1

When and how should we use Cardiac CT for prevention ?

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Conflict of Interest – Grant, GE Healthcare

THE LUNDQUIST INSTITUTE

SCCT
SOCIETY OF CARDIOVASCULAR COMPUTED TOMOGRAPHY

2

ST FRANCIS RANDOMIZED TRIAL

Randomized Double Blind Placebo Controlled Trial of Atorvastatin in the Prevention of Cardiovascular Events Among Individuals With Elevated CAC Score

No Prior CVD

Men, Women 50-70 years

CAC >80%

of age-gender

Atorvastatin 20 mg (N=490)

Placebo (N=515)

duration of treatment was 4.3 years

MI

Stroke

CVD Death

CABG/PTCA

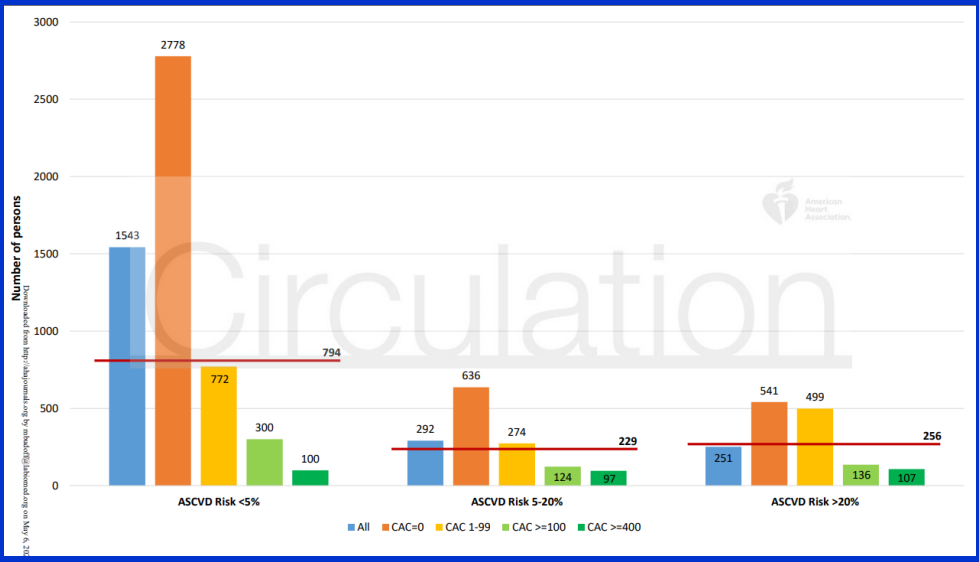
- Treatment with atorvastatin reduced clinical endpoints by 30% (6.9% vs. 9.9%)
- Event rates were more significantly reduced in participants with baseline calcium score >400 (8.7% vs. 15.0%, p=0.046 [42% reduction]).

Arad Y et al. J Am Coll Cardiol 2005: 46: 166-172.

3

Aspirin and Actual Bleeding/Events

Cainzos-Achirica M Circ 2020



4

CAC IN 2018 GUIDELINES

IIa	B-NR	6. In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy (S4.4.2-15, S4.4.2-17, S4.4.2-23).
IIa	B-NR	7. In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND • If the coronary calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking); • If CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; • If CAC score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy (S4.4.2-17, S4.4.2-23).

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CAC IN 2018 GUIDELINES

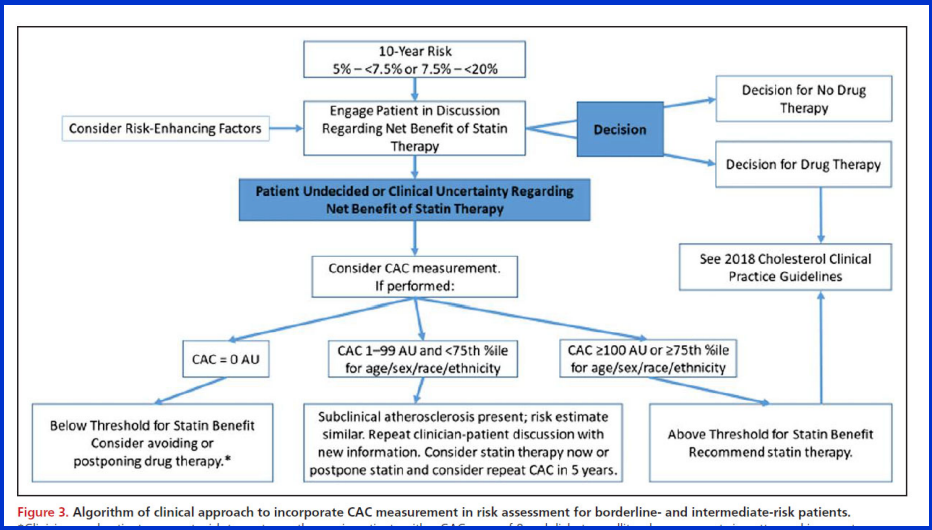

Figure 3. Algorithm of clinical approach to incorporate CAC measurement in risk assessment for borderline- and intermediate-risk patients.

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NNT for CAC >100

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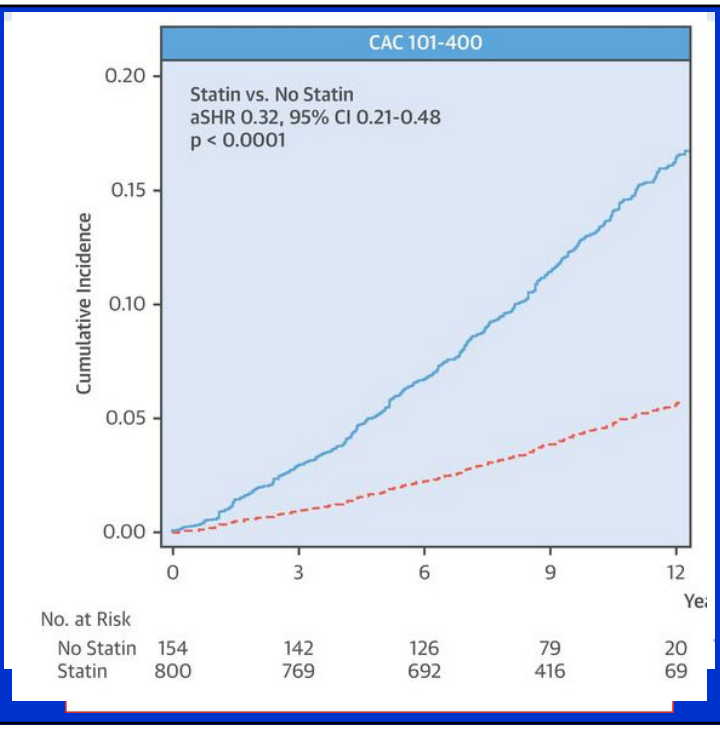

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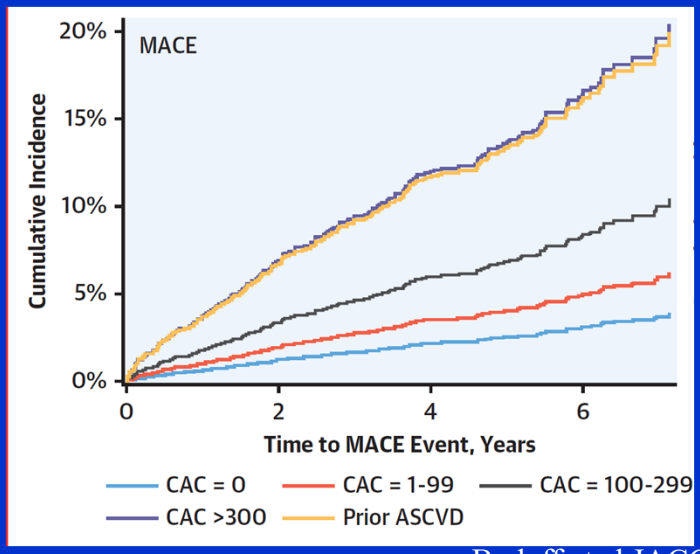
WHEN IS CAC SECONDARY PREVENTION



Budoff et al JACC CI 2023

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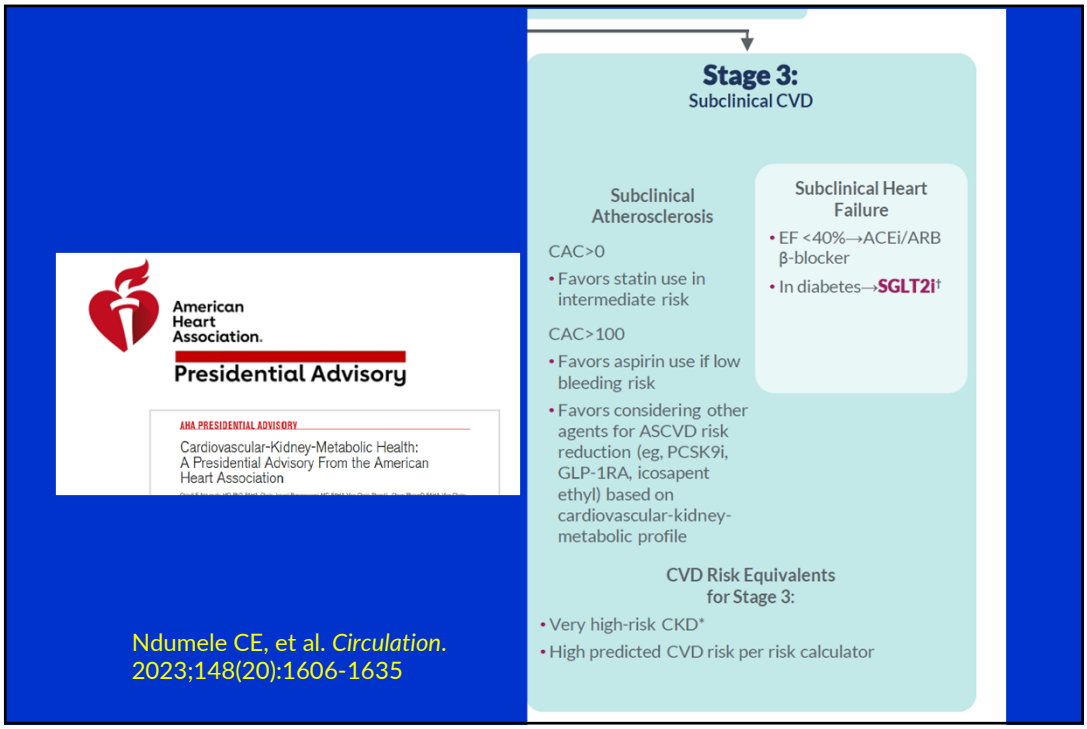
American Heart Association.
Presidential Advisory
AHA PRESIDENTIAL ADVISORY
Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association
Stage 3:
Subclinical CVD
Subclinical Atherosclerosis
CAC>0
• Favors statin use in intermediate risk
CAC>100
• Favors aspirin use if low bleeding risk
• Favors considering other agents for ASCVD risk reduction (eg, PCSK9i, GLP-1RA, icosapent ethyl) based on cardiovascular-kidney-metabolic profile
Subclinical Heart Failure
• EF <40%→ACEi/ARB β-blocker
• In diabetes→SGLT2i†
CVD Risk Equivalents for Stage 3:
• Very high-risk CKD*
• High predicted CVD risk per risk calculator
Ndumele CE, et al. Circulation. 2023;148(20):1606-1635

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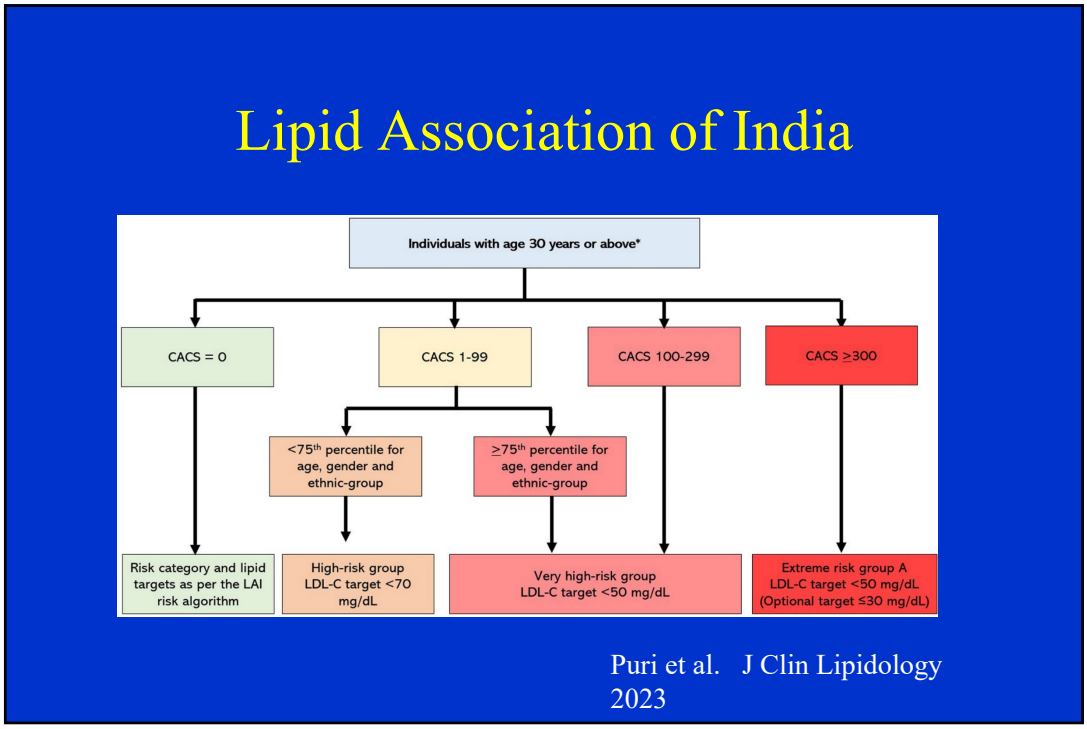
Lipid Association of India
Individuals with age 30 years or above*
CACS = 0
CACS 1-99
CACS 100-299
CACS ≥300
<75th percentile for age, gender and ethnic-group
≥75th percentile for age, gender and ethnic-group
Risk category and lipid targets as per the LAI risk algorithm
High-risk group LDL-C target <70 mg/dL
Very high-risk group LDL-C target <50 mg/dL
Extreme risk group A LDL-C target <50 mg/dL (Optional target ≤30 mg/dL)
Puri et al. J Clin Lipidology 2023

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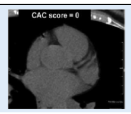
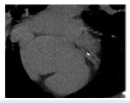
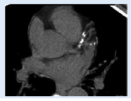
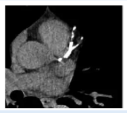
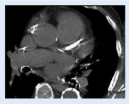
MARON ET AL. JACC ADVANCES 2024

TABLE Proposed Coronary Artery Calcium Staging Guide to Therapy

Stage	CAC Score and Disease Level	Representative Scan Image (White = CAC)	Therapeutic Recommendations Based on ACC/AHA Expert Consensus and Guidelines[2,3]
0	• CAC Score: 0 • No calcified plaque • Visual score: CAC absent		• Promote American Heart Association Life's Essential 8 Optimal Risk Factor Goals[7] • Consider no statin *unless* diabetes, LDL-C ≥190 mg/dL, smoker, family history of premature ASCVD, 10-y ASCVD risk ≥20%, or high Lp(a) • Consider repeat CT for CAC or analysis of nongated chest CT at: ○ 3 y for diabetes or high 10-y risk for ASCVD ○ 3-5 y for intermediate 10-y risk for ASCVD ○ 5-7 y for low 10-y risk for ASCVD
1	• CAC Score: 1-99 and <75th percentile for age and sex • Mild atherosclerotic burden		• Promote American Heart Association Life's Essential 8 Optimal Risk Factor Goals[7] • Statin (+nonstatin) therapy as needed to achieve LDL-C goal <100 mg/dL • Serial monitoring of all risk factors (eg, LDL-C, systolic blood pressure) to achieve critical biometric targets
2	• CAC Score: 100-299 or ≥75th percentile for age and sex • Moderate atherosclerotic burden		• All of the above plus: • Statin (+nonstatin) therapy as needed to achieve LDL-C goal <70 mg/dL • Consider low-dose aspirin therapy
3	• CAC Score: 300-999 • Severe atherosclerotic burden • Very high risk; risk associated with CAC ≥300 is similar to having had a myocardial infarction		• All of the above plus: • High-intensity statin (+nonstatin) therapy as needed to achieve LDL goal <55 mg/dL[3] • Low-dose aspirin
4	• CAC Score: ≥1,000 • Extensive atherosclerotic burden • Extreme risk; risk associated with CAC ≥1,000 similar to having had multiple ASCVD events		• All of the above plus: • Statin (+nonstatin) therapy as needed to achieve LDL-C goal <55 mg/dL[3] • Consider emerging therapies[a]

[a]For example, low-dose anticoagulant in combination with low-dose aspirin, anti-inflammatory therapy (eg, low-dose colchicine).
ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a).

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Top Indications for CAC Testing (primary prevention)

1. "Intermediate" Risk Patient
   - ASCVD 5-20%, Risk Uncertain
   - Family History
2. Statin Reluctant/Intolerant
3. Decisions for Non-Statin Rx (PCSK9i, IPE, GLP1 RA)
4. Decisions For Aspirin Rx
5. MOTIVATION!

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ACC/AHA/ASE/ASNC/ASPC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2023 Multimodality Appropriate Use Criteria for the Detection and Risk Assessment of Chronic Coronary Disease

TABLE 2.1 Asymptomatic Patients Without Known ASCVD

Clinical Scenario Text	ECG Treadmill	Stress Nuclear MPI	Stress Echo	Stress CMR	CAC	CCTA	Cath	No Test
34. ■ Low ASCVD risk <5%*	R (2)	R (1)	R (1)	R (2)	M (4)	R (1)	R (1)	A (8)
35. ■ Borderline ASCVD risk 5% to 7.5%	M (4)	R (2)	R (2)	R (2)	A (7)	R (2)	R (1)	A (7)
36. ■ Borderline ASCVD risk 5% to 7.5% with risk-enhancing factors†	M (4)	R (3)	R (3)	R (3)	A (7)	R (3)	R (1)	A (7)
37. ■ Intermediate ASCVD risk 7.5% to 20% with or without risk-enhancing factors†	M (5)	R (3)	R (3)	R (3)	A (8)	R (3)	R (1)	M (5)
38. ■ High ASCVD risk >20%	M (5)	M (4)	M (4)	M (4)	M (6)	M (4)	R (2)	M (5)

*Risk calculated using the ASCVD risk estimator.
†See Table C, Risk-Enhancing Factors.
A = Appropriate; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium score; cath = cardiac catheterization; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance; ECG = electrocardiogram; echo = echocardiography; M = May Be Appropriate; MPI = myocardial perfusion imaging; R = Rarely Appropriate.

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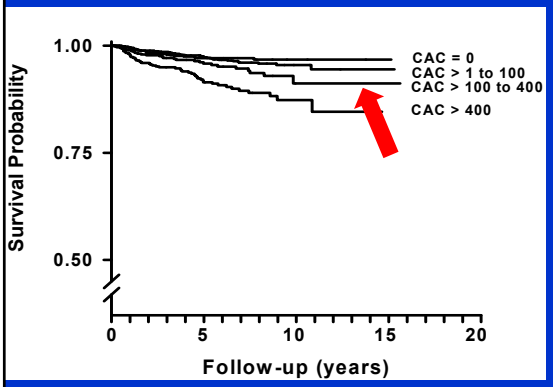
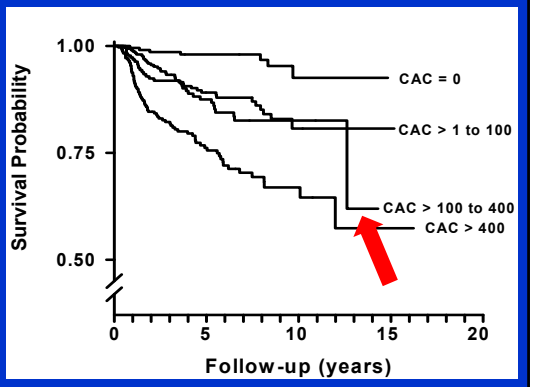
Budoff JACC Imag 2010
4,609 consecutive asymptomatic individuals



In non-progressors



In progressors

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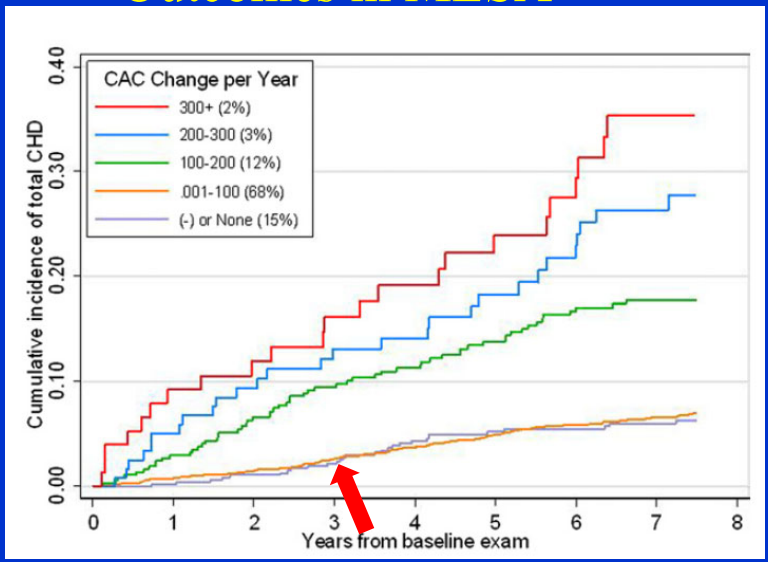
CAC Progression and Outcomes in MESA



Budoff
JACC 2013

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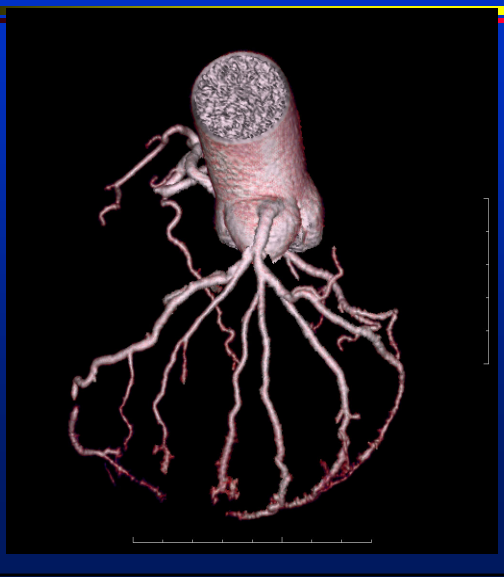
Coronary CTA Under 1 mSv



- **Patient:**
  - Male
  - BMI: 22
  - Cardiac risk factors
  - Heart rate: 54-56 bpm
- **Scan:**
  - Tube: 350 mA & 100 kVp
  - X-ray Exposure: **0.93 sec**
  - Radiation Dose: **0.95 mSv**
- **Findings:**
  - LAD: mild stenosis

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CAC and CTA

Hou JACC CI 2012

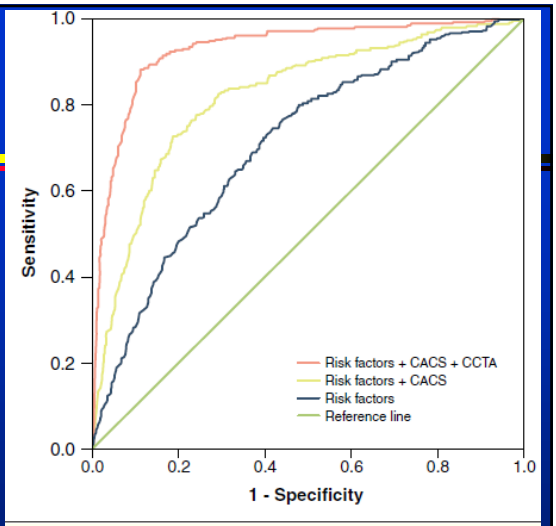

Figure 4. ROC Curves of 3 Models

Receiver-operating characteristic (ROC) curves show the incremental value of coronary artery calcium score (CACS) and coronary computed tomography angiography (CTA): risk factors only (area under the curve [AUC] 0.71; 95% confidence interval [CI]: 0.68 to 0.74, p < 0.001 **[blue line]**). Risk factors plus CACS (AUC 0.82; 95% CI: 0.80 to 0.85, p < 0.001 **[yellow line]**), and risk fac-

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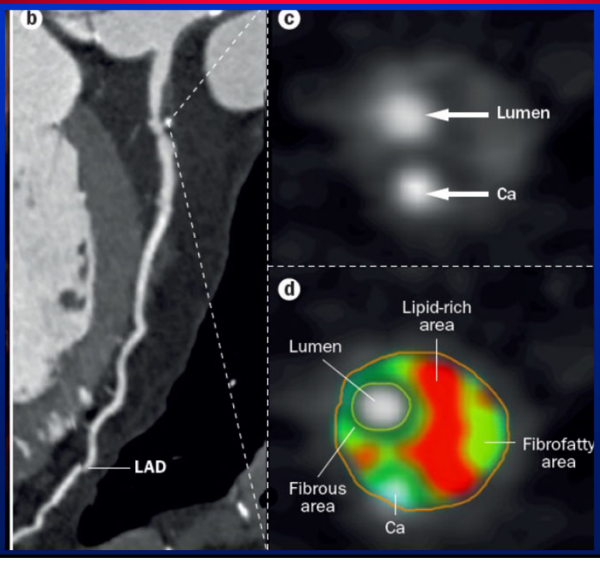
Ability to See Plaque, Stenosis, Remodeling



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Targeted Use of CTA

- 35% of young DM (age <40) had only non-calcified plaques
- Madaj, Karlsberg, Karpman, Budoff
  - Acad Rad 2012

Figure 1. A large noncalified plaque (*arrow*) in the proximal left anterior descending artery.

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ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–71
doi:10.1093/eurheartj/ehz425

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

In high-risk asymptomatic adults (with diabetes, a strong family history of CAD, or when previous risk-assessment tests suggest a high risk of CAD), functional imaging or **coronary CTA** may be considered for cardiovascular risk assessment.

- Class IIb recommendation

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- Addition of coronary CTA imaging clarifies the diagnosis, enables the targeting of preventive therapies and interventions, and potentially reduces the risk of MI

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Intermediate-High Risk Patients With Stable Chest Pain and No Known CAD

Recommendations for Intermediate-High Risk Patients With Stable Chest Pain and No Known CAD Referenced studies that support the recommendations are summarized in Online Data Supplements 29 and 30.		
Index Diagnostic Testing: Selecting the Appropriate Test		
COR	**LOE**	**Recommendations**
Anatomic Testing		
1	A	1. For intermediate-high risk patients with stable chest pain and no known CAD, CCTA is effective for diagnosis of CAD, for risk stratification, and for guiding treatment decisions.

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Intermediate-Risk Patients With Acute Chest Pain and No Known CAD (con't.)

Stress Testing		
1	B-NR	4. For intermediate-risk patients with acute chest pain and no known CAD who are eligible for cardiac testing, either exercise ECG, stress echocardiography, stress PET/SPECT MPI, or stress CMR is useful for the diagnosis of myocardial ischemia.

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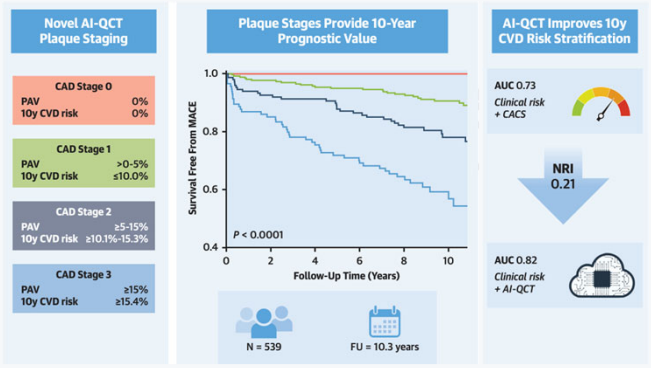
CV Risk Assessment Using Plaque Burden

MACE Prediction:

- CCTA Plaque Stage is a better predictor of short- and long-term MACE events than:
  - Risk Score (ASCVD etc.).
  - CAC Score.
  - Stenosis presence



Nurmohamed et al JACC Imag 2023

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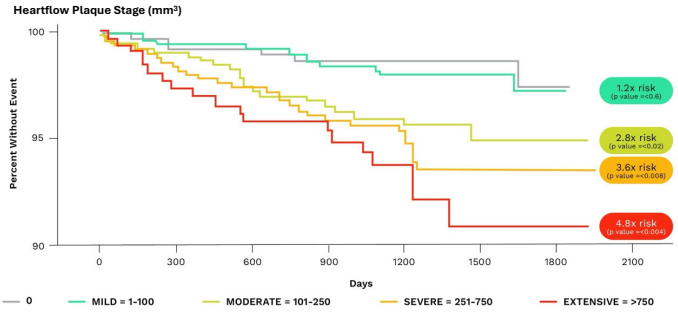
Plaque staging informs cardiovascular outcomes

Study Design

- 2,827 patients from FISH&CHIPS Liverpool cohort were stratified according to Heartflow Plaque Staging* based on total plaque volume
- Patient outcomes (CV death and MI) were reviewed out to 3.3 yrs (median)

FISH&CHIPS Liverpool: Prediction of Cardiovascular Outcomes

Results: Higher TPV-based stages were associated with statistically significant higher CV event rates even after adjusting for risk factors, stenosis, and FFR_{CT}**



Fairbairn, et al. HEART. 2025. doi:10.1136/heartjnl-2025-BSCI.5
*Heartflow Plaque Analysis is an FDA-cleared device. Heartflow Plaque Staging is an investigational only framework and its safety and effectiveness have not been reviewed by the FDA.
** Adjusted for age, sex, hypertension, dyslipidemia, diabetes, stenosis, and FFRCT

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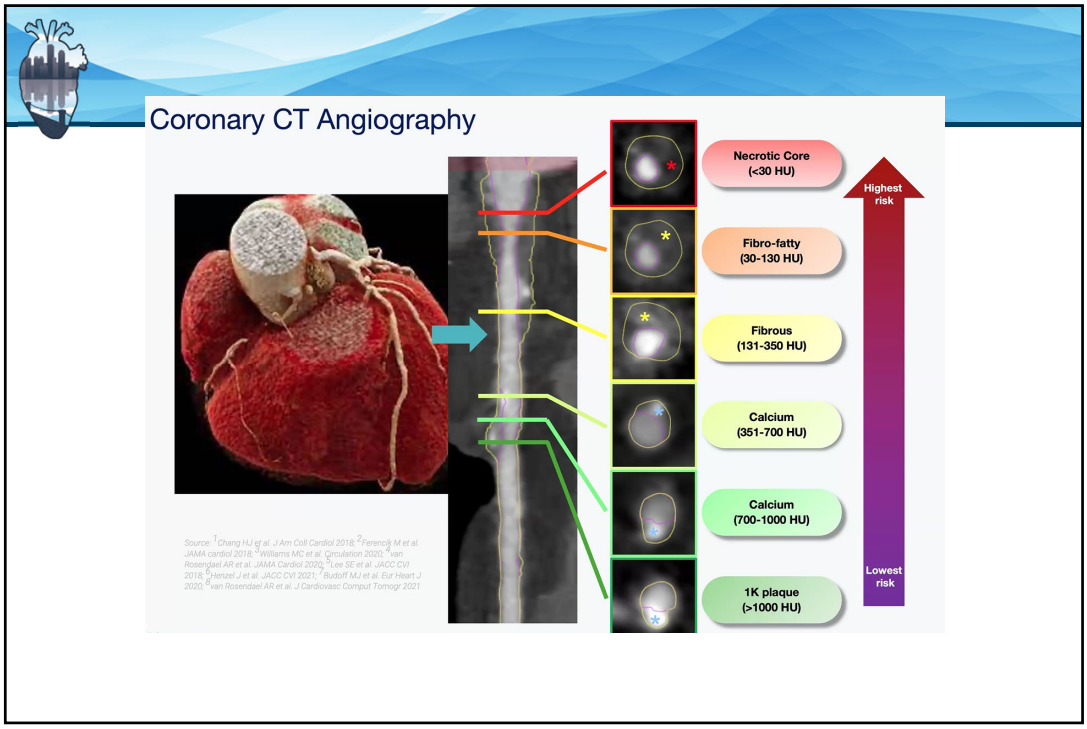
25



Source: [1]Chang HJ et al. J Am Coll Cardiol 2018; [2]Ferencik M et al. JAMA cardiol 2018; [3]Williams MC et al. Circulation 2020; [4]van Rosendael AR et al. JAMA Cardiol 2020; [5]Lee SE et al. JACC CVI 2018; [6]Henzel J et al. JACC CVI 2021; [7]Budoff MJ et al. Eur Heart J 2020; [8]van Rosendael AR et al. J Cardiovasc Comput Tomogr 2021

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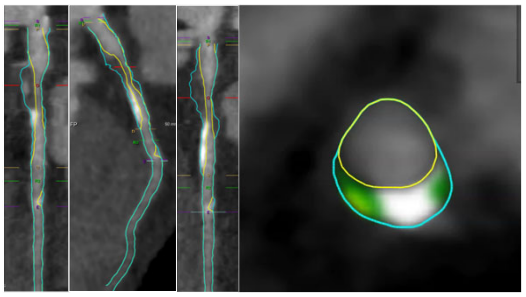
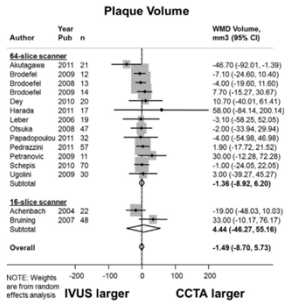
Quantification of Atherosclerotic Plaque Using Coronary CTA Is Highly Concordant with IVUS Measurements



- 3-dimensional measures
- All major epicardial vessels & branches
- 0.5 mm cross-sectional characterization of plaque & lumen

Meta-analysis: 42 studies comparing CT vs. IVUS



- 1,360 patients undergoing CT & IVUS
- 1.5 mm^3 difference between CT / IVUS (p=NS)
- AUC for plaque volume = 0.97

Source: Fischer JCCT 2013;7:256-66.

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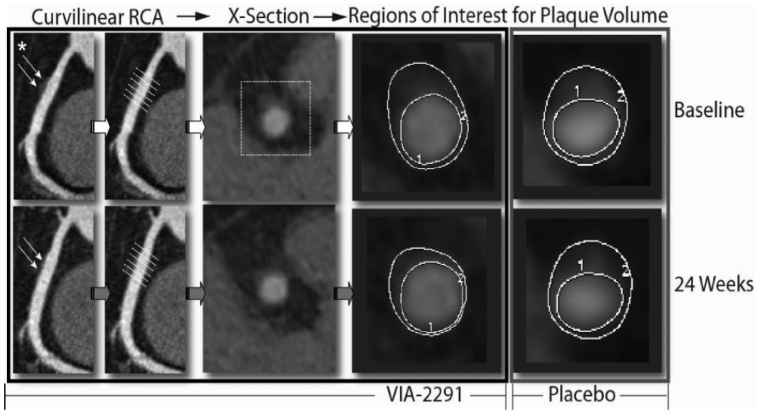
Cardiac CT to Assess Atherosclerosis over Time



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Plaque Progression and Events
Motoyama JACC 2015

TABLE 4 Cardiac Events After CTA-2

	Univariable		Multivariable	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	0.99 (0.94–1.06)	0.85	1.00 (0.95–1.08)	0.87
Male	1.32 (0.24–24.55)	0.78		
Hypertension	1.59 (0.39–10.70)	0.54		
Diabetes	1.13 (0.24–4.27)	0.87		
Dyslipidemia	0.86 (0.22–4.06)	0.83		
BMI >25 kg/m^2	5.58 (1.46–26.52)	0.012	3.27 (0.66–24.42)	0.15
Current smoking	2.35 (0.62–9.51)	0.20		
Previous ACS	6.26 (1.15–116.32)	0.032	8.35 (1.06–209.55)	0.043
Statin use	1.11 (0.27–7.44)	0.90		
Chest pain at CTA-2	3.09 (0.65–11.73)	0.14		
HRP at CTA-1	4.40 (1.08–16.67)	0.039	0.85 (0.07–9.01)	0.89
HRP at CTA-2	9.07 (2.38–43.11)	0.0014	2.18 (0.20–27.78)	0.51
Plaque progression	61.32 (11.24–1,137.73)	<0.0001	33.43 (4.13–78.03)	0.0006

Abbreviations as in Tables 1 and 2.

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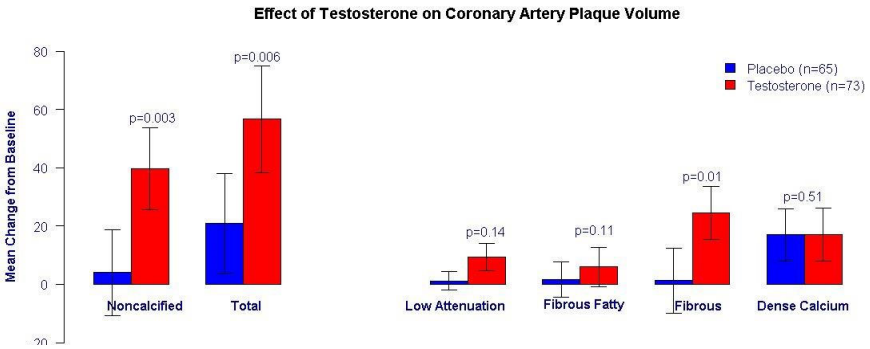
EFFECT OF TESTOSTERONE REPLETMENT ON CORONARY PLAQUE VOLUME

Budoff et al. JAMA. 2017;317(7):708-16



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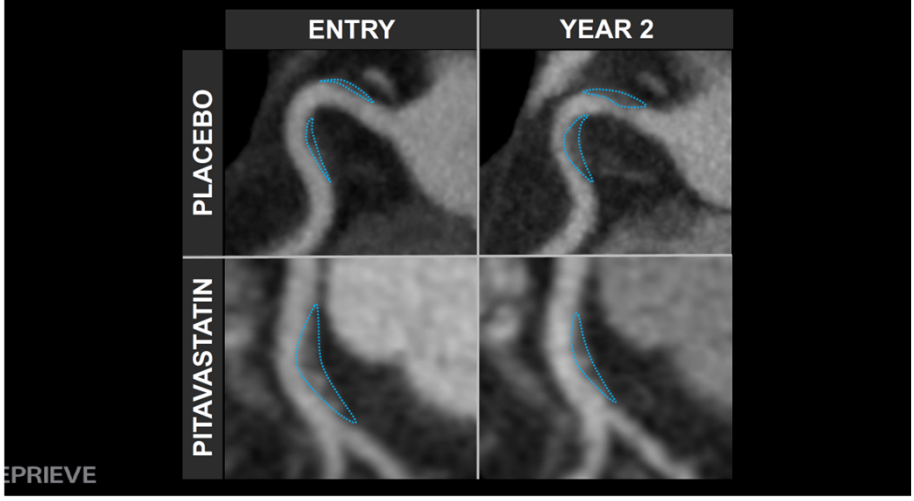
Examples: Plaque Progression & Regression



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REPRIEVE STUDY – Lu et al JAMA Card 2024

2-Year Change in Noncalcified Plaque Volume

Pitavastatin arm:

- -4.3 mm^3 (-7%) decrease in noncalcified plaque volume vs placebo
  - -8.8 mm^3 (-12%) in subgroup with plaque at baseline
- 33% lower risk of noncalcified plaque progression
- Similar in per protocol and multiple imputation analyses

Outcome	Treatment arm: Pitavastatin (N=386)	Treatment arm: Placebo (N=388)	Treatment effect*: Difference (95% CI)	Treatment effect*: P
Noncalcified plaque volume, mm^3				
Change from baseline, mean (SD)	-1.7 (25.2)	2.62 (27.1)	-4.3 (-8.6, -0.1)	0.044
Fold-change from baseline (95% CI)	0.95 (0.91, 1.0)	1.02 (0.99, 1.05)	0.93 (0.88, 0.99)	0.024
Progression of NCP, N (%)	53 (18%)	85 (28%)	0.67 (0.52, 0.88)	0.003
Low attenuation plaque volume, mm^3				
Change from baseline, mean (SD)	-0.9 (9.97)	-0.1 (8.16)	-1.2 (-2.2, -0.1)	0.026

REPRIEVE

* Adjusted for baseline value

ML

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evaporate FINAL — Study Design

Randomized, Double-Blind, Placebo-Controlled Trial

Patient Population (N=80)
- 30–85 years of age
- TG: 135–499 mg/dL
- LDL-C >40 mg/dL and ≤115 mg/dL (on statin)
- ≥1 angiographic stenosis with ≥20% narrowing by CTA
- No history of MI, stroke, or life-threatening arrhythmia within the prior 6 months and no history of CABG

Primary endpoint
- Progression rates of low attenuation plaque

Secondary endpoints include
- Plaque morphology and composition
- (non-calcified, total, fibrous, fibrofatty, calcified)
- Markers of inflammation (Lp-PLA$_2$)
- LDL-C and HDL-C

IPE 4 g/d

Placebo

18 Months

The EVAPORATE study sought to determine whether IPE will reduce plaque progression over 9 to 18 months compared to placebo in statin-treated patients

CABG=coronary artery bypass graft; CTA=computed tomography angiography.

EVAPORATE Clinical Trial. https://clinicaltrials.gov/ct2/show/NCT02926027. **BUDOFF et al. CLIN CARD 2017.**

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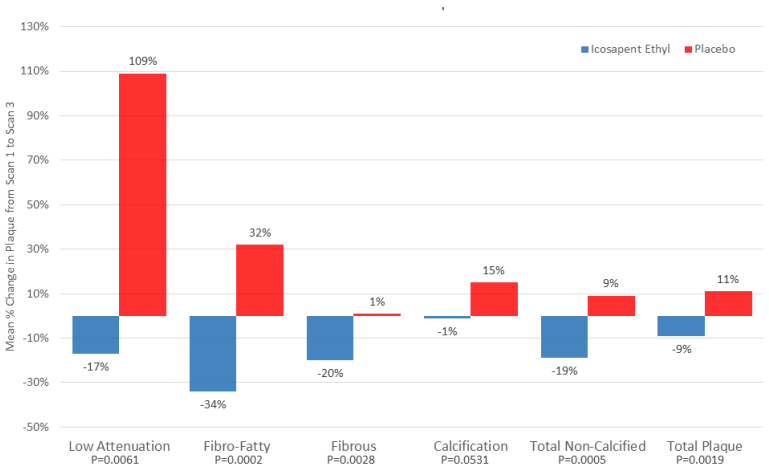
evaporate FINAL — Budoff et al. EHJ 2020



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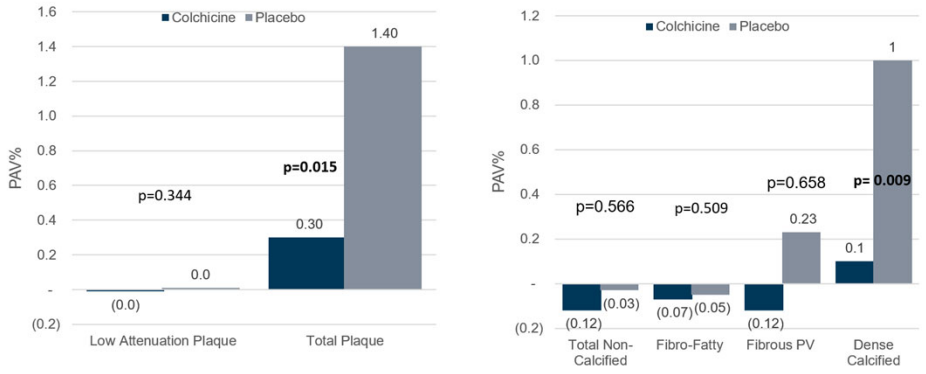
EKSTROM Trial

Results: Plaque Volume Changes at 1 year (Percent Atheroma Volume PAV%)



*p reported adjusted for Age, Gender, BMI, Hypertension, Hyperlipidemia, and Baseline Plaque from multivariable linear regression.

Budoff et al. ACC Abstract 2025

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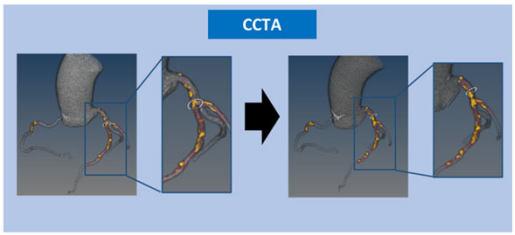
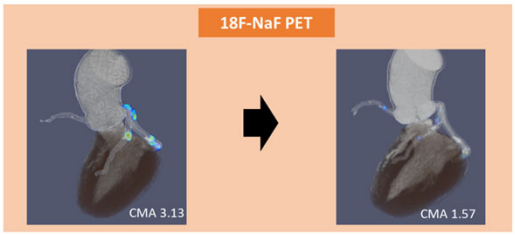
CENTRAL ILLUSTRATION: Effects of Evolocumab on Coronary Atherosclerosis

47 patients with extensive non-calcified plaque volume underwent serial CCTA and 18F-NaF PET imaging to assess plaque changes after 18 months of Evolocumab treatment



Plaque volume and composition

- ↔ Total plaque volume
- ↓ Non-calcified plaque volume
- ↓↓ Low density non-calcified plaque volume
- ↑↑ Calcified plaque volume



Plaque activity

- ↓ Coronary microcalcification activity

Han et al. JACC CI 2025

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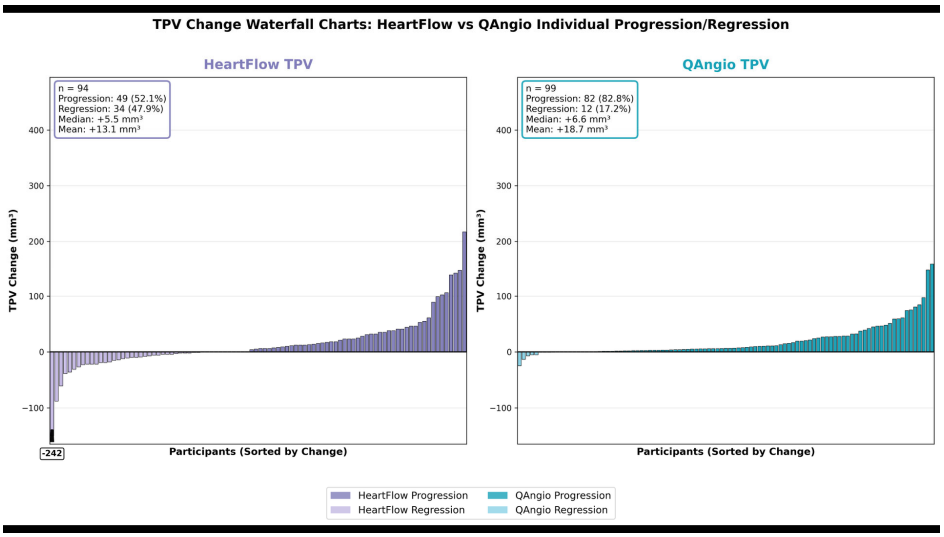
KETO Diet 1 year Follow up



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What have we learned so far

- Changes in atherosclerosis are correlated with outcomes
- CCTA can be used as a non-invasive imaging modality with low cost and low risk
- Plaque progression on Serial CCTA can inform clinician and patient that current therapies are not sufficient
- Additional therapies (PCSK9i, IPE, Colchicine) can be added in those patients who are still progressing
- Tracking atherosclerosis affords the patient and physician the ability to modify treatment plans based on individual responses –

“PERSONALIZED MEDICINE”

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Who needs CT anyway? We should just treat with statins

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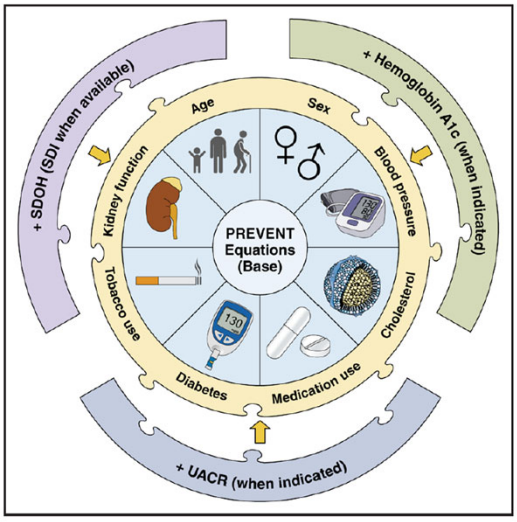
Khan et al Risk of



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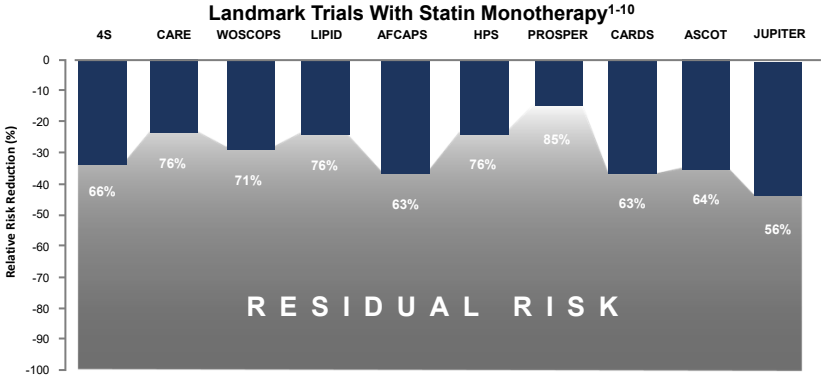
Despite the CV Benefit of LDL-C Lowering, Significant Residual Risk Remains[1-11]

Landmark Trials With Statin Monotherapy[1-10]



1. Adapted from Rader DJ et al. http://www.medscape.org/viewarticle/569095. Accessed Nov. 1, 2024; 2. Shepherd J, et al. *N Engl J Med*. 1995;333(20):1301-1307; 3. Scandinavian Simvastatin Survival Study Group. *Lancet*. 1994;344(8934):1383-1389; 4. Ballantyne CM. *Am J Cardiol*. 1998;82(9A):3Q-12Q; 5. Sacks FM, et al. *N Engl J Med*. 1996;335(14):1001-1009; 6. Downs JR, et al. *JAMA*. 1998;279(20):1615-1622; 7. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med*. 1998;339(19):1349-1357; 8. Brown BG. *Eur Heart J Suppl*. 2005;7(suppl F):F34-F40; 9. Grundy SM, et al. *Circulation*. 2004;110(2):227-239; 10. Ridker PM, et al. *N Engl J Med*. 2008;359(21):2195-2207; 11. Ganda OP, et al. *J Am Coll Cardiol*. 2018;72(3):330-343; 12. Sabatine MS, et al. *N Engl J Med*. 2017;376(18):1713-1722; 13. Schwartz GG, et al. *N Engl J Med*. 2018;379(22):2097-2107.

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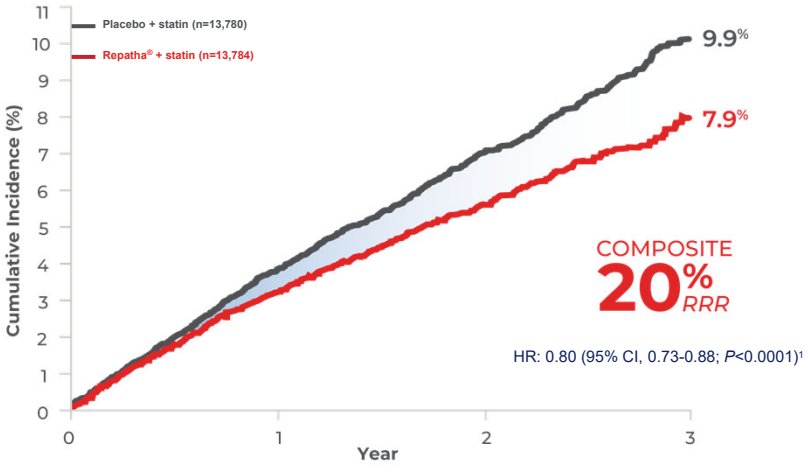
For Patients With Established CVD, Repatha® Added to a Statin Reduced the Risk of Composite CV Events by 20% in a Median of 2.2 Years[1,2]

Key secondary endpoint:
Composite of CV death, MI, or stroke[1,2]



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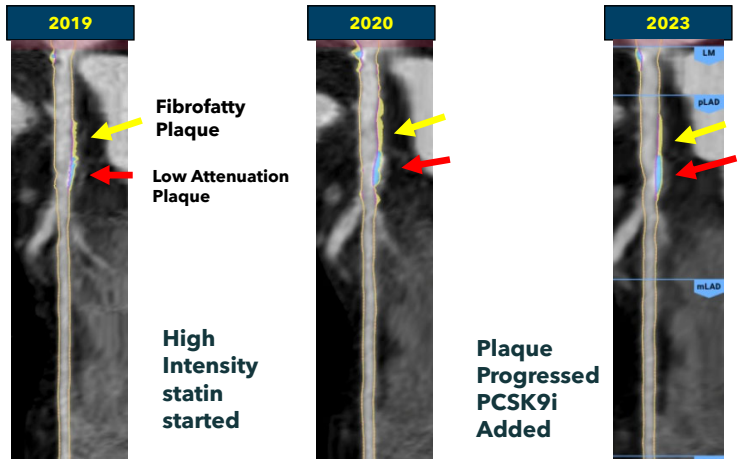
Serial CCTA Images to personalize Lipid Lowering



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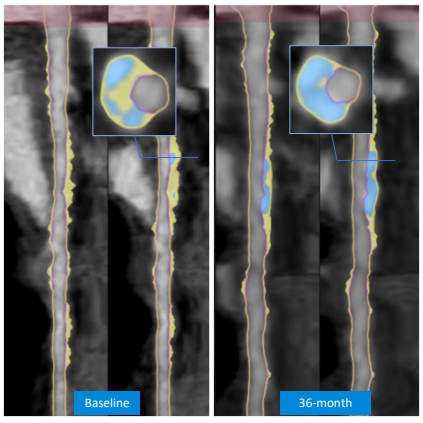
TRACK: Quantify Disease Change



1. Stabilization: Halt New Disease Progression
2. Transformation: Convert to lower risk calcium

57-year-old man taking a statin.

Stage	Baseline	Follow-up	Change
Total Plaque Volume	260.9 mm^3	255.5 mm^3	-2%
Non-calcified Plaque	139.9 mm^3	57.1 mm^3	-59%
Low Density Plaque	0.5 mm^3	0 mm^3	-100%
Calcified Plaque	121 mm^3	198.4 mm^3	+64%

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TREAT: Therapy Based on Plaque Stage + RF

Freeman, A et al Am J Med 2022

Stage	Stenoses	Action	Rescan (until stable):
Stage 0: No Plaque	0	• GDMT / Consider de-escalation	4 years
Stage 1: Mild	<50%	• Statin, Ezetimibe	3 years
Stage 2: Moderate	<50%	Stage 1 Plus • Aspirin, Rivaroxaban • GLP1 if diabetic	2 years
Stage 3: Severe	<50%	Stage 2 plus • Consider PCSK9, Icosapent ethyl, Inclisirin, Bempedoic acid, Colchicine • GLP1 and SGLT2 if diabetic	1 year

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Take Home Messages

- Clinicians need better tools to **identify which patients are not responding** and need more aggressive treatment
- **We have ample treatments available, but we need to know who and when to use them (ezetimibe, PCSK9i, bempadoic acid, inclisiran, icosapent ethyl, colchicine, GLP1 RA, SGLT2i…)**
- CTA-driven plaque progression tools that **quantify disease progression are validated, rapid, and reimbursed**
- These **accurate, patient-specific disease insights impact treatment decisions** which improve long-term disease management

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THOUGHTS ON PREVENTION

- ***…at the beginning a disease is easy to cure but difficult to diagnose; but as time passes, not having been recognized or treated at the outset, it becomes easy to diagnose but difficult to cure.***

- ***Niccolò Machiavelli (1469-1527)***

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