Vulnerable Plaque Imaging

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Dallas VA Medical Center

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Objectives-

1. Understand prevalence of CAD and importance of noninvasive risk stratification of patients with known or suspected CAD
2. Definition of terms for culprit lesion and vulnerable plaque
3. Which imaging modalities can help image vulnerable plaque?
4. Review of recent literature & implications for understanding the natural history of CAD
5. Conclusion

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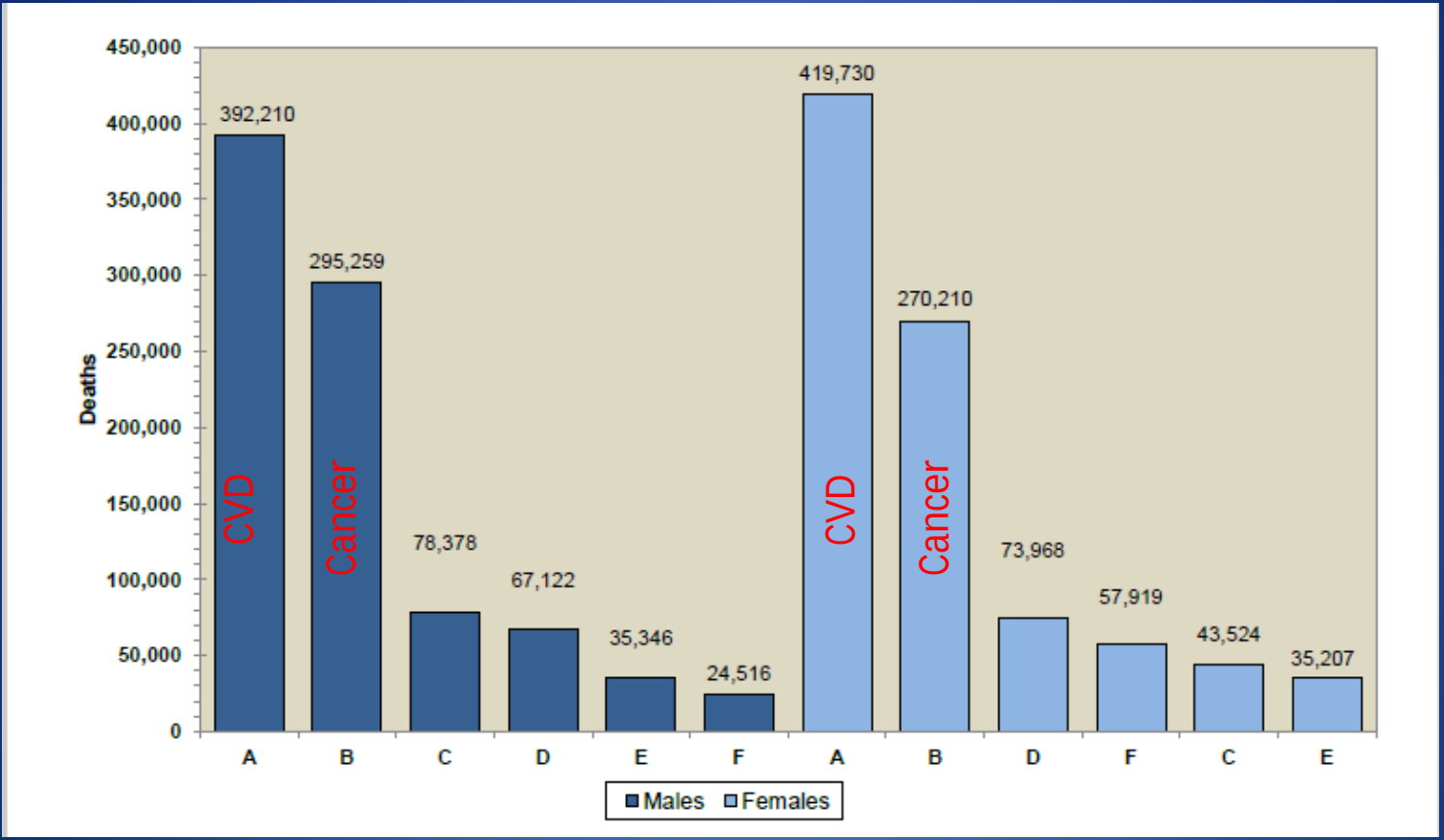
CVD & Other Major Causes of Death for All Males and Females (United States: 2008)



A indicates CVD plus congenital CVD (ICD-10 100-199, Q20-Q28); B, cancer (C00-C97); C, accidents (V01-X59, Y85-Y86; D, CLRD (J40-J47); E, diabetes mellitus (E10-E14); F, Alzheimer disease (G30). Source: NCHS and NHLBI. 2011 American Heart Association, Inc, All rights reserved; Roger VL et al. Published online in Circulation Dec 15, 2011

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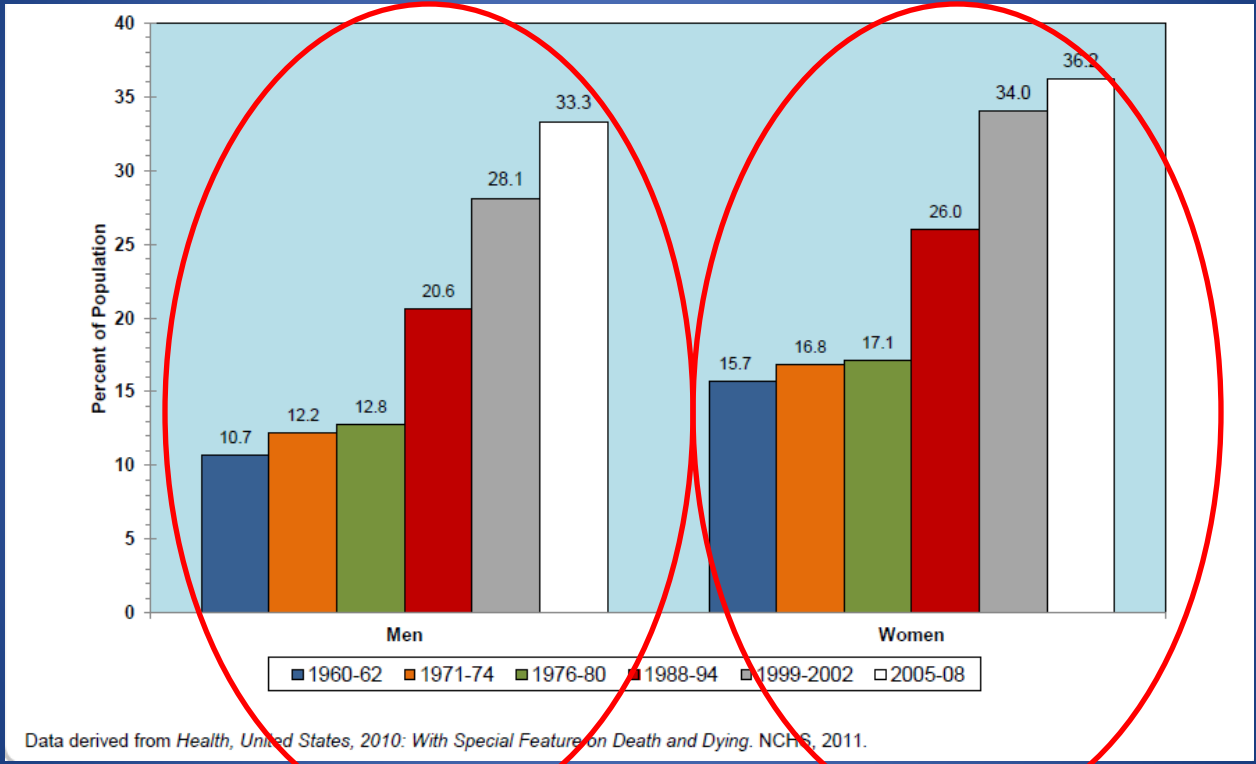
Age-adjusted prevalence of obesity in adults 20-74 years of age, by sex and survey year (NHES: 1960-62; NHANES: 1971-74, 1976-1980, 1988-94, 1999-2002 and 2005-08



Data derived from Health, United States, 2010: With Special Feature on Death and Dying, NCHS, 2011. American Heart Association, Inc. All rights reserved. Roger VL, et. al. Published online in Circulation, Dec 15, 2011

American Heart Association | American Stroke Association

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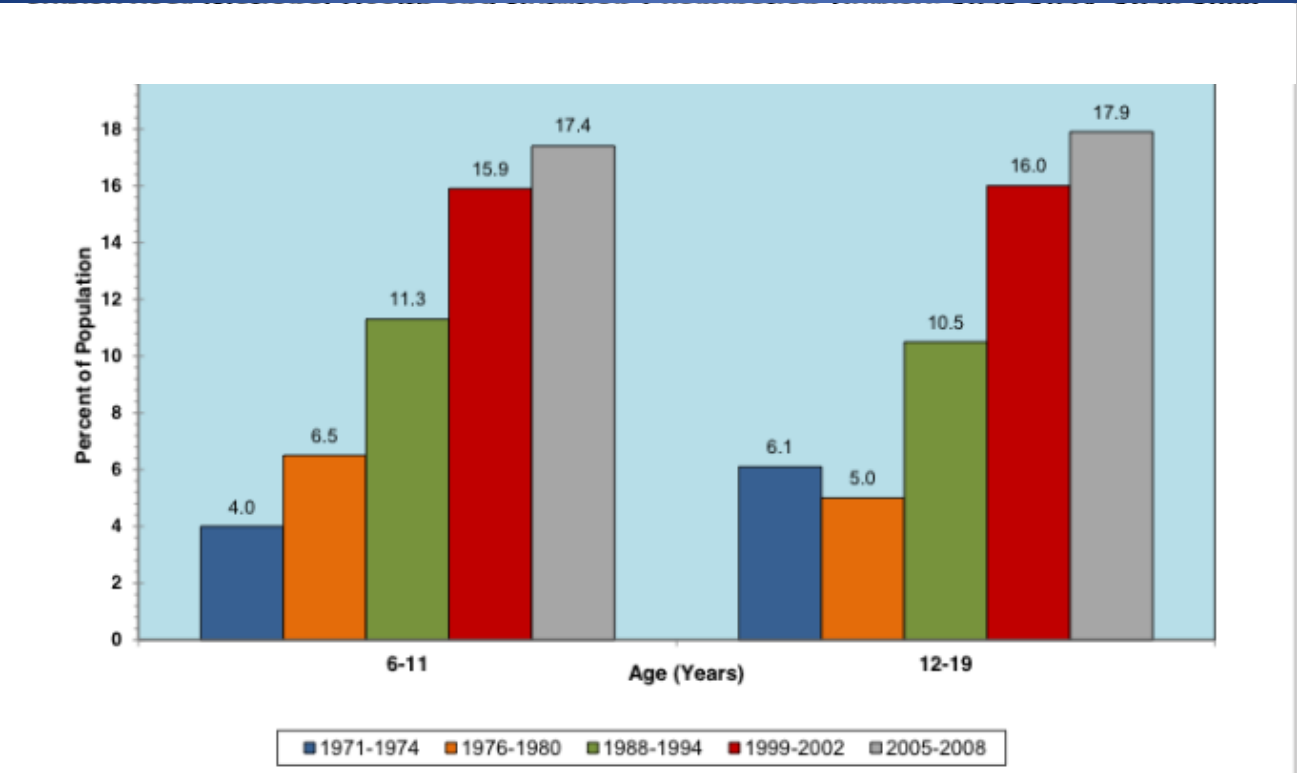
Trends in the Prevalence of Obesity among US Children and Adolescents by Age and Survey Year (National Health and Nutrition Examination Survey: 1971-1974, 1976-1980, 1988-1994, 1999-2002 and 2005-2008



Data derived from *Health, United States, 2010: With Special Feature on Death and Dying NCHS, 2011. Roger VL et al. Published online in Circulation Dec 15, 2011 Copyrighted American Heart Association, Inc.*

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Vulnerable Plaque Imaging

- Culprit lesion- Retrospective identification of plaque in context of ACS (pain, ECG change & troponemia) characterized by:
  - Tight stenosis or occlusion, especially w/acute thrombus
  - Poor TIMI flow
  - Macroscopic evidence of plaque rupture

- Vulnerable plaque- Prospective identification of plaques likely to result in clinical events, characterized by:
  - Thin fibrous cap
  - Large lipid core
  - Inflammation

  - Positive remodeling
  - Spotty calcification
  - Usually nonobstructive

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Vulnerable Plaque Imaging

Histology:	*Imaging Modalities*
• Thin capped fibroadenoma	• IVUS/OCT
• Large lipid core	• IVUS/OCT, CCTA
• Positive remodeling	• IVUS/OCT, CCTA
• Spotty calcification	• CCTA and PET
• Inflammation	• PET (FDG & NaF)

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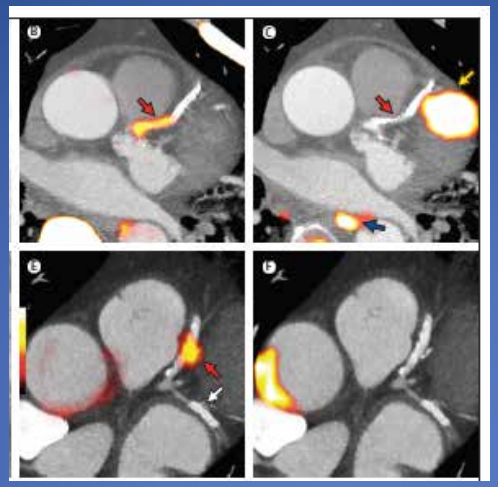
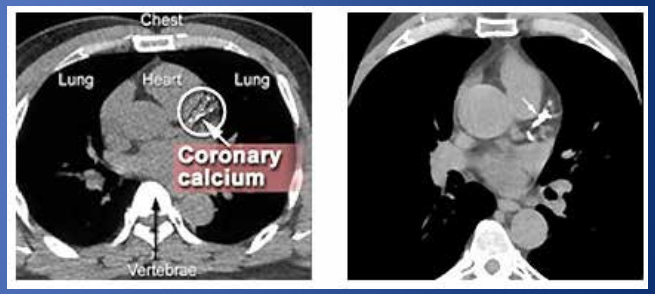
Vulnerable Plaque Imaging

Non invasive imaging options:

- Nuclear



- CT based
  - Coronary calcium scoring
  - CCTA



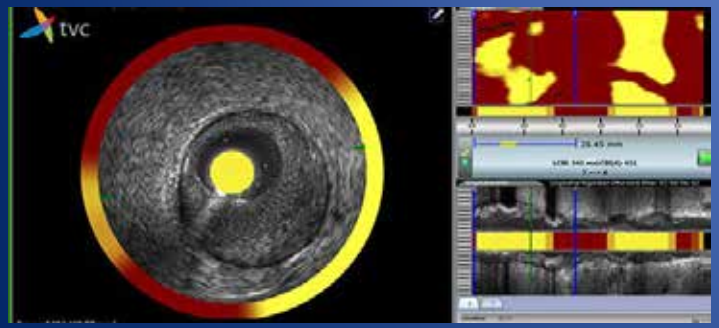
- MR

Vulnerable Plaque Imaging

Invasive imaging options:

Catheter based strategies-

- IVUS
- VH-IVUS
- OCT
- NIR
- Combined modality



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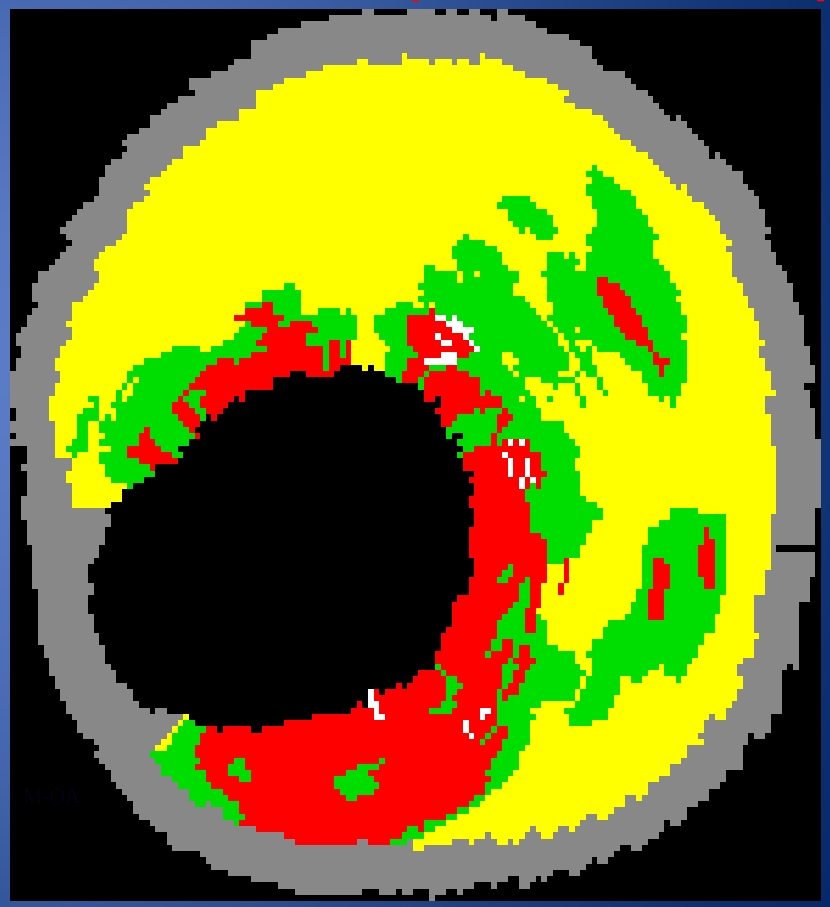
Virtual Histology

Positive remodeling/Glacov's phenomen

VH Legend

- MEDIA
- FIBROUS
- FIBROFATTY
- CALCIUM
- LIPID CORE



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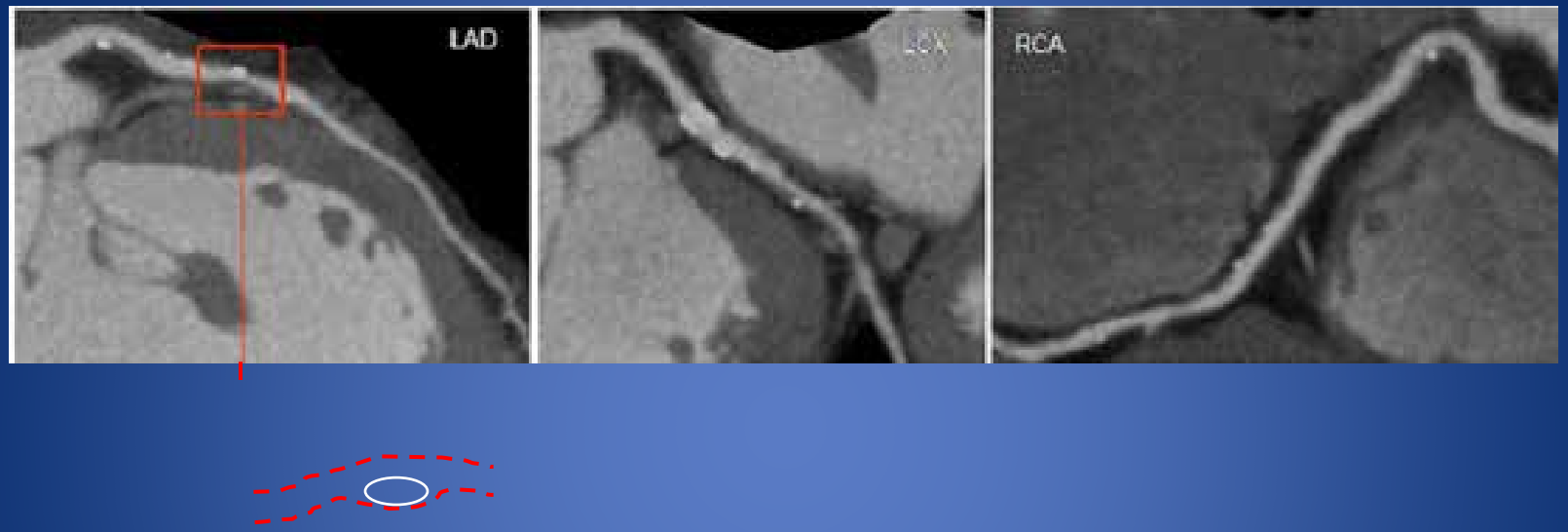
Vulnerable Plaque Imaging: CTA



High Risk plaque features:

- Positive remodeling
- Low attenuation plaque
- Spotty calcification
- Moderate luminal stenosis

Invasive cath 6 months later during ACS shows LAD #6 to be culprit lesion

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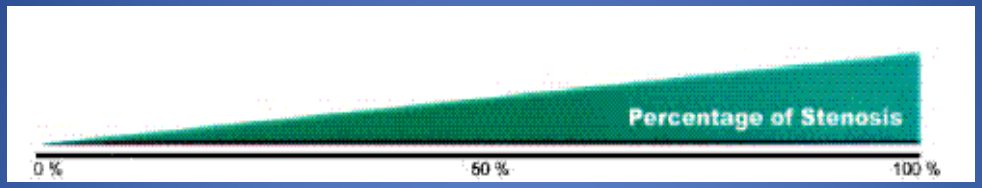
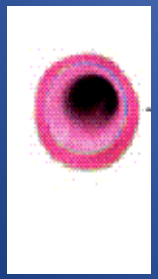
Plaque Severity, Stenosis & Risk of Complication





S. Redwood, St Thomas' Hospital, London

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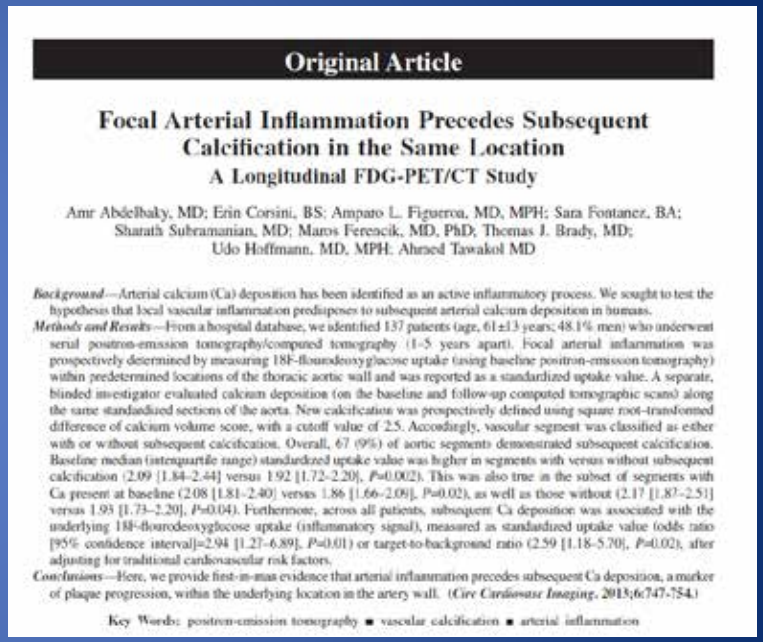
Vulnerable Plaque Imaging

- Study hypothesis-
  - Focal vascular inflammation precedes calcification
- Aorta vs coronary arteries
- Oncology follow up patients identified at Mass Gen from a retrospective image registry
- Exclusion criteria-
  - Age < 35
  - Chronic inflammatory disease
  - Anti-inflammatory drug use
  - Active malignancy
  - Chemotherapy or radiation therapy in past year



Original Article

Focal Arterial Inflammation Precedes Subsequent Calcification in the Same Location
A Longitudinal FDG-PET/CT Study

Amr Abdelbaky, MD; Erin Corsini, BS; Amparo L. Figueroa, MD, MPH; Sara Fontanez, BA; Sharath Subramanian, MD; Maros Ferencik, MD, PhD; Thomas J. Brady, MD; Udo Hoffmann, MD, MPH; Ahmed Tawakol MD

Background—Arterial calcium (Ca) deposition has been identified as an active inflammatory process. We sought to test the hypothesis that local vascular inflammation predisposes to subsequent arterial calcium deposition in humans.

Methods and Results—From a hospital database, we identified 137 patients (age, 61±13 years; 48.1% men) who underwent serial positron-emission tomography/computed tomography (1–5 years apart). Focal arterial inflammation was prospectively determined by measuring 18F-fluorodeoxyglucose uptake (using baseline positron-emission tomography) within predetermined locations of the thoracic aortic wall and was reported as a standardized uptake value. A separate, blinded investigator evaluated calcium deposition (on the baseline and follow-up computed tomographic scans) along the same standardized sections of the aorta. New calcification was prospectively defined using square root–transformed difference of calcium volume score, with a cutoff value of 2.5. Accordingly, vascular segment was classified as either with or without subsequent calcification. Overall, 67 (9%) of aortic segments demonstrated subsequent calcification. Baseline median (interquartile range) standardized uptake value was higher in segments with versus without subsequent calcification (2.09 [1.84–2.44] versus 1.92 [1.72–2.20], P=0.002). This was also true in the subset of segments with Ca present at baseline (2.08 [1.81–2.40] versus 1.86 [1.66–2.06], P=0.02), as well as those without (2.17 [1.87–2.51] versus 1.93 [1.73–2.20], P=0.04). Furthermore, across all patients, subsequent Ca deposition was associated with the underlying 18F-fluorodeoxyglucose uptake (inflammatory signal), measured as standardized uptake value (odds ratio [95% confidence interval]=2.94 [1.27–6.89], P=0.01) or target-to-background ratio (2.59 [1.18–5.70], P=0.02), after adjusting for traditional cardiovascular risk factors.

Conclusions—Here, we provide first-in-man evidence that arterial inflammation precedes subsequent Ca deposition, a marker of plaque progression, within the underlying location in the artery wall. (*Circ Cardiovasc Imaging*. 2013;6:747-754.)

Key Words: positron-emission tomography ■ vascular calcification ■ arterial inflammation

Circ Cardiovasc Imaging. 2013;6:747-754

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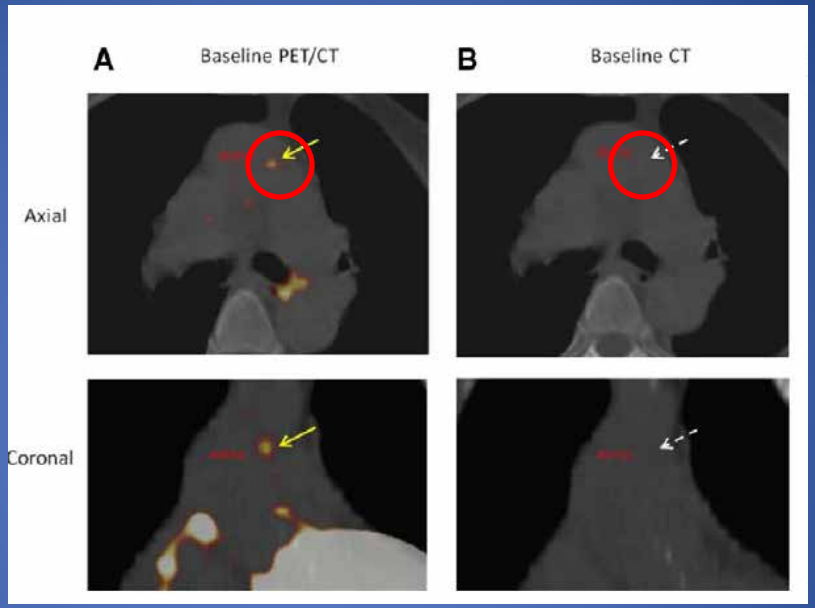
Longitudinal FDG PET/CT

- 137 patients w/serial PET/CT 1-5 years
- Focal inflammation recognized by FDG uptake precedes calcification
- Site of FDG uptake has no calcification on baseline PET/CT
- Follow up CT shows new calcification at site of initial FDG uptake
- Found in 67 of 735 arterial segments (9%)



Circ Cardiovasc Imaging. Abdelbaky et al. 2013;6:747-754

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Vulnerable Plaque Imaging

^{18}F-NaF Uptake by Atherosclerotic Plaque on PET/CT Imaging: Inverse Correlation Between Calcification Density and Mineral Metabolic Activity

Francesco Fiz[1], Silvia Morbelli[1], Arnoldo Piccardo[2], Matteo Bauckneht[1], Giulia Ferrarazzo[1], Emanuela Pestarino[2], Manlio Cabria[2], Alessia Democrito[1], Mattia Riondato[3], Giampiero Villavecchia[2], Cecilia Marini[4], and Gianmario Sambuceti[1]

[1]*Nuclear Medicine Unit, Department of Health Sciences, IRCCS San Martino–IST, University of Genoa, Genoa, Italy;* [2]*Nuclear Medicine Unit, Galliera Hospital, Genoa, Italy;* [3]*Nuclear Medicine Unit, S. Andrea Hospital, La Spezia, Italy; and* [4]*Institute of Molecular Bioimaging and Physiology, CNR, Genoa, Italy*

Several studies have highlighted the role of vascular ^{18}F-NaF uptake as a marker of ongoing calcium deposition. However, accumulation of ^{18}F-NaF is often inconsistent with localization of arterial plaque. Calcification activity and thus ^{18}F-NaF uptake might prevail in the earlier plaque stages. To test this hypothesis, we evaluated ^{18}F-NaF uptake in plaque of 3 different densities, using density as a marker of calcification progression. We also tested whether attenuation-weighted image reconstruction affects ^{18}F-NaF uptake in the different plaque stages. **Methods:** Sixty-four oncologic patients (14 men and 50 women; mean age, 65.3 ± 8.2 y; range, 26–81 y) underwent ^{18}F-NaF PET/CT. A volume of interest was drawn on each plaque within the infrarenal aorta to assess mean standardized uptake value and attenuation (in Hounsfield units [HU]). Plaque was then categorized as light (<210 HU), medium (211–510 HU), or heavy (>510 HU). Standardized uptake value was normalized for blood ^{18}F-NaF activity to obtain the plaque target-to-background ratio (TBR). During this process, several focal, noncalcified areas of ^{18}F-NaF were identified (hot spots). The TBR of the hot spots was computed after isocontour thresholding. The TBR of a noncalcified control region was also calculated. In 35 patients, the TBR of non–attenuation-corrected images was calculated. **Results:** The average TBR was highest in light plaque (2.21 ± 0.88), significantly lower in medium plaque (1.59 ± 0.63, $P < 0.001$), and lower still in heavy plaque (1.14 ± 0.37, $P < 0.0001$ with respect to both light and medium plaque). The TBR of the control region was not significantly different from that of heavy plaque but was significantly lower than that of light and medium plaque ($P < 0.01$). Hot spots had the highest absolute TBR (3.89 ± 1.87, $P < 0.0001$ vs. light plaque). TBRs originating from non–attenuation-corrected images did not significantly differ from those originating from attenuation-corrected images. **Conclusion:** Our results support the concept that ^{18}F-NaF is a feasible option in imaging molecular calcium deposition in the early stages of plaque formation, when active uptake mechanisms are the main determinants of calcium presence, but that retention of ^{18}F-NaF progressively decreases with increasing calcium deposition in the arterial wall. Our data suggest that non–attenuation-corrected reconstruction does not significantly affect evaluation of plaque of any thickness.

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Key Words: ^{18}F-natrium fluoride; plaque imaging; PET/CT
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DOI: 10.2967/jnumed.115.154229

Since the earliest pathologic studies, arterial calcification has been regarded as a focus of ectopically formed skeleton-like tissue, caused by continuous calcium deposition in the arterial intima (*1*). Modern histopathologic research has confirmed this hypothesis, demonstrating the presence of cells deriving from osteoblastic and osteoclastic lineage in areas of vascular calcification (*2,3*). These characteristics allow for the use of CT to assess calcification and generate a clinical calcification score, which is widely regarded as a sound index of the burden and extent of atherosclerotic plaque (*4,5*). However, a calcification score represents only a static picture, not the pathophysiologic behavior of plaque, and may not fully correlate with a patient's clinical status and cardiovascular risk (*6–8*). Therefore, in view of the similarities between calcification formation and osteogenesis, functional studies with ^{18}F-NaF PET have been performed to complement the calcification score with functional data on plaque mineral metabolism (*9–15*). These studies, however, highlighted a striking discrepancy between PET and CT in imaging plaque. In particular, PET-positive areas almost invariably colocalized with calcification, whereas only a fraction of the calcification showed visible ^{18}F-NaF uptake (*9*). Moreover, the fraction of calcification that correlated with tracer uptake varied widely according to the arterial segment studied, being as low as 12% if the average of all calcification sites was considered (*9*), showing great variability in the coronary district (*15*), and peaking in the carotid arteries (*10*).

The mismatch between the morphologic and radioisotopic findings might be grounded on the pathophysiology of plaque buildup, which is a complex and dynamic process involving repeated sequences of inflammation, repair, apoptosis, and necrosis. Arterial calcification is, however, a prominent feature of atherosclerosis and is thus used as an imaging marker of plaque progression (*9,10*). In the earliest calcification stages, the inflammatory environment fosters the release of several bone-forming peptides, which promote the active apposition of a hydroxyapatite matrix in the arterial wall, appearing on CT as soft, inconspicuous,

- Research hypothesis: Calcification might prevail in early stages of CAD
- NaF used as in vivo biomarker for calcification
- Plaque maturity based on density
- Abdominal aorta studied
- 64 Oncology patients
- Correlation made between intensity of PET uptake and plaque density

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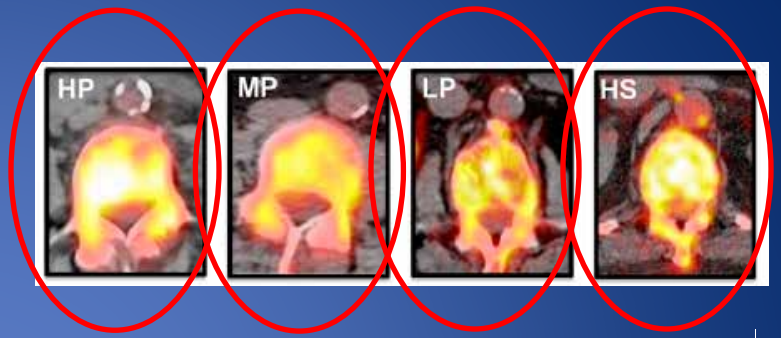
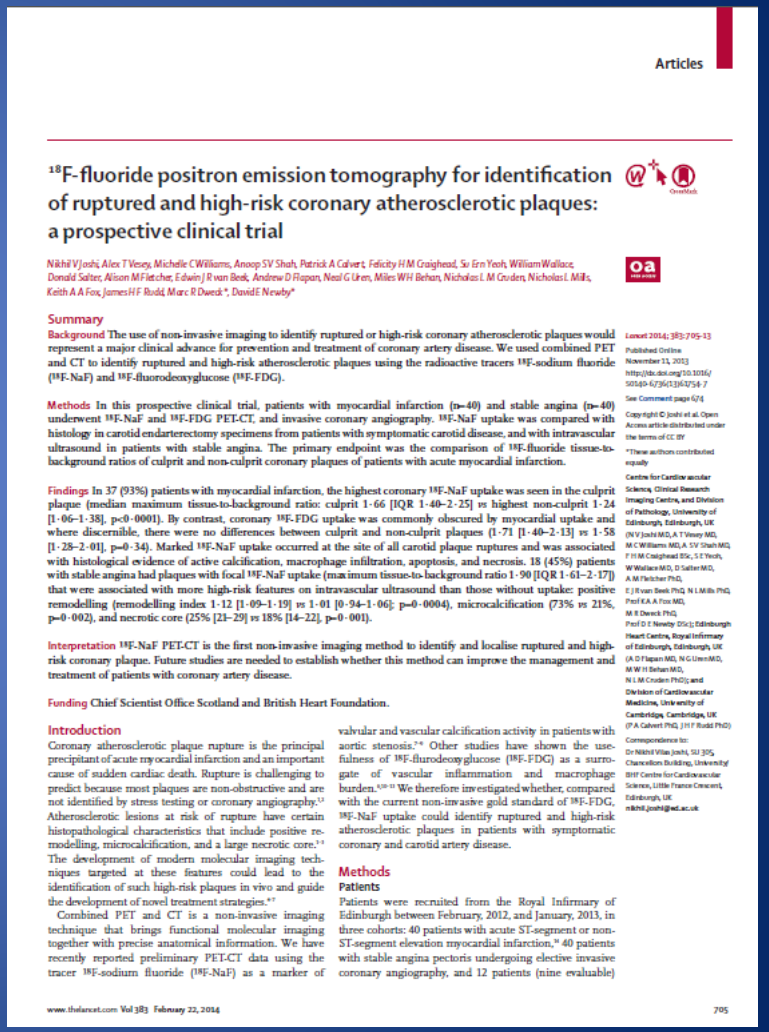
Vulnerable Plaque Imaging



- Study population 78% female
- Abdominal aorta
- Plaque maturity based on HU:
  - Non calcified hot spot
  - LP (<210 HU)
  - MP (211-510 HU)
  - HP (>510 HU)
- Findings-
  - LP 2.2 x blood pool
  - HS most avid at 3.9 x BP
  - No significant difference w/AC
- Conclusion- NaF uptake by atherosclerotic plaque is greatest in early stages of plaque formation when it exhibits no or only spotty/micro calcification

Vulnerable Plaque Imaging: Na F

- Three patient cohorts:
  - Acute MI (n=40)
  - Stable angina (n=40)
  - Elective CEA (n=9)
- All patients w/AMI and SAP had PET/CT w/18F-NaF and 18F-FDG
- Primary endpoint comparison of NaF uptake for AMI patients
- CEA patients compared histologically



Articles

^{18}F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial

Nikhil V Joshi, Alex T Vesey, Michelle C Williams, Anoop S V Shah, Patrick A Calvert, Felicity H M Craighead, Sir Ern Yeoh, William Wallace, Donald Salter, Alison M Fletcher, Edwin J R van Beek, Andrew D Flapan, Neal G Uren, Miles W H Behan, Nicholas L M Cruden, Nicholas L Mills, Keith A A Fox, James H F Rudd, Marc R Dweck*, David E Newby*

Summary

Background The use of non-invasive imaging to identify ruptured or high-risk coronary atherosclerotic plaques would represent a major clinical advance for prevention and treatment of coronary artery disease. We used combined PET and CT to identify ruptured and high-risk atherosclerotic plaques using the radioactive tracers ^{18}F-sodium fluoride (^{18}F-NaF) and ^{18}F-fluorodeoxyglucose (^{18}F-FDG).

Methods In this prospective clinical trial, patients with myocardial infarction (n=40) and stable angina (n=40) underwent ^{18}F-NaF and ^{18}F-FDG PET-CT, and invasive coronary angiography. ^{18}F-NaF uptake was compared with histology in carotid endarterectomy specimens from patients with symptomatic carotid disease, and with intravascular ultrasound in patients with stable angina. The primary endpoint was the comparison of ^{18}F-fluoride tissue-to-background ratios of culprit and non-culprit coronary plaques of patients with acute myocardial infarction.

Findings In 37 (93%) patients with myocardial infarction, the highest coronary ^{18}F-NaF uptake was seen in the culprit plaque (median maximum tissue-to-background ratio: culprit 1·66 [IQR 1·40–2·25] *vs* highest non-culprit 1·24 [1·06–1·38], p<0·0001). By contrast, coronary ^{18}F-FDG uptake was commonly obscured by myocardial uptake and where discernible, there were no differences between culprit and non-culprit plaques (1·71 [1·40–2·13] *vs* 1·58 [1·28–2·01], p=0·34). Marked ^{18}F-NaF uptake occurred at the site of all carotid plaque ruptures and was associated with histological evidence of active calcification, macrophage infiltration, apoptosis, and necrosis. 18 (45%) patients with stable angina had plaques with focal ^{18}F-NaF uptake (maximum tissue-to-background ratio 1·90 [IQR 1·61–2·17]) that were associated with more high-risk features on intravascular ultrasound than those without uptake: positive remodelling (remodelling index 1·12 [1·09–1·19] *vs* 1·01 [0·94–1·06]; p=0·0004), microcalcification (73% *vs* 21%, p=0·002), and necrotic core (25% [23–29] *vs* 18% [14–22], p=0·001).

Interpretation ^{18}F-NaF PET-CT is the first non-invasive imaging method to identify and localise ruptured and high-risk coronary plaque. Future studies are needed to establish whether this method can improve the management and treatment of patients with coronary artery disease.

Funding Chief Scientist Office Scotland and British Heart Foundation.

Introduction

Coronary atherosclerotic plaque rupture is the principal precipitant of acute myocardial infarction and an important cause of sudden cardiac death. Rupture is challenging to predict because most plaques are non-obstructive and are not identified by stress testing or coronary angiography.[1,2] Atherosclerotic lesions at risk of rupture have certain histopathological characteristics that include positive remodelling, microcalcification, and a large necrotic core.[3,4] The development of modern molecular imaging techniques targeted at these features could lead to the identification of such high-risk plaques in vivo and guide the development of novel treatment strategies.[5,6]

Combined PET and CT is a non-invasive imaging technique that brings functional molecular imaging together with precise anatomical information. We have recently reported preliminary PET-CT data using the tracer ^{18}F-sodium fluoride (^{18}F-NaF) as a marker of valvular and vascular calcification activity in patients with aortic stenosis.[7,8] Other studies have shown the usefulness of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) as a surrogate of vascular inflammation and macrophage burden.[9,10,11] We therefore investigated whether, compared with the current non-invasive gold standard of ^{18}F-FDG, ^{18}F-NaF uptake could identify ruptured and high-risk atherosclerotic plaques in patients with symptomatic coronary and carotid artery disease.

Methods

Patients

Patients were recruited from the Royal Infirmary of Edinburgh between February, 2012, and January, 2013, in three cohorts: 40 patients with acute ST-segment or non-ST-segment elevation myocardial infarction,[12] 40 patients with stable angina pectoris undergoing elective invasive coronary angiography, and 12 patients (nine evaluable)

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Lancet 383; Feb 24, 2014 p 705

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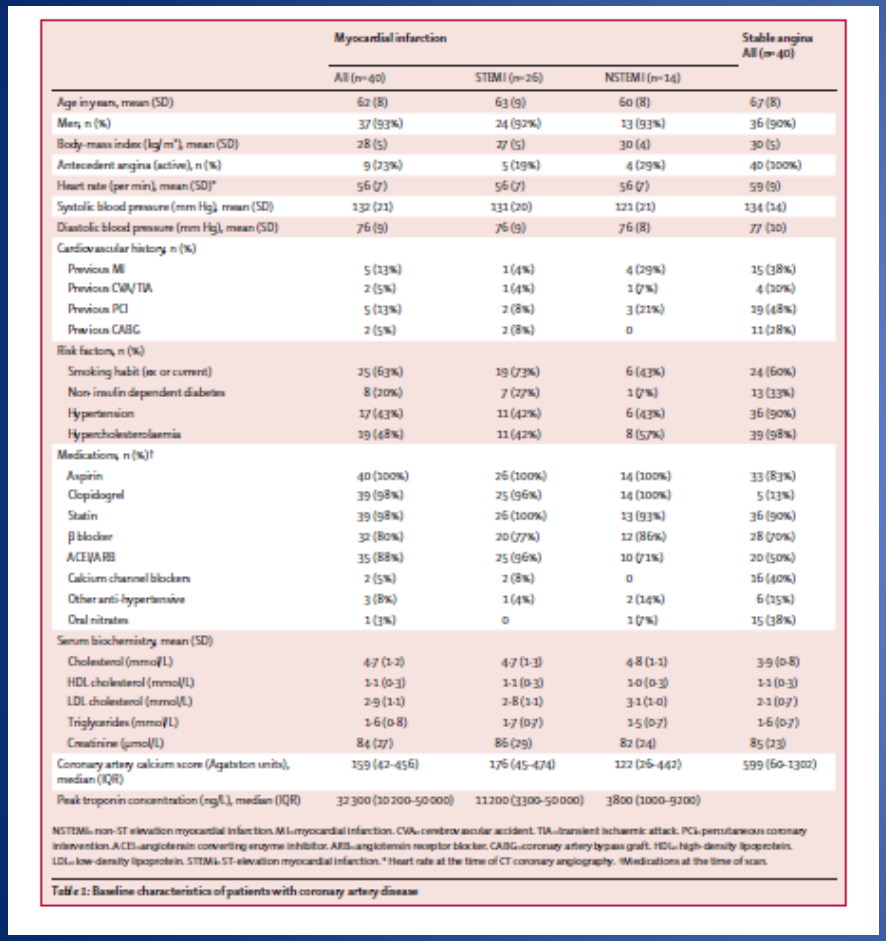
Vulnerable Plaque Imaging: Na F



	Myocardial infarction			Stable angina All (n=40)
	All (n=40)	STEMI (n=26)	NSTEMI (n=14)	
Age in years, mean (SD)	62 (8)	63 (9)	60 (8)	67 (8)
Men, n (%)	37 (93%)	24 (92%)	13 (93%)	36 (90%)
Body-mass index (kg/m²), mean (SD)	28 (5)	27 (5)	30 (4)	30 (5)
Antecedent angina (active), n (%)	9 (23%)	5 (19%)	4 (29%)	40 (100%)
Heart rate (per min), mean (SD)*	56 (7)	56 (7)	56 (7)	59 (9)
Systolic blood pressure (mm Hg), mean (SD)	132 (21)	131 (20)	121 (21)	134 (14)
Diastolic blood pressure (mm Hg), mean (SD)	76 (9)	76 (9)	76 (8)	77 (10)
Cardiovascular history, n (%)				
Previous MI	5 (13%)	1 (4%)	4 (29%)	15 (38%)
Previous CVA/TIA	2 (5%)	1 (4%)	1 (7%)	4 (10%)
Previous PCI	5 (13%)	2 (8%)	3 (21%)	19 (48%)
Previous CABG	2 (5%)	2 (8%)	0	11 (28%)
Risk factors, n (%)				
Smoking habit (ex or current)	25 (63%)	19 (73%)	6 (43%)	24 (60%)
Non-insulin dependent diabetes	8 (20%)	7 (27%)	1 (7%)	13 (33%)
Hypertension	17 (43%)	11 (42%)	6 (43%)	36 (90%)
Hypercholesterolaemia	19 (48%)	11 (42%)	8 (57%)	39 (98%)
Medications, n (%)†				
Aspirin	40 (100%)	26 (100%)	14 (100%)	33 (83%)
Clopidogrel	39 (98%)	25 (96%)	14 (100%)	5 (13%)
Statin	39 (98%)	26 (100%)	13 (93%)	36 (90%)
β blocker	32 (80%)	20 (77%)	12 (86%)	28 (70%)
ACEI/ARB	35 (88%)	25 (96%)	10 (71%)	20 (50%)
Calcium channel blockers	2 (5%)	2 (8%)	0	16 (40%)
Other anti-hypertensive	3 (8%)	1 (4%)	2 (14%)	6 (15%)
Oral nitrates	1 (3%)	0	1 (7%)	15 (38%)
Serum biochemistry, mean (SD)				
Cholesterol (mmol/L)	4·7 (1·2)	4·7 (1·3)	4·8 (1·1)	3·9 (0·8)
HDL cholesterol (mmol/L)	1·1 (0·3)	1·1 (0·3)	1·0 (0·3)	1·1 (0·3)
LDL cholesterol (mmol/L)	2·9 (1·1)	2·8 (1·1)	3·1 (1·0)	2·1 (0·7)
Triglycerides (mmol/L)	1·6 (0·8)	1·7 (0·7)	1·5 (0·7)	1·6 (0·7)
Creatinine (μmol/L)	84 (27)	86 (29)	82 (24)	85 (23)
Coronary artery calcium score (Agatston units), median (IQR)	159 (42–456)	176 (45–474)	122 (26–442)	599 (60–1302)
Peak troponin concentration (ng/L), median (IQR)	32 300 (10 200–50 000)	11 200 (3300–50 000)	3800 (1000–9200)	

NSTEMI=non-ST elevation myocardial infarction. MI=myocardial infarction. CVA=cerebrovascular accident. TIA=transient ischaemic attack. PCI=percutaneous coronary intervention. ACEI=angiotensin converting enzyme inhibitor. ARB=angiotensin receptor blocker. CABG=coronary artery bypass graft. HDL=high-density lipoprotein. LDL=low-density lipoprotein. STEMI=ST-elevation myocardial infarction. *Heart rate at the time of CT coronary angiography. †Medications at the time of scan.

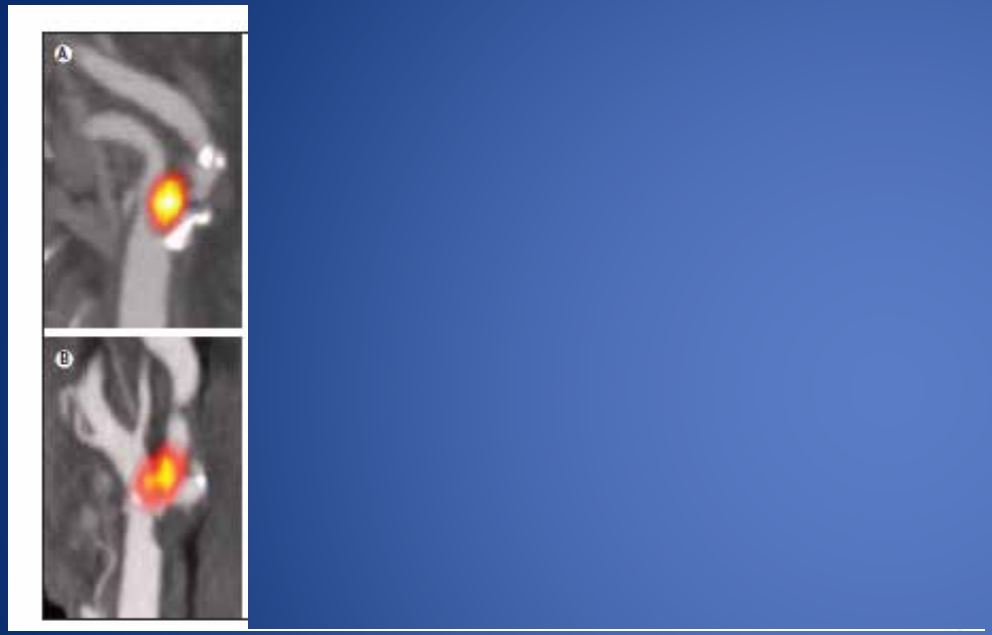
Table 1: Baseline characteristics of patients with coronary artery disease

- Patient population 90% male
- Exclusion-
  - Age < 50 yrs
  - IDDM or poor control
  - Severe renal dz
- Agatston score
- hs-CRP
- hs-TnI
  - Higher in PET + pts w/SAP
    - Subclinical plaque rupture?

Vulnerable Plaque Imaging

- NaF uptake localizes to recent plaque rupture in AMI in 37 patients (93%)
- FDG uptake confounded by variable physiologic myocardial uptake despite prolonged fasting
- Three (3) AMI patients PET negative-
  - 2 were smokers < 60 yo
  - 1 discordant (culprit vessel RCA w/NaF uptake in LCx)
  - Plaque erosion vs rupture

Vulnerable Plaque Imaging



- In-vivo PET in patients undergoing CEA provided histopathological correlation
- F18 flouride uptake A, B
- Ex-vivo imaging C, D
- Macroscopic thrombus E, F
- Large necrotic core G
- Positive alkaline phosphatase as marker for calcification H/I

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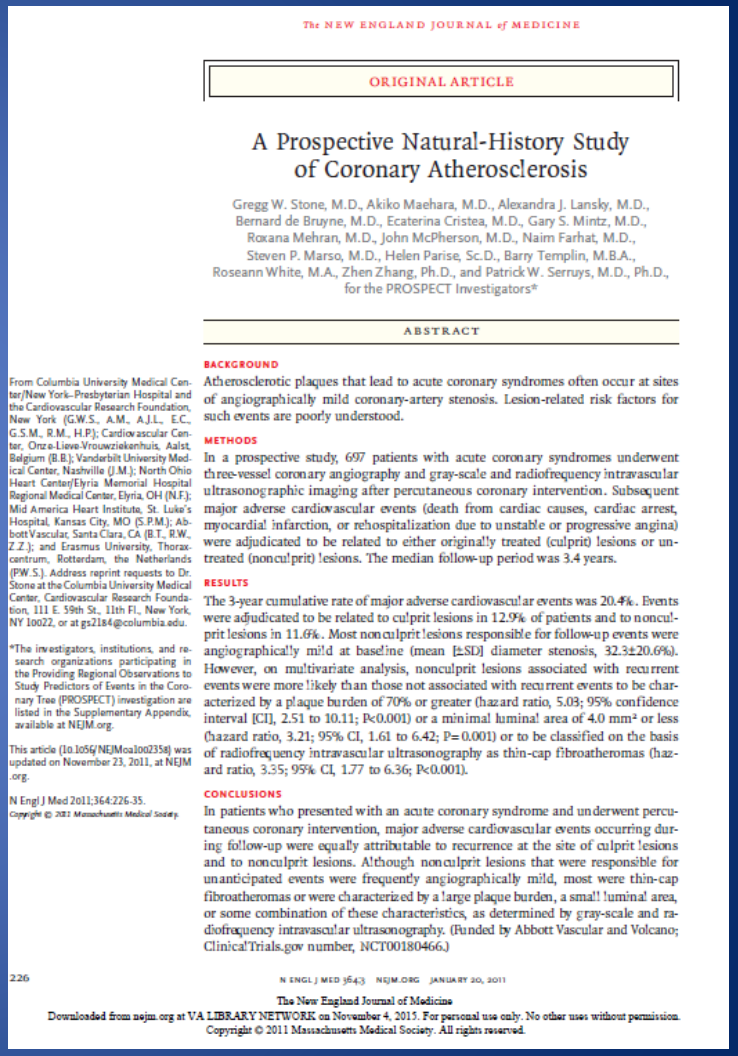
Vulnerable Plaque Imaging

- PROSPECT Study: Natural history of CAD (Providing Regional Observations to Study Predictors of Events in the Coronary Tree)
- 37 sites in US & Europe
- 697 pts w/AMI
  - 3 vessel IVUS after PCI
  - Subsequent MACE (3.4 yrs) occurred in 20% of patients-
    - Culprit vessel 12.9%
    - Nonculprit vessel 11.6%
- 11 patients had IVUS related complications (10 dissections & 1 perforation



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Prospective Natural-History Study of Coronary Atherosclerosis

Gregg W. Stone, M.D., Akiko Maehara, M.D., Alexandra J. Lansky, M.D., Bernard de Bruyne, M.D., Ecaterina Cristea, M.D., Gary S. Mintz, M.D., Roxana Mehran, M.D., John McPherson, M.D., Naim Farhat, M.D., Steven P. Marso, M.D., Helen Parise, Sc.D., Barry Templin, M.B.A., Roseann White, M.A., Zhen Zhang, Ph.D., and Patrick W. Serruys, M.D., Ph.D., for the PROSPECT Investigators*

ABSTRACT

BACKGROUND

Atherosclerotic plaques that lead to acute coronary syndromes often occur at sites of angiographically mild coronary-artery stenosis. Lesion-related risk factors for such events are poorly understood.

METHODS

In a prospective study, 697 patients with acute coronary syndromes underwent three-vessel coronary angiography and gray-scale and radiofrequency intravascular ultrasonographic imaging after percutaneous coronary intervention. Subsequent major adverse cardiovascular events (death from cardiac causes, cardiac arrest, myocardial infarction, or rehospitalization due to unstable or progressive angina) were adjudicated to be related to either originally treated (culprit) lesions or untreated (nonculprit) lesions. The median follow-up period was 3.4 years.

RESULTS

The 3-year cumulative rate of major adverse cardiovascular events was 20.4%. Events were adjudicated to be related to culprit lesions in 12.9% of patients and to nonculprit lesions in 11.6%. Most nonculprit lesions responsible for follow-up events were angiographically mild at baseline (mean [±SD] diameter stenosis, 32.3±20.6%). However, on multivariate analysis, nonculprit lesions associated with recurrent events were more likely than those not associated with recurrent events to be characterized by a plaque burden of 70% or greater (hazard ratio, 5.03; 95% confidence interval [CI], 2.51 to 10.11; P<0.001) or a minimal luminal area of 4.0 mm² or less (hazard ratio, 3.21; 95% CI, 1.61 to 6.42; P=0.001) or to be classified on the basis of radiofrequency intravascular ultrasonography as thin-cap fibroatheromas (hazard ratio, 3.35; 95% CI, 1.77 to 6.36; P<0.001).

CONCLUSIONS

In patients who presented with an acute coronary syndrome and underwent percutaneous coronary intervention, major adverse cardiovascular events occurring during follow-up were equally attributable to recurrence at the site of culprit lesions and to nonculprit lesions. Although nonculprit lesions that were responsible for unanticipated events were frequently angiographically mild, most were thin-cap fibroatheromas or were characterized by a large plaque burden, a small luminal area, or some combination of these characteristics, as determined by gray-scale and radiofrequency intravascular ultrasonography. (Funded by Abbott Vascular and Volcano; ClinicalTrials.gov number, NCT00180466.)

From Columbia University Medical Center/New York–Presbyterian Hospital and the Cardiovascular Research Foundation, New York (G.W.S., A.M., A.J.L., E.C., G.S.M., R.M., H.P.); Cardiovascular Center, Onze-Lieve-Vrouwziekenhuis, Aalst, Belgium (B.B.); Vanderbilt University Medical Center, Nashville (J.M.); North Ohio Heart Center/Elyria Memorial Hospital Regional Medical Center, Elyria, OH (N.F.); Mid America Heart Institute, St. Luke's Hospital, Kansas City, MO (S.P.M.); Abbott Vascular, Santa Clara, CA (B.T., R.W., Z.Z.); and Erasmus University, Thoraxcentrum, Rotterdam, the Netherlands (P.W.S.). Address reprint requests to Dr. Stone at the Columbia University Medical Center, Cardiovascular Research Foundation, 111 E. 59th St., 11th Fl., New York, NY 10022, or at gs2184@columbia.edu.

*The investigators, institutions, and research organizations participating in the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) investigation are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1002358) was updated on November 23, 2011, at NEJM.org.

N Engl J Med 2011;364:226-35.

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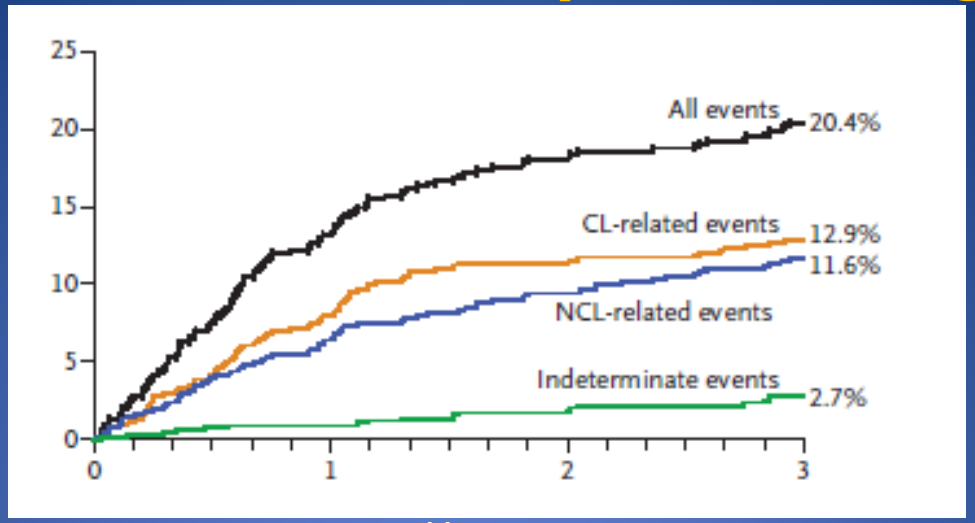
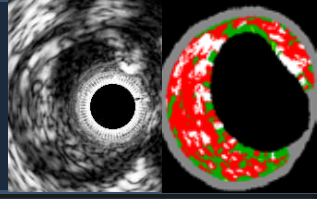
Vulnerable Plaque Imaging



- After PCI 20% of patients had MACE-
  - Nearly equally attributable to culprit and non-culprit vessels
- Most nonculprit lesions were angiographically mild at baseline
- High risk features included:
  - TCFA histology by VH-IVUS (of 595 identified only 26 became culprit during the 3.4 years of follow up)
  - Large plaque burden
  - Small luminal area (high grade stenosis)

PROSPECT: Multivariable Correlates of Non-Culprit Lesion Related Events

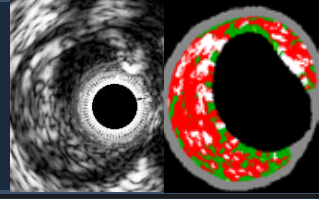


Independent predictors of lesion level events by Cox Proportional Hazards regression

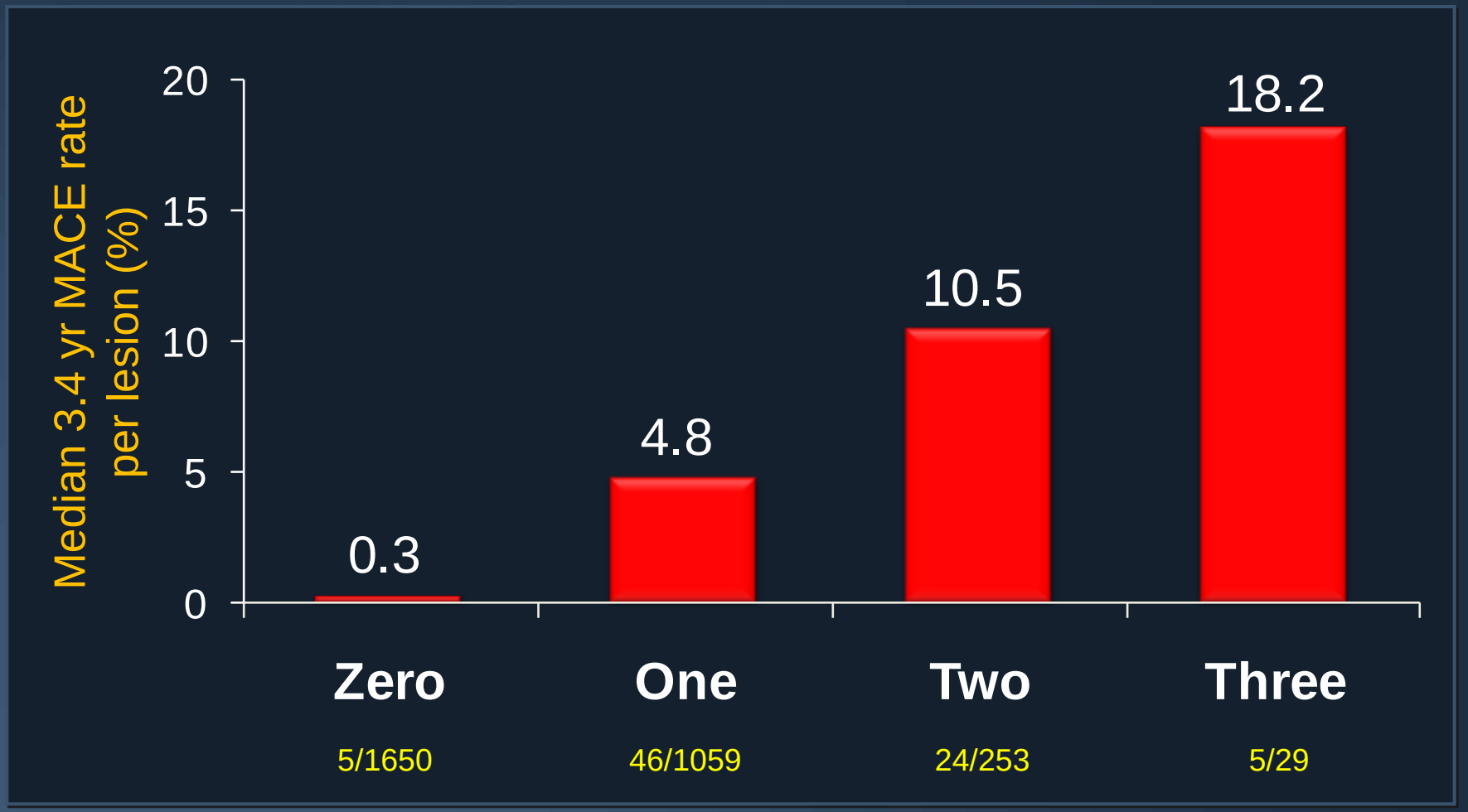
Variable	HR [95% CI]	P value
PB_{MLA} ≥70%	5.03 [2.51, 10.11]	<0.0001
VH-TCFA	3.35 [1.77, 6.36]	0.0002
MLA ≤4.0 mm^2	3.21 [1.61, 6.42]	0.001

Variables entered: minimal lumen area (MLA), plaque burden at the MLA, external elastic membrane at the MLA, lesion length, distance from the coronary ostium to the MLA, remodeling index, thin-cap fibroatheroma, insulin-requiring diabetes and prior percutaneous coronary intervention

PROSPECT: Correlates of Non-Culprit Lesion Related Events

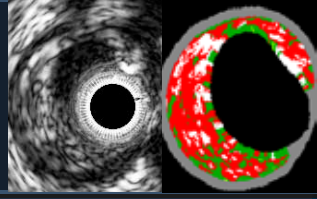


Number of factors present: PB_{MLA} ≥70%, MLA ≤4.0mm^2 or TCFA



PB = plaque burden at the MLA

PROSPECT: Questions



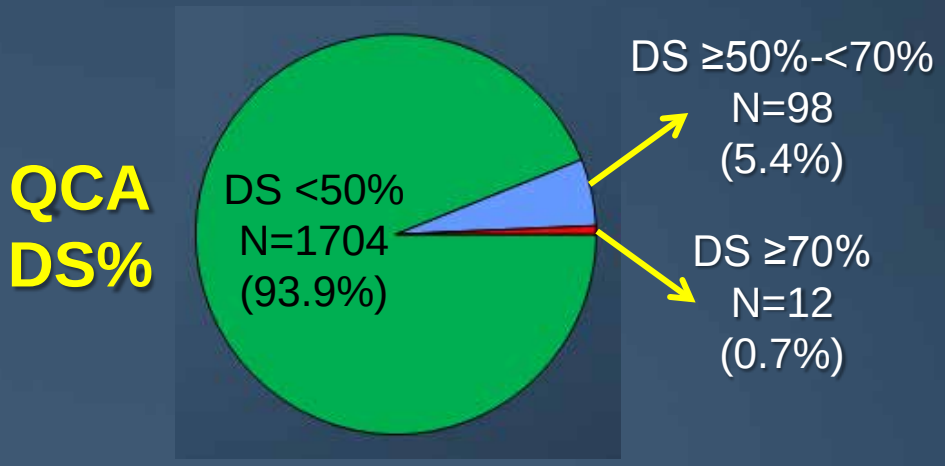
How much disease was left behind after the original PCI in 697 patients?

By angiography

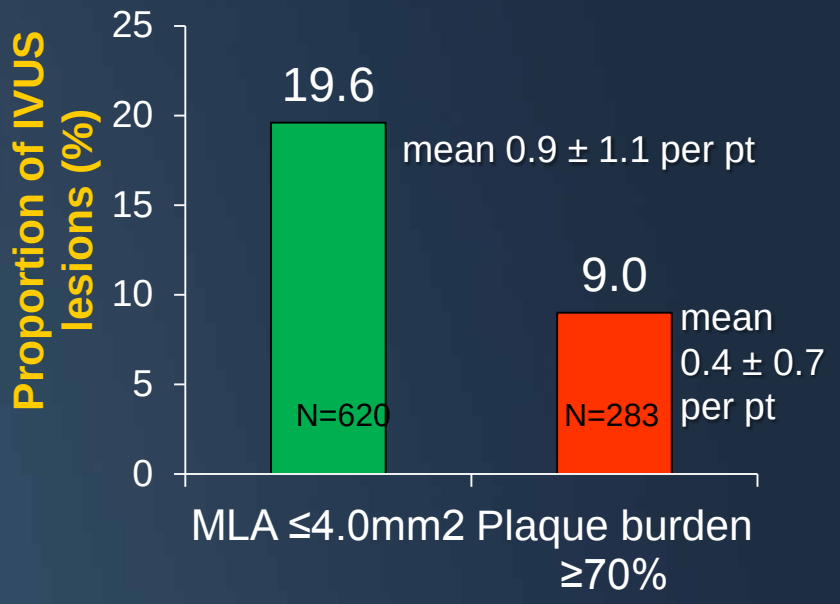
1,814 untreated lesions
(visual DS >30%)
in the entire coronary tree
- mean 2.6 ± 1.8 per pt -

By IVUS (n=673)

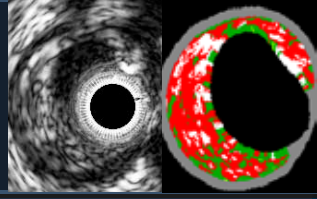
3,160 untreated lesions
(PB ≥40%) in the proximal-to-mid coronary tree
- mean 4.7 ± 2.0 per pt -



DS% mean 33.7 ± 15.7%



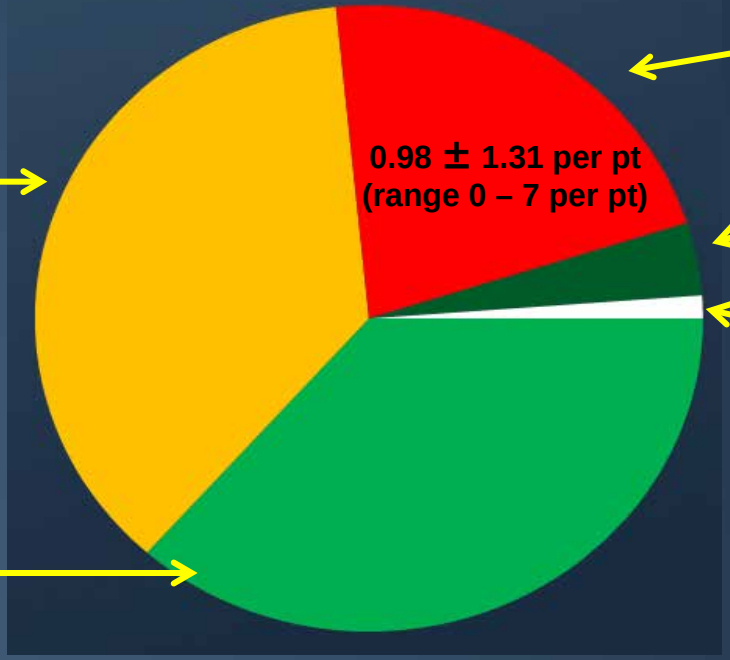
PROSPECT: Questions



How much disease was left behind after the original PCI in 697 patients?

By VH-IVUS (n=623)

2,811 untreated classified lesions in the proximal-to-mid coronary tree



TCFA
N=596 (21.9%)

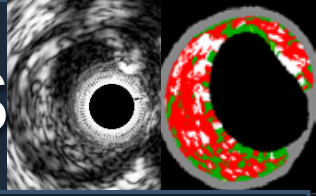
Fibrotic
N=104 (3.8%)

Fibrocalcific
N=33 (1.2%)

ThCFA
N=1018 (37.3%)

PIT
N=1008 (37.0%)

PROSPECT: Conclusions

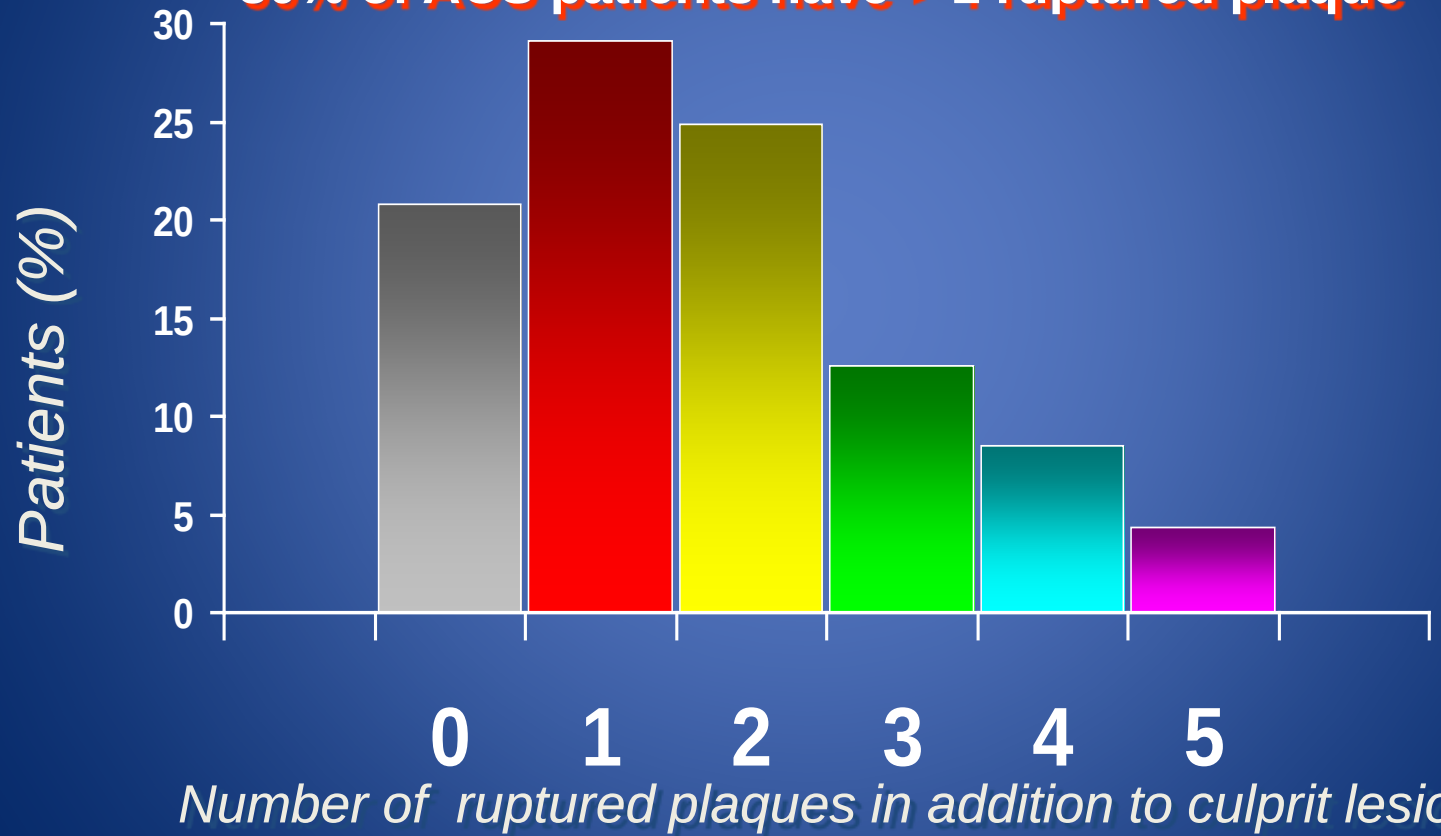


- From this trial, the first prospective, natural history study of atherosclerosis using multimodality imaging to characterize the coronary tree, we can conclude that:
  - Approximately 20% of pts with ACS successfully treated with stents and contemporary medical Rx develop MACE within 3 years, with adverse events equally attributable to recurrence at originally treated culprit lesions (treatment failure) and to previously untreated non culprit coronary segments
  - Approximately 12% of pts develop MACE from non culprit lesions during 3 years of follow-up
- Patients treated with contemporary medical therapy who develop non culprit lesion events present most commonly with progressive or unstable angina, and rarely with cardiac death, cardiac arrest or MI

Diffuse Vulnerability: Vulnerable Arterial Bed

24 patients with ACS, 72 arteries explored with IVUS

80% of ACS patients have > 1 ruptured plaque



Rioufol et al. , Circulation 2002; 106:804-808

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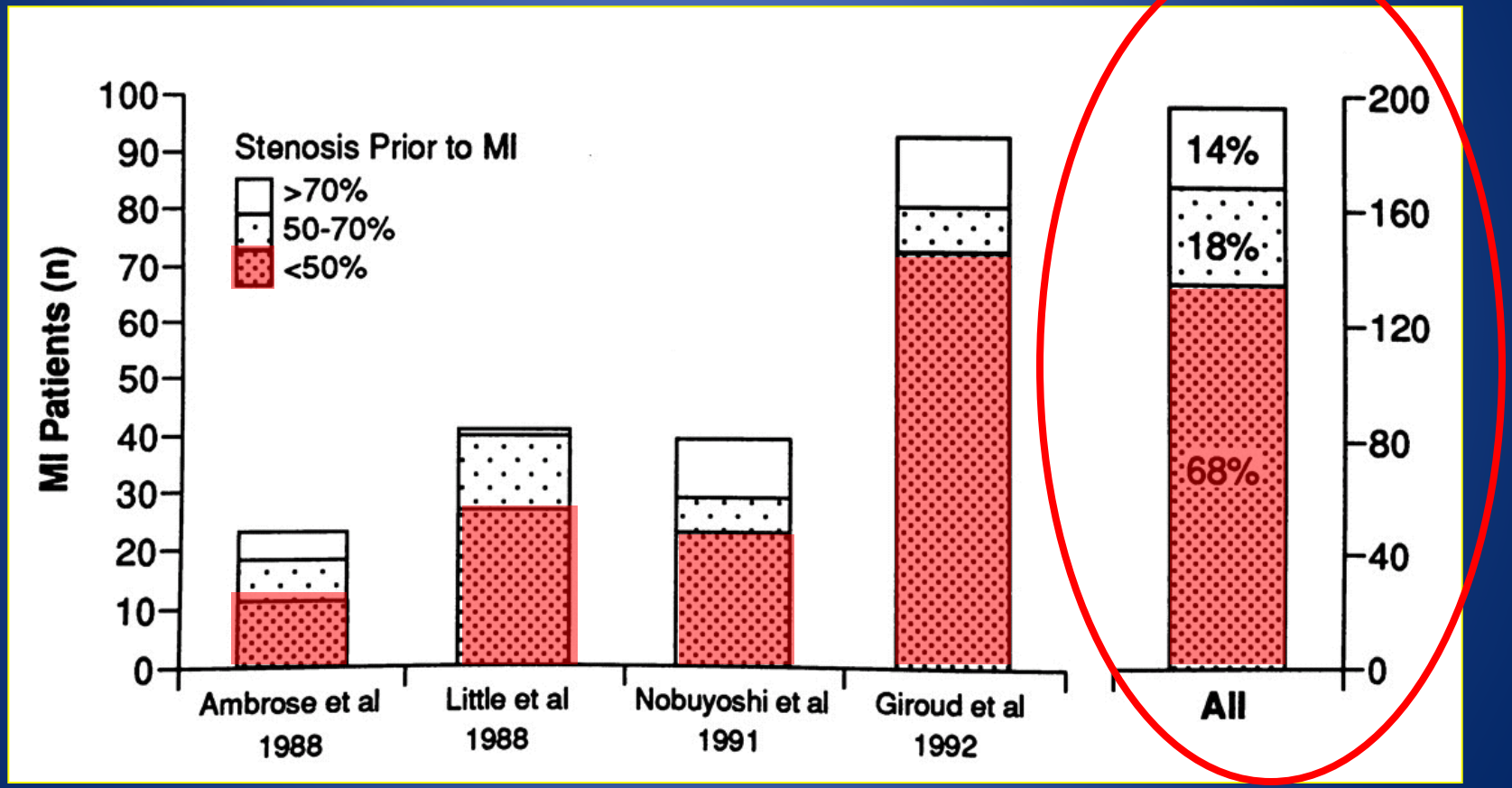
Which Plaques Cause ACS?

"Acute Coronary Syndromes most often occur at the site of mild stenoses"



Falk, Shah and Fuster, Circulation 1995

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Objectives-

1. Understand prevalence of CAD and importance of noninvasive risk stratification of patients with known or suspected CAD
2. Definition of terms for culprit lesion and vulnerable plaque
3. Which imaging modalities can help image vulnerable plaque?
4. Review of recent literature & implications for understanding the natural history of CAD
5. Conclusion

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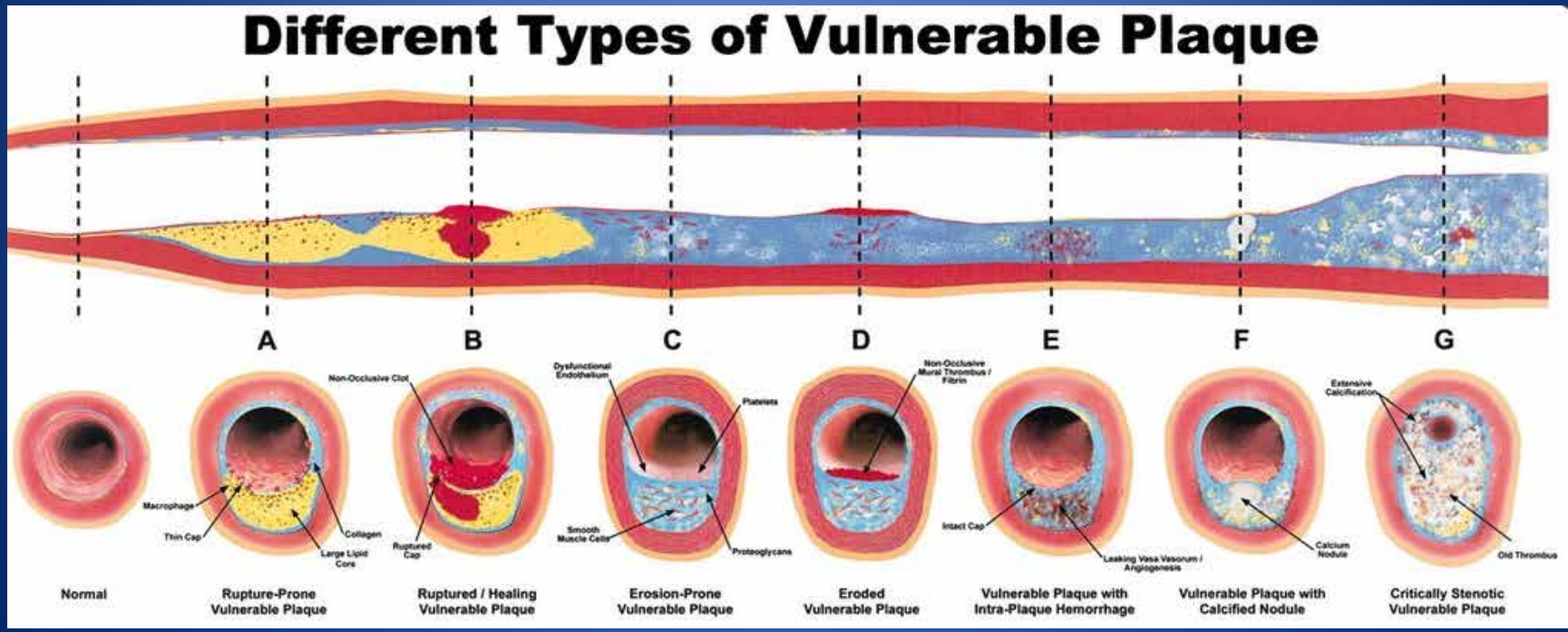
Vulnerable Plaque Imaging



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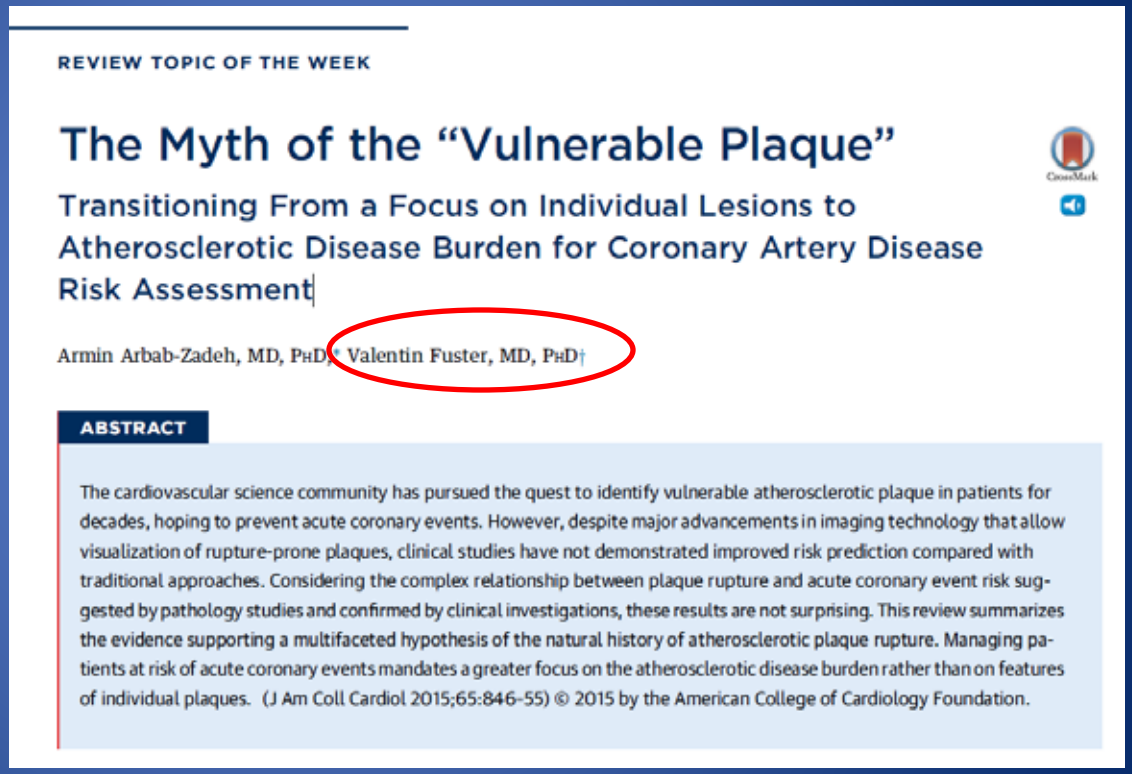
Vulnerable Plaque Myth

- Overall disease burden more predictive of future events than individual plaques
- Most plaque rupture is clinically silent in terms of ACS but does result in progression of CAD



REVIEW TOPIC OF THE WEEK

The Myth of the "Vulnerable Plaque"

Transitioning From a Focus on Individual Lesions to Atherosclerotic Disease Burden for Coronary Artery Disease Risk Assessment

Armin Arbab-Zadeh, MD, PhD,* Valentin Fuster, MD, PhD†

ABSTRACT

The cardiovascular science community has pursued the quest to identify vulnerable atherosclerotic plaque in patients for decades, hoping to prevent acute coronary events. However, despite major advancements in imaging technology that allow visualization of rupture-prone plaques, clinical studies have not demonstrated improved risk prediction compared with traditional approaches. Considering the complex relationship between plaque rupture and acute coronary event risk suggested by pathology studies and confirmed by clinical investigations, these results are not surprising. This review summarizes the evidence supporting a multifaceted hypothesis of the natural history of atherosclerotic plaque rupture. Managing patients at risk of acute coronary events mandates a greater focus on the atherosclerotic disease burden rather than on features of individual plaques. (J Am Coll Cardiol 2015;65:846–55) © 2015 by the American College of Cardiology Foundation.

JACC 2015

Vulnerable Plaque Myth

- CAC is a good tool for overall disease burden assessment
- Vulnerable plaque imaging is likely to require multimodalities that are complementary more than competitive (PET, IVUS/OCT, CCTA, MR)
- Any novel technique to identify vulnerable plaque:
  - § Noninvasive tools would be preferred
  - § Must be better than existing risk stratification
    - § Framingham Risk Score
    - § Coronary Calcium Score
    - § hs CRP

JACC 2015

Conclusion-

1. CAD leading cause of death in US
2. Noninvasive risk stratification of patients with known or suspected CAD-
   - Earlier disease detection
   - Improved patient management
3. Vulnerable plaque imaging
   – Multimodality approach utilizing nuclear, CT & catheter based strategies
4. What to do about intermediate disease
5. Vulnerable patient

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Self Assessment Questions

1. Uptake of NaF by atherosclerotic plaque is
   A. Greatest late in atherosclerosis when plaque levels of calcium is highest and macroscopically visible as heavily calcified vessels.
   B. Significantly affected by whether or not attenuation correction is applied during image reconstruction.
   C. Greatest in the early stages of plaque formation when plaque exhibits spotty microcalcification.
   D. Easier to assess in coronary vessels than the aorta.

Reference- JNM 2015; 56:1019-1023 Fiz et al 18FNa Uptake by Atherosclerotic Plaque on PET/CT Imaging: Inverse correlation between Calcification Density and Mineral Metabolic Activity

Self Assessment Questions

2. When patients undergo serial FDG PET/CT
   A. Patients with the most advanced atherosclerosis exhibit the greatest FDG uptake
   B. Focal vascular uptake has no clinical value in predicting future events
   C. Focal vascular uptake occurs simultaneously with vascular wall calcification
   D. Focal vascular uptake of FDG precedes vessel wall calcification

Reference- CircCVImaging Sept 2013 p. 747-754 Abdebaky et.al.

Self Assessment Questions

3. Vulnerable coronary plaques
   A. Have thick fibrous caps
   B. Are heavily calcified
   C. Do not demonstrate positive remodeling
   D. Often occur in vessels with non-critical stenosis

Reference- Thrombosis & Hemostastis 2013; 110; 706-722

Self Assessment Questions

4. Comparing FDG and NaF uptake by vulnerable coronary plaque
   A. High background FDG uptake by the myocardium limits evaluation in some patients
   B. Special dietary preparation is necessary prior to NaF imaging
   C. Coronary calcium scoring is not a helpful adjunct for risk stratification
   D. In the published series discussed in this presentation all ACS patients studied had increased NaF uptake at the site of a ruptured plaque

Reference- Lancet Vol 383 Feb 2014; 704-713 Joshi et al

Self Assessment Questions

5. In the PROSPECT study independent predictors of future plaque rupture were

   A. Thin-cap fibroatheroma phenotype

   B. Highest CRP (C reactive protein) indicating active inflammatory state

   C. Non-culprit vessels with the most stenotic lesion

   D. Small plaque burden volume

Reference- NEJM 2011; 364:226-35 Stone et.al.

Vulnerable Plaque Imaging, Michael Brophey, MD

1. Uptake of NaF by atherosclerotic plaque is
   A. Greatest late in atherosclerosis when plaque levels of calcium is highest and macroscopically visible as heavily calcified vessels.
   B. Significantly affected by whether or not attenuation correction is applied during image reconstruction.
   C. Greatest in the early stages of plaque formation when plaque exhibits spotty microcalcification. **(KEY)**
   D. Easier to assess in coronary vessels than the aorta.

   The correct answer is C.
   Reference - JNM 2015; 56:1019-1023 Fiz et al 18FNa Uptake by Atherosclerotic Plaque on PET/CT Imaging: Inverse correlation between Calcification Density and Mineral Metabolic Activity

2. When patients undergo serial FDG PET/CT
   A. Patients with the most advanced atherosclerosis exhibit the greatest FDG uptake
   B. Focal vascular uptake has no clinical value in predicting future events
   C. Focal vascular uptake occurs simultaneously with vascular wall calcification
   D. Focal vascular uptake of FDG precedes vessel wall calcification **(KEY)**

   The correct answer is D.
   Reference- CircCVImaging Sept 2013 p. 747-754 Abdebaky et.al.

3. Vulnerable coronary plaques
   A. Have thick fibrous caps
   B. Are heavily calcified
   C. Do not demonstrate positive remodeling
   D. Often occur in vessels with non-critical stenosis **(KEY)**

   The correct answer is D.
   Reference- Thrombosis & Hemostastis 2013; 110; 706-722

4. When comparing FDG and NaF update, the physician should note that:
   A. High background FDG uptake by the myocardium limits evaluation in some patients
   B. Special dietary preparation is necessary prior to NaF imaging

C. Coronary calcium scoring is not a helpful adjunct for risk stratification
D. In the published series discussed in this presentation all ACS patients studied had increased NaF uptake at the site of a ruptured plaque **(KEY)**

The correct answer is A.
Reference- Lancet Vol 383 Feb 2014; 704-713 Joshi et al

5. In the PROSPECT study independent predictors of future plaque rupture were
   A. Thin-cap fibroatheroma phenotype **(KEY)**
   B. Highest CRP (C reactive protein) indicating active inflammatory state
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The correct answer is A.
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