

Association between bone and vascular calcification: evidence from clinical studies

Souvislost mezi kostní a cévní kalcifikací: důkazy z klinických studií

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Abstract

Prior major fragility fracture and, to a smaller extent, lower bone mineral density (BMD), are associated with higher cardiovascular risk. Cardiovascular diseases are associated with higher risk of major osteoporotic fracture. Abdominal aortic calcification (AAC) may be assessed using Kauppila's semiquantitative score. Severe AAC is associated with higher risk of hip and vertebral fracture and, less consistently, with higher risk of other fractures and lower BMD. Greater carotid artery intima-media thickness was associated with lower areal BMD in some, not all, studies. Calcified carotid plaques tended to be associated with lower BMD and higher fracture risk. Severe coronary artery calcification is associated mainly with lower volumetric trabecular BMD (not cortical) in postmenopausal women (not in men). Thus, patients with severe osteoporosis may have high cardiovascular risk and *vice versa*, however, there are no official guidelines for the clinical management of these patients.

Key words: abdominal aortic calcification – cardiovascular disease – carotid artery calcification – coronary artery calcification – fragility fracture – osteoporosis

Abstrakt

Předchozí významná osteoporotická zlomenina a v menší míře nižší hustota kostního minerálu (BMD – bone mineral density) souvisí s vyšším kardiovaskulárním rizikem. Kardiovaskulární choroby jsou spojeny s vyšším rizikem závažných osteoporotických zlomenin. Kalcifikaci břišní aorty (AAC – abdominal aortic calcification) lze vyhodnotit pomocí tzv. Kauppilova semikvantitativního skóre. Závažná AAC je spojena s vyšším rizikem zlomeniny kyčle a obratle, méně pak s vyšším rizikem jiných zlomenin a nižší BMD. Větší poměr intima-media karotid byl v některých, ne však ve všech studiích spojován s nižší plošnou hodnotou BMD. Kalcifikované karotické pláty byly často spojovány s nižší BMD a vyšším rizikem fraktury. Závažná kalcifikace koronárních arterií souvisí převážně s nižší objemovou BMD trabekulární kosti (nikoliv kortikální) u žen v menopauze (netýká se mužů). U pacientů/pacientek s těžkou osteoporózou tedy může existovat vyšší riziko kardiovaskulárního onemocnění a naopak, pro klinické léčení těchto pacientů však nejsou k dispozici žádné oficiální pokyny.

Klíčová slova: kalcifikace břišní aorty – kalcifikace karotidy – kalcifikace koronárních arterií – kardiovaskulární onemocnění – osteoporotická zlomenina – osteoporóza

Osteoporosis and cardiovascular risk

The association between cardiovascular diseases and fracture risk has been shown in a large number of studies published over the last 15 years. History of fragility frac-

ture (mainly hip fracture and clinical vertebral fracture) was associated with higher cardiovascular risk in both sexes [1–2]. This trend was found mainly for major cardiovascular events (stroke, myocardial infarction, death

for cardiovascular reasons), but also for ischemic heart disease, incident heart failure, transient ischemic attack (TIA) and other pathologies. One of the first studies on this subject carried out in a large group of postmenopausal women followed in the placebo arm of a large pharmaceutical trial showed that the risk of major cardiovascular event was 3.5-fold higher in the women with osteoporosis compared to women with osteopenia [3]. In the same study, women with severe or multiple vertebral fractures had higher risk of major cardiovascular event. Similarly, hip fracture was associated with higher risk of myocardial infarction and stroke [4–5]. Overall, the prior hip fracture was associated with a 30% higher risk of myocardial infarction and a 50 % higher risk of stroke [1,5]. Such trends were found in both sexes and in different ethnic groups.

The link between osteoporotic fractures and cardiovascular events is important because of its practical clinical consequences. For instance, the risk of myocardial infarction and stroke was particularly high (13- and 9-fold higher vs. the controls) during the first month after the hip fracture [4]. Such early myocardial infarction or stroke are associated with a four- to sevenfold higher 30-day mortality compared with women who had no fracture [6].

A substantial number of studies show a moderate but significant association between low bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) and higher risk of cardiovascular diseases (e.g. myocardial infarction or incident heart failure) and stroke [1,7–11]. In a large meta-analysis, a decrease in BMD by 1 standard deviation was associ-

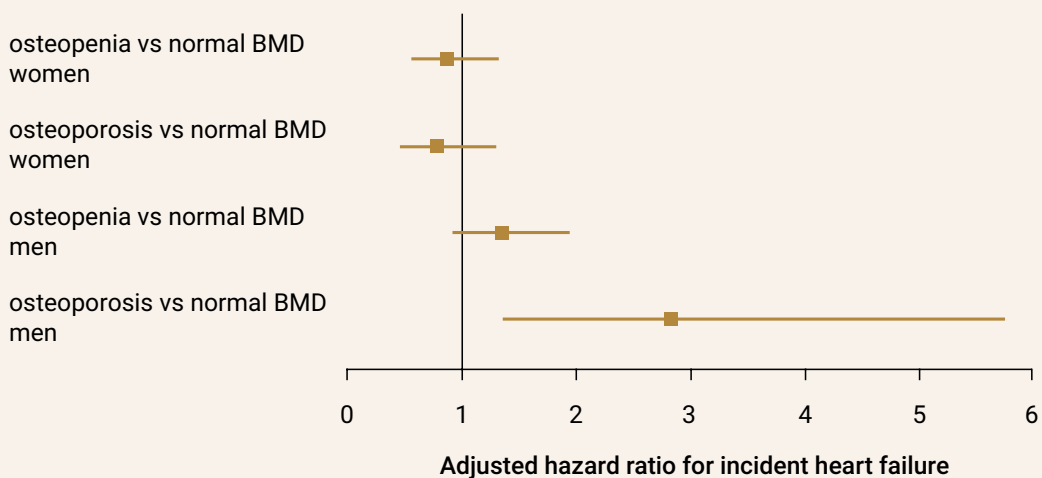
ated with a 16 % higher risk of incident cardiovascular disease (HR = 1.16, 95% CI: 1.09–1.24, $p < 0.001$) [1]. This pattern was found mainly in older men and less consistently in older women [9–10]. For instance, in the Cardiovascular Health Study, higher risk of heart failure was found only in osteoporotic men, but not in osteoporotic women (figure 1).

Cardiovascular diseases and fracture risk

Cardiovascular diseases are associated with higher risk of major osteoporotic fracture, especially hip, vertebral and humerus fracture. Such association was found mainly for severe cardiovascular diseases, such as cerebrovascular diseases, myocardial infarction, heart failure, peripheral artery disease [12–17]. A recent meta-analysis shows that heart failure is associated with a threefold higher risk of hip fracture (RR = 3.45, 95%CI: 1.86–6.40, $p < 0.001$) and with a twofold higher risk of humerus fracture (RR = 1.91, 95%CI: 1.07–3.40, $p = 0.03$) [15]. Furthermore, prior stroke is associated with a twofold higher risk of hip fracture (RR = 2.06, 95%CI 1.68–2.52, $P < 0.001$) [14].

Some discordances between the studies may be related to the methodological factors. Various studies used different criteria and different methods for a given disease. In particular, in large studies using the health-care registers, it is impossible to check which criteria were used for the diagnosis of a given cardiovascular diseases and, most probably, different criteria were used in different hospitals according to their diagnostic equipment. Studies are often poorly controlled for confounding factors (lifestyle, co-morbidities, treatments),

Figure 1 | Risk of incident heart failure in osteoporotic and osteopenic men and women in comparison with the sex-matched controls. The study was performed in 1 250 elderly men and women followed up prospectively for 10.5 years (Cardiovascular Health Study). Reproduced from [9]



which may also contribute to the fracture risk [18–19]. For instance, the use of thiazide diuretics or statins may be associated with a 20–40 % lower risk of fracture [18–19].

Abdominal aortic calcification and its assessment

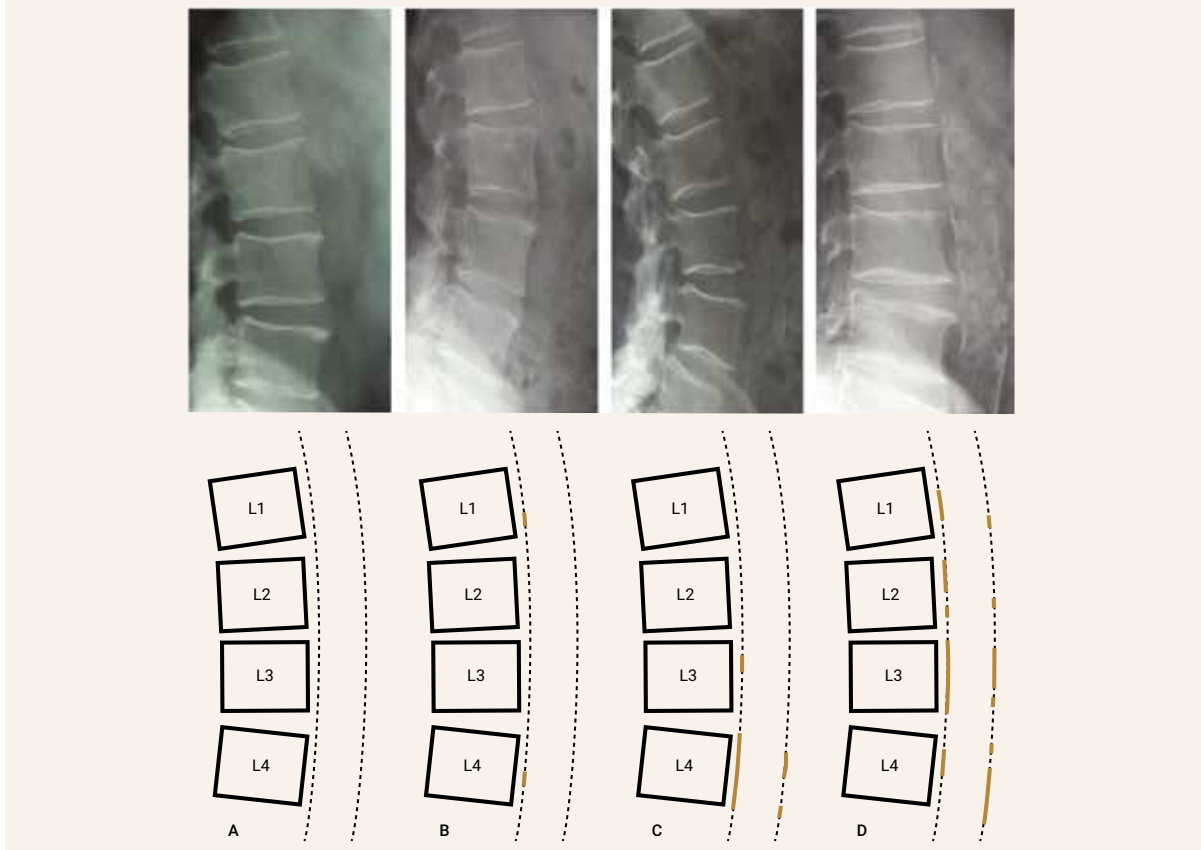
Abdominal aortic calcification (AAC) may be easily assessed on lateral radiographies of lumbar spine and on lateral spine scans obtained by DXA [20–21]. Both are inexpensive, easily available, rapid and safe. AAC is assessed using a 24-point semiquantitative score (AAC-24) [20], which reflects the length of calcification at the posterior and anterior aortic walls adjacent to the first four lumbar vertebrae (figure 2). AAC is assessed in eight segments and lines drawn through the middle of intervertebral spaces are segment boundaries. In every segment AAC is scored from 0 to 3 on the basis of the length of AAC. The agreement of the AAC scores ob-

tained using AAC-24 on the X-ray and on the DXA scan is very good [21–22].

The simplified 8-point semiquantitative score (AAC-8), based on the initial AAC-24 score, is rapid and less influenced by small calcification dispersed in different segments [22]. Speckled calcification dispersed in different segments may result in a falsely elevated AAC-24 score. This limitation is avoided with AAC-8 score. However, for the AAC-8 score, the aggregate length of AAC in different parts of the aortic wall has to be calculated mentally and compared to the average length of the vertebral segment. Despite this limitation, the results from AAC-8 are strongly correlated with those from AAC-24 both on X-rays and on DXA scans [22].

The advantage of DXA compared with X-ray is that the scan is made during the same exam as BMD measurement. In addition, dose of irradiation is lower compared with an X-ray (5 μ Sv vs. 600 μ Sv). Adjustment of brightness and of contrast on the screen of the DXA device

Figure 2 | Semiquantitative score of Kauppila. Reproduced from [117]



A – no abdominal aortic calcification (AAC) – **B** – mild AAC (small calcification at the posterior wall at the level of L1 and L4) **C** – moderate AAC (calcification on the entire length of the posterior wall at the level of L4, smaller calcification in the anterior wall at the level of L4 and at the posterior wall at the level of L3) **D** – severe AAC (calcification on the entire length of the posterior segment of the aortic all at the level of L3, calcification at the posterior wall at the level of L1 and L2 and at the anterior wall at the level of L3 and L4, smaller calcification at the anterior wall at the level of L1 and L2 and at the posterior wall at the level of L4)

permit to improve visibility of AAC. However, DXA has lower resolution compared to X-rays and small calcification may be overlooked on the DXA scan. Hence average AAC score is slightly lower on a DXA scan compared to an X-ray [23]. Consequently, the agreement of AAC score on the X-ray vs the DXA scans was only moderate, when the agreement of the AAC scores on the X-ray vs the DXA scan was analyzed as dichotomized variables (using the same threshold for X-ray and for DXA) [21].

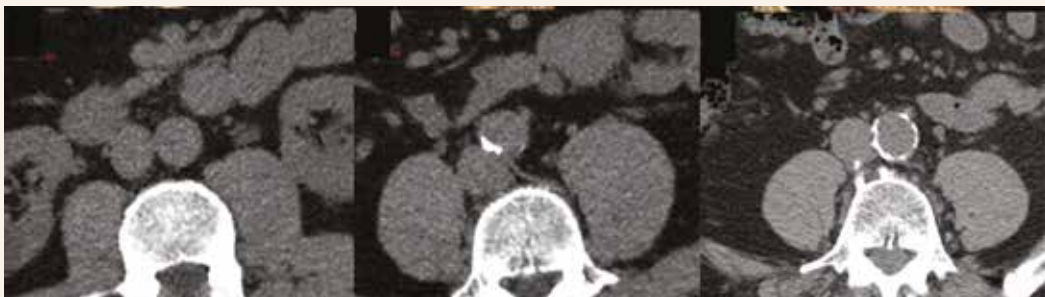
Both methods share some limitations. Poor image quality is the major limitation (insufficient space in front of the lumbar spine, "soft" X-rays with blurred barely visible lines, movement, and rotation). Severe obesity may impair the visibility of calcified aortic walls. The assessment of linear calcification in the anterior or posterior aortic wall is straightforward, whereas the assessment of marble-like calcification present in lateral walls is more subjective. In patients with severe scoliosis and/or lumbar osteoarthritis, abdominal aorta may be tortuous, partly covered by vertebral bodies and/or long osteophytes. Severe fractures of the first four lumbar vertebrae may change the trajectories of intervertebral spaces (which define the segment boundaries) and consequently, the lengths of the segments. Thus, it may be difficult to imagine the reference length of the segment. The posterior height of vertebral body may be used as a reference in case of the wedge vertebral fractures [24]. By contrast, it is impossible to recommend the reference in case of severe crush vertebral fractures. Aortic bifurcation may be situated above the lower boundary of the L4 segment (in front of the fourth lumbar vertebra). In such case, calcification present in the proximal parts of the common iliac arteries is "assigned" to the AAC score using subjective mental operations [24]. AAC cannot be assessed in case of aortic aneurysm. Bones (e.g. ribs) and other ectopic calcification (e.g. in the renal artery wall, in the initial segments

of the superior and inferior mesenteric arteries, kidney stones, calcified non-vascular tissues) should also be assessed and excluded.

AAC may be also assessed using quantitative computed tomography (QCT) [25]. Calcification burden is calculated in the entire investigated vascular bed (e.g. a given part of the aorta) as Agatston score which is a product of calcified lesion area and calcium score reflecting average density expressed in Hounsfield units (HU) or as the volume of calcification in the investigated segment of the aorta (figure 3) [25–26]. AAC severity assessed on DXA scans was significantly correlated with AAC quantified by QCT [27]. Nonetheless, the results provided by these methods (QCT vs X-ray, QCT vs DXA) are not directly comparable. QCT quantifies AAC more accurately than semiquantitative scores on radiograph or DXA scan. However, QCT is not appropriate for the AAC assessment in clinical or epidemiological studies, because it is less available, more expensive and more irradiating than DXA or radiography. As various QCT studies assessed different segments of aorta using different approaches, these studies are not really comparable (although all used QCT). QCT combined with magnetic resonance imaging (MRI) of the aorta permits to evaluate jointly the spatial relationships between calcification and the presence of atherosclerotic plaque areas [28].

The semiquantitative approach of Kauppila's score limits its use in longitudinal studies. AAC is a dynamic process; however, its progression is slow and a long-term follow-up is necessary for a reliable detection of AAC progression in clinical studies in the general population [29]. Follow-up of less than 5 years is insufficient. In particular, a short-term follow-up may be also insufficient to detect or to exclude the change in AAC score in pharmaceutical studies aimed at preventing AAC progression [30–31]. However, age, smoking, hypertension, obesity, and vitamin D deficit are associated with

Figure 3 | Axial slices presenting abdominal QCT scans: no abdominal aortic calcification (left panel), mild calcification limited to right posterior quadrant (middle panel), and severe calcification nearly on the entire circumference (right panel). Reproduced with senior author's permission [26]



more rapid AAC progression in prospective studies [32–33]. Consequently, minimum duration of a follow-up may vary according to the characteristics of the cohort.

Therefore, more accurate, precise and quantitative methods are needed for the assessment of AAC progression. Multidetector computed tomography (MDCT) and electron beam computed tomography (EBCT) improve the sensitivity of the quantification of vascular calcium burden [34–35]. These methods express calcium deposits in Agatston units. They do not necessitate contrast injection. Most studies show good reproducibility of the calcium burden assessment. However, high radiation dose, elevated cost and poor availability limit their use. MDCT has higher reproducibility and increased signal-to-noise ratio, whereas EBCT has lower radiation dose and faster acquisition time. Data on their use for the assessment of AAC are limited [34–36]. The correlation between aortic calcium deposits obtained by MDCT or by EBCT with AAC severity assessed by semiquantitative approach has not been thoroughly studied. Interestingly, they seem to be useful for the assessment of the effect of therapeutic prevention of AAC progression, at least in hemodialysis patients [37–38].

Abdominal aortic calcification and bone mineral density

Data on the association between AAC and areal bone mineral density (BMD) measured by DXA are inconsistent. On the one hand, several studies assessed groups with mild/moderate AAC or groups with mixed, but mainly mild AAC. The analyses adjusted for age show that BMD was similar in individuals with AAC and those without AAC regardless of skeletal site [39–42]. Other studies presented bivariable analyses not adjusted for potential confounders [43–49]. In these studies, BMD was significantly lower in subjects with mild or moderate AAC vs those without AAC. However, the subjects with AAC were significantly older than those without AAC and the differences became non-significant after adjustment for age [43,49]. On the other hand, individuals with severe AAC had lower BMD compared to those without AAC [50–52]. The differences remained significant after adjustment for age and other confounders, at least for some skeletal sites. For instance, in a cohort of older men, BMD was 3–4 % lower at whole body and distal forearm in men with severe AAC (AAC score >6) vs men who had lower AAC score (AAC score 0 to 6). [51]. In a large cohort of Australian older women, total hip BMD was 3 % lower in those with severe AAC (AAC score > 5) vs those without AAC [52].

After adjustment for confounders, more severe AAC is associated with lower trabecular vBMD at the lumbar spine and the hip (total hip, femoral neck) in peri-, post-

menopausal and elderly women in some [25,35,53–56], not all [57–58], studies. For instance, perimenopausal women with severe AAC had 11 % lower trabecular volumetric BMD at the lumbar spine vs women who had no AAC [25]. In another group of older women, severe AAC was associated with a 40 % lower trabecular volumetric BMD at the spine vs women who had no AAC and the difference remained significant after adjustment for age [53]. Similarly, data in men show inconsistent trends in both compartments. Men with more extended AAC had slightly lower trabecular vBMD at the lumbar spine [55–58] or, conversely, lower cortical (but not trabecular) vBMD at the distal radius and distal tibia [59]. By contrast, Chow et al found no association between AAC severity and vBMD in men [58].

Several [50,53,60–62], but not all [63], prospective studies showed faster bone loss in subjects with rapid progression of AAC. In a cohort of 228 older women followed up prospectively for 2 years, women in the highest quartile of AAC gain had fourfold greater bone loss (5.3 vs 1.3 %/year, $p < 0.001$) than women of similar age in the lowest quartile [53]. This association was found mainly in postmenopausal and elderly women, but less consistently in older men [60–61]. However, measurement errors of the changes in AAC and BMD are relatively high in comparison with the individual rates of bone loss and of AAC progression. Therefore, a long-term follow-up is necessary for such analyses, especially in individuals who have slower bone loss (e.g. in men compared to women) [42,60]. Therefore, these results should be interpreted with caution. Some positive results may be fortuitous. The publications bias reflecting the trend that researchers publish positive results, but restrain from publishing negative results, is possible. However, given the low number of studies and methodological differences, a meta-analysis permitting to detect such phenomenon would be difficult to perform.

Overall, these data show that the association between AAC and BMD is weak and strongly dependent on age and other confounders (presumably shared risk factors). In addition, even in the studies showing significantly lower BMD in individuals with severe AAC, the differences are relatively small and limited to some skeletal sites. This is probably one of the reasons the differences attain statistical significance in the multivariable models only in the groups including a sufficient number of individuals with severe AAC. In addition, the link between AAC severity and volumetric BMD seems to be stronger in trabecular bone. Thus, it is plausible that the fraction of trabecular bone at a given skeletal site and the severity of its deterioration determine the strength of the association between

AAC severity and areal BMD. Finally, the presence of artifacts may influence the result. For instance, lumbar spine contains a large fraction of trabecular bone and its volumetric BMD is negatively correlated with severe AAC. However, in the elderly, areal BMD may be falsely elevated by osteophytes and severe AAC itself.

Abdominal aortic calcification and fractures

The association between severe AAC and fractures was assessed in cross-sectional and prospective studies. Cross-sectional studies were focused on vertebral fractures. They show that severe AAC is associated with significantly two- to fourfold higher odds of prevalent vertebral fractures after adjustment for age, weight and bone mineral density (BMD) measured by DXA [40,44,52–54,64–66]. This association was found in men and in women regardless of the ethnic group. The odds were higher for severe vertebral fractures (vs mild fractures) and for multiple fractures (vs simple fractures), table [40,61,64–65]. The results were similar regardless of the method used for the assessment of AAC (X-ray, DXA, QCT) or for vertebral fracture (X-ray, DXA).

However, some limitations should be signaled. Cross-sectional design does not permit to establish the temporal sequence. Vertebral fractures and AAC are assessed side by side on the same image, thus, the assessment of the two variables cannot be really double blind. Of note, in case of abnormality in the lumbar spine (crush fracture, scoliosis), the length of the aortic segment

(denominator) is apparently smaller, thus, for the same length of AAC (numerator) the value of the AAC score may be spuriously high.

Prospective studies assessed the association between baseline AAC severity and the prospectively assessed risk of fracture (figure 4). Severe AAC is associated mainly with higher risk of hip fracture and of vertebral fracture [45,47–48,50,52]. The similar patterns were found for men and women regardless of the ethnicity. After adjustment for confounders, older Chinese women with severe AAC (AAC score > 6) had threefold higher risk of incident vertebral fracture compared with women who had no AAC [45]. In the MrOS cohort (5400 American men aged 65 and over), severe AAC was associated with higher risk of hip fracture (HR = 2.33, 95% CI: 1.41–3.87, p < 0.01), figure 5 [47]. By contrast, data on the association between severe AAC and other non-vertebral fractures are less consistent [41,45,47–48,51,61]. Of note, these associations tended to be significant in the studies, where the group “non-vertebral fractures” included hip fractures [45,51], but not in the analyses of the non-hip-non-vertebral fractures [47]. Mild AAC were not associated with the fracture risk [41–42].

The association between severe AAC and the risk of major fragility fracture remained significant after adjustment for age, BMD and other potential confounders, including shared risk factors, such as smoking, diabetes mellitus, poor renal function or vitamin D level. The association between AAC severity and fracture risk was significant in men and in women. Bone fragility

Table | Odds of vertebral fracture associated with abdominal aortic calcification (AAC score > 6 versus ≤ 6) in 901 men aged 50 and older from the STRAMBO cohort assessed using age-adjusted and multivariable-adjusted logistic regression. Reproduced from [40]

fracture prevalence	age-adjusted OR (95% CI)	multivariable-adjusted ^{a)} OR (95% CI)
grade ≥ 1 (n = 98) vs grade 0	2.1 (1.2–3.6)	2.5 (1.4–4.5)
grade ≥ 2 (n = 80) vs grade ≤ 1	2.1 (1.2–3.9)	2.6 (1.4–5.1)
fracture severity ^{**)}		
grade 1 (n = 18)	1.6 (0.4–6.1)	1.8 (0.4–7.3)
grade 2 (n = 60)	2.0 (1.0–3.9)	2.4 (1.2–5.1)
grade 3 (n = 20)	2.8 (0.99–8.1)	4.4 (1.3–15.1)
number of fractures ^{**)}		
1 fracture	1.7 (0.9–3.4)	2.0 (0.98–4.2)
> 1 fracture	2.7 (1.2–6.0)	3.5 (1.4–8.6)
data are presented as odds ratios (OR) and 95% confidence interval (95%CI)		

^{a)} adjusted for age (years), weight (kilograms), femoral neck BMD (grams per square centimeter), smoking (ever/never), ischemic heart disease (yes/no), and hypertension (yes/no) ^{**)} assessed by polytomous logistic regression using men without vertebral fracture (grade 0) as the reference group

ity measures (BMD, prevalent vertebral fracture) and severe AAC contributed jointly to the higher risk of incident fracture [51–52]. For instance, in the large Australian cohort, the risk of clinical fracture was more than twofold higher (HR=2.43, 95%CI: 1.54–3.85, $p<0.001$) in women who had severe AAC and prevalent vertebral fractures compared to the women who did not have these characteristics [52].

Some observations may explain the discordant results of different studies. Increased fracture risk was found mainly in individuals with severe AAC, but not in those with mild AAC. Therefore, a low threshold of AAC score may not be sufficiently specific and may provide inconsistent results according to the number of subjects with severe AAC among those with AAC. The association between AAC and fracture risk could not be detected in cohorts, in which few individuals had severe AAC, for instance in younger cohorts. Vascular calcification is a dynamic process and its current severity cannot predict its progression over a long period. Therefore, the association between AAC severity and fracture risk has been most often significant in the follow-up of 10 years or less [45,48,50–52]. By contrast, it was not significant in long-term follow-ups, especially when then median follow-up until fracture was long [48,67]. For instance, in the SOF cohort, severe AAC was associated with a significantly twofold higher risk of verte-

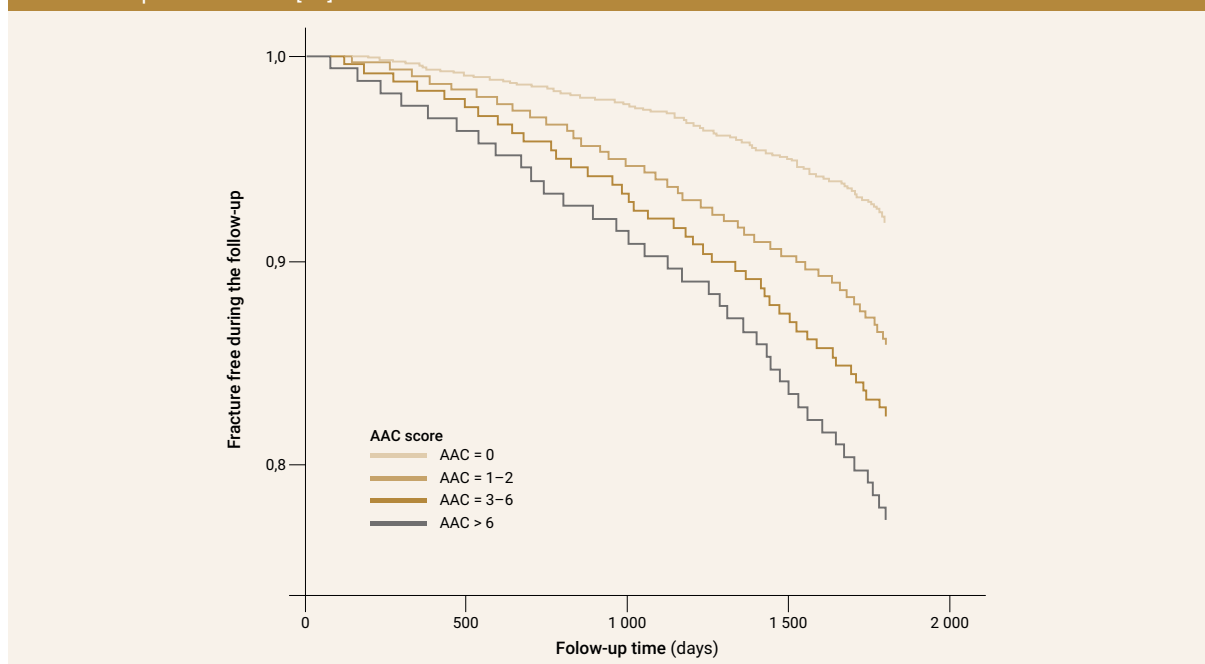
bral fracture during a 4-year follow-up, but not during the 15-year follow-up [48]. Importantly, severe AAC is associated with higher mortality (mainly cardiovascular one). Therefore, in the longer follow-up, the competing risk of death should be taken into account in the analysis of the fracture risk.

Carotid artery calcification and bone

A large number of studies assessed the associations between bone status and atherosclerosis in the carotid common and internal artery. Carotid artery intima-media thickness (CIMT) and carotid plaque number, size, echogenicity and calcification are assessed by ultrasonography. Carotid artery calcification can be also assessed using panoramic radiography.

Overall, the results of the studies were inconsistent. Greater CIMT was associated with lower areal BMD in some [68–77], but not all [78–84], studies. For instance, in postmenopausal women from the Japanese Population-based Osteoporosis Cohort Study, osteoporotic women had 28 % (0.85SD) higher CIMT compared with the women with normal BMD [71]. Similarly, cross-sectional studies on the association between and BMD and carotid plaques provided inconsistent results. In some studies, lower areal and volumetric BMD (or diagnosis of osteoporosis) was associated with higher prevalence of echogenic/calcified carotid plaques [74,85–

Figure 4 | Prospective study of the association between abdominal aortic calcification (AAC) severity at baseline and the risk of fracture during a 5-year follow-up in a cohort of 1 724 postmenopausal Chinese women. Fracture-free survival according to the AAC score: AAC = 0, AAC = 1–2, AAC = 3–6, AAC > 6. Reproduced from [45]



87]. For instance, in a large cohort of older men and women (Tromso study), individuals with echogenic carotid plaques had 3.4 % lower distal forearm BMD compared with the individuals without plaques, whereas BMD did not differ between the subjects with echolucent plaques and those without plaques [86]. Similarly, in older men and women from the MESA study, volumetric BMD at the lumbar spine decreased significantly with the increasing echogenicity of the carotid plaques (p for trend < 0.05) and was 7–8 % lower in the individuals with calcified carotid plaques vs those who did not have plaques [85].

Other studies found significant negative associations only for some but not all the skeletal sites of BMD measurement [57,68,88]. The patterns differed according to the ethnicity, sex and hormone replacement therapy [88]. Finally, studies performed in smaller groups did not find any association between areal BMD (lumbar spine, hip) and the presence of echogenic/calcified carotid plaques [75,89–90].

Furthermore, presence of echogenic/calcified carotid plaques was associated with higher prevalence of osteoporotic fractures (mainly vertebral fractures) in some [89,91], but not all [80, 87], studies. In a large cohort of elderly women followed up prospectively for 20 years, higher CIMT was associated with a significantly higher risk of hip fracture after adjustment for clinical confounders [84]. Similarly, after adjustment for confounders including BMD, presence of echogenic carotid plaques was associated with a slightly higher risk of non-vertebral fracture in postmenopausal women [92].

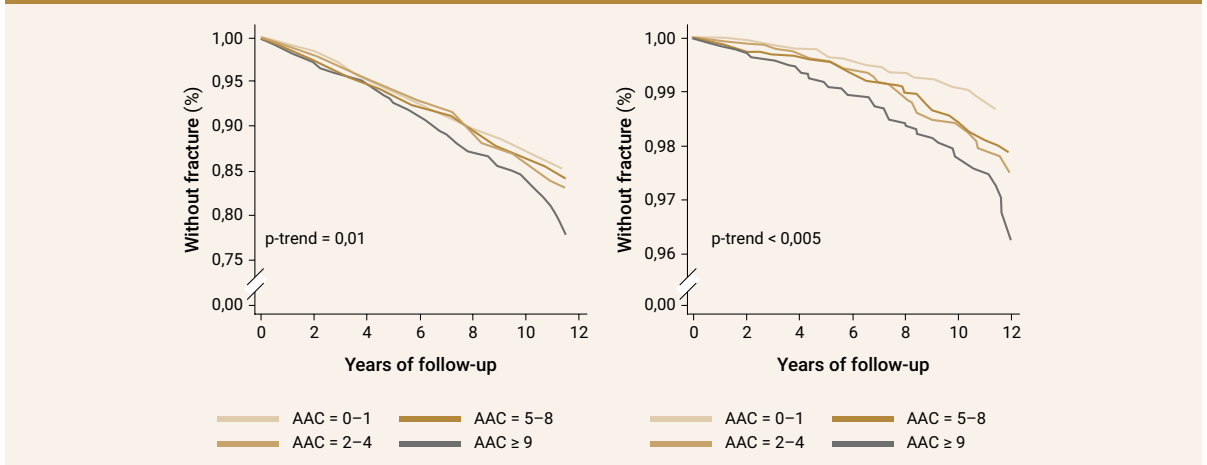
Conversely, lower lumbar spine BMD and prior osteoporotic fracture were associated with higher risk of developing an incident echogenic plaque [91,93]. In a large cohort of older Chinese women, lower lumbar spine BMD (lowest quartile) was associated with a higher risk of developing calcified carotid plaque in comparison with the highest BMD quartile after adjustment for confounders (HR = 2.68, 95% CI: 1.52–3.98) [93].

Several factors may contribute to the discordances between the studies. The associations between CIMT and BMD were negative and significant in postmenopausal women and older men, but not in premenopausal women and young men [82,94–95]. However, one study found positive link between CIMT and BMD in a large cohort of elderly men and women [84]. The associations were similar regardless of the ethnicity and of the health status at baseline (general population, diabetes mellitus, systemic lupus erythematosus). The associations were significant mainly for calcified carotid plaques [57,85–87,93]. By contrast, they were less consistent for CIMT and for somewhat vaguely characterized carotid plaques (present vs absent, echogenic vs echolucent) [71,80–81,89]. The results could also depend on the confounders used in the statistical models. Some significant associations were found in models poorly controlled for confounders.

Coronary artery calcification and bone

A substantial number of studies assessed the association between coronary artery calcification (CAC) and BMD in both sexes. Overall, the majority of the

Figure 5 | Fracture-free survival in 5 400 men aged ≥ 65 from the MrOS cohort followed up prospectively for the median of 10.5 years (interquartile range, 8.5–11.2). Fracture-free survival is presented according to the quartiles of the AAC score (adjusted for age, body mass index, center, race, hip bone mineral density, fall history, prior fracture, smoking, and co-morbidities): (A) non-vertebral fractures ($n = 805$ men); (B) hip fractures ($n = 178$ men). Reproduced from [117]



AAC – abdominal aortic calcification assessed using the 24-point Kauppila's score

studies found no association between CAC and areal BMD measured by DXA in the multivariable models [42,88,96–104]. However, a significant negative link between greater CAC and lower areal BMD in some other studies [39,105–110]. For instance, in a group of postmenopausal Chinese women, average CAC score was fourfold higher in women who were osteoporotic at the femoral neck compared to the women who had normal BMD [108].

Overall, such trends were found mainly in postmenopausal women, but not in men, probably because women have greater bone loss compared with men of similar age [106]. The links were significant mainly at the hip, but less consistently at the lumbar spine [106,109–110], probably because, in older individuals, lumbar spine areal BMD may be influenced by osteoarthritis. However, these weak (although significant) associations may be also due to the type I statistical error (false positive) or due to insufficient control for potential confounders such as shared determinants of the studied variables (age, smoking, diabetes mellitus, low grade inflammatory syndrome, hormones replacement therapy).

Several [35,55,57,88,111–114], but not all [25,115], studies showed that more severe CAC are associated with lower trabecular volumetric BMD at the thoracic and lumbar spine. For instance, in a group of patients with type 2 diabetes mellitus, the presence of calcified coronary artery plaque was associated with a significantly lower trabecular volumetric BMD at the lumbar spine and at the thoracic spine after adjustment for multiple confounders [57]. Again, this negative association was found mainly in postmenopausal women and less frequently in older men [35, 55,57, 88, 112–114]. However, the associations were very weak and the data were inconsistent. By contrast, the association between CAC severity and cortical volumetric BMD was not significant [35] or even astonishingly, positive [112].

In addition, after adjustment for confounders, individuals with severe CAC (Agatston > 400U) had twofold higher odds of prevalent vertebral fractures [116]. By contrast, CAC was not associated with the risk of incident fracture in the prospective studies [102,116].

The association between CAC and BMD seems to be overall weak and determined mainly by the significant negative link between CAC and trabecular volumetric BMD in postmenopausal women. In this population bone loss is relatively rapid, in particular in the trabecular compartment, which has a larger metabolically available surface than cortical bone. Thus, trabecular compartment may be more sensitive to various pathogenic factors, e.g. sex steroid deficit, heavy smoking or inflammatory cytokines.

Vascular calcification and osteoporosis – clinical perspective

Overall, the available data show a significant association between cardiovascular diseases and osteoporosis. Patients with low BMD or prior osteoporotic fracture have higher risk of major cardiovascular event, e.g. myocardial infarction or stroke. Patients with severe cardiovascular disease have higher risk of major osteoporotic fracture, mainly hip or vertebral fracture. These two groups of diseases share risk factors, e.g. smoking, sedentary lifestyle, diabetes mellitus, sex steroid deficit, vitamin D deficit, poor renal function, dyslipidaemia, oxidative stress, low grade inflammatory syndrome, long-term use of systemic glucocorticoids. Osteoporosis and vascular calcification may share underlying pathophysiological mechanisms [117]. Some consequences of one disease may increase the risk of the other one. For instance, prior stroke or arrhythmias are associated with higher risk of dangerous fall, which may result in a fracture [14]. An emergency surgery after a hip fracture may be associated with higher risk of cardiovascular complications compared to an elective surgery for hip osteoarthritis [118].

Thus, a patient with severe osteoporosis may have high risk of cardiovascular disease and *vice versa*. However, there are no official guidelines for the clinical management of these patients. Intuitively, history of myocardial infarction may be considered an indication for the assessment of FRAX, bone densitometry and other exams of bone status. Conversely, a patient with a hip or vertebral fracture would benefit from an in-depth assessment of the cardiovascular status. Of note, severe AAC found incidentally on a radiograph is a signal of higher cardiovascular risk and of higher risk of fracture.

Modification of the lifestyle (cessation of smoking, regular leisure physical activity), optimal pharmacological control of hypertension, arrhythmias or diabetes mellitus as well as reduction of systemic glucocorticoid dose may be beneficial for bone and vascular health. The use of medications increasing fracture risk (e.g. furosemide, selective serotonin uptake inhibitors, proton pump inhibitors) is to be considered with caution in patients with severe cardiovascular diseases [119–120], especially if they also have higher fracture risk for other reasons.

However, these suggestions are only common sense, because no clinical study assessed the impact of modifications of the clinical practice on the incidence of fragility fractures and of cardiovascular events. Further studies are needed to develop clinical recommendations which could improve the clinical management of patients at high risk of these diseases.

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