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The treatment gap: the missed opportunities for osteoporosis therapy

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1 Introduction

The next decade will bear witness to a significant increase in the number of individuals living with osteoporosis and experiencing the morbidity consequent upon fragility fractures. These can be defined as fractures which result from a fall from standing height or less; or that present in the absence of trauma. The most common fragility fractures occur at the hip, wrist, spine, humerus and pelvis. It is timely to take stock of the key challenges facing healthcare professionals and policymakers responsible for providing care for populations in relation to bone health and to identify solutions that will reduce fracture rates and ameliorate their personal and societal burden. These challenges broadly fall into five distinct themes: (a) Perceived benefits and risks of therapy; (b) Case finding and management of individuals at high risk of fracture; (c) Public awareness of osteoporosis and fragility fractures; (d) Reimbursement and health system policy; and (e) Epidemiology of fractures in the developing world [1, 2]. This review will address these important determinants of the osteoporosis "treatment gap" (the 'gap' between those individuals who require treatment and those individuals who actually receive treatment) (Figure 1), and measures that will assist in reducing its magnitude, with the twin objectives of optimising risk assessment and reducing fracture incidence [1, 2].

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2 Pharmacological treatment of osteoporosis

The effectiveness of a broad range of currently available osteoporosis treatments has been comprehensively reviewed elsewhere [4]. The most commonly used agents in Europe are the bisphosphonates alendronate, risedronate, ibandronate and zoledronate. Additionally, raloxifene, agents derived from parathyroid hormone and denosumab. These have all been shown to reduce the risk of vertebral fracture. Some have also been shown to reduce the risk of non-vertebral fractures and, in some cases, agents have been shown specifically to decrease fracture risk at the hip (Table 1) [1].

2.1 Bisphosphonates

2.1.1 Efficacy—Bisphosphonates are stable analogues of pyrophosphate characterized by a P-C-P bond. A variety of bisphosphonates have been synthesized, the potency of which depends on the length and structure of the side chain [5]. Bisphosphonates have a strong affinity for bone apatite, both *in vitro* and *in vivo*, which is the basis for their clinical use. They are potent inhibitors of bone resorption and produce their effect by reducing the recruitment and activity of osteoclasts and increasing their apoptosis. The potency and chemical affinity to bone of bisphosphonates determines their effect to inhibit bone resorption and varies greatly from compound to compound. Potency differences can range 10,000-fold *in vitro*, so that the doses used clinically also vary. The primary action of nitrogen-containing bisphosphonates is to inhibit the farnesyl pyrophosphate synthase enzyme step in the mevalonate pathway, thereby modifying the isoprenylation of multiple guanosine triphosphate binding proteins involved in intracellular signalling and osteoclast function[6–8].

Oral bioavailability of bisphosphonates is low, around 1% of the dose ingested, and is impaired by food, calcium, iron, coffee, tea and orange juice. Bisphosphonates are quickly cleared from plasma, about 50% being deposited in bone and the remainder excreted in urine. Their half-life in bone is very prolonged [9].

Alendronate 70 mg once weekly and risedronate 35 mg once weekly are the most commonly used bisphosphonates worldwide. In the Fracture Intervention (FIT) study, alendronate was shown to reduce the incidence of vertebral, wrist and hip fractures by approximately half in women with prevalent vertebral fractures [10]. In women without prevalent vertebral fractures, there was no significant decrease in clinical fractures in the overall population, but the reduction was significant in the one-third of patients that had a baseline hip BMD T-score lower than -2.5 [11]. In a population of more than 90,000 men and women aged 80 years and older, with a prior fracture, a case-control analysis revealed that alendronate use was associated with a 34% decrease in hip fracture risk, and a 12% lower mortality risk. However there was a 58% increase in the risk of mild upper gastro-intestinal symptoms [12].

Risedronate has been shown to reduce the incidence of vertebral and non-vertebral fractures by 40-50% and 30-36%, respectively in women with prevalent vertebral fractures [13, 14]. In a large population of elderly women, risedronate significantly decreased the risk of hip fractures by 30%, an effect that was greater in osteoporotic women age 70-79 years (-40%), and not significant in women over the age of 80 years without evidence of osteoporosis. A

delayed-release formulation of 35mg risedronate weekly, given before or immediately following breakfast showed a similar or greater effect on spine and hip BMD than traditional immediate-release 5mg risedronate in a daily dose. This formulation allows osteoporotic patients to take their weekly risedronate dose immediately after breakfast, hence offering a potential for improved adherence and persistence to treatment [15].

Ibandronate given daily (2.5 mg) reduces the risk of vertebral fractures by 50-60%. An effect on non-vertebral fractures was only demonstrated in a post hoc analysis of women with a baseline of BMD T-score below -3.0 [17–19]. Bridging studies have shown that oral ibandronate 150 mg once monthly is equivalent or superior to daily ibandronate in increasing BMD and decreasing biochemical markers of bone turnover, giving rise to its approval for the prevention of vertebral fracture in postmenopausal osteoporosis [20]. The efficacy and safety of oral monthly ibandronate was confirmed for up to 5 years in women with post-menopausal osteoporosis [20, 21]. Similarly, bridging studies comparing intermittent intravenous ibandronate to daily oral treatment has led to the approval of intravenous ibandronate 3 mg every 3 months for the same indication [22]. A post-hoc analysis of pooled individual patient-data from the studies assessing the long-term (5 years) efficacy of oral[20] and intravenous[23] ibandronate concluded that for ibandronate regimens with annual cumulative exposure ≥ 10.8mg, time-to-fracture was significantly longer for all clinical fractures, non-vertebral and clinical vertebral fractures versus placebo and that for all fracture types, the rate of fracture appeared stable up to 5 years [24].

Based on the result of a phase II study [25], a large phase III trial in over 7700 postmenopausal osteoporotic patients, assessed the efficacy of yearly infusion of zoledronate 5 mg over 3 years. As compared to the placebo group, zoledronate was found to reduce the incidence of vertebral fractures by 70% and that of hip fractures by 40% [26], and is now available for the treatment of postmenopausal osteoporosis. Intravenous zoledronate has also been shown to decrease the risk of fracture and mortality when given shortly after a first hip fracture [27]. The phase III trial was extended to 6 [28] and 9 [29] years. The overall conclusion was that pursuing treatment beyond 3 years only provided marginal benefits [29]. Some authors even argue that an annual administration of 5mg zoledronate might represent over treatment [30]. A single dose of 5mg zoledronate given to frail elderly women improved spine and total hip BMD over 2 years, compared to placebo but the treated group had an increase in fractures, multiple falls and mortality [31] suggesting that zoledronate may not be an appropriate treatment for such patients. Of course, the intravenous delivery of zoledronate has the potential to improve adherence to bisphosphonates provided that infusions are not missed.

Despite widespread evidence of the efficacy of these agents, there has been a plateau in their use in Europe and North America over recent years (Figure 2).

2.1.2 Safety of bisphosphonates—The overall safety profile of bisphosphonates is favourable. Oral bisphosphonates are associated with mild gastrointestinal disturbances, and some nitrogen-containing bisphosphonates (alendronate and pamidronate) can rarely cause oesophagitis. A network meta-analysis compared the gastro-intestinal safety of all oral and injectable bisphosphonates given to osteoporotic patients. It concluded that zoledronate has the highest probability of causing gastro-intestinal adverse events, possibly related to nausea

[32]. Intravenous nitrogen-containing bisphosphonates can induce a transient acute phase reaction with fever, bone and muscle pain that ameliorates or disappears after subsequent courses [33]. Concerns have been raised about a possible association between bisphosphonate therapy and atrial fibrillation. Subsequent studies have produced conflicting results, but have not excluded the possibility of such an association in people at increased risk of fracture [34]. Patients to whom zoledronate was administered for up to 9 years had a higher risk of cardiac arrhythmias compared to those who discontinued the treatment after 6 years [34]. The possibility that bisphosphonate therapy is associated with increased risk of oesophageal cancer has been raised. Two studies from the General Practice Research Database in the UK have produced conflicting results, one failing to show any association, but another concluding that there was an increased risk with extended use over 5 years [35, 36]. Other database studies have found no excessive risk of oesophageal cancer deaths or incidence[37]. However, the two major adverse effects of bisphosphonate therapy contributing to the treatment gap are atypical femoral fracture and osteonecrosis of the jaw.

2.1.3 Atypical femoral fracture—Schilcher and colleagues reviewed radiographs of Swedish women who sustained a hip fracture in 2008, identifying 59 atypical femoral fractures [38]. Data on medications and coexisting conditions were obtained from national registries. The relative and absolute risk of atypical fractures associated with bisphosphonate use was estimated by means of a nationwide cohort analysis. The 59 case patients were also compared with 263 control patients who had ordinary subtrochanteric or shaft fractures. In this study, the age-adjusted relative risk of atypical fracture was 47.3 (95% confidence interval [CI], 25.6 to 87.3) in the cohort analysis. The increase in absolute risk was 5 cases per 10,000 patient-years (95% CI, 4 to 7). A total of 78% of the case patients and 10% of the controls had received bisphosphonates, corresponding to a multivariable-adjusted odds ratio of 33.3 (95% CI, 14.3 to 77.8). The duration of use influenced the risk (odds ratio per 100 daily doses, 1.3; 95% CI, 1.1 to 1.6). Importantly after drug withdrawal, the risk diminished by 70% per year since the last use (odds ratio, 0.28; 95% CI, 0.21 to 0.38). In a follow-up paper of 172 patients with atypical femoral fractures the age-adjusted relative risk (RR) of atypical fracture associated with bisphosphonate use was 55 (95% CI: 39-79) in women and 54 (CI: 15-192) in men [39]. In bisphosphonate users, women had a 3-fold higher risk than men (RR = 3.1, CI: 1.1-8.4). Alendronate users had higher risk than risedronate users (RR = 1.9, CI: 1.1-3.3). The RR after 4 years or more of use reached 126 (CI: 55-288), with a corresponding absolute risk of 11 (CI: 7-14) fractures per 10,000 person-years of use. The risk decreased by 70% per year since last use. These data are complementary to previous reported figures that suggest the incidence of atypical femoral fracture appears related to duration of exposure. This observation receives some support from preliminary reports from the Southern California Osteoporosis Cohort Study (SOCS) where the risk of radiology adjudicated AFFs declined by 44% in the first year after discontinuation compared to women who continued to use BP (HR 0.56, CI 0.38-0.82). After 4 years or more, the AFF risk was found to be reduced by 78% (HR 0.22, CI 0.08-0.59) compared to current users. The rate of AFFs among current users was reported as 4.6 per 10,000 patient years [40]. A recent systematic review [41] included 23 studies on atypical femoral fractures: 14 on epidemiology and 11 on treatment outcomes (2 articles reported on both aspects). The review showed that the incidence of atypical femoral fractures is low (3.0-9.8 per 100,000

person-years), but relative risk increased with longer duration of bisphosphonates use, especially after more than 3 years.

It should be noted that some of the most recent data in this area come from a study of nearly 200,000 women (over 50 year of age) which modelled the risk-benefit profile from 1 to 10 years with regard to fragility fracture prevention (benefit) and atypical femoral fracture occurrence (risk). This found that the absolute risk was very low and certainly outweighed by the benefits in terms fracture prevention[42].

2.1.4 Osteonecrosis of the jaw—Osteonecrosis of the jaw (ONJ) is a very rare clinical event that was first reported in connection with bisphosphonate use in 2003 [43] and has been addressed in numerous reviews since[44]. The incidence of ONJ is rare and increases with exposure, suggesting an inflection point of 4 years. The American Society for Bone and Mineral Research (ASBMR) estimated ONJ incidence as between 1 in 10, 000-100,000 patient-treatment years. The AAOMS using data from Lo [45] estimated 210/100,000 patient years. Most of the reported cases have been in association with the use of zoledronate or pamidronate used intravenously to control metastatic bone disease [45, 46]. The risk of ONJ in association with the use of oral bisphosphonates is very much less, and was reviewed by Masoodi in 2009, who concluded that the use of oral bisphosphonates did not increase the risk of ONJ in osteoporosis patients [47]. Furthermore, no cases of ONJ were reported in over 3000 patients participating in clinical studies of effectiveness of alendronate and zoledronate [46]. More recent studies have suggested that pre-existing dental disease and prior dental extraction are the strongest risk factors [26]. Danish national health data also suggest a low incidence rate of surgically treated ONJ of 2.5 (95% confidence interval 2.1 to 3.1) per 10,000 patient years for users of oral bisphosphonates, albeit a higher risk in users with 5 years of exposure or more. The risk was higher in patient with rheumatoid disorders or diabetes [48]. Denosumab therapy has also been associated with ONJ. The incidence of adverse and serious adverse events did not increase over time in the denosumab extension study. However, through extension year 5, there were 8 confirmed events of osteonecrosis of the jaw and 2 events of atypical femoral fracture. Very recently, 10-year data have been published for denosumab therapy. Serious adverse event rates were generally stable over time, varying between 11·5 and 14·4 per 100 participant-years. One atypical femoral fracture occurred in each group during the extension. Seven cases of osteonecrosis of the jaw were reported in the long-term group and 6 cases in the crossover group.

There is increasing interest in the potential, non-skeletal benefits of bisphosphonates on lifespan and in conditions including progeria (when used in conjunction with statins)[49], cardiovascular disease[50] neurodegenerative disorders, neoplasia and infections[9] (particularly pneumonia risk reduction[51]).

2.1.5 Treatment discontinuation—These observations have led to a number of position papers and guidelines [4], which generally reinforce the importance of continuing therapy among women who remain at high risk of fracture, as intermission of therapy, even for those with residual effects on bone turnover after intermission such as BPs, will be followed by an increase in fracture incidence in those subjects. Despite these recommendations, many patients discontinue therapy despite remaining at high risk. When

considering long-term therapy though, one has to balance benefits and risks. With the exception of denosumab, the number of patients in RCTs carried through to 10 years or longer is very small. A particular concern of patients and physicians alike is the apparent association of osteoporosis treatment with atypical femoral fractures and ONJ. However, this risk remains less than 1 in 1000 subjects treated even for 10 years according to most long-term extensions of RCTs and observational studies. Although the long-term benefits remain difficult to exactly evaluate in absence of large placebo-controlled extension studies, assuming a long-term reduction of fracture risk in the order of 30% with anti-resorptive therapy, as suggested by the available evidence, particularly among high risk subjects, would result in a benefit: risk ratio (fractures prevented: adverse skeletal event) of at least 100:1. Observational data suggest that patients treated with oral bisphosphonates in excess of 10 dose years maintain a low incidence of both hip fractures and fractures of the subtrochanteric femur and femoral shaft. The available evidence from prospective and retrospective analyses indicates that treatment cessation is associated with an increase in fracture risk. The risk of new clinical fracture was about 20-40% higher in patients who stopped treatment and vertebral fracture risk was approximately doubled. These findings suggest that the concept of a ‘drug holiday’ as routine must be challenged. This is an urgent public health message that should be conveyed to health professionals, policy makers and patients.

3 Other Measures to Close the Treatment Gap

3.1 Secondary prevention: treating those who have already had a fracture

As described by the evidence detailed above, fragility fractures represent a huge burden on societies worldwide. Patient perception of fracture risk is often underestimated as osteoporosis is a silent condition until a fracture happens, so primary prevention initiation is usually reliant on health care practitioners who need to have the time and incentive to assess fracture risk and explain the purpose of treatment to their patients. Secondary prevention, in which patients are identified for treatment on the basis of a previous low trauma fracture, is therefore the approach usually taken.

Several methods have been explored to enable fracture risk assessment and initiation of appropriate treatment – some based upon staff, others on IT and others upon a combination of the two. The multi-disciplinary Fracture Liaison Service (FLS) is one of the most successful of these systems [52, 53], incorporating rheumatologists, ortho-geriatricians, other physicians, clinical nurse specialists and allied health professionals. Members of the FLS multidisciplinary team, coordinated by a lead clinician, work together to optimise the medical management of patients admitted with fracture, both in hospital and for long term fracture prevention [54]. This approach has been demonstrated to optimise osteoporosis treatment (Figure 3).

“Capture the Fracture®”, an initiative instituted by the International Osteoporosis Foundation (http://www.capturethefracture.org/) is “a global campaign to facilitate the implementation of coordinated, multi-disciplinary models of care for secondary fracture prevention.” Capture the Fracture has provided secondary fracture prevention guidance, and also a global map of secondary fracture prevention services, with a quality grading scheme,

graded by assessed application and description of the service [55, 56]. This scheme has helped to document the huge variation in the quality, scope and availability of secondary prevention facilities, not only within, but also between countries. The Capture the Fracture initiative aims to raise the quality and coverage of these fracture liaison services. Vertebral fracture case finding is an additive approach to secondary fracture prevention as many such events go undetected. It has been shown that around 12% of postmenopausal women with osteoporosis have one or more vertebral deformities, but fewer than one in three of these individuals come to clinical attention [57]. Primary care-based screening strategies [58] and history taking methods distinguishing "vertebral fracture-type back pain" from other types of back pain may assist their detection [59]. Different methods for radiological assessment of vertebral fractures exist, including radiographs, CT scans and automatic detection using artificial intelligence modalities are moving nearer to clinical usage[60, 61].

3.2 Primary prevention: starting treatment in individuals at high fracture risk

In osteoporosis, there is ongoing debate regarding the benefits of a widespread systematic screening approach, leading to higher treatment rates (with its associated cost and side-effect risk), and a case-finding approach focused on those at highest individual risk (with its associated issue of under-treatment). Whilst DXA-based osteoporosis screening is officially a standard policy in the US (at age 65 years in women, age 70 in men, and in individuals over 50 years who have suffered a fracture as an adult) [63], in the majority of countries population screening is not judged to be cost-effective. Primary prevention is therefore generally focused on case-finding strategies, reliant on the physician identifying clinical risk factors [64].

In the UK, a randomised controlled trial across 7 centres was recently undertaken (the UK SCOOP study), examining both the clinical and cost-effectiveness of screening older women in primary care for primary fracture prevention. Around 12,500 older women were randomised to either screening and subsequent treatment (stratified using FRAX hip fracture probability) or usual care. The screening intervention was shown to lead to reduction in hip fracture risk by 28% (Figure 4) [65, 66]. Those at highest baseline fracture risk appeared to benefit most from screening (as would be expected, since these were the individuals targeted for treatment) [67], and importantly, was shown to be cost-effective (the cost per quality adjusted life year (QALY) gained was £2772 compared with the control arm) [68]. The finding that women who were identified by FRAX as moderate or high risk of fracture benefited most from a screening programme was supported by the Danish Risk Stratified Osteoporosis Strategy Evaluation (ROSE) study, though this study found no overall effect on fracture incidence of a screening strategy [69]. A recent evidence report and systematic review for the US Preventive Services Task Force, concluded that screening to prevent osteoporosis in women may reduce hip fractures.

Once a patient has been identified as requiring fracture risk assessment, the threshold at which treatment should be given will vary according to factors such as healthcare provision, willingness to pay and cost of medications. The majority of guidelines internationally use FRAX as the arbiter of fracture risk, but 38 of the 120 guidelines identified in a recent systematic review gave no direction on translating FRAX probabilities into a treatment

decision. Threshold setting is as much a philosophical as scientific process, with decisions around whether a level should be fixed, or age dependent, and calibration to the specific country. Given the marked variation in fracture rates between countries, this latter consideration seems mandatory, and the benefits and caveats associated with fixed or age-dependent thresholds are presented in detail in. In the UK, FRAX is linked to the age-dependent (up to the age of 70 years) thresholds of the National Osteoporosis Guideline Group (NOGG), with the threshold predicated on the probability of future fracture conferred by a prior fracture. This approach has been shown to be cost effective in the UK, and contrasts markedly with that of the UK National Institute of Health and Care Excellence (NICE). In the 2017 technology appraisal of bisphosphonates, a pure health economic approach, in the context of a very common disease and extremely inexpensive therapies, led of a 1% risk of major osteoporotic fracture over 10 years as the threshold above which these medications were considered cost-effective. Unfortunately this was often interpreted by payers as an intervention threshold, a situation which if permitted to continue would have resulted in many adults at low risk of fracture being inappropriately treated, but which was later resolved by referral to NOGG guidance for clinical, rather than health economic thresholds.

4.0 Conclusion

Recent decades have seen a dramatic transformation in osteoporosis, from having been historically viewed as an inescapable result of ageing, to now being a well- characterised chronic non-communicable disease, with diagnostic criteria, well-established methods of risk assessment and an enviable range of therapeutic medications. Despite this backdrop, however, there is evidence from the UK, US and continental Europe that treatment rates have declined substantially in the last 5 years. With ageing populations and overstretched health services, osteoporosis may often fall off the bottom of the list of priorities for both clinicians and patients. Although many of the studies included in this review have focussed on women, it is vital to remember that osteoporosis is often more under-diagnosed and under-treated in men. The rare adverse effects of anti-resorptive therapies have become a disproportionately (and inappropriately) major concern, amplified by sensationalised media reports, which have usually been inadequately countered by the clinical academic community. These fears and the resulting reduced prescribing have been exacerbated by reductions in reimbursement in the US, mirrored in new guidance. It is apparent that many patients, doctors and dentists now appear more concerned by the rare but serious side effects of anti-resorptives than they are of the osteoporosis and fragility fractures.

The clear imperative to urgently tackle this issue has been recognised by key organisations such as the International Osteoporosis Foundation and the American Society for Bone and Mineral Research, leading to the publication of recommendations and roadmaps to address the critical care gap in osteoporosis treatment [1, 2]. It is also important to acknowledge that with bisphosphonates now generic compounds, their cost has dropped substantially. This is good news for the accessibility of medications but the field will be reliant on the development of novel therapies to bring in revenue which can be used to educate patients, healthcare professionals and large-scale clinical trials.

Improved public awareness and public health strategies to improve bone health from a young age will also contribute to prevention of osteoporosis in future generations. Given the rapid ageing of the global population and the importance of good musculoskeletal health in old age, we must come together to ensure that during the coming decade, 2020-2030, hailed by the WHO and others as the “Decade of Healthy Ageing”, bone health and fracture prevention become the priority they so urgently need to be.

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Highlights

- Bisphosphonates are effective at reducing the risk of fragility fractures and have an important role to play in closing the osteoporosis treatment gap
- They are generally safe and the rates of osteonecrosis of the jaw and atypical femoral fractures are low
- Secondary fracture prevention services are an effective and cost-efficient method of closing the treatment gap
- The SCOOP trial demonstrated that population screening for primary prevention was clinically effective for hip fractures and cost-effective

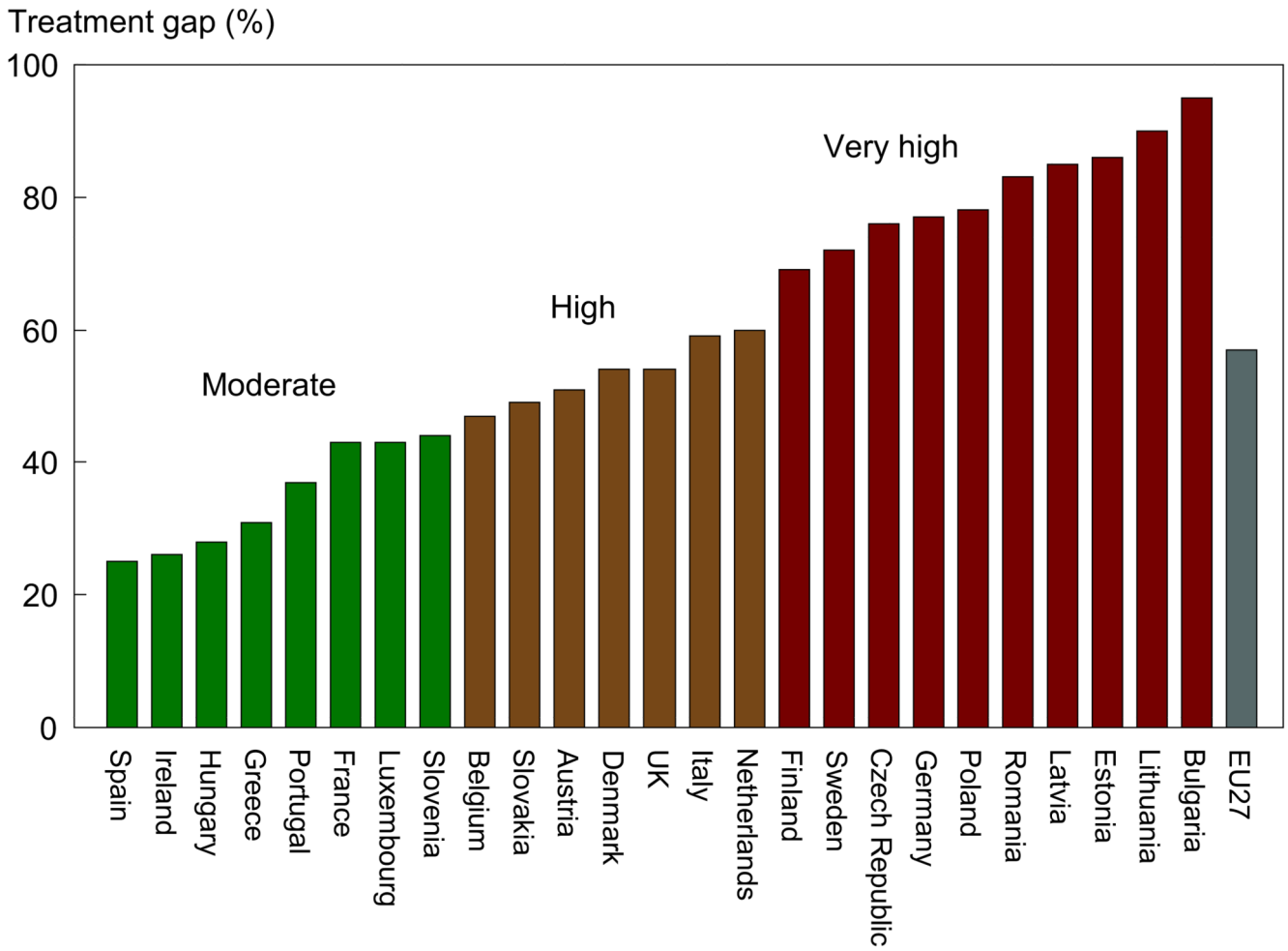

Figure 1.

Proportion of postmenopausal European women at moderate, high and very high risk of osteoporotic fracture who are un-treated – the "treatment gap" according to EU27 country with the EU27 mean in grey Ref [3].

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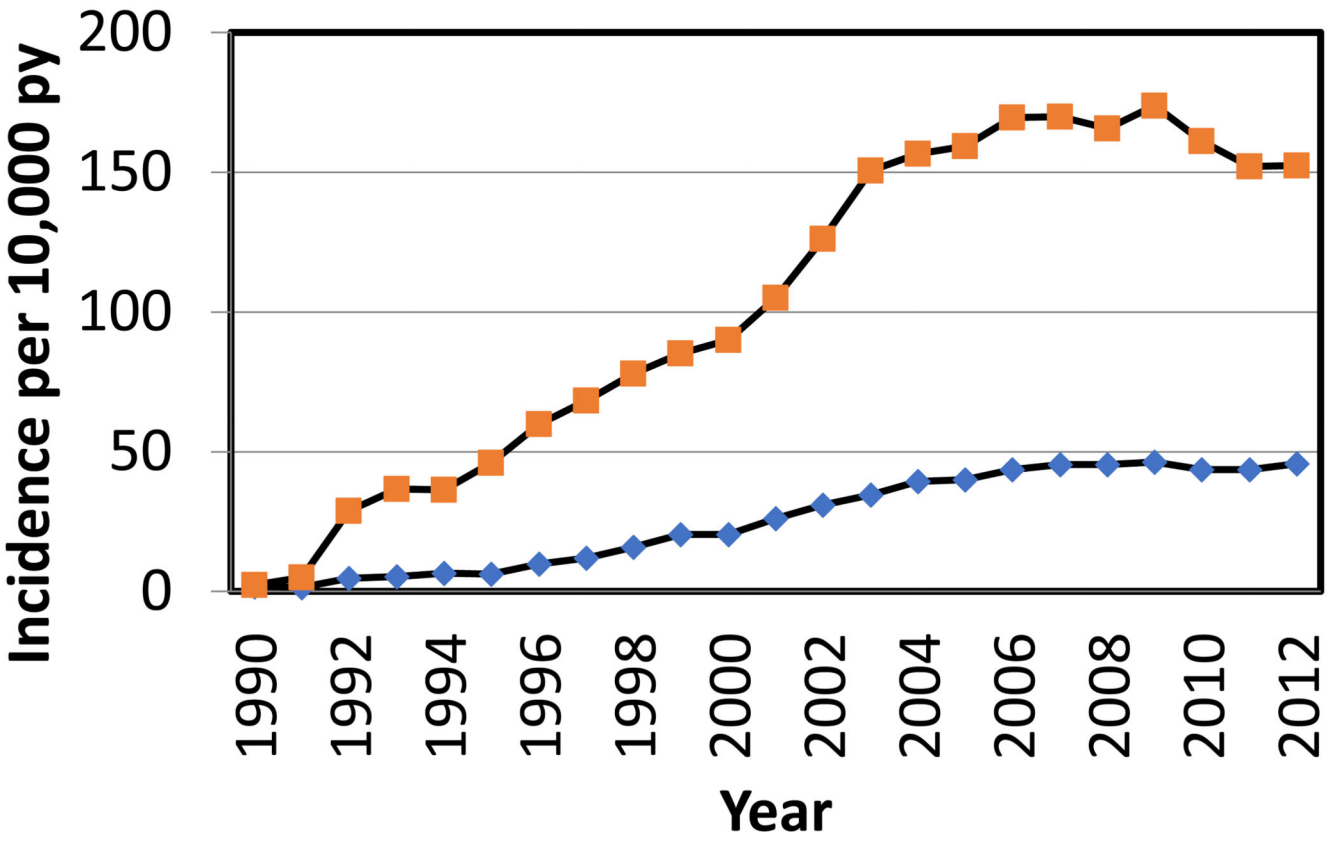

Figure 2.

Frequency of use of anti-osteoporotic medication in England and Wales, 1990-2012. Orange squares denote incidence for women and blue diamonds the incidence for men.[16]

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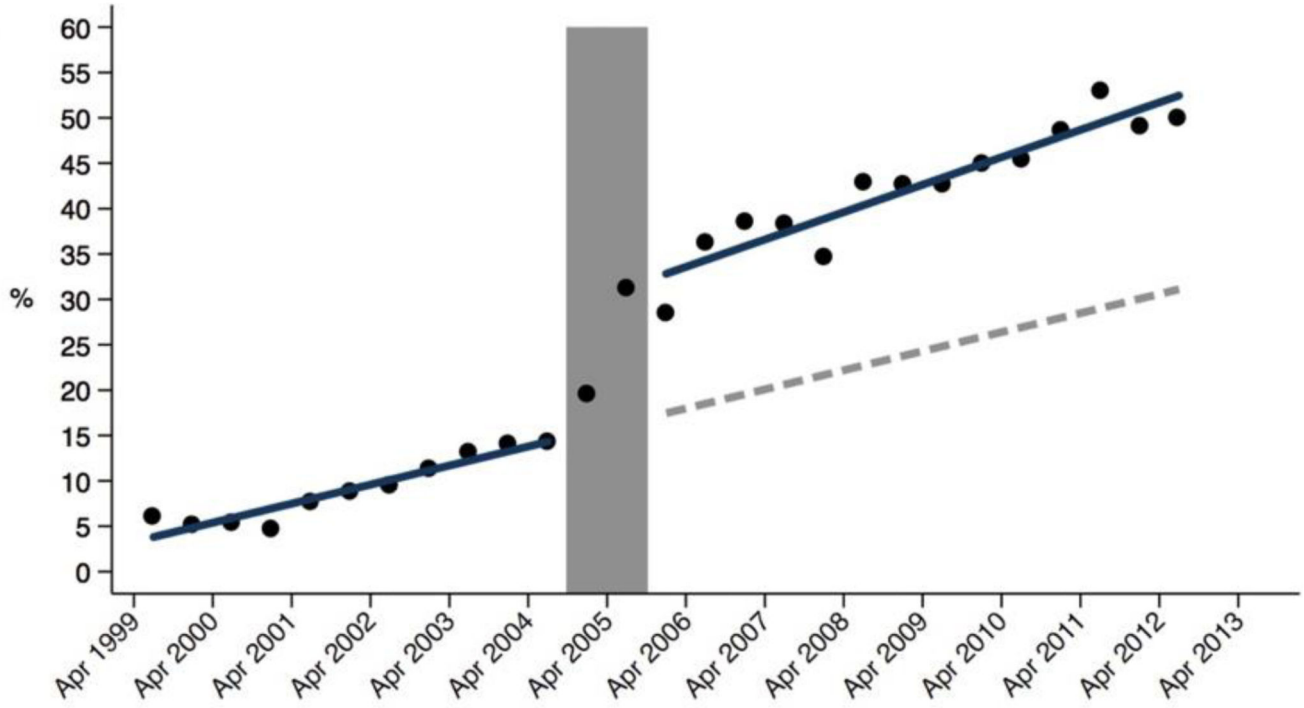

Figure 3.

Increase in frequency of prescribing anti-osteoporotic medication in UK following installment of secondary fracture prevention services nationwide. Percentage of anti-osteoporosis medication in the first year after index hip fracture among treatment naïve patients at baseline before and after the commencement of the secondary fracture prevention service (shown in grey). The blue line represents the actual (observed) increase in the proportion of patients receiving anti-osteoporosis medication before and after the instigation of the secondary fracture prevention service and the dotted line represents the modelled trajectory without the secondary fracture prevention service.[62]

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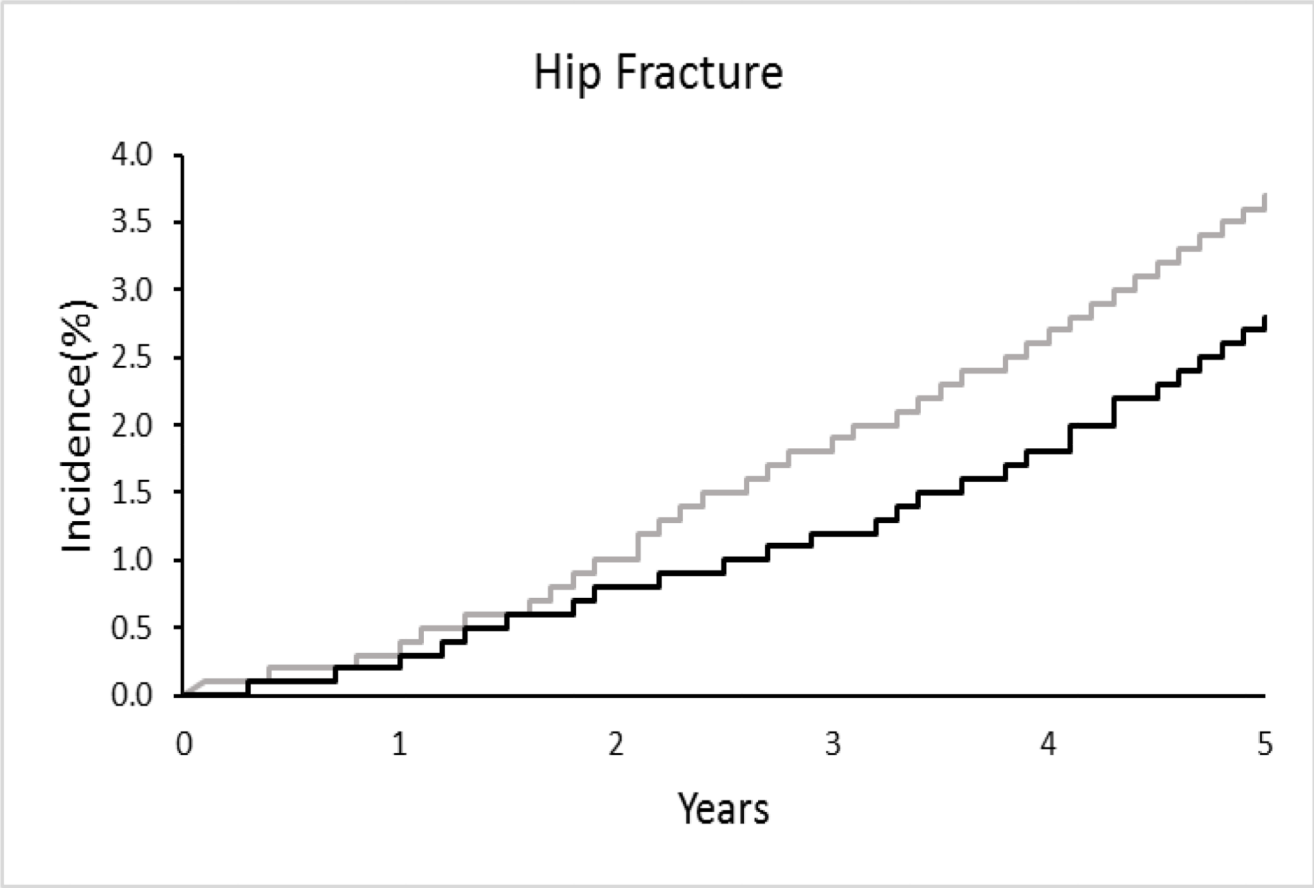

Figure 4.

Results of MRC SCOOP Trial: Over 5 years, risk assessment using FRAX to target bisphosphonate therapy resulted in a 24% ($p<0.01$) reduction in the risk of hip fracture [65]. The grey line shows the incidence of hip fracture in the non-screening (control) arm and the black line shows the lower incidence of hip fracture in the screening (experimental) arm.

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Table 1

Antifracture efficacy of the most frequently used treatments for postmenopausal osteoporosis when given with calcium and vitamin D, as derived from randomized controlled trials[1]. In this table 'established osteoporosis' is defined as osteoporosis in the presence of one or more fragility fractures.

	Effect on vertebral fracture risk		Effect on non-vertebral fracture risk	
	Osteoporosis	**Established osteoporosis**[a]	**Osteoporosis**	**Established osteoporosis**[a]
Alendronate	+	+	NA	+ (including hip)
Risedronate	+	+	NA	+ (including hip)
Ibandronate	NA	+	NA	+[b]
Zoledronate	+	+	NA	+[c]
HRT	+	+	+	+ (including hip)
Raloxifene	+	+	NA	NA
Teriparatide	NA	+	NA	+
Denosumab	+	+[c]	+ (including hip)	+[c]

NA, no evidence available;

+ effective drug;

[a] women with a prior vertebral fracture;

[b] in subsets of patients only (post-hoc analysis);

[c] mixed group of patients with or without prevalent vertebral fractures