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The predictive value of arterial and valvular calcification for mortality and cardiovascular events

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ABSTRACT

A review of the predictive ability of arterial and valvular calcification has shown an additive effect of calcification in more than 1 location in predicting mortality and coronary heart disease, with mitral annual calcification being a particularly strong predictor. In individual arteries and valves there is a clear association between calcification presence, extent and progression and future cardiovascular events and mortality in asymptomatic, symptomatic and high risk patients, although adjustment for calcification in other arterial beds generally renders associations non-significant. Furthermore, in acute coronary syndrome, culprit plaque is normally not calcified. This would tend to reduce the validity of calcification as a predictor and suggest that the association with cardiovascular events and mortality may not be causal. The association with stroke is less clear; carotid and intracranial artery calcification show little predictive ability, with symptomatic plaques tending to be uncalcified.

Introduction

We have previously shown that arterial and valvular calcification is a systemic disease [1]. Its predictive ability was indicated in a large 2009 meta-analysis of 30 studies comprising 218,080, mainly asymptomatic subjects, some of whom were renal patients. This found that after a mean 10 year follow-up the presence of arterial and valvular calcification was significantly associated with all-cause and CV mortality, coronary events and stroke, with CT scanning of the coronary artery giving the highest OR compared to calcification of other arteries [2]. However, this meta-analysis did not consider the predictive ability of individual sites of calcification and several locations, such as the carotid artery, were poorly represented. Since publication of this meta-analysis, there have been a considerable number of studies which are able to shed more light on the situation. In this review we discuss associations found between the prevalence, extent or progression of calcification of arteries and valves and their predictive ability for CV events and mortality in non-renal patients.

Multiple site calcification comparison

A few studies have investigated the predictive ability of several sites of calcification. Among asymptomatic subjects, the presence and extent of mitral annulus calcification (MAC) was more closely associated with cardiovascular (CV) and all-cause mortality than aortic valve calcification (AVC) or abdominal aortic calcification (AAC), although there was an additive effect of calcification in >1 location [3]. In very elderly high risk subjects, a simple score comprising presence of cardiac, carotid and femoral artery and aorta calcification was correlated with all-cause, but not CV, mortality, with the risk rising with calcification score and increasing numbers of calcification sites, although the association came mainly from valves and only MAC was also predictive of CV mortality [4]. In symptomatic type 2 diabetics, mitral and aortic calcification combined were far more predictive of mortality than calcification of an individual valve [5].

A composite score of coronary, carotid and aortic arch calcification significantly improved the C-statistic for coronary heart disease (CHD) over the Framingham model but did not aid cerebrovascular risk prediction. Similarly, this composite score was not associated with cerebrovascular events in asymptomatic elderly subjects followed up for 3.5 years [6]. In heavy smokers, coronary artery calcification (CAC), but not thoracic aorta calcification (TAC), was associated with coronary events, while TAC but not CAC was associated with non-coronary events, although the follow-up was very short [7].

Calcification of the coronary artery

Our earlier review highlighted the significant association between the presence, extent and progression of CAC and mortality and CV events and also presented the conflicting evidence that culprit plaque

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in acute coronary syndrome (ACS) is typically uncalcified [8]. Since then, the MESA, Heinz Nixdorf Recall and other studies have shown similar results in asymptomatic subjects [9–11] and confirmed the utility of CAC for improving risk stratification above conventional risk factors [12]. In contrast, a large study failed to confirm this relationship after adjusting for calcium in other arterial beds [13].

In symptomatic patients, the CAC score was associated with a composite of cardiac death, non-fatal MI and coronary revascularization, although calcified plaques had the lowest predictive value compared to non-calcified and mixed plaque [14]. A similar composite outcome was predicted among type 2 diabetics [15] and heavy smokers [7] but the CAC score did not predict ACS development in chest pain patients [16]. An autopsy study showed that although the extent of CAC correlated with fatal MI, the unstable culprit lesions were not calcified [17].

Calcification of the aorta

Jacobs et al. found an increase in annualized CV event rate with increasing ascending aorta calcium scores. An increase of 1SD in TAC score resulted in a 46% increased CV event risk, with CAC proving to be a stronger predictor of coronary events whereas TAC predicted non-cardiac events [18] several studies showed that TAC and AAC are independent predictors of CVD and CV and all-cause mortality [19–23], although for AAC the results of mortality studies are mixed [2,24]. Nevertheless, after adjustment for calcification in other arterial beds, the association with TAC was no longer significant and did not improve the Framingham risk model [13,25,26]. There may be a gender difference with respect to the predictive ability of TAC. Budoff et al. showed that while TAC had no predictive ability for males after adjustment for CAC, in females TAC remained predictive of coronary events [27]. Likewise, two studies found that TAC [28] and AAC [29] were independent predictors of ischaemic stroke in women only, while Danielsen et al. showed that TAC presence was associated with increased coronary mortality in women only, while in men it was associated with all-cause mortality [30].

In symptomatic patients [31] and heavy smokers [5], there was a significant correlation between the presence of TAC and all-cause and CV mortality and CV events respectively. Among hypertensives, Tanne et al. found that only calcification of ≥ 5 mm in the descending aorta was an independent predictor of ischaemic stroke [32], while in prior stroke patients, the absence of baseline TAC increased the risk of vascular events [33].

Calcification of the carotid/intracranial artery

Although an association has generally been found between carotid or intracranial calcification presence and current or prior cerebral infarcts [34–37], its predictive ability is not so clear. In asymptomatic subjects, Prabhakaran et al. found that carotid artery calcification presence was significantly associated with a combined vascular outcome of ischaemic stroke, MI and vascular death [38]. Nevertheless, Koton et al. found no association between intracranial artery calcification (ICAC) and mortality, although this study had a short follow-up [39] and Allison et al. showed that carotid artery calcification predicted all-cause but not CV mortality but after adjustment for increasing increments of calcium in other arterial beds, the association became non-significant [13]. Small studies of Chinese and Japanese patients found that the carotid calcium score could not predict cerebrovascular events [40,41] although the presence of uncalcified plaque significantly increased stroke risk in males [42]. Similarly, endarterectomy studies have shown that carotid calcification is associated with acute coronary events but not cerebrovascular events [43,44], while calcified plaques showed increased cerebrovascular reactivity, indicating plaque stability [45].

A 2010 systematic review has shown that symptomatic plaques have a lower degree of calcification volume, weight or percentage than asymptomatic plaques, with calcification percentage being the strongest predictor of plaque stability [46]. Since then, Eesa et al. showed that in patients with prior cerebrovascular events, calcification was significantly associated with the asymptomatic side and not with the symptomatic side, suggesting that extensive calcification may reflect plaque stability [47]. A recent study determined that although ICAC volume was associated with prior cardiac or ischaemic cerebrovascular disease, it was not associated with current ischaemic cerebrovascular symptoms [48], while culprit plaque in acute ischaemic events had a thin fibrous cap, large lipid pool and macrophage-dense inflammation, with calcification being associated with stability [49].

Calcification of other arteries

A review of 25 studies of breast artery calcification (BAC), found that a majority showed BAC having high specificity but low sensitivity and negative predictive value for CV events [50]. A number of studies also found that BAC was significantly associated with CHD, heart disease and mortality, although the findings were not consistent for cerebrovascular disease [51,52].

Peripheral artery calcification was shown to be strongly associated with CHD mortality [53] and with all-cause and CV mortality but not stroke mortality in type 2 diabetics [54]. An earlier study had found that the association of calcification with mortality held for diabetics but not non-diabetics [55]. In the renal and iliac arteries, calcification was predictive of mortality but after adjustment for calcium extent in other arterial beds, the association became non-significant [13,56].

Calcification of the aortic valve

The MESA found that in asymptomatic subjects, increasing tertiles of AVC were associated with increased CV event risk, while AVC presence conferred higher risks of CV events and mortality and resuscitated cardiac arrest, although the association with CV events was lost after adjusting for CAC [57]; similarly Blaha et al. showed that after adjustment for CAC presence, AVC remained a significant predictor of all-cause mortality and could improve risk stratification, but when adjustment was made for the CAC score the association became non-significant [58]. In stroke studies Rodriguez et al. found that the presence of calcification of the aortic valve or annulus was significantly associated with a higher prevalence of covert brain infarcts [59] but this finding was contradicted in a study of younger American Indian subjects [60]. Similarly, Boon et al. found no association between AVC and prior or subsequent brain infarct or intracerebral hematoma [61].

In symptomatic or high risk patients, the AVC score was the strongest multivariate predictor of CV events [62], particularly during the peri-operative period. In addition, patients with AVC score >750 had a significantly lower 12 month survival rate compared to those with scores <750 [63].

Calcification of the mitral valve

A large study by Gardin et al. showed that MAC presence in asymptomatic subjects was a multivariate predictor of CHD but not of stroke or all-cause mortality [64]. Nevertheless, in younger subjects Fox et al. found that MAC presence and extent were associated with increased risk of CVD, related mortality and all-cause mortality [65]. A large study of African Americans showed that MAC presence was predictive of fatal or hospitalized MI and revascularization procedures [66], while in Hispanics, MAC >4 mm was an independent predictor of MI and vascular mortality but not ischaemic stroke [67]. In the elderly the presence and extent of MAC was significantly associated with a higher prevalence of stroke after adjustment for risk factors [59,68], although in younger populations the results are mixed [60,69]. Large studies found that all-