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Coronary artery calcium and the competing long-term risk of cardiovascular vs. cancer mortality: the CAC Consortium

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Aims Coronary artery calcium (CAC) is the strongest predictor of cardiovascular disease (CVD), yet is also associated with chronic non-CVD such as cancer. We performed this analysis in order to describe the association of CAC with CVD vs. cancer mortality.

Methods and results The CAC Consortium is comprised of 66 636 scans performed in asymptomatic patients without known CVD. The mean age was 54 ± 11 years and 67% of participants were men. Cause of death was ascertained from death certificates. The association of CAC with cause-specific mortality was calculated using Fine and Gray sub-distribution hazard ratio (SHR) models, which account for competing causes of death. There were 3158 deaths over a median 12 ± 4 years follow-up (37% cancer and 32% CVD). Cancer was the leading cause of death when CAC = 0 (50%) with CVD overtaking cancer when baseline CAC >300. Compared to participants with CAC = 0, the SHR for CVD mortality was 1.44 [95% confidence interval (CI) 1.14–1.81], 2.26 (95% CI 1.76–2.90), and 3.68 (95% CI 2.90–4.67) for patients with CAC 1–99, 100–299, and ≥300, and the SHR for cancer was 1.04 (95% CI 0.88–1.23), 1.19 (95% CI 0.98–1.46), and 1.30 (95% CI 1.07–1.58).

Conclusion Cancer was the leading cause of death for patients with baseline CAC = 0, whereas CVD overtook cancer above a threshold of CAC >300. These results argue for a focused approach for patients at the extremes of CAC scoring while suggesting that combined CVD and cancer primary prevention strategies for patients with intermediate CAC scores may significantly decrease mortality from the two leading causes of death.

Keywords CAC • competing risk • mortality • risk prediction • primary prevention

Introduction

In 2015, cardiovascular disease (CVD) and cancer were the leading causes of death in the United States, accounting for 45% of all deaths.[1] While CVD remains the number one cause of death, there are nearly as many total deaths from cancer, and the Centers for Disease Control projected that cancer will overtake CVD as the number one cause of death by the year 2020.[2] Adding complexity to the prediction of cause of death, CVD, and cancer share many common risk factors such as diabetes, tobacco use, low fitness, and obesity.[3–7] Therefore, more accurate modelling of the competing risk for CVD and cancer mortality has significant public health implications

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for population prevention strategies, guideline-based individual risk stratification, and allocation of limited healthcare resources across the total population.

Coronary artery calcium (CAC) is one of the strongest predictors of incident CVD due to its ability to 'integrate' lifetime risk factor exposures.[8,9] However, through its relationship with subclinical tissue injury, CAC has also been shown to be associated with other non-CVD diseases such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, and dementia.[10–12] Therefore, CAC may be seen as a marker of overall health status and 'biologic age', and not just a marker of increased risk of CVD.[13,14] Despite studies investigating competing risks, the impact of non-CVD in the association of CAC with CVD mortality is unknown.

To better understand, the impact of CAC on the changing epidemiology of CVD vs. non-CVD mortality (including cancer), we used the CAC Consortium to perform novel competing risk analyses for cause-specific mortality. These results add to the existing CAC literature by providing tools for estimating both an individual's most likely cause of death and by providing more precise estimates of the true risk of CVD mortality after accounting for competing risks.

Methods

Study design and population

The CAC Consortium is a retrospective multicentre cohort of 66 636 patients who had a physician referred and clinically indicated CAC scan. The rationale, design, and baseline participant characteristics have been previously published, the latter of which are similar to the contemporary NHANES 2001–02 as well as baseline data from the Multi-Ethnic Study of Atherosclerosis (MESA) characteristics.[15] In summary, four participating centres with expertise in CAC acquisition and scoring contributed consecutive patient data including demographics and risk factors from as early as the year 1991 through 2010. All patients were without known CVD, asymptomatic, and had CAC scoring performed for risk stratification. Each centre collected individual participant consent at the time of CAC scanning. Institutional Review Board approval was obtained at each centre and for coordinating centre activities at Johns Hopkins, which included ascertainment of mortality status and collection of death certificates.

CAC scans

CAC scans were performed using standardized non-contrast cardiac gated computed tomography (CT) protocols at each site and with results reported in Agatston units. Approximately 93% of CAC scans were performed using electron beam tomography with 89% of the total scans performed using an Imatron C-100, C-150, or C-300, which has been shown to have a very high correlation with multi-detector CT scanning (MDCT).[16–18] The remaining 7% of more recently acquired scans were obtained using four-slice MDCT imaging. CAC scores were categorized into the following groups: 0, 1–99, ≥100–299, and ≥300.

Mortality ascertainment

Using a previously validated algorithm, patients were linked to the Social Security Administration (SSA) Death Master File (DMF).[19] Validation studies demonstrated that our algorithm for linkage to the SSA DMF had a >90% specificity and 72–90% sensitivity for the identification of deaths when compared with known deaths identified via the electronic medical record. A total of 3158 deaths were identified and of those 3033 (96%) death certificates were obtained from the National Death Index. The 4% of participants in whom a death certificate was not obtained were treated as alive at the last time of follow-up for competing risk analysis and treated as deceased for all-cause mortality analyses. The cause of death was classified into common groups using the cause of death identified as the underlying (primary) aetiology. In this analysis, we examined CVD (ICD 9 390–459 or ICD 10 I00–I99), CHD (ICD 9 410–414 or ICD 10 I20–I25), non-CVD (total deaths - CVD deaths), pulmonary (ICD 9 460–519 and ICD 10 J00–J99), and cancer (ICD 9 140–239 or ICD 10 C00–D48) mortality. The proportion of deaths due to CVD and cancer along with the distribution of specific types of cancer mortality in the CAC Consortium were similar to the contemporary United States Centers for Disease Control and American Cancer Society mortality data.[20,21]

Risk factors

Patient demographics, risk factors, and laboratory data were obtained from the referral visit during which the CAC scan was ordered and/or a semi-structured interview conducted on the day of the CAC scan. Risk factors aside from age were categorized as categorical variables. Hypertension, dyslipidaemia, and diabetes were defined via prior documented diagnosis or treatment with a disease-specific medication. Among patients with laboratory data, dyslipidaemia was also defined as a low density lipoprotein cholesterol >160 mg/dL, high density lipoprotein cholesterol <40 mg/dL in men, <50 mg/dL in women, or fasting triglycerides >150 mg/dL. Smoking status was categorized as never, current, or former. A family history of CHD was defined as having a first degree relative with CHD by three of the sites, while one site (Columbus, OH, USA) recorded the premature family history of CHD (<55 years of age in a male or <65 years of age in a female). The Pooled Cohort Equation was used to calculate an individual's 10-year risk of developing atherosclerotic CVD (ASCVD) and partially missing risk factor data was imputed using a multivariable adjusted model as described in previous reports.[22]

Statistical analysis

Participant baseline characteristics were calculated both overall and stratified by cause-specific mortality (CVD, CHD, non-CVD, and cancer). The proportion of total and cause-specific deaths within each CAC group was calculated and displayed graphically. Mortality rates of all-cause and cause-specific mortality per 1000 person-years were calculated for each CAC group. Given age differences between cause-specific mortality groups, age-standardized mortality incidence rates based on the overall CAC Consortium cohort age distribution were computed.

Progressively adjusted Cox proportional hazards models were used to calculate the risk of cause-specific mortality within CAC groups for each outcome with CAC = 0 as the reference. Model 1 included age and gender. Model 2 included age, gender, hypertension, dyslipidaemia, smoking status, diabetes, and family history of CHD.

Cox proportional hazards models assume that those who remain in a risk set are representative of the entire study population and thus are known to over-estimate the actual cumulative incidence in the presence of competing risks, since those who are censored for competing events cannot develop the outcome of interest (e.g. those who died of non-CVD cause cannot die for CVD after non-CVD death).[23–26] Therefore, to more accurately account for the competing risks of CVD and non-CVD mortality, we calculated progressively adjusted sub-distribution hazard models using the Fine and Gray method.[27] The cumulative incidence function (CIF) was calculated for each CAC group, which accounts for competing risks, and this was graphically displayed as a survival curve (1-CIF).[28–30] In order to identify where CVD and cancer mortality curves intersect—and where CVD mortality overtakes cancer mortality—we graphically displayed the percent suffering cause-specific mortality as a function of the CAC score on a continuous scale, using locally weighted

Table 1 Participant characteristics

	Total cohort (*n* = 66 636)	CVD mortality (*n* = 971)	CHD mortality (*n* = 524)	Non-CVD mortality (*n* = 2187)	Cancer mortality (*n* = 1129)
Age (years)	54.4 (10.6)	67.1 (11.9)	67.4 (11.7)	64.6 (11.2)	64.3 (10.1)
Men	67.0	69.9	76.0	65.8	64.7
Race					
Caucasian	89.1	83.4	83.0	88.9	92.3
Black	2.3	7.5	7.1	3.8	2.8
Asian	3.8	2.6	2.5	2.9	2.5
Hispanic	3.1	5.6	6.8	3.5	1.8
Hypertension	30.9	55.3	54.0	44.9	41.1
Hyperlipidaemia	54.4	61.7	64.9	56.3	55.9
Diabetes	6.8	18.0	20.4	14.4	12.1
Current smoking	9.6	12.5	12.4	13.3	13.1
Family history CHD	46.1	41.7	44.1	40.0	40.3
Number of risk factors					
0	17.2	10.5	9.9	13.5	13.7
1	35.6	27.5	26.5	31.0	33.2
≥2	47.2	62.0	63.6	55.5	53.1
10-year ASCVD risk	7.4 (9.9)	21.8 (16.7)	22.6 (16.7)	16.9 (14.8)	15.5 (13.5)
ASCVD category (%)					
<5	55.2	14.0	13.6	21.2	22.5
5–20	36.9	39.6	37.6	46.8	50.0
≥20	7.9	46.5	48.9	31.9	27.5
CAC score, median (IQR)	3 (0–95)	295 (0–1016)	403 (86–1194)	109 (0–557)	75 (0–403)

Values are reported as mean (SD) or percent unless otherwise noted.
ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; IQR, interquartile range.

scatterplot smoothing (LOWESS) of the results of a univariable logistic regression model.[31]

Results

Overall, the cohort had a mean age of 54 (±11) years, two-thirds of participants were male, 89% were Caucasian, and had a mean 10-year ASCVD risk score of 7.4% (*Table 1*). Over a median follow-up of 12.4 years, there were 971 deaths due to CVD of which 524 were due to CHD. There were 2187 deaths due to non-CVD of which 1129 were due to cancer. Participants who died due to CVD were older, more likely to have hypertension, hyperlipidaemia, diabetes, and have a higher mean ASCVD score (21.8% vs. 16.9%) compared with participants who died due to non-CVD causes. However, there was a similar proportion smoking and family history among those who died of CVD vs. non-CVD causes.

The median CAC score for the overall cohort was 3 [interquartile interval (IQI) 0–95] Agatston units and 44.7% of participants had no CAC (CAC = 0). The median baseline CAC score for participants who died from CVD was 295 (IQI 0–1016) and the median CAC score was 403 (IQI 86–1194) for participants who died from CHD. Participants who died from non-CVD causes had a median CAC score of 109 and those who died from cancer had a median score of 75. Approximately 90% of participants who died from CHD had CAC present at baseline compared with 74.5% for participants who died from cancer.

The crude mortality rates for individuals with CAC = 0 was 1.6 per 1000 person-years for all-cause mortality, 0.3 for CVD mortality, 0.1 for CHD mortality, and 0.8 for cancer mortality (*Table 2*). A higher CAC score was associated with a higher mortality rate overall and for each cause-specific group. However, the mortality rate was higher for cancer compared with CVD in CAC groups 0 (0.8 vs. 0.3), 1–99 (1.2 vs. 0.8), and ≥100–299 (2.1 vs. 1.9). However, when the CAC score was ≥300, CVD mortality rate was higher than cancer mortality rate (4.7 vs. 3.3). There was no change in the overall relationship after age standardization (bottom of *Table 2*).

The proportion of deaths due to cancer was inversely associated with increasing CAC score. Among individuals with CAC = 0, 50% of deaths were due to cancer while approximately a quarter of deaths were due to cancer among individuals with CAC ≥300 (*Figure 1*). The total proportion of deaths due to CVD was low for individuals with CAC = 0 at approximately 20% and increased to 40% of the deaths for individuals with a CAC score ≥300. The proportion of CVD deaths due to CHD increased with higher CAC scores and 42% of CVD deaths were due to CHD for individuals with CAC = 0, whereas 60% of CVD deaths were due to CHD for individuals in the CAC group ≥300.

Considering CAC as a continuous variable in a threshold analysis, CVD was the leading cause of death when the CAC score was

Table 2 Mortality rate per 1000 person-years follow-up by coronary artery calcium group

	All-cause mortality	CVD mortality	CHD mortality	Non-CVD mortality	Cancer mortality
Crude					
CAC = 0	1.6	0.3	0.1	1.3	0.8
CAC 1–99	3.1	0.8	0.4	2.3	1.2
CAC ≥100–299	5.8	1.9	1.0	3.9	2.1
CAC ≥300	12.1	4.7	2.8	7.4	3.3
Age standardized					
CAC = 0	1.8	0.4	0.2	1.4	0.9
CAC 1–99	3.4	0.8	0.4	2.5	1.4
CAC ≥100–299	3.9	1.3	0.6	2.6	1.4
CAC ≥300	9.8	3.8	2.4	6.0	2.7

CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease.

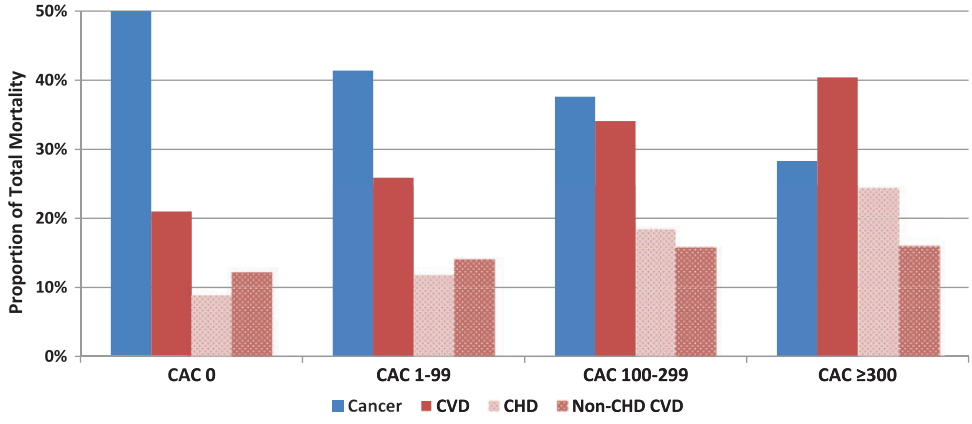

Figure 1 Proportion of deaths due to CVD and cancer within each CAC group. CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease.

greater than approximately 300, while cancer was the leading cause of death for when the CAC score was <300 (*Figure 2*). Among all deaths due to CVD, the proportion due to CHD increased with increasing CAC and above a threshold of approximately 100 Agatston units CHD was the predominant type of CVD-related death.

The Fine and Gray sub-distribution hazard models showed that there was an increase in the sub-hazard for each of the cause-specific mortality groups with increasing CAC scores (*Table 3*). The strongest association was noted between CAC and CHD mortality with an adjusted sub-distribution hazard of 1.49 [95% confidence interval (CI) 1.04–2.11], 2.74 (95% CI 1.90–3.95), and 4.80 (95% CI 3.39–6.80) for CAC groups 1–99, ≥100–299, and ≥300 compared to the group with CAC = 0. A significant adjusted association between CAC and the sub-distribution hazard of cancer mortality was noted only for the CAC group ≥300 with a hazard ratio (HR) of 1.30 (95% CI 1.07–1.58) compared to the group with CAC = 0. The association between CAC and non-CVD mortality was significant, but weaker than the association for CVD and CHD mortality, with a hazard of

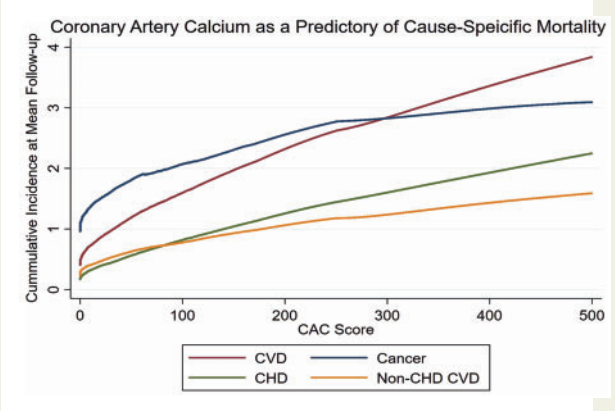

Figure 2 LOWESS curve for cumulative incidence of cause-specific mortality at mean follow-up as a function of CAC score. CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease.

Table 3 Sub-distribution hazards (Fine and Gray method) of cause-specific mortality by coronary artery calcium group

	CVD mortality	CHD mortality	Non-CVD mortality	Cancer mortality
CAC = 0	Reference	Reference	Reference	Reference
CAC 1–99				
Unadjusted	2.35 (1.87–2.94)	2.53 (1.80–3.57)	1.80 (1.59–2.03)	1.58 (1.35–1.85)
Model 1	1.50 (1.19–1.90)	1.57 (1.10–2.24)	1.21 (1.07–1.37)	1.05 (0.89–1.24)
Model 2	1.44 (1.14–1.81)	1.49 (1.04–2.11)	1.19 (1.05–1.35)	1.04 (0.88–1.23)
CAC ≥100–299				
Unadjusted	5.69 (4.51–7.19)	7.24 (5.14–10.21)	3.05 (2.65–3.50)	2.63 (2.19–3.17)
Model 1	2.47 (1.92–3.18)	3.03 (2.10–4.37)	1.45 (1.25–1.68)	1.22 (0.99–1.49)
Model 2	2.26 (1.76–2.90)	2.74 (1.90–3.95)	1.39 (1.20–1.61)	1.19 (0.98–1.46)
CAC ≥300				
Unadjusted	13.66 (11.12–16.67)	19.34 (14.36–26.04)	5.62 (5.01–6.30)	3.99 (3.41–4.67)
Model 1	4.22 (3.34–5.36)	5.64 (3.98–8.01)	1.98 (1.72–2.28)	1.35 (1.10–1.63)
Model 2	3.68 (2.90–4.67)	4.80 (3.39–6.80)	1.85 (1.61–2.13)	1.30 (1.07–1.58)

Model 1: age and gender. Model 2: age, gender, hypertension, hyperlipidaemia, smoking, diabetes, and family history CHD.
CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease.

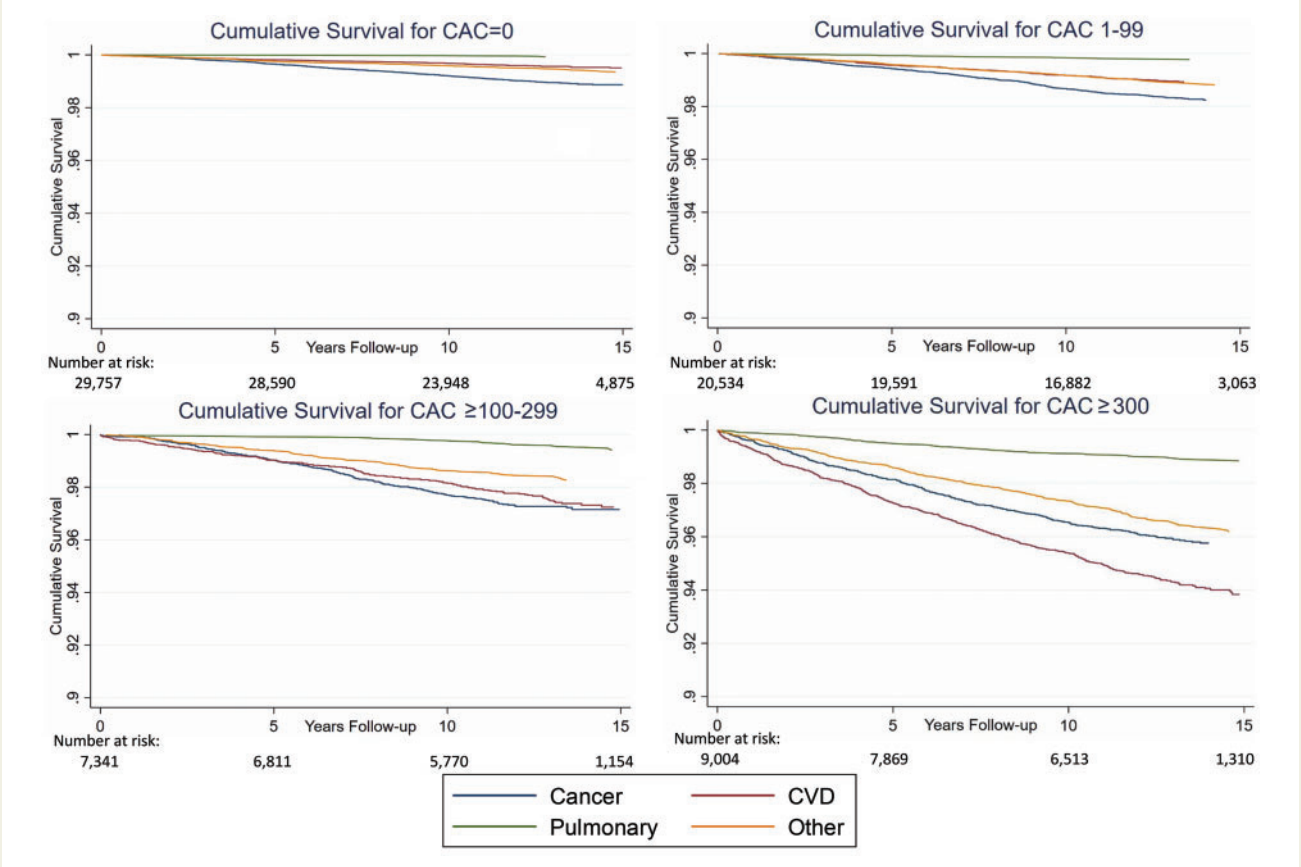

Figure 3 Cumulative incidence survival of cause-specific mortality by CAC group. CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease.

1.19 (95% CI 1.05–1.35), 1.39 (95% CI 1.20–1.61), and 1.85 (95% CI 1.61–2.13) for CAC groups 1–99, ≥100–299, and ≥300. Compared to the sub-distribution hazard models, the cause-specific Cox regression models showed slightly higher HR estimates for the CAC ≥300 and similar estimates for individuals in the CAC groups 1–99 and ≥100–299 (Supplementary data online, *Table S1*).

The competing risk (Fine and Gray method) of cumulative incidence of mortality for individuals with CAC = 0 was very low with CVD mortality <1% and cancer mortality <2% at 15 years of follow-up (*Figure 3*). For individuals with a CAC score ≥300, CVD mortality was the leading cause of death and had a greater cumulative incidence than cancer mortality throughout the entire follow-up period.

Discussion

These novel findings for the association of CAC with the competing risk for cause-specific mortality build upon the well-established relationship between CAC and incident CVD. Over the long-term follow-up of this study, individuals with a higher CAC score were significantly more likely to die due to both of CVD and non-CVD causes, and those who died from CVD (in particular CHD mortality) had a significantly higher median CAC score than individuals who died from cancer or non-CVD. CVD was the most likely cause of death for CAC scores ≥300, while cancer was the most likely cause of death for CAC scores <300. Perhaps most significantly, these results are the first to demonstrate that (i) the proportion of deaths due to CVD increases with an increasing CAC score, while there is an inverse relationship between CAC and the proportion of deaths due to cancer and (ii) at lower CAC scores cancer is the leading cause of death, while CVD is the leading cause of death for participants with a CAC score ≥300.

Multiple studies have shown an increased risk of all-cause mortality with increasing CAC, and while CAC is strongly associated with incident CVD, there is also emerging evidence to show that increasing levels of CAC are significantly associated with non-CVD such as cancer, chronic kidney disease, and chronic obstructive pulmonary disease.[10,11] Therefore, increasing levels of CAC may be considered as not only a risk factor for CVD, but also a marker for individual overall health status. In this regard, the concept of competing risks of mortality is increasingly important. The significant decline in CVD mortality over the last four decades has led the Centers for Disease Control and Prevention to predict that cancer will overtake CVD as the leading cause of death in the United States in the year 2020.[2] Therefore, while CVD risk factors and CVD risk scores have traditionally thought of CVD outcomes in isolation, it is increasingly important to examine competing risks, and our results demonstrate that the interpretation of the CAC score only in the context of CVD risk does not make full use of the available information.

To our knowledge, this analysis is the first that describes the relationship of CAC to cause-specific mortality, and the first that describes the CAC score at which CVD becomes the most likely cause of death. Importantly, our analysis highlights not only the importance of considering competing risks, but also the changing epidemiology of mortality in developed countries. While CVD remains the leading cause of death, the significant decline in CVD mortality over the last four decades has led to an increase in the proportion of non-CVD mortality and, in particular, cancer mortality. Over 40% of the participants in the CAC Consortium have a CAC score between 1 and 300 and while the relative hazard of CVD mortality increases significantly with an increasing CAC score, the absolute risk of CVD and cancer mortality in this group is very similar. This demonstrates that for a large proportion of the general population prevention strategies must be focused on reducing both CVD and cancer risk.

Accordingly, these results may be useful when considering whether the addition of primary prevention medications may be beneficial. We show that individuals with CAC = 0 have a very low long-term risk of CVD mortality that is <1% for individuals with over 15 years of follow-up and these individuals are most likely to experience death from cancer. On the other hand, individuals with CAC ≥300 have an absolute rate of all-cause mortality that is seven times greater than individuals with CAC = 0 and predominantly due to CVD. Therefore, in these two groups the decision regarding initiation of primary prevention medications may be viewed as straightforward.

Conversely, while patients with a low to intermediate CAC score have a significantly higher relative hazard of CVD mortality compared to cancer mortality, the absolute CVD mortality remains relatively low at <2% per 1000 person-years compared to a slightly higher rate of cancer mortality. Providing information on individual's most likely cause of death and their 10–15 year risk of all-cause mortality is important in determining not only the utility of CVD primary prevention strategies, but also the potential life years gained. However, these results should be taken in context of the well-established relationship between CAC and an individual's risk for incident CVD, which can be potentially debilitating and costly.

Therefore, the clinician-patient discussion is of particular importance for individuals with low to intermediate CAC scores in determining what intensity of CVD primary prevention medication therapies are consistent with the patient's treatment goals.[32] Low-dose aspirin therapy for individuals with CAC ≥100 has a demonstrated net benefit for CHD primary prevention and is associated with a reduction in gastrointestinal cancer.[33,34] Indeed, the United States Preventative Services Task Force recommends low-dose aspirin for both CVD and colorectal cancer prevention in high CVD risk individuals who do not have an increased bleeding risk.[35] At a minimum, an emphasis on achieving ideal dietary and lifestyle habits is imperative for these individual as CVD and cancer have many overlapping risk factors including low physical activity, diabetes, obesity, a low consumption of fruits and vegetables, low consumption of fibre, and a high consumption of animal fats.

Potential limitations of this analysis include that the CAC Consortium participants are primarily Caucasian, which may limit the generalizability to other races. The CAC Consortium is also comprised of patients who had a clinically indicated CAC scans, which could potentially lead to indication bias and/or reduce the generalizability of the results. In addition, this analysis uses categorical rather than continuous risk factor variables, although prior studies have suggested that these perform similarly for prediction of CVD.[36] In addition, our death ascertainment algorithm prioritized specificity over sensitivity and there may be a small number of deaths that were not included as outcomes in our study. There are also well-known limitations to using death certificates for ascertainment of cause of death. However, our methods are similar to those used for all national

surveillance programmes in the United States. Finally, follow-up information on lifestyle modification, downstream medications/treatments/procedures, and CVD outcomes is not available. However, adjustment for these results would be expected to bias our results towards the null hypothesis and are therefore unlikely to significantly impact our findings.

These results provide important information on the association of CAC with cause-specific mortality that can be used to improve risk stratification and guide the most appropriate allocation of primary prevention resources at both the individual patient level and population level. In addition, these results advocate for a combined approach to CVD and cancer prevention in persons with a low to intermediate burden of CAC, which may lead to a significant decrease of the two leading causes of death in developed countries.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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