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Critique of evidence put forward by Servier suggesting an association between acid-suppressive medication and fracture risk

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Background

Proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RAs) are both acid-suppressive medications. They are licensed for use both as short-term treatments for gastric and duodenal ulcers, and to relieve gastro-oesophageal reflux disease and also, in the case of PPIs, dyspepsia.[1]

Gastrointestinal disorders are the adverse events most commonly reported in connection with bisphosphonate therapy for osteoporosis or osteopenia; they appear to be more commonly reported in patients taking alendronate or risedronate rather than etidronate.[2] An Australian case-control study found that, after controlling for previous NSAID use, new users with no recent H2RA or PPI use who were prescribed bisphosphonates (primarily alendronate) in general practice were significantly more likely than matched controls who were prescribed other medications to require acid suppression agents (H2RAs, PPIs or other antacids) within 6 weeks of their prescription (odds ratio 3.21, 95% CI 2.02-5.11).[3]

Servier claim that 'acid-suppressing medication significantly reduces, if not completely negates, the anti-fracture benefits of bisphosphonate treatment'.[4] They refer to three papers in support of this claim:

- A case-control study by Vestergaard et al.[5]
- A nested case-control study by Yang et al.[6]
- A prospective cohort study by Yu et al.[7]

They also present some results from a retrospective cohort study using the General Practice Research Database.[4] This study has been published in abstract form by de Vries et al.[8]

All four studies are controlled observational studies. This is appropriate: most RCTs are too small to detect adverse events which are either rare or take a long time to develop,[9] and it is unlikely that any RCT of a PPI would have been powered to detect a significant difference in the incidence of clinical fracture.

However, observational studies suffer from the inherent drawback that, because the subjects select themselves, or are deliberately selected by a physician, for exposure to the putative harmful agent, they may differ from nonexposed persons with respect to important determinants of outcome other than, or additional to, the exposure of interest. Attempts to document subject characteristics and either demonstrate comparability or use statistical techniques to adjust for differences will only account for those prognostic factors (confounders) which the investigators thought of and also measured,[10] and thus all observational studies are susceptible to unmeasured confounders. In the current example, it is impossible to rule out the theoretical possibility that the risk of fracture in patients prescribed acid-suppressive medication is associated with the condition which required the use of such medication rather than with the medication itself. Thus, if the condition which required acid-suppressive medication predated bisphosphonate use, any associated risk of fracture would not be reduced by use of an anti-osteoporosis agent other than a bisphosphonate.

There is a hierarchy of evidence within observational studies, with cohort studies generally recognised as providing higher quality evidence than case-control studies.

Those cohort studies which are planned in advance, and which follow their subjects prospectively, are likely to be more reliable than those which are undertaken retrospectively, both because the data collection is planned and is therefore more likely to be uniformly reliable and complete, and because the selection of participants is unlikely to be influenced by their outcomes.[11]

Because case-control studies identify people who have already developed the outcome of interest (cases), and match them with people who do not have that outcome but who are otherwise similar to cases in respect to important determinants of outcome such as age, sex, concurrent medical conditions (controls), their quality depends largely on the appropriateness of the choice of control group.[11]. Bias may also be introduced because the relative frequency of exposure to the putative harmful agent in cases and controls is assessed respectively. Studies which depend on asking subjects about past exposure are particularly susceptible to recall bias (whereby cases may be more likely than controls to remember exposure to potentially harmful agents) and interviewer bias (whereby the interviewer may probe for information more actively in cases than in controls). However, such bias may be avoided if the information is obtained from routinely collected data,[10] as in both case-control studies assessed here.

In a nested case-control studies, the cases are identified within a cohort which was defined before the case-control study began. Because information relating to the cohort is collected prospectively, such case-control studies are potentially less susceptible to recall bias than non-nested case-control studies. However, they have the drawback that, because of deaths and losses to follow-up, the controls may not be fully representative of the original cohort.

As noted above, in both cohort and case-control studies statistical techniques may be used to adjust for differences between cases and controls in the prevalence of confounders (potential prognostic factors, other than the exposure being studied, which may affect the outcome of interest). Variables which are known securely, without the possibility of conceptual or measurement error, (eg age or sex) can be used with more confidence than those such as smoking or diabetes which are measured less well because duration and severity are not taken into account: the latter will leave unquantifiable residual confounding. It has therefore been suggested that ideally, to minimise the degree of residual confounding, analyses should include only those cases and controls who do not have any such insecurely-known potential prognostic factors.[9]

Summary and critique of study design

Study quality was assessed using quality criteria based on the CRD criteria for cohort and case-control studies,[11] the CASP checklists for cohort[12] and case-control[13] studies, and the SIGN methodology checklists for cohort[14] and case-control[15] studies. The key features of each study are summarised and critiqued below.

Vestergaard et al. 2006[5]

This case-control study addressed the question whether the risk of fracture was different in users of PPIs, H2RAs, and other types of acid-suppressive medication from that in never-users of antacids. It thus cannot distinguish between any difference in risk associated with acid-suppressive medication or with the underlying conditions which necessitated the use of such medication.

The cases were all 124,655 men and women who sustained any clinical fracture in Denmark in the year 2000. They were identified from routine hospital discharge diagnoses of fracture in the National Hospital Discharge Register. These diagnoses had previously been shown to have a validity of around 93% in relation to hip fractures; their validity in relation to other fracture sites is not known. As fracture diagnosis was independent of any inquiry into the use of acid-suppressive medication, it seems unlikely that it could have been influenced by knowledge of exposure to such substances.

Three controls per case, matched only for age and gender, who were not recorded in the National Hospital Discharge Register as having had a fracture during the relevant period, were randomly selected from the background population. It is not clear from what database or register they were sampled. As the validity of fracture discharge diagnoses was not 100%, it is possible that some controls may have suffered a fracture during the relevant period.

It is not clear from the study as published whether any cases or controls refused to participate in the study. However, it seems likely that only routinely-collected data were used, and that therefore consent and active participation were not required, and participation rates may have been 100% in both groups.

Because cases and controls were only matched for age and gender, they were not wholly comparable with respect to potential confounding factors. Cases were more likely than controls to be retired, and to be living alone; they had higher comorbidity and were more likely to use drugs associated with an increased risk of fracture (corticosteroids, antiepileptics, anxiolytics and sedatives, neuroleptics, and antidepressants).

Exposure to acid-suppressive medications was measured using the proxy measure of the cumulated number of defined daily dosages (DDDs) redeemed over a 4 to 5 year period (from 1st January 1996 to the occurrence of fracture or equivalent date for controls in 2000), using routinely-collected prescription data from the Danish Medicines Agency. This is an objective measure, with no possibility of recall bias. However, it could not account for any patients who redeemed but did not take the medication, although such non-compliance was assumed to be relatively rare because

patients paid part of the drug cost when they redeemed the prescription. It also could not take into account drugs administered during episodes of hospitalisation, but this was felt to be a minor factor as the study population did not spend many days in hospital. More seriously, it could not take into account medications available over the counter (OTC) as these could not be linked to a named individual. The investigators sought to overcome this problem (which affected all acid-suppressive medications other than the prescription-only PPIs) by comparing consumption of prescribed acid-suppressive medications among the study population with sales of prescription and OTC acid-suppressive medication among the general population. Data on other potentially relevant exposures (the occurrence of other diseases, and of alcoholism) were obtained from national registers. However, the authors recognised that the fact that H2RAs and other acid-suppressive medications were available over the counter may have led to an underestimation of the risk associated with those drugs.

The measure of effect used was the odds ratio, adjusted for alcoholism, working or not, the Charlson index (an index of 19 comorbid conditions), ever-use of antiepileptics, ever-use of anxiolytics or sedatives, ever-use of antidepressants, ever-use of neuroleptics, ever-use of corticosteroids, number of bed days in 1999, number of contacts with a GP or specialist in 1999, living with someone or living alone, prior fracture, education level, and income in 1999. Potentially important confounding factors which were not adjusted for include smoking, physical activity, differences in body weight, use of calcium/vitamin D supplements, and sun exposure. The actual numbers of cases and controls who received PPIs, H2RAs or other acid-suppressive medications (ie the numbers underlying the crude odds ratio) were not reported.

Yang et al. 2006[6]

This was a nested case-control study which sought to explore the association between PPI therapy and risk of hip fracture, and compare it with the risk associated with H2RA therapy. It was conducted using data from the General Practice Research Database (GPRD) for the period 1987 to 2003. The GPRD contains the computerised medical records of 683 general practices in the UK, and represents about 6% of the UK population,[16] of which it is broadly representative in terms of age and gender.[17] The GPRD contains demographic data, information about prescriptions, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes for each patient.[16]

The cohort within which the case-control study was nested consisted of men and women who were aged 50 years or over at the time of database enrolment; who had at least 365 days of up-to-standard database follow-up; who had either received at least one prescription for PPIs, or at least one prescription for H2RAs but none for PPIs, during their up-to-standard database follow-up, or had no documented prescription for PPI or H2RA therapy; who had not received PPI or H2RA therapy exclusively during non-up-to-standard periods of database follow-up; and who had not had a documented hip fracture before, or during the first year of, up-to-standard database follow-up. The 13,556 cases were variously said to be all patients within that cohort who suffered a first incident hip fracture (other than distal femoral fracture) at least a year after the start of their up-to-standard database follow-up, or to have been sampled from the cohort using incidence density sampling. The GPRD diagnoses of hip fracture had previously been shown to have a validity of over 90%. As fracture diagnosis was

independent of any inquiry into the use of acid-suppressive medications, it seems unlikely that it could have been influenced by knowledge of exposure to such medications.

One to ten controls per case were drawn from the same cohort as the cases, using incidence density sampling and matching for sex, index date, year of birth, and both calendar period and duration of up-to-standard database follow-up before the index date. It is not clear why the number of controls per case varied. As the validity of fracture diagnosis was not 100%, it is possible that some controls may have suffered a fracture during the relevant period.

As only pre-existing data were used, informed consent and active participation were not required. Participation rates may therefore in theory have been as high as 100% in both groups. In practice, however, patients may have died or moved away from their GPRD-participating practice, and the number lost to follow-up in this way is not quantified. As drop-out rates are not presented, it is not possible to determine whether they were similar in exposed and unexposed groups.

Although cases and controls were matched for a number of potential confounding factors, they were not wholly comparable: cases were more likely than controls to have received medications or to have medical diagnoses with known associations with either osteoporosis or the risk of falling.

The primary exposures of interest were PPI or H2RA therapy of more than one year duration before the index date. Individual periods of PPI or H2RA exposure were determined by a proxy measure, namely the intended duration of each prescription recorded in the GPRD. Participants who had received both PPIs and H2RAs were considered in the primary analysis for PPIs only. PPI and H2RA use was thus measured objectively, with no possibility of recall bias. However, it did not take into account any patients who either failed to redeem the prescription, or who redeemed it but did not then take the medication. The possibility that the PPI and H2RA groups contain antacid non-users is therefore higher than in the study by Vestergaard et al.[5] in which the treatment groups did not include patients who failed to redeem their prescription. As in the study by Vestergaard et al., it was not possible to take into account the possible use of OTC acid-suppressive medications, and this may have led to an underestimation of the risk associated with PPIs and H2RAs.

The measure of effect used was the odds ratio. Conditional logistic regression was used to estimate the unadjusted and adjusted odds ratios. The potential confounders which were included in the analysis included BMI, smoking history, alcoholism, health conditions (congestive heart failure, cerebrovascular accident, dementia, impaired mobility, myocardial infarction, COPD or asthma, peptic ulcer disease, PVD, rheumatoid arthritis, vision loss, coeliac disease, Paget disease, osteomalacia, chronic renal failure, Cushing disease, inflammatory bowel disease, seizure disorder, or fracture >3 months before the index date), and use of specific medications (anxiolytics, antidepressants, antiparkinsonian drugs, thiazide diuretics, statins, corticosteroids, hormone therapy, calcitonin, NSAIDs, anticonvulsants, thyroxine, and calcium and vitamin D supplementation). Potentially important confounding factors which were not adjusted for include physical activity, sun exposure, and supplementation with OTC calcium/vitamin D. The actual numbers of participants in

each group who received PPIs, H2RAs or other acid-suppressive medications (ie the numbers underlying the crude odds ratio) were not reported.

de Vries et al. 2007[8]

This was a retrospective cohort study which sought to compare the fracture risk in patients taking a bisphosphonate plus acid-suppressive medication with that in those taking a bisphosphonate alone. As this study has been published only in abstract form, although Servier have provided some additional findings[4] very little detail is available, and a number of questions remain unanswered.

The study used data from the General Practice Research Database (GPRD) on 67,309 men and women aged 40 or over who were starting treatment with bisphosphonates; 20.1% of these had been prescribed PPIs and 7.5% H2RAs. The time period within which bisphosphonate therapy was initiated is not clear, nor is it clear whether the cohort represented all men and women in the GPRD who were prescribed bisphosphonates during that time period. As only pre-existing data were used, informed consent and active participation were presumably not required, and participation rates may in theory have been as high as 100% in both groups. In practice, however, patients may have died or moved away from their GPRD-participating practice, and the number lost to follow-up in this way is not quantified.

There is insufficient information to determine whether the two groups were comparable in terms of potential prognostic factors other than use of acid-suppressive medication. In particular, it is not clear whether they were balanced in terms of disease progression: bisphosphonates may be prescribed for the primary or secondary prevention of osteoporosis, and as the risk of future fracture is lower in primary than in secondary prevention, if the proportion of patients being prescribed bisphosphonates for secondary osteoporosis was not comparable in each group, this would potentially invalidate the study findings. Similarly, patients prescribed bisphosphonates to prevent osteoporotic fracture secondary to other conditions (eg those requiring treatment with corticosteroids) will be at particularly high risk of fracture, and evidence is required, but not available, that they formed a comparable proportion of each of the two groups. Drop-out rates are not presented, and it is therefore not possible to determine whether they were similar in exposed and unexposed groups.

It is not specified how exposure to acid-suppressive medication was measured. Presumably, however, as in the study by Yang et al.,[6] it was determined by a proxy measure, namely prescriptions for PPIs and H2RAs recorded in the GPRD. Although this is an objective measure, it will not take into account any patients who either failed to redeem the prescription, or who redeemed it but did not then take the medication. It also fails to address the possible use of OTC acid-suppressive medication. No indication is given regarding length of therapy.

The outcome of interest was not clearly specified, but was presumably any clinical fracture recorded in the GPRD during the relevant (unspecified) time period. The length of the follow-up period is not clear. The measure of effect used was the relative rate, adjusted using time-dependent Cox regression. The actual numbers of women in

each group who suffered fractures (ie the numbers underlying the relative rate) were not reported.

GPRD data can be used to quantify the absolute risks of adverse events, which case-control studies cannot.[17] However, neither de Vries et al. nor Servier did so.

Yu et al. 2006[7]

This was a prospective cohort study which addressed the question of whether PPI and/or H2RA use was associated with changes in BMD and in the risk of nonvertebral fracture in postmenopausal women who were not taking bisphosphonates or other antiosteoporotic agents.

The cohort of 3432 women was recruited from women enrolled in the Study of Osteoporotic Fractures (ie 9704 non-black women aged ≥65 years recruited from population-based listings and health maintenance membership lists at four sites in the USA between Oct 1986 and Oct 1988[18]). Within this cohort, comparisons were made between PPI users, H2RA users, and non-users of acid-suppressive medication. As no information is provided regarding participation rates at enrolment, it is not clear how representative the cohort is of the population of interest.

There is insufficient information to determine whether the two groups were comparable in terms of potential prognostic factors.

Exposure was measured by 'assessment' of 'current' PPI and/or H2RA use. It is not clear how this was done, and no indication is given as to how long, on average, 'current' users had been using PPIs or H2RAs.

The outcomes of interest were bone loss (apparently assessed by total hip BMD), and hip and other nonvertebral fractures. The fractures were confirmed by central adjudication of x-ray reports; it would appear from another article[18] that they were initially reported by the participants themselves. Thus, while central confirmation of fracture could have been blinded to exposure status, initial reporting of the fracture would not have been. Mean follow-up for BMD data was 4.9 years, when only 72% of the cohort were available to provide information about medication use. Mean follow-up for fracture data was 7.5 years; no information is provided about the number of participants who provided data at that point. Implicitly, drop-out was mainly due to the unavailability of repeat BMD measurements and information about medication use. No information is provided as to whether drop-out rates were comparable in the exposed and unexposed groups. 188 women who had not dropped out were excluded at the follow-up visit because they reported use of bisphosphonates or other osteoporosis medications; as they were women who had either suffered a fracture or were at increased risk of doing so, if they were not distributed between the study cohorts in equal proportions, their exclusion would distort the study findings.

The measure of effect used was the relative hazard. Linear regression and time-dependent proportional hazards regression were used to adjust for age, ethnicity, BMI, calcium intake, health status, exercise, alcohol intake, and use of oestrogens or corticosteroids. It is not clear what comorbidities or medications might be included

under the heading of ‘health status’. Potentially important confounding factors which were not adjusted for include smoking and sun exposure. The actual numbers of participants in each group who suffered fractures (ie the numbers underlying the relative rate) were not reported.

Summary and interpretation of study findings

Vestergaard et al. 2006[5]

Vestergaard et al. found that the use of PPIs within the last year was associated with a small increase in the risk of any fracture (adjusted OR 1.18, 95% CI 1.12, 1.43), as were other antacids (adjusted OR 1.33, 95% CI 1.24, 1.43). This increased risk disappeared if more than a year had elapsed since last use of PPIs (AOR 1.01, 95% CI 0.96, 1.06) or other antacids (AOR 1.02, 95% CI 0.96, 1.08). H2RA use within the last year was associated with a decrease in fracture risk (adjusted OR 0.88, 95% CI 0.82, 0.95).

Because the study design could not distinguish between any difference in risk associated with acid-suppressive medication or with the underlying conditions which necessitated the use of such medication, it is not certain from these whether the risk of fracture is increased by the use of PPIs and other acid-suppressive medication, or whether it is increased by the underlying condition but reduced by the use of H2RAs. However, an analysis which stratified antacid use by average daily dose in the year 2000 may support the latter interpretation: it indicated a dose-response relationship for H2RAs and for other antacids, but not for PPIs, suggesting that there may be no causal relationship between PPI use and changes in fracture risk, but that H2RAs may be associated with a decrease, and other antacids with an increase, in fracture risk. As noted earlier, the authors recognise that the availability of H2RAs and other antacids over the counter may have led to an underestimation of the changes in risk associated with those drugs: in other words, H2RAs may be associated with a greater reduction, and other antacids with a greater increase, in fracture risk than indicated above. However, as Yang et al.[6] observe, Vestergaard et al. assessed the dose-response relationship regardless of length of exposure, although short-term use, even at a high dose, is unlikely to have a significant impact on fracture rates.

An analysis which stratified antacid use among those who had used such drugs during the previous year by the number of defined daily dosages redeemed from 1st January 1996 to the date of fracture or censoring failed to demonstrate a duration-response relationship.

Yang et al. 2006[6]

Yang et al. found that more than one year of PPI therapy was associated with an increase in the risk of hip fracture compared with no acid-suppressive therapy (multivariable adjusted OR 1.44, 95% CI 1.30, 1.59), as was more than one year of H2RA use (multivariable adjusted OR 1.23, 95% CI 1.14, 1.39). As some of the PPI users also used H2RAs, a separate analysis was conducted comparing PPI-only users with acid-suppressive medication non-users; this yielded an adjusted odds ratio for hip fracture of 1.62 (95% CI 1.41, 1.89). As noted earlier, the inability of the study design

to take into account the use of OTC acid-suppressive medications may have led to an underestimation of the increase in risk associated with those drugs.

Long-term PPI use (>1 year of cumulative use) was associated with a higher fracture risk than long-term H2RA use (adjusted OR 1.34, 95% CI 1.14, 1.38). The risk increased with increasing duration of PPI therapy (adjusted OR for one year's therapy 1.22, 95% CI 1.15, 1.30; for 4 years' therapy 1.59, 95% CI 1.39, 1.80); it is not clear whether the comparator here is H2RA use or acid-suppressive medication non-use. The association between long-term PPI use and hip fracture was stronger in men (OR 1.78, 95% CI 1.42, 2.22) than in women (OR 1.36, 95% CI 1.22, 1.53).

Compared with acid-suppressive medication non-users, a significant dose-response effect was observed among patients who had been prescribed PPI therapy for more than one year: the adjusted OR was 1.40 (95% CI 1.26, 1.54) in those prescribed ≤1.75 average daily dose but 2.65 (95% CI 1.80, 3.90) for those prescribed >1.75 average daily dose. No such dose-response effect was observed in relation to H2RA use.

To exclude the possibility that increased fracture risk was associated with gastro-oesophageal reflux disease (GERD), rather than with the medications used to treat it, the investigators conduced an additional analysis restricted to patients with documented chronic GERD (defined as 3 or more diagnoses recorded on different dates in the database). In these patients, the multivariable adjusted OR for hip fracture associated with at least one year's PPI therapy was 1.41 (95% CI 1.02, 1.94), while the corresponding OR for H2RA was 1.21 (95% CI 0.67, 2.22). A dose-response effect was again observed with PPI use.

de Vries et al. 2007[8]

de Vries et al. found that concomitant use of PPIs and bisphosphonates was associated with an increased risk of any fracture (adjusted relative rate 1.08 (1.01, 1.15)) and of hip fracture (ARR 1.21, 95% CI 1.05, 1.38) but not of vertebral fracture (ARR 1.11, 95% CI 0.94, 1.31) compared to bisphosphonate use alone. In contrast, concomitant use of H2RAs and bisphosphonates was associated with an increased risk of vertebral fracture (ARR 1.48, 95% CI 1.17, 1.87) but not of any fracture (ARR 1.07, 95% CI 0.93, 1.22) or of hip fracture (ARR 1.04, 95% CI 0.83, 1.32), compared with bisphosphonate use alone. The inability of the study design to take into account the use of OTC acid-suppressive medications may have led to an underestimation of these changes in fracture risk. However, as no information is available regarding the factors used to produce the adjusted relative rate, other than that they include [redacted] [in confidence, Servier] and other unspecified factors,[4] it is possible that the findings are invalidated by imbalances between the groups in the proportions of patients receiving bisphosphonates for primary or secondary fracture prevention, and for primary or secondary osteoporosis.

De Vries et al stated that consistent dose-dependent trends were observed when data were stratified by daily dose of acid-suppressive medication. Further detail is available in the data submitted by Servier.[4] [redacted]

[redacted] [in confidence, Servier]

Yu et al. 2006[7]

Yu et al. found that, over a mean follow-up period of 7.5 years, using a mulltivariate adjusted relative hazard model, users of acid-suppressant medications were at increased risk of nonvertebral fracture compared with non-users of such medications (1.18, 95% CI 1.01, 1.39). Findings were said to be similar in stratified analyses of PPI users (n=264) and H2RA users (n=594) compared with non-users of acid-suppressant medications. However, statistical significance was not achieved for PPI users. Moreover, without confirmation that the 188 women who were excluded for use of bisphosphonates or other osteoporosis medications were proportionately distributed between the three groups, no confidence can be placed in the findings.

The statement that "with prolonged follow-up, there was an 18% increase in the risk of non-spine fracture among users of acid-suppressive medications" may suggest that no significant increase in fracture risk was seen when BMD outcomes were assessed, after a mean of 4.9 years' follow-up.

Conclusions

The quality of evidence regarding any possible association between the use of acid-suppressive medications and increased risk of fracture is generally poor. Of the two case-control studies, that by Yang et al.[6] found that more than one year of either PPI or H2RA therapy was associated with an increased risk of hip fracture. The risk was higher for long-term PPI use than for long-term H2RA use. However, an analysis conducted to exclude the possibility that the increased fracture risk was associated with the underlying disease for which PPI or H2RA therapy was prescribed failed to demonstrate that H2RA therapy was associated with an increase in fracture risk. The case-control study by Vestergaard et al.[5] did not demonstrate convincingly that fracture risk was increased by PPIs rather than the underlying disease for which they were prescribed, though it did suggest that H2RAs might reduce, and other acid-suppressive medications increase, such risk.

Neither of the cohort studies have been reported in full. No confidence may be placed in the results of the study by de Vries et al.[8] because of its failure to demonstrate comparability between exposure groups in terms of key prognostic factors, in particular whether bisphosphonates were prescribed bisphosphonates for primary or secondary fracture prevention, and for primary or secondary osteoporosis. Similarly, confidence cannot be placed in the results of the study by Yu et al.[7] because of their failure to demonstrate that the exposure groups were comparable in terms of exclusions for use of bisphosphonates or other osteoporosis medications.

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