



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



Rachel Nicoll, Michael Y. Henein*

Department of Public Health and Clinical Medicine and Heart Centre, Umea University, Umea, Sweden
Canterbury Christ Church University, Kent, UK

ARTICLE INFO

Article history:

Received 20 November 2013

Accepted 1 February 2014

Available online 7 February 2014

Keywords:

Calcification

Carotid/intracranial artery

Aortic valve

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 annular 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.

© 2014 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

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

* Corresponding author at: Department of Public Health and Clinical Medicine and Heart Centre, Umea University, Umea, Sweden.

E-mail address: Michael.henein@medicin.umu.se (M.Y. Henein).

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-

cause and CV mortality were significantly higher in those with MAC, although the association with CV mortality only held for women [70]. A smaller study confirmed that MAC was independently predictive of all-cause mortality in males [71].

Among CHD patients MAC was associated with an increased rate of CV events [72], while other studies have generally shown that in symptomatic or high risk patients the presence of MAC was associated with all-cause and CV mortality and morbidity [73,74].

Discussion

Studies of multiple locations have shown an additive effect of calcification in more than one location in predicting mortality and CHD; the predictive ability appears to derive mainly from MAC, although in asymptomatic subjects a total arterial calcification score does not predict cerebrovascular events. In heavy smokers, CAC is associated with coronary events and TAC with non-coronary events. Studies of individual arteries and valves generally show a clear association between calcification presence, extent and progression and future CV events and mortality in asymptomatic, symptomatic and high risk patients, although the association between valve and carotid calcification and stroke alone is less clear. Nevertheless, culprit coronary plaque in ACS is generally not calcified. Adjusting for calcification in other arterial beds renders associations in arteries and valves non-significant, although in women TAC may remain predictive of coronary events. Although the association between carotid or intracranial artery calcification and previous cerebral infarcts is established, there is generally little predictive ability for acute stroke. Similarly, endarterectomy studies show that carotid calcification is associated with ACS but not cerebrovascular events, while symptomatic plaques tend to have less calcification than asymptomatic plaques, suggesting that calcification confers stability.

Our review shows that whether considering arteries or valves, if an adjustment is made for calcification in other locations, then any association with CV events and mortality loses significance. This would tend to reduce the validity of calcification as a predictor and indicate that while it clearly develops prior to CV events and mortality, the association may not be causal. The predictive value of arterial calcification in the elderly has already been questioned [4] and it has been suggested that it serves as a marker of a more generalized vascular disease process, possibly involving inflammation [37].

The repeated lack of association between carotid calcification and ischaemic stroke, primarily embolic, echoes the results of autopsy studies showing that coronary culprit lesions tend to have a large lipid-rich necrotic core with a thin overlying fibrous cap, as indicators of instability which are associated with acute rupture and luminal thrombi [46]. Coronary and carotid calcium are believed to stabilize the plaque by stiffening and protecting against biomechanical stress and subsequent rupture or erosion [41,75], although regions of plaque calcification adjacent to an inflamed soft necrotic core may predispose to increased peak stress [76]. It has also been proposed that calcification is an attempt by the arterial wall to repair existing damage and to reduce the likelihood of plaque rupture [77].

Several authors have pointed out that in the coronary and carotid arteries calcification tends to occur on atherosclerotic plaque and is therefore largely intimal, while in other arteries it may also be medial, where it is unrelated to atherosclerosis but can cause arterial stiffness and is associated with diabetes and renal disease [25,78]. Since no scanning modality can at present distinguish between intimal and medial calcification, it is not possible to assess the contribution of each, although they may have different predictive ability [25]. It has been argued that calcification of valves, particularly the aortic valve is similar to atherosclerosis and may occur as a result of mechanical stress, endothelial damage or through the effect of shared risk factors [79]. Yet statins have failed to slow the

progression of valve calcification or delay clinical outcome, suggesting that the association is coincidental [80].

Conclusion

This review shows that calcification presence, extent and progression in various arterial and valvular sites predicts coronary events and mortality in asymptomatic, symptomatic and high risk patients, with an additive effect of calcification in more than one location. There are mixed results for studies of stroke prediction, with calcification of the coronary artery, aorta and valves generally showing an association, while in the carotid and intracranial arteries calcification was associated with current and prior cerebrovascular events but was not predictive of stroke. Similarly, endarterectomy and symptomatology studies showed that it was uncalcified plaques, rather than calcified plaques, which predicted cerebrovascular disease or its symptoms. This finding was reflected in the coronary artery, where the culprit lesion for ACS was typically uncalcified, suggesting that calcification confers some stability on the plaque. Studies investigating multiple locations found that calcification of valves, and particularly MAC, showed the strongest associations. Nevertheless, studies that adjust for calcification in other arterial beds generally render associations non-significant.

References

- Nicoll R. Arterial and valvular calcification: a systemic diffuse disease. *Int Cardiovasc Forum* 2013;1:19–24.
- Rennenberg RJMW, Kessels AGH, Schurgers LJ, van Engelshoven JMA, de Leeuw PW, Kroon AA. Vascular calcifications as a marker of increased cardiovascular risk: a meta-analysis. *Vasc Health Risk Manag* 2009;5(1):185–97.
- Barasch E, Gottdiener JS, Marino Larsen EK, Chaves PH, Newman AB. Cardiovascular morbidity and mortality in community-dwelling elderly individuals with calcification of the fibrous skeleton of the base of the heart and aortosclerosis (The Cardiovascular Health Study). *Am J Cardiol* 2006;97(9):1281–6.
- Zhang Y, Safar ME, Iaria P, et al. Cardiac and arterial calcifications and all-cause mortality in the elderly: the PROTEGER Study. *Atherosclerosis* 2010;213(2):622–6.
- Rossi A, Targher G, Zoppini G, et al. Aortic and mitral annular calcification are predictive of all-cause and cardiovascular mortality in patients with type 2 diabetes. *Diabetes Care* 2012;35(8):1781–6.
- Elias-Smale SE, Wieberdink RG, Odink AE, et al. Burden of atherosclerosis improved the prediction of coronary heart disease but not cerebrovascular events: the Rotterdam Study. *Eur Heart J* 2011;32(16):2050–8.
- Jacobs PC, Prokop M, van der Graaf Y, et al. Comparing coronary artery calcium and thoracic aorta calcium for prediction of all-cause mortality and cardiovascular events on low-dose non-gated computed tomography in a high-risk population of heavy smokers. *Atherosclerosis* 2010;209(2):455–62.
- Nicoll R, Henein MY. Arterial calcification: friend or foe. *Int J Cardiol* 2013;167(2):322–7.
- Graham G, Blaha MJ, Budoff MJ, et al. Impact of coronary artery calcification on all-cause mortality in individuals with and without hypertension. *Atherosclerosis* 2012;225(2):432–7.
- Hermann DM, Gronewold J, Lehmann N, et al. Coronary artery calcification is an independent stroke predictor in the general population. *Stroke* 2013;44(4):1008–13.
- Budoff MJ, Young R, Lopez VA, et al. Progression of coronary calcium and incident coronary heart disease events: the Multi-Ethnic Study of Atherosclerosis. *J Am Coll Cardiol* 2013;61(12):1231–9.
- Rana JA, Gansar H, Wong ND, et al. Comparative value of coronary artery calcium and multiple blood biomarkers for prognostication of cardiovascular events. *Am J Cardiol* 2012;109(10):1449–53.
- Allison MA, Hsi S, Wassel CL, et al. Calcified atherosclerosis in different vascular beds and the risk of mortality. *Arterioscler Thromb Vasc Biol* 2012;32(1):140–6.
- Hou ZH, Lu B, Gao Y, et al. Prognostic value of coronary CT angiography and calcium score for major adverse cardiac events in outpatients. *JACC Cardiovasc Imaging* 2012;5(10):990–9.
- Kramer CK, Zinman B, Gross JL, et al. Coronary artery calcium score prediction of all-cause mortality and cardiovascular events in people with type 2 diabetes: systematic review and meta-analysis. *BMJ* 2013;346:f1564.
- Versteylen MO, Joosen IA, Winkens MH, et al. Combined use of exercise electrocardiography, coronary calcium score and cardiac CT angiography for the prediction of major cardiovascular events in patients presenting with stable chest pain. *Int J Cardiol* 2013;167(1):121–5.
- Mauriello A, Servadei F, Zoccai GB, et al. Coronary calcification identifies the vulnerable patient rather than the vulnerable plaque. *Atherosclerosis* 2013;229(1):124–9.
- Jacobs PC, Gondrie MJ, Mali WP, et al. Unrequested information from routine diagnostic chest CT predicts future cardiovascular events. *Eur Radiol* 2011;21(8):1577–85.

- [19] Hollander M, Hak AE, Koudstaal PJ, et al. Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam Study. *Stroke* 2003;34(10):2367–72.
- [20] Schousboe JT, Taylor BC, Kiel DP, Ensrud KE, Wilson KE, McCloskey EV. Abdominal aortic calcification detected on lateral spine images from a bone densitometer predicts incident myocardial infarction or stroke in older women. *J Bone Miner Res* 2008;23(3):409–16.
- [21] Golestani R, Tio R, Zeebregts CJ, et al. Abdominal aortic calcification detected by dual X-ray absorptiometry: a strong predictor for cardiovascular events. *Ann Med* 2010;42(7):539–45.
- [22] Van der Meer IM, Bots ML, Hofman A, del Sol AI, van der Kuip DA, Witteman JC. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. *Circulation* 2004;109(9):1089–94.
- [23] Bolland MJ, Wang TK, van Pelt NC, et al. Abdominal aortic calcification on vertebral morphometry images predicts incident myocardial infarction. *J Bone Miner Res* 2010;25(3):505–12.
- [24] Rodondi N, Taylor BC, Bauer DC, et al. Association between aortic calcification and total and cardiovascular mortality in older women. *J Intern Med* 2007;261:238–44.
- [25] Kalsch H, Lehmann N, Berg MH, et al. Coronary artery calcification outperforms thoracic aortic calcification for the prediction of myocardial infarction and all-cause mortality: the Heinz Nixdorf Recall Study. *Eur J Prev Cardiol* 2013 [Epub ahead of print].
- [26] Santos RD, Rumberger JA, Budoff MJ, et al. Thoracic aorta calcification detected by electron beam tomography predicts all-cause mortality. *Atherosclerosis* 2010;209(1):131–5.
- [27] Budoff MJ, Nasir K, Katz R, et al. Thoracic aortic calcification and coronary heart disease events: the multi-ethnic study of atherosclerosis (MESA). *Atherosclerosis* 2011;215(1):196–202.
- [28] Iribarren C, Sidney S, Sternfeld B, Browner WS. Calcification of the aortic arch: risk factors and association with coronary heart disease, stroke and peripheral vascular disease. *JAMA* 2000;283(21):2810–5.
- [29] Levitzky YS, Cupples LA, Murabito JM, et al. Prediction of intermittent claudication, ischemic stroke and other cardiovascular disease by detection of abdominal aortic calcific deposits by plain lumbar radiographs. *Am J Cardiol* 2008;101:326–31.
- [30] Danielsen R, Sigvaldson H, Thorgeirsson G, Sigfusson N. Predominance of aortic calcification as an atherosclerotic manifestation in women: the Reykjavik study. *J Clin Epidemiol* 1996;49(3):383–7.
- [31] Eisen A, Tenenbaum A, Koren-Morag N, et al. Calcification of the thoracic aorta as detected by spiral computed tomography among stable angina pectoris patients: association with cardiovascular events and death. *Circulation* 2008;118(13):1328–34.
- [32] Tanne D, Tenenbaum A, Shemesh J, et al. Calcification of the thoracic aorta by spiral computed tomography among hypertensive patients: associations and risk of ischemic cerebrovascular events. *Int J Cardiol* 2007;120(1):32–7.
- [33] Cohen A, Tzourio C, Bertrand B, Chauvel C, Boussier MG, Amarencu P. Aortic plaque morphology and vascular events: a follow-up study in patients with ischaemic stroke. FAPS Investigators. French Study of Aortic Plaques in Stroke. *Circulation* 1997;96(11):3838–41.
- [34] Chen X, Lam WW, Ng HK, Fan YH, Wong KS. Intracranial artery calcification: a newly identified risk factor of ischemic stroke. *J Neuroimaging* 2007;17:300–3.
- [35] Sohn YH, Cheon HY, Jeon P, Kang SY. Clinical implication of cerebral artery calcification on brain CT. *Cerebrovasc Dis* 2004;18:332–7.
- [36] Elias-Smale SE, Odink AE, Wieberdink RG, et al. Carotid, aortic arch and coronary calcification are related to history of stroke: the Rotterdam Study. *Atherosclerosis* 2010;212(2):656–60.
- [37] Bugnicourt JM, Leclercq C, Chillon JM, et al. Presence of intracranial artery calcification is associated with mortality and vascular events in patients with ischemic stroke after hospital discharge: a cohort study. *Stroke* 2011;42(12):3447–53.
- [38] Prabhakaran S, Singh R, Zhou X, Ramas R, Sacco RL, Rundek T. Presence of calcified carotid plaque predicts vascular events: the Northern Manhattan Study. *Atherosclerosis* 2007;195:e197–201.
- [39] Koton S, Tashlykov V, Schwammenthal Y, et al. Cerebral artery calcification in patients with acute cerebrovascular diseases: determinants and long-term clinical outcome. *Eur J Neurol* 2012;19:739–45.
- [40] Mak HK, Wong CW, Yau KK, et al. Computed tomography evaluation of intracranial atherosclerosis in Chinese patients with transient ischemic attack or minor ischemic stroke – its distribution and association with vascular risk factors. *J Stroke Cerebrovasc Dis* 2009;18(2):158–63.
- [41] Taoka T, Iwasaki S, Nakagawa H, et al. Evaluation of arteriosclerotic changes in the intracranial carotid artery using the calcium score obtained on plain cranial computed tomography scan: correlation with angiographic changes and clinical outcome. *J Comput Assist Tomogr* 2006;30:624–8.
- [42] Kitamura A, Iso H, Imano H, et al. Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men. *Stroke* 2004;35(12):2788–94.
- [43] Ciccone MM, Marzullo A, Mizio D, et al. Can carotid plaque histology selectively predict the risk of an acute coronary syndrome? *Int Heart J* 2011;52(2):72–7.
- [44] Hunt JL, Fairman R, Mitchell ME, et al. Bone formation in carotid plaques: a clinicopathological study. *Stroke* 2002;33(5):1214–9.
- [45] Hashimoto N, Hama S, Yamane K, Kurisu K. Carotid arterial intraplaque haemorrhage and calcification influences cerebral hemodynamics. *Neurosurg Rev* 2013;36(3):421–7.
- [46] Kwee RM. Systematic review on the association between calcification in carotid plaques clinical ischemic symptoms. *J Vasc Surg* 2010;51(4):1015–25.
- [47] Eesa M, Hill MD, Al-Khathaami A, et al. Role of CT angiographic plaque morphologic characteristic in addition to stenosis in predicting the symptomatic side in carotid artery disease. *AJNR Am J Neuroradiol* 2010;31(7):1254–60.
- [48] De Weert TT, Cakir H, Rozie S, et al. Intracranial internal carotid artery calcifications: association with vascular risk factors and ischemic cerebrovascular disease. *AJNR Am J Neuroradiol* 2009;30(1):177–84.
- [49] Nighoghossian N, Derex L, Douek P. The vulnerable carotid artery plaque. Current imaging methods and new perspectives. *Stroke* 2005;36:2764–72.
- [50] Shah N, Chainani V, Delafontaine P, Abdo A, Lafferty J, Rafeh NA. Mammographically detectable breast arterial calcification and atherosclerosis: a review. *Cardiol Rev* 2014;22(2):69–78.
- [51] Iribarren C, Go AS, Tolstykh I, Sidney S, Johnston SC, Spring DB. Breast vascular calcification and risk of coronary heart disease, stroke and heart failure. *J Womens Health (Larchmt)* 2004;13(4):381–9.
- [52] Kemmeren JM, Beijerinck D, van Noord PA, et al. Breast arterial calcification: association with diabetes mellitus and cardiovascular mortality. Work in progress. *Radiology* 1996;201(1):75–8.
- [53] Lehto S, Niskanen L, Suhonen M, Ronnema T, Saikku P, Laakso M. Association between *Chlamydia pneumoniae* antibodies and intimal calcification in femoral arteries of nondiabetic patients. *Arch Intern Med* 2002;162(5):594–9.
- [54] Niskanen L, Siitonen O, Suhonen M, Uusitupa MI. Medial artery calcification predicts cardiovascular mortality in patients with NIDDM. *Diabetes Care* 1994;17(11):1252–6.
- [55] Everhart JE, Pattitt DJ, Knowler WC, Rose FA, Bennett PH. Medial arterial calcification and its association with mortality and complications of diabetes. *Diabetologia* 1988;31(1):16–23.
- [56] Rifkin DE, Ix JH, Wassel CL, Criqui MH, Allison MA. Renal artery calcification and mortality among clinically asymptomatic adults. *J Am Coll Cardiol* 2012;60(12):1079–85.
- [57] Owens DS, Budoff MJ, Katz R, et al. Aortic valve calcium independently predicts coronary and cardiovascular events in a primary prevention population. *JACC Cardiovasc Imaging* 2012;5(6):619–25.
- [58] Blaha MJ, Budoff MJ, Rivera JJ, et al. Relation of aortic valve calcium detected by cardiac computed tomography to all-cause mortality. *Am J Cardiol* 2010;106(12):1787–91.
- [59] Rodriguez CJ, Bartz TM, Longstreth WT, et al. Association of annual calcification and aortic valve sclerosis with brain findings on magnetic resonance imaging in community dwelling older adults: the cardiovascular health study. *J Am Coll Cardiol* 2011;57(21):2172–80.
- [60] Kizer JR, Wiebers DO, Whisnant JP, et al. Mitral annular calcification, aortic valve sclerosis and incident stroke in adults free of clinical cardiovascular disease: the Strong Heart Study. *Stroke* 2005;36(12):2533–7.
- [61] Boon A, Lodder J, Cheriex E, Kessels F. Risk of stroke in a cohort of 815 patients with calcification of the aortic valve with or without stenosis. *Stroke* 1996;27:847–51.
- [62] Messika-Zeitoun D, Aubry MC, Detaint D, et al. Evaluation and clinical implications of aortic valve calcification measured by electron beam computed tomography. *Circulation* 2004;110:356–62.
- [63] Leber AW, Kasel M, Ischinger T, et al. Aortic valve calcium score as a predictor for outcome and TAVI using the CoreValve revalving system. *Int J Cardiol* 2013;166(3):652–7.
- [64] Gardin JM, McClelland R, Kitzman D, et al. M-mode echocardiographic predictors of six- to seven-year incidence of coronary heart disease, stroke, congestive heart failure and mortality in an elderly cohort (The Cardiovascular Health Study). *Am J Cardiol* 2001;87:1051–7.
- [65] Fox CS, Vasan RS, Parise H, et al. Mitral annular calcification predicts cardiovascular morbidity and mortality: the Framingham Heart Study. *Circulation* 2003;107(11):1492–6.
- [66] Fox E, Harkins D, Taylor H, et al. Epidemiology of mitral annular calcification and its predictive value for coronary events in African Americans: the Jackson Cohort of the Atherosclerotic Risk in Communities Study. *Am Heart J* 2004;148(6):979–84.
- [67] Kohnsaka S, Jin Z, Rundek T, et al. Impact of mitral annular calcification on cardiovascular events in a multiethnic community: the Northern Manhattan Study. *JACC Cardiovasc Imaging* 2008;1(5):617–23.
- [68] Aronow WS, Ahn C, Kronzon I, Gutstein H. Association of mitral annular calcium with new thromboembolic stroke at 44-month follow-up of 2,148 persons, mean age 81 years. *Am J Cardiol* 1998;81(1):105–6.
- [69] Boon A, Lodder J, Cheriex E, Kessels F. Mitral annulus calcification is not an independent risk factor for stroke: a cohort study of 657 patients. *J Neurol* 1997;244(9):535–41.
- [70] Volzke H, Haring R, Lohrbein R, et al. Heart valve sclerosis predicts all-cause and cardiovascular mortality. *Atherosclerosis* 2010;209(2):606–10.
- [71] Willens HJ, Chirinos JA, Schob A, Veerani A, Perez AJ, Chakko S. The relation between mitral annular calcification and mortality in patients undergoing diagnostic coronary angiography. *Echocardiography* 2006;23(9):717–22.
- [72] Holtz JE, Upadhyaya DS, Cohen BE, Na B, Schiller NB, Whooley MA. Mitral annular calcium, inducible myocardial ischemia and cardiovascular events in outpatients with coronary heart disease (from the Heart and Soul Study). *Am J Cardiol* 2012;109(8):1092–6.
- [73] Potpara TS, Vasiljevic ZM, Vujisic-Tesic BD, et al. Mitral annular calcification predicts cardiovascular morbidity and mortality in middle-aged patients with atrial fibrillation: the Belgrade Atrial Fibrillation Study. *Chest* 2011;140(4):902–10.
- [74] Kamensky G, Lisy L, Polak E, Pisknova E, Plevova N. Mitral annular calcifications and aortic plaques as predictors of increased cardiovascular mortality. *J Cardiol* 2001;37(Suppl. 1):21–6.
- [75] Nandalur KR, Baskurt E, Hagspiel KD, Phillips CD, Kramer CM. Calcified carotid atherosclerotic plaque is associated less with ischemic symptoms than is noncalcified plaque on MDCT. *AJR Am J Roentgenol* 2005;184(1):295–8.
- [76] Shaalan WE, Cheng H, Gewertz B, et al. Degree of carotid plaque calcification in relation to symptomatic outcome and plaque inflammation. *J Vasc Surg* 2004;40(2):262–9.

- [77] Wexler L, Brundage B, Crouse J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association Writing Group. *Circulation* 1996;94:1175.
- [78] Iribarren C, Molloy S. Breast arterial calcification: a new marker of cardiovascular risk. *Curr Cardiovasc Risk Rep* 2013;7:126–35.
- [79] Back M, Gasser TC, Michel JB, Caligiuri G. Biomechanical factors in the biology of aortic wall and aortic valve diseases. *Cardiovasc Res* 2013;99(2):232–41.
- [80] Owens DS, Otto CM. Is it time for a new paradigm in calcific aortic valve disease? *JACC Cardiovasc Imaging* 2009;2(8):928–30.