Article details: 2014-0060	
Title	Sitagliptin, pancreatitis and older adults: a population-based cohort study
Authors	Kristin Clemens, Eric McArthur, Jamie Fleet, Irene Hramiak, Amit X. Garg
Reviewer 1	**G De Berardis**
Institution	Consorzio Mario Negri Sud, Dept. of Clinical Pharmacology and Epidemiology
General comments	This manuscript describes a well-conducted population-based study of the risk of acute pancreatitis associated to sitagliptin in older patients with type 2 diabetes, based on administrative data in Ontario. Newly prescribed sitagliptin were paired in a 1:1 proportion with those who used other hypoglycemic agents based on propensity-score matching. A great amount of variables were used to balance the two groups and all the reported standardized differences did not exceed the threshold for good balance. The investigators found no evidence of increased risk of acute pancreatitis associated with sitagliptin use compared with other selected hypoglycemic agents. The availability of different and complementary databases together with the use of advanced and appropriate statistical methods made the results of the study extremely reliable. I have only minor questions and comments. Introduction References on animal studies, post-marketing studies suggesting a link between DPP-IV inhibitors and pancreatitis should be provided. Methods Data Sources: The authors should better specify how the databases are linked. Results The Authors should report the figures relative to the whole source population in Ontario from which they identified the cohort. Discussion The Authors fully discuss their results in relation to the other studies. However the study of Singh et al reported results on sitagliptin OR exenatide and pancreatitis. No OR on sitagliptin alone was provided. This aspect should be mentioned in the discussion of the results. Table 1 1. Information reported on Table 1, eTable6, and eTable 7 are for several variables redundant. I suggest to report in Table 1 all the variables incorporated in the propensity score together with the other key characteristics, and all the others in eTables but with no duplication of information. 2. The Authors reported the distribution of "Pancreatitis" assessed in the previous 5 years; did they include acute and chronic pancreatitis or only chronic pancreatitis? 3. The Authors decided to include in the propensity score matching the presence of prescription of specific hypoglycemic agents in the previous 120 days; this method allowed to decrease the standardized differences and balance for such differences. Why they did not take into account also for Pioglitazone (with a standardized difference of 33% before the propensity score matching) but only for Rosiglitazone? Is there a specific reason? Supplementary materials eFigure 1-2: these figures are useful to better understand the selection process of the individuals included in the study. I suggest to include them, as an unique figure in the main text. eTable 8: the results presented in the table are complementary to those reported for the primary outcome. I suggest to report the table in the main text.
Reviewer 2	**John-Michael Gamble**
Institution	University of Alberta, Public Health Sciences
General comments	Synopsis: This cohort study addresses an important drug safety issues in diabetes management and contributes to the existing literature regarding the risk of pancreatitis associated with sitagliptin exposure. The authors used administrative databases from Ontario and compare the risk of acute pancreatitis between sitagliptin users and alternate hypoglycemic users. They measured acute pancreatitis within 90 days of entering the cohort. They did not find any clinically meaningful or statistically significant association between sitagliptin and acute pancreatitis. This is the first study to my knowledge using Canadian data to evaluate this association. Although I feel this manuscript is well

written and the study uses robust methods, I do have concerns regarding the validity of the study cohorts, exposure definitions, and composition of the comparison group. Please find my comments and suggestions below.

General Comments:

1. Validity of study cohorts: The two exposure groups of interest, 'sitagliptin' and ' alternate hypoglycemic agent' had similar eligibility criteria. One of these criteria was that individuals with a prescription record for a DPP-4 inhibitor in the 365 days prior to the index date would be excluded. The first possible index date was in June of 2010 when sitagliptin was added as an open benefit to the ODB formulary. As the ODB database only captures formulary prescription records, individuals receiving sitagliptin via private insurance during the 365 days prior to June 2010 would have been misclassified as unexposed. It is unlikely this misclassification would be non-differential, as those individuals receiving sitagliptin via private insurance would have simply switched payers (i.e., private to public) in June 2010. Therefore, it is possible that the sitagliptin group was composed of several prevalent users, which may introduce several types of bias. The authors could run a sensitivity analysis and redefine the first possible index date as a minimum of June 2011. At the very least, I suggest the authors address this issue in their limitations section. In summary, the sitagliptin group is likely not a new-user cohort.

2. Exposure definition: Please elaborate on the definition of exposure. It appears as though a single prescription record was sufficient to meet the definition of exposed in both the sitagliptin group and comparison group. It also appears as though exposure was time-fixed in that all 90 days of follow-up were considered exposed to the group an individual was initially classified within. It is not clear why exposure was not measured in a time-varying, `as-treated' manner.

3. Comparison group: Although many studies do include a 'mixed' antidiabetic group as a comparator, in my opinion, this makes the interpretation very difficult. The authors should at least address this in their limitations and considering conducting a sensitivity analysis using a cleaner comparison group.

Specific Comments:

1. Title: I suggest revising the title to be more descriptive of the study results.

2. Abstract, background: I suggest specifying that older adults age 66 and older were studied. In my opinion the term elderly is too vague.

3. Abstract, methods: Please include a sentence on what statistical test was used for the main analysis to estimate the independent association between sitagliptin and pancreatitis.

4. Abstract, results: I suggest including a few key patient characteristics to help readers gauge the population studied.

5. Introduction, page 4, lines 29-33: I suggest including references for the first sentence of paragraph 2.

6. Methods, page 6, line 30: My understanding is that only formulary prescription records are captured within the ODB databse, not 'all outpatient prescriptions dispensed'. Please correct. Also, it is important to specific whether sitagliptin was an open benefit or a restricted benefit because in the case of the latter, there may have been substantial drug exposure misclassification. My understanding is that during the study period, sitagliptin was an open benefit (June 2010 listing in ON), however, it was not an open benefit when first marketed (2007 to 2010). This has implications for the validity of the exposure groups given the potential for a higher proportion of missing sitagliptin prescription records prior to June 2010 in the ODB database.

7. Methods, page 7, line 49: Please justify the cohort entry dates given sitagliptin has been available in Canada since 2007. I presume June 2010 was chosen because this is when it was listed on the ODB formulary. Please elaborate.

8. Results, page 11, 1st paragraph: I suggest including some key patients characteristics to provide a clinical context for readers to judge external validity. Although the patient characteristics are listed in table 1, in my opinion it is helpful when reading through the

	paper to have a general sense of the population. 9. Results, page 11, outcomes section: It would be beneficial to report the unweighted incidence rates of acute pancreatitis in the sitagliptin and comparison groups. I suggest also including the average length of follow-up and duration of exposure during follow-up. 10. Discussion, page 12-15, results in relation to other studies: As the authors are likely aware, two recent papers have been published on the topic in the BMJ; A cohort study: BMJ 2014;348:g2780 and a systematic review: BMJ 2014;348:g2366. These papers should be referenced in their discussion. 11. Discussion, page 17, limitations section: Although the authors acknowledge unmeasured confounding in their limitations, I suggest elaborating on other potential bias such as healthy user bias. Upon inspection of table 1, it seems reasonable to me to speculate that the sitagliptin group was a 'healthier group' given the lower charlson score, lower risk of pancreatitis prior to index, and higher use of statins.
Reviewer 3	**Wen-Yuan Lin**
Institution	China Medical University and Hospital, Department of Family Medicine
General comments	Dr. Clemens et al. assessed the potential adverse effect (pancretitis) among elder diabetic patients treated with different type OHAs in Canada. This is a larged scale population-based cohort study and in an important population(elderly). Since the prevalence of diabetes is increasing in past decades, especially in the elder population. The use of DPP4 inhibitor for diabetes treatment is also rapid increased due to the good efficacy and less hypoglycemic adverse effect. I have some comments as below, Major concern: 1. Authors divided those diabetes patients into two groups according to the use of DPP4 inhitos or not. Therefore, there are several same OHAs maybe used among these two groups (for example, metformin is the first line OHA for diabetes treatment; therefore, the use of metformin in two groups may be equal). How to know the study results were due to DPP4 inhibitor or other OHAs? Can authors do more analyses for each OHA? In such large sample size, authors can use divide patients into different combinations (for example, metformin alone, metformin+DPP4 inhibitos, metformin+ SU+DPP4 inhibitos,....), then authors can do more analyses to find out the real adverse effect among different combinations. 2. Since the life expectancy is increasing around the world, the number of older older population (aged over 85 years old) also rapid increased. Can authors divide the elder subjects into different subgroups(ex, 65-74, 75-85, 85-) to do same analyses. Minor concern: 1. Authors chose 90 days of follw-up to avoid crossover in drug therapy. However, the potentital adverse effect for pancretitis may be occurred in later period after DPP4 inhibitos. Therefore, I suggest that authors should follow-up these patients at least 1 year(or report 6 months, 12 months after index date). 2. Sex difference exists in many conditions. Can authors also do these analyses among both genders?
Author response	Thank you for considering a revised version of our manuscript "The risk of pancreatitis with sitagliptin therapy in older adults: a population-based cohort study" for publication in your journal. We have examined each Editor and Reviewer comment in detail and believe that our current manuscript has been significantly strengthened as a result of these valuable suggestions. An itemized list of our responses to each Editor and Reviewer comment is attached below. Thank you once again for considering our manuscript. Responses to editors comments 1. Please could you consider the definition of exposure that you have used. Is it just one prescription? Would this be sufficient exposure and is this OK? Perhaps you could consider other definitions or add something to the discussion on this point. Response: For our primary analysis, we considered an "intention to treat" definition of exposure where patients were followed until they experienced the primary outcome, died, or reached 90 days of follow-up. We clarify this on page 10 of our methods section. It is possible that patients could have received a single prescription for the new hypoglycemic agent. However as indicated in the results on page 13, the majority

	(approximately 80%) filled at least one additional prescription beyond their index prescription. It is important to note that as part of a secondary time to event analysis (detailed in the results section on page 14 and in Table 3), we also used an "as treated" definition of exposure where we extended follow-up beyond 90 days, terminating the observation period for reasons of death, study hypoglycemic agent discontinuation, receipt of a non-study hypoglycemic agent, or the last date of available records (March 31, 2013). Our findings remained consistent with the results of our primary analysis. 2. We also agree with reviewer 3 that the mixed comparator group introduces doubt. Response: The ideal comparator group for sitagliptin is difficult to identify. We chose our comparator group as those who were prescribed a hypoglycemic agent that would be an alternative medication to sitagliptin in clinical practice. To help reduce doubt, in secondary analyses we examined rates of pancreatitis in the sitagliptin, metformin, sulphonylurea and insulin users individually and noted rates to be similar and low. This is detailed in the results section on page 15, in Supplement Table 9, and in our discussion on page 19. 3. Please discuss when adverse effects would be expected. Does the 90 day time period include this time? Response: Although the literature is limited, previous human and animal studies that suggest an association between sitagliptin and pancreatitis have noted that this outcome may occur early within the course of therapy (even within 30 days). Further, studies including a systematic review and recent cohort study have not observed that the risk of pancreatitis differs by exposure duration. We comment on the literature describing the risk of pancreatitis early within the course of therapy in our methods on page 10, and discuss the limitations of our follow-up period in the discussion on page 20. 4. Do you have any information on adherence to medication and any effect of this? Response: We had detailed information of drugs dispensed but little information on whether the patient took the medication or not. However, in a secondary analyses as noted above, we found that the majority of patients (80%) did fill at least one subsequent prescription. This is as mentioned, in our results section on page 13 and as a note in our discussion on page 19. 5. Please include a STROBE Statement checklist with your resubmission. Response: A STROBE checklist was included in our Supplementary Materials in our original submission. We have provided an additional copy as a separate file for the current submission. Responses to minor points from editors 1. Please ensure your final word count is below 2500 words and the abstract is about 250 words. Response: Our final abstract word count is less than 250 words. We did our best to meet a word count of 2500 but with the recommended addition of new analyses and new literature, our final word count was 2755 words. 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. Response: Apart from standard abbreviations we have removed others in the manuscript. 3. Please include up to 1 academic and 1 professional degree after each author's name.

	Response: On our title page, we have included up to 1 academic and 1 professional degree after each author's name. 4. Please structure the abstract into 4 main sections: a. Background: Provide the context for the study. Explain the problem or issue (the reason you decided to conduct your study) in the first sentence. State the objective of your study (the question you set out to answer) in the second sentence. b. Methods: Include 4 elements: setting, patients, study type or design, and key measurements or outcomes. c. Results: Provide data for the key measurements. Describe the data in absolute and relative terms, if applicable. Give confidence intervals for differences where appropriate, or other measures of statistical significance. d. Interpretation: 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. Response: We have structured the abstract as suggested. 5. Please structure the Interpretation section (discussion) into the following 4 main categories: Main findings; explanation and comparison with other studies; limitations; and conclusions and implications for practice and future research. Response: We have structured our discussion accordingly. 6. 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. Response: References have been placed within brackets and we have removed automatic numbering of field codes. 7. Please be sure to include the appropriate reporting guideline (if applicable.) These are available through http://www.equator-network.org/: •STROBE: Required for observational studies in epidemiology (please use appropriate checklist) Response: As detailed above, we have included a STROBE checklist as a separate document. Responses to Reviewer Comments Reviewer: 1 Comments to the Author The question the authors tackle in this manuscript is important – especially given the increasing trend in anti-diabetic drug use. This is also a very good attempt at using the power of existing health records to help give insight on the association of a serious adverse drug event with sitagliptin use. The major issues with the analysis have been clearly stated by the authors themselves: it is a retrospective analysis limited to cases of hospitalization with a diagnosis of acute pancreatitis within 90 days of filling a prescription for sitagliptin. 1. One confounding issue is that most physicians in Ontario prescribing sitagliptin are supposedly aware of this potential serious risk (or at least are aware of the information on its monograph) and would expected to be actively monitoring high risk patients and warning them to be alert for any symptoms (which were previously noted to improve with discontinuation) and providing dietary and lifestyle precautions (perhaps more so than for the comparative drugs used in the analysis). Thus, hospital admission may not be a sensitive outcome for picking up potential events of pancreatitis as a consequence of drug exposure. Response: Thank you for this comment. It is true that physicians might monitor patients on DPP-4 inhibitors differently than those not prescribed the drug. We have attempted to address

	this point using secondary analyses where we determined that a similar proportion of patients in both the sitagliptin and in the alternative hypoglycemic agent group were ordered an amylase or lipase following their new drug prescription. This analyses is outlined on page 15 and in Supplement Table 8 with additional comment on page 21 of the discussion. 2. The argument that "less severe" non-hospital cases missed in the analysis are of a lesser consequence is questionable as any pancreatic damage in this population is serious – and it is important to know whether this class of anti-hyperglycemic agents hold a risk of doing any harm. Response: We have revised this point on page 19 in the discussion. 3. Of note, the time frame is fairly limited – most adverse drug effects of this nature are a consequence of cumulative exposure – a follow-up of at least one year (ideally 3) is required to make an adequate risk-benefit judgment on use. It would be useful if the authors were able to define the time to event in previous reports showing an increased risk of acute pancreatitis with sitagliptin use. Their extended analysis does not seem to extend the time much further (though this was not entirely clear from supplemental etable 8). It is understood these limits on analysis were mainly administrative, not physiological in nature. Response: We recognize that our time frame of study is limited. However as noted in our response to previous comments, in prior studies there has been no indication that the risk of pancreatitis with incretion drugs varies by the duration of drug exposure. To our knowledge there has also been no previous time to event analysis showing an increased risk of pancreatitis to help guide the ideal duration of follow-up. Although it certainly would have been ideal to study patients over a longer term, we feel that 90 days was reasonable as it included a period of time when events could occur based upon previous literature (please see editor comment 3). Also, the mean duration of continuous drug use (defined by the duration of one prescription overlapping with a subsequent prescription allowing for a 10 day grace period between subsequent prescriptions) of the patients in our study ranged from 64 to 108 days (detailed in our results section on page 13). It is correct that our time to event analysis did not extend follow-up much beyond 90 days (median duration of follow-up 65 and 75 days in the sitagliptin and the alternative hypoglycemic agent group respectively as noted in Table 3). The majority of patients were censored because they received a new hypoglycemic agent. We have discussed our rationale and the limitations of our study time frame in the methods on page 11 and in our discussion on page 20. 4. The important question to ask is whether this additional retrospective study with these limitations adds more clarity (for clinical decision making) to the other equally limited (and contradictory) analyses that have already been done on this subject. Given the above points, I do not think it offers reliable assurances on drug safety because of the incomplete information on which the analysis was based. The authors correctly noted that what is needed now is a well-designed longitudinal prospective study in a randomized-controlled trial to more reliably answer the question whether sitagliptin is associated with an increased risk of pancreatitis and/or altered pancreatic function. Response: Our study gives a perspective on the risk of pancreatitis with sitagliptin use in a cohort of elderly Ontarian adults. We have aimed to minimize confounding by providing significant detail of patient comorbidities, concomitant medications and health care utilization and were able to achieve good balance on these characteristics using propensity weighting. With the additional revisions and analyses, we anticipate that although a large prospective cohort study/randomized controlled trial is ideal, our study contributes to and is consistent with the existing literature. 5. As a final point/question – the authors mentioned that previous work that showed an increased risk in acute pancreatitis with sitagliptin was noted in a younger cohort. This raises the question why the analysis was limited to those 65 years and older? Would it not have been informative to see if there is any age-associated risk while also

	confirming or disproving the previous findings? Response: The Ontario Drug Benefits database only contains formulary prescription medications for those aged 65 years and older so we were unable to examine risk in a younger population. Reviewer: 2 Comments to the author: This manuscript describes a well-conducted population-based study of the risk of acute pancreatitis associated to sitagliptin in older patients with type 2 diabetes, based on administrative data in Ontario. Newly prescribed sitagliptin were paired in a 1:1 proportion with those who used other hypoglycemic agents based on propensity-score matching. A great amount of variables were used to balance the two groups and all the reported standardized differences did not exceed the threshold for good balance. The investigators found no evidence of increased risk of acute pancreatitis associated with sitagliptin use compared with other selected hypoglycemic agents. The availability of different and complementary databases together with the use of advanced and appropriate statistical methods made the results of the study extremely reliable. I have only minor questions and comments. 1.Introduction References on animal studies, post-marketing studies suggesting a link between DPP-IV inhibitors and pancreatitis should be provided. Response: We have updated our manuscript with the relevant references as noted. 2. Methods Data Sources: The authors should better specify how the databases are linked. Response: Health care databases are linked using encrypted health card numbers. We note this on page 6 of the methods section. 3. Results The Authors should report the figures relative to the whole source population in Ontario from which they identified the cohort. Response: The source population was the population of Ontario. 4. Discussion The Authors fully discuss their results in relation to the other studies. However the study of Singh et al reported results on sitagliptin OR exenatide and pancreatitis. No OR on sitagliptin alone was provided. This aspect should be mentioned in the discussion of the results. Response: Thank you for this detail. We have corrected the discussion appropriately on page 18. 5. Table 1 a. Information reported on Table 1, eTable6, and eTable 7 are for several variables redundant. I suggest to report in Table 1 all the variables incorporated in the propensity score together with the other key characteristics, and all the others in eTables but with no duplication of information. Response: We had initially created Table 1 as a 1 page summary table. However we have replaced this with a comprehensive table of key baseline characteristics as suggested (Table 1, page 25). Additional baseline characteristics are outlined in Supplement Table 6 with no

	duplication of information. b. The Authors reported the distribution of "Pancreatitis" assessed in the previous 5 years; did they include acute and chronic pancreatitis or only chronic pancreatitis? Response: Our coding definitions are listed in Supplement Table 3. Previous pancreatitis included both acute and chronic pancreatitis. We have also clarified this in Table 1 on page 25. c. The Authors decided to include in the propensity score matching the presence of prescription of specific hypoglycemic agents in the previous 120 days; this method allowed to decrease the standardized differences and balance for such differences. Why they did not take into account also for Pioglitazone (with a standardized difference of 33% before the propensity score matching) but only for Rosiglitazone? Is there a specific reason? Response: Propensity score variables were selected to obtain the most balance between groups. There was no specific reason why rosiglitazone was not accounted for. After weighting, the standardized difference for rosiglitazone use between groups was reduced to 0%. 6. Supplementary materials a. eFigure 1-2: these figures are useful to better understand the selection process of the individuals included in the study. I suggest to include them, as an unique figure in the main text. Response: We have included these figures as part of the main text on page 34 and 35. b. eTable 8: the results presented in the table are complementary to those reported for the primary outcome. I suggest to report the table in the main text. Response: We have also moved this table to the main text (Table 3, page 33). Reviewer: 3 Comments to the Author Synopsis: This cohort study addresses an important drug safety issues in diabetes management and contributes to the existing literature regarding the risk of pancreatitis associated with sitagliptin exposure. The authors used administrative databases from Ontario and compare the risk of acute pancreatitis between sitagliptin users and alternate hypoglycemic users. They measured acute pancreatitis within 90 days of entering the cohort. They did not find any clinically meaningful or statistically significant association between sitagliptin and acute pancreatitis. This is the first study to my knowledge using Canadian data to evaluate this association. Although I feel this manuscript is well written and the study uses robust methods, I do have concerns regarding the validity of the study cohorts, exposure definitions, and composition of the comparison group. Please find my comments and suggestions below. General Comments: 1. Validity of study cohorts: The two exposure groups of interest, 'sitagliptin' and ' alternate hypoglycemic agent' had similar eligibility criteria. One of these criteria was that individuals with a prescription record for a DPP-4 inhibitor in the 365 days prior to the index date would be excluded. The first possible index date was in June of 2010 when sitagliptin was added as an open benefit to the ODB formulary. As the ODB database only captures formulary prescription records, individuals receiving sitagliptin via private insurance during the 365 days prior to June 2010 would have been misclassified as unexposed. It is unlikely this misclassification would be non-differential, as those individuals receiving sitagliptin via private insurance would have simply switched payers (i.e., private to public) in June 2010. Therefore, it is possible that the sitagliptin group was composed of several prevalent users, which may introduce several types of bias. The authors could run a sensitivity analysis and redefine the first possible index date as a minimum of June 2011. At the very least, I suggest the authors address this issue in their limitations section. In summary, the sitagliptin group is likely not a

	new-user cohort. Response: Thank you. We expected a very low proportion of this population to be prescribed sitagliptin through private drug insurance prior to June 2010. However to address this valid concern, we have carried an additional sensitivity analyses where only patients accrued after June 2011 were included in the cohort. Our results remained robust in this analysis which is illustrated in Supplement Table 7 and in the results on page 14. 2. Exposure definition: Please elaborate on the definition of exposure. It appears as though a single prescription record was sufficient to meet the definition of exposed in both the sitagliptin group and comparison group. It also appears as though exposure was time-fixed in that all 90 days of follow-up were considered exposed to the group an individual was initially classified within. It is not clear why exposure was not measured in a time-varying, `as-treated' manner. Response: Please see response to editor comment 1 above. 3. Comparison group: Although many studies do include a 'mixed' antidiabetic group as a comparator, in my opinion, this makes the interpretation very difficult. The authors should at least address this in their limitations and considering conducting a sensitivity analysis using a cleaner comparison group. Response: Please see response to editor comment 3 above. Specific Comments: 1. Title: I suggest revising the title to be more descriptive of the study results. [Editor's note: The title should clearly describe what the study is about (please revise) and include a mention of the type of study, which you have included.] Response: We have revised this title as per the Editor's suggestion, making it one that clearly describes what the study is about and the type of study. 2. Abstract, background: I suggest specifying that older adults age 66 and older were studied. In my opinion the term elderly is too vague. Response: Where relevant, we have specified more clearly that we studied adults 66 years and older. 3. Abstract, methods: Please include a sentence on what statistical test was used for the main analysis to estimate the independent association between sitagliptin and pancreatitis. Response: We have included in our abstract that "to calculate odds ratios we used logistic regression with robust variance estimate to account for inverse probability of treatment weighting" on page 3. This was previously noted in our methods section of the manuscript on page 12. 4. Abstract, results: I suggest including a few key patient characteristics to help readers gauge the population studied. Response: We have included a few baseline characteristics in the abstract on page 3 and in the results section on page 13. 5. Introduction, page 4, lines 29-33: I suggest including references for the first sentence of paragraph 2. Response: Thank you. As noted, references have been added.

	6. Methods, page 6, line 30: My understanding is that only formulary prescription records are captured within the ODB databse, not 'all outpatient prescriptions dispensed'. Please correct. Also, it is important to specific whether sitagliptin was an open benefit or a restricted benefit because in the case of the latter, there may have been substantial drug exposure misclassification. My understanding is that during the study period, sitagliptin was an open benefit (June 2010 listing in ON), however, it was not an open benefit when first marketed (2007 to 2010). This has implications for the validity of the exposure groups given the potential for a higher proportion of missing sitagliptin prescription records prior to June 2010 in the ODB database. Response: We have changed our language appropriately as highlighted in the methods on page 7. Sitagliptin was first covered openly by the province's formulary in June 2010. As noted previously, we have carried out an additional sensitivity analyses to help address the possibility of incomplete DPP-4 prescription drug records prior to this time. 7. Methods, page 7, line 49: Please justify the cohort entry dates given sitagliptin has been available in Canada since 2007. I presume June 2010 was chosen because this is when it was listed on the ODB formulary. Please elaborate. Response: Yes, we chose June 2010 as it was the date when sitagliptin was first listed on the ODB formulary (which was captured in our ODB database). We have elaborated on this in our methods on page 9. 8. Results, page 11, 1st paragraph: I suggest including some key patients characteristics to provide a clinical context for readers to judge external validity. Although the patient characteristics are listed in table 1, in my opinion it is helpful when reading through the paper to have a general sense of the population. Response: Please see response to comment 4 above where we indicate that we have included some key baseline characteristics in the text. 9. Results, page 11, outcomes section: It would be beneficial to report the unweighted incidence rates of acute pancreatitis in the sitagliptin and comparison groups. I suggest also including the average length of follow-up and duration of exposure during follow-up. Response: We have reported the unweighted incidence rates in Table 2 on page 32. As noted in the results on page 13, the average duration of continuous drug exposure ranged from a mean of 63-108 days across study drugs. For our time to event analysis, our median duration of follow-up was 65 and 75 days in the sitagliptin and in the alternative hypoglycemic agent groups respectively (Table 3). 10. Discussion, page 12-15, results in relation to other studies: As the authors are likely aware, two recent papers have been published on the topic in the BMJ; A cohort study: BMJ 2014;348:g2780 and a systematic review: BMJ 2014;348:g2366. These papers should be referenced in their discussion. Response: We have added these studies to our discussion as well as brief summaries on additional new research reports on page 16-18. 11. Discussion, page 17, limitations section: Although the authors acknowledge unmeasured confounding in their limitations, I suggest elaborating on other potential bias such as healthy user bias. Upon inspection of table 1, it seems reasonable to me to speculate that the sitagliptin group was a 'healthier group' given the lower charlson score, lower risk of pancreatitis prior to index, and higher use of statins. Response: We have commented upon the possibility of such biases in our discussion on page 21. Reviewer: 4 Comments to the Author

	Dr. Clemens et al. assessed the potential adverse effect (pancretitis) among elder diabetic patients treated with different type OHAs in Canada. This is a larged scale population-based cohort study and in an important population(elderly). Since the prevalence of diabetes is increasing in past decades, especially in the elder population. The use of DPP4 inhibitor for diabetes treatment is also rapid increased due to the good efficacy and less hypoglycemic adverse effect. I have some comments as below, Major concerns: 1. Authors divided those diabetes patients into two groups according to the use of DPP4 inhitos or not. Therefore, there are several same OHAs maybe used among these two groups (for example, metformin is the first line OHA for diabetes treatment; therefore, the use of metformin in two groups may be equal). How to know the study results were due to DPP4 inhibitor or other OHAs? Can authors do more analyses for each OHA? In such large sample size, authors can use divide patients into different combinations (for example, metformin alone, metformin+DPP4 inhibitos, metformin+ SU+DPP4 inhibitos,....), then authors can do more analyses to find out the real adverse effect among different combinations. Response: Using a new user design we attempted to examine the risk of pancreatitis in those newly prescribed sitagliptin or an alternative hypoglycemic agent. Additionally in secondary analyses we determined the proportion of people with events where the newly initiated study drug was done so as monotherapy or in the setting of additional hypoglycemic drug use. The proportion with events were small and comparable between groups. We highlight this analysis in our results section on page 15 and in the Supplement in Table 10. 2. Since the life expectancy is increasing around the world, the number of older population (aged over 85 years old) also rapid increased. Can authors divide the elder subjects into different subgroups(ex, 65-74, 75-85, 85-) to do same analyses. Response: Our event rate was extremely low and thus we do not feel that we have adequate statistical power to perform meaningful subgroup analyses. We have commented upon this in our discussion on page 20. Minor concerns: 1. Authors chose 90 days of follw-up to avoid crossover in drug therapy. However, the potentital adverse effect for pancretitis may be occurred in later period after DPP4 inhibitos. Therefore, I suggest that authors should follow-up these patients at least 1 year(or report 6 months, 12 months after index date). Response: Please see response to similar comments above. In summary, although it would have been ideal to extend follow-up, given the limited duration of active and continuous drug use, we do not feel that we could meaningfully extend follow-up beyond the 90 days of study. 2. Sex difference exists in many conditions. Can authors also do these analyses among both genders? Response: As noted above, we do not feel that we had adequate statistical power to perform meaningful subgroup analyses.