PEER REVIEW HISTORY

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ARTICLE DETAILS

| TITLE (PROVISIONAL) | Cost-effectiveness of enhancing adherence to oral bisphosphonates treatment in osteoporotic women: an empirical approach based on healthcare utilization databases |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Scotti, Lorenza; Arfè, Andrea; Zambon, Antonella; Merlino, Luca; Corrao, Giovanni                                                        |

VERSION 1 - REVIEW

| REVIEWER            | John T. Schousboe, MD Park Nicollet Institute for Research and Education |
|---------------------|-------------------------------------------------------------------------|
| REVIEW RETURNED     | 22-Sep-2013                                                            |

GENERAL COMMENTS

I think this study is good explication for the Italian population of the incremental costs that would be incurred relative to the fractures that would be prevented if adherence to oral bisphosphonate therapy were better. However, it does not show the cost-effectiveness of enhancing adherence because, as the authors acknowledge, no intervention to actually improve adherence is modeled.

Therefore, this study does not add to a fairly large literature that already exists that show how many fractures might be averted by improving adherence. One can easily take such previously published data and come to the same conclusions by simply then factoring in the local costs of bisphosphonate therapy.

Moreover, I am puzzled why, with access to full utilization and costs in this population, the authors made no attempt to estimate the costs of fractures that would have been averted had adherence been better. Additionally, there are reasonable published estimates of the quality adjusted life years lost from fractures. This would have at least allowed them to do a threshold analysis of how much an intervention might cost and still be cost-effective. This has been done in another country (reference 14) and this would have been a much stronger paper had this study done similar analyses for a European country / population.

| REVIEWER            | Amanda Patrick Brigham and Women's Hospital Boston, MA, United States |
|---------------------|-----------------------------------------------------------------------|
| REVIEW RETURNED     | 03-Oct-2013                                                           |

GENERAL COMMENTS

In this paper, the authors estimate the additional drug cost per fracture-free life year gained associated with improving adherence to bisphosphonates among women with osteoporosis. The study is based on an analysis of data from Italian healthcare databases. The
approach is interesting, although the analysis is less comprehensive than one based on a microsimulation model and the results may be subject to confounding. There are several points that would benefit from further elaboration / discussion:

Methods:
1. Why were subjects censored before one year excluded from the analysis? The disadvantage to excluding these subjects is some loss of generalizability and the possibility of introducing selection bias.
2. The authors should elaborate further on how PDC was incorporated as a time-varying exposure. Was PDC treated as cumulative since treatment initiation or was only the most recent PDC considered? How was the modeling done?
3. Why were data from the year after index included in calculating the Charlson score? Technically speaking, adherence could influence the score since it is being measured after bisphosphonate initiation.
4. Is the benefit of improved adherence assumed to be constant over a six-year period? Is this assumption reasonable?

Discussion:
While the method presented is an interesting alternative to constructing a microsimulation model, it is more limited. The authors mention the fact that they didn't include the costs of an intervention to increase adherence; they also don't include cost-savings from avoided fractures. The results pertain to a 6-year treatment period, but don't allow for an extrapolation of how costs and fracture-free survival would be affected over a longer time-frame. The authors do mention the possibility that their measured association between adherence and fracture-free survival is confounded. I think this point merits a little further discussion. Frailty is another possible confounder – i.e. patients with cognitive impairment/poor balance may have poorer adherence and worse outcomes. Along the same lines, it would be worth considering and commenting on the apparent protective effects of other chronic medications in table 2.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1  I think this study is good explication for the Italian population of the incremental costs that would be incurred relative to the fractures that would be prevented if adherence to oral bisphosphonates therapy were better. However, it does not show the cost-effectiveness of enhancing adherence because, as the authors acknowledge, no intervention to actually improve adherence is modeled.

As properly observed by the Reviewer, our study did not model the impact of an intervention program aimed to improve adherence, simply because our approach did not include costs for intervention implementation. Accordingly, we better discussed this point in the new version of the paper (Discussion section, from Page 17, Lines 24-25 to Page 18, Lines 1-16). In particular we emphasized that (i) "...costs of interventions enhancing adherence are likely not negligible with respect to those directly related to increased drugs use..."; (ii) "... we were not able to include the costs of implementation strategies for enhancing adherence, since ... no studies have been performed in Italy on this topic..."; (iii) "... a general worsening of the reported cost-effectiveness estimates are expected if the corresponding cost source were taken into account..."; however, (iv) "... interventions able enhancing adherence unlikely focus only on one therapeutic class, so that their cost should impact on the adherence of a variety of chronic medicaments...".

2 Therefore, this study does not add to a fairly large literature that already exists that show how many
fractures might be averted by improving adherence. One can easily take such previously published data and come to the same conclusions by simply then factoring in the local costs of bisphosphonate therapy.

We only partially agree on this regard. It is true that data for estimating how many fractures might be avoided by improving adherence can be drawn from the large literature on this issue. However, we did not use as "clinical" outcome the number of avoided fracture, but rather the number of gained fracture-free survival years. This last was derived using the estimates of baseline hazard and parameters of the Cox regression model, which were both directly fitted from the observed data. However, although to our best knowledge literature does not provide estimates of the Cox regression model for the relationship between adherence and time to fracture, also admitting that previously published data on this issue are available, the calculation of the baseline hazard from the data available is still needed.

This is a crucial point of our study and we then thank the Reviewer because his question allowed us to highlight the peculiarity of our approach. For this reason, in the new version of the paper we better clarified how the number of gained fracture-free survival years were estimated from our data (Methods section, Estimating cost and effectiveness of enhancing adherence subsection, Page 9, Lines 10-15).

3 Moreover, I am puzzled why, with access to full utilization and costs in this population, the authors made no attempt to estimate the costs of fractures that would have been averted had adherence been better. Additionally, there are reasonable published estimates of the quality adjusted life years lost from fractures. This would have at least allowed them to do a threshold analysis of how much an intervention might cost and still be cost-effective. This has been done in another country (reference 14) and this would have been a much stronger paper had this study done similar analyses for a European country / population.

Costs for hospitalization, rehabilitation and other cares supplied to patients experiencing fracture have not been included in our cost-effectiveness analysis simply because we used delayed hospitalization as effectiveness measure. Following the Reviewer’s doubts, however, we added a paragraph comparing our ICER estimates with annual cost per patient supported by the NHS for taking care patients who experience bone fracture, including hospitalizations and rehabilitation (Discussion section, Page 16, Lines 1-8).

We also compared our estimates with those obtained from a microsimulation study that used the costs per QALYs gained as outcome measure (Discussion section, Page 16, Lines 21-25).

We thank the Reviewer because both the suggestions allowed us of discussing key issues in the new version of the paper.

Point by point answers - Reviewer 2

1 Why were subjects censored before one year excluded from the analysis? The disadvantage to excluding these subjects is some loss of generalizability and the possibility of introducing selection bias.

With the aim to ensure at least one year of potential exposure at the drugs of interest, patients who did not accumulate at least 1 year of follow-up were excluded from the study. The rationale of this exclusion criterion is that RCTs have consistently showed that reductions in risk of clinical fracture became apparent after six-twelve months of BPs treatment [a,b,c]. As properly observed by the Reviewer, we are conscious that this exclusion criteria can lead to selection bias. This source of bias should however be of irrelevant magnitude since only 3.3% of incident users (1,070/32,901) were excluded for this reason.

Furthermore, we realized that the reasons for exclusion criteria were not justified in the previous version of the paper. Accordingly, we completely rewrote the paragraph in the new version of the paper (Methods section, Cohort selection and follow-up subsection, Page 6, Lines 8-18).

[a] Pols HA, Felsenberg D, Hanley DA, et al. Multinational, placebo controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Fosamax International Trial Study Group. Osteoporos Int 1999;9:461–8
2 The authors should elaborate further on how PDC was incorporated as a time-varying exposure. Was PDC treated as cumulative since treatment initiation or was only the most recent PDC considered? How was the modeling done?

PDC was treated as cumulative since treatment initiation. In addition, as adherence, as well as other factors measured during follow-up, can change over time, assessment of their effects requires properly accounting for the varying nature of these variables. This was done by fitting the Cox model that includes these factors as time-dependent covariates. For instance, by considering the predictor variable of interest (i.e. the two categories of PDC), with this approach each subject's cumulative adherence is recalculated from the start of follow-up until the time of each outcome onset. Thus, the hazard ratio associated with a category of PDC is derived using information concurrent to the observed outcomes, rather than the adherence profile over the full length of follow-up. To better clarify this issue we have now added further details on time-dependent variables in the method section (Estimating the relationship between adherence and outcome subsection, Page 8 Lines 1-14).

3 Why were data from the year after index included in calculating the Charlson score? Technically speaking, adherence could influence the score since it is being measured after bisphosphonate initiation.

Three reasons explain because the year after treatment initiation was included in calculating the Charlson score. First, hospital discharge database provides accurate and complete data since January 1, 2000, so that information about previous hospitalizations occurred at the first patient entering into the cohort (January 1, 2003) were available only for three years. So we added an additional year in the Charlson calculation because we believed that a more complete comorbidity profile might be obtained by adding one year of observation. Second, because all patients experienced at least one dispensation of BPs, we believed that BPs treatment may affect the score of all cohort members with similar intensities. On the other hand, the Reviewer suspects that adherence to BPs could influence the score value. However, empirical evidence (Table 1) show that the Charlson comorbidity score was independent from adherence, having observed that 17.3% and 17.2% of patients with low and high drug coverage respectively, had a Charlson comorbidity score ≥ 1. This is the third and more important reason suggesting that, although the Reviewer’s suggestion has theoretical validity, it does not seem to affect our estimates.

4 Is the benefit of improved adherence assumed to be constant over a six-year period? Is this assumption reasonable?

As correctly observed by the reviewer, the disease free survival time is assumed to be constant over the six year period. This further limitation is now reported in the Discussion section (Discussion section, Page 20, Lines 1-2)

5 While the method presented is an interesting alternative to constructing a microsimulation model, it is more limited. The authors mention the fact that they didn’t include the costs of an intervention to increase adherence; they also don’t include cost-savings from avoided fractures. The results pertain to a 6-year treatment period, but don’t allow for an extrapolation of how costs and fracture-free survival would be affected over a longer time-frame.

The Reviewer raises some issues limiting our approach for estimating cost-effectiveness profile of therapeutics. First, we did not include costs of interventions to increase adherence. Accordingly, we better
discussed this point in the new version of the paper (Discussion section, from Page 17, Lines 24-25 to Page 18, Lines 1-16). In particular we emphasized that (i) “...costs of interventions enhancing adherence are likely not negligible with respect to those directly related to increased drugs use...”;
(ii) “… we were not able to include the costs of implementation strategies for enhancing adherence, since, at our best knowledge, no studies have been performed in Italy on this topic...”; (iii) “… a general worsening of the reported cost-effectiveness estimates are expected if the corresponding cost source were taken into account...”; however, (iv) “… interventions able enhancing adherence unlikely focus only on one therapeutic class, so that their cost should impact on the adherence of a variety of chronic medicaments...”.

Second, costs for hospitalization, rehabilitation and other cares supplied to patients experiencing fracture have not been included in our cost-effectiveness analysis simply because we used disease-free survival time as effectiveness measure and consequently the hospitalization are not avoided but rather delayed. Following the Reviewer’s doubts, however, we added a paragraph comparing our ICER estimates with annual cost per patient supported by the NHS for taking care patients who experience bone fracture, including hospitalizations and rehabilitation (Discussion section, Page 16, Lines 1-8).

Third, although it was not requested, we also compared our estimates with those obtained from a microsimulation study that used the costs per QALYs gained as outcome measure, i.e., through models typical of economic analysis (Discussion section, Page 16, Lines 21-25).

Finally, we agree that a key limitation of our approach is that, in its current application, estimates only concern the time span along which data concerned (i.e., 6 years). This point has been discussed in the new version of the paper (Discussion section, from Page 19, Lines 23-24 to Page 20 Line 1).

The authors do mention the possibility that their measured association between adherence and fracture-free survival is confounded. I think this point merits a little further discussion. Frailty is another possible confounder – i.e. patients with cognitive impairment/poor balance may have poorer adherence and worse outcomes. Along the same lines, it would be worth considering and commenting on the apparent protective effects of other chronic medications in table 2.

Accordingly with the Reviewer's suggestions, in the new version of the paper we:
(i) commented the apparent protective effects of other chronic medications as they appear in table 2 (Discussion section, Page 19, Lines 7-13)
(ii) specified that other factors might exert stronger confounding effect on the relation of interest (e.g., cognitive impairment) (Discussion section, Page 19, Lines 20-22).

| REVIEWER | John T. Schousboe, MD PhD  
| Park Nicollet Institute for Research and Education |
| REVIEW RETURNED | 07-Dec-2013 |

GENERAL COMMENTS

This is a study of the costs of fracture prevention therapy per fracture year averted that would be incurred if medication adherence to said therapy were better. The authors use innovative methods, and clearly a main strength of this study is that it is using real world data in clinical care to populate the estimation models. That said, I think the study has several major weaknesses/omissions (some of which are acknowledged by the authors). If corrected, some would increase the apparent cost per fracture free year gained, and others would decrease the apparent cost per fracture year gained. If these omissions were minor, one could argue that correction of them would not plausibly alter the conclusions of the study. However, I think these weaknesses/omissions are substantial enough that make it very difficult (if not impossible) in my mind to draw any conclusions as to whether or not improvement of adherence among those being treated for primary prevention of
fractures would be a good thing or not.

Major concerns:
1. The health care costs saved by preventing fractures were not included. Their inclusion would significantly decrease the estimated cost per fracture free year gained. I appreciate that the authors attempted to work around this by stating they were estimating costs of additional drug only per fracture free year gained – but it seems to me this latter ICER has no meaning that can be translated into policy or health care practice.
2. Fractures for which the patient was not hospitalized were not captured. This is particularly important issue with respect to vertebral fractures, the majority of which are not hospitalized in most countries. The inclusion of these would significantly decrease the estimated cost per fracture free year gained.
3. Costs for any intervention that might improve adherence were not included. Inclusion of these would significantly increase the costs per fracture free year gained.
4. Other omissions that might have a more modest effect on estimated costs per fracture free year gained;
   a. No discounting of costs or health benefits. This is potentially of modest importance because some of costs (costs of drug therapy and [if they were included] costs of intervention) are occurring in time before the first fracture happens. The gain in fracture free years with treatment is occurring at the distal end of the fracture free period. Discounting both at the same rate would raise the apparent cost per fracture free year gained.
   b. Residual fracture prevention benefit from bisphosphonates after discontinuation. While there is no good estimation how long this persists after bisphosphonates are stopped, it may persist for a few years after discontinuation on account of skeletal retention of the drug
5. Finally, as the authors acknowledge, there is a significant potential selection bias with respect to who chooses to adhere and who does not. If those at higher risk of fracture choose to be more adherent, then the estimated fracture reduction efficacy in those adherent vs. those not adherent is underestimated, and the costs per fracture year gained are overestimated. A major weakness is the lack of risk factors that will not be capture from inpatient claims data, such as parental history of hip fracture and current smoking, that would allow the authors to adjust the estimated fracture reduction efficacy for these fracture risk factors.

Minor concerns:
1. Following sentence page 15 of 29, lines 13 to 16 is unclear. "This implies that if a higher adherence level was observed in the population, a lower number of women would have experienced an hospitalization for bone fracture. Based on our estimates, 0.18 (or 2.77) fracture free years are expected to be gained every 1,000 woman years at risk, provided that average adherence increases at 40% (or at 80%) in the target population."

Are the authors trying to state the absolute increases in fracture-free years by improving PDC to 40% and 80% respectively?
The health care costs saved by preventing fractures were not included. Their inclusion would significantly decrease the estimated cost per fracture free year gained. I appreciate that the authors attempted to work around this by stating they were estimating costs of additional drug only per fracture free year gained – but it seems to me this latter ICER has no meaning that can be translated into policy or health care practice.

R: We agree with the Reviewer’s concern. His/her argumentations are very persuasive. Accordingly, health-care costs saved by preventing fractures have been now included into the ICER. We now specified that health-care costs, rather drug costs, were used for the ICER calculation (Abstract section, Page 2, Line 13; Methods section, Estimating cost and effectiveness of enhancing adherence subsection, Page 8, Line 14 and Page 9, Lines 8-26). Of course results was slightly modified. For example, by setting average adherence at 80%, health-care costs were 265 thousand euro every 1,000 woman-years (rather than 285 thousand euro every 1,000 woman-years), and ICER value was 53 thousand euro (rather than 60 thousand euro). New findings have been reported in:
- Abstract (Page 2, Results subsection),
- Results section, Cost and effectiveness of enhancing adherence subsection (Page 14, Lines 1-13) and Sensitivity analysis subsection (Page 14, Lines 15-24),
- Discussion section (Page 15, Lines 18-24), and
- Figures 1 and 2.

We thank the Reviewer because his/her question allowed us of improving our paper by giving results that can be more easily translated into policy or health care practice.

Fractures for which the patient was not hospitalized were not captured. This is particularly important issue with respect to vertebral fractures, the majority of which are not hospitalized in most countries. The inclusion of these would significantly decrease the estimated cost per fracture free year gained.

R: We agree with the Reviewer’s concern. Accordingly, we have now emphasized this point as a main weakness of our study. In fact, because data on the outcome only regarded hospitalized patients, most vertebral fractures are not included in our calculations. The inclusion of these would significantly decrease the estimated cost per fracture free year gained (Discussion section, Page 18, Lines 10-12).

Costs for any intervention that might improve adherence were not included. Inclusion of these would significantly increase the costs per fracture free year gained.

R: Our study did not include costs to support interventions aimed at improving adherence. This is a crucial question because, as properly observed by the Reviewer, their inclusion would significantly increase the costs per fracture free year gained. Moreover, as we now emphasized, “… interventions that try to change the adherence level in population can be very costly and the objective very hard to obtain …” (Discussion section, Page 17, Lines 20-21).

In the new version of the paper we also specified that “… we are not able to measure, or even only to approximate, costs for supporting interventions aimed at improving adherence since, to our best knowledge, no studies have been performed on this topic in Italy …” (Discussion section, Page 17, Lines 22-24). On the other hand, published studies performed with this aim are mainly randomized trials reporting findings which may poorly generalizable to daily clinical practice. A reference on this topic has been added in the new version of the paper (please see current reference # 41). Since we are conscious that the lack of considerations for intervention costs remains a main weakness of our study, we reasoned along the following two alternative ways. One, we could have imposed different scenarios regarding a range of plausible intervention costs. This way, however, although can be of help to policy makers for decision process, has at least two pitfalls: (i) it introduces
a further source of uncertainty of estimates due to arbitrariness of intervention costs (ii) interventions able to enhance adherence unlikely focus on only one therapeutic class, so that their cost should impact on a variety of chronic therapies. Two, we disregarded intervention costs. This implies that our study “… must to be regarded as aimed to investigate the cost-effectiveness of enhanced adherence, rather than the cost-effectiveness profile of interventions aimed at improving drug adherence …” (Discussion section, from Page 17, Lines 25-6 to Page 18, Lines 1-2).

Accordingly, in the new version of the paper we did not report sentences stating that our study investigated the cost-effectiveness profile for investigations aimed of enhancing adherence”, since our evaluation did not include costs intervention aimed to enhance adherence in the population. On the other hand, we also realized that “…in the last few years substantial improvements of adherence with chronic drug therapies has been noticed in Lombardy Region of Italy, though no specific interventions were implemented on this regard. This suggests that a natural experiment is in progress in our setting, and our estimates can help us to understand the order of magnitude of costs and effectiveness expected from these “unplanned” changes …” (Discussion section, Page 18, Lines 2-6).

4 No discounting of costs or health benefits. This is potentially of modest importance because some of costs (costs of drug therapy and [if they were included] costs of intervention) are occurring in time before the first fracture happens. The gain in fracture free years with treatment is occurring at the distal end of the fracture free period. Discounting both at the same rate would raise the apparent cost per fracture free year gained.

R: We agree with the Reviewer that discounting of costs or health benefits should only weakly affect our estimates. Of course, it would have been necessary should intervention costs have been included in the analysis.

5 Residual fracture prevention benefit from bisphosphonates after discontinuation. While there is no good estimation how long this persists after bisphosphonates are stopped, it may persist for a few years after discontinuation on account of skeletal retention of the drug.

R: We are not sure to have adequately understood the question raised by the Reviewer. We did not censure the observation when a drug discontinuation occurred (see Methods section, Cohort selection and follow-up subsection, Page 6, Lines 17-20). Rather, a discontinuation event contributes at (i) reducing adherence with drug therapy (ii) increasing the fracture risk, not at annulling it since, as properly observed by the Reviewer, the effect of BPs persists for a few years after discontinuation on account of skeletal retention of the drug.

6 Finally, as the authors acknowledge, there is a significant potential selection bias with respect to who chooses to adhere and who does not. If those at higher risk of fracture choose to be more adherent, then the estimated fracture reduction efficacy in those adherent vs. those not adherent is underestimated, and the costs per fracture year gained are overestimated. A major weakness is the lack of risk factors that will not be capture from inpatient claims data, such as parental history of hip fracture and current smoking, that would allow the authors to adjust the estimated fracture reduction efficacy for these fracture risk factors.

R: We agree with the Reviewer's concern. Accordingly, we rewrote this part of the Discussion section (from Page 18, Lines 22-26 to Page19, Lines 1-6). As requested, among uncontrolled risk factors which may have confounded the adherence-outcome association, we also specified the potential role of familiarity and smoking.
Following sentence page 15 of 29, lines 13 to 16 is unclear. "This implies that if a higher adherence level was observed in the population, a lower number of women would have experienced an hospitalization for bone fracture. Based on our estimates, 0.18 (or 2.77) fracture free years are expected to be gained every 1,000 woman years at risk, provided that average adherence increases at 40% (or at 80%) in the target population."

R: According to the reviewer’s comment, in the new version of the manuscript we have rephrased the sentence (Discussion section, Page 15, Lines 13-16).

| REVIEWER                  | John T. Schousboe, MD PhD  
|                          | Park Nicollet Institute for Research and Education  
|                          | University of Minnesota  |
| REVIEW RETURNED         | 30-Jan-2014 |

**GENERAL COMMENTS**
The limitations that potentially lead to overestimation of costs per fracture free year gained (not capturing outpatient fractures & those who are adherent likely having a higher pre-treatment fracture risk) should be grouped together, and contrasted with the limitation that leads to underestimation of costs (cost of intervention to improve adherence. The authors have all of this information in the discussion section, I just think that grouping these together would make the major uncertainties more apparent to the reader.

**VERSION 3 – AUTHOR RESPONSE**
The limitations that potentially lead to overestimation of costs per fracture free year gained (not capturing outpatient fractures & those who are adherent likely having a higher pre-treatment fracture risk) should be grouped together, and contrasted with the limitation that leads to underestimation of costs (cost of intervention to improve adherence. The authors have all of this information in the discussion section, I just think that grouping these together would make the major uncertainties more apparent to the reader.

R: According to reviewer suggestion, in the new version of the manuscript we added a short paragraph reassuming causes of uncertainty leading to overestimation and underestimation of costs per fracture free year gained (Discussion Section Page 19, Lines 12-19).