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Vascular Inflammation: A New Horizon in Cardiovascular Risk Assessment

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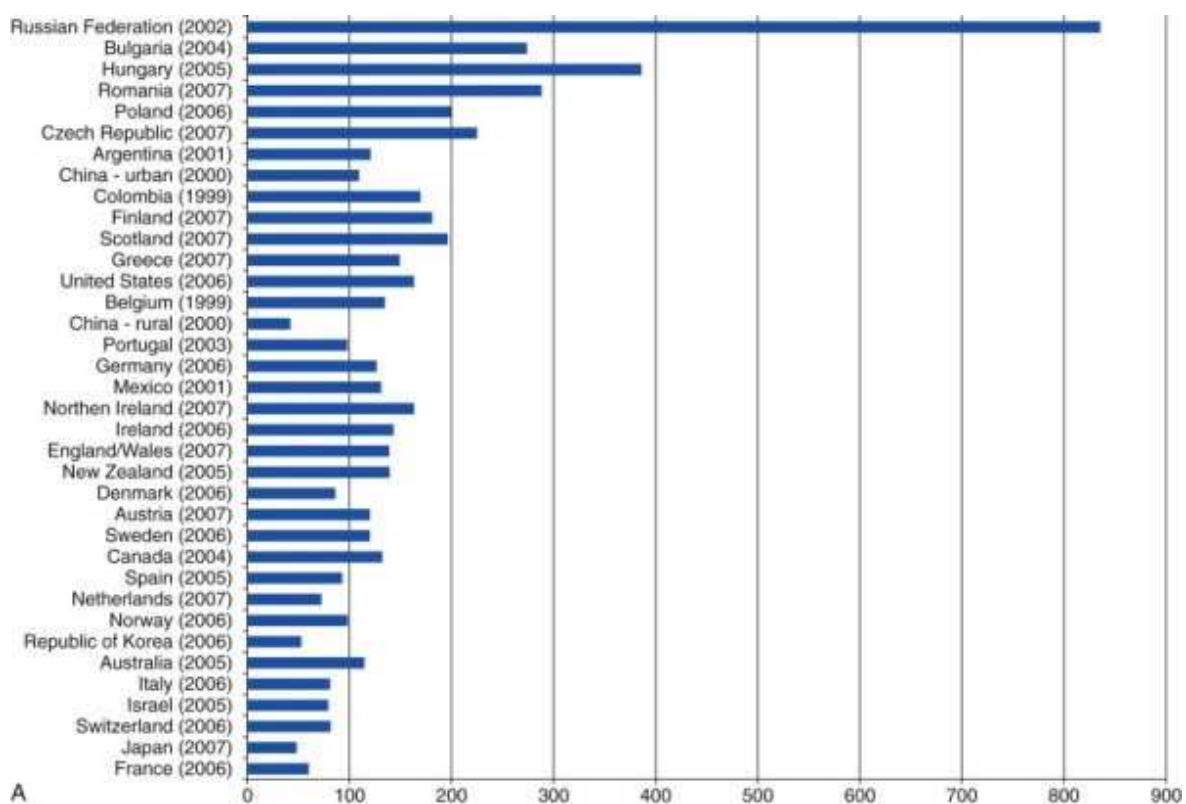
1. Introduction

Coronary artery disease (CAD) remains the leading cause of death across the globe (Rosamond et al., 2008). Although it was thought in the past that coronary artery disease was a disease of the Western world, it is now well known that the developing countries are not spared of the risk (see Figure 1). In fact, recent studies have indicated that in the next decade or so, 80% of the deaths from cardiovascular diseases are projected to occur in developing countries (Yusuf et al., 2001). It is also quite interesting that despite tremendous advances in cardiovascular medicine, myocardial infarction and sudden death are still the initial presentation in half of the patients with coronary artery disease. In the last few decades, cardiac developments have improved the care, and prolonged longevity of patients who suffer an acute coronary syndrome. Unfortunately, the efforts in primary prevention of cardiovascular disease have not quite paralleled the advances in secondary prevention (Rosamond, 2008).

Given the silent nature of the disease and the significant repercussions, it is imperative for physicians to identify at risk individuals early, and implement effective primary prevention of coronary artery disease. Even when selecting pharmacotherapy for cholesterol and blood pressure management, guidelines rely on the patients risk to dictate the intensity of treatment. Thus, cardiovascular risk assessment is the first and most crucial step in the management of the cardiovascular patient. Such risk assessment has traditionally been guided by clinical tools such as the Framingham Risk Score (FRS) from the Framingham Heart Study in the United States, or the Systemic Coronary Risk Evaluation, "SCORE" from European studies on cardiovascular risk assessment (Conroy et al., 2003). Additionally, clinicians use laboratory markers, chiefly total and LDL cholesterol to assess an individual's risk.

Developing a stellar risk determinant requires thorough understanding of the process of atherosclerosis. Atherosclerosis is an ongoing process that occurs through out the life of an individual. We now know that plaque ruptures rather than gradually developing coronary stenoses are the culprits in acute coronary syndromes. A variety of chemokines are involved in the process, and an individual's genetic susceptibility to these enzymes plays a vital role in determining who is at risk for plaque ruptures and cardiac events (KJ Williams et al., 2008). A truly preventative and comprehensive risk assessment algorithm should detect

asymptomatic atherosclerosis by making room for inflammatory markers capable of predicting downstream coronary events. Although lipid panels and Framingham scores provide an assessment of an individual's overall risk, neither of them specifically indicates arterial inflammation or an individual's susceptibility for plaque rupture, the two fundamental culprits in acute coronary syndromes. The goal of medical research is to combine clinical criteria along with pertinent laboratory values and atherosclerosis imaging to generate an inclusive risk assessment tool for patients. Another desirable attribute of this tool is that it should go above and beyond the barriers of gender and ethnicity, and be applicable to a global population. This chapter discusses the role of novel risk factors, focusing mainly on coronary calcium scoring (CCS), while touching upon high sensitivity C reactive protein (CRP), and apolipoproteins in cardiovascular disease. It is important to understand where the traditional risk factors fall short of risk prediction, and where these novel markers could improve our assessment.



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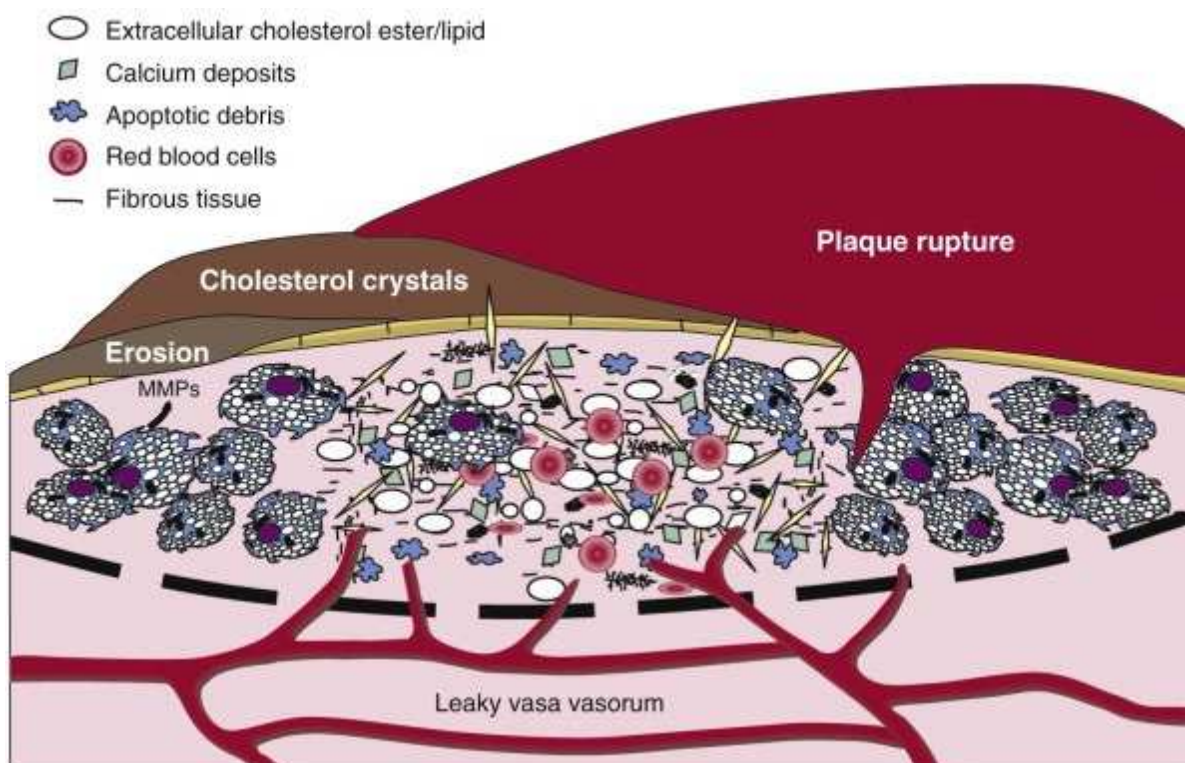
Fig. 1. Age-adjusted rates of death from coronary heart disease (per 100,000 population) among men aged 35 to 74 in selected countries.

1.1 Atherosclerosis an inflammatory process

Atherogenesis in blood vessels has been described to occur in four major steps. The first step is initiation of endothelial activation. Lipoproteins play a key role in this step. During this stage, the intima of susceptible arteries areas (those subjected to hemodynamic stresses) gets infiltrated by atherogenic lipoproteins including low-density lipoproteins (LDL), very low density lipoproteins (VLDL) and other triglyceride rich lipoproteins (TGRL). Under

appropriate genetic and environmental triggers, the modified lipoproteins release inflammatory signals to activate endothelial cells. Recently, the role of platelets has been explored in endothelial activation. Platelets release inflammatory mediators such as interleukin 1 beta (IL-1 β), CD40L, which lead to endothelial activation. This is particularly pronounced in patients with diabetes, hypertension, obesity, dyslipidemia, and in smokers (Vasina et al 2010, Gasparyan et al 2011). The activated endothelial cells express intracellular cell adhesion molecules such as (ICAM)-1 and glycoprotein I-B (GpIB), which promote platelet adhesion and activation. The activated endothelial cells also release chemoattractant and adhesion molecules such as monocyte chemoattractant protein (MCP-1) and vascular cell adhesion molecule1 (VCAM-1). These molecules attract phagocytic cells such as monocytes in to the intima of the vessel wall. These monocytes ingest the modified lipoproteins and turn in to foam cells. In the mean while platelets release platelet derived growth factor (PDGF), which attracts smooth muscle cells (Hopkins & RR Williams, 1981).

During the promotion phase, lipoprotein infiltration continues in proportion to their plasma levels. The growth or necrosis of the plaque is controlled by a balance between lipoprotein entry, foam cell formation and reverse cholesterol transport out of the plaque (Tabas, 2002). During the progression phase, macrophages secrete matrix metalloproteinases (MMPs) that weaken the fibrous cap of the plaque. Additionally, Interferon- γ secreted by activated T cells strongly inhibits collagen synthesis (Libby, 2009). The weakened cap allows cholesterol crystals to erode through the endothelium, causing encroachment of the plaque in to the vessel lumen. Thus, inflammation appears to be the key to plaque destabilization and rupture (Crisby et al., 2001) (see Fig 2).



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Fig. 2. Atherosclerotic plaque destabilization, rupture and calcification.

Shearing stress on the vessel wall from uncontrolled hypertension, contributes to endothelial activation. This stress, in conjunction with other risk factors determines plaque composition with regards to percentage of fibrous versus lipid components (Cheng et al., 2006). Calcium starts to appear inside plaques during the healing and remodeling phase of ruptured plaques. Higher the intimal calcium in a blood vessel, more are the number of prior silent or manifest plaque rupture events inside it (Sangiorgi et al., 1998).

2. Assessment of atherosclerosis and cardiovascular risk

Risk identification and stratification for a clinician begins with an office based assessment of the patient. The presence of CAD/CAD equivalents such as diabetes, peripheral vascular disease automatically places the patient in the high-risk category, needing no further stratification. In the absence of CAD equivalents, risk factors such as hypertension, cigarette smoking, low HDL, family history of premature CAD are considered. When two or more risk factors are present, clinicians currently use risk assessment algorithms such as Framingham Heart Study from the United States or from the Prospective Cardiovascular Münster (PROCAM) study in Germany, or the European risk prediction system called SCORE (Systemic Coronary Risk Evaluation). These algorithms project an individual's 10 year, absolute risk for cardiovascular events such as myocardial infarction (MI), cardiac death (see Table 1). It should be noted that the derived risk is short to intermediate term, and not a lifetime assessment. The cumulative effects of risk factors depend on the duration of an individual's exposure to them. 10-year risk may not be sufficient enough to manifest such effects. It is a known fact that the incidence of coronary artery disease increases exponentially with age (McDermott, 2007; Petersen et al., 2005). Thus, if one decides to go by 10-year prediction algorithms alone, a significant number of patients with coronary artery disease would be classified as low risk. Their lifetime risk would be missed because of the myopic nature of the algorithm.

Long-term risk assessment is particularly relevant for younger patients, in whom initiation of healthy lifestyle modifications and treatment may be delayed or even avoided due to lack of risk awareness. To evade such neglect, the author recommends that physicians should get in to the habit of estimating the lifetime risk. This paradigm has not yet been enforced by clinical guidelines. Lifetime risk assessment is generally performed using the modified technique of survival, and Kaplan Meyer analysis (Lloyd-Jones et al., 2006). These analyses although useful for statistical purposes, are fairly complicated and may not be feasible for day-to-day use in a clinical setting. The alternative is to assess long-term cardiac risk using markers for subclinical atherosclerosis. The traditional risk assessment algorithms suffer from a complete lack of such markers (both biochemical and imaging). Among chemical markers, high sensitivity CRP and apolipoprotein analysis may herald early atherosclerosis. On the imaging front, carotid intimal medial thickness (CIMT) and coronary calcium scoring are two indicators of subclinical atherosclerosis that can be easily measured. CIMT is reviewed elsewhere in this book. The author will focus on coronary calcification in the sections to follow.

2.1 Assessment of coronary artery calcium

As discussed before, the presence of calcium speaks for plaque rupture and healing events within the vessel wall. Calcification of plaques is an active process involving deposition of

hydroxyapatite crystals, as opposed to simple mineral precipitation. The concept of visualizing coronary calcium was first proposed in the early 1980's by a team of physicists at University of California, San Francisco. They invented the Electron Beam Tomography (EBT) scanner, formerly known as the Ultrafast Computed Tomography (CT) (UIC, 2011). It was only in the early 1990's, after years of rigorous testing at major medical centers around the world, that medical institutions began offering Coronary Artery Calcification Scans to the general public.

10-Year Absolute Risk Category	Definition of Category
High risk	CHD*, CHD risk equivalents† including 2+ major risk factors‡ plus a 10-year risk for hard CHD greater than 20%§
Moderately high risk	2+ major risk factors‡ plus a 10-year risk for hard CHD 10% to 20%
Moderate risk	2+ major risk factors plus a 10-year risk for hard CHD less than 10%
Lower risk	0 to 1 major risk factor (10-year risk for hard CHD usually less than 10%)§

*CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or by-pass surgery), or evidence of clinically significant myocardial ischemia.

†CHD risk equivalents include clinical manifestations of non-coronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or greater than 50% obstruction of a carotid artery]), diabetes, and 2 risk factors with 10-year risk for hard CHD less than 20%. ‡Major risk factors include cigarette smoking, hypertension (BP greater than or equal to 140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (less than 40 mg/dL), family history of premature CHD (CHD in male first-degree relative less than 55 years; CHD in female first-degree relative less than 65 years), and age (men greater than or equal to 45 years; women greater than or equal to 55 years). §Almost all people with 0 to 1 risk factor have a 10-year risk less than 10%, and 10-year risk assessment in people with 0 to 1 risk factor is thus not necessary.

Modified with permission from Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; 110: 227-39 (16).

BP blood pressure; CHD coronary heart disease; HDL high-density lipoprotein.

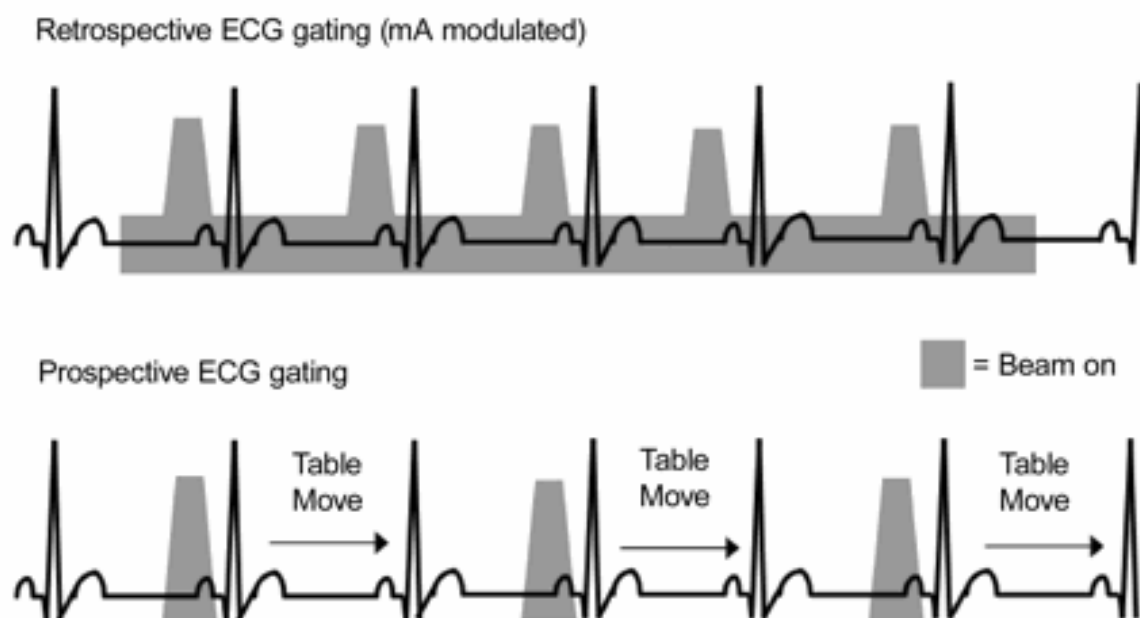
Table 1. Absolute Risk Categories as per the National Cholesterol Education Program (NCEP) Update, 2004

In the present day, there are two modalities for detection of coronary artery calcification. Traditionally, EBT scans were used for this purpose. However, with the development of Multidetector Computed Tomography (MDCT) scanners within the last decade, MDCT has become increasingly popular for the same purpose. Imaging continuously moving structures such as the heart can be fairly challenging. The scan has to be gated off the patient's electrocardiogram (ECG). Coronary arteries are best imaged during diastole, when there is little cardiac motion. Thus, the ECG triggering is done during end systole or early diastole. In clinical practice, 75% of the patient's R-R interval is most favorable for cardiac imaging. Factors such as heart rate irregularities, and tachycardia may necessitate the use of values anywhere between 40-80% of R-R interval for cardiac triggering.

EBT is an ultrafast single slice, high resolution CT scan. Like any form of CT scans, the X-ray source-point moves along a circle in space around an object to be imaged. In EBT, however, the X-ray tube itself is large and stationary, and partially surrounds the imaging circle. Rather than moving the tube itself, the electron-beam focal point (and hence the X-ray source point) is swept electronically along a tungsten anode in the tube, tracing a large circular arc on its inner surface. This motion can be very fast. The resultant scan provides 3

mm thick continuous nonoverlapping slices with an acquisition time of 100 msec/tomogram in a prospective manner (Agatston et al., 1990; Callister et al., 1998a).

As opposed to EBT, MDCT is capable of acquiring clinical images of the heart with multislice imaging technology that captures up to 64 simultaneous anatomical slices of 0.5 mm through an advanced 64-row data acquisition system in a single gantry rotation. In addition, the system's sensitivity and accuracy are enhanced with a process called isotropic scanning. This fast scanning capability allows important diagnostic information concerning the heart to be obtained within a single breath-hold, less than ten seconds, and a CT angiogram can be imaged within 15 seconds. The latest generation of MDCT scanners can acquire up to 320 sections of the heart simultaneously with ECG triggering in either a retrospective or prospective fashion. The patient lies on the CT couch, and the couch is advanced gradually either continuously (helical or spiral scanning) at a fixed speed or in a stepwise fashion (axial/conventional scanning). Figure 3 demonstrates the two scanning modes of MDCT. The gantry speed is up to 330 msec (Agatston, 1990).



Adapted with permission from Shuman W.P. et al. Prospective versus Retrospective ECG Gating for 64-Detector CT of the Coronary Arteries: Comparison of Image Quality and Patient Radiation Dose. August 2008 *Radiology*, 248, 431-437.

Fig. 3. Retrospective and Prospective Gating Techniques for Coronary Computed Tomography Angiography.

2.2 Calcium scoring

Coronary calcium scans are performed using the axial mode and with prospective ECG gating. Either EBT or MDCT scanners can be used for this purpose. No intravenous contrast is necessary. Coronary calcium is diagnosed when as two or three hyperattenuated adjacent pixels with tomographic density of >130 Hounsfield (HU) units for EBT and 90-130 HU for MDCT, are visualized within the coronary tree. The computer software then computes a calcium score for the patient using either the Agatston or Callister methods. The Agatston

method involves multiplying the calculated area of the calcification (measured every 3 mm slice thickness) by the CT density of the same area. Partial volume averaging artifacts could theoretically pose a threat to the validity of this calculation. This artifact results when the computer yields a CT number representative of the average attenuation of the materials within a voxel. Also scanning at 3 mm slice thickness overestimates the area of smaller lesions that are 1mm or less (Barrett & Keat, 2004). As a result, some smaller lesions receive higher peak values for intensity and area. Despite this theoretical concern, there is evidence to suggest that the Agatston score correlates well with that calculated using the Callister method (Callister et al., 1998a). The latter involves computing volume rather than area for lesions with HU density above specified threshold. This partially corrects for slice thickness induced artifacts. Figure 4 summarizes coronary artery calcification (CAC) score calculation.

In comparing EBT and MDCT head to head, studies have revealed an excellent correlation between the two for the presence of calcium (Mao et al., 2009; Daniell et al, 2005; Budoff et al., 2006). This being said, there were some minor differences. Compared to EBT, MDCT had more motion artifacts, and also had higher mean HU for calcific lesions ($p < 0.001$). The Agatston and volumetric scores were not significantly different between EBT and MDCT. However, the study by Mao et al used heart rate control for calcium scoring scans (Mao et al., 2009). Majority of centers do not routinely use heart rate control for this purpose alone, unless a coronary CT Angiogram is also requested. Even in the absence of heart rate control, Daniell et al did not report any significant difference between the two scanners. At our center, MDCT is routinely employed for this purpose, without heart rate control.

Using either of the two methods described above, the computer generates a Calcium Artery Calcification (CAC) Score report. The report compares the patient's calcium score to age and gender matched controls, and generates a percentile value for the patient in question.

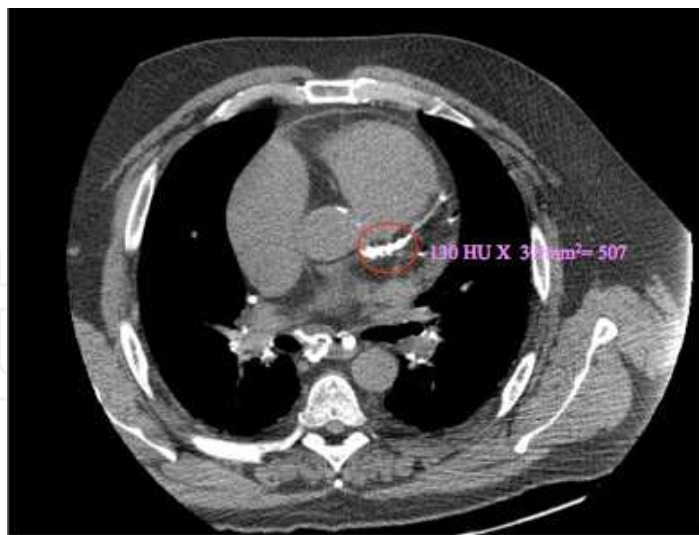


Fig. 4. Coronary Calcium Score (CCS) calculation in a patient with extensive coronary calcification

The figure depicts extensive coronary artery calcification involving the left main and the left anterior descending arteries. Agatston score is calculated by multiplying the area of the calcification (mm^2) by its density in Hounsfield units (HU). The total calcium score is much higher than that for the lesion depicted.

2.3 Radiation dose

Recently, significant concerns have been raised about the radiation exposure to patients from CT scans. Typical radiation dose from a retrospectively gated coronary CT angiograms (CTA) ranges from 10-18 mSv (Gopal & Budoff, 2009). With the introduction of radiation dose reducing techniques such as dose modulation, reduction of kilovoltage for thinner patients, limitation of vertical scan field and prospective gating, the exposure to radiation can be decreased by 80-90%. In fact, studies have reported that the use of prospective gating alone, without any other dose sparing techniques, cuts down radiation exposure by 70-80%. The typical radiation dose for a prospectively gated CTA is about 4.2 mSv (about the same or slightly lower than a diagnostic cardiac catheterization) (Hirai et al., 2008; De Backer et al., 2003).

Although these concerns are valid for coronary CT angiograms (both prospectively and retrospectively gated), radiation exposure is certainly not an issue for calcium scoring. Radiation exposure from CCS scans alone is approximately 1 mSv from either EBT or MDCT scanners. This exposure is negligible, and is nearly equivalent to that from a single X ray. Thus, the benefit of assessing coronary calcium in at risk individuals justifies the minor risk of radiation exposure in most patients.

2.4 Coronary artery calcium scoring in asymptomatic patients

It has been proven that plaque rupture and acute coronary syndromes are generally a function of the total atherosclerotic burden (Kullo & Ballantyne, 2005). Since calcium is known to appear at an advanced stage of atherosclerosis, it has been proposed that patients with calcific plaques also likely have "soft" plaques that could be vulnerable to rupture. The co occurrence of calcific and noncalcific plaques forms the basis of using CCS as a predictor of acute coronary syndromes. Although CAC may not identify a vulnerable plaque per se, it defines a patient's risk for coronary events by virtue of its association with total plaque burden (Rumberger et al., 1995; O'Rourke et al., 2000; Agatston et al., 1990). This is the very basis of testing asymptomatic patients for coronary calcification. Detection of coronary artery calcifications in this group of individuals can help direct decisions on intensity of lipid lowering, aspirin therapy etc. Whether this strategy is useful across all risk groups is questionable, and is discussed later. In the sections to follow, we review data from metaanalyses, observational and prospective cohort studies on prognostic value of CCS.

2.5 Observational studies

Several observational studies have suggested the utility of CCS in cardiac risk stratification. Earlier studies often focused on endpoints such as coronary revascularization. These studies were criticized for a lack of hard endpoints such as cardiac death, myocardial infarctions (MI) etc, and were thought to overestimate the prognostic value of calcium scoring (Pletcher et al., 2004). However, we now have more than a few studies looking at hard endpoints described above. Table 2 summarizes the salient findings of these studies (Arad et al., 2000, 2005; Wong et al., 2000; Raggi et al., 2001; Kondos et al., 2003; Shaw et al., 2003; Greenland et al., et al, 2004; Vliegenthart et al., 2005; Taylor et al., 2005; LaMonte et al., 2005; Budoff et al., 2007; Becker et al., 2008; Anand et al., 2006; Polonsky et al., 2010). Briefly, the study by Arad et al (2000) showed that among 1172 asymptomatic patients observed for 3.6 years after an

initial EBT screening, no events occurred in patients without coronary calcification, and in patients with a CAC score <100 . The negative predictive value of a normal CCS scan was 99.8% for hard cardiac endpoints. Also the authors described increasing cardiac event rates in individuals with a CAC score ≥ 80 , ≥ 160 , and ≥ 600 . Raggi and coworkers (2001) studied more than 600 asymptomatic patients who underwent EBT and were then followed for 32 ± 7 months. They showed that both the absolute CAC score and the relative score percentiles predicted subsequent death and nonfatal MI. Additionally, hard cardiac events occurred in only 0.3% of subjects with a normal CAC score, but increased to 13% in those with a CAC score >400 . The largest observational study with the longest duration of follow up was reported by Budoff and colleagues (2007). They followed 25,253 patients out to 6.8 years, and reported relative risk ratios of 4.5 for CAC scores between 101 and 299, and 12.5 for scores more than 1000. Shaw and colleagues (2003) demonstrated that mortality significantly increased with increasing CAC score, within men and women separately as well as within each Framingham risk group (low, intermediate, and high-risk). This finding contradicts a report from Kondos et al. (2003) describing the futility of CCS in patients with low Framingham risk. With the exception of minor differences, most studies indicate that CAC is an independent predictor of CAD adverse outcome as well as of all-cause mortality after adjusting for traditional risk factors. It should be noted that these studies consistently quote impressive relative risk ratios, but when one looks at the absolute risk, the difference is not as impressive in majority of the studies. Also most data has been reported in Caucasian population. Thus, the author does advise caution in extrapolating these vivid results to one's practice, and ethnically diverse patient population.

2.6 Prospective studies and meta-analysis

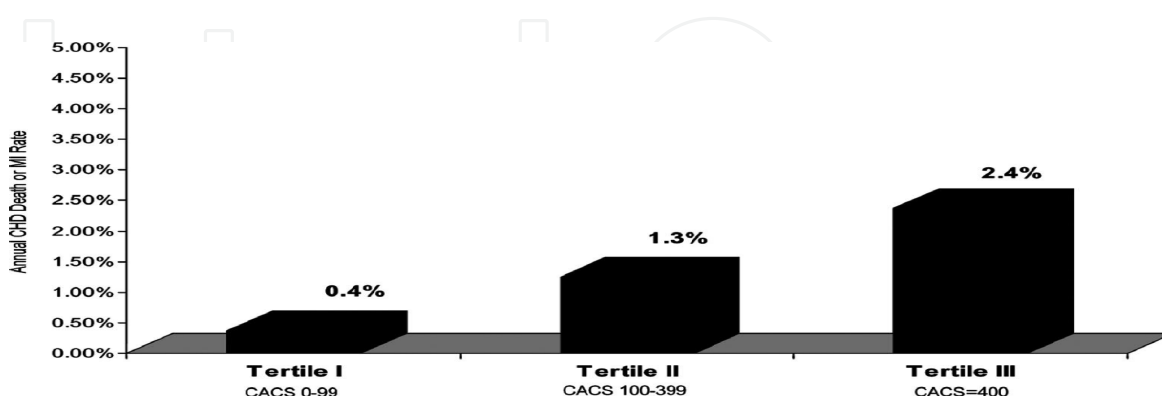
Prospective studies have confirmed these results, and have additionally indicated an independent role for CCS above traditional risk factors. The South Bay Heart Watch study included 1196 asymptomatic patients who were observed for a median of 7.0 years, and it was demonstrated that the CAC score added predictive power beyond that of standard coronary risk factors and C-reactive protein (Greenland et al., 2004). Registry data from the St. Francis Heart Study, a prospective population based study of over 5000 asymptomatic individuals confirmed the higher event rates associated with increasing CAC scores (Arad et al., 2005). CAC scores >100 were associated with relative risks of 12 to 32, thus achieving secondary prevention equivalent event rates $>2\%$ /year (superior to FRS). The Rotterdam Heart Study studied CCS in a slightly older cohort, i.e. 1795 asymptomatic patients with mean age of 71 years (Vliegenthart et al., 2005). During a mean follow-up of 3.3 years, the multivariate-adjusted relative risk of coronary events was 3.1 for calcium scores of 101 to 400, 4.6 for calcium scores of 401 to 1000, and 8.3 for calcium scores >1000 . In a younger cohort of asymptomatic persons, the 3-year mean follow-up in 2000 participants (mean age, 43 years) showed that coronary calcium was associated with an 11.8 fold increased risk for incident CAD ($P < 0.002$) while controlling for the FRS (Taylor et al., 2005).

Budoff and colleagues (2007) showed risk-adjusted hazard ratios of 2.2 for total mortality for CAC score categories of 11-100, and 12.5 for category >1000 . CAC scores provided significant incremental information over traditional risk factors. In Europe, Becker and coworkers (2008) reported their data in 924 patients aged 59.4 ± 18.7 years. During the 3-year follow-up period, the event rates for coronary revascularization, MI, and cardiac death in

patients with volume scores above the 75th percentile were significantly higher compared with the total study group, and no cardiovascular events occurred in patients with scores of zero. In fact, their statistical analysis demonstrated that it outperformed both PROCAM and Framingham models ($P < 0.0001$), in which 36% and 34% of MIs occurred in the high-risk cohorts, respectively.

The studies discussed this far did not include particularly high-risk subgroups. Anand et al (2006) evaluated CCS in asymptomatic diabetic patients. CAC scores were prospectively measured in 510 asymptomatic type 2 diabetic subjects (mean age, 53 ± 8 years; 61% men) without prior CVD, with a median follow-up of 2.2 years. In the multivariable model, the CAC score and extent of myocardial ischemia by nuclear stress testing were the only independent predictors of outcome. Performance analysis using receiver operative curve (ROC) analysis (described in detail later) demonstrated that CCS predicted cardiovascular events with the best accuracy, area under the curve (0.92), significantly better than the United Kingdom Prospective Diabetes Study risk score (0.74) and Framingham score (0.60). The relative risk to predict a cardiovascular event for a CAC score of 101 to 400 was 10.13, and it increased to 58.05 for scores >1000 ($P < 0.0001$). Even in this diabetic population, no cardiac events or perfusion abnormalities occurred in subjects with CAC ≤ 10 Agatston units up until 2 years of follow-up. These results emphasize the value of screening for subclinical disease in diabetics who often do not feel regular symptoms of coronary artery disease and thereby labeled as "asymptomatic".

Combining results of several studies, a meta-analysis of six trials was published in the ACC/AHA consensus document on CCS (Greenland et al., 2007). The meta-analysis reported a relative risk ratio of 4.3 for any measurable calcium, as compared with zero CAC score, thus implying a four-fold increase in the 3-5 year risk. Also, the annual incidence of coronary events increased with increasing tertiles of CAC scores (see fig 5). Although critics tend to point to limitations such as study generalizability of self-referral cohorts, validity of the risk factor measures and risk of test-induced bias, the meta-analysis still remains a stellar piece of evidence supporting the prognostic value of coronary artery calcium scoring.



Adapted with permission from Greenland et al. JACC Vol. 49, No. 3, 2007. ACCF/AHA Expert Consensus Document on Coronary Artery Calcium Scoring January 23, 2007:378 - 402

Fig. 5. Annual incidence of Coronary Artery Disease related events in different tertiles of Coronary Calcium Scores.

Author (Year)	Study and Population	Follow Up (Years)	Number of Events	Results
Arad et al (2000)	Observational N = 1172	3.6	15 nonfatal MI, 21 revascularizations, 3 deaths	OR of 20 for CAC scores ≥ 160
Wong et al (2000)	Observational N = 926	3.3	6 nonfatal MI, 20 revascularizations, 2 CVA	Overall, patients with CAC score ≥ 271 had a risk ratio of 9 for a CAD event.
Raggi et al (2001)	Observational N = 676	2.7	21 nonfatal MI, 9 deaths	OR of 22 for cardiac events for CAC score > 90 percentile
Kondos et al (2003)	Observational N = 5635	3.1	37 nonfatal MI, 166 revascularizations, 21 deaths	RR of 124 for cardiac events in men; incremental prognostic value of CCS
Shaw et al (2003)	Observational N = 10,377	5	249 all-cause mortality	CAC score an independent predictor of mortality with RR 4.0 for score of 401-1000
Greenland et al (2004)	Prospective N = 1312	7	68 nonfatal MI, 16 deaths	RR of 3.9 for CAC score >301 CAC score incremental to FRS
Arad et al (2005)	Prospective N = 4613	4.3	40 nonfatal MI, 59 revascularizations, 7 CVA	RR for CAD events with CAC >100 11. CCS superior to FRS in prediction of cardiac events
Vliegenthart et al (2005)	Prospective N = 1795	3.3	40 nonfatal MI, 38 CVA	RR >8, for CAC scores >1000 regardless of FRS
Taylor et al (2005)	Prospective N=1983	3	9 ACS events	CAC had an independent 12-fold increase in RR.
LaMonte et al (2005)	Retrospective N=10746	3.5	81 MI/CAD death, 206 revascularizations	Increasing cardiac event rates with higher CAC scores
Anand et al (2006)	Prospective N=510 (diabetics)	2.2	Total 22 events (cardiac and cerebral)	Rate of death or MI increased by CAC categories

Budoff et al (2007)	Observation referral-based N = 25,253	6.8	510 all-cause deaths	Rate of death or MI increased by CAC categories
Detrano et al (2008)	Prospective N=6,814	3.4	162 CAD events	FRS-adjusted risk 28% higher with CAC scores doubling. CAC predictive in all ethnic groups
Becker et al (2008)	Prospective	3.3	179 (65 cardiac death, 114 MI)	CAC score \geq 75th percentile associated with higher annualized event rate for MI. No cardiac events in patients with CAC = 0.

(CAC: Coronary Artery Calcium, CAD: Coronary Artery Disease, CVA: Cerebrovascular Accident, FRS: Framingham Risk Score, MI: Myocardial infraction, OR: odds Ratio, RR: relative risk)

Table 2. Clinical Trials summarizing data on Coronary Calcium Scoring.

2.7 Independent prognostic value of CAC scores over cardiac risk factors

Several authors in the preceding section have described an incremental role for CCS. Wong and colleagues (2000) showed that the CAC score severity predicted subsequent cardiovascular events independent of age, gender, and patient risk factor profile. Recent reports have included univariable and multivariable models that have evaluated the independent contribution of CAC in models evaluating risk factors or the FRS. The CAC score strongly predicted mortality, with 43% additional predictive value beyond risk factors alone (Greenland et al., 2004). In the St. Francis Heart Study, both univariable and multivariable models supported CAC scores as independent predictors of CAD outcome above and beyond traditional risk factors (Arad et al., 2000). Of note, CAC scores were also predictive of outcome in a multivariable model containing high-sensitivity C-reactive protein, a relatively newer marker for CAD (Taylor et al., 2005), similar to a previous report by Park et al. (Park et al., 2002). Other authors have evaluated the prognostic contribution of CCS in multivariable models that controlled for risk factors such as a family history of premature CHD or body mass index, that are not in the FRS, and proved CCS to be independently predictive in these settings too (LaMonte et al., 2005; O'Malley et al., 2003).

2.8 Coronary calcium scoring: Complementary to Framingham scores and global risk assessment?

Since CCS has shown to have incremental value over risk factors, the next step is to assess whether it can be integrated in to risk assessment algorithms. The concept of Bayesian theory provides a framework to evaluate the expected relationship between the predictive values of CAC score in individuals with low- to high-risk FRS. As dictated by Bayesian theory, a test's post-test likelihood of events is partially dependent upon a patient's pretest risk estimate. Thus, for patients with a low risk FRS very few events would be expected

during follow-up and the resulting post-test risk estimate for patients with an abnormal CAC score would be expected to remain low. Not surprisingly, several reports have documented the futility of CAC score in risk prediction for low-risk populations (Kondos et al., 2003; Greenland et al., 2004). Such studies demonstrate the importance of selecting optimal cohorts for whom CAC testing will be of greater value. In addition, the recent data provide support for the concept that use of CAC testing is most useful in terms of incremental prognostic value for populations with an intermediate FRS (Redberg et al., 2003). In a secondary analysis of patients with an intermediate FRS from 4 reports (Greenland et al., 2004; Arad et al., 2005; Vliegenthart et al., 2005; LaMonte et al., 2005), annual CAD death or MI rates were 0.4%, 1.3%, and 2.4% for each tertile of CAC score where scores ranged from less than 100, 100 to 399, and greater than or equal to 400, respectively. From this analysis, intermediate-risk FRS patients with a CAC score greater than or equal to 400 would be expected to have coronary event rates that place them in the CAD risk equivalent status i.e >20% event rate in the next ten years.

One way to determine additive utility of a new test is through the use of Receiver Operative Curve (ROC) analyses. The ROC curve is a plot of true-positive rate versus false-positive rate over the entire range of possible cutoff values. The area under the ROC curve (AUC) ranges between 1.0 for the perfect test and 0.5 for a useless test. Studies comparing predictive capacity of conventional and newer biomarkers for prediction of cardiovascular events consistently demonstrate that adding a number of newer biomarkers (such as C-reactive protein, interleukins, and other proposed risk stratifiers) change the C-statistic by only 0.009 ($P = 0.08$). Such small changes such as these in the C-statistic suggest rather limited improvement in risk discrimination with additional risk markers. The costs involved in implementing the use of such biomarkers may not be justified by the magnitude of the observed benefit. However, CAC scanning has been shown to markedly improve the C-statistic in the studies described above, suggesting robust improvement in risk discrimination (Anand et al 2006; Budoff et al 2007).

2.9 Calcium scoring in symptomatic patients

This far, we have discussed the utility of CCS in asymptomatic patients. Researchers have investigated the role of CCS in symptomatic patients also. If a patient does not have coronary artery calcification, it would be very unlikely that they have high grade obstructive CAD. However, once calcium is discovered, theoretically, one cannot definitively opine if the plaque is obstructive or not. Nevertheless, this topic has been a target of active research. Trials investigating this subject have studied symptomatic patients referred for coronary angiography.

A meta-analysis including 3683 patients from 16 studies was performed to evaluate the diagnostic accuracy of coronary calcium scoring (O'Rourke et al., 2000). The entry criteria included diagnostic catheterization for patients without prior history of coronary disease or prior cardiac transplantation. Patients were symptomatic and referred to the cardiac catheterization laboratory for exclusion of obstructive CAD. On average, significant coronary disease (defined as greater than 50% by some or 70% luminal stenosis by others on coronary angiography) was reported in 57.2% of the patients. Presence of CAC was reported on average in 65.8% of patients. The odds of obstructive CAD were found to be elevated 20-

fold with a positive CAC. Additionally, higher coronary calcium scores were associated with higher degrees of obstructive coronary artery disease.

Similar to data in asymptomatic patients, some other authors have described the independent predictability of CAC in symptomatic patients. A large case series by Guerci et al (1998) found that coronary calcium score of greater than 80 (Agatston score) was associated with increased likelihood of obstructive coronary artery disease regardless of the number of risk factors. Also, the series by Kennedy et al (1998) clearly reported that in their multivariate analyses, only male sex and coronary calcium score were significantly related to the extent of angiographic disease. The ROC analysis for CAC showed a much larger area under the curve, as compared to conventional risk factors, thus establishing its role as a disease discriminator.

2.10 CAC in comparison to other tests for diagnosis of coronary artery disease

As a new test for CAD, it is important to assess and compare CCS to the currently accepted modalities for CAD diagnosis. Schermund et al (1999) compared EBT derived CAC measurement to nuclear stress tests using technetium in a cohort of 308 symptomatic patients referred for cardiac catheterization. They found a strong association of CAC score with perfusion defects on Single Photon Emission Computed Tomography (SPECT) scans and angiographically obstructive CAD. This association remained significant after excluding the influence of interrelated risk factors and SPECT variables.

Other authors have reported similar results using thallium exercise stress testing (Kajinami et al., 1995; Yao et al., 1997). In fact, a study by Shavelle et al (2000) indicated that CAC might be more accurate for diagnosis for CAD. The relative risk for obstructive CAD in this study was 4.43, and was significantly higher than that for treadmill ECG (1.72) or technetium stress (1.96). The overall accuracy of CAC was 80%, as opposed to 71 and 74% for exercise treadmill ECG and technetium stress respectively. When combined with an abnormal treadmill ECG response, CAC was found to be 83% specific for obstructive CAD. He et al (2000) suggest a complementary role for CCS based on their finding of a threshold phenomenon. In their study, no myocardial hypoperfusion was noted in patients with CAC less than 100, and a marked increase in perfusion abnormalities with increasing CAC scores. If indeed, the absence of coronary calcium in symptomatic patients can exclude obstructive disease, it can possibly be used in the triage of patients with chest pain in the emergency rooms in the future. Some groups have looked at this possibility, and although their results favor CAC as a triage tool (Georgiou et al., 2001; McLaughlin et al., 1999), the author personally has some concerns about adopting this paradigm as a standard of care, at least for now. This is mainly because of small sample sizes of these studies, and the fact that it may not be safe to discharge every patient with absent coronary calcifications. Some of these patients could have noncalcified soft plaques that may be prone to rupture. Absence of coronary calcification may lead to a false sense of security in such patients, and they may be discharged. A small proportion of these patients could develop a full-blown acute coronary syndrome outside of hospital settings. The medico-legal implications of such mishaps are far from few. In our opinion, until further data become available, CAC scoring should not be recommended as a triage tool in the emergency room setting. This issue is further elaborated in the section on absent coronary artery calcifications in CAD.

2.11 Using CCS in patients with established CAD

While there is limited utility to CCS in patients with documented CAD, a recognized use of CAC screening is to track atherosclerotic changes over time by serial measurements. A large prospective study was designed to evaluate the impact of aggressive lipid-lowering and antioxidant therapy on the progression of CAC. The study included 4613 asymptomatic persons between 50 to 70 years of age, with coronary arteries EBT scanning at baseline and again at 2 years and 4.3 years (Arad et al, 2005). Whereas the intervention did not seem to significantly affect progression of CAC, it was noted that patients who sustained a coronary event demonstrated a median increase in CAC score of 247 as compared to a CAC score increase of 4 in those who did not sustain a coronary event. Multiple logistic regressions demonstrated that 2-year change in calcium score ($P = 0.0001$) was significantly associated with subsequent CAD events. Increasing calcium scores were seen to most strongly correlate with coronary events in this study, as in another observational study by Raggi et al. (2004).

Since statins are known to stabilize coronary artery plaques, one would expect that coronary calcification would not progress, and if anything, regress with aggressive statin therapy. However, the results of clinical trials have been controversial in this regard. In a retrospective study, Callister and associates (1998b) demonstrated a 45% slowing in the rate of CAC progression in patients receiving statins. Budoff and coworkers (2000), in a prospectively designed study, demonstrated a 61% decrease in the rate of CAC score progression in dyslipidemic patients on statin therapy. Similarly, Achenbach and colleagues (2002) showed that with a standard dose of 0.3 mg/day of open-label cerivastatin in dyslipidemic patients, the median annual relative increase in CAC scores was 25% during the untreated period before study entry versus 9% during the treatment period ($P < 0.0001$). Reduction of CAC score was most pronounced in those patients who achieved an LDL level < 100 mg/dL.

On the other hand, at least three randomized controlled trials have failed to replicate these results. The SALTIRE trial (Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression) randomized 102 patients to atorvastatin or placebo and assessed CAC progression during an average follow-up of 2 years. Despite a significant reduction in LDL and C-reactive protein levels, there was a insignificant increase in percentage CAC progression (Houslay et al., 2006). Schermund and coworkers (2006) also failed to show reduced progression of CAC in asymptomatic patients randomized to 80 mg of atorvastatin, despite a 20% reduction in LDL level as compared to the group receiving 10-mg atorvastatin during one year of follow up. Similarly, the BELLES (Beyond Endorsed Lipid Lowering with EBCT Scanning) study, which randomized hyperlipidemic postmenopausal women to atorvastatin 80 mg or pravastatin 40 mg, found no effect on CAC progression in either arms. Although atorvastatin reduced LDL concentration by $47\% \pm 20\%$ and pravastatin reduced LDL by $25\% \pm 19\%$, there was no significant decrease in CAC progression after 12 months, and rather, a statistically insignificant increase of 15% and 14% in CAC scores in the atorvastatin and pravastatin arms, respectively (Raggi et al., 2005). The authors were unable to justify this increase in CAC scores despite LDL reduction.

Based on the conflicting data, the ACC/AHA guidelines do not recommend following CAC scores longitudinally to track coronary atherosclerosis over time (Greenland et al., 2007).

2.12 Absence of coronary artery calcium and its implications

So far, we have reviewed data on the presence and absence of coronary calcium in symptomatic and asymptomatic cohorts. It appears that absence of CAC reliably excludes obstructive coronary disease in asymptomatic and selected symptomatic individuals. Also the absence of coronary calcium appears to be associated with a low cardiovascular event rate, suggesting that less aggressive pharmacotherapy may be acceptable in this population. However, published event rates for individuals with zero CAC vary, probably because of differences in baseline risk, follow-up period, and very different endpoints in studies.

Overall, absence of coronary calcium appears to be favorable in terms of prognosis for coronary events. However, we do need to elaborate on the few patients with coronary artery disease, who are missed by CCS. In a cohort of asymptomatic middle-aged individuals, Blaha et al. (2009) observed that relatively more coronary events occurred among diabetics and smokers, even in the absence of CAC. The likely mechanisms include non-calcified soft plaques, rapid development of atherosclerosis, and plaque destabilization. Even so, whereas the relative risk of events is higher in the presence of low CAC, the absolute event rate remains low. Thus, in an appropriately selected non-high-risk patient, the absence of CAC can likely be used as a rationale to emphasize lifestyle therapy, while refraining from expensive preventive pharmacotherapy, and frequent cardiac imaging or testing.

Given the low 10-year risk in this population, a drug such as a statin that produces a 30% relative risk reduction would have to be given to more than 300 patients for 10 years to prevent one death i.e. number needed to treat (NNT) is approximately 333 for 10 years (Blaha et al., 2009). Although current guidelines do not recommend that preventive therapies such as lipid-lowering medications be stopped or dosed lower in the absence of CAC, data from the aforementioned studies suggest that aggressive management in this cohort is probably not warranted if one does not qualify according to NCEP guidelines. This strategy will allow those with absent CAC to follow healthy lifestyle modifications with little or no medical therapy, whereas intense therapy is focused on a population of patients with an actual higher risk of events demonstrated by atherosclerotic burden on CCS. Again, in implementing this standard of care, one needs to remember the caveat about smokers and diabetic patients described above.

The ACC/AHA guidelines echo these results, recommending against invasive diagnostic procedures or hospital admission in patients with absent CAC (Greenland et al., 2007). The ACC/ASNC appropriateness criteria also mention that the absence of CAC generally precludes the need for assessment by myocardial perfusion imaging (Brindis et al., 2005). This strategy can significantly cut down radiation exposure and coronary angiography related complications.

2.13 Applying coronary calcium screening in every day life: The practicalities and challenges

2.13.1 Is calcium scoring valid across various ethnicities and races?

Demographic data suggest that African American patients have lower incidence of coronary artery calcifications despite a higher overall prevalence of coronary artery disease (Greenland et al., 2007). Most literature on CCS has been described in white populations. Two studies have

addressed the value of CAC in other ethnic groups. First, Nasir and coworkers (2007) in nearly 15,000 ethnically diverse self-referred patients assessed the role of CAC for the prediction of all-cause mortality. In comparison of prognosis by CAC scores in ethnic minorities, relative risk ratios were highest for African Americans, with scores ≥ 400 exceeding 16.1 ($P < 0.0001$). Hispanics with CAC scores ≥ 400 had relative risk ratios from 7.9 to 9.0; Asians with CAC scores ≥ 1000 had relative risk ratios 6.6-fold higher than those of non-Hispanic whites ($P < 0.0001$). The second study to address this question is the prospective Multi-Ethnic Study of Atherosclerosis (MESA) study by Detrano et al., (2008). MESA was designed to investigate the prevalence and progression of subclinical CAD in a population-based sample of 6814 men and women between 45 to 84 years of age. The cohort was selected from six United States field centers and included approximately 38% white, 28% African American, 23% Hispanic, and 11% Asian (primarily of Chinese descent) patients. Their results indicated that when compared with whites, the relative risks for having coronary calcification were 0.78 (95% CI, 0.74 to 0.82) in blacks, 0.85 (95% CI, 0.79 to 0.91) in Hispanics, and 0.92 (95% CI, 0.85 to 0.99) in Chinese. Despite this difference in prevalence of CAC, the predictive value of coronary calcium in various ethnic groups remains valid. These results strongly support the role of CCS as a global coronary event risk stratifier.

2.13.2 Is CCS equally predictive in both men and women?

Women develop atherosclerosis about 10 years later than men. The appearance of coronary calcium tracks with this later onset of CAD. Thus cut off values for CAC scores are different in men and women. However, these differences start to diminish after the age of sixty years. Premenopausal women generally have a low likelihood of obstructive coronary artery disease and vulnerable plaques compared to age matched men. Premenopausal women who have any degree of CAC before sixty years of age are at much higher risk of coronary events and deserve particular attention to aggressive lipid therapy and risk factor modification. These gender differences highlight the importance of age and gender specific reference points for CAC scoring (Hoff et al., 2001). In this regard, one also needs to remember that we presently do not have any guidelines about applying these scores to younger women who have been rendered menopausal iatrogenically via surgical hysterectomy or oophorectomy. Due to small numbers, this cohort has not been systematically studied yet. It is unclear whether these women should be treated as though they have the same level of risk as their age matched male controls.

2.13.3 Is CAC scoring valid in end stage renal disease patients?

It is well known that the subset of patients with end stage renal disease, especially those on hemodialysis have a higher prevalence of coronary artery calcification. Although this cohort as a whole is at higher risk for coronary events, one cannot use coronary artery calcifications to prognosticate this group in the same way as patients without renal disease. Some studies suggest that such patients develop calcification of the tunica media as opposed to the typical intimal calcification associated with atherosclerotic plaques (Moe et al., 2002). The role of medial calcification remains to be explored in CAD. Studies have reported conflicting data about correlation between coronary calcium detected on CT scanning and luminal narrowing on coronary angiography (Haydar et al., 2004; Sharples et al., 2004). In the absence of firm recommendations in this cohort, it is best to individualize care to each patient as much as possible.

2.13.4 Who is an appropriate patient for CCS?

The ACC/AHA consensus document on CCS mentions “it may be reasonable to consider use of CAC measurement in asymptomatic individuals who are at intermediate risk by the FRS” (Greenland et al., 2007pp 378-402). Such individuals are most likely to be reclassified to a higher risk status on the basis of high CAC score, thus modifying subsequent patient management. However, the committee did not find enough evidence for the utility of CAC testing in risk stratification of those considered at low risk as well as of those considered at high risk for CAD in the next 10 years.

Patients with a 10-year risk >20% already qualify for aggressive lipid-lowering management with optional LDL-C goals of <70 mg/dL, and further CAC testing may not change treatment goals. The current guidelines do not recommended CAC testing for those with a 10-year estimated risk of <10% (low risk). However, by current criteria, most non-diabetic women who are younger than 60 years would not be candidates for further risk stratification with CAC testing. This approach will exclude a large number of women at higher risk for CAD from CAC testing. One should remember that those at <10% 10-year risk of CAD are frequently at significant longer term risk of CHD, particularly those women with a family history of premature CAD. Since family history of premature CAD does not factor into most global risk algorithms, it may be advisable to screen a subset of women with low 10-year risk with CAC if they have family history of premature CAD. At least 25% of individuals with family history of premature CAD have significant CAC. Clinical studies have strongly supported family history of premature CAD to be an independent risk factor associated strongly with higher burden of subclinical atherosclerosis. Nasir and coworkers (2007) demonstrated that among those with premature family history of CAD (especially with sibling history), nearly one-third to one-quarter of self-referred patients with no or one CAD risk factor had CAC ≥ 100 .

Another way to work around this problem may be to look for alternative definitions of the “intermediate risk” category. The 2003 American College of Cardiology Bethesda Conference on atherosclerosis imaging defines “intermediate-risk groups” as those at 6% to 20% 10-year risk, as opposed to FRS, which defines intermediate risk as 10-20% 10-year risk (Wilson et al., 2003). By this definition, more higher risk women would be placed in the intermediate-risk group, and thus qualify for risk factor modification, especially regarding LDL-C control, aggressive preventive strategies, such as statin, aspirin, and possibly blood pressure-lowering therapies if they additionally have increased levels of CAC. The recommendations involving low FRS risk category and women with family history of premature CAD were not incorporated in the 2007 consensus document on CCS. The author himself uses these pearls in clinical practice and looks forward to them being integrated in a future consensus document from the ACC/AHA.

2.14 Does CAC scoring improve healthy life style adherence and medication compliance?

Some working groups have demonstrated that the discovery of any calcium on a CAC scan independently lead to initiation of aspirin and/or statin therapy by physicians (Wong et al., 1996). The same group also demonstrated that initiation of healthful lifestyle changes, including losing weight and decreasing dietary fat often accompanied an abnormal CAC

scan. Although the initiation of appropriate lifestyle and pharmacotherapy by physicians correlated with abnormal CAC scores, it is still unclear whether routine atherosclerotic imaging improves medication adherence. Kalia et al (2006) reported that in a study of 505 asymptomatic individuals that continuation of lipid-lowering medication was lowest (44%) among those with a CAC score in the first quartile (0-30), whereas 91% of individuals with a CAC score in the fourth quartile (>526) adhered to lipid-lowering medication. In multivariable analysis, after adjustment for other cardiovascular risk factors, higher baseline CAC scores were strongly associated with adherence to statin therapy. Most data in this regard seem to be coming from only one group of investigators. Moreover, a randomized clinical trial assessing the effects of CAC scanning on estimated risk of CAD after 1 year, determined by changes in FRS, found no difference in mean absolute risk change in 10-year FRS comparing the groups who received CAC score results with those who did not. In this study, the prevalence of CAC was fairly low (15%), with generally low CAC scores even in those with CAC. It is possible that the study was not powered enough to detect the difference between the study groups (O'Malley et al., 2003).

2.15 Is this technology cost effective?

Establishing cost effectiveness of diagnostic tests is quite challenging. To establish effectiveness, CAC measurement has to be shown to enhance quality of life, prolong life or both. While this is feasible for therapies having randomized control trials, no such studies exist for CAC measurement (Douglas & Ginsburg, 1996).

In the absence of clinical trial data, cost effectiveness is approached with simulations in which decisions, test results and outcomes are estimated with as much information from medical literature. Despite significant challenges, three studies have attempted to study cost effectiveness of CAC scoring (O'Malley & Greenberg, 2004; Taylor et al., 2005; Shaw et al., 2003). Most studies assessing cost effectiveness of diagnostic modalities use the Incremental Cost Effectiveness Ratio (ICER) as a measure of cost effectiveness. ICER is defined as the ratio of the change in costs secondary to an intervention/test (compared to the alternative, such as doing nothing or using the best available alternative treatment) to the change in effects of the same (O'Malley & Greenberg, 2004). O'Malley and colleagues (2004) were able to demonstrate an ICER of \$86752. The Prospective Army Coronary Calcium project found an ICER of \$31,500 (Taylor et al., 2005) and Shaw et al (2003) demonstrated an ICER of \$500,000 with estimated coronary risk of <0.6% per year, \$42,339 for an incidence of 1%, and \$30742 for an incidence of 2% per year. The consensus committee felt that neither of these models were strong or grounded enough to justify establishing a policy at this time.

In our opinion, although the proposed cost effectiveness models are weak, their respective authors do offer a valid argument. The basis of their assertion is that both noninvasive testing and invasive angiography rates are low in individuals with low CAC scores. In the absence of CCS data, this patient population will be subjected to functional testing such as myocardial perfusion assessment, and possibly even invasive coronary angiography, both of which drive medical costs up significantly. With its valuable attributes of very little radiation exposure, strong risk stratification evidence, and relative inexpensiveness, CCS appears to be a cost effective alternative in cardiovascular care. Figure 6 summarizes the merits of CAC scoring as an ideal risk stratifier and an economically feasible alternative.

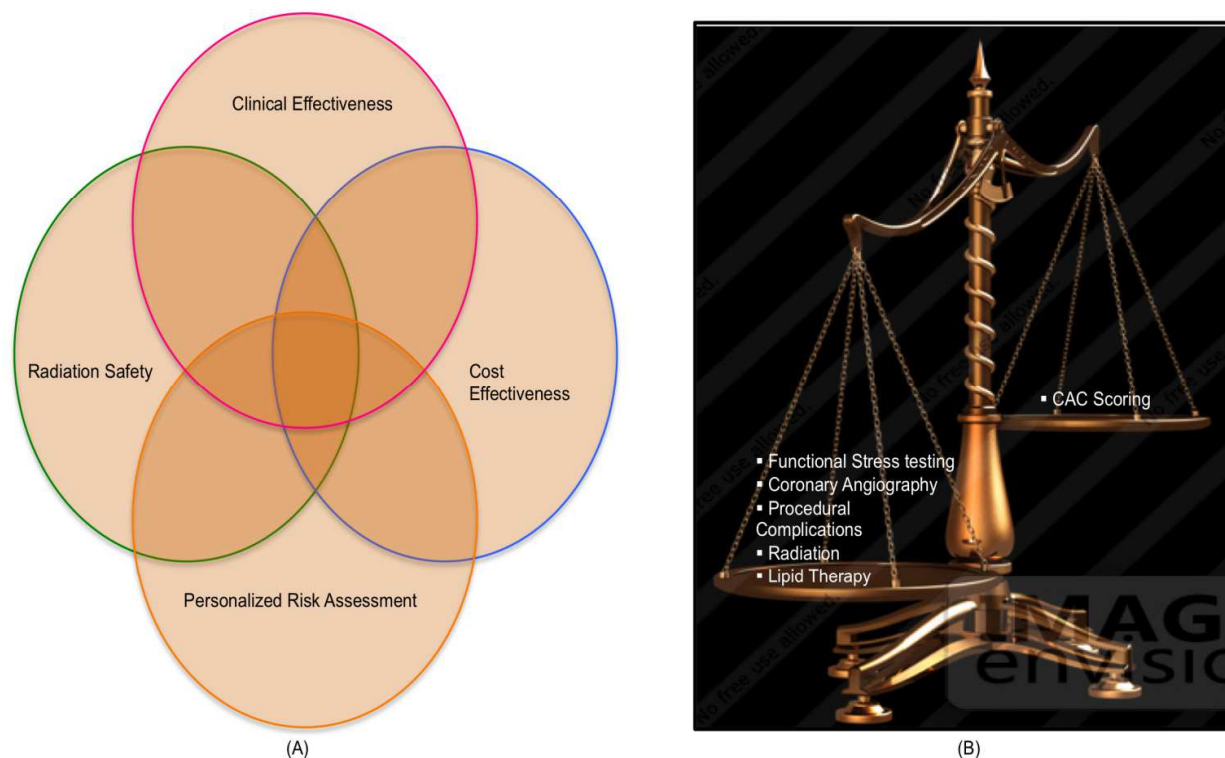


Fig. 6. Clinical (A) and Economic (B) Attributes of Coronary Calcium Scoring (CCS)

3. Other markers for CAD

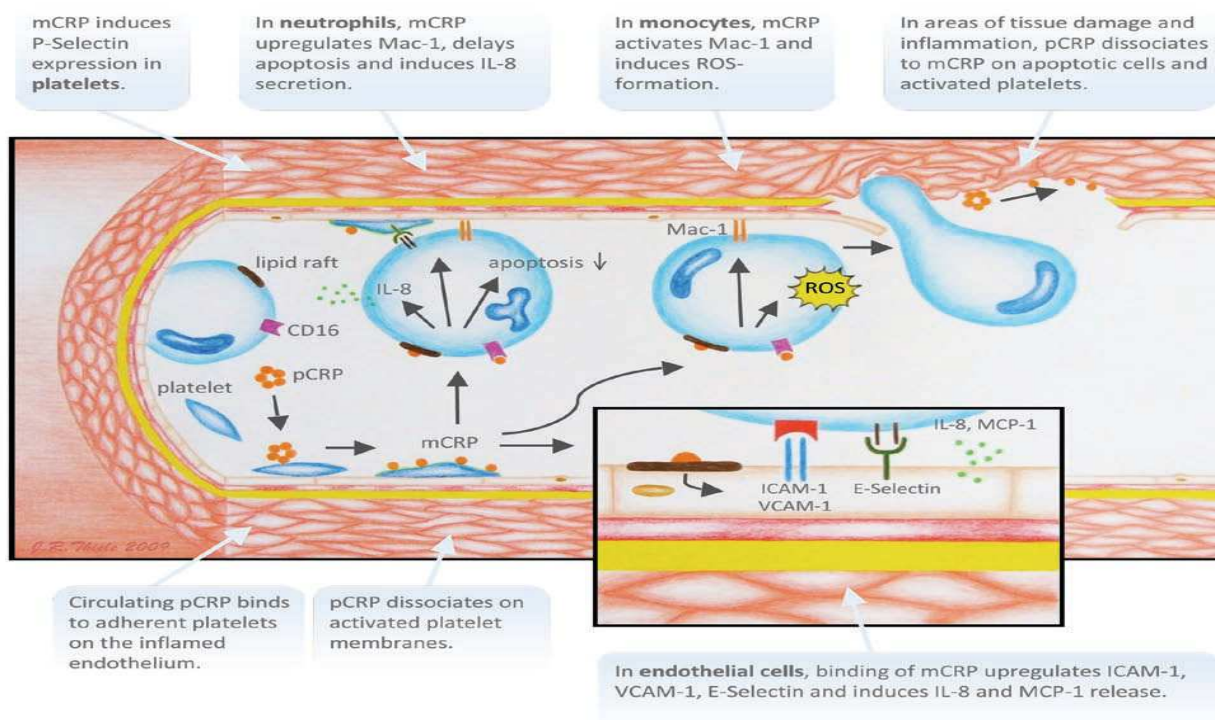
After the extensive discussion on calcium scoring and its role in assessment of CAD, we will now briefly discuss other novel risk markers for CAD.

3.1 C-reactive protein

3.1.1 Historical background and function

C-reactive protein (CRP) is a nonspecific marker of inflammation. C-reactive protein (CRP) was first described by the laboratory of Oswald Avery at the Rockefeller Institute in New York (Ghose, 2004). It was tested for an association with cardiovascular disease when inflammation was implicated as the culprit in the pathogenesis of atherosclerosis (Ross, 1999). CRP occurs in two forms, a pentameric (pCRP) form and a monomeric (mCRP) form (Eisenhardt et al, 2009a). The pentameric form is produced by hepatocytes as an acute phase reactant, elevating up to a 1,000-fold within 24-72 hours in response to infection, inflammation and tissue injury (Pepys & Baltz, 1983). Monomeric CRP is believed to be derived from dissociation of pCRP (Eisenhardt et al., 2009b) and possibly produced in extrahepatic cells such as smooth muscle in arterial walls, adipose tissue and macrophages (Yasojima et al., 2001).

Interestingly, pCRP is believed to promote both inflammatory and anti-inflammatory effects. There is even considerable data suggesting that pCRP may have vasculoprotective potential. mCRP however, has been documented to directly induce expression of VCAM-1 and to play a key role in the promotion of platelet aggregation (Eisenhardt et al., 2009). Fig 7 summarizes the vascular inflammatory process.



Adapted with permission from: Eisenhardt SU, Thiele JR, Bannasch H et al. C-reactive protein: how conformational changes influence inflammatory properties. *Cell Cycle* 2009; 8:23, 3885-3892.

Fig. 7. Role of CRP in vascular inflammation Dissociation and pro-inflammatory effects of mCRP in the peripheral circulation. CRP circulates as a disc shaped pentamer and is dissociated by its exposure to bioactive lipids on cell membranes of activated platelets and apoptotic/necrotic cells. The resulting mCRP then exerts its pro-inflammatory effects that are depicted in the figure.

3.1.2 Nonspecific CRP

The controversy with CRP stems from its nonspecific nature. A great degree of variability was noted in a study in which serial measurements of serum CRP were obtained in 159 patients with stable ischemic heart disease. In this trial, risk stratification was performed using 3 risk categories (CRP <1, 1-3 and >3mg/L). In this process, 40% of patients changed risk categories between the first and second measurements (Ockene et al., 2001). Even a minor inflammatory ailment such as an upper respiratory tract infection can produce significant fluctuations in CRP levels, thus making it difficult to rely on it as a cardiovascular disease marker.

Further, it is extremely difficult to assess CRP in the milieu of other chronic inflammatory disease such as rheumatoid arthritis or systemic lupus erythematosus, which independently raise CRP levels. A study by Breland and associates (2010) evaluated plasma levels of CRP in patients with CAD without inflammatory rheumatologic disease (IRD), CAD with IRD, IRD without CAD, and healthy subjects. They found that plasma levels of CRP in patients with CAD without IRD, CAD with IRD and IRD without CAD were significantly elevated relative to healthy individuals ($p=0.002$). No significant difference was detected in levels of CRP in patients with CAD with or without IRD, and in patients with IRD without CAD.

Gasparyan et al (2010), in their review of the literature, noted that CRP plays a universal role in the enhanced atherogenesis in all rheumatologic diseases. Elevations in CRP levels have been linked to antiphospholipid antibodies in SLE (Feinboom & Bauer, 2005 as cited in Gasparyan et al., 2010) and anti-CCP in RA (del Val Del Amo et al., 2006). CRP as a prognostic marker for CAD in patients with IRD needs further studies with larger sample sizes, however preliminary data is suggestive that an elevated CRP does incur increased risk for CAD. A multiethnic lupus cohort study conducted in the USA determined that CRP independently predicted arterial events (hazard ratio [HR] 3.9, 95%CI 1.5-10.1) (Tolosa et al., 2004 as cited in Gasparyan et al., 2010). While in the UK, a cohort of RA patients with CRP levels >5 mg/L were found to be at risk of cardiovascular death (HR 3.9, 95%CI 1.2-13.4 for men and 4.22, 95% CI 1.4-12.6 for women) (Goodson et al., 2005 as cited in Gasparyan et al., 2010).

Cirrhosis complicates the interpretation of CRP, as it is a cause of decreased production of CRP from the liver. Also medications such as oral contraceptives have also been documented to increase CRP levels (Mackenzie & Woodhouse, 2006). In the recent years, high sensitivity CRP (hs-CRP) has generated significant interest among researchers. hs-CRP detects concentrations down to 0.3 mg/L and below, as compared to more traditional assays which detect in the range of 3 to 5 mg/L. hsCRP assays are used to assess cardiovascular risk because these tests are able to quantify CRP levels normally observed in asymptomatic patients (Marrow, 2011).

3.1.3 CRP and CAD link

The added value of high hsCRP to risk stratification was initially evaluated by Ridker and colleagues (Cook et al., 2006). In their model they added hsCRP to variables utilized in the Framingham risk score (i.e., age, total cholesterol level, high-density lipoprotein cholesterol level, smoking and blood pressure) in the Women's Health Study (Cook et al., 2006). Their results showed only a marginal improvement in the area under the receiver operating characteristic curve (AUC-ROC) (Cook et al., 2006). The same group then explored whether risk prediction of hsCRP could be improved when used together with several other novel biomarkers such as hemoglobin A1c (HbA1c), homocysteine, soluble intercellular adhesion molecule-1, and apolipoproteins (Ridker et al., 2007). The Women's Health Study was divided into a model derivation cohort (n = 16,400) and a model validation cohort (n = 8158) (Ridker et al., 2007). The amalgamation that produced the best fitting model consisted of age, systolic blood pressure, current smoking, hsCRP, parental history of MI < age 60, HbA1c in diabetics, apolipoprotein B-100 level, apolipoprotein A-I level and lipoprotein (a) levels. This algorithm was simplified for more efficient clinical utility into the Reynolds Risk Score (RRS) (Ridker et al., 2007) (see Table 3). The RRS reclassified 40-50% of intermediate-risk, as predetermined by the FRS, to higher risk or lower risk. The FRS and RRS differ in the addition of hsCRP and parental history of MI < age 60 to the latter. However, it is important to point out that none of the subjects were reclassified from a low risk to a high risk category and vice versa, emphasizing the importance of determining prior probability of disease in those recommended to have further testing. The RRS was later validated in men. When compared to a traditional risk stratification model, the RRS reclassified 18% of subjects in the Physicians Health Study II, and was associated with better model fit and discrimination (Ridker et al., 2008a).

Best-Fitting Model	Clinically Simplified Model
Age	Age
Systolic blood pressure	Systolic blood pressure
Current smoking	Current smoking
hsCRP	hsCRP
Parental history of MI <age 60	Parental history of MI <age 60
Hemoglobin A1c (if diabetic)	Hemoglobin A1c (if diabetic)
Apo B-100	Total Cholesterol
Apo A-I	HDL-C
Lp(a) [if apo B-100 \geq 100]	

Adapted with permission from Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007; 297:611-619.

Table 3. Reynolds Risk Score

Most recently, evaluation of the therapeutic benefit of statin therapy in patients with LDL-C levels lower than 130 mg/dL, with elevated hsCRP levels greater than 2mg/L was examined in the Justification for the Use of Statins in Primary Prevention: an Interventional Trial Evaluating Rosuvastatin (JUPITER). Patients who met these criteria were treated with Rosuvastatin. Treatment with this therapy was associated with a 44% relative risk reduction in major cardiovascular events. The trial was discontinued early due to the early observation of clear benefit from such therapy (Ridker et al., 2008b). The Atherosclerosis Risk in Communities (ARIC) study was then conducted analyzing data on participants with the entry criteria of the JUPITER trial (Yang et al., 2009). The results of the ARIC trial suggested that elevated hsCRP conferred high risk regardless of LDL-C levels (<130mg/dL or \geq 130mg/dL) (Yang et al., 2009).

3.2 Lipoprotein associated phospholipase A₂

3.2.1 Form and function

Lipoprotein Associated Phospholipase A₂ (Lp-PLA₂) was first cloned in 1995. It is a modified LDL particle in which a large glycoprotein, apolipoprotein (a), is covalently bound to apo B by a disulfide bridge (Streeter et al., 1994). The apo(a) chain has five cysteine rich domains known as "kringles". The fourth kringle is homologous in structure to the fibrin-binding domain of plasminogen, the plasma protein responsible for dissolving clots. This structural similarity unfortunately sets up a competition between Lp-PLA₂ and plasminogen for binding sites, thus causing interference with fibrinolysis. Lp-PLA₂ induces foam cell formation and encourages cholesterol deposition in atherosclerotic plaques (McLean et al., 1987). Lp-PLA₂ is also thought to propagate inflammation via its action on oxidized phospholipids and nonesterified fatty acids, both of which are capable of inducing expression of adhesion molecules and attracting monocytes (Caslake & Packard, 2005).

3.2.2 Cardiovascular risk and Lp-PLA₂

Studies have contended Lp-PLA₂ as another biomarker associated with both cardiovascular disease and stroke (Ballantyne et al., 2004; Blake et al., 2001). The ARIC study that evaluated the increase in predictive risk provided by 19 markers including hsCRP showed that only Lp-PLA₂ significantly increased the AUC-ROC when added to traditional risk factors for cardiovascular disease (Folsom et al., 2006). The largest prospective analysis, that assessed the association between increased Lp-PLA₂ and coronary artery disease revealed an odds ratio of 1.60 (95% CI 1.09-1.18) for those patients with Lp-PLA₂ values in the upper third tertile as compared to the lowest third tertile after adjusting for traditional risk factors (Bennet et al., 2008). The best data summarizing the relationship between Lp-PLA₂ and cardiovascular disease comes from a meta-analysis of individual patient records from 120,000 subjects in 36 prospective studies (Erqou et al., 2009). This study was able to show that Lp-PLA₂ was associated with a continuous risk for cardiovascular events (Erqou et al., 2009).

3.2.3 Who should be screened?

Although Lp-PLA₂ is a valid cardiovascular disease marker, it may not be feasible to screen everybody for the same. Stein and Rosenson (1997) put forth some recommendations for screening and treatment of Lp-PLA₂. Based on their recommendations, screening should only be performed in the following circumstances:

1. Patients with coronary heart disease and no other identifiable dyslipidemia.
2. Patients with strong family history of coronary heart disease and no other dyslipidemia.
3. Patients with hypercholesterolemia refractory to therapy with LDL cholesterol lowering therapies.

The last recommendation stemmed from the observation that Lp-PLA₂ does not respond to usual the therapy for LDL-C. The Friedewald formula, which is commonly used to calculate LDL cholesterol, does not distinguish between Lp-PLA₂ and LDL-cholesterol. Often, patients who present with elevated LDL may not have true LDL excess, but may instead have significant Lp-PLA₂ accumulation (Berresen et al., 1981). Such patients may be "refractory" to traditional LDL lowering therapy with statins, bile acid sequestrants, fibric acid derivatives etc.

3.2.4 Treatment

The most effective treatment to reduce Lp-PLA₂ levels is nicotinic acid (Carlson et al., 1989). Estrogen replacement therapy has also been reported to reduce Lp-PLA₂ by 50% (Sacks et al., 1994). Apheresis is a newer therapy that has been investigated for treatment of elevated Lp-PLA₂ (Keller, 2007).

3.3 Apolipoprotein B

Forty years ago Fredrickson and associates recognized that atherosclerosis is more closely related to the total number of apolipoprotein B (apo B)-containing particles rather than to LDL-C (Ridker et al., 2007). Apo B is an integral part of LDL, oxidized LDL, VLDL, and triglycerides (TG). It thus provides a direct measure of all circulating atherogenic lipoproteins (Ridker et al., 2008b). Also, measurement of LDL may sometimes be inaccurate

in the setting of hypertriglyceridemia, particularly in diabetic patients. The utility of Apo-B in cardiovascular risk stratification is discussed in the paragraphs to follow. The author and his working group of clinicians use this marker frequently in day-to-day practice.

3.3.1 Combining apolipoproteins with CCS

Having discussed the above biomarkers in detail, it is now time to deliberate on how they can be incorporated in to an algorithm for clinical use. At the present time, there are no randomized trials or guidelines describing such combinations. The thoughts and possibilities presented in this section of the chapter are entirely based on the author's personal clinical experience. We present the risk stratification algorithm followed at our institution. We wish to emphasize that this approach should be considered experimental in the absence of evidence-based data supporting this paradigm.

Like most clinicians, we start our patient risk assessment by calculating Framingham risk scores. When patients are identified to have a 10-year risk of 10-20%, particular attention is paid to their HDL status. When these patients have low HDL, cardiologists consider the possibility of premature atherosclerosis in certain subtypes of patients within this class. Two main categories of dyslipidemias with risk of premature atherosclerosis include Familial hypertriglyceridemia (High TG, Low HDL, near normal LDL; otherwise known as Type IV Hyperlipidemia) and Familial Combined Hyperlipidemia (high TG, high LDL, low HDL; otherwise known as Type IIb Hyperlipidemia). These disorders are not very uncommon, and such patients have high levels of small dense LDL in their circulation (Genest et al, 1992). Particularly, the subgroup with Type IV hyperlipidemias is often clinically undertreated because of normal to near normal LDL levels. While lipoprotein analysis is not the routine standard of care for every patient at our institution, we do recommend checking Apo B 100 levels for further risk stratification in the class patients described above, particularly if they have family history of premature CAD. The apo B levels reflect their potential for early subclinical atherosclerosis.

If the Apo B levels are reported to be within normal limits, further testing is not encouraged and annual follow up of lipid panels, along with statin therapy is advised per the NCEP guidelines. However, in the presence of elevated Apo B 100 levels, these patients are aggressively treated with statins, with or without niacin to achieve LDL goals of <70 mg/dl. We also follow their Apo B levels with therapy with a goal to maintain Apo B levels less than 80 mg/dl. In such patients, a one-time screening with coronary calcium scoring is offered. The rationale for this protocol is that these patients, by virtue of their small dense LDL particles are at much higher risk for plaque inflammation and rupture. In the absence of coronary artery calcifications, no further workup for CAD is recommended, and patients are encouraged to keep up with lifestyle modifications, while maintaining their cholesterol levels at those dictated by the NCEP guidelines. The detection of coronary calcium alerts the physician that the patient in question has already developed vulnerable plaques with silent plaque ruptures. This finding reinforces life style modifications and compliance with/modification of lipid therapy. Further, we quantify the CAC scores. The presence of calcium scores >100, suggests high risk for cardiovascular events, and suggests the need for further assessment of atherosclerotic coronary disease with either functional stress testing or coronary CT Angiography. In the absence of coronary calcification, the life style behaviors

and lipid pharmacotherapy are still recommended, and the option of repeating calcium scoring every 2-3 years with/ without coronary CTA is offered.

Thus, we clinically use Apo B 100 as a surrogate for soft plaque and coronary calcification as a surrogate for ruptured plaques. In our experience, we do find it cost effective to avoid routine stress testing in the presence of normal Apo B levels and absent coronary calcification in asymptomatic patients even with family history of premature CAD. Although our data are not enough to present our thoughts in the form of a study yet, we have had very good success rate with detection of subclinical disease and prevention of acute coronary syndromes in patients with intermediate Framingham risk scores. Our group is working on designing an observational study to test this clinical algorithm. Figure 8 summarizes our algorithm.

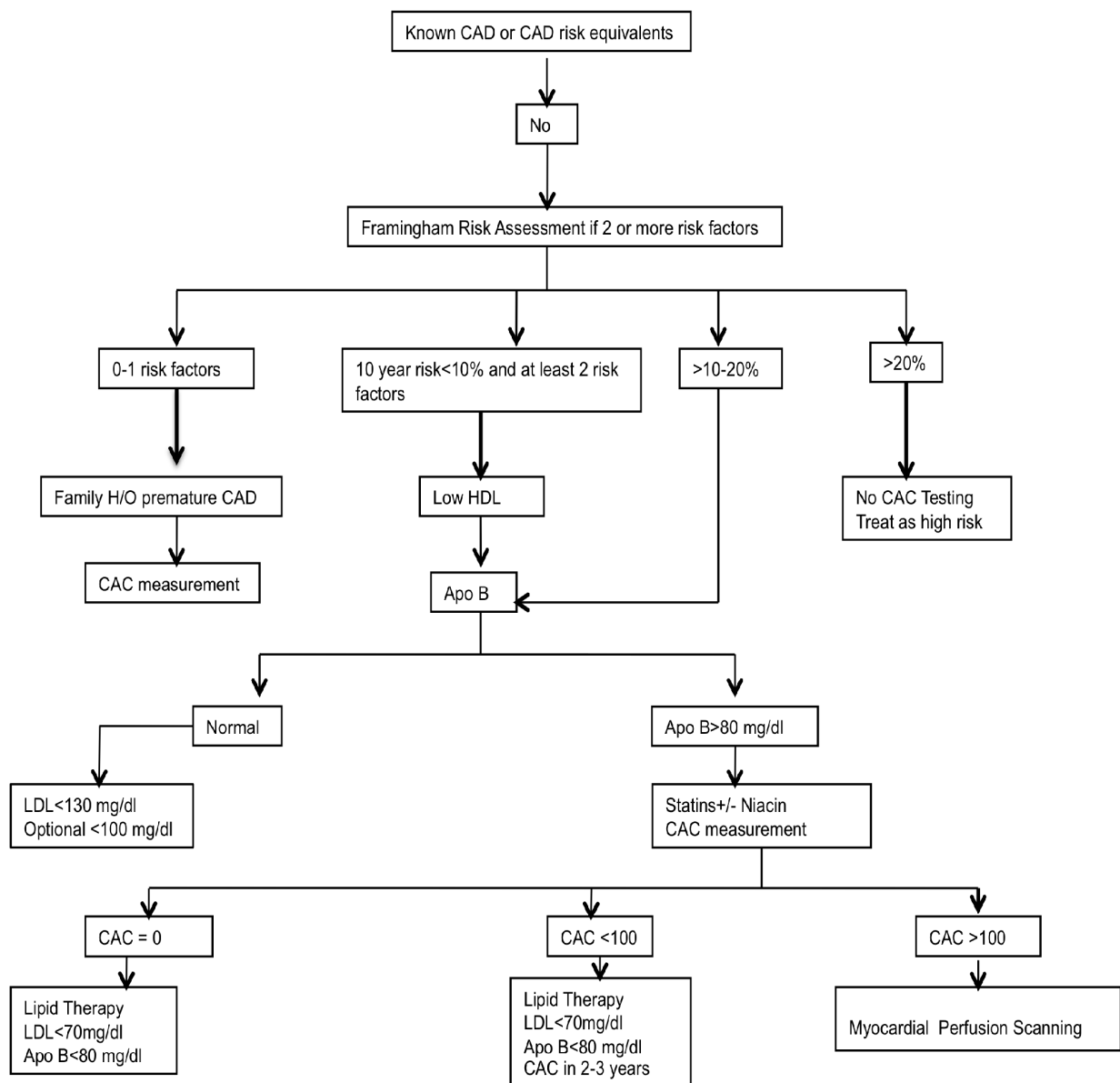


Fig. 8. Cardiovascular Risk stratification Algorithm proposed by Hegde et al

3.3.2 Platelet volume as a marker of cardiovascular risk

Although the author has focused mainly on the role of CCS and lipoproteins in this chapter, there are emerging data on the role of other novel markers such as platelet morphology and volumes as markers of cardiovascular disease. Mean platelet volume (MPV) has been studied as a marker of both vascular inflammation and thromboses (Gasparyan et al 2011). Diabetic patients have hyperactive platelets that are hyposensitive to anti aggregatory effects of prostacyclins and nitric oxide (Watala C. 2005). They also have higher MPV values as compared to normal controls. In fact, Zuberi et al have described that MPV reaches its highest level with increasing insulin resistance, and transition from prediabetes to diabetes, indicating a major increase in the level of risk. Vander Loo and colleagues have indicated that high MPV may herald the occurrence of an acute coronary syndrome in the near future. Inflammatory cytokines such as IL-6 and CRP alter the morphology of platelets released from the bone marrow weeks before an acute coronary syndrome. This finding could potentially be utilized to risk stratify asymptomatic individuals in to low, intermediate versus high risk groups for cardiovascular events. This idea has also been explored in the setting of an actual acute coronary syndrome. Pizzulli et al observed that in subgroups of patients with acute coronary syndromes, patients requiring percutaneous interventions had higher MPV as compared to those with normal MPVs. Although the concept is interesting, the data are not coherent cross studies. Case control studies by other authors such as Glud et al (1986) and Erne et al (1988) have failed to demonstrate such correlation between acute coronary syndromes and MPV. The role of MPV needs to be confirmed in larger clinical trials before we recommend its use as a cardiovascular risk stratifier.

4. Summary and key points

1. Subclinical atherosclerosis is the new target of early detection and treatment strategies to prevent acute coronary syndromes and decrease cardiac mortality.
2. Plaque inflammation and ruptures are the culprits in acute coronary syndromes. Future cardiac event risk stratifiers should include biomarkers that reflect inflammation within vascular tree.
3. Coronary Calcium Scoring (CCS) is a strong indicator of overall atherosclerotic burden in an individual. The total CCS, by virtue of its association with soft plaques, is an indicator of patient's overall risk for future cardiac events. It has established validity across several ethnicities and age groups.
4. CCS appears to be a strong and viable risk stratifier for patients within the intermediate risk category of CAD (10 year FRS 10-20%). CCS may help to redefine goals for life style modifications, lipid therapy and overall management for this patient population.
5. CCS is a valid prognosticator of coronary events across multiple ethnicities including Caucasian, African American, Hispanic and Asian origin.
6. CCS has limited utility and is best avoided in patients with Framingham risk scores of <10%, unless they have strong family history of premature CAD. CCS should also be avoided in patients with FRS of > 20%, since the results are unlikely to change therapeutic decisions anyways.
7. CCS may be useful in symptomatic patients in the setting of equivocal stress testing results.
8. There are insufficient data to support the routine use of CCS as a filter in the triage of symptomatic patients presenting to acute care facilities with chest pain.

9. Apolipoprotein and high sensitivity CRP may be combined with CCS to improve risk stratification in patients with intermediate Framingham scores, although the data are limited in this regard.

5. Future research

Future studies should focus on incorporating simple, yet effective novel imaging and/or biochemical markers in to cardiovascular risk stratification algorithms, with a goal to improve detection of subclinical atherosclerosis. Markers with substantial clinical evidence (Lp-PLA2 and Apo B) should be incorporated in to risk stratification algorithms, along with platelet volume indices. Clinical trials should be designed to assess the performance of such newer algorithms. Genetic and enzymatic markers including matrix metalloproteinases, interferon gamma are on the horizon, and may indeed provide incremental information that could improve cardiovascular care in the future. However, these markers lack sufficient clinical human data. Further evaluation of their efficacy and cost effectiveness is warranted.

6. Acknowledgements

My parents, wife Shwetha Kamath, son to be born Vihaan Hegde, and family for their support

My coauthor Ishmael David Christian Ching, MD for his hard work and assistance with the manuscript

My librarians Judy Knight MLS, Suzanne Cable, Melissa Trace for their help with referencing

Akron General Medical Center for its ongoing support

In Tech publications for this wonderful opportunity

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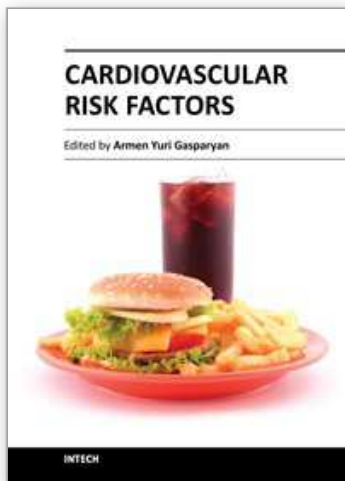
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Cardiovascular Risk Factors

Edited by Prof. Armen Gasparyan

ISBN 978-953-51-0240-3

Hard cover, 498 pages

Publisher InTech

Published online 14, March, 2012

Published in print edition March, 2012

Cardiovascular risk factors contribute to the development of cardiovascular disease from early life. It is thus crucial to implement preventive strategies addressing the burden of cardiovascular disease as early as possible. A multidisciplinary approach to the risk estimation and prevention of vascular events should be adopted at each level of health care, starting from the setting of perinatology. Recent decades have been marked with major advances in this field, with the emergence of a variety of new inflammatory and immune-mediated markers of heightened cardiovascular risk in particular. The current book reflects some of the emerging concepts in cardiovascular pathophysiology and the shifting paradigm of cardiovascular risk estimation. It comprehensively covers primary and secondary preventive measures targeted at different age and gender groups. Attention is paid to inflammatory and metabolic markers of vascular damage and to the assessment of vascular function by noninvasive standardized ultrasound techniques. This is a must-read book for all health professionals and researchers tackling the issue of cardiovascular burden at individual and community level. It can also serve as a didactic source for postgraduate medical students.

How to reference

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Vinayak Hegde and Ishmael Ching (2012). Vascular Inflammation: A New Horizon in Cardiovascular Risk Assessment, Cardiovascular Risk Factors, Prof. Armen Gasparyan (Ed.), ISBN: 978-953-51-0240-3, InTech, Available from: <http://www.intechopen.com/books/cardiovascular-risk-factors/vascular-inflammation-a-new-horizon-in-cardiovascular-risk-assessment>

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