Integrating Biomarkers and Imaging for CV Risk Assessment and Treatment

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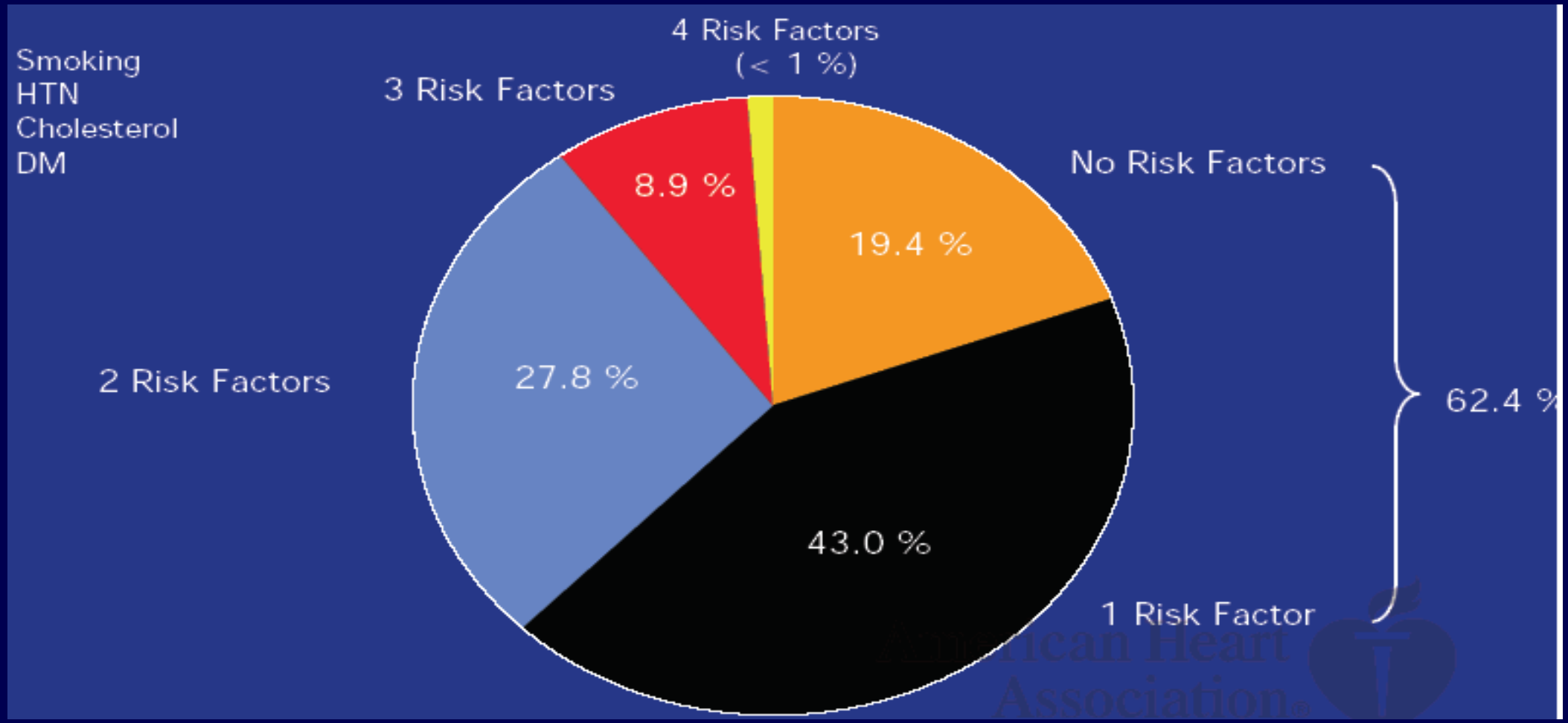
Prevalence of Conventional Risk Factors in Patients with Coronary Heart Disease (N = 87,869)



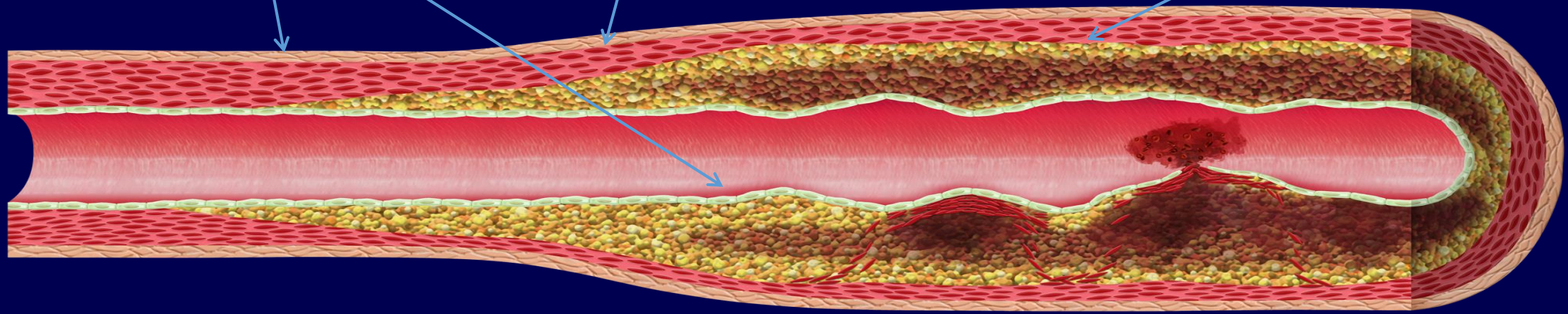
Khot U et al, *JAMA* 2003;290:898-904

Biomarkers Assess the Biology of CVD

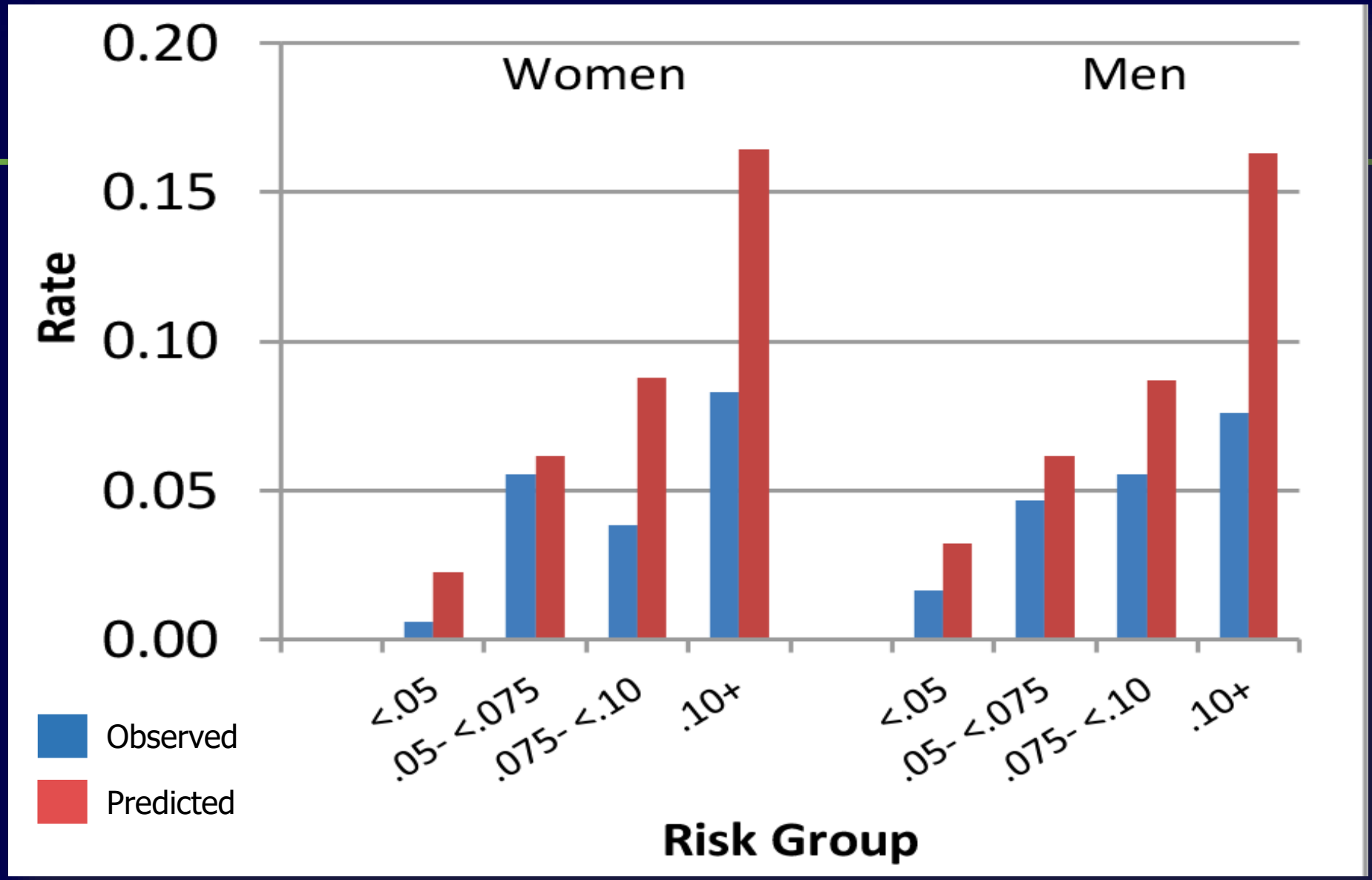
Obesity and Worsening Cardiometabolic Status

Vit D, PTH (Ca,Mg), Testosterone, Glucose, Insulin, HgbA1c, Ferritin, Cortisol, Adiponectin, Leptin

Inflammation	Lipid deposition	Ischemia/ Cardiomyocyte injury
IL-6, IL-17A, TNF-α, Lp-PLA2 hsCRP, Homocysteine (Folate & B12)	TC, LDL, HDL, TG, HDL2b, Apo A-1 sdLDL, ApoB, Lp(a), ApoE	cTnI and NT-proBNP

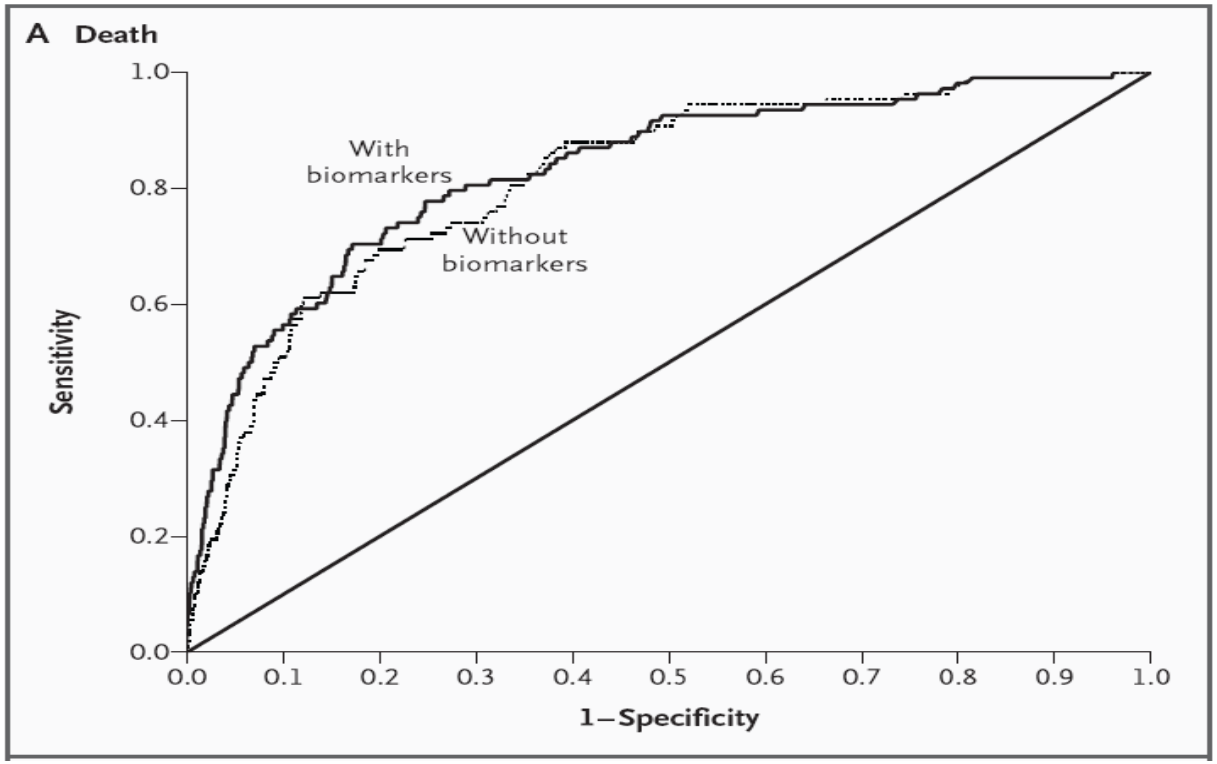


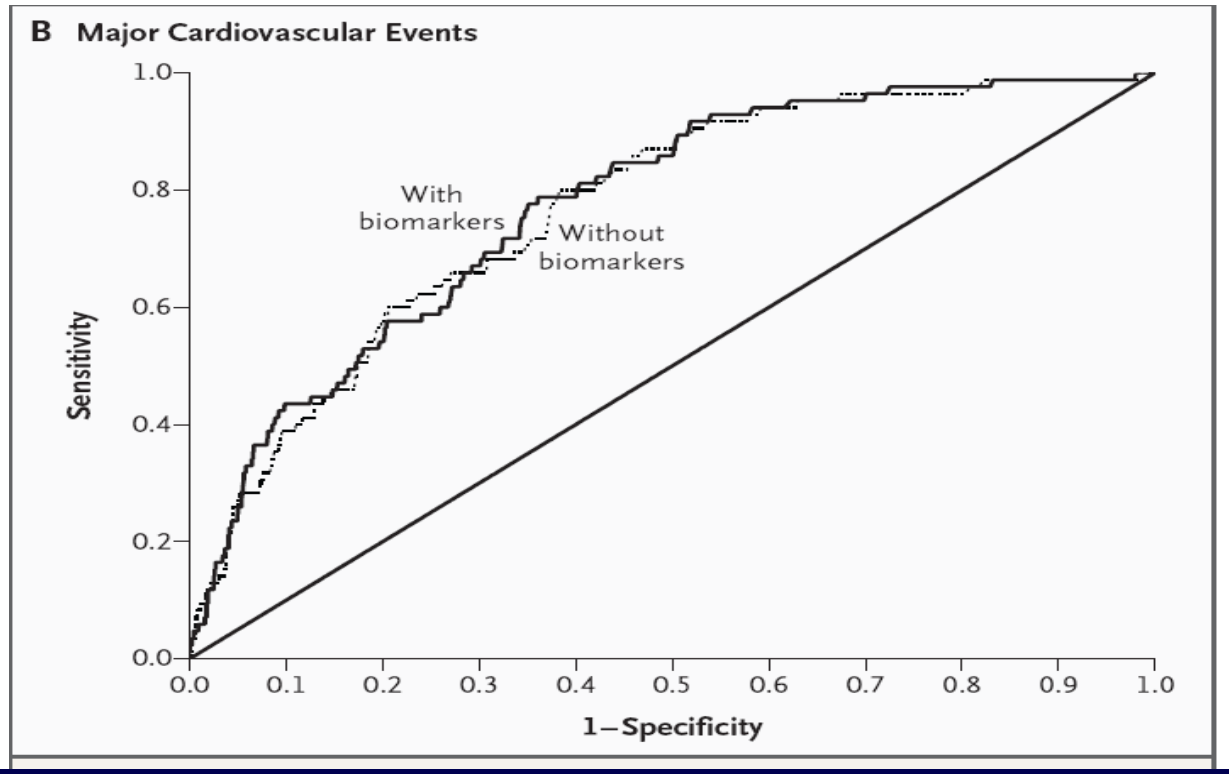
We Can Improve Preventive Screening!



Muntner *JAMA* 2014;311:1406-15. Cook *JAMA Int Med* 2014;174:1964-71. Ridker *Lancet* 2013;382:1762-65.

Biomarkers





10 biomarkers in 3209 participants attending a routine examination of the Framingham Heart Study: the levels of C-reactive protein, B-type natriuretic peptide, N-terminal pro–atrial natriuretic peptide, aldosterone, renin, fibrinogen, D-dimer, plasminogen-activator inhibitor type 1, and homocysteine; and the urinary albumin-to-creatinine ratio.

Wang et al. *N Engl J Med*. 2006;355:2631-2639.

CRP/Fibrinogen

Data Source and Risk Factor	Addition of Biomarker (95% CI)	with Model Including Conventional Risk Factors	Comparison with Reference
25 Studies with 95,733 participants, 6609 with CVD			
Conventional risk factors plus $\log_e$ CRP	0.0035 (0.0018–0.0051)	<0.001	Reference
Conventional risk factors plus fibrinogen	0.0022 (0.0010–0.0035)	<0.001	0.13
Conventional risk factors plus $\log_e$ CRP and fibrinogen	0.0040 (0.0023–0.0057)	<0.001	0.10†
10 Studies with 32,160 participants, 3498 with CVD			
Conventional risk factors plus $\log_e$ CRP	0.0031 (0.0010–0.0053)	0.004	Reference
Conventional risk factors plus $\log_e$ leukocyte count	0.0028 (0.0011–0.0045)	0.002	0.78
17 Studies with 61,002 participants, 8646 with CVD			
Conventional risk factors plus $\log_e$ CRP	0.0038 (0.0023–0.0053)	<0.001	Reference
Conventional risk factors plus albumin	0.0022 (0.0014–0.0030)	<0.001	0.05

Net Reclassification with CRP 1.5%

N Engl J Med. 2012;367:1310-1320.

Highly Sensitive Troponin I

- Troponin I (highest tertile) was associated with a:
  - 7.4-fold increase in all-cause mortality ($p<0.0001$)
  - 7.7-fold increase in major CV events ($p<0.0001$)
- CRP not significant

"Troponin I significantly improved risk stratification for MACEs even after adjustment for traditional risk factors in primary prevention"

Leistner et al. *Clin Chem* 2012;58:200-208.

Highly Sensitive Troponin I: Better Predictor of Risk Than hs-CRP or NT-proBNP

Minnesota Heart Survey

❑ Design:

- 4,451 participants
- 8-15 years follow-up
- Average age 68 years
- hs-cTnI measured in:
  - Cases: 211 CVD deaths (heart disease, stroke, and heart failure)
  - Controls: 253 age, sex and study year matched

❑ Results:

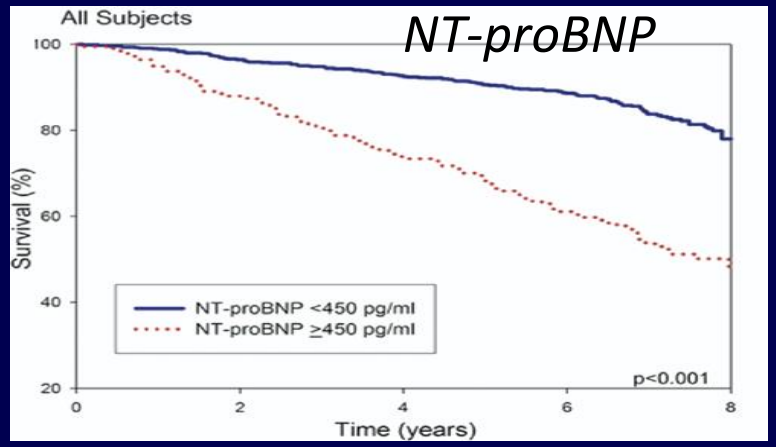
Biomarker	Cut-point (dichotomous)	Odds Ratio CVD Death
hs-CRP	3 ng/mL	1.73
NT-proBNP	>450 pg/mL <50years >900 pg/mL >50 yrs	5.67
cTnI	10.1 pg/mL	8.53

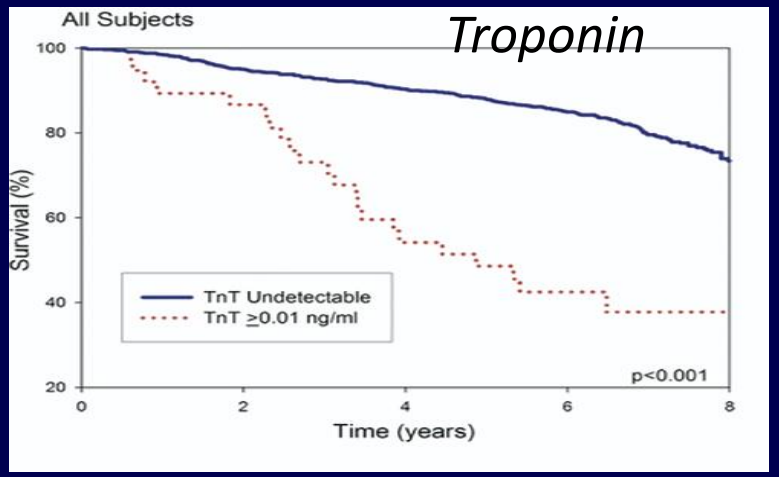
Odds ratio calculations were performed in a model adjusted for CVD risk factors, including: age, sex, race, education, study year, smoking, systolic BP, total cholesterol, abdominal obesity, diabetes, previous hospitalization for CVD events, and other biomarkers (ST2, hs-CRP, NTproBNP and hs-cTnI).

Conclusion: Elevated cTnI is an independent, predictive marker of cardiovascular death in an asymptomatic population.

Apple et al. *Clin Chem.* 2012; 58: 930-935 (Level of evidence: 2)

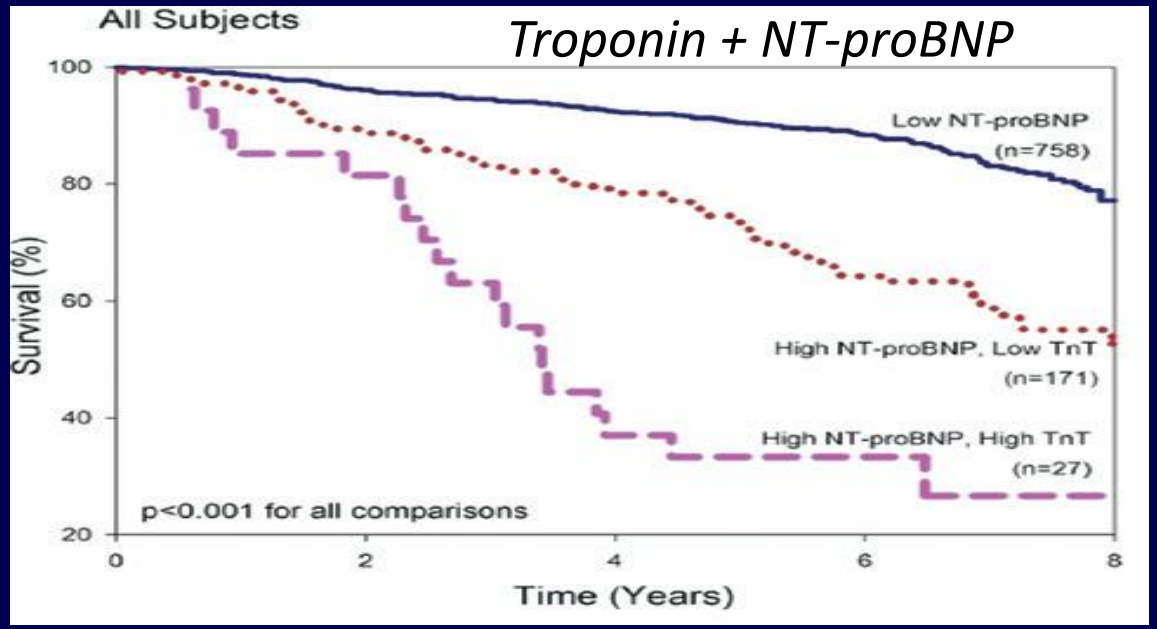
NT-proBNP and Troponin Are Synergistic





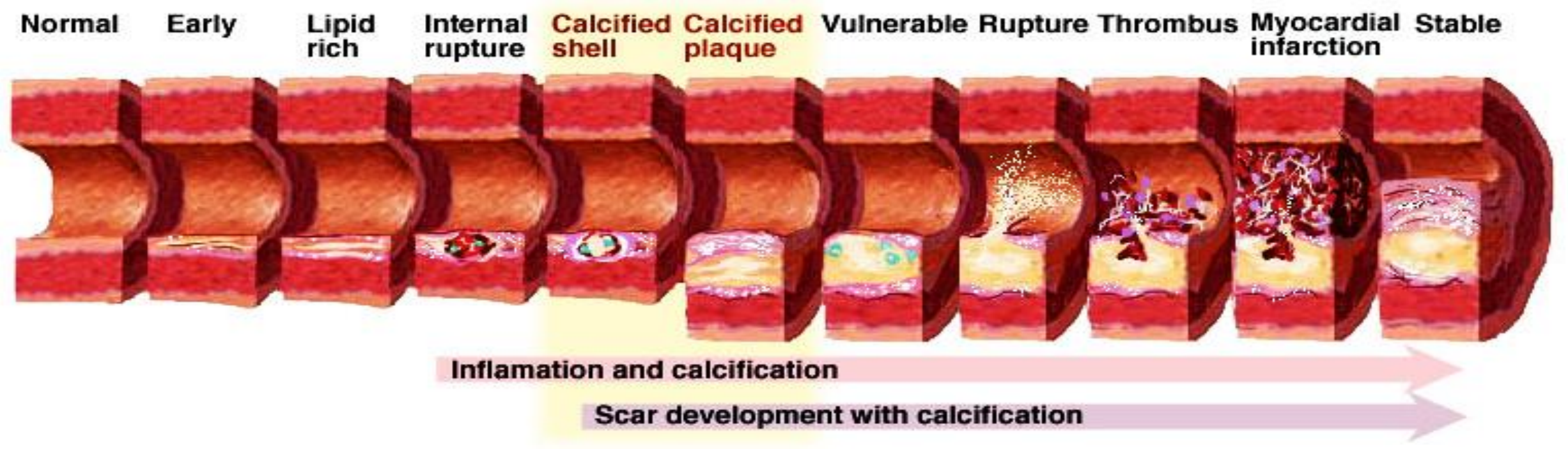
Ranch Bernardo study design

- ✓ 950 subjects
- ✓ One blood sample taken 1998
- ✓ Subjects followed through 2006 for CV-related survival
  Stored blood tested for biomarkers



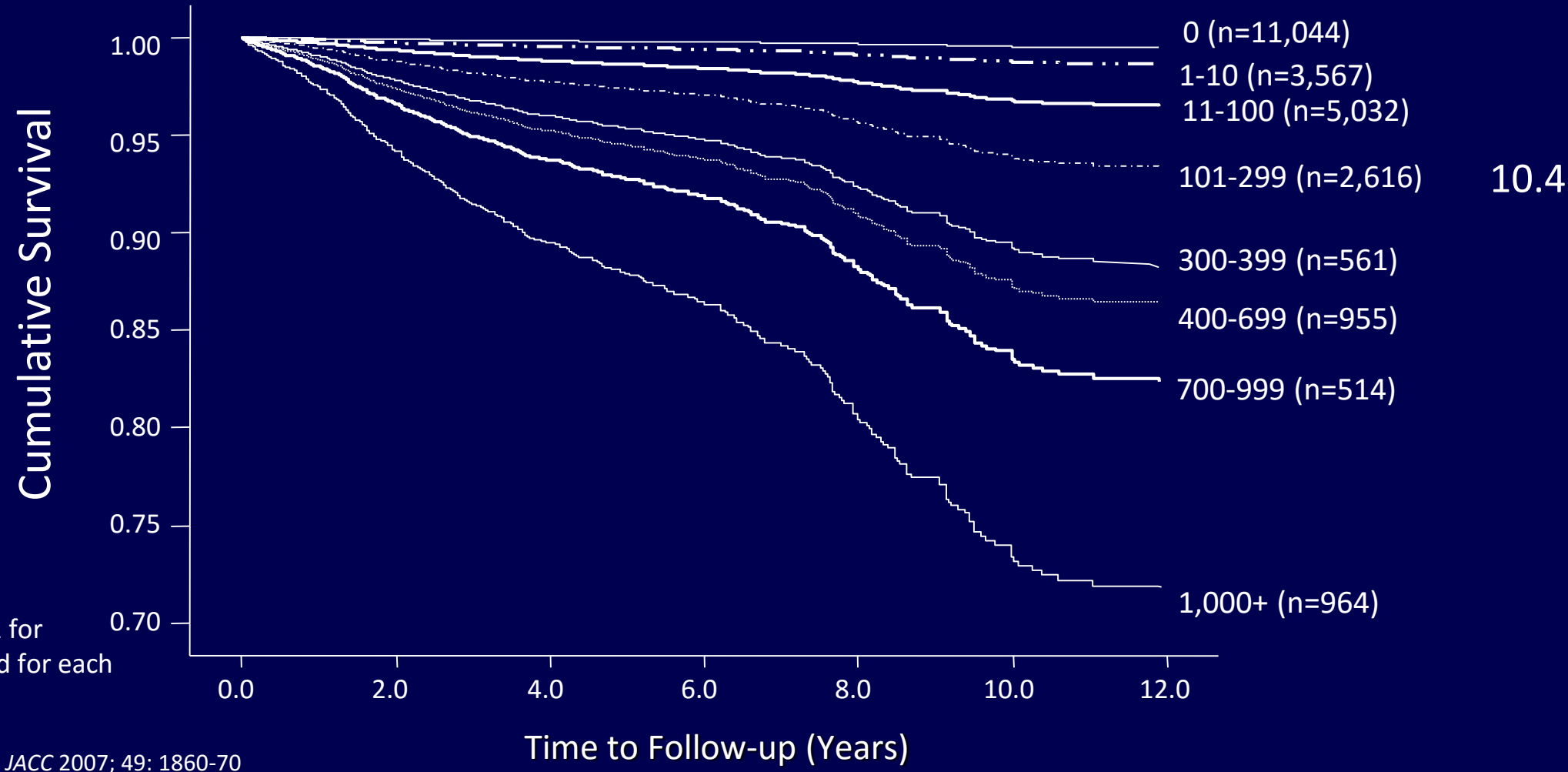
Daniels et al. *J Am Coll Cardiol* 2008;52:450-459.

Historical Development of a Coronary Artery Plaque



This process, in various stages of development, can be seen in many areas of the coronary artery system, consistent with the “diffuse” nature of coronary artery disease.

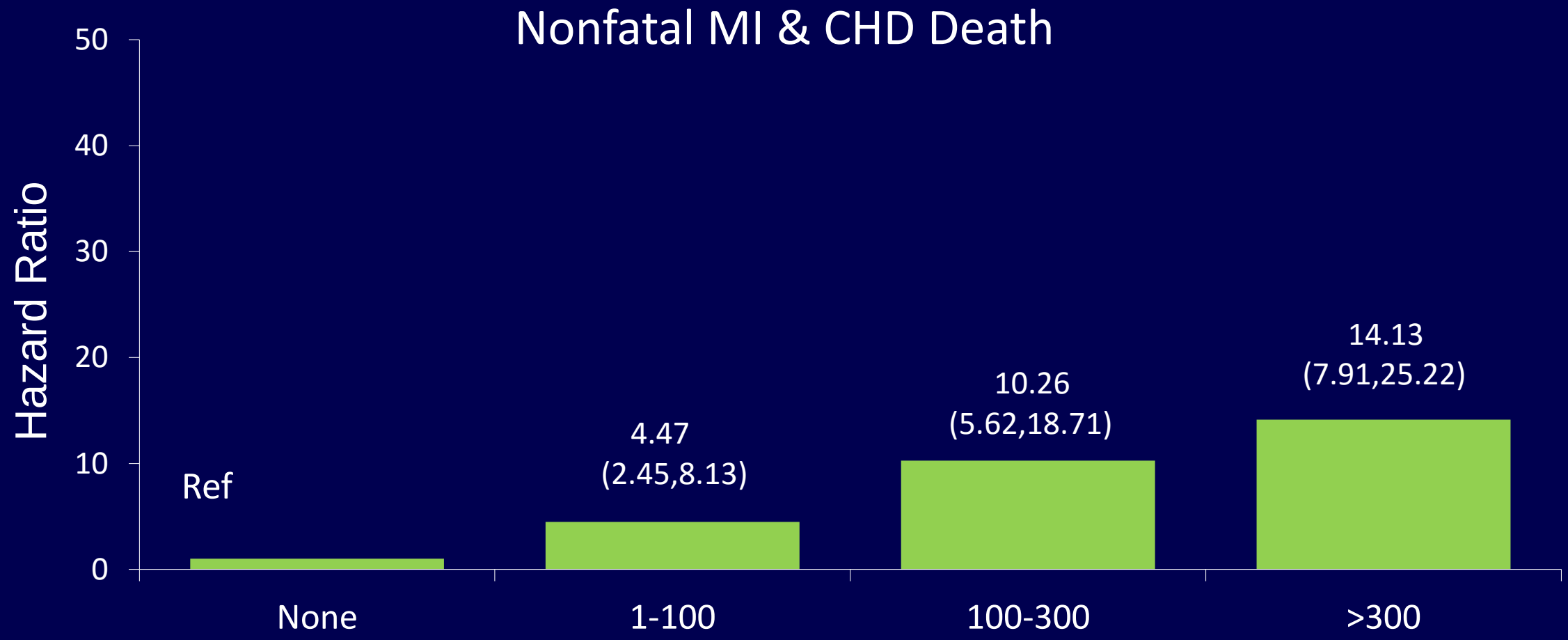
All-Cause Mortality and CAC Scores: Long-Term Prognosis in 25,253 Patients



χ^2=1363, p<0.0001 for variable overall and for each category subset.

Budoff, et al. *JACC* 2007; 49: 1860-70

MESA Study – 6,814 Patients: 3.5-year Follow-up



Fully adjusted – Detrano et al, *NEJM* 2008;358:1336-1345.

Guidelines for Asymptomatic Risk Assessment

2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance

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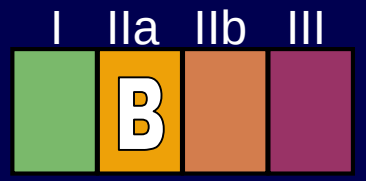
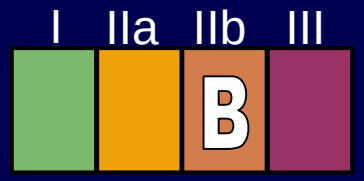
Greenland et al. *Circulation*. 2010;122:e584-636.

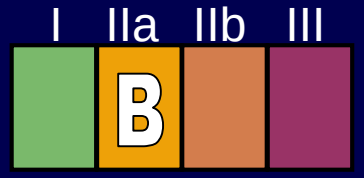
Recommendations for Calcium-Scoring Methods



Measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-year risk).



Measurement of CAC may be reasonable for cardiovascular risk assessment persons at low to intermediate risk (6% to 10% 10-year risk).



In asymptomatic adults with diabetes, 40 years of age and older, measurement of CAC is reasonable for cardiovascular risk assessment.

Greenland et al. *Circulation*. 2010;122:e584-636.

2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk

- If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of 1 or more of the following— family history, hs-CRP, CAC score, or ABI—may be considered to inform treatment decisionmaking.

"Assessing CAC is likely to be the most useful of the current approaches to improving risk assessment among individuals found to be at intermediate risk after formal risk assessment."

Goff et al. *J Am Coll Cardiol*. 2014;63(25 Pt B):2935-2959.

Prevention Guidelines AND Blood Cholesterol Guidelines 2013

High Risk: CAC score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity

Low Risk : <300 Agatston units and <75 percentile for age, sex, and ethnicity

Goff et al. *J Am Coll Cardiol*. 2014;63(25 Pt B):2935-2959; Stone et al. *J Am Coll Cardiol*. 2014;63(25 Pt B): 2889-2934.

Net Reclassification Improvement (NRI)

MESA: Intermediate Risk (n=1,330)

	NRI
FRS + Brachial FMD	0.024
FRS + ABI	0.036
FRS + Hs-CRP	0.079
FRS + Family History	0.160
FRS + C-IMT	0.102
FRS + CAC	**0.659**

FRS: Framingham Risk Score

NRI: Improved Detection of Low & High Risk Individuals

=[*Prob* (being correctly reclassified to higher-risk category/event)
− *Prob* (being incorrectly reclassified to lower-risk category/event)
+[*Prob* (being correctly reclassified to lower-risk category/nonevent)
− *Prob* (being incorrectly classified to higher-risk category/nonevent)

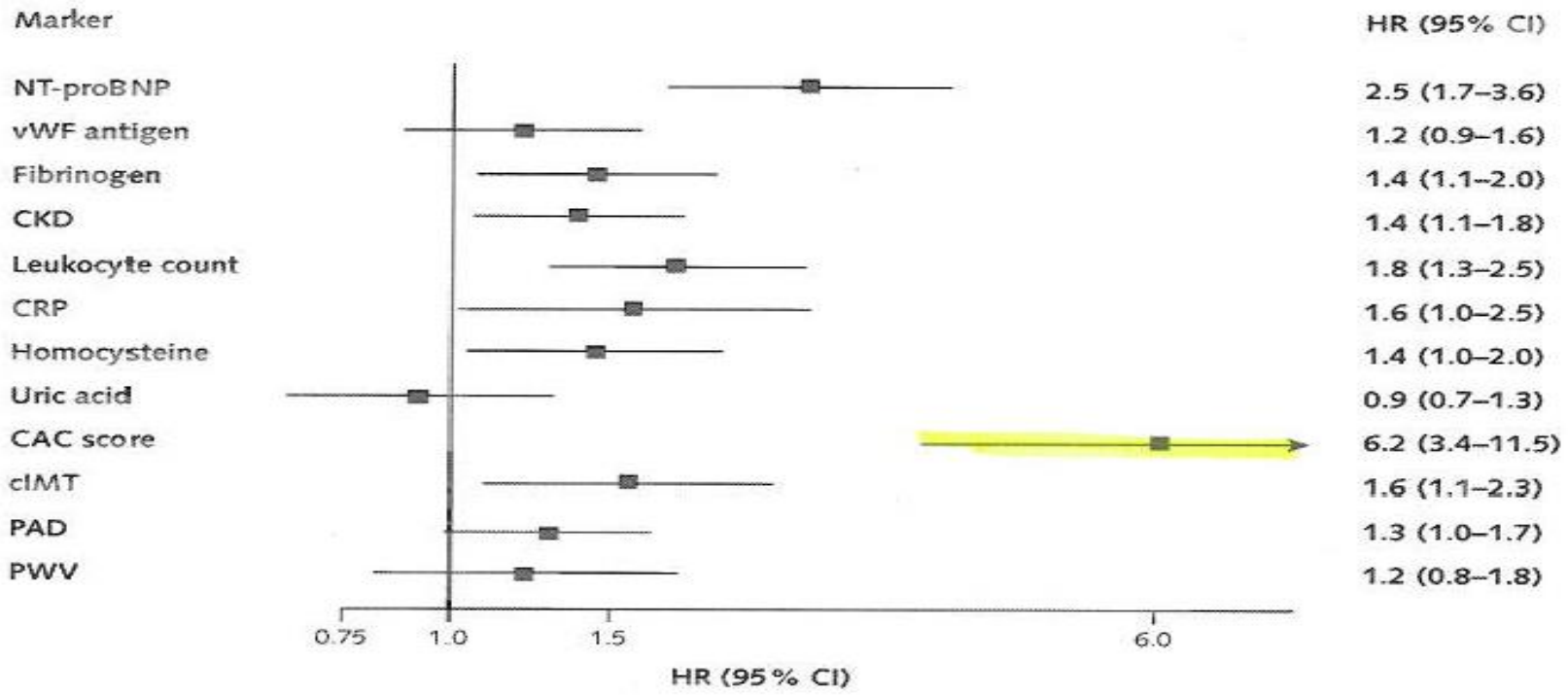
NRI: FRS Model vs. FRS + Screening Test

Models estimating 7-y MI, CHD death, resuscitated cardiac arrest, or angina followed by PCI/CABS

Source: Yeboah JAMA 2012;308:788-95.; Pencina Clin Chem Lab Med 2010;48:1703-11.

Rotterdam Study

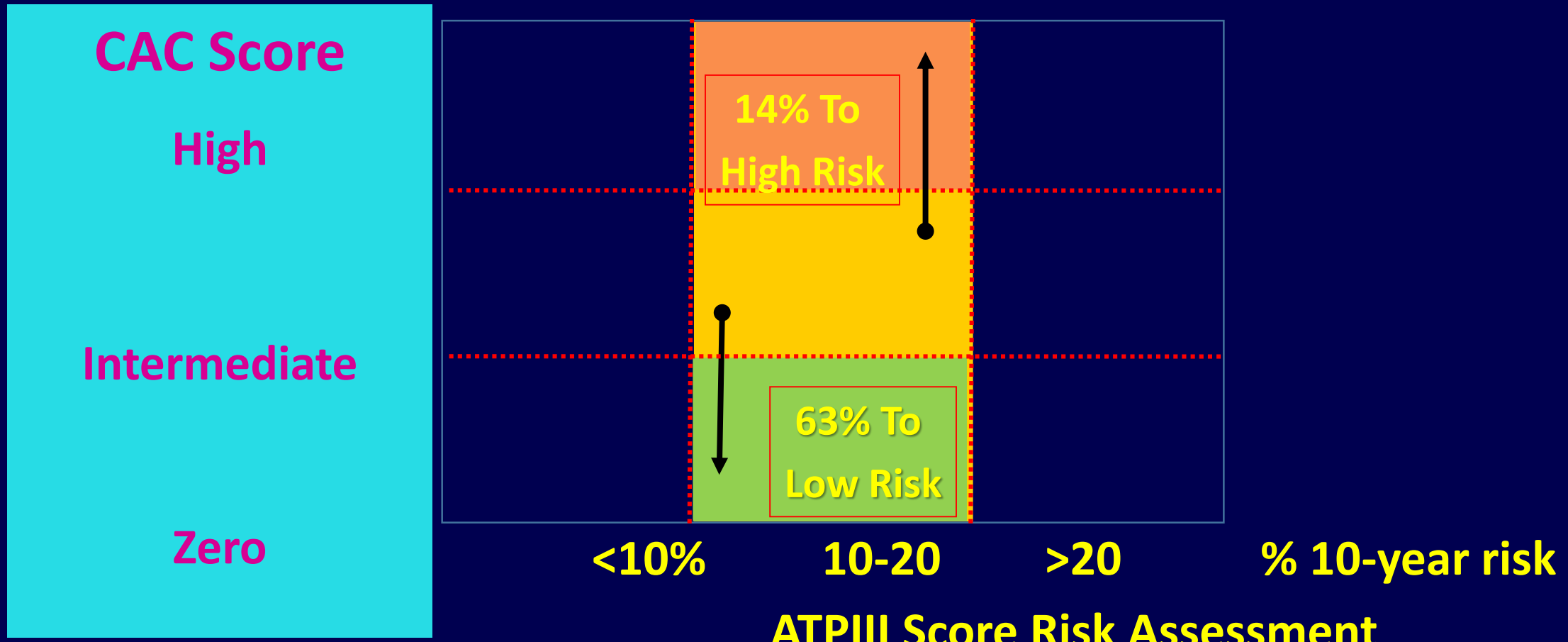
Figure. **Multivariable-adjusted HR for incident coronary heart disease.**



CAC = coronary artery calcium; cIMT = carotid intima–media thickness; CKD = chronic kidney disease; CRP = C-reactive protein; HR = hazard ratio; NT-proBNP = *N*-terminal fragment of prohormone B-type natriuretic peptide; PAD = peripheral arterial disease; PWV = pulse wave velocity; vWF = von Willebrand factor.

Kavousi et al. *Ann Intern Med.* 2012;156:438-44.

Reclassification of ATP III Risk Categories Using CAC



Scheme according to: Wilson et al. *JACC* 2003;41:1898 – 1906 with HNR data

EISNER Randomized Controlled Trial

2137 middle-aged + risk factors without CVD
45-79y without CAD/CVD followed 4 years

No Scan

- Clinical evaluation
- Questionnaire
- Risk factor consultation

Scan

- Clinical evaluation
- Questionnaire
- Risk factor consultation
- CAC scan
- Scan consultation

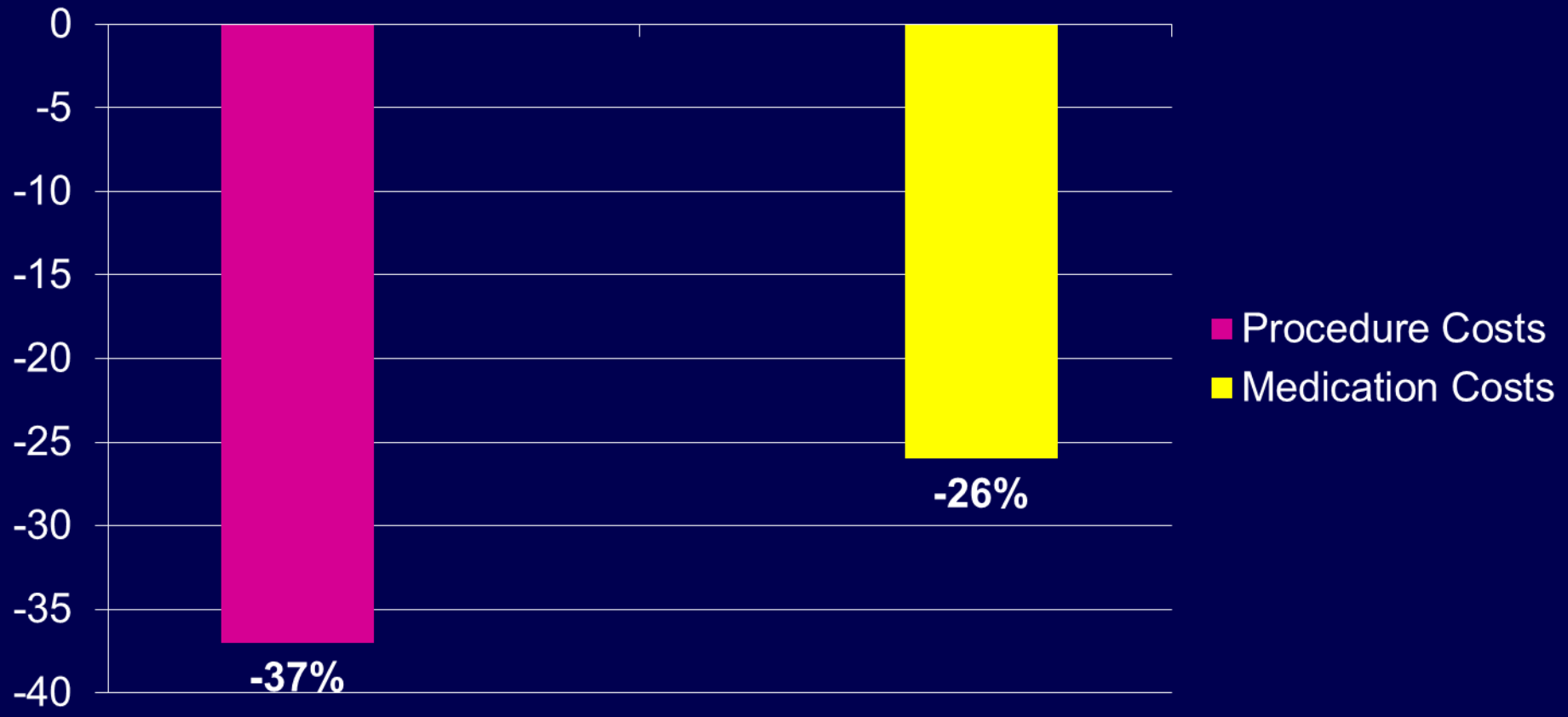
Rozanski. Berman. *JACC* 2011;57:1622.

Does CAC Scanning Improve Outcomes?

Parameters	No SCAN	CACS	P
Change in LDL-C	-11 mg/dL	-29 mg/dL	<0.001
Change in SBP	-5 mm Hg	-9 mm Hg	<0.001
Exercise	36%	47%	0.03
New Lipid Rx	19%	65%	<0.001
New BP Rx	18%	46%	<0.001
New ASA Rx	7%	21%	<0.001
Lipid Adherence	80%	88%	0.04

Rozanski. Berman. EISNER. *JACC* 2011;57:1622. CACS 0 = 631. CACS>400 = 109.

EISNER Study – Costs Compared to No Scan Group



P<0.005 for both measures

Rozanski et al. *JACC* 2011;57:1622-1632.

St Francis Randomized Trial

Randomized Double-Blind Placebo-Controlled Trial of Atorvastatin in the Prevention of Cardiovascular Events Among Individuals With Elevated CAC Score

- **Mean duration of treatment was 4.3 years**
- **Treatment with atorvastatin reduced clinical endpoints by 30% (6.9% vs. 9.9%) and MI/Death by 44% (NNT 30)**
- **Event rates were more significantly reduced in participants with baseline calcium score >400 (8.7% vs. 15.0%, p=0.046 [42% reduction]). (NNT 16)**

Arad et al. *J Am Coll Cardiol* 2005:46:166-172.

Coronary Artery Scanning

- SEVERE CALCIFICATION

A PICTURE IS WORTH 1,000 WORDS

Improving Adherence

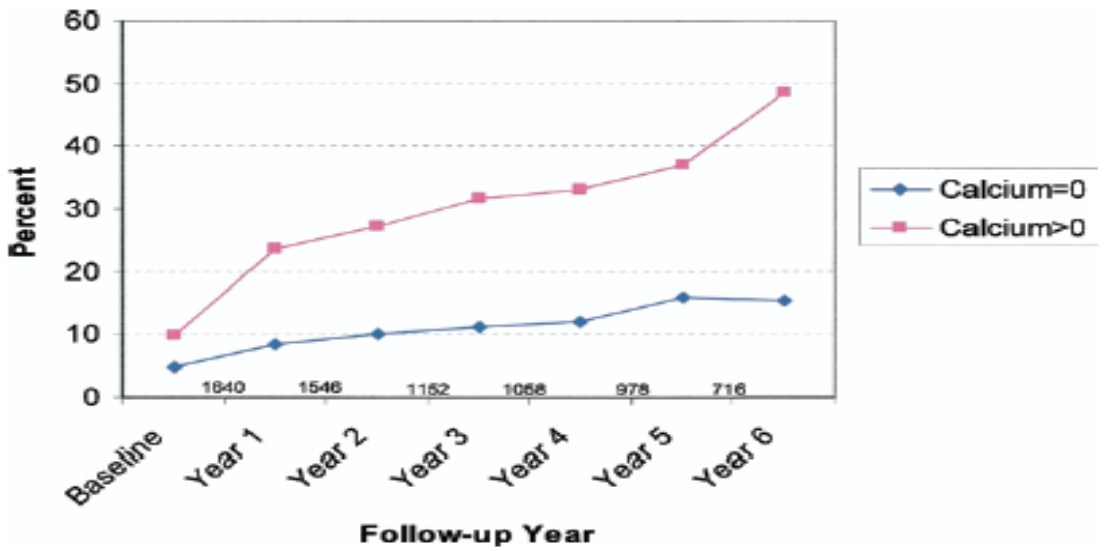


Figure 1 **Incidence of Statin Use During 6-Year Actuarial Follow-Up in the PACC Project Cohort**

Men only; n = 1,640. Ever-use of a statin was noted in 23% of participants, including 48.5% of those with coronary artery calcium and 15.5% of those without coronary artery calcium ($p < 0.001$), which remained significant after controlling for National Cholesterol Education Program risk variables (odds ratio 3.53; 95% confidence interval 2.66 to 4.69).

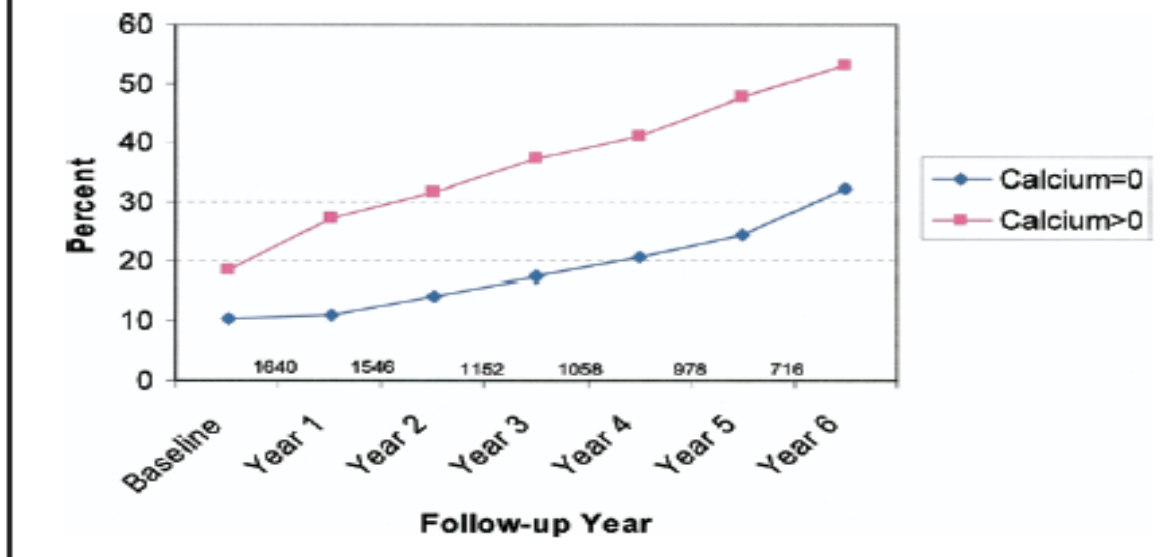


Figure 2 **Incidence of Aspirin Use During 6-Year Actuarial Follow-Up in the PACC Project Cohort**

Men only; n = 1,640. Ever-use of aspirin was noted in 31.2% of participants, including 51.5% of those with coronary artery calcium versus 25.3% of those without coronary artery calcium ($p < 0.001$), which remained significant after controlling for National Cholesterol Education Program risk variables (odds ratio 3.05; 95% confidence interval 2.30 to 4.05).

Taylor et al. *JACC* 2008;51:1337-1341.

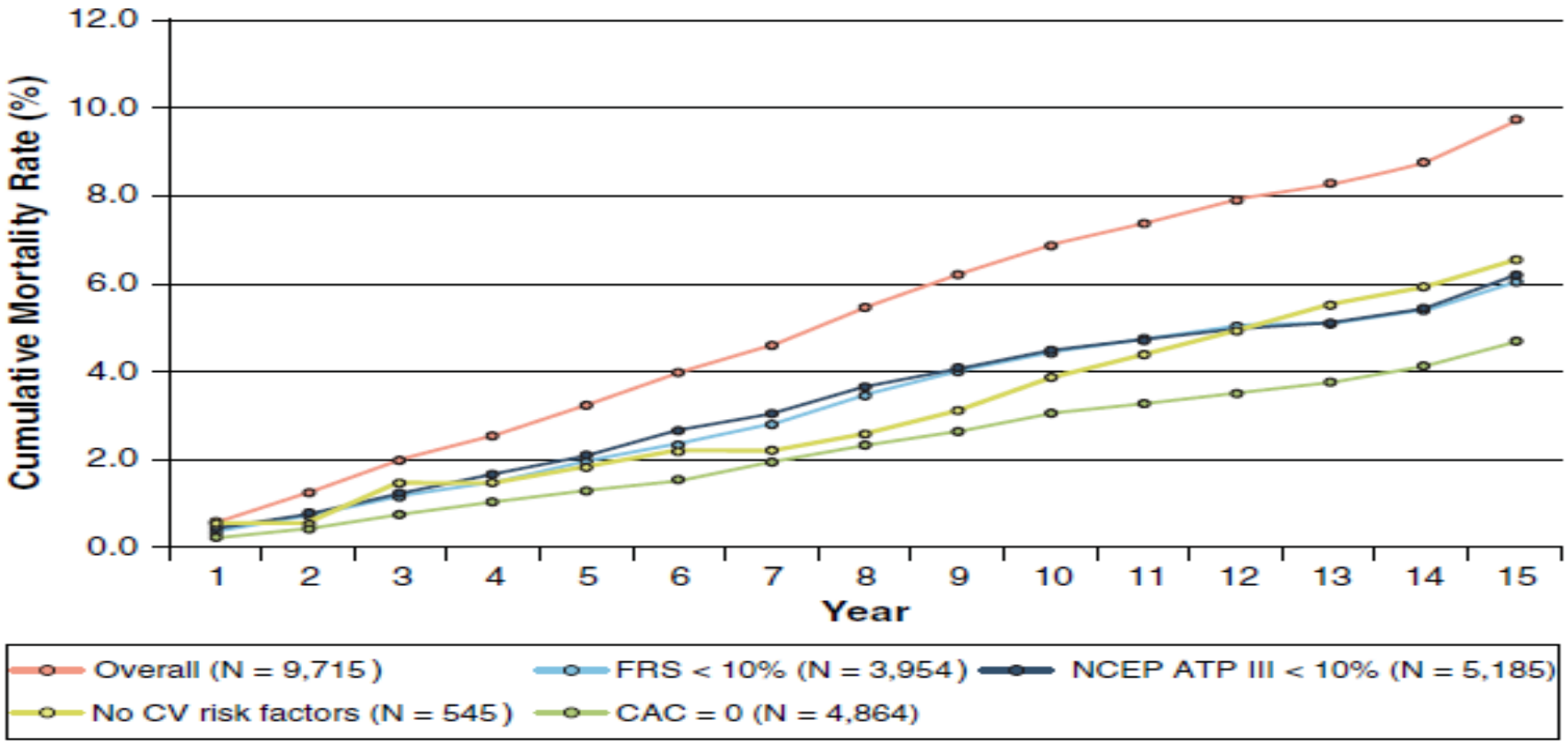
Very High NNT in Almost 50% of Individuals Meeting JUPITER Criteria in MESA

	Percent of Patients in MESA	CHD event rate at 5.8 years	Hazard Ratio (95% CI)	5-year NNT for CHD
JUPITER population				
▪ CAC=0	**47%**	0.48%	**1 (ref)**	549
▪ CAC 1-100	**28%**	2.79%	**4.91**	94
▪ CAC >100	**25%**	10.76%	**27.8**	24

Blaha et al. *Lancet.* 2011;378:684-92.

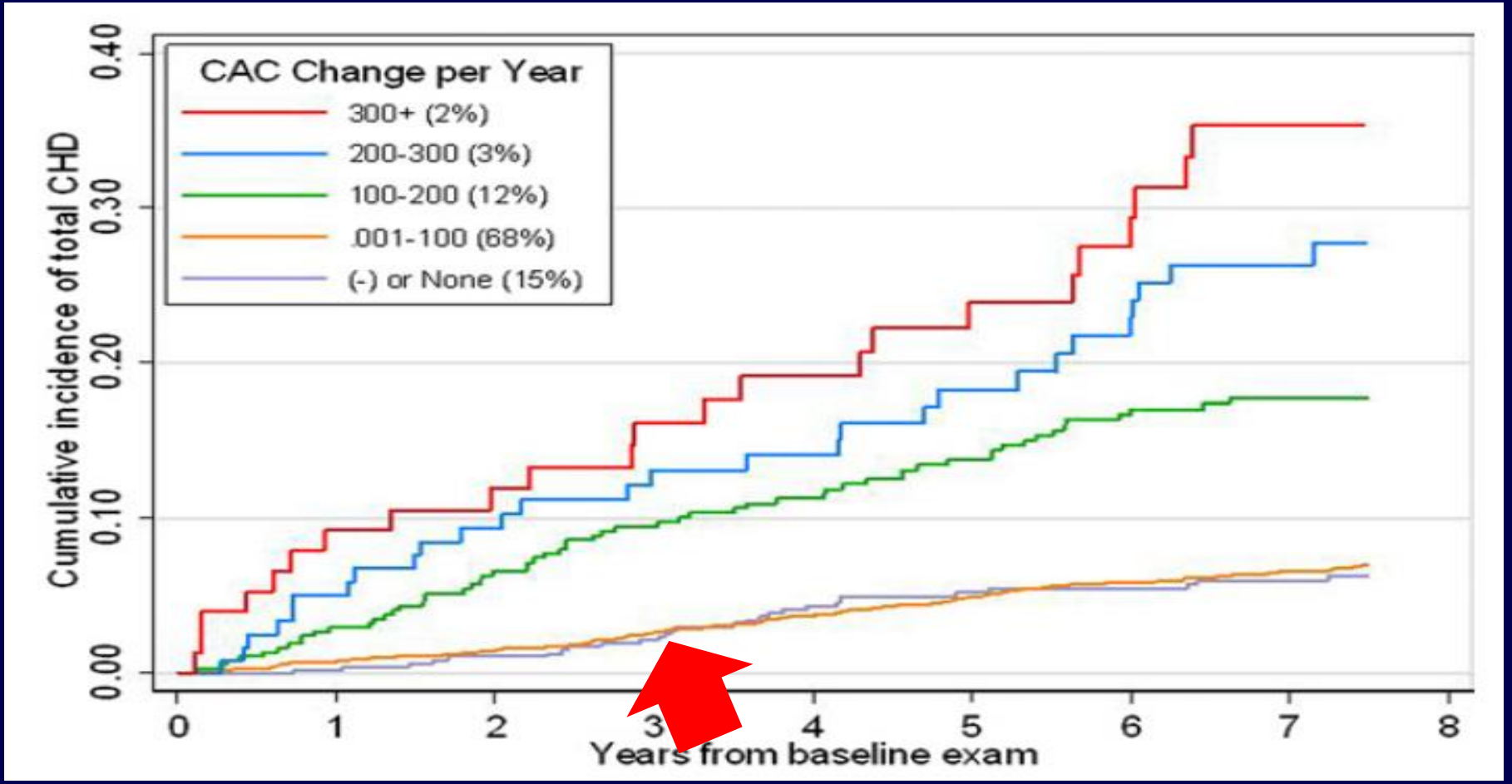
15-Year Warranty Period for Asymptomatic Individuals Without Coronary Artery Calcium

FIGURE 1 The 15-Year Cumulative Mortality Rate for the Study Period



Valenti et al *JACC Cardiovasc Imaging*. 2015;8:900-909.

Progression: MESA



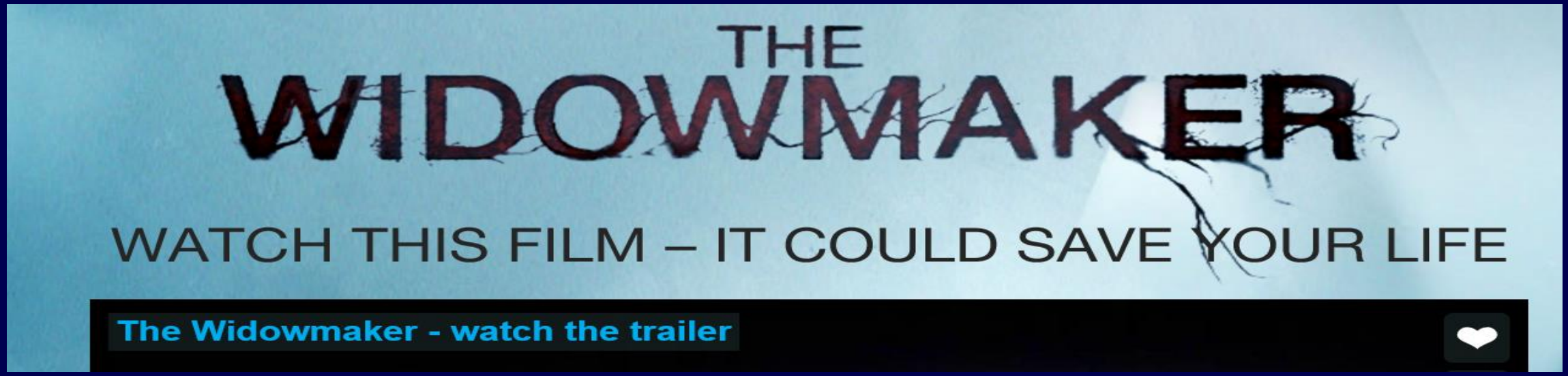
Budoff et al. *J Am Coll Cardiol.* 2013;61:1231-1239.

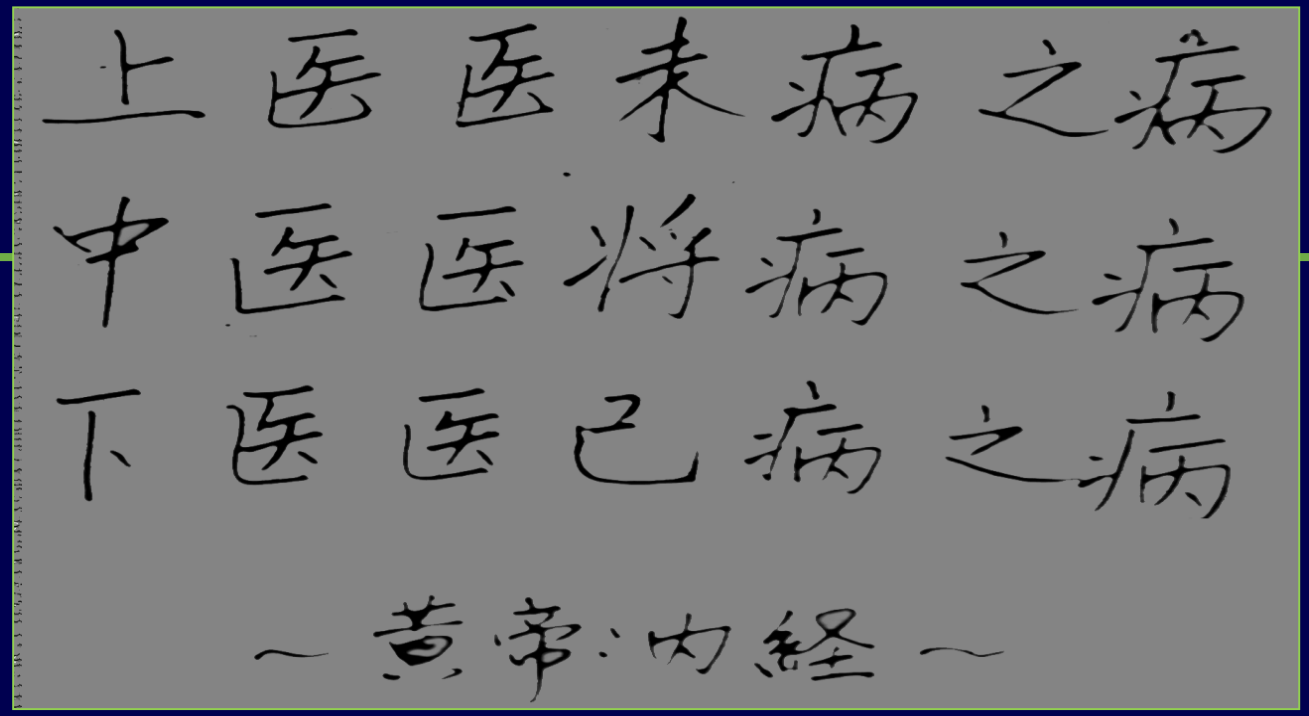
CAC Improves Statin Delivery

- Better Risk Stratification
  - matching risk with intensity of therapy
- 50% (or MORE) will have zero scores*
  - Significant ASCVD risk heterogeneity exists among those eligible for statins according to the new guidelines. The absence of CAC reclassifies approximately one-half of candidates as not eligible for statin therapy.
- IMPROVE COMPLIANCE
  - We all recognize the new guidelines (treat most) will lead to low compliance in asymptomatics

*Nasir et al. *J Am Coll Cardiol*. 2015;66:1657-1668.

Widowmakerthemovie.com





Superior doctors prevent the disease.
Mediocre doctors treat the disease
before evident.
Inferior doctors treat the full-blown disease.
--Huang Dee: Nai-Ching
(2600 BC First Chinese Medical Text)

Coronary Calcium

Cardiometabolic Health Congress - March 4-5 - San Francisco, CA