Bestemmelse av kalsium-score med CT – keiserens nye klær?

Thor Edvardsen

I dette nummeret av Hjerteforum har vi vært så heldige å få tre amerikanske kollegaer til å skrive en oversiktsartikkel om beregning av koronar kalsium-score ved CT. Forfatterne av artikkelen arbeider ved fremtredende amerikanske universitetssykehus og har til sammen mer enn 100 forskningsartikler om temaet. De har jobbet innen feltet i årevis og har samlet enorm kunnskap om hvordan og på hvilke pasienter måling av koronar kalsium-score bør utføres og hvordan resultatene av undersøkelsen bør tolkes. Artikkelen gir også klare råd om hvilke konsekvenser undersøkelsen bør ha for den enkelte pasient.

Artikkelforfatterne bor og arbeider i USA hvor praksis med måling av kalsium-score er mye mer utbredt enn i Norge. Her hjemme har vi så vidt tatt metoden i bruk. Artikkelen gir etter min mening nettopp derfor viktig informasjon til norske kardiologer om hvordan vi kan ta metoden i bruk. Det er viktig med en debatt om metoden og edruelighet i tolkningen av resultatene. Artikkelen til Nasir et al vil etter min mening hjelpe oss til dette.

Det skal ikke stikkes under en stol at bestemmelse av koronar kalsium-score er en omdiskutert undersøkelse. Ikke minst har det blitt slik fordi tallene man får ut av undersøkelsen overtolkes og (mis)brukes som et påskudd til å rettferdiggjøre invasiv utredning med koronar angiografi. Det er da meget interessant lesing i artikkelen til Nasir et al hvilke tiltak de anbefaler ved funn av høy kalsium-score. Et annet viktig poeng som fremholdes i artikkelen, er at sekundærprofylaktiske tiltak etter et hjerteinfarkt er meget gode. Imidlertid har vi sviktet noe i primærprofylaksen, og her kan CT-bestemmelse av koronar kalsium-score være en viktig faktor hos noen utvalgte grupper i populasjonen i tillegg til de mer vanlige risikoscoreberegningene som Framingham Risk Score.

Det er sjelden at en kardiologisk undersøkelsesmetode er så gjennomevaluert i meget store studier som CT-bestemmelse av koronar kalsium-score. Artikkelen gir etter min vurdering en god innføring og oversikt om temaet. God lesing!

Coronary Artery Calcification: Methods and Clinical Value

Khurram Nasir[1], Matthew J Budoff[2], Roger S Blumenthal[3], [1]Cardiac MR PET CT Program, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, [2]Harbor-UCLA Los Angeles Biomedical Research Institute, Torrance, CA, USA, [3]Ciccarone Center for Preventive Cardiology, Johns Hopkins University, Baltimore, MD, USA.

Cardiovascular disease (CVD) is the leading cause of mortality worldwide with coronary heart disease (CHD) accounting for nearly half of all CVD deaths (1-3). Although highly prevalent in the developed world such as USA and Europe, it is important to note that it is estimated that in the next 15 years an estimated 25 million people will die of stroke or heart disease, and only 20% of the burden will be in the developed world whereas the rest would be shared by low and middle-income countries (2). Emerging data suggests that although the mortality rate after the occurrence of clinical heart disease (e.g. myocardial infarc-

tion) has significantly reduced over the last two decades; the incidence of new onset of CHD has remained stable during this period (4-6). This finding points to the fact that although we have made great strides in secondary prevention, we have failed poorly in our primary efforts of decreasing the rate of new onset CHD.

All major Advisory bodies including the American Heart Association and European Society of Cardiology advocate traditional risk factor approach in identifying asymptomatic individuals at high risk of developing CHD as well in determining the aggressiveness of treatment in these individuals at high risk (7,8). These approaches incorporate traditional risk factors such as the patient's age, sex and the presence and extent of established, modifiable coronary risk factors - hypertension, hyperlipidemia, diabetes mellitus, cigarette smoking - in the prediction and reduction of coronary risk. Based on these estimates, a 10-year risk of a myocardial infarction/CHD death can be predicted for a given patient based on these major risk factors. Asymptomatic patients are generally categorized as low (<10%), intermediate (10-20%), or high risk (>20%), based upon their respective scores. According to these guidelines, low-risk patients can be reassured and educated about therapeutic lifestyle changes. Intermediate-risk patients may require further risk stratification, and high-risk patients should be considered candidates for aggressive pharmacological and lifestyle intervention (8).

While the use of office-based risk equations are generally recommended approach in cardiovascular risk screening, they are not without shortcomings as a screening tool. These risk estimates are significantly age dependent and as a result there is a great tendency to underestimate risk in younger individuals, who may be more appropriate candidates for early initiation of aggressive preventing strategies in reducing risk of developing clinical CHD (9). In addition, women are historically known to be underestimated by these approaches and nearly 90% of them below age of 70 years are considered as 'low risk'(10). This point can be illustrated a study by Akosah et al in which the authors assessed a very simple question; how does National Cholesterol Education Panel (NCEP) guidelines classify young men and women presenting with an acute MI as their first mani-

festation of CHD (11)? The study findings demonstrated that among adults aged <65 years with an acute MI, only 25% of patients would have met NCEP criteria, which are based on the Framingham risk score (FRS), for pharmacotherapy at the time of admission. The tendency of NCEP guidelines to under-appreciate the risk of CHD was even more pronounced in women with only 18% of women qualifying for pharmacotherapy for primary prevention; 58% of these patients had LDL-C<3.38 mmol/L and 40% had LDL-C <2.6 mmol/L (11).

Considering the fact that atherosclerosis is the major underlying culprit for the development of clinical CHD, detection of individuals with subclinical atherosclerosis may aid in supplementing the current global risk assessment method by more clearly identifying high risk individuals who harbor preclinical atherosclerosis. There is a large body of evidence that coronary artery calcification (CAC) determined by electron beam tomography (EBT) and multidetector CT is a reasonable surrogate for coronary atherosclerotic burden in adults; a direct relationship has been established between CAC as measured on EBT scanning and histologically measured plaque burden (12). Additionally, there is increasing evidence that measurement of CAC has a significant predictive value for subsequent cardiac events in both symptomatic and asymptomatic individuals. The following discussion examines the methods, value and future of CAC in overall CHD risk stratification strategies.

Coronary Artery Calcium and Atherosclerotic Process

Calcification of the atherosclerotic plaque occurs via an active process of mineralization with deposition of hydroxyapatite crystals and not simple mineral precipitation. It begins in the very early stages of the atherosclerosis. Studies have demonstrated that CAC identified by means of EBT derived is a highly reliable method for identification of arterial calcification, and its sensitivity for the detection of atherosclerosis is close to 95%. Rumberger and colleagues have demonstrated a strong relationship (r=0.90) between CAC measured by EBT with direct histologic plaque areas in autopsy hearts (12). It is also important to note that although the total atherosclerotic plaque burden was

tracked by the total calcium burden, not all plaques were found to be calcified. Also, there is a poor correlation between degree of plaque calcification and extent of luminal stenosis on coronary angiography (13,14). This may be due, at least in part, to individual variations in coronary artery remodeling, whereby the luminal cross-sectional area and/or external vessel dimensions enlarge in compensation for increasing area of mural plaque. Despite the lack of a site-by-site correlation between calcification and luminal stenosis, coronary calcium scores calculated by EBT give a close approximation of the total atherosclerotic burden (14). Since research has shown that the burden of disease contributes more than focal luminal stenosis to the risk of cardiovascular events, EBT is a potentially powerful tool for the identification of patients at risk.

Methods of Assessing Coronary Artery Calcium

Modalities for Coronary Artery Calcium Determination

In the near past, CAC has generally been assessed by EBT. However, with a rapid explosion of use of MDCT in recent years, it has been a frequent modality to assess underlying coronary calcification (15). Both modalities do not require use of intravenous contrast to determine CAC. In general, EBT uses a unique technology enabling ultrafast scan acquisition times in the high-resolution, single-slice mode with continuous, nonoverlapping slices of 3 mm thickness and an acquisition time of 100 ms/tomogram in a prospective manner. Electrocardiographic triggering is done during end-systole or early diastole at a time determined from the continuous ECG tracing done during scanning. Historically, the most common trigger time used is 80% of the R-R interval. However, this trigger occurs on or near the P wave during atrial systole, and the least cardiac motion among all heart rates occurs at 40% to 60% of the R-R interval (15,16). The current generation of MDCT systems is capable of acquiring from 4 up to 320 sections of the heart simultaneously with ECG gating in either a prospective or retrospective mode. These MDCT systems have two principal modes of scanning, which depend on whether the patient on the CT couch is advan-

ced in a step-wise fashion (axial, sequential, or conventional mode) or continuously moved at a fixed speed relative to the gantry rotation (helical or spiral mode). Coronary calcification is determined in axial mode using prospective ECG triggering at predetermined offset from the ECG-detected R wave. With prospective gating, the temporal resolution of MDCT system is proportional to the gantry speed, which determines the time to complete one 360° rotation. To reconstruct each slice, data from a minimum of 180° plus the angle of the fan beam are required (approximately 220° of the total 360° rotation.) The most commonly used 64-slice scanners have rotation gantry speeds up to 330 ms (15).

In brief, this test also exposes the patient to a limited amount of ionizing radiation (0.7 to 3 mSv) that is equivalent to 25% to 100% of the natural background radiation exposure that an individual in the United States receives per year (2.5 to 3 mSv) (15,17). This is less than the dose received during a diagnostic cardiac catheterization (approximately 4.5 mSv) and only a fraction of the occupational exposure limit for a radiation worker in the US (50 mSv per year).

Measurement of Coronary Artery Calcium Burden

On non-contrast cardiac CT, CAC is in general defined as a hyperattenuated lesion above a threshold of 130 "Hounsfield Units" (HU) with an area 3 adjacent pixels (at least 1 mm^2) (18). There are 2 most commonly used methods to calculate the underlying CAC burden. There are currently two CT calcium scoring systems widely used: the original Agatston method and the "volume" score method (15). The Agatston score method which involves multiplication of the calcium area by a number related to CT density and, in the presence of partial volume artifacts, can be variable. With this method, area for all pixels above a threshold of 130 HU are calculated at every 3 mm slice and multiplied by a density factor. Partial volume effects lead to higher peak values for small lesions (but not for large ones) (19). On the other hand, the volume method developed by Callister et al appears to somewhat resolve the issue of slice thickness and spacing by computing a volume above threshold (20). As a result, it appears to be less dependent on minor changes in slice thickness. However, our group has previously demonstra-

ted in nearly 10,000 patients that there appeared to be excellent correlation between both scoring methods, and they show similar characterization when applied properly (21).

Clinical Value of Coronary Artery Calcification in Asymtomatic Individuals

Efforts have been made to develop non-invasive diagnostic tools to help determine the extent of atherosclerosis in asymtomatic patients and improved detection of those who would benefit from more intensive preventive therapies such as lipid lowering medication and aspirin. This potential of coronary CT in the risk assessment protocol and management strategy is in accordance to the current philosophy of the NCEP and other organizations that stress the importance of matching therapy to level of assessed risks. However, in order to establish the role of CAC testing in primary preventive strategies, important questions need to be answered. Is the information gained from coronary CT additive to assessments made by cheaper office-based estimations of risk, and if so, which patient populations are expected to benefit from testing?

Does Coronary artery calcium independently predict CHD events?

Table 1 summarizes the findings of all major studies assessing the prognostic value of CAC burden among asymptomatic individuals (22-34). In general, there appears to be a consensus among all studies that CAC is an independent predictor of CHD adverse outcome as well all cause mortality after taking into account traditional risk factors. For example, Shaw et al. reported on all-cause mortality in a large cohort, consisting of 10,377 asymptomatic individuals, followed for an average of 5±3.5 years (27). At the end of follow-up period, a total of 249 deaths were recorded. A CAC≥1000 was associated with at least 10-fold higher risk of all cause mortality. Coronary artery calcium score was an independent predictor of death (p<0.001) with risk increasing proportionally to the baseline CAC scores. The results of the St Francis Heart Study, which is a prospective registry of 5,585 asymptomatic individuals, mirrored previous retrospective studies and confirmed the higher

Table 1. Summary of Outcomes Studies with Coronary

Author/ Year	Type of study/Population	Follow up (yrs)
Becker A et al (2008)	Prospective population-based study	3.3
Detrano et al (2007)	Prospective population-based study	3.4
Budoff et al (2007)	Observation data series, referral-based n=25,253, mean age 65±11	6.8
Anand et al(2006)	Prospective study 510 asymptomatic type 2 diabetic subjects Age was 53±8 years	2.2
Lamonte et al (2005)	Cohort study 6,835 men, 3,911 women Age 22-96	3.5
Taylor et al (2005)	Prospective cohort study, 1,627 men, 356 women Age 40 to 50 (Army based)	3
Vliegenthart et al (2005)	Prospective population-based study n=1,795 Age 62 to 85	3.3
Arad et al (2005)	Prospective population-based study n=4,613, age 50 to 70	4.3
Greenland et al (2004)	Prospective population-based study n=1,312, age > 45	7
Shaw et al (2003)	Observation data series, referral-based n=10,377, age 30-85	5
Kondos et al (2003)	Observational study, referral-based n=5,635, age 30-76 26% women	3.1
Raggi et al (2001)	Observational referral-based study n=676, mean age 52	2.7
Wong et al (2000)	Observational study, referral-based n=926, mean age 54	3.3
Arad et al (2000)	Observational study, referral-based n=1,172, age 53 +/- 11	3.6

Artery Calcification in Asymptomatic Individuals

Number of events	Results
179 (65 cardiac death, 114 myocardial infarctions)	CACS ≥ 75th percentile was associated with a significantly higher annualized event rate for MI (3.6% vs 1.6%, P < .05). No cardiac events were observed in patients with CAC=0.
162 CHD events (72 myocardial infarctions, 17 CHD deaths, 73 revascularization)	Overall the FRS-adjusted risk was 28% higher with doubling of CAC scores. CAC was equally predictive in all ethnic groups.
510 all cause deaths	As compared to those without CAC, the risk-adjusted relative risk ratios for CAC were 2.2-, 4.5-, 6.4-, 9.2-, 10.4-, and 12.5-fold for scores of 11 to 100, 101 to 299, 300 to 399, 400 to 699, 700 to 999, and >1,000, respectively (p < 0.0001)
22 (2 coronary deaths, 9 non-fatal myocardial infarctions, 3 ACS, 3 CVA, and 3 late revascularizations)	The overall rate of death or MI by CAC categories (<100, 101-400, 401-1000 & >1000) was 0 (n=0), 2.6 (n=2), 13.3 (n=4), and 17.9% (n=5), respectively (P<0.0001).
81 MI/CAD death, 206 revascularization	Age-adjusted rates per 1,000 person years were computed according to 4 CAC categories: 0 CAC and incremental sex- specific thirds of detectable CAC. The rates were 0.4, 1.5, 4.8, and 8.7 in men and 0.7, 2.3, 3.1, and 6.3 in women.
9 ACS events	2% of men with CAC had events versus 0.2% without CAC (P < 0.0001). Controlling for FRS, presence of CAC was associated with an independent 12-fold increase in relative risk. No events in women.
40 nonfatal MI, 11 revascularization, 38 CVA	As compared to those with CAC<100, the RR for events were 3.1, 4.6, and 8.3 for CAC 0-100, 100-400, and 400-1000, respectively. There was a statistically significant high relative risk, > 8, for those with CACS > 1000 regardless of Framingham 10 year risk score ≤ 20% vs. > 20%.
40 nonfatal MI, 59 revascularization, 7 CVA	RR for CAD events with CAC>100 was 11. Overall was superior to FRS in prediction of events (ROC curve of 0.79 vs. 0.69, p=0.006).
68 nonfatal MI, 16 deaths	HR of 3.9 for CACS of >301. CACS able to modify predicted risk obtained from FRS alone (0.73 for FRS alone and 0.78 for FRS and CAC combined).
249 all-cause mortality	CACS an independent predictor of mortality with RR 4.0 for score of 401-1000.
37 non-fatal MI, 166 revascularizations, 21 deaths	RR of 124 in men with soft events in the highest quartile (CAC 170-7,000). Higher CACS added incremental prognostic information to conventional CAD risk assessment in men for hard CHD events.
21 nonfatal MI, 9 deaths	CACS was predictive of hard CAD events, with an OR of 22 for the CACS > 90% percentile.
6 nonfatal MI, 20 revascularization, 2 CVA	Overall patients with CAC≥271 had a risk ratio of 9 for a CHD event.
15 nonfatal MI, 21 revascularization, 3 deaths	OR of 20 for CACS ≥ 160 compared to those with CACS below 160.

event rates associated with increasing CAC scores (29). CAC scores >100 were associated with relative risks of 12 to 32 compared to CAC = 0; achieving secondary prevention equivalent event rates >2 %/year. Similarly Taylor et al. showed CAC was associated with nearly 12-fold increased risk for incident coronary heart disease controlling for the Framingham risk score in men aged 40-50 years of age (31). These findings were nicely summarized by the recent AHA/ACC Expert Consensus Document on Coronary Artery Calcium Scoring which took into account some of these studies, and reported that the relative risk ratio for CAC 100-400, 401-1000, and >1000 was 4.3 (95% CI = 3.5-5.2, p<0.0001), 7.2 (95% CI = 5.2-9.9, p<0.0001), and 10.8 (95% CI = 4.2-27.7, p<0.0001) respectively compared to CAC = 0 (35). Importantly, patients with CAC score of zero have a very low rate of CHD death or MI (0.4%) over 3 to 5 years of observation (35).

However, at the same time it is important to keep in mind that critics tend to point towards minor concerns such as potential study generalizability of self-referral cohorts, validity of the risk factor measures and resultant multivariable models used in the studies, and risk of test-induced bias. However, these concerns have been addressed by a recent report from the Multi-Ethnic Study of Atherosclerosis (MESA), a population based cohort, which reported the utility of CAC scores in predicting future events. According to Detrano et al (36), among nearly 6,800 asymptomatic individuals followed for median of 41 months the hazard ratios for future hard CHD event (myocardial infarction or MI- related death) with CAC 1-100 vs. CAC=0 was 5.3 (95% CI= 2.4-11.7, p<0.0001). The respective hazard ratios with CAC 101-300 and >300 were 10.8 (4.8-24.2, p<0.0001) and 12.0 (5.4-26.5, p<0.0001). These risk ratios are very much similar to previous published studies and confirm the pooled summary findings previously reported and lay to rest of any concern regarding the prognostic value of CAC testing (35).

What is the value of testing for coronary artery calcium across ethnic and racial groups?

Most of the published data to date has related to white Caucasian population; however, two recent studies have addressed the value of CAC in other ethnic groups. Firstly, Nasir et al in nearly 15,000 ethnically diverse self-referred patients assessed the role of CAC for the prediction of all-cause mortality (37). When comparing prognosis by CAC scores in ethnic minorities as compared with non-Hispanic whites (NHW), relative risk ratios were highest for African Americans (AA) with scores ≥400 exceeding 16.1 (p<0.0001) compared to CAC = 0. Hispanics with CAC scores ≥400 had relative risk ratios from 7.9-9.0; while Asians with CAC scores ≥1,000 had relative risk ratios 6.6-fold higher than NHW (p<0.0001). Secondly, the utility of CAC testing has also been reported in the prospective MESA study. According to Detrano et al, the risk associated with a doubling of the CAC score [a 1-unit increase in $\log_2 (CAC+1)$] hard CHD event was 1.3 (1.2-1.4) in Caucasians, 1.5 (1.3-1.7) in African Americans, 1.3 (1.1-1.5) in Hispanics, and 1.4 (1.1-1.8) in Chinese, respectively. These findings firmly establish that CAC scores provide significant information in all four major ethnic groups in the USA.

Does Coronary artery calcium add incremental value to global risk estimates?

The extent of CAC has been shown in several studies to predict cardiac events in symptomatic and asymptomatic individuals. However, decisions about the predictive utility of new tests should be based on their respective additional utility for risk prediction on the test's performance (35). The most important question regarding use for primary CHD risk stratification is whether it is predictive above and beyond the current standard risk assessment method of choice, the FRS, which is an inexpensive, easily available, and office-based tool. One way to determine additive utility of a new test is through the use of receiver operating characteristic (ROC) curves analyses. The ROC curve is a plot of true-positive rate vs 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 the useless test.

In recent years, this important question has been addressed by numerous studies. Raggi et al were among the first to assess the added contribution of CAC over and above the FRS.

In a study of more than ten thousand asymptomatic individuals followed nearly 5 years, the ROC concordance (C-index) index for FRS in estimating risk of all-cause death was 0.67 (95% CI=0.62-0.72, p<0.0001) for women and 0.68 (95% CI=0.64-0.73, p<0.0001) for men. When CAC was added to this analysis, the C-index increased to 0.75 (95% CI=0.70-0.80) for women (p<0.0001) and 0.72 (95% CI=0.68-0.77) for men (p<0.0001), indicating a significant improvement in mortality prediction (38). In a similar fashion, Greenland et al. found that the ROC curves for prediction of CHD death or nonfatal MI was 0.68 for FRS plus CAC, which was significantly greater than that of the FRS alone (0.63; p<0.001) (28). The recent population-based St Francis Heart Study of 5,585 asymptomatic individuals confirmed the findings of previous reports. The coronary calcium score predicted CHD events independently of standard risk factors and C-reactive protein (p=0.004), was superior to the FRS in the prediction of events (area under ROC curve of 0.79±0.03 vs 0.69±0.03, p=0.0006), and enhanced stratification of those falling into the Framingham categories of low, intermediate, and high risk (p<0.0001) (29). Finally, Becker et al in a recent study demonstrated that among 1,726 asymptomatic individuals followed for a median of 40 months, the area under the ROC curve for CAC scores (0.81, 95% CI 0.78-0.84) was significantly larger than that of the FRS risk (0.63, 95% CI: 0.59-0.65), PROCAM (0.65, 95% CI: 0.6-0.68), and European Society of Cardiology scores(0.66, 95% CI: 0.62-0.6), respectively, (P = 0.03) (23). Importantly, these findings not only support the contention that established cardiac risk factors possess a limited ability to quantitate CHD risk, but also provide evidence that CAC may provide unique information for risk assessment.

Who are candidates for CAC Testing?

In 2007, the Expert Consensus Document (CECD) by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) provided recommendations to provide a perspective on the current state of the role of CAC testing in clinical practice. The consensus was that, "it may be reasonable to consider use of CAC measurement in among asymptomatic individuals who are at intermediate risk based on FRS" (35). This conclusion was based on the possibility that such individuals might be reclassified to a higher risk status based on high CAC score, and subsequent patient management may be modified. However, at the same time, the committee did not find enough evidence regarding the utility of CAC testing in further risk stratifying in those considered low as well high risk of CHD in next 10 years.

As far as those with 10 year risk >20%, they already meet eligibility criteria for aggressive lipid lowering management with lipid goals of <1.82 mmol/L, as a result further CAC testing, although may provide prognostic information, however may not lead to changes in treatment goals. On the other hand, not considering those with 10 year estimated risk of <10% (low-risk) for CAC testing is problematic for the following reasons. If these guidelines are followed, then majority of non-diabetic women who are less than 70 years of age don't reach 10 year risk of 10% and thus would not be candidates for further risk stratification with CAC testing (10). As a result, a large number of women may be at higher risk of CHD risk, but may never become candidates for CAC testing. At the same time, the practicality of conducting additional screening for all such women becomes an important question. One approach would be to identify a subgroup of women in low risk group who are more likely to harbor significant CAC and testing them may potentially be a cost effective approach. Recent emerging evidence has strongly implicated presence of family history of premature CHD as an independent risk factor associated strongly with higher burden of subclinical atherosclerosis (39-41). Nasir et al demonstrated that among those with premature family history of CHD (especially with sibling history) nearly one third to one quarter of self-referred patients in presence of 0-1 CHD risk factors had CAC ≥ 100 (41). In addition, among women with presence of family history of premature CHD along with presence of multiple CHD risk factors identify a subgroup of women with FRS<10% who will have significant atherosclerosis (40). Alternatively, based on 2003 American College of Cardiology Bethesda Conference on Atherosclerosis Imaging, intermediate-risk group should be reclassified as those at 6-20%
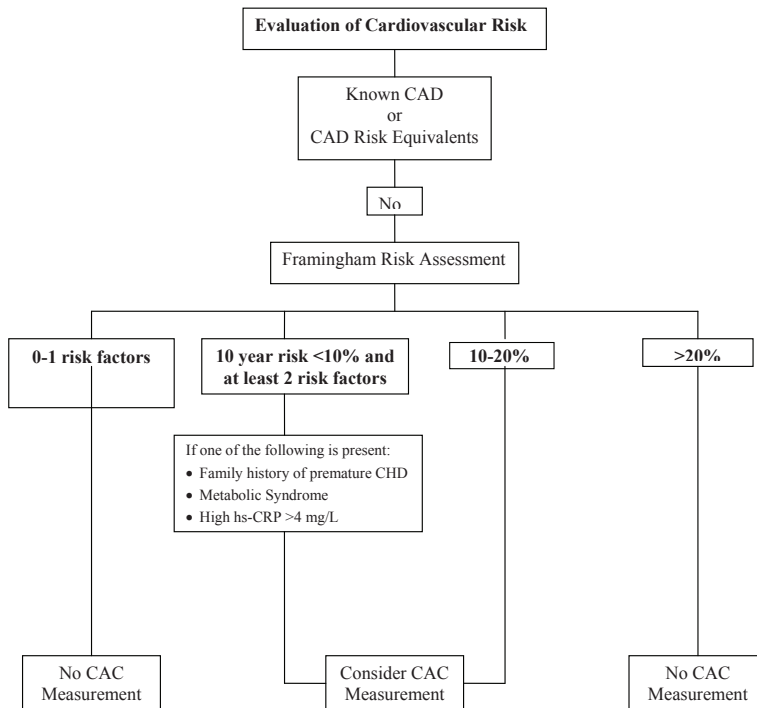
Evaluation of Cardiovascular Risk

Known CAD
or
CAD Risk Equivalents

No

Framingham Risk Assessment

0-1 risk factors

10 year risk <10% and at least 2 risk factors

10-20%

>20%

If one of the following is present:
- Family history of premature CHD
- Metabolic Syndrome
- High hs-CRP >4 mg/L

No CAC Measurement

Consider CAC Measurement

No CAC Measurement

Figure 1.

risk, at least for women (42). This strategy will identify high-risk women among those with FRS<10%, who may benefit from aggressive preventive strategies such as statin, aspirin, and possibly blood pressure lowering therapies. Figure 1 provides a schematic algorithm in identifying ideal candidates for CAC testing.
How information from CAC testing can be used to modify treatment plans?

Incorporation of CAC into preventive strategies applied in the context of conventional clinical profiles can potentially refine risk definition and/or understanding of the consequences of risk factors into a more complete or comprehensive assessment in any given person. At the moment some experts consider that the CAC scoring can be used to modify the number of points assigned to chronological age when determining global risk assessment such as in the Framingham risk or European risk score estimates for more accurate prediction of 10-year cardiovascular risk (43). The utilization of CAC scoring in combination with conventional risk factor assessment to define a "modified" FRS allows the inclusion of subclinical disease definition into the context of modifiable risk

factors. The employment of CAC scores to identify the "heart age" allows accounting for the variability in atherosclerotic burden at a given age, and can be easily used to modify current treatment plans. An example of the incorporation of the CAC score with estimation of global risk score is shown in Figure 2.
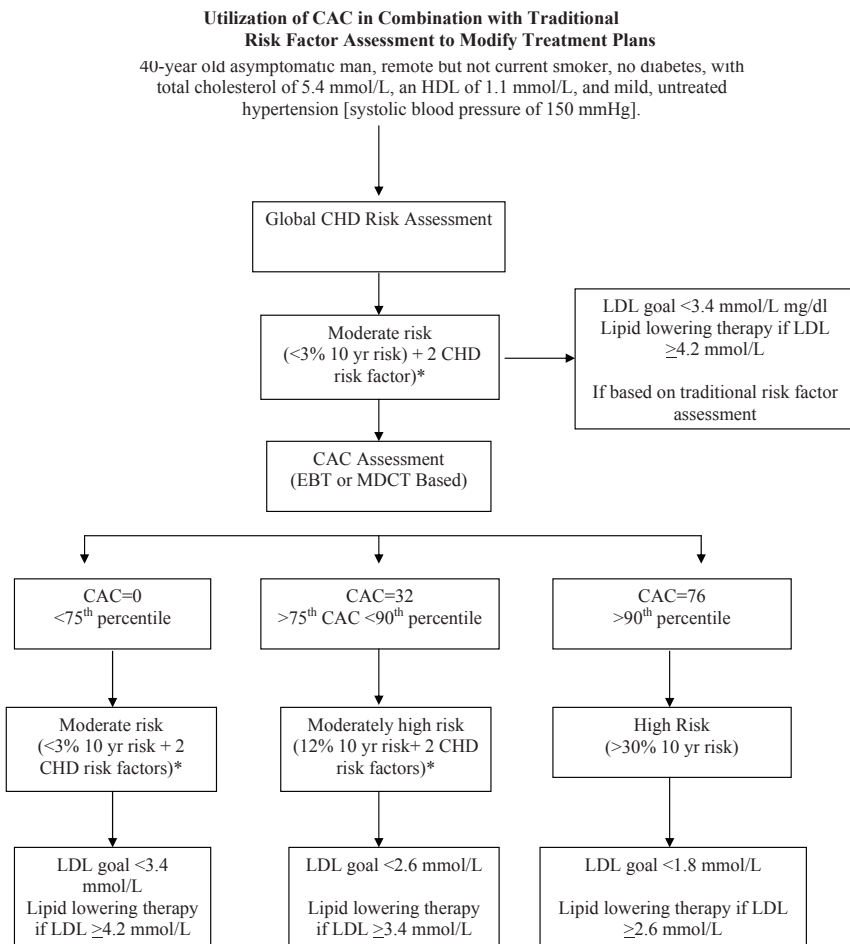
The notion of CAC percentile helps conceptualize the extent of the disease relative to that of others with same age and sex. The employment of CAC scores to identify the "heart age" allows accounting for the variability in atherosclerotic burden at a given age, and can be easily incorporated into the FRS and NCEP guidelines. However, the efficacy of the above approaches can only be assessed in a definitive manner in longitudinal studies such as the Multi-Ethnic Study of Atherosclerosis (MESA) and the Heinz-Nixdorf RECALL (Risk Factors Evaluation of Coronary Calcium and Lifestyle) study including both information on Framingham or equivalent risk factors and CAC; unfortunately, the results of these studies will not be available before the end of the current decade.

Future Directions

One of the most important topics that need further clarification is not whether CAC testing is predictive of adverse outcomes, but whether this approach will be cost effective? To date little evidence exists in this regard. The Society of Heart Attack Prevention and Eradication (SHAPE) attempted to assess this question in a cost-effectiveness analysis which based on comparing competing choices for screening to prevent CHD, with the result being the incremental price of an additional outcome for a given strategy as compared with an alternative approach

**Utilization of CAC in Combination with Traditional
Risk Factor Assessment to Modify Treatment Plans**

40-year old asymptomatic man, remote but not current smoker, no diabetes, with total cholesterol of 5.4 mmol/L, an HDL of 1.1 mmol/L, and mild, untreated hypertension [systolic blood pressure of 150 mmHg].

Global CHD Risk Assessment

Moderate risk
(<3% 10 yr risk) + 2 CHD risk factor)*

LDL goal <3.4 mmol/L mg/dl
Lipid lowering therapy if LDL ≥4.2 mmol/L

If based on traditional risk factor assessment

CAC Assessment
(EBT or MDCT Based)

CAC=0
<75th percentile

CAC=32
>75th CAC <90th percentile

CAC=76
>90th percentile

Moderate risk
(<3% 10 yr risk + 2 CHD risk factors)*

Moderately high risk
(12% 10 yr risk+ 2 CHD risk factors)*

High Risk
(>30% 10 yr risk)

LDL goal <3.4 mmol/L
Lipid lowering therapy if LDL ≥4.2 mmol/L

LDL goal <2.6 mmol/L
Lipid lowering therapy if LDL ≥3.4 mmol/L

LDL goal <1.8 mmol/L
Lipid lowering therapy if LDL ≥2.6 mmol/L

If only one risk factor than LDL goals <4.2 mmol/L in presence of 10-year risk <10%
* Risk factors considered were cigarette smoking, hypertension (BP 140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40 mg/dl), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men 45 years; women 55 years).

Figure 2.

(44). Their initial economic models examined the cost-effectiveness of treating selected at-risk adults with evidence of subclinical atherosclerosis compared with the existing risk factor based guideline. The SHAPE model demonstrated that use of screening for subclinical atherosclerosis with CAC is a cost-effective approach resulting in cost-effectiveness ratios <$50,000 per year of life saved with a potential of reducing US$21.5 billion each year in care for patients with CHD(44).

Secondly, it is vital to establish whether utilization of CAC testing will be associated with improved outcomes. In order to understand the clinical utility of CAC testing as a screening tool, it is imperative to demonstrate that it alters clinical management (such as the use of preventive medications). In a recent study, Kalia et al showed that lipid lowering medication adherence increased from 44% over 3 years to >90% in those with baseline calcium scores in the top 75th percentile for age and sex (p <0.001). This finding was independent of underlying cardiovascular risk factors, age, and sex thus suggesting that actually seeing their coronary artery can improve patients' adherence to treatments such as lipid-lowering therapy (45).

Although these initial results are very promising, there is an urgent need for a resolute effort from concerned stakeholders to initiate a

clinical study that will truly identify the accurate role of CAC testing, which has shown actual promise, in reducing the overall burden of CHD in the society in a cost-effective manner.

Summary

In summary, common global risk assessment seems to underestimate the CAC burden as well as longer term CHD risk especially in the young and in women. CAC is an independent predictor of CAD events and provides prognostic information above and beyond the FRS. Assessment of CAC with non-contrast CT appears to have high predictive value among individuals with "intermediate risk group". In general, it is thought that it would be unlikely to be beneficial as a screening tool for the low-risk patients. However, even among this group those with a family history of premature CHD are a group that may potentially benefit from this testing. On the other end of spectrum, those with high pretest probability are essentially at CAD-equivalent risk regardless of calcium score, and treatment of risk factors rather than screening would be more appropriate. Integrating the information generated from the FRS with CAC, especially by modification of age factor, appears to be an effective system for assessing actual cardiac risk to optimally target and follow the effect of preventive measures.

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