VALUE IN HEALTH 14 (2011) 571–581

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# A Meta-Analysis of Osteoporotic Fracture Risk with Medication Nonadherence

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ABSTRACT

**Objectives:** Therapy for osteoporosis reduces the risk of fracture in clinical trials; real-world adherence to therapy is suboptimal and may reduce the effectiveness of intervention. The objective was to assess the fracture risk among patients nonadherent versus adherent to therapy for osteoporosis. **Methods:** Medline, Embase, and CINAHL were searched for English-language publications of observational studies (January 1998–February 2009). Proceedings from two recent meetings of five relevant conferences were hand searched. Prospective and retrospective observational studies of patients with osteoporosis receiving bisphosphonates, parathyroid hormone, or selective estrogen receptor modulators denosumab were included. Studies were required to consider both fracture risk and adherence (compliance and/or persistence); any definition of adherence/fracture was acceptable. Data were analyzed using pooled comparisons of the odds and hazard ratios of fracture in noncompliance versus compliance and nonpersistence versus persistence. Sensitivity analyses were conducted to determine the effect of clinical heterogeneity on the results. **Results:** Twenty-seven citations were identified, the majority of which were retrospective database analyses considering the effect of adherence to bisphosphonate therapy on fracture at any skeletal site. The absolute frequency of fracture ranged from 6% to 38% with noncompliance and from 5% to 19% with nonpersistence (104–159 weeks). Meta-analysis indicates that fracture risk increases by approximately 30% with noncompliance (odds ratio [95% confidence interval] 1.29 [1.22–1.38]; hazard ratio 1.28 [1.18–1.38]) and by 30% to 40% with nonpersistence (odds ratio 1.40 [1.29–1.52]; hazard ratio 1.32 [1.23–1.42]). **Conclusions:** Poor medication adherence is associated with a significantly increased risk of fracture versus optimal adherence. Improving medication adherence in patients with osteoporosis may lead to a greater reduction in fracture.

*Keywords:* adherence, compliance, fracture, meta-analysis, osteoporosis.



## Introduction

Osteoporosis, a skeletal disorder characterized by reductions in bone mass (estimated by measurement of bone mineral density) and bone quality, is associated with an increased frequency of fractures. Osteoporosis-related fractures represent a significant burden on society in terms of severe morbidity, increased mortality, and high health care expenditures [1]. In the United States alone there are as many as 8 million women and 2 million men with osteoporosis [1], which is estimated to result in at least 1.5 million fractures per year [2] costing approximately $19 billion [3]. It is predicted that this will increase to more than 3 million fractures at a cost of approximately $25.3 billion by 2025 [4]. The high incidence of fracture within the population with osteoporosis is therefore an important focus for preventative action. The 2004 *US Surgeon General's Report on Bone Health and Osteoporosis* [5] notes that preventative action is needed to reduce fractures experienced by older individuals to reduce both the human and economic costs of this public health problem.

The current pharmacologic management of osteoporosis in the United States includes the use of bisphosphonates, selective estrogen receptor modulators denosumab, intranasal calcitonin, and the anabolic agent teriparatide (human recombinant parathyroid hormone 1–34). Hormone therapy is approved for the prevention of osteoporosis. These drug treatments have been shown to increase bone mass and significantly reduce the risk of fracture in clinical trials [6–11]. However, real-world adherence, comprising compliance ("the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [12]) and persistence ("the duration of time from initiation to discontinuation of therapy" [12]), associated with such prescribed medication is suboptimal and may reduce the effectiveness of these interventions. Indeed, it is estimated that between one-third and one-half of patients do not take their medication as directed [13].

Poor adherence has been associated with increased fracture risk and increased frequency of hospitalization and other resource use in comparison with optimal adherence [14–16]. In a qualitative review of the literature, Siris et at. [17] conclude that an increased risk of fracture with poor adherence to osteoporosis medication can be observed across a range of studies investigating a variety of medications and fracture locations. Although the definitions of adherence were varied, the most common measure of compliance reported was the Medication Possession Ratio (MPR), defined as the sum of the

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1098-3015/$36.00 – see front matter 

doi:10.1016/j.jval.2010.11.010

days' supply of medication divided by the number of days between the first fill and the last refill plus the days' supply of the last refill [18], while the most frequently used measure of persistence was the absence of a prescription refill over a duration exceeding 30 days.

Recently, a systematic review and meta-analysis has been published that measures the degree of compliance and persistence with bisphosphonate therapy [19]. The authors of that publication also present a quantitative analysis of the effects of compliance to bisphosphonate therapy on the risk of fracture. Although it appears that their systematic review was not designed specifically to identify studies presenting data on the risk of fracture with noncompliance, the analysis of the included studies reporting such data suggests that there is an increase in fracture risk with noncompliance compared to compliance. However, no systematic review of the literature conducted to date has been specifically designed to quantitatively analyze the increase in fracture risk associated with nonadherence (noncompliance and/or nonpersistence) versus optimal adherence (compliance and/or persistence) through meta-analysis. Specifically, the quantitative increase in fracture risk with nonpersistence compared to persistence has not been addressed.

Therefore, our systematic review was designed to assess the magnitude of fracture risk in a nonadherent compared to an adherent osteoporosis patient population, using meta-analytic techniques. It was hypothesized that individuals with osteoporosis who were nonadherent to their prescribed medication would experience a greater incidence of fracture than patients who were adherent to therapy. A secondary aim was to determine the predictors of adherence, as well as the risk of hospitalization and the change in direct costs associated with fracture in the nonadherent versus adherent osteoporosis population, as identified within the included studies.

## Methods

### Data sources

Medline, Embase, and CINAHL were searched from January 1, 1998, to February 17, 2009, for English-language publications of observational studies. Standard filters developed by the Scottish Intercollegiate Guidance Network [20] were used to search for study design (observational study), while clinical keywords and medical subject headings were used to search for disease ("osteoporosis") and outcome ("adherence" and "fracture"). An example search strategy is presented as supplementary material; all further search strategies used are available upon request. In addition, the proceedings from the two most recent meetings of five relevant symposia were hand-searched (European Symposium on Calcified Tissue International 2007 and 2008; International Symposium on Osteoporosis 2007 and 2008; European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis 2008 and 2009; American Society for Bone and Mineral Research 2007 and 2008; International Bone and Mineral Society Scientific Meeting 2007 and 2009). The conference proceedings from the International Osteoporosis Foundation World Osteoporosis Congress were not searched due to the cancellation of the 2008 congress. Finally, the bibliographies of all included studies were reviewed to identify any studies not retrieved through the database search. No efforts were made to contact authors.

### Study eligibility

Studies with an observational design (case-control, cohort, or cross-sectional), both retrospective and prospective, and published in English from January 1998 to February 2009 were included in the review. Studies were not excluded on the basis of follow-up duration. Given the rapidly evolving treatment options for patients with osteoporosis, studies published before 1998 were considered unlikely to contain information relevant to the current clinical situation. Similarly, randomized controlled trials are assumed to not accurately reflect real-world clinical practice and so were not included in the review.

The patients of interest were those with evidence of osteoporosis (as assessed by the individual study investigators; for example, patients identified through the use of osteoporosis-related ICD-9 or ICD-10 codes) and treatment with a qualifying osteoporosis medication (bisphosphonate, parathyroid hormone, or selective estrogen receptor modulators). The identified studies were required to consider both fracture risk and adherence to be included. Any clinical definition of compliance/persistence (e.g., MPR, treatment refill gap $>$ 30 days, but not self-reported adherence) and fracture (e.g., osteoporosis-related and identified using ICD-9 or ICD-10 codes or through radiological documentation, but not self-reported fracture) used by the authors was acceptable for inclusion into the systematic review; stricter criteria were used to determine inclusion into the pooled quantitative analyses (see below).

The included population was originally restricted to female post-menopausal osteoporosis (PMO) patients aged 45 years and older; a protocol amendment expanded this population to include studies of both male and female patients of any age receiving therapy with an osteoporosis medication. The planned PMO cohort analysis thus became a subgroup analysis secondary to the main research question. The a priori protocol is available upon request.

### Study selection

Bibliographic details and abstracts of all citations detected by the literature search were downloaded into the Heron Systematic Review Database, a bespoke, SQL-based Internet database. A team of reviewers—information scientists specializing in evidence-based medicine—independently determined the eligibility of each publication by applying the defined set of selection criteria (see above). Two different reviewers considered each publication, with discrepancies resolved by a third reviewer. Citations were first screened based on the abstract supplied with each citation. Full-text copies of all references that might meet the eligibility criteria were ordered alongside those where it was not possible to exclude or include based on the abstract. The eligibility criteria were applied to the full-text citations in a second pass of the studies.

### Data extraction

Two reviewers extracted data from eligible publications in parallel; a third reviewer checked the resulting extractions and resolved any discrepancies through team discussion. Only one extraction dataset per study was compiled from all publications relating to that study so as to avoid the error of double-counting patients in subsequent analyses. Data extracted included study design; patient population characteristics; fracture rate by level of adherence; and odds, hazard, and risk ratio data relating to fracture risk and nonadherence/adherence.

Quality scoring of observational studies is controversial because the constructs may not be valid or represent the actual quality of the study [21]. Instead, key aspects of design are important considerations in the assessment of study quality. As such, each study was subject to a qualitative critical appraisal of quality at the time of data abstraction using a project-specific assessment of quality (risk of bias). This assessment was made for each publication based upon the existence of a study question, the methodology employed to answer the study question, the appropriateness of the defined population and the data collection methods used, the clarity in the presentation of results and statistical analyses conducted (including consideration of confounding factors), and the reliability of the conclusions drawn. Although the questions are subjective, they give an overall indication of the strengths and

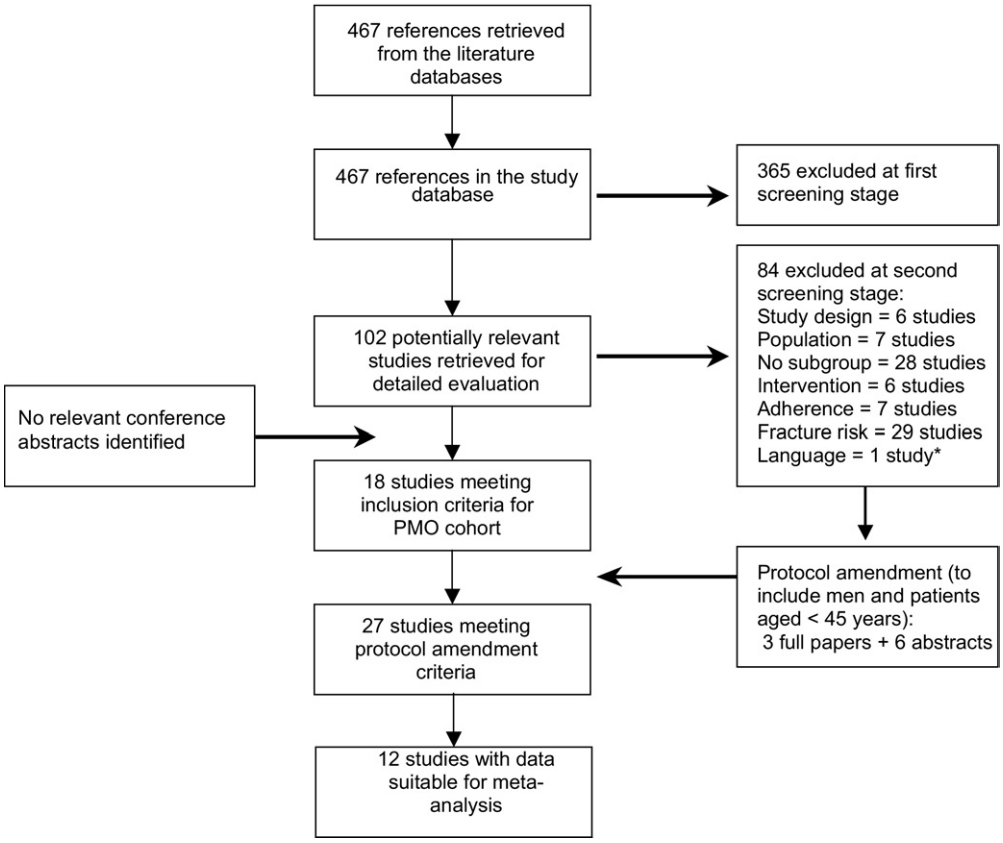



**Fig. 1 – Flow of citations through the review. Exclusion definitions included study design—randomized controlled trials, case series and case studies, systematic reviews, letters, and editorials; population—patient groups without osteoporosis; no subgroup—studies involving a mixed patient population without presentation of data by subgroup; intervention—non-pharmacological intervention or hormone replacement therapy only; adherence—no data relating to adherence (compliance and/or persistence) to medication presented; fracture risk—no data relating to fracture risk as a result of adherence/non-adherence; language—non-English language publications. Population originally involved exclusion of studies involving men and/or women aged < 45 y; this exclusion criterion was relaxed following protocol amendment.**

weaknesses within each study that can be used to determine the validity of pooling the results in a meta-analysis.

### *Quantitative data synthesis*

Pooled direct comparisons were made using conventional meta-analysis techniques. When conducting the meta-analyses, Stata statistical software was used to run the metan meta-analysis command, where the Mantel-Haenszel method is used to weight the studies [22]. The following meta-analyses were conducted:

- Odds ratio for fracture in noncompliant (MPR $<$ 80%) versus compliant (MPR $\geq$ 80%) patients;
- Hazard ratio for fracture in non-compliant (MPR $<$ 80%) versus compliant (MPR $\geq$ 80%) patients;
- Odds ratio for fracture in nonpersistent (defined as $>$30 days treatment gap) versus persistent patients ($\leq$30 days treatment gap); and
- Hazard ratio for fracture in non-persistent (defined as $>$30 days treatment gap) versus persistent patients ($\leq$30 days treatment gap).

There is no consistently applied cutoff for MPR assessment; rather there is a continuum of compliance onto which a dichotomy is applied to aid analysis. As a result, the cutoff selected varies between studies. Although this dichotomy of "compliant" versus "noncompliant" patients may be based on an arbitrary point rather than a clinically meaningful value, 80% is generally regarded to be the standard cutoff point. As such, this cutoff is used here to determine compliance versus noncompliance.

The appropriateness of pooling data was considered for each ratio (odds or hazard) based on an assessment of the data available and the comparability of the studies reporting the data. The minimum requirements for inclusion in the meta-analysis were: 1) at least two comparable studies reporting data for the odds or hazard ratio and compliance or persistence definition specified above; and 2) both the ratio (odds or hazard) and the associated 95% confidence interval (95% CI) for noncompliant/nonpersistent versus compliant/persistent cohorts for each study identified. Studies were excluded when the data were presented in such a way as to not allow calculation of the odds or hazard ratio (i.e., risk ratio) and where the data presented did not meet the standard compliance/persistence definitions selected (i.e., MPR $\geq$ 80% vs. MPR $<$ 50%). Where absolute fracture frequencies were presented for the compliant/persistent and noncompliant/nonpersistent cohorts, the odds ratio and the rate ratio (with associated 95% CIs) were calculated. The rate ratio was used as a close approximation to the hazard ratio.

A detailed description of the methodology and handling of statistical heterogeneity is provided as supplementary material. In addition to assessing statistical heterogeneity, judgments about clinical heterogeneity were qualitative and involved the evaluation of the similarities and differences between studies to assess the appropri-

**Table 1 – Selected characteristics of included studies.**

| Study | Design | Interventions received (naïve/prior users) | Studied population (% women) | Data collection period | Follow-up (wks) | Fracture type | Definition of compliance/ persistence | Compliance and/or persistence |
|---|---|---|---|---|---|---|---|---|
| Blouin 2008 [44] | Case-control (retrospective claims database) | BP (naïve) | 21,105 (100%) | 2002 to 2005 | 100 (mean) | Non-vertebral fractures | MPR ≥ 80% (vs. MPR < 80%) | Compliance |
| Briesacher 2007 [27] | Cohort (retrospective database) | BP (naïve) | 17,988 (94%) | 2000 to 2004 | 156 | Wrist, hip, or proximal humerus | MPR < 20% (vs. MPR 20%–39%, MPR 40%–59%, MPR 60%–79%, MPR 80%–100%) | Compliance |
| Caro 2004* [15] | Cohort (retrospective database) | BP, C, HRT (unclear) | 11,249 (100%) | 1996 to 2001 | 104 (mean) | All fractures | MPR ≥ 80% (vs. MPR < 80%) | Compliance |
| Cotte 2008* [23] | Case-control (retrospective database) | BP, Ral, SR (naïve) | 2468 (100%) | 2001 to 2006 | 159 (mean) | All fractures | MPR ≥80% (vs. MPR <20%, MPR 20% to <40%, MPR 40% to <60%, MPR 60% to <80%)<br>Time from initial prescription to discontinuation (permissible gap ≤ 30 d) | Compliance + persistence |
| Curtis 2008 [36] | Cohort (retrospective claims database) | BP (naïve) | 101,038 (100%) | 1998 to 2005 | 116 (mean) | All fractures | MPR ≥ 80% (vs. MPR < 50%) | Compliance |
| Curtis 2007 [abstract] [45] | Cohort (retrospective claims database) | BP (naïve) | 103,038 (NR) | — | — | Non-vertebral fractures | MPR ≥ 80% (vs. MPR < 50%) | Compliance |
| Davie 2007 [abstract] [41] | Prospective cohort | BP, HRT (naïve) | 254 (100%) | — | — | Hip and wrist fractures | 5-y compliance | Compliance |
| de Lusignan* 2006 [46] | Cross-sectional (GP records) | BP, HRT, Ca, Vit D, SERM, C (unclear) | 1286 (100%) | March 2005 to May 2005 | — | All fractures | MPR ≥ 80% (vs. MPR < 80%) | Compliance |
| Feldstein 2009 [47] | Case-control (retrospective database) | BP, C, HRT, Ral (naïve) | 3658 (100%) | 1995 to 2006 | 140 (mean) | Any closed fracture excluding face, skull, finger, or toe | MPR ≥ 80% (vs. MPR < 80%) | Compliance |
| Gallagher 2008* [35] | Cohort (retrospective database) | BP (naïve) | 44,531 (81%) | 1987 to 2006 | — | All fractures | Current use vs. past use (current use 0–6 mo after starting, 6+ mo after starting, 6–24 mo after starting, 24+ mo after starting, all vs. past use 6+ mo after discontinuation) measured via repeat prescription within 3 mo after the expected end of the previous prescription | Persistence |
| Gold 2007* [37] | Cohort (retrospective claims database) | BP (naïve) | 4769 (100%) | 1996 to 2003 | 104 | All fractures | Prescription refill gap of ≤ 30 d over 24 mo | Persistence |
| Gothe 2007* [abstract] [24] | Cohort (retrospective database) | BP (naïve) | 4451 (NR) | 2000 to 2004 | — | All fractures | MPR ≥80% (vs. MPR <80%)<br>Persistence vs. nonpersistence defined by the duration of continuous therapy (no further information) | Compliance + Persistence |
| Huybrechts 2006* [16] | Cohort (retrospective claims database) | BP, HRT (unclear) | 38,120 (100%) | 1997 to 2002 | 88 (mean) | All fractures | MPR ≥ 80% (vs. MPR < 80%) | Compliance |
| ICARO Study (Adami 2006) [48] | Cohort (retrospective) | BP, Ral, Ca, Vit D (prior users) | 880 (100%) | — | 104 (median) | Vertebral or non-vertebral fragility fractures | MPR > 75% (vs. MPR ≤ 75%) | Compliance |
| ICARO Study (Adami 2008) [49] | Cohort (prospective) | BP, Ral, Ca, Vit D (prior users) | 862 (100%) | — | 59 (mean) | Vertebral or non-vertebral fragility fractures | MPR > 75% (vs. MPR ≤ 75%) | Compliance |
| Jaglal 2007* [abstract] [50] | Cohort (retrospective database) | BP, SERM (naïve) | 74,085 (NR) | 2002 to 2004 | — | All fractures | MPR ≥ 80% (vs. MPR < 80%) and MPR ≥ 68% (vs. MPR < 68%) | Compliance |

(continued on next page)

**Table 1 (*continued*)**

| Study | Design | Interventions received (naïve/prior users) | Studied population (% women) | Data collection period | Follow-up (wks) | Fracture type | Definition of compliance/persistence | Compliance and/or persistence |
|---|---|---|---|---|---|---|---|---|
| Kun 2008 [abstract] [51] | Cohort (prospective) | BP (unclear) | 244 (98%) | 2004 to 2007 | — | All fractures | Continuation with therapy (no further information) | Persistence |
| McCombs 2004 [25] | Cohort (retrospective database) | BP, Ral, HRT (naïve) | 58,109 (99%) | 1998 to 2001 | — | Vertebral, Colles (lower arm and wrist), and hip fractures | Total days of therapy in the first year<br>Prescription refill gap of ≤ 2 wk | Compliance + Persistence |
| Penning-van Beest 2008* [42] | Cohort (retrospective database) | BP (naïve) | 8822 (100%) | 1999 to 2004 | — | All fractures | MPR ≥ 80% (vs. MPR < 80%) | Compliance |
| Perreault 2008 [52] | Case-control (retrospective database) | BP, Ral, C (unclear) | 35,853 (100%) | 1995 to 2003 | 218 (mean) | All fractures | MPR ≥ 80% for short-, intermediate-, and long-term treatment durations and MPR < 80% (vs. no treatment) | Compliance |
| Rabenda 2008 [abstract] [53] | Case-control (retrospective) | SR (unclear) | 1710 (100%) | — | 156 | Non-vertebral fractures | MPR ≥ 80% (vs. MPR <80%) | Compliance |
| Rabenda 2008* [26] | Case-control (retrospective claims database) | BP (naïve) | 54,807 (100%) | 2001 to 2004 | 40 (mean) | Hip fracture | MPR ≥ 80% (vs. MPR < 80%)<br>Time from initial prescription to discontinuation (permissible gap ≤ 5 wk) | Compliance + Persistence |
| Rietbrock 2009 [38] | Cross-sectional (GP records) | BP (naïve) | 44,531 (100%) | — | — | Hip, vertebral, radius, ulna, rib, sternum, tibia, fibula, and other, non-osteoporotic fractures | MPR > 90% (very good compliance; vs. tertiles < 90% defined as good, medium, and bad compliance) | Compliance |
| Siris 2006* [14] | Cohort (retrospective claims database) | BP (naïve) | 35,537 (100%) | 1999 to 2003 | 104 | All fractures | MPR ≥ 80% (vs. MPR < 80%)<br>Prescription refill gap of ≤ 30 d over 24 mo | Compliance + Persistence |
| van den Boogaard 2006* [39] | Case-control (retrospective database) | BP (naïve) | 14,760 (100%) | 1996 to 2003 | — | All fractures | Prescription refill gap < 1/2 the period of the given dispensing or < 7 d for 1 or 2 y | Persistence |
| Weycker 2007 [54] | Case-control (retrospective claims database) | BP, C, HRT, Ral (naïve) | 2613 (100%) | 1998 to 2003 | — | All fractures | MPR ≥ 90% (vs. MPR < 30%, MPR 30%–69%, MPR 70%–89%) | Compliance |
| Zambon 2008 [40] | Cohort (retrospective database) | BP (naïve) | 11,863 (100%) | 2003 to 2005 | — | All fractures | Percentage of time covered by treatment | Compliance |

BP, bisphosphonates (alendronate, risedronate, etidronate, and/or ibandronate); C, calcitonin; Ca, calcium; HRT, hormone replacement therapy; Ral, raloxifene; SERM, selective estrogen receptor modulators; SR, strontium ranelate; Vit D, vitamin D.

* The study was suitable for inclusion in pooled analyses; the reasons for study exclusion from the pooled analyses are presented in the Supplementary Material.

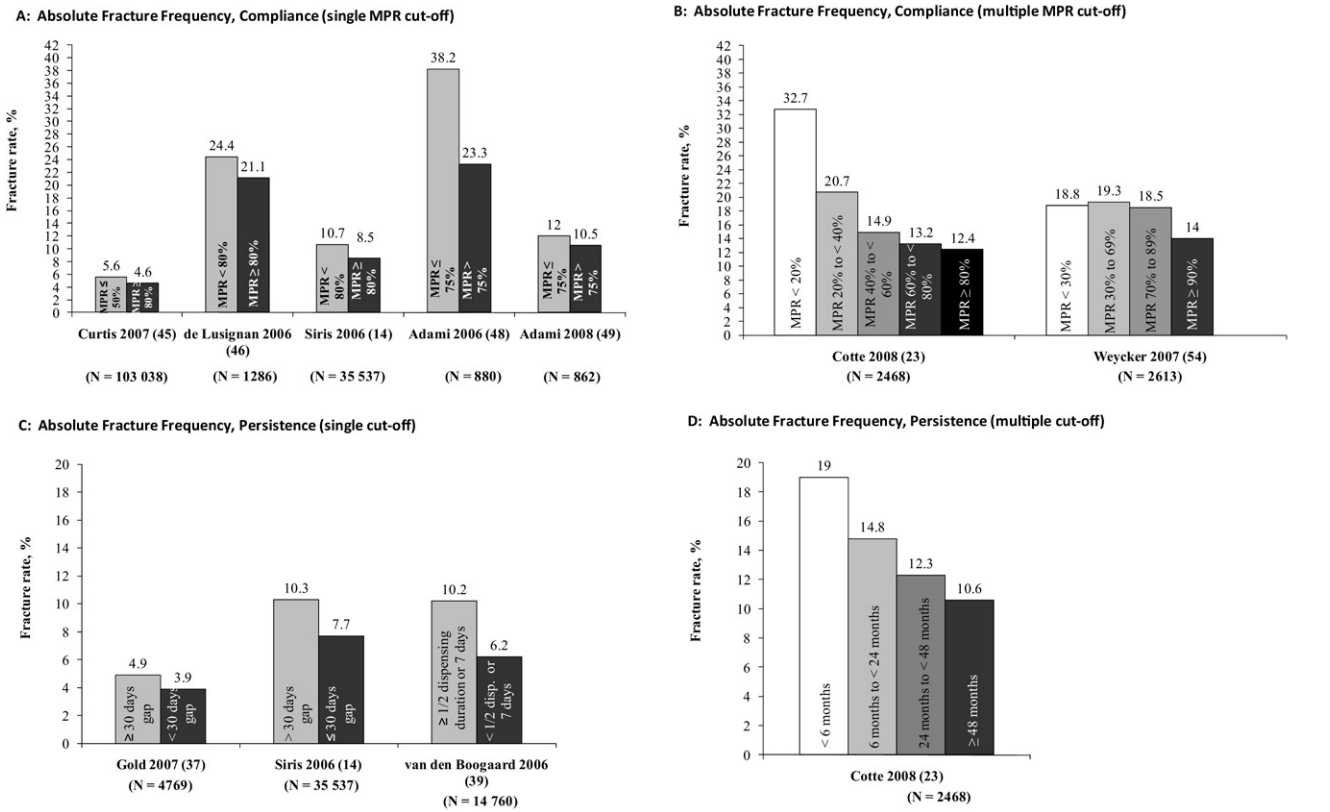
ateness and relevance for combining the results [21]. The evaluation of clinical heterogeneity was made before conducting the meta-analysis and informed a series of sensitivity analyses whereby studies were excluded based on differences in study design, publication type, population size, mean follow-up period, interventions received, fracture location, ratio adjustment, and persistence cut-off (further detail is provided in the supplementary material available at: doi:10.1016/j.jval.2010.11.010).

## Results

### *Study flow*

The flow of citations through the review is given in Figure 1. Eighteen studies met the original inclusion criteria; following protocol amendment 21 studies were included for data abstraction, and six conference abstracts were identified as meeting the inclusion criteria. Of these 27 studies, 12 (44%) contained data suitable for at least one of the four meta-analyses conducted. Two of the included studies were abstracts. It was deemed appropriate to include data from abstracts to avoid potential bias in the results (toward those studies where a stronger relationship detected allowed easier full-text publication). The reasons for study exclusion from the meta-analyses are presented in the supplementary material available at: doi:10.1016/j.jval.2010.11.010. None of the studies were excluded from the analysis based upon a qualitative assessment of poor quality; the outcome of the quality assessment is available upon request.

The characteristics of the 27 included studies are given in Table 1. The majority of studies were retrospective database analyses considering adherence in new users of bisphosphonate therapy. Twenty-three (85%) of the studies presented data relating to compliance, while nine (33%) considered persistence. Five (19%) considered both compliance and persistence [14,23–26]. The follow-up




NOTE: Fracture rates were recorded across 159 weeks for Cotte 2008, 104 weeks for Siris 2006, Adami 2006, Gold 2007, and van den Boogaard 2006, whilst follow-up was only 59 weeks for Adami 2008 (not reported for Curtis 2007, de Lusignan 2006, or Weycker 2007)

**Fig. 2 – Absolute fracture frequencies (%) with nonadherence: compliance (Panels A–B) and persistence (Panels C–D).**

duration in these studies (where reported) ranged from 40 weeks to 218 weeks, with 10 (37%) studies reporting a follow-up of 2 years or longer. Overall, 698,631 patients were involved in the 27 studies identified: 634,327 patients contributed to the assessment of fracture and compliance and 219,676 patients contributed to the analysis of persistence.

### *Compliance*

Twenty studies used the MPR to assess compliance and commonly took 80% as the cutoff point at which to define compliant (MPR ≥ 80%) and noncompliant (MPR < 80%) patients (Table 1). Across those studies presenting the absolute fracture rates in compliant and non-compliant cohorts, the frequency of fracture was considerably higher in non-compliant patients (Fig. 2a). Importantly, in studies reporting several MPR cutoff points the frequency of fracture appears to increase as the level of compliance decreases (Fig. 2b), suggesting that there may not be one point at which compliance can be dichotomized.

Eight studies were suitable for pooled comparison in the meta-analysis of compliance: four were included in the odds ratio analysis, constituting data from 113,376 patients, and seven within the hazard ratio analysis, constituting data from 101,933 patients. The meta-analyses suggest that noncompliance (vs. compliance) increases the risk of all fractures by 28% (18%–38%) and 29% (22%–38%) when using the hazard and odds ratios, respectively (Figs. 3a and 3b).

Sensitivity analysis based on study design, population size, publication type, intervention assessed, and ratio adjustment indicated that these variables had minimal effect on the pooled odds ratio, with fracture risk still found to be increased at between 27% and 37% in noncompliant compared to compliant patients (Table 2). In contrast, the skeletal sites considered within these studies do appear to be important: Rabenda et al. [26] contained data potentially suitable for inclusion in the main analyses but considered only hip fractures, while all other studies included in the analysis considered fractures at any location. As a result, this study was not included in the main analysis but was included in sensitivity analysis to determine the effect of fracture location on the pooled result: the inclusion of Rabenda et al. [26] reduced the fracture risk to 24% and increased the statistical heterogeneity within the analysis.

Sensitivity analysis found that most variables had little effect on the overall risk of fracture with noncompliance based on the hazard ratio, with the increase generally estimated at between 28% and 30% (Table 2). However, it should be noted that exclusion of studies with fewer than 10,000 patients reduced the estimated increase in fracture risk to 21%.

### *Persistence*

A range of definitions have been used to assess persistence with osteoporosis therapy in the nine studies identified (Table 1). The most frequently utilized measure was the prescription refill gap, where between seven and 90 days was permissible before it was concluded that the patient was nonpersistent with therapy. Despite the differences in the definition of persistence, it is clear that the absolute fracture frequency is higher in the cohort classed as nonpersistent than in patients seen to persist with therapy (Fig. 2c). Further, the duration for which a patient per-

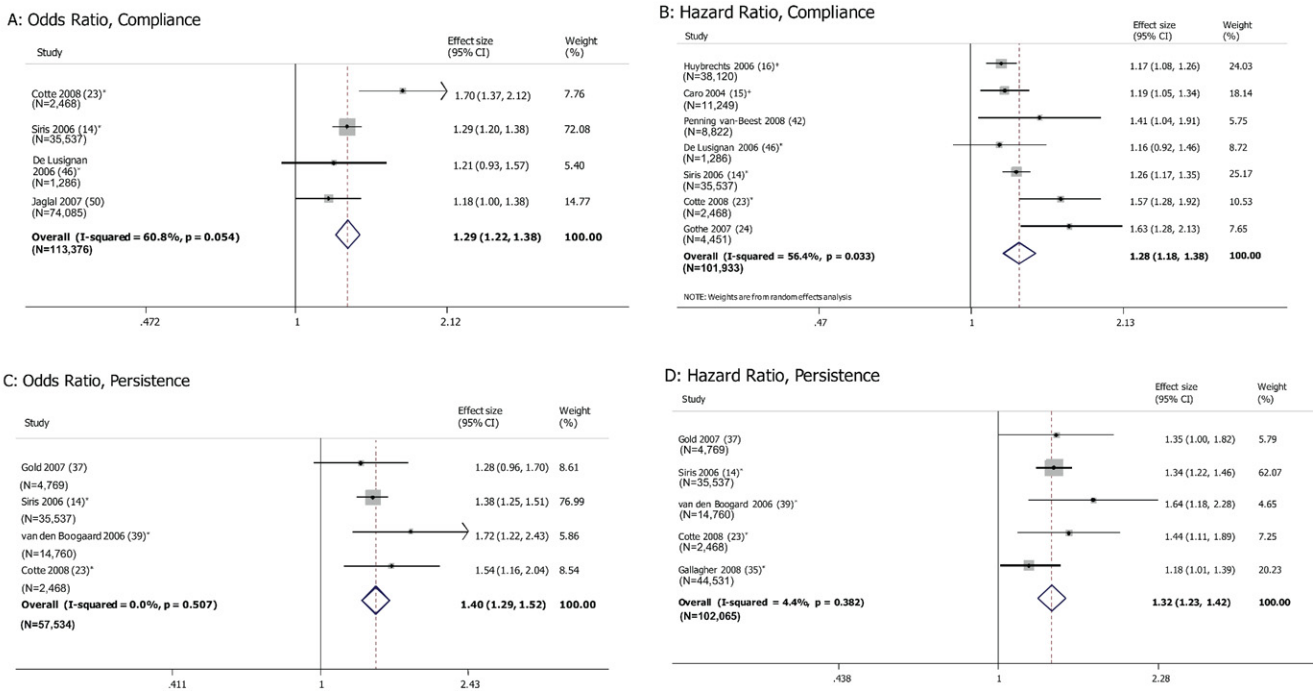



**Fig. 3 – Meta-analysis of fracture rate with nonadherence to therapy in all patients. *Data calculated from absolute fracture rates (rate ratio calculated as a close approximation to the hazard ratio), +95% confidence interval (CI) calculated from P value. #Less than 30-d treatment gap except for van den Boogaard et al. [39], where continuous persistence was required and defined as a treatment gap of less than half the dispensing duration or 7 d, and Gallagher et al. [35], where the definition of persistence was not described. ≠The compliance hazard ratio analysis for all patients contained significant statistical heterogeneity; as such the random effects model was used for these analyses. All other analyses did not contain significant statistical heterogeneity (P > 0.05) and were analyzed using a fixed effects model. Although Rabenda et al. [26] also contained data potentially suitable for inclusion in these analyses, the study considered only hip fractures while all other studies included fractures at any location. As a result, this study was not included in the main analyses but was included in sensitivity analysis to determine the affects of fracture location on the pooled result.**

sists has an important impact on fracture frequency, whereby longer durations of persistence are associated with a lower frequency of fracture (Fig. 2d).

Five studies were suitable for pooled comparison in meta-analysis: four were included in the odds ratio analysis, constituting data from 57,534 patients, and all five within the hazard ratio analysis, constituting data from 90,565 patients (Table 2). The pooled analyses indicate that nonpersistence (vs. persistence) increases the risk of all fractures by 40% (29%–52%) and 32% (23%–42%) when using the odds and hazard ratios, respectively (Figs. 3c and 3d).

Within the meta-analysis of the odds ratio data for persistence, the sensitivity analyses indicated that the risk of fracture with non-persistence was only minimally affected by this clinical heterogeneity (Table 2). However, as discussed for compliance, only hip fractures were included in Rabenda et al. [26]. Inclusion of this study in the pooled hazard ratio increased the risk of fracture with nonpersistence to 53% (16%–101%) but introduced significant statistical heterogeneity within the analysis. In contrast, the remaining sensitivity analyses demonstrated that the impact of all other variables on the pooled result was minimal (Table 2).

### *PMO subgroup analysis*

The results of the subgroup analyses (Fig. 4) are similar to the results of the main analyses (Fig. 3): noncompliance appears to increase the risk of fracture in a PMO patient by 37% (95% CI 15%– 65%) and 23% (95% CI 18%–29%) when using the odds and hazard ratio, respectively. Nonpersistence increases the risk of fracture in a PMO cohort by 40% (95% CI 29%–52%) and 36% (95% CI 26%–48%), when using the odds and hazard ratio, respectively. Sensitivity analyses conducted on these results confirm that the only variable to influence the associated increase in risk with nonadherence is fracture location, where the inclusion of the study focused solely on hip fracture (Rabenda et al. [26]) reduces the association between compliance and fracture risk and increases the association between persistence and fracture risk (data not shown).

### *Direct costs and resource use*

Data in the included studies relating to the risk of hospitalization and the effect on total health care costs as a result of nonadherence and fracture were limited. Patients who are nonadherent to their prescribed therapy had both an increased risk of hospitalization [16] and an increase in the total cost of health care incurred [16,23,25,27]. For example, a large database study involving almost 40,000 patients reports that the risk of hospitalization increases by approximately 50% in poorly compliant patients (MPR $<$ 50%) when compared to highly compliant patients (MPR $\geq$ 90%), while the total direct costs per month increase by 76% from $340 to $600 (MPR $>$ 80% vs. MPR $\leq$ 80%) [16]. This increase in hospitalization rate and direct health care costs with nonadherence is not surprising given the results of an earlier database study that found an increase in overall expenditure in osteoporosis patients experiencing fracture compared to patients without fracture [28]. In-

**Table 2 – Sensitivity analysis results.**

| Factor | Study exclusion | OR/HR (95% CI) | P |
|---|---|---|---|
| Compliance OR | | | |
| Study design* | de Lusignan 2006 [46] | 1.341 (1.143–1.574) | <0.001 |
| Fracture location* | Rabenda 2008 [26]† | 1.238 (1.038–1.478) | 0.018 |
| Population size | de Lusignan 2006 [46] and Cotte 2008 [23] | 1.268 (1.188–1.355) | <0.001 |
| Intervention | Cotte 2008 [23] and Jaglal 2007 [50] | 1.282 (1.196–1.375) | <0.001 |
| Unadjusted ratio/publication type | Jaglal 2007 [50] | 1.316 (1.232–1.406) | <0.001 |
| Compliance HR | | | |
| Study design* | de Lusignan 2006 [46] | 1.291 (1.181–1.411) | <0.001 |
| Population size | Penning van-Beest 2008 [42], Cotte 2008 [23], Gothe 2007 [24], and de Lusignan 2006 [46] | 1.212 (1.156–1.271) | <0.001 |
| Unadjusted ratio | Huybrechts 2006 [16], Penning van-Beest 2008 [42], Caro 2004 [15], and Gothe 2007 [24] | 1.276 (1.199–1.359) | <0.001 |
| Intervention | Huybrechts 2006 [16], Cotte 2008 [23], and Caro 2004 [15] | 1.299 (1.224–1.378) | <0.001 |
| Publication type | Gothe 2007 [24] | 1.229 (1.175–1.285) | <0.001 |
| Persistence OR | | | |
| Population size | Gold 2007 [37] and Cotte 2008 [23] | 1.397 (1.275–1.531) | <0.001 |
| Intervention | Cotte 2008 [23] | 1.386 (1.270–1.512) | <0.001 |
| Persistence cut-off point | Gold 2007 [37] | 1.410 (1.292–1.538) | <0.001 |
| Persistence HR | | | |
| Fracture location* | Rabenda 2008 [26]† | 1.526 (1.159–2.011) | 0.003 |
| Population size | Cotte 2008 [23] and Gold 2007 [37] | 1.312 (1.215–1.416) | <0.001 |
| Interventions received | Cotte 2008 [23] | 1.314 (1.220–1.416) | <0.001 |
| Persistence cut-off point/unadjusted ratio | Gallagher 2008 [35] and Gold 2007 [37] | 1.364 (1.255–1.483) | <0.001 |

OR, odds ratio; HR, hazard ratio; CI, confidence interval.

* A random effects analysis was conducted due to the presence of significant statistical heterogeneity, all other analyses use a fixed effects model.

† Sensitivity analysis involved the inclusion (rather than exclusion) of this study.

deed, costs in this study were more than double for patients with fracture compared to patients without.

## Discussion

This systematic review and meta-analysis of observational studies provides the first focused quantitative summary and comparison of fracture risk in patients who are adherent versus patients who are nonadherent to treatment with osteoporosis medication. Our analysis indicates that the risk of fracture is increased by approximately 30% with noncompliance (MPR < 80%) and by approximately 30% to 40% with nonpersistence (discontinuation before 2 years of therapy) when compared to the risk of fracture in compliant and persistent patients, respectively. The associated risk appears to be similar across all patients and within a subgroup of PMO patients.

The results presented here are in agreement with the results of the qualitative review conducted recently by Siris et al. [17], where the importance of adherence for therapeutic benefit and reduction of clinical and economic burden was emphasized, and are similar to the 46% increase in fracture risk with noncompliance to bisphosphonates reported recently [19]. It should be noted that there are important differences between the analysis presented here and that reported by Imaz et al. [19]. First, our review was designed specifically to identify all studies presenting fracture risk and adherence data, while the Imaz publication [19] was primarily focused on quantifying level of adherence to bisphosphonates through an update of two previous systematic reviews focused on adherence to treatment [13,29]. Secondly, Imaz et al. [19] restrict their analysis to the consideration of compliance, and use only Cox proportional hazard ratio or conditional logistic regression data from the studies included. While this gives an indication of the increase in fracture risk with nonadherence, by considering separately the odds ratio and the hazard ratio for both compliance and persistence, our analysis provides a more complete picture of the association between adherence and fracture risk. Indeed, the fact that all four analyses provide a similar estimate of increased fracture risk with nonadherence compared to adherence supports the robustness of the quantitative estimates produced. Finally, our meta-analysis has been driven by robust statistical methodology. For example, the Mantel-Haenszel method of study weighting was specifically selected because this was designed to be used in meta-analyses combining ratio data [30]. Similarly, in pooling data across studies we have been careful to select only data arising from studies that can be considered sufficiently homogeneous as to be estimating the same effect and thus provide a meaningful overall estimate of risk when combined. For example, studies defining compliance and non-compliance using nonstandard MPR cutoffs were excluded from the pooled analysis (MPR < 30% and MPR < 50%). Our review thus provides an important and robust quantitative estimate of the importance of adherence to osteoporosis medication in maximizing clinical benefit.

Potential limitations of this meta-analysis include clinical heterogeneity among the studies. An important source of this heterogeneity is the location of the fracture that is the outcome measure. For example, in two of the included studies the association of increased risk of fracture with nonadherence is significant for vertebral fracture but not for wrist and forearm fracture [23,25]. Fractures of the hip may also be affected by nonadherence to a larger degree than other fracture locations [14,25,26]. Given the high degree of clinical burden associated with both vertebral and hip fracture, this finding is of particular importance and may deserve further attention from a clinical management perspective. A second source of heterogeneity between studies may relate to the fracture history of the included population; this information was lacking in the majority of in-

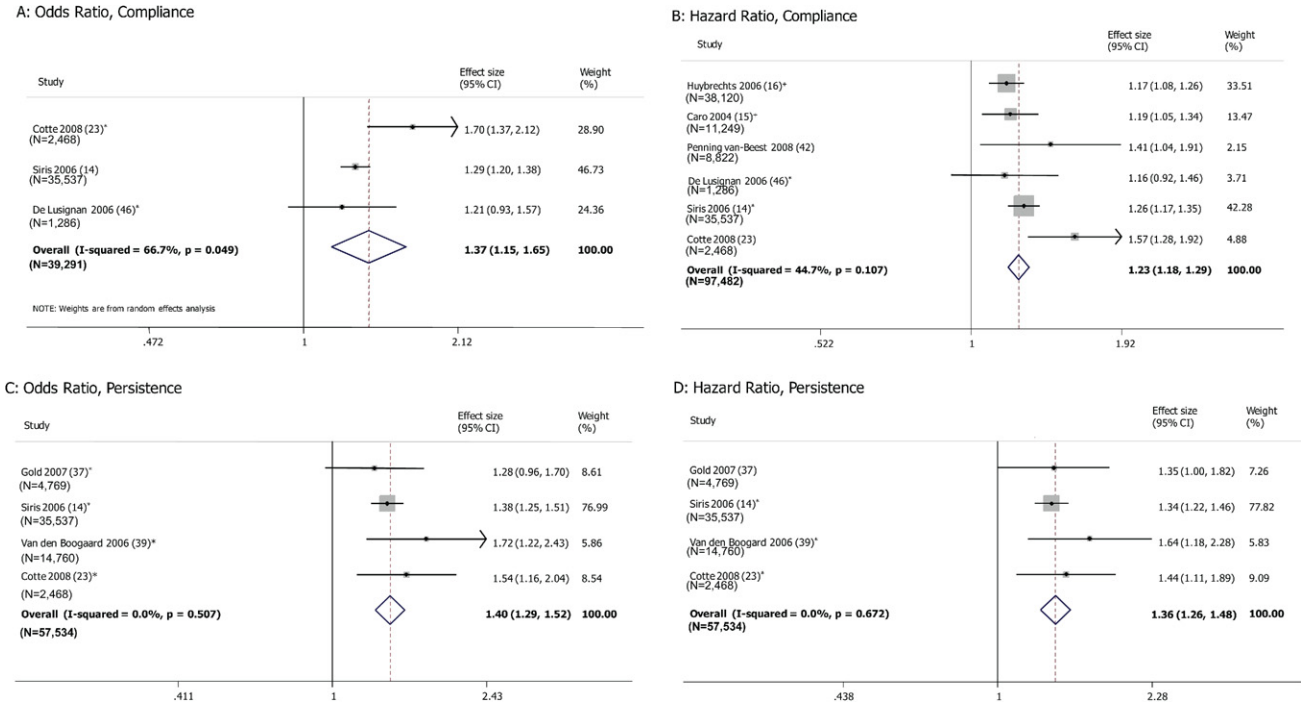



**Fig. 4 – Meta-analysis of fracture rate with nonadherence to therapy in a post-menopausal osteoporosis cohort. *Data calculated from absolute fracture rates (rate ratio calculated as a close approximation to the hazard ratio), +95% confidence interval (CI) calculated from P. †Less than 30 d treatment gap except for van den Boogaard et al. [39], where continuous persistence was required and defined as a treatment gap of less than half the dispensing duration or 7 d, and Gallagher et al. [35], where the definition of persistence was not described. ‡The compliance odds ratio analysis for postmenopausal patients with osteoporosis contained significant statistical heterogeneity; as such the random effects model was used for these analyses. All other analyses did not contain significant statistical heterogeneity ($P > 0.05$) and were analyzed using a fixed effects model. Although Rabenda et al. [26] also contained data potentially suitable for inclusion in these analyses, the study considered only hip fractures, while all other studies included fractures at any location. As a result, this study was not included in the main analyses but was included in sensitivity analysis to determine the effect of fracture location on the pooled result.**

cluded studies but may have important implications for the risk of fracture with nonadherence.

There are limitations to the measures employed by included studies to measure compliance. It is widely recognized that the presence of a refill prescription does not necessarily mean that the patient was taking the medication as prescribed [13]. Further, some claims database analyses consider patients who switch providers or whose clinician terminated the prescription as having poor adherence [31]. Similarly, patients who show a treatment gap of greater than 30 days (or any alternative persistence definition) may continue or restart therapy following their categorization as nonpersistent. However, these biases are likely to attenuate the effect of poor adherence on fracture risk, by including potentially adherent patients within the non-adherent patient group. It has also been recognized that patient-reported compliance and persistence, the alternative to database analyses, is limited by inaccuracies [32], resulting from a reluctance to report noncompliance and nonpersistence and/or recall bias [33,34]. Thus refill compliance and persistence can be considered as useful measures of adherence in the absence of a feasible alternative [17,31].

Publication bias is another potential limitation of this review. The implication of this bias is that small studies detecting no relationship between adherence and fracture risk may not have been published, as was suggested by Imaz et al. [19] for their analysis of all site fracture risk. However, given the broader search, the large sample size of the majority of studies included in our review, and the more conservative estimate of the association of adherence and fracture risk, publication bias may be considered to be minimal and to have a low effect on the conclusions drawn.

Study design bias is another potential limitation of the meta-analysis, given that many of the included studies used retrospective database analyses. Although most studies controlled for the impact of confounding factors such as age, sex, bone mineral density, prior medications, and fracture history in adjusted analyses, the confounding factors selected were not consistent across studies. As a result of this heterogeneity the unadjusted results, where available, were selected for inclusion into our meta-analysis. This fact should be considered when interpreting the results and applying them to the osteoporotic population as a whole. Despite these limitations, the observational study design is recognized to have greater external validity than a randomized controlled trial and thus the results are more easily generalizable to the whole population with osteoporosis. Further, the studies tended to be comparable in terms of study design (mainly retrospective database analyses), treatments received (largely restricted to bisphosphonates), and fracture location (generally all fractures were considered).

Although predictors of poor adherence to osteoporosis treatments were of interest in this review, many of the included studies did not directly consider this. From the studies that did consider risk factors, several variables arise as clear predictors of adherence to therapy. Patients of younger age appear to be less adherent to medication than older patients [14,25,35,36], while treatment regimens requiring more frequent administrations are associated

with poor adherence to therapy [26,35,37–40]. The length of time from treatment initiation may also be important [16,41,42]. Given the clinical importance of adherence to osteoporosis therapy observed in the current review, future research should focus on determining further the factors that underlie poor adherence and how adherence might be increased. This may involve the development of therapies with less frequent administration alongside research into new management programs for improving adherence. It should also be recognized that the relationship between adherence and fracture rate may reflect the fact that an adherent individual is more likely to lead a healthier lifestyle and to exert greater care to avoid activities that could increase the likelihood of sustaining a fracture [43].

A final important consideration is the economic implication of poor adherence. The, albeit limited, data reported in the studies in this review suggest that the direct cost of poor adherence is significant. However, this area warrants further, specific research to quantify the effect of poor compliance and persistence on fracture-related resource use and costs.

## Conclusions

This systematic review highlights the importance of compliance and persistence to medications known to be effective in the treatment of osteoporosis. Poor adherence is associated with a significantly increased risk of fracture. Given that one-third to one-half of patients do not take their medication as directed [13], the additional burden on society due to nonadherence is likely to be high. Enhancing both compliance and persistence to osteoporosis therapy could significantly reduce the burden of osteoporosis in terms of fracture frequency, hospitalizations, and direct medical costs.

Source of financial support: This research was funded by Amgen Inc., USA, and conducted in collaboration with Heron Evidence Development Ltd., UK. A summary of the PMO subgroup data has previously been presented in poster format at the American College of Rheumatology Annual Scientific Meeting 2009 (Philadelphia, PA, October 19, 2009, presentation No. 868). Dr. Ross and Dr. Siris were commissioned by Amgen to collaborate on this project with Dr. Samuels and K. Gairy, employees of Heron Evidence Development, who were contracted to conduct the project presented. Dr. Siris serves as a consultant and participates in Speaker's Bureaus for Amgen, Eli Lilly, and Novartis. Dr. Ross, Dr. Samuels, and K. Gairy declare no financial conflicts of interest that might affect the conduct or reporting of this work. Dr. Iqbal and Dr. Badamgarav are employees of Amgen Inc.

## Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at doi:10.1016/j.jval.2010.11.010, or if hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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