Published in final edited form as:

Osteoporos Int. 2013 December ; 24(12): . doi:10.1007/s00198-013-2408-4.

Fear of falling, fracture history and comorbidities are associated with health-related quality of life among European and US women with osteoporosis in a large international study

F. Guillemin,

Université de Lorraine, Université Paris Descartes, EA 4360 Apemac, Nancy, France

L. Martinez,

Department of General Practice, Pierre et Marie Curie University, Paris, France

M. Calvert,

University of Birmingham, Edgbaston, Birmingham, UK

C. Cooper,

MRC Epidemiology Resource Centre, University of Southampton, Southampton, UK and Institute of Musculoskeletal Sciences, University of Oxford, Oxford, UK

T.G. Ganiats,

University of California, San Diego, CA, USA

M. Gitlin,

(former position), Health Economics, Amgen (Europe) GmbH, Zug, Switzerland; (current position) Health Economics, Amgen Inc., Thousand Oaks, CA, USA

R. Horne,

Centre for Behavioural Medicine, UCL School of Pharmacy, University College London, London, UK

A. Marciniak*,

Health Economics, Amgen Ltd, Uxbridge, UK

J. Pfeilschifter,

Alfried Krupp Krankenhaus, Essen, Germany

S. Shepherd,

Biostatistics, Amgen Ltd, Uxbridge, UK

A.N.A. Tosteson,

The Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine at Lebanon, NH, USA

S. Wade,

Wade Outcomes Research and Consulting, Salt Lake City, UT, USA

D. Macarios, and

Health Economics, Amgen Inc., Thousand Oaks, CA, USA

N. Freemantle

(former position), University of Birmingham, Edgbaston, Birmingham, UK; (current position) Department of Primary Care and Population Health, University College London, London, UK

Abstract

Purpose—Health-related quality of life (HRQoL) is impaired in women treated for postmenopausal osteoporosis (PMO). The objective of this study was to examine the relationship

between clinical characteristics, comorbidities, medical history, patient demographics and HRQoL in women with PMO.

Methods—Baseline data were obtained and combined from two large and similar multinational observational studies: Prospective Observational Scientific Study Investigating Bone Loss Experience in Europe (POSSIBLE EU®) and in the US (POSSIBLE US™) including postmenopausal women in primary care settings initiating, switching or who had been on bone loss treatment for some time. HRQoL measured by health utility scores (EQ-5D™) were available for 7,897 women (94% of study participants). The relationship between HRQoL and baseline clinical characteristics, medical history and patient demographics was assessed using parsimonious, multivariable, mixed-model analyses.

Results—Median health utility score was 0.80 (interquartile range 0.69–1.00). In multivariable analyses, young age, low body mass index, previous vertebral fracture, increased number of comorbidities, high fear of falling and depression were associated with reduced HRQoL. Regression-based model estimates showed that previous vertebral fracture was associated with lower health utility scores by 0.08 (10.3%) and demonstrated the impact of multiple comorbidities and of fear of falling on HRQoL.

Conclusions—In this large observational study of women with PMO, there was substantial inter-individual variability in HRQoL. An increased number of comorbidities, fear of falling and previous vertebral fracture were associated with significant reductions in HRQoL.

Keywords

Osteoporosis; Postmenopausal; Health-related quality of life; Falls; Fracture; Observational study

Introduction

Osteoporotic fractures are a major cause of morbidity among postmenopausal women, and are associated with increased mortality [1]. Among patients with postmenopausal osteoporosis (PMO), women who have previously experienced vertebral or non-vertebral fractures have lower health-related quality of life (HRQoL) than those who have not experienced such fractures [2-4], and this impairment increases with an increasing number of previous fractures [5, 6]. The societal disease burden of osteoporosis, measured in disability-adjusted life-years, is twice as great as that of rheumatoid arthritis, and is higher than that of any single cancer except lung cancer [7].

However, a history of fracture may not be the only factor affecting the health status of women with PMO [8-10]. Indeed, a recent Italian multicenter study indicated that comorbidities (the simultaneous presence of one or more health conditions in a patient with a defined index condition), assessed by generic and osteoporosis-specific instruments, may be just as important a contributor to reduced HRQoL as previous fractures [11]. Similarly, the presence of multi-morbidity (the simultaneous presence of multiple health conditions in a patient with no defined index condition [12]) is associated with poorer HRQoL [13, 14]. The number of morbidities that a person has increases with age [15]; hence, women with PMO are often subject to multiple challenges to HRQoL in addition to those directly resulting from osteoporosis-related events. Furthermore, older women at high risk of hip fracture may be concerned about falling and the potential consequences of a hip fracture [16]. They may therefore be concerned about performing their day-to-day activities, which could have a considerable impact on HRQoL [17].

The impact of comorbidities and fear of falling on health status in women with PMO has not been as widely studied as the effect of fractures. Bianchi and colleagues reported that pain

and depressed mood were associated with lower HRQoL in women with PMO. Their study excluded women with comorbidities likely to affect quality of life (e.g. cancer, renal insufficiency, chronic respiratory disease, uncontrolled hypertension and diabetes) [8]. We aimed to investigate the relationship between clinical characteristics, comorbidities, medical history, patient demographics and HRQoL in European and US women with PMO participating in the Prospective Observational Scientific Study Investigating Bone Loss Experience in Europe (POSSIBLE EU[®]) [18] and Prospective Observational Scientific Study Investigating Bone Loss Experience in the USA (POSSIBLE US[™]) [19].

Methods

Source data

POSSIBLE EU and POSSIBLE US are longitudinal cohort studies, for which methods and baseline data have previously been published [18, 19]. The similar designs of the studies allowed the data to be combined. Both studies assessed the use of bone loss treatment by postmenopausal women in primary care settings who were initiating or switching bone loss treatment, or who had been on such therapy for some time. Postmenopausal osteoporosis was defined as a need for antiosteoporosis medication in postmenopausal women. Women aged 18 years or older who had been postmenopausal for at least 1 year and who were receiving or about to receive treatment for bone loss were enrolled during a routine clinical visit to their general practitioner at 196 study sites in five European countries (France, Germany, Italy, Spain and the UK) and 134 sites in the USA. The following exclusion criteria were used: current or recent participation in other research studies; receiving experimental treatments; and presence of medical conditions that could impact on ability to participate in the study. Women receiving bone loss treatment other than hormone replacement therapy were assigned to one of three subgroups: inception (newly starting treatment); established (receiving bone loss treatment); and switch (receiving bone loss treatment, but switched at enrollment).

Physicians and sites were chosen for their willingness or ability to take part in the study and as being representative of their country with respect to a range of characteristics, including broad geographical region, urban/rural distribution, gender and size of practice. Patients were invited to participate in the study during routine clinical visits to their GPs.

Data were collected on patient demographics and clinical characteristics, comorbidities, HRQoL (patient-reported outcome) and treatment. Comorbidities were assessed using a list of 28 pre-specified conditions. HRQoL was measured using the EuroQol 5 Dimensions (EQ-5D[™])¹ instrument [20] and the Osteoporosis Assessment Questionnaire-Short Version (OPAQ-SV), an osteoporosis-specific instrument for quantifying health status [21]. EQ-5D health states were converted into health utility scores ranging from -0.594 to 1.0 (where 1.0 is full health and 0 is dead; negative scores are considered by the general population as being 'worse than death') using a set of weighted preferences produced from the UK and US general population samples by the time trade-off technique [22]. Data presented use weighted preferences from the UK general population samples.

Fear of falling was obtained from the OPAQ-SV. The 34-item OPAQ-SV has three dimensions (physical function, emotional status and back pain) [21]. A high score indicates better health status than a low score. Fear of falling, one of three domains from the emotional status dimension, is assessed from the answers to five questions scored between 0 and 100, with a low score representing a high perceived fear of falling (see Appendix) [21].

¹The EQ-5D-3L version was used in this study

Statistical analyses

Women who were recruited to the two studies and who completed the EQ-5D instrument at baseline were included in the analyses. The characteristics of included participants were described by the median and interquartile range for continuous measures and frequency for categorical measures. Analyses were performed using the SAS statistical software (version 9.2, SAS Institute, Cary, NC, USA) and the GNU R statistical package (R Development Core Team, <http://www.r-project.org>).

Model specification and validity

A limited number of clinically relevant patient characteristics that might explain observed differences in HRQoL among individuals were specified for inclusion as independent variables. These variables were selected *a priori* based on clinical knowledge, and were limited to reduce the potential for over-fitting (model optimism). They included age, body mass index (BMI), history of fractures, comorbidities, bone loss treatments (number and duration since initiation) and number of concomitant medications at enrollment (Table 1). The fear of falling OPAQ-SV domain was included as a candidate variable in an attempt to capture aspects of the patients' perspectives of osteoporosis risk. Assigned cohort was also included as a covariate in the model. No interactions were included in the model.

Multivariable models were developed initially on the POSSIBLE EU data set, then applied separately to the US data set and the combined EU and US data set when the US data became available. The model fit was good in all three data sets. Data presented are based on the combined data set.

Generalized mixed models were developed in which the health utility score for each patient was the response variable, and candidate variables were included using a stepwise backward selection process, for which the criterion for retention in the model was $\alpha=0.05$, using the general approach described by Harrell et al [23]. The model included cohort as a fixed effect and investigator sites as random effects. The functional form of continuous candidate variables that were statistically associated in univariate models was examined through a log transformation and, if that demonstrated a significantly better fit, a restricted cubic spline. More complex functional forms were included in the final model only when they provided a statistically significantly improved model fit, in order to minimize the risk of model optimism. Model fit was assessed using the Akaike Information Criterion, a penalized measure of residual likelihood [24]. To assess the degree of model optimism, and thus the risk of poor external validity, we used the internal bootstrap model validation process described by Harrell and colleagues [23], taking a value of less than 5% to indicate a model with acceptable fit. Additionally, we described the degree of residual covariance explained by the final model fit.

The extent of missing data for the included participants was described. The final statistical model was rerun using multiple imputation techniques to account for missing data. The model was developed according to a pre-specified statistical analysis plan.

Owing to the importance of the fear of falling score, and because this score is likely to be influenced by other patient characteristics, such as fracture history and comorbidities, we conducted further exploratory analyses to examine the extent to which our selected patient characteristic scores were associated with fear of falling, and developed a parsimonious model using the same methods as in the analyses of health utility scores.

Supportive analyses

We conducted supportive analyses to examine the extent to which model fit was sensitive to the choice of utility weights, replacing the EQ-5D score based on the UK weights with that derived from the US data [22, 25]. We assessed the relationship between health utility estimates based on the US and UK weights, and forced the final model derived from the UK weighted utility estimate onto the US weighted utility estimate and described model fit. Finally, we fitted the model directly onto the combined EU and US database. We conducted a further supportive analysis to examine the effect of country.

Results

Of 3,402 women providing data in POSSIBLE EU, HRQoL data were available for 3,011 (89%). Diagnosis of postmenopausal osteoporosis was obtained from dual energy X-ray absorptiometry (DEXA) (55% of patients, of whom 31% were osteopenic and 68% osteoporotic), X-ray (25%) and clinical history (11%). POSSIBLE US HRQoL data were available for 4,886 women of 5,015 recruited (97.4%), of whom 50% were osteopenic and 44% osteoporotic. There were no differences in fracture history and patient demographics among individuals with HRQoL data and those without. The characteristics of these 7,897 women are described in Table 1. There was considerable variability in HRQoL, with a median health utility score of 0.80 (mean 0.75) and an interquartile range of 0.69–1.00. Some patient responses resulted in negative scores.

Model specification and validity

The effects of each candidate explanatory variable on health utility scores in univariate models are shown in Table 2. Several candidate variables proved to be highly statistically significantly associated with utility outcome in the univariate setting. Models fitted for the candidate variable ‘age’ and ‘number of previous fractures’ were substantially better when the variables were log transformed, but because no further advantage was gained through fitting restricted cubic splines to these variables, the log-transformed variables were included in the model.

The final reduced multivariable model (Table 3) included assigned cohorts, investigator sites and the following variables: age (log-transformed), BMI, any previous vertebral fracture, number of ongoing comorbidities and fear of falling score. The following baseline comorbidities were also included: heart valve problems, hypertension, hyperlipidemia, congestive heart failure, asthma, chronic obstructive pulmonary disease, diabetes, lower gastrointestinal tract disorders, hyperparathyroidism, hyperthyroidism, depression, vision disorders and cancer. The final model explained 45.1% of the residual variance. On its own, the fear of falling score accounted for 35.7% of the residual variance. From the bootstrap internal validation process, the final model optimism was estimated to be 0.6%, indicating an acceptable degree of model fit.

For women with available health utility data, there were few missing data for the candidate explanatory variables. BMI data were missing for 1.4% of women, fear of falling score for 0.5% and total number of fractures for 0.1%. Re-analysis using multiple imputation according to our statistical analysis plan provided almost identical results to the model based on women with complete data.

To explore the implications of the model, we ran several simulations to provide estimated health utility scores (Table 4). For example, for a patient in the inception subgroup with median values for continuous variables (age 64 years, BMI 26.1 kg/m² and fear of falling score 65), no previous fractures and no ongoing comorbidities, predicted mean health utility would be 0.78. The predicted health utility would be reduced by 0.08 in a woman who has

experienced a vertebral fracture. If there was also a decrease in (i.e. worsening of) the fear of falling score to the 25th percentile value (score of 45), the predicted health utility would be further reduced by 0.10. Retaining these changes and adding six comorbidities, including depression, hypertension and diabetes, would further reduce predicted health utility by 0.26. For a patient in the switch cohort, all these values would be 0.034 higher, and for a patient in the established cohort, they would be 0.044 higher.

The results of the exploratory analyses of our selected patient characteristic scores indicated that age (log-transformed), BMI, number of previous fractures (log-transformed) and a history of hip or vertebral fracture were all strongly associated with fear of falling (Table 5).

Supportive analyses

Applying the US weights to the EQ-5D responses provided a new estimate of health utility for each patient. The mean US weighted health utility score was 0.81 and the median was 0.83. The minimum value was -0.11, the 25th percentile was 0.78, and both the 75th percentile and maximum value were 1.0. As expected, there was a very strong relationship between the UK and US health utility estimates. On average, the US health utility estimate was 4.1% higher than the UK health utility estimate (95% CI 3.8%, 4.4%; $p < 0.0001$). Applying the model derived from the UK health utility estimate to the US health utility estimates led to a similar overall model fit, and all model parameters remained statistically significant. The model forced onto the US health utility weights explained 46% of the residual variance, and the fear of falling score on its own accounted for 36% of the residual variance. Fitting the model onto the combined UK and US weights databases resulted in a model with virtually unchanged parameters.

When country was added to the final model, the country parameter estimates were highly statistically significant ($p < 0.0001$ across country stratum), but the main model parameter estimates and the degree of residual variance explained were essentially unchanged, indicating that there were systematic differences among patients in different countries that may reflect disease severity. European women on average had lower health utility than their US counterparts. Compared with US values, the mean health utility score was 10.6% lower in Italy (95% CI 8.1%, 13.1%), 6.7% lower in France (95% CI 4.3%, 9.0%), 6.3% lower in Germany (95% CI 4.1%, 8.6%), 4.1% lower in the UK (95% CI 1.8%, 6.3%) and 3.8% lower in Spain (95% CI 1.3%, 6.4%).

Discussion

This analysis of the HRQoL of women included in this large observational study demonstrated that patients with PMO have, on average, slightly lower health utility than the population norms (see Table 6) [25, 26]; this is particularly true of the initiation cohort. While there is a risk of more severe subjects being more prepared to join the study, this is to some degree mitigated by the design (noninterventional and based on chart review and patient-reported outcomes); even the population-based studies from which the norms are taken require subjects to consent and thus the norms may also be subject to the problem of non-response bias. Our findings confirm the results of previous research showing that patients with osteoporosis have lower HRQoL, the magnitude of the reduction varying according to fracture number and type [27]. Furthermore, our model is the first to explore how a range of clinical characteristics may contribute to this reduced HRQoL using a cross-sectional analysis of multinational individual patient data and societal valuations of health utility.

The model identified characteristics that may explain the heterogeneity of health utility scores in this sample, including some related to osteoporosis, such as fractures and fear of

falling, and others related to comorbidities. The inclusion of the total number of comorbidities per patient in the model, as well as each individual's specific comorbidities (e.g. angina and depression), was pre-specified in the analysis plan. The interplay of these variables made interpretation complex; most comorbidities appeared to be associated with improved quality of life unless the contribution of total comorbidity number was taken into account, so it was necessary to have information on multiple morbidities before the role of a specific condition could be assessed. For example, although it may seem paradoxical that a patient with cancer has a higher health utility than someone with the same number of comorbidities but without cancer, the explanation is due to the association between comorbidities. Thus, in the 375 individuals with cancer in this analysis, the median number of comorbidities was 3, and the maximum was 23. Comorbidities affected the model in two different respects: by their number (decreasing the score) and individually (each comorbidity slightly increasing the score, buffering the effect of comorbidity number). The person with 10 comorbidities would have a predicted health utility reduced by 10×0.047 , but would have it increased again if they have any of the comorbidities identified in the model apart from depression. This means that comorbidities affect HRQoL differently, because the number of comorbidities overestimates the decrease in HRQoL, whereas some individual comorbidities had less effect on the decrease than others. The only comorbidity that was individually associated with a reduction in health utility was depression, which was associated with a loss of 0.41 points on the average health utility scale, in addition to the reduction of 0.047 points associated with each comorbidity included. This demonstrates the major impact that depression can have on health utility compared with other comorbidities. Depression may be more common in patients with PMO than in those without the condition [28]. These findings also underline the importance of accounting for comorbidities by nature rather than simply by number (sum).

Fear of falling was strongly associated with a decreased HRQoL in our model, and could indicate a sense of infirmity in women. The size of the apparent effect of fear of falling was associated with the scaling of the domain, because the model provided a parameter estimate associated with a change of a single point. Our finding is in accordance with a previous study in older women, in which fear of falling (a health state generated from qualitative research and clinical opinion, rather than using the OPAQ-SV) was associated with a health utility of 0.67, derived using the time trade-off technique [16]. Fear of falling is specific to a limited number of conditions including osteoporosis. While generic instruments are not designed to capture it, a disease-targeted questionnaire is more appropriate to understand the consequences of osteoporosis. In a supplementary analysis, we showed that variables associated with fear of falling included objective data such as the number and type of fractures, as well as factors that increased the risk of falls such as advancing age and low BMI. Effective interventions to address fear of falling have not yet been demonstrated, but could provide an additional tool to increase HRQoL in women with PMO.

In our model, previous vertebral fracture had a strong impact on HRQoL, being associated with an 8% decrease in health utility. However, the number of previous fractures did not explain additional inter-patient variability in the final model. Owing to the fact that 165 of the 538 (30.7%) women who experienced a vertebral fracture also experienced at least one other fracture, it seems that the impact of vertebral fracture on HRQoL may, in part, reflect the number of previous fractures. In a review of health utility scores in patients with osteoporosis, Peasgood and colleagues showed that individuals who had previously experienced fractures (vertebral, hip and wrist fractures) had health utility scores broadly consistent with those from the present study, whereas the health utility scores for patients without fractures appeared to be somewhat better [29]. It is possible that population characteristics are driving the low scores in the population who have not experienced a fracture, as shown by some of the modeling exercises in this study.

In the final model, health utility scores increased with age (log-transformed) – younger patients in our analysis experienced a lower HRQoL than older patients, possibly because younger individuals have higher expectations. The nature of the log transformation indicated that the greatest effect of age on HRQoL was in the youngest age group. The non-linear impact of age on HRQoL, however, was relatively small compared with the effect of comorbidity, fear of falling and fractures, with an increase of less than 3% in health utility score for patients aged 73 (75th percentile inception subgroup) relative to those aged 56 years (25th percentile). BMI was also associated with a significant but relatively small change in HRQoL.

The statistical results of our model are illustrated in the simulations that we performed to show the cumulative result of combining key explanatory variables in one patient: for a woman in the inception subgroup, an increased fear of falling, a previous vertebral fracture and the presence of six comorbidities was associated with a reduction in mean health utility of 0.44, from 0.78 to 0.34. Women in the switch and established subgroups had a higher median health utility score (0.80 for both) than those in the inception subgroup (0.73), which is a substantial difference. Therefore, further interpretation of the role of other factors on health utility in women in POSSIBLE EU and POSSIBLE US should take account of the women's cohort by using the corresponding health utility estimate. The large impact of the assigned cohorts on HRQoL could be due to differences in disease duration and severity among the cohorts. We can also speculate that as women in the inception cohort are more likely to be newcomers to osteoporosis, they perceive it as threatening, while switch and established subgroups may be more familiar with their – mostly silent on average – condition. In addition, it is possible that women in the inception cohort have experienced a fracture more recently than those in other cohorts. Finally, the stability of the model, no matter which country set health utility weights were used (including those from the USA), shows that our findings have good generalizability.

Our study had some limitations. First, although the analysis was based on data from two large observational cohorts in the USA and Europe, and despite controlling for the effect of country in the statistical modeling, the findings cannot be fully extrapolated to all of Europe and the USA. This is because characteristics of healthcare systems or societies in countries not represented in the source studies may influence HRQoL; such characteristics could include the management of PMO, such as treatment delivery, and indices of social deprivation. Second, the statistical model includes a large number of variables, which increases the risk that identification of a contributing factor as significant might have been due only to chance. To limit this risk, the modeling was controlled for multiple testing (model optimism) by limiting the number of variables included and assessing the degree of model optimism; however, the model did not include interaction factors. Third, the EQ-5D has limitations, including a significant ceiling effect even in this elderly population [30]. Finally, this analysis was conducted on baseline data from POSSIBLE EU and POSSIBLE US, and modeling of cross-sectional data does not allow one to infer that the contributory factors we have identified have an impact. This will need further investigation using follow-up data. The cross-sectional approach provides clinicians with an indication of which factors may influence current health state and disease burden. Our findings raise the question of whether these determinants also predict future changes in HRQoL. Longitudinal data analysis will show whether the model is valid for predicting future health states, and could indicate whether interventions to ameliorate fear of falling are as good as drug interventions. If findings are confirmed, they can be used to advise women and improve their perception of the necessity to take treatment.

In conclusion, this analysis of HRQoL based on a large observational study including multinational data from women with various PMO treatment histories in Europe and the

USA at different stages of therapy shows a low health utility associated with the condition compared with the general population, with wide variability across the sample. This highlights the need to encourage stakeholders to pay attention to the impact of the disease and the importance of prevention. Through the use of a robust statistical model, we have shown that several factors, notably the patient's fear of falling, history of fracture and comorbidity burden, play a role in HRQoL in women with PMO.

Footnotes

F. Guillemin (corresponding author): Francis.Guillemin@univ-lorraine.fr, Tel: +33 3 83 68 35 12, Fax: +33 3 83 68 35 19

* Currently at Daichii-Sankyo Europe, Gerrards Cross, UK

Author contributions: N. Freemantle had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial disclosures: M. Gitlin, S. Shepherd and D. Macarios are employees of and may hold stock in Amgen; A. Marciniak was an employee of Amgen during the conduct of the study and manuscript preparation, and may hold stock in Amgen. S. Wade is an independent consultant contracted to Amgen.

Acknowledgments

Funding/support:

F. Guillemin has received funding for travel and consultancy from Amgen and GlaxoSmithKline, and research grants from Merck, Pfizer, sanofi-aventis and Expanscience.

M. Calvert has received funding for travel and consultancy from Amgen.

L. Martinez has received consulting fees or other remuneration from Amgen, sanofi-aventis, Pfizer, Roche, Novo Nordisk, Ipsen and Mayoly Spindler.

T.G. Ganiats has received funding for consultancy from Amgen.

R. Horne has received research funding from Amgen.

J. Pfeilschifter has received research grants from Roche Diagnostics and Merck Sharp & Dohme, is on the Speaker's bureau for Amgen, GlaxoSmithKline, Lilly Deutschland, Novartis, Roche and Merck Sharp & Dohme, and is an advisory board member for Amgen, Novartis and Roche.

A. Tosteson has received funding for consultancy from Amgen.

S. Wade has received funding for consultancy from Amgen.

N. Freemantle has received funding for research, travel and consulting from Amgen and for research and consulting from Pfizer and Eli Lilly.

Role of the sponsor: Both the POSSIBLE EU[®] and POSSIBLE US[™] studies were sponsored by Amgen Inc. Amgen (Europe) GmbH and GlaxoSmithKline sponsored the joint analysis for this paper. Editing support was provided by Bioscript Stirling Ltd and Oxford Pharmagenesis, funded by Amgen (Europe) GmbH and GlaxoSmithKline, and by Lucy Hyatt of Amgen (Europe) GmbH. Amgen and GlaxoSmithKline were given the opportunity to review the manuscript, but inclusion of their comments was at the discretion of the authors.

Appendix

Items in the OPAQ-SV fear of falling domain [21]

Questions

20.How often were you afraid that you would fall?

21. How often were you afraid that you would accidentally break or fracture a bone?
22. How often did you feel that you were losing balance?
23. How often did you use a hand rail or other support when walking up or down stairs?
24. How often did your fear of falling keep you from doing what you want to do?

Answer options

Always, Very often, Sometimes, Almost never, Never

References

1. Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, Rizzoli R. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int.* 2008; 19:399–428. [PubMed: 18266020]
2. Lips P, Cooper C, Agnusdei D, Caulin F, Egger P, Johnell O, Kanis JA, Kellingray S, Leplege A, Liberman UA, McCloskey E, Minne H, Reeve J, Reginster JY, Scholz M, Todd C, de Vernejoul MC, Wiklund I. Quality of life in patients with vertebral fractures: validation of the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO). Working Party for Quality of Life of the European Foundation for Osteoporosis. *Osteoporos Int.* 1999; 10:150–160. [PubMed: 10501796]
3. Adachi JD, Ioannidis G, Olszynski WP, Brown JP, Hanley DA, Sebaldt RJ, Petrie A, Tenenhouse A, Stephenson GF, Papaioannou A, Guyatt GH, Goldsmith CH. The impact of incident vertebral and non-vertebral fractures on health related quality of life in postmenopausal women. *BMC Musculoskelet Disord.* 2002; 3:11. [PubMed: 11967146]
4. Randell AG, Nguyen TV, Bhalerao N, Silverman SL, Sambrook PN, Eisman JA. Deterioration in quality of life following hip fracture: a prospective study. *Osteoporos Int.* 2000; 11:460–466. [PubMed: 10912850]
5. Oleksik A, Lips P, Dawson A, Minshall ME, Shen W, Cooper C, Kanis J. Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. *J Bone Miner Res.* 2000; 15:1384–1392. [PubMed: 10893688]
6. Silverman SL, Minshall ME, Shen W, Harper KD, Xie S. The relationship of health-related quality of life to prevalent and incident vertebral fractures in postmenopausal women with osteoporosis: results from the Multiple Outcomes of Raloxifene Evaluation Study. *Arthritis Rheum.* 2001; 44:2611–2619. [PubMed: 11710717]
7. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int.* 2006; 17:1726–1733. [PubMed: 16983459]
8. Bianchi ML, Orsini MR, Saraifogor S, Ortolani S, Radaelli G, Betti S. Quality of life in postmenopausal osteoporosis. *Health Qual Life Outcomes.* 2005; 3:78. [PubMed: 16321148]
9. Romagnoli E, Carnevale V, Nofroni I, D'Erasmo E, Paglia F, De Geronimo S, Pepe J, Rajejntroph N, Maranghi M, Minisola S. Quality of life in ambulatory postmenopausal women: the impact of reduced bone mineral density and subclinical vertebral fractures. *Osteoporos Int.* 2004; 15:975–980. [PubMed: 15118812]
10. Dhillon V, Hurst N, Hannan J, Nuki G. Association of low general health status, measured prospectively by EuroQol EQ5D, with osteoporosis, independent of a history of prior fracture. *Osteoporos Int.* 2005; 16:483–489. [PubMed: 15875094]
11. Salaffi F, Cimmino MA, Malavolta N, Carotti M, Di Matteo L, Scendoni P, Grassi W. The burden of prevalent fractures on health-related quality of life in postmenopausal women with osteoporosis: the IMOF study. *J Rheumatol.* 2007; 34:1551–1560. [PubMed: 17516618]
12. Starfield B. Threads and yarns: weaving the tapestry of comorbidity. *Ann Fam Med.* 2006; 4:101–103. [PubMed: 16569711]
13. Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes.* 2004; 2

14. Fortin M, Bravo G, Hudon C, Lapointe L, Almirall J, Dubois MF, Vanasse A. Relationship between multimorbidity and health-related quality of life of patients in primary care. *Qual Life Res.* 2006; 15:83–91. [PubMed: 16411033]
15. van den Akker M, Buntinx F, Metsemakers JF, Roos S, Knottnerus JA. Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. *J Clin Epidemiol.* 1998; 51:367–375. [PubMed: 9619963]
16. Salkeld G, Cameron ID, Cumming RG, Easter S, Seymour J, Kurrle SE, Quine S. Quality of life related to fear of falling and hip fracture in older women: a time trade off study. *BMJ.* 2000; 320:341–346. [PubMed: 10657327]
17. Suzuki M, Ohya N, Yamada K, Kanamori M. The relationship between fear of falling, activities of daily living and quality of life among elderly individuals. *Nurs Health Sci.* 2002; 4:155–161. [PubMed: 12406202]
18. Freemantle N, Cooper C, Roux C, Díez-Pérez A, Guillemin F, Jonsson B, Ortolani S, Pfeilschifter J, Horne R, Kakad S, Shepherd S, Möller G, Marciniak A, Martinez L. Baseline observations from the POSSIBLE EU study: characteristics of postmenopausal women receiving bone loss medications. *Arch Osteoporos.* 2010; 5:61–72. [PubMed: 21258637]
19. Barrett-Connor E, Ensrud K, Tosteson AN, Varon SF, Anthony M, Daizadeh N, Wade S. Design of the POSSIBLE US™ Study: postmenopausal women's compliance and persistence with osteoporosis medications. *Osteoporos Int.* 2009; 20:463–472. [PubMed: 18607669]
20. EuroQoL EQ-5D™; EuroQol Group. 2010 <http://www.euroqol.org/>.
21. Silverman SL. The Osteoporosis Assessment Questionnaire (OPAQ): a reliable and valid disease-targeted measure of health-related quality of life (HRQOL) in osteoporosis. *Qual Life Res.* 2000; 9:767–774.
22. Dolan P. Modeling valuations for EuroQol health states. *Med Care.* 1997; 35:1095–1108. [PubMed: 9366889]
23. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med.* 1996; 15:361–387. [PubMed: 8668867]
24. Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Contr.* 1974; 19:716–723.
25. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care.* 2005; 43:203–220. [PubMed: 15725977]
26. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. Discussion paper 172. York: University of York Centre for Health Economics. 1999 <http://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf>.
27. Lips P, van Schoor NM. Quality of life in patients with osteoporosis. *Osteoporos Int.* 2005; 16:447–455. [PubMed: 15609073]
28. Coelho R, Silva C, Maia A, Prata J, Barros H. Bone mineral density and depression: a community study in women. *J Psychosom Res.* 1999; 46:29–35. [PubMed: 10088979]
29. Peasgood T, Herrmann K, Kanis JA, Brazier JE. An updated systematic review of health state utility values for osteoporosis related conditions. *Osteoporos Int.* 2009; 20:853–868. [PubMed: 19271098]
30. Bharmal M, Thomas J 3rd. Comparing the EQ-5D and the SF-6D descriptive systems to assess their ceiling effects in the US general population. *Value Health.* 2006; 9:262–271. [PubMed: 16903996]

Table 1

Baseline characteristics for all patients with EQ-5D data

Selected demographic and clinical characteristics (continuous variables)	N	Median	25th, 75th percentile
Cohort			
Inception	2,951	–	–
Established	2,963	–	–
Switch	2,010	–	–
Age at baseline (years)	7,897	65.0	57.0, 73.0
Body mass index (kg/m ²)	7,786	25.6	22.8, 29.2
Number of ongoing comorbid conditions	7,897	2.0	1.0, 3.0
Number of unique bone loss medications before enrollment	7,897	1.0	1.0, 1.0
Number of unique concomitant medications taken at baseline	7,897	3.0	2.0, 5.0
Number of previous fractures	7,893	0.0	0.0, 1.0
Fear of falling score (0–100)	7,856	70.0	50.0, 85.0
Time since first recorded bone loss medication (months)	7,897	2.6	0.0, 33.1
EQ-5D score ^a	7,897	0.80	0.69, 1.00
Comorbidities and fractures (categorical variables)		n	%
Hypertension	7,897	3,411	43.2
Hyperlipidemia	7,897	2,991	37.9
Osteoarthritis	7,897	2,044	25.9
Depression	7,897	1,123	14.2
Vision impairment	7,897	797	10.1
Diabetes	7,897	619	7.8
Asthma	7,897	486	6.2
Lower gastrointestinal tract disorders	7,897	435	5.5
Chronic obstructive pulmonary disease	7,897	394	5.0
Cancer	7,897	375	4.8
Heart valve problems	7,897	334	4.2
Rheumatoid arthritis	7,897	324	4.1
Angina	7,897	257	3.3
Hyperthyroidism	7,897	216	2.7
Other inflammatory disorders	7,897	207	2.6
Thromboembolic diseases	7,897	180	2.3
Renal disease	7,897	138	1.8
Congestive heart failure	7,897	135	1.7

Selected demographic and clinical characteristics (continuous variables)	<i>N</i>	Median	25th, 75th percentile
Ulcers	7,897	111	1.4
Chronic liver disease	7,897	77	1.0
Coagulopathy	7,897	70	0.9
Seizure disorders	7,897	64	0.8
Hyperparathyroidism	7,897	51	0.7
Any fractures during adulthood	7,893	2,608	33.0
Any previous vertebral fractures	7,896	538	6.8
Any previous hip fractures	7,896	198	2.5

^aThe theoretical range of EuroQol 5 Dimensions (EQ-5D) scores is from −0.594 to 1.0

Table 2Effect of each candidate explanatory variable on health utility score from univariate analysis^a

Variable	Estimated change in health utility score (95% confidence limit)	p value
Age (log-transformed)	-0.177 (-0.215, -0.139)	<0.001
Body mass index	-0.007 (-0.008, -0.006)	<0.001
Number of comorbidities	-0.044 (-0.047, -0.040)	<0.001
Presence of comorbidity at baseline		
Angina	-0.109 (-0.139, -0.079)	<0.001
Chronic liver disease	-0.109 (-0.163, -0.054)	<0.001
Congestive heart failure	-0.083 (-0.124, -0.041)	<0.001
Chronic obstructive pulmonary disease	-0.076 (-0.101, -0.051)	<0.001
Depression	-0.135 (-0.151, -0.120)	<0.001
Diabetes	-0.073 (-0.093, -0.053)	<0.001
Hypertension	-0.051 (-0.062, -0.040)	<0.001
Lower gastrointestinal tract disorders	-0.048 (-0.072, -0.025)	<0.001
Osteoarthritis	-0.113 (-0.126, -0.100)	<0.001
Renal disease	-0.101 (-0.143, -0.060)	<0.001
Rheumatoid arthritis	-0.113 (-0.141, -0.084)	<0.001
Thromboembolic diseases	-0.103 (-0.139, -0.067)	<0.001
Ulcers	-0.124 (-0.169, -0.078)	<0.001
Other inflammatory disorders	-0.074 (-0.108, -0.040)	<0.001
Coagulopathy	-0.100 (-0.157, -0.043)	0.001
Asthma	-0.028 (-0.050, -0.005)	0.02
Hyperlipidemia	-0.013 (-0.024, -0.001)	0.03
Vision impairment	-0.024 (-0.046, -0.003)	0.03
Seizure disorders	-0.056 (-0.115, 0.003)	0.06
Heart valve problems	-0.011 (-0.038, 0.016)	0.42
Hyperthyroidism	-0.013 (-0.046, 0.021)	0.46
Hyperparathyroidism	-0.014 (-0.080, 0.053)	0.69
Cancer	-0.004 (-0.030, 0.021)	0.74
Number of different bone loss medications	-0.011 (-0.020, -0.003)	0.09
Time since first recorded bone loss medication (months)	0.000 (0.000, 0.000)	0.14
Number of ongoing concomitant medications at enrollment	-0.022 (-0.024, -0.020)	<0.001
Any fractures during adulthood	-0.052 (-0.064, -0.040)	<0.001
Number of previous fractures (log-transformed)	-0.064 (-0.077, -0.051)	<0.001
Any previous vertebral fracture	-0.138 (-0.160, -0.116)	<0.001
Any previous hip fracture	-0.092 (-0.126, -0.058)	<0.001
Fear of falling score	0.006 (0.005, 0.006)	<0.001

^aStudy cohort is included as a fixed effect and investigator sites as random effects

Table 3Final reduced multivariable model showing change in health utility score for each explanatory parameter^a

Effect	Estimate (95% confidence limit)	p value
Intercept	0.140 (−0.013, 0.293)	0.07
Cohort		
Inception	−0.044 (−0.054, −0.033)	<0.001
Switch	−0.010 (−0.021, 0.002)	0.09
Established	Ref	–
Age (log-transformed)	0.094 (0.059, 0.128)	<0.001
Body mass index	−0.002 (−0.003, −0.001)	<0.001
Any previous vertebral fracture	−0.079 (−0.097, −0.061)	<0.001
Number of ongoing comorbidities	−0.047 (−0.053, −0.042)	<0.001
Fear of Falling score	0.005 (0.005, 0.005)	<0.001
Heart valve problems	0.069 (0.046, 0.092)	<0.001
Hypertension	0.038 (0.026, 0.049)	<0.001
Hyperlipidemia	0.056 (0.044, 0.067)	<0.001
Congestive heart failure	0.090 (0.053, 0.126)	<0.001
Asthma	0.049 (0.029, 0.069)	<0.001
Chronic obstructive pulmonary disease	0.036 (0.014, 0.057)	0.001
Diabetes	0.030 (0.012, 0.048)	0.001
Lower gastrointestinal tract disorders	0.040 (0.019, 0.061)	<0.001
Hyperparathyroidism	0.071 (0.016, 0.127)	0.01
Hyperthyroidism	0.056 (0.028, 0.084)	<0.001
Depression	−0.041 (−0.055, −0.026)	<0.001
Vision disorders	0.058 (0.040, 0.076)	<0.001
Cancer	0.049 (0.027, 0.070)	<0.001

Cohort effect $p < 0.001$

Final model explains 45.1% of residual variance

Model optimism approximately 0.6% (signifies acceptable fit)

^aValues for inception and switch subgroups are contrasts relative to established cohort value. Investigator sites are included as random effects

Table 4

Simulations to illustrate effect of key variables on health utility scores (examples shown are for patients in Inception cohort)

Simulation number	Simulation scenario	Mean health utility score (95% confidence limit)
S1	Median values ^a from cohort (age 64 years, BMI 26.1 kg/m ² , fear of falling score 65) with no comorbidities and no previous fracture	0.78 (0.73, 0.82)
S2	S1 plus previous vertebral fracture	0.70 (0.65, 0.75)
S3	S2 plus Fear of Falling score of 45 (25th percentile)	0.60 (0.55, 0.65)
S4	S3 plus six comorbidities including depression, hypertension and diabetes	0.34 (0.29, 0.40)

^aRefers to the other input values in the model, which in each case follow the median observed in the data set *BMI* body mass index

Table 5Multivariable analysis of patient characteristics associated with fear of falling score^a

Effect	Estimate (95% confidence limit)	p value
Intercept	274.49 (259.71, 289.27)	<0.0001
Age, log-transformed (years)	-45.8534 (-49.3232, -42.3837)	<0.0001
Body mass index (kg/m ²)	-0.6778 (-0.7715, -0.5840)	<0.0001
Number of previous fractures, Log _e (1+n)	-7.0238 (-8.3382, -5.7094)	<0.0001
Hip fracture, yes/no	-8.5320 (-11.7217, -5.3424)	<0.0001
Vertebral fracture, yes/no	-4.7535 (-6.9051, -2.6018)	<0.0001

^aFear of falling score is derived from the answers to five questions scored between 0 and 100, with a low score indicating a high perceived fear of falling.

Table 6

Norms of EQ-5D_{index} for women by age, mean (standard deviation) [26] and comparable data from the current analysis of POSSIBLE EU and POSSIBLE US

Age (years)	N	EQ-5D norms	N	EQ-5D
45-54	267	0.85 (0.23)	1143	0.81 (0.23)
55-64	288	0.81 (0.26)	2638	0.78 (0.25)
65-74	260	0.78 (0.25)	2366	0.74 (0.26)
75	206	0.71 (0.27)	1686	0.67 (0.29)