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### Title

Coronary Artery Calcium Dispersion and Cause-Specific Mortality: Results from the Coronary Artery Calcium Consortium

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1 Coronary Artery Calcium Dispersion and Cause-specific Mortality: Results from the Coronary  
2 Artery Calcium Consortium

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4 Running Head: CAC Dispersion and Cause-Specific Mortality

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- 1 ABBREVIATIONS
- 2 ASCVD – Atherosclerotic Cardiovascular Disease
- 3 CAC – Coronary Artery Calcium
- 4 CHD – Coronary Heart Disease
- 5 CI – Confidence Interval
- 6 CVD – Cardiovascular Disease
- 7 HDL-C – High-density Lipoprotein Cholesterol
- 8 HR – Hazard Ratio
- 9 HU – Hounsfield Units
- 10 ICD – International Statistical Classification of Diseases and Related Health Problems
- 11 ID – Index of Diffusion
- 12 KM –Kaplan-Meier
- 13 LDL-C – Low-density Lipoprotein Cholesterol
- 14 SD – Standard Deviation
- 15 SSDIDMF – Social Security Death Index Death Master File
- 16

1 ABSTRACT

2 **Background and Aims:** CAC is a measure of subclinical atherosclerosis and a powerful tool for  
3 improving risk stratification. CAC characteristics—including vessel(s) involved, number of  
4 vessels, volume, and density —have been shown to differentially impact risk. We assessed how  
5 dispersion—either the number of calcified vessels or a diffuse CAC phenotype—impacted cause-  
6 specific mortality. We sought to assess coronary artery calcium (CAC) dispersion and its  
7 association with cause-specific mortality.

8  
9 **Methods:** The CAC Consortium is a retrospective, multi-site cohort of 66,636 participants  
10 without CHD who underwent CAC scoring. Risk factor data were collected at time of enrollment  
11 or CAC scan. Individuals with CAC>0 were included—CAC area, CAC density, and the CAC  
12 index of diffusion (ID=1- (CAC in most concentrated vessel/total Agatston score) were  
13 calculated and the association between CAC characteristics and CVD- and CHD-specific  
14 mortality was assessed.

15  
16 **Results:** In 28,147 study participants, with mean age of 58.3 years, 25% female, and 89.6%  
17 white, ~66% had 2 or more calcified vessels. Diabetes, hypertension, and hyperlipidemia were  
18 predictors of multivessel involvement (p<0.001). After controlling for overall CAC score, those  
19 with 4-vessel CAC had more CAC area involved with less dense calcification compared to those  
20 with 1-vessel involvement. There was a graded increase in the association between number of  
21 vessels with CAC and all-cause, CVD- and CHD-specific mortality compared with 1-vessel  
22 CAC. Among those with 2 or more vessels involved (N=18,516), there was a trend towards  
23 higher all-cause, CVD- and CHD-specific mortality in those with a diffuse CAC phenotype  
24 compared with a concentrated CAC phenotype.

25  
26 **Conclusion:** Diffuse CAC involvement was characterized by less dense calcification, more CAC  
27 area, multiple coronary vessel involvement, and presence of certain traditional risk factors. There  
28 is a graded increase in all-cause, CVD- and CHD-specific mortality with increasing CAC  
29 dispersion.

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33 Word Count: 291 (300 Max)

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35  
36 Key Words: Coronary Artery Calcium, Index of Diffusion, Computed Tomography, Coronary  
37 Heart Disease

1 CONDENSED ABSTRACT

2

3 In a large retrospective, cohort study of patients referred for coronary artery calcium (CAC)

4 scoring and followed for over 12 years, there was a graded increase all-cause, CVD- and CHD-

5 specific mortality with each additional calcified vessel. There was a trend towards higher all-

6 cause, CVD- and CHD-specific mortality in those with a diffuse phenotype compared with a

7 concentrated phenotype. Diabetes, hypertension, and hyperlipidemia were associated with

8 multivessel disease. Given non-invasive imaging modalities role in risk stratification, the degree

9 of CAC dispersion can help clinicians identify and treat higher-risk patients who are more likely

10 to experience all-cause or cardiovascular related mortality events.

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13 Word Count: 100 (100 Max)

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1 1. INTRODUCTION

2 The absence of coronary artery calcium (CAC) has been firmly established as the best  
3 predictor of low risk among clinical parameters used to assess patients noninvasively (1). In  
4 contrast, the burden of CAC—a strong correlate of total coronary atherosclerotic plaque (2)—has  
5 been shown to be associated with the risk of coronary heart disease (CHD) and cardiovascular  
6 disease (CVD) events (3-5). As such, CAC scoring is now incorporated in clinical practice  
7 guidelines given its demonstrated use as a powerful adjunct to both traditional risk factors (6-8)  
8 and risk-prediction models for helping to characterize risk (9,10).

9 However, the full utility of CAC scanning as a predictive tool has yet to be realized. The  
10 original and still longstanding means for calculating CAC, the widely used Agatston score, is  
11 derived by summing the scores of all individual lesions (determined by multiplying the total  
12 lesion area by a weighting factor accounting for maximum density in Hounsfield units) (11).  
13 However, contrary to the initial assumptions of the Agatston score, CAC density has since been  
14 shown to be inversely related to CHD and CVD events (12). Other potential characteristics that  
15 may improve upon the Agatston score’s predictive ability—but not yet accounted for—include  
16 the number and identity of vessels affected, the overall CAC distribution (13), and the number of  
17 calcified plaques (14). For example, both left main calcification and number of calcified plaques  
18 have been shown to be associated with increased risk of all-cause mortality (15,16). In addition,  
19 the number of vessels involved may also provide additive prognostic information depending on  
20 the individual’s gender (17).

21 Given these considerations, we sought to understand how measures of CAC dispersion—  
22 considered as either the number of calcified vessels involved or by CAC phenotype, using an  
23 index of diffusion (ID), which apportions how much each vessel contributes to the total Agatston

1 score—high indices reflect diffuse disease, whereas low indices reflect concentrated disease—are  
2 associated with all-cause and cause-specific mortality. We also examined the interplay of CAC  
3 area and density and whether clinical risk factor data might predict diffuse CAC involvement.

4

## 5 2. METHODS

### 6 2.1 Study Design

7 The complete details and rationale behind the CAC Consortium have been published  
8 elsewhere (18). Briefly, the CAC Consortium is a retrospective cohort study including 66,636  
9 participants from four institutions—Cedars-Sinai Medical Center in Los Angeles, CA;  
10 PrevaHealth Wellness Diagnostic Center in Columbus, OH; Harbor-UCLA Medical Center in  
11 Torrance, CA; and the Minneapolis Heart Institute in Minneapolis, MN (18). Eligible  
12 participants were at least 18 years of age, were asymptomatic and without clinical evidence of  
13 CHD, and underwent CAC testing after a clinically indicated physician referral (18). For these  
14 analyses, only participants with CAC>0 were included (N=28,147). Analyses for ID were further  
15 restricted to only those with two or more calcified vessels (N=18,516). Consent was obtained at  
16 participating institutions at time of CAC scanning (18).

### 17 2.2 Coronary Artery Calcium Scans

18 CAC scans were obtained by using either electron beam tomography (~93% of scans) or  
19 multi-detector computed tomography (CT) (~7% of scans) (18). Each site performed these non-  
20 contrast, cardiac-gated scans using common protocols (18) and calcium score was quantified  
21 using the Agatston method (11). Mean vessel area that contained calcium was calculated.  
22 Directly measured CAC density data was confined to the Minneapolis site and was available for  
23 20,052 (30%) of participants in the CAC Consortium (18), or 10,374 for the purposes of this

1 analysis of patients with prevalent CAC. Mean density, rather than calculated peak density, was  
2 used for the purpose of density-based analyses as this was measured directly at the patient level.  
3 In order to determine the relationship between calcified vessels involved to mean density and  
4 mean area, we performed linear regression separately for mean density (modeled as a continuous  
5 variable) and mean area (log-transformed and modeled as a continuous variable) with  
6 adjustments for age, sex, study site, and CAC score.

### 7 2.3 Number of Vessels and Index of Diffusion

8 For any given calcium score, vessel involvement was categorized from 1 to 4 vessels. For  
9 those with  $\geq 2$  vessel CAC involvement, diffuseness was described using ID. Consistent with  
10 prior literature, this was calculated by taking each vessel's Agatston score and dividing it by the  
11 total Agatston score, i.e. the proportion that each vessel contributes to the total Agatston score  
12 ( $ID = 1 - (CAC \text{ in most concentrated vessel} / \text{total Agatston score})$ ) (13). A higher ID indicates  
13 more diffuse calcified coronary disease, and a lower ID indicates a less diffuse phenotype. For  
14 each grouping of number of vessels (i.e., 2-, 3-, or 4-vessel involvement), we identified the  
15 25<sup>th</sup> & 75<sup>th</sup> percentile for ID. Consistent with prior literature, a "diffuse" phenotype was defined  
16 when the ID was greater than the 75<sup>th</sup> percentile for the respective number of vessel  
17 category. Similarly, the phenotype was categorized as "concentrated" if the ID was less than the  
18 25<sup>th</sup> percentile. Given that the Agatston score takes area into consideration, we have performed  
19 sensitivity analyses using an area-based ID, which considers the area of each calcified vessel as a  
20 proportion of the total calcified area.

### 21 2.4 Risk factor data

22 Clinical risk factors and laboratory-based data were collected either at the visit when  
23 CAC testing was ordered or at the time of CAC testing (18). Hypertension was defined as



1 having a prior diagnosis of hypertension or being treated with anti-hypertensives; dyslipidemia  
2 was defined as having a prior diagnosis of hyperlipidemia or dyslipidemia, being treated with  
3 lipid-lowering therapies, or having low-density lipoprotein cholesterol (LDL-C) >160 mg/dL,  
4 high-density lipoprotein cholesterol (HDL-C) <40 mg/dL in men and <50 mg/dL in women, or  
5 fasting triglycerides >150 mg/dL; Diabetes was defined as a prior diagnosis of diabetes or being  
6 treated with oral hypoglycemics or insulin (18). Family history of CHD was defined as having a  
7 first-degree relative with a presence of CHD; the Columbus, OH site used a definition of  
8 premature family history, i.e., age <55 years old in men or age <65 years in women (18).  
9 Smoking was defined as either a never smoker, a current smoker, or a former smoker (18).

## 10 2.5 Mortality Outcomes

11 Mortality data was ascertained by linking participant data to the Social Security Death  
12 Index Death Master File (SSDIDMF) using a validated algorithm (19). This algorithm uses a  
13 hierarchical matching process of patient identifiers to link to the SSDIDMF database (18).  
14 Mortality data was obtained through June 1<sup>st</sup>, 2014 (18). Cause of death data was obtained  
15 through the National Death Index and were reported using ICD coding and then categorized as  
16 “CVD, cancer, pulmonary disease, gastrointestinal disease, nervous system disorders, endocrine  
17 and metabolic disease, injury and poisoning, or other” (18). CVD includes CHD, stroke,  
18 congestive heart failure, and other circulatory disorders.

## 19 2.6 Statistical Analysis

20 Continuous data are presented as mean (standard deviation) and categorical data as total  
21 number (percentage). Data are presented by the number of vessels that have calcium involvement  
22 and/or ID phenotype. Using ordinal logistic regression, the marginal predicted probability of  
23 number of vessels involved was determined by risk factor status. Predicted probabilities were

1 based on a model which included the CAC score and traditional cardiovascular risk factors.  
2 Increased probability of multi-vessel involvement was expressed as a marginal percentage  
3 increase for each individual risk factor.

4 Absolute event rates of all-cause and cause-specific mortality are presented per 1,000  
5 person-years. Kaplan-Meier curves were used to plot all-cause and cause-specific mortality by  
6 diffusivity group (concentrated, normal, and diffuse), and used the log rank test to determine  
7 whether survival differed among diffuse groups. Multivariable-adjusted Cox proportional hazards  
8 models were used to determine the relative hazard of all-cause and cause specific death  
9 according to number of vessels involved. Models were presented by CAC strata and adjusted for  
10 age, sex, Log(CAC+1), and study site.

11 Data was analyzed using Stata/SE 15. A p-value of <0.05 was considered statistically  
12 significant.

### 13 3. RESULTS

#### 14 3.1 Baseline Characteristics

15 Among the 66,636 participants in the CAC Consortium, 28,147 (58.3 years old (SD  
16 10.3), 25% female, and 89.6% white) met inclusion criteria. The percentage of participants with  
17 calcium in only a single vessel was 34.2%, in 2 vessels was 27.1%, and in 3 or 4-vessels was  
18 38.7%. Participants with multivessel involvement were more likely to be older, male, and non-  
19 white. With increasing CAC strata, the proportion of participants with 3- or 4-vessel involvement  
20 also increased (55.4% of participants with CAC  $\geq$  300 vs. 18.1% of participants with CAC=1-  
21 99). Additionally, there were significant differences in number of vessels involved based on the

1 presence of diabetes mellitus ( $p < 0.001$ ), hypertension ( $p < 0.001$ ), hyperlipidemia ( $p < 0.001$ ), and  
2 current smoking ( $p < 0.001$ ) (**Table 1**).

### 3 3.2 CAC Density, Area, and Vessel Involvement

4 In unadjusted analyses, there was a graded decrease in mean calcium density with each  
5 additional vessel involved for those at intermediate CAC scores (100-299) (**Figure 1**). After  
6 adjustment, there was a graded decrease in mean density in all CAC groups. For example, in the  
7 CAC scores  $\geq 300$  group, compared to single vessel involvement, the mean density was lower in  
8 2-, 3-, and 4-vessels (-23.0 HU, -38.7 HU, and -42.9 HU, respectively) (all  $p < 0.001$ ) (**Table 2**).  
9 Full results for mean CAC density and mean CAC area as a function of number of vessels with  
10 CAC abnormality are shown in **Table 2**. A sensitivity analysis was conducted stratifying by area  
11 tertiles rather than CAC groupings and was consistent with these results (**Appendix Table 2A**).  
12 Among those with CAC scores greater than 300, there was a 4 unit increase in area among 2-  
13 vessels, 6 unit increase in area among 3-vessels, and 6 unit increase in area among 4-vessels,  
14 compared to single vessel involvement. A sensitivity analysis was performed excluding MDCT  
15 scans and was consistent with these findings.

### 16 3.3 Index of Diffusion Phenotypes and Predictors

17 Of the 18,516 participants with  $\geq 2$  vessels with CAC involvement there was substantial  
18 heterogeneity in CAC phenotype. Among our cohort, 5,133 (27.7%) had a concentrated  
19 phenotype, 7,158 (38.7%) had a normal phenotype, and 6,225 (33.6%) had a diffuse phenotype.  
20 Those with a concentrated, normal and diffuse phenotype had an ID of 10.3 (SD 6.1), 32.7 (SD  
21 8.3) and 49.3 (SD 8.1), respectively.

1 Through ordered logistic regression diabetes mellitus ( $p < 0.001$ ), hypertension ( $p < 0.001$ ),  
2 and hyperlipidemia ( $p < 0.001$ ) were predictive of increased vessel involvement. The presence of  
3 diabetes, hypertension, and hyperlipidemia were associated with an increase of 11.1%, 9.9%, and  
4 7.5%, respectively, in the likelihood of having 3- or 4-vessel disease compared to the absence of  
5 each risk factor, respectively.

### 6 3.4 Cause-specific mortality

#### 7 Absolute Event Rates per 1,000 patient-years

8 There was a graded increase in all-cause mortality and cause-specific mortality based on  
9 the number of vessels involved. For all-cause mortality, there was a 4-fold increase comparing 4-  
10 vessel involvement to 1-vessel involvement; for CVD-specific mortality, there was a 7-fold  
11 increase comparing 4-vessel involvement to 1-vessel involvement; and for CHD-specific  
12 mortality, there was 10-fold increase comparing 4-vessel involvement to 1-vessel involvement  
13 (**Table 3**). When analyzing only those with  $\geq 2$  vessel involvement in ID groupings, comparing  
14 a diffuse phenotype to a concentrated phenotype, the effect size was more modest—1.7-fold  
15 increase for all-cause mortality, 1.9-fold increase for CVD-specific mortality, and 2.2-fold  
16 increase for CHD-specific mortality (**Table 3**). Absolute event rates using an area-based ID  
17 demonstrated similar trends with a stepwise increase from concentrated to diffuse for all-cause,  
18 CVD-specific, and CHD-specific (**Appendix Table 3A**).

#### 19 Mortality Estimates by Vessel Number and Index of Diffusion

20 In both a minimally adjusted model, there was a significant increase in All-Cause  
21 mortality for those with 3- or 4-vessel disease compared to those with 1-vessel disease (1.3 [95%  
22 CI 1.2 to 1.5] and 1.5 [95% CI 1.2 to 1.7], respectively). For both CVD-specific and CHD-

1 specific, there was a stepwise increase with each successive vessel included (**Table 4**). After  
2 further adjustment with clinical risk factors, such as hypertension, diabetes, and dyslipidemia,  
3 there was a 2-fold higher risk of CHD-specific mortality with 2-vessel disease (2.0 [95% CI 1.3  
4 to 3.0]), and roughly a 3-fold higher increase for 3-vessel and 4-vessel disease (3.0 [95% CI 2.0  
5 to 4.5] and 3.2 [95% CI 2.1 to 5.0], respectively) (**Table 4**).

6 In unadjusted survival analyses stratified by ID phenotype, there were significant  
7 differences in all-cause mortality ( $p < 0.001$ ) and a trend towards significance for CVD-specific  
8 mortality ( $p = 0.06$ ). After adjustment these differences were not significant and there was only a  
9 trend towards higher all-cause, CVD-specific, or CHD-specific mortality. Full results are  
10 reported in **Table 4** and **Figure 2**.

#### 11 4. DISCUSSION

12 In this retrospective analysis of participants with any CAC, we explored CAC dispersion  
13 —defined either by vessel number or by ID phenotypes—and its association with cause-specific  
14 mortality. Diffuse disease, determined by vessel number, was associated with increased mortality  
15 from CVD, CHD, or any cause. When restricting to individuals with 2 or more calcified vessels,  
16 there was a similar all-cause and cause-specific mortality trend comparing the diffuse phenotype  
17 to a concentrated phenotype, though this did not reach significance.

18 We found significant differences in the prevalence of diffuse disease based on sex, race,  
19 and CAC score groupings. Traditional risk factors such as diabetes, hypertension, and  
20 hyperlipidemia were significant predictors of more diffuse 3- or 4-vessel involvement. Previous  
21 studies using other testing modalities have found that diabetes (20-24), hypertension (24), and  
22 dyslipidemia (24) are associated with more extensive disease. Autopsy data ( $n = 2,029$ ) has shown

1 high-grade multivessel atherosclerotic disease in 58% of diabetic patients compared to 41% non-  
2 diabetic patients ( $p < 0.001$ ) (22). In decedents who did not have clinical signs of atherosclerosis,  
3 50% of diabetic individuals were found to have multivessel disease compared to 31% of non-  
4 diabetic individuals (22), raising the specter of diabetes being an important marker of subclinical  
5 multivessel disease. Angiographically, in a study of over 600 participants, individuals 3-vessel  
6 disease were more like to have diabetes compared to those without diabetes ( 47.1% vs 27.6%,  
7  $p < 0.001$ ) (25). Valsania et al. similarly found that not only was diabetes associated with more  
8 severe 3-vessel disease (47% with  $>70\%$  stenosis compared to 6%), but was also associated with  
9 more distal coronary involvement compared to nondiabetic individuals (26).

10 Prior studies involving coronary computed tomography angiography (CCTA) have since  
11 demonstrated the power of non-invasive detection of multivessel disease among patients with  
12 diabetes, hyperlipidemia, or hypertension (21,24). Blanke et al. found that diabetic participants  
13 had 2-vessel or 3-vessel/left main disease at almost 50% higher rates of their non-diabetic  
14 counterparts and that this was associated with a 2.6 higher hazard ratio of all-cause mortality  
15 (21). Tomizawa and colleagues described similar findings among participants with hypertension  
16 or hyperlipidemia (24). In their study of 1,161 participants, they found much higher segmental  
17 severity scores in participants with hypertension, dyslipidemia, and diabetes— $2.7 \pm 4.3$  segments  
18 involved for hypertension,  $4.0 \pm 4.8$  for diabetes, and  $2.0 \pm 3.7$  for hyperlipidemia—compared to  
19 no risk factors ( $0.8 \pm 1.8$  segments, all  $p < 0.0005$  compared to none) (24). The authors also found  
20 that these risk factors were associated with higher CAC scores but did not describe the  
21 distribution of CAC disease (24). Other studies have demonstrated associations between CAC  
22 score in subgroups of participants with diabetes, hypertension, and dyslipidemia, but do not  
23 describe the extent of disease or vessel involvement (27). To the best of our knowledge, our

1 study is the first to demonstrate these risk factors can predict more diffuse involvement on CAC  
2 testing.

3 The ability to non-invasively characterize, quantify, and describe the phenotypes of  
4 calcific disease is an important new paradigm in risk characterization. This paradigm emphasizes  
5 the notion that total plaque burden and diffuse involvement may present a more precise  
6 assessment of risk, which, in turn, will provide more targeted, aggressive therapeutics. The  
7 CCTA literature provides evidence for this—Bittencourt et al., in a study of over 3,000  
8 individuals without a prior history of coronary artery disease, provide evidence that those with  
9 extensive disease (defined as multiple segments involved) had higher rates of CVD mortality and  
10 myocardial infarctions (28). Building on this, they found that a risk prediction model that  
11 included plaque distribution—defined by segment involvement score—in addition to disease  
12 severity (obstructive vs. nonobstructive) and traditional clinical variables—performed best (28).

13 Tota-Maharaj and colleagues, in a study of almost 1,000 individuals, reported significant  
14 heterogeneity in CAC distribution, particularly among those with intermediate CAC scores  
15 (CAC 1-400) (29). For instance, 54% of individuals with CAC>400 had 4-vessel disease  
16 compared to 20% and 2% of individuals with CAC = 101-400 and CAC 1-100, respectively (29).  
17 They also demonstrated that multivessel CAC involvement better approximated increases in  
18 segmental involvement score on CTA (29). In a subsequent study of 23,058 participants, Tota-  
19 Maharaj et al. found a stepwise increase in mortality rates per 1000 person-years for each  
20 additional calcified vessel (30). Our findings echo these and highlight that increasing vessel  
21 involvement is a poor prognostic marker among those with calcified coronary vessels.

22 Building on these earlier observations, the Society of Cardiovascular Computed  
23 Tomography (SCCT), developed a way of incorporating vessel number into CAC reports—the

1 CAC-Data Reporting System (CAC DRS) (31). The CAC DRS proposes a standardized  
2 approach to reporting that incorporates the Agatston score or visual assessment with the vessel  
3 number (31). As this would help to more accurately stratify individuals, increasing CAC DRS  
4 scores could lead to more intensive therapy and risk factor modification (31). Subsequent  
5 analyses that have specifically incorporated the CAC DRS score have confirmed its performance  
6 in stratifying ASCVD events (32).

7         Our findings provide additional evidence for the importance of incorporating markers of  
8 CAC dispersion into both reporting and practice. It stands to reason that incorporating CAC  
9 distribution, in addition to total CAC score, allows for a better approximation of total plaque  
10 burden, which is a more precise predictor of subsequent cardiovascular death. Blaha et al.  
11 confirmed this in a study from the Multi-Ethnic Study of Atherosclerosis cohort, which  
12 demonstrated that diffuse disease within CAC groupings portends a significantly poorer  
13 prognosis (13) and by including these regional findings to CAC score the discriminatory  
14 capabilities improve (13). As a result, a working group proposed that the next iteration of CAC  
15 scoring might incorporate these findings—regional distribution, diffusivity, lesion-specific  
16 characteristics, and location of calcified disease—and might be particularly important for those  
17 with CAC scores in an intermediate range (33). Our findings provide evidence of incorporating  
18 these methods into clinical practice.

19         Our study has a few limitations to note—first, those who were referred for CAC testing  
20 were done so at physician discretion for the purpose of ASCVD risk-stratification, and as such,  
21 may not be representative of individuals who undergo testing for other reasons. Second, this  
22 study is also a retrospective, observational design study and suffers from the possibility of  
23 additional unmeasured confounding despite our best attempt to control for these. Third, our



1 description of dispersion does not approximate other types of diffuse phenotypic definitions, such  
2 as proximal versus distal disease and overall number of plaques. Lastly, measurements of mean  
3 CAC density were calculated at the patient level rather than the lesion-specific level, and it  
4 remains uncertain whether lesion-specific CAC features meaningfully add to risk prediction.

5         In summary, we have shown that specific traditional risk factors are associated with a  
6 more diffuse CAC distribution and that increasing vessel number is associated all-cause and  
7 cause-specific mortality. Further restricting to individuals with 2 or more calcified vessels using  
8 the ID demonstrated a modest trend of increasing all-cause and cause-specific mortality but was  
9 not statistically significant. Incorporating details of CAC distributions is important to consider in  
10 future CAC score algorithms and in guiding clinical management towards intensification of  
11 preventive measures.

12

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4

5 7. AUTHOR CONTRIBUTIONS

6 RD, MJB designed the study and contributed most to manuscript preparation. ZAD

7 performed data analysis. All other authors contributed equally with conceptualization, access to

8 data and critical editing.

9

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1 9. FIGURES AND TABLES

2 **Table 1. Baseline Characteristics of Study Cohort\***

Characteristic	Number of Vessels with CAC				
	1 Artery (N= 9,631)	2 Arteries (N= 7,622)	3 Arteries (N= 7,434)	4 Arteries (N= 3,460)	All (N=28,147)
Age, mean (SD) ‡	54.6 (9.5)	57.6 (10.0)	60.9 (10.0)	64.2 (10.0)	58.3 (10.3)
Sex ‡					
Female	3,112 (32.3)	1,947 (25.5)	1,457 (19.6)	526 (15.2)	7,042 (25.0)
Male	6,519 (67.7)	5,675 (74.5)	5,977 (80.4)	2,934 (84.8)	21,105 (75.0)
Race (N=23,039) †					
Black	167 (2.1)	135 (2.2)	158 (2.6)	66 (2.3)	526 (2.3)
White	7,206 (90.8)	5,523 (89.5)	5,328 (88.6)	2,590 (89.0)	20,647 (89.6)
All Others	565 (7.1)	516 (8.3)	531 (8.8)	254 (8.7)	1,866 (8.1)
Current Smoking‡	893 (9.3)	781 (10.3)	839 (11.3)	370 (10.7)	2,883 (10.2)
Diabetes‡	538 (5.6)	579 (7.6)	864 (11.6)	540 (15.6)	2,521 (9.0)
Family History of CHD	4,746 (49.3)	3,699 (48.5)	3,648 (49.1)	1,705 (49.3)	13,798 (49.0)
Hypertension‡	2,814 (29.2)	2,804 (36.8)	3,278 (44.1)	1,758 (50.8)	10,654 (37.9)
Hyperlipidemia‡	5,616 (58.3)	4,824 (63.3)	4,975 (66.9)	2,439 (70.5)	17,854 (63.4)
CAC Score Group‡					
CAC = 1-99	8,845 (91.8)	4,861 (63.8)	1,745 (23.5)	228 (6.6)	15,679 (55.7)
CAC = 100-299	717 (7.4)	1,963 (25.8)	2,255 (30.3)	634 (18.3)	5,569 (19.8)
CAC = 300+	69 (0.72)	798 (10.5)	3,434 (46.2)	2,598 (75.1)	6,899 (24.5)
Index of Diffusion‡					
Concentrated	9,631 (100)	3,170 (41.6)	1,624 (21.9)	339 (9.8)	14,764 (52.5)
Normal	0 (0)	2,128 (27.9)	3,305 (44.5)	1,725 (49.9)	7,158 (25.4)
Diffuse	0 (0)	2,324 (30.5)	2,505 (33.7)	1,396 (40.4)	6,225 (22.1)
*Data are presented as No. (%) unless otherwise indicated					
† $p < 0.05$ , ‡ $p < 0.001$					

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1 **Table 2. Mean CAC Density and Mean CAC Area by Number of Vessels with CAC**

		<b>Number of Vessels</b>			
		<b>1 Artery</b>	<b>2 Arteries</b>	<b>3 Arteries</b>	<b>4 Arteries</b>
<b>Mean Density</b> <sup>*,‡</sup>	CAC Score Group CAC = 1-99	1 (ref)	-19.4 (-20.9 to -17.9)	-33.0 (-35.4 to -30.6)	-40.6 (-46.6 to -34.4)
	CAC = 100-299	1 (ref)	-29.9 (-34.9 to -24.8)	-43.8 (-48.9 to -38.8)	-51.6 (-57.9 to -45.4)
	CAC = 300+	1 (ref)	-23.0 (-36.3 to -9.7)	-38.7 (-51.6 to -25.9)	-42.9 (-55.9 to -30.0)
<b>Area</b> <sup>*</sup>	CAC Score Group CAC = 1-99	1 (ref)	1.10 (1.08 to 1.11)	1.11 (1.09 to 1.14)	1.09 (1.03 to 1.15)
	CAC = 100-299	1 (ref)	1.02 (1.01 to 1.03)	1.05 (1.04 to 1.06)	1.07 (1.06 to 1.09)
	CAC = 300+	1 (ref)	1.04 (1.02 to 1.06)	1.06 (1.04 to 1.08)	1.06 (1.04 to 1.08)
Density is measured in HU, Area is measured in mm <sup>2</sup>					
*Model includes age (as a continuous variable), sex, calcium score, and study site.					
† p<0.05, ‡ p<0.001					

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3 **Table 3. Absolute Event Rates per 1000 patient-years by Vessel Number and Diffusivity**

		<b>All-cause Mortality</b>	<b>CVD* Mortality</b>	<b>CHD Mortality</b>
<b>Number of Vessels</b>	1-Vessel	3.3 (3.0 to 3.7)	0.7 (0.6 to 0.9)	0.3 (0.2 to 0.4)
	2-Vessel	4.9 (4.4 to 5.3)	1.5 (1.3 to 1.8)	0.8 (0.6 to 1.0)
	3-Vessel	8.2 (7.6 to 8.9)	3.2 (2.8 to 3.6)	1.8 (1.6 to 2.2)
	4-Vessel	12.9 (11.8 to 14.2)	5.1 (4.4 to 5.9)	3.0 (2.5 to 3.7)
<b>Index of Diffusion</b>	Concentrated	5.3 (4.8 to 6.0)	1.8 (1.5 to 2.2)	0.9 (0.7 to 1.2)
	Normal	8.2 (7.6 to 8.8)	3.1 (2.7 to 3.5)	1.7 (1.4 to 2.0)
	Diffuse	8.9 (8.2 to 9.6)	3.4 (2.9 to 3.8)	2.0 (1.7 to 2.4)

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2 **Table 4. Hazard Ratios of All-cause and cause-specific mortality by number of vessels and Index of Diffusion (ID)**

	Model 1			Model 2		
	All-Cause Mortality	CVD-specific Mortality	CHD-specific Mortality	All-Cause Mortality	CVD-specific Mortality	CHD-specific Mortality
<b>Vessel Number</b>						
<b>1-Vessel</b>	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
<b>2-Vessel</b>	1.1 (0.99 to 1.3)	<b>1.6</b> <b>(1.2 to 2.1)</b>	<b>2.0</b> <b>(1.3 to 3.1)</b>	1.1 (0.97 to 1.3)	<b>1.5</b> <b>(1.2 to 2.0)</b>	<b>2.0</b> <b>(1.3 to 3.0)</b>
<b>3-Vessel</b>	<b>1.3</b> <b>(1.2 to 1.5)</b>	<b>2.2</b> <b>(1.7 to 2.9)</b>	<b>3.2</b> <b>(2.1 to 4.8)</b>	<b>1.3</b> <b>(1.1 to 1.5)</b>	<b>2.1</b> <b>(1.6 to 2.7)</b>	<b>3.0</b> <b>(2.0 to 4.5)</b>
<b>4-Vessel</b>	<b>1.5</b> <b>(1.2 to 1.7)</b>	<b>2.4</b> <b>(1.8 to 3.2)</b>	<b>3.5</b> <b>(2.3 to 5.5)</b>	<b>1.4</b> <b>(1.2 to 1.6)</b>	<b>2.2</b> <b>(1.7 to 3.0)</b>	<b>3.2</b> <b>(2.1 to 5.0)</b>
<b>Index of Diffusion (Only ≥ 2 vessels)</b>						
<b>Concentrated</b>	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
<b>Normal</b>	1.04 (0.9 to 1.2)	1.04 (0.9 to 1.3)	1.04 (0.8 to 1.4)	1.02 (0.91 to 1.2)	1.02 (0.8 to 1.3)	1.03 (0.8 to 1.3)
<b>Diffuse</b>	1.1 (0.98 to 1.3)	1.1 (0.9 to 1.4)	1.2 (0.9 to 1.6)	1.1 (0.97 to 1.3)	1.1 (0.9 to 1.4)	1.1 (0.8 to 1.6)
†Model 1 includes age (as a continuous variable), sex, study site, and Agatston CAC score (continuous).						
‡Model 2 includes Model 1 + hypertension, dyslipidemia, and diabetes						
* CVD mortality includes the following: other circulatory disorder, CHD, stroke, and congestive heart failure.						

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**1 Figure 1. Density of Calcium per Vessel Stratified by CAC Groupings**

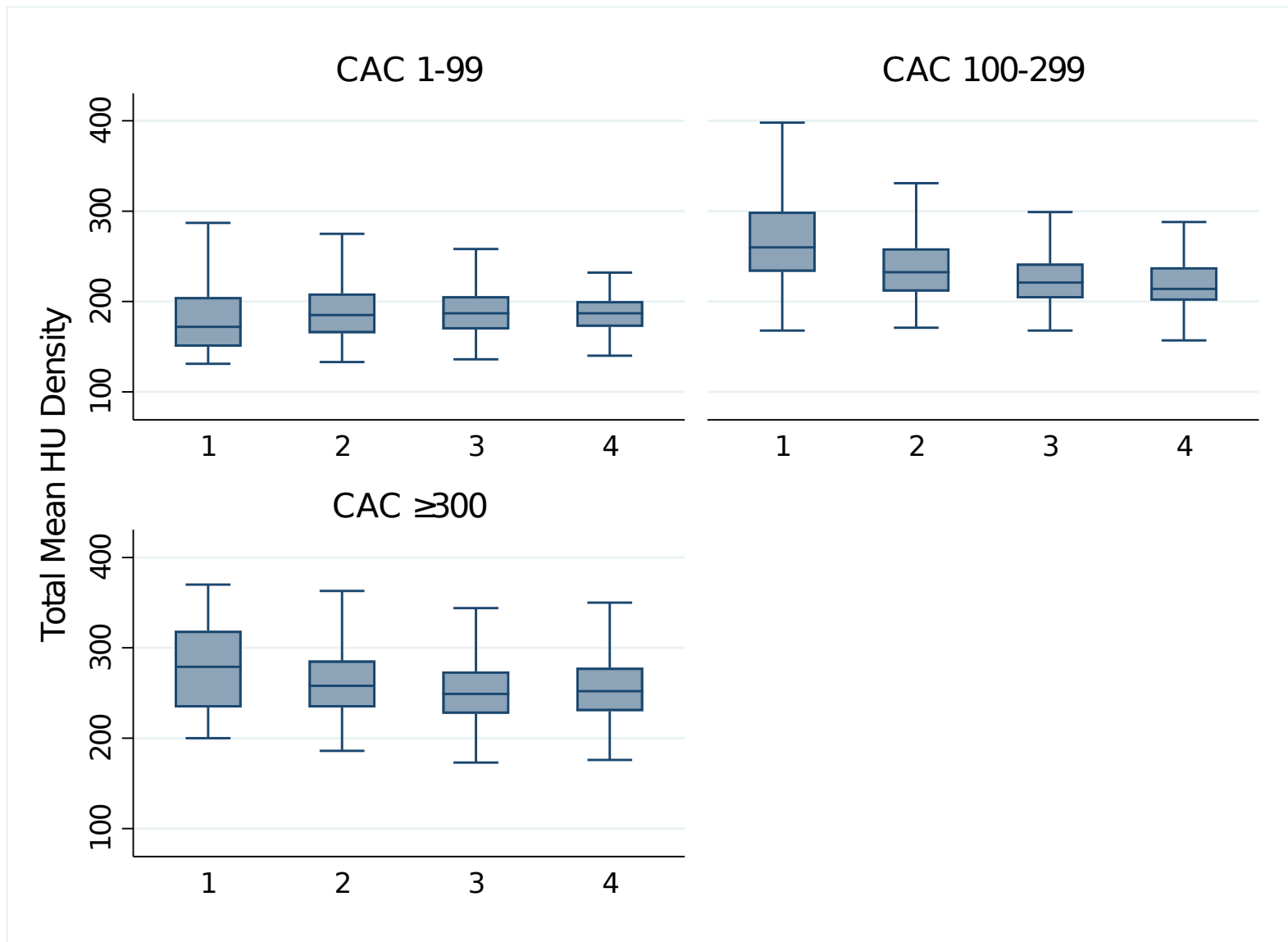
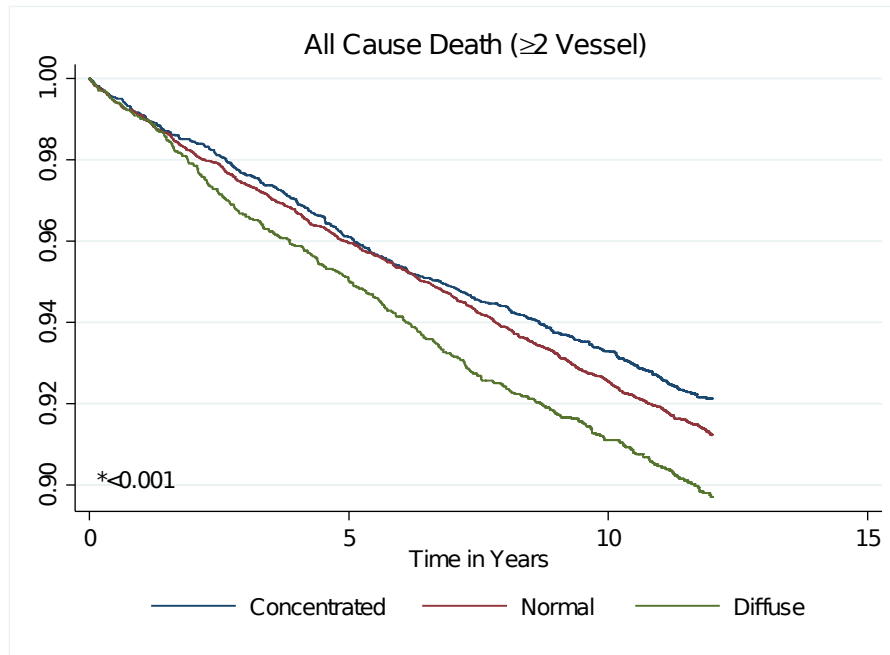
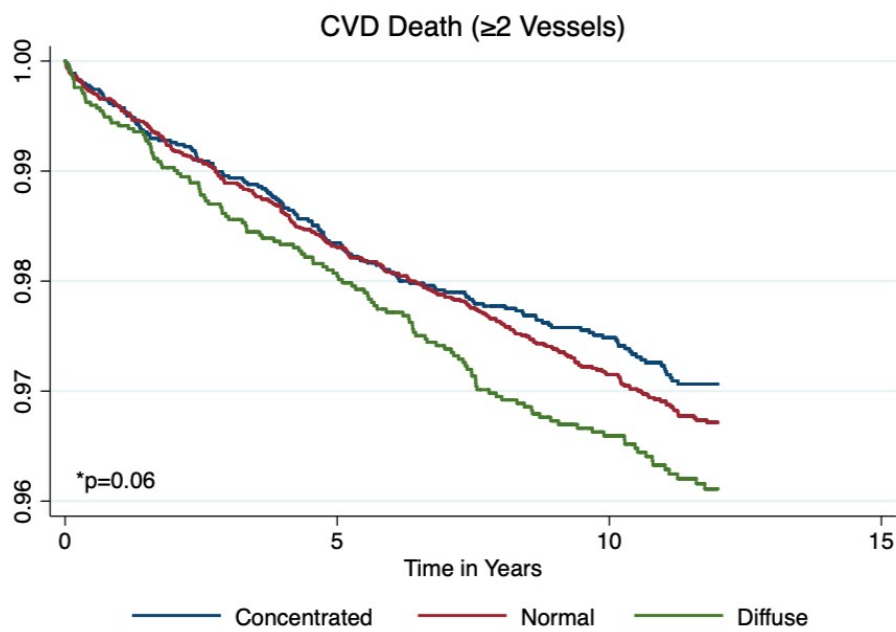


Figure 2. All-cause

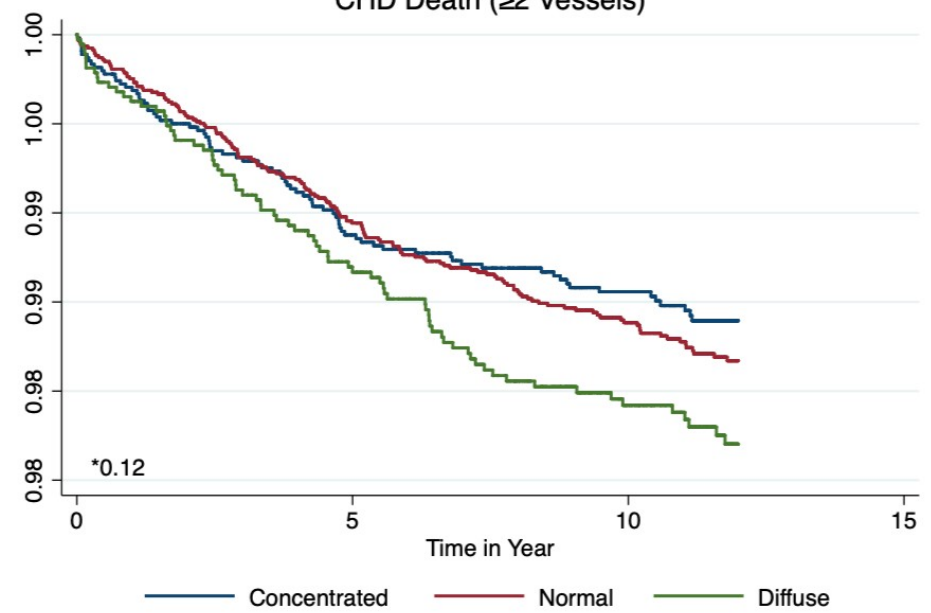
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2 and cause-specific mortality Kaplan-Meier Curves by Index of Diffusion



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**CHD Death ( $\geq 2$  Vessels)**



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1 Appendix Tables

2 **Table 2A. Mean CAC Density and Mean CAC Area by Number of Vessels with Area**  
 3 **Tertiles**

		Number of Vessels			
		1 Artery	2 Arteries	3 Arteries	4 Arteries
<b>Mean Density</b> <sup>*‡</sup>	CAC Area Tertiles				
	1 <sup>st</sup> Tertile	1 (ref)	-14.6 (-15.9 to -13.3)	-24.7 (-27.7 to -21.8)	-28.7 (-40.4 to -17.1)
	2 <sup>nd</sup> Tertile	1 (ref)	-27.4 (-30.2 to -24.7)	-40.9 (-44.1 to -37.7)	-48.4 (-54.1 to -42.7)
	3 <sup>rd</sup> Tertile	1 (ref)	-32.3 (-40.4 to -24.2)	-48.9 (-56.7 to -41.1)	-53.7 (-61.7 to -45.7)
<b>Area</b> <sup>*‡</sup>	CAC Area Tertiles				
	1 <sup>st</sup> Tertile	1 (ref)	1.13 (1.11 to 1.16)	1.17 (1.11 to 1.22)	1.1 (0.9 to 1.4)
	2 <sup>nd</sup> Tertile	1 (ref)	1.05 (1.04 to 1.06)	1.09 (1.08 to 1.10)	1.11 (1.09 to 1.13)
	3 <sup>rd</sup> Tertile	1 (ref)	1.02 (1.00 to 1.03)	1.03 (1.02 to 1.04)	1.04 (1.03 to 1.05)
Density is measured in HU, Area is measured in mm <sup>2</sup>					
*Model includes age (as a continuous variable), sex, calcium score, and study site.					
† $p < 0.05$ , ‡ $p < 0.001$					

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 5 **Table 3A. Absolute Event Rates per 1000 patient-years by Area-based Diffusivity**

		All-cause Mortality	CVD* Mortality	CHD Mortality
<b>Index of Diffusion</b>	Concentrated	8.5 (7.5 to 9.6)	2.9 (2.3 to 3.6)	1.5 (1.1 to 2.0)
	Normal	9.1 (8.4 to 10.0)	3.1 (2.6 to 3.5)	1.6 (1.3 to 2.0)
	Diffuse	9.9 (8.8 to 11.1)	3.8 (3.1 to 4.6)	2.0 (1.5 to 2.6)

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