CORONARY ARTERY CALCIUM DETERMINATION USING NON-GATED COMPUTED TOMOGRAPHY:

HISTORICAL BACKGROUND AND CLINICAL APPLICATION

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ABOUT JOHN A. RUMBERGER, PHD, MD, FACC:

Dr. John A. Rumberger has trained in engineering [BAAE, MSc, Ph.D. - The Ohio State University, 1972 and 1976, respectively – Aerospace Engineering, Bio-Medical Engineering, Fluid Dynamics and Applied Mathematics] and in medicine [MD - University of Miami, 1978]. He did his internal medicine training at The Ohio State University [1978-1981] and his Cardiovascular Diseases Fellowship [1981-1984] under Dr. Melvin Marcus at the University of Iowa. He specialized in cardiac imaging [especially Cardiac CT], cardiac/coronary physiology and dynamics, and Preventive Cardiology.

In 1984, Dr. Rumberger began his study of Cardiac CT and continued his clinical and research studies at the University of Iowa, as an Assistant Professor, from 1984 to 1987. In 1987 Dr. Rumberger became a Consultant in the Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota. During his tenure at the University of Iowa and his subsequent years at the Mayo Clinic [1987-1998], Dr. Rumberger established himself as a leader in the development of cardiac imaging using Computed Tomography as it relates to cardiovascular disease and in practical and clinical applications of Computed Tomography in understanding cardiac physiology and coronary atherosclerosis. Dr. Rumberger became Professor of Medicine, Department of Internal Medicine, and Division of Cardiovascular Diseases at the Mayo Clinic in 1996.

He has published over 250 scientific papers, 250 abstracts, 35 book chapters, numerous invited editorials, and two books dealing with the development and application of cardiac CT. He is also author of 'The Way Diet' – a lifestyle plan of diet, exercise, and stress management. Dr. Rumberger was supported by research grants from the National Institutes of Health and, in 1989, became an Established Investigator of the American Heart Association.

Dr. Rumberger also continued his clinical work as a member of the prestigious Coronary Intensive Care Staff at the Mayo Clinic. From 1998 until 2006, Dr. Rumberger was Medical Director of HealthWise/PrevaHealth Wellness Diagnostic Center in Columbus, Ohio. He was appointed Clinical Professor of Medicine at the Ohio State University, Columbus, Ohio in 2001. In 2006 he joined the staff of the Princeton Longevity Center, Princeton, NJ as Director of Cardiac Imaging. Dr. Rumberger is recognized as an authority on the use of Cardiac CT, CT physics, and in developing practice guidelines for its interpretation in patients. Currently Dr. Rumberger remains active in clinical practice, epidemiological research, Preventive Cardiology/Medicine and teaching Cardiologists and Radiologists methods to interpret Cardiac CT in clinical practice. In the past decade, Dr. Rumberger and his colleagues have trained >3000 physicians from all over the world in the use and application of Cardiac CT Angiography.

Dr. Rumberger continues his research and education and clinical practice in Preventive Cardiology. He is a Permanent Member of Who's Who in Health Care and has received numerous sponsored lectureships. He continues his research interests in early diagnosis of coronary disease and continues to lecture and travel extensively, and conduct numerous physician seminars regarding cardiac imaging. Dr. Rumberger, under the auspices of ccta.instructor has continued his training of physicians via an expanding series of instructional videos placed on YouTube.

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BRIEF OVERVIEW:

The discussion provides firstly an understanding of what is coronary artery calcification [CAC] as defined by pathology and clinical investigations using non-contrast CT scanning. The current 'standard' for defining CAC clinically is using gated CT. However, due largely to the interest of performing low dose non-gated lung cancer screening, which includes non-contrast imaging of the heart, more and more data have been published regarding the alternative of non-gated CT for quantification of CAC. Secondly, this review focuses on currently available literature comparing gated versus non-gated CT for assessment of coronary artery atherosclerotic plaque burden. The application of CAC scanning by non-gated CT greatly extends the application of CAC scanning universally and allows small imaging facilities to duplicate imaging techniques largely heretofore afforded to academic institutions.

KEY WORDS:

Cardiac CT
Non-gated cardiac CT
CAC – coronary artery calcium
Agatston Score
Volume Score
Atherosclerosis
Plaque

WHAT IS CORONARY ARTERY CALCIFICATION?

An intimate relationship between the formation of coronary artery calcification in the mural surfaces of the coronary arteries and mural atherosclerotic plaque has been noted for centuries. Perhaps best stated by Virchow in Cellular Pathology, 1863[1] "….the coronary arteries in atherosclerosis represent "an ossification, and not mere calcification; the plates which pervade the inner wall of the vessel are real plates of bone...." Early imaging studies of heart and arterial wall calcification were done using fluoroscopy and reported in the 1960's.[2] Later clinical studies identified fluoroscopic presence and extent [i.e. involving 1 or more coronary arteries] of coronary artery calcification as related to the presence of 1, 2, and 3 vessel obstructive disease determined at cardiac catheterization.[3] However, what does coronary arterial mural 'calcification' actually signify?

As commonly believed the first event in the vascular atherosclerotic process is damage to the single-cell endothelium lining all arterial walls allowing passage from lumen to wall of cholesterol and inflammatory proteins and setting up what I characterize as an indolent 'response to foreign body/injury reaction' resulting in the appearance of various white blood cell types, the later appearance of 'foam' cells and continued mural oxidative stress. Cytokines released by inflammatory cells induce smooth muscle cell apoptosis and/or trans-differentiation to osteochondrogenic phenotypes. These ectopic 'bone' proteins contribute to mineral deposition in the plaque. At first micro-calcifications appear that likely cannot be adequately visualized by conventional x-ray methods. But fusion of the micro-calcifications over time provides macro-calcifications that may well be visualized using various clinical methods. This 'calcification' has little to do with serum calcium levels, although there have been suggestions that the process can be influenced by hormonal and vitamin D interactions regarding bone densities and abnormal calcium metabolism. Both high or toxic vitamin D levels and low or deficient vitamin D levels can be associated with vascular calcification demonstrating a bi-phasic dose response [or J-shaped curve].[4] The proper term for calcium deposition in arterial vessel walls is 'calcium hydroxyapatite' and can be identified in non-decalcified arterial segments using a Mason-Goldner-Trichrome stain. Figure 1 shows examples of direct histologic cross sections of non-calcified coronary arteries and corresponding direct contact microradiography demonstrating the intimate relationship of hydroxyapatite [dark green to black staining] to macrocalcification by x-ray.[5]

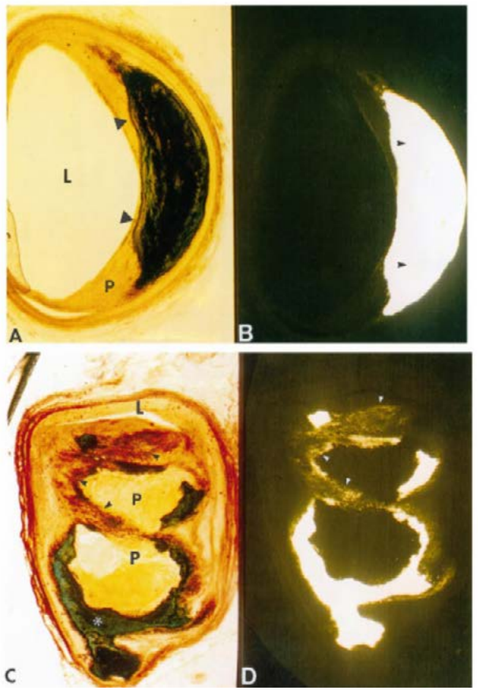

Figure 1:
Photomicrographs of non-decalcified human coronary arteries. A and B, extensive calcium [arrowheads] is deposited relatively uniformly within a noncritical plaque [P], as shown by light microscopy and by microradiography [B]. C and D – in contrast a large plaque with near total lumen [L] occlusion shows a large peripheral focus of dense calcium and a rim of microfocal mineralization [arrowheads] scatter distributed around the vessel circumference by light microscopy.

Fitzpatrick and colleagues[6] demonstrated that calcium deposition in the form of hydroxyapatite was widely present within atherosclerotic plaques and that the messenger ribonucleic acid [mRNA] for proteins associated with normal bone calcification, osteopontin and osteonectin, were similarly present in cells within the plaque. Normal arterial segments without evidence of atherosclerotic disease and calcification had no evidence of osteopontin expression.

Rumberger and colleagues demonstrated a direct relationship between calcified plaque area by CT [heretofore termed 'CAC'] with histologic atherosclerotic plaque area in the same coronary segments, as noted in Figure 2.[7] Schmermund and colleagues[8] extended the assessment of CAC using CT to the 'clinical' standard of defining atherosclerotic plaque in vivo using intravascular ultrasound [IVUS, figure 3]. These studies provided credence for CAC using CT as a valid surrogate to individual atherosclerotic plaque formation and burden. The next steps were to utilize CAC to determine if it provided not only diagnostic information but prognostic information.

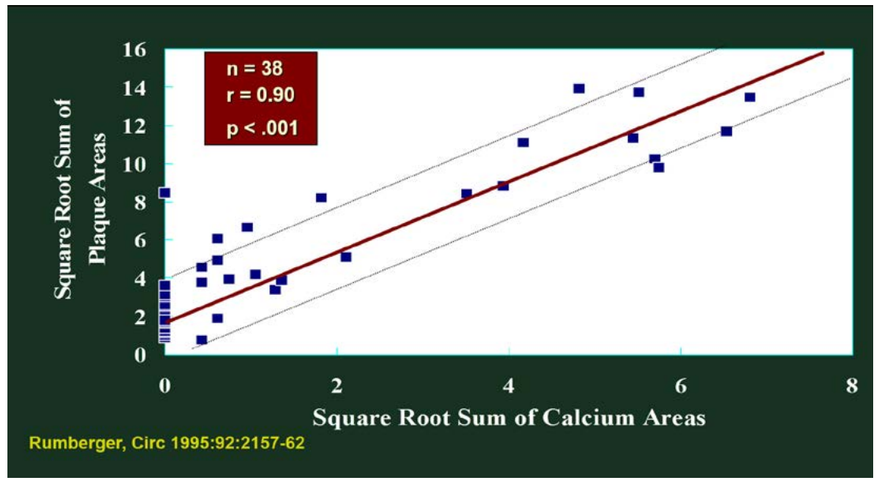

Figure 2:
Atherosclerotic plaque area [from histology] and calcified plaque area [EBCT] in the same pathologic coronary artery segments; adapted from data presented in reference 7.

The pathologic and clinical studies defining CAC as an intimate indicator of mural coronary atherosclerotic plaque by histopathology, IVUS, and cardiac CT were done in the 1980's and 1990's – but long term prognostic information regarding CAC took much longer. Subsequent decades of research have focused on the prognostic value of CAC with data derived from population and clinical cohorts. The population studies, largely based on asymptomatic and otherwise healthy volunteers, are diverse, including the NIH-NHLBI-sponsored Multi-Ethnic

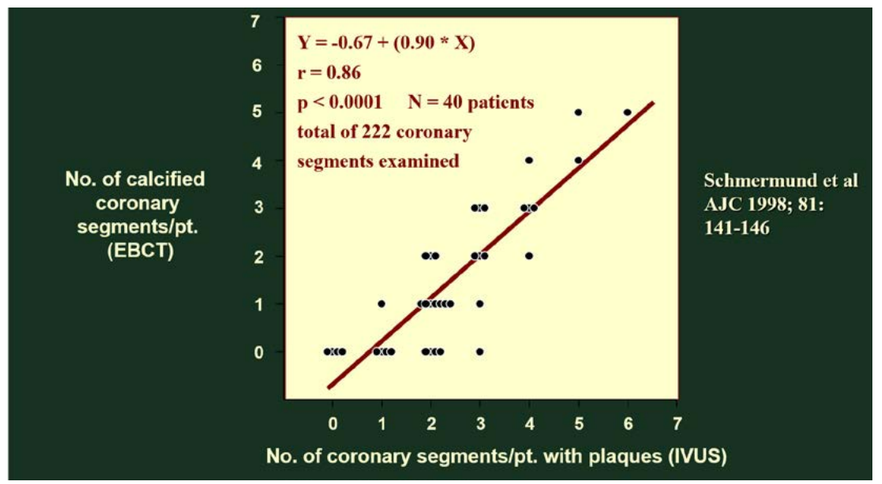

Figure 3:
Number of coronary artery segments per patient with atherosclerotic plaque [derived from invasive intravascular ultrasound] versus number of calcified coronary artery segments per patient [derived from EBCT scans]; modified from data presented in reference 8.

Study of Atherosclerosis (MESA)[9] and Framingham Heart Study[10] and other large cohorts such as the Dallas Heart Study[11] and BioImage[12], as well as international cohorts such as the Heinz Nixdorf Recall study[13]. Figure 4 shows published early data from MESA looking at CAC 'score' [as discussed below]. From these data as well as data published in populations referred to clinical centers[14,15] have confirmed CAC and the CAC 'score' provide incremental prognostic information regarding future coronary related and stroke events totally independent of conventional cardiovascular 'risk factors'.

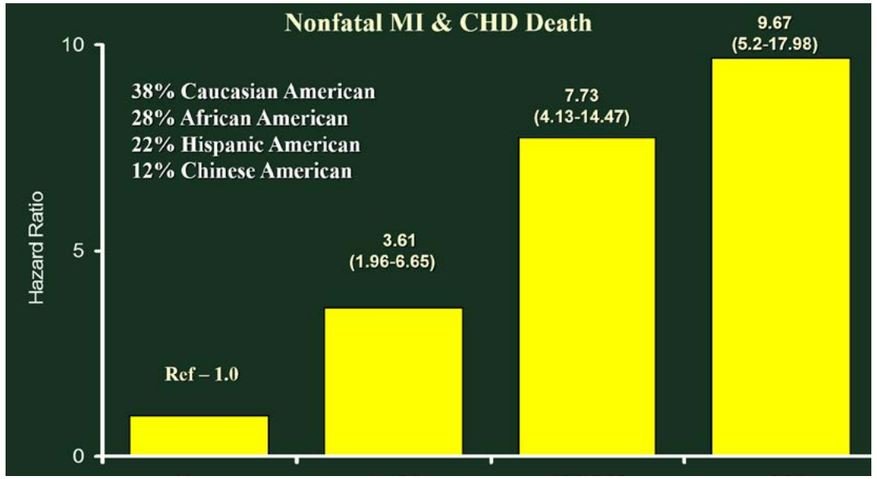

Figure 4:
36 months [median] follow up in MESA study [adapted from data presented in reference 9] – initial Agatston CAC score versus subsequent nonfatal myocardial infarction or coronary heart disease related death

Calcification of the coronary arteries and the aorta is now known as a systemic phenomenon designating an arterial wall [i.e. mural surface] problem and only late in the progression of atherosclerosis contributing to a lumen problem and clinical manifestations. In short, definition of CAC is a surrogate to atherosclerotic plaque burden and can thus define the presence, location, and severity of coronary atherosclerotic plaque years to decades prior to a clinical cardiac event such as myocardial infarction or sudden cardiac death.

HOW IS CORONARY ARTERY CALCIFICATION USING CARDIAC CT DETERMINED?

Coronary artery calcification (CAC), is now largely imaged using electrocardiographic [ECG] gated multidetector, computed tomography (MDCT) or 'ECG-triggered' electron beam CT (EBCT), and its relationship to coronary atherosclerosis diagnosis, plaque extent, and cardiac prognosis is discussed above.

EBCT was developed in the late 1970's as the first commercially developed CT scanner designed to image the beating heart. Throughout the 1980's and 1990's EBCT remained the only valid CT method to provide 'stop action' images of the beating heart and that is why there is so much published literature available using this technique.

The first reported attempt to define CAC using conventional CT was 1987.[16] The first EBCT study defining coronary artery calcification [CAC] in comparison with angiography was published by Tennenbaum, et al in 1989.[17] This study used the low resolution 'cine' mode obtaining eight tomographic images with a slice thickness of 8 mm covering 76 mm of the coronary arteries and including 4 mm gaps between alternate level pairs. No attempt was made to quantify the calcification; however qualification of coronary calcium was noted with results of obstructive disease at invasive angiography.

However, it was the publication by Agatston, et al two years later that set up a specific protocol for CAC imaging and quantitation using CT.[18] The protocol was set up to provide a series of non-contrast thin slice, contiguous [no gaps] coronary artery cross-sections taken at the same phase of the cardiac cycle imaging the heart from base of the aorta/left main coronary artery and ending at the apex including the region of the posterior descending coronary artery.

At that time in 1989 and essentially until approximately 2005 EBCT was the 'reference standard' for CAC scanning. With the advent of 16-slice multidetector CT [MDCT] and especially the introduction of what is now state of the art 64+-slice MDCT such unique CAC protocols as outlined above have been possible using conventional CT.

It is the systematic quantification [i.e. CAC 'scoring'] of the calcified coronary artery plaque that provides the most clinical usefulness for CAC scanning regardless of the CT imaging platform. But it is very important to note that coronary calcium score measurements are 'rules based'. The rules are based on the original EBCT scan studies. Comparisons of scores between individuals or in relationship with established and published databases are valid only regarding scans that are performed according to the 'rules'.

The original description of the method of Agatston et. al[18] for quantification of the coronary calcium score [now universally referred to as the 'Agatston' score] is as follows:

- A tomographic slice thickness of 3 mm [or 2.5 mm interpolated to 3.0 mm] and non-overlapping slices
- To determine the presence and quantity of coronary artery calcium, each of the tomographic images are evaluated sequentially.
- The threshold for a calcific lesion is set at a CT density of 130 Hounsfield units and at an area of greater than or equal to 0.51 mm2 [essentially 2 contiguous pixels]. This eliminates single pixels with Hounsfield number of greater than 130 due to noise.
- At each level, using validated software, all pixels with a CT density equal to or greater than 130 are displayed.
- A 'region of interest' is placed around all lesions found within a coronary artery. Automated measurement of the lesion area in square millimeters and the maximum Hounsfield number of each region of interest are recorded.
- A lesion score is determined based on the maximum Hounsfield number [the cofactor] in the following manner: 1 = 130 to 199; 2 = 200 to 299; 3 = 300 to 399, and 4 >400 Hounsfield units. A score for each region of interest is calculated by multiplying the density score by the area.
- A total coronary calcium score is determined by adding up each of these scores for all tomographic slices. A score may also be obtained for each vessel or vessel segment [depending on the software program employed],
- Mathematically the formula is as shown in Equation 1:

EQUATION 1

$$\text{Agatston Score} = \frac{\text{Slice Increment}}{\text{Slice Thickness}} \times \sum (\text{calcium area} \times \text{cofactor})$$

[Note: The use of a 'threshold' of >130 Hounsfield [or CT density] for coronary calcification was chosen rather arbitrarily but essentially is >2 standard deviations from the non-contrast CT density of the cardiac myocardium [roughly 60 Hounsfield Units].

EQUATION 2

$$\text{Volume Score} = \sum (\text{calcium area} \times \text{slice increment})$$

The establishment of a CAC score in a given individual potentially defines a surrogate to the atherosclerotic plaque burden at that time. The

question, which remains unfortunately not fully addressed 'is of the use of the Agatston CAC score to define the atherosclerotic plaque progression, stabilization, or even regression in a given individual over time'? To potentially address this issue Callister and colleagues developed the 'volume score'.[19] The volume score is based on a principle called isotropic interpolation.[20] The values obtained with this method represent a volume and not an abstract number [i.e. the weighted assigned value to the maximum pixel density as for the Agatston score]; this volume is derived from the multiplication of the attenuation and area of a calcified plaque. Mathematically as shown in Equation 1, the sum [mathematically expressed as 'Σ'] includes the sum of the values in parenthesis obtained from each individual lesion found within the tomographic slice. The volume score [Equation 2] was found to be much more reproducible than the directly compared Agatston score in scans done in the same patients one year apart. At present nearly all vendor created calcium score reports report both the Agatston score [which is a non-dimensional number] and the volume score expressed as mm3 calcium $x10^{-3}$.

Clinically, Agatston scores run from zero to as high as 3,000 to 5,000 with even higher values found in some individuals with renal failure [where it is unclear if this represents intimal or medial calcification or both]. Rumberger et al[21] initially separated Agatston CAC scores as 0, 1 to 100, <100 to 400, >400 to 1,000, and >1,000 to define very low, low, intermediate, high, and very high future cardiac risk. But there is also significant value in looking at a given score in an age matched, gender matched, and even race matched database in asymptomatic individuals. This then makes it possible to determine if one individual score, regardless of physical 'score,' places them at higher or lower 'risk' than age/gender/race matched individuals.

Defining Agatston score percentile ranking allows for examining differences across gender and age as we age. Rumberger et al[21] suggested that Agatston CAC scores for age and gender at >75th percentile would add further intermediate term 'risk' not necessarily found based on CAC score alone. An example would be a score of 100 in a 45-year-old man versus the same score in a 70-year-old man. Although the score in the elder individual would be close to the median for an asymptomatic man at that age, it would represent >90th percentile for the same score in the younger man. This tacitly implies that the 'rate of change' of score in the years prior to the CAC scan in that 45-year-old man is totally out of what might have been expected in the average man, implying a much higher intermediate term 'risk' than the same CAC score in the 70-year old man.

The best known and most commonly used database for CAC scoring [derived solely from EBCT studies but easily used for MDCT studies] was published by Hoff, et al.[22] in 2001. This paper detailed scores and percentile scoring for a >35,000 asymptomatic adults referred by their doctor for CAC scanning in Chicago, Illinois.

Issues of potential differences in CAC scores between specific or mixed ethnic races was raised many years ago as the primary clinical databases were largely confined [but not limited] to Caucasian Americans. The MESA [multi-ethnic study of atherosclerosis] was an NIH defined multi-site investigation done, in part, to study CAC scores in various ethnic sub-groups. McClelland et al.[23] initially published the MESA database results as a function of age, gender, and 4 ethnic races. The participants were individuals between 45-84 years old who identified themselves as Caucasian [white], African-American, Hispanic, or Chinese. Again, although these results are somewhat different than the ranges of scores in previously published databases, limited ethnic differences were noted. The MESA study has a web site where one can enter information on traditional Framingham 'risk factors' [age, gender, total cholesterol, HDL cholesterol, smoking status, systolic blood pressure and use of anti-hypertensive medications] and the individuals' Agatston CAC score to calculate an absolute 10 year risk [www.mesa-nhlbi.org/Calcium/input.aspx].

In 2007 McCullough and colleagues[24] published a study using a cardiac calcification thoracic phantom comparing various scoring algorithms between EBCT and conventional CT scanners. Although variations were noted, the bottom line was that the variation between Agatston scoring was approximately 4% and considered by most to not be clinically significantly different.

In summary, published databases of CAC scores as a function of age and gender, whether from EBCT or MDCT or ethnically diverse individuals tend to overlap significantly and thus can be interchanged, at least for categorical ranges of CAC Agatston scores. Although there still remains controversy regarding the incremental risk value in looking at percentile ranking [compared to database information for age and gender] above absolute CAC score – the value at >75th percentile based on age and gender does imply a certain level of 'prematurity' of plaque formation and thus can also be used, with the score, to suggest aggressiveness of treatment for 'modifiable' risk factors.

APPLICATION OF NON-GATED CT TO CAC SCORING

Heretofore we have discussed studies utilizing either ECG triggered EBCT or ECG-gated MDCT in quantifying of CAC scores [either traditional Agatston Score or the Volume Score] in asymptomatic individuals who are generally at 'intermediate risk' for the future development of coronary heart disease.

The extension of non-gated CT low radiation dose of the chest has now expanded into 'screening' for lung cancer. One of the major 'risk factors' for lung cancer and heart disease is smoking; importantly, the imaging of the chest includes imaging of the heart. Why not extend the application of lung screening to screening for CAC and atherosclerotic plaque formation? As noted by Hecht et al[25], excluding screening lung scan eligible patients who also have established coronary disease, there is an overlap in the United States of 6.6 million lung scan patients who would be expected to benefit from CAC scanning; this is only a subset of potentially 33 million CAC screening eligible patients [i.e. those at 'intermediate risk' for developing coronary disease] in the US alone. But what are the data on CAC scanning using non-gated MDCT?

Up to the early 1990's conventional CT [as opposed to EBCT] acquired single slice images using a 'step and shoot' protocol – i.e. one slice at a time. The introduction of helical/spiral CT scanning, facilitated by 'slip ring' technology ushered in a new era in clinical CT. Soon the race was on to allow for multiple tomographic slices for each sweep of the x-ray gantry. Shemesh et al[26] measured coronary artery calcium with non-gated dual-slice helical CT and compared results with obstructive disease in the same subjects defined at coronary angiography. They demonstrated that sensitivity in detecting CAC was very high in localizing obstructive lesions, although the specificity was much lower – mainly due to calcification of also non-obstructed plaque.

Subsequently 4-slice and 8-slice MDCT began appearing in the late 1990's/early 2000's; but it was not until the introduction of 16-slice MDCT [circa 2005], capable of isotropic imaging, proved to be a viable alternative to cardiac imaging using EBCT.

In 2013 Xie and colleagues[27] performed a systematic review and meta-analysis regarding validation and prognosis of CAC using 16-slice non-gated MDCT. Five studies looking at validation of calcium scoring in gated vs non-gated CT were included. Additionally, 5 studies [comprising 34,028 asymptomatic patients with mean follow-up of 45 months] were included to evaluate prognosis in non-gated CT scans. They made the following key observations:

- The correlation in CAC scores between nontriggered and electrocardiography-triggered CT was excellent on a group level [r=0.94]
- In broad CAC categories, there was high agreement between nontriggered and ECG-triggered CT
- In a given individual, although variability in absolute CAC scores between CT methods did exist, using broad CAC score categories can potentially be used for cardiovascular risk stratification using nontriggered CT.

In 2016 the Society of Cardiovascular Computed Tomography and the Society of Thoracic Radiology [recognizing the utility of standard or screening lung scans to also contain potentially diagnostic images of the heart] published a joint scientific statement regarding guidelines for CAC scoring of non-contrast, non-gated CT scanning of the chest.[25] They reiterated that for any utilization for CAC scoring, thoracic CT images should employ at least 8-slice MDCT and allow for image reconstruction at 2.5 mm or 3 mm increments [see discussion on CAC scoring above]. Performing direct Agatston scoring using validated software was preferred to visual estimation of CAC severity or use of ordinal scoring systems. They also indicated acceptability of categorical CAC score ranges for non-gated CAC scoring as used routinely for gated CT examinations in terms of estimating cardiac 'risk' [see table below]:

CAC Gated and Nongated Agatston Score

0	Very Low Risk
1-99	Mildly Increased Risk
100-299	Moderately Increased Risk
>300	Moderately to Severely Increased Risk

These suggestions then could be incorporated into the standard Radiology Report to alert the Referring Physician of the findings.

Hecht and colleagues[29] have most recently updated and expanded the original CAC Guidelines[21] for Clinical Interpretation of CAC scoring and percentile ranking via an Expert Consensus Statement from the Society of Cardiovascular Computed Tomography; this furthermore provides clinical incremental risk categories and treatment recommendations [for both gated and non-gated CT scanning] as follows:

CAC Score Determined Risk Classifications and Treatment Recommendations in Asymptomatic Individuals at Intermediate Cardiac Risk

SCORE	INCREMENTAL RISK	TREATMENT RECOMMENDATIONS
0	Very Low	Statin Not Recommended
1-99	Mildly Increased	Moderate Intensivy Statin if <75th Percentile Moderate to High Instensity if ≥75th Percentile
100-299	Moderately Increased	Moderate to High Intensity Statin + 81 MG Aspirin
≥300	Moderately To Serverly Increased	High Intensity Statin + 81 MG Aspirin

Such additional information could also be included in the Radiology Report to further guide the Referring Physician as to therapy.

CONCLUSIONS:

1. Coronary artery mural calcification [CAC] has been shown to be true 'bone formation' [calcium hydroxyapatite] and is intimately associated with the active and indolent inflammatory pathways responsible for atherosclerotic plaque formation
2. The site and extent of CAC provides a valid surrogate for the burden of atherosclerotic plaque
3. Gated/triggered EBCT/MDCT and non-gated MDCT [16 slice or better] has been shown to allow for a useful, valid, and highly reproducible measurement of CAC via the application of CAC scoring algorithms [both Agatston and Volume Scoring]
4. Non-gated MDCT provides similar diagnostic and most importantly prognostic information across categories of Agatston CAC scores indistinguishable from similar data provided by ECG-gated MDCT
5. Application of CAC scoring to low-dose non-gated diagnostic and/or screening CT scans of the lung and thorax affords a validated extension of assessment also of cardiac risk in asymptomatic, intermediate risk patients

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