Atherosclerosis xxx (2017) 1–9

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

Is there a role for coronary artery calcification scoring in primary prevention of cerebrovascular disease?

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ARTICLE INFO

Article history:
Received 12 September 2016
Received in revised form
29 November 2016
Accepted 12 January 2017
Available online xxx

Keywords:
Cerebrovascular disease
Coronary artery calcification

ABSTRACT

Cerebrovascular disease (CVA) is one of the most prevalent causes of death and disability in the United States, and its primary prevention is crucial. For the primary prevention of CVA, it is commonly recommended that all adults should initially undergo an office-based traditional risk assessment using established predictive models, such as the Framingham Stroke Profile Score or the atherosclerotic cardiovascular disease (ASCVD) risk calculator from the American College of Cardiology/American Heart Association (ACC/AHA). Coronary artery calcification (CAC) is an independent risk predictor of cardiovascular disease (CVD), which often includes CVA. A CAC score can improve discrimination for CVD in the general population beyond established risk prediction tools. Several recent major prospective studies have assessed the use of CAC data to predict CVA events in asymptomatic patients. The CAC score itself is a reliable independent risk factor for predicting CVA events after adjusting for traditional risk factors. Regarding discriminative value, there is little value afforded by the addition of the CAC score to current CVA risk prediction tools. In this review, we summarize the current key literature regarding the CAC score and CVA. We focus on its diagnostic value in identifying patients at risk and the utility of the CAC score for stratification of individuals.

1. Introduction

Cerebrovascular disease (CVA) is one of the most prevalent causes of death and disability in the United States [1], as 3.4 million people have had a stroke in the U.S., and this number is expected to increase by 20.5% by the year 2030 [2,3]. In addition, the total direct stroke-related medical costs are projected to triple during this period [2]. Primary prevention is currently difficult because most strokes occur in people without known CVA.[2] Guidelines from the American Heart Association/American Stroke Association (AHA/ASA) recommend that all adults should initially undergo an office-based traditional risk assessment using an established predictive model, such as the Framingham Stroke Profile Score [4]. In addition, the American College of Cardiology/American Heart Association (ACC/AHA) has included CVA risk in addition to CVD risk in the new risk equation for the atherosclerotic cardiovascular disease (ASCVD) risk score in the most recent prevention guidelines [5]. The lifetime prognostic abilities of these risk assessments have been established; however, their prognostic effects depend on the magnitude of the deviation of the risk factors from normal and on the duration of exposure [6]. Additionally, these risk assessments do not offer any information about the severity of actual vascular disease.

Coronary artery calcification (CAC) can form during the early stages of atherosclerosis and represents a linear estimate of the total plaque burden of coronary artery atherosclerosis [7]. A CAC score, which is based on a quantification of calcification, allows direct visualization of the cumulative effect of all risk factors in an individual patient and enables personalized risk assessment. Individuals with a high CAC score have a high risk of coronary heart disease (CHD) [8–10]. Moreover, CAC has a close relationship with the extra-coronary plaque burden [11–13] and, thus, can also be considered as manifestation of atherosclerotic disease at other sites within the vascular network.

Numerous studies have investigated whether CAC predicts CVD or coronary heart disease events. After the aforementioned ACC/AHA prevention guidelines were released, however, data from major prospective studies to determine whether the CAC score is useful for predicting CVA events in asymptomatic patients are now available. This review will focus on the use of CAC testing in stratifying patients for risk of CVA, with implications for patient

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http://dx.doi.org/10.1016/j.atherosclerosis.2017.01.007
0021-9150/

management based on these tests.

2. The association between CAC and intra- and extracranial artery atherosclerosis

Most CVA events are due to ischemic infarction (87%, ischemic; 10%, intracerebral hemorrhage; 3%, subarachnoid hemorrhage) [1] and are commonly derived from an arterial obstruction resulting from a thrombus or embolism. Hence, it is important to evaluate intra- and extracranial vessels to identify asymptomatic individuals at high risk of CVA. Increased carotid intima-media thickness (IMT) and carotid plaque volume are strongly associated with cardiac and stroke events. A meta-analysis of eight population-based studies including over 37000 individuals showed that an increase in the common carotid artery IMT is significantly associated with future CVA events [14]. In addition, the BioImage study, a prospective observational study that followed >5800 asymptomatic adults in the U.S., demonstrated that carotid artery plaque (CAP) burden, as assessed by three-dimensional ultrasound, is a strong predictor of future major adverse cardiac events (MACE), with individuals in the highest CAP burden category being 2.3-fold more likely to have a MACE (hazard ratio [HR] 2.36, 95% confidence interval [CI] 1.13–4.92) [15].

Atherosclerosis is a systemic disease, and individuals with CAP could have plaques present within other vascular beds, such as the coronary artery.[16] Based on pathology, carotid and coronary arteries undergo a similar process of atherosclerosis.[17] In both vascular beds, the first manifestation of atherosclerosis is pathological intimal thickening and the development of advanced atheromatous plaques with necrosis that could lead to both cardiovascular and cerebrovascular events. Several studies have demonstrated an association between CAC and carotid plaques. The Multi-Ethnic Study of Atherosclerosis (MESA), a National Institutes of Health (NIH)-sponsored prospective population cohort study, indicated that carotid stenosis of >50% as measured by ultrasound was associated with the presence of CAC (odds ratio [OR] 1.73; 95% CI 1.20–2.49) and with the log-transformed Agatston score (OR per 1-point increase 1.18; 95% CI 1.04–1.35) as a measure of the extent of coronary artery calcification.[18] Likewise, the BioImage study showed that carotid plaque burden, as determined by three-dimensional ultrasound, had a strong correlation with CAC score (Chi-squared 450, $p < 0.0001$) and patients in the highest tertile of carotid plaque burden (>4.21 cm^2) had a 4.79-fold (95% CI 4.11–6.22) greater odds of being in the highest category of CAC scores (CAC score > 400), as compared with patients without CAP.[19] In addition, in an analysis of 10550 participants [20], intracranial arterial stenosis of >50%, as detected by transcranial Doppler, showed a strong association with CAC score. Compared with individuals with a CAC score of zero, those with a CAC score ≥400 showed a significantly increased OR of 2.75 (95% CI 1.33–5.69) for having intracranial arterial stenosis.[20] Table 1 provides a summary of the studies examining the association between CAC and intra- and extracranial artery atherosclerosis. Overall, there was a good association between CAC and both intra- and extracranial artery atherosclerosis, and a CAC sore of >400 was significantly associated with an OR of ~3.0 for having intra- and extracranial artery stenosis. Moreover, carotid plaque burden, as determined by the sum of the areas of atherosclerosis in the carotid artery based on three-dimensional ultrasound, was correlated more strongly with the CAC score, which was also obtained with three-dimensional methods by computed tomography (CT), than with carotid intima-media thickness (c-IMT) assessment by conventional ultrasound. An association between CAC and cerebral small vessel disease as detected by magnetic resonance imaging was investigated in individuals of ≥65 years old without alleged cardiac or neurological disease. A CAC score of ≥100 was significantly associated with an adjusted OR of 4.69 (95% CI 1.30–16.98, $p = 0.02$) for having white matter lesions, an adjusted OR of 5.04 (95% CI 1.86–13.63, $p < 0.01$) for having silent lacunar infarction and an adjusted OR of 6.07 (95% CI 1.54–23.94, $p = 0.01$) for having cerebral microbleeds.[21]

Thus individuals with a positive or increased CAC score may be more likely to have a higher prevalence of intra- and extracranial vessel disease, suggesting that CAC is a risk factor for future strokes, and, thus, such subjects should be considered as having a high risk of CVA and treated accordingly.

3. The CAC score as an independent risk predictor for CVA events

Several population-based cohort studies have consistently demonstrated that elevated CAC scores are associated with increased risk of new-onset CVD including stroke, independently of standard risk factors.[15, 22–28] Table 2 provides a summary of the studies examining the association between CAC and CVA events. Using data from the MESA study, we demonstrated that a CAC score >0 was a strong and graded predictor of incident atherosclerotic CVD (including stroke and transient ischemic attack) at a median follow-up of 10.2 years. As compared with a CAC score of zero, CAC ranges of 1–100 (HR 2.1, 95% CI 1.6–2.6), 101–300 (HR 3.1, 95% CI 2.4–4.0) or >300 (HR 4.5, 95% CI 3.5–5.8) were all predictive of ASCVD events at 10 years.[53]

Similarly, several studies have focused on only CVA risk and investigated the association between CAC and the risk of a CVA event.[23, 29–37] In short- or middle-term follow-up studies, there remained an active debate about the association between CAC and the risk of CVA events. In the Cardiovascular Health Study, consisting of 559 elderly U.S. subjects who were followed for 5 years, CAC score was strongly related to stroke risk and the adjusted HR for the CAC scores in the 2nd, 3rd and the highest quartile versus those in the lowest quartile was 2.51, 4.09 and 3.29, respectively.[36] Likewise, in a matched case-control study, moderate to extensive CAC (corresponding to a CAC score ≥ 100) was strongly associated with ischemic stroke, with an OR of 1.72 as compared with subjects with a CAC score of zero.[31] Moreover, among a cohort of 1137 individuals with suspected CAD during a median 26-month follow-up, Lee et al. reported that the presence and the extent of CAC were associated and were independent predictors of ischemic stroke.[35] In contrast, Folsom et al. showed no relationship between CAC and stroke median follow-up of 3.9 years in the MESA study.[23] They showed that the maximum c-IMT was statistically significantly associated with stroke with a multivariate adjusted HR of 1.3 (95% CI 1.1–1.7), but this was not true for CAC. Likewise, in the Rotterdam study, no clear association was found between CAC and CVA events (stroke + transient ischemic attack [TIA]) during a follow-up of 3.5 years. Compared with individuals with CAC scores falling within the lowest tertile, those with scores in the second and third tertiles had a reduced risk of CVA events of 0.8 (95% CI 0.4–1.5) and 0.5 (95% CI 0.2–1.0), respectively.[37]

In contrast with these short- to mid-term follow-up studies, the long-term follow-up studies showed the robustness of the relationship between CAC and CVA events regardless of CVA subtypes (Table 2). In MESA, CVA events defined as all strokes or TIAs were observed in 234 of 6779 events (3.5%) during a mean follow-up of 9.5 years.[33] Individuals with a CAC score > 0 had a higher risk of a CVA event as compared with those with a CAC score of zero (log rank chi squared = 59.84, $p < 0.0001$), and log-transformed CAC was an independent predictor for CVA events.[33] Likewise, in MESA, the presence of CAC was an independent predictor of CVA events (ischemic stroke + TIA) with a HR of 1.54 (95% CI 1.09–2.18, $p = 0.015$). [34] Similarly, the Heinz Nixdorf Recall study, which is a

Please cite this article in press as: K. Osawa, et al., Is there a role for coronary artery calcification scoring in primary prevention of cerebrovascular disease?, Atherosclerosis (2017), http://dx.doi.org/10.1016/j.atherosclerosis.2017.01.007