Transforming Cardiovascular Care: Non-Wire Based Coronary Physiology

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Chief Medical Officer

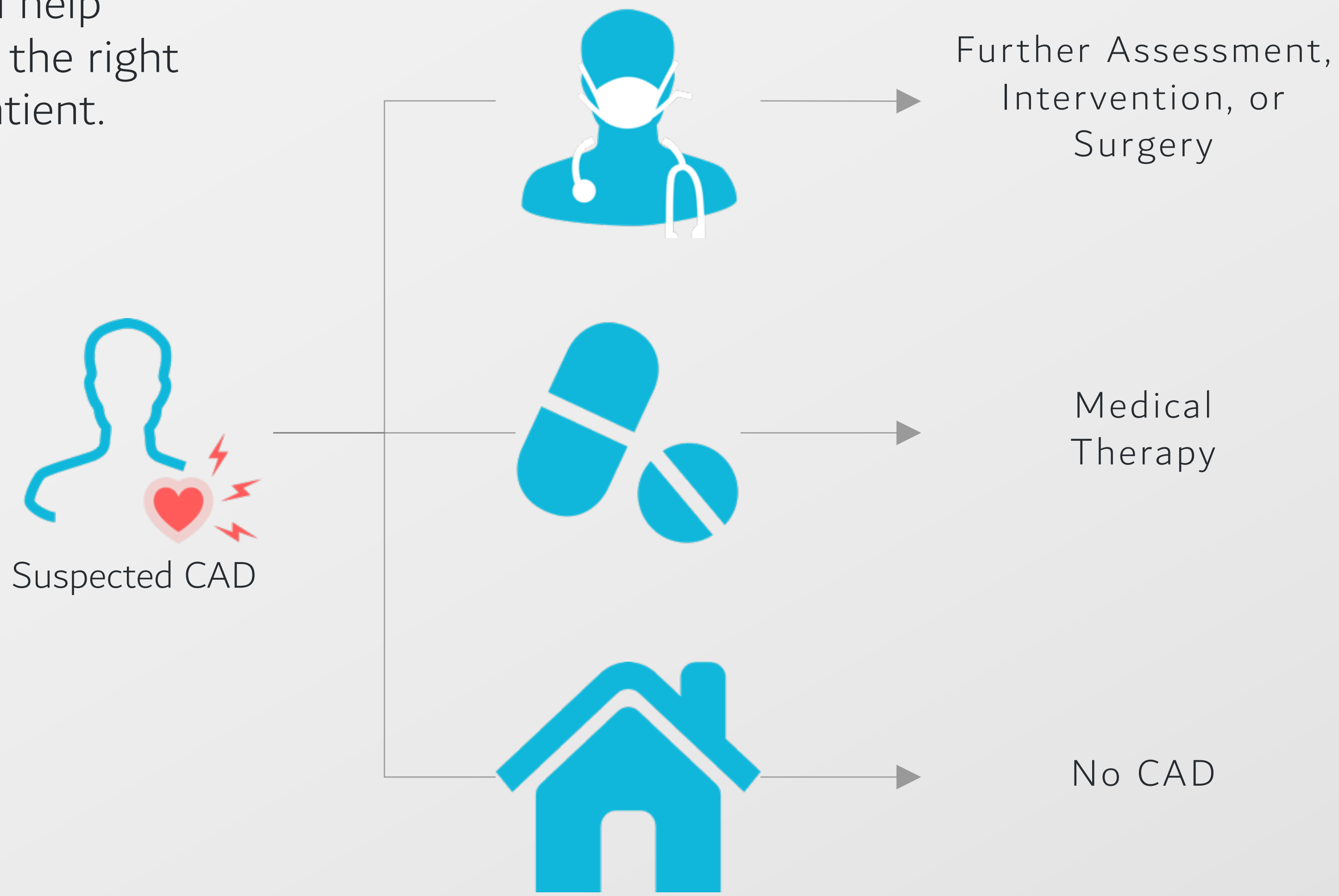
INTEGRIS Heart Hospital

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.



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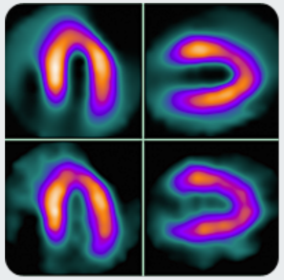
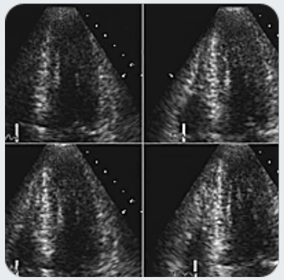
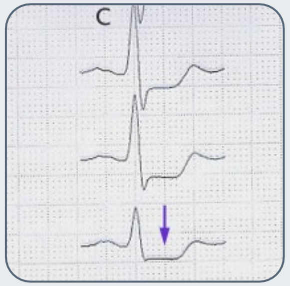
A finding of No CAD does not diminish the role of initiating or continuing primary prevention efforts

Current reality of non-invasive cardiac testing


SPECT


Stress Echo



Treadmill

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 test[2]

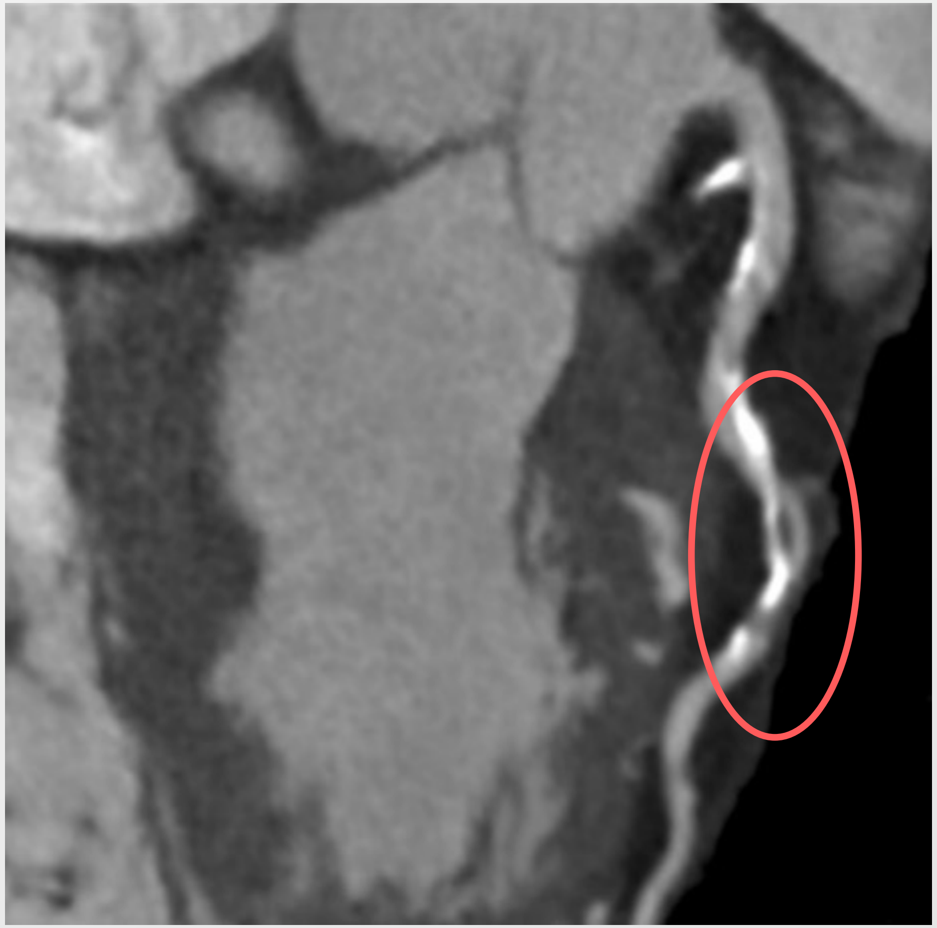
1. Patel, et al. N Engl J Med 2010. Patel, et al. AHJ 2014. Danad, et al. JAMA Cardiology 2017.
2. Arbab-Zadeh, Heart Int 2012. Yokota, et al. Neth Heart J 2018. Nakanishi, et al. J Nucl Cardiol 2018.

Common scenarios with today's non-invasive cardiac tests

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%)

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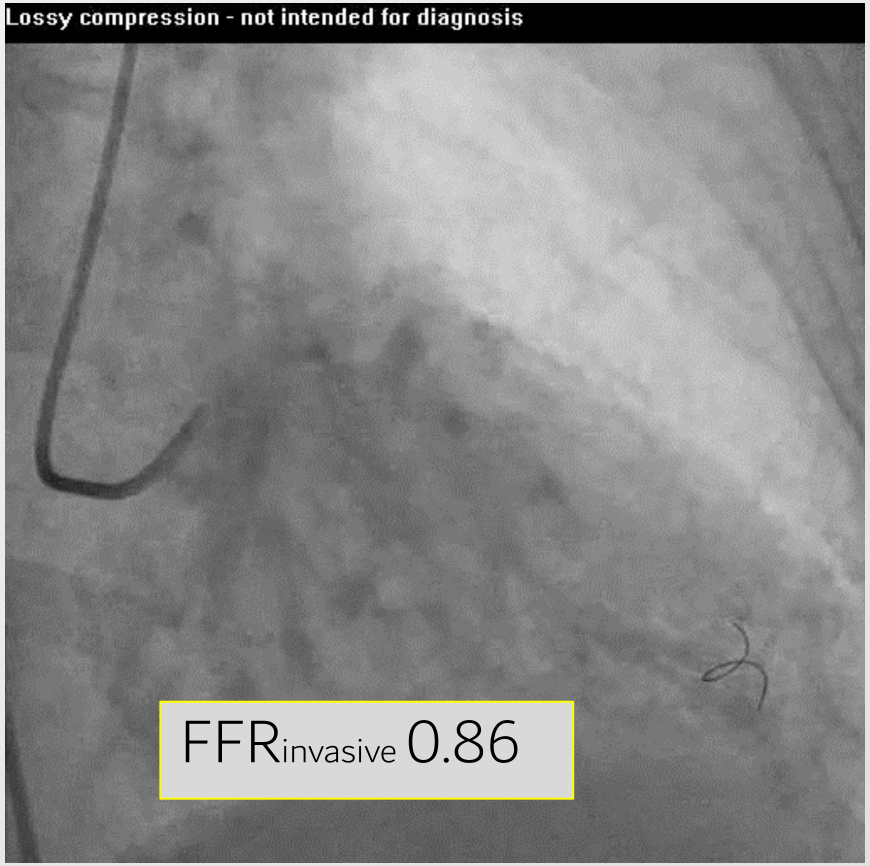
CASE WESTERN RESERVE
UNIVERSITY

Courtesy of Dr. Daniel Simon

Case Study: A Common Clinical Occurrence

Invasive Angiogram

No meaningful blockage:
Invasive FFR suggests no intervention is needed



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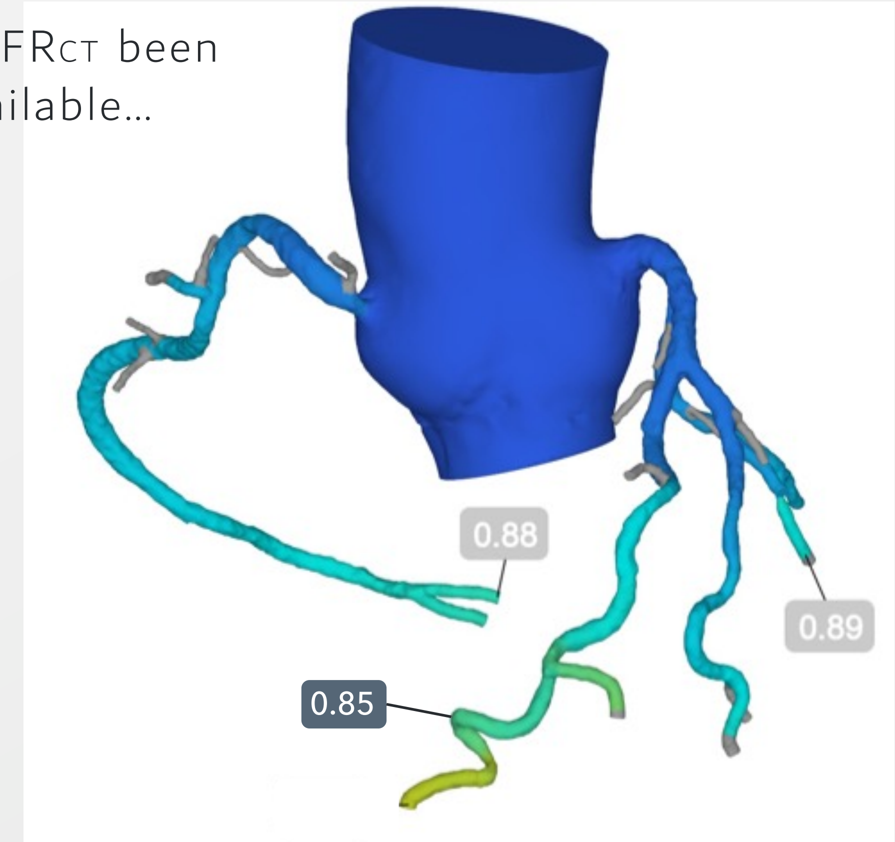
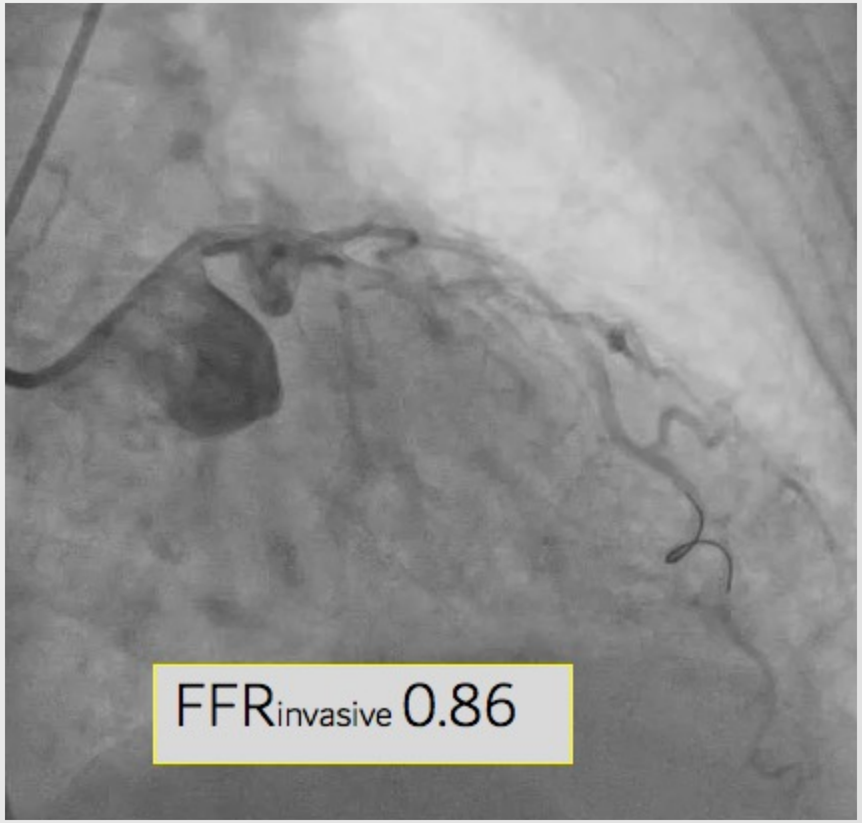
Courtesy of Dr. Daniel Simon

Case Study: A Common Clinical Occurrence

Had FFR_{CT} been available…





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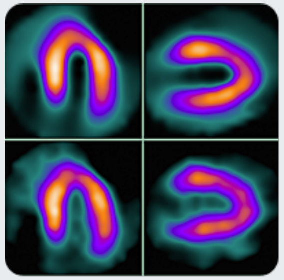
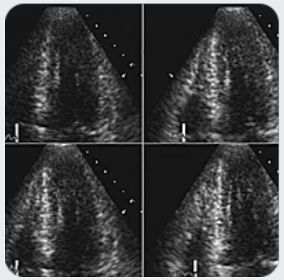
Current reality of non-invasive cardiac testing


SPECT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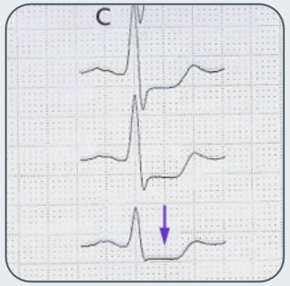

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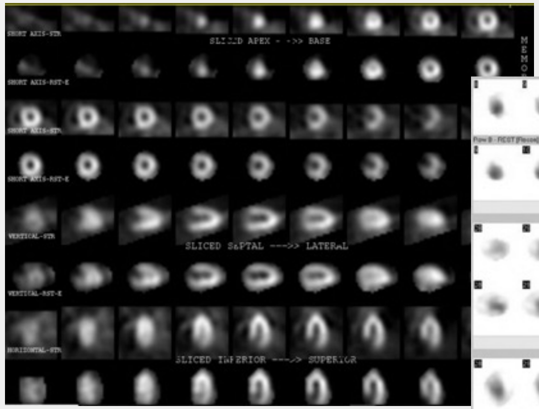
1. Patel, et al. N Engl J Med 2010. Patel, et al. AHJ 2014. Danad, et al. JAMA Cardiology 2017.

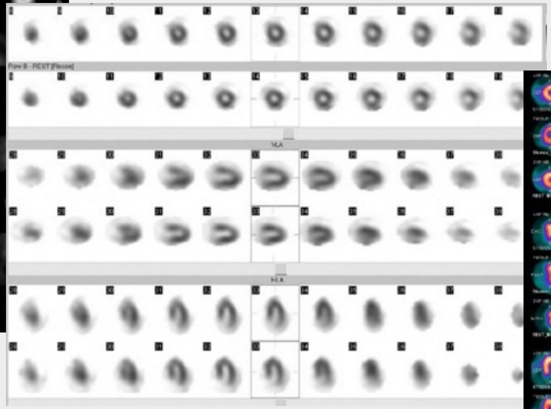
Case Study: Under-diagnosing disease

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

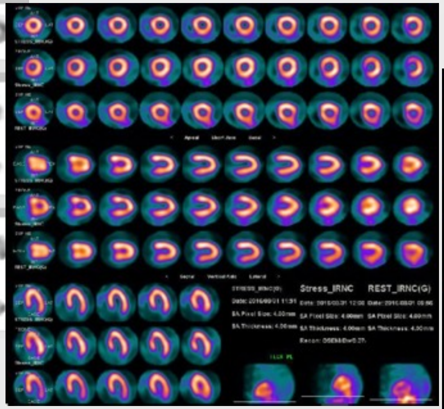
2005: Negative SPECT



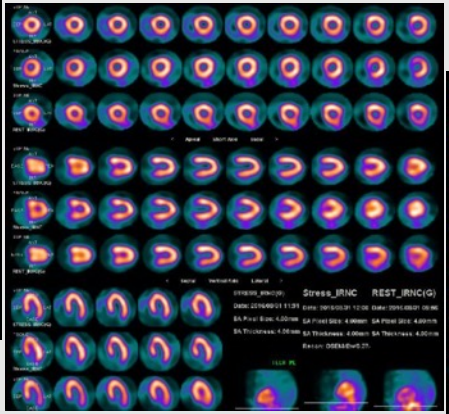
2011: Negative SPECT



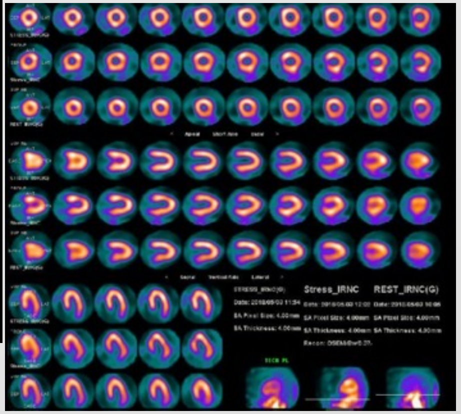
2015: Negative SPECT



2016: Negative SPECT



2018: Negative SPECT



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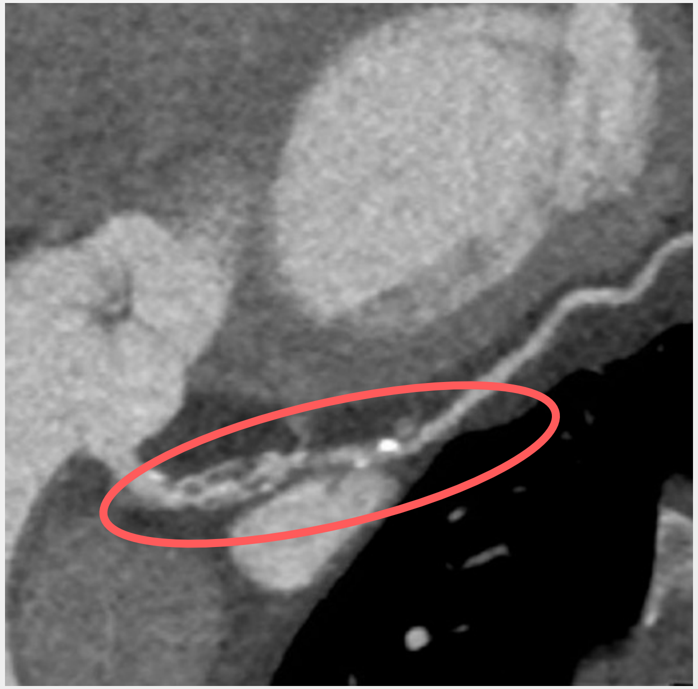
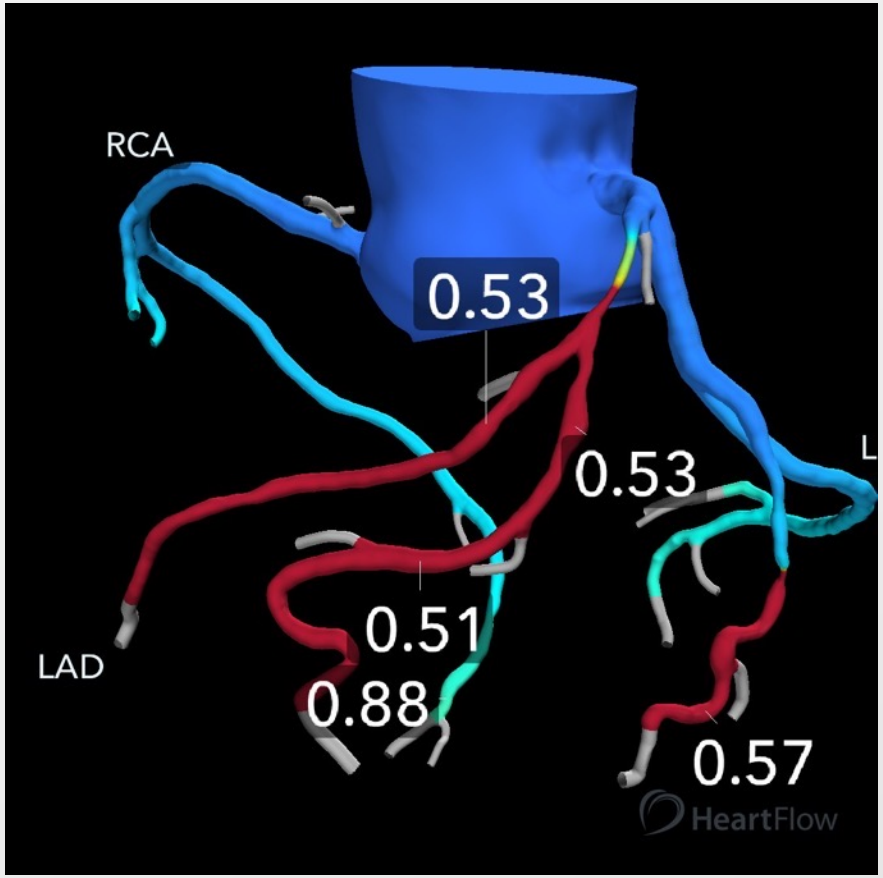
Courtesy of Dr. Michael Grantham

Case Study: Under-diagnosing disease



CCTA shows narrowings of multiple coronary arteries



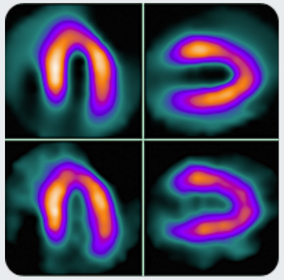
FFRCT shows two coronary arteries with functionally-significant disease and low FFRCT values (0.50-0.60 range) enabling invasive treatment and resolution of symptoms

Invasive angiogram validates findings of narrowings in two coronary arteries

Memorial Hospital of South Bend®

Courtesy of Dr. Michael Grantham

Current reality of non-invasive cardiac testing



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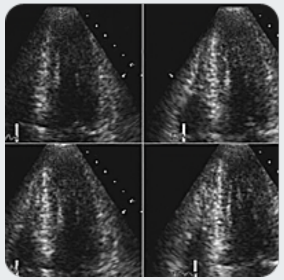

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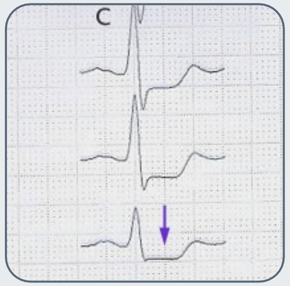

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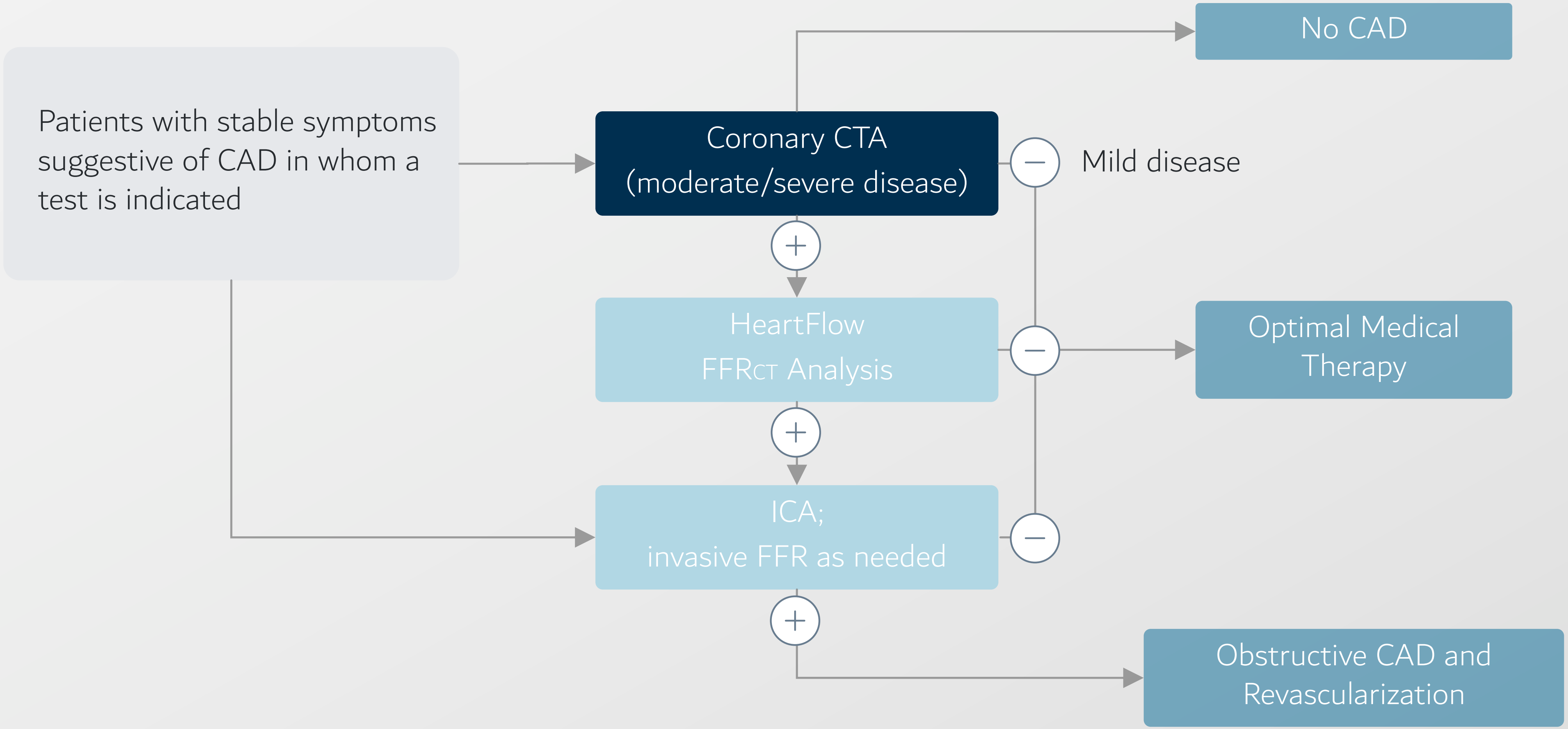
A better cardiac testing pathway starts with coronary CTA

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



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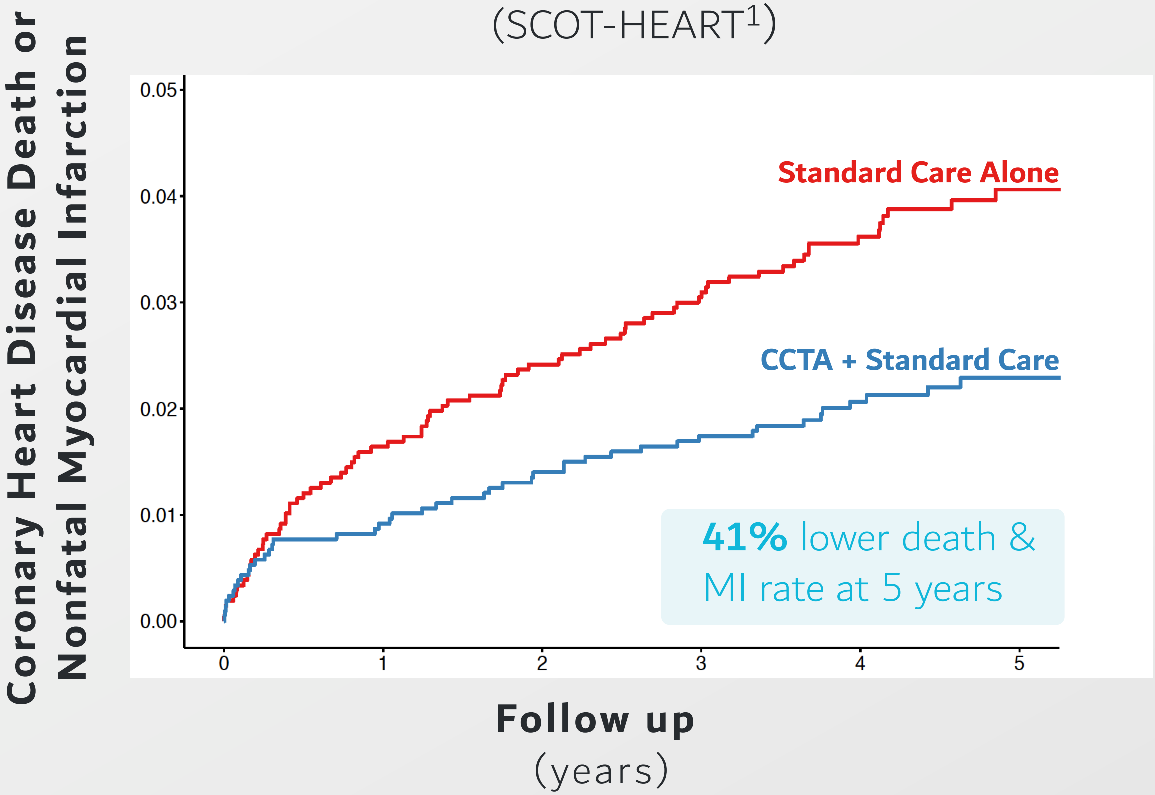
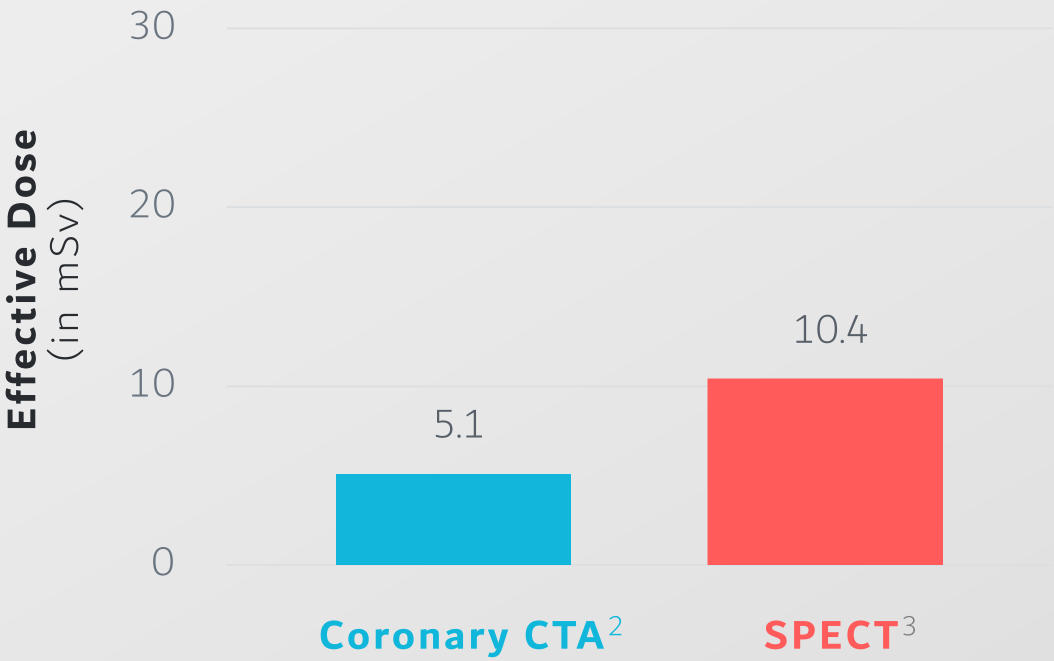
A better cardiac testing pathway starts with coronary CTA

Improved Long-term Outcomes:
Coronary CTA + Standard Care
(SCOT-HEART[1])



Lower Radiation than SPECT:
Coronary CTA
(PROTECTION VI[2])



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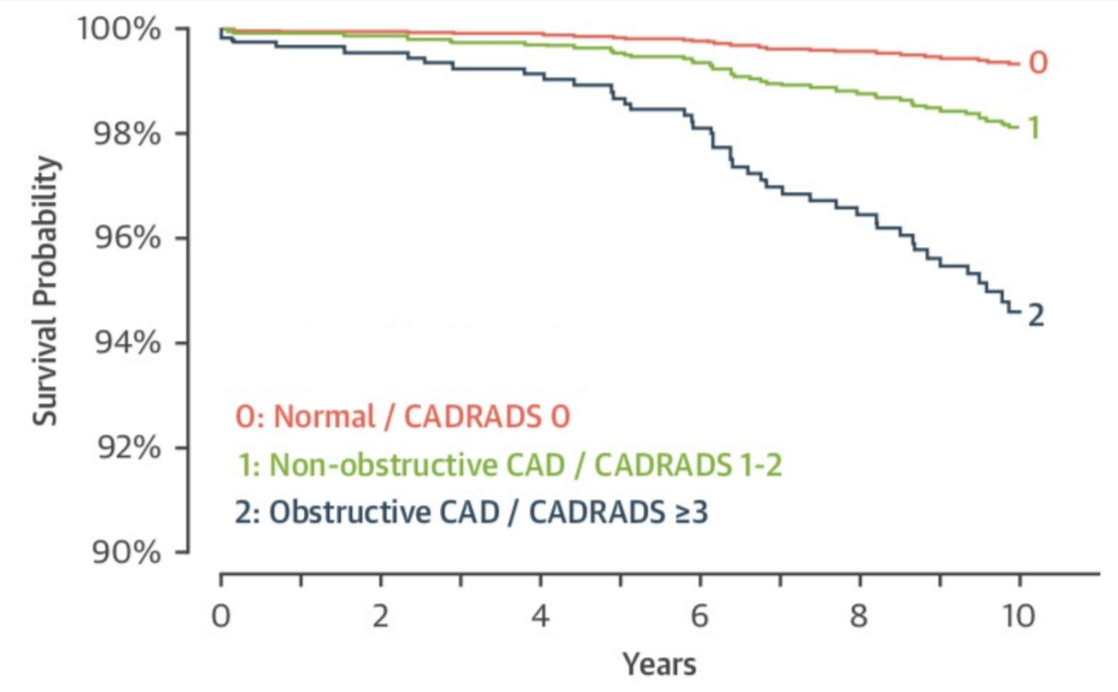
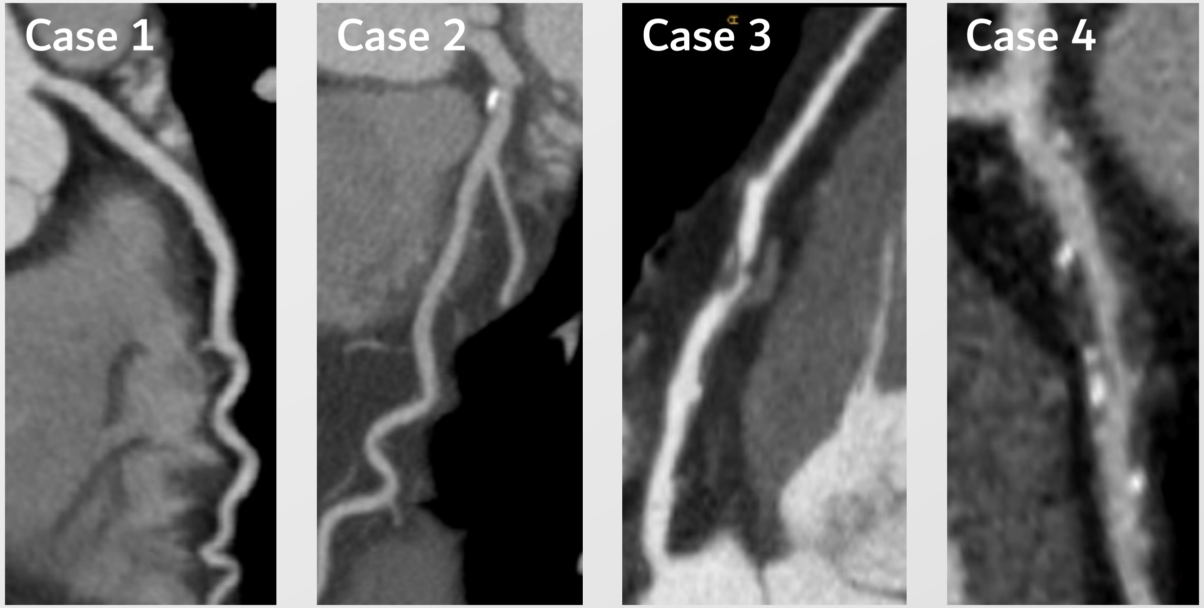
1. Newby, et al. N Engl J Med 2018. | 2. Stocker, et al. Euro Heart J 2018. | 3. Einstein, et al. Euro Heart J 2015.

A better cardiac testing pathway starts with coronary CTA

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



"Warranty Period" of a normal CCTA > 8 years



CADRADS 0 | CADRADS 1-2 | CADRADS 3 | CADRADS ≥3

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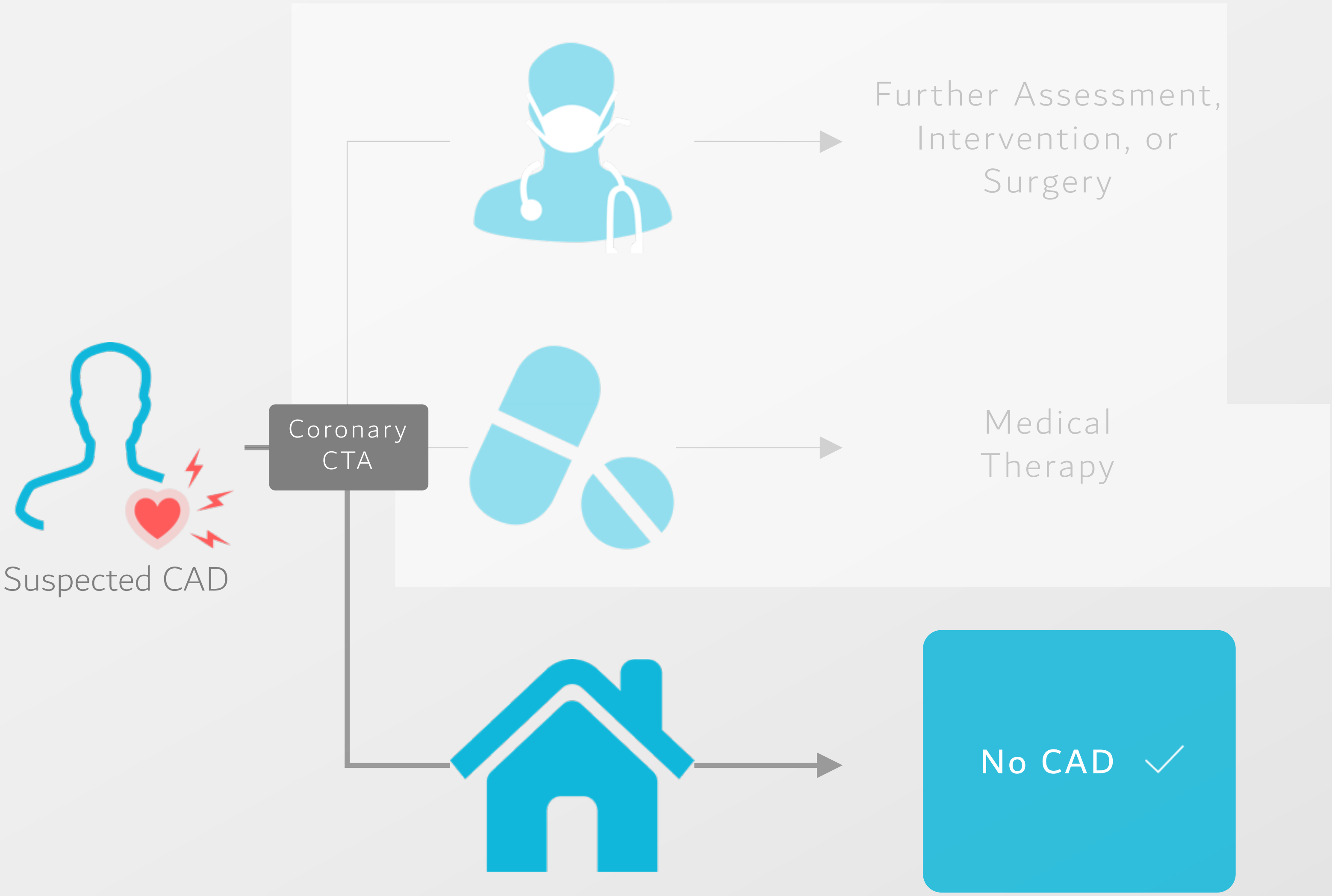
Finck, et al. JACC: Cardiovascular Imaging 2018.

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



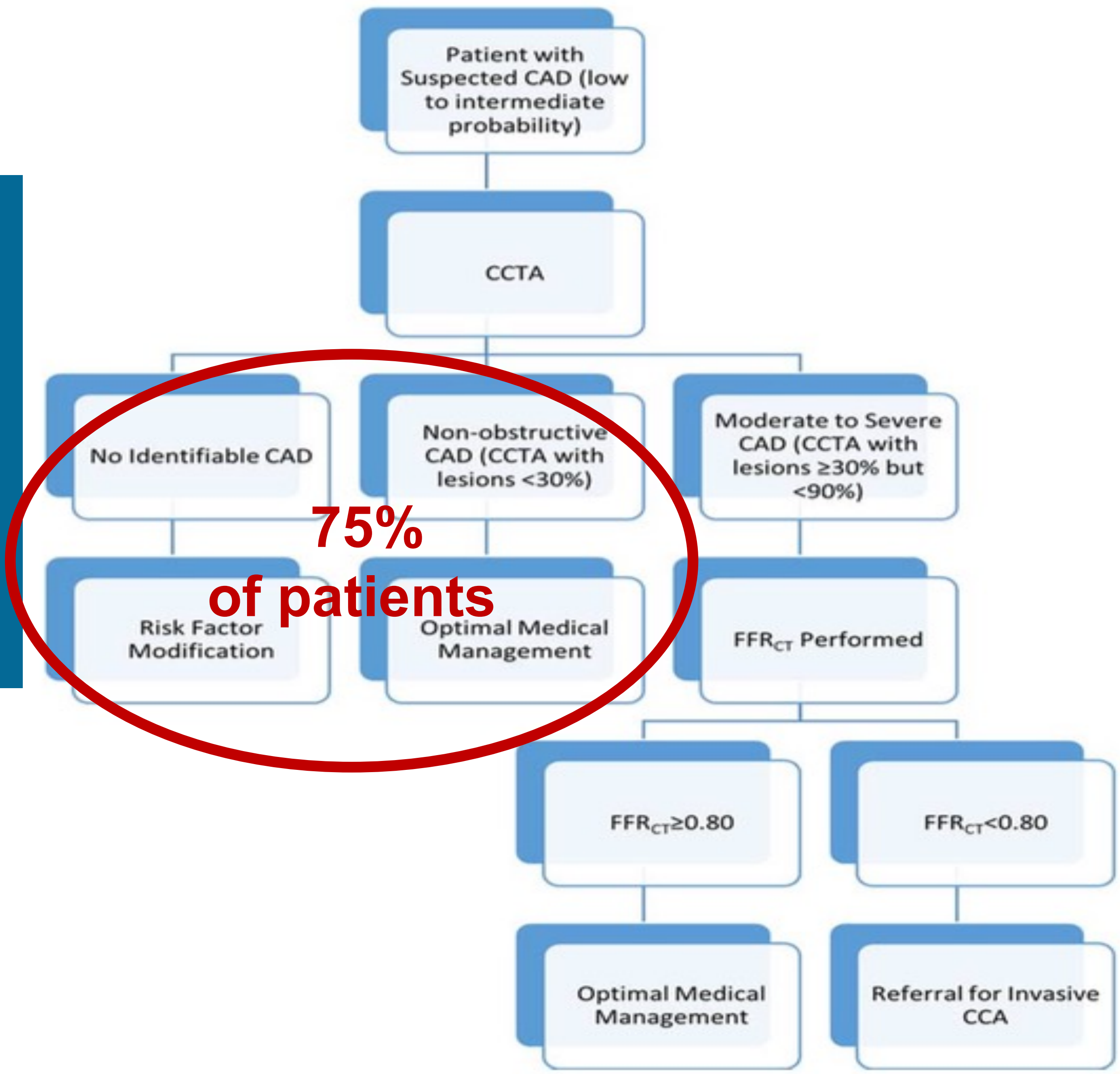
Only coronary CTA **differentiates** patients with **moderate to severe CAD**...

... **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.



Benton et al., J Thorac Imaging 2017.

A better cardiac testing pathway starts with coronary CTA

Coronary CTA is the preferred pathway in the UK…

NHS
National Institute for Health and Clinical Excellence

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 Shaw[2], Y.S. Chandrashekhar[3], Jeroen J. Bax[4], and Jagat Narula[1]

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).

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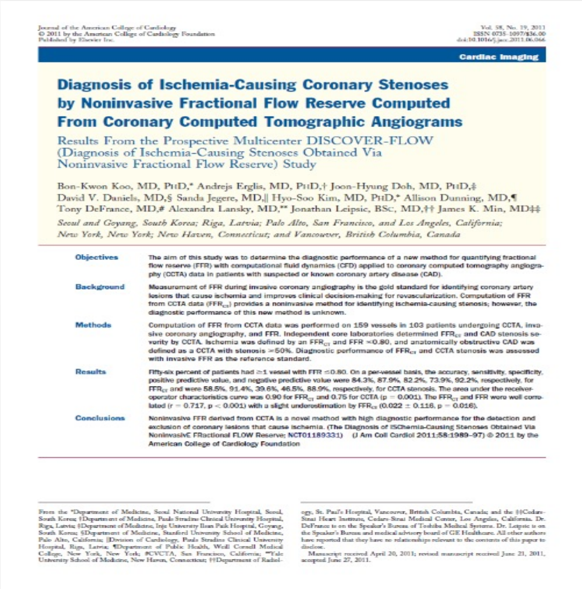
Accuracy of FFR_{CT} Compared to Gold Standard

DISCOVER-FLOW

- Completed 2011
- N=103 patients


Journal of the American College of Cardiology

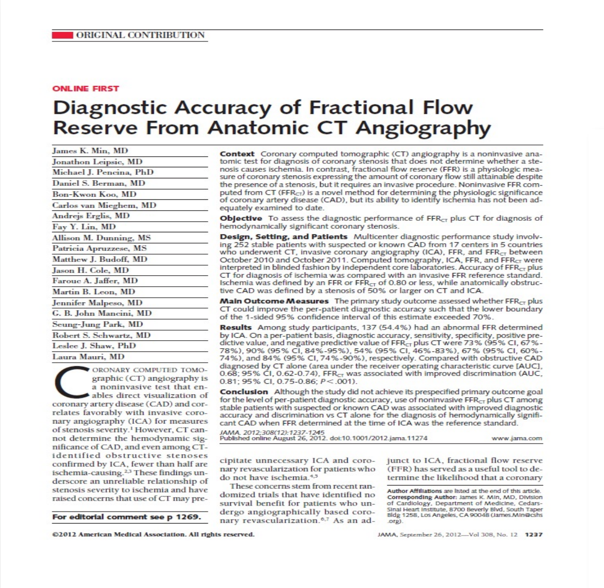
Cardiac Imaging

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

DeFACTO

- Completed 2012
- N=252 patients


ORIGINAL CONTRIBUTION

ONLINE FIRST

Diagnostic Accuracy of Fractional Flow Reserve From Anatomic CT Angiography

NXT

- Completed 2013
- N=254 patients


Journal of the American College of Cardiology

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)

NXT Per-Vessel Performance

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

Data supported 2014 FDA Clearance

Koo et al., JACC 2011.

Min et al., JAMA 2012.

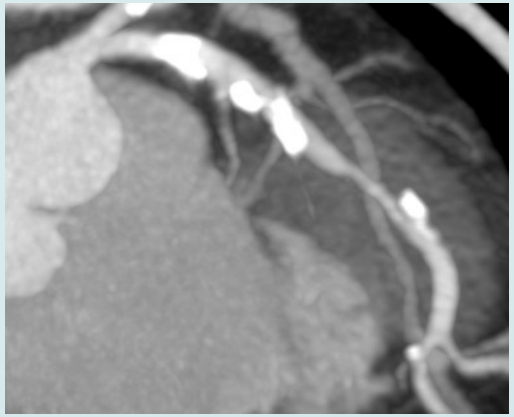
Norgaard et al., JACC 2014.

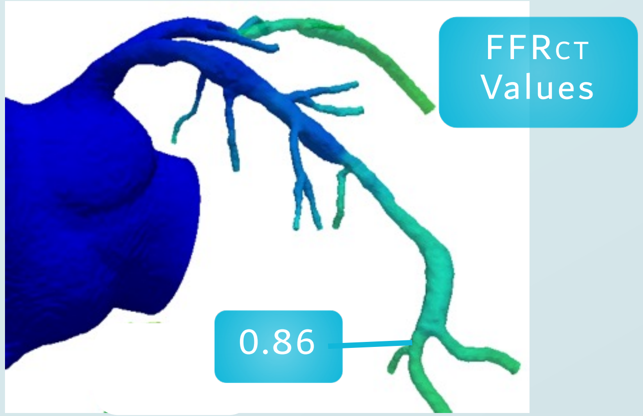
The Need for Physiology:
When does a 70% LAD stenosis by CCTA impact flow?

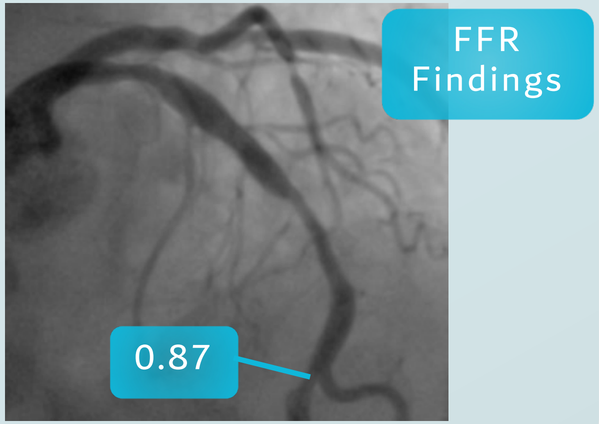
CTA 70% LAD Stenosis

Angio 70% LAD Stenosis

Patient A



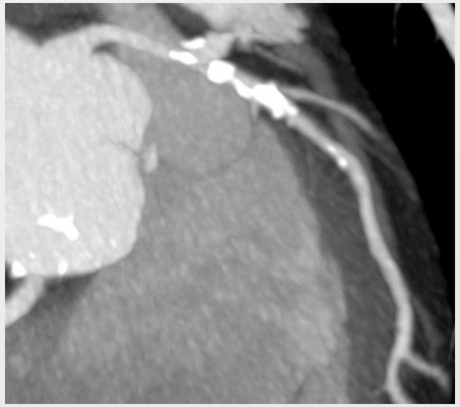


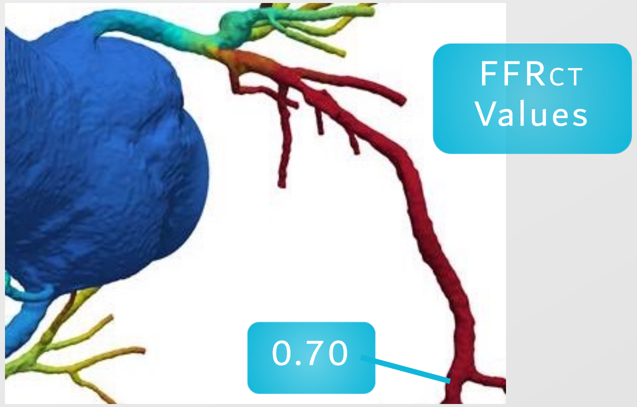


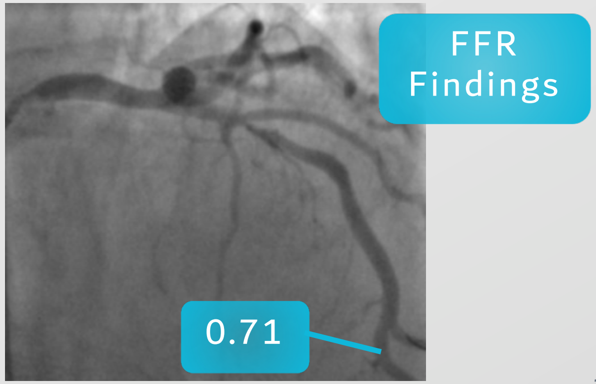
CTA 70% LAD Stenosis

Angio 70% LAD Stenosis

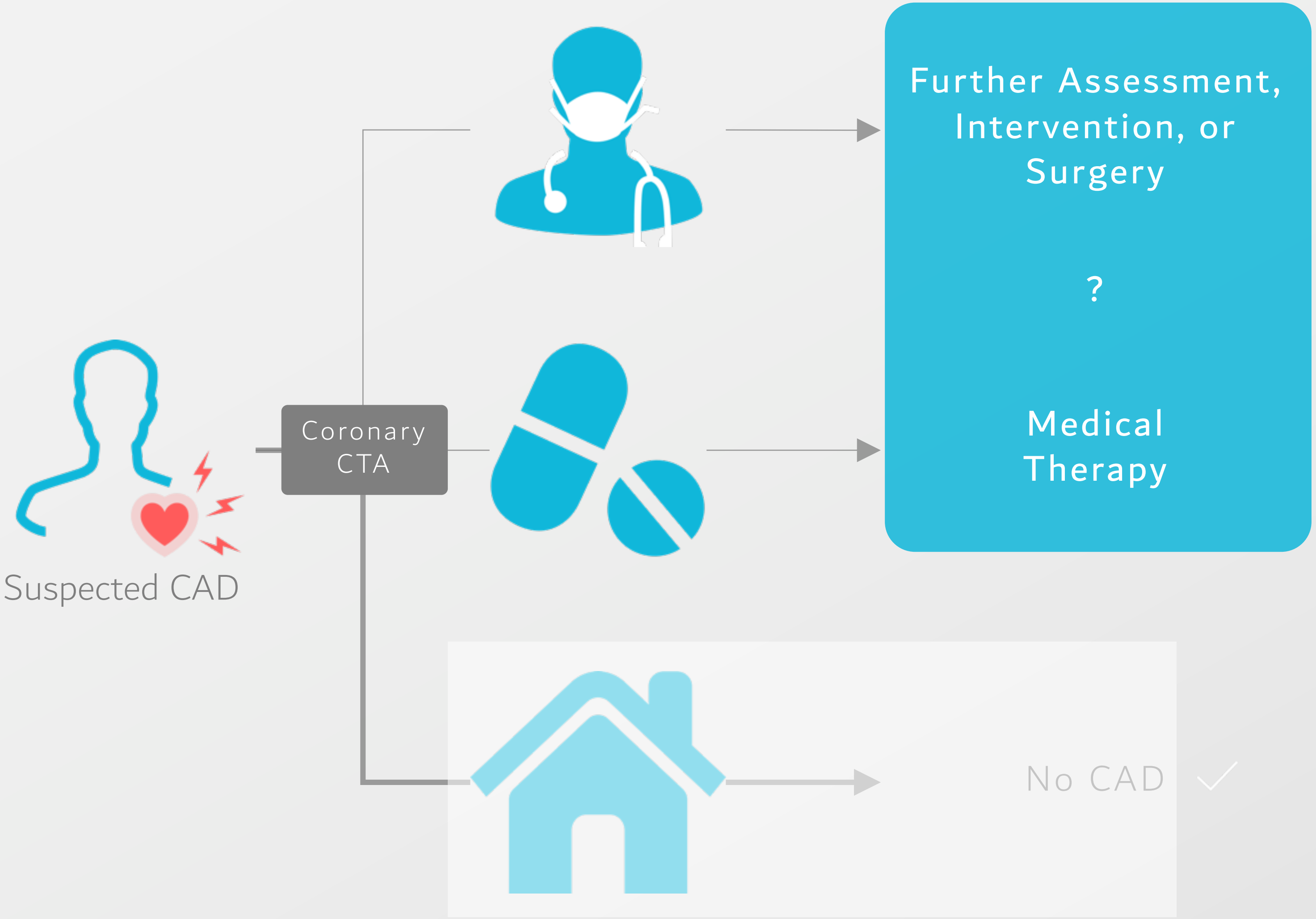
Patient B







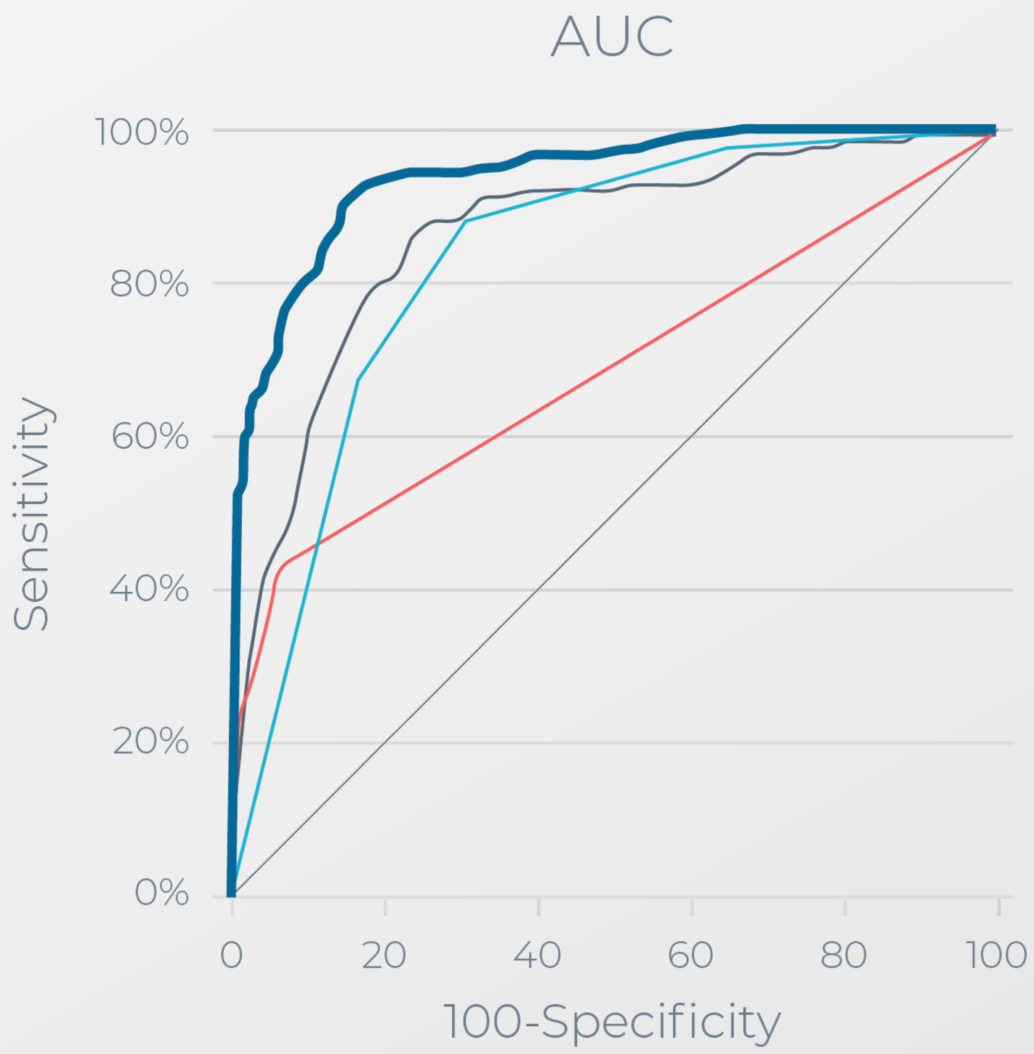
A better cardiac testing pathway starts with coronary CTA



CCTA + FFRCT
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 FFRCT
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 FFRCT Analysis

Diagnostic accuracy:

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

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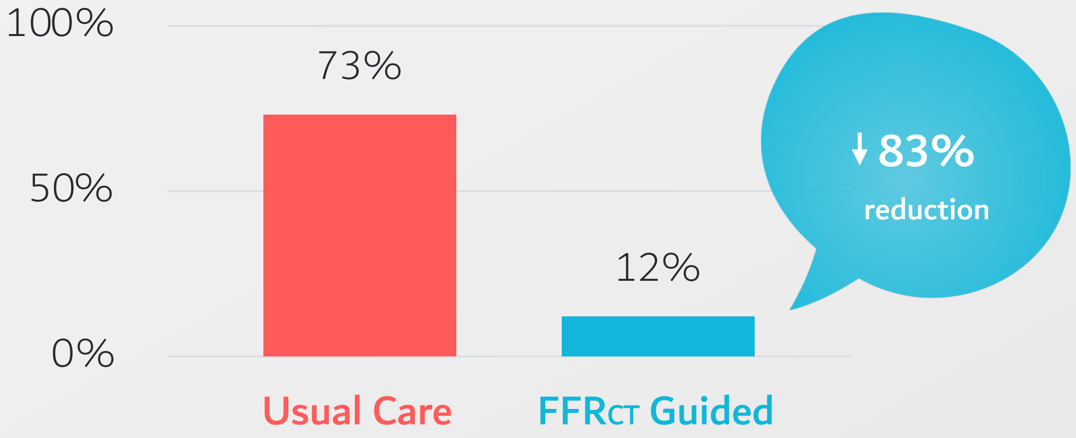
Driessen, et al. J Am Coll Cardiol 2019. | Nørgaard, et al. J Am Coll Cardiol 2014.

A better cardiac testing pathway: Coronary CTA + HeartFlow FFRCT

Reduce Overutilization of Invasive Testing[1]
by reducing **false positives**

Rate of Negative ICAs



NOTE: No Change in the revascularization rate[1]

Safe to defer ICA for patients with FFRCT >0.80

Low adverse clinical event rates in patients whose ICA was canceled based on the findings from an FFRCT-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]

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1. Douglas, et al. Eur Heart J 2015. | 2. Patel, et al. JACC CV Imaging 2019. | 3. Douglas, et al. JACC 2016. | 4. Nørgaard, et al. JACC 2018.
*At 1 year, 3 of 1592 (0.19%) patients who had an FFRCT >0.80 also had an MI. Zero of these 1592 patients experienced cardiovascular death.

A better cardiac testing pathway: Coronary CTA + HeartFlow FFRct

Reduce Overutilization of Invasive Testing[1]
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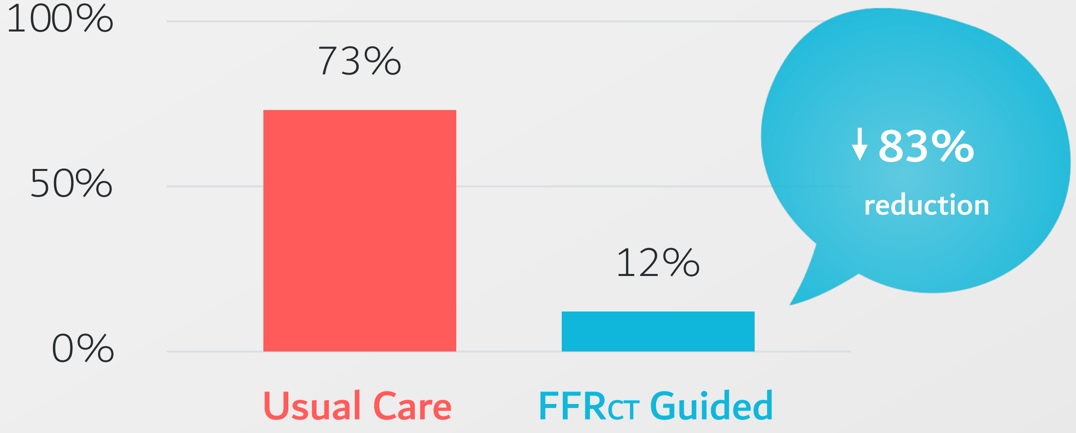
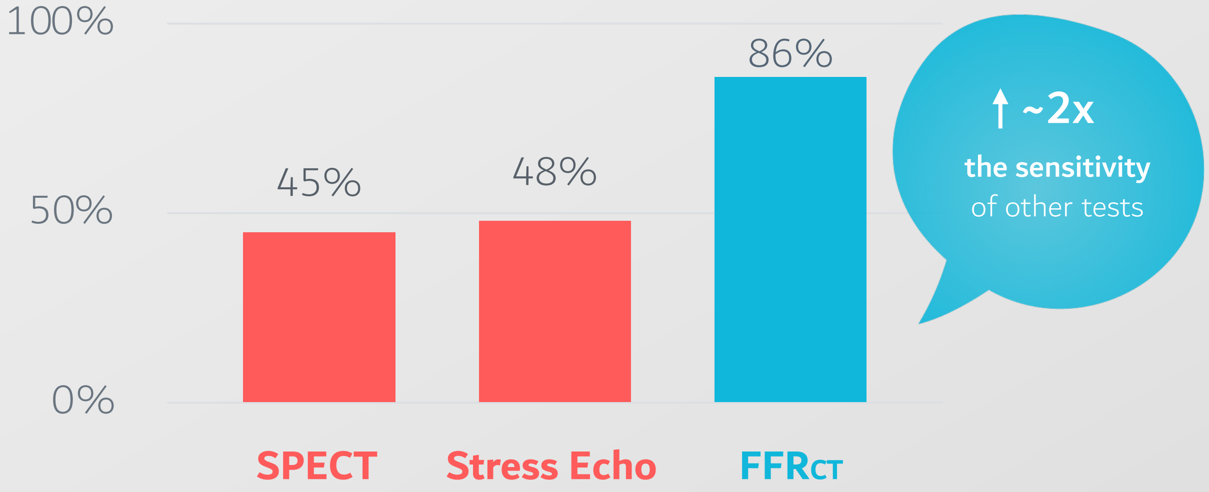


NOTE: No Change in the revascularization rate[1]

Identify Functional Disease Other Tests Miss[2]
by reducing **false negatives**

Sensitivity vs Invasive FFR
(per vessel)



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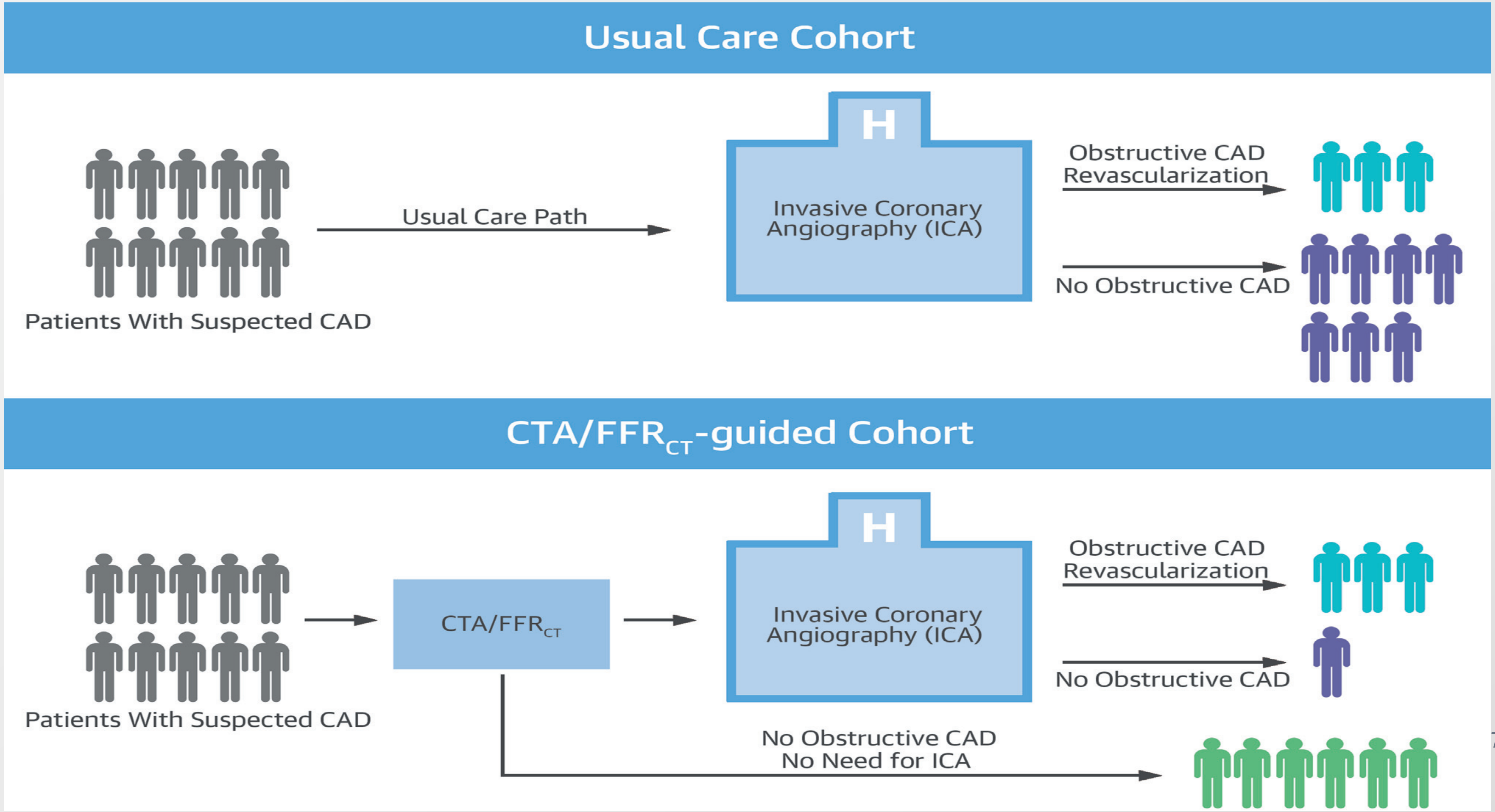
1. Douglas, et al. Eur Heart J 2015. | 2. Nørgaard, et al. Euro J Radiol 2015. Incl. Jung, et al. Euro Heart J 2008. Melikian, et al. JACC Cardiovasc Interv 2010. Koo, et al. JACC 2011. Min, et al. J Am Med Assoc 2012. Nørgaard, et al. JACC 2014. Danad, et al. JAMA Cardiol 2017. Driessen, et al. JACC 2019.

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

The PLATFORM Study

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

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



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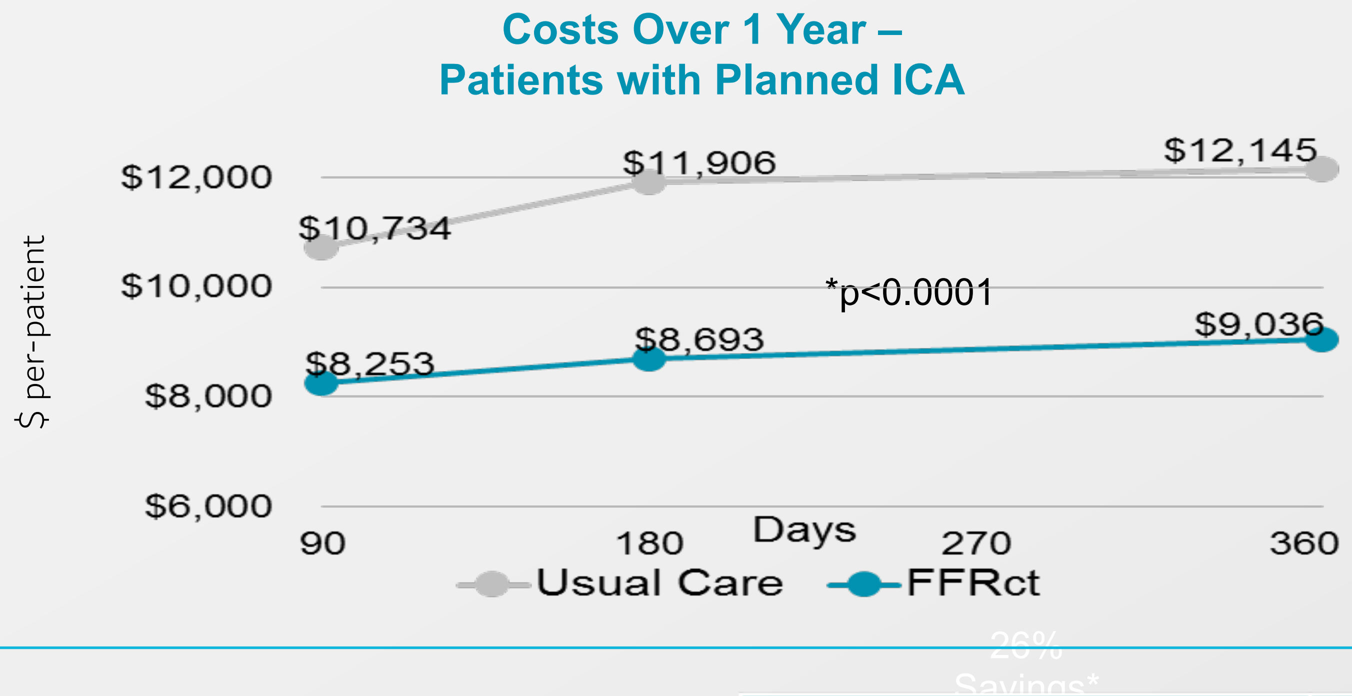
Douglas, P.S. et al. J Am Coll Cardiol. 2016;68(5):435–45.

Cost Savings Over Time



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

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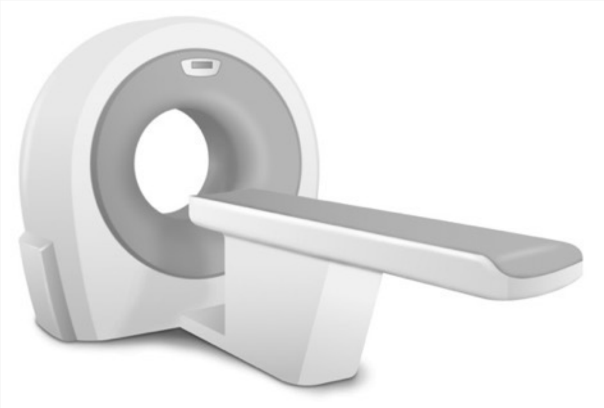
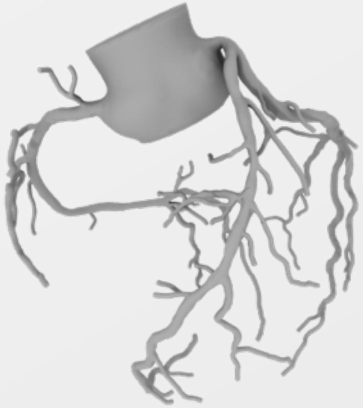
Hlatky, et al. JACC 2015

Douglas, et al. JACC 2016.

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***

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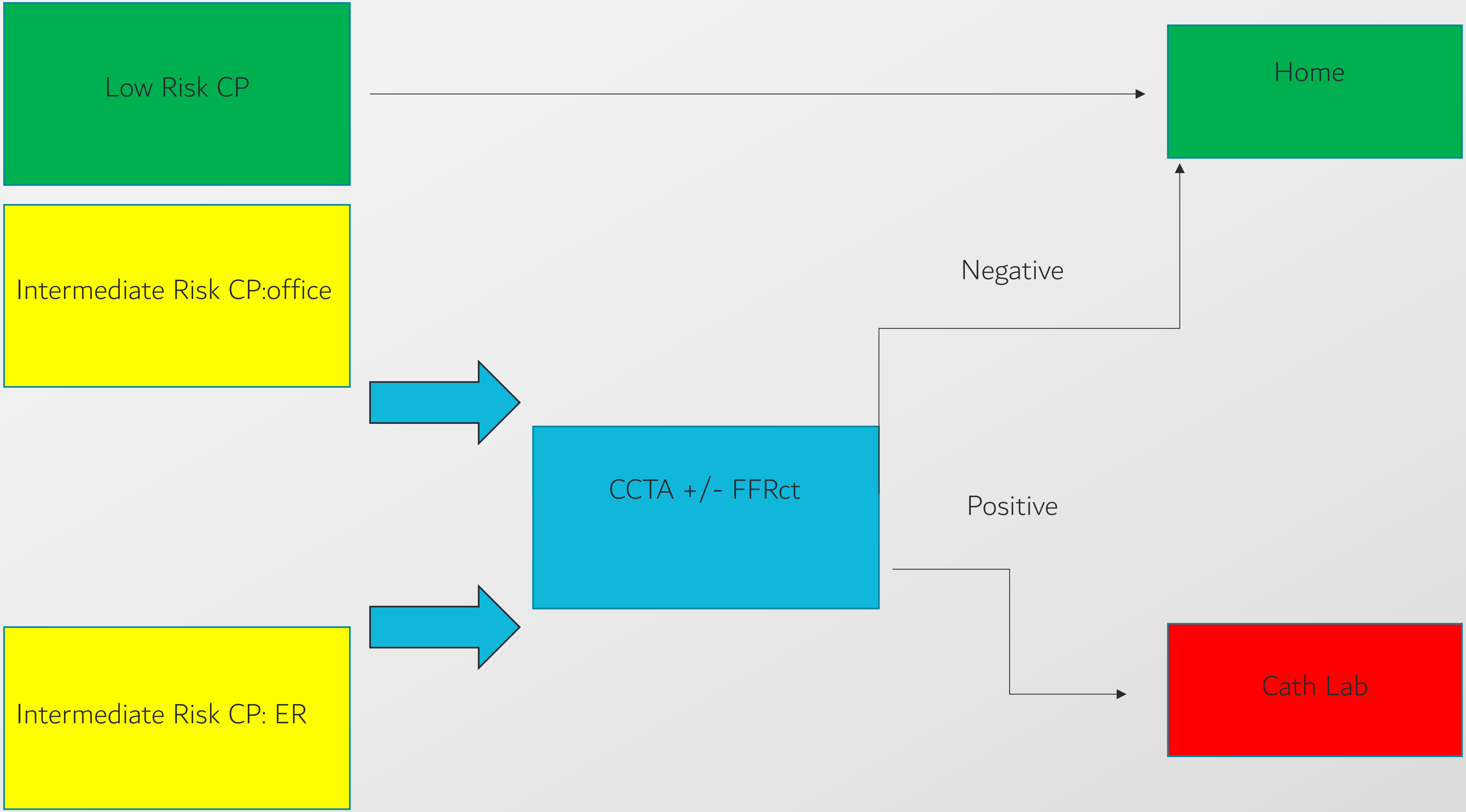
*As of 31 December 2018. Data subject to change.

Outpatient clinic pathway + Low-intermediate risk ER pathway


Low Risk CP
Intermediate Risk CP:office
Intermediate Risk CP: ER
CCTA +/- FFRct
Negative
Positive
Home
Cath Lab

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

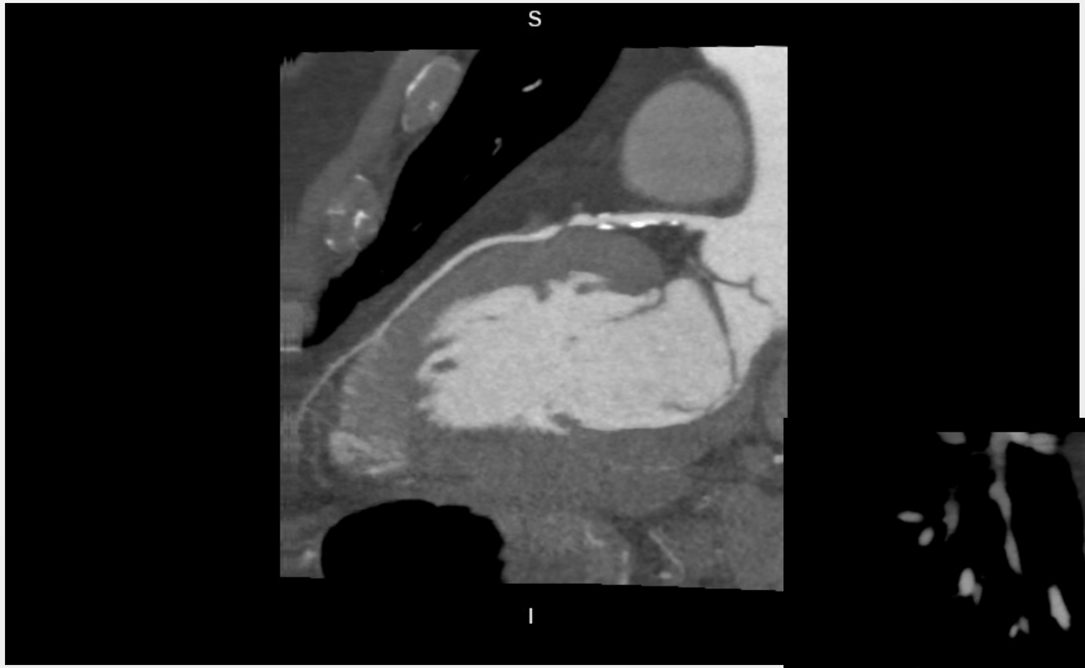
Low rate of False - studies

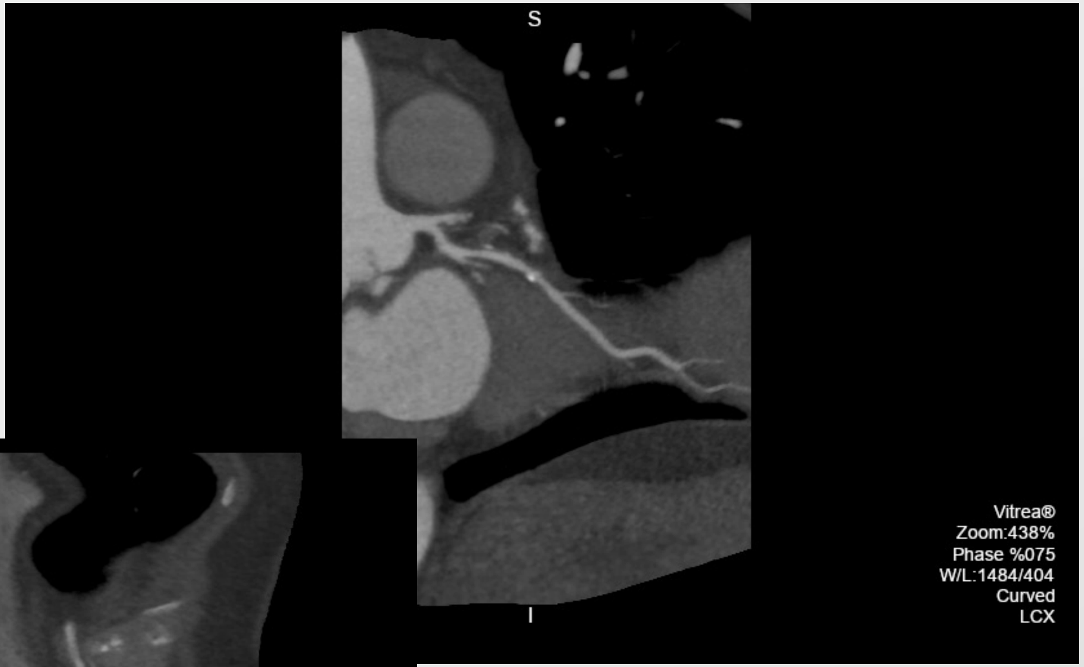
Case Example - KB - Patient History and Overview

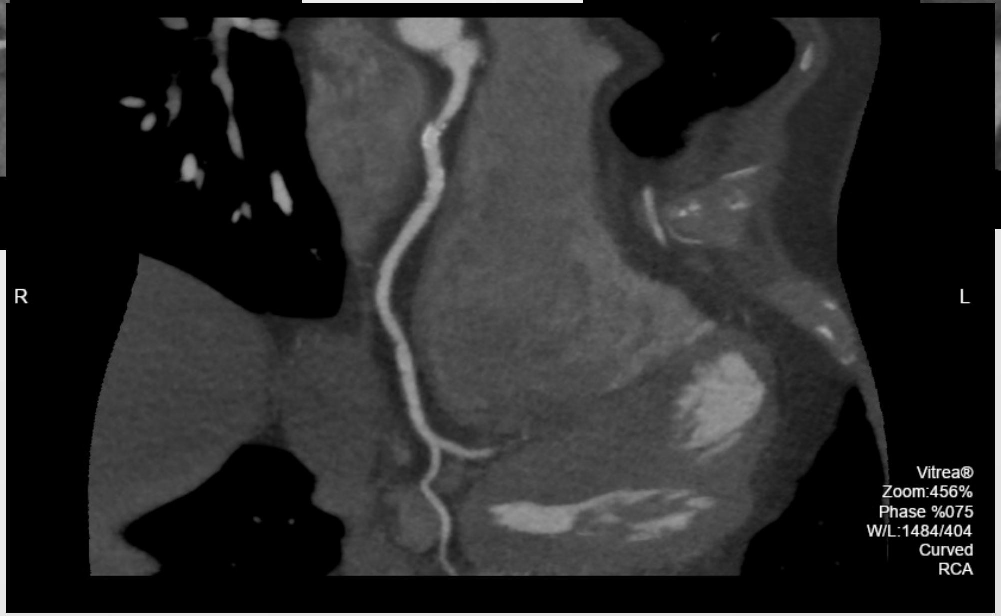
- 65 yo gentleman
- HTN, HL, +FH
- 3-4 months of exertional dyspnea
- Mild non-radiating CP lasting 30 seconds to 1 minute before resolving spontaneously
- Never has had any cardiac testing
- Calcium score: 740
  - LM- 11
  - RCA- 411
  - LAD- 216
  - LCX- 102

Case Example – KB – CT Image Review

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



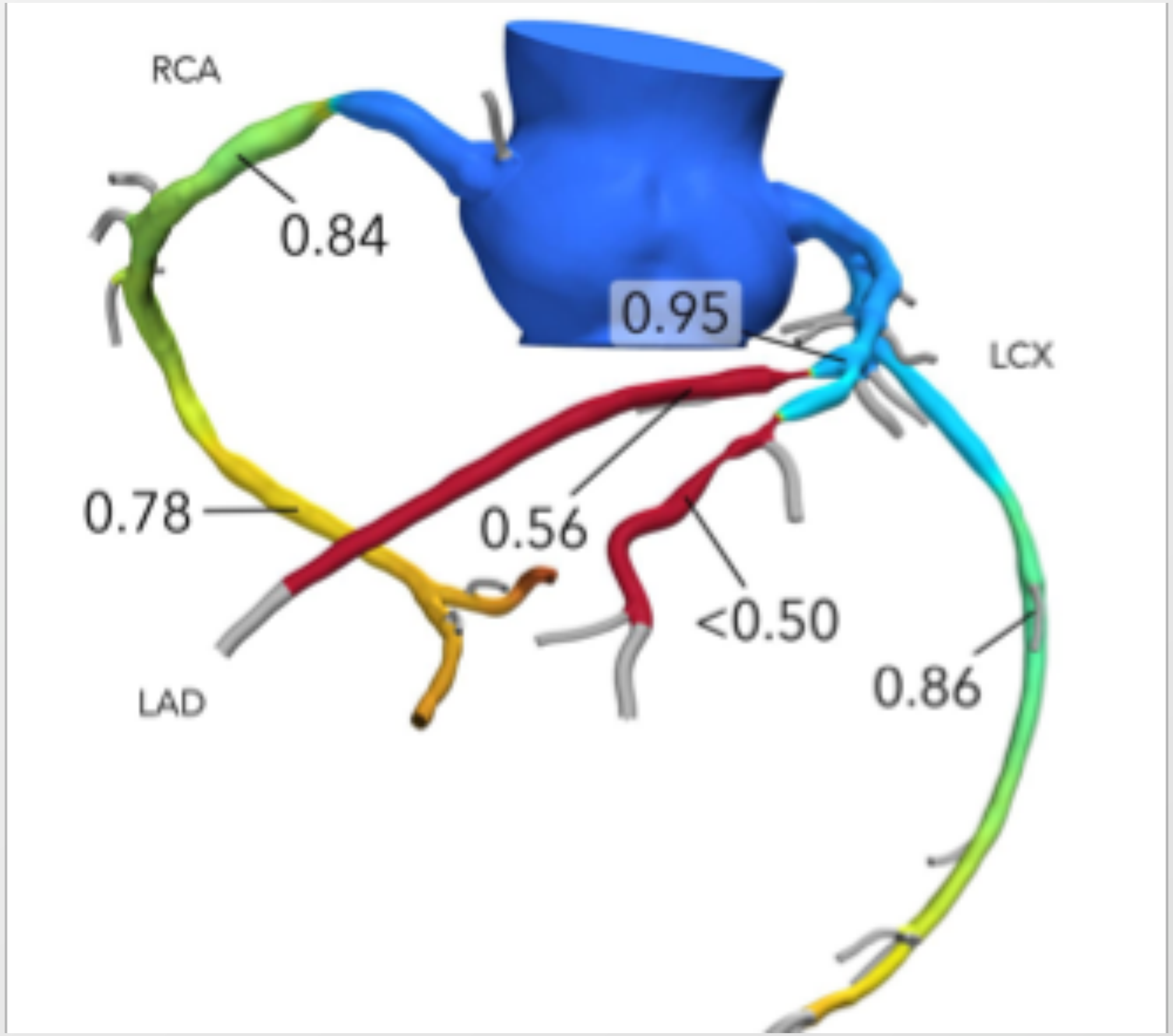




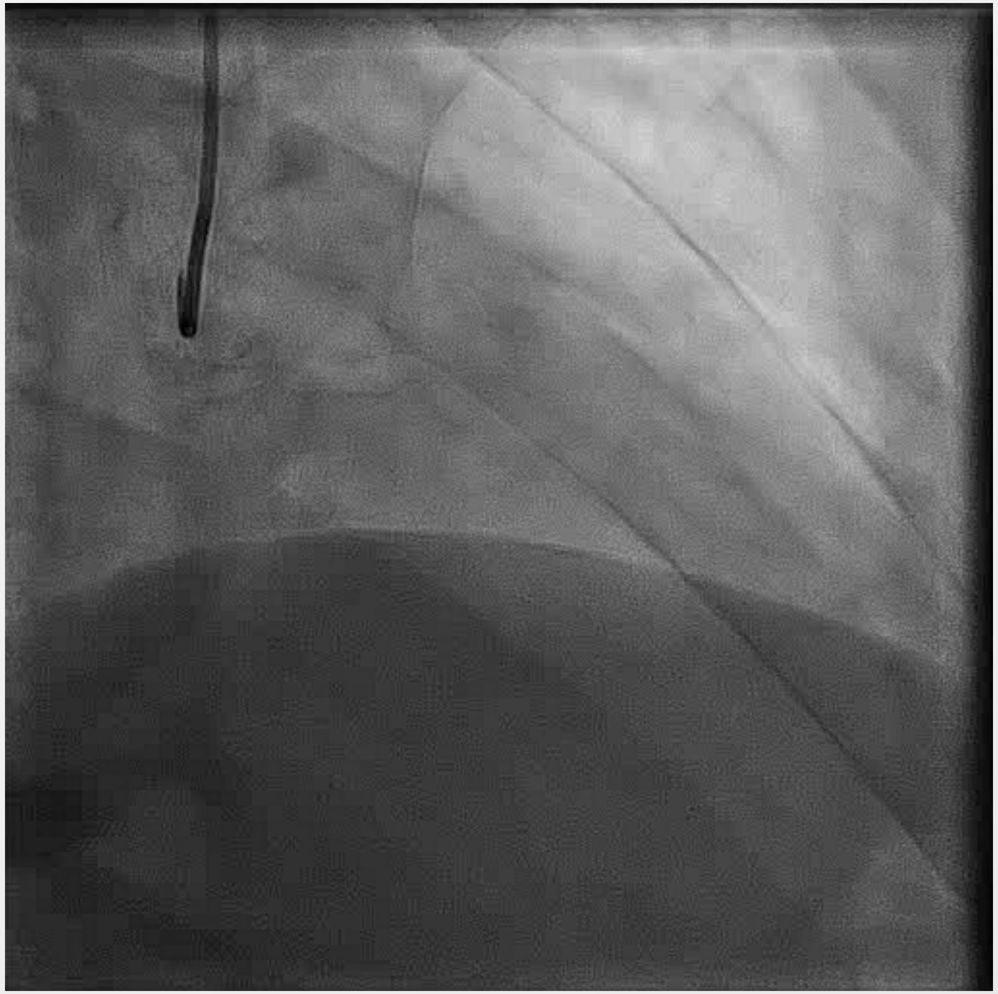
- Next Steps?

Case Example – KB – FFRCT Image Review

- FFRCT Image Review – Multivessel CAD

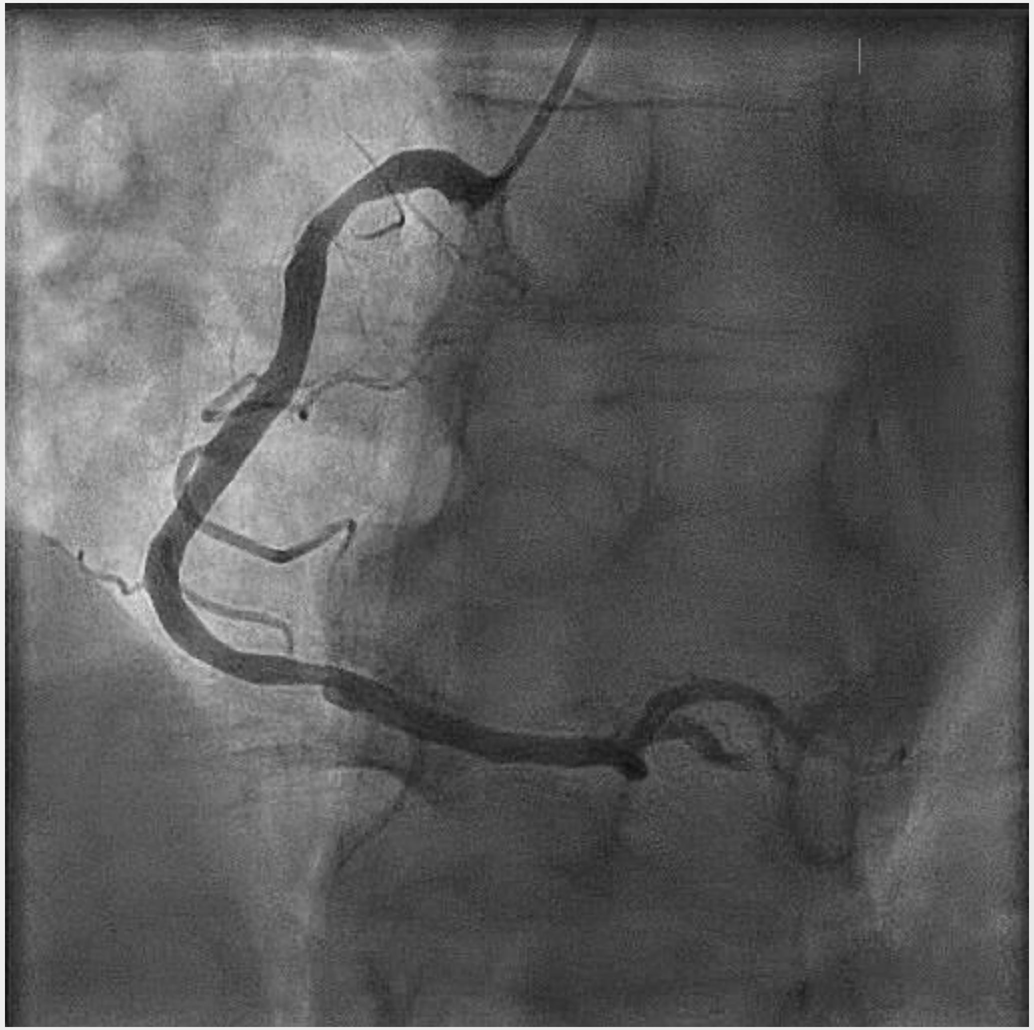


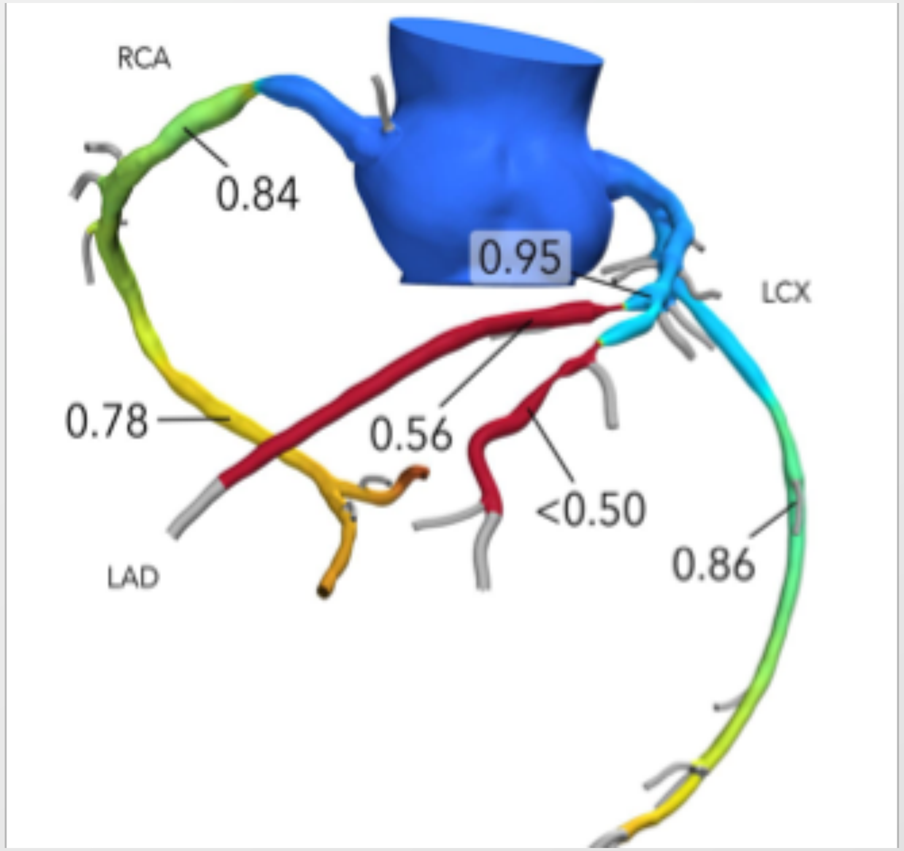
Case Example: KB – Angio/FFR



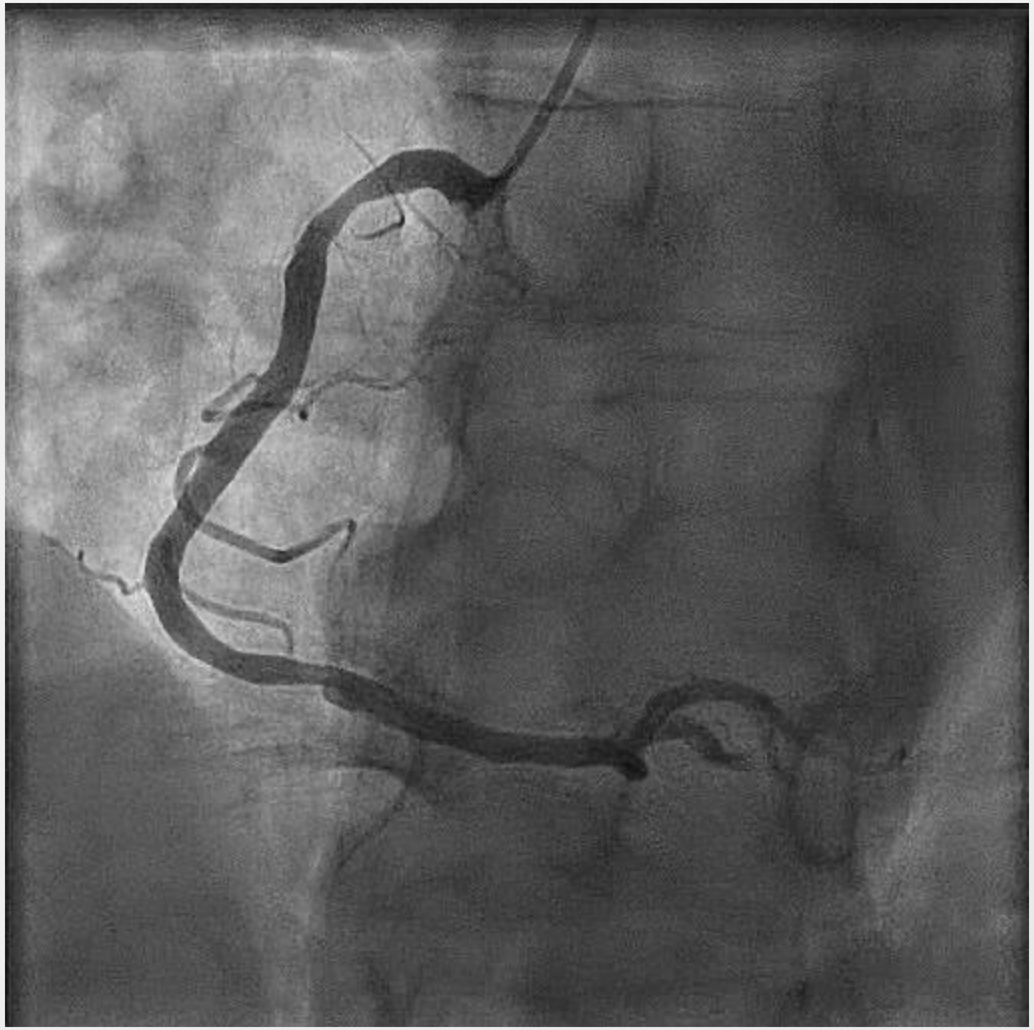
- After consultation with CV surgery and patient: Decision made to proceed with PCI

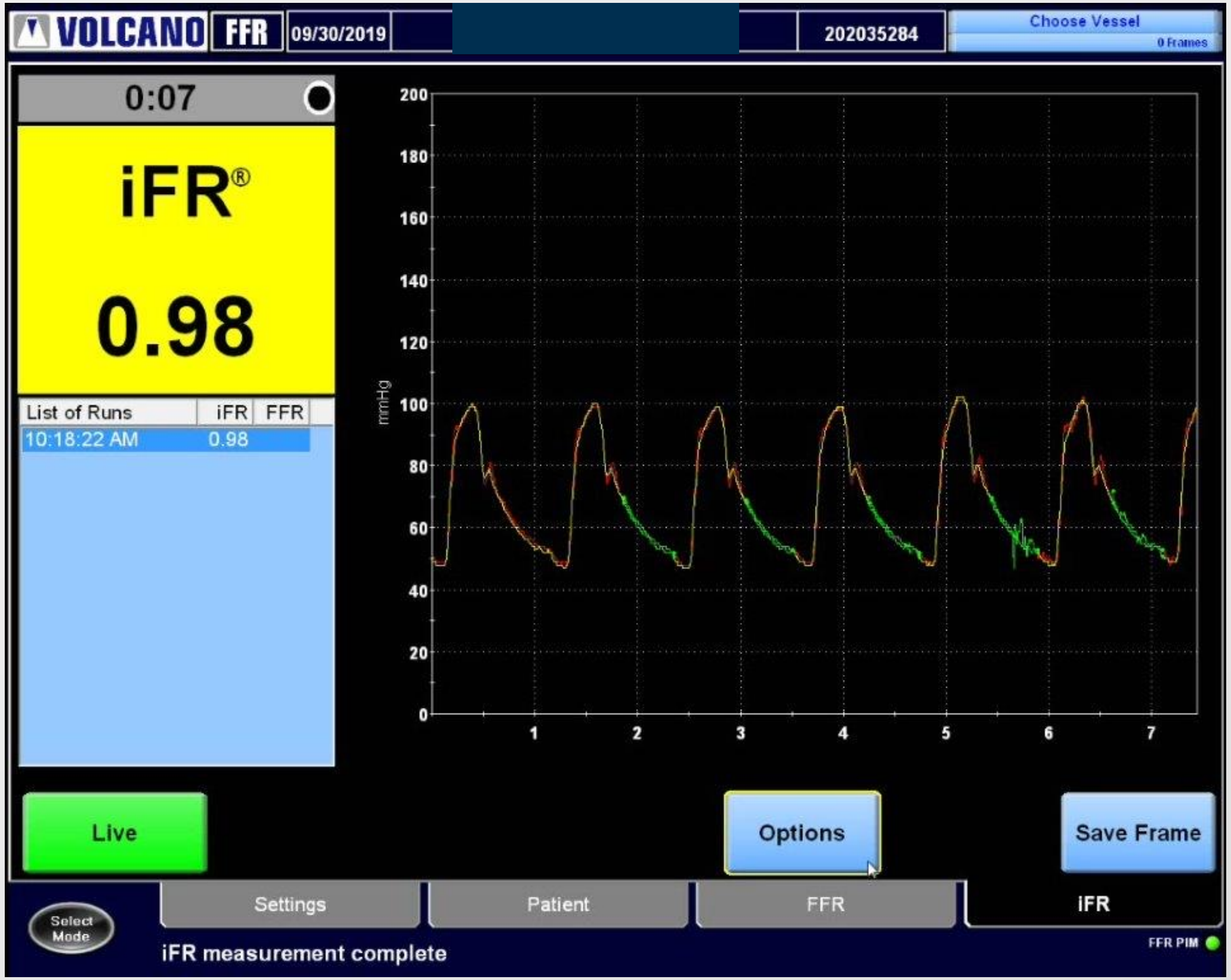
What about the RCA?: Does it affect the decision for CABG or not?



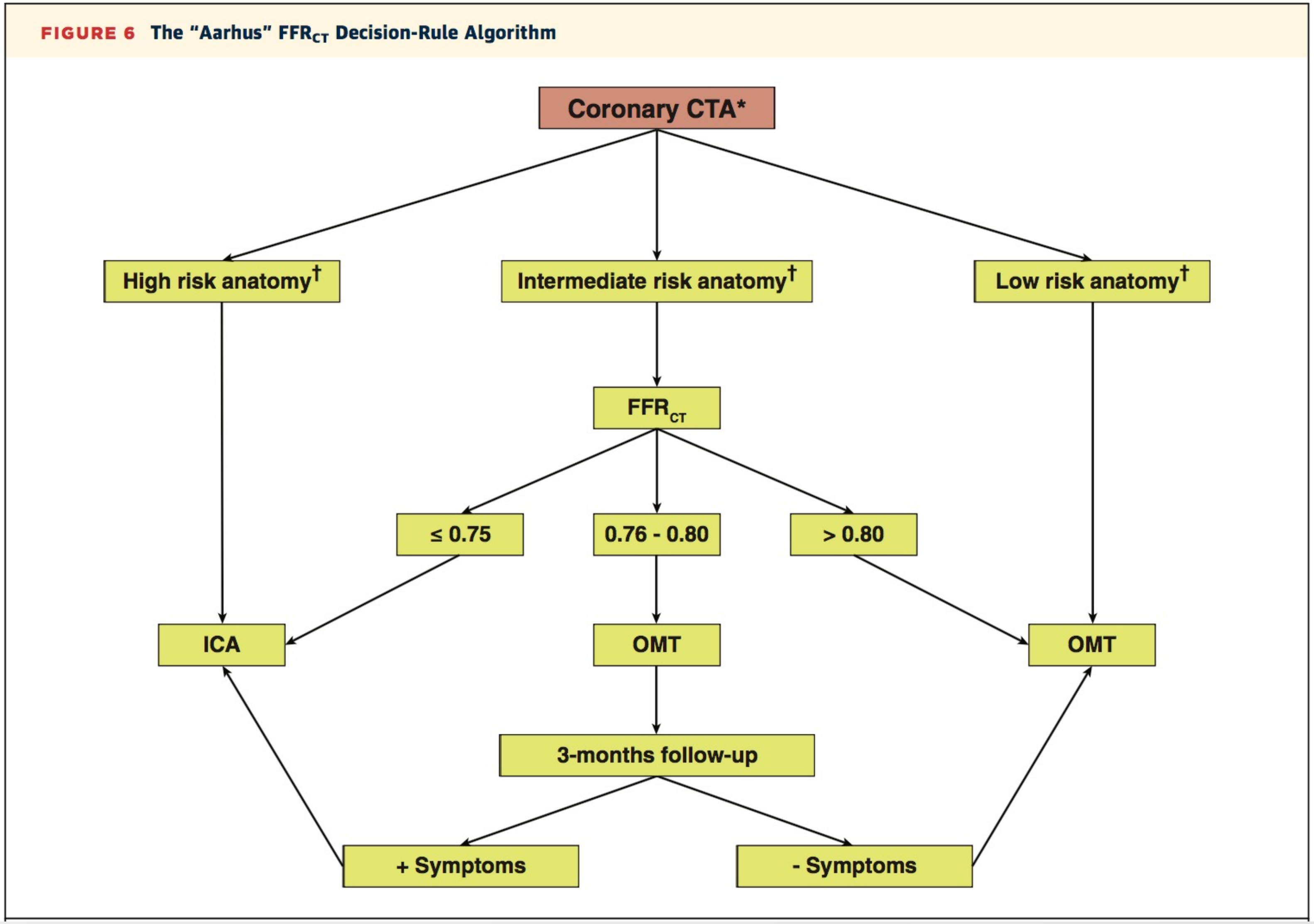


RCA: Invasive physiology vs FFRct





Consider an FFRCT grey zone



Aarhus real-world FFRCT experience:

OMT and 3-month follow-up for 0.76-0.80 FFRCT values.

"In the event of FFRCT <0.75, the probability of having ischemia was high (92%). **If FFRCT ranged between 0.76-0.80, ischemia was present in only 55% of patients."**

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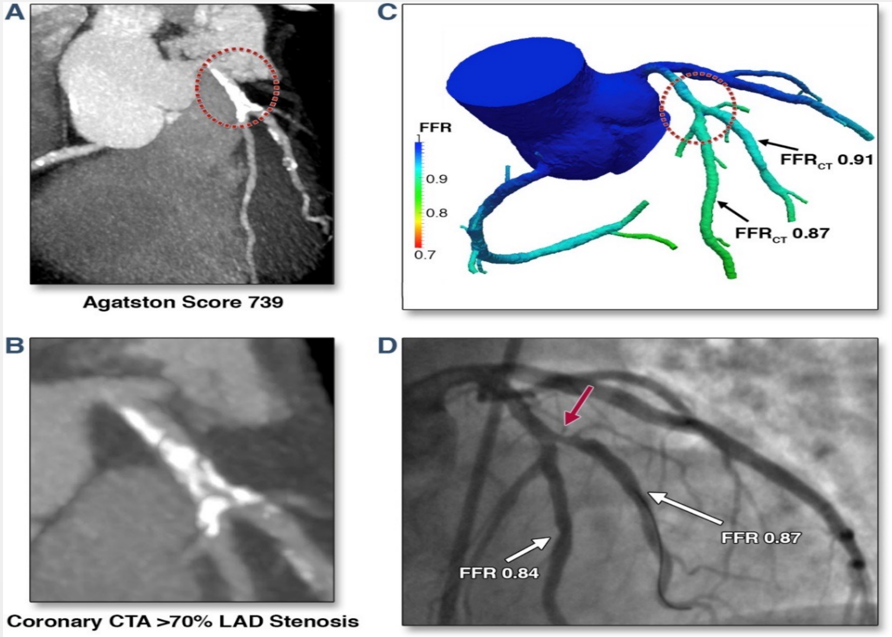
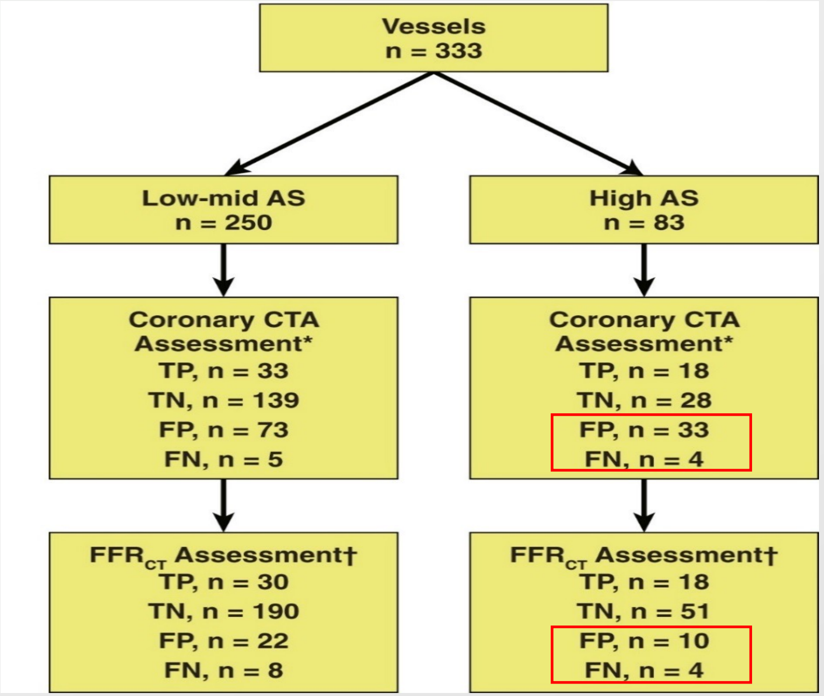
Nørgaard, et al. JACC Cardiovascular Imaging 2016.

FFR_{CT} performs well with high calcium





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

73474022 v1

Nørgaard et. al., Influence of Coronary Calcification on the Diagnostic Performance of CT Angiography Derived FFR in Coronary Artery Disease, JACC: Cardiovascular Imaging, Volume 8, Issue 9, Pages 1045-1055

Inpatient Pathway

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 Knegt, 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]

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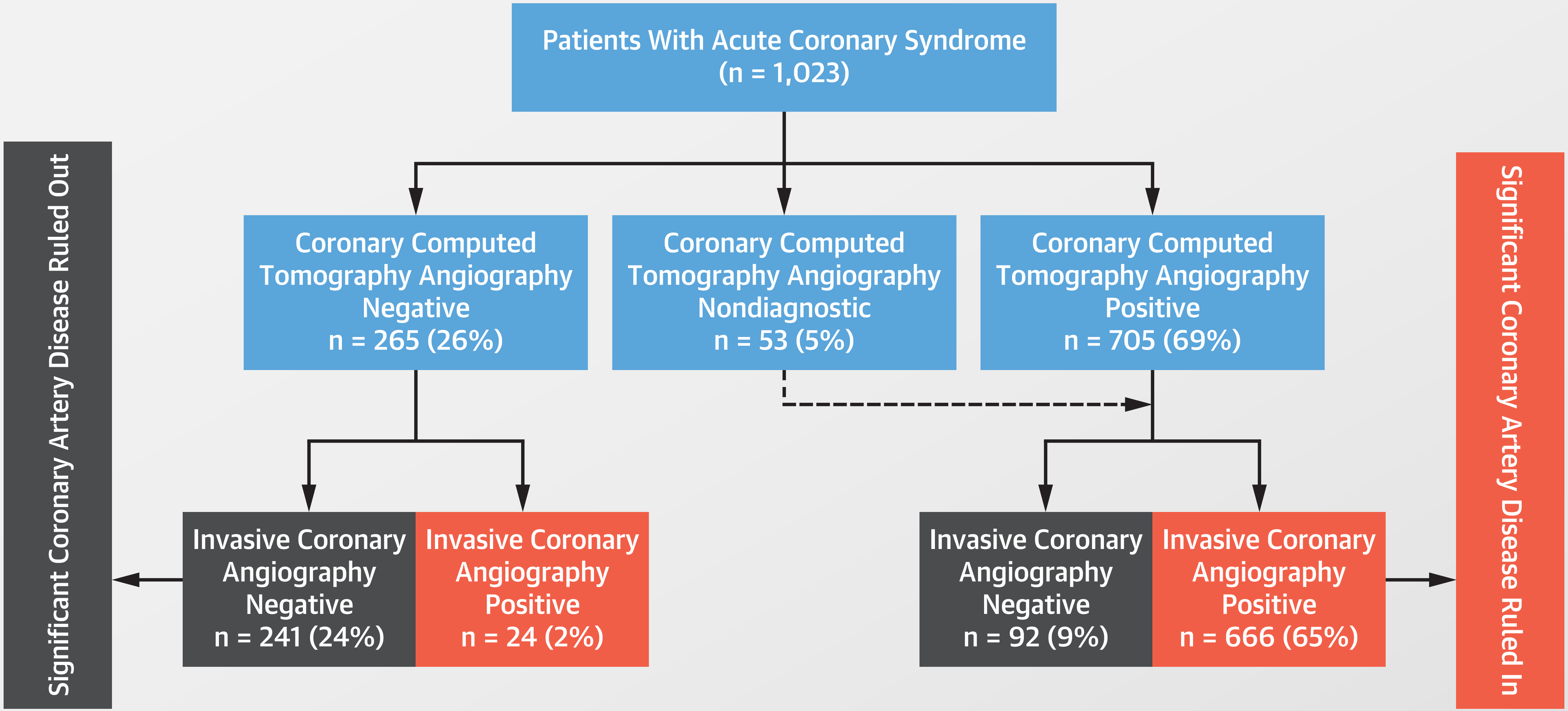
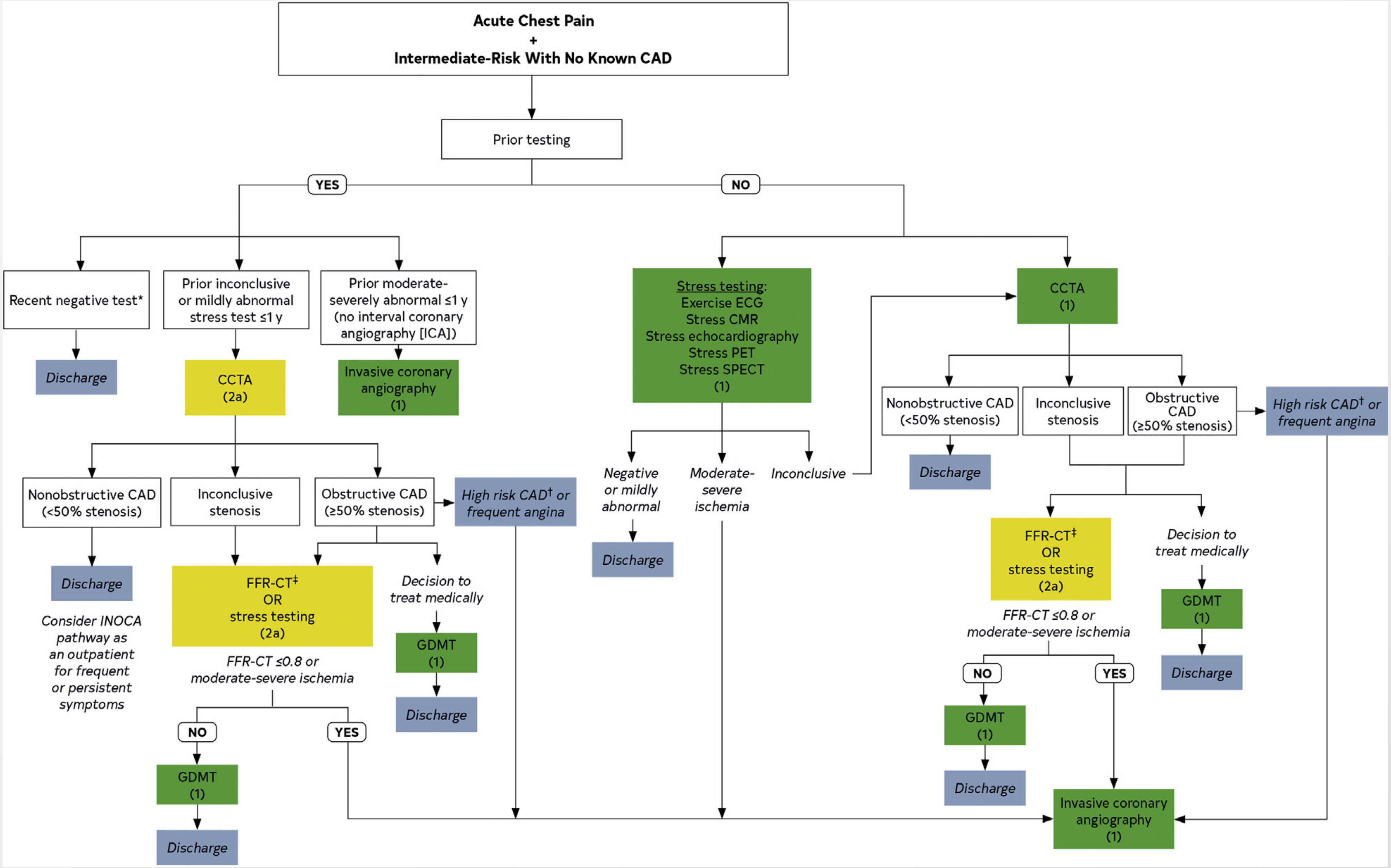


Negative Predictive Value (95% CI)	90.9% (86.8-94.1)	**Positive Predictive Value (95% CI)**	87.9% (85.3-90.9)
Sensitivity (95% CI)	96.5% (94.9-97.8)	**Specificity (95% CI)**	72.4% (67.2-77.1)

73474022 v1

Linde, J.J. et al. J Am Coll Cardiol. 2020;75(5):453-63.


Acute Chest Pain
+
Intermediate-Risk With No Known CAD
Prior testing
YES
NO
Recent negative test*
Discharge
Prior inconclusive or mildly abnormal stress test ≤1 y
CCTA (2a)
Prior moderate-severely abnormal ≤1 y (no interval coronary angiography [ICA])
Invasive coronary angiography (1)
Nonobstructive CAD (<50% stenosis)
Discharge
Consider INOCA pathway as an outpatient for frequent or persistent symptoms
Inconclusive stenosis
Obstructive CAD (≥50% stenosis)
High risk CAD† or frequent angina
FFR-CT‡ OR stress testing (2a)
FFR-CT ≤0.8 or moderate-severe ischemia
NO
GDMT (1)
Discharge
YES
Decision to treat medically
GDMT (1)
Discharge
Stress testing: Exercise ECG Stress CMR Stress echocardiography Stress PET Stress SPECT (1)
Negative or mildly abnormal
Discharge
Moderate-severe ischemia
Inconclusive
CCTA (1)
Nonobstructive CAD (<50% stenosis)
Discharge
Inconclusive stenosis
Obstructive CAD (≥50% stenosis)
High risk CAD† or frequent angina
FFR-CT‡ OR stress testing (2a)
FFR-CT ≤0.8 or moderate-severe ischemia
NO
GDMT (1)
Discharge
YES
Decision to treat medically
GDMT (1)
Discharge
Invasive coronary angiography (1)

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Catheterization Pathway: Inpatient/Outpatient/OBL/ASC

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 ρ=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 ≤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

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.

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Circulation

ORIGINAL RESEARCH ARTICLE

Accuracy of Fractional Flow Reserve Derived From Coronary Angiography

Editorial, see p 485

William F. Fearon, MD
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Ran Kornowski, MD
Gabriel Greenberg, MD
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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

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≤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%.

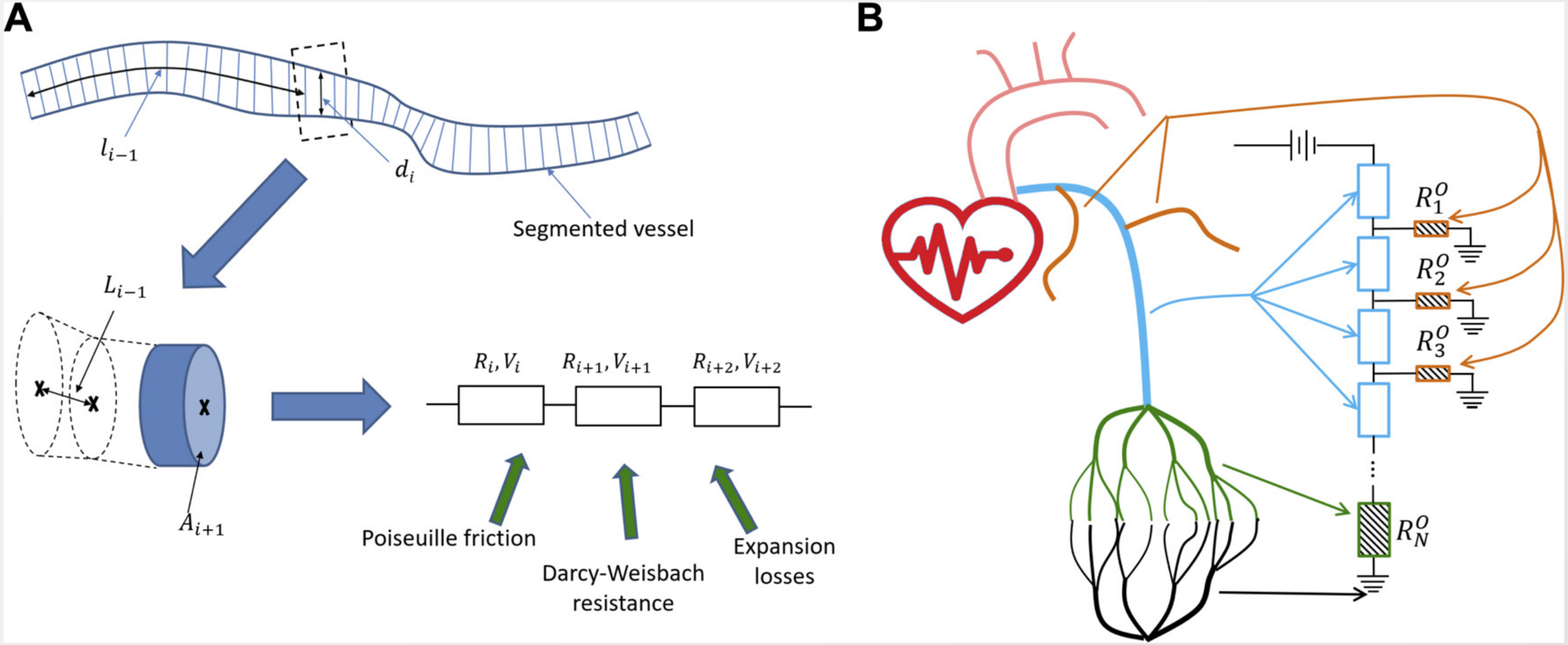
CONCLUSIONS: FFR_{angio} measured from the coronary angiogram alone has a high sensitivity, specificity, and accuracy compared with pressure wire–derived FFR. FFR_{angio} has the promise to substantially increase physiological coronary lesion assessment in the catheterization laboratory, thereby potentially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

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

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

Sources of Funding, see page 483

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



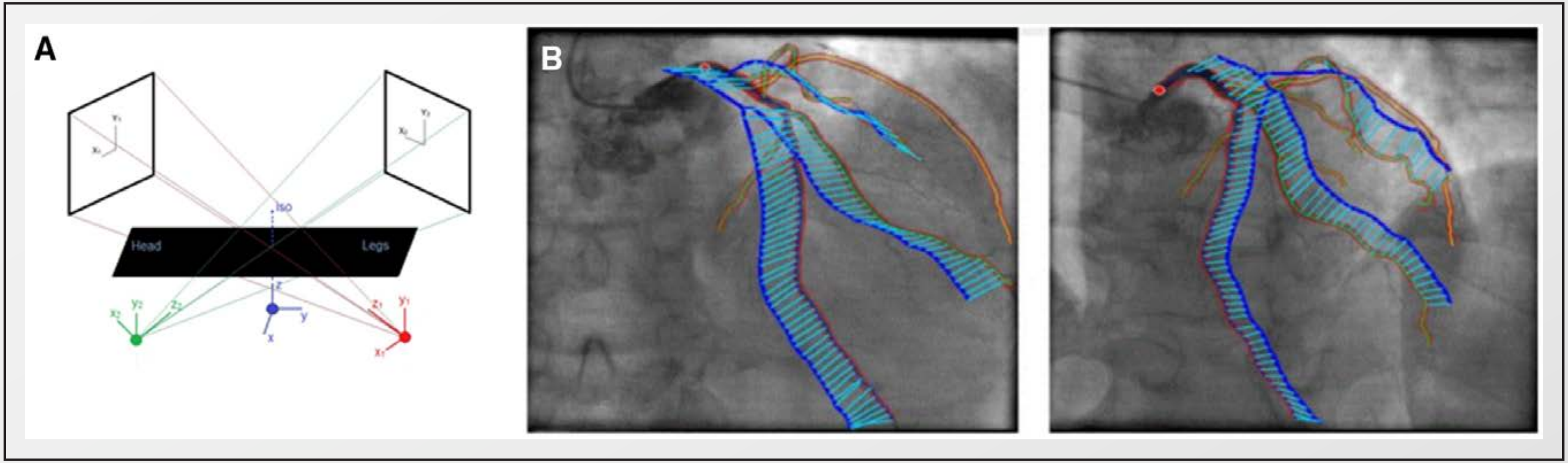
$$\Delta P = \frac{8\eta LQ}{\pi r^4}$$

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

73474022 v1

From Ono et al *Am Heart J.* 2021

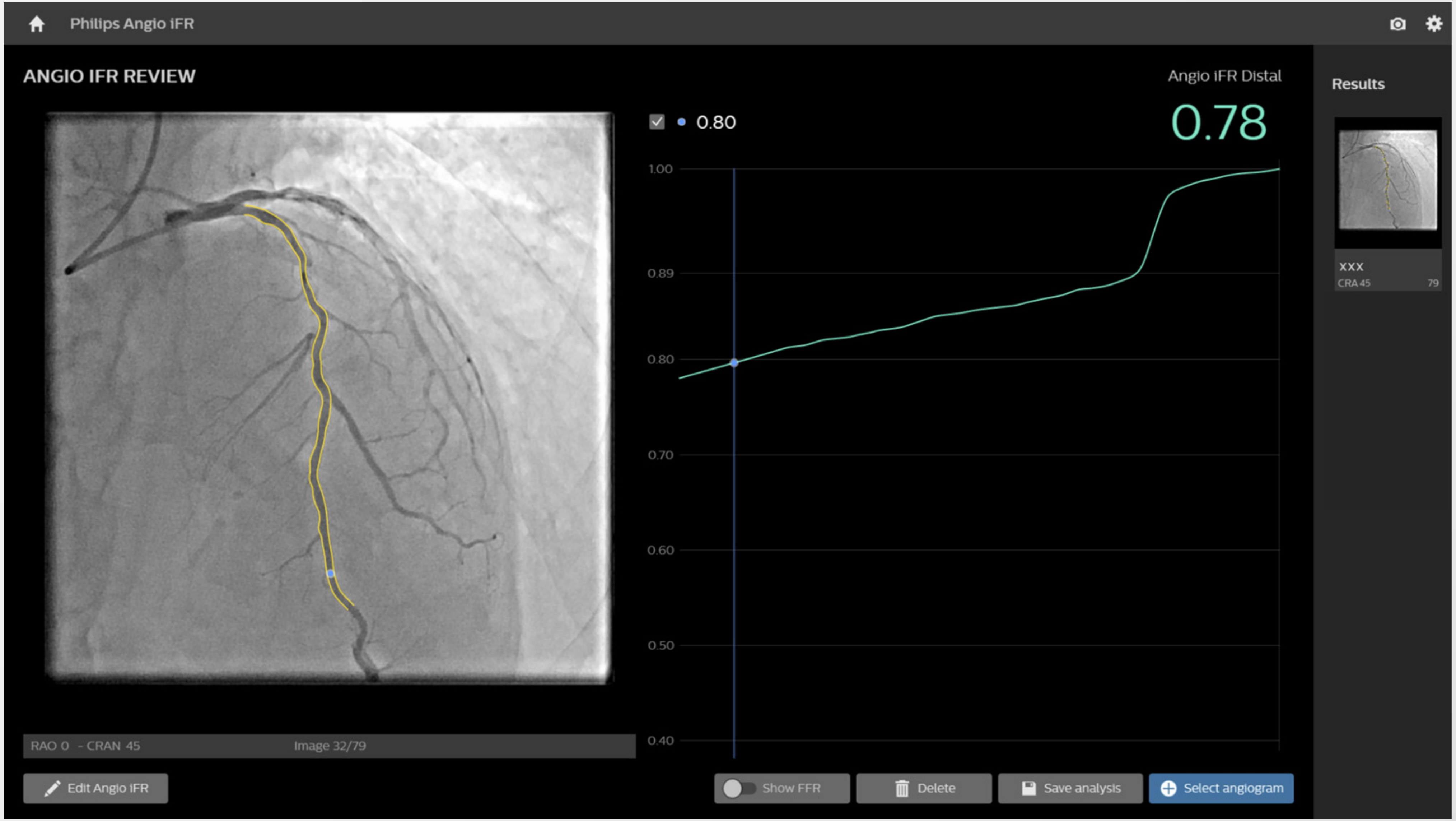
3D Reconstruction



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.

73474022 v1

From Pellicano et al. *Circ Cardiovasc Interv*. 2017



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

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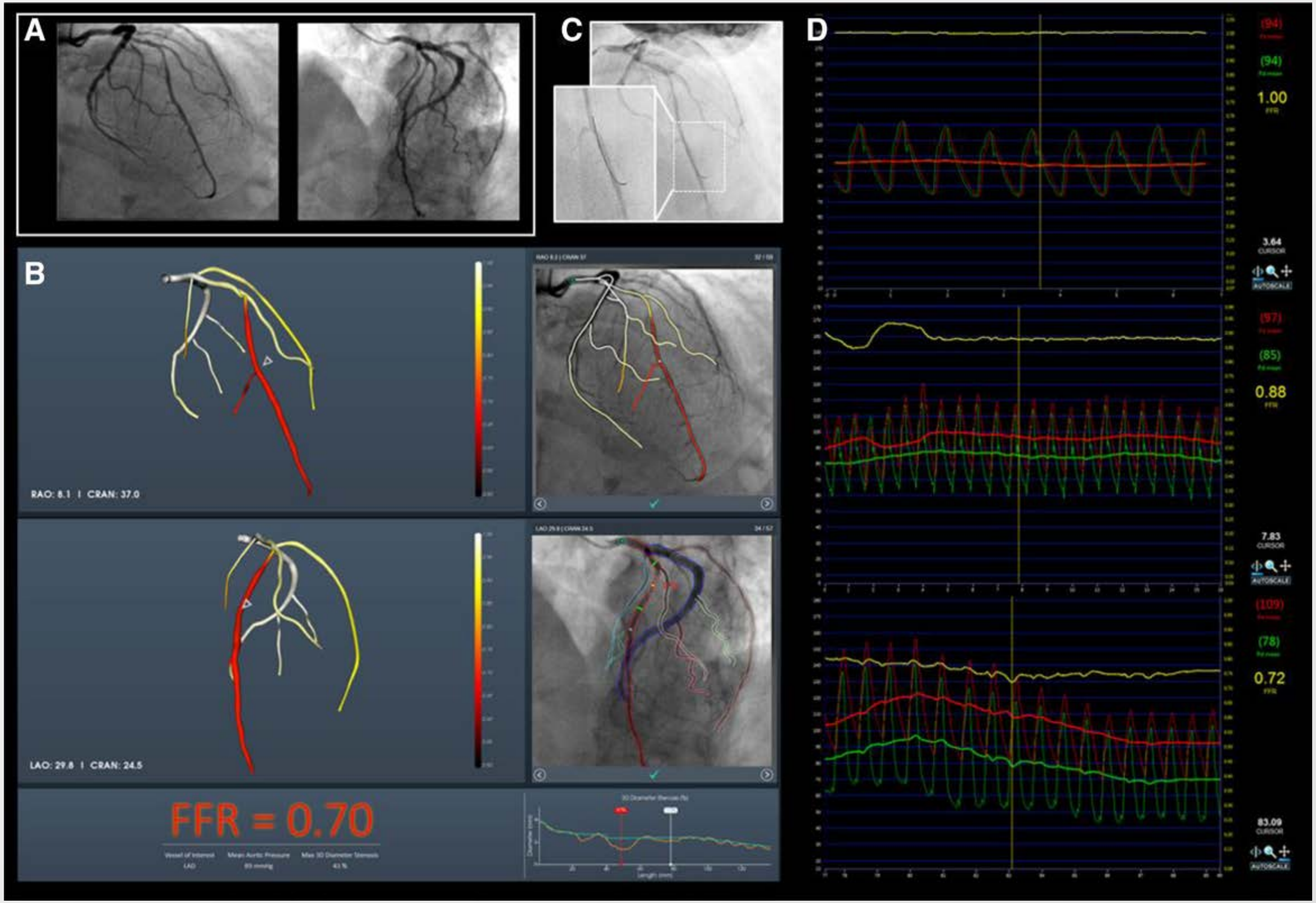
From Ono et al *Am Heart J.* 2021

Example

FFRangio



Equalization

Resting FFR

Hyperemia

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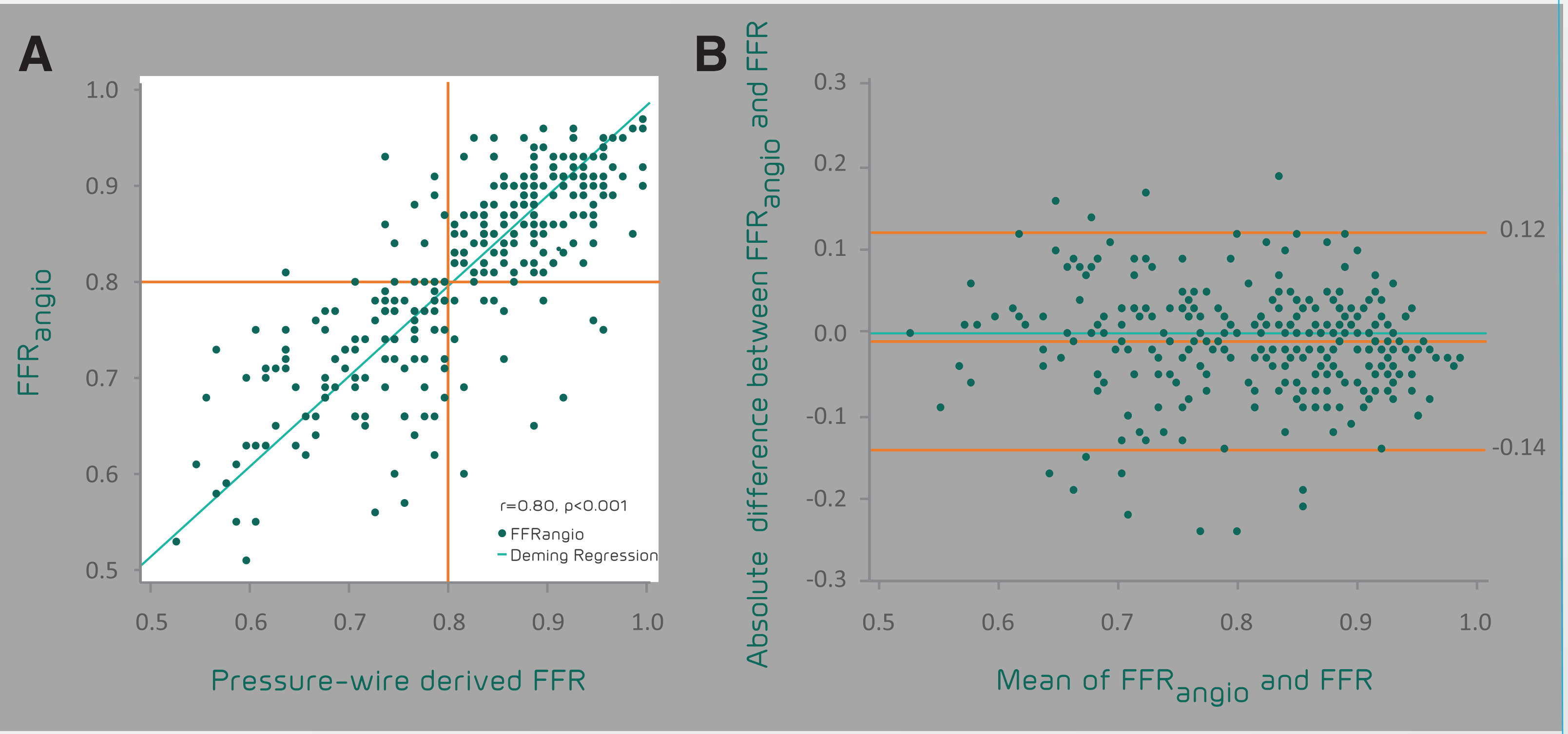
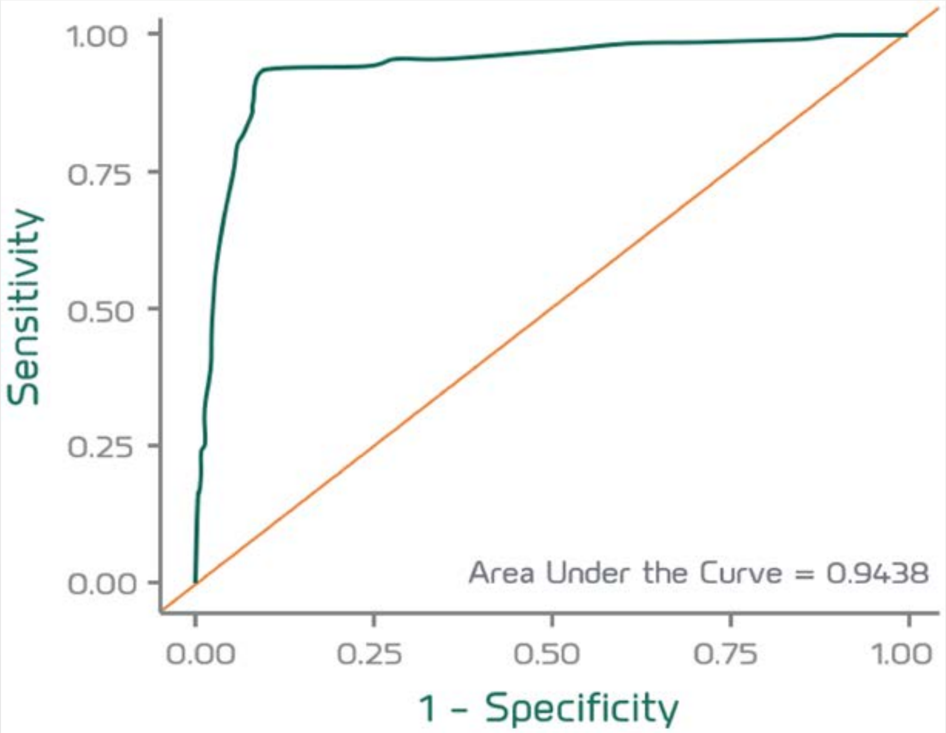
Correlation between FFR and FFRangio

ROC 94%

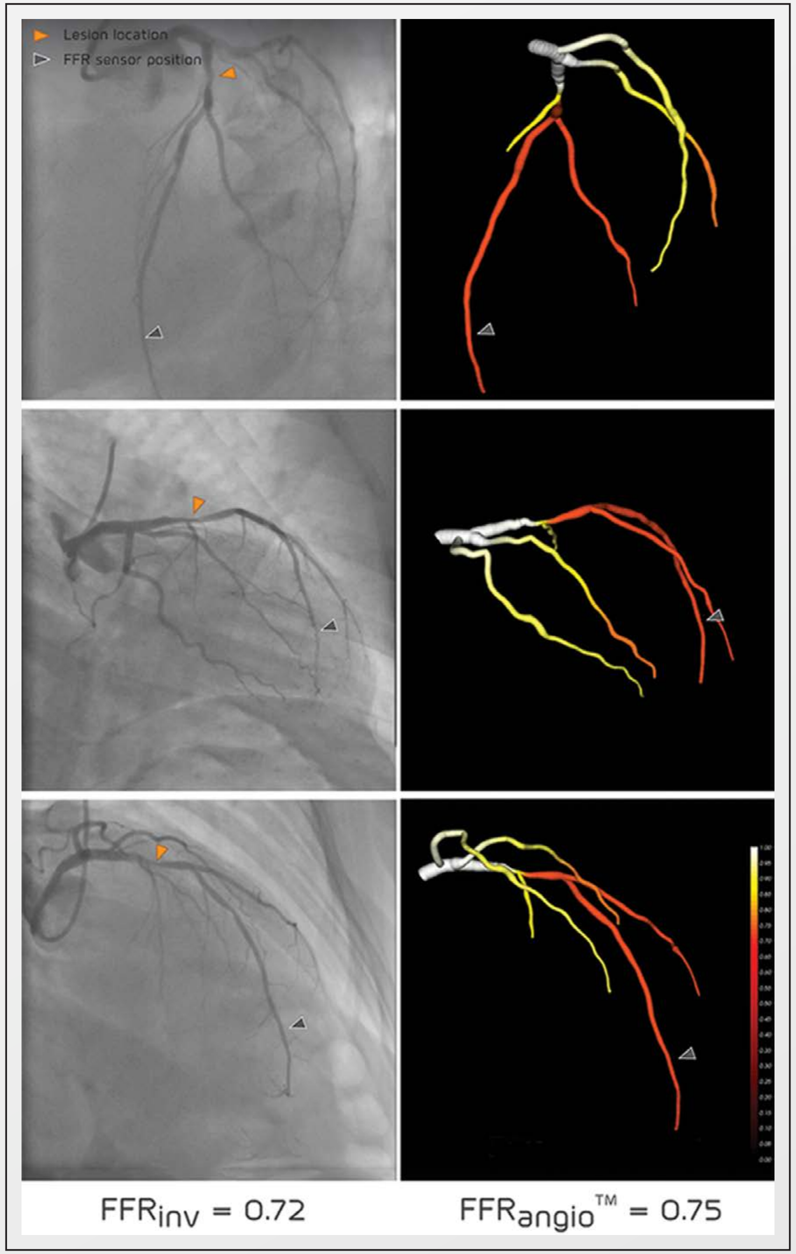


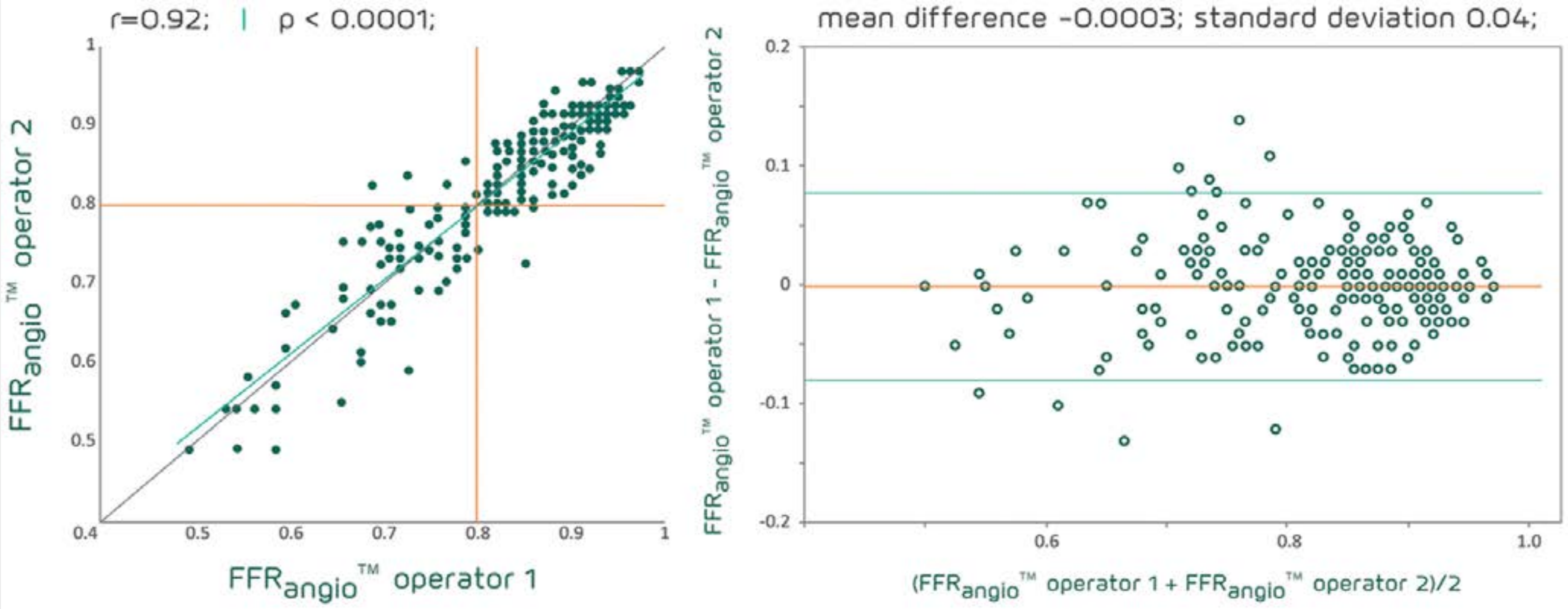


73474022 v1

From Fearon et al. *Circulation.* 2019

Case Example and Correlation between FFR and FFRangio





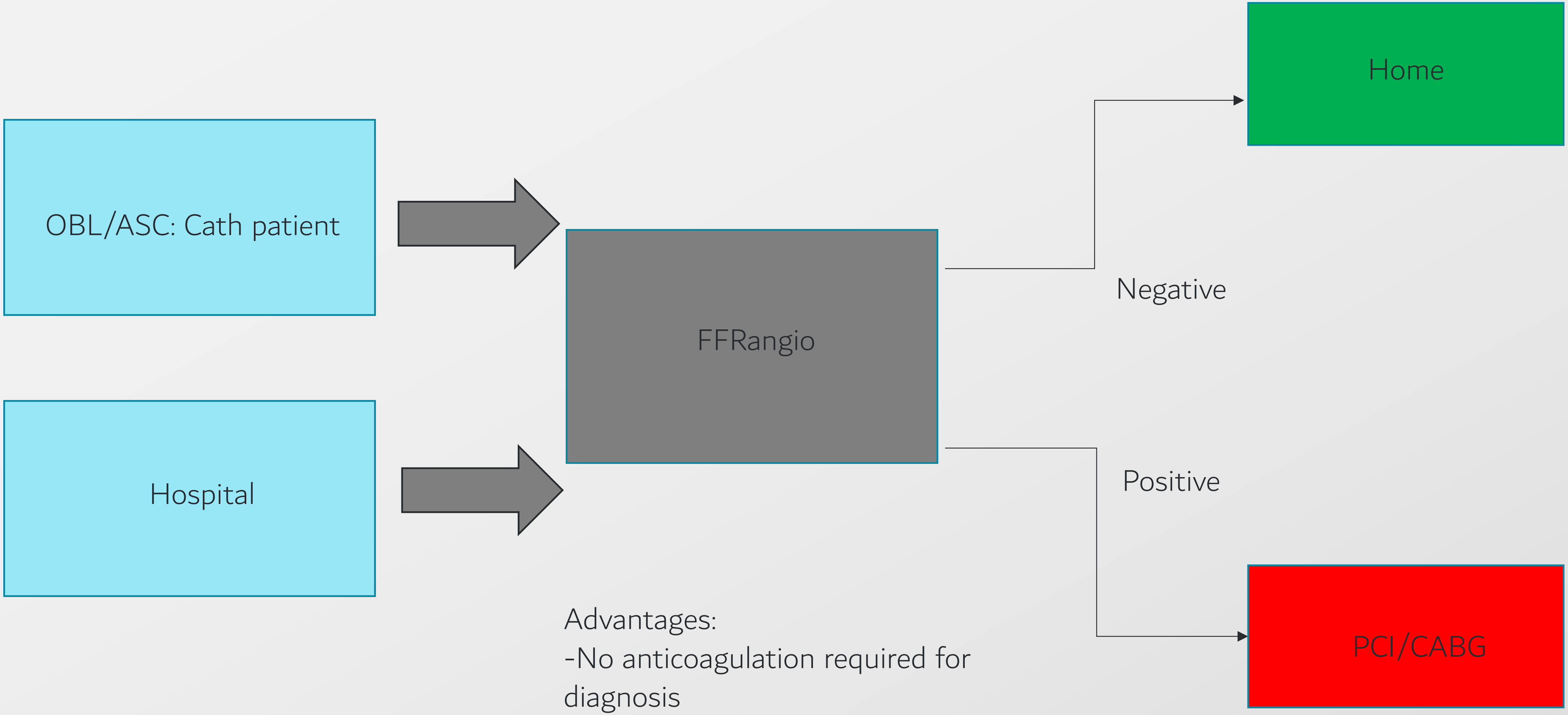
73474022 v1

From Pellicano et al. *Circ Cardiovasc Interv.* 2017

Currently available angio-based physiology systems

	Angio-iFR	μQFR	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	Incorporated	Incorporated	Not incorporated	Incorporated	Not incorporated	Not incorporated
Studies	ReVEAL iFR	Tu S, et al.	FAVOR pilot FAVOR II China FAVOR II EJ WiFi II FAVOR III	FAST-FFR	FAST	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±22 seconds	4.36 ± 2.55 min	*2.7 min	NA	4.54±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.



Advantages:
-No anticoagulation required for diagnosis
-No wire needed for diagnosis
-No hyperemic agents

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

Thank you!