General Comorbidity Indicators Contribute to Fracture Risk Independent of FRAX: Registry-Based Cohort Study

Short title: Medical comorbidity and fracture prediction

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Abstract

Context: FRAX® estimates 10-year fracture probability from osteoporosis-specific risk factors. Medical comorbidity indicators are associated with fracture risk but whether these are independent from those in FRAX is uncertain.

Objective: We hypothesized Johns Hopkins Aggregated Diagnosis Groups (ADG®) scores or recent hospitalization number may be independently associated with increased risk for fractures.

Design: Retrospective cohort study.

Setting: Manitoba BMD Registry (1996-2016).

Participants: Women and men age ≥ 40 with at least 3 years prior health care data

Exposures: Using linked administrative databases, ADG® scores were constructed along with number of hospitalizations for each individual. **Main measures**: Incident Major Osteoporotic Fracture and Hip Fracture was ascertained during average follow up of 9 years; Cox regression analysis determined the association between increasing ADG® score or number of hospitalizations and fractures.

Results: Separately, hospitalizations and ADG® score independently increased the hazard ratio for fracture at all levels of comorbidity (hazard range 1.2-1.8, all $p<0.05$), irrespective of adjustment for FRAX, BMD and competing mortality. Taken together, there was still a higher than predicted rate of fracture at all levels of increased comorbidity, independent of FRAX and BMD but attenuated by competing mortality. Using an intervention threshold of major fracture

risk > 20%, application of the comorbidity hazard ratio multiplier to the patient population FRAX scores would increase the number of treatment candidates from 8.6% to 14.4%.

Conclusions: Both complex and simple measures of medical comorbidity may be used to modify FRAX-based risk estimates to capture the increased fracture risk associated with multiple comorbid conditions in older patients.

Introduction

Osteoporotic fractures constitute a major contributor to pain, disability, health care costs (direct and indirect)[12] and mortality[3]. Effective anti-fracture therapies exist[45] and the present medical paradigm suggests such therapies be offered to individuals at high risk of fracture[6]. The primary tasks of the bone health assessment is to determine which patients are at high risk for fracture, particularly in the primary prevention setting. The development of several population-based and validated fracture risk assessment scores have been useful for this purpose[78] although it is recognized that the existing tools have imperfect discrimination[910111213]. The characteristics of individual patients may either increase or decrease their predicted fracture risk and may account for the imperfect categorization of existing risk assessment systems. A number of health conditions have been studied in this regard, including diabetes[14], prostate cancer[15], chronic kidney disease[16], Parkinson's disease[17], falls[18] and frailty[17] among others. For each health condition, population fracture risk studies have shown an increased fracture rate. However, in many cases, unless the study is undertaken in conjunction with existing fracture risk assessment tools, it is unknown whether any observed increased risk is

independent of that which might already be predicted using a more widely validated tool comprising common risk factors or bone density (BMD).

It is therefore impractical and unrealistic, given the number of permutations for individual patients' special considerations, to have a unique fracture risk tool or adjustment for every medical problem. A more general approach would be to derive and validate fracture risk multipliers for existing risk assessment tools that may account for these additional factors. Given the real-world complexity of patient care, it would be preferable to design such multipliers in a sufficiently broad fashion to capture medical complexity without needing to account for every possible health condition and interactions amongst conditions. This may involve cumulative medical comorbidity scores or, more generally, a consideration of recent hospitalizations as an easily identifiable and broadly applicable marker of ill health. In particular, the number of hospitalizations may be a proxy indicator of comorbidity as greater healthcare use may reflect general comorbidity. As a first step to address this need, we performed a fracture outcomes-based population risk analysis within a well-characterized administrative database to determine whether a general index of medical comorbidity or the number of recent hospitalizations might be a FRAX®-independent risk factor for subsequent fracture.

Methods

Study population and setting

This study was approved by the Health Research Ethics Board of the University of Manitoba and the Health Information Privacy Committee of Manitoba Health. We used the population-based

Manitoba BMD program registry to identify women and men over the age of 40 years undergoing a first (baseline) BMD test between January 1, 1996 to March 31, 2016 and in whom at least 3 years of prior provincial health care data were available. In Manitoba, Canada, all health care is provided through a single, government-payor health system such that each interaction with the health system may be tabulated and interrogated. For each encounter, information including demographics, date, type of service and diagnostic codes was recorded. Hospital discharge abstracts containing diagnoses, procedures and physician billing claims are coded using ICD-9, Clinical Modification (i.e., ICD-9-CM) prior to 2004 and ICD-10 Canadian version (i.e., ICD-10-CA), thereafter. Data on dispensation of prescribed medication, available from 1995 onwards, were collected via the provincial retail pharmacy system[19]. The Manitoba BMD program registry has been used in many validated studies of osteoporosis risk factors and fracture rates[20121421] since it can be linked through anonymous identifiers to the administrative databases listed where completeness and accuracy rates of > 99% have been demonstrated[22232425].

Definition and classification of general medical comorbidity

Two measures were used to define severity-stratified general medical comorbidity: number of hospitalizations in the three years prior to the BMD test, and Johns Hopkins Aggregated Diagnosis Groups™ (ADGs®) score created using The Johns Hopkins Adjusted Clinical Group® (ACG®) Case-Mix System version 9. Each patient's ADG® score was computed from hospital and physician claims data for the year prior to the BMD assessment. The ADG® score is a patient-focused, diagnosis-based means of categorizing medical conditions[2627]. Each ICD-9-CM or ICD-

10-CA code is categorized into one of 32 clusters known as an Aggregated Diagnosis Group based upon duration of the condition, severity, diagnostic certainty, etiology and requirement for specialty care. ICD codes in the same ADG® are alike in clinical aspects and demand for health system utilization; any patient may have diagnoses belonging to 0 - 32 ADG®s. The ADG® groupings use both inpatient and ambulatory health data so that both ICD codes and physician billing codes may be combined as unique contributing sources. Although originally designed to permit study of system healthcare resource use[28], the ADG® system has been validated in secondary populations[2930] and shown to predict mortality in general adult populations[31] as well as hospitalization in specific patient groups[32]. The ADG® score is potentially superior to other comparable scores such as the Charlson Comorbidity Index or Elixhauser method given direct comparison between methods has shown slightly higher discriminative ability for the ADG®s score[33]. Hospitalization was determined from the Hospital Discharge Abstract Data (DAD) system and includes records of both Manitoba residents hospitalized in Manitoba facilities with detailed information about inpatient and day surgery services. The Hospital Abstracts Data consist of hospital forms/computerized records containing summaries of demographic and clinical information completed at the point of discharge from the hospital by trained health records data abstracters.

Fracture and outcome ascertainment

Fracture incidence was ascertained using hospital discharge abstract and physician billing claims between the index date (BMD testing) and March 31, 2016 which were assessed for evidence of occurrence of a hip fracture or major osteoporotic fracture(MOF). Fractures of the face, hands,

feet and ankles were excluded as were any fractures associated with severe trauma codes as previously described[24]. Hip and forearm fractures were verified by the co-existence of a fracture reduction, fixation or casting code. Duplication of fracture counting was minimized by requiring that there be no hospital or billing code for the same fracture site in the year prior to an incident fracture[25]. Hospitalization was determined from the Hospital Discharge Abstract Data and mortality verified from the registration file which is updated against Vital Statistics.

Bone densitometry and FRAX® score calculation

All BMD measures in the province of Manitoba are performed under the provincial BMD program using cross-calibrated DXA devices under the direct supervision of a medical physicist (Lunar DPX, Prodigy or iDXA; GE Health Care, Madison, WI, USA). The Manitoba database was not used to generate the relevant FRAX®-Canada tool but has been previously used in validation studies of calibration and discrimination[34]. Prior fracture and other FRAX®-input variables were assessed using a combination of self-report and linkage to administrative data. Weight and height were measured at the time of BMD, and BMI was calculated as weight (kg) divided by height (m) squared. We defined prior fragility fracture as any non-traumatic fracture that occurred before the baseline BMD test examining medical records back to 1979; the mean (SD) look-back period was 22.0 (6.6) years. Parental hip fracture was self-reported after 2005 and in earlier years was ascertained from linkage to parental hospitalization records dating back to 1970. [35] Current smoking was self-reported after 2005 and for earlier years used data linkage to a diagnosis of chronic obstructive lung disease as a proxy for significant smoking in earlier years[36,37]. High alcohol use was by self-report of weekly alcohol intake from 2012 onwards and

from administrative data (i.e., alcohol substance abuse diagnosis codes in hospital and physician billing records) in earlier years. Rheumatoid arthritis from 2012 onwards was from patient self-report followed by physician review of medical and pharmacy records, and from administrative data in earlier years using a validated definition.[38] Prolonged oral corticosteroid use (>90 days dispensed in the 1 year prior to BMD) was obtained from the provincial pharmacy system.

Statistical analysis

Descriptive analyses of cohort characteristics included means +/- standard deviations (SD) for continuous variables and frequency(%) for categorical data. For each individual, we determined the number of hospitalizations and number of ADG®s and created categorical covariates in the 3 years preceding the index BMD. For ADG®s, the categories were 0-2 [none; reference], 3-5 [mildly increased comorbidity], 6-8 [moderately increased comorbidity] and ≧9 [markedly increased comorbidity]. Based on prior observations regarding hospitalization and incident fractures[39], for the present study, hospitalizations were categorized as 0 [none; reference] and 1 [mildly increased], 2 [moderately increased], and 3+ [markedly increased]. Multivariable Cox proportional hazards semi-parametric regression models were used to estimate the risk gradient associated with incident hip fracture or MOF for the ADG® score and the number of hospitalizations in separate models, and then in a combined model. Hazard ratios (HR) and 95% confidence intervals (95% CI) are reported. We adjusted for the following covariates in four separate models: 1) age and sex, 2) FRAX® predicted 10-year MOF or HF risk including BMD, 3) FRAX® predicted 10-year MOF or HF risk with BMD and competing mortality and 4) FRAX®

individual risk factors. There was no evidence of collinearity between the ADG® and hospitalization measures. Secondary analyses were conducted to show effect of hospitalization over three years compared to hospitalization in the past 12 months only. These models were stratified by age group(40-64 versus 65 years or older), sex (male versus female), and diabetes mellitus diagnosis at baseline (presence versus absence). A final sensitivity analysis restricted the cohort to patients with baseline FRAX® 10-year predicted MOF risks < 20% and lacking prior fracture in order to estimate the proportion in whom application of the comorbidity multiplier might re-classify the patient into a high-risk, treatment-recommended category (i.e. adjusted 10-year MOF risk > 20%). Statistical analyses were performed with Statistica (V13.0, StatSoft Inc, Tulsa, OK) and a nominal $\alpha = 0.05$ was used to define statistical significance.

Results

The study population baseline demographics are displayed in Tables 1 and 2 where it may be seen that of the entire population of 86,400, 90% were women and the average(SD) age was 64.6(11.0) years. The mean baseline femoral neck T-score was -1.4(1.0) and 11.7% had a T-score less than -2.5. Estimated 10-year hip and MOF risks by FRAX® with BMD were relatively low on average but 9.1% had a 10-year MOF risk $\geq$ 20%. The distribution of comorbidity indices showed that 18.9% of patients had an ADG® score of 0-2 while 10.8% classified as having markedly increased comorbidity (i.e., ADG® score≥9). There was 20.1% of the population with prior hospitalization, approximately half of whom were hospitalized more than once in the prior 3 years. Over an average follow up of 9.0(5.5) years, there were 8416 unique MOF and 2665 hip fractures, occurring in 10.1% and 3.2% of the population, respectively.

The primary analysis to test the association between incident fracture and ADG® score and hospitalization (either separately or combined) is shown in Tables 3 and 4. Taken separately (Table 2), hospitalization and ADG® score independently increased the HR for MOF fracture at all levels of comorbidity (HR range 1.2-1.8, all $p<0.05$), irrespective of adjustment for FRAX®, BMD, competing mortality and risk factors. The same was true for hip fracture. However, after adjustment for FRAX®predicted 10-year HF risk and BMD, an increased HR for hip fracture was no longer associated with one prior hospitalization. In the models that contained both ADG® score and hospitalization, after controlling for age and sex (Table 4, model 1), there was still a clear, statistically significant increasing gradient of risk for both hip fracture and MOF according to the ADG® score and number of hospitalizations, ranging from a HR of 1.16 (95% CI 1.09-1.24) in the mildly increased ADG® score group to a HR of 1.67 (95% CI 1.54-1.82) in the markedly increased ADG® score group. FRAX®-based adjustments in models 2, 3 and 4 did not affect the hazard ratios by gradient or direction of increase when applied to the ADG® risk scoring groups, demonstrating independence of FRAX®-based factors including competing mortality for both MOF and hip fracture incidence. However, in this combined analysis, increased HRs associated with hospitalization were attenuated by adjustment for FRAX® predicted 10-year MOF risk with BMD and eliminated by adjustment for FRAX® predicted 10-year MOF risk with BMD and competing mortality (p=NS). The pre-specified secondary analyses showed slightly higher adjusted HR when considering patients < age 65 years or men, but using number of hospitalizations in the previous 12 months (rather than 3 years) and further adjustment for diabetes mellitus did not generate any difference in observed HRs (data not shown).

The potential clinical implications of a general comorbidity FRAX® risk multiplier is shown in Table 5 (ADG® scores) and Table 6 (prior hospitalizations). Where an intervention threshold is set at 10-year MOF risk ≥ 20% or 10-year hip fracture risk ≥ 3%, applying HRs for ADG® (Table 2, Model 3 FRAX® with BMD and competing mortality) would change the decision to offer anti-fracture therapy in 35.8% to 100% of patients with initial 10-year MOF risk 15.0-19.9% and 39.8% to 75.9% of patients with initial 10-year hip fracture risk 2.0-2.9%. For patients with lower initial predicted risk, even high comorbidity counts rarely reclassified patients to high risk. Overall, 6.4% were reclassified to MOF risk ≥ 20% and 5.6% were reclassified to hip fracture risk ≥ 3%. Age-specific multipliers to adjust FRAX® MOF risk for number of past hospitalizations were generated from Model 3 (FRAX® model with BMD and competing mortality) that included a significant age*hospitalization interaction term (p-interaction = 0.004); multipliers showed a gradient related to both age (larger in younger patients) and number of prior hospitalizations (Figure 1). Once again, almost all the risk reclassification was seen in those with initial 10-year MOF risk 15.0-19.9% (range 20.7% to 67.3%), with overall 1.0% reclassified to MOF risk ≥ 20%.

Discussion

The present study provides clear evidence for a FRAX® and BMD-independent increase in estimated fracture risk according to increasing levels of general medical comorbidity as defined using the ADG® score or multiple prior hospitalizations. The target population for whom a comorbidity multiplier could be most usefully applied includes young patients in whom predicted fracture risk is only slightly below the usual intervention threshold. The impact of the adjustment is substantial with a nearly 30-50% increase in observed fracture risk once a patient

reaches a moderate level of associated medical comorbidity. Notably, the increased fracture risk persisted even after adjustment for competing mortality, an important consideration to avoid over-inflation of risk estimates[40]. This is especially surprising given that increasing ADG®scores themselves predict increased mortality risk[31] and so the statistical adjustment confirms the robustness of the findings with relevance to the impact of multi-comorbidity upon fractures occurring prior to comorbidity-predicted death. Although ADG® scores are not intended for bedside clinical decision making, a clinician might now choose to consider their more medically complex patients as being at 30-50% higher risk for fracture than estimated from FRAX® with BMD alone. On the other hand, number of prior hospitalizations is more reliably assessed in clinical practice and is therefore more amenable to the use of FRAX® risk multipliers. The HR for fracture after hospitalization in our analysis are very similar to those reported previously[39], suggesting probable agreement on the magnitude of impact that hospitalization has upon incident fracture risk.

The use of FRAX® fracture risk multipliers is not new; previous population studies have suggested possible adjustments based upon lumbar spine and hip BMD discordance[41], trabecular bone score[42], glucocorticoid dosage[43], diabetes mellitus[44], type of and time since prior fractures[45] and frequency of falls[46]. These adjustments for FRAX® will shortly be accessible through the FRAX® web site under the banner of FRAXplus®. It is unknown whether each of these unique and independent additions to FRAX® scores are themselves independent from each other. Additionally, there is disagreement as to the value of making certain adjustments based on risk factors such as falls, which may not be amenable to pharmacologic

fracture prevention strategies[47]. Therefore, while it is conceivable that a single risk score adjustment might be considered in uncomplicated cases (e.g., spine-hip T score discordance), adjusted risk estimations become far more uncertain in the presence of multiple potentially relevant additional factors. It is perhaps this type of scenario where a general medical comorbidity index may prove to be of broadest use; with so many newly described independent factors, some are already calling for a new approach to fracture risk estimation[48]. In the interim, it is likely unnecessary to be concerned about the precisely-adjusted numeric risk estimate for a given patient unless one is following a treatment strategy whereby patients at an especially high estimated risk threshold are considered for primary anabolic therapy first[49]. Rather, the greatest benefit of a comorbidity-adjusted fracture risk estimate may be to help appropriately move patients into a treatment-recommended risk category where such treatment is otherwise not considered based upon FRAX® and BMD alone.

Other data have demonstrated that general measures of medical comorbidity have a meaningful albeit imperfect relationship with fracture risk. A Danish study of an older (1987) and newer (2011) version of the Charlson Comorbidity Index had a receiver operating characteristics (ROC) AUC of around 0.6 to predict MOF for both men and women. The authors demonstrated that hip fracture prediction could be slightly improved (AUC 0.72-0.76) with a re-weighting of certain specific diagnoses (such as dementia, alcoholic liver disease, Parkinson's disease) according to their associated odds ratios for fracture. However, for MOF, a sensitivity analysis showed that the inclusion of multiple diagnoses did not outperform an age-only index[50]. The authors commented that such tools may perform better if combined with a risk

tool that incorporates variables more immediately associated with osteoporosis. In the same population, a different and even more complex medical comorbidity measure (Danish Fracture Risk Evaluation Model, FREM) has been developed as a tool to predict short term (1-year) MOF and hip fractures[51]. In a 5-year validation study for that population, the AUC was around 0.71 for MOF and 0.83 for hip fracture[52]. The value of the FREM tool in addition to FRAX® for 10-year prediction has been recently confirmed in the Canadian population with hazard ratios of 1.05-1.49 for higher FREM scores, again with more consistent results in predicting hip fractures compared to MOF and with a significant attenuating effect from competing mortality[53]. However, the FREM tool is complex and not designed for individual application in routine care[50] and thus we have chosen to emphasize a more general awareness of comorbidity-related impact upon estimated fracture risk. In our study, the effect of co-morbidity upon fracture risk was greatest in younger individuals, possibly because a major fracture risk modifier will have a larger impact in a background low-risk population. It may also be explained by the effect of adjustment for competing mortality; if the comorbidity predicts death as well as fracture then the full risk increment for fracture alone will appear less, in a 10-year prediction window.

Other strictly osteoporosis-oriented risk tools exist for fracture risk prediction besides FRAX® and some consider fewer risk factors[7] whereas others consider even more; the QFracture tool being one of the better-known risk estimating tools that accounts for >25 potential factors including a long list of chronic medical conditions[54]. Although one might speculate that a more complex tool such as QFracture may perform better than FRAX® in calibration and discrimination, that has not generally been the case[55]. Even where slightly better performance

has been suggested, it may simply be an artifact of the tool construction[56] and validation study design wherein an abundance of lowest-risk younger individuals exaggerates the observed discrimination[57]. The hazards of comparing fracture risk prediction tools by receiver-operator-characteristics curves has been highlighted elsewhere[58]. Clearly, there must be a difference when it comes to the prediction of fracture risk, between the medical complexity ADG® score and the medically complex QFracture tool, given the impressively increased hazard ratios seen independent of FRAX® using ADG® scores. We suggest that this may be explained by the broader scope of diagnoses included in ADG® as well as the "severity" factors built into the ADG® model.

Some have wondered why the predictive AUC is only modest (AUC 0.5-0.7) for most fracture risk models and why more complicated prediction tools seem to offer only minor improvements over simpler ones[55]. Our data, and the data from other FRAX®-based risk modifier studies suggest that fracture risk is a multi-factorial set of factors and circumstances; a simplified, general comorbidity adjustment as shown here may represent the most practical way forward to permit capturing the "excess risk" beyond a formal risk tool result, recognizing that it is still just an estimate to facilitate a clinical discussion with individual patients. Indeed, the patient's own view of risk and willingness to accept pharmacotherapy may show significant variation compared to guideline recommendations[59] so as to add another large element to the overall discussion.

Our study had several strengths including the use of a very large population receiving comprehensive health care from a single-payer administration and followed over a sufficiently long time. This permitted comprehensive capture of all relevant fracture risks, medical comorbidity conditions and incident fractures. The use of the ADG® tool for comorbidity definitions took advantage of the availability of both outpatient and inpatient health encounters and was ideal as a more global index of medical complexity. There were some study limitations; as in many population studies of osteoporosis, men were under-represented as were those using higher dose, prolonged glucocorticoids, both of which may have yielded very different HRs for these subgroups if studied in larger numbers. Another limitation was our categorization of ADG® according to baseline status; annualized over the mean of nine years' observation, it is likely that population ADG® would change and likely in a direction that favoured a higher proportion of patients moving into the modestly and markedly increased comorbidity groups. However, the impact of population comorbidity shift in this analysis is likely predictable and would suggest that if anything, the fracture hazard ratios might be over-estimated for those who remain healthy the entire time whereas the fracture hazard ratios are likely under-estimated for those who start with modest comorbidity and progress to marked comorbidity with age. However, change in BMD over time, while unaccounted for in this analysis, is unlikely to have affected the results given the ability of a single BMD to predict long term fracture risk[60] and the lack of effect upon numeric risk estimates from serial BMD measures[6162]. Finally, another important caveat is that ADG® scores are not available or even intended to be used in individual clinical consultations, although they might still be useful for case finding strategies in healthcare systems with electronic medical records. However, we

have shown number of hospitalizations to be a useful multiplier and that would be readily available to any clinician. ADG scores certainly could be used in health informatics where a comprehensive clinical electronic record is available. As well, the importance of the analysis here lies in the concept and not necessarily the actual ADG® scores; the online FRAX® tool already advises users to add clinical judgement when calculating fracture risk. We have demonstrated a general linear relationship between 3 simple tiers of medical comorbidity, and it is likely that most clinicians will have sufficient clinical experience to similarly categorize their patients even without ADG® scoring. Thus, one only requires knowledge of the risk relationship in order to improve the clinical judgement input already required.

Summary

Using a comprehensive and validated measure of general medical comorbidity, the ADG® score, we have shown that increasing levels of co-morbidity and recent hospitalizations are each associated with a clear gradient effect upon increasing fracture risk and this effect is independent of the other common risk factors captured in FRAX® with BMD. ADG® scores are not feasible or intended to be calculated for individual patients in routine clinical practice, but rather, the general relationship between increasing comorbidity and fracture is the key feature that may inform clinical decision-making. Number of hospitalizations in the past 3 years might represent a reasonable way of denoting relevant comorbidity. Using a 20% 10-year fracture risk as a treatment threshold, clinicians should consider upward adjustment of their patient's FRAX®-generated risk estimates by an additional relative 30-50% if moderate-to-severe medical comorbidity is present and baseline risk is between 15-19.9%.

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Data availability

Study data are not publicly available. In order to access data from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba, an individual must prepare a research proposal, complete an accreditation process, obtain ethical and data access approval, and complete a researcher agreement with the provincial ministry of health.

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Table 1: Study population characteristics by ADG score for general medical comorbidity. Data shown includes means with standard deviations or frequency percentage as applicable. ADG, Aggregated Diagnosis Group score, BMD, bone mineral density, MOF, major osteoporotic fracture.

	All subjects, N=86,400	Reference (ADG 0-2), N=16,211	Mildly increased (ADG 3-5), N=38,039	Moderately increased (ADG 6-8), N=22,760	Markedly increased (ADG >9), N=9,390
Age (years)	64.6 (11.0)	62.0 (10.0)	64.4 (10.8)	65.9 (11.2)	66.9 (11.8)
Sex (% female)	90.2%	94.3%	91.2%	88.4%	83.4%
Femoral neck T-score	-1.4 (1.0)	-1.3 (0.9)	-1.3 (1.0)	-1.4 (1.0)	-1.5 (1.1)
FRAX hip fracture risk with BMD (%)	2.4 (3.9)	1.7 (3.0)	2.2 (3.7)	2.7 (4.2)	3.3 (4.7)
FRAX MOF risk with BMD (%)	10.1 (7.2)	8.6 (5.9)	9.9 (6.9)	10.8 (7.6)	11.9 (8.3)
Observation time (years)	9.0 (5.5)	10.1 (5.5)	9.3 (5.5)	8.5 (5.4)	7.6 (5.4)
Incident hip fracture (%)	3.2	2.1	3.0	4.0	4.4
Incident MOF (%)	10.1	7.9	9.6	11.7	13.3
No hospitalization (%) in previous 3 years	79.9	94.3	86.3	72.2	48.0
1 hospitalization (%)	8.4	1.3	5.8	12.8	20.1
2 hospitalizations (%)	7.1	3.6	5.8	8.9	14.2
≥3 hospitalizations (%)	4.6	0.8	2.2	6.1	17.8
Death (%)	19.9	11.8	18.1	24.0	32.8

Table 2: Study population characteristics by number of hospitalizations in past 3 years as a marker of medical comorbidity. Data shown includes means with standard deviations or frequency percentage as applicable. BMD, bone mineral density, MOF, major osteoporotic fracture

	All subjects, N=86,400	Reference (no hospitalizations), N=69,037	1 hospitalization, N=7215	2 hospitalizations, N=6134	≥ 3 hospitalizations, 4014
Age (years)	64.6 (11.0)	64.3 (10.7)	66 (11.8)	65.8 (11.6)	66.1 (12.5)
Sex (female)	90.2%	91.8%	85.1%	85.9%	78.9%
Femoral neck T-score	-1.4 (1.0)	-1.3 (1.0)	-1.4 (1.1)	-1.4 (1.0)	-1.6 (1.1)
FRAX hip fracture risk with BMD (%)	2.4 (3.9)	2.1 (3.6)	3.1 (4.6)	3.0 (4.7)	3.9 (5.5)
FRAX MOF risk with BMD	10.1 (7.2)	9.7 (6.7)	11.7 (8.3)	11.2 (8.2)	12.7 (9.2)
Observation time (years)	9.1 (5.5)	9.4 (5.5)	7.9 (5.2)	8.4 (5.3)	7.4 (5.2)
Incident hip fracture (%)	3.2	3.0	3.6	4.5	4.9
Incident MOF (%)	10.2	9.7	11.5	12.6	14.2

Table 3: Adjusted Hazard ratios (HR) for incident major osteoporotic fracture (MOF) or hip fracture (HF), separate assessment of ADG score and hospitalizations.

Adjustment model, per comorbidity marker category	**ADG score** HR for **MOF** (95% CI)	**Hospitalizations** HR for **MOF** (95% CI)	**ADG score** HR for **HF** (95% CI)	**Hospitalizations** HR for **HF** (95% CI)
Model 1: age/sex				
Mild increase	**1.18 (1.11-1.26)**	**1.36 (1.27-1.47)**	**1.25 (1.10-1.41)**	**1.27 (1.12-1.46)**
Moderate increase	**1.48 (1.39-1.59)**	**1.43 (1.33-1.55)**	**1.55 (1.36-1.76)**	**1.60 (1.41-1.82)**
High increase	**1.90 (1.76-2.06)**	**1.82 (1.67-1.99)**	**1.88 (1.62-2.18)**	**1.88 (1.62-2.18)**
Model 2: FRAX with BMD				
Mild increase	**1.19 (1.11-1.27)**	**1.24 (1.15-1.34)**	1.29 (1.14-1.46)	1.14 (1.00-1.30)
Moderate increase	**1.47 (1.38-1.58)**	**1.37 (1.27-1.47)**	**1.59 (1.40-1.81)**	**1.47 (1.29-1.67)**
High increase	**1.82 (1.68-1.97)**	**1.54 (1.41-1.68)**	**1.80 (1.55-2.09)**	**1.40 (1.21-1.63)**
Model 3: FRAX with BMD and competing mortality				
Mild increase	**1.13 (1.06-1.21)**	**1.11 (1.03-1.19)**	**1.19 (1.06-1.35)**	0.95 (0.84-1.09)
Moderate increase	**1.33 (1.24-1.42)**	**1.20 (1.11-1.29)**	**1.35 (1.19-1.54)**	**1.20 (1.05-1.36)**
High increase	**1.50 (1.38-1.63)**	**1.20 (1.09-1.31)**	**1.35 (1.16-1.57)**	0.99 (0.85-1.15)
Model 4: FRAX individual risk factors				
Mild increase	**1.16 (1.09-1.24)**	**1.17 (1.09-1.26)**	**1.23 (1.09-1.40)**	1.06 (0.93-1.22)
Moderate increase	**1.40 (1.31-1.50)**	**1.28 (1.19-1.39)**	**1.44 (1.26-1.64)**	**1.41 (1.24-1.60)**
High increase	**1.66 (1.53-1.81)**	**1.36 (1.24-1.49)**	**1.60 (1.37-1.86)**	**1.30 (1.11-1.53)**

Comorbidity marker categories: ADG score referent = 0-2. ADG mild increase = score 3-5, ADG moderate increase = score 6-9, ADG high increase = score 9+. Hospitalization referent = 0. Hospitalization mild increase = 1, moderate increase = 2, high increase = 3+. Bold numbers denote $p < 0.05$.

FRAX individual risk factors include age, sex, BMI, smoking history, alcohol excess, rheumatoid arthritis, maternal hip fracture, secondary osteoporosis.

Table 4: Adjusted Hazard ratios (HR) for incident major osteoporotic fracture (MOF) or hip fracture (HF), <u>combined</u> assessment of ADG score and hospitalizations (ADG scores controlled for hospitalization numbers and vice versa). ADG, Aggregate Diagnosis Group.

Adjustment model, per comorbidity marker category	**ADG score** HR for **MOF** (95% CI)	**Hospitalizations** HR for **MOF** (95% CI)	**ADG score** HR for **HF** (95% CI)	**Hospitalizations** HR for **HF** (95% CI)
Model 1: age/sex				
Mild increase	**1.16 (1.09-1.24)**	**1.20 (1.12-1.30)**	**1.19 (1.05-1.34)**	0.99 (0.86-1.13)
Moderate increase	**1.40 (1.31-1.50)**	**1.32 (1.22-1.43)**	**1.37 (1.20-1.56)**	**1.26 (1.11-1.44)**
High increase	**1.67 (1.54-1.82)**	**1.56 (1.42-1.70)**	**1.43 (1.22-1.67)**	**1.21 (1.03-1.41)**
Model 2: FRAX with BMD				
Mild increase	**1.17 (1.10-1.25)**	**1.10 (1.02-1.19)**	**1.28 (1.13-1.45)**	1.02 (0.89-1.16)
Moderate increase	**1.42 (1.33-1.53)**	**1.26 (1.16-1.36)**	**1.55 (1.36-1.76)**	**1.36 (1.19-1.55)**
High increase	**1.67 (1.54-1.82)**	**1.32 (1.20-1.44)**	**1.68 (1.43-1.96)**	**1.23 (1.05-1.44)**
Model 3: FRAX with BMD and competing mortality				
Mild increase	**1.13 (1.06-1.20)**	1.01 (0.93-1.09)	**1.20 (1.06-1.36)**	0.89 (0.77-1.02)
Moderate increase	**1.31 (1.23-1.41)**	**1.12 (1.04-1.21)**	**1.37 (1.20-1.56)**	**1.14 (1.0-1.30)**
High increase	**1.47 (1.35-1.60)**	1.06 (0.97-1.16)	**1.38 (1.18-1.61)**	0.91 (0.78-1.07)
Model 4: FRAX individual risk factors				
Mild increase	**1.16 (1.08-1.23)**	1.06 (0.98-1.15)	**1.19 (1.05-1.34)**	0.86 (0.75-0.99)
Moderate increase	**1.37 (1.28-1.47)**	**1.20 (1.11-1.30)**	**1.34 (1.17-1.52)**	1.12 (0.98-1.28)
High increase	**1.58 (1.45-1.72)**	**1.21 (1.10-1.33)**	**1.33 (1.14-1.56)**	0.93 (0.79-1.09)

Comorbidity marker categories: ADG score referent = 0-2. ADG mild increase = score 3-5, ADG moderate increase = score 6-9, ADG high increase = score 9+. Hospitalization referent = 0. Hospitalization mild increase = 1, moderate increase = 2, high increase = 3+. Bold numbers denote $p < 0.05$.

FRAX individual risk factors include age, sex, BMI, smoking history, alcohol excess, rheumatoid arthritis, maternal hip fracture, secondary osteoporosis.

Table 5: Reclassification from ADG scores – (A) percentage of patients with FRAX+BMD predicted 10-year MOF risk of < 20% in whom adjustment for ADG comorbidity level reclassifies 10-year MOF risk to ≥ 20%. (B) percentage of patients with FRAX+BMD predicted 10-year hip fracture (HF) risk < 3% in whom adjustment for ADG comorbidity level reclassifies 10-year HF risk to ≥ 3%. BMD, bone density, MOF, major osteoporotic fracture, HF hip fracture, ADG, Aggregated Diagnosis Group

FRAX+ BMD 10-year MOF risk	ADG comorbidity level	% of 75,856 patients with initial MOF < 20%	% Reclassified to MOF risk ≥ 20%
0 – 4.9%	None	5.8%	0%
	Mild	11.1%	0%
	Moderate	5.8%	0%
	High	2.1%	0%
5.0-9.9%	None	9.1%	0%
	Mild	19.9%	0%
	Moderate	11.2%	0%
	High	4.2%	0%
10.0-14.9%	None	3.4%	0%
	Mild	9.3%	0%
	Moderate	5.8%	0%
	High	2.5%	26.4%
15.0-19.9%	None	1.4%	0%
	Mild	4.2%	35.8%
	Moderate	2.9%	98.6%
	High	1.4%	100.0%
FRAX+ BMD 10-year HF risk	**ADG comorbidity level**	**% of 63,958 patients with initial HF risk < 3 %**	**% Reclassified to HF risk ≥ 3%**
0 – 0.9%	None	14.6%	0%
	Mild	29.7%	0%
	Moderate	15.9%	0%
	High	5.7%	0%
1.0-1.9%	None	4.2%	0%
	Mild	9.9%	0%
	Moderate	5.7%	0%
	High	2.3%	0%
2.0 - 2.9%	None	2.0%	0%
	Mild	5.3%	39.8%
	Moderate	3.3%	73.0%
	High	1.4%	75.9%

Table 6: Reclassification from prior hospitalizations – percentage of patients with FRAX+BMD predicted 10-year MOF risk of < 20% in whom adjustment for number of previous hospitalizations reclassifies 10-year MOF risk to ≥ 20%. BMD, bone density, MOF, major osteoporotic fracture.

FRAX+ BMD 10-year MOF risk	Hospitalization events	% of 75,856 patients with initial MOF < 20%	% Reclassified to MOF risk ≥ 20%
0 – 4.9%	None	20.6%	0%
	1	1.8%	0%
	2	1.6%	0%
	≥3	0.9%	0%
5.0-9.9%	None	36.6%	0%
	1	3.3%	0%
	2	2.9%	0%
	≥3	1.6%	0%
10.0-14.9%	None	16.5%	0%
	1	1.9%	0%
	2	1.5%	0%
	≥3	1.1%	2.9%
15.0-19.9%	None	7.4%	0%
	1	1.0%	20.7%
	2	0.8%	39.0%
	≥3	0.6%	67.3%

Figure 1: MOF Risk multiplier according to age categories and number of hospitalizations in the preceding 36 months; estimates based upon baseline FRAX plus BMD-estimated risk of MOF and with competing mortality. MOF, major osteoporotic fracture