Article details: 2013-0036	
Title	Comparison of orally administered bisphosphonate drugs in reducing the risk of hip fracture in older adults: a population-based cohort study
Authors	Suzanne M. Cadarette PhD, Linda Lévesque BScPhm PhD, Muhammad Mamdani PharmD MPH, Sylvie Perreault BScPhm PhD, David N. Juurlink MD PhD, J. Michael Paterson MSc, Greg Carney BSc, Nadia Gunraj MPH, Gillian A. Hawker MD MSc, Mina Tadrous PharmD MS, Lindsay Wong, Colin R. Dormuth ScD
Reviewer 1	William Leslie
Institution	Department of Internal Medicine, St. Boniface General Hospital
General comments	Despite widespread use of bisphosphonates for treatment of osteoporosis and fracture protection there are relatively limited head-to-head comparative data regarding the relative benefits (if any) of one agent versus another. Analyses of observational data (predominantly from US insurance plans and HMOs) have yielded contradictory results. In the past, there were large cost differentials between these agents, and therefore identifying the agent with the best effectiveness to cost ratio had important implications for the healthcare system. This is much less relevant under the current cost structure given access to generic versions of all three of the agents that were addressed in this study (cyclical etidronate, alendronate and risedronate). Although the methodologic approach (propensity score matching) and availability of large healthcare databases in two Canadian provinces (BC and Ontario) are obvious strengths to the current study, there are a major limitations that effectively negate the value of the study's findings. The authors found few differences, and those differences that were observed were felt to most likely relate to a variety of biases (confounding by indication, imbalance in baseline BMD which was not available, or residual differences in unmeasured characteristics between exposure groups in BC). Given the lower hip fracture rate among men treated with etidronate relative to alendronate and lower cost this might be seen as the preferred agent, but the authors dismiss this as likely due to selection bias. The opposite pattern is seen among women with 3 years of follow up (higher fracture risk with etidronate versus alendronate) but this was only apparent in the BC users and there was no parallel effect in Ontario users. Importantly, without an untreated control group, it is difficult to know whether agents were equally effective or equally ineffective in preventing hip fractures, and the authors acknowledge the difficulty of translating clinical trial efficacy into population effectiveness due to poor adherence among other factors. Given these limitations, it is difficult to find any "take home messages" other than an appeal for further studies that can address the identified study limitations.

Reviewer 2	KE Martin
Institution	WellPoint, Clinical Pharmacy Policy
General comments	Introduction: page 3, line 25 I don't agree that risedronate has quality data showing reduction in hip fracture risk. The sentence speaks to it being "effective", but the trials cited are secondary studies that included primary efficacy studies, so the sentence should use the word "efficacious". The MacLean 2008 analysis included many studies with high drop-out rates. This was also a problem for Cranney 2002, in which the drop-out rates for included studies were 14-43%, threatening validity. No sensitivity analysis was performed surrounding drop-out in these secondary studies. In our review of these products we have relied on 2 quality studies, the 2005 Papapoulos 2005 meta-analysis and 1996 Black primary study, to support the efficacy of alendronate for hip fracture prevention. In the Papapoulos meta-analysis, although there were high drop-out rates in some studies, this was explored through sensitivity analyses and found to not affect results. The studies with high non-completer rates only accounted for 11% of the total meta-analysis population. Methods: page 4, line 30 I propose striking the following: "….that restricted alendronate and risedronate coverage to those at higher fracture risk between 2001 and 2007. Since 2007, all three oral bisphosphonates have been open listed in Ontario." This is confusing. It makes it sound like BC doesn't have any restriction in place. Are they indeed still restrictive on these drugs? Page 4, line 39 Propose combining the 2 sentences as follows: In the current study, we restricted inclusion to new users of an oral bisphosphonate from April 1, 2001 to March 31, 2008, with no evidence of prior osteoporosis treatment, thereby ensuring their use of the oral bisphosphonate as first line therapy. Page 4, line 49 What do you mean by "were available"; available on the market or available without restriction? If available without restriction, is this also true for BC? Interpretation: page 7, line 55 Recommend striking "risedronate" if my argument is accepted about lack of hip fracture data with risedronate Introduction: page 3, line 25
Author response	We provide point-by-point responses to the minor revisions that were requested. To facilitate review of our revisions, we have accepted all changes in the original submission to *CMAJ Open*, and use the Microsoft Word track changes feature to document new edits to the manuscript text.

	<u>Points raised by *CMAJ Open* editors</u>
	
	1. Abstract: the objective (one sentence) of the study needs to be included in the background section.
	
	• The abstract "background" is now one sentence – we deleted the second sentence, page 2.
	
	2. Title: should include the type of cohort study (e.g., retrospective)
	
	• We understand and appreciate the efforts that editors are making to encourage all papers to explicitly state the study design. However, the terms "retrospective" and "prospective" in the context of a cohort study may be less critical compared to distinguishing between different types of observational study designs, such as "case-control," or "case-crossover." In light of STROBE guidelines that do not support the use of the terms "retrospective" and "prospective," we respectfully ask that editors consider permitting us to keep our title as submitted.
	
	As detailed in the STROBE guidelines, the terms "retrospective" and "prospective" in the context of observational research studies are ill-defined, and thus STROBE guidelines do not support the use of the terms (*Ann Inter Med* 2007; 147(8):W-168). The STROBE statement acknowledges that many researchers do use these terms, yet not consistently, which leads to confusion. Indeed, Dr. Cadarette sees this first hand in her teaching at the University of Toronto – both professional pharmacy students and physicians gaining graduate level research training are confused by the "retrospective" cohort, as it often only refer to whether the data are available at the time of study design. The analysis is indeed prospective, starting with drug exposure and following patients forward. Although we kindly request that editors consider our request in light of the fact that STROBE guidelines do not support use of the term "retrospective," we also understand and appreciate editors' efforts to be consistent in study design reporting, and will thus modify the title should editors continue to support the term "retrospective."
	
	3. Figure: The figure can be included in the article, rather than as an appendix.
	
	• We have moved the appendix figure to the main article, and thus renamed all figures:
	  ○ "Appendix Figure" is now "Figure 1"
	  ○ "Figure 1" is now "Figure 2"
	  ○ "Figure 2" is now "Figure 3"
	
	4. Interpretation:
	
	a. Begin with a sentence that answers your research question (What did the study show?). The second sentence should be a brief statement about implications for practice or research (What do the findings mean?). Avoid speculation and generalization.
	
	• We have modified the first few sentences of our interpretation

	section on page 8:
	
	"We identified little difference in the effectiveness of alendronate or risedronate in reducing 1-year hip fracture risk among men or women, yet inconsistent results comparing etidronate and alendronate. With alendronate and risedronate demonstrating similar drug effectiveness, physicians may be comforted in prescribing their first-line oral bisphosphonate agent of choice to patients. More evidence with better clinical data is needed to understand the relative benefits of etidronate compared with alendronate or risedronate."
	
	b. Please structure the Interpretation section (discussion) into the following 4 main categories:
	
	***Main findings**
	
	***Explanation and comparison with other studies**
	
	***Limitations**
	
	***Conclusions and implications for practice and future research.**
	
	• The interpretation section was reorganized as suggested, for example:
	  ○ The first paragraph was restructured to focus on the main findings and implications for practice,
	  ○ We have added two subheadings: "limitations," and "conclusions and implications for practice and future research," and
	  ○ Several sections were moved to align with the 4 main categories structure.
	
	5. It's not clear whether you have directly addressed the comments made by Reviewer 2 in the version submitted to CMAJ Open. I have appended these at the end of this letter for your consideration.
	
	[Some may no longer apply.]
	
	• Our apologies for not clearly responding to reviewer 2 comments. Indeed, we did respond to several of the reviewer comments, yet in taking the time to provide point-by-point responses, noticed that we also neglected some of the comments. Please see below for detailed point-by-point responses.
	
	1. Introduction: page 3, line 25 - I don't agree that risedronate has quality data showing reduction in hip fracture risk. The sentence speaks to it being "effective", but the trials cited are secondary studies that included primary efficacy studies, so the sentence should use the word "efficacious"…
	
	• We agree that there is a clear distinction between the terms "efficacy" and "effectiveness," and that the term "effective" in reference to RCT data is incorrect. Our apologies for not catching this error during our initial revisions, and we thank *CMAJ Open* editors for requesting that we provide point-by-point responses to cue us to the required revision! As suggested by the reviewer, we have replaced the word "effective" with "efficacious" in the

	abstract (page 2) and introduction (page 4) that references placebo-controlled trial evidence of drug efficacy. **2. Methods: page 4, line 30 - a. I propose striking the following: "….that restricted alendronate and risedronate coverage to those at higher fracture risk between 2001 and 2007. Since 2007, all three oral bisphosphonates have been open listed in Ontario." This is confusing. It makes it sound like BC doesn't have any restriction in place. Are they indeed still restrictive on these drugs?** • Rather than striking the sentences as proposed, we previously (before submission to *CMAJ Open*), clarified that BC data are comprehensive and include all drugs dispensed: *"British Columbia PharmaNet data are comprehensive and include all drugs dispensed in community pharmacies. These data therefore include drugs covered by the public system, as well as drugs paid through private insurance or out of pocket. In contrast, Ontario data available for analysis were drugs covered through the public Ontario Drug Benefit Program that restricted alendronate and risedronate coverage to those at higher fracture risk between 2001 and 2007. Since 2007, all three oral bisphosphonates have been open listed in Ontario."* **b. Page 4, line 39 - Propose combining the 2 sentences as follows: In the current study, we restricted inclusion to new users of an oral bisphosphonate from April 1, 2001 to March 31, 2008, with no evidence of prior osteoporosis treatment, thereby ensuring their use of the oral bisphosphonate as first line therapy.** • We did not combine the two sentences as proposed because doing so creates a lengthy sentence. Instead, we shortened the second sentence before combining the two sentences, first sentence on page 6: *"In the current study, we restricted inclusion to new users of an oral bisphosphonate from April 1, 2001 to March 31, 2008; and therefore restricted inclusion to oral bisphosphonates as first line therapy."* **c. Page 4, line 49 - What do you mean by "were available"; available on the market or available without restriction? If available without restriction, is this also true for BC?** • We previously (before initial submission to *CMAJ Open*) addressed this comment by adding "on the market" to the sentence, third sentence on page 6: *"We selected April 2001 as the earliest exposure period to restrict analyses to when all three oral bisphosphonates were available on the market."* **<u>RE: other minor points:</u>** **1. Please ensure your final word count is below 2500 words and the abstract is about 250 words.** • Our final word count is 2305 in the main text, and 244 in the abstract.

	2. Abbreviations: For only the most standard abbreviations (i.e., 95% CI, SD, OR, RR, HR), please spell out at first mention and include the abbreviation in parentheses. The abbreviations may be used throughout the remainder of the manuscript. Please remove all other abbreviations. • Hazard ratio is now defined in the abstract and on first mention (middle of page 8) in the main text. We have also removed two abbreviations -- BC (British Columbia) and BMD (bone mineral density) -- from the manuscript abstract and text. **3. Please include up to 1 academic and 1 professional degree after each author's name.** • Author degrees now comply fully with this guideline. **4. Please use plain numbers in brackets for your references and do not use automatic numbering of field codes as these do not carry over well into our publishing software.** **We have updated our referencing style to use plain numbers in brackets without field codes.** • We now use plain numbers in brackets without field codes.