Approach to Risk Stratifying of ASCVD

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Learning Objectives

At the conclusion of this presentation, participants should be able to:

Risk Assessment Tools

Determine an individual's **10-year and 30-year risk** of developing ASCVD and CVD using current assessment tools (PCE, PREVENT).

Modifiable Risk Factors

Identify and quantify **major modifiable risk factors** such as high blood pressure, dyslipidemia, diabetes mellitus, and tobacco use.

Diagnostic Testing

Apply **selective diagnostic testing** (e.g., CAC, Lp(a)) to assess for subclinical atherosclerosis when treatment decisions are uncertain.

Intervention Benefit

Recognize interventions with **unclear benefit** in primary prevention, including aspirin, Omega-3 fatty acids, and single pill combinations.

02

Section

Tools & Calculators

Clinical Update

Risk Estimation Tools

From PCE to PREVENT

Understanding the paradigm shift from traditional 10-year ASCVD risk assessment to the new equations incorporating comprehensive 10- and 30-year predictions.

PCE
10-Year ASCVD

→

PREVENT™
Total CVD • ASCVD • HF
(10 & 30 Years)

Pooled Cohort Equations (PCE): 10-Year ASCVD

Standard Risk Assessment Tool for Primary Prevention

Target Population

Valid for adults **aged 40–79 years** without pre-existing clinical ASCVD.

Primary Output: Estimated 10-year risk of a first hard ASCVD event (fatal/non-fatal MI or fatal/non-fatal stroke).

Key Inputs

- Age (40-79)
- Sex
- Race (AA vs. White/Other)
- Total Cholesterol
- HDL-Cholesterol
- Systolic BP
- HTN Treatment
- Diabetes Status
- Smoking Status

Caveats & Limitations

While the PCE remains the guideline-recommended initial step, clinicians must be aware of its limitations in modern populations.

Calibration Issues:

May **overestimate risk** in higher socio-economic groups and those with high uptake of preventive therapies (e.g., extensive statin use in population).

May **underestimate risk** in certain high-risk subgroups (e.g., South Asians, chronic inflammatory conditions, HIV).

Addressing Uncertainty

Risk Enhancers: Use to refine risk estimation when decision is unclear.

CAC Scoring: The best tool for reclassification when PCE estimates are borderline or intermediate.

Shared Decision Making: Essential when predicted risk is near treatment thresholds.

Sources: Goff DC Jr et al. *J Am Coll Cardiol*. 2014;63:2935-2959; USPSTF. *JAMA*. 2022;327:1577-1584.

AHA PREVENT™ Calculator

10- & 30-Year Risk Stratification

Comprehensive Risk Assessment

Provides risk estimates for Total CVD (ASCVD + Heart Failure), ASCVD alone, and Heart Failure alone.

Extended Time Horizon

Calculates both 10-year and 30-year risk. Crucial for identifying younger patients (ages 30–59) with high lifetime risk who may benefit from early intervention.

Novel Inputs

Incorporates renal function (eGFR, albuminuria) and social determinants of health (SDOH), removing race as a variable for more equitable assessment.

Clinical Utility Focus

Especially valuable for adults aged 30–59 not yet eligible for statins under 10-year models. Helps inform lifetime risk discussions and emphasizes the urgency of lifestyle modifications early in the disease course.

Source: Khan SS, et al. The American Heart Association PREVENT™ Risk Calculator. Circulation. 2024.

Choosing Between PCE and PREVENT

Risk Assessment Algorithm & Decision Support

Patient Assessment

Primary Prevention Evaluation

Age 30–59

PREVENT Calculator

Estimates **30-Year** & 10-Year Risk for CVD, ASCVD, and Heart Failure.

Goal: Guide earlier lifestyle modification and lifetime risk reduction.

Age 40–79

PCE Calculator

Pooled Cohort Equations. Estimates **10-Year ASCVD** Risk (MI & Stroke).

Goal: Guide statin initiation decisions based on 10-year probability.

Indication for Refinement

If risk is **Borderline (5%–<7.5%)** or **Intermediate (7.5%–<20%)**, or decision is uncertain:

- Risk Enhancers
- CAC Score

Source: ACC/AHA 2019 Primary Prevention Guidelines

AHA PREVENT™ Online Calculator 2024

Risk Categories and Treatment Thresholds

Primary Prevention: Assessing 10-Year ASCVD Risk (Ages 40–75 Years)

Risk Category	10-Year Risk	Clinical Recommendation	Statin Intensity
Low Risk LOW	< 5%	Emphasize lifestyle to reduce risk factors. No medication typically recommended.	*None*
Borderline Risk BORDERLINE	5% to < 7.5%	Discussion of risk and lifestyle. If risk enhancers present, discuss moderate-intensity statin.	**Moderate Intensity** (If enhancers present)
Intermediate Risk INTERMEDIATE	7.5% to < 20%	Initiate moderate-intensity statin if risk enhancers present. If decision is uncertain, consider measuring CAC.	**Moderate Intensity** (Consider High Intensity)
High Risk HIGH	≥ 20%	Initiate high-intensity statin to lower LDL-C by ≥50%. Aggressive risk factor control.	**High Intensity**

Source: Grundy SM, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. *J Am Coll Cardiol*. 2019;73(24):e285-e350.

Arnett DK, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.

Risk-Enhancing Factors

Refining Risk Assessment Beyond Standard Calculators (ACC/AHA 2019)

History & Metabolic Factors

Family History: Premature ASCVD (males <55y, females <65y).

Primary Hypercholesterolemia: LDL-C 160–189 mg/dL (4.1–4.8 mmol/L); LDL-C ≥190 mg/dL is high risk by default.

Metabolic Syndrome: increased waist circumference, elevated triglycerides, elevated BP, elevated glucose, and low HDL-C (count of 3 factors).

Chronic Kidney Disease: eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria.

Specific Conditions

Chronic Inflammatory Conditions: Psoriasis, RA, lupus, HIV/AIDS.

Pregnancy-Associated Conditions: History of preeclampsia or premature menopause (<40 years).

Lipid & Inflammatory Biomarkers

Persistently Elevated Triglycerides: ≥175 mg/dL (≥1.97 mmol/L).

High-Sensitivity CRP: ≥2.0 mg/L.

Elevated Lipoprotein(a): ≥50 mg/dL or ≥125 nmol/L.

Elevated Apolipoprotein B: ≥130 mg/dL.

Ancestry & Subclinical Markers

High-Risk Race/Ethnicity: E.g., South Asian ancestry.

Ankle-Brachial Index (ABI): <0.9 (indicative of PAD).

Clinical Implication:

Presence of these factors favors initiation of statin therapy in borderline (5% to <7.5%) or intermediate (7.5% to <20%) risk patients.

Source: Arnett DK et al. *Circulation*. 2019;140:e596–e646 (2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease).

CVD | ASCVD | Heart Failure

Sex*

( ) Male ( ) Female

Current Smoking

Any cigarette use within the last 30 days

( ) No ( ) Yes

Lipid-lowering medication

Current use of statin medication to lower cholesterol

( ) No ( ) Yes

Age (years)*

30-79

HDL Cholesterol (mg/dL)*

20-100

BMI (kg/m^2)*

18.5-39.9

Total Cholesterol (mg/dL)*

130-320

SBP (mmHg)*

90-200

eGFR (mL/min/1.73m^2)*

15-140

Diabetes

Any history of diabetes.

( ) No ( ) Yes

Anti-hypertensive medication

Current use of any medication for hypertension

( ) No ( ) Yes

The following three predictors are optional for further personalization of risk assessment. When they are clinically indicated or available,

If avaliable or indicated, select "Yes" and enter the value.

UACR (mg/g)

UACR is clinically indicated for individuals with chronic kidney disease, diabetes, or hypertension

( ) No ( ) Yes

HbA1C

HbA1c is clinically indicated for individuals with diabetes, prediabetes, overweight, or obesity, or those with history of gestational diabetes

( ) No ( ) Yes

Zip Code

valid 5-digit zip code is needed to estimate social deprivation index [SDI]

( ) No ( ) Yes

Calculate | Reset

Shared Decision-Making Algorithm

Clinician-Patient Risk Discussion Pathway

1 **Estimate Risk**

Use PCE (10-yr) or PREVENT calculator

2 **Discuss Risk Enhancers**

Review comorbidities, family history, biomarkers

3 **Decision Uncertainty?**

Is risk status or treatment benefit unclear?

Borderline / Intermediate Risk

4 **Obtain CAC Score**

Reclassify risk based on calcium burden

If Certain:

Proceed directly to therapy alignment based on clear high/low risk.

03

Section

Subclinical Atherosclerosis

Targeted Evaluation

Selective Diagnostic Testing

Clarifying Uncertain Risk

Utilizing diagnostic tests to detect subclinical atherosclerosis when treatment decisions remain uncertain—moving away from universal screening toward precision risk assessment.

Uncertainty → **Testing** → **Decision**

- **Uncertainty**: Intermediate Risk
- **Testing**: CAC • Biomarkers
- **Decision**: Treat or Defer

ACC/AHA 2019 Guideline on the Primary Prevention of Cardiovascular Disease

AAFP 2022: Coronary Artery Calcium Scoring for Prevention of CVD

Biomarkers: When and Why

Selective Testing to Refine Risk Assessment

Key Principle: Selective Use

"Will the result change my management?"

Reserve biomarker testing for specific scenarios where risk status is unclear after standard assessment:

Borderline Risk (5% - <7.5%)

Intermediate Risk (7.5% - <20%)

Younger adults (<40 years) with premature family history

Not recommended for universal screening or low-risk patients.

Recommended Options

Consider these risk-enhancing factors to guide decisions:

hsCRP: Inflammation marker; ≥2.0 mg/L indicates higher risk.

Lp(a): Genetic risk factor; ≥50 mg/dL (≥125 nmol/L) is a risk enhancer.

ApoB: Atherogenic particle burden; ≥130 mg/dL corresponds to risk.

Emerging Utility: hs-cTn

High-sensitivity cardiac troponin (hs-cTn) in stable patients.

Prognostic Value: Elevations in stable outpatients signal structural heart disease and higher future ASCVD risk.

Application: Can help refine risk prediction in selected older adults or those with multiple comorbidities.

What to Avoid: Homocysteine

Routine testing is NOT recommended.

Rationale: While associated with CVD risk, lowering homocysteine levels with B-vitamins has **not** been shown to reduce cardiovascular events in RCTs.

Exception: Specific metabolic or genetic evaluation (e.g., homocystinuria).

Clinical Pearl

Prioritize CAC scoring over biomarkers for reclassification if available, as it provides a direct measure of disease burden.

Sources: Arnett DK et al. *Circulation*. 2019;140:e596–e646 (2019 ACC/AHA Primary Prevention); USPSTF Recommendation Statement. *JAMA*. 2022;327(16):1577-

High-Sensitivity CRP (hsCRP)

Inflammation as a Risk Enhancer

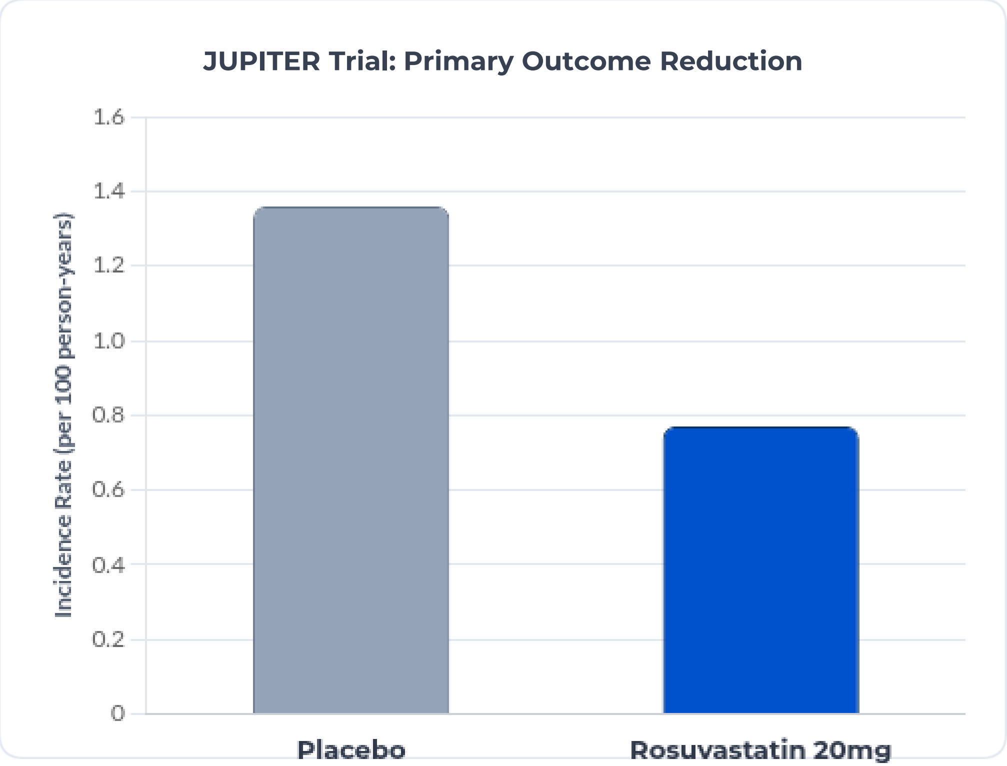
Risk Enhancer Threshold: hsCRP ≥2.0 mg/L is formally recognized as a risk-enhancing factor. It signals chronic systemic inflammation associated with plaque instability.

Decision Aid: Measurement is most useful in borderline or intermediate-risk patients (5% to <20% 10-year risk) where the decision to start a statin is uncertain.

Clinical Utility: Presence of elevated hsCRP reclassifies patients to a higher risk category, favoring the initiation of moderate- to high-intensity statin therapy.

Evidence: The JUPITER Trial

In patients with normal LDL-C (<130 mg/dL) but elevated hsCRP (≥2 mg/L), rosuvastatin 20mg significantly reduced major cardiovascular events compared to placebo.



44% Relative Risk Reduction (HR 0.56, P<0.00001)

Sources: Ridker PM, et al. NEJM. 2008;359:2195-2207; Arnett DK, et al. 2019 ACC/AHA Primary Prevention Guideline. Circulation. 2019.

Lipoprotein(a) [Lp(a)]

Genetically Determined Risk Enhancer for ASCVD

Measurement Strategy

Lp(a) levels are largely genetically determined and remain stable throughout a lifetime.

One-time measurement is reasonable in most adults to identify hidden risk.

Particularly important for those with premature ASCVD or strong family history.

Helps reclassify risk in borderline or intermediate risk patients.

Clinical Implications

Elevated Lp(a) changes management by intensifying overall risk reduction efforts.

Favor earlier initiation of statin therapy in borderline risk patients.

Intensify LDL-C lowering goals (e.g., target <70 or <55 mg/dL) to offset Lp(a) risk.

Cascade screening for family members.

Clinical Thresholds

Defined levels for risk stratification:

Risk Enhancing Level:	≥ 50 mg/dL
Molar Equivalent:	≥ 125 nmol/L

**Values above this threshold independently increase ASCVD risk.*

Emerging Therapies

While lifestyle and statins have minimal effect on Lp(a) levels directly:

PCSK9 inhibitors can lower Lp(a) by ~20-30% (secondary benefit).

Novel RNA therapeutics (e.g., pelacarsen, olpasiran) in Phase 3 trials show potent Lp(a) reduction (>80%).

Apolipoprotein B and Triglycerides

Secondary Lipid Parameters for Risk Refinement

Apolipoprotein B (ApoB)

ApoB is the primary protein on atherogenic particles (LDL, VLDL, IDL). It provides a direct measure of particle number, often more predictive than LDL-C alone.

Clinical Utility: Useful when LDL-C and particle number are discordant (e.g., hypertriglyceridemia, diabetes, metabolic syndrome).

Elevated Triglycerides

Persistent hypertriglyceridemia is an independent ASCVD risk enhancer.

Threshold: Persistently **≥ 175 mg/dL** (fasting or non-fasting).

Implication: Indicates elevated remnant cholesterol and metabolic risk.

ApoB Risk Thresholds

Used as a "Risk Enhancer" to guide decision-making in borderline/intermediate risk patients.

≥ 130 mg/dL: Standard risk enhancer for primary prevention.

≥ 120 mg/dL: Consider as elevated in high-risk patients or secondary prevention contexts.

Clinical Management

Focus on addressing underlying factors before intensifying pharmacotherapy.

Secondary Causes: Evaluate for poorly controlled diabetes, hypothyroidism, alcohol use, and medications.

Therapy: Intense lifestyle modification is first-line. Consider adjuncts (e.g., Icosapent ethyl) in select high-risk patients already on statins.

Sources: Lloyd-Jones DM et al. *J Am Coll Cardiol*. 2022;80(14):1366-1418 (ACC Nonstatin ECDP); Arnett DK et al. *Circulation*. 2019;140:e596–e646.

High-Sensitivity Troponin

hs-cTn for Risk Stratification

Prognostic Value in Stable Patients: Elevated hs-cTn levels in asymptomatic individuals are strongly associated with higher long-term risk of ASCVD events, heart failure, and mortality.

Risk Refinement: Can help reclassify risk in borderline or intermediate cases where traditional risk factors may underestimate true cardiovascular burden.

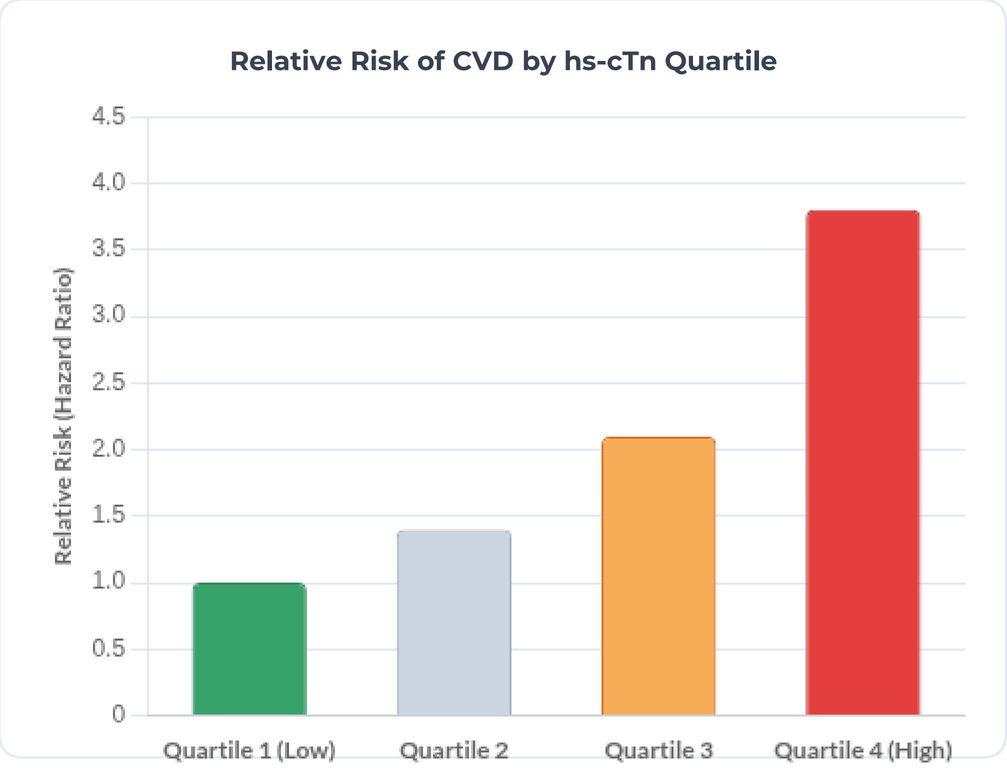
Structural Context: Reflects subclinical myocardial injury, often related to structural heart disease (LVH) or microvascular dysfunction rather than just plaque burden.

Clinical Interpretation

Consider CKD Status

Structural Heart Disease

Interpret results within the context of renal function and structural heart abnormalities. Not recommended for universal screening but valuable in select high-risk phenotypes.



Graded association between hs-cTn and outcomes

Source: Circulation. 2019;140:e993-e1011; Circulation. 2021;144:e1-e45; ACC/AHA 2019 Primary Prevention Guideline.

Homocysteine

Understanding its Limited Role in Contemporary Risk Assessment

Assessment Recommendation

Current Guideline Status

Not recommended for routine ASCVD risk assessment.

Although elevated homocysteine levels are associated with increased cardiovascular risk in observational studies, causality remains unproven.

Routine screening does not improve risk stratification beyond standard risk factors in the general population.

May be considered in specific clinical scenarios (e.g., premature atherosclerosis without other risk factors), but utility is limited.

Intervention Outcomes

Lack of Therapeutic Benefit

Lowering homocysteine with B-vitamin supplementation does not reduce cardiovascular events.

HOPE-2 Trial (2006): Supplementation with folic acid and vitamins B6/B12 lowered homocysteine levels but did not reduce the risk of major cardiovascular events in patients with vascular disease.

NORVIT Trial (2006): In patients with acute myocardial infarction, treatment with B vitamins lowered homocysteine but did not lower the risk of recurrent cardiovascular disease; some data suggested potential harm.

***Clinical Pearl:** While useful for diagnosing homocystinuria or specific nutritional deficiencies, homocysteine remains a "marker" rather than a proven "target" for ASCVD prevention.*

Sources: Lonn E et al. *N Engl J Med*. 2006;354:1567-1577 (HOPE-2); Bønaa KH et al. *N Engl J Med*. 2006;354:1578-1588 (NORVIT); ACC/AHA 2019 Primary Prevention Guideline.

CIMT vs. ABI: Selective Diagnostic Testing

Comparing utility in ASCVD risk assessment and stratification

Diagnostic Test	Recommendation	Clinical Utility & Evidence	Key Thresholds & Implications
CIMT Carotid Intima-Media Thickness	**Not Routine**	**Limited Value:** Adding CIMT to traditional risk factors provides minimal improvement in risk prediction (c-statistic change ~0.01). **Measurement Issues:** Highly operator-dependent; lack of standardization across labs. **Current Stance:** Not recommended for routine assessment of ASCVD risk in current guidelines.	**No specific threshold** recommended for risk reclassification due to variability. Does not reliably reclassify individuals into higher or lower risk categories compared to CAC.
ABI Ankle-Brachial Index	**Selective**	**Indication:** Measure when Peripheral Artery Disease (PAD) is suspected (claudication, non-healing wounds). **Risk Enhancer:** Presence of abnormal ABI is an independent predictor of future ASCVD events. **Prognostic Value:** Identifies high-risk patients who may benefit from more intensive risk factor modification.	**ABI $<$ 0.9:** Diagnostic for PAD; considered a **Risk Enhancer**. **ABI $>$ 1.4:** Indicates non-compressible vessels (calcification), also associated with increased CV risk.

CLINICAL TAKEAWAY

While CIMT was historically used, evidence now favors **Coronary Artery Calcium (CAC)** scoring over CIMT for subclinical atherosclerosis detection due to better predictive value. ABI remains crucial for symptomatic patients and as a risk enhancer.

Source: Arnett DK, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *Circulation*. 2019;140:e596–e646. Gerhard-Herman MD, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity PAD. *Circulation*. 2017;135:e726–e779.

Coronary Artery Calcium (CAC)

Evidence & Clinical Application

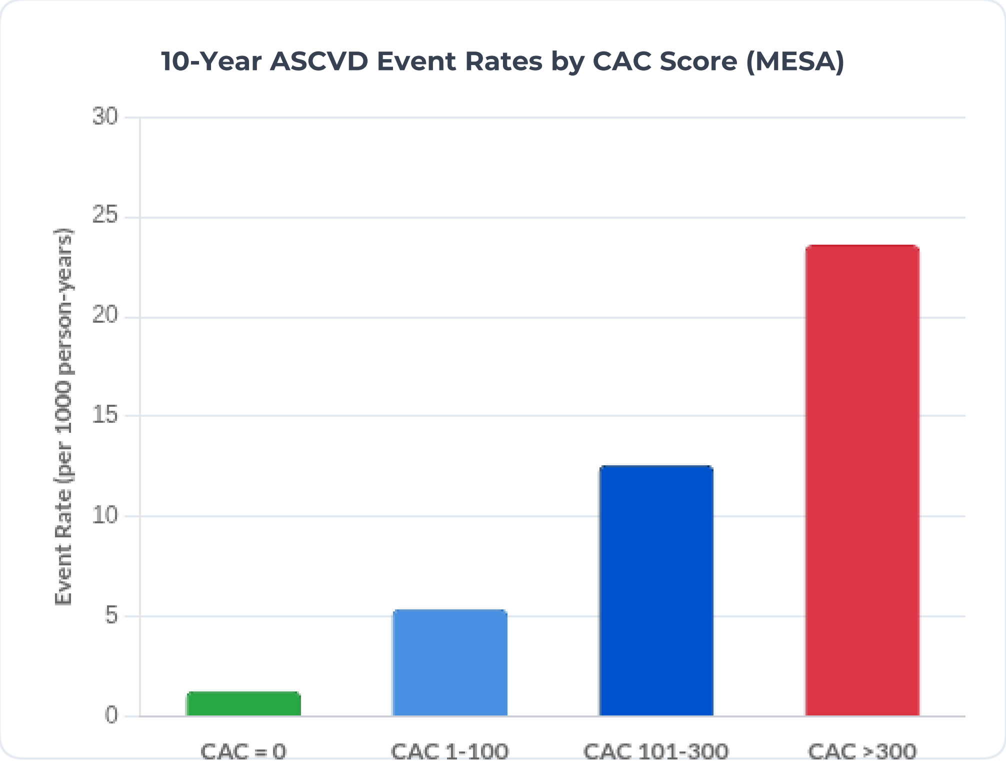
Predictive Value: CAC score is a direct measure of subclinical atherosclerosis burden and predicts ASCVD events beyond traditional risk factors, significantly improving risk reclassification.

CAC = 0 (Zero): Indicates very low 10-year risk ("Power of Zero"). Statin therapy can typically be deferred in non-diabetic patients unless other high-risk features exist (e.g., strong family history, smoking).

High Risk Thresholds: A score of **≥100** or **≥75th percentile** for age/sex/race indicates high risk, strongly favoring statin initiation.

Safety & Feasibility

Non-contrast CT scan with low radiation exposure (typically ~1 mSv, comparable to mammography). Cost-effective for intermediate risk refinement.



Data derived from Multi-Ethnic Study of Atherosclerosis (MESA)

CAC to Guide Statin Therapy

Decision Matrix for Borderline to Intermediate Risk (5% – <20%)

Clinical Context: Use this matrix when the decision to initiate statin therapy is uncertain after quantitative risk assessment (10-year risk 5-20%).

CAC Score	Risk	Recommendation
0	**Low Risk** Subclinical atherosclerosis absent or very low	**Defer Statin Therapy** Reassess in 5-10 years. **Exception:** Consider statin if Diabetes, Family History of Premature ASCVD, or Current Cigarette Smoking.
1-99	**Increased Risk** Mild to moderate subclinical atherosclerosis	**Favor Statin Therapy** Initiate moderate-intensity statin. Strongly favor if age ≥55 years.
≥100 or ≥75th%	**High Risk** Significant subclinical atherosclerosis burden	**Initiate Statin Therapy** Consistent with high-risk secondary prevention protocols.

References:

1. Grundy SM, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. Circulation. 2019.
2. Virani SS, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies. J Am Coll Cardiol. 2022.
3. MESA (Multi-Ethnic Study of Atherosclerosis) Risk Calculator Data.

CAC: Special Populations & Follow-Up

Exceptions to the Rule of Zero and Monitoring Recommendations

When CAC=0 May Not Mean "Defer"

While a CAC score of 0 generally indicates very low risk and supports deferring statin therapy, certain high-risk conditions warrant treatment regardless of calcification status.

Key Exceptions:

Diabetes Mellitus: Especially with duration >10 years, or with albuminuria/retinopathy.

Severe Hypercholesterolemia: LDL-C ≥190 mg/dL (Familial Hypercholesterolemia).

Current Cigarette Smoking: Active smokers remain at high risk for soft plaque rupture.

Strong Family History: Premature ASCVD in first-degree relative.

⚠ **Clinical Pearl:** Absence of calcified plaque does not rule out non-calcified plaque in these high-inflammatory states. Statins are often indicated based on the underlying condition.

Rescreening Strategy

For patients with an initial CAC score of 0 who are not on statin therapy, repeat testing helps track disease progression.

Standard Interval: 3–5 Years

If initial CAC = 0 and patient remains untreated, repeat scanning is reasonable to detect incident calcification.

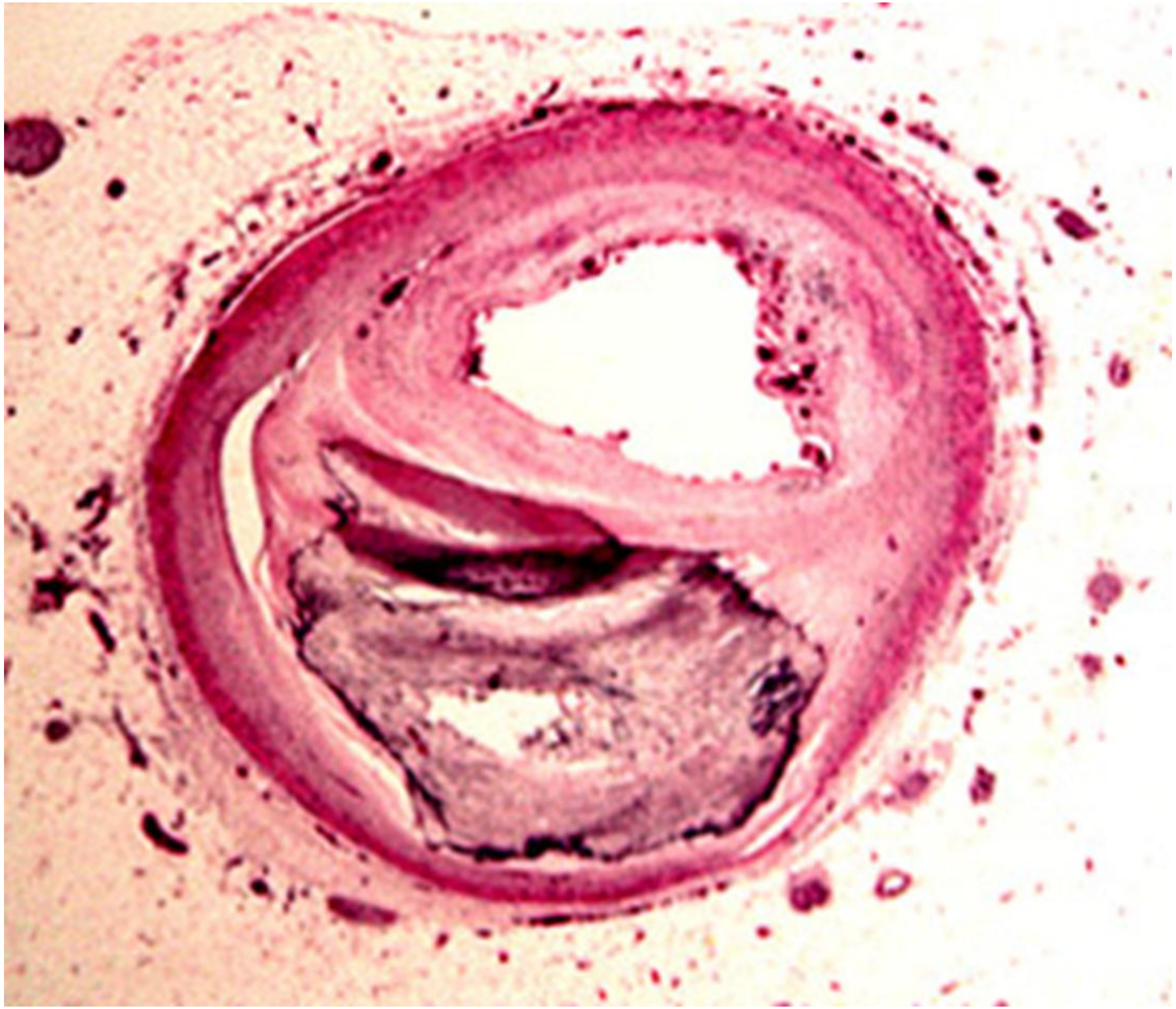
Why Repeat?

Conversion from CAC=0 to CAC>0 ("Warranty Period" expiration) reclassifies risk and often triggers statin initiation.

If Initial CAC > 0:

Repeat scanning is generally **not recommended** for monitoring therapy response. Statins may increase calcification density (a stabilizing effect), confounding score interpretation.

Sources: Arnett DK et al. *Circulation*. 2019;140:e596–e646 (2019 ACC/AHA Primary Prevention); Orringer CE et al. *J Clin Lipidol*. 2021;15(1):15-28.



Coronary CTA

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY (CCTA)

A non-invasive imaging modality that visualizes coronary artery lumen and vessel wall, enabling direct assessment of stenosis severity and atherosclerotic plaque burden.

Clinical Advantages

High Diagnostic Accuracy: Excellent negative predictive value (99%) to rule out CAD [8].

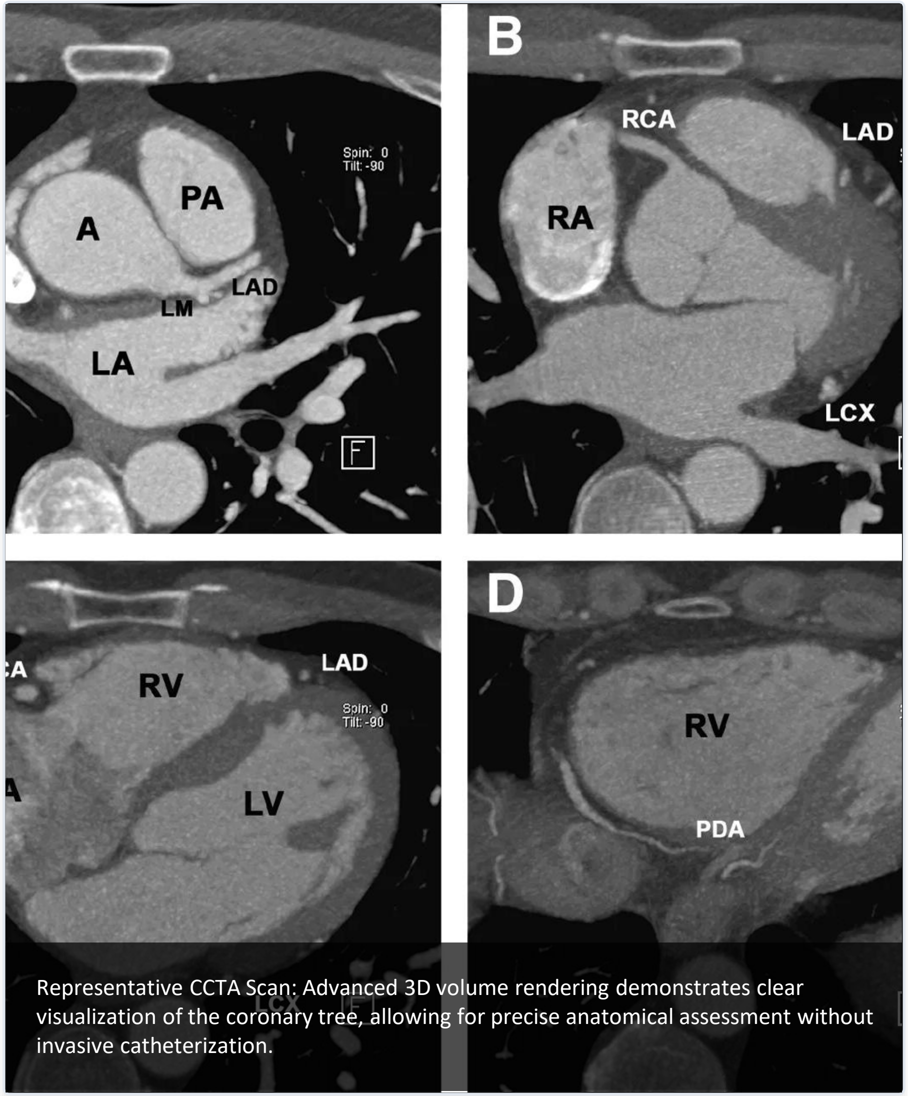
Rapid Acquisition: Full coronary tree imaging in 10–15 seconds (single breath-hold).

Sub-millimeter Resolution: 0.23–0.5 mm spatial resolution for fine detail.

Quantitative Plaque Capability: Measures calcified, non-calcified, and total plaque volumes [1][4].

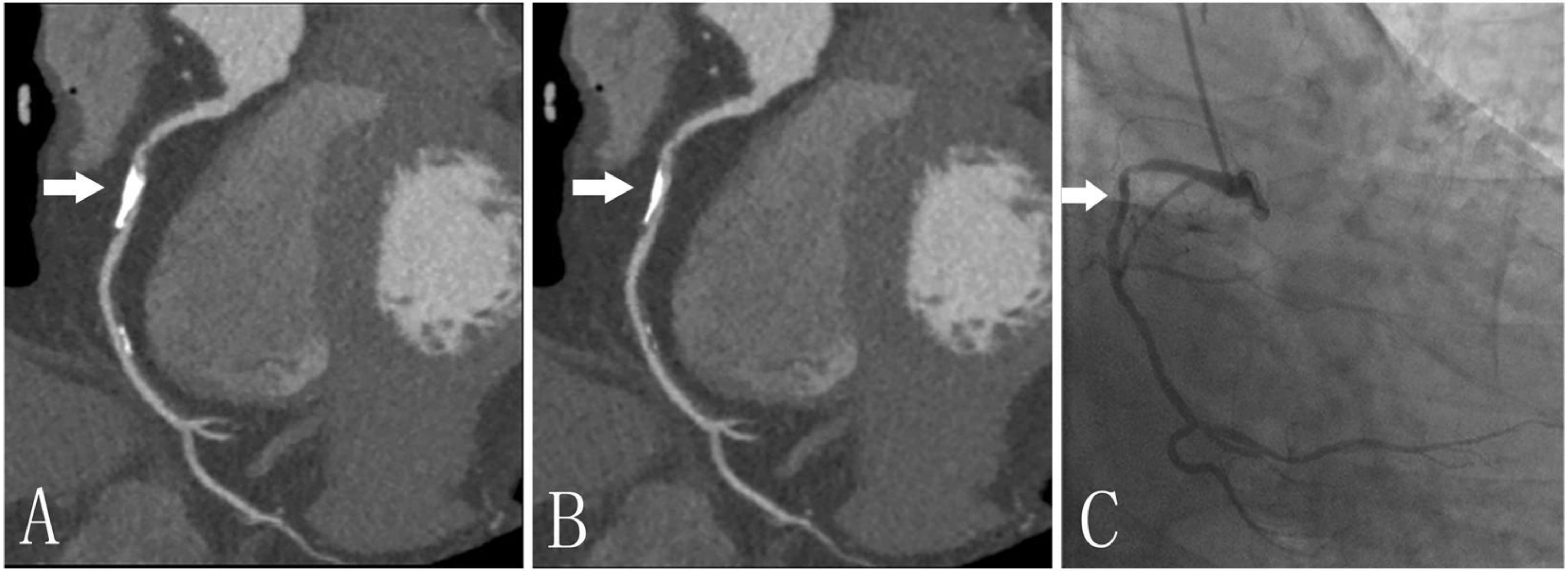
Modality Comparison

Feature	Coronary CTA	Stress Testing	Invasive Angiography
Primary Target	Anatomy & Plaque	Ischemia / Function	Lumen Silhouette
Plaque Assessment	Full Vessel Wall	None	Limited (Luminogram)
Non-Obstructive Disease	Detected	Often Missed	Often Underestimated
Risk Stratification	Plaque Phenotyping	Ischemia Driven	Stenosis Driven



Representative CCTA Scan: Advanced 3D volume rendering demonstrates clear visualization of the coronary tree, allowing for precise anatomical assessment without invasive catheterization.

References: [1] Narula J et al. Nature Rev Cardiol 2025; [4] NIH/NLM Syst Rev 2024; [8] ACC/AHA Guidelines 2024

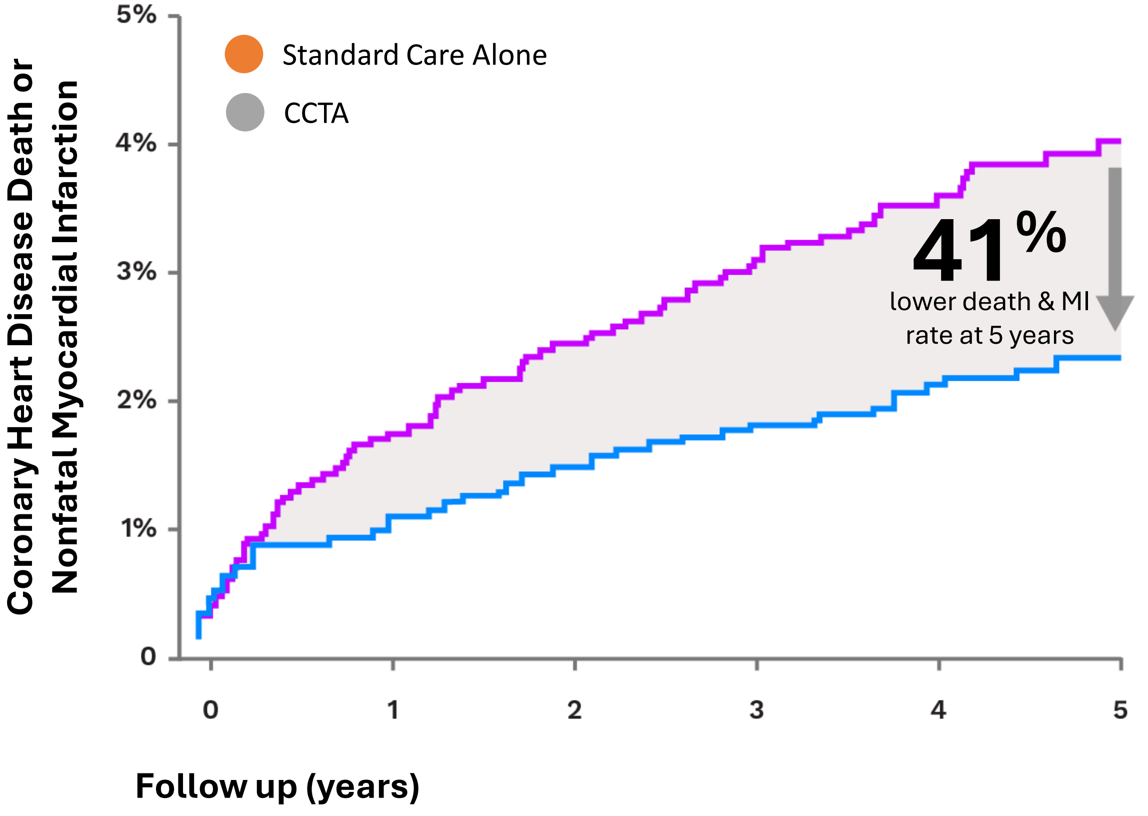


A 77-year-old man with calcified plaque (arrow) of the right coronary artery. A and B, Curved planar reformation (CPR) images without (A) and with (B) de-blooming algorithm show the volume reduction of calcified plaque and improvement of lumen evaluation by using this algorithm; (C) Invasive coronary angiography confirms mild stenosis in the right coronary artery. Without de-blooming algorithm, the right coronary artery was almost occluded; while with use of de-blooming algorithm, the right coronary artery was almost 50% stenosis, being consistent with findings from invasive coronary angiography.

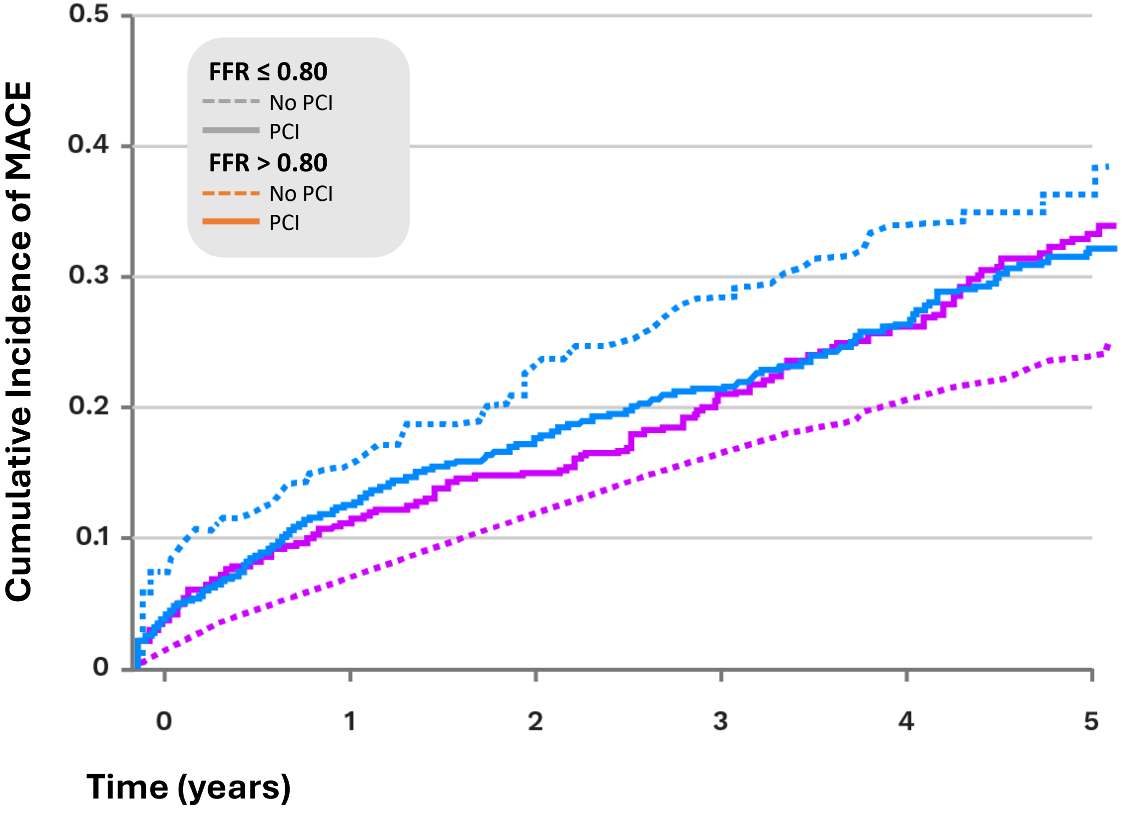
Li, P., Xu, L., Yang, L. *et al.* Blooming Artifact Reduction in Coronary Artery Calcification by A New De-blooming Algorithm: Initial Study. *Sci Rep* **8**, 6945 (2018).
https://doi.org/10.1038/s41598-018-25352-5

Coronary CTA-guided and FFR-inclusive Management Improves Outcomes

Coronary CTA + Standard Care (SCOT-HEART[1])



Using FFR in decision-making for revascularization[2]



1. SCOT-HEART Investigators, et al. *N Engl J Med.* 2018;379(10):924-933. doi:10.1056/NEJMoa1805971
2. Sud M, et al. *JAMA*. 2020;324(23):2406-2414. doi:10.1001/jama.2020.22708

2021 ACC/AHA Guidelines[1]

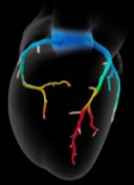
Patients with stable chest pain

Coronary CTA

To diagnose CAD and guide treatment decisions

Class 1 Recommendation

Level A Evidence



FFR_{CT}

To help guide treatment decisions

Class 2a Recommendation

Level B Evidence

2024 ESC Guidelines[2]

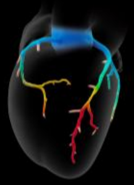
Patients with chronic coronary syndrome

Coronary CTA

To diagnose CAD in patients with suspected coronary artery disease

Class 1 Recommendation

Level A Evidence



FFR_{CT}

In high-risk cases, stenosis >70% in proximal LAD

Class 2a Recommendation

Level B Evidence

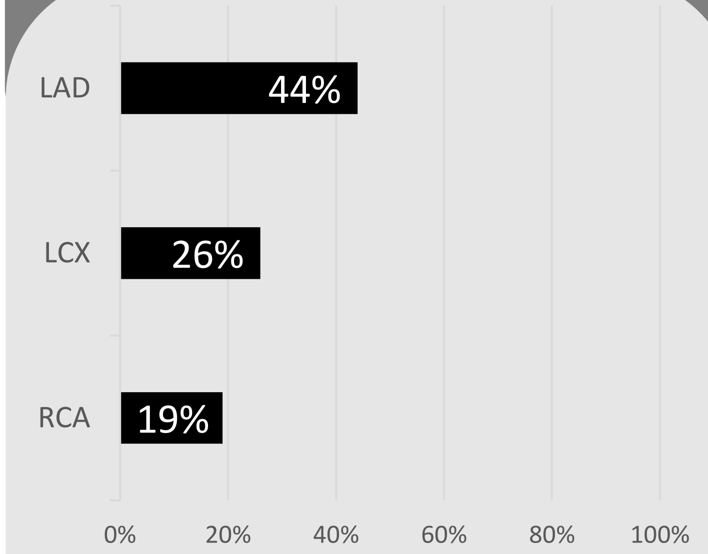
ACC/AHA Guidelines Anatomic Testing[1]

2a	For patients with known coronary **stenosis from 40% to 90% on CCTA**, FFR can be useful for diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of ICA
B-NR	

1. Gulati M, et al. *Circulation*. 2021;144(22):e368-e454. doi:10.1161/CIR.0000000000001029
2. Vrints C, et al. *Eur Heart J.* 2024;45(36):3415-3537. doi:10.1093/eurheartj/ehae177

CAD % stenosis and positive FFRCT stratified by coronary artery*

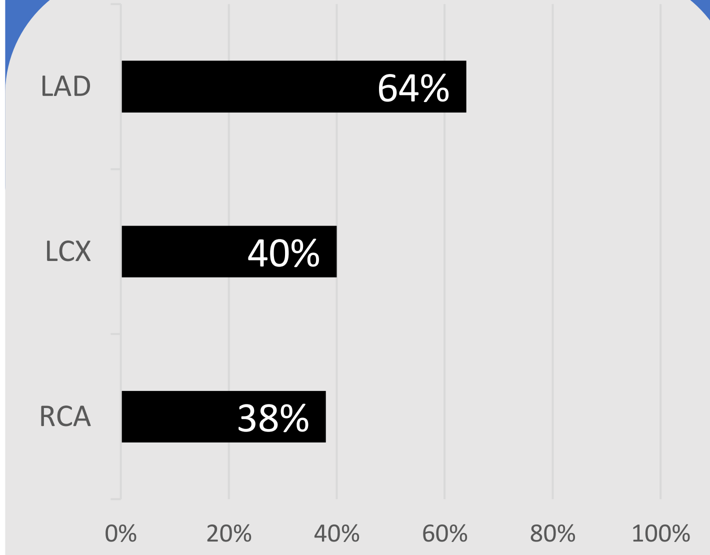
30-50% Stenosis



1 in 3

30-50% anatomic lesions will be discordant with physiology

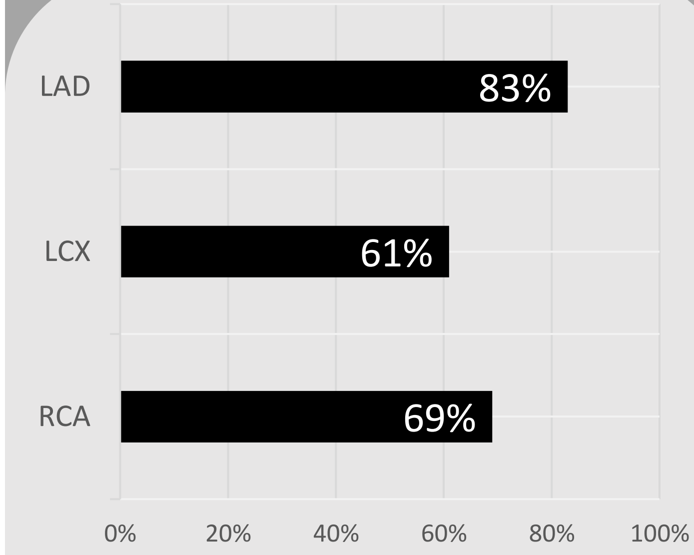
50-70% Stenosis



1 in 2

50-70% anatomic lesions will be discordant with physiology

70-90% Stenosis



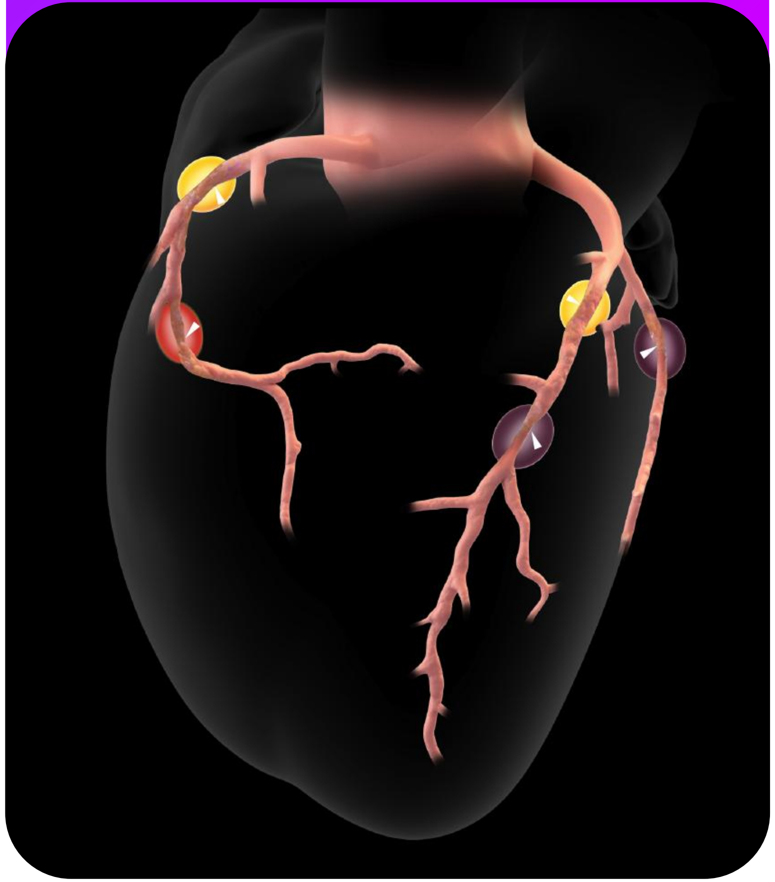
1 in 4

70-90% anatomic lesions will be discordant with physiology

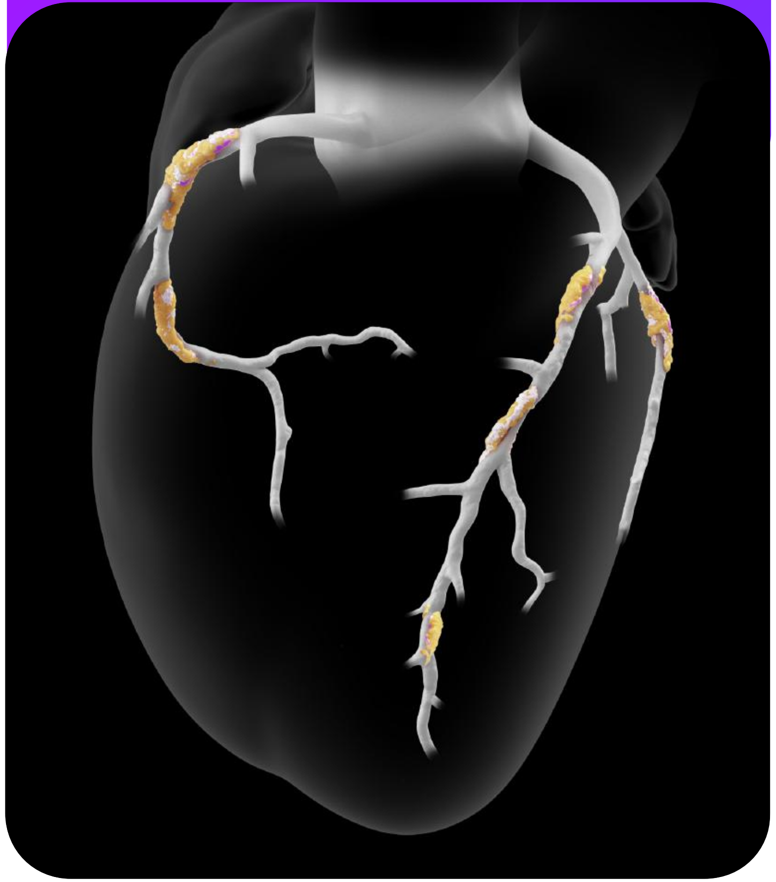
% of stenoses with FFR_{CT} ≤0.80

1. , et al. Circulation. 2021: 144(22):e368-e454. doi:10.1161/CIR0000000000001029
2. Fairbairn TA, et al. Eur Heart J. 2018:39(41):3701-3711. doi:10.1093/eurheartj/ehy530
3. *FFRCT values ≤0.80 were deemd physiologically significant in the ADVANCE Registry.

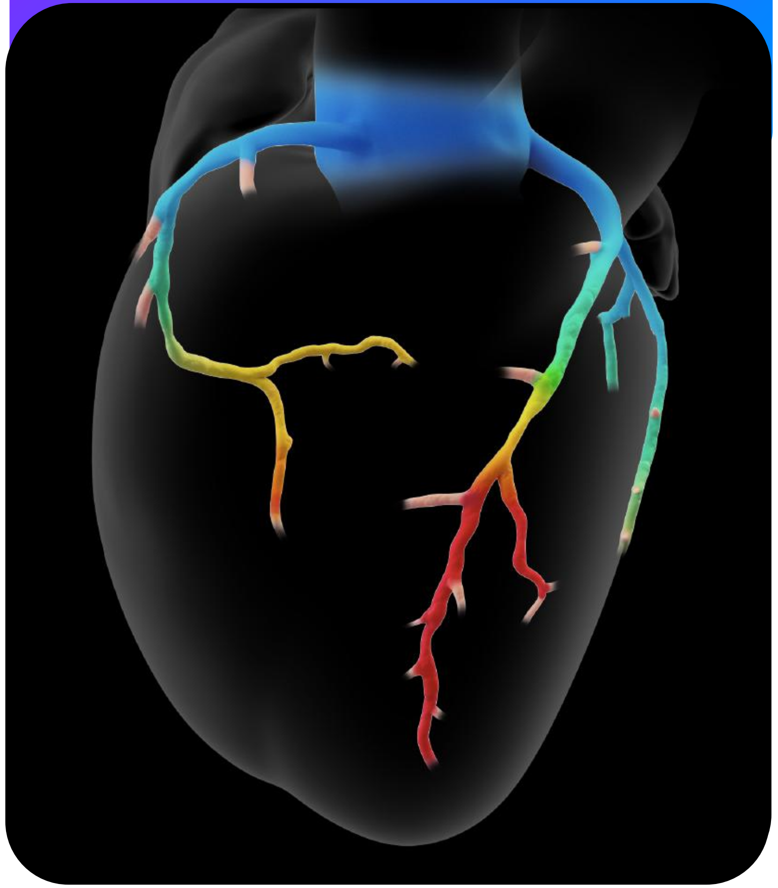
Roadmap Analysis



Plaque Analysis



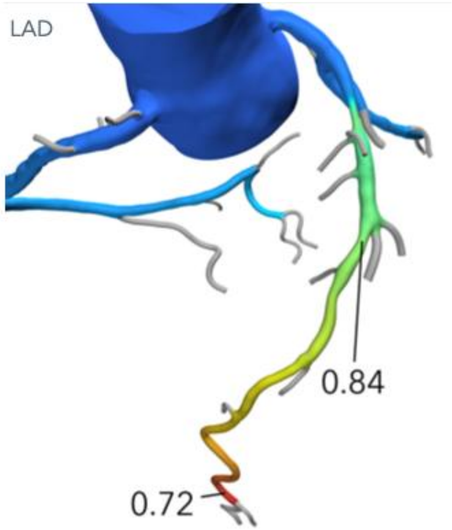
FFR_{CT} Analysis



H&P: F/64

- Chest pain, nonspecific.
- CP with exertion.

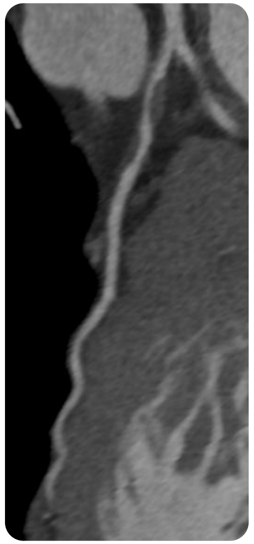
CCTA + FFRCT Findings: Calcified and noncalcified plaque in proximal LAD artery with estimated stenosis >70% by CCTA (CAD-RADS 4)

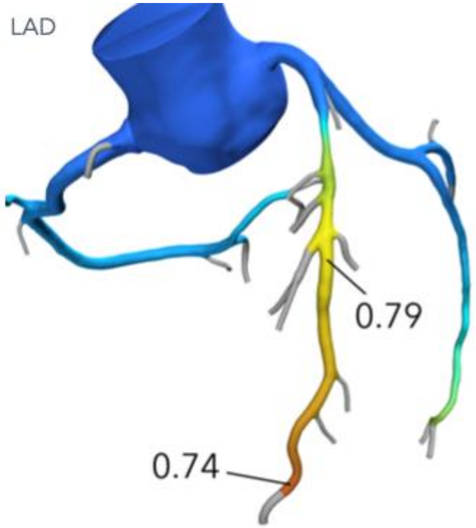


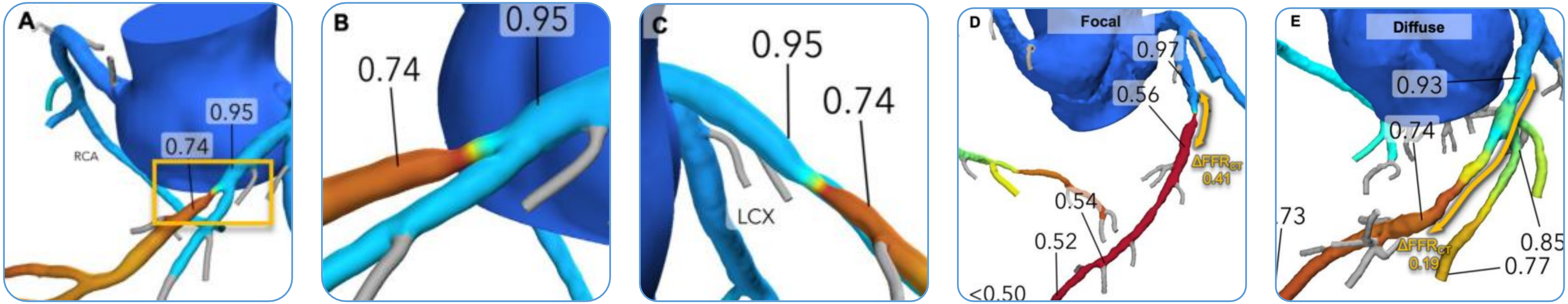
H&P: F/53

- Chest pain/anginal equivalent, high CAD risk.
- CP w/ exertion and family history CAD.

CCTA Findings: A prominent eccentric, soft, noncalcified plaque in the very proximal LAD producing severe luminal diameter narrowing of >70% (CAD RADS: 4, 70-99% severe stenosis)







Steps Determining ΔFFR_{CT} **Stenosis Type**

- Calculate: FFR_{CT} 1-2 cm proximal to the lesion – FFR_{CT} value 1-2 cm distal to the lesion
- Delta >0.12 is considered significant in the grey zone of physiology 0.76-0.80

Takagi, Hidenobu et al. *J Cardiovasc Comput Tomogr*. 2021; 16(1): 19-26. doi: 10.1016/j.jcct.2021.08.003

Photon-Counting CT: Revolutionizing Coronary CTA

Ultra-High Resolution

0.2mm isotropic spatial resolution for precise visualization

Spectral Imaging

Intrinsic multi-energy capabilities in every scan

Dose Efficiency

Up to 40% radiation dose reduction vs. conventional CT

The Clinical Challenge: Conventional CT Limitations

Calcium Blooming Artifacts

High-density calcium creates distinct halo effects, causing overestimation of stenosis severity and false positives.

Limited Spatial Resolution

Standard 0.5-0.6mm resolution struggles with distal vessels and complex lesions, leading to partial volume effects.

Stent Assessment Challenges

Metallic struts cause beam hardening and blooming, obscuring in-stent lumen visibility for restenosis evaluation.

Unnecessary Invasive Procedures

Diagnostic uncertainty often triggers downstream invasive coronary angiography (ICA) with no actionable disease found.

References:
1. DISCHARGE Trial Group. CT or Invasive Coronary Angiography in Stable Chest Pain. NEJM 2022.
2. Shaw et al. CAD-RADS 2.0 - 2022 Coronary Artery Disease-Reporting and Data System. JCCT 2022.
3. McCollough et al. Clinical Applications of Photon Counting Detector CT. Eur Radiol 2023.

Diagnostic Uncertainty Gap

Conventional EID-CT vs. Truth

ICA Referral Rate: ~13.1%

Clinical Impact

Diagnostic Confidence

False Positive Rate

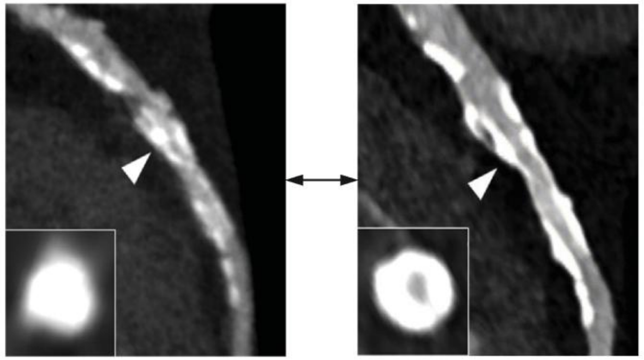
Resolution Limit: 0.5mm

Noise Floor: Electronic Noise Present

CENTRAL ILLUSTRATION: Clinical Impact and Diagnostic Performance of Photon-Counting Detector-Computed Tomography Imaging in the Evaluation of Coronary Artery Disease

Single-Center Experience With Photon-Counting Detector CT in Evaluation of CAD

Energy-Integrating Detector CT (EID-CT) (N = 3,957)	Photon-Counting Detector CT (PCD-CT) (N = 3,876)
• Scintillator/photodiode • Indirect conversion of photon energies • Reflective Septa	• Semiconductor • Direct conversion of photon energies • Elimination of septa



Improved Spatial Resolution, Less Noise, Less Blooming Artifact

Clinical Impact of PCD-CT	Excellent Diagnostic Performance of PCD-CT
▼ ICA referral (9.9% vs 13.1%) ▼ Unnecessary ICA (5.6% vs 8.4%) ▲ Revascularization if referred (43.4% vs 35.5%)	↑ Accuracy: 97.2% ↑ PPV: 83.3% ↑ Specificity: 98.0%

Sakai K, et al. JACC. 2025;85(4):339-348.

Technology Overview:
How Photon-Counting Detectors Work

Direct Conversion

Semiconductors (CdTe/CZT/Si) directly convert X-ray photons into electrical signals, bypassing the scintillator light-step of conventional CT.

Noise Elimination

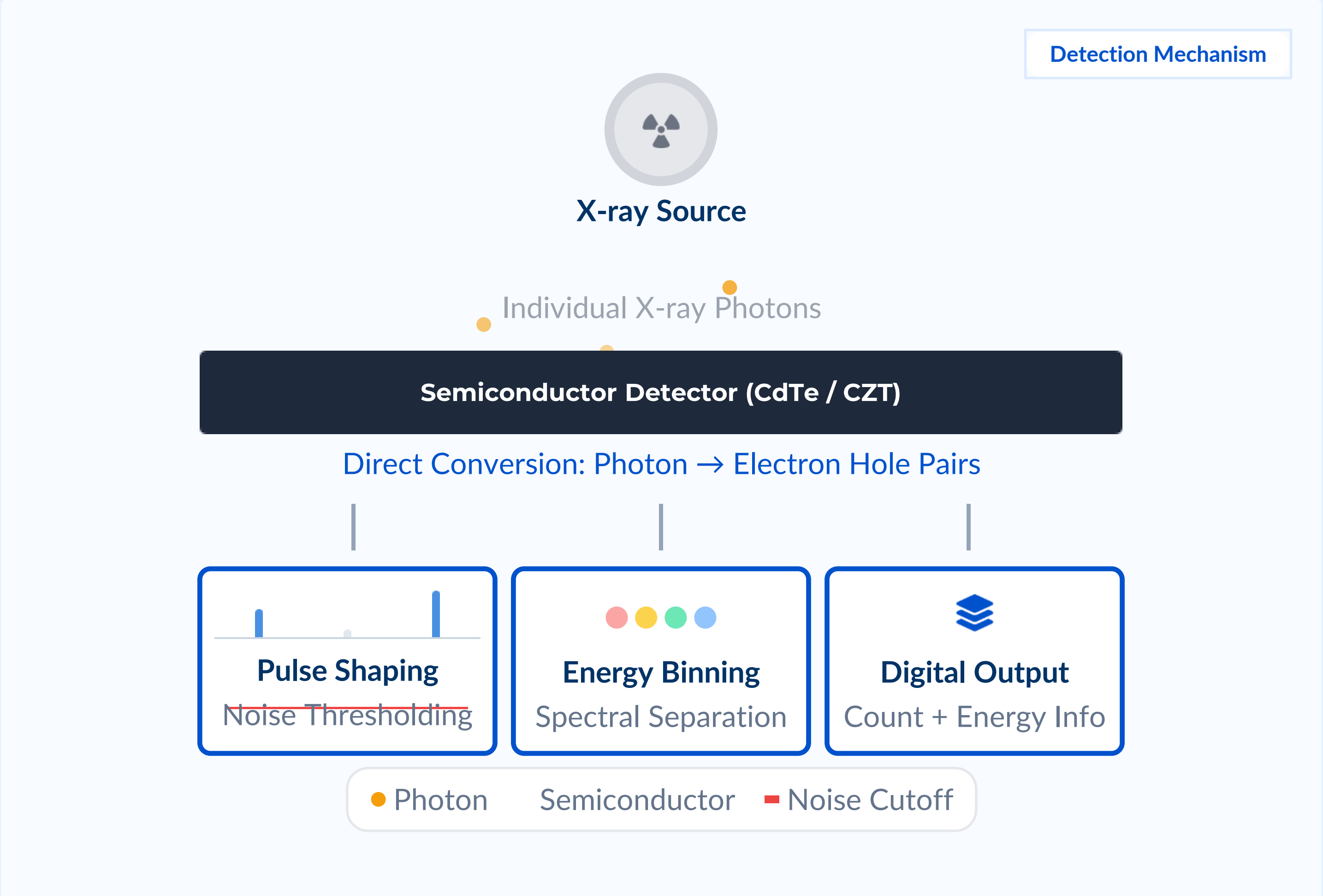
Electronic noise is filtered out by setting a lower energy threshold, counting only true photon events for superior signal-to-noise ratio.

Ultra-High Resolution

Smaller detector pixels enable 0.2mm resolution without the need for inter-pixel septa, reducing dead space and improving dose efficiency.

Spectral Capabilities

Energy binning allows simultaneous multi-energy acquisition in every scan for material decomposition and Virtual Monoenergetic Images (VMI).



References: 1. Flohr T, et al. Photon-counting CT review. Phys Med 2020. 2. McCollough CH, et al. Clinical Applications of Photon Counting Detector CT. Eur Radiol 2023. 3. Technical Development of Photon Counting Detector CT. PMC 2023.

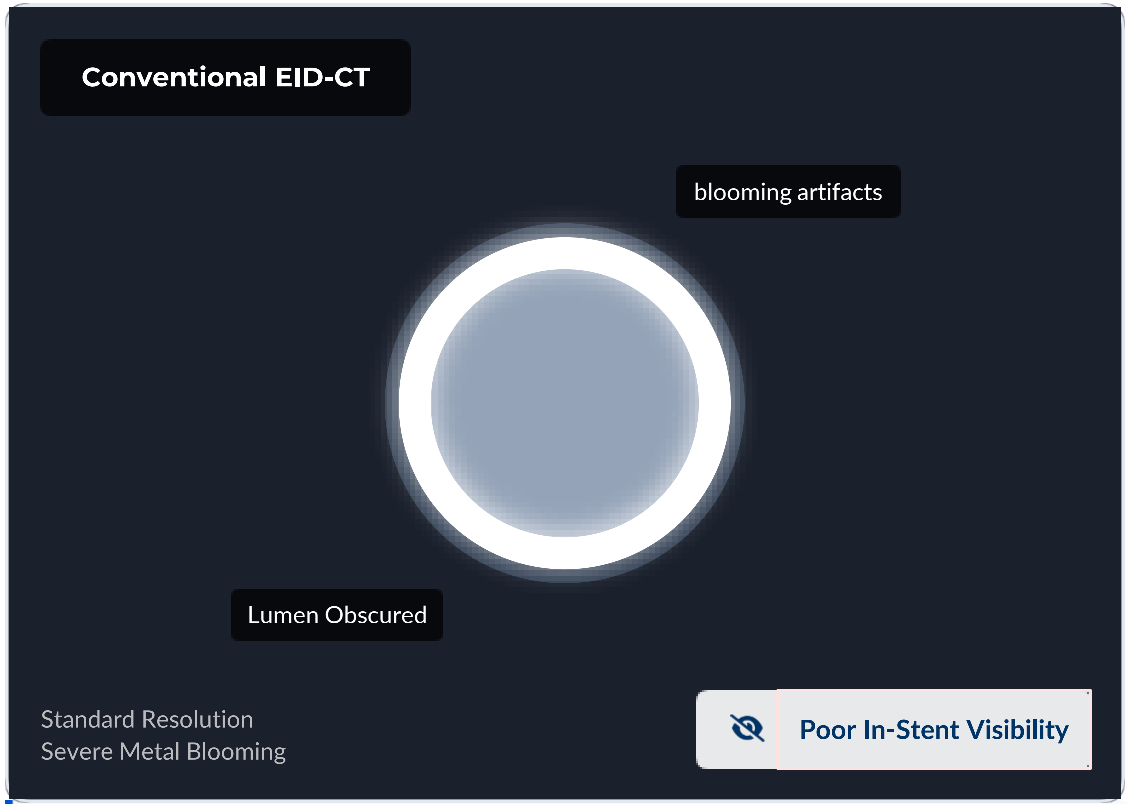
PCD-CT vs EID-CT: Head-to-Head Comparison

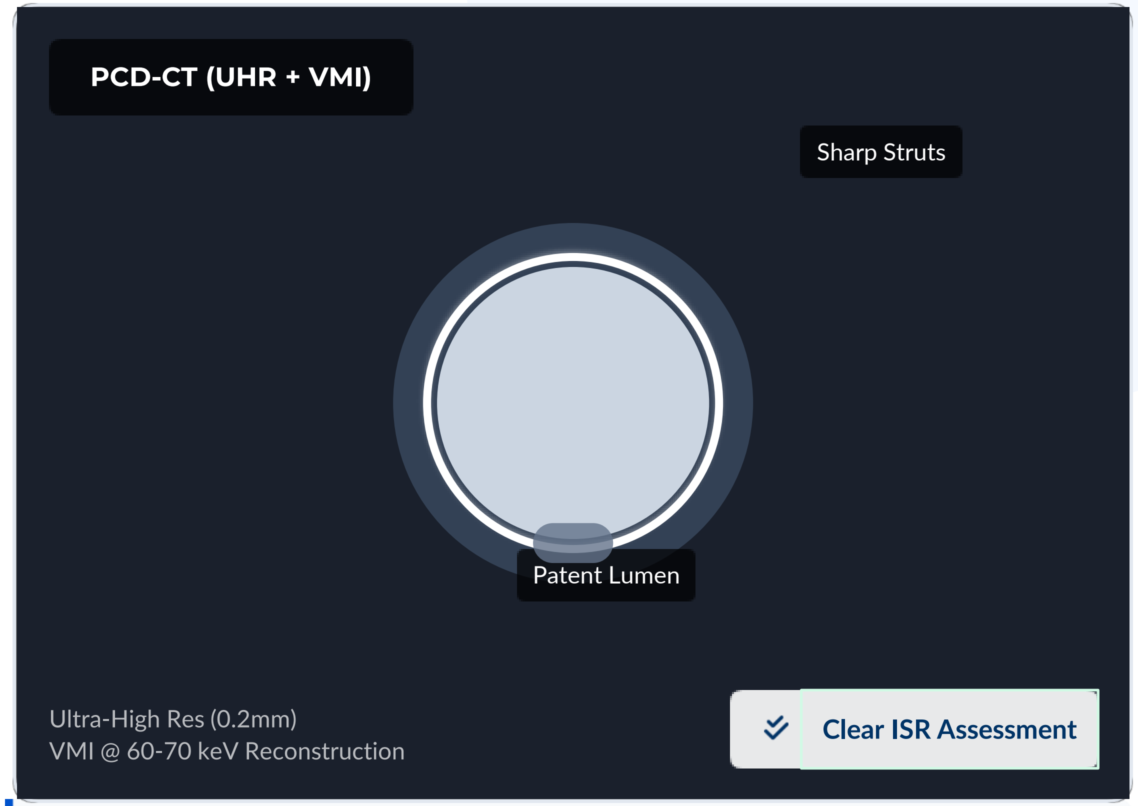
parameter	Conventional EID-CT	Photon-Counting CT
Detector Technology	Indirect Conversion (Scintillator + Photodiode) Light step causes blurring	Direct Conversion (Semiconductor) CdTe / CZT / Si - No light scatter
Spatial Resolution	~0.5 - 0.6 mm Limited by septa & light spread	0.2 mm Isotropic Ultra-High Res Defined by pixel size only
Electronic Noise	Integrated into Signal Degrades low-dose image quality	Eliminated (Thresholded) Zero Noise Counts only photons above noise floor
Spectral Capability	Limited Dual-Energy Modes Often requires specific protocols	Intrinsic Multi-Energy Always on, every scan, perfectly registered
Dose Efficiency	Standard Reference	Up to 40% Reduction -40% Dose Higher geometric efficiency
Blooming Artifacts	Moderate to Severe Calcium overestimates stenosis	Significantly Reduced Better lumen visualization in calcified vessels

EID-CT: Energy-Integrating Detector CT

PCD-CT: Photon-Counting Detector CT

Coronary Stent Visualization
Conventional vs PCD-CT

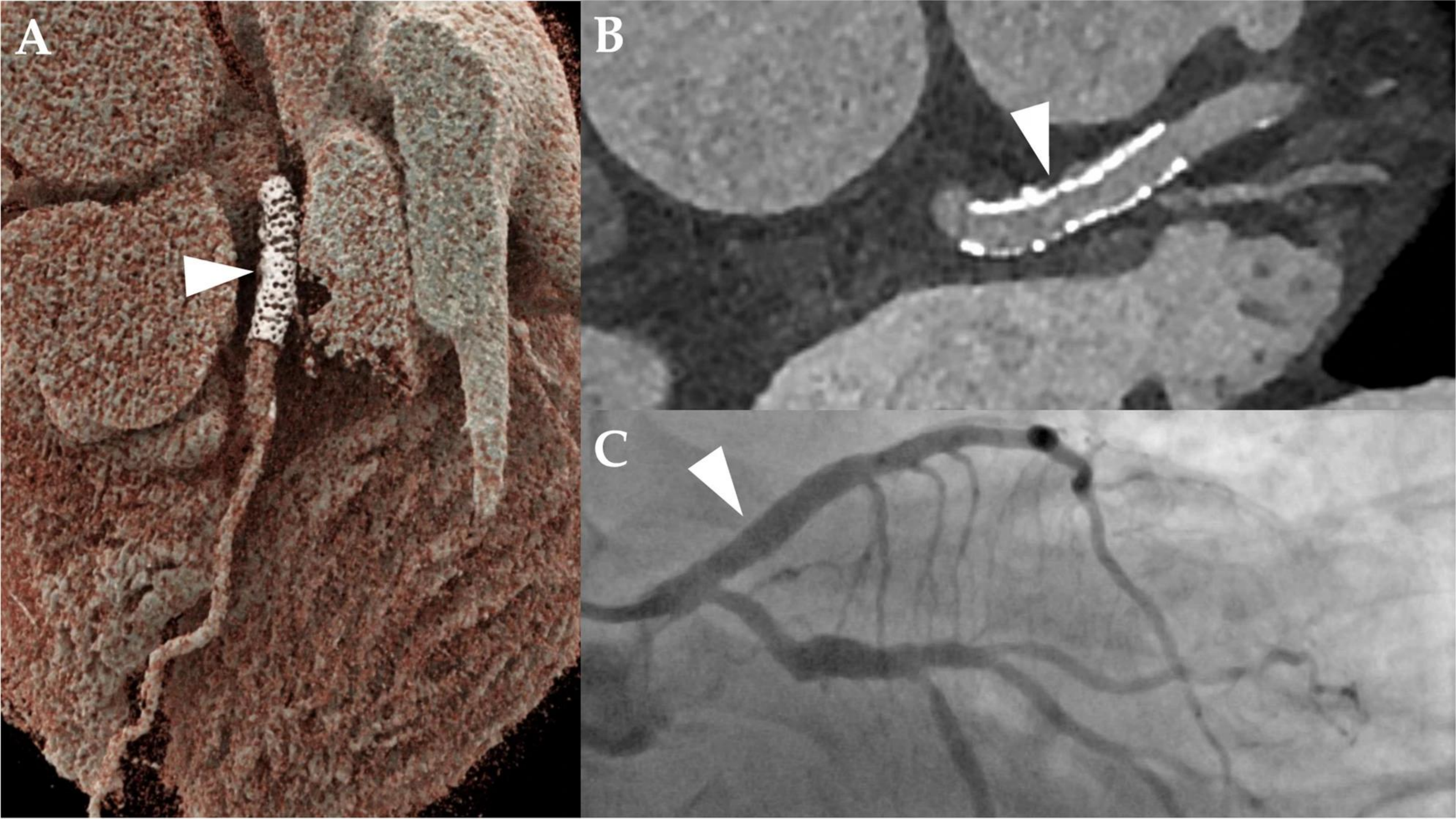


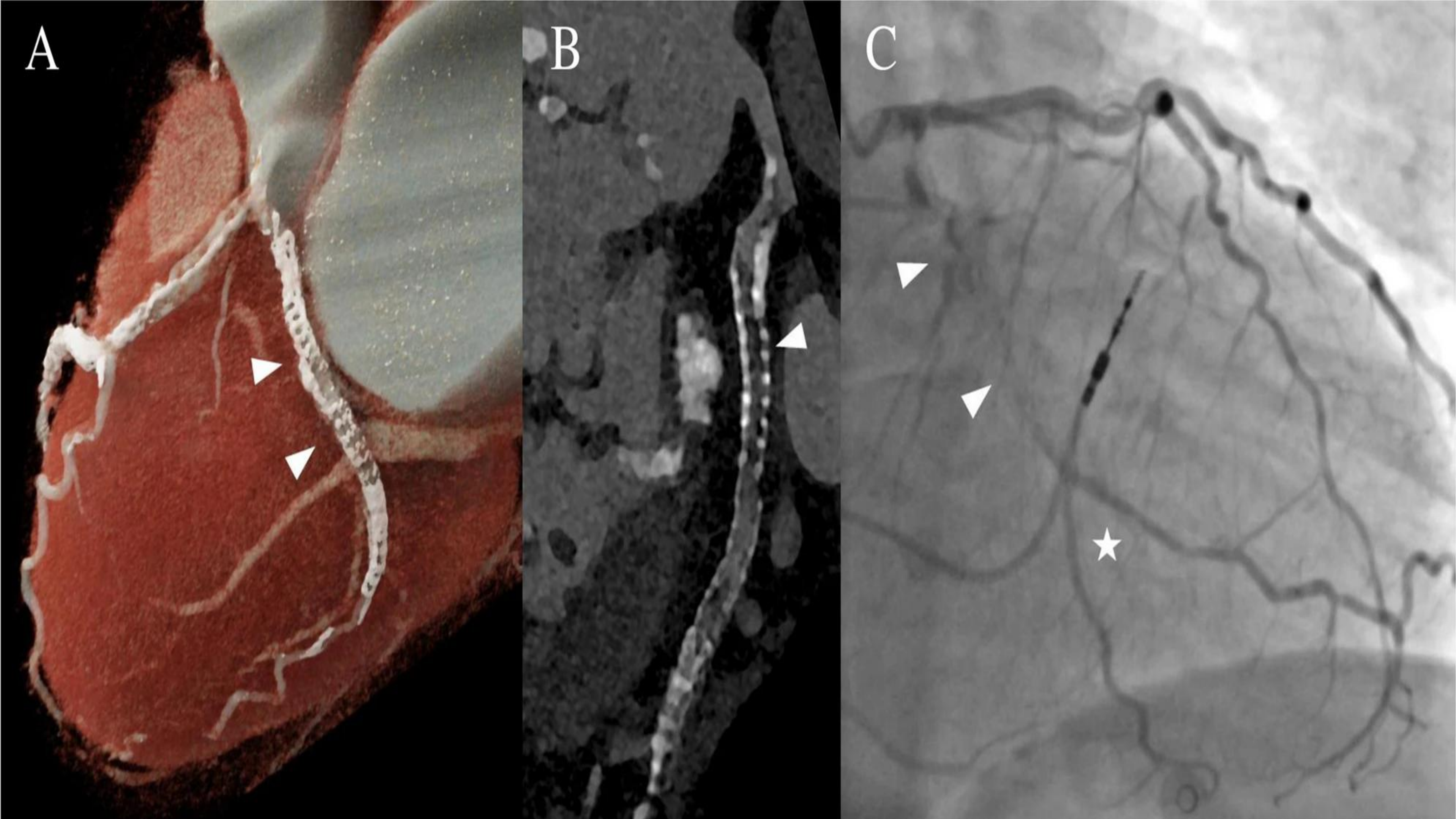


Optimal VMI Settings, Ultra-High Resolution Benefit

Reconstruction at 60-70 keV provides optimal balance between contrast enhancement and suppression of metal blooming glare.

0.2mm isotropic resolution enables precise visualization of individual stent struts and in-stent lumen, critical for ruling out restenosis.


A
B
C


A
B
C

JACC 2025 Clinical Impact Study
Real-World Outcomes (n=7,833)

ICA Referral Rate
9.9% vs 13.1%

Reduced Unnecessary Caths — -24% Relative

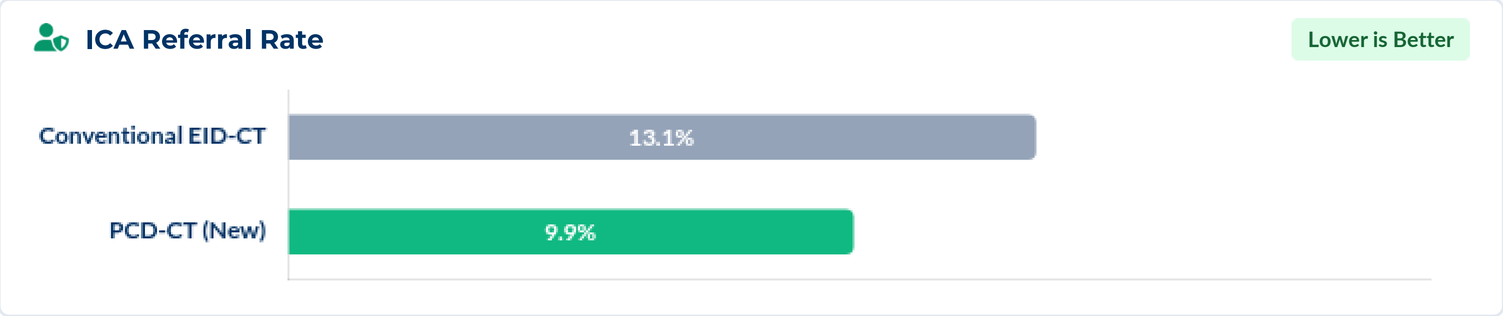
Revascularization Yield
43.4% vs 35.5%

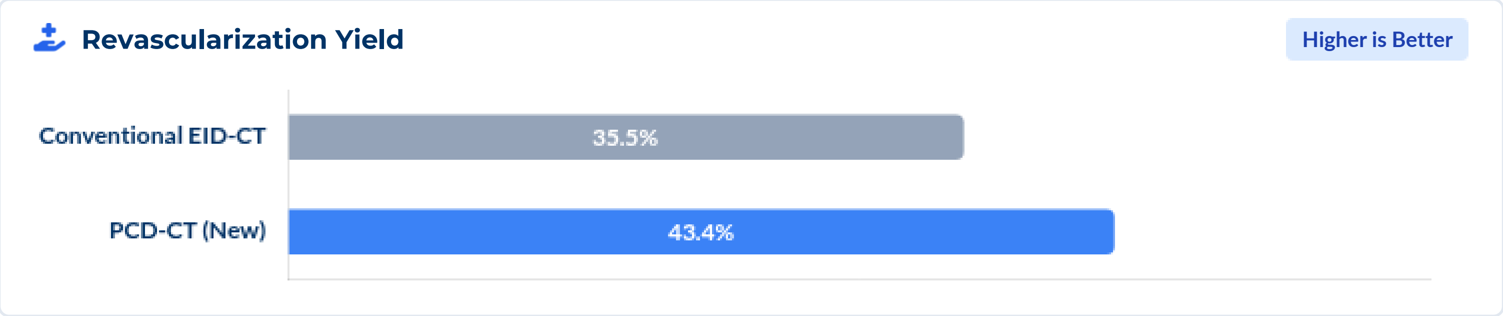
Higher Procedural Value — +22% Yield

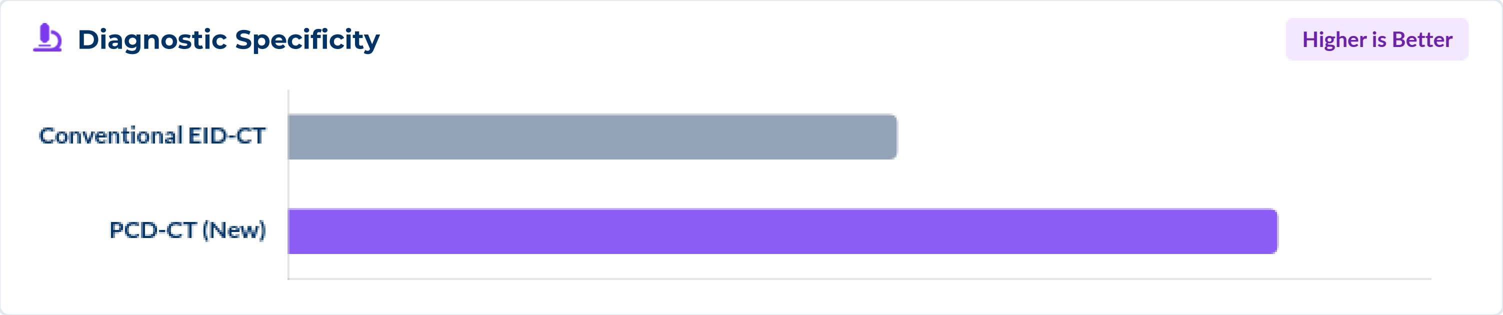
Diagnostic Specificity
98.0% vs 93.0%

Superior Accuracy — +5% Abs.

Study Cohort Details
Large-scale comparative analysis of 7,833 symptomatic patients. Assessed downstream clinical management and procedural outcomes between conventional EID-CT and photon-counting PCD-CT.







References: Sakai et al., Diagnostic Performance and Clinical Impact of Photon-Counting Detector CT in Coronary Artery Disease, J Am Coll Cardiol. 2025.

Head-to-Head Comparison: PCD-CT vs EID-CT
Diagnostic Performance Metrics

Positive Predictive Value

63.0%
EID-CT

83.3%
PCD-CT

20.3% Absolute Increase

Major reduction in false positives due to calcium de-blooming

Overall Diagnostic Accuracy

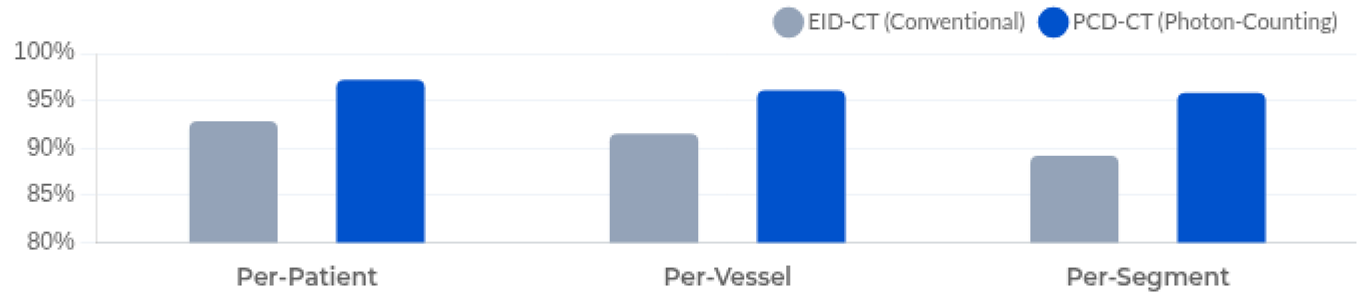
92.8%
EID-CT

97.2%
PCD-CT

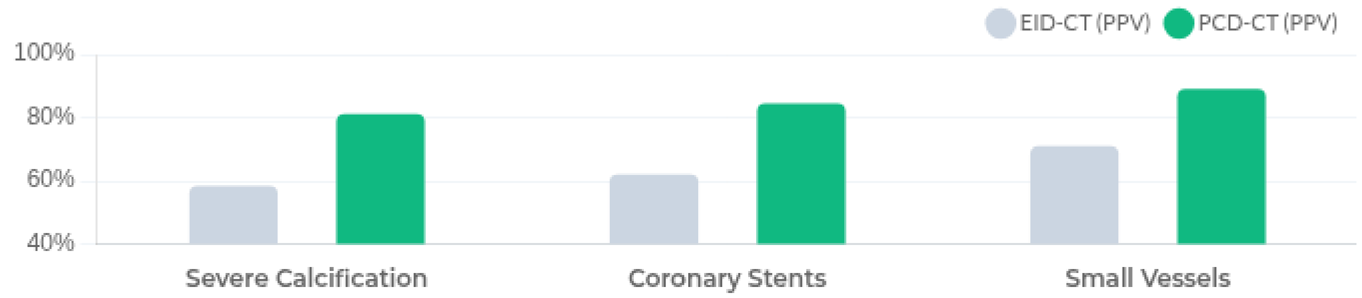
Statistically Significant ($p<0.05$)

Consistent improvement across patient & vessel levels

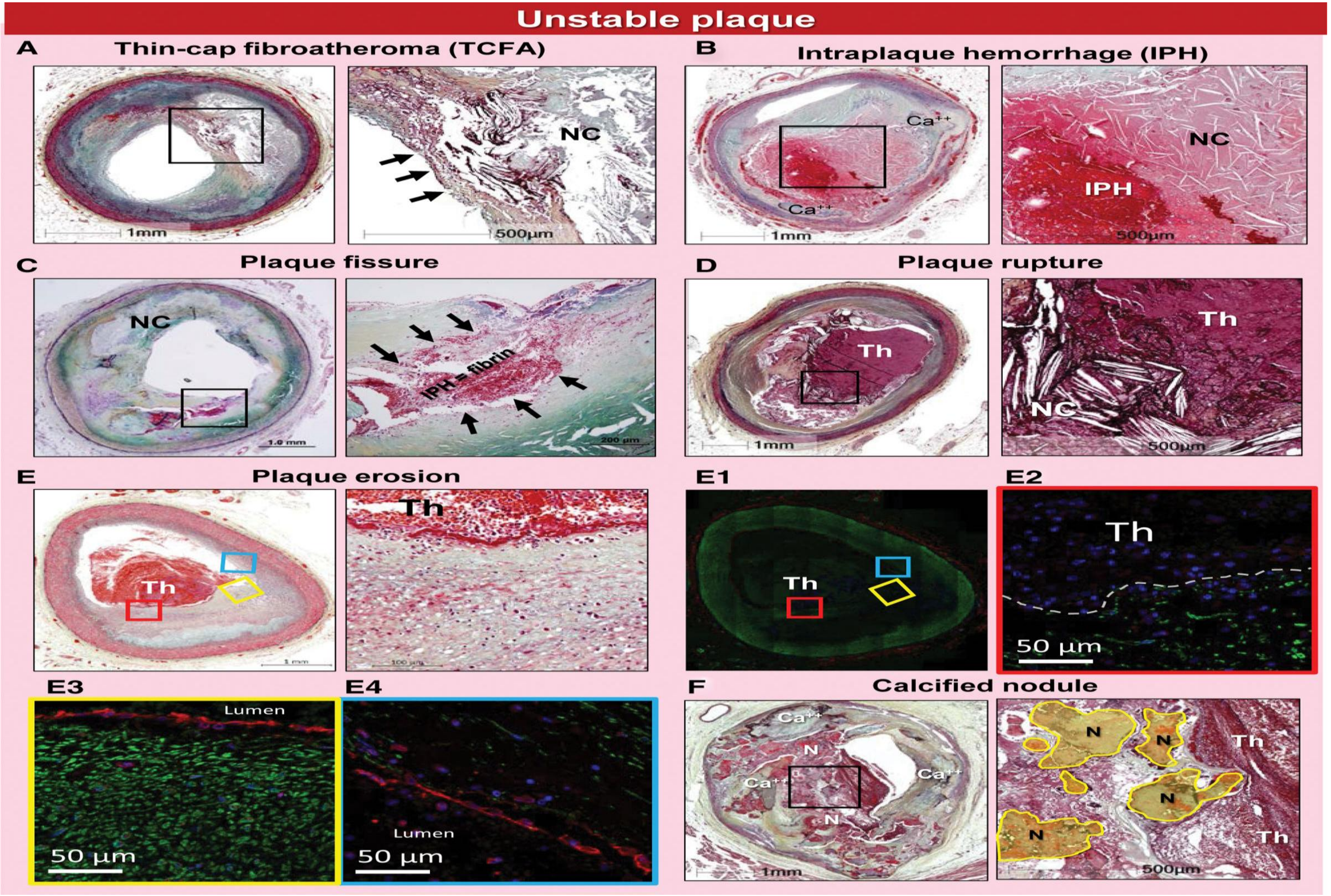
Diagnostic Accuracy by Analysis Level



Performance in Challenging Scenarios (Calcified/Stents)



References: 1. Vecsey-Nagy et al., Comparative Analysis of PCD vs EID CT, 2024/2025. 2. JCCT Comparative Studies Pooled Analysis 2024-2026.



Kawai K, Kawakami R, Finn AV, Virmani R. Differences in stable and unstable atherosclerotic plaque. *Arterioscler Thromb Vasc Biol*. 2024 Jun 26.

High-Risk Plaque Features on CCTA

Part I: Napkin-Ring Sign & Low-Attenuation Plaque

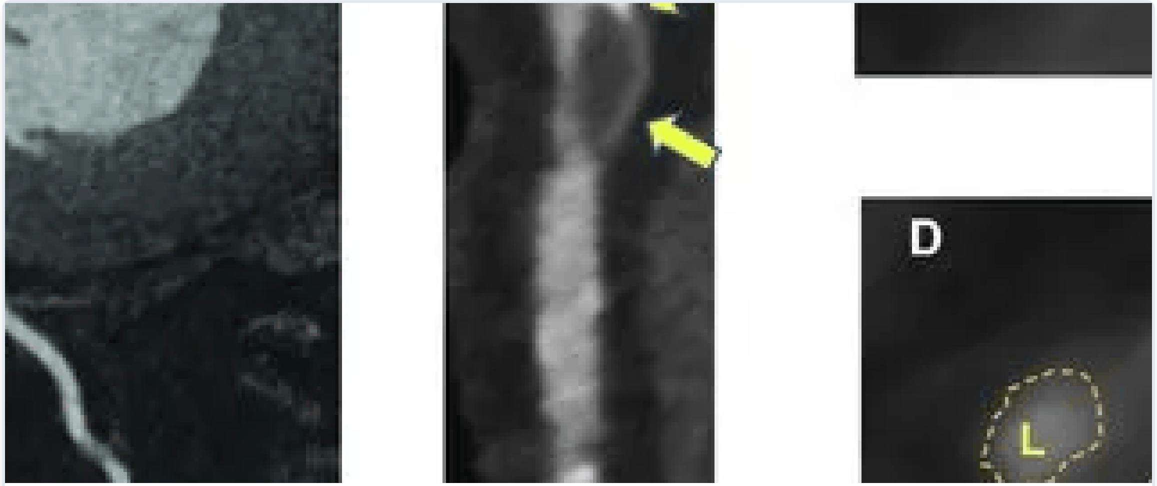
DEFINITION: High-Risk Plaque (HRP)

Plaque morphologies that predict acute coronary syndrome (ACS) independent of stenosis severity. Identifying Identifying these features shifts treatment from ischemia-guided to prevention-guided strategies.

ROMICAT-II EVIDENCE

Increased ACS Risk with HRP

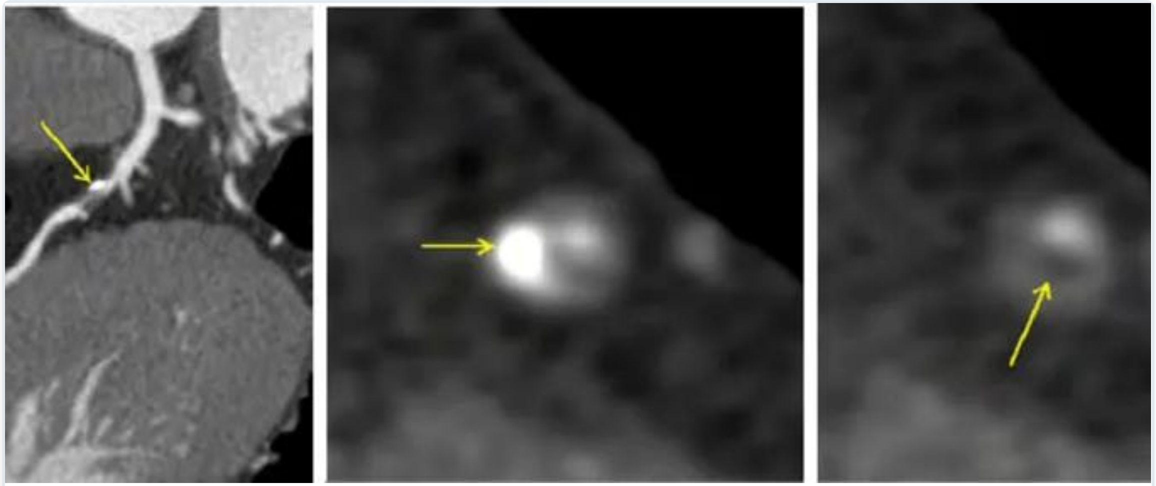
8.2x



1 Napkin-Ring Sign

Characterized by a ringlike peripheral enhancement with a central area of low attenuation. This specific pattern on CCTA corresponds directly to the thin-cap fibroatheroma seen on OCT.

Marker: Thin-cap fibroatheroma (TCFA)



2 Low-Attenuation Plaque

Defined as non-calcified plaque with mean CT attenuation values <30 HU (Hounsfield Units). This low density signifies a large lipid-rich necrotic core vulnerable to rupture.

Marker: Lipid-rich necrotic core

References: [3] Ihdayhid AR et al. Nature Cardiol Rev 2024; [6] ROMICAT-II Trial JACC 2014

High-Risk Plaque Features on CCTA

Part II: Positive Remodeling & Spotty Microcalcifications

INCREMENTAL PROGNOSTIC VALUE

Combining HRP features (e.g., remodeling + spotty calcium) significantly improves risk stratification beyond stenosis severity. HRP presence is an independent predictor of future adverse events.

CLINICAL IMPACT

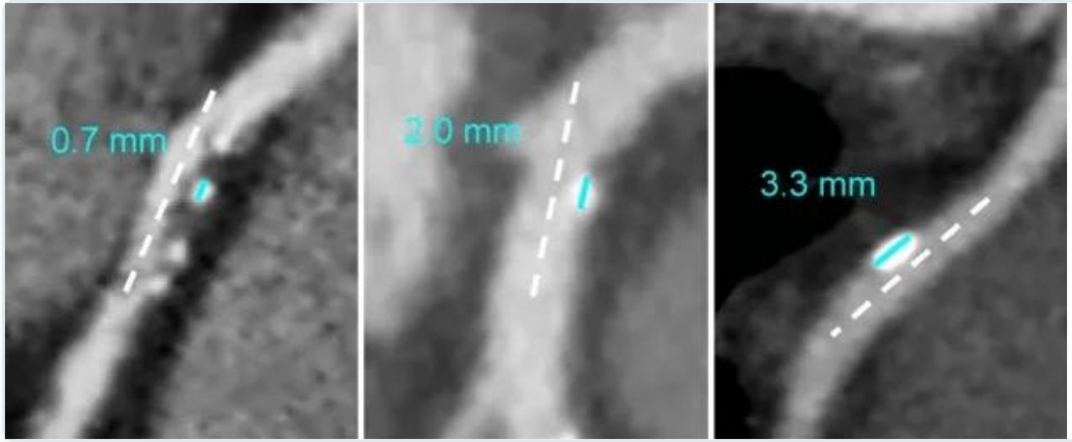
Therapy Strategy

Escalation

3 Positive Remodeling

Defined by a remodeling index >1.1, where the vessel wall expands outward to accommodate plaque growth without compromising the lumen initially. This "outward bulging" is a hallmark of unstable plaque.

Marker: Expansive remodeling (Index >1.1)



4 Spotty Microcalcifications

Small, scattered calcifications (<3mm) within the plaque burden. Unlike large stable calcifications, these "spotty" deposits are associated with active inflammation and increased plaque vulnerability.

Marker: Active inflammation & vulnerability

References: [3] Ihdayhid AR et al. Nature Cardiol Rev 2024; ROMICAT-II Trial

AI and Deep Learning in CCTA Analysis

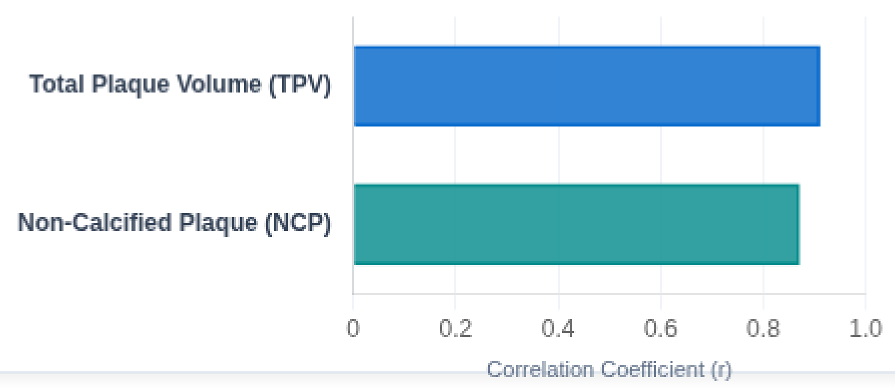
Automated Quantification and Predictive Modeling

Roles of Artificial Intelligence

- Automated, objective quantification of TPV, CP, and NCP volumes
- Consistent interpretation across readers; reduces inter-observer variability
- Enhanced workflow efficiency (minutes vs. hours for manual analysis)
- Predictive modeling for future cardiac events beyond stenosis

Deep Learning Capabilities

- Automated vessel segmentation and high-risk high-risk plaque detection
- Phenotyping of plaque composition and detailed morphology
- Integration with clinical data for personalized risk prediction



CONFIRM2 Study (2024) [5]

AI-based quantitative CCTA demonstrated superior accuracy in predicting serious cardiac events compared to visual assessment alone.

TRANSFORM Trial (Ongoing)

Evaluating the clinical impact of AI-guided intensive medical therapy for patients identified with high-risk plaque.

References: [1] Narula J et al. Nature Rev Cardiol 2025; [4] NIH/NLM Syst Rev 2024; [5] Cleerly/CONFIRM2 TCT 2024

AI Plaque Assessment Workflow

End-to-End Pathway from Acquisition to Treatment

Rapid Turnaround
Scan-to-report in <5 minutes

CMS Coverage
Reimbursable under LCD-39851

Seamless Integration
EMR & Clinical Decision Support

1 Data Acquisition

Patient undergoes standard Coronary CTA scan. DICOM images are pushed to AI server. server.

2 Automated Processing

AI algorithm automatically segments coronary vessels and and identifies lumen/wall boundaries.

3 Quantitative Analysis

Measurement of TPV, NCP, CP volumes. Phenotyping of composition and distribution.

4 Risk Stratification

Algorithm integrates imaging biomarkers (HRP) with clinical risk risk factors.

5 Personalized Care

Report generates tailored recommendations for therapy intensification and follow-up.

Aligned with 2024 ACC/AHA Guidelines for Quantitative Coronary Plaque Analysis

References: [7] CMS Coverage Determination LCD-39851; [8] ACC/AHA Guidelines 2024

Clinical Trials and Evidence Base

Evolution of CCTA Evidence: From Anatomy to Outcomes

2014

ROMICAT-II
COMPLETED

n=1,000+ ACS Risk

Established low-attenuation plaque as a potent predictor of Acute Coronary Syndrome.

2015/24

SCOT-HEART
LANDMARK

n=4,146 10yr Follow-up

CCTA-guided care reduced CHD death/MI. HR 0.79 at 10 years. Validated preventive strategy.

2015

PROMISE
COMPLETED

n=10,003 Functional vs CT

Demonstrated prognostic value of anatomical CCTA comparable to functional testing; incremental value of HRP.

2024

CONFIRM2
NEW 2024

Multi-center AI Validation

AI-enabled quantitative CCTA significantly improves event prediction accuracy versus visual assessment alone.

2025+

TRANSFORM
ONGOING

Intervention Lipid Therapy

Evaluating impact of AI-guided intensive therapy for patients with HRP on long-term outcomes.

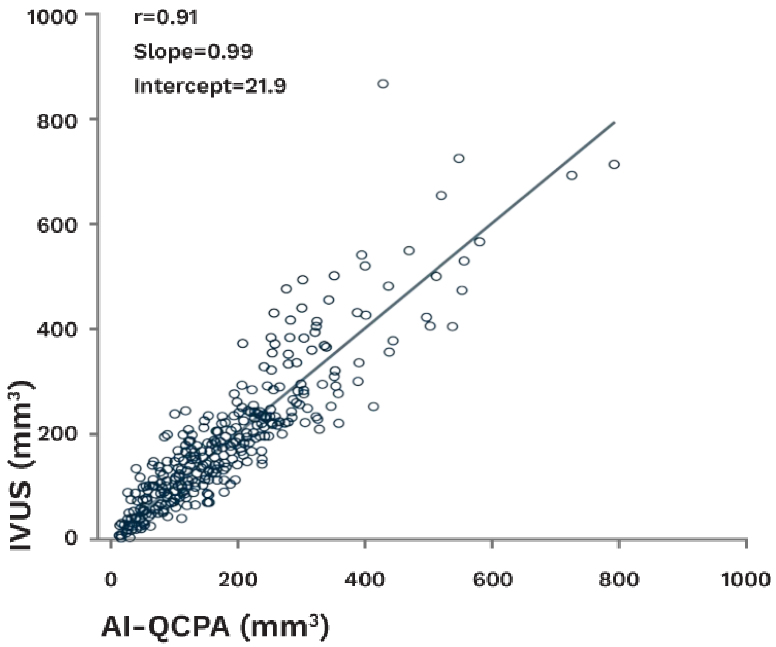
Evidence Synthesis

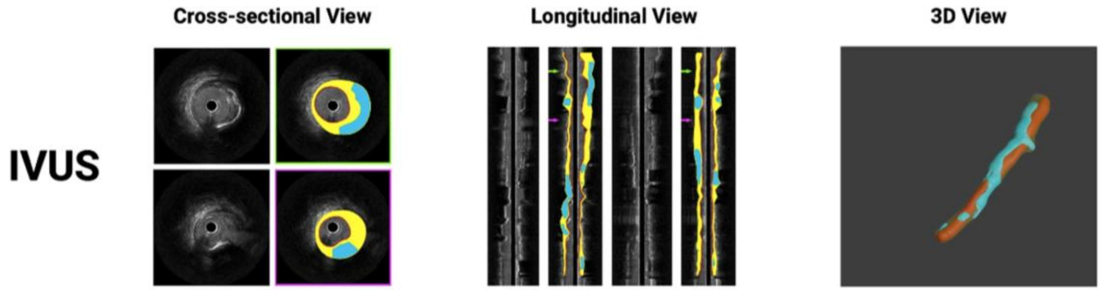
A decade of clinical trials confirms that CCTA not only diagnoses CAD but, when combined with AI and HRP assessment, provides a superior substrate for guiding preventive therapy and reducing myocardial infarction.
reducing myocardial infarction.

References: [2] SCOT-HEART Lancet 2015/2024; [5] CONFIRM2 TCT 2024; [8] ACC/AHA Guidelines 2024

REVEALPLAQUE Study

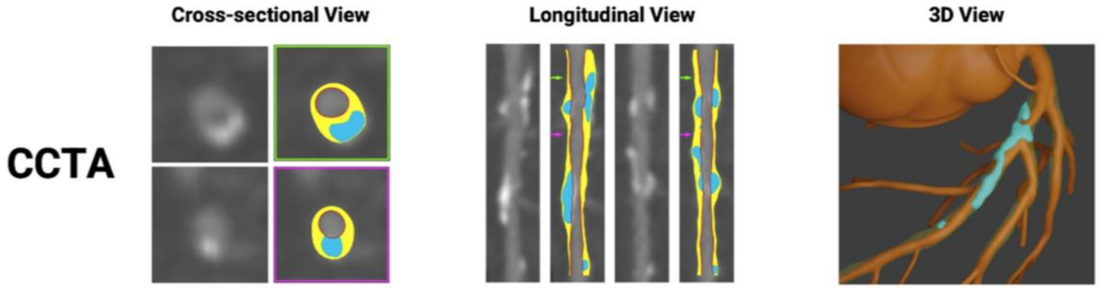
Prospective, blinded RCT, published showing **95% agreement with IVUS** to quantify and characterize coronary plaque.





CCTA vs IVUS Plaque Volume Correlations

Total Plaque Volume	0.91
Calcified Plaque Volume	0.91
Non-calcified Plaque Volume	0.87



Personalized Prevention Strategies

Tailoring Intervention Intensity Based on Plaque Phenotype

High-Risk Plaque Patients (Intensified)

PHARMACOTHERAPY OPTIMIZATION

- Lipid Lowering: High-intensity statins + Ezetimibe. Consider PCSK9 inhibitors for LDL-C <55 mg/dL.
- Antiplatelet: Optimize therapy; consider DAPT based on bleeding risk/ischemic benefit.
- Targets: BP <130/80 mmHg; Strict glycemic control (SGLT2i/GLP-1 RA).

STRICT LIFESTYLE TARGETS

- Diet: Mediterranean or DASH
- Exercise: 150m mod / 75m vig
- BMI Target: 18.5 – 24.9
- Sleep: 7–9 hours/night

SURVEILLANCE

→ Serial CCTA to assess plaque progression/stabilization (regression of LAP).

General Prevention (All Patients)

- Tobacco Cessation: Complete avoidance of smoking/vaping.
- Diet Quality: Limit processed foods, sugar, and sodium.
- Physical Activity: Reduce sedentary time; active daily living.
- Risk Factor Control: Regular screening for BP and glucose.

Precision Medicine Approach

Treatment intensity is no longer solely based on systemic risk scores but is tailored to the individual's plaque phenotype (HRP features) and quantitative burden.

References: [8] ACC/AHA Guidelines 2024; [9] World Heart Federation 2024; [10] CDC Guidelines 2024

03

Section

Management & Targets

Evidence-Based Management

Core Modifiable Risk Factors

Measure • Treat-to-Goal • Re-estimate

Comprehensive management of traditional risk factors remains the cornerstone of ASCVD prevention, emphasizing strict target adherence and regular reassessment.

Hypertension
ACC/AHA 2017/2020

Dyslipidemia
ACC/AHA 2018

Diabetes Mellitus
ADA 2024

Tobacco Use
Ask, Advise, Assist

ACC/AHA 2017/2020 HTN; ACC/AHA 2018 Chol; ADA 2024

Hypertension: Targets and Treatment

Accurate Screening, Evidence-Based Goals, and Management

Accurate Assessment

Proper measurement technique is critical for diagnosis.

In-Office: Use validated device, proper cuff size, seated for 5 mins, feet flat, arm supported at heart level.

Confirmation: Verify with **Out-of-Office** measurement (ABPM or HBPM) when feasible to rule out white-coat or masked hypertension.

Average: Base diagnosis on ≥2 readings on ≥2 occasions.

BP Treatment Targets

Guideline-directed goals to reduce ASCVD risk.

<130/80 mm Hg

Recommended for:

Patients with established ASCVD

10-year ASCVD risk ≥10%

Diabetes Mellitus or CKD

Lifestyle First & Concurrent

Non-pharmacologic interventions are foundational.

DASH Diet: Rich in fruits, vegetables, whole grains, low-fat dairy.

Sodium Restriction: Aim for <1.5–2.0 g/day sodium intake.

Potassium: Increase dietary potassium (3.5–5.0 g/d) unless CKD contraindicated.

Physical Activity: 150 min/week moderate-intensity aerobic exercise.

Weight Loss: Expect ~1 mm Hg reduction per 1 kg weight loss.

Pharmacotherapy

Initiate if targets unmet after lifestyle or high initial risk.

First-line Agents: Thiazide diuretics, CCBs, ACE inhibitors, or ARBs.

Combination: Consider single-pill combination for stage 2 HTN (≥140/90).

Optimization: Titrate doses or add agents to reach goal.

Sources: Whelton PK et al. *J Am Coll Cardiol*. 2018;71:e127–e248 (2017 ACC/AHA Guideline); Unger T et al. *Hypertension*. 2020;75:1334-1357.

Dyslipidemia: Statin-Centered Therapy

Primary Prevention Strategy (Ages 40–75) & Non-Statin Intensification

Patient Group	Assessment Strategy	Statin Intensity	Non-Statin Considerations
Intermediate Risk (7.5% to <20%) **INTERMEDIATE**	**Risk Enhancers:** Review factors. **CAC Score:** If uncertain. **CAC 1-99:** Favors statin. **CAC ≥100:** Strongly favors statin.	**Moderate Intensity** Goal: Lower LDL-C by 30-49%	*Typically not indicated initially unless risk is significantly underestimated.*
High Risk (≥20%) **HIGH**	**Direct Therapy:** No further testing needed. **Lipid Panel:** Baseline LDL-C.	**High Intensity** Goal: Lower LDL-C by ≥50%	**Ezetimibe** considered if LDL-C remains ≥70 mg/dL on max statin.
Diabetes Mellitus (Age 40-75) **DIABETES**	**Risk Assessment:** Calculate 10-year risk. **Enhancers:** Duration ≥10y, albuminuria, retinopathy.	**Moderate Intensity** **High Intensity** if multiple risk factors or 10-yr risk ≥20%.	**Ezetimibe** if 10-yr risk ≥20% and LDL-C reduction <50%.
Non-Statin Add-on Therapy **ADJUNCT**	For patients not meeting LDL-C goals or with statin intolerance.	*Max tolerated statin dose first.*	**Ezetimibe (First line add-on)** **PCSK9 Inhibitor (mAb)** **Bempedoic Acid (if statin intolerant)**

Non-Statin Consensus (ACC 2022): If LDL-C remains above threshold despite max statin + lifestyle, add ezetimibe first. If goals still unmet, consider PCSK9i or bempedoic acid (especially in statin-associated muscle symptoms).

Source: Grundy SM, et al. 2018 AHA/ACC Guideline on the Management of Blood Cholesterol. *J Am Coll Cardiol*. 2019.
Lloyd-Jones DM, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies. *J Am Coll Cardiol*. 2022.

Diabetes Mellitus

Optimizing Glycemic Control & Cardiovascular Risk Reduction

Optimize Glycemic Control

Glycemic targets should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, CVD, and hypoglycemia awareness.

General Target: HbA1c < 7.0% for most non-pregnant adults.

Individualization: More stringent (<6.5%) if achievable safely; less stringent (<8.0%) for complex patients.

Cardioprotective Therapies

For T2D with ASCVD or high cardiovascular risk (regardless of baseline A1c):

GLP-1 RA: Reduces MACE (CV death, MI, stroke).
Examples: Liraglutide, Semaglutide, Dulaglutide.

SGLT2 Inhibitors: Reduces MACE and Heart Failure hospitalization; renoprotective.
Examples: Empagliflozin, Canagliflozin, Dapagliflozin.

Evidence **CVOTs demonstrated benefit:**

LEADER, SUSTAIN-6 (GLP-1 RA); EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58 (SGLT2i)

Weight Management

Weight loss delays progression and improves cardiometabolic factors.

Goal: ≥5% weight loss for overweight/obese patients.

Strategy: Lifestyle modification + consider weight-loss promoting anti-hyperglycemic agents (GLP-1 RA, SGLT2i, GIP/GLP-1 RA).

Associated Risk Factors

Comprehensive management reduces ASCVD events more than glucose control alone.

Blood Pressure: Target <130/80 mmHg. ACEi or ARB first-line if albuminuria present.

Lipids: High-intensity statin for T2D + ASCVD or high risk. Add ezetimibe if LDL-C ≥70 mg/dL.

Tobacco: Cessation counseling and pharmacotherapy at every visit.

Sources: ADA Standards of Care 2024; Zinman B et al. *NEJM* 2015 (EMPA-REG); Marso SP et al. *NEJM* 2016 (LEADER); Neal B et al. *NEJM* 2017 (CANVAS); Wiviott SD et al. *NEJM* 2019 (DECLARE).

Tobacco Use & Cessation Strategy

Core Modifiable Risk Factor Management

Clinical Approach: The 5 A's

Every patient, every visit. Consistent intervention is key to behavioral change.

Ask: Systematically identify all tobacco users at every visit.

Advise: Strongly urge all tobacco users to quit.

Assess: Determine willingness to make a quit attempt.

Assist: Aid the patient in quitting (counseling + pharmacotherapy).

Arrange: Schedule follow-up contact.

ASCVD Risk Reduction

Cessation yields immediate and long-term benefits.

Within 1-2 years of quitting:
Risk of heart attack drops dramatically.

Within 5 years:
Stroke risk can fall to that of a non-smoker.

Effective Treatment Modalities

Pharmacotherapy combined with counseling is more effective than either alone.

Counseling: Individual, group, or telephone counseling (e.g., 1-800-QUIT-NOW).

- Nicotine Replacement Therapy (NRT): Patch, gum, lozenge, inhaler, spray.
- Varenicline (Chantix): Partial nicotine agonist.
- Bupropion SR: Non-nicotine oral medication.

Recommendation: Use FDA-approved medications unless contraindicated.

Post-Cessation Management

Address potential metabolic changes proactively.

Weight Gain: Common post-cessation (avg 2-4 kg).

Mitigation: Concurrent lifestyle modification (diet/exercise) is crucial.

Net Benefit: Health benefits of cessation outweigh risks of mild weight gain.

Monitoring: Re-evaluate BP and lipids after cessation.

Sources: USPHS Clinical Practice Guideline 2020; AHA Scientific Statement 2018; ADA Standards of Care 2024.

06

Section

Selective vs. Routine Use

Therapeutic Decision Making

Interventions with Unclear or Selective Benefit

Evidence supports selective, not routine, use in primary prevention

Reviewing the shift away from universal prescribing for primary prevention toward individualized risk-benefit assessment for specific therapies.

Aspirin	Omega-3s	Polypill
USPSTF 2022	ACC/AHA	Clinical Context

Citations: USPSTF 2022; ACC/AHA Statements

“ Primum non nocere (First, do no harm)

Aspirin for Primary Prevention

Interventions with Unclear or Selective Benefit

Initiation: Age 40–59

Shared Decision-Making is Essential

Criteria: Adults aged 40–59 years with ≥10% 10-year CVD risk.

Benefit: Evidence suggests only a *small net benefit* for primary prevention.

Recommendation: The decision to initiate low-dose aspirin should be individualized. Persons who place a higher value on potential benefits than potential harms may choose to initiate.

Dosing: If chosen, low-dose aspirin (81 mg/day) is the standard.

Age ≥60 & Safety Concerns

Initiation in Older Adults (≥60 years)

Do Not Initiate: USPSTF recommends *against* initiating low-dose aspirin for primary prevention in adults ≥60 years.

Rationale: Risk of bleeding harms generally outweighs potential cardiovascular benefits in this age group.

Bleeding Risk & Deprescribing

Bleeding Risk: Assess for history of GI bleeding, peptic ulcer disease, or other bleeding risks before any initiation.

Stopping: For those already on aspirin for primary prevention, consider stopping use around age 75 due to increasing bleeding risk.

*Note: These recommendations apply only to **primary prevention**. Aspirin remains a cornerstone for secondary prevention in patients with established CVD.*

Omega-3 Fatty Acids and Polypill

Evidence-Based Review of Adjunctive Therapies in Prevention

Intervention	Key Trials	Evidence & Findings	Clinical Status
Icosapent Ethyl Purified EPA (4g/day)	**REDUCE-IT** (Bhatt et al. NEJM 2019)	**Population:** Established CVD or Diabetes + Risk Factors with elevated TG (135–499 mg/dL) on statin. **Outcome:** Significant 25% relative risk reduction in MACE.	**Select Benefit** FDA approved for specific high-risk groups
Mixed Omega-3 EPA + DHA / Fish Oil	**STRENGTH** (Nicholls et al. JAMA 2020)	**Population:** High CV risk with high TG. **Outcome:** Trial halted early for futility. No significant benefit compared to corn oil placebo. **Routine Use:** General OTC fish oil supplements are not recommended for ASCVD prevention.	**No Benefit** Routine use not recommended
Polypill Single Pill Combination	**TIPS-3 / SECURE** (Yusuf NEJM 2021; SECURE NEJM 2022)	**TIPS-3:** Modest benefit in intermediate risk (primary prevention), largely driven by BP/lipid lowering components. **SECURE:** Improved adherence and outcomes in post-MI secondary prevention.	**Select Benefit** Not standard in US primary prevention

Clinical Pearl: Do not conflate prescription Icosapent Ethyl with dietary supplements. The benefits seen in REDUCE-IT were specific to the purified EPA formulation and dose, and have not been replicated with mixed omega-3 products.

Sources: Bhatt DL, et al. *N Engl J Med*. 2019;380:11-22 (REDUCE-IT). Nicholls SJ, et al. *JAMA*. 2020;324:2268-2280 (STRENGTH).
Yusuf S, et al. *N Engl J Med*. 2021;384:216-228 (TIPS-3). Castellano JM, et al. *N Engl J Med*. 2022;387:967-977 (SECURE).

COLCHICINE & ASCVD: MECHANISM OF ACTION

Colchicine targets the specific inflammatory pathways that drive atherosclerosis progression, offering a novel mechanism for cardiovascular risk reduction beyond lipid lowering.

Dosing 0.5 mg Daily

FDA Approved June 2023 for CV Risk

THREE KEY MECHANISMS OF ACTION

1. Inhibits Tubulin

Binds to β-tubulin to prevent polymerization, disrupting microtubule formation essential for cell trafficking.

→

2. Blocks NLRP3

Prevents NLRP3 inflammasome assembly, directly reducing production of IL-1β, IL-6, and IL-18 cytokines.

→

3. Clinical Result

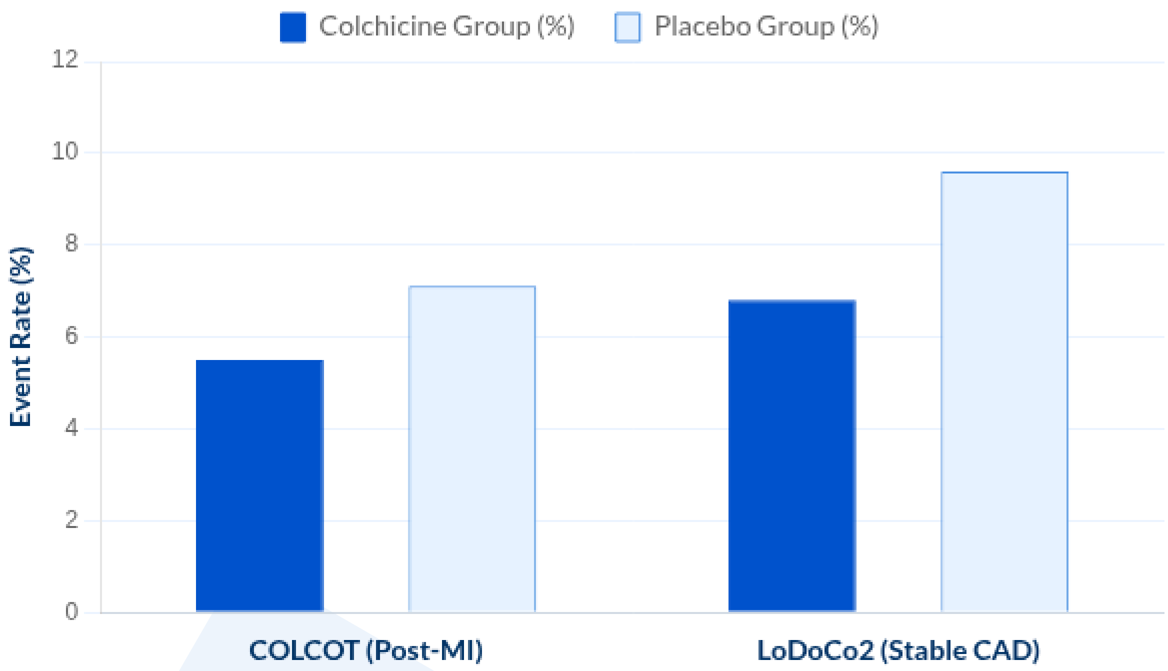
Decreased systemic inflammation (hs-CRP) and stabilization of atherosclerotic plaque.

References: Tardif JC et al. NEJM 2019;381:2497-505; Nidorf SM et al. NEJM 2020;383:1838-47; González L et al. PMC 2022.

PIVOTAL RCTS: COLCOT AND LODOCO2

Comparative analysis of landmark trials demonstrating colchicine efficacy in ASCVD

Primary Endpoint Reduction



Trial Summary Data

Trial	Population (N)	Primary Outcome	Hazard Ratio (95% CI)
COLCOT 2019	Post-MI <30d (4,745)	**23% Reduction** 5.5% vs 7.1%	**0.77** (0.61-0.96) p=0.02
LoDoCo2 2020	Stable CAD (5,522)	**31% Reduction** 6.8% vs 9.6%	**0.69** (0.57-0.83) p<0.001

Key Takeaway

Both trials demonstrated consistent, significant reductions in major adverse cardiovascular events (MACE) when adding 0.5mg colchicine to standard of care therapy.

References: Tardif JC et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med. 2019;381:2497-2505. | Nidorf SM et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med. 2020;383:1838-1847.

SIGNIFICANT MORBIDITY REDUCTION

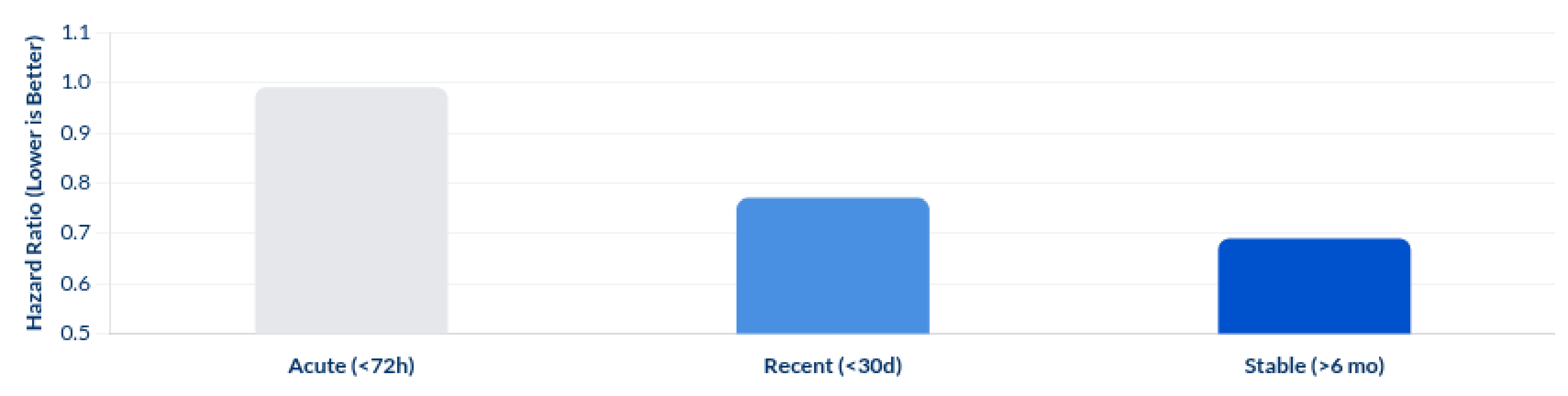
Meta-analysis confirms substantial reductions in non-fatal events, with efficacy dependent on timing.

27%
MACE Reduction
Pooled Risk Ratio 0.73

74%
Stroke Reduction
COLCOT Data (HR 0.26)

50%
Urgent Revasc.
COLCOT Data (HR 0.50)

EFFICACY BY TIMING OF INITIATION



CV Mortality
Neutral
RR 0.95 (CI 0.78-1.17)

References:

1. Samuel M, et al. Eur Heart J. 2021;42(1):31-39 (Meta-analysis). 2. Tardif JC, et al. N Engl J Med. 2019;381:2497-2505 (COLCOT). 3. Nidorf SM, et al. N Engl J Med. 2020;383:1838-1847 (LoDoCo2). 4. Jolly SS, et al. N Engl J Med. 2025;392:633-642 (CLEAR SYNERGY).

SAFETY PROFILE

Common Side Effects

10% — **GI Upset / Diarrhea**
Most common dose-limiting effect

2% — **Nausea**
Mild and transient

<0.9% — **Pneumonia**
Small signal in COLCOT trial

CONTRAINDICATION

Avoid use in patients with **severe renal or hepatic impairment**.

GUIDELINES

Clinical Recommendations

ESC 2024
Class IIa

Recommended for stable CAD patients.

AHA/ACC 2023
Class IIb

Consider for reducing recurrent ASCVD events.

FDA APPROVED (2023)
0.5 mg Daily

Approved for CV risk reduction in established ASCVD.

1. Tardif JC et al. N Engl J Med. 2019 (COLCOT). 2. Nidorf SM et al. N Engl J Med. 2020 (LoDoCo2). 3. FDA Prescribing Information 2023. 4. 2024 ESC Guidelines for Chronic Coronary Syndromes. 5. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for Chronic Coronary Disease.

CLINICAL IMPLEMENTATION WORKFLOW

Simplified 4-step protocol for integrating low-dose colchicine into practice

1 SELECT

Target Patient

- Stable CAD
- Residual inflammatory risk
- Suboptimal control

2 SCREEN

Safety Check

- Renal function (eGFR)
- Hepatic function
- Drug interactions (CYP3A4)

3 START

Initiation

- **0.5 mg daily**
- Avoid loading dose
- Counsel on GI effects

4 MONITOR

Follow-up

- GI tolerance check
- Infection signs
- Reassess at 2-4 weeks

TIMING MATTERS

Wait ≥1-2 weeks post-MI before initiation. Recent data (CLEAR SYNERGY) shows no benefit when started within 72 hours of acute event.

References: Tardif JC et al. N Engl J Med. 2019;381:2497-2505; Nidorf SM et al. N Engl J Med. 2020;383:1838-1847; Jolly SS et al. (CLEAR SYNERGY). N Engl J Med. 2025;392:633-642; ACC 2025 Review.

Key Takeaways & Action Items

Summary of ASCVD Risk Stratification Evidence

01

Select the Right Risk Tool

Standard of Care: Use PCE to estimate 10-year ASCVD risk in adults aged 40–79.

Early Prevention: Utilize the PREVENT calculator to estimate 30-year risk in younger adults (ages 30–59) to guide earlier lifestyle modification discussions.

02

Resolve Uncertainty

Decision Aids: When risk status is borderline/intermediate or treatment decision is unclear, use risk-enhancing factors (e.g., family history, metabolic syndrome).

Tie-Breaker: Order CAC scoring to reclassify risk; CAC = 0 typically allows for deferring statin therapy (with specific exceptions).

03

Prioritize & Target

Core Factors: Aggressively manage hypertension, lipids, and diabetes to guideline-directed targets.

Selective Testing: Use biomarkers like Lp(a) (once per lifetime) and ApoB selectively to refine risk assessment, not for universal screening.

04

Avoid Routine Low-Value Care

Aspirin: Do not use routinely for primary prevention, especially in adults ≥60 years. Individualize for high risk ages 40-59.

Supplements: Generic omega-3 fatty acids and multivitamins have unclear benefit for ASCVD reduction and are not recommended.

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