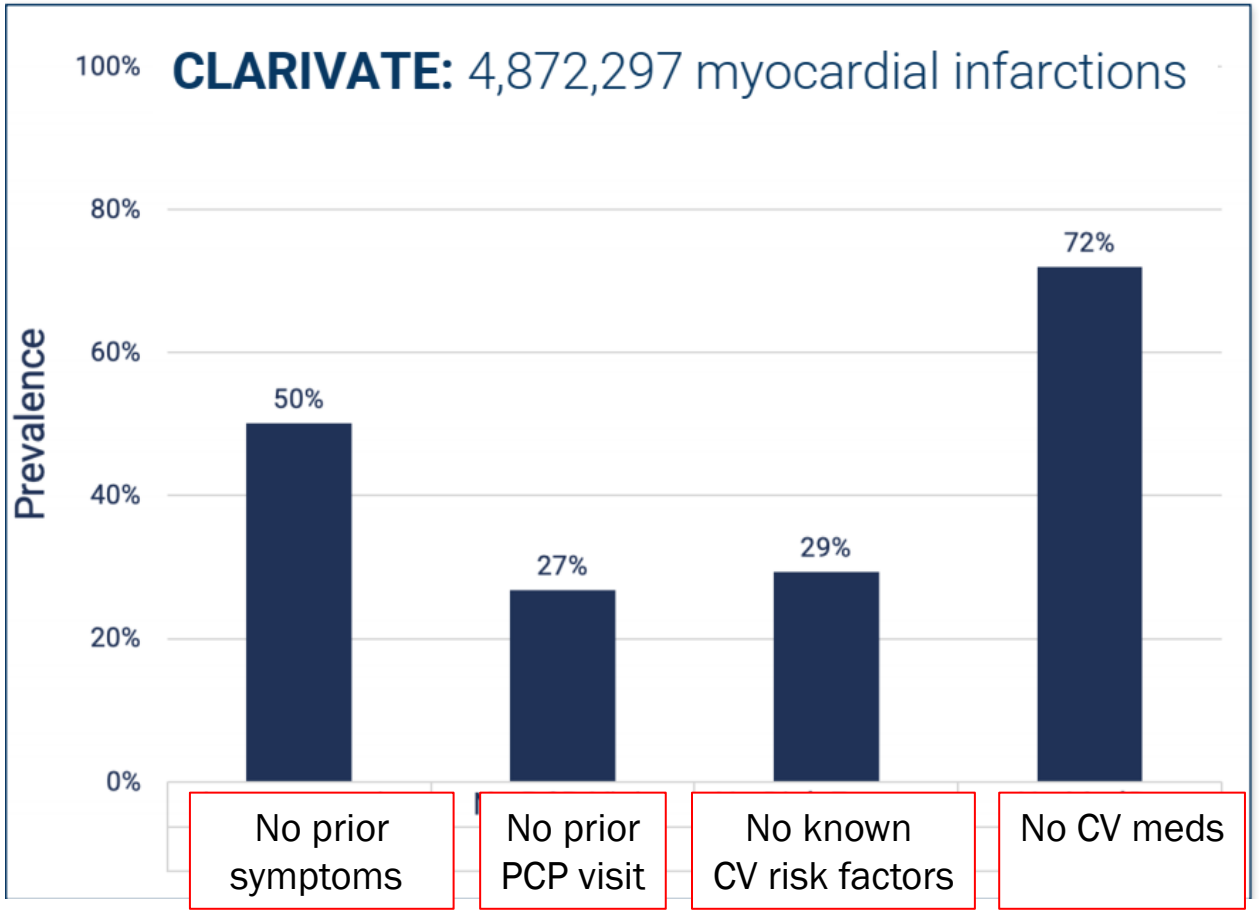
Atherosclerosis Timeline



Adapted from Stary HC et al. Circulation. 1995; 92:1355-1374.

Strategies for ASCVD Risk Mitigation Still Unable to Prevent Many MI's

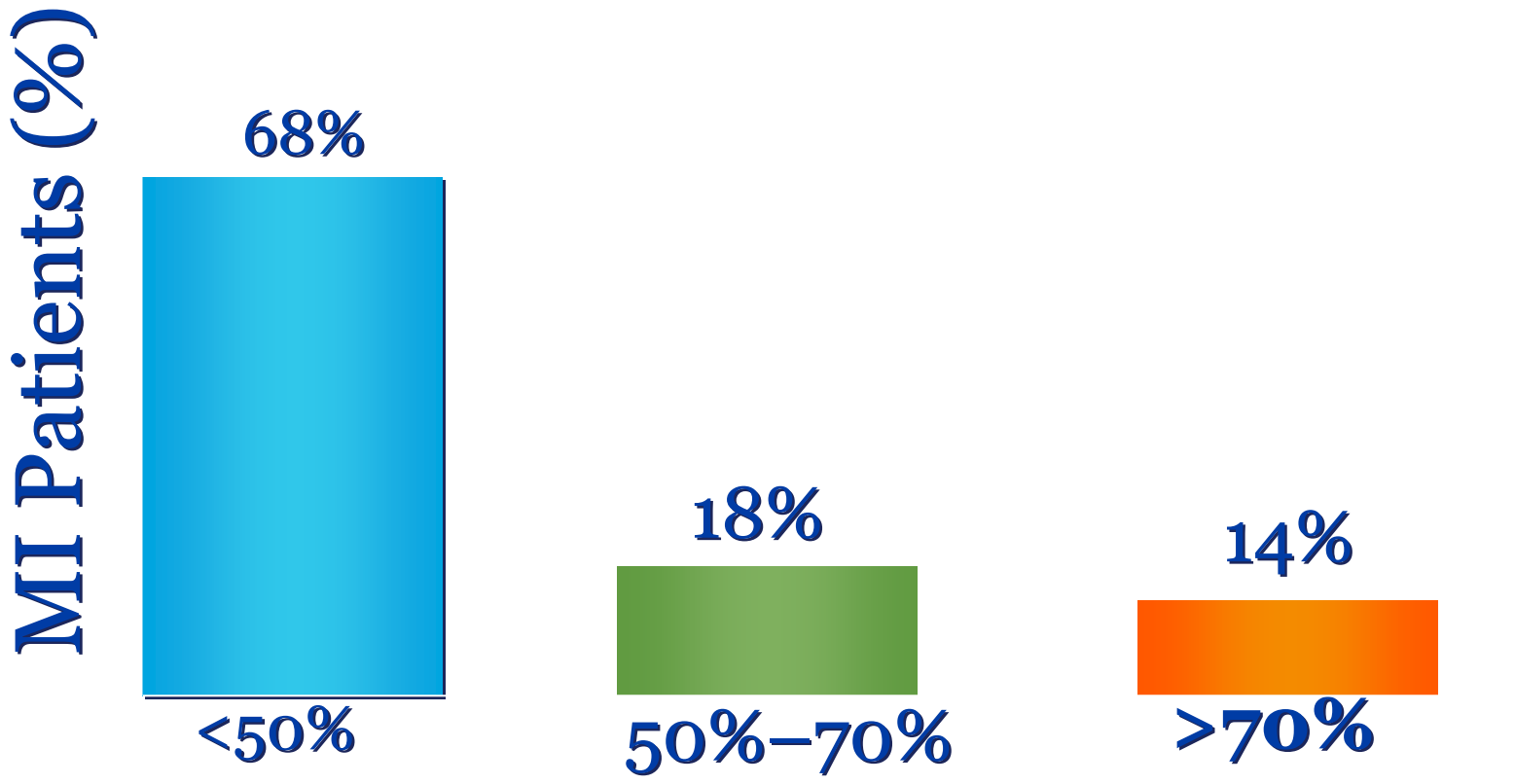
- Most patients with 1st MI unaware beforehand that they had CAD
- 72% of individuals not on preventive therapy prior to 1st MI. 50% were asymptomatic (no h/o dyspnea/chest pain/reduced exercise tolerance)
- Risk scoring systems (PCE, SCORE2 etc) for MI prediction miss 33% of MI cases
- Even when ASCVD risk is predicted as intermediate or higher, >40% of pts don't receive optimal preventive therapy (→ ability of CT to improve adherence)



Figtree et al, Lancet 2019
Benjamin et al, Circ 2019

MYOCARDIAL INFARCTION

STENOSIS SEVERITY AND RISK

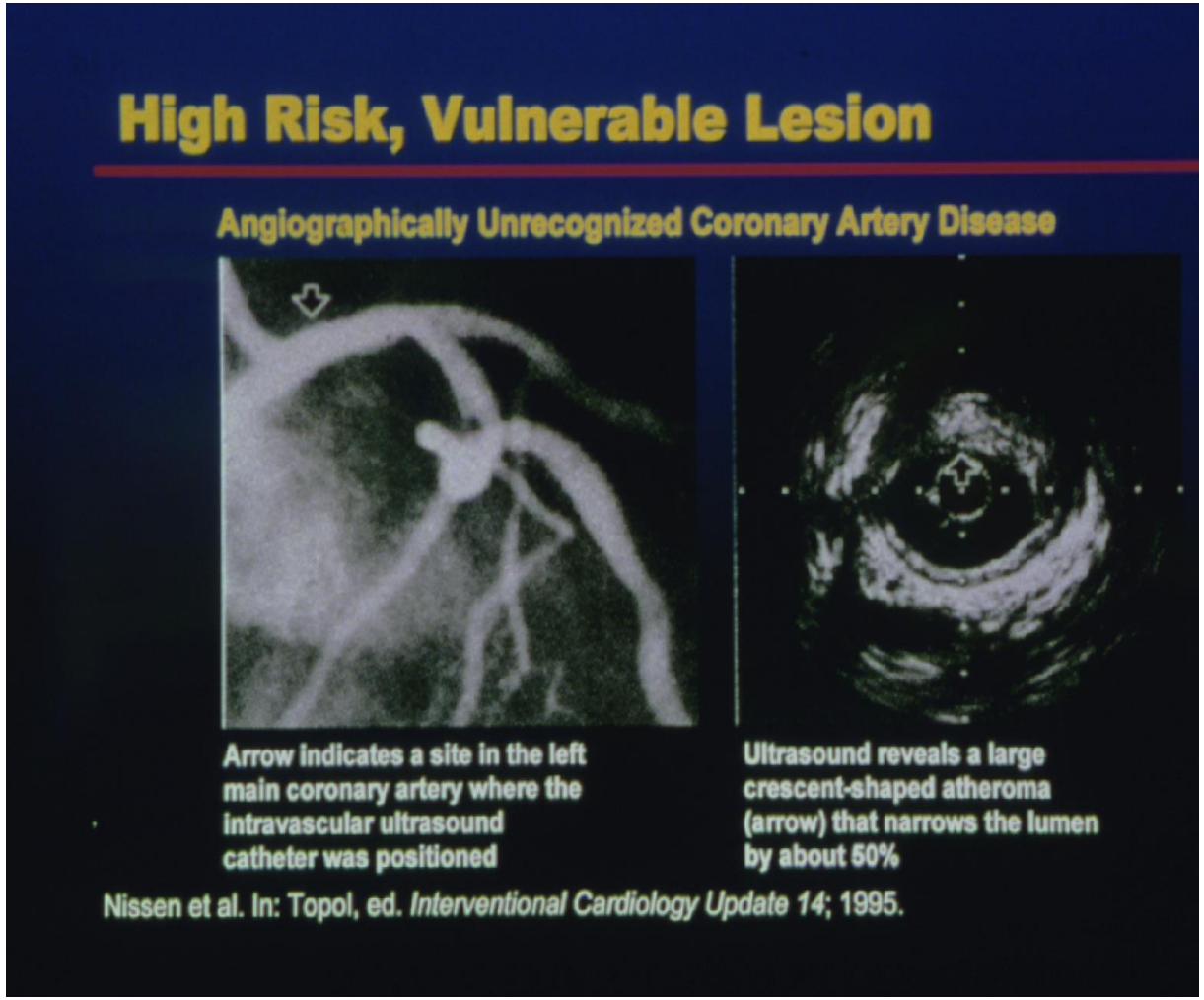


DEGREE STENOSIS PRIOR TO A MYOCARDIAL INFARCTION

Falk E, et al. Circulation. 1995; 92: 657-671.

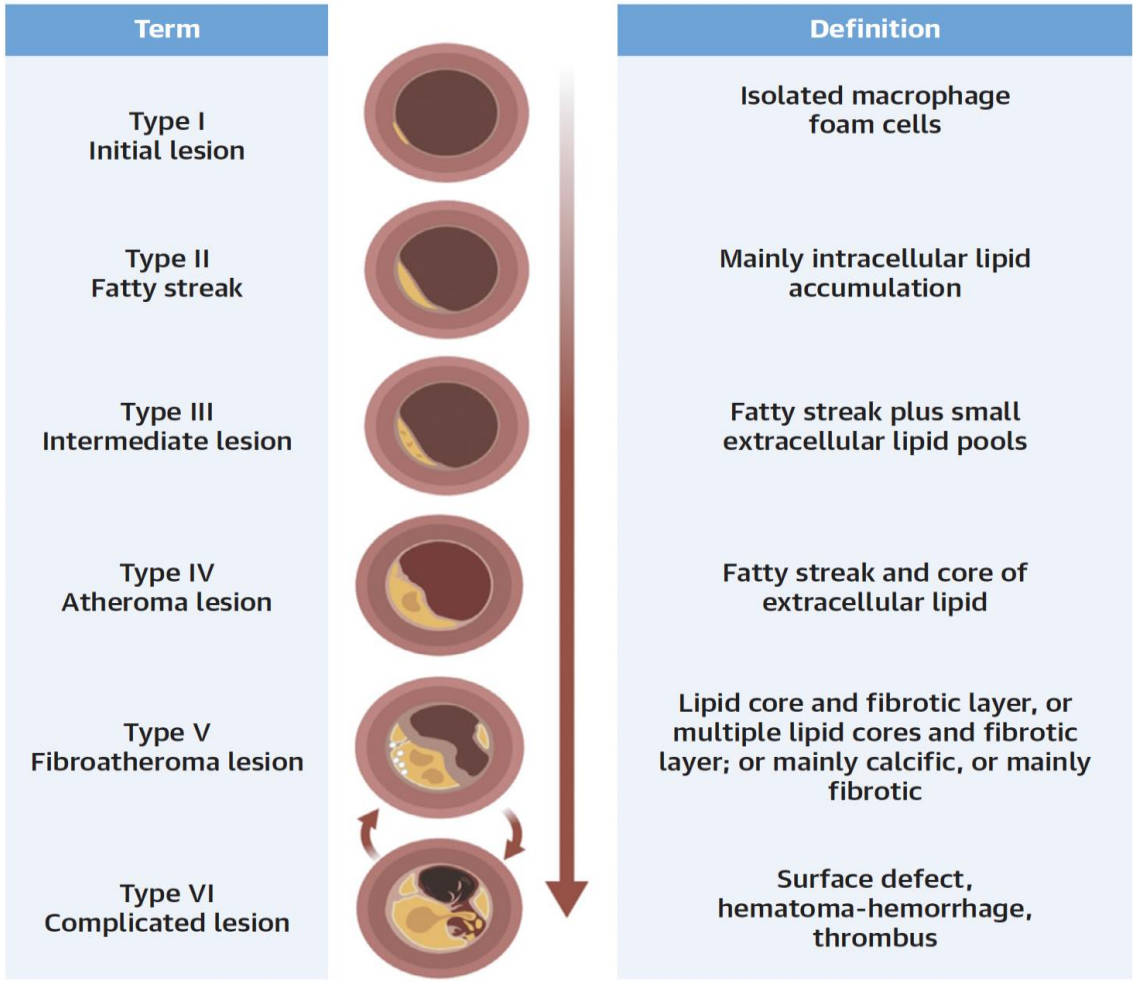
PLAQUE: TO REGRESS OR NOT TO REGRESS-THAT IS THE QUESTION

- **Imaging Modalities can be used to evaluate plaque characteristics**
- **Changes in plaque volume & composition in response to treatment can be assessed**
- **Improved cardiovascular outcomes by changes in plaque**
- **Treatment Approaches to affect coronary plaque**



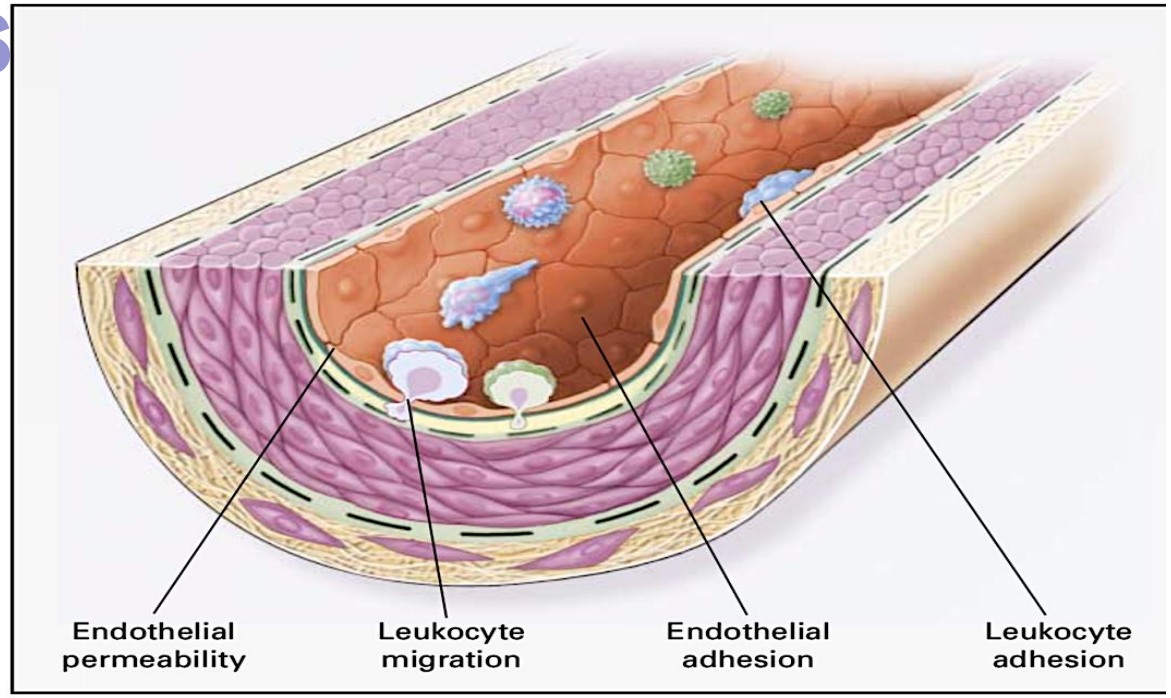
JOURNEY OF PLAQUE FORMATION

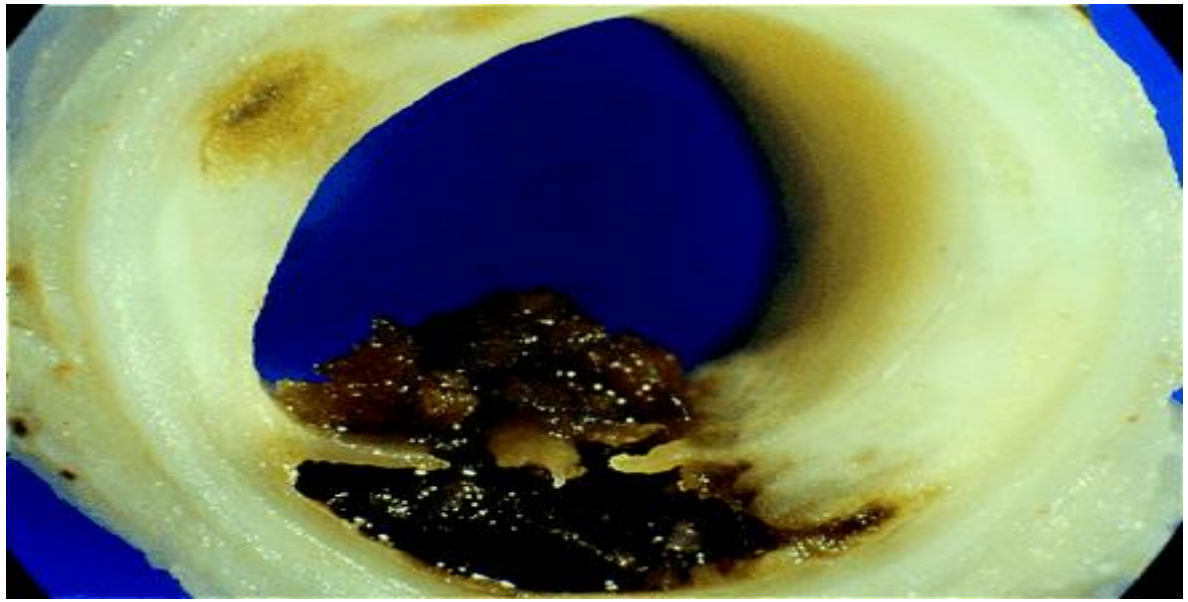
- Atherosclerotic Plaque begins with endothelial dysfunction
- Oxidized LDL moves into the intima of damaged endothelium which initiates an inflammatory process
- LDL ingested by macrophages to form foam cells, smooth muscle cells proliferate-fibrous cap
- Plaque propagates over time leading to progression
  - **Stable:** intimal thickening, thick cap
  - **Unstable:** Thin fibrous cap, inflammatory cells
- Positive remodeling: Glagov Phenomenon in which internal elastic lumen area accommodates an increase of 40%.....



INFLAMMATION AND ATHEROSCLEROSIS

- Inflammation may determine plaque stability
  - Unstable plaques have increased leukocytic infiltrates
  - T cells, macrophages predominate rupture sites
  - Cytokines and metalloproteinases influence both stability and degradation of the fibrous cap
- Lipid lowering may reduce plaque inflammation
  - Decreased macrophage number
  - Decreased expression of collagenolytic enzymes (MMP-1)
  - Increased interstitial collagen
  - Reduced calcium deposition

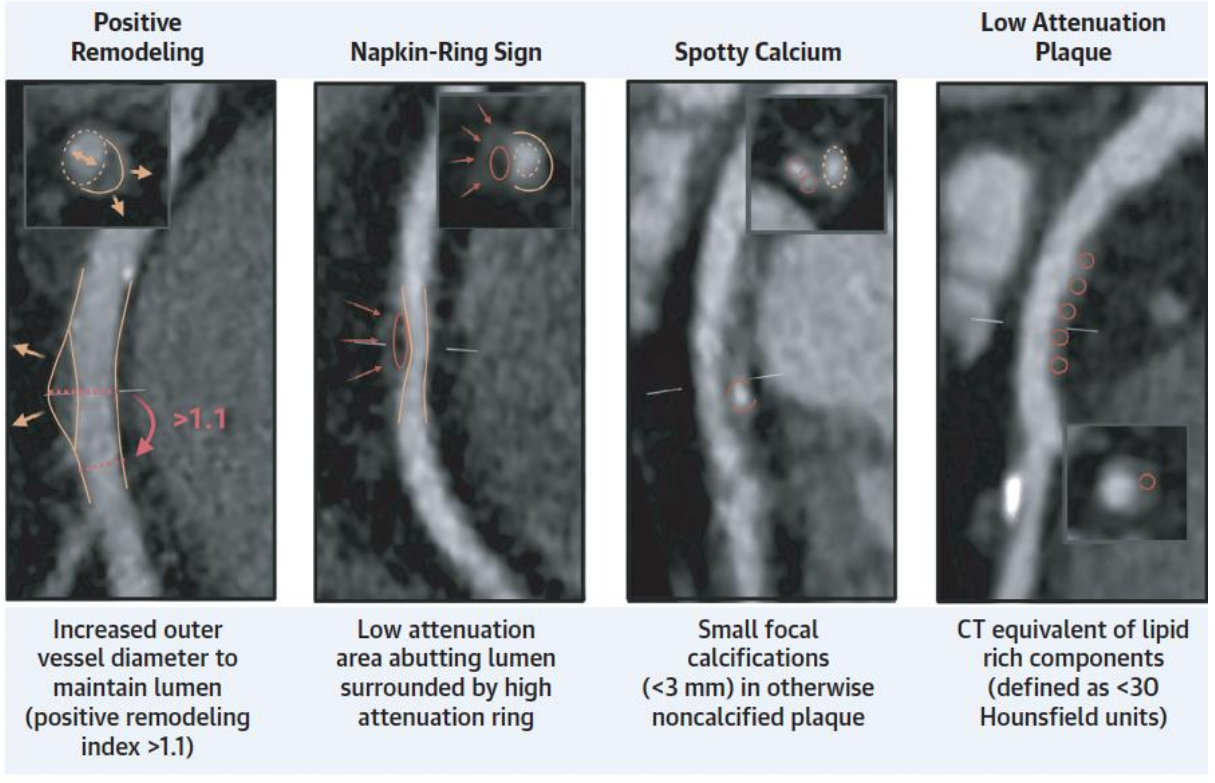




Ross, NEJM, 1999

IMAGING STUDIES HAVE DEMONSTRATED

- In 10-20% of non-culprit lesions progress 8-12 months before Acute Coronary Syndrome event
- Lesions with large plaque burden or thin fibrous cap, and positive remodeling are more likely to progress
- Plaque Progression have higher rates of coronary events, up to 15-20% at 1 year vs. <1% without progression
- MISSION: Identify plaque progression and high risk plaque



Plaque features associated with increased risk of cardiac events (11). Positive remodeling: presence of an outer vessel diameter which is 10% greater than the mean of the diameter of the normal adjoining vessel (ie, a remodeling index >1.1 shown by the ratio of **dotted red line** at enlarged region to **dotted red line** at normal vessel); Napkin-ring sign: area of low CT attenuation area **(red outline)** that abuts the lumen with a high attenuation ring surrounding **(red arrows)**; spotty calcium: small focal calcifications of <3 mm in any direction **(red tracings)**; low attenuation plaque: presence of a central focal area within the plaque that has low CT attenuation, usually defined as at least 1 voxel with <30 HU **(red tracings)**.

Barbato E, et al.JACC 2016;68:2247. Yamamoto MH, et al. Circ Cardiovasc Imaging. 2017:10(9),. Puncher SB, et al. JACC 2014;64;684.
Shaw LJ, et al. J Cardiovasc Comput Tomogr. 2021; 15:93. Dawson L, et al. JACC;79:66. Motoyama S, et al JACC. 2009; 54: 49.

PLAQUE REGRESSSION

- **Reduction in plaque lipid content, macrophages and cooling the inflammatory state**
- **Coronary Angiography: All about the lumen with regression assumed with increases in luminal diameter**
- **Advanced Imaging:**
  - **Reduction Plaque Volume**
  - **Improvement plaque composition: fibrous cap thickness, necrotic core volume, positive remodeling to decrease risk of plaque rupture**
  - **Caveat : Not all plaque is modifiable- calcified plaque rarely changes**
  - **Act Early**

TABLE 1 An Overall Comparison of the Main Imaging Modalities

Modality	IVUS	OCT	CCTA	PET/CT
Imaging type	Invasive		Noninvasive	
Resolution	Axial: 100-150 µm Lateral: 200-300 µm	Axial: 15-20 µm Lateral: 20-40 µm	Spatial: 0.5-0.625 mm (z-axis), 0.5 mm (x- to y-axes)	
Tissue penetration	4-8 mm	0.5-1.5 mm	-	-
Luminal stenosis	Detectable	Detectable	Detectable	Detectable
Plaque volume	Detectable	Detectable	Detectable	Detectable
Plaque composition	With postprocessing	Detectable	Detectable	Detectable

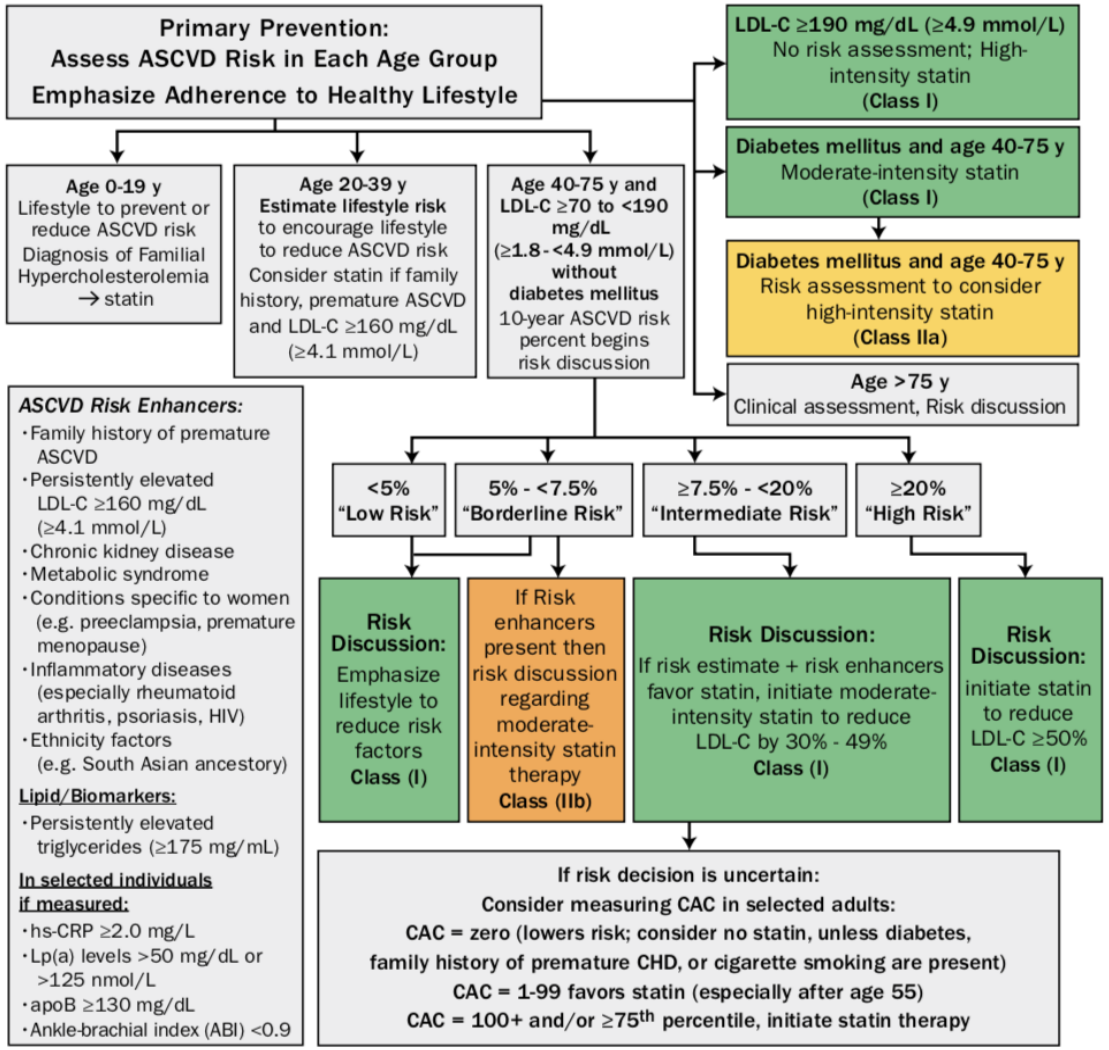
CCTA = coronary computed tomography angiography; CT = computed tomography; IVUS = intravascular ultrasound; OCT = optical coherence tomography; PET = positron emission tomography.

Dawson, L. et al. J Am Coll Cardiol.2022; 79: 66-82.

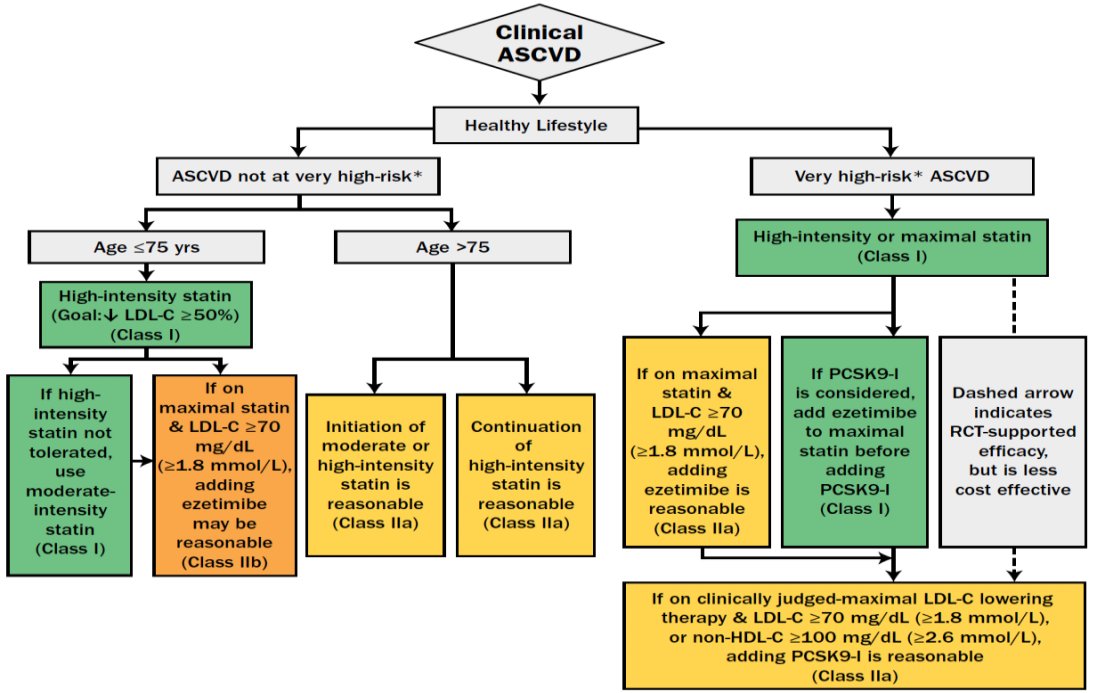
CARDIOLOGIST VS. “PLAQUE-OLOGIST”

THERAPEUTIC TREATMENT OF PLAQUE

2018 AHA/ACC CHOLESTEROL GUIDELINES



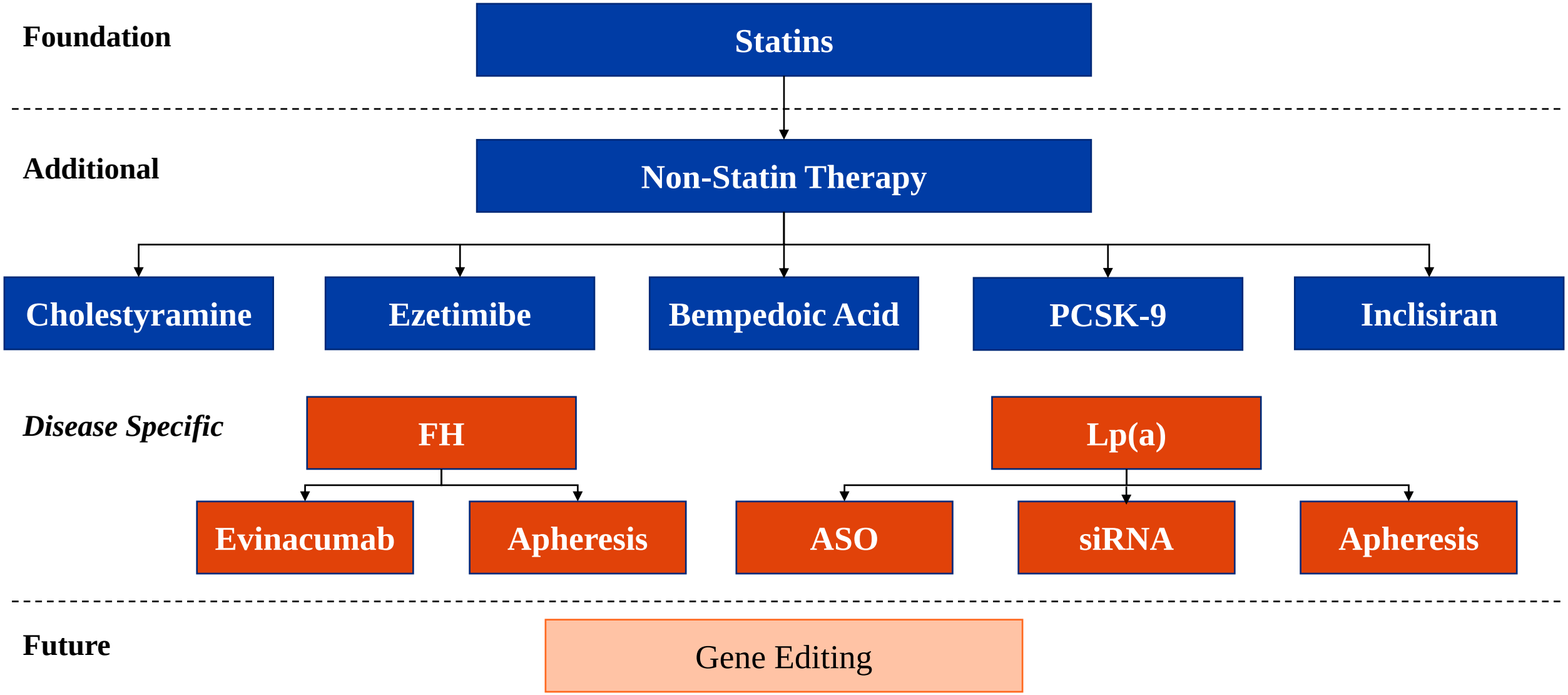
Secondary Prevention in Patients with Clinical ASCVD



Major ASCVD Events
Recent acute coronary syndrome (within the past 12 months)
History of myocardial infarction (other than recent acute coronary syndrome event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ankle brachial index <0.85, or previous revascularization or amputation)
High-Risk Conditions
Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)
Diabetes Mellitus
Hypertension
Chronic kidney disease (eGFR 15-59 mL/min/1.73 m²)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL (≥2.6 mmol/L)) despite maximally tolerated statin therapy and ezetimibe
History of congestive heart failure

*Very High Risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.

Lipid Lowering Therapy 2024



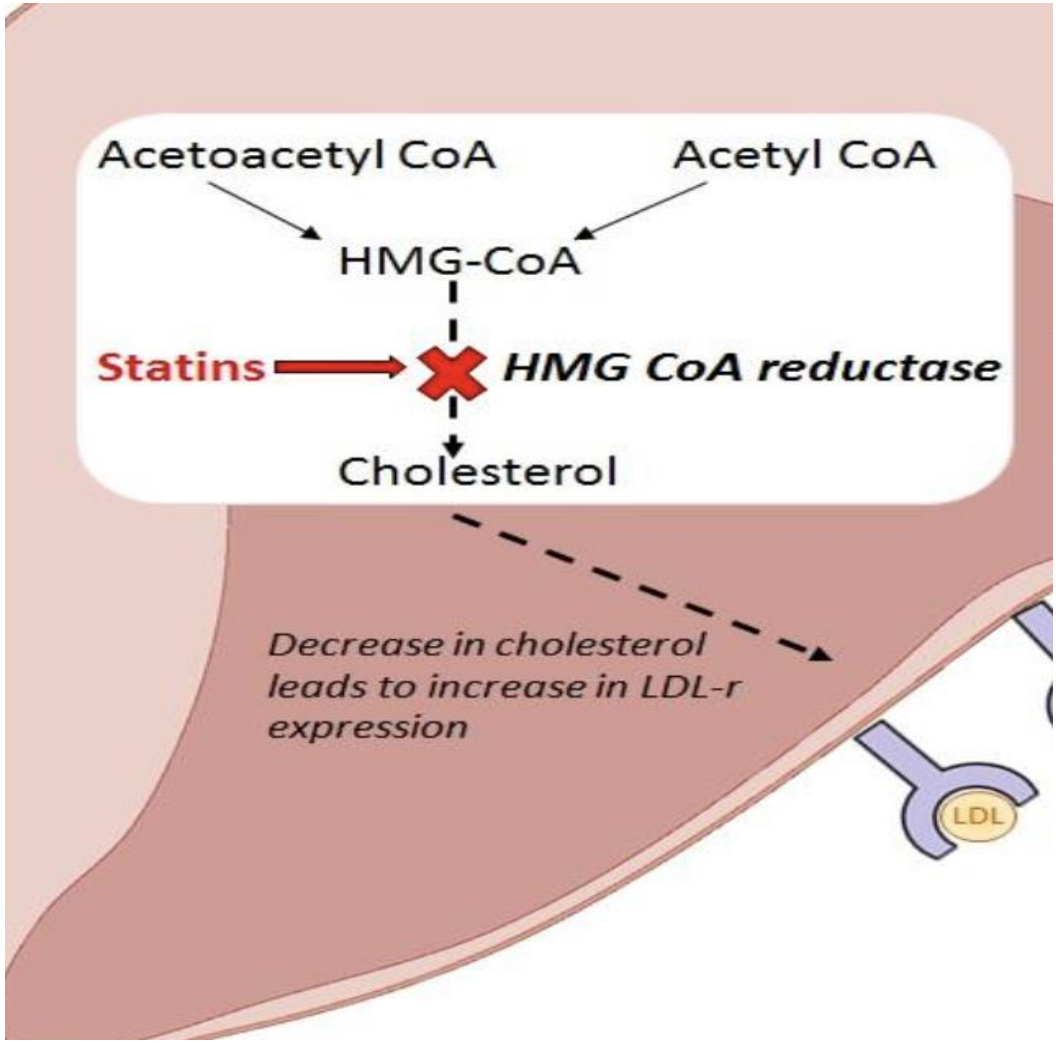
DIETARY & LIFESTYLE CHANGES

- Greatest role in risk factor modification to prevent atherosclerosis
- Ornish, 1998, 48 patients intensive lifestyle change, vegetarian diet, exercise, smoking cessation and psychological support, demonstrated reduced coronary artery degree progression by angiography at 5 years
- Dietary control arms of statin trials had increase in plaque volume
- Diet strategy alone not deterrent for plaque
- IVUS Trial post hoc analysis > 7,000 steps a day had greater plaque regression than < 7,000 steps/day
- Exercise is of some benefit

Ornish D, et al. JAMA,1998,280;2001. Hattori K, et al. J AM Coll Cardiol Img. 2012;5:169. Takagi T, et al. Am J Cardiol 1997; 79:1673
Nishitani.-Yokoyami M et al. Circ J 2018; 83: 101.

STATIN EFFECTS ON PLAQUE

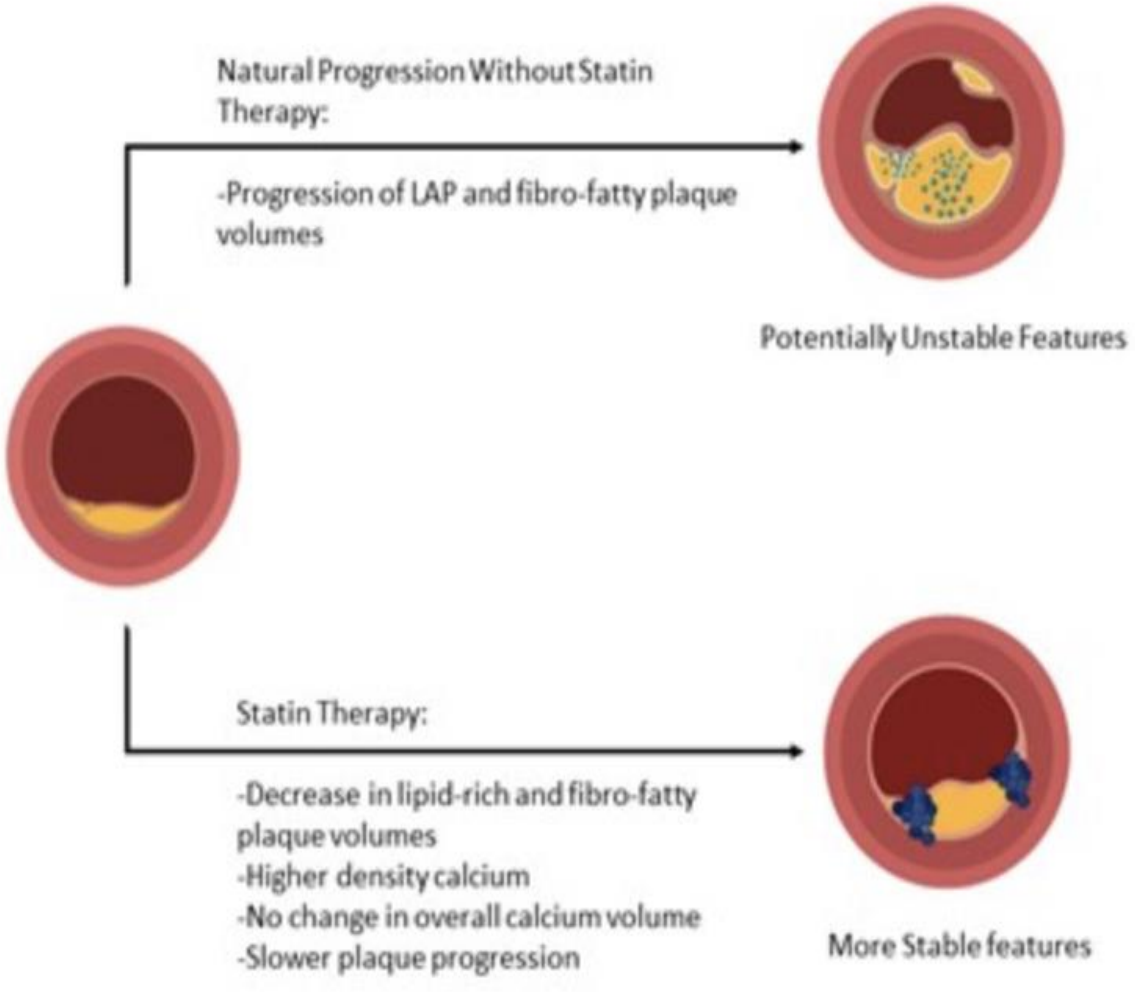
- Reduction in lipid content and macrophages-on rosuvastatin 40 mg- (reduction in inflammation)
- Increased fibrous cap thickness
- Increases in calcified plaque, reductions in non calcified plaque, reductions in high risk plaque defined (> than 2 features: low attenuation, positive arterial remodeling, or spotty calcification) with CCTA
- Statins induce plaque regression in a dose dependent fashion proportional to LDL-C reduction
  - Non-calcified fibrofatty plaque & necrotic core decrease
  - Fibrous & calcified plaque volume increase
- IVUS was mostly used , now CCTA use increased



Lee SE, et al. J Am Coll Cardiol Img. 2018; 11:1475. Raber L, et al. J Am Coll Cardiol. Img. 2019; 12: 1518. Komukai K, et al. J Am Coll Cardiol. 2014; 64:2207

PLAQUE ATTACK: STATINS

- **Statin Benefits:**
  - Plaque Regression
  - Reduce Total Atheroma volume 0-20%
  - Progression in controls about 10%
  - Intravascular ultrasound and CCTA to evaluate plaque burden; and few studies looked at plaque composition with IVUS, OCT, NIRS, PET
- IVUS Trial: Pravastatin 10mg v. placebo; reduction in plaque atheroma at 3 yrs, -7% vs +41%,($p < 0.01$)
- Asteroid Trial: 40 mg rosuvastatin, 2 years, 507 pts, 6.1% in total atheroma with IVUS
- PREDICT Trial: Diabetic patients with CAD had greater plaque volume, more unstable plaque then CAD pts without diabetes; IVUS Trial, Blunted statin effect???



Takagi T, et al. Am L Cardiol. 1997; 79: 1673 Nissen SE, et al. JAMA. 2006; 295: 1556. Kovarnik T, et al. Cardiovascular Diabetology.2017; 16:156.

Kazzi, BE, Feldman D, Blumenthal RS, Zadeh AA; Commentary ACC, Effect of Statin Therapy on Progression and Composition of Coronary Plaque on CCTA 11,12,2021

STATIN: PLEIOTROPIC & CLINICAL EFFECTS

Plaque Stabilization

↓Macrophage cell content, ↑ collagen synthesis

Anti-Inflammatory Benefit

-Reduction of hs-CRP via ↓ IL-6, inflammatory cytokines

-↓ Adhesion Molecules, LDL oxidation, matrix metalloproteinases

Anti- Proliferative Effect

↓ Proliferation & Migration of Smooth Muscle Cells, ↑ Collagen synthesis

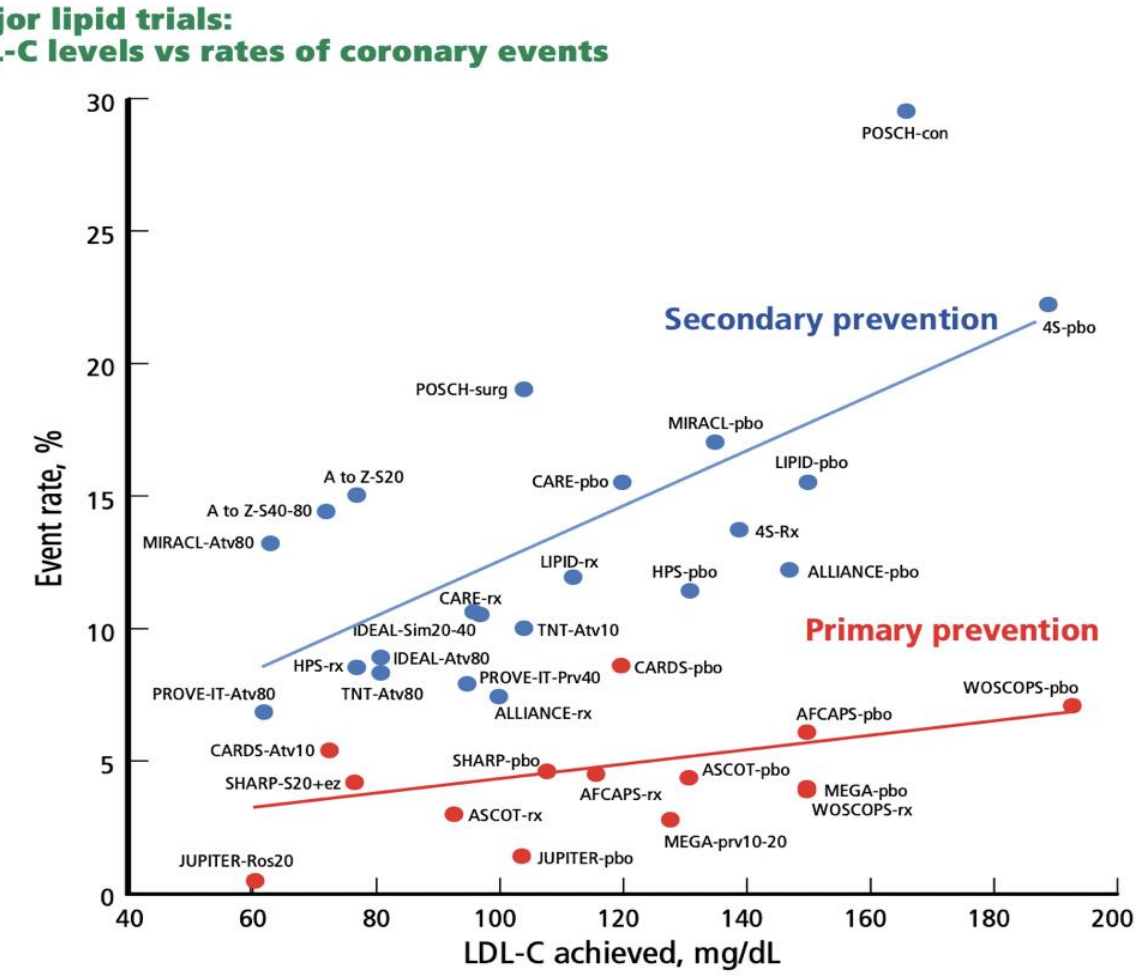
Anti-Thrombotic Effect

↑ PAI-1 Inhibitor,

Endothelial Function

Nitric Oxide synthesis ↑

↓ Endothelin 1 expression



Davignon J. Circulation, 2004 ;109, 39-43, Rosenson R et al, JAMA 1998;279 (20): 1643-1650.

HIGH INTENSITY VERSUS LOW INTENSITY STATIN THERAPY

Target 70mg/dl:

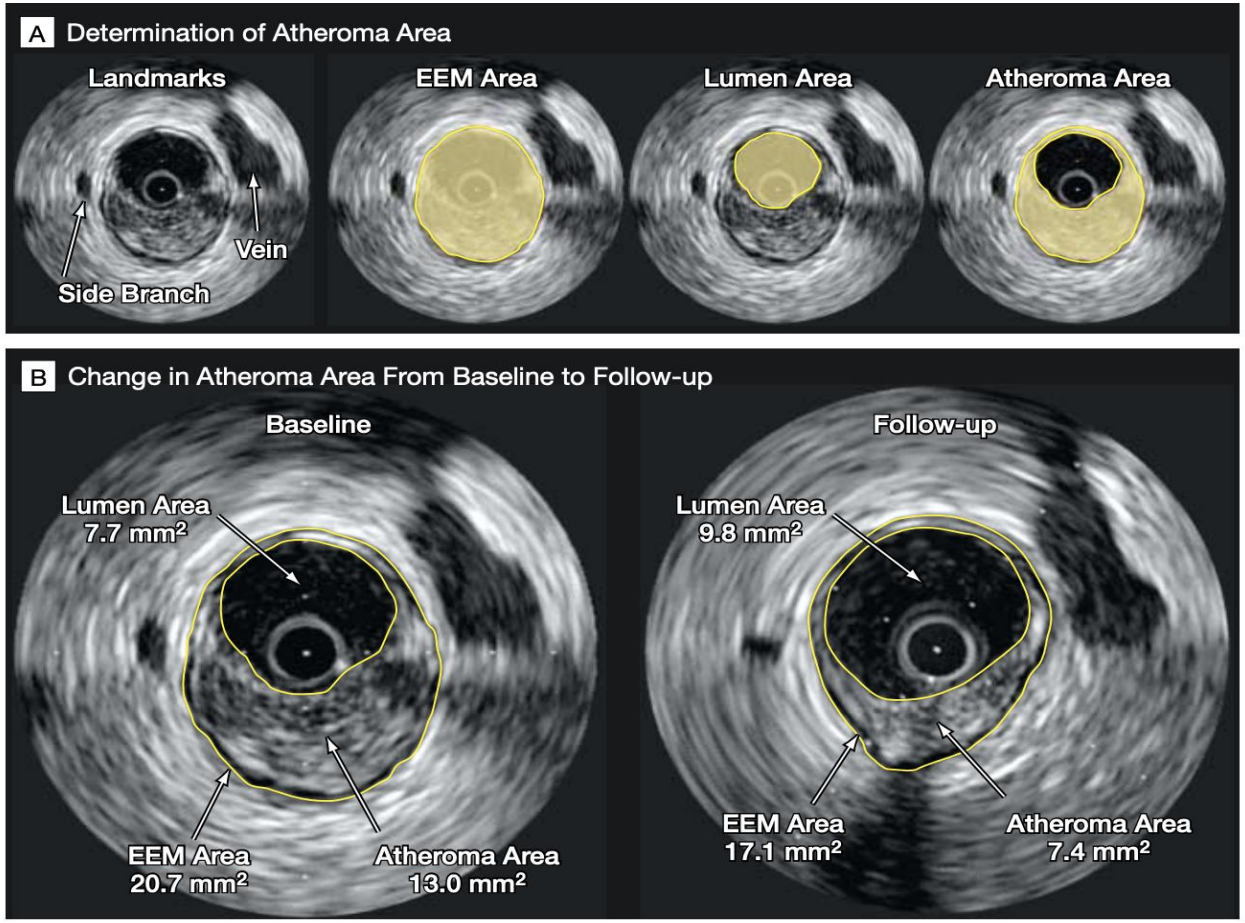
- Achievement of LDL < 70 mg/dl with statins, reduced progression, compared to > 70mg/dl with CCTA , TAV+4.6% vs. 11.6% (p <.0.05)

High Intensity Statin Trials:

- Plaque regression-IVUS for plaque evaluation
- **Reversal Trial:** atorvastatin 80mg v. pravastatin 40 mg reduction in TAV @ 18 months (-0.4% v. + 2.7%; (p <0.05)
- **Japan ACS Trial:**
  - Plaque regression -18% v.16.9% atorvastatin 20 mg v. pitavastatin 4 mg @ 1 year.

– Plaque Composition:

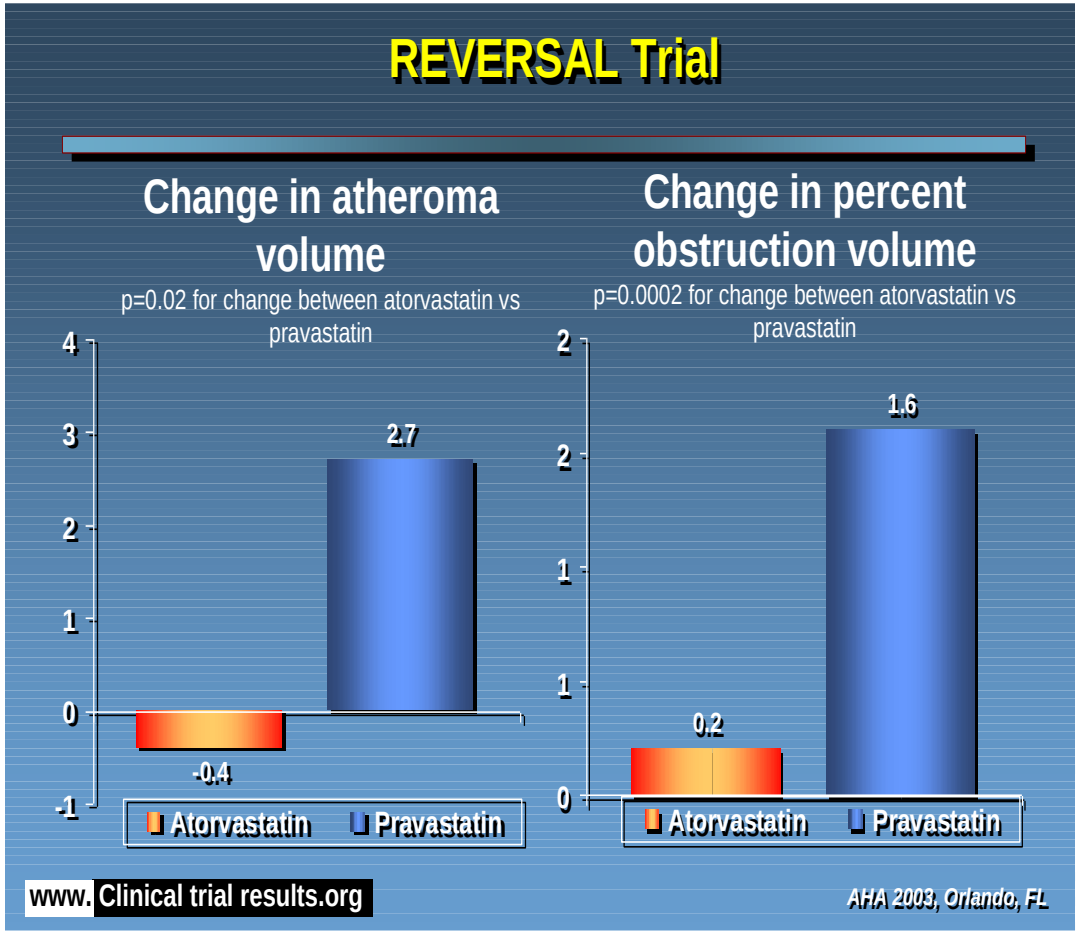
- Increases in fibrous volume & calcified plaque
- Reduction in necrotic core thickening fibrous cap
- Reduction in non-calcified plaque

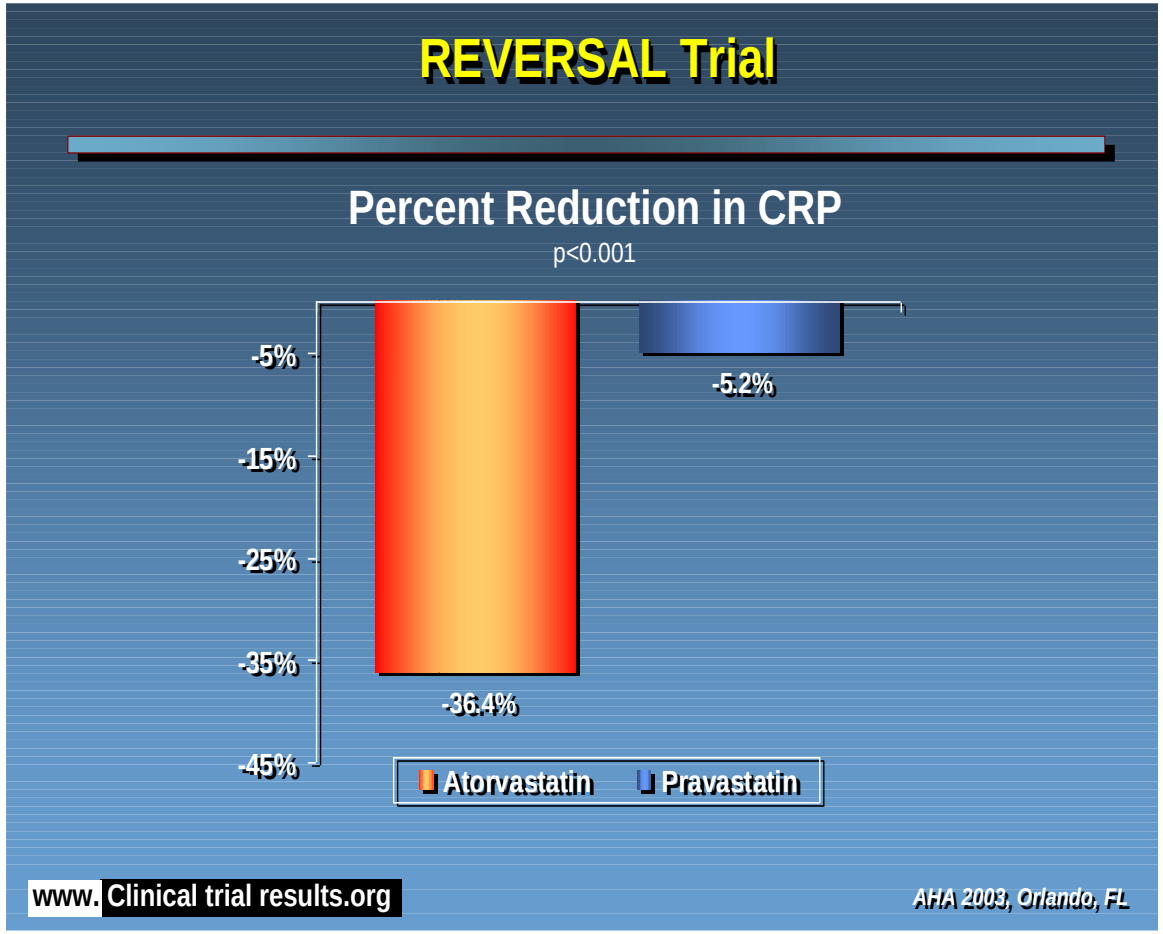


A, Atheroma area is calculated by subtracting the lumen area from the area of the external elastic membrane (EEM). B, Patient randomized to 80 mg of atorvastatin. There is substantial reduction in atheroma area (from 13.0 to 7.4 mm²). A lesser increase in lumen area is noted (from 7.7 to 9.8 mm²). See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

Shin S. et al, J Am Coll Cardiol Img. 2017;10:437. Nissen SE, et al. JAMA 2004; 291:1071. Hiro T, et al. J Am Coll Cardiol. 2009; 54: 293.

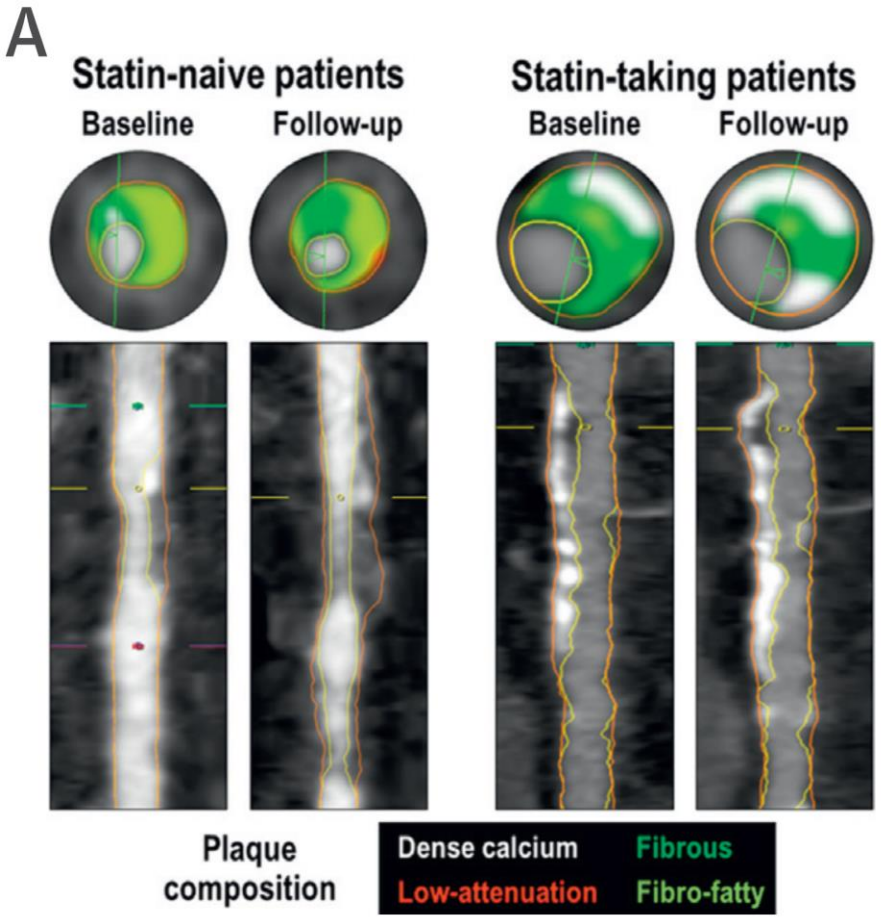
REVERSAL TRIAL: CHANGE ATHEROMA & HS CRP

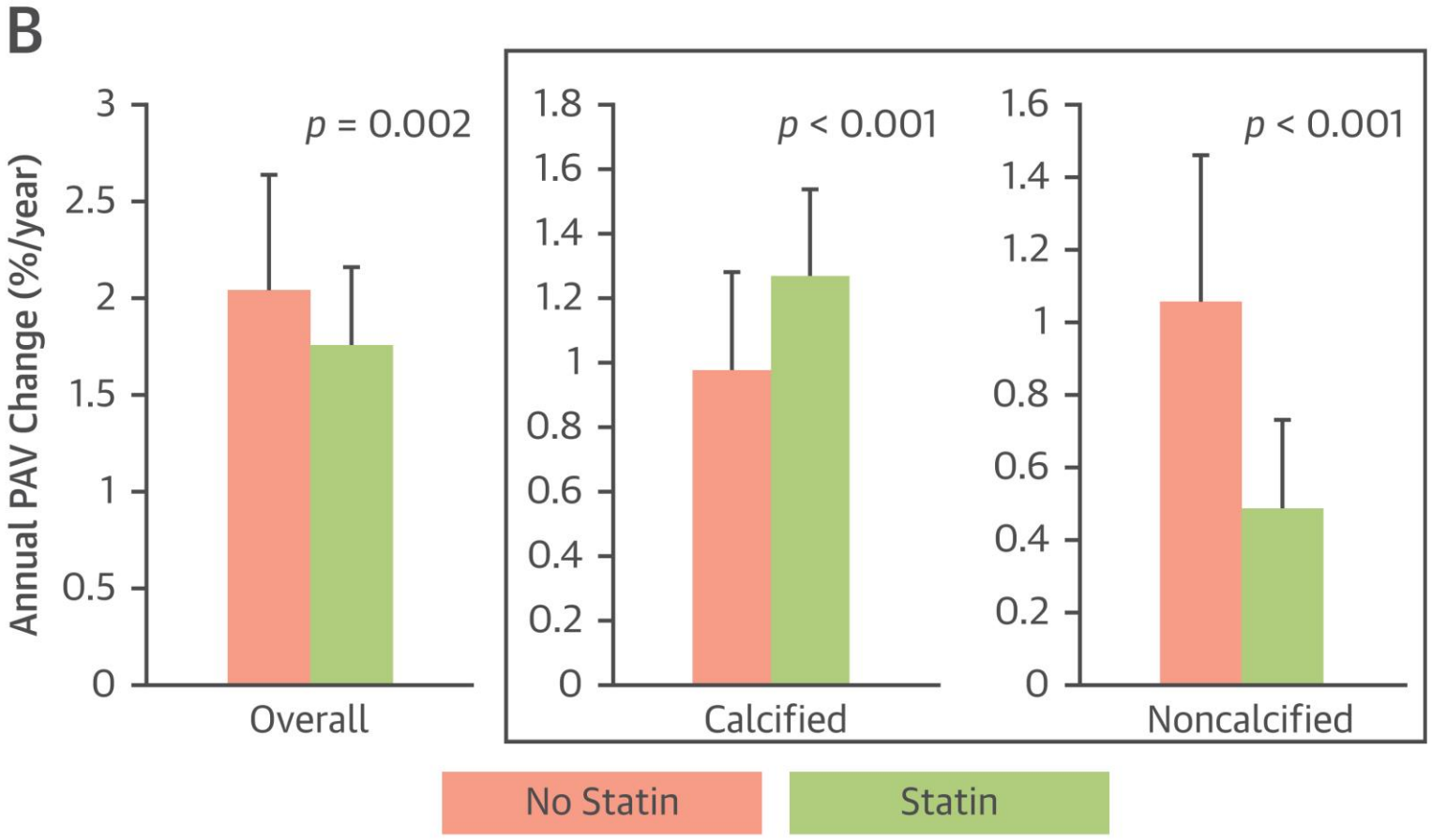




Nissen SE, et al. JAMA 2004; 291:1071

Plaque Regression With Statins





- PARADIGM registry – 1255 pts, 474 statin naïve and 781 on statin, had 2 CTs > 2 yrs apart
- Statins reduced the rate of plaque progression (annual change in percentage atheroma volume) and they increased plaque calcification
- Observational registry. No outcomes data were reported. Selecetion bias and confounding

Lee et al, JACC imaging 2018

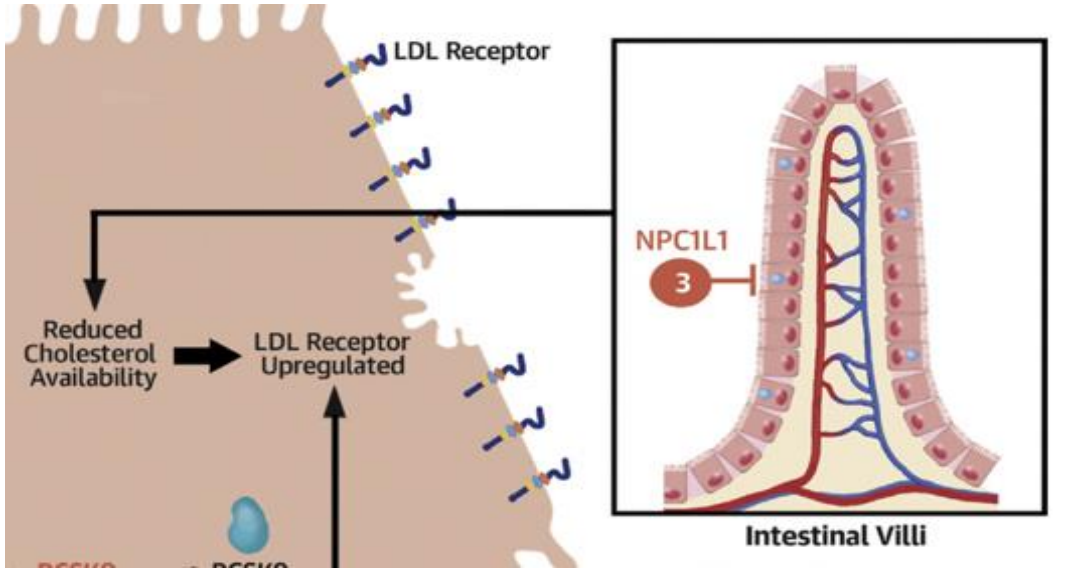
NON STATIN EFFECTS ON PLAQUE

Ezetimibe:

- Most studies with optimal medical therapy
- Regression rates: -2.9% to – 13.9%
- Reduction total atheroma volume, 40 pts, -13.2% @ 6 months
- Multiple larger studies showed plaque regression with OMT plus ezetimibe, but not statistically different from just OMT
- Effect on Plaque regression appears small

Bempedoic Acid:

- One case study using CCTA reduced low attenuation plaque compared to baseline



 Masuda J, et al. Int Heart J. 2015;56: 278. Dawson L, et al. J Am Coll Cardiolo; 2022; 79: 66, Korosoglou, G., et al. Cardiovascular Imaging; 2023, 10:

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 INHIBITORS

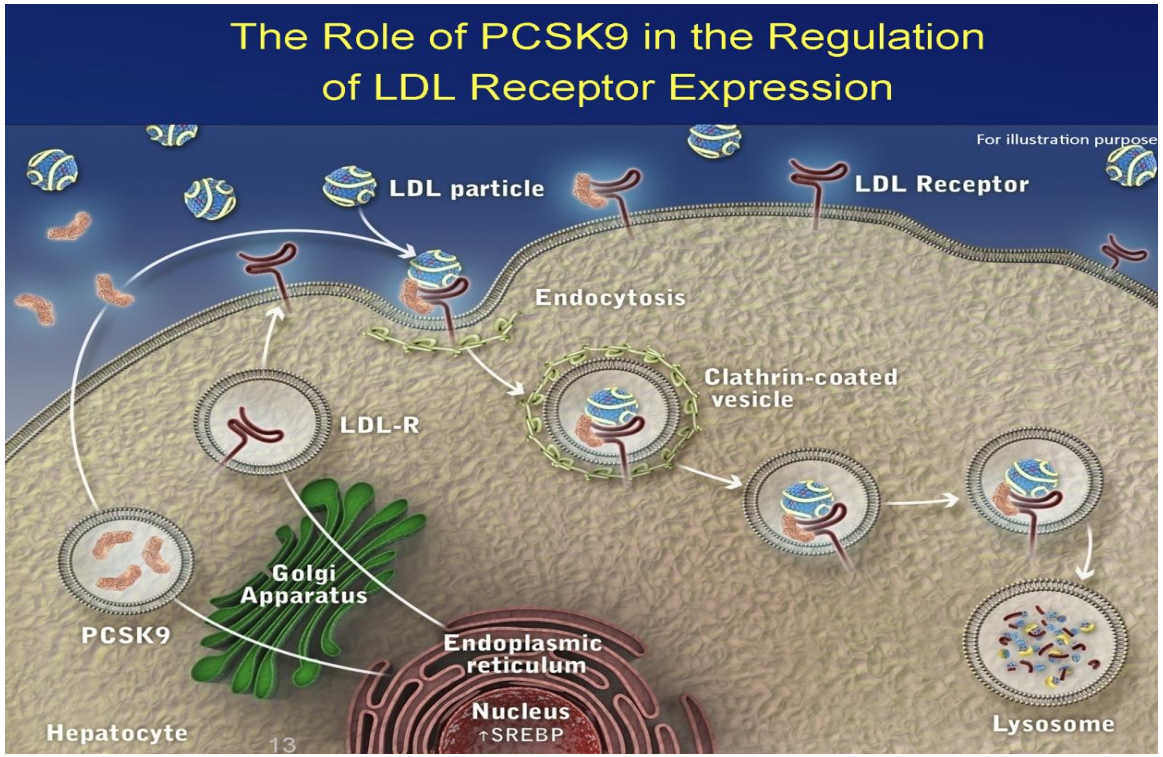
Glagov Trial: Global Assessment Plaque Regression PCSK9

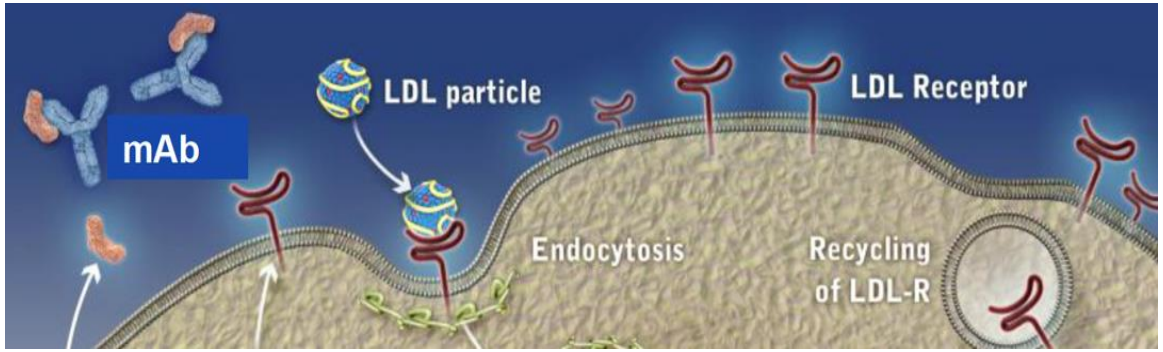
- IVUS Trial, 968 patients Evolucumab vs. Optimal medical therapy (statin), 1.5 years
- Greater reduction: total atheroma volume -2.9 % v. – 0.4% ($p < 0.05$)

ODYSSEY J-IVUS:

- Effect Alirocumab on Coronary Atheroma Volume Japanese patients ACS; IVUS Trial
- 75 mg dose in 206 pts ACS vs. OMT
- Slight Reduction in total atheroma volume @ 36 weeks not significant

Smaller changes in plaque, compared to significant LDL-C reduction & event reduction will require further and longer investigation





Nicholls SJ, et al. JAMA 2016; 316: 2373. Ako J, et al. Circ J. 2019;83: 2025.

PCSK9 EFFECTS ON PLAQUE REGRESSION

Glagov Trial:

- **968 patients with ASHD treated with Evolocumab 420mg/month v. OMT ~ 1.5 years**
- **Stable statin dose 4 weeks, LDL>80 mg/dl or 60-80mg/dl with 1 major or 3 minor risk factors**
- **Serial IVUS to measure coronary atheroma volume**
- **LDL: 36 mg/dl v. 93 mg/dl**
- **Atheroma reduction:.95% v. +0.05% placebo**
- **Plaque regression 64.3% v. 47.3 %**
- ***PCSK9 had favorable effect on IVUS measured plaque progression in patients on moderate or high intensity statin***

PACMAN-AMI Trial:

Alirocumab 150mg biweekly within 24 hours of AMI & PCI; 300 patients on high intensity rosuvastatin

-LDL>125 mg/dl no statin or > 70mg/dl if on statin

-LDL reduced 85% on combination v. 51% rosuvastatin 20mg

-Primary Endpt: Change in percent atheroma volume (PAV) was -2.13 % PCSK9, v. -0.92% statin (p<0.001)

2nd Endpt: Regression: 84.6% v. 65.9% (p<0.001)

-Administration PCSK9 within 24 hrs after PCI for AMI resulted in greater reduction in plaque burden and plaque regression at 1 year in non culprit vessel.

- *Both studies emphasize the role for aggressive LDL reduction with PCSK9 therapy in high risk patients*
- *Statins can also induce regression in dose dependent fashion proportional LDL reduction; plaque morphology changes to fibrous & calcified plaque whereas fibrofatty and necrotic core volume decreases.*

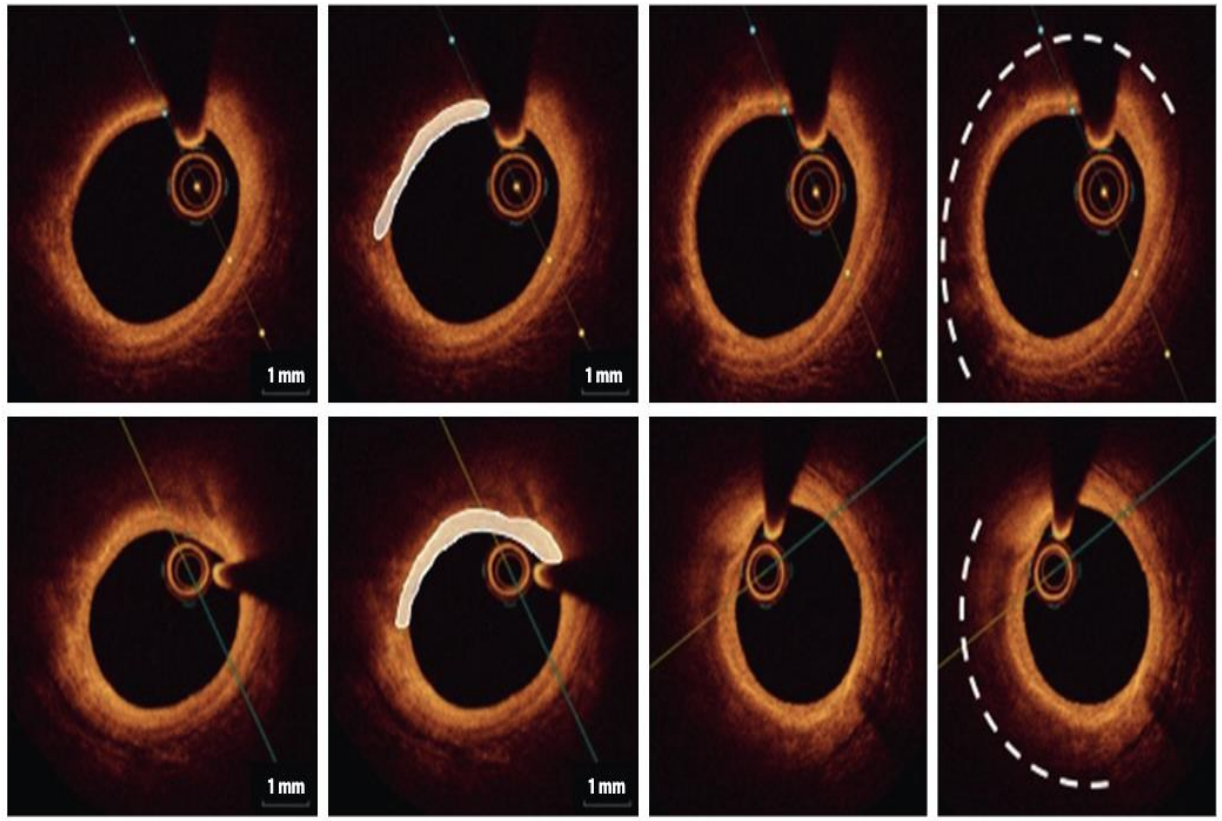
Nicholls S, et al. JAMA 2016; 316(22):2373-2384.

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

Dawson L, et al. J Am Cardioll 2022;79:66-82.

MORE INTENSIVE LIPID LOWERING WITH EVOLOCUMAB IMPROVES PLAQUE

- **Evolucumab added to intensive statin therapy in patients with NSTEMI had effects on stabilizing effects on plaque**
  - **Primary Endpoint: Minimum fibrous cap thickness increased in the target vessel in patients treated with the PCSK9 therapy compared to statin therapy alone; avg LDL-C = 28.1 mg/dl**
  - **Secondary Endpoint: Greater decrease in maximum lipid arc which complemented the IVUS findings in the group that could have IVUS.**
  - **Conclusion:**
    - **Patients with NSTEMI & very low cholesterol had favorable changes in their plaque contributing to plaque stabilization**
    - **High Intensity statin therapy group also had favorable changes in cap thickness and lipid arc (pool)**
    - **Evolucumab group with LDL-C , 30mg/dl had a greater improvement**



Nicholls SJ, et al. J Am Coll Cardiol Img. 2022;15(7):1308-1321.

Reduction in minimum fibrous cap thickness **(left)** and lipid arc **(right)** from baseline **(top)** to follow-up **(bottom)** with evolocumab.

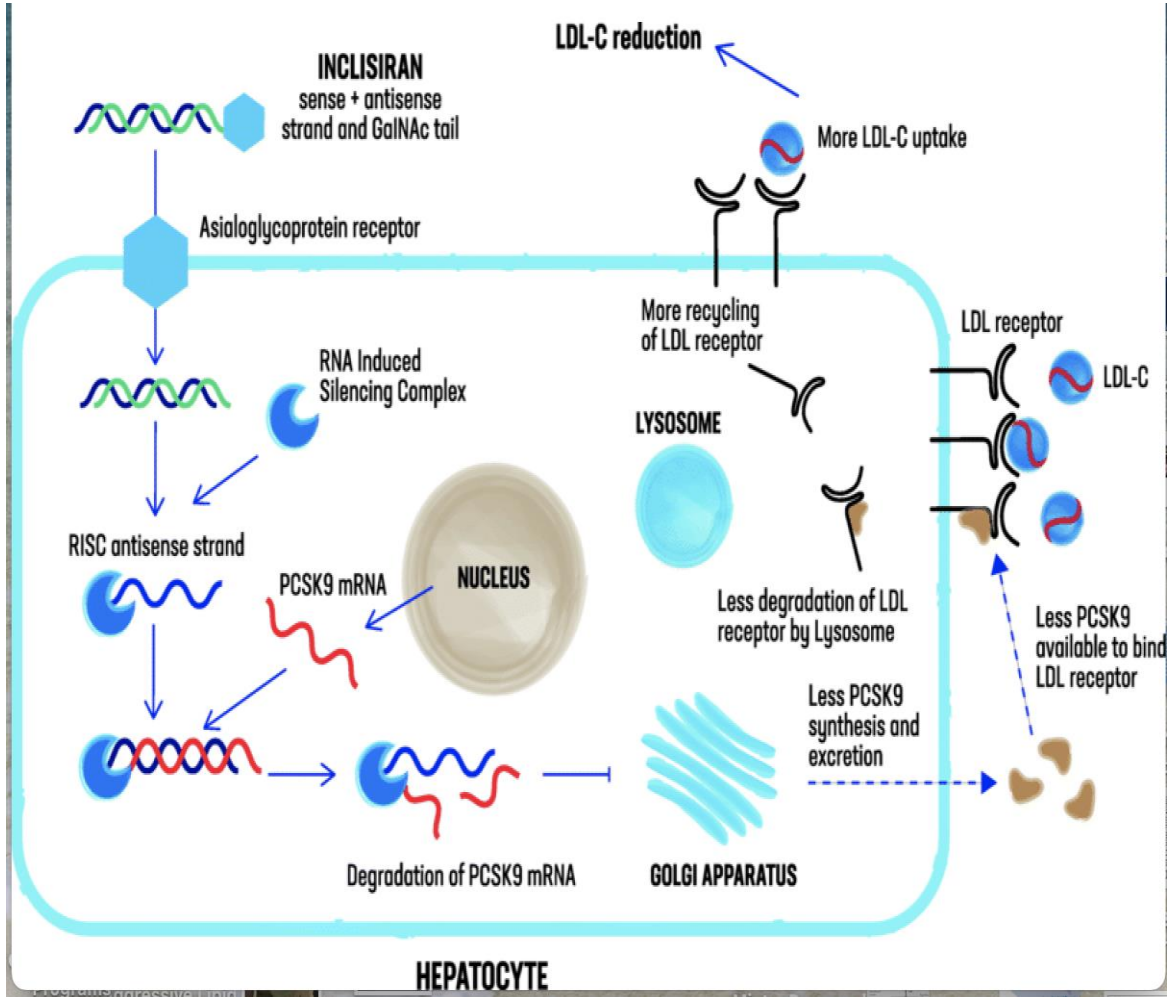
Nicholls SJ, et al. J Am Coll Cardiol Img 2022; 15: 1308

SI-RNA INCLISIRAN AFFECTS PLAQUE

- Double stranded small interfering RNA (siRNA) reduces production of PCSK9 by degrading relevant RNA in hepatocyte
- Less PCSK9 - more LDL Receptors & lower LDL-C

- NIRS (near infrared spectroscopy) at baseline & 15 months 36 pts CAD; plaque evaluation on statin +/- ezetimibe (17) vs. triple therapy (19) Inclisiran, statin +/- ezetimibe
  - Lipid Core burden (content) significantly reduced (p=0.041)
- Victorian Plaque:
  - CCTA for effect Inclisiran on plaque progression in patients with mild CAD without h/o CVS event

- Advantage: Prolonged effect on PCSK9, allowing for SQ dose every 6 months
  - Population Health - improve compliance
- Reduction of LDL about 50% (49.2-53.8%), in addition to maximally tolerated statin (90% on high intensity statin)
- Effect reversed 2%/month, effects persist 2 years; undetectable plasma- 48 hours



Kausik K, et al. N Engl J Med 2020;382:1507-19. Trusinskis K, et al. Euro Heart J. 2023:44 (suppl 2)

EICOSAPENTAENOIC ACID

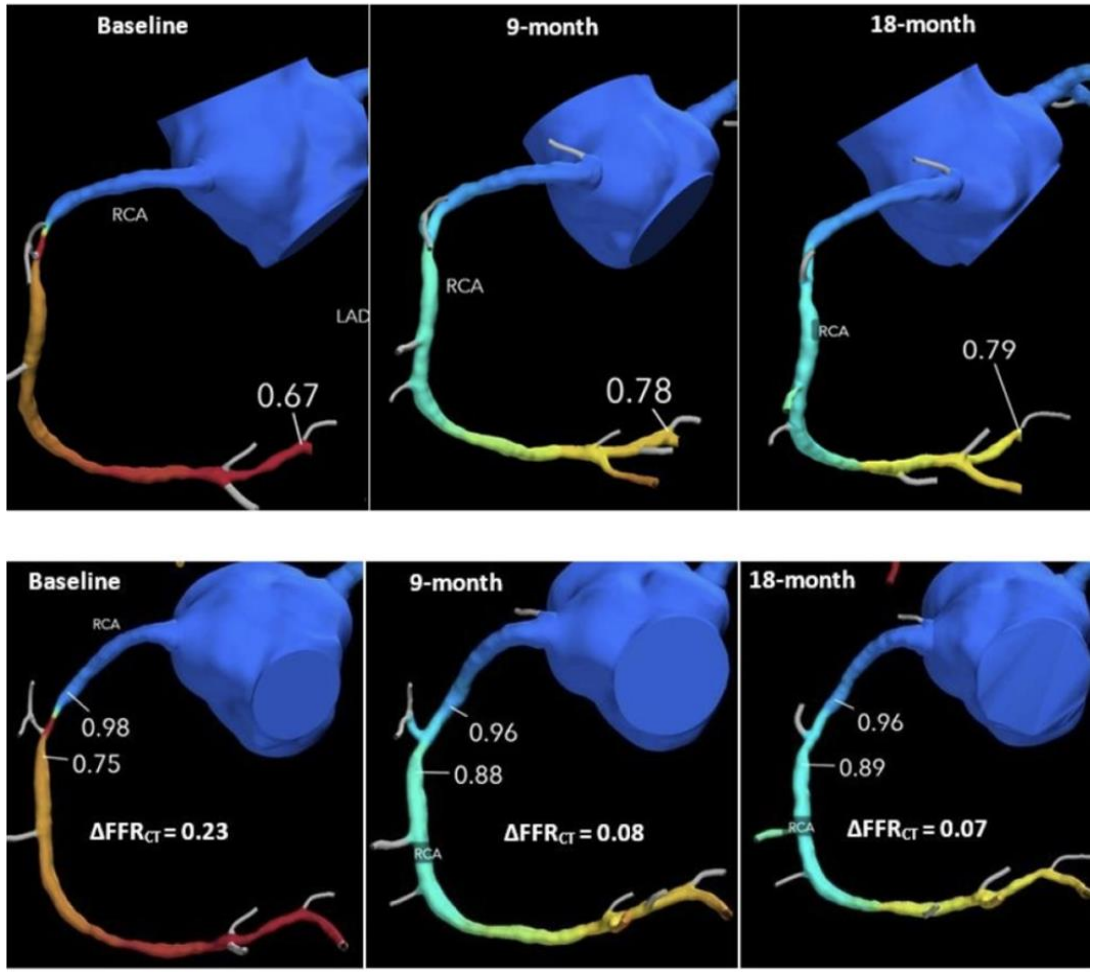
Icosapent EPA:

- Increase in fibrous volumes, reduction in lipid volume
- Reduced plaque progression on CCTA
- Increases in fibrous cap thickness

– **EVAPORATE Trial:**

- EPA- 4 gms, 80 patients CAD, high TG on statins, CCTA 9 & 18 months
- Primary Endpoint- Reduce Low attenuation plaque “LAP”
- Primary Endpoint: 17% reduction in LAP (p< 0.0061)
- Greater plaque regression seen with EPA, -9.0% v. + 11% , (p< 0.05) at 18 months
- Reduced low attenuation plaque, reduced fibrofatty volume, and fibrous volume
- Comment: groups had different plaque burden at baseline and control group received mineral oil

– **EPA have anti-inflammatory effects and affect plaque**



Change in distal FFR @ 18 months, 47 pts, Reduce It & Evaporate Trials:

Reduced 0.01 +/- 0.09,v. -.0.09 +/- 0.12, p=0.03; Trans-lesional FFR-0.06 +/-0.08 v. -0.09 =/- 0.1 (p=0.054)

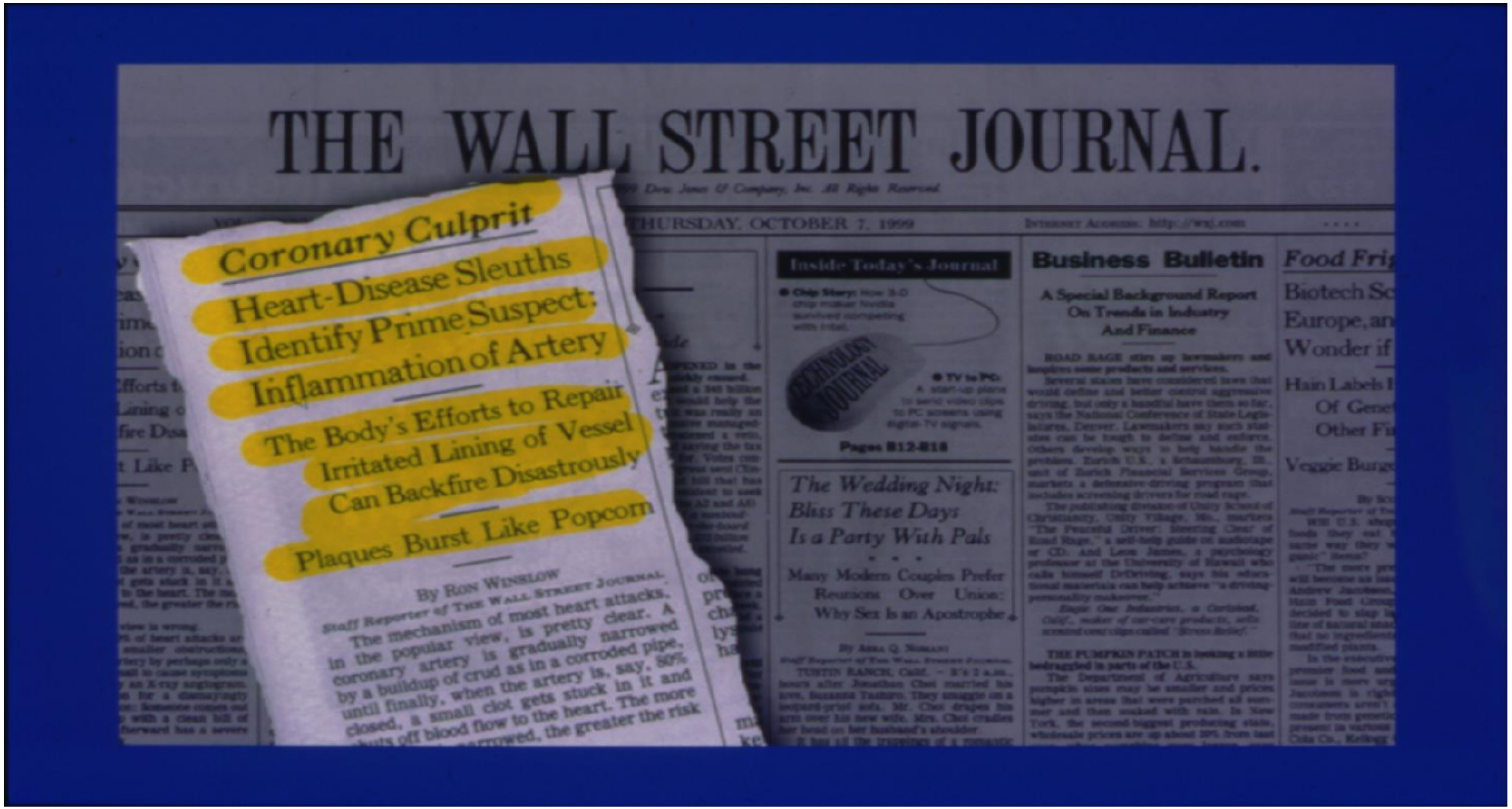
Niki T, et al. Circ J. 2016;80: 450. Alfaddagh A, et al. J Am Heart Assoc. 2017; 6 (12):e006981. Kuroda K, et al. Euro-Intervention. 2019; 15: e1099.
Nishio R, et al.Atherosclerosis. 2014; 234: 114. Budoff MJ , et al. Eur Heart J. 2020; 29:29. . Rabbat et al, EHJ CI 2023

EFFECTS OF LIPID THERAPY ON PLAQUE CHARACTERISTICS

Medication	Mechanism	Abundance of data on plaque effects	Modalities to assess coronary plaque	Most common effects on coronary artery plaque	MACE reduction
Statins	HMG-CoA reductase inhibitor	+++	CCTA, CAC, Angioscopy, ICA, IVUS, OCT, NIRS	• Plaque stabilization • Decreased lipid content • Increased dense calcium volume • Increased fibrous cap thickness • Variable change in plaque volume • Decreased inflammatory cytokines • Decreased oxidation-sensitive inflammatory pathways • Altered T-cell differentiation and leukocyte-endothelial cell interaction	Yes
Ezetimibe	NPC1L1 inhibitor	++	ICA, IVUS, OCT	• Plaque volume reduction • Plaque regression • Increased fibrous cap thickness	Yes
PCSK9 inhibitors	monoclonal antibodies to free plasma PCSK9 protein	++	ICA, IVUS, OCT	• Decreased plaque volume • Increased fibrous cap thickness • Regression of lipid-rich plaque • Attenuation of plaque inflammation	Yes
Bempedoic acid	ATP-citrate lyase inhibitor	+	Animal studies only	• Attenuated plaque inflammation • Potential plaque stabilization	Unknown
Bile acid se-questrants	Interrupt enterohepatic homeostasis	+	Animal studies only	• Borderline plaque regression	No
Fibrates	PPAR alpha agonists	+	Animal studies only	• Reduced plaque thrombogenicity • Decreased fibrinogen and C-reactive protein • Improved flow-mediated dilatation	Variable
Omega-3 fatty acids	Not fully understood; likely multiple effects	+	IVUS, Laboratory and clinical studies	• Modulation of T-cell differentiation • Plaque-stabilization • Reduced coronary plaque volume • Decrease in inflammatory cytokines	Variable
Niacin	Likely multiple effects	+	ICA, IVUS	• Anti-inflammatory effects • Protection against endothelial dysfunction • Reduced coronary plaque volume	No
Effects of emerging lipid-lowering medications on coronary plaque characteristics					
Evinacumab	monoclonal antibody to Angiopoietin-like protein 3	+	Animal studies only	• Regression of atherosclerotic lesion size • Decrease in macrophage accumulation	Unknown

Pulipati, VP, et al. J ASPC; 8; 2021; 100294

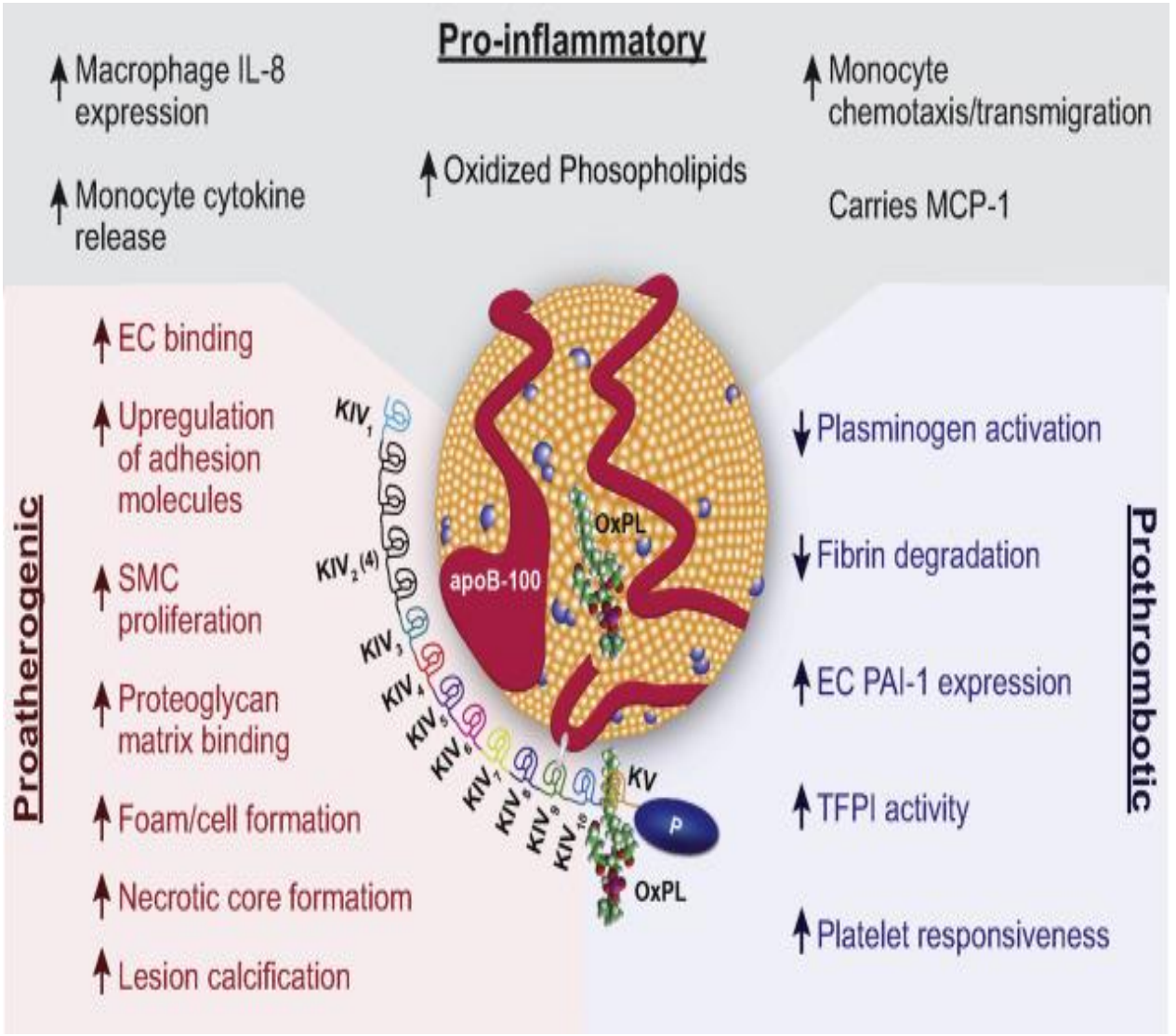
INFLAMMATION PLAYS A ROLE IN PLAQUE INSTABILITY



LIPOPROTEIN (A) EFFECTS ON PLAQUE

- Associated with increased plaque volume and high risk plaque features in observational studies.
- PCSK9 inhibitors can lower Lp(a) up to 20-30% which may account for some of their effects on plaque

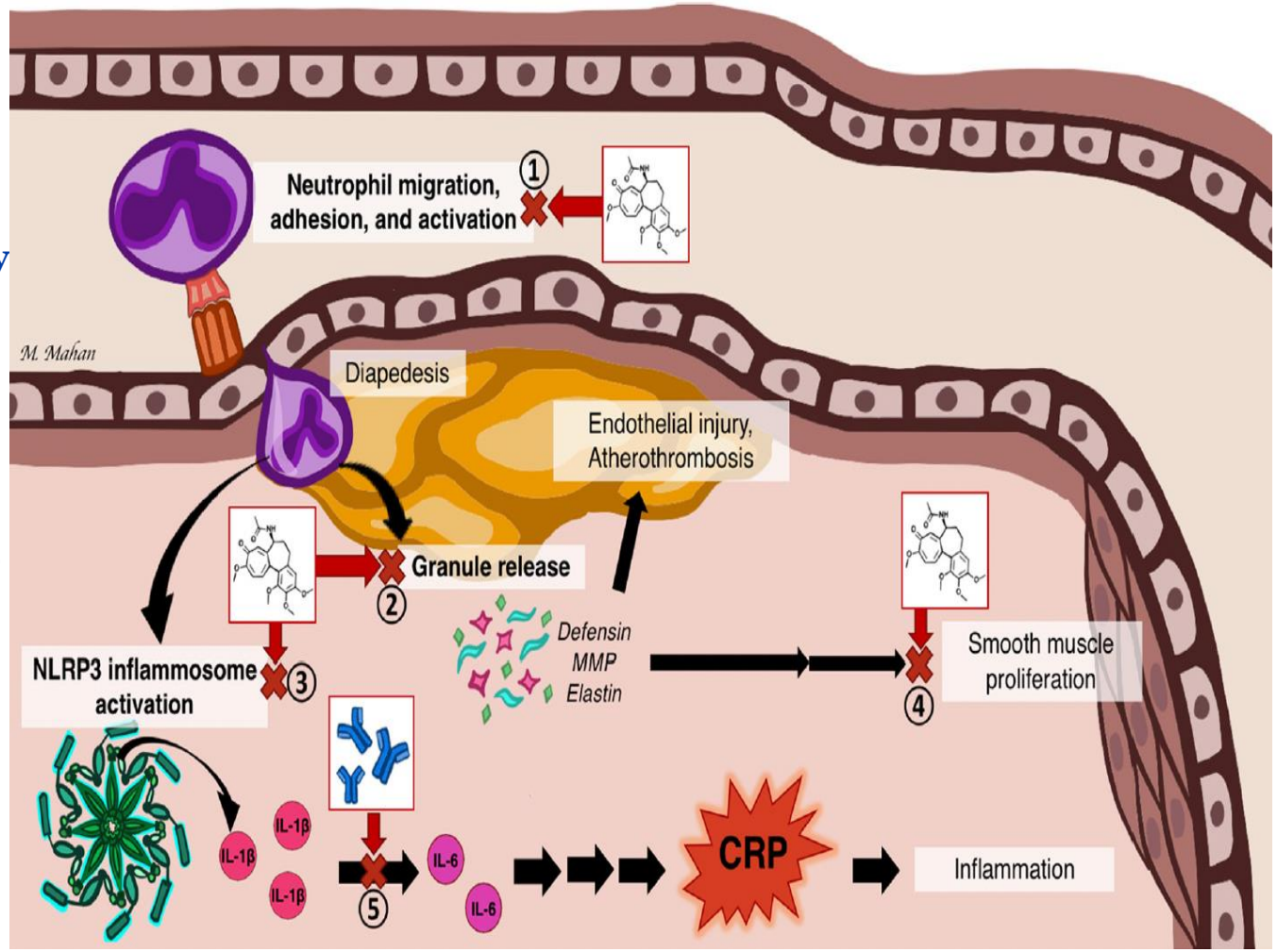
- LDL molecule with lipoprotein antigen (variable weight & sequence) attached via disulfide bond thru cysteine side chain of Apo B; two kringle folded sections
- Deposits in arterial wall & taken up by macrophages; promotes monocyte adhesion carries atherogenic oxidized phospholipids in plasma
- Binds to fibrin & interferes with conversion of plasminogen to plasmin; structure similar to plasminogen
- Measure in patients with strong family history of CVS events, Premature ASHD, FH, Recurrent Events, Premature aortic stenosis
- Lp(a) > 50 mg/dl, > 125 nmol/L: Risk Enhancing
- Therapy: Apheresis, LDL reduction, PCSK9, niacin
- Future: Antisense oligonucleotides and siRNA against Lp(a)



Tsimikas,S; JACC VOL. 69, NO. 6, 2017:692 – 711

COLCHICINE: MECHANISM OF ACTION

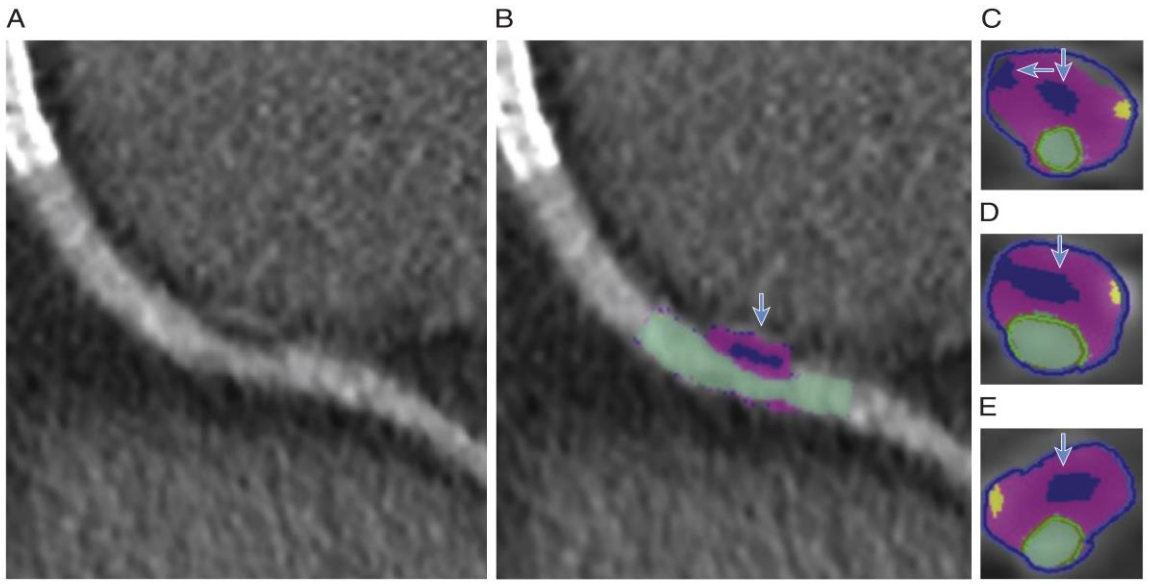
- Colchicine binds tubulin and inhibits tubulin polymerization with disruption of the cellular cytoskeleton, mitosis and intracellular transport activities.
- Accumulates in neutrophils and affects their activity due to lack of efflux pump
  - Colchicine inhibits neutrophil migration to inflamed foci, adhesion and activation
  - Inhibits mobilization & release of matrix metalloproteinases, neutrophil elastase, alpha-defensins
  - Inhibits assembly & activation of the inflammasome- decrease production interleukin 1Beta & IL-18
  - May Suppress myofibroblasts, SMC proliferation & Fibrosis
  - Decrease IL-6 & CRP production



COLCHICINE EFFECTS ON PLAQUE

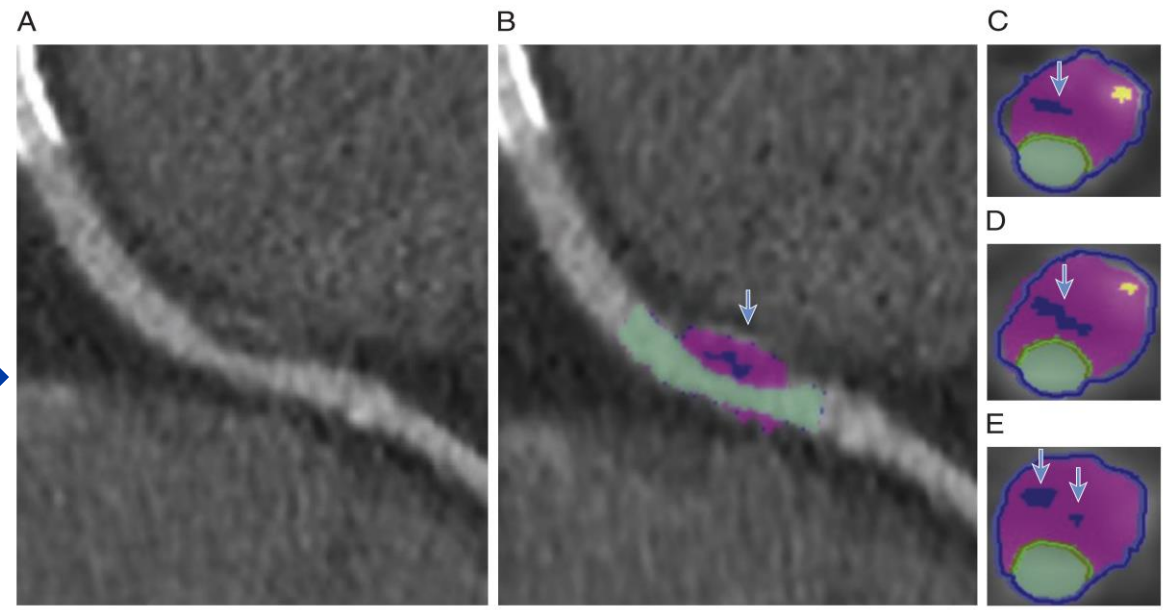
- Non-randomized open label CCTA study in 80 patients with ACS treated with Optimal medical therapy (OMT) or OMT plus colchicine 0.5 mg/day for one year
- Colchicine caused a significant reduction in low attenuation plaque volume 15.9 mm2 v. 6.6 mm2, ($p < 0.05$), and non calcified plaque volume, but the TAV was similar in both groups

FIGURE 2 Distal Right Coronary Artery Plaque Identified at Baseline



(A) Curved planar reformat; **(B)** curved planar reformat with color overlay coded image map to identify plaque components; **(C to E)** representative cross-sectional views with color overlay. **Light blue arrows** indicate low attenuation plaque **(dark blue)**; noncalcified plaque, **purple**; dense calcified plaque, **yellow**; lumen **green**. LAP volume = 4.2 mm^3, NCP volume = 46.5 mm^3, DCP volume = 2.2 mm^3, lumen volume = 41.4 mm^3. DCP = dense calcified plaque; LAP = low attenuation plaque; NCP = noncalcified plaque.

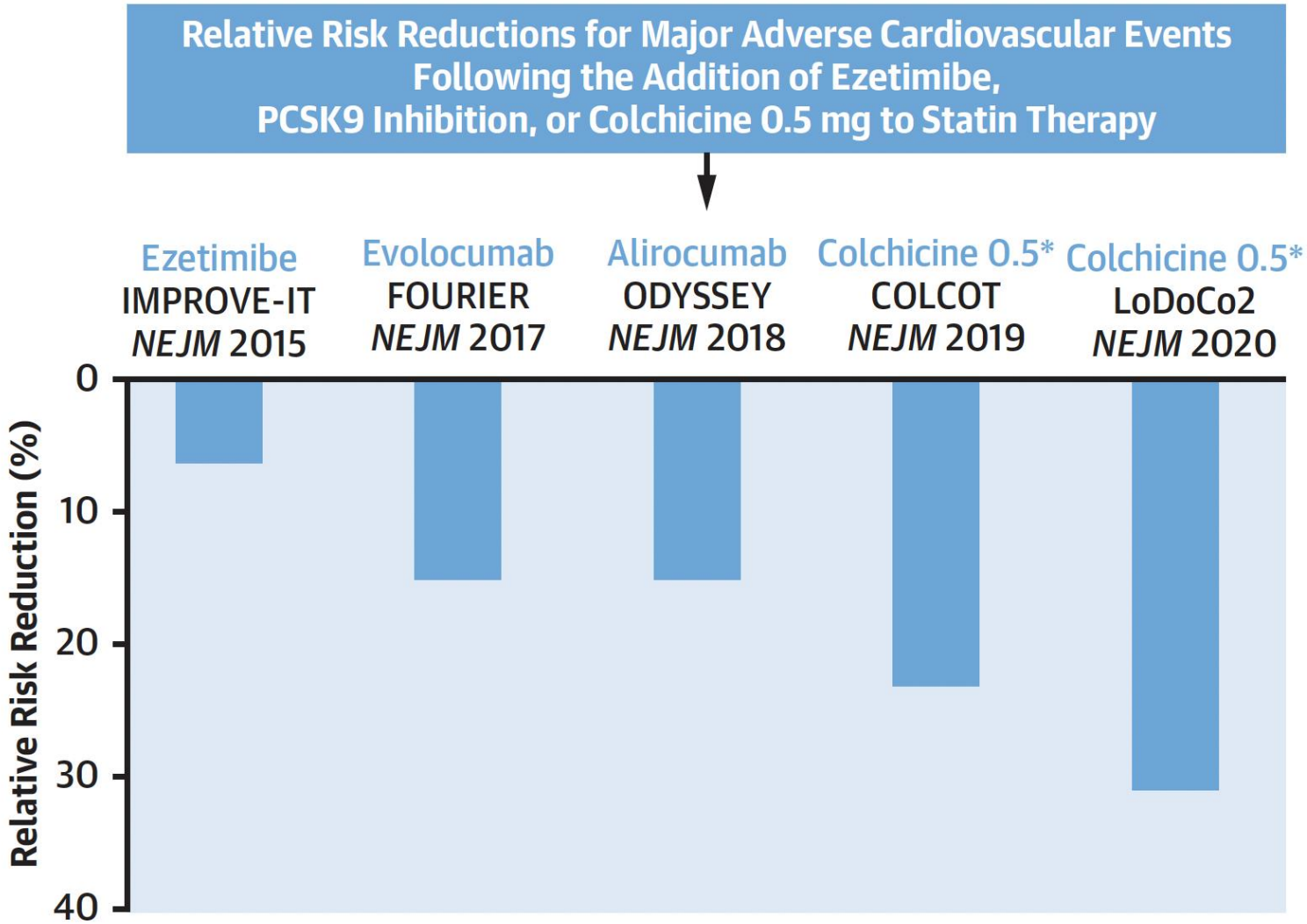
FIGURE 3 Distal Right Coronary Artery Plaque Reimaged After 12 Months of Oral Colchicine (0.5 mg/day)



(A) Curved planar reformat; **(B)** curved planar reformat with color overlay coded image map to identify plaque components; **(C to E)** representative cross-sectional views with color overlay. See Figure 1 legend for color descriptions. LAPV = 3.2 mm^3 (−23.8%), NCPV = 65.8 mm^3 (+41.5%), DCPV = 0.3 mm^3 (−86.4%), lumen volume = 47.2 mm^3 (+14.0%). DCPV = dense calcified plaque volume; LAPV = low attenuation plaque volume; NCPV = noncalcified plaque volume.

Vaidya K, et al. J Am Coll Cardiol Img. 2018; 305

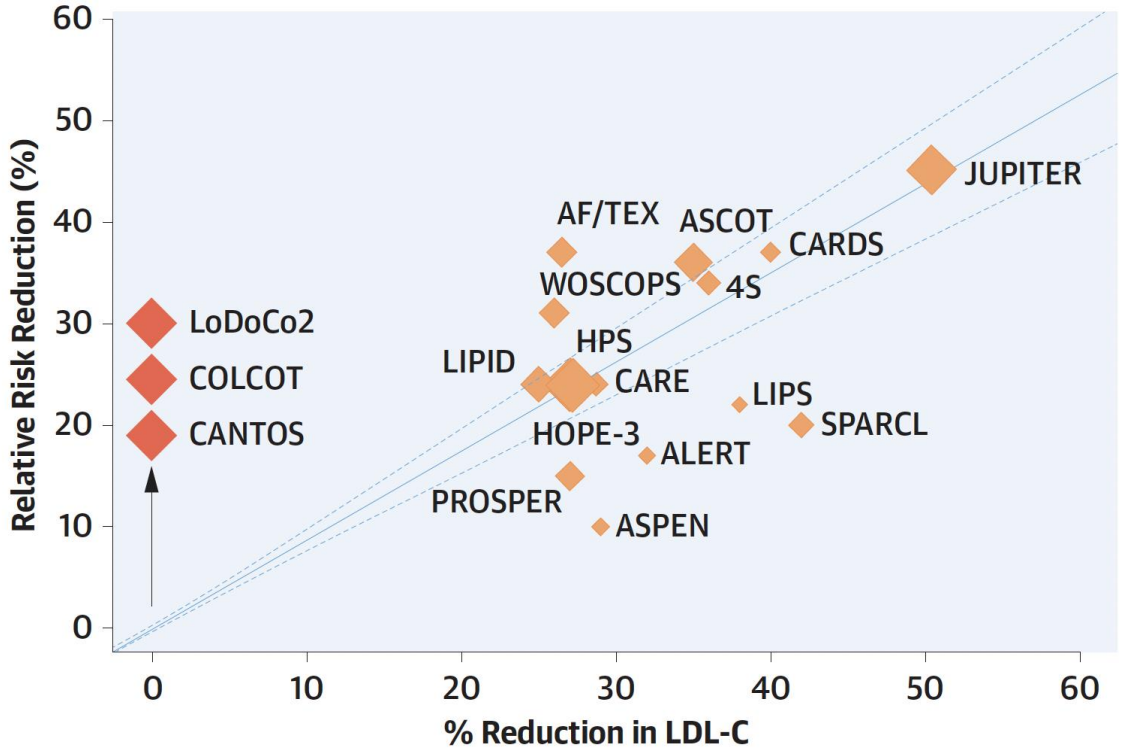
REDUCTION IN CARDIOVASCULAR EVENTS BASED ON TREATMENT



Nelson, K et al. J Am Coll Cardiol 2023; 82: 648-660

ANTI-INFLAMMATORY THERAPY DEMONSTRATES CVS RISK REDUCTION WITHOUT CHANGE IN LDL-C

- **Reduction in LDL-C by statin therapy demonstrates a linear reduction in CVS events**
- **Anti-Inflammatory Therapy Reduced Cardiovascular Events without effecting LDL**
  - **Canakinumab, SQ monoclonal antibody, Cantos Trial (*Canakinumab Anti-Inflammatory Outcomes Trial*) reduced CVS events 15%**
  - **Low dose colchicine, 0.5mg in COLCOT (*Colchicine Cardiovascular Outcomes Trial*) and LoDoCo2 (*Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease*) reduced CVS events about 23% & 31%**



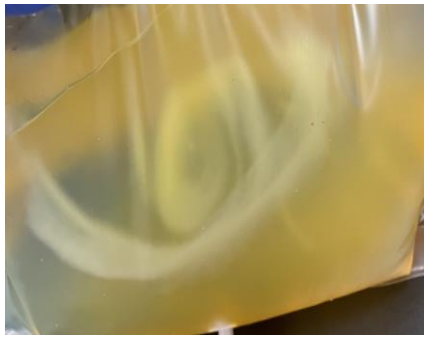
Ridker PM. Anti-inflammatory therapy for cardiovascular disease. In: Ballantyne CM. Clinical Lipidology: A Companion to Braunwald's Heart Disease. Third ed. Elsevier; 2023: chapter 24.

LIPID APHERESIS

LACMART Trial:

- **LDL Apheresis Coronary Morphology & Reserve Trial**
- **18 patients apheresis vs. usual care for a year**
- **Plaque Regression in apheresis group**
- **(- 8.2% vs. + 12.4%, p < 0.05)**

Matsuzaki M, et al. J AM Coll Cardiol. 2002; 40: 220.



Marker	DSA
MCP-1	-20
MMP-9	-20
TIMP-1	-30
ET-1	-75
LBP	-27
Lp-PLA$_2$	-21
VCAM-1	-10
ICAM-1	-10
E-Selectin	-6
Fibrinogen	-20
Oxidized LDL	-65
CRP	-65
Gal-3	-23

MCP-1 = monocyte chemoattractant protein-1

MMP-9= matrix metalloproteinase-9

TIMP-1=tissue inhibitor of metallproteinase-1

ET-1 = endothelin-1

LBP = lipopolysaccharide binding protein

sCD40L = soluble CD40 ligand

Lp-PLA$_2$= Lipoprotein-Associatee Phospholipase A$_2$

sCD430L = soluble CD40 Ligand

VCAM-1 = Vascular Cellular Adhesion Molecule-1

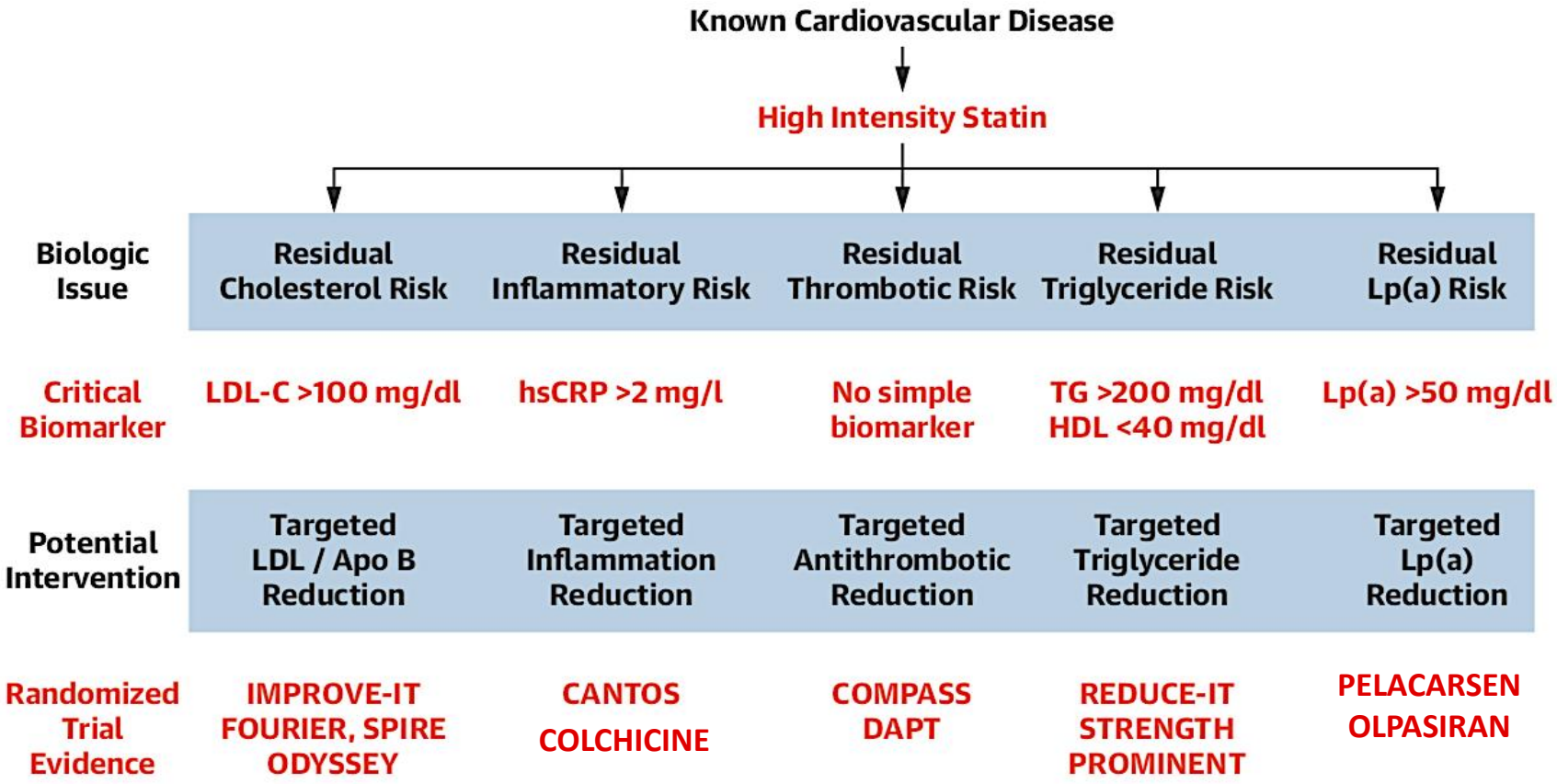
ICAM-1 = Intercellular Adhesion Molecule-1

CRP = C-Reactive Protein

Gal-3= Galactin-3

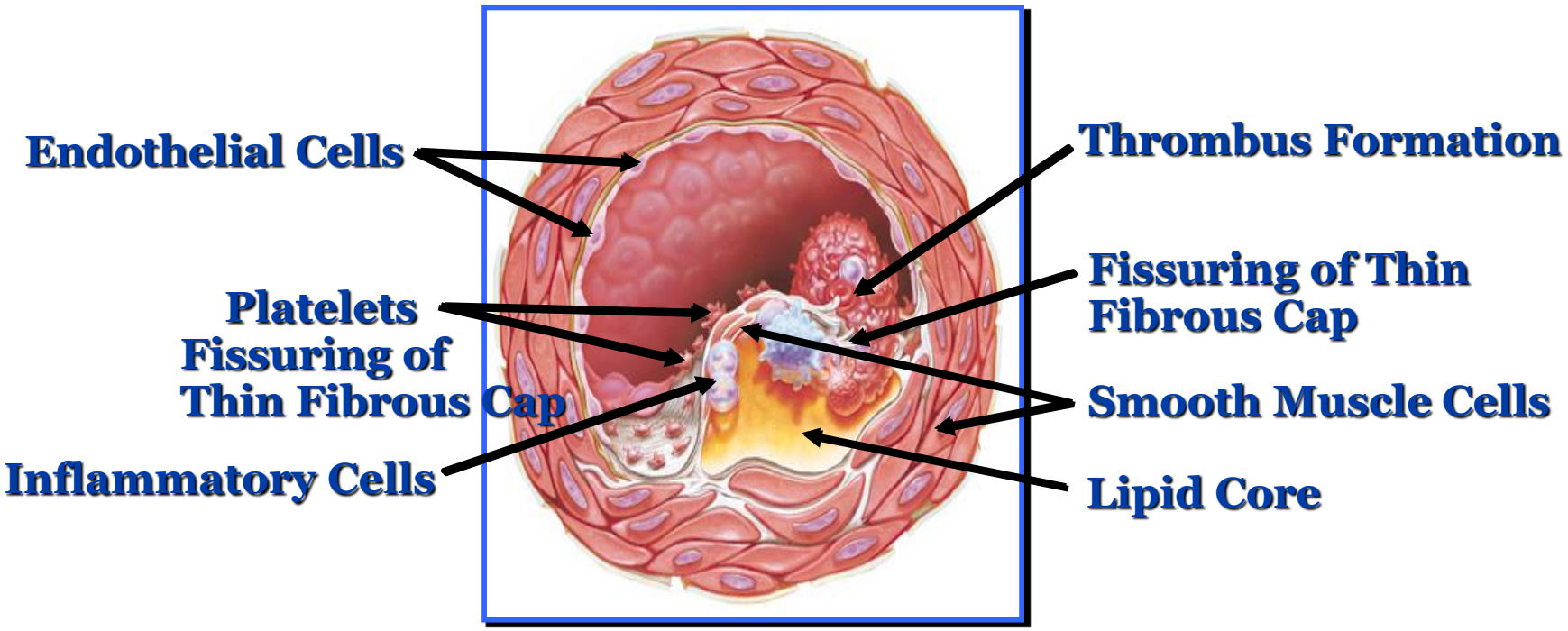
Moriarty PM. Future Lipidology. 2006, Eliaz I., et al. J Clin Apher.2016.

RESIDUAL RISK AND A MOVEMENT TOWARD PERSONALIZED MEDICINE



Ridker, P.M. J Am Coll Cardiol. 2018;72(25):3320–31.

CARDIOVASCULAR EVENTS SUCH AS MI ARE OFTEN COMPLEX AND UNPREDICTABLE

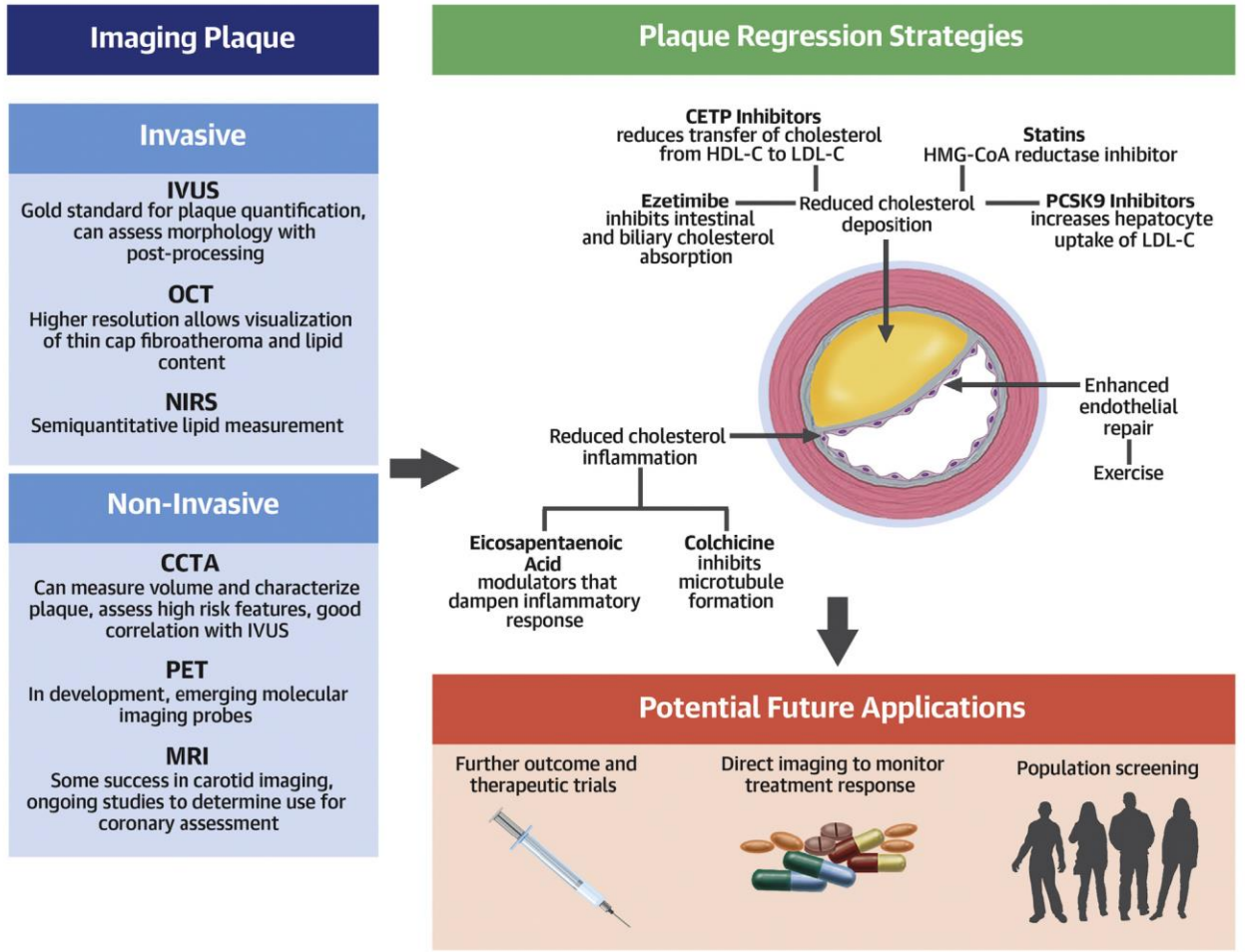


This complexity emphasizes the need to rely on clinical proof of cardiovascular protection, not on LDL-C lowering alone.

Libby. Circulation. 1995;91:2844-50. Falk et al. Circulation. 1995;92:657-71.
Davies. Circulation. 1996;94:2013-20. Brown. Circulation. 1993;87:1781-91.

PLAQUE ATTACK: BATTLE PLAN SUMMARY

- **Lower LDL-C is associated with reduced cardiovascular events**
- **Reduction in LDL-C correlates with plaque regression, but no direct relationship for reduction in cardiovascular events**
- **Imaging has allowed us to evaluate plaque- low risk and high risk, plaque burden- volume, plaque content.**
- **Plaque regression can occur with effective therapy**
  - **Cost**
  - **Protocols- serial imaging, monitor treatment response; radiation exposure**
  - **Assess treatment effects**
  - **Identify early risk**
  - **Role of inflammation ????? – treatments targeting inflammation can reduce plaque rupture.**



Dawson, L.P. et al. J Am Coll Cardiol. 2022;79(1):66-82.

Plaque regression definitions, plaque imaging modalities, plaque regression therapeutic strategies, and potential future directions. CCTA = coronary computed tomography angiography; CETP = cholesteryl ester transfer protein; HDL-C = high-density lipoprotein-cholesterol; IVUS = intravascular ultrasound; LDL-C = low-density lipoprotein-cholesterol; NIRS = near infrared spectroscopy; OCT = optical coherence tomography; OMT = optimal medical therapy; PCSK9 = proprotein convertase subtillisin/kexin type 9 inhibitors; PET = positron emission tomography.

Yamamoto E, et al. J Am Heart Assoc. 2019; 8 e012322. Partida RA, et al. Eur Heart J. 2018; 39: 2070. Libby P, et al. Cir Res 2019; 124:150.

REGRESSION

LACK OF PROGRESSION

PLAQUE STABILIZATION

WHAT TO DO.....

THANK YOU

Northwell[SM]
Cardiovascular Institute

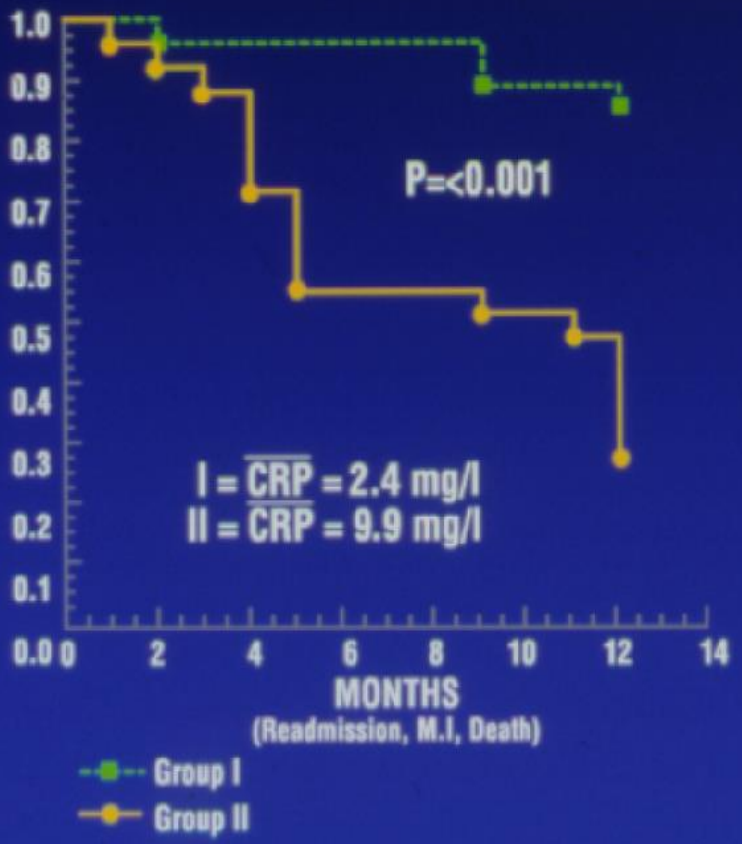
CURRENT LP(A) INTERVENTIONS

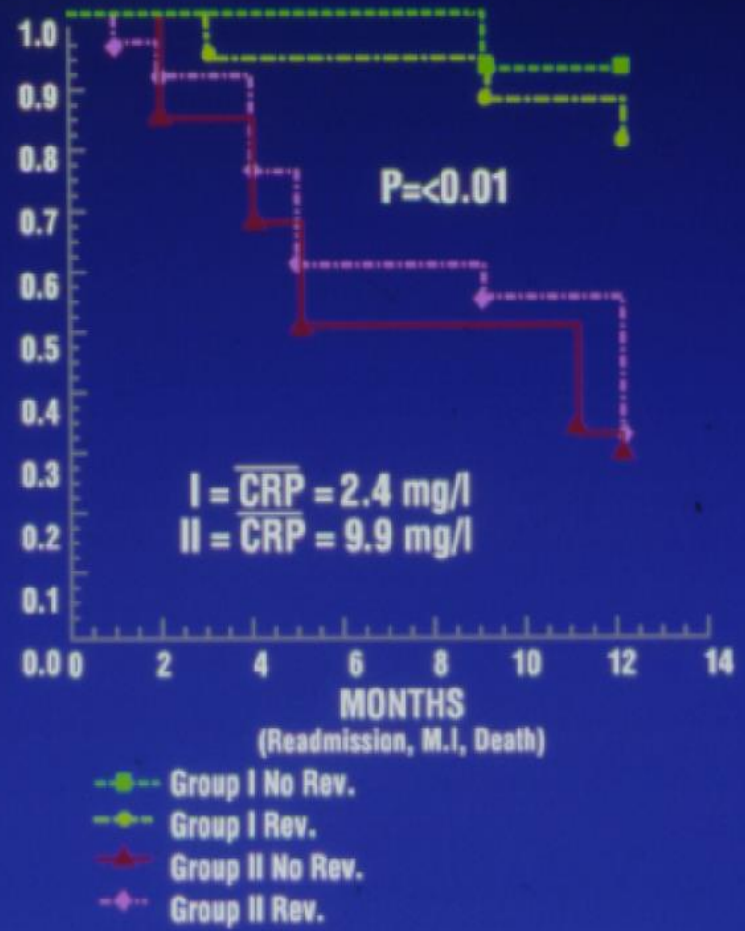
Lp(a)-Lowering Therapy	Lp(a) Effect	Possible Mechanism of Lp(a) Lowering	Best Level of Evidence
Lipid apheresis	70% acute, 35% time-averaged reduction	Removal of Lp(a) and other lipoproteins using adsorption columns	Several longitudinal prospective trials (45)
Nicotinic acid	20% to 30% reduction	Inhibition of LPA promoter via cyclic AMP (46)	Randomized control trials (12)
PCSK9 inhibitors	14-30% reduction	Unknown, possibly due to decreased apo(a) secretion	Multiple, large, randomized trials (16,17,47)
Mipomersen	20% to 40% reduction	Inhibits synthesis of apoB-100	4 phase 3 randomized, placebo-controlled trials (24)
Lomitapide	17% reduction	Decrease in VLDL synthesis via microsomal triglyceride transfer protein inhibition	Small phase 2 and 3 randomized, placebo-controlled trials (48)
Statins	8% to 24% increase	Unknown, possibly due to increase in apo(a) secretion via PCSK9 (22)	Large meta-analysis and smaller single studies (22)
Ezetimibe/fibrates/bile acid sequestrants	? neutral	N/A	Small clinical studies, more data needed (49)

apo(a) = apolipoprotein(a); apoB = apolipoprotein B; Lp(a) = lipoprotein(a); N/A = not available; PCSK9 = proprotein convertase subtilisin kexin type 9; VLDL = very low-density lipoprotein.

Tsimmikas S, et al. J Am Coll Cardiol 2021; 77: 1576-1589

One Year Survival Free Events Based on CRP





Biasucci, LM et al. Elevated levels of C-Reactive Protein at Discharge in Patients with Unstable Angina Predict Recurrent Instability. Circ 1999; 99:855