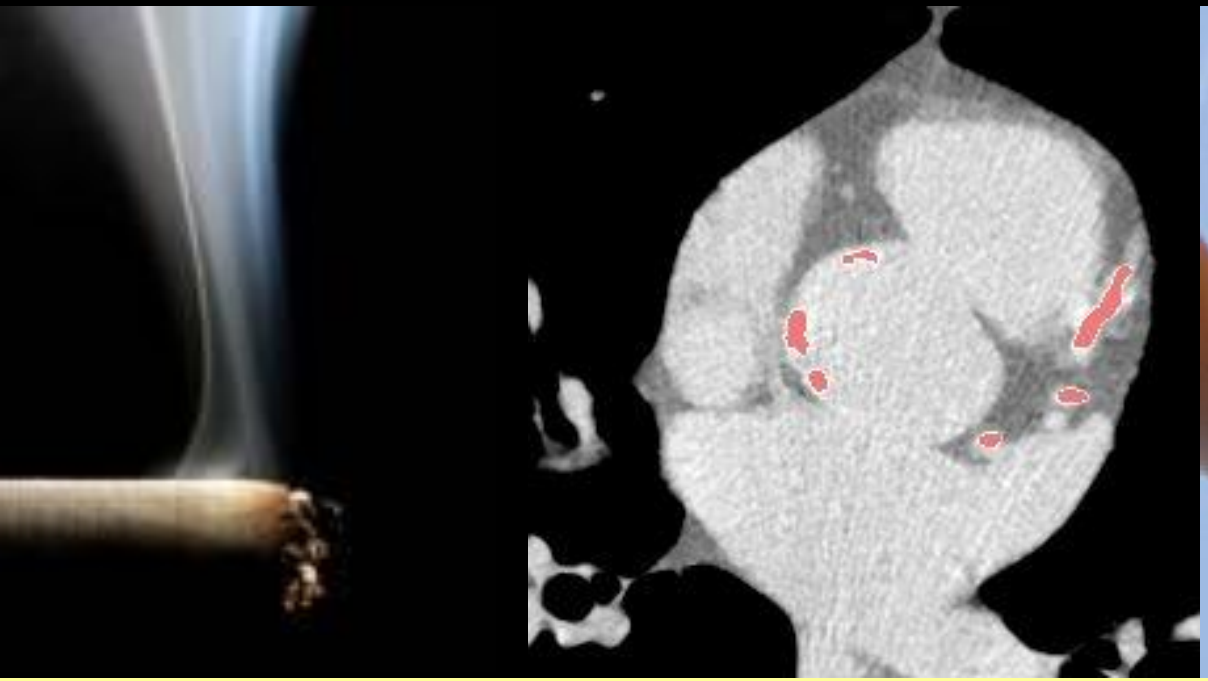
LUNG CANCER WORKSHOP

prevent cancer FOUNDATION

State of the Art Calcium Scoring



Disclosure: Philips Medical Systems Consultant

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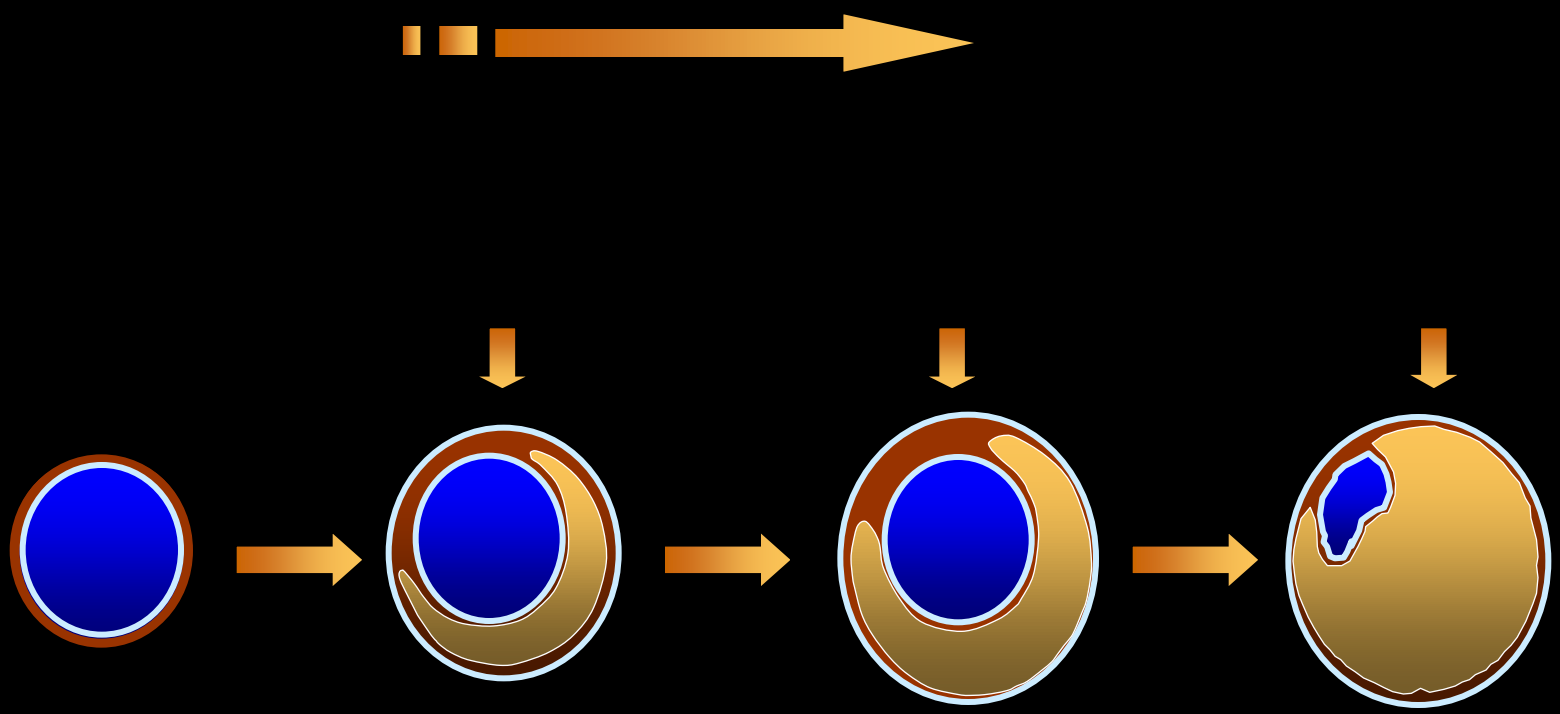
Associate Director of Cardiovascular Imaging
Professor of Medicine, Mount Sinai School of Medicine

Coronary Arterial Remodeling



Examples of Coronary Artery Scans

Coronary Calcium Scores as Function of Patient Age and Gender – Results of National Database

MEN (n=28,250)	**EBCT Coronary Calcium Scores in Asymptomatic Patients as a Function of Patient Age at the Time of the Examination**						
Percentiles /Age (yrs)	40-45	46-50	51-55	56-60	61-65	66-70	70+
10	0	0	0	1	1	3	3
25	0	1	2	5	12	30	***69***
50	2	3	15	54	117	166	350
75	11	36	110	229	386	538	844
90	***69***	151	346	588	933	1151	1650
WOMEN (n=14,540)							
10	0	0	0	0	0	0	0
25	0	0	0	0	0	1	***4***
50	0	0	1	1	3	25	51
75	1	2	6	22	68	148	231
90	***4***	21	61	127	208	327	698

1. Risk Prediction

Coronary artery calcium (CAC) is unequivocally the most powerful predictor of cardiac risk in the asymptomatic primary prevention population and should replace risk factor based analyses (FRS, Procam, ESC).

Prognostic Power of CAC in Asymptomatic Patients

	N	Mean Age (years)	Follow up (years)	Calcium Score Cutoff	Comparator Group for RR Calculat	Relative Risk Ratio
Arad (1)	1,173	53	3.6	CAC>160	CAC< 160	20.2
Park (2)	967	67	6.4	CAC >142.1	CAC <3.7	4.9
Raggi (3)	632	52	2.7	Top Quartile	Lowest	13
Wo						.8
Kor						0.5
Gre						.9
Sha						.4
Ara						0.7
Tay						1.8
Vliegenthart (10)	1795	71	3.3	CAC>1000	CAC<100	8.3
				CAC 400-1000	CAC<100	4.6
Budoff (11)	25,503	56	6.8	CAC>400	CAC 0	9.2
Lagoski (12)	3601	45-84	3.75	CAC>0	CAC 0	6.5
Becker (13)	1726	57.7	3.4	CAC>400	CAC 0	6.8 men 7.9 women
Detrano (14)	6814	62.2	3.8	CAC>300	CAC 0	14.1
Erbel (15)	4487	45-75	5	>75th%	<25th%	11.1 men 3.2 women

In every study, CAC has been superior to and significantly added to the area under the ROC curve for all risk factor based aalyses!

Prognostic Studies of a Zero Coronary Calcium Score

Study	Total Patients	Zero CAC Patients N (%)	F/U yrs	MI+Death %/yr (N)	All Events %/yr (N)
Prospective					
Arad	5585	1504 (26.9)	4.3 mean	not available	0.13% (8)
Becker	1726	379 (21.9)	3.4 mean	0% (0)	0.9% (12)
Detrano	6722	3409 (50.7)	3.9 median	0.06% (8)	0.11% (15)
Pooled prospective	14,303	5282 (36.9)	3.9	not available	0.17%(35)
Meta-analysis 2000-2008 Prospective and Retrospective					
Sarwar	71,595	29,132 (41.0)	4.2	not available	0.1% (154)
Retrospective All Cause Mortality 2009					
Blaha	44,052	19,898 (45.5)	5.6	not available	0.1% (104)

Summary of CAC Absolute Event Rates

CAC	FRS Risk	10 yr event rate
0	very low	1.1-1.7 %
1-100	low	2.3-5.9 %
100-400	intermediate	12.8-16.4 %
>400	high	22.5-28.6 %
>1000	very high	37 %

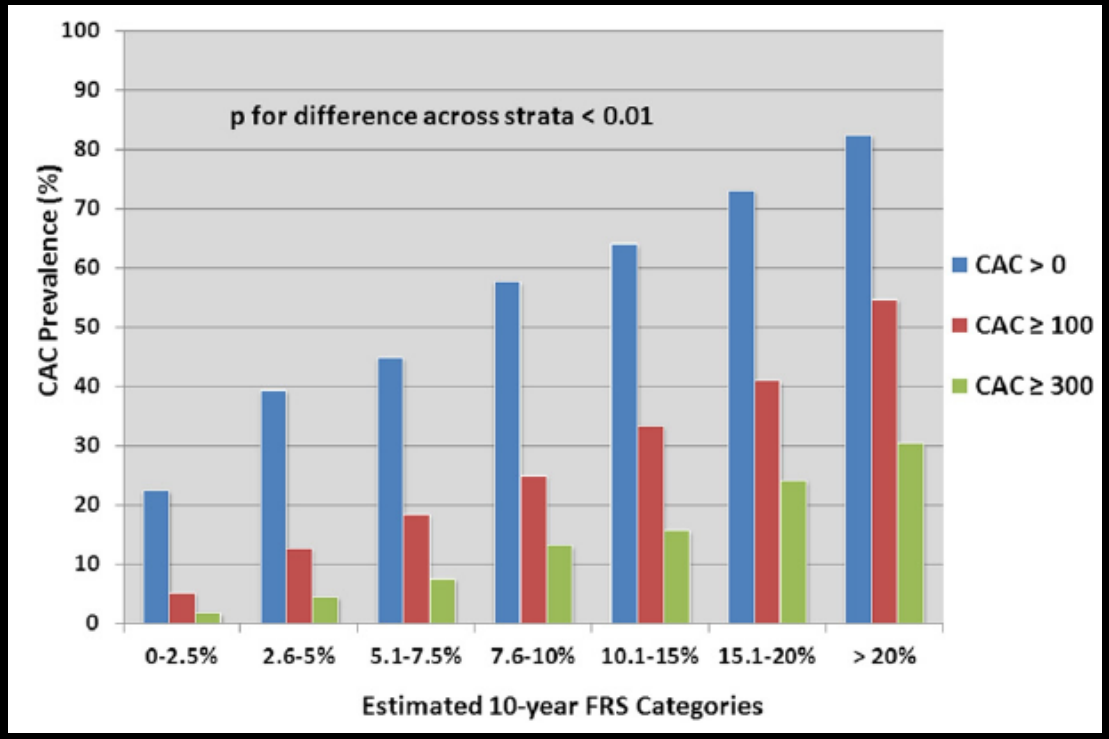
Reclassification of FRS Risk by CAC
Primary Prevention Outcome Studies

Study	% Reclassified	N	Age	Follow up (yrs)
MESA		5878	62.2	5.8
FRS 0-6%	11.6%			
FRS 6-20%	54.4%			
FRS>20%	35.8%			
NRI	25%			
Heinz Nixdorf		4487	45-75	5.0
FRS<10%	15.0%			
FRS 10-20%	65.6%			
FRS>20%	34.2%			
NRI	22.4%			
Rotterdam		2028	69.6	9.2
FRS<10%	12%			
FRS 10-20%	52%			
FRS>20%	34%			
NRI	19%			

Hecht. J Diabetes. 2012: In Press

Distribution of CAC by FRS in MESA: Potential Implications for Coronary Risk Assessment

5660 asymptomatic pts



CAC	Prevalence
>0	46.4%
>100	20.6%
>300	10.1%

FRS	CAC>300	NNS
0-2.5%	1.7%	59.7
2.6-5%	4.4%	22.7
5.1 -7.5%	7.5%	13.4
7.6-10%	13.1%	7.6
10.1-15%	15.6%	6.4
15.1-20%	24%	4.2
>20%	30%	3.3

Okwuosa. JACC 2011;57:1838–45

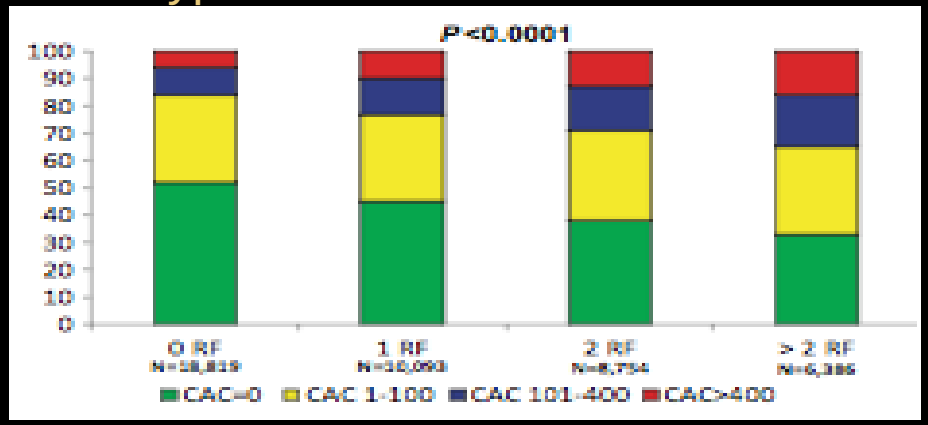
Interplay of CAC and Traditional Risk Factors for Prediction of All-Cause Mortality in Asymptomatic Individuals

44, 052 asymptomatic pts

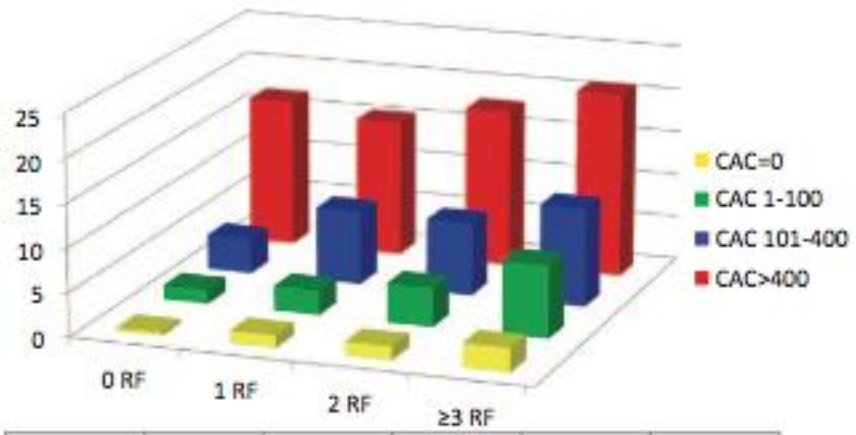
5.6 2.6y f/u

RF: current cigarette smoking
dyslipidemia
diabetes mellitus
hypertension

	0 CAC			
RF	0	1	2	≥3
5 y all cause mortality	99.7%	99.3%	99.3%	99.0%



	Events/1000 person y
0 RF, CAC 400	16.89
≥3 RFs, CAC 0	2.72



	0 RF	1 RF	2 RF	≥3RF	Total
CAC=0	9,805	4,558	3,322	2,123	19,898
CAC 1-100	5,994	3,250	2,913	2,204	14,181
CAC 101-400	1,883	1,301	1,371	1,184	5,739
CAC>400	1,047	984	1,148	1,055	4,234
Total	18,819	10,093	8,754	6,386	44,052

Nasir. Circ Cardiovasc Imaging. 2012; 5:467-473

Interplay of CAC and Traditional Risk Factors for Prediction of All-Cause Mortality in Asymptomatic Individuals

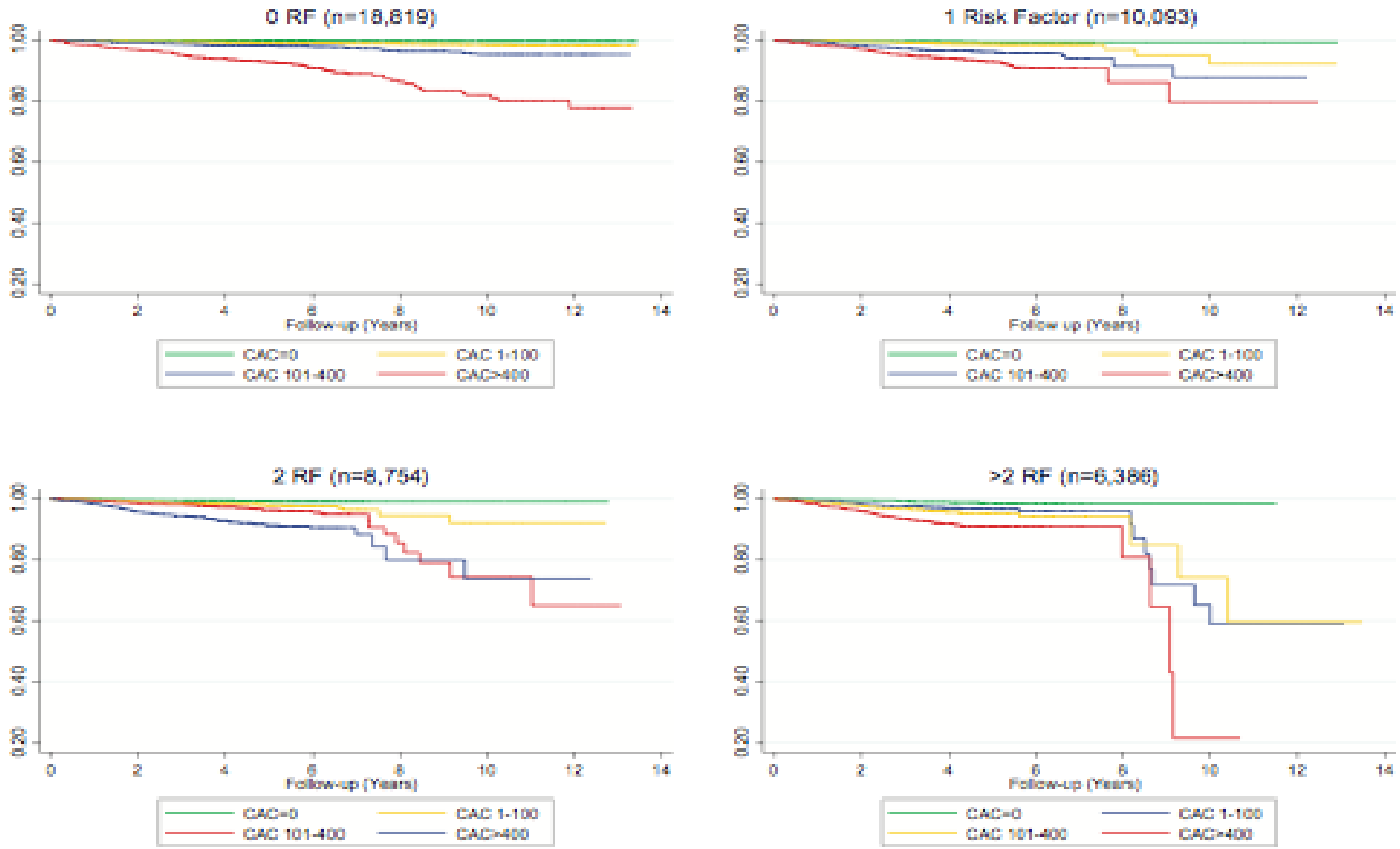


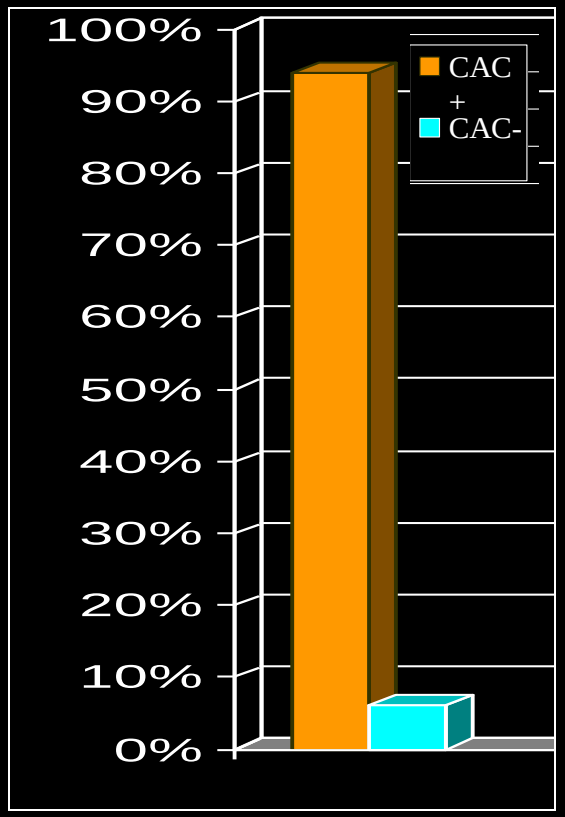
Figure 2. Kaplan-Meier survival curves by coronary artery calcium (CAC) scores across increasing risk factor (RF) burden.

Nasir. Circ Cardiovasc Imaging. 2012; 5:467-473

Coronary Calcium in Patients with First MI or UA

114 pts: MI (97) or UA (17)
57±11 yrs

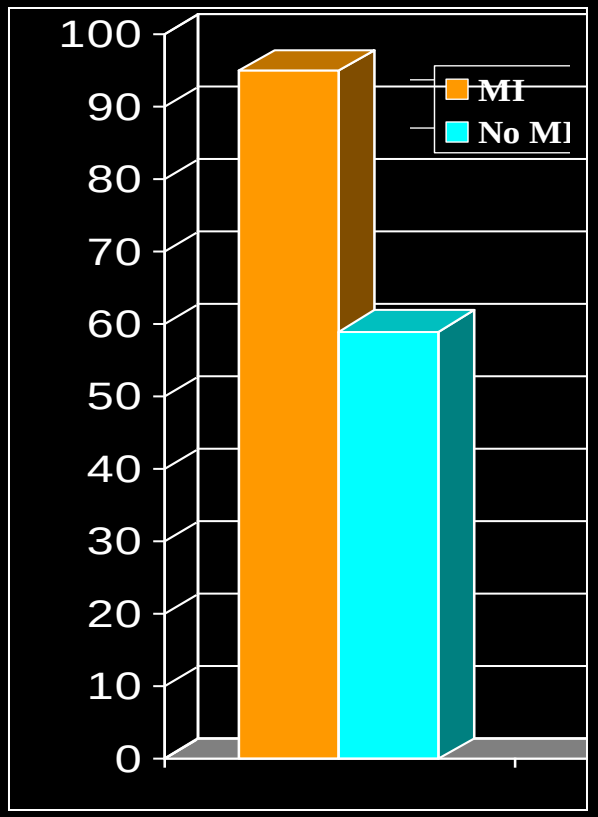
% of ASHD pts



Schmermund, et al. Circulation 1997;96:1461-9

102 pts < 60 with MI
41±7 yrs

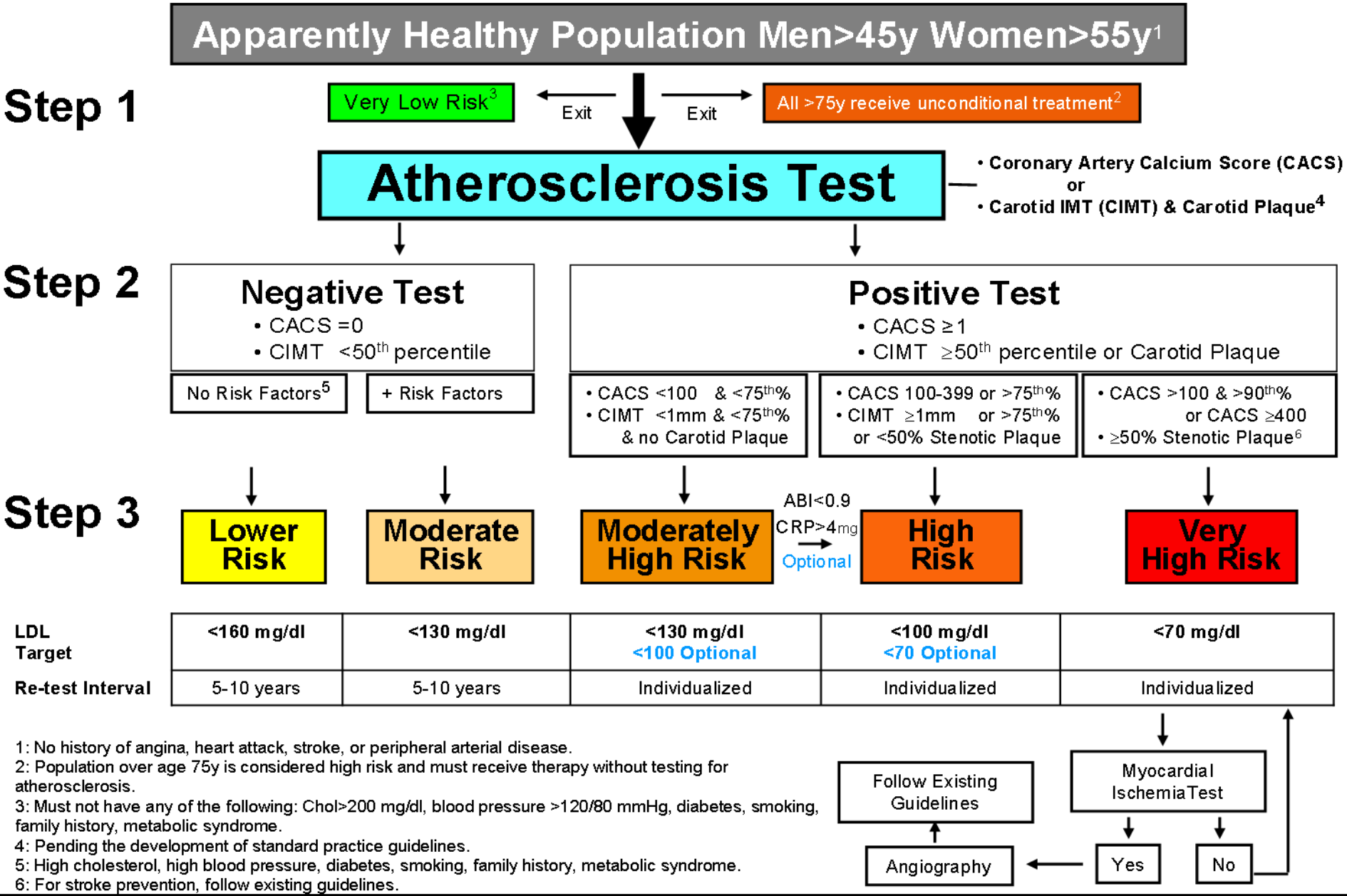
Calcium Present



Pohle et al. Heart 2003;89:625-8

The 1st S.H.A.P.E. Guideline

Towards the National Screening for Heart Attack Prevention and Education (SHAPE) Program



1: No history of angina, heart attack, stroke, or peripheral arterial disease.
2: Population over age 75y is considered high risk and must receive therapy without testing for atherosclerosis.
3: Must not have any of the following: Chol>200 mg/dl, blood pressure >120/80 mmHg, diabetes, smoking, family history, metabolic syndrome.
4: Pending the development of standard practice guidelines.
5: High cholesterol, high blood pressure, diabetes, smoking, family history, metabolic syndrome.
6: For stroke prevention, follow existing guidelines.

Naghavi, Falk, Hecht., et al. AJC 2006

The Asymptomatic Low Risk Patient

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

CLASS IIb

1. Measurement of CAC may be reasonable for cardiovascular risk assessment in persons at low to intermediate risk (6% to 10% 10-year risk) (348–350). (*Level of Evidence: B*)

ACCF/SCCT/ACR/AHA/ASE/ASNC/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography

Detection of CAD/Risk Assessment in Asymptomatic Patients Without Known CAD

	Appropriate Use Score (1–9)		
Noncontrast CT for CCS			
Global CHD Risk Estimate	**Low**	**Intermediate**	**High**
• Family history of premature CHD	A (7)		
• Asymptomatic • No known CAD	I (2)	A (7)	U (4)

The Asymptomatic Intermediate Risk Patient

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

2.5.10. Computed Tomography for Coronary Calcium

CLASS IIa

1. Measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-year risk) (18,348). (*Level of Evidence: B*)

ACCF/SCCT/ACR/AHA/ASE/ASNC/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography

	Appropriate Use Score (1–9)		
Noncontrast CT for CCS			
Global CHD Risk Estimate	**Low**	**Intermediate**	**High**
• Family history of premature CHD	A (7)		
• Asymptomatic • No known CAD	I (2)	A (7)	U (4)

The Asymptomatic High Risk Patient

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

ACCF/SCCT/ACR/AHA/ASE/ASNC/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography

Detection of CAD/Risk Assessment in Asymptomatic Patients Without Known CAD

	Appropriate Use Score (1–9)		
Noncontrast CT for CCS			
Global CHD Risk Estimate	**Low**	**Intermediate**	**High**
• Family history of premature CHD	A (7)		
• Asymptomatic • No known CAD	I (2)	A (7)	U (4)

Diabetes

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

2.6.1.1. RECOMMENDATIONS FOR PATIENTS WITH DIABETES

CLASS IIa

1. In asymptomatic adults with diabetes, 40 years of age and older, measurement of CAC is reasonable for cardiovascular risk assessment (344,397–399). (*Level of Evidence: B*)

2. Risk Factors Revisited

"The most important role of risk factors is to identify the modifiable targets of risk reduction in patients with risk already established by CAC."

Hecht. AJC 2008;101: 1085-7

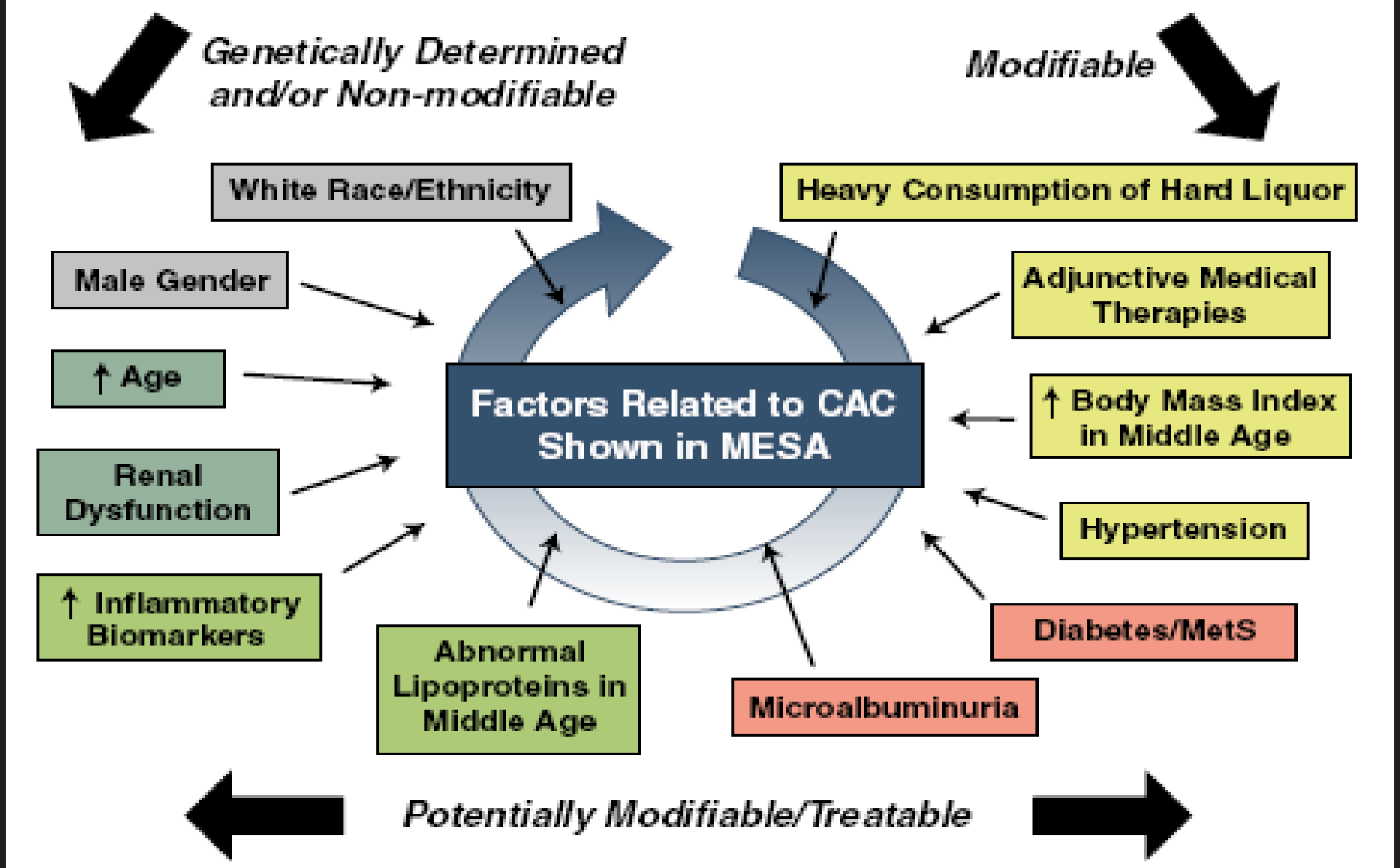


Figure 1. Factors Shown to Be Associated With the Incidence and/or Progression of CAC From MESA

3. Redefinition of Normal Lipids

There are no “normal cholesterol” values that apply to the individual patients in the population based studies from which they were derived

“normal” : cholesterol values at which level there is *no* subclinical atherosclerosis

“abnormal”: cholesterol values at which level there *is* subclinical atherosclerosis, with the severity of “abnormal” depending on the degree of subclinical atherosclerosis.

4. Redefinition of Residual Risk

Old Definitions: The gap between attained and ideal "normal" cholesterol levels dictated by guidelines, i.e., the difference between 2 blood tests

or

Occurrence of events despite treatment

New Definition: Disease progression measured by serial CAC evaluation of subclinical atherosclerosis

The "ideal" lipid level at which disease stabilization occurs will vary from patient to patient, and cannot possibly be accurately assessed by lipid values provided in guidelines

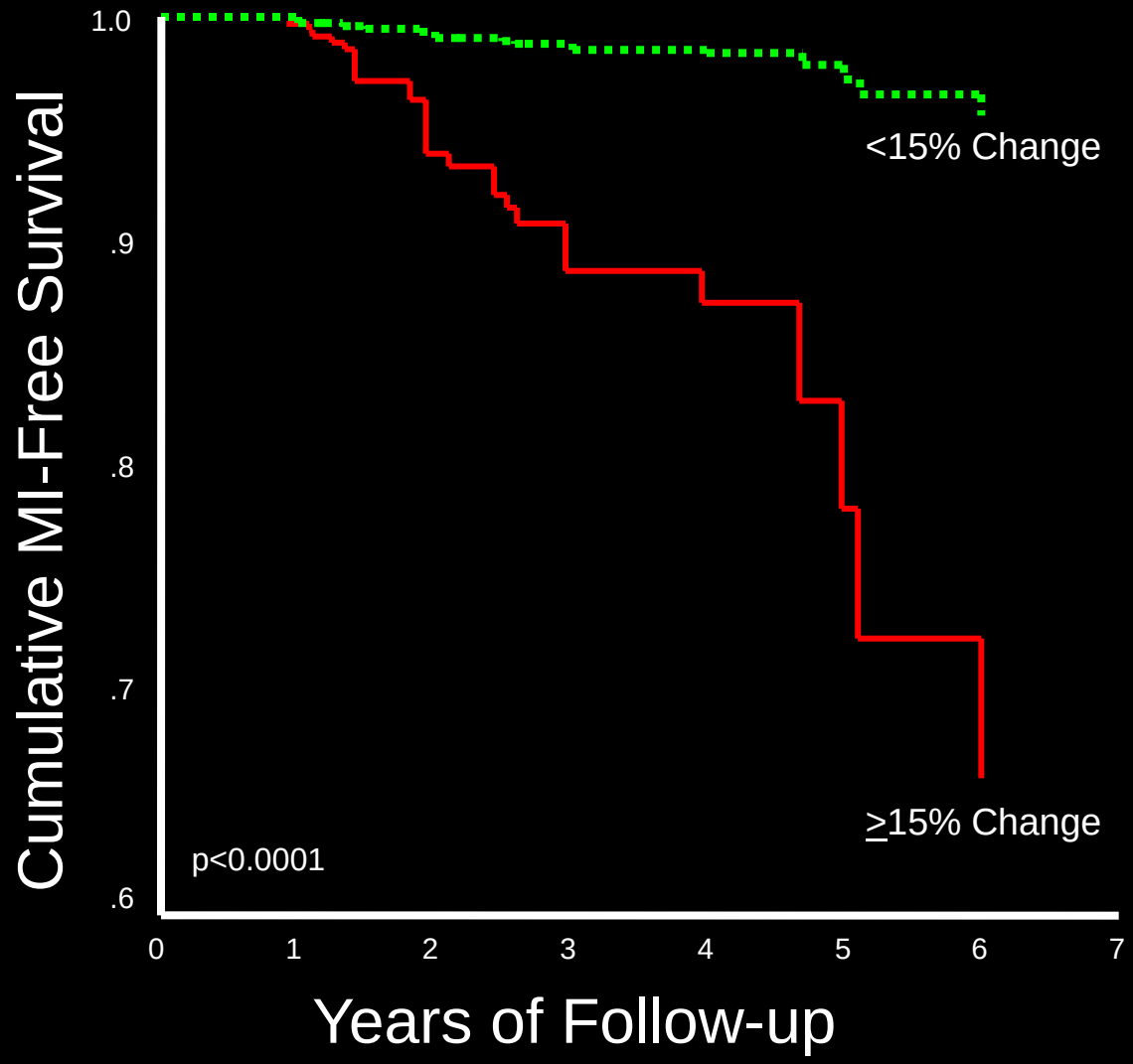
Measures of subclinical atherosclerosis rather than lipids define residual risk just as they define pre-treatment risk

4. CAC Progression

CAC Progression Trials in Asymptomatic Patients

Trial/ Duration	N	Δ CAC	Δ LDL	Final LDL
Belles 2005 / 1 year	615			
atorvastatin 80 mg		+15.1%	-46.6%	92.2
pravastatin 40 mg		+14.3%	-24.5%	129.0
St. Francis 2005 / 4.3 yrs	1000			
atorvastatin 20 mg		+18.8%	-43.4%	NA
placebo		+17.0%	-39.1%	NA
Schmermund 2006 / 1 yr	366			
atorvastatin 80 mg		+27%	-19%	87.3
atorvastatin 10 mg		+25%	+2%	109.3

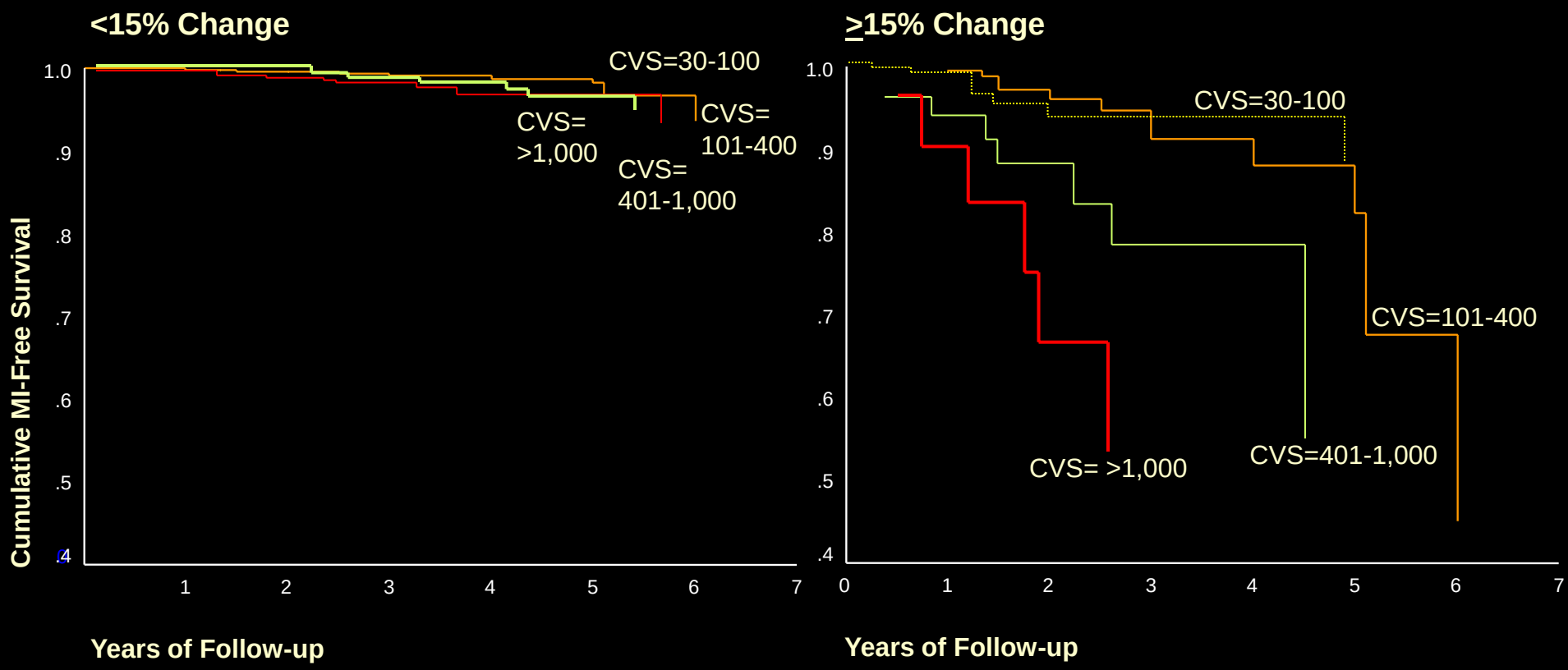
Progression of CAC and Risk of First MI in Patients Receiving Cholesterol-Lowering Therapy



Raggi, Callister, Shaw, ATVB 2004

Progression of CAC and Risk of First MI in Patients Receiving Cholesterol-Lowering Therapy

3.2 + 0.7 years of follow-up



p<0.0001

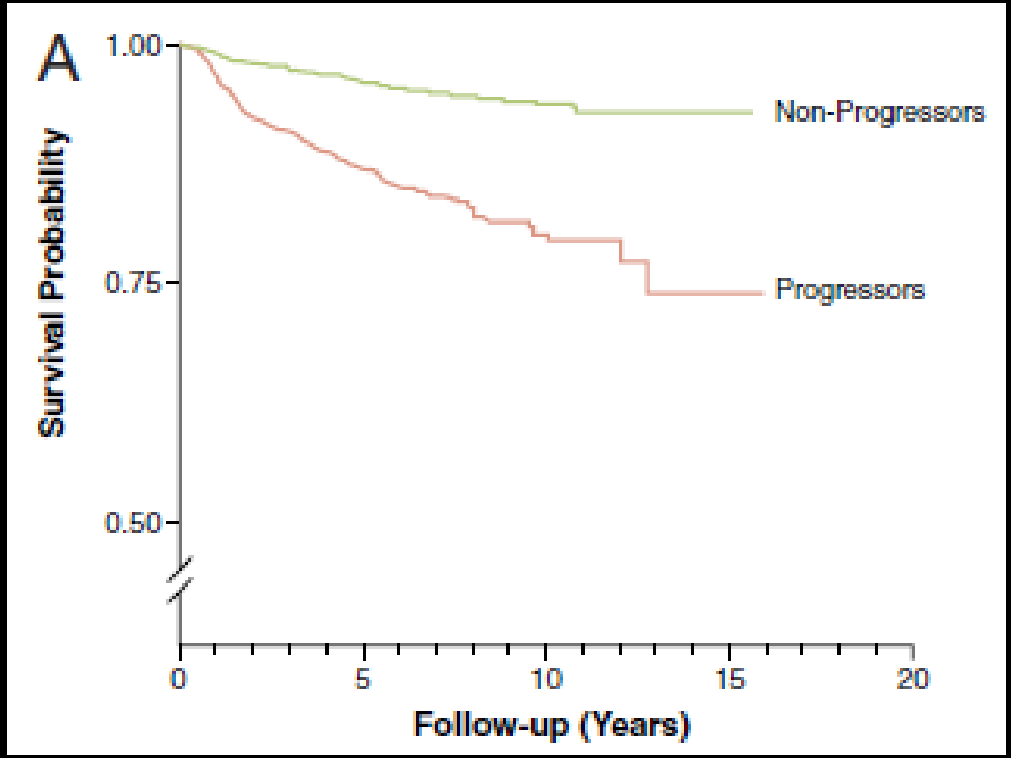
Raggi, Callister, Shaw, ATVB 2004

Progression of CAC Predicts All-Cause Mortality

4609 consecutive asymptomatic pts
Interscan time 3.1 yrs; 288 deaths

After adjusting for baseline score, age, sex, and time between scans:

SQRT method HR: 3.34
>15% yearly increase HR: 2.98



CONCLUSION: Serial assessment
may have clinical value in assessing plaque progression
and future cardiovascular risk.

Budoff. JACC Img 2010;3:1229–36

Metabolic Syndrome, DM and Incidence and Progression of CAC: MESA

5,662 pts, 51% female, 61.0+ 10.3 yrs, 4.9 yr f/u
2 scans 2.4 yrs apart
2,927 - 0 baseline CAC
2,735 - >0 baseline CAC: MetS without DM (25.2%)
DM without MetS (3.5%)
DM and MetS (9.0%)
neither MetS nor DM (58%)

Wong. JACC Imaging

Metabolic Syndrome, DM and Incidence and Progression of CAC: MESA

	CAD RR for CAC Progression		
	o prog	2nd tert	3rd tert
+MetS/-DM	1	2.3	4.1
+MetS/+DM	1	4.1	8.5
P		<.05	<.05

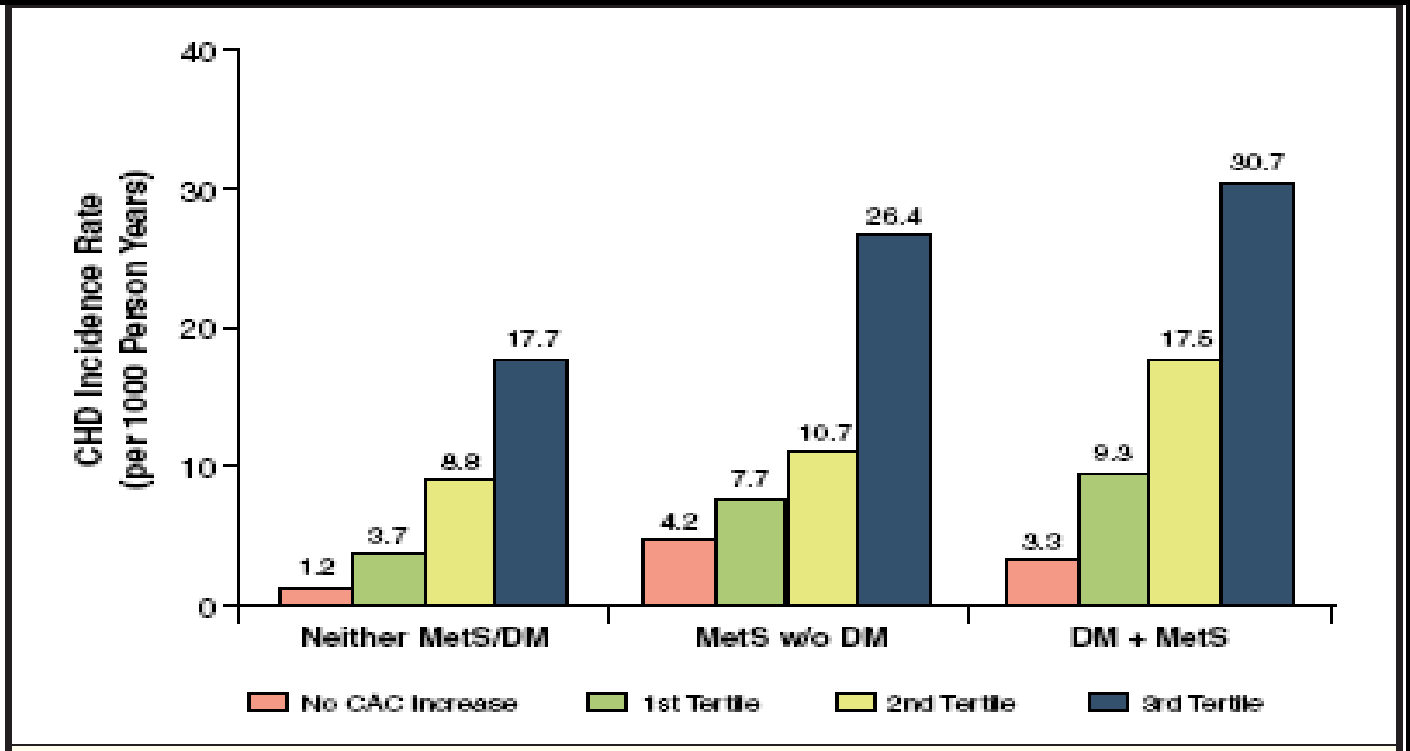


Figure 3. CHD Event Rates (per 1,000 Person Years) According to Tertile of CAC Progression by Presence of MetS and DM

Impact of CAC Progression and Statin Therapy on Outcome in Subjects with and without Diabetes

296 asymptomatic DM
300 controls
59+/-6years, 29%women
Scan interval 1-2 yrs
f/u 5 6+/-11 mos

	Event-Free Survival	
ΔCAC	DM	No DM
<10%	97.9%	100%
10-20%	95.9%	97.2%
21-30%	92.7%	94%
>30%	79.6%	90.6%

Death HR: DM vs Controls (N=596)

ΔCAC	Matched Control Group	DM	p
10-20% vs. <10%	1.0	1.88	0.0001
21-30% vs. <10%	1.0	2.29	0.0001
>30% vs. <10%	1.0	6.95	0.0001

*Adjusted for age, gender, HTN, HLP, Family History of CHD, Baseline CAC and Smoking.

Kiramijyan. AJC: In Press

CAC Progression and Incident CHD Events in MESA

6,778 (52.8% female) 45-84 y
5,682 baseline and f/u 2.5y apart
Baseline f/u 7.6y; 343 total, 206 hard events
CAC increased 24.9+65.3/y

Adjusted HR (RF + baseline CAC)

0 CAC	3,396 Total	3,382 Hard
Per 5AU/y	1.4	1.5
>0 CAC		
Per 100AU/y	1.2	1.3
>300/y	3.8	6.3
<5%/y		
5-14%/y	1.1	1.0
15-29%/y	1.6	1.4
>30%/y	1.5	1.4

Progression (AU)

No statins	46.2/y
Statins	60.0/y
P	< 0.001
Events	
No statins	55.7/y
Statins	119.3/y

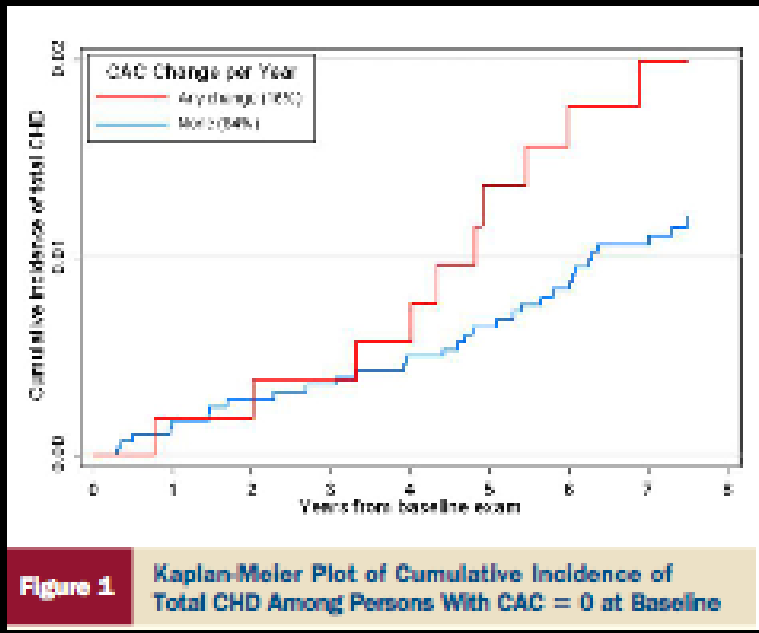


Figure 1 Kaplan-Meier Plot of Cumulative Incidence of Total CHD Among Persons With CAC = 0 at Baseline

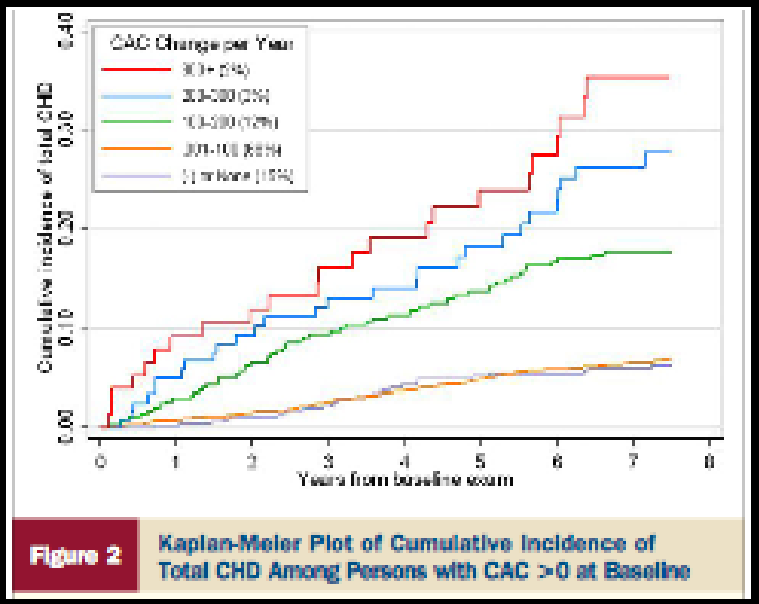


Figure 2 Kaplan-Meier Plot of Cumulative Incidence of Total CHD Among Persons with CAC >0 at Baseline

Budoff JACC 2013;61:1231-9

Issues

Decrease radiation without increasing noise:

- Lower mAs
- 100 kV: redefine Ca
- Convert 0 CAC into >0 CAC

Improve reproducibilty:

- Definition of significant change in individuals

Effects of iterative reconstruction algorithms:

- Too much smoothing?

Coordinate with cardiology community

Adjusted HR (RF + baseline CAC)

	3,396 Total	3,382 Hard
0 CAC		
Per 5AU/y	1.4	1.5
>0 CAC		
Per 100AU/y	1.2	1.3
>300/y	3.8	6.3
<5%/y		
5-14%/y	1.1	1.0
15-29%/y	1.6	1.4
>30%/y	1.5	1.4

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

What is already known about this topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

Studies of free fall do not show 100% mortality

What this study adds

No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

Conclusions: As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Smith. BMJ 2003;327:1459–61

"The prospective convert came before Shammai and requested, 'Convert me on condition that you teach me the Torah of Preventive Cardiology while I stand on one foot.' He [Shammai] pushed him out with the ruler in his hand. He then came before Hillel, who converted him. Hillel addressed to him the immortal words, “Coronary artery calcium scanning. That is the entire Torah; the rest is commentary. Go and learn.'"