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MANAGEMENT OF CHRONIC STABLE ANGINA IN CURRENT PRACTICE

Brain twisters

- What is the best and no cost diagnostic tool to diagnose stable angina?
- Do you believe that the stable angina is the reason for ACS
- Do you accept treatment should be based on symptoms not on plaque morphology
- Do you believe that atypical symptoms of angina is unbelievable

Continuum of stable angina

Chronic stable angina

Acute coronary syndrome

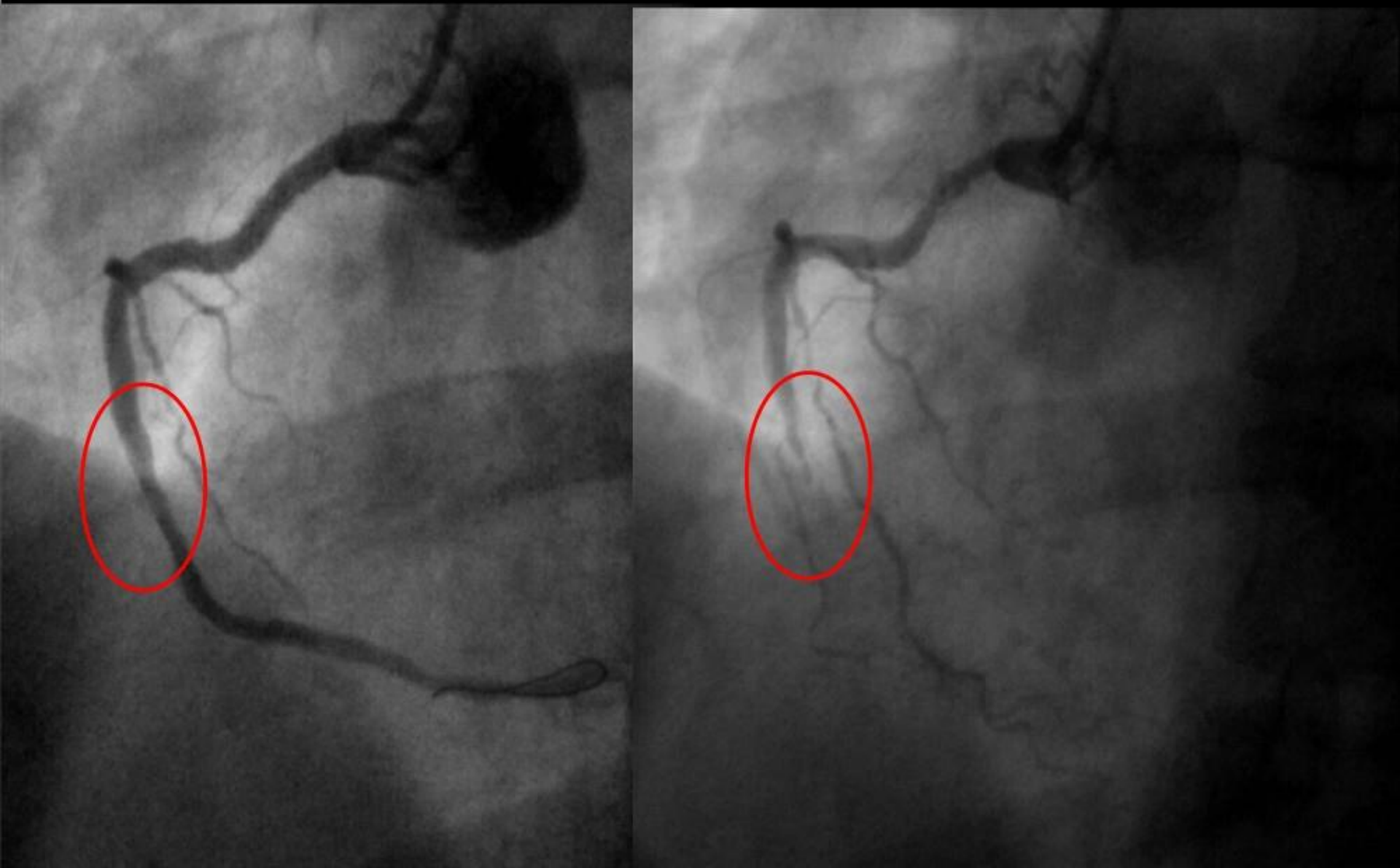
CHF ESHF

What leads to ACS?

- Undermining risk factors
- No appropriate biological markers to detect future event
- Underestimating plaque biology and morphology
- Still we are lacking proper guidelines to manage chronic stable angina
- Not giving proper attention to patients angina equalant symptoms

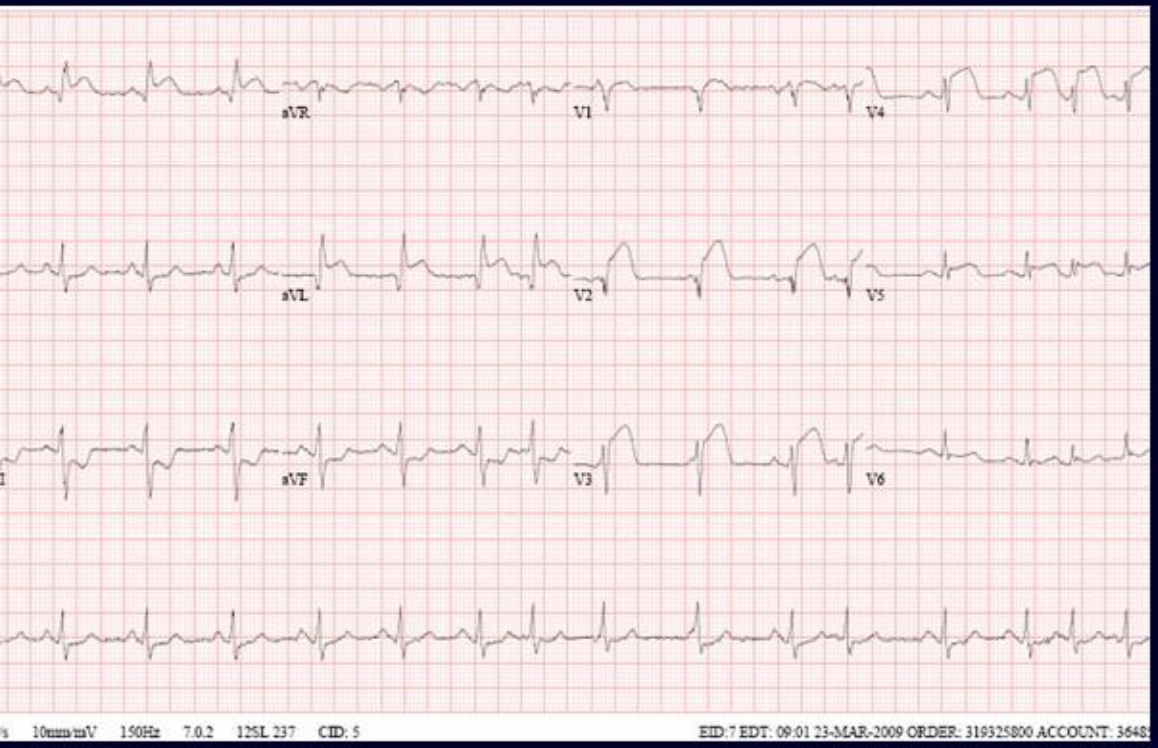
April 2001

July 2002
Acute Inferior Wall MI



Courtesy of Drs. Madder and Goldstein, William Beaumont Hospital, 2010

One year later



IABP and LAD stent
Hospital course complicated by:
Atrial fibrillation, **EF 20%, LV Thrombi**
Transferred to inpatient **rehab** one week later on **coumadin**
Embolic Stroke while at rehab

PET/CT for Cardiology….

Early Detection → Non-Invasive Diagnosis → Pre-Procedural Planning → Follow-Up

Stable High risk of CAD | Stable Angina | Unstable Angina | NSTEMI | STEMI

50 Million patients* | **4-6 Million patients** | **1.4 Million patients** | **xx Million patients**

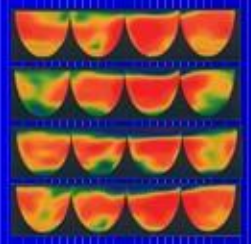
asymptomatics

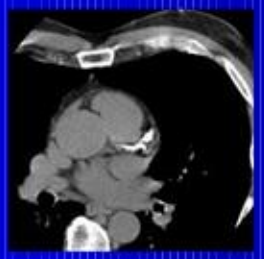
73 y.o woman
3-vassel CAD
angio confimred

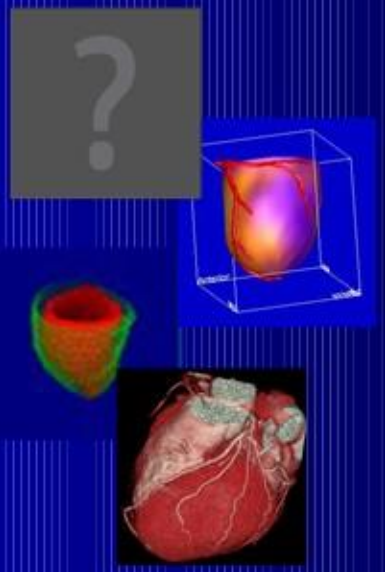
Son #1

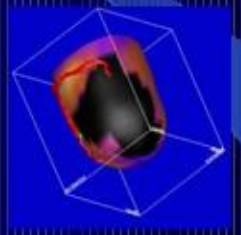
Son #2

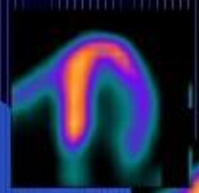
Son #3





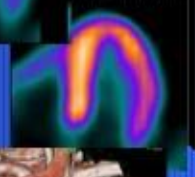






before

after



Primary Prevention

Secondary Prevention

Intervention

Monitor the Vascular Response

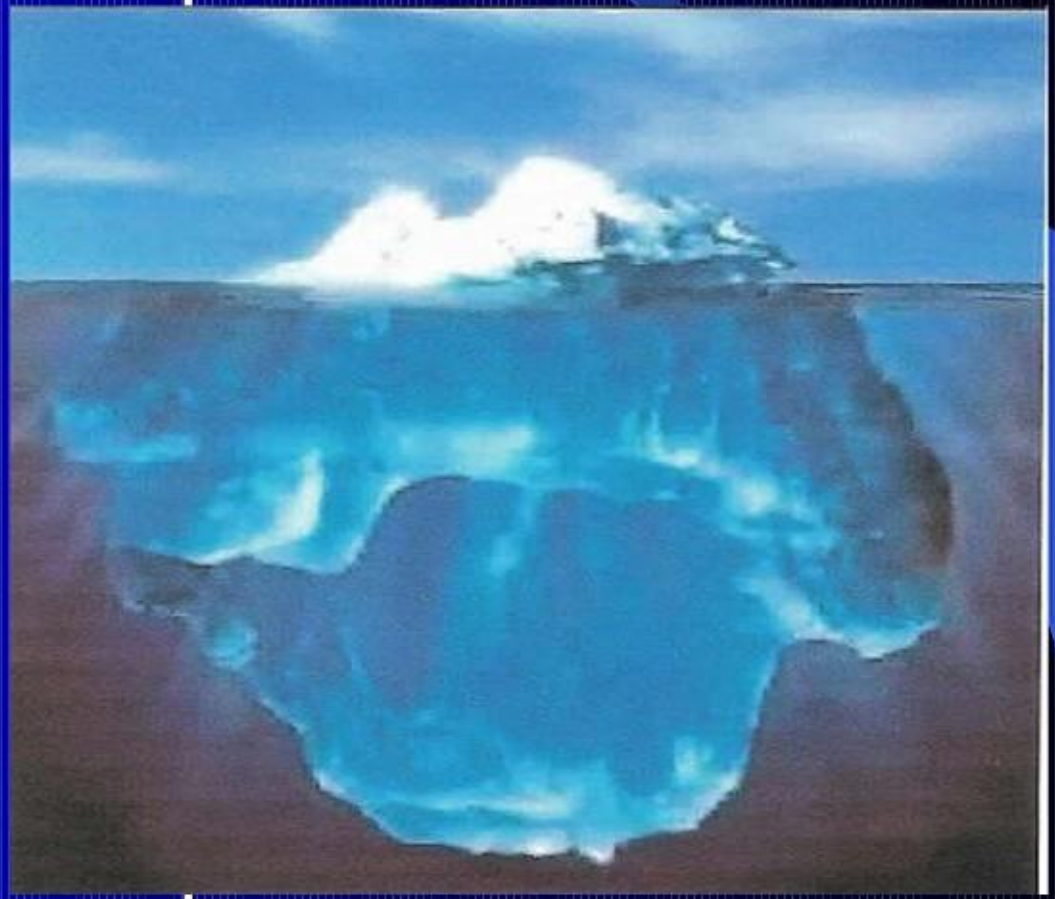
Total Coronary Artery Plaque Burden

20% Calcified

Fibrotic

80%

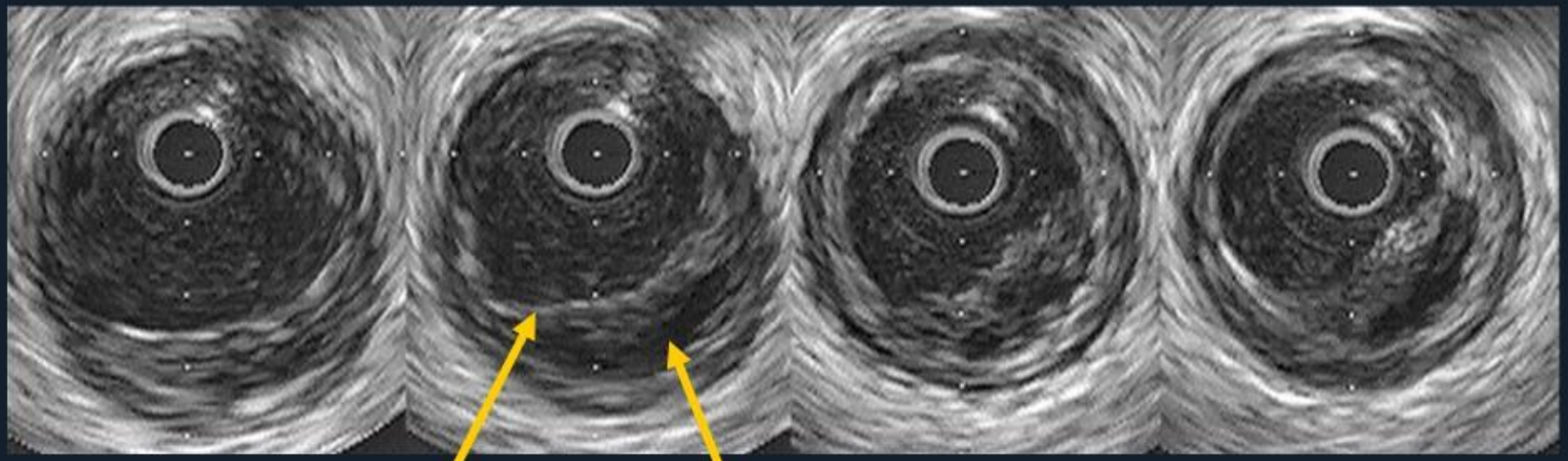
Lipid Rich



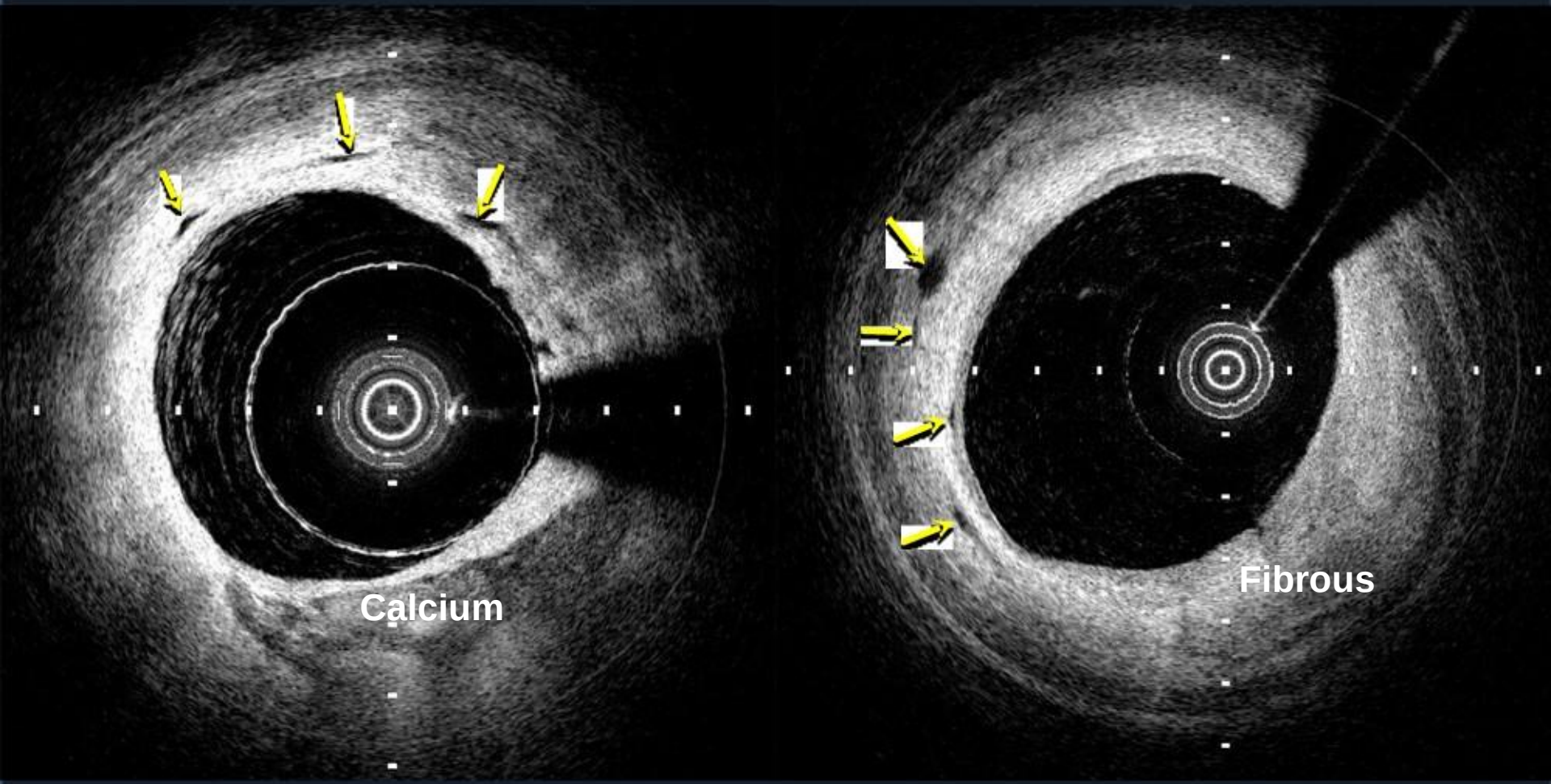
Imaging of plaque is playing vital role in treating CAD

IVUS, FFR, OCT NEW TECHNIQUE IN TREATING CAD

Thin Cap Fibro-Atheroma in IVUS



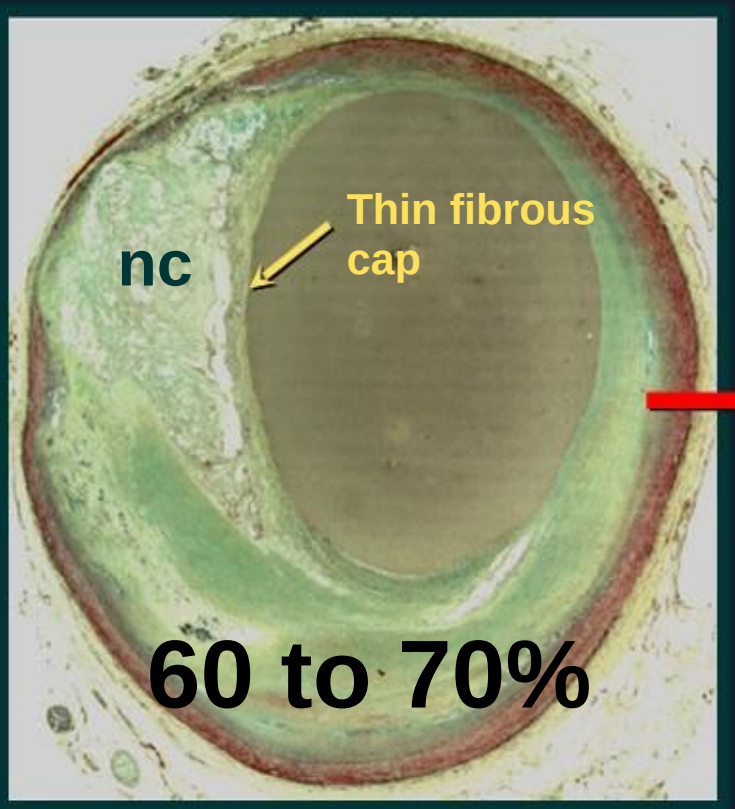
Plaque morphology imaging



Columbia Medical Center

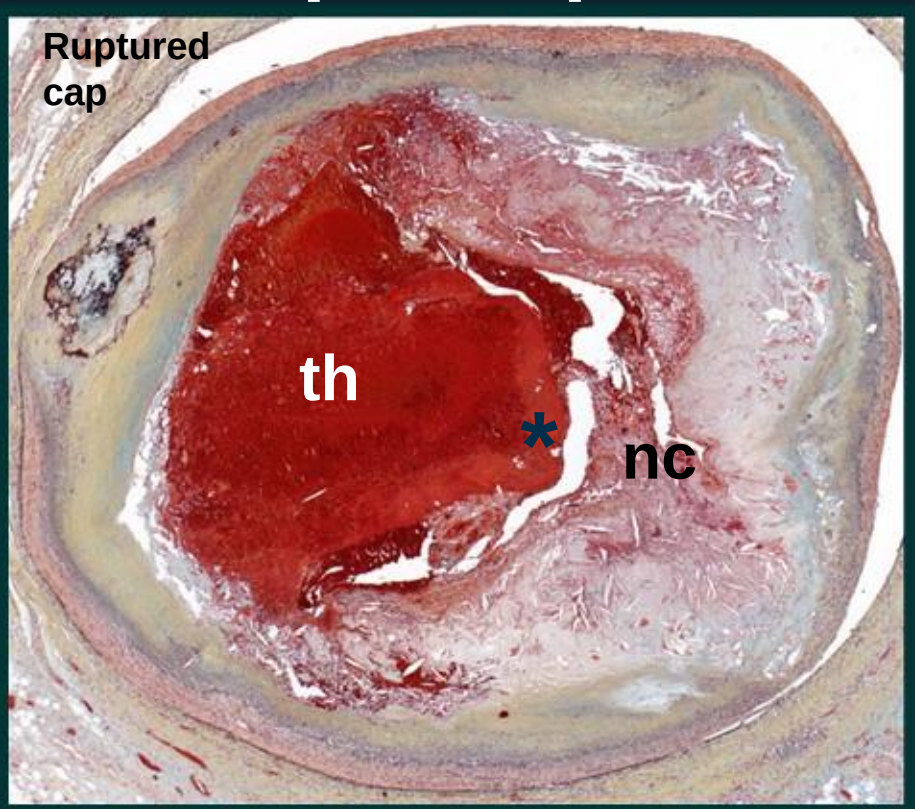
Is the TCFA Always the Precursor Lesion of Plaque Rupture?

TCFA



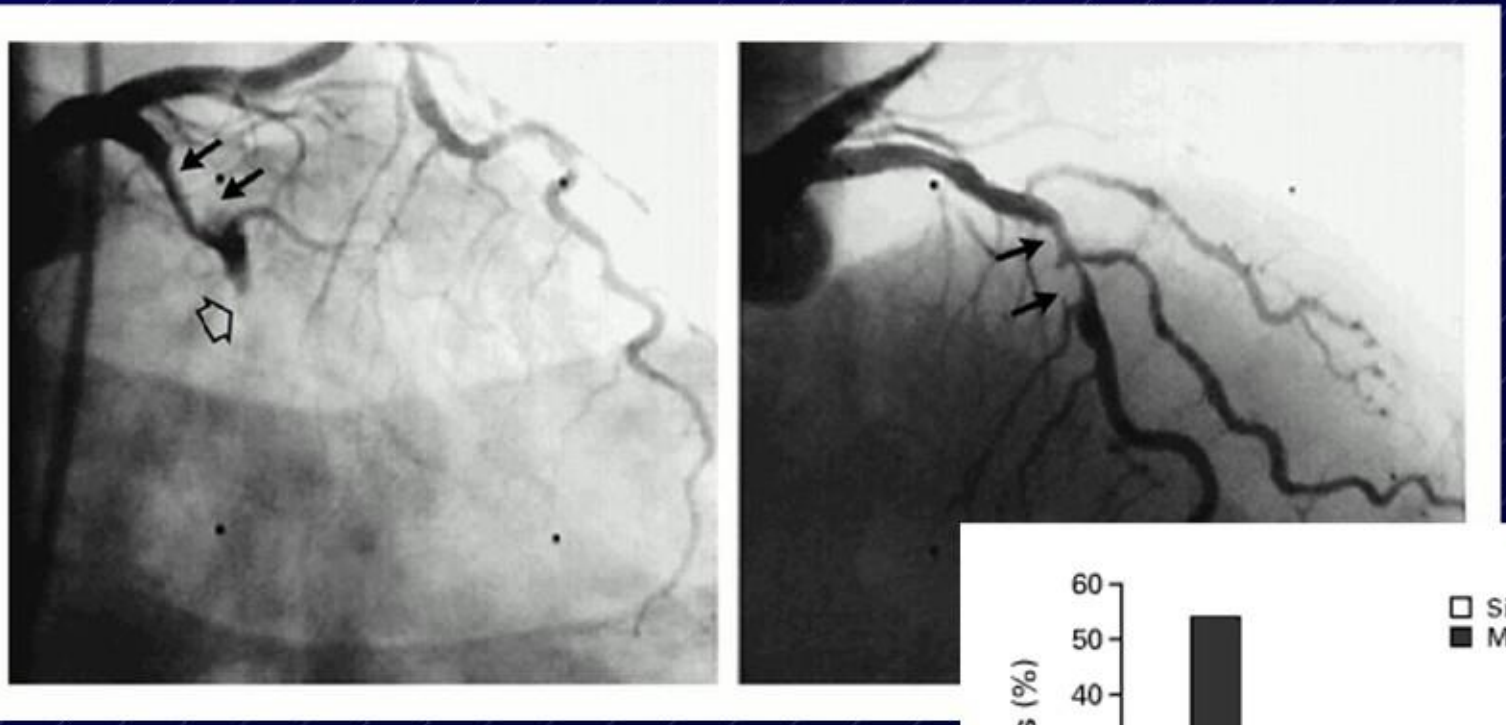
- Lipid rich necrotic core
- Thin fibrous cap (<65 um)

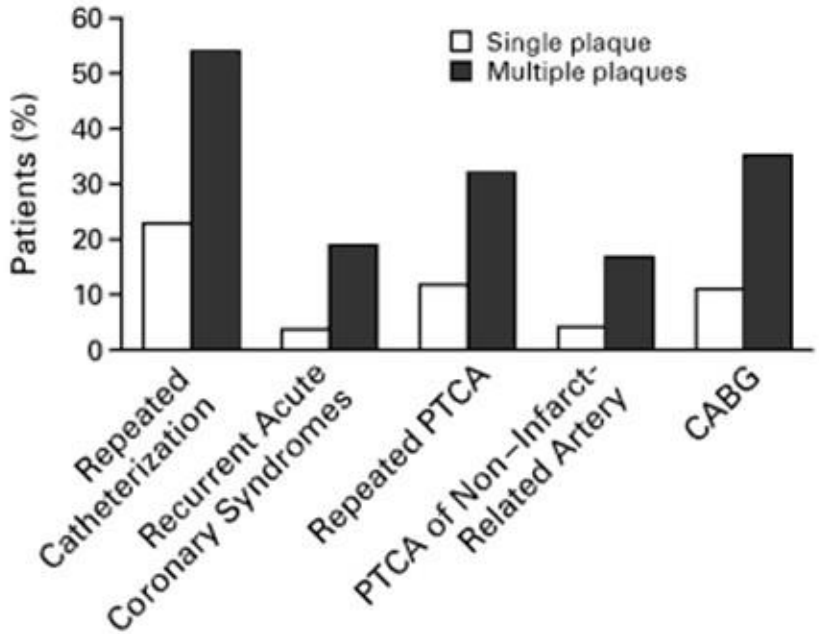
Plaque Rupture



- Cap = Collagen type I with few SMC
- Cap infiltrated by macrophages

Multiple vulnerable plaques





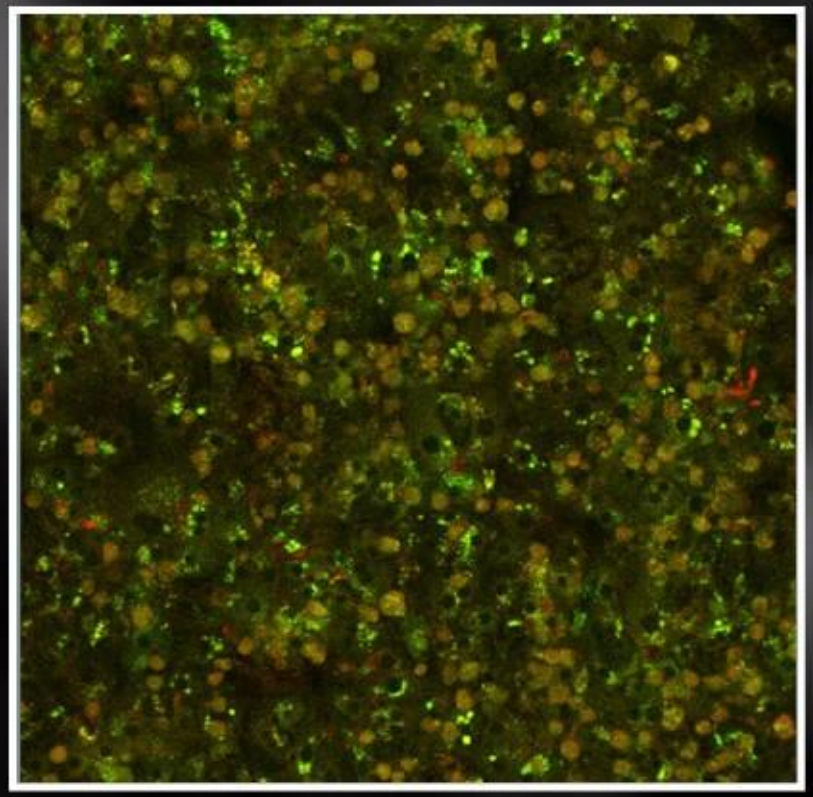
Goldstein et al. *N Engl J Med* 2000;343:915-22

Lipoproteins

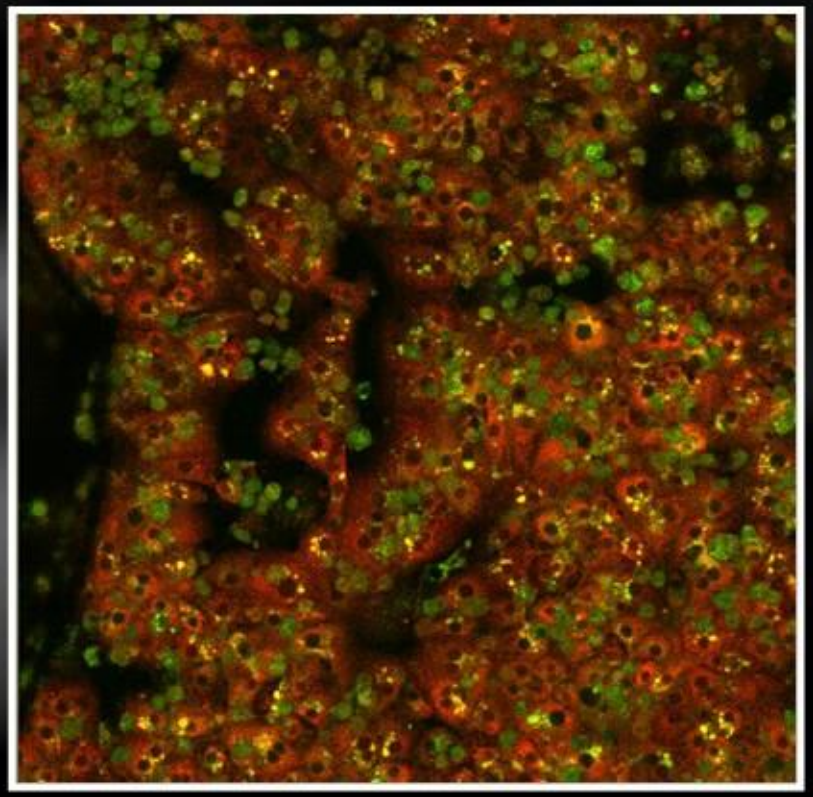
ApoB48 and ApoB100 in Hepatocyte Culture

Fuqua Heart Center of Atlanta

ApoB48



ApoB100

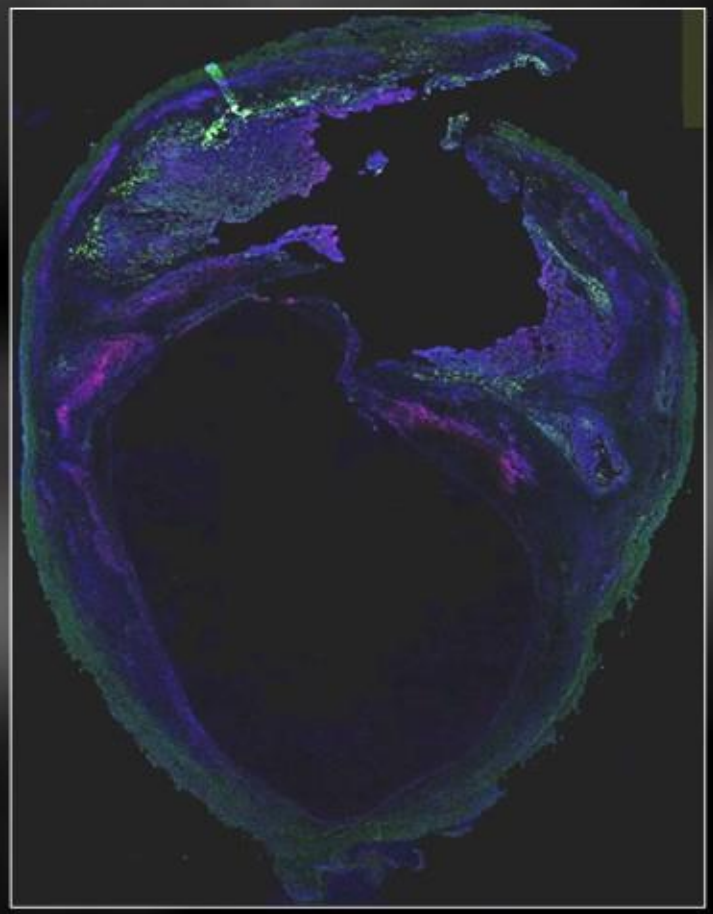


LeCluyse, Vazquez, Pryor, Blackman, Voros. 2010 Unpublished.

Lipoproteins

Hepatic and Intestinal Lipoproteins in Human Plaque

B100/B48
Dual Stain



Red: ApoB100
Blue: ApoB48

Vazquez, Pryor, Blackman, Battey, Voros. 2009.

‘Do not’ recommendations

Do not :

- X exclude people from treatment based on their age
- X investigate or treat symptoms differently in men and women or in different ethnic groups
- X offer vitamin or fish oil supplements
- X offer TENS, EECP or acupuncture
- X routinely offer drugs for secondary prevention of cardiovascular disease to people with suspected cardiac syndrome X.

CCSC Angina Classification

- Class I
- Class II
- Class III
- Class IV

- Angina only with extreme exertion
- Angina with walking 1 to 2 blocks
- Angina with walking 1 block
- Angina with minimal activity

Stable Angina Classes

- Exertional
- Variant or Prinzmetal's Angina
- Anginal Equivalent Syndrome
- Syndrome-X
- Silent Ischemia
- Decubitus angina
- Nocturnal angina

Angina Pectoris

- Classic angina is characterized by substernal squeezing chest pain, occurring with stress and relieved with rest or nitroglycerin.
- May radiate down the left arm
- May be associated with nausea, vomiting, or diaphoresis.

Angina: Exertional

- Coronary artery obstructions are not sufficient to result in resting myocardial ischemia. However, when myocardial demand increases, ischemia results.

Angina: Variant Angina

- Transient impairment of coronary blood supply by vasospasm or platelet aggregation
- Majority of patients have an atherosclerotic plaque
- Generalized arterial hypersensitivity
- Long term prognosis very good

Angina: Anginal Equivalent Syndrome

- Patient's with exertional dyspnea rather than exertional chest pain
- Caused by exercise induced left ventricular dysfunction

Angina: Prinzmetal's Angina

- Spasm of a large coronary artery
- Transmural ischemia
- ST-Segment elevation at rest or with exercise
- Not very common

Angina: Syndrome X

- Typical, exertional angina with positive exercise stress test
- Anatomically normal coronary arteries
- Reduced capacity of vasodilatation in microvasculature
- Long term prognosis very good
- Calcium channel blockers and beta blockers effective

Angina: Silent Ischemia

- Very common
- More episodes of silent than painful ischemia in the same patient
- Difficult to diagnose
- Holter monitor
- Exercise testing

Investigations for CSA

- Nuclear thallium
- Stress echo
- Tread mill test
- Coronary angiography is a gold standard
- Intra vascular ultrasound
- Fractional flow reserve

Stable Angina
Guidelines for Nuclear EST

Defined CAD

- Post infarct risk stratification
- Risk stratification to determine need for revascularization (viability study)

Stable Angina
Stress Echo

- Ischemia may cause wall motion abnormalities, no rise of fall in LVEF
- Sensitivity/specificity same as nuclear testing
- May be better in women

Exercise Testing Contraindications

- MI—impending or acute
- Unstable angina
- Acute myocarditis/pericarditis
- Acute systemic illness
- Severe aortic stenosis
- Congestive heart failure
- Severe hypertension
- Uncontrolled cardiac arrhythmias

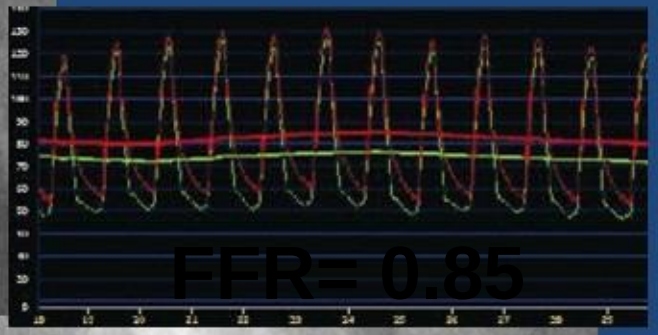
Cardiac Catheterization Indications

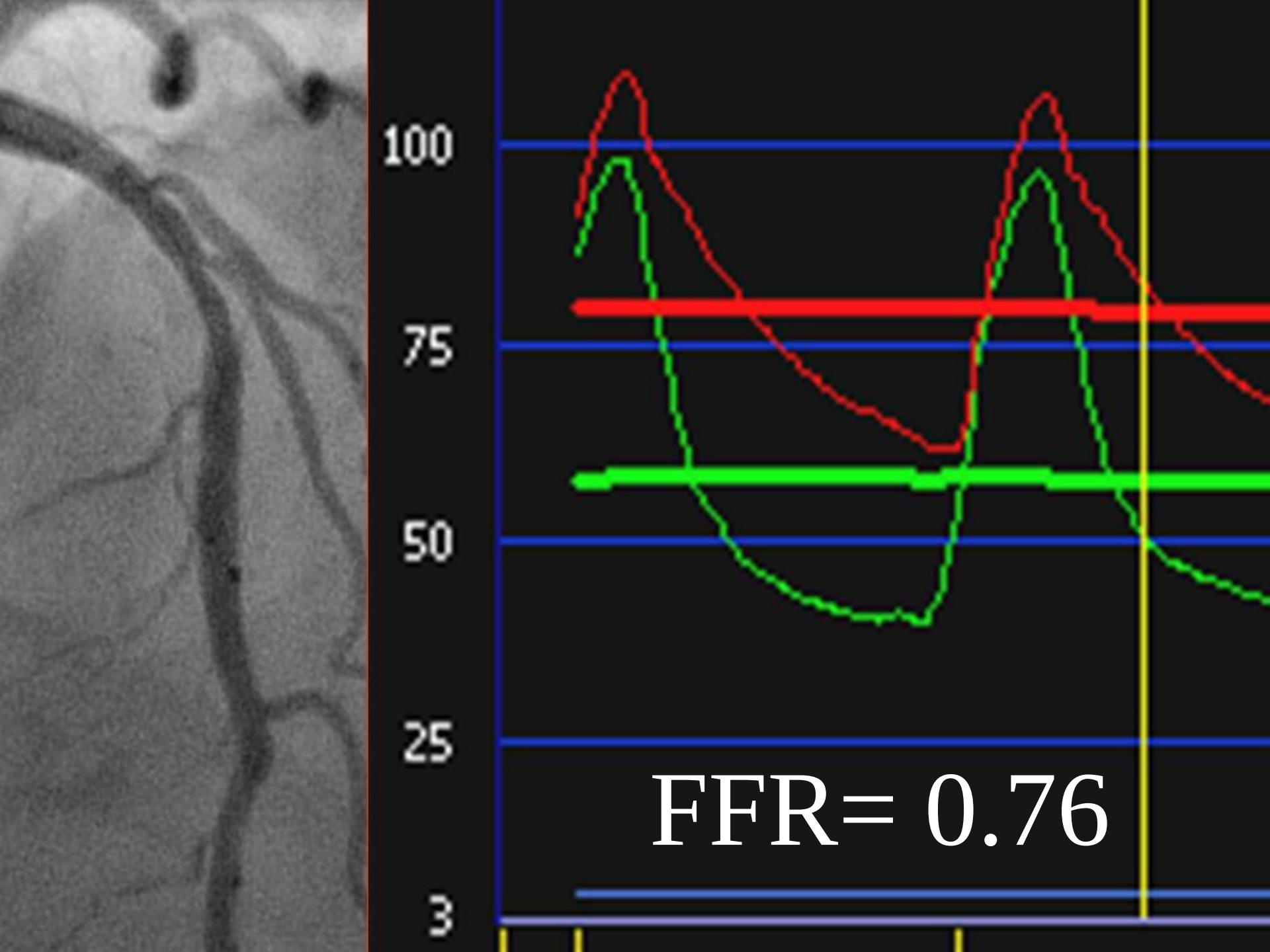
- Suspicion of multi-vessel CAD
- Determine if CABG/PTCA feasible
- Rule out CAD in patients with persistent/disabling chest pain and equivocal/normal noninvasive testing

Mean Diameter
0
10
20
30
40
mm
31
Distal << Proximal, 54.0 mm
MLA 13.38 mm2
MLA 3.72 mm2
M
MLA 11.49 mm2

Class CCS 2 Effort Angina

64 Yo Photographer
Hypertension
Hypercholesterolaemia
Smoking

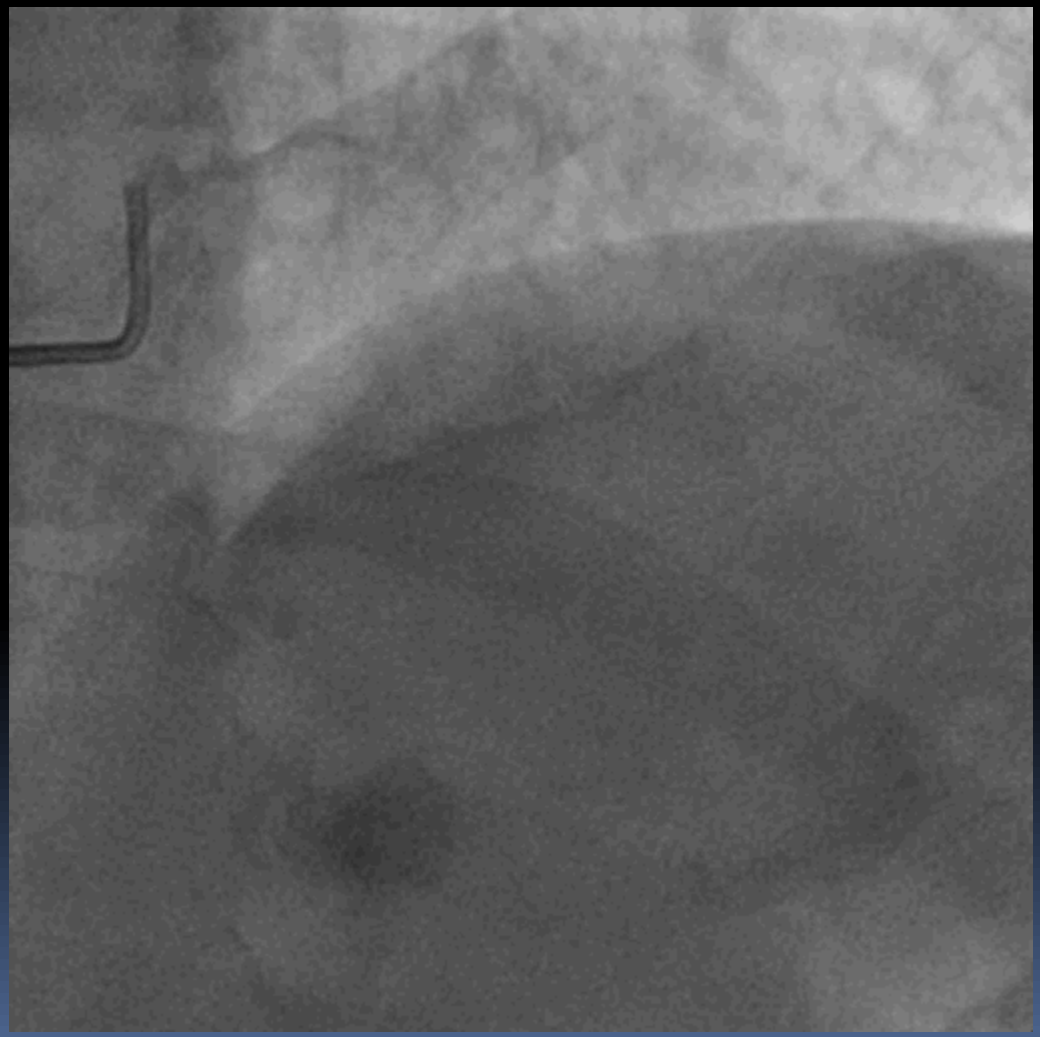



100
75
50
25
3
FFR= 0.76

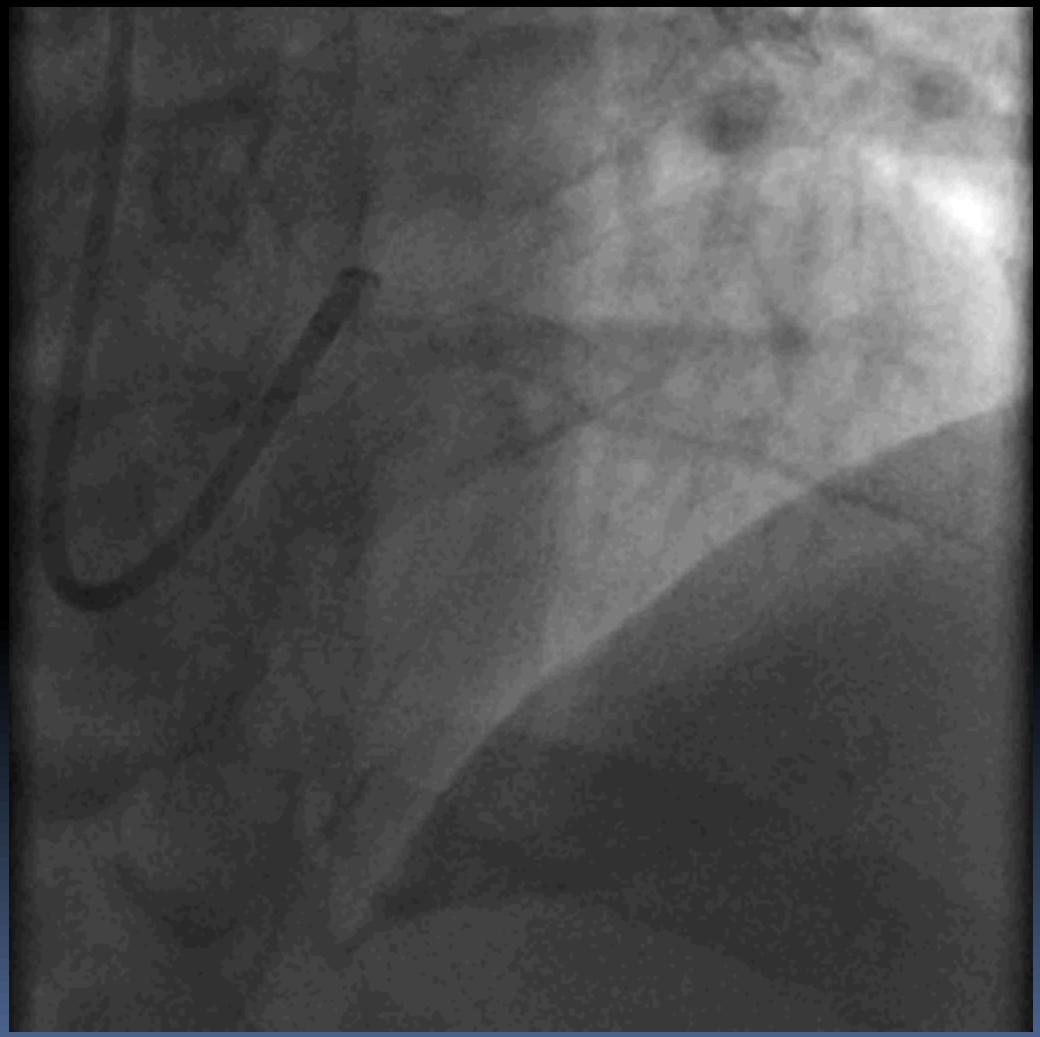
LAD Angiography in 7 Views

54 Yo Woman Chest Pain for 6 months, severe hypercholesterolaemia

76 yrs Male with DOE for 1 y



48yrs male with DOE 5yrs



45yrs male DOE & AOE class2

Selection of drugs

- Effect on myocardium
- Effect on cardiac conduction system
- Effect on coronary/systemic arteries
- Effect on venous capitance system
- Circadian rhythm

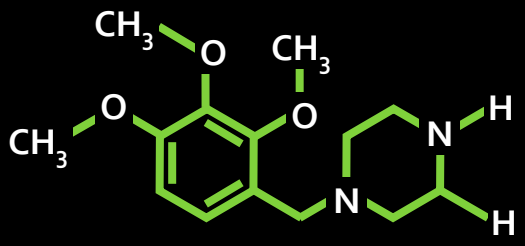
Stable Angina
Current Pharmacotherapy

- Beta-blockers
- Calcium channel blockers
- Nitrates
- Aspirin
- Statins
- ? ACE inhibitors

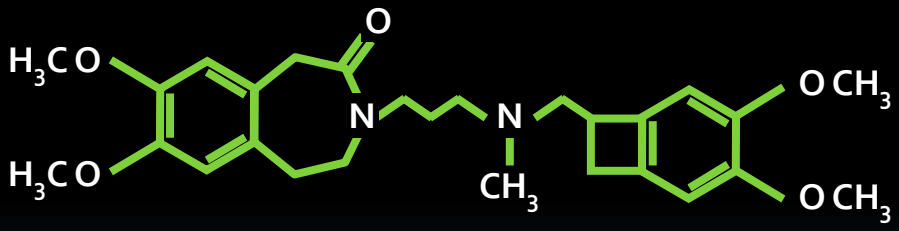
New mechanistic approaches to chronic stable angina

Rho kinase inhibition (fasudil)

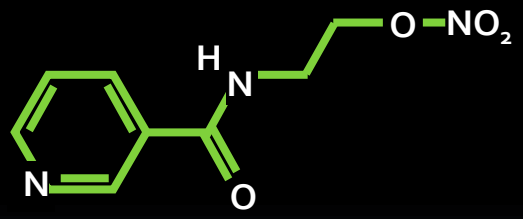
Metabolic modulation (trimetazidine)



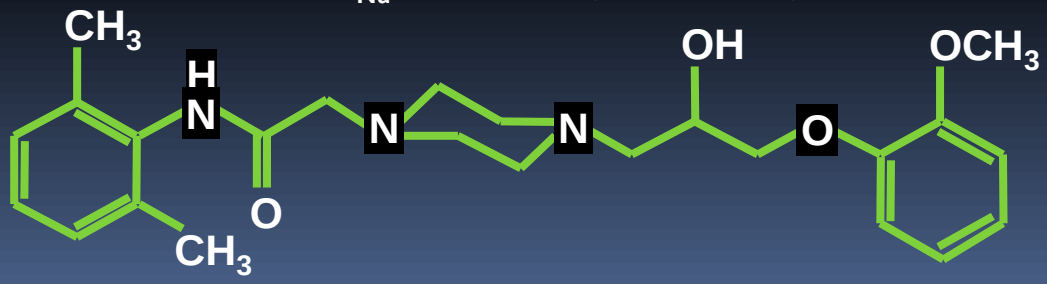
Sinus node inhibition (ivabradine)



Preconditioning (nicorandil)



Late I_{Na} inhibition (ranolazine)



Beta-Blockers

- Decrease myocardial oxygen consumption
- Blunt exercise response
- Beta-one drugs have theoretical advantage
- Try to avoid drugs with intrinsic sympathomimetic activity
- First line therapy in all patients with angina if possible

Beta-Blockers

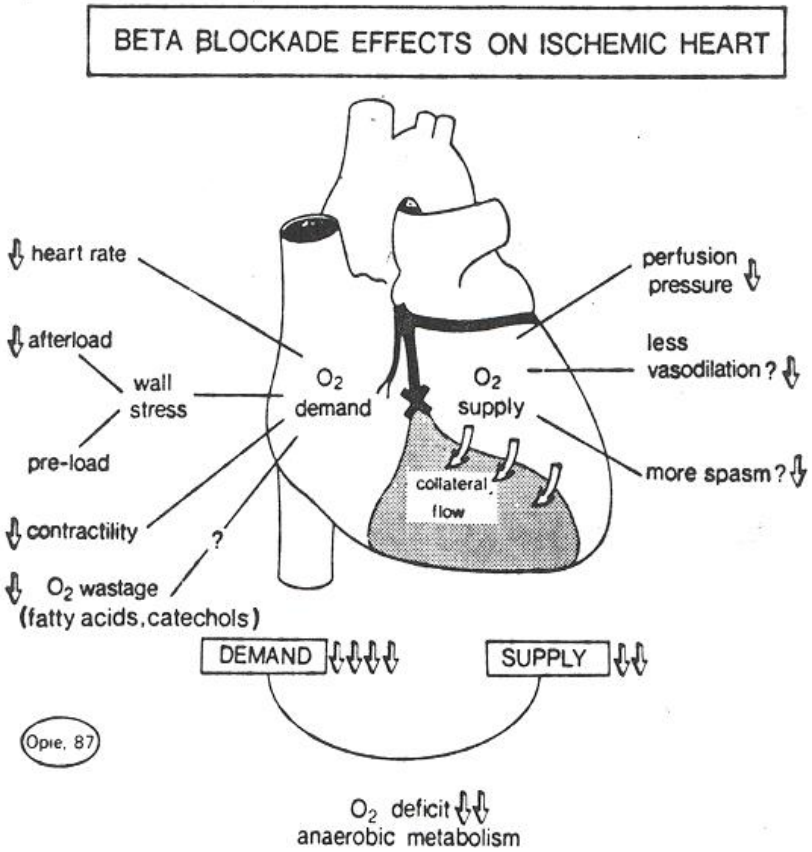


Fig. 1-2. Effects of β-blockade on ischemic heart. β-blockade has a beneficial effect on the ischemic myocardium, unless (1) the preload rises substantially as in left heart failure or (2) there is vasospastic angina when spasm may be promoted in some patients.

Beta Blockers Side Effects

- Bronchospasm
- Diminished exercise capacity
- Negative inotropy
- Sexual dysfunction
- Bradyarrhythmia
- Masking of hypoglycemia
- Increased claudication
- Hair loss

Calcium Channel Blockers Mechanisms of Action

- Arterial dilation/after-load reduction
- Coronary arterial vasodilation
- Prevention of coronary vasoconstriction
- Enhancement of coronary collateral flow
- Improved subendocardial perfusion
- Slowing of heart rate with diltiazem, verapamil

Calcium Channel Blockers Side Effects

- Palpitations
- Headache
- Ankle edema
- Gingival hyperplasia

Nitrates
Mechanisms of Action

- Nitric oxide has been identified as endothelium-derived relaxing factor
- Organic nitrates are therapeutic precursors of endothelium-derived relaxing factor

Nitrates
Mechanisms of Action

- Venous vasodilation/pre-load reduction
- Arterial dilation/after-load reduction
- Coronary arterial vasodilation
- Prevention of coronary vasoconstriction
- Enhancement of coronary collateral flow
- Antiplatelet and antithrombotic effects

Nitrates
Reducing Tolerance

- Smaller doses
- Less frequent dosing
- Avoidance of long-acting formulations unless a prolonged nitrate-free interval is provided
- Build-in a nitrate-free interval o 8-12 hours

Nitrates
Side Effects

- Headache
- Flushing
- Palpitations
- Tolerance

Ranolazine in Ischemic Heart Disease

MERLIN TIMI 36

Background

- Anti-anginal & anti-ischemic effects without clinically significant effect on HR or BP
- Approved for treatment of chronic angina
  - ↑ exercise time, ↓ angina in selected pts
- Novel mechanism of action
  - Inhibition of late I_{Na} → ↓ Ca^{2+} overload → ↓ adverse energetic, mechanical, electrical consequences
- Experimental evidence
  - ↑ LV performance during ischemia
  - ↑ recovery of LV function, ↓ infarct size

Morrow DA et al. JAMA 2007; 297: 1775-83

TIMI

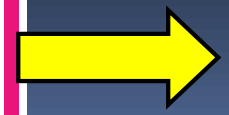
Ranolazine in Ischemic Heart Disease

MERLIN TIMI 36

Background

- Ranolazine associated with an ↑ in QTc (average ~5 msec)
- However, experimental data suggest *suppression* of pro-arrhythmic markers
- *Indication in chronic angina*: "Because ranolazine prolongs the QT interval, it should be reserved for patients who have not achieved an adequate response with other anti-anginal drugs."

Need for additional safety information



Morrow DA et al. JAMA 2007; 297: 1775-83

TIMI

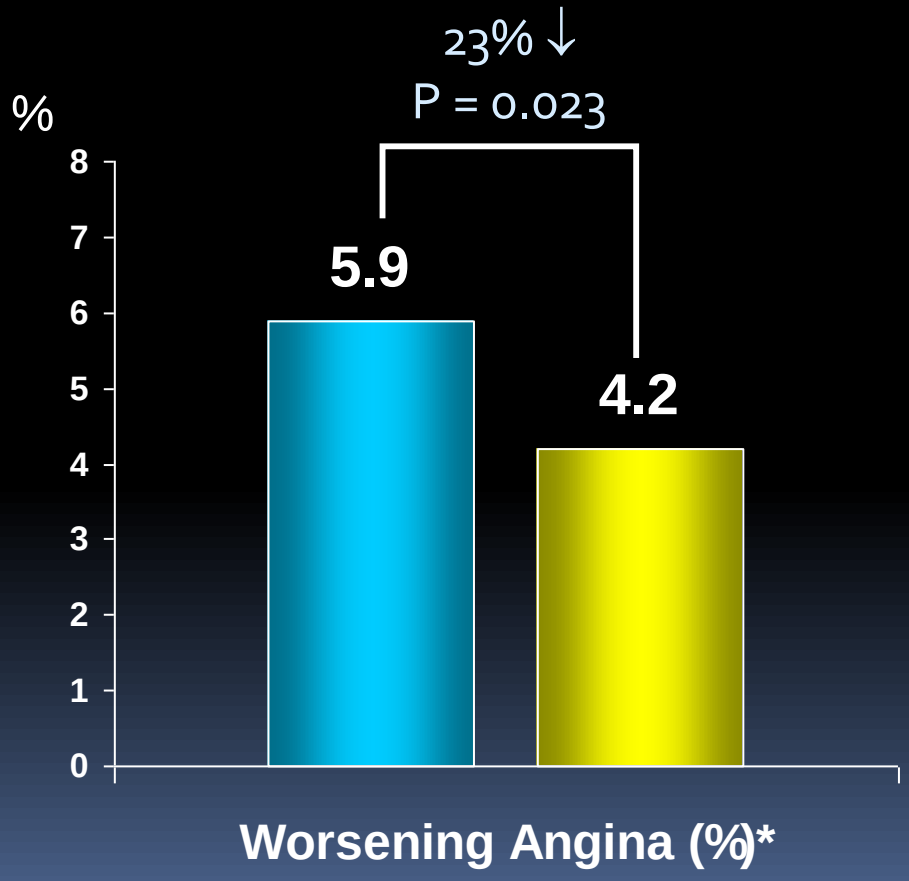
Assessment of Anti-anginal Effects

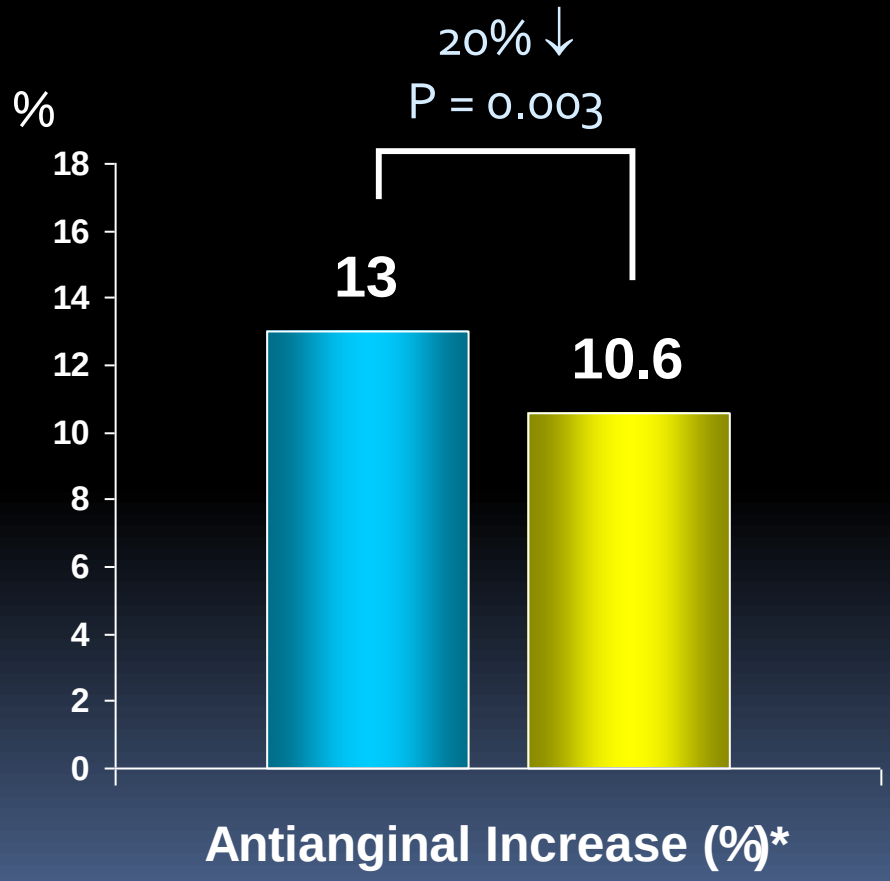
MERLIN TIMI 36

Results

PLACEBO (N=3,281)

RANOLAZINE (N=3,279)





Morrow DA et al. JAMA 2007; 297: 1775-83

*KM Cumulative Incidence at 12 months

Shift Study: ivabradine in heart failure and angina

- Ivabradine
  - An I(f) blocker
  - Slows the sinus node rate without other effects of beta blockers
  - Only effective if in sinus rhythm
- Contraindicated with diltiazem, verapamil, antifungal, microlides, grape juice and etc

Q-1 which drug is contraindicated in AF?

- A) nicorandil
- B) Mononitrate
- C) Ivabradine
- D)Trimetazidine

Q-2, What is best symptom to diagnose CSA?

- A) Angina on exertion
- B) Diaphoresis
- C) Palpitation
- D)Dyspnea on exertion

Q-3, which type of lipoprotein is found in the plaque of CSA?

- A) ApoB100 and ApoB26
- B) ApoB100 and ApoB28
- C) ApoB100 and Apo A
- D) ApoB100 and Lpa

Q-4, how does ranolazine work on cardiac pathway?

- A) ,Inhibiting Ca channel
- B), Inhibiting K ATP channel
- C), Inhibiting Late Na channel
- D), inhibiting late K channel

Q-5, contraindication with ivabradine?

- A), amiodarone
- B), Beta blockers
- C), ACEIs
- D), Fluconazole

How to avoid CSA to ACS?

- Using appropriate tool to diagnose CAD
- Assessing plaque morphology
- Molecular based treatment
- Periodical assessment

Thank you for your attention