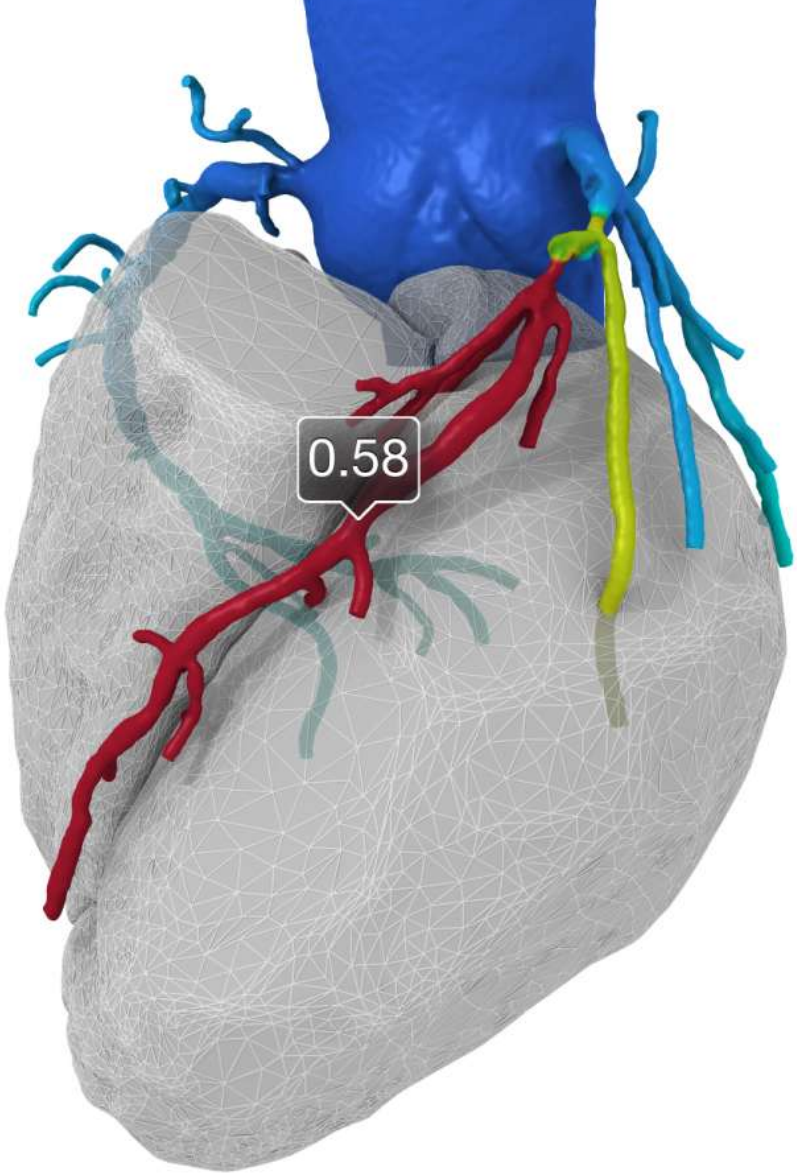
HeartFlow™

FFR_{CT} – Update on Algorithms, Validation Studies and Planned Clinical Trials



Charles A. Taylor, Ph.D.

Founder and Chief Technology Officer
HeartFlow, Inc.

Consulting Professor of Bioengineering
Stanford University

April 23, 2014

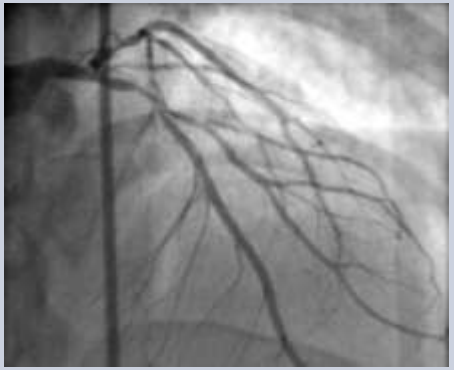
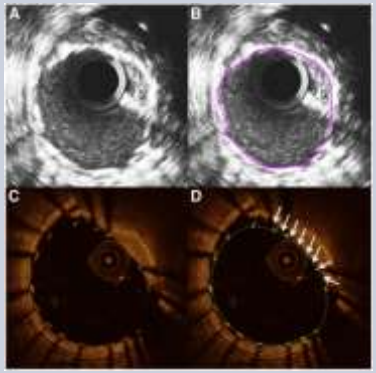
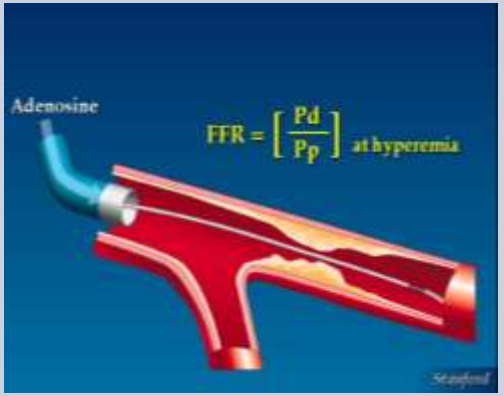
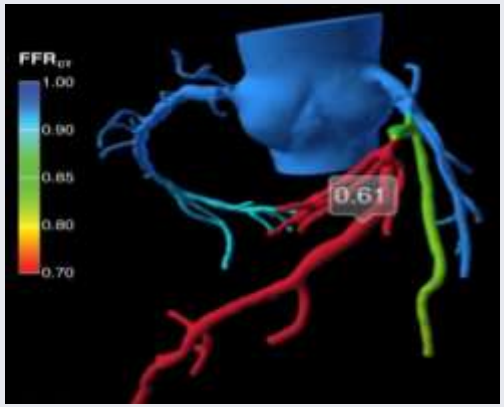
Potential conflicts of interest

Charles A. Taylor, Ph.D.

I have the following potential conflicts of interest to report:

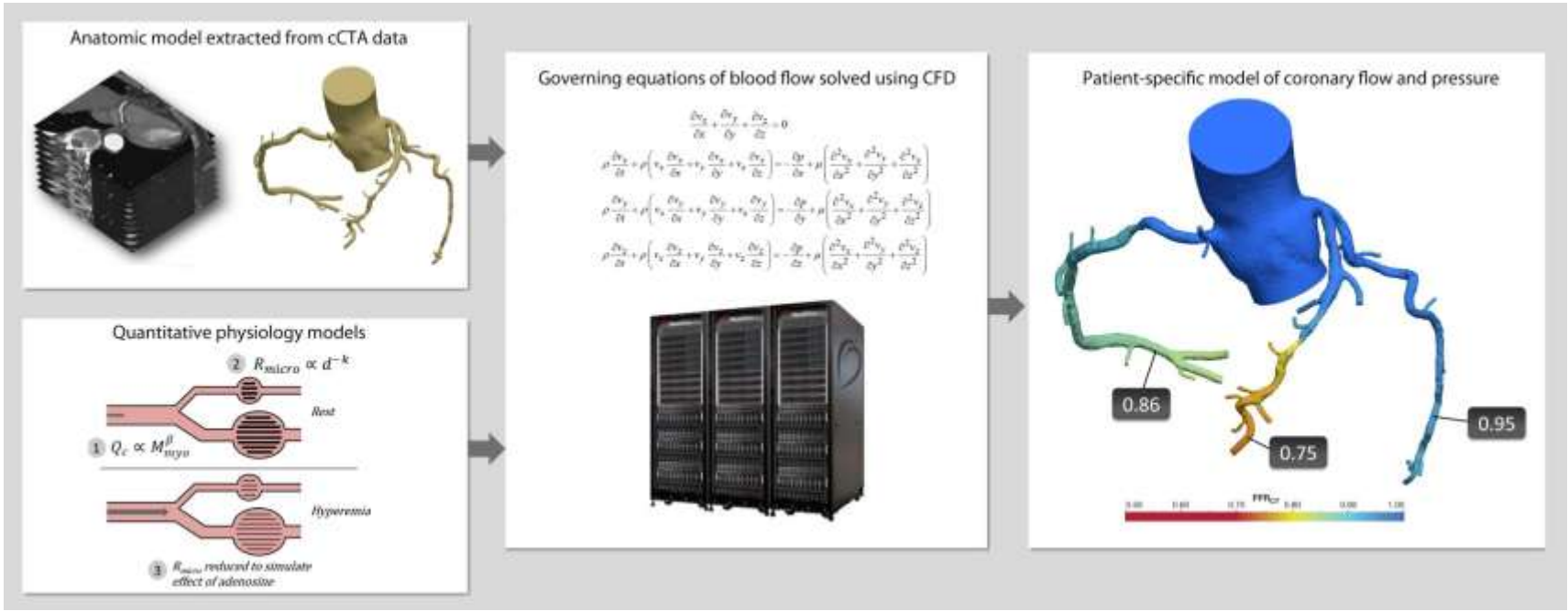
- Employment in industry
- Stockholder of a healthcare company

Diagnosing anatomic and functionally-significant CAD

	ANATOMY ***Identify focal obstructive CAD***	***FUNCTION*** ***Identify lesion-specific ischemia that may benefit from PCI***
Invasive	 	
Non-invasive		

FFR_{CT} - Noninvasive Functional Assessment of CAD

Unique patient-specific modeling technology based on over 20 years of research



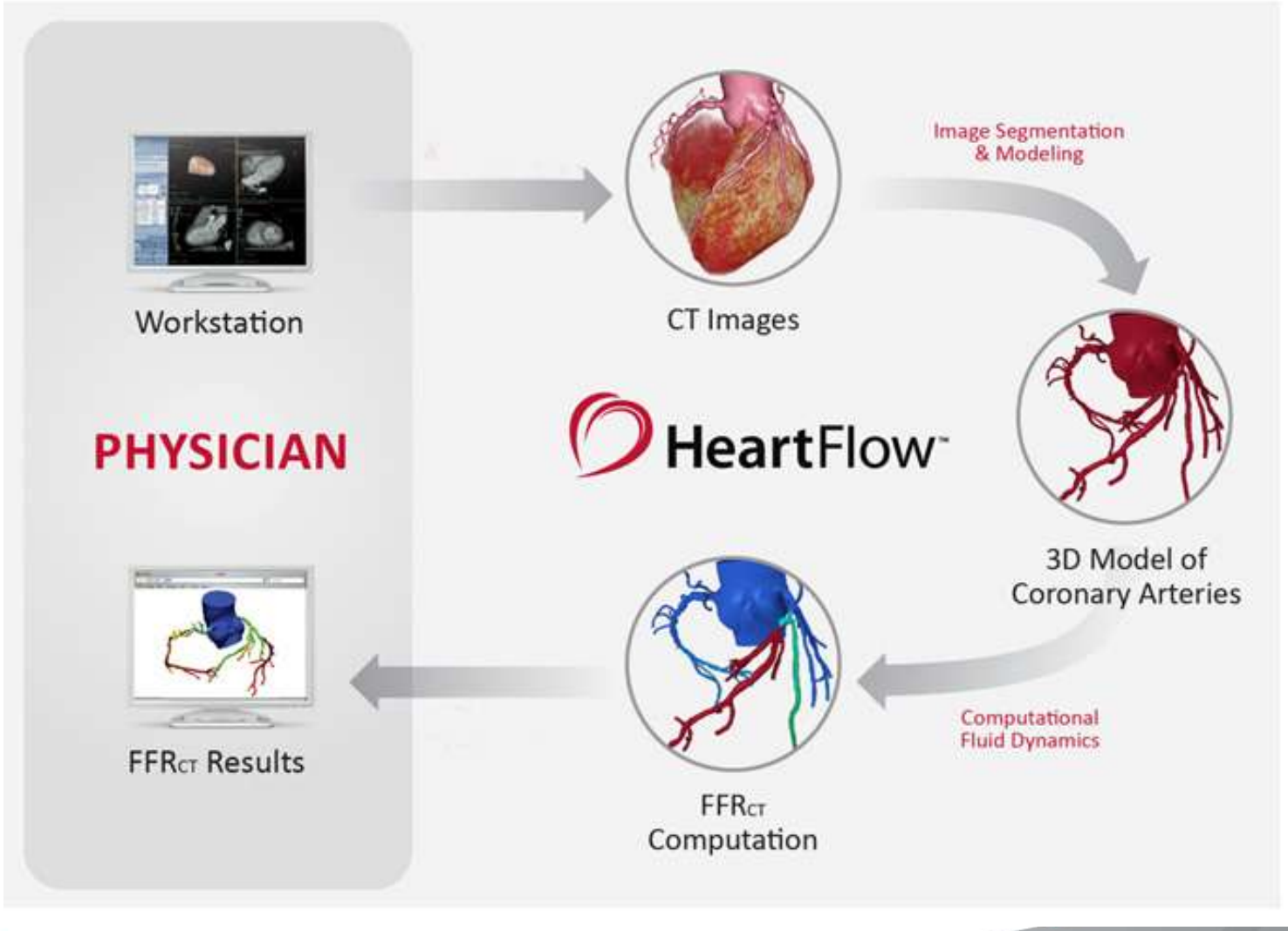
Clinically validated in over 600 patients

DISCOVER-FLOW - 2011

DeFACTO - 2012

NXT – 2013/2014

HeartFlow provides FFR_{CT} as a service to physicians to aid in assessing significance of CAD



HeartFlow™

Overview of the FFR_{CT} Process

Hospital / Physician Workflow

Sample of Clinical Report Provided to Physician

HeartFlow

FFR$_{CT}$ Results

Lincolnopolis, Abraham

Patient ID KEPO-3820KEKO-38
Birth Date 07-24-1961

CT Study Date 10-27-2013
Referring Physician Hawkeye Pierce
Provider Anytown Cardiology

Summary:

This patient has an FFR$_{CT}$ ≤ 0.80 in the LAD system.

CORONARY ARTERIES & SYSTEMS		FFR$_{CT}$
Left Main Artery	LM	0.98
Left Anterior Descending System	LAD	0.56
Left Circumflex System	LCx	0.93
Right Coronary System	RCA	0.94

FFR$_{CT}$ 0.00 0.20 0.40 0.60 0.80 1.00

MAY BE FUNCTIONALLY SIGNIFICANT (1-3)

0.56

LAO 23° / Cran 29°

0.56

0° / Caud 90°

Legend:

< 1.5 mm lumen diameter

FFR$_{CT}$ 0.00 0.60 0.70 0.80 0.90 1.00

MAY BE SIGNIFICANT | MAY NOT BE SIGNIFICANT

Created with FFR$_{CT}$ v1.6.0.123 Product on 0-29-2013 8:43 PM UTC. HFID 073b20ab-f523-497d-b34e-1910435f1a0a4

1400 Seaport Blvd • Building B • Redwood City, CA 94063 USA • tel +1.650.241.1221 • fax +1.650.368.2594 • www.heartflow.com

page 1 of 2

FFRCT is not commercially available in the US

HeartFlow Clinical Trial Data

- **DISCOVER-FLOW**
  - P.I. Bon Kwon Koo, M.D., Ph.D.
  - Completed 2011
  - N=104 patients

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,* Andrejs Erglis, MD, PhD,† Joon-Hyung Doh, MD, PhD,‡ David V. Daniels, MD,§ Sanda Jegere, MD,‖ Hyo-Soo Kim, MD, PhD,* Allison Dunning, MD,¶ Tony DeFrance, MD,# Alexandra Lansky, MD,** Jonathan Leipsic, BSc, MD,†† James K. Min, MD‡‡

Seoul and Goyang, South Korea; Riga, Latvia; Palo Alto, San Francisco, and Los Angeles, California; New York, New York; New Haven, Connecticut; and Vancouver, British Columbia, Canada

- **DeFACTO**
  - P.I. James Min, M.D.
  - Completed 2012
  - N=252 patients

ONLINE FIRST

Diagnostic Accuracy of Fractional Flow Reserve From Anatomic CT Angiography

JAMA. 2012;308(12):doi:10.1001/2012.jama.11274

- **NXT**
  - P.I. Bjarne Norgaard, M.D., Ph.D.
  - Completed 2013
  - N=254 patients
  - 10 Worldwide Sites
    - EU
    - Japan
    - Korea
    - Australia

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)

Bjarne L. Nørgaard, MD, PhD,* Jonathon Leipsic, MD, PhD,† Sara Gaur, MD,* Sujith Seneviratne, MBBS,‖ Brian S. Ko, MBBS, PhD,‖ Hiroshi Ito, MD, PhD,§ Jesper M. Jensen, MD, PhD,* Laura Mauri, MD, PhD,‖ Bernard De Bruyne, MD, PhD,¶ Hiram Bezerra, MD, PhD,# Kazuhiro Osawa, MD,§ Mohamed Marwan, MD, PhD,** Christoph Naber, MD, PhD,†† Andrejs Erglis, MD, PhD,‡‡ Seung-Jung Park, MD, PhD,§§ Evald H. Christiansen, MD, PhD,* Anne Kaltoft, MD, PhD,* Jens F. Lassen, MD, PhD,* Hans Erik Bøtker, MD, DMSci,* Stephan Achenbach, MD, PhD,** on behalf of the NXT Trial Study Group

HFNXT Study Endpoints

Primary Endpoint:

- Per-patient diagnostic performance as assessed by the area under the receiver operating characteristic curve (AUC) of FFR_{CT} vs. coronary CTA for the diagnosis of ischemia.
  (Reference standard: FFR ≤ 0.80)

Secondary Endpoints:

- Diagnostic performance (accuracy, sensitivity, specificity, PPV and NPV) of FFR_{CT}, coronary CTA, and invasive coronary angiography

Subject Inclusion / Exclusion Criteria

Inclusion Criteria:

- Underwent ≥64-row CT and ICA scheduled
- < 60 days between CT and ICA

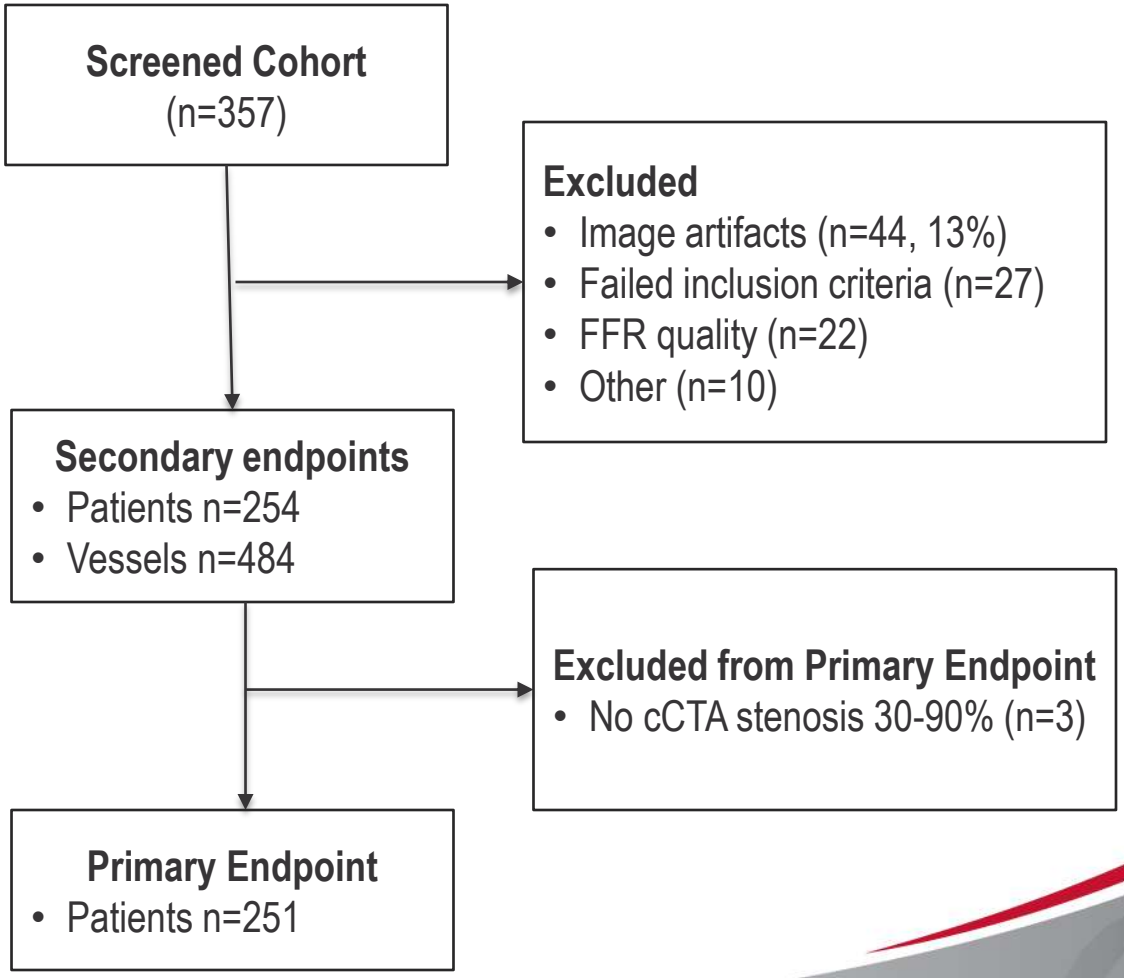
Exclusion Criteria:

- Prior CABG or PCI
- Suspected ACS
- Recent MI within 30 days of CT
- Contraindication to nitrates, beta blockade or adenosine

ICA = Invasive coronary angiography; CABG = coronary artery bypass surgery; ACS = acute coronary syndrome; MI = myocardial infarction; PCI = percutaneous coronary intervention

Patient Enrollment

- Study enrollment 9/2012 – 8/2013
- 10 sites in Europe, Asia, and Australia



Study Population

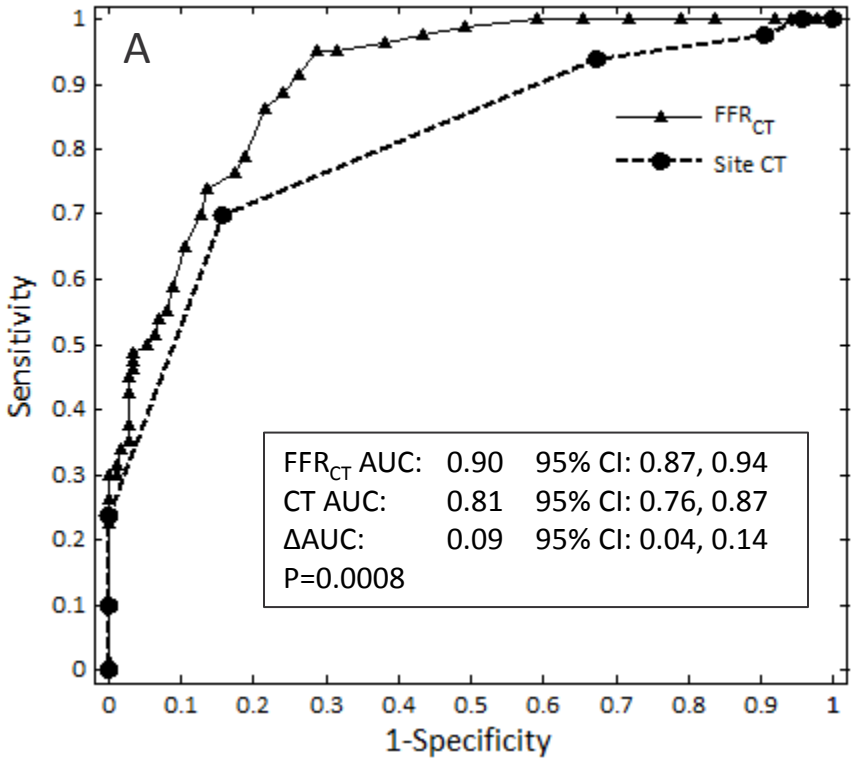
Patient Characteristics	
Age (years) [mean ± SD]	64 ± 10
Male gender	64%
Prior MI	2%
Diabetes mellitus	23%
Hypertension	69%
Pre-test Likelihood of CAD	58%
FFR≤0.80	32%

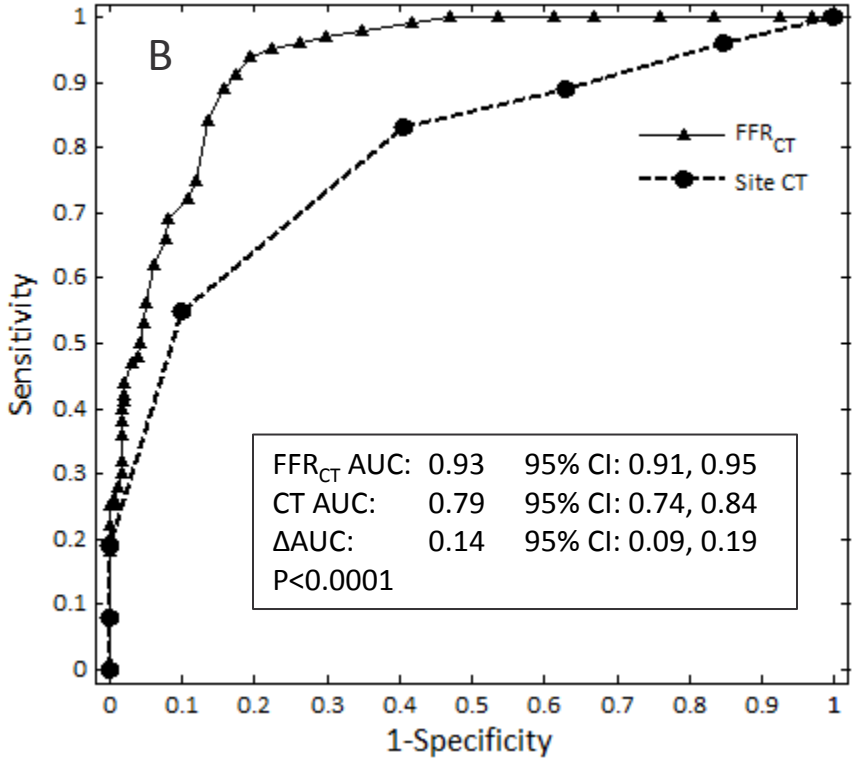
CT Characteristics

– Nitrates	99.6%
– Beta Blockers	78%
– Heart Rate (bpm)	63
Range	37-110
– Prospective	54%
mean dose (mSv)	3
– Retrospective	46%
mean dose (mSv)	14
– Calcium score*	
Mean	302
>400	26%

*Available for 214 patients

Discrimination of Ischemia

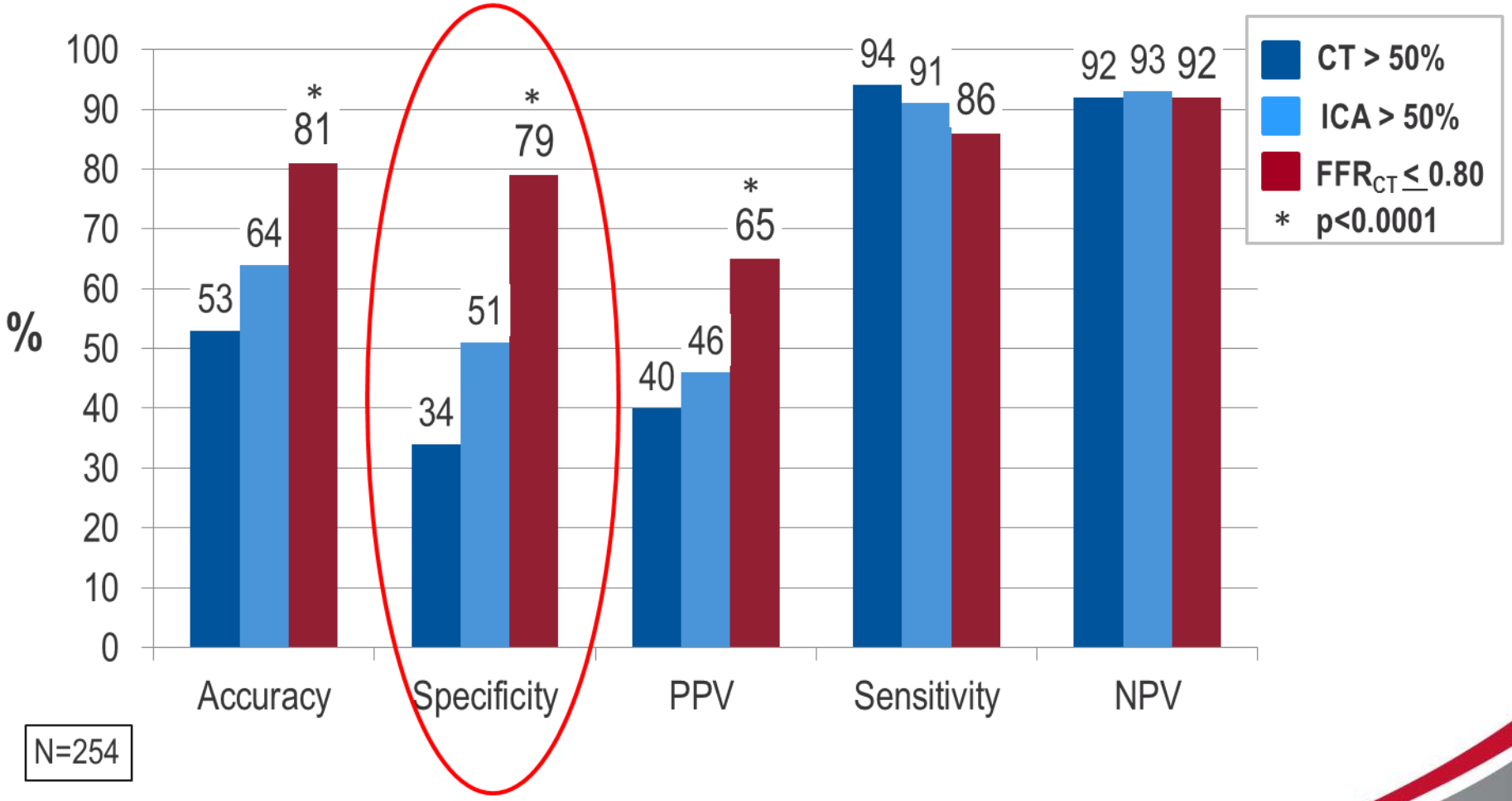




Greater discriminatory power for FFR$_{CT}$ versus CT stenosis

Patient (Δ 0.09, p<0.0008) Vessel (Δ 0.14, p<0.0001)

Per-Patient Diagnostic Performance



FFR_{CT} reclassification

Per-patient

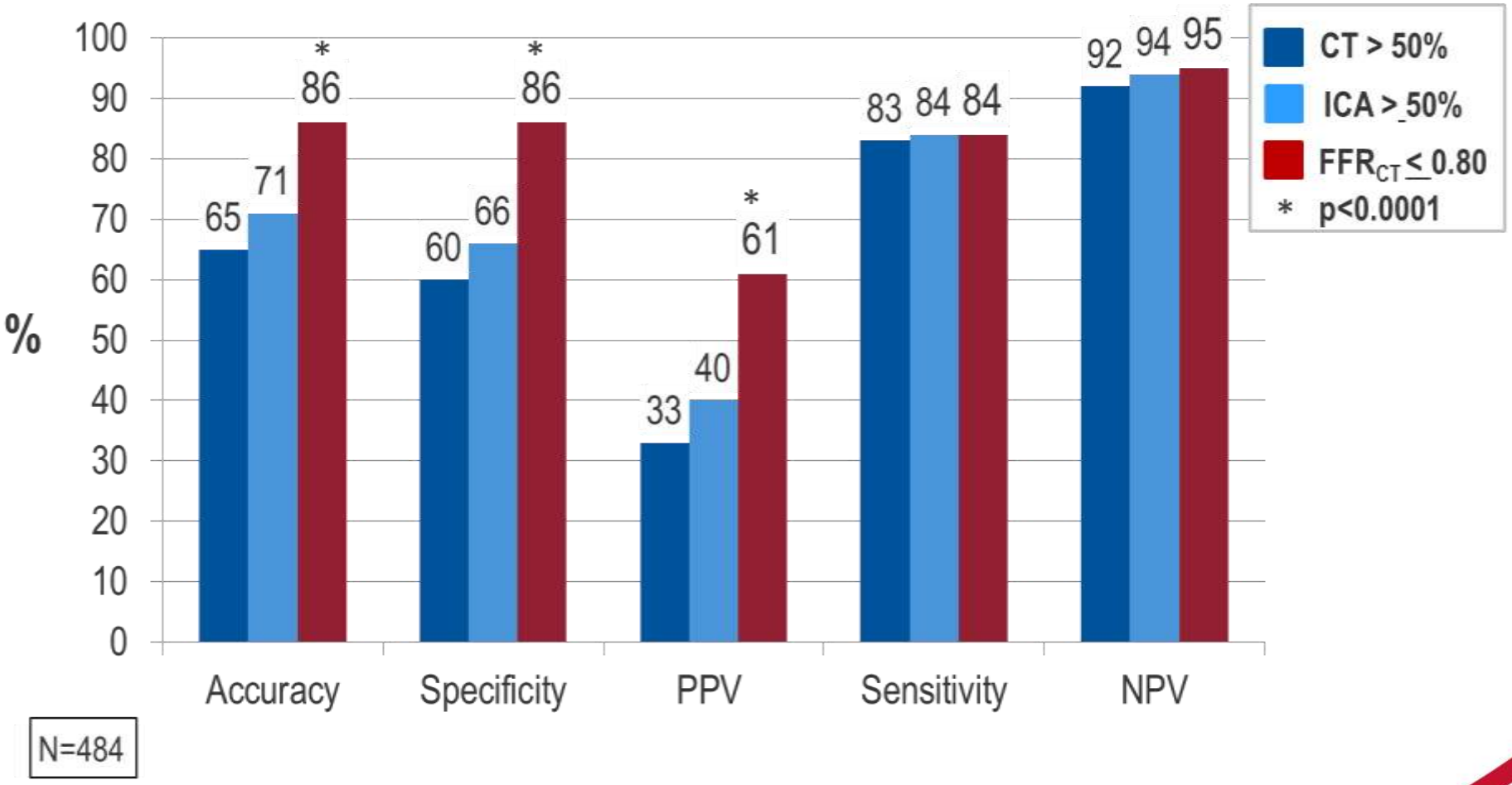
FFR	Coronary CTA stenosis ≥50%	Coronary CTA stenosis <50%
≤0.80	75 (30%)	5 (2%)
>0.80	115 (45%)	59 (23%)

FFR	FFR_{CT} ≤0.80	FFR_{CT} >0.80
≤0.80	69 (27%)	11 (4%)
>0.80	37 (15%)	137 (54%)

- FFR_{CT} reclassified **68%** of CT false positives as true negatives
- If FFR_{CT} were used prospectively, 148 of 254 patients could have been deferred from diagnostic cath

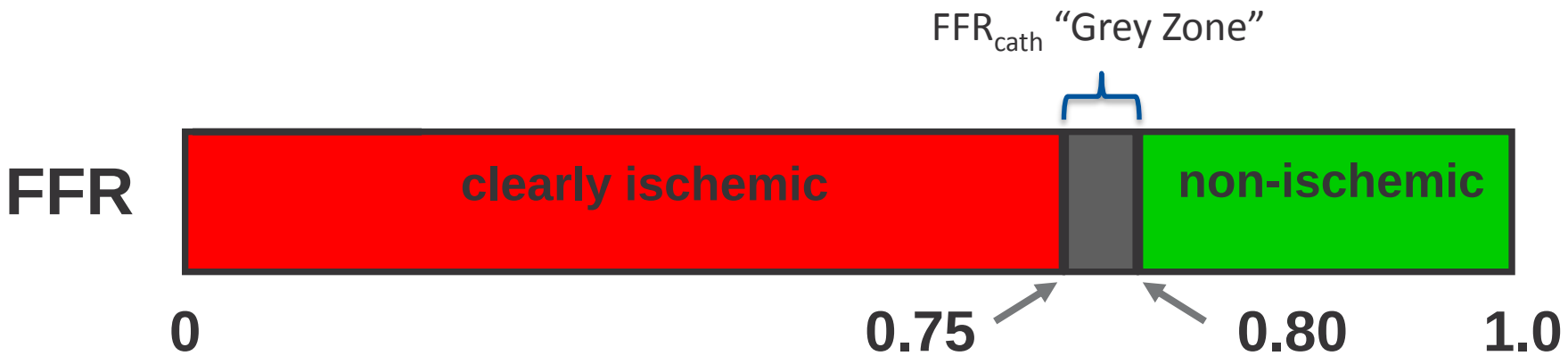
Nørgaard et al, JACC 2014: ePub ahead of print; DOI: 10.1016/j.jacc.2013. 11.043

Per-Vessel Diagnostic Performance



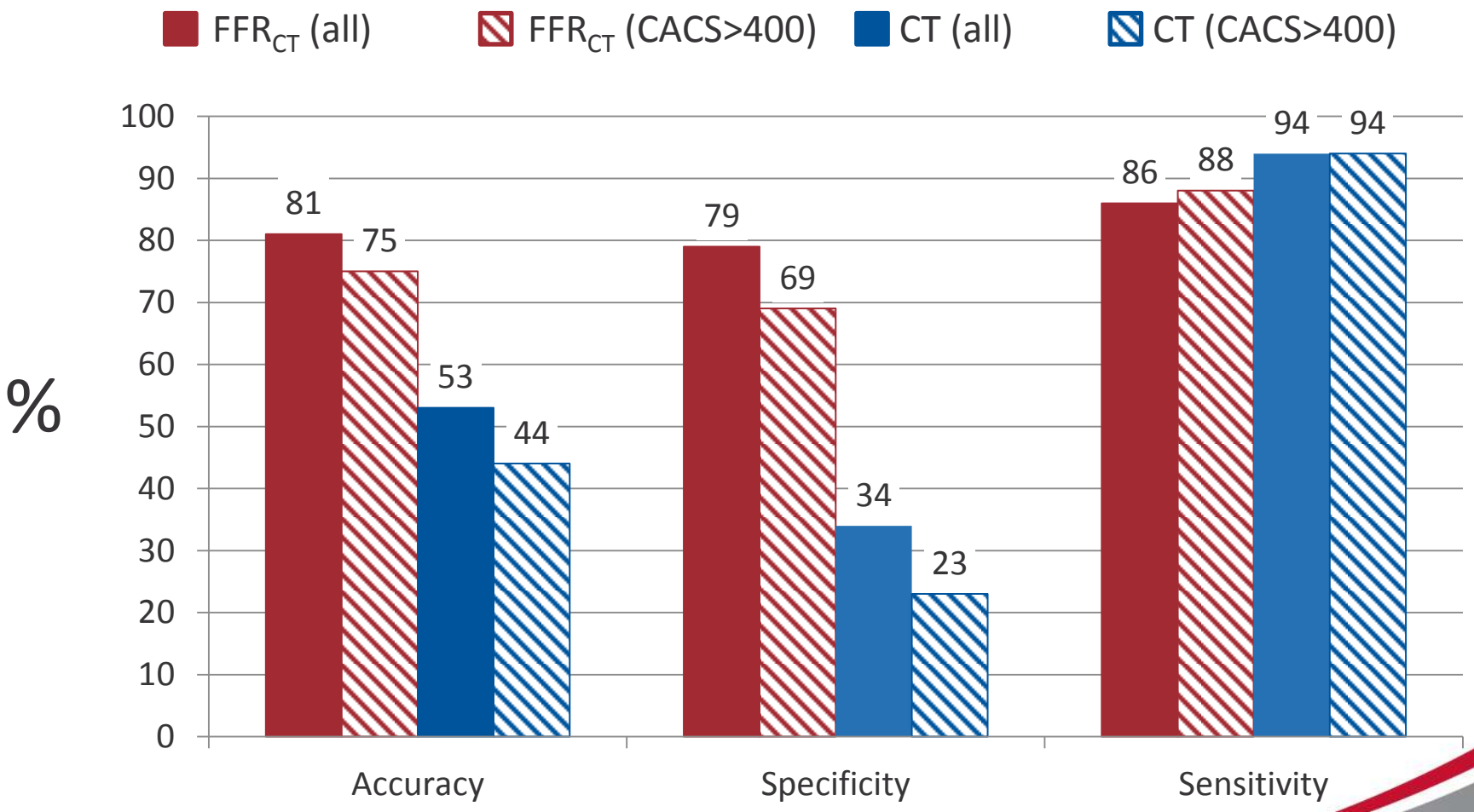
NXT Grey Zone analysis

- FFR "Grey Zone" defined as $0.75 < FFR \leq 0.80$
- Among vessels with $FFR \leq 0.75$ (i.e. outside of "grey zone"), only 3 were negative by FFR_{CT} (i.e. $FFR_{CT} > 0.80$)
- NPV for FFR_{CT} in this subset = 98%



If FFR_{CT} is > 0.8, there is only a 2% chance FFR < 0.75, i.e. clearly ischemic

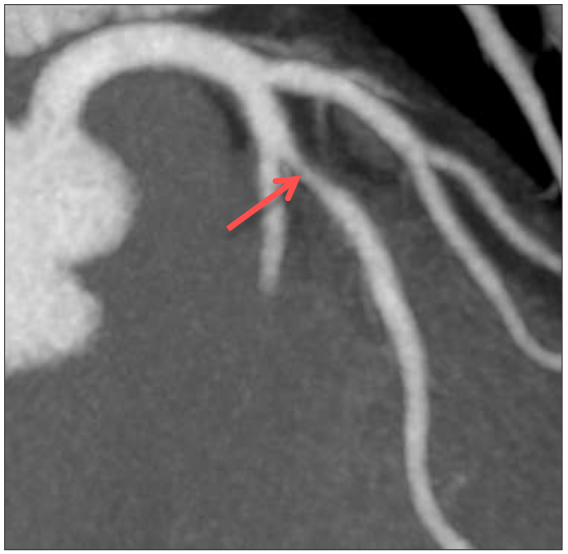
Diagnostic Performance of CT and FFR_{CT}: Effect of Calcium

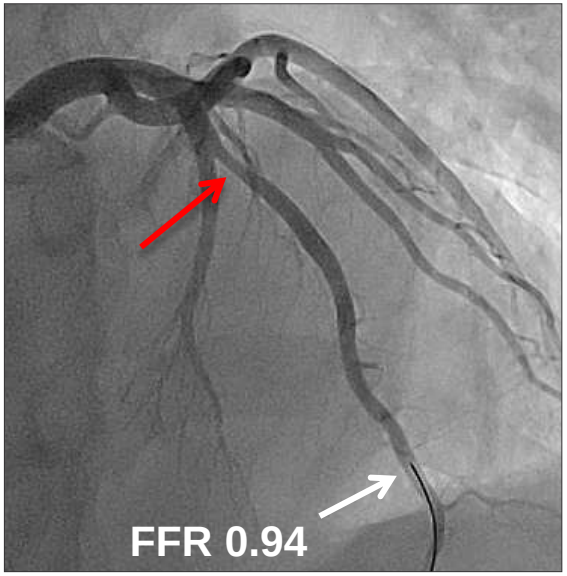


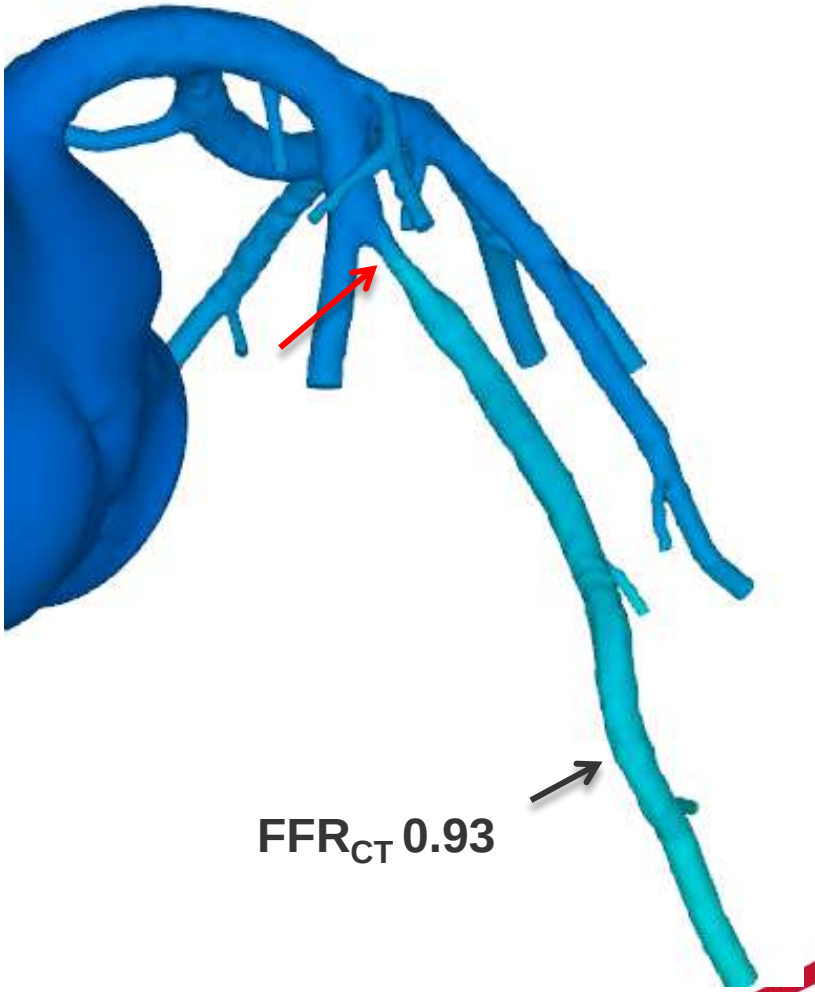
Nørgaard et al, JACC 2014: ePub ahead of print; DOI: 10.1016/j.jacc.2013. 11.043

Case Example

LAD stenosis 70-90%







FFR$_{CT}$ Model

DISCOVER-FLOW → DeFACTO → NXT

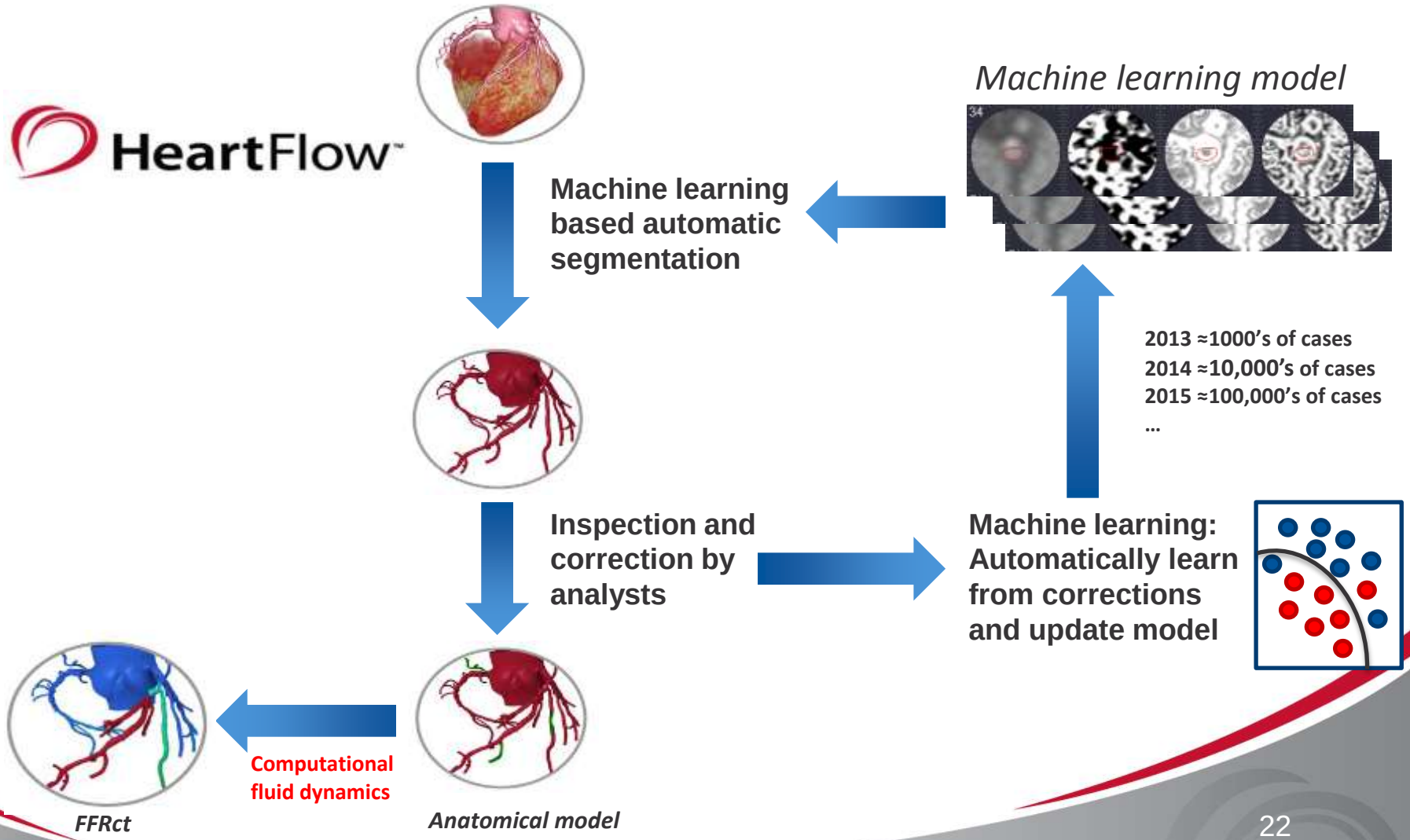
Evolution of Technology, core scientific principles remain the same

- Changes and advances in technology
  - Manual model building → semi-automated/automated image processing
  - Improved boundary condition inputs
  - Reproducibility/quality control/analyst training

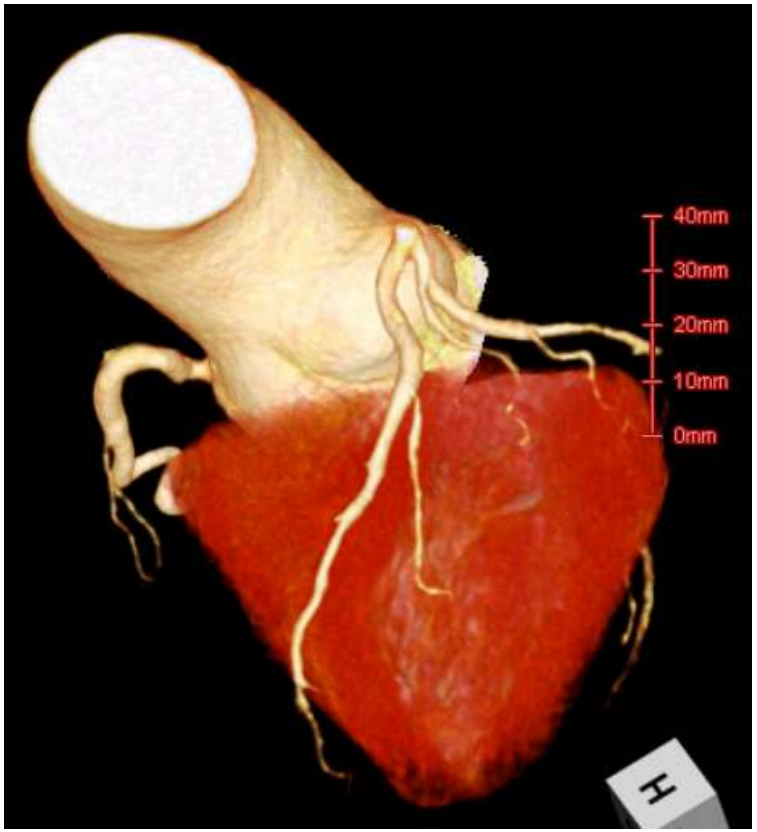
- Image quality
  - Prequalification of site CT: education re SCCT guidelines
  - Pre-specified image quality standards for initiation and enrollment
  - Use of NTG (99% vs 75% in DeFACTO)

- FFR measurement
  - Site education
  - Core lab control

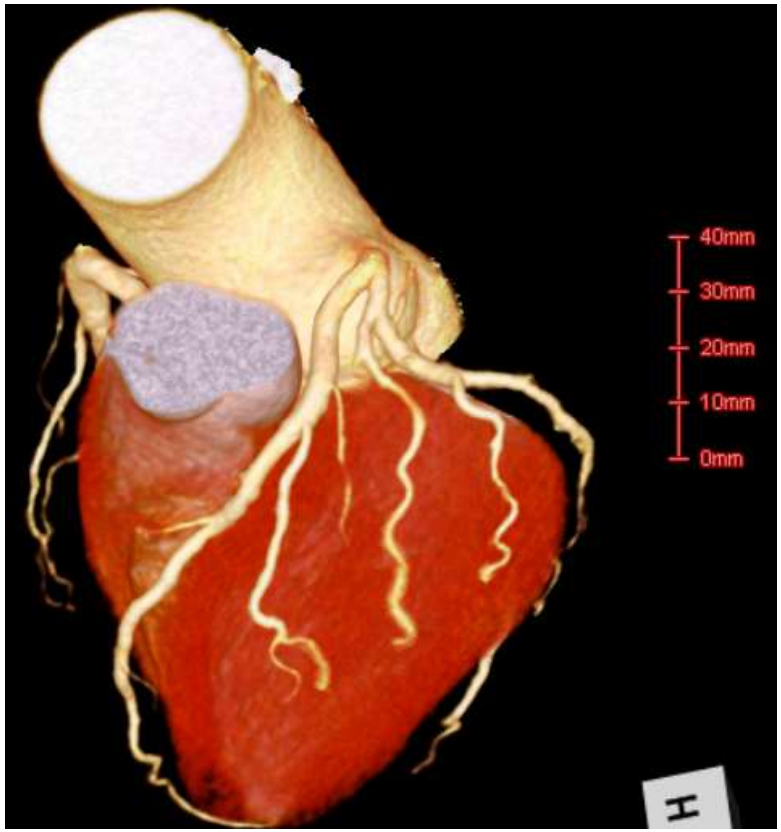
Machine Learning used to further improve image processing algorithms



Impact of SL NTG on cCTA



Prior to Sublingual Nitrate administration



5 min after Sublingual Nitrate administration

79 y.o. female patient

Image courtesy of Munemasa Okada, Department of Radiology, Yamaguchi Medical Center

Primary Peer-reviewed Publications

1.	DISCOVER-FLOW study results	Koo	JACC 2011; 58: 1989
2.	DISCOVER-FLOW intermediate stenosis	Min	Am J Cardiol 2012; 971
3.	DISCOVER-FLOW image quality	Min	JCCT 2012; 6: 191
4.	DeFACTO rationale and design	Min	JCCT 2011; 5: 3011
5.	DeFACTO study results	Min	JAMA 2012; 308(12): 1237
6.	DeFACTO intermediate stenosis	Nakazato	Circulation: CV Imaging 2013 ; 6: 881
7.	DeFACTO image quality, patient prep	Leipsic	Am J Radiology 2013, in press
8.	Non-invasive FFR: scientific basis	Serruys	EuroIntervention 2012; 8: 511
9.	Scientific basis of FFR_{CT}	Taylor	JACC 2013, 61: 2233-41
10.	FFR_{CT} derived from cCTA	Zarins	J Cardiovasc Transl Res 2013
11.	Non-inv dx of ischemia-causing stenosis	Yoon	JACC Imaging 2012; 5: 1088
12.	CT-FFR next level in cardiac imaging	Meijs	Neth Heart J 2012; 20: 410
13.	Noninvasive FFR using CT	Yoon	Cardiovasc Dx and Rx 2012; 2: 105
14.	Integrating physiology and anatomy	Arsanjani	Curr Cardiovasc Imaging Rep 2012; 5: 301
15.	Modeling of FFR based on cCTA	Grunau	Curr Cardio Rep 2013; 15: 336
16.	ABSORB trial 5 year follow up	Serruys	JACC Interventions 2013, 6: 999
17.	FFR_{CT} anatomic-functional integration	Al-Hassan	Future Cardiol 2013; 9: 243
18.	New frontiers in CTA	Min	Heart 2013; 99: 661
19.	Virtual FFR by CT	Rajani	Eurointervention 2013; 9:277
20.	Physiologic assessment of CAD by CT	Kochar	Korean Circ J 2013; 43: 435
21.	Virtual coronary stenting and FFR_{CT}	Kim	JACC Interventions 2013
22.	Cost-consequences of FFR_{CT}	Hlatky	Clinical Cardiology 2013, 36: 743
23.	HeartFlowNXT rationale and design	Gaur	JCCT 2013, 7: 279
24.	HeartFlowNXT study results	Norgaard	JACC 2014, 63, No. 12, 1146-55

FFR_{CT}: Building the Body of Evidence

PLATFORM

PROMISE, ACRIN PA, …

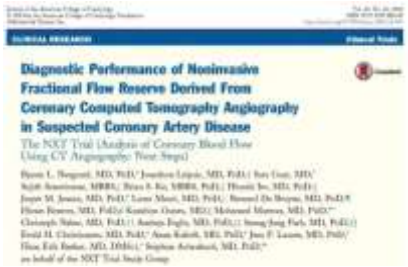
Randomized Control Trial
(planning underway)

DISCOVER-FLOW

DeFACTO

Cath lab
Population
Dx Accuracy

HFNXT



30-90%
Stenosis
Dx Accuracy

Stable
Angina
Outcomes and resources

ACS
(- enzyme)
Outcomes and resources

2012 *2013* *2014* *2015* *…*

PLATFORM:
Comparing Current Care to FFR_{CT}

Principal Investigators: Pam Douglas, Bernard de Bruyne, Mark Hlatky, Gianluca Pontone

Symptomatic subjects with suspected CAD and intermediate likelihood of CAD(20%–80%)[1] and no contraindications to cCTA or FFR_{CT} referred for invasive coronary angiography (with or without prior non-invasive coronary ischemia testing)

[1] per Updated Diamond Forrester clinical risk score

	Time period 1: Current standard practices	Time period 2: FFR_{CT} based diagnosis
Enrollment	Invasive coronary angiogram	CT/FFR_{CT}
Definitive treatment decision	Invasive Standard practice	Medical or invasive CT/FFR_{CT} guided practice

Primary endpoint (90 days)

- Frequency of ICA showing no significant CAD

Secondary endpoints

- 6 and 12 month MACE
- QOL (EQ5D and SAQ)
- Medical Radiation

HeartFlow

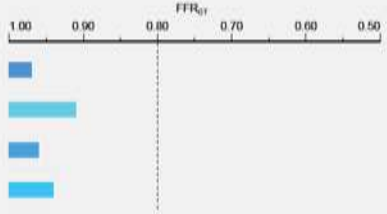
FFR_{CT} Results

[redacted]

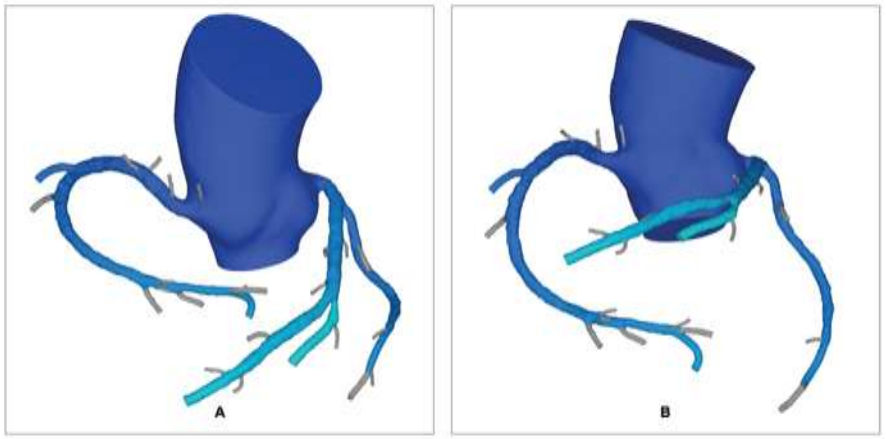
Patient ID 19-0062-S-L
Birth Date 4/23/1959
CT Study Date 1/21/2014

Summary

CORONARY ARTERY		FFR_{CT}
Left Main	LM	0.97
Left Anterior Descending System	LAD	0.91
Left Circumflex System	LCx	0.96
Right Coronary Artery System	RCA	0.94



Measured Fractional Flow Reserve (FFR) values ≤ 0.80 suggest hemodynamic (functional) significance (1,2,3).



HeartFlow

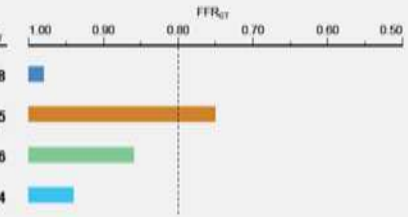
FFR_{CT} Results

[redacted]

Patient ID 29-0070-G-C
Birth Date *Not provided*
CT Study Date 1/14/2014

Summary

CORONARY ARTERY		FFR_{CT}
Left Main	LM	0.98
Left Anterior Descending System	LAD	0.75
Left Circumflex System	LCx	0.86
Right Coronary Artery System	RCA	0.94



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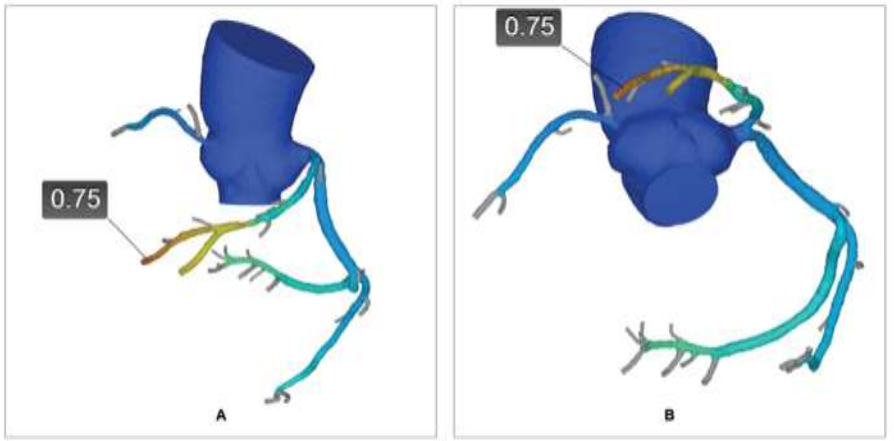
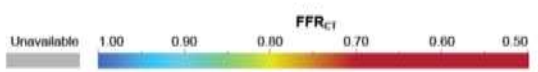
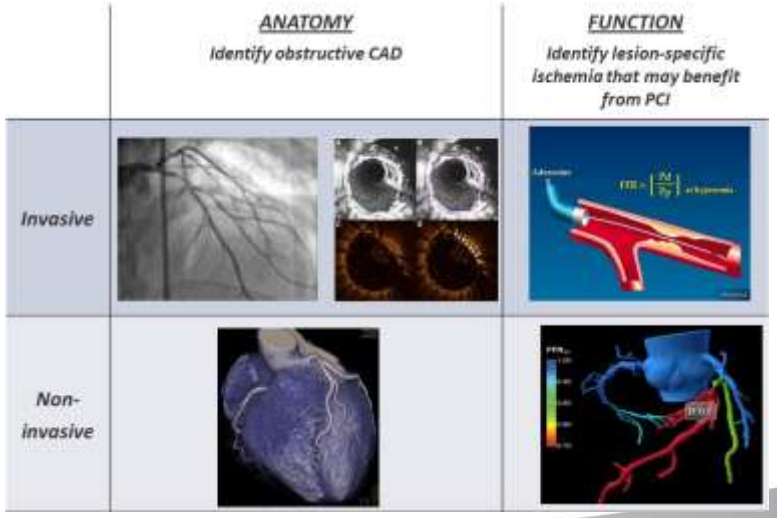




FFR_{CT} - Delivering Anatomical AND Functional Capabilities in One Noninvasive Test

- Clear need for a better noninvasive CAD diagnostic test combining anatomy and function
- FFR_{CT} demonstrates high diagnostic accuracy validated in 3 prospective multicenter clinical trials
- FFR_{CT} leverages high-fidelity image processing, well established physiology principles and robust computational fluid dynamics methods to solve the laws of physics governing blood flow



Thank you