

# Osteoporosis, (bone) fractures and fracture liaison services

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## SUMMARY

Osteoporosis, (bone) fractures and metabolic bone diseases are associated with significant morbidity, reduction in health-related quality of life, excess mortality as well as considerable healthcare expenditures, representing therefore an important public health challenge. A prior fracture is a well-documented major risk factor for subsequent fractures. Pharmacological treatments including anabolic and anti-resorptives agents as well as sequential therapy have proven efficacy in reducing increased fracture risk. Despite the wide availability of these pharmacologic interventions, a substantial proportion of patients with osteoporosis or at high risk of (recurrent) fractures remain underdiagnosed and/or undertreated, leading to substantial treatment gap. Poor adherence and persistence to osteoporotic medication remains a major problem increasing the treatment gap. In further response to this treatment gap, post-fracture care program such as fracture liaison service (FLS), is nowadays widely advocated as the most appropriate and effective approach for secondary fracture prevention in persons aged 50 years and older with a recent bone fracture. Recently, with the international endorsement by scientific societies, an increasing number of FLSs have been implemented throughout the world. Several questions remain concerning the effect of the FLS on various outcomes. Correspondingly, studies were conducted to investigate the effectiveness and cost-effectiveness of anti-osteoporosis medications as well as the implementation of an FLS in country-specific hospital settings.

**Part I** of this dissertation focused on economic evaluations in both women and men with osteoporosis, on factors involved in adherence or persistence to medication and behaviours; and on understanding the complexities of the communication of fracture risk to an individual.

Part I contains three chapters. In **Chapter 2**, we conducted a systematic review to update information on cost-effectiveness of drugs in women with osteoporosis and critically appraised the quality of included economic evaluations using an osteoporosis-specific guideline. In this chapter, 27 studies published between 1 July, 2013 and 31 December, 2019 were included, representing the perspective of 15 countries and evaluating 12 different active drugs. Compared to traditional oral bisphosphonates, newer interventions (denosumab, zoledronic acid, gastro-resistant risedronate, and teriparatide) were generally cost-effective or even dominant (better health outcome for lower costs) in women aged 50 years and older with osteoporosis. Sequential therapy (anabolic first followed by an antiresorptive) opposed to monotherapy (such as oral alendronate)

as initial treatment in postmenopausal women indicated extra health benefits (larger gains in quality-adjusted life years), and potential cost-effectiveness in very high risk population although the cost-effectiveness of sequential therapy depends on acquisition costs of anabolic agents even when accounting for low costs of bisphosphonates that were out of patent. In terms of study quality, the average score for quality assessment was 17 out of 25 (range 2–15). Items such as ‘an additional effect on costs and/ or utility after multiple fractures’, ‘adverse events’ as well as ‘proportion of excess mortality attributed to the fracture’ were frequently unreported and room for improvement was observed for most studies which could potentially be explained by the fact that most studies were published prior to the osteoporosis-specific guideline. We concluded that newer interventions were generally cost-effective or even dominant when compared to oral bisphosphonates. Greater adherence to guideline recommendations (in particular the ESCEO-IOF guideline) was expected for future studies.

In **Chapter 3**, a systematic review was conducted to summarize information on the cost-effectiveness of treating men with osteoporosis, to compare the cost-effectiveness results between men and women, and to critically appraise study quality including inspection the source of model input data. In this chapter, a total of 25 studies published between 1 January, 2000 and 30 June, 2022 were included. These studies were classified into economic evaluations of active anti-osteoporosis drugs (n=8) or nutrition supplements (n=4), medication intervention thresholds (n=5), screening strategies (n=6), and post-fracture care programs (n=2). Most studies were conducted in European countries, followed by North America. Bisphosphonates and nutrition supplements were shown to be generally cost-effective compared to no treatment in men aged over 60 years with osteoporosis or prior fractures. Two studies suggested that denosumab was cost-effective in men aged 75 years and older with osteoporosis compared to bisphosphates and teriparatide. Intervention thresholds at which bisphosphonates were found to be cost-effective varied among studies focusing on men with a 10-year probability of a major osteoporotic fracture ranging from 8.9% to 34.2% for different age categories. A few studies suggested cost-effectiveness of screening strategies and post-fracture care programs in men aged 65 years and older with osteoporosis or a recent fracture. Similar findings regarding the cost-effectiveness of drugs and intervention thresholds in women and men were captured, with slightly greater ICERs in men. The quality of the studies included had an average score of 18.8 out of 25 (range 13-23.5). Hip fracture incidence and mortality risk were mainly derived from studies in men, while fracture cost, treatment efficacy,

and disutility were commonly derived from studies in women or studies combining both sexes. We concluded that medicines and nutrition supplements are generally cost-effective in men over 60 years of age with osteoporosis or prior fractures, reimbursement for these active drugs should be considered as part of the standard of care. Similar findings regarding the cost-effectiveness of interventions in women and men with osteoporosis were captured, fracture risk reduction should therefore be the primary consideration in the treatment for osteoporosis irrespective of sex.

In **Chapter 4**, we conducted a scoping review to study the current status of patient adherence to osteoporosis medications, the determinants and consequences of non-adherence as well as the complexities of fracture risk communication. Low adherence to osteoporotic medications is well recognized by published studies, leading to increased risk of fractures and representing a substantial clinical and economic burden. Studies reported that multiple factors were identified for non-adherence, including patient-related factors such as older age and misconceptions about osteoporosis, therapy-related factors such as higher dosing frequency and medication side effects. Besides, patient perceptions and preferences for osteoporosis medications were also shown to impact adherence behavior including persistence. Interventions including patient education, drug regimen implementation, monitoring and supervision, interdisciplinary collaboration, and shared decision-making were common initiatives to facilitate interaction/communication between patients and doctors, to help patients improve health literacy related to osteoporosis or fracture, and to further improve the medication adherence. To quantify individuals' fracture risk, several risk algorithms have been developed, the majority of guidelines internationally use FRAX® as the measure of fracture risk over 10 years. Developing online tools to convert output of those fracture risk algorithms into friendly and visual presentation could facilitate professionals communicating with patients about fracture risk. Using available and effective educational materials in daily practice to communicate in a highly efficient manner about risk could be an important step in enhancing patient education, self-management of the disease, acceptance of treatment and, ultimately, adherence to treatment. We concluded that patient understanding of risk of fracture should be confirmed by making sure that patients feel free to ask questions and express their concerns. This will contribute to an optimal patient-centered approach. Visual aids could help patients understand their fracture risk and further improve their adherence to medication.

**Part II** of this dissertation focuses on clinical and economic outcomes of FLS. Five chapters were contained in Part II. In **Chapter 5**, we summarized the current evidence by conducting a systematic

review and meta-analysis to investigate the impact of FLS on subsequent fractures and mortality. A total of 16 studies published between January 1, 2010, and April 30, 2020 and comparing FLS to no-FLS were included. Twelve studies compared outcomes before (pre-FLS) and after (post-FLS) FLS implementation, two studies compared outcomes between hospitals with and without FLS, and two other studies performed both comparisons. The meta-analysis suggested that the FLS care was associated with a significantly lower probability of subsequent fractures (odds ratio: 0.70, 95% CI: 0.52–0.93,  $P=0.01$ ). The reduction was even larger (odds ratio: 0.57, 95% CI: 0.34–0.94,  $P=0.03$ ) in studies with relatively longer follow-up ( $>2$  years). Overall, no significant difference in mortality was observed (odds ratio: 0.73, 95% CI: 0.49–1.09,  $P=0.12$ ), however, a significantly lower probability of mortality was identified in the six pre-post FLS comparisons (odds ratio: 0.65, 95% CI: 0.44–0.95,  $P=0.03$ ). No difference was further observed in mortality stratified by follow-up time. The average score for quality assessment using self-designed tool (by combining and modifying criteria of existing quality assessment tools, i.e. ROBINS-I, Newcastle–Ottawa scale, and NIH tool) was 5.4 out of 10 (range 3–8.5). Only 50% of studies fulfilled more than half of the criteria. We concluded that FLS is associated with a significantly lower probability of subsequent fractures and mortality although the latter was only found in studies comparing outcomes before and after the introduction of an FLS. Some important methodological issues were unmet in the currently available studies, the most important one was all eligible patients (not only attenders) should be included in the FLS group and all analyses, otherwise the results would be biased (these studies were regarded as very high selection bias and were excluded from the main meta-analysis in our study, i.e. only tested in sensitivity analysis).

In **Chapter 6**, we assessed the 3-year health state utility value (HSUV) (as measured by EQ-5D-5L and SF-6D) in patients with a recent fracture presenting at an FLS after a mean of 3.5 months (SD: 1.0) post-fracture, and explored factors associated with HSUV. We found that the EQ-5D HSUV in patients aged 50 years and older presenting the FLS because of a recent fracture did not change significantly over 3 years following their first visit ( $P=0.52$ ), although slightly but significantly higher HSUV was captured at 6 months (mean difference: 0.015,  $P=0.02$ ) and 12 months (mean difference: 0.018,  $P=0.01$ ). There was no significant difference in the course of EQ-5D HSUV across fracture locations ( $P=0.86$ ). A significant increase in HSUV was only captured for patients had shorter time period ( $<107$  days) between FLS visit and their index fracture, indicating the recovery from the fracture in this group. Sustaining a subsequent fracture was

associated with significant loss of health utility (mean difference:  $-0.078$ ,  $P < 0.001$ ). Subsequent fracture, previous treatment with anti-osteoporosis medication, a prevalent vertebral fracture (grade 2 or 3), use of a walking aid, previous falls, and higher BMI were negatively associated with mean EQ-5D HSUV over 3 years. We concluded that the 3-year change in HSUV was not statistically significant, although significant improvements were observed at 6 and 12 months post-fracture in comparison with baseline.

In **Chapter 7**, we compared the psychometric properties (construct validity, known-group validity, and responsiveness/longitudinal validity) of EQ-5D-5L and SF-6D to assess the interchangeability of both instruments in patients with a recent fracture presenting at an FLS. Moderate agreement between the (UK and Dutch) EQ-5D-5L and SF-6D was identified with intra-class correlation coefficients of 0.625 and 0.654, respectively. Bland-Altman plots revealed proportional bias, as the differences in utilities between two instruments were highly dependent on the health states. Notwithstanding, high correlation between instruments was found (UK:  $\rho = 0.758$ ; Dutch:  $\rho = 0.763$ ). EQ-5D-5L and SF-6D utilities showed high correlation with physical component but low correlation with mental component score of SF-36. Both instruments showed moderate discrimination (effect size (ES)  $> 0.5$ ) for subgroup by baseline fracture type, and moderate responsiveness ( $0.5 < \text{standardized response mean (SRM)} < 0.8$ ) in patients that sustained a subsequent fracture. We concluded that both EQ-5D-5L and SF-6D appeared to be valid utility instruments in patients with fractures attending the FLS. Construct validity and responsiveness (change after recurrent fracture) were comparable. However, these two instruments cannot be used interchangeably given only moderate agreement and differences in utilities and ceiling effect were revealed. Of note, trial discrimination could not be tested.

In **Chapter 8**, we assessed the potential economic benefits of the FLS from the Chinese healthcare perspective with a lifetime horizon using a Markov microsimulation model. We found when compared with no-FLS, that FLS was dominant (lower costs, higher QALYs) in China at the FLS cost of \$200 per patient. The FLS was however not cost-effective in patients aged 80 years and older. We concluded that FLS care could potentially lead to lifetime cost-saving in patients who have experienced a fracture in China. More future research incorporating Chinese-specific real-world data are needed to confirm the results of our study and to better evaluate the cost-effectiveness of FLS in China.

In **Chapter 9**, we assessed the cost-effectiveness of FLS in patients with a recent fracture from the Dutch societal perspective using real-life data. We found that for patients with a recent fracture aged 50 years and older, the availability of an FLS was associated with a €45 higher cost and 0.11 additional QALY gained leading to an ICER of €409 per QALY gained, indicating FLS was cost-effective compared to no-FLS at the Dutch threshold of €20,000/QALY. For every 1,000 patients attending the FLS, 53 subsequent fractures were avoided during their lifetime. For patients at the ages of 50, 60, 70 and 80 years, FLS was consistently cost-effective; patients aged 80 years resulted in slightly greater QALY gained compared to younger groups. Our results were robust in all one-way sensitivity analyses. At a threshold of €20,000 per QALY gained, FLS was cost-effective compared to no-FLS in 90% of the simulations. This study provides the first economic results of FLS in the Netherlands. We concluded that the availability of an FLS is cost-effective compared to no-FLS in patients with a recent fracture aged 50 years and older in the Netherlands. The implementation of FLS could lead to lifetime health-economic benefits.