AMERICAN COLLEGE of CARDIOLOGY | Ohio CHAPTER

The 26th Annual Meeting

FFR and CTA:
When Evaluating Anatomy Isn't Enough

October 15, 2016

Subha V. Raman, MD, MSEE, FACC, FAHA
Professor and Joseph M. Ryan, MD Chair in Cardiovascular Medicine
Program Director, Cardiovascular Diagnostics Fellowship
Medical Director, CMR/CCT

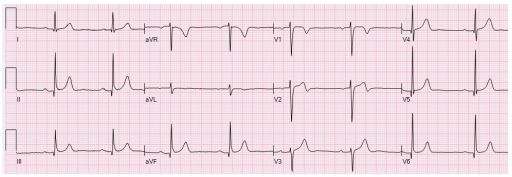
Wexner Medical Center

Disclosures

- Research support from NIH, Siemens

64 year-old male with bradycardia pre-colonoscopy

- Atropine given, cardiology evaluation advised; 'asymptomatic'
- PMH: OSA on CPAP
- SocH: karate instructor, nonsmoker
- FH: father died of suspected MI in his 70s
- Exam: 150/80, HR 78, 71 kg, 1.8 m
- Labs: LDL 121, HDL 60, TG 68, total 195

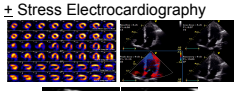


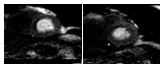
Typical evaluation of stable patients with suspected CAD:

History, Physical, Labs, ECG

☐ Pre-test Likelihood

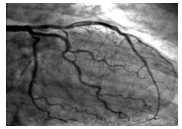
± Stress Electrocardiography

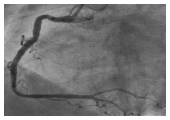




± Imaging
(Nuclear, echo, CMR, PET)

☐ Post-test Likelihood
☐ Presence/location of ischemia



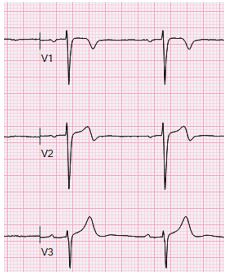


Invasive coronary
Angiography ± FFR

☐ Stenosis + ischemia
☐ Therapeutic revascularization

64 y/o active male with bradycardia, OSA, HTN

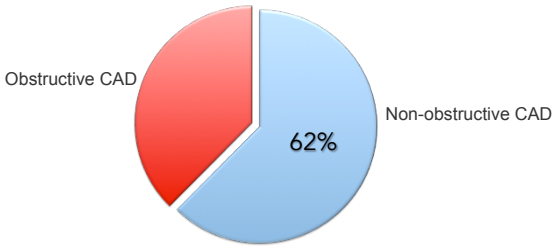
- What next?
  1. Reassurance
  2. Stress testing
  3. Coronary CTA
  4. Invasive angiography



Outline

- Room for improvement? Established utility of CTA
- FFR-CT – underlying principles
- FFR-CT – trial data
- FFR-CT – Practical aspects (time to process, quality of CTA data, cost/reimbursement) & case illustrations
- Ongoing trials, future directions/other apps (anomalies, stents, ACS prediction)

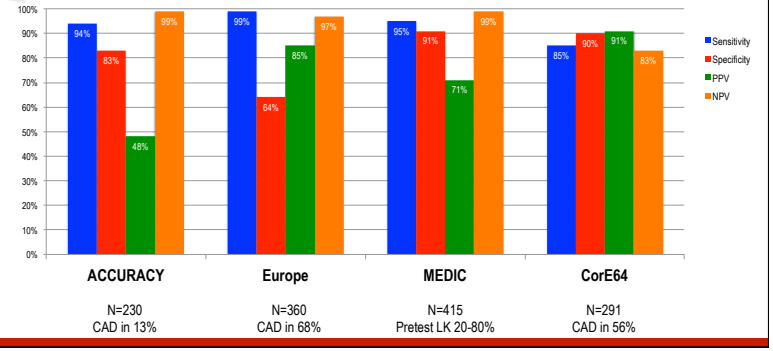
Suspected but no known CAD: nearly 2/3 without obstructive disease by ICA



analysis of ~400,000 patients at > 650 US hospitals

Patel M *et al.* NEJM 2010.

Diagnostic Performance of Coronary CTA



Accuracy Requires ≥64 Detector Rows, HR Control

- Meta-analysis of 89 CTA studies, N=7,516 patients
  - Five (5) multi-center trials; per-patient analysis

Table. Diagnostic Accuracy Data for CT, MRI, and Covariate Analyses

Imaging Method	Mean Sensitivity (95% CI), %	Mean Specificity (95% CI), %	Area Under the Curve (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)
MRI (1					(0.14–0.25)
CT (89					(0.02–0.04)
Suspe					(0.02–0.04)
Suspe					(0.02–0.19)
Covariates					
Scanner rows					
>16†			98.1 (97.0–99.0)	89.4 (86.0–92.0)	
Heart rate					
<60 beats/min			99.0 (98.1–99.5)	85.8 (79.4–90.5)	
≥60 beats/min			96.2 (94.7–97.3)	87.7 (84.1–90.5)	
P value			<0.001	0.55	
≥60 beats/min	96.2 (94.7–97.3)	87.7 (84.1–90.5)			
P value	<0.001	0.55			

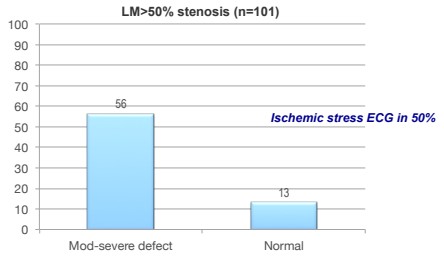
Ann Int Med 2010.

Diagnosis of Obstructive CAD

Test	Sensitivity	Specificity
Exercise ECG treadmill[1]	68%	77%
Exercise Echo treadmill[2]	86%	81%
Dobutamine Echo[2]	~85%	~85%
Treadmill stress nuclear[3]	87%	73%
Pharmacologic stress nuclear[3]	89%	75%
Coronary CTA[4]	94%	83%

1. ACC/AHA 2002 Guideline Update for Exercise Testing
2. ACC/AHA/ASE 2003 Guideline Update for the Application of Echocardiography
3. ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging
4. ACCURACY study

We Don't Want to Miss Significant Left Main Disease



Berman D *et al.* J Nuc Cardiol 2007.

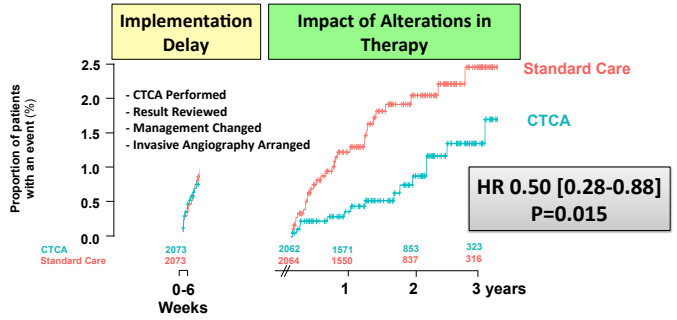
Clinical Outcomes: PROMISE Trial

- 10,003 patients presenting for new CAD evaluation
- Randomized to CTA or stress testing (referring doc's choice)

	Favors CT	Neither	Favors Stress Testing	
Outcomes at 2 years		X		
Outcomes at 1 year	X			33% decrease death/ MI (p=0.04)
Radiation dose			X	12 vs. 10 mSv
Radiation dose vs. SPECT	X			12 vs. 14 mSv
Diagnostic Performance	X			Cath Normalcy 3.4 vs 4.3%
Triage to surgical revascularization	X			2-fold increase CABG
Primary Preventive Tx	X			2-fold increase statins
Quality of Life		X		Similar
Cost		X		~$50 difference

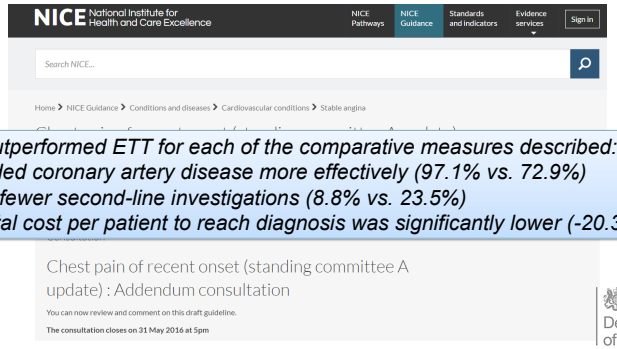
NEJM 2015

SCOT-HEART: randomized trial of >4100 CP patients



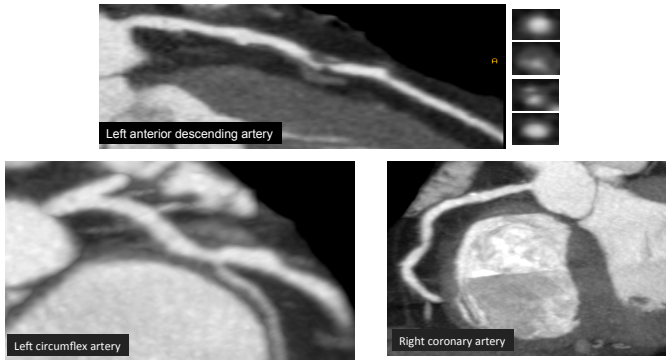
JACC 2016

National Institute for Health and Care Excellence

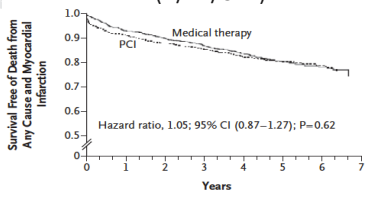


CTA outperformed ETT for each of the comparative measures described:
-excluded coronary artery disease more effectively (97.1% vs. 72.9%)
-led to fewer second-line investigations (8.8% vs. 23.5%)
-the total cost per patient to reach diagnosis was significantly lower (-20.3%)

"Should I be revascularized?"

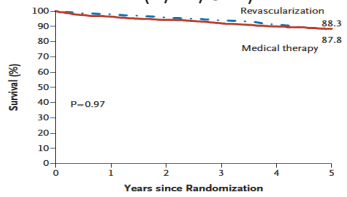


COURAGE Trial (D/MI/CVA)



2,287 individuals with angiographically obstructive CAD and ischemia assigned to PCI or medical tx and followed for 4.6 years

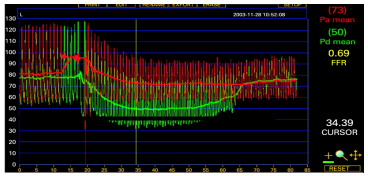
BARI 2D Trial (D/MI/CVA)

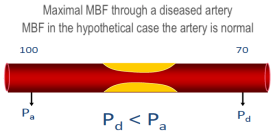


2,368 diabetic patients assigned to revascularization or medical tx and followed for 5 years

NEJM 2007; NEJM 2009

Reference "Gold" Standard for Ischemia: Fractional Flow Reserve

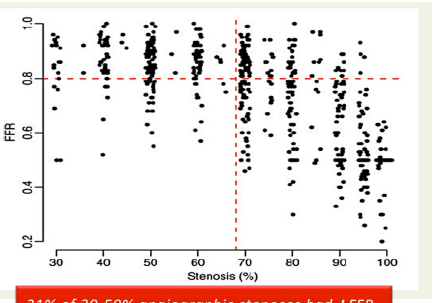




FFR ≤ 0.80 or ≤ 0.75 considered diagnostic of lesion-specific ischemia

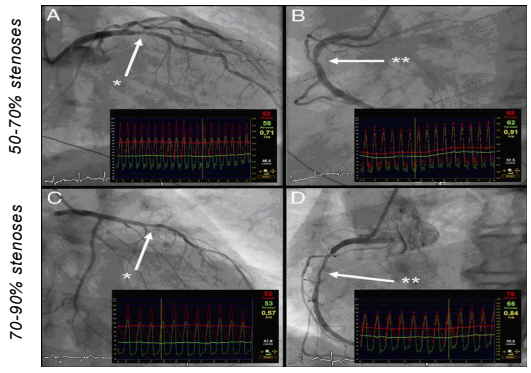
Pijls NH et al. J Am Coll Cardiol. 2007; Pijls NH et al. J. Am. Coll. Cardiol. 2010

Lesion-specific ischemia exhibits an unreliable relationship with angiographic stenosis



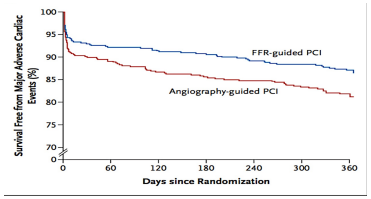
21% of 30-50% angiographic stenoses had +FFR, 19% of 90-95% stenoses have -FFR

Layland et al EHJ 2014

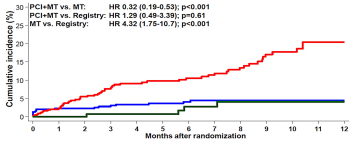


Tonino PA *et al.* JACC 2010.

FAME : FFR-Guided Therapy is Superior to Angiography-Guided Therapy



FAME 2: FFR-Guided Revascularization is Superior to OMT Alone

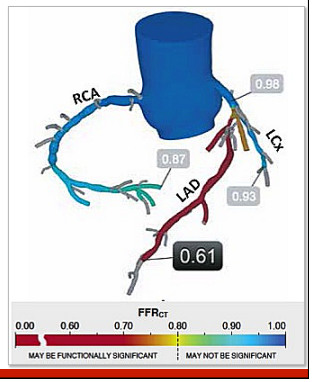


Tonino *et al.* NEJM 2009; Debruyne *et al.* NEJM 2012.

FFR can now be derived from CTA

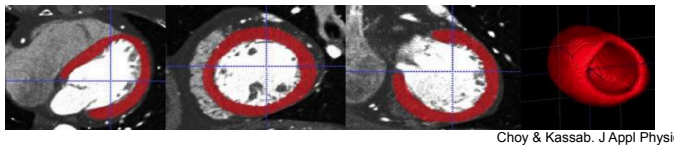
1. Uses standard (high quality) CTA images
2. No added radiation, contrast, medications

→ FFR at any point in the coronary tree

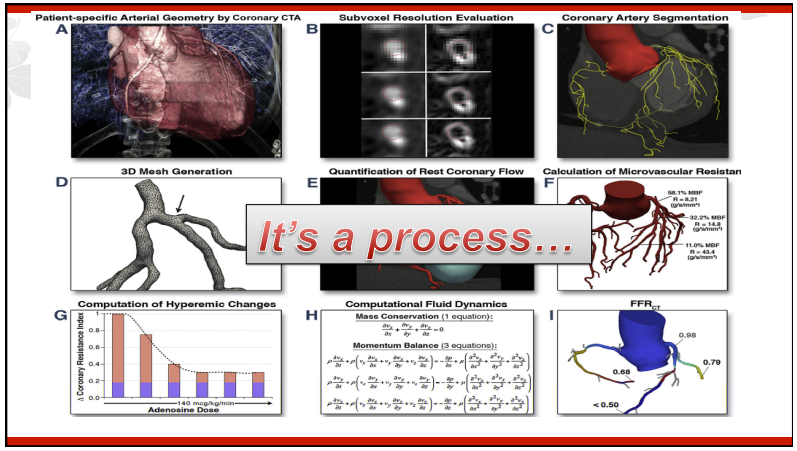


Functional Significance of CAD: FFR-CT

- Pressure loss determined by serial lesions
- Perfusion territory affects flow and pressure loss
- Allometric scaling: Q_{cor} proportional to $LVM^{0.75}$
- Maximum reduction in coronary resistance i.e. response to adenosine can be modeled

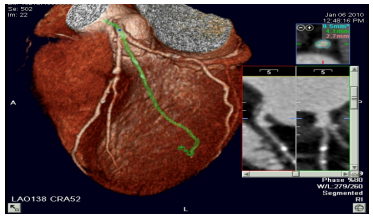


Choy & Kassab. J Appl Physiol 2008.
Wilson RF *et al*. Circ 1990.



1 – Patient Specific Arterial Geometry

- Finite Element Modeling for pulsatile blood flow
- Millions of vertices and elements, more at boundaries



C.A. Taylor, T.J.R. Hughes, and C.K. Zarins, (1996) Computers in Physics, Vol. 10, No. 3, pp. 224-232; C.A. Taylor, T.J.R. Hughes, and C.K. Zarins, (1998) Finite Element Modeling of Blood Flow in Arteries. Computer Methods in Applied Mechanics and Engineering. Vol. 158, Nos. 1-2, pp. 155-196.

2 – Form-Function Relationships

- **Allometric Scaling (Morphometry) Laws:** Relate mass (size) of object to shape, anatomy and physiology
  - Abundant physiologic information from anatomic data
  - Examples:
    - AV fistula enlargement d/t chronic incr. in blood flow
    - High-grade stenosis vessel smaller d/t chronic decrease in blood flow


Coronary Flow Related to Size

- **Murray's Law is a Homeostatic process**
  - Adaptive mechanism
  - Endothelium → remodel coronary size to maintain homeostatic level of shear stress
- **Poiseuille's Equation:** Q / Diameter Relationship
  - Describes steady flow of viscous fluid in circular cylinder
  - Blood vessels change in caliber based on flow and wall shear stress sensed by endothelial cells
    - Q = flow rate
    - D = diameter of vessel
    - T_w =wall shear stress
    - η = fluid viscosity

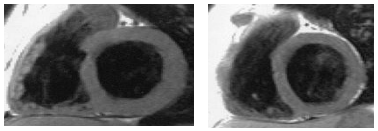
$$Q = \frac{\pi}{32\mu}\tau_w d^3$$

Flow = d^3 if wall shear stress maintained

Taylor et al. J Am Coll Cardiol 2010; Leipsic et al AJR 2013 Schuijf et al. J Am Coll Cardiol 2006, Schuijf et al. Heart 2008

Form-Function Relationships (cont.)

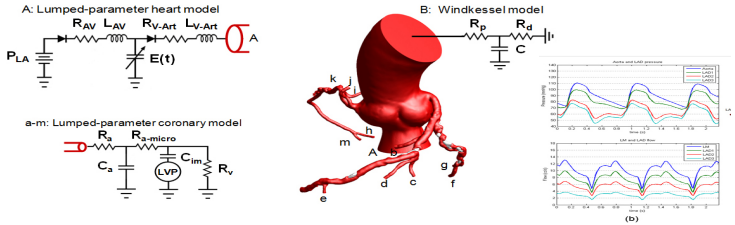
Resting coronary flow proportional to myocardial mass



$Q_c^{rest} \alpha M_{myo}^{\beta}$

3 – Patient-Specific Physiology

- **Boundaries**: aortic inlet, aortic outlet, coronary outlets and lateral surface
- Lumped parameter model to enforce relationship b/w pressure and flow

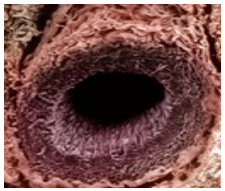


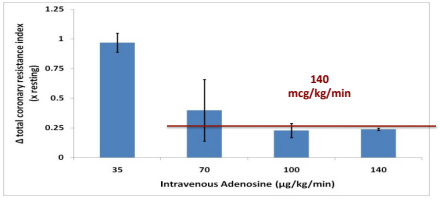
- Pulsatile flow in relation to time-varying intramyocardial pressure

Leipsic et al AJR in press ; Leipsic et al JCCT 2012 Taylor CA and Min JK J Am Coll Cardiol 2013, C.A. Taylor, T.J.R. Hughes, and C.K. Zarins, (1996) Computers in Physics, Vol. 10, No. 3, pp. 224-232; C.A. Taylor, T.J.R. Hughes, and C.K. Zarins, (1998)

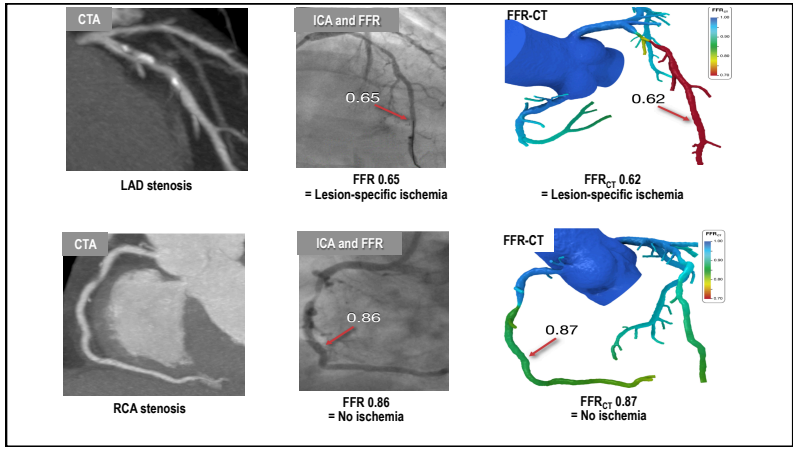
4 – Induction of Hyperemia

1. Heart lacks O_2, breakdown of ATP results in release of adenosine → vasodilation
2. Exogenous adenosine elicits hyperemia by forcing complete smooth muscle cell relaxation





- FFR_{CT} includes adenosine effect on resistance of microcirculation
- Underlies dose for pharmacologic stress testing and invasive FFR

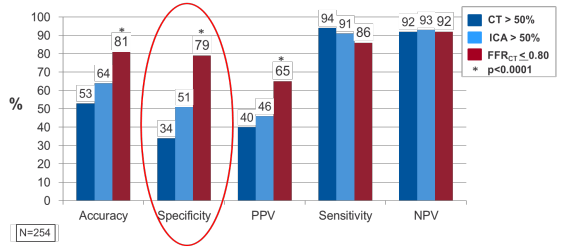


Does It Work? 3 Prospective Multicenter Trials

	DISCOVER-FLOW	DeFACTO	NXT
Primary end point	Per pt. diag accuracy	Per pt. diag accuracy; lower limit 95% CI 0.7	Per pt. AUC
Study sites/ countries	4 / 3	17 / 5	10 / 8
CT training of site	Yes	No	Yes
FFR training of site	No	No	Yes
CT quality check	No	No	Yes
CT results reading	Core lab	Core lab	Site
FFR results report	Site	Site	Site with core lab overview
Vessel size for inclusion	≥ 2.0 mm	≥ 1.5 mm	≥ 2.0 mm
Use of NTG with CT	?	75%	99.6%

Koo et al. JACC 2011; Min JK et al. JAMA 2012; Norgaard BL et al. JACC 2014

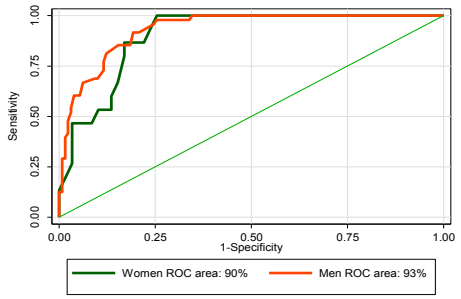
Per-Patient Diagnostic Performance: NXT Trial



FFR-CT correctly reclassified 68% of CT false⊕ to true negatives

Nørgaard BL *et al.*JACC 2014.

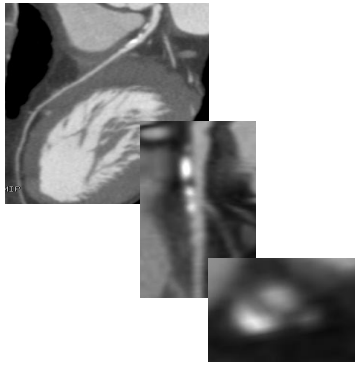
Comparable Diagnostic Performance in Men and Women



Thompson A G *et al.* JCCT 2014

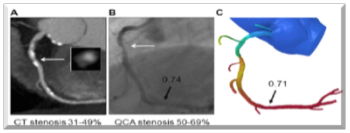
Intermediate Stenoses

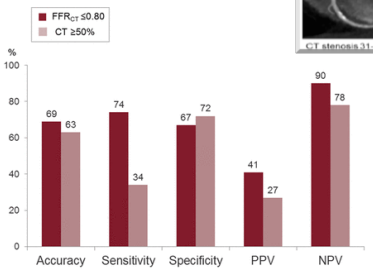
	50% to 70% (n = 620, 47%)
FFR >0.80	402 (65)
FFR ≤0.80	218 (35)
Mean FFR for all lesions	0.81 ± 0.12
Mean FFR >0.80	0.89 ± 0.05
Mean FFR ≤0.80	0.68 ± 0.10



Tonino *et al.* JACC 2010.

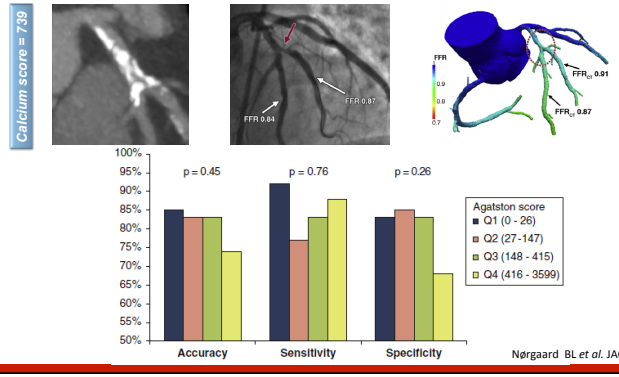
Substudy of DeFACTO: 30-69% CTA Lesions





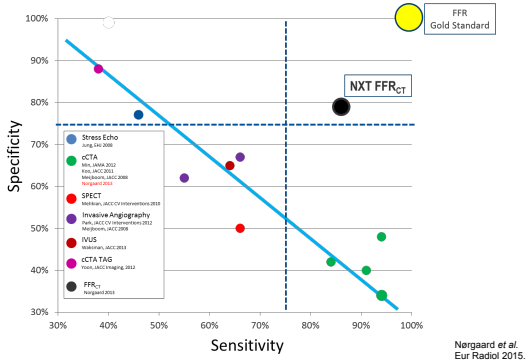
Nakazato *et al.* Circ Im 2013.

FFR-CT works across varying degrees of CACS



Nørgaard BL *et al.* JACC Imaging 2015.

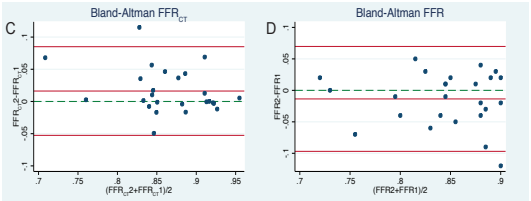
FFR-CT: A New Standard in Noninvasive Testing?



Nørgaard *et al.*
Eur Radiol 2015.

Reproducibility

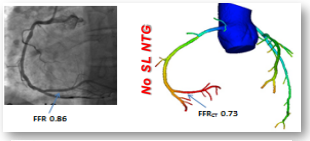
- 28 patients/58 vessels analyzed by FFR-CT and iFFR
  - Repeat analysis of CTA data sets
  - Repeat iFFR – replace pressure wire and re-infuse adenosine
- SD of FFR-CT vs. iFFR: 0.034 vs. 0.033 (p=0.72)

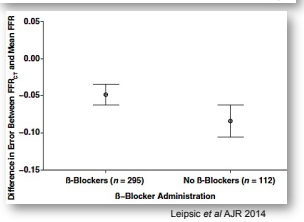


Gaur S *et al.*
JCCT 2014.

Importance of adherence to best practice for CTA

- SL NTG
- HR control
- Contrast opacification of the coronaries
- Minimal right heart/SVC contrast
- Minimal respiratory artifact



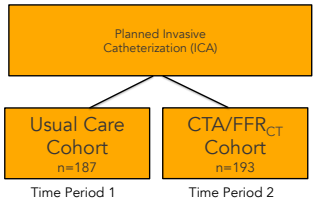


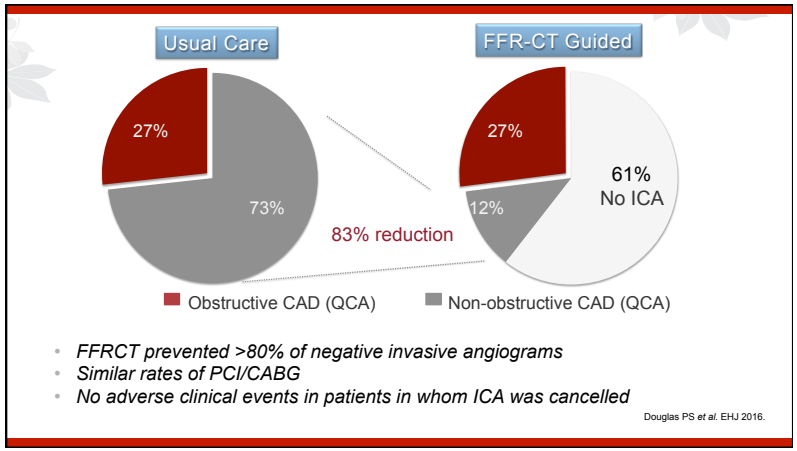
Leipsic *et al* AJR 2014

Clinical Utility: PLATFORM Trial

- **P**rospective **L**ongitudin**A**l **T**rial of **F**FR$_{CT}$: **O**utcome and **R**esource I**M**pacts
  - Prospective, controlled, pragmatic comparative effectiveness trial utilizing a comparative cohort design
  - 584 patients with suspected CAD (pre-test likelihood of 20-80%) were enrolled at 11 centers in 6 EU countries

- **Primary Endpoint:** Patients with a planned ICA
  - Are patients evaluated using a **CTA/FFR$_{CT}$ guided strategy** less likely to undergo ICAs that show **no obstructive CAD**?



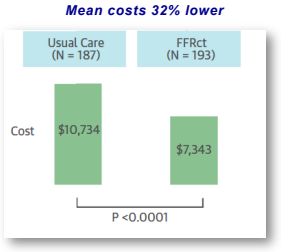


- *FFRCT prevented >80% of negative invasive angiograms*
- *Similar rates of PCI/CABG*
- *No adverse clinical events in patients in whom ICA was cancelled*

Douglas PS *et al.* EHJ 2016.

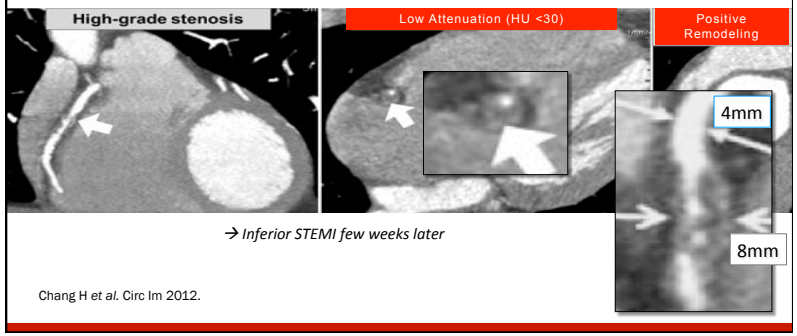
PLATFORM: Cost-Effectiveness Analysis

	Usual Care (n = 187)	FFR_{CT} (n = 193)
Stress tests		
ECG	2 (2)	8 (8)
Echo	0 (0)	1 (1)
Nuclear	2 (2)	0 (0)
CT angiograms	1 (1)	193 (193)
FFR_{CT}	0 (0)	117 (117)
Invasive tests		
Diagnostic ICA	153 (153)	37 (36)
ICA with PCI	40 (38)	51 (45)
FFR_{INV}	11 (11)	27 (26)
IVUS	7 (7)	4 (4)
Coronary revascularization		
PCI	44 (42)	51 (45)
Stents (mean)	1.82	1.80
CABG	17 (17)	10 (10)
Hospital days	445 (109)	259 (54)
Clinic visit	45 (35)	37 (36)
ED visits	8 (8)	2 (2)
Medications at 90 days		
Aspirin	133	117
Statin	114	107
Clopidogrel	38	46
Prasugrel	3	3
Ticagrelor	1	0



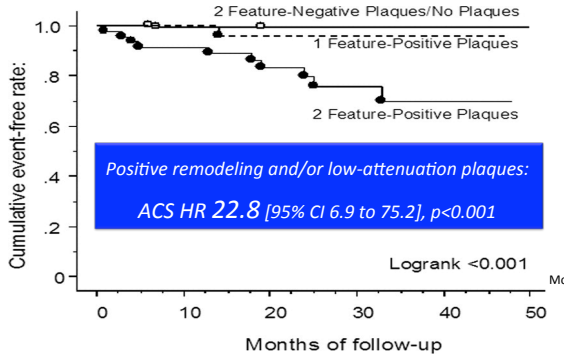
Hlatky ME *et al.* JACC 2015.

High Risk Plaque by CTA



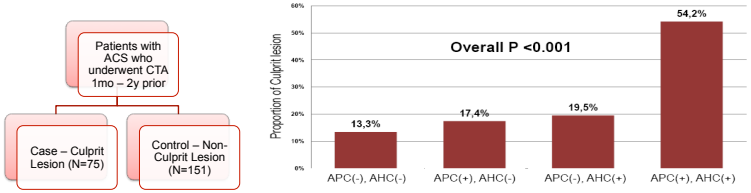
→ *Inferior STEMI few weeks later*

Chang H *et al.* Circ Im 2012.



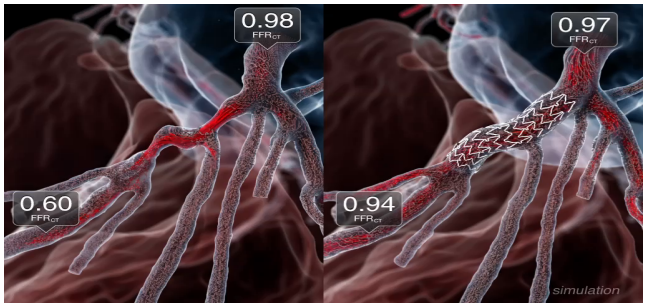
Motoyama S *et al.* JACC 2009.

Which Dictates ACS – Adverse Plaque or Adverse Hemodynamic Characteristics?



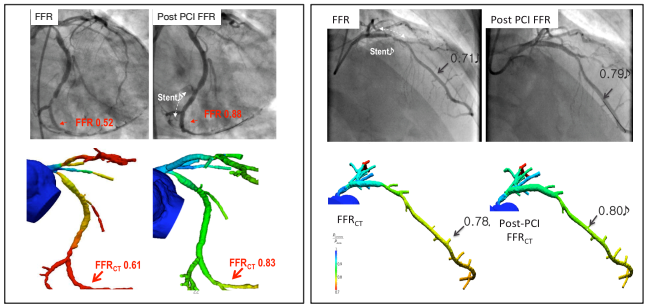
Koo BK *et al.* Euro PCR 2016 (abstract).

Future of FFR-CT: Virtual Stenting



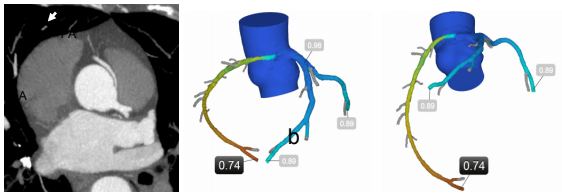
Courtesy J Min, MD

44 patients
Accuracy 96%
Sens / Spec 100% / 96%

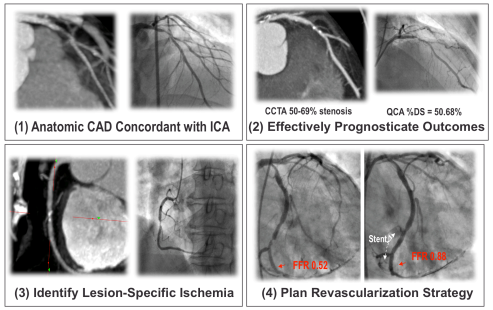


Koo BK et al. JACC CV Interventions 2013

Other Applications



Optimal Diagnostic Approach to Symptomatic CAD?



Back to our patient:

64 y/o active male with bradycardia, OSA, HTN

Summary

- CAD anatomy + physiology → better outcomes
  - FFR-CT represents a significant advance in evaluating CAD
  - Superior diagnostic accuracy of 86% for lesion-specific ischemia
- Typical referrals to coronary CTA may need to change to realize full incremental value
- Availability, cost, & processing time should improve

Thank you

- Team OSU CMR/CCT
- Johnathon Leipsic, MD - University of British Columbia
- James Min, MD - Dalio Institute/Weill-Cornell Medical Center