Why Are Imaging RCTs Different?
Lessons from Chest Pain Evaluation Trials

Pamela S. Douglas, MD, MACC, FASE, FAHA

Ursula Geller Distinguished Professor of Research in Cardiovascular Diseases

Duke University

Past President, American College of Cardiology

Past President, American Society of Echocardiography

Relationships With Industry

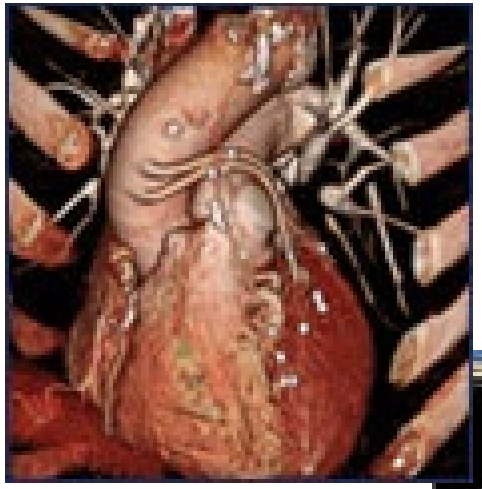
I have one industry relationship relevant to this presentation.

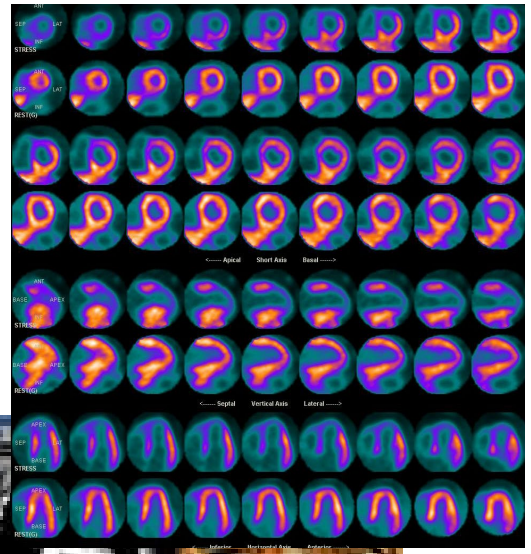
All relationships with industry may be found online:
http://www.dcri.duke.edu/research/coi.jsp

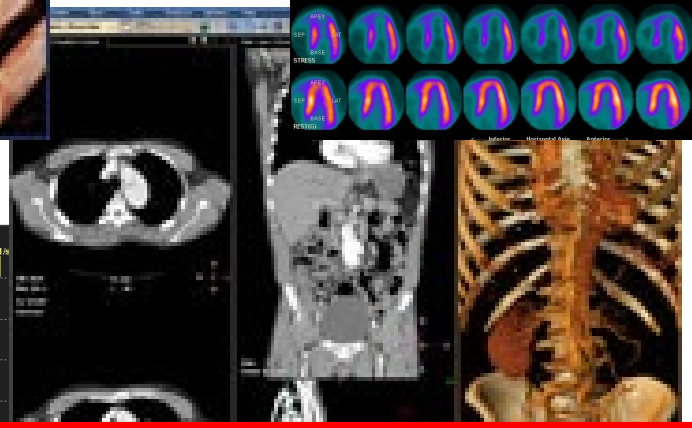
Caption Health
Foresite Labs
HeartFlow
UpToDate/Kluwer

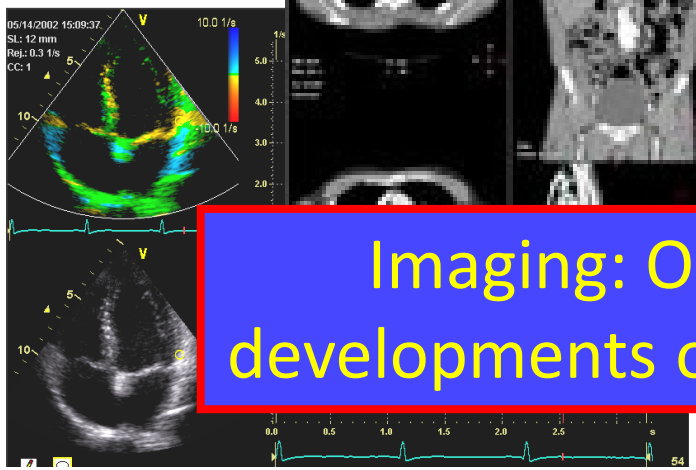
I will not discuss any off label or investigational uses in this presentation.

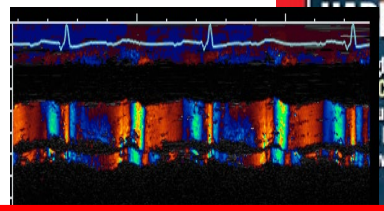
Imaging Has Transformed the Cardiovascular Enterprise

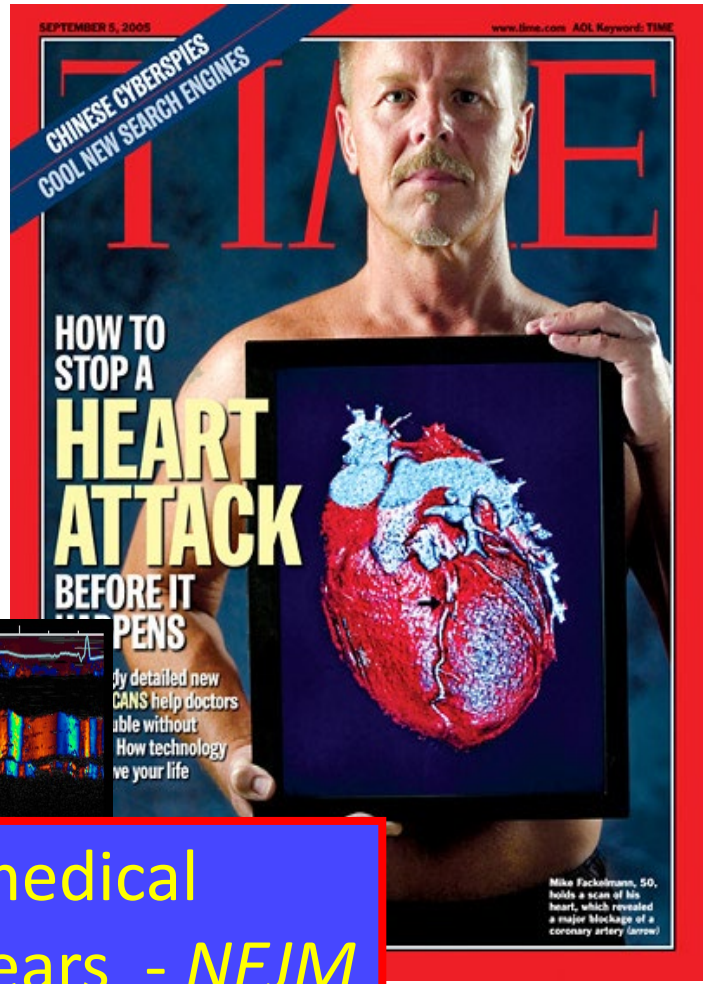












Imaging: One of the top 11 medical developments of the past 1000 years - *NEJM*

Imaging Clinical Trials: Evaluation of Stable Chest Pain in 2024

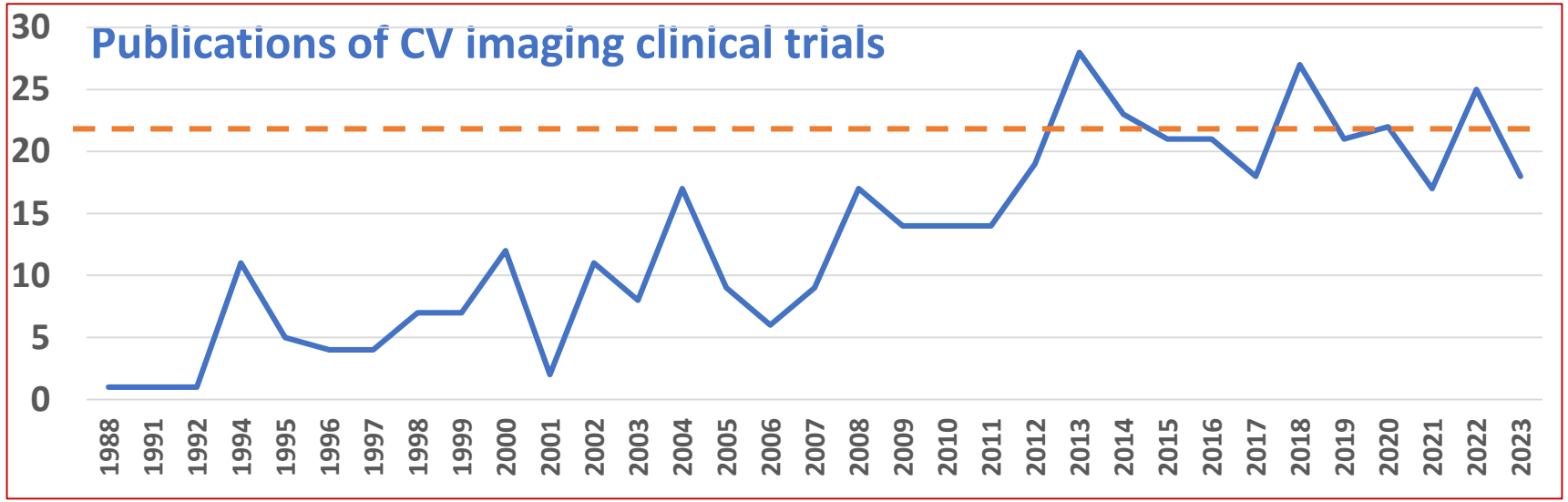
- CVD is the #1 killer; Often presents with chest pain
- >10 million new stable CP pts in US each year; many receive imaging
- AHA/ACC Chest Pain Guideline 2021: Many Class 1 imaging approaches
- In 2024, despite several large RCTs comparing evaluation approaches
  - No universal consensus on initial imaging strategies: who to test and how
  - Ongoing concerns about over imaging lowest risk patients but no consensus on testing deferral pathways
  - New imaging technologies may offer value but are untested

Why Isn't There a Consensus on "Best" Imaging Pathways for Chest Pain Evaluations?

- Under studied: Cardiology is disease and mgmt focused; symptoms are an entry point
- Imaging information is separated from hard outcomes; identifying causality is difficult
- A few myths related to chest pain imaging
  - Stress testing already provides excellent results – no need to improve
  - Information from noninvasive tests is largely interchangeable
  - Coronary artery disease is simple
- Funding and interest are limited, but stakes are high
  - No FDA required efficacy testing for imaging (510K) → Limited business case for industry
  - No FDA-validated biomarker/prognostic marker → Barrier to drug development and innovation
  - A validated imaging biomarker would markedly reduce cost and time to market

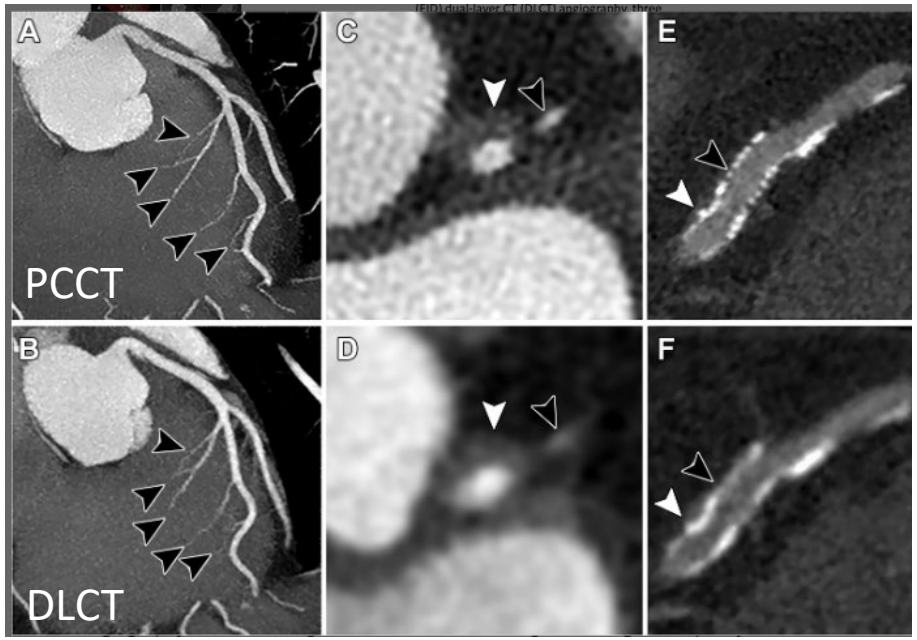
CV Imaging Trials: An Evidence Gap

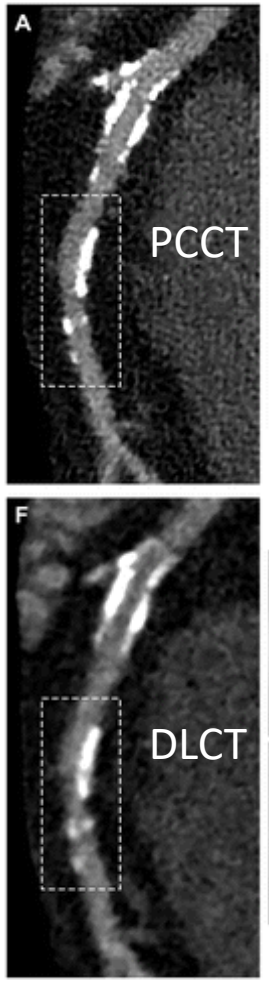
- Medicare CV dx testing rates in 2016: 316/1000; Roughly **21 M tests** in US/y
- Annually US cost **~$10B** (est $200/test)
- The evidence base is small ~ 22 trials pubs/y; No growth x 10 years
- Given high utilization and costs, research expenditures are very low
  - Imaging: 1 publication per $455K expenditure
  - In contrast: HF costs are 4-5x higher, but >800 trial pubs/y, or 1 paper/$62K in costs



Rapid Technological Change is the Norm

- Machine learning and AI
  - As of Jan 2024; FDA lists >500 ML/AI devices
  - 155 listed 8/2022 – 7/2023: 79% radiology, 9% cardiology, 5% neuro, 4% GI
  - Radiology applications increasingly hybrid
    - Safe and effective device
    - Classification of disease
- Image acquisition: Photon Counting CTA
  - Image resolution similar to IVUS, ~ 200 µm
- Many other acquisition and interpretation advances outpacing ability to test prospectively





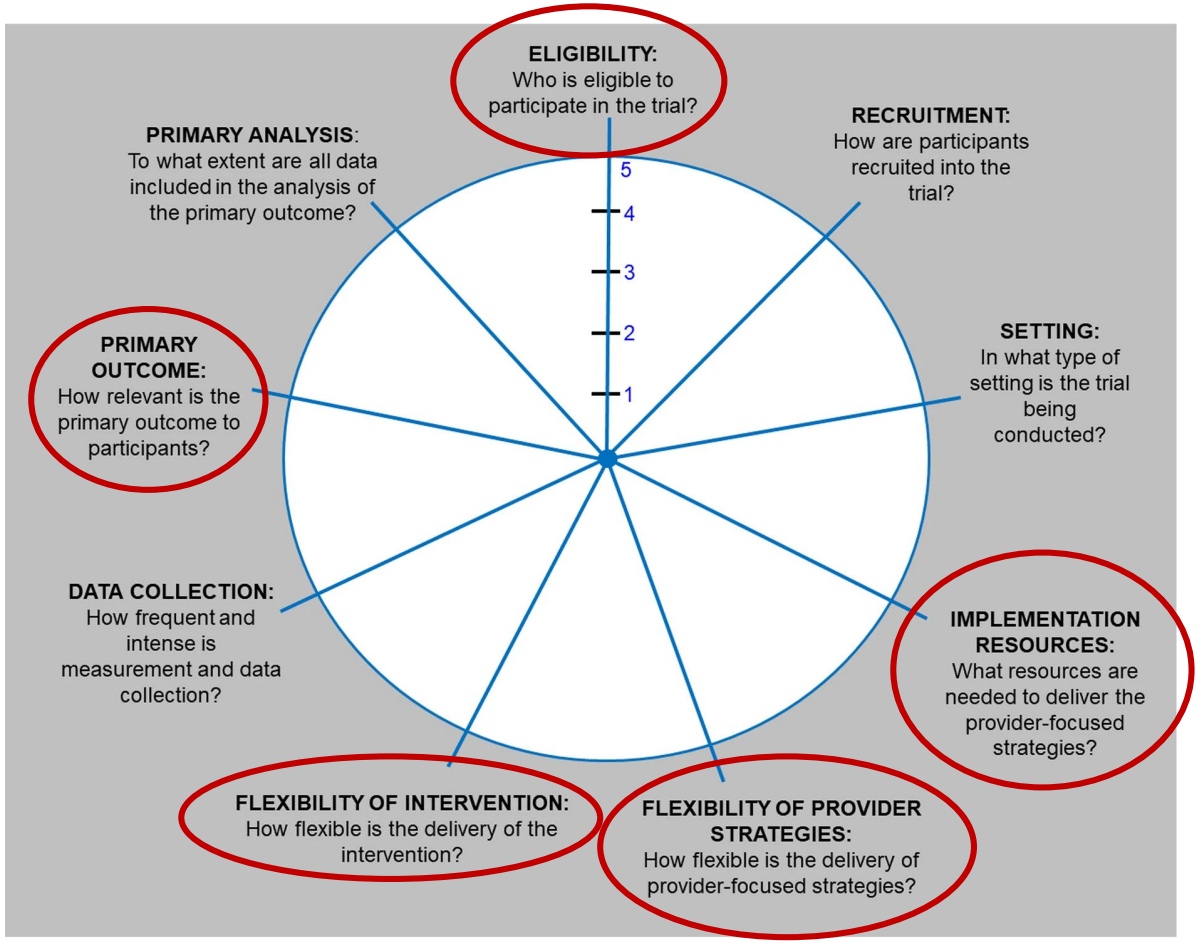
Imaging Trials: Chest Pain Evaluation

- Pragmatic design considerations
- Who is the patient we want to study?
- What is the disease?
- Flexibility of the intervention
- What events are we trying to avoid?

Pragmatic Imaging Trial Design

- Similar to most types of trials, there are pros and cons to both pragmatic and explanatory designs in imaging trials
- Feasibility and generalizability vs scientific hypothesis affect design choices including
  - Inclusion/exclusion criteria
  - Flexibility of imaging intervention being tested (incl use of core lab)
  - Guidance/control of subsequent care after imaging (medical management, procedures)
  - Endpoints and outcomes

PRECIS - 2



Implementation Science 2021

Imaging Trials: Chest Pain Evaluation

- Pragmatic design considerations
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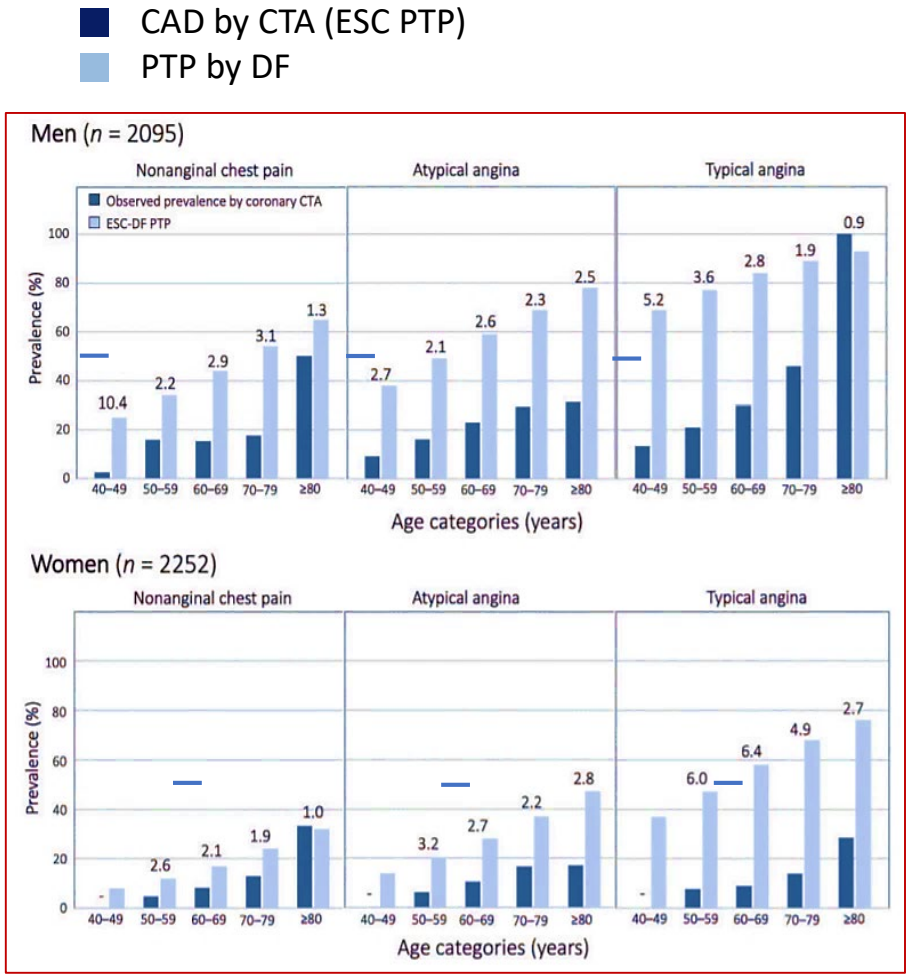
Who is the Patient We Want to Study: Cohort Selection

- People with angina-like symptoms are often not patients with a disease
- Most don't have obstructive CAD, but a few are very high risk
  - Potential for over testing with significant false positive rate (specificity ~80%)
  - Potential for missed diagnosis with stress imaging (sensitivity ~80%)
- Obstructive CAD in stable CP is unlikely (10-20%) and outcomes are excellent (CV death MI ~ 1%/yr) wo revascularization
- Many possible approaches from all-comer (with MD referral) to those who truly need testing (PTP) to only those with recurrent or resistant symptoms

Determining CAD Likelihood: Updating PTP Algorithms

Pretest probability for patients with suspected obstructive coronary artery disease: re-evaluating Diamond–Forrester for the contemporary era and clinical implications: insights from the PROMISE trial

- Old Diamond and Forrester PTP based on cath and autopsy data from 1970's
- New PTP derived from contemporary CTA cohorts
- PROMISE: 4415 pts with chest pain and CTA imaging
- *Actual* anatomy by CTA→PTP 'estimate'
- Result: ↓ **PTP by 50-70%** vs old D-F (2012 ACC/AHA GL)

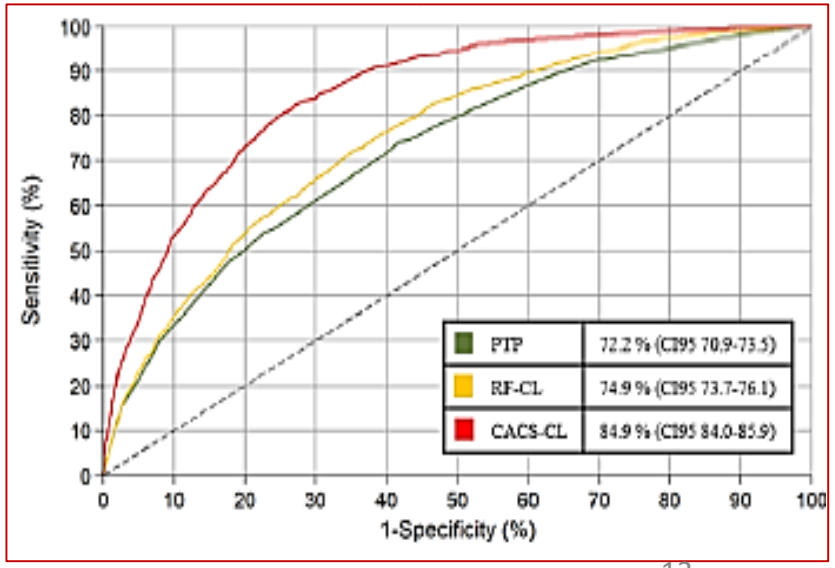


EHJ CVI 2019; 20: 574

Improving on the New PTP Estimates for CAD

- Can the updated PTP be improved by strategies? Specifically, does adding RFs or RF+CAC to 2019 PTP improve CAD prediction?
- Machine Learning model: 41,177 pts; Validation: 15,411 pts: PROMISE, Dan-NICAD
- Results: Adding RFs or RF+CAC reduces testing (max 43% reclass) and improves accuracy
- Use of CAC '*instead of testing*' now a Class 2a recommendation in 2021 CP Guidelines
- Watch for ESC 2024 guidelines…

Model	<5% PTP: No testing	>5% PTP: Testing	AUC for CAD
2019 PTP alone	11%	89%	72%
2019 PTP+RF	38%	62%	75%
2019 PTP+RF+CAC	54%	46%	85%

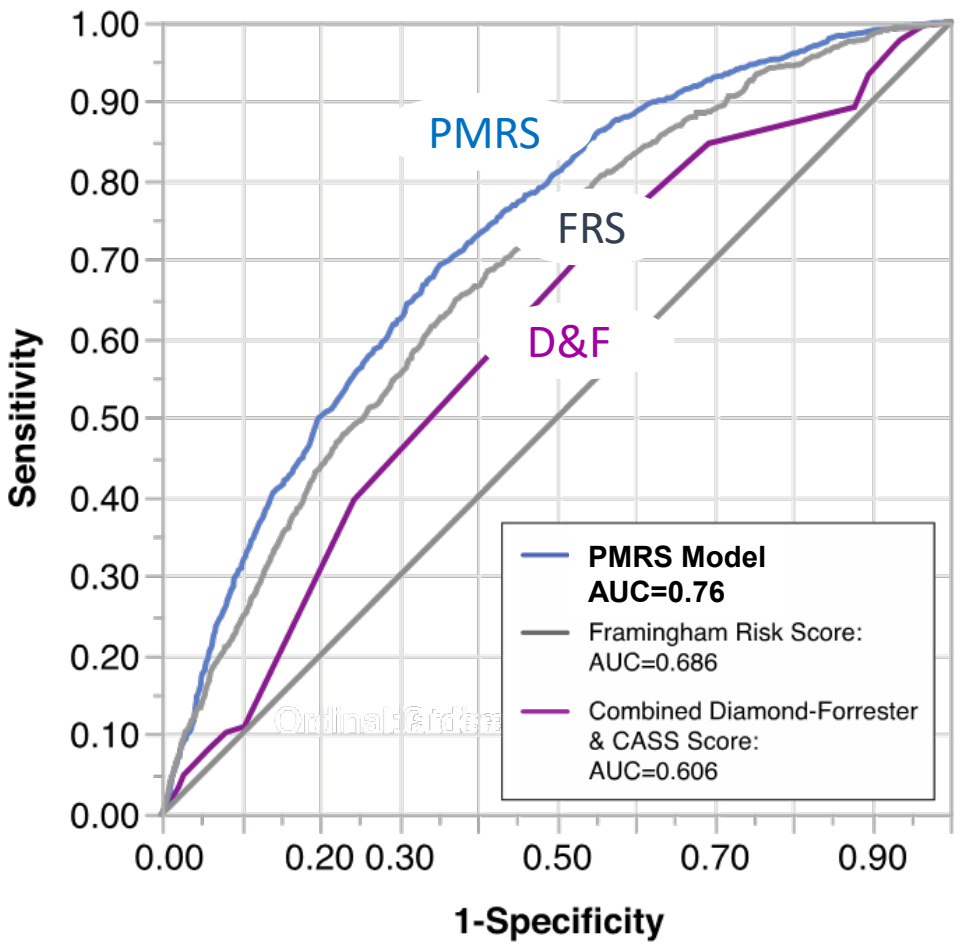


JAMA Cardiology | Original Investigation

Identification of Patients With Stable Chest Pain Deriving Minimal Value From Noninvasive Testing

The PROMISE Minimal-Risk Tool, A Secondary Analysis of a Randomized Clinical Trial

- 4,631 PROMISE cCTA pts, model 'No' Risk: 27% w/o CAC, plaque or events (*not only obs CAD*)
- Result: 10 clinical variables predicted 'No' Risk
- Validated in SCOT-HEART, Dan-NICAD (n=3,439)
- Combined in all 3 cohorts: C stat 0.76



Calculator: https://heartcenter.shinyapps.io/PROMISE_Minimal_Risk_Tool/

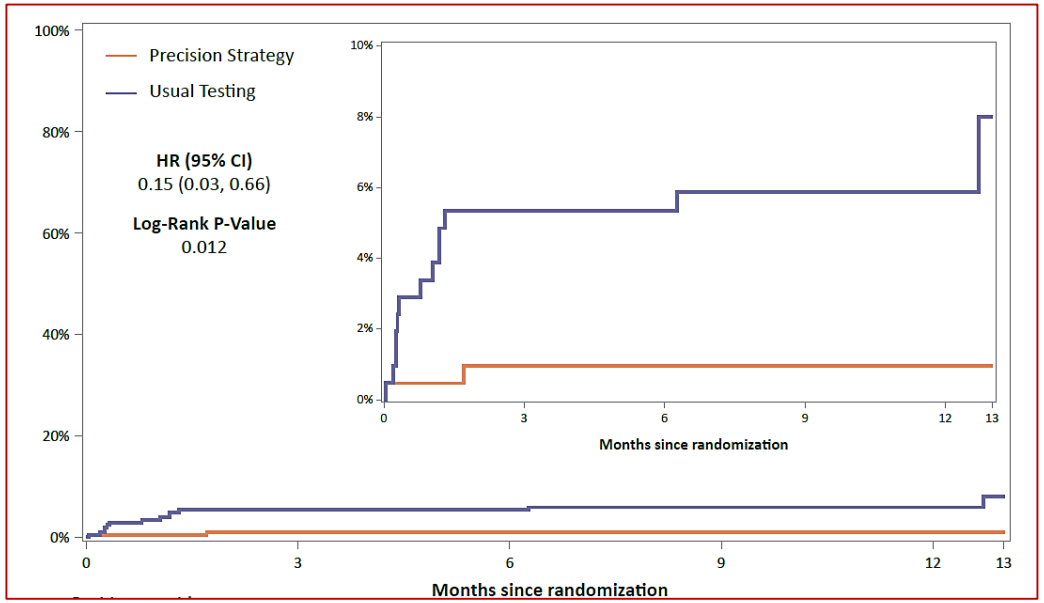
JAMA Cardiology 2017 2:400-408
Intl J Cardiology 2018 252:31-34
Intl J CV Imaging 2021 37:699–706

JAMA Cardiology | Original Investigation

Deferred Testing in Stable Outpatients With Suspected Coronary Artery Disease

A Prespecified Secondary Analysis of the PRECISE Randomized Clinical Trial

- 422 of 2103 PRECISE participants identified as low risk by PMRS
  - Prespecified cut point to achieve ~20% of cohort
- Randomized to usual care (MD choice) or deferred testing
- Deferred testing vs usual care:
  - 64% never tested vs 36%
  - Testing was later 48 vs 15 days; 96% normal
  - Primary endpoint (death, MI, cath wo CAD)
    2 vs 13 participants
- Similar reduction in angina in both groups



JAMA Cardiol 2023; 8:915

Clinical Implications: Who is the Patient We Want to Study?

- Heterogeneity of chest pain patients with varying clinical need to diagnosis a treatable disease (CAD)
- If seeking intermediate risk patients with suspected obstructive CAD, cohort selection best done using risk factors as well as age, sex and symptoms
  - Exclude lowest risk patients (via PMRS or updated PTP) vs
  - Alternative: all-comer, pragmatic trial
- Consider the role of OMT failure before imaging
- Implications for enrolling a more homogenous cohort likely to benefit in a trial

Imaging Trials: Chest Pain Evaluation

- Pragmatic design considerations
- Who is the patient we want to study?
- What is the disease?
- Flexibility of the intervention
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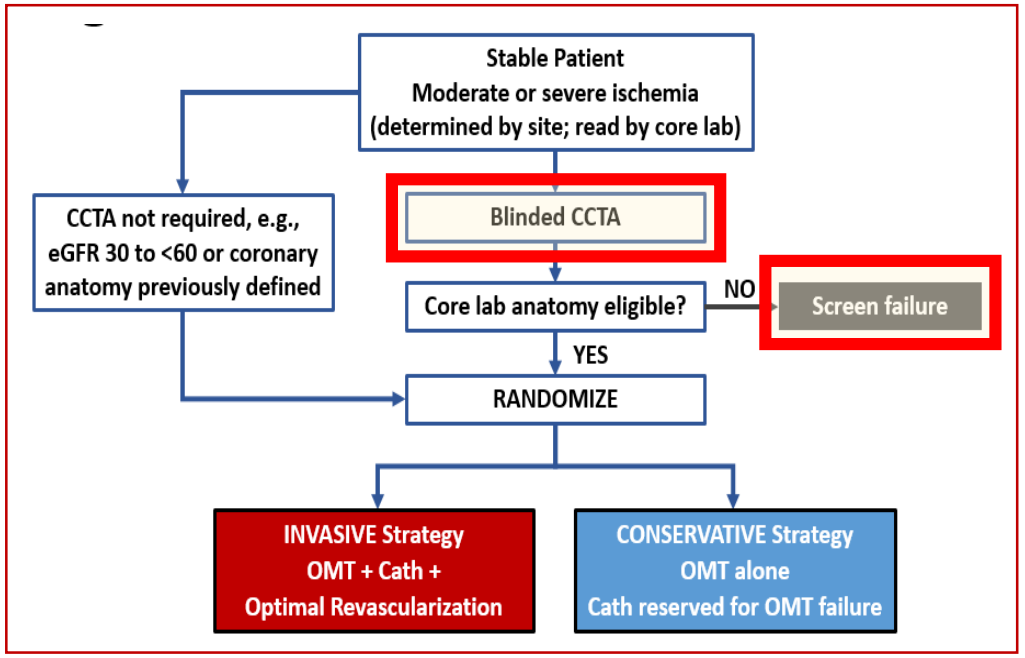
CAD Has Multiple Phenotypes: Which Imaging Targets Should RCTs Investigate?

- RCT design will vary depending on which CAD manifestation(s) are reflected in the information provided by the imaging test being studied.
- This in turn affects the treatment target(s) being evaluated in a therapeutic trial
- A partial list – more than one may be relevant
  - Any plaque
  - Obstructive stenosis
  - Ischemia
  - Disrupted flow
  - High risk/vulnerable plaque
  - Microvascular dysfunction
  - Inflammation

Stress Testing vs CTA For Eligibility in ISCHEMIA

Cohort characterization for eligibility: How do anatomy and physiology relate in stable patients with mod-severe ischemia on a core lab interpreted stress test?



Among otherwise eligible pts with core lab confirmed moderate-severe ischemia:

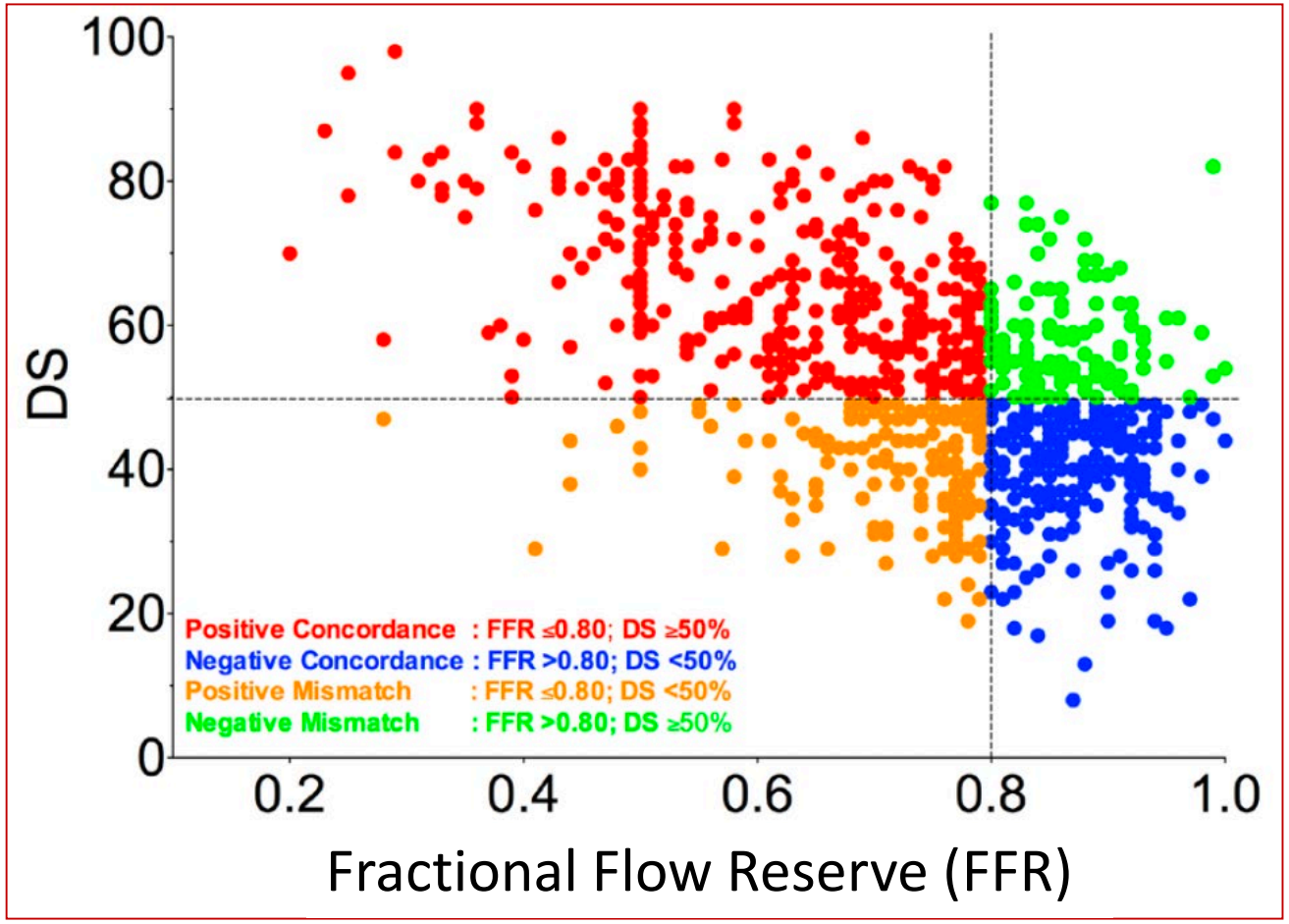
1829/5757 (31.8%) were excluded by CTA

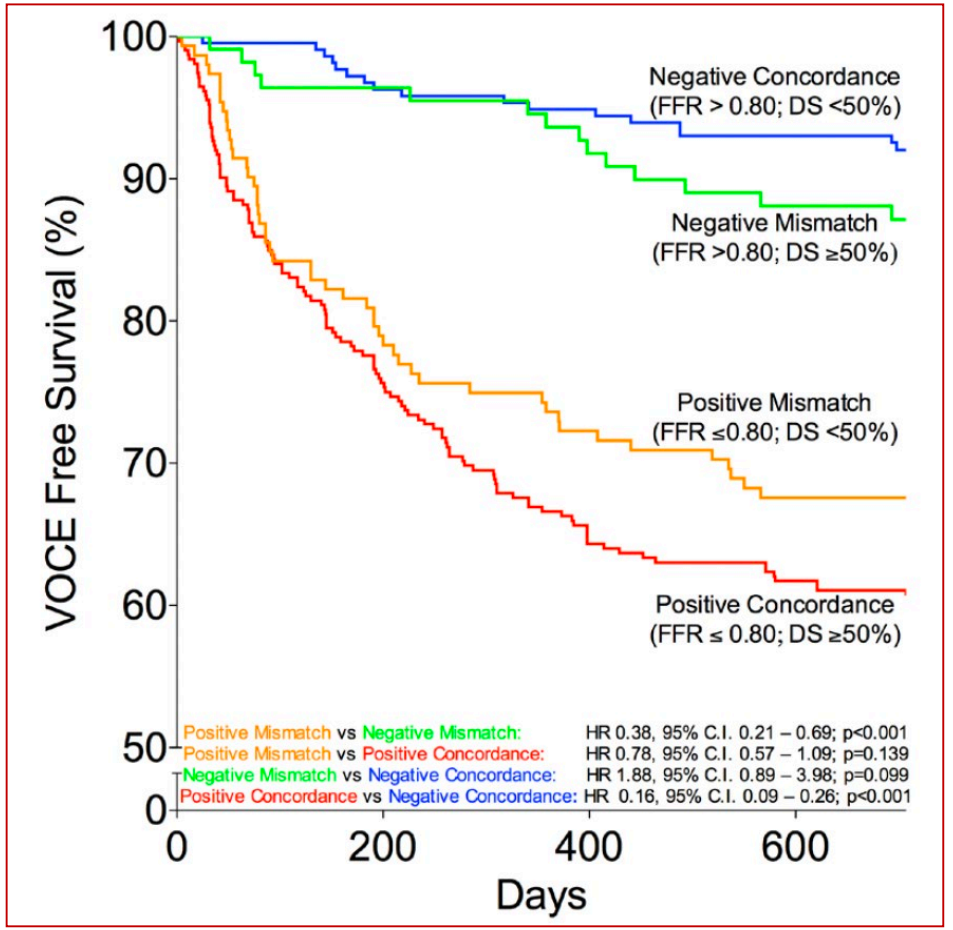
- 66.6% no obstructive CAD
- 23.7% unprotected left main**
- 9.7% other

** "….clinical and stress testing parameters [echo and ECG] were weakly predictive of LMD on CTA. For most patients with moderate or severe ischemia, **anatomical imaging is needed to rule out Left Main Disease**."

JAMA Card 2019; 4(3):273
JACC 2022; 79:651

Coronary Physiology ≠ Anatomy; Physiology Is More Important: Invasive FFR

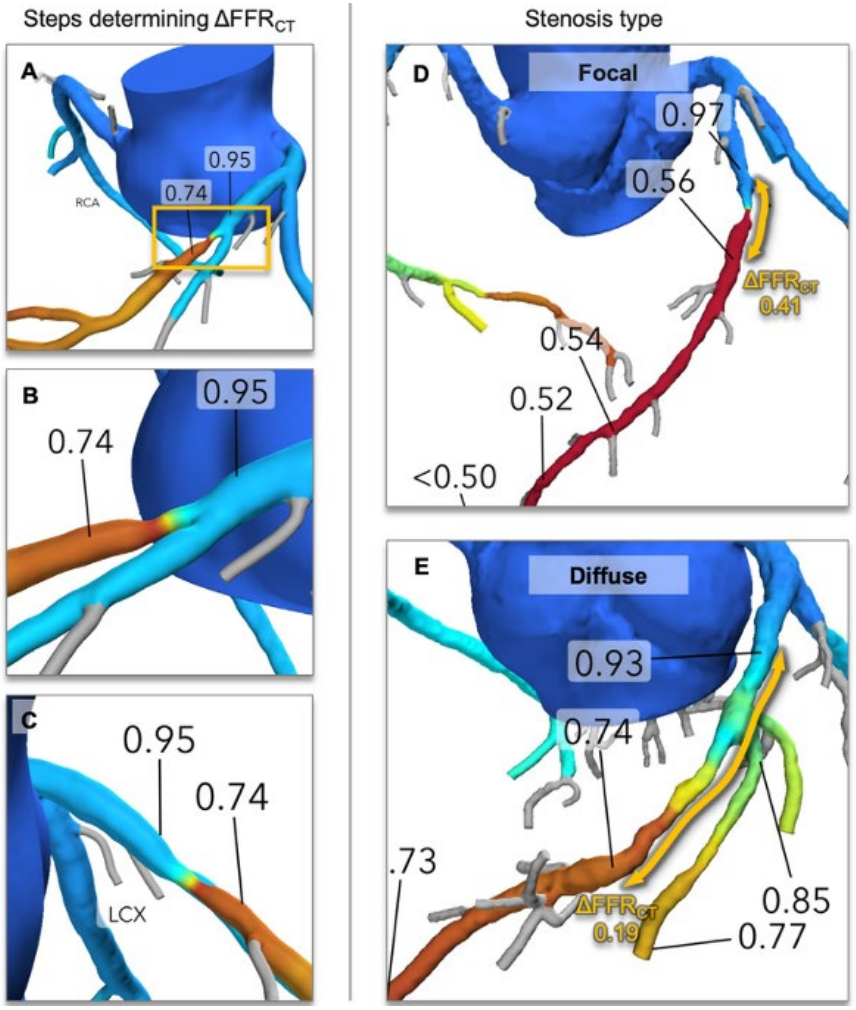




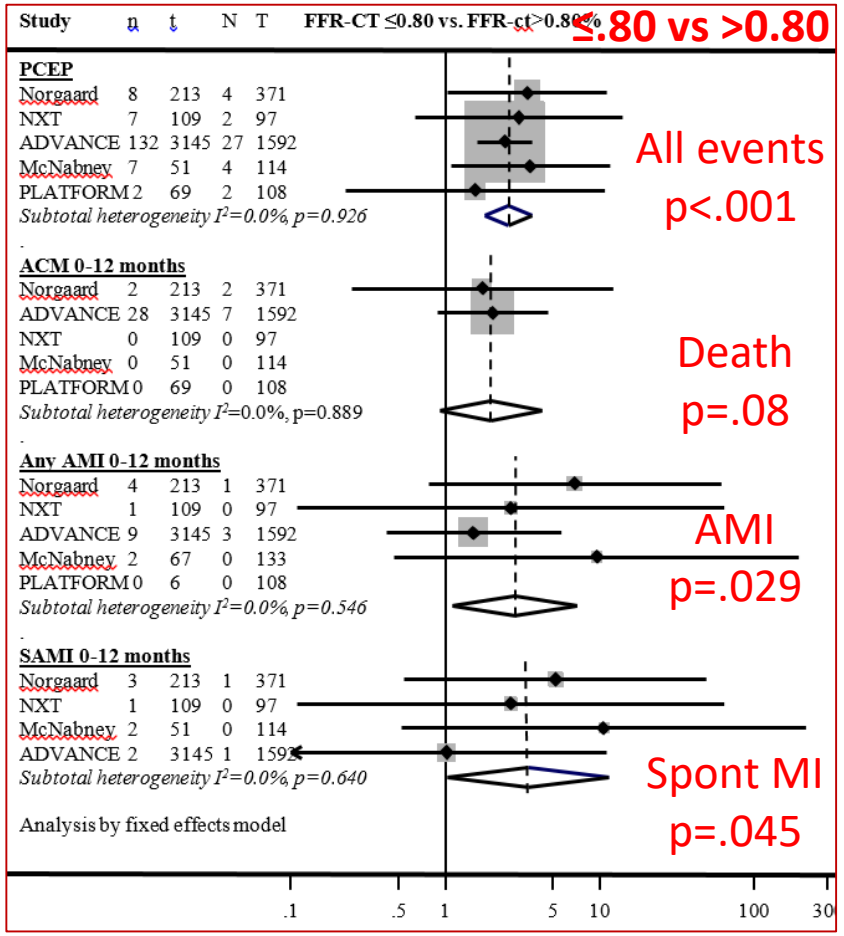
FAME 2
Circ 2018;137:1475

Measuring Coronary Physiology Noninvasively: FFR_{CT}

FFR_{CT} – ML estimation of flow reserve



- Meta-analysis: 5 FFR_{CT} studies; N= 5869
- Endpoints: Death, MI, unplanned revasc

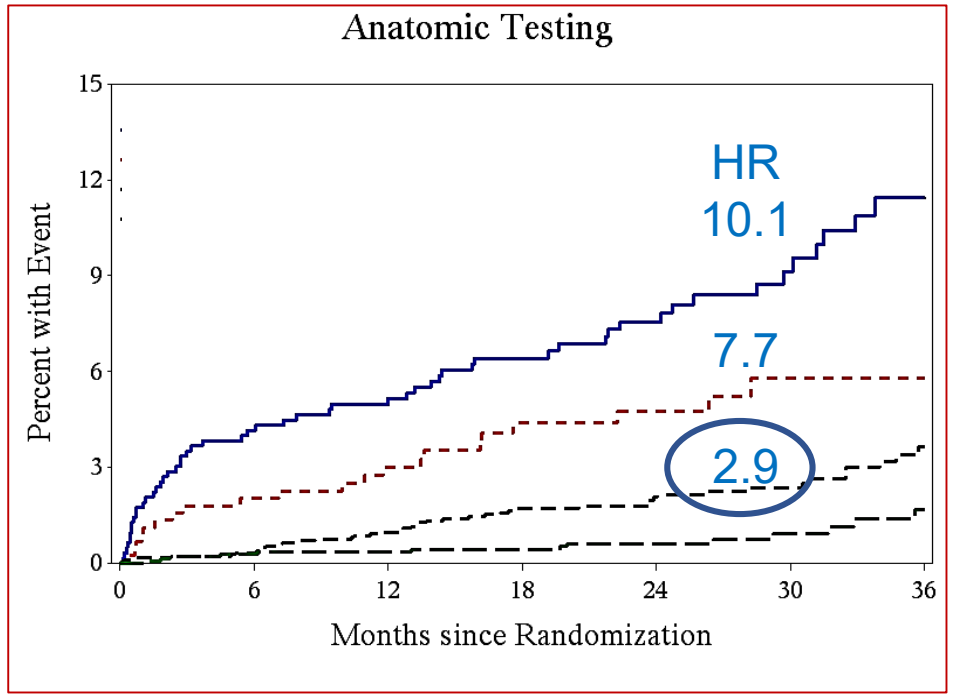


Heart 2022 doi: 10.1136/heartjnl-2021-319773

Non Obstructive CAD Carries an Unfavorable Prognosis (and is Not Detected by Stress Tests)

PROMISE CTA

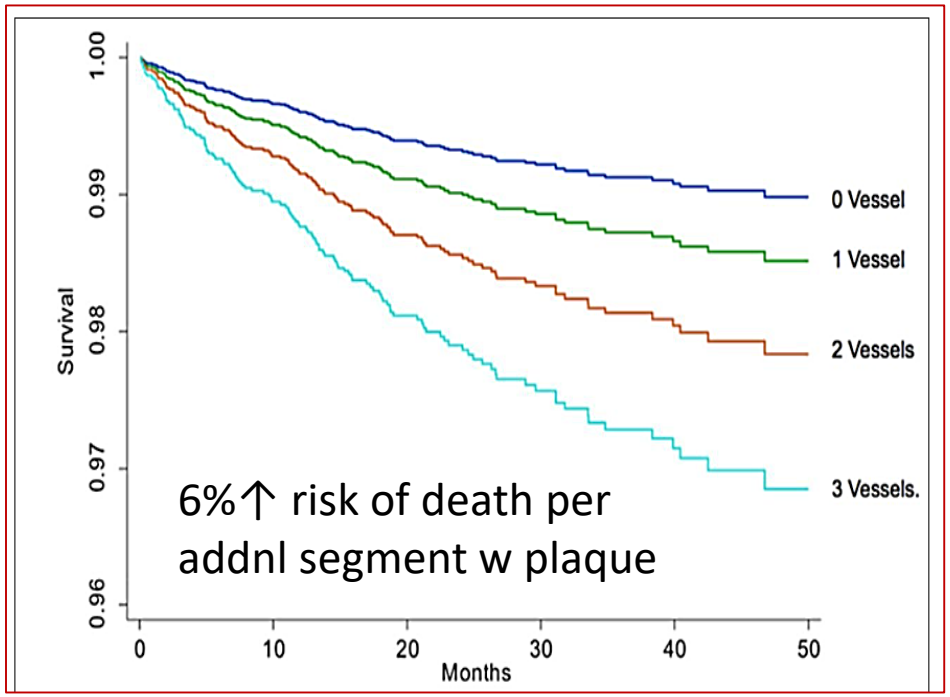
Death, MI, and Unstable Angina



Mild CAD (1%–49%)

CONFIRM CTA

All cause death



Non-obstructive CAD (1%–49%)

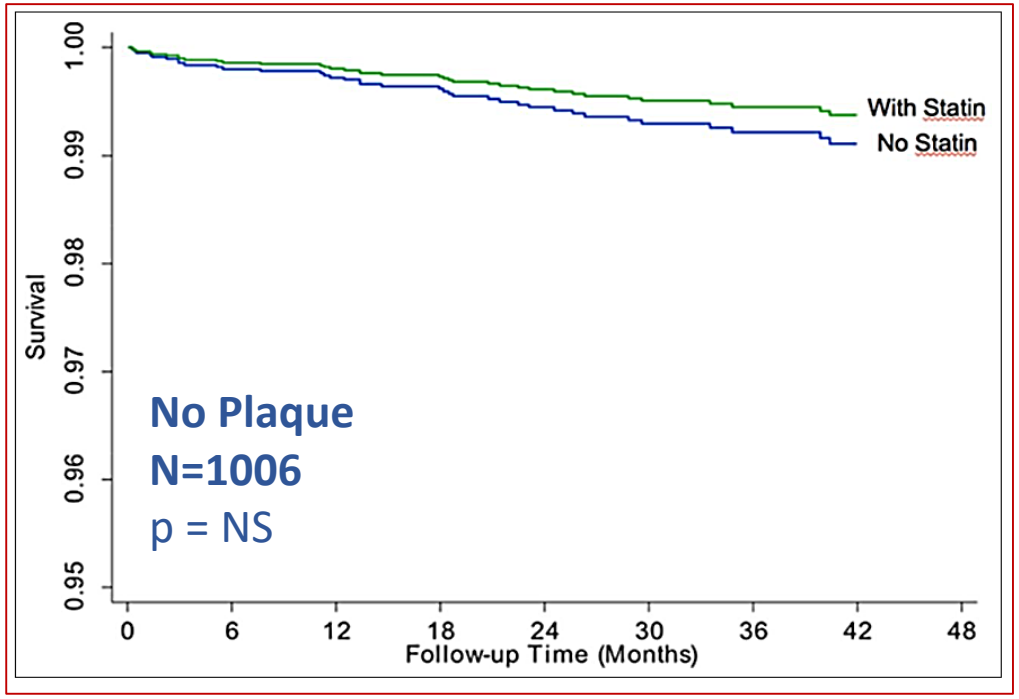
promise

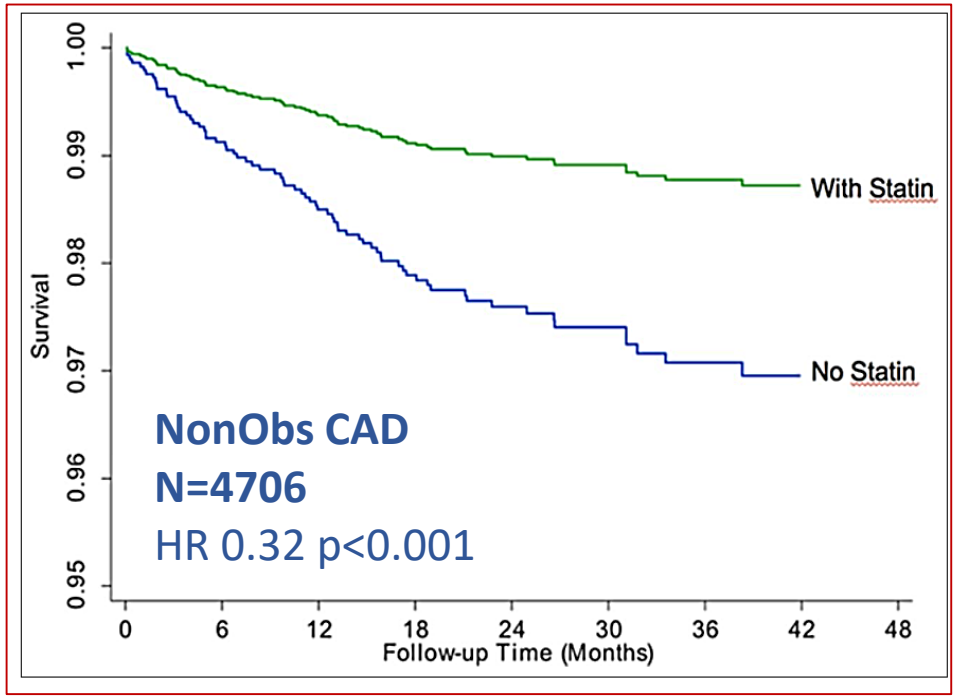
ATVB 2015; 35:981; Circ 2017;135:2320

Prognostic and Therapeutic Implications of Statin and Aspirin Therapy in Individuals With Nonobstructive Coronary Artery Disease - CONFIRM

- 10,418 pts w CTA; F/u median 27 months
- Statins reduce all cause death by 68%, but only in those with plaque

Prognosis with Statin Use vs Non Use



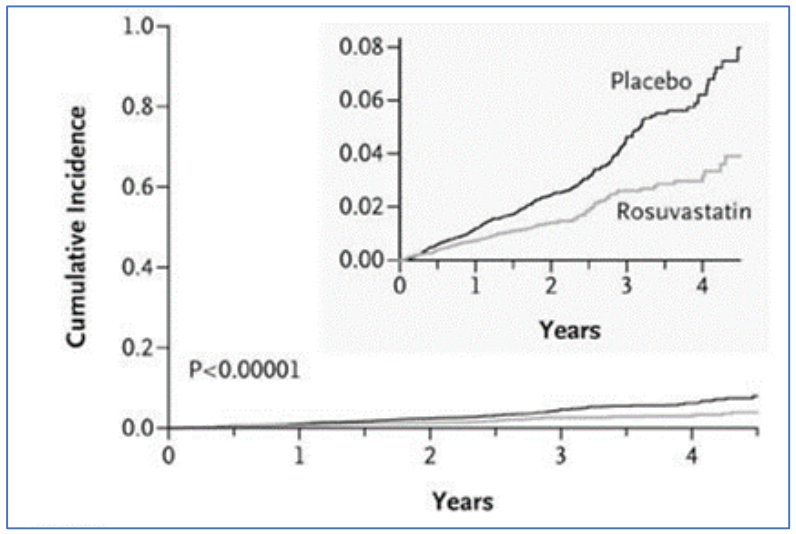


ATVB 2015; 35: 981

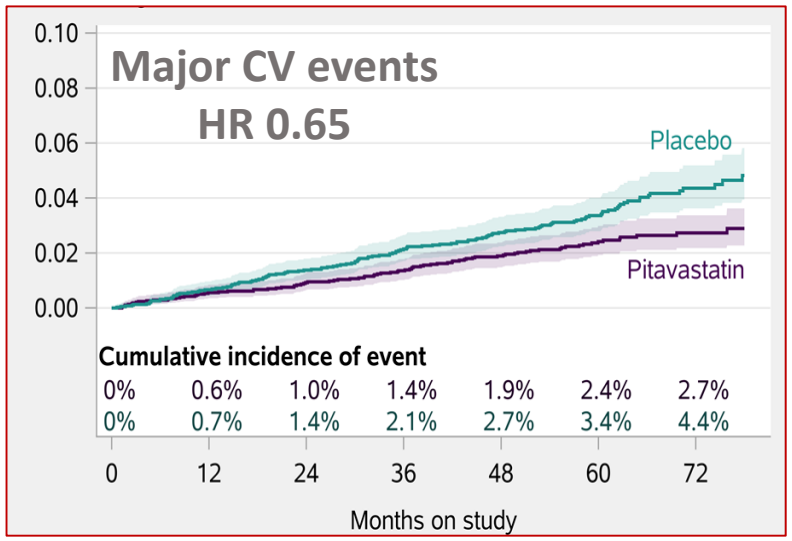
What About Inflammation?

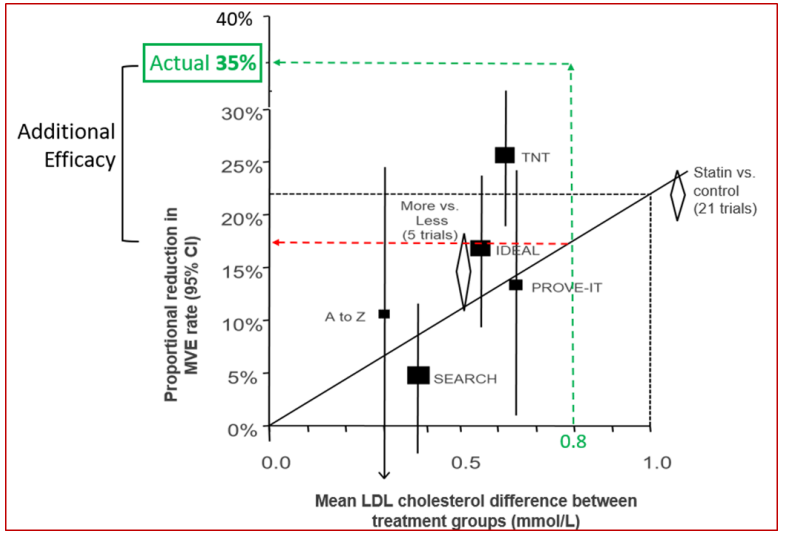
- JUPITER: 17,802 with LDL<130 and CRP>2.0; HR 0.56
- REPRIEVE: 7800 PWH, Statin vs placebo RCT

JUPITER



REPRIEVE

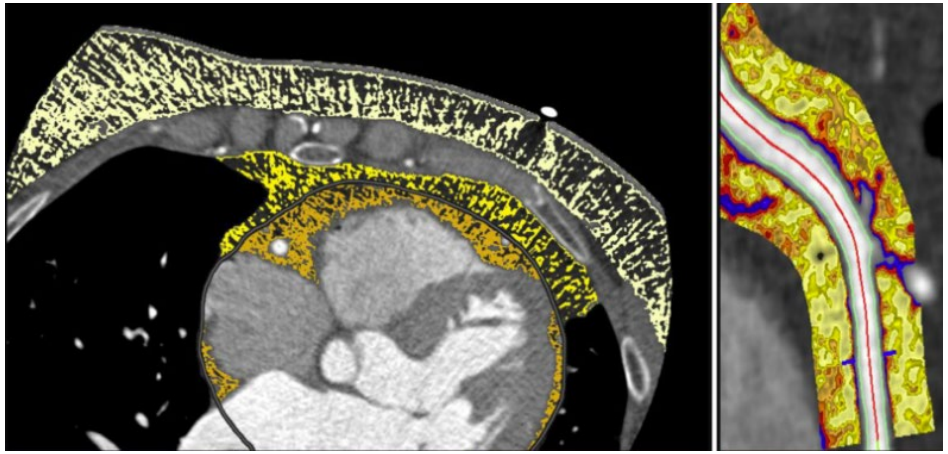


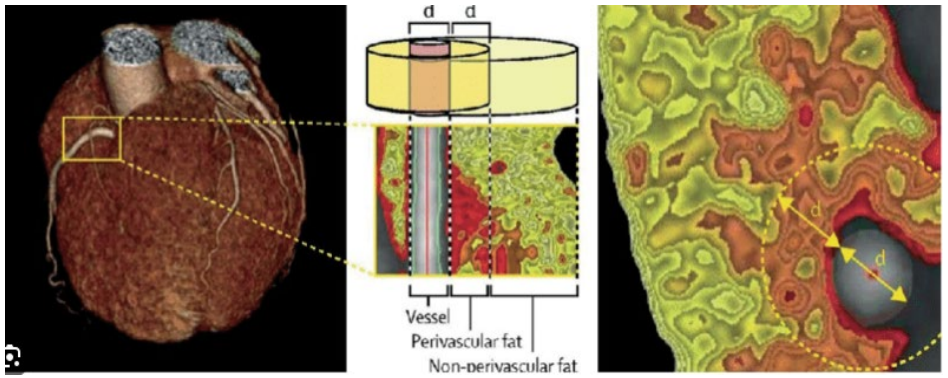


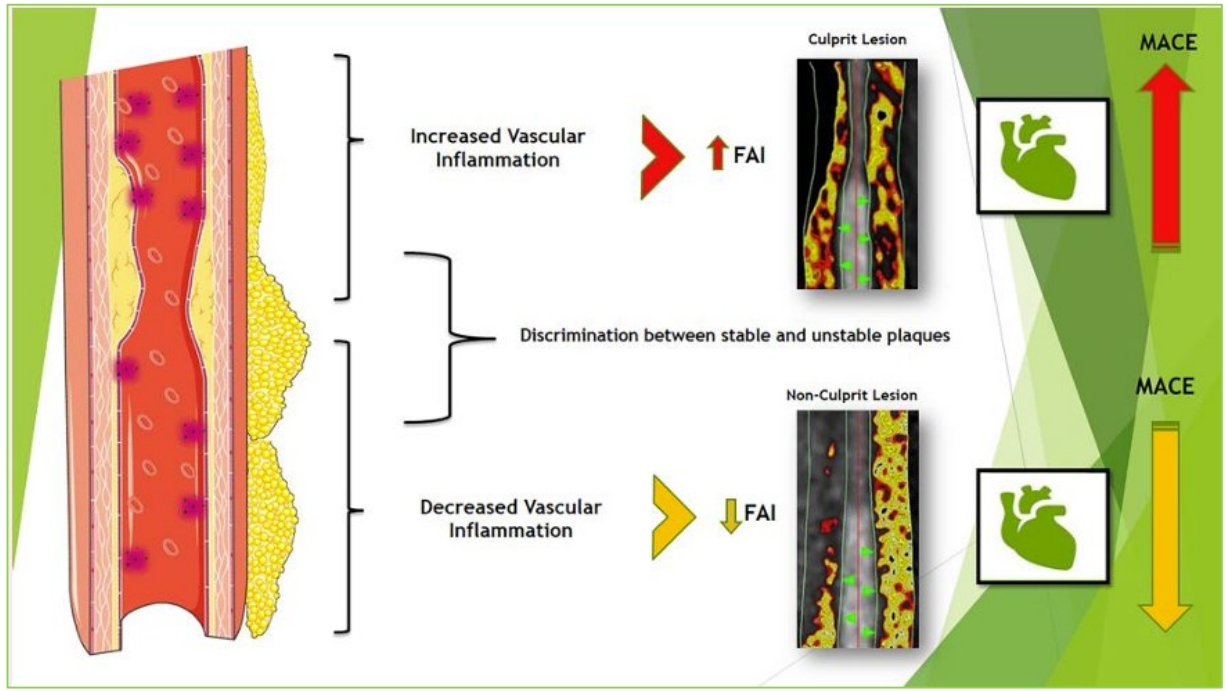
NEJM 2008; 359:2195
NEJM 2023; 389:687

Emerging Imaging Biomarkers of Inflammation: Epicardial and Pericoronary Fat Attenuation

- Intriguing, but not yet ready for prime time







Lancet 2018;392:929

Clinical Implications: What is the Disease?

- Many imaging findings (targets) are important for optimal care
- Ischemia (stress imaging) is not a reliable way to exclude high risk, obstructive CAD
- Obstructive CAD is not necessarily hemodynamically important and requires further functional information to interpret correctly
- Nonobstructive CAD is prognostically important and can be treated effectively
- Inflammation is prognostically important and can be treated effectively
- Paradigm shift: There is no single CAD phenotype which can be targeted diagnostically or therapeutically. Imaging strategies must be multidimensional or account for this heterogeneity

Imaging Trials: Chest Pain Evaluation

- Pragmatic design considerations
- Who is the patient we want to study?
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Selecting and Controlling Imaging and Subsequent Care

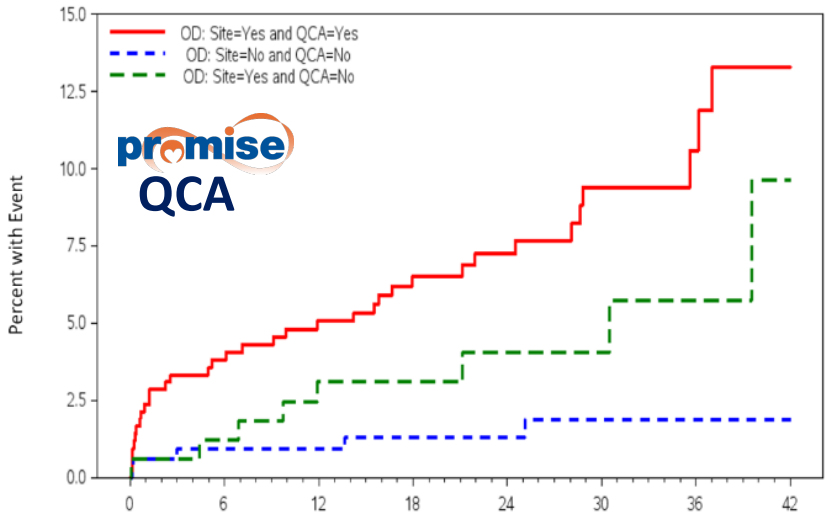
- When evaluating imaging strategies, is 'usual testing' the appropriate comparator?
  - Stress ECG vs stress imaging; Nuclear vs PET; Angiographic gold standard
  - What about direct to cath? (10% of PRECISE; DISCHARGE cath=CTA)
- CTA may be the preferred test. What is the optimal CTA intervention?
  - Tiered testing (CAC first): CRESCENT - 97 vs 90% event-free survival, more rapid dx, less downstream testing, lower cost, less angina
  - CTA alone: PROMISE - 51% more caths, 93% more revascularizations
  - Selective FFR_{CT}: PLATFORM – 61% ordered caths cancelled; Up to $4000 saved per ppt
  - CTA vs CTA +/-FFR_{CT}: FORECAST - 60% CTA among UC; no diff events or costs; 24% fewer caths
- Should downstream care be mandated depending on imaging findings?

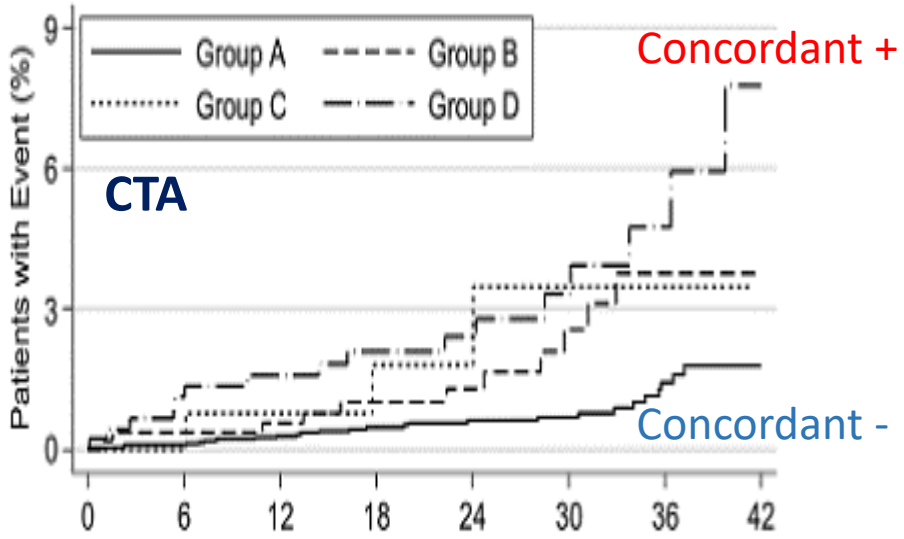
EHJ 2016; 37:1232 NEJM 2015; 372:1291
JACC 2016; 68:435 EHJ 2021; 42:3844

Sites and Core Laboratories Differ in Eligibility and Outcomes Determinations

- Core laboratories and site interpretations do not align
- Significant 'over-enrollment' by sites vs core lab measurements
  - STICH echo - 18% of enrolled participants did not meet EF requirements (ie: had EFs >35%)
  - PARTNER I echo – 45% mean AV <40mmHg; 18% had AVAs >0.8cm^2; 13% mod-severe AR
- Similar 'overreading' by sites of coronary stenosis severity
  - PROMISE QCA –19% disagreement rate; Higher events than QCA= <50%
  - PROMISE CTA – 16% disagreement rate; Higher events than core lab <50%

JASE 2012; 25:327
JASE 2015;28:210-17
AHJ 2017; 184:1
Radiology 2018; 287:87





Imaging Trials: Chest Pain Evaluation

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Usual Evidentiary Standards for Imaging Evaluation

Technical capabilities

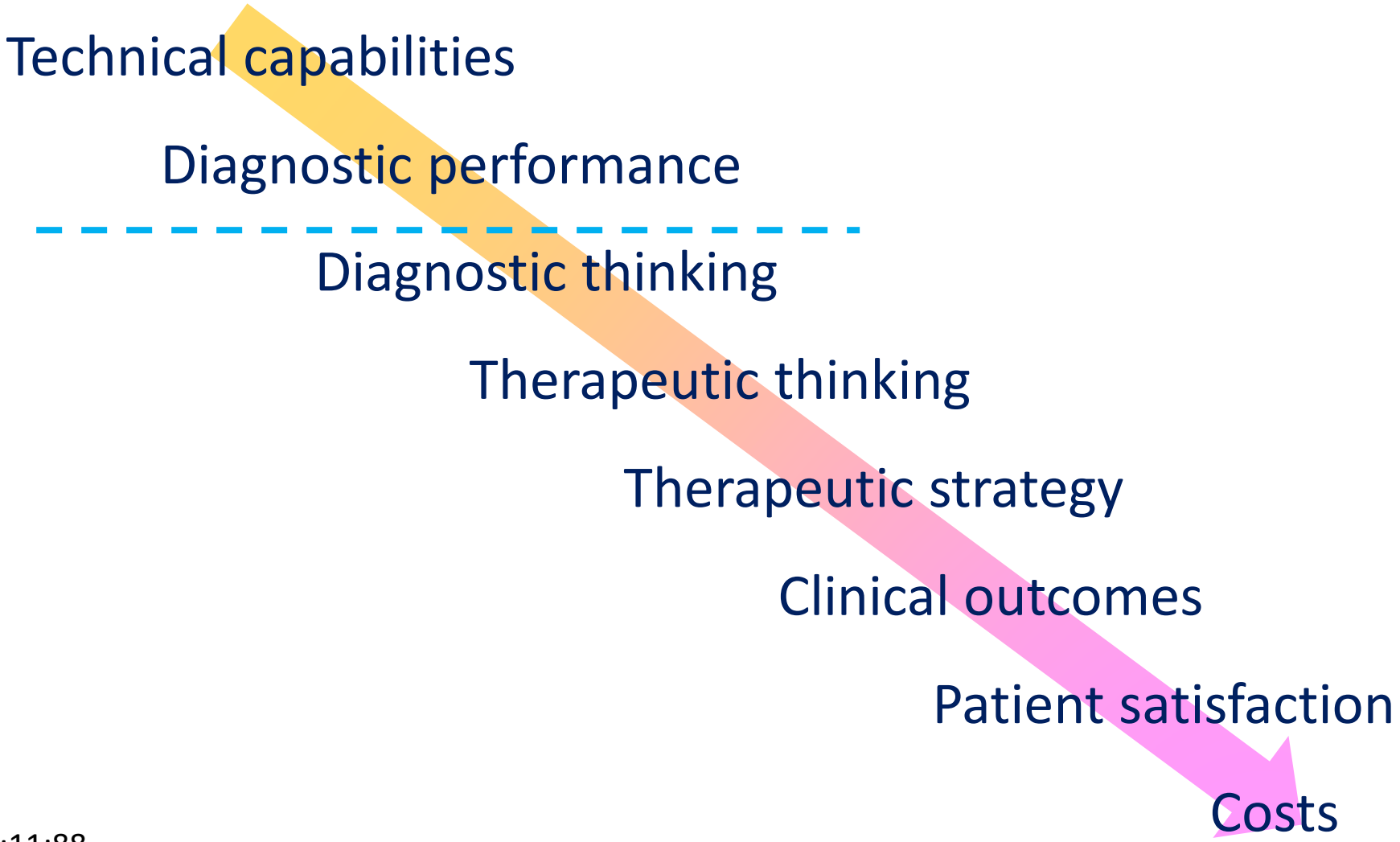
Diagnostic performance

Bench to bedside pathway

- 510K approval
- Reimbursement
- Clinical use

CMAJ 1986;134:587
Med Decis Making 1991;11:88

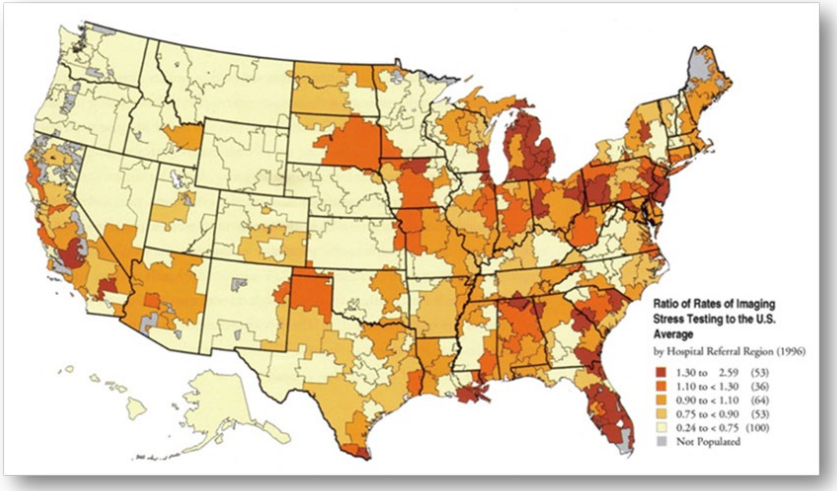
Higher Evidentiary Standards can be Used to Evaluate Imaging Outcomes



CMAJ 1986;134:587
Med Decis Making 1991;11:88

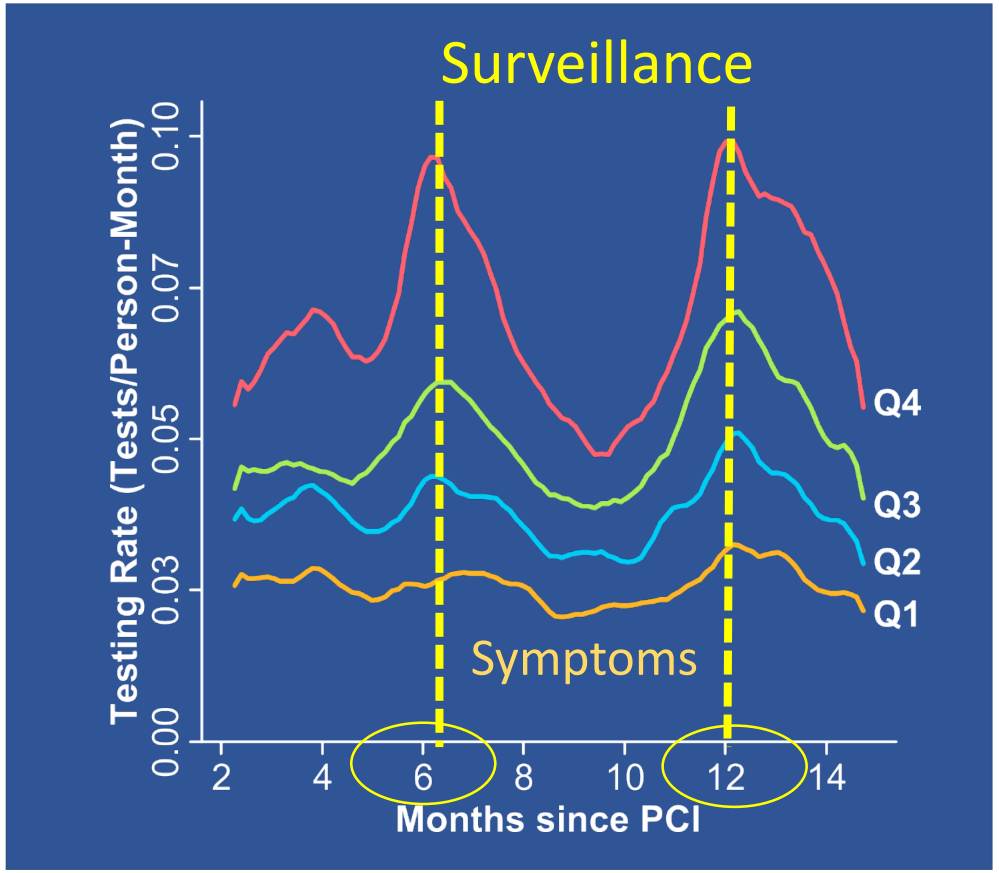
What are Appropriate Endpoint(s) for Imaging RTCs?

- Testing utilization
  - Appropriate Use Criteria
  - Geographic variation
- Efficiency/Gatekeeper function
  - % ‘normal’ results/New findings
- Diagnostic or therapeutic certainty
- Angina and QOL
- Major adverse events
  - Death, CV death, MI, unstable angina, urgent revascularization, etc
- Optimization of medical therapy

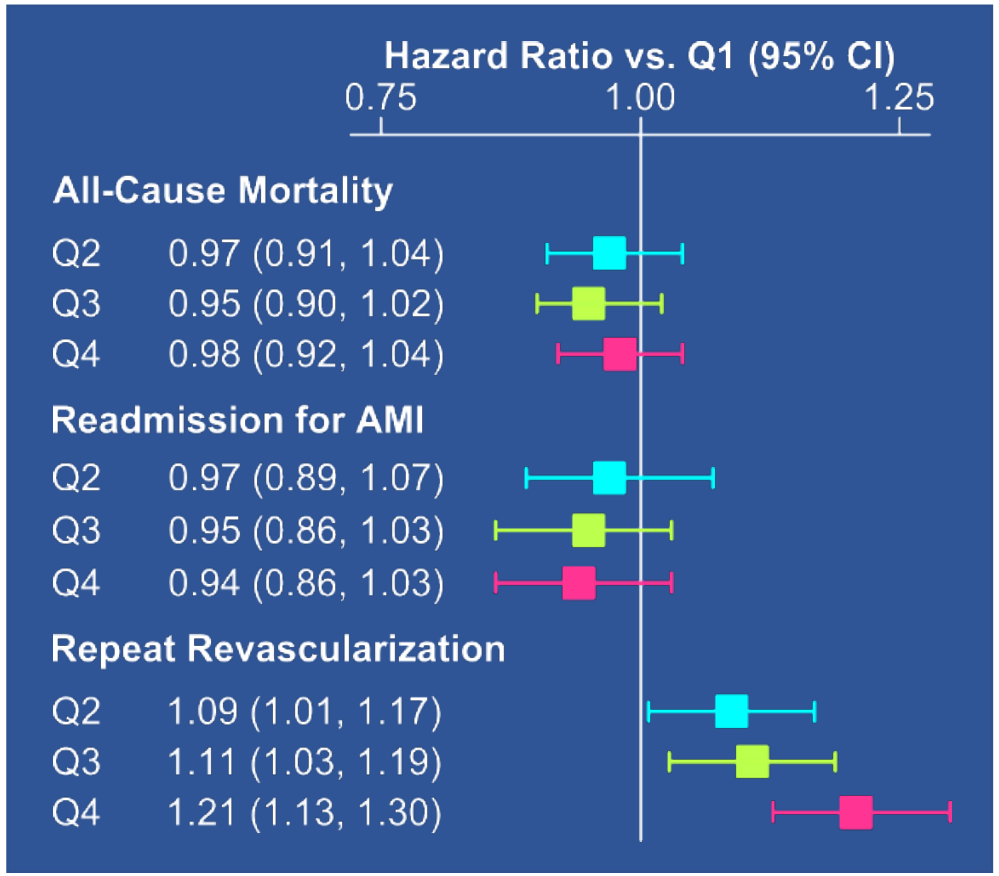


Early Post PCI Stress: Rarely Appropriate By AUC Variable Intensity of Testing Use by Hospital

Overall Testing Intensity Related to Temporal Use



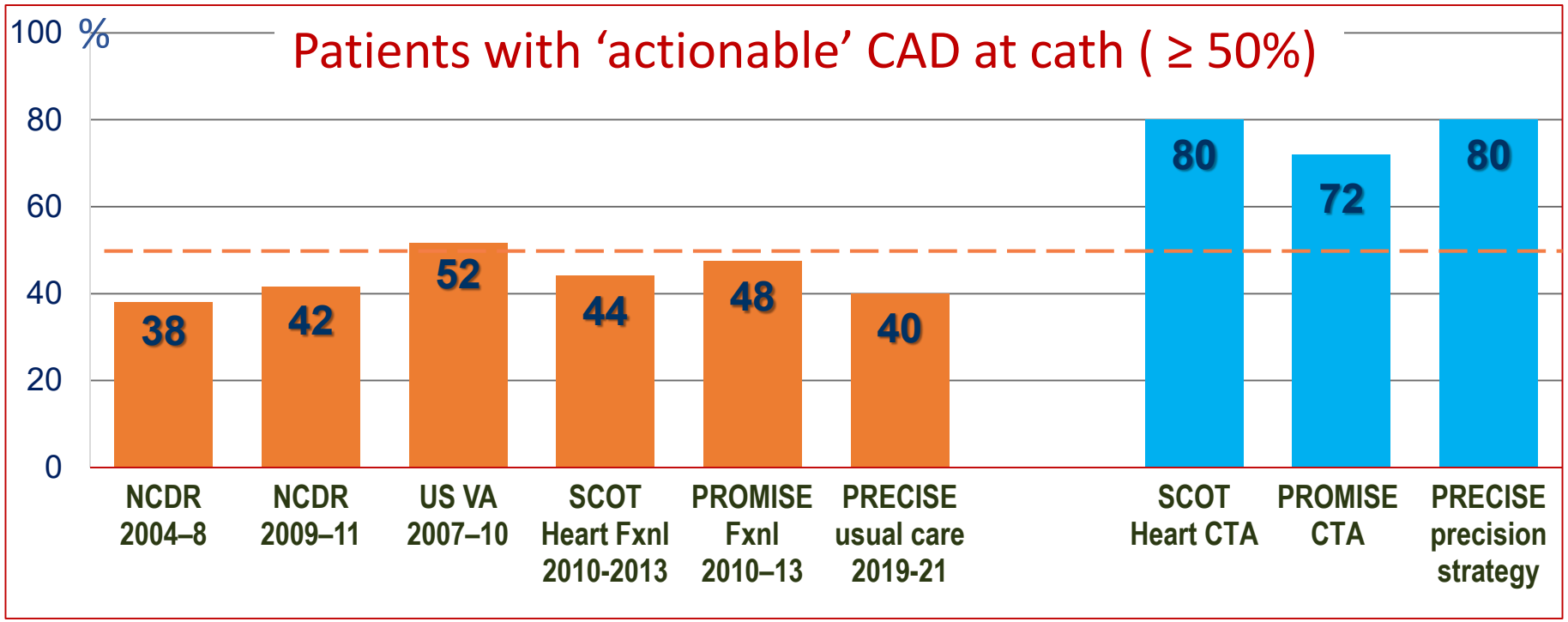
Overall Testing Intensity Related to Outcomes



JACC 2013 62:436

Is CTA a Better Gateway to Cath Lab Than Stress Testing?

- Standard NI testing has frequent false + and false – results.
- A CTA first testing strategy increases the proportion with obs CAD at cath
- A CTA first strategy reduces cath w/o actionable CAD and improves cath lab efficiency with increased conversion rate of dx cath to PCI ('yield')



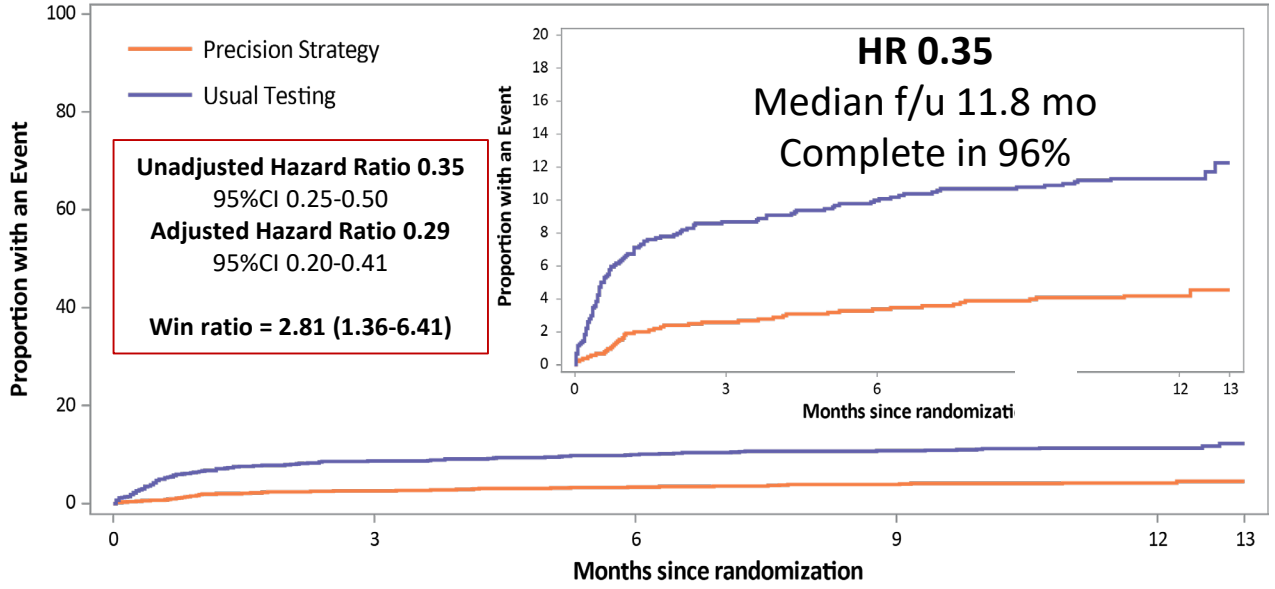
JAMA Cardiology | Original Investigation

PRECISE

Comparison of an Initial Risk-Based Testing Strategy vs Usual Testing in Stable Symptomatic Patients With Suspected Coronary Artery Disease

The PRECISE Randomized Clinical Trial

- 2103 stable angina patients requiring testing
- Randomized to precision strategy (CTA +/-FFR_{CT} or deferred testing) versus site choice of usual testing (including invasive cath)
- Primary Endpoint: Death, MI, or Cath w/o Obstructive CAD at 12 months
- Less testing w higher positive rate (18 vs 13%)
- 24% fewer catheterizations
- Higher rate obs CAD (80 vs 40%)
- 135% higher cath yield for revasc
- 1.8x more revasc

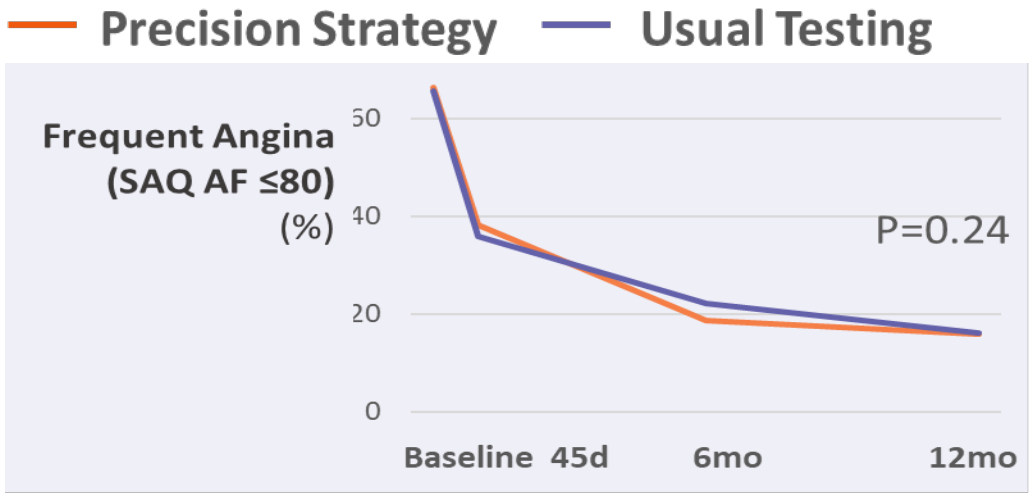


JAMA Cardiol 2023; 8:904

Although Important, Angina is not a Good Discriminator of Imaging Effectiveness

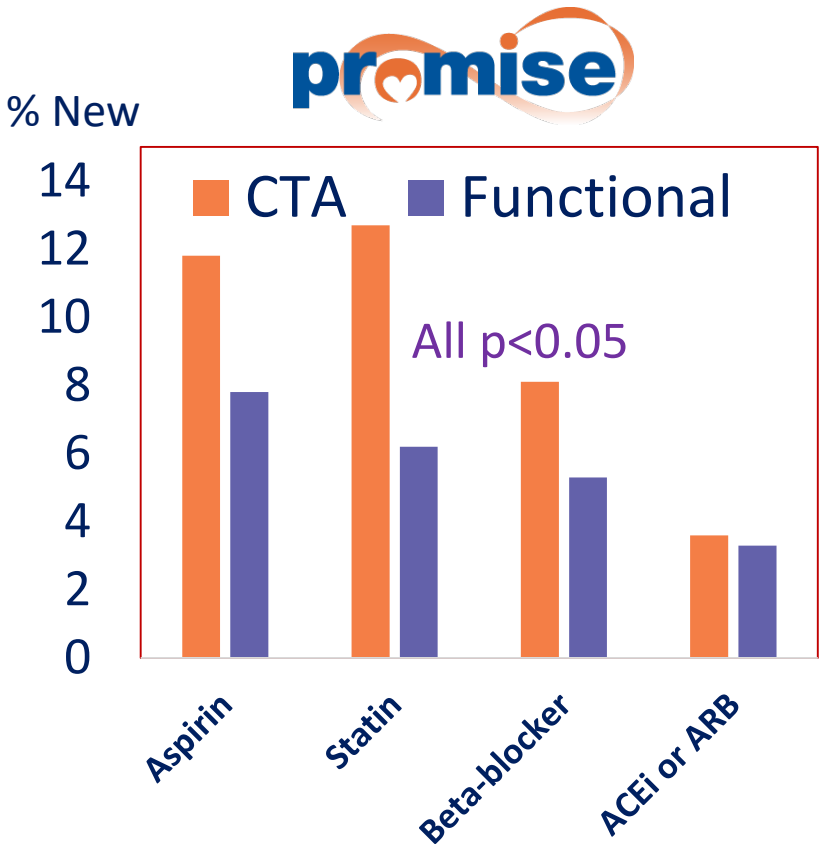
- CLARIFY registry: 32,691 pts with stable CAD
- Among the 7212 with angina, this 'disappeared' in 40% wo intervention at 1 y
  - 5 y outcomes similar to those who had never had angina
- Among those w/o angina, new onset 2-5%/y
- At 5 years, 7773 had controlled angina (84% wo intervention, 11% med Rx, 5% revasc)
- ORBITA1 &2: No difference in exercise time but less angina at 12 wks with PCI vs sham

PRECISE

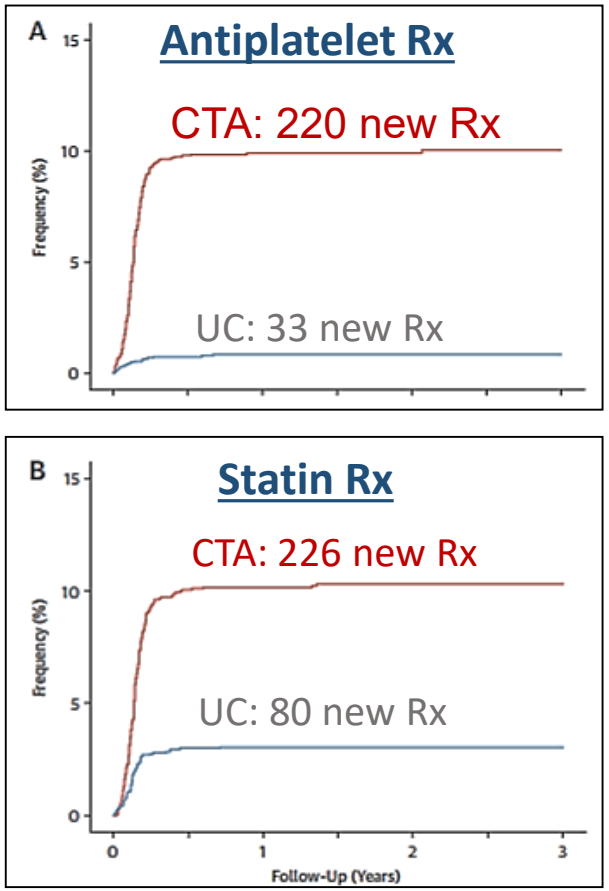


Circulation 2021;144:512
Lancet 2018; 391:31
NEJM 2023; 389:2319
JAMA Cards 2023; 8:904

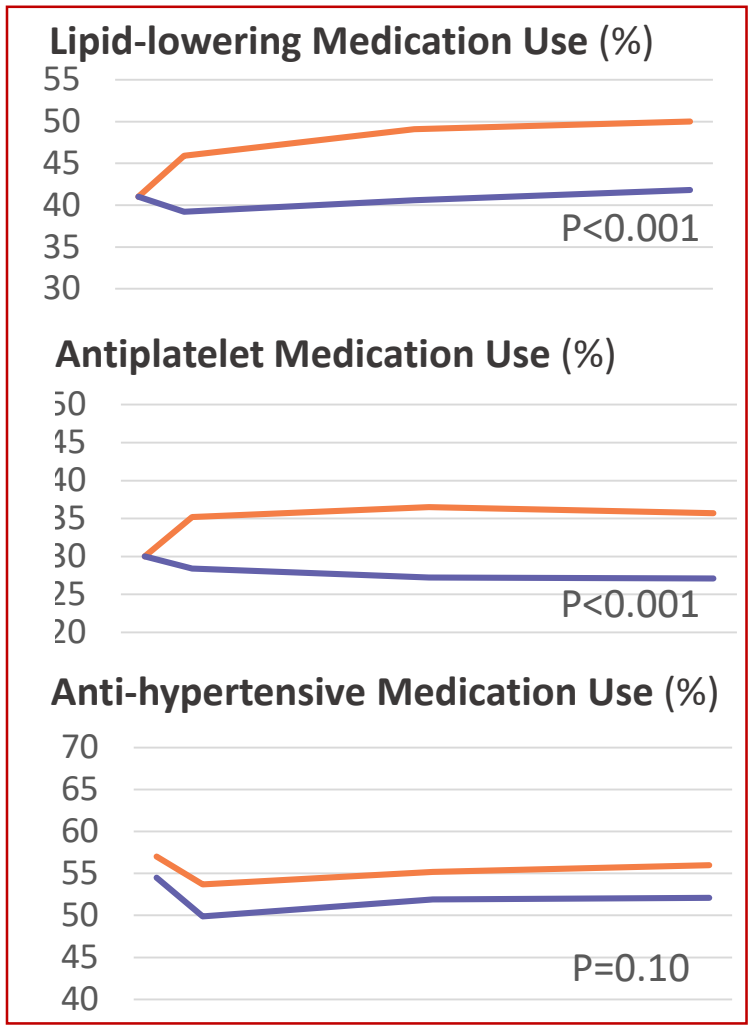
CTA: Enhanced Use of Preventive Medications: Diagnostic and Therapeutic Thinking



SCOT-HEART

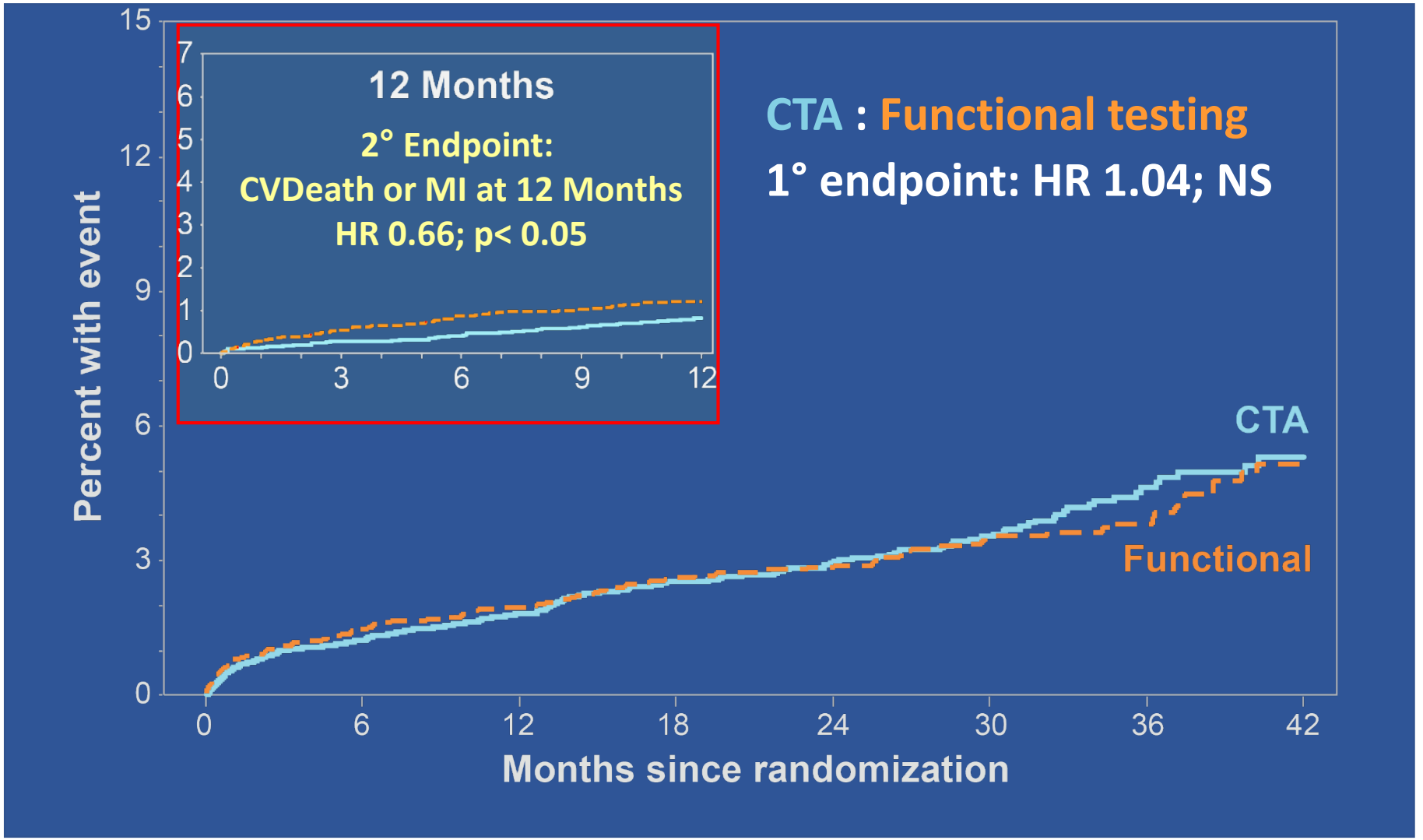


PRECISE



JAHA 2016; 5 pii: e003807
JACC 2016; 67:1759
JAMA Cards 2023; 8: 904

PROMISE 1° and 2° Endpoints: Results Depend on Endpoint and Timeframe

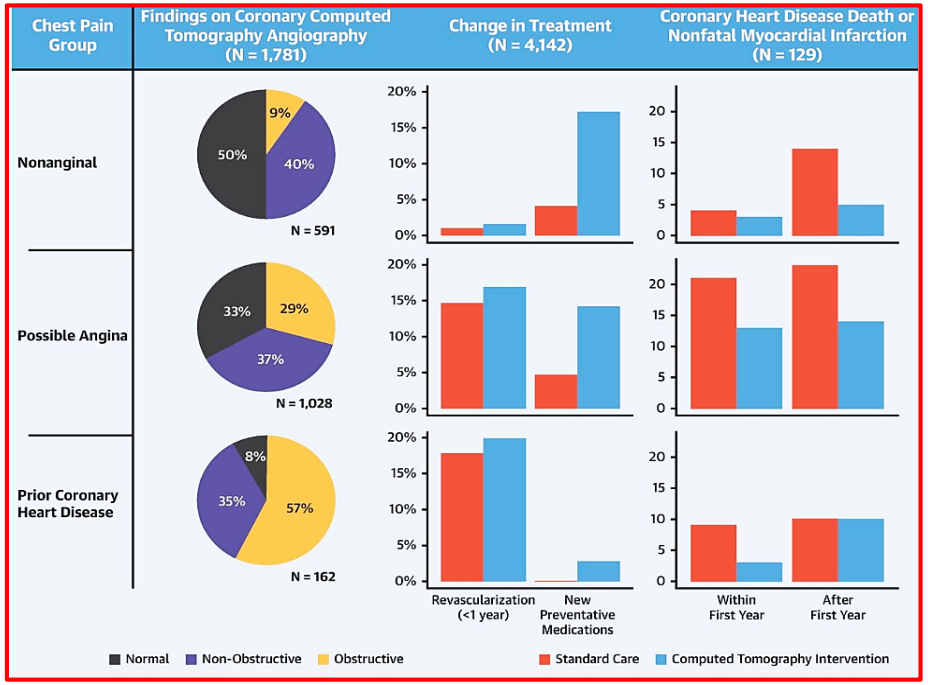


NEJM 2015; 372:1291

SCOT-HEART: Six Week and Five Year Results

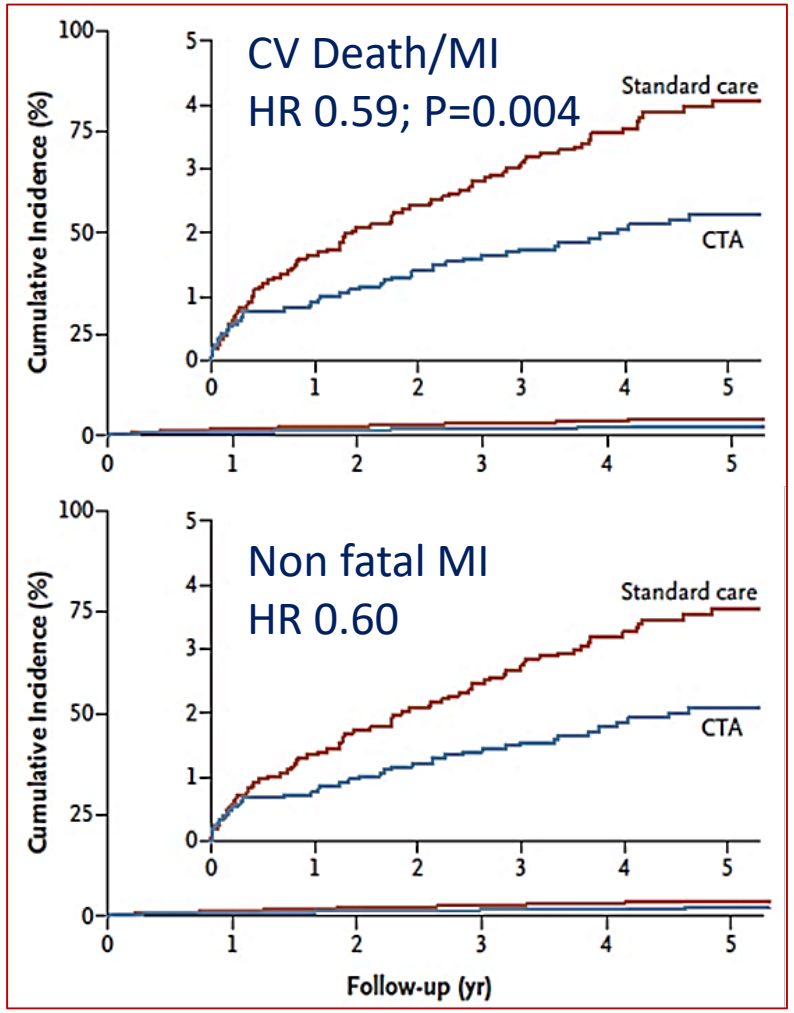
Six week results (Primary report)

- 1° endpoint: Dx of angina due to CAD
  - Improved dx thinking
- 2° endpoint: ↓ CV Death/MI (NS)
  - Improved outcomes



Lancet 2015; 385:2383

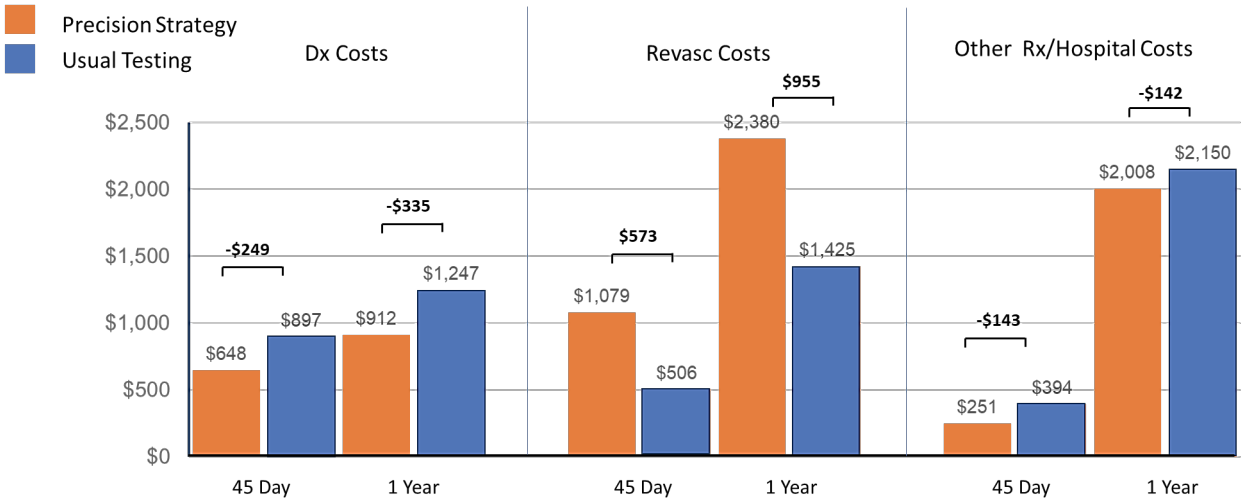
Five year results



NEJM 2018 379:924
JACC 2019 74:2058

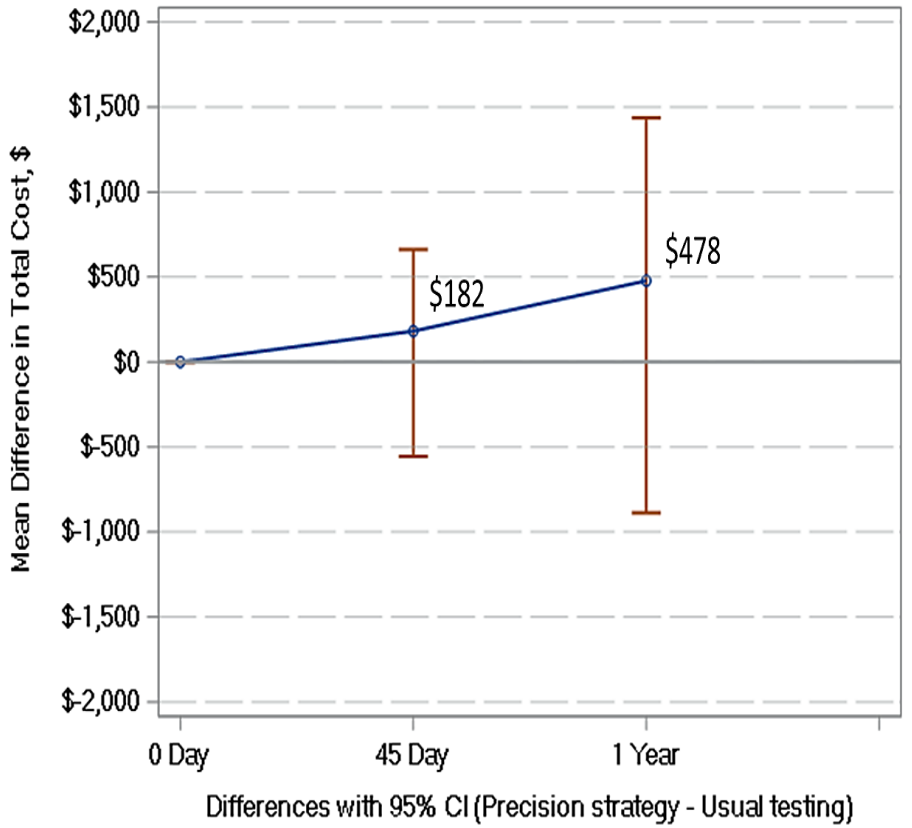
Cost in Chest Pain RCTs

- RCT 2103 stable sx pts
- Precision : CTA +/-FFR_{CT} or deferred testing
  vs Usual care (incl cath)
- Some variation in types of costs
- Improved efficiency with little net effect on costs



Mean Costs by Category

Overall Cost Differences at 1 Year



AHA 2023

Clinical Implications: What Events are We Trying to Avoid?

- Angina may not effectively discriminate between strategies
- Given the low risk of the stable chest pain population, use of MACE - type endpoints is largely infeasible (although still important for safety)
  - Little room for improvement in outcomes
  - Low death/MI event rates require large sample size and long follow up, and limit precision
- Intermediate endpoints such as diagnostic and therapeutic thinking are useful with impact on treatment (preventive medications, revascularization) being a major determinant of long term value
- Process of care/efficiency measures are important
- Costs are rarely a significant factor in comparing different testing approaches

Imaging Trials: Chest Pain Evaluation

- Pragmatic design considerations
- Who is the patient we want to study?
- What is the disease?
- Flexibility of the intervention
- What events are we trying to avoid?

THANK YOU !!