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ORIGINAL ARTICLE

# Comparative statistical analysis of osteoporosis treatment based on Hungarian claims data and interpretation of the results in respect to cost-effectiveness

**P. Lakatos · E. Tóth · L. Szekeres · G. Poór · G. Héjj · I. Marton · I. Takács**

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**Abstract**
*Summary* The efficacy of interventions used in real life for the treatment of osteoporosis has not been evaluated on a national basis. We analysed the database of the single Hungarian health care provider between 2004 and 2010. A marked reduction in fracture incidence and hospitalization was seen, which also proved to be cost-effective.
*Introduction* Osteoporosis and its consequences place a significant burden on the health care systems of developed countries. Present therapeutic modalities are effective in reducing the risk of fractures caused by osteoporosis. However, we do not know whether the interventions introduced in the past 15 years have significantly reduced the number of osteoporotic fractures in real life, and if yes, how cost-effectively.
*Methods* The database of the National Health Insurance Fund Administration in Hungary was analysed for the period between 2004 and 2010. Two specific patient groups were identified within the population. Patients, who were under osteoporosis treatment in more than 80 % of the potential treatment days in three consecutive years (patients with high compliance), were compared with patients where this ratio was under 20 % (patients with low compliance). Several statistical comparative models were implemented in order to capture a complete picture on the differences. Because of natural data heterogeneity of administration databases, propensity matching was applied as well.
*Results* Comparing treated vs. control subjects, patients with high compliance showed a significant decrease in fracture risk and hospitalization, which was more robust after propensity adjustment. On the basis of the observed statistically significant differences, cost-effectiveness analysis was implemented. Utility loss due the observed fractures was compared with the total cost differences of the two arms based on modelling. Our calculations proved the cost-effectiveness of the long-term high compliance in real world settings.
*Conclusion* Our findings infer that the standardized and uniform health care of osteoporotic patients in a country may reduce general fracture incidence and hospitalization in a cost-effective way.

**Keywords** Cost-effectiveness · Fractures · Hospitalization · Osteoporosis · Treatment

P. Lakatos · I. Takács (✉)
1st Department of Medicine, Semmelweis University, Korányi u. 2/A, Budapest 1083, Hungary
e-mail: Takacs.Istvan@med.semmelweis-univ.hu

E. Tóth
Healthware Consulting Ltd, Budapest, Hungary

L. Szekeres · G. Poór · G. Héjj
National Institute of Rheumatology and Physiotherapy, Budapest, Hungary

I. Marton
Hungarian Society for Osteoporosis and Osteoarthrology, Budapest, Hungary

## Introduction

The ageing of society is a global phenomenon, which no longer challenges the health care and social security systems only of the countries with the most developed economies. As a result of the continuously increasing ratio of the aged population, the prevalence of several different illnesses has increased markedly [1]. These include osteoporosis, which at the same time also brings up serious problems of morbidity and mortality. Between the 1950s and 1980s, a fast increase in osteoporotic fracture incidence was seen in all countries. From the 1990s, stabilization and even a slight reduction were registered in some regions [2, 3]. However, remarkable fracture reduction in a whole country over longer period has not been published to date. According to some forecasts, in the next

30 years, the number of osteoporotic fractures will increase two or threefold, consequently resulting in the multiplication of treatment costs [4].

Over the past 10–15 years, the pharmaceutical treatment of osteoporosis has developed significantly, thanks to the effective medications introduced and approved for clinical practice, as proven by the results of several clinical studies [4–8]. However, treatment compliance remains a significant challenge in daily practice. Osteoporosis is often described as a "silent disease", since there are no clinically obvious signs or symptoms characterizing substantial parts of the progression pathway. This factor notably affects the patients' attitude for adherence and for that reason, changes in the treatment context, e.g. reimbursement rate could have significant effect on therapeutic outcomes. Attributes of medication highlight the importance of patient's adherence as well, since the effects of treatment evolve after a longer period, which result in early dropouts as sunk cost in treatment reimbursement.

Hungary has a special place among the countries in Europe, as its social insurance system comprises a single fund, the National Health Insurance Fund Administration (NHIFA). As a result, 99 % of the country's population is registered in a unified, homogenous database. However, the entire population is subject to a standard treatment—and health care model, with diagnostic work also being performed along the lines of standard professional criteria in the various osteoporosis centres. This makes possible the long-term monitoring of large, homogenous patient groups.

In the present study, we performed an analysis of the NHIFA database, with the objective of examining long-term osteoporosis treatment efficacy in comparison to early dropouts in a real-world setting. The results of our research will help the evaluation of system performance as well as the identification of the intervention point with the best benefit/expenditure ratio.

## Methods

### NHIFA data management

The objective of our research was to collect information on the osteoporotic population in Hungary from the database maintained by the NHIFA. Thanks to the data made available in a time series, it was possible to describe temporal trends.

The research is based on the financing data registered at NHIFA. Our work was performed in the context of a data request cooperation arrangement, in the course of which analytic definitions specified with the assistance of experts directly triggered inquiries among the available data, for which we employed the help of NHIFA. The scope of NHIFA data analysis covered the comprehensive health insurance treatment records (redemption of prescriptions for medicine and medical appliances, in and outpatient treatments) of in and outpatients registered in the period analysed (which is between 1 January 2004 and 31 December 2010), under the International Statistical Classification of Diseases and Related Health Problems (ICD) codes for osteoporosis (M80-82) as a primary or secondary diagnosis or as having perused osteopathic therapy. A social security number can be assigned to the various treatments in all instances, which makes it possible to follow the full life cycle of patients and to avoid double counting; consequently, in our paper, we always specified distinct patient numbers. Accuracy of the information used in the analysis was preliminary validated through published sources, like epidemiology studies regarding fracture occurrence.

### Definitions

#### *Patients*

*Hungarian osteoporosis population* We have considered those patients as suffering from osteoporosis who were treated at least once during the period analysed as in or outpatients under one of the ICD codes for osteoporosis or have redeemed osteoporotic treatment (bisphosphonates—oral and parenteral, strontium ranelate, teriparatide, raloxifene) on at least two occasions. In addition, according to our classification, all women having had an osteoporotic fracture at the age of 60+ were also placed in this patient category.

*Analysis population* Hungarian osteoporotic patients were narrowed down for the analysis of the effects of long-term treatment. Patients having started osteoporotic therapy between 01.01.2006 and 31.12.2007 were eligible for inclusion with at least 3 year's follow-up data. Inclusion criteria allow us to have a 2-year baseline period for each patient to describe their osteoporotic status. Patients who died within the period of analysis were excluded.

The analysis population consisted of two different subpopulations according to how long they received osteoporosis treatment. Those patients were considered with high compliance who were under osteoporosis treatment in more than 80 % of the potential treatment days in three consecutive years (i.e. where the so-called MPR—medication possession ratio—was higher than 0.8). In the control arm, those patients were classified whose value was under 20 %, so after treatment initiation there was a constant dropout from osteoporosis therapy. The comparison of two extreme subgroups aimed to highlight remarkable differences of outcomes with high MPR against low MPR. We may have measured a marginal effect of a one-unit increase in MPR as a continuous variable but our purpose was to underline the benefit of outstanding MPR> 80 %. The results may reveal the importance of achieving high MPR in osteoporosis treatments.

*Clinical outcomes*

*Fractures* Fractures were considered as the main clinical outcome. Inpatient and outpatient services of the NHIFA database were analysed to identify fracture-related health services based on ICD codes (M48, M84, S12, S22, S32, S42, S52, S62, S72, S82, T08, T14). The main types of osteoporotic fractures (femur, hip, wrist, spine, other) were differentiated assuming maximum one occurrence per year for every type. This represents a conservative approach, as ignoring multiple fractures may result in an underestimation of actual occurrences. Fractures were captured as a total number of events regardless of type and also for groups of the classical osteoporotic sites (spine, hip, wrist, all other).

*Hospitalization* Fracture-related hospitalization was defined to estimate the occurrence of serious fractures. The ICD codes of fractures were searched under the main diagnosis of active hospitalization event. Data accuracy is guaranteed by the internal verification process of NHIFA before payment of the accomplished services.

*Costs* All available patient records (medications and medical appliances, in and outpatient care, diagnostics, lab) of NHIFA were processed for the analysis of fracture costs (exchange rate 230 HUF/USD). By filtering for ICD codes of osteoporosis and fractures listed earlier, we used the individual patient records of health services for calculation in the arms compared. In the case of medical appliances, we calculated with the items to be used in the course of rehabilitation after a fracture (physical medicine prosthetic devices). Medication for pain management (analgesics) and best supportive care (calcium and vitamin D) was considered relevant as well. The cost of medications was calculated at their reimbursement value to capture direct costs from the perspective of the financer.

Methodology

*Descriptive analysis*

The simple identification of the patients and events fitting our definition constituted the outcome of the exploratory phase of our work. Patients included in statistical comparison were characterized by the occurrence of fractures and the costs of health care biannually after the index date of the analysis for a 3-year time horizon. Relative risk for patients with high compliance compared to the patients with low compliance was calculated for the total analysis period (3 years) and biannually as well, for clinical and cost outcomes.

*Statistical comparison*

Statistical comparison was implemented on the raw data to determine relative risks for the total analysis period (3 years) and biannually as well, for clinical and cost outcomes.

Interruption of osteoporosis therapy is accompanied by several factors, resulting in differences between the analysis arms. In order to identify the causal differences between the arms, we provided a propensity analysis based on a 2-year time period before starting the analysis.

*Propensity modelling* The clinical background (demographic data, disease and therapeutic antecedents, associated diseases) of the patients in the therapeutic arms impacts the happenings of the period after the baseline, regardless of the therapeutic arm. The comparison of the raw data of therapeutic arms can show such relations, whose casual interpretation cannot be justified clearly (for instance, the statistically significant difference between the therapeutic arms of single outcome variables can be caused not only by the different therapy—but also by the different patient composition of the two arms). Therefore, the patients of the two arms are compared by the propensity method [9], whereby the bias caused by different patient composition can be reduced and the different effect of the therapies can be measured with reduced bias for known variables [10, 11]. During propensity modelling, the variables prior to the baseline are used (Table 1). The goodness of fit of the propensity model had been verified before the adjusted results were used. The propensity score was stratified into quintiles. There were a sufficient number of patients of each arm in each quintile. For each covariate recorded before the baseline period, we tested the propensity-adjusted difference between the means of the compliant and noncompliant arms by ANOVA. Propensity score adjustments were made by including propensity quintiles as an additional factor in the ANOVA models. No significant differences were detected at the 5 % significance level. It means that the differences of covariates between the two arms recorded before the baseline period were eliminated by propensity score adjustment.

Difference was estimated in the whole analysis period and biannually in the case of fractures and hospitalization. Different models were used for sensitivity analysis; these scenarios will be presented as well.

*ANOVA tests* The significance of the differences studied during the analysis period was investigated by ANOVA models with and without propensity quintile adjustment. Type I error was set to 5 %.

*Cox proportional hazard model* The occurrence of different fractures and hospital care were analysed with the Cox proportional hazard model [12, 13]. The Cox regression, alias Cox proportional hazard model, based on the assumption that

**Table 1** Baseline characteristics in last half year before follow-up period

| Propensity adjustment factors | Average per one patient[a] | |
|---|---|---|
| | Active | Control |
| Patient older than 70 years | 53 % | 50 % |
| Total fractures (any type of fracture) | 0.0462 | 0.0366 |
| Days of hospitalization | 0.1475 | 0.0718 |
| Number of hospitalization | 0.0198 | 0.0114 |
| DEXA bone density scans | 0.5681 | 0.4255 |
| Usage of medical devices | 3.00 % | 2.07 % |
| Visits in outpatient care | 1.4091 | 0.9471 |
| Days of treatment on painkillers | 1.4915 | 1.8596 |
| MPR of other not osteoporosis treatment | 0.2603 | 0.1938 |
| MPR of painkillers | 0.008 | 0.0099 |
| Mean costs of other treatment | 23.40 USD | 18.45 USD |
| Mean costs of all medical care for fractures | 25.73 USD | 14.36 USD |
| Mean costs of medical devices | 0.94 USD | 0.58 USD |

[a] Average per one patient calculated by total number of patients on compared arms

the so-called hazard-function (instantaneous risk) can be specified by the product of one follow-up period dependent factor and the exponential function of the explanatory variables. The outcome of this model is the RR value, which shows relative risk, which is a ratio that compares the risk of the event in the compliant arm to the risk of the event in the noncompliant arm.

*Repeated-measure Poisson regression with subject-specific random effect* The frequency of events is generally modelled with the Poisson regression. Examples of such events are numbers of fractures, hospitalizations or deaths within a fixed time interval. However, Poisson regression models assume perfectly homogeneous data. The heterogeneity of patients can lead to overdispersion in statistical models, which can be identified through the relationship of mean and variance. The Poisson regression has a strict condition of equality of mean and variance. In the case of overdispersion, the estimated confidence intervals of the Poisson regression are unrealistically shortened. Heterogeneity of fractures in the dataset means, e.g. volatile circumstances, such as osteoporosis treatments. We may control overdispersion caused by heterogeneity by repeated-measure Poisson regression with subject-specific random effect including subject-specific random terms in the model [10].

We modelled the frequencies of fractures, hospitalizations and deaths of patients within a fixed time period with repeated-measure Poisson regression, including subject-specific random intercept.

Denoting the expected number of events by $\mu_{it}$ for patient $i$ repeatedly at each time point $t$, the functional relationship expressed by this model is $\log(\mu_{it})=u_i+X_t\beta_t$, where $u_i$ is a random intercept that depends on patient $i$ but does not depend on time $t$, and $X_t\beta_t$ are fixed (i.e. nonrandom) effects of possibly time-dependent covariates [10]. The model usually contains covariates that do not depend on time, e.g. gender, age at the onset of treatment, propensity quintiles etc.

*Generalized linear model* During the comparison of the cost variables, the generalized linear model was built assuming Gamma distribution and applying a logarithmic link function. Thus, the estimates of the coefficients of the comparison can be interpreted only on a logarithmic scale and the adjusted differences are presented by transformation with an exponential function [10]. The bias caused by the different patient compositions of the two arms was eliminated by propensity score adjustment.

*Cost-effectiveness analysis*

In the cost-effectiveness analysis, the risk of fractures and social insurance spending in the two groups of patients were reviewed. We determined the total loss of health incurred as a result of nonfatal fractures and specified the total cost thereof.

Loss of health related to fractures was expressed in quality-adjusted life years (QALY), using international efficiency measurement publications as our sources [14, 15]. These values were adapted for Hungarian normal population tariffs on the basis of national survey [16] and published method for calculating QALY [17]. In the international papers cases, the disutility was determined with the EQ-5D method, the most widely accepted measurement tool. These values represent data accepted at European level and have previously served as input data for several Hungarian and international cost-effectiveness analysis publications. In Table 2, we present the utility values taken into account in our calculation. The definition of costs was the same as presented in the section on cost analysis.

## Results

Descriptive data of the Hungarian osteoporosis population

Inclusion criteria of the Hungarian osteoporosis population identified a potential of 1,000,000 female patients. Taking yearly prevalence into account, we can estimate approximately 300,000 patients treated per year. Previous studies showed approximately 50,000–80,000 fractures per year for the whole population (excluding vertebral fractures). In our study, those patients were excluded whose MPR value of osteoporosis treatment was higher than 20 % and lower than 80 %.

**Table 2** Disutility of fractures

| Type of fracture | Distribution in the analysis (%) | Disutility in the 1st year | Disutility in the 2nd year | Source |
|---|---|---|---|---|
| Femur | 3.83 | 0.074 | 0.023 | [14] |
| Hip | 18.95 | 0.232 | 0.156 | [15] |
| Wrist | 34.10 | 0.041 | | [15] |
| Other fractures | 29.94 | 0.074 | 0.023 | [14] |
| Spine | 9.43 | 0.234 | 0.652 | [14] |
| Tibia | 3.75 | 0.074 | 0.023 | [14] |

Descriptive and comparative data of the analysis population

In the compliant arm, there were 8,636 patients based on the definition above, 53 % of whom were over 70 years of age. Patients (17,084) were classified in the control arm, where 50 % of the patients were over 70 years old. Detailed baseline characteristic of the population is presented in Table 1. The number of noncompliant and compliant patients is much less than the overall osteoporotic population because the hypothesis refer to extreme subgroups and we had to limit the baseline selection period to 3 years of follow-up and 2 years of retrospective period.

In last half-year before follow-up period, there were 399 fractures in the compliant arm and 626 fractures in the noncompliant arm meaning 0.046 fracture per patient (compliant) and 0.037 fracture per patient (noncompliant), respectively.

*Occurrence of clinical outcomes*

Defined clinical outcomes occurrence is presented for the 3-year observation period for the compared patient subgroups in Tables 3 and 4. Numbers per arms represent the number of patients concerned with the type of events at any time during the analysis period. These data were compared using the Cox model to estimate relative risks. The raw RR derived from the Cox model without propensity adjustment. There were significant differences identified in fractures and hospitalization; however, the statistical inference of relative risks for subgroups of fractures was not conclusive due to the low number of events. Despite the relatively low numbers of occurrence, hip fractures occurred significantly less frequently in patients treated permanently (compliant subgroup) compared to the control subgroup. As hip fracture is the most progressive site of the relevant types, this outcome has a crucial importance if we consider the fact that fatal fractures were excluded from our analysis.

*Sum of fractures (events)*

The total number of fractures was determined biannually after the first prescription of medication. Raw estimation for difference of average fracture per patient for the compared arms was calculated with two sample *t* tests (Welch tests). Results are presented in Table 5. Despite the clear differences in the rate of fractures per patients, raw estimation of the mean difference showed significance only in the last year of the observation. In this case, the bias caused by censoring was negligible owing to the definition of the two arms (e.g. patients who died in the analysis period were excluded).

*Hospitalization (events)*

The total number of fracture-related hospitalizations was determined biannually after the first prescription of medication. Raw estimation for difference of average fracture-related hospitalization per patient for the compared arms was calculated using two sample *t* tests (Welch tests). Results are presented in Table 6. Similarly to the fractures, despite the clear differences in the rate per patients, raw estimation showed significance only in the last year of the observation.

**Table 3** Relative risk of events without propensity adjustment

| Type of event | Active | Control | Raw RR | *p* value |
|---|---|---|---|---|
| Total fractures (any type of fracture) | 847 | 1936 | 0.8742 | 0.0047* |
| Spine fractures | 90 | 201 | 0.9489 | 0.7199 |
| Hip fractures | 115 | 380 | 0.5538 | 0.0000* |
| Wrist fractures | 430 | 887 | 0.9640 | 0.5883 |
| Other fractures | 296 | 690 | 0.8823 | 0.1188 |
| Fracture-related hospitalization | 443 | 929 | 0.7200 | 0.0000* |

*Significant $p<0.05$

**Table 4** Relative risk of events after propensity adjustment

| First event | Raw RR (CI) | *p* value | Adjusted RR (CI) | *p* value |
|---|---|---|---|---|
| Total fractures (any type of fracture) | 0.8742 (0.80–0.96) | 0.0047* | 0.7931 (0.72–0.87) | 0.0000* |
| Spine fractures | 0.9489 (0.71–1.26) | 0.7199 | 0.8974 (0.67–1.21) | 0.4746 |
| Hip fractures | 0.5538 (0.43–0.72) | 0.0000* | 0.4850 (0.37–0.63) | 0.0000* |
| Wrist fractures | 0.9640 (0.84–1.10) | 0.5883 | 0.8698 (0.76–1.00) | 0.0448* |
| Other fractures | 0.8823 (0.75–1.03) | 0.1188 | 0.8046 (0.68–0.95) | 0.0087* |
| Fracture-related hospitalization | 0.7200 (0.62–0.84) | 0.0000* | 0.6306 (0.54–0.74) | 0.0000* |

*Significant $p<0.05$

*Cost of fractures*

The cost of fractures was determined biannually after the first prescription of medication. Average costs per patient are presented in USD. The raw ratio of average expenditure per affected patient (patients with no costs are excluded) for the compared arms was calculated with the Gamma GLM model without propensity adjustment, as presented in Table 7. After the first half year, the cost of fractures was significantly lower for the compliant arm despite the descriptive data, which is explained by the exclusion of patients without fracture-related services (in the first half year, the raw ratio is not significant ($p>0.1$).

Comparative analysis with propensity

*Analysis of time to events*

Time-to-event risk estimation for the whole period is analysed by the Cox model. Estimation without propensity showed benefits in the compliant arm, but the differences appeared to be nonsignificant for spine, wrist and other fractures. After propensity adjustment (Table 4), the advantages further improved for constant therapy on a 3-year horizon. Spine fracture differences remained nonsignificant, but other outcomes became significantly different.

*Analysis of fractures*

Estimation on the whole period showed 0.79 relative risk for the first fracture in the compliant arm in comparison with the noncompliant arm, according to the Cox modelling. Different scenarios were modelled on the basis of changes in the starting point of analysis. Relative risk estimates based on Poisson regression showed increasing benefit after a longer time on osteoporotic treatment—Table 8. Modelling after 1.5 years of constant treatment, the risk of fracture is almost 30 % lower than in the control arm.

Repeated Poisson regression was used to compare fracture occurrences biannually to reflect disease progression. Results are presented in Table 9. Model estimates adjusted RR for the compliant arm in comparison to patients of the noncompliant group. Descriptive statistics gave similar tendencies to the raw estimation, but after propensity score adjustment, the benefit on the compliant arm increased. Estimation showed higher differences after the propensity score adjustment presented in the last two columns of Table 9.

The adjusted mean difference is based on adjusted RR. In the first place, the raw average of fractures in the control arm was multiplied by adjusted RR; thereafter, this has become the adjusted average of fractures in the compliant arm. This compliant arm is theoretical; it is not the original compliant arm. The adjusted mean difference is the difference between the

**Table 5** Raw difference for fractures from the ANOVA model without propensity adjustment

| Period | Active | Control | Difference | *p* value |
|---|---|---|---|---|
| 1st half year | 178 (2.06 %) | 319 (1.87 %) | 0.0019 | 0.3202 |
| 2nd half year | 165 (1.91 %) | 315 (1.84 %) | 0.0007 | 0.7356 |
| 3rd half year | 141 (1.63 %) | 303 (1.77 %) | −0.0014 | 0.4689 |
| 4th half year | 130 (1.51 %) | 307 (1.80 %) | −0.0029 | 0.1187 |
| 5th half year | 112 (1.30 %) | 332 (1.94 %) | −0.0065 | 0.0007* |
| 6th half year | 132 (1.53 %) | 331 (1.94 %) | −0.0041 | 0.0304* |
| SUM | 858 | 1907 | | |

*Significant $p<0.05$

**Table 6** Raw difference for hospitalization events from the ANOVA model without propensity adjustment

| Period | Active | Control | Difference | *p* value |
|---|---|---|---|---|
| 1st half year | 60 | 130 | −0.0007 | 0.6172 |
| 2nd half year | 52 | 107 | −0.0002 | 0.8355 |
| 3rd half year | 43 | 118 | −0.0019 | 0.1418 |
| 4th half year | 46 | 128 | −0.0022 | 0.1020 |
| 5th half year | 34 | 167 | −0.0058 | 0.0000* |
| 6th half year | 44 | 159 | −0.0042 | 0.0020* |
| SUM | 279 | 809 | | |

*Significant $p<0.05$

**Table 7** Adjusted ratio of total cost of fractures based on Gamma GLM with propensity adjustment. Raw ratio based on the Gamma GLM model without propensity adjustment

| Period | All patients | | Affected patients | | Raw ratio | *p* value |
|---|---|---|---|---|---|---|
| | Active (USD) | Control (USD) | Active (USD) | Control (USD) | | |
| 1st half year | 37.83 | 33.58 | 267.90 | 371.57 | 1.0829 | 0.1355 |
| 2nd half year | 32.58 | 26.83 | 197.31 | 326.12 | 0.8359 | 0.0010* |
| 3rd half year | 28.33 | 24.40 | 368.65 | 372.30 | 0.8047 | 0.0003* |
| 4th half year | 28.44 | 23.72 | 332.35 | 423.44 | 0.8529 | 0.0178* |
| 5th half year | 23.91 | 25.47 | 183.91 | 302.00 | 0.7000 | 0.0000* |
| 6th half year | 24.50 | 25.01 | 221.20 | 286.70 | 0.7219 | 0.0000* |
| SUM | 175.59 | 159.01 | 1,571.32 | 2,082.14 | | |

*Significant $p<0.05$

raw average and the adjusted average of fractures in the original control arm. Adjusted mean difference confirmed the beneficial effect of constant osteoporosis treatment. After 2 years of therapy, relative risks showed significant reductions of a clinically considerable magnitude and comparable to clinical evidence.

*Analysis of hospitalization*

Estimation on the whole period showed 0.63 relative risk for the first fracture-related hospitalization in the compliant arm in comparison with the noncompliant arm, according to the Cox modelling. Different scenarios were modelled on the basis of changes in the starting point of analysis. Results in Table 10 showed similar patterns; depending on the length of compliance, health benefits are increasing.

The presence of heterogeneity affects estimation for hospitalization events as well. The extent of changes appears to be greater than in the case of fractures, since the estimated confidence intervals are broader.

With repeated Poisson regression, risks were compared biannually to reflect disease progression. Results in Table 11 showed similar tendencies to the raw estimation, but after the adjustment, the benefit in the compliant arm decreased. This means that biannual risks are lower for the compliant arm, but propensity affects lowering these benefits.

*Analysis of fracture-related costs*

Modelling of fracture-related costs with propensity score adjustment resulted in lower relative risks for constant osteoporosis treatment. The adjusted ratio of average for the compared arms was calculated with the Gamma GLM model with propensity score adjustment. Results are presented in Table 12.

Cost-effectiveness analysis

On the basis of Table 8, 0.0722 fractures occurred per patient in the compliant arm during the analysis period, while 0.0929 events are calculated for the noncompliant arm. It resulted in a 0.0207 event-per-patient difference.

Calculating with the distribution of the different types of fractures, a weighted average disutility of 0.2075 was determined per event in our analysis based on the values in Table 2.

The total cost of fractures is presented in Table 7 for each modelling arm. On the basis of the GLM model, approximately 350 USD savings can be realized by osteoporosis therapy. If we calculated the therapeutic costs on the basis of the trade data published by NHIFA, we can determine the needed expenditure to achieve these savings. A weighted average daily cost of 0.6 USD results in a total cost of 531.7 USD taking into account 80 % MPR on treatment. The cost of

**Table 8** Relative risk for fractures after propensity adjustment (active vs control arm)

| Model | Follow-up | RR | Confidence interval | | *p* value |
|---|---|---|---|---|---|
| | | | Lower limit | Upper limit | |
| Poisson regression | From 1st half year | 0.8025 | 0.7386 | 0.8720 | 0.0000* |
| | From 2nd half year | 0.7716 | 0.7035 | 0.8464 | 0.0000* |
| | From 3rd half year | 0.7348 | 0.6613 | 0.8165 | 0.0000* |

*Significant $p<0.05$

**Table 9** Biannual relative risk for fractures after propensity score adjustment

| Period | Adjusted RR | *p* value | Control | Active | Adjusted mean difference | Raw mean difference |
|---|---|---|---|---|---|---|
| 1st half year | | 0.3202 | | | | 0.0019 |
| 2nd half year | 0.9439 | 0.7356 | 0.0184 | 0.0174 | −0.0010 | 0.0007 |
| 3rd half year | 0.8066 | 0.4689 | 0.0177 | 0.0143 | −0.0034 | −0.0014 |
| 4th half year | 0.7437 | 0.1187 | 0.0180 | 0.0134 | −0.0046 | −0.0029 |
| 5th half year | 0.6407* | 0.0007* | 0.0194 | 0.0125 | −0.0070 | −0.0065 |
| 6th half year | 0.7551* | 0.0304* | 0.0194 | 0.0146 | −0.0047 | −0.0041 |

*Significant $p<0.05$

osteoporosis treatment for the control arm was 51 USD, which showed lower than 8 % MPR in the whole analysis.

If we compare the total costs and health outcomes, we can see an incremental cost-effectiveness ratio (ICER) of 28,158 USD (incremental cost of 121 USD and a 0.0043 utility gain for the compliant arm).

## Discussion

Hungary with its 10 million inhabitants is considered a middle-sized country. Approximately 300,000 osteoporotic patients are diagnosed and treated by standardized protocols. Their drug consumption, fracture incidence and hospitalization data are kept in a uniform database due to the general health care system and single insurance company model. Thus, our results reflect representative changes in response to osteoporosis treatment in a homogenous population of a 10 million country.

In the 7-year period we studied, the number of osteoporotic fractures were reduced by 46 % (from an annual 88,290 to 47,747) and hip fracture incidence decreased by 37.5 % (from 17,992 to 11,242/year) in Hungary. This reduction rate was also seen when the number of fractures was standardized to the number of patients treated. This reduction in fracture incidence can be demonstrated in the Hungarian osteoporotic population despite the fact that the expected life span increased by 2.5 years during the 7 years of the study period.

The number of osteoporotic fractures varies between broad limits worldwide [18, 19]. Hungarian fracture data are similar to the ones in the neighbouring countries [18]. However, the direction of changes is quite the opposite. In the neighbouring Austria, a steady increase in hip fracture incidence was demonstrated between 1994 and 2006 [20]. Based on the Austrian hospital discharge register, hip fracture incidence was increased by 13 % in the elderly population over a 12-year study period. A 16 % increase was shown in Romania between 2005 and 2009 as well [21]. Total fracture reduction in a country of that magnitude over a 7-year period as demonstrated in our case has not been published to date. The explanation of this significant reduction is not completely clear. Improving adherence would be a reasonable solution [22] but the figures from a smaller pilot research show that the rate of adherence (54 % among women) in the country is not outstanding and has not changed considerably during the studied period in Hungary [23]. One-year persistence among all osteoporosis medicines was 32 %, with 2- and 3-year persistence results only amounting to 18 and 13 %, respectively [23]. These results are similar to those measured in France [24] and in the USA [25], but lag behind Swedish rates [22]. Therefore, the observed reduction in bone fracture must be due to other factors than changes in adherence or persistence. At least part of this achievement might probably be attributed to the efficient work of the Hungarian osteoporosis network. Other causative factors may be the uniform nature of the healthcare service or the excessive number of treated patients. The number of treated osteoporotic patients changed between 70,000

**Table 10** Relative risk for hospitalization after propensity adjustment

| Model | Follow-up | RR | Confidence interval | | *p* value |
|---|---|---|---|---|---|
| | | | Lower limit | Upper limit | |
| Poisson regression | From 1st half year | 0.8146 | 0.7245 | 0.9158 | 0.0006* |
| | From 2nd half year | 0.7707 | 0.6756 | 0.8792 | 0.0001* |
| | From 3rd half year | 0.7282 | 0.6286 | 0.8436 | 0.0000* |

*Significant $p<0.05$

**Table 11** Biannual relative risk for hospitalization after propensity score adjustment

| Period | Adjusted RR | *p* value | Control | Active | Adjusted mean difference | Raw mean difference |
|---|---|---|---|---|---|---|
| 1st half year | | 0.6172 | | | | −0.0007 |
| 2nd half year | 0.9569 | 0.8355 | 0.0063 | 0.0060 | −0.0003 | −0.0002 |
| 3rd half year | 0.8108 | 0.1418 | 0.0069 | 0.0056 | −0.0013 | −0.0019 |
| 4th half year | 0.9437 | 0.1020 | 0.0075 | 0.0071 | −0.0004 | −0.0022 |
| 5th half year | 0.8506* | 0.0000* | 0.0098 | 0.0083 | −0.0015 | −0.0058 |
| 6th half year | 0.9437* | 0.0020* | 0.0093 | 0.0088 | −0.0005 | −0.0042 |

and 150,000 during this period (data on file). Considering these numbers, we could assume that a growing number of patients during the observed term received effective treatment for longer or shorter period of time.

To determine the efficacy of treatment, we not only estimated the changes in fracture incidence but also examined the outcomes of the high-compliance (MPR>80 %) vs low-compliance (MPR<20 %) population in time. Patients on active treatment for 3 years suffered fewer fractures, including hip fracture as well, and needed less hospitalization compared to nontreated osteoporotic patients. The raw estimation did not see significant difference in vertebral and wrist fractures; however, after propensity adjustment, only vertebral fractures remained insignificant. This could partly be explained by the fact that vertebral fractures might be frequently hidden without appropriate radiological work-up [26].

After 3 years of active treatment, the risk of all fractures decreased by 23 %, the risk of hip fracture was reduced by 55 % and fracture-related hospitalization was also lower by 38 % compared to the nontreated group. Ross et al. [27] have demonstrated similar data in a meta-analysis including mostly retrospective data published between 1998 and 2007. They demonstrated that bad compliance increases fracture incidence by 30 % in osteoporotic patients. Olsen et al. [28] have found smaller reduction after a 2-year treatment based on Danish data; however, the definition of low MPR level was set higher than in our study. In the group exhibiting an MPR> 80 %, the risk of all fractures decreased by 21 %, while that of hip fracture was reduced by 28 % compared to a group of patients with an MPR<50 %. These authors could not show a significant difference in vertebral fractures either. The slight difference in the magnitude of changes between their work and our data might be explained by the different populations, MPR borderlines and the fact that we did include all available anti-osteoporotic treatments in the evaluation, and not only alendronate. Nevertheless, the trends observed are similar in both studies.

We studied the time-dependent appearance of the efficacy of osteoporosis treatment. The high-compliance (MPR> 80 %) group showed a significant fracture risk reduction after the 2nd year, compared to the low-compliance (MPR<20 %) patients. After the adjustment of the raw data, this effect was seen after 6 months of treatment. Our results are in accordance with the clinical trials where the risk of patients on active treatment decreased quickly compared to the controls on calcium and vitamin D [5, 7, 8, 29, 30]. This fracture reduction has become significant in most cases after 3 years of treatment [4, 5], but it was also observed after 1 year with other treatment modalities [8, 31]. The difference between these data and our results might be due to the difference in the treated populations and the lack of calcium and vitamin D supplementation in our control group.

In the Hungarian health care system, patients do not pay for hospitalization; thus, admission depends only on the severity of the patient's condition. In our study, active treatment decreased the need for hospitalization among osteoporotic patients by 47 % during 3 years. This reduction was 30 % after 1.5 years, but it reached significance only after 2 years of treatment. However, after the propensity adjustment, this benefit in the compliant arm decreased. Adjusted mean difference confirmed the beneficial effect of constant osteoporosis treatment in both approaches (with and without propensity fitting). This means that biannual risks are lower for the compliant arm, but the propensity effect is lowering these benefits, which could be explained by the study design regarding the exclusion of patients who died within the analysis period.

**Table 12** Adjusted ratio of total cost of fractures based on the Gamma GLM model with propensity adjustment

| Period | Adjusted Ratio | Confidence interval | | *p* value |
|---|---|---|---|---|
| | | Lower limit | Upper limit | |
| 1st half year | 1.0459 | 0.9411 | 1.1624 | 0.4046 |
| 2nd half year | 0.8186 | 0.7353 | 0.9113 | 0.0003* |
| 3rd half year | 0.7842 | 0.6999 | 0.8786 | 0.0000* |
| 4th half year | 0.8495 | 0.7519 | 0.9598 | 0.0088* |
| 5th half year | 0.6873 | 0.6107 | 0.7735 | 0.0000* |
| 6th half year | 0.7240 | 0.6413 | 0.8173 | 0.0000* |
| SUM | | | | |

*Significant $p<0.05$

Huybrechts et al. [32] have shown that low compliance (MPR <50 %) was associated with a 37 % increase in the risk of all-cause hospitalization. Our results corroborate these findings, except for the fact that our follow-up period was longer (3 vs 1.7 years) and our study population was much larger.

The uniform insurance database has provided a valid basis for calculating osteoporosis-related costs for the whole country. Active osteoporosis treatment already reduced fracture-related expenses after 6 months. In its 2002 World Health Report, the WHO makes recommendations concerning the assessment of cost-effectiveness [33]. These recommendations are taken into account in the Hungarian HTA guideline as well. Pursuant to it, treatments which are capable of generating one QALY increase at an incremental cost of less than three times the per capita GDP (Hungarian Central Statistical Office data for 2011: 12,178 USD) are considered to be cost-effective from a societal perspective. This means that in Hungary, one QALY increase is cost-effective up to 36,522 USD. According to these data, the incremental cost of one QALY increase in case of continuous treatment amounts to 28,158 USD, putting the ICER below the threshold proposed by WHO (36,522 USD). The costs captured in the study reflect the 'true' attributable to fracture only since it is based on BNO classification. In view of the above, continuous osteoporosis treatment (MPR>80 %) in Hungary should be considered as cost-effective. Our findings infer that the standardized and uniform health care of osteoporotic patients in a country may reduce general fracture incidence and hospitalization in a cost-effective way.

Limitations of this study include that available data contain less information than a specific patient register whose main purposes are identified before the data collection and can fully address the research objectives. Furthermore, the fact that reported items are the determinants of finance (i.e. the funding system defines higher subsidy rate on particular registry codes than others) may distort the results since every health care provider has a vested interest to report the most high-valued financing code which results in a tendency to 'up-code'. This makes harder to find the patients by financing code. 'Cause codes' indicating low-energy fractures are infrequently used in practice which makes it necessary to extend the ICD codes for any fractures at typical osteoporotic fracture sites (vertebrae, humerus, radius, ulna, clavicle, pelvis, femoral neck, and femur). This could bias the analysis as we might take into account nonosteoporotic fractures as well, but considering only postmenopausal osteoporotic patients on the basis of the selection period, the bias will be negligible. Another limiting aspect is that reasons relating to loss to follow-up are unknown. This means, we are not able to distinguish a patient who stopped osteoporosis medication but still having other health services from a patient who left the country. However, the number of patients who represents this kind of a special subgroup of dropout events is assumed to be relative low which results in a small biasing effect only. Moreover, it may, regardless of the length of the follow-up time, be difficult to relate poor persistence and compliance to any outcome variable due to unknown confounders. It will not be possible to obtain patient level data to control for all potential confounders. However, with these limitations in mind, the analysis was carried out with as many control variables as possible, and thereby, the relationships found in the statistical analysis are fairly robust.

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