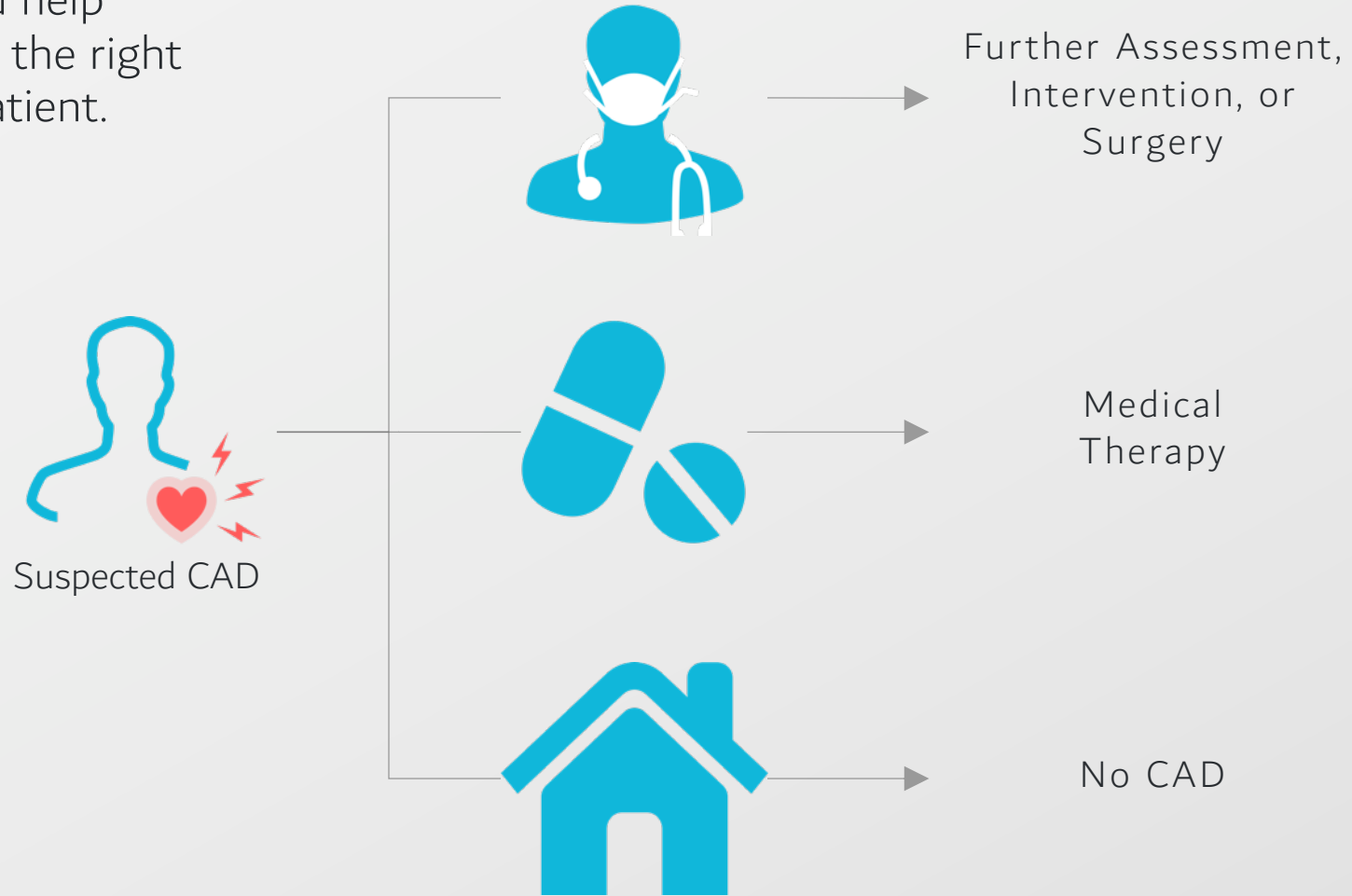


Outline

- ▶ Current ischemic evaluation strategies
- ▶ CCTA Background
- ▶ FFRct data
- ▶ FFRangio data
- ▶ Clinic pathway
- ▶ Cath pathway

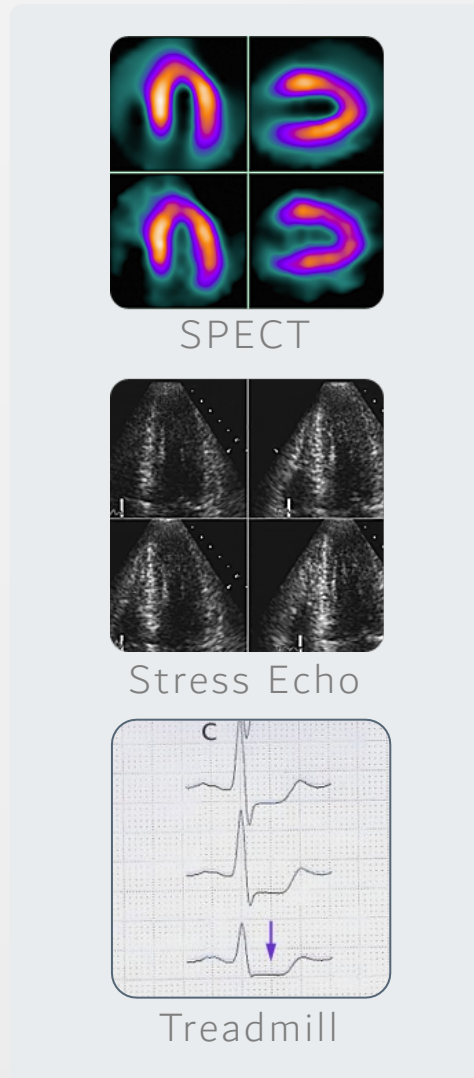
Non-invasive cardiac testing

Cardiac tests should help clinicians determine the right pathway for each patient.



A finding of No CAD does not diminish the role of initiating or continuing primary prevention efforts

Current reality of non-invasive cardiac testing



No **lesion-specific** information provided

High rate of **false positives**

55% of patients sent for an elective ICA following a non-invasive test have **no obstructive CAD**¹

High rate of **false negatives**

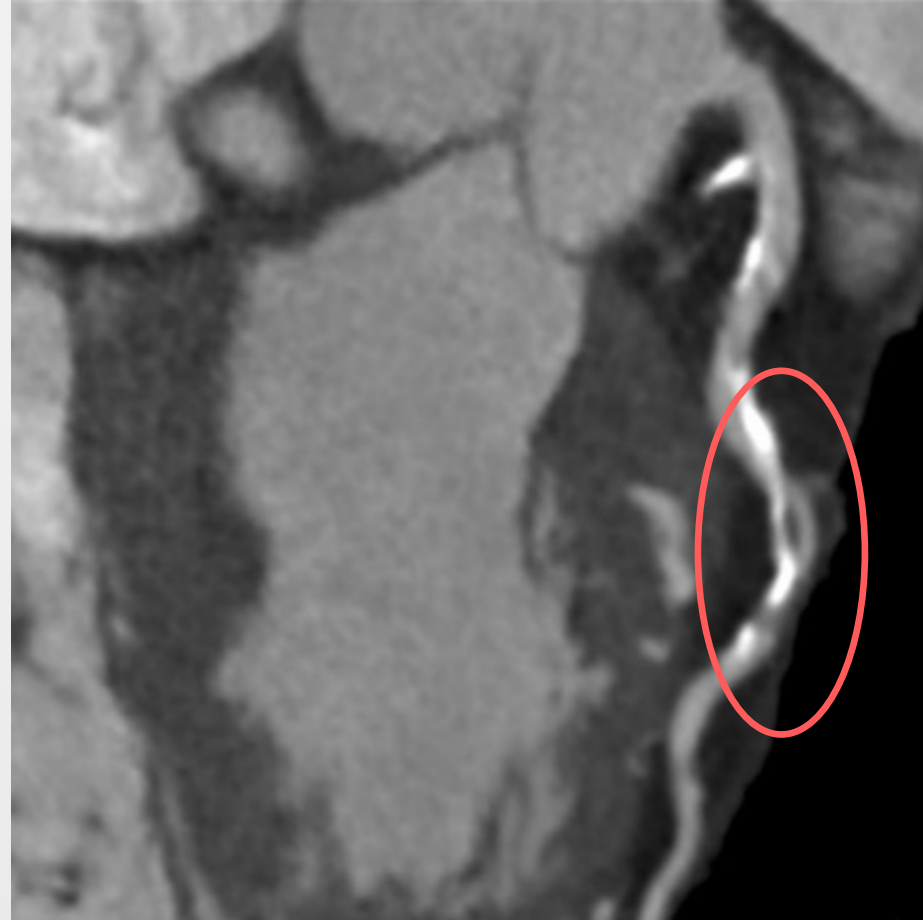
20-30% of patients will have a false negative result for obstructive CAD from a non-invasive test²

1. Patel, et al. N Engl J Med 2010. Patel, et al. AHJ 2014. Danad, et al. JAMA Cardiology 2017.
2. Arbab-Zadeh, Heart Int 2012. Yokota, et al. Neth Heart J 2018. Nakanishi, et al. J Nucl Cardiol 2018.

Case Study: A Common Clinical Occurrence

Patient Presentation

- ▶ 79 y/o female
- ▶ History: Shortness of breath, diabetes, previous silent myocardial infarction
- ▶ SPECT positive



Coronary CTA findings

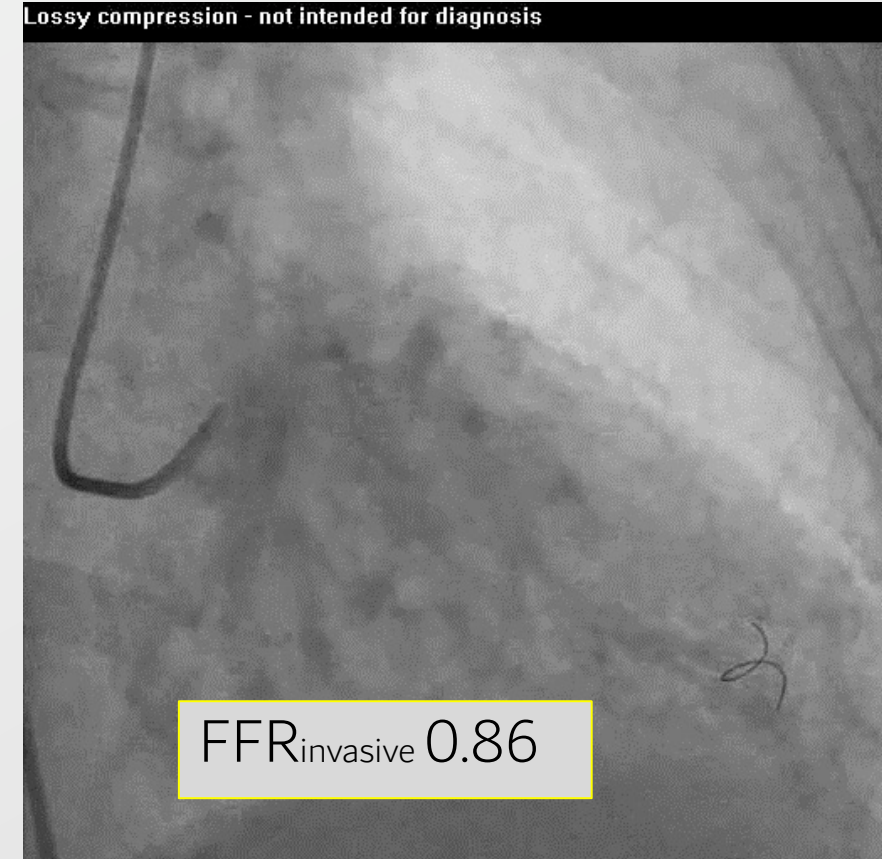
- ▶ Moderate-severe mid-LAD stenosis (70-80%)

Case Study: A Common Clinical Occurrence

Invasive Angiogram

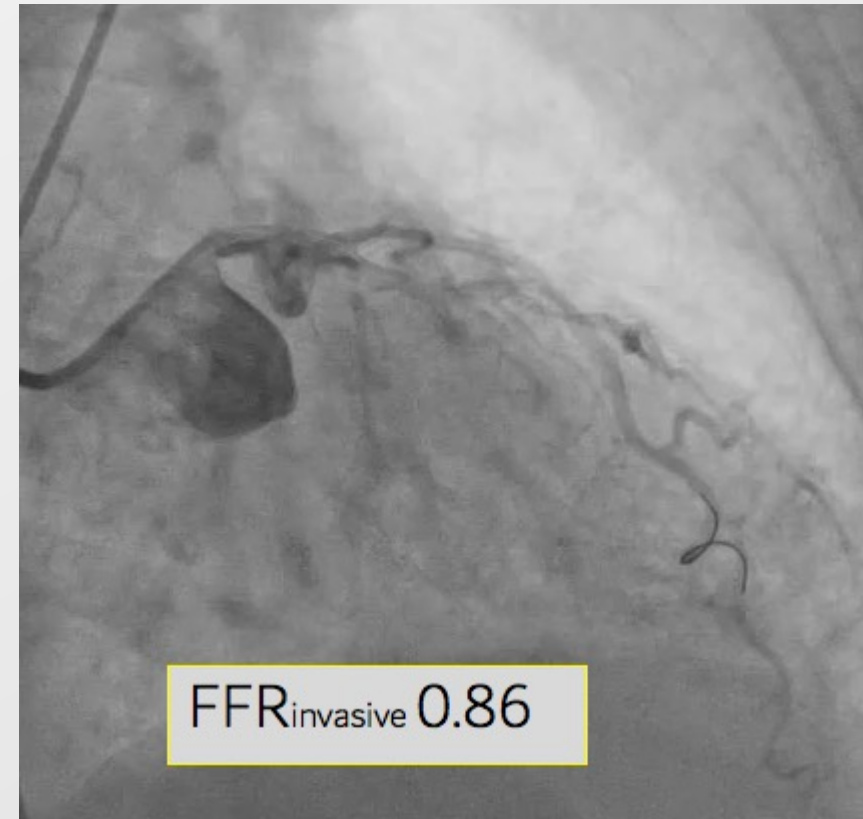
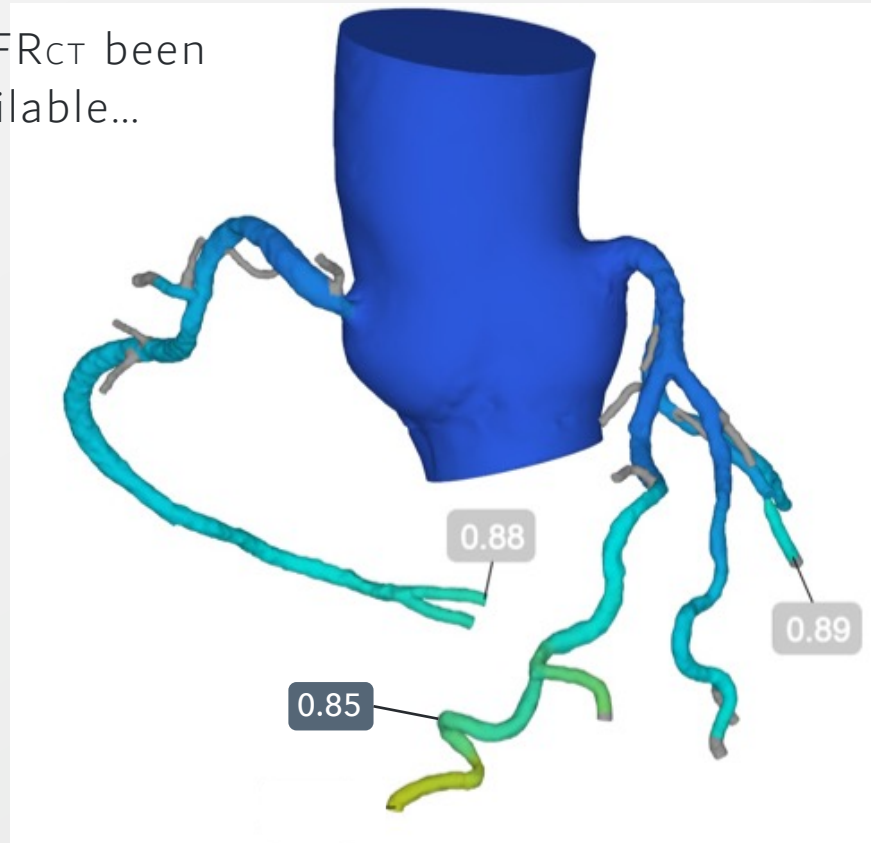


No meaningful blockage:
Invasive FFR suggests no intervention is needed

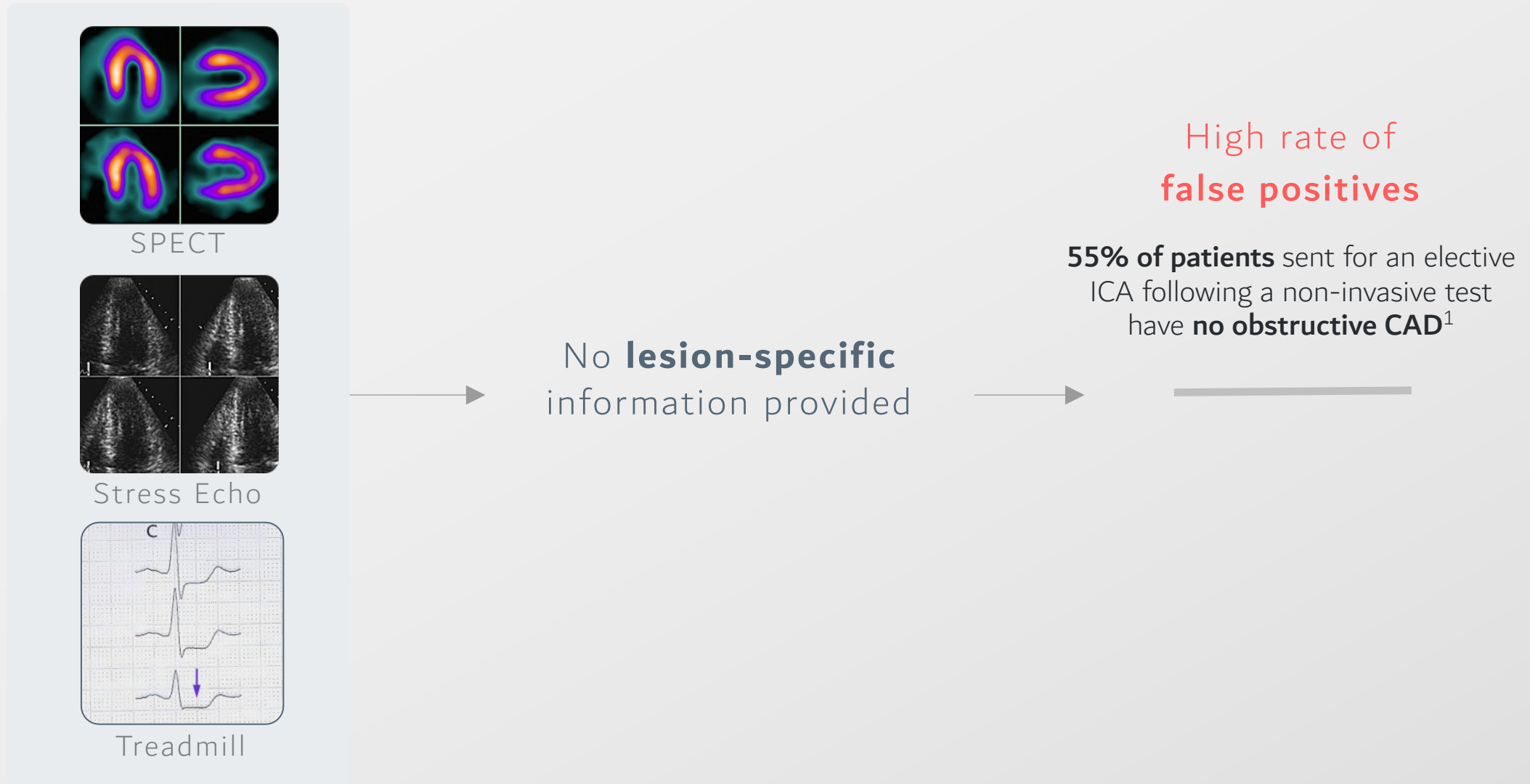


Case Study: A Common Clinical Occurrence

Had FFR_{CT} been available...



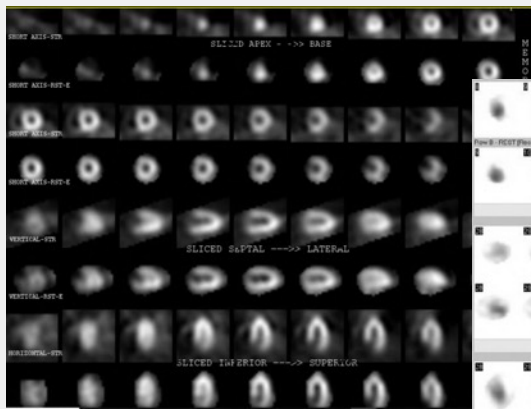
Current reality of non-invasive cardiac testing



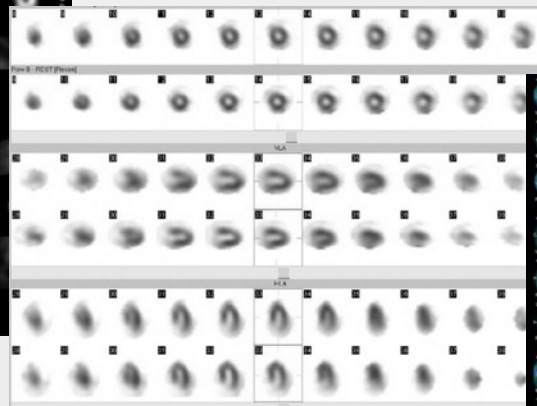
Case Study: Under-diagnosing disease

- ▶ 87 y/o female
- ▶ History: Persistent chest pain
- ▶ Repeated negative SPECT tests over 13 years

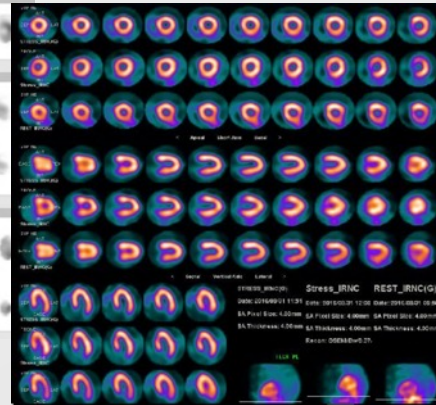
2005: Negative SPECT



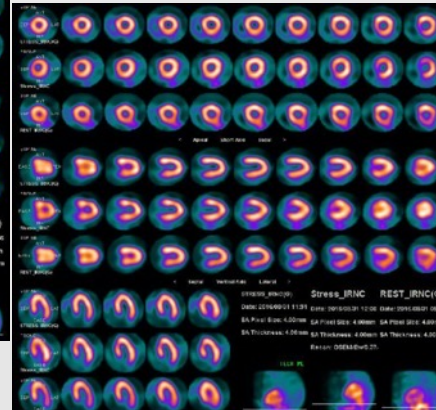
2011: Negative SPECT



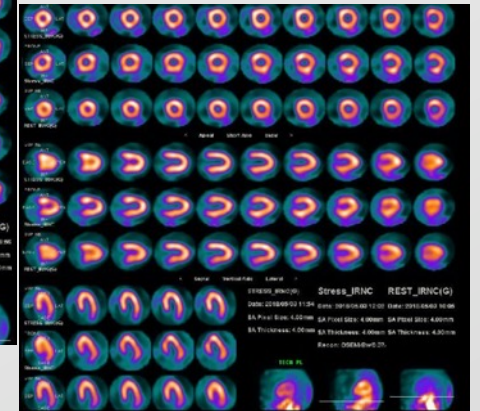
2015: Negative SPECT



2016: Negative SPECT



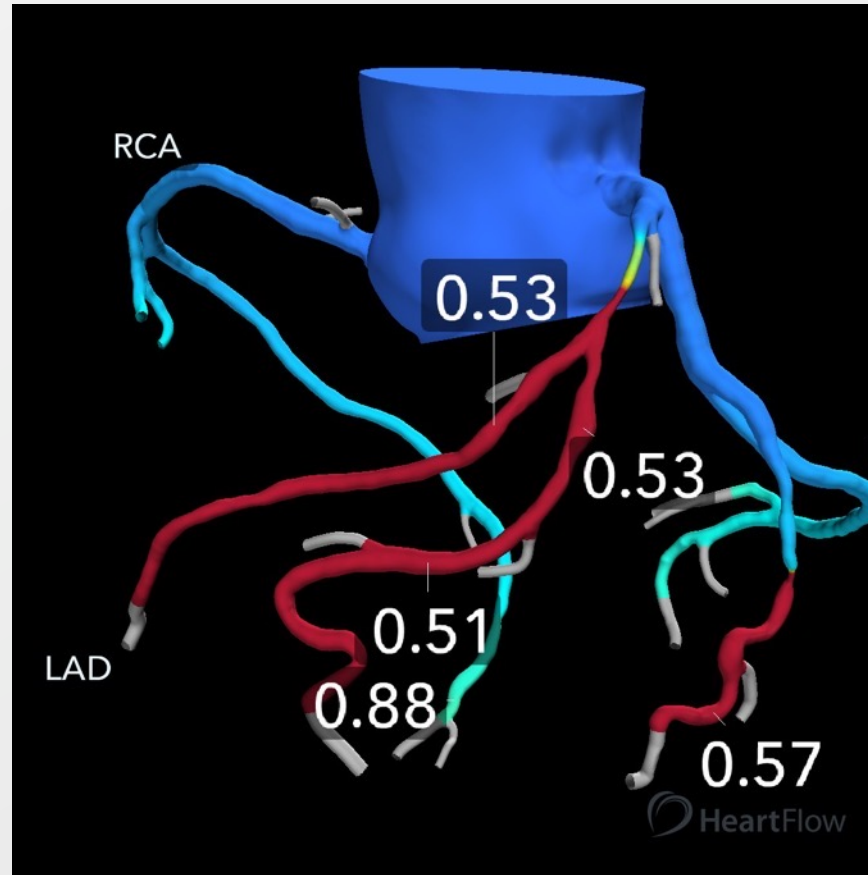
2018: Negative SPECT



Case Study: Under-diagnosing disease



CCTA shows narrowings of multiple coronary arteries

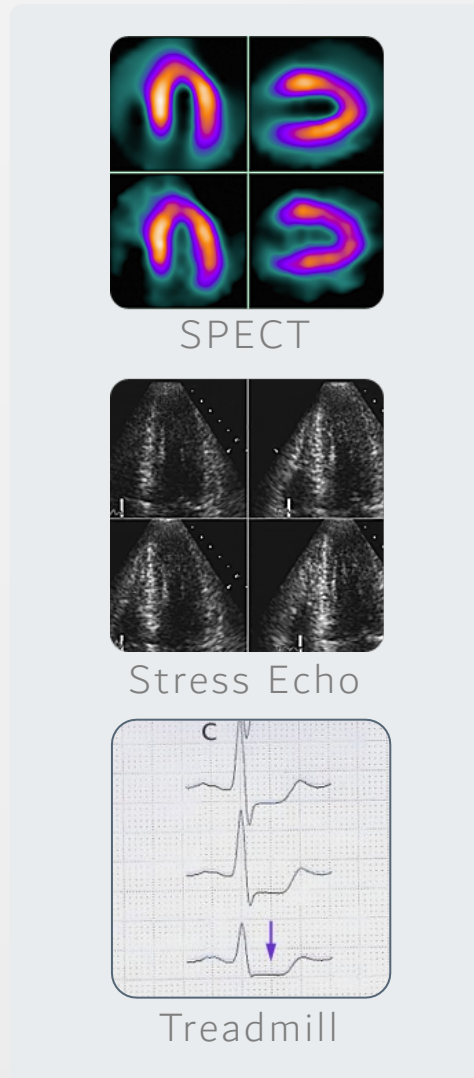


FFR_{CT} shows two coronary arteries with functionally-significant disease and low FFR_{CT} values (0.50-0.60 range) enabling invasive treatment and resolution of symptoms



Invasive angiogram validates findings of narrowings in two coronary arteries

Current reality of non-invasive cardiac testing



No **lesion-specific** information provided

High rate of **false positives**

55% of patients sent for an elective ICA following a non-invasive test have **no obstructive CAD**¹

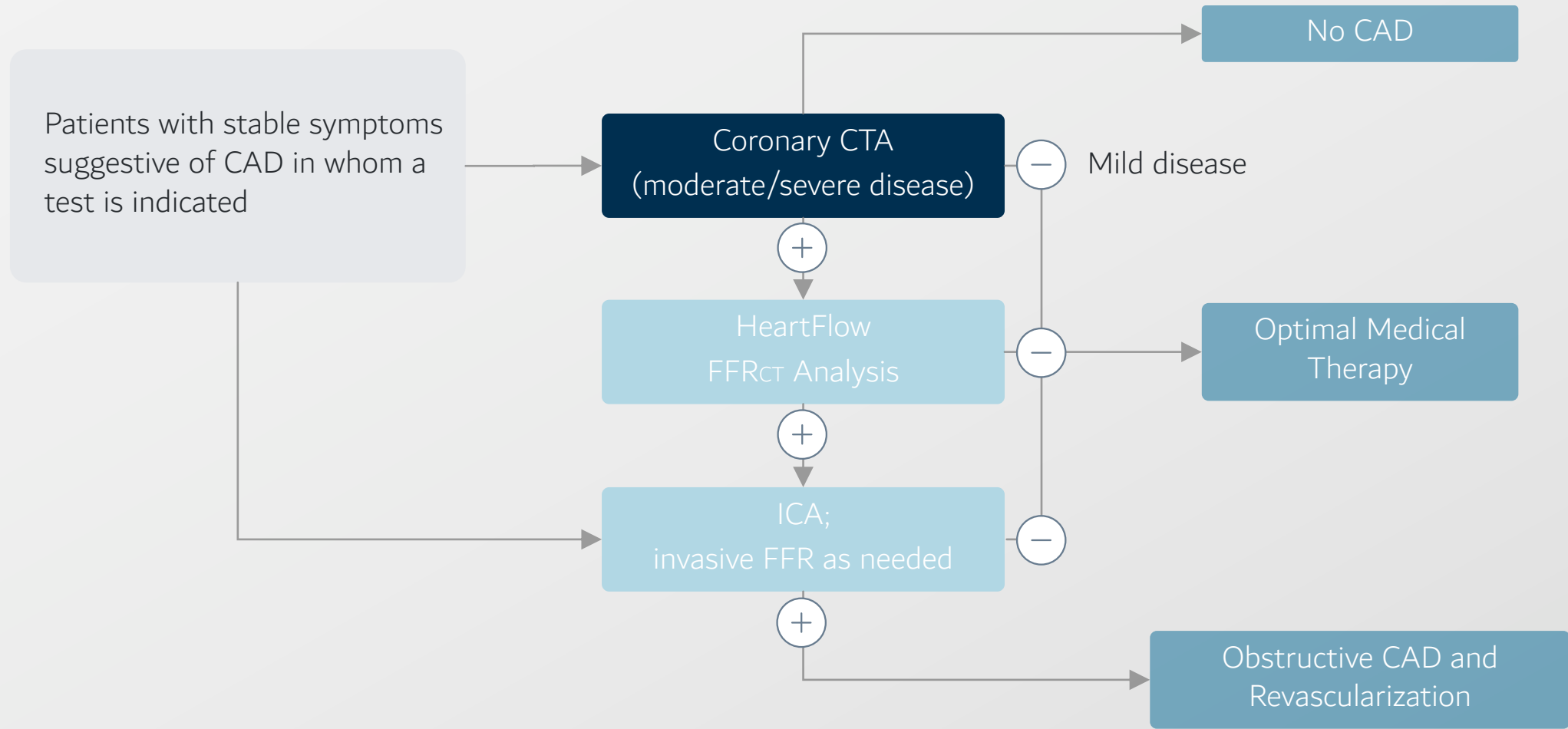
High rate of **false negatives**

20-30% of patients will have a false negative result for obstructive CAD from a non-invasive test²

1. Patel, et al. N Engl J Med 2010. Patel, et al. AHJ 2014. Danad, et al. JAMA Cardiology 2017.
2. Arbab-Zadeh, Heart Int 2012. Yokota, et al. Neth Heart J 2018. Nakanishi, et al. J Nucl Cardiol 2018.

A better cardiac testing pathway starts with coronary CTA

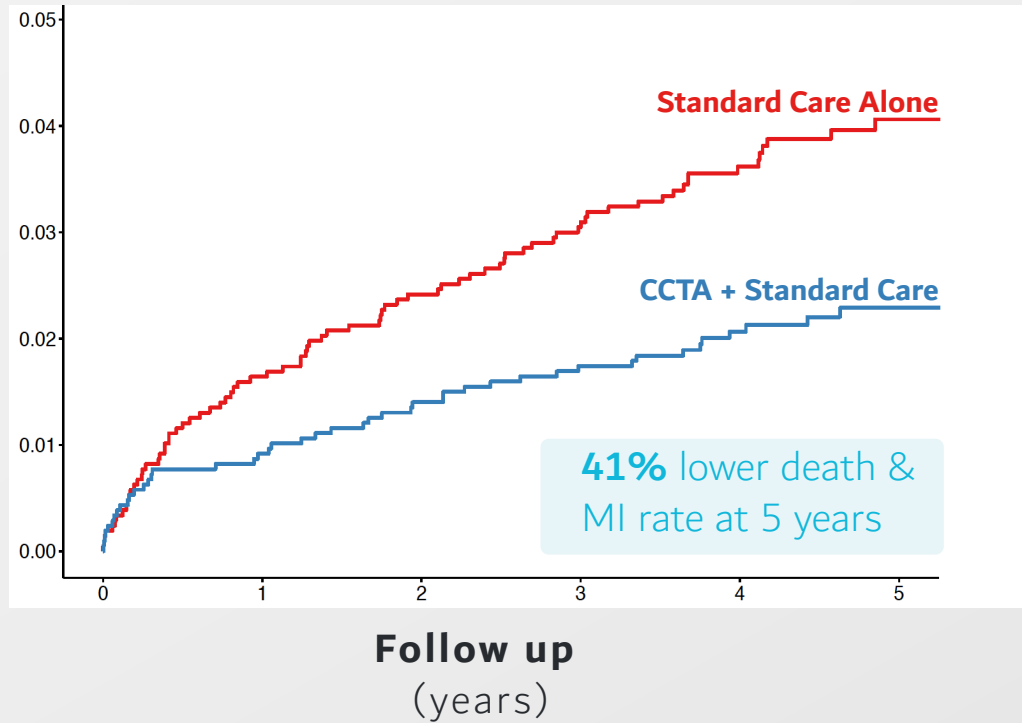
Coronary CTA answers the clinically relevant questions for patients with suspected CAD



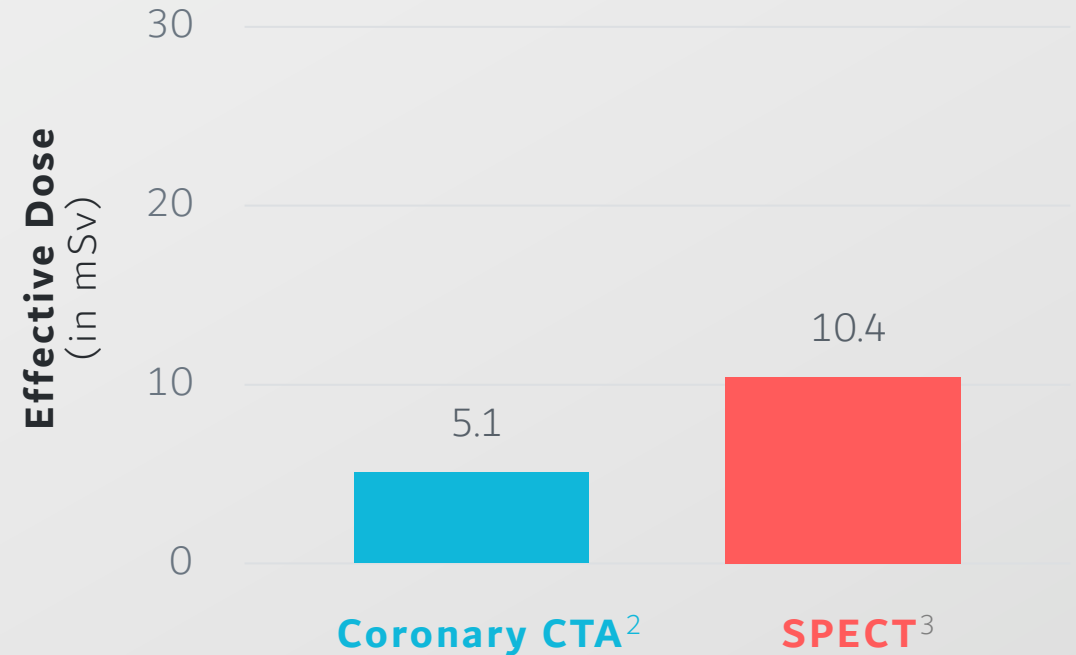
A better cardiac testing pathway starts with coronary CTA

Improved Long-term Outcomes: Coronary CTA + Standard Care (SCOT-HEART¹)

Coronary Heart Disease Death or
Nonfatal Myocardial Infarction



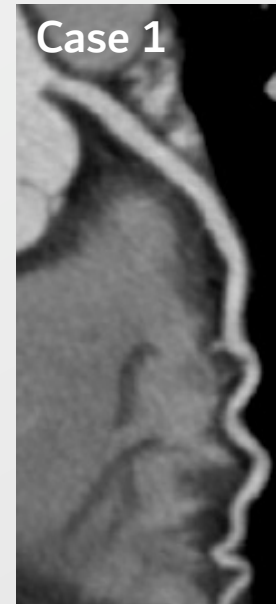
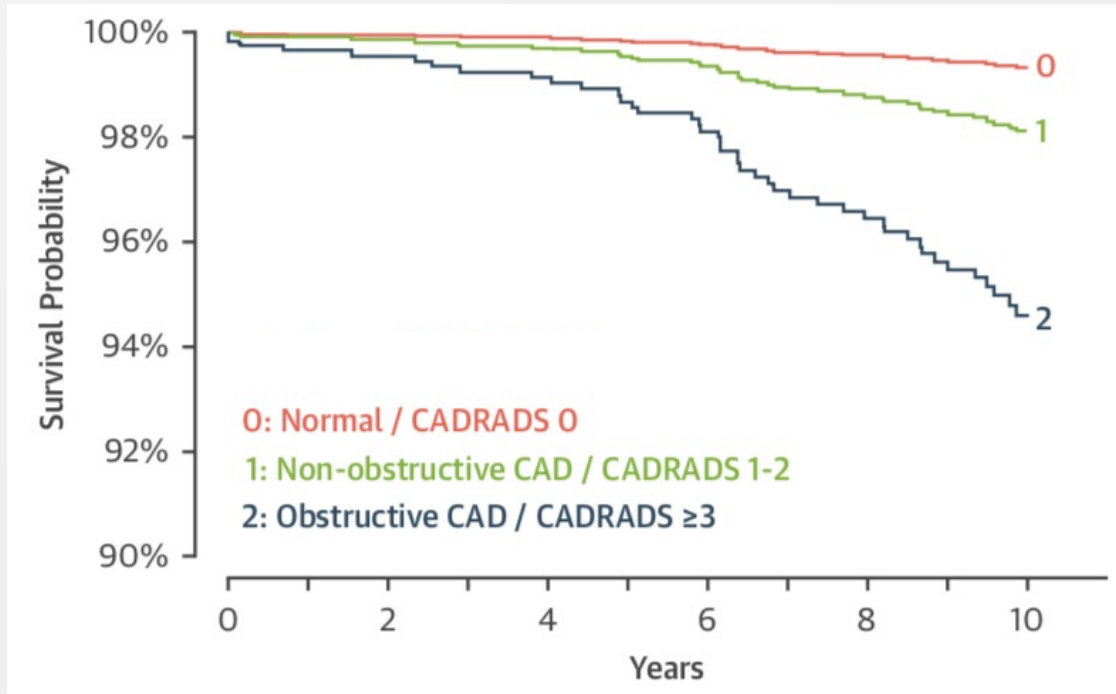
Lower Radiation than SPECT: Coronary CTA (PROTECTION VI²)



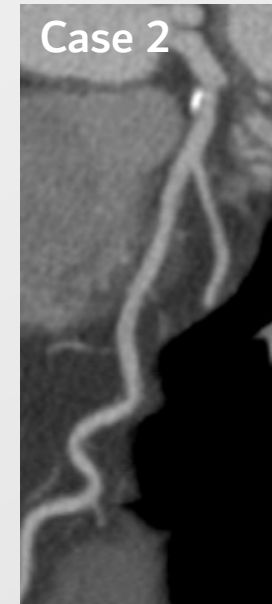
73474022 v1

A better cardiac testing pathway starts with coronary CTA

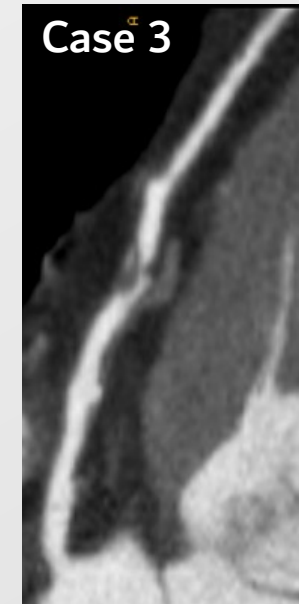
Coronary CTA's high negative predictive value gives confidence when no disease is found



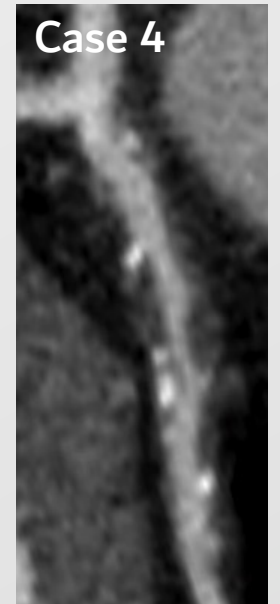
CADRADS 0



CADRADS 1-2



CADRADS 3



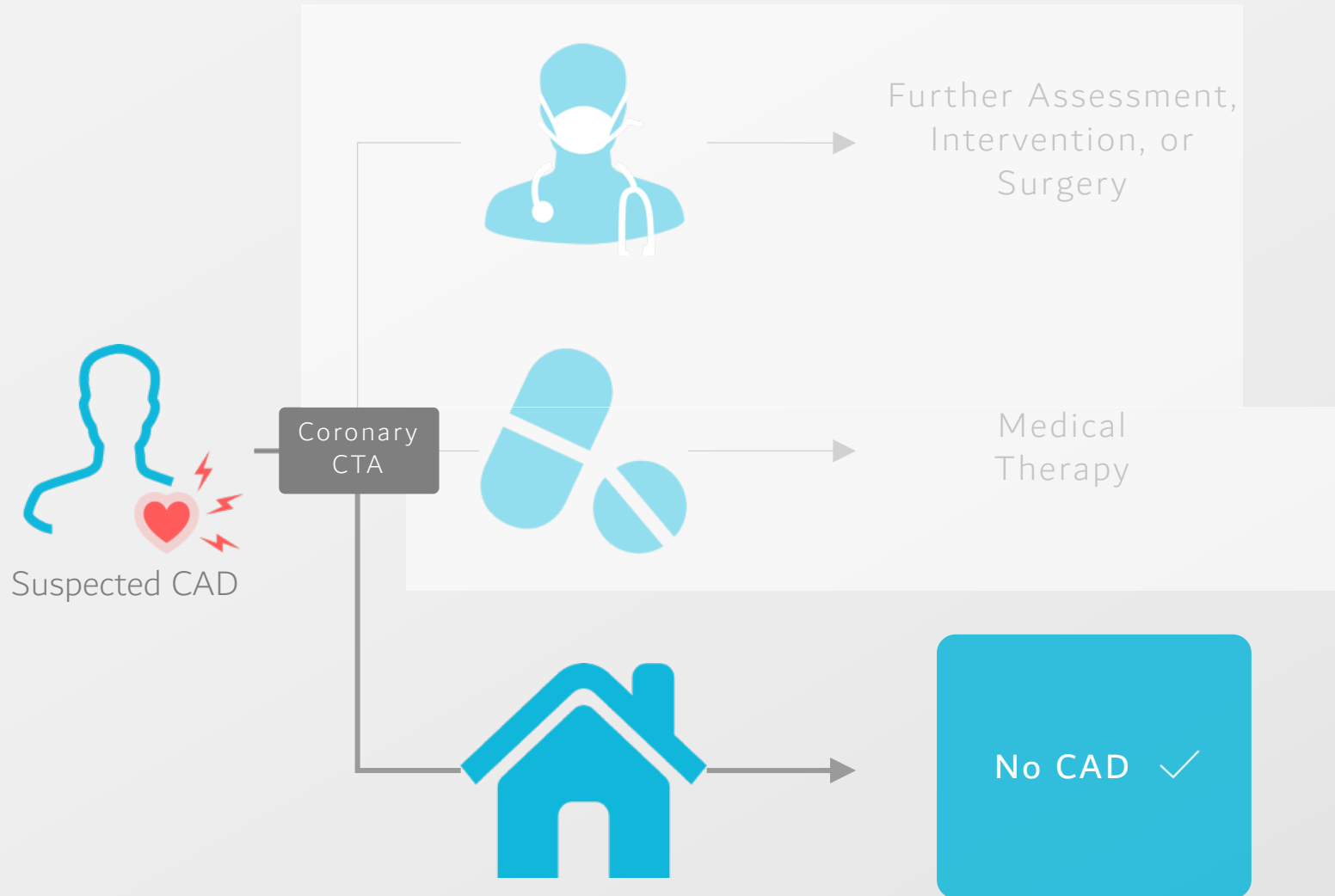
CADRADS ≥3

“Warranty Period” of a normal CCTA > 8 years

CAD-RADS reporting for patients with stable chest pain

CAD-RADS Classification	Degree of Maximal Coronary Stenosis	Interpretation	Further Cardiac Investigation	Management
CAD-RADS 0	0% (No plaque or stenosis)	Documented absence of CAD*	None	Reassurance. Consider non-atherosclerotic causes of chest pain
CAD-RADS 1	1-24% - Minimal stenosis or plaque with no stenosis**	Minimal non-obstructive CAD	None	Consider non-atherosclerotic causes of chest pain Consider preventive therapy and risk factor modification
CAD-RADS 2	25-49% - Mild stenosis	Mild non-obstructive CAD	None	Consider non-atherosclerotic causes of chest pain Consider preventive therapy and risk factor modification, particularly for patients with non-obstructive plaque in multiple segments.
CAD-RADS 3	50-69% stenosis	Moderate stenosis	Consider functional assessment	Consider symptom-guided anti-ischemic and preventive pharmacotherapy as well as risk factor modification per guideline-directed care*** Other treatments should be considered per guideline-directed care***
CAD-RADS 4	A - 70-99% stenosis or B - Left main >50% or 3-vessel obstructive (≥70%) disease	Severe stenosis	A: Consider ICA or functional assessment B: ICA is recommended	Consider symptom-guided anti-ischemic and preventive pharmacotherapy as well as risk factor modification per guideline-directed care*** Other treatments (including options of revascularization) should be considered per guideline-directed care***
CAD-RADS 5	100% (total occlusion)	Total coronary occlusion	Consider ICA and/or viability assessment	Consider symptom-guided anti-ischemic and preventive pharmacotherapy as well as risk factors modification per guideline-directed care*** Other treatments (including options of revascularization) should be considered per guideline-directed care***

A better cardiac testing pathway starts with coronary CTA



Only coronary CTA
differentiates patients with
moderate to severe CAD...

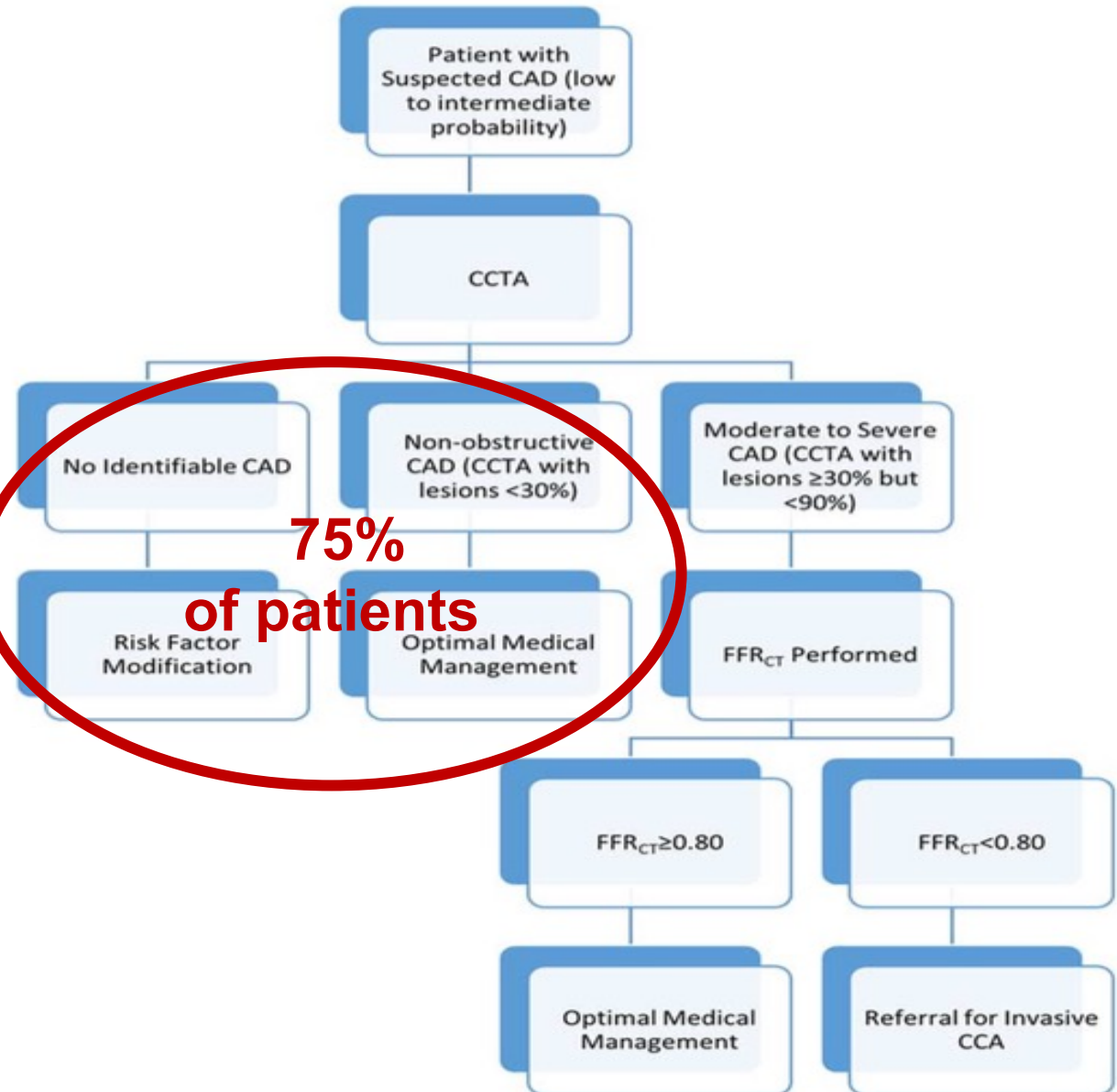
... **from** patients with
mild to no CAD.

What happens to patients in this pathway?



cCTA is a high value test.

cCTA alone provides enough information to completely diagnose 3 out of 4 patients and, as appropriate, to enable initiation of medical treatment for early-stage disease.



A better cardiac testing pathway starts with coronary CTA


Coronary CTA is the preferred pathway in the UK...



Coronary CTA as a frontline test* for patients with:

- typical or atypical chest pain, or
- abnormal 12-lead resting EKG


... and is being called for **globally**

 **ESC** European Society of Cardiology
European Heart Journal (2019) 0, 1–14
doi:10.1093/eurheartj/ehz024

CLINICAL REVIEW
Controversies in cardiovascular medicine

Should NICE guidelines be universally accepted for the evaluation of stable coronary disease? A debate

Harvey S. Hecht^{1*}, Leslee Shaw², Y.S. Chandrashekar³, Jeroen J. Bax⁴, and Jagat Narula¹

EDITORIAL COMMENT  **JACC**
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Coronary CT Angiography in New-Onset Stable Chest Pain
Time for U.S. Guidelines to Be NICEr*

Michael J. Blaha, MD, MPH,^{a,b} Miguel Cainzos-Achirica, MD MPH^{a,c,d}

*See NICE Guidance for Chest Pain of Recent Onset (CG95)

2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain

A Report of the American College of Cardiology/American Heart Association
Joint Committee on Clinical Practice Guidelines

COR	LOE	RECOMMENDATIONS
Index Diagnostic Testing		
Anatomic Testing		
1	A	1. For intermediate-risk patients with acute chest pain and no known CAD eligible for diagnostic testing after a negative or inconclusive evaluation for ACS, CCTA is useful for exclusion of atherosclerotic plaque and obstructive CAD (1-11).
1	C-EO	2. For intermediate-risk patients with acute chest pain, moderate-severe ischemia on current or prior (≤ 1 year) stress testing, and no known CAD established by prior anatomic testing, ICA is recommended.
2a	C-LD	3. For intermediate-risk patients with acute chest pain with evidence of previous mildly abnormal stress test results (≤ 1 year), CCTA is reasonable for diagnosing obstructive CAD (12,13).

Accuracy of FFR_{CT} Compared to Gold Standard



DISCOVER-FLOW

- ▶ Completed 2011
- ▶ N=103 patients

DeFACTO

- Completed 2012
- N=252 patients

NXT

- Completed 2013
- N=254 patients

NXT Per-Vessel Performance

- Specificity: 86%
- Sensitivity: 84%
- Accuracy: 86%

Data supported 2014 FDA Clearance

Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 55, No. 18, 2011
ISSN 0735-1017/11/\$36.00
doi:10.1016/j.jacc.2011.06.016

Cardiac Imaging

Diagnosis of Ischemia-Causing Coronary Stenoses by Noninvasive Fractional Flow Reserve Computed From Coronary Computed Tomographic Angiograms

Results From the Prospective Multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) Study

Bon-Kwon Koo, MD, PhD,² Andrejs Erglis, MD, PhD,¹ Joon-Hyung Doh, MD, PhD,³ David V. Daniels, MD,⁵ Sandra Jegere, MD,¹ Hyo-Soo Kim, MD, PhD,⁴ Allison Dunning, MD,⁶ Tony DeFranco, MD,⁷ Alexandra Lansky, MD,⁸ Jonathan Leipsic, BSc, MD,¹ James K. Min, MD,¹†
Soul and Gyeongju, South Korea; Riga, Latvia; Palo Alto, San Francisco, and Los Angeles, California; New York, New York; New Haven, Connecticut; and Vancouver, British Columbia, Canada

Objectives The aim of this study was to determine the diagnostic performance of a new method for quantifying fractional flow reserve (FFR) with noninvasive fractional flow reserve (FFR_{CT}) applied to coronary computed tomography angiography (CTA) data in patients with suspected or known coronary artery disease (CAD).

Background Measurement of FFR during invasive coronary angiography is the gold standard for identifying coronary artery lesions that cause ischemia and improves clinical decision-making for revascularization. Computation of FFR from CTA data (FFR_{CT}) provides a noninvasive method for identifying ischemia-causing stenoses; however, the diagnostic performance of this new method is unknown.

Methods Computation of FFR from CTA data was performed on 159 vessels in 103 patients undergoing CTA, invasive coronary angiography, and FFR. Independent core laboratories determined FFR_{CT} and CAD diagnosis concurrently by CTA, ischemia was defined by an FFR_{CT} and FFR <0.80, and anatomically obstructive CAD was defined as a CTA with stenosis ≥50%. Diagnostic performance of FFR_{CT} and CTA stenosis was assessed with invasive FFR as the reference standard.

Results Fifty-six percent of patients had ≥1 vessel with FFR <0.80. On a per-vessel basis, the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 84.2%, 87.0%, 82.2%, 73.9%, 92.2%, respectively, for FFR_{CT} and were 88.8%, 91.4%, 29.6%, 46.8%, 88.9%, respectively, for CTA stenosis. The area under the receiver-operator characteristic curve was 0.80 for FFR_{CT} and 0.76 for CTA (p < 0.0003). The FFR_{CT} and FFR were well correlated (r = 0.737, p < 0.0001) with a slight underestimation by FFR_{CT} (0.022 ± 0.116, p = 0.016).

Conclusions Noninvasive FFR derived from CTA is a novel method with high diagnostic performance for the detection and location of coronary lesions that cause ischemia. (The Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve: NCT01189333.) (J Am Coll Cardiol 2011;58:1989–97) © 2011 by the American College of Cardiology Foundation

From the ¹Department of Medicine, Saint Michael's University Hospital, Seoul, South Korea; ²Department of Medicine, Puh-Sook Chul University Hospital, Riga, Latvia; ³Department of Medicine, National University School of Medicine, Puh-Sook Chul University Hospital, Seoul, South Korea; ⁴Department of Medicine, Seoul National University School of Medicine, Seoul, South Korea; ⁵Department of Medicine, Stanford University School of Medicine, Palo Alto, California; ⁶Division of Cardiology, Puh-Sook Chul University Hospital, Riga, Latvia; ⁷Department of Public Health, Weill Cornell Medical College, New York, New York; ⁸UCSF, San Francisco, California; ⁹Department of Cardiology, Puh-Sook Chul University Hospital, Seoul, South Korea; ¹⁰Department of Radiology, Puh-Sook Chul University School of Medicine, New Haven, Connecticut; ¹¹Department of Radi-

ology, St. Paul's Hospital, Vancouver, British Columbia, Canada; and the ¹²Cardiac MRI Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California. Dr. Daniels is the Speaker's Bureau and medical advisory board of GE Healthcare. All other authors have reported that they have no relationship relevant to the contents of this paper to disclose.

Manuscript received April 26, 2011; revised manuscript received June 21, 2011; accepted June 27, 2011.

CORONARY COMPUTED TOMOGRAPHIC (CT) ANGIOGRAPHY IS A noninvasive test that enables direct visualization of coronary artery disease (CAD) and correlates favorably with invasive coronary angiography (ICA) for measures of stenosis severity.¹ However, CT cannot determine the hemodynamic significance of CAD, and even among CT-identified obstructive stenoses confirmed by ICA, fewer than half are ischemia-causing.^{2,3} These findings underscore an unreliable relationship of stenosis severity to ischemia and have raised concerns that use of CT may precipitate unnecessary ICA and coronary revascularization for patients who do not have ischemia.^{4,5}

These concerns stem from recent randomized trials that have identified no survival benefit for patients who undergo angiographically based coronary revascularization.^{6,7} As an ad-

For additional comment see p 1269.

© 2011 American Medical Association. All rights reserved.

JAMA, September 26, 2011; Vol. 306, No. 12 1237

ORIGINAL CONTRIBUTION

ONLINE FIRST

Diagnostic Accuracy of Fractional Flow Reserve From Anatomic CT Angiography

James K. Min, MD
Jonathan Erglis, MD
Michael J. Penciner, PhD
Daniel S. Herman, MD
Bon-Kwon Koo, MD
Carlos van Marrewijk, MD
Andrejs Erglis, MD
Pao Y. Liu, MD
Allison M. Dunning, MS
Patricia Apeztegui, MS
Matthew J. Budoff, MD
Jason H. Cole, MD
Farooq A. Jaffer, MD
Martin B. Leon, MD
Jennifer Maloney, MD
G. B. John Mancini, MD
Seung-Jung Park, MD
Robert S. Schwartz, MD
Leslee J. Shaw, PhD
Laura Mauri, MD

Context Coronary computed tomographic (CT) angiography is a noninvasive anatomic test for diagnosis of coronary stenosis that does not determine whether a stenosis causes ischemia. In contrast, fractional flow reserve (FFR) is a physiologic measure of coronary stenosis expressing the amount of coronary flow distal to a stenosis despite the presence of a stenosis, but it requires an invasive procedure. Noninvasive FFR computed from CT (FFR_{CT}) is a novel method for determining the physiologic significance of coronary artery disease (CAD), but its ability to identify ischemia has not been adequately examined to date.

Objective To assess the diagnostic performance of FFR_{CT} plus CT for diagnosis of hemodynamically significant coronary stenosis.

Design, Setting, and Patients Multicenter diagnostic performance study involving 252 stable patients with suspected or known CAD from 17 centers in 5 countries who underwent CT, invasive coronary angiography (ICA), FFR, and FFR_{CT} between October 2010 and October 2011. Computed tomography, ICA, FFR, and FFR_{CT} were interpreted in blinded fashion by independent core laboratories. Accuracy of FFR_{CT} plus CT for diagnosis of ischemia was compared with an invasive FFR reference standard. Ischemia was defined by an FFR or FFR_{CT} of 0.80 or less, while anatomically obstructive CAD was defined by a stenosis of 50% or larger on CT and ICA.

Main Outcome Measures The primary study outcome assessed whether FFR_{CT} plus CT could improve the per-patient diagnostic accuracy such that the lower boundary of the 1-sided 95% confidence interval of the estimate exceeded 70%.

Results Among study participants, 137 (54.4%) had an abnormal FFR determined by ICA. On a per-patient basis, diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of FFR_{CT} plus CT were 73% (95% CI, 62%–78%), 90% (95% CI, 84%–95%), 54% (95% CI, 46%–62%), 67% (95% CI, 60%–74%), and 84% (95% CI, 74%–90%), respectively. Compared with obstructive CAD diagnosed by CT alone (area under the receiver operating characteristic curve [AUC], 0.68; 95% CI, 0.62–0.74), FFR_{CT} was associated with improved discrimination (AUC, 0.81; 95% CI, 0.75–0.86, P < .001).

Conclusion Although the study did not achieve its prespecified primary outcome goal for the level of per-patient diagnostic accuracy, use of noninvasive FFR_{CT} plus CT among stable patients with suspected or known CAD was associated with improved diagnostic accuracy and coronary revascularization decisions in patients with stable CAD. The potential for FFR_{CT} to noninvasively identify ischemia in patients with suspected CAD has not been sufficiently investigated.

Published online August 26, 2011. doi:10.1001/2011.jama.11274

www.jama.com

Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 53, No. 12, 2014
ISSN 0735-1017/14/\$36.00
doi:10.1016/j.jacc.2014.06.013

Clinical Research

Clinical Trials

Diagnostic Performance of Noninvasive Fractional Flow Reserve Derived From Coronary Computed Tomography Angiography in Suspected Coronary Artery Disease

The NXT Trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps)

Bjorne L. Nørgaard, MD, PhD,¹ Jonathan Leipsic, MD, PhD,¹ Sara Gaur, MD,² Sujith Seneviratne, MBBS,³ Brian S. Ko, MBBS, PhD,⁴ Hiroshi Ino, MD, PhD,⁵ Jesper M. Jensen, MD, PhD,⁶ Laura Mauri, MD, PhD,⁷ Bernard De Bruyne, MD, PhD,⁸ Hiron Bezerra, MD, PhD,⁹ Kazuhiko Ogasawa, MD,¹⁰ Mohamed Marwan, MD, PhD,¹¹ Christoph Naber, MD, PhD,¹² Andrejs Erglis, MD, PhD,¹³ Seung-Jung Park, MD, PhD,¹⁴ Evald H. Christiansen, MD, PhD,¹⁵ Anne Kaltoft, MD, PhD,¹⁶ Jens F. Lassen, MD, PhD,¹⁷ Hans Erik Bøtker, MD, DMSc,¹⁸ Stephan Achenbach, MD, PhD,¹⁹ on behalf of the NXT Trial Study Group
Aarhus, Denmark; Vancouver, British Columbia, Canada; Victoria, Australia; Okayama, Japan; Boston, Massachusetts; Jala, Belgium; Cleveland, Ohio; Erlangen and Essen, Germany; Riga, Latvia; and Seoul, South Korea

Objectives The goal of this study was to determine the diagnostic performance of noninvasive fractional flow reserve (FFR) derived from standard acquired coronary computed tomography angiography (CTA) datasets (FFR_{CT}) for the diagnosis of myocardial ischemia in patients with suspected stable coronary artery disease (CAD).

Background FFR measured during invasive coronary angiography (ICA) is the gold standard for lesion-specific coronary revascularization decisions in patients with stable CAD. The potential for FFR_{CT} to noninvasively identify ischemia in patients with suspected CAD has not been sufficiently investigated.

Methods This prospective multicenter trial included 254 patients scheduled to undergo clinically indicated ICA for suspected CAD. Coronary CTA was performed before ICA. Evaluation of stenosis (<50% luminal reduction) in coronary CTA was performed by local investigators and ICA by an independent core laboratory. FFR_{CT} was calculated and interpreted in a blinded fashion by an independent core laboratory. Results were compared with invasively measured FFR, with ischemia defined as FFR_{CT} or FFR <0.80.

Results The area under the receiver-operating characteristic curve for FFR_{CT} was 0.80 (95% confidence interval [CI], 0.87 to 0.94) versus 0.82 (95% CI, 0.76 to 0.87) for coronary CTA (p = 0.0008). Per-patient sensitivity and specificity (95% CI) to identify myocardial ischemia were 86% (95% CI, 77% to 92%) and 79% (95% CI, 72% to 84%) for FFR_{CT} versus 84% (95% CI, 80% to 87%) and 84% (95% CI, 77% to 91%) for coronary CTA, and 64% (95% CI, 53% to 74%) and 83% (95% CI, 77% to 88%) for ICA, respectively. In patients (n = 235) with intermediate stenosis (95% CI, 30% to 70%), the diagnostic accuracy of FFR_{CT} remained high.

Conclusions FFR_{CT} provides high diagnostic accuracy and discrimination for the diagnosis of hemodynamically significant CAD with invasive FFR as the reference standard. When compared with standard testing by using coronary CTA, FFR_{CT} led to a 16% increase in specificity, decrease in NXT heart flow analysis of coronary blood flow analysis of coronary CT angiography (NXT2014-0707). (J Am Coll Cardiol 2014;63:1145–56) © 2014 by the American College of Cardiology Foundation

From the ¹Department of Cardiology, Aarhus University Hospital, Skejby, Aarhus, Denmark; ²Department of Radiology, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; ³Mitak Hospital, Mitak, Mexico; ⁴Center and Mirrah, University, Victoria, Australia; ⁵Department of Cardiology, Okayama University Hospital, Okayama, Japan; ⁶Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts; ⁷Cardiologist

Koo et al., JACC 2011.

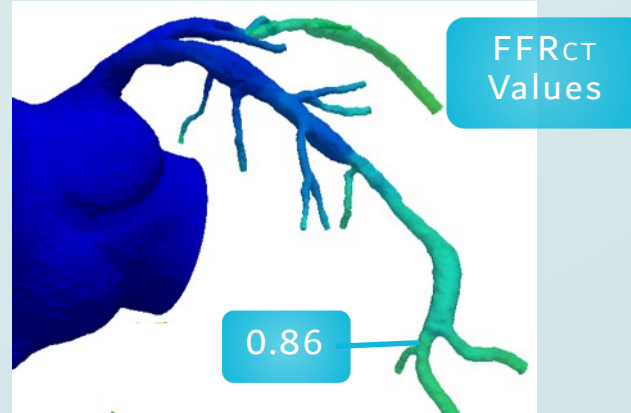
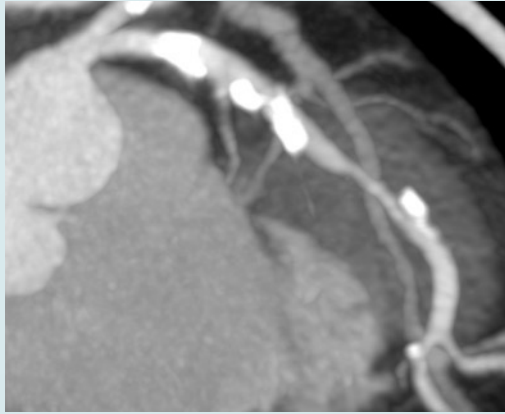
Min et al., JAMA 2012.

Norgaard et al., JACC 2014.

The Need for Physiology: When does a 70% LAD stenosis by CCTA impact flow?

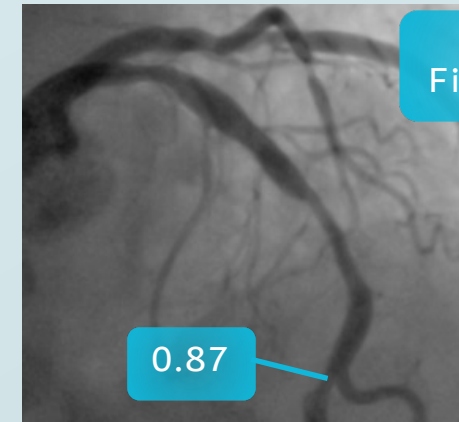
CTA 70% LAD Stenosis

Patient A



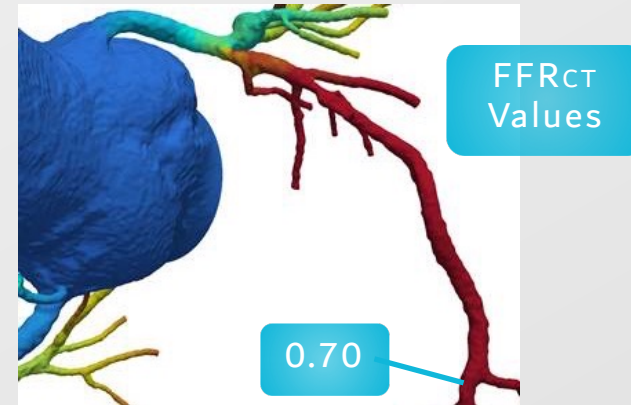
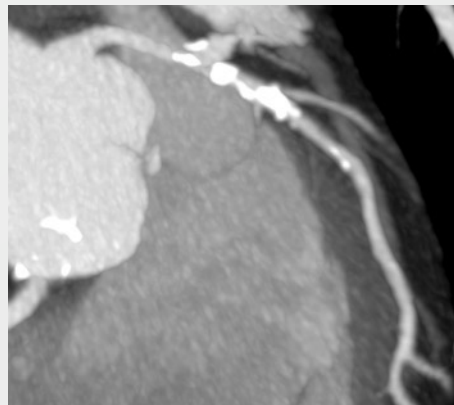
Angio 70% LAD Stenosis

FFR Findings



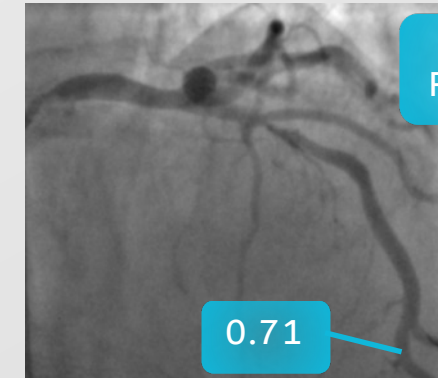
CTA 70% LAD Stenosis

Patient B

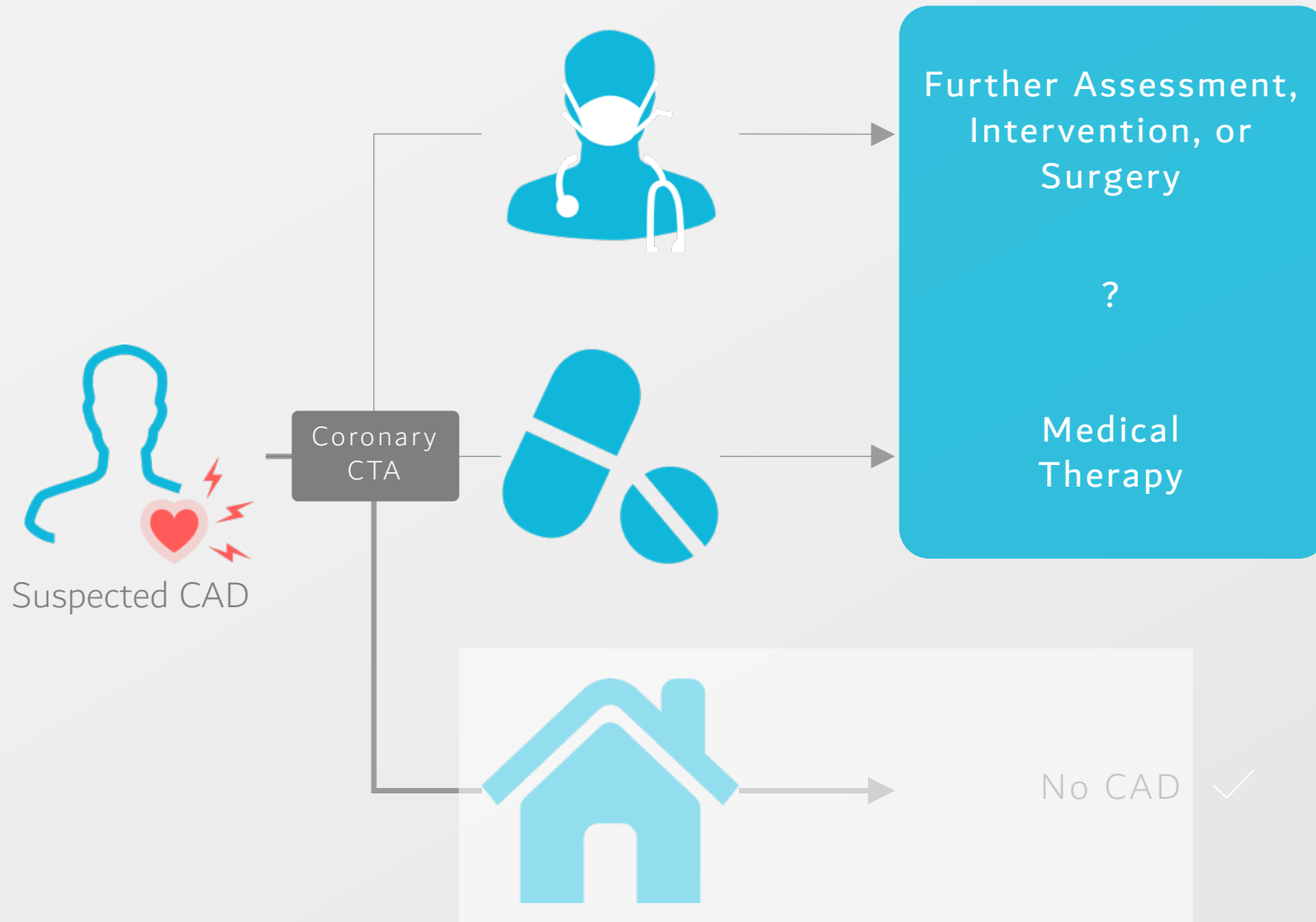


Angio 70% LAD Stenosis

FFR Findings



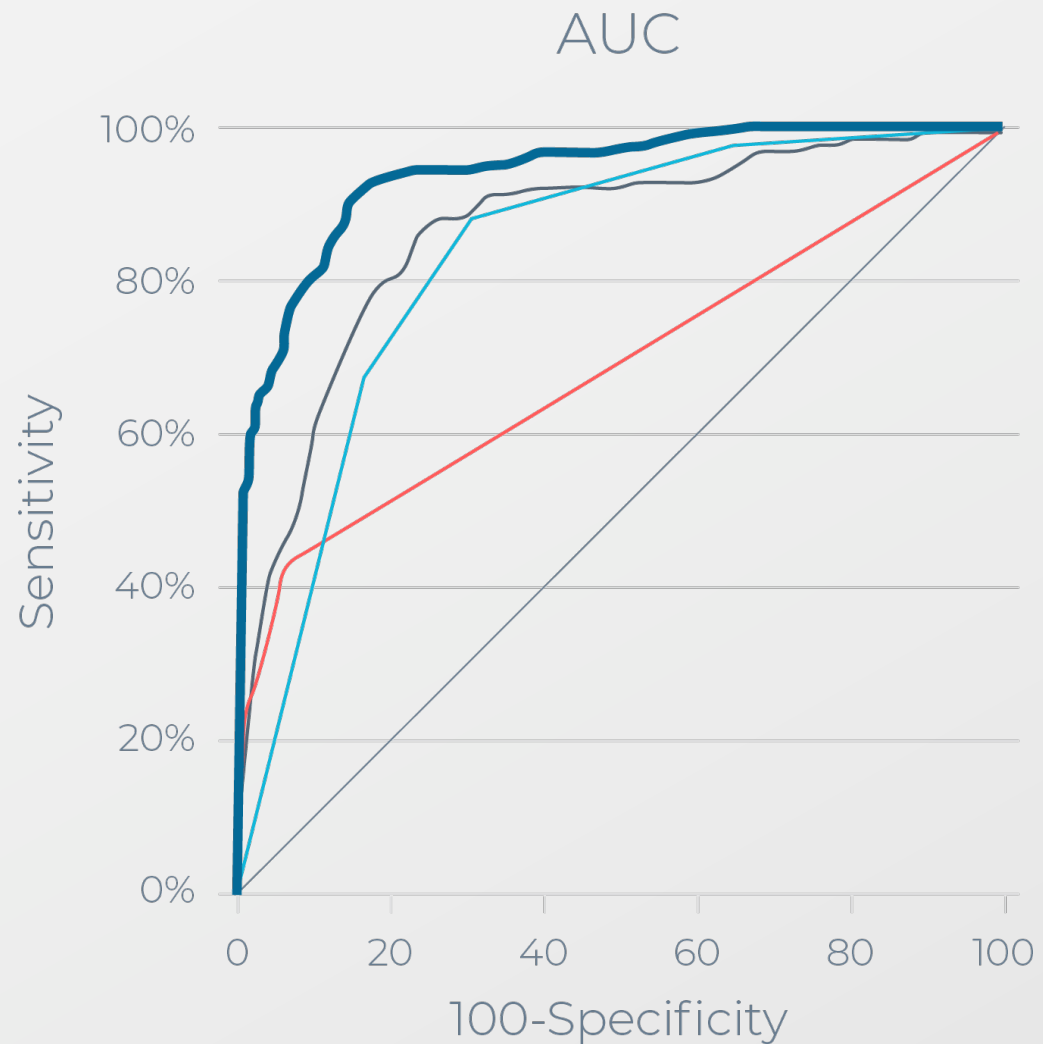
A better cardiac testing pathway starts with coronary CTA



CCTA + FFR_{CT}
clarifies the pathway
for patients with CAD...

... by improving the
accuracy and performance
of non-invasive cardiac testing.

Diagnostic performance of common cardiac tests



HeartFlow FFR_{CT}
0.94

PET
0.87 (p < 0.001)

Coronary CTA
0.83 (p < 0.001)

SPECT
0.70 (p < 0.001)

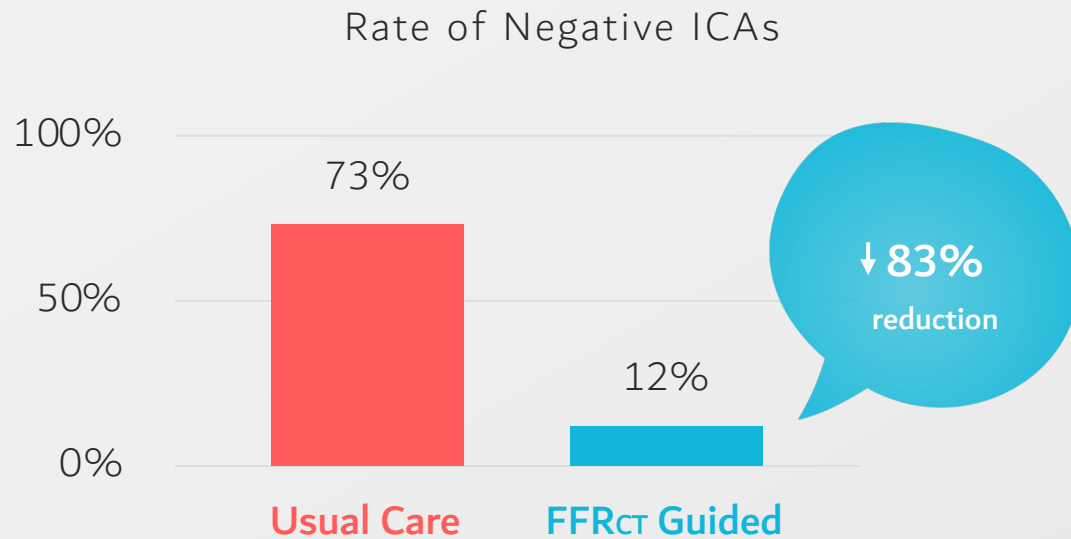
P-values reflect comparison to the HeartFlow FFR_{CT} Analysis

Diagnostic accuracy:

- **87%** (PACIFIC, JACC 2019)
- **86%** (NXT, JACC 2014)

A better cardiac testing pathway: Coronary CTA + HeartFlow FFR_{CT}

Reduce Overutilization of Invasive Testing¹
by reducing **false positives**



NOTE: No Change in the revascularization rate¹

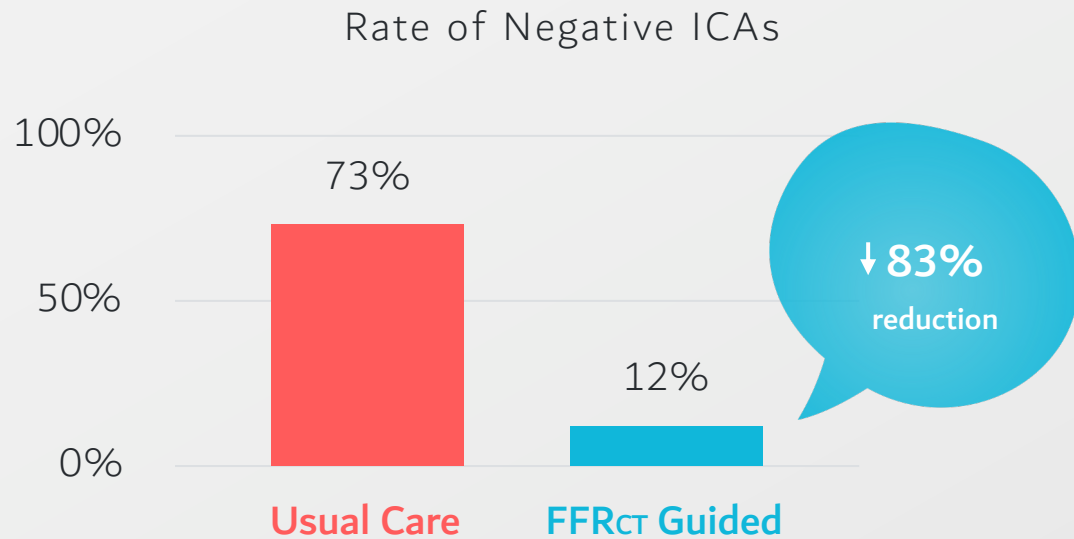
Safe to defer ICA for patients with FFR_{CT} >0.80

Low adverse clinical event rates in patients whose ICA was canceled based on the findings from an FFR_{CT}-guided strategy

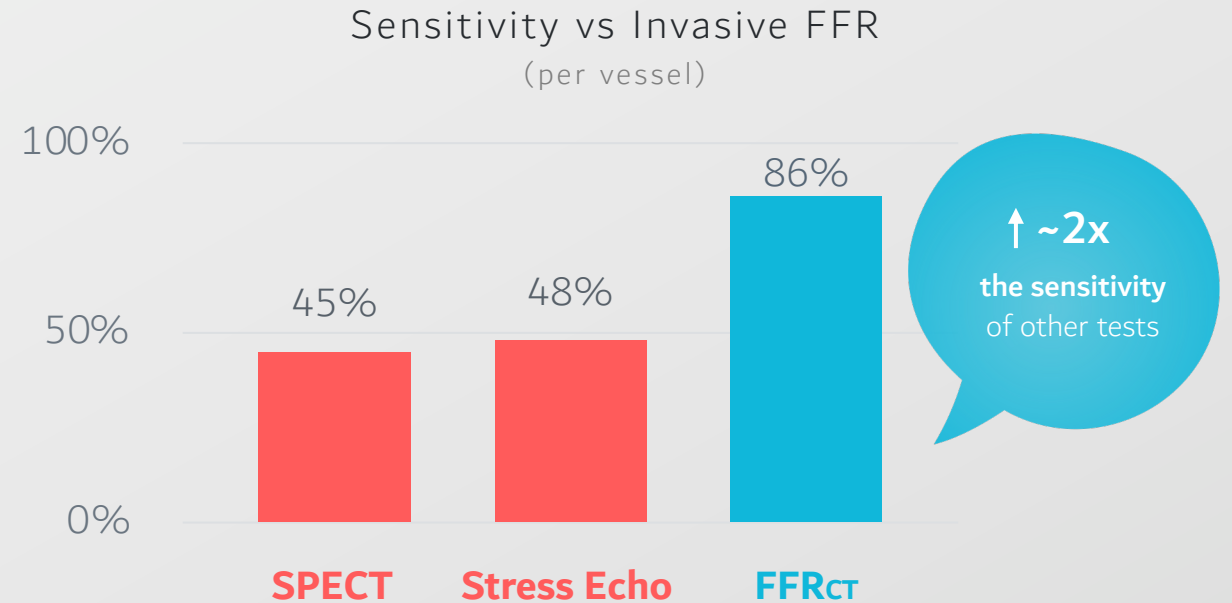
- Deferred patients had **significantly lower** CV death & MI through 1 year* (n=1592) (ADVANCE, JACC CV Imaging 2019)²
- All deferred patients were **event free** through 1 year (n=117) (PLATFORM, JACC 2016)³
- Deferred patients had an **event rate not different** from patients with 0-30% stenoses by CT through 2 years (n=410 deferred) (Aarhus, JACC 2018)⁴

A better cardiac testing pathway: Coronary CTA + HeartFlow FFR_{CT}

Reduce Overutilization of Invasive Testing¹
by reducing **false positives**



Identify Functional Disease Other Tests Miss²
by reducing **false negatives**

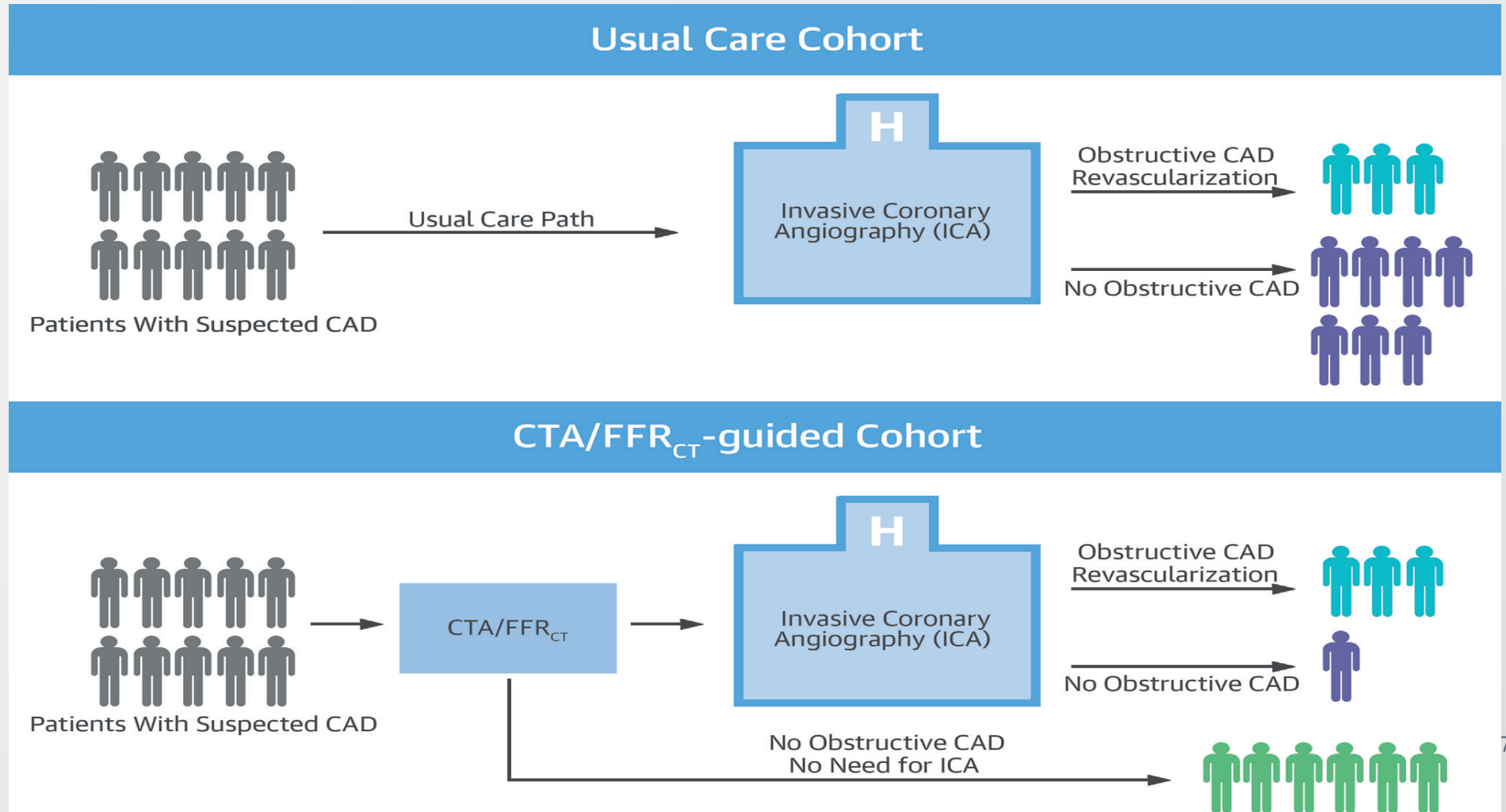


NOTE: No Change in the revascularization rate¹

1-Year Outcomes of FFR_{CT}-Guided Care in Patients With Suspected Coronary Disease

The PLATFORM Study

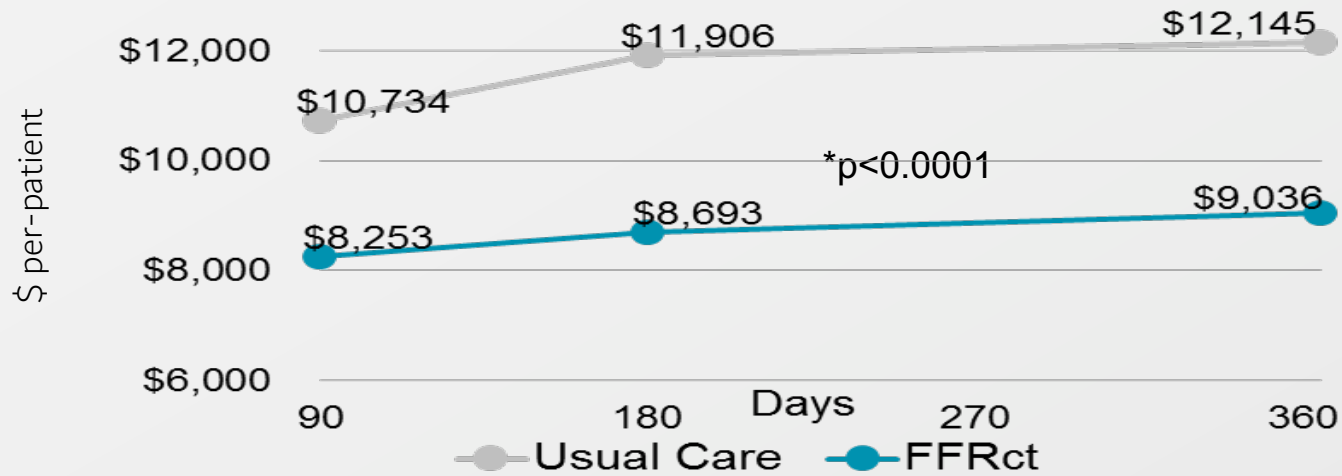
CENTRAL ILLUSTRATION FFR_{CT}-Guided Care in Patients With Suspected CAD



Equal outcomes, QOL and cost between 2 strategies at 1 year



Costs Over 1 Year – Patients with Planned ICA



Cost savings increase:
 23% (\$2,481) at 90 days 26% (\$3,109) at 12 months
 after accounting for \$1,500 cost of the HeartFlow
 Analysis.

Utilization over 1 year
 In patients referred for ICA

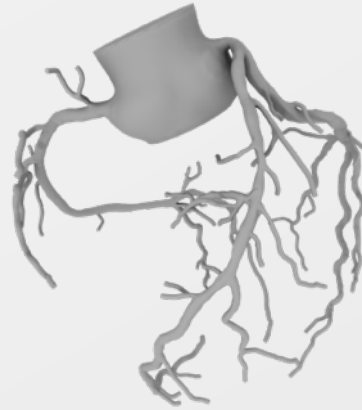
	Hospital days	Clinic visits
Standard Care (n=187)	514	283
FFRct strategy (n=193)	162	111

26% Savings*

FFRct information within hours



A **standard cardiac CT scan** is performed and the data is uploaded to HeartFlow.



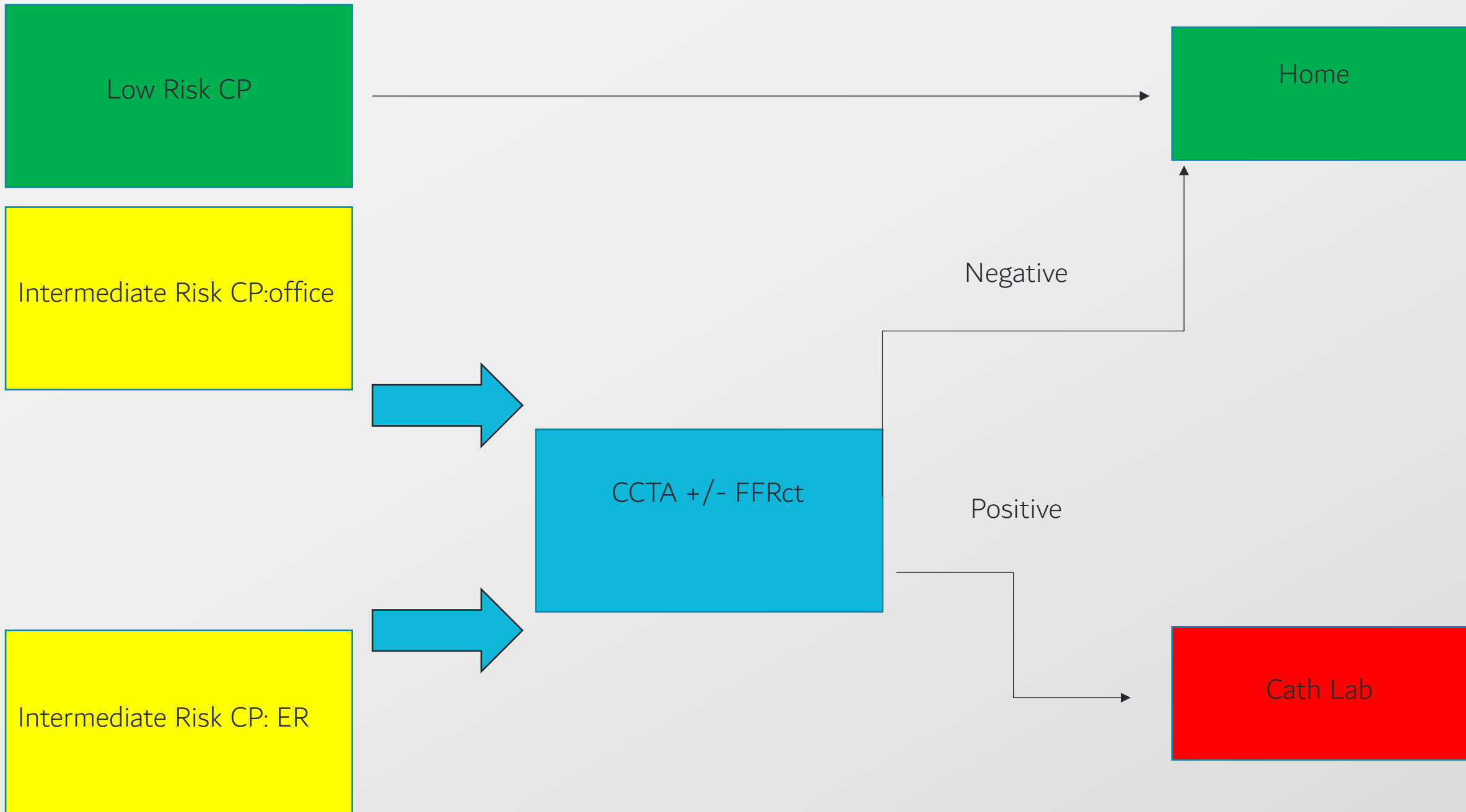
Our **proprietary software** uses certified analysts and AI-driven algorithms to develop a **personalized, digital 3D model** of the the coronary arteries.



FFRct values can be accessed via computer, iPhone, iPad or printable overview to assess, vessel by vessel, if sufficient blood flow is reaching the heart.

Median turnaround time is **<5 hours***

*As of 31 December 2018. Data subject to change.



Case Studies

Examples that have helped transform our group's approach to chest pain evaluation.

Participation in PROMISE and now PRECISE Trials

Quick turnaround of low risk ER chest pain: + Economic benefit of low ER dwell time

In line with Beaumont experience and ROMICAT studies

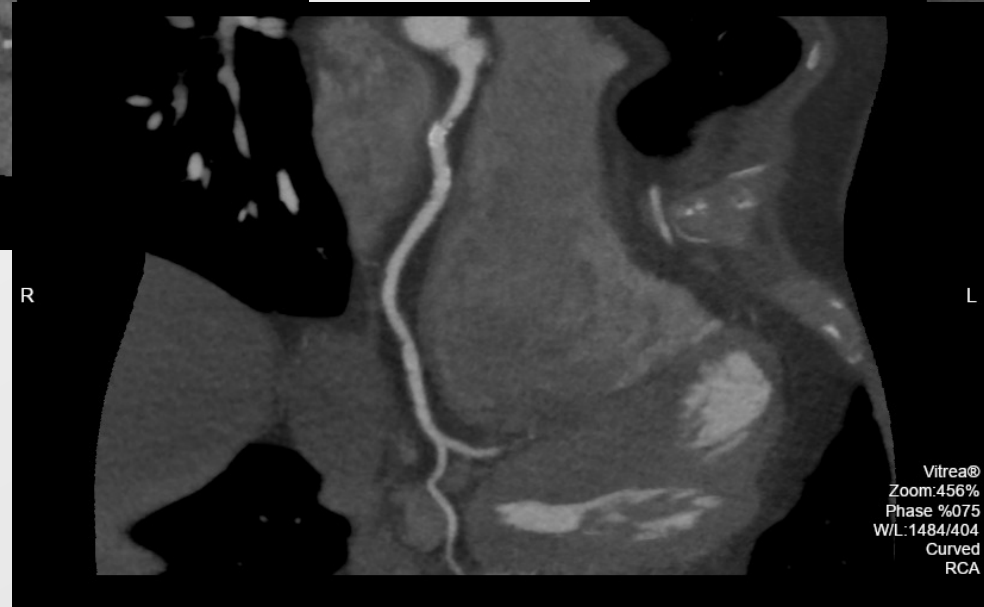
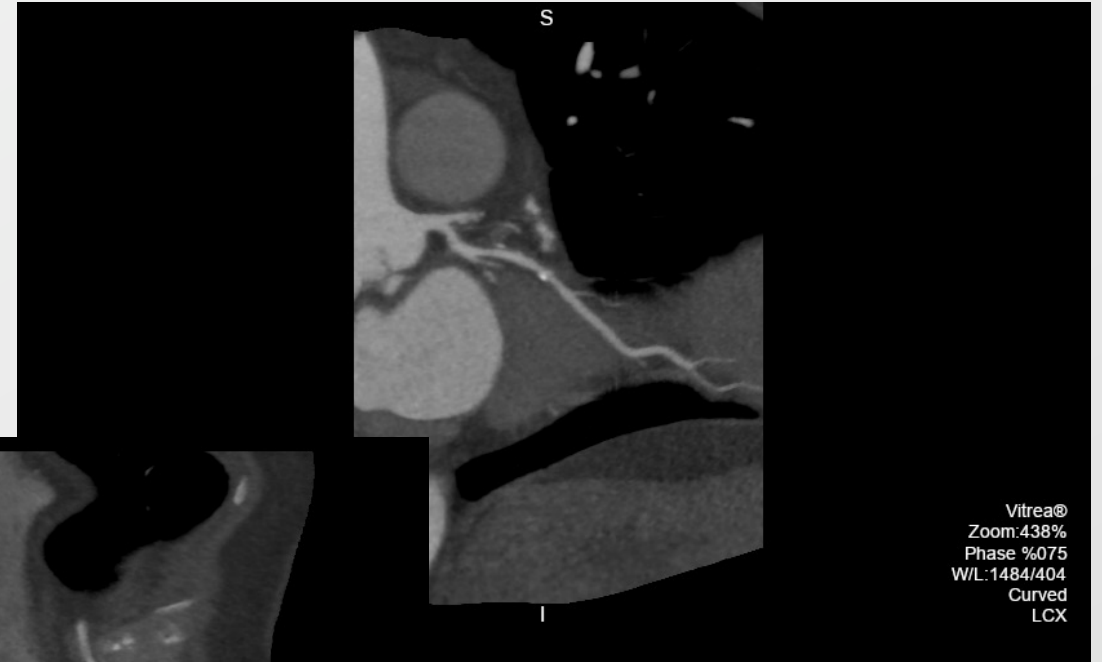
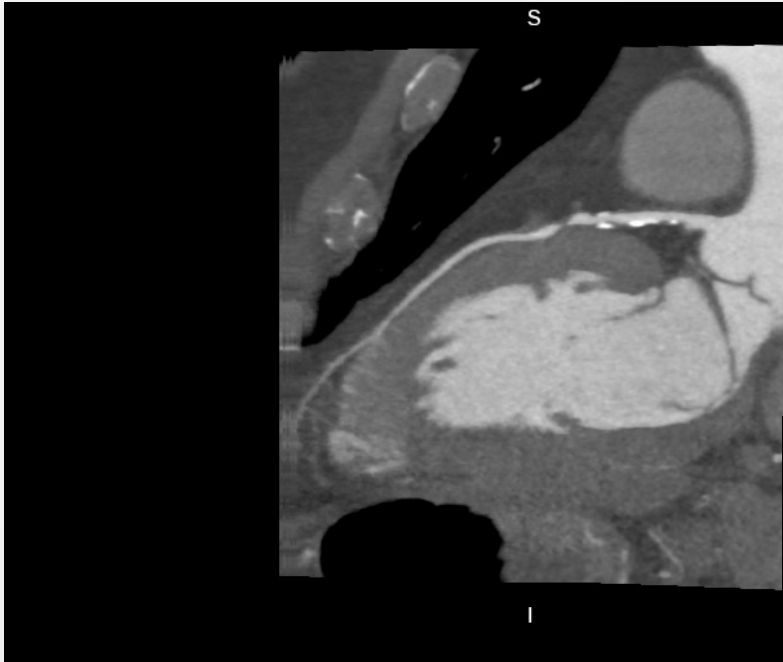
Low rate of False - studies

Case Example - KB - Patient History and Overview

- ▶ 65 yo gentleman
- ▶ HTN, HL, +FH
- ▶ 3-4 months of exertional dyspnea
- ▶ Mild non-radiating CP lasting 30 seconds to 1 minute before resolving spontaneously
- ▶ Never has had any cardiac testing
- ▶ Calcium score: 740
 - ▶ LM- 11
 - ▶ RCA- 411
 - ▶ LAD- 216
 - ▶ LCX- 102

Case Example – KB – CT Image Review

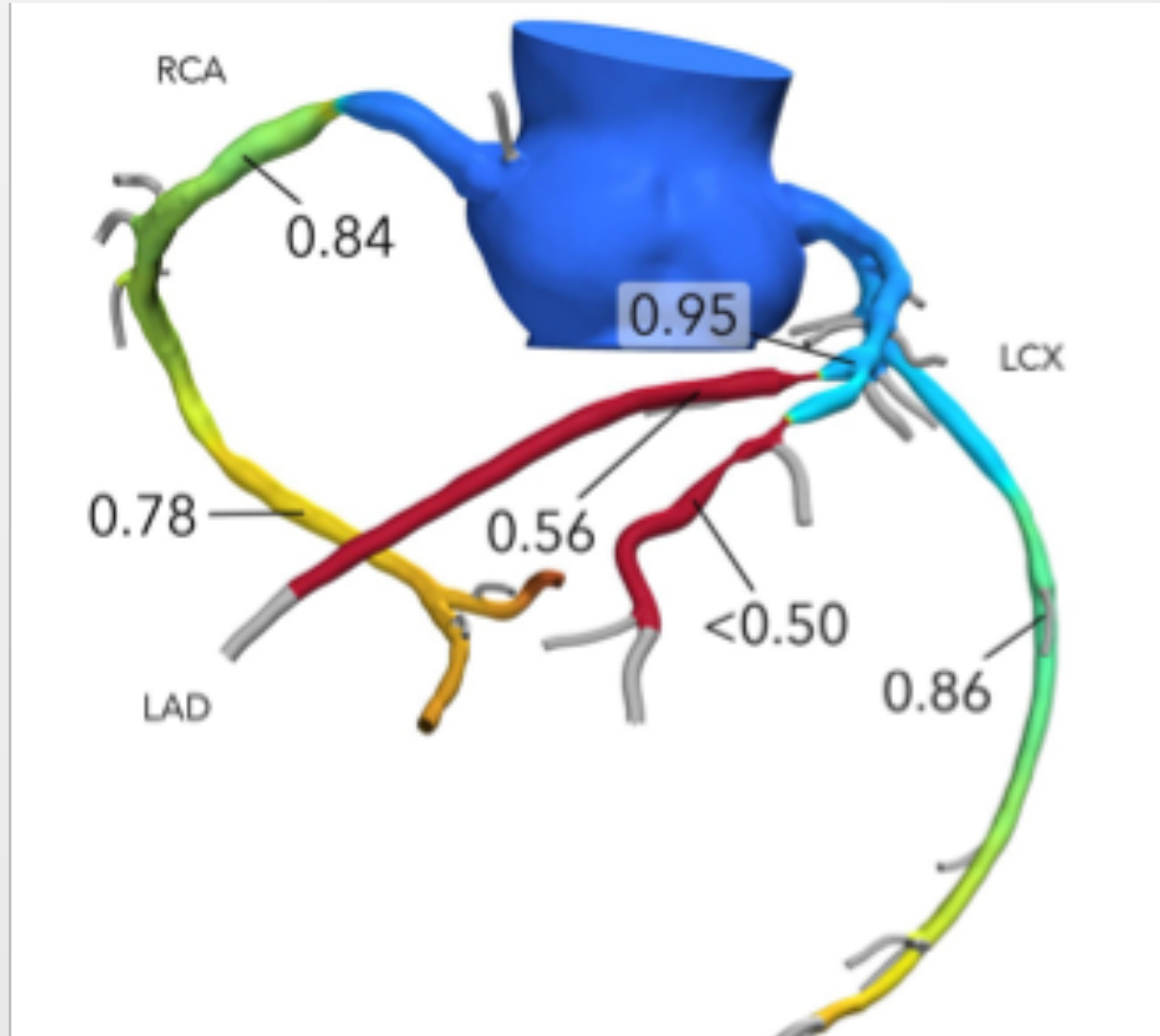
- ▶ LAD looks significant. LCX looks mild-moderate. RCA looks at least moderate



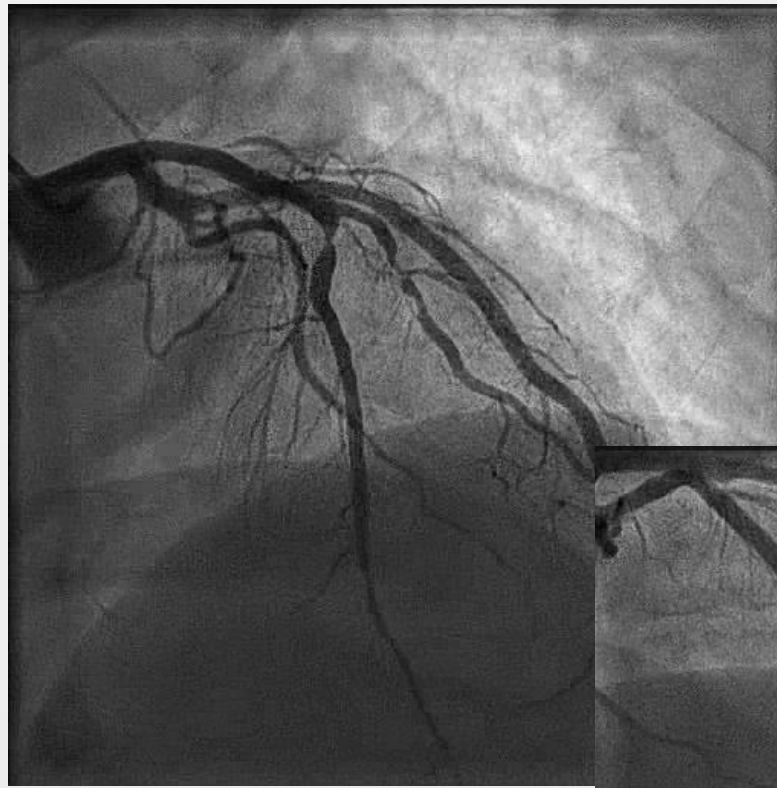
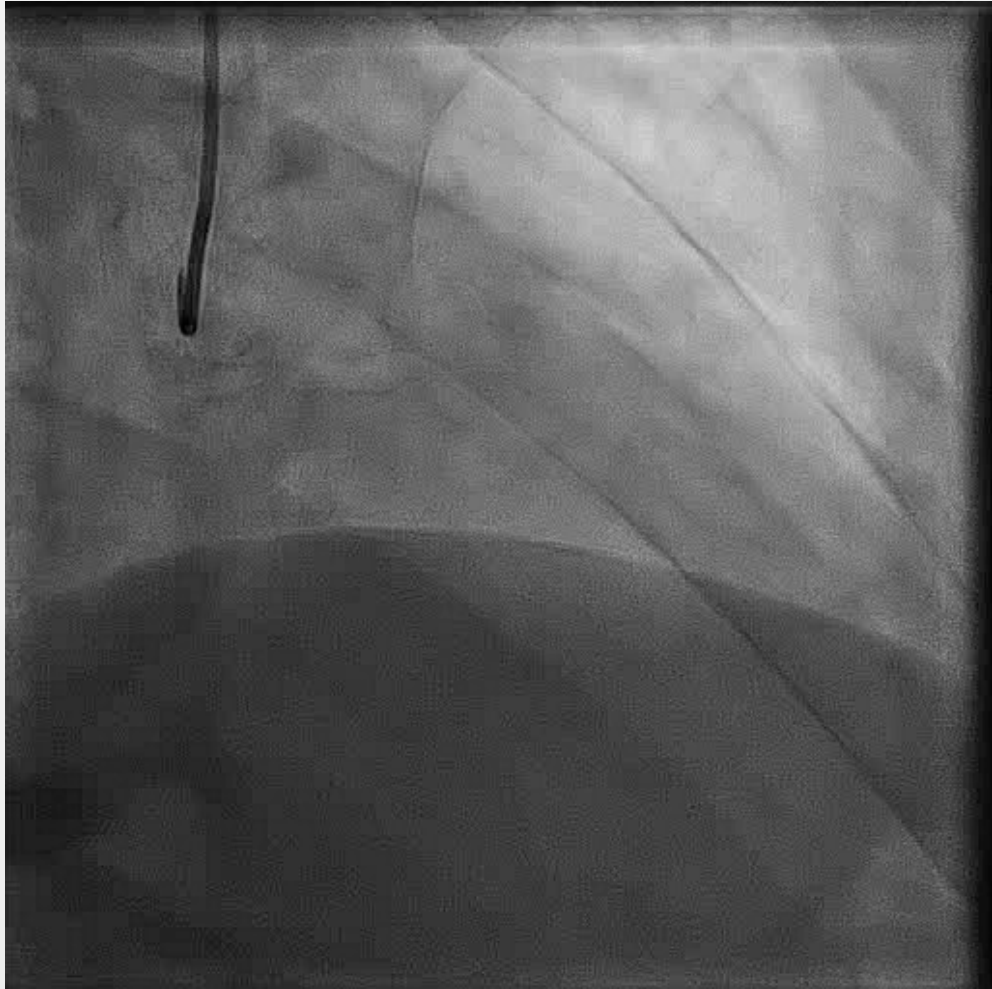
- ▶ Next Steps?

Case Example – KB – FFRCT Image Review

► FFRCT Image Review – Multivessel CAD

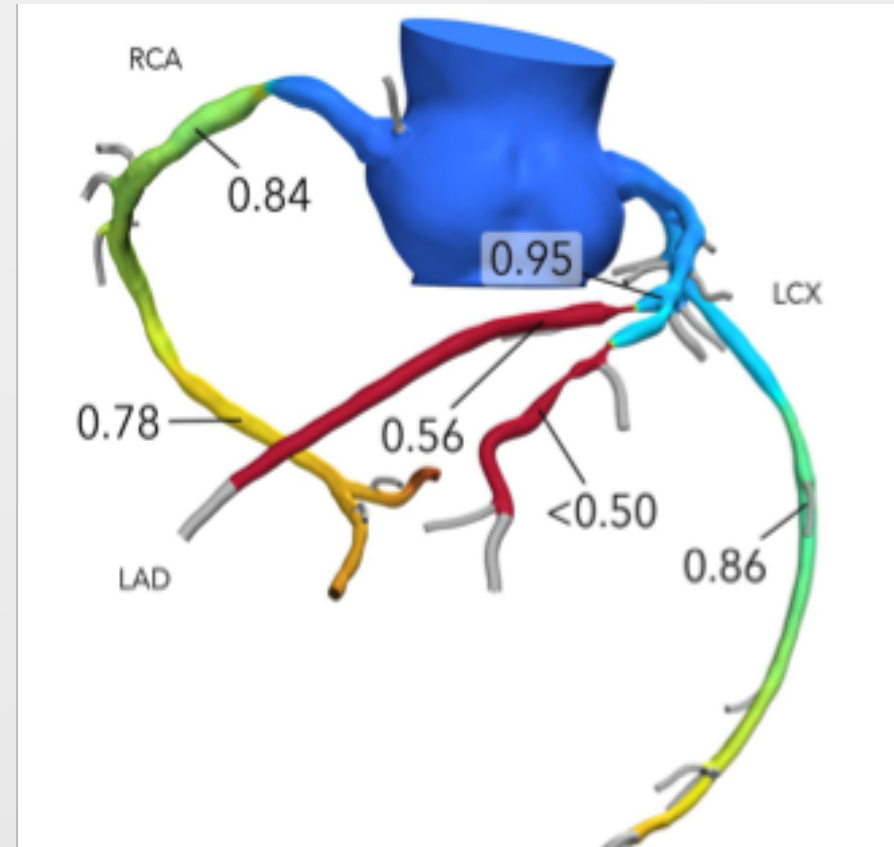
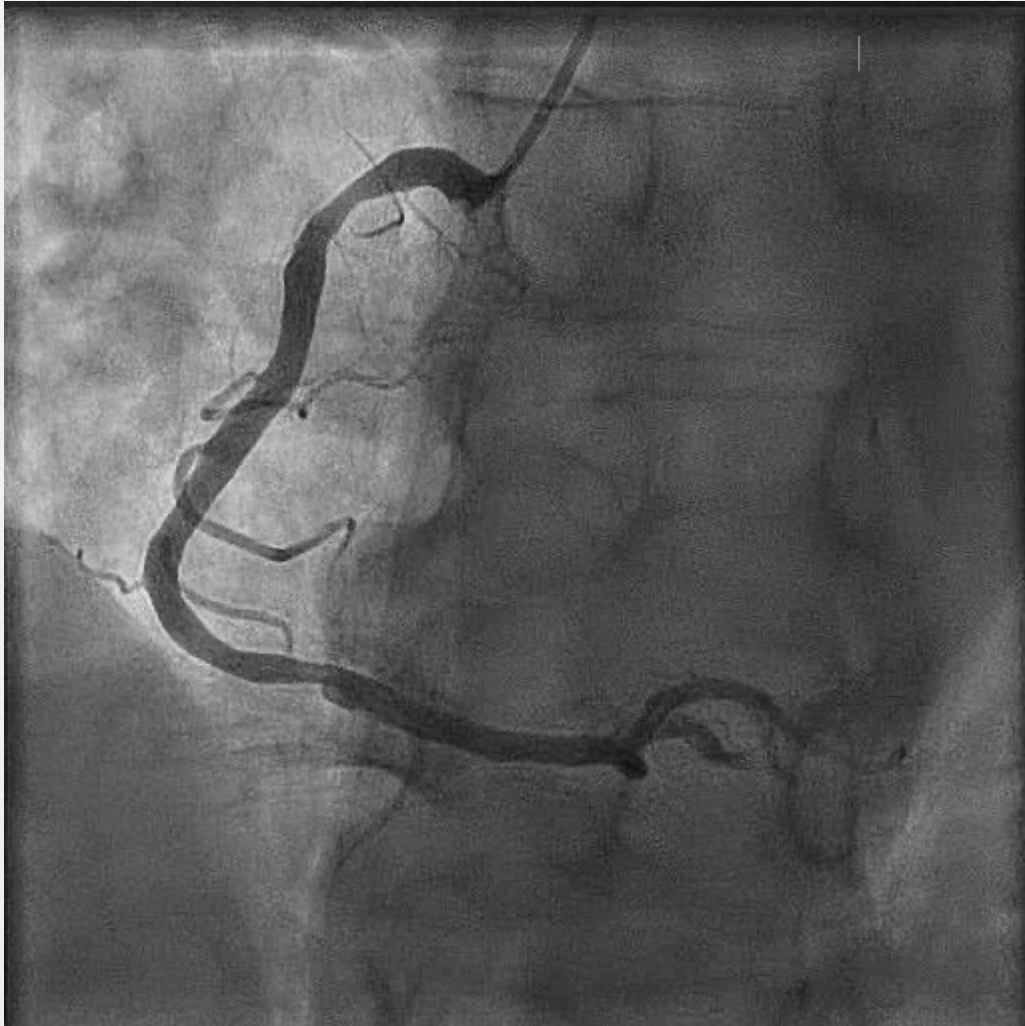


Case Example: KB – Angio/FFR

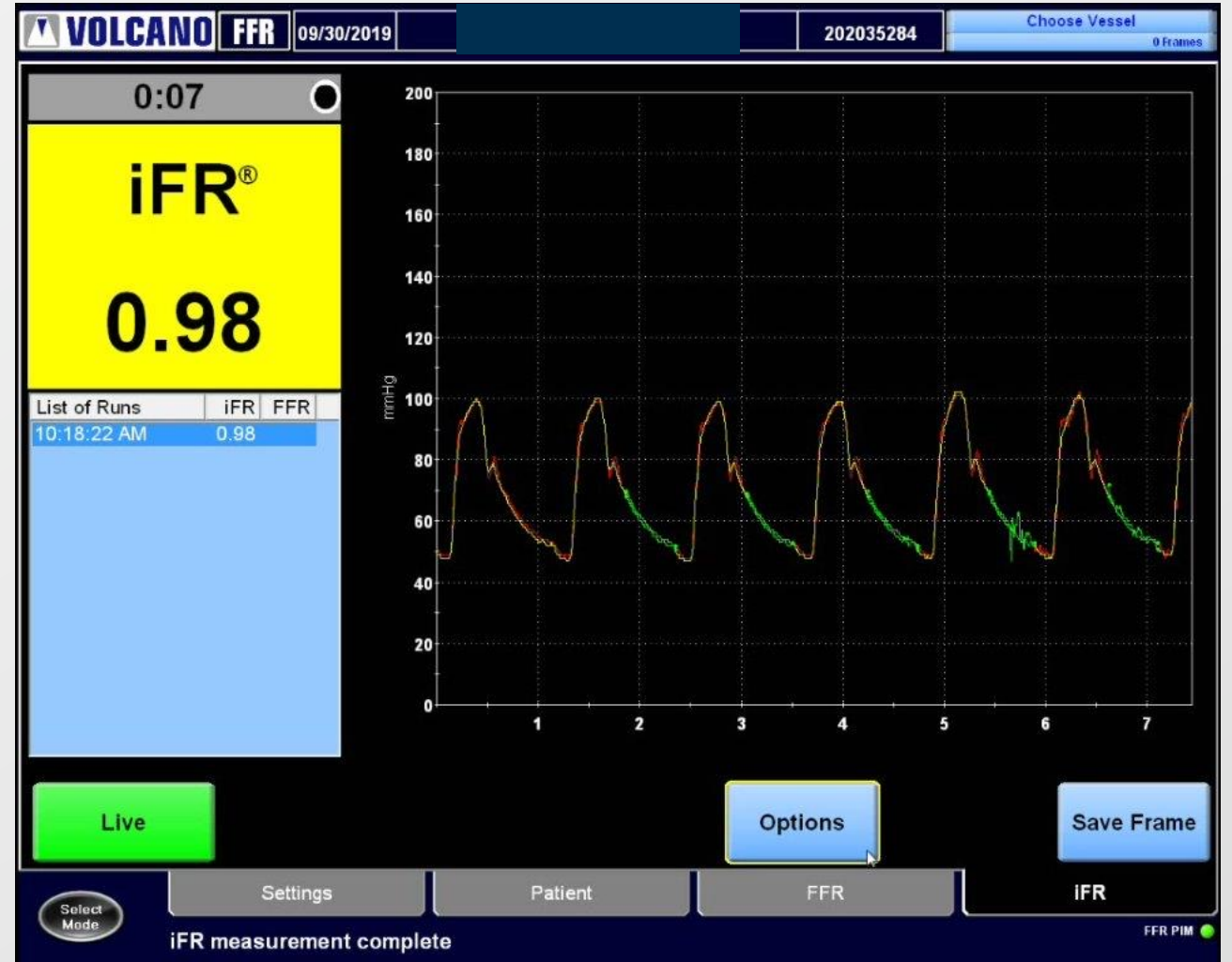


- ▶ After consultation with CV surgery and patient: Decision made to proceed with PCI

What about the RCA?: Does it affect the decision for CABG or not?

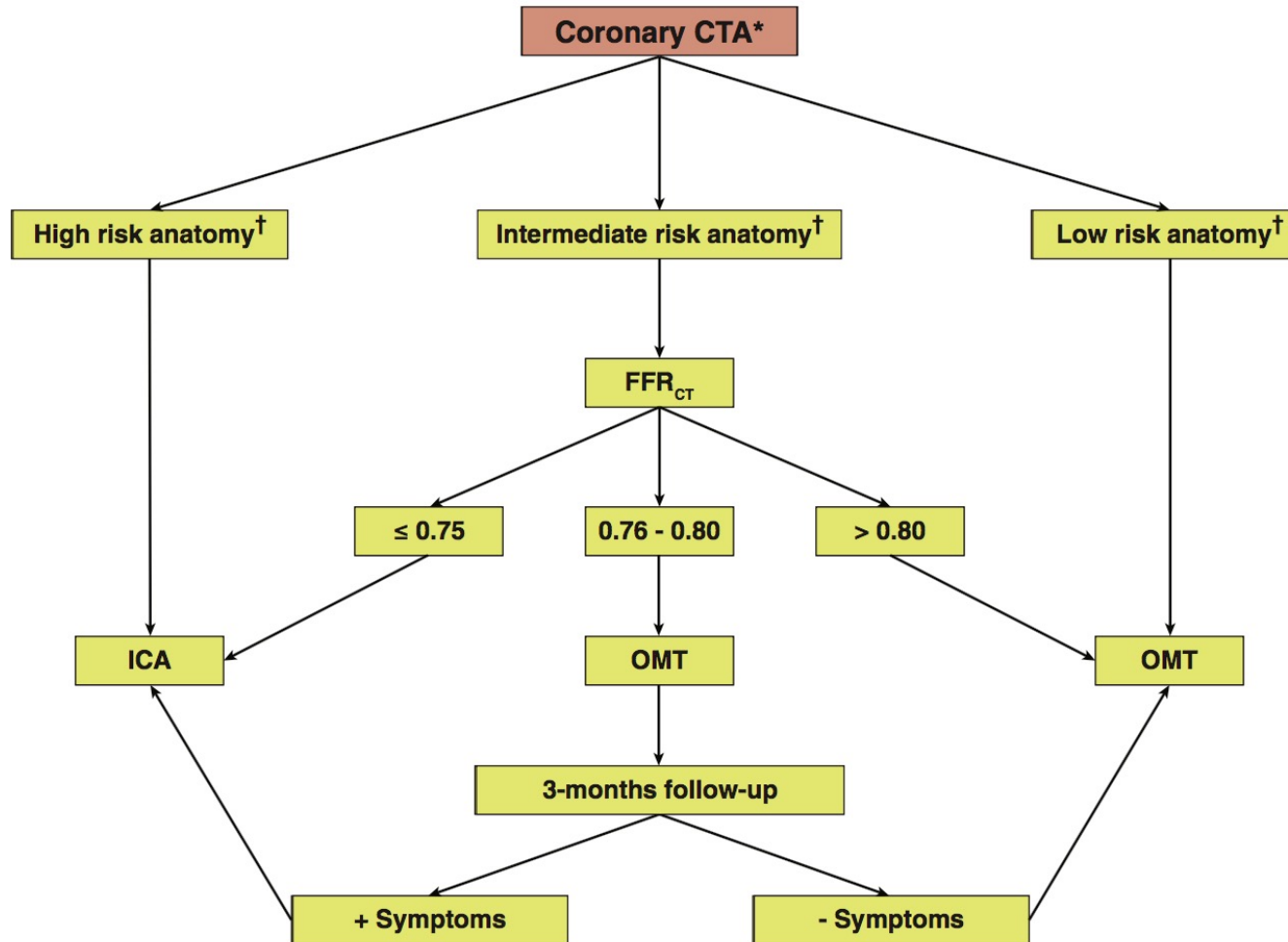


RCA: Invasive physiology vs FFRct



Consider an FFR_{CT} grey zone

FIGURE 6 The "Aarhus" FFR_{CT} Decision-Rule Algorithm

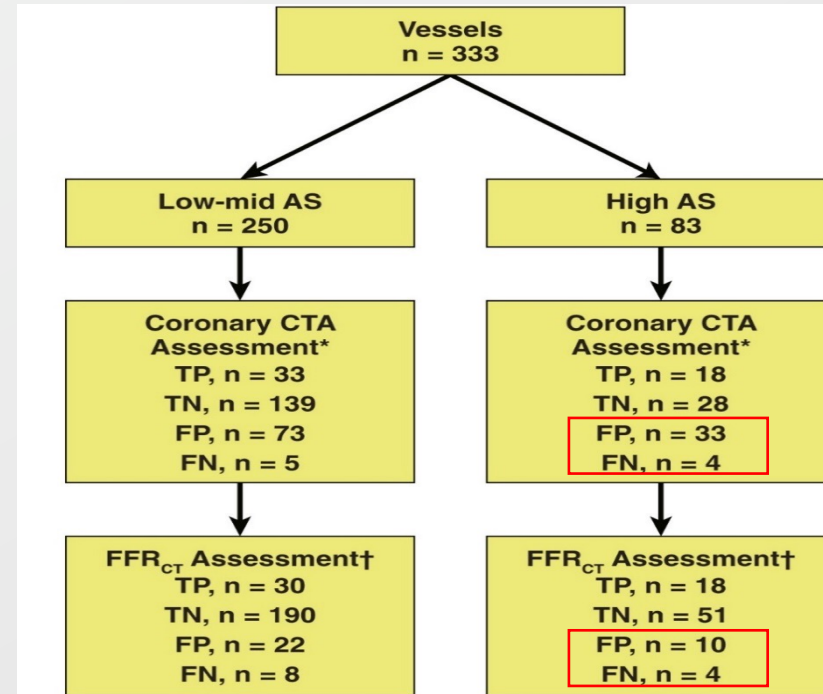
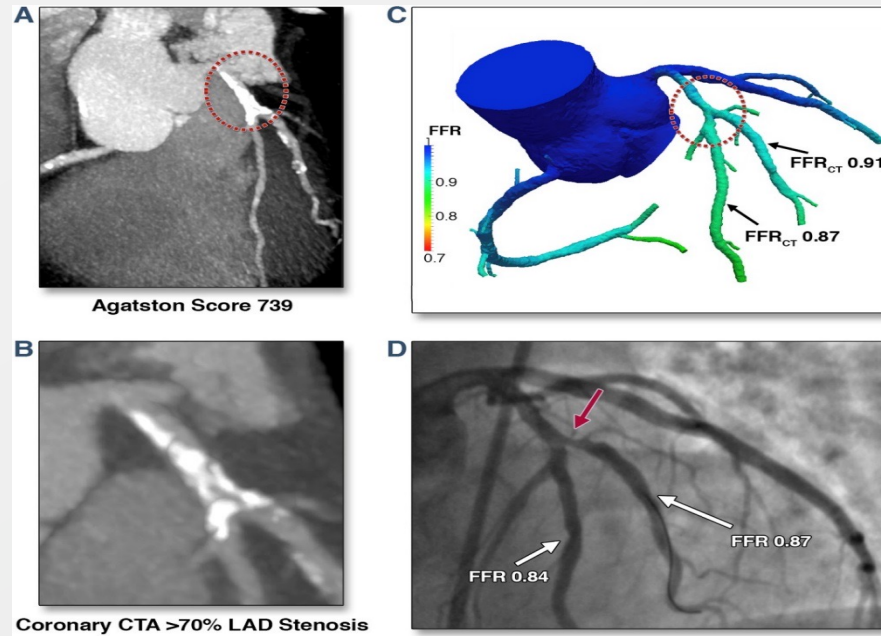


Aarhus real-world FFR_{CT} experience:

OMT and 3-month follow-up for 0.76-0.80 FFR_{CT} values.

“In the event of FFR_{CT} <0.75, the probability of having ischemia was high (92%). If FFR_{CT} ranged between 0.76-0.80, ischemia was present in only 55% of patients.”

FFR_{CT} performs well with high calcium

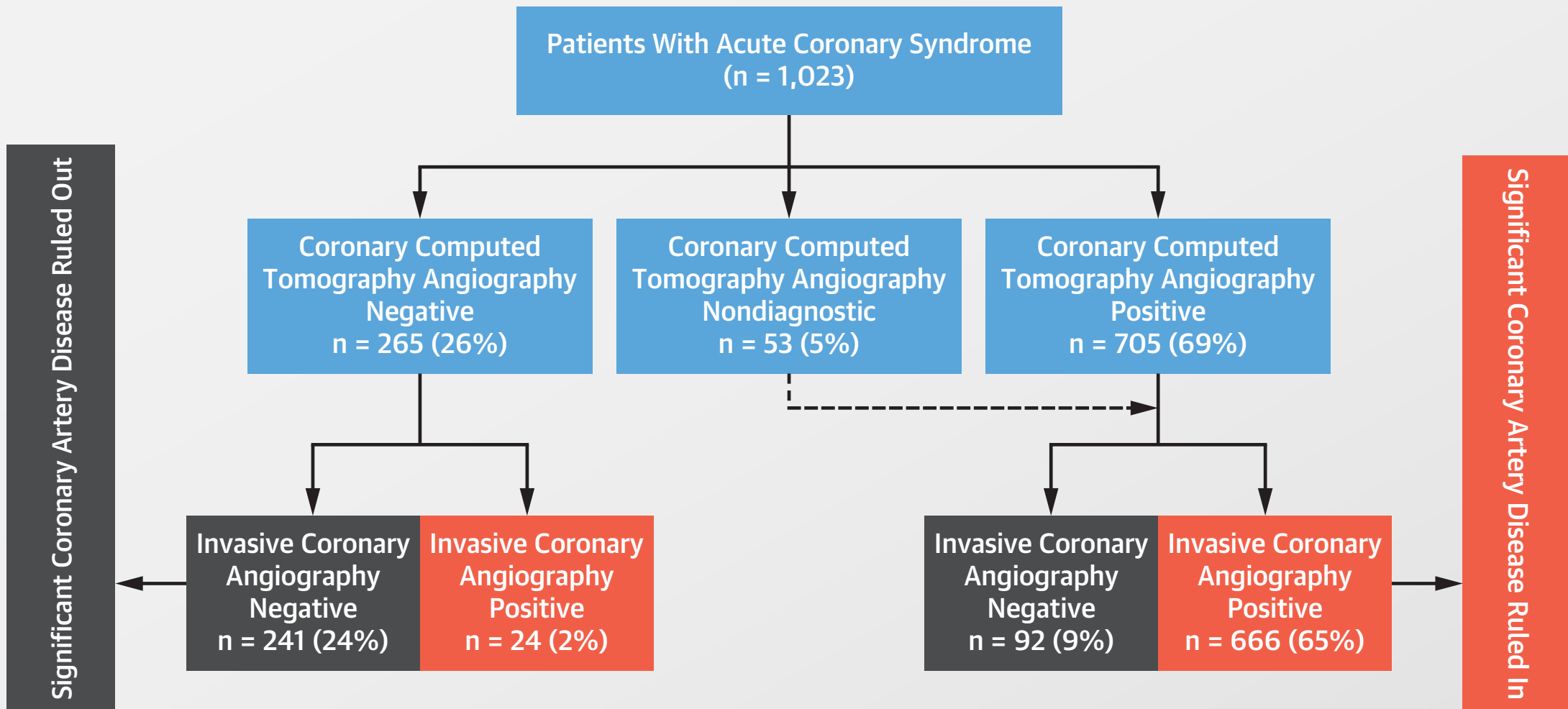


3-fold reduction in false positives by adding FFR_{CT} to coronary CTA, even with high Agatston calcium score

Coronary CT Angiography in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome



Jesper J. Linde, MD, PhD,^a Henning Kelbæk, MD, DMSc,^b Thomas F. Hansen, MD, PhD,^c Per E. Sigvardsen, MD,^a Christian Torp-Pedersen, MD, DMSc,^c Jan Bech, MD, PhD,^d Merete Heitmann, MD, PhD,^d Olav W. Nielsen, MD, DMSc,^d Dan Høfsten, MD, PhD,^a Jørgen T. Kühl, MD, DMSc,^b Ilan E. Raymond, MD, PhD,^d Ole P. Kristiansen, MD, PhD,^d Ida H. Svendsen, MD, PhD,^d Maria H.D. Vall-Lamora, MD, PhD,^d Charlotte Kragelund, MD, PhD,^c Martina de Knecht, MD, PhD,^a Jens D. Hove, MD, PhD,^e Tem Jørgensen, MD,^e Gitte G. Fornitz, MD, PhD,^e Rolf Steffensen, MD,^f Birgit Jurlander, MD, PhD,^f Jawdat Abdulla, MD, PhD,^g Stig Lyngbæk, MD, PhD,^g Hanne Elming, MD, PhD,^b Susette K. Therkelsen, MD, PhD,^b Erik Jørgensen, MD,^a Lene Kløvgaard, RN,^a Lia Evi Bang, MD, PhD,^a Peter Riis Hansen, MD, DMSc,^c Steffen Helqvist, MD, DMSc,^a Søren Galatius, MD, DMSc,^c Frants Pedersen, MD, PhD,^a Ulrik Abildgaard, MD, PhD,^c Peter Clemmensen, MD, DMSc,^h Kari Saunamäki, MD, DMSc,^c Lene Holmvang, MD, DMSc,^a Thomas Engstrøm, MD, DMSc,^a Gunnar Gislason, MD, DMSc,^c Lars V. Køber, MD, DMSc,^a Klaus F. Kofoed, MD, DMSc^a

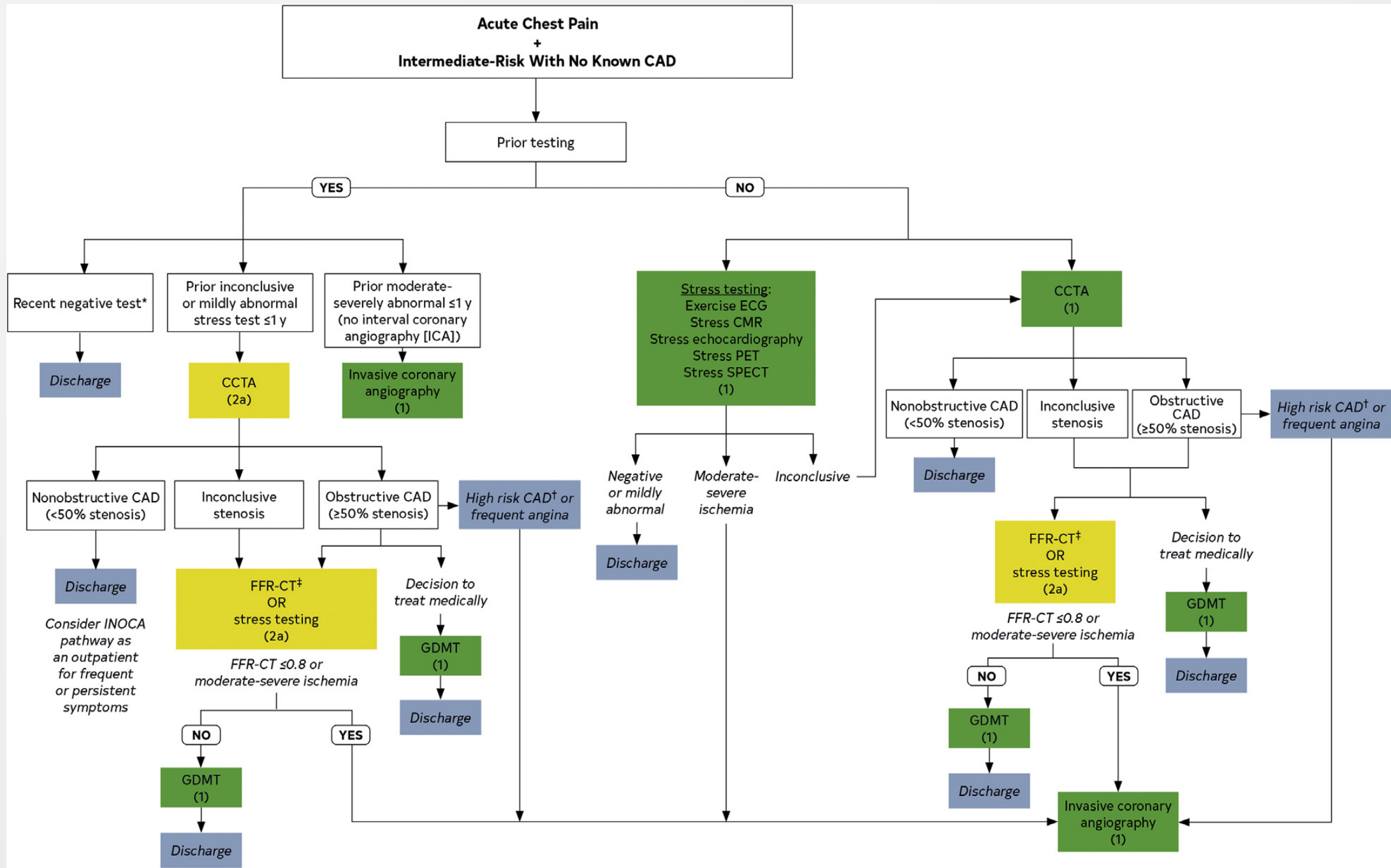


Negative Predictive Value 90.9%
(95% CI) (86.8-94.1)

Sensitivity 96.5%
(95% CI) (94.9-97.8)

Positive Predictive Value 87.9%
(95% CI) (85.3-90.9)

Specificity 72.4%
(95% CI) (67.2-77.1)



Validation Study of Image-Based Fractional Flow Reserve During Coronary Angiography

Mariano Pellicano, MD; Ifat Lavi, PhD; Bernard De Bruyne, MD, PhD;
 Hana Vaknin-Assa, MD; Abid Assali, MD; Orna Valtzer, DMD; Yonit Lotringer, MSc;
 Giora Weisz, MD; Yaron Almagor, MD; Panagiotis Xaplanteris, MD, PhD;
 Ajay J. Kirtane, MD, SM; Pablo Codner, MD;
 Martin B. Leon, MD; Ran Kornowski, MD

Background—Fractional flow reserve (FFR), an index of the hemodynamic severity of coronary stenoses, is derived from invasive measurements and requires a pressure-monitoring guidewire and hyperemic stimulus. Angiography-derived FFR measurements (FFR_{angio}) may have several advantages. The aim of this study is to assess the diagnostic performance and interobserver reproducibility of FFR_{angio} in patients with stable coronary artery disease.

Methods and Results— FFR_{angio} is a computational method based on rapid flow analysis for the assessment of FFR. FFR_{angio} uses the patient's hemodynamic data and routine angiograms to generate a complete 3-dimensional coronary tree with color-coded FFR values at any epicardial location. Hyperemic flow ratio is derived from an automatic resistance-based lumped model of the entire coronary tree. A total of 203 lesions were analyzed in 184 patients from 4 centers. Values derived using FFR_{angio} ranged from 0.5 to 0.97 (median 0.85) and correlated closely (Spearman $\rho=0.90$; $P<0.001$) with the invasive FFR measurements, which ranged from 0.5 to 1 (median 0.84). In Bland–Altman analyses, the 95% limits of agreement between these methods ranged from -0.096 to 0.112 . Using an FFR cutoff value of 0.80, the sensitivity, specificity, and diagnostic accuracy of FFR_{angio} were 88%, 95%, and 93%, respectively. The intraclass coefficient between 2 blinded operators was 0.962 with a 95% confidence interval from 0.950 to 0.971, $P<0.001$.

Conclusions—There is a high concordance between FFR_{angio} and invasive FFR. The color-coded display of FFR values during coronary angiography facilitates the integration of physiology and anatomy for decision making on revascularization in patients with stable coronary artery disease.

Clinical Trial Registration—URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT03005028. (*Circ Cardiovasc Interv*. 2017;10:e005259. DOI: 10.1161/CIRCINTERVENTIONS.116.005259.)

Key Words: angiography ■ catheterization ■ microcirculation ■ tomography ■ workflow

Fractional flow reserve (FFR) is a physiological index that quantifies the hemodynamic impact of epicardial atherosclerotic stenoses. It is defined as the ratio of hyperemic myocardial flow in the presence of stenosis, to the hyperemic flow in its absence, and is obtained by measuring the ratio of distal coronary pressure and the aortic pressure, respectively, using pressure-measuring guidewires during maximal hyperemia.^{1–3} FFR is considered the standard of reference for clinical decision making, particularly of angiographically indeterminate coronary lesions. Clinical outcome studies have shown that for nonsignificant lesions ($FFR >0.80$), medical therapy should be preferred, whereas in cases of significant stenoses ($FFR \leq 0.80$), coronary revascularization should be considered.^{4–11} Accordingly, both the US and European guidelines

recommend using FFR to guide the treatment strategy in stable coronary lesions.^{12,13}

See Editorial by Morris and Gunn

Nevertheless, for a variety of practical reasons, FFR measurements remain underused. Therefore, the ability to derive FFR values from routinely performed coronary angiograms, without the need for a pressure guidewire or hyperemic stimulus, could have an important impact on daily clinical practice by streamlining the workflow within the catheterization laboratory and avoiding the need for invasive coronary measurements.^{14–16}

Several image-based FFR methodologies have recently been introduced. Computational fluid dynamics (CFD) simulation applied to cardiac computed tomographic images and

ORIGINAL RESEARCH ARTICLE

Accuracy of Fractional Flow Reserve Derived From Coronary Angiography

Editorial, see p 485

BACKGROUND: Measuring fractional flow reserve (FFR) with a pressure wire remains underutilized because of the invasiveness of guide wire placement or the need for a hyperemic stimulus. FFR derived from routine coronary angiography (FFR_{angio}) eliminates both of these requirements and displays FFR values of the entire coronary tree. The FFR_{angio} Accuracy versus Standard FFR (FAST-FFR) study is a prospective, multicenter, international trial with the primary goal of determining the accuracy of FFR_{angio} .

METHODS: Coronary angiography was performed in a routine fashion in patients with suspected coronary artery disease. FFR was measured in vessels with coronary lesions of varying severity using a coronary pressure wire and hyperemic stimulus. Based on angiograms of the respective arteries acquired in ≥ 2 different projections, on-site operators blinded to FFR then calculated FFR_{angio} using proprietary software. Coprimary end points were the sensitivity and specificity of the dichotomously scored FFR_{angio} for predicting pressure wire–derived FFR using a cutoff value of 0.80. The study was powered to meet prespecified performance goals for sensitivity and specificity.

RESULTS: Ten centers in the United States, Europe, and Israel enrolled a total of 301 subjects and 319 vessels meeting inclusion/exclusion criteria which were included in the final analysis. The mean FFR was 0.81 and 43% of vessels had an $FFR \leq 0.80$. The per-vessel sensitivity and specificity were 94% (95% CI, 88% to 97%) and 91% (86% to 95%), respectively, both of which exceeded the prespecified performance goals. The diagnostic accuracy of FFR_{angio} was 92% overall and remained high when only considering FFR values between 0.75 to 0.85 (87%). FFR_{angio} values correlated well with FFR measurements ($r=0.80$, $P<0.001$) and the Bland–Altman 95% confidence limits were between -0.14 and 0.12 . The device success rate for FFR_{angio} was 99%.

CONCLUSIONS: FFR_{angio} measured from the coronary angiogram alone has a high sensitivity, specificity, and accuracy compared with pressure wire–derived FFR. FFR_{angio} has the promise to substantially increase physiological coronary lesion assessment in the catheterization laboratory, thereby potentially leading to improved patient outcomes.

CLINICAL TRIAL REGISTRATION: URL: <https://www.clinicaltrials.gov>. Unique Identifier: NCT03226262.

William F. Fearon, MD
 Stephan Achenbach, MD,
 PhD
 Thomas Engstrom, MD,
 PhD
 Abid Assali, MD
 Richard Shlofmitz, MD
 Allen Jeremias, MD
 Stephane Fournier, MD
 Ajay J. Kirtane, MD
 Ran Kornowski, MD
 Gabriel Greenberg, MD
 Rami Jubeh, MD
 Daniel M. Kolansky, MD
 Thomas McAndrew, PhD
 Ovidiu Dressler, MD
 Akiko Maehara, MD
 Mitsuaki Matsumura, BS
 Martin B. Leon, MD
 Bernard De Bruyne, MD,
 PhD
 For the FAST-FFR Study
 Investigators

Key Words: coronary artery disease
 ■ coronary circulation ■ fractional flow
 reserve, myocardial

Sources of Funding, see page 483

© 2017 American Heart Association, Inc.

<https://www.ahajournals.org/journal/circ>

Received March 13, 2017; accepted July 17, 2017.

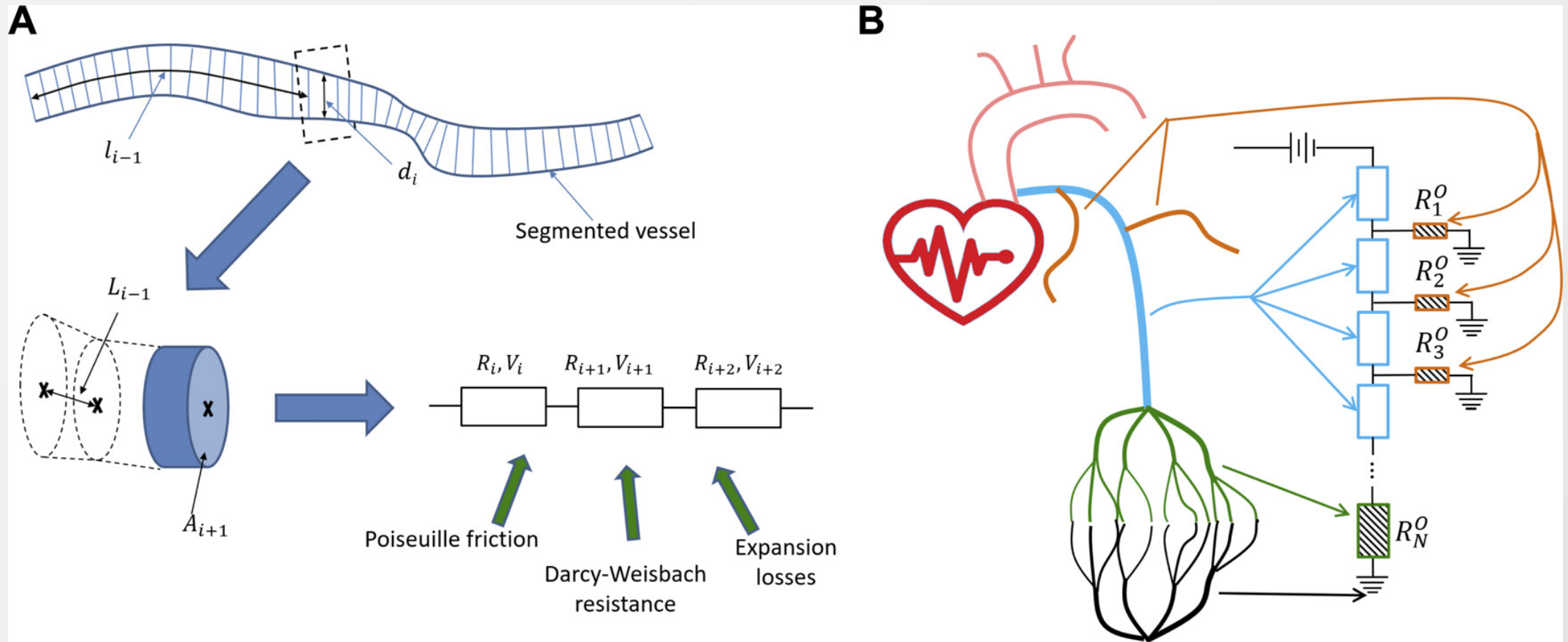
From the Cardiovascular Center Aalst, OLV Hospital, Belgium (M.P., B.D.B., P.X.); Rabin Medical Center, Petach Tikva, Israel (I.L., H.V.-A., A.A., O.V., P.C., R.K.); Department of Advanced Biomedical Sciences, Federico II University of Naples, Italy (M.P.); CathWorks Ltd, Ra'anana, Israel (I.L., O.V., Y.L.); Columbia University Medical Center, New York-Presbyterian Hospital (A.J.K., P.C., M.B.L.); and Shaare Zedek Medical Center, Jerusalem, Israel (G.W., Y.A.).

The Data Supplement is available at <http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.116.005259/-DC1>. Correspondence to Bernard De Bruyne, MD, PhD, Cardiovascular Center Aalst, OLV-Clinic, Moorselbaan, 164, B-9300 Aalst, Belgium. E-mail bernard.de.bruyne@olvz-aalst.be

© 2017 American Heart Association, Inc.

Circ Cardiovasc Interv is available at <http://circinterventions.ahajournals.org>

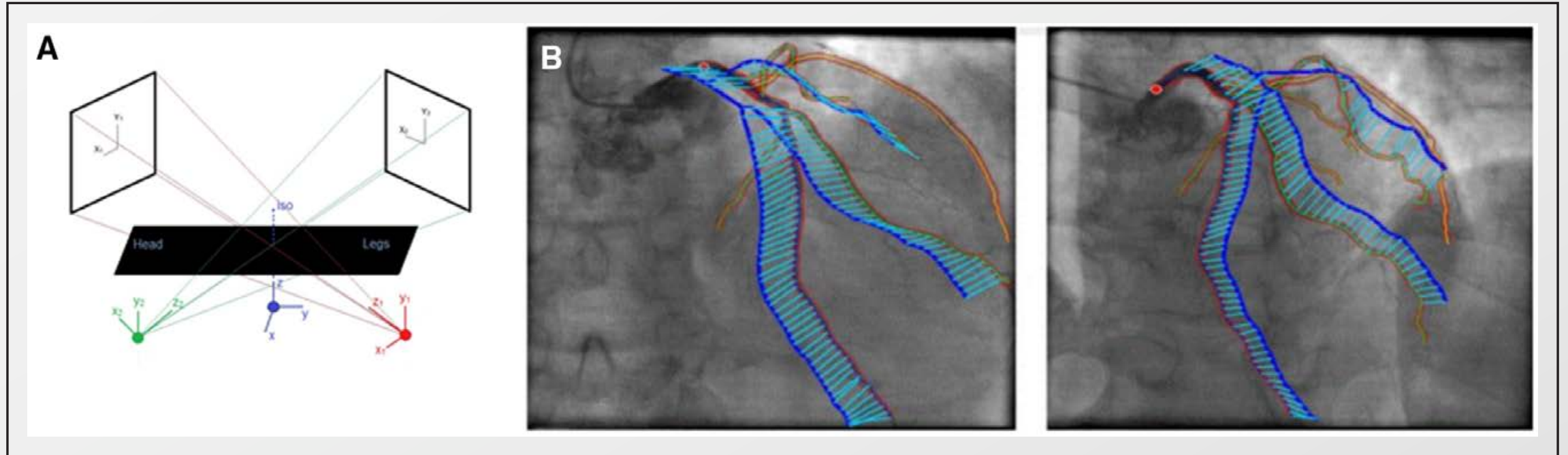
DOI: 10.1161/CIRCINTERVENTIONS.116.005259



$$\Delta P = \frac{8\eta LQ}{\pi r^4}$$

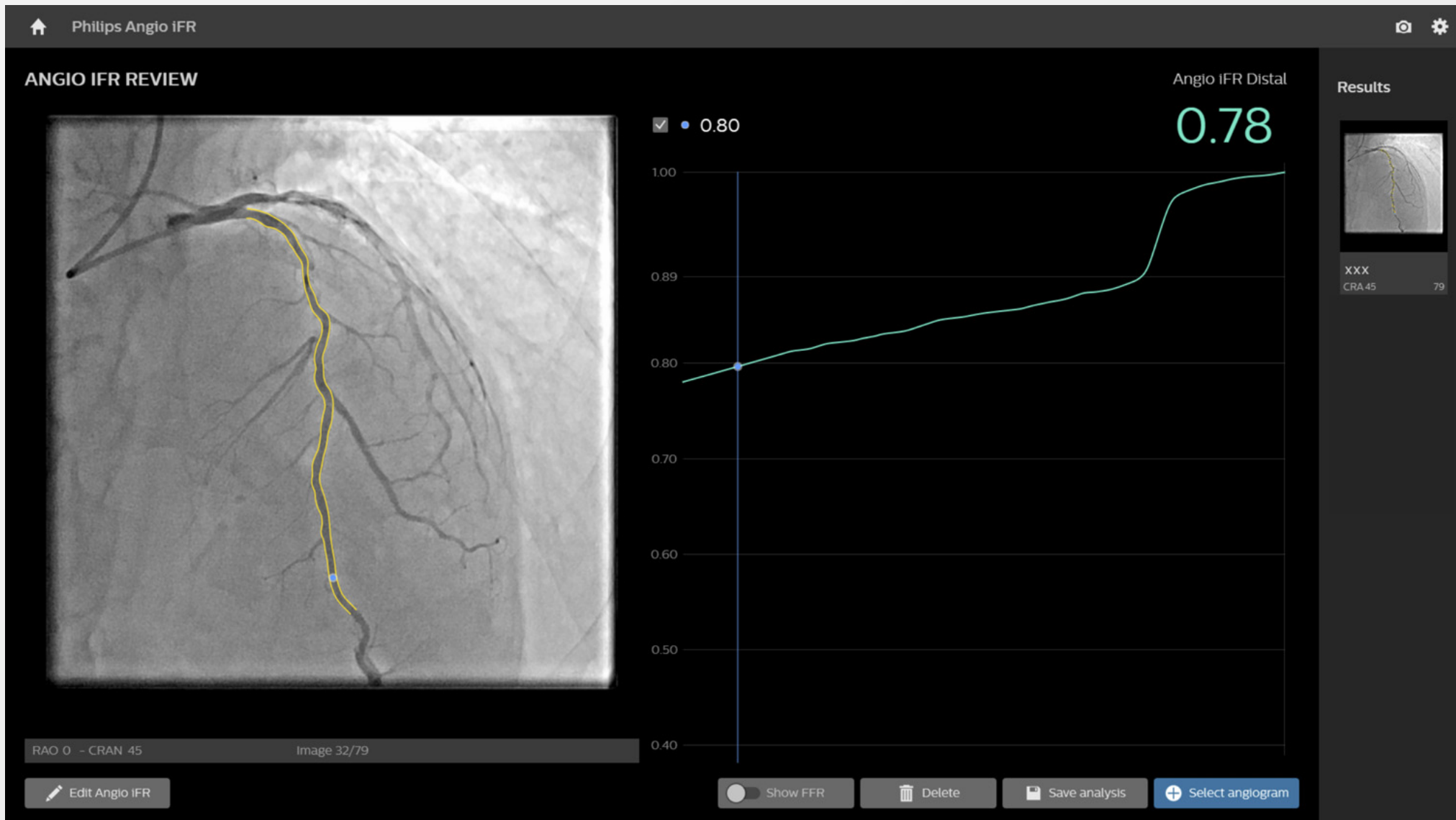
Pressure drop across the vessel length
 L and r are measured directly from the angiogram
 Q is a model parameter determined by the outlet
 conditions of the vascular system derived from aortic
 pressure

3D Reconstruction



Coronary tree is reconstructed from at least 2 orthogonal projections (usually 30 degrees or more) using centerline tracing and cross section analysis.

Geometry of vessel is created and vessel is broken down into nodes.



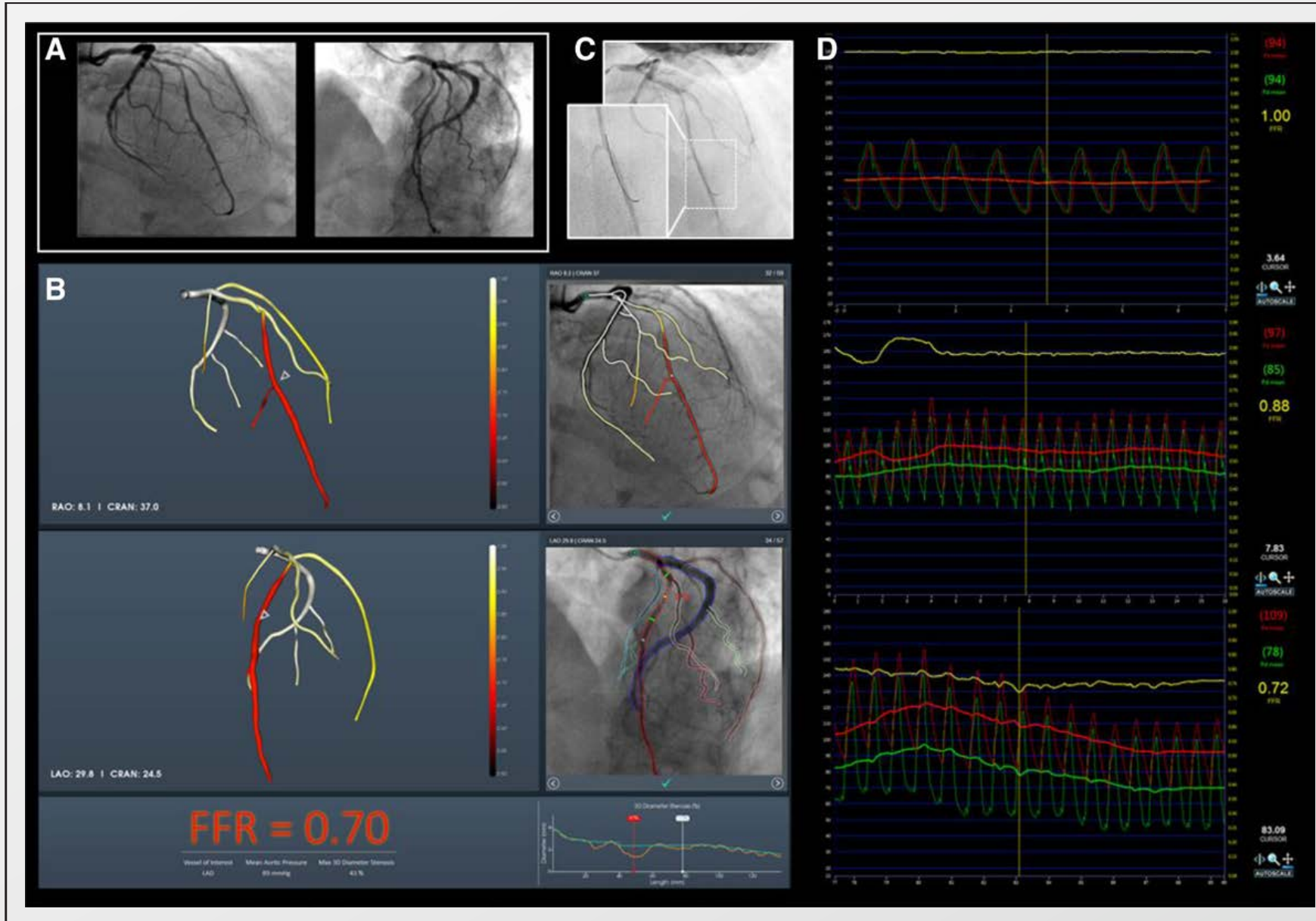
Angio-iFR medical software. The image is preliminary, which may be changed in the commercial version.

73474022 v1

From Ono et al *Am Heart J.* 2021

Example

FFRangio



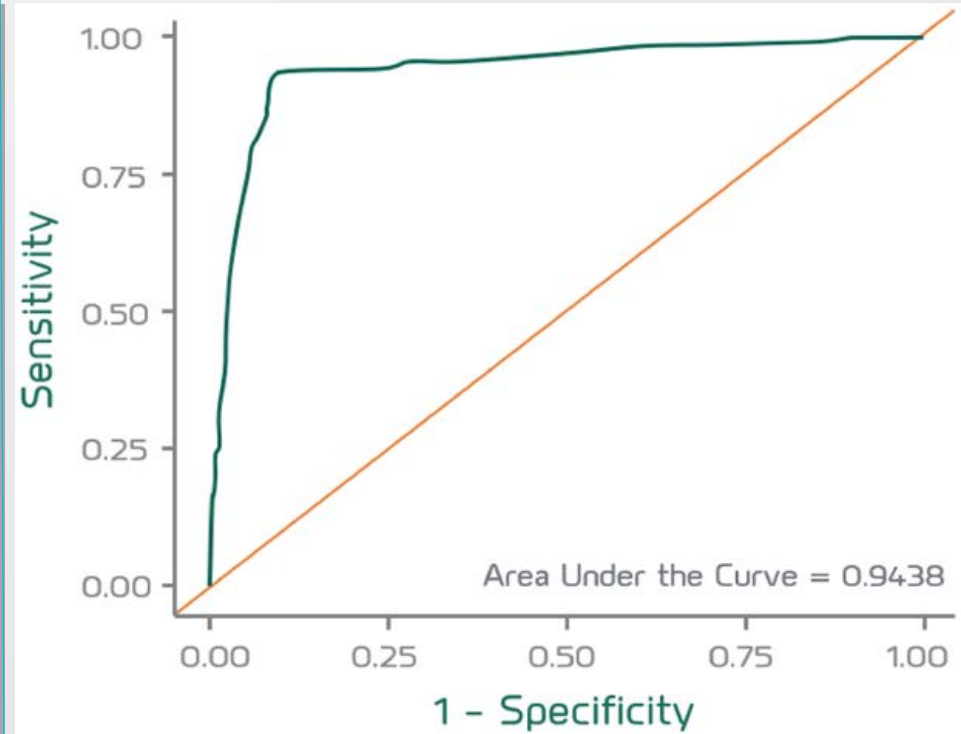
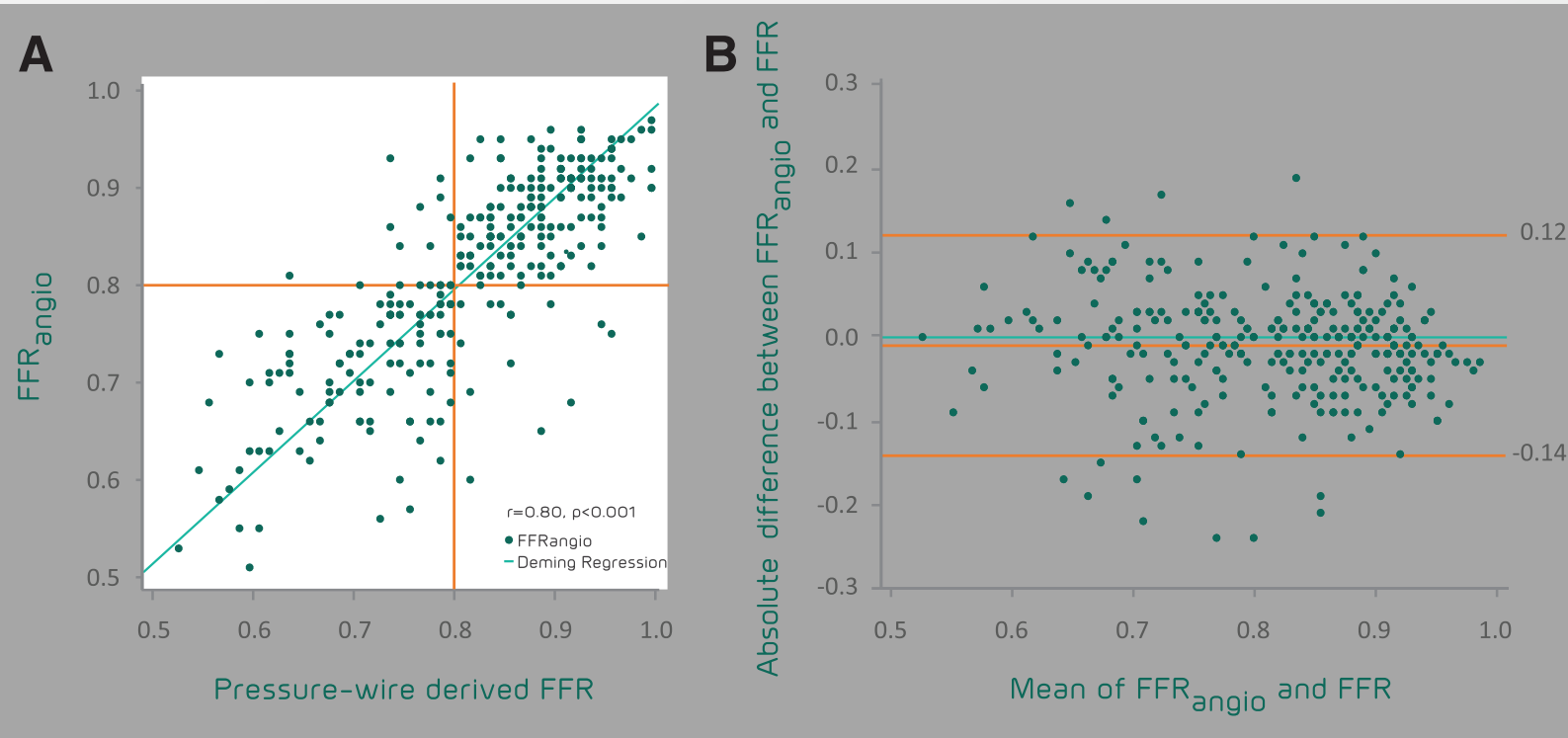
Equalization

Resting FFR

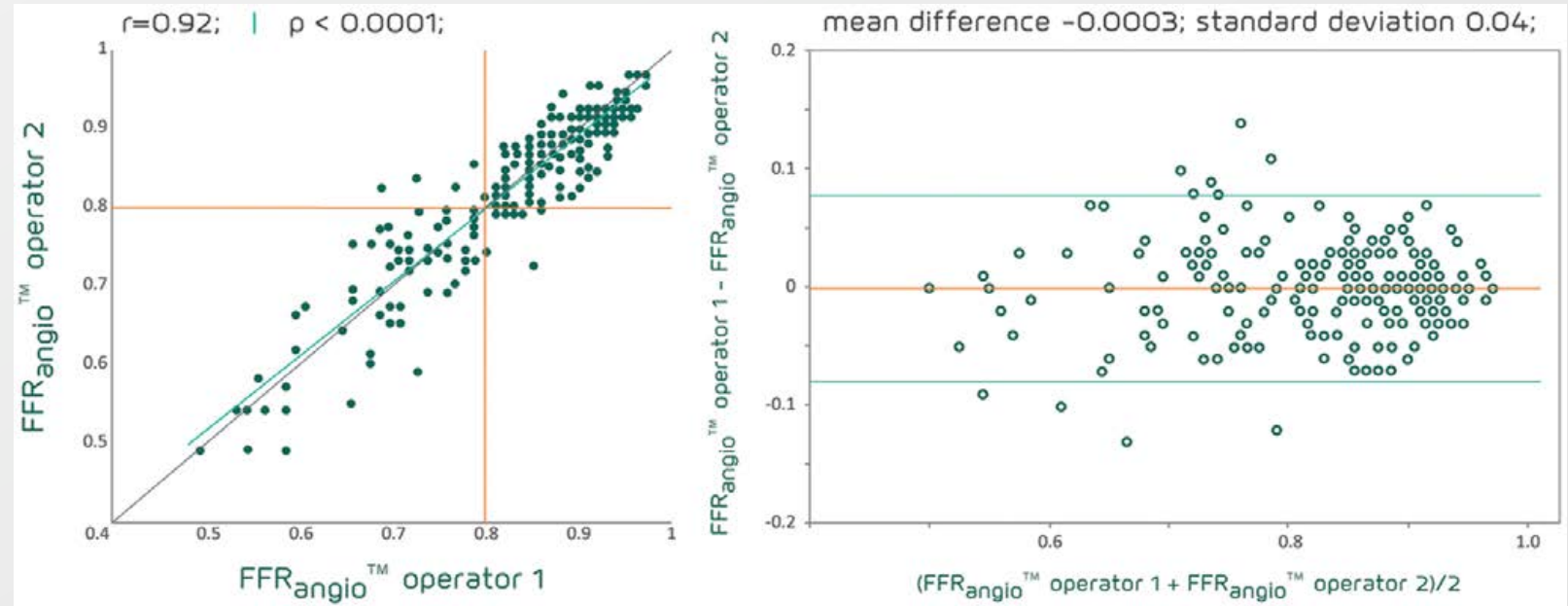
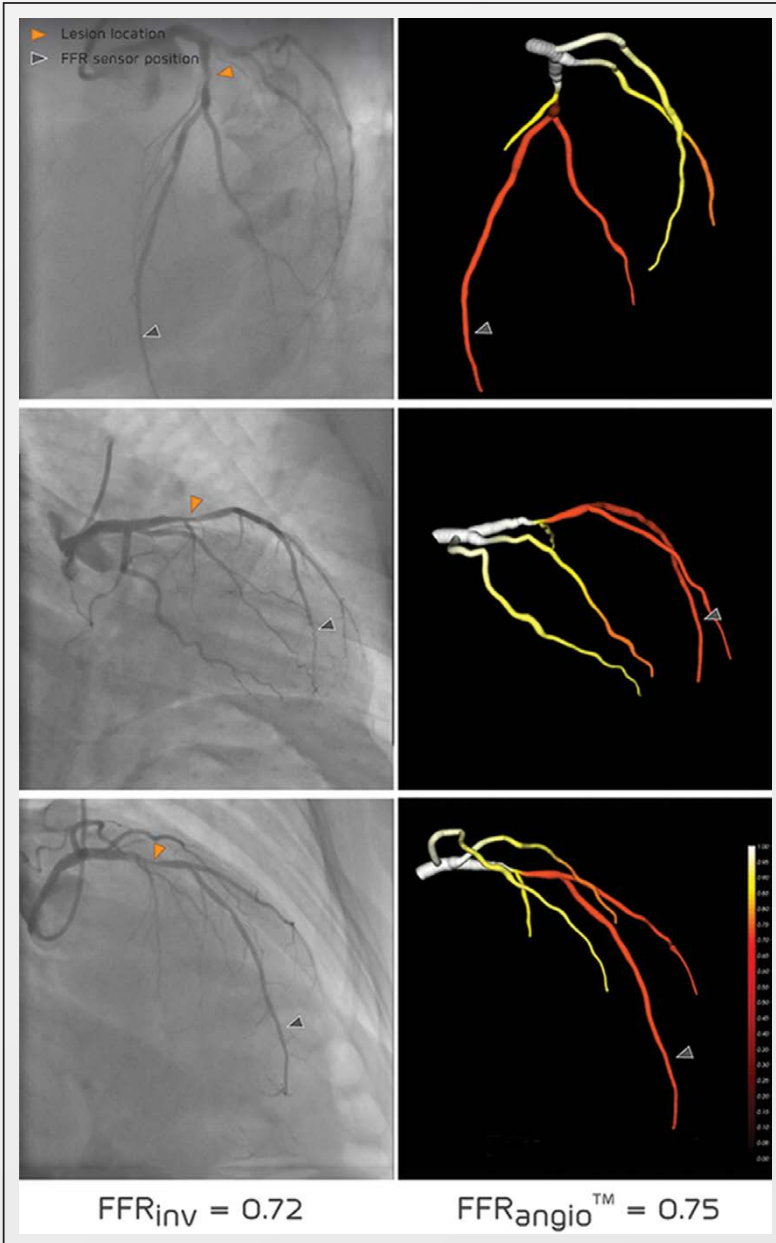
Hyperemia

Correlation between FFR and FFR_{angio}

ROC 94%



Case Example and Correlation between FFR and FFRangio

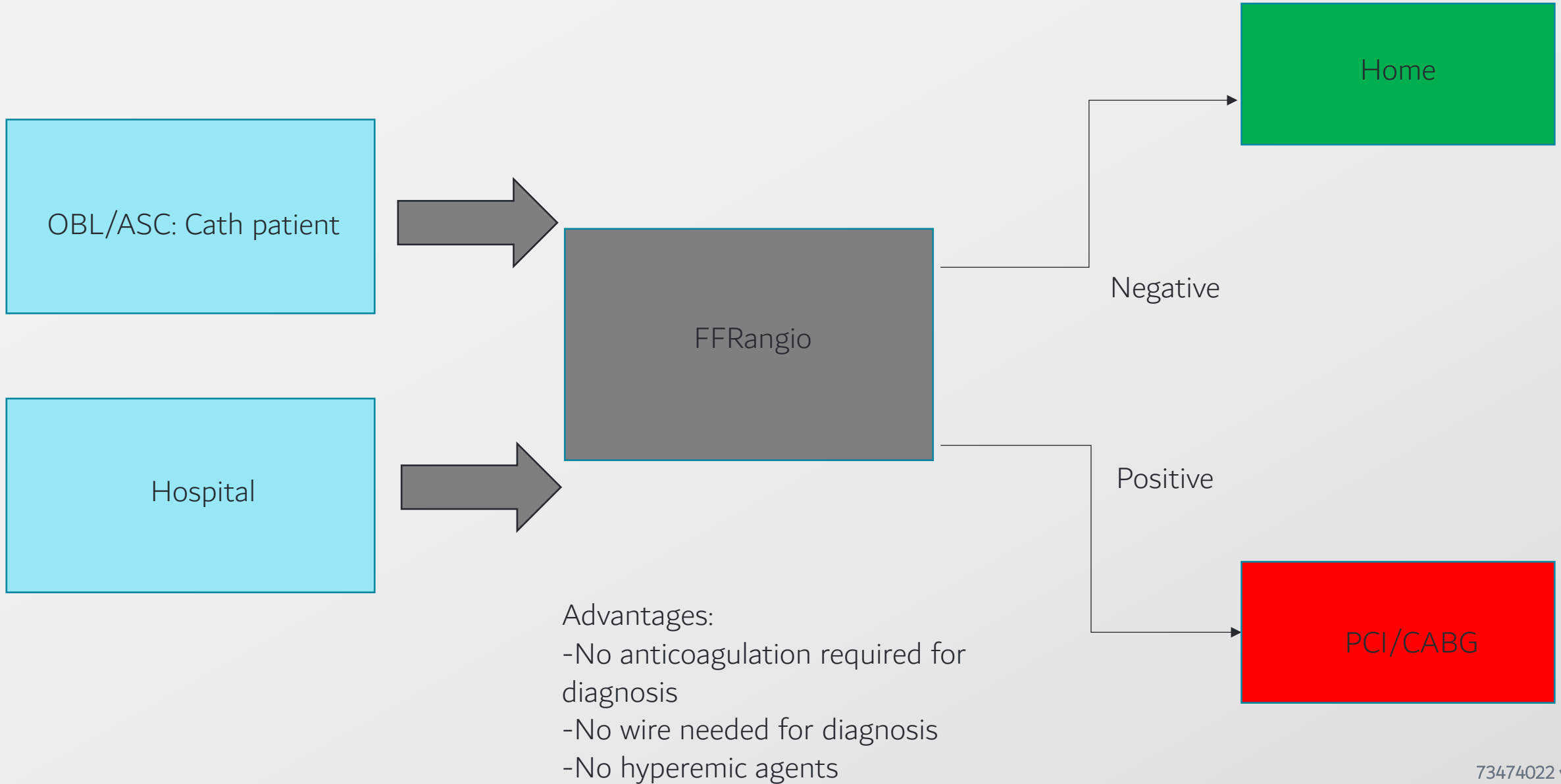


Currently available angio-based physiology systems

	Angio-iFR	μ QFR	QFR	FFR _{angio}	vFFR	caFFR
Company	Philips	Pulse Medical	Medis/Pulse Medical	CathWorks	Pie Medical	RainMed
Estimated reference	iFR and FFR	FFR	FFR	FFR	FFR	FFR
Required angio projections	1 projection	1 projection	2 projections 25 degrees apart	≥ 2 projections 30 degrees apart	2 projections	2 projections 30 degrees apart
Required pressure data	No	No	No	No	Need	Need
Side branches Studies	Incorporated ReVEAL iFR	Incorporated Tu S, et al.	Not incorporated FAVOR pilot FAVOR II China FAVOR II EJ WiFi II FAVOR III	Incorporated FAST-FFR	Not incorporated FAST	Not incorporated FLASH-FFR
C-statistics for predicting FFR ≤ 0.8	NA	0.97	0.92-0.96	0.94	0.93	0.979
Time to computation	NA (expected to be very short time)	67 \pm 22 seconds	4.36 \pm 2.55 min	*2.7 min	NA	4.54 \pm 1.48 min

FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; QFR: quantitative flow ratio.

*Time for manual correction and lesion identification were not included.



Summary

- ▶ CCTA has Guideline backing and payors are following: It is here to stay
- ▶ Noninvasive coronary physiology and FFRangio are disruptive
- ▶ Correlation of FFRct and FFRangio to invasive FFR is impressive: more data to come
- ▶ Diagnostic angiography is at risk, NOT revascularization
- ▶ Could lead to major improvements in work efficiency
- ▶ Could lead to significant cost-savings over the mid- to long-term
- ▶ Will make us better cardiologists

