

Optimal Drug Regimen in Asymptomatic Patients With High Calcium Score in CT

Soon Jun Hong

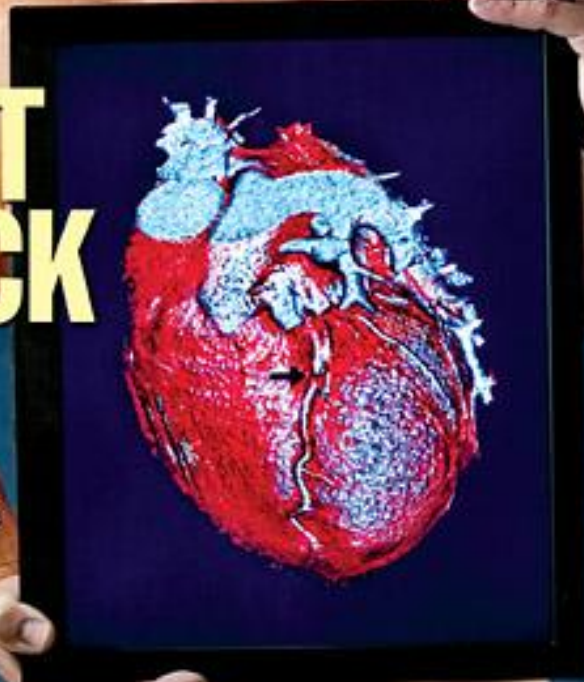
**Cardiovascular Center
Korea University Anam Hospital**

CHINESE CYBERSPIES
COOL NEW SEARCH ENGINES

TIME

HOW TO STOP A **HEART ATTACK** BEFORE IT HAPPENS

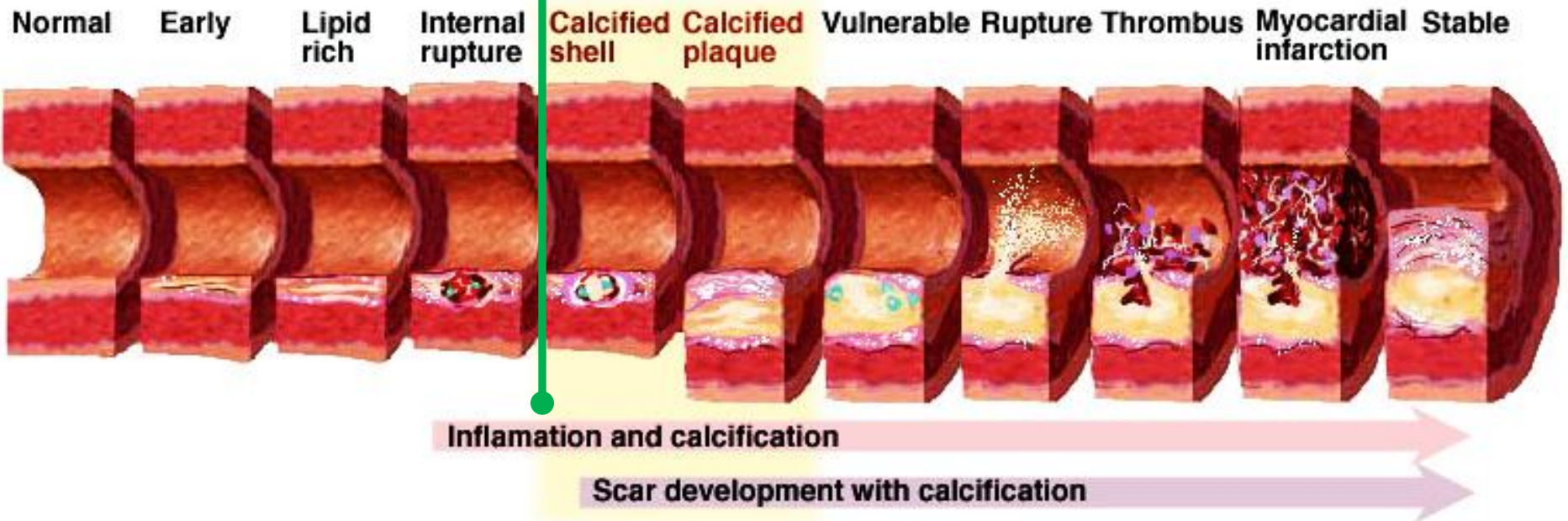
Amazingly detailed new
HEART SCANS help doctors
spot trouble without
surgery. How technology
could save your life



Mike Fackelmann, 50,
holds a scan of his
heart, which revealed
a major blockage of a
coronary artery (arrow)

Coronary Disease Progression

Calcified Plaque Detected by CT →

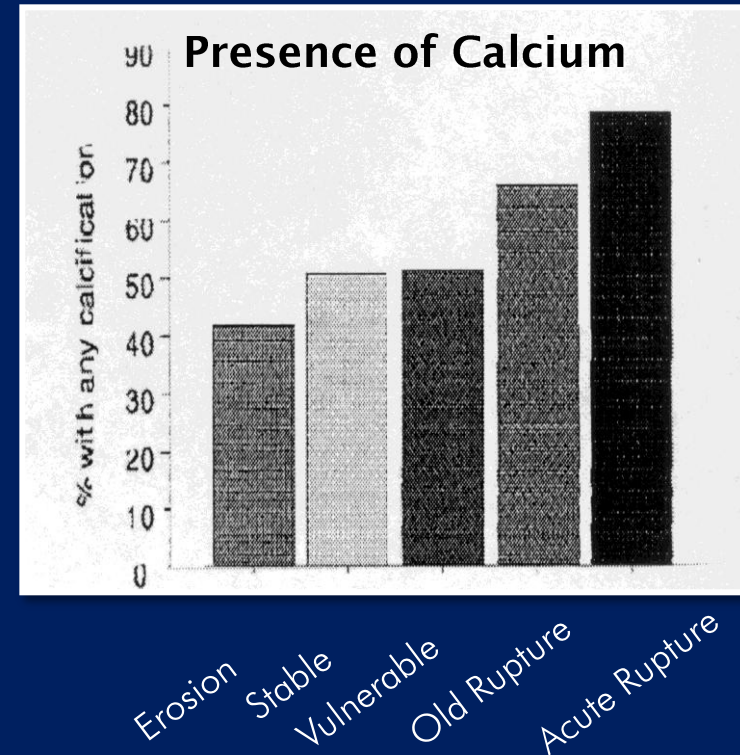


Calcium Score

- The calcium scale is a linear scale with 4 calcium score categories:
 - 0 none
 - 1–99 mild
 - 100–400 moderate
 - >400 severe
- Calcium score correlates directly with risk of CV events and likelihood of obstructive CAD

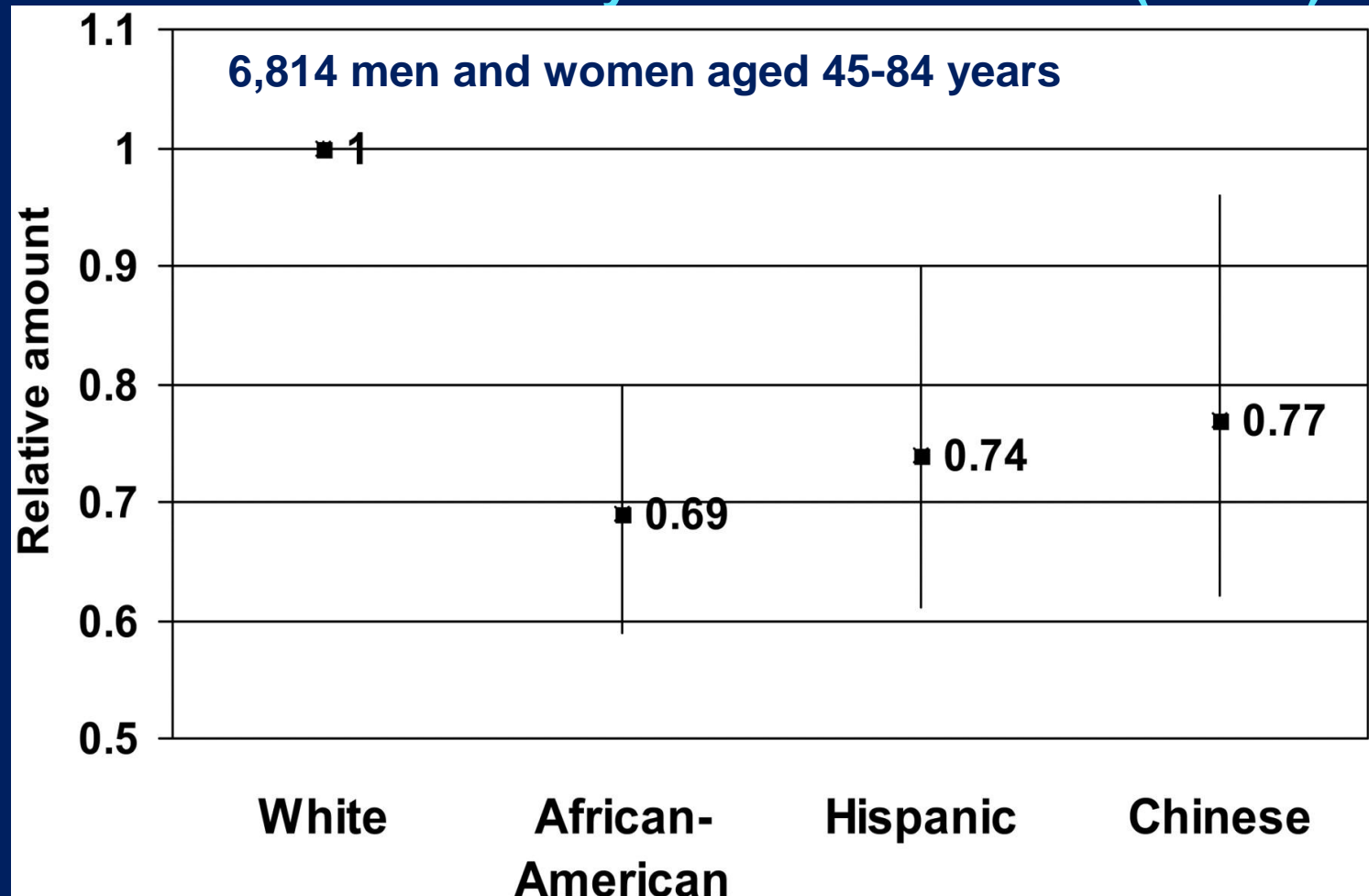
Coronary Calcium & Atherosclerosis

- The amount of calcium roughly correlates to the overall amount of plaque.
- Calcium is not a sign of plaque stability.

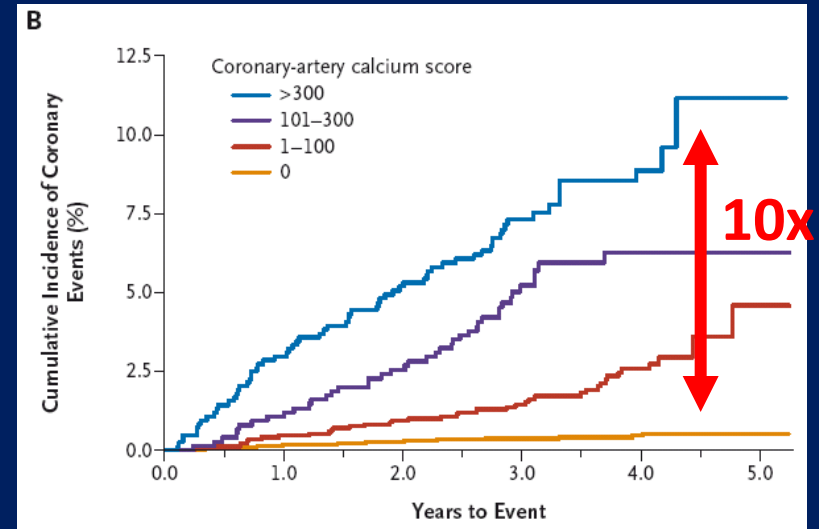
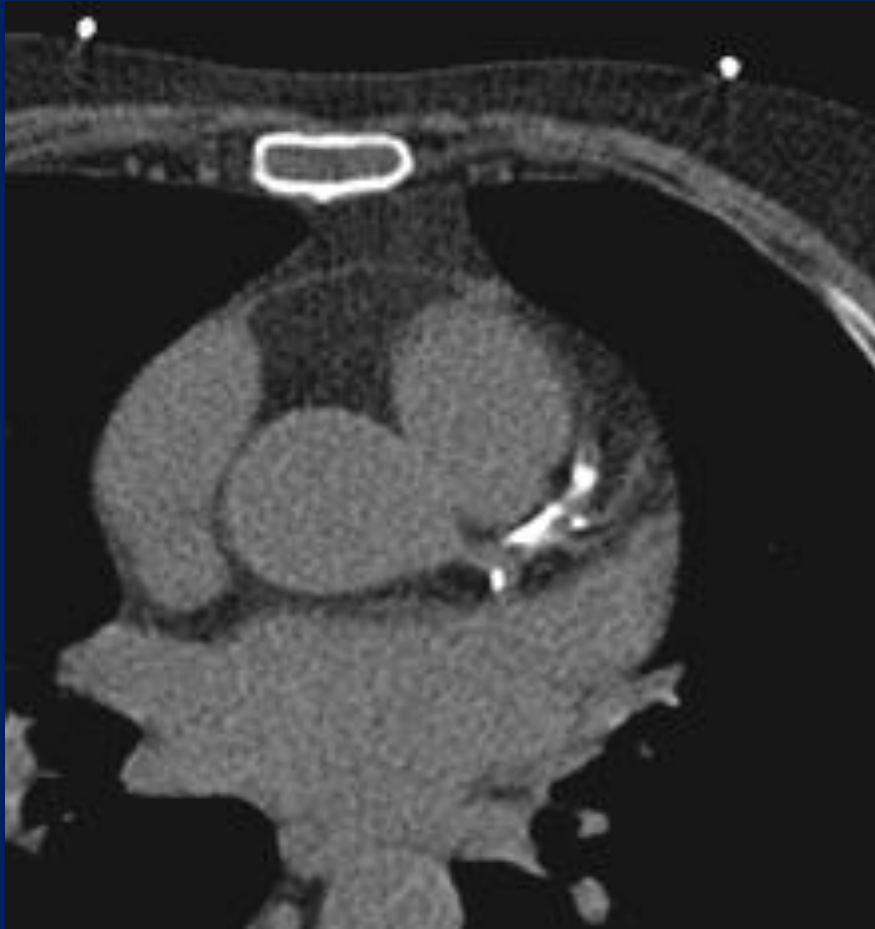


Ethnic Differences in Coronary Calcification

The Multi-Ethnic Study of Atherosclerosis (MESA)



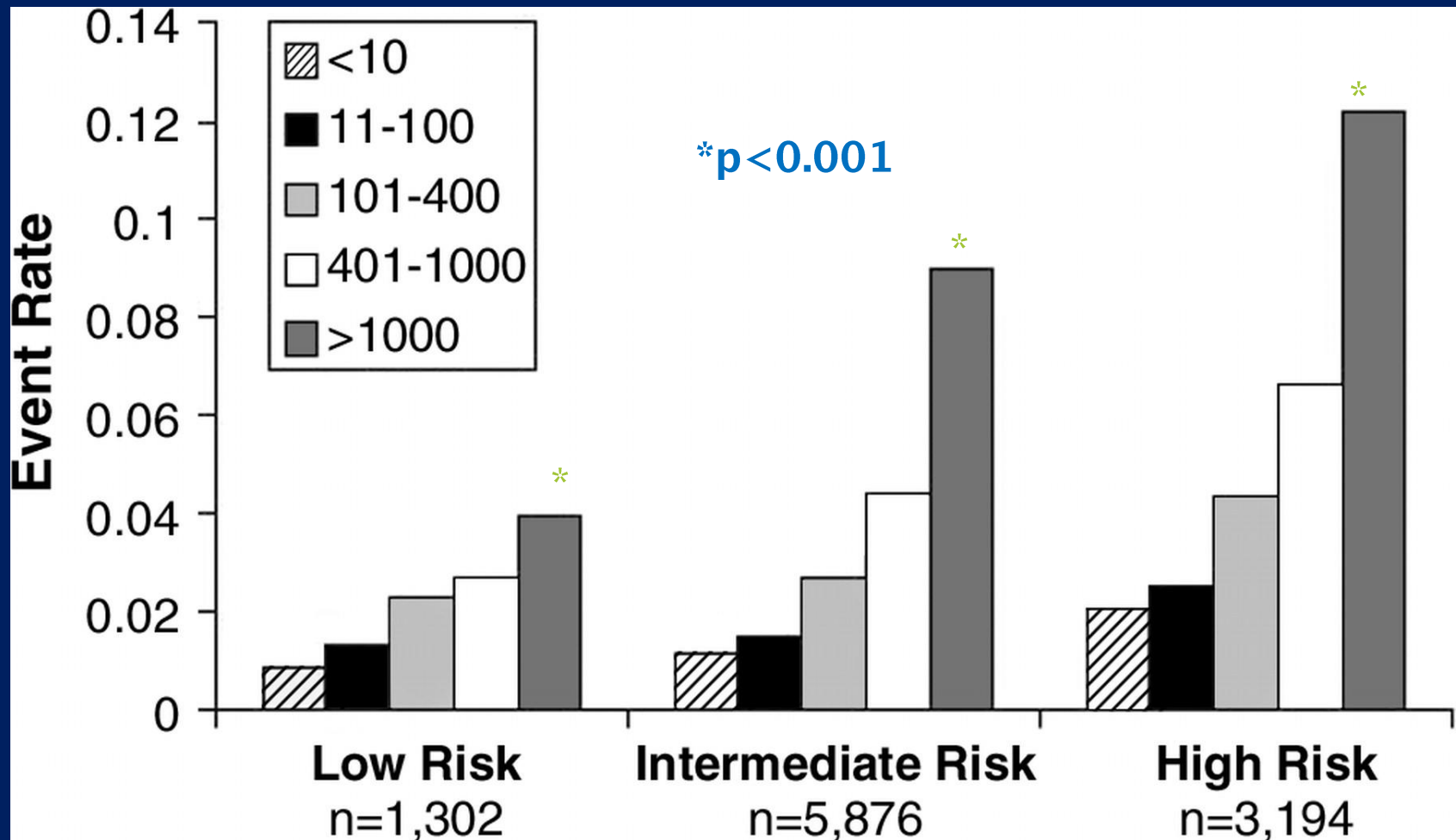
Coronary Calcium in CT



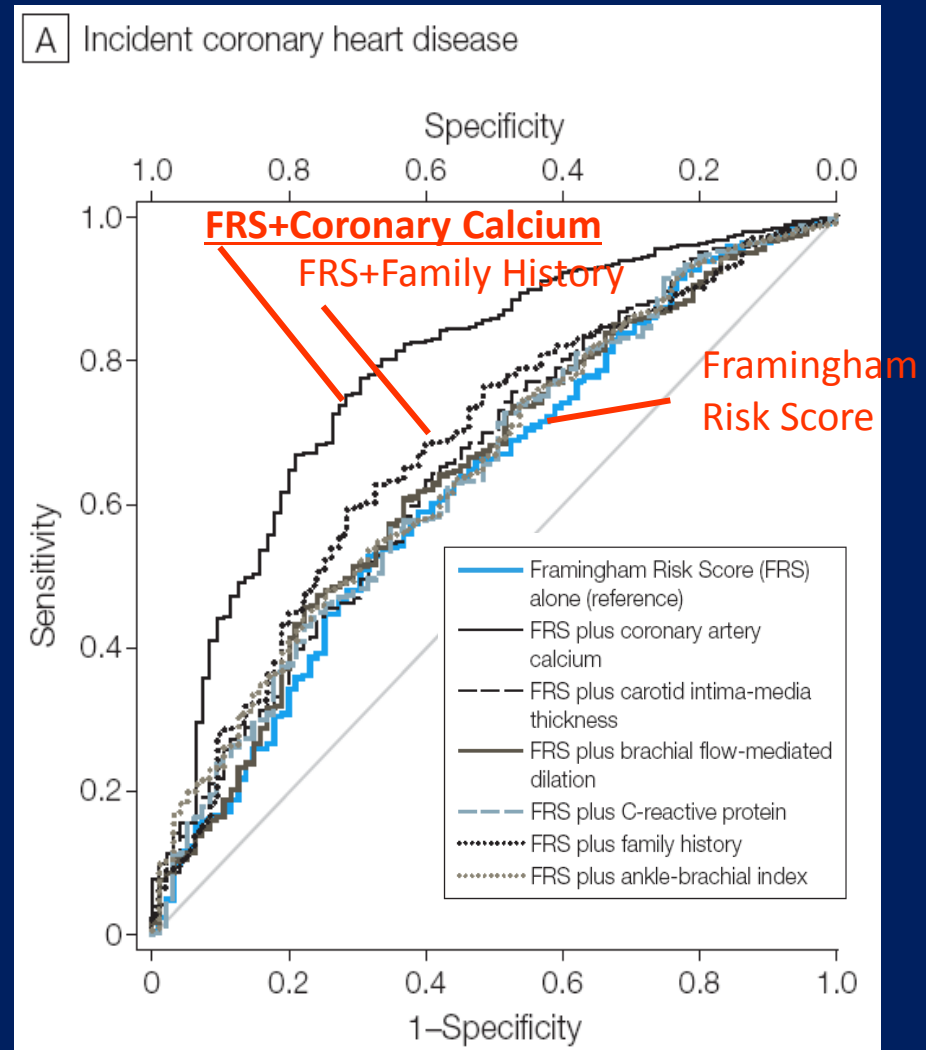
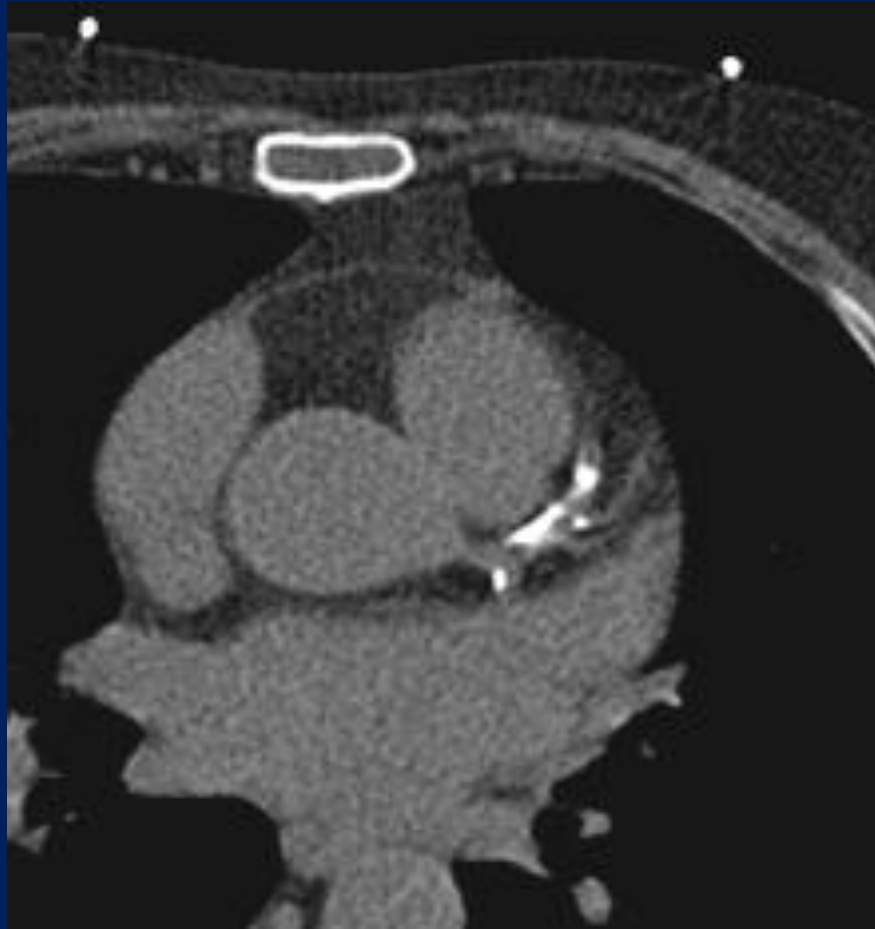
Major Coronary Event†			Any Coronary Event		
AUC for Risk Factors Alone	AUC for Risk Factors plus Coronary-Artery Calcium Score	P Value	AUC for Risk Factors Alone	AUC for Risk Factors plus Coronary-Artery Calcium Score	P Value
0.79	0.83	0.006	0.77	0.82	<0.001

MESA Study - 6722 individuals - 4 years

5-Year Mortality Rates in Framingham Risk Subset by Coronary Calcium Score



Coronary Calcium in CT



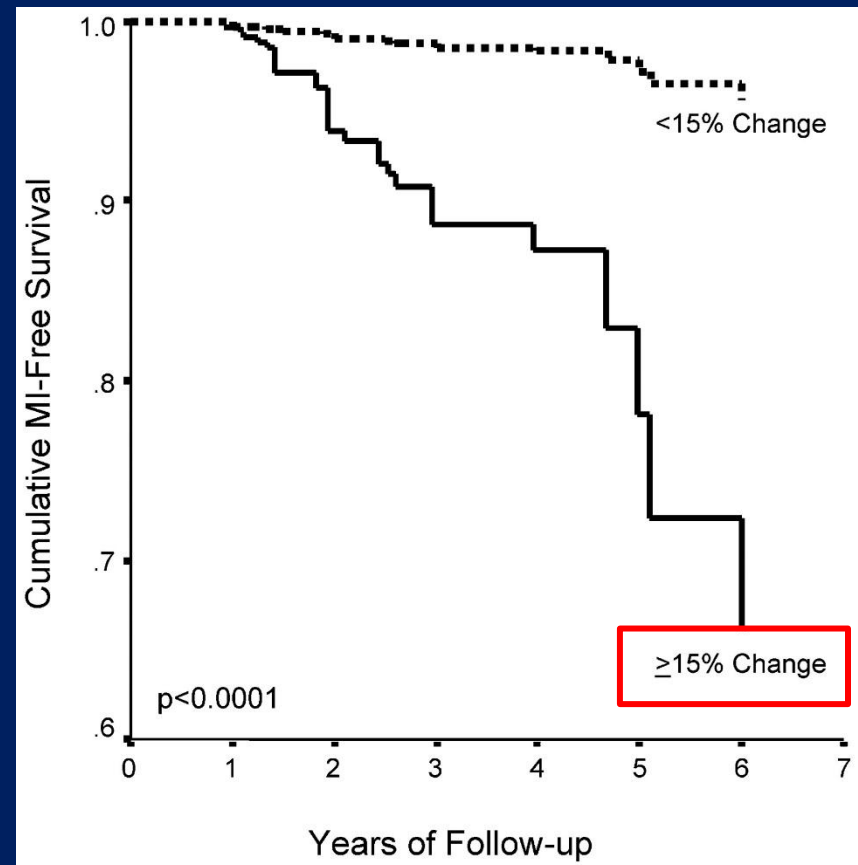
N = 6814, 8 yrs Follow-up

Comparison of Novel Risk Markers
for Improvement in Cardiovascular Risk
Assessment in Intermediate-Risk Individuals

Progression of Coronary Artery Calcium and Risk of First MI

495 Asymptomatic Patients Started on Statin Therapy

- MI in 41 pts during 3.2 ± 0.7 years
- LDL levels similar in MI and non-MI pts
- Relative risk of MI in presence of CAC progression was 17.2-fold higher ($P < 0.0001$)

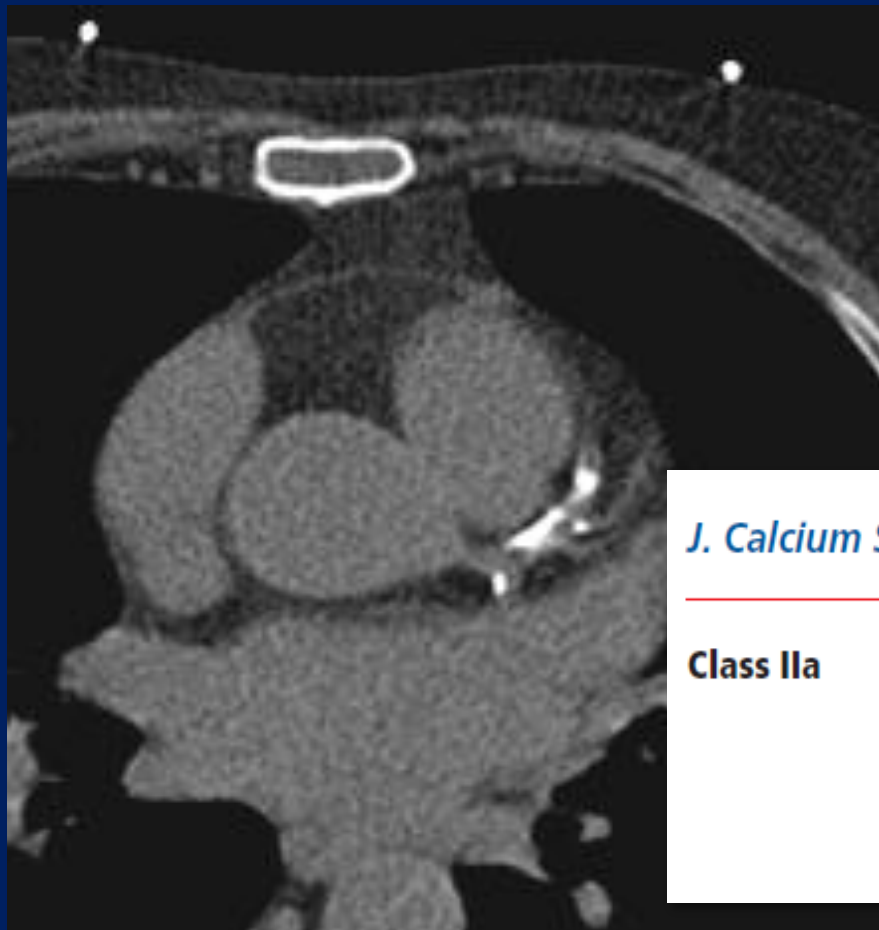


Clinical Indications for MSCT

- Calcium Scoring → risk stratification
- Non-invasive coronary angiography (CTA) in the symptomatic low-risk patient or asymptomatic intermediate-risk patient

→ *A negative test (normal CTA) has a 98% chance of revealing normal coronary arteries on invasive angiography*

Coronary Calcium in CT



Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

November 2010

ACCF/AHA Writing Committee

J. Calcium Scoring Methods Recommendations

- Class IIa** 1. Measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-year risk). (Level of Evidence: B)

N = 6814, 8 yrs Follow-up

Case Presentation

M/64

Asymptomatic subject

검진 coronary CT angiography상 high calcium score, r/o diffuse variable stenosis in all coronary arteries로 순환기 내과 외래 방문

Current presentation

HTN/DM/dyslipidemia (+/-/-)

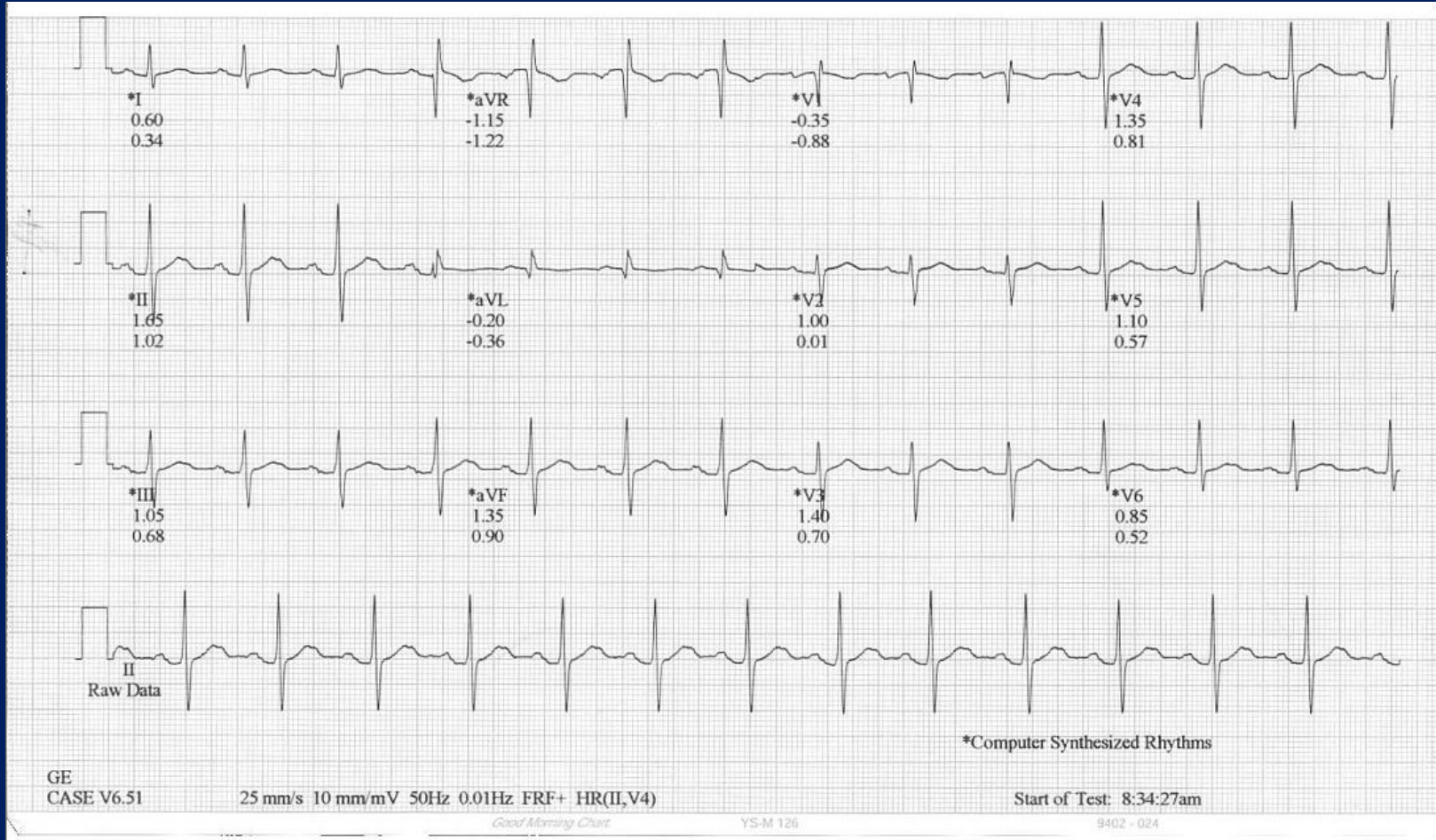
Premature CVD Family history (-)

Smoking (-)

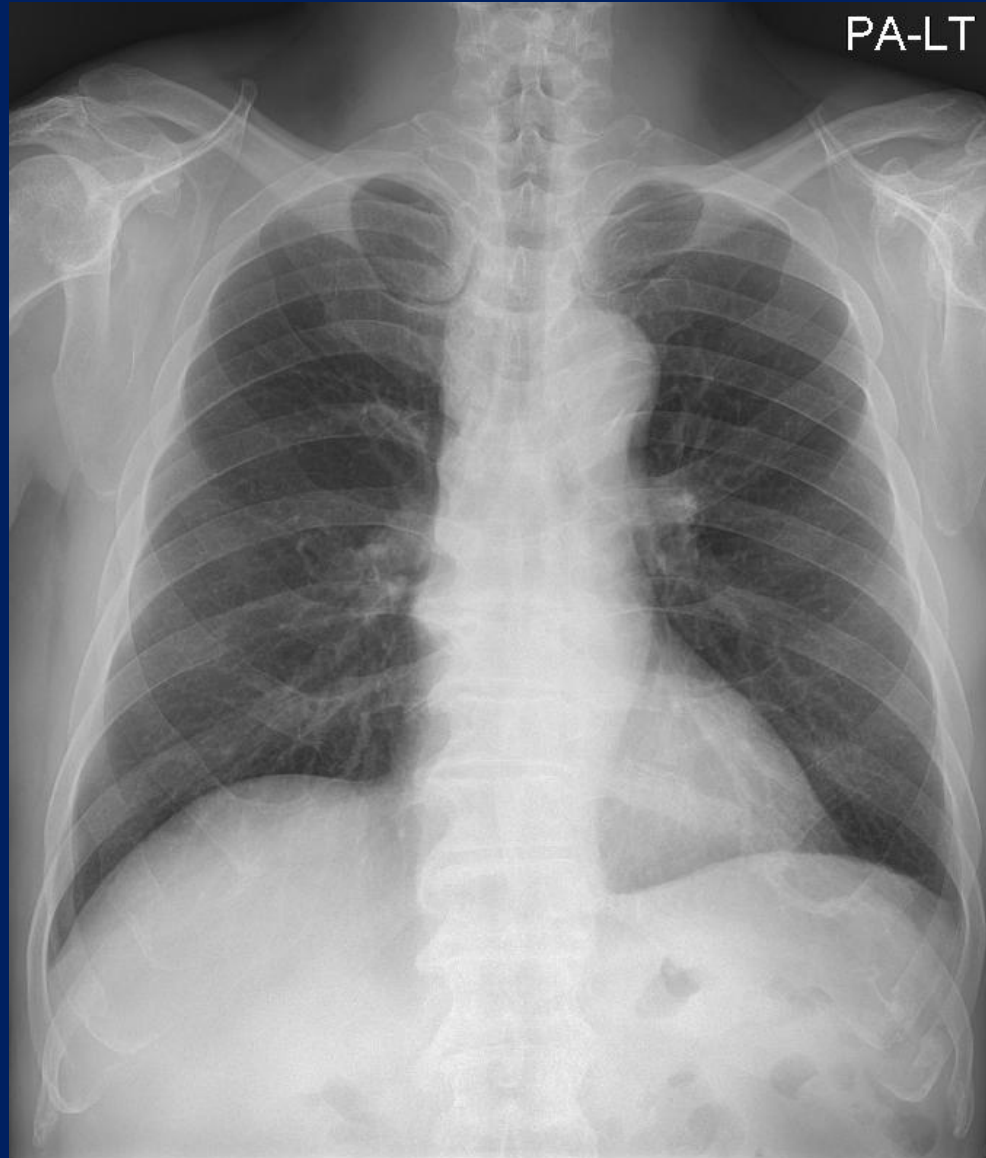
Alcohol (-)

**Medications : Adalat oros 30mg 1T QD,
Coaprovel 150/12.5mg 0.5T QD**

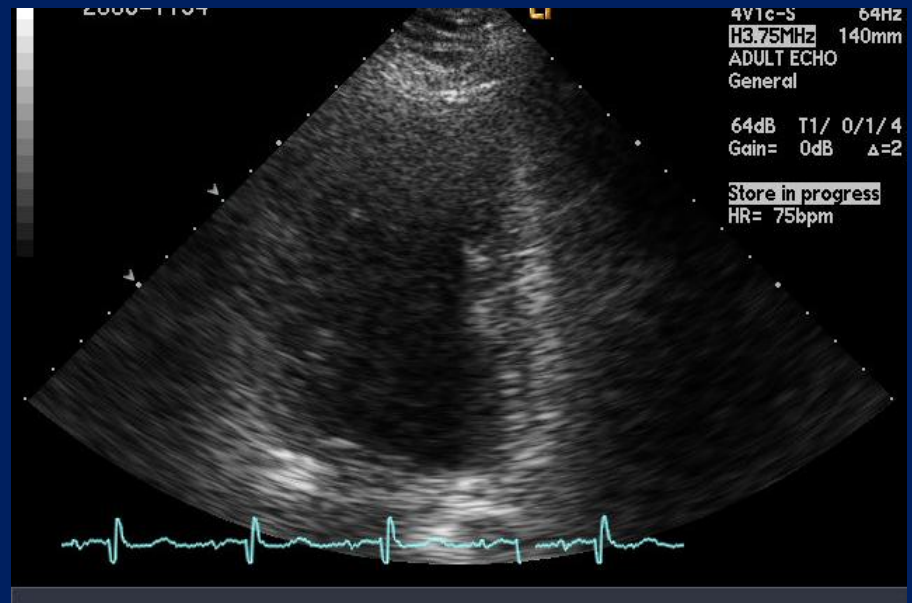
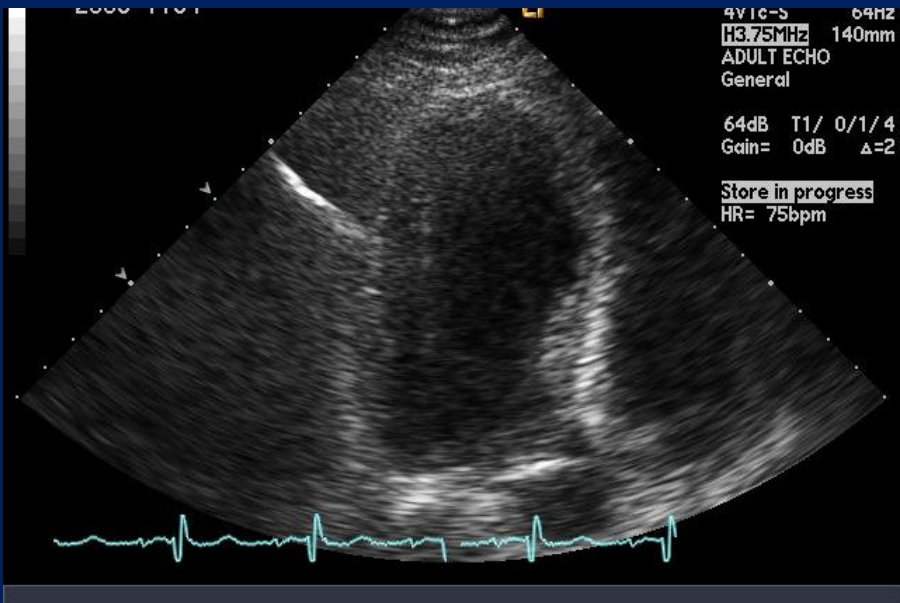
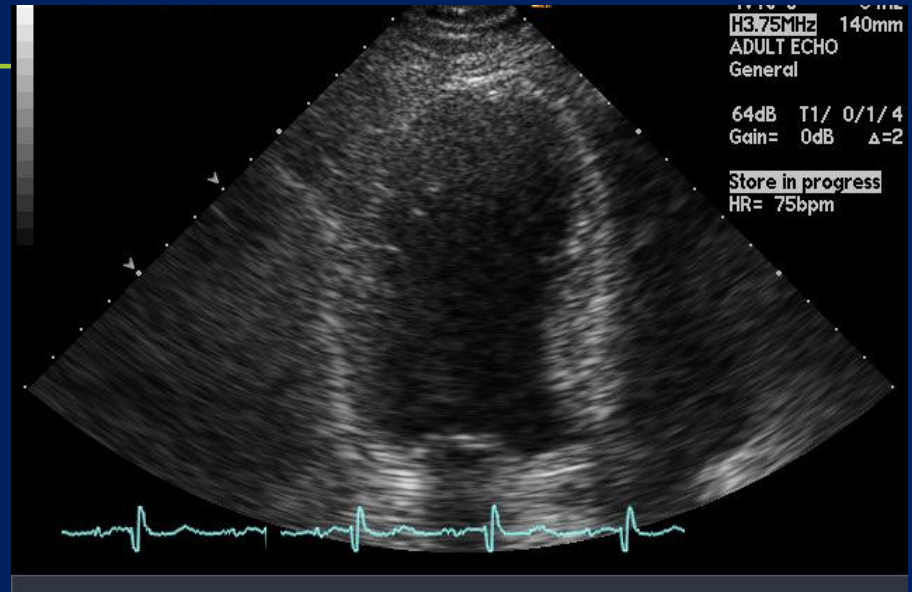
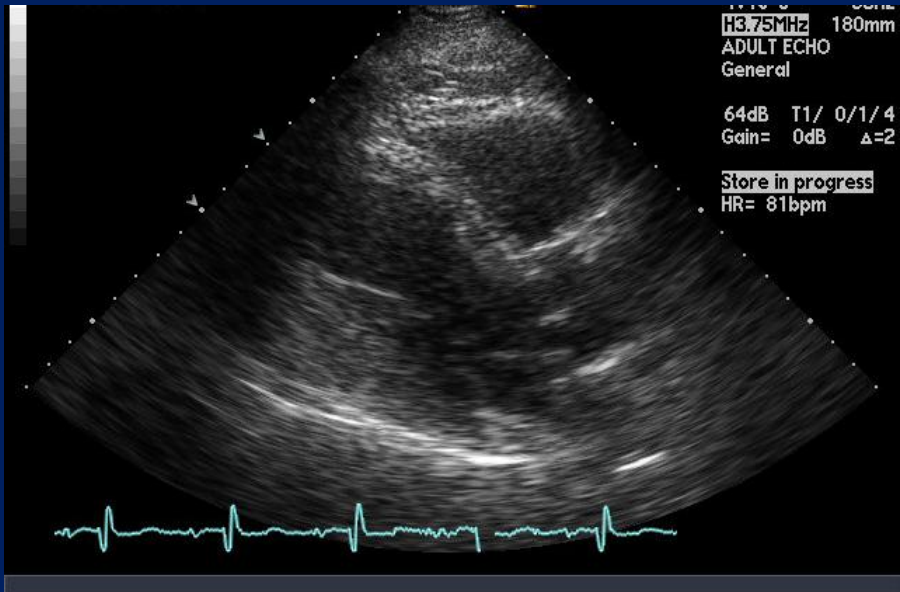
EKG



Chest X-Ray



Echocardiography



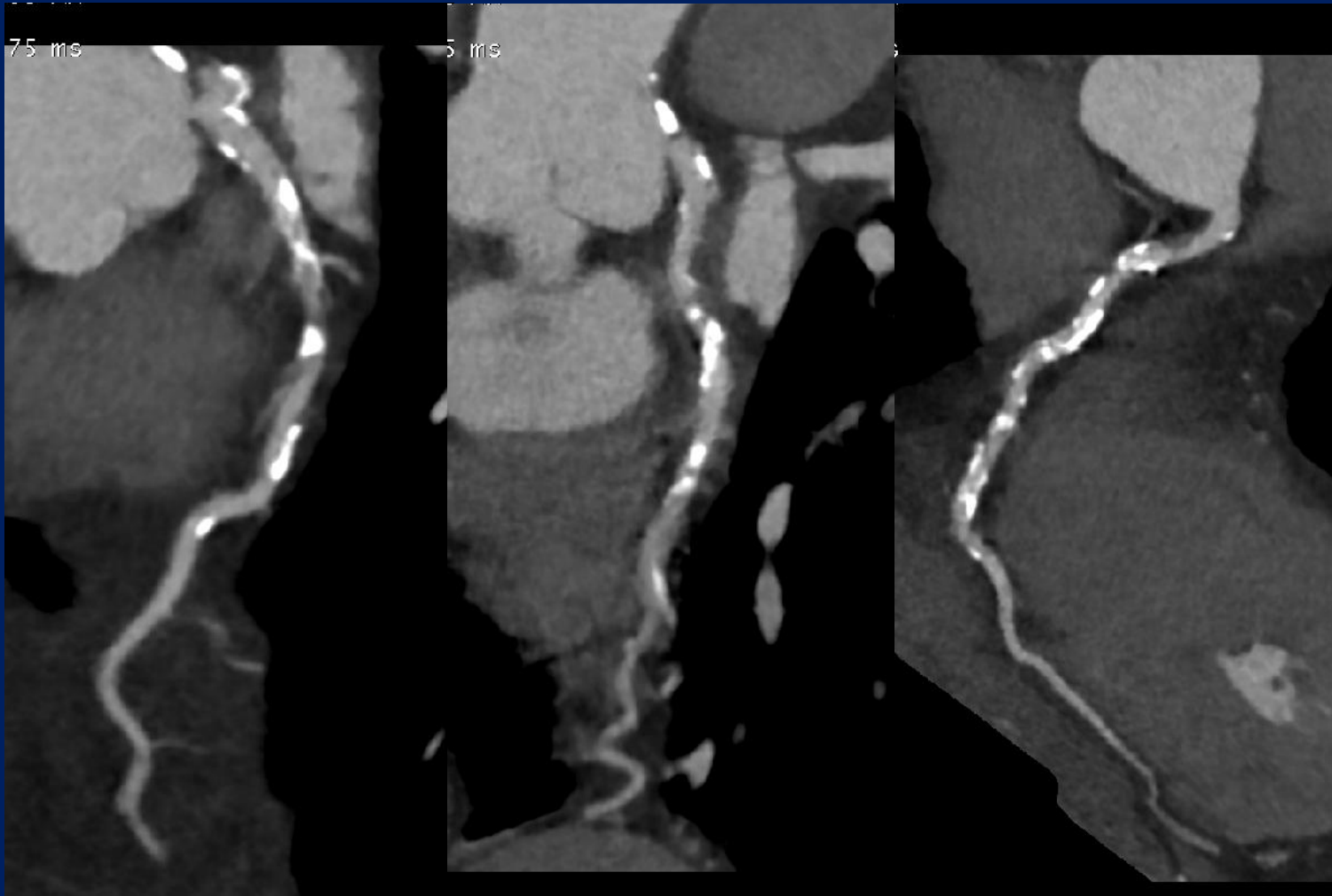
Coronary CT Angiography

Coronary artery calcium score: 3336.35

LAD

LCX

RCA



Initial Laboratory Findings

CBC	Hb 16.4 g/dL - WBC 4,100 /uL – PLT 136,000 /uL
Electrolyte	Na 139 - K 4.2 – Cl 105 mmol/L
Chemistry	BUN / Cr 9.5 / 0.79 mg/dL Protein / Albumin 7.1 / 3.9 g/dL AST / ALT 62 / 102 IU/L ALP 68 IU/L CRP 3.83 mg/L
Coagulation	PT / aPTT 1.03(INR) / 35.9 sec
Others	TC 223 mg/dL, TG 127mg/dL, HDL 38 mg/dL, LDL 159 mg/dL

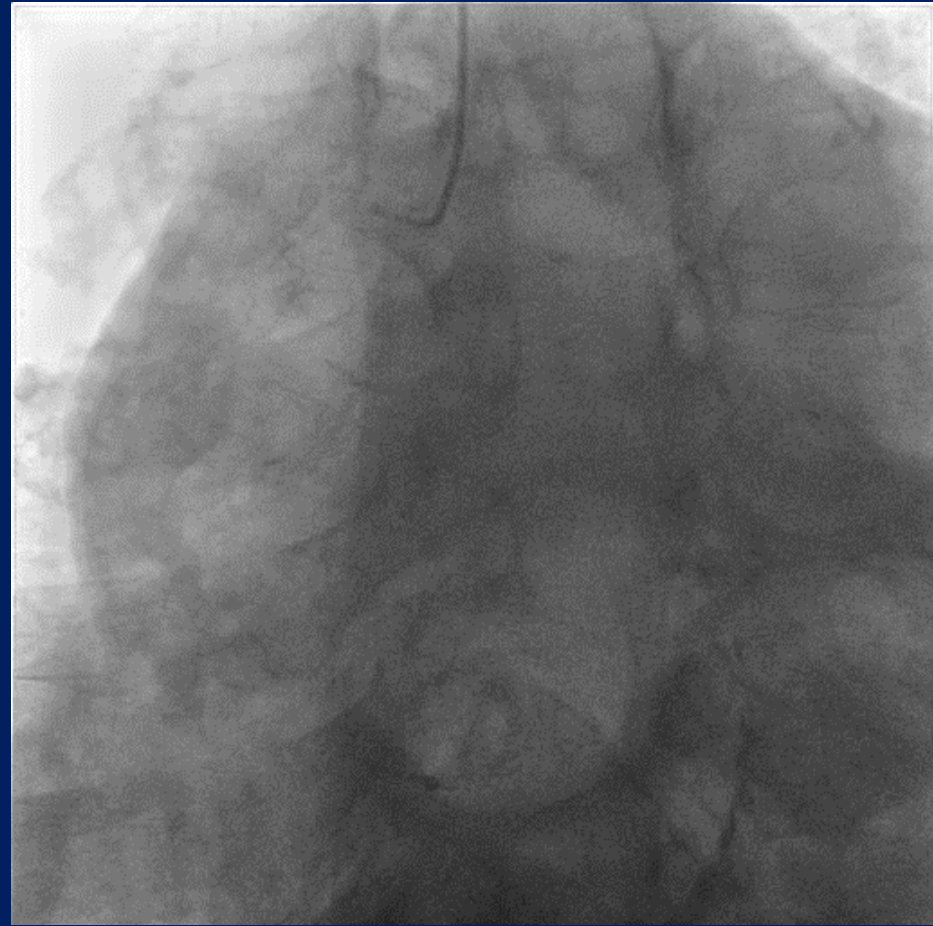
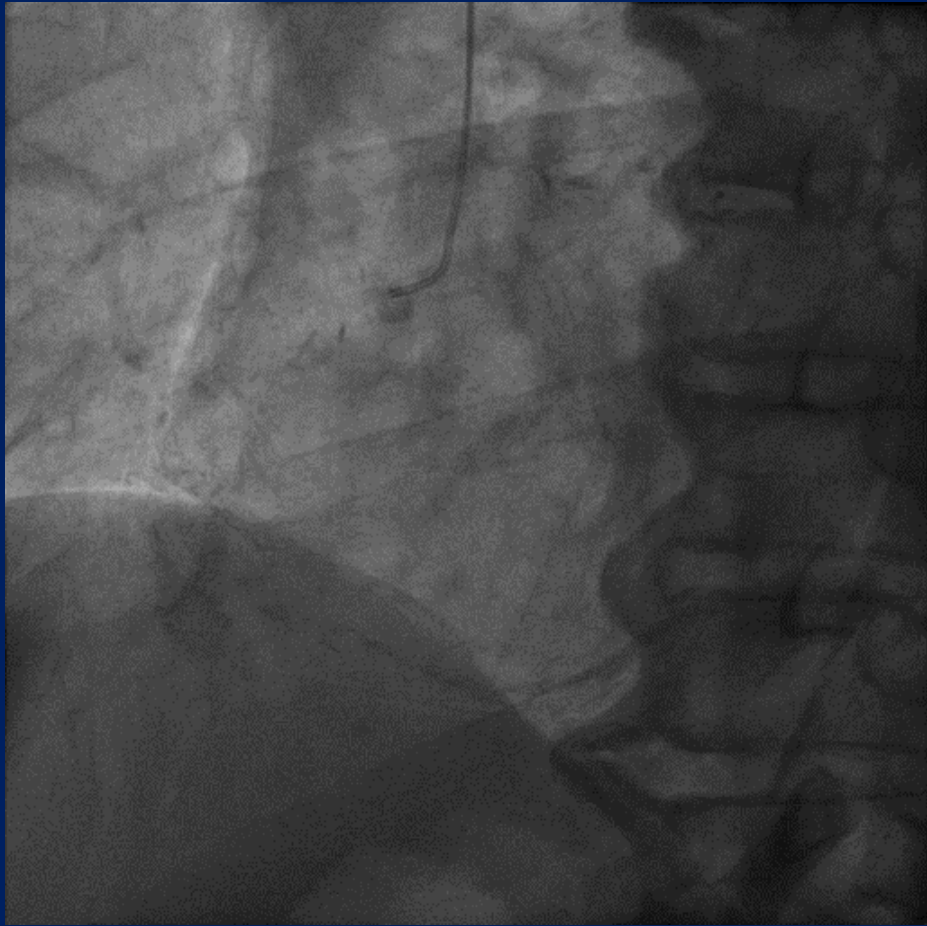
10-Year Framingham Risk Score

Age:	64
Gender:	male
Total Cholesterol:	223 mg/dL
HDL Cholesterol:	38 mg/dL
Smoker:	No
Systolic Blood Pressure:	120 mm/Hg
On medication for HBP:	Yes
Risk Score*	17%

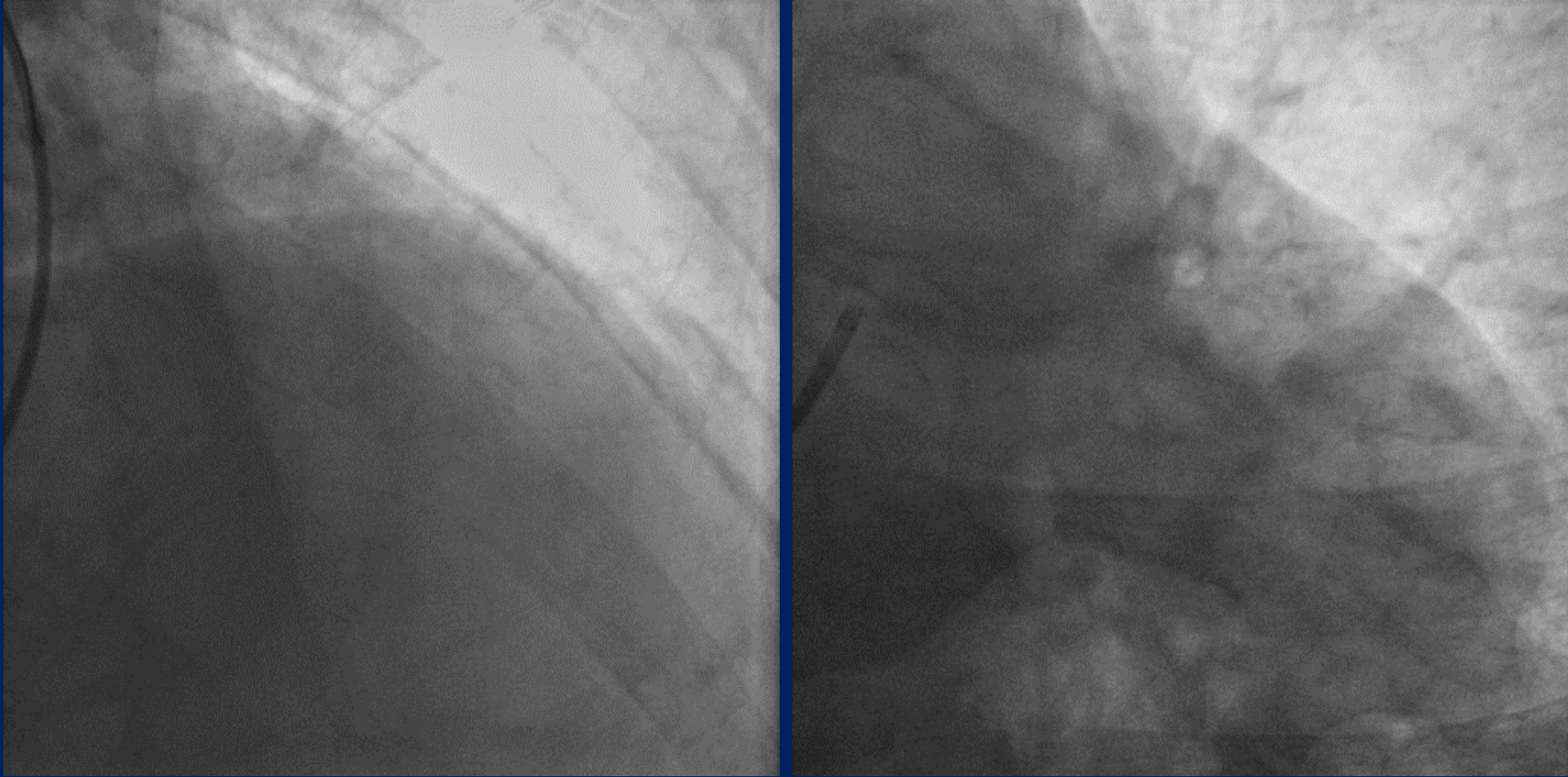
Means 17 of 100 people with this level of risk will have a heart attack in the next 10 years.

→ Asymptomatic Intermediate risk patient

Coronary Angiography



Coronary Angiography



Follow-Up Medication

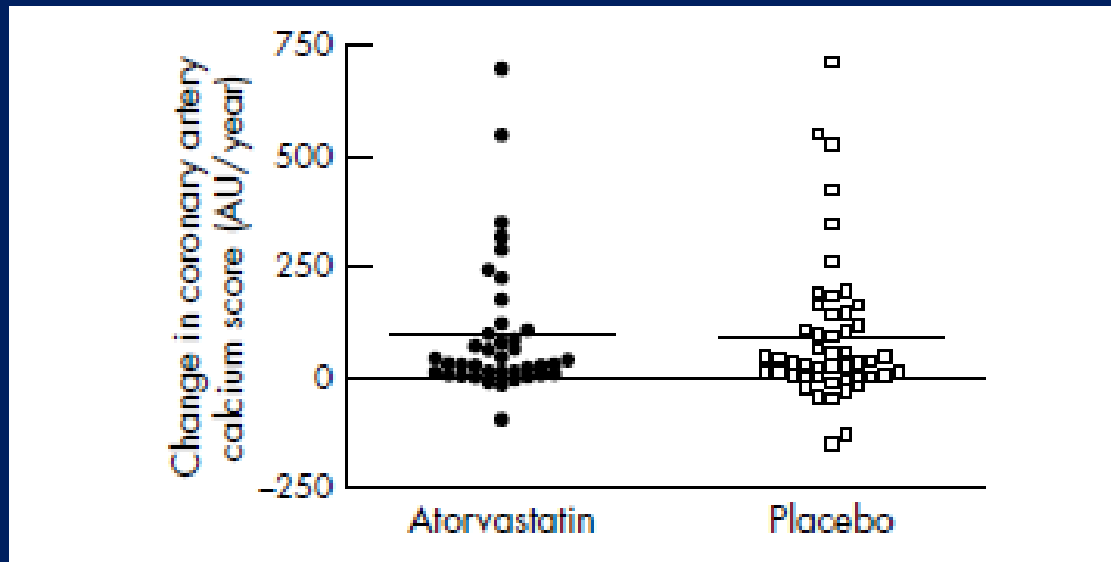
- Aspirin 100mg 1T QD
- Adalat oros 30mg 1T QD
- Coaprovel 150/12.5mg 0.5T QD
- Atorvastatin 20mg QD

Possible Effects of Treatment in Asymptomatic Patients

Statin: Coronary Calcium Score

- To evaluate the effect of intensive lipid-lowering treatment on coronary artery calcification
- In a substudy of a trial recruiting patients with calcific aortic stenosis.
- A double blind RCT
- 102 patients with calcific aortic stenosis and coronary artery calcification
- 48 patients receiving atorvastatin 80mg vs. 54 to placebo
- A median follow-up of 24 months

Statin: Coronary Calcium Score



- Absolute rate of change in coronary calcium score expressed in arbitrary units (AU) per year
- Despite reduction in LDL and CRP, atorvastatin 80mg did not affect the rate of progression of the coronary artery calcium score compared with the placebo group (26 % vs. 18 %) respectively.

Statin: Coronary Calcium Score

- Hypothesis: compared with placebo, simvastatin would reduce the progression of coronary artery calcium (CAC) in participants asymptomatic for vascular disease.
- A randomized trial with participants receiving simvastatin 80 mg or matching placebo for 12 months.

Statin: Coronary Calcium Score

Treatment effects on lipids

Lipids (mg/dl)	Placebo				Active				p Value*
	Baseline	6 [†]	12	%Δ [‡]	Baseline	6	12	%Δ	
Total cholesterol	200 ± 3	200 ± 3	197 ± 3	↓1	198 ± 3	136 ± 3	140 ± 3	↓30	<0.0001
Triglycerides	149 ± 11	156 ± 10	154 ± 10	↑3	160 ± 11	120 ± 10	131 ± 10	↓18	<0.0001
HDL	41 ± 1	43 ± 1	41 ± 1	↑1	40 ± 1	39 ± 1	39 ± 1	↓2	0.014
LDL	129 ± 3	127 ± 3	126 ± 3	↓2	127 ± 2	72 ± 3	74 ± 3	↓42	<0.0001

* Significance level for average treatment effect for 6- and 12-month follow-up adjusted for baseline and using natural log transformed data.
[†] Least-square mean ± SE for 6- plus 12-month follow-up adjusted for baseline value.
[‡] Percentage change (Δ) at 12 months versus baseline.

Treatment effects on coronary calcium

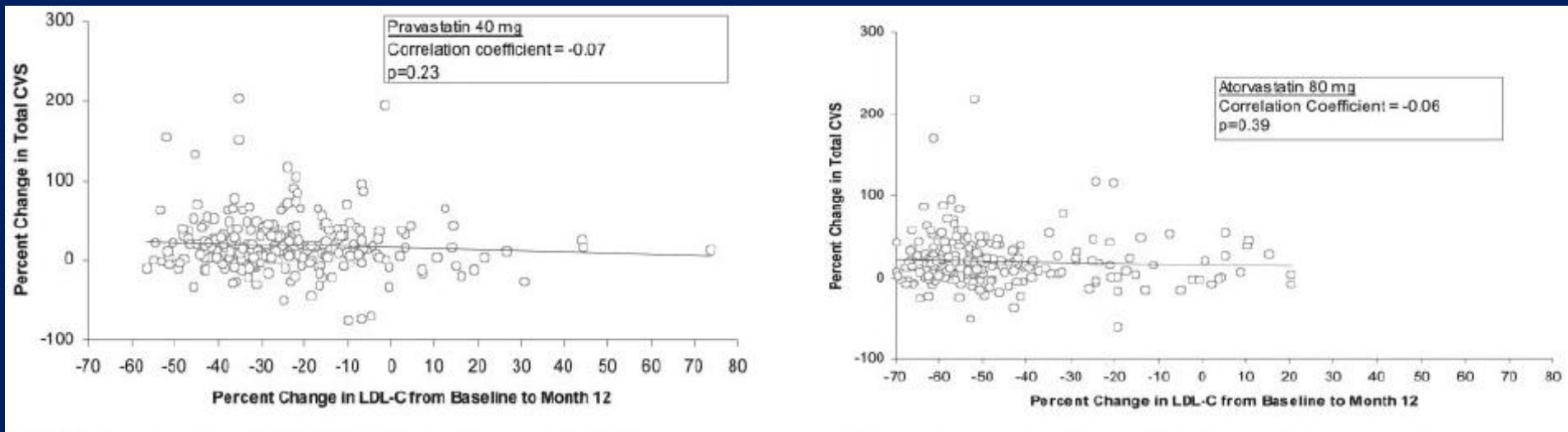
Calcium measures (U)	Placebo				Active				p Value*
	Baseline	6 [†]	12	%Δ [‡]	Baseline	6	12	%Δ	
CAC									
Volume	872 ± 138	809 ± 26	845 ± 32	↓3	751 ± 133	799 ± 26	820 ± 32	↑9	0.61
Agatston	659 ± 116	651 ± 16	691 ± 24	↑5	593 ± 132	631 ± 16	645 ± 24	↑9	0.12

- Despite significant reduction in LDL, simvastatin 80mg does not reduce progression of CAC compared with placebo (9 % vs. 5 %), respectively.

Statin: Coronary Calcium Score

- The effect of different intensities of statin therapy on CAC in hyperlipidemic postmenopausal women was evaluated in the BELLES trial
- 615 patients were randomly assigned to intensive (atorvastatin 80 mg/day) or moderate (pravastatin 40 mg/day) lipid lowering

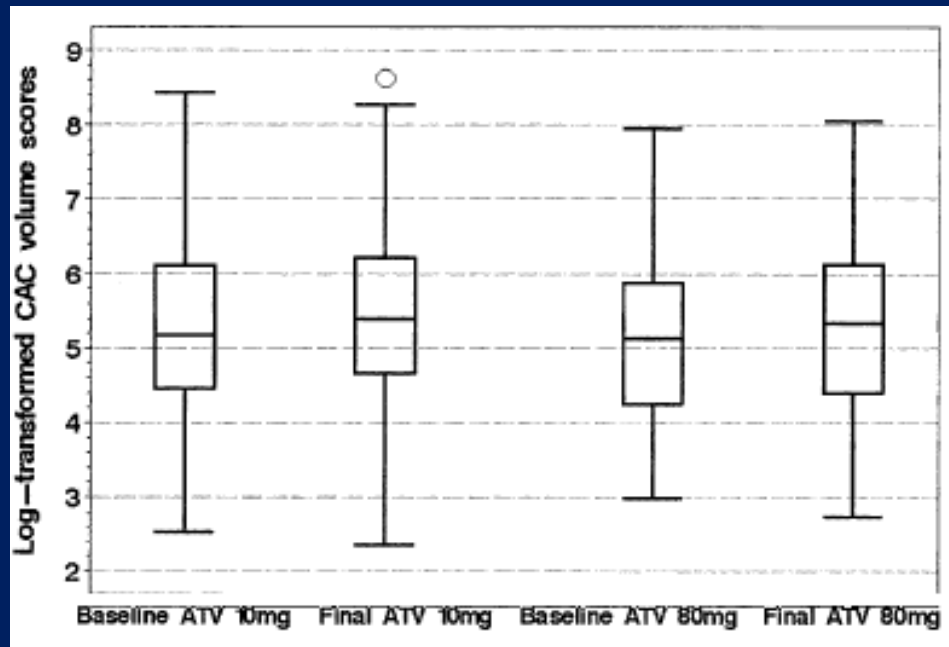
Statin: Coronary Calcium Score



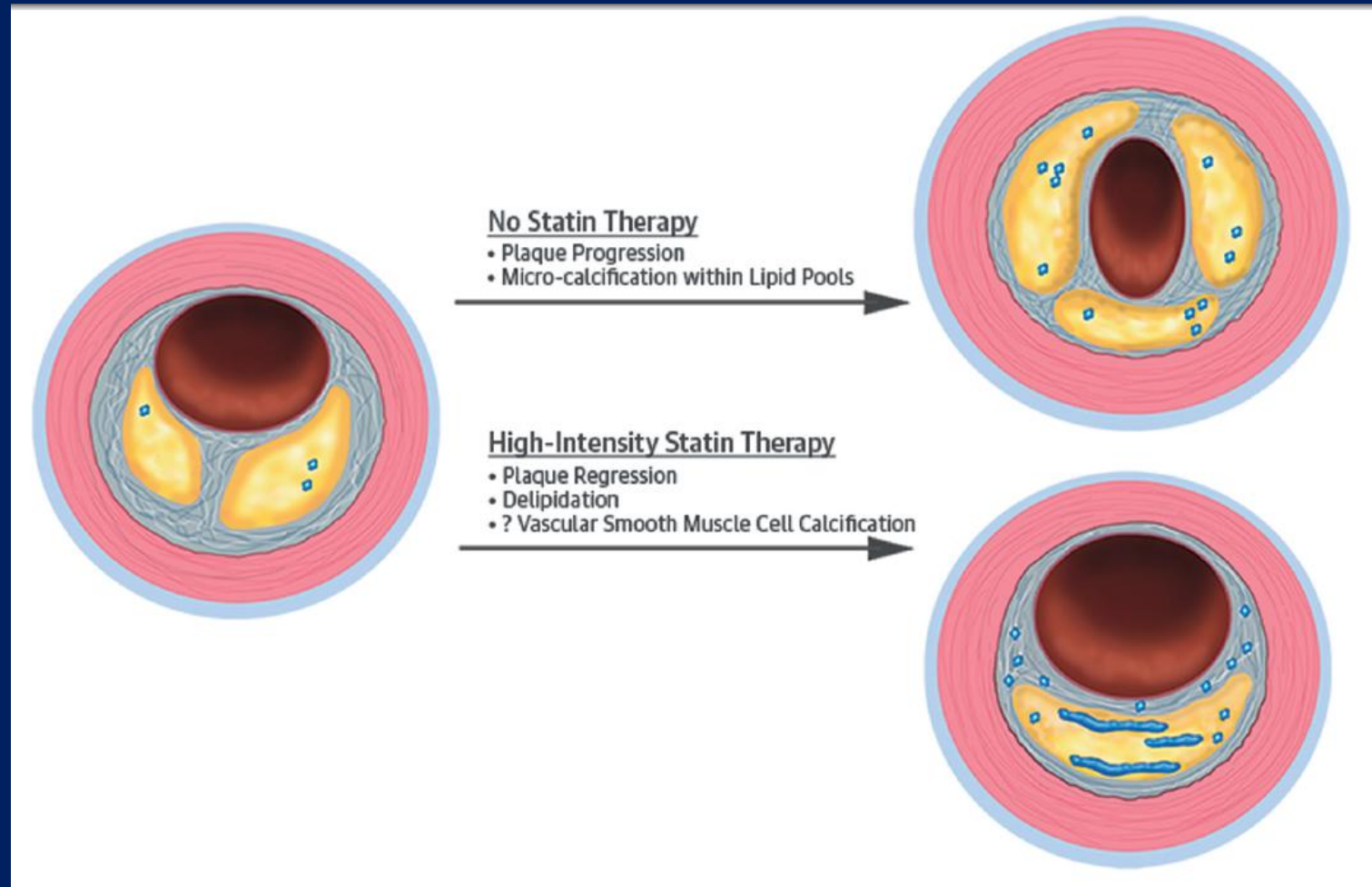
- % change in total calcium volume score (CVS) vs. % change in LDL after 12 months
- There was no difference between the two groups in the degree of CAC progression (15.1 vs. 14.3 percent).

Statin: Coronary Calcium Score

- A multicenter RCT to evaluate the effect of 80 mg vs. 10 mg atorvastatin on CAC progression over 12 months period.
- The mean progression of CAC volume score was non-significantly different between two groups [27 % in 80mg vs. 25 % in 10 mg, $p = 0.65$].



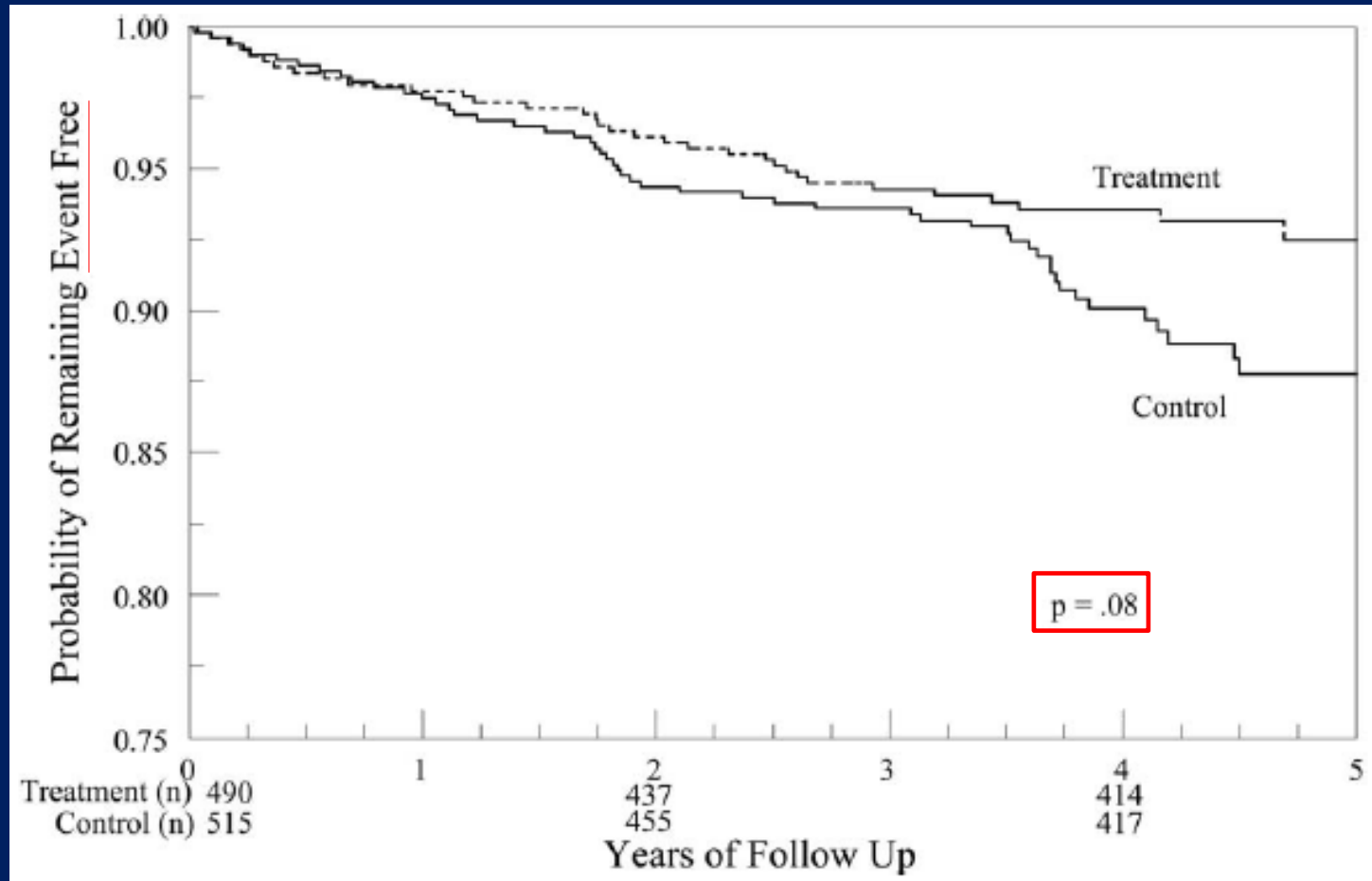
Plaque Calcification in the Setting of No-Statin vs. High-Intensity Statin



Statin: Cardiac Events

- A double-blinded, placebo-controlled RCT of atorvastatin 20 mg daily, vitamin C 1 g daily, and vitamin E 1,000 U daily, vs. placebos
- 1,005 asymptomatic men and women age 50–70 years
- Coronary calcium scores $\geq 80^{\text{th}}$ % for age and gender.
- Followed for 4.3 years for occurrence of cardiac events.

Statin: Cardiac Events



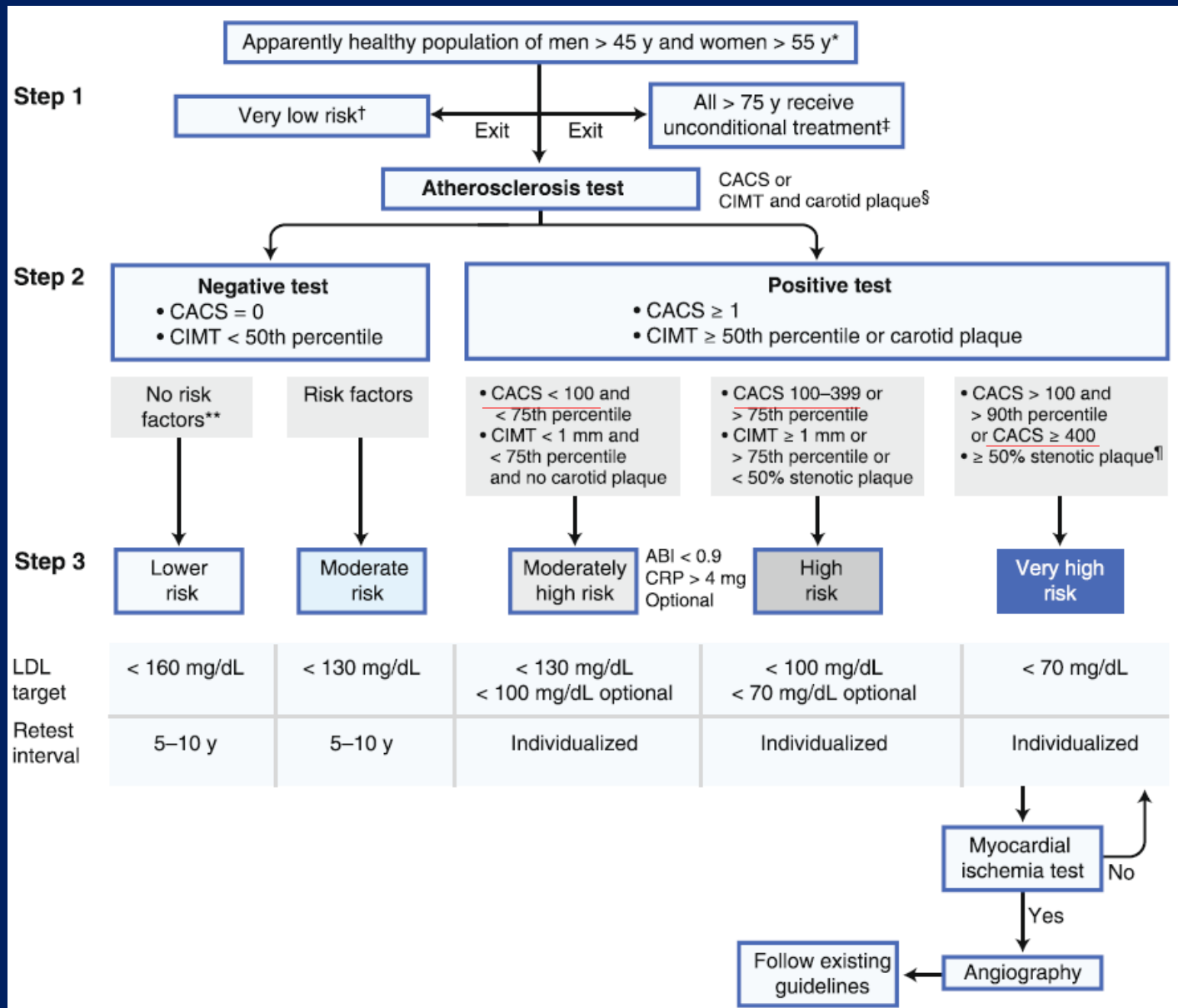
Limitations → underpowered, relatively lower dose of atorvastatin, low-risk patients

CAC and Clinical Guideline



- The SHAPE (Screening for Heart Attack Prevention and Education) Guideline of 2006 was the first to recommend **statin treatment in primary prevention** based primarily on subclinical atherosclerosis as defined by **coronary artery calcium** and **carotid intima medial thickening**.

SHAPE Guideline



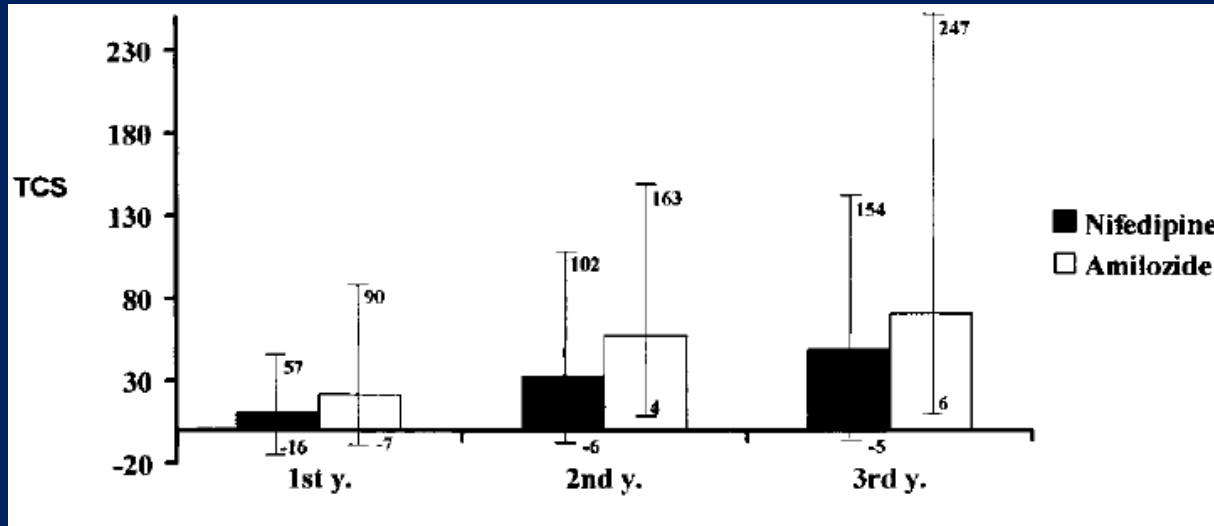
Aspirin

- We studied 4,229 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) who were not on aspirin at baseline and were free of diabetes mellitus.
- Using data from median 7.6-year follow-up
- For the primary prevention of CHD, MESA participants with CAC \geq 100 had favorable risk/benefit estimations for aspirin use while participants with zero CAC were estimated to receive net harm from aspirin.

Calcium Channel Blocker

- A study to compare the effect of nifedipine once daily to co-amilozide diuretic treatment of high-risk hypertensive patients on progression of CAC over 3-year time interval.
- A total of 201 patients with a total calcium score of ≥ 10 at the onset of study who underwent an annual double-helix computerized tomography for 3 years were analyzed for efficacy.

Calcium Channel Blocker



- Median and interquartile range of absolute change in Total calcium score (TCS) for nifedipine vs co-amilozide.
- Treatment with nifedipine once daily was associated with significant slower progression of CAC in hypertensive patients compared with co-amilozide over 3 years (40 % vs. 78 %, $p = 0.02$), respectively.

Estrogen Therapy

The NEW ENGLAND JOURNAL of MEDICINE

Estrogen Therapy and Coronary-Artery Calcification

- Substudy of the Women's Health Initiative trial of conjugated equine estrogens (0.625 mg per day) as compared with placebo
- Women who had undergone hysterectomy, performed CT of the heart in 1,064 women aged 50 to 59 years at randomization.
- Imaging was conducted at 28 of 40 centers after a mean of 7.4 years of treatment and 1.3 years after the trial was completed (8.7 years after randomization).

Estrogen Therapy

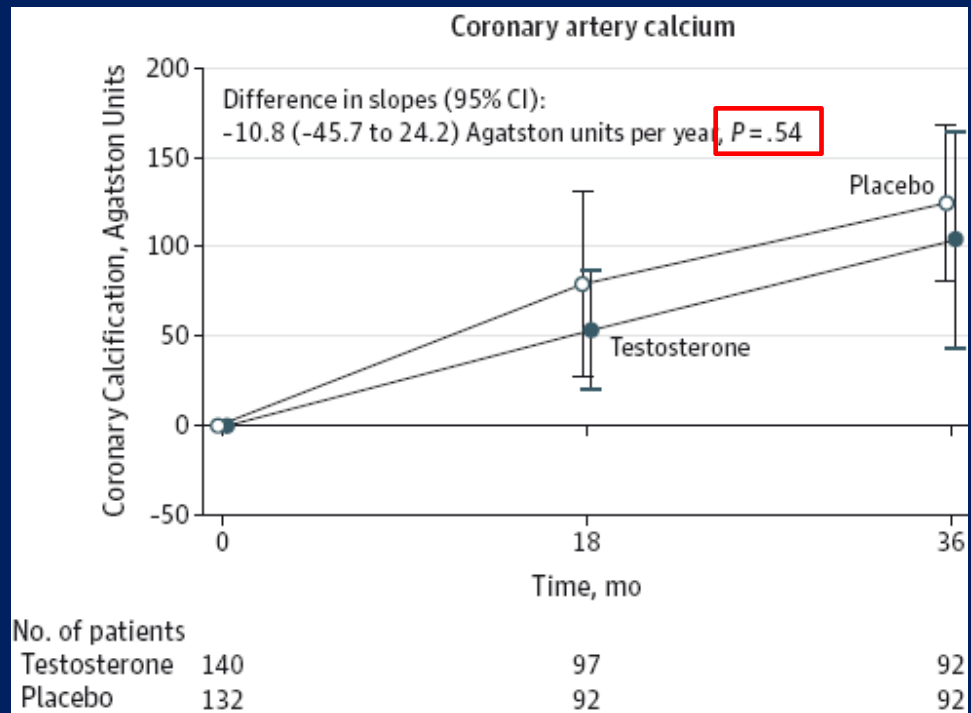
- The mean CAC score after trial completion was lower among women receiving **estrogen (83.1)** than among those receiving **placebo (123.1)** (P=0.02).

Table 2. Distribution of Coronary-Artery Calcium Scores after Trial Completion, According to Randomized-Group Assignment.*

Score and Model	Conjugated Equine Estrogens (N=537)	Placebo (N=527)	Wald Chi-Square Statistic (1 df)	P Value
Mean score	83.1±250.2	123.1±348.6		0.02†
Score distribution				
50th percentile	0	0		
60th percentile	3	17		
75th percentile	43	84		
95th percentile	452	689		
Tobit model with transformation‡:				
Intention-to-treat analyses§				
Unadjusted			5.89	0.02
Multivariate¶			4.83	0.03
Analyses restricted to participants with ≥80% adherence to study medication				
Unadjusted			10.0	0.002
Multivariate¶			9.4	0.002

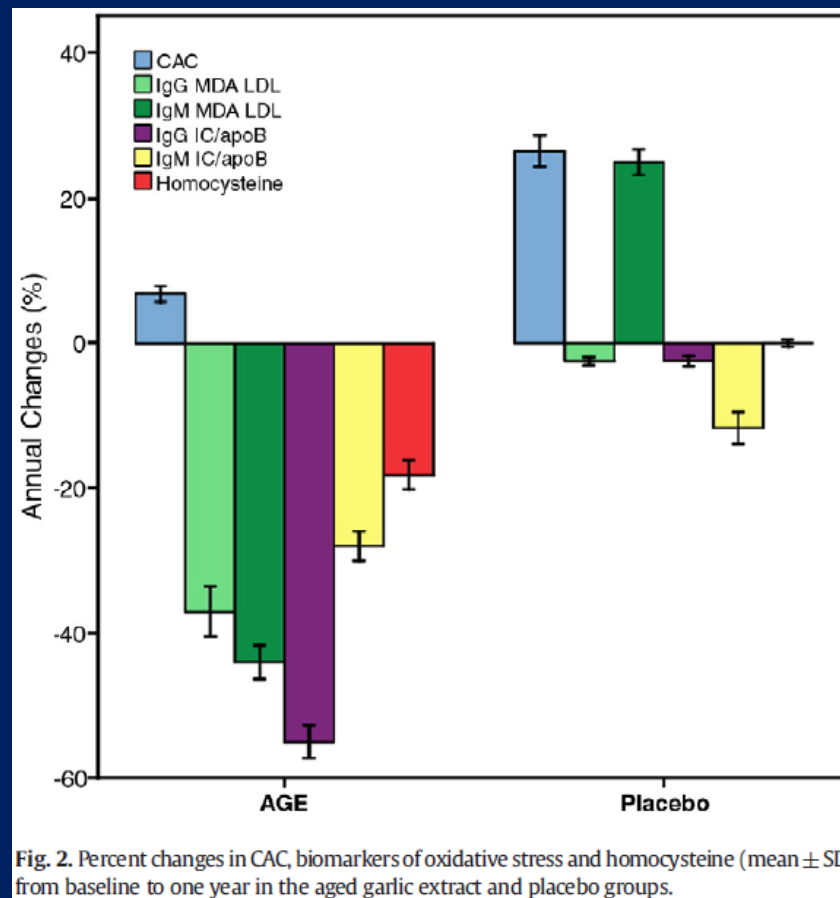
Testosterone

- Testosterone's Effects on Atherosclerosis Progression was a placebo-controlled, double-blind, randomized trial involving 308 men 60 years or older with low or low-normal testosterone levels (100-400 ng/dL; free testosterone <50 pg/mL).
- 156 participants were randomized to receive 7.5 g of 1% testosterone and 152 were randomized to receive placebo gel packets daily for 3 years.



Aged Garlic Extract

- Aged garlic extract and supplements have also been shown to reduce the progression of CAC over 1 year compared with placebo in a double blind randomized clinical trial.



Summary

- ✓ The absence of coronary calcified plaque conveys an extraordinarily low long term cardiovascular risk.
- ✓ **Statins** did not decrease coronary calcium score with favorable benefit in clinical outcomes.
- ✓ Anecdotal data:

Conclusions

- There is no specific treatment available that stops or lowers coronary calcium.
- Treatment of individuals with high calcium scores should aim at reducing risk.
 - ✓ Treating lipid disorders, high blood pressure, and diabetes if present.
 - ✓ Refraining from smoking is essential.
 - ✓ Regular, moderate exercise is advised.

Conclusions

- Due to the overwhelming evidence of benefit in individuals with atherosclerotic heart disease, treatment with aspirin and statins is often advised.

Thank You For Your Attention !