Expert Opinion

informa
healthcare

Improving adherence in osteoporosis: a new management algorithm for the patient with osteoporosis

Gianluca Baio, Mario Barbagallo, Giovanni D'Avola, Andrea Di Luccio, Gian Luca Di Tanna, Paolo Falaschi, Giovanni Iolascon, Nazzarena Malavolta, Federico Robbiati & Fabio Massimo Ulivieri[†]
[†]Fondazione Ca' Granda, Ospedale Maggiore Policlinico IRCCS, Milan, Italy

Introduction: Bisphosphonates are the first-choice treatment for osteoporosis. They effectively increase bone mineral density, reduce markers of bone resorption, and lower the incidence of new fractures in patients with osteoporosis-related fracture. However, the efficacy observed in clinical trials may not be realized in a real-life setting, partly due to poor adherence to therapy, with a significant worsening of clinical outcomes. Several issues contribute to poor adherence to osteoporosis medication, including inconvenient dosing regimens and concerns about possible adverse events. Although strategies to improve adherence have been investigated, new approaches are required.

Areas covered: We review available data and propose a new approach to improve adherence to osteoporosis therapy in clinical practice. We present the current evidence and personal experience from a group of Italian osteoporosis experts.

Expert opinion: To improve adherence, we propose a multifaceted approach, which includes the Triad Model suggested by the World Health Organization, direct observed therapy and the use of drugs with longer administration intervals, e.g., zoledronic acid. The integration of these strategies may provide the basis for a marked increase in adherence to osteoporosis therapy, and improved clinical outcomes in a real-life scenario.

Keywords: adherence, bisphosphonates, bone density, medication possession ratio, osteoporosis, treatment algorithm

1. Introduction

Although often neglected, osteoporosis presents a heavy burden to patients and communities in all countries where data are available [1-3]. The incidence, clinical consequences and costs of osteoporotic fractures are widely accepted [1,2].

Osteoporosis management involves several well-studied screening, diagnostic and therapeutic tools [2,4]. In addition, detailed meta-analyses for each agent used in osteoporosis treatment are available [5]. Nevertheless, it is well known that there is a wide gap between knowledge (such as that included in treatment guidelines) and clinical reality [6], and a quantitative relationship between lack of adherence and loss of fracture risk reduction.

At least two large gaps need to be filled if the potential of available diagnostic and treatment tools is to be fully exploited. The first is the lack of secondary prevention after fractures that require surgical repair, irrespective of the higher risk to incur further, more severe, fractures (the so-called 'domino effect') [6,7]. The second is

---

Article highlights.

- Adherence is a key factor in the management of osteoporosis. However, adherence in 'real-life' is much lower than that observed in clinical trials. New approaches to improve adherence are thus required.
- Adherence to osteoporosis treatment is a relevant clinical issue for the following reasons:
  - Clinical implications of poor patient adherence and persistence: low adherence to osteoporosis treatment is associated with a significant increase in the risk of fractures.
  - Measuring the gap in adherence to osteoporosis treatment: improving adherence requires the direct involvement of local health authorities in clinical audit and follow-up programmes.
  - Identification of low-adherence patients: at present, patients at risk of low adherence are unlikely to be identified before the initiation of therapy; moreover, a clinical parameter precisely relating to low adherence is still lacking.
  - It may not be possible to manage the reasons for poor adherence: there appear to be many reasons for poor adherence to BP therapy. With the exception of lack of confidence in efficacy and fear of side effects, most of the reasons for low adherence seem unlikely to be easily manageable.
  - Improving adherence in osteoporosis: some possible methods to improve adherence to osteoporosis treatment are represented by the WHO Triad model, directly observed therapy, and the widespread use of intermittent osteoporosis therapies.
  - Impact of improving adherence in osteoporosis on clinical and cost outcomes: improving adherence reduces fracture incidence and related costs, although increases treatment costs, and as a result, programs targeted to improve adherence might be costly.
- We propose a patient-centric diagnosis–treatment pathway to be used as a working draft in clinical audit with local health authorities.
- The use of drug administrative databases to monitor adherence to osteoporosis treatment and, by consequence, the development of a 'Triad model' among patients, physicians and healthcare administrations may have an impact on low adherence, and thus further improve treatment effectiveness and clinical outcomes in a real-life scenario.
- Low adherence in osteoporosis is a widespread issue that has severe clinical and economic consequences, both for patients as well as communities. Our proposal is to develop patient-centric pathways, tailored communication and supporting programmes that utilize the information potential coming from administrative drug databases.

This box summarizes key points contained in the article.

---

the large proportion of patients who stop treatment before a meaningful threshold (6 – 12 months) and/or have an intermittent pattern of drug use, resulting in adherence below that needed to confer a positive clinical impact [6-8]. With few local or time-limited exceptions, analysis of the literature shows no trend in establishing a new management culture

capable of supporting a strong, worldwide improvement in either issue.

We believe that combining a standard multidisciplinary clinical audit approach with innovative use of information technology (IT) may lead to a new approach to solve this issue. We decided to focus on low adherence, with the hope that addressing this issue will enable better clinical outcomes for primary and secondary prevention. A multidisciplinary working group (WG) was set up, bringing together clinicians, healthcare statisticians and healthcare managers previously involved in the development and application of health outcome models in osteoporosis (GDT, GB, FMU, NM, GI, GDA, MB), the development of clinical audit projects (ADL, PF), use of IT and administrative databases in audit and follow-up projects (ADL), analysis of local administrative databases to study adherence in osteoporosis (FMU, ADL), epidemiology and cost of hip fractures (GI), the role of osteoporosis within local health authorities (ADL, GDA) and the development of programs to improve adherence (FR). The WG methodology largely followed the National Institute of Clinical Excellence (NICE) path on clinical audit principles and recognized that a detailed plan on how to implement changes in osteoporosis management and how to sustain the change process requires deeper analysis at the regional/local level because of the regionalization of the Italian National Health System (NHS). In this paper, we propose a new Triad-like, IT-supported method to improve adherence in osteoporosis in a cost-conscious manner.

2. Adherence to osteoporosis treatment: a relevant clinical issue

2.1 Clinical implications of poor patient adherence and persistence

Adherence (or compliance) is currently defined as the extent to which patients take medication as prescribed by their physicians [9]. It is expressed as a percentage of prescribed doses taken over a specified period, often referred to as the medication possession ratio (MPR). Although adherence and compliance are often used interchangeably, for the purposes of this article we will refer to adherence only. The persistence with a medication is defined as continuing to take the prescribed therapy, i.e., the duration of time from initiation to discontinuation of therapy.

The full clinical benefit of osteoporosis therapy is reached only when adherence is high [8]. Thus, poor patient adherence to therapy is of particular concern, and its relationship to fracture risk reduction has been studied in detail, particularly for bisphosphonates (BPs). A large observational experience suggested that fracture risk, all-cause hospitalization risk and healthcare costs in patients with poor adherence, i.e., MPR < 50%, were higher than in patients with an MPR of 80 – 90% (**Figure 1**) [8]. Given that oral BPs are usually thought to reduce fracture risk by 40 – 50%, an MPR < 50% may significantly reduce, if not abolish, any
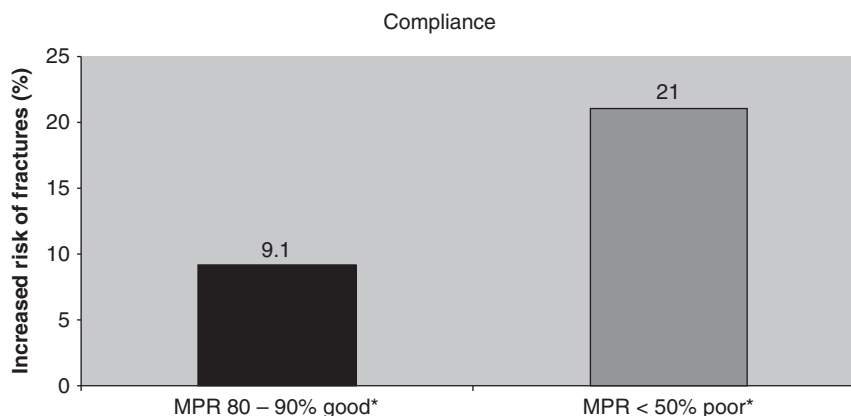
Figure 1. The effects of adherence with osteoporosis medication on fracture risk in 38,120 postmenopausal women with osteoporosis [8].

*Risk gradient of adherence effects (multivariate estimation).

MPR: Medication possession ratio.

potential efficacy [6]. These findings are overall confirmed by data from two US claims databases; this study indicated that the 'classic' 80% adherence threshold used in many studies might not be as optimal as previously assumed, given that only half of the nominal drug efficacy is observed [10]. Poor adherence has also been associated with smaller increments in bone mineral density (BMD): in a study on 176 patients, a 3.80% per year increase in spine bone density for subjects whose adherence with therapy was $\geq$ 66%, versus 2.11% per year ($p < 0.005$) for those whose adherence was < 66% [11]. These results [8,10,11], and those from another study [12], led Seeman *et al.* [6] to suggest that optimal antifracture efficacy was reached only with > 90% adherence. It has been questioned whether < 50 – 60% adherence, or treatment periods of < 6 – 12 months, are actually effective [13] and the latter study suggests there is little or no residual efficacy 'tail effect' after BP discontinuation, which would negatively impact upon pharmacoeconomic models that take into consideration such an effect.

Although MPR has limitations [14], it is probably the most commonly used measure of adherence and its correlation to fracture risk. Moreover, it allows repeated measures to check improvements during audit and feedback projects. Persistence is also an important predictor of clinical outcomes, with the relative risk of experiencing hip/femur fractures being lower in patients treated for > 24 months [13].

Differing from BMD and risk of fractures, data supporting the use of markers to monitor patients' adherence and persistence are still scant [15].

2.2 Measuring the gap in adherence to osteoporosis treatment

The efficacy observed in clinical trials for BPs and other agents in the treatment of osteoporosis may not be fully realized in clinical practice for various reasons; for example,

adherence issues, less stringent monitoring and the lack of eligibility criteria [16]. Siris *et al.* found that only 43% of the > 35,000 patients considered in their study had an MPR > 80%, an adherence threshold that the same study found to be associated with a 50% drop in efficacy [10]. Penning-van Beest *et al.* found that after 1 year only $\approx$ 40% of patients had an MPR > 70% [17].

Data on treatment adherence and persistence collected in Italy are consistent with those observed in the US when based on administrative prescription database analyses (e.g., tracking prescriptions reimbursed from the Regional Health Systems [RHS]) [18-20]. In an analysis conducted in the Tuscany region [20], only 2% of patients with hip fracture achieved a level of adherence sufficient to maximize hip fracture prevention (i.e., a MPR > 90%, according to Seeman *et al.* [6]). In the Molise region, adherence measured by MPR was lower in patients treated with generic weekly alendronate than branded weekly BPs, and the lowest adherence was found for daily treatment regimens, in this case strontium ranelate (**Figure 2**; data on file, reported here for the first time).

These findings highlight an immediate need for initiatives to improve adherence to achieve optimal fracture protection. At least in Italy, the use of administrative prescription databases makes measuring adherence feasible and inexpensive. Such databases are also easily searchable and constantly updated (at least monthly), allowing the entire population to be evaluated. However, this requires the direct involvement of local health authorities in clinical audit and follow-up programmes, all targeted at improving adherence.

2.3 Identification of low-adherence patients

As most dropouts occur within a few months of beginning therapy, close control of adherence and persistence is
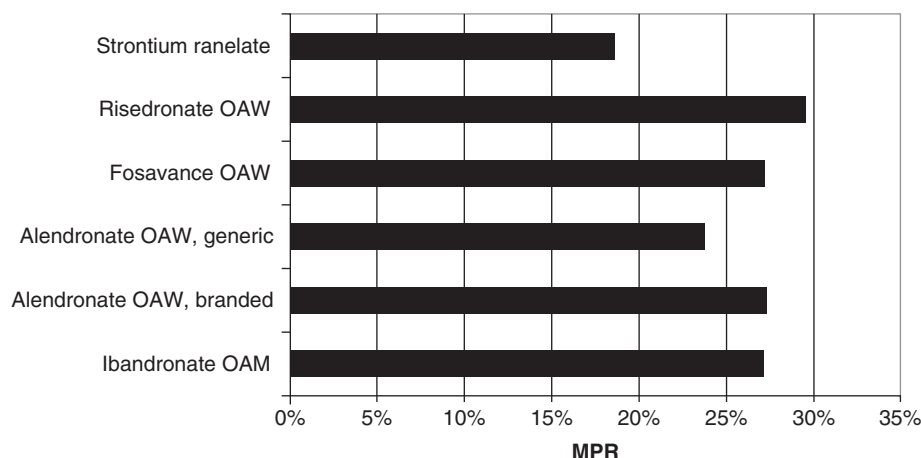
Figure 2. Adherence to anti-osteoporosis agents in Molise region, Italy.
MPR: Medication Possession Ratio; OAM: Once a month; OAW: Once a week.

needed [6]. However, at present, patients at risk of low adherence are unlikely to be identified before the initiation of therapy, partly due to the lack of a clinical parameter precisely relating to low adherence [21]. In Italy, identification of poorly adherent patients is difficult, as shown by the large gap between self-reported patient BP adherence rates and assessments based on administrative databases [18,19]. Thus, there is a need for a method of early (within a few months) identification of patients at risk of low adherence [6]. Preliminary data collected in the Molise region by mining administrative databases suggested that MPR during the first trimester of therapy can predict the long-term adherence (Table 1) (ADL and FR, manuscript in preparation). This analysis reflects clinical practice (i.e., 'poorly adherent patients will worsen') and shows the power of administrative database analyses in providing physicians with early warning signals helpful in identifying patients with behaviours and/or conditions likely to impact adherence.

2.4 Are reasons for poor adherence manageable?

There appear to be many reasons for poor adherence to BP therapy. An International Osteoporosis Foundation survey found that women considered most of the disadvantages of oral BP therapy to be related to inconvenient dosing regimens and concerns about possible adverse events [22], in particular those at the gastrointestinal level, which are minimized by complex administration procedures [23-26]. Other reasons for poor adherence include multiple concomitant treatments [16] and frequency of treatment: less frequent dosing usually results in better adherence and persistence [19,27]. In addition, across different drug classes, daily dosing seems to be linked to lower MPR values (Figure 3; data on file). With the exception of lack of confidence in efficacy and fear of side effects (which may be attenuated by better education and patient-physician relationships), most of the reasons for low adherence seem unlikely to be easily manageable.

2.5 Improving adherence in osteoporosis

Randomized trials have evaluated the possible effect of closer monitoring of nursing staff and bone markers [28,29]. New dosage regimens [30] and clinical interventions, such as consultations, bone densitometry referrals and educational materials [31,32], have also been tested. However, none of these approaches has proven to be particularly effective in clinical practice [28-33]. These findings indicate that, despite the various approaches investigated to date, new approaches to improve adherence are required. A selection of approaches to improve adherence to medication regimens is presented in Table 2 and are discussed in detail below.

2.5.1 WHO Triad model

The so-called Triad model was identified by the World Health Organization (WHO) from best practice to improve adherence [34]. In accordance with the Innovative Care for Chronic Conditions Framework, the Triad model proposes a partnership (with the Triad at the centre of the concept) comprising patients and families, healthcare teams and community supporters. Clinical outcomes are greatly improved when each member of the Triad is informed, motivated and prepared to work together to manage chronic conditions, and the importance of communication and cooperation among all the members of the Triad is emphasized. The Triad may also include other components involved to varying degrees in the clinical decision-making process, such as healthcare organizations and health administrators. When the integration of the different components is optimal, the patient and family become active participants in caring for chronic conditions, supported by the community and the healthcare team, thus enhancing adherence to treatment.

As mentioned previously, evaluation of administrative databases by healthcare providers may have a critical role in identifying and measuring critical issues and warnings. For instance, Kaiser Permanente is an integrated

Table 1. Three-month analysis of medication possession ratios (MPR) in patients receiving oral bisphosphonates or strontium ranelate in the Molise region, Italy (ADL, manuscript in preparation).

1st trimester		Distribution of each group of patients by MPR[*] in the 2nd trimester			
MPR[*]	% of treated patients	MPR 100%	MPR 67%	MPR 33%	MPR 0%
MPR 100%	33.9%	35.9%	27.9%	25.4%	10.9%
MPR 67%	41.2%	6.5%	37.0%	35.4%	21.1%
MPR 33%	24.9%	1.9%	10.1%	16.5%	71.4%

*All drugs sold in 28- or 30-day packs: one pack provides approximately 1 month of therapy.

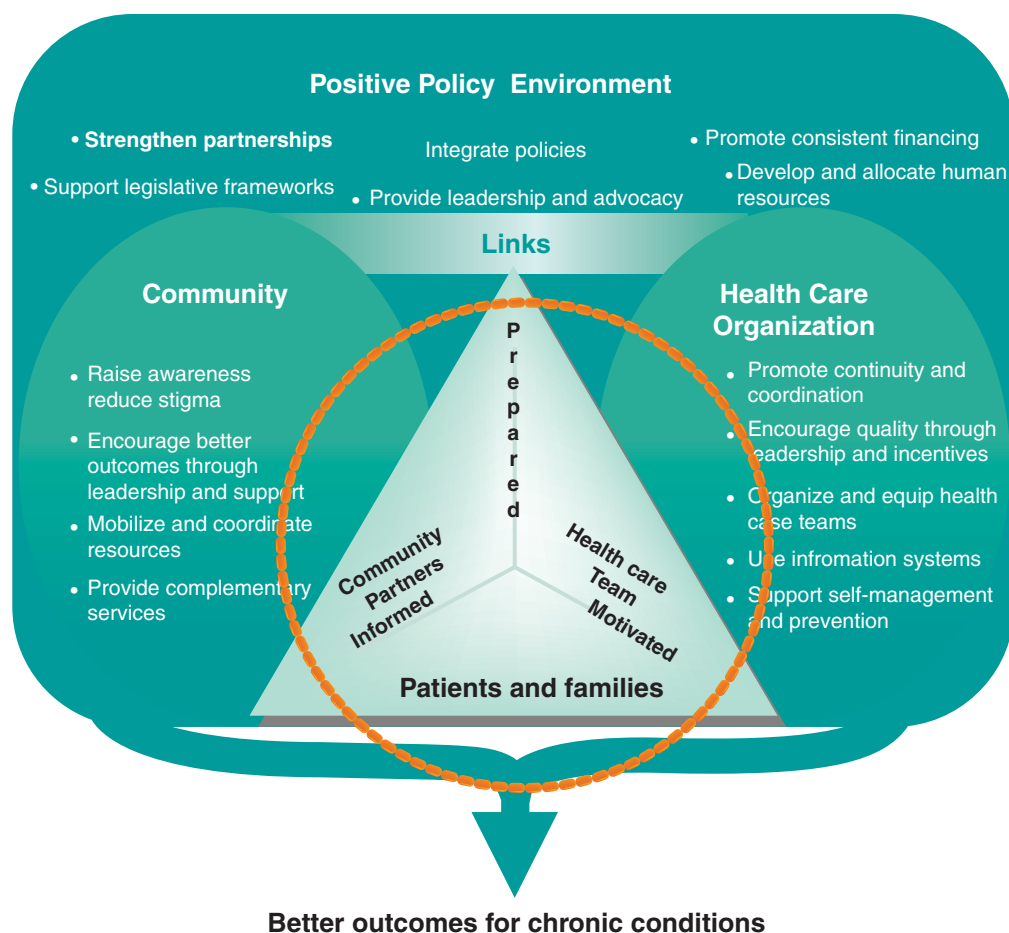*Innovative care for chronic conditions framework*

Figure 3. The Triad concept: the WHO Innovative Care for Chronic Conditions (ICCC) framework (World Health Organization [34]).

managed-care consortium based in Oakland, California, United States. This database was mined to assess the gaps between guidelines and actual management of osteoporosis patients by analyzing data on demographics, diagnoses, drugs dispensed by the pharmacy and the measurement of BMD [35]. Moreover, an analysis of > 46,000 patients included in the Kaiser Permanente database allowed an accurate description of the incidence of myocardial infarction from 1999 to 2008 [36]. A 62% decrease in the incidence of ST-segment elevation myocardial infarction was reported,

Table 2. Possible approaches for improving adherence to bisphosphonate therapy.

Approach	Description
WHO Triad model	A partnership (triad) comprising patients and families, healthcare teams, and community supporters to maximize clinical outcomes thorough a direct interaction. Triad may include others involved in the clinical decision-making process
Directly observed therapy	Close monitoring through direct observation of patients' medication taking, to improve adherence

and authors attributed this improvement, at least in part, to the implementation of adequate prevention and management programs.

Such analyses, which can be updated regularly, can support tailored communication programmes targeted to patients and healthcare providers and help physicians to identify patients in daily care.

2.5.2 *Directly observed therapy*

Directly observed therapy (DOT) is a WHO initiative involving the close monitoring (through direct observation) of patients taking their medications, with the aim of improving adherence and avoiding drug resistance for diseases such as tuberculosis and HIV. The concept has been adopted by the WHO as the standard of care in tuberculosis treatment [37]. The WHO strategy consists of political commitment, improved laboratory analysis, direct patient observation when they swallow each dose of medication, standardized treatment and patient support, and standardized monitoring and evaluation of treatment results. In addition to the aforementioned indications, the US experience of the Kaiser Permanente database may support the use of DOT for the monitoring of therapy adherence and clinical outcomes in patients with osteoporosis. However, the effectiveness of DOT is debatable [38]. Among critical issues were the fact that daily observation of patients was cumbersome and DOT might not be sufficient unless integrated into a wider programme; however, such a strategy might be more effective with osteoporosis therapies that have less frequent dosing intervals in osteoporosis.

2.5.3 *Role of intermittent osteoporosis therapies*

The BPs are now accepted as the first-choice treatment of osteoporosis [39] and are available with various administration frequencies. Recently, once-yearly intravenous zoledronic acid demonstrated efficacy in the secondary prevention of fractures [40,41]. There was also a 46% reduction in the relative risk of death in the zoledronic acid group, which may be explained in part by the reduction in new fractures, further supporting the benefits of treatment with zoledronic acid in the secondary prevention of fractures [42].

Recently, zoledronic acid was shown to provide the greatest reduction in the risk of vertebral fracture when compared with alendronate, ibandronate and risedronate in a Bayesian analysis of seven randomized, placebo-controlled trials involving > 20,000 patients [43]. Of note, Bayesian analyses provide a methodology for analyzing multiple treatments even when results of different head-to-head studies are conflicting [44,45].

Zoledronic acid is the first BP to be available for intravenous once-yearly administration [46,47] and it has been suggested that a low frequency of administration of zoledronic acid may enhance adherence to treatment [48]. These results were confirmed for other drugs, e.g., alendronate, ibandronate and denosumab [30,49-51]. For instance, once-monthly oral ibandronate was associated with a 47% relative improvement in persistence at 6 months, with respect to oral once-weekly alendronate [49] and quarterly intravenous ibandronate administration was associated with greater adherence than oral monthly administration [50]. In a recent multicentric study, adherence in the first 12 months was 76.6% for oral alendronate once weekly and 87.3% (110/126) for subcutaneous denosumab every 6 months. At 12 months, risk ratios for denosumab, compared with alendronate, were 0.58 for non-adherence and 0.54 for non-persistence ($p < 0.05$ for all comparisons) [51]. Moreover, the reduction of the frequency of oral BP administration from daily to weekly was found to be associated with improvements in patient persistence with therapy in a real-life setting, although even weekly administration resulted in suboptimal adherence [52,53].

Collectively, these findings suggest that a low administration frequency of a bisphosphonate may further improve patient adherence [48]. In any case, a careful evaluation of every reason for poor adherence is required before switching to any therapy with a low administration frequency.

3. Impact of improving adherence in osteoporosis on clinical and cost outcomes

Despite the causes, prevalence, population distribution and consequences of low adherence on fracture risk being well studied, attempts to develop health economic models that include these variables are few.

A model that used data from the UK General Practitioner Research Database showed that improving persistence of weekly BPs by 10% would prevent an additional 1.4 fractures/100 patients over 3 years; an annual treatment that would potentially guarantee 100% adherence for at least 1 year would prevent an additional 6.8 hip fractures/1000 patients (14.7 if persistence increased by 10%) [54]. This model, in which adherence with oral bisphosphonates was quite high (62 – 72%, depending on age), demonstrates that decision making that is based purely on efficacy shown in clinical studies might overestimate cost effectiveness. These findings are in line with another model in which the

incremental cost-effectiveness ratio (ICER) was better for more severe patients because the higher the risk, the higher the number of fractures prevented [55]; this was also the case with a Monte Carlo simulation that compared usual adherence and optimal adherence with weekly and daily BPs [56]. The authors of this latter study suggest that modelled cost analyses that include adherence should also include costs to improve adherence, given that they would exceed $US200/year [57].

In the Italian NHS, which – like Italy – is strongly regionalized, costs (e.g., weighted average cost of drugs) and diagnosis-related group costs may vary from region to region. In a study led by Pammolli, cost-effectiveness analyses focused specifically on the adoption of zoledronic acid versus risedronate or alendronate in five regions: Lombardia [58], Emilia Romagna [59], Lazio, Campania [60] and Sicilia [61]. The model was built within a Bayesian Health Technology Assessment approach that included adherence and real treatment data [62]. Using Lombardia as an example, the cost-effectiveness analysis shows that zoledronic acid is predominantly a dominant strategy (less costly, better efficacy) compared with risedronate or alendronate (**Figure** 4). In Lombardia (about 10 million people), adoption of zoledronic acid would bring savings of about €7.5 million versus risedronate and €4 million versus alendronate (priced as generic).

Thus, improving adherence reduces fracture incidence and related costs, although it increases treatment costs. As a result, programmes targeted to improve adherence might be costly.

4. A proposal for a new osteoporosis treatment algorithm

Taking all of the above into consideration, we propose a patient-centric Diagnosis-Treatment Pathway (DTP) to be used as a working draft in clinical audit with local health authorities. In this DTP, the classic 'patient–physician' dual relationship becomes a 'patient–physician–local health administrator' triad-like relationship that, together with supporting data from administrative drug-reimbursement databases, provides an easy, low-cost, and effective means of helping physicians identify patients with low adherence and those with a higher probability of becoming poorly adherent or stopping therapy.

This algorithm is illustrated in **Figure** 5. Adherence to osteoporosis medication is reviewed at regular follow-up visits, calculated according to MPR data provided by the health administration authorities. Patients with an MPR > 90% (adherent) continue with their osteoporosis medication. The physician works together with patients with an MPR < 90% to analyze the causes of poor adherence, and discusses treatment goals, means of improving medication adherence and alternative therapeutic options to current osteoporosis medication A joint decision is reached on whether the patient will stop the current therapy, continue with the current therapy or consider a change in medication from the options

available: oral (including generic drugs, which are cheaper than any injected therapy) and subcutaneous therapies, or 3-monthly or annual intravenous therapies. The implications and costs of each option are considered carefully. The results of some studies, however, suggest that zoledronic acid and denosumab are associated with a more favourable cost/effectiveness ratio than generic alendronate [62,63]. If the decision reached leads to self-administered therapy (i.e., oral BPs), the patient has to sign an informed consent about risks associated with insufficient adherence to instruction and schedule. If intravenous therapy is chosen, the patient is referred to an osteoporosis centre (in Italy, zoledronic acid can be prescribed only in a hospital-like setting). One Italian Local Health Authority (ASL 3 Foligno) recently approved a similar pilot project based on secondary use of administrative data to find patients with an MPR < 80% [64]. The reasons for low adherence for each patient are verified by a questionnaire and reviewed by a team of general practitioners; patients might be referred to a local hospital for once-a- year bisphosphonate infusion. However, definite data from this pilot programme are not available to date.

5. Conclusions

We suggest that the use of drug administrative databases to monitor adherence to osteoporosis treatment and, by consequence, the development of a 'Triad model' among patients, physicians and healthcare administrations, has the potential to have a widespread and economically feasible impact on low adherence, and thus further improve treatment effectiveness and clinical outcomes in a real-life scenario.

6. Expert opinion

Low adherence in osteoporosis is a widespread issue that has severe clinical and economic consequences, both for patients and communities. Our proposal is to develop patient-centric pathways, tailored communication and supporting programmes that leverage the information potential coming from administrative drug databases.

Clinical databases have been used successfully to describe the phenomenon of low adherence in osteoporosis, including the length of persistence on treatment, adherence, distribution of patients by these variables and, more recently, the impact of adherence on clinical outcomes, namely the reduction of fractures. We propose that administrative databases are used as a way to support patients and physicians in improving adherence in osteoporosis and that the availability of intravenous once-a-year bisphosphonates is leveraged to implement feasible DOT programmes to further improve adherence.

Use of administrative databases means that health authorities (or other budget holders, depending on the local healthcare system) will be involved not only in clinical audit projects but will be the third corner of the Triad model described by the WHO, regularly providing patients and
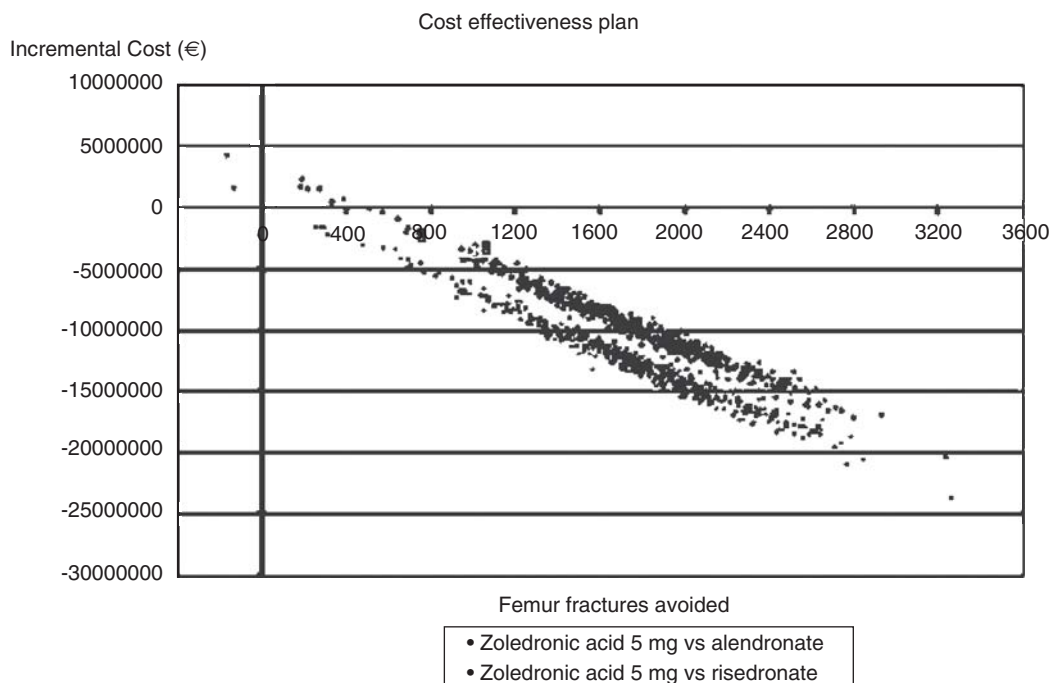
Figure 4. Number of secondary femur fractures avoided and costs associated with three different bisphosphonates following either a vertebral fracture or a primary fracture, as derived from an analysis of data collected in the Lombardia region, Italy (Sole 24 Ore, May 2009).

physicians with tailored communication and programmes. For instance, reminders could be mailed to all patients shortly after treatment starts, or specifically directed to patients who cease to participate after 1 – 2 months. As early as 3 months after starting therapy, educational materials or programmes can be directed specifically to patients who appear to be poorly adherent or at risk of low adherence. General practitioners could be helped to identify low-adherence patients by being mailed a monthly list of patients who interrupted therapy and/or fell below a certain adherence threshold, and could be provided with tools tailored for specific patient behaviour models or training programmes targeted to facilitate the patient-physician interaction on these themes.

A pilot programme based on the use of administrative databases has recently been implemented in Italy to improve adherence in osteoporosis patents [64]. Similar initiatives have been conducted in the United States to monitor patients' adherence and clinical outcomes on osteoporosis and cardio-vascular disease [35,36]. These findings may suggest that a management algorithm based on the analysis of administrative databases can be applied to different chronic conditions.

However, all initiatives must ensure that the patient–physician relationship is not undermined. Usually, only physicians are entitled to discuss issues with patients and, if necessary, to evaluate potential reasons underlying the suggestions made by prescription analyses. Prescription

analyses should be considered only as the starting point of a classic patient–physician interaction. Cultural, professional ethics and legal constraints must be considered carefully when defining activities. Special care should also be taken to ensure privacy, with laws to restrict both data analyses and personal data being shared between various health authorities and physicians. This might even apply when all healthcare-related costs (drug use, laboratory tests, hospitalization, etc.) are regularly collected for administrative purposes and stored in individualized patient files.

In general, patients should be given the choice of adhering to an initiative that will involve specific communication with their GP or specialist. Discussing the opportunity of adhering to this programme and obtaining patient consent should be managed by doctors at the beginning of therapy or by healthcare organizations through *ad hoc* information programmes. There must be no prescription restrictions or limitation of access to healthcare services for patients who do not adhere to such initiatives.

Analysis of adherence using drug records has all of the limitations previously described when this approach was used to describe the low-adherence phenomenon. Patients might be in possession of pills but not necessarily taking them, and even those who are complying with the treatment schedule might not be complying with administration rules. In all these cases, MPR tends to overestimate adherence and might be too
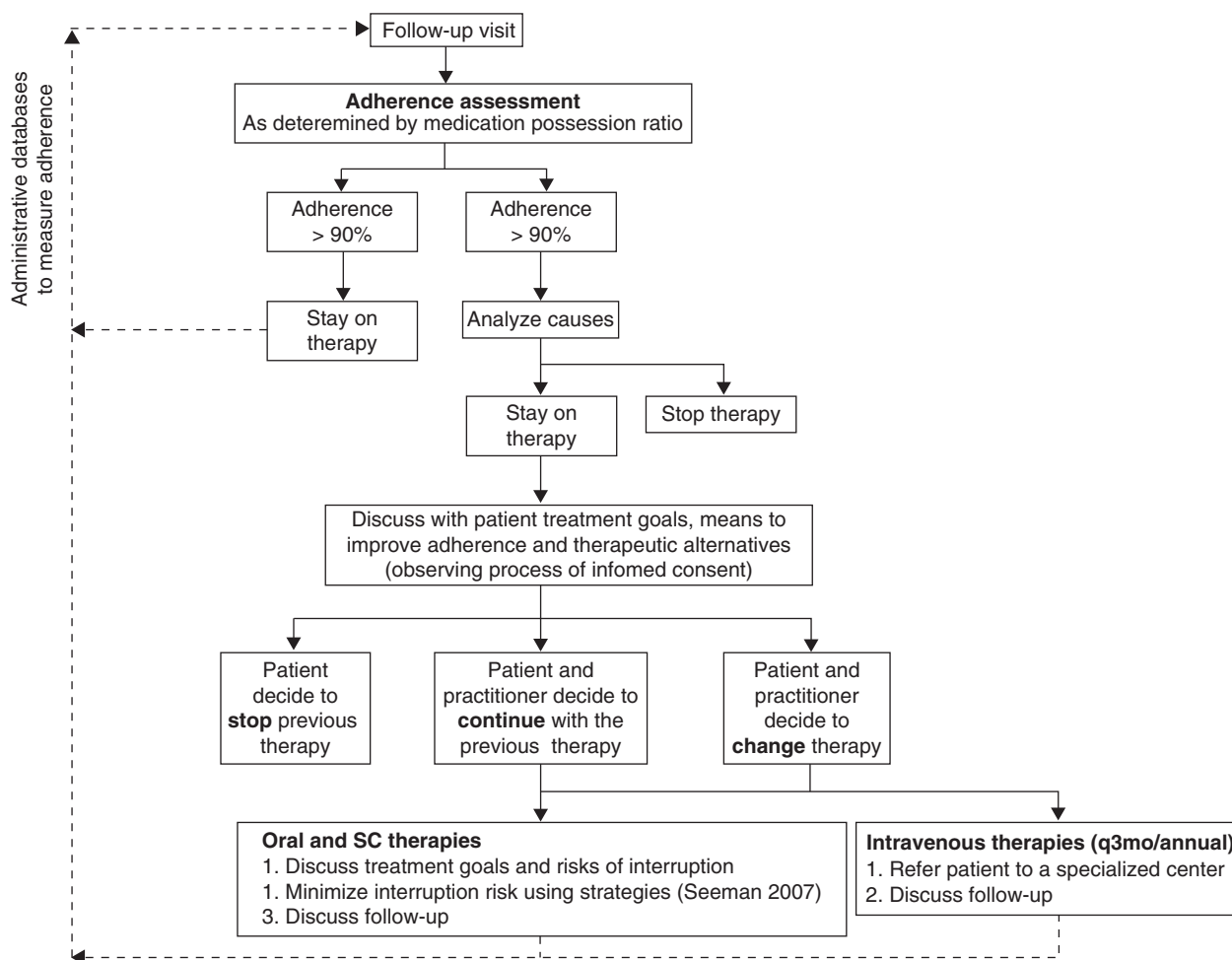
Figure 5. Management algorithm of an osteoporosis patient. Adherence is measured as medication possession rate (MPR: percentage of days on therapy either since therapy begun or in the last 3 and 12 months). This parameter is evaluated monthly by local health authorities using the refilling prescription database. Data for each poorly adherent or at-risk patient are mailed monthly to the general practitioner.

time-consuming for a single physician to analyse if not provided by *ad hoc* software, although privacy laws may restrict the range of feasible communication initiatives. However, administrative database analysis has many advantages. It is cheap; can be implemented quickly because hardware, data collection and storage are already in place; and it can be easily repeated, at almost no additional cost, to monitor progress. In most parts of Italy, local health administrations already analyze monthly or quarterly prescription volumes and send tailored detailed reports to every GP; these could easily be extended to include adherence to osteoporosis therapies. Unlike epidemiological studies, patient surveys and market research, prescription data collection does not require additional work by physicians or additional administrative staff and, unlike standard surveys, may cover almost 100% of patients. Moreover, the ability to tailor programmes and communication will improve programme efficacy and keep costs down, and avoids the need to mail all osteoporosis patients on treatment.

The best way to implement this model is through local clinical audits (see the NICE Best Practice Guidelines on Clinical Audit) [65] and the involvement of all stakeholders is essential. Variables (well identified in the NICE guidelines) that might prevent the development and implementation of such projects include lack of a common culture and language, conflict of interests, different goals across different stakeholders, and lack of time and resources. This initiative should include information, training and follow-up activities and would benefit from pay-for-better-quality programmes. The latter could be easily planned and monitored because key process indicators (based on patient adherence) can be routinely monitored through administrative drug databases.

Given the current pressure on health budgets in most countries, the fact that if an adherence programme is successful, especially in the short term, the total costs for the NHS will increase should be borne in mind. Currently, at least in Italy, this seems to be more of a concern

with osteoporosis, which is often neglected as a disease, whereas other areas with costs of a similar magnitude – such as acute MI – receive a much greater portion of the drug budget. For example, although the cost of acute MI equals the cost of hip fracture, NHS spending for statins and antihypertensives is 14-fold greater than for osteoporosis drugs [66]. One solution for keeping costs under control is to develop different models of interaction between local health authorities and drug manufacturers. Pharmaceutical companies often invest in programmes targeted to improve adherence as a way of increasing sales; it should be possible for health authorities to include them in the scenario.

Acknowledgements

Declaration of interest

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Osteoporosis in the European Union in 2008: ten years of progress and ongoing challenges. International Osteoporosis Foundation 2008. Available from: http://www.iofbonehealth.org/download/osteofound/filemanager/publications/pdf/eu-report-2008.pdf. [Last accessed 9 July 2010]

2. Kanis JA, Burlet N, Cooper C, et al.; European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2008;19:399-428

3. Piscitelli P, Iolascon G, Gimigliano F, et al.; SIOMMMS study group; CERSUM research group. Incidence and costs of hip fractures compared to acute myocardial infarction in the Italian population: a 4-year survey. Osteoporos Int 2007;18:211-19

4. Adami S, Bertoldo F, Brandi ML, et al.; Società Italiana dell'Osteoporosi, del Metabolismo Minerale e delle Malattie dello Scheletro. Guidelines for the diagnosis, prevention and treatment of osteoporosis. Reumatismo 2009;61:260-84

5. Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk. Osteoporosis evidence review: systematic reviews of clinical effectiveness. National Institute for Clinical Excellence 2008. Available from: http://www.nice.org.uk/nicemedia/pdf/

OsteoporosisEvidenceReviews190908.pdf. [Last accessed 9 July 2010]

6. Seeman E, Compston J, Adachi J, et al. Non-compliance: the Achilles' heel of anti-fracture efficacy. Osteoporos Int 2007;18:711-19
•• Extensive review of the major issues in ensuring optimal adherence to osteoporosis treatment.

7. Siris ES, Bilezikian JP, Rubin MR, et al. Pins and plaster aren't enough: a call for the evaluation and treatment of patients with osteoporotic fractures. J Clin Endocrinol Metab 2003;88:3482-6
• This landmark article points out the need for a better evaluation and treatment of osteoporotic patients.

8. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone 2006;38:922-8
•• Large population study evaluating non-adherence with osteoporosis medications as well as its implications for health and economic outcomes in actual practice.

9. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. Value Health 2008;11:44-7

10. Siris ES, Harris ST, Rosen CJ, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc 2006;81:1013-22
• This study characterized the relationship between adherence to bisphosphonate therapy and risk of specific fracture types in postmenopausal women.

11. Yood RA, Emani S, Reed JI, et al. Compliance with pharmacologic therapy for osteoporosis. Osteoporos Int 2003;14:965-8

12. Caro JJ, Ishak KJ, Huybrechts KF, et al. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. Osteoporos Int 2004;15:1003-8

13. Gallagher AM, Rietbrock S, Olson M, van Staa TP. Fracture outcomes related to persistence and compliance with oral bisphosphonates. J Bone Miner Res 2008;23:1569-75

14. Canadian Institute for Health Information. Available from: secure.cihi.ca/cihiweb/products/npduis_aib_bisphosphonates2009_e.pdf. [Last accessed 9 July 2010]

15. Seibel MJ. Biochemical markers of bone turnover part II: clinical applications in the management of osteoporosis. Clin Biochem Rev 2006;27:123-38

16. Dowd R, Recker RR, Heaney RP. Study subjects and ordinary patients. Osteoporos Int 2000;11:533-6

17. Penning-van Beest FJ, Erkens JA, Olson M, Herings RM. Loss of treatment benefit due to low compliance with bisphosphonate therapy. Osteoporos Int 2008;19:511-17

18. Rossini M, Bianchi G, Di Munno O, et al.; Treatment of Osteoporosis in clinical Practice (TOP) Study Group. Determinants of adherence to osteoporosis treatment in clinical practice. Osteoporos Int 2006;17:914-21

19. Zambon A, Baio G, Mazzaglia G, et al. Discontinuity and failures of therapy with bisphosphonates: joint assessment of predictors with multi-state models.

Pharmacoepidemiol Drug Saf 2008;17:260-9

20. Rizzuti C, Girani M, Brandi M. Use of administrative database in region Tuscany to set goals for Triad-like intervention to increase osteoporosis treatment rate and adherence rate after hip fracture. American Society for Bone and Mineral Research (ASBMR) 31st Annual Meeting; 11 – 15 September 2009; Denver, Colorado, US

21. The hidden epidemic: finding a cure for unfilled prescriptions and missed doses. The Boston Consulting Group 2003: Available from: http://www.bcg.com/publications/publications_splash.jsp. [Last accessed 9 July 2010]

22. The adherence gap: why patients don't continue with treatment. International Osteoporosis Foundation 2005. Available from: http://www.iofbonehealth.org. [Last accessed 9 July 2010]

23. Reginster JY, Rabenda V. Patient preference in the management of postmenopausal osteoporosis with bisphosphonates. Clin Interv Aging 2006;1:415-23

24. Actonel 30 mg film coated tablets: summary of product characteristics. Electronic Medicines Company (2009). Available from: http://emc.medicines.org.uk/medicine/3341/SPC/Actonel+30mg+Film+Coated+Tablets/. [Last accessed 9 July 2010]

25. Fosavance 70 mg/2800 IU tablets: summary of product characteristics. European Medicines Agency 2009. Available from: http://www.emea.europa.eu/humandocs/PDFs/EPAR/Fosavance/emea-combined-h619en.pdf. [Last accessed 9 July 2010]

26. Bonviva 150 mg film-coated tablets: summary of product characteristics. European Medicines Agency 2009. Available from: http://www.emea.europa.eu/humandocs/PDFs/EPAR/Bonviva/emea-combined-h501en.pdf. [Last accessed 9 July 2010]

27. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. Osteoporos Int 2007;18:1023-31

28. Clowes JA, Peel NF, Eastell R. The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomized controlled trial. J Clin Endocrinol Metab 2004;89:1117-23

29. Delmas P, Vrijens B, Roux C, et al. Osteoporosis treatment using reinforcement with bone turnover marker data reduces fracture risk: the IMPACT study. J Bone Miner Res 2004;19:S444

30. Simon JA, Lewiecki EM, Smith ME, et al. Patient preference for once-weekly alendronate 70 mg versus once-daily alendronate 10 mg: a multicenter, randomized, open-label, crossover study. Clin Ther 2002;24:1871-86

31. Cuddihy MT, Amadio PC, Gabriel SE, et al. A prospective clinical practice intervention to improve osteoporosis management following distal forearm fracture. Osteoporos Int 2004;15:695-700

32. Guilera M, Fuentes M, Grifols M, et al. Does an educational leaflet improve self-reported adherence to therapy in osteoporosis? The OPTIMA study. Osteoporos Int 2006;17:664-71

33. Gleeson T, Iversen MD, Avorn J, et al. Interventions to improve adherence and persistence with osteoporosis medications: a systematic literature review. Osteoporos Int 2009;20:2127-34

34. The Innovative Care for Chronic Conditions framework (ICCC). World Health Organization. Available from: http://www.who.int/diabetesactiononline/about/ICCC/en/. [Last accessed 9 July 2010]

35. Feldstein AC, Nichols GA, Elmer PJ, et al. Older women with fractures: patients falling through the cracks of guideline-recommended osteoporosis screening and treatment. J Bone Joint Surg Am 2003;85-A:2294-302

36. Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010;362:2155-65

37. Pursue high-quality DOTS expansion and enhancement. World Health Organization. Available from: http://www.who.int/tb/dots/en/. [Last accessed 9 July 2010]

38. Volmink J, Garner P. Directly observed therapy for treating tuberculosis [review]. Cochrane Database Syst Rev 2006:CD003343. Update in: Cochrane Database Syst Rev 2007:CD003343

39. Epstein S. Update of current therapeutic options for the treatment of postmenopausal osteoporosis. Clin Ther 2006;28:151-73

40. Lyles KW, Colon-Emeric CS, Magaziner JS, et al.; HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007;357:1799-809

41. Colon-Emeric CS, Eriksen EF, Lyles KV, et al. Timing of dosing of zoledronic acid 5mg after recent hip fracture affects antifracture efficacy and reduction in mortality: HORIZON-Recurrent Fracture Trial. American Geriatrics Society Annual Scientific Meeting; 30 April – May 4 2008; Washington DC

42. Calis KA, Pucino F. Zoledronic acid and secondary prevention of fractures. N Engl J Med 2007;357:1861-2

43. Jansen JP, Bergman GJ, Huels J, Olson M. Prevention of vertebral fractures in osteoporosis: mixed treatment comparison of bisphosphonate therapies. Curr Med Res Opin 2009;25:1861-8

44. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 2005;331:897-900

45. Miksad RA, Gonen M, Lynch TJ, Roberts TG Jr. Interpreting trial results in light of conflicting evidence: a Bayesian analysis of adjuvant chemotherapy for non-small-cell lung cancer. J Clin Oncol 2009;27:2245-52

46. Reclast: US prescribing information. Food and Drug Administration 2009. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021817s004lbl.pdf. [Last accessed 9 July 2010]

47. Aclasta 5 mg solution for infusion: summary of product characteristics. European Medicines Agency 2009. Available from: http://www.emea.europa.eu/humandocs/PDFs/EPAR/aclasta/emea-combined-h595en.pdf. [Last accessed 9 July 2010]

48. Boonen S, Vanderschueren D, Venken K, et al. Recent developments in the management of postmenopausal osteoporosis with bisphosphonates: enhanced efficacy by enhanced compliance. J Inter Med 2008;264:315-32

49. Cooper A, Drake J, Brankin E, PERSIST Investigators. Treatment persistence with once-monthly ibandronate and patient

support vs. once-weekly alendronate: results from the PERSIST study. Int J Clin Pract 2006;60:896-905

50. Lewiecki EM, Babbitt AM, Piziak VK, et al. Adherence to and gastrointestinal tolerability of monthly oral or quarterly intravenous ibandronate therapy in women with previous intolerance to oral bisphosphonates: a 12-month, open-label, prospective evaluation. Clin Ther 2008;30:605-21

51. Kendler DL, McClung MR, Freemantle N, et al.; on behalf of the DAPS Investigators. Adherence, preference, and satisfaction of postmenopausal women taking denosumab or alendronate. Osteoporos Int 2010. [Epub ahead of print]

52. Cramer JA, Amonkar MM, Hebborn A, Altman R. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. Curr Med Res Opin 2005;21:1453-60

53. Recker RR, Gallagher R, MacCosbe PE. Effect of dosing frequency on bisphosphonate medication adherence in a large longitudinal cohort of women. Mayo Clin Proc 2005;80:856-61

54. Rietbrock S, Olson M, van Staa TP. The potential effects on fracture outcomes of improvements in persistence and compliance with bisphosphonates. QJM 2009;102:35-42

55. Strom O, Borgstrom F, Kanis JA, Jonsson B. Incorporating adherence into health economic modelling of osteoporosis. Osteoporos Int 2009;20:23-34

56. Danese MD, Badamgarav E, Bauer DC. Effect of adherence on lifetime fractures in osteoporotic women treated with daily and weekly bisphosphonates. J Bone Miner Res 2009;24:1819-26

57. Murray MD, Young J, Hoke S, et al. Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. Ann Intern Med 2007;146:714-25

58. Ulivieri FM, Baio G, Di Tanna GL, et al. Region lombardia adoption of zoledronic could be cost effective when compared to other bisfosfonate in the treatment of postmenopausal osteoporosis. Clin Case Min Bone Metab 2008;5:409. P 4-65

59. Malavolta N, Baio G, Di Tanna GL, et al. In emilia romagna adoption of zoledronic acid to treat postmenopausal osteoporosis could be cost effective when compared to other bisfosfonates. Clin Case Min Bone Metab 2008;5:410. P 4-66

60. Iolascon G, Baio G, Di Tanna GL, et al. In region campania zoledronic acid is cost effective when compared to both alendronate and risedronate and this choice shows a small uncertainty range. Clin Case Min Bone Metab 2008;5:421. P 4-77

61. D'Avola G, Baragallo M, Baio G, et al. In sicilia zoledronic acid is cost-effective when compared to both alendronate and risedronate and this choice shows a small uncertainty range. Clin Case Min Bone Metab 2008;5:422. P 4-78

62. Baio G, Di Tanna GL, Integlia D, Pammolli F. Health economic evaluation of the treatment of osteoporosis in five Italian regions (poster). ISPOR 12th Annual European Congress; 24 – 27 Oct 2009; Paris

63. Jonsson B, Strom O, Eisman JA, et al. Cost-effectiveness of Denosumab for the treatment of postmenopausal osteoporosis. Osteoporos Int 2010. [Epub ahead of print]

64. Decisioni amministrative del Direttore Generale in pubblicazione dal 24.03.2010 al 07.04.2010. Available from: portale.asl3.umbria.it. [Last accessed 26 October 2010]

65. NICE Best Practice Guidelines on Clinical Audit. Available from: http://www.nice.org.uk/media/796/23/BestPracticeClinicalAudit.pdf [Last accessed 02-12-2010]

66. L'Uso dei farmaci in Italia: rapporto nazionale gennaio – settembre 2009. National Observatory on the Use of Medicines 2009. Available from: http://www.agenziafarmaco.it/allegati/rapporto_osmed_gen-set2009.pdf. [Last accessed 9 July 2010]

Affiliation

Gianluca Baio[1,11], Mario Barbagallo[2], Giovanni D'Avola[3], Andrea Di Luccio[4], Gian Luca Di Tanna[5], Paolo Falaschi[6], Giovanni Iolascon[7], Nazzarena Malavolta[8], Federico Robbiati[9] & Fabio Massimo Ulivieri[†10]
†Author for correspondence
[1]University College London, Department of Epidemiology and Public Health, London, UK
[2]University of Palermo, Deptartment of Internal Medicine and Emergent Pathologies, Geriatric Unit, Palermo, Italy
[3]Servizio Reumatologia Osteoporosi Azienda Sanitaria 3, Catania, Italy
[4]Azienda Sanitaria Regionale del Molise, Azienda Unita' Sanitaria Locale No. 3 Centro Molise Via G Marconi, 9 Molise, CB 86020, 86020, Italy
[5]Sapienza University of Rome, Department of Experimental Medicine, Via del Policlinico 155, 00161, Rome, Italy
[6]'Sapienza' University of Rome. S. Andrea Hospital, Department of Aging Sciences, via di Grottarossa 1035, 00189 Rome, Italy
[7]Second University of Naples, Department of Orthopedics and Rehabilitation, Naples, Italy
[8]Bologna University Hospital Policlinico S. Orsola-Malpighi, Bologna, Italy
[9]Novartis Pharma, Origgio, Italy
[10]Ulivieri: Fondazione Ca' Granda, Ospedale Maggiore Policlinico IRCCS, U.O. Medicina Nucleare, Milan, Italy
Tel: +39 0255033554;
Fax: +39 0255034382;
E-mail: ulivieri@policlinico.mi.it
[11]University of Milan Bicocca, Department of Statistics, Milan, Italy