Anti-osteoporosis medication prescriptions and incidence of subsequent fracture among primary hip fracture patients in England and Wales: an interrupted time-series analysis

Samuel Hawley1, MSc; Jose Leal2, DPhil; Antonella Delmestri1, PhD; Daniel Prieto-Alhambra1, 3-4, PhD; Nigel K Arden1,3, MD; Cyrus Cooper1,3, MD; M Kassim Javaid1,3\*, PhD; Andrew Judge1,3\*, PhD; The REFReSH study group

1 Oxford NIHR Musculoskeletal Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Windmill Road, Headington, Oxford, OX3 7LD, UK

2 Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Old Road Campus, OX3 7LF

3 MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, SO16 6YD, UK

4 IMIM (Hospital del Mar Medical Research Institute), Universitat Autònoma de Barcelona and RETICEF, Instituto de Salud Carlos III, Barcelona, Spain

5 GREMPAL Research Group, IDIAP Jordi Gol Primary Care Research Institute, Universitat Autònoma de Barcelona, Spain

\* AJ and MKJ are joint senior authors

Corresponding Author

Andrew Judge

NIHR Musculoskeletal Biomedical Research Unit,

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences,

University of Oxford,

Windmill Road, Headington,

Oxford, OX3 7LD, UK.

Tel: +44 (0) 1865 737 837

Key words: epidemiology, osteoporosis, hip fracture, secondary prevention, bisphosphonates, guidelines, health services research

ABSTRACT

In January 2005 the National Institute for Health and Care Excellence (NICE) in England and Wales provided new guidance on the use of anti-osteoporosis therapies for the secondary prevention of osteoporotic fractures. This was shortly followed in the same year by market authorisation of a generic form of alendronic acid. We here set out to estimate the actual practice impact of these events among hip fracture patients in terms of anti-osteoporosis medicationprescribing and subsequent fracture incidence using primary care data (Clinical Practice Research Datalink) from 1999-2013. Changes in level and trend of prescribing and subsequent fracture following publication of NICE guidance and availability of generic alendronic acid were estimated using an interrupted time series analysis. Both events were considered in combination within a 1-year ‘intervention period’. We identified 10,873 primary hip fracture patients between April 1999 and Sept 2012. Taking into account prior trend, the intervention period was associated with an immediate absolute increase of 14.9% (95% C.I. 10.9 – 18.9) for incident anti-osteoporosis prescriptions and a significant and clinically important reduction in subsequent major and subsequent hip fracture: -0.19% (95% C.I.-0.28 to -0.09) and -0.17% (95% C.I. -0.26 to -0.09) per six months, respectively. This equated to an approximate 14% (major) and 22% (hip) reduction at three years post-intervention relative to expected values based solely on pre-intervention level and trend. We conclude that among hip fracture patients, publication of NICE guidance and availability of generic alendronic acid was temporally associated with increased prescribing and a significant decline in subsequent fractures.

INTRODUCTION

Hip fractures are associated with major distress, disability, dependency (1), and significant costs to health and social care (2). Hip fracture patients are at increased risk of subsequent fracture, premature death (1), and a decline in quality of life that is comparable to severe neurological diseases (3). The projected cost of hip fracture for the year 2025 is approximately $18 billion (4) in the US and £1.5 billion in the UK (2).

Data from randomised controlled trials (RCTs) have demonstrated that bisphosphonate treatment is highly effective for the secondary prevention of osteoporotic fracture (5), including among hip fracture patients (6). This is reflected in many clinical guidelines from around the world that recommend the use of bisphosphonate for patients having sustained a minimal trauma fracture (7). In January 2005, the National Institute for Health and Care Excellence (NICE) in England and Wales published new guidance recommending bisphosphonate use as a first-line therapy for the secondary prevention of osteoporotic fracture (8). Moreover, the first-time UK market authorisation of generic bisphosphonate alendronic acid occurred in August 2005, after which the cost of therapy fell substantially.

We therefore aimed to evaluate these “real world” events within the English and Welsh National Health Service (NHS) setting in terms of subsequent change in anti-osteoporosis medication prescribing and incidence of clinical outcomes such prescriptions were intended to prevent, i.e. secondary osteoporotic fractures.

MATERIALS AND METHODS

Study population and source of data

We used primary care data from the Clinical Practice Research Datalink (CPRD) for the period 1999-2013. CPRD covers approximately 11.3 million patients from 674 UK practices and has a current representative coverage of approximately 7% of the UK (9). Mortality data was linked to the Office for National Statistics (ONS) database. Primary hip fractures occurring between 1st April 1999 and 30st Sept 2012 were identified using READ codes (supplementary table 1) as defined a-priori by two clinicians with experience in both clinical practice and epidemiological research into osteoporosis independently identifying available codes and reaching consensus. To focus on proximal femoral fractures, subtrochanteric/shaft fractures were not included. To focus on proximal femoral fractures, subtrochanteric/shaft fractures were not included. Patients below 60 years of age were excluded, as were patients with a history of a hip fracture diagnosis in the preceding three years or with less than three years of clinical data from registration. Patients registered in a GP practice outside England or Wales were excluded as guidance pertained only to these countries.

Intervention

Publication of NICE TA 87 (8) in January 2005 and the first authorisation of generic forms of alendronic acid in August 2005 were considered as a combined intervention due to their close temporal proximity (10) . NICE TA 87 gave for the first time guidance on clinical thresholds for prescribing various anti-osteoporosis medications among post–menopausal women having sustained a clinically apparent osteoporotic fracture (i.e. in secondary prevention). It recommended the use of bisphosphonates for the treatment of women aged 75 years or older without the need for prior dual energy X-ray absorptiometry (DEXA) scanning. The authorisation of generic alendronic acid led to a substantial reduction in price, to what is now approximately £1 per month (11).

Outcomes

The proportion of patients initiating anti-osteoporosis medications within 1 year of their hip fracture was calculated among treatment naïve patients (no such prescription within prior 6 months). Medications included were oral bisphosphonates, strontium ranelate, teriparatide, denosumab, and selective oestrogen receptor modulators. Given concerns regarding low therapy adherence, we also modelled separately the proportion of patients who received at least one bisphosphonate prescription between 10 and 14 months (excluding those patients not surviving to 14 months).

To examine the effect on re-fracture, we derived the proportion of patients (including prevalent users of anti-osteoporosis medications) sustaining a subsequent major (hip, pelvis, proximal-humerus, rib, spine, or wrist/forearm) fracture within 3-years of their primary event. Hip fractures were only included if sustained between 6-36 months so as to avoid counting of re-coding events. Second hip fracture was also considered separately.

As a sensitivity analysis, we analysed women separately because although treatment is typically offered to both genders following hip fracture, NICE TA 87 guidance pertained only to women. We repeated analyses excluding patients who either transferred out or were registered to a practice whose last data upload was within 1 year (for incident prescriptions timeseries) or 3 years (for re-fracture timeseries) of their primary hip fracture. We also repeated analyses for subsequent fracture outcomes stratified by therapy status at index hip-fracture.

Statistical analysis

We used an interrupted time series approach (12) to estimate changes in outcomes immediately following the intervention period while controlling for baseline levels and trends. In order to take into account temporal changes in the age and sex structure of the population, we modelled aggregated data points in the form of age and sex standardised biannual proportions of each outcome of interest using segmented linear regression (10): Yt=β0 + β1\*timet + β2\*interventiont + β3\*post\_int\_timet + et. Here, Yt is the proportion of index hip fracture patients with the outcome at time point (i.e. 6-month period) t. β0 estimates the baseline level of the outcome at the beginning of the time series. β1 estimates the pre-intervention trend, β2 the change in level immediately following the intervention and β3 the change in post-intervention trend. The intervention period spanned a 1-year period, from the beginning of Oct 2004 to the end of Sept 2005. All analyses were therefore based on 11 pre-intervention data points (Apr 1999 – Sept 2004), and between 10-14 post-intervention data points (Oct 2005 – Sept 2012) according to the follow-up time required for each outcome measure. Full models including all regression terms and final ‘conservative’ models were derived, the latter by way of removing non-significant terms in a backward step-wise process (p‐entry 0.049; p‐exit 0.10). The presence of autocorrelation was tested using the Durban-Watson test. All Durban-Watson statistics were close to the value of 2 and above the higher bound, thereforewe did not reject the null hypothesis of no autocorrelation.

For ease of interpretation, we expressed regression coefficients for level and slope in the form of a single estimate of absolute change between estimated post-intervention values and their counterfactual values (10, 13), i.e. estimates for the same time point but based on pre-intervention level and trend only. We used the Oct 2007 – Mar 2008 time point as the end of Mar 2008 was the middle of the post-intervention period (for the fracture time series). All analyses were performed using Stata v13.1.

RESULTS

We identified 10,873 eligible patients as having sustained an incident hip fracture within the period April 1999 to Sept 2012. There was an increase in the proportion of men (21.8% vs. 25.0%), proportion aged 85 years and older (41.9% vs. 44.3%), severe rated co-morbidities (2.4% vs. 7.1%) and prior bisphosphonate use (5.8% vs. 24.2%) (supplementary table 2).

Table 1 reports study outcomes by financial year. Comparing years 1999-2000 to 2011-2012, the initiation of anti-osteoporosis medication within 12 months increased markedly from 5.4 to 50.3%, although there were significant differences by gender and age band (Figure 1a-b). The overall increase was mainly driven by alendronic acid (Figure 1c/1d). Between 1999-2000 and 2009-2010, the proportion of patients sustaining a subsequent major or second hip fracture (as defined above) declined from 6.2 to 4.7%, and 3.4 to 2.1%, respectively.

Results from the interrupted time series analyses are reported as derived from parsimonious regression models. Regression coefficients from ‘full’models are provided in supplementary table 4.

Prescription data

We found a pre-intervention increase in anti-osteoporosis prescriptions of 1.05% per six months of the study period, then a marked step change of 14.9% (95% C.I. 10.9-18.9; p=<0.001) taking place between pre- and post-intervention periods (figure 2a, supplementary table 3). Also found was a post-intervention trend increase of 0.46% per six months (95% C.I. -0.05 to 0.96; p=0.075). This equated to an overall estimated 17.2% (95% C.I. 11.0 to 23.3) absolute increase in incident anti-osteoporosis use within one year of hip fracture for the time point three years following the start of the intervention period (table 2), representing an approximate relative increase of 79%. Similar although slightly lower increases in prescribing were seen when restricted to ≥1 bisphosphonate prescription between 10-14 months (figure 2b, supplementary table 3, table 2).

Subsequent major re-fracture and hip re-fracture

The pre-intervention level of subsequent major re-fracture was stable at 6.3% (95% C.I. 5.9 to 6.8). Following the intervention there was a significant (p=0.001) downward trend by -0.19% per six months (95% CI: -0.28 to -0.09; p=0.001). This equated to an absolute reduction of -1.0% (95% C.I. -1.4 to -0.5) at three years after the start of the intervention period (Table 2), and an approximate relative 14% decrease. A similar reduction was demonstrated for subsequent hip fracture (Figure 3b): an initial stable rate of 3.8% (95% C.I. 3.4 to 4.2) followed by a post-intervention downward trend of -0.17% (95% C.I. -0.26 to -0.09; p=0.001) per six months. This equated to an absolute reduction of -0.9% three years following the start of the intervention period, and an approximate relative reduction of 22%.

The same time series terms were included in final models in sensitivity analyses including only women (results not shown) and excluding patients with incomplete follow-up (supplementary table 5), with the exception that no trend change was detected in incident prescriptions and a significant step-change decrease in subsequent major fractures was found when patients with incomplete follow-up were excluded. We report analyses stratified by therapy status at time of index hip fracture in supplementary table 6. For patients not on therapy at baseline, these were the same as for the main analysis. Amongst prevalent users however there was no significant impact of intervention identified although this is likely to have been a consequence of the much smaller sample size in this sub-group, especially in the pre-intervention period.

DISCUSSION

Our study identifies that following the introduction of NICE TA 87 and first UK market authorisation of generic alendronic acid, prescriptions of anti-osteoporosis medications increased markedly amongst hip fracture patients. This was contemporary with a significant decline in the incidence of subsequent fractures and estimated hospital costs.

Considering the official and widespread use of NICE guidance within the NHS, the finding of significantly increased prescribing following NICE TA 87 is somewhat an expected finding and is consistent with previous reports of temporal associations between NICE publications and the health or prescription outcomes they were intended to impact (14, 15). Whilst we did not disentangle the effect of the NICE TA 87 publication from availability of generic alendronic acid, the increase in prescriptions across genders and age groups (figure 1a-b) and divergence of alendronic acid vs. other types of bisphosphonates (figure 1d) suggests availability of generic therapy was influential.

Although a decline in subsequent fracture incidence was concomitant with increased bisphosphonate prescribing, we have not here been able to establish whether increased prescribing caused the reduction in subsequent fractures. Therapy recommendations contained within NICE TA 87 were based on data from 39 published RCTs (8), with reference made to the Fracture Intervention Trial where the relative risk (RR) between alendronate vs. placebo arms for subsequent ‘any clinical’ or hip fracture was 0.74 (95% C.I. 0.59-0.92) and 0.49 (95% C.I. 0.23-0.99), respectively - amongst women with an existing vertebral fracture (16). Our use of an interrupted time series approach that controls for baseline level and trend is considered a strong quasi-experimental modelling strategy, allowing for “real world” estimation of longitudinal effects when a RCT is unfeasible (10, 12). The reverse of this ecological correlation has also been previously demonstrated, i.e. recent increases in hip fracture incidence alongside a reduction in bisphosphonate use (17), itself likely due to reports of atypical femoral fractures associated with long-term bisphosphonate use. The large number of primary hip fractures and the generalisability of the CPRD cohort to the general UK population (9) are further strengths of the analysis.

One main limitation is that changes in outcomes may have been confounded by events other than the defined intervention (1, 18). In this context, studies from other countries have identified downward trends in fracture rates to an extent that is beyond that attributable to increased bisphosphonate use alone (19, 20), there prompting explanations of other contributory factors such as changes in BMI, smoking, and vitamin D status or improvement in falls prevention services. On the other hand, a significant decline in hip fracture incidence in Canada has previously been reported for the time period 1985-2005 (21), pre-dating the era of large-scale anti-osteoporosis medication use and therefore dependant on alternative explanations than improvement in treatment rates. One such candidate there suggested was a birth-cohort effect, which may have been a factor in the observed decline in our study were such a phenomenon to be concomitant with our defined intervention period. One issue is the speed of change in prescription and re-fracture rates that suggest that slower changes in demographics such as obesity are less likely to be the main cause of the findings of this study. Furthermore, lack of association between bisphosphonate use and hip fracture incidence across Canadian provinces has also recently been reported (22), although those data didn’t distinguish between primary and secondary prevention of fractures or address the issue of confounding by indication.

Whilst the discrete intervention here evaluated was the publication of NICE guidance and availability of generic alendronate, other changes in the health care system such as in the introduction of Fracture Liaison Service (FLS) models of care (23, 24) may also have contributed to the findings. Given that the FLS operates to improve case-finding, assessment, therapy initiation and monitoring after a fragility fracture and that such services have become increasingly common in the NHS, it’s plausible these models of care contributed to the steeper andsustained post-intervention increase in prescribing of the therapies that were recommended and became substantially cheaper during the intervention period. An economic evaluation of an FLS in the UK health setting has demonstrated FLS to be a cost-effective model for improving secondary fracture prevention within the UK (25), although the fracture reduction was based on prescribing rates only. Other studies have reported no observed difference in fracture rates by FLS status (26), one possible explanation being poor medication adherence. Further work is required given the wider availability of parenteral therapies with significantly greater adherence rates (27).

It is worth noting that in a post-hoc analysis we found our decline in 3-year re-fracture rate to be occurring in the context of a stable 3-year mortality rate, although 1-year mortality did improve over the course of the study period (25.3 vs. 19.8% for years 1999/2000 to 2012/13). However, given fracture risk after hip fracture is high, improved survival at 1-year would likely increase rather than reduce the re-fracture rates as patients live longer at an elevated risk of re-fracture (28). Acknowledging that persistence with bisphosphonates is poor (29), it is reassuring that the intervention was here associated with increased prescribing between 12-14 months.

Reporting absolute difference between estimated post-intervention values compared to estimated contralateral values does involve extrapolation and therefore uncertainty, although 95% confidence intervals incorporating the standard error of regression coefficients are included (13). We also had more than the minimum number of eight time points before and after the intervention to have sufficient power to estimate the regression coefficients (30). Main findings were derived from parsimonious regression models, but estimated changes in fracture outcomes were larger when ‘full’ models were used (supplementary figure 1, supplementary table 4). Using routinely collected data with no individual validation of fracture events is another limitation, however validation of hip and vertebral fracture coding has been carried out previously and been shown to be accurate (31). Our definition of second hip fracture is based on previous work (32) and incorporates a 6-month wash out from the index fracture to minimise the inclusion of recoding events although such occurrences cannot be ruled out.

While we set out to investigate the potential impact on prescribing and the clinical outcomes such prescribing was intended to improve, we did not model the unintended consequences of bisphosphonate use. Widespread concern exists regarding adverse events (e.g. gastrointestinal problems) and safety issues associated with bisphosphonate use, most notably osteonecrosis of the jaw and atypical fractures (33). However, given that the absolute risk of these safety issues is low at approximately one in 300 patients sustaining an atypical fracture among those treated for three years (34) and the high rate of discontinuation among bisphosphonate users (29),we would be underpowered to investigate such events here. Furthermore, whilst we acknowledge that adverse events from the use of some anti-osteoporosis medications are important to include, there is no READ code for atypical fractures and so this could not be included in the model and remains an area for future research.

Our time series of prescriptions data is consistent with secular trends of similar outcomes reported in the literature (35). Despite the observed increase in prescribing, our findings support previous reports of under treatment of high-risk patients, contrary to guideline recommendations (36, 37). For example, a national audit within the UK indicated in 2010 that 40% of hip fracture patients did not receive appropriate bone health treatment (38). One caveat here is we weren’t able to consider Zoledronic Acid use as this is rarely administered in a primary care setting.

Exact comparison of re-fracture rates to other studies is difficult due to the difference in definitions, outcome measures and time periods used (26, 39, 40). Particularly, our UK cohort of hip fractures was smaller and our secular trend in re-fracture different to that reported elsewhere (41), although in order to be highly specific that we included true incident hip fractures, our inclusion criteria required three years registration in a CPRD participating GP practice and only considered proximal femoral fractures. However we may have created an artificially stable study sample with respect to GP practice in only including those with three years of GP registration prior to their index hip fracture.

In summary, although this is an observational study and we have not proven a cause-effect relationship, we have demonstrated that among hip fracture patients, publication of NICE guidance and availability of generic alendronic acid was temporally associated with an increase in anti-osteoporosis medication prescribing and a clinically important and cost effective reduction in the incidence of subsequent fracture.

Declaration of interests

JL, DPA, NKA, CC, MKJ and AJ received grants from NIHR HS&DR during the conduct of the study. Outside the submitted work, MKJ reports personal fees from Lilly UK, Amgen, Sevier, Merck, Medtronic, Internis, Consilient Health and serves on the Scientific Committee of the National Osteoporosis Society and International Osteoporosis Foundation; DPA received grants from Bioiberica S.A. and Amgen Spain S.A.; CC received personal fees from Servier, Amgen, Eli Lilly, Merck, Medtronic and Novartis. NKA reports personal fees from Merck, Smith and Nephew, Q-Med, Nicox, Flexion, Bioiberica, Servier and grants and personal fees from Roche. AJ has received consultancy, lecture fees and honoraria from Servier, UK Renal Registry, Oxford Craniofacial Unit, IDIAP Jordi Gol, Freshfields Bruckhaus Deringer, has held advisory board positions (which involved receipt of fees) from Anthera Pharmaceuticals, INC., and received research sponsorship from ROCHE. SH and AD have no competing financial interests relevant to the submitted work.

Figure Legends

Figure 1: descriptive trends among primary hip fracture patients in: (a) anti-osteoporosis medication use within 12 months stratified by gender, (b) anti-osteoporosis medication use within 12 months stratified by age, (c) anti-osteoporosis medication use within 12 months stratified by type, (d) bisphosphonate use within 12 months stratified by type

Figure 2: (a) results from segmented linear regression of incident anti-osteoporosis medication in the first year after index hip fracture and (b) results from segmented linear regression of bisphosphonate medication use between 10-14 months after index hip fracture, among treatment naïve patients at baseline who survived to 14 months

Figure 3: (a) results from segmented linear regression of subsequent major fracture within three years after index hip fracture and (b) results from segmented linear regression of subsequent hip fracture within three years (6-36 months) after index hip fracture

ACKNOWLEDGEMENTS

This project was funded by the NIHR Health Services and Delivery Research programme (project number 11/1023/01). Partial support was also received from the Oxford NIHR Musculoskeletal Biomedical Research Unit, Nuffield Orthopaedic Centre, University of Oxford. The funding source had no role in the design and conduct of the study, in the collection, analysis and interpretation of the data, or in the preparation, review, or approval of the manuscript. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HS&DR programme, NIHR, NHS or the Department of Health. This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency.

TheReFRESH study group consists of Dr Andrew David Judge, Dr Muhammad Kassim Javaid, Professor Nigel Arden, Professor Cyrus Cooper, Professor Andrew Farmer, Dr Daniel Prieto-Alhambra, Dr Jose Leal, Professor Michael Goldacre, Professor Alastair Gray, Dr Janet Lippett, Dr Rachael Gooberman-Hill and Laura Graham.

CONTRIBUTORS

AJ, MKJ, and SH take responsibility for design of the study. SH and AJ take responsibility for the integrity of the prescriptions and incidence data and the accuracy of the statistical analysis. AD takes responsibility for data management. All authors provided inputs and comments to the article and approved the final version. AJ and MKJ supervised the study and are joint senior authors.

REFERENCES

1. The care of patients with fragility fractures: British Orthopaedic Association (BOA); 2007 [Available from: http://www.bgs.org.uk/pdf\_cms/pubs/Blue Book on fragility fracture care.pdf.

2. Leal J, Gray AM, Prieto-Alhambra D, Arden NK, Cooper C, Javaid MK, et al. Impact of hip fracture on hospital care costs: a population-based study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2016;27(2):549-58.

3. Griffin XL, Parsons N, Achten J, Fernandez M, Costa ML. Recovery of health-related quality of life in a United Kingdom hip fracture population. The Warwick Hip Trauma Evaluation--a prospective cohort study. Bone Joint J. 2015;97-B(3):372-82.

4. BurgeR, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. Journal of Bone and Mineral Research. 2007;22(3):465-75.

5. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008(1):CD001155.

6. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. The New England journal of medicine. 2007;357(18):1799-809.

7. Ganda K, Puech M, Chen JS, Speerin R, Bleasel J, Center JR, et al. Models of care for the secondary prevention of osteoporotic fractures: a systematic review and meta-analysis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2013;24(2):393-406.

8. NICE. Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. National Institute for Health and Care Excellence: Technological Appraisal 87; 2005.

9. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). International journal of epidemiology. 2015.

10. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27(4):299-309.

11. Alendronic Acid (Non-proprietary): British National Formulary; 2015 [Available from: https://www.evidence.nhs.uk/formulary/bnf/current/6-endocrine-system/66-drugs-affecting-bone-metabolism/662-bisphosphonates-and-other-drugs-affecting-bone-metabolism/bisphosphonates/alendronic-acid/alendronic-acid.

12. Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. Bmj. 2015;350:h2750.

13. Zhang F, Wagner AK, Soumerai SB, Ross-Degnan D. Methods for estimating confidence intervals in interrupted time series analyses of health interventions. J Clin Epidemiol. 2009;62(2):143 PubMed -8.

14. Audit NP. Impact of NICE guidance on rates of haemorrhage after tonsillectomy: anevaluation of guidance issued during an ongoing national tonsillectomy audit. Quality & safety in health care. 2008;17(4):264-8.

15. Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. Incidence of infective endocarditis in England, 2000-13: a secular trend, interrupted time-series analysis. Lancet. 2015;385(9974):1219 PubMed -28.

16. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. The Journal of clinical endocrinology and metabolism. 2000;85(11):4118-24.

17. Fisher A, Martin J, Srikusalanukul W, Davis M. Bisphosphonate use and hip fracture epidemiology: ecologic proof from the contrary. Clin Interv Aging. 2010;5:355-62.

18. (NICE). Falls: assessment and prevention of falls in older people. National Institute for Clinical Excellence 2004;Clinical Guideline 21.

19. Abrahamsen B, Vestergaard P. Declining incidence of hip fractures and the extent of use of anti-osteoporotic therapy in Denmark 1997–2006. Osteoporos International. 2010;21:373-80.

20. Korhonen N, Niemi S, Parkkari J, Sievanen H, Palvanen M, Kannus P. Continuous decline in incidence of hip fracture: nationwide statistics from Finland between 1970 and 2010. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2013;24(5):1599-603.

21. Leslie WD, O'Donnell S, Jean S, Lagace C, Walsh P, Bancej C, et al. Trends in hip fracture rates in Canada. JAMA : the journal of the American Medical Association. 2009;302(8):883-9.

22. Crilly RG, Kloseck M, Chesworth B, Mequanint S, Sadowski E, Gilliland J. Comparison of hip fracture and osteoporosis medication prescription rates across Canadian provinces. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2014;25(1):205-10.

23. Drew S, Sheard S, Chana J, Cooper C, Javaid MK, Judge A, et al. Describing variation in the delivery of secondary fracture prevention after hip fracture: an overview of 11 hospitals within one regional area in England. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2014;25(10):2427-33.

24. Drew S, Judge A, Cooper C, Javaid MK, Farmer A, Gooberman-Hill R. Secondary prevention of fractures after hip fracture: a qualitative study of effective service delivery. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2016.

25. McLellanAR, Wolowacz SE, Zimovetz EA, Beard SM, Lock S, McCrink L, et al. Fracture liaison services for the evaluation and management of patients with osteoporotic fracture: a cost-effectiveness evaluation based on data collected over 8 years of service provision. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2011;22(7):2083-98.

26. Hawley S, Javaid MK, Prieto-Alhambra D, Lippett J, Sheard S, Arden NK, et al. Clinical effectiveness of orthogeriatric and fracture liaison service models of care for hip fracture patients: population-based longitudinal study. Age Ageing. 2016;45(2):236-42.

27. Hadji P, Papaioannou N, Gielen E, Feudjo Tepie M, Zhang E, Frieling I, et al. Persistence, adherence, and medication-taking behavior in women with postmenopausal osteoporosis receiving denosumab in routine practice in Germany, Austria, Greece, and Belgium: 12-month results from a European non-interventional study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2015;26(10):2479-89.

28. Curtis JR, Arora T, Matthews RS, Taylor A, Becker DJ, Colon-Emeric C, et al. Is Withholding Osteoporosis Medication After Fracture Sometimes Rational? A Comparison of the Risk for Second Fracture Versus Death. J Am Med Dir Assoc. 2010;11(8):584-91.

29. Li L, Roddam A, Gitlin M, Taylor A, Shepherd S, Shearer A, et al. Persistence with osteoporosis medications among postmenopausal women in the UK General Practice Research Database. Menopause. 2012;19(1):33 PubMed -40.

30. Penfold RB, Zhang F. Use of Interrupted Time Series Analysis in Evaluating Health Care Quality Improvements. Acad Pediatr. 2013;13(6): PubMed S38-S44.

31. Van Staa TP, Abenhaim L, Cooper C, Zhang B, Leufkens HGM. The use of a large pharmacoepidemiological database to study exposure to oral corticosteroids and risk of fractures: Validation of study population and results. Pharmacoepidem Dr S. 2000;9(5):359-66.

32. Hawley S, Javaid MK, Rubin KH, Judge A, Arden NK, Vestergaard P, et al. Incidence and Predictors of Multiple Fractures Despite High Adherence to Oral Bisphosphonates: A Binational Population-Based Cohort Study. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2015.

33. Jarvinen TLN, Michaelsson K, Jokihaara J, Collins GS, Perry TL, Mintzes B, et al. TOO MUCH MEDICINE Overdiagnosis of bone fragility in the quest to prevent hip fracture. Bmj-Brit Med J. 2015;350.

34. Jarvinen TLN, Michaelsson K, Aspenberg P, Sievanen H. Osteoporosis: the emperor has no clothes. J Intern Med. 2015;277(6):662 PubMed -73.

35. Klop C, Gibson-Smith D, Elders PJ, Welsing PM, Leufkens HG, Harvey NC, et al. Anti-osteoporosis drug prescribing after hip fracture in the UK: 2000-2010. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National OsteoporosisFoundation of the USA. 2015;26(7):1919-28.

36. Elvey MH, Pugh H, Schaller G, Dhotar G, Patel B, Oddy MJ. Failure in the application of fragility fracture prevention guidelines. Ann Roy Coll Surg. 2014;96(5):381-5.

37. Feldstein A, Elmer PJ, Orwoll E, Herson M, Hillier T. Bone mineral density measurement and treatment for osteoporosis in older individuals with fractures - A gap in evidence-based practice guideline implementation. Arch Intern Med. 2003;163(18):2165-72.

38. Tremi J HJ, Lowe D, Vasilakis N. Falling standards, broken promises: Report of the national audit of falls and bone health in older people. Royal College of Physicians, 2011.

39. Omsland TK, Holvik K, Meyer HE, Center JR, Emaus N, Tell GS, et al. Hip fractures in Norway 1999-2008: time trends in total incidence and second hip fracture rates: a NOREPOS study. European journal of epidemiology. 2012;27(10):807-14.

40. Melton LJ, 3rd, Kearns AE, Atkinson EJ, Bolander ME, Achenbach SJ, Huddleston JM, et al. Secular trends in hip fracture incidence and recurrence. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2009;20(5):687-94.

41. Gibson-Smith D, Klop C, Elders PJM, Welsing PMJ, van Schoor N, Leufkens HGM, et al. The risk of major and any (non-hip) fragility fracture after hip fracture in the United Kingdom: 2000-2010. Osteoporosis Int. 2014;25(11):2555 PubMed -63.

**TABLES**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 1: outcomes of interest following primary hip fracture: stratified by year (N=10,873) | | | | | | | | | |
| Year        (Apr-Mar) | Index hip fracture | Incident anti-osteoporosis medication prescriptiona (1-year) | | ≥1 Bisphosphonate prescriptionb (10-14 months) | | Subsequent Major Fracturec (3-year) | | Subsequent Hip Fracturec (3-year) | |
| n | n | % | n | % | n | % | n | % |
| 1999 | 861 | 47 | 5.7 | 30 | 5.0 | 50 | 5.8 | 27 | 3.1 |
| 2000 | 855 | 42 | 5.2 | 30 | 4.9 | 56 | 6.6 | 31 | 3.6 |
| 2001 | 830 | 65 | 8.4 | 49 | 8.1 | 54 | 6.5 | 34 | 4.1 |
| 2002 | 861 | 84 | 10.5 | 78 | 13.4 | 59 | 6.9 | 34 | 4 |
| 2003 | 878 | 112 | 14 | 87 | 14.4 | 56 | 6.4 | 34 | 3.9 |
| 2004 | 817 | 126 | 17.1 | 93 | 16.6 | 61 | 7.5 | 33 | 4 |
| 2005 | 841 | 225 | 29.9 | 165 | 29.7 | 48 | 5.7 | 25 | 3 |
| 2006 | 825 | 267 | 37.1 | 184 | 33.8 | 48 | 5.8 | 26 | 3.2 |
| 2007 | 816 | 256 | 36.5 | 159 | 30.6 | 39 | 4.8 | 23 | 2.8 |
| 2008 | 795 | 290 | 42.6 | 167 | 31.9 | 47 | 5.9 | 25 | 3.1 |
| 2009 | 756 | 278 | 43.6 | 166 | 34.3 | 36 | 4.8 | 17 | 2.3 |
| 2010 | 719 | 283 | 46.2 | 172 | 34.2 | 17^ | 4.6^ | 7^ | 1.9^ |
| 2011 | 667 | 293 | 50.9 | 187 | 39.4 |  |  |  |  |
| 2012^ | 352^ | 148∧ | 48.8∧ |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| Overall | 10,873 | 2,516 | 25.9 | 1,599 | 21.8 | 571 | 6.0 | 316 | 3.3 |
| a only amongst treatment naïve primary hip fracture patients (defined as no anti-OP prescription in 6 months prior to index fracture) | | | | | | | | | |
| b only amongst BP treatment naïve primary hip fracture patients surviving to 14 months (defined as no BP prescription in 6 months prior to index fracture) | | | | | | | | | |
| c second hip fractures only counted between 6-36 months | | | | | | | | | |
| ∧ Based on months Apr-Sept | | | | | | | | | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Table 2: Estimated absolute change in outcomes under study, associated with the publication of NICE TA 87 and first UK market authorisation of generic alendronic acid\* | | | | | |
|  | Oct 2007 - Mar 2008 estimatea, e | | Absolute changea, e | | |
|  | Without intervention (%) | With intervention  (%) | estimate (%)e | lower 95% CI | upper 95% CI |
| Subsequent anti-OP medication (0-12m) b | 21.7 | 38.9 | 17.2 | 11.0 | 23.3 |
| Subsequent BP medication (10-14m) b, c | 19.9 | 32.1 | 12.2 | 6.6 | 17.7 |
| Subseqent major fractures (0-36 months) d | 6.3 | 5.4 | -1.0 | -1.4 | -0.5 |
| Subsequent hip fractures (6-36 months) d | 3.8 | 3.0 | -0.9 | -1.2 | -0.5 |
| \* calculated by comparing estimated values in the period Oct07 - Mar08 (three years after the beginning of the intervention phase) to counterfactual values for the same period (i.e. those expected for Oct 2007 - Mar 2008 based only on the pre-intervention level and trend) | | | | | |
| a estimated from final/parsimonious models specified using backward-stepwise selection (p‐entry 0.049 and p‐exit 0.10). Percentages rounded to one decimal place | | | | | |
| b amongst treatment naïve index hip fracture patients | | | | | |
| c amongst survivors at 14 months | | | | | |
| d subsequent hip fractures only counted between 6-36 months | | | | | |
| e rounded to one decimal place | | | | | |