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In Which Patients Does Lumbar Spine Trabecular Bone Score (TBS) Have the Largest Effect?

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Abstract

Background—Lumbar spine TBS, a texture index derived from lumbar spine dual-energy x-ray absorptiometry (DXA) images, enhances fracture prediction. No studies to date have studied a broad range of clinical variables to determine which patients might experience the greatest benefit from the use of TBS.

Methods—Using the Manitoba BMD Registry, we identified 37,176 subjects with baseline DXA, FRAX®-based fracture probability, lumbar spine TBS, and minimum 5 years of observation.

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Roles

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Subgroups considered were based on sex, age, body mass index (BMI), prior fracture, chronic obstructive lung disease (COPD), high alcohol use, rheumatoid arthritis (RA), high glucocorticoid use, osteoporotic femoral neck T-score, number of comorbidities, diabetes, secondary osteoporosis, and prior osteoporosis treatment. Non-traumatic major osteoporotic fractures (MOF, n=3741) and hip fractures (HF, n=1008) were identified using population-based health services data. We analyzed baseline TBS using analysis of covariance (ANCOVA). FRAX-adjusted hazard ratios (HR) per SD reduction in TBS were estimated and tested for interactions. Categorical net reclassification improvement (NRI) was estimated using fixed FRAX-based intervention cut-offs.

Results—Adjusted baseline TBS was significantly lower ($p \leq 0.001$) for women (-4.2%), osteoporotic hip T-score (-4.0%), COPD (-2.8%), diabetes (-2.6%), high alcohol use (-2.3%), prior fracture (-2.2%), glucocorticoid use (-1.5%), RA (-0.9%) and secondary osteoporosis (-0.8%), whereas recent osteoporosis therapy was associated with greater TBS (+1.5%). HRs per SD reduction in TBS for fracture prediction were larger for age <65 vs 65+ (MOF p-interaction=0.004, HF p-interaction<0.001), without vs with prior fracture (MOF p-interaction=0.003, HF p-interaction=0.048), without vs with glucocorticoid use (HF p-interaction=0.029), lower vs higher comorbidity score (HF p-interaction<0.001), and without vs with osteoporosis treatment (MOF p-interaction=0.005). NRI for using the TBS adjustment to FRAX in all subjects was 1.2% for MOF (p=0.002) and 1.7% for HF (p=0.016). NRI was greater in subjects age <65 y (MOF: 1.7%, HF: 5.6%), no prior fracture (HF: 2.4%), non-osteoporotic T-score (HF: 3.0%), and high glucocorticoid use (MOF: 3.9%).

Conclusion—TBS is sensitive to the effects of multiple risk factors for fracture. TBS-adjusted fracture risk assessment resulted in significant improvements for multiple subgroups.

Keywords

Osteoporosis; fracture prediction; FRAX; trabecular bone score

1 Introduction

Trabecular bone score (TBS) is a bone texture index derived from lumbar spine dual-energy x-ray absorptiometry (DXA) images. Multiple studies and a mixture of study designs have demonstrated an association between reduced TBS and increased fracture risk [1]. More recently, a technique to incorporate TBS in FRAX for improved fracture-risk assessment has been developed [2] with TBS-adjusted FRAX predictions shown to result in small but significant improvements in risk classification over conventional FRAX risk estimates [3–6].

Studies involving older subjects [7–9], patients exposed to glucocorticoids [10–13], hyperparathyroidism [14–16], diabetes mellitus [17–20], and renal disease [21,22] have shown that these groups typically have decreased TBS values and increased fracture risk compared to controls. With the exception of [9,12,16,17,22], all of these studies were retrospective. A recent retrospective study by Martineau *et al* [5] showed that fracture risk reclassification from the use of TBS-adjusted FRAX was greatest in women close to an intervention threshold and in women under 65 years of age; however, that study was not designed to identify other clinical factors for which the use of TBS might significantly impact on management.

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The clinical utility of TBS, as with any risk factor, is largely determined by its impact on management decisions. TBS can potentially alter the fracture risk assessment and, in those patients close to an intervention threshold, management decisions in two major ways: if a given risk factor is associated with significantly lower TBS, and/or if a given TBS reduction associated with a particular risk factor is in turn associated with a larger fracture risk hazard ratio (HR). The former assumes that TBS has the same effect in the presence/absence of the risk factor under consideration (i.e., no interaction) whereas the latter indicates a larger effect on fracture risk (i.e., significant interaction). Either or both together can result in TBS having an impact on management.

To date, no studies have simultaneously explored the relationship between multiple clinical variables and their effect on baseline TBS, HR for TBS to predict fracture, and risk reclassification using the TBS-adjusted FRAX. The purpose of the current study was to examine the relative impact of commonly encountered clinical variables on TBS in routine clinical practice in order to determine those subgroups in which TBS is most likely to be beneficial.

2 Materials and Methods

2.1 Patient population

In the Province of Manitoba, Canada, health services are provided to virtually all residents through a single public health care system. Manitoba Health maintains computerized databases of physician billing claims and hospital separations for all residents of the province eligible to receive health services. The Manitoba Bone Density Program is a targeted case-finding clinical program with the associated database validated and described elsewhere [23,24]. This database has been shown to exceed 99% in terms of completeness and accuracy. We performed a historical cohort study in men and women, age 40 years or older, who had undergone baseline BMD measurement of the spine and hip by DXA using a narrow, fan-beam scanner configuration (Prodigy, GE Healthcare, Madison, WI, USA) with at least 5 years of follow up for assessing incident fractures. We excluded individuals with BMI <15 or >37 kg/m^2 since TBS is not recommended in extremes of body size [1]. All participants had medical coverage during the observation period ending March 31, 2013. In cases of multiple eligible data sets, only the first record was included in the analysis. The study was approved by the Health Research Ethics Board for the University of Manitoba.

2.2 Measurement of BMD and TBS

All DXA scans were performed and analyzed in accordance with the manufacturer's recommendations. BMD measurements were recorded for the lumbar spine BMD for L_1 through L_4 (L_1–L_4, excluding obvious artifacts) and the femoral neck. The resulting data approximated a normal distribution. Instruments were cross-calibrated using anthropomorphic phantoms. No clinically significant differences were identified; therefore, all analyses are based on unadjusted numerical results generated by the instrument.

All TBS measurements were performed in the Bone Disease Unit at the University of Lausanne, Lausanne, Switzerland (TBS iNsight Software, Version 2.1, Med-Imaps, Pessac,

France), using anonymized spine DXA files from the Manitoba database to ensure blinding of the Swiss investigators to all clinical parameters and outcomes. No significant differences in mean TBS measurements were seen for the three DXA scanners used. All three instruments used for this study exhibited stable long-term performance (coefficient of variation [CV] < 0.5%) and satisfactory in vivo precision. Short-term reproducibility (CV) for TBS was 2.1% and for lumbar spine BMD was 1.7% in 92 individuals with repeat spine DXA scans performed within 28 days.

2.3 Fracture Outcomes

Each health system contact includes information on a patient's demographics, date and type of service, and diagnoses from (1) physician billing claims (inpatient, outpatient, and private office) coded using the *International Classification of Disease*, 9th edition, *Clinical Modification* (ICD-9-CM) system and (2) hospital discharge abstracts, for which the diagnoses and procedures have been coded using the ICD-9-CM system prior to 2005 and the ICD-10-CA system thereafter. Anonymous linkage of these databases to the BMD database was possible via a unique scrambled health identification number, thereby allowing for the creation of a longitudinal record of health services and outcomes. Longitudinal health service records were examined for the presence of fracture codes before and after BMD testing that were not associated with trauma codes using previously validated algorithms [25]. Hip fracture (HF) and major osteoporotic fracture (MOF) (hip, clinical spine, forearm, and humerus fractures) were studied as these are the basis for the 10-year absolute fracture risk estimates generated by FRAX. We required that hip and forearm fractures be accompanied by a site-specific fracture reduction, fixation, or casting code, which enhances the diagnostic and temporal specificity of an acute fracture.

2.4 Fracture Probability and Other Covariates

The ten-year probabilities for MOF and for HF were calculated using FRAX, fracture risk assessment tool, developed by the World Health Organization Collaborating Centre at Sheffield, UK, (Canadian version (FRAX® Desktop Multi-Patient Entry, version 3.7). The Canadian FRAX tool was calibrated using nationwide hip fracture data [26], and its predictions agreed closely with observed fracture rates in Manitoba and the general Canadian population [27,28]. Data required for calculating fracture probability with FRAX were assessed through a combination of data from the BMD registry, self-reported information at the time of BMD testing, hospital discharge abstracts, physician claims and a province-wide retail pharmacy database as previously described [29]. Anthropomorphic data (height and weight) were measured at the time of DXA, and BMI was calculated. In addition to prior osteoporotic fractures, we identified prior diagnoses of diabetes, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD, a proxy for smoking), alcohol/substance abuse (a proxy for high alcohol intake), prolonged (>3 months) systemic corticosteroid use in the last year, and osteoporosis medication use (>6 months) in the year before BMD testing. Secondary osteoporosis was defined from the following previously diagnosed conditions: hyperthyroidism, ankylosing spondylitis, inflammatory bowel disease, cerebrovascular disease, Parkinson’s disease, muscular dystrophy, celiac disease or other disorders of malabsorption, chronic liver disease, organ transplantation, gastrectomy or small bowel resection. To define burden of comorbidity in the 1-year prior to their baseline

DXA test for each subject we used the Johns Hopkins Adjusted Clinical Group® (ACG®) Case-Mix System (version 9) [30,31]. Aggregated Diagnosis Groups (ADGs) represent 32 comorbidity clusters of every ICD diagnostic codes.

We then derived TBS-adjusted FRAX fracture probability using a method previously described in detail by McCloskey *et al* [2]. This procedure incorporates both competing mortality and an age-TBS interaction in the calculation. This resulted in both FRAX and TBS-adjusted FRAX fracture probabilities of MOF and HF being available for all subjects. For all participants, the FRAX probabilities for MOFs and HFs were calculated initially using the femoral neck BMD and other covariates, and then recalculated including the TBS in the FRAX assessment.

2.5 Clinical variable subgroups

Our analysis examined subgroups based on multiple clinical variables: age (above or below 65 years of age), sex, BMI (greater or less than 30 kg/m^2), history of prior osteoporotic fracture, COPD, prior diagnosis of rheumatoid arthritis, high alcohol intake, prolonged (>3 months) systemic corticosteroid use in the last year, secondary osteoporosis, osteoporotic femoral neck T-score, ADG comorbidity score (low <3, moderate 3-5, or high >5), prior diagnosis of diabetes, and osteoporosis treatment. These subgroups were chosen due to their association with increased MOF and HF risk.

2.6 Statistical Analysis

All statistical analyses were performed using Statistica (Version 12.0, StatSoft, Inc., Tulsa, OK, USA). The criterion for statistical significance was set at a p value of 0.05. Descriptive statistics for demographic and baseline characteristics are presented as mean ± SD for continuous variables or count (percent) for categorical variables. All models were age- and BMI-adjusted.

Analysis of covariance (ANCOVA) was used to assess independent effects of the clinical variables on TBS considered simultaneously. Results were reported as the percent change with 95% confidence intervals (CI). Hazard ratios (HR) per SD reduction in TBS for both MOF and HF were determined along with 95% CI using Cox proportional hazards regression. Stratified models were constructed to assess the effect of TBS within subgroups defined from the clinical variables. Two-way interaction terms between the clinical variables and TBS (e.g., sex*TBS, diabetes*TBS) were examined and tested for significance.

Using fixed FRAX-based intervention criteria - MOF ≥ 20% or HF ≥ 3% - we computed the percentage of patients reclassified within each subgroup defined from the clinical variables. These intervention cutoffs are the basis of the US National Osteoporosis Foundation (NOF) guidelines, and we have previously shown that the NRI results from the use of TBS-adjusted FRAX are comparable when using different guidelines [5]. Using logistic regression, we also estimated the odds ratio (OR) for reclassification with 95% CI for reclassification using the TBS adjustment to FRAX where all clinical variables were considered simultaneously. Impact on reclassification was studied using the Net Reclassification Improvement (NRI). NRI [32] is a technique which measures the impact of including an additional clinical variable on the classification of predicted risk. NRI was used to examine the clinical impact

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of applying the TBS adjustment to FRAX for fixed MOF risk of 20% or HF risk of 3% within subgroups defined by various clinical variables, as detailed above. The NRI was calculated as per the method detailed by Pencina *et al* [32] and reported as recommended by Leening *et al* [33]. For individuals that sustain a fracture in follow up, NRI cases is the probability of moving 'up' to a higher FRAX risk category minus the probability of moving 'down' to a lower FRAX risk category. Conversely, for individuals who remain fracture-free in follow up, NRI non-cases is the probability of moving into a lower FRAX risk category minus the probability of moving into a higher FRAX risk category. Values of NRI cases and NRI non-cases greater than zero indicate an improvement in risk classification, whereas negative values indicate worse risk classification. An asymptotic test of significance for the null hypothesis of NRI=0 based upon the multinomial distribution was performed [32].

3 Results

3.1 Population characteristics

A total of 37,176 subjects, with a mean age of 64 years, satisfied the eligibility criteria. Table 1 summarizes the baseline characteristics. On average, TBS was significantly lower ($p < 0.001$) in subjects with incident fractures (MOF and HF) than in those without.

3.2 Baseline TBS

Factors affecting baseline TBS are shown in Figure 1. Significant reductions in age- and BMI-adjusted TBS (rank ordered) were associated with women (-4.2%), osteoporotic hip T-score (-4.0%), COPD (-2.8%), diabetes (-2.6%), high alcohol use (-2.3%), prior fracture (-2.2%), glucocorticoid use (-1.5%), RA (-0.9%) and secondary osteoporosis (-0.8%). Recent osteoporosis therapy was associated with greater TBS (+1.5%). No statistically significant differences in TBS were noted for subjects with different levels of comorbidity scores. Supplementary Table 1 summarizes all factors and their independent effects on baseline least-squares mean TBS.

3.3 Fracture prediction

Over a mean follow-up period of 8.7 (±2.7) years, 3741 (10.1%) of these subjects suffered incident MOFs, with a total of 1008 (2.7%) incident HFs recorded. Numbers of MOFs and HFs within each subgroup are shown in Table 2. The calculated HRs associated with the various clinical subgroups for both MOF and HF are shown in Table 3, with significant values plotted in Figure 2. Each SD reduction in TBS was significantly associated with greater risk of MOFs for each subgroup considered (with the exception of men, RA, and high alcohol consumption), with the largest effects in subjects aged < 65 years and those with low comorbidity. For HFs, each SD reduction in TBS was significantly associated with greater risk for women, subjects less than 65 years of age, low or moderate comorbidity, and those with BMIs less than 30 kg/m^2, whereas associations with other clinical variables were non-significant.

No significant interactions were detected for sex (men vs women), BMI (< 30 kg/m^2 vs ≥ 30 kg/m^2), COPD (with vs without), RA (with vs without), diabetes (with vs without) or secondary osteoporosis (with vs without). In contrast, significant interactions were noted for

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some clinical variables. Our analysis revealed significant interactions with larger effects for age <65 vs ≥65 (MOF p=0.004, HF p<0.001), without vs with prior fracture (MOF p=0.003, HF p=0.048), without vs with glucocorticoid use (HF p=0.029), lower vs higher comorbidity score (HF p <0.001), and without vs with osteoporosis treatment (MOF p=0.005).

3.4 Risk reclassification

Percentages of patients reclassified using the TBS-adjustment to FRAX and ORs for reclassification according to the subgroups defined by the clinical variables are presented in Table 4. Overall reclassifications using the MOF criterion were similar to using the HF criterion with a total of 2.5% (1.0% into a lower risk and 1.5% into a higher risk category) and 3.0% (0.9% lower and 2.1% higher), respectively. For most clinical subgroups, reclassification 'up' into higher risk categories exceeded reclassification 'down' into lower risk categories; however, for the HF intervention criterion in patients with femoral neck osteoporosis, downwards reclassification at 3.4% was more common than upwards reclassification at 1.8%. For the MOF criterion, upwards reclassifications ranged from 0.6% in older patients (≥65 years) to 5.0% in patients with femoral neck osteoporosis, while downwards reclassifications ranged from 0.2% in older patients to 4.2% in those with femoral neck osteoporosis. For the HF criterion, upwards reclassifications ranged from 1.1% in older patients to 3.8% in those with diabetes, while downwards reclassifications varied between 0.6% in those without femoral neck osteoporosis to 3.4% in those with femoral neck osteoporosis. ORs for MOF reclassification (OR: 3.45, 95% CI 2.89-4.11) and HF reclassification (1.92, 95% CI1.68-2.19) were greater for younger compared to older patients. Of note, TBS had opposing effects on reclassification in men compared to women, lower for MOF (OR: 0.37, 95% CI 0.26-0.51) but greater for HF (1.62, 95% CI1.35-1.94). Prior osteoporosis treatment vs no treatment was associated with lower MOF reclassification (OR: 0.79, 95% CI0.67-0.95) and HF reclassification (0.80, 95% CI 0.68-0.94).

Table 2 and Figure 3 present the NRI analysis overall and for each subgroup using the TBS-adjustment to FRAX. The detailed breakdown of NRI for cases and non-cases separately is shown in Supplementary Table 2. Overall correct reclassification from including TBS in the fracture risk assessment was modest with an NRI of 1.2% for MOFs and 1.7% for HFs (both p<0.001). For MOFs, a greater NRI was seen for subjects with a history of glucocorticoid use (3.9%, p=0.039), COPD (3.2%, p=0.019), diabetes (2.5%, p=0.030), and age < 65 years (1.7%, p<0.001). In the case of HFs, a greater NRI was seen for age < 65 years (5.6%, p=0.017), non-osteoporotic femoral neck T scores (3.0%, p=0.008), and subjects with no prior fracture (2.4%, p=0.006). Compared to MOFs, fewer subgroups demonstrated significant NRIs for HF.

4 Discussion

We identified various clinical variables which are associated with baseline TBS, and determined that female sex, femoral neck osteoporosis, COPD and diabetes are associated with the greatest decreases in age- and BMI-adjusted TBS, whilst recent osteoporosis treatment is associated with increased TBS. Several other studies have reported clinical factors that correlate with lower TBS (e.g., increasing age [7], glucocorticoid use [10–13],

and diabetes [17–20]) but this is the first study to examine the relative and independent effect of multiple clinical variables on TBS within a single population. Importantly, we have been able to show that, with the exception of comorbidity score and prior osteoporosis treatment, all clinical variables considered were associated with a significantly lower age- and BMI-adjusted TBS. Previous studies that have explored the utility of TBS in specific subgroups have examined effects on baseline TBS, TBS for fracture prediction or NRI. The strength of the current paper is that it looks at all three simultaneously across a wide range of conditions/subgroups. Supplementary Table 3 provides a comprehensive summary of the salient results.

Another strength of this work is that we were able to assess interactions between clinical risk factors. Statistically significant interactions were noted between TBS and age for both MOF and HF prediction, with HRs in older patients attenuated compared to younger patients. TBS interactions were also significant according to prior fracture and previously osteoporosis treatment (at least for MOF). The latter may reflect the fact that TBS is relatively unresponsive to anti-resorptive therapies [34–36]. Although the effect of TBS in assessing MOF risk is slightly weaker in patients previously treated for osteoporosis, this population still demonstrated a small but statistically significant increase in NRI. These results can be contrasted to those of the conventional FRAX tool which has been shown to provide accurate fracture risk prediction in patients treated for osteoporosis [37]

Our findings are in keeping with previously published results. In particular, our results can be compared to those of McCloskey *et al* [3] which concluded that TBS-adjusted FRAX performed similarly in men and women. Likewise, we found that the interaction term for sex*TBS was not significant. Our results are also compatible with those of Schousboe *et al* [38] who found that an increasing BMI attenuated the predictive effect of TBS in men with incident vertebral fractures. In our study, obese patients (BMI ≥30 kg/m^2) showed no significant improvement in NRI. Previous studies have suggested that TBS may be particularly useful in patients with diabetes [17,18,20]. Our results support this conclusion with NRI being higher in patients with versus without diabetes for both MOF (2.5% vs 1.0%, respectively) and HF (3.1% vs 1.3%, respectively), suggesting that TBS may help guide management in this patient population. Likewise, our results are also consistent with reports that TBS was effective in improving fracture risk assessment and influencing therapeutic choices in patients undergoing glucocorticoid therapy [10–12].

Our results show that the use of TBS-adjusted FRAX scores resulted in the larger HR/SD for younger subjects (<65 years of age), and in those with low comorbidity, and women, compared with older subjects, those with comorbidity and men, respectively. It is interesting to note that, despite not demonstrating corresponding statistically significant differences in TBS, a low or moderate comorbidity score was still associated with a greater HR for HF per SD TBS-adjusted FRAX score than in those with high comorbidity.

Certain limitations of this study should be acknowledged. In particular, the population studied was from a clinical registry and may be prone to referral bias. Conversely, this suggests that our results are applicable to patients encountered in routine clinical practice. Our study population was almost exclusively Caucasian, which may limit applicability to

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other ethnic populations, although no significant population heterogeneity was seen in the meta-analysis by McCloskey et al [3]. In addition, our analysis was limited to examining the impact of TBS-adjusted FRAX on reclassification of patients in the context of fixed FRAX-based intervention cut-offs (MOF ≥ 20%, HF ≥ 3%); however, we have previously shown that the significant improvement in overall NRI was independent of the specific intervention thresholds used [5]. Another limitation of this exploratory study is that we did not correct for multiple comparisons. Some of our results could have occurred by chance. Subsequent studies will be important in confirming our findings. Finally, the TBS adjustment for FRAX was developed using the Manitoba cohort, the same cohort used for the current analysis.

5 Conclusion

The use of TBS-adjusted fracture risk assessment resulted in significant improvements overall. We found that TBS is sensitive to the effects of multiple risk factors for fracture. TBS was beneficial for most subgroups considered, either in terms of improved fracture-risk prediction or fracture-risk reclassification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Baseline TBS was sensitive to most of the clinical variables tested.
- TBS predicted major osteoporotic fractures and/or hip fracture overall, and several of the clinical variables considered showed significant interactions with TBS.
- TBS-adjusted FRAX resulted in significant risk reclassification and/or improved fracture risk classification for most of the clinical variables considered.

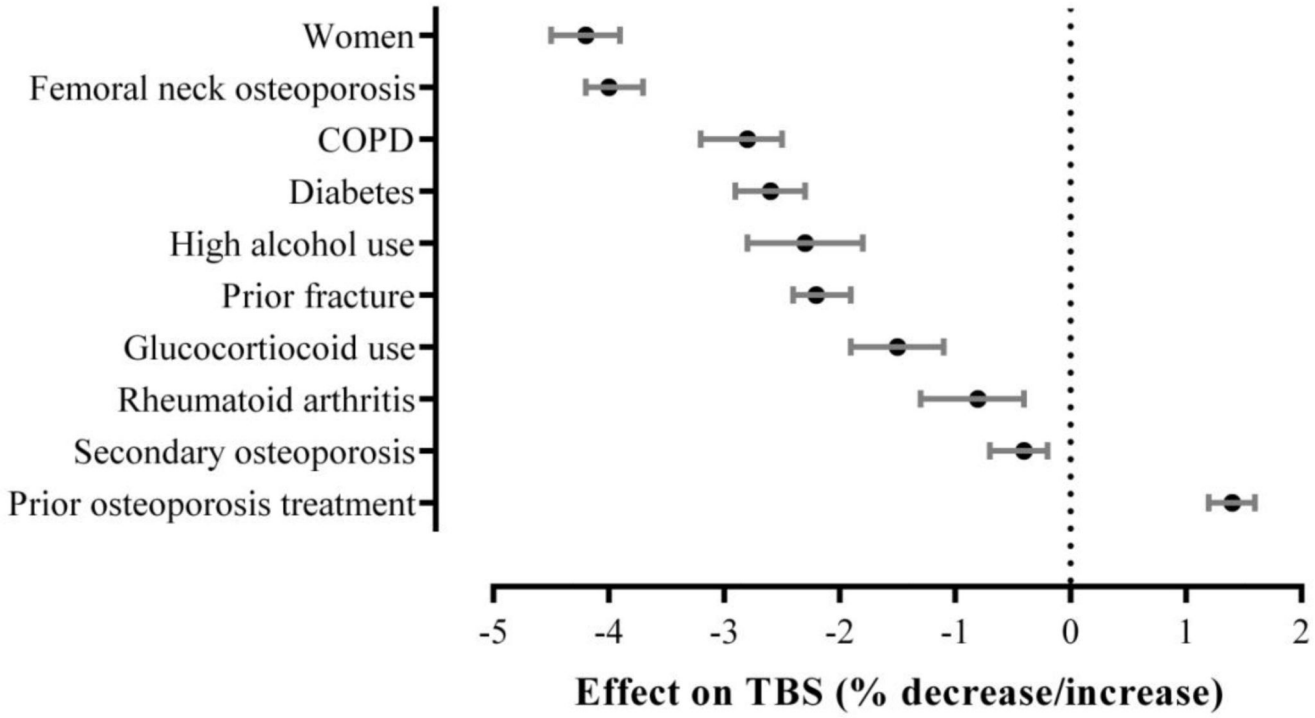

Figure 1.

Rank-ordered relative change in TBS with 95% CI bars attributable to the presence (versus absence) of clinical variables from multivariable ANCOVA models (age and BMI-adjusted).

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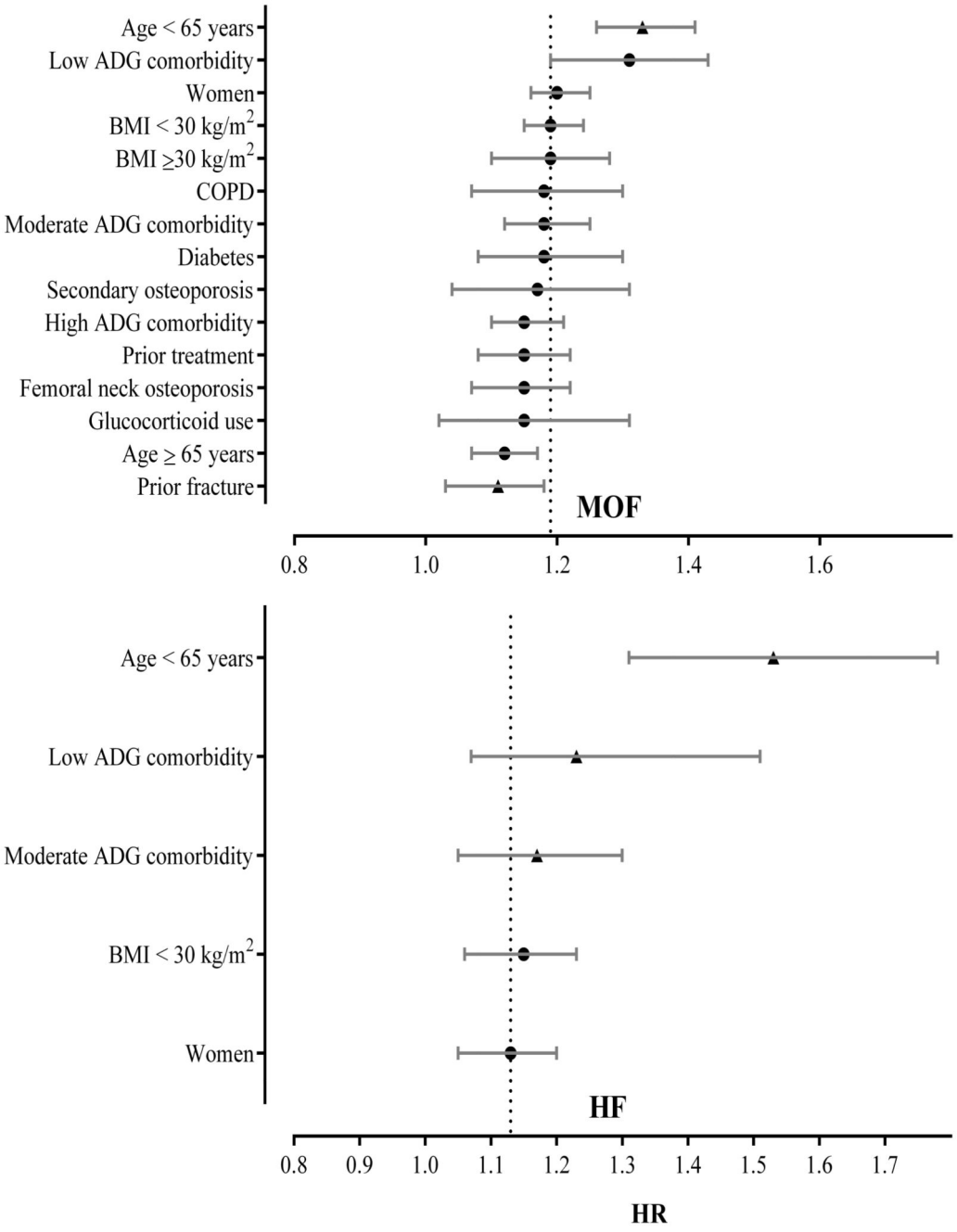

Figure 2.

Rank-ordered HRs with 95% CI bars for each SD reduction in TBS to predict MOF (panel above) and HF (panel below) stratified by clinical variables. Only statistically significant HRs are included. The dashed line indicates the HR for all cases. Variables with statistically significant interactions are denoted by a triangle.

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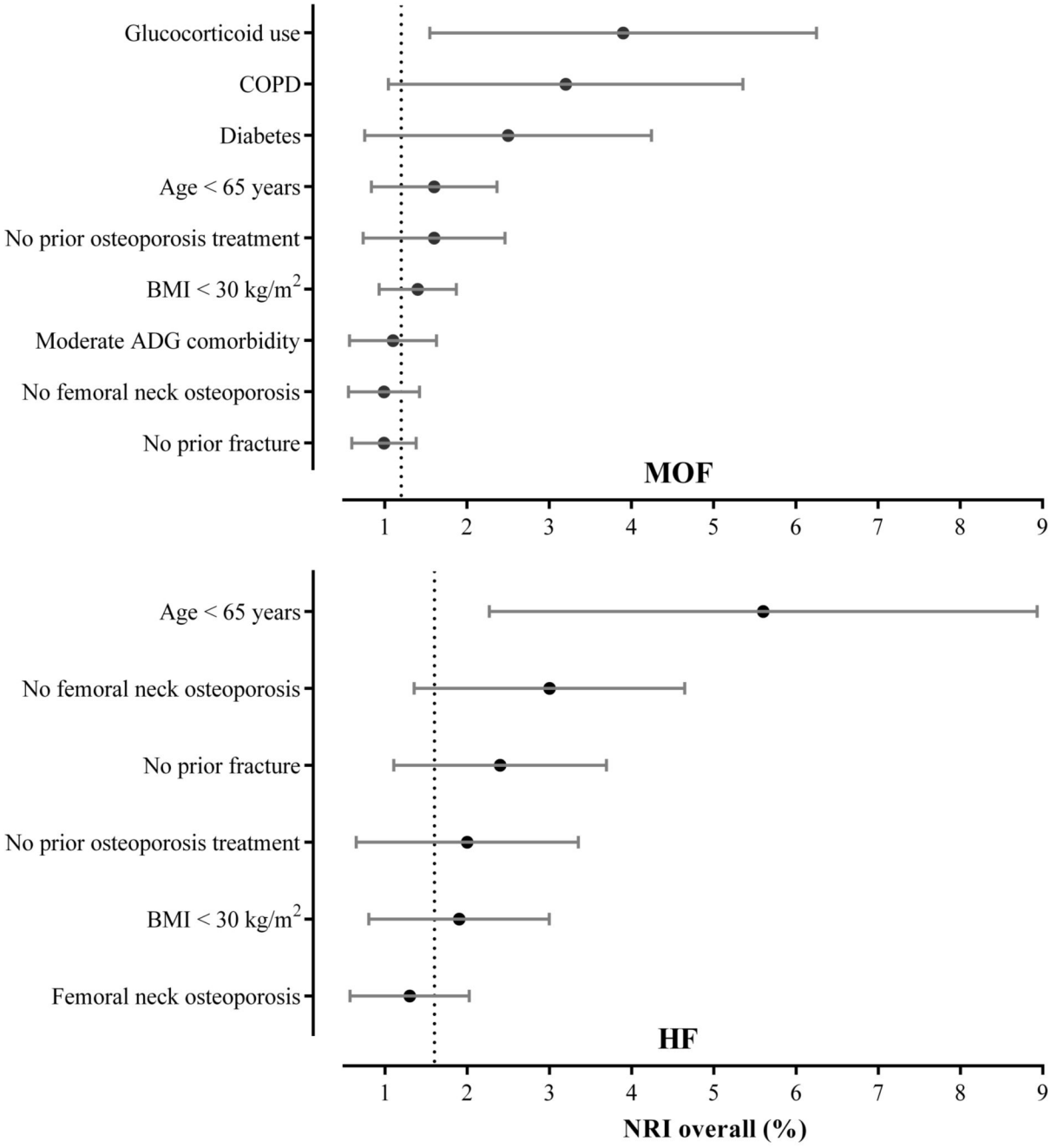

Figure 3.

Rank-ordered overall NRI with 95% CI bars for TBS-adjustment to FRAX for predicting incident MOF (panel above) and HF (panel below) stratified by clinical variables. The dashed line indicates the HR for all cases.

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Table 1

Baseline characteristics stratified by incident major osteoporotic fracture (MOF) and incident hip fracture (HF).

	All Cases	MOF	No MOF	p-value	HF	No HF	p-value
N	37,176	3741	33,435		1008	36,168	
Age (years)	63.6 ± 10.9	68.5 ± 11.0	63.0 ± 10.7	<0.001	73.8 ± 9.3	63.3 ± 10.8	<0.001
Sex (women)	34,316 (92.3%)	3503 (93.6%)	30,813 (92.2%)	0.001	945 (93.8%)	33,371 (92.3%)	0.081
BMI (kg/m^2)	26.1 ± 4.3	25.6 ± 4.3	26.1 ± 4.3	<0.001	25.0 ± 4.2	26.1 ± 4.3	<0.001
Prior fracture	5070 (13.6%)	955 (25.5%)	4115 (12.3%)	<0.001	274 (27.2%)	4796 (13.3%)	<0.001
Femoral neck T-score	-1.4 ± 1.0	-1.9 ± 0.9	-1.3 ± 1.0	<0.001	-2.3 ± 0.8	-1.4 ± 1.0	<0.001
FRAX 10 year MOF risk without TBS (%)	10.7 ± 7.8	16.0 ± 10.3	10.1 ± 7.3	<0.001	20.6 ± 10.7	10.5 ± 7.6	<0.001
FRAX 10 year HF risk without TBS (%)	2.6 ± 4.3	5.1 ± 6.2	2.3 ± 4.0	<0.001	7.7 ± 7.0	2.4 ± 4.1	<0.001
Lumbar spine TBS	1.32 ± 0.12	1.27 ± 0.12	1.33 ± 0.12	<0.001	1.25 ± 0.12	1.32 ± 0.12	<0.001

BMI=Body mass index

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Table 2

Net reclassification improvement (NRI) for incident major osteoporotic fracture (MOF) and hip fracture (HF) cases using the TBS-adjustment to FRAX assuming MOF ≥ 20% and HF ≥ 3% intervention cut-offs, respectively.

Clinical variables	Subgroups	N (overall %)	MOF			HF		
			Number of fractures (subgroup %)	NRI	p-value	Number of fractures (subgroup %)	NRI	p-value
All subjects		37,176	3,741 (10.1%)	**1.2%**	**0.002**	1,008 (2.7%)	**1.7%**	**0.016**
Sex	**Women**	34,316 (92.3%)	3,503 (10.2%)	**1.1%**	**0.006**	945 (2.8%)	**1.8%**	**0.010**
	Men	2,860 (7.7%)	238 (8.3%)	2.3%	0.054	63 (2.2%)	-0.9%	0.78
Age (years)	**< 65**	20,431 (55.0%)	1,353 (6.6%)	**1.7%**	**<0.001**	170 (0.8%)	**5.6%**	**0.017**
	≥ 65	16,745 (45.0%)	2,388 (14.3%)	0.8%	0.14	838 (5.0%)	-0.1%	0.92
BMI (kg/m^2)	**< 30**	29,952 (80.6%)	3,090 (10.3%)	**1.4%**	**0.001**	871 (2.9%)	**1.9%**	**0.012**
	≥ 30	7,224 (19.4%)	651 (9.0%)	0.2%	0.80	137 (1.9%)	0.7%	0.74
Diabetes	**Yes**	3704 (10.0%)	437 (11.8%)	**2.5%**	**0.030**	155 (4.2%)	3.1%	0.15
	No	33,472 (90.0%)	3304 (9.9%)	**1.0%**	**0.016**	853 (2.5%)	1.3%	0.074
Prior fracture	**Yes**	5,070 (13.6%)	955 (18.8%)	1.0%	0.32	274 (5.4%)	-0.5%	0.68
	No	32,106 (86.4%)	2,786 (8.7%)	**1.0%**	**0.011**	734 (2.3%)	**2.4%**	**0.006**
COPD	**Yes**	3,214 (8.6%)	429 (13.3%)	**3.2%**	**0.019**	126 (3.9%)	1.1%	0.63
	No	33,962 (91.4%)	3,312 (9.8%)	**0.8%**	**0.030**	882 (2.6%)	**1.7%**	**0.019**
High alcohol use	**Yes**	1,030 (2.8%)	132 (12.8%)	4.0%	0.094	30 (2.9%)	-4.7%	0.42
	No	36,146 (97.2%)	3,609 (10.0%)	**1.0%**	**0.006**	978 (2.7%)	**1.9%**	**0.007**
Rheumatoid arthritis	**Yes**	1,335 (3.6%)	181 (13.6%)	-0.6%	0.69	50 (3.7%)	0.6%	0.77
	No	35,841 (96.4%)	3,560 (9.9%)	**1.2%**	**0.001**	958 (2.7%)	**1.7%**	**0.017**
Glucocorticoid use	**Yes**	2,164 (5.8%)	254 (11.7%)	**3.9%**	**0.039**	83 (3.8%)	-0.3%	0.87
	No	35,012 (94.2%)	3,487 (10.0%)	**1.0%**	**0.012**	925 (2.6%)	**1.9%**	**0.012**
Secondary osteoporosis	**Yes**	2,690 (7.2%)	357 (13.3%)	0.2%	0.90	114 (4.2%)	-0.2%	0.91
	No	34,486 (92.8%)	3,384 (9.8%)	**1.2%**	**0.002**	894 (2.6%)	**1.9%**	**0.012**

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Clinical variables	Subgroups	N (overall %)	MOF			HF		
			Number of fractures (subgroup %)	NRI	p-value	Number of fractures (subgroup %)	NRI	p-value
Femoral neck osteoporosis	**Yes**	4,713 (12.7%)	1,051 (22.3%)	1.5%	0.15	430 (9.1%)	**2.3%**	**<0.001**
	No	32,463 (87.3%)	2,690 (8.3%)	**1.0%**	**0.007**	578 (1.8%)	**3.0%**	**0.008**
Osteoporosis treatment*	**Yes**	9,698 (26.1%)	1,354 (14.0%)	**1.6%**	**0.020**	352 (3.6%)	0.9%	0.35
	No	27,478 (73.9%)	2,387 (8.7%)	0.7%	0.10	656 (2.4%)	**2.0%**	**0.029**
Comorbidity	**High**	12,330 (33.2%)	1639 (13.3%)	1.2%	0.064	488 (4.0%)	1.6%	0.10
	Moderate	16,808 (45.2%)	1546 (9.2%)	**1.1%**	**0.032**	409 (2.4%)	1.1%	0.27
	Low	8,038 (21.6%)	556 (6.9%)	0.9%	0.28	111 (13.8%)	2.9%	0.26

Significant effects are in bold. BMI body mass index, COPD chronic obstructive pulmonary disease.

*Treatment in the year before BMD testing.

Table 3

Hazard ratios (HR) per 1 SD reduction in TBS with 95% confidence intervals (CI) for incident major osteoporotic fracture (MOF) and hip fracture (HF).

Clinical variables	Subgroups	MOF			HF		
		HR (95% CI)	p-value	p-interaction	HR (95% CI)	p-value	p-interaction
All Cases		1.19 (1.15-1.23)	<0.001		1.13 (1.05-1.20)	<0.001	
Sex	**Women**	**1.20 (1.16-1.25)**	**<0.001**	0.25	**1.13 (1.05-1.21)**	**<0.001**	0.84
	Men	1.10 (0.97-1.24)	0.13		1.14 (0.90-1.44)	0.27	
Age (years)	**< 65**	**1.33 (1.26-1.41)**	**<0.001**	**0.004**	**1.53 (1.31-1.78)**	**<0.001**	**<0.001**
	≥ 65	**1.12 (1.07-1.17)**	**<0.001**		1.05 (0.98-1.13)	0.18	
BMI (kg/m^2)	**< 30**	**1.19 (1.15-1.24)**	**<0.001**	0.86	**1.15 (1.06-1.23)**	**<0.001**	0.26
	≥ 30	**1.19 (1.10-1.28)**	**<0.001**		1.03 (0.88-1.21)	0.69	
Diabetes	**Yes**	**1.18 (1.08-1.30)**	**<0.001**	0.73	1.17 (1.00-1.37)	0.053	0.36
	No	**1.19 (1.14-1.23)**	**<0.001**		**1.09 (1.02-1.18)**	**0.017**	
Prior fracture	**Yes**	**1.11 (1.03-1.18)**	**0.004**	**0.003**	**1.02 (0.89-1.16)**	**0.81**	**0.048**
	No	**1.19 (1.15-1.23)**	**<0.001**		**1.13 (1.05-1.20)**	**<0.001**	
COPD	**Yes**	**1.18 (1.07-1.30)**	**<0.001**	0.44	1.08 (0.90-1.29)	0.41	0.59
	No	**1.19 (1.15-1.23)**	**<0.001**		**1.14 (1.06-1.23)**	**<0.001**	
High alcohol use	**Yes**	1.16 (0.97-1.37)	0.096	0.55	0.99 (0.69-1.43)	0.96	0.21
	No	**1.19 (1.15-1.23)**	**<0.001**		**1.13 (1.06-1.21)**	**<0.001**	
Rheumatoid arthritis	**Yes**	1.15 (0.99-1.34)	0.072	0.61	0.89 (0.66-1.21)	0.47	0.083
	No	**1.19 (1.15-1.24)**	**<0.001**		**1.14 (1.06-1.22)**	**<0.001**	
Glucocorticoid use	**Yes**	**1.15 (1.02-1.31)**	**0.027**	0.51	**0.93 (0.74-1.17)**	**0.53**	**0.029**
	No	**1.19 (1.15-1.24)**	**<0.001**		**1.14 (1.07-1.23)**	**<0.001**	
Secondary osteoporosis	**Yes**	**1.17 (1.04-1.31)**	**0.007**	0.94	1.14 (0.93-1.39)	0.21	0.92
	No	**1.19 (1.15-1.24)**	**<0.001**		**1.13 (1.05-1.21)**	**0.001**	
Femoral neck osteoporosis	**Yes**	**1.15 (1.07-1.22)**	**<0.001**	0.19	1.08 (0.98-1.20)	0.13	0.36
	No	**1.21 (1.16-1.26)**	**<0.001**		**1.15 (1.06-1.26)**	**0.001**	
Osteoporosis treatment*	**Yes**	**1.15 (1.08-1.22)**	**<0.001**	**0.005**	1.12 (1.00-1.25)	0.057	0.58
	No	**1.22 (1.16-1.27)**	**<0.001**		**1.15 (1.06-1.25)**	**<0.001**	
Comorbidity	**High**	**1.15 (1.10-1.21)**	**<0.001**	0.091	1.06 (0.97-1.17)	0.21	
	Moderate	**1.18 (1.12-1.25)**	**<0.001**		**1.17 (1.05-1.30)**	**0.003**	**<0.001**
	Low	**1.31 (1.19-1.43)**	**<0.001**		**1.23 (1.01-1.51)**	**0.044**	

Significant effects are in bold. BMI body mass index, COPD chronic obstructive pulmonary disease.

*Treatment in the year before BMD testing.

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Table 4

Percentage reclassified and odds ratios (OR) for reclassification from multivariable logistic regression using the TBS-adjustment to FRAX assuming fixed MOF ≥ 20% and HF ≥ 3% intervention cut-offs.

Clinical variables	Subgroups	MOF			HF		
		% Reclassified Overall (Down : Up)*	OR (95% CI)	p-value	% Reclassified Overall (Down : Up)*	OR (95% CI)	p-value
All subjects		2.5 (1.0 : 1.5)			3.0 (0.9 : 2.1)		
Sex	**Women**	2.6 (1.1 : 1.5)	1.00 (ref)		2.8 (0.8 : 2.0)	1.00 (ref)	
	Men	1.4 (0.5 : 0.9)	**0.37 (0.26-0.51)**	**<0.001**	5.6 (2.3 : 3.2)	**1.62 (1.35-1.94)**	**<0.001**
Age (years)	**< 65**	4.5 (2.0 : 2.5)	**3.45 (2.89-4.11)**	**<0.001**	4.2 (1.0 : 3.2)	**1.92 (1.68-2.19)**	**<0.001**
	≥ 65	0.9 (0.2 : 0.6)	1.00 (ref)		2.0 (0.8 : 1.1)	1.00 (ref)	
BMI (kg/m^2)	**< 30**	2.0 (0.7 : 1.3)	0.91 (0.75-1.10)	0.31	2.9 (0.7 : 2.2)	0.93 (0.80-1.09)	0.38
	≥ 30	2.6 (1.1 : 1.5)	1.00 (ref)		3.0 (1.0 : 2.0)	1.00 (ref)	
Diabetes	**Yes**	3.4 (1.0 : 2.4)	**1.22 (1.00-1.49)**	**0.049**	4.7 (0.9 : 3.8)	**1.45 (1.22-1.72)**	**<0.001**
	No	2.4 (1.0 : 1.4)	1.00 (ref)		2.8 (0.9 : 1.9)	1.00 (ref)	
Prior fracture	**Yes**	7.3 (2.8 : 4.4)	**2.94 (2.55-3.39)**	**<0.001**	5.4 (1.9 : 3.5)	**1.80 (1.56-2.08)**	**<0.001**
	No	1.7 (0.7 : 1.0)	1.00 (ref)		2.6 (0.8 : 1.9)	1.00 (ref)	
COPD	**Yes**	4.5 (1.2 : 3.3)	**1.37 (1.13-1.67)**	**0.001**	5.2 (1.5 : 3.6)	**1.51 (1.26-1.80)**	**<0.001**
	No	2.3 (1.0 : 1.3)	1.00 (ref)		2.8 (0.9 : 1.9)	1.00 (ref)	
High alcohol use	**Yes**	4.4 (1.3 : 3.1)	**2.01 (1.44-2.79)**	**<0.001**	4.8 (1.7 : 3.0)	**1.57 (1.16-2.12)**	**0.003**
	No	2.4 (1.0 : 1.4)	1.00 (ref)		2.9 (0.9 : 2.0)	1.00 (ref)	
Rheumatoid arthritis	**Yes**	4.9 (2.2 : 2.7)	**1.66 (1.24-2.22)**	**<0.001**	4.9 (1.7 : 3.1)	**1.46 (1.11-1.92)**	**0.006**
	No	2.4 (1.0 : 1.4)	1.00 (ref)		2.9 (0.9 : 2.0)	1.00 (ref)	
Glucocorticoid use	**Yes**	4.9 (2.2 : 2.7)	**2.21 (1.74-2.81)**	**<0.001**	5.3 (2.5 : 2.8)	**1.50 (1.20-1.87)**	**<0.001**
	No	2.3 (0.9 : 1.4)	1.00 (ref)		2.8 (0.8 : 2.0)	1.00 (ref)	
Secondary osteoporosis	**Yes**	2.6 (0.9 : 1.6)	1.01 (0.81-1.24)	0.96	3.5 (1.4 : 2.1)	1.09 (0.91-1.31)	0.36
	No	2.5 (1.0 : 1.5)	1.00		2.9 (0.9 : 2.1)	1.00	

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Clinical variables	Subgroups	MOF			HF		
		% Reclassified Overall (Down : Up)*	OR (95% CI)	p-value	% Reclassified Overall (Down : Up)*	OR (95% CI)	p-value
Femoral neck osteoporosis	**Yes**	9.2 (4.2 : 5.0)	**3.65 (3.16-4.22)**	**<0.001**	5.2 (3.4 : 1.8)	**1.34 (1.15-1.57)**	**<0.001**
	No	1.5 (0.6 : 1.0)	1.00 (ref)		2.7 (0.6 : 2.1)	1.00 (ref)	
Osteoporosis treatment	**Yes**	2.1 (1.0 : 1.1)	**0.79 (0.67-0.95)**	**0.010**	2.4 (0.9 : 1.5)	**0.80 (0.68-0.94)**	**0.007**
	No	2.6 (1.0 : 1.6)	1.00 (ref)		3.2 (0.9 : 2.2)	1.00 (ref)	
Comorbidity	**High**	3.4 (1.3 : 2.1)	**1.26 (1.01-1.57)**	0.105	3.5 (1 : 2.5)	1.04 (0.86-1.25)	
	Moderate	2.3 (1.1 : 1.2)	1.17 (0.95-1.45)		2.9 (0.9 : 2.0)	1.07 (0.90-1.27)	0.73
	Low	1.5 (0.4 : 1.1)	1.00 (ref)		2.3 (0.8 : 1.5)	1.00 (ref)	

Significant effects are in bold.

*Down: Reclassification from treatment to non-treatment; Up: Reclassification from non-treatment to treatment, BMI body mass index, COPD chronic obstructive pulmonary disease.