Rational Allocation of Limited Health Care Resources: The Contributions of Epidemiological, Clinical, and Health Economic Studies

Schwenkglenks, M
HABILITATIONSSCHRIFT

Rational Allocation of Limited Health Care Resources:
The Contributions of Epidemiological, Clinical,
and Health Economic Studies

Zur Erlangung der Venia Legendi der Universität Zürich

Matthias Schwenkglenks

10. Dezember 2008
Zusammenfassung der Habilitationsschrift

For at least two decades, the health care expenditures of virtually all industrialised countries have been increasing faster than gross domestic products. In this situation, health care sectors are rarely perceived as contributors to the creation of societal value but are rather associated with a - much debated - cost problem. At the health system level, most countries have experimented with interventions in the fields of health care financing, health insurance, and reimbursement of health care providers. Managed care and patient co-payments were introduced or extended. The successes of these measures were highly variable and sometimes, dysfunctional effects (e.g. unintended rationing) were triggered. The field of macro-level health economics strives to address these issues.

In parallel, but more at the meso- and micro-levels, health economic evaluation aims at contributing to a more rational use of health care resources by analysing the costs and benefits of individual medical interventions, or groups of interventions, as a basis for decision making. According to the underlying paradigm, the final goal is to achieve an optimal use of limited resources, and thus maximise population health. Therefore, full-scale health economic evaluation studies (cost-effectiveness and cost-utility analyses) always imply two sides of a coin: an integration of clinical and economic evidence. Other health economic studies, such as budget impact analyses, cost-of-illness studies and studies of the medical resource use associated with disease entities or medical interventions, are more limited in scope but provide important auxiliary information. Epidemiological studies contribute background data on patterns of disease occurrence (incidence, prevalence, and geographical distribution). Moreover, studies with a clinical epidemiology or primarily clinical focus can at times yield important direct hints on how health care resources can be used more efficiently. This is for example the case where genetic or biological markers are identified that allow predict if an expensive treatment will be effective in a given patient, or where risk factors for diseases, clinical events or treatment side effects can be identified and used to efficiently target screening and preventive measures.

The following six publications selected for habilitation span most of the above-described range of possibilities. They all have, in a less or more direct manner, implications for the efficient use of medical resources. The first publication introduces and discusses risk models for the occurrence of febrile neutropenia in patients with non-Hodgkin lymphoma undergoing chemotherapy [1]. The second publication, a research letter, establishes a link between reduced chemotherapy delivery, a frequent consequence of myelosuppression, and long-term survival, in patients with the same disease [2]. In the third publication, the clinical and medical resource use implications of severe oral mucositis, another major side effect of anti-malignant chemotherapy, are assessed [3]. The forth publication reports a population-representative cross-sectional study of gastroesophageal reflux disease and its cost-of-illness implications [4]. The last two papers describe modelling studies of postmenopausal
osteoporosis. The first predicts future osteoporotic fracture occurrence in Switzerland and its economic consequences for the health system [5]. The second reports a full-scale health economic evaluation of the implications of adopting a population-based screening strategy for osteoporosis, with subsequent treatment where applicable, in Switzerland [6].

The febrile neutropenia risk model publication is based on a prospective observational study of patients from five European countries. The multivariate risk models proposed require further validation but appear to have the potential to predict febrile neutropenia with good precision. In particular, low risk patients are successfully identified. This may allow to better target, and hence improve the cost-effectiveness of, expensive prophylactic measures. A randomised clinical trial with an accompanying health economic sub-study should ideally be conducted to confirm this potential, if initial external validation of the risk models is successful.

As a side-finding, the analysis of febrile neutropenia occurrence demonstrates that patient risk is influenced by patient and treatment characteristics but also by clinical practice patterns, e.g. the tendency to delay chemotherapy cycles or reduce doses. In consequence, the administered chemotherapy dose intensity (a composite measure of dose and timeliness of delivery) can be substantially compromised. The second publication shows a negative impact of compromised chemotherapy delivery on long-term survival, based on data from two independent retrospective studies conducted in Belgium and Great Britain. Apparently, administering full chemotherapy dose intensity is important enough to justify expenditures on prophylactic measures. Again, further study is required and could be accompanied by a formal health economic assessment.

The oral mucositis publication is based on a pan-European prospective observational study of patients with non-Hodgkin lymphoma and multiple myeloma. By linking the clinical correlates of oral mucositis with medical resource use implications, it is shown that better management of this adverse condition would not only improve patient well-being but might also lead to savings. This notion is supported by a Poisson regression analysis of influences on duration of hospitalisation which includes severe oral mucositis occurrence as a highly significant predictor variable.

Telephone surveys are a valid and efficient alternative approach to gain information on the occurrence (prevalence, in the present case) of frequent medical conditions and the structure of associated medical resource use and costs, as is exemplified by the study on gastroesophageal reflux disease. The contributions of different cost components are shown and patient characteristics associated with increased total costs (e.g. urban versus rural dwelling) are identified. Such information supports the planning and development of health services and provides input data for subsequent health economic modelling.
The publications on osteoporosis are literature-based and make use of decision-analytic modelling techniques. A Markov model of osteoporotic fracture occurrence was developed and populated with demographic scenarios provided by the Swiss Federal Statistical Office, published epidemiological data, and publicly available Swiss data on duration of hospitalisation, nursing home residency and cost per day of stay. Fracture numbers and the burden to the Swiss health care budgets are projected until 2020.

The original Markov model was adapted to perform a cost-utility analysis of a population-based screen-and-treat strategy for osteoporosis (dual X-ray absorptiometry followed by bisphosphonate (alendronate) treatment if osteoporosis, or osteopenia and a fracture, were found to be present) from the perspective of the Swiss health care system. Population-based screening was found to be cost-effective in women aged 75 or older but not in men. Internationally, several other studies assessed the cost-effectiveness of alendronate but most of them used unrealistic compliance assumptions, disregarded the process of screening and diagnosis, or ignored disease-related events that occurred before a defined screening age. It is shown in the publication that the latter has led to too optimistic judgements on the benefits of screening later in life. The main limitation of the present analysis is that, due to a lack of data, it could not be assessed to what extent cost-effectiveness could be improved by targeting the screening to persons with known risk factors for osteoporosis or falls. Further work is currently being planned to address this issue.

In conclusion, independent of macro-level interventions, improving the efficiency of health care on the basis of emerging scientific evidence and rational decision making can contribute to patient well-being and cost-containment. In some cases, clinical epidemiology or primarily clinically oriented studies make direct contributions to this goal, by providing information that helps to better target screening, prevention, or treatment. In these situations, it is fundamental to achieve a thorough understanding of the underlying disease process and to ensure that any identified associations between predictors and risk factors on the one hand, and patient outcomes on the other hand, are valid. This typically implies the use of appropriate techniques of multivariate statistical analysis and independent validation. In other cases, explicitly health economic studies are needed to generate a sufficient knowledge base for improving the efficiency of health care delivery. Such studies often make use of decision-analytic modelling techniques, in order to integrate data from different sources and to extrapolate beyond the limited observation times of most randomised clinical trials. In these cases, careful selection of model input parameters, transparency, appropriate sensitivity analyses, and adherence to good modelling practice guidelines are of paramount importance. At the same time, oversimplification must be avoided. As is shown in the last of the publications selected for habilitation, health economic models must not ignore important elements of the disease and medical management process, such as disease occurrence before a given screening age. Otherwise, biased results may occur that cannot be detected by standard sensitivity analyses, and the goal of improving the efficiency of health care delivery may not be achieved.
Publications selected for habilitation


Multivariate analysis of febrile neutropenia occurrence in patients with non-Hodgkin lymphoma: Data from the INC-EU Prospective Observational European Neutropenia study.

British Journal of Haematology 2008 Dec 1. [Epub ahead of print]
Multivariate analysis of febrile neutropenia occurrence in patients with non-Hodgkin lymphoma: data from the INC-EU Prospective Observational European Neutropenia Study

Ruth Pettengell,1 André Bosly,2 Thomas D. Szucs,3 Christian Jackisch,4 Robert Leonard,5 Robert Paridaens,6 Manuel Constenla,7 and Matthias Schwenkglenks3 for the Impact of Neutropenia in Chemotherapy - European Study Group (INC-EU)

1Cellular and Molecular Medicine, St George’s University of London, Cranmer Terrace, London, UK, 2Service d’Hematologie, Cliniques Universitaires UCL, Godinne, Belgium, 3European Centre of Pharmaceutical Medicine, University of Basel, c/o ECPM Executive Office, University Hospital, Basel, Switzerland, 4Department of Gynaecology and Obstetrics, Klinikum Offenbach, Offenbach, Germany, 5Cancer Services & Clinical Haematology, Charing Cross Hospital, London, UK, 6Department of Medical Oncology, University Hospital Gasthuisberg, Leuven, Belgium, and 7Servicio de Oncologia, Complexo Hospitalario de Pontevedra, Pontevedra, Spain

Received 29 August 2008; accepted for publication 16 October 2008
Correspondence: Dr Ruth Pettengell, Cellular and Molecular Medicine, St George’s University of London, Cranmer Terrace, London SW17 0RE, UK. E-mail: rpetteng@sgul.ac.uk
Re-use of this article is permitted in accordance with the Creative Commons Deed, Attribution 2.5, which does not permit commercial exploitation.

Summary
Myelosuppression, particularly febrile neutropenia (FN), are serious dose-limiting toxicities that occur frequently during the first cycle of chemotherapy. Identifying patients most at risk of developing FN might help physicians to target prophylactic treatment with colony-stimulating factor (CSF), in order to decrease the incidence, or duration, of myelosuppression and facilitate delivery of chemotherapy as planned. We present a risk model for FN occurrence in the first cycle of chemotherapy, based on a subgroup of 240 patients with non-Hodgkin lymphoma (NHL) enrolled in our European prospective observational study. Eligible patients had an International Prognostic Index of 0–3, and were scheduled to receive a new myelosuppressive chemotherapy regimen with at least four cycles. Clinically relevant factors significantly associated with cycle 1 FN were older age, increasing planned cyclophosphamide dose, a history of previous chemotherapy, a history of recent infection, and low baseline albumin (<35 g/l). Prophylactic CSF use and higher weight were associated with a significant protective effect. The model had high sensitivity (81%) and specificity (80%). Our model, together with treatment guidelines, may rationalise the clinical decision of whether to support patients with CSF primary prophylaxis based on their risk factor profile. Further validation is required.

Keywords: Non-Hodgkin lymphoma, neutropenia, chemotherapy, risk factors.
Physicians wishing to identify those patients that should be supported with prophylactic CSF are faced with an array of patient-related and treatment-related factors to consider. Current guidelines recommend CSF support for chemotherapy treatment regimens associated with a high risk of FN (>20%) (Aapro et al., 2006; Smith et al., 2006). One such regimen is combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), which has long been the standard treatment for patients with aggressive non-Hodgkin lymphoma (NHL) (Fisher et al., 1993). The addition of rituximab to the CHOP regimen (R-CHOP) has further improved patient outcomes (Coiffr et al., 2002; Pfreamschuh et al., 2006; National Comprehensive Cancer Network Inc, 2008a), making R-CHOP the current standard of care (National Comprehensive Cancer Network Inc, 2008a). CHOP-like chemotherapy carries a significant risk of FN (17–50%) (Morrison et al., 2001; Lyman et al., 2003; Osby et al., 2003; Aapro et al., 2006; Boudry et al., 2008; Pettengell et al., 2008b). In addition to the risk associated with the chemotherapy regimen, other risk factors should be considered in order to determine the patient’s overall FN risk (Aapro et al., 2006; Smith et al., 2006; National Comprehensive Cancer Network Inc, 2008b).

Several retrospective studies have identified potential risk factors for FN in lymphoma patients, including older age, low baseline blood cell counts, low serum albumin, anaemia, abnormal bone marrow, increased lactate dehydrogenase (LDH), co-morbid renal, cardiovascular or hepatic disease, full or high-risk planned chemotherapy regimen, and lack of CSF prophylaxis (Lyman & Delgado, 2003; Lyman et al., 2005; Rabinowitz et al., 2006; Teegala et al., 2007). However, it is not possible to give a weighting to these risk factors and accurately determine their individual importance. The potential for risk factors identified in retrospective studies to guide targeted CSF use needs to be validated in prospective investigations.

Early, prospective clinical models in lymphoma patients not receiving CSF prophylaxis identified high levels of serum LDH and tumour necrosis factor (TNF) and bone marrow involvement as risk factors for FN (Intragamtoch et al., 2000; Voog et al., 2000). Data from several large prospective registries have led to the development of risk models for chemotherapy-induced FN, and the risk factors they have identified are broadly consistent with those highlighted by retrospective studies (Casas et al., 2006; Lyman et al., 2006; Shayne et al., 2007a). However, these studies were in patients with solid tumours (Casas et al., 2006) or in patients with solid tumours or lymphoma (Lyman et al., 2006; Shayne et al., 2007a), and therefore did not specifically examine the risk of FN in lymphoma patients.

Several studies have demonstrated that the risk of FN is greatest in the first cycle of chemotherapy, with >50% of patients who develop FN experiencing an episode during cycle one (Lyman & Delgado, 2003; Lyman et al., 2003). The Impact of Neutropenia in Chemotherapy – European Study Group (INC-EU) Prospective Observational European Neutropenia Study was conducted to assess the incidence and predictors of neutropenia, FN and reduced chemotherapy administration for breast cancer and lymphoma patients in European practices. Multivariate regression models for lymphoma patients indicated that first cycle FN, age >65 years, disease status, and type of chemotherapy regimen predicted low relative dose intensity (RDI), while primary prophylaxis with CSF was protective (Pettengell et al., 2008b).

Here we present a subgroup analysis of NHL patients from the INC-EU prospective study with the aim of establishing a multivariate risk model of FN occurrence in the first cycle of chemotherapy. Such models may help to target high-risk patients for prophylactic treatment in order to decrease the incidence of myelosuppression and enable full-dose chemotherapy to be delivered on schedule.

Methods

Study design and patient selection

Data were obtained for 749 patients with histologically confirmed breast cancer, NHL and Hodgkin lymphoma (HL) who were enrolled in the INC-EU Prospective Observational European Neutropenia Study between January 2004 and May 2005. A subset of 240 patients with NHL were included in this sub-analysis. The study was conducted in 66 centres in Belgium, France, Germany, Spain and the UK. Of these, 39 centres contributed NHL patients for this subanalysis. Ethical approval was obtained from the institutional review boards of all centres. Patients with NHL and an International Prognostic Index (IPI) of 0–3, and who were scheduled to receive a new myelosuppressive chemotherapy regimen with at least four cycles, were eligible for inclusion. All participants provided their informed consent. Further details of the overall study design and patient selection have been described previously (Pettengell et al., 2008b).

Statistical methods

Multivariate logistic regression models of FN occurrence in cycle 1 were developed. In line with established definitions (e.g. National Comprehensive Cancer Network Inc, 2008b), FN was defined as Grade 4 CIN [absolute neutrophil count (ANC) <0.5 x 10^9/l] and a body temperature ≥38°C. General estimating equations (GEE)-based robust standard error (SE) estimates were used to allow for clustering by study centre. The impact of this choice was assessed by comparison with results based on conventional SE estimates.

Candidate predictors were selected based on clinical and statistical grounds (P ≤ 0.25 in univariate analysis). To rule out circularity effects, potential direct correlates of the dependent variables of interest were not used. In the model-building process, main effects were identified by manually exploring all plausible combinations of covariates. A model for the occurrence of FN in any cycle of chemotherapy was also developed using similar techniques.
In an effort to make full use of the available information, missing categories were introduced for candidate predictors with more than 5% missing values. Concerns have been raised that this approach can lead to biased estimation results, particularly where covariates have a high proportion of missing values and are strong confounders (Vach & Blettner, 1991; Greenland & Finkle, 1995). Therefore, as an additional sensitivity analysis, alternative models omitting all covariates with more than 5% missing values were estimated and the parameter estimates and standard errors for the remaining covariates were assessed for deviation; these sensitivity analyses did not reveal any relevant distortions.

The Hosmer–Lemeshow goodness of fit test and plots of mean observed versus mean predicted event probabilities, by deciles of the linear predictor, were used to assess model fit. The risk of cycle 1 FN is presented as an odds ratio (OR) with 95% confidence interval (CI). Predictive ability of the models was characterised by sensitivity (percentage of the FN occurrences that were correctly predicted) and specificity (percentage of the FN non-occurrences that were correctly predicted). Positive predictive value (percentage of patients predicted to have an FN who had FN), negative predictive value (percentage of patients predicted not to have an FN who did not have FN), the area under the receiver operating characteristic (ROC) curve, and the total proportion of correct predictions. Additionally, in the absence of an independent validation dataset, 10-fold cross-validation was performed. In a final step, the model was applied to hypothetical scenarios.

### Variables considered for multivariate models

The following variables were considered for logistic regression model building for both cycle 1 FN and any cycle FN: previous chemotherapy (vs. chemotherapy-naïve); planned doses (for sequential regimens, of first part of chemotherapy); chemotherapy treatment within a clinical trial protocol; CSF prophylaxis (for the purpose of statistical modelling, defined as any CSF use before a FN occurred); antibiotic prophylaxis (for the purpose of statistical modelling, defined as any cotrimoxazole or quinoline use before a FN occurred) cancer stage (Ann Arbor); number of haematology laboratory tests before a grade IV CIN occurred; recent infection (<60 d prior to start to chemotherapy); baseline ANC <3 x 10^9/l; baseline white blood cell count (WBC) <5 x 10^9/l; baseline haemoglobin <100 g/l; baseline glucose >8.8 mmol/l; baseline albumin <35 g/l; baseline total bilirubin >17.1 μmol/l; baseline alkaline phosphatase >250 IU/l; number of comorbidities at baseline; cardiac comorbidity at baseline; vascular comorbidity at baseline; cardiovascular comorbidity at baseline; liver disease at baseline; renal comorbidity at baseline; age; glomerular filtration rate (GFR; estimated using the Cockcroft-Gault formula); height; weight; body surface area (BSA); and body mass index (BMI). Assessment of comorbidities at baseline used Medical Dictionary for Regulatory Activities (Med-DRA®)-coded medical history entries with the following system organ class and preferred term names: cardiac disorders; vascular disorders; renal and urinary disorders; hepatobiliary disorders; infections and infestation; diabetes mellitus. For the any cycle model, the following covariates were also considered: planned dose intensities (for sequential regimens, of first part of chemotherapy); use of a dose dense regimen (cycle length 2 weeks instead of 3 weeks); planned cycle length; planned cycle number; dose reduction (≥10% of planned dose of at least one drug in at least one cycle) before FN occurred; and dose delay (a delay ≥4 d in at least one cycle) before FN occurred.

### Results

Patient and baseline disease characteristics are shown in Table I. The majority of patients (75%) received a CHOP-21-like treatment regimen and a high percentage (82%) of patients received rituximab (Table II). An average of six chemotherapy cycles were planned (mean 6.2, SD 1.5). Overall, 28% of patients received primary CSF prophylaxis and 29% had other CSF use. CSFs used were: filgrastim, 40%; pegfilgrastim, 34%; lenograstim, 10%. The remaining 16% of patients with any CSF use received two or three of these substances. Primary antibiotic prophylaxis with cotrimoxazole was seen in 8% of patients and prophylaxis with quinolones in 14%. During cycle 1, FN occurred in 9% of patients and the incidence of FN across all cycles of chemotherapy was 22% (Fig 1). Grade IV CIN occurred in 35% of patients in cycle 1 and in 54% of patients across all cycles.

The results of the multivariate logistic regression analysis used to model risk factors for cycle 1 FN are shown in Table III. Clinically relevant factors that were significantly associated with cycle 1 FN were older age, increasing planned cyclophosphamide dose, increasing planned etoposide dose, a history of previous chemotherapy, a history of recent infection, and low baseline albumin <35 g/l. Prophylactic CSF use and higher weight were associated with a significant protective effect. The effect of antibiotic prophylaxis with cotrimoxazole or quinolones remained non-significant [OR (95% CI): 0.36 (0.08–1.62), P = 0.181] when added to the final model. Replacing age with GFR (to which it is inversely related) and replacing weight with height yielded similar models.

The model correctly classified 192 of the 240 patients (80%). The area under the ROC curve, which describes the ability of the model to discriminate between those at risk from cycle 1 FN and those not at risk, was 0.86 (95% CI 0.79–0.94) (Fig 2). (An area under the ROC curve of 0.5 implies an ability to discriminate that is no better than chance, while a value of 1 represents perfect ability to discriminate). When the optimal probability cut-off was used to predict cycle 1 FN, test characteristics were: sensitivity 81%; specificity 80%; positive predictive value 28% (proportion of patients classified as high risk who suffered cycle 1 FN); negative predictive value 98% (the proportion of patients classified as low FN risk who did not suffer cycle 1 FN). Predictive ability was only slightly lower...
under 10-fold cross-validation conditions (area under the ROC curve 0.72).

A similar model was developed to predict the risk of FN in any cycle. In agreement with the first cycle FN model, the following factors were also significantly associated with FN occurrence in any cycle: age [OR (95% CI): 1.79 (1.16–2.78) per additional 10 years, \(P = 0.009\)]; increasing planned cyclophosphamide dose [OR (95% CI): 1.33 (1.16–1.52) per additional 50 mg/m², \(P < 0.001\)]; increasing planned etoposide dose [OR (95% CI): 1.88 (1.10–3.20) per additional 50 mg/m², \(P = 0.021\)]; and recent infection [OR (95% CI): 3.32 (1.03–10.71), \(P = 0.044\)]. Likewise, prophylactic CSF use [OR (95% CI): 0.21 (0.10–0.44), \(P < 0.001\)] and higher weight [OR (95% CI): 0.62 (0.44–0.88) per additional 10 kg, \(P = 0.007\)] were associated with a significant protective effect. In addition, the following clinically relevant factors were associated with a significantly increased risk of any cycle FN: low baseline ANC or WBC [ANC <3.0 × 10⁹/l or WBC <5 × 10⁹/l]; OR (95% CI): 4.18 (1.82–9.60), \(P = 0.001\), high baseline alkaline phosphatase (>250 IU/ml; OR (95% CI): 9.07 (4.11–38.30), \(P = 0.020\), cardiovascular comorbidity [OR (95% CI): 2.56 (1.04–6.29), \(P = 0.041\)], and increasing planned cytarabine dose [OR (95% CI): 1.09 (1.05–1.13) per additional 50 mg/m², \(P < 0.001\)]. Use of a dose dense regimen (cycle length 2 weeks instead of 3 weeks) may influence FN but did not attain statistical significance in our model [OR (95% CI): 1.84 (0.71–3.83), \(P = 0.208\); see Discussion]. In the any cycle model, dose reductions before an FN event occurred [OR (95% CI): 0.24 (0.09–0.63), \(P = 0.004\)] and dose delays before an FN event occurred [OR (95% CI): 0.17 (0.07–0.40), \(P < 0.001\)] had a significant protective effect against FN. In contrast to the cycle 1 model, a history of chemotherapy [OR (95% CI): 1.76 (0.49–6.36), \(P = 0.390\)] and low baseline albumin [OR (95% CI): 1.62 (0.54–5.04), \(P = 0.391\) when added to the final model] were non-significant in the any cycle model. Antibiotic prophylaxis showed no effect.

The any cycle model correctly classified 180 of 237 patients (76%). The area under the ROC curve was 0.83 (95% CI 0.76–0.90). When the optimal probability cut-off was used to predict any cycle FN, test characteristics were: sensitivity 76%; specificity 76%; positive predictive value 48%; negative predictive value 92%. Predictive ability was slightly lower under 10-fold cross-validation conditions (area under the ROC curve 0.72).

Based on our models, the estimated risk of FN in cycle 1 or any cycle during R-CHOP therapy for lymphoma (without CSF prophylaxis) in a hypothetical 80 kg subject (average weight of our male subsample) is shown in Table IV. The risk of FN increased as the number of risk factors and age increased in both models. Assigning a lower weight (e.g. 55 kg) to the subject increased the risk for all possible scenarios shown in Table IV.

### Discussion

This study identified several clinically relevant factors that were predictive or protective for cycle 1 FN. Patient and baseline characteristics of older age and low baseline albumin were predictive of cycle 1 FN, as were a clinical history of previous chemotherapy or recent infection. Treatment characteristics, specifically increasing planned chemotherapy dose, also significantly increased risk of cycle 1 FN. In contrast, higher weight and prophylactic CSF use were associated with significant protective effects.

Older age (>65 years) is recognised as a risk factor for FN by current European guidelines (Aapro et al, 2006). Indeed,
Table II. Treatment characteristics.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>Distribution (%)</th>
<th>Primary CSF prophylaxis</th>
<th>Other CSF use*</th>
<th>Rituximab administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td>Total</td>
<td>240</td>
<td>100</td>
<td>27.5 (66)</td>
<td>28.8 (69)</td>
<td>81.7 (196)</td>
</tr>
<tr>
<td>CHOP-21-like†</td>
<td>178</td>
<td>74.2</td>
<td>19.7 (35)</td>
<td>34.3 (61)</td>
<td>86.5 (154)</td>
</tr>
<tr>
<td>CHOP-14-like</td>
<td>41</td>
<td>17.1</td>
<td>75.6 (31)</td>
<td>9.8 (4)</td>
<td>65.9 (27)</td>
</tr>
<tr>
<td>ACVBP-like</td>
<td>9</td>
<td>3.8</td>
<td>66.7 (6)</td>
<td>33.3 (3)</td>
<td>77.8 (7)</td>
</tr>
<tr>
<td>Other regimens</td>
<td>12</td>
<td>5.0</td>
<td>66.7 (8)</td>
<td>8.3 (1)</td>
<td>66.7 (8)</td>
</tr>
</tbody>
</table>

ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CSF, colony-stimulating factor.

*Secondary prophylaxis or treatment.
†Includes six patients with a cycle length of 28 d.
‡Denominator values for percentage calculations are the regimen n-values in column 2.

Fig 1. Incidence of febrile neutropenia (FN) in cycle 1 and across all cycles. Error bars represent 95% exact binomial confidence intervals. ACVBP = doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone. Data taken from Pettengell et al, 2008b.

European Organisation for Research and Treatment of Cancer (EORTC) Elderly Guidelines recommend primary prophylaxis with CSF for all elderly patients receiving curative CHOP-like chemotherapy (Repetto et al, 2003). Although many of the other patient risk factors identified in this study do not necessarily reflect risk factors highlighted in the guidelines, it is important to recognise that the EORTC guidelines (Aapro et al, 2006) are based on a literature review of studies across tumour types and are not specific for NHL.

The increased risk for cycle 1 FN associated with age and low baseline albumin, and the protective effects of CSF prophylaxis, are consistent with data from retrospective studies specific to NHL patients (Lyman & Delgado, 2003; Rabinowitz et al, 2006; Teegala et al, 2007). An increased risk of FN in patients with low serum albumin (Intragumtornchai et al, 2000) or higher cyclophosphamide dose (Voog et al, 2000) was also reported in early prospective studies in this patient population. Data on the potential relationship between prior chemotherapy, weight or recent infection and the risk of cycle 1 FN in NHL is limited. However, a US nationwide prospective cohort study of 3468 patients with solid tumours or lymphoma identified prior chemotherapy and concurrent antibiotics as risk factors for neutropenic complications in cycle 1. We assume that antibiotics are not in themselves a risk factor for FN, but that they are prescribed to patients who are perceived to be at higher FN risk. Other risk factors identified in the US study were the number of myelosuppressive agents, anthracycline-based regimens, planned chemotherapy delivery >85% of standard, cancer type, phenothiazines, abnormal alkaline phosphatase, elevated bilirubin, low platelets, elevated glucose

Table III. Logistic regression model for predicting cycle 1 FN occurrence*.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age†</td>
<td>2.20</td>
<td>1.21–4.01</td>
<td>0.010</td>
</tr>
<tr>
<td>Weight‡</td>
<td>0.62</td>
<td>0.43–0.89</td>
<td>0.010</td>
</tr>
<tr>
<td>Previous chemotherapy§</td>
<td>6.39</td>
<td>1.72–23.68</td>
<td>0.006</td>
</tr>
<tr>
<td>Planned cyclophosphamide dose§</td>
<td>1.16</td>
<td>1.02–1.32</td>
<td>0.023</td>
</tr>
<tr>
<td>Planned cytarabine dose§</td>
<td>1.06</td>
<td>0.98–1.16</td>
<td>0.151</td>
</tr>
<tr>
<td>Planned etoposide dose§</td>
<td>1.59</td>
<td>1.20–2.11</td>
<td>0.001</td>
</tr>
<tr>
<td>CSF before an event occurred¶</td>
<td>0.18</td>
<td>0.03–0.94</td>
<td>0.042</td>
</tr>
<tr>
<td>Baseline albumin low**</td>
<td>4.76</td>
<td>1.35–16.71</td>
<td>0.015</td>
</tr>
<tr>
<td>Baseline albumin missing**</td>
<td>0.52</td>
<td>0.09–2.99</td>
<td>0.464</td>
</tr>
<tr>
<td>Recent infection††</td>
<td>3.07</td>
<td>0.99–9.52</td>
<td>0.052</td>
</tr>
</tbody>
</table>

CI, confidence interval; CSF, colony-stimulating factor.
*Number of observations = 240, Wald $\chi^2 = 26.59$, prob $> \chi^2 = 0.003$, log pseudolikelihood = −52.41.
†Per additional 10 years of age.
‡Per additional 10 kg body weight.
§Planned doses in mg/m² body surface area; per additional 50 mg/m².
¶Myelopoietic growth factor use before a FN occurred in cycle 1.
**Baseline albumin <35 g/dl, missing category introduced to avoid loss of observations (sensitivity analyses did not reveal any relevant distortions with the use of this technique).
††During 60 d prior to chemotherapy or ongoing infectious comorbidity.
and reduced GFR, whereas CSF prophylaxis was protective (Lyman et al., 2006). Results from a subset of older patients from the same registry (n = 1378) supported some of these findings and additionally highlighted chemotherapy regimens containing cyclophosphamide, etoposide or ifosfamide as increasing the risk of early neutropenic events (Shayne et al., 2007a). Overall, the findings of the US prospective study (Lyman et al., 2006; Shayne et al., 2007a) and the present study were generally consistent and differences observed may be related to the patient populations studied, treatment regimens and sample size.

It is noteworthy that increasing planned chemotherapy dose was predictive of FN in our model, in keeping with a previously published model (Voog et al., 2000) and a recent validated risk model that found that regimens containing cyclophosphamide, etoposide or ifosfamide were associated with an increased risk of early neutropenic events (Shayne et al., 2007a). In our model, planned cyclophosphamide use also correlated with the use of other anti-malignant agents, which could potentially mask the contribution of these other agents to the neutropenic potential of the chemotherapy regimen. Planned etoposide dose was identified as a significant predictor of cycle 1 FN; however, very few patients received this agent. Similarly, risk estimates for recent infection were based on a small number of observations (11 patients) and require careful interpretation. CSF primary prophylaxis had a significant protective effect against cycle 1 FN. The protective effects of CSF have been validated previously (Komrokji & Lyman, 2004; Aapro et al., 2006; Smith et al., 2006).

The high number of patients correctly classified by the model (80%) suggests that it may have potential clinical utility. The model showed good ability to discriminate between patients at risk from cycle 1 FN and those not at risk. Model test characteristics were comparable to, or better than, values published for other risk models of neutropenia (Morrison et al., 2001; Lyman & Delgado, 2003; Lyman et al., 2006; Rabinowitz et al., 2008). The high number of patients correctly classified by the model (80%) suggests that it may have potential clinical utility. The model showed good ability to discriminate between patients at risk from cycle 1 FN and those not at risk. Model test characteristics were comparable to, or better than, values published for other risk models of neutropenia (Morrison et al., 2001; Lyman & Delgado, 2003; Lyman et al., 2006; Rabinowitz et al., 2008).}

![Fig 2. Receiver operating characteristic (ROC) curve for the multivariate analysis of factors predicting cycle 1 febrile neutropenia. Area under ROC curve = 0.86 (95% confidence interval 0.79–0.94).](image)

**Table IV.** Estimated risk [%] of cycle 1 FN and any cycle FN following R-CHOP treatment for NHL (cycle length 3 weeks) in an 80 kg subject (average weight of male subsample) according to age and risk factor profile. Estimated risks for a lower assigned weight (55 kg) are given in parentheses.

<table>
<thead>
<tr>
<th>Cycle/risk factors</th>
<th>Age, years; weight 80 kg (55 kg), [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Cycle 1</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0 (1)</td>
</tr>
<tr>
<td>Previous CT</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Low albumin*</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Recent infection†</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Previous CT + low albumin*</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Previous CT + low albumin* + recent infection†</td>
<td>19 (44)</td>
</tr>
<tr>
<td>Any cycle</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Previous CT</td>
<td>8 (22)</td>
</tr>
<tr>
<td>ANC/WBC low‡</td>
<td>17 (41)</td>
</tr>
<tr>
<td>Alkaline phosphatase high‡</td>
<td>31 (60)</td>
</tr>
<tr>
<td>CV comorbidity</td>
<td>11 (30)</td>
</tr>
<tr>
<td>Recent infection†</td>
<td>14 (35)</td>
</tr>
<tr>
<td>ANC/WBC low‡ + CV comorbidity</td>
<td>35 (64)</td>
</tr>
<tr>
<td>ANC/WBC low‡ + CV comorbidity + recent infection†</td>
<td>64 (85)</td>
</tr>
</tbody>
</table>

ANC, absolute neutrophil count; CT, chemotherapy; CV, cardiovascular; WBC, white blood cell count.

*Baseline albumin <35 g/l.
†During 60 d prior to treatment.
‡Baseline ANC <3·0 × 10⁹/l or WBC <5·0 × 10⁹/l; baseline alkaline phosphatase >250 IU/ml.
et al, 2006; Shayne et al, 2007a,b). The 98% negative predictive value showed that the model successfully identified patients at low risk of developing FN. The 28% positive predictive value (PPV) indicated that the model identified as high risk some patients who did not ultimately have a cycle 1 FN event. While a higher PPV is desirable, it should be remembered that the PPV in this setting was partially driven by a low absolute frequency of cycle 1 FN events and that not every patient who is at high risk of FN will actually experience FN.

The potential clinical utility of the model was explored by applying our dataset to hypothetical scenarios of NHL patients and estimating the risk of developing FN in cycle 1 or any cycle. Whilst the presence of some risk factors alone (e.g. low baseline albumin) did not predict a high risk of FN, a combination of risk factors increased the predicted risk for developing cycle 1 FN substantially. In addition, patient characteristics of older age or lower weight increased the predicted risk for developing cycle 1 FN for any of the given risk factor scenarios.

Owing to the sample size, the relatively infrequent occurrence of cycle 1 FN (9%) and the high number of covariates used, the logistic regression model generated has some potential limitations in its ability to correctly assess the impact of rare risk factors and there is the possibility of artefacts. This caveat particularly applies to the effects of some comorbidities and baseline laboratory abnormalities. The standard approach to randomly split the study dataset into a training dataset (on which the model is estimated) and a test dataset (on which the model is validated) was considered to be inefficient for the same reasons. Ten-fold cross-validation has been shown to be superior in small datasets (Goutte, 1997) and showed favourable results in the present case. However, additional validation in an independent data set from a different population is clearly required.

The any cycle model correctly classified 76% of patients, and the test characteristics were comparable to a recent model of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. European Journal of Cancer, 42, 2433–2453.


© 2008 The Authors
Journal Compilation © 2008 Blackwell Publishing Ltd, British Journal of Haematology


Pettengell R, Schwenkglenks M, Bosly A.

Association of reduced relative dose intensity and survival in lymphoma patients receiving CHOP-21 chemotherapy.

Dear Editor,

Reductions in average relative chemotherapy dose intensity (ARDI; i.e. administered compared with planned) compromise patient outcomes [3], and a recent Belgian study showed that survival for non-Hodgkin lymphoma (NHL) patients receiving CHOP-21 was reduced when ARDI fell below 90% [2]. We support these findings with similar data from the UK Audit of Lymphoma Patients (n=78 patients who received CHOP-21 chemotherapy in 1999–2000) and from the combined Belgian and UK data (n=289) [4].

Patient, disease and treatment characteristics were similar between the two studies, except that the UK patients were younger (mean age ± SD was 55±15 years versus 63±14 years) and fewer UK patients received colony stimulating factor (CSF). First cycle CSF use was 4% in the UK study compared to 25% in the Belgian study. During an average time to death or censoring of 72 months, 35% of patients in the UK study died. In the Belgian study, the average observation time was 30 months, during which 31% of patients died. After adjusting for the higher mean age of the Belgian patients, Kaplan–Meier survival functions were similar between the two populations (log-rank test stratified by 10-year age groups, p=0.38).

Kaplan–Meier plots for patients with >90% ARDI versus ≤90% ARDI showed reduced survival for the patients with ≤90% ARDI (Fig. 1). A trend towards reduced survival was apparent in the UK dataset alone (Fig. 1a; log-rank test-based p=0.090). For the combined dataset, the effect was statistically significant (p<0.001; Fig. 1b), as for the Belgian data alone [2].

Potential predictors of reduced survival were assessed using an extended Cox proportional hazards regression model with robust standard errors allowing for clustering by centre. Using the UK dataset, reduced survival was significantly associated with a higher Ann Arbor disease stage (hazard ratio (HR) at treatment initiation 2.59 per stage increase by 1, 95% CI 1.45–4.66, p=0.001) and showed a trend towards association with age (HR 1.02 per year of age, CI 1.00–1.04, p=0.058) and RDI ≤90% (HR 1.42, CI 0.88–2.28, p=0.146). Using the combined dataset, reduced survival was associated with more advanced disease stage (HR 2.00, CI 1.44–2.77, p<0.001), age (HR 1.03, 95% CI 1.01–1.05, p=0.002) and RDI ≤90% (HR 1.77, CI 1.12–2.79, p=0.014). In both models, the strength of the association with disease stage decreased over time.

Approximately 23% and 30% of UK and Belgian patients, respectively, received ARDI ≤90% and were, therefore, at risk of reduced survival. There are many factors that result in a decision to reduce or delay chemotherapy, including local institutional practice. Particularly relevant is the higher proportion of elderly patients in the Belgian dataset; elderly patients are at high FN risk [1] and often receive lower doses of chemotherapy [3]. Despite this common practice, dose-dense CHOP-14 chemotherapy...
supported with G-CSF has been shown to be efficacious and well tolerated in both young and elderly NHL patients. This study highlights the potential impact of receiving ARDI ≤ 90% on survival. While further investigation is needed, delivering full chemotherapy dose intensity remains an important goal in NHL patients who receive CHOP-21 chemotherapy.

Acknowledgements The authors wish to thank the following for contributing data: D Bron (Bruxelles, Belgium), P Johnson (Southampton, UK), A Van Hoof (Brugge, Belgium), B Hancock (Sheffield, UK), R De Bock (Antwerpen, Belgium), A Pagliuca (London, UK), Z Berneman (Edegem, Belgium), R Thomasi (Cambridge, UK), A Ferrant (Bruxelles, Belgium), M Joyner (Exeter, UK), M Dauwe (Bruxelles, Belgium), G Verhoef (Leuven, Belgium) and P Hoskins (Northwood, UK). The authors also wish to thank Amgen (Europe) GmbH, Zug, Switzerland for supporting this work with an unrestricted, educational grant, and Dr L. Woodford who provided medical writing services on behalf of medcept Ltd, Switzerland.

Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

References


The Prospective Oral Mucositis Audit: relationship of severe oral mucositis with clinical and medical resource use outcomes in patients receiving high-dose melphalan or BEAM-conditioning chemotherapy and autologous SCT.

Bone Marrow Transplantation 2008 Sep 8. [Epub ahead of print]
ORIGINAL ARTICLE

The Prospective Oral Mucositis Audit: relationship of severe oral mucositis with clinical and medical resource use outcomes in patients receiving high-dose melphalan or BEAM-conditioning chemotherapy and autologous SCT

S McCann1, M Schwenkglenks2, P Bacon3, H Einsele4, A D’Addio5, J Maertens6, D Niederwieser7, W Rabitsch8, A Roosaat9, T Ruutu10, H Schouten11, R Stone12, S Vorkurka13, B Quinn14 and N Blijlevens15, on behalf of the EBMT Mucositis Advisory Group

1Department of Haematology, St James’s Hospital, Dublin, Ireland; 2European Center of Pharmaceutical Medicine, II Department of Internal Medicine, Hematology/Oncology, University of Basel, Basel, Switzerland; 3Amen (Europe) GmbH, Zug, Switzerland; 4Department of Internal Medicine II, Julius Maximilian’s University of Würzburg, Würzburg, Germany; 5Institute of Haematology and Medical Oncology ‘L. and A. Seragnoi’, Bologna, Italy; 6Department of Haematology, Universitaire Ziekenhuizen Leuven, Catholic University, Leuven, Belgium; 7Department of Haematology and Oncology, University of Leipzig, Leipzig, Germany; 8BMT Unit, Medical University of Vienna, Vienna, Austria; 9Karolinska Institutet, Institute of Odontology, Huddinge, Sweden; 10Helsinki University Central Hospital, Helsinki, Finland; 11University Hospital Maastricht, Maastricht, The Netherlands; 12Nottingham City Hospital NHS Trust, Nottingham, UK; 13University Hospital Alej Scobody 80, Plzen, Czech Republic; 14St George’s Hospital, London, UK and 15Department of Haematology, University Medical Centre St Radboud, Nijmegen, The Netherlands

The Prospective Oral Mucositis Audit was an observational study in 197 patients with multiple myeloma (MM) or non-Hodgkin’s lymphoma (NHL) undergoing, respectively, high-dose melphalan or BEAM chemotherapy and autologous SCT at 25 European centres. We evaluated the relationship between severe oral mucositis (SOM; WHO Oral Toxicity Scale grade 3–4) and local and systemic clinical sequelae and medical resource use. SOM occurred in 44% of patients. The duration of SOM (mean 5.3 days) correlated with time to neutrophil engraftment. The following parameters increased gradiently with maximum grade of oral mucositis: duration of pain score ≥4, opioid use, dysphagia score ≥4, total parenteral nutrition (TPN) use, incidence and/or duration of fever and infection, and duration of antibiotic use. SOM increased the duration of TPN use by 2.7 days (P<0.001), opioids by 4.6 days (P<0.001), and antibiotics by 2.4 days (P=0.045). SOM prolonged hospital stay by 2.3 days (P=0.013) in MM patients, but not in NHL patients (who tended to have a longer hospital stay). In conclusion, this analysis of prospectively collected observational data provides important insight into the scope and impact of SOM in the European transplant setting.

Bone Marrow Transplantation advance online publication, 8 September 2008; doi:10.1038/bmt.2008.299

Keywords: oral mucositis; multiple myeloma; non-Hodgkin’s lymphoma; high-dose chemotherapy; medical resource use

Introduction

Oral mucositis (OM) is a very common debilitating adverse event in patients receiving high-dose chemotherapy and SCT, and results from damage to both epithelial and submucosal tissues by the conditioning regimen. Clinical manifestations of OM include signs and symptoms of an inflammatory process, ranging from mild erythema, oedema and soreness to extreme pain and ulceration. Severe OM interferes with daily activities such as speaking, eating and swallowing and has a negative impact on quality of life. It can lead to dehydration, malnutrition and serious infections and has been linked to inferior overall survival after SCT.

Several US-based analyses from various cancer settings have demonstrated that severe OM increases healthcare resource utilization by necessitating opioid analgesia, anti-infective treatment, total parenteral nutrition (TPN) and subsequently prolonging hospitalization. However, medical resource use in relation to OM has not been systematically assessed in the European SCT setting, although a recently published overview provided insights in the management of OM in European transplantation centres. The Prospective Oral Mucositis Audit (POMA), conducted by our group in 25 centres across 13 European countries, was the first multi-country audit study with OM...
occurrence as the primary objective. The first part of the analysis (described in our initial paper) revealed a high incidence of severe (World Health Organization (WHO) oral toxicity scale grade 3–4) OM (44%) in patients with multiple myeloma (MM) or non-Hodgkin’s lymphoma (NHL) who underwent high-dose dose melphalan or BEAM conditioning, respectively and autologous SCT. Severe OM risk and/or duration were significantly associated with higher chemotherapy dose per kg body weight and poor performance status, but in contrast to some previous reports they were not related to age.

The POMA design has been described previously. Study design and patient population

The POMA design has been described previously. In brief, this prospective, observational audit recruited 197 adult patients with MM or NHL who received high-dose melphalan (200 mg/m²; MM patients) or BEAM (carmustine 300 mg/m², etoposide 800 mg/m², cytarabine 800–1600 mg/m² and melphalan 140 mg/m²; NHL patients) conditioning chemotherapy followed by autologous SCT. Exclusion criteria were previous SCT/BMT, palifermin administration and presence of oral abnormalities at baseline. Prophylaxis and treatment for OM and its clinical sequelae were according to local clinical practice. Ethical approval was obtained according to country-specific requirements and all patients provided written informed consent.

Patients were selected from European transplant units, which had a history of reporting patients to the European Society for Bone and Marrow Transplantation registry. Centres were selected in which patients received autografts as inpatients to monitor ‘mucositis’ accurately. Centres were selected to represent a wide spectrum of European countries and to allow training of nurses to be a practical proposition.

Study assessments and data collection

Data collection included baseline demographic and medical characteristics and type and dosage of conditioning chemotherapy. OM assessments were conducted daily from day 1 of conditioning chemotherapy until 30 days post transplantation or hospital discharge (whichever occurred first), using the five-point WHO oral toxicity scale (grade 1: soreness and erythema, no further symptoms; grade 2: ulcers present, but solid diet possible; grade 3: only liquids can be swallowed; grade 4: oral alimentation impossible). To achieve consistent high-quality OM assessment, on-site nurse assessors and physicians underwent an intensive training programme. Ulcerative OM was defined as WHO scale score 2–4 and severe OM as WHO scale score 3–4. Specific 10-point scales were used to record local signs and symptoms of severe OM (0 = no symptoms present; 10 = worst possible symptoms, as judged by patients). Body temperature was recorded on the daily OM assessment forms. Time to neutrophil engraftment (>0.5 × 10⁹/l) was retrieved from the European Society for Bone and Marrow Transplantation Promise database. Information on infections and use of medical resources, including medications used for OM prophylaxis and treatment was obtained from the study sites. Medication categories included mouthwashes, opioid analgesics, antibiotics, antifungals, antivirals and other medications. These categories were not prospectively defined and were therefore open to interpretation by site staff. However, drug names were requested for verification purposes (except in the case of mouthwashes, as local preparations were often used). No on-site monitoring was performed for this study.

Statistical methodology

Clinical end points included in this analysis were: WHO oral toxicity scale score; duration of pain score ≥ 4, and dysphagia score ≥ 4; incidence and duration of fever (≥38.0°C), incidence of infection (clinically defined or microbiologically confirmed) and of microbiologically confirmed bacterial infection before day 30 post transplantation, and time to neutrophil engraftment. Medical resource utilization end points were duration of TPN, opioid analgesic and antibiotic use and duration of hospitalization.

The WHO scoring system was chosen because most European transplant centres were familiar with this instrument based on a survey by the nurses’ group of the European Society for Bone and Marrow Transplantation. Missing WHO scale and pain score values during the audit period were interpolated and missing values at the beginning or end of the audit period extrapolated. For the purpose of longitudinal assessments, a grade of 0 was also imputed after patient discharge and fever and dysphagia were assumed to be absent after patient discharge. Temporal patterns were assessed by plotting mean daily WHO scale-based OM scores and applicable symptom-specific scores over the audit period. The proportion of patients with fever was plotted in a similar way.

Using univariate analyses, associations of interest were assessed using the χ² test, the non-parametric Mann-Whitney U-test or the Spearman’s correlation coefficient and its P-value, as appropriate. Multivariate Poisson regression was used to further assess the impact of severe OM on the duration of hospitalization. Parameters that were explored as potential determinants of length of hospital stay included baseline characteristics (age, sex, weight, height, body surface area, Eastern Cooperative Oncology Group (ECOG) performance status, type and dosage of chemotherapy), time to neutrophil engraftment, as well as infection-related parameters (incidence and duration of fever and incidence of infection and microbiologically confirmed bacterial infection before day 30 post transplantation—which would be difficult to interpret in models of OM occurrence).

Random effects modelling was used to assess possible distortions of the main study results by centre effects.
Poisson regression used generalized estimation equations (GEE)-based robust s.e. estimates to allow for clustering by study centre. Statistical analyses were performed using the STATA/SE version 9 statistical software package. Statistical tests were two-sided at the 5% significance level. Two-sided 95% confidence intervals are shown.

Results

Study population
Patient baseline characteristics and conditioning chemotherapy doses for the 197 evaluable patients enrolled into POMA (109 patients (55.3%) with MM and 88 (44.7%) with NHL) are summarized in Table 1. Mean recruitment per centre ± s.d. was 7.9 ± 4.8 patients (range, 1–18). In the MM group, the mean age was higher and there were fewer women, consistent with the epidemiology of this disease. The audit period lasted (mean ± s.d.) 19.8 ± 4.5 days in the MM group and 22.4 ± 3.7 days in the NHL group. The time from first chemotherapy administration to transplantation was longer in the NHL group than in the MM group (median 7 vs 3 days), as BEAM is typically administered over 5 days and high-dose melphalan over 1–2 days. Patients received various types of OM prophylaxis, including mouthwashes (78% of patients), antibiotics (36%), antifungals (54%) and antivirals (44%), according to local practice. The most frequently used antifungal substance was fluconazole, followed by itraconazole, systemic or local amphotericin B, and nystatin. Antivirals were aciclovir or valaciclovir.

Evolution of OM
A total of 87 (44.2%), of 197 patients experienced severe OM (46% in patients with MM and 42% in patients with NHL), with a mean duration of 5.3 ± 3.2 days: there were no relevant differences between MM and NHL patients with regard to these end points. A significant amount of variation between centres with respect to these end points was noted but random effects modelling yielded no indication of a related distortion of the overall results. The temporal relationship of WHO scale score with pain and dysphagia scores, fever and neutrophil engraftment is shown in Figure 1. The median onset of ulcerative OM and of severe OM was on days 11 and 12, respectively, after the start of conditioning chemotherapy. This coincided with median onset of fever, infection and microbiologically confirmed bacterial infection, both in patients with and in patients without severe OM. The peak level of discomfort was experienced on days 12–13 and this coincided with the beginning of neutrophil engraftment (Figure 1). The relationship of maximum grade of OM and clinical and healthcare resource outcomes is summarized in Table 2.

Pain and opioid use
Not surprisingly, the duration of pain score ≥ 4 increased gradually with the maximum WHO OM scale score (P < 0.001), reaching a mean duration of 6.5 days in patients with WHO grade 4 OM. Opioid analgesic use also increased across the OM grades (P < 0.001), patients with

Table 1 Patient demographics, baseline medical characteristics and treatment regimens, mean ± s.d. (range) except where indicated

<table>
<thead>
<tr>
<th></th>
<th>Multiple myeloma</th>
<th>Non-Hodgkin’s lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>109</td>
<td>88</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>109</td>
<td>88</td>
</tr>
<tr>
<td>ECOG status, n (%)</td>
<td>108</td>
<td>88</td>
</tr>
<tr>
<td>Melphalan dose, mg/m² BSA</td>
<td>105</td>
<td>85</td>
</tr>
<tr>
<td>Carmustine, mg/m² BSA</td>
<td>105</td>
<td>85</td>
</tr>
<tr>
<td>Cytarabine, mg/m² BSA</td>
<td>105</td>
<td>85</td>
</tr>
<tr>
<td>Observation time, median days (range)</td>
<td>109</td>
<td>88</td>
</tr>
</tbody>
</table>

Abbreviations: BSA = body surface area; ECOG = Eastern Cooperative Oncology Group.

Figure 1 Evolution of mean WHO oral toxicity scale, pain and dysphagia scores and proportions of patients with fever and neutrophil engraftment. This assumes a standardized observation time of 39 days and zero score values and proportions after the patients’ individual audit periods. Based on n = 197 patients (193 with engraftment data).
severe OM requiring an additional 4.6 days of opioid use ($P<0.001$) compared with those without severe OM (Table 2).

**Dysphagia and TPN use**
The duration of dysphagia score $\geq 4$ increased with increasing maximum WHO OM scale score ($P<0.001$), reaching a mean duration of 8.4 days in patients with WHO grade 4 OM. Duration of use of TPN (averaged across all patients including those who did not receive TPN) also increased across OM grades (Table 2), patients with severe OM receiving an additional 2.7 days of TPN compared with those without severe OM; ($P<0.001$). The incidence of TPN use ranged from 19% in patients with no OM to 59% in patients with WHO grade 4 OM. It was 35% across all patients.

**Fever and antibiotic use**
Fever, infection and microbiologically confirmed infection, increased with increasing grade of OM (Table 2). Comparison of patients with and without severe OM showed that patients with severe OM had a higher incidence of fever (68 vs 47% of patients; difference 21%; $P=0.004$), infection (42 vs 24%; $P=0.013$) and microbiologically confirmed bacterial infection (27 vs 12%; $P=0.013$), and a longer duration of fever (4.2 vs 3.0 days; $P=0.033$). The duration of severe OM (in patients who developed severe OM) mostly showed the same associations, but it was not significantly associated with the incidence of infection or of microbiologically confirmed bacterial infection (data not shown).

Combined duration of antibiotic use with prophylactic and therapeutic intent also increased across OM grades (Table 2), patients with severe OM receiving an additional 2.4 days of antibiotics ($P=0.045$) compared with those without severe OM.

**Neutrophil engraftment**
Time to neutrophil engraftment did not show any clear correlation with the maximum grade of OM (Table 2) or severe OM incidence, but it was positively correlated with the duration of severe OM (Spearman’s correlation coefficient 0.27; $P=0.012$). This observation was confirmed when time to neutrophil engraftment was tentatively allowed as an additional covariate in the multivariate analysis of severe OM duration ($P<0.001$), as noted in our earlier analysis.

**Length of hospital stay**
Length of hospital stay increased with increasing severity of OM in patients with MM, ranging from 17.0±5.4 days in patients with no OM to 21.5±3.7 days in patients with grade 4 OM, with severe OM prolonging hospital stay by 2.3 days ($P=0.013$). However this trend was less clear in patients with NHL, who tended to have a longer hospital stay than patients with MM (Table 2).

Multivariate Poisson regression analysis showed that higher age, higher baseline Eastern Cooperative Oncology Group performance status, longer duration of severe OM, longer time from start of conditioning to transplantation and longer time from transplantation to neutrophil engraftment were associated with significantly longer hospitalization (Table 3). The impact of duration of severe OM on duration of hospitalization was attenuated by both time to transplantation and time to neutrophil engraftment (Table 3) (indicating that the effect of duration of severe OM on hospital stay is reduced if hospitalization is prolonged anyway). When indicators of fever or infection were added to the model, the effect of severe OM duration...
Increasing grade of OM.

of fever and/or febrile neutropenia (FN) increases with the process that is induced by conditioning chemotherapy...

Previous studies in the SCT setting have shown that the risk of fever may be a manifestation of the inflammatory duration of fever 1.2 days longer, in those with severe OM.

An alternative hypothesis is that fever may be a manifestation of the inflammatory duration of fever 1.2 days longer, in those with severe OM.

severity of OM was closely related to development of fever, instead of duration, of severe OM in the analysis.

Factors influencing duration of hospitalization (Poisson Model)

<table>
<thead>
<tr>
<th>Coefficient (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.004 (0.002 to 0.006)</td>
</tr>
<tr>
<td>Baseline ECOG status</td>
<td>0.052 (0.019 to 0.085)</td>
</tr>
<tr>
<td>Severe OM duration</td>
<td>0.058 (0.024 to 0.091)</td>
</tr>
<tr>
<td>Time to transplantation</td>
<td>0.058 (0.036 to 0.080)</td>
</tr>
<tr>
<td>Interactions to neutrophil engraftment</td>
<td>0.026 (0.014 to 0.038)</td>
</tr>
<tr>
<td>Interaction of time to transplantation and severe OM duration</td>
<td>-0.005 (0.009 to -0.001)</td>
</tr>
<tr>
<td>Interaction of time to neutrophil engraftment and severe OM duration</td>
<td>-0.002 (-0.004 to -0.000)</td>
</tr>
<tr>
<td>Constant</td>
<td>2.162 (1.869; 2.456)</td>
</tr>
</tbody>
</table>

Multiplying the coefficients of Poisson Models by 100 yields a value approximating to percentage changes of the expected values of the response variable.

N = 191 on account of missing covariate values. One patient who died around the time of transplantation was hospitalized for only 3 days and one patient with an outlying time from transplantation to neutrophil engraftment of 65 days was also excluded.

The association of fever with oral mucositis has been attributed to local and systemic infections, as disruption of the mucosal barrier may provide an entry point for pathogens. However, infection frequently cannot be documented in febrile patients. An alternative hypothesis is that fever may be a manifestation of the inflammatory process that is induced by conditioning chemotherapy and driven by acute phase cytokines such as tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6). Mucositis itself is also a potential source of local and systemic cytokines. These cytokines can induce sepsis-like signs and symptoms when administered exogenously to humans. Indeed, one study found that blood levels of TNF-α and IL-6 were significantly correlated with changes in body temperature in cancer patients who were administered TNF.

We found that severe OM duration was positively correlated with time to neutrophil engraftment and that engraftment coincided with peak OM scores (Figure 1). This supports previous observations that healing of OM coincides with neutrophil recovery. Although some investigators have failed to find a link between OM and neutropenia, Rapoport et al. noted that duration of neutropenia was a risk factor for OM and the severity of OM has been linked to the degree of neutropenia. Oral neutrophil kinetic studies (using mouth rinses) in patients recovering from profound neutropenia have demonstrated that neutrophils are present in the tissues before peripheral neutrophils recover. Consistent with their important role in mucosal defence and repair. A study in the BMT setting found that neutrophil levels in mouth rinses decreased to undetectable levels during the neutropenic period, but recovered 1–2 and 3–9 days before peripheral neutrophil counts reached 0.1 and 1.0 x 10^9/L, respectively, regardless of whether or not patients received granulocyte-colony stimulating factor (G-CSF) support. A study in paediatric SCT patients found that the return of neutrophils to the oral cavity marked the beginning of the mucosal recovery phase. Moreover, the time span between oral and peripheral neutrophil recovery was inversely related to the number of infection-related febrile episodes occurring after peripheral engraftment.

Duration of severe OM was associated with the duration of hospitalization, and development of severe OM prolonged the hospital stay by 2.3 days (P = 0.013) in MM patients. However, fever and infection were cofactors in prolonging hospitalization. Therefore, if severe OM is itself a causative factor in fever and infection (Table 2), including these covariates may lead to underestimation of the effect of severe OM on duration of hospitalization, a major driver of costs in this setting. Other factors influencing hospital stay were age, baseline Eastern Cooperative Oncology...
Group status, time to transplantation and time to neutrophil engraftment. Duration of use of TPN, opioids and antibiotics also increased with increasing grade of OM, patients with severe OM requiring an additional 2.7 days of TPN, 4.6 days of opioids and 2.4 days of antibiotics. All three associations are further supported by the very similar temporal patterns of OM occurrence, pain, dysphagia and fever (Figure 1).

Our findings are consistent with earlier data from the United States. An earlier prospective, multicentre study in blood or marrow transplant recipients (n = 92)\(^8\) and a retrospective chart review in SCT recipients (n = 281)\(^9\) found that resource use and clinical outcomes, including duration of hospitalization, were significantly correlated with the severity of OM. A retrospective case–control study in 24 patients who developed z-haemolytic streptococcal bacteraemia following autologous BMT\(^5\)\(^6\) found that OM prolonged hospital stay both independently and as a cofactor associated with bacteraemia.

Systemic drug exposure was a key determinant of severe OM risk in our previous analysis,\(^1\) in line with other observations.\(^29,\(^30\)\) Indeed, a recent study by a German group found that patients treated with a melphalan dose ≥70 mg/m\(^2\) had a 23-fold increased risk of developing mucositis (P < 0.001) compared with those receiving lower doses.\(^30\) Thus, we tentatively evaluated whether there was an association between melphalan dose per kg body weight and medical resource use, in MM patients only. No relationship was found, indicating that the observed associations of OM with medical resource use were not directly on account of higher drug doses.

Changes in guidelines to prevent or treat OM have recently been reviewed\(^13\) and include the use of cryotherapy (ice-water or chips) during the infusion of high-dose melphalan; however, the authors also state: ‘However, additional and sustained efforts will be required to gain a fuller understanding of the pathobiology, impact on overall patient status, optimal therapeutic strategies, and improved educational programs for health professionals, patients, and caregivers’.

In conclusion, our analysis of prospectively collected observational data has provided important insights into the scope and impact of severe OM in patients undergoing SCT in routine clinical practice in Europe. The correlation of severe OM with serious systemic sequelae such as infection and increased use of healthcare resources, together with the adverse impact on patient quality of life, underlines the need for effective measures for preventing OM. It is hoped that our findings will help to guide the use of novel preventive treatments.

Acknowledgements

Roisin Cínneide and Kim Champion were data manager and study coordinator, respectively. The EBMT Oral Mucositis Advisory Group wishes to thank Amgen (Europe) GmbH, Zug, Switzerland, for supporting this work. Julia Balfour (Consultant Medical Writer, Kilonquhar, Scotland) and Claire Foster (Amgen (Europe) GmbH) assisted with the writing of the paper. We also gratefully acknowledge the participation of the investigators, staff and patients from the study centres.

References


Schwenkglenks M, Marbet UA, Szucs TD.

Epidemiology and costs of gastroesophageal reflux disease in Switzerland: a population-based study.

Epidemiology and costs of gastroesophageal reflux disease in Switzerland: a population-based study

Summary

Objectives: Assessment of the prevalence, health care resource use and cost of gastroesophageal reflux disease in Switzerland.

Methods: A population-based telephone survey was conducted in German and French speaking Switzerland. Reflux cases were defined using a questionnaire proposed by the German Gastro League and answered additional questions on their personal characteristics and resource use.

Results: 1274 out of 7222 participants were positively screened. The prevalence of reflux disease in Swiss adults was estimated at 17.6% (95% CI: 15.6%–19.7%) or 993,000 individuals. Regular treatment with medication was reported by 38.0% of the reflux positive sample. Reflux-induced general practitioner consultations during the last year were reported by 25.9%. On average, there were 0.84 general practitioner consultations, 0.19 specialist consultations, 0.08 gastroscopies and 0.01 hospitalisations annually. Mean direct medical costs, dominated by medication costs, were CHF 185 per patient-year (95% CI: CHF 140–230) or 0.5% of Switzerland’s total health care expenditures. Total costs were CHF 234 (95% CI: CHF 185–284) per patient-year.

Conclusions: The prevalence of reflux disease in Switzerland is similar to that in other industrialised countries. Reflux disease causes considerable costs, in the medical system and at the societal level.

Keywords: Gastroesophageal reflux – Epidemiology – Economics – Cost of illness – Switzerland.

Recent studies addressing the epidemiology of oesophageal reflux disease have reported a tenfold increase in prevalence during the last 30 years (El-Serag & Sonnenberg 1998). During the same time span, reflux may have developed from a problem mainly affecting males to one being equally distributed between genders (Ter 2000). Surveys in France, Great Britain, Italy, Sweden, and Germany have shown that 18% to 40% of the populations of these countries suffer from reflux symptoms (Kennedy et al. 1998; Rösch & Hotz 2000). U.S. prevalence figures are in the same range (Spechler 1992; Locke et al. 1997). Quality of life studies in patients with reflux disease show these to be seriously incapacitated (Rösch & Hotz 2000). Reflux disease is associated with a risk of developing Barrett’s Esophagus (BE), and of subsequently developing adenocarcinoma of the oesophagus, with a very poor prognosis (Skinner et al. 1983). The causes of the increase in reflux disease remain unclear. Environmental factors such as stress, stimulus satiation, and changes in dietary practices are discussed, as well as decreasing infection rates with Helicobacter pylori and the introduction of medications promoting reflux by relaxing the lower oesophageal sphincter (Lagergren et al. 2000). The development of proton pump inhibitors (PPIs) has revolutionised the treatment of reflux disease and the approach to BE. PPIs allow for a continuous suppression of gastric acid production, generally achieving a healing of oesophagitis (Janknegt et al. 1999). In order to avoid recurrences, costly continued treatment with this class of substances is usually necessary (O’Connor et al. 2000). The overall economic impact of reflux disease appears to be significant. Cost of illness studies performed in the U.S. and Great Britain reported annual costs of several hundred Swiss francs per person (Levin et al. 1997; Eggleston et al. 1998). Information on the cost of illness of reflux disease in Switzerland has not been published so far.
Objectives
To address the epidemiology and economics of reflux disease in Switzerland, with a principal focus on prevalence, on the utilisation of health care resources, and on associated costs.

Methods
Data collection
A population-based survey using computer-assisted telephone interviews (CATIs) was conducted in November 2000. Interviewees were selected and interviews performed by IPSO, Dübendorf, Switzerland, a company experienced in the field of health-related survey research and collaborator of several federal agencies including the Swiss Federal Statistical Office. All interviewers were part-time employees of IPSO. They had no medical training, but received a project-specific introduction and continuous supervision by the CATI lab's leading staff.

The target population were persons domiciled in the French- and German-speaking parts of Switzerland, aged 18 years or more. Interviewee selection was based on a two-step random quota procedure using an address database listing all Swisscom fixed telephone connections. A proportion of three German speaking households to one French speaking was maintained, reflecting the relative size of language groups in the Swiss population. Within households, one person was selected at random, but proceedings were modified to fulfil age and gender quota corresponding to the mean 1998 permanent resident population (Bundesamt für Statistik 1999). Households exclusively relying on mobile telephones and persons living in institutions could not be included. At the time of the survey, fixed telephone coverage was very high in Switzerland, with more than 4 200 000 fixed telephone connections in a population of 7.164 Million (Bundesamt für Kommunikation 2000).

Calls were made Monday to Friday from 5 p.m. to 9 p.m., thus ensuring a high availability of professionally active as well as other persons. 17654 telephone numbers were called. In 646 cases, there was no contact after 10 calls, or the number belonged to a modem/fax device or a company, or it was invalid. In 3592 cases, no person in the household met the age and gender quota requirements. 1102 interviews could not take place due to language problems or because the person selected was too old or ill. Of the remaining 12314 persons, 5092 (41 %) refused or interrupted their interview. 7222 interviews (59 %) were realised.

Screening was performed by recording reflux symptoms on the basis of a questionnaire (Tab. 1) developed and applied by the German Gastro League (Anonymous 2001). This instrument is referring to the present, without explicitly specifying a time span of observation. Focusing on heartburn and acid regurgitation, it comprises eight easily understandable questions divided into two sets of four. Persons answering at least one question in each set positively are defined as reflux cases.

All positively screened interviewees were questioned in greater detail to assess their utilisation of medical resources and direct medical costs. Absences from work were recorded to allow for the calculation of indirect costs. Additional sociodemographic, physiologic and anamnestic data were recorded to be used in the analysis of prevalence (age, gender, language region), in the description of the characteristics of the reflux positive sample (age, gender, height, weight, smoking status, presence of asthma, percentage of women pregnant during the observation period), and as potential influences on resource use and cost (all afore mentioned, education, employment status, household income, familial status, insurance status, urban or rural character of place of domicile) to be taken into account in multivariate analysis (Schneeweiss & Sangha 2000).

Body mass index (BMI), smoking status, presence of asthma and pregnancy have been previously reported to be positively associated with the presence of reflux symptoms (Isolauri & Laippala 1995; Mokhlesi et al. 2001). Screening interviews lasted about five, in-depth interviews about 12 minutes.

Cost analysis
Cost of illness studies usually divide costs into direct costs, for which payments are made; indirect costs or losses of resources; and intangible costs related to facts that are difficult to express in monetary terms, e.g., the consequences of decreased quality of life (Rice 1994). Direct costs are estimated as the product of the number of services performed and their unit prices or charges. Following the human capital approach, the human capital costs are estimated as the product of the number of losses of human capital and a value of one’s working day (Laippala & Voutilainen 2000). Indirect costs are estimated as the product of the number of absences from work and a value of one’s working day (Laippala & Voutilainen 2000).

To address the epidemiology and economics of reflux disease in Switzerland, with a principal focus on prevalence, on the utilisation of health care resources, and on associated costs.
or lost productivity due to the disease in question. Intangible costs are difficult to assess and, as in most studies, were not included in our calculations. Direct medical cost factors comprised outpatient costs (consultation costs and outpatient endoscopy costs), hospital costs and medication costs. All expenditures on these resources were taken into account independently of the payer (patient, third-party, or state). In this sense, a societal perspective of cost assessment was adopted. All costs are indicated in their original currency and in Swiss currency (CHF). On November 30, 2000, at the end of the data collection period, CHF 1 equaled 0.57 US Dollars ($) and 0.40 British Pounds (£).

Regional tariff lists (Kantonale Tarifvereinbarungen zwischen Ärzten und Krankenkassen) valid in 1999 were used to estimate mean consultation costs. Conservatively assuming ordinary consultations without any particularities causing extra charges resulted in an approximation of CHF 24.50 for a consultation with a non-specialist as well as a specialist physician. Using the same lists, outpatient endoscopies were estimated to cost CHF 425 on average. It was assumed that, in cases of a suspected diagnosis of reflux disease, complete endoscopies of the oesophagus, stomach, and duodenum were performed, but biopsies and other additional procedures rarely needed.

A day on the general ward of a public hospital was reimbursed with an intercantonal mean of CHF 320 in 1999 (Konkordat der Schweizerischen Krankenversicherer 1999). Additional public subsidies to the Swiss hospitals amounted to CHF 4 700.5 Million in 1998 (Bundesamt für Statistik 2001). Assuming these subsidies to support hospitals’ inpatient and ambulatory expenditures proportionally, and dividing the 90% share of inpatient expenditures by the estimated number of 1998 hospital days, results in a mean subsidy of CHF 300 per day (Bundesamt für Statistik 2002). The sum of CHF 620 is used as an estimate of average daily hospitalisation costs. This figure assumes that persons with a semi-private or private complementary insurance are not excluded from the benefits of public subsidies. Proceeding differently would be difficult as the exact proportion of these persons is not known (Bundesamt für Sozialversicherung 2000). Costs of reflux-related operations were not assessed additionally, as this would have raised a problem of double-counting. Reflux-related medication costs during the 12 month period preceding the survey were directly estimated by our interviewees.

For the calculation of indirect costs, only the days off work of persons with a full- or part-time work contract, and of those self-employed or following a job-training were included. The costs of caring for relatives, of early retirement, and of premature death should also be accounted for in theory, but presumably can be neglected in the case of reflux. A one day absence from work was estimated to cost CHF 230, on the basis of a population-level standardised median salary of CHF 4 988 as reported by the 1998 Salary Structure Survey of the Swiss Federal Statistical Office (Bundesamt für Statistik 1999).

Statistical methods
Sample weights were applied to correct for small deviations from the age and gender quota requested, thus allowing for population-adjusted prevalence estimates and ensuring comparability of the characteristics of the positively screened individuals with population-level data from other sources including the 1997 Swiss Health Survey (SHS ‘97). SHS ‘97 results, originally covering persons aged 15 or older, were recalculated by the Swiss Federal Statistical Office, to meet the age range of this survey.

All statistical analyses were performed using SPSS 10.0®. To analyse bivariate associations of categorical variables, odds ratios (ORs) were calculated. In case of one continuous variable, Mann-Whitney U tests and Kruskall-Wallis tests were used, due to the skewed distributions observed (Glick & Polsky 1999). Correlations of two continuous or ordinal variables were assessed by Spearman’s correlation coefficient. Two-tailed p = 0.05 was used as the level of statistical significance. Confidence intervals (CIs) are given at the 95% level. As there was no access to the SHS ‘97 data at the individual observation level, comparisons with these were not based on statistical tests.

To further investigate significant bivariate associations and correlations of potential influence factors on direct medical costs, multivariate least squares regression on the logarithm of direct medical costs was performed. Before taking the logarithm, CHF 0.10 was added to all observations in order to avoid undefined values.

Results

Prevalence of reflux disease and history of illness
The prevalence of reflux disease in the adult population was 17.6% (95% CI: 15.6%–19.7%), based on 1 274 cases among 7 222 persons aged at least 18 years who were interviewed. Using these data, the number of persons in Switzerland with reflux disease can be estimated at approximately 993 000 (95% CI: 944 000 – 1 043 000). Of the persons interviewed, 5 538 (76.7%) lived in the German-speaking part of Switzerland, and 1 683 (23.3%) lived...
in the French-speaking part. The proportion of the positively screened was 16.4% in the German-speaking part (907 persons) and 21.9% in the French-speaking part (368 persons). This translates into a statistically significant OR of 1.34 (95% CI: 1.20–1.49).

There was a constant but moderate rise with age, from 11.7% in those aged 18 to 29 to a peak of 23.1% in persons of age 70 to 79 (Tab. 2). The highest age group (80 and over) reported a lower prevalence of 18.7%.

The proportion of the positively screened was 18.2% in the women and 17.1% in the men, corresponding to a non-significant OR of 1.11 (95% CI: 0.97–1.25).

Mean disease duration was 9.8 years (median 6 years). Stratification by 10-year age groups shows mean values ranging from 3.1 years in those aged 29 or younger to 14.2 years in those aged 70–79 (Tab. 2). Here too, persons aged 80 or older reported a lower figure. Medians followed a similar pattern.

### Sociodemographic, physiologic and anamnestic variables

Table 3 shows characteristics of the persons identified to suffer from reflux disease. These are contrasted to population level estimates derived from all 7 222 interviews of this survey if available, or from the SHS ‘97.

Mean age was slightly but significantly higher in the positively screened persons (p < 0.0005). The share of women was 2.0% higher in the positively screened group, which corresponds to a non-significant OR of 1.11 (95% CI: 0.97–1.25). Both absolute body weight and BMI results suggest a distinctly higher proportion of overweight persons in the reflux positive compared to the general population. A history of current or past smoking was reported by 48.6% of the reflux positive persons, compared to 52.6% in the SHS ‘97. Reflux positive interviewees reported to suffer from asthma in 110 cases (8.6%).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Prevalence and disease duration by 10-year age intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>N (total)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>7 222</td>
</tr>
<tr>
<td>18–29</td>
<td>745</td>
</tr>
<tr>
<td>30–39</td>
<td>1 438</td>
</tr>
<tr>
<td>40–49</td>
<td>1 440</td>
</tr>
<tr>
<td>50–59</td>
<td>1 263</td>
</tr>
<tr>
<td>60–69</td>
<td>961</td>
</tr>
<tr>
<td>70–79</td>
<td>736</td>
</tr>
<tr>
<td>≥ 80</td>
<td>638</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Characteristics of positively screened persons and population level estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Positively screened persons (N = 1 274)</td>
</tr>
<tr>
<td></td>
<td>Average value ± standard deviation or %</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.4 ± 17.3</td>
</tr>
<tr>
<td>Women (%)</td>
<td>53.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.0 ± 11.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.8 ± 14.7</td>
</tr>
<tr>
<td>BMI groups (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt; 20</td>
</tr>
<tr>
<td></td>
<td>20, &lt;25</td>
</tr>
<tr>
<td></td>
<td>25, &lt;30</td>
</tr>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td>History of smoking (%)</td>
<td>48.6</td>
</tr>
<tr>
<td>Asthma (%)</td>
<td>8.6</td>
</tr>
<tr>
<td>Presence of pregnancy in women aged 18–45 years (%)</td>
<td>6.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> All interviewees of our telephone survey
<sup>b</sup> Swiss Federal Statistical Office, 1997 Swiss Health Survey. Reference: persons aged 18 or older. Standard deviations not available
<sup>c</sup> Unit of BMI: kg/m<sup>2</sup>
Utilisation of medical resources

Only 796 (62.4%) of the reflux cases reported to “do something against the disease”. Regular treatment with medication was reported by 458 (38.0%). Information on the names of the drugs used was provided by 349 persons, of which 114 (32.6%) took prescription drugs. Combining these figures lead to an estimate of 11.8% of the persons with reflux taking prescription drugs (mainly PPIs) regularly.

Treatment by a general practitioner in the 12 months preceding the survey was reported by 330 (25.9%) patients, who saw their doctor 3.1 times on average (95% CI: 2.7–3.5, median 2). The maximum number of consultations due to reflux was 25. Specialists were consulted up to 12 times by 134 patients (10.6%), 1.8 times on average (95% CI: 1.6–2.1, median 1.8). A history of gastroscopy was reported by 382 patients (30.0%). This procedure took place within the previous year in 95 patients (7.5%). A history of reflux-related hospitalisation was reported by 55 persons (4.3%), and by 14 patients (1.1%) with reference to the previous year. Mean duration of hospitalisation was 9.7 days (median 7). Hospitalisations during the year preceding the survey only lasted 6.3 days (median 4.8).

Mean consultation frequencies for all positively screened persons and utilisation frequencies of other health care resources are shown in Table 4. At this level, medians were 0 for all resource use variables, due to heavily right-skewed distributions.

Reflux-related absences from work during the last 12 months were remembered by 48 persons (3.8% or 7.7% of those being professionally active or on a job training). Mean duration of absence from work was 5.6 (median 2.3) days, which corresponds to 0.4 (median 0) days per year in the professionally active, and to 0.2 (median 0) days per year in all positively screened persons.

Costs of gastroesophageal reflux in Switzerland

Direct costs: The mean contribution of different cost parameters to reflux-associated direct medical costs is shown in Table 5. Medians were CHF 0, due to heavily right-skewed distributions. This was mirrored in the reflux-associated direct medical costs themselves. These amounted to CHF 185 (95% CI: CHF 140–230) per year on average, and were clearly dominated by medication costs, with hospital, endoscopy, and general practitioner costs being second to fourth in importance.

Higher direct medical costs were weakly correlated with age (Spearman’s correlation coefficient 0.16, p < 0.005) and disease duration (Spearman’s correlation coefficient 0.07, p = 0.013). Correlations with weight (0.01, p = 0.745) and BMI (0.05, p = 0.092) were not statistically significant. There was virtually no cost difference between men and women (CHF 184 vs CHF 186, p = 0.835). Cost differences between persons with and without a history of smoking (CHF 156 vs CHF 213, p = 0.930), and between asthma patients and non-asthma patients (CHF 217 vs CHF 182, p = 0.500) were not statistically significant.

Higher costs in the French versus German speaking areas (CHF 191 vs CHF 183) and in persons living in urban versus rural surroundings (CHF 235 vs CHF 150) reached statistical significance (p = 0.018 and p = 0.020). The level of education also had a significant effect on treatment costs (p = 0.046). Persons having completed compulsory education and/or a professional training incurred costs of CHF 203 per year, those with a high school diploma incurred costs of CHF 121, and those with a technical school diploma or a university degree costs of CHF 154. Costs of persons with statutory health insurance were CHF 187 per year on average, whereas persons with an additional semi-private or private insurance incurred costs of CHF 174 and CHF 228 per year, respectively (p = 0.270). Correlation with household income was negative, but weak and non-significant (Spearman’s correlation coefficient -0.05, p = 0.165).

Multivariate least squares regression on the logarithm of direct medical costs confirmed that all associations and correlations found to be significant in bivariate analysis were also significant or near-significant in regression, with their directions unchanged. Disease duration was the only exception. Other potential influences did not reach p-values < 0.20. The

Table 4

<table>
<thead>
<tr>
<th>Resource</th>
<th>No. of patients using resource or being affected during reference period</th>
<th>Units consumed</th>
<th>Rate/patient/year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>General practitioner consultations</td>
<td>330 (25.9%)</td>
<td>1 071</td>
<td>0.84</td>
</tr>
<tr>
<td>Specialist consultations</td>
<td>134 (10.6%)</td>
<td>245</td>
<td>0.19</td>
</tr>
<tr>
<td>Endoscopies</td>
<td>95 ( 7.5%)</td>
<td>95</td>
<td>0.08</td>
</tr>
<tr>
<td>Hospitalisations</td>
<td>14 ( 1.1%)</td>
<td>14</td>
<td>0.01</td>
</tr>
<tr>
<td>Hospital days</td>
<td>-</td>
<td>91</td>
<td>0.07</td>
</tr>
<tr>
<td>Days off work</td>
<td>49 ( 3.8%)</td>
<td>272</td>
<td>0.21</td>
</tr>
</tbody>
</table>

© Birkhäuser Verlag, Basel, 2004
explanatory power of all possible models remained minimal, with R-squared values consistently below 0.05. Table 6 shows the final model.

Indirect costs: Calculation based on reflux-related days off work as reported by our interview partners lead to an estimate of mean indirect costs of CHF 49 (95% CI: CHF 28–70) per person-year for all reflux cases, and of CHF 90 (95% CI: CHF 52–128) per person-year in those professionally active or on a job training. Medians were 0 in both cases.

Total costs: Total costs summed up to CHF 234 (95% CI: CHF 185–284) per person-year.

Extrapolation to the whole of Switzerland
Assuming 993000 Swiss persons with reflux disease lead to an estimate of the total costs of reflux disease in Switzerland of CHF 0.23 billion per year. Direct medical costs amounted to CHF 0.18 billion per year.

According to the Swiss Federal Statistical Office, total health care expenditures in Switzerland amounted to CHF 39.8 billion in 1998 (Bundesamt für Statistik 2001). Thus, the direct medical costs of reflux disease account for approximately 0.5% of total Swiss health care expenditures.

Discussion
The main methodological issues to be addressed are the advantages and disadvantages of population-based data collection, the choice of risk score, and cost assessment.

Data collection: Any approach to the study of reflux disease relying solely on medical records would necessarily underestimate prevalence at the population-level and overestimate resource use per person, as many of those affected do not seek medical assistance. A population-based approach to data collection is necessary. Thus, the distortions occurring if non-representative samples of study participants are recruited in physician’s offices can largely be avoided. In addition, out-of-pocket expenses never showing up in medical records can be accounted for. On the other hand, population-based data collection has its own pitfalls, the most important being limited quality of information, recall bias and selection bias.

The most important potential reason of selection bias despite correct sampling is non-response. Comparisons of face-to-face, mailed and telephone surveys addressing health-related issues showed small differences between modes of administration and small non-response effects with respect to prevalence estimates (Marcus & Crane 1986; O’Toole et al. 1986). Non-response in telephone surveys was found to be less content-oriented than in mailed surveys (Fowler et al. 2002). Also, bias due to different sociodemographic characteristics of persons inaccessible by telephone affected reports of illness and related use of services only marginally, if the general population was addressed and if telephone coverage was at least 90% (Marcus & Crane 1986; Ford 1998). It can be assumed that these preconditions were fulfilled in Switzerland at the time of our data collection, when exclusive use of mobile phones was still infrequent. Persons living in institutions could not be included, which would be critical in the study of a disease affecting the higher ages differentially or directly causing institutionalisation. In the case of reflux, it should be of minor importance. The overall risk of relevant selection bias can be assumed to be relatively small in this study.

Information quality clearly is a more critical problem. Assessments of health related issues and resource use by survey methods are prone to error and recall bias. Comparisons with medical records have revealed relevant potential shortcomings, notwithstanding the fact that the completeness and correctness of medical record information is an issue in itself.

Table 5 Costs of reflux disease in Switzerland, per patient-year (N = 1274)

<table>
<thead>
<tr>
<th>Resource</th>
<th>Costs/patient/year (CHF)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>General practitioner consultations</td>
<td>21</td>
</tr>
<tr>
<td>Specialist consultations</td>
<td>5</td>
</tr>
<tr>
<td>Endoscopies</td>
<td>32</td>
</tr>
<tr>
<td>Medication</td>
<td>84</td>
</tr>
<tr>
<td>Total ambulant costs</td>
<td>141</td>
</tr>
<tr>
<td>Hospital costs</td>
<td>44</td>
</tr>
<tr>
<td>Direct medical costs</td>
<td>185</td>
</tr>
<tr>
<td>Indirect costs</td>
<td>49</td>
</tr>
<tr>
<td>Total costs</td>
<td>234</td>
</tr>
</tbody>
</table>

Table 6 Multivariate least squares regression on the logarithm of direct medical costs (N = 1 266)

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Prob &gt; F = 0.000</th>
<th>Adjusted R-squared = 0.029</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.024</td>
<td>0.012</td>
<td>0.035</td>
</tr>
<tr>
<td>German language region</td>
<td>0.764</td>
<td>1.188</td>
<td>0.340</td>
</tr>
<tr>
<td>Rural dwelling</td>
<td>0.478</td>
<td>0.865</td>
<td>0.091</td>
</tr>
<tr>
<td>Education:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>0.256</td>
<td>0.859</td>
<td>0.347</td>
</tr>
<tr>
<td>University or equivalent</td>
<td>0.679</td>
<td>1.189</td>
<td>0.168</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.992</td>
<td>0.221</td>
<td>2.205</td>
</tr>
</tbody>
</table>

* N < 1 274 due to missing values

* Compared to French language region

* Compared to urban dwelling

* Compared to compulsory education and/or professional training

© Birkhäuser Verlag, Basel, 2004
(McKinnon et al. 1997). Studies of chronic conditions like lower back pain and asthma hint at a moderate underreporting of medium to long term prevalence, in the range of 5–20%, while forward telescoping of earlier events may partially compensate for this effect (Carey et al. 1995; Mathiowetz & Dipko 2000). Recall of resource use has been observed to deteriorate seriously after 10 months, and up to 20% of information may be lost after one year (Brown & Adams 1992). Reports of the exact number of disease-specific and overall physician consultations during the previous 12 months differed from medical record-based information in up to 70% of cases, but similar rates of under- and over-reporting greatly reduced overall error (McKinnon et al. 1997; Mathiowetz & Dipko 2000). Hospitalisations and their causes were well remembered, while the validity of reports of drug use was judged more critically (Brown & Adams 1992). All modes of administration seem to be affected by these problems in about the same way, despite some advantages of face-to-face and telephone interviews in comparison with mailed questionnaires (Marcus & Crane 1986; O’Toole et al. 1986; McKinnon et al. 1997; Galobardes et al. 1998; Brogger et al. 2002).

In summary, collection of health-related data in general populations using survey methods is an accepted, while not entirely unproblematic alternative to medical record review (Marcus & Crane 1986; Brown & Adams 1992). It was justified in this study as a medical record-based approach could not have produced population-level estimates. Nevertheless, some measurement error and bias may be present in the results. Reports of earlier studies indicate that this may have induced an under- as well as an overestimation of some parameters, but probably no major distortions.

**Choice of risk score:** A variety of questionnaires have been used to measure the presence of reflux disease. These were designed to be used in self-reporting (Isolauri & Laippala 1995; Ledson et al. 1998), in face-to-face interviews with trained interviewers (Eggleston et al. 1999), or in physician interviews (Klauser et al. 1990). Until today, no standard has emerged, and results strongly depend on the reference periods used, ranging from one day to one year (Isolauri & Laippala 1995). All instruments address heartburn and acid regurgitation, while in part considering additional symptoms such as dysphagia, globus, nausea, belching, or chest-pain. Validation is complicated by a lack of gold standard, as even invasive procedures such as pH monitoring and gastroscopy are of limited sensitivity and specificity (Johnson et al. 1987; Klauser et al. 1990). Only the instruments developed by Andersen et al. (1987) and Locke et al. (1994) and, to a certain extent, the DIGEST instrument have been formally validat-ed (Eggleston et al. 1999). All three are clearly too extended to be used in a population-based screening study using CATIs. Measures specifically designed or validated for use in a CATI framework are not available. The questionnaire by Locke et al. was used in a telephone setting once, but for reassessment purposes only (Newton et al. 1999). Facing the lack of a formally validated instrument suitable for this study, we selected a measure which relied on easily understandable questions with good face value. It covered the symptoms jointly addressed by all instruments proposed, and it could be assessed by phone without problems, renouncing highly elaborated formal definitions in favour of interviewee compliance.

**Cost assessment:** Cost assessment can follow a top-down or a bottom-up approach (Tolpin & Bentkover 1983). The latter derives healthcare costs from aggregated sources (e.g., national statistical records). Due to a lack of central databases, this approach can hardly be adopted in Switzerland. The bottom-up approach, which we used, determines resource use at the single patient level and multiplies per capita resources with the appropriate epidemiological figures like prevalence or incidence. Using a population-based approach to derive these figures allows for a relatively high degree of external validity. Assessment of unit costs, however, often has to be based on approximations. This is particularly true for Switzerland’s very decentralised health care system.

Medication costs dominate medical resource costs in reflux disease. Interviewees’ estimates of these costs are certainly far from being exact. In diseases mainly requiring continuous medication, it would be more appropriate to ask for the daily doses, to which public prescription prices could be applied. Treatment of reflux disease, however, is in many cases characterised by on demand medication, whose intensity may be remembered in even less detail. Direct estimates should be more reliable under such circumstances.

**Epidemiologic results:** Most of our epidemiologic results are a confirmation of previous findings from other industrialised countries. Our prevalence estimate of 17.6%, referring to the adult population, is in the range to be expected from many studies (Spechler 1992; Locke et al. 1997; Kennedy et al. 1998; Rösch & Hotz 2000; Ter 2000). The findings of the Domestic/International Gastroenterology Surveillance Study (DIGEST), however, contradict our result (Eggleston et al. 1999; Stanghellini 1999). Based on 5600 interviews in 10 industrialised countries, DIGEST found an overall prevalence of reflux-like symptoms of 7.7%, and a prevalence in Switzerland of 4.8% (Stanghellini 1999). Several metho-
been reported earlier (Mokhlesi et al. 2001). A reference period of three months was used. Reflux symptoms had to reach a certain level of “relevance” to be counted, and were not considered if other upper gastrointestinal (GI) symptoms were more prominent. Total Swiss prevalence of relevant upper GI symptoms was found to be 17.7% (Stanghellini 1999).

The observation of a significantly higher prevalence rate in the French speaking part of Switzerland may be due to a real epidemiologic difference or due to a higher awareness of reflux disease in this region. A rise of reflux prevalence with age has been previously reported (Isolauri & Laippala 1995; Eggleston et al. 1999). Spechler (1992) even found a dramatic increase in those over age 40. Our additional finding of a reduced prevalence in the highest age group, which has not been described before, can be assumed to be an artefact. It possibly results from a reduced awareness of reflux due to an increased presence of other, more threatening health problems. Disease duration also rose with age, but had lower values in the highest age group. Recall bias may be an important factor here. Nevertheless, our results suggest that disease duration is limited in many cases, or at least that disease intensity often regresses to a level which is not remembered over prolonged periods of time. Reflux disease develops at all adult ages. The absence of a gender gap in the reflux-positive sample is consistent with the findings of several observational studies (El-Serag & Sonnenberg 1998; Kennedy et al. 1998; Eggleston et al. 1999; Ter 2000).

Comparisons of our data with population-level estimates from the SHS ‘97 (Table 3) may be affected by selection bias in one or both data sources. If no relevant distortions of this kind are assumed, our results support an association between reflux and overweight, which is controversial in the literature, but confirmed by DIGEST (Isolauri & Laippala 1995; Eggleston et al. 1999; Lagergren et al. 2000). Some studies reported an increased prevalence of reflux disease in persons with a history of smoking and, nearly undisputed, a negative influence of smoking on disease severity (Isolauri & Laippala 1995; Pandolfino & Kahrilas 2000). Thus, the finding of a reduced number of smokers in the reflux-positive persons compared to the SHS ‘97 estimate could potentially result from an influence of reflux symptoms on smoking habits. The asthma prevalence in the reflux-positive interviewees of 8.6% is best compared with an earlier report of a prevalence of 6.7% in the adult Swiss population (Leuenberger 1995). A positive association between reflux disease and asthma has been reported earlier (Mokhlesi et al. 2001).

Our population-level estimate of 993,000 persons with reflux disease in Switzerland is conservative as it does not include persons under 18 years of age with reflux.

Cost results: Our cost estimates are seemingly low. While several of the methodological issues addressed above may have contributed to this, the main reason lies in the fact that we included all reflux-positive persons identified, unregarding the question if they were medically treated or not. During the 12 months preceding their interview, only 26% of our reflux positive sample reported a general practitioner consultation due to this condition. Studies only including persons undergoing medical treatment must yield higher resource use and cost estimates. This is the case in most research addressing the economics of reflux disease (Viljakka et al. 1997; Sonnenberg et al. 1999; Gerson et al. 2000). Eggleston et al. (1998), e.g., refer to a period of initial medical activity. They report costs in the range of £136 to £189 (CHF 341 to CHF 474) and a mean of 2.4 to 2.9 general practitioner consultations during six months. We observed 3.1 consultations per one year in those interviewees who reported reflux-induced consultations. (Except by chance, these were not in their initial treatment phases.) Levin et al. (1997) found annual treatment costs in the range of $471 (CHF 826) in a U.S. managed care setting. Our results, referring to a population with a distinctly lower mean intensity of disease and being based on a different health care system, are compatible with these findings.

Most significant bivariate associations we found between direct medical costs and possible influence variables (age, language region, urban or rural dwelling, educational level) were confirmed in regression analysis. Our observation of a moderate rise of costs with age can be assumed to be of indirect nature. Longer disease duration in older persons may be the true reason. Higher costs of reflux disease in the French compared to the German language region probably are a reflection of higher total health care costs (Frei & Ting 1996). An above-average density of health care providers may have contributed to the observation of higher costs in urban areas. Despite their plausibility, the explanatory value of all influences identified is minimal. Treatment intensity may largely be ruled by personal attitudes of the patients and physicians involved, and chance may also have an important role. Other studies might try to find better explanatory variables than those we measured, to allow for a better prediction of costs.

In addition, further methodological research should in greater depth address the difficulties and relationship of medical record-based and survey-based collection of health-related data. Optimised future study designs might combine the use of...
survey methods for case identification and of medical record review for the collection of resource use and additional data. Epidemiologic, resource use and cost results demonstrate that reflux disease is of considerable importance medically, but also economically. Our estimate of reflux disease accounting for approximately 0.5% of the total Swiss health care expenditures has probably to be viewed as conservative, due to the implications of study design.

Acknowledgements
The study was supported by an unrestricted research grant from AstraZeneca AG, Zug, Switzerland.

Zusammenfassung
Epidemiologie und Kosten der gastroösophagealen Refluxkrankheit in der Schweiz: eine bevölkerungsrepräsentative Studie

Fragestellung: Messung der Prävalenz, des medizinischen Ressourcenverbrauchs und der Kosten der gastroösophagealen Refluxkrankheit in der Schweiz.


Ergebnisse: 1274 von 7222 TeilnehmerInnen wurden als Refluxfälle definiert. Die Prävalenz der Refluxkrankheit unter Schweizer Erwachsenen wurde auf 17.6% (95%-KI: 15.6%–19.7%) oder 993000 Personen geschätzt. Eine regelmäßige medikamentöse Behandlung wurde von 38.0% dieser Personen angegeben. Durch Reflux bedingte Allgemeinarztkonsultationen während des letzten Jahres wurden von 25.9% berichtet. In Durchschnitt betrug die Zahl der Allgemeinarztkonsultationen 0.84, die Zahl der Spezialistenkonsultationen 0.19, die Zahl der Gastroskopien 0.08 und die der Hospitalisationen 0.01 pro Patientenjahr. Die durchschnittlichen direkten medizinischen Kosten wurden durch die Medikamentenkosten dominiert und betrugen CHF 185 pro Patientenjahr (95%-KI: CHF 140–230) oder 0.5% der gesamten Gesundheitsausgaben der Schweiz. Die totalen Kosten beliefen sich auf CHF 234 (95%-KI: CHF 185–284) pro Patientenjahr.

Schlussfolgerungen: Die Prävalenz der gastroösophagealen Refluxkrankheit in der Schweiz ähnelt der in anderen industrialisierten Ländern beobachteten. Die Kosten der Refluxkrankheit sind sowohl auf der medizinischen als auch auf der gesellschaftlichen Ebene beträchtlich.

Résumé
Epidémiologie et coûts du reflux gastro-oesophagien en Suisse: une étude dans la population générale

Objectifs: Evaluation de la prévalence, de la consommation de prestations médicales et des coûts du reflux gastro-oesophagien en Suisse.

Méthodes: Une enquête téléphonique a été menée dans la population générale en Suisse alémanique et Suisse romande.

Les cas de reflux ont été identifiés en utilisant un questionnaire proposé par la ligue allemande contre les maladies gastriques et interrogés sur leurs caractéristiques personnelles et leur consommation de prestations médicales.

Résultats: On a dépisté 1274 cas positifs sur 7222 participants. La prévalence du reflux parmi les adultes en Suisse a été estimée à 17.6% (IC 95%: 15.6%–19.7%), correspondant à 993 000 personnes. Un traitement médicamenteux a été suivi par 38.0% des cas positifs, et 25.9% ont déclaré avoir consulté leur médecin généraliste pour cause de reflux pendant l’année précédente. En moyenne, on a dénombré 0.84 consultations au cabinet généraliste, 0.19 consultations d’un spécialiste, 0.08 gastroscopies et 0.01 hospitalisations par personne-année. Les coûts médicaux directs, dominés par les coûts médicamenteux, se sont montés en moyenne à CHF 185 par personne-année (IC 95%: CHF 140–CHF 230) ou à 0.5% des dépenses de santé en Suisse. Les coûts totaux ont été de CHF 234 (IC 95%: CHF 185–CHF 284) par personne-année.

Conclusions: La prévalence du reflux gastro-oesophagien en Suisse est comparable à celles des autres pays industrialisés. Le reflux est à l’origine de coûts considérables au niveau du système de santé et au niveau de la société.


Address for correspondence
Matthias Schwenkglenks, M.A., M.P.H.
ECPM Executive Office
University Hospital
CH-4031 Basel
Tel.: +41 61 261 4583
Fax: +41 61 261 4584
E-mail: m.schwenkglenks@unibas.ch

To access this journal online:
http://www.birkhauser.ch
Schwenkglenks M, Lippuner K, Häuselmann HJ, Szucs TD.


A model of osteoporosis impact in Switzerland 2000–2020

Matthias Schwenkglenks · Kurt Lippuner
Hans Jörg Häuselmann · Thomas D. Szucs

Received: 19 September 2003 / Accepted: 18 August 2004 / Published online: 26 October 2004
© International Osteoporosis Foundation and National Osteoporosis Foundation 2004

Abstract The aim of our study was to develop a modeling framework suitable to quantify the incidence, absolute number and economic impact of osteoporosis-attributable hip, vertebral and distal forearm fractures, with a particular focus on change over time, and with application to the situation in Switzerland from 2000 to 2020. A Markov process model was developed and analyzed by Monte Carlo simulation. A demographic scenario provided by the Swiss Federal Statistical Office and various Swiss and international data sources were used as model inputs. Demographic and epidemiologic input parameters were reproduced correctly, confirming the internal validity of the model. The proportion of the Swiss population aged 50 years or over will rise from 33.3% in 2000 to 41.3% in 2020. At the total population level, osteoporosis-attributable incidence will rise from 1.16 to 1.54 per 1,000 person-years in the case of hip fracture, from 3.28 to 4.18 per 1,000 person-years in the case of radiographic vertebral fracture, and from 0.59 to 0.70 per 1,000 person-years in the case of distal forearm fracture. Osteoporosis-attributable hip fracture numbers will rise from 8,375 to 11,353, vertebral fracture numbers will rise from 23,584 to 30,883, and distal forearm fracture numbers will rise from 4,209 to 5,186. Population-level osteoporosis-related direct medical inpatient costs per year will rise from 713.4 million Swiss francs (CHF) to CHF946.2 million. These figures correspond to 1.6% and 2.2% of Swiss health care expenditures in 2000. The modeling framework described can be applied to a wide variety of settings. It can be used to assess the impact of new prevention, diagnostic and treatment strategies. In Switzerland incidences of osteoporotic hip, vertebral and distal forearm fracture will rise by 33%, 27%, and 19%, respectively, between 2000 and 2020, if current prevention and treatment patterns are maintained. Corresponding absolute fracture numbers will rise by 36%, 31%, and 23%. Related direct medical inpatient costs are predicted to increase by 33%; however, this estimate is subject to uncertainty due to limited availability of input data.

Keywords Economics · Epidemiology · Europe · Modeling studies · Osteoporosis · Switzerland

Introduction

Osteoporosis is an important health problem in elderly women and, to a lesser extent, in elderly men [1]. Osteoporotic fragility fractures occur at multiple sites of the skeletal system [2], but the main focus of research is on fractures of the hip, vertebrae and distal forearm [1]. These fracture types occur frequently and show a steep rise in incidence with age, more pronounced in women than in men [1, 3]. Most serious consequences are observed in hip and vertebral fracture patients. The impact of hip fracture is dramatic in terms of morbidity, mortality, loss of functional independence, and cost [1, 4]. Worldwide projections have predicted a doubling of hip fracture cases from 1990 to 2025, with the ageing of the populations being one of the most important causes [5, 6]. The expected rise will be particularly pronounced in Asia, but Western societies will be affected, too [5, 7].

Despite an awareness of these general trends, detailed simulations of the future impact of osteoporosis are rare. Several Markov-based modeling studies have assessed lifetime fracture risk and long-term fracture
compares the age distribution to the current situation and the developments to be expected for 2000 and 2020. The share of those aged 65 or over will rise from 33.3% in 2000 to 41.3% in 2020. For the application to Switzerland, two different kinds of simulation were used. First, a cohort representing the Swiss population of a certain year aged 50 years or older was observed for 1 year. Based on a random assignment of gender and age, 500,000 simulated persons were run through the model. Total and osteoporosis-related hip, vertebral, and distal forearm fractures were counted. We observed fracture-related resource use and costs for another 6 months, without allowing for additional fracture entries, in order to achieve a mean follow-up time of 1 year after fracture entry. Second, a cohort representing all Swiss persons aged 50 years in a certain year was observed for the remainder of their lives. Based on a random assignment of gender, 12,500 simulated persons were run through the model. Costs were calculated undiscounted and discounted by 3% per year. Inflation or changes in inpatient care cost due to changing medical practice were not modeled. Owing to the extended observation period per subject, the relative importance of long-term nursing home costs was adequately taken into account. On this basis, estimates of mean yearly inpatient costs due to recent, as well as earlier, fractures could be calculated.

Model inputs

Published or publicly available Swiss data sources were used wherever possible. Otherwise, European data and, if necessary, data from the USA and Australia were used. Plausibility of all model inputs was assessed by comparison with published literature.

Demographic data: The Swiss Federal Statistical Office (SFSO) has issued a series of demographic scenarios projecting the development of the Swiss population between 2000 and 2060 [19]. Age and gender distributions used in the main analysis are those described by the SFSO main scenario, which extrapolates current demographic trends and thus avoids extreme assumptions. In this scenario, the proportion of the population aged 50 years or over will rise from 33.3% in 2000 to 41.3% in 2020. The share of those aged 65 or over will rise from 15.4% to 20.0%. Figure 1 compares the age distributions expected for 2000 and 2020.

Fracture incidences: Swiss hospitals are obliged to report patient-level inpatient data to the SFSO. Gender- and age-specific hip fracture incidences were estimated from the ICD-10 S72.0–S72.2 cases reported to the SFSO in 2000, with the assumption of a hip fracture hospitalization rate of 100%. Reporting was incomplete, and the SFSO calculated a relation of reported to expected cases of 0.811. This figure was used with the assumption of a random distribution of non-reporting. Cases reported to the SFSO could not be used here, as valid Swiss data on hospitalization probabilities do not exist. Published data show that hip fracture rates are
similar in Switzerland and in Western Europe [6, 20]. It was assumed that the same relationship exists for other types of osteoporotic fractures, and morphometric vertebral fracture incidences for Western Europe reported by the EPOS group were used [21]. Missing data points after age 79 years were estimated by linear extrapolation [21, 22, 23, 24]. In the case of distal forearm fracture, the incidences reported by Kanis et al. for Malmö, Sweden, provided sufficient detail [23]. These were multiplied by a correction factor of 0.55, derived from the EVOS data, as distal forearm fracture incidences are higher in Northern Europe than in Western Europe [1, 25]. Incidences above age 89 years were assumed to be identical to those in the age group 85–89 years [22, 23, 24]. The incidence rates used are summarized in Table 1.

Osteoporosis-attributable fractures: The share of osteoporosis-attributable fractures, i.e., of fractures that would not have occurred if no osteoporotic changes had been present in the skeletal system, by fracture type, gender and age was modeled by way of a stochastic process that used the attribution probabilities described by Melton et al. for the white population in the USA [26]. Calculation of osteoporosis-attributable fracture incidences and numbers at the total population level assumed no osteoporosis-related fractures under the age of 50 years.

Mortality: All-cause mortality by year, gender and age was taken from the SFSO main demographic scenario [19]. Short- and long-term excess mortality after hip fracture was modeled from data collected by Trombetti...
et al. in canton Geneva, Switzerland [27]. Those authors observed an unadjusted in-hospital mortality rate of 8% in women and 15% in men. The combination of their original data and the Swiss age distribution starting at age 50 years led to an age-adjusted excess mortality rate of 53 per 1,000 person-years in women and 206 per 1,000 person-years in men, in the first year after fracture. In the second to fifth years, excess mortality rates per year were 103 per 1,000 person-years in women and 127 per 1,000 person-years in men. Long-term excess mortality after vertebral fracture was modeled on relative risks of 1.6 in women and 1.2 in men, as found in the EPOS study after hip fracture was assumed to occur in 68% of women and 36% of men, with a length of stay of 59 and 54 days, respectively [26]. Excess mortality was limited to a period of 5 years after fracture event [1, 27, 29, 31, 32]. Excess mortality after distal forearm fracture and short-term excess mortality after vertebral fracture were not modeled [1]. To avoid an overestimation of total mortality, all-cause mortality was reduced by the approximate population-level impact of fracture-associated mortality.

The probability that a vertebral fracture would come to clinical attention and be treated was estimated to be 30% [33, 34, 35]. The probability of an acute hospitalization episode was assumed to be 33% after a vertebral fracture had come to clinical attention [1, 35]. In the case of distal forearm fracture, a hospitalization probability of 53.0% was estimated from the incidence data used and the inpatient cases with ICD-10 codes S52.5–6 reported to the SFSO in 2000. This estimate takes into account all patients that occupy a hospital bed, even be it for a few hours only.

Year 2000 acute care lengths of stay were calculated from the SFSO data. In the case of vertebral fracture, ICD-10 codes M48.5, M80.0–9, M84.0, M84.4 and T08 were taken into account. Participation in an inpatient rehabilitation program after hip fracture was assumed to occur in 68% of women and 36% of men, with a length of stay of 59 and 54 days, respectively [27]. Rehabilitation programs after vertebral or distal forearm fracture were not taken into account.

### Table 1 Gender- and age-specific fracture incidence rates, per 1,000 person-years, as used in the main analysis

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Hip fracture</th>
<th>Vertebral fracture*</th>
<th>Distal forearm fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>50–54</td>
<td>0.31</td>
<td>0.49</td>
<td>3.6</td>
</tr>
<tr>
<td>55–59</td>
<td>0.68</td>
<td>0.79</td>
<td>5.5</td>
</tr>
<tr>
<td>60–64</td>
<td>1.09</td>
<td>0.91</td>
<td>9.5</td>
</tr>
<tr>
<td>65–69</td>
<td>2.15</td>
<td>1.59</td>
<td>12.3</td>
</tr>
<tr>
<td>70–74</td>
<td>4.14</td>
<td>2.29</td>
<td>17.9</td>
</tr>
<tr>
<td>75–79</td>
<td>8.51</td>
<td>4.49</td>
<td>29.3</td>
</tr>
<tr>
<td>80–84</td>
<td>17.71</td>
<td>7.46</td>
<td>34.4</td>
</tr>
<tr>
<td>85–89</td>
<td>32.31</td>
<td>14.84</td>
<td>39.6</td>
</tr>
<tr>
<td>90–94</td>
<td>41.43</td>
<td>24.96</td>
<td>44.7</td>
</tr>
<tr>
<td>95+</td>
<td>44.04</td>
<td>46.28</td>
<td>49.8</td>
</tr>
</tbody>
</table>

*Extrapolated fractures

a Assumed to remain constant after age 85–89 years

### Swiss year 2000 census data were used to estimate gender- and age-specific probabilities of being cared for in a nursing home, and of being admitted to such an institution, for any reason. The overall share of fracture-induced nursing home admissions was assumed to be 8%, following a German source [36]. Based on data from canton Geneva, Switzerland, the overall probability of long-term nursing home admission after hip fracture in those living in an apartment before the fracture event was assumed to be 18% [27, 37]. Gender- and age-specific admission probabilities were estimated under the assumption of a linear increase with age. Residency in a nursing home for any reason and the event of being admitted to a nursing home due to hip fracture were modeled in parallel. Residency in a nursing home was counted as fracture-induced until a nursing home admission for any reason would have occurred. Nursing home admissions due to vertebral or distal forearm fractures were not taken into account.

### Adopting a societal perspective, we assessed direct medical costs of acute inpatient hospital care, inpatient rehabilitation and nursing home care by multiplying length of stay with the estimated daily real costs by type of institution as reported by the SFSO for the year 2000. The results were verified against Swiss and international data sources [38, 39, 40, 41]. All costs are indicated in year 2000 Swiss francs (CHF). On 31 Dec 2000, CHF1 equaled 0.66 euros.

### Analysis of model output

Using STATA/SE (version 8.0, Stata Corporation, College Station, Tex., USA) and standard statistical procedures, we analyzed the output data. Calculation of 95% confidence intervals (95% CIs) was based on bias-corrected bootstrapping using 1,000 repetitions. Due to limitations of available computation time, calculation of CIs was restricted to key output parameters.

### Internal and external model validation

Correct reproduction of main input parameters was examined to test the internal validity of the model. Comparisons included the gender and age distributions and life expectancies of the underlying demographic scenario, as well as gender- and age-specific incidence rates. External plausibility of results was assessed by comparison with published data as detailed in the Discussion.

### Sensitivity analysis

While Monte Carlo simulation was used to deal with first-order uncertainty (individual variation in gender and age), the impact of second-order parameter uncertainty was assessed by classic deterministic sensitivity...
analysis. Ranges of variation are shown in Table 2. In order to limit calculation time, we combined several parameter changes that prompted fewer fracture events and lower costs, and tested them simultaneously in a best-case scenario. Parameter changes that prompted more fracture events and higher costs were tested in a worst-case scenario. Varied parameters comprised: gender- and age-specific incidences; osteoporosis attribution probabilities; treatment, hospitalization and rehabilitation probabilities; the probability of a new admission to a nursing home after hip fracture; lengths of stay; acute care, rehabilitation and nursing home costs per day. In a separate analysis, approximate outpatient hip fracture costs of CHF6,442 per case were added [42]. Background nursing home residency and disease-specific mortality were also varied separately. Additional analyses modeled disease-specific mortality as age-specific or replaced the SFSO main demographic scenario with alternative scenarios that described either a less or a more pronounced ageing of the population [19]. Finally, we repeated the main analysis but included a secular 1% per year rise of gender- and age-specific hip fracture incidence rates [1, 6].

Results

Internal validation

The gender and age distributions of the underlying demographic scenario were reproduced correctly. The proportion of women in the population aged 50 years or older was 54.6% (95% CI 54.4–54.7) in 2000, 53.8% (95% CI 53.7–53.9) in 2010 and 53.5% (95% CI 53.3–53.6) in 2020. Mean age ± SD of those aged 50 years or older rose from 65.0 ± 11.0 (95% CI 64.9–65.0) years in 2000 and 65.2 ± 10.9 (95% CI 65.2–65.2) years in 2010 to 65.6 ± 10.8 (95% CI 65.6–65.6) years in 2020. Predicted life expectancy at age 50 years was 31.8±10.4 (95% CI 31.7–32.0) years in 2000, 32.8±10.1 (95% CI 32.6–32.9) years in 2010 and 33.4±9.6 (95% CI 33.3–33.6) years in 2020. These results compare well with the SFSO estimates of 32.0 years in 2000, 32.8 years in 2010 and 33.4 years in 2020. Gender- and age-specific fracture incidences used on the input side were also reproduced correctly. First hip fractures were estimated to occur at an age of 79.8 years, on average, in 2000. This compares well with a broad estimate of 80.5 years as directly derived from the SFSO data. In the latter case, no distinction between first and repeated fractures could be made.

Fractures

Tables 3 and 4 summarize total and osteoporosis-attributable fracture incidences and absolute fracture numbers by gender. For all parameters a rise is seen between 2000 and 2020, with the exception of the inci-
Table 3 Female population: fracture incidences per 1,000 person-years (95% CIs) and total fracture numbers in Switzerland

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hip fracture</th>
<th>Vertebral fracture&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Distal forearm fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Female population from age 50 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>5.56</td>
<td>5.59</td>
<td>5.88</td>
</tr>
<tr>
<td>Incidence attributable to osteoporosis</td>
<td>5.07</td>
<td>5.15</td>
<td>5.34</td>
</tr>
<tr>
<td><strong>Total fracture number</strong></td>
<td>7,266</td>
<td>8,171</td>
<td>9,589</td>
</tr>
<tr>
<td><strong>Incidence attributable to osteoporosis</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.80</td>
<td>2.00</td>
<td>2.30</td>
</tr>
<tr>
<td><strong>Total fracture number attributable to osteoporosis</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6,618</td>
<td>7,518</td>
<td>8,702</td>
</tr>
</tbody>
</table>

<sup>a</sup>Radiographic fractures. For estimates on clinical fractures, divide values by 3
<sup>b</sup>Assuming no osteoporosis-related fractures in the population under age 50 years

Table 4 Male population: fracture incidences per 1,000 person-years (95% CIs) and total fracture numbers in Switzerland

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hip fracture</th>
<th>Vertebral fracture&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Distal forearm fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Male population from age 50 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>2.07</td>
<td>2.20</td>
<td>2.31</td>
</tr>
<tr>
<td></td>
<td>(1.89–2.25)</td>
<td>(2.02–2.38)</td>
<td>(2.13–2.52)</td>
</tr>
<tr>
<td>Incidence attributable to osteoporosis</td>
<td>1.61</td>
<td>1.71</td>
<td>1.86</td>
</tr>
<tr>
<td></td>
<td>(1.45–1.77)</td>
<td>(1.55–1.87)</td>
<td>(1.70–2.04)</td>
</tr>
<tr>
<td><strong>Total fracture number</strong></td>
<td>2,249</td>
<td>2,764</td>
<td>3,274</td>
</tr>
<tr>
<td><strong>Total male population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence attributable to osteoporosis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.59</td>
<td>0.60</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Total fracture number attributable to osteoporosis</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1,755</td>
<td>2,149</td>
<td>2,644</td>
</tr>
</tbody>
</table>

<sup>a</sup>Radiographic fractures. For estimates on clinical fractures, divide values by 3
<sup>b</sup>Assuming no osteoporosis-related fractures in the population under age 50 years
idence of distal forearm fractures in women aged 50 years and over, which is constant at the all-fracture level and slightly decreases when only osteoporosis-attributable fractures are taken into account. Related absolute minima will occur in 2010.

For all ages combined, osteoporosis-attributable hip fracture incidence will rise from 1.16 to 1.54 per 1,000 person-years (+32.8%), osteoporosis-attributable vertebral fracture incidence from 3.28 to 4.18 per 1,000 person-years (+27.4%), and osteoporosis-attributable distal forearm fracture incidence from 0.59 to 0.70 per 1,000 person-years (+18.6%). Osteoporosis-attributable fracture numbers at the total population level will rise from 8,375 to 11,353 (+35.6%) in the case of hip fracture, from 23,584 to 30,883 (+30.9%) in the case of vertebral fracture, and from 4,209 to 5,186 (+23.2%) in the case of distal forearm fracture.

Lifetime fracture risk

For all combinations of fracture type and gender, lifetime risk at age 50 years will rise between 2000 and 2020. Lifetime hip fracture risk will rise from 14.7% to 16.4% (women: 20.9% to 23.1%, men: 8.7% to 9.7%). Lifetime vertebral fracture risk will rise from 30.7% to 33.8% (women: 42.6% to 46.1%, men: 19.1% to 21.7%), and distal forearm fracture risk from 8.1% to 8.9% (women: 13.8% to 14.9%, men: 2.7% to 3.1%). Osteoporosis-attributable lifetime risk will rise from 13.0% to 14.4% (women: 19.2% to 21.2%, men: 7.0% to 7.6%) in the case of hip fracture, from 27.8% to 30.7% (women: 39.0% to 42.5%, men: 17.0% to 19.0%) in the case of vertebral fracture, and from 5.6% to 6.1% (women: 10.1% to 10.9%, men: 1.2% to 1.5%) in the case of distal forearm fracture.

Resource use

Table 5 shows the number of acute hospitalizations and the days spent in acute care hospitals, inpatient rehabilitation facilities, and nursing homes, due to fractures, in 1000 persons aged 50 years and over, in 2000, 2010 and 2020. Results for the Swiss population from age 50 on are added. Days of stay occurring until 1 year after fracture entry are taken into account. For all parameters, a rise is seen between 2000 and 2020. However, estimates per 1,000 persons show a non-monotonic development in some cases, with their maxima or minima in 2010. Population-level increases are more pronounced due to the growth of population size.

Costs

Figure 2 shows direct medical inpatient costs arising in the Swiss population from age 50 on, induced by fractures in 2000, 2010 and 2020, during the first year after fracture entry, due to hip, vertebral and distal forearm fractures occurring in the year of reference.
fracture. Costs of all fractures and of those attributable to osteoporosis are presented in parallel.

Total first-year inpatient costs will rise by 31.5% at the all-fracture level, from CHF443.7 million (CI 422.8–462.9 million) to CHF583.5 million (CI 559.2–609.7 million). Point estimates correspond to 1.0% and 1.3% of Swiss health care expenditure in 2000. At the osteoporosis-attributable fracture level there will be a rise by 33.5%, from CHF388.2 million (CI 369.1–406.4 million) to CHF518.3 million (CI 494.9–544.7 million). Point estimates correspond to 0.9% and 1.2% of Swiss health care expenditure in 2000.

The relative shares of acute care hospital, inpatient rehabilitation and nursing home costs in the first year after osteoporosis-related fracture will remain fairly constant over time. In 2000, acute hospital care contributes 51.5% (2020: 51.3%), inpatient rehabilitation contributes 33.4% (2020: 33.1%), and nursing home care 15.1% (2020: 15.7%). Results at the all-fracture level are similar.

The relative importance of nursing home costs is much higher if undiscounted lifetime inpatient costs from age 50 years on are considered. Long-term cost consequences of fractures are included in this perspective, which results in a proportion of nursing home costs that is near constant over time at 53.3%–54.3%.

These percentages broadly reflect the contribution of nursing home costs to yearly fracture- and osteoporotic fracture-induced inpatient costs taking into account the consequences of earlier fractures. If an average value of 53.8% is adopted, yearly fracture-related inpatient costs can be estimated at CHF817.2 million in 2000 and at CHF1,072.4 million in 2020 (+31.2%), which correspond to 1.9% and 2.5% of Swiss health care expenditure in 2000. Osteoporosis-attributable costs can be estimated at CHF713.4 million in 2000 and at CHF946.2 million in 2020 (+32.6%), which correspond to 1.6% and 2.2% of Swiss health care expenditure in 2000.

Lifetime fracture-related inpatient costs from age 50 on, per 1,000 persons observed, will rise from CHF13.7 million in 2000 (CI 12.3–15.4 million; discounted by 3%: CHF5.4 million) to CHF15.2 million in 2020 (CI 13.8–16.6 million; discounted: CHF5.7 million). If only osteoporosis-attributable fractures are regarded, the rise will be from CHF11.9 million in 2000 (CI 10.6–13.3 million; discounted: CHF4.6 million) to CHF13.5 million in 2020 (CI 12.3–15.0 million; discounted: CHF5.0 million).

Sensitivity analysis

The effects of input parameter variation on key outcome parameters are shown in Table 6. Implementation of the best and worst case scenarios described in the Methods strongly impacted on all epidemiologic and economic outcome parameters. For example, the incidence of year 2000 osteoporosis-attributable hip fractures, for all ages combined, was changed by \( \pm 31.9\% \). Population level, osteoporosis-attributable, first-year inpatient costs were reduced by 57.7% in the best case and increased by 93.7% in the worst case. If estimated outpatient hip fracture costs of CHF6,552 per case were taken into account, this led to an absolute increase of osteoporosis-attributable costs.
Table 6 Effects of input parameter variation on key outcome parameters (see Materials and methods section and Table 2 for details and ranges of input parameter variation)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Year</th>
<th>Main analysis</th>
<th>Best case scenario(^a)</th>
<th>Worst case scenario(^a)</th>
<th>Inclusion of out-patient hip fracture costs</th>
<th>Disease-specific mortality</th>
<th>Proportion of population living in nursing homes</th>
<th>Less-pronounced ageing(^b)</th>
<th>More-pronounced ageing(^b)</th>
<th>Secular rise in hip fracture incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population from age 50 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of hip fracture per 1,000 person-years</td>
<td>2000</td>
<td>3.97</td>
<td>3.20</td>
<td>4.83</td>
<td>No effect</td>
<td>3.97</td>
<td>No effect</td>
<td>3.97</td>
<td>3.97</td>
<td>3.97</td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>4.23</td>
<td>3.41</td>
<td>5.02</td>
<td>No effect</td>
<td>4.20</td>
<td>No effect</td>
<td>4.13</td>
<td>4.29</td>
<td>5.07</td>
</tr>
<tr>
<td>Days in acute care hospitals due to osteoporotic fractures per 1,000 persons</td>
<td>2000</td>
<td>82.7</td>
<td>35.4</td>
<td>162.9</td>
<td>No effect</td>
<td>81.0</td>
<td>No effect</td>
<td>82.7</td>
<td>82.7</td>
<td>82.7</td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>86.3</td>
<td>38.6</td>
<td>166.2</td>
<td>No effect</td>
<td>86.4</td>
<td>No effect</td>
<td>86.9</td>
<td>87.5</td>
<td>101.1</td>
</tr>
<tr>
<td>Total population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of osteoporotic hip fracture per 1,000 person-years</td>
<td>2000</td>
<td>1.16</td>
<td>0.79</td>
<td>1.53</td>
<td>No effect</td>
<td>1.16</td>
<td>No effect</td>
<td>1.16</td>
<td>1.16</td>
<td>1.16</td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>1.54</td>
<td>1.05</td>
<td>1.97</td>
<td>No effect</td>
<td>1.53</td>
<td>No effect</td>
<td>1.47</td>
<td>1.64</td>
<td>1.87</td>
</tr>
<tr>
<td>Number of osteoporotic hip fractures</td>
<td>2000</td>
<td>3.875</td>
<td>5.710</td>
<td>11.001</td>
<td>No effect</td>
<td>3.822</td>
<td>No effect</td>
<td>3.875</td>
<td>3.875</td>
<td>3.875</td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>11,353</td>
<td>7,782</td>
<td>14,542</td>
<td>No effect</td>
<td>11,305</td>
<td>No effect</td>
<td>11,252</td>
<td>11,682</td>
<td>13,783</td>
</tr>
<tr>
<td>First-year inpatient costs due to osteoporotic fractures (million CHF)</td>
<td>2000</td>
<td>388.2</td>
<td>164.4</td>
<td>751.9</td>
<td>441.6</td>
<td>380.1</td>
<td>392.9</td>
<td>388.2</td>
<td>388.2</td>
<td>388.2</td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>518.3</td>
<td>228.7</td>
<td>965.2</td>
<td>590.6</td>
<td>518.1</td>
<td>523.9</td>
<td>523.2</td>
<td>611.4</td>
<td>667.1</td>
</tr>
</tbody>
</table>

\(^a\)Combined variation of gender- and age-specific incidences; osteoporosis attribution probabilities; treatment, hospitalization and rehabilitation probabilities; probability of new admission to nursing home after hip fracture; lengths of stay; acute care, rehabilitation and nursing home costs per day

\(^b\)Alternative SFSO demographic scenarios, “less pronounced ageing of the population” and “more pronounced ageing of the population”
by 13.8%. In contrast, if we varied the proportion of the population that were living in a nursing home, varied the level of disease-specific mortality, or modeled disease-specific mortality as age-specific, it hardly affected the absolute results. Relative parameter changes between 2000 and 2020 were only marginally affected by all modifications named so far. When the SFSO main demographic scenario was replaced by alternative scenarios that described a less-pronounced or a more-pronounced ageing of the population, relative increases in the incidence of osteoporosis-attributable fractures between 2000 and 2020 were slightly less pronounced in the former case and more pronounced in the latter (in the case of hip fracture, +26.7% and +41.2% compared to +32.8% in the main analysis). However, there was no impact on the resource use and cost results. When a 1% per year secular rise in the incidences of gender- and age-specific hip fractures was modeled, relative changes between 2000 and 2020 were inflated by a factor of 2 to 4 when compared with the main analysis. The incidence of osteoporosis-attributable hip fractures increased by +61.2%, and population level, osteoporosis-attributable, first-year inpatient costs by +57.5%.

Discussion

The modeling framework described here allows one to assess the epidemiologic and economic consequences of osteoporotic hip, vertebral and distal forearm fractures. There is a particular focus on change over time, e.g., related to demographic developments. If suitable input data are available, the model can be applied to a wide variety of countries and settings. While the application to Switzerland, presented here as a test case, was purely descriptive, the epidemiological and economic impact of new preventive or treatment strategies, or of any changes occurring in medical practice, can easily be modeled as soon as related effect estimates are available.

To our knowledge this is the second study, internationally, that used a Markov process model, and the first one that used the Monte Carlo technique, to simulate the development of osteoporotic fracture incidences and numbers, associated resource use, and cost over an extended period of time [12]. While future fracture occurrence alone could be estimated by simpler means, the synthesis of data from various sources and the assessment of several interlinked output parameters are most consistently achieved by the use off the Markov approach. More importantly, long-term observation of numbers, associated resource use, and cost over an extended period of time [17]. The advantages of Monte Carlo simulation in particular are highlighted by a comparison with the methodological approach described in a recently published work by Burge et al., who assessed the epidemiology and economic impact of osteoporosis in Florida for 2000–2025 [12]. Relying on a conventional Markov cohort model, Burge et al. had to run a large number of separate simulations, one for each combination of year of age and race. Simulation outputs were combined, and the impact of demographic change was assessed by way of separate procedures outside the Markov module. By contrast, the Monte Carlo technique enabled us to forego additional modeling steps. Additional calculations were limited to the statistics required to address the chance component inherent in all Monte Carlo-based results.

While models are generally characterized by a reduction in complexity compared to reality, some simplifications in the present case were dictated by an anticipated lack of appropriate input data. For example, we relied on a set of Markov states that solely described fracture event history, in contrast to some osteoporosis models that incorporated functional status or type of residence at the disease state level [8, 10, 16]. Owing to a lack of detailed fracture incidence data that distinguished between persons without and with osteoporosis, modeling of fracture entries was not based on the absence or presence of the underlying disease [10]. Different fracture incidences in persons without or with previous fractures, or in persons living either in the community or in nursing homes, were not taken into account [10]. The model was built in such a way that the simplifications described can be abandoned easily when adequate input data become available. Technical correctness of the model was assessed by comparison of output parameters with related input parameters, with completely satisfactory results.

Besides developing and testing methodology, this study aimed at closing a gap of information on the future occurrence and consequences of osteoporosis-attributable hip, vertebral, and distal forearm fractures in Switzerland. According to our results, the incidence of these fracture types at the Swiss population level will rise by 19%–33% between 2000 and 2020. Corresponding absolute fracture numbers will rise by 23%–36%. Related direct medical inpatient costs per year are predicted to increase by 33%.

The expected increase in the number of osteoporosis-related hip fractures, from 8,375 in 2000 to 11,353 in 2020, confirms the magnitude of earlier estimates [1, 6, 7]. For Switzerland in 2020, Meine et al. [15] expected 15,000 hip fractures and Lippuner and Jaeger [14] expected 14,436, for all ages combined and without excluding non-osteoporotic fractures. Calculated lifetime risks are well in the range to be expected from the literature. For example, our result of a 21% lifetime hip fracture risk in women aged 50 years in 2000 compares well with published estimates from various industrialized countries, indicating a risk of 14%–23% at this age [4, 8, 10, 20, 23]. In men aged 50 years, our result of 9% compares with published estimates of from 6%–11% [23, 35, 43].

Constant or slightly decreasing incidence rates of distal forearm fractures, as observed in women aged 50 years and over, and non-monotonic developments over time in some resource use parameters, are explained by
shifts in the age structure above age 50 as modeled by the SFSO main scenario. Residual influences of chance may have played an additional role.

For the fracture types taken into account here, Lippuner et al. reported 290,972 osteoporosis-attributable days spent in acute care hospitals in 1992 and related costs of CHF245.9 million [13]. Our corresponding results of 197,987 hospital days and costs of CHF199.8 million in 2000 are distinctly lower. While the different registration methods and coding systems used might have contributed to this effect, the main reason lies in reduced lengths of stay. In particular, mean acute care length of stay after hip fracture fell dramatically, from 29.1 days in 1992 to 17.7 days in 2000 [13]. It can be assumed that this decrease was enabled by improved medical practice but also encouraged by budgetary constraints in the Swiss health care system. It may have been accompanied by a still unmeasured increase in the use of outpatient medical and nursing services and, consequently, in outpatient costs. Missing information on outpatient costs hindered a realistic assessment of total direct medical costs.

The finding that long-term nursing home costs contributed 54% of total inpatient costs is consistent with findings from 1998 onwards, which indicated that long-term care costs are responsible for 40%–75% of osteoporosis-related inpatient costs in the USA [12].

Sensitivity analyses demonstrated stable relative parameter changes between 2000 and 2020 except for when a 1% per year secular rise of fracture incidence was modeled. In fact, there is no strong evidence for an ongoing secular rise in Europe or in the USA [1, 6]. Absolute results, however, showed considerable variation, which highlighted that relevant uncertainty was present in some of the input parameters available. These were of different quality and, in part, of non-Swiss origin. For example, for vertebral and distal forearm fractures, European incidence data had to be used and, in the latter case, adjusted for geographic differences. This was justified by various literature sources, but, still, the inputs derived may, to a certain extent, deviate from Swiss reality [22, 25, 35, 44].

The osteoporosis attribution probabilities applied, reported by Melton et al., were estimated by an expert panel that used a Delphi process, and they compare well with earlier estimates published by Phillips et al. [26, 45]. Attribution probabilities have been used by several authors to model osteoporosis-related fracture occurrence [12, 13].

Modeling of hip fracture mortality was based on Swiss short-term and long-term data reported by Trombetti et al. [27], which are in line with various Swiss and international data sources [31, 37, 46]. In particular, 1-year cumulative mortality was near identical in the study by Trombetti et al. (women: 19%, men: 39%), in an earlier Swiss study by Schüürch et al. (women: 21%, men: 35%) [37], and in the Australian study by Center et al. (women: 20%; men: 37%) [31].

The estimate of a 53% hospitalization probability after distal forearm fracture in the population aged 50 years or older reflects Swiss hospitalization data and, thus, ensures consistency in our economic results. Patients that occupy a hospital bed for only a few hours were taken into account here, which may explain, in part, why this value is in accordance with a Swiss source that indicated a hospitalization probability of 70% at age 85 years, but not with two international sources that hinted at a probability of approximately 10% only from age 40 onwards [9, 35, 47]. The latter value was used as a lower boundary in sensitivity analysis.

This study focused on the occurrence and impact of osteoporosis-attributable hip, vertebral, and distal forearm fractures. An assessment of total osteoporosis-related fracture occurrence, resource use and cost would have to take into account additional fracture sites, such as the humerus, ribs and pelvis, but it was not undertaken for reasons of data availability. Another slight tendency for the model to underestimate the impact of osteoporosis may have been introduced by our not considering osteoporotic fracture occurrence under the age of 50 years. Due to a lack of data, inpatient rehabilitation episodes caused by vertebral and distal forearm fractures could not be taken into account, which may have impacted on costs estimates.

In summary, in Switzerland the incidences of osteoporotic hip, vertebral and distal forearm fractures will rise, respectively, by 33%, 27%, and 19%, between 2000 and 2020, if current prevention and treatment patterns are maintained. Corresponding absolute fracture numbers per year will rise by 36%, 31%, and 23%. The increase in hip fractures will be most pronounced. Main causes are (1) a shift toward higher ages within the population from age 50 years on, (2) a relative growth of the population from age 50 on within the total population, and (3) absolute population growth. Main assumptions are that demographic reality will essentially confirm the SFSO main scenario and that age- and gender-specific incidence rates will remain constant. Related direct medical inpatient costs per year are predicted to increase by 33% (CHF232.8 million), but this result is affected by uncertainty due to a lack of knowledge of future developments of treatment patterns, economic circumstances, and resource unit prices. Moreover, currently, total direct medical costs cannot be estimated due to missing data on outpatient costs. When additional information becomes available, this modeling framework can be used for a re-assessment.

In more general terms, this modeling framework, which focuses on hip, vertebral, and distal forearm fractures, can be applied to a wide variety of situations in order to forecast future developments and assess the impact of changing medical practice and changing economic circumstances. The incorporation of additional fracture sites is also feasible. Limitations will usually be due to the limited availability of adequate input data.
Acknowledgments
This study was supported by an unrestricted, educational grant from Merck Sharp & Dohme-Chibret AG, Glattbrugg, Switzerland.

References
Schwenkglenks M, Lippuner K.

Simulation-based cost-utility analysis of population screening-based alendronate use in Switzerland.

Simulation-based cost-utility analysis of population screening-based alendronate use in Switzerland

M. Schwenkglenks · K. Lippuner

Received: 15 November 2006 /Accepted: 25 April 2007 /Published online: 26 May 2007
© International Osteoporosis Foundation and National Osteoporosis Foundation 2007

Abstract
Summary A simulation model adopting a health system perspective showed population-based screening with DXA, followed by alendronate treatment of persons with osteoporosis, or with anamnestic fracture and osteopenia, to be cost-effective in Swiss postmenopausal women from age 70, but not in men.

Introduction We assessed the cost-effectiveness of a population-based screen-and-treat strategy for osteoporosis (DXA followed by alendronate treatment if osteoporotic, or osteopenic in the presence of fracture), compared to no intervention, from the perspective of the Swiss health care system.

Methods A published Markov model assessed by first-order Monte Carlo simulation was refined to reflect the diagnostic process and treatment effects. Women and men entered the model at age 50. Main screening ages were 65, 75, and 85 years. Age at bone densitometry was flexible for persons fracturing before the main screening age. Realistic assumptions were made with respect to persistence with intended 5 years of alendronate treatment. The main outcome was cost per quality-adjusted life year (QALY) gained.

Results In women, costs per QALY were Swiss francs (CHF) 71,000, CHF 35,000, and CHF 28,000 for the main screening ages of 65, 75, and 85 years. The threshold of CHF 50,000 per QALY was reached between main screening ages 65 and 75 years. Population-based screening was not cost-effective in men.

Conclusion Population-based DXA screening, followed by alendronate treatment in the presence of osteoporosis, or of fracture and osteopenia, is a cost-effective option in Swiss postmenopausal women after age 70.

Keywords Alendronate · Bone densitometry · Cost-utility analysis · Modelling studies · Osteoporosis · Switzerland

Introduction
Osteoporosis is a chronic, systemic disease, characterised by low bone mass and deterioration of bone micro-architecture, leading to increased fracture risk [1]. Osteoporotic fragility fractures may occur at any skeletal site [2]. However, fractures of the hip, the spine and the distal forearm are the most frequent osteoporotic fracture types [3], representing 82% and 75% of all incident osteoporotic fractures in Swiss women and men, respectively [4]. The lifetime risk of any osteoporotic fracture approximates 50% in women and 20% in men [5]. Fractures result in significant morbidity [6, 7], mortality [8, 9], and reductions in quality of life [10].

Osteoporosis has a profound and growing impact on health care resource utilization, especially in industrialized countries. The direct expenditures for the treatment of osteoporotic fractures were estimated at US dollar (USD) 10–15 billion per year for the USA [11], a figure which is consistent with Swiss francs (CHF) 713 million reported for Switzerland for the year 2000 [4]. These costs are expected to substantially increase in the coming decade, due to the overall ageing of the population and to the exponential increase of fracture incidence with age [4, 12].
Drug therapy of osteoporosis is generally indicated in patients who have had a prior fragility fracture and in patients who have osteoporosis according to the WHO densitometric definition (i.e., T-score ≤−2.5 SD) [1]. Alendronate, an aminobisphosphonate, has been previously shown, in randomised controlled primary endpoint fracture trials [13–15] and in meta-analyses of such trials [16, 17], to reduce fracture risk at all clinically relevant sites, including the hip, in postmenopausal women with osteoporosis defined as low BMD with or without prevalent vertebral fractures. In addition, the efficacy and safety of long-term treatment of osteoporosis with alendronate was established for up to 10 years of continuous therapy [18]. Furthermore, the efficacy profile of alendronate for reducing fracture risk was established in men with primary osteoporosis [19, 20] and in the most frequent form of secondary osteoporosis, glucocorticosteroid-induced osteoporosis, in women and in men [21].

Several studies have suggested that the treatment of osteoporosis with alendronate is cost-effective [22–30] with an incremental cost-utility ratio (ICUR) of less than USD 50,000 per quality adjusted life year (QALY) gained. However, these studies generally did not consider the cost involved with the identification of cases of osteoporosis which deserve therapeutic intervention, with only two exceptions, one study in glucocorticosteroid-induced osteoporosis [30] and one recent publication by Schousboe et al. [27]. In the latter work, the health benefits and costs of universal screening of elderly women, followed by alendronate treatment of those identified with osteoporosis (screen-and-treat strategy) were assessed from the societal perspective. The cost per QALY gained was estimated at USD 43,000 and USD 5,600 for 65 and 75-year-old women, respectively, while the intervention was found to be cost-saving for older women [27]. However, this model observed the screened populations from the age of mass screening onwards only and did not take into account the effect of cases identified and treated earlier (e.g., due to fractures occurring before the main screening age).

In Switzerland, as in many other European countries, bone densitometry with DXA is not accepted for mass screening of osteoporosis and reimbursement is limited to indications resulting from case-finding strategies. Drug treatment is reimbursed for persons with a T-score ≤−2.5 SD or in the presence of one or more fragility fractures. Whether and for which subset of the population mass screening with DXA, followed by drug treatment where indicated, would be cost-effective remains unknown.

Using an adapted version of our published model [12], the present study aimed at assessing the cost-effectiveness of mass bone densitometry screening plus subsequent alendronate therapy, compared to no drug treatment of osteopenia and osteoporosis, in the Swiss population from age 50 onwards, from the perspective of the Swiss health care system. We took into account the impact of earlier fracture events, which have already led to “pre-screening age” diagnostic activities. We hypothesized that even if the diagnostic process is taken into account in the modelling, the cost-effectiveness of subsequent drug intervention will still be preserved in specific patient groups.

### Materials and methods

The cost-effectiveness of two alternative strategies was evaluated in a simulation-based incremental cost-utility analysis from the perspective of the Swiss health care system. For this purpose, a non-intervention strategy was compared to a screen-and-treat strategy defined as i) bone densitometry screening with DXA at a predefined main screening age or if a fracture occurred after age 50, and ii) alendronate (FOSAMAX®; Merck & Co) treatment in subjects with osteoporosis (T-score ≤−2.5 SD), or with confirmed osteopenia (T-score >−2.5 SD but ≤−1.0 SD) after a fracture event [31]. The time horizon for analysis was life-long from age 50 on in the main analysis. Direct medical costs were taken into account regardless of payer.

For women and men, the outcomes of the screen-and-treat strategy were assessed for main screening ages of 65, 75, and 85 years, and for three treatment options each: treatment with alendronate for 5 years [25] with full persistence (to assess the theoretical potential); treatment with alendronate for 5 years with realistic persistence; and treatment with alendronate for 10 years with realistic persistence.

Additional specifications were: re-screening once after 3 years if osteopenic at first measurement (in the absence of fracture); assessment of all persons presenting with a fracture and treatment if osteopenic or osteoporotic; treatment initiation without additional screening if a fracture occurred and an earlier screening had already confirmed the presence of osteopenia; no repeated initiation of alendronate treatment in the same person; no initiation of treatment after age 95.

The main outcome was the incremental cost per QALY gained (incremental cost-utility ratio; ICUR) of each screen-and-treat scenario vs. the no intervention scenario.

In the absence of an accepted cost-effectiveness threshold for Switzerland, ICUR results of less than CHF 50,000 per QALY gained were regarded as cost-effective. Taking different price structures into account [32], one can regard this choice as roughly equivalent to the thresholds of USD 50,000 per QALY, and of British pound (GBP) 20,000–30,000 per QALY, which have been used for the USA and the United Kingdom, respectively [33, 34]. CHF 1 equalled USD 0.80 on June 30, 2006.
Model characteristics

Key model characteristics were previously described [12]. Briefly, a Markov state transition model with four mutually exclusive health states (alive without fracture; alive with at least one distal forearm or vertebral fracture, but no hip fracture; alive with at least one hip fracture; dead) was developed to simulate the number of osteoporotic hip, vertebral, and distal forearm fractures as a function of demographic change and other influences. This model was analysed using individual, first-order Monte Carlo simulation, and was pre-designed to be adaptable for assessing the impact of different screening, prophylactic, and treatment strategies on fracture occurrence and associated cost, allowing for a wide variety of scenarios regarding planned medication usage, drug efficacy, and individual persistence with treatment. Cycle length was one month. For the purpose of this study, the model was adapted as follows:

1. The increase in relative fracture risk observed in persons with a history of previous fracture; in those suffering from osteopenia or osteoporosis; and in nursing home residents was additionally modelled. The technical implementation was such that the average gender- and age-specific fracture incidences remained unaffected.

2. The probability of having osteopenia or osteoporosis at model entry, or of developing any of these conditions, was modelled using gender- and age-specific prevalence estimates and transition probabilities derived from these.

3. The impact of alendronate usage was modelled using published relative risks (RRs).

4. Age at model entry was kept constant while screening age was considered variable in the different scenarios, in order to accommodate for the fact that at a given main screening age, some persons may already have been identified with and treated for osteoporosis.

5. In order to take into account the difference between fracture-associated mortality and mortality causally related to fracture, the estimates of life years gained through alendronate usage were corrected downwards in a separate step, outside the main model. The “life expectancy component” of the QALY results was corrected in the same way.

Model inputs

Published or publicly available Swiss data sources were used whenever available. Otherwise, European data were preferred to US data, and were adjusted for regional differences within Europe. Gender- and age-specific population-level fracture risks and other models inputs used in the previously published model version were retained with the exception of osteoporosis attribution probabilities, which were no longer used to model osteoporotic causation of fracture events [12]. Additional inputs comprised the following.

Prevalence of osteopenia/osteoporosis was assumed to be similar as seen in the NHANES III study for a caucasian US population, based on femoral neck BMD measurements [35, 36]. In the absence of published Swiss BMD data, a local DXA reference database from the Bern Canton supported this assumption. Technical implementation used the results of the Rotterdam Study, with data points available for both genders and all relevant age groups [37]. Compared with NHANES III, the Rotterdam data showed a higher prevalence, consistent with the north-south gradient of osteoporosis prevalence in Europe. Therefore, a downwards adjustment was performed, using the following correction factors: 0.80 for osteopenia and osteoporosis in women; 0.65 for osteoporosis and 0.75 for osteopenia in men. This resulted in average prevalences of 23% and 8% (osteoporosis), and of 49% and 46% (osteopenia), in women and men from age 50, respectively. These figures are consistent with the NHANES III results [35, 36]. The incidence of osteopenia and osteoporosis was estimated using transition probabilities derived from these prevalence data.

Prevalence of any previous fracture was derived from a recent meta-analysis exploring the relationship of any previous fracture with age, sex and bone mineral density in 15,259 men and 44,902 women from 11 cohorts followed for a total of 250,000 person-years [38].

Relative fracture risks In the presence of osteoporosis or osteopenia, RRs of 2.7 or 1.3, respectively, as reported in the Rotterdam Study, were used for non-vertebral fractures in women and men [37]. Identical RRs were assumed for vertebral fractures [39]. BMD-adjusted RRs of 1.7 for women and of 2.0 for men were used to take into account the presence of previous fracture [38]. For nursing home residents, a RR for hip fracture of 3.5 was assumed, based on the only recent Swiss publication available [40]. This figure is consistent with previously published Swiss [41] and US data [42, 43]. No increased risk of vertebral and distal forearm fracture was assumed for this group [44, 45]. The above RRs compare persons who have the risk factor of interest with persons who do not have it. In combination with absolute fracture risk (gender- and age-specific, but averaged across other risk factors), and gender- and age-specific patterns of risk factor prevalence, they provided a basis for deriving individualised fracture risks as they were finally used in the modelling.

The RR of fracture during alendronate treatment in women with osteoporosis was generally assumed to be 0.5, in accordance with published primary endpoint trials and
meta-analyses [13–17, 28]. However, a more conservative RR of 0.6 was assumed for non-vertebral fractures after age 85 [29, 46]. In women with osteopenia, the RR was conservatively assumed to be 0.7 for vertebral fractures [15] and 1.0 for other fractures. Identical assumptions were used for men [20]. The effect of alendronate has been shown to be present early in treatment [47]. For the purpose of this analysis, it was assumed to be present from day 1 of therapy, given that the above RR estimates represent averages across the entire observation periods of the underlying studies. After the end of alendronate administration, we assumed a linear decline of the alendronate effect to zero over a 5-year period [18, 48], or over a period equal to the given person’s treatment duration, whichever was shorter.

Persistence with alendronate treatment was assumed to decline linearly from 100% to 65% during year 1 and from 65% to 45% between end of year 1 and the end of the intended duration of use [49]. It was assumed that those who stopped drug treatment prematurely did no longer accrue drug costs.

Mortality Twenty-five percent of the deaths associated with hip fracture were considered to be causally related in the base case scenario [50]. Consequently, the life years gained through alendronate usage, as reported by the model, were multiplied with a correction factor of 0.25. No such adjustment was made for vertebral fracture-associated excess deaths whose number was considered to be too low to meaningfully impact on the overall results, especially when compared to the remaining uncertainty about hip fracture-related excess mortality [48, 51]. To account for an increased general morbidity of persons admitted to nursing homes, in the absence of published data, a correction factor of 0.9 was applied to the crude hip fracture-related excess mortality [48, 51]. All-cause mortality was assumed to be 33% after a vertebral fracture coming to clinical attention [3, 55] and 53% after a distal forearm fracture [12]. Participation in an inpatient rehabilitation program after hip fracture was assumed to occur in 68% of women and 36% of men, with a length of stay of 59 and 54 days, respectively [56]. Ambulatory treatment costs post fracture was estimated at CHF 6,442 for a hip fracture, based on published data [57]. They were estimated at CHF 2,250 for a vertebral fracture and at CHF 1,750 for a distal forearm fracture, irrespective of whether an initial hospitalisation

Utilities associated with health states As no Swiss data were available, population-based European (Danish) data were used as shown in Table 1 [23, 52]. These baseline utilities were adjusted downwards after fracture occurrence, by applying multiplication factors as reported by Kanis et al. (Table 2) [53]. It was assumed that 2nd year factors would also apply for subsequent years. In addition, 1st year and subsequent years factors for the combination of a hip and a clinical vertebral fracture were assumed to be 0.489 and 0.714 [27, 54]. Utility and multiplication factor measurements involved the time trade off method and the EQ-5D [52–54].

Costs Unit cost estimates were real cost estimates for the year 2000. The monthly cost of alendronate treatment was set at CHF 61.36, based on the public price of marketed alendronate in Switzerland in 2005 adjusted for the health system-specific price inflation between 2000 and 2005 of 3.4%, as published by the Swiss Federal Office of Statistics (SFOS). Based on expert opinion and Swiss tariff lists, the cost of each screening episode was estimated at CHF 300, covering bone densitometry and a medical consultation with typical services performed. Daily inpatient costs were CHF 1,009 for acute care hospitals, CHF 440 for inpatient rehabilitation facilities, and CHF 187 for nursing homes, as reported by the SFOS for the year 2000. Overall inpatient costs were modelled individually as previously described [12]. To give some reference points, average acute care length of stay was 17.4 days for hip fracture, 18.0 days for vertebral fracture and 6.4 days for distal forearm fracture. The probability of being hospitalised was assumed to be 33% after a vertebral fracture coming to clinical attention [3, 55] and 53% after a distal forearm fracture [12]. Participation in an inpatient rehabilitation program after hip fracture was assumed to occur in 68% of women and 36% of men, with a length of stay of 59 and 54 days, respectively [56]. Ambulatory treatment costs post fracture was estimated at CHF 6,442 for a hip fracture, based on published data [57]. They were estimated at CHF 2,250 for a vertebral fracture and at CHF 1,750 for a distal forearm fracture, irrespective of whether an initial hospitalisation.

Table 1 European (Danish) population utility values1

<table>
<thead>
<tr>
<th>Age</th>
<th>Average utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.917</td>
</tr>
<tr>
<td>55</td>
<td>0.9199</td>
</tr>
<tr>
<td>60</td>
<td>0.8992</td>
</tr>
<tr>
<td>65</td>
<td>0.8882</td>
</tr>
<tr>
<td>70</td>
<td>0.8939</td>
</tr>
<tr>
<td>75</td>
<td>0.863</td>
</tr>
<tr>
<td>80</td>
<td>0.8529</td>
</tr>
<tr>
<td>85</td>
<td>0.8339</td>
</tr>
</tbody>
</table>

1 Pedersen et al. 2003 [23, 52].

Table 2 Utility correction factors

<table>
<thead>
<tr>
<th>Fracture site</th>
<th>Female, 1st year</th>
<th>Male, 1st year</th>
<th>Female, subsequent years</th>
<th>Male, subsequent years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist1</td>
<td>0.977</td>
<td>0.977</td>
<td>0.999</td>
<td>0.999</td>
</tr>
<tr>
<td>Vertebræ2</td>
<td>0.820</td>
<td>0.777</td>
<td>0.913</td>
<td>0.912</td>
</tr>
<tr>
<td>Hip1</td>
<td>0.792</td>
<td>0.792</td>
<td>0.813</td>
<td>0.813</td>
</tr>
<tr>
<td>Hip and clinical vertebral fracture2</td>
<td>0.489</td>
<td>0.489</td>
<td>0.714</td>
<td>0.714</td>
</tr>
</tbody>
</table>

1 Kanis et al. 2004 [53].
2 Estimated based on Tosteson et al. 2001 [54] and Schousboe et al. 2005 [27].
occurred. These estimates were based on expert opinion as there were no published Swiss data available.

**Discount rate** The discount rate for costs and QALYs was set at 3%.

Sensitivity analysis

In the base case scenarios, model entry was at age 50 for all persons, which allowed to take into account the impact of cases of osteoporosis or osteopenia with intercurrent fracture, identified before the main screening age. In alternative scenarios, intended for comparison purposes, the simulated persons entered the model at the main screening age, i.e., their previous diagnosis and treatment history was neglected.

Additional, univariate sensitivity analyses were conducted to identify influential input parameters. Specifically, average population fracture risks; the risk reduction achieved with alendronate; the utility reduction due to fracture events; and most cost parameters were varied by ±30%. The cost of outpatient fracture treatment was varied by ±50%, due to the higher level of uncertainty present in the underlying estimates. The linear offset post alendronate administration was set to 0.4 or 1.6 times the treatment duration, corresponding to a 2-year or 8-year linear offset for a treatment duration of 5 years. Persistence with alendronate treatment was assumed to decline from 100% to either 40% or 80% during year 1, and to decline further to either 20% or 60% between end of year 1 and the end of the intended duration of use [49]. The correction for non-causally related hip fracture-associated deaths was set to 15% or 50%, and the correction of hip fracture-related nursing home time for increased general co-morbidity of nursing home residents was set to 0.6 or 1.0, the latter representing no correction. The probability of a new nursing home admission after hip fracture was set to 10% or 25% [12]. The discount rate was set to 0% or 6%.

Subsequently, probabilistic sensitivity analyses were run on the main scenarios. Triangular distributions, based on the base case values and the above described ranges of variation, were used to vary the above-listed parameters jointly. As an exception, a uniform distribution was used to vary the correction of hip fracture-related nursing home time for increased general co-morbidity of nursing home residents, in the absence of published values. The discount rate was not varied in probabilistic sensitivity analysis.

Technical implementation

The model was implemented using TreeAge Pro 2006 Suite® (TreeAge, Williamstown, USA). TreeAge’s option to independently seed each model iteration allowed to greatly reduce the amount of random variation present in the simulation results. Additional statistical analyses were performed in Stata/SE®, version 9 (Stata Corporation, College Station, USA). Main scenarios and univariate sensitivity analyses were based on 100,000 simulated persons per arm, for each scenario. Probabilistic sensitivity analyses used 500 different sets of input parameters (randomly drawn from the above-mentioned triangular distributions) and 2,000 simulated persons per set of input parameters and arm [27].

Model validation

All validations performed on the previously published model [12] retained their validity. Expected gender- and age-specific prevalences of osteoporosis and osteopenia were reproduced correctly. After model calibration, the overall fracture incidence rates found for a cohort followed for the rest of their lives from age 50 onwards, without alendronate treatment, deviated only slightly from the incidence rates calculated from the previously published model (deviations in women: hip fracture 0.7%; vertebral fracture 0.2%; distal forearm fracture 0.2%, deviations in men: hip fracture −0.3%; vertebral fracture 0.0%; distal forearm fracture −3.3%). A simulation of 50,000 virtual persons receiving alendronate, under the assumption of perfect persistence and a relative risk of fracture of 0.5, correctly reduced fracture incidences by 50%. Two scenarios mimicking the previously published models of Christensen et al. [23] and Johnell et al. [25] delivered similar results in terms of expected relative fracture risk reduction. Calculation of 95% confidence intervals based on bias-corrected bootstrapping using 1,000 repetitions confirmed standard errors for the main outcomes of interest to be sufficiently small compared to effect sizes. (Data not shown).

**Results**

Results for the primary outcome measure, incremental cost per QALY gained (ICUR), are shown in Table 3, for both genders. Table 3 covers the base case scenarios (where all persons entered the model at age 50) as well as the alternative scenarios (where all persons entered the model at the main screening age; to enhance comparability with results published earlier by Schousboe et al. [27]). The incremental costs of, and QALYs gained with a screen-and-treat strategy compared to no intervention, assuming model entry at age 50 and 5 years of intended treatment with alendronate if applicable, under realistic persistence assumptions, are shown for women and men in Table 4.
ICUR results were better when model entry was at the main screening age (i.e., when the possibility of earlier diagnosis and treatment was disregarded); better in women than in men; better if perfect persistence was assumed; and better if the intended treatment duration was extended from 5 to 10 years under realistic persistence assumptions. However, the latter was not observed when the main screening age was set to 85 years.

In women, the ICUR of the screen-and-treat strategy compared to no intervention was less than CHF 50,000 for a main screening age of 75 years or higher, in the base case scenario. In the alternative scenarios, ICUR results were below or around CHF 50,000 for all main screening ages considered. Although the alternative scenarios showed overall improved cost-effectiveness results, the relative rank order of the assessed strategies remained identical. An additional analysis under realistic persistence assumptions showed that, in women, a screen-and-treat strategy using a main screening age of 70 years lead to ICURs of CHF 49,101 and CHF 42,141 for 5 and 10 years of intended alendronate treatment, respectively. However, the screen-and-treat approach did not appear to be cost-effective for a main screening age of 65 years or below, or in men.

The impact of univariate sensitivity analysis on the ICUR is shown in Table 5, for a representative scenario (women; model entry at age 50; main screening age 75 years; intended duration of alendronate treatment 5 years; realistic persistence). For this scenario, parameter changes favouring the comparator strategy yielded moderate increases of the ICUR, which remained below or very close to CHF 50,000 in all instances. Variation of the risk reduction achieved with alendronate, of the duration of the residual alendronate effect after the end of drug administration, and of the cost of drug treatment had the strongest impact. The parameters which exerted the smallest influence were the correction for increased general morbidity of persons admitted to nursing homes, the probability of a new nursing home admission after hip fracture, and the cost of outpatient fracture treatment.

For this same scenario, probabilistic sensitivity analysis indicated that the cost-effectiveness criterion of CHF 50,000 per QALY gained was met in 79% of cases, with a 95% confidence interval for the ICUR reaching from cost-saving to CHF 79,525 per QALY gained (Fig. 1). Under identical assumptions, but with the main screening age set to 65 years, the CHF 50,000 per QALY threshold was only reached in 16% of the cases.

Discussion

The present study demonstrates that, from the perspective of the Swiss health care system, mass bone densitometry screening at or after age 70, plus subsequent alendronate therapy for 5 or 10 years (screen-and-treat strategy for osteoporosis and osteopenia), is a cost-effective intervention in women, with an ICUR around or below CHF 50,000 per QALY gained. This finding is based on realistic assumptions with respect to persistence with drug treatment and takes into account the impact of diagnostic and treatment activities before the age of mass screening, induced by “pre-screening age” fracture occurrence. It is
hence in line with the stated hypothesis. In contrast, a screen-and-treat strategy for osteoporosis and osteopenia does not appear to be cost-effective in men. Increasing the intended duration of alendronate treatment from 5 to 10 years leads to improved ICUR results in most cases. However, for a main screening age of 85 years, this was no longer true. At this age, all-cause mortality rates are very high and cost savings due to avoided fracture events may no longer be able to outweigh the additional cost of further treatment.

Our results demonstrate further that in situations where fixed upfront costs (not influenced by persistence; such as screening costs) have a substantial role, sub-optimal persistence can have a relevant negative impact on ICUR results. Our screen-and-treat strategy assumed, in contrast to current clinical practice in Switzerland and other countries [58], that all persons fracturing before the main screening age would immediately be assessed, and treated with alendronate if osteopenic or osteoporotic. Not allowing for such “pre-screening age” diagnostic and treatment activities leads to improved cost-effectiveness results because on average, alendronate is now administered at a higher age and when fracture incidences are also higher, at the cost of not protecting an easily identifiable risk group at an earlier age.

To our knowledge, the only other modelling study assessing a mass screen-and-treat strategy for osteoporosis was recently published by Schousboe et al. [27]. These authors compared the combination of DXA screening plus alendronate treatment from a US perspective. Their approach was conceptionally close to ours, with some remarkable differences. The present model used Swiss or European data whenever available; all scenarios were assessed for women and for men; the strategies modelled took into account osteopenia in addition to osteoporosis; and realistic assumptions were made with respect to persistence with alendronate treatment in the base case analysis. Most importantly, we observed the target population from age 50 onwards (and not from the age of mass screening onwards, which scotomizes any diagnostics performed earlier, and treatments administered earlier, due to fracture occurrence before the main screening age). This scotomization and a related difficulty to individually model “pre-screening age” fracture-induced changes in health-related quality of life and utility may have lead to an overestimation of the cost-effectiveness of the screen-and-treat approach, in particular when a very high main screening age was chosen. In order to clarify this point, we performed alternative assessments with model entry at

Table 5 Univariate sensitivity analysis of incremental cost-utility ratio for women

<table>
<thead>
<tr>
<th>Parameter varied</th>
<th>Range of variation</th>
<th>Favours screening/alendronate use</th>
<th>Baseline</th>
<th>Favours comparator strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture risk (average population risk)</td>
<td>+30%−30%</td>
<td>22,775</td>
<td>35,412</td>
<td>45,512</td>
</tr>
<tr>
<td>Fracture risk, effect of alendronate</td>
<td></td>
<td>18,062</td>
<td>35,412</td>
<td>52,543</td>
</tr>
<tr>
<td>Duration of effect of alendronate after end of administration</td>
<td>Relative reduction of risk, +30%−30%</td>
<td>25,409</td>
<td>35,412</td>
<td>50,131</td>
</tr>
<tr>
<td>Persistence (persons taking drug)</td>
<td>Decline to 40%/80% in year 1, further decline to 20%/60% between end of year 1 and end of intended duration of use</td>
<td>30,149</td>
<td>35,412</td>
<td>46,374</td>
</tr>
<tr>
<td>Causally related hip fracture-associated deaths</td>
<td>50%/15%</td>
<td>25,525</td>
<td>35,412</td>
<td>41,904</td>
</tr>
<tr>
<td>Correction for increased general morbidity in persons admitted to nursing homes</td>
<td>1.0/0.6</td>
<td>34,751</td>
<td>35,412</td>
<td>37,395</td>
</tr>
<tr>
<td>Probability of new nursing home admission after hip fracture</td>
<td>10%/25%</td>
<td>31,334</td>
<td>35,412</td>
<td>37,989</td>
</tr>
<tr>
<td>Disutility factors</td>
<td>Relative utility reduction, +30%−30%</td>
<td>29,272</td>
<td>35,412</td>
<td>44,812</td>
</tr>
<tr>
<td>Cost of alendronate</td>
<td>−30%/+30%</td>
<td>22,002</td>
<td>35,412</td>
<td>48,822</td>
</tr>
<tr>
<td>Cost of diagnostic work-up before initiation of alendronate therapy</td>
<td>−30%/+30%</td>
<td>29,988</td>
<td>35,412</td>
<td>40,836</td>
</tr>
<tr>
<td>Cost of inpatient treatment inclusive of nursing home stays</td>
<td>+30%/−30%</td>
<td>28,325</td>
<td>35,412</td>
<td>42,499</td>
</tr>
<tr>
<td>Cost of outpatient fracture treatment</td>
<td>−50%/+50%</td>
<td>34,289</td>
<td>35,412</td>
<td>36,535</td>
</tr>
<tr>
<td>Discount rate</td>
<td>0%/6%</td>
<td>20,904</td>
<td>35,412</td>
<td>47,807</td>
</tr>
</tbody>
</table>

Specifications: model entry at age 50, main screening age 75 years; intended duration of alendronate treatment 5 years; realistic persistence
the main screening age. The resulting set of more favourable ICUR values was entirely consistent with the results reported by Schousboe et al. \[27\]. In both cases, the gain in cost-effectiveness achieved by choosing a higher main screening age was distinctly bigger than in our analyses observing the target population from age 50 onwards. Observing the target population from the age of mass screening onwards only, or otherwise disregarding diagnostic and treatment activities before the main screening age, tends to overestimate cost-effectiveness in general, and the advantages of choosing a high screening age in particular.

This study has some limitations. The proposed results and conclusions are model-based, which always implies a simplification of reality. This remains true although we adapted our published model \[12\] to incorporate the screening and diagnostic process (in contrast to other modelling studies addressing the cost-effectiveness of alendronate \[23, 25\]); to take into account increases in relative fracture risk in persons with anamnestic fractures or with low BMD; and to correct for the discrepancy between fracture-associated deaths and deaths causally related to fracture \[23, 25\]. The co-morbidity patterns of osteoporotic fracture patients are likely to differ from those of the general population and we implemented a correction for increased general morbidity in persons who were admitted to a nursing home post hip fracture. However, little detailed knowledge is available on this topic, which may have a significant impact on patient outcomes and on the cost-effectiveness of intervention which could not be adequately reflected in our model and deserves further research.

The model did not encompass all types of osteoporotic fractures but was limited to three typical fracture sites. About 18–25% of osteoporotic fractures were shown to occur at other skeletal sites not considered in the present analysis \[4\]. This may have led to a certain underestimation of the cost-effectiveness of the screen-and-treat approach.

We made realistic assumptions with respect to persistence with drug treatment, but in order to limit complexity, it was assumed that no further drug costs were accrued by those persons who stopped taking the drug prematurely. Moreover, given that alendronate is currently taken as a weekly tablet, the possibility of additional compliance effects (such as reduced effectiveness due to omission of individual doses or taking the drug in the wrong way) was neglected. This may have caused a certain overestimation of the cost-effectiveness of the screen-and-treat approach.

Only some of our model inputs could be based on published or official Swiss data \[12\]. Other model inputs had to be derived from various European or US sources, had to be based on expert opinion, or were subject to relevant uncertainty otherwise (e.g., persistence with drug treatment; residual treatment effect after the end of drug administration). However, univariate and probabilistic sensitivity analyses confirmed the robustness of the ICUR results. Based on variation within a ±30% range, the risk reduction achieved with drug treatment was the most sensitive single parameter.

The applicability of our results is in essence limited to Switzerland, as Swiss cost and resource use data were used. Some transferability to other industrialised countries with similar cost and age structures can be assumed, but cannot be taken for granted. Transferability to other treatments of osteoporosis may neither be without problems. Separate calculations would be required, based on a thorough assessment of reported effect sizes, related levels of empirical evidence, and other related input parameters (e.g., expected persistence).

Finally, this study did not assess the cost-effectiveness of scenarios involving a pre-selection of sub-populations at high risk of osteoporosis. Earlier studies have shown that selective case-finding based on a combination of risk factors, with or without radiographic absorptiometry,
provided a better sensitivity and specificity in identifying women with underlying osteoporosis than the currently accepted criteria for reimbursement of DXA measurements in Switzerland [59]. In addition, the pre-selection of women and men at highest risk of osteoporosis, and who should therefore undergo BMD measurement by DXA, based on the determination of their 10-year absolute fracture risk may considerably improve the cost-effectiveness of the population-based screen-and-treat approach [60–64]. More research work is required in this field.

In Switzerland, as in other European countries, universal screening for osteoporosis with bone densitometry using DXA is not recommended and patient identification solely relies on case-finding strategies based on anamnestic fractures and/or other risk factors for osteoporosis. For the USA, medical interventions have been considered as cost-effective from a societal point of view if their cost was below USD 50,000–100,000 per QALY gained [33]. Allowing for different price structures in the USA vs. Switzerland, the cost-effectiveness threshold adopted here, of CHF 50,000 per QALY, is at the lower end of this range, and was used in an assessment only taking into account direct medical costs. It corresponds to 0.9 times the Swiss gross domestic product (GDP) per capita in the year 2000 (while use of a factor of 1.4–2.1 times the GDP per capita has been tentatively estimated for the UK [65]), and must, thus, be considered as conservative. With this restrictive assumption, this is the first European study to demonstrate that population-based screening with bone densitometry by DXA and subsequent alendronate treatment in the presence of osteoporosis, or of anamnestic fracture and osteopenia, is cost-effective in women from age 70 onwards and should, therefore, be regarded as a valid option from a Swiss health care system point of view.

Generic alendronates may become available in Switzerland in the future. By Swiss law, no cost-effectiveness assessment of new generics is required if they are marketed at least 30% below the price of the original drug [66]. Based on their lower price, such generic alendronates may contribute to further improve the cost-effectiveness of the screen-and-treat option. Our corresponding univariate sensitivity analysis result of CHF 22,002 per QALY gained reflects this theoretical potential, if it is assumed that the clinical efficacy, tolerability and safety of the original compound will be matched.

Although the incremental cost-utility ratio remains superior if a high main screening age is chosen, the difference seen is distinctly smaller than reported earlier [27], leaving more room for the notion that it may be more important from an individual, but also from a societal perspective to avoid fracture events at a younger rather than at a later age, despite higher absolute budget implications due to differences in the size of the populations to be screened. If and for which population segments the cost-effectiveness of the screen-and-treat approach can be further improved, e.g., by pre-selection of eligible candidates for screening based on clinical risk factor profiles, should be subject to further research.

Acknowledgements We are grateful to Dr Philippe Kress for his invaluable contribution to the manuscript.

Funding This study was partially funded by an unrestricted research grant from Merck Sharp & Dohme-Chibret AG, Glattbrugg, Switzerland.

References


32. Organisation for Economic Co-operation and Development (OECD) (2007) Purchasing Power Parities (PPP). http://www.oecd.org/department/0.2688,en_2649_34357_1_1_1_1_1,00.html


