Vulnerable Plaque Imaging: Lessons Learn from PROSPECT, ATHEROREMO, and VIVA

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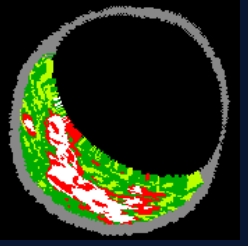
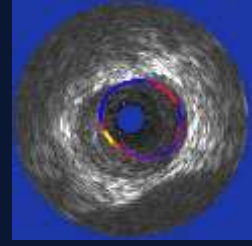
Cardiovascular Research Foundation



The PROSPECT Trial



700 pts with ACS UA (with ECG Δs) or NSTEMI or STEMI
>24º
undergoing 1 or 2-vessel PCI followed by 3-vessel imaging

QCA of entire coronary tree

IVUS

Virtual Histology

Proximal 6-8 cm of each coronary artery

Medications
Aspirin
Plavix ≥1yr
Statins

F/U: Until there were 100 VP events

Repeat imaging in patients with events

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PROSPECT: Multivariable Correlates of Non Culprit Lesion Related Events

Independent predictors of lesion level events by Cox Proportional Hazards regression

Variable	HR [95% CI)	p
PB_{MLA} ≥70%	5.03 [2.51, 10.11]	<0.0001
VH-TCFA	3.35 [1.77, 6.36]	0.0002
MLA ≤4.0 mm^2	3.21 [1.61, 6.42]	0.001

Variables entered into the model: minimal luminal area (MLA) ≤4.0 mm^2; plaque burden at the MLA (PB_{MLA}) ≥70%; external elastic membrane at the MLA (EEM_{MLA}) <median (14.1 mm^2); lesion length ≥median (11.2 mm); distance from ostium to MLA ≥median (30.4 mm); remodeling index ≥median (0.94); VH-TCFA.

Stone et al. N Engl J Med 2011;361:226-35

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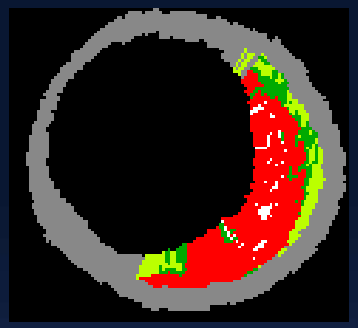
PROSPECT: Predictors of Non Culprit Lesion Events



Stone et al. N Engl J Med 2011;361:226-35

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VIVA: Virtual Histology in Vulnerable Atherosclerosis

- 932 non-culprit lesions in 170 pts were identified with 3-vessel IVUS imaging
- At a median follow-up of 625 days, there were 18 culprit and non-culprit MACE in 16 pts (14 revascularizations, 2 MIs, and 2 deaths)
- *Univariate* predictors of non-culprit MACE
  - Non-calcified VH-TCFA (p=0.025)
  - MLA <4mm^2 (p=0.021)
  - Plaque burden >70% (p<0.001)
  - Remodeling index (p=0.014)

Calvert et al. JACC Cardiovasc Imaging 2011;4:894-901

European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis – IVUS (ATHEROREMO-IVUS) study

- 1 non-culprit artery imaged in 581 pts (stable CAD or ACS): LAD>RCA>LCX
- At 1 year of follow-up, 56 pts had at least 1 event: 4 PCI in pts without baseline PCI, 11 culprit events, 27 non-culprit events, 18 indeterminate events
- 18 deaths, 8 from cardiac or unknown causes; 14 ACS (7 MI); 24 unplanned revascularization
- Presence of VH-TCFA was significantly associated with the composite of Death/ACS (adjusted HR=2.51, p=0.021)

Cheng et al. Eur Heart J 2014;35:639-47

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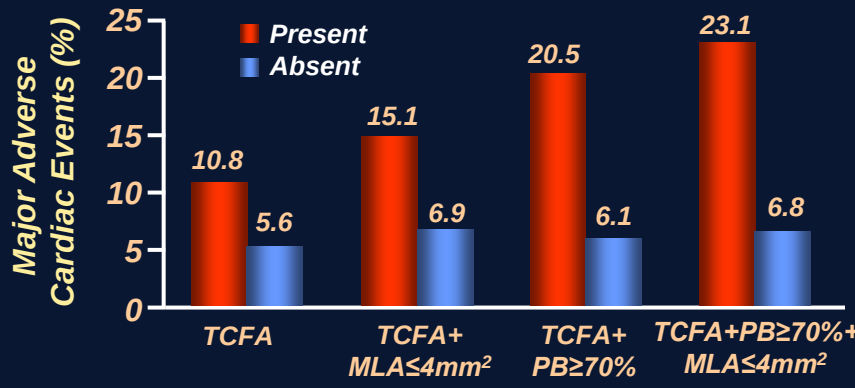
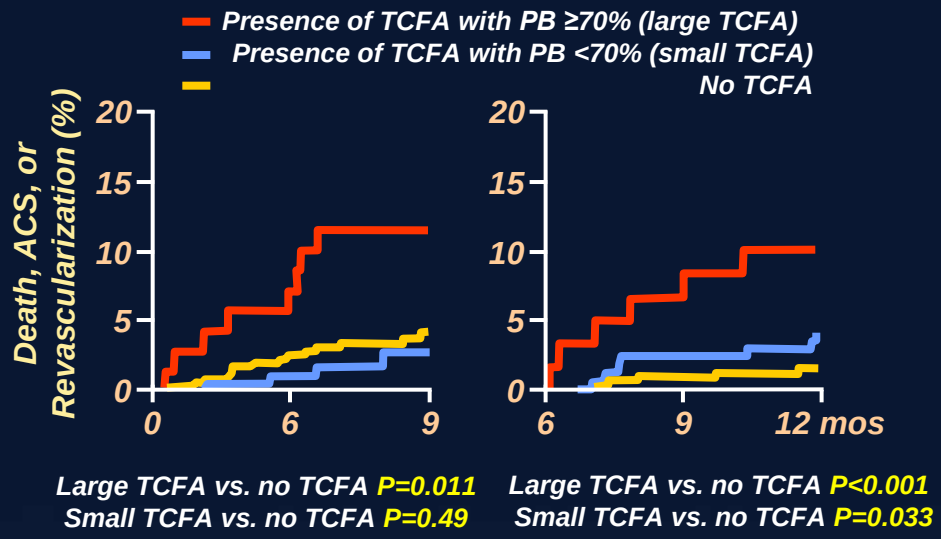


Prevalence (%)	41.7	58.3	10.5	89.5	11.9	88.1	6.0	94.0
No. at risk at 1 yr (n)	211	312	50	473	52	471	52	471
HR	1.96		2.26		3.47		3.70	
P value	0.024		0.025		<0.001		<0.001	



- *A VH-TCFA (present 10.8% vs. absent 5.6%; adjusted HR: 1.98, P=0.026) and a plaque burden ≥70% (present 16.2% vs. absent 5.5%; adjusted HR: 2.90, P<0.001), but not an MLA ≤4.0mm², were independently associated with MACE.*
- *Risk for MACE was further increased if the VH-TCFA had an MLA ≤4.0mm², plaque burden ≥70%, or a combination of these three characteristics*
- *VH-TCFAs with a plaque burden ≥70% were associated with a higher MACE rate both in the first 6 months (P=0.011) and after 6 months (P<0.001), while smaller TCFA lesions were only associated with a higher MACE rate after 6 months (P=0.033)*

Cheng et al. Eur Heart J 2014;35:639-47

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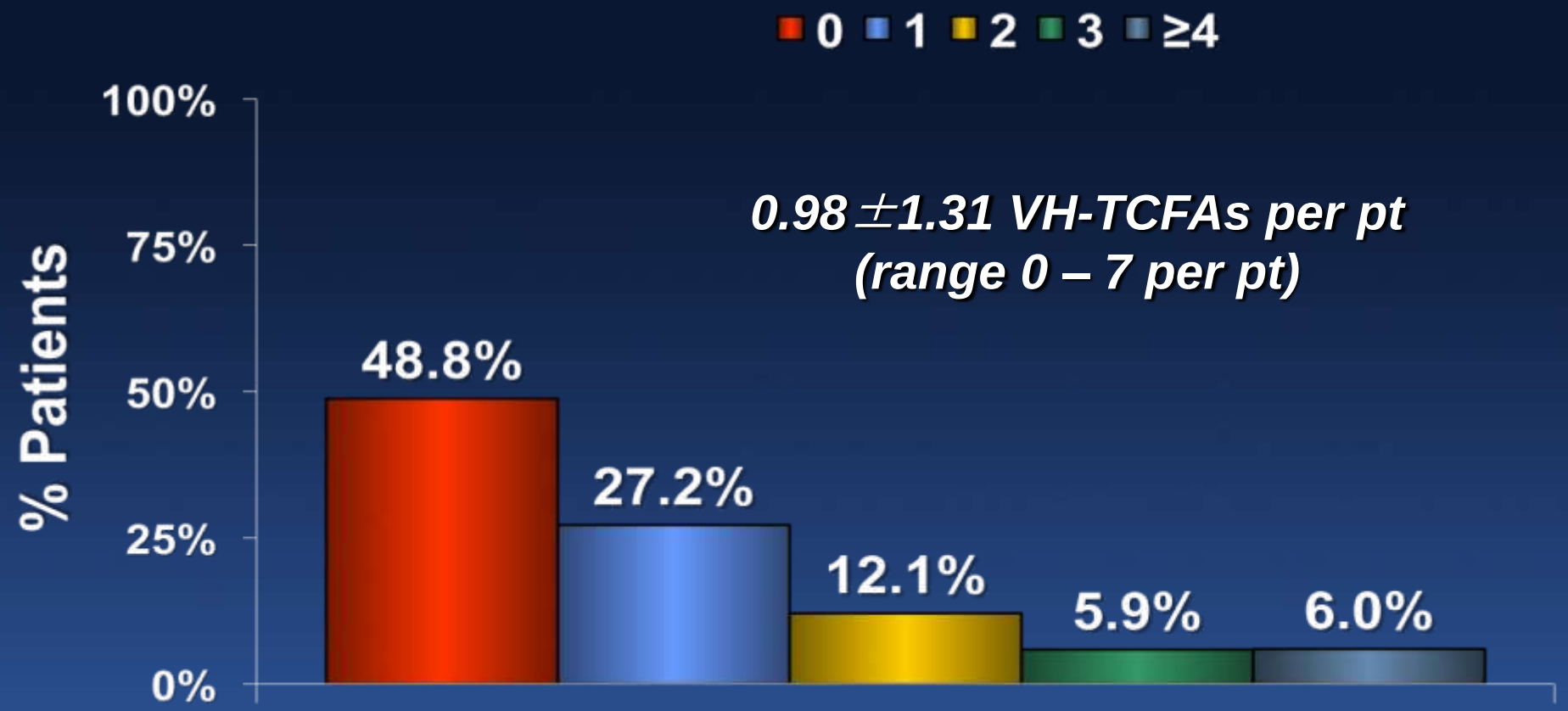
PROSPECT: *596 TCFAs were identified in 51.2% of the patients (vs 1005 thick cap fibroatheromas)*



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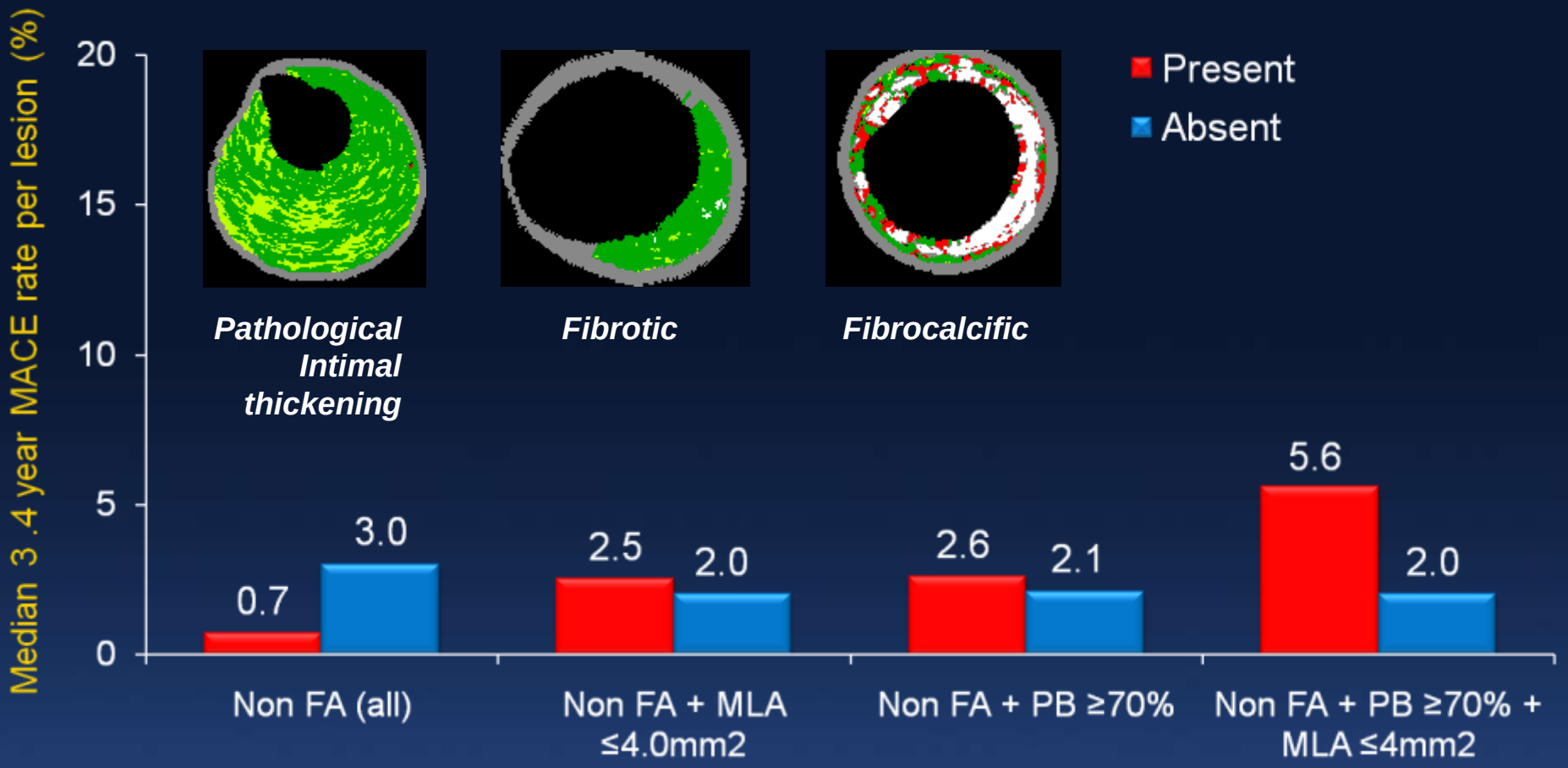
Non Fibroatheromas and Non Culprit Lesion Events



Lesion HR	0.22 [0.10, 0.49]	1.49 [0.44, 3.39]	1.25 [0.17, 9.01]	2.60 [0.36, 18.84]
P-value	0.0002	0.70	0.83	0.34
Prevalence	67.9%	19.7%	5.6%	2.7%

Stone et al. N Engl J Med 2011;361:226-35

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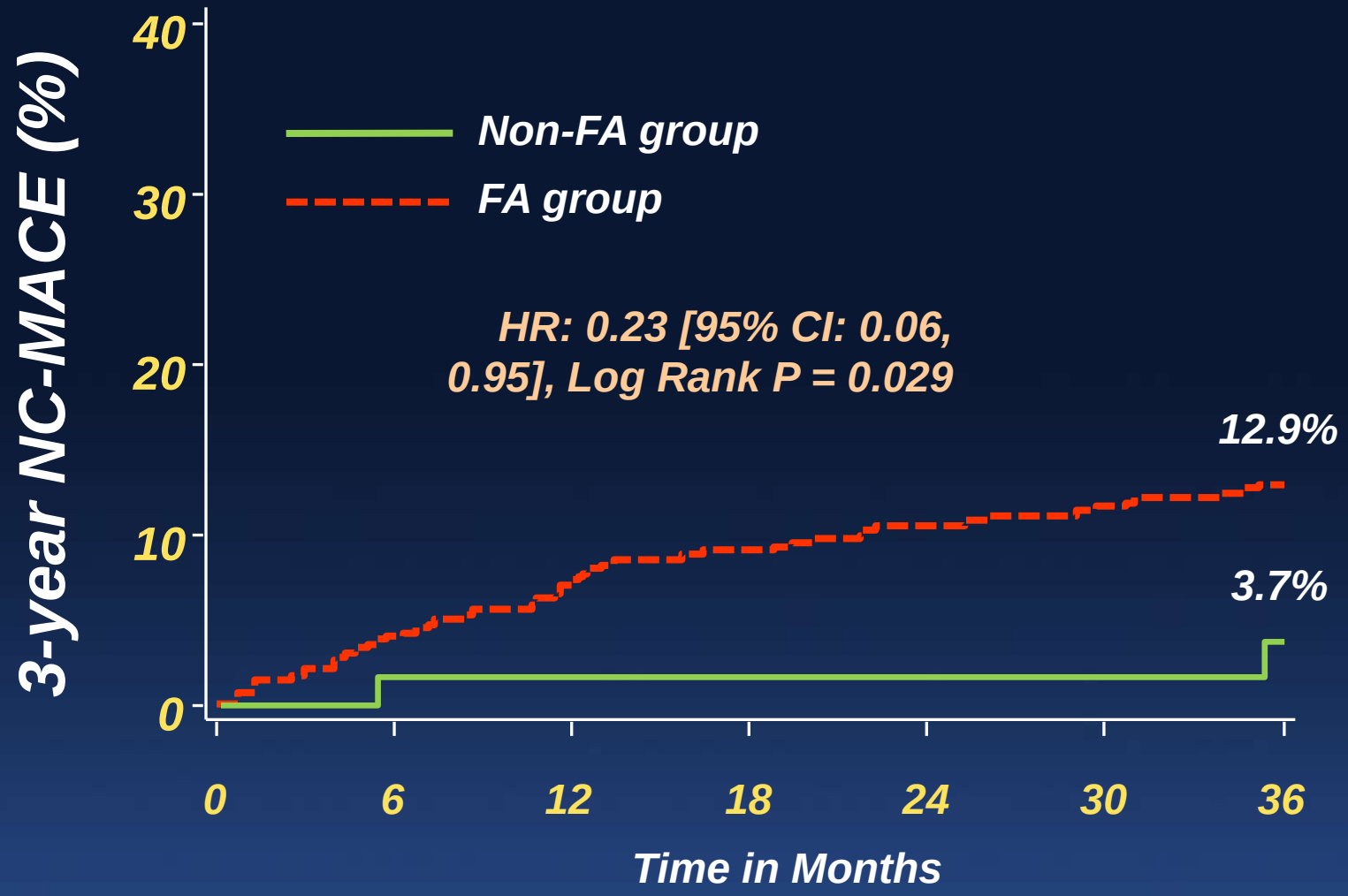


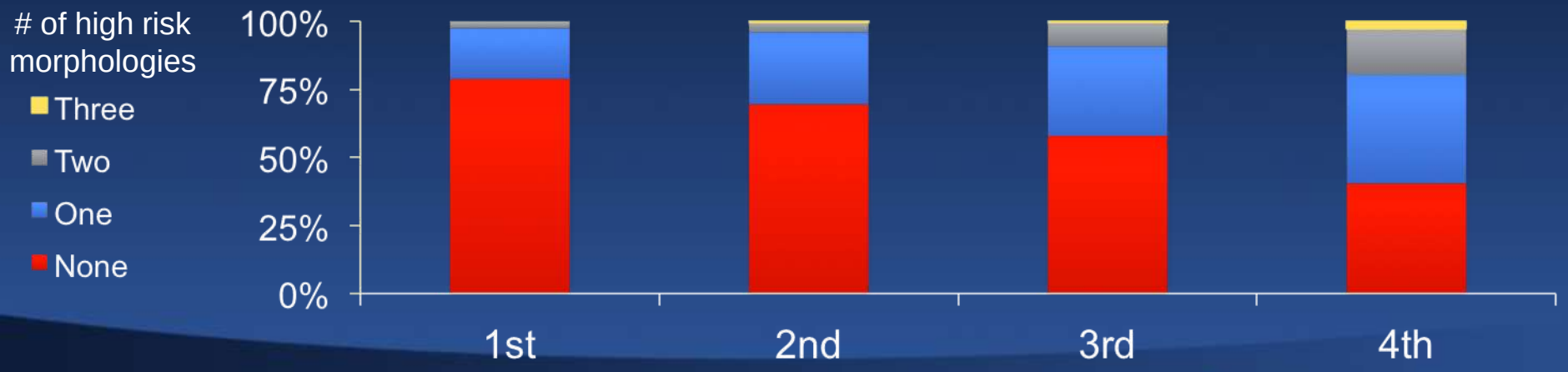
Number at risk

Non-FA group	67	62	61	61	60	57	29
FA group	542	485	463	443	424	406	248

Dohi et al. JACC Cardiovasc Imaging 2013;6:908-16

PROSPECT: Angiographic severity vs high risk morphology (n=3115)

	Quartile			
	1st	2nd	3rd	4th
QCA DS (%)	2.82 (2.56, 3.08)	9.95 (9.82, 10.08)	17.67 (17.47, 17.88)	33.52 (32.90, 34.14)
NC volume, %	12.3 (11.6, 13.0)	12.5 (11.8, 13.2)	13.0 (12.3, 13.7)	14.0 (13.3, 14.7)
VH-TCFA	13.4%	22.0%	24.4%	30.3%
FA	48.6%	56.2%	62.3%	72.3%



Yun et al. Am J Cardiol 2012;110:471-7

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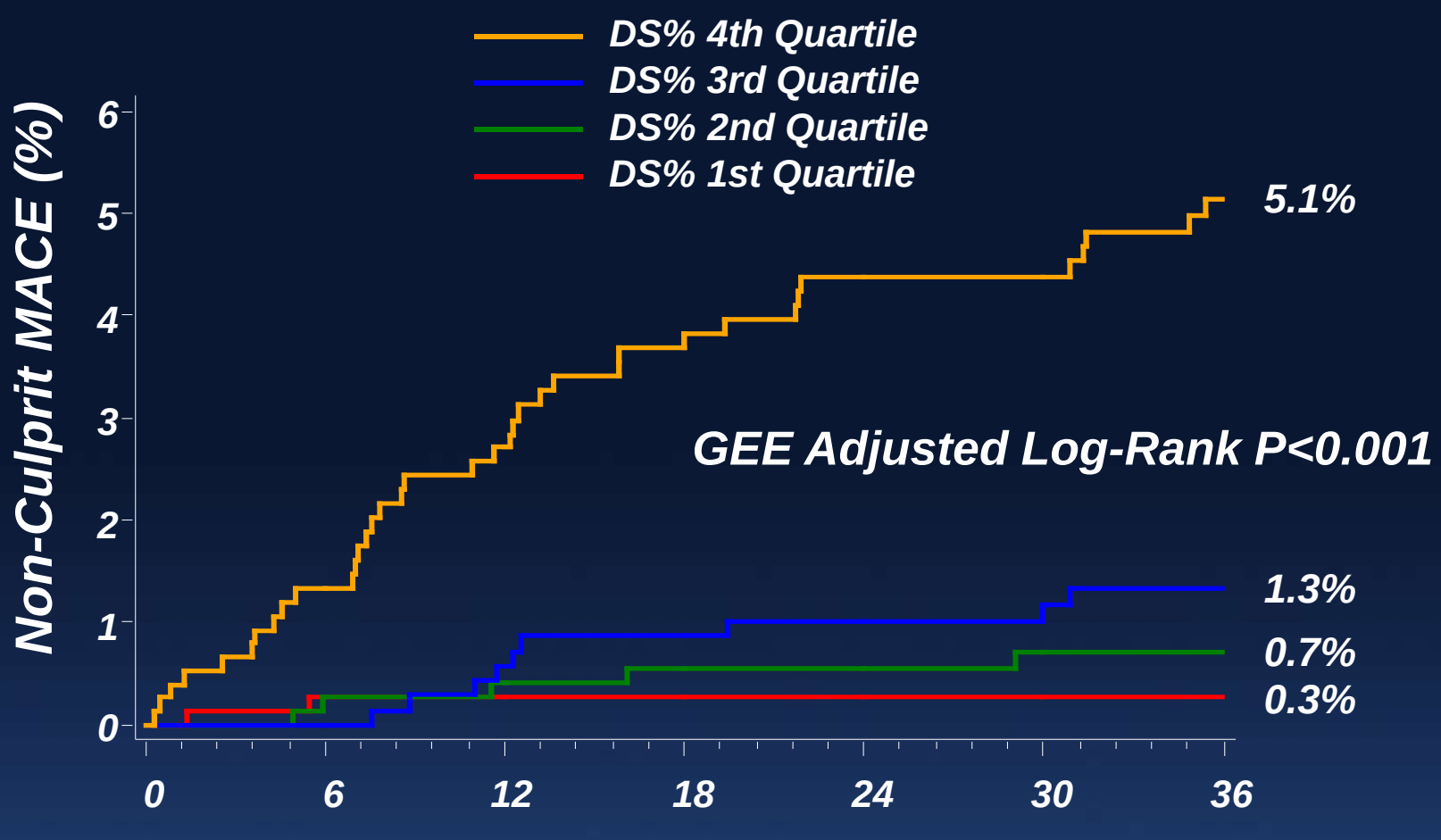

Number at risk

1st quartile	778	726	717	693	680	655	416
2nd quartile	779	721	711	692	679	659	411
3rd quartile	779	707	693	675	652	630	379
4th quartile	779	722	706	684	668	654	430

Yun et al. Am J Cardiol 2012;110:471-7

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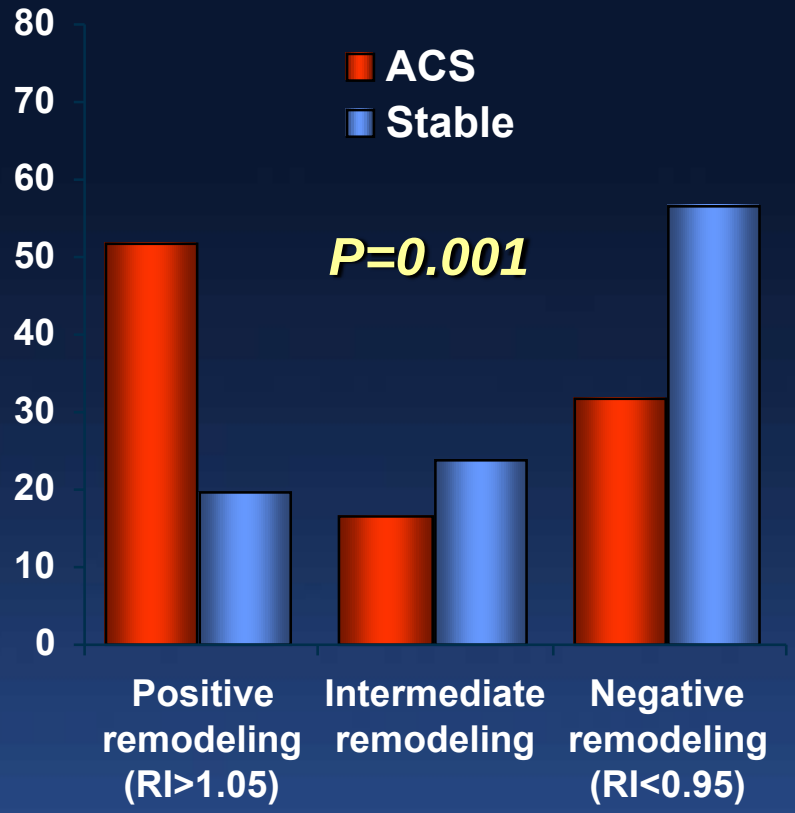
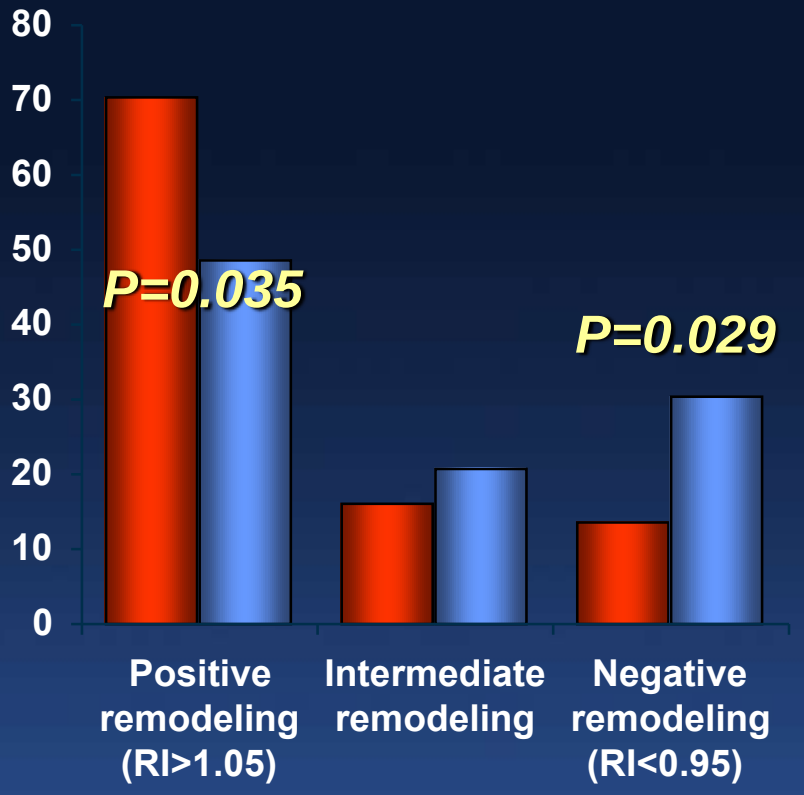
Despite the fact that more than a dozen histopathologic and IVUS studies showed a relationship between positive remodeling and unstable lesion morphology, neither the remodeling index nor positive remodeling were independent predictors of events in PROSPECT, VIVA, or ATHEROREMO-IVUS

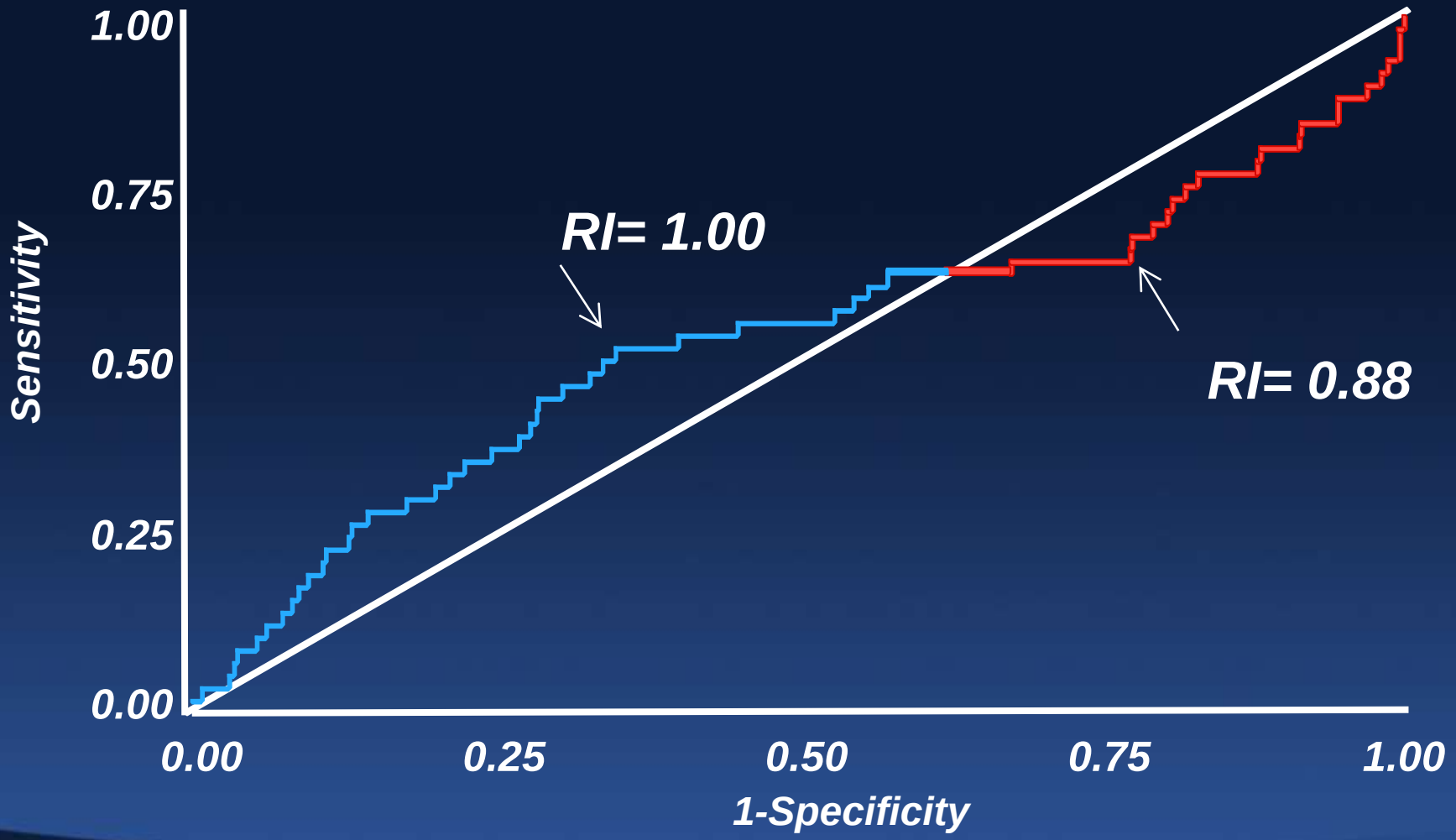


(Schoenhagen et al. Circulation 2000;101:598-603)



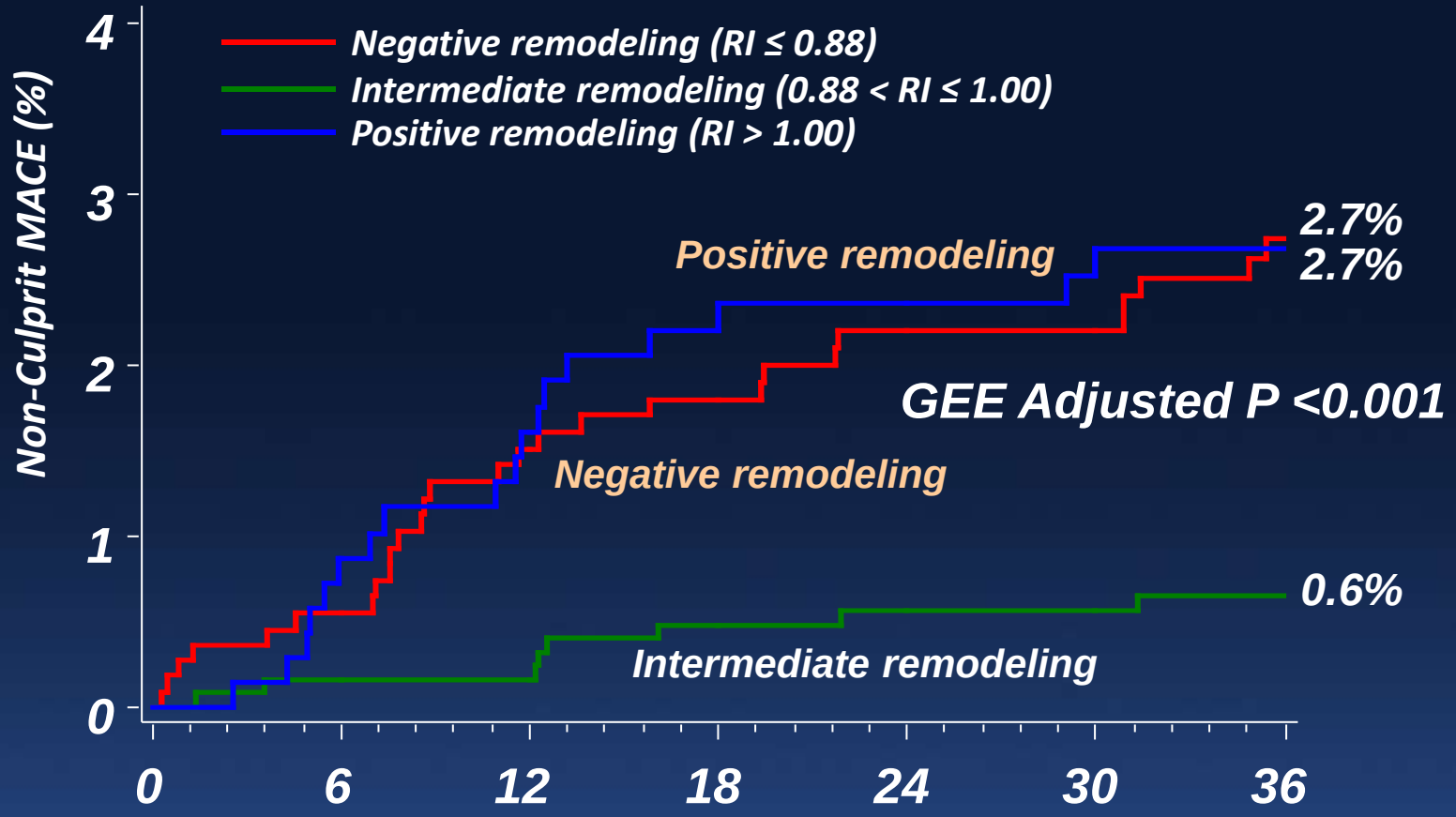
(Prati et al. Circulation 2003;107:2320-5)

Remodeling index that predicted MACE in PROSPECT (Training set: 1041 lesions in 214 pts)



Inaba et al. JACC Cardiovasc Imaging 2014;7:70-8

Impact of Positive and Negative Remodeling in PROSPECT (Test set: 2182 lesions is 443 pts)



Number at risk							
Negative Remodeling	1137	1041	1019	996	970	940	598
Intermediate Remodeling	1355	1262	1244	1209	1186	1154	712
Positive Remodeling	731	675	666	640	622	601	385

Inaba et al. JACC Cardiovasc Imaging 2014;7:70-8

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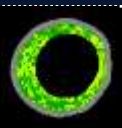
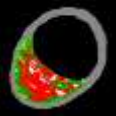
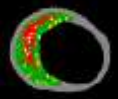
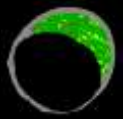
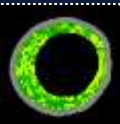
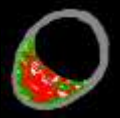
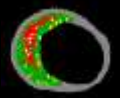
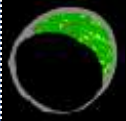
8-month change in non-culprit lesion phenotype in 106 pts (201 lesions) with stable CAD with plaque burden >40% from the Global VH Registry

Baseline		Follow-up: PIT (n=48)	TCFA (n=17)	ThCFA (n=109)	Fibrotic (n=23)	Fibrcalcific (n=20)
						
PIT (n=62)		44	6	12	0	0
TCFA (n=20)		0	5	14	2	0
ThCFA (n=93)		0	6	83	3	1
Fibrotic (n=22)		4	0	0	18	0
Fibrocalcific (n=19)		0	0	0	0	19

Kubo et al. J Am Coll Cardiol 2010;55:1590-7

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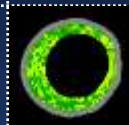
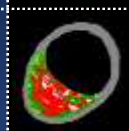
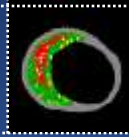
13-month change in non-culprit lesion phenotype in 100 pts (100 lesions) with plaque burden >40% from the HORIZONS-AMI Trial

Baseline			*Follow-up*		
			PIT (n=11)	TCFA (n=54)	ThCFA (n=32)
					
	PIT (n=16)		6	3	7
	TCFA (n=43)		2	33	8
	ThCFA (n=40)		1	19	20

Zhao et al. JACC Cardiovasc Imaging 2013;6:86-95

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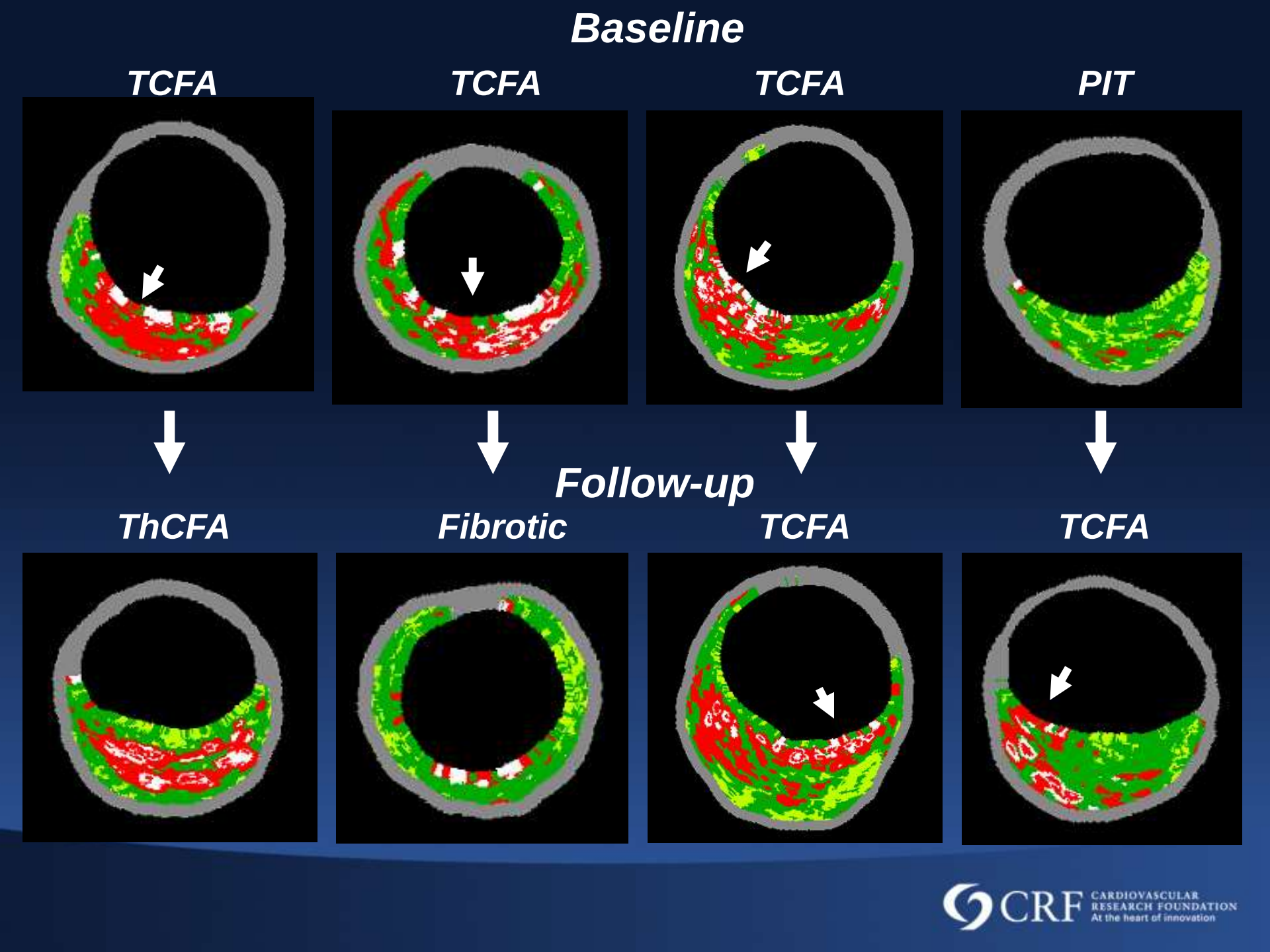

PROSPECT: 3-year follow-up hierarchical MACE (assuming indeterminant events are non-culprit lesion related)

	All	Culprit lesion related	Non culprit lesion related
Cardiac death	1.9% (12)	0.2% (1)	1.8% (11)
Cardiac arrest	0.3% (2)	0.3% (2)	0% (0)
MI (STEMI or NSTEMI)	2.7% (17)	1.7% (11)	1.2% (7)
Rehospitalization for unstable or progressive angina	15.4% (101)	10.4% (69)	10.5% (67)
Composite MACE	20.4% (132)	12.9% (83)	13.3% (85)
Cardiac death, arrest or MI	**4.9% (31)**	**2.2% (14)**	**2.9% (18)**

Stone et al. N Engl J Med 2011;361:226-35

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Composite MACE	20.4% (132)	12.9% (83)	13.3% (85)
Cardiac death, arrest or MI	**4.9% (31)**	**2.2% (14)**	**2.9% (18)**

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PROSPECT: Completeness of 3-vessel IVUS and VH-IVUS imaging

Event type	Total # of events	Baseline QCA at event site	Baseline IVUS at event site	Baseline VH at event site
All MACE	245	227	140	132
Culprit lesion related	120	120	84	76
Non culprit lesion related	**107**	**107**	**56**	**56**
- With RLP	51	51	31	31
- Without RLP	56	56	25	25
Indeterminate	18	0	0	0

PROSPECT: Complications attributed to the 3-vessel IVUS imaging procedure (n=697, non-hierarchical)

Death	0 (0%)
MI	3 (0.4%)
- Q-wave (from dissection)	1
- non Q-wave (from dissection)	2
PCI or CABG	10 (1.4%)
- CABG (from perforation)	1
- CABG (from dissection)	2
- PCI (from dissection)	9
Any imaging complication*	11 (1.6%)

Some pts had more than one complication

Searching for Vulnerable Plaques: Will It Ever Make Clinical Sense?

Yes	No
Intravascular imaging can identify rupture-prone TCFAs	With modern medical therapy, hard events (death/MI) that are related to plaque rupture occur in only 1% per year
	TCFAs are not ubiquitous, 50% of high-risk patients have no identifiable TCFAs, and intravascular imaging identifies only 50% of TCFAs that cause future events
	Three-vessel intravascular imaging is associated with a small, but finite rate of complications
	TCFAs develop, heal, and/or rupture asymptomatically
	TCFAs account for only approximately 50% of lesions that cause acute events. Other causes are erosions, severe stenoses, calcified nodules, and spontaneous dissections.