A systematic review assessing the effectiveness of interventions to improve persistence with anti-resorptive therapy in women at high risk of clinical fracture

H J Whitea, S S Bettiolb, R Pererac, N W Robertsd, M K Javaide and Andrew J Farmerc,*

aUniversity of Oxford Clinical School, John Radcliffe Hospital, Oxford, UK, bDepartment of Pathology, School of Medicine, 43 Collins Street, Hobart, Tasmania 7000, Australia, cNational Institute for Health Research (NIHR), School of Primary Care Research, Department of Primary Health Care, University of Oxford, Oxford, dBodleian Health Care Libraries, University of Oxford, Oxford and eNIHR Musculoskeletal Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK.

*Correspondence to Andrew Farmer, Department of Primary Health Care, University of Oxford, Rosemary Rue Building, Old Road Campus, Headington, Oxford OX3 7LF, UK; E-mail: andrew.farmer@dphpc.ox.ac.uk

Received 19 January 2010; Revised 26 May 2010; Accepted 28 June 2010.

Background. Despite availability of effective treatments for osteoporosis, impact on fracture rates may be suboptimal because of failure to adhere to recommended anti-resorptive therapy.

Objective. To identify randomized controlled trials (RCTs) evaluating interventions intended to improve persistence with anti-resorptive therapy for treating women with osteoporosis or osteopenia. The design of the study is a systematic review and meta-analysis of RCTs.

Methods. Included trials were those reporting interventions to improve persistence with or adherence to anti-resorptive treatment compared to a control medication or usual care. A search of MEDLINE, EMBASE, CINAHL and the Cochrane Library was supplemented by review of cited literature. Reports were reviewed and data pooled where appropriate. The primary outcome was duration of persistence with medication.

Results. Six trials met inclusion criteria, including four reporting persistence as an outcome measure indicating a relative reduction in non-persistence of 22% (pooled relative risk: 0.78, 95% confidence interval 0.65–0.95) for active compared to control interventions. Heterogeneity between the trial effects was present but not significant ($I^2 = 47\%$, $P = 0.11$). Interventions were varied in design, and some measurements of adherence were subject to self-report bias. Two trials included the majority of participants (3386/3497), accounting for >90% of the weight in the pooled estimate.

Conclusions. Trials to date suggest potential for improving persistence with medication taking thus improving treatment outcomes and reducing fracture risk. More precise measurement of medication taking and promoting fidelity to a precisely defined intervention protocol may lead to better assessment of impact on clinically important outcomes.

Keywords. Adherence, anti-resorptive therapy, meta-analysis, osteoporosis, persistence.

Background

Osteoporosis is a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to bone fragility and increased fracture risk. The disease places a great burden on both patients and health services, with around half of all women and one in five men sustaining an osteoporosis-related fracture after the age of 50 years. Such fractures lead to high mortality and morbidity. In the context of an ageing population in most developed countries, osteoporosis prevention has become imperative and bisphosphonates, which act by osteoclast inhibition, are now recommended worldwide both for primary osteoporosis prevention and for secondary prevention after a fragility fracture has been sustained. In the UK, the National Institute for Health and Clinical Excellence recommends alendronate, taken orally, as the first-line treatment for primary and secondary fracture prevention. Randomized controlled trials (RCTS) have demonstrated that alendronate substantially increases bone mineral density (BMD), leading to a reduction in
the rate of vertebral and non-vertebral fractures over 2 years, with a number needed to treat (NNT) of 72 [95% confidence interval (CI) 61–99] and 24 (95% CI 19–37), respectively, in postmenopausal women. Despite such clear benefits, low compliance (the extent to which the patient acts in accordance with the prescribed interval and dose as well as the dosing regimen) and failure of persistence (the proportion of patients continuing with therapy), particularly with bisphosphonate medications, have been identified as major problems. A recent systematic review of retrospective data from administrative databases demonstrated a wide variation in persistence, ranging from 17.9% to 78.0% at 1 year, and a mean medication possession ratio (number of days' supply of medication divided by the length of follow-up) varying from 0.59% to 0.81%. A proportion of patients prescribed bisphosphonates will never pick up their prescription due to a lack of acceptance of the need for treatment, and of those who discontinue bisphosphonate therapy or fail to take it as advised, many do so due to complex administration instructions, which must be followed to prevent upper gastrointestinal irritation and improve bioavailability. Other reasons proposed for such poor adherence include troublesome gastrointestinal effects, the overall pill burden (as patients are required to take concurrent calcium and vitamin D and may be taking medications for other illnesses) forgetfulness, lack of obvious benefit of the medication and disillusionment due to fractures or persistent pain despite treatment. Poor adherence with anti-resorptive medication has widespread consequences, both for the individual and in terms of resulting medical costs. Patients who persist with and adhere to bisphosphonate therapy are known to have significantly lower rates of vertebral and non-vertebral fractures compared to those who do not take the medication as prescribed. A variety of interventions to improve patient adherence with anti-resorptives have been investigated. However, these interventions are not without cost, and if applied to all patients prescribed, oral anti-resorptive medication would result in significant health care burden. To justify these costs, the incremental benefit in adherence from these various interventions needs to be quantified and at present is not known. In this systematic review, we aimed to identify RCTs assessing interventions intended to improve persistence or adherence with anti-resorptive therapy in those at high risk of clinical fracture, and where possible, to pool data to determine the efficacy of the interventions.

Methods

Literature search
We searched Ovid versions of MEDLINE (1950–2009), EMBASE (1980–2009) and CINAHL (1982–2009), as well as the Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Register, Cochrane Library issue 2, 2009 (search date 5 May 2009). High-sensitivity filters developed by the Health Information Research Unit at McMaster University were used to limit our searches to RCTs where possible. All registers on Current Controlled Trials, http://www.controlled-trials, were searched to locate ongoing studies. In addition, we hand searched the reference lists of retrieved full-text papers.

The search strategy was based on two criteria, defining the population and outcome required, and can be viewed in Appendix 1. The population was defined using bisphosphonates as a broad term, as well as specific bisphosphonates (alendronate, etidronate, clodronic acid, risedronate, ibandronate and pamidronate), all types of osteoporosis including osteopenia and all types of fracture including hip, wrist, vertebral and non-vertebral. The outcomes were defined using the terms persistence, non-persistence, adherence, non-adherence, compliance, non-compliance, concordance, non-concordance, cooperation, dropouts and treatment refusal.

Selection
We included RCTs studying persistence or adherence with anti-resorptive medication in women with high risk of clinical fracture comparing interventions with standard care. Studies were included only if the two groups were treated equally except for the provision of an intervention aiming to improve medication adherence to one group. Our primary outcome of interest was the proportion of patients who persisted with anti-resorptive medication. We also considered different measures of adherence as secondary outcomes, such as rate of fragility fracture, BMD measured by dual energy X-ray absorptiometry (DEXA) scan and measurement of bone turnover markers.

Trials evaluating the effectiveness of treatment with hormone replacement therapy, strontium ranelate or active vitamin D were excluded as these agents are no longer recommended as first-line therapy in osteoporosis. Studies with non-clinical outcomes, such as patient level of knowledge of osteoporosis, were excluded.

Two reviewers (HJW and SSB) independently assessed articles and abstracts and each put forward articles for inclusion, which fulfilled the inclusion criteria. Data were extracted by one reviewer (HJW), with the second reviewer (SSB) checking and verifying each data item. Relevant information was summarized into a predefined grid (study reference, study period, study population, interventions examined, duration of follow-up, quality score and method of analysis and outcome(s) measured) and a summary of key results was compiled and then evaluated. Non-English language publications were not excluded.
Data analysis
To evaluate the trials identified, we used a scale of trial quality developed by Jadad et al. for randomized trials in pain research. Trials were designated a score from 0 to 5, taking into account randomization (1 point for randomization and 1 point for description of appropriate method of randomization, including allocation concealment), blinding (1 point if blinded and 1 point for description of blinding) and loss to follow-up (1 point if loss to follow-up reported adequately). However, as blinding participating physicians with an educational or motivational intervention are impractical, we expected all trials identified to score 0 for blinding, giving a maximum score of 3. The characteristics of the interventions were tabulated and the summarized information used to determine the broad categories used for this analysis.

We used Review Manager Version 5.0.22 for the statistical analysis and calculated relative risks (RRs) and 95% CIs as summary statistics (as our primary outcome was binary). We used a random-effects model with the Mantel–Haenszel method to calculate the pooled RR. We examined heterogeneity between trials using the I^2 statistic.16 Where the trial design included comparison of two intervention groups with a control group, for the purposes of pooling the control group was divided into two (both the events and the total sample size) to provide separate control groups for each of the two interventions reported. If enough trials were available for inclusion, we aimed to examine publication bias by constructing a funnel plot of precision [standard error of the log odds ratio (OR)] against RRs for the primary outcome. We did a post hoc subgroup analysis according to the type of intervention given (biomarker or motivational). NNTs were calculated based on the pooled RR reduction and the event rate in the control group of the largest trial.

Results
Our search identified 1755 published papers (410 from MEDLINE, 754 from EMBASE, 55 from CINAHL and 536 from the Cochrane Library Databases), and after removal of duplicates, 1158 potentially relevant records were identified (Fig. 1). Only 18 abstracts were identified as RCTs evaluating educational or motivational interventions, which could potentially affect persistence with anti-resorptive therapy. All of these articles were in English language. After obtaining and reviewing the full reports, 12 further publications were excluded (Fig. 1).

Six publications were identified as reporting RCTs assessing biomarker or motivational interventions intending to improve adherence with anti-resorptive medication, four reported persistence with medication17–20 and two reported only data on adherence defined as the extent to which patient’s behaviour coincided with the clinical prescription.21,22 Table 1 summarizes the characteristics of these trials. On the basis of an assessment of the interventions used in the trials, they were broadly divided into those involving biomarker monitoring with feedback to patients17,19 and other motivational interventions, including educational leaflets,21 nurse-led education,17,20 decision aids22 and telephone reminders.18 (Table 2).

The trials identified had marked heterogeneity in their outcomes (Table 1). Although all of the identified trials included only postmenopausal women, a range of risk factors for increased fracture risk were identified, including low BMD (osteoporosis or osteopenia) using DEXA or the Simple Calculated Osteoporosis Risk Estimation (SCORE) questionnaire, based on age, weight, race, fracture history, rheumatoid arthritis history and oestrogen use.23 The six trials identified recruited patients in a range of settings, including primary and secondary care. One of the trials identified was multinational, including data from 171 centres in 21 countries across Australia, North and South America, Europe and Africa.18 The other trials identified ranged from multi-centre trials to those conducted in a single primary care practice.22 The quality of the six trials, as defined by both the power of the trial and the Jadad score, also varied considerably. The number of patients randomized in the trials ranged from 2382 patients to 33 patients, and values of the Jadad score varied between 3 and 0.22

Interventions indentified included two examples of biomarker feedback, in which patients had periodic blood tests for urinary N-telopeptide of type 1 collagen (uNTX), a marker of bone resorption, and were subsequently presented with a graphical representation and standardized interpretation of the results by a nurse.17,19 One of these trials also included a second intervention group, receiving a nurse interview alone, without measurement of uNTX.17 The other trials identified utilized motivational interventions, including a variety of educational methods ranging from simple leaflets21 and nurse-led education to more complex decision aids aiming to encourage patients to make informed decisions about their treatment options.22 One further trial involved a change in drug regimen and anti-resorptive used, as well as a telephone reminder system from trained nurses for patients in the group receiving medication less frequently.18

Several different anti-resorptives were studied. Four of the trials focused on patients prescribed bisphosphonates, one focused on patients prescribed risedronate,19 one compared alendronate with ibandronate18 and two included patients prescribed any type of bisphosphonate.20,22 Two further trials focused on raloxifene.17,21
Methods of measuring medication usage also varied among the trials identified. Two trials used electronic monitoring devices, which recorded the date and frequency the prescription bottle was opened. A further two trials measured medication use based on the proportion of prescriptions for anti-resorptive medications dispensed to patients from their pharmacy. Self-reported adherence and persistence were also measured in several trials, either through a telephone interview assessing initiation and persistence of therapy at trial conclusion or through a formal questionnaire, such as the Medication Adherence Report Scale (MARS) and the Morisky Test, which uses four questions to categorize patients into low, moderate or high adherence.

**Primary outcome**
Four of the six trials identified reported the percentage of patients persisting with therapy at trial conclusion, three trials after 1 year and one after 6 months. Pooled data from these four trials are shown in Figure 2. The combined data from all four trials indicated that these biomarker feedback and motivational interventions led to a relative reduction in non-persistence of 22% (pooled RR: 0.78, 95% CI 0.65–0.95, \(P\)-value = 0.01) in the intervention compared to the control group. However, two trials accounted for >90% of the weight of these results, and one trial demonstrated a slight increase in non-persistence in the intervention arm. The degree of heterogeneity between the trials, \(I^2 = 47\%\), was non-significant (test for homogeneity \(P = 0.11\)).

As the six trials identified varied in the interventions evaluated, we have categorized them according to biomarker feedback or motivational interventions (Table 2). The design of one of the trials compared two intervention groups (nurse monitoring and marker monitoring) with a control group. Pooled results from the two trials using uNTX measurements for monitoring (including a subgroup of one of the trials) show
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Duration Setting*</th>
<th>Age (years)</th>
<th>Risk factor for increased fracture risk</th>
<th>Use of HRT</th>
<th>Primary or secondary preventionb</th>
<th>Anti-resorptive used</th>
<th>Intervention (n)</th>
<th>Comparator (n)</th>
<th>Total randomized</th>
<th>Quality scorec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clowes et al.17, comparison 1. Nurse monitoring versus control</td>
<td>Single centre RCT</td>
<td>1 year</td>
<td>1 and 2 50–80</td>
<td>Osteopenia diagnosed by DEXA scan</td>
<td>Excluded if taken in past 6 months</td>
<td>Unclear</td>
<td>Oral raloxifene 60 mg/day</td>
<td>Nurse monitoring at 12, 24 and 36 weeks (25)</td>
<td>No monitoring (25)</td>
<td>75</td>
<td>2 0 1</td>
</tr>
<tr>
<td>Clowes et al.17; comparison 2. Marker-monitoring versus control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooper et al.18</td>
<td>Multi-centre RCT</td>
<td>6 months 1</td>
<td>67.8 (mean)</td>
<td>Osteoporosis judged by a GP</td>
<td>Not specified</td>
<td>Unclear</td>
<td>Oral ibandronate 150 mg once monthly (intervention) Oral alendronate 70 mg once weekly (comparator) Oral risedronate 5 mg/day</td>
<td>Marker monitoring at 13 and 25 weeks (1228)</td>
<td>No reinforcement (1154)</td>
<td>1103</td>
<td>2 0 0</td>
</tr>
<tr>
<td>Delmas et al.19</td>
<td>Multinational cluster RCT</td>
<td>1 year</td>
<td>Unclear 65–80</td>
<td>Osteoporosis diagnosed by DEXA scan or osteopenia with history of fragility fracture aged &lt;45 years</td>
<td>Excluded only if given specifically for osteoporosis</td>
<td>1 and 2</td>
<td>Oral risedronate 5 mg/day</td>
<td>Marker monitoring at 13 and 25 weeks (1228)</td>
<td>No reinforcement (1154)</td>
<td>2382</td>
<td>1 0 1</td>
</tr>
<tr>
<td>Guilera et al.21</td>
<td>Multi-centre RCT</td>
<td>1 year</td>
<td>1 &gt;50</td>
<td>Osteoporosis diagnosed by DEXA scan</td>
<td>Not specified</td>
<td>Unclear</td>
<td>Oral raloxifene 60 mg/day</td>
<td>Educational leaflet about osteoporosis plus 15-minute leaflet review with attending physician (366)</td>
<td>Current information only (379)</td>
<td>745</td>
<td>1 0 1</td>
</tr>
<tr>
<td>Oakley and Walley22</td>
<td>Single centre RCT</td>
<td>4 months 1</td>
<td>61–90</td>
<td>Osteoporosis diagnosed by DEXA scan or radiological evidence of fragility fracture aged &gt;65 years</td>
<td>Not specified</td>
<td>1 and 2</td>
<td>Any bisphosphonate</td>
<td>Workshop followed by decision aid for home use before GP appointment (16)</td>
<td>Normal care (17)</td>
<td>33</td>
<td>0 0 0</td>
</tr>
<tr>
<td>Schousboe et al.20</td>
<td>Single centre RCT</td>
<td>1 year</td>
<td>1 50+</td>
<td>Low BMD suggested by SCORE Questionnaire</td>
<td>Excluded if currently on HRT</td>
<td>Unclear</td>
<td>Any bisphosphonate</td>
<td>Nurse education (158)</td>
<td>Brochure on osteoporosis plus usual care (152)</td>
<td>310</td>
<td>0 0 1</td>
</tr>
</tbody>
</table>

---

*a1 = primary care; 2 = secondary care.

*b1 = no previous fracture; 2 = previous fracture.

cBased on Jadad et al.15, R = randomization, B = blinding, FU = loss to follow-up and HRT = hormone replacement therapy.
<table>
<thead>
<tr>
<th>Intervention type</th>
<th>Paper</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker feedback</td>
<td>Clowes et al.</td>
<td>Patients taking raloxifene 60 mg/day were randomized to either:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● No feedback given.</td>
</tr>
<tr>
<td></td>
<td>Delmas et al.</td>
<td>Patients taking risedronate 5 mg/day were randomized to either:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● No feedback given.</td>
</tr>
<tr>
<td>Motivational educational leaflet</td>
<td>Guilera et al.</td>
<td>Patients taking raloxifene 60 mg/day were randomized to either:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Feedback on changes in bone turnover markers (uNTX) given on two occasions at 13 and 25 weeks.</td>
</tr>
<tr>
<td>Nurse-led</td>
<td>Schousboe et al.</td>
<td>Following a DEXA scan, patients were stratified into three groups according to BMD. They were then randomized either:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● nurse education involving a 15-minute consultation with a nurse, discussing their preliminary BMD results, fracture risk and lifestyle advice. Those with osteoporosis were advised that anti-resorptive treatment should be considered. They also received a leaflet about osteoporosis and increasing their calcium and vitamin D intake and telephone consultations at 3, 6 and 9 months advising on medication use, lifestyle and follow-up.</td>
</tr>
<tr>
<td>Nurse-led</td>
<td>Clowes et al.</td>
<td>Patients taking raloxifene 60 mg/day were randomized to either:</td>
</tr>
<tr>
<td></td>
<td>nurse</td>
<td>● No feedback given.</td>
</tr>
<tr>
<td>Decision Aid</td>
<td>Oakley and Walley</td>
<td>Women already being prescribed bisphosphonates were randomized to either:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Attend a workshop and receive an information booklet, audiocassette and worksheet to be used before an appointment with their doctor, aiming to allow them to consider the advantages and disadvantages of their prescribed medication and to decide whether they would like to be involved in making decisions about their therapy</td>
</tr>
<tr>
<td>Telephone reminders</td>
<td>Cooper et al.</td>
<td>Patients were randomized to receive either:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Once weekly alendronate (70 mg) with no added support.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Once monthly ibandronate (150 mg) with a Patient Support Programme available to all UK patients receiving this drug regime (initial telephone call, welcome pack with information about osteoporosis and a telephone call from a nurse 1–3 days before each scheduled monthly dose).</td>
</tr>
</tbody>
</table>
a smaller reduction in the proportion of people failing to persist RR 0.86 (95% CI 0.74–1.01) with no heterogeneity ($I^2 = 0\%$, $P = 0.57$). On combining the results of the three trials, which did not involve biomarker measurement, a larger reduction in non-persistence was obtained RR 0.76 (95% CI 0.50–1.15), with reduced heterogeneity ($I^2 = 38\%$, $P = 0.20$). The effect for both subgroups was not statistically significant.

Results of within trial subgroup analyses
Two of the trials evaluated also undertook a subgroup analysis, assessing the effect of different reinforcement messages (based on good, moderate or poor uNTX changes) on persistence and adherence. One trial found that after reinforcement, the message given significantly affected the likelihood of non-persistence. Reinforcement based on a positive response, defined as more than a 30% decrease in uNTX, resulted in a 29% improvement in persistence compared to no reinforcement (HR 0.71, 95% CI 0.53–0.95, $P = 0.020$). Reinforcement based on a stable response, with an uNTX change of −30% to +30%, resulted in a similar likelihood of discontinuation compared to no reinforcement (HR 1.02, 95% CI 0.74–1.40, $P = 0.920$). In contrast, reinforcement based on a poor response, defined as more than a 30% increase in uNTX, resulted in patients being more than twice as likely to discontinue treatment compared to no reinforcement (HR 2.22, 95% CI 1.27–3.89, $P = 0.0005$).

Similarly, in a post hoc analysis of a second trial, subjects informed that they had a positive treatment response increased adherence by 92% compared to no monitoring ($P = 0.04$) and by 140% compared to those who were given a negative message due to poor response to therapy ($P = 0.03$). However, non-adherence often preceded the negative message in those with poor treatment response and that in fact 81% in the non-responder group who were adherent at 12 weeks were still adherent at 1 year after negative reinforcement.

Two trials also included analysis of persistence data over time. Both studies demonstrated that the difference in persistence rates between intervention and comparator groups increased with time, with one trial showing the impact starting to appear after 30 days and the second trial demonstrating a longer delay of ~200 days.

Secondary outcomes
Secondary outcomes of interest are summarized in Table 3. One trial reported adherence (percentage tablets taken over 1 year) and percentage of patients with good cumulative adherence over 1 year (defined as taking >75% tablets), recording data using electronic monitoring, in patients receiving feedback from a nurse with or without measurement of the biomarker uNTX. This trial demonstrated a trend towards greater cumulative adherence to therapy in both nurse-monitored ($P = 0.05$) and marker-monitored groups ($P = 0.15$), and the difference between the two intervention groups was not significant in terms of cumulative adherence.

A second trial, which reported the percentage of patients with high self-reported adherence among those receiving an educational leaflet compared to those receiving normal care, showed lower adherence in the
intervention group compared to control, although this was not statistically significant. A further trial measured percentage of medication use by each patient by monitoring bisphosphonate prescription requests, as well as reporting self-assessed compliance using the MARS. However, only median and ranges for adherence after 4 months in the intervention and control groups were reported, and therefore, the data could not be pooled. In the intervention group, the median final adherence measured by prescription requests was 100%, with a range of 50–100%, and in the comparator group, the median final adherence was 100% with a range of 0–100%. Self-reported adherence using MARS was reported to be 98% in the intervention and 97% in the control groups throughout the trial.

We identified one trial, which reported both vertebral fractures (identified by lateral thoracic and lumbar spine radiographs) and non-vertebral fractures after 1 year. In the reinforcement group, 8 patients (1.2%) had 9 new vertebral fractures at 1 year compared to 17 patients (2.7%) with 18 new vertebral fractures in the group without reinforcement. (OR 0.4, 95% CI 0.2–1.0). The incidence of new non-vertebral fractures (fractures of the clavicle, hip, humerus, leg, pelvis or wrist not associated with a fall) was a total of 22 (1.85%) in the reinforcement group compared to 24 (2.16%) in the group without reinforcement (OR 0.9, 95% CI 0.5–1.5).

One of the papers identified described the measurement of both BMD change and uNTX change after 1 year of treatment, and both the percentage change in hip BMD and the uNTX were significantly correlated with patient adherence to therapy.

### Discussion

#### Summary of main findings

This systematic review provides a comprehensive assessment of randomized trials of educational and motivational interventions to improve adherence with anti-resorptive therapy. The combined data from four of the six trials identified suggests that such interventions lead to a relative reduction in non-persistence of 22%, equivalent to an absolute reduction of 5% in non-persistence (based on the proportion of non-persistence in the control group of the largest trial); a benefit of one person persisting with therapy for every 20 receiving an intervention. Two of the trials identified also reported results of subanalyses, assessing the effect of different reinforcement messages on adherence. Although this data could not be pooled, both studies demonstrated that those subjects informed that they had a positive treatment response (based on bone turnover marker measurements) and had high adherence rates, whereas those given a negative message were more likely to discontinue therapy. The reporting of biomarkers findings to patients may identify non-compliance but does not, in itself, improve compliance.

#### Strengths and weaknesses

By including only data from RCTs, this review has the advantage of reducing the potential bias introduced by the use of retrospective data. However, our study is limited by several important factors. Although pooled data suggest a positive impact of educational and motivational interventions in comparison with
normal care, individual trials did not demonstrate consistent effects. The results of this review are dominated by two large studies which account for >90% of the weight in the pooled estimate and the majority of the participants (3386/3497); however, a single different trial demonstrated a non-significant increase in non-persistence.

The conclusions of our review are limited by the great degree of clinical heterogeneity between the trials identified. The population of patients recruited into the trials was diverse and the interventions ranged from educational leaflets to feedback based on biomarker measurements. Methods of measuring medication usage also differed and included subjective self-report questionnaires as well as more objective measures using electronic monitoring devices, and there was no unified outcome measure of persistence or adherence. Given the poor bioavailability of oral bisphosphonates, even minor deviations from the administration regime may lead to a significant reduction in bioavailability, suggesting that in addition to monitoring persistence, monitoring of biomarkers of treatment effect may be required.

Our systematic review is further limited by the quality of the trials included, which was often low, with some small trials with as few as 33 patients and trial quality scores ranging from 0 to 3. The method of individual randomization used was not reported in two of the trials and another trial randomized at the level of osteoporosis treatment centres. Additional limitations of the evidence include the limited capacity of RCTs, to establish external validity, and potential for results to be affected by detection bias.

Several different anti-resorptive treatments were studied, including bisphosphonates (alendronate, ibandronate and risedronate) and raloxifene. Differences between trial results may also arise from differences in dosing administration [30 minutes before breakfast (alendronate and risedronate), after at least 6 hours overnight fast and then 1 hour before breakfast (ibandronate) or at any time (raloxifene)], dose frequency (daily, weekly or monthly) and adverse effect profile differs markedly between anti-resorptive agents.

**Explanation of our results**
As part of our analysis, we grouped the interventions studied into biomarker and motivational categories, allowing comparison of the different types of interventions studied. This post hoc subgroup analysis demonstrated that those trials involving biomarker feedback resulted in a smaller reduction in the proportion of people failing to persist (RR 0.87) than the motivational interventions studied (RR 0.76). This may be explained by the variable reinforcement messages given to patients following biomarker measurement, depending on their results. In contrast, trials in which all patients in the intervention group receive positive feedback, in the form of nurse-led support, leaflets and telephone reminders, the magnitude of the change in persistence appears to be greater. Further analysis would be desirable, including grouping by intervention characteristics, such as duration and intensity, but power would be limited by the small number of trials identified.

**Comparison with other studies**
The rates of non-persistence reported in this review are lower than those reported in a recent survey of cohort studies of persistence and adherence with bisphosphonates. In the data previously published, levels of non-persistence varied between 22.0% and 82.1% at 1 year, whereas the rates reported in the six trials we identified range between 23.0% and 61.4% in the comparator groups. The low rates of non-adherence reported may be accounted for by selection bias in recruiting patients for RCTs compared to the use of retrospective data from administrative databases by Cramer et al. The studies reported in our review suggest that educational and motivational interventions have a positive effect, even on a population already self-selected to have good adherence, so we may infer that these effects may be more significant when interventions are applied to the general population.

Similar interventions aiming to increase adherence have been investigated across a wide spectrum of diseases. A systematic review has identified 37 RCTs investigating methods of improving adherence with medications in the treatment of chronic illnesses, categorizing the interventions as informational, family and social or combined. The results of the interventions studied varied greatly, both in terms of adherence and in terms of clinical outcomes. Fifty per cent of the informational interventions led to a significant increase in adherence, although only 33% trials demonstrated improvement in clinical outcomes. Within the motivational category, all three trials of dosage simplification led to improved adherence, but with mixed effect on clinical outcomes, and all three studies of monitoring and feedback showed significant improvement in adherence. Five of the 13 studies combining informational and motivational components led to improvements in adherence, although none of these studies showed significant improvement in clinical parameters, and no trials were identified that investigated family or social interventions alone.

**Implications for research and practice**
To gain better insight into the most effective educational and motivational interventions in improving adherence with bisphosphonates, further research is needed. Our systematic review of the current literature has identified only six relevant RCTs, which are heterogeneous and of variable quality. Future trials should include standardized measures of compliance.
and persistence outcomes, such as electronic monitoring devices on prescription bottles, should also be used more consistently, in place of self-report questionnaires, which are likely to introduce considerable bias. Trials should focus on in clinical areas where there is most clinical need, i.e., those with osteoporosis, recent fracture, the elderly and those approved therapies. Similar time points for assessing the outcome should be used as anti-fracture treatments are continued for 5–10 years. Interventions studied also need to be feasible when applied to clinical practice on a wider scale, both in terms of cost and in terms of time demands placed on medical practitioners in the community. Notably, our systematic review did not identify any health economic studies, and the economic impact of such interventions should be considered in future research. Despite its limitations, the results of this systematic review have important implications for clinical practice. Our pooled analysis suggests that both educational and motivational interventions may improve patient adherence and continuation with bisphosphonate therapy, with consequent improvements in BMD and reduced fracture rates in women at high risk of fragility fracture. The intervention associated with the greatest magnitude of effect is less frequent dosing (monthly compared to weekly) combined with a regular newsletter and telephone support from the Patient Support Programme. This programme is available to all patients taking monthly ibandronate in the UK; however, the proportion of persistence was only 56.6% in the intervention arm and it is not known which component of the intervention has greatest benefit. Furthermore, 3-monthly contact by trained nurses for all patients on anti-resorptive therapy has considerable resource implications. This systematic review has also identified two trials that demonstrate a positive effect of monitoring individual responses to treatment using bone turnover markers (uNTX in both cases) and using results to encourage patients to continue with anti-resorptive therapy. Although patient responses to reinforcement varied according to the message delivered, overall the evidence presented suggests that measurement of such markers and feedback to patients about their response may be beneficial in promoting adherence. Simpler interventions, such as the provision of an educational leaflet, have also been identified in this review of the literature, although the study identified only documented self-reported adherence, introducing bias and in fact demonstrated a negative effect of the intervention. Further research is needed to provide stronger evidence for the effectiveness of this simple and cheap educational intervention.

Conclusions
In summary, the pooled data from the identified trials suggest a relative reduction in non-persistence of only 22% resulting from biomarker-based feedback and motivational interventions in postmenopausal women taking anti-resorptive medications. However, the conclusions that can be drawn from this review are limited by the degree of clinical heterogeneity between the trials identified and the dominance of two large trials in the analysis. Further RCTs are needed to clarify which interventions, which have the greatest effect on patient adherence and how they may best be implemented as current evidence-based interventions are not effective in 78% of non-compliant patients.

Declarations
Funding: none.
Ethical approval: none.
Conflicts of interest: none.

References
Appendix 1

MEDLINE® search strategy used to identify publications for assessment in the systematic review assessing the effectiveness of educational and motivational interventions to improve persistence with anti-resorptive therapy in women at high risk of clinical fracture

1. “fractures, bone”[Mesh] OR (“osteoporosis”[Mesh] OR “osteoporosis, postmenopausal”[Mesh]) OR “bone demineralization, pathologic”[Mesh] OR osteopeni* OR diphosphonates”[Mesh]) OR (“etidronic acid”[Mesh] OR “clodronic acid”[Mesh] OR “pamidronate” [Substance Name]) OR (“risedronic acid” [Substance Name] OR “ibandronic acid” [Substance Name]) OR (“alendronate”[Mesh] OR “etidronic acid”[Mesh]) OR bisphosphonate*

2. 1 OR 2

3. 3 AND 4

4. medication adherence”[Mesh] OR “patient compliance”[Mesh] OR “guideline adherence”[Mesh]) OR “patient dropouts”[Mesh]) OR “treatment refusal”[Mesh] OR persisten* or non-persisten* or compliant* or non-compliant* or adheren* or non-adheren* or concordan* or non-concordan* or dropout* or drop-out* or cooperat* or co-operat* or discontinu*

5. 3 AND 4