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Original Research Article

All-cause mortality in asymptomatic persons with extensive Agatston scores above 1000

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ABSTRACT

Background: Risk assessment in the extensive calcified plaque phenotype has been limited by small sample size.
Objective: We studied all-cause mortality rates among asymptomatic patients with markedly elevated Agatston scores > 1000.
Methods: We studied a clinical cohort of 44,052 asymptomatic patients referred for coronary calcium scans. Mean follow-up was 5.6 years (range, 1–13 years). All-cause mortality rates were calculated after stratifying by Agatston score (0, 1–1000, 1001–1500, 1500–2000, and >2000). A multivariable Cox regression model adjusting for self-reported traditional risk factors was created to assess the relative mortality hazard of Agatston scores 1001 to 1500, 1501 to 2000, and >2000. With the use of post-estimation modeling, we assessed for the presence of an upper threshold of risk with high Agatston scores.

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Dr Patel and Dr Blaha contributed equally to this work.

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Calcified plaque in coronary arteries paradox

Results: A total of 1593 patients (4% of total population) had Agatston score > 1000. There was a continuous graded decrease in estimated 10-year survival across increasing Agatston score, continuing when Agatston score > 1000 (Agatston score 1001–1500, 78%; Agatston score 1501–2000, 74%; Agatston score > 2000, 51%). After multivariable adjustment, Agatston scores 1001 to 1500, 1501 to 2000, and >2000 were associated with an 8.05-, 7.45-, and 13.26-fold greater mortality risk, respectively, than for Agatston score of 0. Compared with Agatston score 1001 to 1500, Agatston score 1501 to 2000 had a similar all-cause mortality risk, whereas Agatston score > 2000 had an increased relative risk (Agatston score 1501–2000: hazard ratio [HR], 1.01 [95% CI, 0.67–1.51]; Agatston score > 2000: HR, 1.79 [95% CI, 1.30–2.46]). Graphical assessment of the predicted survival model suggests no upper threshold for risk associated with calcified plaque in coronary arteries.

Conclusion: Increasing calcified plaque in coronary arteries continues to predict a graded decrease in survival among patients with extensive Agatston score > 1000 with no apparent upper threshold.

1. Introduction

Calcified plaque in coronary arteries detected by using noncontrast cardiac CT is closely associated with the total burden of coronary atherosclerosis and the subsequent development of clinical coronary heart disease (CHD).[1–3] Calcified plaque in coronary arteries has been shown to predict events independent of traditional Framingham risk variables across diverse populations.[4] Current guidelines from the American Heart Association and American College of Cardiology have suggested that asymptomatic, intermediate-risk patients (defined by a Framingham risk score of between 10% and 20% for 10-year risk of CHD) may be reasonable candidates for coronary calcium measurement as a means of refining cardiovascular risk and guiding pharmacologic therapy (class IIa, level of evidence B).[5,6]

Although an Agatston score of zero has been associated with a very low risk of cardiovascular events,[7,8] Agatston scores of >100 or >400 have been predominantly used to define patients at the highest risk of incident CHD events.[9] Severe coronary calcification (Agatston score > 1000) is a less commonly encountered phenotype presumably associated with advanced coronary disease. However, because individual highly calcified plaques are frequently thought of as mature and clinically stable,[10] and the preponderance of data suggest that noncalcified lipid-laden plaques are more likely to be associated with acute coronary syndromes,[11] some have speculated that this extensive calcified plaque phenotype might be associated with an overall stable patient and a plateau in overall risk.

In this study population of asymptomatic persons, which represents the largest cohort of clinical Agatston scoring yet undertaken, we describe the risk of all-cause mortality among persons with Agatston score > 1000.

2. Methods

The study cohort consisted of 44,052 asymptomatic persons referred for electron beam CT (EBCT) for the assessment of subclinical atherosclerosis. This study incorporated data from 3 centers during the time period 1991 to 2004 (Torrance, CA; Columbus, OH; Nashville, TN), and all centers used a common scanning protocol. Methods of data collection were similar for all centers.

Participants were referred by their primary physicians on the basis of established cardiovascular risk factors for atherosclerosis. As an inclusion criterion, patients were determined to be free of baseline clinical CHD according to prior assessment by the referring physician. All participants provided informed consent to undergo EBCT and for the use of their blinded data for epidemiologic research. The study was conducted in accordance with the Declaration of Helsinki and received approval from the Humans Investigations Committee at all 3 sites.

2.1. Risk factor data collection

Participants completed a questionnaire for the collection of demographic and clinical characteristics, including baseline cardiovascular risk factors. Cigarette smoking was present if a subject was a smoker at the time of scanning.[12] Dyslipidemia was defined by the reported presence of a history of high total cholesterol, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, hypertriglyceridemia, or current use of lipid-lowering therapy. Study subjects were considered to have diabetes mellitus if they reported a history of diabetes or current use of oral antidiabetes medications or insulin.

Hypertension was defined as a self-reported history of hypertension or use of antihypertensive medication. Family history of CHD was determined by the presence of a first-degree relative with a history of CHD (male aged <55 years/female aged <65 years in 36,010 [82% of the study population]; age < 55 years for both male and female relatives in 8042 participants from the center in Columbus, OH [18% of the study population]).

2.2. Screening protocol

All subjects underwent EBCT with either a C-100 or C-150 Ultrafast CT scanner (GE-Imatron; GE Healthcare, South San Francisco, CA). With the use of a tomographic slice thickness of 3 mm, a total of approximately 40 sections were obtained from the level of the carina to the diaphragm. Image acquisition was electrocardiographically triggered at 60% to 80% of the R–R interval, using a 100 ms/slice scanning time. A