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Prognostic implications of coronary artery calcium in the absence of coronary artery luminal narrowing

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ABSTRACT

Background and aims: Coronary artery calcium (CAC) scoring is a predictor of future adverse clinical events, and a surrogate measure of overall coronary artery plaque burden. Coronary computed tomographic angiography (CCTA) is a contrast-enhanced method that allows for visualization of plaque as well as whether that plaque causes luminal narrowing. To date, the prognosis of individuals with CAC but without stenosis has not been reported. We explored the prevalence of CAC>0 and its prognostic utility for future mortality for patients without luminal narrowing by CCTA.

Methods: From 17 sites in 9 countries, we identified patients without known coronary artery disease, who underwent CAC scoring and CCTA, and were followed for >3 years. CCTA was graded for % stenosis

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according to a modified American Heart Association 16-segment model. We calculated hazard ratios (HR) with 95% confidence intervals (95% CI) for incident mortality and compared risk of death for patients as a function of presence or absence of CAC and presence or absence of luminal narrowing by CCTA.

Results: Among 6656 patients who underwent CCTA and CAC scoring, 399 patients (6.0%) had no coronary luminal narrowing but CAC>0. During a median follow-up of 5.1 years (IQR: 3.9–5.9 years), 456 deaths occurred. Compared to individuals without luminal narrowing or CAC, individuals without luminal narrowing but CAC>0 were older, more likely to be male and had higher rates of diabetes, hypertension, and dyslipidemia. Individuals without luminal narrowing but CAC experienced a 2-fold increased risk of mortality, with increasing risk of mortality with higher CAC score. Following adjustment, incident death persisted (HR, 1.8; 95% CI, 1.1–2.9, $p = 0.02$) among patients without luminal narrowing but with CAC>0 compared with patients whose CACS = 0. Individuals without luminal narrowing but CAC ≥ 100 had mortality risks similar to individuals with non-obstructive CAD (0 < stenosis < 50%) by CCTA [HR 2.5 (95% CI 1.3–4.9) and 2.2 (95% CI 1.6–3.0), respectively].

Conclusions: Patients without luminal narrowing but with CAC experience greater risk of 5-year mortality. Patients with CAC score ≥ 100 and no coronary luminal narrowing experience death rates similar to those with non-obstructive CAD.

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1. Introduction

Coronary artery calcium (CAC) scoring is a useful non-contrast enhanced imaging method for visualization of calcified coronary plaque, and represents a surrogate marker of overall plaque burden independent of stenosis severity. Prior population-based studies have established the relationship between CAC and worsened cardiovascular prognosis [1–3]. Coronary computed tomographic angiography (CCTA) is a non-invasive imaging modality with high diagnostic accuracy for diagnosis of coronary luminal stenosis and atherosclerotic plaque [4,5], the latter of which may exist in the absence of coronary luminal diameter reduction due to positive arterial remodeling. To date, the prognostic implications of CAC in the absence of coronary luminal narrowing remains unknown. The present prospective multicenter study was set out to examine the prevalence and prognosis of CAC, in the absence of coronary luminal narrowing, in patients without clinical manifestations of coronary artery disease (CAD).

2. Materials and methods

The initial study design and rationale of the CONFIRM (COronary CT Angiography EvaluationN For Clinical Outcomes: An InteRnational Multicenter) registry has been described previously [6]. In brief, the CONFIRM registry was designed to evaluate the ability of CCTA findings to predict mortality and major adverse cardiac events in patients with chronic CAD. For the current study, we utilized data from the CONFIRM long-term follow-up registry, which only included patients who had a follow-up duration of more than 3 years. Overall, 17181 patients who underwent CCTA at 17 centers in 9 countries (Austria, Canada, Germany, Israel, Italy, Portugal, South Korea, Switzerland, and United States) were enrolled between February 2003 and May 2011 for long-term follow-up. Inclusion criteria were age 18 years or older, an evaluation by CCTA scanner with 64-detector rows or greater, and the presence of interpretable CCTA. For the current study, we excluded patients according to the following exclusion criteria: the absence of CAC data ($n = 9626$) or CCTA stenosis information ($n = 214$), the absence of age or gender information ($n = 12$), or prior history of CAD ($n = 639$). The analytic sample comprised 6656 patients. Each of the study centers' institutional review boards approved the study protocol, and all study participants provided written informed consent.

CCTA and CAC data were acquired using multi-detector row CT scanners consisting of 64-rows or greater. Expert imagers

(cardiologists and radiologists) analyzed all CCTA images and measured CAC. Data acquisition, image post-processing, and data interpretation were performed according to the guidelines of the Society of Cardiovascular Computed Tomography (SCCT) [7–9]. CAC were measured using the scoring system (in units) developed by Agatston et al. [10]. For CCTA, we defined the coronary atherosclerosis as any tissue structures larger than 1 mm², which were either within the lumen of the coronary artery or adjacent to the coronary artery lumen that could be distinguished from adjacent epicardial fat, pericardial tissue, or the artery lumen itself. We examined all identified lesions by maximum-intensity-projection and multi-planar reconstruction techniques, along multiple longitudinal axes, and in the transverse plane. For the current analyses, we used a modified American Heart Association (AHA) 16-segment coronary artery tree model [11]: left main; proximal, mid and distal left anterior descending (LAD) artery; first and second diagonal branches of the LAD; proximal and distal left circumflex artery; first and second obtuse marginal branches of the left circumflex artery; proximal, mid and distal right coronary artery; posterior descending artery; and postero-lateral branches (left or right). Coronary artery luminal narrowing was defined as the presence of any plaque resulting in a % diameter reduction >0: obstructive stenosis was defined as coronary artery plaques imparting luminal diameter stenosis $\geq 50\%$, while non-obstructive stenosis was defined as coronary artery segments displaying plaque with a luminal diameter stenosis 1–49%. The total mean dose length product for CCTA and coronary artery calcium scans was estimated to be 883 ± 379 mGy \times cm, corresponding to an estimated radiation dose of 12 ± 5 mSv [12].

2.1. Patient follow-up

The primary outcome of the current study was all-cause mortality. Trained personnel from each participating institution adjudicated the study endpoint via direct interview with physicians, next-of-kin and/or witnesses, by review of hospital records, or by querying of national medical databases. All patients were questioned using a scripted interview, and all procedures were confirmed by review of the patients' medical record.

2.2. Statistical methods

Continuous variables are expressed as means \pm standard deviation (SD), and categorical variables are presented as numbers with proportions. Differences between continuous variables among

patient groups according to CCTA and CAC findings were performed using one-way ANOVA with Bonferroni correction for *post-hoc* analyses. Differences between categorical variables were analyzed by χ^2 test or Fisher's exact test, as appropriate. We fashioned a Kaplan–Meier curve to obtain the cumulative event rates as a function of time, with each survival curve compared using the log-rank test. Univariable and multivariable Cox regression models, with adjustment of Framingham risk scores reporting hazard ratios (HR) with 95% confidence limits (95% CI), were calculated to identify associations between CCTA and CAC variables with the study outcome. We evaluated the risk of death specifically comparing patients without luminal narrowing by CCTA but with CAC score >0 with subgroups of patients classified on the background of CAC and non-obstructive or obstructive CAD, as detected by CCTA.

3. Results

Among 6656 patients who underwent both CCTA and CAC scanning, 2166 (32.5%) individuals were identified as having no luminal stenosis by CCTA and CACS = 0 (Table 1). Conversely, 399 (6.0%) patients had no luminal narrowing by CCTA but CAC score >0 (Fig. 1). Among these, 296 (4.4%) and 103 (1.6%) patients without stenosis by CCTA were identified as having a CAC score between 1 and 99 and ≥ 100 , respectively. Patients without luminal narrowing by CCTA but CAC score >0 tended to be older, predominantly male, more hypertensive, diabetic, and dyslipidemic than those without luminal narrowing by CCTA and CACS = 0 (all $p < 0.001$) (Table 2). Compared to patients with non-obstructive or obstructive stenosis, patients without luminal narrowing by CCTA but CAC >0 were younger ($p < 0.001$), with a lower prevalence of hypertension ($p < 0.001$), dyslipidemia ($p = 0.017$), and active smoking ($p = 0.005$).

During a median follow-up of 5.1 years (interquartile range: 3.9–5.9 years), 456 deaths occurred. Patients without luminal narrowing by CCTA but with CAC experienced a significantly higher rate of death than patients without luminal narrowing by CCTA and no CAC ($p = 0.005$) (Fig. 2). This increased risk was similar to that imparted by the presence of non-obstructive coronary stenosis by CCTA ($p = 0.229$), but lower than that conferred by the presence of obstructive coronary stenosis by CCTA ($p < 0.001$).

Among the 2166 patients without stenosis and no CAC, 61 deaths occurred with a 5-year cumulative mortality of 2.9% (95% CI, 2.2%–3.8%) (Table 3). In contrast, 23 deaths occurred among the 399 patients without luminal narrowing but with CAC >0 , with a 5-year cumulative mortality of 6.2% (95% CI, 4.0%–9.6%). The mortality incidence for the 103 patients without stenosis but CAC ≥ 100 was 7.1% (95% CI, 3.2%–15.0%), a rate similar to patients with non-obstructive stenosis [8.1% (95% CI, 7.0%–9.4%)]. Among all groups, patients with obstructive coronary stenosis experienced the highest rates of death (11.6%; 95% CI, 10.0%–13.4%).

Table 1

Distribution of patients according to coronary CT angiography findings and coronary artery calcium score.

CCTA	CAC score	No of patients (%)
No stenosis	0	2166 (32.5%)
	>0	399 (6.0%)
0% < stenosis < 50%	0	2404 (36.1%)
	>0	430 (6.5%)
$\geq 50\%$ stenosis	>0	1974 (29.6%)
	0	1687 (25.4%)
	>0	172 (2.6%)
	>0	1515 (22.8%)

CCTA, coronary CT angiography; CAC, coronary artery calcium.

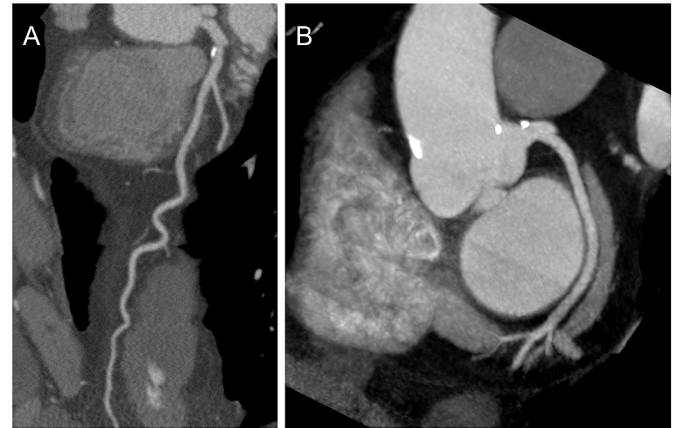


Fig. 1. Representative images of arteries without coronary luminal stenosis but coronary artery calcium.

Calcified plaque in (A) proximal left anterior descending (LAD) and (B) left main coronary artery without luminal narrowing was observed in multiplanar reconstruction images.

In Table 4, univariable Cox regression analyses revealed the presence of CAC in patients without coronary luminal narrowing to be a significant predictor of death (HR, 2.0; 95% CI 1.3–3.3, $p = 0.003$) compared with those without coronary luminal narrowing and no CAC. In those individuals with no coronary luminal narrowing but CAC >0 , risk of all-cause death grew as CAC score increased. After adjustment for the FRS, a 2-fold increased risk of death was observed for individuals with CAC but without coronary luminal narrowing (HR, 1.8; 95% CI, 1.1–2.9, $p = 0.020$) compared with patients without coronary luminal narrowing and no CAC. In subgroup analysis, patients with a CAC score ≥ 100 had a significantly increased risk of death (HR, 2.5; 95% CI, 1.3–4.9) compared with those without coronary luminal narrowing and no CAC and similar risk of death compared with non-obstructive luminal narrowing patients (HR, 2.2; 95% CI, 1.6–3.0).

4. Discussion

In this global multicenter study, we evaluated the prevalence of CAC and its associated prognosis in patients without luminal narrowing by CCTA. Given the long-term follow-up, the multinational enrollment and the large population studied, these findings should be considered to be highly generalizable. We identified a non-negligible frequency of individuals without stenosis but with evident coronary calcium, with 1 of 17 individuals exhibiting this pattern. Individuals with CAC but without luminal narrowing, as compared to individuals without CAC and stenosis, tended to be older, male and with a higher prevalence of traditional coronary heart disease risk factors, including hypertension, dyslipidemia and diabetes. Indeed, the prevalence of diabetes was 2-fold higher for individuals without stenosis and CAC when compared to individuals without stenosis or CAC.

Importantly, we observed a worsened prognosis of individuals without luminal narrowing but with CAC. Compared to individuals without luminal narrowing or CAC, there was a more than 2-fold increased risk of mortality during the 5 years of follow-up. This increased risk exhibited a dose-response curve, with risk of 5-year mortality exceeding 7% for individuals without luminal narrowing but CAC score ≥ 100 , a rate similar to the 8.1% mortality observed for individuals with non-obstructive stenosis by CCTA. The absolute event rates mirrored the relative risk wherein the hazards for death was 2.5 and 2.2 for individuals without luminal narrowing but CAC score ≥ 100 and individuals with non-obstructive stenosis by CCTA,

Table 2
Baseline characteristics of study patients.

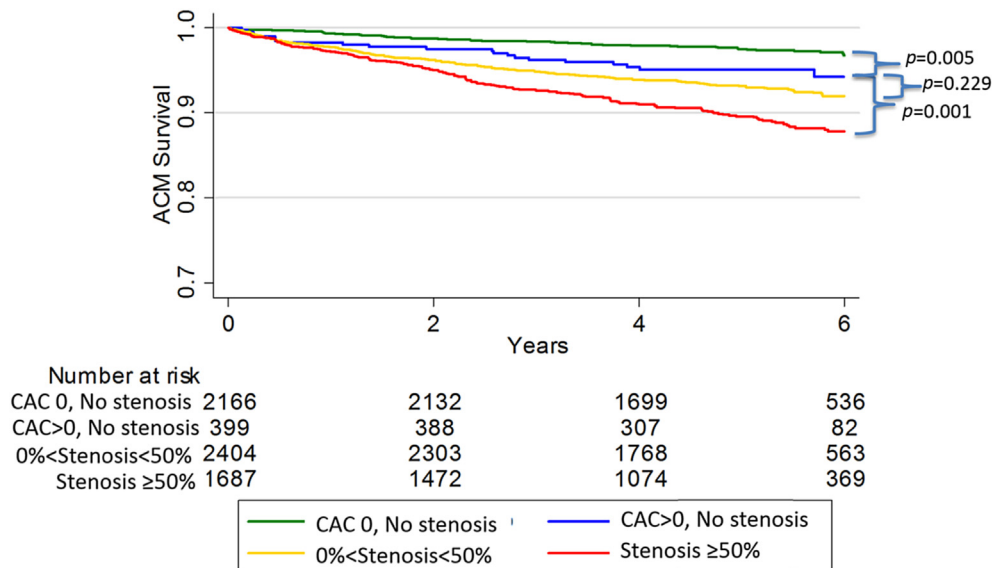
Variables	Total (N = 6656)	CCTA: No stenosis, CAC score = 0 (N = 2166)	CCTA: No stenosis, CAC score > 0 (N = 399)	CCTA: Any stenosis (N = 4091)	p-value for ANOVA
Age (years)	59 ± 13	52 ± 12	60 ± 12*	63 ± 11*†	<0.001
Gender (male)	3947 (59%)	1007 (47%)	250 (63%)*	2690 (66%)*	<0.001
Hypertension	3476 (53%)	858 (40%)	199 (50%)*	2419 (59%)*†	<0.001
Diabetes	973 (15%)	171 (8%)	62 (16%)*	740 (18%)*	<0.001
Current smoking	1216 (18%)	341 (16%)	58 (15%)	817 (20%)*†	<0.001
BMI (kg/m ²)	28 ± 5	27 ± 5	28 ± 6	28 ± 5*	<0.001
Dyslipidemia	3646 (55%)	893 (41%)	223 (57%)*	2530 (62%)*†	<0.001
Total cholesterol, mg/dL	191 ± 45	197 ± 42	181 ± 44*	187 ± 47*	<0.001
LDL cholesterol, mg/dL	113 ± 37	117 ± 35	107 ± 37*	111 ± 38*	<0.001
HDL cholesterol, mg/dL	54 ± 18	57 ± 19	51 ± 17*	52 ± 17*	<0.001

Continuous values are mean ± standard deviation and categorical values are number and percentage (%).

*p < 0.001 compared with patients without luminal narrowing by CCTA and with zero CACS.

†p < 0.05 compared with patients without luminal narrowing by CCTA but with CAC score above zero.

BMI, body mass index; CACS, coronary artery calcium score; CCTA, cardiac computed tomographic angiography; HDL, high density lipoprotein; LDL, low density lipoprotein; N, number.

**Fig. 2.** Kaplan-Meier survival curve for all-cause mortality according to coronary artery calcium score and coronary computed tomographic angiography findings.**Table 3**
Prevalence and rates of mortality as a function of CAC score and CCTA findings.

CCTA	CAC score	Number of events/Total population	5-year KM estimates of event, % (95% CI)
No stenosis	0	61/2166	2.9 (2.2–3.8)
	>0	23/399	6.2 (4.0–9.6)
	1–99	13/296	5.9 (3.5–9.9)
	≥100	10/103	7.1 (3.2–15.0)
0% < stenosis < 50%		156/1974	8.1 (7.0–9.4)
≥50% stenosis		161/1515	11.6 (10.0–13.4)

CCTA, coronary CT angiography; CAC, coronary artery calcium; No, number; KM, Kaplan-Meier; CI, confidence interval.

respectively. The presence of non-obstructive coronary artery disease on CCTA, defined by stenosis of 1–49%, has previously been shown to be associated with increased mortality rates [13]. The results of this study suggest that the finding of CAC but no luminal narrowing on CCTA is another form of non-obstructive CAD and should not be considered normal. Thus, aggressive risk factor control should perhaps be considered among this patient population.

The reasons for classification of individuals with CAC but without luminal narrowing warrant consideration. Expansive remodeling of coronary arteries to accommodate increasing plaque burden is a well-recognized compensatory mechanism to preserve coronary luminal integrity. Given the ability of CCTA to evaluate both the arterial lumen and wall, imagers evaluating CCTA can identify atherosclerotic plaques that do *versus* do not cause luminal narrowing. In the present study cohort, the overall plaque burden

Table 4

Univariate and multivariate Cox regression models for all-cause mortality according to CAC and CCTA findings.

CCTA	CAC score	Unadjusted		Adjusted for FRS	
		HR (95% CI)	p-value	HR (95% CI)	p-value
No stenosis	0	Reference	NA	Reference	NA
	>0	2.0 (1.3–3.3)	0.003	1.8 (1.1–2.9)	0.020
	1–99	1.6 (0.9–2.9)	0.140	1.4 (0.8–2.6)	0.230
0% < stenosis	<50%	3.3 (1.7–6.5)	<0.001	2.5 (1.3–4.9)	0.008
	≥50% stenosis	2.7 (2.0–3.6)	<0.001	2.2 (1.6–3.0)	<0.001
		4.1 (3.0–5.5)	<0.001	2.9 (2.2–4.0)	<0.001

CCTA, coronary CT angiography; CAC, coronary artery calcium; CI, confidence interval; FRS, Framingham risk score; HR, hazard ratio; NA, not applicable.

associated with no luminal narrowing by CCTA, yet CAC is expectedly low. Despite this, however, the prognosis associated with its presence exhibited impactful adverse consequences. Prior studies evaluating positive arterial remodeling by CCTA have shown its collinearity with other atherosclerotic plaque features, such as plaque burden and necrotic intra-plaque core [14]. Indeed, plaques undergoing positive arterial remodeling exhibit higher rates of ischemia when compared to invasive fractional flow reserve, and are associated with higher rates of downstream acute coronary syndromes compared to those that do not [15].

Our study findings should serve to raise awareness with respect to current CCTA reporting. Further to prior investigations that have reported the importance of atherosclerotic plaque features to more precisely define prognosis, the present study data indicates the importance of these characteristics, even when coronary luminal compromise is not present. Allowing for the importance of these findings, the most recent guidelines, which were published in 2009 and 2014, requested that the presence of coronary atherosclerosis should be reported, and specifically stated that intraluminal plaque without luminal stenosis should be reported as minimal (grade 1) in the qualitative scales and quantitative scales [9,16]. However, given that the patient enrollment and CCTA interpretation had been done between February 2003 and May 2011 in CONFIRM registry, our study findings showed that non-negligible proportion of those patients were classified and reported as normal (grade 0). Another potential method for reporting this may be to couple CCTA and CAC reporting, but this method may not fully embody the totality of adverse plaque findings, and future studies should be performed to identify the most parsimonious methods to comprehensively define risk and promote salutary therapeutic interventions.

The current study is not without limitations. CCTAs were interpreted by experts at each site rather than a dedicated core laboratory. As such, we attempted to minimize potential biases by applying standardized data definitions that included only sites where interpretation of CCTAs were led by cardiologist/radiologists with adequate proficiency. Patients with both CCTA and CACS results were only included in the current analysis, hence the potential for selection bias may have influenced our study findings. Further, CCTA and CAC both possess intrinsic technological limitations that may introduce imaging artifacts that may have affected our study findings. Future generation CT scanners may address these artifacts, but we employed CT scanners of ≥64 detector rows, which is considered the clinical standard for performance of CCTA and CAC. Further, we observed important prognostic findings with the use of this standard-of-care technology. Finally, our study did not evaluate the findings of non-calcified plaque in patients with no luminal narrowing. We also did not systematically evaluate other important plaque features, such as plaque volume or low attenuation plaque as a surrogate marker of necrotic lipid-laden intra-plaque cores. Given the high number of CTs evaluated and the lack of diagnostic

software at the time of initiation of this study, we were unable to perform this important task, which should be addressed in future studies.

In this prospective multicenter international study, the presence of CAC in the absence of coronary luminal narrowing is associated with increased 5-year risk of mortality. Individuals with CAC score ≥100 and no coronary luminal narrowing experience death rates similar to those with non-obstructive CAD.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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