Predictors of Imminent Risk of Nonvertebral Fracture in Older, High-Risk Women: The Framingham Osteoporosis Study

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ABSTRACT
Osteoporosis treatment decisions are often based solely on BMD or on 10-year fracture risk; little is known about factors increasing imminent fracture risk. Understanding factors contributing to imminent risk of fracture is potentially useful for personalizing therapy, especially among those at high risk. Our aim was to identify predictors of nonvertebral fracture for 1- and 2-year periods in women at high risk for fracture. The Framingham Osteoporosis Study cohort included 1470 women (contributing 2778 observations), aged ≥65 years with BMD hip T-score ≤ −1.0, or history of fragility fracture (irrespective of T-score). Nonvertebral fractures were ascertained prospectively over 1 year and 2 years following a baseline BMD scan. Potential risk factors included age, anthropometric variables, comorbidities/medical history, cognitive function, medications, history of fracture, self-rated health, falls in the past year, smoking, physical performance, hip BMD T-score, Activities of Daily Living (ADL) score, and caffeine and alcohol intakes. Predictive factors with p value ≤ 0.10 in bivariate Cox proportional hazards regression models were subsequently considered in multivariable models. Mean baseline age was 75 years (SD 6.0). During 1-year follow-up, 89 nonvertebral fractures occurred; during 2-year follow-up, 176 fractures occurred. Of the variables considered in the bivariate models, significant predictors of nonvertebral fractures included age, history of fracture, self-rated health, falls in the prior year, BMD T-score, ADL, renal disease, dementia, and current use of nitrates, beta-blockers, calcium channel blockers, or antidepressants. In multivariable models, significant independent risk factors were history of fracture, self-rated health, hip BMD T-score, and use of nitrates. Significant 1-year results were attenuated at the 2-year follow-up. In addition to the traditional factors of BMD and fracture history, self-rated health and use of nitrates were independently associated with imminent risk of fracture in older, high-risk women. These specific risk factors thus may be useful in identifying which women to target for therapy. ©2018 The Authors JBMR Plus published by Wiley Periodicals, Inc. on behalf of American Society for Bone and Mineral Research.

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Introduction
Rates of fractures of the hip, forearm, vertebrae, humerus, pelvis, and ankle increase with advancing age, especially after age 75 years.1 Lifetime risk of symptomatic fracture for a 50-year-old white woman has been estimated to be 13% for the forearm and 14% for the hip, several-fold higher than corresponding risks among men of similar age.2,3 These fractures are a major cause of morbidity, mortality, and healthcare costs, especially those involving the hip. Excess mortality is often seen in the year following a fracture in older adults.3 Loss of cortical and trabecular bone mass with advancing age, and resulting osteoporosis and associated bone fragility, is widely considered to be the major cause of fractures in older people.

In light of the substantial clinical and economic burden of osteoporotic fractures, the National Osteoporosis Foundation (NOF) promulgated guidelines for fracture prevention in 2010.4 In addition to nonpharmacological recommendations and maintenance of adequate intake of calcium and vitamin D, specific pharmacologic therapy (eg, bisphosphonates, calcitonin) is recommended for persons with: (1) BMD T-scores ≤ −2.5;
and (2) T-scores between $-1.0$ and $-2.5$, and 10-year predicted risk of hip fracture $\geq 3\%$ or major osteoporosis-related fracture $\geq 20\%$ based on WHO’s absolute Fracture Risk Assessment Tool (FRAX). The FRAX model is based on 12 risk factors, one of which is hip BMD, but a risk score can be calculated with or without information on BMD.

Despite endorsements of FRAX by both NOF and WHO, it has a number of limitations: (1) the general nature of some of the items (eg, fracture history does not take into account the timing or number of fractures); (2) the exclusion of falls information$^{10,61}$; (3) a relatively low area-under-the-curve (AUC) in validation studies (only about 60% for major osteoporosis-related fracture); and (4) application only to persons who are untreated for osteoporosis.$^{7,8}$ The importance of some of the items in FRAX also may be questionable. One study, for example, reported that there was no significant difference in predictive accuracy as measured by AUC between FRAX and simple models based only on BMD and age.$^{16}$ Finally, 10-year fracture risk is not necessarily indicative of short-term fracture risk because the annual incidence of fracture increases substantively with age; thus, the risk in the first year of a given 10-year interval is undoubtedly lower than that in year 10. Moreover, the relative risk of fracture for those with (versus without) a history of fracture is highest in the period soon after the event (ie, within the 1-to-2-year period) and declines thereafter.$^{10}$ Identifying these patients can reinvigorate the treatment discussions in this undertreated population.

For older women with established osteoporosis, short-term risk prediction may be much more important than 10-year risk, especially within the context of decisions regarding the use of new, high-cost bone anabolic agents. Moreover, the importance of age, BMD, and other risk factors may be different in the prediction of short-term fracture risk among older women with established osteoporosis compared with the prediction of long-term fracture risk among the general population of postmenopausal women. Identification of women with high risk of fracture may be especially important in elderly women with osteoporosis or osteopenia. To better understand the risk factors for imminent (ie, within 1 to 2 years) fracture in this population, we conducted a cohort study using prospectively collected data from the large, well-characterized Framingham Osteoporosis Study cohort. Our objective was to determine the factors that are independently associated with imminent nonvertebral fracture, for 1-year and 2-year time frames, in women aged 65 years and older, and at high risk of fracture.

**Participants and Methods**

We used a cohort study design using previously collected prospective data to discern predictive factors associated with subsequent nonvertebral fractures in older women from a large, well-characterized cohort, the Framingham Osteoporosis Study. The institutional review board at Hebrew SeniorLife approved this study; all participants signed an informed consent form prior to study enrollment.

**Participants**

The Framingham Study Original Cohort is a large, longitudinal population-based study that in 1948 enrolled two-thirds of the adults in the town of Framingham, Massachusetts, USA. In 1971 the Framingham Offspring Study enrolled the adult offspring (and their spouses) of the original cohort participants. Framingham Study participants undergo an extensive clinical examination and questionnaire battery every 2 or 4 years, depending upon the cohort. DXA scans of the hip and spine were obtained up to 3 times every 2 years between 1986 and 1998 for the original cohort, and up to 3 times every 4 years between 1996 and 2008 for the offspring cohort, using a Lunar DPX-L densitometer (GE Lunar Corp, Madison, WI, USA). For the current study, each BMD assessment was considered as the unit of observation, with the date of BMD assessment as baseline for the 1- and 2-year fracture follow-up periods. Thus, the same individual could have up to three separate observations included in the study sample for analysis (see Fig. 1). Our sample included women from both cohorts who were aged 65 years and older, and met at least one of the following criteria at baseline: (1) having osteoporosis defined as a T-score $\leq -2.5$ at the femoral neck or lumbar spine; (2) osteopenia defined as a T-score $>-2.5$ to $\leq -1.0$ at the femoral neck or lumbar spine; or (3) a history of nonvertebral or vertebral fracture, regardless of T-score. These selection criteria are based in large part on the NOF treatment guidelines.$^{24,11}$ The study source sample comprised 1010 original cohort participants and 3025 offspring cohort participants. Of these women, 1470 met the study eligibility criteria.

**Assessment of fractures**

Fracture of any nonvertebral site was defined as first occurrence during the follow-up period of fracture of the hip, leg, knee, ankle, foot, clavicle, humerus, elbow, hand (excluding fingers), pelvis, or rib. Follow-up information on mortality and fracture is complete for well over 95% of the cohort. Fracture ascertainment is performed through review of all participant contacts or study visits during which all hospitalizations and physician contacts are reported, including any fractures that occurred since their last visit. Fractures are adjudicated through an ongoing process using several overlapping sources including the clinic exam, fracture logs, hospitalization and death records, discharge summaries, reports from emergency department visits, operative reports, radiographic procedures, medical history updates, and other medical reports. The circumstances of each fracture are documented (degree of trauma, details of event, and treatment). Pathological fractures and fractures caused by high-energy trauma (motor vehicle accident or assault) were excluded because it is not hypothesized that these high-impact fractures will be related to factors for fragility fractures.

**Covariables**

Each participant contributed up to three separate risk factor assessments, each considered in light of 1- and 2-year risks of subsequent fracture. Potential predictive factors for fracture were evaluated at each eligible BMD assessment and included age, BMD, BMI, history of fracture, falls in the past 12 months, alcohol use, smoking status, caffeine use, history of medical comorbidities (eg, cardiovascular disease [CVD]), medication use (eg, anticonvulsants, benzodiazepines, bisphosphonates, and other osteoporosis drugs), cognitive function as assessed by the Mini-Mental Status Examination (MMSE) score,$^{12}$ physical function as assessed by self-reported ability to perform activities of daily living (ADLs), and instrumental activities of daily living (IADLS), observed physical performance assessed by chair stands and measured walks, self-rated health$^{13-16}$ (queried as excellent, good, fair, or poor), and depressive symptom (Center for...
Epidemiologic Studies Depression Scale (CES-D) score. Categorizing persons scoring ≥16 on the CES-D as exhibiting depression symptoms has been validated in a general population, as well as in elderly persons. Candidate risk factors were based largely on those identified in a review of published literature on predictors of fractures and/or falls, and an ongoing similar evaluations presented in abstract form at scientific meetings.

Follow-up
Following each risk factor assessment, 1- and 2-year follow-up periods were assessed for fracture occurrence. The one-year follow-up period began on the day after the date of the risk factor assessment and DXA scan, and ended at the date of occurrence of fracture, last contact, death, or 365 days later, whichever occurred earliest. For the 2-year follow-up, the maximum duration of follow-up was 730 days. Only one (ie, the first) fracture event in each follow-up interval for an observation was considered; multiple first fracture events occurring in different follow-up periods for the same participant were considered (see Fig. 1).

Statistical analysis
Each qualifying examination for each woman in the study population was considered as a separate observation in analyses, assessed over 1- and 2-year follow-up periods. Each participant contributed up to three such groupings of baseline and follow-up observations. All observations were considered in a single analysis, taking into account clustering at the level of the participant based on repeated assessments. Risk factors were allowed to vary by assessment, such that a participant’s age, comorbidities, etc., at each assessment were taken into account.

Potential risk factors that were continuous in nature were also evaluated using multilevel categorical (ie, ordinal or interval) variables; thresholds separating categories for a given factor were defined based on the quantiles of the distribution, and subsequently modified based on clinical and/or statistical considerations. Crude risk (numbers of participants with fracture events divided by person-years or risk) of fracture were computed, and estimated relative risks were obtained comparing each variable grouping to referent categories. Following this, we modeled the risk of fracture using a clustered Cox proportional hazards model with robust variance estimated, employed to obtain validity in the presence of repeated assessments and outcomes. All risk factors with a p value <0.10 in the bivariate analyses were initially included simultaneously in a single multivariable model; grouped multilevel factors were included if any level had a p value <0.10. Variables that were no longer significant or important predictors in the multivariate context were excluded from the model (ie, other than age, no variables were retained based on a priori considerations), and the final parsimonious model was calculated. The importance of interactions between potential risk factors was examined. Model discrimination was evaluated based on the concordance index (c-index).

Results
There were 1470 Framingham Study women who met the study criteria of age ≥65 years with a baseline DXA indicating either osteoporosis (T-score ≤−2.5), osteopenia (T-scores for osteopenia were >−2.5 and included values as high as −1.0), or having a history of nonvertebral or vertebral fracture, regardless of T-score. Mean age was 75 years (±5-year SD). Table 1 shows the baseline characteristics of the study sample. These 1470 women contributed 2778 observations (up to three per woman) to both the 1- and 2-year follow-up analyses. Of these observations, 612 women contributed one observation, 408 women contributed two observations, and 450 women contributed three observations.
During the 1-year follow-up, 89 nonvertebral fractures occurred; during the 2-year follow-up, 176 fractures occurred. Hip fracture as well as wrist/forearm was the most frequent type of fracture in the 1-year follow-up (Table 2). Of 31 variables considered in unadjusted, bivariate models, those associated \((p < 0.10)\) with nonvertebral fracture included age, history of fracture, self-rated health, falls in the prior year, BMD \(T\)-score, ADL score, renal disease, dementia, and current use of nitrates, beta-blockers, calcium channel blockers, or antidepressants (Tables 3a, 3b). There were no statistically significant interactions.

In the 1-year multivariable model, significant independent risk factors were history of fracture, self-rated health, hip BMD \(T\)-score, and use of nitrates (Table 4). Significant associations from the 1-year time frame were mostly attenuated when considered over 2 years of follow-up. Discrimination of the 1-year model, based on the \(c\)-index, was 0.71 (SE 0.03), indicating good discrimination, with the 2-year model \(c\)-index of 0.64 (SE 0.02).

Discussion

The purpose of this study was to better understand the risk factors for imminent nonvertebral fracture in a population of older postmenopausal women with osteoporosis, osteopenia, and/or fracture history in whom fracture risk may be elevated. This study found several factors were independently associated with the 1-year risk of fracture including history of fracture, poor self-reported health status, osteoporosis indicated by \(T\)-score level, and use of nitrates in the past 2 years or more. Additional factors including falls history, renal disease, and use of antidepressants met our bivariate criterion for inclusion in the multivariate model, but were not statistically significant once other variables were considered. Several recent studies have also examined risk of imminent fracture and report similar factors derived from claims databases and clinical studies. Two recent studies\(^{[10,24]}\) on the 1- and 2-year risk from the Medicare 20% sample and the Truven Commercial and Medicare Claims Dataset supported the importance of older age, history of other adult fracture, prior recent falls, poorer health status, diagnosis of osteoporosis, and comorbidities that trigger more frequent falls (Alzheimer disease, CNS diseases), as well as medications and equipment that linked to poorer cognition, physical function, and motor skills (use of wheelchair, walker, cane, narcotics, centrally sedating anticholinergic medications, and sedative hypnotic medications). Other research from observational cohorts (Study of Fractures, Canadian Multi-Center Osteoporosis Study, Kaiser, Swedish Registry Data) have demonstrated similar findings with older age, BMD \(T\)-score, prior fracture, falls, and falls-related risk factors (comorbidities, medications) being the dominant predictors. The results support many of the fracture risk prediction tools that focus on longer term risk prediction (5 to 10 years) with the exception that falls and fall-related factors (diseases and medications) are also quite important. Currently, only tools such as Q-Fracture capture these important risk factors, whereas FRAX and others do not consider them. Previous research has reported that falls represent at least 30% of the risk of fracture, which would be accurate for these risk factors to factor so consistently and prominently into defining the imminent risk fracture patient across data source and type.\(^{[5]}\)

Imminent (1 to 2 year) risk of fracture appears to be an important, yet relatively understudied, time frame that may be relevant to stimulate more patient interest in therapeutics aimed at fracture prevention.

There is a strong inverse relationship between bone density and risk of fracture, with a two- to threefold increased risk per standard deviation decline in BMD. Nonetheless, at any given level of BMD, fracture risk increases with advancing age, highlighting the fact that factors other than bone density are independently related to risk of fracture. Although some of these factors affect skeletal integrity (eg, bone turnover, trabecular architecture), nonskeletal factors may also play an important role to the extent that they increase the risk of falls, which are the precipitating factor in the vast majority of osteoporotic fractures.

Not surprisingly, falls were predictive of imminent fracture risk in our study despite data on falls occurrence being somewhat limited in scope (self-reported yes/no for past year at BMD scan visit). Once other important variables were considered in our study, however, falls were no longer statistically significant in the multivariable model. A 2016 case-control study of short-term fracture risk using US claims data reported higher imminent fracture risk for older adults with falls, poor health, specific comorbidities, psychoactive medication use, and mobility impairment.\(^{[10]}\) A 2017 cohort study of women in the Study of Osteoporotic Fractures (SOF) also found prior falls as well as prior fracture, walking speed, Parkinson disease, smoking, and stroke to be predictive factors.\(^{[20]}\) A select list of medications used in the past year also predicted short-term fracture risk in our study. The claims data study examined class of medications rather than specific medications, but reported similar findings for antidepressants\(^{[20]}\); however, our study did not have sufficient numbers of users of medication categories to closely examine many medications. Although a previous study found nitrates to

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**Table 1. Characteristics of the First Observation for Women in the Study Sample, Aged ≥65 Years With Osteoporosis, Osteopenia, or Fracture History (N = 1470)**

| Characteristic                  | Mean ± SD        |
|--------------------------------|------------------|
| Age, mean ± SD, (years)        | 75.4 ± 6.0       |
| Age category, n (%)            |                  |
| <75 years                      | 674 (45.9)       |
| 75–84 years                    | 686 (46.7)       |
| 85 + years                     | 110 (7.5)        |
| Weight, mean ± SD (pounds)     | 144.2 ± 28.5     |
| Height, mean ± SD (inches)     | 61.7 ± 2.5       |
| BMI, mean ± SD (kg/m²)         | 26.7 ± 5.0       |
| Hip BMD \(T\)-score, mean ± SD| −2.20 ± 0.83     |

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**Table 2. Types of Nonvertebral Fractures Experienced Over Follow-Up in Study Women**

| Frequency at 1 year | Frequency at 2 year |  |
|--------------------|---------------------|---|
| Hi                 | 18                  | 33 |
| Wrist/forearm      | 18                  | 33 |
| Foot/ankle/leg     | 15                  | 34 |
| Upper arm/shoulder | 16                  | 28 |
| Ribs               | 10                  | 14 |
| Other              | 12                  | 34 |
| Total              | 89                  | 176 |
| Covariates                      | No. of observations | No. of Fx | % Fx | Rel. risk | HR     | 95% CI   | p value |
|--------------------------------|---------------------|-----------|------|-----------|--------|----------|---------|
| **Age**                        |                     |           |      |           |        |          |         |
| <75 years                      | 1274                | 32        | 2.5  | REF       | 1.5    | 0.93, 2.28| 0.10    |
| 75–84 years                    | 1296                | 47        | 3.6  | 1.5       | 1.9    | 0.95, 3.92| 0.07    |
| 85+ years                      | 208                 | 10        | 4.8  | 1.9       | 1.9    | 0.88, 2.41| 0.14    |
| **History of fracture**        |                     |           |      |           |        |          |         |
| Yes                            | 939                 | 41        | 4.4  | 1.7       | 1.7    | 1.12, 2.57| 0.01    |
| No                             | 1839                | 48        | 2.6  | REF       | REF    |          |         |
| **Falls in last year**         |                     |           |      |           |        |          |         |
| 0                              | 1585                | 41        | 2.6  | REF       | REF    |          |         |
| 1                              | 467                 | 22        | 4.7  | 1.8       | 1.8    | 1.09, 3.07| 0.02    |
| 2+                             | 636                 | 24        | 3.8  | 1.5       | 1.5    | 0.88, 2.41| 0.14    |
| **Smoking**                    |                     |           |      |           |        |          |         |
| No, not current                | 2539                | 81        | 3.2  | REF       | REF    |          |         |
| Yes, current                   | 237                 | 8         | 3.4  | 1.1       | 1.1    | 0.51, 2.17| 0.90    |
| **Estrogen use**               |                     |           |      |           |        |          |         |
| No                             | 2391                | 82        | 3.4  | REF       | REF    |          |         |
| Yes, current                   | 235                 | 4         | 1.7  | 0.5       | 0.5    | 0.18, 1.33| 0.16    |
| Yes, former                    | 150                 | 3         | 2.0  | 0.6       | 0.6    | 0.19, 1.88| 0.04    |
| **Total ADL score**            |                     |           |      |           |        |          |         |
| 0–2 Severe impairment          | 6                   | 1         | 16.7 | 5.4       | 6.2    | 0.86, 44.6| 0.07    |
| 3–4 Moderate impairment        | 18                  | 1         | 5.6  | 1.8       | 1.8    | 0.25, 13.1| 0.55    |
| 5–6 Full function              | 2730                | 85        | 3.1  | REF       | REF    |          |         |
| **Self-related health**        |                     |           |      |           |        |          |         |
| Excellent                      | 886                 | 17        | 1.9  | REF       | REF    |          |         |
| Good                           | 1486                | 53        | 3.6  | 1.9       | 1.9    | 1.08, 3.21| 0.03    |
| Fair                           | 325                 | 13        | 4.0  | 2.1       | 2.1    | 1.02, 4.33| 0.04    |
| Poor                           | 26                  | 3         | 11.5 | 9.7       | 6.0    | 1.8, 20.4 | 0.004   |
| **T-score category**           |                     |           |      |           |        |          |         |
| ≤ −2.5 or lower (osteoporosis) | 980                 | 54        | 5.5  | 3.3       | 3.3    | 0.80, 13.5| 0.10    |
| > −1.0 to −2.499 (osteopenic)  | 1680                | 33        | 2.0  | 1.2       | 1.2    | 0.3, 4.81 | 0.84    |
| ≥ −1.0 or better (normal)      | 118                 | 2         | 1.7  | REF       | REF    |          |         |
| **Medical history/comorbidities**|                   |           |      |           |        |          |         |
| Hypertension                   | Yes                 | 1420      | 40   | 2.8       | 0.8    | 0.50, 1.15| 0.19    |
| No                             | 1318                | 48        | 3.6  | REF       | REF    |          |         |
| Renal disease                  | Yes                 | 169       | 9    | 5.3       | 1.8    | 1.8, 3.66 | 0.08    |
| No                             | 2597                | 78        | 3.0  | REF       | REF    |          |         |
| Emphysema                      | Yes                 | 70        | 4    | 5.7       | 1.8    | 1.8, 6.7  | 0.24    |
| No                             | 2698                | 85        | 3.2  | REF       | REF    |          |         |
| Degenerative joint disease     | Yes                 | 1032      | 32   | 3.1       | 1.0    | 1.0, 6.3  | 0.90    |
| No                             | 1722                | 55        | 2.9  | REF       | REF    |          |         |
| Dementia                       | Yes                 | 50        | 3    | 6.0       | 1.9    | 2.0, 6.19 | 0.25    |
| No                             | 2689                | 84        | 3.1  | REF       | REF    |          |         |
| High thyroid                   | Yes                 | 188       | 6    | 3.2       | 0.9    | 0.9, 0.41 | 2.18    |
| No                             | 1965                | 68        | 3.5  | REF       | REF    |          |         |
| Parkinson disease              | Yes                 | 10        | 0    | 0.0       | --     | --       | --      |
| No                             | 2103                | 72        | 3.4  |          |        |          |         |
| Diabetes                       | Yes                 | 214       | 8    | 3.7       | 1.2    | 1.2, 5.9  | 0.61    |
| No                             | 2564                | 81        | 3.2  | REF       | REF    |          |         |
| CVD                            | Yes                 | 1261      | 48   | 3.8       | 1.4    | 1.4, 9.3  | 0.11    |
| No                             | 1517                | 41        | 2.7  | REF       | REF    |          |         |
| Cancer                         | Yes                 | 631       | 18   | 2.8       | 0.8    | 0.8, 0.50 | 0.40    |
| No                             | 2127                | 71        | 3.3  | REF       | REF    |          |         |
| Medication use                 | Nitroglycerine      | Yes       | 90   | 3         | 3.3    | 0.9, 1.0  | 0.31    |
| No                             | 2416                | 82        | 3.4  | REF       | REF    |          |         |

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Table 3a. One-Year Follow-Up Bivariate Analyses of Potential Risk Factors and Nonvertebral Fracture in Women Aged ≥65 Years With Osteoporosis, Osteopenia, or Fracture History
protect against hip fracture, we found use in the past 2 years increased the risk of hip fracture. This could be because of the disease for which they were prescribed (CVD) or because of the hypotensive effects of taking nitrates. Because persons with CVD manifest by aortic calcification, they may also have greater fracture risk. The study from claims data supports the limited medications data from our cohort. Attributing risk to medication prescribing may suffer from bias by indication, making it quite difficult to discern the disease from the medication used to treat the disease, as the causal risk factor. Understanding the factors that elevate short-term fracture risk are important for identifying patients at imminent risk of fracture, as they merit prompt evaluation and treatment for osteoporosis. It is important to note that falls and other variables (as seen in Table 4) were most predictive of short-term fracture risk in the 1-year time frame than 2-year follow-up time. Whether the risk factors of primary importance in a broad group of postmenopausal women (eg, older age and low BMD), retain their relative importance in this high-risk subgroup is largely unknown. Perhaps for this group of women, identification of the subset at imminent risk of falling is much more important from the perspective of risk stratification. Moreover, in older postmenopausal women and in women with a recent fracture, ascertainment of risk factors for imminent fracture may have greater clinical relevance than identification of risk factors that have long-term prognostic importance, but poorer predictive accuracy over the short-run. The NOF guidelines list more than 75 conditions, diseases, and medications that cause or contribute to osteoporosis and fractures; they also identify 21 risk factors for falls. Among the risk factors for falls that have been identified are muscle weakness, gait and balance deficits, visual impairment, arthritis, impaired ADLs, depression, cognitive impairment, and age >80 years. There have been numerous studies of these and other risk factors for osteoporotic fractures and falls. Major studies included those based on the SOF, the Framingham Osteoporosis Study, the National Osteoporosis Risk Assessment (NORA) Study, the Canadian Multicentre Osteoporosis Study (CaMos), Women’s Health Initiative (WHI), the Million Women Study, and the Global Longitudinal Study of Osteoporosis in Women (GLOW). The current study results winnow this long list of potential factors to several that may be particularly pertinent for imminent risk of fracture. The unadjusted findings of this study may indicate those items of interest to consider in a clinical examination or check-up examination for older women at high-risk of nonvertebral fracture. The parsimonious results from analyses considering all factors showed that history of fracture, poor self-reported health status, osteoporosis indicated by T-score level, and use of nitrates in the past 2 years or more were indicators of imminent nonvertebral fractures in our study. These factors may be of particular interest to clinicians and helpful in highlighting persons who may warrant strong consideration for falls-prevention programs. Relatively sparse information (compared to long-term fracture risk) exists in the published literature to compare with our results on imminent risk of nonvertebral fractures. The attenuation of results over 2 years compared to the results over 1 year suggests that the effects of risk factors

| Table 3a. (Continued) |
|------------------------|
| Women with osteoporosis, osteopenia, fracture history (n observations = 2778) |
| Covariates | No. of observations | No. of Fx | % Fx | Rel. risk | HR | 95% CI | p value |
| Nitrateyes | 98 | 11 | 11.2 | 3.7 | 3.9 | 2.06, 7.31 | <.0001 |
| Niten | 2408 | 74 | 3.1 | REF | REF |
| Beta blocker yest | 471 | 23 | 4.9 | 1.6 | 1.6 | 1.01, 2.63 | 0.05 |
| Niten | 2040 | 62 | 3.4 | REF | REF |
| Calcium channel blockeryes | 385 | 19 | 4.9 | 1.6 | 1.6 | 0.96, 2.67 | 0.07 |
| Niten | 2126 | 66 | 3.1 | REF | REF |
| Diureticsyes | 516 | 14 | 2.7 | 0.8 | 0.8 | 0.44, 1.39 | 0.40 |
| Nitrateyes | 1946 | 67 | 3.4 | REF | REF |
| Antihyperseques | 58 | 2 | 3.4 | 0.9 | 0.9 | 0.23, 3.75 | 0.91 |
| Nitrateyes | 1920 | 71 | 3.7 | REF | REF |
| Anti-anxietyyes | 121 | 5 | 4.1 | 1.2 | 1.2 | 0.50, 3.03 | 0.66 |
| Nitrateyes | 2393 | 80 | 3.3 | REF | REF |
| Sleepingyes | 45 | 2 | 4.4 | 1.3 | 1.4 | 0.33, 5.52 | 0.67 |
| Nitrateyes | 2469 | 83 | 3.7 | REF | REF |
| Antidepressantsyes | 132 | 8 | 6.1 | 1.9 | 1.9 | 0.91, 3.92 | 0.09 |
| Nitrateyes | 2381 | 77 | 3.2 | REF | REF |
| Anticonvulsantsyes | 21 | 1 | 4.8 | 1.3 | 1.2 | 0.17, 8.97 | 0.83 |
| Nitrateyes | 1852 | 69 | 4.2 | REF | REF |
| Progesteroneyes | 83 | 1 | 1.2 | 0.4 | 0.4 | 0.05, 2.61 | 0.31 |
| Nitrateyes | 2677 | 88 | 3.3 | REF | REF |

Any sum <2778 observations is based on missing values of a variable.
FX = fractures; ADL = activities of daily living; CVD = cardiovascular disease; REF = Referent Category.
| Covariates                          | Women with osteoporosis, osteopenia, fracture history (n = 2778) | Cox PH model |
|------------------------------------|-----------------------------------------------------------------|--------------|
|                                    | No. of observations | No. of Fx | % Fx | Rel. risk | HR      | 95% CI    | p value |
| **Age**                            |                    |           |      |           |         |           |         |
| <75 years                          | 1274               | 63       | 4.9  | REF       |         |           |         |
| 75–84 years                        | 1296               | 97       | 7.5  | 1.5       | 1.12, 2.12 | 0.007     |
| 85+ years                          | 208                | 16       | 7.7  | 1.6       | 0.93, 2.80 | 0.09      |
| **History of fracture**            |                    |           |      |           |         |           |         |
| Yes                                | 939                | 75       | 8.0  | 1.5       | 1.11, 2.01 | 0.009     |
| No                                 | 1839               | 101      | 5.5  | REF       | REF      |           |         |
| **Falls in last year**             |                    |           |      |           |         |           |         |
| 0                                  | 1585               | 96       | 6.1  | REF       | REF      |           |         |
| 1                                  | 467                | 39       | 8.4  | 1.4       | 0.96, 2.03 | 0.08      |
| 2+                                 | 636                | 36       | 5.7  | 0.9       | 0.63, 1.35 | 0.68      |
| **Smoking**                        |                    |           |      |           |         |           |         |
| No, not current                    | 2539               | 161      | 6.3  | REF       | REF      |           |         |
| Yes, current                       | 237                | 15       | 6.3  | 1.0       | 1.0     | 0.58, 1.68 | 0.96 |
| **Estrogen use**                   |                    |           |      |           |         |           |         |
| No                                 | 2391               | 161      | 6.7  | REF       | REF      |           |         |
| Yes, current                       | 235                | 8        | 3.4  | 0.5       | 0.24, 0.99 | 0.05      |
| Yes, former                        | 150                | 7        | 4.7  | 0.7       | 0.34, 1.53 | 0.39      |
| **Total ADL score**                |                    |           |      |           |         |           |         |
| 0–2 Severe impairment              | 24                 | 4        | 16.7 | 2.4       | 2.6     | 0.97, 7.10 | 0.06 |
| 3–4 Moderate impairment            | 620                | 20       | 3.2  | 0.5       | 0.31, 0.78 | 0.003     |
| 5–6 Full function                  | 2110               | 149      | 7.1  | REF       | REF      |           |         |
| **Self-related health**            |                    |           |      |           |         |           |         |
| Excellent                          | 886                | 42       | 4.7  | REF       | REF      |           |         |
| Good                               | 1486               | 96       | 6.5  | 1.4       | 1.4     | 0.95, 1.95 | 0.10 |
| Fair                               | 325                | 29       | 9.1  | 1.9       | 1.9     | 1.21, 3.12 | 0.006 |
| Poor                               | 26                 | 3        | 11.5 | 2.4       | 2.5     | 0.78, 8.08 | 0.12 |
| **T-score category**               |                    |           |      |           |         |           |         |
| ≤ –2.5 or lower (osteoporosis)     | 980                | 94       | 9.6  | 2.3       | 0.4     | 0.18, 1.08 | 0.07 |
| > –1.0 to –2.499 (osteopenic)      | 1680               | 77       | 4.6  | 1.1       | 0.5     | 0.35, 0.63 | <0.0001 |
| ≥ –1.0 or better (normal)          | 118                | 5        | 4.2  | REF       | REF      |           |         |
| **Medical history/comorbidities**  |                    |           |      |           |         |           |         |
| Hypertension                       | Yes                | 1427     | 85   | 6.0       | 0.9     | 0.65, 1.19 | 0.40 |
| No                                 | 1318               | 88       | 6.7  | REF       | REF      |           |         |
| Renal disease                      | Yes                | 169      | 14   | 8.3       | 1.3     | 1.4     | 0.82, 2.45 | 0.21 |
| No                                 | 2597               | 160      | 6.2  | REF       | REF      |           |         |
| Emphysema                          | Yes                | 70       | 7    | 10.0      | 1.6     | 1.6     | 0.77, 3.49 | 0.20 |
| No                                 | 2698               | 169      | 6.3  | REF       | REF      |           |         |
| Degenerative joint disease         | Yes                | 1032     | 65   | 6.3       | 1.0     | 1.0     | 0.73, 1.36 | 0.99 |
| No                                 | 1722               | 109      | 6.3  | REF       | REF      |           |         |
| Dementia                           | Yes                | 50       | 6    | 12.0      | 1.9     | 2.0     | 0.88, 4.48 | 0.10 |
| No                                 | 2689               | 167      | 6.2  | REF       | REF      |           |         |
| High thyroid                       | Yes                | 188      | 12   | 6.4       | 1.0     | 1.1     | 0.58, 1.91 | 0.86 |
| No                                 | 1965               | 125      | 6.4  | REF       | REF      |           |         |
| Parkinson                          | Yes                | 10       | 0    | 0.0       | --      | --      |          |
| No                                 | 2103               | 134      | 6.4  |           |         |         |          |
| Diabetes                           | Yes                | 214      | 14   | 6.5       | 1.0     | 1.1     | 0.63, 1.88 | 0.76 |
| No                                 | 2564               | 162      | 6.3  | REF       | REF      |           |         |
| CVD                                | Yes                | 1261     | 88   | 7.0       | 1.2     | 1.2     | 0.89, 1.60 | 0.24 |
| No                                 | 1517               | 88       | 5.8  | REF       | REF      |           |         |
| Cancer                             | Yes                | 651      | 39   | 6.0       | 0.9     | 0.9     | 0.66, 1.35 | 0.76 |
| No                                 | 2127               | 137      | 6.4  | REF       | REF      |           |         |
| Medication use                     | Nitroglycerine     | Yes      | 90   | 7         | 7.8     | 1.2     | 1.2     | 0.56, 2.55 | 0.64 |
|                                   | No                 | 2416     | 160  | 6.6       | REF     | REF      |           |         |

continued
diminish with time, even with this short time frame, such that the estimations of long-term risk of fracture may not be as useful clinically in those at high risk.

Strengths and limitations

A strength of this study is that the sample population was derived from the Framingham Study, a well-characterized cohort that contains large numbers of women ages 65 years and older. Reproducibility of BMD measurement is good in studies such as the Framingham Study (coefficient of variations of 2% to 3% at the proximal femur); it may be worse in clinical practice where quality assurance factors and operator experience may be less. Thus, women in this study were unlikely to be misclassified in terms of their T-score, and unlikely to be erroneously included or excluded from the study population. Another strength is the ability to focus on a large number of older women at high risk for fracture—the group most susceptible to long-term risk of fracture as well. Also we were able to include consideration of many major factors that are likely to be available clinically, including comorbidities and medications.

However, a number of limitations need to be considered when interpreting the findings in this study. The Framingham Study is primarily comprised of whites; thus, the results may not be generalizable to non-white groups. Although Framingham Study participants undergo examinations every 2 or 4 years and are followed for fractures, it is possible that not all fractures are captured and appropriately adjudicated. Another limitation is that several of the comorbidities included in our study had low prevalence (eg, only 50 subjects had medical history of dementia and only 6 of them had a subsequent fracture. Similarly, only 10 persons had Parkinson disease, limiting the statistical power to detect an imminent fracture risk for these conditions. Also, practice patterns, technology, and other largely unobservable or quantifiable factors may have changed over the period of observation in our cohort, which could have an impact upon measurements of risk factors over time and estimated relationships with fracture. Finally, information on risk factors was limited to those available at the Framingham Study examinations. Although use of selected medications is confirmed by interview and examination of medication containers, whether patients continued to take medications during follow-up is uncertain. Although the timing of clinical fractures between visits is accurately detailed in the data source, subclinical or asymptomatic fractures may not be identified on a continuous basis in the Framingham Study cohorts. The true timing of such events is unknown. Also, this study did not examine risks for specific sites of fracture. In the Framingham Study cohorts, fractures are tracked via self-report on an ongoing basis, and confirmed via medical records review. It thus is not possible to capture potentially important changes in time-dependent risk factors that occurred between visits or prior to the occurrence of fracture during a given interval. The follow-up interval used in our study was quite short, so this possible concern is unlikely to have had a major impact on our results. Yet, as such information is not available, the precise nature of

| Covariates              | No. of observations | No. of Fx | % Fx | Rel. risk | HR   | 95% CI    | p value |
|-------------------------|--------------------|-----------|------|-----------|------|-----------|---------|
| Nitrates Yes            | 98                 | 14        | 14.3 | 2.3       | 2.5  | 1.43, 4.27| 0.001   |
| No                      | 2408               | 153       | 6.4  | REF       | REF  |           |         |
| Beta blockers Yes       | 471                | 40        | 8.5  | 1.4       | 1.4  | 0.98, 1.99| 0.07    |
| No                      | 2040               | 127       | 6.2  | REF       | REF  |           |         |
| Calcium channel blockers Yes | 385            | 33        | 8.6  | 1.4       | 1.4  | 0.95, 2.04| 0.09    |
| No                      | 2126               | 134       | 6.3  | REF       | REF  |           |         |
| Diuretics Yes           | 516                | 36        | 7.0  | 1.1       | 1.1  | 0.74, 1.56| 0.69    |
| No                      | 1946               | 1257      | 6.4  | REF       | REF  |           |         |
| Anticholesterol Yes     | 412                | 21        | 5.1  | 0.8       | 0.8  | 0.51, 1.27| 0.36    |
| No                      | 2362               | 155       | 6.6  | REF       | REF  |           |         |
| Thyroid med Yes         | 401                | 27        | 6.7  | 1.0       | 1.0  | 0.68, 1.54| 0.92    |
| No                      | 2104               | 139       | 6.6  | REF       | REF  |           |         |
| Oral glucocorticoids Yes | 58               | 6         | 10.3 | 1.5       | 1.5  | 0.67, 3.45| 0.32    |
| No                      | 1920               | 131       | 6.8  | REF       | REF  |           |         |
| Anti-anxiety Yes        | 121                | 6         | 5.0  | 0.7       | 0.7  | 0.33, 1.66| 0.46    |
| No                      | 2393               | 161       | 6.7  | REF       | REF  |           |         |
| Sleeping Yes            | 45                 | 5         | 11.1 | 1.7       | 1.8  | 0.72, 4.26| 0.22    |
| No                      | 2469               | 162       | 6.6  | REF       | REF  |           |         |
| Antidepressants Yes     | 132                | 12        | 9.1  | 1.4       | 1.4  | 0.78, 2.53| 0.26    |
| No                      | 2381               | 155       | 6.5  | REF       | REF  |           |         |
| Anticonvulsants Yes     | 21                 | 3         | 14.3 | 2.1       | 2.1  | 0.67, 6.65| 0.20    |
| No                      | 1852               | 124       | 6.7  | REF       | REF  |           |         |
| Progesterone Yes        | 83                 | 3         | 3.6  | 0.6       | 0.6  | 0.18, 1.71| 0.30    |
| No                      | 2677               | 172       | 6.4  | REF       | REF  |           |         |

Any sum <2778 observations is based on missing values of a variable. 
FX = fractures; ADL = activities of daily living; CVD = cardiovascular disease; REF = Referent Category.
the relationships between selected risk factors (e.g., use of medications) and occurrence of fracture may be mischaracterized in analyses. Moreover, because not all self-reported fractures are confirmed by medical records, some fractures were self-reported only.

**Conclusion**

In conclusion, this study found several factors were associated with the imminent 1-year risk of nonvertebral fracture in older women at high risk for fracture. These results imply that the risk for fractures is increased in high-risk women based on factors, in addition to BMD, that are easily obtained at a clinical visit. These factors may be useful in identifying which women to target for therapy and/or other interventions. Fractures remain devastating events for older adults. Insights from imminent fracture occurrences may lead to better interventions, especially for those women at high-risk of future fracture. Future work should highlight the short-term benefits of interventions on decreasing the risk for nonvertebral fractures.

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**Table 4. Multivariable Analysis of Potential Risk Factors and Risk of Nonvertebral Fracture Over 1 Year and 2 Years of Follow-Up (n Observations = 2778)**

| Predictors of Imminent Fracture Risk in Older, High-Risk Women | 1-year fracture risk Cox PH model | 2-year fracture risk Cox PH model |
|---------------------------------------------------------------|----------------------------------|----------------------------------|
|                                                               | N  | Fx  | HR   | 95% CI | p value | N  | Fx  | HR   | 95% CI | p value |
| Age |                                                               |    |     |      |        |         |    |     |      |        |         |
| <75 years                                     | 1274 | 32 | REF |        |         | 1274 | 63 | REF |        |         |
| 75–84 years                                  | 1296 | 47 | 1.0 | 0.58,1.57 | 0.85 | 1296 | 97 | 1.2 | 0.85,1.73 | 0.29 |
| 85+ years                                    | 208  | 10 | 1.1 | 0.49,2.26 | 0.90 | 208  | 16 | 1.0 | 0.57,1.92 | 0.89 |
| History of fracture                          |     |     |      |        |         |     |     |      |        |         |
| Yes                                         | 939  | 41 | 1.4 | 0.89,2.19 | 0.14 | 939  | 75 | 1.4 | 1.00,1.91 | 0.05 |
| No                                          | 1839 | 48 | REF |        |         | 1839 | 101 | REF |        |         |
| ADL score                                    |     |     |      |        |         |     |     |      |        |         |
| 0–4 impaired                                 | 24   | 2  | 0.9 | 0.12,6.57 | 0.91 | 24   | 4  | 0.6 | 0.08,4.40 | 0.62 |
| 5–6 functional                               | 2730 | 85 | REF |        |         | 2730 | 169 | REF |        |         |
| Self-rated health                            |     |     |      |        |         |     |     |      |        |         |
| Excellent                                    | 886  | 17 | REF |        |         | 886  | 42 | REF |        |         |
| Good/fair                                    | 1811 | 66 | 1.5 | 0.84,2.75 | 0.16 | 1811 | 125 | 1.4 | 0.91,2.00 | 0.13 |
| Poor                                        | 26   | 3  | 4.0 | 1.10,14.3 | 0.04 | 26   | 3  | 2.1 | 0.64,7.05 | 0.22 |
| BMD T-score                                  |     |     |      |        |         |     |     |      |        |         |
| ≤ −2.5 (osteoporosis)                        | 980  | 54 | 2.8 | 1.75,4.54 | <.0001 | 980  | 94 | 2.0 | 1.46,2.81 | <.0001 |
| > −1.0 (osteopenic/normal)                   | 1798 | 35 | REF |        |         | 1798 | 82 | REF |        |         |
| Falls in past year                           |     |     |      |        |         |     |     |      |        |         |
| Yes 1+                                      | 1103 | 46 | 1.3 | 0.83,2.04 | 0.25 | 1103 | 75 | 1.0 | 0.66,1.27 | 0.60 |
| No                                          | 1585 | 41 | REF |        |         | 1585 | 96 | REF |        |         |
| Medication use in last year                  |     |     |      |        |         |     |     |      |        |         |
| Nitrates                                     |     |     |      |        |         |     |     |      |        |         |
| Yes                                         | 98   | 11 | 2.6 | 1.22,5.39 | 0.01 | 98   | 14 | 1.8 | 0.95,3.40 | 0.07 |
| No                                          | 2408 | 74 | REF |        |         | 2408 | 153| REF |        |         |
| Beta blockers                                |     |     |      |        |         |     |     |      |        |         |
| Yes                                         | 471  | 23 | 1.3 | 0.78,2.20 | 0.30 | 471  | 40 | 1.2 | 0.82,1.76 | 0.36 |
| No                                          | 2040 | 62 | REF |        |         | 2040 | 127| REF |        |         |
| Calcium channel blockers                     |     |     |      |        |         |     |     |      |        |         |
| Yes                                         | 385  | 19 | 1.1 | 0.60,1.92 | 0.82 | 385  | 33 | 1.1 | 0.75,1.74 | 0.55 |
| No                                          | 2126 | 66 | REF |        |         | 2126 | 134| REF |        |         |
| Antidepressants                              |     |     |      |        |         |     |     |      |        |         |
| Yes                                         | 132  | 8  | 1.7 | 0.76,3.64 | 0.20 | 132  | 12 | 1.3 | 0.72,2.47 | 0.36 |
| No                                          | 2381 | 77 | REF |        |         | 2381 | 155| REF |        |         |

Concordance index (SE) for 1-year model is 0.71 (0.03) and for 2-year model is 0.64 (0.02). Each variable adjusted in models for all other listed variables. FX = fractures; REF = Referent Category.
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References

1. Johansen A, Evans RJ, Stone MD, Richmond PW, Lo SV, Woodhouse KW. Fracture incidence in England and Wales: a study based on the population of Cardiff. Injury. 1997;28(10):655–60.
2. Bliuc D, Alaraki D, Nguyen TV, Eisman JA, Center JR. Risk of subsequent fractures and mortality in elderly women and men with fragility fractures with and without osteoporotic bone density: the Dubbo Osteoporosis Epidemiology Study. J Bone Miner Res. 2015;30(4):637–46.
3. Cooper C. Epidemiology and definition of osteoporosis. In Compston J, editor. Osteoporosis: new perspectives on causes, prevention, and treatment. London: Royal College of Physicians; 1996. p. 1–10.
4. National Osteoporosis Foundation, editor. Clinician’s guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation; 2013.
5. Masud T, Binkley N, Boonen S, Hannan MT, FRAX® Position Development Conference Members. Official positions for FRAX(R) clinical regarding falls and frailty: can falls and frailty be used in FRAX(R)? From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX(R). J Clin Densitom. 2011;14(3):194–204.
6. Berry SD, McLean RR, Hannan MT, Cuppers LA, Kiel DP. Changes in bone mineral density may predict the risk of fracture differently in older adults according to fall history. J Am Geriatr Soc. 2014;62(12):2345–9.
7. Kanis JA, W.H.O.Scientific Group. Assessment of osteoporosis at the primary health-care level. In: W.H.O.Collaborative Centre for Metabolic Bone Diseases, editor. Technical report. Sheffield, UK: University of Sheffield; 2007. p. 2–4.
8. Gogate Y, Bhadada SK. FRAX: facts and fantasy. Indian J Endocrinol Metab. 2012;16(Suppl 2):S224–6.