Title

Usefulness of Regional Distribution of Coronary Artery Calcium to Improve the Prediction of All-Cause Mortality

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Regional Distribution of Coronary Artery Calcium and Incremental Improvement in Prediction of All-Cause Mortality: A Study of 23,058 Patients.

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Abstract

Background: While the traditional Agatston coronary artery calcium (CAC) score is a powerful predictor of mortality, it is unknown if inclusion of regional distribution of calcified plaque further improves cardiovascular risk prediction.

Methods: We retrospectively studied 23,058 patients referred for CAC scoring. Approximately 61% of patients had CAC (N=14,084). CAC distribution was defined as the number of vessels with CAC (0-4, including the left main). For multi-vessel CAC, "diffuse" CAC was defined by decreasing percentage of CAC found in the single most affected vessel, and by the presence of ≤75% of the Agatston CAC score in the most calcified vessel. All-cause mortality was ascertained in 100% of patients via the social security death index.

Results: Mean age of the population was 55 ± 11 years, with 69% men. There were 584 deaths (2.5%) over 6.6 ± 1.7 years. Considerable heterogeneity existed between CAC score group and number of vessels with CAC. In each CAC group, increasing number of vessels with CAC was associated with increased mortality. In Cox models adjusted for age, gender, Agatston CAC score, and cardiovascular risk factors, increasing number of vessels with CAC was associated with incrementally higher risk (2-vessel: hazard ratio [HR] 1.61, 3-vessel: HR 1.99, 4-vessel: HR 2.22). A "Diffuse" CAC pattern was associated with an increase in mortality in the CAC 101-400 and >400 groups. Increasing CAC score in the left main artery was incrementally associated with mortality risk after adjustment for the Agatston Score and other risk factors.

Conclusions: Increasing number of vessels with CAC, a more diffuse CAC pattern, and involvement of the left main improve the prognostic power of the traditional Agatston CAC score.

Introduction

Accurate cardiovascular risk prediction is a pre-eminent topic, emphasized in the most recent ACC/AHA cardiovascular prevention guidelines (1). Coronary artery calcium (CAC) scoring using the method defined by Agatston et al (2) has been shown to refine cardiovascular risk stratification along a wide spectrum of CAC scores (3, 4), and its use is endorsed in the latest cardiovascular prevention guidelines (1). However, the additive value of regional CAC scores of individual coronary arteries in predicting cardiovascular events in addition to the overall Agatston CAC score has not been extensively studied.

CAC scoring has been shown to correlate with the overall burden of coronary atherosclerosis, inclusive of both non-calcified and fully calcified coronary atheromatous plaque (5). While the Agatston CAC score (2) is the most widely used method for CAC determination, it does not account for the regional distribution of CAC. While a high Agatston CAC score may correlate with more diffuse coronary atherosclerosis, a single calcified coronary atherosclerotic lesion may account for the majority of CAC seen in a given patient. A burgeoning body of evidence supports the finding that more diffuse coronary atherosclerosis is associated with a worse prognosis (6-8). Whether multi-vessel, diffuse CAC portends a worse prognosis compared to single vessel CAC involvement in patients with similar overall CAC scores is unknown.

We sought to describe the heterogeneity between the Agatston CAC score and simple measures of CAC distribution. We then sought to assess the added impact of CAC distribution in addition to the overall Agatston CAC score on the prediction of all-cause mortality in a large cohort of patients referred for CAC scoring based on cardiovascular risk factors.

Methodology

The study cohort consisted of 23,058 asymptomatic individuals referred for electron

beam computed tomography (EBCT) for the assessment of subclinical atherosclerosis. This study incorporated data from two centers during the time period 1991–2004 (Torrance, CA [n=14,657]; Columbus, OH [n=8401]), both of whom utilized a common CAC scanning protocol (9). Methods of data collection were similar for both centers. Participants were referred by their primary physicians on the basis of established cardiovascular risk factors for atherosclerosis. As an inclusion criterion, patients were determined to be free of known CAD based on prior assessment by the referring physician. All participants provided informed consent to undergo EBCT and for the use of their de-identified data for epidemiological research. The study was conducted in accordance with the Declaration of Helsinki and received approval from the Humans Investigations Committee at each site. Separate Committee approval was also obtained for patient interviews and collection of baseline and follow-up data.

Risk factor data collection

Participants completed a questionnaire for the collection of demographic and clinical characteristics, including baseline cardiovascular risk factors. Cigarette smoking was present if a subject was a smoker at the time of scanning. Dyslipidemia was defined by the presence of a history of high total cholesterol, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, hypertriglyceridemia, or current use of lipid-lowering therapy. Study subjects were considered to have diabetes mellitus if they reported using oral anti-diabetes medications or insulin. Hypertension was defined as a self-reported history of hypertension or use of antihypertensive medication. Family history of CAD was determined by the presence of a first-degree relative with a history of CAD [male <55 years old/female <65 years old (Torrance, CA); <55 years old for both male and female relatives in 8042 participants (Columbus, OH)].

Scanning protocol

All subjects underwent CAC scoring with either a C-100 or a C-150 Ultrafast computed tomography scanner (GE-Imatron, South San Francisco, CA, USA). Using a tomographic slice thickness of 3 mm, a total of approximately 40 sections were obtained from the level of the carina to the diaphragm. Image acquisition was electrocardiographically triggered at 60–80% of the R-R interval, using a 100-ms/slice scanning time. A calcified lesion was defined as ≥3 contiguous pixels with a peak attenuation ≥130 Hounsfield units. Lesions were scored using the method developed by Agatston et al (2).

CAC Definitions

Participants' overall Agatston CAC scores were categorized into four distinct CAC groups, representing increasing severity of CAC (CAC=0, CAC 1-100, CAC 101-400, CAC>400).

The number of vessels with CAC was described as an ordinal variable, accounting for the cumulative involvement of the left main, left anterior descending, left circumflex, and right coronary arteries (range 0-4). For patients with multi-vessel CAC (≥2 vessels involved), concentrated CAC was defined as the presence of >75% of the overall Agatston CAC score in the single most affected vessel, whereas diffuse CAC was defined as ≤75% overall Agatston CAC score in the most affected vessel (10).

In order to express the dispersion of CAC as a continuous variable, the maximal percentage of CAC in the most affected vessel was also determined. "CAC Diffusivity" was defined by the following equation: (1 – maximal percentage of CAC in most affected vessel), and represented the relative dispersion of CAC within the coronary tree in patients with multi-vessel CAC. If CAC was highly concentrated in the single most affected vessel, this would result in a low "diffusivity" score. Conversely, if CAC was widely dispersed within the coronary tree

leading to a low fraction of overall CAC in the single most affected vessel, the “diffusivity” score would be higher.

Follow-up and mortality ascertainment

Patients were followed for a mean of 5.6±2.6 years (range 1–13years). The primary endpoint for the study cohort was all-cause mortality. Ascertainment of mortality was conducted using the Social Security Death Index, and was verified by individuals blinded to baseline historical data and EBT results. The United States Social Security Death Index is a national registry of all deaths that occurred within the USA. Follow-up, therefore, occurred by studying this database for the reporting of the deaths of patients enrolled in the study, allowing for mortality ascertainment in 100% of participants. Follow-up was not obtained by direct contact with patients, either by clinic visits or by telephone.

Statistical Analysis

Chi-square testing was used to determine statistical significance between categorical variables, while Analysis of Variance (ANOVA) was used to compare the means across continuous variables. Using standard survival statistics, the death rate/1000 person-years was calculated per number of vessels with CAC, stratifying by CAC groups. A similar analysis was conducted for diffuse CAC. Multi-variable Cox regression analysis was employed to determine the hazard ratio of mortality for each measure of regional CAC distribution: number of vessels with CAC, concentrated vs. diffuse CAC, CAC diffusivity, and the Agatston score in individual coronary arteries. Adjustment included age, gender, Agatston CAC score (to adjust for residual confounding within each CAC group), hypertension, diabetes, hyperlipidemia, smoking and a family history of premature CAD. As appropriate, the Agatston score was modeled as both the continuous score and by conventional CAC score groups. When modeling the number of vessels

with CAC, single vessel CAC was considered the reference group. CAC "diffusivity", a measure of the extent of regional involvement of CAC, was modeled per 10% more diffuse distribution.

All statistical analyses were performed with STATA version 13 (STATA Corp., College Station, TX, USA).

Results

The mean age of the study population was 58 ± 11 years old. The population was predominantly male (78%). CAC was present in 61% of the overall study cohort (14,084/23,058). The proportion of patients with hypertension, diabetes, hyperlipidemia, smoking and a family history of premature CAD increased progressively with increasing number of vessels with CAC (Table 1). Data on BMI were available for 6839 patients, demonstrating a progressive increase in BMI with increasing coronary vessel involvement from 26.7 to 28.1 kg/m^2 ($p<0.001$, data not shown). Similarly, ethnicity data were available for 48% of the population, with this data showing more CAC with a more diffuse CAC distribution pattern in Caucasians compared to other races ($p<0.001$, Supplemental Figure).

Of the 14,084 patients with CAC, the mean Agatston CAC score was 63 units (Table 2), while the mean number of vessels with CAC per patient was 2.2 ± 1.0. The majority of patients had CAC in the left anterior descending artery territory (84%), with a decreasing frequency in the right coronary (67%), circumflex (50%), and left main (17%) arteries. Among patients with multi-vessel CAC (≥2 vessels), the mean maximal percentage of CAC in one vessel was 69%, while the proportion of patients with a diffuse CAC pattern was 62%.

<u>Heterogeneity between CAC Score Group and Number of Vessels with CAC</u>

In the CAC 1-100 group, 85% of patients had one- or two-vessel CAC, with a much smaller proportion of patients with three- (14%) and four-vessel CAC (2%). Conversely, for patients with CAC>400, there was a predominance of patients with three- and four-vessel CAC,

with only 1% and 11% of patients having one- or two-vessel CAC respectively. The intermediate CAC range (101-400) was far more heterogeneous, with a wider dispersion of the number of vessels involved (Figure 1).

Mortality Rates by Regional Measures of CAC

Within both the CAC 1-100 and 101-400 groups, the annual mortality rate increased as the number of vessels with CAC increased (Figure 2A). The mortality rate for the CAC>400 group was uniformly elevated regardless of the number of vessels with CAC.

Diffuse CAC was associated with a higher annual mortality rate compared to concentrated CAC, both in the overall multi-vessel CAC subset, as well as in patients with moderate and high CAC (101-400 and >400) (Figure 2B). In patients with mild CAC (1-100), there was no difference in mortality rate between patients with diffuse or concentrated CAC.

Hazard Ratio of Adding Regional CAC to Agatston CAC Score

After adjusting for demographic variables, cardiovascular risk factors, and the Agatston CAC score, increasing number of vessels with CAC was associated with an incrementally increased risk of all-cause mortality compared to single-vessel CAC, regardless of whether the Agatston CAC score was adjusted for as a continuous variable or by CAC score groups (Table 3A). Patients with three- and four-vessel CAC were at an approximately two-fold increased risk of death after adjusting for overall Agatston CAC score.

When mortality risk was stratified by individual CAC groups, there was a trend towards increased mortality risk in the mild-moderate CAC groups (CAC 1-400) with increasing number of vessels with CAC, which achieved borderline statistical significance (Table 3B). The addition of increasing number of vessels with CAC was not associated with an incremental increased

mortality risk in the CAC>400 group.

For every 10% increase in CAC “diffusivity”, there was an incrementally increased all-cause mortality risk after adjustment for overall Agatston CAC score (Table 4). CAC “diffusivity” lost statistical significance after adjusting for cardiovascular risk factors. Similar to the finding for an increase in number of vessels with CAC, an increase in CAC diffusivity did not confer an increased mortality risk in the CAC>400 group. When diffuse CAC was defined by <75% CAC in the most affected vessel, there was no statistically increased mortality risk after adjusting for overall Agatston CAC score and cardiovascular risk factors.

For every 100 Agatston units increase in left main and LAD CAC, there was an incremental, statistically significantly increased all-cause mortality risk, even after adjusting for the overall Agatston score and the number of coronary vessels with CAC (Table 5). Conversely, increasing RCA CAC was associated with decreased all-cause mortality [hazard ratio (p-value), Left main: 1.18 (0.001), LAD: 1.05 (0.04), RCA: 0.99 (0.003)], while increasing circumflex artery CAC had no independent impact on all-cause mortality prediction after adjustment for the total Agatston CAC score and other variables (hazard ratio 1.03, p=0.18).

Discussion

In this study of all-cause mortality risk prediction over mean 5.6 years, we demonstrated that regional measures of CAC improve the overall prognostic value of CAC beyond traditional Agatston scoring. Furthermore, we have shown that an increase in left main CAC is associated with incremental mortality risk even after adjusting for the traditional Agatston score.

<u>Traditional Agatston CAC Scoring- Strengths and Limitations</u>

In 1990, Agatston et al (2) described a method of CAC scoring, which remains the most widely used today. The Agatston CAC score has demonstrated utility in improving cardiovascular risk prediction in patients with an intermediate Framingham risk score (11), as well as many patient subsets not fully captured by the Framingham risk score (9, 12).

However, there are two limitations worthy of mention. The score is computed by multiplying each area of calcification within large epicardial coronary arteries $>1mm^2$ by a factor related to the density of the calcified plaque, and adding each of these values to determine an aggregate score. This leads to increased weighting of more densely calcified plaque, and less effect on the overall Agatston score for less calcified "soft" plaque. Recent research suggests that mixed calcified plaque is more likely to rupture leading to an acute myocardial infarction compared to fully calcified plaque (13). Imaging of culprit coronary plaque morphology at the time of acute myocardial infarction has demonstrated that a "spotty" pattern of calcification was more closely associated with acute plaque rupture than extensively calcified plaque (14). This suggests that mixed calcified plaque may be more predictive of acute myocardial infarction than fully calcified plaque, and that less emphasis on plaque density may improve cardiovascular risk prediction.

In addition, The Agatston CAC score does not account for the regional dispersion of CAC. Bittencourt et al (6) and many others have demonstrated that more diffuse coronary atherosclerosis has a higher long-term risk of major cardiovascular events compared to more focal CAD. This suggests that an estimate of the dispersion of CAC throughout the coronary arterial tree may also incrementally improve its ability to predict cardiac events.

Regional CAC Measures and Correlation with Coronary Atherosclerotic Burden

Bartel et al (15) used coronary angiography to demonstrate that the angiographic severity of CAD increased with more diffuse involvement with CAC. As the number of vessels with CAC

increased from one to three, the prevalence of triple-vessel CAD increased from 45% to 82% respectively. This concept has been subsequently highlighted with the use of non-contrast coronary CT (16), and in the histologic analysis of coronary artery segments (17). In the latter study, CAC quantification was an excellent predictor of coronary artery plaque burden within each coronary artery (left anterior descending coronary artery: $r=0.89$, $p < 0.0001$; left circumflex coronary artery: $r=0.7$, $p < 0.001$; right coronary artery: $r=0.89$, $p < 0.0001$). Our study supports the suggestion that increasing diffuse CAC may suggesting increasingly diffuse CAD burden, which is associated with higher risk.

Regional CAC and Cardiac Event Prediction

Stone et al (18) studied the relative morbidity and mortality of patients presenting with ST-elevation myocardial infarction, stratifying by culprit vessel. This study noted that patients with a myocardial infarction involving the left main or left anterior descending arteries have a significantly worse prognosis than left circumflex or right coronary artery territory myocardial infarction. A more recent analysis of the Atherosclerosis Risk in Communities (ARIC) study demonstrated that even in the era of primary coronary intervention, anterior location of myocardial infarction and the presence of multi-vessel disease both predict a higher 28-day mortality after acute myocardial infarction compared to inferior location (19). Our study validates both these findings with the use of non-contrast coronary CT in a primary prevention setting. We have shown that increasing number of vessels with CAC, corresponding to more diffuse atherosclerosis, predicts a higher all-cause mortality risk (Table 3A). Furthermore, we demonstrated the independent prognostic significance of left main and LAD CAC in predicting mortality, even after adjusting for the overall Agatston CAC score and increasing number of vessels with CAC.

Limitations

There is the potential for referral bias, given the fact that patient were referred by their primary care physicians based on cardiovascular risk factors. This may limit the applicability of the findings to the general population. Additionally, the presence of cardiovascular risk factors was assessed by a questionnaire format, suggesting that recall bias may affect the results.

For this cohort of patients, we did not assess cardiovascular causes of death, or non-fatal myocardial infarction. However, all-cause mortality is an established, objective cardiovascular endpoint upon which accurate conclusions can be drawn.

For the purpose of studying regional CAC variability, our definitions of diffuse and concentrated CAC, as well as CAC "diffusivity" were arbitrary, and require further study to validate the ideal separation of patients into concentrated and diffuse CAC.

Conclusion

Our study suggests that measures of the regional dispersion of CAC within the coronary tree incrementally add to the Agatston CAC score for prediction of all-cause mortality. After future confirmation studies are conducted, attempts should be made to construct an improved algorithm for CAC scoring.

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