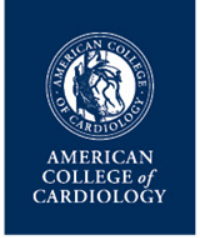
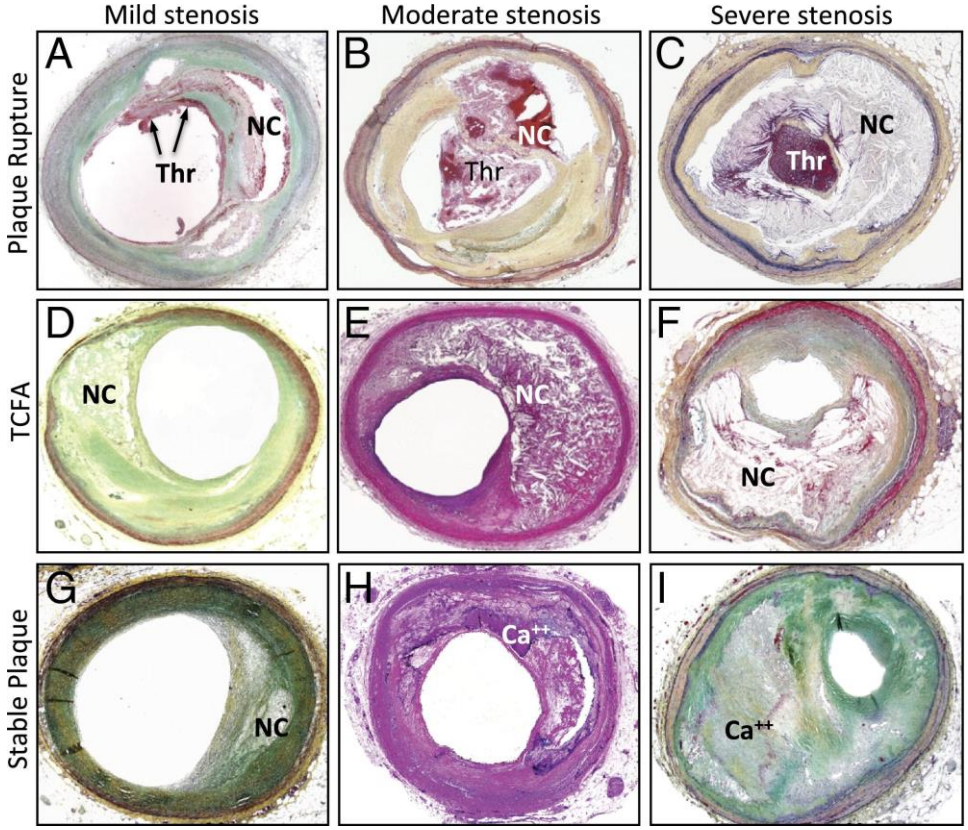
Invasive Evaluation of High Risk or Vulnerable Plaque
A Powerful Tool to Address Potential Pharmacological Agents?

Jagat Narula, MD PhD MACC



No Conflicts of Interest to Declare

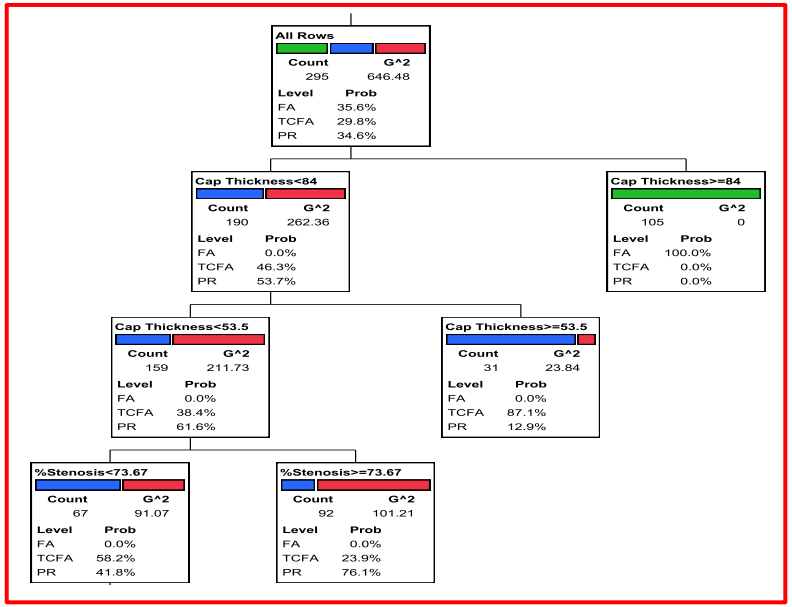
Histological Signatures of High-Risk Plaques



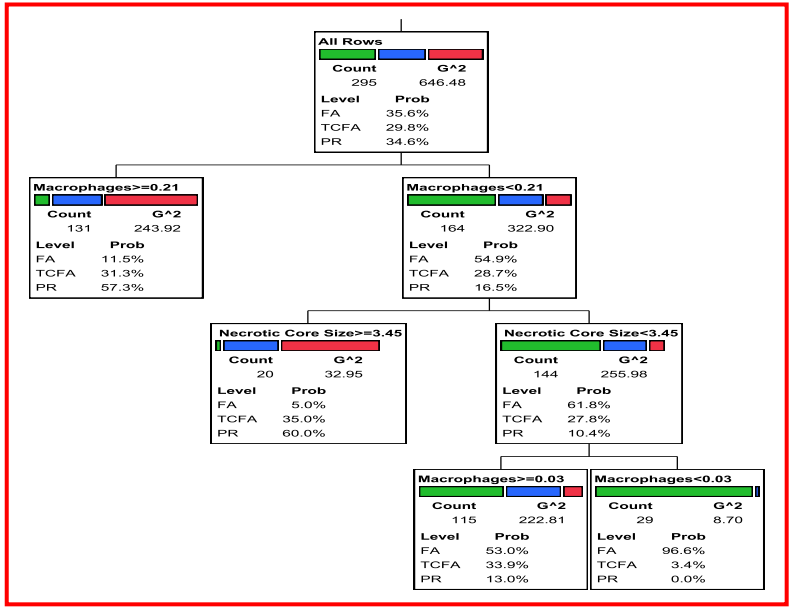
Narula et al.
JACC 2013;61:1041-1051

Hierarchical Importance of Morphological Characteristics for the Plaque Vulnerability

Recursive Partitioning Analyses



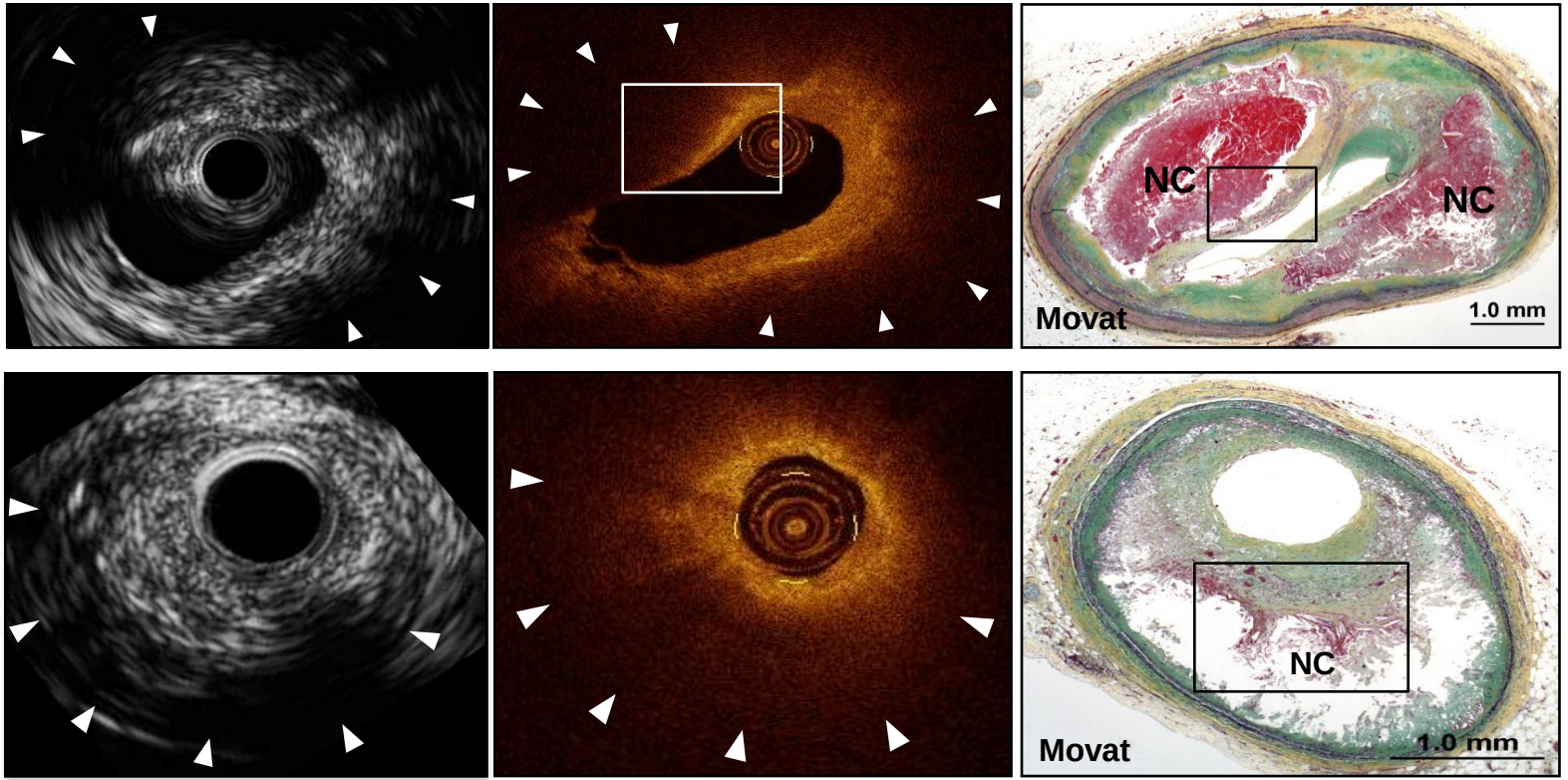
1. Fibrous Cap Thickness <55μ for PR and >85μ for Plaque Stability



2. Extent of Inflammation, and
3. Necrotic core Size

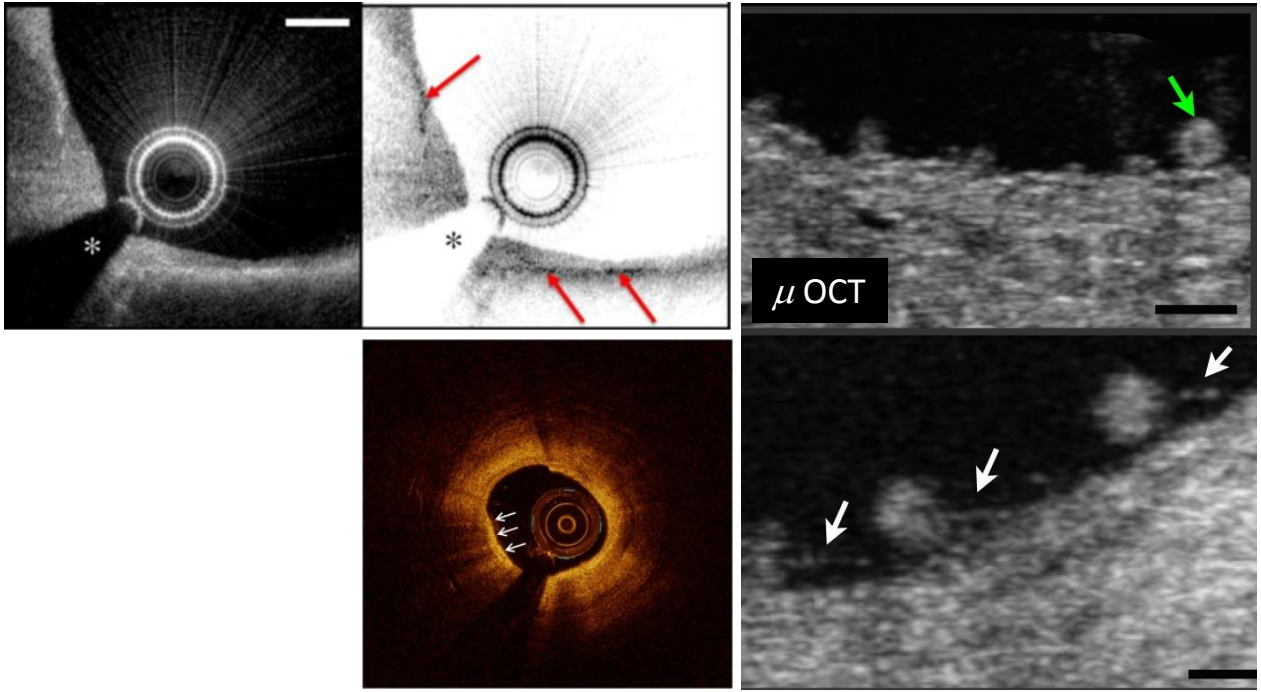
Narula et al. JACC 2013

Thin & *Thick-Cap* Fibroatheroma



Otsuka, Narula et al. Nature Rev Cardiology 2014

Invasive Assessment of Plaque Inflammation



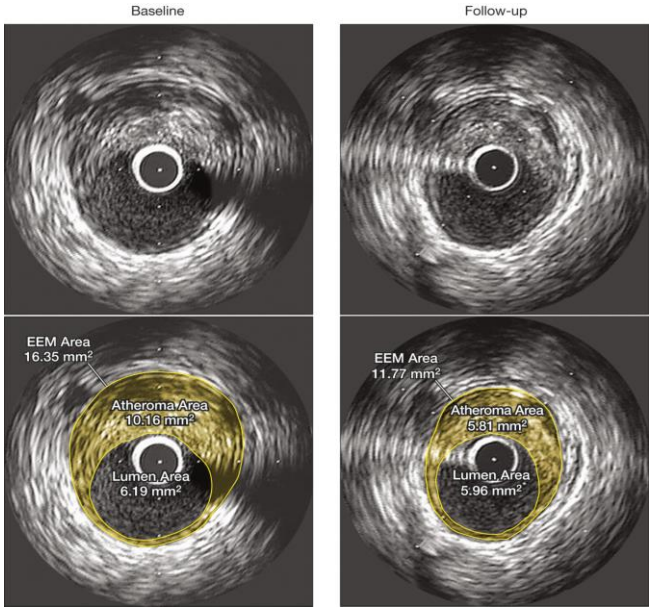
Tearney et al. JACC 2012;59:1058 & Nature Med 2011;17:1010
Kini et al. JACC (submitted)

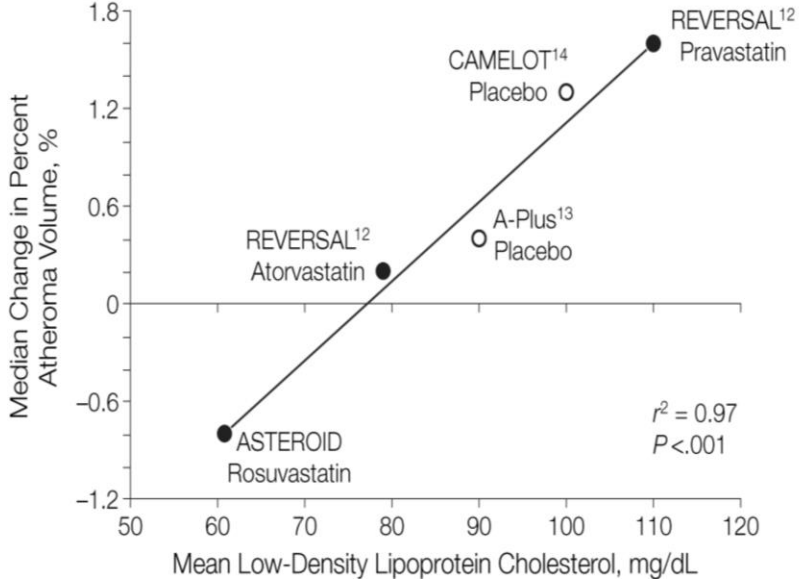
Could imaging endpoints offer an appropriate replacement for hard endpoints in clinical trials?

Premise

… that the surrogate primary end point may offer potential in terms of evaluating the progression or regression of atherosclerotic process, and allow for comparatively smaller clinical trials and for shorter duration in comparison with those powered for clinical events!

WE HAVE HAD HITS AND MISSES!!

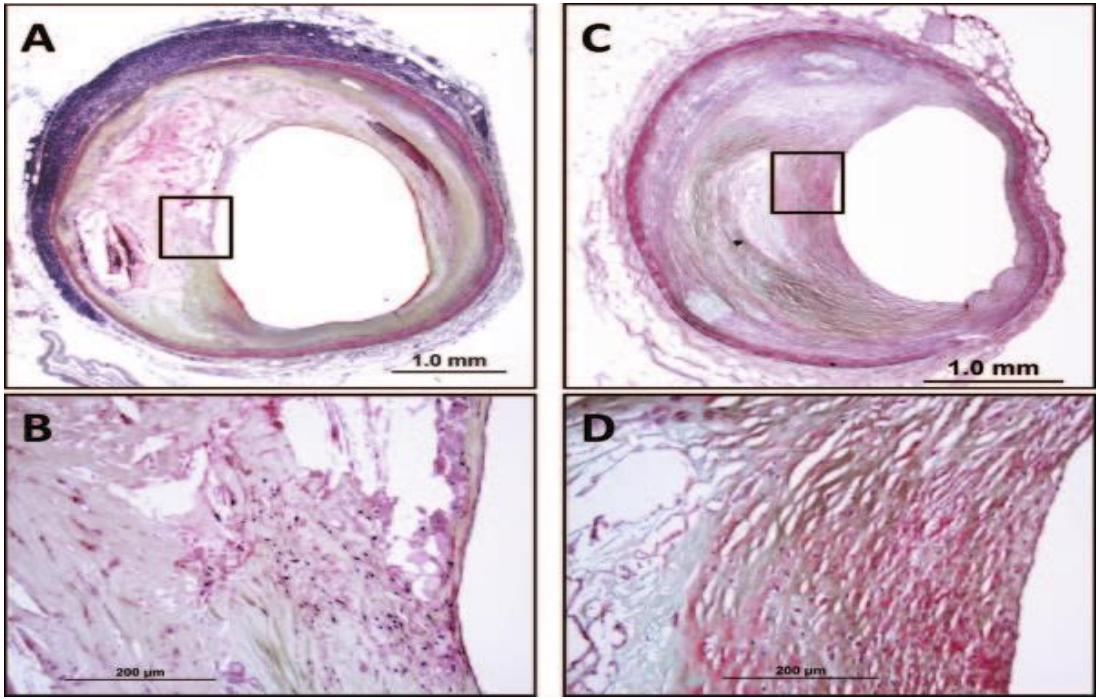




	Baseline	Follow-up	Change
Primary efficacy parameters			
Percent atheroma volume (n = 349)			
Mean (SD)	39.6 (8.5)	38.6 (8.5)	−0.98 (3.15)
Median (IQR)	39.9 (33.8-45.3)	38.5 (32.6-44.3)	−0.79 (−1.21 to −0.53)*†
Atheroma volume in most diseased 10-mm subsegment, mm^3 (n = 319)			
Mean (SD)	65.1 (27.0)	59.0 (24.5)	−6.1 (10.1)
Median (IQR)	65.1 (45.2-82.2)	58.4 (40.6-76.3)	−5.6 (−6.82 to −3.96)*†

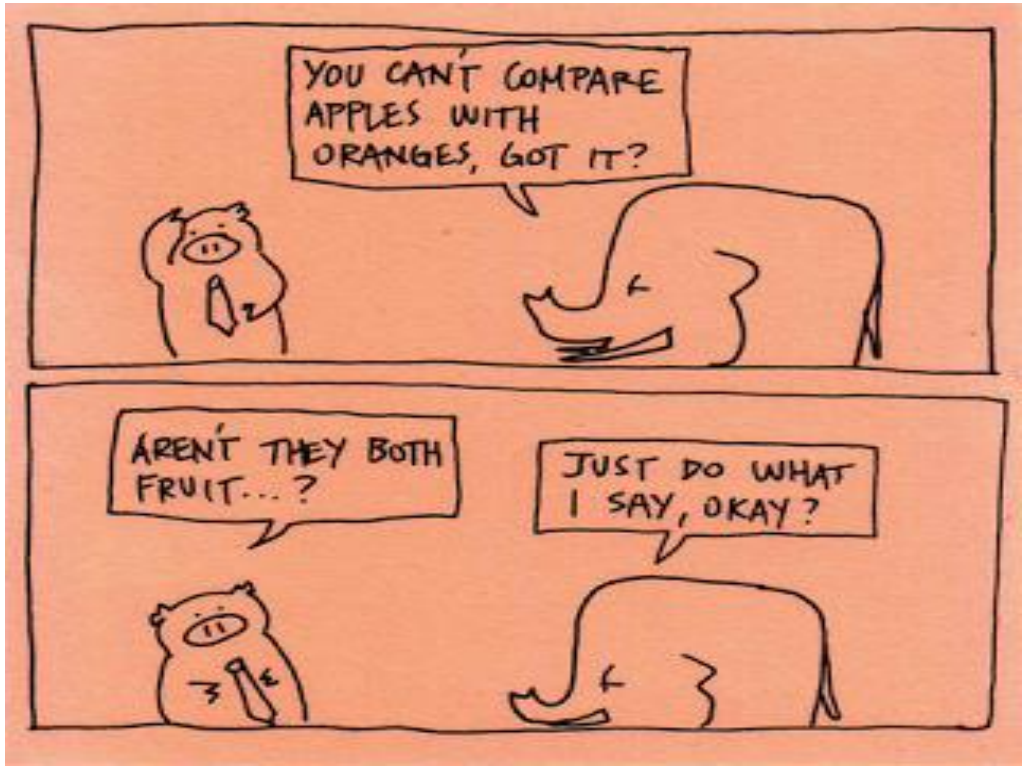
Nissen et al.
JAMA. 2006;295:1556
NEJM. 2005 352:29

PAV may not accurately estimate CV risk because it does not address plaque morphology

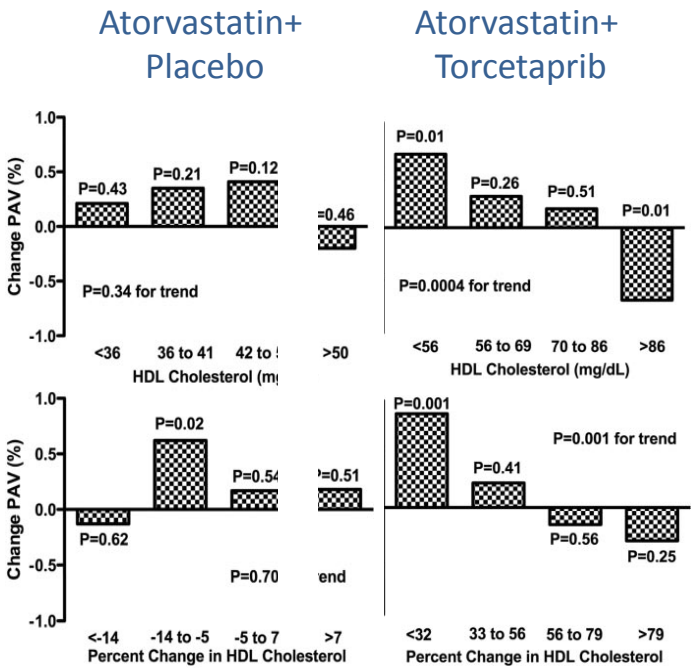


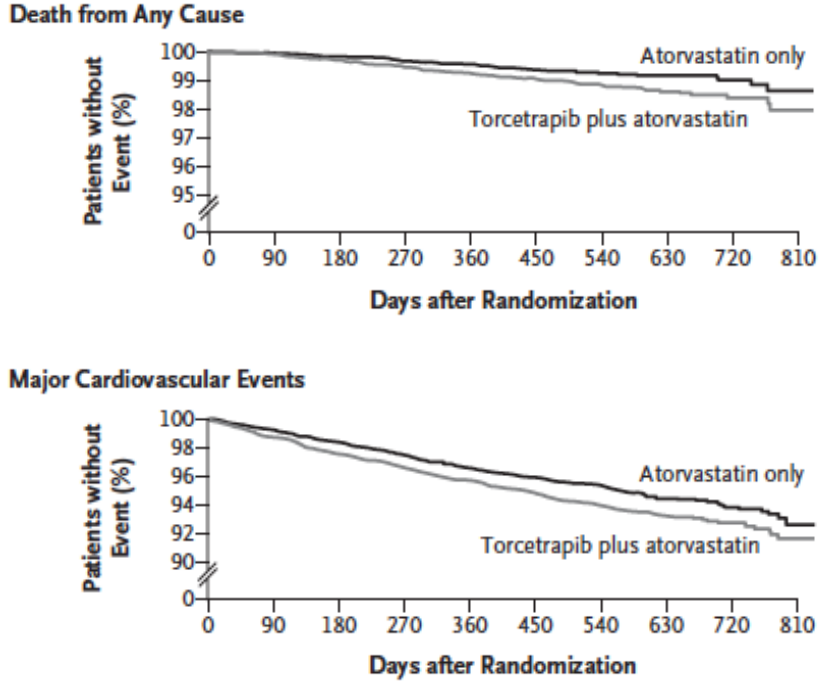
A reduction in IVUS-verified lipid volume with intervention may show corresponding increase in fibrous volume. As such, IVUS studies, of the kind reported in recent years, would offer only a coarse lens toward the otherwise dynamic plaque biology. It is of paramount importance that we exploit imaging techniques to help answer more pressing questions, such as: Is there a regression in the lipid core, or is attenuation of progression simply inferior to achieving frank regression?

Validity of Surrogate End Points



ILLUSTRATE to ILLUMINATE…

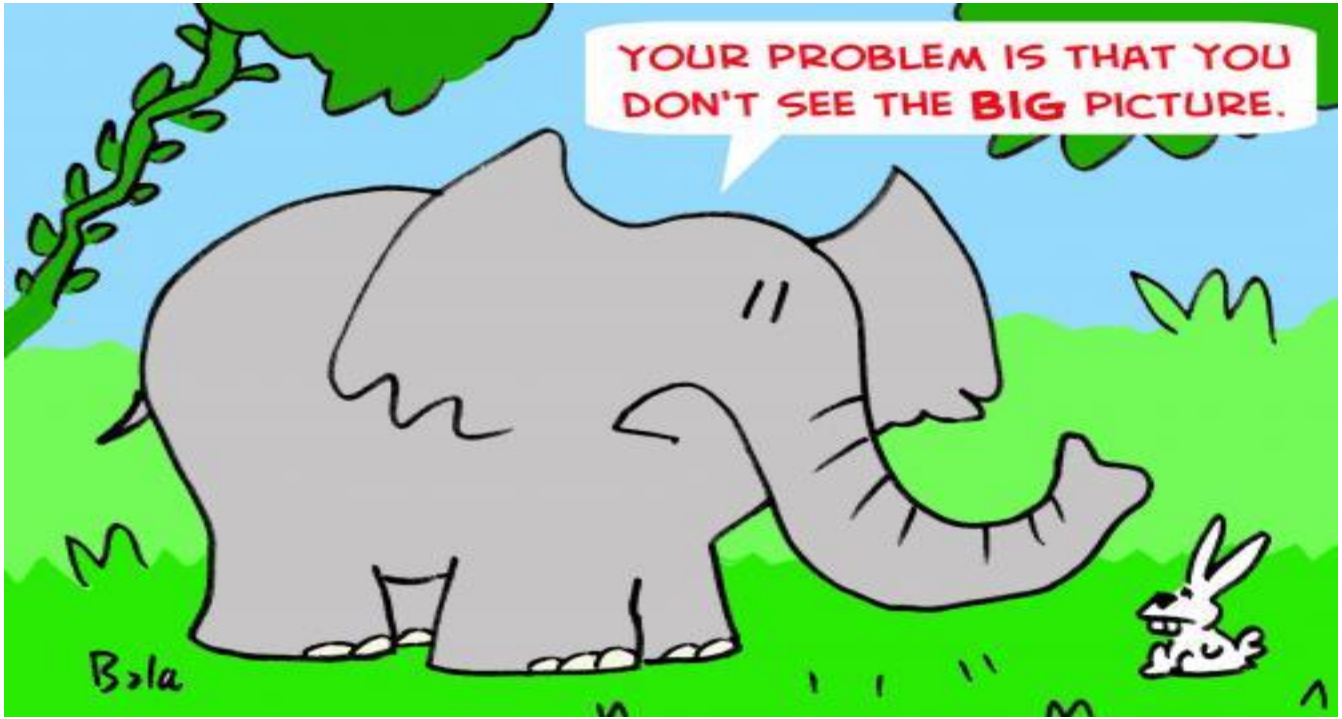




Nicolls et al., Circulation 2008

Barter et al., NEJM 2007

Surrogacy for Safety…



Evaluation of Incremental or Complementary Effects of Pharmacologic Intervention

- TZD favorable for inflammation and endothelial function in T2D, and could retard or reverse IVUS-verified plaque progression. Prospective evaluation of glucose-independent effects of TZD have been compared with sulphonylurea; rosiglitazone (Vs. glipizide in APPROACH) or pioglitazone (Vs. glimepiride in PERISCOPE)
- Noncritical plaque progression was expressed as a change in PAV;

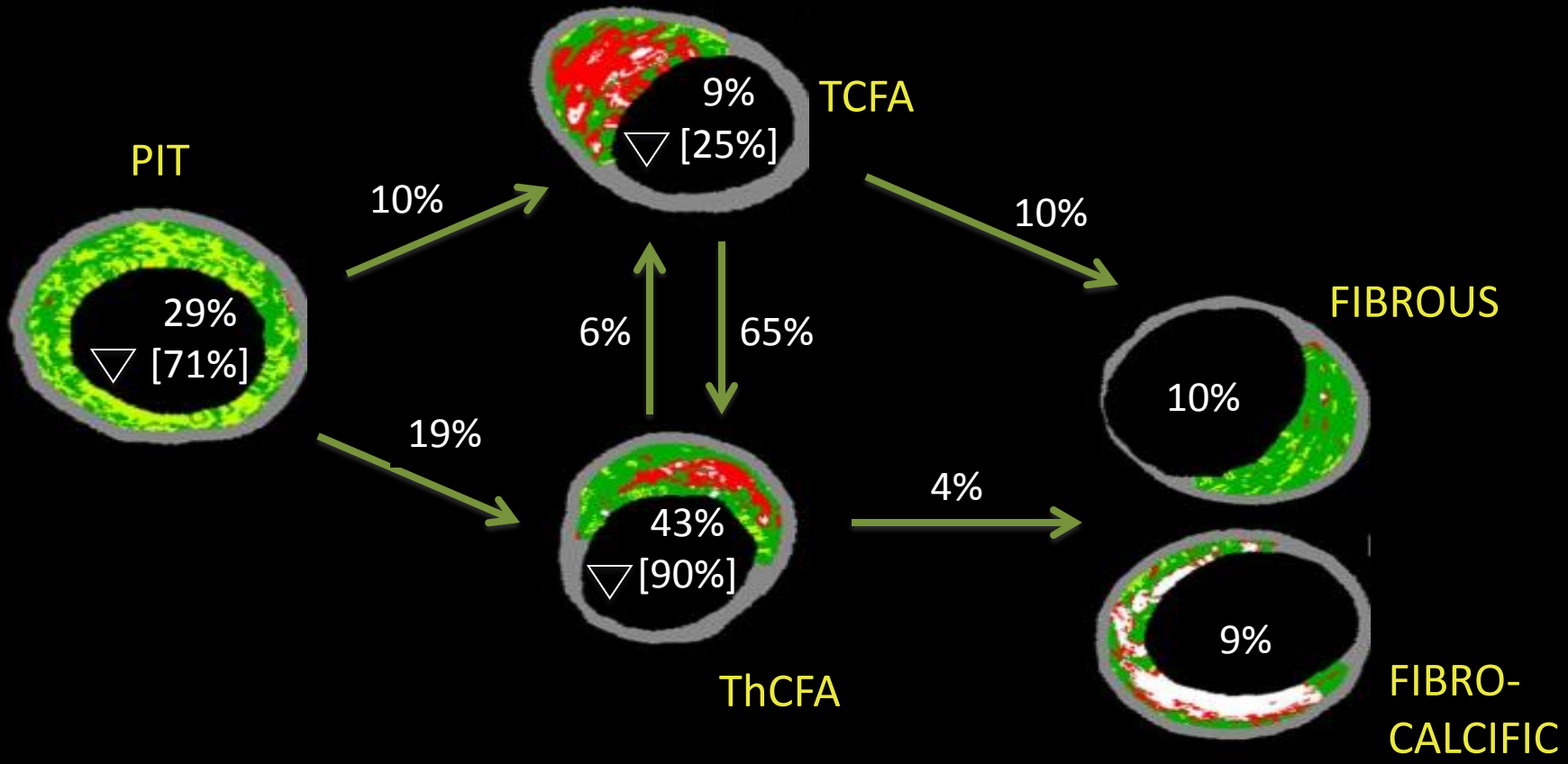
PERISCOPE: pioglitazone (-0.16%), glimiperide (+0.73%); P = 0.01, or TZD better

APPROACH: rosiglitazone (-0.21%), glipizide (+0.43%); P= NS, or TZD bad!

- 23% patients had received insulin in PERISCOPE compared to 9% in APPROACH! And, PAV reduction is a rather slow process

The Extent of Expectations…

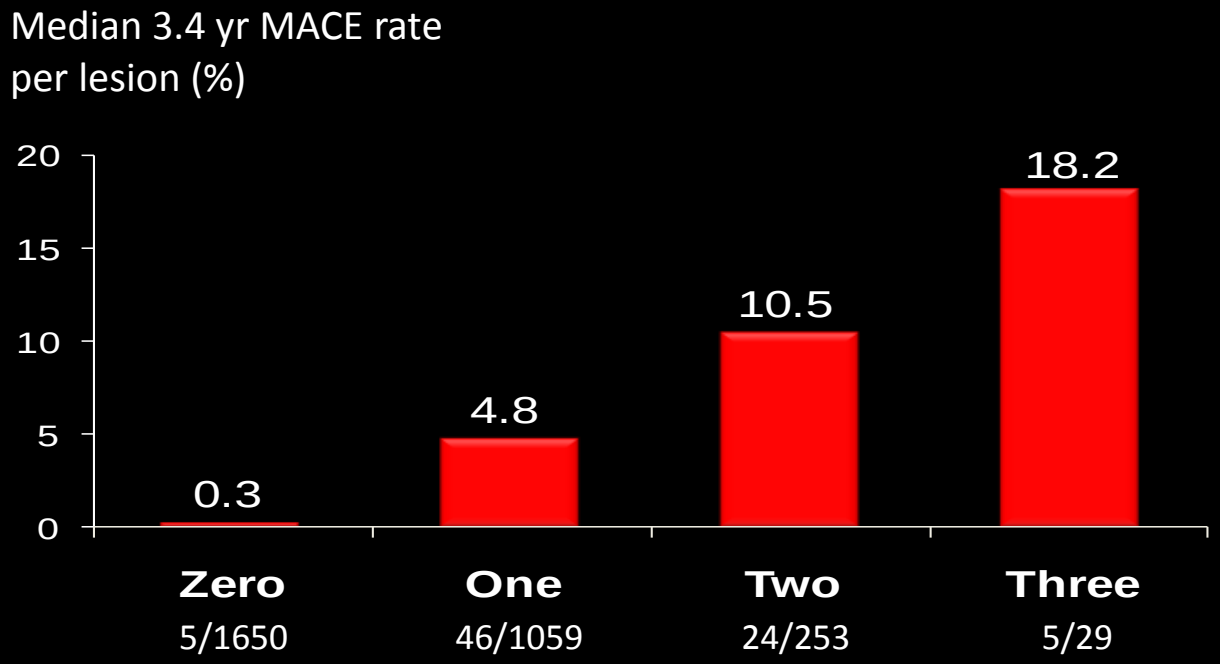
IVUS with Radiofrequency Analysis



Narula & Kovacic [Editorial] JACC August 2014; data extracted from Kubo et al. 2010

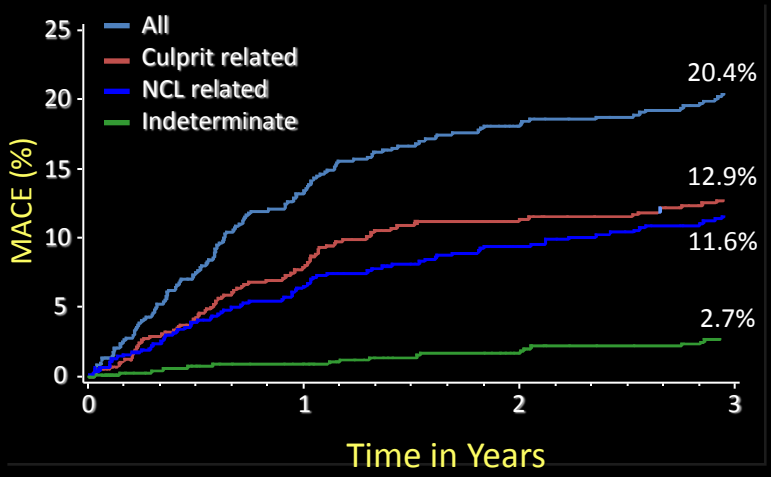
PROSPECT: Correlates of NCL Related Events

Variable	HR [95% CI]	PB_{MLA}
≥70%	5.03 [2.51, 10.11]	VH-
TCFA	3.35 [1.77, 6.36]	MLA
≤4.0mm^2	3.21 [1.61, 6.42]	



PROSPECT: MACE

3-year follow-up, hierarchical

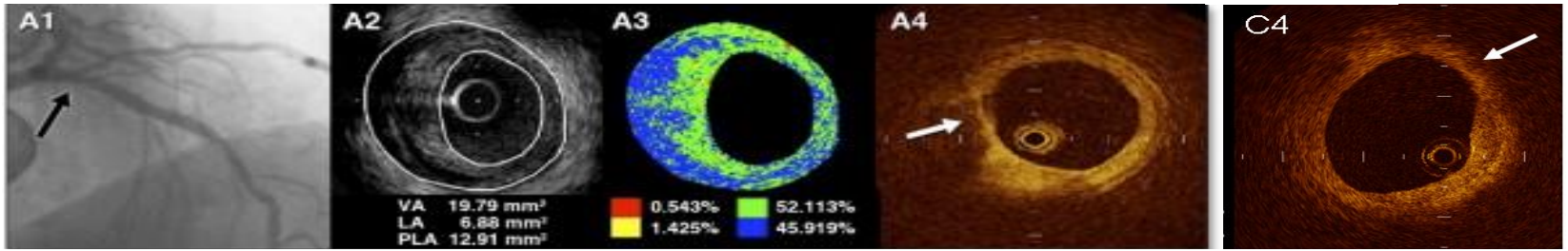


	All	Culprit lesion related	Non culprit lesion related	Indeter-minate
Cardiac death	1.9% (12)	0.2% (1)	0% (0)	1.7% (11)
Cardiac arrest	0.3% (2)	0.3% (2)	0% (0)	0% (0)
MI (STEMI or NSTEMI)	2.7% (17)	1.7% (11)	1.0% (6)	0.2% (1)
Hospitalization: unstable/progressive angina	15.4% (101)	10.4% (69)	10.7% (68)	0.8% (5)
Composite MACE	20.4% (132)	12.9% (83)	11.6% (74)	2.7% (17)
Cardiac death, arrest, MI	4.9% (31)	2.2% (14)	1.0% (6)	1.9% (12)

Rates are 3-yr Kaplan-Meier estimates (n of even

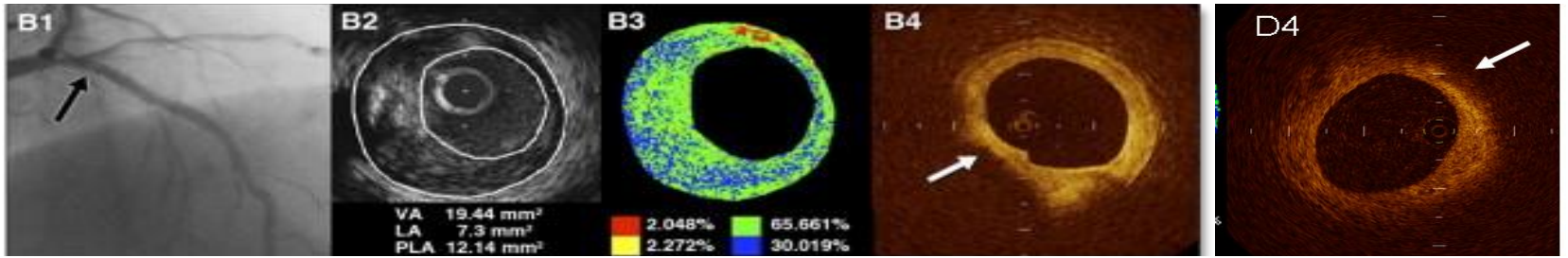
Baseline: Pre-Statin

Pre-Diet

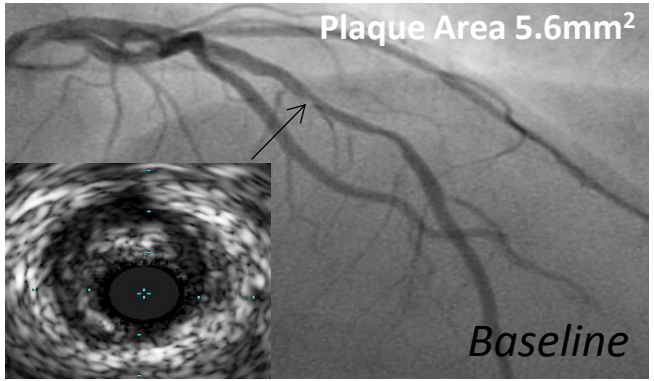


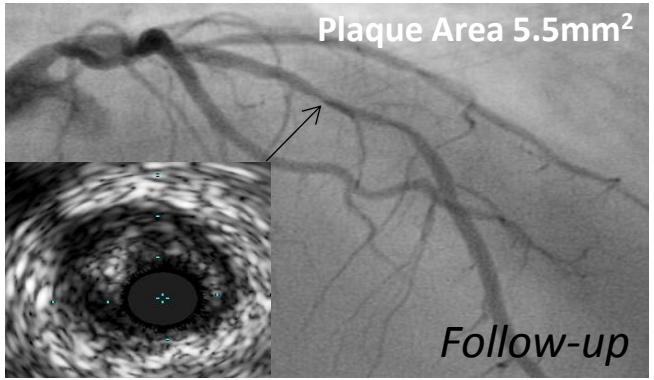
Follow up: Post-Statin

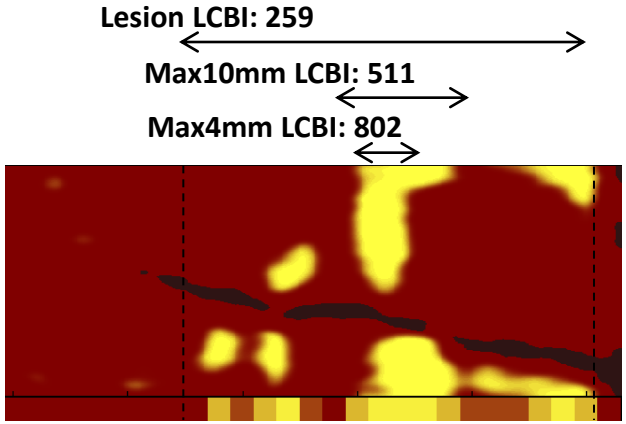
Post-Diet

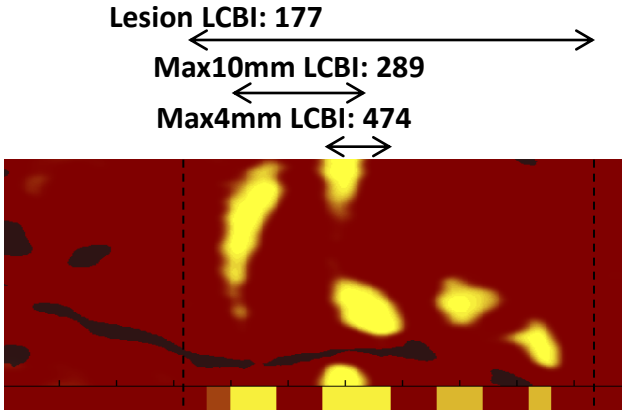


Hattori, Narula et al. JACC-Imaging 2012;5:169-77



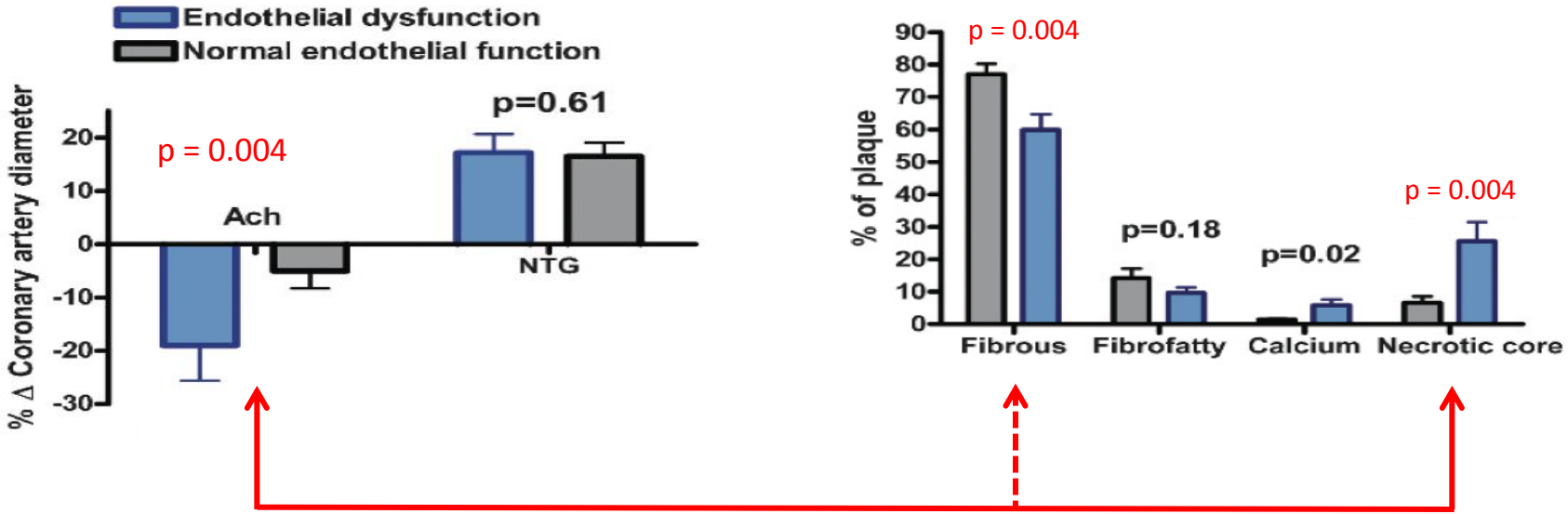






YELLOW
Kini et al. JACC 2013

Is Necrotic Core Predictive of Endothelial Dysfunction ?



Lerman et al. *Heart* 2009; **95**:1525-30

- Surrogates have always been a moving target – IMT yesterday, PAV today and plaque type tomorrow. While a death is death, the surrogate is “flavor of the day,” could go in and out of favor, and may even be wrong, e.g. EF change as a surrogate for reducing HF death, PVC as surrogate for anti-arrhythmic therapy.
- With so much uncertainty in “truth,” truth becoming difficult to show with rapidly improving “pre trial” event rates and with so many post marketing reversals based on shaky surrogate data, most definitive studies would need to show hard end points.
- THEREFORE, the best use of imaging is to develop the hypothesis further, understand mechanisms, and to show who may BENEFIT from PROVEN therapies rather than using it to PROVE therapy (unless we move over to MORE DEFINITIVE STUDIES).

- What should an imaging surrogate tell us then– an *"imaging"* marker intended to substitute for a clinical end point should predict clinical benefit and harm, or lack of both.
- *Imaging should demonstrate: 1. Causal relationship to outcome, 2. Strong specificity and sensitivity for outcome, and 3. Robust estimate of clinical effect* that is better than traditional markers. (we are not there yet)
- Imaging surrogate provides a cumulative snapshot –it may not demonstrate as to (1) how the change in result is important for outcome, and (2) the off target effects. (clinical outcome trials thus are still needed before approval process)
- All current and future imaging techniques, while ever increasingly informative, should be vetted, not for their ability ONLY to image, but their ability to predict the outcome.

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Prognostic Performance of Plaque Characteristics

Trial (Ref. #), Follow-Up	Cohort	Endpoint	Lesion Variable	Event Rate % (n/N) + Lesion Variable	Event Rate % (n/N) − Lesion Variable	OR/HR	Sn	Sp	PPV	NPV	LR+	LR−	AUC (95% CI)
Intravascular Imaging Studies													
PROSPECT(3), 3.4 yrs (lesion-specific risk)	ACS	MACE	TCFA	4.4 (26/595)	1.2 (25/2,114)	3.8	0.51	0.79	0.04	0.99	2.38	0.62	0.71 (0.62-0.79)
			PB ≥70%	8.7 (25/288)	1.0 (30/2,941)	9.6	0.46	0.92	0.09	0.99	5.59	0.59	0.82 (0.76-0.87)
			MLA ≤4 mm^2	4.9 (30/616)	1.0 (25/2,522)	5.11	0.55	0.81	0.05	0.91	2.87	0.56	0.75 (0.67-0.82)
			All 3	18.2 (8/44)	1.6 (44/2,665)	13.6	0.16	0.99	0.18	0.98	11.58	0.85	0.86 (0.76-0.92)
PROSPECT (3), 3.4 yrs (patient-specific risk)	ACS	MACE	PB ≥70%	19.1 (42/220)	7.0 (31/440)	3.1	0.58	0.70	0.19	0.93	1.90	0.61	0.68 (0.60-0.75)
VIVA (4), 1.8 yrs (lesion-specific risk)*	ACS + SCAD	MACE	NC-VHTCFA	2.9 (5/175)	1.1 (8/756)	7.53†	NA	NA	NA	NA	NA	NA	NA
			PB ≥70%	NA	NA	8.13	NA	NA	NA	NA	NA	NA	NA
VIVA (4), 1.8 yrs (patient-specific risk)*	ACS + SCAD	MACE	NC-VHTCFA	NA	NA	1.79	NA	NA	NA	NA	NA	NA	NA
ATHEROREMO-IVUS (6), 1 yr (patient-specific risk)	ACS + SCAD	MACE	TCFA	10.8 (23/211)	5.6 (17/312)	1.98	0.57	0.61	0.11	0.94	1.46	0.71	0.62 (0.51-0.72)
			PB ≥70%	16.2 (20/124)	5.5 (21/384)	2.90	0.24	0.91	0.16	0.95	2.74	0.84	0.69 (0.55-0.80)
			MLA ≤4 mm^2	9.4 (16/182)	7.1 (23/326)	1.23‡	0.13	0.90	0.10	0.93	1.34	0.96	0.55 (0.38-0.72)
			All 3	23.1 (12/52)	6.8 (32/471)	3.70	0.27	0.92	0.23	0.93	3.27	0.79	0.72 (0.61-0.82)
ATHEROREMO-NIRS (2), 1 yr (patient-specific risk)	ACS + SCAD	MACE	LCP ($LCBI_{4mm}$ ≥43)	16.7 (17/102)	4.0 (4/101)	4.20	0.81	0.53	0.17	0.96	1.73	0.36	0.74 (0.56-0.87)
		ACM/ACS		8.8 (9/102)	1.0 (1/101)	9.36	0.90	0.52	0.09	0.99	1.87	0.19	0.82 (0.52-0.97)
		ACM/ACS/Stroke		11.8 (12/102)	1.0 (1/101)	11.9	0.92	0.53	0.12	0.99	1.95	0.15	0.85 (0.57-0.97)
PREDICTION (5), 1 yr (patient-specific risk)	ACS	PCI	PB ≥58%	22	2	17.6	0.94	0.54	0.22	0.98	1.97	0.15	0.85 (0.67-0.94)
			Low ESS	25	9	3.18	0.42	0.82	0.25	0.91	2.30	0.71	0.69 (0.56-0.79)
			Both	41	8	NA	0.42	0.91	0.41	0.92	4.92	0.63	0.80 (0.68-0.88)
Noninvasive Imaging Study													
CTA (7), 2 yrs (patient-specific risk)	SCAD	ACS	Positive remodeling + low attenuation plaque	22.2 (10/45)	0.49 (4/820)	45.6	0.71	0.96	0.22	1.00	17.4	0.30	0.95 (0.87-0.98)
Invasive Hemodynamic Assessment													
FAME-2 (8), 30 days (patient-specific risk)§	SCAD	MACE (D/MI/UR)	FFR ≤0.80	12.7 (56/441)	3.0 (5/166)	4.22	0.92	0.29	0.13	0.97	1.30	0.28	0.74 (0.59-0.85)
		D/MI		3.9 (17/441)	1.8 (3/166)	2.13‡	0.85	0.28	0.04	0.98	1.18	0.54	0.63 (0.41-0.81)

Kaul & Narula JACC [Editorial] Dec 2014