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REVIEW

Association between cardiovascular diseases and osteoporosis—reappraisal

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Positive association between cardiovascular diseases and osteoporosis is important because it concerns two major public health problems. Men and women with cardiovascular diseases (including severe abdominal aortic calcification (AAC) and peripheral arterial disease) tend to have lower areal and volumetric bone mineral density (BMD) as well as faster bone loss, although findings vary according to skeletal site. On one hand, severe forms of cardiovascular diseases (heart failure, myocardial infarction, hypertension, severe AAC) are associated with higher risk of osteoporotic fracture, especially hip fracture. This link was found in the studies based on healthcare databases and the cohort studies. On the other hand, low BMD, history of fragility fracture, vitamin D deficit and increased bone resorption are associated with higher risk of major cardiovascular events (myocardial infraction, stroke, cardiovascular mortality). Moreover, osteocalcin secreted by osteoblasts may be involved in the regulation of energetic and cardiovascular metabolism. The association between both pathologies depends partially on the shared risk factors, and also on the mechanisms that are involved in the regulation of bone and cardiovascular metabolism. Interpretation of the data should take into account methodological limitations: representativeness of the cohorts, quality of the registers and the information obtained from questionnaires, severity of diseases, number of events (statistical power) and their temporal closeness, availability of the information on potential confounders. It seems that patients with severe form of osteoporosis would benefit from assessment of the cardiovascular status and vice versa. However, official guidelines for the clinical practice are still lacking.

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Many studies published over the past 20 years show a significant positive association between cardiovascular diseases (CVD) and osteoporosis. This association is important because it concerns two major public health problems. The investigation of shared biomarkers (clinical, radiological, biochemical) may improve identification of subjects at high risk of both diseases. The investigation of shared pathophysiological mechanisms may help to understand the pathophysiology of these diseases and to establish new treatments that could be efficient in both diseases. Below, I have tried to analyze various groups of clinical studies to better understand the association between osteoporosis and CVD as well as discrepancies between the studies. My review is focused on the epidemiological studies of the general population, and I have not analyzed the association between bone and CVD in chronic renal failure.

Association between Cardiovascular Diseases and Bone Mineral Density

Several studies showed that CVD and arterial calcification are associated with decreased bone mineral density (BMD), although findings vary according to skeletal site and gender. Severe abdominal aortic calcification (AAC) was associated with lower BMD at the spine and hip in older women,[1] at the hip and whole body (but not spine) in older women (but not men),[2] at the lumbar spine (but not femoral neck) in a cohort of men and women,[3] at the femoral neck in women[4] and at whole body and distal forearm (but not at the spine or hip) in older men.[5] Severe AAC was associated with lower trabecular volumetric BMD at the spine in postmenopausal women,[6] in peri- and postmenopausal black and white women,[7] and in men and women aged $\geqslant$45 years.[8] In a group of siblings concordant for type 2 diabetes, severity of the coronary and aortic calcification was correlated negatively with spine volumetric BMD.[9] In other studies, the association between AAC severity and BMD was weak or non-significant.[10–13]

Limited data also suggest a weak but significant association between severe peripheral arterial disease (PAD) and lower BMD at the hip.[14–16] Elevated diastolic (but not systolic) blood pressure was associated with lower BMD at the total body, trochanter and Ward's triangle in a small group of 47 men aged 24 to 77 years.[17]

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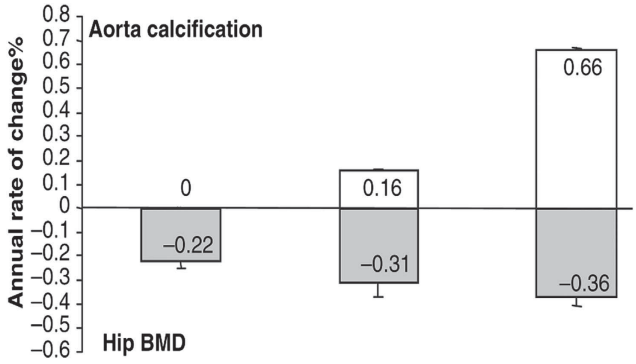

Figure 1 Annualized rate of change (%) in total hip bone mineral density (grey bars) according to the tertiles of change in the abdominal aortic calcification score (white bars) in 2662 older women from the PERF study followed up prospectively for 7.5 years on average. Bars show mean±s.e.m. *P*-value for trend = 0.019 after adjustment for age and baseline BMD. Reproduced from Bagger *et al.*[1] with permission from Blackwell Publishing Ltd.

CVD were also associated with the accelerated bone loss. Faster progression of AAC was associated with faster bone loss at the hip in older women,[1] at the lumbar spine (but not femoral neck),[3] at the spine in postmenopausal women,[7] at the metacarpal in women followed up across the menopause,[18] and at the metacarpal in women, but not men[19] (**Figure 1**). Hypertension was associated with faster bone loss in elderly white women.[20] Moreover, in the MrOS cohort, the elderly men with PAD had faster bone loss at the total hip and its components.[21]

Thus, the cross-sectional studies show an association between CVD and BMD. The observed differences between the studies may be related to the various populations, age range, sex, skeletal site and method of BMD measurement. The associations of lumbar spine BMD, measured by dual X-ray absorptiometry, with AAC are weak and not reliable because of the frequent arthritis in the elderly. The associations are similar for the predominantly cortical and predominantly trabecular skeletal sites. The difference in BMD is greater for subjects with more severe CVD or severe AAC. Adjustment for confounders may influence the results. In particular, adjustment for the shared risk factors of both diseases (for example, smoking, sedentary lifestyle) may falsely attenuate the existing relationship. The association between CVD and bone loss is stronger in women, probably because in postmenopausal women bone loss is faster than in older men. Therefore, estimation of bone loss may be more accurate in women than in men (because the effect of the measurement error is smaller). Lower BMD and faster bone loss at the lower limbs in patients with the PAD suggest that the local effect related to the decreased blood flow may also contribute to this association.

Association between the Prevalent Cardiovascular Pathology and Incident Fracture

Epidemiological studies on the association between CVD and fractures can be divided into two groups. The first group is based on the healthcare databases and large epidemiological studies, which were not specifically designed to study osteoporosis. These studies show that severe forms of CVD are associated with higher risk of fragility fracture.

In the Swedish Twin Registry, individuals with heart failure, ischemic heart disease or PAD had significantly, two- to fourfold higher risk of hip fracture.[22] In a study that was a part of the Rochester Epidemiology Project, myocardial infarction was associated with higher risk of all types of osteoporotic fracture.[23] In a large Danish study carried out in about 500 000 individuals using the data from the National Health Service, a trial fibrillation was associated with higher risk of the fracture of hip, distal forearm or spine during the first 3 years after the incident.[24] In addition, patients with myocardial infarction had higher risk of hip fracture (but not spine or forearm fracture), during first 3 years. Finally, elderly patients with heart failure and patients with other cardiovascular diagnoses were identified in the healthcare databases of the province Alberta, Canada.[25] The controls with CVD were selected because they can share some cardiovascular risk factors and potentially be eligible for similar medications. Patients with heart failure had a fourfold higher risk of sustaining any fracture requiring hospitalization compared with other cardiovascular diagnoses.

The advantage of the population-based studies is the large representative cohort, large number of individuals with different forms of CVD, in particular, large number of subjects with severe forms of CVD and large number of fractures. Follow-up data are available instantly and the investigated group is not influenced by participation bias, which is quite frequent in the cohort studies.

However, these studies also have limitations. The quality of the data depends on the quality and the exhaustiveness of the register and on the completeness of the follow-up. There is no formal ascertainment of the investigated diseases, both false positives and false negatives are possible. The use of the same diagnostic criteria for a given disease is not guaranteed; they change with time over long follow-ups and may vary according to the physician or hospital. Such studies capture better hip fractures (almost all hospitalized) than other peripheral fractures (often treated on the outpatient basis). In many studies, the low number of investigated covariates may have a confounding role in a study of fracture, especially BMD, circumstances of the fracture, prevalent fractures, prevalent falls or use of vitamin D and calcium, which may be available without prescription. Similar to other long-term prospective studies, these studies cannot account for changes in medications during the follow-up. It is a limitation in case of the study on fractures, because some medications may induce bone loss or increase the risk of falling.

The second group comprises epidemiological studies focused on osteoporosis or CVD. Most of them show that CVD are associated with a higher risk of fragility fracture. In a cohort of home-dwelling men and women followed up prospectively for 11.5 years, incident heart failure conferred higher subsequent risk of hip fracture[26]. After adjustment for confounders, the relative risk slightly attenuated and marginally lost statistical significance. Thus, the association between heart failure and hip fracture may be partly explained by shared risk factors. However, BMD was not measured. Interestingly, in a cohort of 45 509 subjects followed up for up to 10 years, recently diagnosed heart failure remained significantly associated with a higher risk of fragility fracture after adjustment for confounders including baseline BMD at the spine or hip.[27]

In a cohort of older Caucasian women (SOF study) followed up prospectively for 3.5 years, higher resting heart rate was

associated with a progressive increase in the risk of fragility fracture (vertebra, hip, pelvis, rib) after adjustment for confounders.[28] Heart failure and rapid heart rate may reflect poor health status and/or frailty. However, the adjustment for the measures of general health and frailty had a limited impact on these associations.

Some,[1,4,5] but not all,[2,29,30] prospective studies showed that severe AAC is associated with higher risk of fragility fracture. This association was found both in men and in women, for various types of fracture (hip, vertebra, all osteoporotic fractures) and remained significant after adjustment for BMD. However, the increased fracture risk was found mainly in the individuals with severe AAC, but not in the subjects with mild (limited) AAC. In addition, the results of the analyses are influenced by the higher mortality in the subjects with severe AAC and by the duration of the follow-up. Similar positive association between the presence of fragility fracture and calcifications in the abdominal aorta or carotid artery was also found in the cross-sectional studies.[6,31,32]

In the elderly men (MrOS cohort), PAD was associated with higher risk of peripheral fracture.[21] The association lost marginally the significance after adjustment for hip BMD and falls, which indicates that it may partly depend on the lower BMD and higher risk of fall in men with impaired blood flow in the lower limbs. By contrast, in the Rancho Bernardo Study, PAD was not associated with the fracture risk in men or in women.[33] However, the number of individuals followed up prospectively and the number of incident fractures were relatively low, most of the subjects had mild form of PAD and the individuals with PAD were less likely to return for the follow-up visit.

Finally, studies using large administrative registers showed that hypertension is associated with a higher risk of fracture (especially during the first 3 years after diagnosis).[22,24] By contrast, such association was not found in a study based on self-reported data on hypertension obtained using self-administered questionnaires.[34]

Sennerby *et al.*[35] compared postmenopausal women having sustained a hip fracture with controls from the same region. The information on the cases and the controls was based on questionnaire and hospital records. Heart failure, cerebrovascular lesion and hypertension were associated with higher risk of hip fracture. More importantly, the risk of hip fracture increased progressively with the number of hospitalizations for CVD before the study and was highest during the first 6 months after hospitalization.

Jointly, these studies show that various types of CVD are associated with higher risk of fracture. These studies allow us to assess this association in a well-characterized cohort and to include in the statistical models a large number of confounding factors. In such cohorts, it is possible to use standardized methods to assess and to ascertain the investigated variables. However, participation bias may limit representativeness of the cohort. In particular, the elderly with severe diseases often decline to participate in epidemiological follow-ups. In addition, such studies necessitate long follow-ups. This relationship holds mainly for severe CVD and for major osteoporotic fractures (especially hip fracture). It remains significant after adjustment for BMD, which indicates the existence of shared mechanisms underlying both diseases, which are not explained by BMD. This association attenuates after adjustment for shared risk factors, which indicates that it depends partially on the risk factors that are common for both diseases. The relationship between prevalent CVD and fracture incidence has been studied more thoroughly in women than in men. In addition, it seems to be more significant in women; however, the incidence of fragility fractures in men is lower, which results in poorer statistical power.

Association between the Prevalent Bone Abnormality and Incident CVD

Similarly, a substantial number of studies have assessed for the past 20 years the risk of CVD in patients with low BMD, fragility fractures, vitamin D deficit and abnormalities of bone turnover. In a cohort of American elderly women, low calcaneus BMD was associated with higher risk of stroke during a 2-year follow-up.[36] Similarly, in a cohort of Swedish elderly men and women, low femoral neck BMD was associated with higher risk of stroke during a follow-up of 5.5 years.[37]

In the placebo branch of the MORE study, osteoporosis (*T*-score < -2.5 at the spine or the femoral neck) was associated with a fivefold higher risk of cardiovascular event (for example, stroke, myocardial infarction).[38] In a group of 6800 men and women (MONICA and Västerbotten Intervention Programme databases), low hip BMD was associated with higher risk of myocardial infarction.[39] In men, this association remained significant after adjustment for confounders including cardiovascular risk factors. In the Framingham cohort, lower cortical mass of the second metacarpal was associated with a higher incidence of coronary heart disease in postmenopausal women but not in older men.[40] In the Health ABC cohort, incident CVD was defined as the onset of coronary heart disease, cerebrovascular disease, PAD or carotid artery disease.[41] In this cohort, low hip BMD was associated with higher incidence of the above CVD in black, but not white, women. Moreover, low lumbar spine volumetric BMD was associated with higher CVD incidence in white, but not black, men.

Finally, in postmenopausal Danish women recruited for various clinical studies, low bone mass was also associated with higher cardiovascular mortality after adjustment for confounders, including age and cardiovascular risk factors.[42]

Furthermore, presence of fragility fracture is predictive of CVD. In the MORE study, the risk of cardiovascular event was higher in women with prevalent vertebral fractures and increased progressively with the number and with the severity of vertebral fractures[38] (**Figure 2**). In the above Danish study, presence of vertebral fracture was associated with higher cardiovascular mortality.[42] In a case–control study conducted in 8404 men and women identified in the Taiwanese healthcare database, the history of hip fracture conferred 50% higher risk of stroke after adjustment for heart disease, diabetes, hypertension and hyperlipidemia.[43] Given the design of the study, BMD or negative lifestyle factors were not assessed. Finally, in the Rochester Epidemiology Project, history of hip fracture was associated with higher risk of heart failure.[44]

Lower 25OHD level is associated with higher incidence of CVD, especially myocardial infarction, and faster progression of AAC.[45–48] This relation was observed in various populations, in both sexes and regardless of the design of the study (prospective cohort study, prospective nested case–control study, case–control study). This association remained significant after adjustment for potential confounders, which can be associated

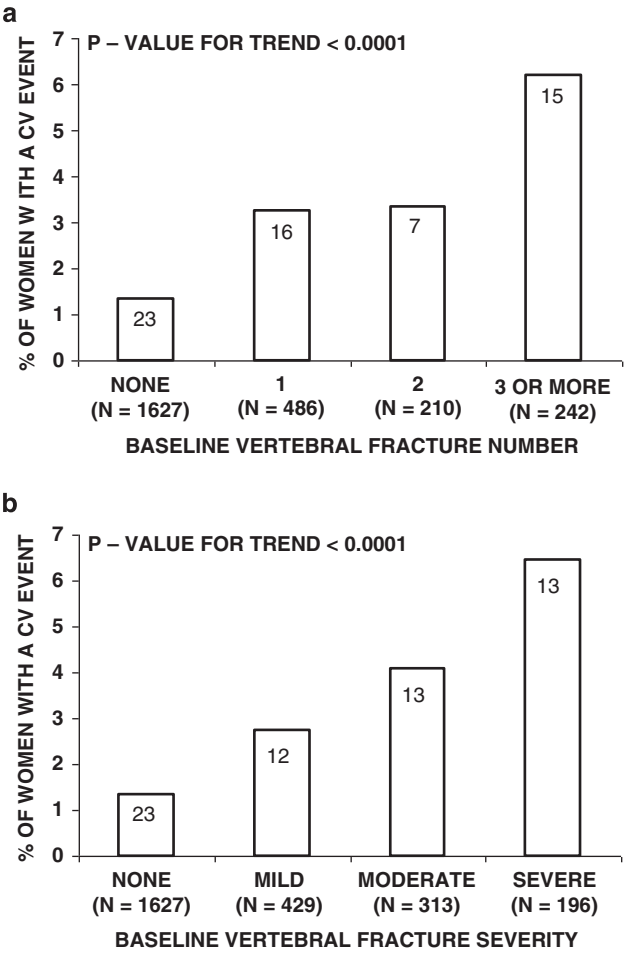

Figure 2 Relationship between the (**a**) number and (**b**) severity of osteoporotic vertebral fractures and the risk of cardiovascular events in 2565 postmenopausal women from the placebo branch of the MORE study. *P*-value is from Cochrane–Armitage trend test. Numbers in bars represent number of women with a cardiovascular event. Cardiovascular event is defined as the incident myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, or a stroke. Vertebral fractures were diagnosed using the semiquantitative method described by Genant. Fracture severity is shown in terms of magnitude of vertebral height reduction. Reproduced from Tanko *et al.*[38] with permission from the American Society for Bone and Mineral Research.

with bone and cardiovascular status independently of each other, such as age, exposure to sunlight, physical activity, smoking and season. Moreover, low 25OHD level was associated with higher cardiovascular mortality in a large group of men and women scheduled for coronary angiography and followed up prospectively for 7.7 years.[49]

In a cohort of 744 men aged 50 years and older and followed up for 7.5 years, elevated levels of bone resorption markers were associated with higher risk of major cardiovascular events (myocardial infarction, stroke) after adjustment for confounders[50] (**Figure 3**).

An important point that has emerged recently is the hormonal role of osteocalcin (OC) as a regulator of energetic metabolism. Experimental studies show that OC, especially its undercarboxylated form, promotes β-cell proliferation, insulin β-cell secretion and insulin sensitivity.[51] Some,[52–54] but not all,[55] clinical studies showed that lower OC level is associated with higher prevalence of metabolic syndrome, more severe AAC, higher brachial-ankle pulse wave velocity and higher intima-media thickness.[52–54] In Chinese men and women, higher OC level was associated with lower prevalence of ischemic heart disease.[56] In a cohort of elderly men, men in the highest OC quintile and those in the lowest OC quintile had higher all-cause mortality compared with the second quintile.[57] Cardiovascular mortality was also significantly higher in the highest OC quintile, whereas in the lowest OC quintile, the risk of cardiovascular mortality was not significant (HR = 1.35, 95% CI: 0.82–2.22). Until now, clinical data on the association between OC and cardiovascular morbidity are scanty; however, they raise an interesting possibility of the pathophysiological pathway: bone–glucose metabolism–CVD.

Osteoporosis and CVD—Consistency and Inconsistency

The association between osteoporosis and CVD is driven by severe forms of both diseases. The associations are significant in the studies, which assess fragility fractures, mainly hip fracture on the side of osteoporosis and, on the side of CVD, myocardial infarction, stroke, heart failure or severe AAC.[1,5,6,25,35,38,43] By contrast, the results are less consistent in the studies in which mild forms of these pathologies were also taken into account.[2,10,11,21,41] More importantly, concomitant heart failure is a risk factor of mortality in hip fracture patients, whereas hip fracture confers a risk of mortality in patients with heart failure.[58–60]

The associations between CVD (especially AAC) and measures of osteoporosis (BMD, rate of bone loss, fracture incidence) are stronger in women than in men. In postmenopausal women, bone loss is faster than in men. Thus, in women, BMD and fracture risk depend more strongly on the postmenopausal bone loss, whereas in older men, BMD is more strongly determined by the peak BMD. This difference between men and women may accentuate the importance of the aging-related factors as the determinants of the association between osteoporosis and CVD. Obviously, the importance of the genetic and growth-related factors should not be underestimated; however, their role in the pathogenesis of these disease in older individuals remains to be established.[61]

Furthermore, the sufficient number of events and temporal closeness are necessary to detect the association. The association has not been detected in small groups, especially composed of younger individuals without severe CVD, or in the long-term follow-up with a large time-lapse between the cardiovascular event (or the assessment of cardiovascular status) and fracture event. In addition, low BMD, fragility fractures, severe AAC and CVD, especially major cardiovascular events, are all associated with higher mortality. Thus, the individuals with severe forms of these diseases are less likely to survive and this differential survival can make the association harder to detect.

The association between both diseases remains significant after adjustment for shared risk factors. However, the presence and intensity of some risk factors (for example, lifestyle factors or comorbidities) are self-reported and not further ascertained. Then, in the analysis, they are often dichotomized or categorized into a small number of classes. Comorbidities are most often dichotomized and their duration and severity are not taken into account. Treatment and its duration as well as dose of drug and compliance to treatment are not taken into account either.

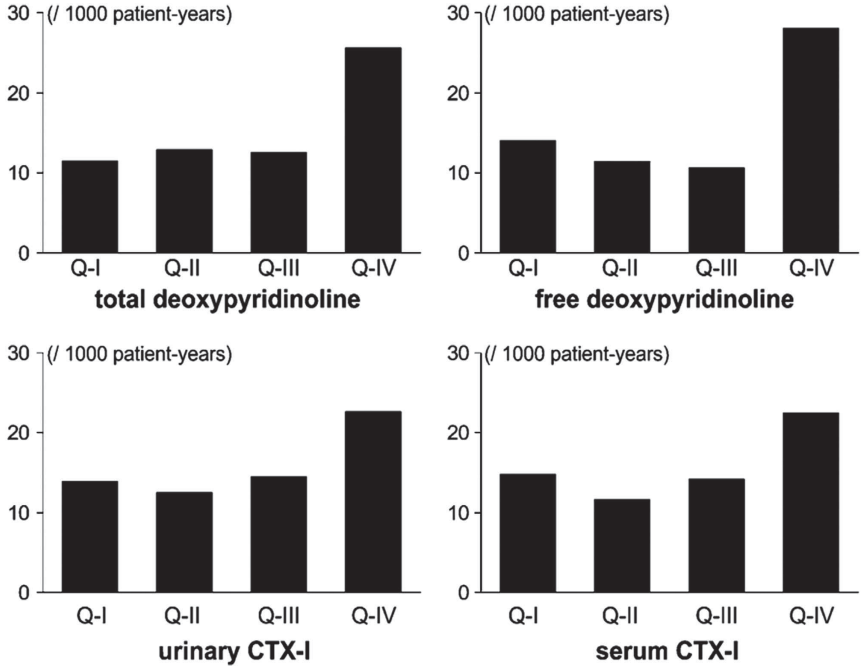

Figure 3 Age-adjusted incidence of the major cardiovascular event in 744 men from the MINOS cohort according to the quartiles of the urinary excretion of total deoxypyridinoline (DPD) (top left graph), free DPD (top right graph), urinary CTX-I (bottom left graph) and serum CTX-I (bottom right graph). Reproduced with permission from Szulc *et al.*[50] with permission from the American Society for Bone and Mineral Research.

However, in some types of CVD for which various classes of medications are available, for example, hypertension, medication as well as its dose and duration of treatment may also impact on the fracture risk.[62]

The assessment of some risk factors, such as hyperlipidaemia or inflammatory markers, is based on one measurement. Thus, their real effect cannot be correctly appreciated. This limitation of the statistical analyses may underestimate the role of the shared risk factors and falsely overestimate the strength of the part of the link between osteoporosis and CVD, which is independent of the shared risk factors.

Many studies show the role of the 'bone risk factors' in the regulation of cardiovascular metabolism and vice versa. Vitamin D deficit may be associated with higher activity of the renin–angiotensin system and impaired glucose tolerance.[63,64] Some factors may have parallel, independent negative effects on bone and cardiovascular metabolism. For instance, homocysteine may promote aortic calcification and reduce bone resistance.[65,66] Higher levels of the glycation end products (AGEs), for example, pentosidine, were associated with poor bone and cardiovascular status. On one hand, accumulation of pentosidine in the trabecular bone was associated with lower bone strength after adjustment for BMD.[67] On the other hand, higher AGE levels were associated with higher risk of cardiovascular event.[68]

General Summary and Conclusions

The experimental and clinical studies show a significant positive association between severe forms of osteoporosis and of CVD. They suggest that this association depends partially on the shared risk factors, for example, smoking, sedentary lifestyle, hormonal deficits, vitamin D deficit, AGE accumulation. From the clinical point of view, it seems that patients with severe form of osteoporosis would benefit from a detailed assessment of the cardiovascular status, whereas patients with severe CVD would benefit from the assessment of BMD and other bone-related parameters. However, official guidelines that could be recommended for the clinical practice are still lacking.

Conflict of Interest

The author declares no conflict of interest.

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