Seminar: Coronary Artery Calcification

George Isitt, Christopher Kane, Wei Ren Lau & Oluwatobiloba Oyefeso

Overview

- The pathophysiology of atherosclerotic coronary artery calcification
- Coronary artery calcification: good or bad?
- Imaging techniques
- The use of CAC scoring in the diagnosis, prognosis and monitoring of CAD

NOTES:

Pathobiology of Coronary Artery Calcification (CAC)

Pathobiology of Coronary Artery Calcification (CAC)

- Begins as early as second decade of life
- More frequent and more pronounced
  - –In the elderly
  - –In advanced lesions
- In a study of 65 hearts on autopsy, 94% of coronary arteries showed some degree of calcification

- Postmortem studies have show prevalence of coronary calcium deposits in a given decade of life as 10-100x higher than expected

- Therefore, determining threshold levels of coronary calcium content would be important in order to make appropriate management decisions

- Within advanced lesions, mineralization dominates alongside components such as increased fibrous tissue and lipid deposits

- Accumulation of calcium within coronary arteries develops in an age-related manner and appears to be exponential

- Presence of calcification strong indicator of atherosclerosis, and extent directly relates to overall burden of atherosclerotic disease

Associated Literature

- Lewis Wexler et al. Coronary Artery Calcification: Pathophysiology, Epidemiology, Imaging Methods, and Clinical Implications. Circulation. 1996; 94: 1175-1192
- Chapman I. Anatomic and clinical significance of calcification of the aortic knob visualized radiographically. *Am J Cardiol*. 1960;6:281–286.
- Rumberger et al. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation*. 1995;92:2157–2162.

NOTES:

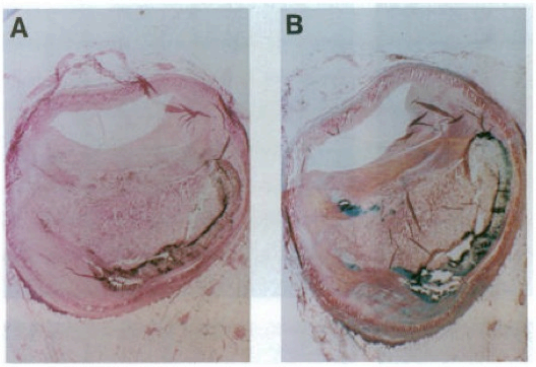
- Main form: calcium Phosphate (Hydroxyapatite $Ca_3[-PO_4]_{2-}\times Ca[OH]_2$)
- Calcification process similar to endochondral ossification:
  - Vesicles exocytose from osteoblast-like cells in the vessel wall
  - Vesicles may also derive from dead foam & SM cell debris

- Calcium phosphate (hydroxyapatite), almost 50% calcium, thrives in diseased coronary arteries
- Similar to that found in active bone formation and remodeling
- Hydroxyapatite formed in vesicles that pinch off from arterial wall, in a very similar way to which matrix vesicles pinch off from chondrocytes in developing bone
- A very close spatial association between cholesterol deposits and hydroxyapatite has also been demonstrated, suggesting that atherosclerosis may lead to calcification

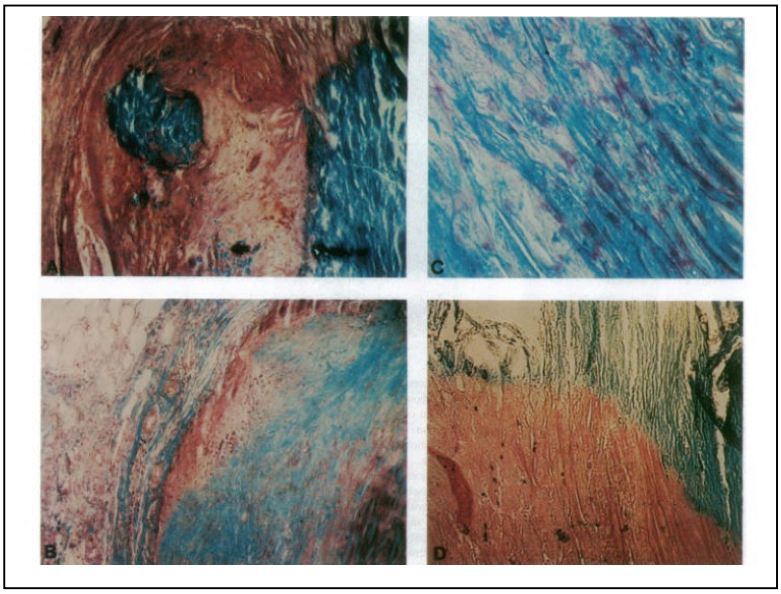
Associated Literature

- Bostrom K, Watson KE, Horn S, Wortham C, Herman IM, Demer LL. Bone morphogenetic protein expression in human atherosclerotic lesions. J Clin Invest.. 1993;91:1800-1809.
- Tanimura A, McGregor DH, Anderson HC. Calcification in atherosclerosis, I: human studies. J Exp Pathol.. 1986;2:261-273.
- Hirsch D, Azoury R, Sarig S, Kruth HS. Colocalization of cholesterol and hydroxyapatite in human atherosclerotic lesions. Calcif Tissue Int.. 1993;52:94-98.

NOTES:



NOTES:



Dyslipidaemia and calcification

- Dyslipidaemia implicated in the development of calcification foci
- Investigations looking into possible benefits of statins in reducing calcium accumulation

NOTES:

Molecular pathogenesis of CAC

1. Osteogenesis
2. Loss of inhibitors of mineralisation

Osteogenesis: Pivotal role of VSMCs

- De-differentiation of vascular smooth muscle cells (VSMCs) appears to be central
- Stimuli like oxidative stress, BMPs etc cause:
- VSMCs → osteoblast/chondrocyte-like cells
- Mediated by an upregulation of osteogenic differentiation markers:
  - BMP2
  - Transcription factors – RUNX2 &MSX 2

- Speculated that may be an attempt to protect the myocardium by strengthening weakened atherosclerotic plaque prone to rupture - an attempt by the artery to stabalise itself

- Calcification of the lesions causes them become much stiffer (about 5x stiffer than a cellular lesion) and are unlikely to be the source of plaque rupture

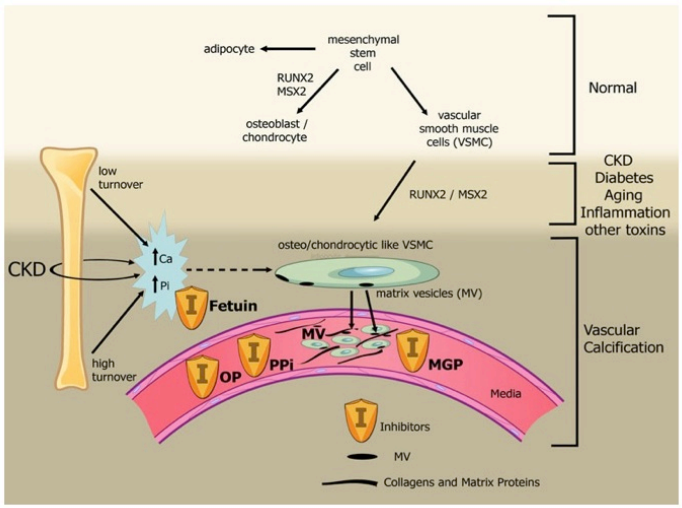
- Vascular smooth muscle cells (VSMCs) originate from similar mesenchymal stem cells as those for osteoblasts, chondrocytes and adipocytes.

- Osteoblasts occurring via the upregulation of the transcription factor core binding factor α-1 (Cbfa-1) now known as Runt-related transcription factor 2 (RUNX2) or msh homeobox 2 (MSX-2)

Associated Literature

- Lee RT, Grodzinsky AJ, Frank EH, Kamm RD, Schoen FJ. Structure-dependent dynamic mechanical behavior of fibrous caps from human atherosclerotic plaques. Circulation. 1991;83:1764-1770.
- Cheng GC, Loree HM, Kamm RD, Fishbein MC, Lee RT. Distribution of circumferential stress in ruptured and stable atherosclerotic lesions: a structural analysis with histopathological correlation. Circulation.. 1993;87:1179-1187.

NOTES:



- The osteoblast-like cell lays down collagen & noncollagenous proteins in the intima/media and incorporates calcium and phosphorus into matrix vesicles (MVs) to initiate mineralization

NOTES:

Inducers of osteogenesis: Bone morphogenic protein (BMP)

- Member of TGFβ superfamily
- BMP 2a: Factor for osteoblastic differentiation
- Vascular wall cell cultures
  - Formed calcified nodules
  - Secreted BMP2a
  - Contained microvascular pericytes (known to be capable of osteoblastic differentiation)

- Many different matrix proteins identified:
  - Potent factor for osteoblastic differentiation called bone morphogenic protein-2a (BMP-2a)
  - Cell attachment protein, osteopontin, protein associated with calcium, osteonectin, and γ-carboxylated protein involved in regulating mineralisation, osteocalcin

NOTES:

Other factors inducing bone formation

- Pro-inflammatory cytokines
- Oxidised low-density lipoprotein (oxLDL)
- Monocyte/macrophage release products

- In vitro studies - highlighted importance of pro-inflammatory cytokines, oxidised low-density lipoprotein (oxLDL) and monocyte/macrophage release products in promoting osteogenesis and the accumulation of calcium deposits

- However, some studies have shown an increase in antioxidant factors such as HDL, may reduce mineralization (via influence on IL-1, IL-6 and oxLDL)

NOTES:

Atherosclerotic calcification is a balance

Balance between inhibitors of calcification and pro-mineralizing factors

Table 2. Factors involved in arterial calcification.

Stimulators	Inhibitors
Inorganic phosphate	Pyrophosphate
TGF-β	Statins
25-hydroxycholesterol	N-3 fatty acids
cAMP	Tropoelastin
MAP kinase	Bisphosphonates
Acetylated LDL	Matrix Gla Protein
Homocysteine	BMP-7
Glucose	Osteopontin
Endothelin-1	Osteoprotegerin
Elastin degradation products	NPP-1
Pit-1	Ahsg (Fetuin-A)
Leptin	
BMP2-Msx2-Wnt	
MMPs	

TGF – Transforming growth factor; *cAMP* – cyclic adenosine monophosphate; *MAP* – mitogen-activated protein kinase; *LDL* – low-density lipoprotein; *Pit-1* – sodium dependent phosphate transporter; *NPP* – nucleotide pyrophosphatase phosphodiesterase; *PPi* – inorganic pyrophosphate. *BMP* – bone morphogenic protein; *BMP2-Msx2-Wnt* – wingless signaling pathway; *MMPs* – metalloproteinases (adapted from Guzman RJ: Clinical, cellular, and molecular aspects of arterial calcification. J Vasc Surg. 2007; 45: 57A–63A).

- Appears to be a balance between inhibitors of calcification and pro-mineralizing factors (e.g. transforming growth factor beta (TGF-b), vitamin D3 (Vit. D3)

Molecular pathogenesis of CAC

1. Osteogenesis
2. Loss of inhibitors of mineralisation

Inhibitors of mineralisation: Matrix Gla Protein (MGP)

- Inhibits action of BMP2
- Requires γ-carboxylation to be fully functional:
- γ-carboxylated MGP binds calcium
  → allows formation BMP/MP2 complex
  → prevention BMPR2 reactions
  → ↓ osteogenesis

- Decarboxylation of Gla residues, by γ-glutamate carboxylase, to glutamyl residues greatly diminishes the affinity of Gla-containing proteins for hydroxyapatite

- Believed that nonhepatic Gla-containing proteins, which are actively involved in the transport of calcium out of vessel walls and have a very high affinity for hydroxyapatite, are suspected to have key roles in the pathogenesis of coronary calcification

Associated Literature

- Vermeer C. Gamma-carboxyglutamate-containing proteins & vitamin K-dependent carboxylase. Biochem J. 1990;266:625-636.
- Deboervanderberg MAG, Van Haarlem LJM, Vermeer C. Vitamin-K-dependent carboxylase in human vessel wall. Thromb Res. 1986:(S6):134.

NOTES:

Matrix Gla Protein (MGP)

- MGP–null mice develop massive artieral calcification.
- Immunohistological studies:
  - Initially: ↑ in MGP at pre-calcified lesions – attempt to maintain homeostasis
  - Eventually: **expression of MGP ↓s globally before atherosclerotic calcification**
- Warfarin**:** inhibits MGP

- Thought that atherosclerotic processes inhibit the synthesis and activity of γ-glutamate carboxylase - atherosclerotic arteries contain only about 30% of the carboxylase activity found in normal arterial segments

NOTES:

- Osteopontin is a phosphorylated glycoprotein, is a known mediator in the formation and calcification of bone and has a role in cell adhesion, regulated by local cytokines

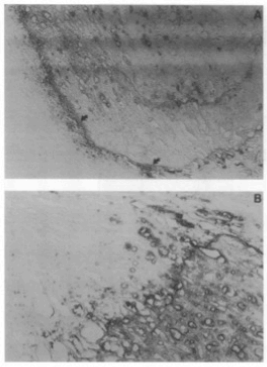
- It has been demonstrated that osteopontin mRNA expression is related to severity of atherosclerosis

Associated Literature

- Fitzpatrick LA, Severson A, Edwards WD, Ingram RT. Diffuse calcification in human coronary arteries: association of osteopontin with atherosclerosis. J Clin Invest.. 1994;94:1597-1604.

Inhibitor of mineralisation: Osteopontin

- Calcium-binding glycoprotein involved in formation and calcification of bone
- Present in areas of atherosclerosis
- Levels related to severity of disease
  - Low levels of mRNA present in SMCs in arterial wall
  - On injury: time-dependent ↑ in mRNA & protein levels



- Immunohistochemistry stain for osteopontin. Small amount in body of plaque but strong around edges ("leading edge") of plaque

NOTES:

- These and other recent findings indicate that calcification is an active process and not simply a passive precipitation of calcium phosphate crystals, as once thought.

Atherosclerotic calcification: Good or bad?

- Virmani et al: high physical stress exerted by calcific nodules may lead to plaque rupture
- Abedin et al: plaque rupture risk has a biphasic response to increasing calcification
- Intravascular ultrasound studies: calcification to stabilise plaque

- Still debated as to whether there is a positive or negative contribution of atherosclerotic calcification to plaque rupture

Associated Literature

- Virmani R, Burke AP, Farb A. Plaque morphology in sudden coronary death. Cardiologia. 1998; 43: 267–271.
- Abedin M, Tintut Y, Demer LL. Vascular calcification: mechanisms and clinical ramifications. Arterioscler Thromb Vasc Biol. 2004; 24: 1161–1170.

NOTES:

Imaging Techniques

3 main techniques

1. Electron beam computed tomography (EBCT)
2. Intravascular ultrasound (IVUS)
3. Fluoroscopy

NOTES:

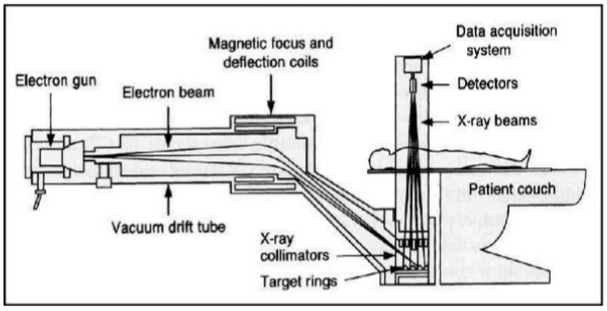
- Electron beam computed tomography (EBCT) uses an electron gun and a stationary tungsten "target" (four tungsten targets underneath the patient) rather than a standard x-ray tube to generate x-rays, permitting very rapid scanning times

- Different from a conventional CT scan in that it uses harmless electron beams instead of X-rays to create multiple images of the heart

Associated Literature

- Lewis Wexler et al. Coronary Artery Calcification: Pathophysiology, Epidemiology, Imaging Methods, and Clinical Implications. Circulation.1996; 94: 1175-1192

Electron Beam Computed Tomography (EBCT)



http://www.medizin.uni-essen.de/cardio/images/ebct2.jpg

EBCT

- Motion artifact is virtually eliminated due to:
  - Fast scanning times (100ms per image)
  - Use of ECG gating
- High spatial resolution: 0.8x 0.8x 2.5mm^3.
- Radiation dose: 1.5mSv

- EBCT images are obtained in 100 ms with a scan slice thickness of 3 mm and due to the rapid image acquisition time, this virtually eliminates motion artifact related to cardiac contraction

- To further eliminate motion artifact one or two separate breath-holding actions are performed and the scan itself is triggered by ECG signal at 80% of the RR interval, near the end of diastole

NOTES:

Associated Literature

- Agatston AS, Janowitz WH. Coronary calcification: detection by ultrafast computed tomography. In: Stanford W, Rumberger JA, eds. Ultrafast Computed Tomography in Cardiac Imaging: Principles and Practice. Mt Kisco, NY: Futura; 1992:77-95.

EBCT Clinical Trial Evidence

- 1992 - first large clinical series in which EBCT was used to detect calcification of the coronary arteries.
- 584 consecutive patients with a mean age of 48 years underwent 100 ms EBCT scans
- 50 also underwent fluoroscopic examination

- Electron beam CT showed calcium in 90%, and fluoroscopy showed it in 52% of patients with established coronary artery disease

Agatston AS, Janowitz WH. Coronary calcification: detection by ultrafast computed tomography. In: Stanford W, Rumberger JA, eds. Ultrafast Computed Tomography in Cardiac Imaging: Principles and Practice. Mt Kisco, NY: Futura; 1992:77-95.

EBCT: Coronary Artery Calcium Scoring

- Obtained by unenhanced EBCT
- Can be use to quantify coronary calcium by means of the Agatston scoring system
- Calculated based on calcium densities & area of calcification
- Provides information on total atherosclerotic burden, not location or extent of individual stenoses

- Total calcium score is a prognostic tool and is strongly associated with total atherosclerotic plaque burden

- It works by calcium densities of 130-200 HU are assigned a score of 1, between 201-300 HU a score of 2, between 301-400 HU a score of 3, and more than 401 HU a score of 4

- Peak calcium density values are multiplied by the actual area of calcification per tomogram to obtain the score - score is given per specific coronary artery or for the entire coronary system.

Associated Literature

- Rumberger J.A., Simons D.B., Fitzpatrick L.A., Sheedy P.F., Schwartz R.S.; Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area: a histopathologic correlative study, Circulation 92 1995 2157-2162

NOTES:

Calcium Score	Plaque Burden	Probability of CAD	Cardiac Event Risk*	Relative Risk	Recommendations
0	No identifiable plaque	Very unlikely, <1%	10 yr risk < 2% Annual risk less than 0.11%.	1	Reassure patient. Discuss risk factors. Repeat scans no more often than every 5 years.
1-80	Small plaque	Low probability	50% (2 fold) reduction from FRS predicted risk. Annual event rate 0.2%.	2	Risk factor modification. Repeat scans in 2 to 5 years.
81-400	Moderate atherosclerotic plaque burden	Non-obstructive CAD likely, although obstructive disease possible	50% increase in FRS predicted risk. Annual event rate 1%.	10	Secondary prevention guidelines of AHA. Exercise testing if clinically indicated. Daily ASA, Statins. Repeat scans annually.
>400	Extensive atherosclerotic plaque burden	High likelihood of at least one significant coronary stenosis	FRS predicted risk increases 8 fold. 10 year event risk ranges from 20% to 70%. Annual event rate up to 4.8%.	25	Secondary prevention guidelines of AHA. Evaluate for inducible ischemia. Daily ASA, Statins. Repeat scans annually.

EBCT

- Advantages:
  - High spatial resolution
  - High temporal resolution
  - High sensitivity in detecting CHD
- Disadvantages:
  - Radiation to patient
  - Poor localisation of stenoses
  - Low reproducibility
  - Low specificity

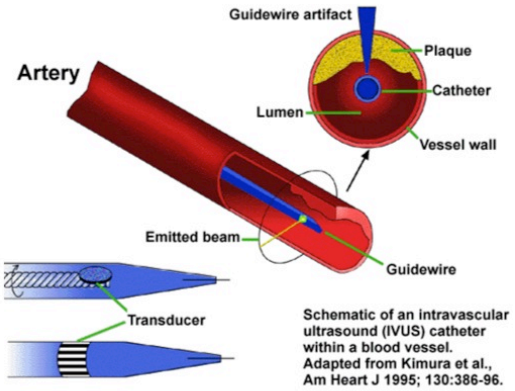
NOTES:

- Intravascular ultrasound is a newer method for detecting coronary atherosclerosis
- Using a method of mounting transducers with rotating reflectors on catheter tips, it is possible to acquire cross-sectional images of the coronary arteries
- Calcification within a plaque obscures the underlying wall and produces an area of shadowing

Associated Literature

- Honye J, Mahon DJ, Tobis JM. Intravascular ultrasound imaging. Trends Cardiovasc Med. 1991;1:305-311.
- Waller BF, Pinkerton CA, Slack JD. Intravascular ultrasound: a histological study of vessels during life—the new 'gold standard' for vascular imaging. Circulation.. 1992:85:2305-2310.

Intravenous Ultrasound (IVUS)



Schematic of an intravascular ultrasound (IVUS) catheter within a blood vessel. Adapted from Kimura et al., Am Heart J 1995; 130:386-96.

IVUS: Clinical Trial Evidence

- Sensitivity for dense, coherent calcification was 90%, with a specificity of 100%[1].
- Angiography was significantly less sensitive than IVUS in detecting calcification at the site of a target lesion[2].

[1]Friedrich et al. Detection of intralesional calcium by intracoronary ultrasound depends on the histologic pattern. Am Heart J.. 1994;128:435-441.

[2]Mintz et al. Patterns of calcification in coronary artery disease: a statistical analysis of intravascular ultrasound and coronary angiography in 1155 lesions. Circulation.. 1995;91:1959-1965.

- However, for small accumulations of micro-calcification and scattered calcification, sensitivity is only 64% but specificity remains high

Associated Literature

- Friedrich et al. Detection of intralesional calcium by intracoronary ultrasound depends on the histologic pattern. Am Heart J.. 1994;128:435-441.
- Mintz et al. Patterns of calcification in coronary artery disease: a statistical analysis of intravascular ultrasound and coronary angiography in 1155 lesions. Circulation.. 1995;91:1959-1965.

NOTES:

- **Advantages:**
  - No radiation
  - High sensitivity & specificity for dense calcificaiton
- **Disadvantages:**
  - Invasive
  - Visualises only a limited portion of the coronary tree
  - Expensive

Fluoroscopy

- Fluoroscopy has frequently been used to detect calcification in coronary arteries - involves imaging the coronary arteries using X-ray screening with real-time display on a fluoroscope

- To detect coronary calcification, fluoroscopy is performed with the patient in a 60^{o} oblique relationship (anterior oblique projection) to the film cassette

- Calcium deposits are seen as densely parallel tracks moving perpendicular to their long axes in a to-and-fro motion.

Associated Literature

- Detrano R, Froelicher V. A logical approach to screening for coronary artery disease. Ann Intern Med.. 1987;106:846-852.

NOTES:

Fluoroscopy

- For detecting significant stenoses (>50% occlusion)
  - **Sensitivity:** 40% to 79%
  - **Specificity**: 52% to 95%[9].

Fluoroscopy

- Advantages:
  - Widely available
  - Low cost
- Disadvantages:
  - Low to moderate sensitivity
  - Operator dependent
  - Radiation risk
  - Quantification of calcium not possible

NOTES:

Calcium scoring in prognosis, diagnosis and monitoring of CHD

Calcium scoring in prognosis, diagnosis and monitoring of CHD

- Can calcium scoring predict risk?
- Can calcium scoring diagnose CHD?
- Can calcium scoring be used to monitor the progression of CHD?

NOTES:

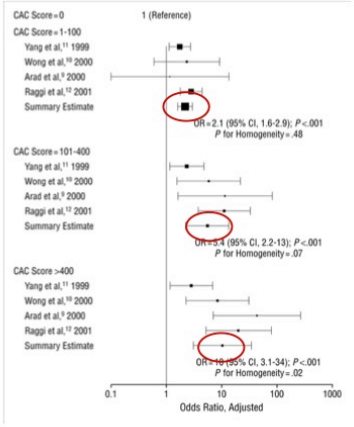
- The coronary artery calcium score is an independent predictor of coronary heart disease events.

Associated Literature

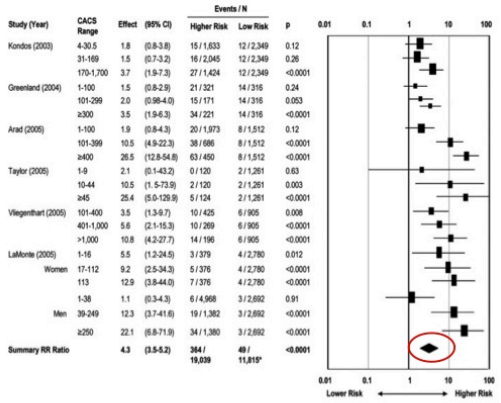
- Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the Coronary Artery Calcium Score to Predict Coronary Heart Disease Events: A Systematic Review and Meta-analysis. *Arch Intern Med.* 2004;164(12):1285-1292.

Risk Assessment

- Pletcher et al. 2004
- Odds ratio increases with increasing levels of CAC



Risk Assessment



Study (Year)	CACS Range	Effect	(95% CI)	Events / N Higher Risk	Low Risk	p
Kondos (2003)	4-30.5	1.8	(0.8-3.8)	15 / 1,633	12 / 2,349	0.12
	31-169	1.5	(0.7-3.2)	16 / 2,045	12 / 2,349	0.26
	170-1,700	3.7	(1.9-7.3)	27 / 1,424	12 / 2,349	<0.0001
Greenland (2004)	1-100	1.5	(0.8-2.9)	21 / 321	14 / 316	0.24
	101-299	2.0	(0.98-4.0)	15 / 171	14 / 316	0.053
	≥300	3.5	(1.9-6.3)	34 / 221	14 / 316	<0.0001
Arad (2005)	1-100	1.9	(0.8-4.3)	20 / 1,973	8 / 1,512	0.12
	101-399	10.5	(4.9-22.3)	38 / 686	8 / 1,512	<0.0001
	≥400	26.5	(12.8-54.8)	63 / 450	8 / 1,512	<0.0001
Taylor (2005)	1-9	2.1	(0.1-43.2)	0 / 120	2 / 1,261	0.63
	10-44	10.5	(1.5-73.9)	2 / 120	2 / 1,261	0.003
	≥45	25.4	(5.0-129.9)	5 / 124	2 / 1,261	<0.0001
Vliegenthart (2005)	101-400	3.5	(1.3-9.7)	10 / 425	6 / 905	0.008
	401-1,000	5.6	(2.1-15.3)	10 / 269	6 / 905	<0.0001
	>1,000	10.8	(4.2-27.7)	14 / 196	6 / 905	<0.0001
LaMonte (2005)	1-16	5.5	(1.2-24.5)	3 / 379	4 / 2,780	0.012
Women	17-112	9.2	(2.5-34.3)	5 / 376	4 / 2,780	<0.0001
	113	12.9	(3.8-44.0)	7 / 376	4 / 2,780	<0.0001
	1-38	1.1	(0.3-4.3)	6 / 4,968	3 / 2,692	0.91
Men	39-249	12.3	(3.7-41.6)	19 / 1,382	3 / 2,692	<0.0001
	≥250	22.1	(6.8-71.9)	34 / 1,380	3 / 2,692	<0.0001
Summary RR Ratio		**4.3**	**(3.5-5.2)**	**364 / 19,039**	**49 / 11,815***	**<0.0001**

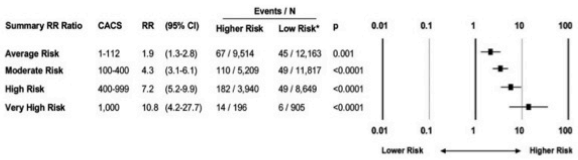
- Greenland et al. 2007

Associated Literature

- Greenland et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force. Circulation. 2007; 115: 402-426

NOTES:

Risk Assessment

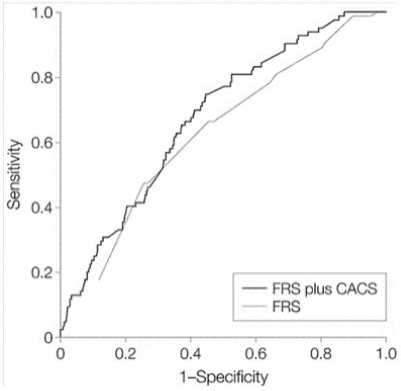


Summary RR Ratio	CACS	RR	(95% CI)	Events / N Higher Risk	Low Risk*	p
Average Risk	1-112	1.9	(1.3-2.8)	67 / 9,514	45 / 12,163	0.001
Moderate Risk	100-400	4.3	(3.1-6.1)	110 / 5,209	49 / 11,817	<0.0001
High Risk	400-999	7.2	(5.2-9.9)	182 / 3,940	49 / 8,649	<0.0001
Very High Risk	1,000	10.8	(4.2-27.7)	14 / 196	6 / 905	<0.0001

- Greenland et al. 2007

Risk Assessment

- Greenland et al. 2004
- CACS can improve the Framingham risk score
- *"high CACS can modify predicted risk obtained from FRS alone, especially among patients in the intermediate-risk category in whom clinical decision making is most uncertain."*



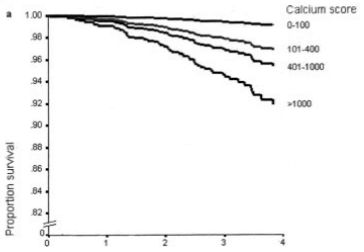
NOTES:

- Performed a study in the elderly that suggested that CACS>1000 meant that these patients were of high risk regardless of other risk factors

Associated Literature

- Rozemarijn Vliegenthart, PhD; Matthijs Oudkerk, MD, PhD; Albert Hofman, MD, PhD; Hok-Hay S. Oei, MD, PhD; Wim van Dijck, MSc; Frank J.A. van Rooij, MSc; Jacqueline C.M. Witteman, PhD. Coronary Calcification Improves Cardiovascular Risk Prediction in the Elderly. Circulation. 2005; 112: 572-577

- Vliegenthart et al. 2005
- *"a high calcium score (>1000) implies a high risk of CHD events, regardless of a low or high Framingham risk score"*



Can CACS be used in the risk assessment of coronary artery disease?

- Increasing levels of CAC are correlated with increased risk of CHD events
  - Any detectable calcium (CAC > 0) is correlated with a relative risk of 4.3
- Using CACS can improve risk assessment based on Framingham risk factors alone
  - Especially useful patients with intermediate FRS

NOTES:

Associated Literature

- Knez et al. 2004

Diagnosis

- Sensitivity & specificity of CAC for the detection of obstructive disease:
- **Knez et al (2004)**
  - Overall values:
    - Sensitivity: 99%
    - Specificity: 28%
  - With volume calcium score > 100:
    - Sensitivity: 87%
    - Specificity: 79%

Comparisons with other tests

Data from various studies:

Test	Sensitivity	Specificity
CACS (Greenland et al. 2007)	99%	28%
Exercise ECG (Gianrossi et al. 1989)	68%	77%
Exercise ECHO (Fleischmann et al. 1998)	85%	77%
Nuclear perfusion imaging (Fleischmann et al. 1998)	87%	64%

NOTES:

Associated Literature

- Kouji Kajinami, Hiroyasu Seki, Noboru Takekoshi, Hiroshi Mabuchi, Noninvasive prediction of coronary atherosclerosis by quantification of coronary artery calcification using electron beam computed tomography: Comparison with electrocardiographic and thallium exercise stress test results, Journal of the American College of Cardiology. 1995. 26(5). 1209-1221
- David M Shavelle, Matthew J Budoff, Daniel H LaMont, Robert M Shavelle, John M Kennedy, Bruce H Brundage. Exercise testing and electron beam computed tomography in the evaluation of coronary artery disease. Journal of the American College of Cardiology. Vol. 36, No. 1, 2000

Comparisons with other tests

- Direct comparison studies
- Kajinami et al. 1995

Test	Sensitivity	Specificity
CACS	77%	86%
Exercise ECG	74%	73%
Nuclear perfusion imaging	83%	60%

- Shavelle et al. 2000

Test	Sensitivity	Specificity
CACS	96%	47%
Exercise ECG	76%	60%
Nuclear perfusion imaging	78%	67%

Localising Lesions

- Fallavollita et al. 1994
- *"a significant number of patients with single-vessel CAD failed to have detectable calcification (25%)"*
- *"similar to the frequency with which CT calcification was absent in individual arteries with angiographically significant stenoses (30%)"*

Associated Literature

- J A Fallavollita; A S Brody; I L Bunnell; K Kumar; J M Canty Jr. Fast computed tomography detection of coronary calcification in the diagnosis of coronary artery disease. Comparison with angiography in patients < 50 years old. Circulation.1994; 89: 285-290
- Lewis Wexler, MD, Chair; Bruce Brundage, MD; John Crouse, MD; Robert Detrano, MD, PhD; Valentin Fuster, MD, PhD; Jamshid Maddahi, MD; John Rumberger, MD, PhD; William Stanford, MD; Richard White, MD, Members; Kathryn Taubert, PhD; AHA Staff. Coronary Artery Calcification: Pathophysiology, Epidemiology, Imaging Methods, and Clinical Implications. Circulation. 1996; 94: 1175-1192

NOTES:

- 30% of arteries with angiographically significant stenoses had no detectable calcification on EBCT
- Lack of calcification implies a low atherosclerotic burden and hence a low chance of stenosis being present.

- Wexler et al. 1996
- *"The absence of calcific deposits on an EBCT scan implies the absence of significant angiographic coronary narrowing; however, it does not imply the absence of atherosclerosis, including unstable plaque. Similarly, calcification may frequently be seen in the absence of significant angiographic narrowing"*

Can CACS be used to diagnose CHD?

- CAC scoring has a high sensitivity for detecting CAD, including when compared to other tests, but specificity is limited
- However, unable to reliably localise lesions – should not be used to detect specific stenoses
- Effective filter before undertaking invasive diagnostic procedures or hospital admission

NOTES:

Monitoring

- Greenland 2007
- 4 requirements for CACS to be used in monitoring:

1. that progression of coronary calcium has biologic relevance to atherosclerosis activity
2. that progression of coronary calcium can be detected relative to inter-test variability
3. that changes in coronary calcium severity have prognostic relevance
4. that modification of cardiovascular risk factors modulates the progression of coronary calcium

1) Does progression of coronary calcium have biologic relevance to atherosclerosis activity?

- Most heavily calcified lesions are those that cause stable angina (Beckman 2001)
- Age and gender have largest correlation with CACS progression (Allison 2005)
- Others have found that baseline CAC is more predictive of CACS progression (Schermund 2001; Yoon 2002)
- Appears that CACS progression has little correlation with modifiable risk factors

Associated Literature

- Joshua A. Beckman, Jason Ganz, Mark A. Creager, Peter Ganz, Scott Kinlay. Relationship of Clinical Presentation and Calcification of Culprit Coronary Artery Stenoses. Arteriosclerosis, Thrombosis, and Vascular Biology. 2001; 21: 1618-1622.
- Allison MA, Wright CM. Age and gender are the strongest clinical correlates of prevalent coronary calcification (R1). Int J Cardiol. 2005 Feb 15;98(2):325-30.
- Schmermund A, Baumgart D, Möhlenkamp S, Kriener P, Pump H, Grönemeyer D, Seibel R, Erbel R. Natural history and topographic pattern of progression of coronary calcification in symptomatic patients: An electron-beam CT study. Arterioscler Thromb Vasc Biol. 2001 Mar;21(3):421-6.
- Mao S, Bakhsheshi H, Lu B, Liu SC, Oudiz RJ, Budoff MJ. Effect of electrocardiogram triggering on reproducibility of coronary artery calcium scoring. Radiology. 2001 Sep;220(3):707-11.
- Budoff MJ, Lane KL, Bakhsheshi H, Mao S, Grassmann BO, Friedman BC, Brundage BH. Rates of progression of coronary calcium by electron beam tomography. Am J Cardiol. 2000 Jul 1;86(1):8-11.

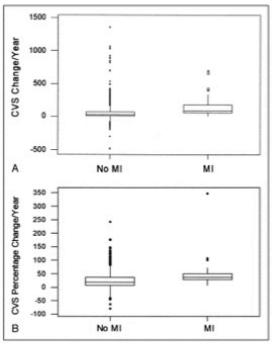
NOTES:

2) Accuracy of serial CAC assessments

- Low inter-test variability: 11.5% (Mao 2001)
- Progression rates: 24-39%/year (Budoff 2000; Maher 1999)
- Therefore CAC progression can be accurately monitored between 2 relatively close time points (1-2 years)

3) Prognostic relevance of CAC score changes

- Raggi 2003:
- Compared change in CACS over 2 years
- Patients who developed MI had higher rates of progression

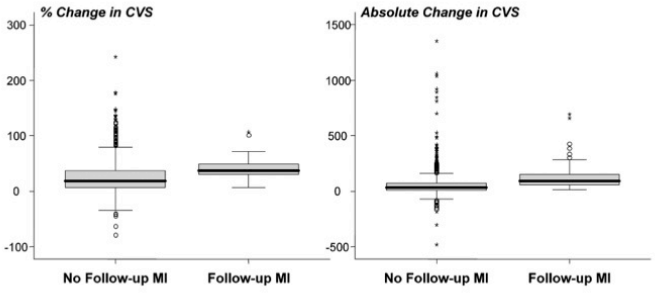


Associated Literature

- Raggi P, Cooil B, Shaw LJ, Aboulhson J, Takasu J, Budoff M, Callister TQ. Progression of coronary calcium on serial electron beam tomographic scanning is greater in patients with future myocardial infarction. Am J Cardiol. 2003 Oct 1;92(7):827-9.
- Raggi P, Callister TQ, Shaw LJ. Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy. Arterioscler Thromb Vasc Biol. 2004 Jul;24(7):1272-7.

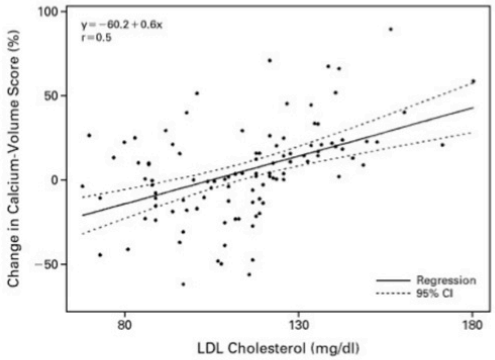
NOTES:

One year later…



- Raggi 2004

4. Modification of cardiovascular risk factors & the progression of coronary calcium



- Callister 1998

Associated Literature

- Callister TQ, Raggi P, Cooil B, Lippolis NJ, Russo DJ. Effect of HMG-CoA reductase inhibitors on coronary artery disease as assessed by electron-beam computed tomography. N Engl J Med. 1998 Dec 31;339(27):1972-8.
- Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. J Am Coll Cardiol. 2005 Jul 5;46(1):166-72.

NOTES:

However…

- Arad 2005
- Large randomised controlled trial

Table 3. Effect of Treatment on Coronary Calcium Score

	Treatment	Control	p Value
Baseline			
n	490	515	
Mean	526	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	166 ± 368	0.86
Percent	38 ± 75	36 ± 68	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

Can CACS be used to monitor CHD?

1. that progression of coronary calcium has biologic relevance to atherosclerosis activity
2. that progression of coronary calcium can be detected relative to inter-test variability
3. that changes in coronary calcium severity have prognostic relevance
4. that modification of cardiovascular risk factors modulates the progression of coronary calcium