The role of coronary artery calcium score on the detection of subclinical atherosclerosis in metabolic diseases

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The History of Atherosclerosis

RESEARCH LETTER

Computed Tomographic Assessment of Atherosclerosis in Ancient Egyptian Mummies

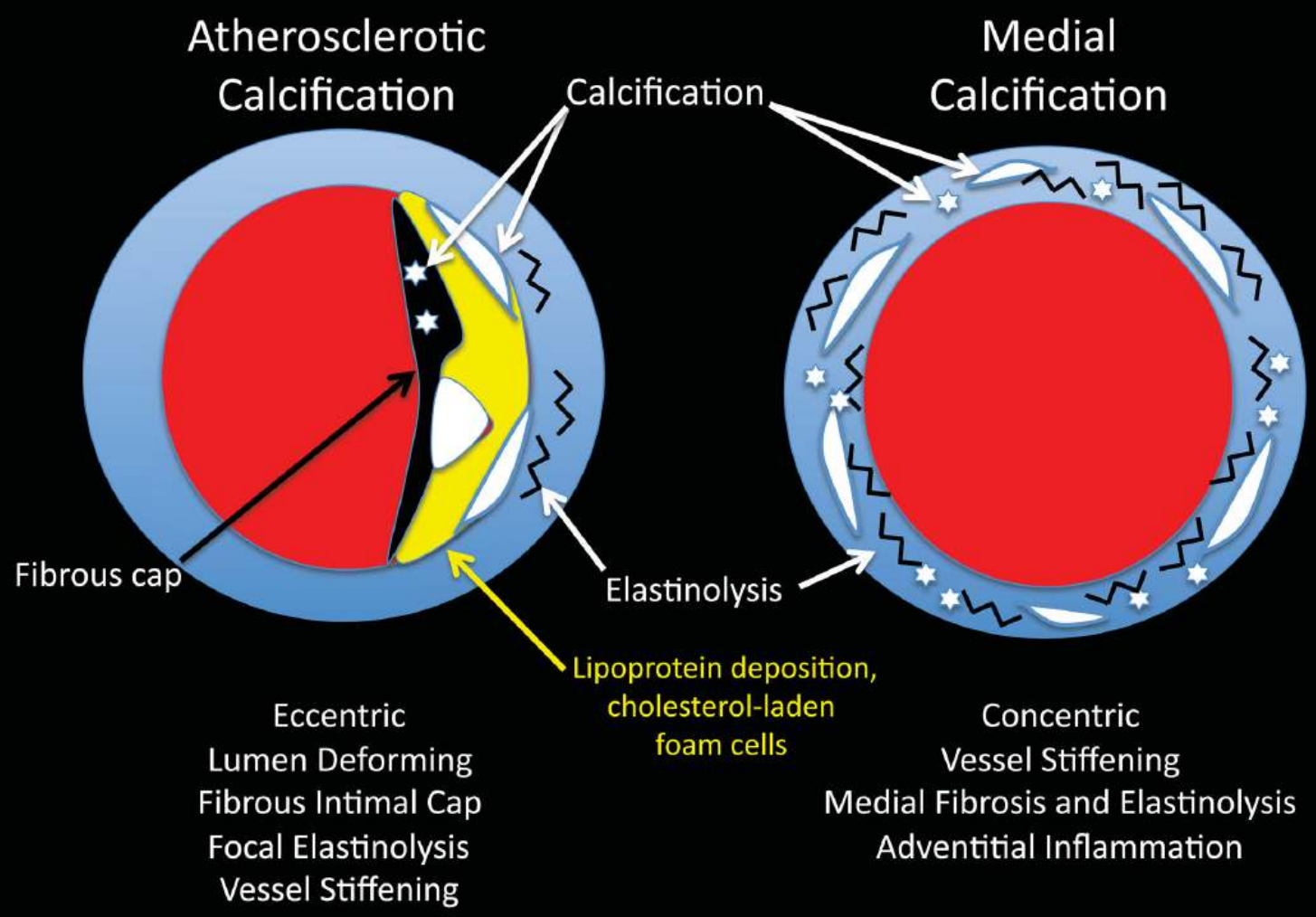
JAMA®
2009;302(19):2091-2094

Among those who died when 45 years or older, calcification was present in 7 of 8 (87%) compared with 2 of 8 (25%) who died when younger than 45 years.

Contents

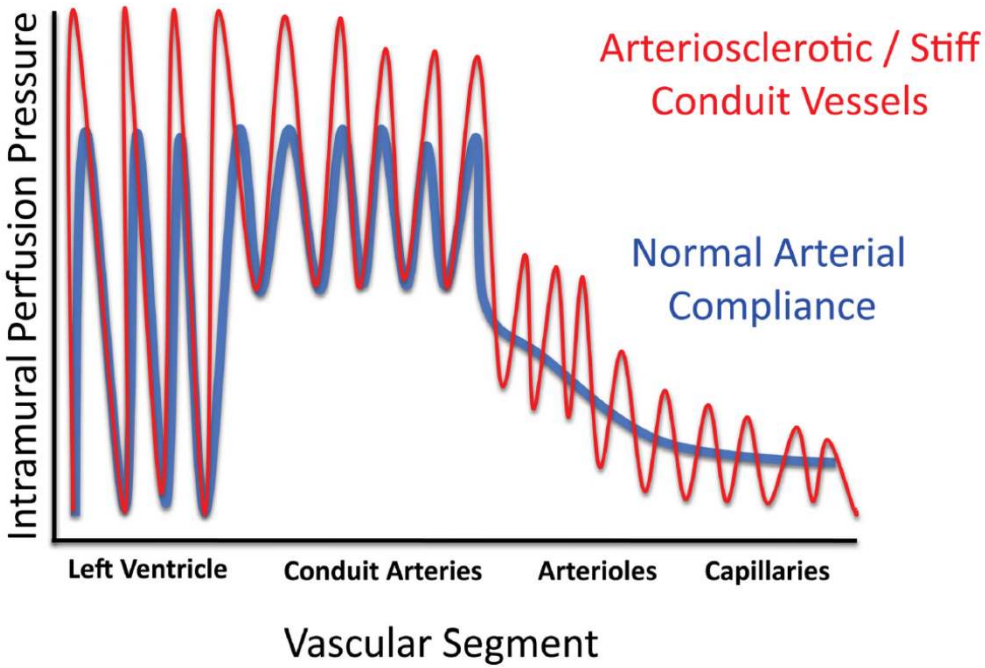
- Vascular calcification
- How to measure CAC?
- MESA and HNR cohort
- Association of risk factors and CAC
- CAC and diabetes
- Modification of CAC?
- Candidate for CACS testing

Atherosclerotic vs. medial arterial calcification



Thompson B et al. Nat Rev Endocrinol, 2012

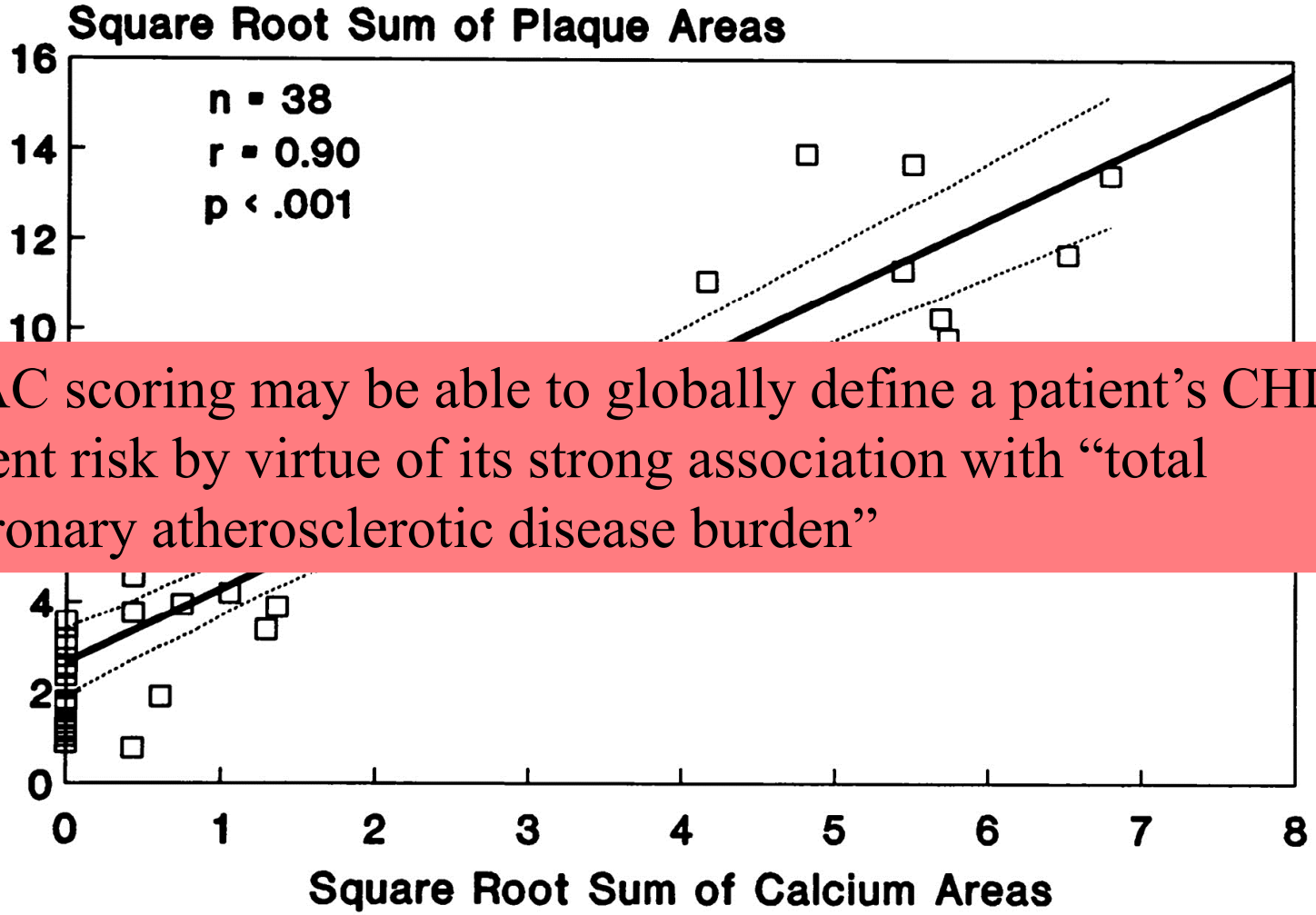
Consequences of arterial stiffening and impaired Windkessel physiology



- ✓ During systole, some kinetic energy is stored as potential energy in the elastic conduit arteries for the coronary perfusion and smooth distal capillary perfusion during diastole
- ✓ With arteriosclerotic stiffening, less potential energy is stored during systole, giving rise to impaired, pulsatile and erratic flow during diastole

Thompson B et al. Nat Rev Endocrinol, 2012

Graph showing square-root sum of coronary calcium areas (mm) by electron-beam computed tomography vs square-root sum of atherosclerotic plaque areas (mm) for each of the individual coronary arteries studied (n=38).



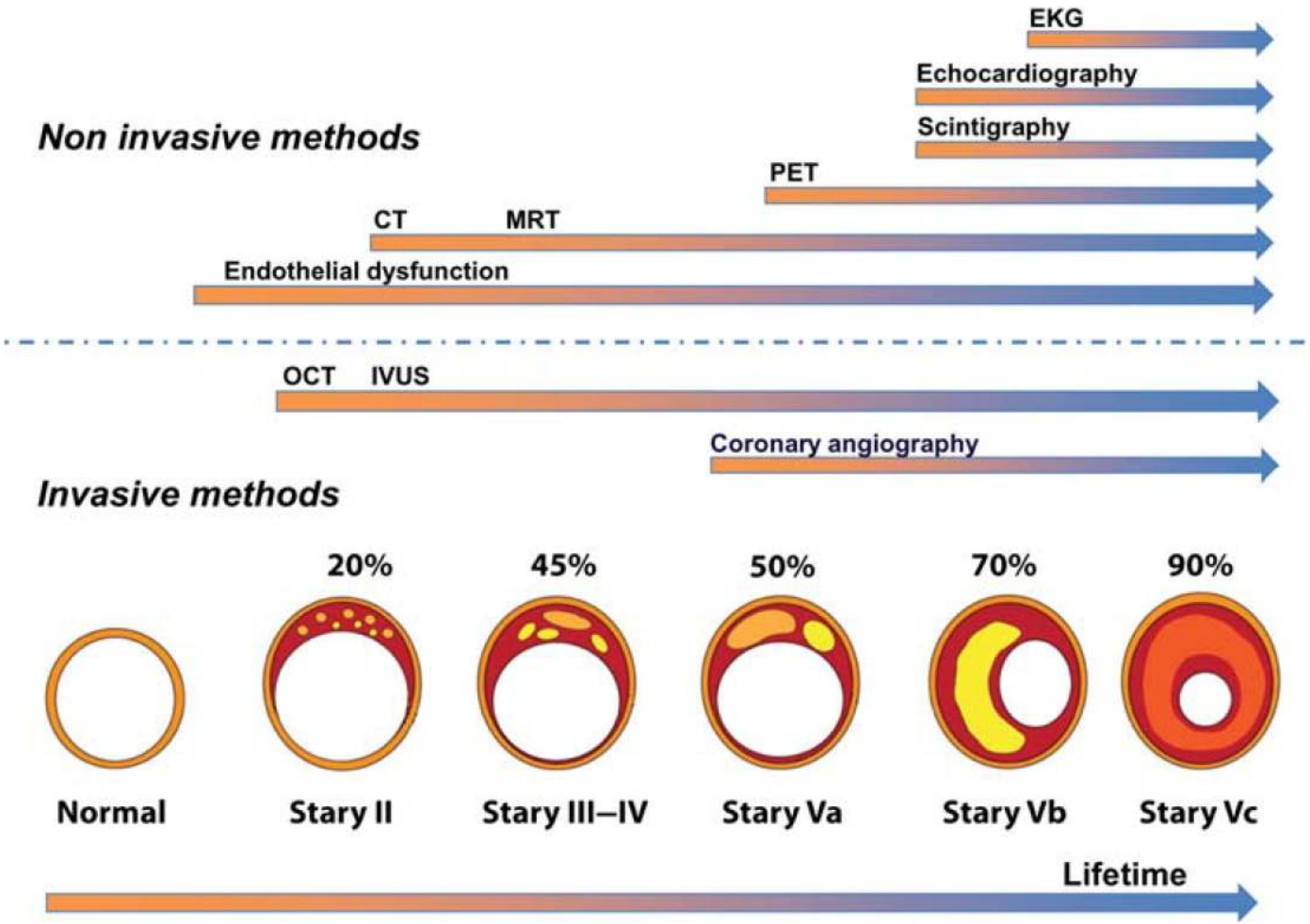
CAC scoring may be able to globally define a patient's CHD event risk by virtue of its strong association with "total coronary atherosclerotic disease burden"

Rumberger J A et al. Circulation 1995;92:2157-2162

American Heart Association
Learn and Live

How to measure CACS?

Development of coronary arteriosclerosis and detection methods



Erbel et al. Eur Heart J, 2012

What is CAC score?

- A validated marker for cardiovascular risk and currently regarded as a feasible surrogate marker for screening of coronary artery disease
- Electron beam computed tomography (EBCT) and multidetector computed tomography (MDCT) have been used in quantification of CAC
- Compared to EBCT, MDCT have the advantage of higher spatial resolution and less noise, while EBCT has less motion artifacts and lower radiation
- Scanned in a prospectively ECG-triggered mode with 2.5-3.0mm thick axial slices
- Radiation dose is low, with typical effective dose of approximately 1.0mSv (about the same dose of radiation of 1.5 screening mammograms performed)

Agatston Score

- Calcium density multiplied with the area of the plaque using 3 or 4 pixels and the detection threshold of 130 IU Hounsfield for differentiation between calcium and surrounding tissue structures

Agatston score	Calcium score categories	Probability of significant CAD	Cardiovascular risk	Recommendation
0	Absent	Very unlikely (<5 %)	Very low	Reassure patient. General guidelines for primary prevention of CV diseases
1-10	Minimal	Very unlikely (<10 %)	Low	General guidelines for primary prevention of CV diseases
11-100	Mild	Mild or minimal coronary stenosis likely	Moderate	Counsel about risk factors modification, strict adherence with primary prevention goals. Daily ASA
101-400	Moderate	Non obstructive CAD, highly likely, obstructive CAD possible	Moderately high	Institute risk factor modification and secondary prevention goals. Consider exercise testing
>400	Extensive	High likelihood of significant coronary stenosis (>90 %)	High	Institute very aggressive risk factor modification. Consider exercise or pharmacological nuclear stress testing for the detection o inducible ischemia

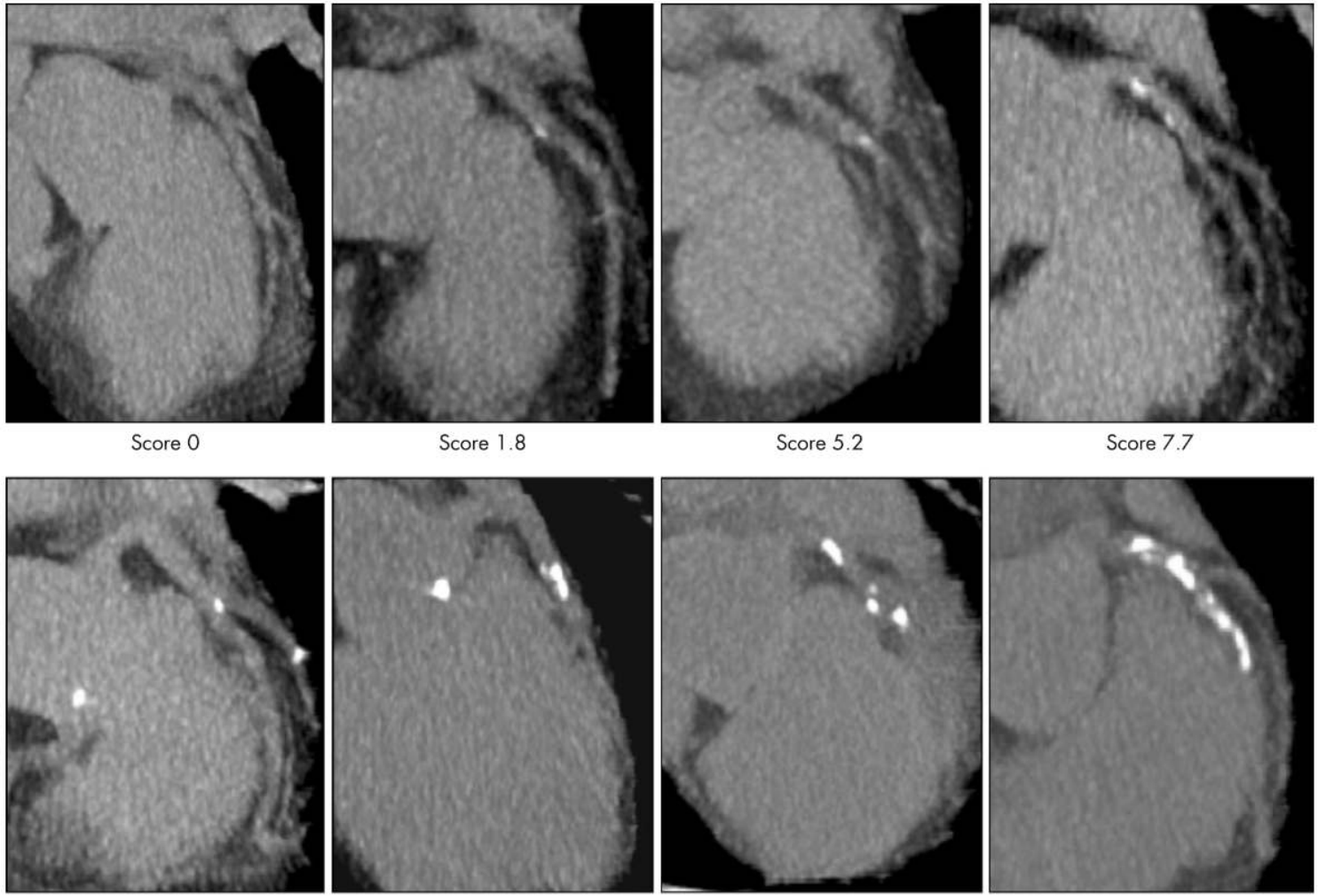
Adapted from Cademartiri F et al., 2012

Principle of calculating the Agatston score

Score = MC
Maximal c

1
2
3
4

EBT-score-e
Lesion with
Density of
Area-size:
EBT-score:



Erbel R et al. Heart, 2007

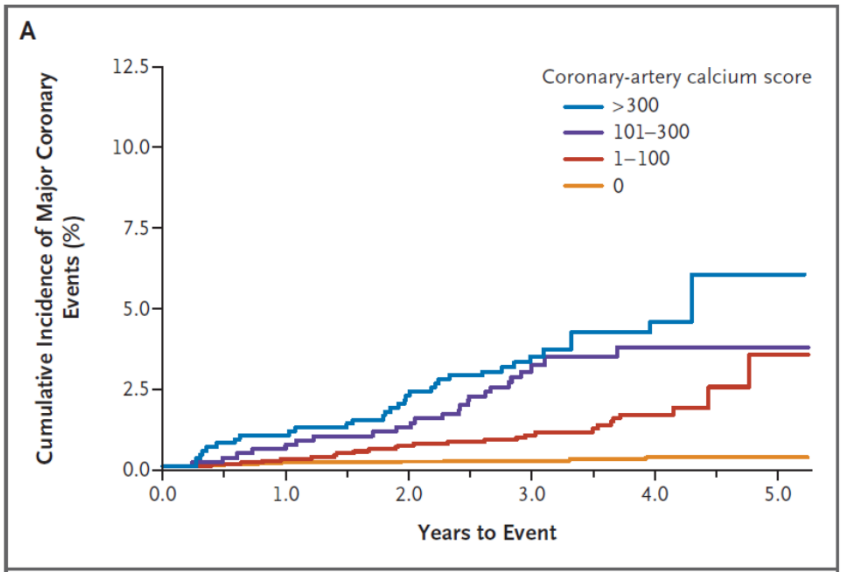
Multi-Ethnic Study of Atherosclerosis (MESA) and Heinz Nixdorf Recall (HNR) study groups

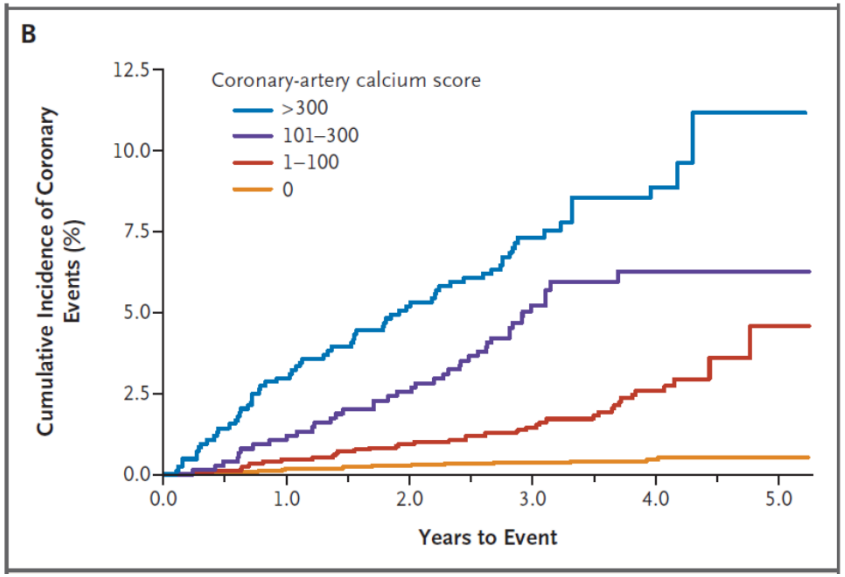
Multi-Ethnic Study of Atherosclerosis (MESA)

- A prospective observational study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced signs and symptoms) that predict progression to clinically overt cardiovascular disease in a diverse and representative population-based sample of men and women aged 35-84.
- CACS, cardiac MRI, FMD, carotid IMT, ABI, ECG and other metabolic parameters from 2000-2002, 3 subsequent exam of the cohort between 2002 and 2007
- White (38%), African-American (28%), Hispanic (22%), Chinese American (12%)

CAC as a predictor of coronary event - MESA

In 6722 subjects in MESA, followed up for a median of 3.8 years





Detrano R et al. NEJM, 2008

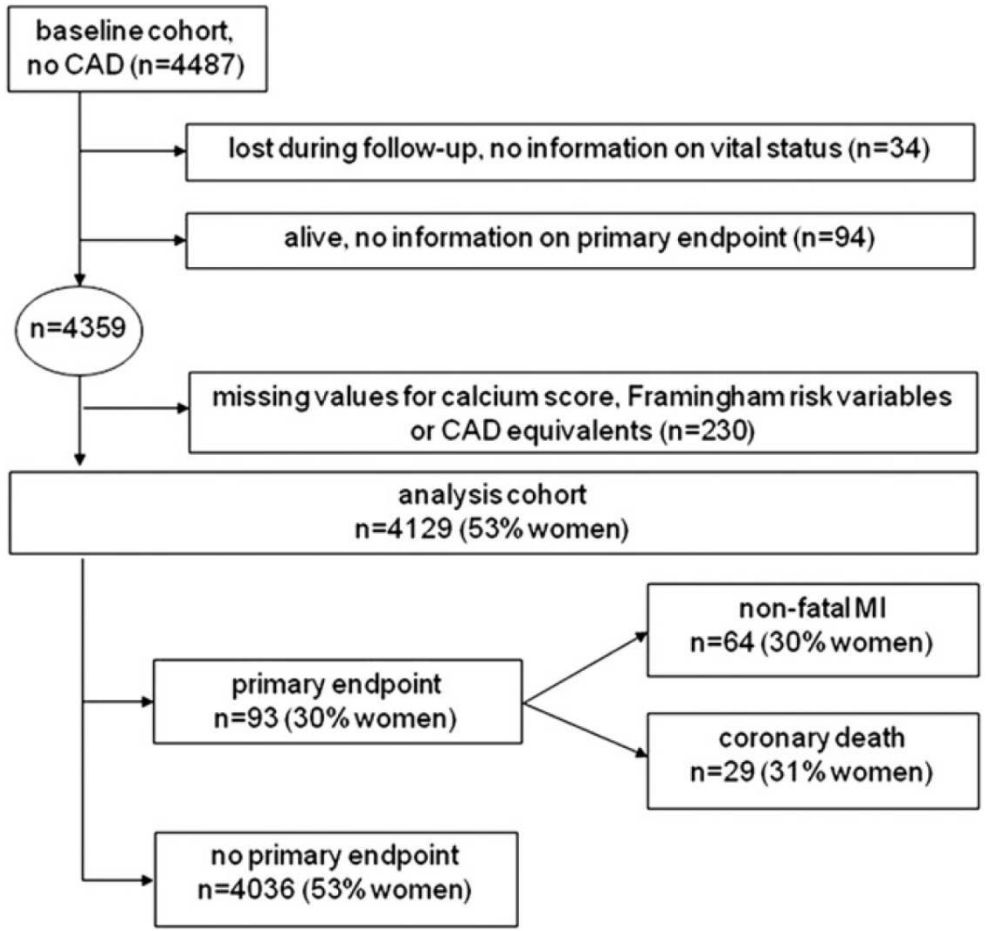
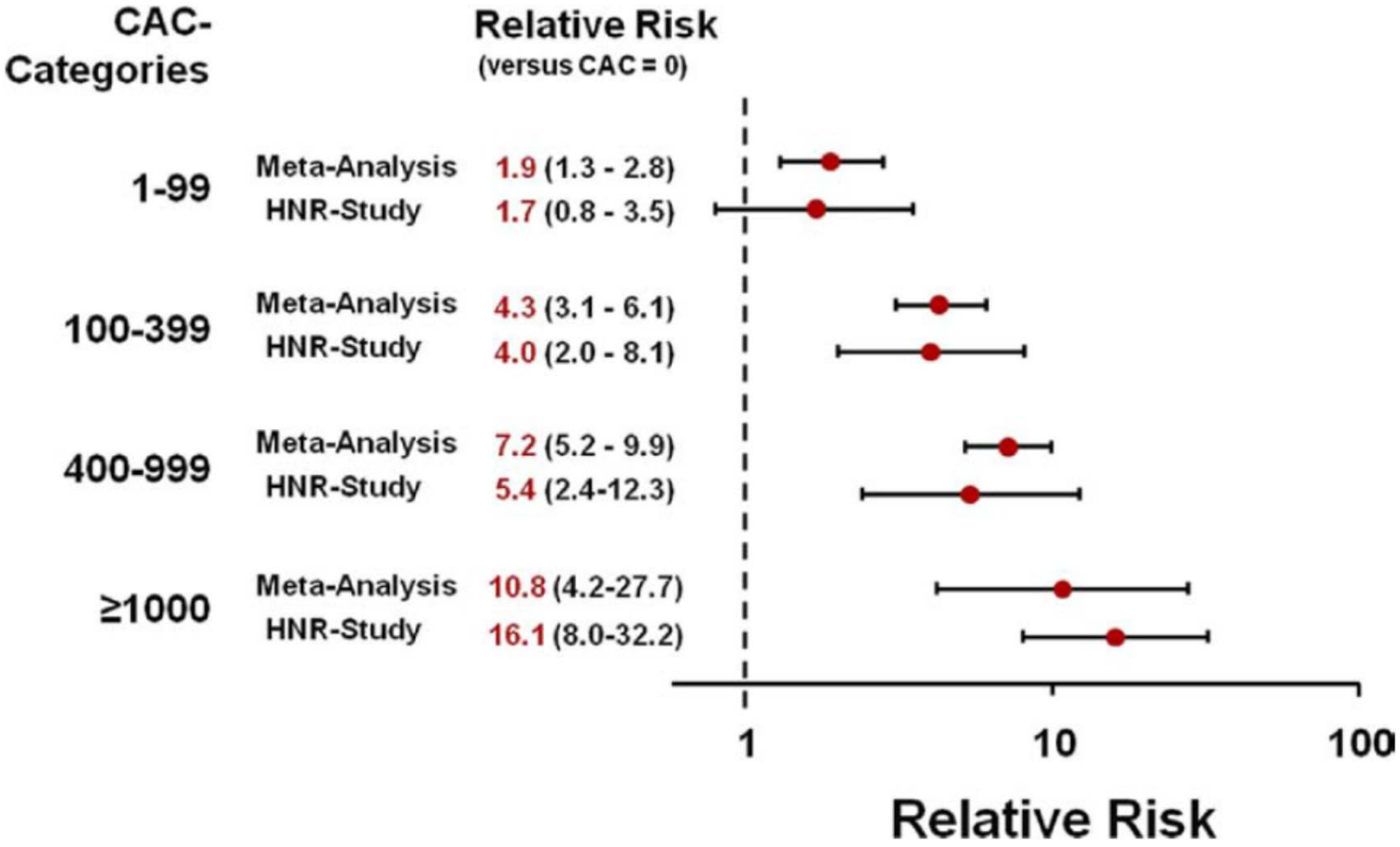


Figure 1 **Flow Chart of the HNR Study Cohort**

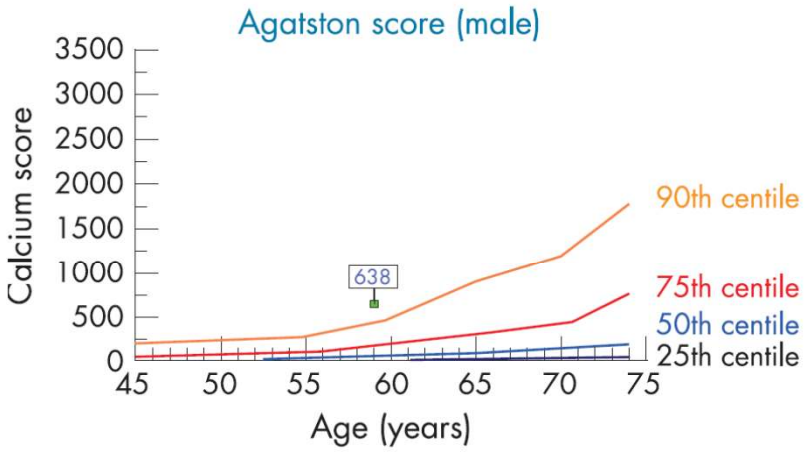
Study cohort includes 4,487 participants 45 to 75 years of age without coronary artery disease (CAD). MI = myocardial infarction.

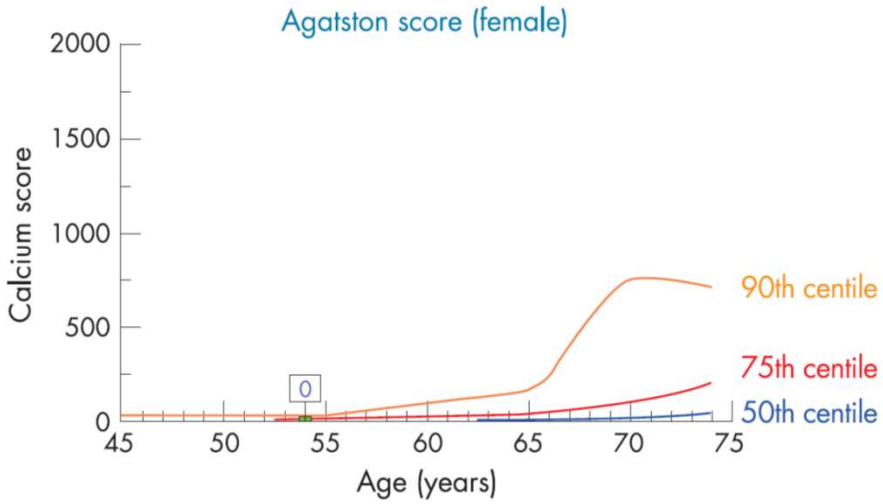
Relative risks and 95% CIs of CAC categories



Erbel E et al. JACC, 2010

Prevalence of CACS

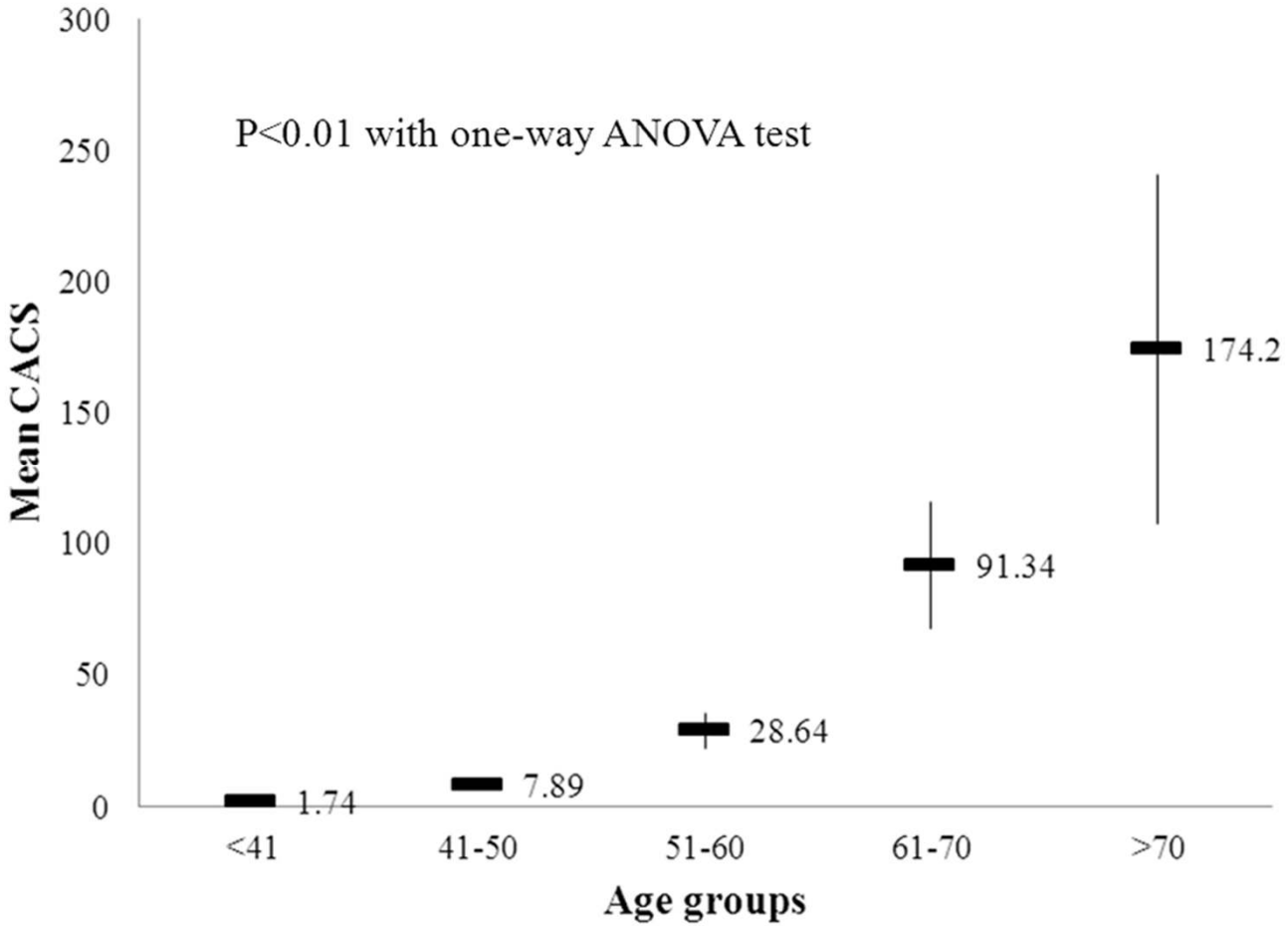




- Age-dependent
- Gender differences; In women, CAC develops 10-15 years later in life than in men, the amount 5-7 times lower at any given age

- In HNR study (n=4487, 45-75 years), more than 20% of men have CAC>100 and up to 8% CAC >1000
- The prevalence of higher degrees of CAC is much lower in women
- Totally, 82% of men and 55% of women demonstrated CAC

Mean CACS according to age groups in 24,063 Korean participants in Health Screening Program



Rhee eJ et al. Plos ONE, 2013

Ethnic differences in coronary calcification in MESA

TABLE 2. Distribution of Coronary Calcification by Gender and Ethnicity in MESA

	Men					Women				
	White (n=1259)	Black (n=845)	Hispanic (n=719)	Chinese (n=390)	*P*	White (n=1360)	Black (n=1053)	Hispanic (n=774)	Chinese (n=413)	*P*
Prevalence, %	70.4	52.1	56.5	59.2	<0.001	44.6	36.5	34.9	41.9	<0.0001
Calcium score										
Mean±SD	298±601	176±508	203±545	127±322	<0.001	96±254	82±296	59 ±201	65±199	0.006
50th Percentile	48	3	8	11		0	0	0	0	
75th Percentile	298	87	122	116		54	24	18	38	
90th Percentile	1595	1044	1098	583		291	193	143	155	
Maximum	6316	6047	5148	3774		2528	4013	2434	2440	

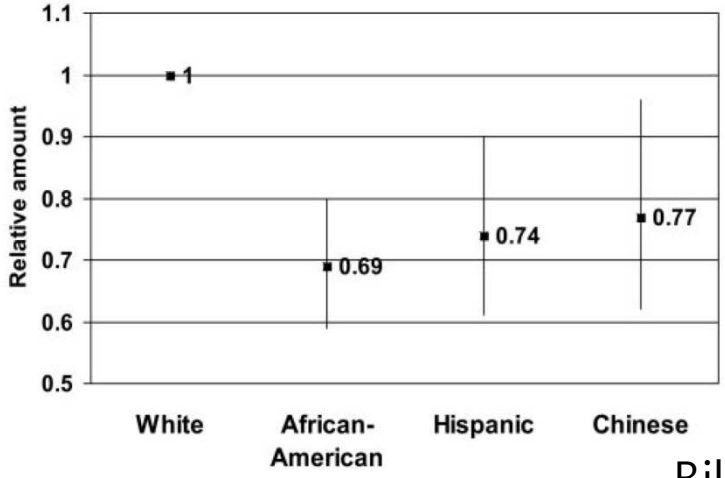
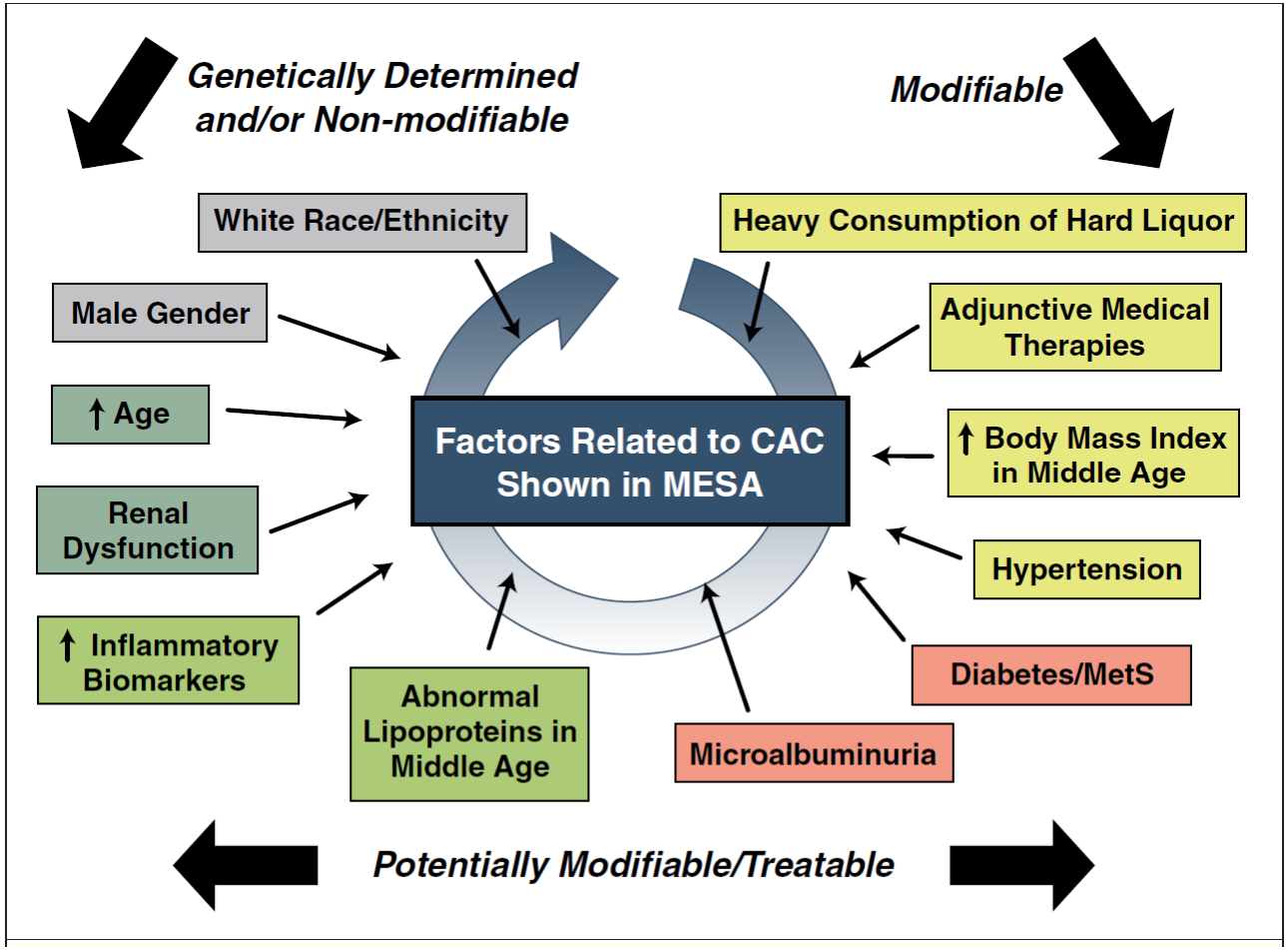


Bild DE et al. Circulation, 2005

Association of risk factors and coronary artery calcification

Factors associated with the incidence and/or progression of CAC from MESA



Kovacic JC et al. JACC Cardiovasc Imag, 2012

Early adult risk factor levels and subsequent coronary artery calcification

In CARDIA study, in 3043 US citizens aged 18-30y, risk factors measured at 0,2,5,7,10 and 15, as CAC assessed at 15 years

Table 1 Prevalence of CAC at Year 15 in the CARDIA Study, 2000 to 2001

	n	%	p Value
Any CAC			
Overall	3,043	9.6	
Race-gender group			<0.0001
African-American women*	800	4.9	
African-American men†	576	11.3	
White women*	860	5.2	
White men†	807	17.6	
Gender			<0.0001
Men	1,383	15.0	
Women	1,660	5.1	
Age			<0.0001
33 to 39 yrs	1,464	5.5	
40 to 45 yrs	1,579	13.3	
Agatston score			
>0–10	95	3.1	
>10–20	46	1.5	
>20–100	102	3.3	
>100–400	40	1.3	
>400	8	0.3	

Table 5 ORs for Having CAC at Year 15 by Age, Race, Gender, and Presence of Above* Optimal Levels of Cardiovascular Disease Risk Factors at Baseline in the CARDIA Study (n = 2,756)

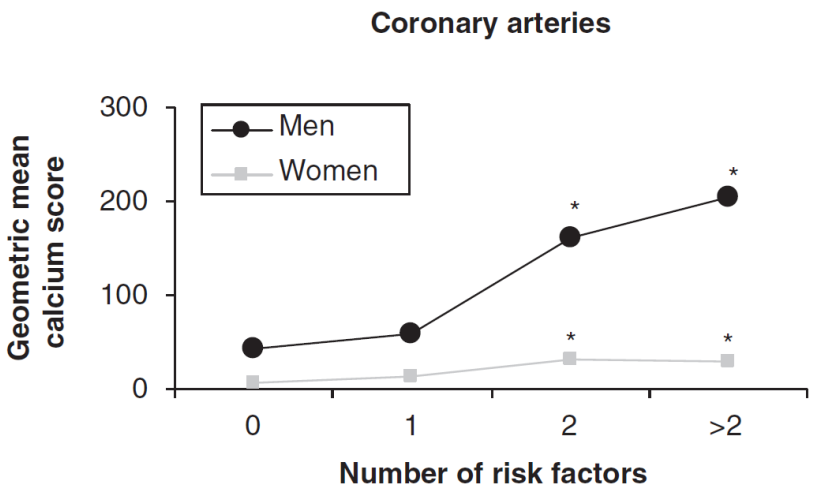
	Minimally Adjusted†		Multivariate Adjusted‡	
Year 0 Risk Factors	OR	95% CI	OR	95% CI
Age, 5 yr	2.54	(2.03–3.18)	2.44	(1.93–3.08)
White race	1.32	(0.99–1.75)	1.62	(1.20–2.19)
Male gender	3.35	(2.52–4.46)	2.93	(2.16–3.97)
Current smoker	2.10	(1.58–2.78)	2.17	(1.62–2.91)
Above optimal cut points*				
LDL-C ≥130 mg/dl	2.42	(1.83–3.20)	2.23	(1.68–2.98)
Systolic/diastolic BP ≥120/80 mm Hg	1.62	(1.21–2.16)	1.52	(1.12–2.06)
BMI ≥25 kg/m^2	1.81	(1.38–2.38)	1.62	(1.21–2.17)
HDL-C <40 mg/dl	1.46	(1.02–2.08)	1.01	(0.69–1.49)
Glucose ≥110 mg/dl	3.19	(1.29–7.88)	3.04	(1.20–7.68)

Loria CM et al. JACC, 2007

Risk factors for coronary artery calcification: The Rotterdam Study

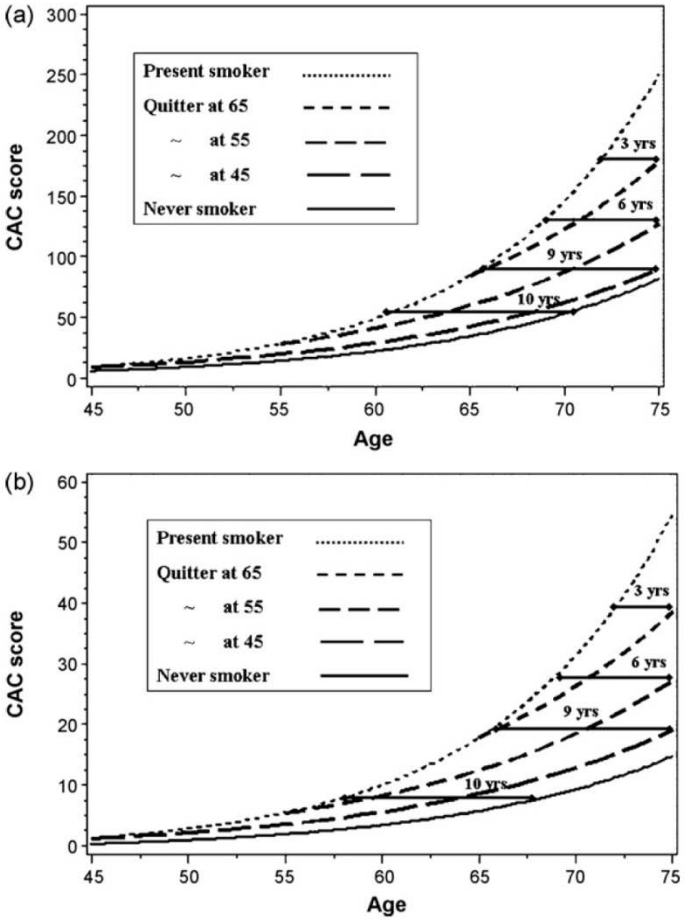
Table 2 Relation between putative risk factors and presence of severe calcification in the coronary arteries (upper quartiles versus lower three)

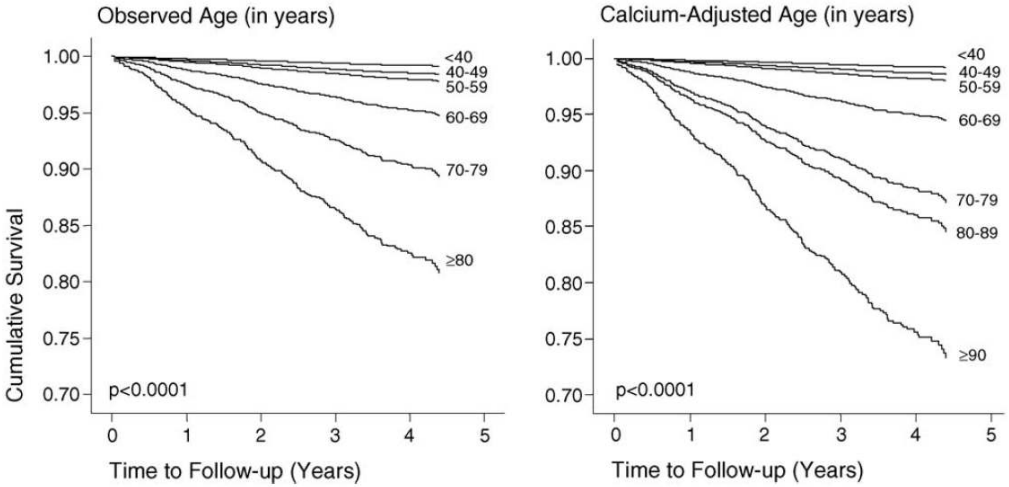
Variable	*(Exposed (%))*	*Model 1*	*Model 2*
		OR (95% CI)	*OR (95% CI)*
Men			
Age (years)		1.1 (1.0–1.1)[b]	1.0 (1.0–1.1)
BMI ⩾ 30 kg/m^2	92 (20)	1.4 (0.8–2.3)	1.0 (0.5–1.8)
Hypertension	263 (57)	2.1 (1.3–3.4)[b]	1.6 (1.0–2.7)
Hypercholesterolemia	191 (41)	2.6 (1.7–4.1)[a]	1.9 (1.2–3.1)[b]
HDL < 1.0 mmol l^{-1}	67 (14)	0.8 (0.4–1.5)	0.7 (0.4–1.4)
Current smoking	59 (13)	1.1 (0.4–2.5)	1.2 (0.5–3.1)
Past smoking	337 (72)	1.3 (0.7–2.5)	1.1 (0.6–2.3)
Diabetes	57 (12)	2.5 (1.4–4.4)[b]	1.9 (1.0–3.6)[c]
Women			
Age (years)		1.1 (1.1–1.1)[a]	1.1 (1.0–1.1)[a]
BMI ⩾ 30 kg/m^2	131 (26)	1.1 (0.7–1.7)	0.8 (0.4–1.3)
Hypertension	268 (53)	2.6 (1.6–4.1)[a]	2.3 (1.4–3.7)[a]
Hypercholesterolemia	276 (54)	1.7 (1.1–2.6)[c]	1.5 (1.0–2.3)
HDL < 1.0 mmol l^{-1}	34 (7)	1.3 (0.6–2.8)	0.8 (0.3–2.0)
Current smoking	76 (15)	2.0 (1.1–3.6)[c]	1.8 (1.0–3.6)
Past smoking	212 (42)	1.2 (0.8–1.9)	1.3 (0.8–2.0)
Diabetes	52 (10)	2.0 (1.1–3.7)[b]	2.0 (1.0–4.0)[c]



Odink AE et al. J Human Hypertension, 2010

Smoking cessation and subclinical atherosclerosis-HNR study



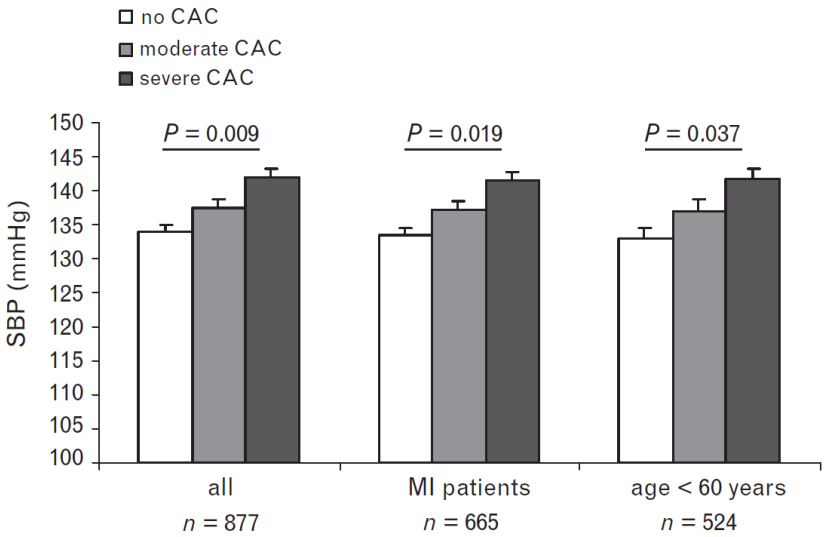


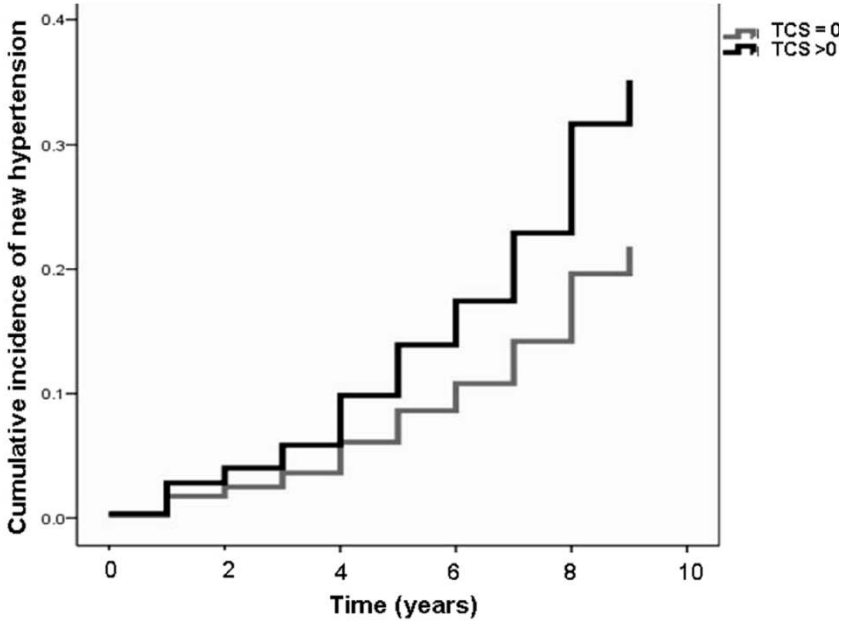
Cumulative 5-yeasr survival comparing observed age with calcium-adjusted age estimates

Jockel KH et al. Atherosclerosis, 2009
Shaw LJ et al. Atherosclerosis, 2006

Blood pressure and CACS

In 483 normotensive subjects followed up for 7 years



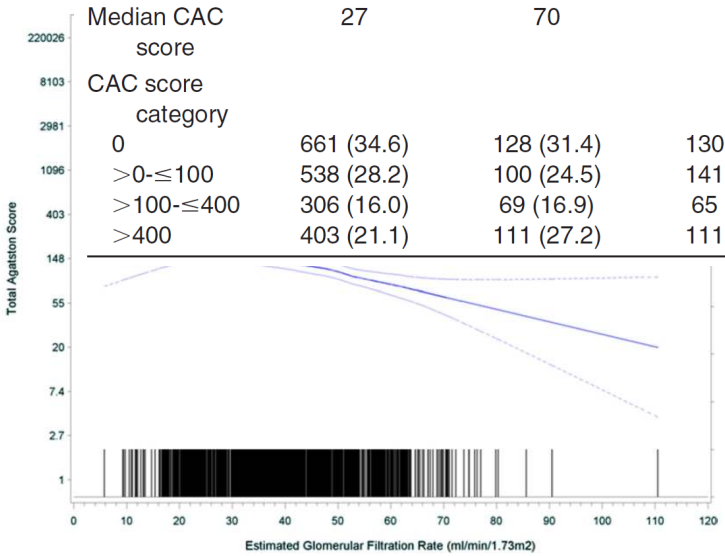


Grossman C et al. Am J Hypertens, 2013
Mayer B et al. J Hypertens, 2007

Relationship of eGFR and CAC

Table 2. Bivariate Associations Between eGFR and CAC

		eGFR (mL/min/1.73 m^2) at EBT Visit					
	All (N = 1,908)	<30 (n = 408)	30-<40 (n = 447)	40-<50 (n = 471)	50-<60 (n = 368)	>60 (n = 214)	*P*
Mean CAC score[a]	327.94 ± 737.51	406.13 ± 747.68	369.24 ± 804.44	356.81 ± 785.72	229.26 ± 591.01	198.75 ± 657.12	<0.001
Median CAC score	27	70	47	53	7	0	<0.001
CAC score category							
0	661 (34.6)	128 (31.4)	130 (29.1)	146 (31)	143 (38.9)	114 (53.3)	
>0-≤100	538 (28.2)	100 (24.5)	141 (31.5)	124 (26.3)	115 (31.3)	58 (27.1)	
>100-≤400	306 (16.0)	69 (16.9)	65 (14.5)	97 (20.6)	57 (15.5)	18 (8.4)	
>400	403 (21.1)	111 (27.2)	111 (24.8)	104 (22.1)	53 (14.4)	24 (11.2)	



In 1908 participants in Chronic Renal Insufficiency Cohort (CRIC) study, CACS were analyzed with eGFR

Budoff MJ et al. AJKD, 2011

Family history of premature coronary heart disease and coronary artery calcification

In 5347 asymp subjects in MESA study

TABLE 3. Presence of Any CAC and CAC ≥75th Percentile According to Parental and Sibling FamHx of Premature CHD*

	CAC >0	CAC ≥75th Percentile
Model 1		
No FamHx of CHD	1 (Reference)	1 (Reference)
FamHx of premature CHD in a parent only	1.52 (1.19 to 1.93)	1.60 (1.25 to 2.04)
FamHx of premature CHD in a sibling only	2.06 (1.64 to 2.58)	2.12 (1.70 to 2.66)
FamHx of premature CHD in both a parent and a sibling	2.74 (1.64 to 4.59)	2.83 (1.74 to 4.59)
Model 2		
No FamHx of CHD	1 (Reference)	1 (Reference)
FamHx of premature CHD in a parent only	1.48 (1.15 to 1.91)	1.68 (1.29 to 2.18)
FamHx of premature CHD in a sibling only	1.90 (1.49 to 2.40)	2.13 (1.67 to 2.71)
FamHx of premature CHD in both a parent and a sibling	3.23 (1.85 to 5.63)	3.18 (1.88 to 5.35)

Nasir K et al. Circulation, 2007

Waist-hip ratio is a significant predictor for coronary artery calcification in healthy Koreans

Table 4. Logistic Regression Analyses with Coronary Artery Calcification as the Dependent Variable

Model	*P* value	Exp (B)	95% CI	
			Lower	Upper
Age	<0.01	1.135	1.108	1.163
Gender	<0.01	0.169	0.095	0.302
Fasting blood glucose	0.001	1.013	1.005	1.021
Systolic blood pressure	0.184	1.010	0.995	1.024
Percent body fat	0.541	0.976	0.905	1.054
Lean body mass	0.699	0.992	0.950	1.035
Waist-hip ratio 1st Q	0.163	1.000	-	-
Waist-hip ratio 2nd Q	0.073	2.546	0.917	7.070
Waist-hip ratio 3rd Q	0.115	2.306	0.815	6.524
Waist-hip ratio 4th Q	0.030	3.125	1.119	8.728
HOMA-IR	0.712	1.046	0.823	1.331
Total cholesterol	0.185	1.004	0.998	1.010
Triglyceride	0.128	0.999	0.996	1.001

CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance.

Table 5. AUROC Curve of the Variables for the Prediction of Coronary Calcification

Variable	Cutoff values	Sens/spec (%)	AUC
Age	52.5	70.5/74	0.790
Fasting glucose	105.5	39.7/82.1	0.646
HbA1c	5.55	58.9/64.8	0.660
Weight (Men)	70.85	48.8/44.9	0.461
Weight (Women)	55.2	81/45.3	0.572
BMI	23.5	74/44.7	0.605
WC (Men)	83.4	67.2/43.9	0.549
WC (Women)	79.4	76.2/65.2	0.719
Waist-hip ratio	0.885	79.5/48.6	0.696
Lean mass	42.75	83.6/37.5	0.561
Percent body fat	21.45	74/27.9	0.485
HOMA-IR	2.22	61.6/54.3	0.602

AUROC, area under the receiver operating characteristic curve; Sens, sensitivity; spec, specificity; AUC, area under the curve; HbA1c, hemoglobin A1c; BMI, body mass index; WC, waist circumference; HOMA-IR, homeostasis model assessment of insulin resistance.

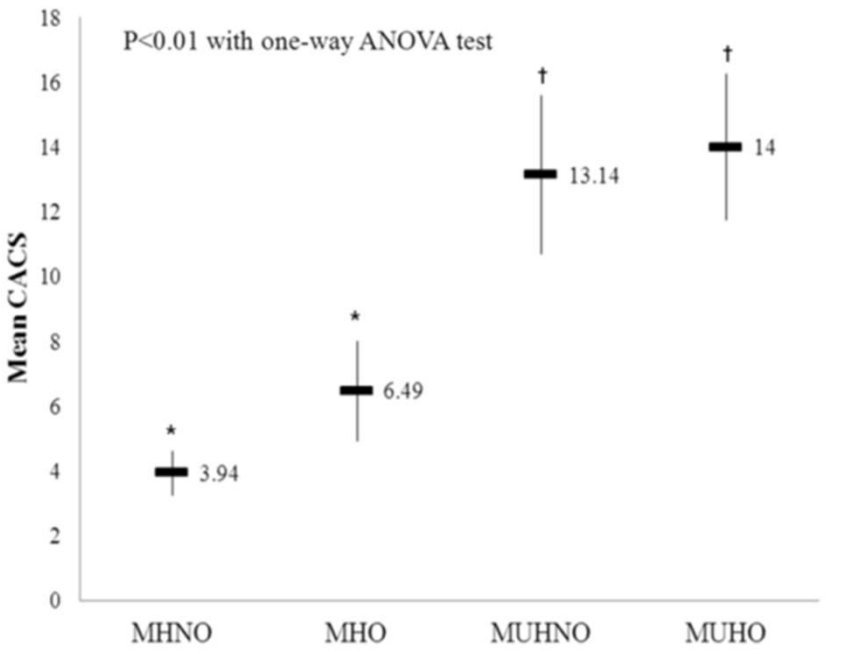
In 945 participants in medical check-up program (mean age 49 years), body composition analyses done with BIA methods

Yu JH et al. EnM, 2013

Metabolic Health Is More Closely Associated with Coronary Artery Calcification than Obesity

- In 24063 participants in Kangbuk Samsung Health Study, multi-detector computed tomography (MDCT) for coronary calcium scoring was undertaken by 64-slice spiral computed tomography scan.
- Being metabolically healthy was defined by satisfying less than 2 components among 6 metabolic factors (high TG, low HDL-C, high FBS, high BP, hs-CRP ≥ 0.2mg/L and being in the highest decile of HOMA-IR)
  - MHNO (metabolically healthy non-obese): Metabolically healthy & BMI <25 kg/m^2
  - MHO (metabolically healthy obese): Metabolically healthy & BMI ≥25 kg/m^2
  - MUHNO (metabolically unhealthy non-obese): Metabolically unhealthy & BMI <25 kg/m^2
  - MUHO (metabolically unhealthy obese): Metabolically unhealthy & BMI ≥25 kg/m^2

Metabolic Health Is More Closely Associated with Coronary Artery Calcification than Obesity



CACS categories		1~10		11~100	
variables	**Reference**	**OR**	**95% CI**	**OR**	**95% CI**
Model 1					
Age	+1 year	1.107	1.097~1.116	1.149	1.140~1.158
Sex	1:men, 2:women	0.262	0.203~0.338	0.273	0.216~0.334
Smoking	0:no smoking, 1:smoking	1.101	0.967~1.254	1.295	1.140~1.470
MHNO		1.000	–	1.000	–
MHO		1.348	1.129~1.919	1.250	1.049~1.489
MUHNO		1.513	1.264~1.811	1.733	1.471~2.042
MUHO		2.229	1.919~2.589	2.38	2.063~2.744
Model 2					
Age	+1 year	1.107	1.097~1.117	1.150	1.140~1.159
Sex	1:men, 2:women	0.275	0.210~0.352	0.275	0.217~0.348
SBP	+1 SD	1.139	1.028~1.261	1.133	1.079~1.190
Calcium	+1 SD	1.012	0.952~1.075	1.035	0.978~1.096
FBS	+1 SD	1.067	1.003~1.136	1.083	1.050~1.118
TC	+1 SD	1.283	1.197~1.377	1.285	1.197~1.377
TG	+1 SD	1.000	1.000~1.000	1.000	1.000~1.000
Hs-CRP	+1 SD	0.966	0.892~1.046	1.000	0.952~1.024
Smoking	0:no smoking, 1:smoking	1.077	0.945~1.227	1.281	1.127~1.455
MHNO		1.000	–	1.000	–
MHO		1.234	1.032~1.475	1.159	0.971~1.383
MUHNO		1.212	0.996~1.475	1.447	1.208~1.734
MUHO		1.667	1.397~1.989	1.896	1.602~2.245

Rhee EJ et al., Plos ONE, 2013

Power of Zero CAC

- Despite an excellent risk prediction related to the different levels of CAC, coronary events rarely occur in the presence of zero CAC…

"Myth of Zero CAC"

Joshi PH et al. J Nucl Cardiol, 2012

Diagnostic and prognostic value of absence of CAC

•A total of 13 studies were selected
•154 (0.47%) of 29312 pt without CAC had a CVD during a mean time of 4 years compared with 1749 (4.14%) of 42283 pt with CAC
•Sensitivity reached 98% and negative predictive value of 93% for significant CAD

Study	Cumulative Statistics		
	Point	Lower CI	Upper CI
Arad (2000)	0.05	0.001	0.25
Raggi (2001)	0.04	0.01	0.17
Wong (2002)	0.10	0.04	0.25
Kondos (2003)	0.10	0.05	0.21
Shaw (2003)	0.13	0.07	0.23
Shemesh (2004)	0.15	0.09	0.25
Greenland (2004)	0.18	0.12	0.26
Arad (2005)	0.18	0.14	0.22
LaMonte (2005)	0.18	0.12	0.26
Taylor (2005)	0.17	0.11	0.25
Budoff (2007)	0.16	0.11	0.23
Becker (2008)	0.15	0.11	0.22
Detrano (2008)	0.15	0.11	0.21
Summary Risk Ratio	**0.15**	**0.11**	**0.21**

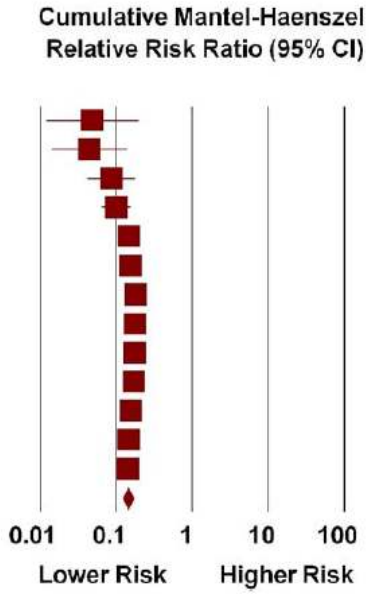


Figure 1. Forest Plot of the Cumulative Relative Risk Ratio for Events in No CAC Versus CAC Asymptomatic Patients

The relative risk ratio is calculated using a Mantel-Haenszel relative risk ratio (95% confidence interval [CI]). The individual study relative risks are reported, but the Forest plot details a cumulative relative risk ratio. All $p < 0.0001$. CAC = coronary artery calcium.

Sarwar A et al. JACC Cardiovasc Imag, 2009

What is the "Warranty period" for remaining normal?

- In 422 individuals with normal CAC scan undergoing annual scanning for 5 years
- Conversion from CAC 0 to >0 in 0.5, 1.2, 5.7, 6.2, 11.6% in 1,2,3,4,5 years
- 4 year as the warranty period for zero CAC patients
- Diabetes and smoking was the strongest predictors

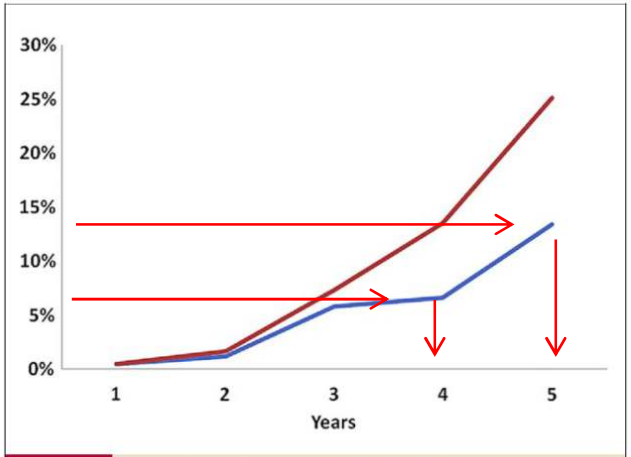


Figure 1 Conversion of Individuals With a Baseline Score of CAC = 0 to CAC >0 Over Time

Both cumulative percent **(red line)** as well as yearly incidence **(blue line)** of coronary artery calcium (CAC) conversion is low before the first 4 years.

Table 6 Univariate and Multivariate Cox Proportional Hazards Ratio Comparison for CAC Progression in Propensity-Matched Cohort

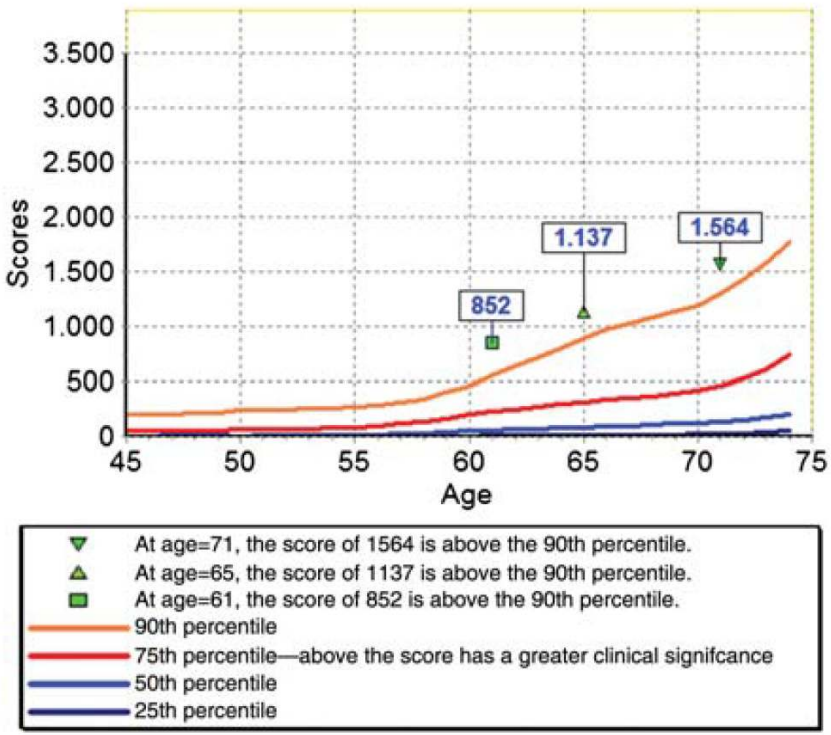
	Univariate HR	p Value	Multivariate HR	p Value
Age (per yr)	1 (0.98–1.01)	0.834		
Male	0.85 (0.67–1.07)	0.17		
Cholesterol	1.08 (0.83–1.41)	0.545		
Hypertension	1.28 (1.02–1.61)	0.031		
Diabetes mellitus	1.63 (1.17–2.26)	0.004	2.07 (1.47–2.9)	<0.001
Smoking	1.33 (1.05–1.67)	0.015	1.29 (1.02–1.63)	0.029
CAC >0	11.7 (8.75–15.64)	0.828	14.96 (11.22–19.96)	<0.001

Abbreviations as in Table 3.

Min JK et al. JACC, 2010

Progression of coronary artery calcification

- CAC progression rate ranges from 15 to 25% per year
- Mean annual increase 24-33%
- Risk of progression predicted by male sex, hyperlipidemia, smoking, baseline CAC scores, HTN, diabetes older age



Erbel R et al. Eur Heart J, 2012

Progression of coronary calcium and incident coronary heart disease events

In 6778 subjects in MESA (45-84 years) with CACS measurement average 2.6 years apart. Average 5.4 yrs F/U after second scan

Table 2 Hazard Ratio Examining the Likelihood of Total CHD and Hard CHD by Progression of CAC Among Those With CAC = 0 at Baseline (Multi-Ethnic Study of Atherosclerosis MESA)

	Total CHD	Hard CHD
Event rate per 1,000 person-years, annualized rate (%) [events/subjects]		
Absolute Δ in CAC/yr		
No change	1.6 (0.16) [34/2,861]	1.1 (0.11) [24/2,861]
Any progression	2.6 (0.26) [10/535]	1.8 (0.18) [7/535]
Total	1.8 (0.18) [44/3,396]	1.3 (0.13) [31/3,396]
Hazard ratio (95% confidence interval)		
Unadjusted absolute Δ in CAC/yr	[44/3,396]	[31/3,396]
No change	Reference	Reference
Any progression	1.5 (0.7–3.5)	1.5 (0.6–3.9)
Adjusted absolute Δ in CAC/yr*	[44/3,396]	[31/3,396]
No change	Reference	Reference
Any progression	1.0 (0.4–2.3)	1.1 (0.4–2.8)
Unadjusted absolute Δ in CAC/yr (per 5 U)	[44/3,396] 1.3† (1.1–1.8)	[31/3,396] 1.4† (1.1–1.9)
Adjusted absolute Δ in CAC/yr* (per 5 U)	[44/3,396] 1.4† (1.0–1.9)	[31/3,396] 1.5† (1.1–2.1)

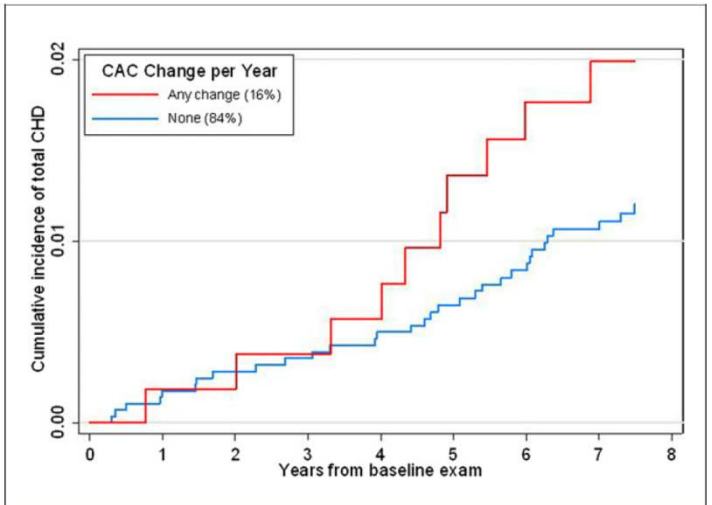


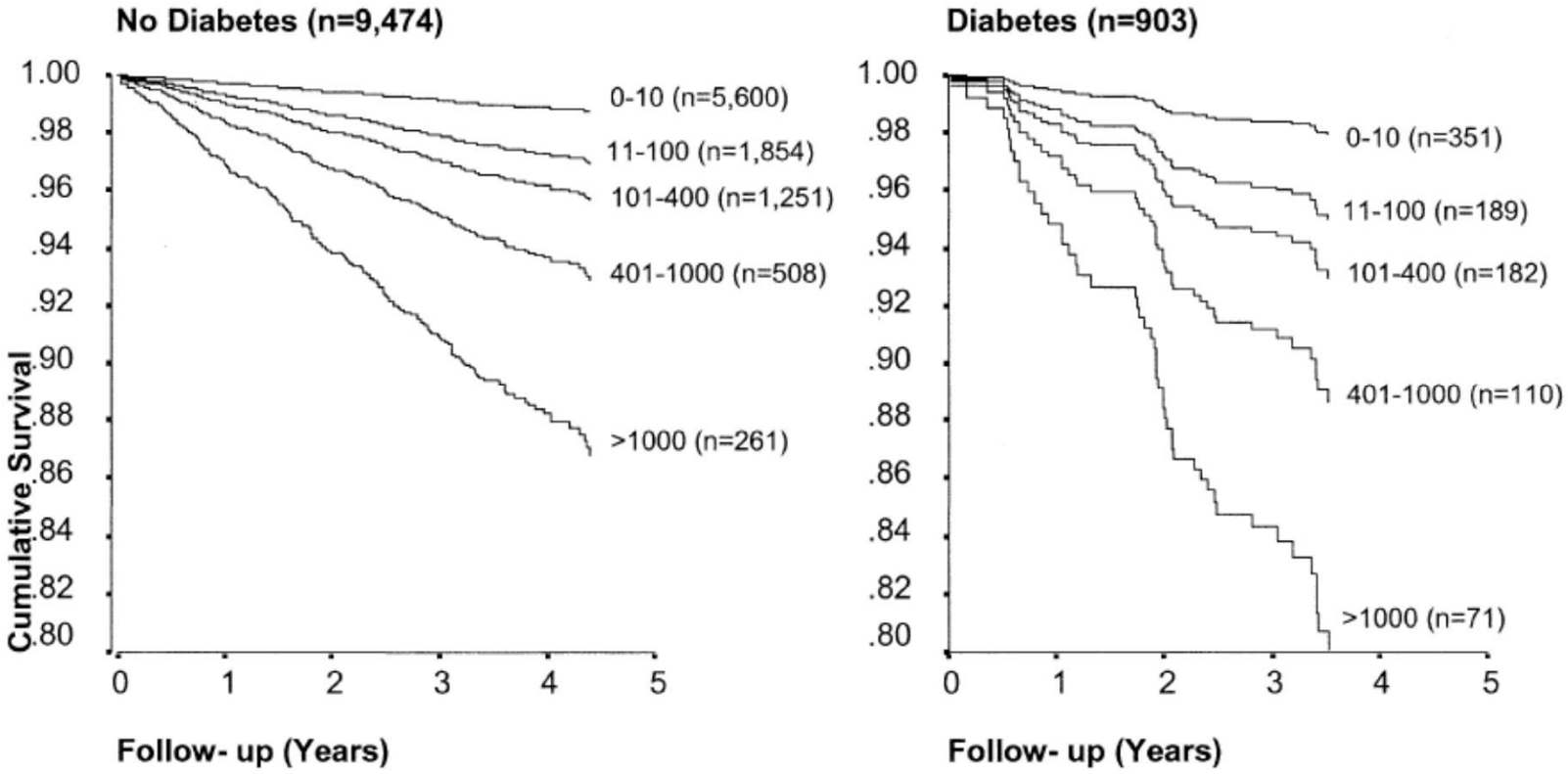
Figure 1 Kaplan-Meier Plot of Cumulative Incidence of Total CHD Among Persons With CAC = 0 at Baseline

Budoff MJ et al. JACC, 2013

CAC and diabetes

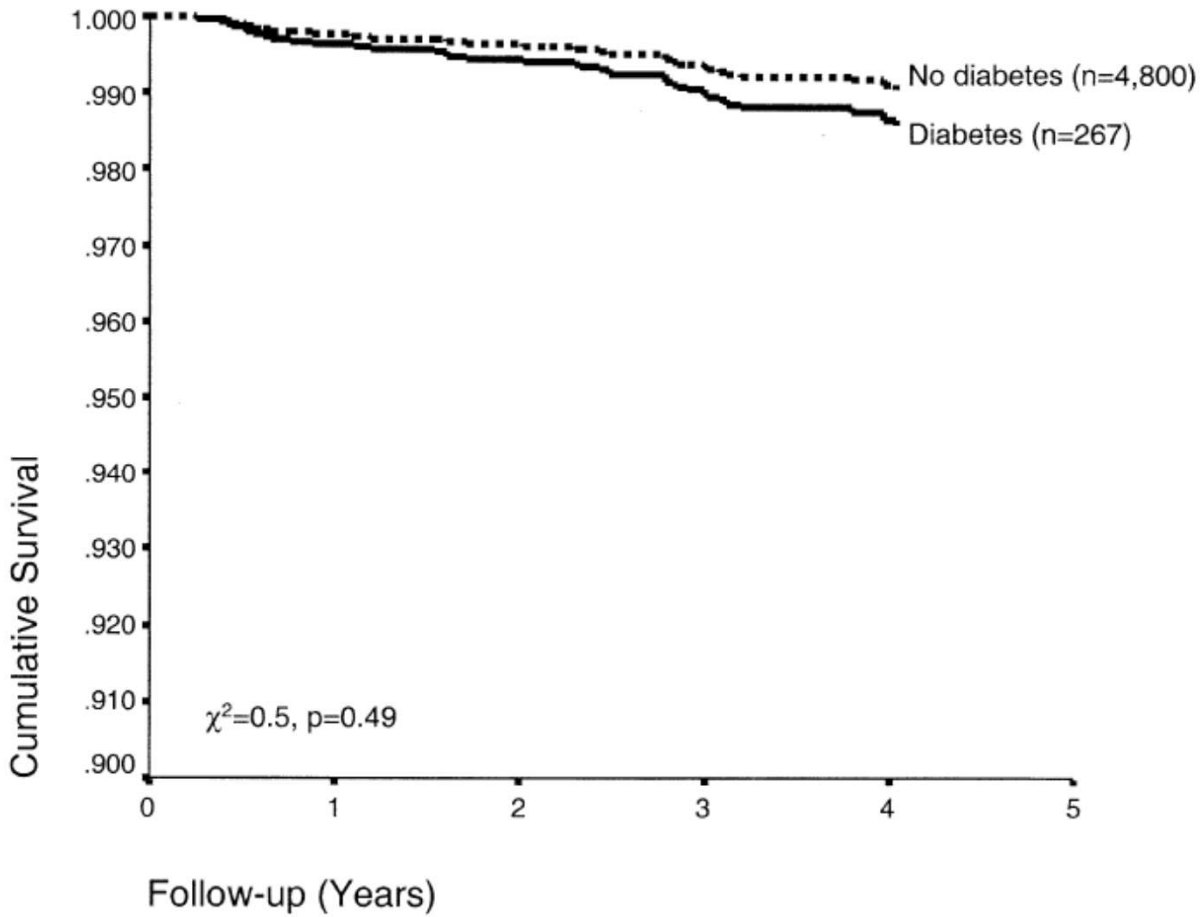
Prognostic value of CACS in subjects with and without diabetes

- 10,377 asympt subjects with a mean age of 54 years (903 diabetes) followed up for 5 years after baseline CACS screening
- Death rates were 3.5% and 2.0% in subjects with and without diabetes



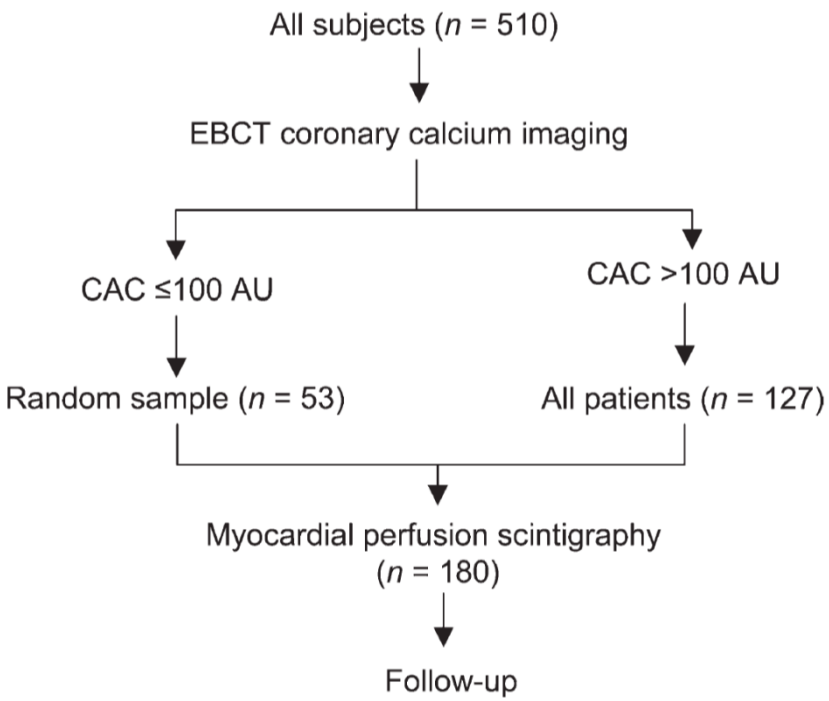
Raggi P et al. JACC, 2004

Patients with zero CAC showed similar CVD risk compared with the patients without diabetes

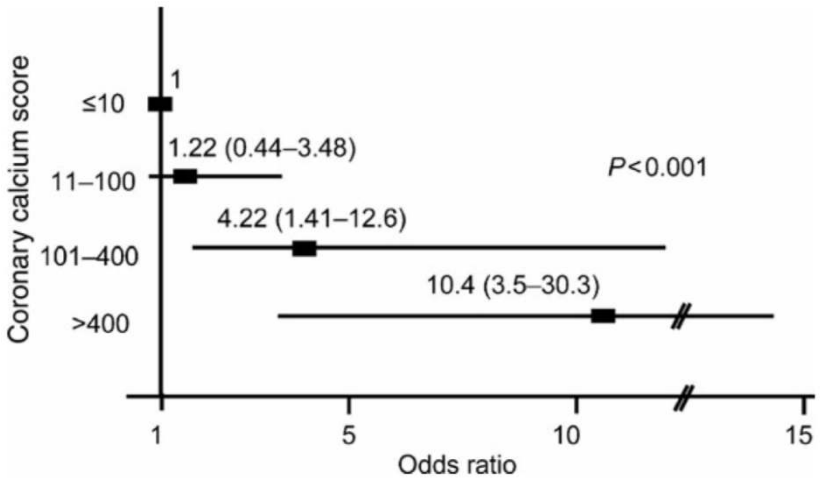


Raggi P et al. JACC, 2004

CAC superior to CV risk factors for predicting silent MI in patients with T2DM



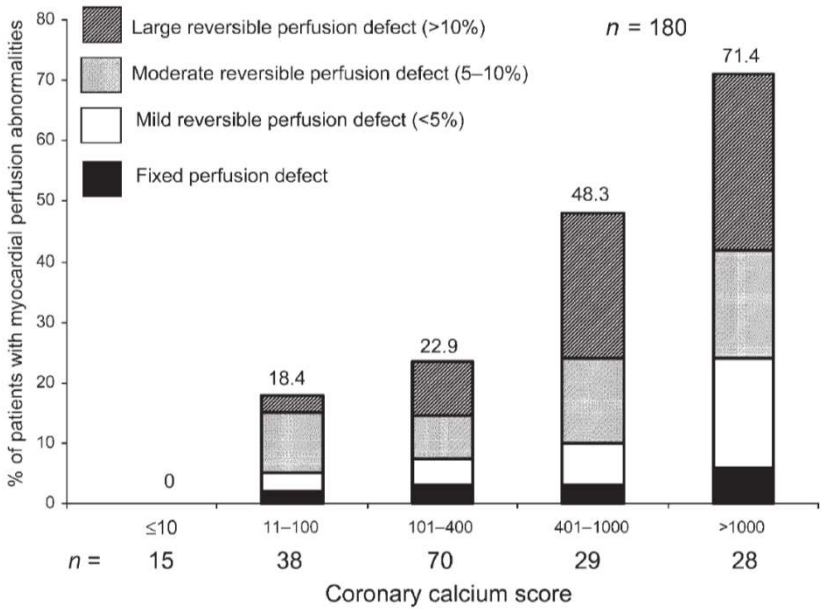
2.2 years

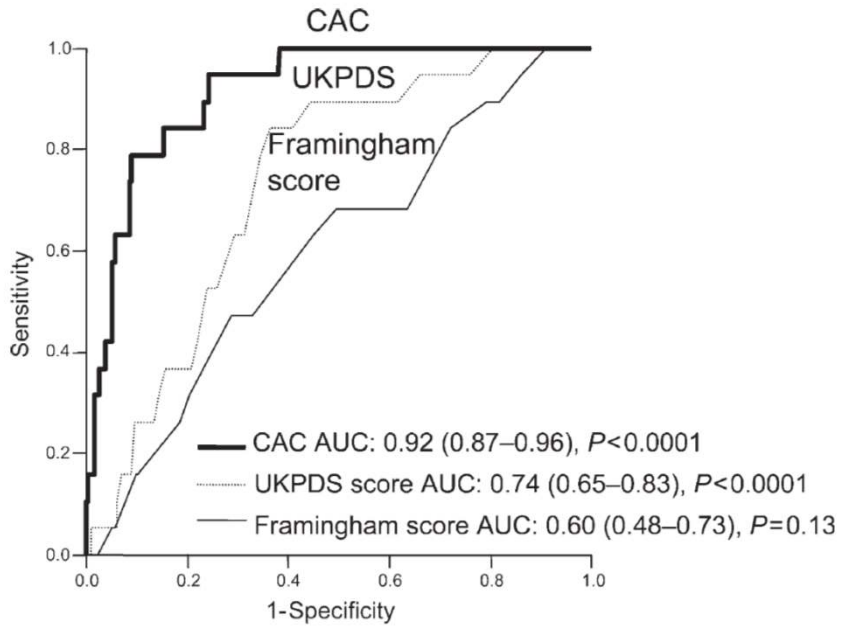


Predictors for MP abnormality

Anand DV et al. Eur Heart J, 2006

CAC superior to CV risk factors for predicting silent MI in patients with T2DM





Anand DV et al. Eur Heart J, 2006

The relationship between CACS, plasma OPG level and arterial stiffness in asymptomatic T2DM patients

In 110 T2DM patients, with DM duration of 6.5 years, mean age of 57.2 years

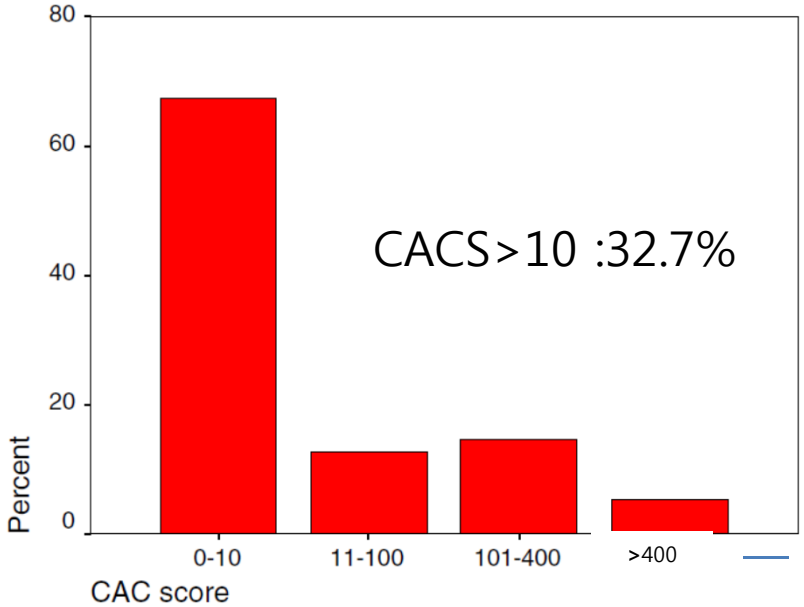


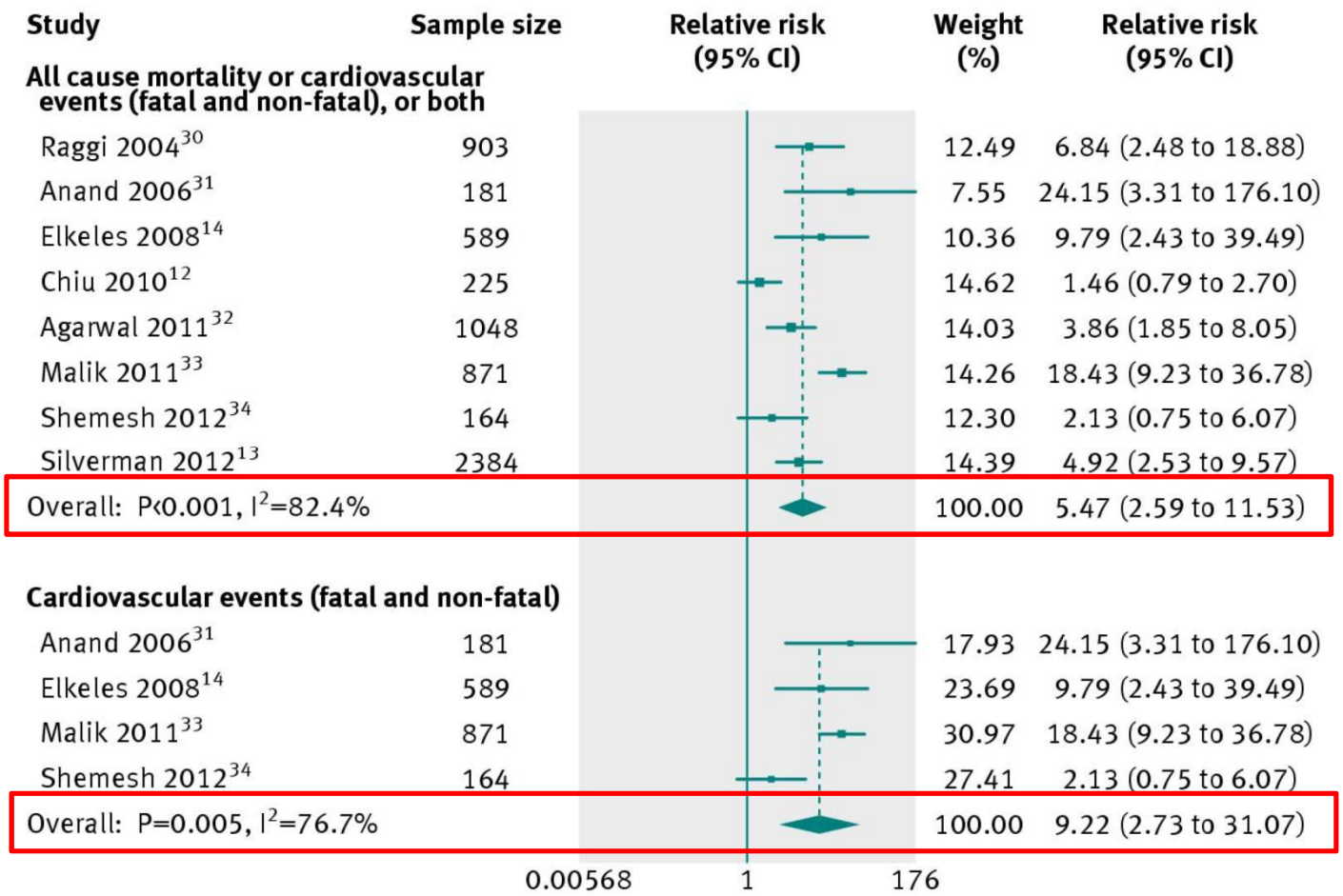
Fig. 1 Distribution of CAC score in all subjects

Table 3 Bivariate correlation analyses between CACS, OPG, baPWV and variables

	CAC		OPG		PWV	
	r	*P*	*r*	*P*	*r*	*P*
Age	0.366	<0.001	0.373	0.002	0.636	<0.001
CAC	–	–	0.336	0.005	0.239	0.024
OPG	0.336	0.005	–	–	0.282	0.031
PWV	0.239	0.024	0.282	0.031	–	–
BMI	0.008	0.944	0.015	0.920	−0.091	0.458
FBS	0.092	0.344	0.140	0.251	0.217	0.041
HbA1C	−0.061	0.534	0.077	0.535	0.050	0.649
T-Chol	−0.090	0.358	−0.053	0.666	0.064	0.551
HDL-C	0.027	0.782	−0.019	0.875	−0.008	0.940
LDL-C	−0.057	0.563	−0.116	0.351	−0.040	0.713
TG	0.072	0.468	0.031	0.805	0.171	0.114
Systolic BP	0.230	0.021	0.142	0.271	0.517	<0.001
Diastolic BP	0.162	0.106	0.035	0.787	0.297	0.006
Duration of DM	0.118	0.270	0.065	0.635	0.041	0.724
Creatinine	0.071	0.467	−0.137	0.266	0.010	0.924
hsCRP	−0.70	0.500	−0.230	0.075	0.096	0.393

Jung CH et al. Acta Diabetol, 2010

CACS prediction of all-cause mortality and cardiovascular events in people with T2DM: systemic review



Kramer CK et al. BMJ, 2013

CAC score is a better predictor of subsequent CVD events than carotid IMT

The Multi-Ethnic Study of Atherosclerosis (MESA)

- In 6698 subjects free of CVD were follow-up for 5.3 years
- Standardized carotid IMT and CAC were measured at baseline

Table 2. Hazard Ratios (HRs) for an Incident CVD, CHD, or Stroke Event in Relation to a 1-SD Increment of Maximal Carotid IMT or CAC Score (MESA, 2000-2004)

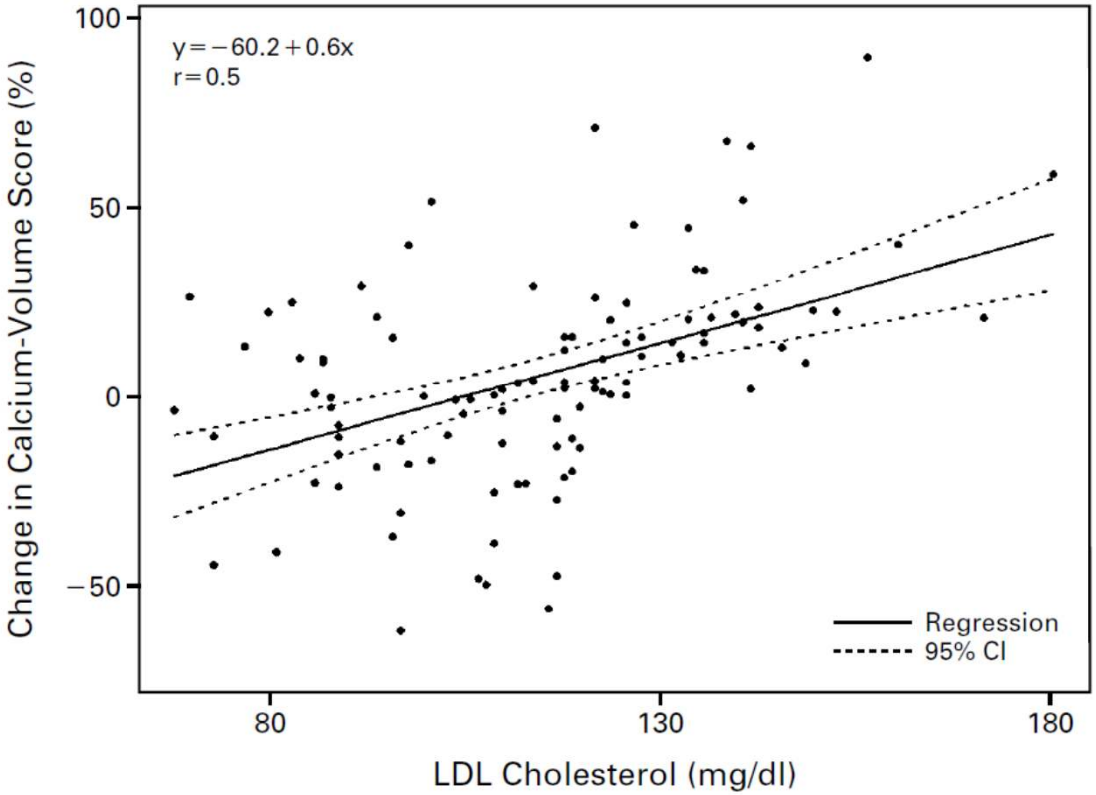
Measure[a]	HR Per 1-SD Increment (95% CI)	*z* Statistic	*P* Value
CVD (n = 222)			
Age-, race-, and sex-adjusted			
z Score max IMT	1.3 (1.1-1.4)	4.1	<.001
ln(CAC score + 1)	2.1 (1.8-2.5)	8.6	<.001
Multivariable-adjusted[b]			
z Score max IMT	1.2 (1.0-1.3)	2.7	.007
ln(CAC score + 1)	1.9 (1.6-2.2)	7.5	<.001
CHD (n = 159)			
Age-, race-, and sex-adjusted			
z Score max IMT	1.2 (1.0-1.4)	2.5	.01
ln(CAC score + 1)	2.5 (2.1-3.1)	8.8	<.001
Multivariable-adjusted[b]			
z Score max IMT	1.1 (1.0-1.3)	1.5	.12
ln(CAC score + 1)	2.3 (1.9-2.8)	7.9	<.001
Stroke (n = 59)			
Age-, race-, and sex-adjusted			
z Score max IMT	1.4 (1.2-1.8)	3.5	.001
ln(CAC score + 1)	1.1 (0.8-1.5)	0.8	.41
Multivariable-adjusted[b]			
z Score max IMT	1.3 (1.1-1.7)	2.5	.01
ln(CAC score + 1)	1.1 (0.8-1.4)	0.4	.71

Folsom AR et al. Arch Intern Med, 2008

Modification of CAC progression?

Statin is effective in coronary calcium volume reduction

In 149 patients with treatment with statin or no statin; F/U for 1 year



Callister TQ et al. NEJM, 1998

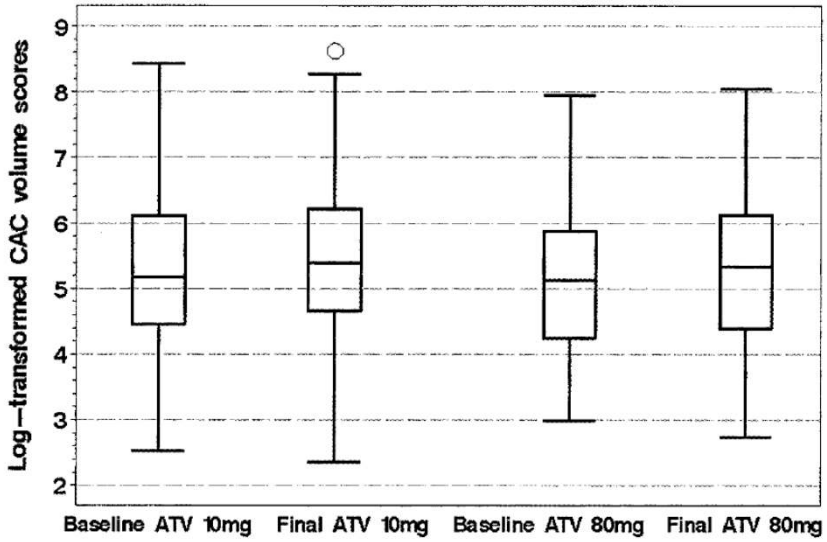
No effect of statins on CAC progression

In 1005 asympt subjects; atorva 20mg vs. placebo; aspirin in all participants; mean duration of 4.3 years

In 471 subjects without CVD; atorva 10 mg vs. 80 mg for 12 months

Table 3. Effect of Treatment on Coronary Calcium Score

	Treatment	Control	p Value
Baseline			
n	490	515	
Mean	528	563	—
Median	379	370	0.96
25th, 75th percentiles	184, 636	183, 671	—
Year two			
n	417	431	—
Mean	647	723	—
Median	482	505	—
25th, 75th percentiles	231, 820	251, 901	
Change (year two minus baseline)			
Absolute	137 ± 310	155 ± 358	0.86
Percent	38 ± 75	36 ± 58	0.86
Year four			
n	281	288	
Mean	846	922	—
Median	623	673	—
25th, 75th percentiles	335, 1,077	343, 1,138	—
Change (year four minus baseline)			
Absolute	331 ± 421	323 ± 385	0.80
Percent	81 ± 89	73 ± 93	0.76



Arad Y et al. JACC, 2005
Schmermund A et al. Circulation, 2006

Explanation for the discrepancy..?

- Longer periods of monitoring of CAC necessary to detect an effect of statin Tx
- Statins fundamentally alter the relationship between calcified plaque extent and CV outcomes; statins are affecting the non-calcified plaque and no change is detectable by CAC measurement
- At the molecular level, the removal of lipid deposits by statin may induce vascular calcification by macrophages, VSMC and osteoclast-like cells..("vascular healing"?)

Who is the candidate for CACS testing?

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

Coronary calcium score	
Class IIa	Measurement of CAC is reasonable for CV risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-year risk) : B
Class IIb	Measurement of CAC may be reasonable for CV risk assessment in persons at low to intermediate risk (6% to 10% 10-year risk) : B
Class III (no benefit)	Persons at low risk (<6% 10-year risk) should not undergo CAC measurement for CV risk assessment : B

Among intermediate-risk patients, the use of CAC is associated with a net reclassification improvement of 55%

Greenland P et al. Circulation, 2010

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

Recommendation for patients with diabetes	
Class IIa	In asymptomatic adults with diabetes, 40 years of age and older, measurement of CAC is reasonable for CV risk assessment : B
Class IIb	1. Measurement of HbA1c may be considered for CV risk assessment in asymptomatic adults with diabetes : B
	2. Stress MPI may be considered for advanced CV risk assessment in asymptomatic adults with diabetes or when previous risk assessment testing suggests a high risk of coronary heart disease, such as a CAC score of 400 or greater : C

Greenland P et al. Circulation, 2010

Screening for Coronary Artery Disease in Patients With Diabetes

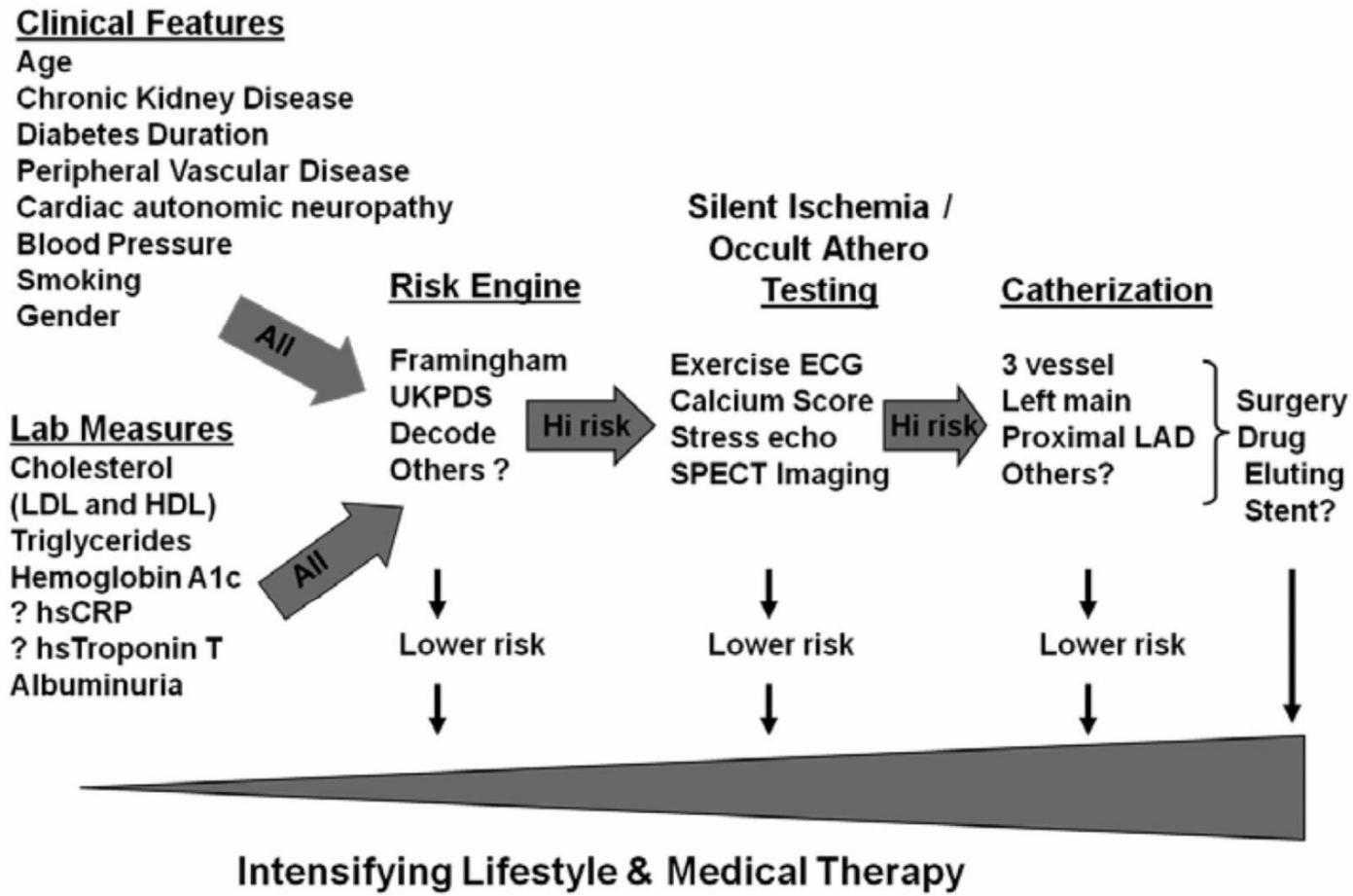
If coronary calcium testing is performed, it appears reasonable to proceed with further testing in diabetic patients with calcium scores >400, considering factors such as age and renal function.

If a patient with diabetes shows a CACS > 400, actions should be taken for the further cardiac testing looking for coronary lesion…

Diabetes Care 30:2729–2736, 2007

Screening for Coronary Artery Disease in Type 2 Diabetes

Charles T
University o



(*J Clin Endocrinol Metab* 97: 1434–1442, 2012)

Summary and conclusion

- CACS is a useful, non-invasive and accurate method for the assessment of CV risk
- Zero CACS is a useful marker for reduced CV risk – warranty for 4 years
- CACS higher than 400 in patients with diabetes is a warning for the existence of CHD – further testing is needed
- CACS is recommended only in intermediate global risk group in asymptomatic subjects
- More evidences are accumulating for the high predictability of CACS in CVD
- The effect of statin on CACS progression is under debate

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- Prof. Se Eun Park

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