Article details: 2014-0078	
Title	Trends in the coprescription of proton pump inhibitors with clopidogrel: an ecological analysis
Authors	Juurlink, David; Gomes, Tara; Paterson, Michael; Hellings, Chelsea; Mamdani, Muhammad
Reviewer 1	
Name	BR Dalton
Institution	Alberta Health Services
General comments	Major: 1. For those who are interested in maximizing the effect of releasing a research report on prescribing behaviour, could there be more description of the traction and path in the media and scientific press? eg. Was a press release made? How many news networks covered the story? How many interviews of authors occurred? Were results discussed at scientific or continuing education meetings (or other speaking engagements)? Similarily, did the JAMA study (ref 14) or regulatory alerts (Health Canada or FDA) have public and professional media attention. 2. Could data on the trends of pantoprazole and other PPIs not co prescribed with clopidogrel be obtained & included? If a no effect (or only a minor effect) in those trends was observed at that time, it would strengthen the case that the 2009 study caused what has been observed. 3. If data of admission for AMI in patients co-prescribed clopidogrel and PPI were analyzed previously for your 2009 study, why has this not been done again? Readers may rightly ask "with this change in prescribing, did it have any impact on outcome?" I can only assume that a report will be forthcoming. Minor: 1. Page 4 line 31-33: "In early 2009, we published the first observational study of the clinical consequences of this newly described drug interaction.13" It would benefit readers if you could be explicit about the clinical consequences of this drug interaction in this paragraph. 2. Page 7 line 17"During the 11-year study period, the number of people aged 66 years or older dispensed clopidogrel during each quarter increased from 330 in the second quarter of 1999 to 62,843 by the first quarter of 2010" Awkward - "number of people clopidogrel was dispensed to"
Author response	Thank you for the invitation to review this manuscript. It is an interesting study of the effect of the release of a study on prescribing behaviour in a natural setting. The report is very well written. The methods are well described and they completed the tasks stated in the methods. The statistical analysis appears to be rigorous although this reviewer is not well acquainted with the techniques, so would not be a good judge. Response: We thank the reviewer for these positive comments. There are a few major and minor points listed below that I believe could enhance the quality of the report. Major: 1. For those who are interested in maximizing the effect of releasing a research report on prescribing behaviour, could there be more description of the traction and path in the media and scientific press? eg. Was a press release made? How many news networks covered the story? How many interviews of authors occurred? Were results discussed at scientific or continuing education meetings (or other speaking engagements)? Similarly, did

	the JAMA study (ref 14) or regulatory alerts (Health Canada or FDA) have public and professional media attention. Response: The media coverage of this issue was extensive. An accurate determination of the number of media 'hits' cannot be readily attained with confidence, but the study was covered by Canada AM, The National, CTV National News, The Globe and Mail, the Canadian Press and others. Another testament to the study's reach is that in just 5 years, it has been cited approximately 341 times. The FDA notice and JAMA study that followed ours also elicited media attention, but it is not possible to determine how much. We have elected not to expand upon this in the revised manuscript but could if the editors wish. 2. Could data on the trends of pantoprazole and other PPIs not co prescribed with clopidogrel be obtained & included? If a no effect (or only a minor effect) in those trends was observed at that time, it would strengthen the case that the 2009 study caused what has been observed. Response: The reviewer asks if we could ascertain PPI trends in patients not taking clopiodgrel. We haven't undertaken an analysis of this for two reasons. First, it wouldn't advance our conclusions regarding co-prescription of an interacting drug pair in a meaningful way. Second, the dramatic rise of pantoprazole likely did have some "spillover" into patients not taking clopidogrel, if for no other reason than clopidogrel is generally stopped after a period of time (for example, after a bare-metal or drug eluting stent) while PPIs are often continued. 3. If data of admission for AMI in patients co-prescribed clopidogrel and PPI were analyzed previously for your 2009 study, why has this not been done again? Readers may rightly ask "with this change in prescribing, did it have any impact on outcome?" I can only assume that a report will be forthcoming. Response: This is a fair question. The objective of this analysis was to examine the influence of our paper on prescribing trends only. We have not undertaken an analysis of outcomes following the publication, because under an ecologic design, any signal in such an analysis would be dwarfed by the associated noise. This is particularly true because the absolute risk associated with omeprazole use relative to pantoprazole (or non-use for that matter) use is very small and subject to a host of influences (drug timing, pharmacogenetics, etc). A detailed exposition of the omeprazole-clopidogrel interaction (Juurlink Circulation 2009;(23):2310-2) explains this in more detail. Minor: 1. Page 4 line 31-33: "In early 2009, we published the first observational study of the clinical consequences of this newly described drug interaction.13" It would benefit readers if you could be explicit about the clinical consequences of this drug interaction in this paragraph. Response: We thank the reviewer for this suggestion and have added a sentence briefly summarizing the conclusions of our 2009 CMAJ publication. 2. Page 7 line 17"During the 11-year study period, the number of people aged 66 years or older dispensed clopidogrel during each quarter increased from 330 in the second quarter of 1999 to 62,843 by the first quarter of 2010" Awkward - "number of people clopidogrel was dispensed to" Response: We have revised the sentence in the interest of clarity

	and grammatical correctness.
Reviewer 2	
Name	John S. Sampalis
Institution	JSS Medical Research and McGill University, Surgical Epidemiology
General comments	The authors must be commented for taking on this work to clarify issues and prevent misinterpretation or use of the results of other studies. This is a good ecological study and must be identified as such. 1. Therefore as a first comment I would suggest that the title must be changed to reflect the fact that this is an ecological study. Assuming that at this point further analyses would not be ideal, the authors should address the following limitations and perhaps consider addressing some of the following questions: 2. This is an ecological study and hence should be generating hypotheses rather than testing them. The authors should present and interpret the results in this context. 3. There is no longitudinal patient - level follow up. For the periods of interest as an example, a very relevant question would be one of treatment changes such as treatment termination and switching. More specifically, could the authors determine for the patients on a PPI in 2009: how many stopped treatment and how many switched from one PPI to another with emphasis on how many were switched to pantoprazole. This is the key question in the assessments of the impact of media and science literature on prescribing behaviors. 4. The authors should present some data or make assumptions about the population at risk and what happens to them. More precisely, the question is: how many patients treated with clopidogrel are also candidates to be treated with PPIs. We may assume that this will not change over time (an assumption that needs to be proven or well supported). We can then determine the population at risk and hence derive an estimated (standardized) expected rate of PPI use. Then we can assess whether there has been a shift in the management of these patients. Given the access to data I would also assume that a diagnosis with GI diseases indicating treatment with a PPI as a co-morbidity would give us more precise estimates of the population at risk. This will also allow us to assess what alternative treatments, if any, were used for these patients. The question here is whether these patients were treated with something else or were there patients not managed for their GI. These decisions have significantly different implications with respect to the quality of care or treatment gaps in these patients.
Author response	The authors must be commented for taking on this work to clarify issues and prevent misinterpretation or use of the results of other studies. This is a good ecological study and must be identified as such. Response: We thank the reviewer for this comment. 1. Therefore as a first comment I would suggest that the title must be changed to reflect the fact that this is an ecological study. Response: We have revised the title to indicate the nature of the study design Assuming that at this point further analyses would not be ideal, the authors should address the following limitations and perhaps consider addressing some of the following questions:

	2. This is an ecological study and hence should be generating hypotheses rather than testing them. The authors should present and interpret the results in this context. Response: We respectfully disagree with the reviewer. The analysis was done to test the hypothesis, driven in part by clinical observation, that our 2009 publication in CMAJ influenced PPI prescribing trends among clopidogrel recipients. Accordingly, no change has been made. 3. There is no longitudinal patient - level follow up. For the periods of interest as an example, a very relevant question would be one of treatment changes such as treatment termination and switching. More specifically, could the authors determine for the patients on a PPI in 2009: how many stopped treatment and how many switched from one PPI to another with emphasis on how many were switched to pantoprazole. This is the key question in the assessments of the impact of media and science literature on prescribing behaviors. Response: We have now extended our study period and examined the degree of switching from non-pantoprazole PPIs, as noted in our reply to the Editors. 4. The authors should present some data or make assumptions about the population at risk and what happens to them. More precisely, the question is: how many patients treated with clopidogrel are also candidates to be treated with PPIs. We may assume that this will not change over time (an assumption that needs to be proven or well supported). We can then determine the population at risk and hence derive an estimated (standardized) expected rate of PPI use. Then we can assess whether there has been a shift in the management of these patients. Given the access to data I would also assume that a diagnosis with GI diseases indicating treatment with a PPI as a co-morbidity would give us more precise estimates of the population at risk. This will also allow us to assess what alternative treatments, if any, were used for these patients. The question here is whether these patients were treated with something else or were there patients not managed for their GI. These decisions have significantly different implications with respect to the quality of care or treatment gaps in these patients. Response: The reviewer poses questions that are beyond the resolution of administrative databases. However, most patients treated with clopidogrel also receive ASA, and many physicians reflexively prescribe a PPI in patients receiving dual antiplatelet therapy. There is fair evidence that PPIs reduce the risk of gastrointestinal hemorrhage in this setting.
Reviewer 3	
Name	Petra Alwine Thürmann
Institution	Helios Klinikum Wuppertal, Germany
General comments	The authors present a carefully conducted pharmacoepidemiological study on the use of PPIs and clopidogrel. Background for this analysis are controversial study results and to some extent contradictory recommendations on the concurrent use of clopidogrel and PPIs. 1. The analysis is restricted to patients 66 years and older. The interaction should also occur in younger patients with coronary artery disease, what was the reason for their exclusion? The lower rate of other risk factors for GI bleeding and the fact that age per se

	represents a risk factor? 2. The authors conclude that PPI withdrawal in some patients may be dangerous and an overreaction towards warnings. However, misuse of PPIs is a commonly observed problem and may have been corrected by this warning (e.g. Heidelbaugh JJ et al. Overutilization of proton pump inhibitors: a review of cost-effectiveness and risk [corrected]. Am J Gastroenterol. 2009 Mar;104 Suppl 2:S27-32) and they show no proof for an increase in GI bleeding events. 3. Moreover, the potential side effects of PPIs should also be mentioned, i.e. risk for osteoporosis and fractures (e.g. Ngamruengphong S et al. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. Am J Gastroenterol. 2011 Jul;106(7):1209-18) and clostridium difficile infections (e.g. Janarthanan S et al. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am J Gastroenterol. 2012 Jul;107(7):1001-10) – although the evidence for both risks is still rather weak. 4. As advocated by some recommendations and guidelines (Abraham NS et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines: A Focused Update of the ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use. Am J Gastroenterol 2010;105:2533–2549) clinicians may have preferred in some patients the use of an antihistaminic drug. 5. Thus, the issue of underuse of gastroprotection during clopidogrel therapy can be illustrated much better, when prescriptions of H2-antagonists are considered as well. This would add valuable information and should be available for the authors. [Editor's note: We are not convinced that the inclusion of H2-antagonists in the analysis is necessary]
Author response	The authors present a carefully conducted pharmacoepidemiological study on the use of PPIs and clopidogrel. Background for this analysis are controversial study results and to some extent contradictory recommendations on the concurrent use of clopidogrel and PPIs. 1. The analysis is restricted to patients 66 years and older. The interaction should also occur in younger patients with coronary artery disease, what was the reason for their exclusion? The lower rate of other risk factors for GI bleeding and the fact that age per se represents a risk factor? Response: While younger patients tend to have fewer risk factors for bleeding and may be less likely to receive a PPI with clopidogrel, our databases contain prescription drug information only for patients aged 65 years and older. Our analyses are necessarily limited to these patients. 2. The authors conclude that PPI withdrawal in some patients may be dangerous and an overreaction towards warnings. However, misuse of PPIs is a commonly observed problem and may have been corrected by this warning (e.g. Heidelbaugh JJ et al. Overutilization of proton pump inhibitors: a review of cost-effectiveness and risk [corrected]. Am J Gastroenterol. 2009 Mar;104 Suppl 2:S27-32) and they show no proof for an increase in GI bleeding events. Response: We agree with the reviewer that PPIs are overprescribed, although inappropriate use is less likely in patients taking clopidogrel. We have opted not to act on this comment because it is only of peripheral relevance to our manuscript.

	3. Moreover, the potential side effects of PPIs should also be mentioned, i.e. risk for osteoporosis and fractures (e.g. Ngamruengphong S et al. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. Am J Gastroenterol. 2011 Jul;106(7):1209-18) and clostridium difficile infections (e.g. Janarthanan S et al. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am J Gastroenterol. 2012 Jul;107(7):1001-10) – although the evidence for both risks is still rather weak. Response: Controversy surrounds many of these suspected adverse events from PPI therapy. Because our study focuses on a changes in clinical practice related to a novel drug interaction, rather than adverse drug events as a whole, we have elected not to act on this suggestion. If the editors disagree with this approach we will add mention of these other adverse effects. 4. As advocated by some recommendations and guidelines (Abraham NS et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines: A Focused Update of the ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use. Am J Gastroenterol 2010;105:2533–2549) clinicians may have preferred in some patients the use of an antihistaminic drug. Response: This is true, but it is not directly relevant to our study question. No action has been taken. 5. Thus, the issue of underuse of gastroprotection during clopidogrel therapy can be illustrated much better, when prescriptions of H2-antagonists are considered as well. This would add valuable information and should be available for the authors. [Editor's note: We are not convinced that the inclusion of H2-antagonists in the analysis is necessary] Response: Our study question focused on changes in the prescribing of PPIs with clopidogrel following publication of out study. Our findings in regard to pantoprazole are quite striking, and are independent of whether or not H2 blocker prescribing changed as well. Accordingly, we have followed the editor's suggestion and not examined prescribing of H2 receptor antagonists.
Reviewer 4	
Name	Laure Huot,
Institution	Unite de recherche Clinique, Hospices Civils de Lyon, Lyon, France
General comments	The manuscript presents the results of an observational study on trends in prescriptions of proton pump inhibitor (PPI) in patients treated with clopidogrel. The manuscript is well written, however some clarifications could be added to the text. Major comments: 1. In the Introduction section, results from the various pharmacodynamic studies could be more detailed, e.g. (1) the results published by Angiolillo et al. are from 4 randomized placebo-controlled studies (not only one); (2) the authors should have detailed the study published by Fontes-Carvalho et al., which is also a randomized crossover design that measured platelet function after clopidogrel treatment concomitant with omeprazole or pantoprazole. 2. Although early communication had been made by the FDA in January 2009 without distinction between PPIs, an update was published in November 2009 focusing on omeprazole and

	esomeprazole drug interaction, and specifying that "At this time, FDA does not have enough information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to advise on their use together". Moreover, the pharmacodynamic studies mentioned in the Introduction section (ref. 8-12) were performed after the FDA published its first advisory. 3. The manuscript presents the results of a 11-year period ending on the first quarter of 2010. Considering the foregoing, it may be unfortunate that the study was not extended after the beginning of 2010 to establish a trend and the decline in PPI prescriptions much further. Since claims data are available as a continuous ongoing process, there is no reason to stop the analysis at year 2010. This should be discussed in the Interpretation section. Moreover, it seems that the bibliography has not been updated since July 2011. [Editor's note: Please update data and references] 4. Formally, the ARIMA model was not used to evaluate the changes in PPI prescribing, but rather to anticipate (starting first quarter of 2009) the expected continuous trend based on a steady-state hypothesis and on the previous collected data. The purpose of the ARIMA model should be better explained by the authors. It should be clarified in the Results section that the projected estimate is from the ARIMA model (page 8 line 2). What were the results of the stationarity and auto-correlation tests? These results allow to ascertain the reliability of the proposed model. 5. The statistical tests performed to compare the various proportions and the overall decline of PPIs prescriptions should be specified in the Methods section. 6. The conclusion (page 9 lines 8-15) should be modified. It refers only to the prescription of pantoprazole and is not in line with what was discussed above about the overall trend of PPI. What is the clear message mentioned by the authors, since the recommendations of the agencies were for the whole class? 7. For the same reason, the last sentence of the abstract is neither understandable nor established from a scientific perspective. The conclusion should be changed. Minor comments: Abstract: 1. Background line 7, precise that "two observational studies and a FDA advisory addressed the clinical consequences of the drug interaction…". It should be mentioned that the study examined prescriptions in a Canadian population. 2. Methods: It should be specified that the study was cross-sectional. The data source should be announced. 3. Results: Please add the numbers corresponding to the presented percentages. The result "Decline of roughly 10%…" appears in the Abstract but not in the Result section. Manuscript: 4. Page 4 line 10, please include the abbreviation "CYP2C19", which is used in the rest of the manuscript. 5. When reading the second paragraph of the Introduction section, the reviewer wonders what were the results and conclusions of the previous observational study (page 4 line 33) and why these were controversial. The first part of the last paragraph of the Introduction could be moved here, for better understanding. 6. Page 4 line 38, suppress "a" before "conclusion". 7. The authors mainly point to the FDA advisory, while their observational study had been performed on a Canadian population: little emphasis is made about the national Canadian advisory. 8. The authors must precise the study period. Has the second

	quarter of 1999 been chosen in relation with the market authorization of clopidogrel? This should be clarified. 9. Only one Figure is presented in the manuscript, please harmonize page 7 line 26 and line 40. 10. The number of PPIs prescriptions among studied patients should appear in the text (page 7 line 24), and not only the percentages. What was the number and percentage of rabeprazole prescriptions in the last quarter of 2008 among PPIs? 11. Page 7 lines 55-57, the sentence in parenthesis should be removed. 12. In the Interpretation section page 8, lines 31-43 should be re-written: the sentence is too long and carry two different ideas. 13. Would it have been possible to observe the clinical outcomes (page 9 line 2), and if so how? 14. In the Figure legend: From 1999 through 2010 (instead of 2009)? Please specify that the grey lines representing projected co-prescriptions rates were based on ARIMA modeling.
Author response	The manuscript presents the results of an observational study on trends in prescriptions of proton pump inhibitor (PPI) in patients treated with clopidogrel. The manuscript is well written, however some clarifications could be added to the text. Major comments: 1. In the Introduction section, results from the various pharmacodynamic studies could be more detailed, e.g. (1) the results published by Angiolillo et al. are from 4 randomized placebo-controlled studies (not only one); (2) the authors should have detailed the study published by Fontes-Carvalho et al., which is also a randomized crossover design that measured platelet function after clopidogrel treatment concomitant with omeprazole or pantoprazole. Response: A large body of work has explored the interaction between PPIs and clopidogrel. The reviewer notes some of the ex vivo studies. For the most part, these have shown that omeprazole influences the platelet response to clopidogrel but pantoprazole does not. Given the goals of our study and the intended audience, we believe that a general comment about the conclusions of these studies is preferable to a detailed exposition of the basic science itself. Accordingly, we have not acted on this comment, but could if the editors wish. 2. Although early communication had been made by the FDA in January 2009 without distinction between PPIs, an update was published in November 2009 focusing on omeprazole and esomeprazole drug interaction, and specifying that "At this time, FDA does not have enough information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to advise on their use together". Moreover, the pharmacodynamic studies mentioned in the Introduction section (ref. 8-12) were performed after the FDA published its first advisory. Response: We agree, but reiterate that the change in practice we observed relates to the two observational studies (Juurlink CMAJ Jan 2009 CITE and Ho JAMA Feb 2009 CITE) and the FDA's "Early Warning" of January 26th 2009. Our impression is that the reviewer's comment does not seem to warrant modification of the manuscript. 3. The manuscript presents the results of a 11-year period ending on the first quarter of 2010. Considering the foregoing, it may be unfortunate that the study was not extended after the beginning of 2010 to establish a trend and the decline in PPI prescriptions much

	further. Since claims data are available as a continuous ongoing process, there is no reason to stop the analysis at year 2010. This should be discussed in the Interpretation section. Moreover, it seems that the bibliography has not been updated since July 2011. [Editor's note: Please update data and references] Response: As noted in our response to the editors, we have now extended the study period to the third quarter of 2013. 4. Formally, the ARIMA model was not used to evaluate the changes in PPI prescribing, but rather to anticipate (starting first quarter of 2009) the expected continuous trend based on a steady-state hypothesis and on the previous collected data. The purpose of the ARIMA model should be better explained by the authors. It should be clarified in the Results section that the projected estimate is from the ARIMA model (page 8 line 2). What were the results of the stationarity and auto-correlation tests? These results allow to ascertain the reliability of the proposed model. Response: The purpose of the interventional ARIMA model was to assess the impact of the study on PPI utilization rates. As the reviewer notes, this is done by comparing the expected trends in PPI utilization to the actual trends. Accordingly, we have modified the Results section to include the text As with the primary analysis, the observed trends were significantly different from expected. Autocorrelation was assessed using the Ljung-Box chi-square statistic and were conducted for up to 12 lags. The test statistics suggested that autocorrelation was sufficiently handled by the final model. Stationarity was assessed using the Augmented Dicky-Fuller test and test results suggested that a first order difference was sufficient in making the data stationary. Should further information be needed (e.g. test plots) we can provide them, but we anticipate that few readers would wish this information. 5. The statistical tests performed to compare the various proportions and the overall decline of PPIs prescriptions should be specified in the Methods section. Response: Please see the response above. 6. The conclusion (page 9 lines 8-15) should be modified. It refers only to the prescription of pantoprazole and is not in line with what was discussed above about the overall trend of PPI. What is the clear message mentioned by the authors, since the recommendations of the agencies were for the whole class? Response: The messages we wish to convey are: 1. In early 2009, a major shift occurred in the prescribing of PPIs among clopidogrel recipients, such that pantoprazole became the most commonly used agent. 2. This most likely reflected our publication in CMAJ, which conveyed the message that, until the PPI-clopidogrel interaction was better characterized, pantoprazole should be the preferred PPI. (Parenthetically, this same message was not conveyed by the contemporaneous FDA advisory or the subsequent JAMA publication, making it unlikely that they explain the shift to pantoprazole.) 3. A modest reduction in overall PPI use also occurred, which may reflect inappropriate generalization of the drug interaction warning to all PPIs. If so, this may reflect a lack of specificity in public messaging about the interaction.

	These are now reflected in the first paragraph under Main Findings. 7. For the same reason, the last sentence of the abstract is neither understandable nor established from a scientific perspective. The conclusion should be changed. Response: We have modified the Interpretation section of the abstract, and now believe it conveys our findings accurately. Minor comments: Abstract: 1. Background line 7, precise that "two observational studies and a FDA advisory addressed the clinical consequences of the drug interaction…". It should be mentioned that the study examined prescriptions in a Canadian population. Response: This change has been made. 2. Methods: It should be specified that the study was cross-sectional. The data source should be announced. Response: We have outlined the data source and made clear that the study design is that of a serial cross-sectional time series. 3. Results: Please add the numbers corresponding to the presented percentages. The result "Decline of roughly 10%…" appears in the Abstract but not in the Result section. Response: This change has been made. Manuscript: 4. Page 4 line 10, please include the abbreviation "CYP2C19", which is used in the rest of the manuscript. Response: We have removed the abbreviation in response to the editors' suggestion in that regard. We defer to the editors on whether CYP should be used. 5. When reading the second paragraph of the Introduction section, the reviewer wonders what were the results and conclusions of the previous observational study (page 4 line 33) and why these were controversial. The first part of the last paragraph of the Introduction could be moved here, for better understanding. Response: We thank the reviewer for this comment. As noted above, we now briefly summarize the findings of our 2009 study in CMAJ. 6. Page 4 line 38, suppress "a" before "conclusion". Response: We thank the reviewer for noting this typo. This change has been made. 7. The authors mainly point to the FDA advisory, while their observational study had been performed on a Canadian population: little emphasis is made about the national Canadian advisory. Response: We agree. This is because the Canadian advisory was not issued until August 2009. Moreover, that advisory did not distinguish among PPIs. These observations are noted in the introduction section. No change has been made. 8. The authors must precise the study period. Has the second quarter of 1999 been chosen in relation with the market authorization of clopidogrel? This should be clarified. Response: We thank the reviewer for noting this. Q2 1999 represents the first full quarter of the availability of Plavix on the Ontario formulary.

	This is now noted in the manuscript. 9. Only one Figure is presented in the manuscript, please harmonize page 7 line 26 and line 40. Response: This has been clarified. 10. The number of PPIs prescriptions among studied patients should appear in the text (page 7 line 24), and not only the percentages. What was the number and percentage of rabeprazole prescriptions in the last quarter of 2008 among PPIs? Response: We have made this change, but the manuscript is now rather 'number-dense.' We defer to the editors on whether this change should remain. 11. Page 7 lines 55-57, the sentence in parenthesis should be removed. Response: This change has been made. 12. In the Interpretation section page 8, lines 31-43 should be re-written: the sentence is too long and carry two different ideas. Response: This section has now been revised. 13. Would it have been possible to observe the clinical outcomes (page 9 line 2), and if so how? Response: Please see our detailed response to Dr Dalton. 14. In the Figure legend: From 1999 through 2010 (instead of 2009)? Please specify that the grey lines representing projected co-prescriptions rates were based on ARIMA modeling. Response: We have extended the study period and now better clarify the nature of the lines in the legend.
Version 2	
Name	Avgil Tsadok, Meytal
Institution	McGill University Health Centre, Internal Medicine and Clinical Epidemiology
General comments	The main missing information is the trends of the different PPIs in general, and not only among clopidogrel users. It is possible that the patterns of use among the clopidogrel users only reflect the general patterns of PPI use. The authors do not rule out the option of different factors that may contribute the trends seen in Ontario except for their previous publication. These factors can be differences in drug costs or other regulatory factors. An interesting note: around the end of 2007 a generic version of pantoprazole by Teva finally became available and the manufactures were sued during 2008, but eventually the drug was made commercially available. This could also have affected the increase in use during 2009 as the price would have decreased drastically. As the Juurlink paper was not published until March 2009, and as their graph shows that a major increase in use occurred in the first quarter of 2009, there conclusion could have been more inclusive to other possible explanations. There are some bold statements in the discussion: "The mass shift toward preferential use of pantoprazole may have favourably influenced cardiac outcomes among some clopidogrel recipients. Conversely, because overall PPI prescribing among clopidogrel recipients declined slightly following our publication, this may have been associated with harm". These speculation should be

	attenuated, and have some supporting evidence from the literature.
Author response	1. The main missing information is the trends of the different PPIs in general, and not only among clopidogrel users. It is possible that the patterns of use among the clopidogrel users only reflect the general patterns of PPI use. Response: Please see our new analysis described above and the accompanying interpretation. 2. The authors do not rule out the option of different factors that may contribute the trends seen in Ontario except for their previous publication. These factors can be differences in drug costs or other regulatory factors. An interesting note: around the end of 2007 a generic version of pantoprazole by Teva finally became available and the manufactures were sued during 2008, but eventually the drug was made commercially available. This could also have affected the increase in use during 2009 as the price would have decreased drastically. As the Juurlink paper was not published until March 2009, and as their graph shows that a major increase in use occurred in the first quarter of 2009, their conclusion could have been more inclusive to other possible explanations. Response: Our paper was released ahead of print on January 28th 2009, contemporaneously with the FDA advisory and a few weeks before a related publication in JAMA. By their timing alone, the phenomena noted by the reviewer are not relevant. No action has been taken. 3. There are some bold statements in the discussion: "The mass shift toward preferential use of pantoprazole may have favourably influenced cardiac outcomes among some clopidogrel recipients. Conversely, because overall PPI prescribing among clopidogrel recipients declined slightly following our publication, this may have been associated with harm". These speculation should be attenuated, and have some supporting evidence from the literature. Response: The comments noted by the reviewer are clearly labelled as speculative, but more importantly they are accurate. We are not inclined to remove them because they address the potential clinical consequences of our findings. We defer to the editor in this regard. Reference List (1) Blumenthal-Barby JS, Krieger H. Cognitive Biases and Heuristics in Medical Decision Making: A Critical Review Using a Systematic Search Strategy. Med Decis Making 2014.
Reviewer 2	
Name	Burry, Lisa D.
Institution	Department of Pharmacy, Mount Sinai Hospital
General comments	Major comments: - The findings would be strengthened by examining whether the same shift occurred in PPI prescribing non-clopidogrel patients. If the shift only occurred in clopidogrel recipients, readers would be better persuaded that the shift was because of the new evidence. - Page 5, paragraph starting on line 34. Considerable text is dedicated to reviewing studies which support the interaction. Suggest dedicating a similar amount of text to references 15 and 16 to ensure a balanced review of the evidence. - Page 7, line 6. 'Influenced' is too strong a statement for an ecologic study. Perhaps 'we examined the extent to which PPI prescribing patterns shifted after the drug advisories were issued and publication of these studies'. - Page 7, line 20. Please verify that the date range on this line and elsewhere in the text are correct and consistent. 1999 - 2010 or

	1999-2013. ? - Page 9, line 24. The 20.0% (12,433 of 62129) statistic is repeated on page 9, line 32. Is this a coincidence that the values are identical? Odd. - Wonder about patient level shifts from non-pantoprazole PPI to pantoprazole. Would be more compelling. - consider emphasizing in the discussion that the shift in prescribing occurred years after the introduction of generic pantoprazole and after the ODB listing. This is noted earlier in the manuscript but I believe it is worth restating. - Page 6, paragraph starting on line 12. Suggest deleting the 1st sentence as the points - both the study findings and the media attention - are made elsewhere in the introduction. Similarly, suggest deleting the phrase 'In both the abstract and the media attention that accompanied our study' as this is adequate emphasized elsewhere in the introduction. Continue with 'In our study we emphasized that patients need not....' - Page 10, line 43. Correct citation manager reference to Wedemeyer. - Consider adding to the discussion that clopidogrel-treated patients who would have been non-pantoprazole PPI would not have shifted to prasugrel/ticagrelor as these agents were not available on the market at that time.
Author response	Major comments: 1. The findings would be strengthened by examining whether the same shift occurred in PPI prescribing non-clopidogrel patients. If the shift only occurred in clopidogrel recipients, readers would be better persuaded that the shift was because of the new evidence. Response: We have now conducted such an analysis, and we do identify a significant increase in the use of pantoprazole among patients not receiving clopidogrel. However, this begins approximately one year after our paper was published (see appended figure). We believe tis observation has several contributing explanations: 1. The "bandwagon effect"- accelerated diffusion through a group of a pattern of behaviour.(1) In this instance, the preferential use of pantoprazole in a sizeable subset of patients (those on clopidogrel) leaves physicians more familiar with pantoprazole and its dosing, increasing the likelihood that they will prescribe it to other patients in whom a PPI is indicated. 2. Institutional policies – Many hospitals have on formulary a PPI of choice, andsome employ an automatic substitution policy for that agent. We understand thatsome hospitals changed their PPI of choice to pantoprazole following our publication, in the interest of simplicity. 3. The addition of Tecta® to the Ontario formulary - This is likely the most important factor underlying the new findings. This new formulation of pantoprazole was was heavly promoted by its manusfacturer and added to the Ontario formulary on June 14th, 2010. This coincides exactly with the rise in pantoprazole use in the analysis requested by the reviewer, and more than a year after the surge in pantoprazole use among clopidogrel recipients documented in our main analysis. Please note that we have not added the new figure to the manuscript because of the other explanations for the finding, most notably the launch of Tecta in mid-2010. This figure neither informs our study's message nor vitiates our original observations. If the editors disagree, we can revisit this decision. 2. Page 5, paragraph starting on line 34. Considerable text is

	dedicated to reviewing studies which support the interaction. Suggest dedicating a similar amount of text to references 15 and 16 to ensure a balanced review of the evidence. Response: We cite these studies because either preceded (Li) or were near-contemporaneous (Cuisset, Ho and the FDA warning) with our publication. As such, they bear on the state of knowledge at the time, which is the crux of this section. This is not true of References 15 and 16, which by virtue of being published later have no bearing on the immediate surge in pantoprazole use. No action has been taken. 3. Page 7, line 6. 'Influenced' is too strong a statement for an ecologic study. Perhaps 'we examined the extent to which PPI prescribing patterns shifted after the drug advisories were issued and publication of these studies'. Response: This sentence has been removed. 4. Page 7, line 20. Please verify that the date range on this line and elsewhere in the text are correct and consistent. 1999 - 2010 or 1999-2013. ? Response: We have verified the dates reported in the manuscript. 4. Page 9, line 24. The 20.0% (12,433 of 62129) statistic is repeated on page 9, line 32. Is this a coincidence that the values are identical? Odd. Response: We noted that as well. It is correct and simply a coincidence. 5. Wonder about patient level shifts from non-pantoprazole PPI to pantoprazole. Would be more compelling. Response: In response to this comment, we identified all patients taking a non-pantoprazole PPI with clopidogrel in Q4 2008 (the quarter preceding our publication) and examined their prescription patterns over the subsequent 6 months. Of 14,318 patients receiving a non-pantoprazole PPI with clopidogrel in Q4 2008: - 10,318 (72.1%) remained on a non-pantoprazole PPI - 2,717 (19.0%) switched to pantoprazole - 1,283 (9.0%) received no other PPI (presumed discontinuation) - 628 (4.4%) received a H2 blocker instead of a PPI Overall, more than a quarter of patients taking a non-pantoprazole PPI with clopidogrel experienced a change in therapy after our publication. We have taken the liberty of adding these findings to the results section of the revised manuscript 6. Consider emphasizing in the discussion that the shift in prescribing occurred years after the introduction of generic pantoprazole and after the ODB listing. This is noted earlier in the manuscript but I believe it is worth restating. Response: We appreciate this suggestion, but as the reviewer notes we already mention this in the manuscript, and neither phenomena could explain the surge in pantoprazole use after our publication. No action has been taken. 7. Page 6, paragraph starting on line 12. Suggest deleting the 1st sentence as the points - both the study findings and the media attention - are made elsewhere in the introduction. Similarly, suggest deleting the phrase 'In both the abstract and the media attention that accompanied our study' as this is adequately emphasized elsewhere in the introduction. Continue with 'In our study we emphasized that patients need not....' Response: We respectfully suggest that these are worth retaining for emphasis, as they are central to the hypothesis of our study. Is the editor wishes, we will make this change. 8. Page 10, line 43. Correct citation manager reference to

	Wedemeyer. Response: We do not find this citation in our manuscript. No change has been made. Please let us know if we have misunderstood the suggestion. 9. Consider adding to the discussion that clopidogrel-treated patients who would have been non-pantoprazole PPI would not have shifted to prasugrel/ticagrelor as these agents were not available on the market at that time. Response: Note is now made of this