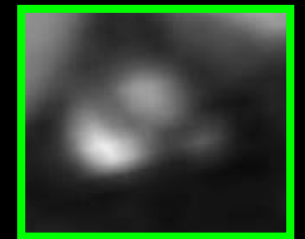
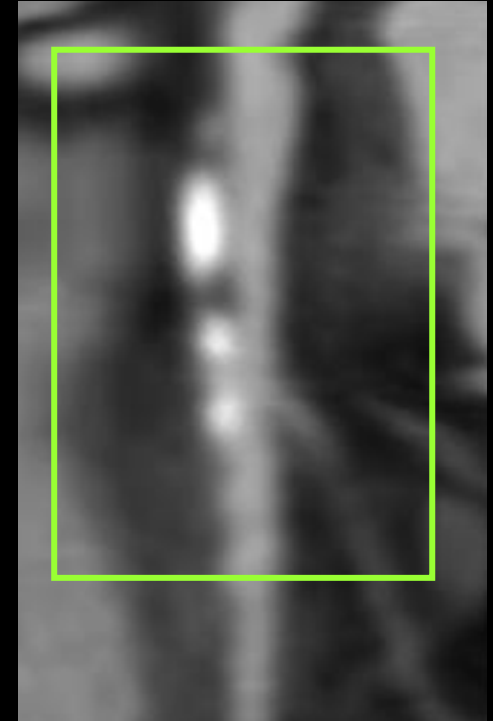
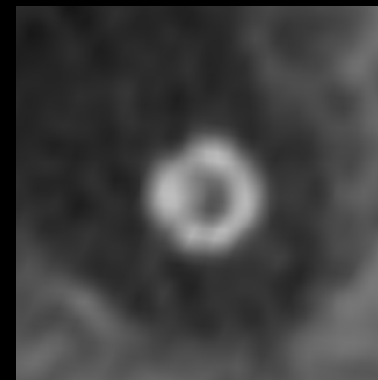
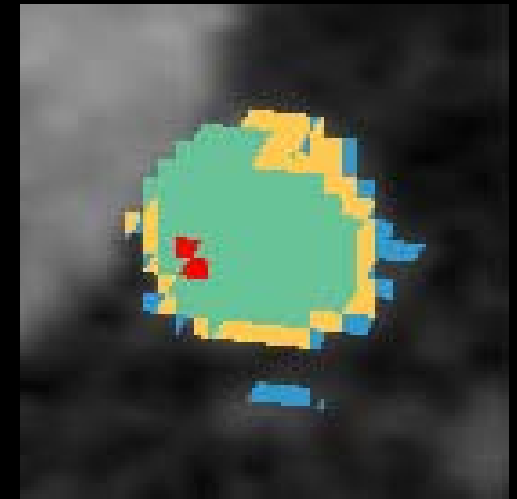
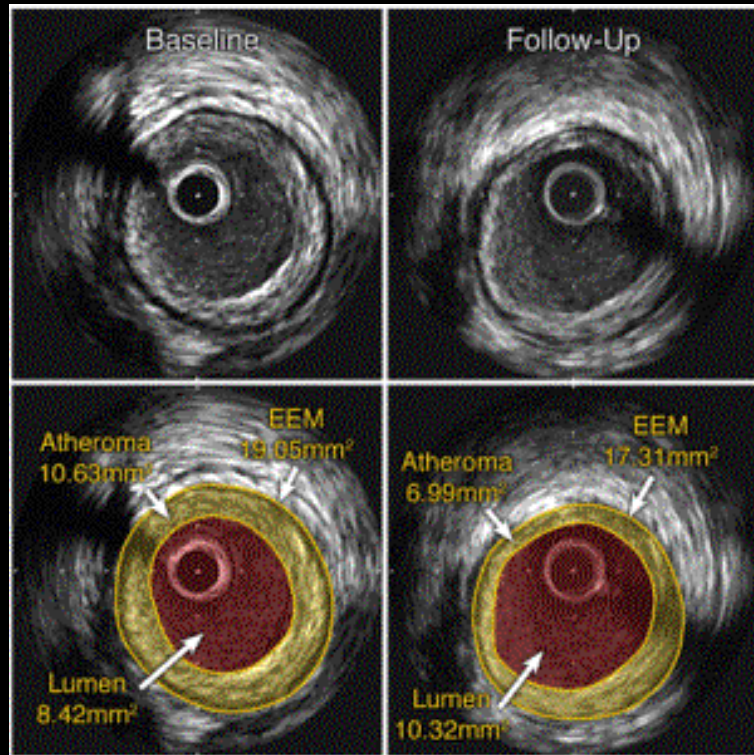

Detection of Vulnerable Plaque: Non-Invasive Imaging Is More Clinically Relevant

**James K. Min, MD FACC
Assistant Professor of Medicine and Radiology
Cornell University Medical Center
The New York Presbyterian Hospital**

Can non-invasive methods effectively image "vulnerable" plaques?

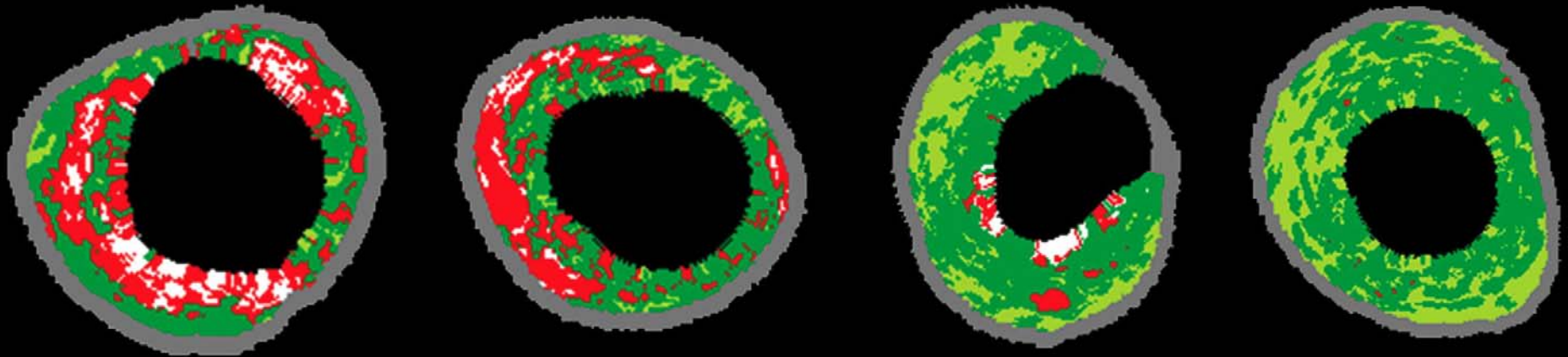


No.



- ✓ Spatial resolution
- ✓ Temporal resolution
- ✓ Plaque composition

Non-invasive imaging does not have the ability to identify important plaque features.



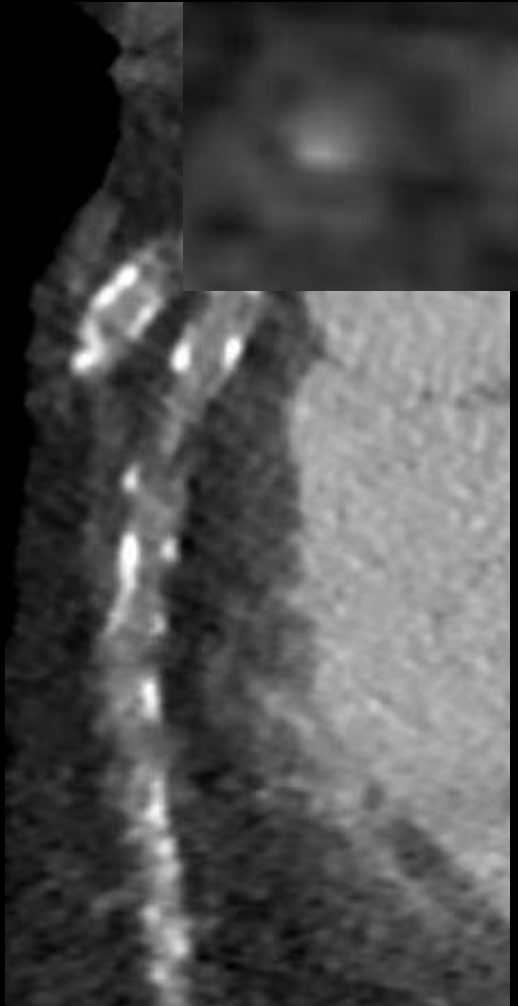
- Thin cap fibroatheroma
- Necrotic core
- Plaque rupture
- Plaque erosion
- Calcified nodule

Why is non-invasive imaging preferable for assessing 'at-risk' individuals?

REASON #1:

Non-invasive imaging offers
measure of overall coronary
artery plaque burden.

Plaque Characteristics by CCTA



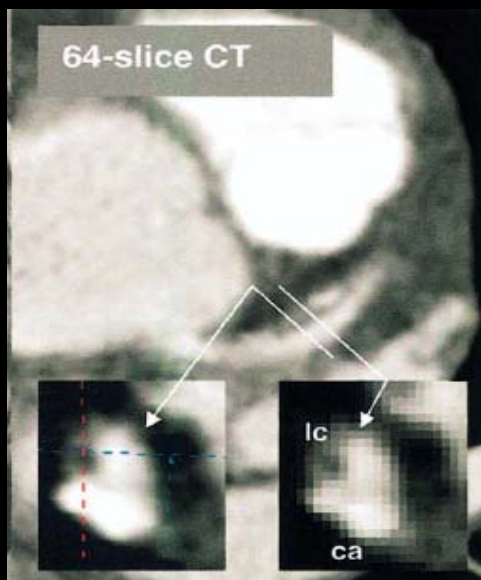
	Sensitivity	Specificity	PPV	NPV
ACCURACY	94	83	48	99
<i>N=230, Stable Chest Pain; No known CAD; No exclusion (CACS, HR, BMI); CAD prevalence 13%</i>				
CorE64	85	90	91	83
<i>N=291, Stable Chest Pain; No known and Known CAD; Exclusion CACS>600; CAD prevalence 56%</i>				
Meijboom	99	64	85	97
<i>N=360, Acute and Stable Chest Pain; No known CAD; CAD prevalence 68%</i>				

	Detected	Not Detected
Plaque thickness	1.5 ± 0.3 mm	0.9 ± 0.3 mm
Vessel size (EEM CSA)	4.5 ± 1.2 mm	3.6 ± 1.1 mm
% Plaque cross-sectional area	42 ± 16%	22 ± 5%

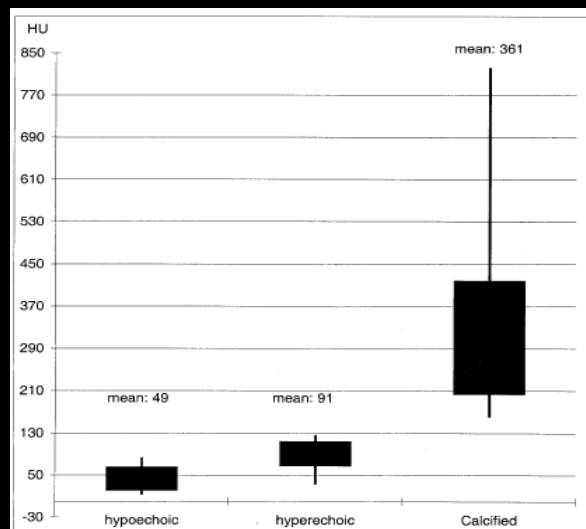
n < 0.05 for all categories.

Plaque Features by CCTA

Volume (+/-)



Composition (+/-)

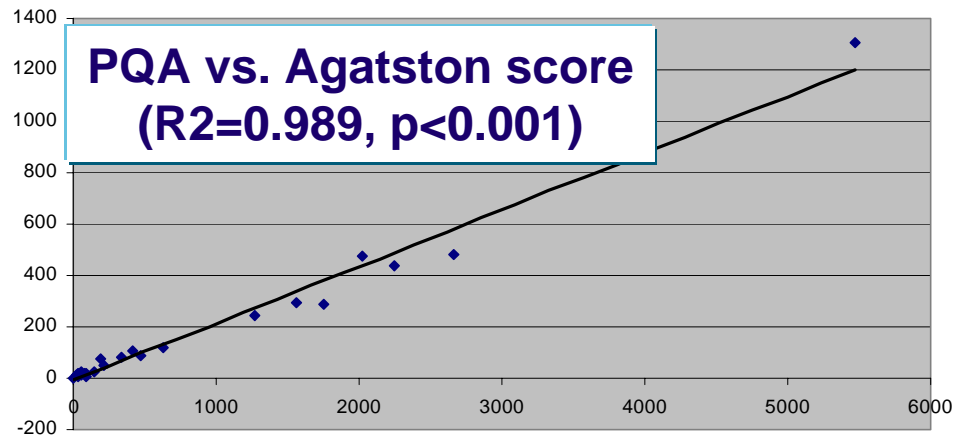
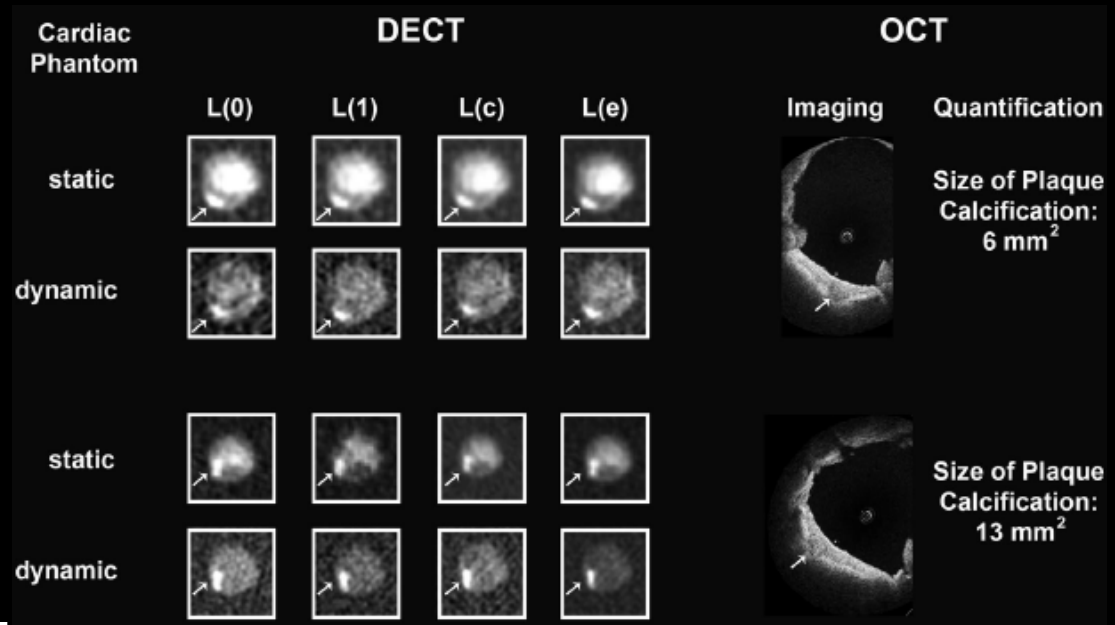
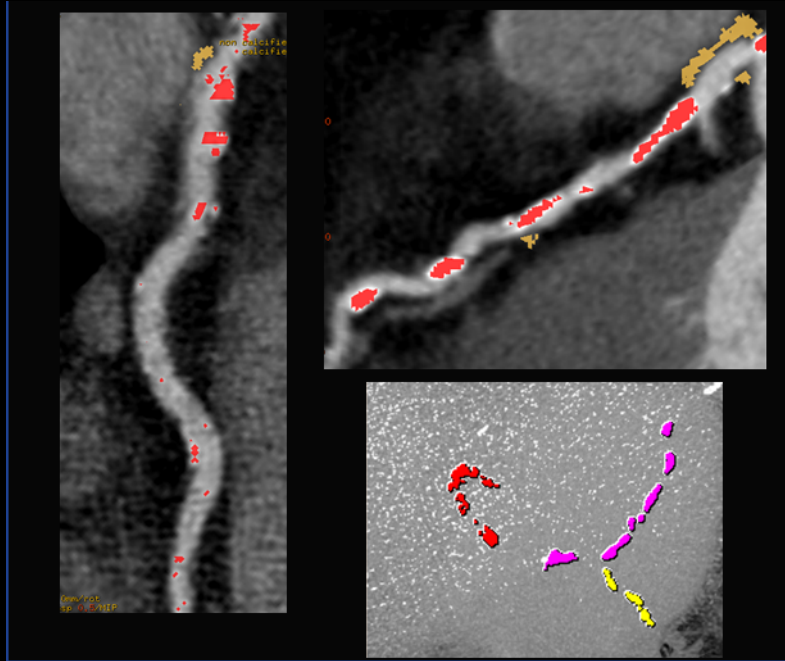


Remodeling (+)



- **Plaque volume/vessel $r^2=0.69$, $p<0.001$**
 - **Underestimates non-calcified**
 - **Overestimates calcified**
- **Interobserver variability**
 - **Any plaque ($\kappa = 0.75$)**
 - **Plaque volume ($\kappa = 0.37$)**
- **Overlap of HU for fibrous, and lipioid**
- **Remodeling generally high agreement**

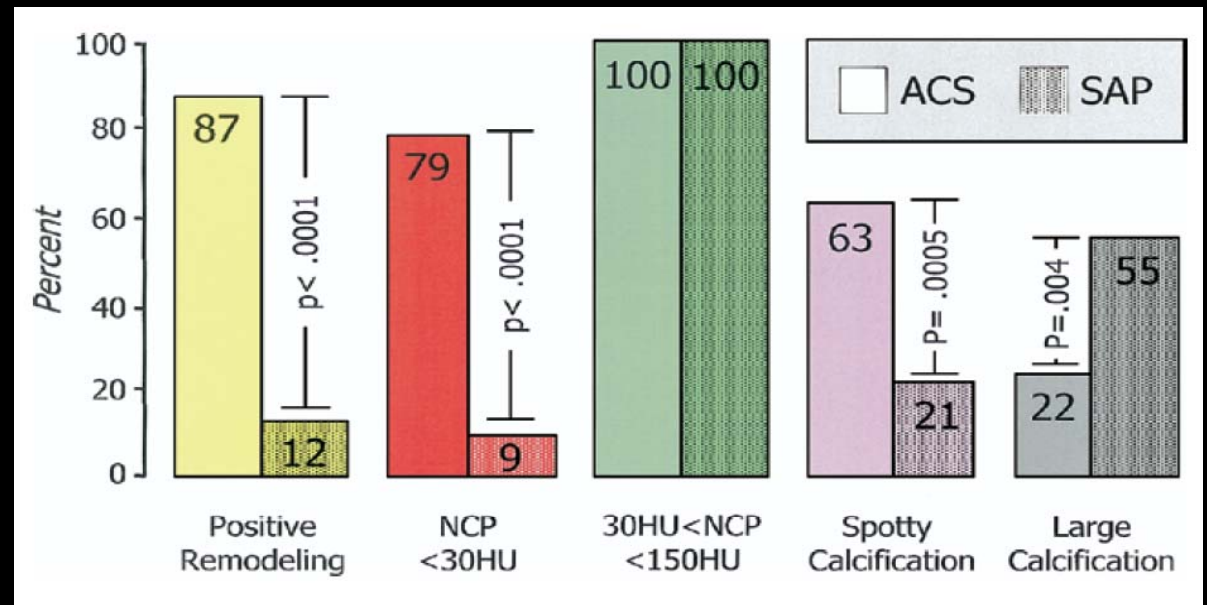
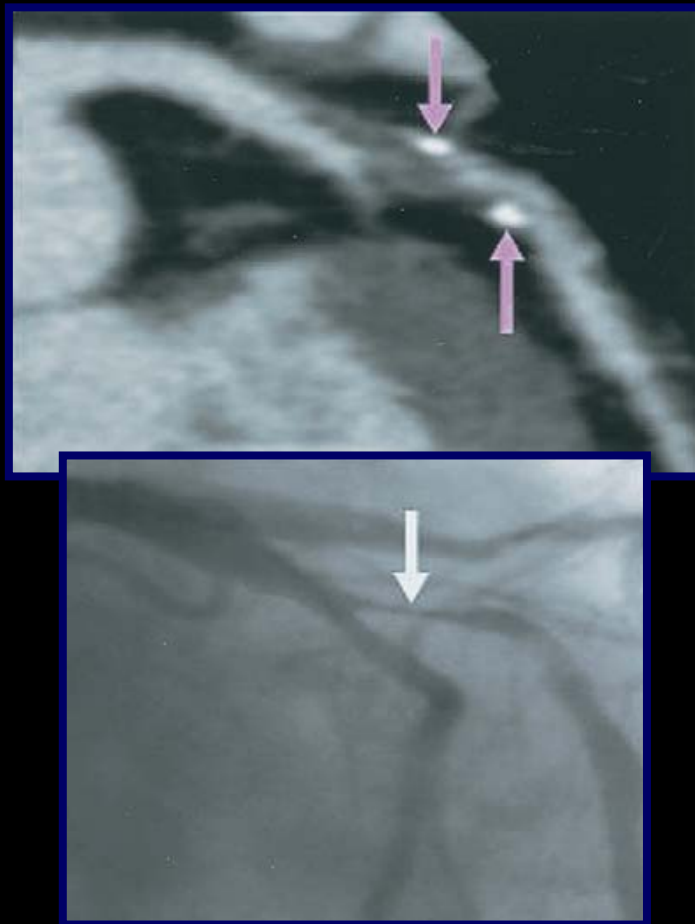
Plaque features by CCTA



Dual Energy CCTA

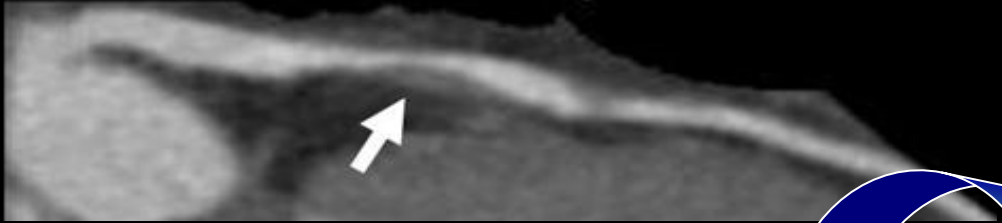
CCTA Characteristics of Coronary Lesions in ACS

38 pts with ACS and 33 pts with SAP prior to PCI studied by CCTA.

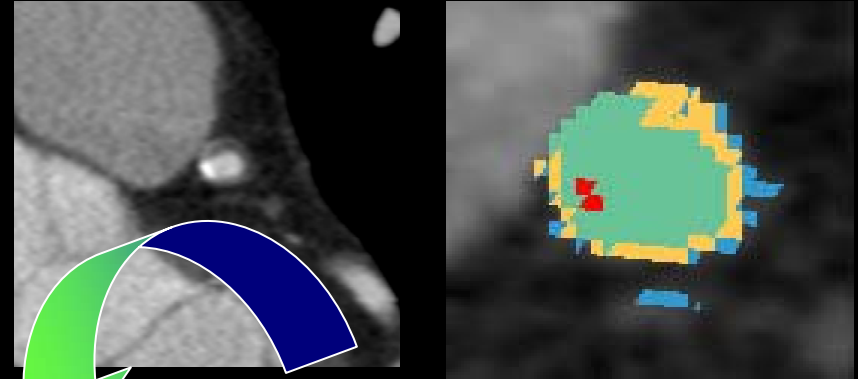


Positive remodeling, NCP <30 HU and spotty calcification more frequent in culprit ACS lesions than SAP.

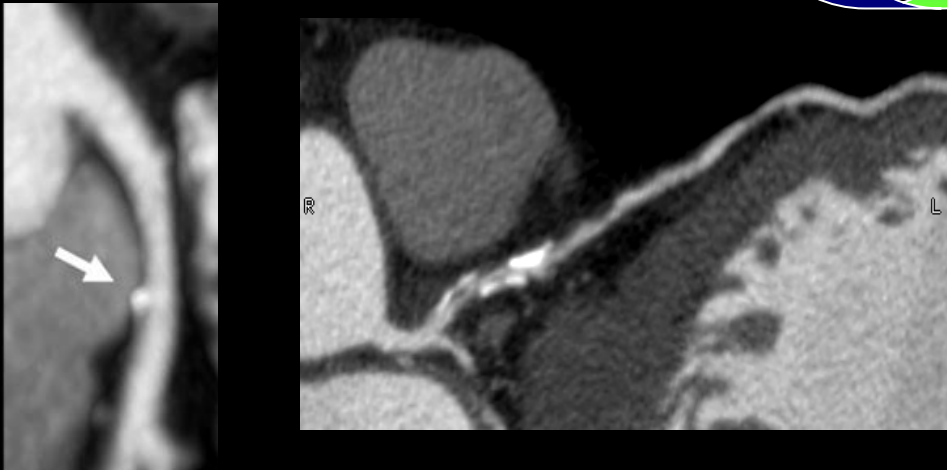
PLAQUE SEVERITY/VOLUME



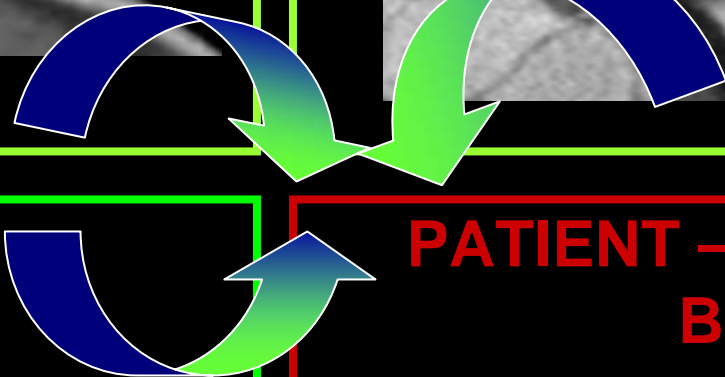
PLAQUE COMPOSITION/REMODELING



PLAQUE LOCATION/DISTRIBUTION



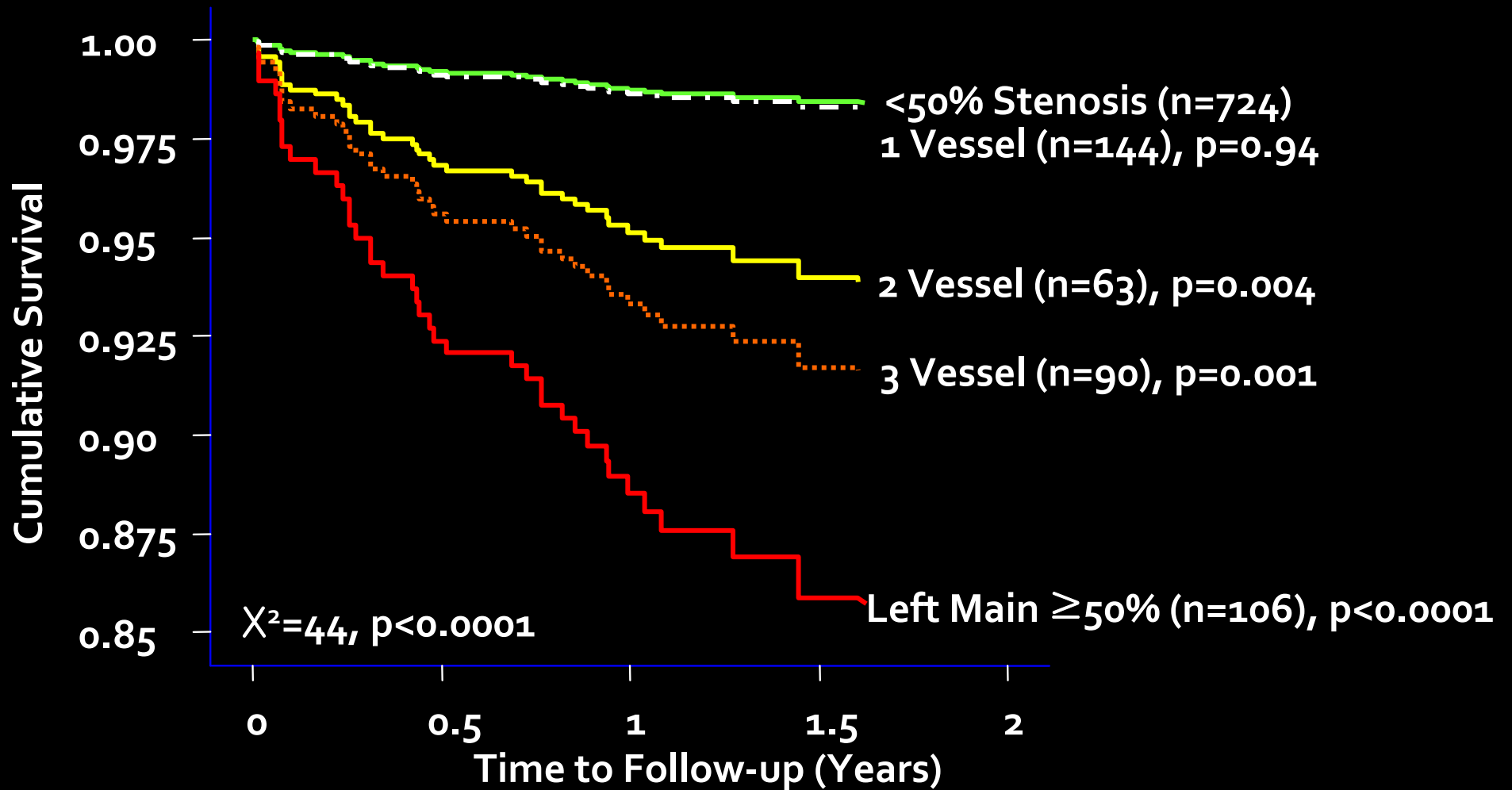
PATIENT-LEVEL PLAQUE BURDEN



REASON #2:

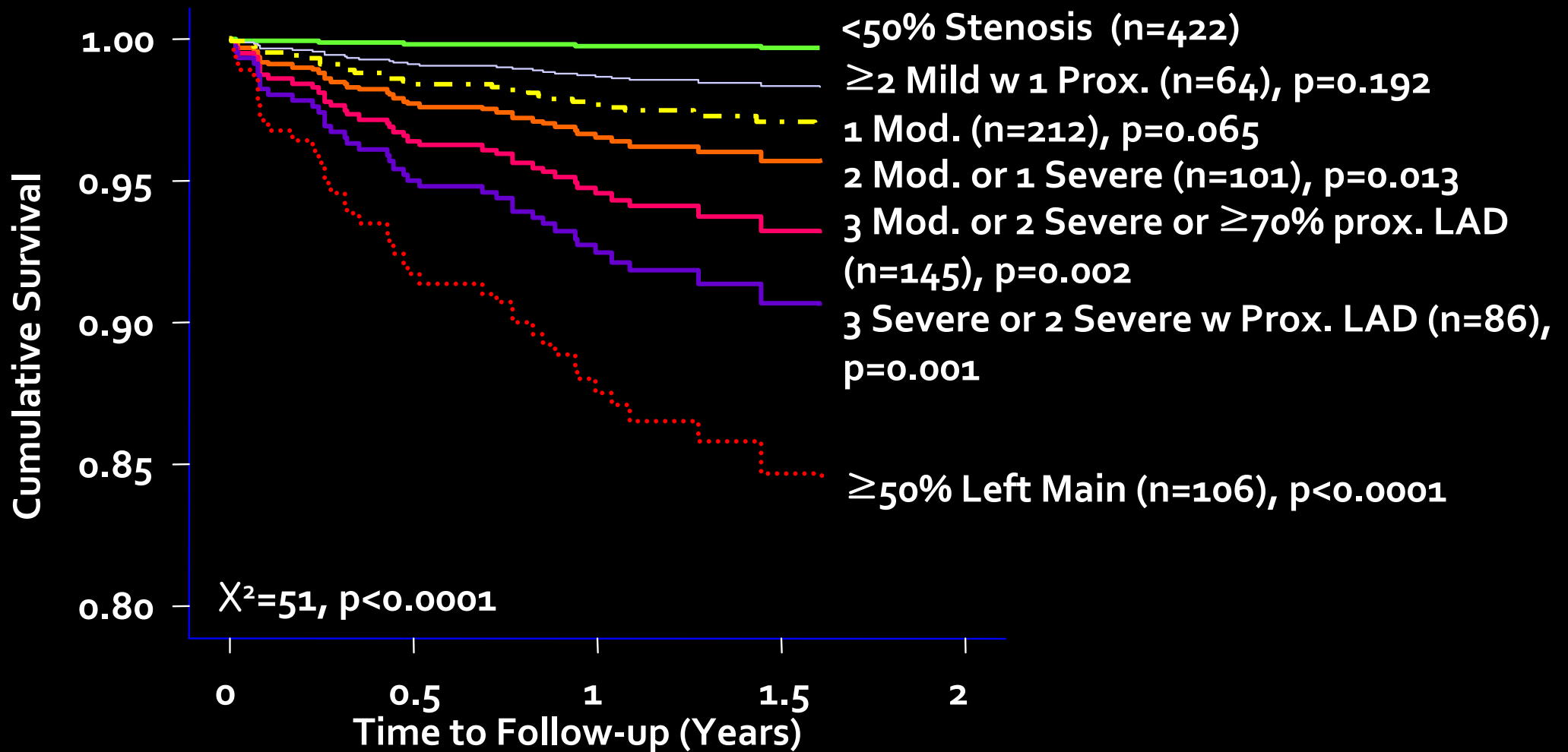
Non-invasive imaging is prognostically valuable for identifying 'at-risk' individuals **BEFORE** events occur.

Plaque Severity



R-A p<0.001 (controlling for risk factors + chest pain).

Plaque Location



R-A p<0.0001 (adjusting for risk factors, chest pain, + dyspnea), Mild (30%-49%), Mod. (50%-69%), & Severe ($\geq 70\%$).

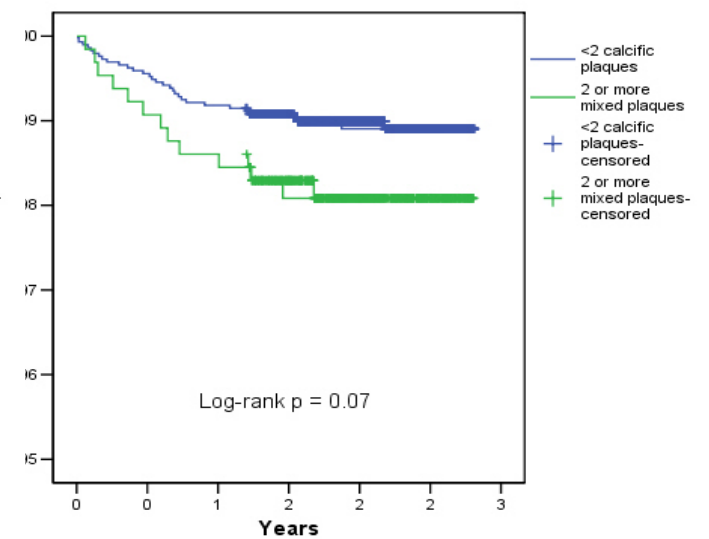
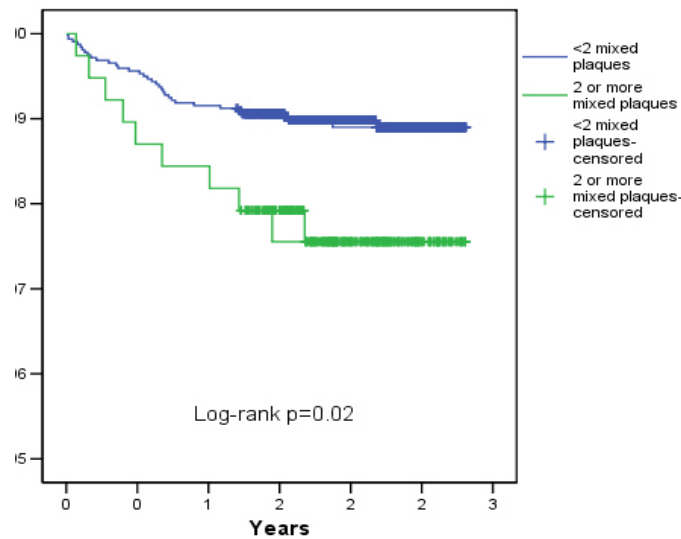
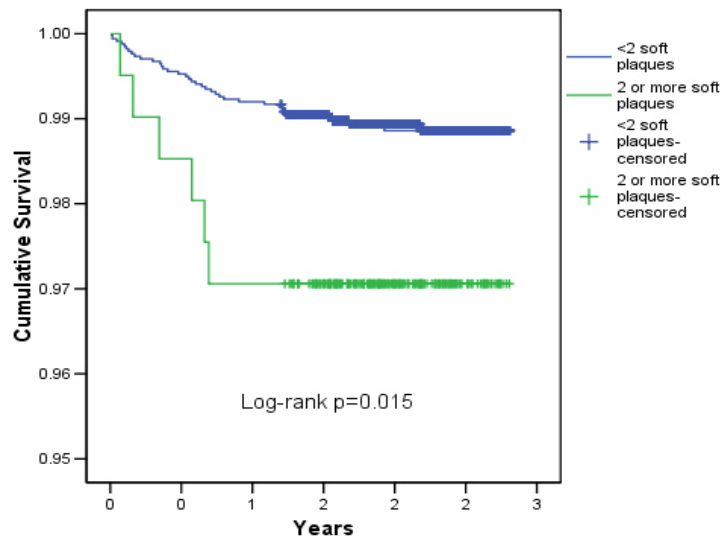
Plaque Composition and Mortality

Two-center study of 3,576 patients without obstructive CAD followed for 2.3 years.

Non-obstructive –
Non-calcified

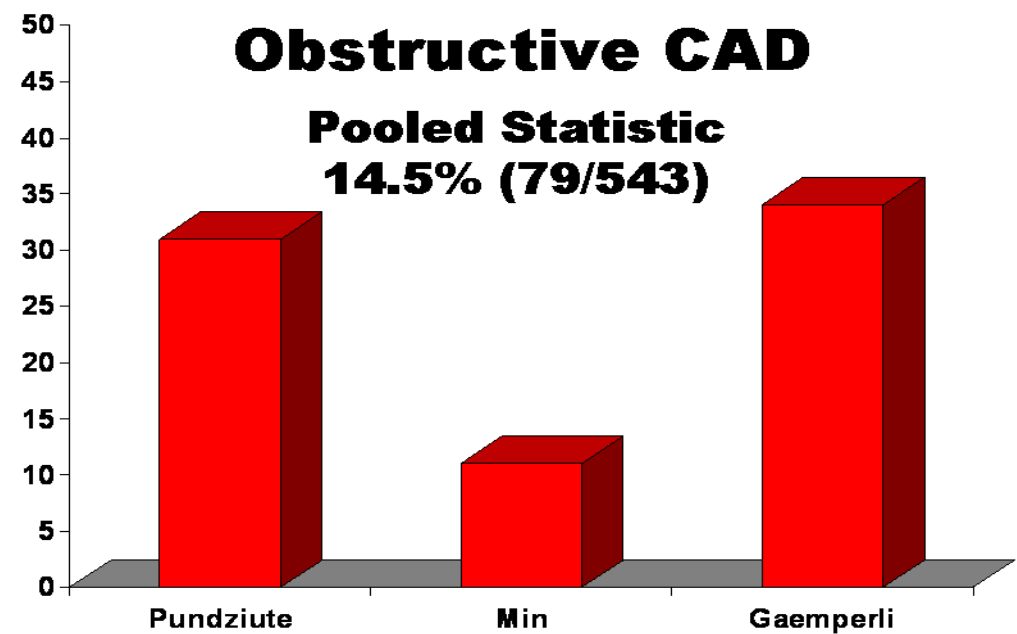
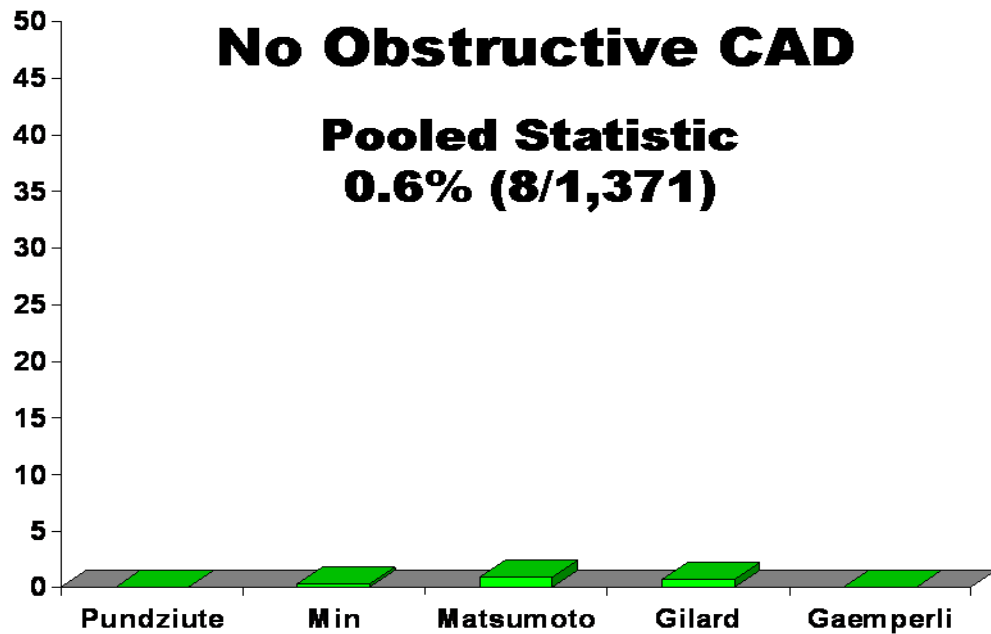
Non-obstructive and Obstructive –
Mixed

Obstructive –
Calcified



Min, preliminary data

Prognosis by Non-invasive Imaging



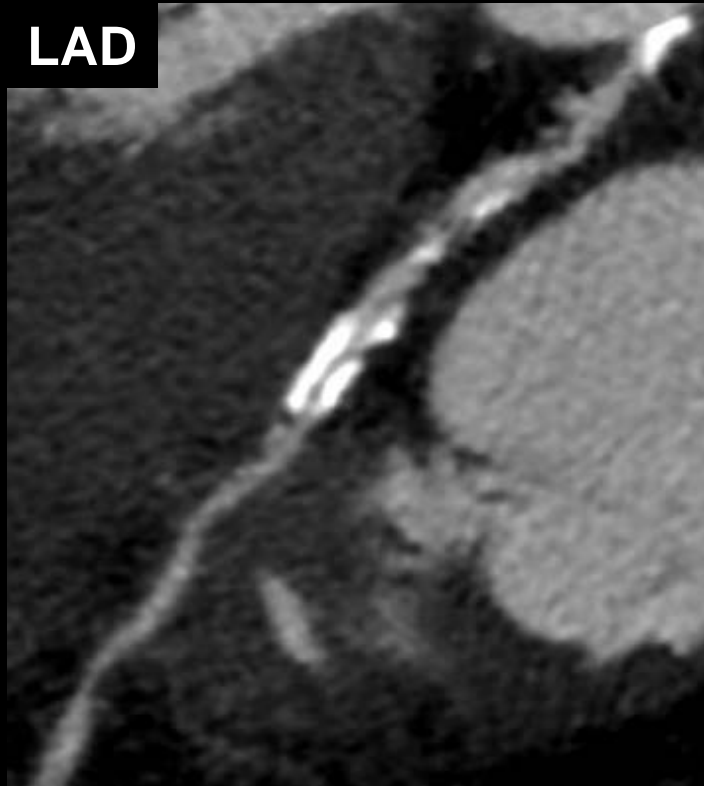
Totality of Prognostic Data Associated with Invasive Plaque Imaging

REASON #3:

Non-invasive imaging
concurrently identifies other
information capable of
predicting risk.

Which factors portend vulnerability?

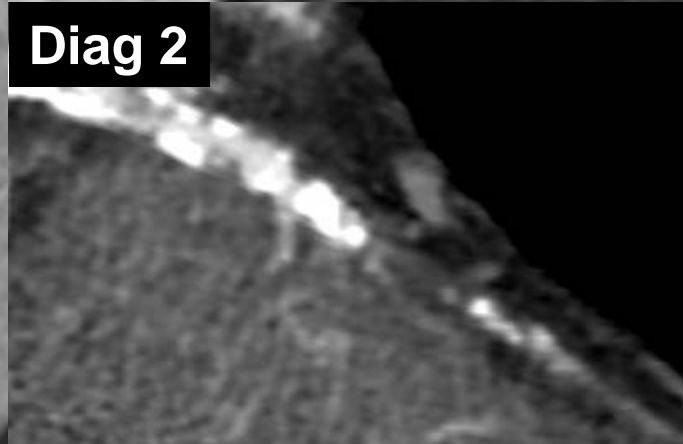
LAD



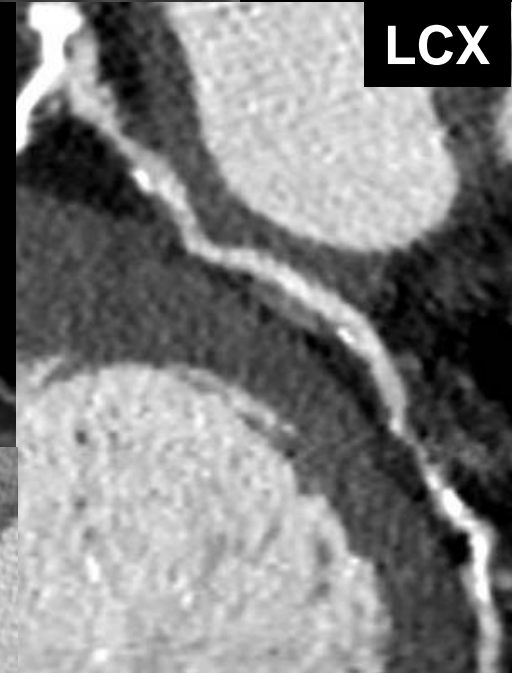
Diag 1



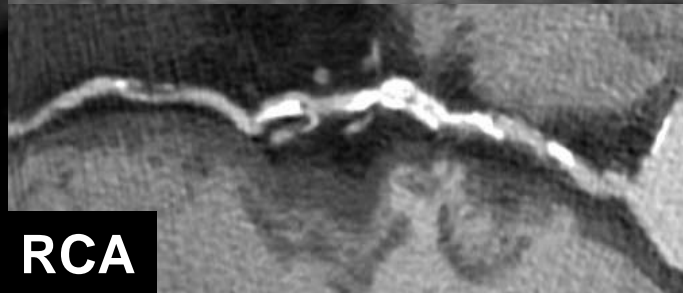
Diag 2



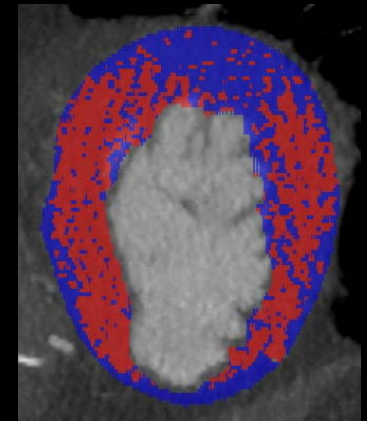
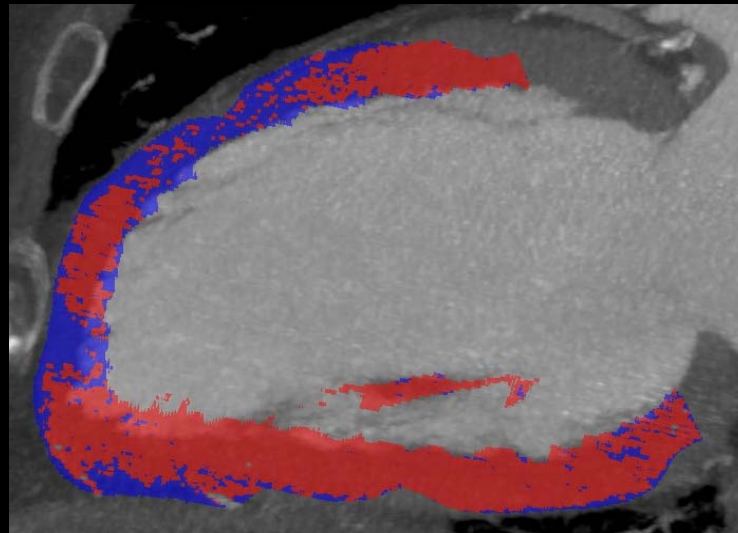
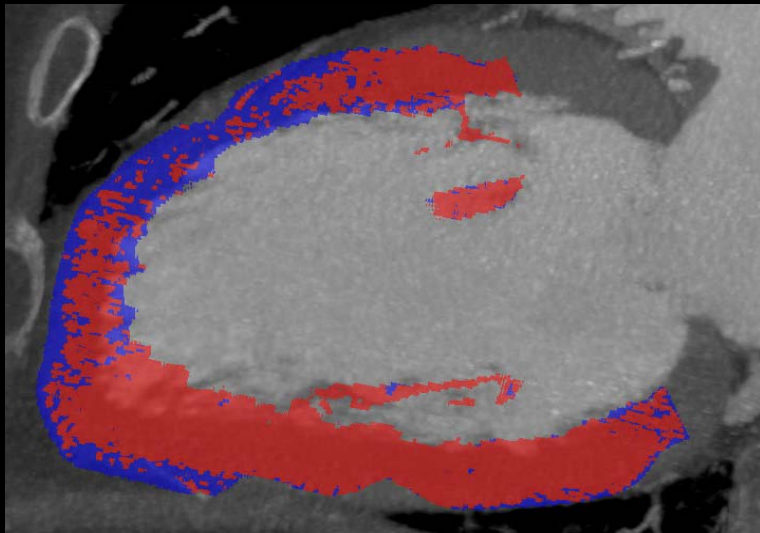
LCX



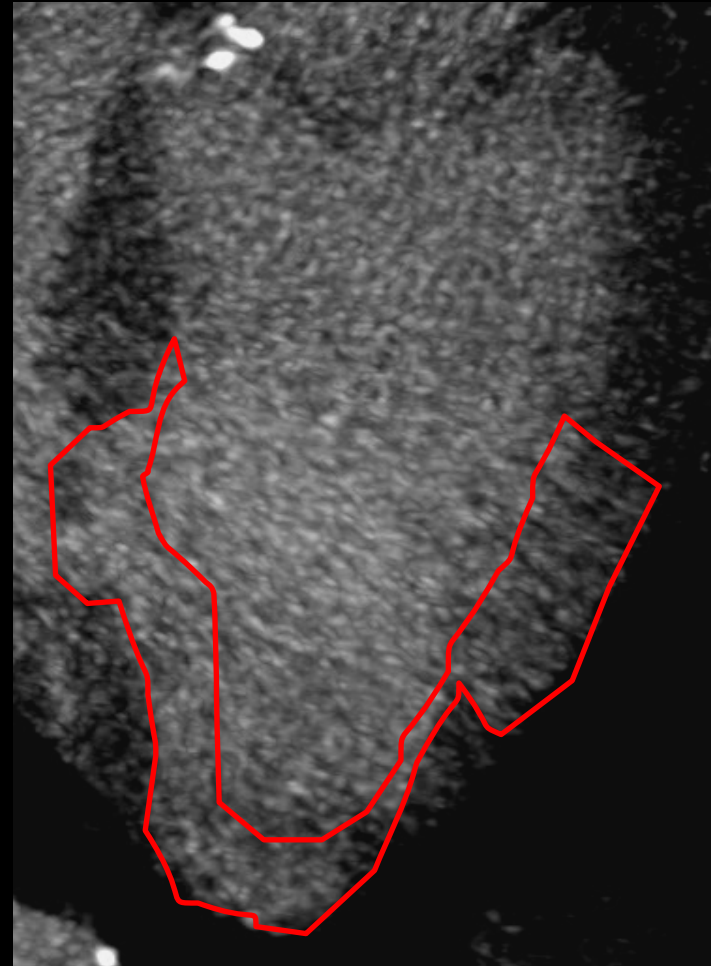
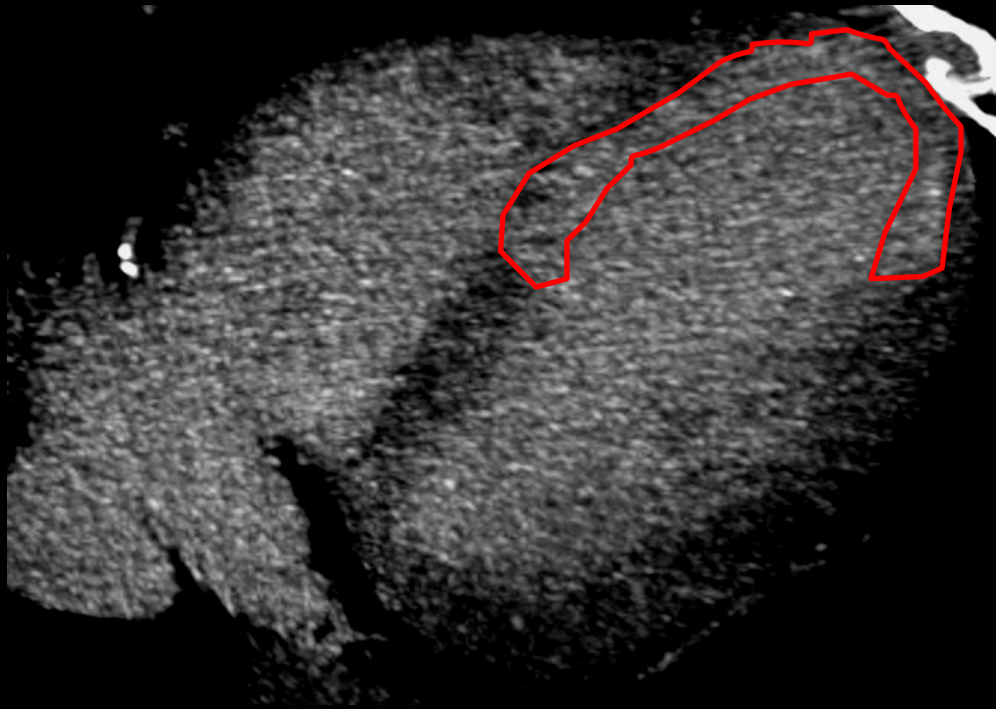
RCA



Perfusion



Myocardial scar



Function

AW VolumeShare 3
sdc

Patient List Volume Viewer Viewer Filmer

Review Steps
Save_State_layout_preset
Angiographic View
Tree VR
Coronary Analysis
Heart Graft
Cardiac Transparency
Auto Ejection Fraction
Protocols List

Auto Ejection Fraction

LV RV LA RA

ES: 46 ED: 124

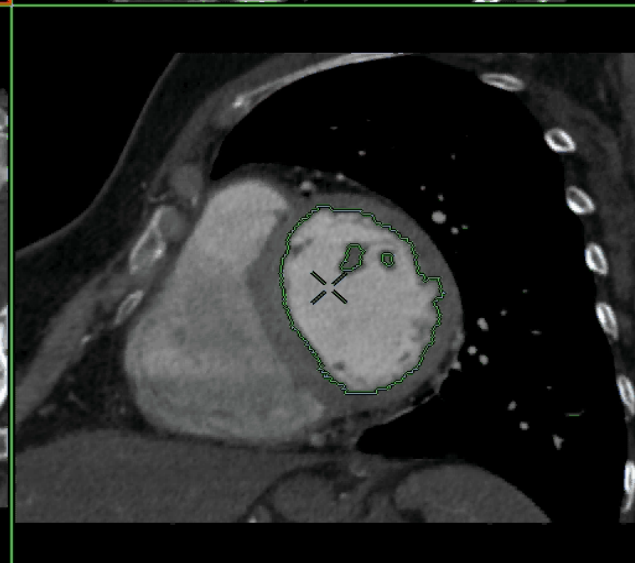
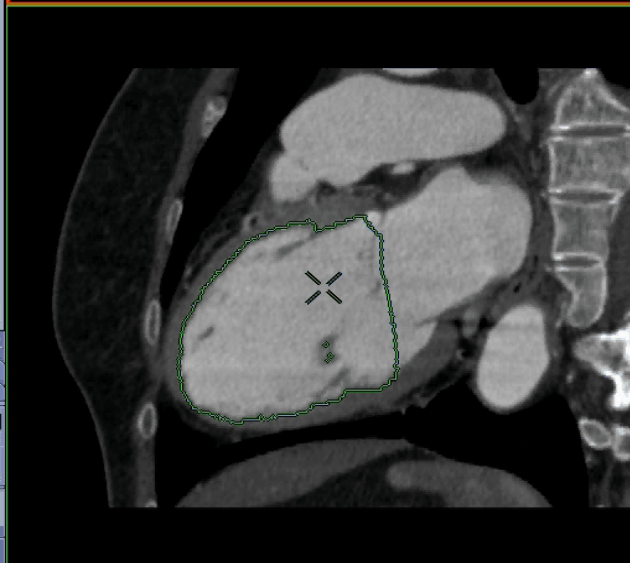
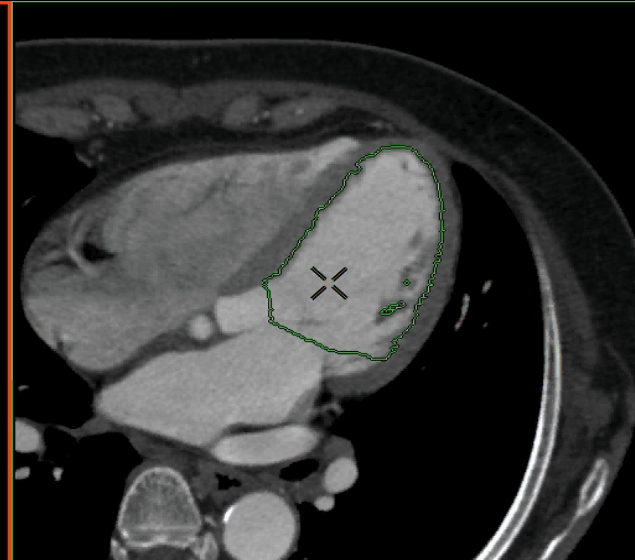
StrokeVolume 78.0 ml
Ejection Fraction 62.0 %
Cardiac Output 3354.0 ml/min
Myocardial Mass 97.3 g
ES Volume (35%) 46.0 ml
ED Volume (95%) 124.0 ml
PVR calculate
SVR calculate
BSA 1.9 m2
Heart Rate 43 bpm

Myocardium Analysis

VR My Tools Film/Save
Display Segment Report

Auto Select Threshold Remove Object
Advanced Processing

Exit Hide Panels

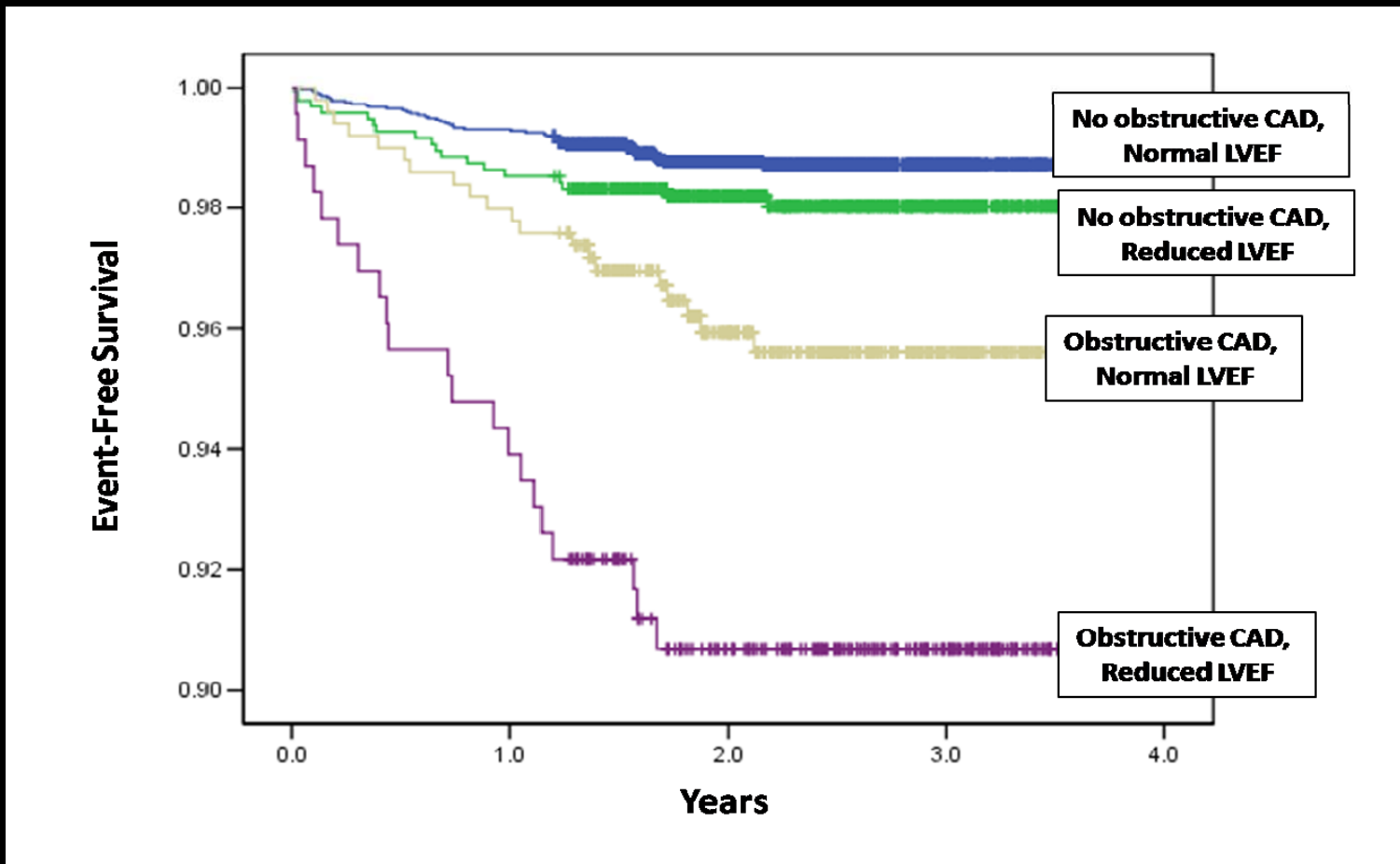


Incremental Value of Perfusion to Anatomy

517 pts undergoing CCTA and MPS studied for $SSS \geq 4$ or coronary stenosis $\geq 50\%$

Incremental Value of LVEF to Anatomy

5,646 consecutive patients undergoing CCTA followed for 2.3 years.

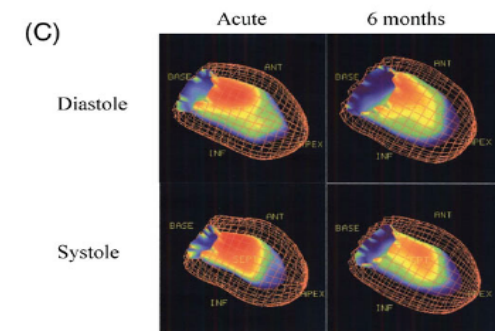
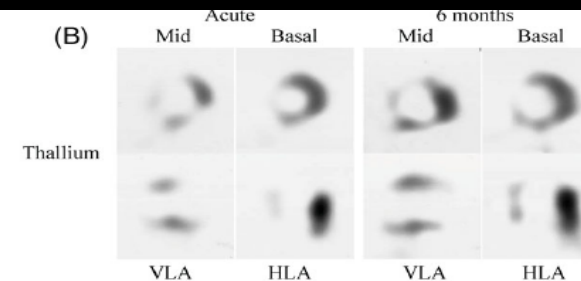
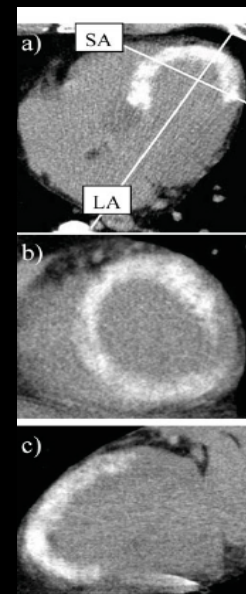
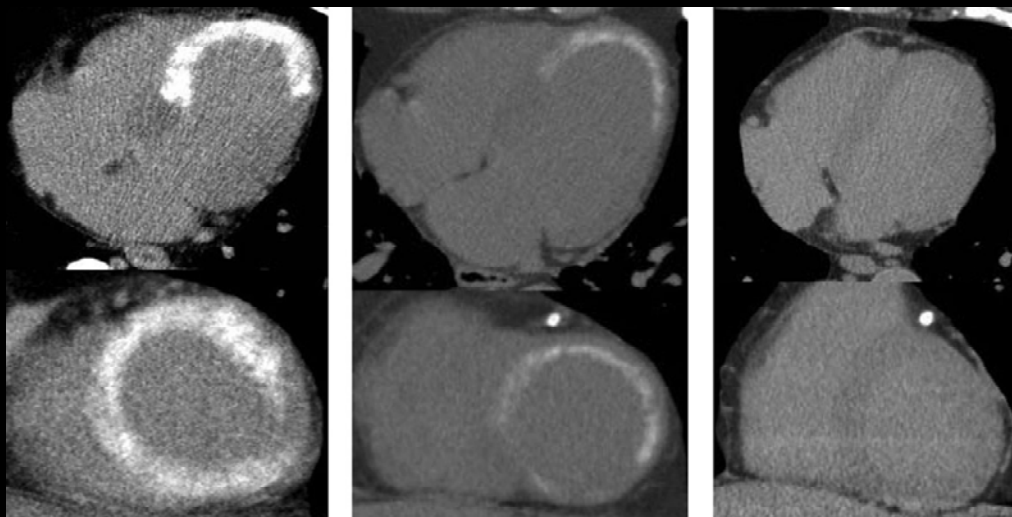


Min, preliminary data

Incremental Value of Scar to Anatomy

Adverse LV remodelling ($p=0.001$) and # of rehospitalizations for CHF ($p=0.0017$) higher in TM DE.

	TM DE (n=18)	SE DE (n=20)	No DE (n=14)	P value
Peak CKMB	497	182	85	0.0004
Myocardial blush grade 3	22%	67%	75%	0.001
LVEF	41%	53%	62%	0.0001

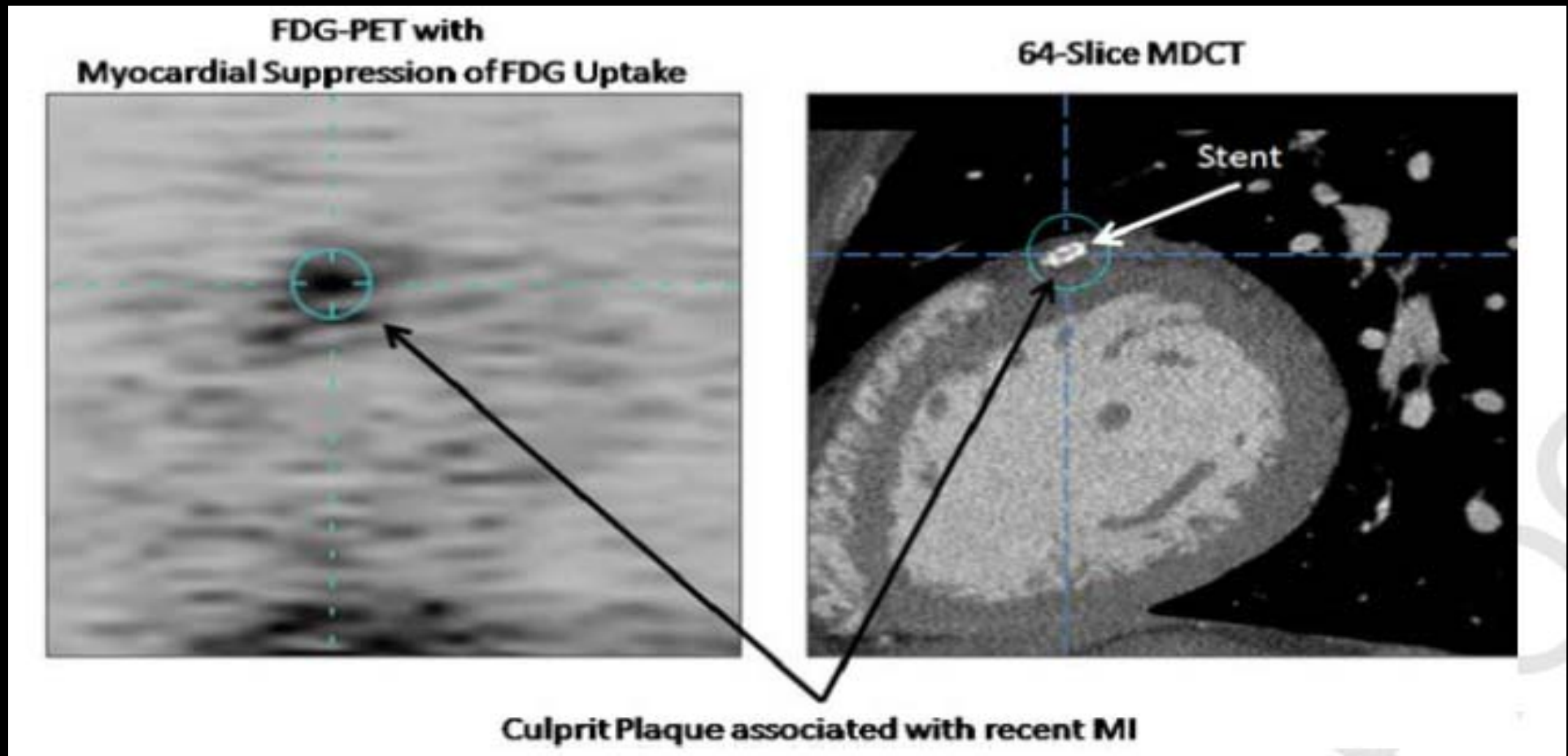


REASON #4:

Non-invasive imaging offers assessment beyond anatomy.

Inflammation and ACS (PET and CCTA)

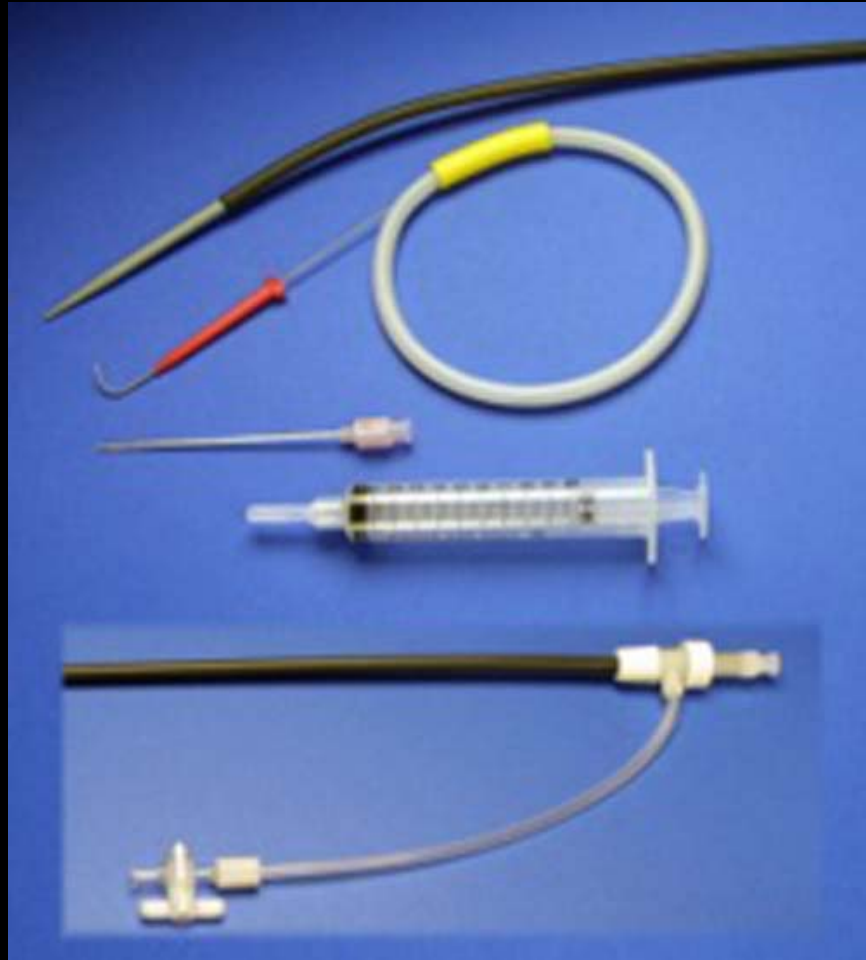
Glycolytic activity by FDG uptake in the LM artery greater for pts with ACS than those who were stable (2.4 vs. 1.8, p 0.001).



REASON #5:

Non-invasive imaging by CCTA
is safer than invasive imaging.

Near-term complications: Invasive Evaluation



■ Complication Rate, IVUS

- Any 1.1-2.9%
 - Spasm
- Major 0.4%
 - Occlusion
 - Dissection
 - Guidewire entrapment

Hausmann D et al *Circulation* 1995; Batkoff BW et al. *Cathet Cardiovasc Diagn* 1996;
Pinto FJ et al. *Circulation* 1993

Near-term complications: Non-invasive imaging

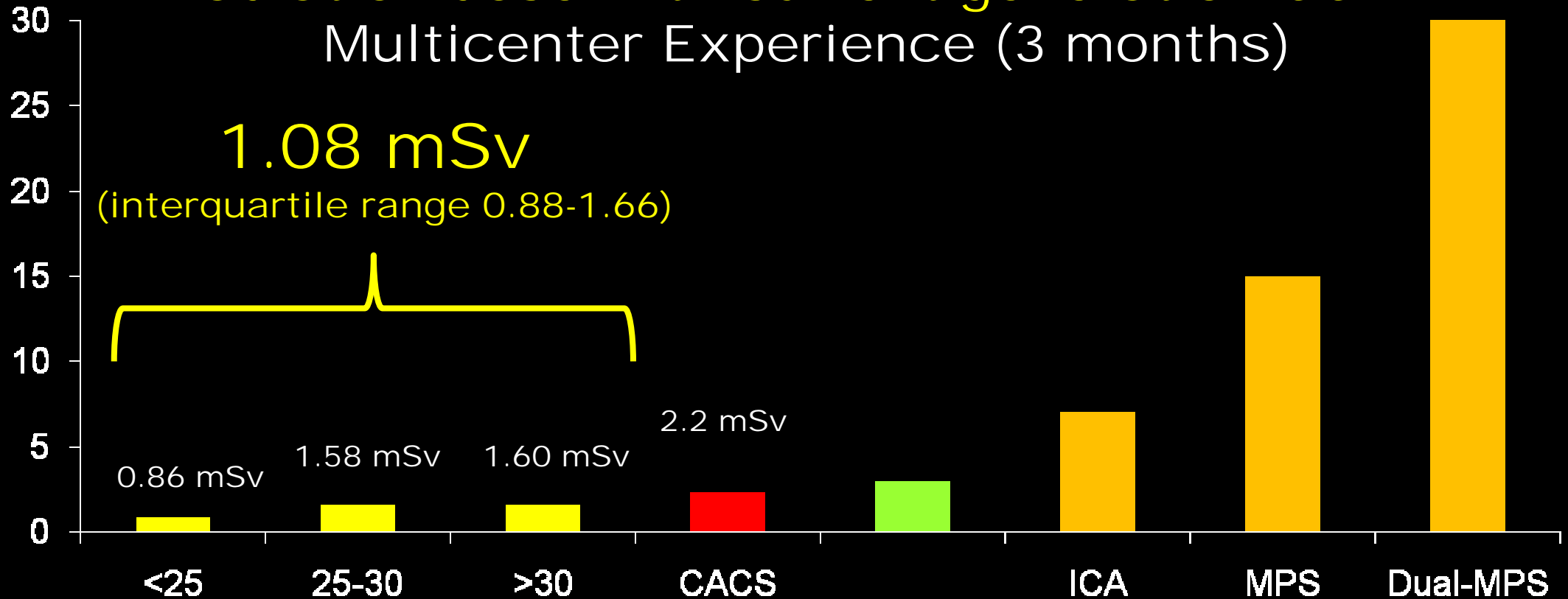
Complication*	Rate
Symptomatic bradycardia	0%
Hypotension	0%
Contrast-induced nephropathy	0%
Heart block	0%
Anaphylactic reaction	0%
Any complication	0%

***Using standard protocol involving 5mg increments of Iopressor and iodixanol as contrast agent**

Results from prospective multicenter ACCURACY trial, Budoff MJ et al. JACC 2008

Long-term Safety

Radiation dose with current generation CCTA:
Multicenter Experience (3 months)



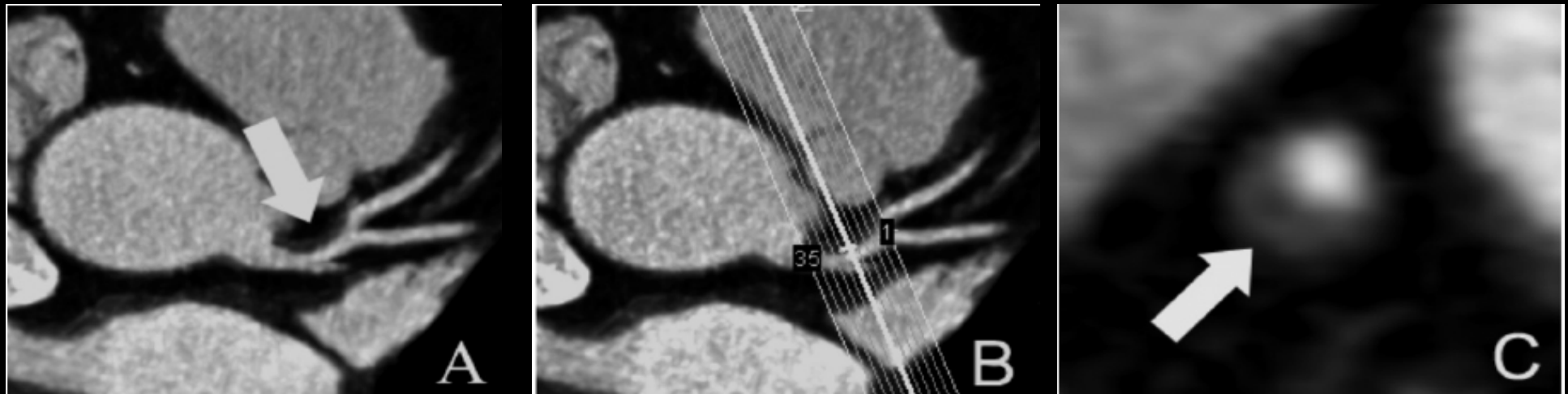
ICA dose 5X the CCTA.

REASON #6:

Non-invasive imaging by CCTA permits assessment of plaque progression.

Assessing Changes in Non-Calcified Atherosclerotic Plaque Volume in LM and LAD Over Time by 64-slice CCTA

50 patients with non-calcified plaque at baseline underwent f/u CCTA after 17 ± 6 months. Mean plaque volumes were 92 ± 81 mm³ at baseline MDCT and 115 ± 110 mm³ on follow-up CCTA ($p < 0.001$). Mean annualized volume change was 22% (95%CI, 14.7% vs. 29.7%). Weak but significant correlation to LDL levels for amount of baseline plaque volume, $r = 0.37$, $p < 0.001$



Plaque areas manually traced. (PA = CSA – Luminal area)
Volume calculated by PA x (reconstruction increment)
Plaque volume = [PA1 + PA2 + PA30] x 0.5mm

REASON #7:

You cannot invasively
evaluate everyone.

Implicit in the evaluation of the “vulnerable”
plaque is identification BEFORE clinical
events occur



Non-invasive assessment of 'at-risk' patients is
clinically more relevant than invasive assessment of
'at risk' plaques.

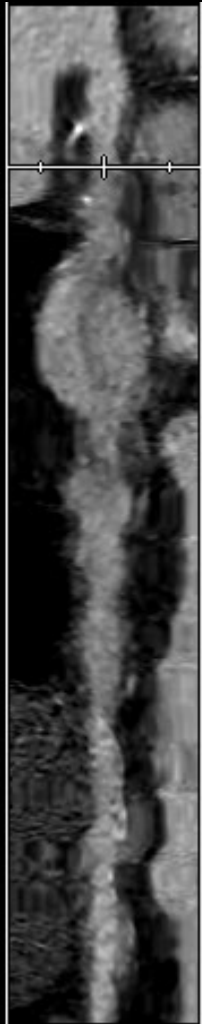
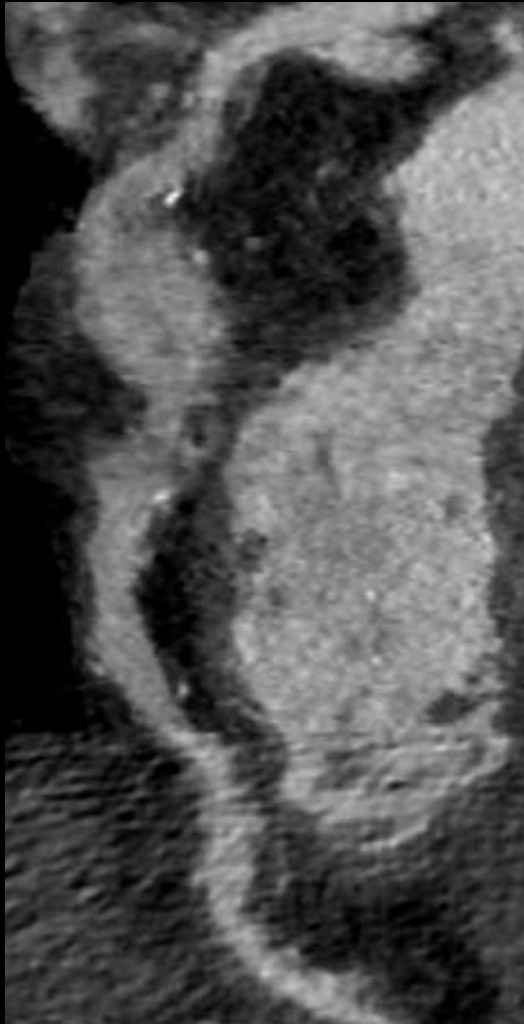
Thank you.

Non-invasive assessment of plaque vulnerability is preferable because:

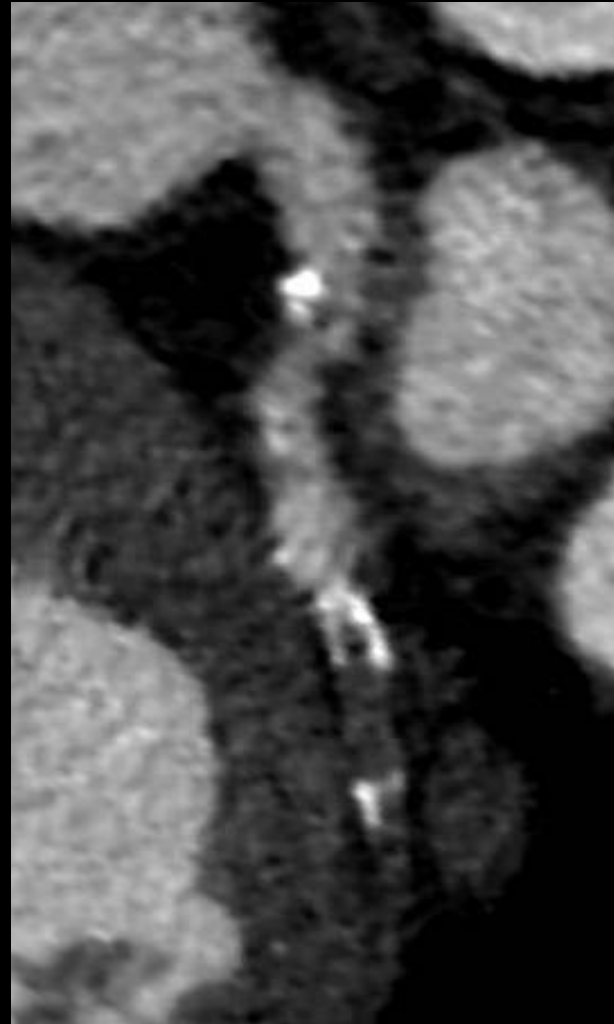
1. People will do it.
2. It is safer.
3. It permits serial assessment.
4. It permits assessment of overall plaque burden.
5. It is prognostic.
6. It offers data beyond plaque.
7. It permits concurrent evaluation of anatomy and physiology.

BEAL 2.5 mSv

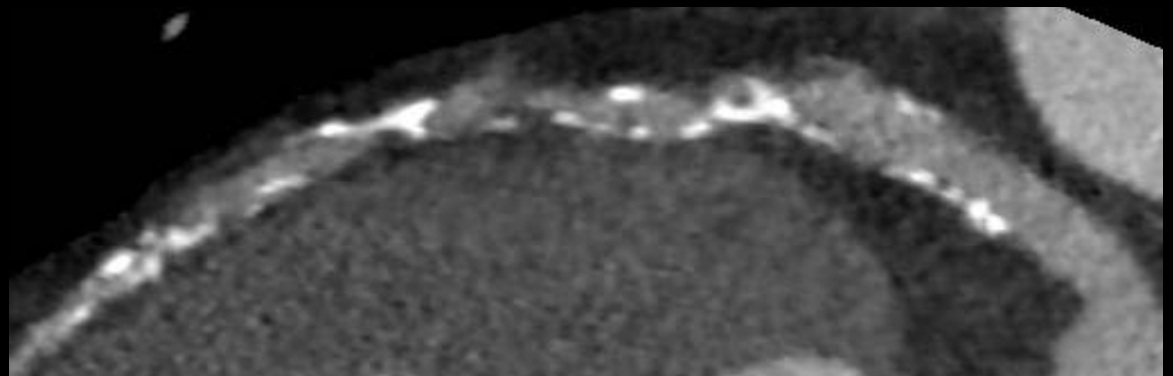
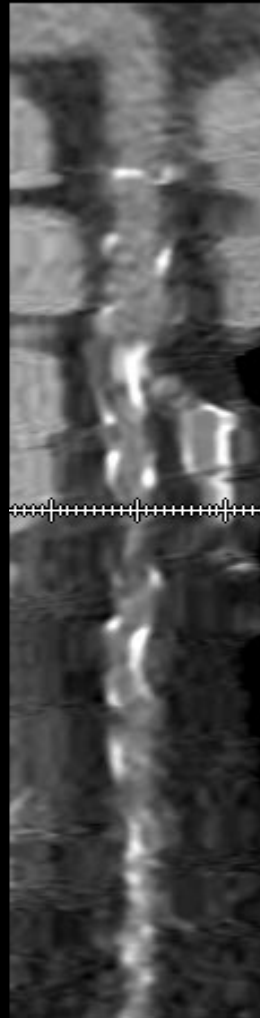
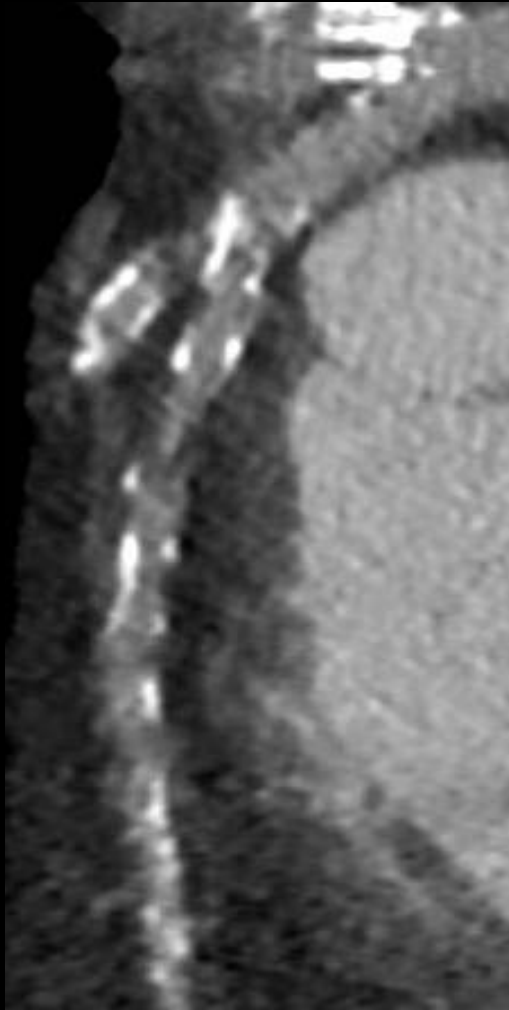
RCA aneurysm



Totally occluded OM

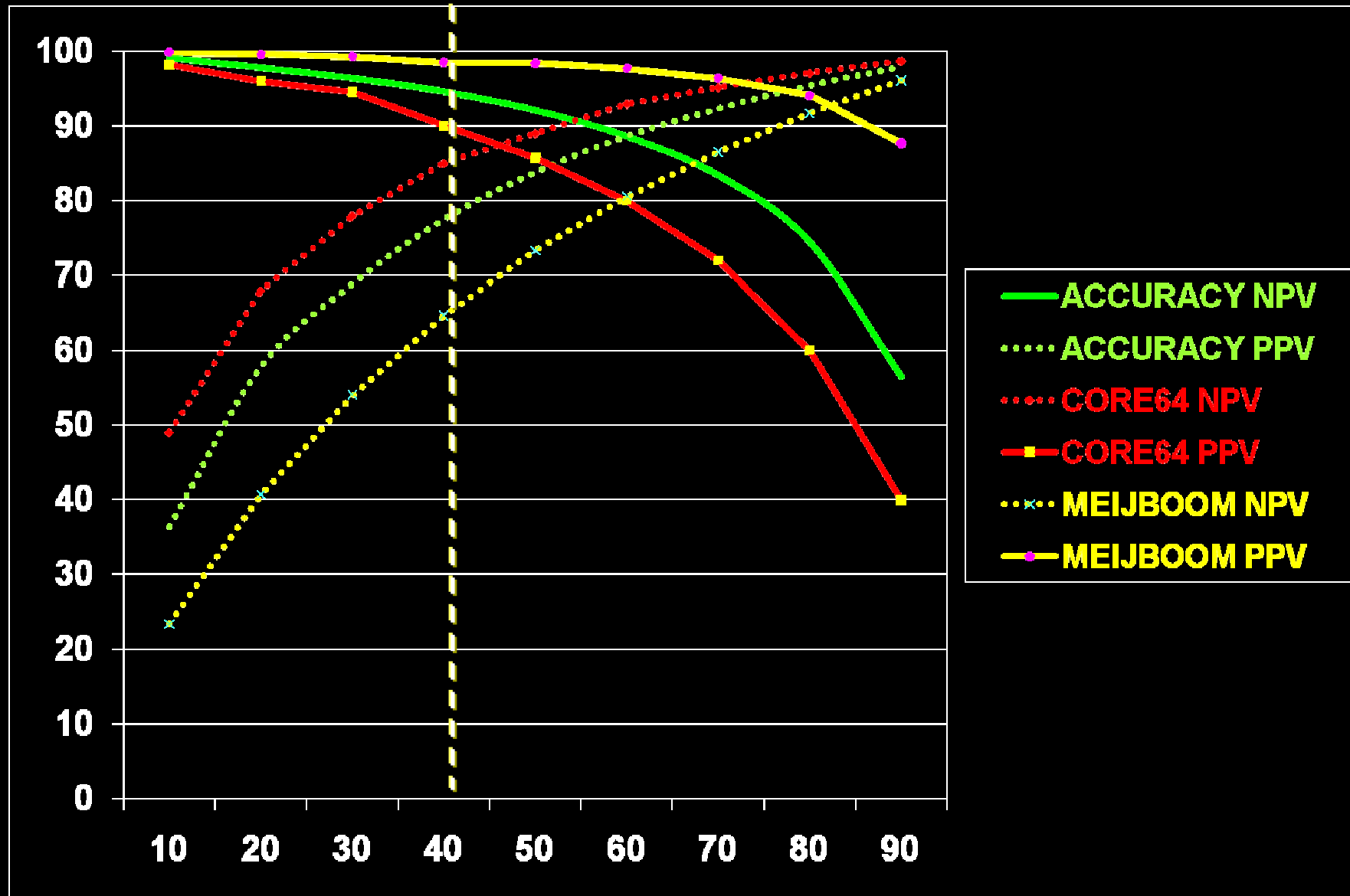


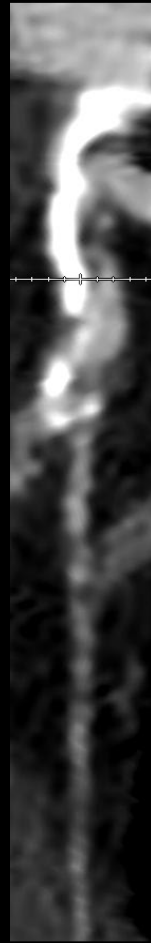
Severely diseased LAD

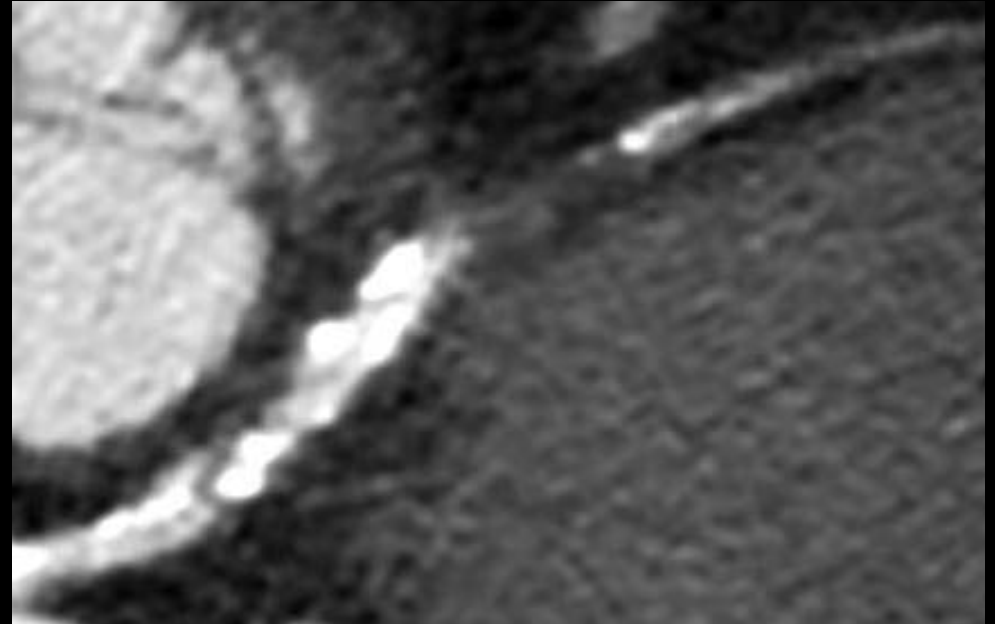
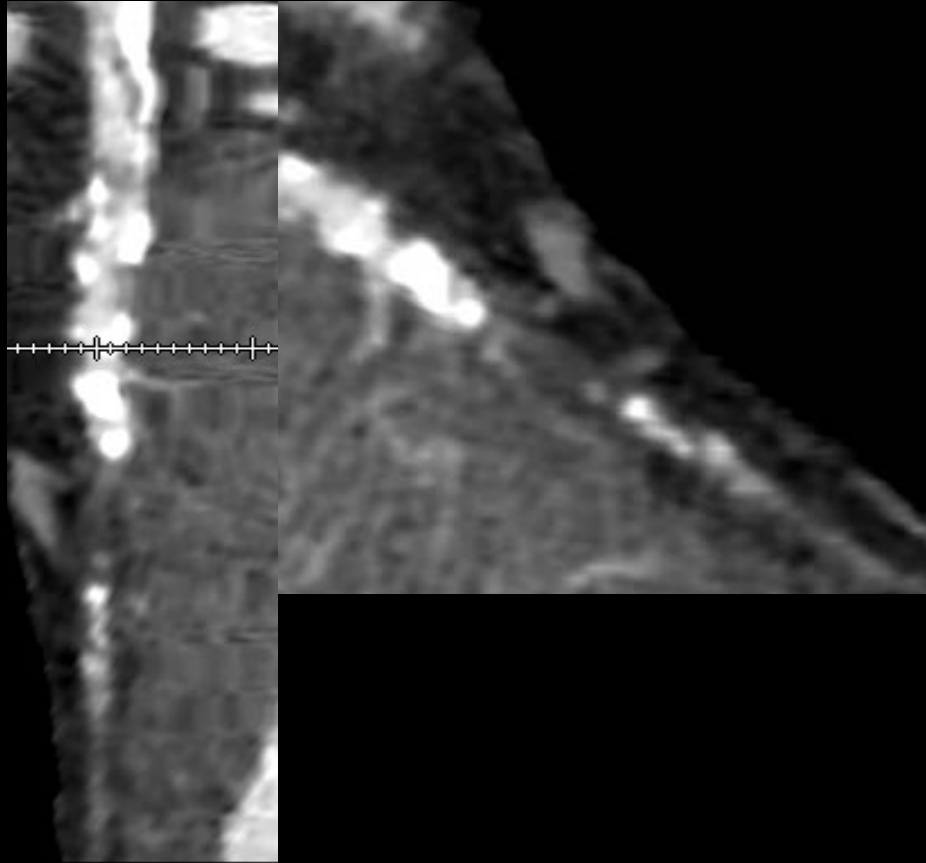


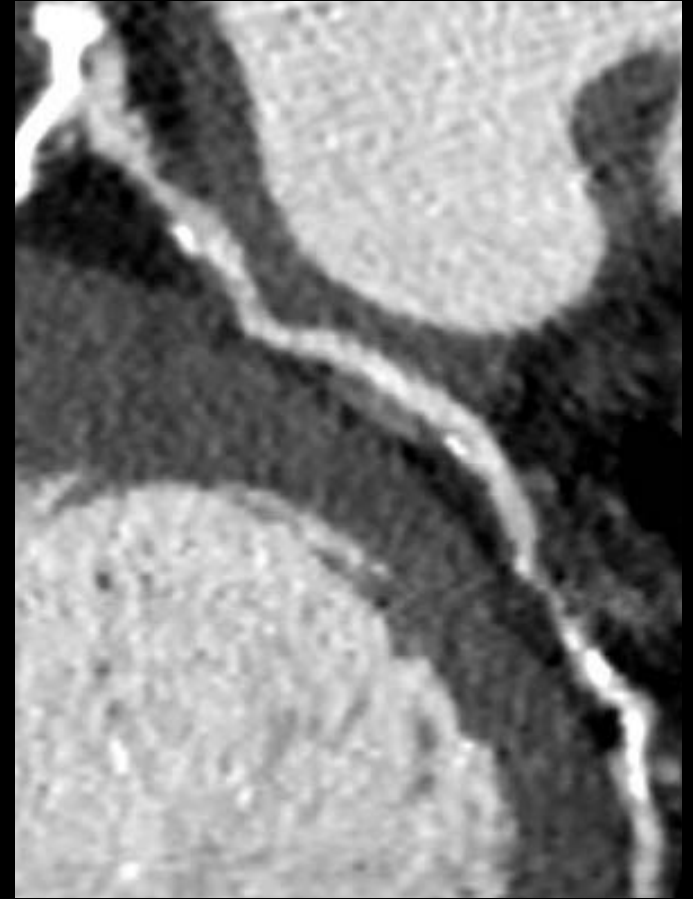
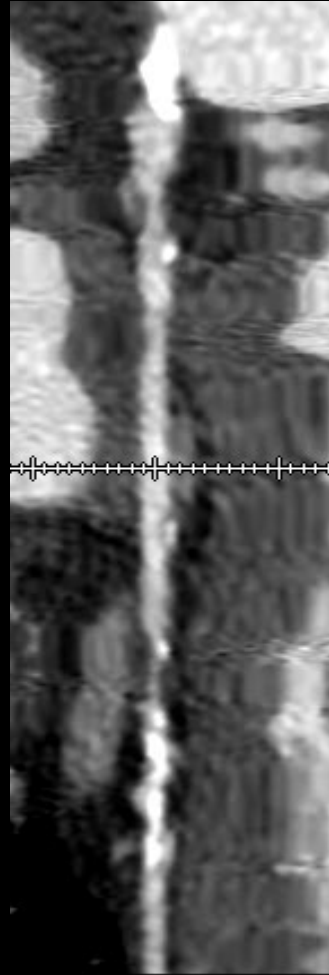
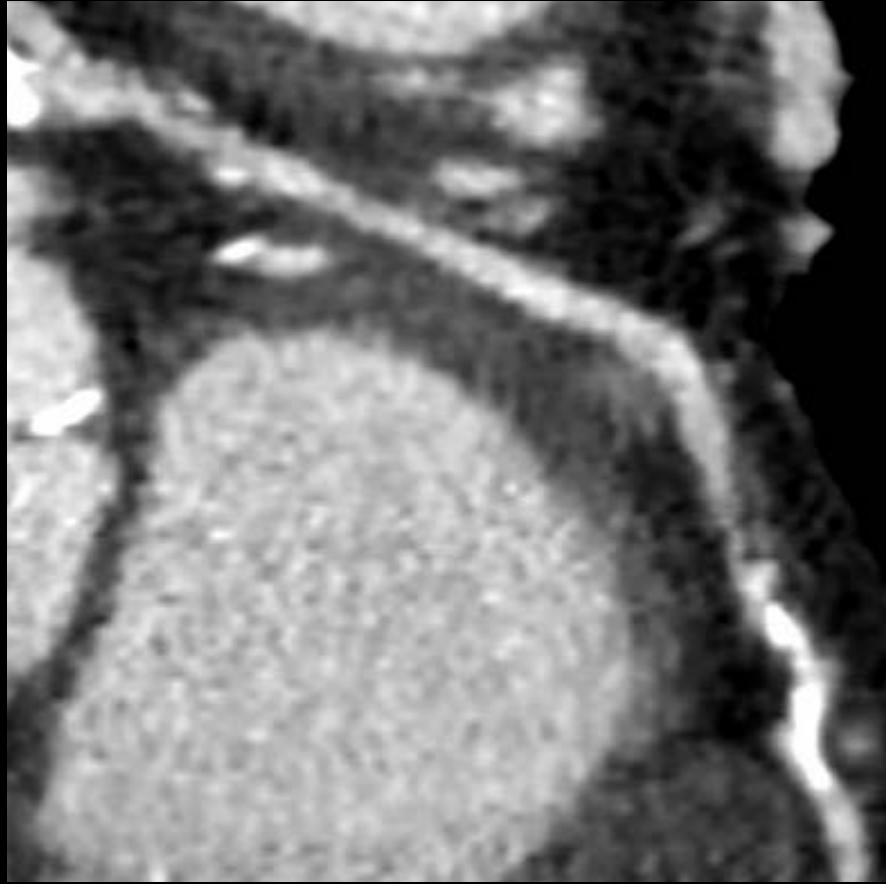
Chronic Total Occlusions

NPV / PPV based upon disease prevalence



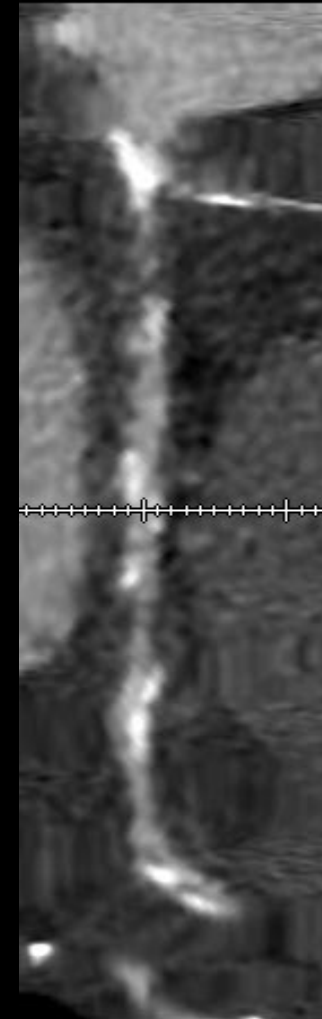
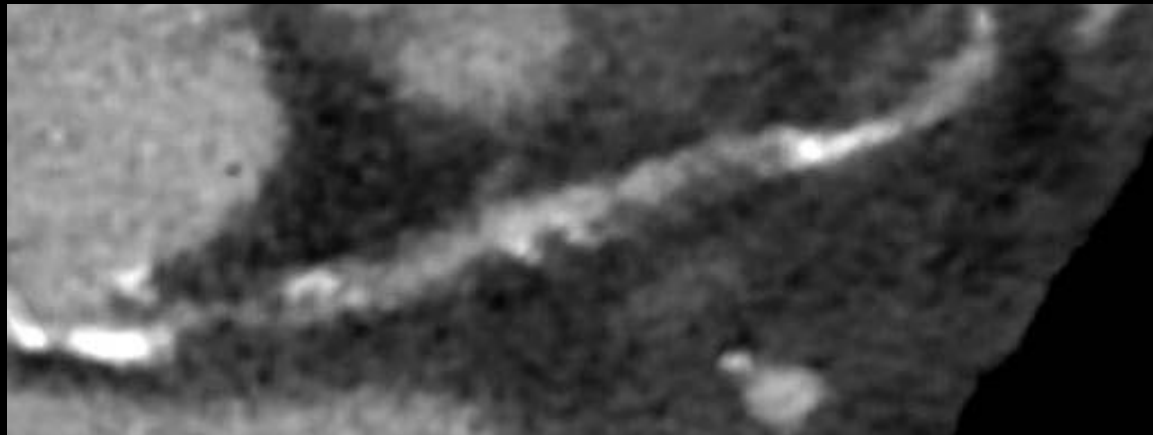






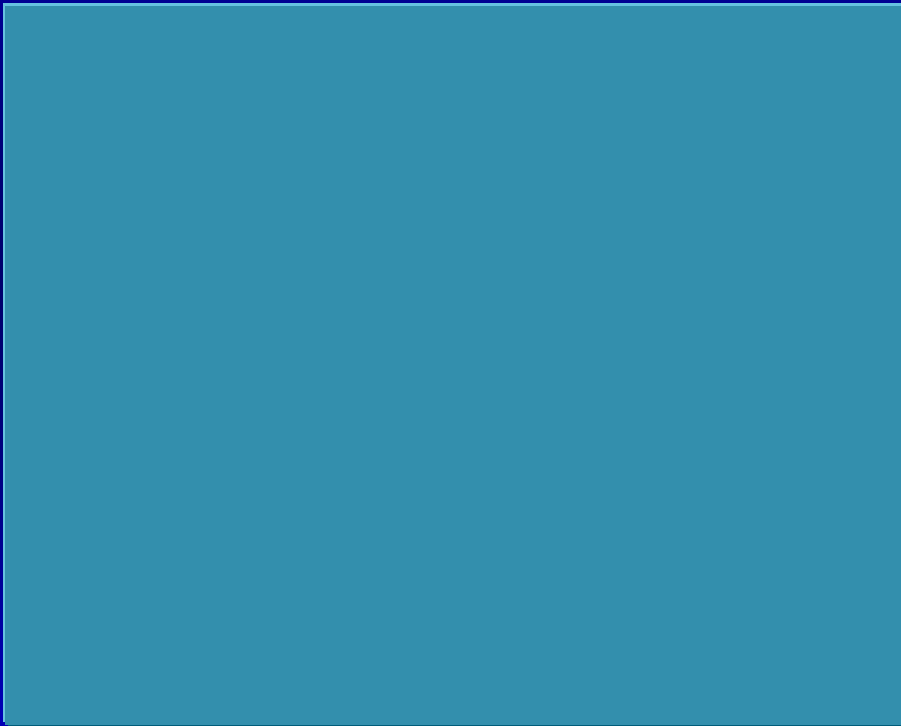
SVG to OM; SVG to RPL

LM and LAD



Plaque Composition

810 patients who underwent CCTA with non-obstructive CAD but with low dense plaques with CT HU density <68 HU, accompanied by mild-moderate coronary artery stenosis (25-75%). Follow-up 1,062 \pm 544 days for MACE (ACS, incl AMI and UA; cardiac death).



**Only prior MI and low dense CT plaques predictive of MACE.
Low density plaques OR 4.60 (95% CI, 1.08-5.92)**

MDCT: CABG 64-row MDCT Studies

Author	# Pts	MDCT Rows	# Grafts	% Assessable	Basis	Sens	Spec	PPV	NPV
Pashka Eur Heart J 2006	31	64	96	94	Sten & Occl	97.8	89.3	90	87.7
Ropers et al Circulation. 2006	50	64	138	100	Sten	100	94	100	92
Dijkers J Cardio Imag 2006	34	64	69		Sten Occl	100 100	100 98.7		
Meyer J Am Coll Cardiol 2007	138	64	418		Sten & Occl	97	97	93	99

TAKE HOME POINT 1:

Spatial resolution is the most needed improvement to cardiac CT.

CASE #1: No known CAD

- 60 y/o female
 - H/o dyslipidemia, HTN
 - Chest pain: exertional, better with rest

HDCT

LAD



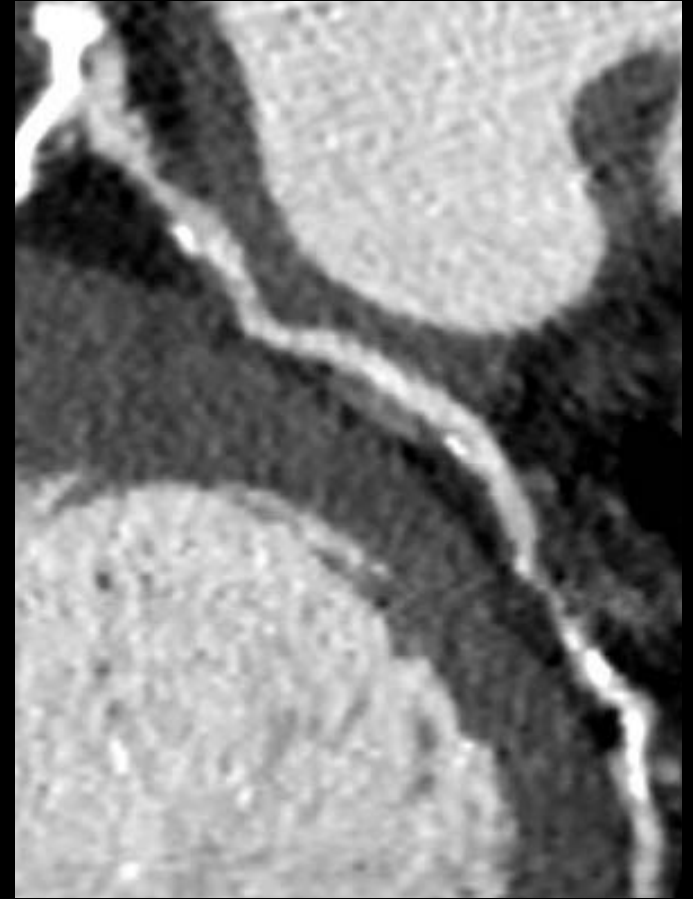
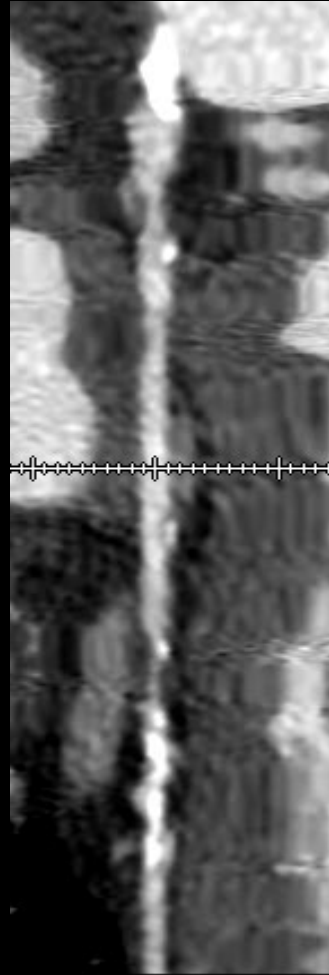
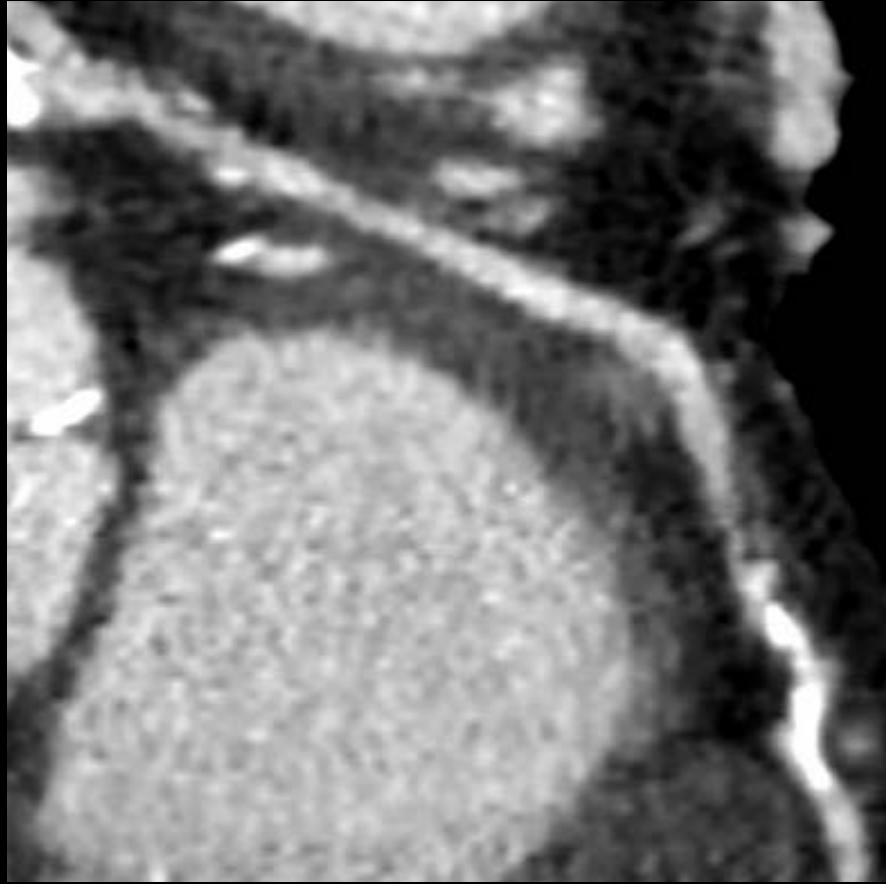
LCX



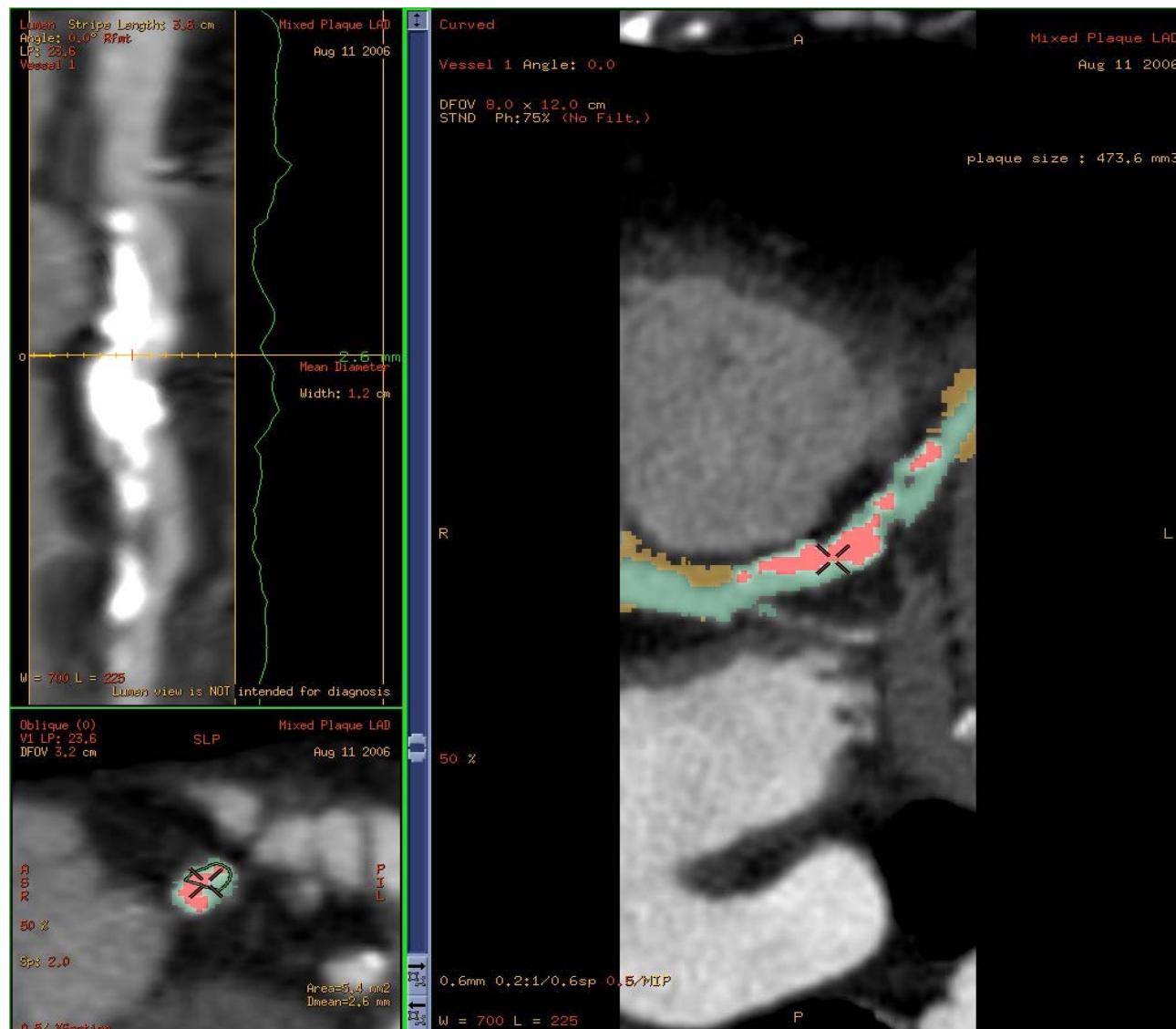
RCA



0.5 mSv



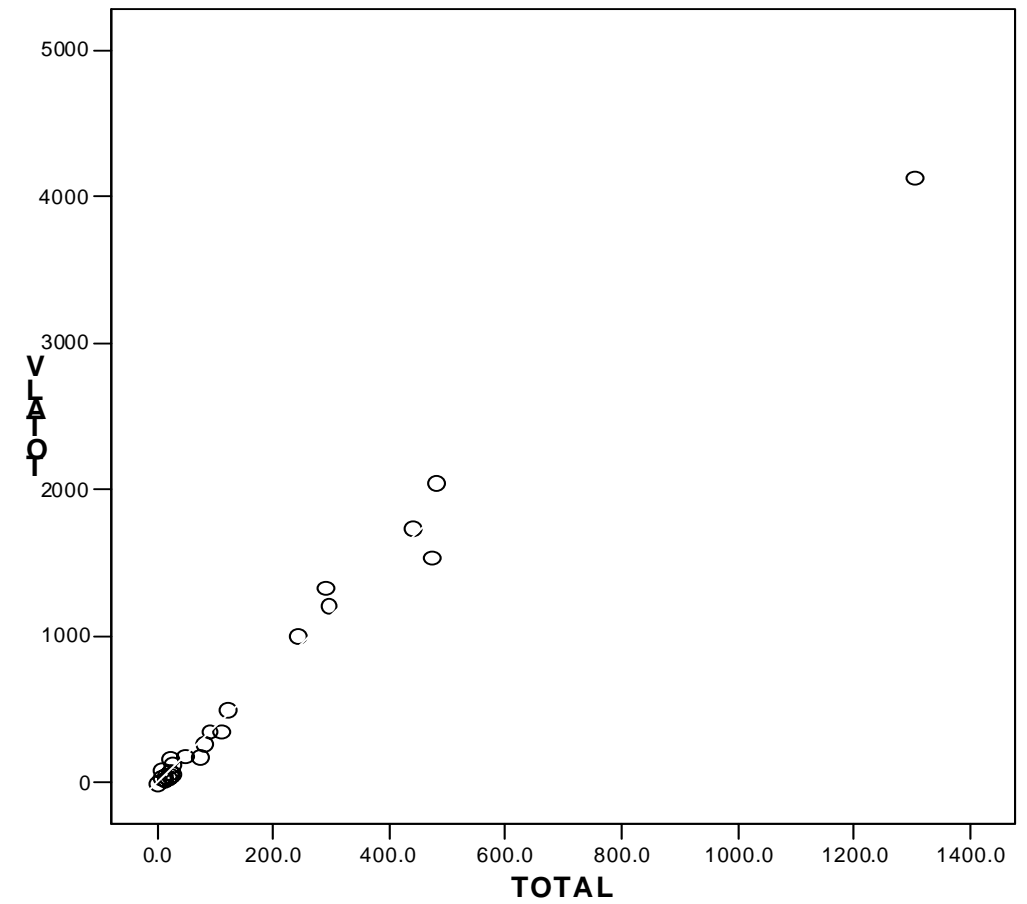
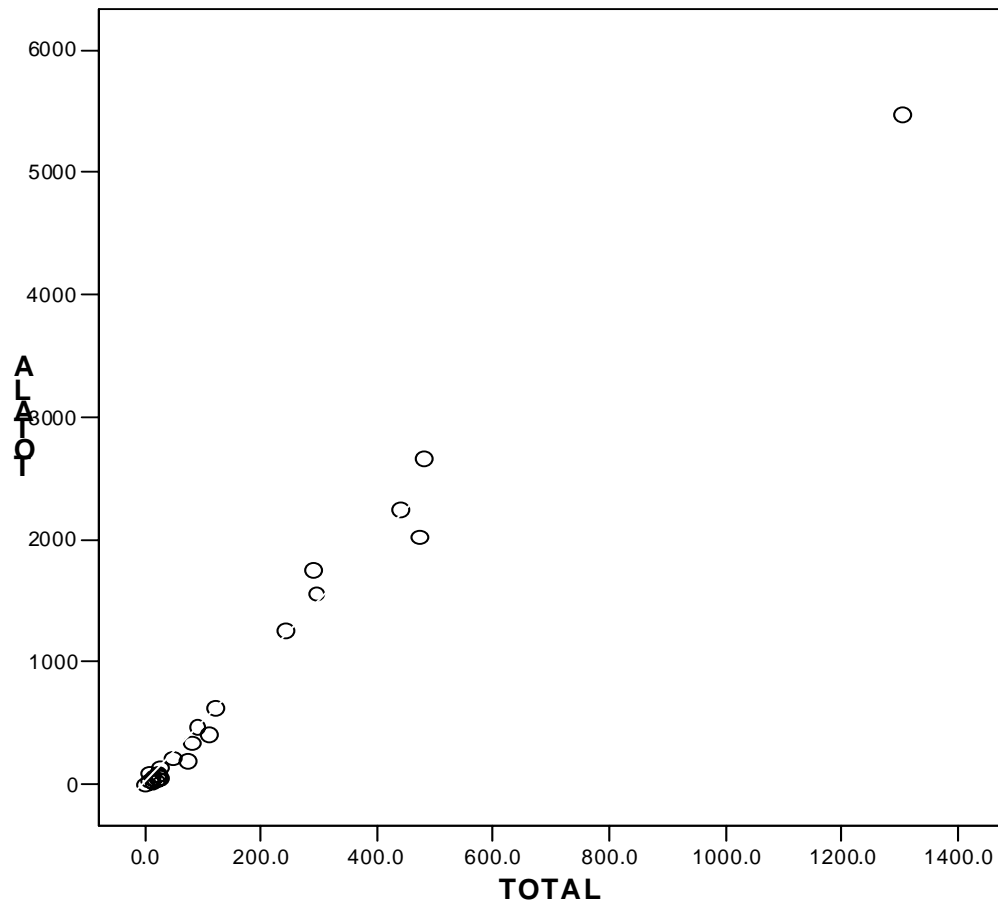
Contrast-enhanced Quantification of Plaque Volumes



Calcium score vs. Contrast-enhanced calcium measurement

By total calcium score

Volumetric vs. Contrast-Enhanced Calcium Score

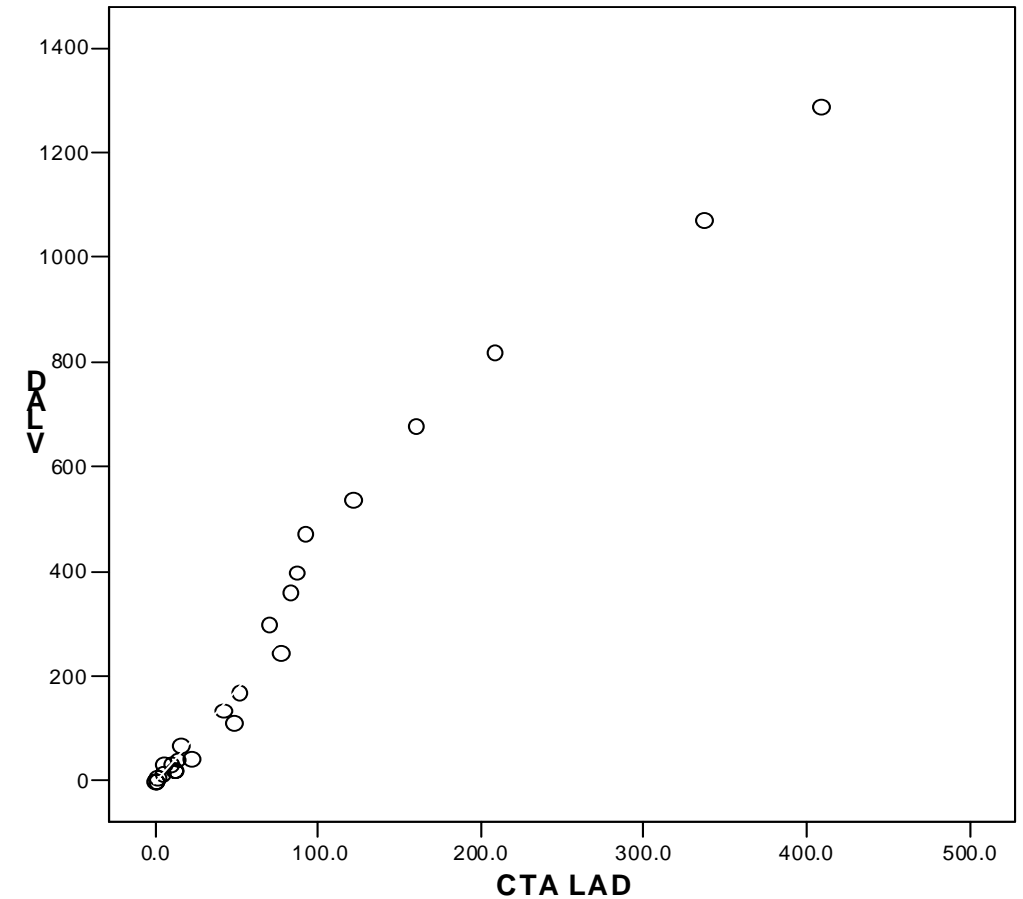
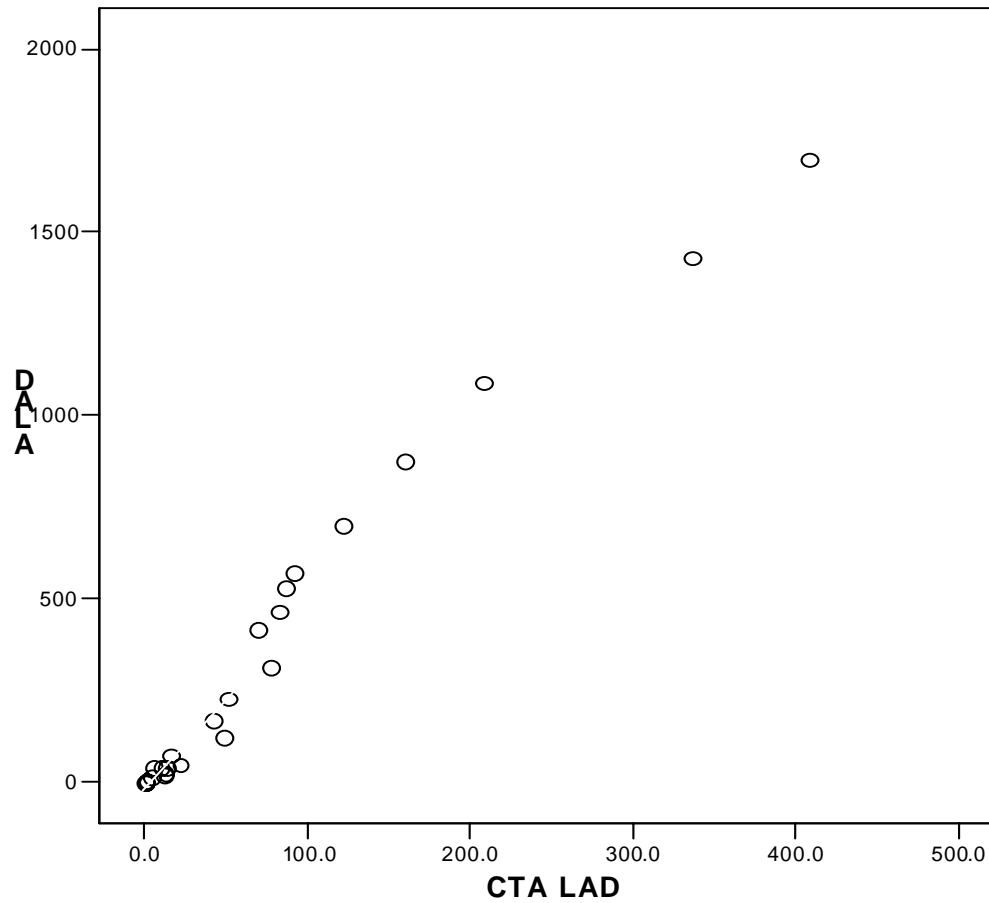


Agatston vs. Contrast-Enhanced Calcium Score

Calcium score vs. Contrast-enhanced calcium measurement

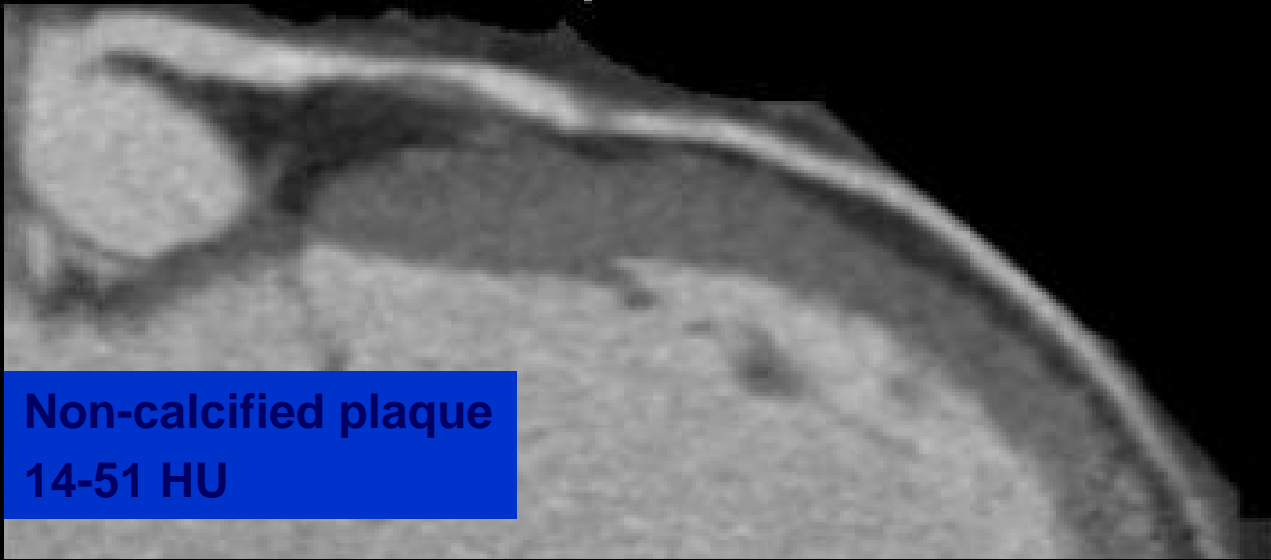
By artery

Volumetric vs. Contrast-Enhanced Calcium Score

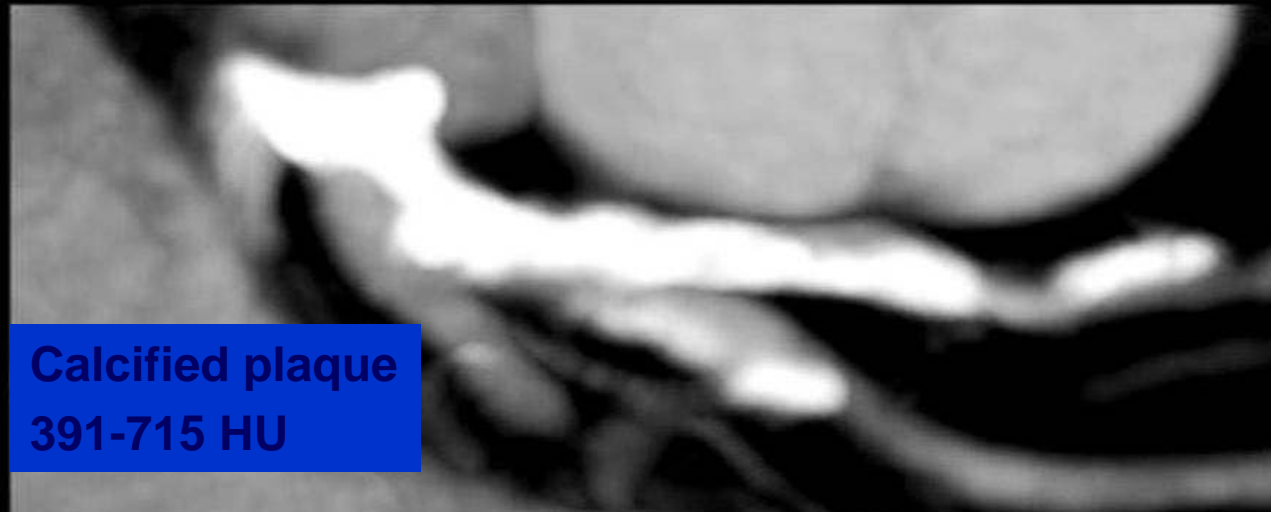


Agatston vs. Contrast-Enhanced Calcium Score

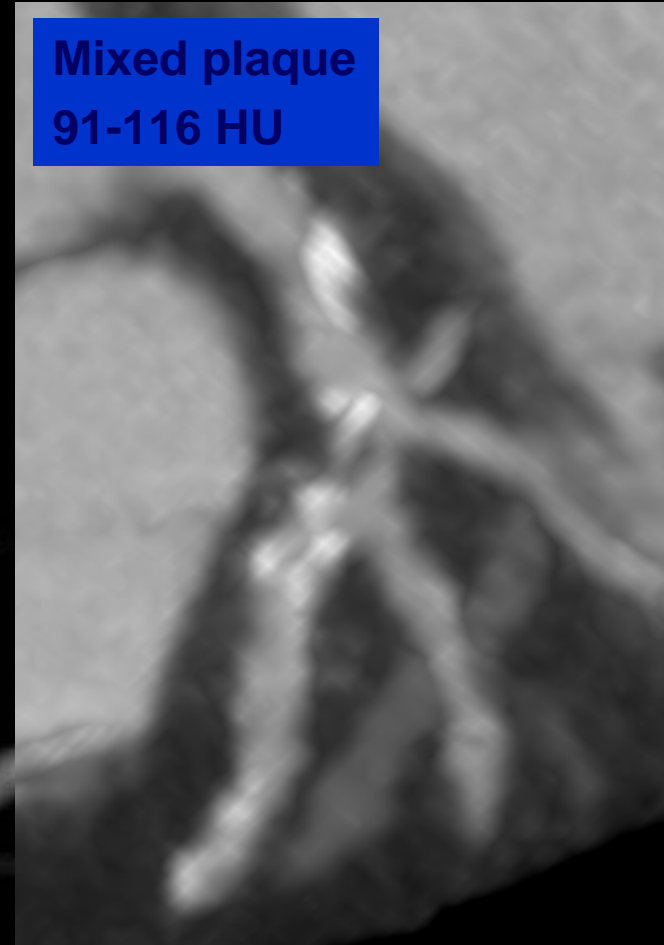
Plaque composition



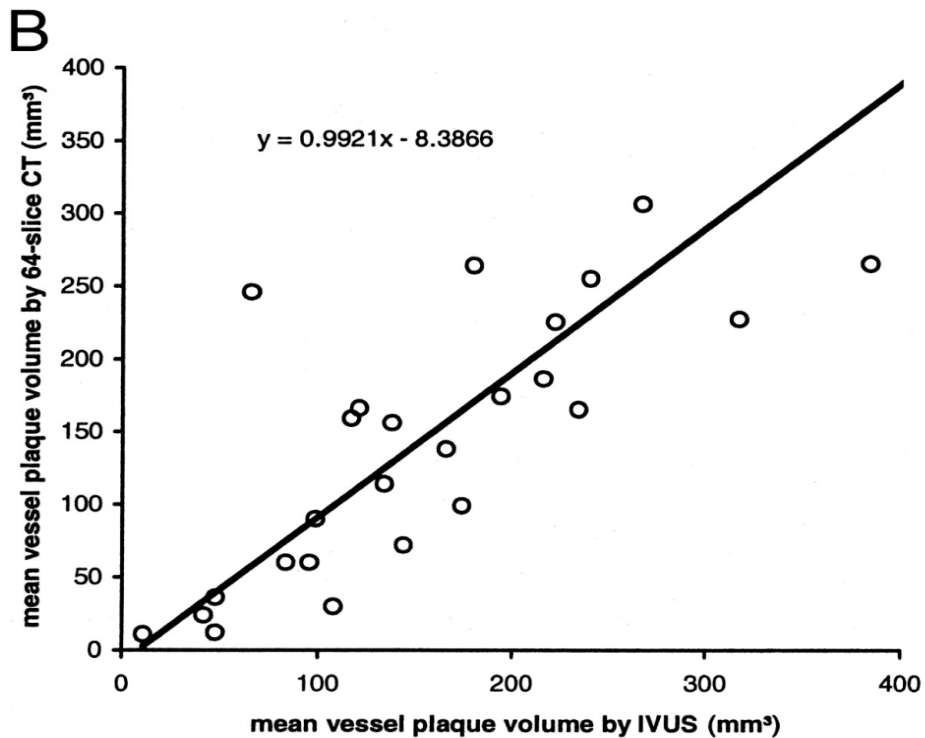
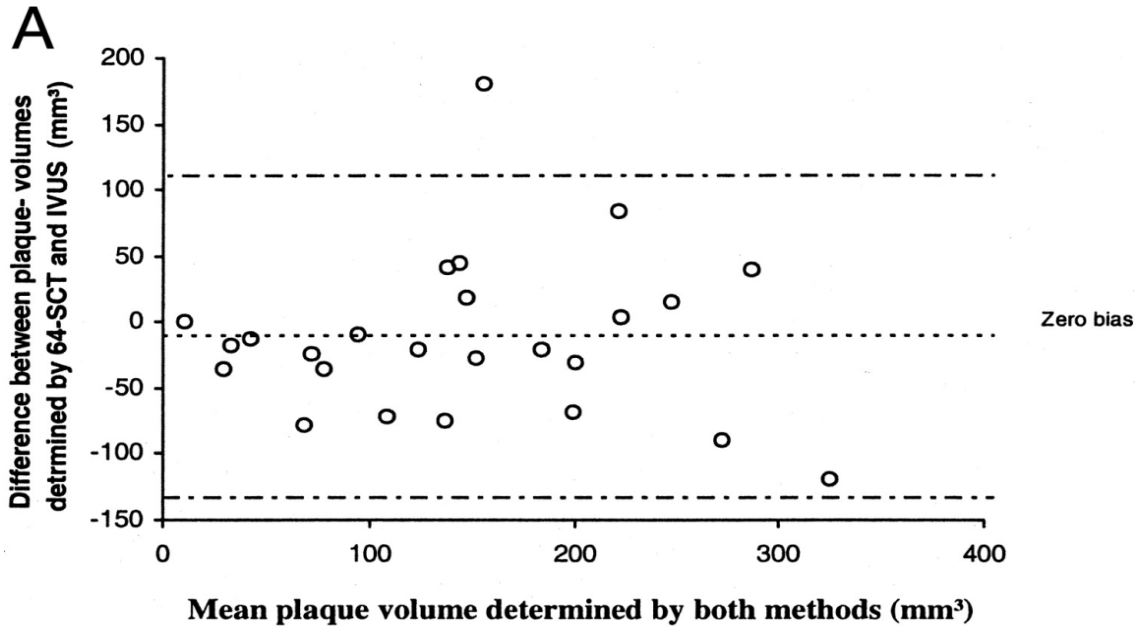
Non-calcified plaque
14-51 HU



Calcified plaque
391-715 HU

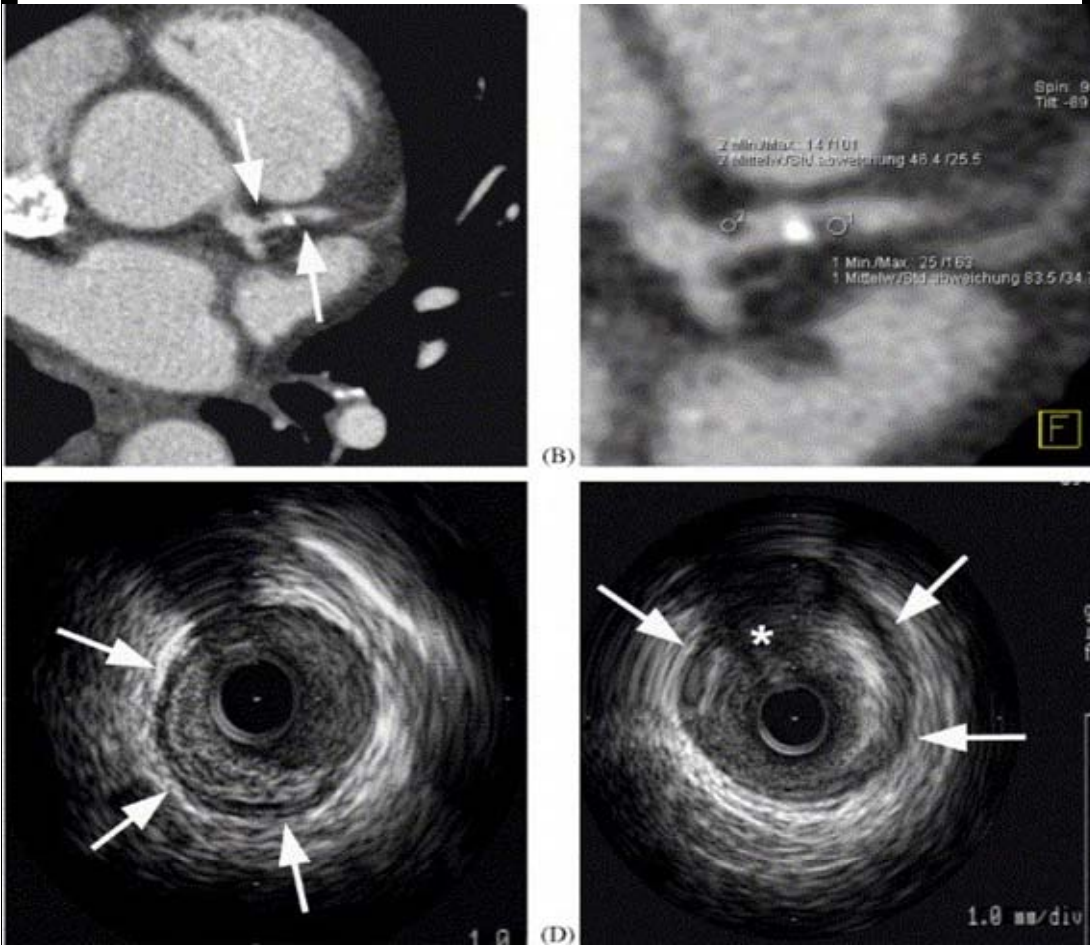


Mixed plaque
91-116 HU



- 20 patients – 64-row CT
- Comparison to IVUS
 - 54/65 (83%) non-calcified
 - 50/53 (94%) mixed
 - 41/43 (95%) calcified
 - 192/204 (94%) accurate identification
- $r^2=0.69$
 - Underestimate mixed and non-calcified plaque

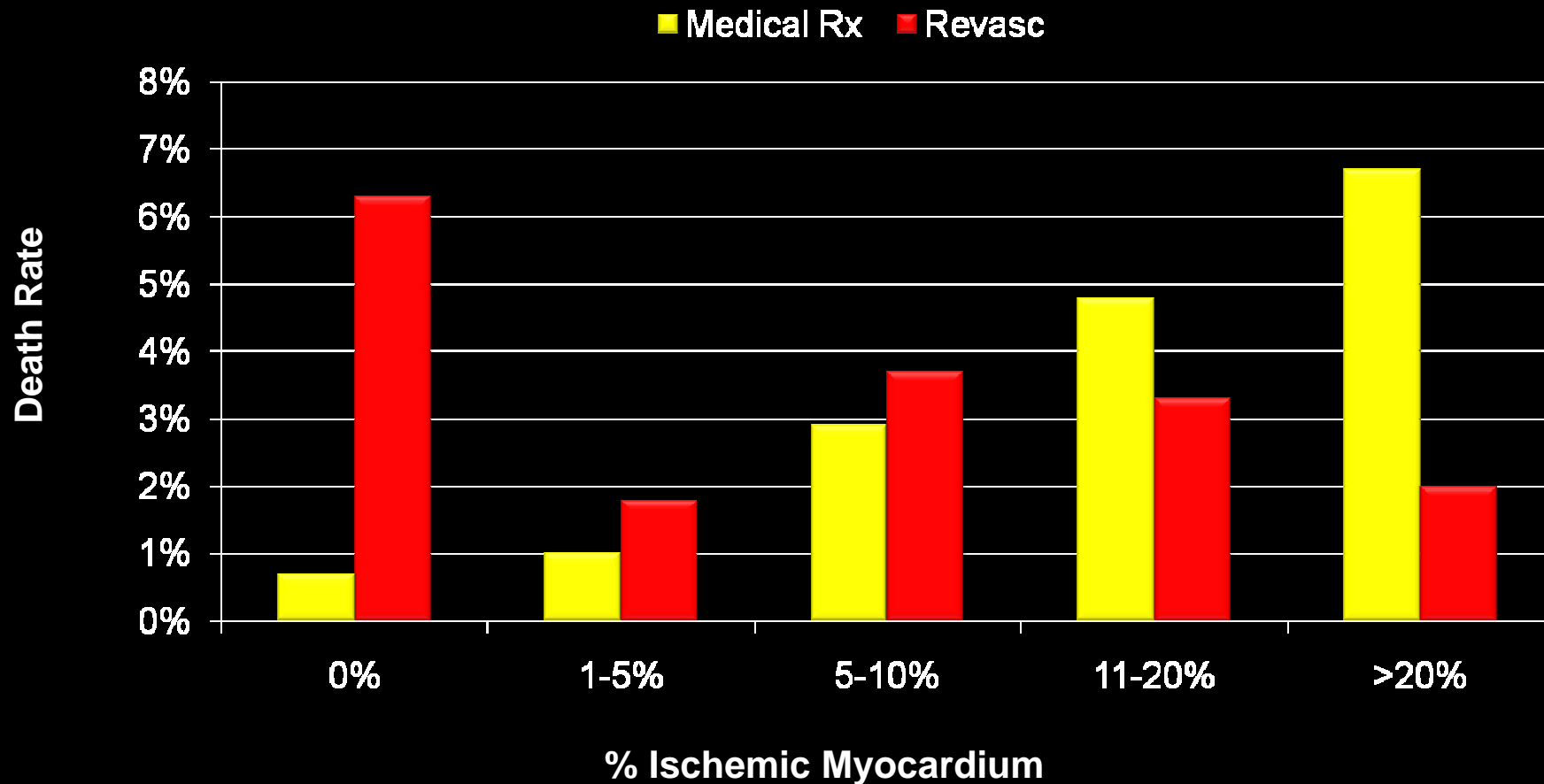
Plaque Characterization - IVUS



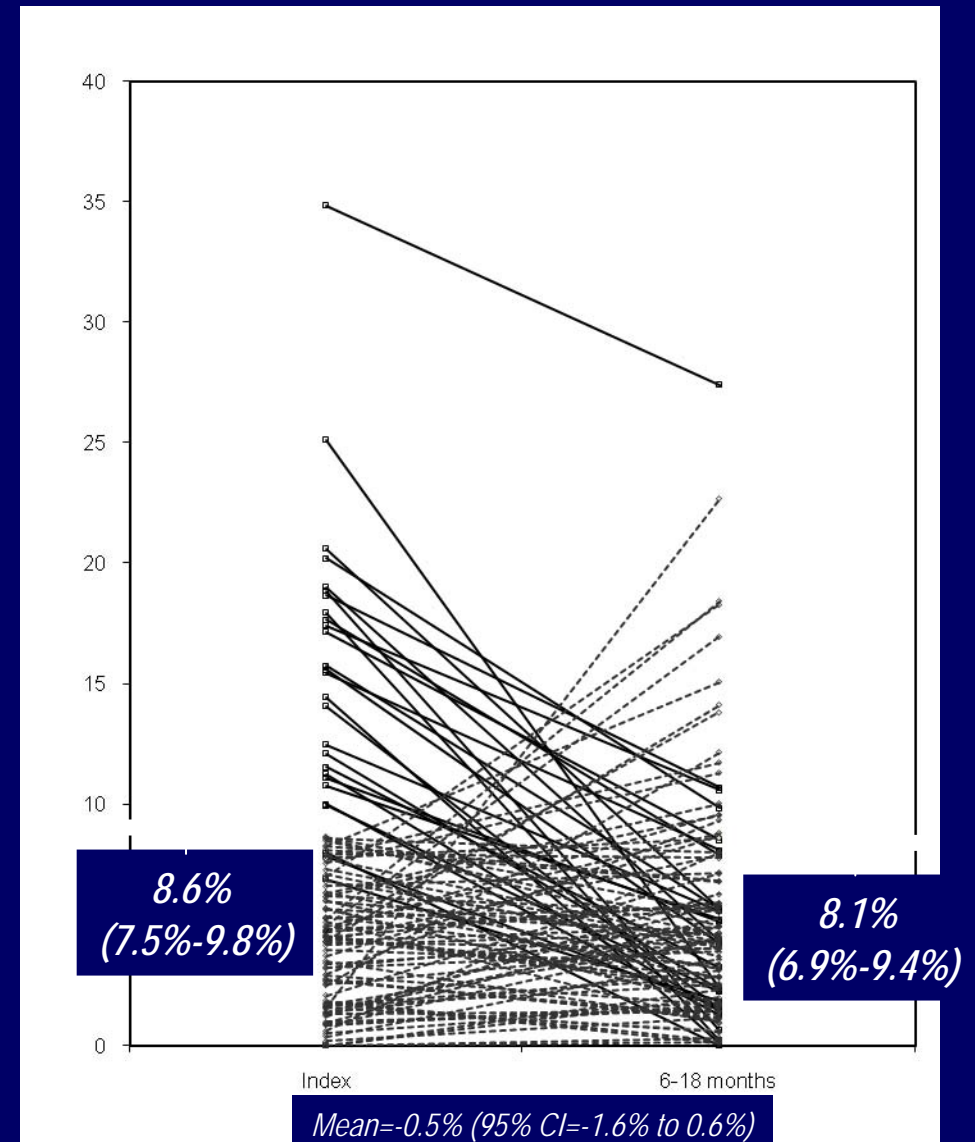
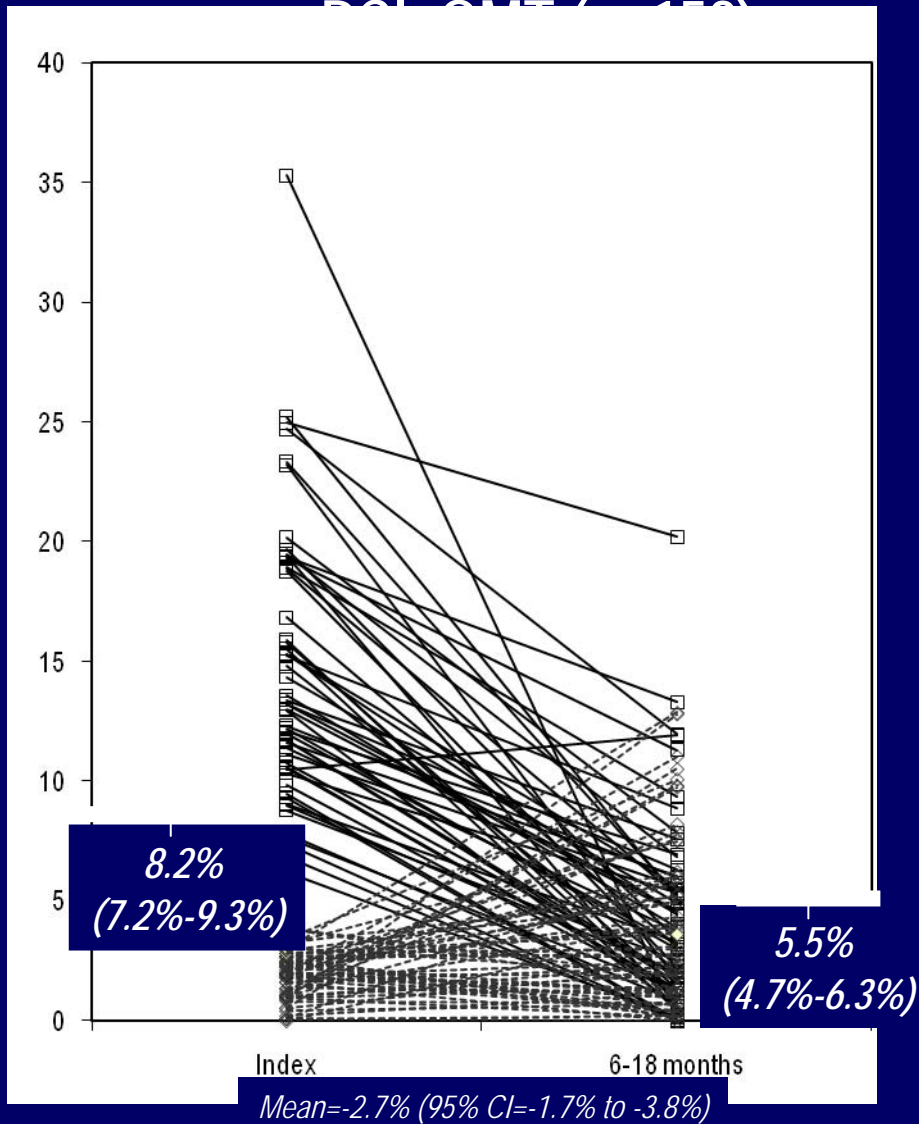
- 32 patients – 16-row CT
- IVUS 252 sites
- Hyper-echogenic IVUS
– 121 ± 34 HU
- Hypo-echogenic IVUS
– 43 ± 58 HU

Risk of Death with Medical Therapy vs. Revascularization: Observational Data

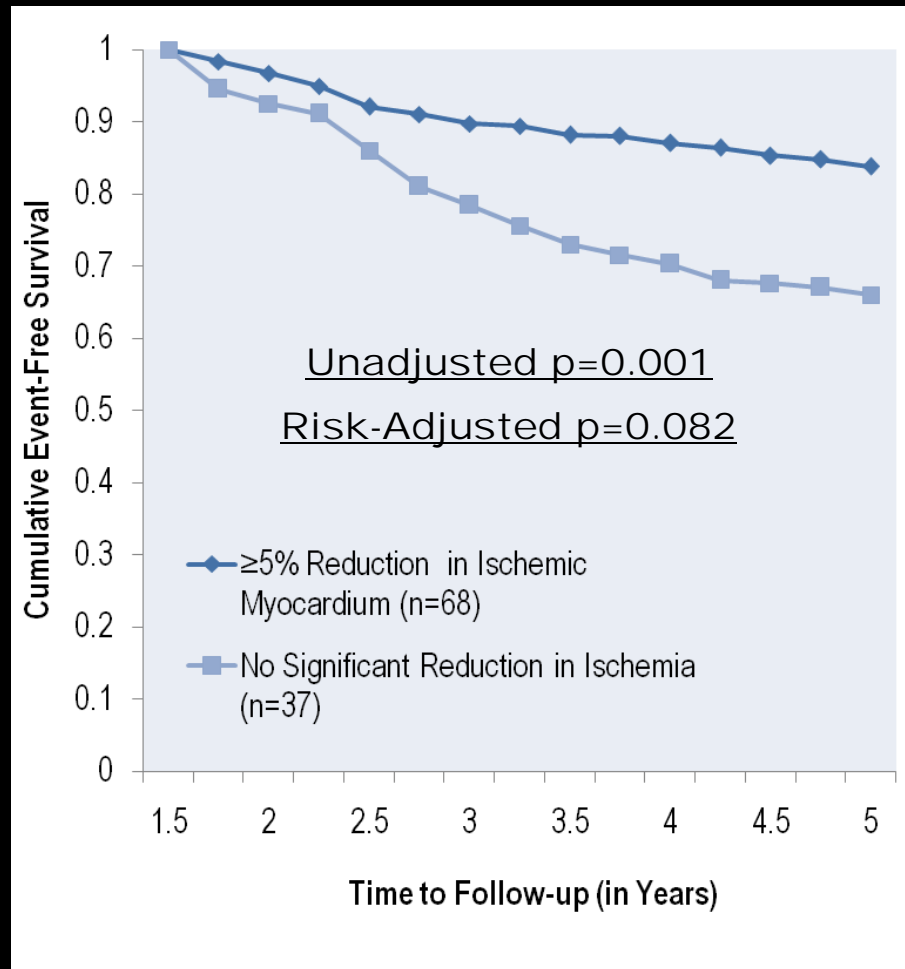
N=13,555; 3,893 deaths; F/U 8.7 yrs



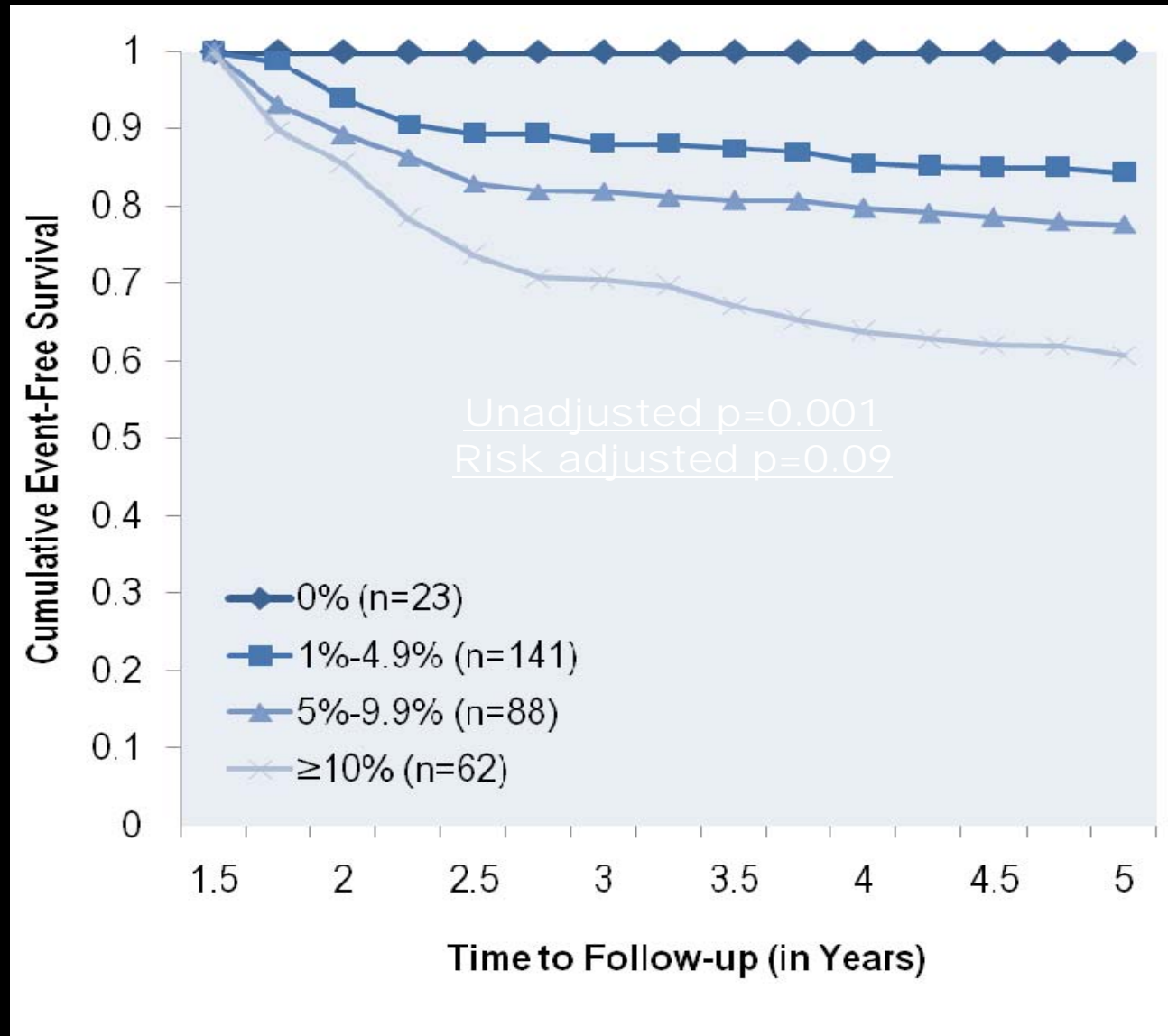
Inducible Ischemia Pre-Treatment and Following 6-18 Months of OMT with or without PCI



*Changes by treatment were adjusted by index ischemia. Dotted lines indicate no significant reduction in ischemia. Solid lines indicate $\geq 5\%$ reduction in myocardial ischemia.



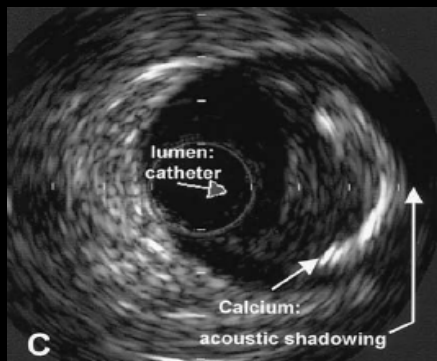
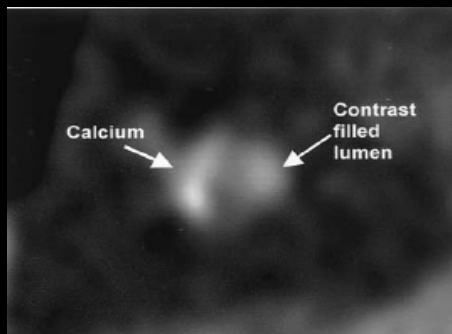
Residual Ischemia and Outcome



Accuracy of CCTA (16-slice) to Identify and Differentiate Plaque Composition

58 vessels in 37 consecutive patients (33 male, 63±8yrs) patients undergoing CCTA and IVUS, examined for accuracy of CCTA for detection of any plaque and plaque composition.

92% (484/525) atherosclerotic lesions correctly excluded.



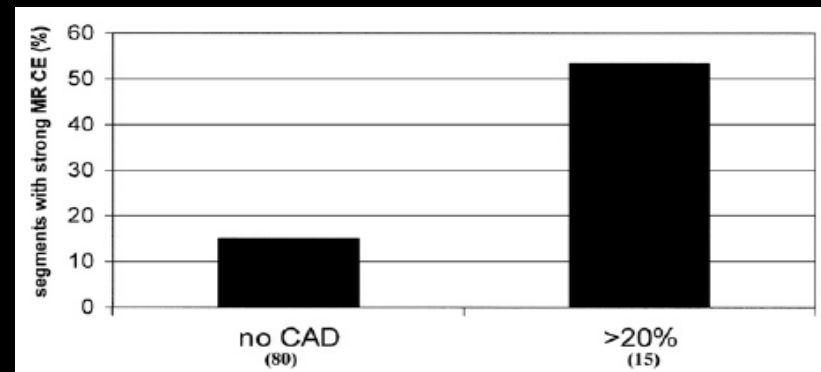
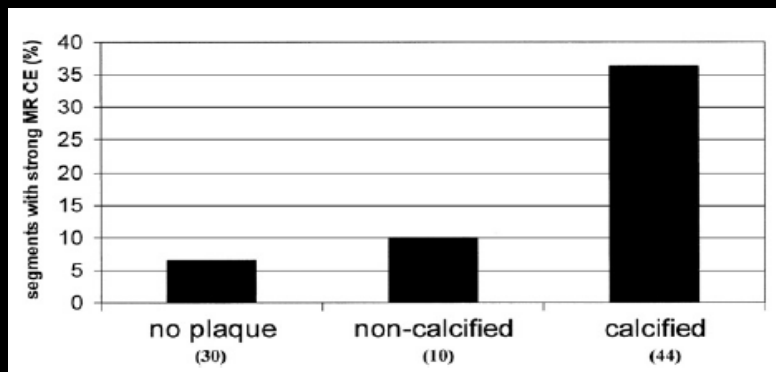
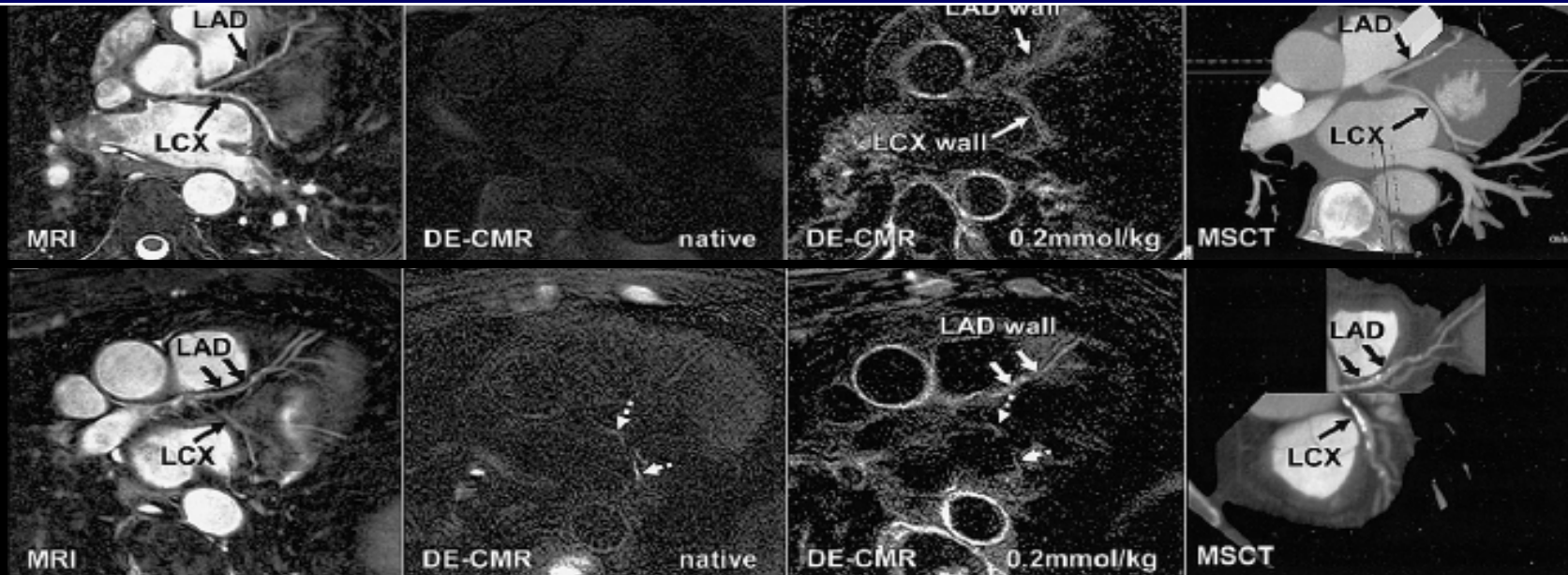
	Soft Sensitivity	Fibrous Sensitivity	Calcified Sensitivity	Total Specificity
RCA	(12/16) 75% (48%–92%)	(27/34) 79% (62%–91%)	(49/49) 100% NA	94/102 92% (85%–97%)
LAD	(44/54) 81% (69%–91%)	(47/62) 76% (63%–88%)	(76/83) 92% (83%–97%)	294/315 93% (90%–96%)
RCX	(6/10) 60% (26%–88%)	(12/16) 82% (54%–95%)	(25/26) 96% (80%–99%)	96/108 89% (81%–94%)
Total	(62/80) 78% (67%–86%)	(87/112) 78% (69%–85%)	(150/158) 95% (90%–98%)	484/525 92% (89%–94%)

	Detected	Not Detected
Plaque thickness	1.5 ± 0.3 mm	0.9 ± 0.3 mm
Vessel size (EEM CSA)	4.5 ± 1.2 mm	3.6 ± 1.1 mm
% Plaque cross-sectional area	42 ± 16%	22 ± 5%

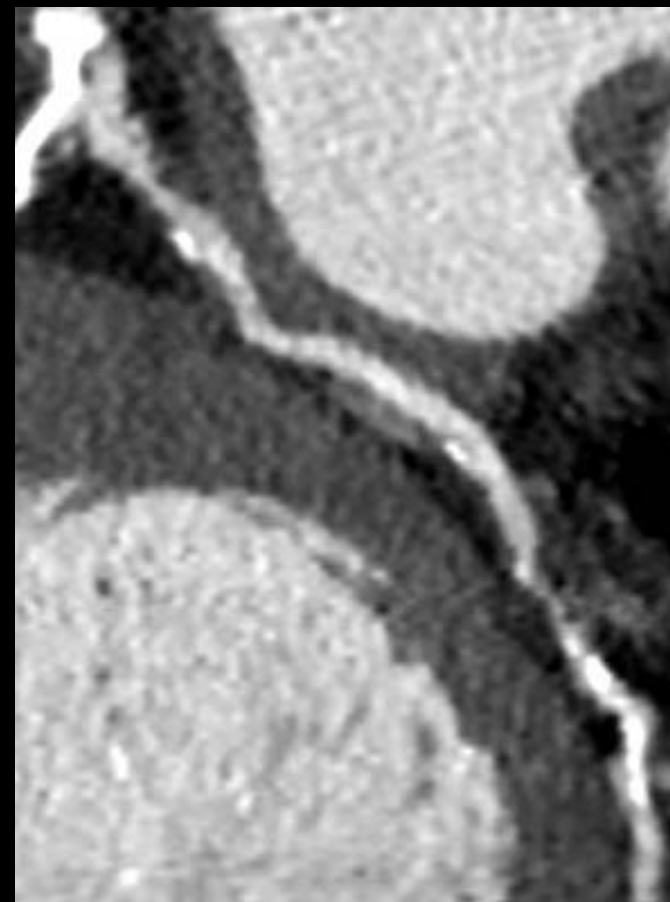
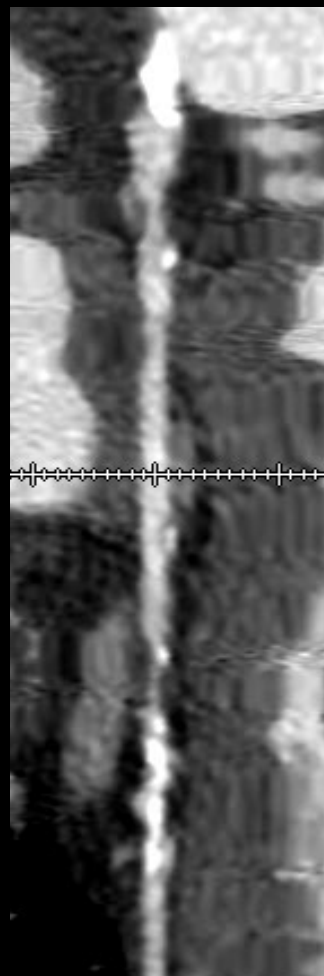
p < 0.05 for all categories.

DE-CMR of the Coronary Arteries and CCTA

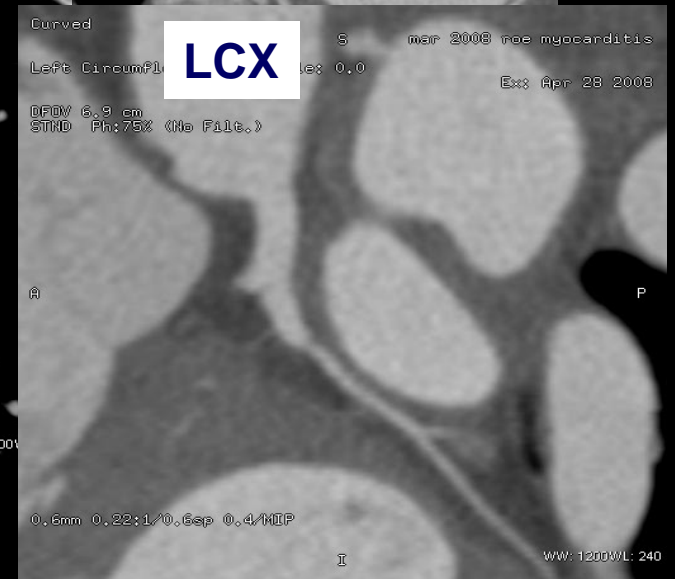
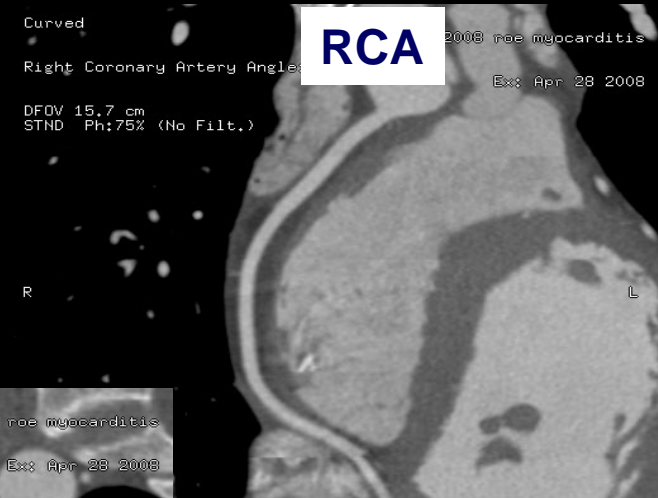
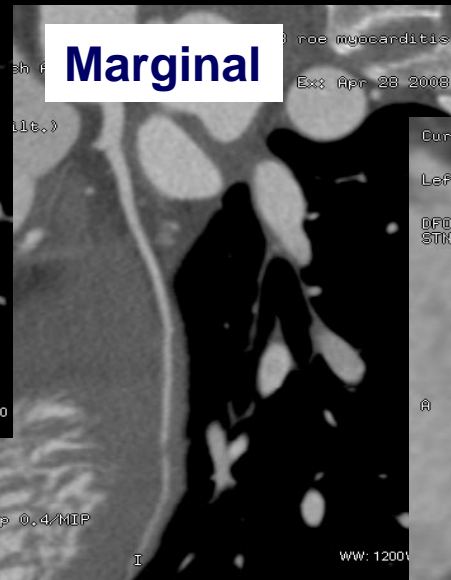
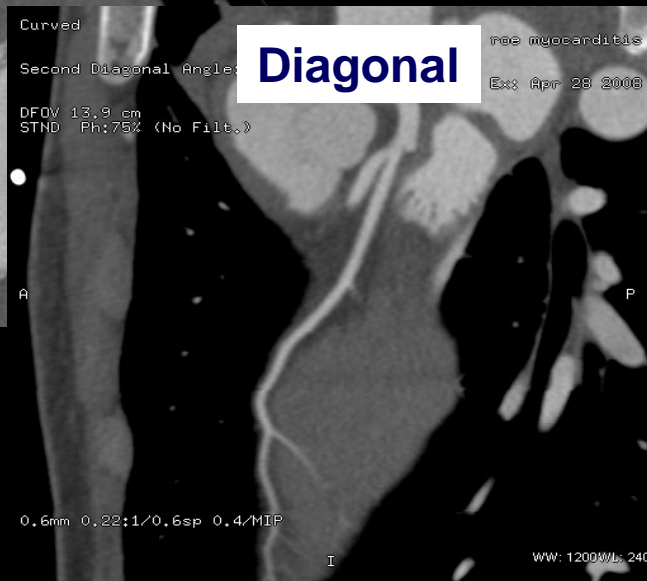
20 pts (14 with CV risk factors, 6 healthy subjects without RF). DE-CMR noted in 2/30 (7%) coronary segments with no plaque by CCTA, 1/10 (10%) segments with non-calcified plaque, 16/44 (36%) segments with calcified plaque ($p=0.035$). DE-CMR noted in 8/15 (53%) segments with $>20\%$ coronary artery stenosis by QCA but also in 12/80 (15%) segments w/o stenosis ($p=0.01$).



A patient.

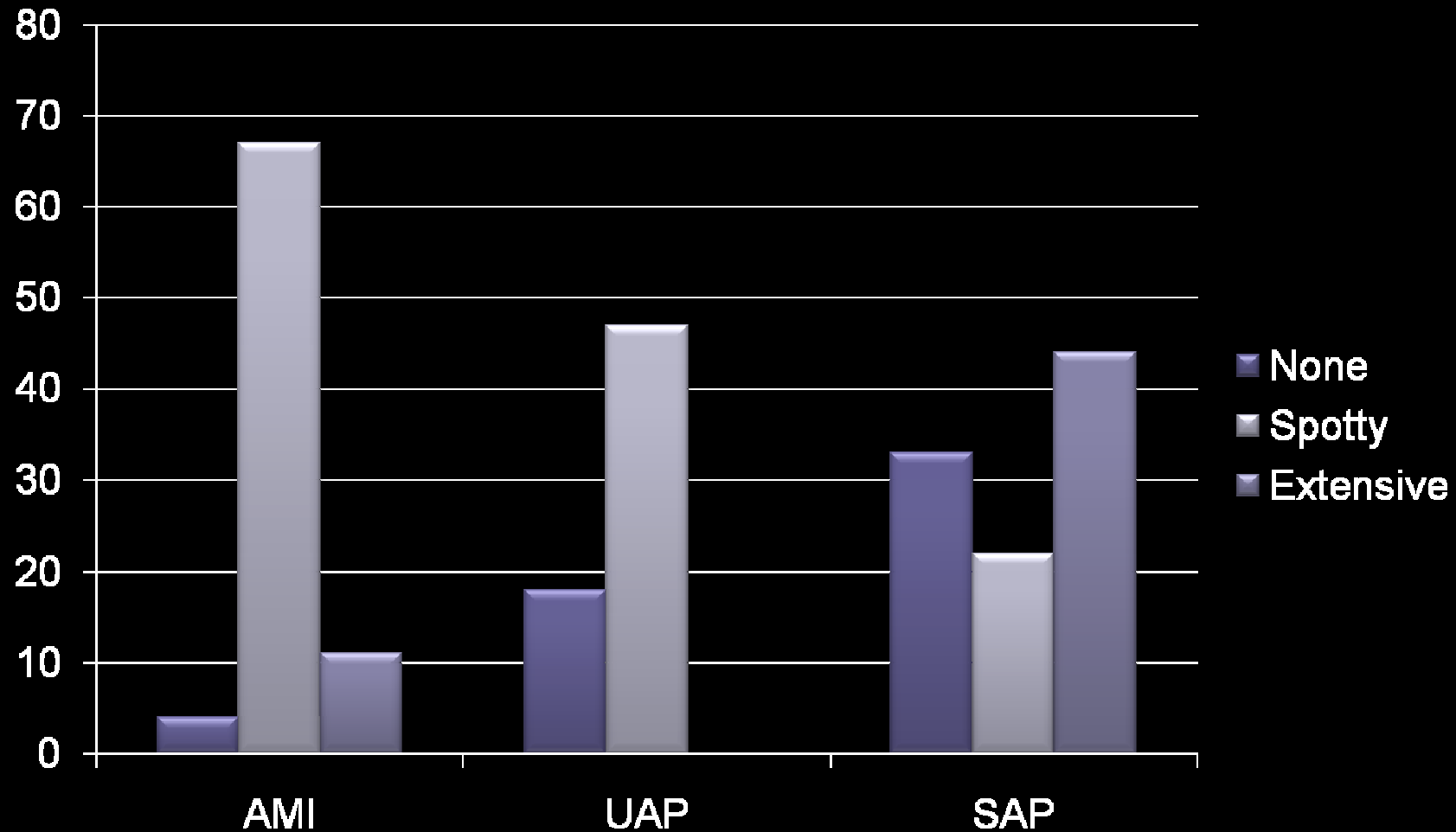


Another patient.

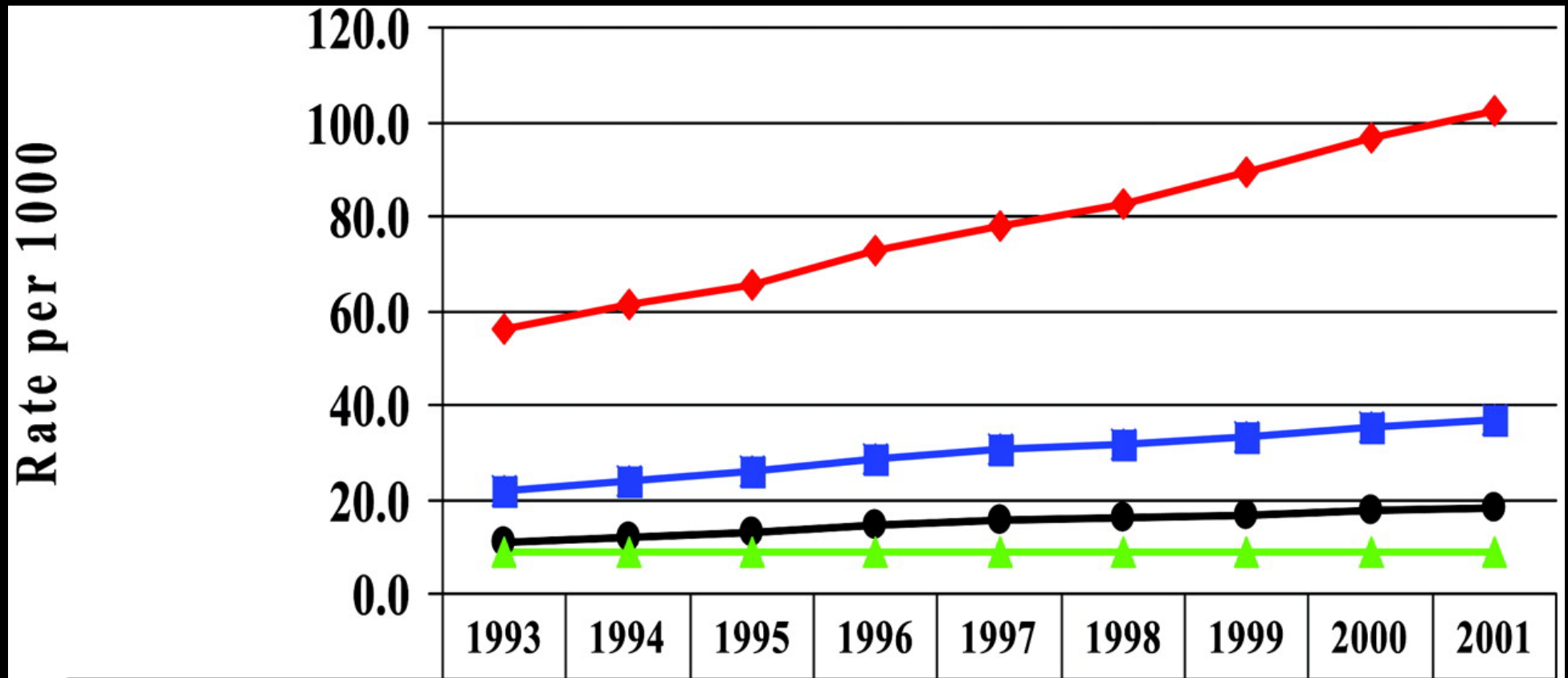


Spotty Calcification Typifies the Culprit Plaque in AMI (IVUS)

% Patients with Positive Remodeling and Calcification Patterns



Utilization of non-invasive and invasive testing.



- 50% of all imaging relates to CV imaging
- 3 fold increase non-invasive imaging '93-'01

Non-invasive imaging is more clinically relevant because . . .

- It can identify vulnerable patients before not after an acute coronary event.
- It is prognostically valuable.
- It provides incremental information about risk beyond plaque.
- It is safer.
- Patients will do it.

Stable Chest Pain

NPV for death

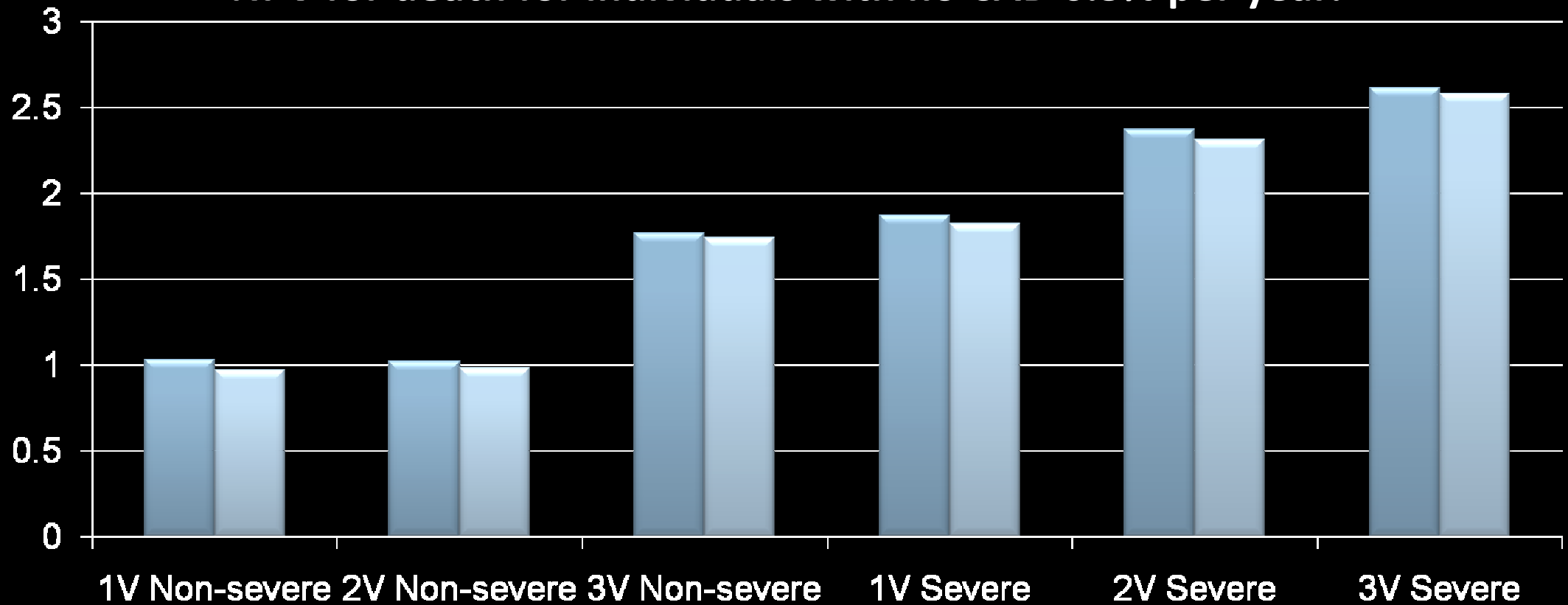
RISK FACTOR	PATIENTS (N)	DEAD (N)	%
Coronary artery plaque score= 0	333	1	0.3%
No left main plaque	951	20	2.1%
No proximal LAD plaque	551	9	1.6%

Negative predictive value 97.9-99.7% for death.

Stable Chest Pain

Long-term Risk Stratification for All-Cause Death

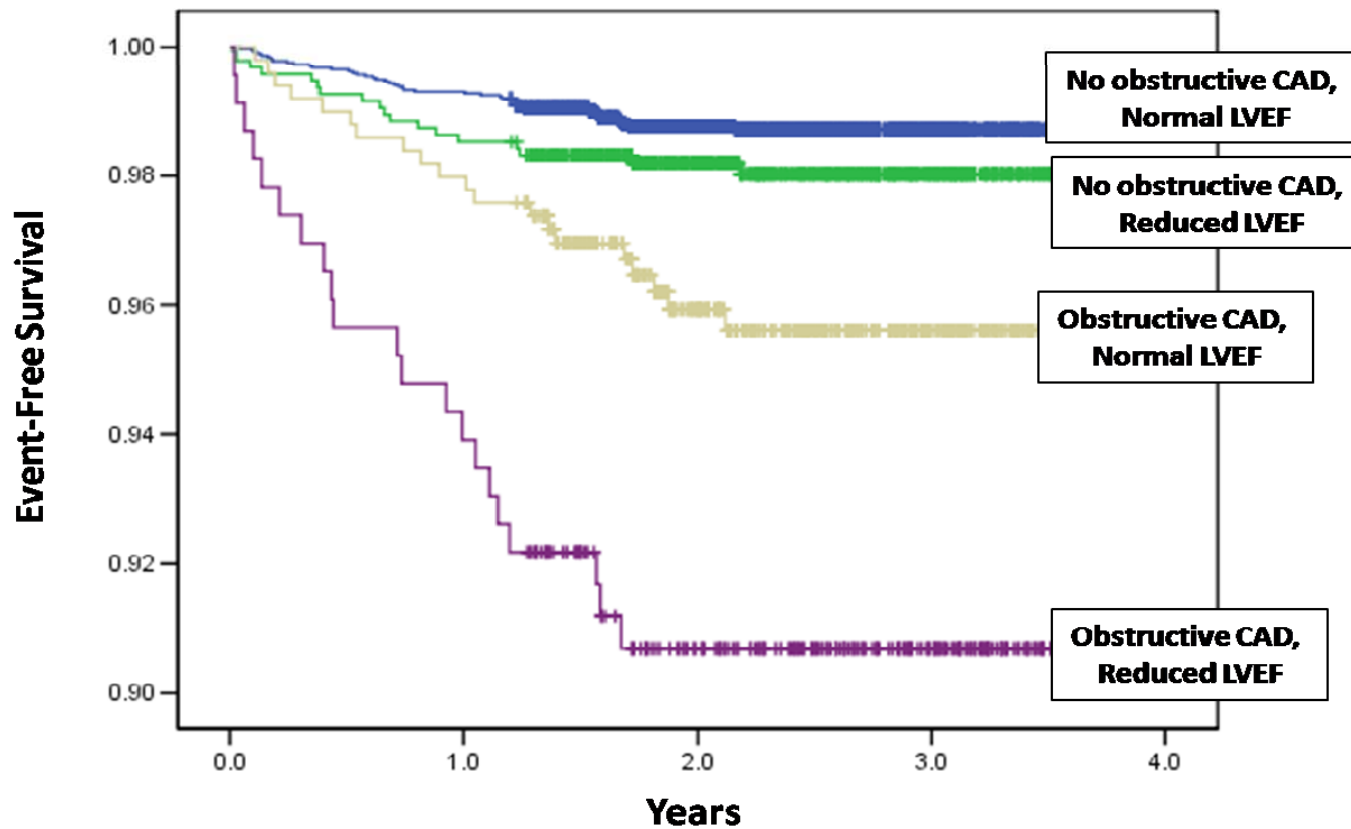
2,538 consecutive patients undergoing CCTA by EBCTA followed for 6.5 years.
NPV for death for individuals with no CAD 0.3% per year.



Stable Chest Pain

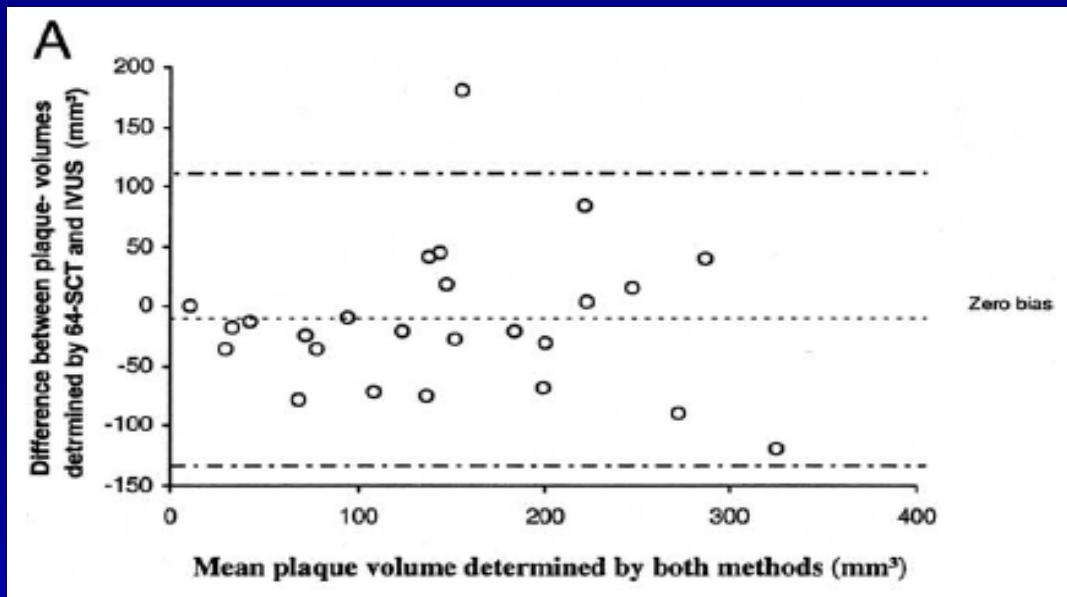
Two Center 64-Detector Row CCTA Risk Stratification for All-Cause Death

5,646 consecutive patients without prior bypass surgery undergoing CCTA followed for 2.3 years.



64-slice CCTA for Classification and Quantification of Plaque Volume in Proximal Coronary System

19 patients underwent 64-slice CCTA and IVUS in 36 vessels. Vessels divided into 3mm sections, evaluated for correct detection of plaque.

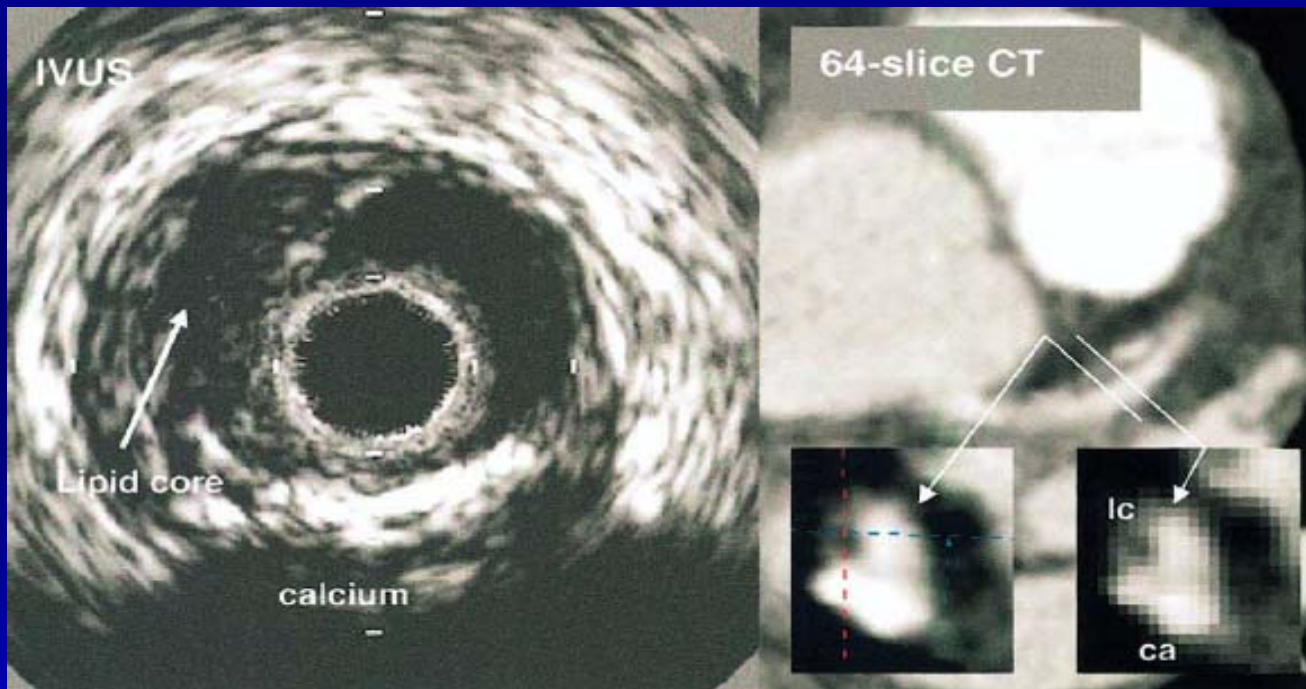


Non-calcified plaque: 54/65 (83%)
Mixed Plaque: 41/43 (94%)
Calcified Plaque: 41/43 (95%)



64-slice CCTA for Classification and Quantification of Plaque Volume in Proximal Coronary System

19 patients underwent 64-slice CCTA and IVUS in 36 vessels. Vessels divided into 3mm sections, evaluated for correct detection of plaque.



Plaque volume/vessel: $r^2=0.69$, $p<0.001$

‡ Underestimates mixed and non-calcified volumes
‡ Overestimates calcified plaque volume

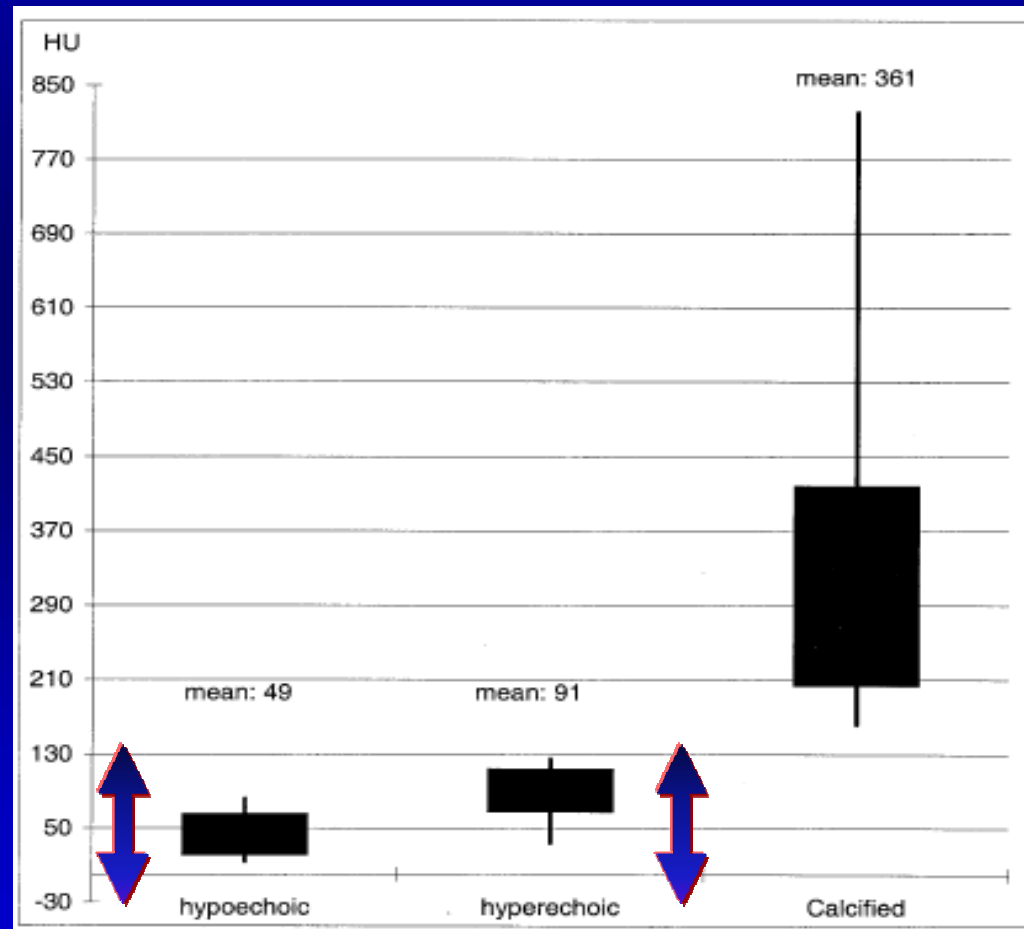
Interobserver variability:

‡ Any plaque ($\kappa=0.75$)
‡ Plaque volume ($\kappa=0.37$)

7/10 (70%) correct for “lipid pool”
27/30 (90%) correct for spotty calcification.

Accuracy of CCTA to Identify and Differentiate Plaque Composition

Current generation CCTA can NOT differentiate effectively between lipid, fibrolipoid or fibrous plaque because HU densities overlap.

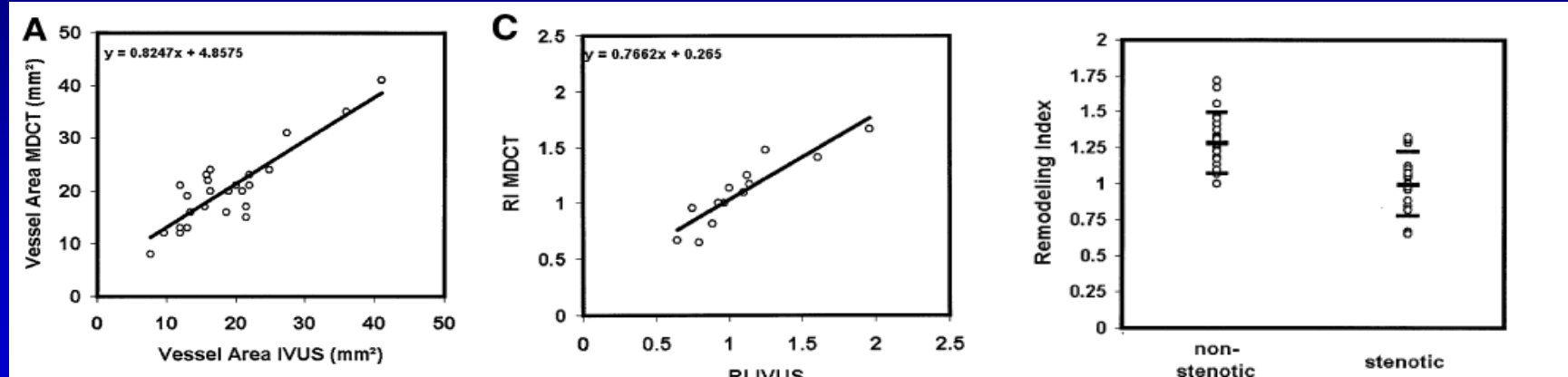
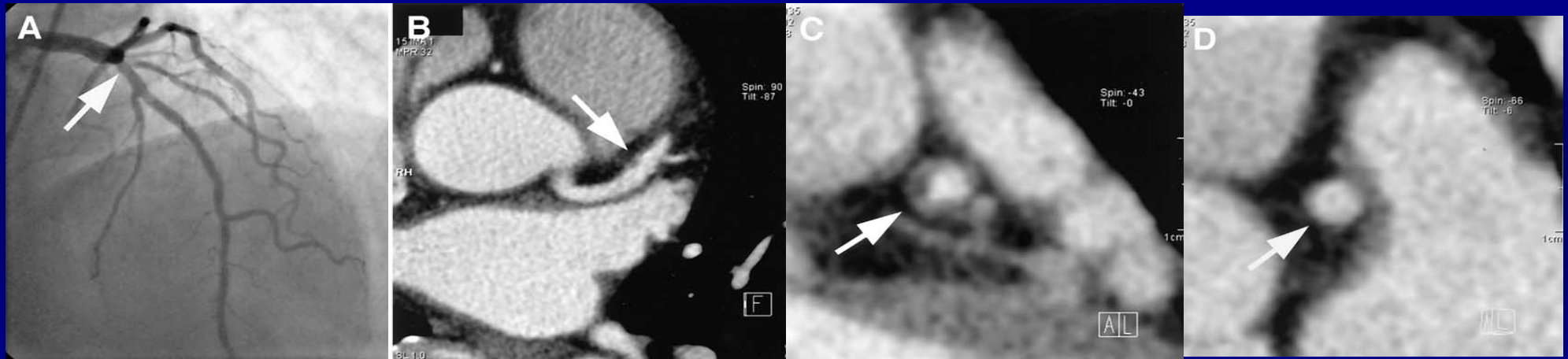


Assessment of Coronary Remodeling by CCTA

44 patients undergoing CCTA and ICA. CSA measured for respective lesion and for reference segment proximal to the lesion.

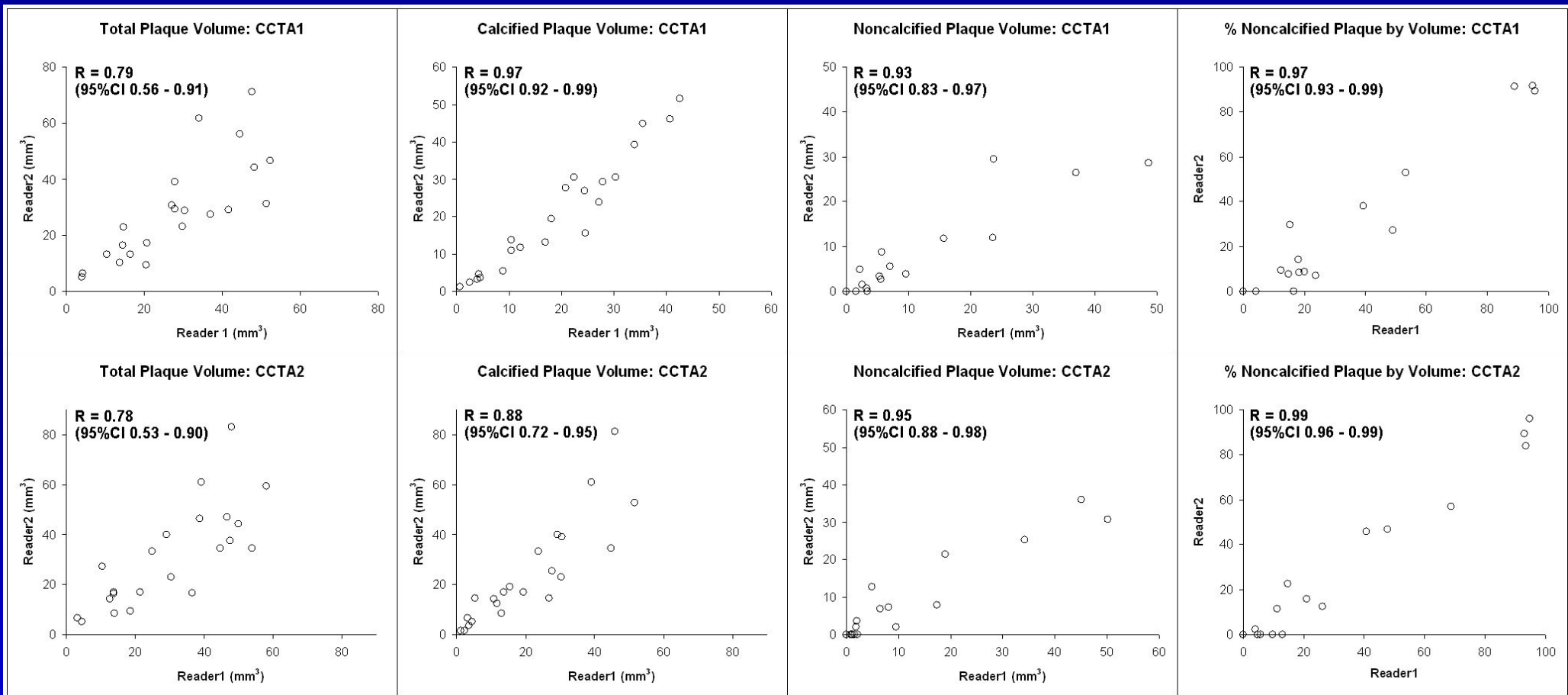
'Remodeling Index' = vessel area/ reference segment.

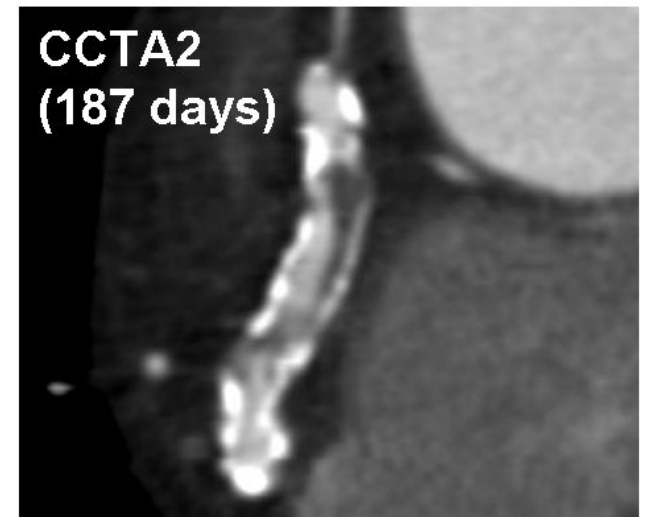
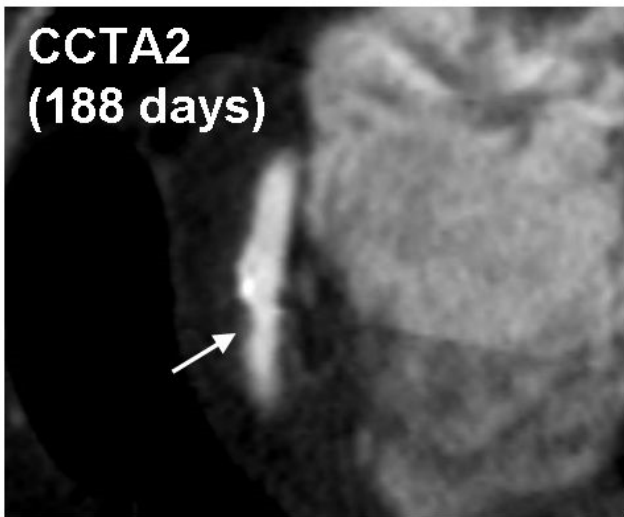
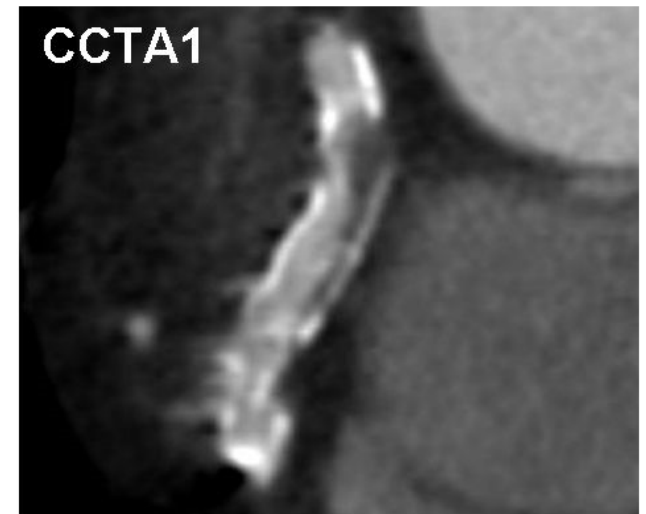
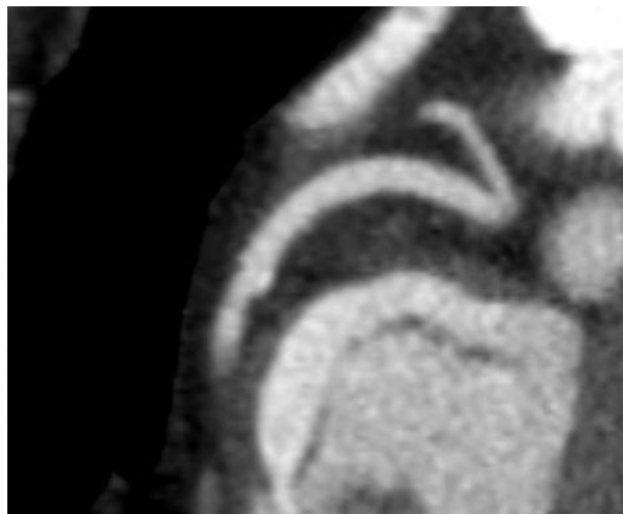
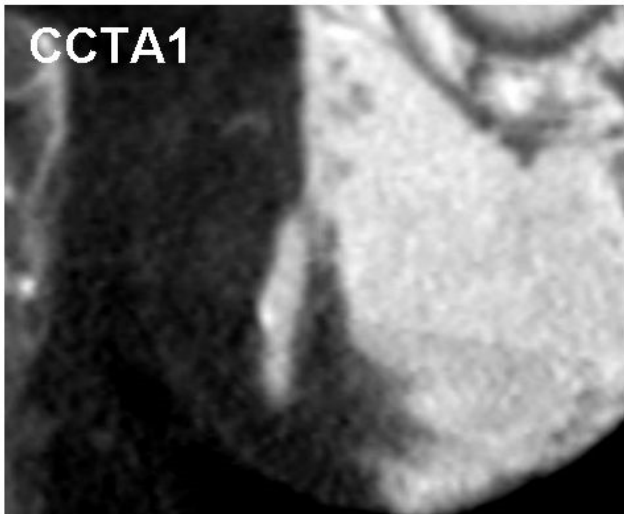
Results correlated to IVUS and ICA stenosis measurements >50%.



Vulnerable Plaque

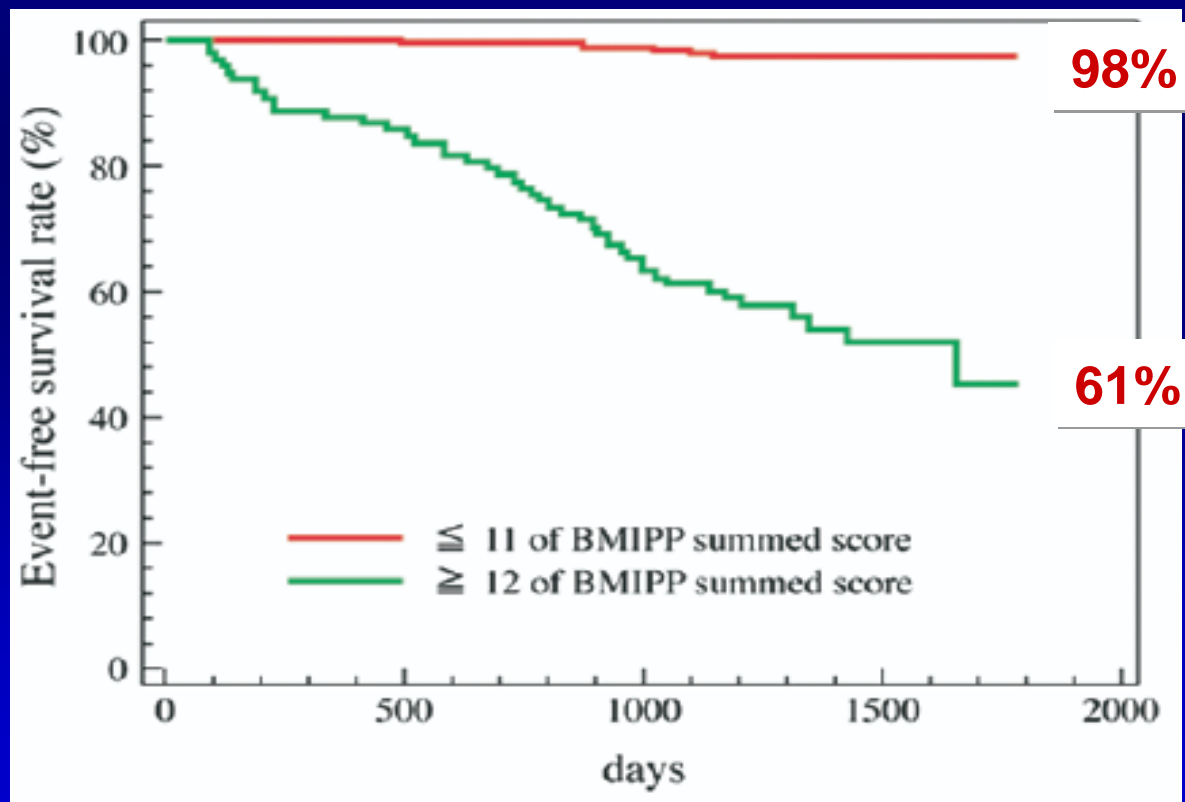
- A **vulnerable plaque** is an atheromatous plaque, an unstable collection of white blood cells (primarily macrophages) and lipids (including cholesterol) in the wall of an artery which is particularly prone to produce sudden major problems, such as heart attack
- Susceptible to physical injury.
 - Implies a state which has not yet occurred, i.e., before the event occurs





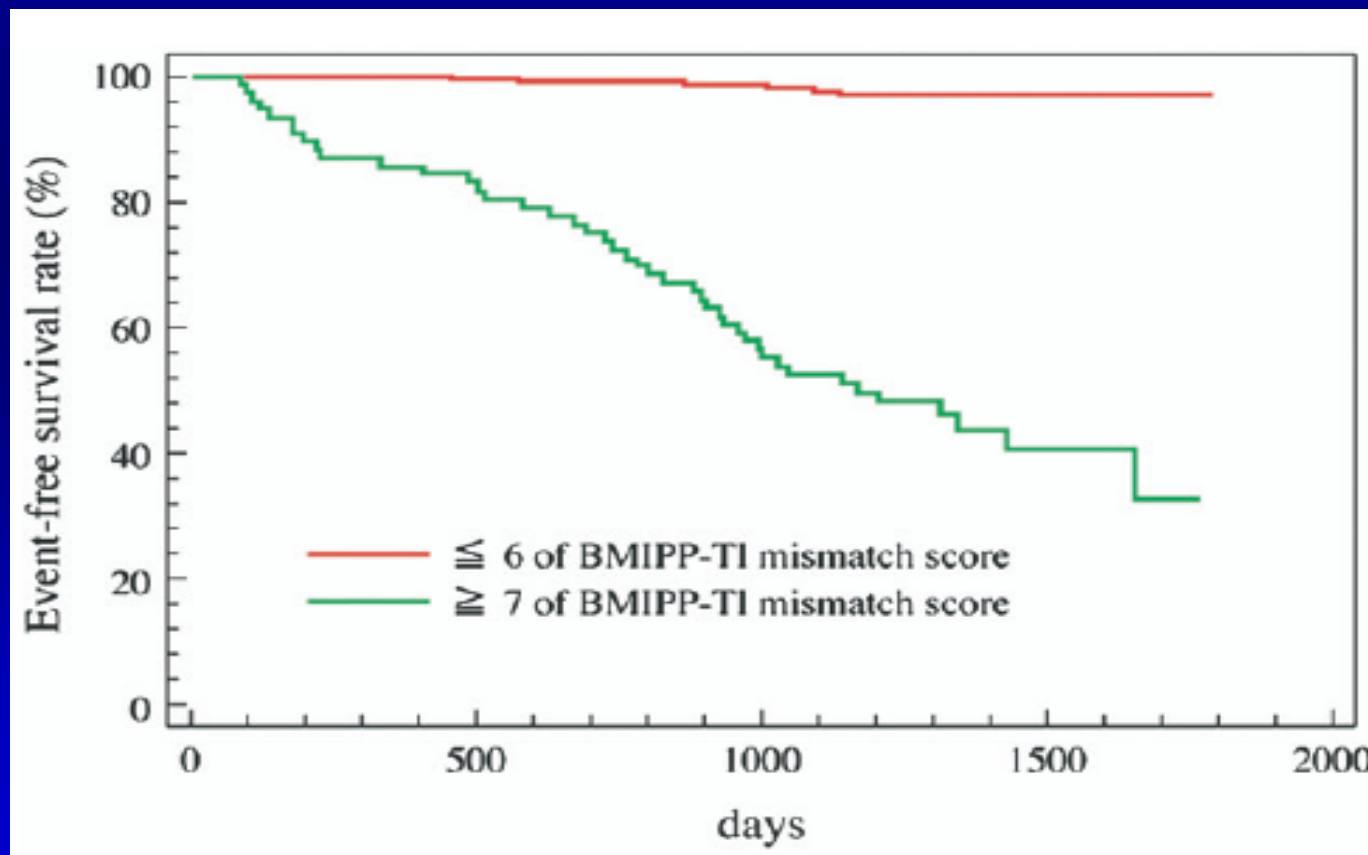
Prediction of Cardiac Death in Hemodialysis Patients by Myocardial Fatty Acid Imaging

Prospective enrollment of 318 asymptomatic HD patients (male/female: 170/148; 64 yrs), without known CAD who underwent dual SPECT using ^{123}I -BMIPP and ^{201}Tl -thallium. 3.6 \pm 1.0 yr f/u. 50 died of cardiac events (MI=22, CHF=17, SCD=11). Cox hazard analysis associated cardiac death with age (70 years) and with abnormal BMIPP SPECT images (BMIPP SSS $>$ 12: HR 21.9; p 0.0001).



Prediction of Cardiac Death by Myocardial Fatty Acid Imaging

Mean BMIPP-TI mismatch score higher in pts with cardiac death than in those w/o (14.0 ± 8.1 [n = 50] vs. 2.9 ± 4.6 [n = 268]; $p < 0.001$).

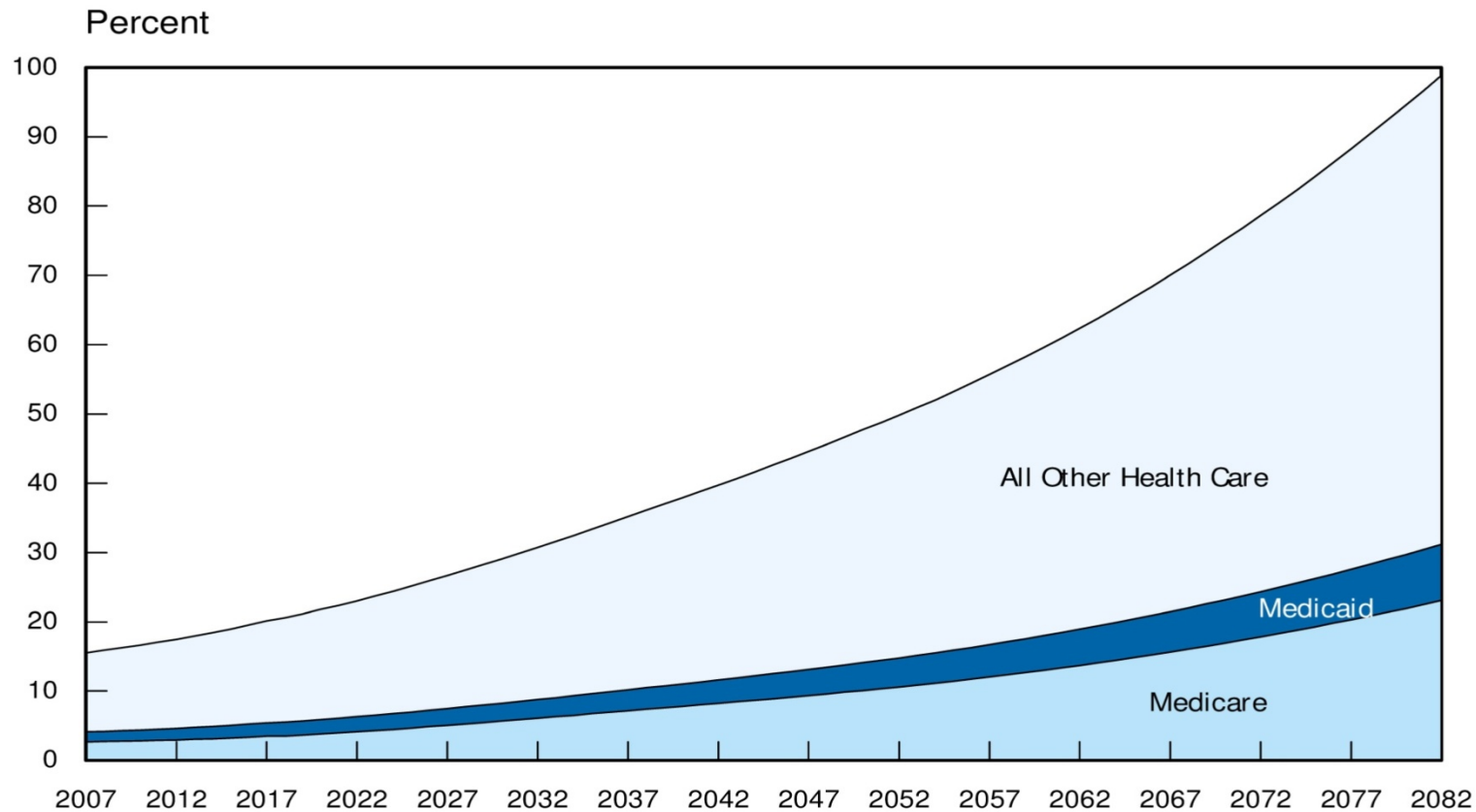


REASON #8:

Non-invasive imaging is less costly.

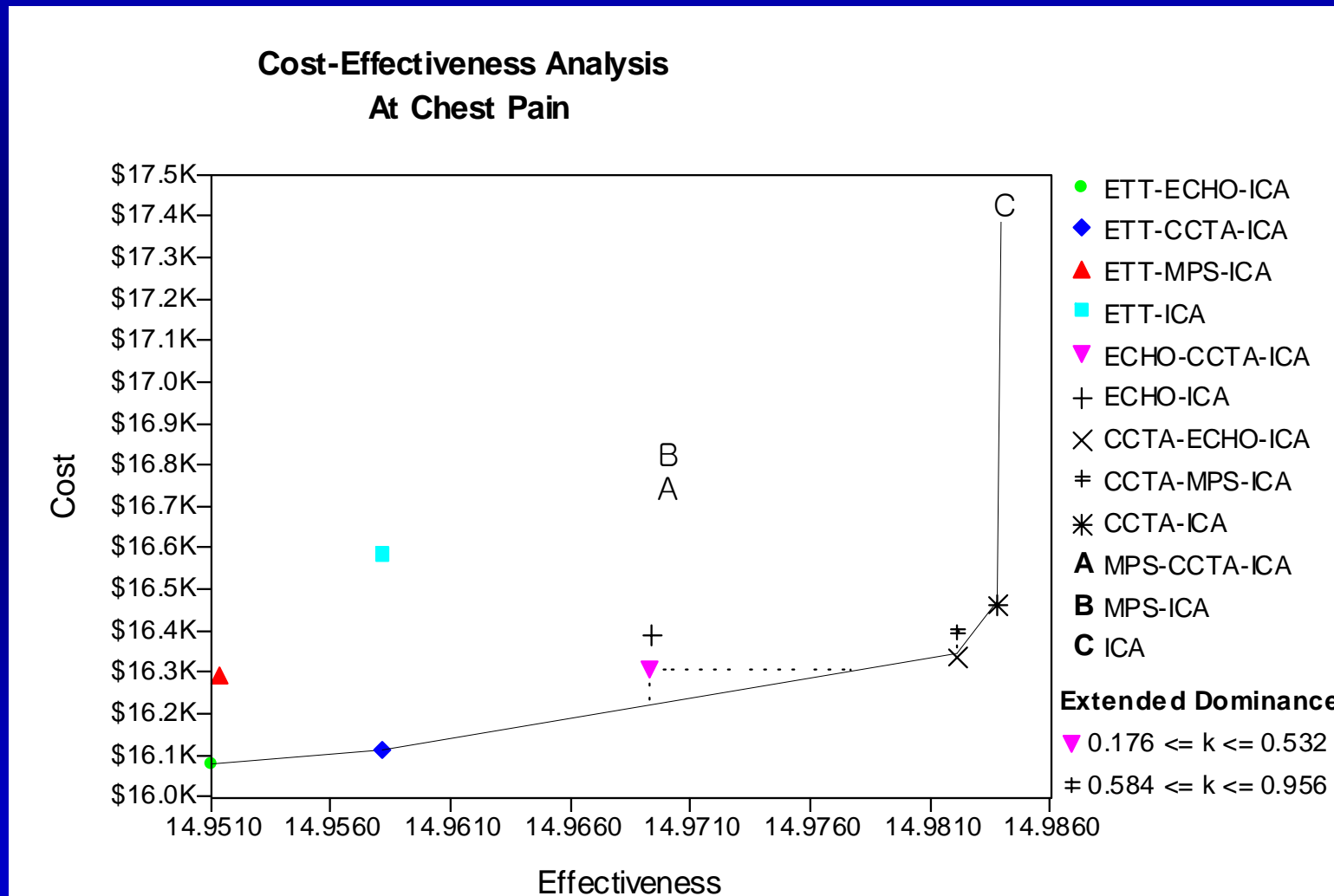


Spending on Health Care as a Percentage of Gross Domestic Product Under an Assumption That Excess Cost Growth Continues at Historical Averages



Ezekiel J. Emanuel, MD, PhD: NIH

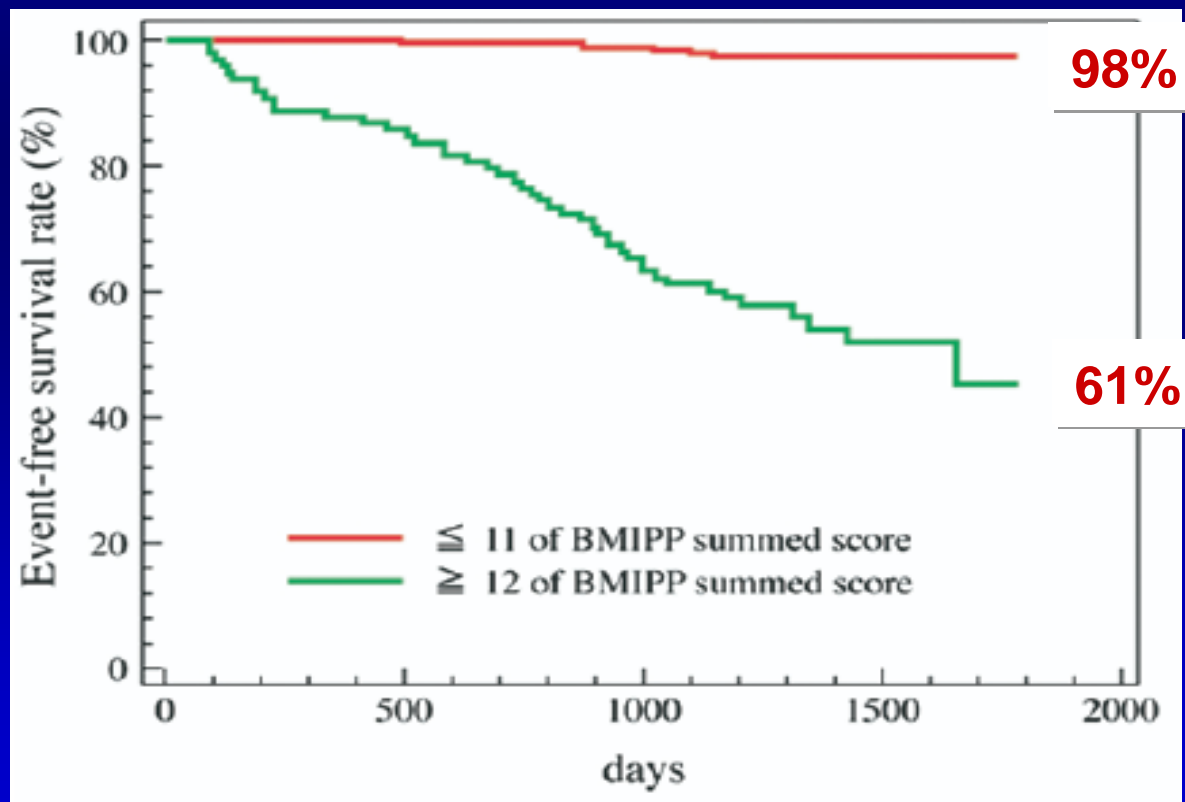
Noninvasive imaging is cost effective.



Min, preliminary data

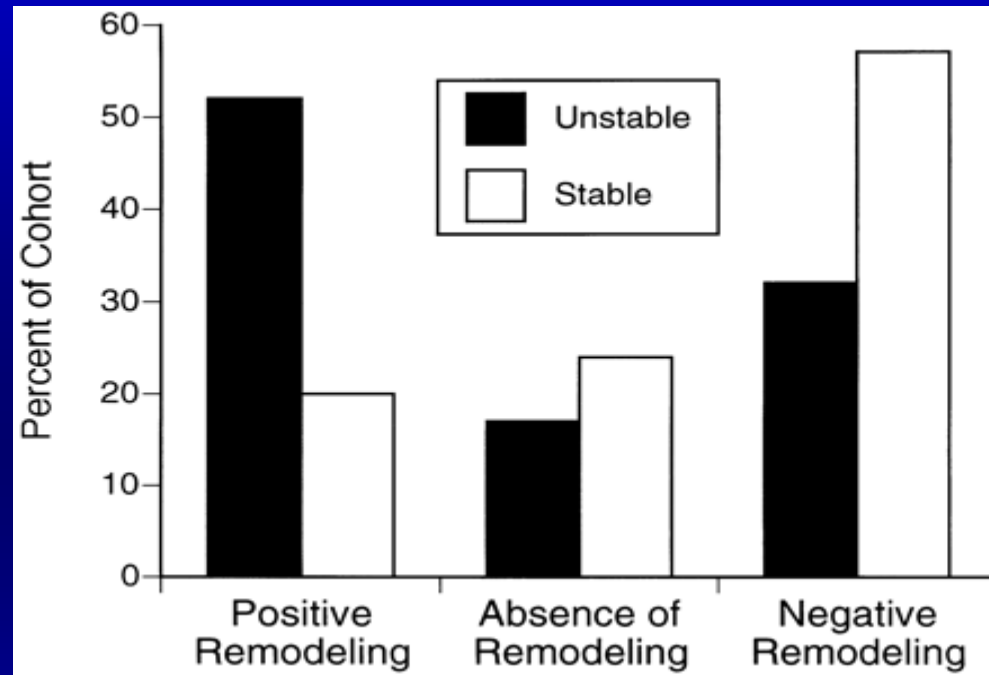
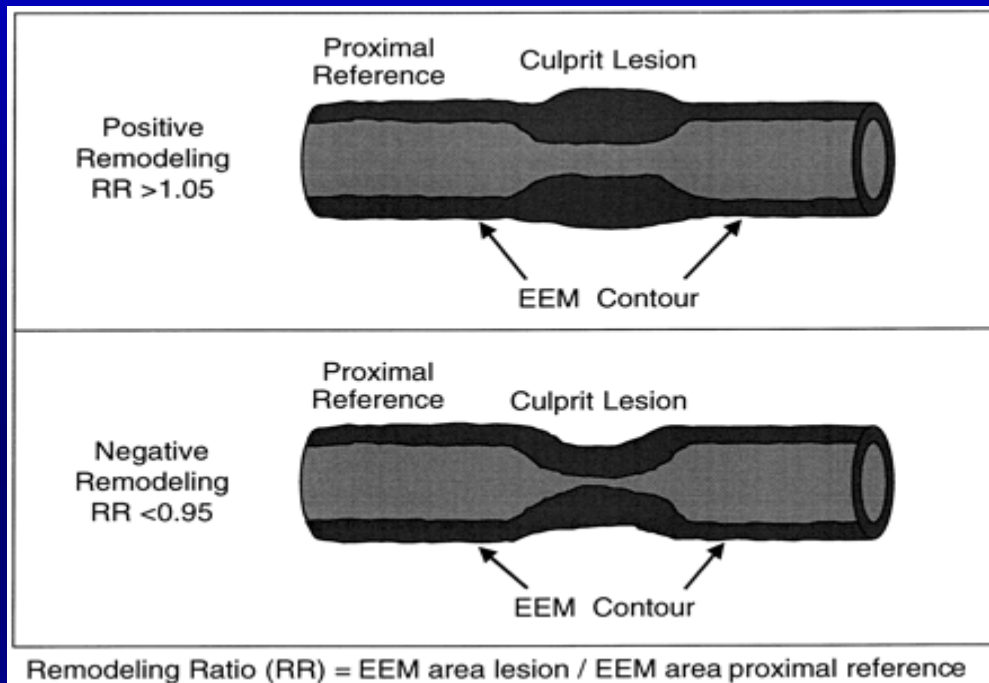
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Extent and Direction of Arterial Remodeling in Stable Versus Unstable Coronary Syndromes: An IVUS Study

85 pts with ACS and 46 pts with stable coronary syndromes studied by IVUS prior to PCI.

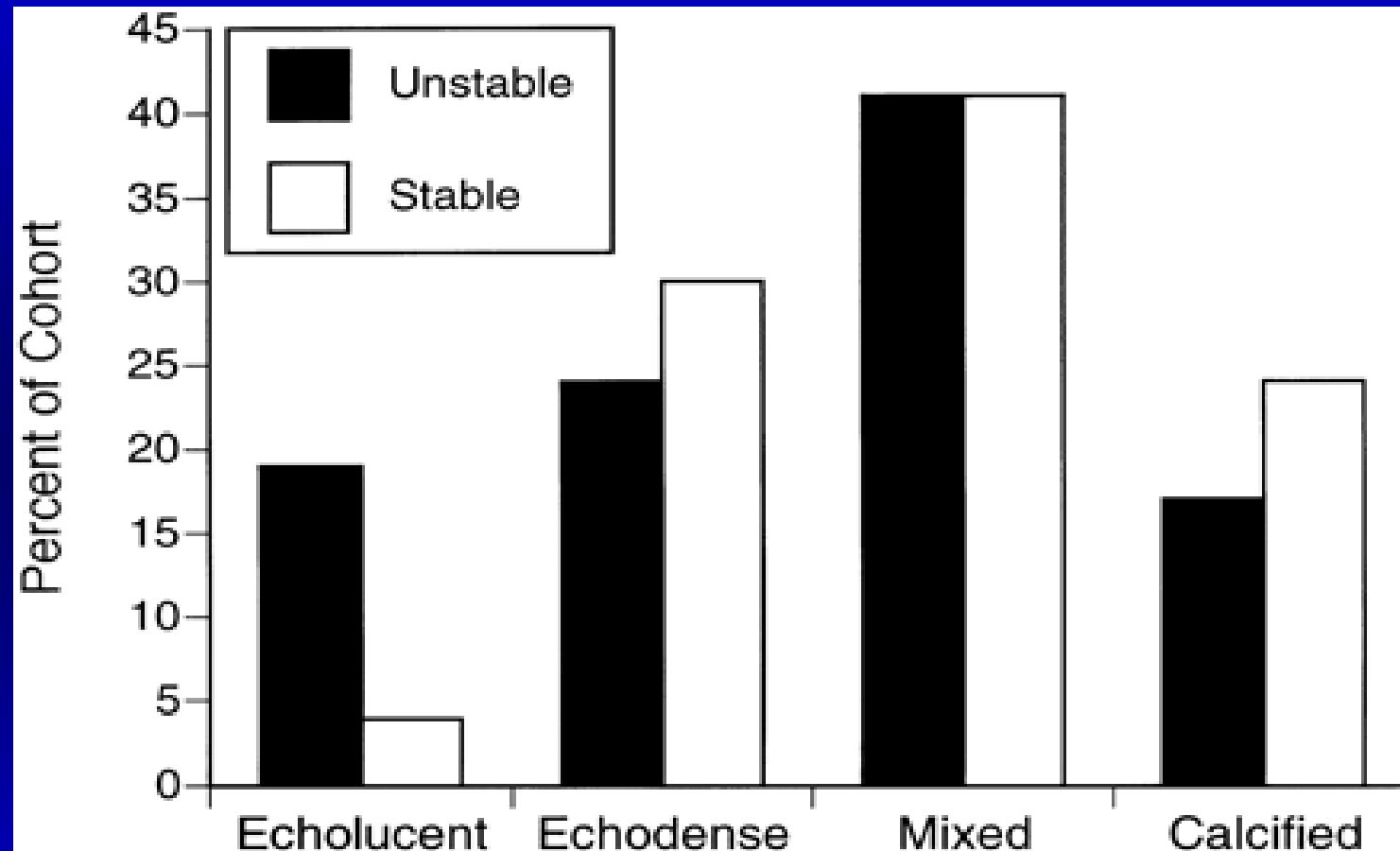


Remodeling ratio (RR) = $(EEM_{lesion}) / (EEM_{prox})$.
 Positive remodeling: RR > 1.05;
 Negative remodeling: RR < 0.95.

ACS vs. Stable Angina:

1. **Plaque area**
(13.9 ± 5.5 vs 11.1 ± 4.8 mm²; $P=0.005$)
2. **EEM area**
(16.1 ± 6.2 vs 13.0 ± 4.8 mm²; $P=0.004$)
3. **Relative Remodeling**
(1.06 ± 0.2 vs 0.94 ± 0.2 ; $P=0.008$)

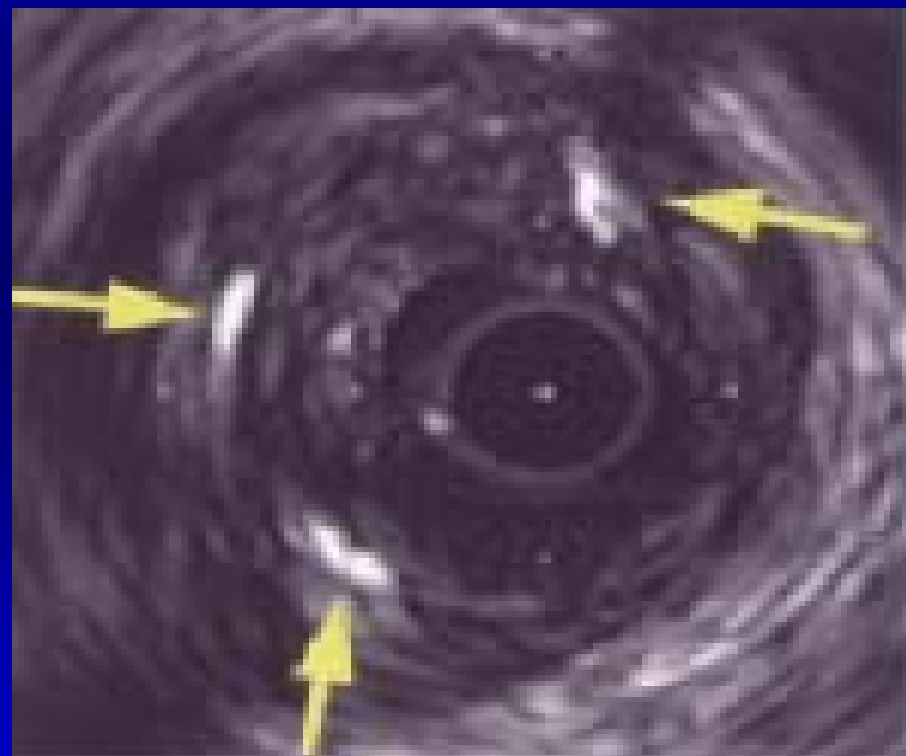
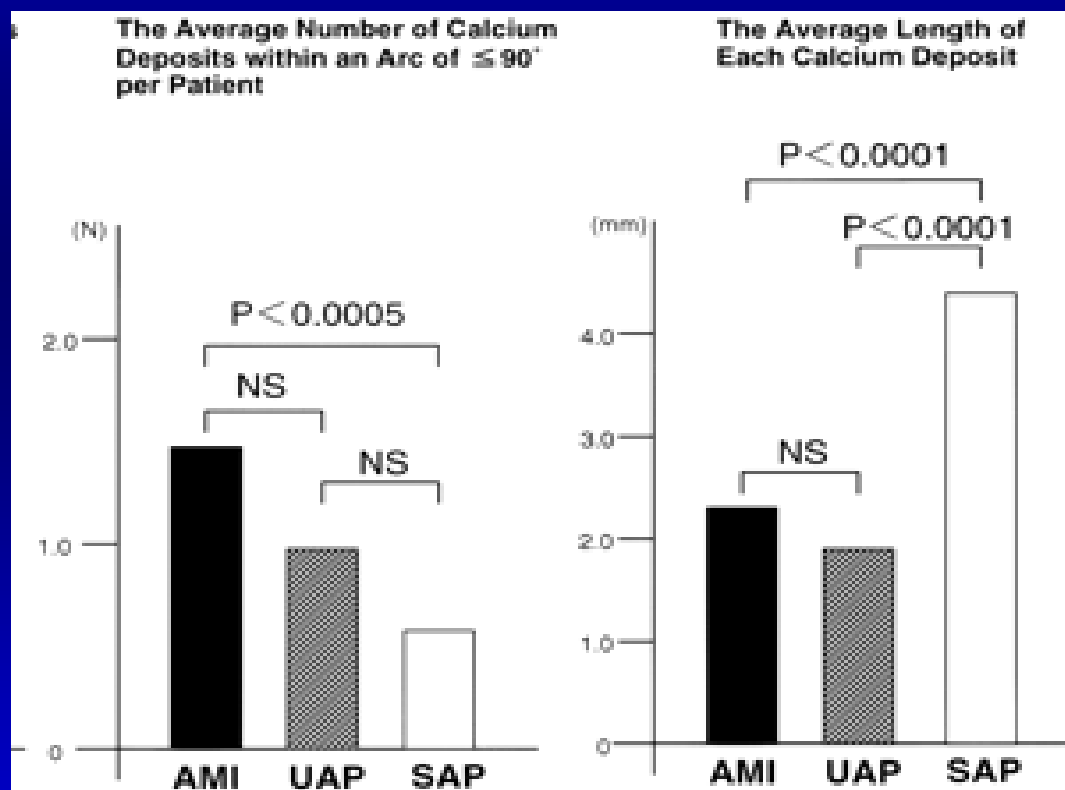
Plaque Composition in Stable Versus Unstable Coronary Syndromes



Compared with the 3 other morphology groups, echolucent plaques were more frequent in the unstable than in the stable angina group (19% versus 4%; $P=0.02$).

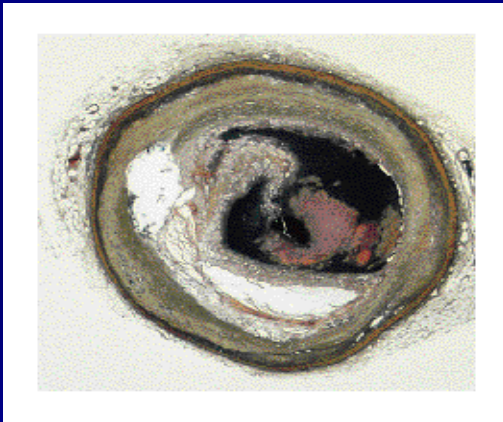
Spotty Calcification in Culprit Plaques in AMI: An IVUS Study

171 pts—61 AMI, 70 UAP, 47 SAP. Frequency and # of calcium deposits within arc $<90^\circ$ for all calcium deposits measured.

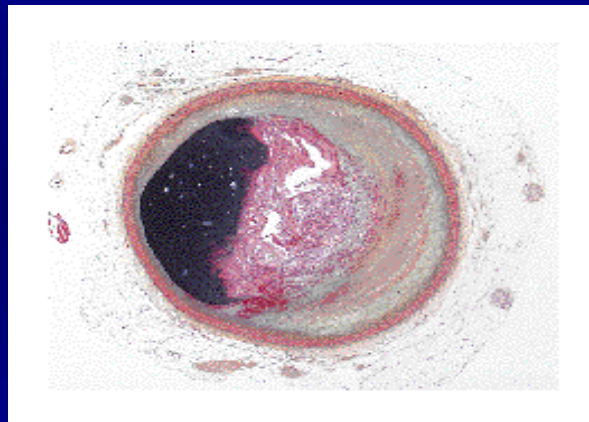


Plaque Morphology in Men with CAD Who Died Suddenly

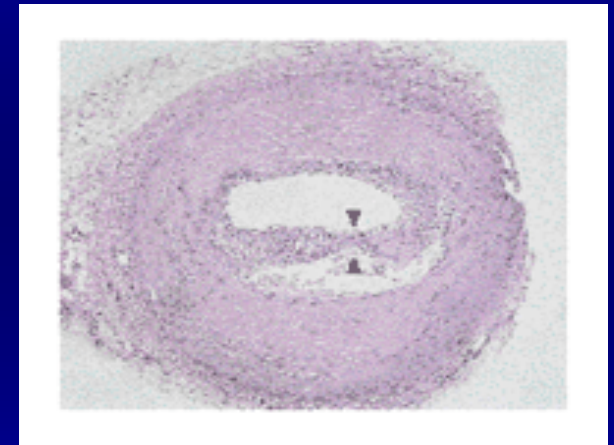
113 men: 59 acute thrombus; 54 severe narrowing by plaque without thrombosis (stable plaque). Thrombosis divided into 2 groups: 41 from rupture of a vulnerable plaque (a thin fibrous cap overlying a lipid-rich core); 18 resulting from the erosion of a fibrous plaque rich in smooth-muscle cells and proteoglycans.



**PLAQUE
COMPOSITION**



**PLAQUE
VOLUME**



**PLAQUE
REMODELING**

**MULTIFACTORIAL ASSESSMENT OF PLAQUE IDENTIFIES
PATIENTS WITH UNHERALDED SUDDEN CARDIAC DEATH**