Title

The relationship between coronary artery calcium score and the long-term mortality among patients with minimal or absent coronary artery risk factors

Authors

Nakanishi, Rine
Li, Dong
Blaha, Michael J
et al.

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All-cause mortality by Age and Gender based on Coronary Artery Calcium Scores

Rine Nakanishi MD PhD [a], Dong Li MD PhD [a], Michael J Blaha MD MPH [b], Seamus P. Whelton MD MPH [b], Sirous Darabian MD [a], Ferdinand R. Flores BS [a], Christopher Dailing BS [a], Roger S. Blumenthal MD [b], Khurram Nasir, MD [c,b], Daniel S. Berman, MD [d], and Matthew J. Budoff, MD [a]

[a] Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, California, USA
[b] The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, Maryland, USA
[c] Center for Prevention and Wellness Research, Baptist Health Medical Group, Miami Beach, FL, USA.
[d] Cedars Sinai Medical center, Los Angeles, California, USA

Address for correspondence

Matthew J. Budoff, MD FACC
Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, California, USA
Tel: +1-310 2224107
Fax: +1-3107829652
Email: mbudoff@labiomed.org

DISCLOSURES

Dr. Matthew Budoff is a consultant for General Electric; the other authors have no conflict of interest.

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ABSTRACT

Purpose: We investigated the long-term association of coronary artery calcium (CAC) and all-cause mortality stratified by age and gender groups.

Materials and Methods: Although CAC has been established as a robust tool for predicting total mortality during intermediate follow-up, less is known about the long term predictive value of CAC. This study included 13,092 asymptomatic patients without known cardiovascular disease (CVD) who underwent a clinically indicated CAC. CAC was categorized as an Agatson score of 0, 1-99, 100-399 and ≥400. We used multivariable Cox proportional hazards to calculate adjusted hazard ratios for mortality stratified by age (younger, intermediate or older) and gender. This study was approved by the institutional review board, and informed consent was obtained from all patients.

Results: The mean age of participants was 58±11 years (67% men). During a median follow-up of 11.0±3.2 years, 522 deaths occurred (4.0%). Compared with CAC=0, increasing CAC was associated with higher mortality rate: 1-99 (HR1.5, 95%CI1.1-2.1); 100-399 (HR1.8, 95%CI1.3-2.5); ≥400 (HR2.6, 95%CI1.9-3.6). Relative risk according to CAC category did not differ between genders. When patients with CAC≥400 were compared with CAC=0, strong differences in mortality were present among younger-females (HR4.7, 95%CI0.4-55.5), younger-males (HR4.9, 95%CI0.5-51.0), intermediate-females (HR5.8, 95%CI5.8-12.4), and intermediate-males (HR4.5, 95%CI2.8-7.1). These differences in mortality were still present but to a lesser degree in older-females (HR2.7, 95%CI0.99-7.5) and older-males (HR1.5, 95%CI0.7-3.1) in whom the mortality rate of patients with CAC=0 was significantly higher than in the younger

patients. Nonetheless, the mortality rate of the older patients with CAC=0 was far lower than that of the general U.S. population. Greater incremental value of CAC scanning over traditional risk factors was shown in predicting long term (15 year) mortality than shorter term (5 year) mortality.

Conclusion:

CAC shows strong stratification of long term risk in young and middle age groups of both genders. In older patients, the long-term risk stratification by CAC is lower, due principally to increased mortality rate in patients with low calcium scores; however, even in the older patients, absent or low CAC define a group at much lower risk than that of the general population.

Key word: Coronary artery calcium score, mortality risk, age, gender

Abbreviations

CAC Coronary artery calcium

CVD Cardiovascular disease

INTRODUCTION

Cardiovascular disease (CVD) has the highest morbidity and mortality rate of any disease process [1]. Effective preventive therapies are available that can reduce CVD events. Population-based risk prediction models calculated by traditional clinical risk scoring, which form the basis for recommendation of therapies for individual patients in current CVD prevention guidelines, may overestimate or underestimate risks in individual patients [2, 3].

Numerous studies have demonstrated the prognostic utility of coronary artery calcium (CAC) for risk stratification among asymptomatic patients [4-8]. An increasing CAC is associated with a higher mortality and CVD risk regardless of age [9], gender [10], or ethnicity [11] during an intermediate follow-up period. Its CVD risk prediction is superior to that of traditional CVD risk factors, novel biomarkers or other measures of sub-clinical atherosclerosis [7, 12-15]. However, the results of these studies were reported with a follow-up time of only 5 to 7 years. The longer term mortality associated with CAC has not been well defined. Moreover, CVD risk has been shown to increase with age and to be higher in men than in women, and the long term implications of CAC scanning according to these groups has not been explored. Therefore, the aim of this current study is to investigate the relationship between CAC and all-cause mortality, used as a proxy for CVD risk, stratified by age and gender after a median follow-up of at least 10 years.

MATERIALS and METHODS

Study population

We studied 13,092 consecutive asymptomatic individuals without known coronary artery disease with a mean age of 58±11 years (67% men) clinically referred for a CAC scan between July 1997 to December 2011 at our institution. We stratified the population in groups by age [younger (<45 years for male, <55 years for female), intermediate (45-74 years for male and 55-74 years for female) or older (≥75 years for both male and female)] and gender, as has been previously proposed [13].

All subjects completed a questionnaire for ethnicity (Caucasian, Hispanic/Latino, African-American, Asian or other), and CVD risk factors including hypertension, hypercholesterolemia, diabetes mellitus, current cigarette smoking, and any family history of CVD determined as whether any member of their immediate family (parents or siblings) had a history of fatal or nonfatal myocardial infarction and/or coronary revascularization, as previously described [16]. Exclusion criteria included age <20 years, any chest pain, prior known CVD (prior coronary revascularization or myocardial infarction), or follow-up of ≤365 days. This study was approved by the Institutional Review Board of our institution. Informed consent was obtained from all patients.

Non-contrast CT Image Acquisition Protocol

All subjects underwent EBCT with an Imatron C-150XL Ultrafast computed tomography scanner (GE-Imatron, South San Francisco, California) or multi-detector 64-slices coronary CT (Lightspeed VCT, General Electric Healthcare Technologies, Milwaukee, WI). Each scan extended from 1 cm below the carina to the bottom of the heart to include the entire coronary tree. Scan parameters included as follows:

prospective electrocardiogram-triggering (typically 60–80% of the R–R interval for EBCT, 65-80% for multi-detector CT), 35 cm field-of-view, 512×512 matrix size, and peak tube voltage of 120 kVp. Slice thickness was 3 mm. CAC measurements were performed on a dedicated workstation (AW Volume Share™, GE Medical Systems, Milwaukee, WI), and CAC was quantified using the Agatson score [17].

Statistical analysis

Continuous variables are expressed as the mean ± SD. The unpaired Student t test or the Wilcoxon rank-sum test was used to conduct the group comparisons by age (younger vs. older subjects) and/or gender, or ethnicity groups. Categorical variables were compared using the Pearson chi-square test.

All-cause death was defined as the end-point of this current study and verified using linkage with the Social Security Death Index [18] through December 2012 at the time when we ran the analysis. A full Social Security Death Index search was completely performed by patient name and date of birth in all of patients.

The thresholds of CAC for the mortality risk were defined as 0, 1-99, 100-399 and ≥400. The prevalence of CAC was assessed among age and gender groups. The mortality risk was analyzed across the spectrum of CAC categories. Kaplan-Meier models investigating the association between CAC groups and mortality were calculated. We also calculated multivariable Cox Proportional hazards models adjusted for hypertension, hyperlipidemia, diabetes, current smoking and family history, and ethnicity among CAC groups in each age and gender group. The mortality event rates per 1,000 person-years were assessed among age and gender group based on CAC

with 0, 1-99, 100-399 and ≥400.

We also compared the mortality event rates per 1,000 person-years between patients with CAC 0 and the general adult population in the U.S from the data based on the Center for Disease Control and Prevention [19] across various age groups for males and females.

Relative risk of mortality rate among males and females was assessed based on CAC with 0, 1-99, 100-399 and ≥400. Area under the curves (AUC) by receiver operator characteristics (ROC) was used to predict all-cause mortality at 5 years and 15 years between traditional risk factors alone and risk factors plus the continuous CAC score among males and females.

Scaled Schoenfeld residuals were used to verify the assumption of proportional hazards within the Cox models [20]. A hazard ratio (HR) and 95% confidence interval (CI) were calculated from the Cox models. P values <0.05 were considered statistically significant. All statistical calculations were performed using SAS (Version 9.3, SAS Inc., Cary, NC) for Windows.

RESULTS

Baseline Characteristics

The median follow-up of this study was 11.0±3.2 years. Among the 13,092 patients, 8713 (66.55%) were males and 4379 (33.45%) were females. Females were older (58.7±11.3 years vs. 57.7±11.5 years, p=0.0001) and had greater number of risk factors compared to males (1.77±0.99 vs. 1.64±1.01, p=0.0001). By age and gender,

there were 1664 younger-females (38.0%), 1213 younger-males (13.9%), 2321 intermediate-females (53.0%), 6813 intermediate-males (78.2%), 394 older-females (9.0%) and 687 older-males (7.9%). Baseline characteristics are shown in the Table1. Younger-females and males were less likely to have hypertension, diabetes and hyperlipidemia, resulting in a lower number of risk factors compared to other groups. Between gender, females had more family history and a greater number of risk factors than males across a board spectrum of age groups (Table1).

The prevalence and severity of coronary artery calcium

Figures 1a and b display the prevalence of CAC categories by age and gender. The prevalence of CAC 0 ranged from 73.6% in younger females to 10.6% in older males, and CAC ≥400 ranged from 1.8% in younger females to 51.8% in older males. Males were more likely to have higher CAC across various age groups compared to females.

Figures 2a and b also illustrate the prevalence of CAC categories by number of risk factors among males and females. Among both gender, patients with greater risk factors possessed more CAC burden. This trend was more manifest in females than in males, while approximately 30% of females and 60% of males without risk factors had CAC>0. Compared to females, males had approximately 2-fold higher prevalence of CAC at any level of number of risk factors, whereas similar prevalence was observed between genders when patients had all of risk factors.

Mortality risk

Of the 13,107 patients, 522 (4.0%) died. Of these, 15 (0.9%) were younger-females, 11 (0.9%) were younger-males, 84 (3.6%) were intermediate-females, 234 (3.4%) were intermediate-males, 55 (14.0%) were older-females and 123 (17.9%) were older-males. There was no significant difference of mortality risk between gender in the total, younger, intermediate or older age group ($p>0.05$ for all). By CAC categories, compared to CAC 0, increased CAC with 1-99, 100-399 and ≥400 were associated with higher mortality rates among males (1.5% vs. 2.9% vs. 4.7% vs. 9.9%, $p<0.001$) and females (1.6% vs. 3.1% vs. 7.0% vs. 12.9%, $p<0.001$).

Kaplan Meier curves for all-cause mortality stratified by CAC among males and females are shown in Figure 3. During a mean follow-up of 11 years, mortality rate was extremely low in patients with CAC 0, and increased progressively with each of CAC category for both males and females ($p<0.001$ for all). Among males, subjects with CAC 1-99, 100-399 and ≥400 experienced approximately 2.1-fold, 3.6-fold ad 7.1-fold higher mortality risk compared to those with CAC 0 (Figure 3a). By contrast, in females, this trend was more remarkable at 3.1-fold, 4.2-fold and 13.3-fold higher mortality risk (Figure 3b). However, relative risk (RR) in males at any level of CAC with 0 (RR 1.47, 95% CI 0.9-2.4, $p=0.13$), 1-99 (RR 1.51, 95% CI 0.99-2.30, $p=0.06$), 100-399 (RR 0.82, 95% CI 0.53-1.28, $p=0.39$) and ≥400 (RR 1.05, 95% CI 0.72-1.53, $p=0.79$) did not differ compared to females.

Figures 4a and 4b demonstrate the mortality rate per 1,000 person-years stratified by age and gender. Among younger subjects, the mortality rates among those with CAC 0 were very low at 0.4 and 0.9 per 1,000 person-years of follow-up in males and females, 0.8 and 1.0 per 1,000 person-years follow-up for intermediate-males and females, and 11.9 and 9.5 per 1,000 person-years follow-up for older-males and females. Mortality increased progressively with each higher CAC category in all groups. Similar findings were observed in the risk adjusted cox proportional hazard models for all-cause mortality, stratified by CAC among age and gender groups (Table 2).

Figure 5 illustrates the trend of the mortality rates per 1000 person-years by gender among patients with CAC of zero and the general adult population in the U.S from The Centers for Disease Control and Prevention. Across a board spectrum of various age groups, patients with CAC of zero had much lower mortality rates when compared to general population in the U.S. regardless of gender with the greatest differences seen in the older age group (Figure 5b).

The additive value of CAC to traditional risk factors to predict all-cause mortality

Figures 6a-d demonstrate the additive value of CAC to traditional risk factors including hypertension, diabetes, hyperlipidemia, smoking and family history to predict all-cause mortality among males and females at 5 and 15 years after CAC testing. In males, at 5 years, CAC showed the incremental prognostic value over risk factors alone (AUC: 0.702 vs. 0.655, $p=0.02$). This incremental value was greater at 15 years (AUC: 0.723 vs. 0.656, $p<0.0001$). In females, there was a trend towards incremental value of

CAC over risk factors in predicting mortality risk at 5 years (AUC: 0.650 vs. 0.612, p=0.065). In females at 15 years, CAC more significantly improved this prediction over risk factors alone (AUC: 0.690 vs. 0.624, p<0.0001).

DISCUSSION

This is the first study demonstrating the prognostic utility of CAC over a median follow-up of >10 years in asymptomatic patients by age and gender. This long-term observational study builds on previous studies which demonstrated the added prognostic information provided by CAC among asymptomatic patients during intermediate follow-up [4, 16, 21]. In patients who are less than 75 years old, the ability of CAC to stratify risk at 10 years is similar to what it has previously been described at 5 years [9].

An interesting novel finding of this study is the observation that long term risk stratification by CAC is attenuated in the older patients. In patients older than 75 years, the ability of CAC to stratify risk was still present, but was lower than in the other groups and lower than was previously described [9]. Compared to patients <75 years old who had a 10-fold difference in annualized mortality risk between CAC 0 and ≥400, those ≥75 years old had only a 5-fold difference in risk between these CAC categories. This finding may be explained by an increased overall mortality rate of older patients with CAC 0. In contrast to the younger and intermediate age patients in whom the mortality rate in our study was 0.35%/year, the annualized mortality rate in the patients 75-84 years of age was still relatively low but higher (0.7-1.1%/year) and was even higher in

the ≥85 year old patients (3.7%/year). This increase in mortality rates for the older patients with low CAC may be due to the increased in non-cardiac death in these age groups. Of importance, however, in these older patients with 0 or low CAC (1-99), the mortality risk at 10 years is much lower than that of the general population.

A CAC 0 has been shown to confer an extremely low mortality risk over an intermediate duration follow-up, regardless of traditional risk factors [16, 22]. A prior study reported by Budoff and colleagues demonstrated findings similar to those of this manuscript in 25,253 patients over a duration mean follow-up of 6.8 years [4]. Blaha et al. similarly reported an excellent survival rate of CAC 0 with >99% in 44,052 patients at a mean follow-up of 5.6 years [23]. The results of our study expand on these intermediate term findings by demonstrating the consistent associations between CAC 0 and very low long-term all-cause mortality, except on the older group. In the current study, annualized mortality risk among patients <75 years old with CAC 0 (30% in males and 56% in females of this age group) was only <0.35%/year, which is comparable to the results of a prior study in this age group showing <0.2%/year of mortality risk [9]. In patients ≥75 years of age with CAC 0 (10.6% of males and 17.8% of females of this age group), our study demonstrated that annualized mortality rate is higher than in the younger and intermediate age groups; however, it is still relatively low. Importantly, this risk is 70% lower than that of the general U.S adult population in this age group.

A recent prevention guideline has recommended to use a 10-year Atherosclerotic Cardiovascular Disease (ASCVD) risk score for determining the need for statin therapy among asymptomatic individuals [24]. This guideline considers patients with a >7.5% ASCVD risk to be at high risk and suggests that they should be treated with statins.

However, Kavousi et al. have recently reported that nearly all of men ≥55 years of age and women ≥65 years of age would have a >7.5% predicted 10-year risk and be recommended for treatment intervention with a statin regardless of the risk factor burden, since an estimated 10-year ASCVD risk is heavily weighted based on age [2]. By showing that a substantial proportion of the patients in this age group have a CAC score of 0 and that this is associated with low long term risk, the findings of this study support the concept that selection of the intensity of therapy might be better based on observed atherosclerosis in individual patients rather than on population-based risk.

With respect to gender, while lower prevalence of CAC in females than males, CAC equally predicted mortality risk among males and females in the current study. A previous systematic meta-analysis of 17850 males and 17779 females with CAC scanning similarly demonstrated that there was no difference in stratifying risk between males and females [25]. Our study also did not show any difference in predicting mortality risk at any level of CAC burden between genders ($p>0.05$). Regarding incremental value of CAC scanning over traditional risk factors, numerous previous studies have shown an independent prognostic value of CAC over clinical risk factors during an intermediate term follow-up [5, 7, 11]. In this study, we similarly demonstrate that CAC has an incremental value in predicting mortality over risk factors alone among males and a trend toward incremental value in females at the intermediate 5 year follow-up. This incremental value of CAC burden was more prominent in both genders at 15 years.

We recognize several limitations in the current study. This is a single center study. Since CAC scanning was referred for clinical purposes in our cohort, the association between CAC and long-term mortality rate among population-based cohorts

remains unclear. In addition, risk factors were self-reported by patients, which may underestimate their true prevalence. Although numerous previous studies demonstrated the prognostic value of CAC beyond other risk scoring such as Framingham Risk Score [7, 26], we did not have information allowing us to calculate this or other conventional scores. Further studies examining the comparative ability of CAC and risk scores to predict long term CVD events appear warranted. The Multi-Ethnic Study of Atherosclerosis (MESA) has reported differences in CAC scores and their prognostic implications in various ethnicities [11]. We did not separately analyze the ethnic groups in this predominantly Caucasian patient population. There were no data regarding medication use after CAC scanning. Since increased CAC has been associated with increased use of statins and aspirin [27, 28], the long term event rates observed in our study in patients with CAC >0 may be lower than would be observed in patients who had not undergone scanning. The outcome variable in this study was all-cause mortality. While CVD mortality is the most common cause of death in middle aged individuals, the risk of death from cancer and other causes increases with age. Further studies examining the relationship between CAC and cardiovascular events during a long-term follow-up would be needed.

CONCLUSION

CAC shows strong stratification of risk at 11 years in young and middle age groups of both genders. In older patients, the long-term risk stratification by CAC is lower, due principally to increased mortality rate in patients with low calcium scores;

however, even in the older patients, absent or low CAC define a group at much lower risk than that of the general population.

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Figure legends

Figure1a. Prevalence of coronary artery calcium scores among males by age groups

Figure 1b. Prevalence of coronary artery calcium among females by age groups

Abbreviations: CAC- coronary artery calcium

Figure 2a. Prevalence of coronary artery calcium among males by number of risk factors

Figure 2b. Prevalence of coronary artery calcium among females by number of risk factors

Abbreviations as in Figure1.

Figure 3a. Kaplan Meier curves for all-cause mortality among males with 0, 1-99, 100-399 and ≥400.

Figure 3b. Kaplan Meier curves for all-cause mortality among females with 0, 1-99, 100-399 and ≥400.

Abbreviations as in Figure1.

Figure 4a. Annualized mortality risk per 1000 person stratified by CAC categories among younger, intermediate and older patients in males

Figure 4b. Annualized mortality risk per 1000 person stratified by CAC categories among younger, intermediate and older patients in females

Figure 5a. Annual mortality rates per 1000 person-years among males with CAC 0 compared to males from general population in the U.S (2012)

Figure 5b. Annual mortality rates per 1000 person-years among females with CAC 0 compared to males from general population in the U.S (2012)

Figure 6 a-d. Receiver operator characteristics curves for prediction of all-cause mortality by traditional risk factors alone and risk factors plus the CAC score among males and females at 5 years (a: males, c: females) and 15 years (b: males, d: females).

Abbreviations as in Figure1.