Increasing Risk of Osteoporotic Fracture Is Associated With Vascular Dysfunction and Abnormal Vascular Structure in Both Men and Women

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Background: Osteoporosis and cardiovascular disease are major public health problems. A number of clinical studies have shown a link between osteoporosis and cardiovascular disease, but there is no information on the associations of risk of osteoporotic fracture with vascular function and vascular structure.

Methods and Results: The risk of major osteoporotic fracture was calculated using the World Health Organization fracture risk assessment tool (FRAX); vascular function was assessed using flow-mediated vasodilation (FMD) and nitroglycerine-induced vasodilation (NID), and vascular structure was assessed on brachial artery intima-media thickness (IMT) in 414 subjects (241 men and 173 women) who underwent health examinations. On univariate regression, FRAX was negatively correlated with FMD (total, r=–0.16, P<0.001; men, r=–0.19, P=0.003; women, r=–0.25, P<0.001) and NID (total, r=–0.22, P<0.001; men, r=–0.19, P=0.003; women, r=–0.30, P<0.001) and was positively correlated with brachial artery IMT (total, r=0.12, P=0.02; men, r=0.22, P<0.001; women, r=0.33, P<0.001). On multivariate analysis FRAX remained an independent predictor of FMD, NID, and brachial artery IMT in both men and women.

Conclusions: Increase in the risk of osteoporotic fracture evaluated on FRAX is associated with vascular dysfunction and abnormal vascular structure in both men and women. Osteoporosis should be monitored in order to reduce the risk of cardiovascular events.

Key Words: Atherosclerosis; Brachial artery intima-media thickness; Risk of osteoporotic fracture; Vascular function
This suggests that osteoporosis may be related to cardiovascular disease. Recently, the World Health Organization proposed the fracture risk assessment tool (FRAX): a risk calculator of 10-year major osteoporotic and hip fracture probabilities. Several investigators have reported an association between osteoporosis evaluated by bone mass and atherosclerosis, but there is no information on the associations of risk of osteoporotic fracture with vascular function and vascular structure. In this study, we evaluated the association between FRAX and subclinical atherosclerosis on measurement of FMD. Brachial artery IMT is also considered as a surrogate marker for cardiovascular disease.

Clinical and epidemiological studies have shown a link between osteoporosis and cardiovascular disease. Although osteoporosis and cardiovascular disease share many common risk factors, growing evidence also indicates that there are common pathophysiological mechanisms underlying these diseases. Both vascular calcification and bone mineralization are regulated by several shared bone-associated proteins, such as osteocalcin, osteopontin, bone morphogenetic proteins (BMP), and osteoprotegerin. This suggests that osteoporosis may be related to cardiovascular disease.

### Table 1. Subject Clinical Characteristics

| Variables                        | Total (n=414) | Men (n=241) | Women (n=173) | P value |
|----------------------------------|---------------|-------------|---------------|---------|
| Age (years)                      | 67±11         | 66±11       | 67±12         | 0.41    |
| BMI (kg/m²)                      | 23.7±3.9      | 24.0±3.7    | 23.2±4.1      | 0.02    |
| SBP (mmHg)                       | 131±20        | 132±21      | 129±19        | 0.11    |
| DBP (mmHg)                       | 77±12         | 78±13       | 75±11         | 0.01    |
| Heart rate (beats/min)           | 69±12         | 68±12       | 71±12         | 0.06    |
| Total cholesterol (mmol/L)       | 4.86±0.98     | 4.73±1.01   | 5.07±0.96     | <0.001  |
| Triglycerides (mmol/L)           | 1.50±0.95     | 1.59±1.10   | 1.38±0.67     | 0.02    |
| HDL-C (mmol/L)                   | 1.55±0.44     | 1.50±0.44   | 1.63±0.41     | <0.001  |
| LDL-C (mmol/L)                   | 2.84±0.88     | 2.74±0.85   | 2.97±0.91     | 0.01    |
| Glucose (mmol/L)                 | 6.55±2.16     | 6.66±2.28   | 6.38±1.94     | 0.20    |
| Medical history                  |               |             |               |         |
| Hypertension                     | 302 (72.9)    | 180 (74.7)  | 122 (70.5)    | 0.35    |
| Dyslipidemia                     | 289 (69.8)    | 176 (73.0)  | 113 (65.3)    | 0.09    |
| Diabetes mellitus                | 127 (30.7)    | 76 (31.5)   | 51 (29.5)     | 0.65    |
| Previous CAD                     | 87 (21.0)     | 72 (29.9)   | 15 (8.7)      | <0.001  |
| Previous stroke                  | 47 (11.4)     | 35 (14.5)   | 12 (6.9)      | 0.01    |
| Current smoker                   | 51 (12.3)     | 41 (17.0)   | 10 (5.8)      | <0.001  |
| Medications                      |               |             |               |         |
| Antiplatelets                    | 128 (30.9)    | 90 (37.3)   | 38 (22.0)     | <0.001  |
| CCB                              | 190 (45.9)    | 111 (46.1)  | 79 (45.7)     | 0.94    |
| RAS inhibitors                   | 154 (37.2)    | 92 (38.2)   | 62 (35.8)     | 0.63    |
| Statins                          | 172 (41.5)    | 104 (43.2)  | 68 (39.3)     | 0.43    |
| Medically treated DM             |               |             |               |         |
| Any                              | 80 (19.3)     | 49 (20.3)   | 31 (17.9)     | 0.54    |
| Insulin-dependent                | 18 (4.3)      | 14 (5.8)    | 4 (2.3)       | 0.07    |
| Activated vitamin Ds             | 8 (1.9)       | 4 (1.7)     | 4 (2.3)       | 0.64    |
| Bisphosphonates                  | 6 (1.4)       | 1 (0.4)     | 5 (2.9)       | 0.03    |
| CaCO₃s                           | 3 (0.7)       | 2 (0.8)     | 1 (0.6)       | 0.76    |
| FMD (%)                          | 3.4±2.9       | 3.3±2.7     | 3.7±3.2       | 0.14    |
| NID (%)                          | 11.5±5.6      | 11.5±5.5    | 11.6±5.7      | 0.90    |
| Brachial artery IMT (mm)         | 0.34±0.07     | 0.35±0.07   | 0.32±0.06     | <0.001  |
| Framingham risk score (%)        | 11.5±9.1      | 13.4±10.2   | 8.8±6.4       | <0.001  |
| FRAX (%)                         | 12.1±9.7      | 8.4±4.9     | 17.2±12.2     | <0.001  |
| Previous fracture                | 158 (38.2)    | 98 (40.7)   | 60 (34.7)     | 0.22    |
| Parent fractured hip             | 48 (11.6)     | 23 (9.5)    | 25 (14.5)     | 0.13    |
| Glucocorticoid use               | 10 (2.4)      | 2 (0.8)     | 8 (4.6)       | 0.01    |
| Rheumatoid arthritis             | 10 (2.4)      | 4 (1.7)     | 6 (3.5)       | 0.24    |
| Secondary osteoporosis           | 55 (13.3)     | 31 (12.9)   | 24 (13.9)     | 0.77    |
| Alcohol (≥3 units/day)           | 94 (22.7)     | 84 (34.9)   | 10 (5.8)      | <0.001  |

Data given as mean ± SD or n (%). BMI, body mass index; CaCO₃, calcium carbonate; CAD, coronary artery disease; CCB, calcium-channel blockers; DBP, diastolic blood pressure; DM, diabetes mellitus; FMD, flow-mediated vasodilation; FRAX, fracture risk assessment tool; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; NID, nitroglycerine-induced vasodilation; RAS, renin-angiotensin system; SBP, systolic blood pressure.
in a sitting position, on at least 3 different occasions. Diabetes mellitus was defined according to the American Diabetes Association. Dyslipidemia was defined according to the third report of the National Cholesterol Education Program. Framingham risk score was calculated by summing points for risk factors: age, total cholesterol, high-density lipoprotein cholesterol (HDL-C), SBP, and smoking status. This study was approved by the ethics committee of Hiroshima University. All subjects gave written informed consent for participation in the study.

### Methods

#### Subjects
Between January 2013 and January 2016, 414 consecutive subjects aged 40–89 years who underwent health screening at Hiroshima University Hospital were enrolled. Hypertension was defined as systolic blood pressure (SBP) >140mmHg or diastolic blood pressure (DBP) >90mmHg, in a sitting position, on at least 3 different occasions. Diabetes mellitus was defined according to the American Diabetes Association. Dyslipidemia was defined according to the third report of the National Cholesterol Education Program. Framingham risk score was calculated by summing points for risk factors: age, total cholesterol, high-density lipoprotein cholesterol (HDL-C), SBP, and smoking status. This study was approved by the ethics committee of Hiroshima University. All subjects gave written informed consent for participation in the study.

### Table 2. Clinical Subject Characteristics vs. FRAX

| Variables                     | Total (n=414) | Median FRAX (%) | Men (n=241) | Women (n=173) | ≤9.4 (n=207) | >9.4 (n=207) | ≤7.5 (n=120) | >7.5 (n=121) | ≤14.9 (n=85) | >14.9 (n=88) |
|-------------------------------|---------------|-----------------|-------------|--------------|--------------|--------------|-------------|--------------|--------------|--------------|
| **Age (years)**               | 60±11         | 73±7*†          | 60±10       | 73±7*         | 59±10        | 75±7*        |             |              |              |              |
| M/F                           | 155/52        | 86/121†         |             |              |              |              |             |              |              |              |
| **BMI (kg/m²)**               | 24.6±4.2      | 22.8±3.4*†      | 25.0±4.1    | 23.1±3.2*     | 24.1±4.5     | 23.2±3.5*    |             |              |              |              |
| **SBP (mmHg)**                | 131±21        | 132±20          | 132±21      | 134±20       | 129±19       | 130±20       |             |              |              |              |
| **DBP (mmHg)**                | 79±13         | 74±11*†         | 80±13       | 76±12*        | 78±11        | 73±11*       |             |              |              |              |
| **Heart rate (beats/min)**    | 71±12         | 68±12*†         | 70±12       | 67±12         | 71±11        | 71±12        |             |              |              |              |
| **Total cholesterol (mmol/L)**| 4.86±1.06     | 4.86±0.93       | 4.89±1.06   | 4.55±0.91*‡   | 5.09±1.06    | 5.04±0.80    |             |              |              |              |
| **Triglycerides (mmol/L)**    | 1.50±0.44     | 1.60±0.44*†     | 1.45±0.47   | 1.53±0.41     | 1.63±0.41    | 1.66±0.44    |             |              |              |              |
| **HDL-C (mmol/L)**            | 2.87±0.91     | 2.79±0.85       | 2.90±0.91   | 2.59±0.78*‡   | 3.03±1.01    | 2.92±0.80    |             |              |              |              |
| **Glucose (mmol/L)**          | 6.44±2.05     | 6.66±2.28       | 6.49±2.22   | 6.83±2.33     | 6.27±1.72    | 6.49±2.11    |             |              |              |              |

Data given as mean±SD or n (%). *P<0.05 (†vs. FRAX ≤9.4% group; ‡vs. FRAX ≤7.5% group; §vs. FRAX ≤14.9% group). Abbreviations as in Table 1.
Protocol
All of the subjects completed the FRAX questionnaire; vascular function was assessed on FMD and NID, and vascular structure was assessed using brachial artery IMT. We investigated cross-sectional associations of 10-year probability of a future major osteoporotic fracture with vascular function and vascular structure. The subjects were instructed to abstain from eating, drinking alcohol, smoking and taking caffeine for at least 12 h prior to the measurements. Measurements were performed while each subject was in the supine position in a quiet, dark, air-conditioned room (constant temperature, 22–25°C). Venous blood samples were obtained from the left antecubital vein. Brachial artery IMT was measured after 30 min of resting in the supine position. FMD and NID were then measured. The observers were blind to the purpose of this study.

FRAX
The 10-year probability risk of major osteoporotic fracture was estimated using FRAX version 3.9 for Japan. FRAX is calculated using clinical variables (age, sex, body mass index [BMI], previous fracture as an adult, parental hip fracture, current cigarette smoking, current use of glucocorticoids, diagnosis of rheumatoid arthritis, consumption of ≥3 units alcohol daily, and secondary osteoporosis) with or without bone mineral density (BMD) at the femoral neck. In this study, FRAX was used without BMD at the femoral neck.

Vascular Function and Structure
High-resolution ultrasonography (UNEXEF 18G; UNEX, Nagoya, Japan) was used to evaluate FMD, NID, and brachial artery IMT. The protocol for FMD, NID, and brachial artery IMT measurement has been described in detail previously. Briefly, the longitudinal image of the brachial artery was assessed before and after generation of vascular response to reactive hyperemia by a 5-min period of forearm occlusion to evaluate FMD. FMD was defined as the maximum percentage change in vessel diameter from baseline. After FMD measurement, the longitudinal image of the brachial artery was assessed before and after consumption of a sublingual tablet (75 μg nitroglycerine) to evaluate NID. Images of the artery were recorded continuously until the dilation reached a plateau. NID was defined as the maximum percentage change in vessel diameter from baseline. Brachial artery IMT was measured at the far wall of the brachial artery at 5–10 cm above the elbow.

Statistical Analysis
Data are given as mean ± SD for continuous variables and as percentages for categorical variables. Statistical significance was set at P < 0.05. Comparison of continuous variables between 2 groups was performed using the Mann-Whitney U-test or the chi-squared test for categorical data. Separate analyses were conducted for men and women due to significant sex-specific differences in FRAX (P < 0.001, Table 1). Associations between variables were determined on Spearman rank correlation analysis. Multivariate linear regression analysis was performed to determine the association between vascular function and FRAX before (model 1) and after adjustment for presence of hypertension, dyslipidemia, diabetes (model 2), further adjusted for presence of hypertension, dyslipidemia, diabetes, concomitant treatment with antiplatelets, renin-angiotensin system (RAS) inhibitors, calcium-channel blockers (CCB), statins, and diabetes agents (model 3), and further adjusted for Framingham risk score (model 4). FRAX incorporates age, BMI, and smoking status as risk factors, therefore these were not included in the multiple linear regression analysis. The data were processed using Stata version 9 (Stata, College Station, TX, USA).

Results
Clinical Characteristics
The baseline characteristics of the 414 subjects are summarized in Table 1. Of the 414 subjects, 241 (58.2%) were men and 173 (41.8%) were women. Three hundred

Figure. World Health Organization fracture risk assessment tool (FRAX) vs. (A) flow-mediated vasodilation, (B) nitroglycerine-induced vasodilation, and (C) brachial intima-media thickness in (○) men and (●) women.
and two (72.9%) had hypertension, 289 (69.8%) had
dyslipidemia, 127 (30.7%) had diabetes mellitus, and 51
(12.3%) were current smokers. Mean FRAX was 12.1±9.7%
(men, 8.4±4.9%; women, 17.2±12.2%, P<0.001).

**FRAX and Cardiovascular Risk Factors**

The subjects were divided into 2 groups according to
median FRAX (Table 2). There were significant differences
between the 2 groups in age, gender, BMI, DBP, heart
rate, triglycerides, HDL-C, use of RAS inhibitors, use of
statins, FMD, NID, and brachial artery IMT. There were
significant associations between FRAX and FMD
(r=−0.16, P<0.001; Figure A), NID (r=−0.22, P<0.001;
Figure B), and brachial artery IMT (r=0.12, P=0.02;
Figure C). After adjustment for cardiovascular risk factors,
FRAX remained independently associated with FMD and
NID (Table 3).

**Sex Differences**

We next performed separate analyses for men and women
given that the significant sex-specific differences in FRAX
(P<0.001, Table 1). The subjects were divided into 2 groups
according to median FRAX (Table 2).

In men, there were significant differences between the 2
groups in age, BMI, DBP, total cholesterol, triglycerides,
low-density lipoprotein cholesterol, FMD, NID, and
brachial artery IMT. There were significant associations
between FRAX and FMD (r=−0.19, P=0.003; Figure S1A),
NID (r=−0.21, P=0.002; Figure S1B), and brachial artery
IMT (r=0.12, P=0.001; Figure S1C).

In women, there were significant differences between the
2 groups in age, BMI, DBP, proportion of current smokers,
use of RAS inhibitors, use of activated vitamin D₃, FMD,
NID, and brachial artery IMT. There were significant
associations between FRAX and FMD (r=−0.25, P<0.001;
Figure S2A), NID (r=−0.31, P<0.001; Figure S2B), and
brachial artery IMT (r=0.33, P<0.001; Figure S2C).

After adjustment for confounders, FRAX remained
independently associated with FMD, NID, and brachial
artery IMT in both men and women (Table 3).

**Discussion**

In the present study, risk of osteoporotic fracture evaluated
on FRAX was negatively correlated with FMD and NID
and was positively correlated with brachial artery IMT.
We also confirmed that risk of osteoporotic fracture was
an independent predictor of vascular function and vascular
structure in both men and women after adjustment for
various confounders.

Several observational studies have shown an association
between BMD and atherosclerosis, but there is little
information on the association between risk of osteoporotic
fracture and cardiovascular risk factors. Chen et al showed
that women with cardiovascular disease were at increased
risk of osteoporotic fracture. Makovey et al reported that
risk of osteoporotic fracture was significantly correlated
with Framingham risk score. In the present study, vascular
function assessed on FMD and NID and vascular structure
assessed using brachial artery IMT were impaired as
FRAX risk of osteoporotic fracture increased. This suggests
that risk of osteoporotic fracture is associated with vascular
function and vascular structure.

Several experimental studies have shown that numerous
factors affect disease development in both the bones and
arteries. BMP-2, which is originally found in cartilage and
bone, plays an important role in the development of
atherosclerosis. Expression of BMP-2 is regulated by
nuclear factor-κ-B (NF-κB) activation, and BMP-2 impairs
endothelial function through production of NADPH
oxidase-derived reactive oxygen species. Osteoprotegerin
is a key cytokine that inhibits receptor activator of NF-κB
ligand (RANKL)-mediated osteoclastic bone resorption.
Osteoprotegerin is expressed in endothelial cells and plays
a pivotal role in vascular calcification and osteoporosis.
In addition, osteoprotegerin may be associated with
endothelial dysfunction by inducing the expression of
ICAM-1, VCAM-1, and E-selectin on endothelial cells and

| Table 3. Correlations Between FRAX, FMD, NID, and Brachial Artery IMT |
|-------------------------|----------------|----------------|----------------|
|                         | FMD            | NID            | Brachial artery IMT |
|                         | β              | P value        | β              | P value        | β              | P value        |
| Total (n=414)           |                |                |                |
| Model 1                 | −0.16          | <0.001         | −0.22          | <0.001         | 0.12           | 0.02           |
| Model 2                 | −0.15          | 0.001          | −0.22          | <0.001         | 0.10           | 0.04           |
| Model 3                 | −0.15          | 0.003          | −0.24          | <0.001         | 0.10           | 0.052          |
| Model 4                 | −0.15          | 0.002          | −0.20          | <0.001         | 0.10           | 0.03           |
| Men (n=241)             |                |                |                |
| Model 1                 | −0.19          | 0.003          | −0.21          | 0.002          | 0.22           | <0.001         |
| Model 2                 | −0.16          | 0.009          | −0.21          | 0.002          | 0.20           | 0.001          |
| Model 3                 | −0.16          | 0.01           | −0.22          | 0.001          | 0.20           | 0.001          |
| Model 4                 | −0.17          | 0.01           | −0.18          | 0.01           | 0.19           | 0.003          |
| Women (n=173)           |                |                |                |
| Model 1                 | −0.25          | <0.001         | −0.30          | <0.001         | 0.33           | <0.001         |
| Model 2                 | −0.25          | <0.001         | −0.31          | <0.001         | 0.31           | <0.001         |
| Model 3                 | −0.24          | 0.002          | −0.31          | <0.001         | 0.27           | <0.001         |
| Model 4                 | −0.23          | 0.003          | −0.31          | <0.001         | 0.27           | <0.001         |

Abbreviations as in Table 1. Model 1, unadjusted model; model 2, adjusted for presence of hypertension, dyslipidemia, diabetes; model 3, adjusted for presence of hypertension, dyslipidemia, diabetes, concomitant treatment with antplatelets, RAS inhibitors, CCB, statins, and diabetes agents; model 4, adjusted for Framingham risk score.
consequently promoting leukocyte adhesion to endothelial cells, which is considered to be an early step of endothelial dysfunction.\textsuperscript{31} These observations support the interaction between osteoporosis and endothelial dysfunction. An association between osteoporosis and atherosclerosis has been reported, especially in women,\textsuperscript{15,16,17,22,32} but there have been only a few studies on the association between osteoporosis and atherosclerosis in men.\textsuperscript{33,34} In the present study, we confirmed that FRAX was significantly associated with vascular function and vascular structure in men as well as women, but FRAX was correlated with Framingham risk score in women but not in men (Table S1). The associations of FRAX with vascular function and vascular structure were significantly greater in women than in men. This suggests that osteoporosis may be more significantly associated with atherosclerosis in women than in men.

A number of studies have shown that osteoporosis and atherosclerosis share many risk factors such as hypertension, dyslipidemia, and diabetes.\textsuperscript{15,18} Several investigators, including us, have reported that bone mineral loss is independently associated with vascular dysfunction.\textsuperscript{18,22,23,32} In the present study, on multivariate regression analysis increased risk of osteoporotic fracture was associated with vascular dysfunction in both sexes. Moreover, FRAX was independently associated with vascular function after adjustment of Framingham risk score. The present subjects were taking several drugs that are known to improve endothelial function. It is well known that the use of statins and RAS inhibitors improves BMD, vascular function and vascular structure and reduces the risk of osteoporotic fractures.\textsuperscript{45,46} We confirmed that the association between FRAX and vascular function remained significant after adjustment for the use of these medications. Several investigators including us have reported that NID is decreased in subjects with coronary atherosclerosis or established cardiovascular disease.\textsuperscript{7,14,27,37,38} NID reflects vascular structural changes such as arterial calcification and increase in IMT. In the present study, FRAX was independently associated with endothelium-independent vasodilation. These findings support the results of previous prospective studies showing that increasing severity of aortic calcification is associated with increasing risk of fracture.\textsuperscript{23,39} These harmful effects on the vasculature may contribute to an increase in the prevalence of cardiovascular events in subjects with high risk of osteoporotic fracture. We should pay close attention to osteoporosis in order to reduce the risk of cardiovascular events.

Study Limitations
The present study has a number of limitations. First, the cross-sectional design meant that a definitive causal relationship between risk of osteoporotic fracture and vascular function and vascular structure was unable to be established. In this study, brachial-ankle pulse wave velocity (baPWV) was examined in 370 of the 414 subjects. There were significant relationships between FRAX and baPWV (total subjects, $r=0.20$, $P<0.001$; men, $r=0.22$, $P=0.001$; women, $r=0.38$, $P<0.001$; Figure S3). After adjustment for cardiovascular risk factors, FRAX remained independently associated with baPWV in both men and women (Table S2). These findings support the possibility of a link between osteoporosis and atherosclerosis. Second, FRAX is designed for use in adults aged ≥20 years. Menopausal status is also a risk factor for endothelial dysfunction.\textsuperscript{40} In the present study, 145 of the 173 female subjects were menopausal. We confirmed that FRAX significantly correlated with FMD ($r=-0.17; P=0.04$; Figure S4A), NID ($r=-0.29; P=0.002$; Figure S4B), and brachial artery IMT ($r=0.18; P=0.04$; Figure S4C) in menopausal women. In 28 of the 173 premenopausal women, FRAX did not correlate with FMD, NID or brachial artery IMT. Third, we estimated risk of osteoporotic fracture using FRAX. Although FRAX does not take into account some of the risk factors for osteoporosis such as frequency of bone fracture and previous glucocorticoid use,\textsuperscript{41} FRAX has been found to be significantly associated with future osteoporotic fractures.\textsuperscript{42} In addition, FRAX includes determinants of cardiovascular risk factors such as age, smoking, and glucocorticoid use. Therefore, in the primary analysis we evaluated the associations between FRAX and vascular function and structure after adjustment for Framingham risk score on multivariate linear regression analysis. In addition, in the sensitivity analysis we performed exploratory analysis to evaluate the associations between FRAX and vascular function and structure before and after adjustment for the presence of hypertension, dyslipidemia, and diabetes and after adjustment for the presence of hypertension, dyslipidemia, and diabetes, and concomitant treatment with antiplatelets, RAS inhibitors, CCB, statins, and diabetes agents. We cannot deny the possibility, however, that unobserved confounders and cardiovascular risk factors included in FRAX may have affected the relationships between risk of osteoporotic fracture and vascular function and vascular structure. Finally, FRAX was calculated without BMD. Assessment of BMD and markers of bone turnover such as bone alkaline phosphatase and tartrate-resistant acid phosphate would have provided more information on bone quality for osteoporosis in the enrolled subjects. FRAX has the advantage of enabling evaluation of the risk of osteoporotic fracture without measurements of bone morphometric markers.\textsuperscript{21,42} In addition, several investigators have reported that fracture prediction using FRAX without BMD is as good as that for FRAX with BMD.\textsuperscript{43} Future studies are needed to confirm the associations between risk of osteoporotic fracture and endothelial function and vascular structure in a larger population.

In conclusion, increase in the risk of osteoporotic fracture assessed on FRAX was associated with vascular dysfunction and abnormal vascular structure in both men and women. Osteoporosis should therefore be considered in the development of novel approaches to prevent cardiovascular disease.

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Supplementary Files

**Figure S1.** World Health Organization fracture risk assessment tool (FRAX) vs. (A) flow-mediated vasodilation, (B) nitroglycerine-induced vasodilation, and (C) brachial intima-media thickness in men.

**Figure S2.** World Health Organization fracture risk assessment tool (FRAX) vs. (A) flow-mediated vasodilation, (B) nitroglycerine-induced vasodilation, and (C) brachial intima-media thickness in women.

**Figure S3.** World Health Organization fracture risk assessment tool (FRAX) vs. brachial-ankle pulse wave velocity in (A) all subjects, (B) men, and (C) women.

**Figure S4.** World Health Organization fracture risk assessment tool (FRAX) vs. (A) flow-mediated vasodilation, (B) nitroglycerine-induced vasodilation, and (C) brachial intima-media thickness in menopausal women.

**Table S1.** Univariate indicators of FRAX

**Table S2.** Multivariate correlation between FRAX and baPWV

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