Test in Subjects with Suspected CAD
Anatomic Study is Better

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Functional Test

Two Issues

- Accuracy of stress-tests
- Do literature summaries reflect reality?

Functional Test

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- Do literature summaries reflect reality?

Accuracy of stress tests

Duke Stress Perfusion Study

- Consecutive patients referred for elective diagnostic CAG with suspected CAD

- All patients with intermediate risk of CAD

  (no prior MI, known CAD)

- Exclusion: routine contralxs to MRI

  or adenosine stress-testing

Klem et al, JACC 2006

Accuracy of stress tests

Duke Stress Perfusion Study

- Results
  - 100 patients enrolled
  - **76%** had priori abnormal stress-test
    : Nuclear (48%), Echo (21%), Treadmill (8%)

→ **53%** had insignificant disease (<50% stenosis)
60% had insignificant disease (<70% stenosis)

Klem et al, JACC 2006

Accuracy of stress tests

- Morise and Duval
  - 1,681 patients referred for exercise stress test
  - Positive 436 patients underwent ICA (within 2 months of exercise stress test) for the first time
  - → **62% had insignificant disease (<50% stenosis)**

<div align="right">Am J Cardiol 1989</div>

- Cecil et al
  - 2,688 referred for thallium SPECT
  - Positive 471 pts underwent ICA (within 3 months of SPECT) for the first time
  - → **58% had insignificant disease (<50% stenosis)**
  - → **65% had insignificant disease (<70% stenosis)**

<div align="right">J Clin Epidemiol 1996</div>

Accuracy of stress tests

ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging)

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Table 5. Sensitivity and Specificity of Exercise Myocardial Perfusion Single-Photon Emission Computed Tomography for Detecting Coronary Artery Disease (Greater Than or Equal to 50% Stenosis)—Generally Without Correction for Referral Bias

Year	Author	Radiopharmaceutical	Prior MI (%)	Sensitivity Pts. with CAD	%	Specificity Pts. w/out CAD	%
2001	Elhendy (65)	Sestamibi/Tetrofosmin	0	183/240	76	67/92	73
1999	Azzarelli (66)	Tetrofosmin	66	199/209	95	20/26	77
1998	San Roman (67)	Sestamibi	0	54/62	87	21/30	70
1998	Budoff (68)	Sestamibi	0	12/16	75	12/17	71
1998	Santana-Boado (69)	Sestamibi	0	91/100	91	57/63	90
1998	Acampa (70)	Sestamibi	47	23/25	92	5/7	71
1998	Acampa (70)	Tetrofosmin	47	24/25	96	6/7	86
1998	Ho (71)	Tl-201	22	19/24	79	15/20	75
1997	Iskandrian (72)	Tl-201	21	717/820	87	120/173	69
1997	Candell-Riera	Sestamibi	0	53/57	93	32/34	94
1997	Yao (74)	Sestamibi	55	34/36	94	14/15	93
1997	Heiba (75)	Sestamibi	31	28/30	93	2/4	50
1997	Ho (76)	Tl-201	33	29/38	76	10/13	77
1997	Taillefer (77)	Sestamibi	17	23/32	72	13/16	81
1997	Van Eck-Smit (78)	Tetrofosmin	NR	46/53	87	6/7	86
1996	Hambye (79)	Sestamibi	0	75/91	82	28/37	75
1995	Palmas (80)	Sestamibi	30	60/66	91	3/4	75
1995	Rubello (81)	Sestamibi	57	100/107	93	8/13	61
1994	Sylven (82)	Sestamibi	37	41/57	72	5/10	50
1994	Van Train (83)	Sestamibi	19	91/102	89	8/22	36
1993	Berman (84)	Sestamibi/Tl-201	0	50/52	96	9/11	82
1993	Forster (85)	Sestamibi	0	10/12	83	8/9	89
1993	Chae (86)	Tl-201	42	116/163	71	52/80	65
1993	Minoves (87)	Sestamibi/Tl-201	42	27/30	90	22/24	92
1993	Van Train (88)	Sestamibi	16	30/31	97	6/9	67
1992	Quinones (89)	Tl-201	NR	65/86	76	21/26	81
1991	Coyne (90)	Tl-201	NR	38/47	81	39/53	74
1991	Pozzoli (91)	Sestamibi	19	41/49	84	23/26	88
1990	Kiat (92)	Sestamibi	45	45/48	94	4/5	80

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1990	Mahmarian (93)	Tl-201	43	192/221	87	65/75	87
1990	Nguyen (94)	Tl-201	NR	19/25	75	5/5	100
1990	Van Train (95)	Tl-201	35	291/307	95	30/64	47
1989	Iskandrian (96)	Tl-201	45	145/164	88	36/58	62
	Total			2971/3425		772/1055	
	Average				87		73

Another Functional Test?

Two Issues

- Accuracy of stress-tests
- Do literature reflect reality?

Biased Populations: Pre/Post-test referral bias

- Appropriate population are those with intermediate risk of CAD

  (i.e. exclude known prior MI, known prior CAD)

- Intermediate risk population?
    - Pre-test referral ("spectrum") bias
    - Post-test referral ("work-up") bias

    " *Sickest of the sick VS. the wellest of the well*"

Ransahaff et al, NEJM 1978

Rozanski et al, NEJM 1983

Biased Populations:
Pre-test referral (spectrum) bias

Factors Affecting Sensitivity and Specificity of a Diagnostic Test:
The Exercise Thallium Scintigram

- Meta-analysis, 56 publications on exercise thallium scintigraphy (1977 to 1986)

- 6,083 patients with catheterization correlation

- Multivariable analysis: *" the % of patients with prior MI (in each individual study) had the highest correlation with test sensitivity (0.45, P<0.001)"*

- Without vs. With MI: sensitivity, 17% lower

"Reported sensitivity of thallium scintigraphy is higher than that expected in clinical practice because of the presence of the inappropriate inclusion of post-infarct patients"

Detrano et al., Am J Med 1988

Biased populations:
Post-test referral bias

- Post-test referral ("work-up") bias
  - Extreme case:

  ..once the test used as the absolute "gate-keeper" to ICA

  "If only positive test responders sent to ICA, 100% sensitivity, 0% specificity..

  even if the test in question had a true sensitivity of 90% and a true specificity of 90%... because only positive test responders are catheterized"

  Ransohoff, NEJM 1978

Although exercise radionuclide ventriculography was initially reported to be a highly specific test for CAD, later studies reported a high false-positive rate. Why?

	Study Period		P-Value
	Early Period (1978-1979)	Recent Period (1980-1982)	
Angiographically Normal Patients	32	45	
Normal response rate	94% (EF) 84% (WM)	49% (EF) 36% (WM)	<0.001
Probability of CAD before testing	7%	38%	<0.001
Radionucleotide imaging before CAG	22%	78%	<0.001
Abnormal results	6%	55%	<0.001

2 factors are responsible for the temporal decline in specificity:
➜ a change in the population being tested **(pre-test referral bias)**
➜ a preferential selection of patients with a positive test response for CAG
(post-test referral bias)

Rozanski et al, NEJM 1983

Biased populations: Posttest referral bias

Post-test referral ("work-up") bias: Solutions

- Have patients with negative stress test get catheterization
- **Correction algorithms**
    - Assumption: Predictive values are constant for the catheterized and general population, thus the sensitivity and specificity can be corrected by knowing the proportion of abnormal SPECT test
        - Diamond method
        - Begg & Greenes method

Am J Cardiol 1986

Biometrics 1983

Biased populations:
Post-test referral bias

ACC/AHA PRACTICE GUIDELINES—FULL TEXT

ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging)

Non-invasive test before & after adjustment for referral bias

Year	Author	Modality	Total Patients	Sensitivity Biased	Sensitivity Adjusted	Specificity Biased	Specificity Adjusted
2002	Miller et al. (108a)	Exercise SPECT sestamibi/Tl-201	Overall: 1853	98	65	13	67
1998	Santana-Boado et al. (69)	Exercise/dipyridamole and SPECT sestamibi	Men: 100	93	88	89	96
			Women: 63	85	87	91	91
1996	Cecil et al. (108b)	Exercise SPECT Tl-201	Overall: 2688	98	82	14	59
1993	Schwartz et al. (282)	Tl-201	Men: 845	67	45	59	78
1986	Diamond (108c)	Exercise planar Tl-201	Overall: 2269	91	68	34	71

- 3/52 (6%) corrected for post-test referral bias
- 2 studies excluded prior MI, known CAD, and corrected for posttest referral bias

Miller et al. Am J Med 2002; Cecil et al., J Clin Epidemiol 1994

Noninvasive test before & after adjustment for referral bias
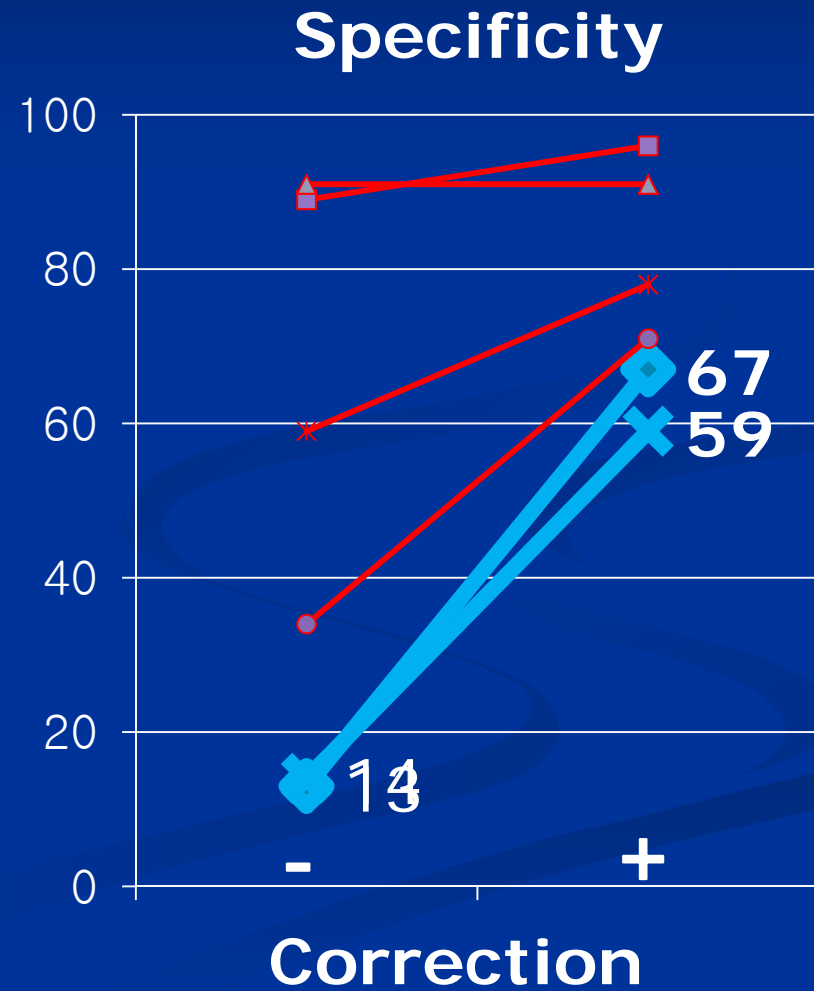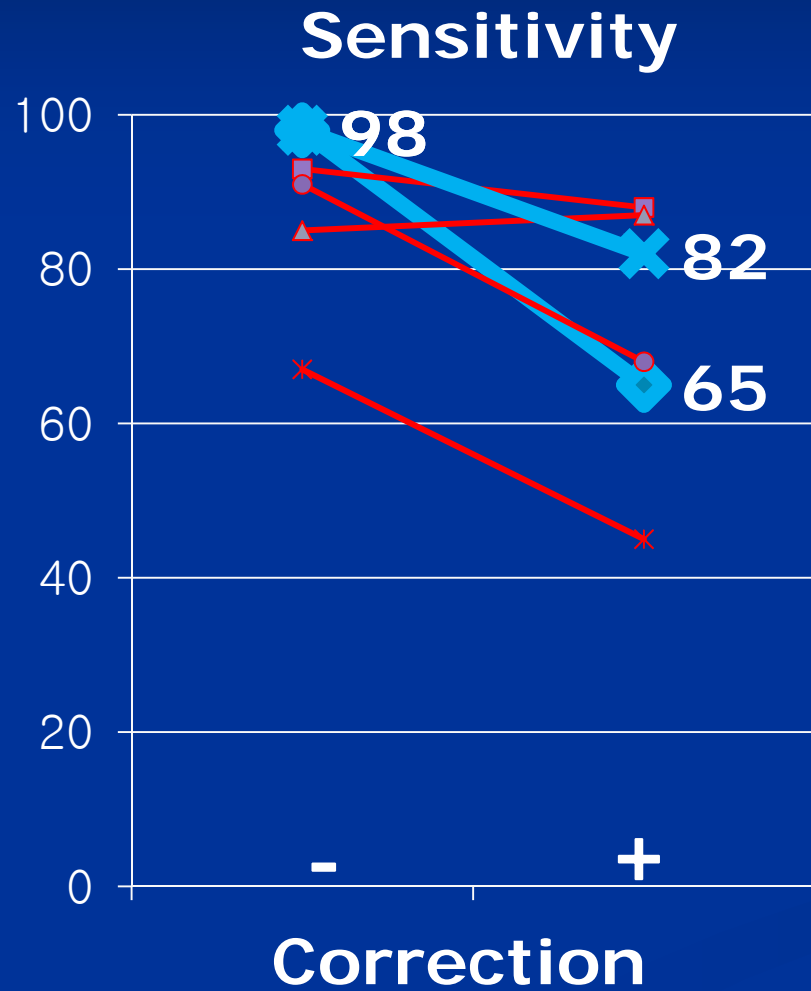
Another Functional Test ?
Summary

- Myocardial stress imaging
  - High rate of ICA with insignificant CAD
  - Accuracy of stress testing in appropriate population (intermediate pretest probability and after correction for posttest referral bias) is lower than literature summaries

→ *Non-invasive functional test: Not enough!*

Then…
What Test Should We Count On?

Inherent Relationship between Lumen and Flow

$$F = \frac{\Delta P}{R_s + R_b}$$

Gould KL. Circ. Res. 1985
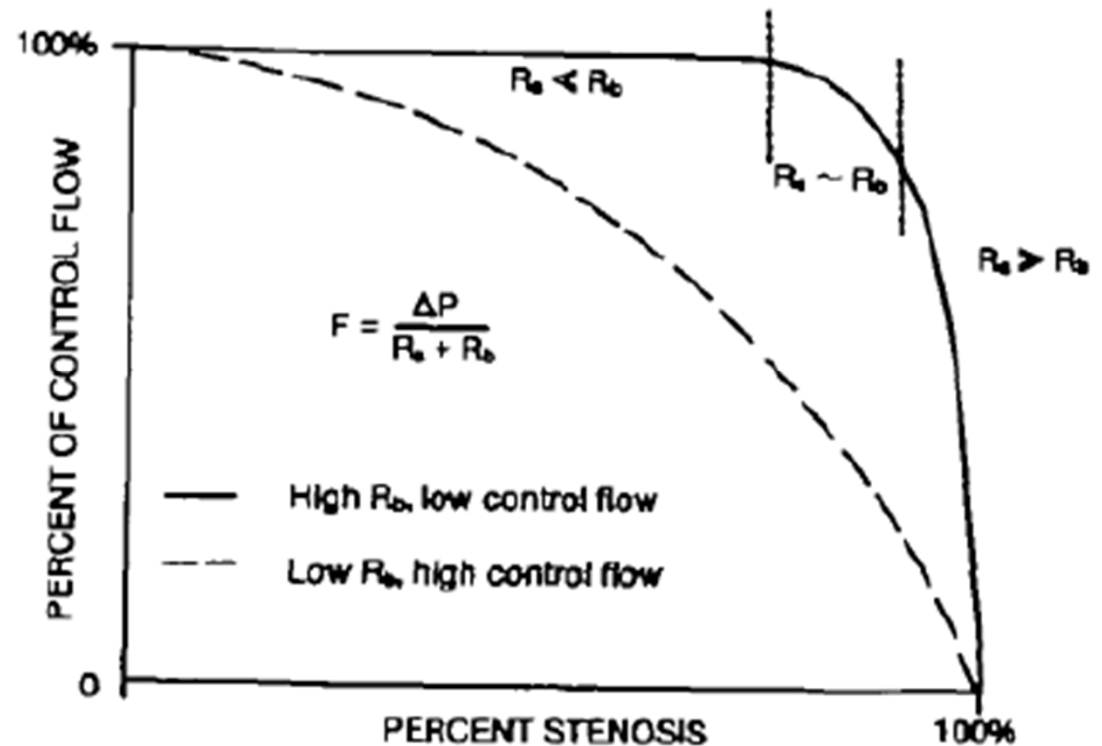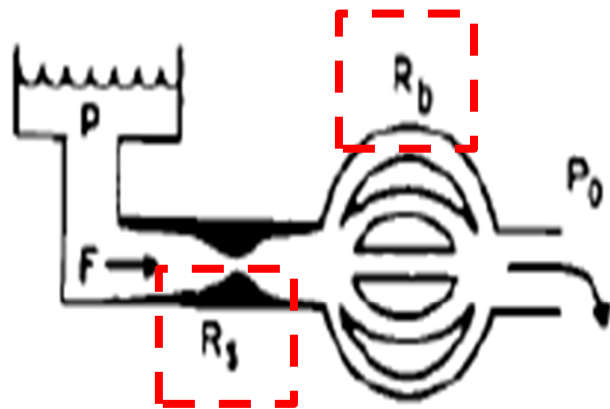
Inherent Relationship between Lumen and Flow

Flow is predominantly determined
by the smallest cross-sectional area
in the coronary bed: the Minimal Luminal Area (MLA)..

$$FFR = 1 - \frac{\rho v_o^2}{2P_o}\left(\frac{LA_{ref}^2}{MLA^2} - 1\right)$$
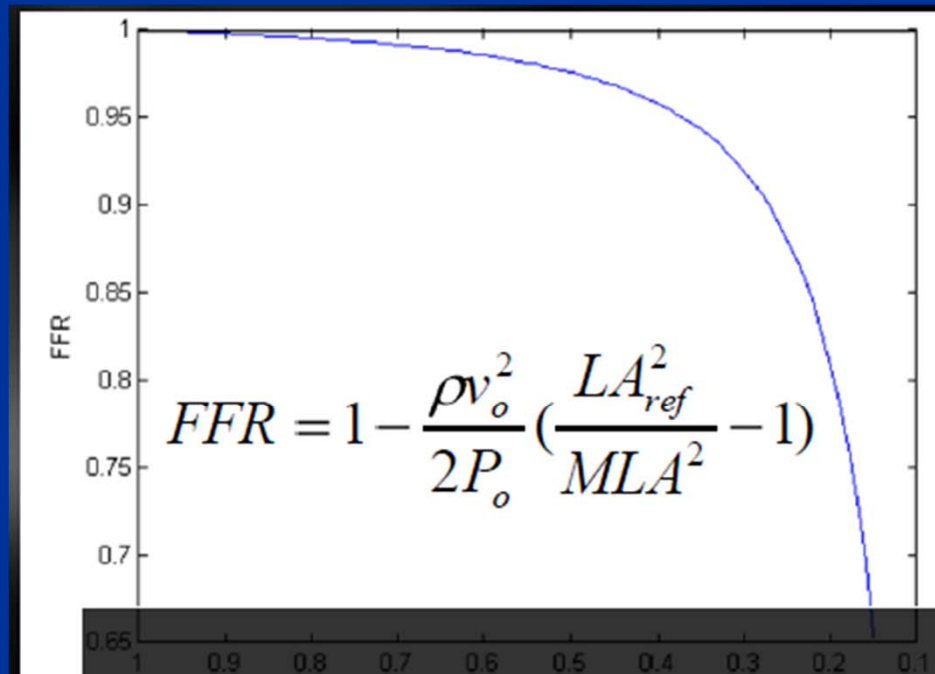
...ANATOMY DETERMINES PHYSIOLOGY...

We can measure the lumen
in non-invasive manner

- **If we can measure the lumen, we can predict physiology!**

- MLD: % DS
  (2D concept, XA)
- MLA: % area stenosis
  (IVUS, CCTA)
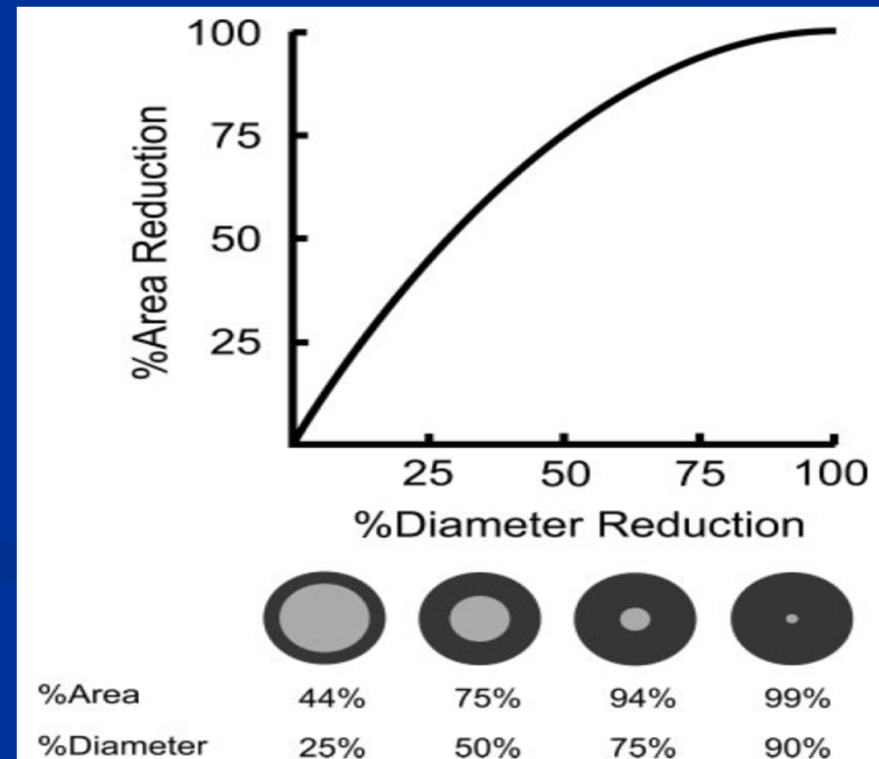
Diagnostic Performance of CCTA
Diagnosis of obstructive CAD
compared to other modalities

Test	Sensitivity	Specificity
Exercise ECG treadmill[1]	68%	77%
Exercise Echo treadmill[2]	86%	81%
Dobutamine Echo[2]	~85%	~85%
Exercise nuclear treadmill[3]	87%	73%
Pharmacologic nuclear[3]	89%	75%
Coronary CTA[4]	**95%**	**83%**

1. ACC/AHA 2002 Guideline Update for Exercise Testing
2. ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography
3. ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging
4. ACCURACY study
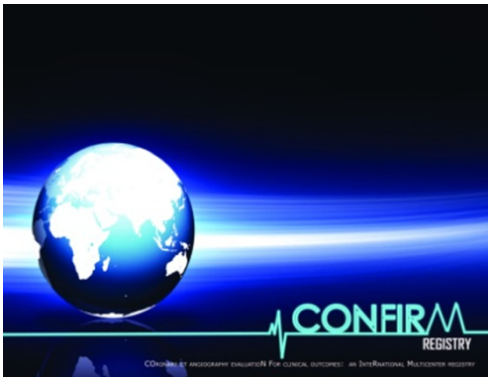
Prognostic Value of CCTA
KM Survival by Per-Vessel Obstructive CAD

5-year NPV for death 99%

Normal

Non-Obstructive
p<0.0001

1-Vessel CAD
p<0.0001

2-Vessel CAD
p<0.001

3-Vessel/Left Main
p<0.0001

Survival Probability vs. Survival Time (Years)
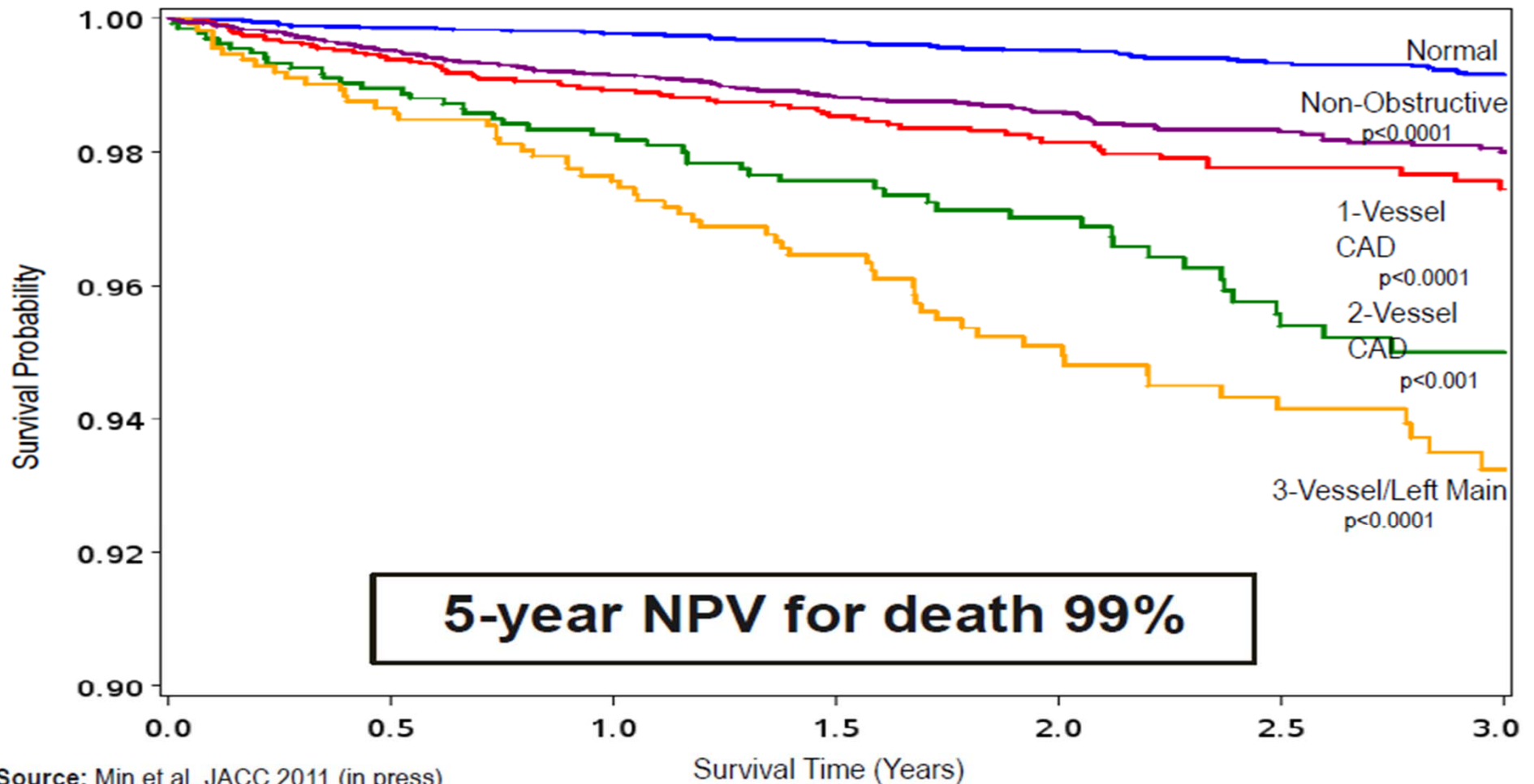
Source: Min et al. JACC 2011 (in press)

Prognostic Value of CCTA applies to individuals with mild CAD

❖ 2,583 consecutive patients undergoing CCTA with ≤50% stenosis

Min JK, et al, ACC 2011

Cost & clinical outcome of CCTA compared to functional study

>10 million insured lives

142,535 individuals underwent CCTA or SPECT

CCTA (n=3676)

SPECT (n=138,859)

Matched CCTA (n=2313)

Matched SPECT (n= 9,252)
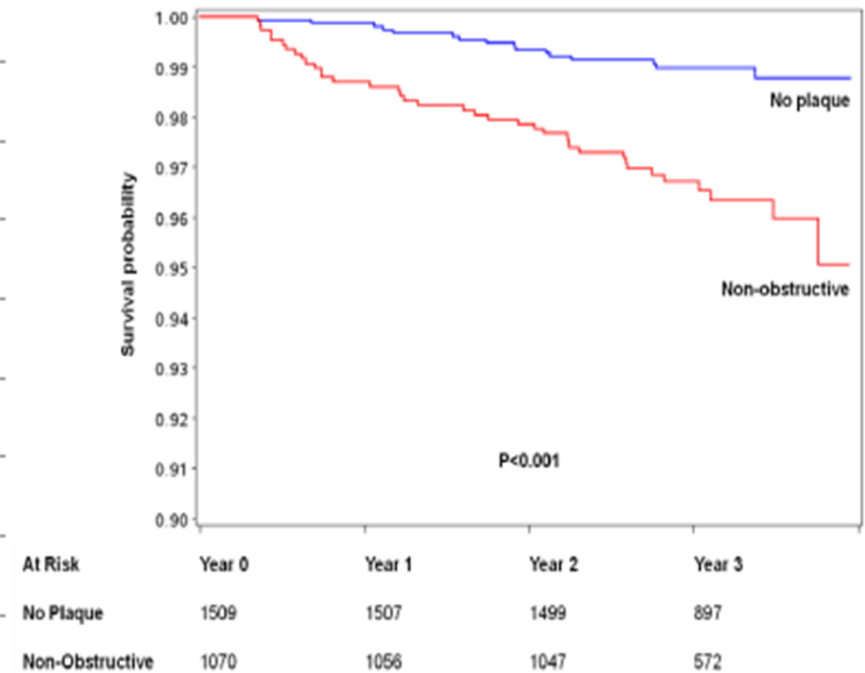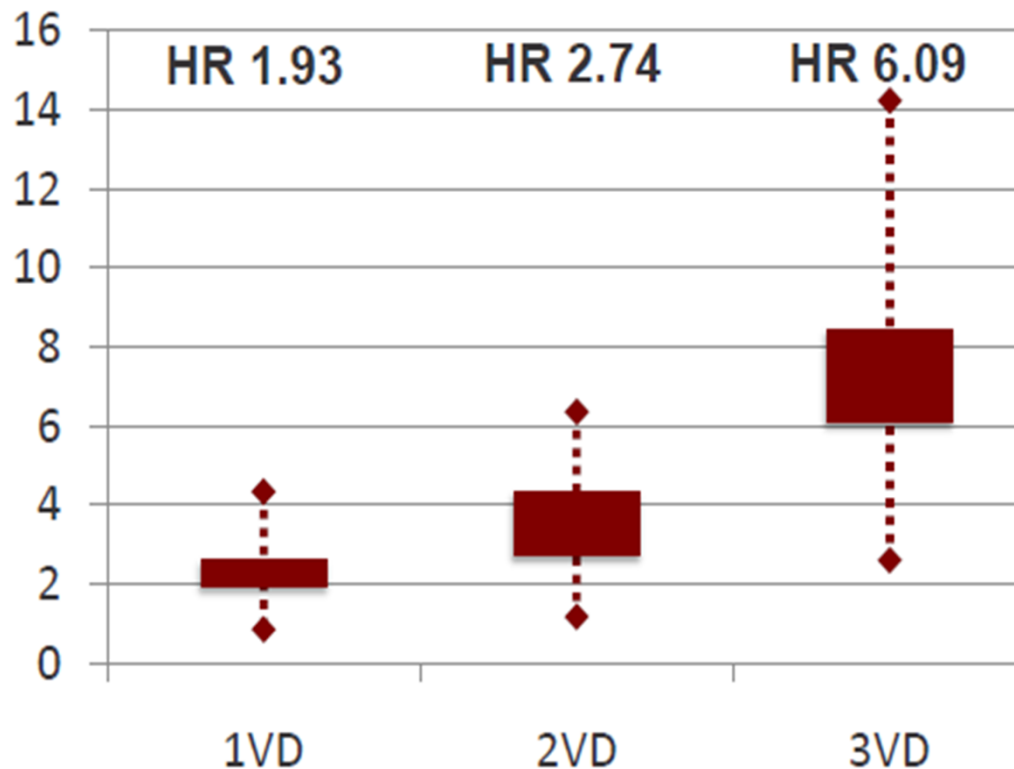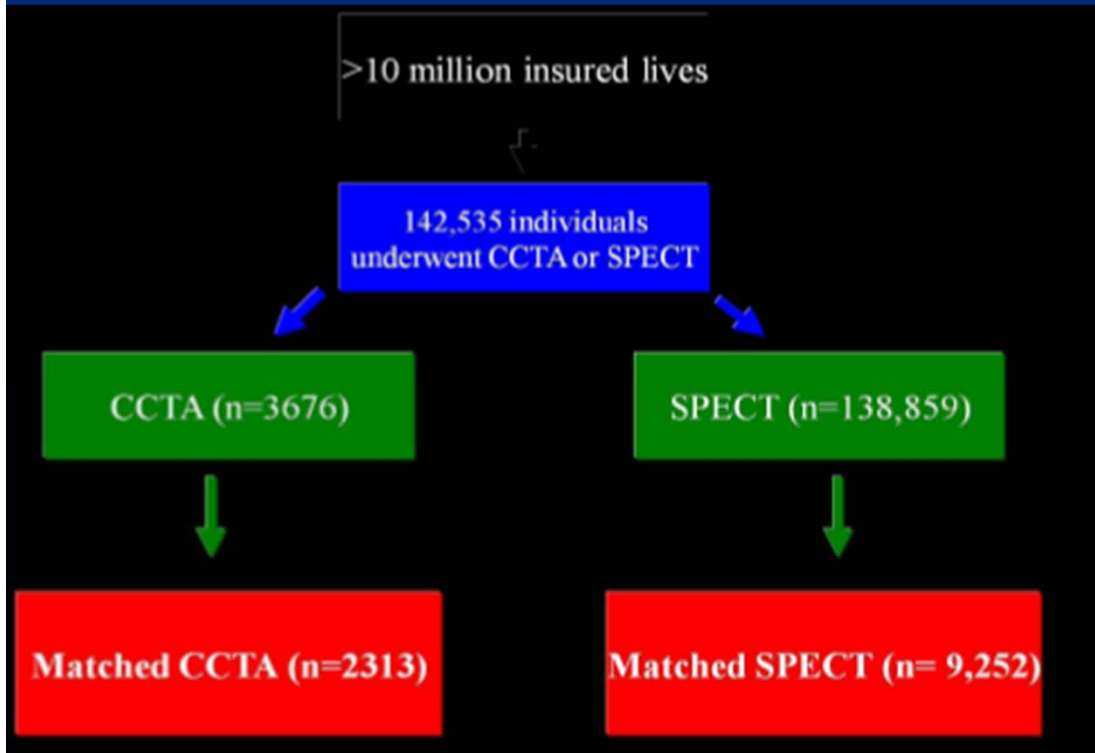
HEALTHCARE COSTS:
- --Additional testing
- --Medical therapies
- --Interventional therapies
- --CAD-related hospitalization

CLINICAL OUTCOMES:
- --Myocardial infarction
- --Angina
- --CAD-related hospitalization
- --CAD-related outpatient visits

Multi-center study of 142,535 patients undergoing

CCTA vs. MPS: Cost and clinical outcomes

Min JK, et al, AJC 2008

Cost & clinical outcome of CCTA compared to functional study

■ CCTA ■ MPS

CCTA: Greater rates of medications for primary prevention of CAD events

Aspirin — 21.8, 8.1 — P=0.04

Statin — 6.9, -3.5 — P=0.03

Beta blocker — 4.6, 0 — P=0.25
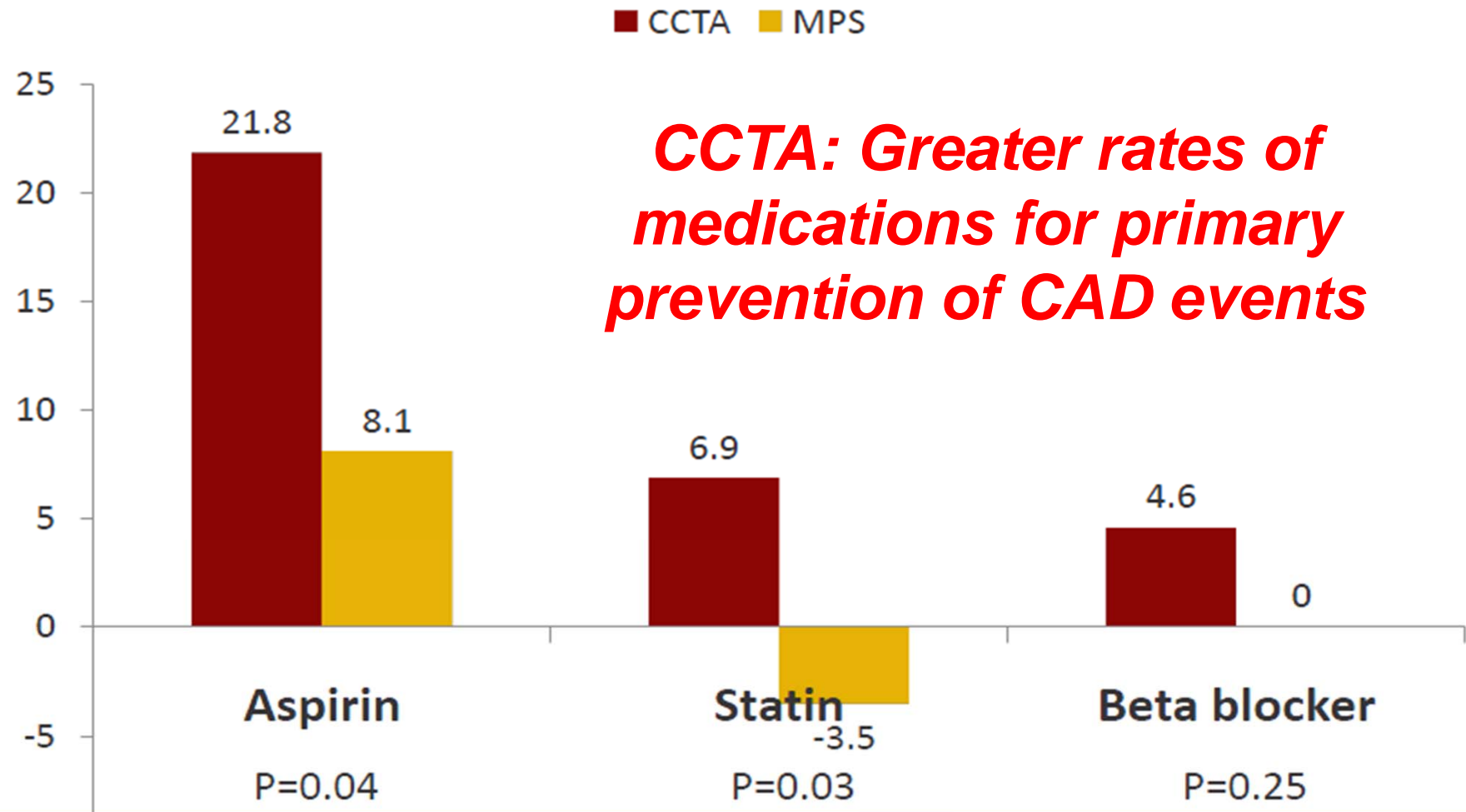
Cost & clinical outcome of CCTA compared to functional study
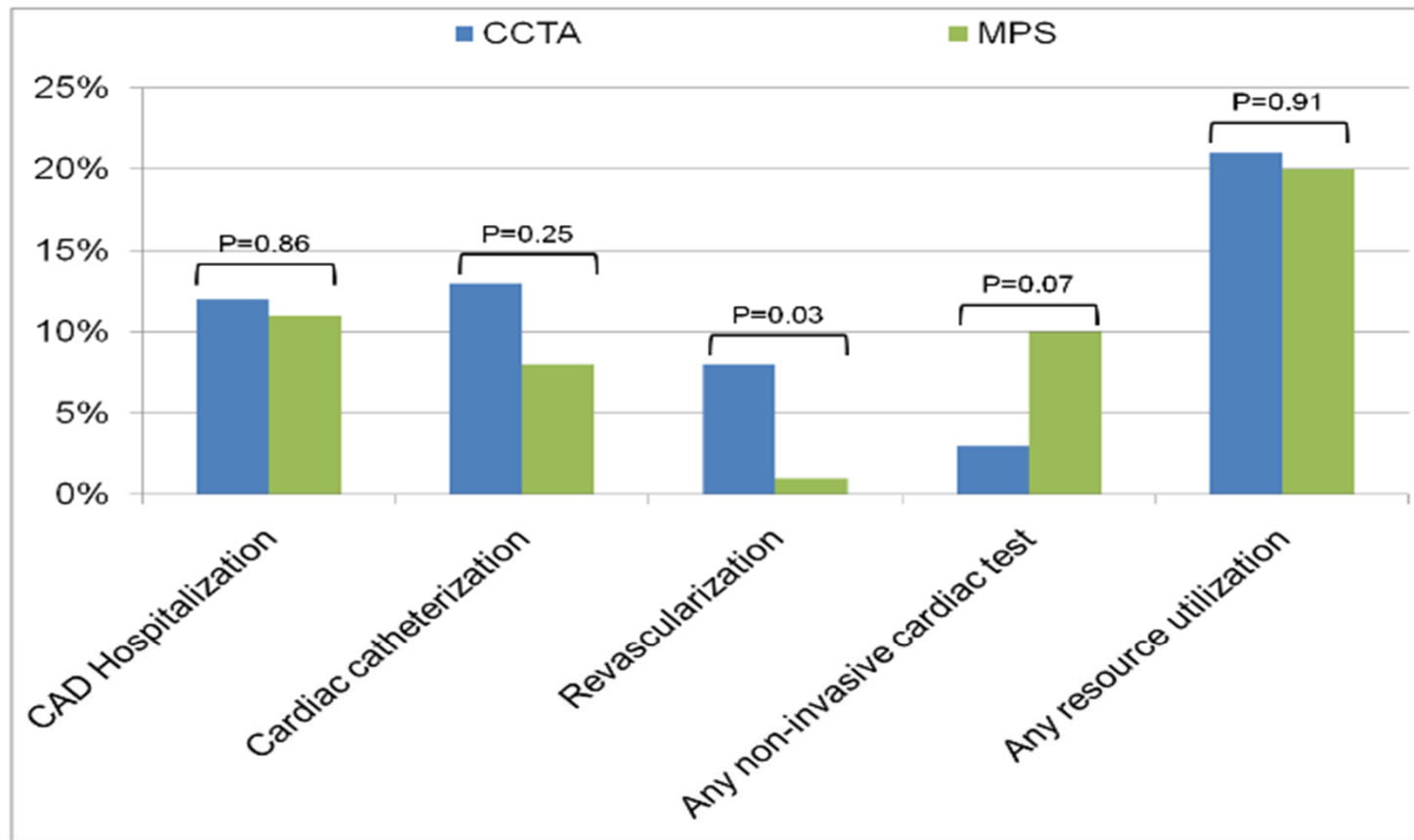
➤ No differences in angina-specific (SAQ) or general QoL (EQ5D)

Cost & clinical outcome of CCTA compared to functional study

Similar incurred costs between CCTA and MPS
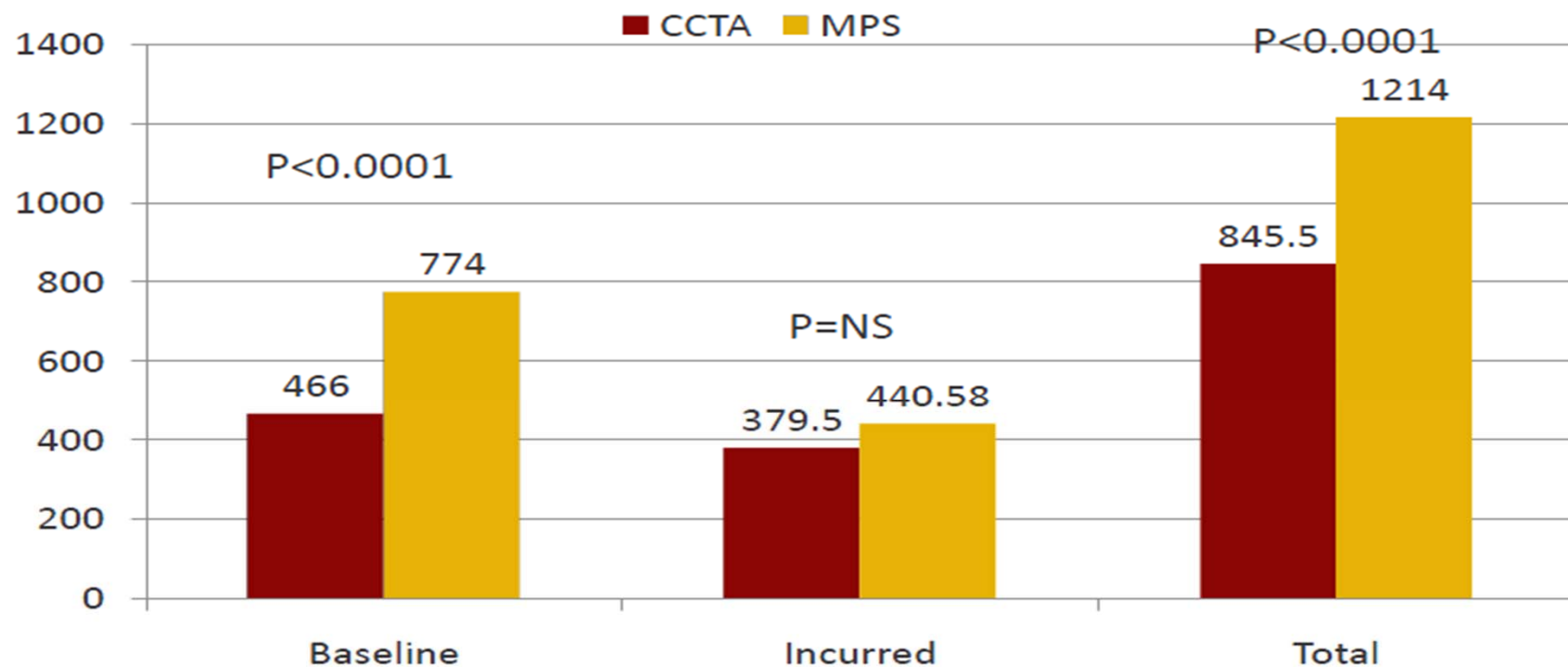
CT STAT Trial:
Efficiency, Cost, and Safety in Acute Chest Pain

Figure 1 - Study Algorithm
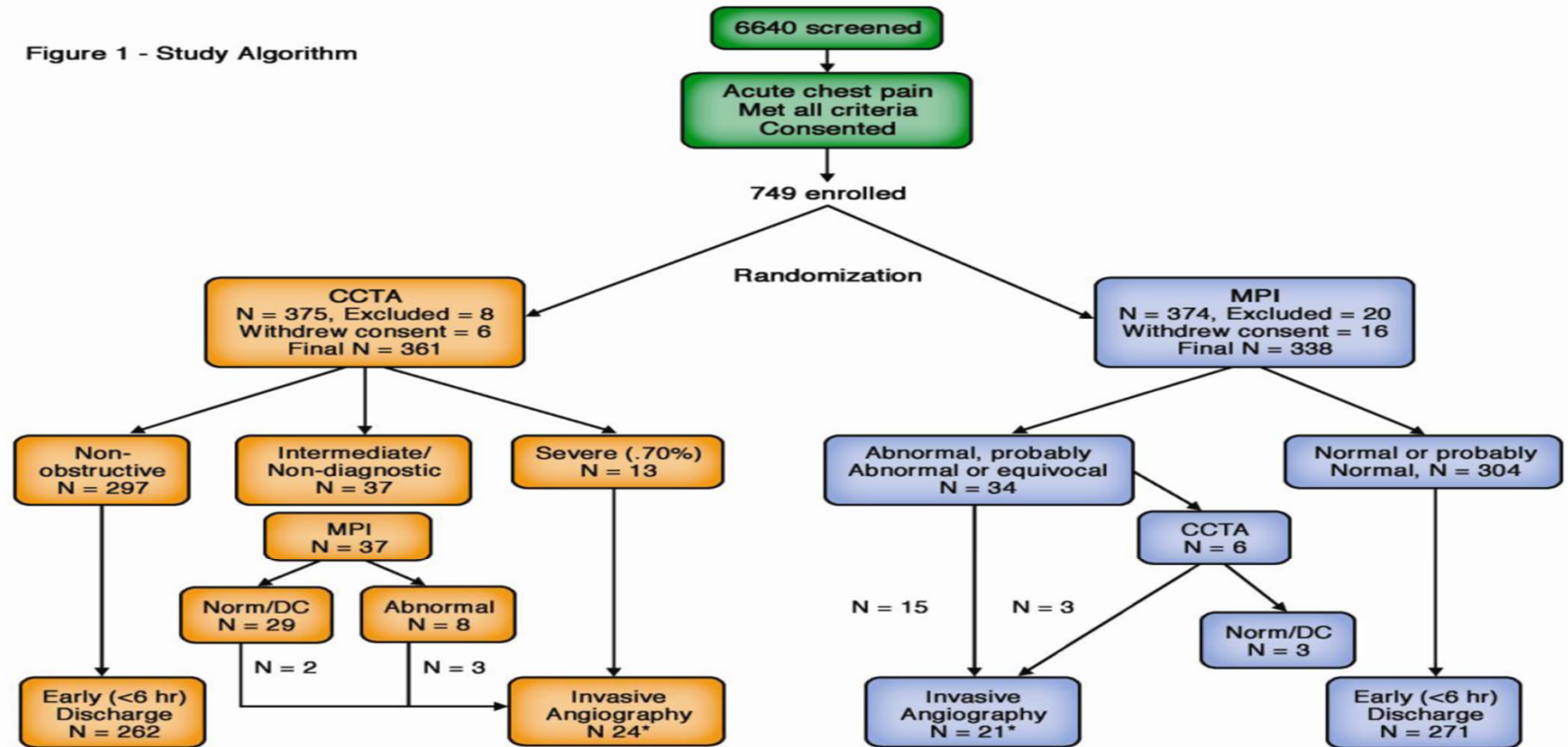
CT STAT Trial
Study outcomes: Efficiency, Cost, and Safety

	CCTA Group N=361	MPI Group N=338	P Value
Time-to-diagnosis (hours) Median (25th, 75th percentile)	2.9 (2.1, 4.0)	6.2 (4.2, 19.0)	<0.0001
Total ED costs (dollars) Median (25th, 75th percentile)	2137 (1660, 3077)	3458 (2900, 4297)	<0.0001
MACE events in patients With normal index test	2/268 (0.8%)	1/266 (0.4%)	0.29

Raff et al. JACC 2011

CCTA
Refining Risk Prediction Through Plaque   Imaging:

Plaque Quantitation

Plaque quantifitation: Volume
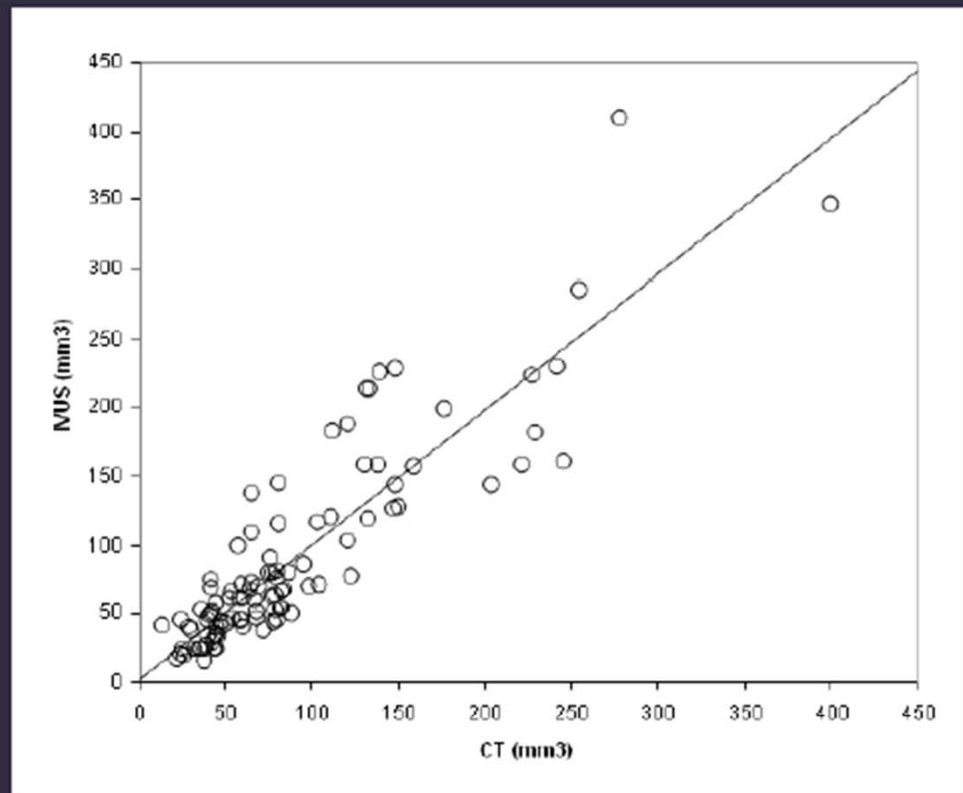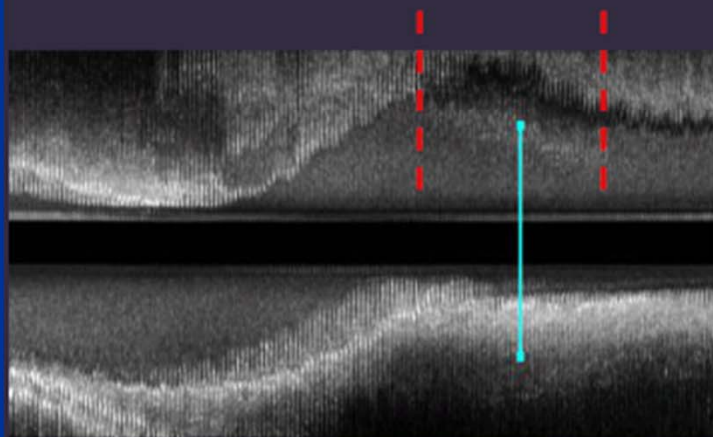
100 Plaques, CT vs. IVUS

Schepis et al, r = 0.9

Plaque Characterization by CCTA

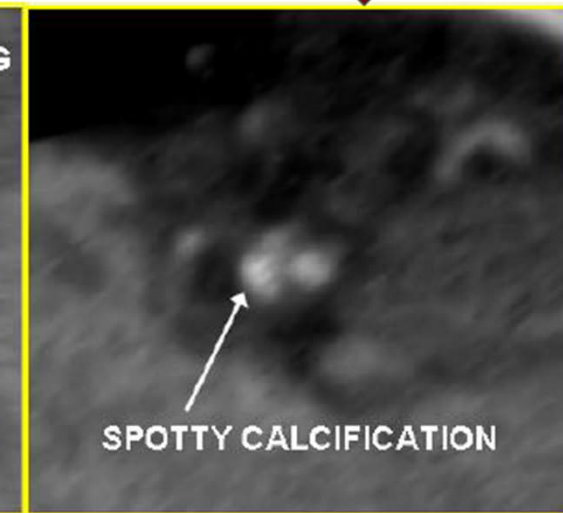47 patients with CCTA and MPS within 6 months without coronary intervention and with % Diameter stenosis = 70-89%
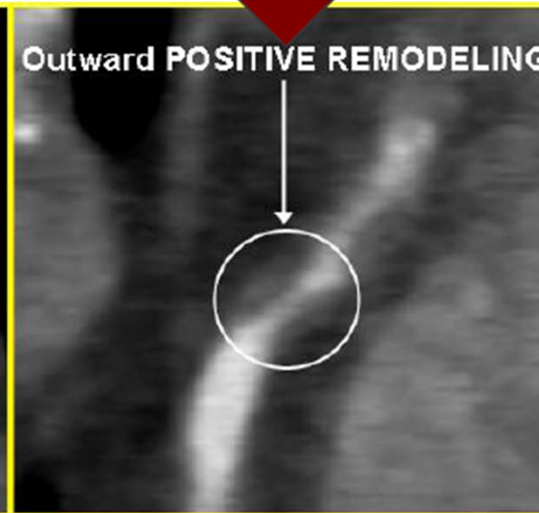
Low Attenuation Core
Tissue attenuation ≤40 HU
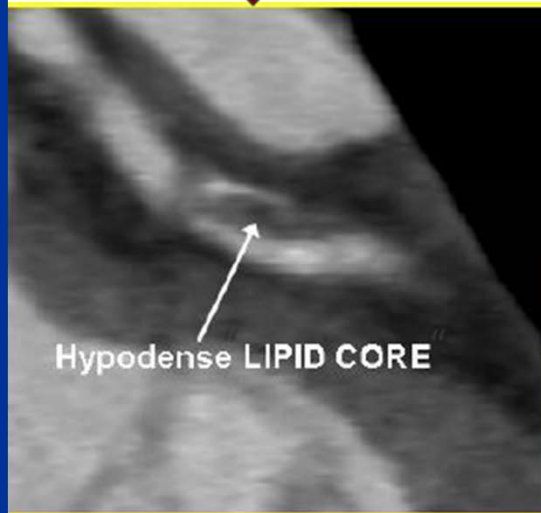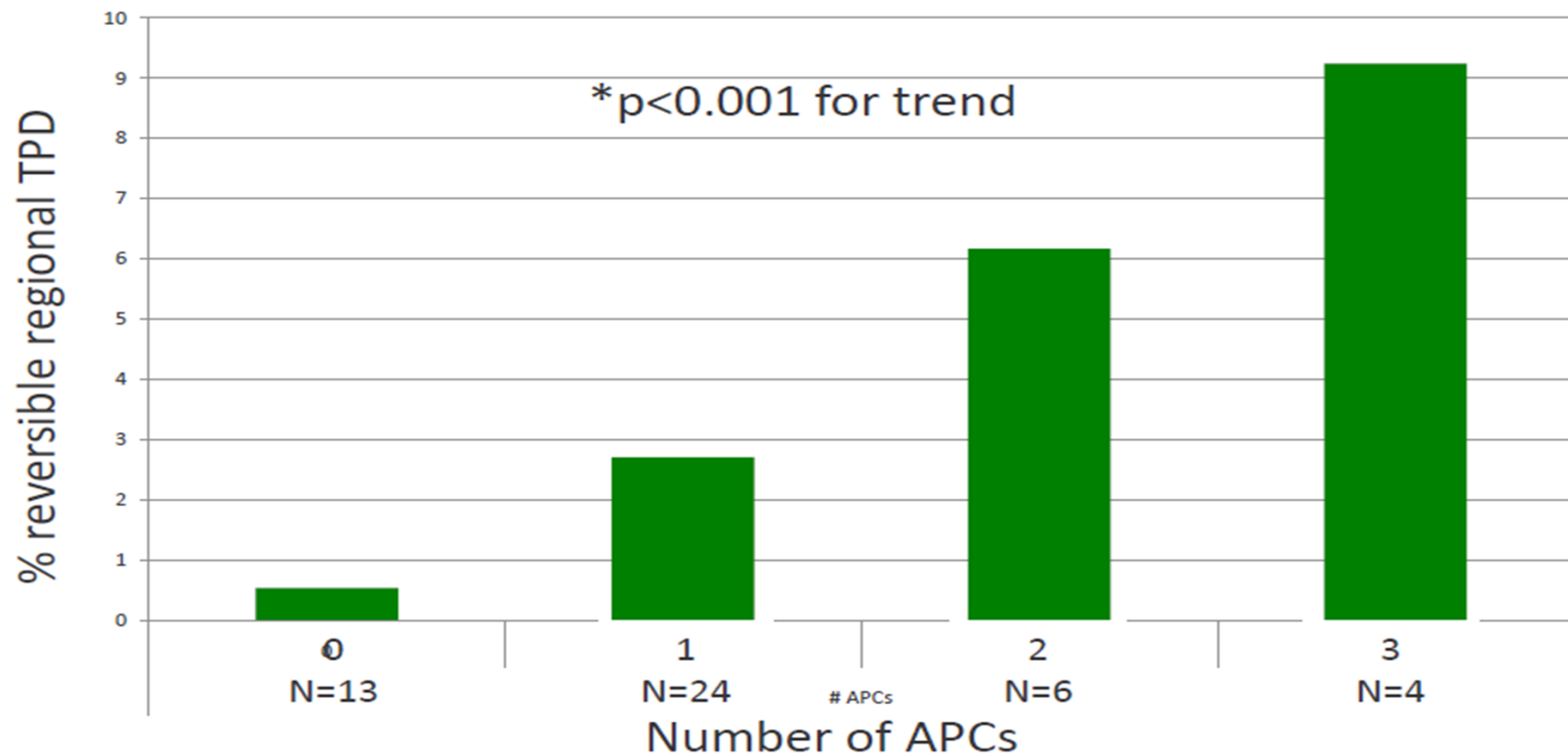
Spotty Calcification
Speckle of Ca ≤3 mm & ≤90

Positive remodeling
Diseased/normal diameter ratio ≥5%

Hypodense LIPID CORE

Outward POSITIVE REMODELING

SPOTTY CALCIFICATION

Shmilovich et al. J Nucl Med. 2010

Plaque Characterization by CCTA

%revTPD related to number of APCs:

*p<0.001 for trend

y-axis: % reversible regional TPD (0 to 10)

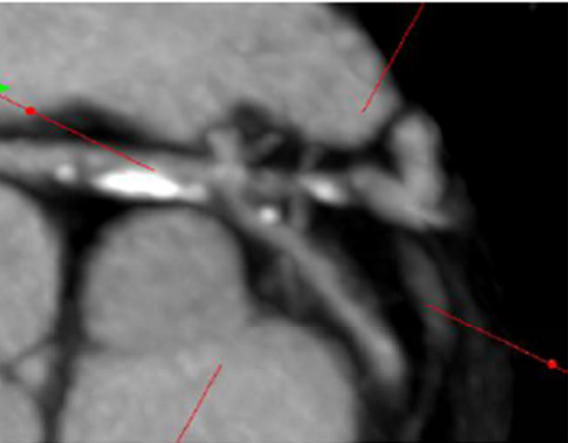x-axis: Number of APCs

# APCs	0	1	2	3
	N=13	N=24	N=6	N=4

revTPD: reversible total perfusion defect
APC: Adverse plaque characteristics

Shmilovich et al. J Nucl Med. 2010
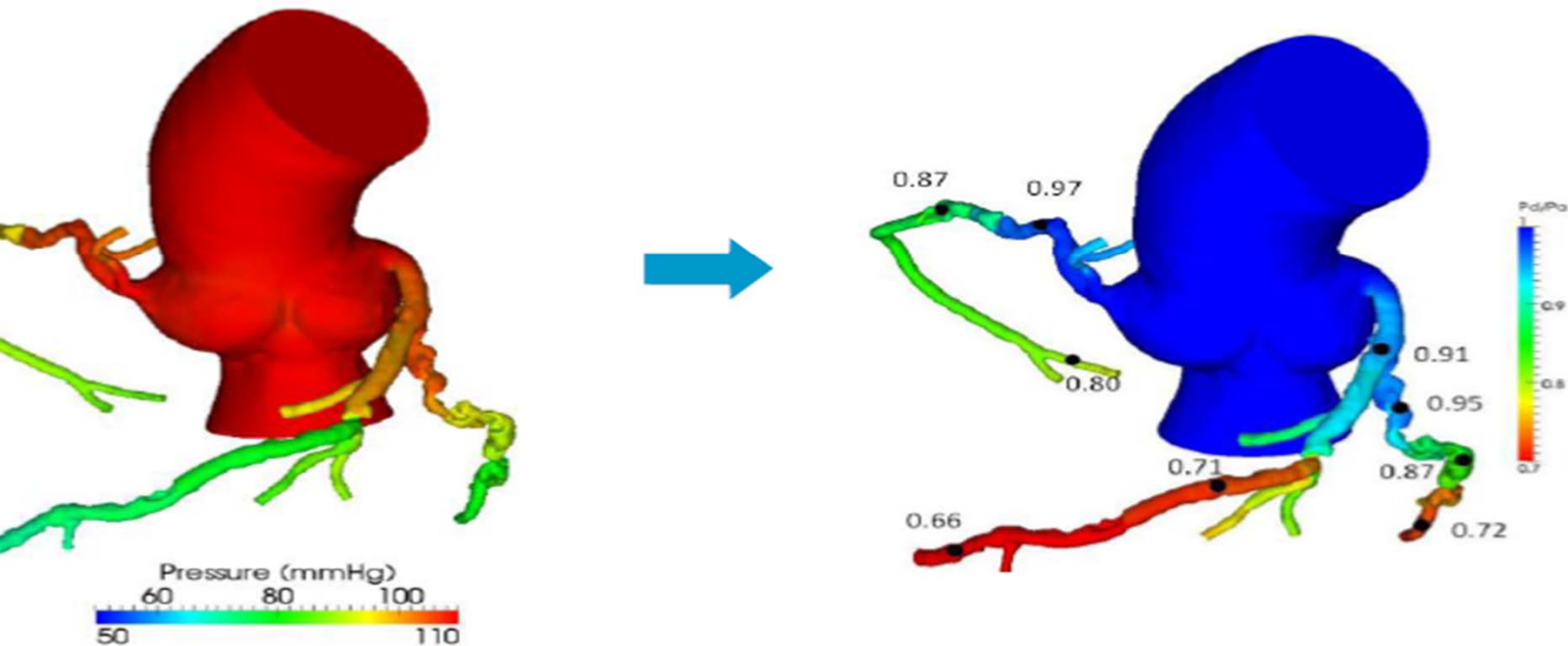
ase#1: LAD (Equivocal CCTA, Positive cFFR)
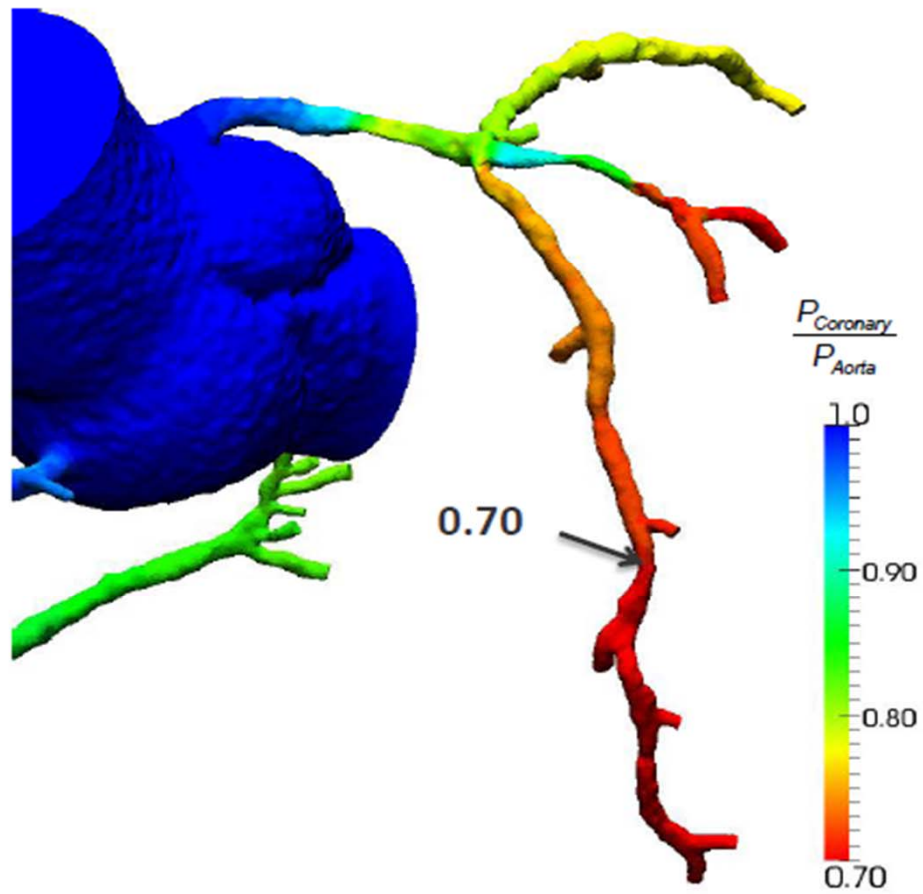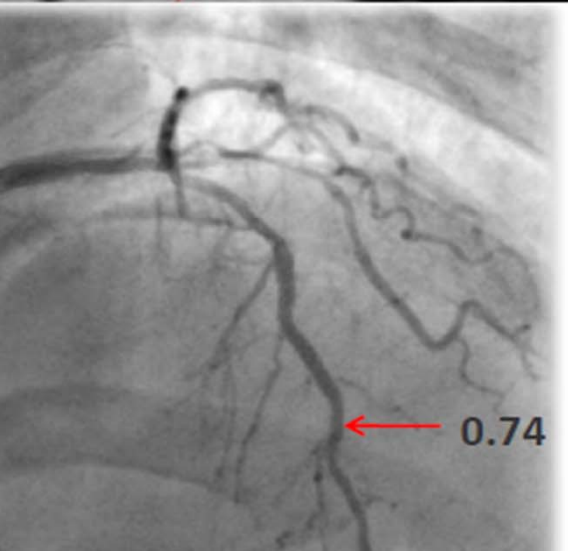
The DeFACTO Trial

(Determination of Fractional Flow Reserve by Anatomic Computed TomographicAngiOgraphy)

The DeFACTO study will be a prospective, 20-center study of 238 patients to evaluate the **diagnostic performance of CCTA plus CT-FLOW for detection and exclusion of HD-significant coronary artery disease** (CAD), as defined by invasive FFR as the reference standard

Enrollment began in 11/10

Summary

Functional test has limitations:

- High rate of invasive angiography with insignificant CAD

- Accuracy of stress testing in appropriate population is lower than literature summaries

Anatomic test with CCTA

• High diagnostic performance for detection and exclusion of angiographically-obstructive CAD

• Significant improvements in CT technology enhance diagnostic performance and prediction of prognosis.