Imaging For Prevention? Role of Coronary Calcium Scoring in High Risk Asymptomatic Patients

May 5, 2016

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Coronary Artery Disease: Silent Killer Symptoms are a poor surrogate of risk!

4 out of every 10 individuals who develop a heart attack or sudden death from CAD *have no prior warning or symptoms.*

American Heart Association. Heart disease and stroke update 2005. Available at: http:www.americanheart.org. Accessed July 27, 2006.

Approaches to Rx of CV Risk

- Global: Polypill
- Selective: Imaging

The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials

Cholesterol Treatment Trialists' (CTT) Collaborators*

Summary

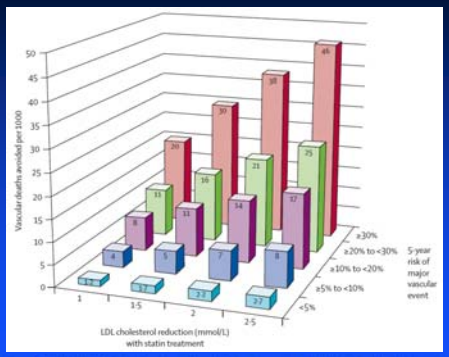
Background Statins reduce LDL cholesterol and prevent vascular events, but their net effects in people at low risk of vascular events remain uncertain.

Methods This meta-analysis included individual participant data from 22 trials of statin versus control (n=134 537; mean LDL cholesterol difference 1·08 mmol/L; median follow-up 4·8 years) and five trials of more versus less statin (n=39 612; difference 0·51 mmol/L; 5·1 years). Major vascular events were major coronary events (ie, non-fatal myocardial infarction or coronary death), strokes, or coronary revascularisations. Participants were separated into five categories of baseline 5-year major vascular event risk on control therapy (no statin or low-intensity statin) (<5%, ≥5% to <10%, ≥10% to <20%, ≥20% to <30%, ≥30%); in each, the rate ratio (RR) per 1·0 mmol/L LDL cholesterol reduction was estimated.

Findings Reduction of LDL cholesterol with a statin reduced the risk of major vascular events (RR 0·79, 95% CI 0·77–0·81, per 1·0 mmol/L reduction), largely irrespective of age, sex, baseline LDL cholesterol or previous vascular disease, and of vascular and all-cause mortality. The proportional reduction in major vascular events was at least as big in the two lowest risk categories as in the higher risk categories (RR per 1·0 mmol/L reduction from lowest to highest risk: 0·62 [99% CI 0·47–0·81], 0·69 [99% CI 0·60–0·79], 0·79 [99% CI 0·74–0·85], 0·81 [99% CI 0·77–0·86], and 0·79 [99% CI 0·74–0·84]; trend p=0·04), which reflected significant reductions in these two lowest risk categories in major coronary events (RR 0·57, 99% CI 0·36–0·89, p=0·0012, and 0·61, 99% CI 0·50–0·74, p<0·0001) and in coronary revascularisations (RR 0·52, 99% CI 0·35–0·75, and 0·63, 99% CI 0·55–0·70; both p<0·0001). For stroke, the reduction in risk in participants with 5-year risk of major vascular events lower than 10% (RR per 1·0 mmol/L LDL cholesterol reduction 0·76, 99% CI 0·63–0·95, p=0·0012) was also similar to that seen in higher risk categories (trend p=0·3). In participants without a history of vascular disease, statins reduced the risks of vascular (RR per 1·0 mmol/L LDL cholesterol reduction 0·85, 95% CI 0·77–0·95) and all-cause mortality (RR 0·91, 95% CI 0·85–0·97), and the proportional reductions were similar by baseline risk. There was no evidence that reduction of LDL cholesterol with a statin increased cancer incidence (RR per 1·0 mmol/L LDL cholesterol reduction 1·00, 95% CI 0·96–1·04), cancer mortality (RR 0·99, 95% CI 0·93–1·06), or other non-vascular mortality.

Interpretation In individuals with 5-year risk of major vascular events lower than 10%, each 1 mmol/L reduction in LDL cholesterol produced an absolute reduction in major vascular events of about 11 per 1000 over 5 years. This benefit greatly exceeds any known hazards of statin therapy. Under present guidelines, such individuals would not typically be regarded as suitable for LDL-lowering statin therapy. The present report suggests, therefore, that these guidelines might need to be reconsidered.

Overall vascular risk is more important than LDL-reduction in determining statin outcome as judged by vascular deaths avoided per 1000



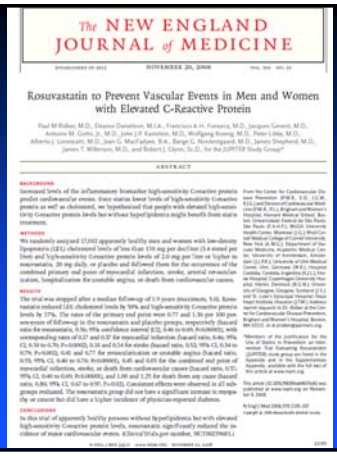
Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012; 380: 581–90

JUPITER Trial
NEJM 2008

N=17,802 apparently healthy men and women
LDL < 130 mg/dl
Hs-CRP ≥ 2.0 mg/l

Rx: Rosuvastatin 20 mg qd v placebo

Finding: Significant and substantial reduction of incidence of major CV events.

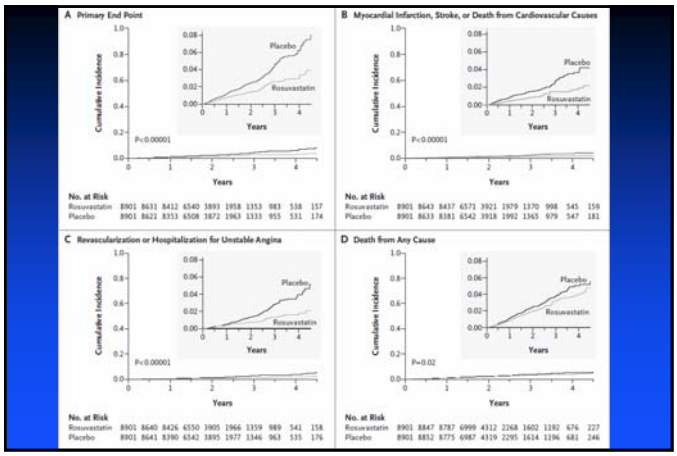


The NEW ENGLAND JOURNAL of MEDICINE

NOVEMBER 20, 2008

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

ABSTRACT



Questions:

1. Is CAD present?
   If so, how much risk of MI & death?

2. If CAD is present, is the treatment effective?
   What is the residual risk on Rx?

59-Year-Old Asymptomatic Man

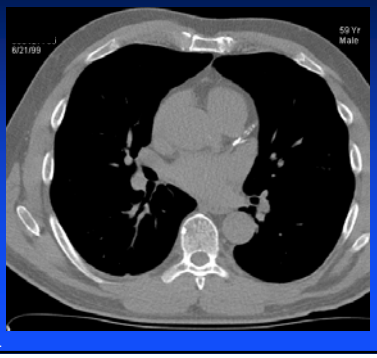
Would you treat this patient with aspirin and a statin?

LDL,
100 mg/dL
HDL,
53 mg/dL
+ FH

Cedars Sinai Medical Center.

59-Year-Old Asymptomatic Man

Would you treat this patient with aspirin and a statin?



LDL,
100 mg/dL
HDL,
53 mg/dL
+ FH

CCS, 526
(87th %)

Cedars Sinai Medical Center.

Nov 2013 ACC AHA Consensus Statement to Simplify Prevention

Stone NJ. Circulation. 2013;doi:10.1161/01.cir.0000437738.63853.7a.
Stone NJ. J Am Coll Cardiol. 2013;doi:10.1016/j.jacc.2013.11.002.

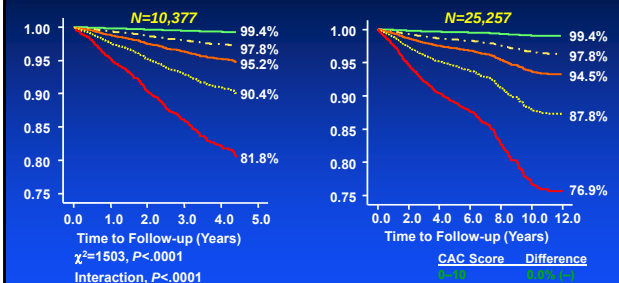
2013 CV Risk Calculator:
http://static.heart.org/ahamah/risk/Omnibus_Risk_Estimator.xls

FOUR STATIN GROUPS:

1. People with atherosclerosis-related CVD, defined as ACS; history of MI, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack presumed to be of atherosclerotic origin; and peripheral arterial disease or revascularization.
2. People with LDL ≥190 mg/dL.
3. People with type 2 diabetes aged 40 to 75 years.
4. People with an estimated 10-year risk for CVD of 7.5% or higher aged 40 to 75 years.

- High-intensity statin dose: daily dose lowers LDL by ≥50%.
- Moderate statin dose: daily dose lowers LDL by 30% to <50%.

Near- & Long-Term Survival From 2 EBT Centers: Nashville, TN and Los Angeles, CA



Adapted from *J Am Coll Cardiol*. Vol 43, Raggi P, Shaw LJ, Berman DS, Callister TQ. 1663-1669, ©2004 with permission from the American College of Cardiology Foundation; Budoff D et al. In press.

Case 2: Is coronary atherosclerosis adequately treated?

- 58 years old, sedentary, non-smoker. Negative family history
- Type 2 diabetic
- HDL low, triglycerides high
- Obese, waist 40”
- Coronary CA++ 219
- Rx HBP, cholesterol pills
- LDL “not high”, CRP ok
- Negative stress echo, LVH

Has treatment response been identified adequately?

Tim Russert
05/07/1950 – 6/13/2008

- 58 years old, sedentary, non-smoker. Negative family history
- Type 2 diabetic
- HDL low, triglycerides high
- Obese, waist 40”
- Coronary CA++ 219
- Rx HBP, cholesterol pills
- LDL “not high”, CRP ok
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How could inadequate treatment response have been identified?

MPS detects CAD, predicts outcome, directs treatment and monitors treatment response across a broad spectrum of CV risk.

- MPS integrates true myocardial perfusion with flow effects of CAD at all levels of coronary tree: focal, diffuse, and vasospasm
- Continuous predictor of morbid events incremental to ECG Duke TES
- TID, Post-stress LV volume indices, EF identify CV risk missed by perfusion alone
- Similar prognostic power as coronary arteriography
- Prognostic Value - With or Without known CAD
- Identifies subsets at high risk of cardiac death that benefit from revascularization
- Identifies very low risk (<<1%) from intermediate risk pre-test patients with suspected CAD that will not benefit substantially from costly medical treatments
- Identifies early CAD (altered flow reserve) in DM and multiple CRFs that benefit from lifestyle and medical Rx
- Gender
- Stress Modality Exercise / Pharmacologic
- Age Young / Older
- Post MI
- Post Revascularization PCI / CABG
- Prior to non-cardiac surgery
- Complementary to CAC for risk assessment in at risk asymptomatic patients
- Monitors effectiveness of medical therapy
- END: Cost effectively Gatekeeper to coronary angiography
- Like any test, its value is underestimated when results are not quantified

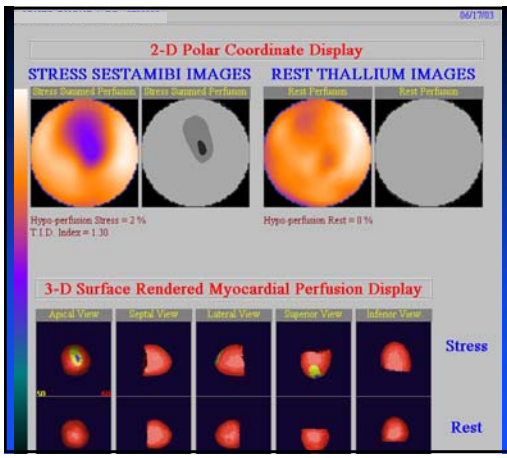
URMC CARDIOLOGY

52 y.o. anxious asymptomatic woman with anklyosing spondylitis, hs-CRP 4.4

+ FH mother age 52 had USA and CABG

Should this patient be treated for CAD?

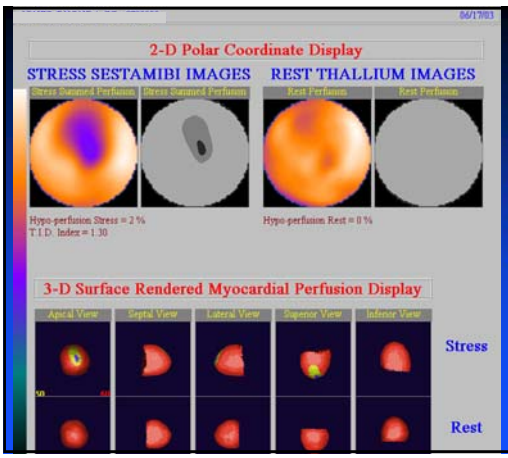
URMC CARDIOLOGY



52 y.o. anxious asymptomatic woman with anklyosing spondylitis, hs-CRP 4.4

+ FH mother age 52 had USA and CABG

Should this patient be treated for CAD?

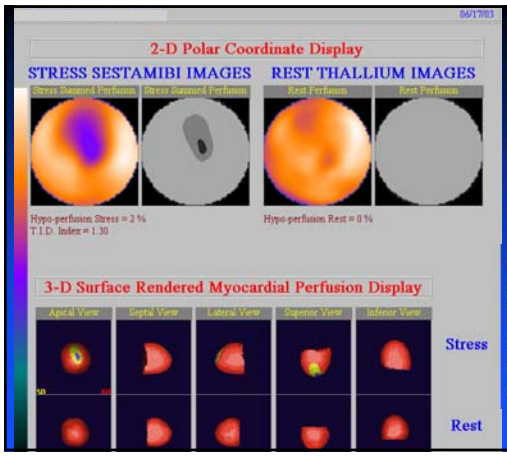


52 y.o. woman with anklyosing spondylitis, hs-CRP 4.4

+ FH

Coronary angiography: Normal

Rx?



52 y.o. woman with anklyosing spondylitis, hs-CRP 4.4

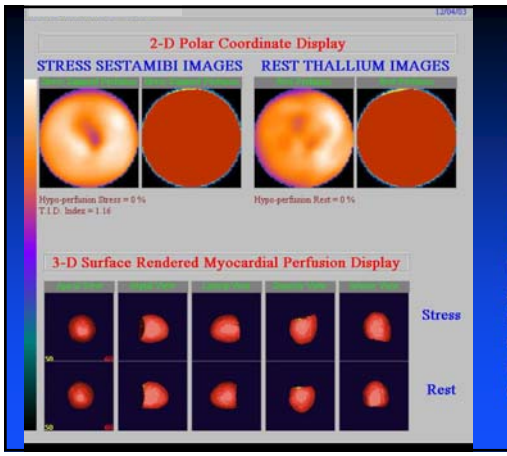
Coronary angiography: Normal

Rx?

ASA 162 mg qd
Clopidogrel 75 mg qd
Pravastatin 40 mg qhs
Ramipril 5 mg qd
Naproxen prn

Benefit of TLC and Medical Therapy: Reflected in the Lipid Profile?

DATE	CHOL	HDL	RATIO	LDL	TG	Weight	BMI	COMMENTS
1/03								HsCRP 6.6
3/4/03	186	47	4.0	121	90			TSH 0.22; hsCRP 2.8
5/29/03	177	52	3.4	111	70			TSH 0.15; hsCRP 4.4
7/2/03						5ft 4" 147 #	25.2	CBC WNL; Profile 8 WNL
8/21/03	161	51	3.2	98	59			Pravastatin 40 mg qhs hsCRP 2.7
11/03	173	59	2.9	104	51			Pravastatin 40 mg qhs



52 y.o. woman with anklyosing spondylitis, hs-CRP 4.4

Coronary angiography: Normal

Rx?

ASA 162 mg qd
Clopidogrel 75 mg qd
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53M mild chest pain at start of exercise, gets better with exercise.

Diagnostic test?

53M mild chest pain at start of exercise, gets better with exercise.

Coronary arteriography (Elmira, 2005):

50 - 75% left main
80% LAD prox, 60% mid stenosis

Treatment recommendation: CABG

53M mild chest pain at start of exercise, gets better with exercise.

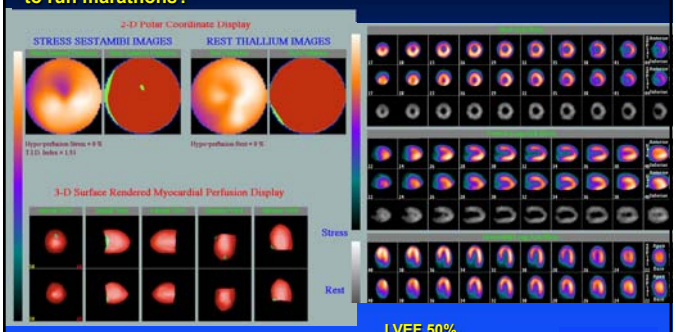
Coronary arteriography (Elmira, 2005):

50 - 75% left main
80% LAD prox, 60% mid stenosis

Treatment recommendation: CABG

Patient refuses CABG: Starts strict Vegan diet. (Diet advocated by Caldwell B. Esselstyn, MD, CCF)
Simvastatin 20 mg daily
FLP: 128 / 55 / 2.3 / 60 / 63

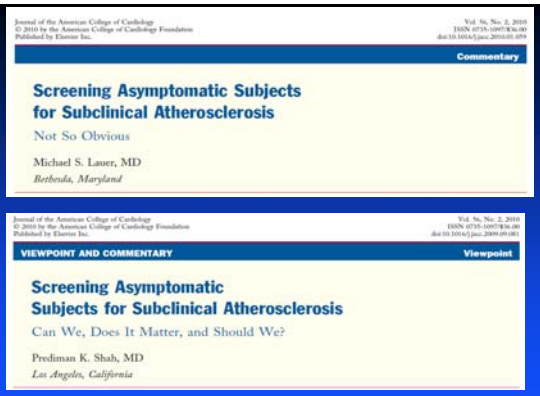
58M vegan asymptomatic, known LM CAD, marathoner, 9 min Bruce protocol, limited by RN d/t 2 mm HSTD, post-exercise LVEF 50%. Safe to run marathons?



June 2010

LVEF 50%

ESVI 58 ml/m2



Commentary

Screening Asymptomatic Subjects for Subclinical Atherosclerosis

Not So Obvious

Michael S. Lauer, MD

Bethesda, Maryland

VIEWPOINT AND COMMENTARY

Viewpoint

Screening Asymptomatic Subjects for Subclinical Atherosclerosis

Can We, Does It Matter, and Should We?

Prediman K. Shah, MD

Los Angeles, California

Dr. Lauer's Key Points

- Large-scale randomized trials have been conducted on a variety of screening tests, and screening tests for coronary artery disease should be subject to the same level of rigor.
- It is "not at all clear" that a risk stratification paradigm is the best way to reduce substantially the burden of clinically active coronary artery disease in our population.
- *"Our next step is to have the humility to admit that we do not know which approach or combination of approaches is best, but that, in the public interest, we will join forces to design and implement the definitive large-scale randomized trials that our patients and the public should rightly demand."*

Dr. Shah's Points - 1

- "Despite the lack of randomized clinical trial evidence, the totality of observational evidence supports imaging-guided management because:"

–Detecting disease in order to prevent its consequences is likely better than simply identifying risk factors that have only a modest specificity and a highly variable relationship to the development of disease.

–Imaging can reclassify intermediate- and low-risk FRS subjects into higher-risk strata for which more aggressive medical therapy would be recommended.

–Imaging-based identification of at-risk people may improve adherence to risk-modifying interventions.

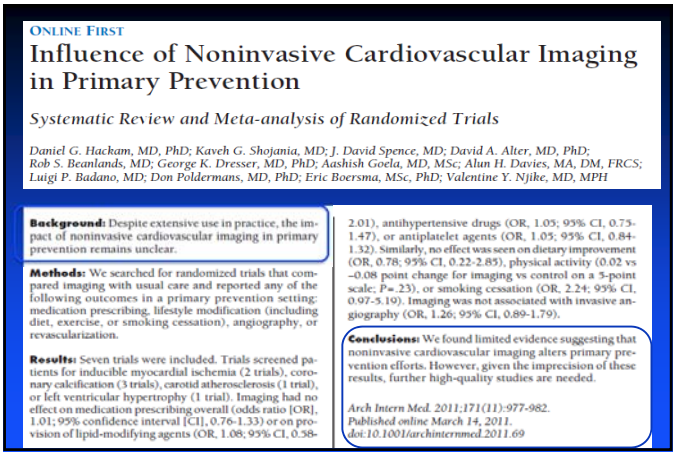
Dr. Shah's Points - 2

- "An important consideration in any recommendation for large-scale screening is the cost-effectiveness of such an approach."

–Diamond and Kaul (2007) compared the costs and effectiveness of unconditional treatment of all risk factor– based treatment recommended by the NCEP and imaging-based treatment.

–The analysis supported cost-effectiveness of the imaging-based algorithm over the current NCEP strategy, but suggested that unconditional treatment was most cost- effective.

–They also pointed out that if the imaging-based approach improves adherence to preventive therapy, its cost-effectiveness could surpass unconditional treatment.



ONLINE FIRST

Influence of Noninvasive Cardiovascular Imaging in Primary Prevention

Systematic Review and Meta-analysis of Randomized Trials

Daniel G. Hackam, MD, PhD; Kaveh G. Shojania, MD; J. David Spence, MD; David A. Alter, MD, PhD; Rob S. Beanlands, MD; George K. Dresser, MD, PhD; Aashish Goela, MD, MSc; Alun H. Davies, MA, DM, FRCS; Luigi P. Badano, MD; Don Poldermans, MD, PhD; Eric Boersma, MSc, PhD; Valentine Y. Njike, MD, MPH

Background: Despite extensive use in practice, the impact of noninvasive cardiovascular imaging in primary prevention remains unclear.

Methods: We searched for randomized trials that compared imaging with usual care and reported any of the following outcomes in a primary prevention setting: medication prescribing, lifestyle modification (including diet, exercise, or smoking cessation), angiography, or revascularization.

Results: Seven trials were included. Trials screened patients for inducible myocardial ischemia (2 trials), coronary calcification (3 trials), carotid atherosclerosis (1 trial), or left ventricular hypertrophy (1 trial). Imaging had no effect on medication prescribing overall (odds ratio [OR], 1.01; 95% confidence interval [CI], 0.76-1.33) or on provision of lipid-modifying agents (OR, 1.08; 95% CI, 0.58-2.01), antihypertensive drugs (OR, 1.05; 95% CI, 0.75-1.47), or antiplatelet agents (OR, 1.05; 95% CI, 0.84-1.32). Similarly, no effect was seen on dietary improvement (OR, 0.78; 95% CI, 0.22-2.85), physical activity (0.02 vs −0.08 point change for imaging vs control on a 5-point scale; $P = .23$), or smoking cessation (OR, 2.24; 95% CI, 0.97-5.19). Imaging was not associated with invasive angiography (OR, 1.26; 95% CI, 0.89-1.79).

Conclusions: We found limited evidence suggesting that noninvasive cardiovascular imaging alters primary prevention efforts. However, given the imprecision of these results, further high-quality studies are needed.

Arch Intern Med. 2011;171(11):977-982.
Published online March 14, 2011.
doi:10.1001/archinternmed.2011.69

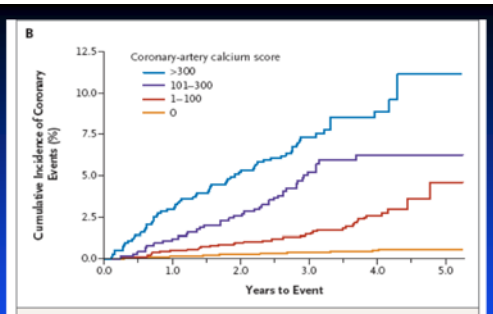


Figure 1. Unadjusted Kaplan–Meier Cumulative-Event Curves for Coronary Events among Participants with Coronary-Artery Calcium Scores of 0, 1 to 100, 101 to 300, and More Than 300.

Panel A shows the rates for major coronary events (myocardial infarction and death from coronary heart disease), and Panel B shows the rates for any coronary event. The differences among all curves are statistically significant (P<0.001).

Coronary Artery Calcium Score and Risk Classification for Coronary Heart Disease Prediction

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Robyn L. McClelland, PhD
Neal W. Jorgensen, BS
Diane E. Bild, MD, MPH
Gregory L. Burke, MD, MSc
Alan D. Guerci, MD
Philip Greenland, MD

Context The coronary artery calcium score (CACS) has been shown to predict future coronary heart disease (CHD) events. However, the extent to which adding CACS to traditional CHD risk factors improves classification of risk is unclear.

Objective To determine whether adding CACS to a prediction model based on traditional risk factors improves classification of risk.

Design, Setting, and Participants CACS was measured by computed tomography in 6814 participants from the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based cohort without known cardiovascular disease. Recruitment spanned July 2000 to September 2002; follow-up extended through May 2008. Participants with diabetes were excluded from the primary analysis. Five-year risk estimates for incident CHD were categorized as 0% to less than 3%, 3% to less than 10%, and 10% or more using Cox proportional hazards models. Model 1 used age, sex, tobacco use, systolic blood pressure, antihypertensive medication use, total and high-density lipoprotein cholesterol, and race/ethnicity. Model 2 used these risk factors plus CACS. We calculated the net reclassification improvement and compared the distribution of risk using model 2 vs model 1.

Main Outcome Measures Incident CHD events.

JAMA 2010

Coronary Artery Calcium Score and Risk Classification for Coronary Heart Disease Prediction

During a median of 5.8 years of follow-up among a cohort of 5,878, 209 CHD events occurred, of which 122 were myocardial infarction, death from CHD, or resuscitated cardiac arrest.

Model 2 (with CAC added) resulted in significant improvements in risk prediction compared with model 1 (net reclassification improvement=0.25; 95% confidence interval, 0.16-0.34; *P*.001).

In model 1, 69% of the cohort was classified in the highest or lowest risk categories compared with 77% in model 2. An additional 23% of those who experienced events were reclassified as high risk, and an additional 13% without events were reclassified as low risk using model 2.

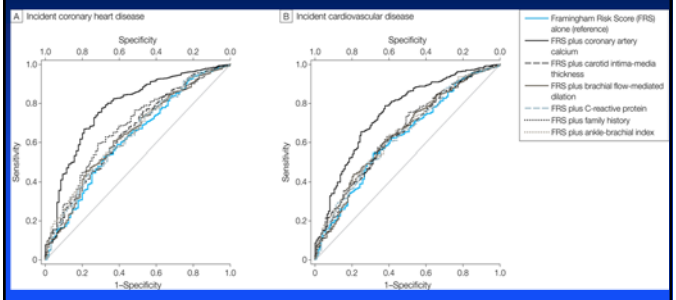
73 % of participants were not reclassified by CAC in MESA

	5-Year Risk from Model with CAC		
5-Year Risk from Model without CAC	0% to <3%	3% to 10%	>10%
0% to <3%, **n=3,746**	**3,310**		
Events, n	**34**		
Proportion with events	**0.9**		
3% to 10%, **n=1847**		**843**	
Events, n		**52**	
Proportion with events		**5.4**	
>10%, **n=285**			**183**
Events, n			**28**
Proportion with events			**14.4**

The JAMA Network

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

JAMA. 2012;308(8):788-795. doi:10.1001/jama.2012.9624



The JAMA Network

Table 3. Net Reclassification Improvement (NRI) for Incident Coronary Heart Disease Events With Addition of Novel Risk Markers to the Framingham Risk Score in Intermediate-Risk MESA Participants (N = 1330)

Variable	% Reclassified	Risk Category, No. of Events FRS Events (n = 94) Low	Intermediate	FRS Nonevents (n = 1236) High	% Net Correct Reclassification	NRI
FRS plus carotid IMT						.102
Events	7.4	0	87	7	7.4	
Nonevents	5.3	50	1170	16	2.8	
FRS plus CAC						.659
Events	51.1	12	46	36	25.5	
Nonevents	54.9	589	557	90	40.4	
FRS plus brachial FMD						.024
Events	0.0	0	94	0	0	
Nonevents	3.2	35	1196	5	2.4	
FRS plus ABI						.036
Events	4.3	1	90	3	2.1	
Nonevents	4.0	34	1186	16	1.5	
FRS plus high-sensitivity CRP						.070
Events	4.3	0	90	4	4.3	
Nonevents	5.2	54	1172	10	3.6	
FRS plus family history						.160
Events	8.5	0	86	8	8.5	
Nonevents	11.2	148	1097	39	7.5	

Abbreviations: ABI, ankle-brachial index; CAC, coronary calcium score; CRP, C-reactive protein; FMD, flow-mediated dilation; FRS, Framingham Risk Score; IMT, intima-media thickness; MESA, Multi-Ethnic Study of Atherosclerosis.

Table 2 | Discrimination and risk reclassification for several novel risk markers[26]*

Marker	NRI (TOTAL POP*N)	CHANGE IN C-STAT
Coronary artery calcium score	19.3 (12.5–26.2)	0.05 (.02- .06)
N-terminal fragment of prohormone B-type natriuretic peptide	7.6 (2.8–12.5)	0.02 (.01- .04)
Fibrinogen	2.9 (-0.2 to 6.0)	0.00 (.00- .01)
Chronic kidney disease	2.7 (-0.2 to 5.7)	0.00 (.00- .00)
C-reactive protein	2.0 (-2.3 to 6.4)	0.00 (-.01- .00)
Carotid intima–media thickness	1.6 (-1.1 to 4.4)	0.00 (.00- .00)
Leukocyte count	1.5 (-1.5 to 4.6)	0.01 (.00- .02)
Uric acid	0.8 (-0.5 to 2.1)	0.00 (.00 - .00)
Peripheral arterial disease	0.6 (-1.8 to 2.9)	0.00 (.00 - .00)
von Willebrand factor antigen	0.4 (-1.7 to 2.5)	0.00 (.00 - .00)
Pulse wave velocity	0.0 (-2.1 to 2.1)	0.00 (.00 - .00)
Homocysteine	-0.3 (-3.0 to 2.3)	0.00 (.00 - .00)

*Data were obtained from the Rotterdam study,[26] a population-based cohort study of adults aged >55 years. NRI values can also be written as proportions (i.e. coronary artery calcium score would be 0.193). Abbreviation: NRI, net reclassification improvement.

Rotterdam Study – Annals 2012

Are Other Tests As Good as CAC?

Adds Incremental Information to Traditional Risk Factors?

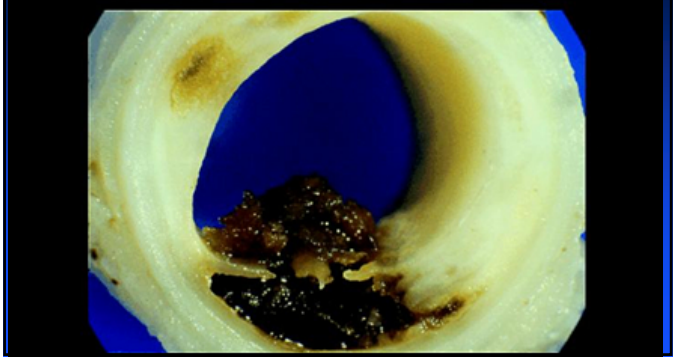
Biomarker	Association with Outcomes?	Improves Discrimination?	Improves Calibration?	Reclassifies Large Proportion?	Reclassification is Useful?	Result Will Affect Clinical Outcome?
CRP	YES	NO	+/-	+/-	+/- (NRI ~ 5%)	Unknown
Genomics	YES	NO	NO	NO	+/- (NRI ~ 1%)	Unknown (Probably Not)
Newer Lipid Markers	YES	NO	NO	NO	NO < 1.0%	Probably Not
CAC	YES	YES	+/-	YES	YES (NRI ~ 25%) NRI higher in intermediate risk	Unknown

Questions

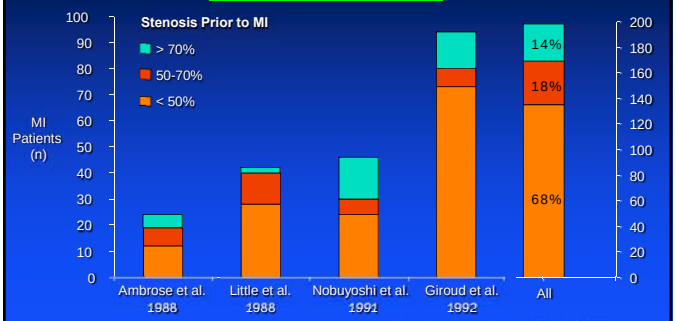
- Would a coronary calcium testing strategy be cost-effective?
- What is the cost of not identifying preclinical CAD?

39

Plaque Fissure and Rupture

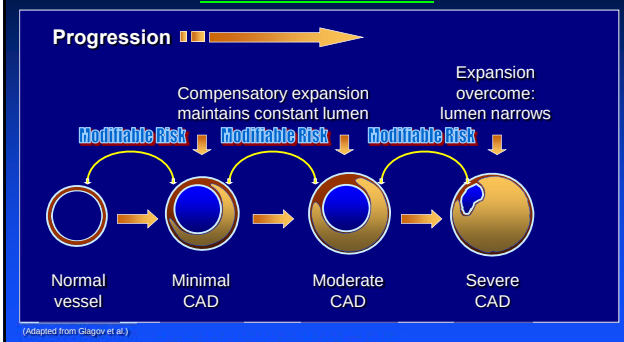


Majority of MIs are Associated with Non-flow Limiting, Unstable Lesions



Falk et al. *Circulation.* 1995;92:657-71.

CURRENT CONCEPT: Coronary Remodeling

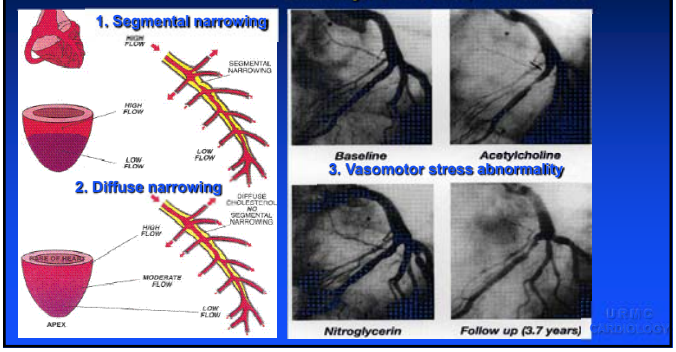


Glagov et al, N Engl J Med, 1987.

Alterations of Coronary Flow in CAD and Rx Response

Gould KL Circ 2000;101:1931

Schachinger V *Circ 2000;101:1899-1906*



Screening

Key Concepts for CAD

- Potential benefit measured by cardiac death/MI, not by angina
- Absolute risk of death/MI vs risk/cost of intervention
- Increase in relative risk (risk ratio) is not the key issue
- Enrichment strategy to identify higher risk cohort, but most patients are at low risk
- Conflict of responsibilities – indiv pt vs public health

Screening Test

General Requirements

- Detect target condition earlier with sufficient accuracy to avoid large number of false ⊕ and false ⊖
- Treating persons with early disease should improve outcomes compared to treating persons when they have symptoms

U.S. Preventive Services Task Force, 1996

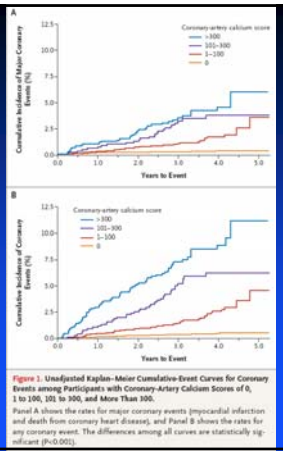
Limitations of Framingham Risk Scoring System

- Population Specific
  - –Variability by country
  - –Underestimates risk in special populations in USA
    - »Women
    - »+ FH primary relative with CVD
    - »Metabolic Syndrome
    - »Renal insufficiency
    - »Diabetes Mellitus

CT for Coronary Artery Calcification

- Objective, reproducible measurement
- Highly specific: abnormal study implies coronary atherosclerosis
- Strong quantitative relationship between coronary calcium score and total plaque burden
- Independent and incremental information over risk factors for predicting cardiac events
- Easily added to routine SPECT/CT, PET/CT

Berman DS et al. *J Nucl Med.* 2006;47:74-82; Taylor AJ et al. *J Am Coll Cardiol.* 2005;6;46:807-814.



MESA

Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups

Detrano et al. NEJM 2008; 358, 1336-45.

MESA

Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups

Detrano et al. NEJM 2008; 358, 1336-45.

Table 5. Use of Area under the Curve for Risk Factors Alone and for Risk Factors plus Coronary-Artery Calcium Score to Predict Major Coronary Events and Any Coronary Event, According to Racial or Ethnic Group.*

Racial or Ethnic Group	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
White	0.76	0.79	0.10	0.75	0.79	0.02
Chinese	0.83	0.88	0.05	0.74	0.85	<0.001
Black	0.79	0.87	0.04	0.81	0.87	0.005
Hispanic	0.84	0.86	0.11	0.80	0.84	0.10
Total	0.79	0.83	0.006	0.77	0.82	<0.001

* Separate models are fitted for each racial or ethnic group. AUC denotes area under the receiver-operating-characteristic curve. P values are for the comparison between AUC without and AUC with the coronary-artery calcium score.
† Major coronary events were myocardial infarction and death from coronary heart disease.

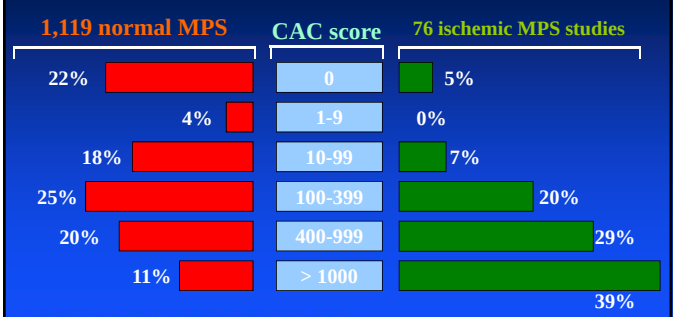
Predicting Cardiovascular Events with Coronary Calcium Scoring

Weintraub WS and Diamond GS. ***NEJM 2008;358:1394-1396.***

The MESA results confirm previous studies that showed that calcium scoring does predict events, as do other risk factors.14-16 But is this relatively small improvement in accuracy worth it? Does calcium scoring provide value? Here the issue is uncertain….

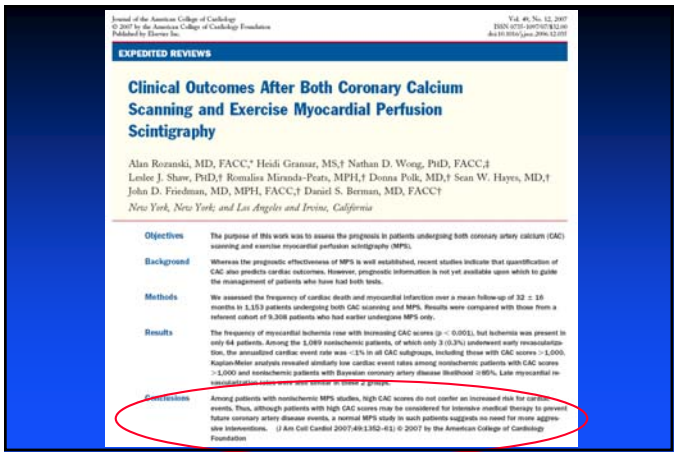
Thus, coronary calcium scoring remains an interesting technique for predicting events, in addition to the simple Framingham score. Nonetheless, the role of coronary calcium screening — and of risk stratification in general, beyond the Framingham score — remains unknown.

Distribution of CAC Scores in Patients with Normal MPS and Patients with Ischemic MPS



Berman DS et al, JACC 2004; 44:923-30.

Does Radionuclide MPS Further Assess Risk of Coronary Calcification?



EXPEDITED REVIEWS

Clinical Outcomes After Both Coronary Calcium Scanning and Exercise Myocardial Perfusion Scintigraphy

Alan Rozanski, MD, FACC,* Heidi Gransar, MS,† Nathan D. Wong, PhD, FACC,‡
Leslee J. Shaw, PhD,† Romalisa Miranda-Peats, MPH,† Donna Polk, MD,† Sean W. Hayes, MD,†
John D. Friedman, MD, MPH, FACC,† Daniel S. Berman, MD, FACC†
New York, New York; and Los Angeles and Irvine, California

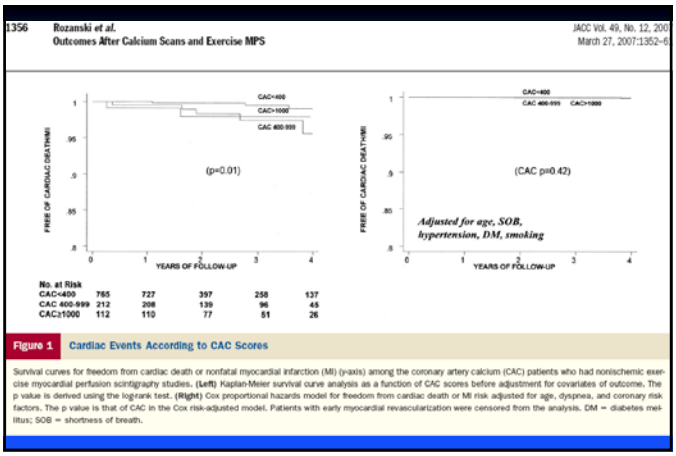
Objectives The purpose of this work was to assess the prognosis in patients undergoing both coronary artery calcium (CAC) scanning and exercise myocardial perfusion scintigraphy (MPS).

Background Whereas the prognostic effectiveness of MPS is well established, recent studies indicate that quantification of CAC also predicts cardiac outcomes. However, prognostic information is not yet available upon which to guide the management of patients who have had both tests.

Methods We assessed the frequency of cardiac death and myocardial infarction over a mean follow-up of 32 ± 16 months in 3,153 patients undergoing both CAC scanning and MPS. Results were compared with those from a referent cohort of 9,308 patients who had earlier undergone MPS only.

Results The frequency of myocardial ischemia rose with increasing CAC scores ($p < 0.001$), but ischemia was present in only 64 patients. Among the 1,089 nonischemic patients, of which only 3 (0.3%) underwent early revascularization, the annualized cardiac event rate was <1% in all CAC subgroups, including those with CAC scores >1,000. Kaplan-Meier analysis revealed similarly low cardiac event rates among nonischemic patients with CAC scores >1,000 and nonischemic patients with Bayesian coronary artery disease likelihood ≤85%. Late myocardial revascularization was very similar in these 2 groups.

Conclusions Among patients with nonischemic MPS studies, high CAC scores do not confer an increased risk for cardiac events. Thus, although patients with high CAC scores may be considered for intensive medical therapy to prevent future coronary artery disease events, a normal MPS study in such patients suggests no need for more aggressive interventions. (J Am Coll Cardiol 2007;49:1352–61) © 2007 by the American College of Cardiology Foundation

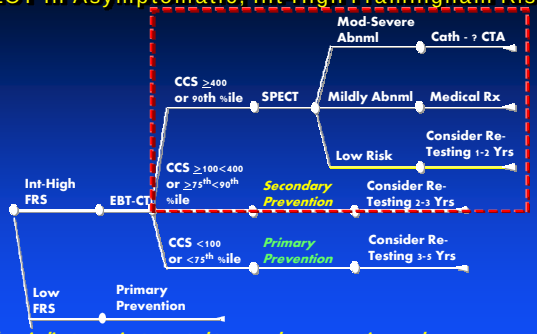


1356 Rozanski *et al.*
Outcomes After Calcium Scans and Exercise MPS
JACC Vol. 49, No. 12, 200
March 27, 2007:1352–6

Figure 1 Cardiac Events According to CAC Scores

Survival curves for freedom from cardiac death or nonfatal myocardial infarction (MI) (y-axis) among the coronary artery calcium (CAC) patients who had nonischemic exercise myocardial perfusion scintigraphy studies. **(Left)** Kaplan-Meier survival curve analysis as a function of CAC scores before adjustment for covariates of outcome. The p value is derived using the log-rank test. **(Right)** Cox proportional hazards model for freedom from cardiac death or MI risk adjusted for age, dyspnea, and coronary risk factors. The p value is that of CAC in the Cox risk-adjusted model. Patients with early myocardial revascularization were censored from the analysis. DM = diabetes mellitus; SOB = shortness of breath.

ASNC Patient Management Strategy for CT Imaging & SPECT In Asymptomatic, Int-High Framingham Risk



Dotted box indicates patients treated to secondary prevention goals

Source: Shaw LJ, Berman DS, Bax JJ, Brown KA, Cohen MC, Hendel RC, Mahmarian JJ, Williams KA, Ziffer JA. The complementary roles of nuclear cardiology and cardiac CT in the current healthcare environment. J Nuc Cardiol 2005;12:131-142.

APPROPRIATE USE CRITERIA

ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 Multimodality Appropriate Use Criteria for the Detection and Risk Assessment of Stable Ischemic Heart Disease

A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons

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2009 AUC Terminology[1]

Appropriate	Uncertain	Inappropriate
(median score 7 to 9)	(median score 4 to 6)	(median score 1 to 3)

1. Hendel RC, et al. J Am Coll Cardiol 2009;53:2201-2229.

2013 AUC Terminology[1]

Appropriate Care (median score 7 to 9)	May Be Appropriate Care (median score 4 to 6)	Rarely Appropriate Care (median score 1 to 3)
▪ An appropriate option because the benefits generally outweigh the risks	▪ At times an appropriate option due to variable evidence or agreement regarding benefit/risk ratio ▪ May be reasonable for the indication	▪ Rarely an appropriate option due to lack of clear benefit/risk advantage ▪ Not generally reasonable for the indication

1. Wolk MJ, et al. J Am Coll Cardiol 2014;63:380-406.

64-Year-Old Male, Asymptomatic

- Hypertension
- Diabetes mellitus
- Obesity
- Physically inactive
- Prior calcium Agatston score was 376

Stress RNI?

Appropriate
May be appropriate
Rarely appropriate

2009 AUC: Risk Assessment With Prior Test Results and/or Known Chronic Stable CAD[1]

	Indication	Stress RNI
	Asymptomatic Prior Coronary Calcium Agatston Score	
33.	• Agatston score <100	I
34.	• Low to intermediate CHD risk • Agatston score between 100 and 400	U
35.	• High CHD risk • Agatston score between 100 and 400	A
36.	• Agatston score >400	A

A = appropriate; U = uncertain; I = inappropriate.

64-year-old male: inactive, hypertension, diabetes, obesity, prior Agatston score 376

1. Hendel RC, et al. J Am Coll Cardiol 2009;53:2201-2229.

2013 AUC: Follow-up Test (>90 days): Asymptomatic or Stable Symptoms[1]

	Indication	Stress RNI
	Prior Coronary Calcium Agatston Score, Asymptomatic (Without Ischemic Equivalent) or Stable Symptoms	
41.	• Agatston score <100	R
42.	• Low to intermediate global CAD risk • Agatston score between 100 and 400	M
43.	• High global CAD risk • Agatston score between 100 and 400	M
44.	• Agatston score >400	M

A = appropriate; M = may be appropriate; R = rarely appropriate.

64-year-old male: inactive, hypertension, diabetes, obesity, prior Agatston score 376

1. Wolk MJ, et al. J Am Coll Cardiol 2014;63:380-406.

Summary

- Evaluating arterial wall thickness, area, volume, and plaque composition and burden with imaging technology may enable[1-3]
  - Early detection of atherosclerosis
  - Refinement of risk assessments
  - Monitoring of atherosclerosis progression/regression
- CT calcium scoring, CT angiography, B mode ultrasound, and high-resolution MRI technologies are emerging as useful noninvasive tools for enhancing atherosclerosis detection and management[1,2]

1. Crouse JR. J Lipid Res. 2006;47:1677-1699;
2. Schoenhagen P, et al. Clev Clin J Med. 2005;72:487-496;
3. Raggi P, et al. Arch Intern Med. 2005;165:2345-2353.

Concepts: Imaging for Prevention

- Pre-symptom risk assessment in intermediate-high risk patients based on risk factor profiles (FRS > 10%)
- Consider lifetime attributable risk and substantial benefit in lower risk patients in society.
- Committee statement is intended to stimulate research
- Current guidelines support use of CAC and CIMT as effective risk stratifiers
  - Further work needed to assess value of these methods in diverse patient subsets
- Addition of an atherosclerotic imaging test may be appropriate patients with intermediate to high FRS
- Clinicians should take care to examine vulnerable low FRS patient subsets whose risk may be underestimated, notably women and younger men, and who may benefit from atherosclerosis imaging.

URMC CARDIOLOGY

Imaging for Prevention: Potential Candidates for Imaging

- **Assessment of Pretest Risk is critically important.**
- **Is imaging likely to change assessment, Rx or outcome?**
- **CRFs not included in the FRS: + FH premature CHD; MBS**
- **Patients with higher risk of atherosclerosis: women w PCOS (polycystic ovaries) or early menopause**
- **Autoimmune diseases: e.g., RA, SLE, psoriatic arthritis**
- **Assess CAD presence and progression in "CAD risk equivalents": T2DM (>5 yrs), PAD, cerebrovascular disease, CKD, abnormal ABI's.**
- **Current testing guidelines include: preoperative risk detection, new onset atrial fibrillation or LVH.**
- **Incremental risk assessment is necessary but insufficient: Value in QALY saved.**

URMC CARDIOLOGY

Imaging for CAD Prevention and Management

- Noninvasive, low risk to perform
- Role of CAC progression (15% threshold) has been challenged by recent data showing no difference in progression of CAC with aggressive statin Rx
- SPECT / PET provide superior risk and Rx assessment compared to clinical, exercise and stenosis information
  - Stenosis information anatomy by integrating flow effects of entire arterial tree
  - Reflects tissue perfusion rather than vascular space perfusion provided by CTA / MRA
  - MPS identifies those with benefit from PCI; role in OMT requires further evaluation
- Detect preclinical CAD for earlier Rx & greater benefit
- Can identify effective response to therapy prior to clinical events.
- Well established gatekeeper role of SPECT / PET
- Initial evaluation of CTA in ED setting suggests greater downstream test and rx utilization in lower risk patients
- Allow successful broadening and intensification of Rx to ameliorate outcome? - *More data needed!*

How to Treat Asymptomatic At Risk Patients More Effectively

- Identify appropriate, at-risk individuals (>1%/year risk; NOT low risk individuals)
- Given a lack of infinite resources, target these individuals for intensive treatment to reduce risk.
- Identify the 10-25% patients who fail to show improvement or stability and target these patients for more intensive lifestyle and medical Rx.

URMC CARDIOLOGY

Why nuclear cardiology (SPECT / PET)?

- Safest and most accurate test for CHD management
  - > 20X incremental risk assessment vs. Exercise ECG Duke TES
    - » >2 x incremental risk assessment of stress echo vs. Exercise ECG Duke TES
  - SPECT identifies "Normal" 6X more accurately than stress echo
  - Gatekeeper: Identifies patients who benefit from revascularization
- Tracks effectiveness of Rx (TLC, medical, Revasc)
  - Perfusion response correlates with outcome (COURAGE)
- Exercise +/- regadenoson "RegEx"
- Ultra low dose radiation (1 – 2 mSv): < 100 mSv NOT a measurable risk!
- Noninvasive – much safer than coronary angiography
- No contrast risk (renal dysfunction; allergies)
- Fast – about one hour (stress only)
- Cost effective
  - Stress only – similar cost to stress echocardiography with contrast
  - END – more cost effective than direct coronary angiogrpaphy
  - Avoid anatomy based downstream testing costs (CTA) and unnecessary revascularization (direct angiography)

URMC CARDIOLOGY

Table 1.2. Asymptomatic (Without Symptoms or Ischemic Equivalent)

Refer to pages 17 and 18 for relevant definitions

Indication	Text	Exercise ECG	Stress RNI	Stress Echo	Stress CMR	Calcium Scoring	CCTA	Invasive Coronary Angiography
7.	• Low global CHD risk • Regardless of ECG interpretability and ability to exercise	R	R	R	R	R	R	R
8.	• Intermediate global CHD risk • ECG interpretable and able to exercise	M	R	R	R	M	R	R
9.	• Intermediate global CHD risk ECG uninterpretable OR unable to exercise		M	M	R	M	R	R
10.	• High global CAD Risk • ECG interpretable and able to exercise	A	M	M	M	M	M	R
11.	• High global CAD Risk • ECG uninterpretable OR unable to exercise		M	M	M	M	M	R

Appropriate Use Key: A = Appropriate; M = May Be Appropriate; R = Rarely Appropriate.
A = Appropriate; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CHD = coronary heart disease; CMR = cardiac magnetic resonance; ECG = electrocardiogram; Echo = echocardiography; M = May Be Appropriate; R = Rarely Appropriate; RNI = radionuclide imaging.

MEDICAL POLICY

Excellus

SUBJECT: CORONARY CALCIUM SCORING	EFFECTIVE DATE: 10/15/99 REVISED DATE: 02/21/02, 06/19/03, 05/19/04, 04/21/05, 02/16/06, 01/18/07, 01/17/08, 12/18/08, 01/21/10, 01/20/11, 01/19/12, 03/21/13
POLICY NUMBER: 6.01.13 CATEGORY: Technology Assessment	PAGE: 1 OF: 5

- *If the member's subscriber contract excludes coverage for a specific service it is not covered under that contract. In such cases, medical policy criteria are not applied.*
- *Medical policies apply to commercial and Medicaid products only when a contract benefit for the specific service exists.*
- *Medical policies only apply to Medicare products when a contract benefit exists and where there are no National or Local Medicare coverage decisions for the specific service.*

POLICY STATEMENT:

I. As a screening technique for asymptomatic patients:

Based on our criteria and review of the peer reviewed literature, coronary calcium scoring is considered **medically appropriate** when:

A. Coronary artery disease has not been documented by prior abnormal imaging stress test; or coronary revascularization; or prior catheterization; or cardiac CT angiogram; AND
B. Low cardiovascular risk based on the Adult Treatment Panel III (ATP) risk calculation score (less than 10%); and
   1. Father or brother with coronary heart disease diagnosed at age 55 or less; or
   2. Mother or sister with coronary heart disease diagnosed at age 65 or less; OR
C. Intermediate cardiovascular risk (10-19%) based on the Adult Treatment Panel III (ATP) risk calculation score and there are no symptoms of chest pain or shortness of breath.

Recommendation

It's time for a high quality RCT of CAC vs. no imaging on adherence and CV outcomes in an appropriate population at risk.


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CARDIOLOGY