

Electron Beam CT Coronary Calcium as a Surrogate for Coronary Atherosclerosis

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Cardiovascular Biomarkers

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Subclinical Atherosclerosis

- Atherosclerotic changes start at a young age
 - Autopsy results on young soldiers identified advanced atherosclerosis
 - Pathobiological Determinants of Atherosclerosis in Youth and Bogalusa Heart Study reported association between traditional risk factors and early atherosclerosis
- Need for a method that identifies presence and extent of atherosclerosis in asymptomatic individuals

Useful Characteristics of Biomarker

- Should reflect the pathophysiology of atherosclerosis
- Should predict clinical outcome
- Should reflect modification of risk by interventions e.g. lipid lowering
- If it is to be used in asymptomatic individuals, i.e. as a screening tool, it must accurately detect disease, should carry low risk, be fast and be inexpensive

Association between amount of Calcification and Atherosclerosis

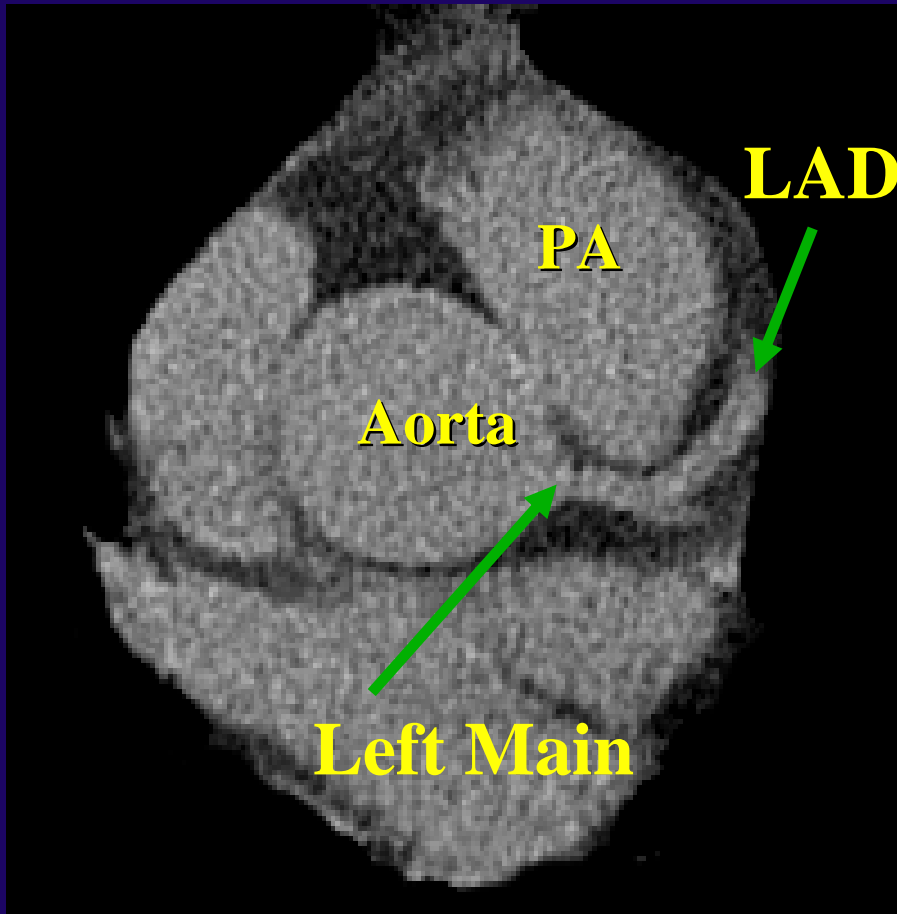
- Calcium is absent in normal vessel wall
- Calcification has been found in small amounts in early lesions occurring in 2nd and 3rd decade of life
- Calcification is found more frequently in advanced lesions
- Strong relationship between coronary calcium score (CAC) and severity of angiographic disease

Electron Beam CT

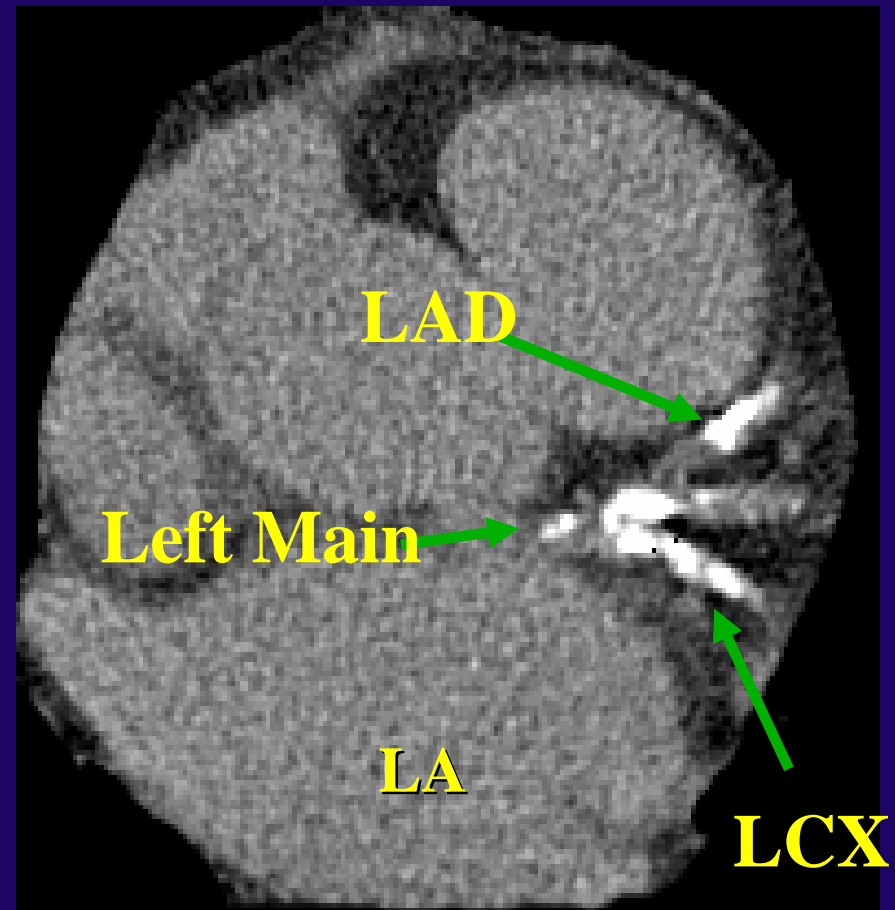
- Cardiovascular computed tomography scanner with subsecond imaging times (100 msec)
- Thirty to forty 3-6 mm thick adjacent transverse slices image the entire coronary tree
- Scans usually obtained during 1-2 breath holding sequences and are triggered by the ECG at 80% of RR interval to obtain end-diastolic image
- Detects and quantifies coronary artery calcium, defined as pixels > 130 Hounsfield units
- Quantification of coronary calcium most often uses technique of Agatson with a score derived for the sum of left main, LAD, LCx and RCA calcium score

Non-Contrast EBCT Scans at the Base of the Heart

No Calcification

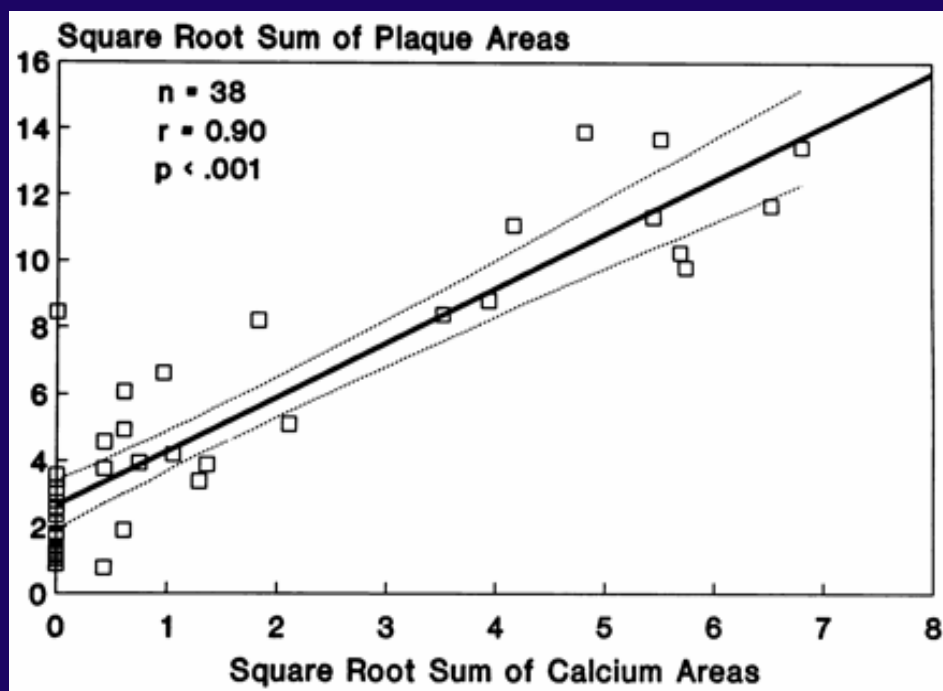


Severe Calcification



Coronary Artery Calcium Score and Angiographic Disease

Correlation between EBCT CAC and
histopathologic atherosclerotic plaque area



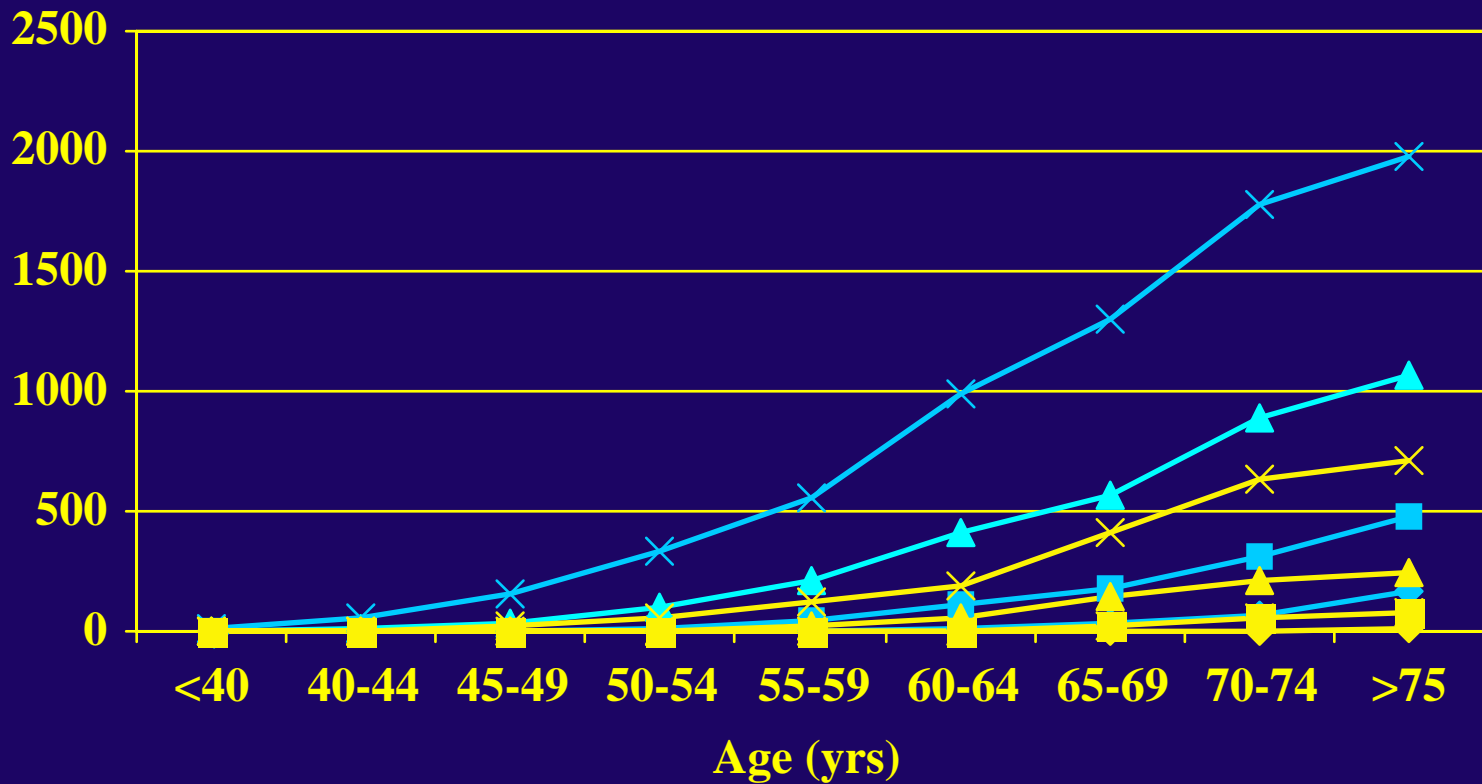
- Relationship between CAC and coronary luminal stenosis by angiogram is non linear
- Relations of CAC and probability of plaque rupture is unknown

Rumberger et al: Circulation 1995;92:2157

Identification of Asymptomatic Atherosclerosis

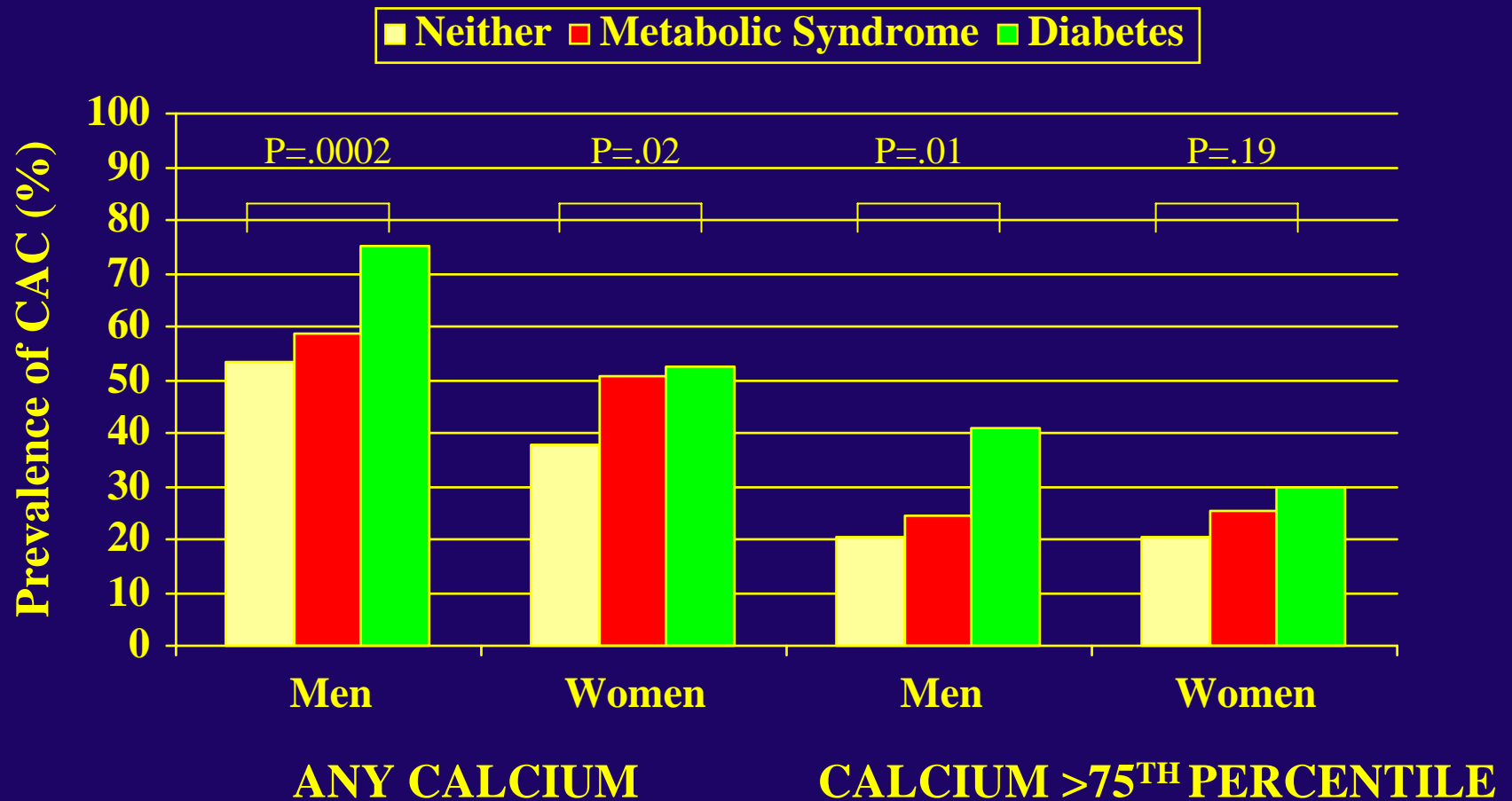
- As many as half of initial coronary events occur in asymptomatic people
- Treatment of risk factors has potential to reduce CHD events as primary prevention
- CAC increases with age and differs by gender and ethnic group

Coronary Calcium Distribution in Asymptomatic Men and Women (25th, 50th, 75th and 90th percentiles)



Prevalence of CAC by Disease and Gender

Wong et al, JACC 2003;41:1547



Ethnic Differences in CAC

- Several studies have shown that CAC is lower in African American US populations than whites
- Less is known about other ethnic groups
- The Multi-Ethnic Study of Atherosclerosis (MESA) is an NHBLI funded prospective cohort study of 6,800 men and women aged 45-84 with no CVD recruited from 6 communities in the US

Prevalence of coronary calcium, by ethnicity and gender, MESA

- Significant differences were present in prevalence of CAC in the ethnic groups in MESA
 - White men had the highest prevalence of 70% compared to 51% in AA, 56% in Hispanic and 50% Chinese
 - Prevalence in white women was 46%, 42% in Chinese, 36% in AA and 34% in Hispanic women
- After adjustment for significant risk factors, the prevalence ratio for CAC compared to white men was 0.74 for AA, 0.88 for Hispanics and 0.91 for Chinese men

Factors independently associated with presence of CAC

	<u>Men</u>	<u>Women</u>
Age, yrs	1.10 (1.08-1.11)	1.11 (1.10-1.12)
Waist, cm	1.01 (1.004-1.02)	1.01 (1.001-1.01)
SBP, mmHg	1.01 (1.002-1.01)	1.005 (1.003-1.01)
LDL-C, mg/dl	1.01 (1.002-1.01)	1.005 (1.003-1.01)
Smoking	1.50 (1.16-1.94)	1.93 (1.48-2.51)
Diabetes	1.30 (1.01-1.66)	1.26 (1.12-1.42)
Income >50K	1.35 (1.10-1.66)	1.16 (0.95-1.42)
AUC	0.77	0.78

Adjusted for ethnicity; factors retained after backward stepwise regression

Prediction of Cardiac Events by CAC in Asymptomatic Subjects

- Arad et al 1996, 1173 subjects who were self referred and followed for 19 months. There were 26 events in 18 patients (majority were revascularization). CAC >160 associated with OR 23 for any cardiac event, and was only 2 for death or MI (NS). With longer follow up of 3.6 yr and 18 additional cardiac events the OR increased to 22 for death or MI.

Correlation between CAC and Traditional Tests of CAD

- EBCT is not superior to other available diagnostic procedures (exercise or pharmacologic imaging testing) to diagnose angiographic coronary disease
- Coronary angiography is considered a “gold standard” but has the limitations of identifying only luminal encroachment of coronary plaque

Does CAC add Prognostic Information to Angiography?

- Keelan et al Circulation 2001;104:412
- 317 patients underwent both coronary angiography and EBCT. Follow-up was obtained in 288 (91%) subjects after 6.9 yrs
- Univariate analysis showed both CAC and angiographic variables were predictive of coronary death or nonfatal MI

Unadjusted RR of Cardiac Death/nonfatal MI

Risk Factor	Unadjusted RR	P-value
Age	2.15 (1.35-3.45)	0.001
Presence of CAC	2.83 (0.38-21.05)	0.310
Log (CAC score + 1)	2.44 (1.35-4.40)	0.003
CAC \geq 100	3.2 (1.17-8.71)	0.023
Log angiographic burden	2.55 (1.19-5.45)	0.016
No vessels \geq 50% stenosis	1.58 (1.11-2.23)	0.010

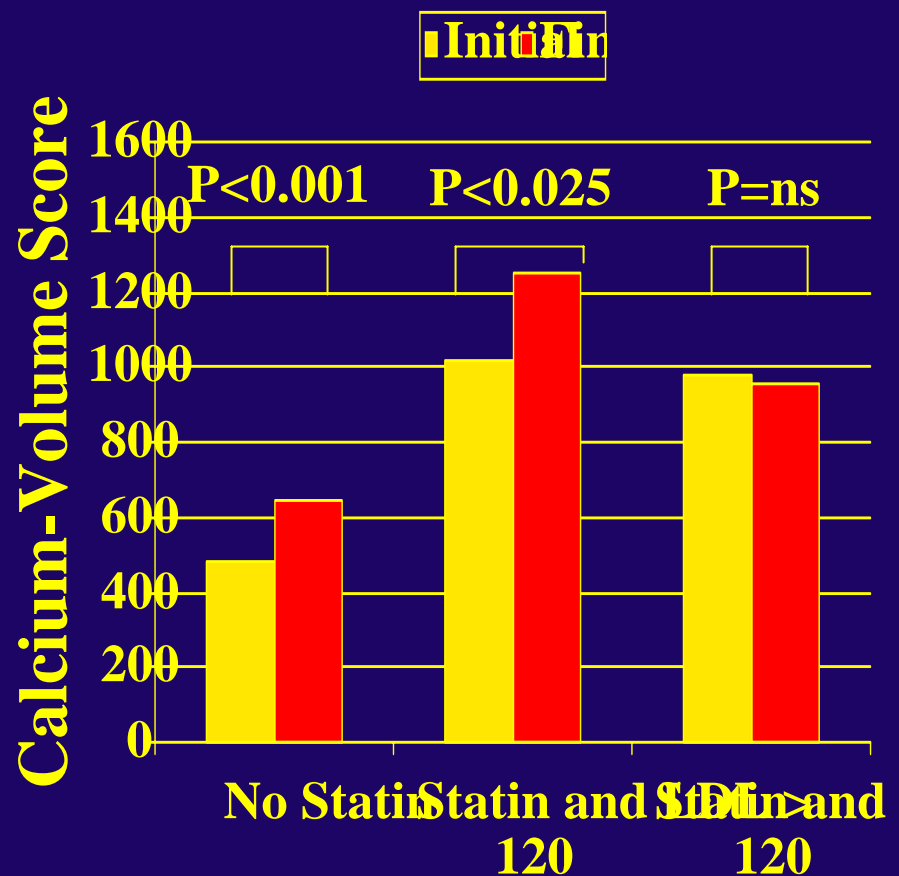
Stepwise Multivariate Regression for Cardiac Death/Nonfatal MI including Risk Factors, CAD history, CAC and Angiographic Data

	RR* (95% CI)	P-value
Age	1.72 (1.01-2.91)	0.043
Log (CAC score + 1)	1.88 (1.02-3.48)	0.044

* For 1-SD increase in continuous variable

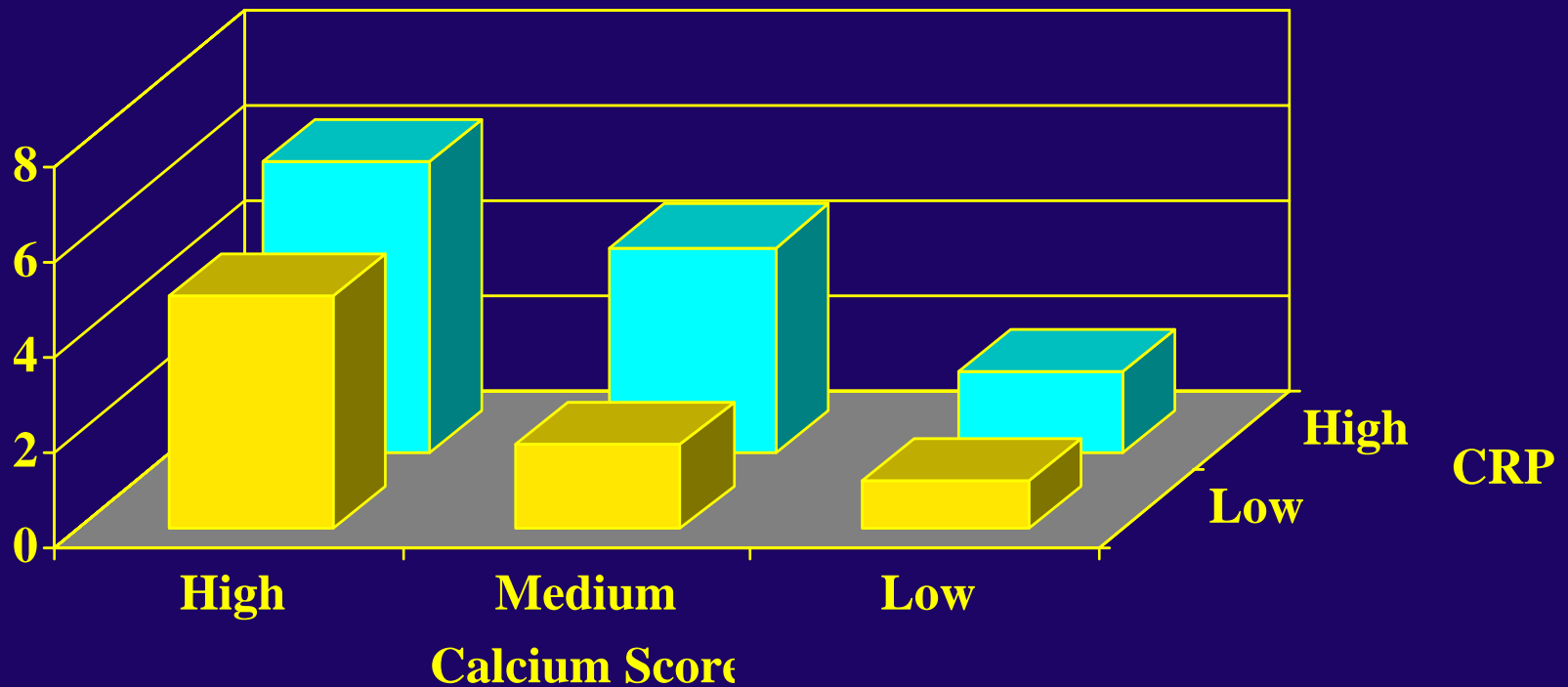
Assessment of Effect of Statins

- Retrospective study of 149 pts with no known CAD and 2 scans 12 mo apart
- Compared subjects not on statin, those with final LDL of ≥ 120 mg/dl and those with final LDL of <120 mg/dl



RR of nonfatal MI or coronary death associated with ≥ 75 th %tile CRP and with tertile of CAC score in nondiabetics

Park R et al. Circulation 2002;106:2073



No significant interaction between CAC and CRP

Special Considerations in Use of EBCT in Research

- Reproducibility: improved by newer scanning protocols, volume scores, timing of image acquisition
- Standardized protocol and a central reading laboratory are needed if several clinical sites involved

Coronary Calcium Score as Surrogate Of Atherosclerotic Burden

- CAC identifies the overall burden of atherosclerosis and is increased in the presence of established risk factors
- No published randomized clinical trial has shown that CAC will decrease with interventions that reduce atherosclerotic progression or result in regression, such as lipid lowering
- Utility of CAC score as a surrogate for atherosclerosis and the change in score as a surrogate for coronary arterial response to interventions is not clear