European Heart Journal

Azerbaijan Society of Cardiology

The New Coronary Paradigm: Vulnerable Atheroma, Inflammatory Risk & Intelligent Imaging–Physiology Integration

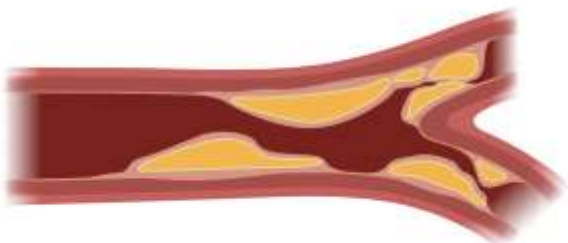
Ulvi Mirzoyev, MD, PhD,
MBA, MSc, MHA

FESC FSCAI

Shifting Focus to Vulnerable Plaque

Obstructive CAD Focus

Blockages limit blood flow



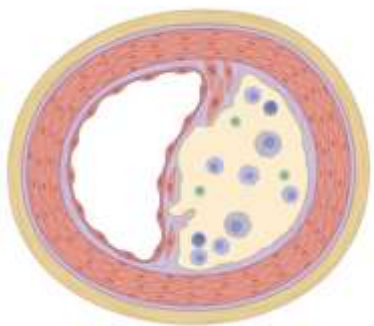
Non-invasive Imaging & Drugs

Visualize high-risk plaque

Reduce inflammation in arteries

Non-obstructive CAD Focus

Atheroma is the new target



SCIENCE
http://www.aaas.org

1996

EDITORIAL

Heart Attacks: Gone with the Century?

This issue of *Science* highlights the progress and promise of research in cardiovascular disease, the most frequent cause of death in men over age 35 and women over age 65 in the United States. Heart attacks were recognized as a public health problem only in this century. They are likely to lose this notoriety early in the next. The reason? Four decades of progress in understanding cholesterol and the lipoproteins that carry it in blood plasma.

Atherosclerosis begins when plasma lipoproteins of intermediate and low density (here called LDL) are deposited in artery walls. Evidence for the causative role of LDL comes from three sources. (i) Experimental: Animals with low levels of LDL have no atherosclerosis, and manipulations that raise LDL universally cause the disease. (ii) Epidemiologic: Human populations with low LDL levels have very little atherosclerosis; the disease increases in proportion to LDL in all populations studied. (iii) Genetic: Mutations that impair the receptor-mediated removal of LDL from plasma cause fulminant atherosclerosis. The final (therapeutic) line of evidence has now been supplied by three clinical trials, all completed in the past 18 months.

All three trials used drugs called statins, which inhibit 3-hydroxy-3-methyl glutaryl CoA reductase, a key enzyme of cholesterol synthesis. Statins slow cholesterol production and enhance receptor-mediated removal of LDL from plasma. The three studies followed 15,198 people for 5 years. The studies from Scandinavia (4S)* and from North America (CARE)† enlisted patients with coronary disease. The study from Scotland‡ enrolled asymptomatic individuals with high cholesterol. All studies yielded similar results: Plasma levels of LDL fell by 26 to 35% and heart attacks declined by 25 to 31%. In the 4S study, heart attack deaths were reduced by 42% and deaths from all causes fell by 30%. We believe that the results would be even more striking if cholesterol were lowered further and earlier.

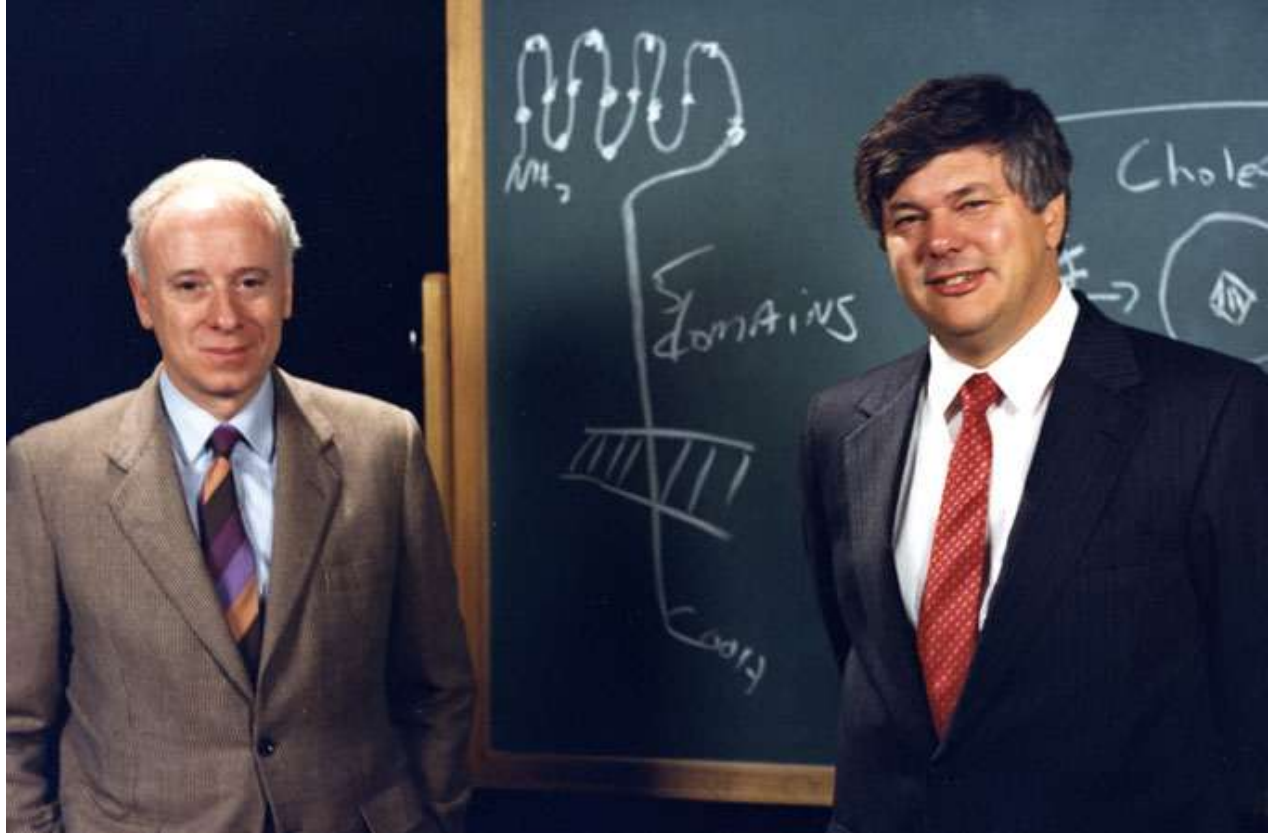
The 4S and CARE studies found that coronary events were reduced in patients with "normal" plasma cholesterol levels around 210 mg/dl. This is not surprising, as a cholesterol level of 210 mg/dl, which is near the median in the United States and Europe, is above the 90th percentile for the human species worldwide. Individuals with such levels who develop atherosclerosis have arteries that are unusually susceptible to LDL. As cholesterol rises above 210 mg/dl, the incidence of atherosclerosis increases; and at very high levels, atherosclerosis is rampant even when patients are not especially susceptible.

Well-documented susceptibility factors include smoking, hypertension, diabetes, a lipoprotein called Lp(a), and low levels of high density lipoproteins. More recently discovered are genetic polymorphisms that raise blood homocysteine or disrupt regulation of blood clotting. All of these should be treated when possible, but the therapeutic trials tell us that atherosclerotic events can be reduced by lowering of LDL even when these factors are present.

Statins are effective, but are they safe? In the three trials, statins were taken by 7500 people for 5 years without a significant increase in deaths from noncardiac diseases. These studies are reassuring but brief. Will some hidden toxicity emerge when individuals take these drugs for most of their adult lives? Long-term studies are needed.

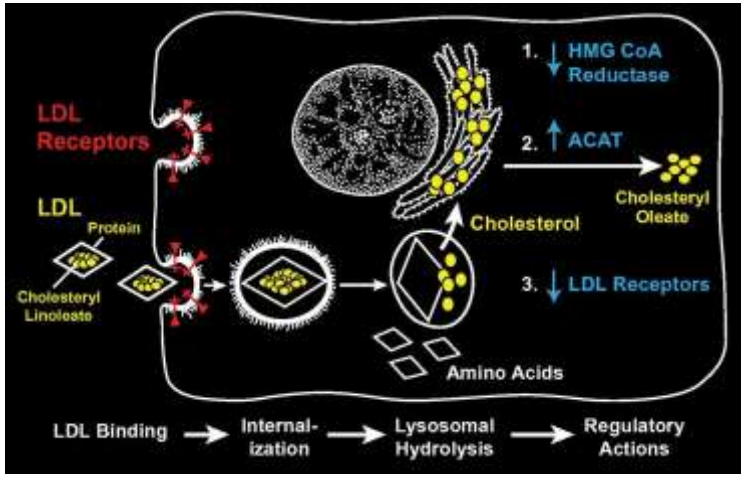
In middle-aged people with cholesterol levels greater than 240 mg/dl, the potential for coronary heart disease warrants aggressive cholesterol lowering with diet and drugs. People with normal cholesterol levels of 210 mg/dl have a lower relative risk, but their absolute numbers are greater. If we wait for susceptible individuals to develop symptoms before deciding to treat, the earliest symptom is often sudden death. The challenge is to develop noninvasive screening methods to detect coronary atherosclerosis in its earliest stages. Exploitation of recent breakthroughs—proof of the cholesterol hypothesis, discovery of effective drugs, and better definition of genetic susceptibility factors—may well end coronary disease as a major public health problem early in the next century.

Michael S. Brown and Joseph L. Goldstein



Michael Brown and Joseph Goldstein

1985



Development of Atherosclerotic Plaque

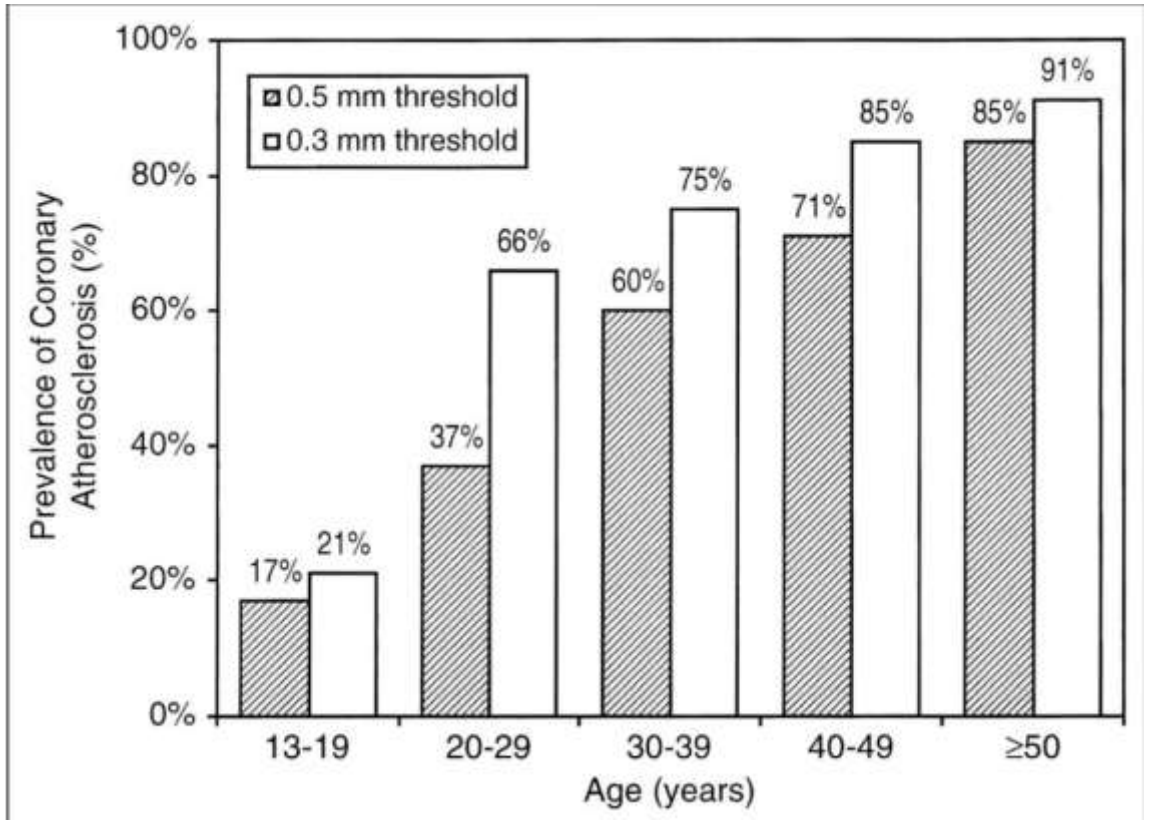
Circulation
Volume 103, Issue 22, 5 June 2001; Pages 2705-2710
https://doi.org/10.1161/01.CIR.103.22.2705

CLINICAL INVESTIGATION AND REPORTS

High Prevalence of Coronary Atherosclerosis in Asymptomatic Teenagers and Young Adults

Evidence From Intravascular Ultrasound

E. Murat Tuzcu, Samir R. Kapadia, Eralp Tutar, Khaled M. Ziada, Robert E. Hobbs, Patrick M. McCarthy, James B. Young, and Steven E. Nissen



Introduction: Why a Paradigm Shift Is Necessary

For >40 years, coronary disease assessment was **stenosis-centric**

Yet **~70% of ACS** originates from *mild or intermediate stenoses*

We must shift from **lumen narrowing** to **plaque biology**

Modern tools enable this transition:

IVUS, OCT, NIRS

CTA-based inflammatory assessment (FAI)

AI-driven plaque analysis

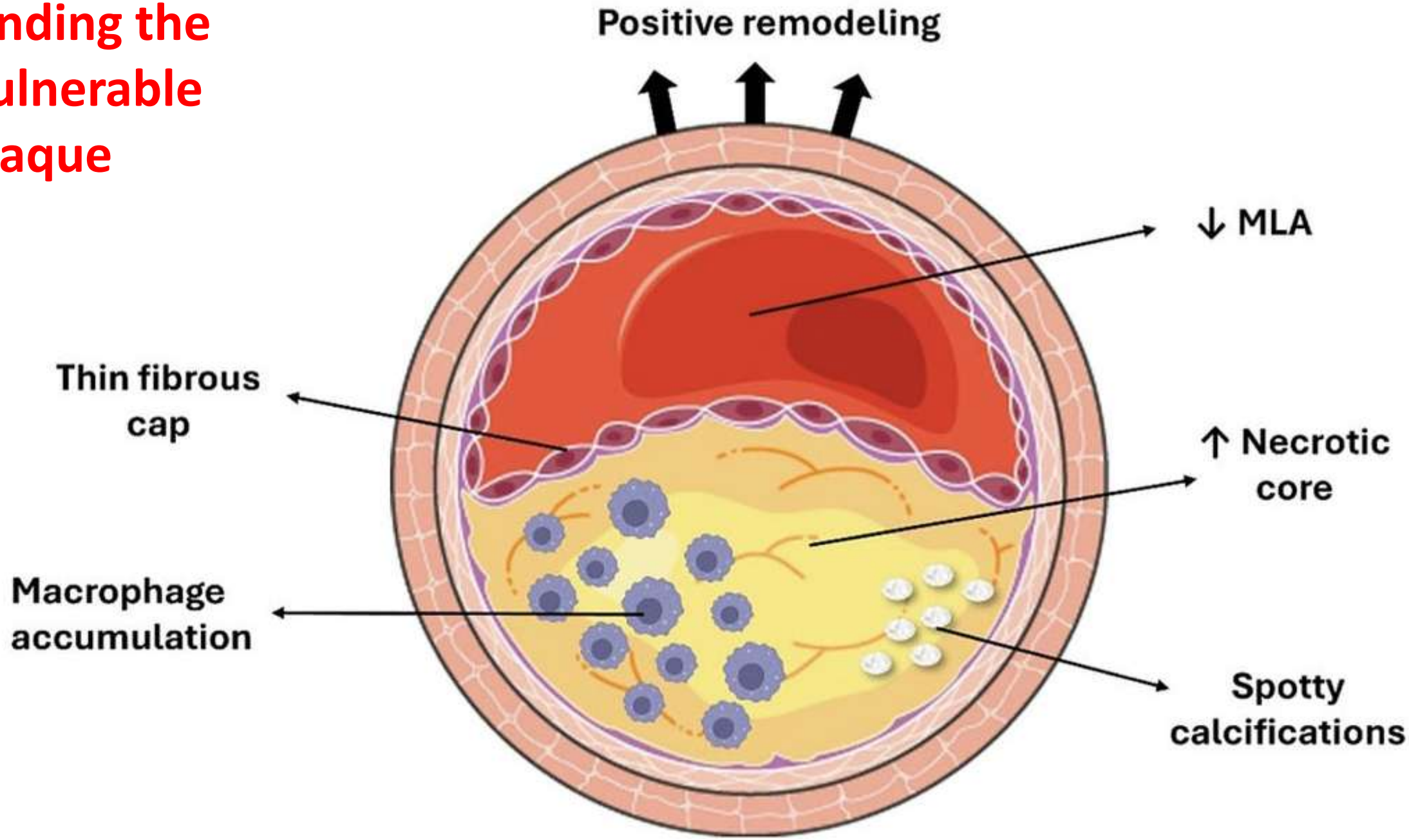
FFR/iFR physiology

Stenosis Is a Poor Surrogate for Risk

Stenosis ≠ Vulnerability

- 30–50% lesions cause most MIs
- Angiography shows **anatomy**, not **danger**
- A “normal-looking” lesion may be biologically unstable
- PROSPECT, CLIMA, COMBINE OCT–FFR → consistent message:
  Biology predicts events better than lumen diameter

Finding the Vulnerable Plaque




JOHN BLACK
44 YEARS
CALCIUM SCORE 0

Circulation
Volume 92, Issue 8, 15 October 1995; Pages 2333-2342
https://doi.org/10.1161/01.CIR.92.8.2333

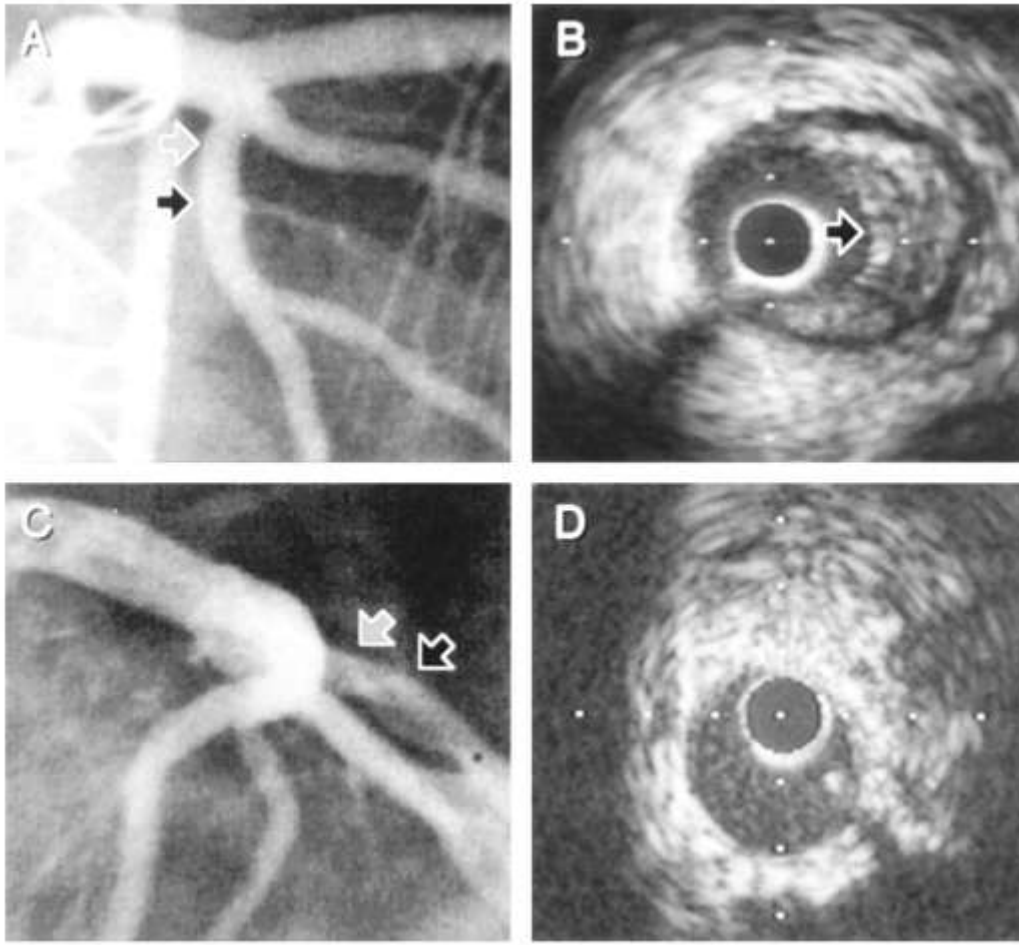
American Heart Association.

ARTICLE

Our Preoccupation With Coronary Luminology

The Dissociation Between Clinical and Angiographic Findings in Ischemic Heart Disease

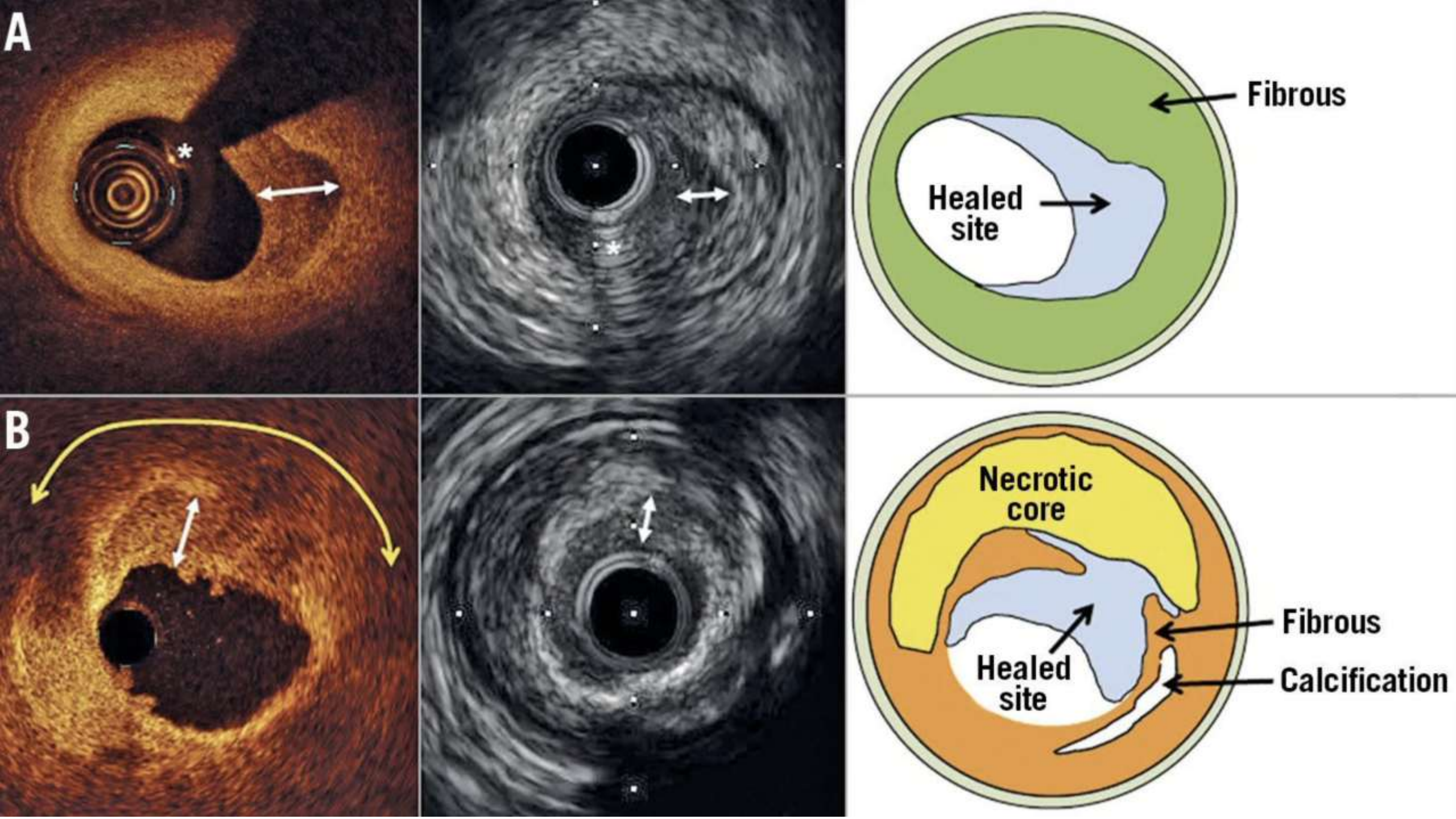
Eric J. Topol and Steven E. Nissen



CLINICAL RESEARCH
DOI: 10.4244/EIJ-D-18-01175

Characteristics and significance of healed plaques in patients with acute coronary syndrome and stable angina: an in vivo OCT and IVUS study

Chao Wang[1], MD; Sining Hu[1], MD; Jianjun Wu[1], MD; Huai Yu[1]; Weili Pan[1], MD; Yuhan Qin[1], MD; Luping He[1], MD; Lulu Li[1], MS; Jingbo Hou[1], MD, PhD; Shaosong Zhang[1], MD, PhD; Haibo Jia[1], MD, PhD; Bo Yu[1], MD, PhD;


A
Fibrous
Healed site
B
Necrotic core
Fibrous
Healed site
Calcification

What Intracoronary Imaging Taught Us About Atheroma Progression
Natural History of Atheroma: Beyond the Angiogram

A prospective study of **~700 patients**, followed for **3.4 years**, showed that **most major cardiovascular events** originated from plaques that appeared **mild or non-obstructive on angiography**.

•**Angiogram misses biological risk**—these "mild" lesions had high-risk features on IVUS:

- **Thin-Cap Fibroatheroma (TCFA)**
- **High Plaque Burden (PB)**
- **Small Minimal Lumen Area (MLA)**

•These vulnerable characteristics are **invisible on angiography** but **predict future events**.

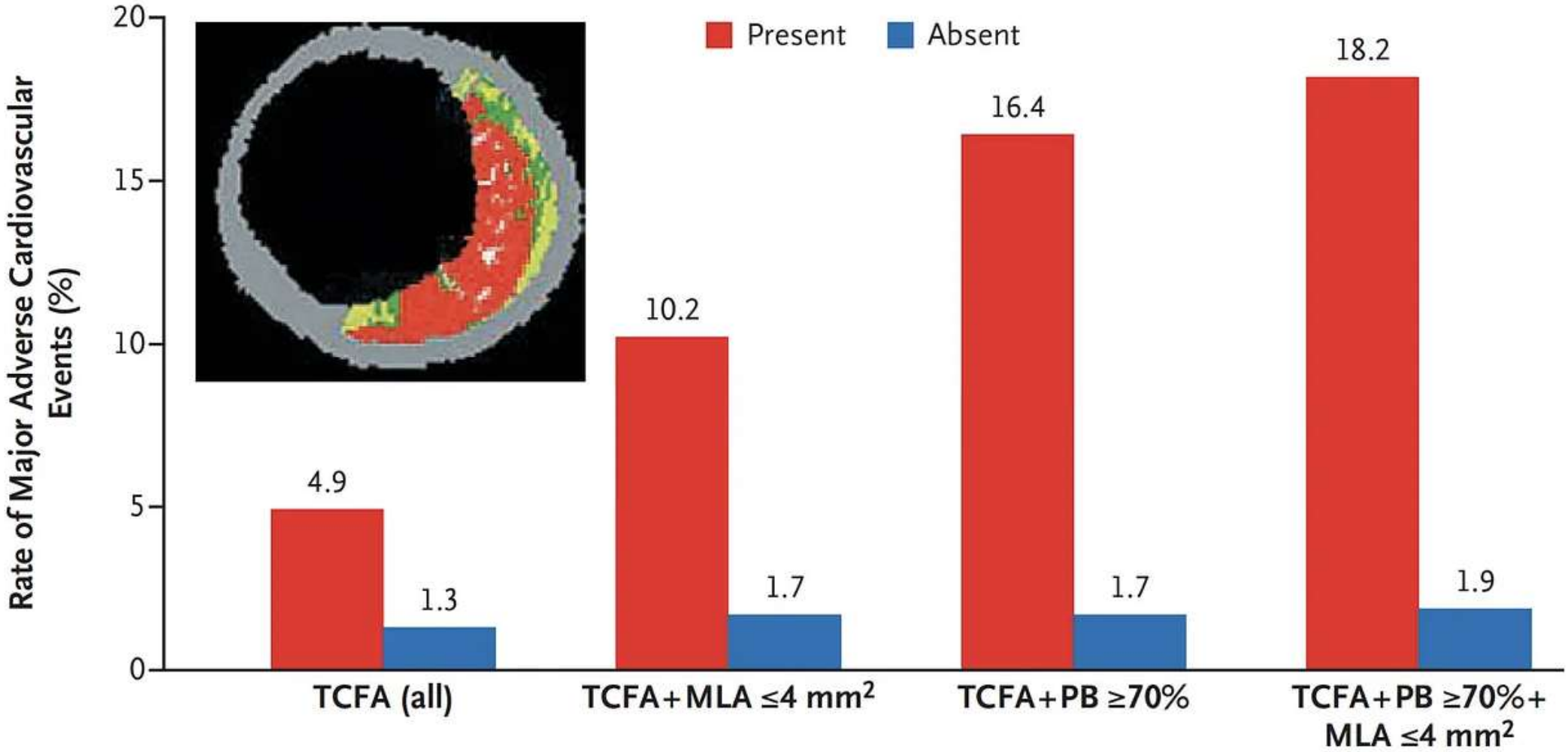
•Key Message:
Atheroma progression and rupture are driven by biology—not stenosis severity.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Prospective Natural-History Study of Coronary Atherosclerosis

Gregg W. Stone, M.D., Akiko Maehara, M.D., Alexandra J. Lansky, M.D., Bernard de Bruyne, M.D., Ecaterina Cristea, M.D., Gary S. Mintz, M.D., Roxana Mehran, M.D., John McPherson, M.D., Naim Farhat, M.D., Steven P. Marso, M.D., Helen Parise, Sc.D., Barry Templin, M.B.A., Roseann White, M.A., Zhen Zhang, Ph.D., and Patrick W. Serruys, M.D., Ph.D., for the PROSPECT Investigators*



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

So now that we could identify these high-risk atheroma—vulnerable plaques—there was thought they might be stabilized or “sealed” with ballon angioplasty

MINI-SYMPOSIUM

Plaque sealing by coronary angioplasty

B Meier

Heart 2004;**90**:1395–1397. doi: 10.1136/hrt.2004.034983

Circulation
Volume 103, Issue 25, 26 June 2001; Pages 3142-3149
https://doi.org/10.1161/01.CIR.103.25.3142

American Heart Association.

CLINICAL CARDIOLOGY: NEW FRONTIERS

Evaluation of the Culprit Plaque and the Physiological Significance of Coronary Atherosclerotic Narrowings

Morton J. Kern and Bernhard Meier

ARTICLES · Volume 403, Issue 10438, P1753-1765, May 04, 2024

Download Full Issue

Preventive percutaneous coronary intervention versus optimal medical therapy alone for the treatment of vulnerable atherosclerotic coronary plaques (PREVENT): a multicentre, open-label, randomised controlled trial

Prof Seung-Jung Park, MD [a,*] · Jung-Min Ahn, MD [a,*] · Do-Yoon Kang, MD [a] · Sung-Cheol Yun, PhD [b] · Prof Young-Keun Ahn, MD [c] · Won-Jang Kim, MD [d] · et al. Show more

Affiliations & Notes · Article Info · Linked Articles (7)

The **PREVENT**ive Coronary Intervention on Stenosis With Functionally Insignificant Vulnerable Plaque

PREVENT Trial

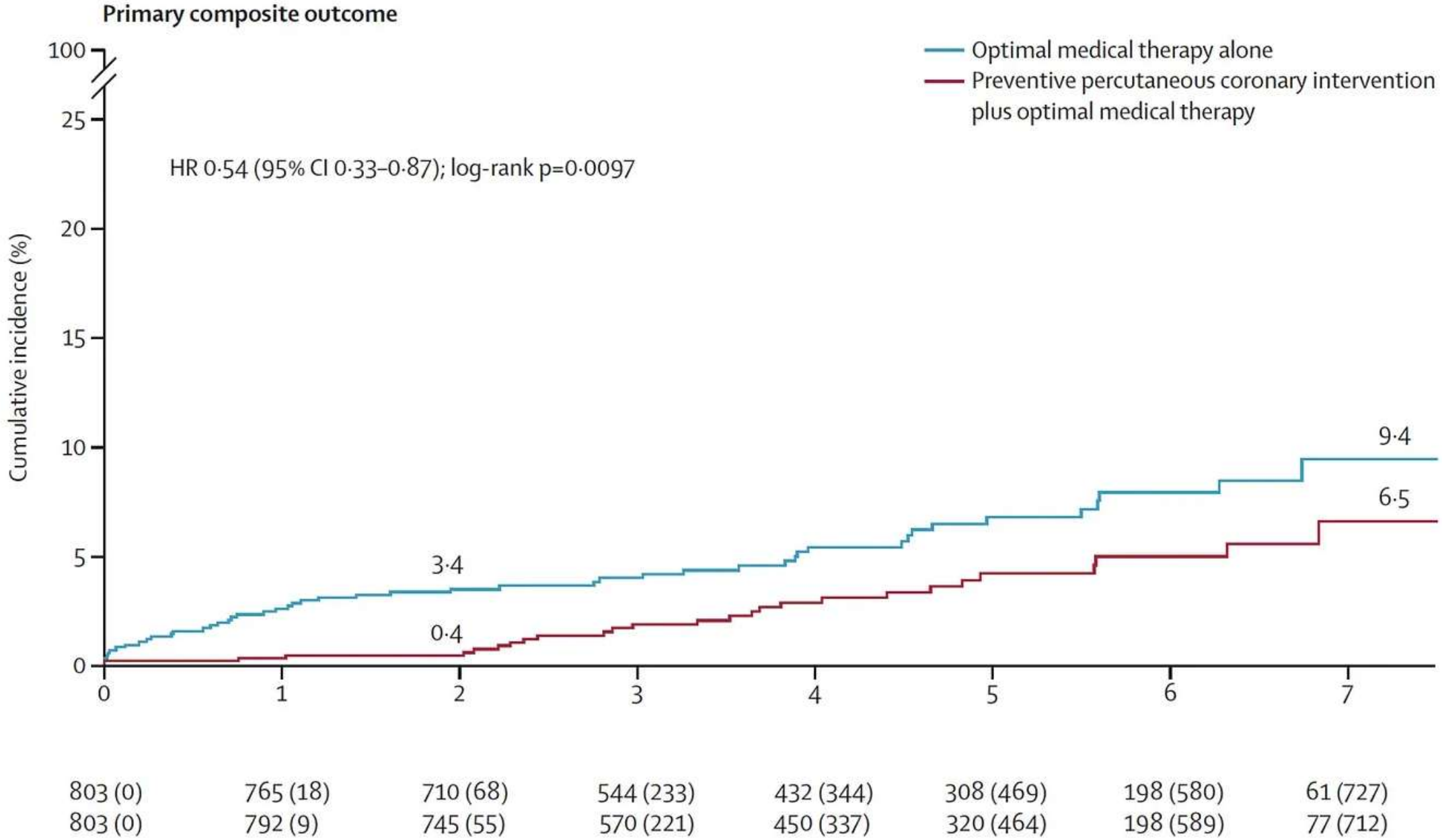
Any Significant Epicardial Coronary Stenosis (DS>50%) with *FFR >0.80* and with *Two* of the following

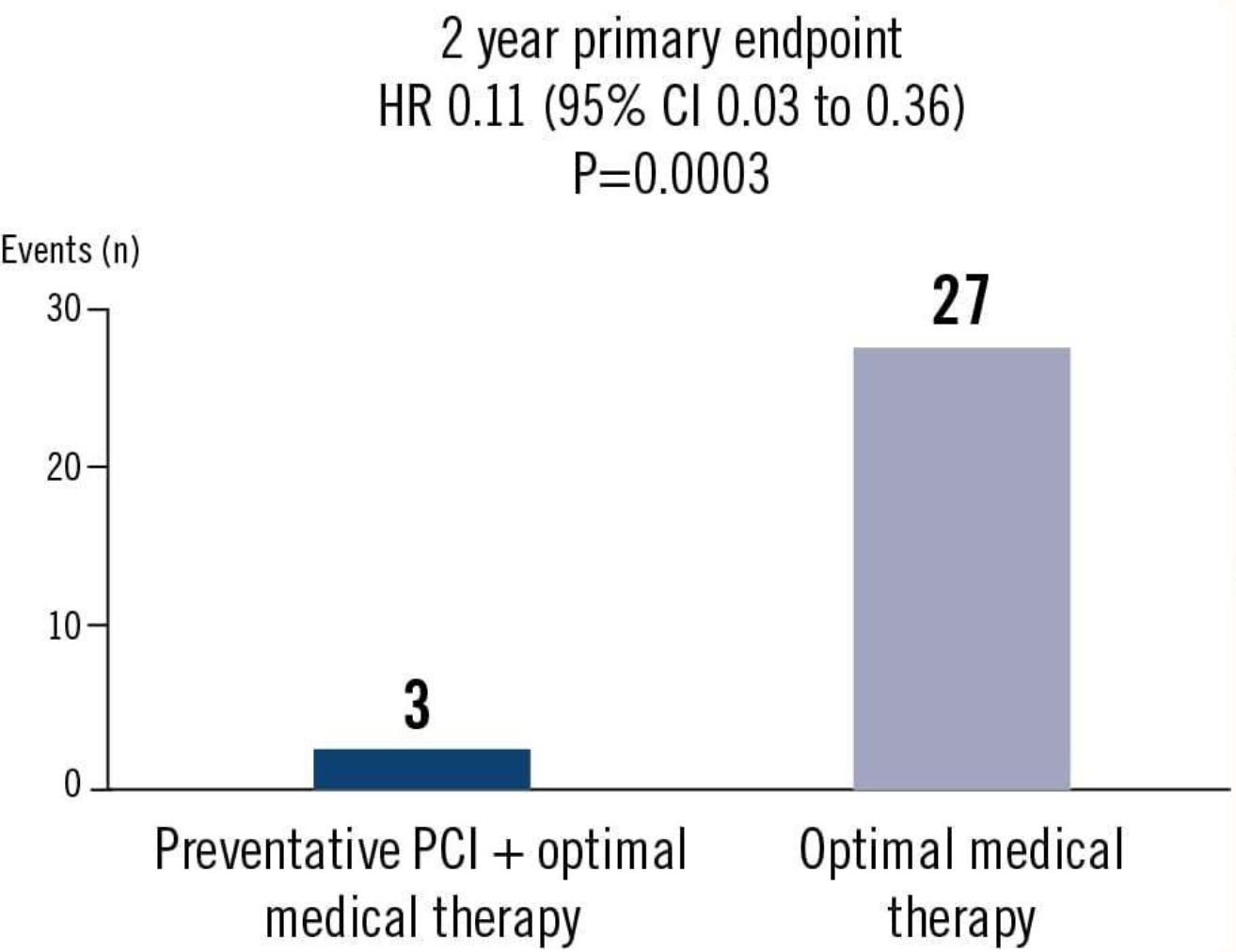
1. IVUS MLA <4.0mm^2
2. IVUS Plaque Burden >70%
3. Lipid-Rich Plaque on NIRS ($_{max}LCBI_{4mm}$>315)
4. TCFA by OCT or VH-IVUS

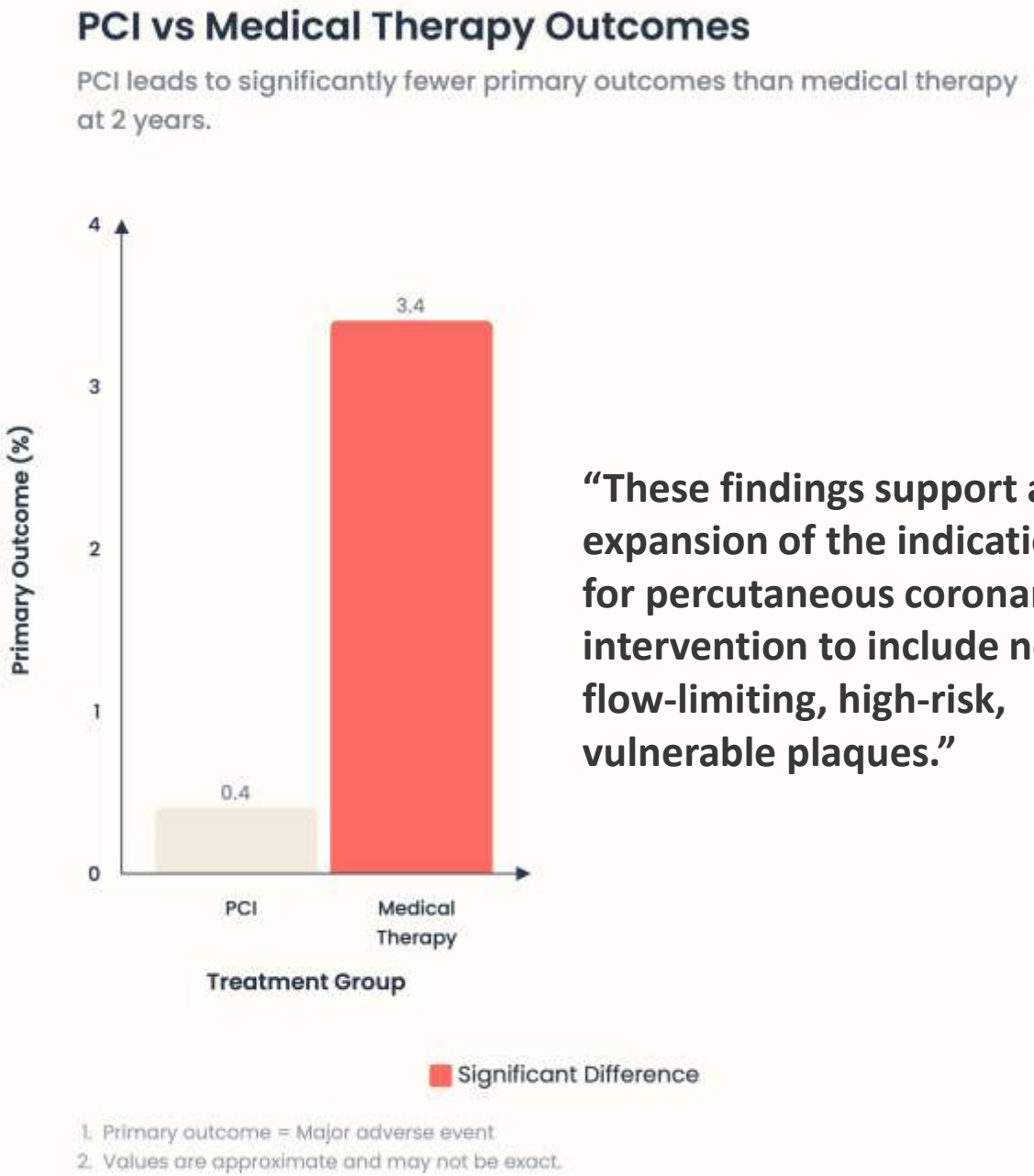
PCI+GDMT	GDMT
N=800	N=800

Primary endpoint: Target Vessel Failure at 2 years

(Death from cardiac cause, target vessel myocardial infarction, ischemic-driven target vessel revascularization, or unplanned hospitalization due to unstable or progressive angina)


Primary composite outcome
Optimal medical therapy alone
Preventive percutaneous coronary intervention plus optimal medical therapy
HR 0·54 (95% CI 0·33–0·87); log-rank p=0·0097
Cumulative incidence (%)
100
25
20
15
10
5
0
9·4
6·5
3·4
0·4
0
1
2
3
4
5
6
7
803 (0) 765 (18) 710 (68) 544 (233) 432 (344) 308 (469) 198 (580) 61 (727)
803 (0) 792 (9) 745 (55) 570 (221) 450 (337) 320 (464) 198 (589) 77 (712)



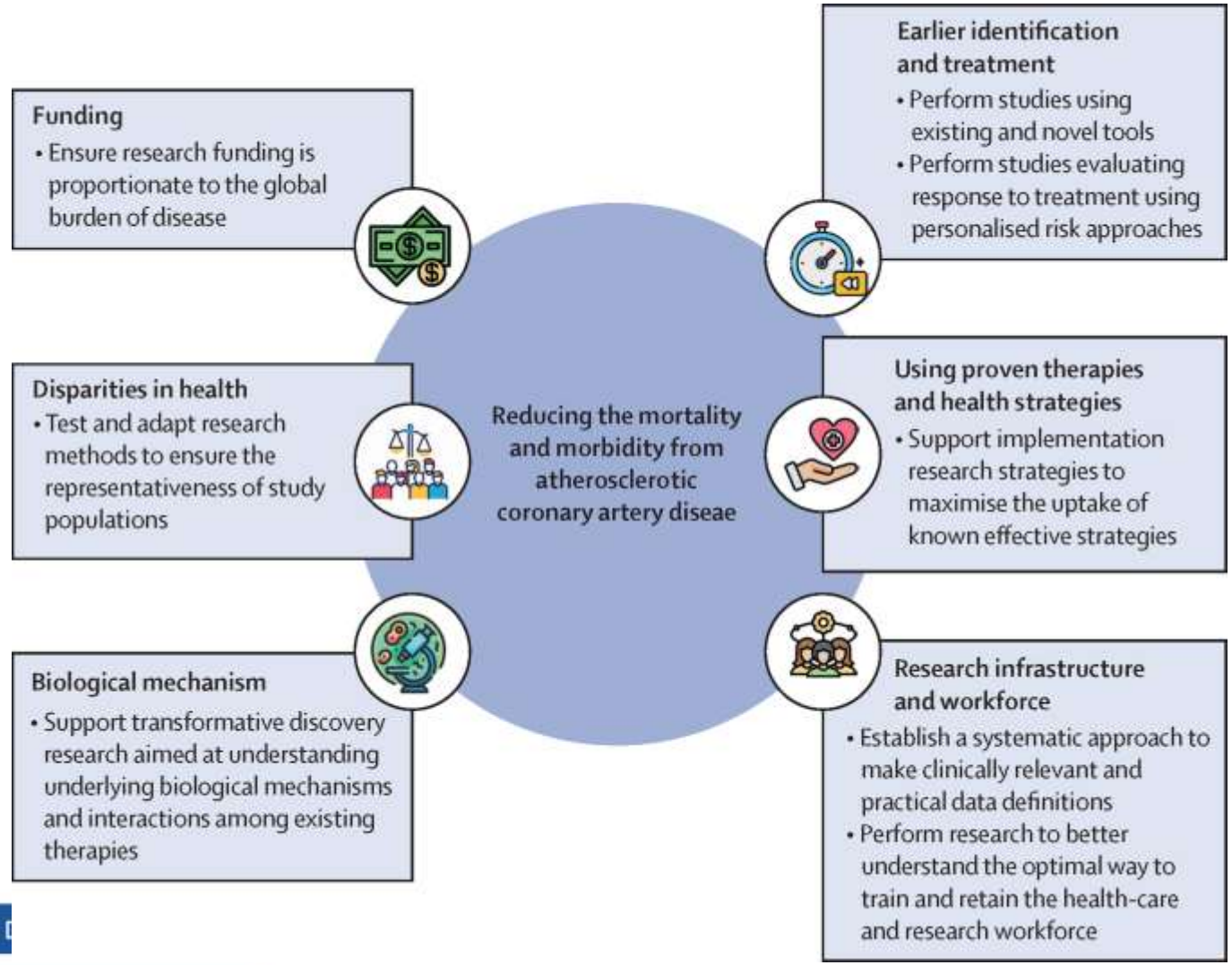


“These findings support an expansion of the indications for percutaneous coronary intervention to include non-flow-limiting, high-risk, vulnerable plaques.”

THE LANCET

Volume 405 · Number 10486 · Pages 1203-1312 · April 12-18, 2025 www.thelancet.com

"Refocusing and reframing the definition and discussion of coronary artery disease [towards] early detection of coronary artery atheroma... has the potential to save 8·7 million lives globally every year."



THE LANCET COMMISSIONS · Volume 405, Issue 10486, P1264-1312, April 12, 2025

The *Lancet* Commission on rethinking coronary artery disease: moving from ischaemia to atheroma

Sarah Zaman, MD PhD [a,b] · Jason H Wasfy, MD PhD [c,d] · Vikas Kapil, MD PhD [e] · Boback Ziaeian, MD PhD [f] · Prof William A Parsonage, MD [g,h] · Sira Sriswasdi, PhD [i,j] · et al. Show more

The Role of Systemic Inflammation

Elevated hsCRP

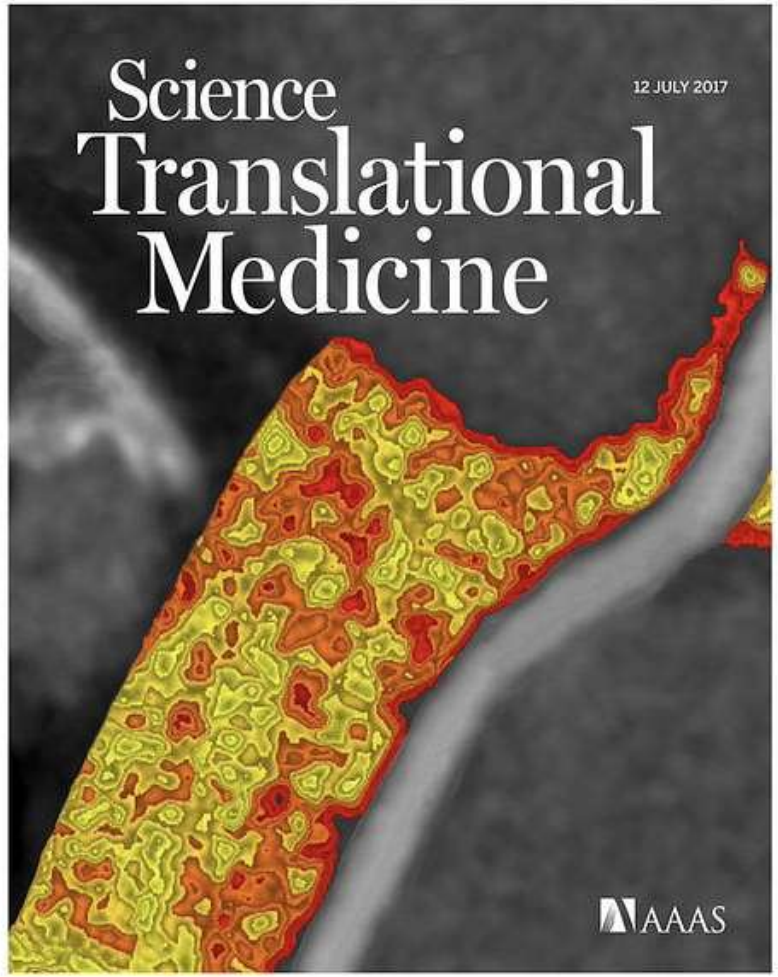
Diabetes

Obesity and metabolic syndrome

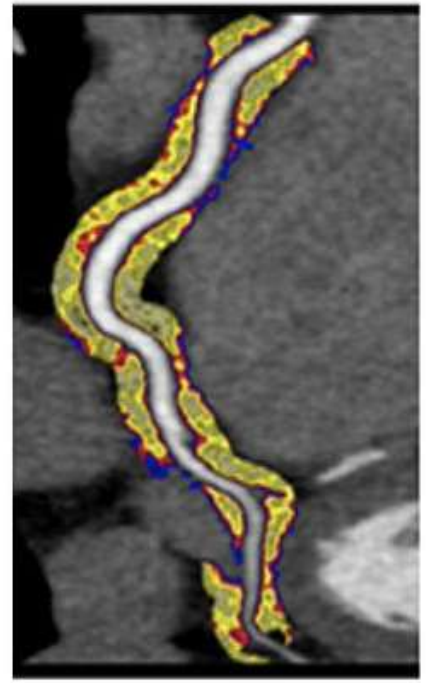
Perivascular fat inflammation (CTA FAI)

Chronic immune activation

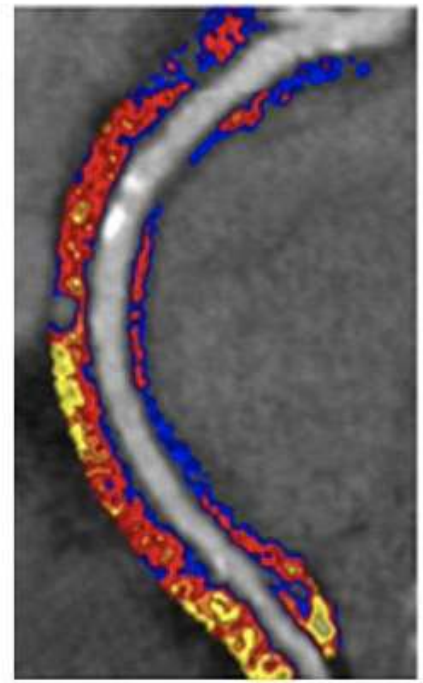
Inflammation links the plaque to the patient's overall cardiovascular risk



Inflammation in Heart Arteries Without A Narrowing or Obstruction



Low FAI Score



High FAI Score

FAI is the fat attenuation index, using A.I. to gauge the extent of inflammation in the epicardial artery fat tissue that surrounds the artery

JACC
VOL. ■, NO. ■, 2025

PUBLISHED BY ELSEVIER

ACC SCIENTIFIC STATEMENT

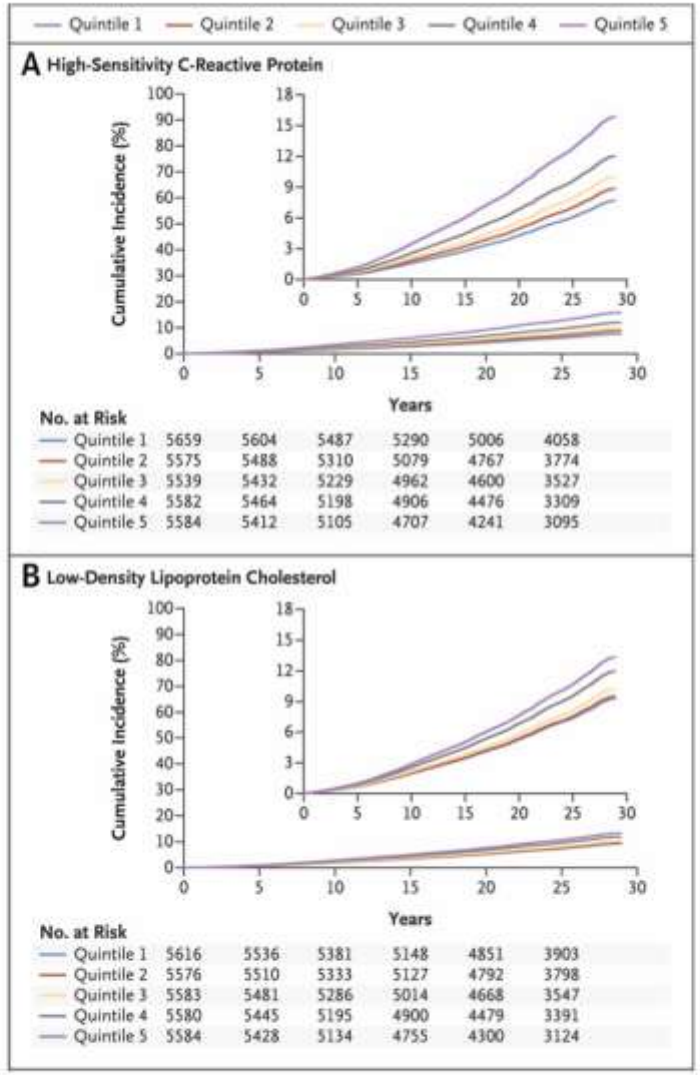
Inflammation and Cardiovascular Disease: 2025 ACC Scientific Statement

A Report of the American College of Cardiology

Writing Committee Members

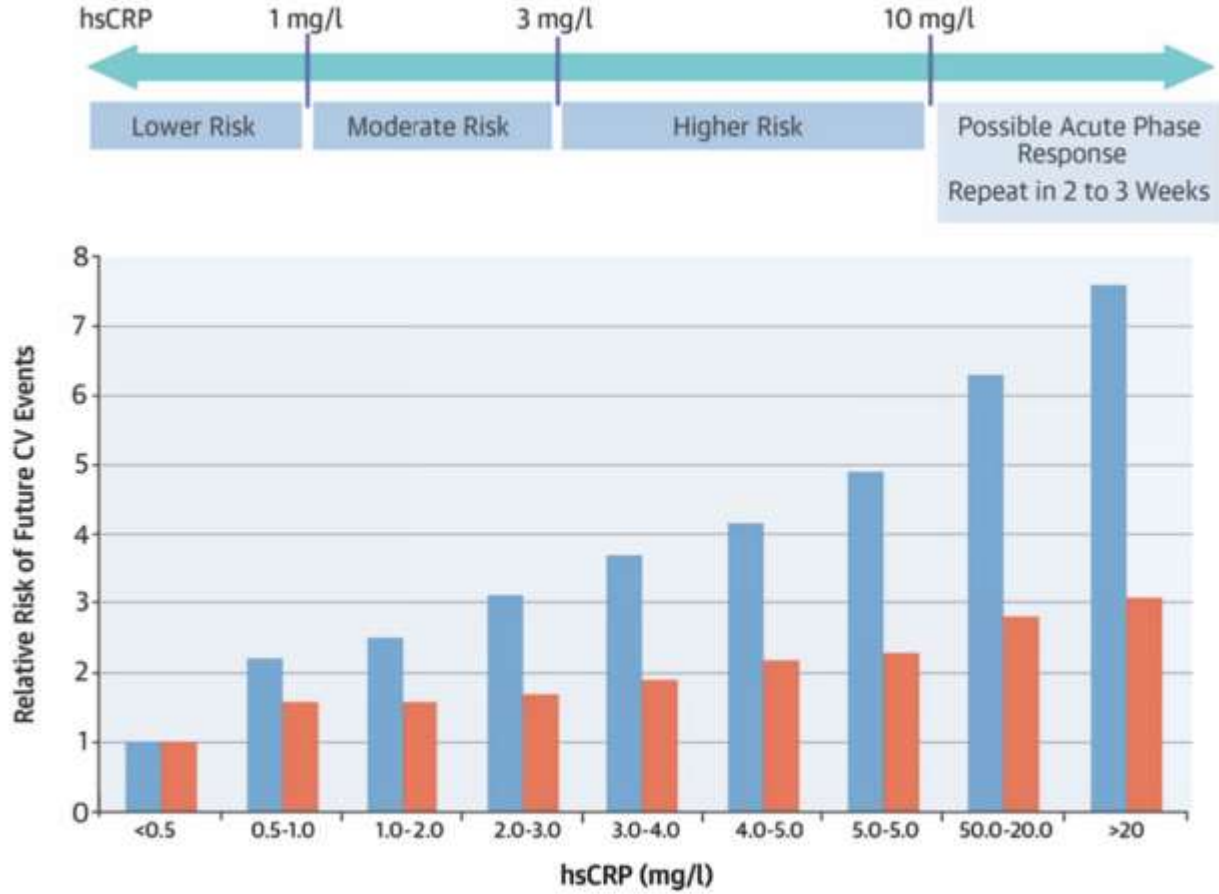
George A. Mensah, MD, FACC, *Chair*
Natalie Arnold, MD
Sumanth D. Prabhu, MD, FACC
Paul M Ridker, MD, MPH, FACC
Francine K. Welty, MD, PhD, FACC

FIGURE 2 Cumulative Incidence of First Major Cardiovascular Events According to Baseline Levels of hsCRP and LDL-C



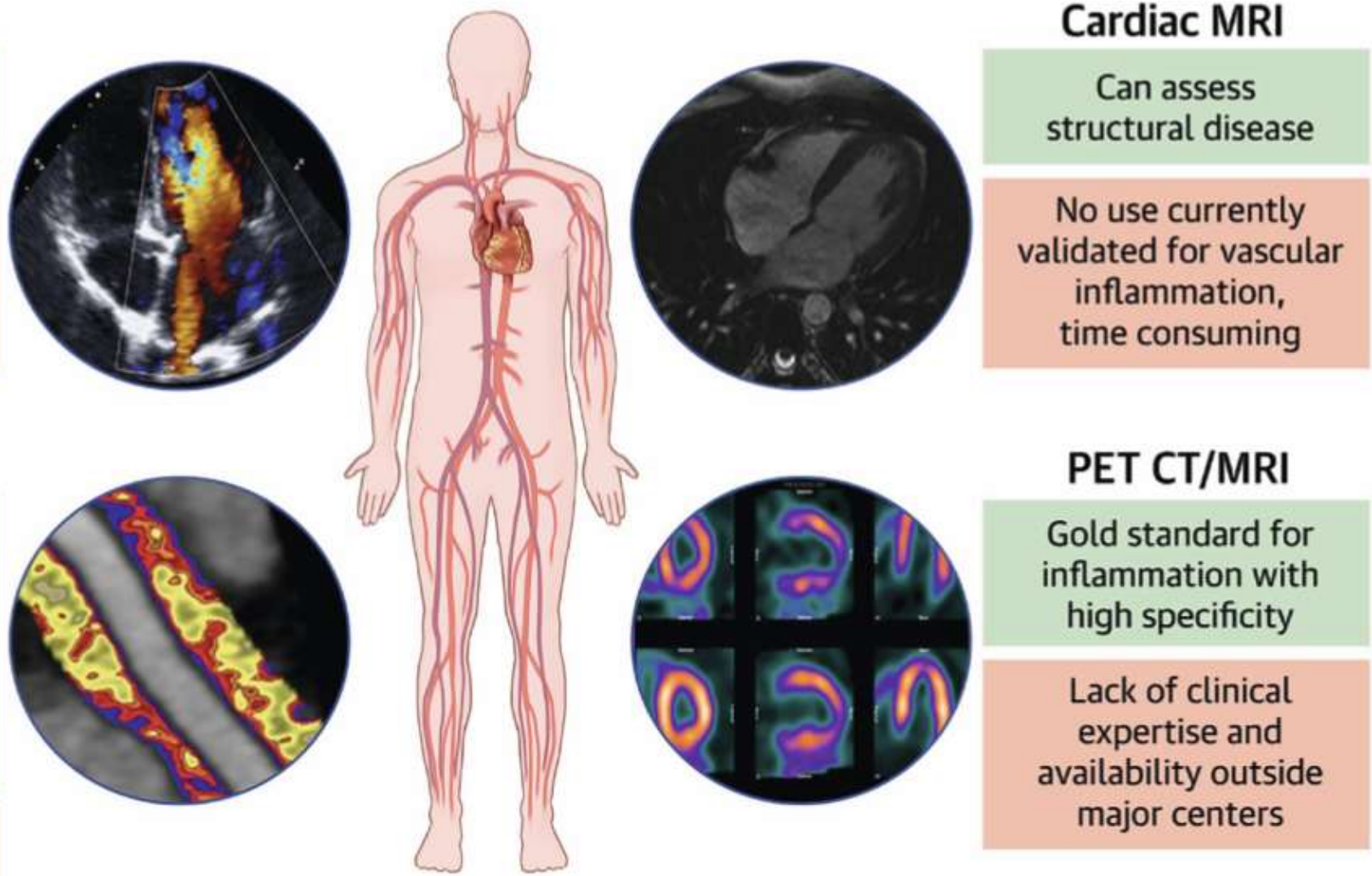
30-year HRs and cumulative incidence for first major adverse cardiovascular events among 27,939 initially healthy American women, according to increasing quintiles of baseline level of low-density lipoprotein cholesterol (LDL-C) (bottom) and high-sensitivity C-reactive protein (hsCRP) (bottom). As shown, the magnitude of risk is greater for inflammation than for cholesterol. Data are adjusted for age, smoking status, diabetes, blood pressure, estimated glomerular filtration rate, and body mass index. Adapted with permission from Ridker et al.[26]

FIGURE 1 Clinical Interpretation of hsCRP for Cardiovascular Risk Prediction



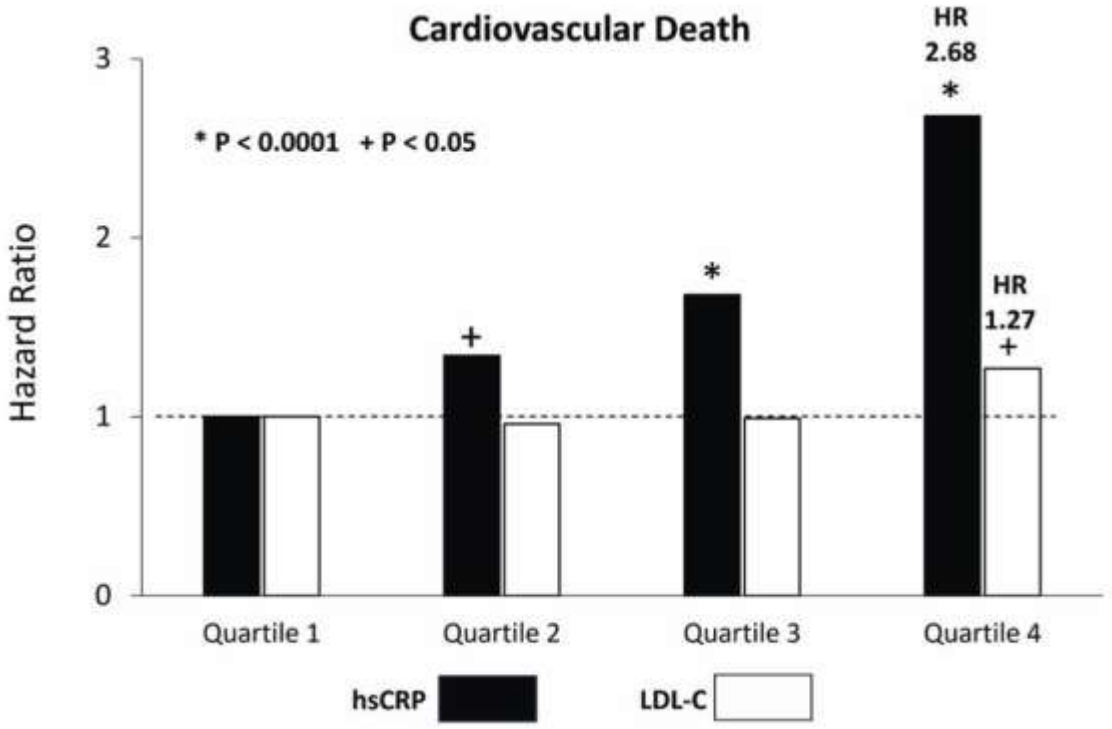
The relationship of inflammation to cardiovascular (CV) risk is linear across a wide range of high-sensitivity C-reactive protein (hsCRP) values. Blue bars represent crude relative risks; red bars represent relative risks adjusted for traditional Framingham Risk Score factors. Data from Ridker et al.[28] Reproduced from Ridker et al.[23]

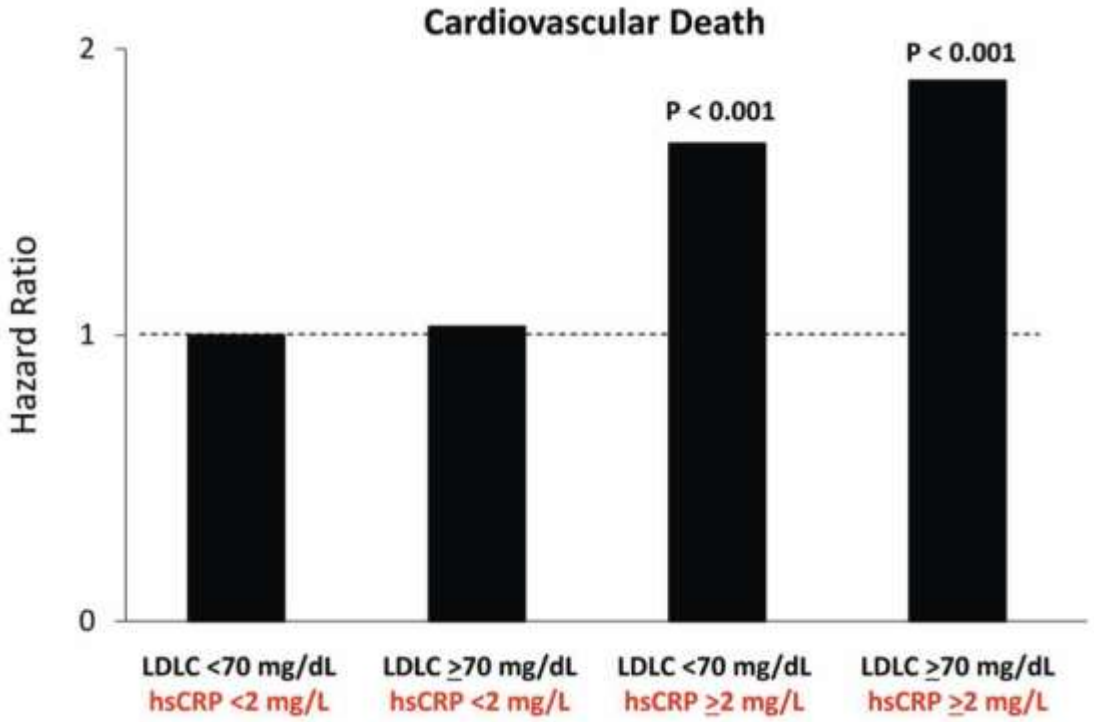
FIGURE 3 **Imaging Modalities to Detect Vascular Inflammation**



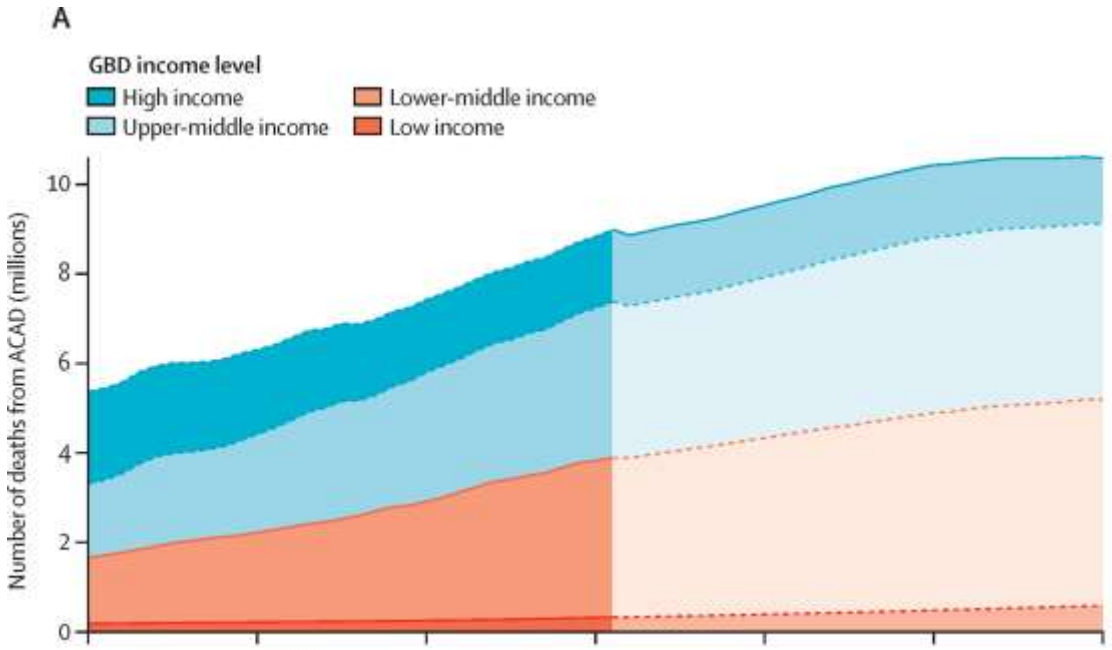
Summary of the clinical imaging modalities in use or under development for the noninvasive detection of vascular inflammation. Reproduced with permission from West et al.[30] CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.

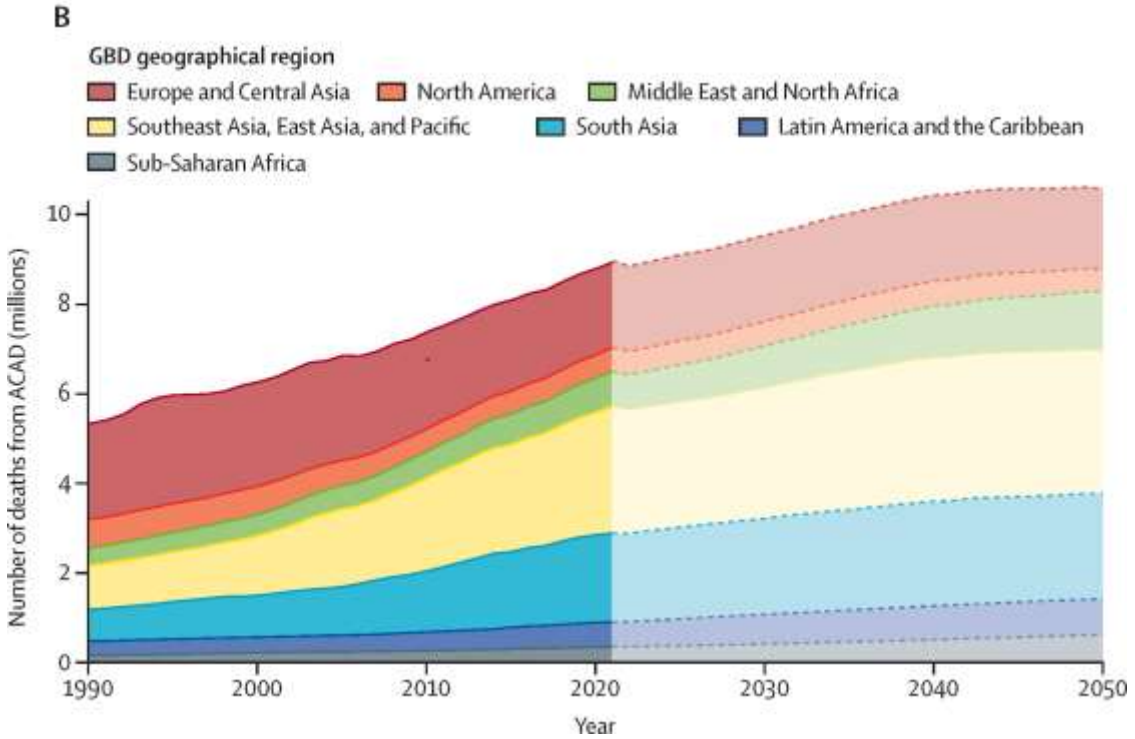
Residual Inflammatory Risk as Assessed by hsCRP and Residual Cholesterol Risk as Assessed by LDL Cholesterol as Predictors of Future Cardiovascular Events and Death

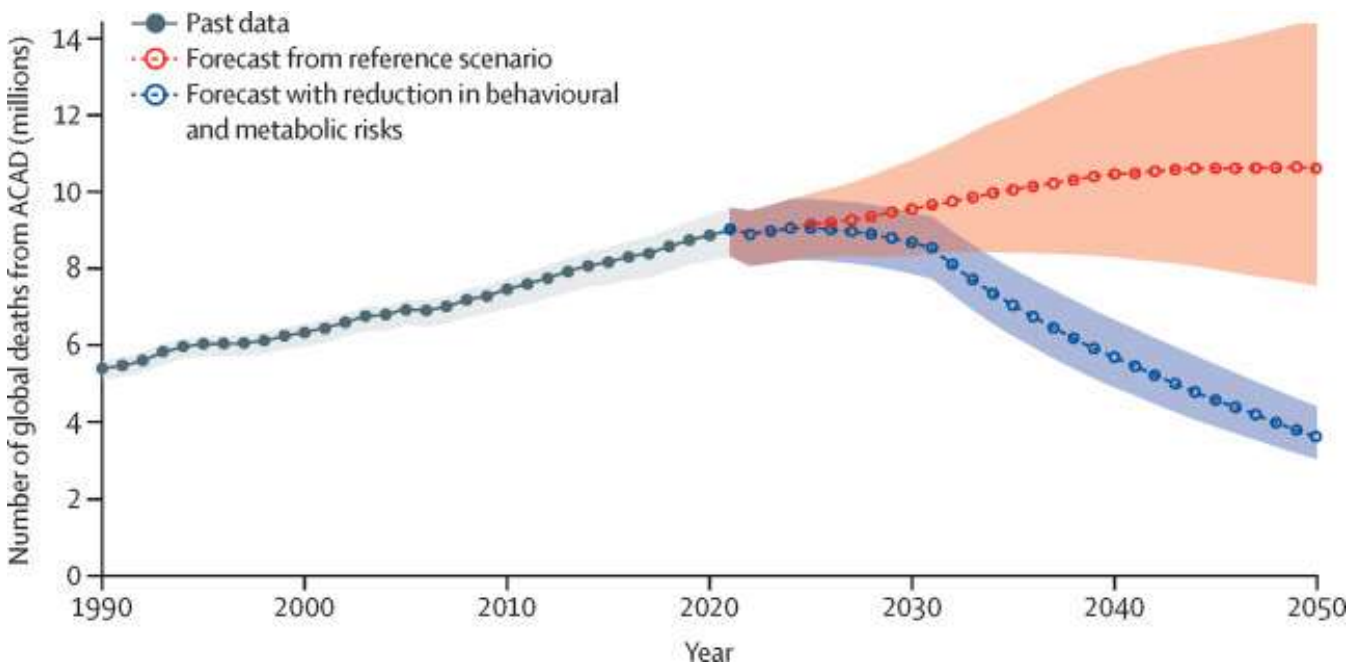




- Following statin therapy, risks of cardiovascular death are greater for individuals with increasing levels of high-sensitivity C-reactive protein (hsCRP) (black) than for individuals with increasing levels of low-density lipoprotein (LDL) cholesterol (white).
- Following statin therapy, risks of cardiovascular death are high among those with elevated hsCRP and low LDL cholesterol, but conversely low among those with low hsCRP and elevated LDL cholesterol *Ridker et al*





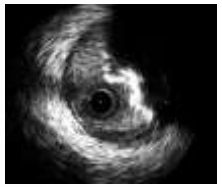


"The time is also ripe for the development of strategies to promote increased physician awareness of the crucial role of inflammation in CVD and accelerate the adoption of evidence-based, guideline-directed anti-inflammatory therapy through dissemination and implementation research."

Modern Coronary Imaging: Seeing the Biology

IVUS

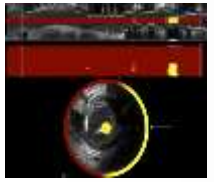
- Determines plaque burden
- Identifies remodeling
- Useful in diffuse disease



OCT

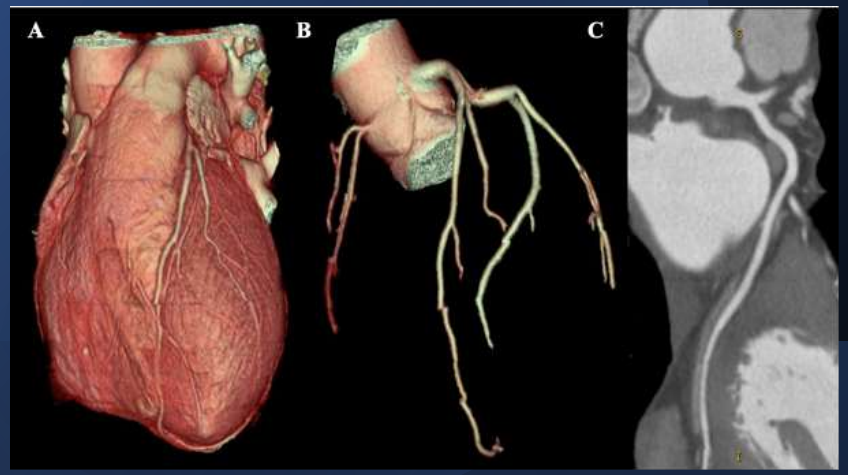
- Measures **fibrous cap thickness**
- Detects macrophages, microchannels
- Best for detailed structural assessment

NIRS



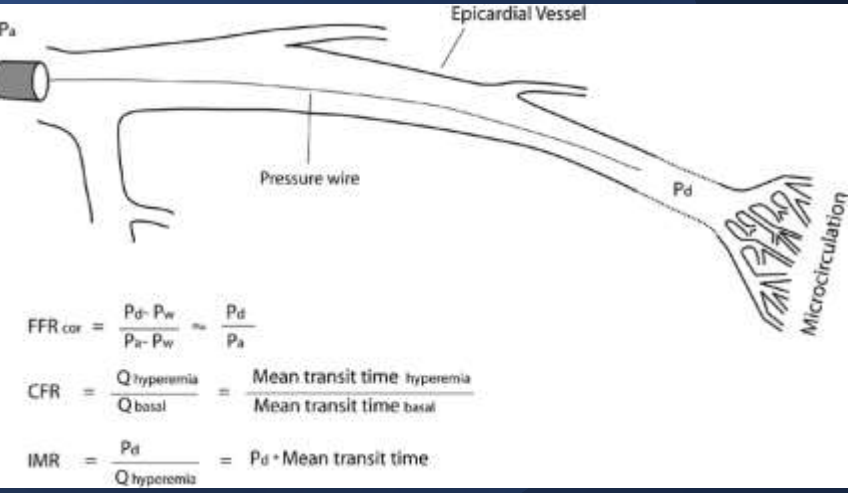
- Quantifies lipid core burden (LCBI)
- LCBI > 400 → strong predictor of future events

CTA as the First-Line Biological Tool



- Non-invasive plaque characterization
- Identifies non-calcified plaque
- Measures perivascular inflammation (FAI)
- AI-enhanced CTA rivals invasive insights in early detection

Physiology: The Other Dimension



FFR / iFR / NHPR / CRR

FFR: pressure-based ischemia assessment

iFR/NHPR: resting physiology, wire-based alternative

CRR: coronary resistance reserve → microvascular function

Physiology determines **whether the lesion is flow-limiting**

Imaging = *what it is*, physiology = *what it does*

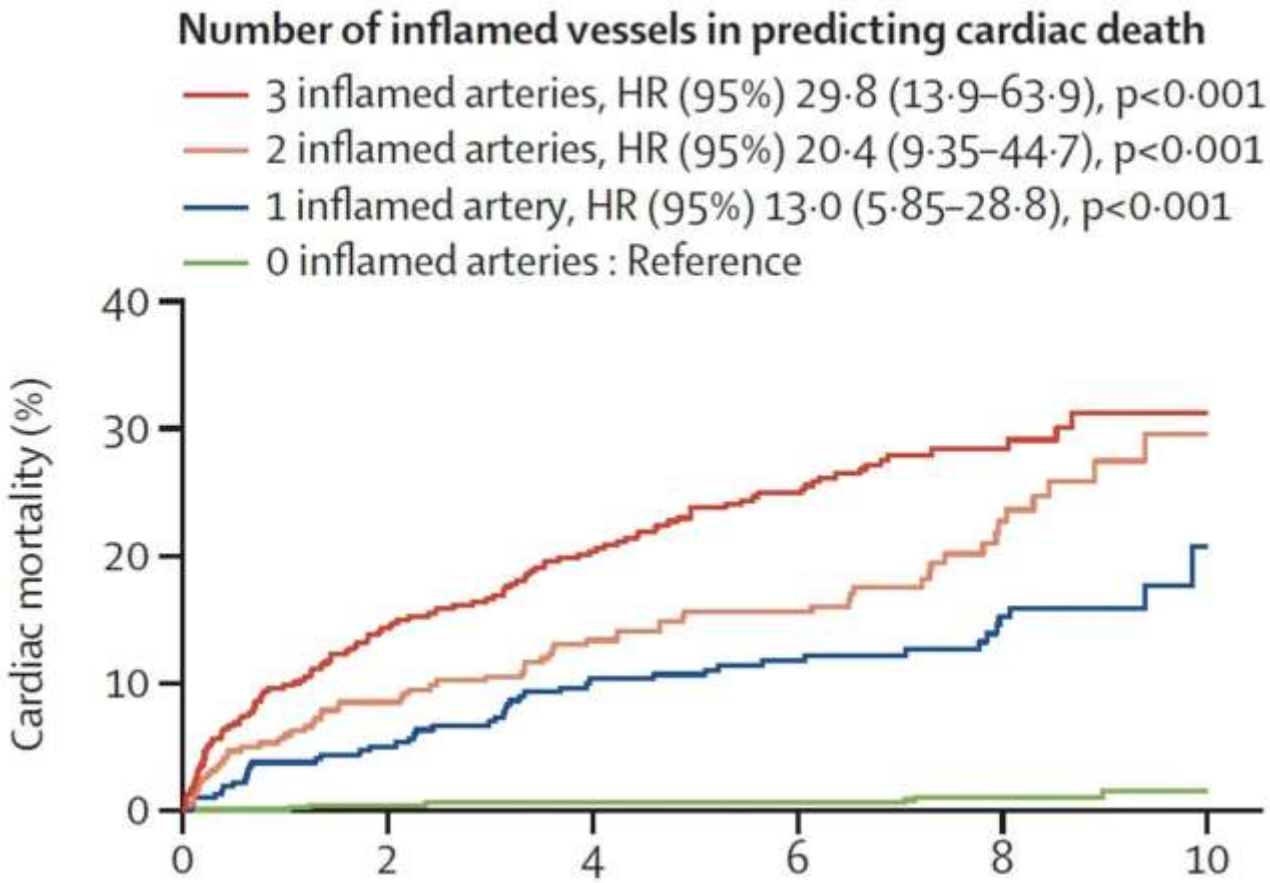
Non-Invasive Coronary Imaging With A.I.

A.I. Imaging Company	Focus	Biomarker	Reference marker(s)	Clinical Validation Studies
CLEERLY	Plaque Morphology	Total Plaque Volume, Low-Density Non-Calcified Plaque	IVUS, QCA, FFR	Griffin, JACC CV Imaging, 2023
ELUCID	Plaque Composition	Lipid Rich Necrotic Core	Histology, Invasive FFR	Histology; None with clinical events
CARISTO	Coronary Inflammation	FAI, Perivascular inflammation	Cardiac mortality	Chan, Lancet 2024
HEARTFLOW	Ischemia; Computational Fluid dynamics	3D Plaque Quantification, FFR	Invasive FFR	Madsen, Radiology 2023

FFR-fractional flow reserve, QCA-quantitative coronary angiography, IVUS-intravascular ultrasound, FAI-fat attenuation index

Data from 40,000 consecutive patients with CCTA in 8 centers in the UK with up to 10-year follow-up using the **CARISTO FAI**.

Even 1 inflamed artery raised the risk of death 13-fold compared with no inflamed arteries!



THE LANCET

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Inflammatory risk and cardiovascular events in patients without obstructive coronary artery disease: the ORFAN multicentre, longitudinal cohort study

Kenneth Chan, MRCP [a,b,†] · Elizabeth Wahome, PhD [a,†] · Apostolos Tsiachristas, PhD [c] · Alexios S Antonopoulos, PhD [a] · Parijat Patel, BSc [a] · Maria Lyasheva, MPhil [a] · et al. Show more

Imaging + Physiology = Complete Cardiac Decisions

Only combined imaging and physiology features enable truly optimal cardiac treatment decisions.

Feature Pair		Decision Impact		
Imaging Feature	Physiology Feature	Decision Value	Optimal Outcome	Treatment Example
Plaque composition	Ischemia presence	Complete	✓	Targeted stenting of culprit lesion
Cap thickness	Flow limitation	Complete	✓	Risk assessment for rupture and intervention
Lipid load	Microvascular involvement	Complete	✓	Microvascular angina management
Inflammation	Functional significance	Complete	✓	Anti-inflammatory therapy guidance

1. Complete = Both features used
2. Optimal Outcome = Best possible patient result

AI: The Integrating Intelligence Layer

AI Applications:

- **AI-CT (Cleerly):** quantifies plaque types & volumes
- **Caristo FAI:** quantifies coronary inflammation
- **AI-OCT:** automated cap thickness & macrophage detection
- **AI-FFR (CT-FFR, Angio-FFR):** physiology without wires

Key message:

- **AI connects anatomy, biology, and function into a cohesive risk map.**

PULSE MEDICAL

μFR®

AngioPlus® Core
Quantitative Flow Ratio Analysis Software

Non-invasive
Free of hyperemic agent & wire

Automated
AI enpowered more intelligent

Simple
Single/two views based higher feasibility

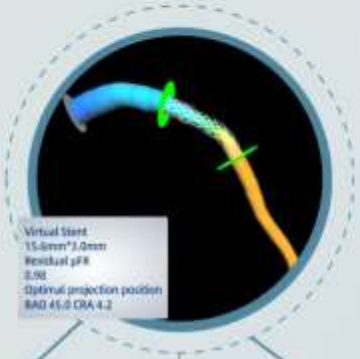
More
RWS*, main vessel & side branches & microcirculation

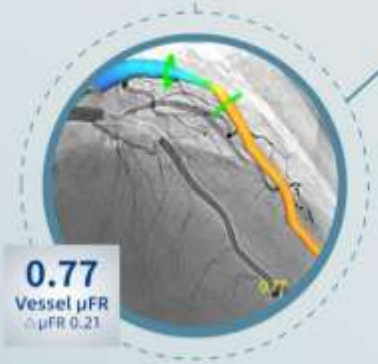
Pre-PCI
DECISION MAKING

- OMT, PCI or CABG
- μFR® can identify significant flow-limited lesions/vessels
- ΔμFR® can identify culprit lesions

Post-PCI
OUTCOME EVALUATION

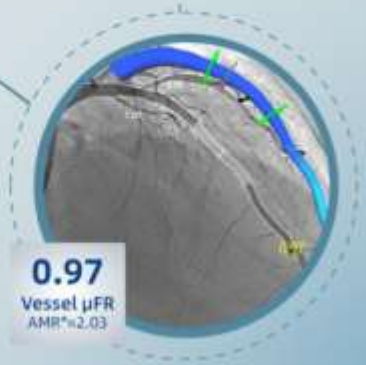
- Post-PCI μFR® can identify suboptimal revascularization and predict prognosis
- Post-PCI AMR* can evaluate microvascular function



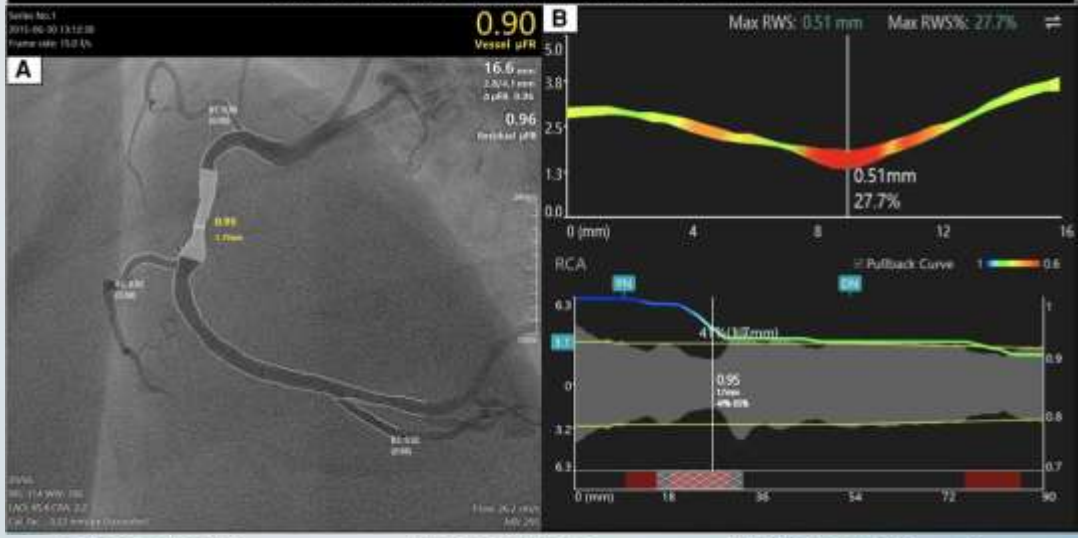


Intra-PCI
STRATEGY OPTIMIZATION

- Recommended stent location, stent length & diameter, and No. of stents
- Residual μFR® can predict post-PCI outcomes
- Recommended angiographic view with minimum foreshortening

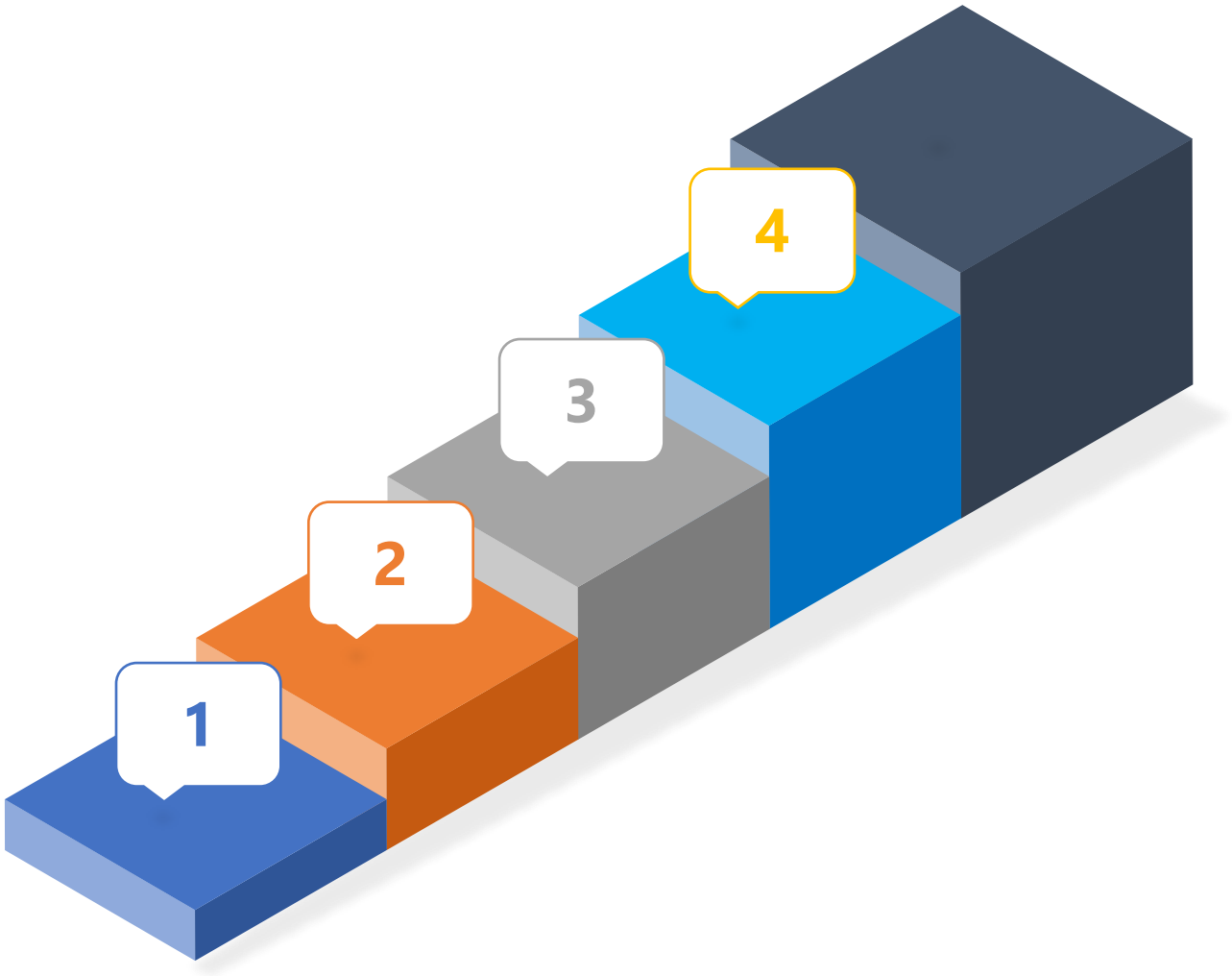


PHYSIOLOGY AND VULNERABILITY COMPUTATION



FAVOR II China	FAVOR III China	FAVOR III China-2yr
92.7%	**35%**	**34%**
Accuracy	**MACE risk reduction**	**MACE risk reduction**
Fast real-time analysis Good correlation & agreement with FFR.[1]	Less contrast used, less radiation exposure, shorter procedural time.[2] Significant outcome improvement.	The benefit of AngioPlus-guidance were incrementally increasing benefit over time.[3]
Released at TCT 2017,published at JACC	*Released at TCT2021, published at LANCET*	*Released at TCT2022, published at JACC*

The New Diagnostic Paradigm



Step 4 — Precision therapy
- Maximal LDL lowering
- Anti-inflammatory therapies
- PCI only when physiology & imaging both support intervention
- Long-term imaging follow-up

Step 3 — Physiology (FFR/iFR/CRR)
Determine flow limitation and microvascular contribution

Step 2 — Catheter-based imaging (OCT/IVUS/NIRS)
Assess vulnerability + plaque morphology

Step 1 — CTA + AI for plaque & inflammation mapping
Identify diffuse, non-calcified, high-risk plaques

Patients Have More Choices To Tackle High Cholesterol

Researchers present latest study results of alternatives beyond statins that are on the horizon

By Betsy McKay

A statin isn't the only answer anymore to lowering cholesterol.

The lipid-reducing medicines, among the most widely prescribed drugs in the U.S., have been a mainstay of heart-disease prevention and treatment for decades. But they don't work for everyone, and can only reduce harmful "bad" cholesterol so much.

Now some patients have other cholesterol-busting medicines available as options—and even more alternatives are on the horizon.

Certain patients already can take a twice-yearly injection, sold by **Novartis** as Leqvio, that uses an RNA-based technology, or a more frequent injection that targets a protein called PCSK9 that interferes with the body's ability to clear the bad form of cholesterol.

Biotech **Amgen** has been doing testing to expand use of its PCSK9 drug Repatha to more patients, while **Merck** is developing an easier-to-take pill version. Biotechs are working on therapies that use gene-editing technology to lower people's cholesterol, perhaps permanently.

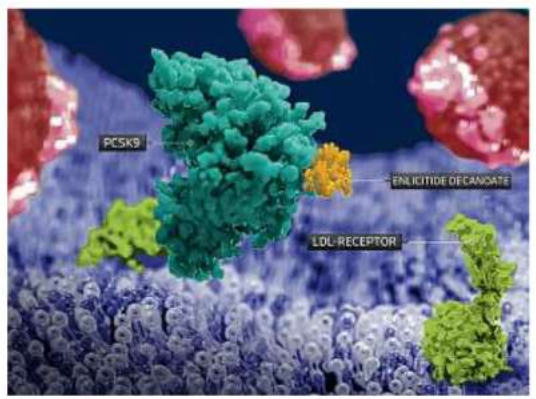
Researchers presented the latest study results recently at the American Heart Association's annual meeting.

"This is an amazing time, a very, very exciting time for patients," said Dr. Leslie Cho, cardiologist and director of the Cleveland Clinic Women's Cardiovascular Center, who wasn't involved in the latest studies. She cautioned, however, that most patients can be helped by diet, exercise and statins, and some of the newer therapies can be very expensive.

In a late-stage study, Merck's PCSK9 pill reduced bad, or LDL, cholesterol up to 60% over six months in adults with or at risk of atherosclerotic cardiovascular disease, researchers reported.

Amgen's PCSK9 drug, Repatha, reduced the risk of heart disease, stroke and other cardiovascular events by 25% in a large Phase 3 study of subjects taking a statin and at high risk of an event but haven't had one.

An early, or Phase 1, study found that a gene-editing drug from **CRISPR Therapeutics** cut cholesterol levels by 49% in two months in patients who received the highest dose, study investigators reported. The study included 15 patients.



Clockwise from top, CRISPR Therapeutics' lab in Boston; an image showing Merck's enlicitide decanoate; Amgen is conducting tests to expand use of Repatha.

The therapy also reduced levels of triglycerides, a type of fat in the body, by 55%. The therapy uses so-called Crispr-Cas9 technology to knock out a cholesterol-promoting gene called ANGPTL3 that pushes up levels of cholesterol and triglycerides.

The goal is to offer a "one and done" therapy, said Dr. Luke Laffin, a preventive cardiologist at the Cleveland Clinic and lead author of the study, published in the New England Journal of Medicine.

While it is still early, "ultimately technologies like this will likely play a role in supplanting every two weeks injections and taking daily pills," he said.

High cholesterol is a major driver of heart disease. Statins, like Lipitor and Zocor, emerged as powerful antidotes starting in the 1980s. With blood-pressure medicines, antismoking campaigns and advances in treating heart attacks, the medicines contributed to a sharp decline in heart-disease deaths.

Yet those declines stalled nearly a decade and a half ago, and heart disease is still the nation's biggest killer.

More than a quarter of Americans have levels of LDL cholesterol that are considered high—130 milligrams per deciliter—according to the most recent data from AHA. Doctors generally recommend that people at high risk of a heart attack or stroke keep their LDL cholesterol less than 70 mg/dL, and those at very high risk keep it below 55 mg/dL. People at very high risk have had a heart attack or stroke and have multiple high-risk conditions like hypertension, diabetes or are age 65 or older.

"Often statins are not enough," said Dr. Jamal Rana, a cardiologist and professor of clinical science with Kaiser Permanente in Oakland, Calif.

Because statins don't reduce cholesterol levels low enough in certain high-risk patients, Rana adds other medicines to their prescriptions like the pill Zetia that also goes by the generic name ezetimibe, a PCSK9 drug or Leqvio, also known as inclisiran.

A little over half of people who could benefit from a cholesterol medicine are on one, according to the Centers for Disease Control and Prevention. Many quit within a year of starting a statin. Some drop off due to side effects like muscle pain or headaches.

Mary-Ellen Conway, 78, of Houston, has taken two statins over several years but got leg cramps taking one, while her LDL cholesterol levels were higher than she wanted on the other medicine.

Her LDL cholesterol has dropped significantly while a subject in the Phase 3 study of Merck's experimental PCSK9 pill. Her LDL cholesterol at last check was 35 mg/dL. It had been 166 mg/dL in 2003, and 62 mg/dL in 2024, when she took a statin and another drug.

The adults in Conway's trial also took statins. Merck said its drug, called enlicitide decanoate, is now being studied to see how effective it is at preventing heart attacks and strokes, with results expected in a couple of years. Merck said it plans to file for FDA approval early next year.

No serious side effects were reported among the 15 patients in the trial of CRISPR Therapeutics' experimental therapy, called CTX310.

Such gene-editing therapies must be tested in thousands more patients to assess their effectiveness and safety, said Dr. Kiran Musunuru, cardiologist, geneticist and professor for translational research at Penn Medicine, who wasn't involved in the CRISPR Therapeutics study.

A subject in a trial of a different gene-editing therapy died a few days ago, according to biotech **Intellia Therapeutics**. Studies testing the drug are now on hold.

Musunuru expects gene-editing therapies will become available by the 2030s and provide permanent and more targeted treatment to certain patients depending on the genetics of their conditions. "In my opinion, the more options, the better," he said.

CLOCKWISE FROM TOP: CRISPR; MERCK; AMGEN

New Drugs for Heart Health

PCSK9 Blockers
Potent oral drugs that lower cholesterol levels.

Lp(a) Inhibitors
Drugs that target lipoprotein(a), a risk factor for heart disease.

ANGPTL3 Blockers
Drugs that lower triglyceride levels and improve lipid profiles.

Anti-inflammatory Drugs
Interleukin blockers and GLP-1 drugs that reduce inflammation.

Missed Innovations in Heart Risk

Many validated heart risk tools remain underused in clinical practice.

Current Gaps

Missed Opportunities

Many validated tools not yet routine in heart risk assessment

10+ PRS Providers

Multiple companies offer validated PRS tests

Limited Health System Uptake

PRS not yet in general clinical use

Polygenic Risk Scores

CAD PRS

PRS value is independent of family history or classic ris...

Unique insight

No CHIP Assay

CHIP linked to CVD, but not routinely tested

Retina Imaging

OCT or photo can reveal subclinical atherosclerosis

Protein Organ Clocks

Quantify artery & heart aging pace

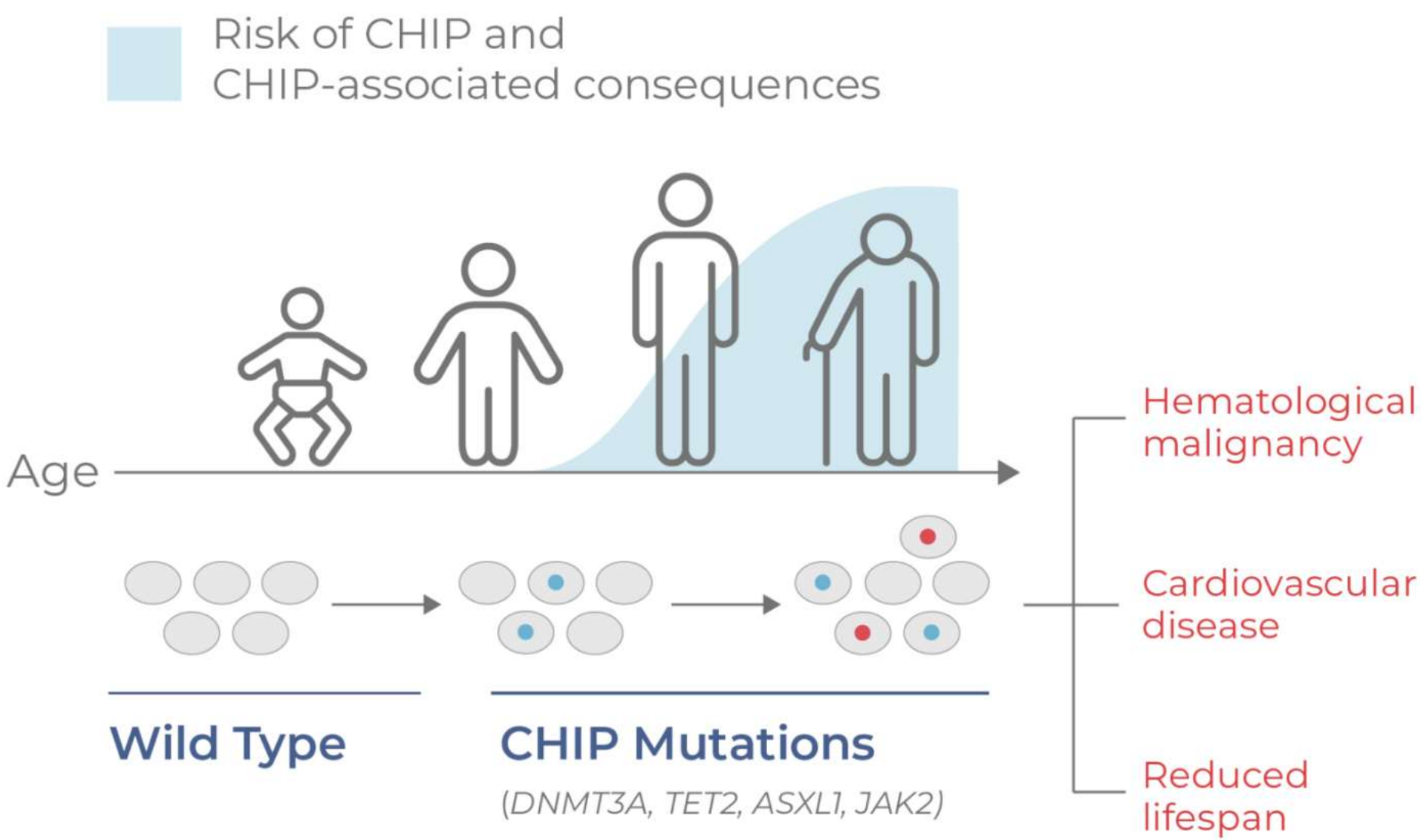
Inflammation Markers

hs-CRP rarely measured in practice

A.I. Heart Attack Prediction

AI can predict risk from eye images

1. PRS = Polygenic Risk Score
2. CHIP = Clonal Hematopoiesis of Indeterminate Potential


Risk of CHIP and
CHIP-associated consequences
Age
Wild Type
CHIP Mutations
(DNMT3A, TET2, ASXL1, JAK2)
Hematological malignancy
Cardiovascular disease
Reduced lifespan

JAMA Cardiology

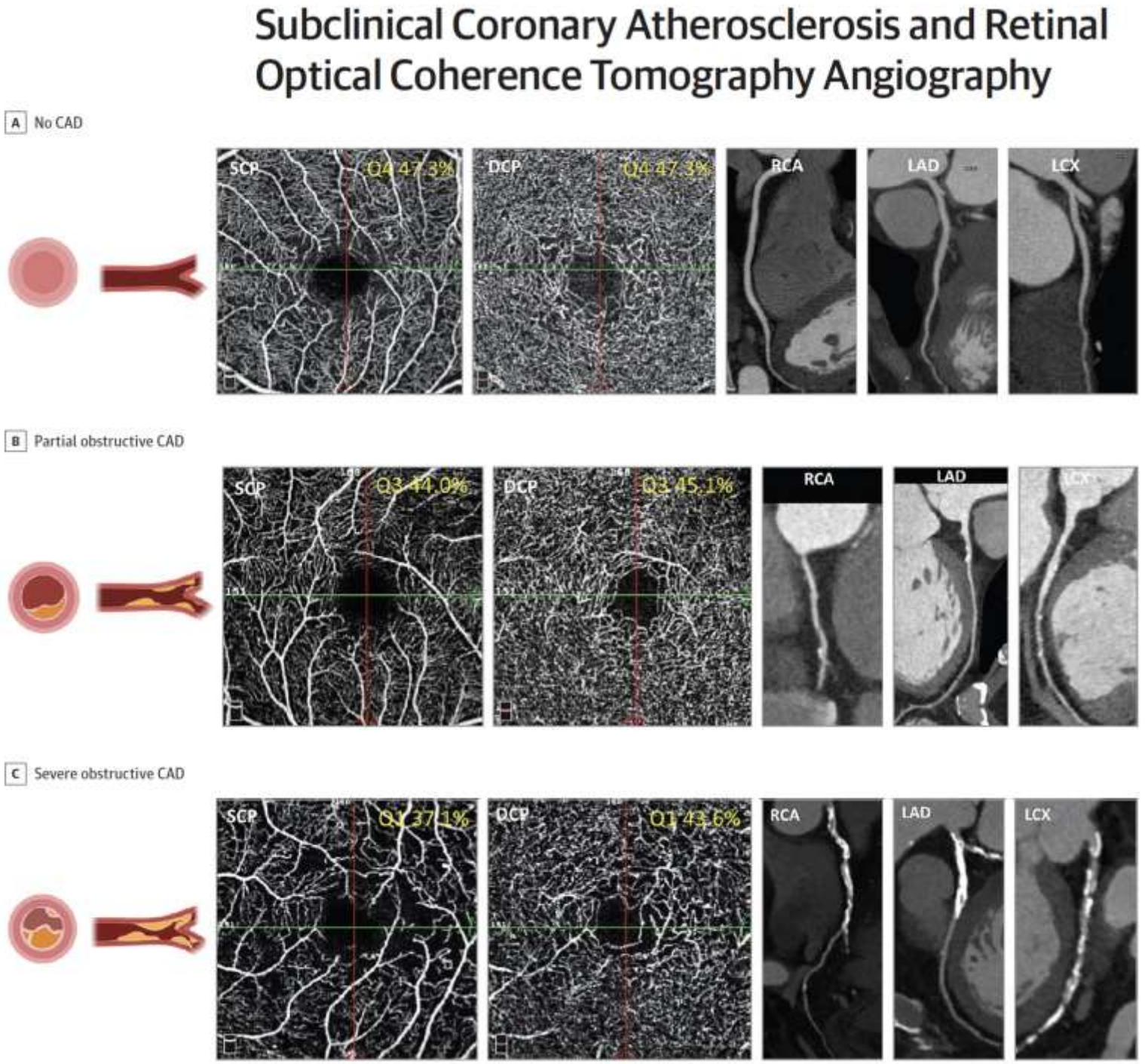
Original Investigation

Subclinical Coronary Atherosclerosis and Retinal Optical Coherence Tomography Angiography

Jee Myung Yang, MD, PhD[1]; Dong Hyun Yang, MD, PhD[2]; Seung-Whan Lee, MD, PhD[3] ; et al

Author Affiliations | Article Information

"Our results indicate that one could identify patients at high risk of future myocardial infarction from retinal imaging available in every optician and eye clinic."



ESC guidelines for Coronary Artery Disease

1 Clinical examination

Initial clinical data (Medical history, vitals labs, ECG)

2 Calculation of Clinical Likelihood for obstructive CAD

Cardio Explorer

3 Guidelines Recommendations for diagnostic pathway

Clinical likelihood		
Very low	≤5%	Defer further testing
Low	>5–15%	Rule out OR Adjust clinical likelihood
Moderate	>15–50%	CCTA
High	>50–85%	PET/SPECT, CMR, Stress ECHO
Very high	>85%	Invasive coronary angiography

4 Treatment

Cardio Explorer: Closing the Diagnostic Biomarker Gap

Single markers

ECG

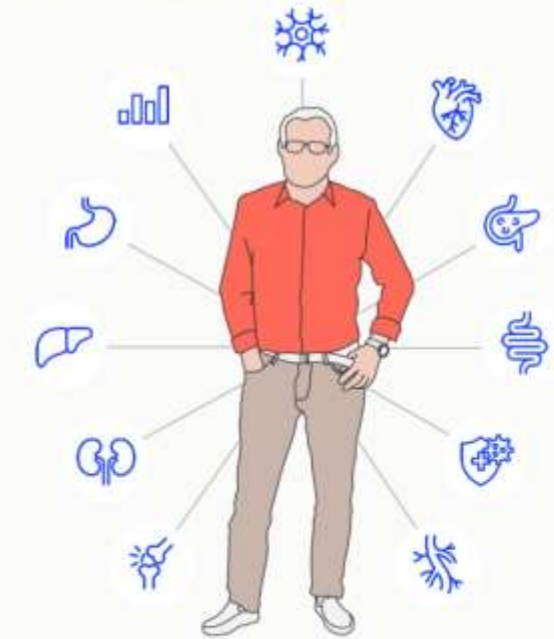
LDL

...

Piecemeal

- Focus on **isolated issues**
- **CAD complexity missed**
- **Informed guessing** if CAD is present or not

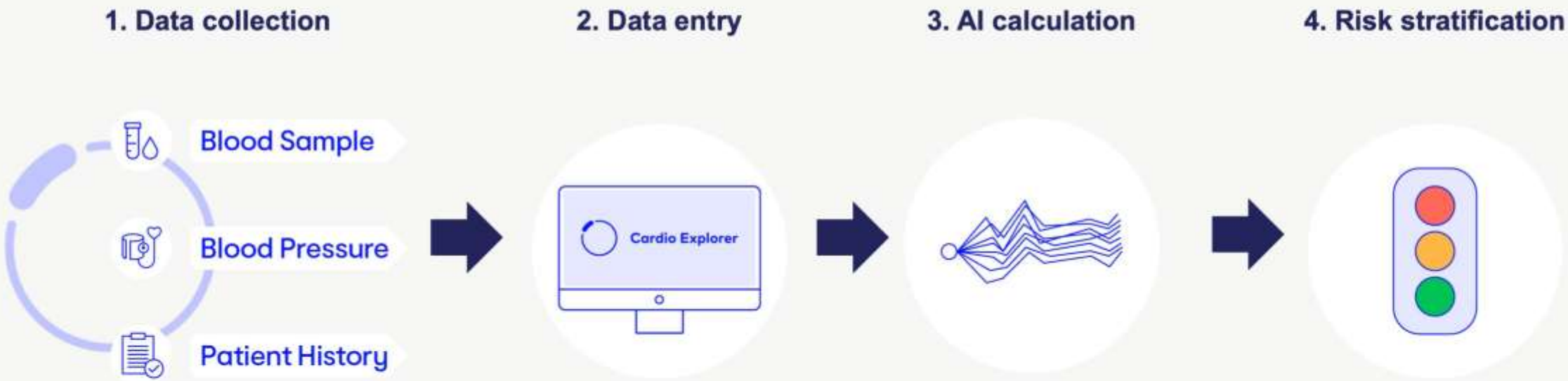
Cardio Explorer



Holistic

- **Right underlying multi-marker combination** discovered with AI to capture complex interactions
- **Personalized diagnosis** with dynamic weighting of each marker
- **Standardized** for all healthcare professionals

From Data collection to Risk Stratification



Data Collection

Symptoms & History

Collected during consultation. Includes chest pain characteristics, smoking status, and ECG findings.

Clinical Parameters & Medications

Entered by the physician or imported from the record. Includes blood pressure, BMI, diabetes therapy, and prescribed medications such as statins and antihypertensives.

Blood panel

Uploaded from lab systems or entered manually. Includes key biomarkers such as Hs-troponin T, cholesterol, and liver function markers.

Anamnesis

- Age, years
- Sex
- Height, cm
- Weight, kg
- Chest pain
- Nicotine consumption (NC)

Medication

- Diabetes
- Cholesterol-lowering agents
- Antiplatelet agents
- RAS inhibitors
- Calcium antagonist
- Beta-blocker
- Diuretics
- Organic nitrates

Examination

- Blood pressure systolic
- Blood pressure diastolic
- Resting ECG: Pathological Q w

Blood parameters

- Cholesterol (total)
- HDL
- LDL
- Bilirubin (total)
- Urea
- Uric acid
- Protein (total)
- Albumin
- Pancreatic amylase
- Alkaline phosphatase
- hs Troponin T
- ALT (GPT)
- Glucose
- Leukocytes
- MCHC

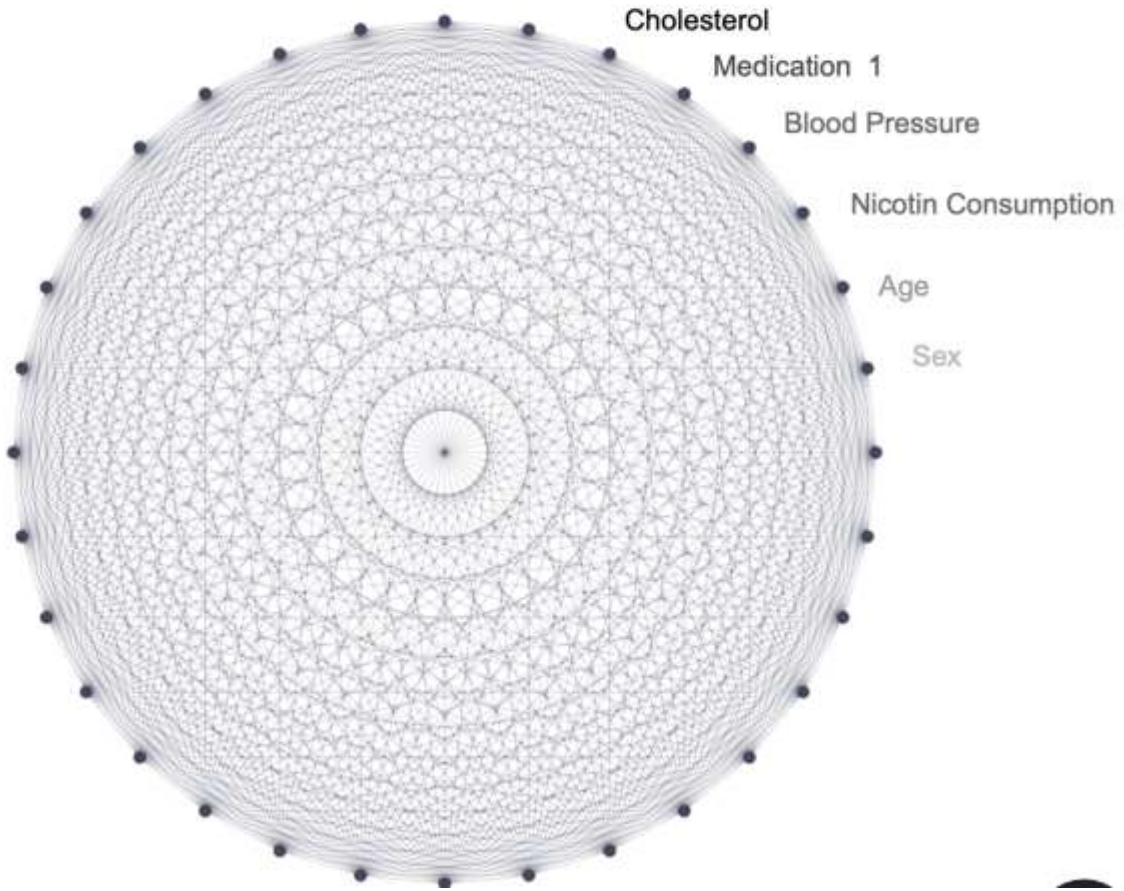
Laboratory Information System

Comprehensive Pattern Analysis leads to high accuracy

The Cardio Explorer® analyzes 32 parameters with > **4 billion possible interactions**, identifying complex, non-linear relationships that cannot be comprehended by the human brain.

By creating **personalized models** that take into account each patient's individual context, it delivers the highest precision and CT-like accuracy – based on routine clinical parameters, at a fraction of the cost and time.

Comprehensive pattern analysis with 32 parameters



Prof. Michael Zellweger
Head of Non-Invasive Cardiology, University Hospital Basel

Prof. Hans-Peter Brunner
Deputy Chair of Cardiology, Head of Heart Failure Clinic, Maastricht University Medical Centre (MUMC)

Univ. Prof. Dr. Winfried März
Director of the SYNLAB Academy

Zellweger et al. 2014[15]
Validation of the model published in the International Journal of Cardiology, hospital co-prevalence 69% AUC 0.82, NPV 94%

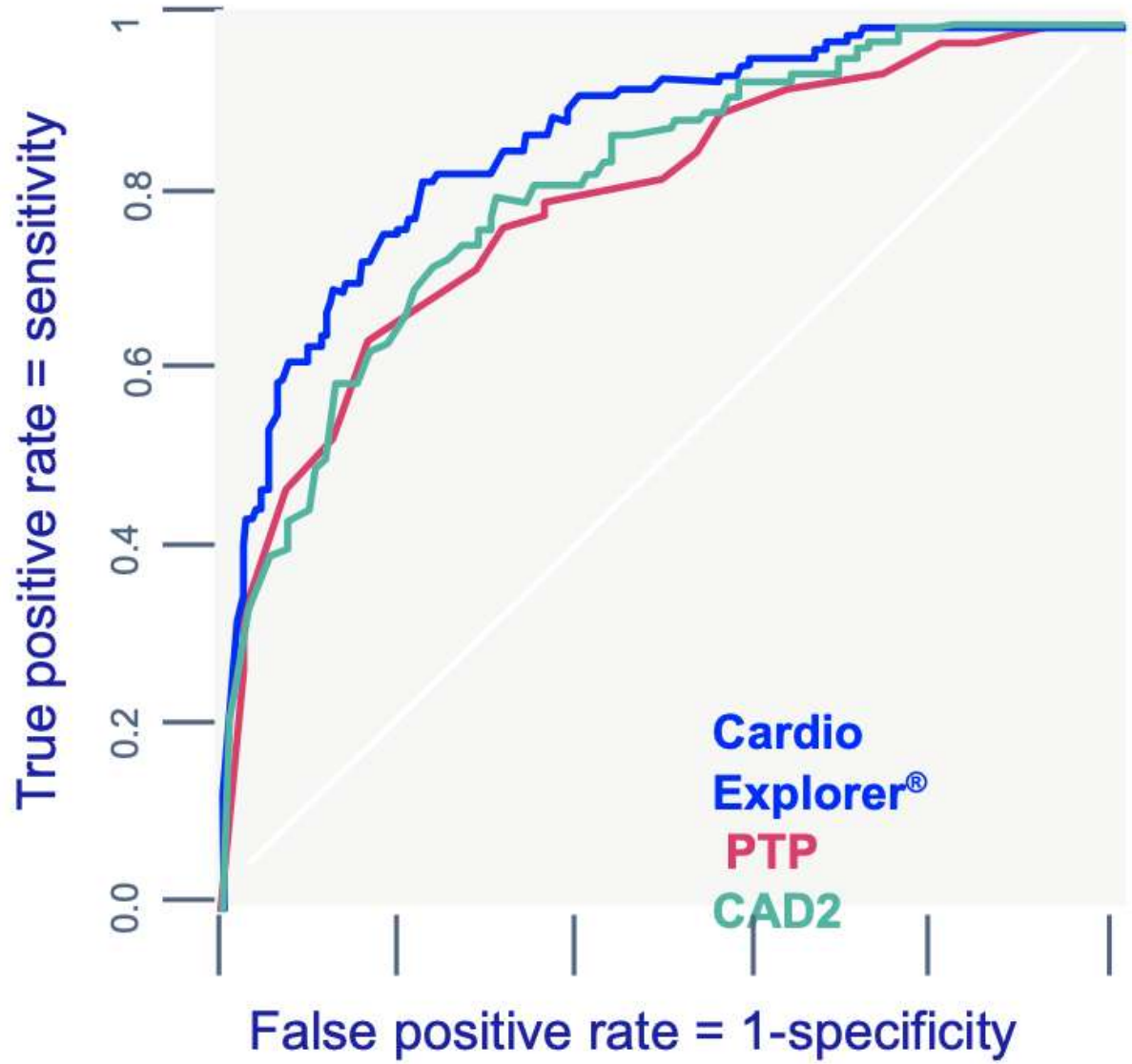
Eurlings et al. 2022[17]
Validation of an optimised model, published in BMJ Open Primary Care Cohort, prevalence 16%, AUC 0.87, NPV 96%

Zellweger et al. 2018[16]
Validation of the optimised model published in the EPMA Journal Hospital cohort, prevalence 69% AUC 0.87, NPV 95% simulated cohort, prevalence 23%, AUC 0.97, NPV 98%

Frey et al. 2023[18]
Confirmation of the optimised model, which improves the assessment of ischaemia probability prior to testing, AUC 0.76, published in the EPMA Journal

15 Zellweger et al. (2014).
16 Zellweger et al. (2018)
17 Eurlings et al. (2022).
18 Frey et al. (2023).

In the study by **Eurlings et al. (2022)[17],** Cardio Explorer achieved an AUC of 0.87, outperforming both the PTP and CAD2 models



The Future of Coronary Care

- Integration of **AI + imaging + physiology**
- Treating ***plaque biology***, not stenosis
- Earlier detection of high-risk patients
- Reduction of MI through preventive targeting
- Precision cardiology for Eastern Europe & Azerbaijan

Implementation Barriers in Our Region

The New Paradigm to Prevent Myocardial Infarction

Therapies now match the biology

- LDL lowering + Lp(a) therapies
- Anti-inflammatory treatments
- Imaging-guided interventions
- Personalized prevention strategies

The real issue is not knowledge- It is Implementation

We have the science, evidence, and tools. What is missing is the **action** to use them systematically..

Change the strategy now

Heart attacks are rarely caused by severe stenosis alone.
Risk emerges from **atheroma biology**, **inflammation**, and **patient vulnerability**

Breakthrough: Early identification

We can now detect high-risk individuals *and* high-risk plaques — long before symptoms or significant narrowing appear.

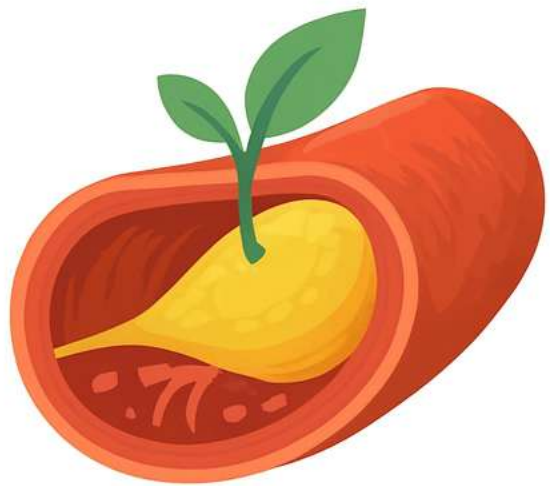
Vulnarable plaques + Vulnarable patients

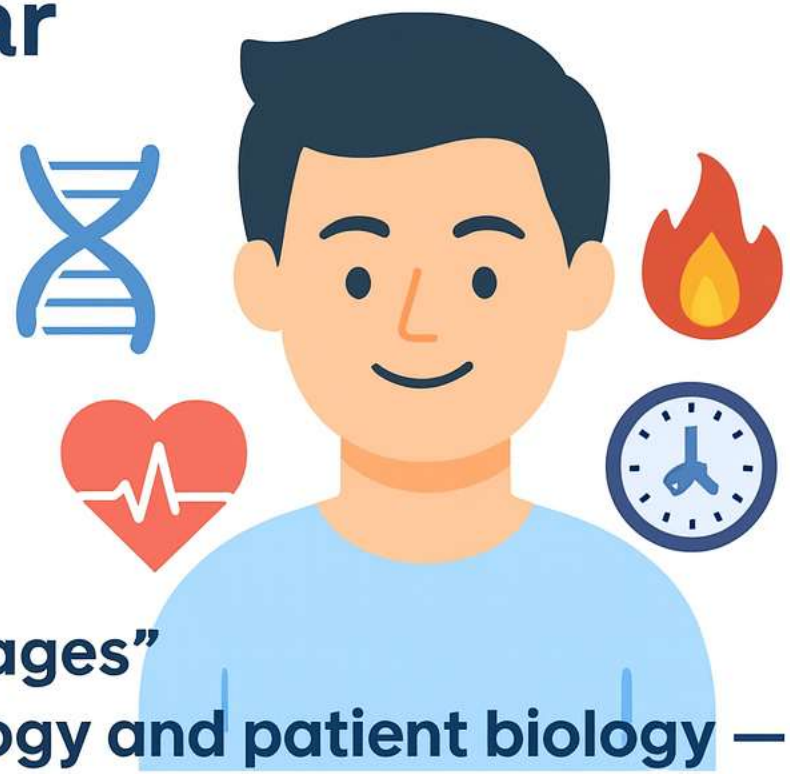
A modern risk framework integrates:

- **Genomics (PRS)**
- **Proteins / Organ Clocks**
- **Inflammation markers** (hs-CRP, CHIP)
- **Targeted imaging** (CTA, OCT, AI)

Conclusion:

The next step is clear





Shift from focusing on “blockages”
to understanding plaque biology and patient biology —
a unified approach that can finally prevent myocardial infarctions