PEER REVIEW HISTORY

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ARTICLE DETAILS

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<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Lipid-Lowering Drugs and Risk of New-Onset Diabetes: A Cohort Study Using Japanese Healthcare Data Linked to Clinical Data for Health Screening</th>
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<td>AUTHORS</td>
<td>Ooba, Nobuhiro; Setoguchi, Soko; Sato, Tsugumichi; Kubota, Kiyoshi</td>
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VERSION 1 - REVIEW

<table>
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<th>Bennett, Kathleen</th>
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<td>RCSI Ireland</td>
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<td>REVIEW RETURNED</td>
<td>03-Mar-2017</td>
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GENERAL COMMENTS

It is a large study of claims data examining the exposure to fibrates and statins and the subsequent risk of incident diabetes. The following comments are made:

- Strengths and limitations – might be helpful to make it clearer which are strengths and which limitations.
- Introduction – the study looks at fibrates and statins but the evidence on fibrates is less obvious and was the hypothesis here that fibrates would also increase the risk of diabetes or not? The rationale for including fibrates is not as clear.
- Perhaps say that the adverse effects of statins are fairly rare. There is some inconsistency throughout this section where statins and then LLD as a whole are referred to as increasing incident diabetes risk - care is needed when referring so it is clear what is meant.
- The sentence ‘important subject … prevention of CVD’ but this is about increasing risk of diabetes – it was not clear what this sentence meant?
- Although this study includes more confounders, it still has several other biases e.g retrospective design etc.
- Methods – How representative of the population is the cohort included here? It appears it includes mainly those who are working and aged 20-74 years.
- How were the different datasets linked together? Is there a unique identifier – was permission given by the participants?
- Exposure – how was discontinuation defined? Similarly switching – no explanations provided. Was there any information on doses given? Could you look at dose response relationships?
- Covariates – some of the covariates are included but not referenced – why were there adjusted for? How was the metabolic syndrome score adjusted for BMI instead of waist circumference? no details provided.
- Statistical analysis – Multiple imputation was used for missing data but normally this would be considered in a sensitivity analysis not the main analysis. Did the authors run the analysis without MI? were the findings similar?
- Results – It would be helpful to have percentages after the numbers.
given. There is description of the covariates as main effects, the focus of this paper is on the exposures of LLD.

Table 1 – what does +, ++, etc refer to?
Table 2 – It looks like the non-users had longer follow-up on average (2 years) than the LLD users (average 6 months??) from the table. Is this correct? Is this sufficient follow-up to evaluate incident diabetes?

Discussion – The mechanisms of action of LLD on diabetes are not explored fully in relation to the potency of statins and the difference in fibrates and statins – is there any evidence to support mechanism?

Limitation might also be the generalizability of the findings to non-working populations and older ages etc.

The English could be improved throughout with a careful proof-read. For example, HR that ‘got away’ from 1, and CIs ‘was’ wide rather than CIs were wide.

REVIEWER
Iskandar Idris
University of Nottingham

REVIEW RETURNED
03-Mar-2017

GENERAL COMMENTS
This study by Ooba et al investigated the possible role/association of statins with new-onset diabetes in a Japanese population.

Please consider the comments/queries below:

Abstract.
1. Lines 12: With the use of data of employees/relatives of large cooperates in Japan; please discuss if findings of this study be generalised to the Japanese population?
3. Line 33: The word “non-use” should be better defined.

Page 4: Strengths and Limitations
1. Line 6: Spelling error- laboratory not “laboraory”
2. Lines 19 -24: Please consider revision to make sentence clearer

Page 5: Introduction
1. Line 6: should read “Statins are widely…” are was omitted
2. Lines 11 – 15: Unclear meaning. Please revise
3. Given the large number of studies investigating the association between statins and new onset diabetes, it is important to add novelty statement to this work.
5. Please revise the introduction to be more logical, coherent, and to give a strong rationale and novelty for your study.

Pages 5-8: Methods
1. Lines 54 – 57: It is very difficult to know how you arrived at the choice of your data source. What was the selection process? How representative of the local and national demographics was this data source? Has it been validated by previous studies?
2. Page 6, line 4: What are domestic codes? Are they internationally recognised? Are they validated?
3. Lines 9 -11: While this screening was not compulsory for the
employees’ relatives, is this not a huge source of bias to this data?
Need to discuss in limitations
4. Very good definition of inclusion, exclusion and censorship of the study participants
5. Lines 53 – 57: Your definition of new onset of diabetes using prescription of insulin and/or oral hypoglycaemic agents may risk the introduction of misclassification bias and may overestimate your effect, moving the hypothesis away from null. Can you use codes for diabetes as the definition
6. Page 7, line 3: It is unclear why you will censor patients who switched to another lipid-lowering medication, especially if they fall within the same lipid class or category.
7. Lines 21 – 30: It is unclear what you did here and how these data were obtained and classified. The use of high BMI, high FBG, high etc is confusing.
8. Lines 47 -57. This is an incidence study- new onset diabetes (among statin users). The use of Cox regression is inappropriate because this will show the hazard (risk) of diabetes in statin users. This is not the aim of your study as you outlined above. Instead, Poisson’s regression model is most appropriate here to determine the incidence rates/ ratios in the users’ categories.

Page 8. Results:
1. Lines 36 – 41. The result here is correct but in conflict with the Figure in page 21. I wonder what the figure “68567” stands for and how it was obtained in figure 1 page 21.
2. Line 54. Should read crude incidence rate and not just crude rate
3. Table 2. Page 18. It will be better to stick to one definition of cases of new-onset diabetes. The best will be to use the diagnostic codes for diabetes and not use of anti-diabetic medication.
4. Page 9. Lines 23-25. The sentence is needless and inappropriate and must be revised or entirely removed as it is already in Table 3 (Page 19)

Pages 9 – 11. Discussion:
1. Page 10: Lines 47 – 54. This is not scientifically sound and convincing. The sentences made in lines 51-54 needs to be revised, to temper your rationale for your definition of new onset diabetes. This, no doubt, will lead to an over estimation of effects.
2. Lines 54 -57: The short follow-up duration may not be adequate for the outcome. Studies have shown this association to be both dose and time dependent. A shorter time will drive the hypothesis to the null, underestimate the effect, and add some residual confounding from prevalent users.
3. Lines 28 -35: The conclusion did not flow from the aim. In lines Page 5, lines 47 – 49, your aim was “…association between the use of lipid-lowering drugs and new-onset diabetes (NOD)” but your conclusion and even the title were on the risk of NOD. This is confusing whether this study is about the incidence of diabetes in statin users or the risk of diabetes associated with statin-use.
The authors have utilized health screening and insurance claims databases from large Japanese corporations to examine the question of whether statins and fibrates are associated with increased risk of developing new-onset diabetes. The population at risk is about 70,000 subjects with dyslipidemia. Since one of the criteria for abnormal lipids is low HDL cholesterol, "dyslipidemia" is a more appropriate term than "hyperlipidemia."

The use of observational data to create a quantitative estimate of the relative risk of developing diabetes between lipid medication users and nonusers is fraught with inaccuracy. At best one can say that the increased risk for statin users found in this database is consistent with the far more reliable increased risk shown in randomized controlled trials.

Adjustment for confounders, especially when variables are dichotomized – i.e., hypertriglyceridemia as 150 mg/DL or greater versus normal triglyceride – probably does not fully adjust for selection bias. This is to say, patients selected for fibrate therapy or even statin therapy may simply have had more extreme deviation in the confounding variables than is usually encountered. This is the reason that one should be very wary of quantitative estimates of relative risk. Even if adjustment for confounders is performed by continuous variables rather than dichotomously, linearity versus nonlinearity of response can still introduce uncertainty.

It is all right to do a study such as this, but the results should be interpreted very cautiously and always with the proviso that randomized controlled trials give more reliable quantitation.

The incidence rates listed in Abstract Results suggest a decreased, rather than increased, risk of new-onset diabetes among statin and fibrate users. It seems possible that some numbers have become confused. The rates in lipid drug users appear to be low by a factor of 10.

I think that the authors should probably delete the data and conclusions regarding fibrates. It strains credulity to suggest that any real estimate of increased risk of diabetes should be based on only 19 cases. This is especially true when adjustment for confounders reduces the hazard ratio by about half.

In table 2, there is a column enumerating cases of new-onset diabetes in patients who used anti-diabetic medication, but did not have a diagnosis of diabetes listed. This does not seem to be the condition listed in Methods for the sensitivity analysis. Instead, I assume the sensitivity analysis counted cases of new onset diabetes by all patients who used anti-diabetic medication regardless of whether they had a diagnosis of diabetes. One would suppose that the numbers of cases identified in this way would be fairly similar to those in the column headed "diagnosis or use of antidiabetic."

Page 10, line 34. "The insulin-sensitizing action on adiponectin..." I think this should read "The insulin-sensitizing action of adiponectin..." In reading this paragraph, I can't tell whether fibrates and statins actually raise or lower adiponectin.
Reviewer(s)' Comments to Author:

Reviewer: 1
K Bennett
RCSI Ireland
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
It is a large study of claims data examining the exposure to fibrates and statins and the subsequent risk of incident diabetes.
The following comments are made
Strengths and limitations – might be helpful to make it clearer which are strengths and which limitations.

We revised the section of the ‘Strengths and Limitations’ and included an additional limitation for the generalizability or “Our study population included those who worked in relatively large corporations and their relatives, aged between 20 to 74 years, which means our findings might not be readily generalized to those working in small corporations or self-employed individuals and old people aged ≥75 years.”

Introduction – the study looks at fibrates and statins but the evidence on fibrates is less obvious and was the hypothesis here that fibrates would also increase the risk of diabetes or not? The rationale for including fibrates is not as clear.

We agree. This point was also commented by another reviewer who recommended not mentioning anything about fibrates. We however mentioned the high risk of new-onset diabetes of fibrates as observed in our study but we added our interpretation in the revision that “it is quite possible that the higher risk of fibrates compared to non-use was obtained just by chance in the current study.” in the Discussion section.

Perhaps say that the adverse effects of statins are fairly rare. There is some inconsistency throughout this section where statins and then LLD as a whole are referred to as increasing incident diabetes risk - care is needed when referring so it is clear what is meant. The sentence ‘important subject … prevention of CVD’ but this is about increasing risk of diabetes – it was not clear what this sentence meant?

In the first paragraph of Discussion section, we added “As the incidence rate of new-onset diabetes was estimated as 22.6 per 1,000 person-years during the period of non-use in our study, the absolute increase of the rate potentially due to the use of statins, corresponding to hazard ratio of 1.5 to 3.1, may be approximately 10 to 45 per 1000 person-years.” which may or may not indicate that “the adverse effects of statins are fairly rare”. In the revision, we tried to indicate that we believe that the increased risk of new-onset diabetes by statins was likely to be the truth while the increased risk of fibrates can be a chance observation because the number of cases was small for fibrates. Also, the sentence ‘important subject … prevention of CVD’ was improved in the revision.

Although this study includes more confounders, it still has several other biases e.g retrospective design etc.

In the Discussion section of the revision, we mentioned that there may be residual confounders and
indicated some of potentially important factors for which we did not have the information such as smoking and physical exercise.

Methods – How representative of the population is the cohort included here? It appears it includes mainly those who are working and aged 20-74 years.

In the Discussion section of the revision, we explicitly stated that our cohort consists of those working in relatively large corporations and their relatives and did not include those aged 75 or older, therefore our findings might not be generalized to those working in small corporates and self-employed, and older ages.

How were the different datasets linked together? Is there a unique identifier – was permission given by the participants?

Three types of data owned by the insurer were linked by the insurer due to the legal obligations. In the Methods section of the revision, we explained the obligations of the insurer and why they had to link those data.

Exposure – how was discontinuation defined? Similarly switching – no explanations provided. Was there any information on doses given? Could you look at dose response relationships?

In “Exposures and outcomes data” of the Methods section of the revision, we defined the discontinuation and switching. We did not examine the dose response relationships as the number of patients with new-onset diabetes was relatively small and not enough to examine details including the risk of individual statins and dose response relationships. This point is added as one of the limitations in the Discussion section of the revision.

Covariates – some of the covariates are included but not referenced – why were there adjusted for? How was the metabolic syndrome score adjusted for BMI instead of waist circumference? no details provided.

In “Covariates” of the Methods section of the revision, we added how we selected the covariates incorporated in the statistical model.

We did not use the definition of MS using waist circumference simply because data of waist circumference was not available. This point is explained also in “Covariates” of the Methods section.

Statistical analysis – Multiple imputation was used for missing data but normally this would be considered in a sensitivity analysis not the main analysis. Did the authors run the analysis without MI? were the findings similar?

To address this comment, we added the results of the complete case analysis that were similar to the results of the analysis using MI. However, in the revision, the analysis with MI is still used as the main analysis as the complete case analysis and other methods (e.g., single imputation and the creation of the “unknown” category) are known to give the biased results.

Results – It would be helpful to have percentages after the numbers given. There is description of the covariates as main effects, the focus of this paper is on the exposures of LLD.

In the first paragraph of “Results” section of the revision, we gave percentages after the numbers. We deleted the description which may be potentially interpreted that the covariates are considered as main effects.
Table 1 – what does +, ++, etc refer to?

In footnote of Table1, we gave what “+, ++ etc” mean and the typical concentrations they correspond to.

Table 2 – It looks like the non-users had longer follow-up on average (2 years) than the LLD users (average 6 months??) from the table. Is this correct? Is this sufficient follow-up to evaluate incident diabetes?

It is correct that the average length of the follow-up time is short. It is therefore not possible to evaluate the long-term effect of the LLD but the short-term effect may be evaluated. These points are discussed as one of limitations of the study in the Discussion section of the revision.

Discussion – The mechanisms of action of LLD on diabetes are not explored fully in relation to the potency of statins and the difference in fibrates and statins – is there any evidence to support mechanism?

We believe that the mechanism of action has not been fully explored even if the increased risk of diabetes has been observed repeatedly in the previous studies on the association of LLDs and new-onset diabetes. In the Discussion section of the revision, we indicated that the details are unclear.

Limitation might also be the generalizability of the findings to non-working populations and older ages etc.

In the Discussion section of the revision, we mentioned that our finding may not be generalized to those who are working in small corporates and self-employed as well as those aged 75 or older.

The English could be improved throughout with a careful proof-read. For example, HR that ‘got away’ from 1, and CIs ‘was’ wide rather than CIs were wide.

This manuscript was proofread by the editor in the professional language editing service.

Reviewer: 2
Iskandar Idris
University of Nottingham
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
This study by Ooba et al investigated the possible role/association of statins with new-onset diabetes in a Japanese population.

Please consider the comments/queries below:

Abstract.

1. Lines 12: With the use of data of employees/relatives of large cooperates in Japan; please discuss if findings of this study be generalised to the Japanese population?

In the section of the ‘Strengths and Limitations’ and Discussion of the revision, we mentioned that our findings may not be generalized to those who are working in small corporates and self-employed as well as those aged 75 or older"
3. Line 33: The word “non-use” should be better defined.

In the abstract of the revision, we defined “non-use” as “non-use of any lipid-lowering drugs before starting a lipid-lowering drug”. We hope that this way of the definition is acceptable.

Page 4: Strengths and Limitations

1. Line 6: Spelling error- laboratory not “laboraory”

Thank you. We changed “laboraory” to “laboratory”.

2. Lines 19 -24: Please consider revision to make sentence clearer

We revised the sentence in the revision and hope it is clearer than that in the original.

Page 5: Introduction

1. Line 6: should read “Statins are widely…” are was omitted

We inserted “are” after “Statins” in Line 4 of Introduction section.

2. Lines 11 – 15: Unclear meaning. Please revise

We revised the sentence so that the meaning is clear. It now reads in the revision as follows: “As with hyperlipidaemia, diabetes is an established risk factor for cardiovascular diseases and therefore the possible increased risk of new-onset diabetes by the drugs used to treat hyperlipidaemia may attenuate the effect of reducing the risk of cardiovascular diseases.”

3. Given the large number of studies investigating the association between statins and new onset diabetes, it is important to add novelty statement to this work.

5. Please revise the introduction to be more logical, coherent, and to give a strong rationale and novelty for your study.

To give rationale and novelty, we added the following sentence in the revision: “there have been few reports on the association between statins and the incidence of diabetes in the Asian population” We believe that this statement can give rationale and novelty as patient characteristics and the magnitude of the cardiovascular risk in Asian patients with diabetes or dyslipidaemia are known to differ from those in the Western countries.

Pages 5-8: Methods

1. Lines 54 – 57: It is very difficult to know how you arrived at the choice of your data source. What was the selection process? How representative of the local and national demographics was this data source? Has it been validated by previous studies?

As stated in “Data sources” of the Methods section of the revision, we needed to use three types of data of claims, enrollment and regular health screening. In general, there are only a limited number of databases that can be used in the research in Japan in particular when those 3 types of data are available. The database we used had the 3 types of the information. The data has not been validated by previous studies and this is stated as a limitation of the study in the Discussion section.
2. Page 6, line 4: What are domestic codes? Are they internationally recognised? Are they validated?

We gave some details of codes for drugs and medical procedures in the revision.

3. Lines 9 -11: While this screening was not compulsory for the employees’ relatives, is this not a huge source of bias to this data? Need to discuss in limitations

The possible selection bias due to the non-compulsory nature of the health screening for the relatives is addressed as a limitation in the Discussion section of the revision.

4. Very good definition of inclusion, exclusion and censorship of the study participants

5. Lines 53 – 57: Your definition of new onset of diabetes using prescription of insulin and/or oral hypoglycaemic agents may risk the introduction of misclassification bias and may overestimate your effect, moving the hypothesis away from null. Can you use codes for diabetes as the definition

The diagnosis codes of diabetes have been not validated in Japan. In the textbook (Strom BL. Overview of Automated Databases in Pharmacoepidemiology. Chapter11, In Strom BL, Kimmel SE, Hennessy S, eds., Pharmacoepidemiology 5th, Willey Blackwell, 2012), the definition of the condition by prescription of the medication to treat that condition (e.g., new onset diabetes defined by prescription of antidiabetics) is recommended in such a scenario. In our sensitivity analysis we followed this recommendation and for statins, RR in this sensitivity analysis got close to the null as compared to RR in the main analysis where new-onset diabetes was defined as diagnosis code of diabetes or prescription of an antidiabetic.

6. Page 7, line 3: It is unclear why you will censor patients who switched to another lipid-lowering medication, especially if they fall within the same lipid class or category.

Thank you very much for pointing out this. In the second paragraph of the “Exposures and outcomes data “ of the Methods section of the revision, we clarified this point as follows: “We considered that an LLD was used continuously when an LLD was switched to another LLD under the same category of LLDs”.

7. Lines 21 – 30: It is unclear what you did here and how these data were obtained and classified. The use of high BMI, high FBG, high etc is confusing.

In the revision, we presented the results of the analyses where BMI, FBG, SCre, Blood pressure and serum creatinine were incorporated as continuous variables in all multivariate analyses. We changed all the relevant descriptions in the text and figures though the results were almost identical to those in the original.

8. Lines 47 -57. This is an incidence study- new onset diabetes (among statin users). The use of Cox regression is inappropriate because this will show the hazard (risk) of diabetes in statin users. This is not the aim of your study as you outlined above. Instead, Poisson’s regression model is most appropriate here to determine the incidence rates/ ratios in the users’ categories.

We do not think that the contention that “the Poisson regression model rather than the Cox regression model should be used in an incident study” is the view widely accepted. For example, the Cox regression model was used in the previous studies to estimate the association between new-onset diabetes and LLDs (Reference No. 5, 6 and 26). In the revision, we used the Cox regression model.
Page 8. Results:

1. Lines 36 – 41. The result here is correct but in conflict with the Figure in page 21. I wonder what the figure “68567” stands for and how it was obtained in figure 1 page 21.

   In the Results section and Figure 1 of the revision, we gave better description for the number of subjects including what the figure “68567” stands for.

2. Line 54. Should read crude incidence rate and not just crude rate

   In “Lipid-lowering drugs and new-onset diabetes” of the Results section of the revision, we changed “crude rate” to “crude incidence rate”.

3. Table 2. Page 18. It will be better to stick to one definition of cases of new-onset diabetes. The best will be to use the diagnostic codes for diabetes and not use of anti-diabetic medication.

   As in the answer to the comments on Page 6, Line 53-57 in the Methods section, the diagnosis codes of diabetes have been not validated in Japan and we followed the recommendation for such a situation in the standard textbook of pharmacoepidemiology and in the sensitivity analysis we used the definition of diabetes by prescription of antidiabetics only.

4. Page 9. Lines 23-25. The sentence is needless and inappropriate and must be revised or entirely removed as it is already in Table 3 (Page 19)

   We deleted the sentence.

Pages 9 – 11. Discussion:

1. Page 10: Lines 47 – 54. This is not scientifically sound and convincing. The sentences made in lines 51-54 needs to be revised, to temper your rationale for your definition of new onset diabetes. This, no doubt, will lead to an over estimation of effects.

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2. Lines 54 -57: The short follow-up duration may not be adequate for the outcome. Studies have shown this association to be both dose and time dependent. A shorter time will drive the hypothesis to the null, underestimate the effect, and add some residual confounding from prevalent users.

   We agree. As the average follow-up time is short, we cannot know the long-term effect but we can still know the short-term effect. The point is addressed as a limitation in the Discussion session of the revision.

3. Lines 28 -35: The conclusion did not flow from the aim. In lines Page 5, lines 47 – 49, your aim was “…association between the use of lipid-lowering drugs and new-onset diabetes (NOD)” but your conclusion and even the title were on the risk of NOD. This is confusing whether this study is about the incidence of diabetes in statin users or the risk of diabetes associated with statin-use.

   If the relative risk is higher than 1, this indicates that the risk in the study drug is higher than that in the reference drug. We believe that they state actually the same thing. Therefore, we did not make any
substantial change.

Reviewer: 3
John R Guyton
Duke University, USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The authors have utilized health screening and insurance claims databases from large Japanese corporations to examine the question of whether statins and fibrate’s are associated with increased risk of developing new-onset diabetes. The population at risk is about 70,000 subjects with dyslipidemia. Since one of the criteria for abnormal lipids is low HDL cholesterol, "dyslipidemia" is a more appropriate term than "hyperlipidemia."

In this manuscript, we changed “hyperlipidemia” to “dyslipidaemia”.

The use of observational data to create a quantitative estimate of the relative risk of developing diabetes between lipid medication users and nonusers is fraught with inaccuracy. At best one can say that the increased risk for statin users found in this database is consistent with the far more reliable increased risk shown in randomized controlled trials.

Adjustment for confounders, especially when variables are dichotomized – i.e., hypertriglyceridemia as 150 mg/DL or greater versus normal triglyceride – probably does not fully adjust for selection bias. This is to say, patients selected for fibrate therapy or even statin therapy may simply have had more extreme deviation in the confounding variables than is usually encountered. This is the reason that one should be very wary of quantitative estimates of relative risk. Even if adjustment for confounders is performed by continuous variables rather than dichotomously, linearity versus nonlinearity of response can still introduce uncertainty.
In the revision, we presented the results of the analyses where BMI, FBG, SCre, Blood pressure and serum creatinine were incorporated as continuous variables in all multivariate analyses. We changed all the relevant descriptions in the text and figures though the results were almost the same as those in the original.

It is all right to do a study such as this, but the results should be interpreted very cautiously and always with the proviso that randomized controlled trials give more reliable quantitation.

The incidence rates listed in Abstract Results suggest a decreased, rather than increased, risk of new-onset diabetes among statin and fibrate users. It seems possible that some numbers have become confused. The rates in lipid drug users appear to be low by a factor of 10.

Thank you very much. In the Abstract section, we checked the numbers and corrected them.

I think that the authors should probably delete the data and conclusions regarding fibrates. It strains credulity to suggest that any real estimate of increased risk of diabetes should be based on only 19 cases. This is especially true when adjustment for confounders reduces the hazard ratio by about half.

We toned down the description on the risk of new-onset diabetes associated with fibrates and mentioned that the increased risk of new onset fibrates in patients with fibrates is derived from a small number of cases and therefore it is possible we got the results just by chance.

In table 2, there is a column enumerating cases of new-onset diabetes in patients who used anti-diabetic medication, but did not have a diagnosis of diabetes listed. This does not seem to be the condition listed in Methods for the sensitivity analysis. Instead, I assume the sensitivity analysis counted cases of new onset diabetes by all patients who used anti-diabetic medication regardless of whether they had a diagnosis of diabetes. One would suppose that the numbers of cases identified in this way would be fairly similar to those in the column headed "diagnosis or use of antidiabetic."

To clarify the definition of outcome in Table2, we changed “use of antidiabetic only” to “use of antidiabetic”.

Page 10, line 34. "The insulin-sensitizing action on adiponectin…" I think this should read "The insulin-sensitizing action of adiponectin…" In reading this paragraph, I can't tell whether fibrates and statins actually raise or lower adiponectin.

We corrected the error of "on" which should be "of". In this paragraph, we revised the relevant descriptions on adiponectin.

**General Comments**

Thank you. The investigators have made appropriate revision to their manuscript. I have no further comments.

**Reviewer**

Iskandar Idris
University of Nottingham

**Review Returned**

18-Apr-2017

**Reviewer**

John Guyton MD
**GENERAL COMMENTS**

The Discussion lists 5 limitations of this study. The most glaring limitation is that this is an observational cohort study and not a randomized controlled trial, and it is mandatory that this limitation head the list. The discussion does not seem to recognize the greater validity of RCTs.

Page 10. “In our study, fibrates (fenofibrate and bezafibrate) were associated with an increased risk of new-onset diabetes, compared to that for non-use.” This is wrong. Since the multivariate hazard ratio confidence interval included 1.00, the correct statement is “Our study did not find fibrates (fenofibrate and bezafibrate) to be associated with an increased risk of new-onset diabetes, compared to that for non-use. However, we cannot rule out a possible increased risk, due to small numbers of patients taking fibrates.” This null result should also be reflected in the language describing fibrate effects in Results as well.

Given the many factors that go into clinical decisions to prescribe a fibrate, I do not find the “significant” hazard ratios for unadjusted rates of diabetes onset with fibrates compelling at all.

On the basis of 19 cases of new-onset diabetes (3 cases if defined by anti-diabetic drugs) associated with fibrate use, this study simply does not have the power to make a statement about diabetogenic effects of fibrates. The fact that it’s an observational cohort study compounds the problem of lack of significant effect.

In the sensitivity analysis of diabetes defined by anti-diabetic drug alone, the numbers of cases of “new-onset diabetes” were approximately 10 times less than cases defined by either diagnosis or drug or both. Is it really true that 90% of new diabetes cases did not receive anti-diabetic medication?

Moreover, this sensitivity analysis did NOT confirm the results of the main analysis, since all of the confidence intervals in the sensitivity analysis crossed 1.00.

**VERSION 2 – AUTHOR RESPONSE**

Reviewer(s)’ Comments to Author:

Reviewer: 2
Iskandar Idris
University of Nottingham
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
No further comments

Reviewer: 3
John Guyton MD
Duke University, USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The Discussion lists 5 limitations of this study. The most glaring limitation is that this is an
observational cohort study and not a randomized controlled trial, and it is mandatory that this
limitation head the list. The discussion does not seem to recognize the greater validity of RCTs.

The first sentence of the 'Strengths and Limitations of this study' as well as the first sentence of the
paragraph of Discussion section mentioning the limitations (5th paragraph) in the revision now read
"This was not a randomized controlled trial but a retrospective cohort study ---"

Page 10. “In our study, fibrates (fenofibrate and bezafibrate) were associated with an increased risk of
new-onset diabetes, compared to that for non-use.” This is wrong. Since the multivariate hazard ratio
confidence interval included 1.00, the correct statement is “Our study did not find fibrates (fenofibrate
and bezafibrate) to be associated with an increased risk of new-onset diabetes, compared to that for
non-use. However, we cannot rule out a possible increased risk, due to small numbers of patients
taking fibrates.” This null result should also be reflected in the language describing fibrate effects in
Results as well.

Given the many factors that go into clinical decisions to prescribe a fibrate, I do not find the
“significant” hazard ratios for unadjusted rates of diabetes onset with fibrates compelling at all.

On the basis of 19 cases of new-onset diabetes (3 cases if defined by anti-diabetic drugs) associated
with fibrate use, this study simply does not have the power to make a statement about diabetogenic
effects of fibrates. The fact that it’s an observational cohort study compounds the problem of lack of
significant effect.

In the sensitivity analysis of diabetes defined by anti-diabetic drug alone, the numbers of cases of
“new-onset diabetes” were approximately 10 times less than cases defined by either diagnosis or
drug or both. Is it really true that 90% of new diabetes cases did not receive anti-diabetic medication?

As in Table 2, the number of patients who had new-onset diabetes mellitus was 3,000 while the use of
an anti-diabetic was observed only for 273 during the study period. This is not surprising as the first
treatment of non-type 1 diabetes is normally not the drug therapy. We are not certain about whether
or not 90% of new diabetes cases did not receive the drug therapy eventually. What we could know
was only that 90% of patients who had newly diagnosed as having diabetes had not yet started the
drug therapy during the study period.

Moreover, this sensitivity analysis did NOT confirm the results of the main analysis, since all of the
confidence intervals in the sensitivity analysis crossed 1.00.

In Table3 of the Result section, we changed “the confidence intervals was wide.” to “the confidence
intervals were wide and crossed 1.00.”

We revised the 3rd paragraph of the Discussion section according to the kind suggestion as follows:
“Our study did not find fibrates (fenofibrate and bezafibrate) to be associated with an increased risk of
new-onset diabetes, compared to that for non-use. However, we cannot rule out a possible increased
risk, due to small numbers of patients taking fibrates.”

In addition, in the 6th paragraph of the Discussion section, we simply deleted the followings:” Fibrates
were also associated with the increased risk but the number of patients with new-onset diabetes was small."

| REVIEWER | John R Guyton  
Duke University, USA |
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| GENERAL COMMENTS | I appreciate the authors’ responses and congratulate them on a useful paper. |
Lipid-lowering drugs and risk of new-onset diabetes: a cohort study using Japanese healthcare data linked to clinical data for health screening

Nobuhiro Ooba, Soko Setoguchi, Tsugumichi Sato and Kiyoshi Kubota

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