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Publication Date

2019-07-01

DOI

10.1016/j.atherosclerosis.2019.03.015

Peer reviewed

Title **The association between left main coronary artery calcium and cardiovascular-specific and total mortality: The Coronary Artery Calcium Consortium**

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Words Abstract – 250 words; manuscript – 2615 words

Figures

Tables

References

Funding The authors did not receive any funding to write this article.

Disclosures

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Abstract

Background and aims

Left main (LM) coronary artery disease is associated with greater myocardial infarction-related mortality, however, coronary artery calcium (CAC) scoring does not account for disease location. We explored whether LM CAC predicts excess mortality in asymptomatic adults.

Methods

Cause-specific cardiovascular and all-cause mortality were studied in 28,147 asymptomatic patients with non-zero CAC scores in the CAC Consortium. Multivariate regression was performed to evaluate if the presence and burden of LM CAC predicts mortality after adjustment for clinical risk factors and the Agatston CAC score. We further analyzed the per-unit hazard associated with LM CAC in comparison to CAC in other arteries.

Results

The study population had mean age of 58.3 ± 10 years and CAC score of 301 ± 631. LM CAC was present in 21.7%. During 312,398 patient-years of follow-up 1,907 deaths were observed. LM CAC was associated with an increased burden of clinical risk factors, total CAC, and was independently predictive of increased hazard for all-cause (HR 1.2 [1.1, 1.3]) and cardiovascular disease death (HR 1.3 [1.1, 1.5]). The hazard for death increased proportionate to the percentage of CAC localized to the LM. On a per-100 Agatston unit basis, LM CAC was associated with a 6-9% incremental hazard for death beyond knowledge of CAC in other arteries.

Conclusions

Presence and high burden of left main CAC are independently associated with a 20-30% greater hazard for cardiovascular and total mortality in asymptomatic adults, arguing that LM CAC should be routinely noted in CAC score reports when present.

Introduction

Coronary artery calcium (CAC) detected with imaging correlates with the histopathological presence of calcified atherosclerotic plaque, providing a specific marker of subclinical coronary artery disease (CAD)[1]. Quantification of CAC, as first described by Agatston et al. using non-contrast cardiac-gated computed tomography (CT)[2] is highly predictive of incident cardiovascular disease (CVD) events and all-cause mortality, and provides predictive value beyond that of traditional clinical risk factors[3–6]. Accordingly, in clinical practice, CAC scans are increasingly used to stratify CVD risk in asymptomatic adults[7].

Considering its prognostic performance, the Agatston CAC score is remarkably simple in its calculation. The Agatston CAC score is the sum of the scores of all individual calcified coronary lesions (areas with >130 Hounsfield units multiplied by a density weighting factor) visually-confirmed to be coronary calcifications under standard image acquisition parameters[2]. A criticism of this scoring protocol is that it does not account for the potential differential risk associated with plaque localization within the coronary tree[8–10]. For example, the Agatston method weights CAC in the left-main (LM) coronary artery equally to that in the distal right coronary artery (RCA), despite a vast difference in the quantity of subtended at-risk myocardium and, consequently, a faster progression from symptoms to death in patients with LM disease[11–14]. Accordingly, it has been suggested—but not

convincingly demonstrated—that LM CAC in asymptomatic patients confers incremental risk beyond that predicted by its contribution to the total CAC score[15].

Limited prior data suggests a possible signal for increased risk with LM CAC. In an analysis of more than 25,000 asymptomatic adults, the Agatston score in the LM was associated with a higher relative risk for death compared to scores from the circumflex (CIRC), RCA, and left anterior descending (LAD) arteries[16]. In a separate study by the same authors, among vessel-specific CAC scores, only those from the LM and LAD were significantly associated with mortality after adjustment for traditional clinical risk factors[17]. However, because this study did not control for the total CAC score, or study CVD-specific mortality, it remains unclear if LM CAC confers greater CVD-specific risk *per se* or by association with higher total CAC or other traditional risk factors.

We hypothesized that LM CAC, in a sufficiently large sample with long follow-up, confers higher risk for both CVD-specific and all-cause mortality compared to CAC in other distributions. We further hypothesized that this effect would be strongest in patients with intermediate CAC scores (1-399). To explore this possibility, we measured the burden of LM CAC among patients in the CAC Consortium, and evaluated if its presence conferred incremental cause-specific and total mortality risk to that predicted by the total Agatston CAC score and traditional cardiac risk factors.

Methods

Study design

The Coronary Artery Calcium Consortium is a multi-center population-based retrospective cohort of asymptomatic patients ≥18 years of age, without known

coronary heart disease (CHD, defined as history of MI, obstructive CAD, PCI, or CABG), who were referred for clinical CAC scoring for CVD risk stratification. The study population comprised 66,636 men and women undergoing CAC testing between 1991 and 2010. The CAC Consortium includes data from 4 different centers, each having a CAC scanning program for at least 10 years, contributing at least 5000 patients, and able to provide nearly complete individual patient-level CVD risk factor data (>90% of all fields). Informed consent was provided by all participants at the time of enrollment at each contributing center. Institutional review board approval for data coordinating center activities was obtained at the Johns Hopkins Hospital.

Study Population

For the present analysis, all CAC Consortium participants with CAC>0 were considered for inclusion. In addition to the total CAC score, the presence of LM CAC and all vessel-specific contributions to the total CAC score had to be reported for each patient. This yielded a study population of 28,147 participants (76.3% of all patients with CAC>0) with complete baseline demographics and clinical characteristics.

CT Data

Non-contrast cardiac-gated CT scans were performed at baseline using electron beam tomography (EBT) (93%) or multi-detctor CT (MDCT) (7%) with CAC scores calculated by the Agatston method[2]. EBT was conducted with the Imatron C-100 in 13%, C-150 in 38%, C-300 in 38%, and with the e-Speed scanner in 3.5% (GE-Imatron). The MDCT scanners included a 4-slice device (Somatom Volume Zoom,

Siemens Medical Solutions) and a 64-slice device (General Electric LightSpeed, GE Healthcare).

Risk factor Data

Patient-level data on demographics, CVD risk factors, and medical history were collected by self-report and from the electronic medical record from the initial clinical visit associated with referral for CAC testing[18]. Baseline information collected included hypertension (prior diagnosis or current treatment), hyperlipidemia (prior diagnosis of hyperlipidemia, dyslipidemia, use of lipid-lowering drug therapy, or laboratory data, where available), current smoking, diabetes (prior diagnosis or treatment with oral hypoglycemic agents or insulin), and family history of CHD in a first degree relative. In the 28% of cases where there was incomplete ascertainment of at least one risk marker, multiple imputation was performed using a multivariable model adjusting for age, sex, race, total CAC score, and the non-missing traditional risk factors to impute data.

Follow-up for Cause-Specific Mortality

Ascertainment of death was determined through linkage to the Social Security Death Index using a previously validated algorithm[18]. Classification of death into common categories was performed by review of ICD-9 coded death certificates obtained from the National Death Index. Participants were followed for a mean of 12 ± 4 years for the incidence of CVD death or non-CVD death. All cause-death included both CVD and non-CVD mortality, with CVD mortality encompassing all CHD, as well as stroke, heart failure, and other cardiovascular mortality.

Statistical methods

Baseline demographics and clinical characteristics of the study population were analyzed in aggregate and according to LM CAC status (present or absent). Continuous data were presented as mean ± standard deviation and categorical as the total number and as proportions. The two groups defined by LM CAC status were compared using the Student's t-test and Chi-square test for continuous and categorical variables, respectively.

For descriptive purposes, the prevalence of LM CAC was calculated by CAC score group (intermediate CAC: 1-399 and elevated CAC: ≥400) and by number of vessels with CAC (1-4)[10]. These results were then presented graphically.

Absolute event rates of all-cause and cause specific death for those with LM CAC and those without LM CAC were calculated by dividing the total number of events by the total number of person-years at risk. Additionally, analyses were performed after stratifying by CAC score group. These results were then presented graphically.

To determine if the presence of LM CAC predicts time to all-cause and CVD death independently of the total Agatston CAC score, we used multivariable Cox proportional-hazards regression models. For each outcome, CAC-only adjusted and then sequentially more adjusted models were presented. Model 1 additionally adjusted for age and sex, while the fully adjusted model (Model 2) further adjusted for hyperlipidemia, smoking, hypertension, diabetes and family history. These models were then repeated after stratification by intermediate CAC (1-399) and high CAC (≥400).

To assess if the burden of LM CAC has predictive value beyond its qualitative presence, we constructed additional models using the following LM CAC burden cutpoints: 0% (reference), 1-25%, >25%. For these analyses, LM CAC burden was

calculated by taking the CAC score in the LM and dividing by the total CAC score, expressing this quotient as a percentage.

Finally, to determine if CAC in the LM on a per Agatston unit basis was more strongly associated with adverse outcomes compared to CAC in other coronary arteries, additional regression analysis were performed entering the CAC score of each coronary artery into the model at the same time. Models were additionally adjusted for the variables from Model 2 above. The incremental predictive value of the LM CAC score (presented per 100 Agatston units) was then interpreted as the exponentiated model coefficient for LM CAC from this adjusted model (i.e. the incremental hazard ratio).

All statistical analyses were performed using STATA 14 (Stata Corp, College Station, TX). A two-tailed p-value of <0.05 was consider significant.

Results

Baseline Characteristics

Baseline characteristics of the study population are shown in **Table 1.** Mean age was 58.3 ± 10 and 25% were female. Overall, LM CAC was observed in 21.7% of the asymptomatic population studied with CAC>0. Patients with LM CAC were more likely to have traditional CVD risk factors, including hypertension, hyperlipidemia, diabetes mellitus and smoking ($p<0.05$). They also had a higher mean CAC score (647 vs. 205) and were more likely to have CAC scores ≥400 (43% vs. 13%). The proportion of subjects with LM CAC involvement increased as the total CAC score and number of involved vessels increased (**Figure 1a & 1b).**

Survival analysis by presence of LM CAC

We observed 1,907 deaths during the 312,398 patient-years of follow-up, of which 1000 (52%) were attributable to CVD, and 907 (48%) were from other causes. **Figure 2** demonstrates a graded increase in both all-cause and CVD mortality rates across CAC groups, with those with LM CAC having higher mortality rates than those with no LM CAC.

In the fully adjusted multivariate adjusted analysis, presence of LM CAC was associated with increased hazard for all-cause death (HR 1.2 [1.1–1.3]) and CVD death (HR 1.3 [1.1–1.5]) beyond the total CAC score and traditional risk factors **(Table2/Figure 3)**.

Survival analysis by burden of LM CAC

There was a graded increase in all-cause and CVD death observed across groups with increasing LM CAC %. This trend remained statistically significant upon correction for clinical risk factors in the fully adjusted multivariate model. The hazard for all-cause and CVD death was 20% higher when the percentage of total CAC in the LM was 1-25% and 40% higher when LM CAC comprised >25% of the total. There was no difference in the hazard for all-cause as compared to CVD-specific mortality within groups with similar burden of LM CAC **(Table 3)**.

Predictive value of LM CAC compared to CAC in other vessels

In the multivariate analysis adjusting for the CAC scores in each individual coronary artery, and additionally adjusted for clinical risk factors, the incremental hazard for all-cause and CVD death was significantly higher for the LM as compared to the other vessel-specific scores**.** Per 100 Agatston units, the incremental hazard for CVD death associated with LM CAC was 6-9% greater than that associated with the LAD, CIRC, and RCA **(Table 4)**.

Discussion

In this large, multicenter retrospective cohort study from the CAC Consortium, we demonstrate that LM CAC is a somewhat common finding in asymptomatic patients with CAC>0 (21.7%), and is associated with more clinical CVD risk factors, higher total CAC scores, and more diffuse disease. Within individual CAC score groups, LM involvement is associated with higher crude rates of CVD and total mortality, and independently predicts a 20-30% mortality increase risk beyond the total CAC score and traditional risk factors. Moreover, per Agatston unit, the CAC score contribution from the LM leads to more increased risk than any other of the coronary arteries. Taken together, the findings suggest that LM CAC serves as a marker of a higher risk phenotype, and may be considered a modest independent risk factor for mortality beyond the traditional risk assessment and Agatston CAC scoring.

Much has been written about LM disease since Herrick's classic case series first described the natural history of LM coronary artery occlusion[19]. It is now known that acute coronary syndromes in this territory progress rapidly from the onset of symptoms and, without intervention, often culminate in massive myocardial infarction, cardiogenic shock, and sudden cardiac death[20]. LM CAD is also a well-established prognostic factor and predictor of benefit from surgical or percutaneous revascularization in the setting of symptomatic but stable coronary artery disease[11–14,21]. Previously, it was unknown if the high CVD risk associated with obstructive LM disease extended to asymptomatic LM CAC, which might represent its earliest clinically-recognizable manifestation.

In the most extensive prior analysis of LM CAC, Williams et al. showed that among the four coronary artery specific CAC scores, only the LM and LAD appeared to be

significant predictors of all-cause mortality. Likely due to differences in statistical power, here we observe that each of the vessel-specific CAC scores, except the RCA, are independent predictors of all-cause mortality, however the greatest hazard per Agatston unit is associated with the LM. The authors of the Williams et al study also observed particularly high mortality among patients with frequent calcifications in the LM[17], suggesting that LM CAC, particularly frequent discontinuous calcification, contributed a disproportionate amount of the mortality risk predicted by CAC scoring in asymptomatic populations. Correspondingly, it is demonstrated here that both LM CAC presence and burden are associated with clinical cardiovascular risk factors, higher total CAC score, and higher CVD and total mortality.

Taken together, these findings support the hypothesis that LM calcification predisposes patients to excess risk compared to its presence in other vessels and should be routinely noted in clinical CAC scoring. We hypothesize that a large portion of the excess mortality observed is related to the greater likelihood of fatal complications immediately after acute coronary events in the LM distribution, or attendant to surgical revascularization among survivors. Based on this hypothesis it was anticipated that LM CAC would be more strongly associated with CHD as compared to all-cause mortality, however, we did not have sufficient power to detect small between-vessel differences in cause-specific mortality to all-cause mortality rate ratios.

Our findings build on the accumulating evidence that the regional distribution of CAC significantly modifies the risk of events predicted by the Agatston method[8,10,22]. However, if vessel-specific CAC scoring, including LM CAC, is clinically actionable remains uncertain. The findings here suggest that LM CAC is a notable high-risk

finding on CAC scans that should be specifically noted on study interpretations. Further research will be needed to determine if the presence of LM CAC should be used to modify the decision to initiate risk-modifying therapy. However, based on current guidelines and evidence, the presence of LM CAC should not be used to justify unnecessary and potentially harmful stress testing or cardiac catheterization in the absence of symptoms[23].

The main strength of the present study is its design and size. This was a multisite cohort study with ample size to study LM-specific CAC and adjust for the total CAC score and relevant confounders. Since this is a clinical population, findings should be generalizable to practicing physicians. However, results are not necessarily generalizable to the general asymptomatic community-dwelling population, as our study may be subject to selection bias since all patients were referred by their physician for clinical CAC scoring. An additional limitation of the study is the subjective aspect of classifying CAC as residing within the left main, as experience suggests it often is contiguous with aortic, LAD, and/or circumflex calcification, and the CAC Consortium did not include core lab reading. Finally, our study is limited by lack of data on LM CAC density, which has an inverse relation to risk in whole heart CAC scoring, although specific effects in the LM are unknown. Future work may be directed at determining if there are LM CAC characteristics such as volume, density, or lesion count that can identify a subset of patients at even higher risk in need of even more aggressive therapies.

Conclusion

LM CAC is present in approximately one in five asymptomatic patients referred for clinical CAC scoring with non-zero CAC score, and LM CAC presence and burden is

associated with greater morality risk independent of the total Agatston score and clinical risk factors. LM CAC may therefore represent a high-risk phenotype that should be routinely reported on CAC scans and that may warrant close scrutiny to ensure adequate control of CVD risk.

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Table 1: *Baseline characteristics of the study population and by left main coronary artery involvement*

Abbreviations: LM, left main; SD, standard deviation; IQR, interquartile range; CAC, coronary artery calcium

Figure 1a: *Left main CAC prevalence by CAC score groups*

Abbreviations: LM, left main; CAC, coronary artery calcium

Figure 1b: *Left main CAC prevalence by number of coronary vessels with CAC*

Abbreviations: LM, left main; CAC, coronary artery calcium

Figure 2: *Absolute Mortality Rates (All-cause and CVD Death) Per 1000 Person-Years, by the presence or absence of left main CAC*
Abbreviations: LM, left main; CAC, coronary artery calcium; CVD, cardiovascular disease

Figure 3: *Hazard Ratios for the association of left main CAC with the study endpoints*

Table 2: *Hazard Ratios for the study endpoints, by presence of left main CAC*

*All models adjusted for total CAC score on its native scale

Model 1: Age and Sex. Model 2: Model 1 + hyperlipidemia, smoker, hypertension, diabetes, and family history

Abbreviations: LM, left main; CAC, coronary artery calcium; CVD, cardiovascular disease

Table 3: *Hazard Ratios for the association of left main CAC burden with the study endpoints*

†Left main CAC burden defined as the percentage of total CAC score contributed by the left main

*All models adjusted for total CAC score on its native scale

**Model 1: Age and Sex. Model 2: Model 1 + hyperlipidemia, smoker, hypertension, diabetes, and family history

Abbreviations: LM, left main; CAC, coronary artery calcium; CVD, cardiovascular disease

Table 4: *Incremental Hazard Ratios for the association of vessel-specific CAC score (per 100 Agatston units) with the study endpoints adjusted for each individual vessel CAC scores*

*Adjusted for the total CAC score of each vessel + age, sex, hyperlipidemia, smoking, hypertension, diabetes, and family history

Abbreviations: LM, left main; CAC, LAD, left anterior descending; RCA, right coronary artery; CIRC, circumflex; CVD, cardiovascular disease

Supplemental Table 1: *Hazard Ratios for the study endpoints, by CAC score groups*

*All models adjusted for total CAC score on its native scale

Model 1: Age and Sex. Model 2: Model 1 + hyperlipidemia, smoker, hypertension, diabetes, and family history

Abbreviations: LM, left main; CAC, coronary artery calcium; CVD, cardiovascular disease