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Long-term prognosis for individuals with hypertension undergoing coronary artery calcium scoring

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ABSTRACT

Background: To examine the performance of coronary artery calcification (CAC) for stratifying long-term risk of death in asymptomatic hypertensive patients.
Methods and results: 8905 consecutive asymptomatic individuals without cardiovascular disease or diabetes who underwent CAC testing (mean age 53.3 ± 10.5, 59.3% male) were followed for a mean of 14 years and categorized on the background of hypertension as well as age above or below 60 years (in accordance with the 2014 Guidelines from the Joint National Committee 8). The prevalence and severity of CAC were higher for those with hypertension versus without hypertension ($P < 0.001$), and the extent increased proportionally with advancing age ($P < 0.001$). Following adjustment, the presence of CAC in hypertensive with respect to normotensive, was associated with worse prognosis for individuals above the age of 60 years (HR 7.74 [95% CI: 5.15–11.63] vs. HR 4.83 [95% CI: 3.18–7.33]) than individuals below the age of 60 (HR 3.18 [95% CI: 2.42–4.19] vs. HR 2.14 [95% CI: 1.61–2.85]), respectively. A zero CAC score in hypertensive over the age of 60 years was associated with a lower but persisting risk of mortality for (HR 2.48 [95% CI: 1.50–4.08]) that was attenuated non-significant for those below the age of 60 years ($P = 0.09$). In a "low risk" hypertensive population, the presence any CAC was associated with an almost five-fold (HR 4.68 [95% CI: 2.22–9.87]) increased risk of death.
Conclusion: The presence and extent of CAC effectively may help the clinicians to further discriminate the long-term risk of mortality among asymptomatic hypertensive individuals, beyond conventional cardiovascular risk and current guidelines.

1. Introduction

One third of the adult population in the United States is affected by hypertension which remains a primary cause of mortality, accounting for approximately 14% of all US deaths [1]. Recently, the Joint National Committee set forth new guidelines regarding the clinical management of high blood pressure in adults [2]. These guidelines diverge from prior recommendations, with an age-stratified difference in recommendation for targeted blood pressure goals. Specifically, in hypertensive subjects younger than 60 years free from diabetes and kidney disease, these guidelines further state that the management of blood pressure should be determined based upon clinical evaluation and use of the global cardiovascular risk assessment scores.

To this end, novel tools that effectively stratify risk of younger and older individuals with hypertension are needed [3,4]. In short- and intermediate-term follow-up, the assessment of coronary artery calcification (CAC) scoring by computed tomography (CT) imaging is a non-invasive tool that enables accurate stratification of risk [5–9]. Specifically, the presence [10,11], severity [12], and progression [13,14] of CAC have been shown to be independently associated with major adverse cardiovascular events [10–15] and death [6,10,15–20], while a low risk of adverse outcomes has been observed in the absence of CAC [21–23]. Nevertheless, these investigations lack insight towards the

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long-term efficacy of CAC for risk stratification, are limited in their focus among the hypertensive population, and have not yet examined the prognostic utility of CAC for hypertensive individuals when stratified by age.

To address this, in a large consecutive cohort of asymptomatic hypertensive individuals followed for 14 years, we sought to examine whether CAC could accurately stratify the risk of mortality.

2. Methods

2.1. Study population

The study cohort comprised 9715 consecutive asymptomatic individuals (41% female) without known coronary artery disease (CAD). All individuals referred by their physicians for electron beam computed tomography (EBCT) underwent CAC testing from a single site. Of 9715 individuals, 810 were excluded due to the presence of diabetes. The remaining 8905 individuals (mean age 53.3 ± 10.5, 59.3% male) who represented the study population were divided into 2 groups based on hypertension status (Table 1). From the remaining cohort, we identified a sub-population of individuals without other traditional cardiovascular risk factors, as defined by the absence of dyslipidemia, family history of premature CAD, and smoking status (n = 781). Those individuals are considered by definition [21], at low Framingham Risk Score (FRS) risk (herein referred to as low-risk subgroup). All screened individuals provided informed consent to undergo EBCT and the study received approval from the appropriate Human Investigations Committee.

2.2. Risk factor collection

All study participants were prospectively provided with a questionnaire for the collection of demographic characteristics as well as baseline cardiovascular risk factors. The following risk factors were considered in this study: 1) cigarette smoking was present if a subject was an active smoker at the time of scanning; 2) dyslipidemia was considered to be present for any individual reporting a history of high total cholesterol, high low density lipoprotein cholesterol, low high-density lipoprotein cholesterol, high triglycerides, or current use of lipid-lowering therapy; 3) diabetes was defined as baseline use of anti-diabetic medication or had a history of elevated blood glucose measurement of >126 mg/dl; 4) hypertension was defined as a self-reported history of high blood pressure or had a documented blood pressure ≥140/90 mm Hg or use of antihypertensive medication; and 5) family history of premature CAD was determined by asking individuals whether any member of their immediate family (parents or siblings) had a history of fatal or nonfatal myocardial infarction and/or coronary revascularization in a male relative <55 years or a female relative <65 years.

2.3. EBCT screening protocol

All subjects underwent EBCT on either a C-100 or C-150 Ultrafast CT scanner (GE-Imatron, South San Francisco, California). With a tomographic slice thickness of 3 mm, a total of approximately 40 sections were obtained beginning at the level of the carina and proceeding caudally to the level of the diaphragm. Images were obtained with a 100-ms/slice scanning time, with image acquisition electrocardiographically triggered at 60% to 80% of the R–R interval. A calcified lesion was defined as >3 contiguous pixels with a peak attenuation of at least 130 Hounsfield units. Each lesion was then scored using the method developed by Agatston et al. [24] (Agatston units).

2.4. Study outcome

The primary endpoint of this study was death from all-causes. Ascertainment of mortality status was conducted by individuals masked to baseline historical data and EBCT results, and was verified using the Social Security Death Index. The Social Security Death Index is a national registry of all deaths that have occurred in the United States, allowing for 100% mortality ascertainment among study participants.

2.5. Statistical methods

Categorical variables are presented as counts with proportions (%) and continuous variables as mean ± SD or median and interquartile range. The chi-square test was employed for comparison of categorical variables. Between-group comparisons for continuous variables were computed using the independent samples t-test or the Mann–Whitney U test as appropriate. A Kaplan–Meier survival curve with log-rank test was employed to compare survival rates for hypertensives versus normotensives above or below the age of 60 years, according to existing or absent CAC. Cox proportional hazard regression reporting hazard ratios (HRs) with 95% confidence intervals (95% CI) was performed to examine the risk of death from all causes in the overall study population. Separately, we repeated the Cox analyses for the low-risk sub-group (i.e., with no traditional cardiovascular risk factors). All Cox models were stratified according to hypertension status, age above and below 60 years, and the presence or absence, as well as severity of CAC. Additionally, all Cox models were adjusted for gender, smoking, dyslipidemia, and family history of premature CAD. We additionally tested the incremental prognostic value of CAC over and above an established risk algorithm, the Framingham Risk Score (FRS), using the area under the receiver operator characteristic curve (AUC). Further, we computed the net reclassification improvement (NRI) [26], which provides an estimate in percentage gain in reclassification for a pre-specified set of cut-off points. For the latter analysis, we chose risk categories based on low (<10%), intermediate (10% to 20%), and high (>20%) 10-year Framingham risk [6]. Statistical analyses were performed using SAS

Table 1
Clinical characteristics of the study population.

Variable	Total n (N = 8905)	Hypertension status								
		All subjects			Classified by age					
					<60 years			≥60 years		
		No (N = 5186)	Yes (N = 3719)	P value	No (N = 3881)	Yes (N = 2654)	P value	No (N = 1305)	Yes (N = 1065)	P value
Mean follow-up (years)	14.6 ± 1.0	14.6 ± 1.0	14.6 ± 1.0	0.49	14.6 ± 1.0	14.6 ± 1.1	0.32	14.5 ± 1.1	14.5 ± 1.1	0.55
Death events (%)	748 (8.4)	340 (6.6)	408 (11.0)	<0.001	199 (5.1)	210 (7.9)	<0.001	141 (10.8)	198 (18.6)	<.0001
Age (years)	53.3 ± 10.5	52.8 ± 10.5	53.9 ± 10.3	<0.001	48.1 ± 6.9	48.8 ± 6.7	<0.001	66.9 ± 5.8	66.6 ± 5.4	0.34
Gender (female)	3621 (40.7)	2123 (40.9)	1498 (10.3)	0.53	1478 (38.1)	935 (35.2)	0.0189	645 (49.4)	563 (52.9)	0.0958
Dyslipidemia	5540 (62.2)	2975 (57.4)	2565 (69.0)	<0.001	2227 (57.4)	1823 (68.7)	<0.001	748 (57.3)	742 (69.7)	<.0001
Current smokers	3473 (39.0)	1965 (37.9)	1508 (40.6)	0.01	1474 (38.0)	1081 (40.7)	0.0252	491 (37.6)	427 (40.1)	0.2196
Family history premature CAD	6140 (69.0)	3491 (67.3)	2649 (71.2)	<0.001	2658 (68.5)	1879 (70.8)	0.0464	833 (63.8)	770 (72.3)	<.0001
CAC > 0 (%)	4316 (48.5)	2225 (42.9)	2091 (56.2)	<0.001	1595 (41.1)	1434 (54.0)	<0.001	630 (48.3)	657 (61.7)	<0.001

CAD: Coronary artery disease; CAC: coronary artery calcification.