BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

**ARTICLE DETAILS**

| TITLE (PROVISIONAL)                      | Assessment of statin-associated muscle toxicity in Japan: A cohort study conducted using a claims database and laboratory information |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| AUTHORS                                 | Akazawa, Manabu; Chang, Chia-Hsien; Kusama, Makiko; Ono, ShunSuke; Sugiyama, Yuichi; Orii, Takao                              |

**VERSION 1 - REVIEW**

| REVIEWER                                 | Christopher G. Rowan Phd  
Senior Epidemiologist  
Outcome, A Quintiles Company  
USA |
|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
|                                          | I conducted a study titled "Clinical importance of the drug interaction between statins and CYP3A4 inhibitors: a retrospective cohort study in THIN" |

| REVIEW RETURNED | 14-Sep-2012 |
|-----------------|-------------|

**THE STUDY**

The authors could more clearly describe the inclusion and exclusion criteria. In particular, the authors should state if the excluded patients who had previously experienced the outcome.

The methods section could be further developed. I'd like to see more verbiage around how the following were handled: gaps in statin therapy, outcome timing relative to statin therapy, classification of concomitant therapy, etc.

Also, the outcome definitions in this study deviate substantially from other statin AE studies. I described the secondary analyses that would make this study stronger and more consistent with prior research.

**GENERAL COMMENTS**

- In the introduction, the author should provide more details to explain why the Asian population is more sensitive to statins (e.g., genetic polymorphisms of important metabolic enzymes).
- The discussion of MIHARI in the introduction, while important, seems unrelated to the background or rationale for the study. If the MIHARI database was used for this analysis, I would consider including the MIHARI description in the methods section.
- It's not clear why the authors are excluding the 4 patients with a muscle-related diagnosis AND an elevated CK. These seem like important, and perhaps more severe adverse events that should be included.
  - Please consider elaborating on this statement. It is not clear what the author is attempting to convey: "Given concerns that the infrastructure of the database might restrict the presentation of information, the identification of severe muscle toxicity was conducted by using these two criteria separately."
- I appreciate the authors attempt to study severe muscle toxicity, however, it is likely difficult to determine disease severity through...
codes. The authors should consider conducting several secondary analyses.
  o One may include adding less restrictive muscle toxicity codes for “myopathy” or “myalgia” and see how the incidence of adverse events with these codes compared to “myositis” and “rhabdo”.
  o In the US and EU, rhabdomyolysis is frequently misclassified. The authors should consider evaluating changes in serum creatinine or eGFR from baseline or a single measurement above a certain threshold (e.g., 2X ULN).
  o The classification of severe muscle toxicity with a CK value of 10X ULN is very high. I would like to see a secondary analysis at CK >5X ULN.
  o A composite endpoint is preferred. I would not exclude patients who had both a code and an elevated CK.
    • I would consider revising your inclusion criteria to include a 12 month baseline period. There seems to be sufficient person-years to do this.
    • I suggest including only patients with no statin during the 12 month baseline period
    • And no evidence of the outcome during the baseline period.
  ▶ The authors do not state if they excluded statin initiators with prior evidence of the outcome.
    • It’s been shown that statin related toxicity is related more so to the potency rather than statin dose. The authors should consider revising the statin dose into equipotent dosages.
    • It’s not clear how the author classified concomitant administration of interacting drugs. More details around the timing of concomitancy would be helpful.

REVIEWER
Elis, Avishay
Meir Medical Center

REVIEW RETURNED
01-Nov-2012

GENERAL COMMENTS
This is an interesting and important study, concerns muscular side effects in statin treated japanese patients. Although these patients are more susceptible to statins and their side effects, we lack data on these subjects. Never the less, the study reviewed only severe myopathies, which rare in all populations including this one, but did not evaluated myalgia which is more common and bathering in the everyday life.

VERSION 1 – AUTHOR RESPONSE
Reviewer 1: Dr. Christopher G. Rowan

Comment 1: The authors could more clearly describe the inclusion and exclusion criteria. In particular, the authors should state if the excluded patients who had previously experienced the outcome.

Response:
We excluded prevalent cases with muscle toxicity as suggested. To clearly describe the inclusion and exclusion criteria of the study population, we have revised the manuscript on p. 10, lines 8-16 as follows: “Because the median duration of statin prescription in the database was 28 days, a patient would be enrolled if there was no existing claim of statin prescription within 3 months after the first date of any claim. To avoid enrolling prevalent cases with muscle toxicity, patients who exhibited the following conditions would be excluded: a diagnosis of rhabdomyolysis/myositis; or the possibility of
muscle-related CK elevation (i.e., patients whose CK elevation did not present with myocardial infarction, myocarditis, trauma, or hypothyroidism, and who had no claims of obtaining nitrate or levothyroxine prescriptions within 3 days after concurrent elevation of CK). In addition, the eligible population was required to have undergone at least one blood test during statin therapy, for avoidance of information bias.”

Comment 2: The methods section could be further developed. I'd like to see more verbiage around how the following were handled: gaps in statin therapy, outcome timing relative to statin therapy, classification of concomitant therapy, etc.

Response:
No gaps in statin therapy were considered. In Japan, patients usually make an appointment for the subsequent visit, and the quantity of drugs prescribed is adjusted for the period between visits. Therefore, we assumed that the patients received consecutive treatment once they initiated the statin until the end of the last prescription. Awareness of disease control is sufficiently high in Japan that patients are monitored regularly for adherence to medication regimens. (Eur J Clin Pharmacol. 1999;55:145-9, Clin Exp Hypertens. 2010;32:234-8). We have added two references and have revised the manuscript on p. 11, lines 7-9 as follows: “We assumed that the patients received consecutive treatment from the initiation of statin therapy until the end of the last prescription, because the patients were monitored regularly. [18-19]”

We identified a muscle toxicity event occurring any time during the statin therapy as an outcome. Patients were observed until the first muscle toxicity event and were censored when statin therapy was discontinued or when passing the end of the observational period (31 December 2010). As a sensitivity analysis, we extended the follow-up for 30 days after the statin therapy was terminated; however, no additional events were captured. To clarify the timing of outcome detection, we have revised on p. 14, lines 6-8 as follows: “Patients were observed until occurrence of the first muscle toxicity event, and were censored when statin therapy was discontinued or when the end of the observational period was reached (31 December 2010).”

For the concomitant drugs, we were particularly interested in drugs that have some pharmacokinetic interactions with statins because they may increase the risk of muscle toxicity. Therefore, we selected these drugs from information contained in the package inserts of the statins. Interacting drugs that are listed as contraindicated or to be used with caution in the package inserts are rarely used concomitantly with statins. Therefore, we pooled all interacting drugs together rather than identifying specific drug interactions according to severity. We have revised the manuscript on p. 11, line 15 and p. 12, line 12 as follows: “We also defined drugs that have some pharmacokinetic interactions with statins and that may increase risk of muscle toxicity. Lists of potentially interacting drugs were compiled from package inserts for statin medications, excluding topical and ophthalmic preparations.[20] We determined whether patients had used any of the following interacting drugs while undergoing statin therapy: fibrate (benzafibrate, fenofibrate, clofibrate), macrolide antibiotics (clarithromycin, erythromycin, telithromycin), triazole antimycotics (fluconazole, itraconazole, fosfluconazole, voriconazole), immunosuppressant (cyclosporine), antiarrhythmic drug (amiodarone), and HIV/AIDS drugs (saquinavir/ritonavir, atazanavir, etravirine, and efavirenz). Statin therapy administrated concurrently with an interacting agent was treated as a time-varying covariate. Subjects could contribute person-time to the statin both with and without a concomitant interacting drug. Because the package inserts list the aforementioned interacting drugs as contraindicated or to be used with caution, concomitant use of these drugs with statins is rare. Therefore, we pooled all interacting drugs together rather than assessing specific drug interactions.”
Comment 3: Also, the outcome definitions in this study deviate substantially from other statin AE studies. I described the secondary analyses that would make this study stronger and more consistent with prior research.

Response:
For clarification, we have revised the manuscript on p. 12, line 15 and p. 13, line 1 as follows: “Since databases based on insurance claims do not contain laboratory results, differences in risk estimation would occur when the varying composition of available data. Therefore, we identified severe muscle toxicity using the following two criteria to explore the deviation between differing definitions.”

Comment 4: In the introduction, the author should provide more details to explain why the Asian population is more sensitive to statins (e.g., genetic polymorphisms of important metabolic enzymes).

Response:
There have been many studies on racial differences in statin pharmacokinetics; however, there is no definite genetic polymorphism that can explain the difference in statin sensitivity between races. It is well known that the pharmacokinetics of rosuvastatin differ between Asians and Caucasians. The AUC (Area Under the Curve) was 2.5-fold higher in Japanese compared to Caucasians in clinical pharmacology trials, while the Japanese starting dose of rosuvastatin is one-fourth that of the United States, which is based on efficacy and safety. Further, the range of approved doses differs between the two countries. Considering these facts, we have stated that the Asian population is more sensitive to statins and investigated safety concerns that could be compared with Caucasian data. The starting doses for hyperlipidemia for JPN and US are as follows:

| Statin     | JPN (mg) | US (mg) |
|------------|----------|---------|
| Atorvastatin | 10, 10 – 20 | 10      |
| Rosuvastatin | 2.5, 10  |         |
| Pravastatin | 10, 40   |         |
| Pitavastatin | 1 – 2, 2 |         |
| Simvastatin | 5, 10 – 20 |        |
| Fluvastatin | 20, 40 – 80 |        |

We have revised the manuscript on p. 7, lines 10-13 and added one reference as follows: “Moreover, the Asian population is more sensitive in its clinical response to statins than is the Western population, and approved statin doses in Japan are relatively low compared to those approved for use in the US. [6-9]”

*We have cited the following article:
Statin dose in Asians: is pharmacogenetics relevant?
Wang P. Pharmacogenomics 2011;12:1605-15.

Comment 5: The discussion of MIHARI in the introduction, while important, seems unrelated to the background or rationale for the study. If the MIHARI database was used for this analysis, I would consider including the MIHARI description in the methods section.

Response:
We did not use the MIHARI database because it is in the trial phase and access to the data is very limited. The discussion of the MIHARI project in the introduction is used to explain the status of drug-safety monitoring in Japan. This study, using a relatively small-scale commercial database with similar data composition to the MIHARI database (for example, the claims database with laboratory information), could point out obstacles and applicability of the pilot scale for future investigative research. For clarification, we have revised the manuscript on p. 8, lines 16-19 as follows: ”Before
researchers and regulators begin working with large automated databases (including the MIHARI database) for drug safety monitoring, pilot studies are needed to evaluate the pros and cons of database studies under the Japanese healthcare system.

Comment 6: It’s not clear why the authors are excluding the 4 patients with a muscle-related diagnosis AND an elevated CK. These seem like important, and perhaps more severe adverse events that should be included.

Response:
Four patients identified by both criteria A and B were not excluded. Because 23 cases met only criterion A, 16 cases met only criterion B, and 4 cases met both criteria A and B, the total number of cases should be 43. We have revised Figure 1 and Tables 2-4 to avoid this misunderstanding.

Comment 7: Please consider elaborating on this statement. It is not clear what the author is attempting to convey: “Given concerns that the infrastructure of the database might restrict the presentation of information, the identification of severe muscle toxicity was conducted by using these two criteria separately.”

Response:
In the MIHARI project, two types of data sources would be used. One is insurance claims that contain one million beneficiaries but lack confirmation by laboratory results. The other is the electronic health records in participating hospital settings that contain detailed clinical information but are limited to fragmented observations. By considering the pros and cons of the different data sources, we established two criteria for outcome measurement for comparison. We have revised the manuscript as suggested. Please refer to comment 3.

Comment 8: I appreciate the authors attempt to study severe muscle toxicity, however, it is likely difficult to determine disease severity through codes. The authors should consider conducting several secondary analyses. One may include adding less restrictive muscle toxicity codes for “myopathy” or “myalgia” and see how the incidence of adverse events with these codes compared to “myositis” and “rhabdo”.

Response:
We agree. We did not rely on ICD-10 codes to identify cases. Under the Japanese healthcare system, more detailed disease names should be submitted for reimbursement purposes, and the dataset includes this information written in Japanese text. Further, we found that when all muscle-related symptoms were included for the case definition, in Japanese text the terms “myopathy” and “myalgia” were used interchangeably and not differentiated. Because these definitions were considered to be too ambiguous to evaluate the associations with drug exposure, and many confounding factors were not available (such as physical activity), we finally concluded that we should focus only on severe cases to avoid the misclassification of cases.

Comment 9: In the US and EU, rhabdomyolysis is frequently misclassified. The authors should consider evaluating changes in serum creatinine or eGFR from baseline or a single measurement above a certain threshold (e.g., 2X ULN).

Response:
Regarding the renal function change during rhabdomyolysis, the current study found that 17 out of 31 patients (55%) met criterion A or B, accompanied by worsened renal function. We have added the clinical information in Table 4 and revised on p. 20, lines 9-11 as follows: “The majority of cases of discontinuation of statins resulted in hospitalization accompanied by acute changes in renal function.”
Comment 10: The classification of severe muscle toxicity with a CK value of 10X ULN is very high. I would like to see a secondary analysis at CK >5X ULN.

Response:
We have revised Table 2 and added Table 3 as suggested.

Comment 11: A composite endpoint is preferred. I would not exclude patients who had both a code and an elevated CK.

Response:
Please refer to the response to comment 6.

Comment 12: I would consider revising your inclusion criteria to include a 12 month baseline period. There seems to be sufficient person-years to do this. I suggest including only patients with no statin during the 12 month baseline period and no evidence of the outcome during the baseline period.

Response:
Our data sources were taken from 16 participating hospitals, and patient information covered individuals that received services from these hospitals. Different from the insurance claims, no information was included for individuals that did not receive hospital services. We attempted to minimize the baseline periods for defining new statin users. For statin users in the database, the median duration of statin prescriptions was 28 days, with 1st and 3rd quintiles of 14-50 days. Statins prescribed for more than 90 days were less than 0.5% among all statin prescriptions. Thus, it is efficient enough to identify the new statin users by using 3 months as the baseline period based on clinical practice. On the other hand, if we extend the baseline period to 12 months, we might include patients who did not use statins but received any other medical services from the hospital. This selecting process would threaten the generalizability of our findings. We have revised the manuscript on p. 10, lines 8-10 as follows: "Because the median duration of statin prescription in the database was 28 days, a patient would be enrolled if there was no existing claim of statin prescription within 3 months after the first date of any claim."

Response:
The statement for excluding prevalent cases is added for clarification. Please refer to response to comment 1.

Comment 14: It's been shown that statin related toxicity is related more so to the potency rather than statin dose. The authors should consider revising the statin dose into equipotent dosages.

Response:
We assumed that safety profiles of the statins would differ among drugs and doses, and pursued this investigation by stratifying all statins and doses. In this cohort the majority of the subjects were prescribed statins at the lower limit of the approved doses, which we considered equipotent among statins because it is the lowest effective dose. We have revised the manuscript on p. 19, lines 5-7 as follows: "The majority of prescribed doses were at the lower limits of approved dosage levels, implying comparable potency among statins at the lowest effective dose."

Comment 15: It's not clear how the author classified concomitant administration of interacting drugs. More details around the timing of concomitancy would be helpful.
Response:
For clarification, the concomitant drug in the baseline period is used for identifying comorbidities (Table 1). Accordingly, we have revised as suggested on p. 12, lines 6-9 as follows: “Statin therapy administered concurrently with an interacting agent was treated as a time-varying covariate. Subjects could contribute person-time to the statin both with and without a concomitant interacting drug.”

Reviewer 2: Dr. Avishay Elis

Comment 1: Never the less, the study reviewed only severe myopathies, which rare in all populations including this one, but did not evaluated myalgia which is more common and bothering in the everyday life.

Response:
Indeed, the complaint of myalgia is common comparing to rhabomyolysis/myositis; however, it is a challenge to evaluate the association with the use of statin because many confounding factors cannot be measured, such as physical activity or falls. Therefore, we used severe muscle toxicity, which is judged by the physicians and/or clinically significant changes in CK level, as the conservative outcome definition. Please refer to the reply to reviewer 1, comment 8.

Comment 2: table 1 - only percents are needed, please compare between medications, please short it - too much data.

Response:
We have reduced the data according to your suggestion (Table 1).

Comment 3: table 3 - please explain mean daily dose 0.36

Response:
To avoid confusion, we have deleted this data in Table 4.

Comment 4: please provide more clinical data on the characteristics of the study group (table 3)

Response:
We added the information according to your suggestion (Table 4). Further, we have revised the manuscript on p. 17, lines 14-15 as follows: “In addition, clinical characteristics were similar among cases defined by diagnosis and cases defined by laboratory results.”

### VERSION 2 – REVIEW

| REVIEWER                  | Christopher G. Rowan PhD
|                          | Senior Epidemiologist
|                          | Quintiles | Outcome
|                          | Real-World and Late Phase Research
|                          | USA
|                          | I have no competing interests. I conducted a similar study for my dissertation research. Therefore, I am familiar with this research area, but have no interest in this study beyond academic.
| REVIEW RETURNED           | 17-Dec-2012 |
| PAGE  | COMMENT |
|-------|---------|
| 4 Line 14: | Consider changing the wording of the objective. The current verbiage gives the impression you're doing hypothesis testing rather a purely descriptive study. |
| 5 Line 58: | 10x ULN is pretty high...it would be interesting to see CK outcomes @ 5x ULN. |
| 5 Line 38: | Please revise the last sentence of the paragraph beginning in "As a result...". |
| 9 Line 27: | Consider shortening the discussion of the MIHARI project. This is not required for this research. Also consider, including more detail about the data source as it relates to ascertainment of exposure, outcome, and confounder data...and any inherent bias (specifically I would address the following: selection bias, information bias, and generalizability). |
| 11 Line 33: | A 3 month baseline period is not typical in pharmacoepidemiology. It is presumed this short duration was selected to increase sample size. Please consider presenting a sensitivity analysis with a six and 12 month baseline period. |
| 11 Line 56: | Please revise the language in the sentence ending in bias. Requiring cohort members (statin initiators) to have at least one blood test during statin therapy does not avoid information bias. Rather, it attempts to construct a cohort with the potential for equal ascertainment of the outcome. |
| 12 Line 4: | This is not important to the study of muscle toxicity associated with statin therapy. It is not clear why the authors are including this analysis in this manuscript. I recommend this be removed. |
| 12 Line 24: | Please consider adding a simple sensitivity analysis to show the assumption about continuous exposure is reliable. Patients stop and start therapy frequently. The denominator (p-y) may be overestimated. You could also do a small sensitivity analysis to show how the IRs would change if the p-yys were reduced. |
| 13 Line 47: | Please consider revising your outcome definition verbiage. You're using the term "severe muscle toxicity" to describe ICD9 codes (for myositeis and rhabdo) and or CK elevation. There's no medical record adjudication to verify that in fact the muscle toxicity was severe. From experience, I can tell you that physicians frequently use different language to describe muscle toxicity (e.g., myalgia, myositis, or rhabdomyolysis). Additionally, a diagnosis of rhabdo should be accompanied by renal dysfunction. Since you have renal function laboratory data, you should consider creating another outcome category for renal dysfunction. You could then separate the myositis/ck "muscle toxicity code/lab" from the rhabdo/sCr "renal toxicity" code lab. |
| 14 Line 28: | Please consider adding a sensitivity analysis for 5x...
ULN for CK. While 10x ULN has been used in prior research, it is very high and suggestive of rhabdo and/or sever muscle toxicity. Your myositis code however does not have this level of severity.

Page 15 line 7: It's true that a muscle toxicity event may lead to discontinuation of statin therapy. It's also true that physicians may switch statins. I recommend you also evaluate and describe patients who switch statins following a muscle event.

Page 17 line 15: The results further support that you're not studying only "severe muscle toxicity" rather you're studying a spectrum of myalgia to myositis to rhabdomyolysis.

I recommend the authors create multiple outcome definitions to reflect the varying severity of the muscle toxicity outcome. For example:
- myositis code only
- myositis code & ck >5x uln
- myositis code & ck >10x uln
- rhabdomyolysis code only
- rhabdomyolysis code & ck >5x uln
- myoshrhabdomyolysis its code & ck >10x uln

Page 17 line 30: Again, I don't think your overall incidence truly reflect "severe muscle toxicity". I believe your outcome definition needs modification.

Page 18 line 24: Other studies of severe muscle toxicity (e.g., the MacAfee study) required hospitalization.

Page 19 line 12 - consider changing incidence to percent, proportion, or frequency.

**VERSION 2 – AUTHOR RESPONSE**

Responses to reviewer, Dr. Christopher G. Rowan:

Thank you very much for your thoughtful suggestions and comments. We have revised our manuscript by following your recommendations as much as possible.

Comment 1:
Page 4 line 14: Consider changing the wording of the objective. The current verbiage gives the impression you're doing hypothesis testing rather a purely descriptive study. This is a descriptive study.

Response:
We agree. We have revised the wording of our objective as follows: To estimate the incidence of muscle toxicity in patients receiving statin therapy by examining study populations, drug exposure status, and outcome definitions. All changes in the manuscript are highlighted in blue.

Comment 2
Page 5 line 58: 10x ULN is pretty high...it would be interesting to see CK outcomes @ 5x ULN.
Responses:
We selected 10x ULN as a base case because many database studies used this definition. However, as suggested, we have re-analyzed the data by changing CK outcomes as 5x ULN. These results are shown in Table 2. Also, the sentence on Page 3 Line 18 (in the Abstract) has been reworded as follows: Statin-associated muscle toxicity (the ‘event’) was identified based on a diagnosis of muscle-related disorders (myopathy or rhabdomyolysis) and/or abnormal elevation of creatine kinase (CK) concentrations.

Comment 3
Page 5 line 38: Please revise the last sentence of the paragraph beginning in “As a result...”.

Response:
We have revised several sentences in the results (and in the Abstract) as follows: The incidence of muscle toxicity in the patients treated with statins was 1.02 (95% CI: 0.76–1.37) per 1,000 person-years. The estimates varied when outcome definitions were modified from 0.09 per 1,000 person-years, which met both diagnosis and CK 10x greater than the upper limit of normal range (ULN) criteria, to 2.06 per 1,000 person-years, which met diagnosis or CK 5x ULN criterion. The incidence of muscle toxicity was also influenced by the statin therapies selected, but no significant differences were observed. Among 2,430 patients (13.5%) received interacting drugs with statins, only 3 muscle toxicity cases were observed (incidence: 1.69 per 1,000 person-years).

Comment 4
Page 9 line 27: Consider shortening the discussion of the MIHARI project. This is not required for this research. Also consider, including more detail about the data source as it relates to ascertainment of exposure, outcome, and confounder data and any inherent bias (specifically I would address the following: selection bias, information bias, and generalizability).

Response:
The following sentences explaining the MIHARI project were deleted. “The MIHARI project aggregates electronic medical information with appropriate methodologies for risk evaluation, and ensures the accessibility and applicability of claims databases and electronic healthcare records for use. The Japanese national claims database has been accessible to researchers by a peer-reviewed proposal process, beginning in April 2011.”

Then, in the data resource session of Methods, we added the following explanation of the MDV database. Although the source of information was limited to 16 facilities, the age and gender distribution of patients in the database was similar to that of the national demographics. Furthermore, the database had been used for various epidemiological studies including an observational study examining a national estimate of acute pancreatitis risk among diabetes patients in Japan. We have added the reference below which explains the database and provides an example of a study using the MDV data.

Urushihara H, Taketsuna M, Liu Y, et al. Increased risk of acute pancreatitis in patients with type 2 diabetes: an observational study using a Japanese hospital database. PLoS One. 2012;7(12):e53224.

Comment 5
Page 11 Line 33: A 3 month baseline period is not typical in pharmacoepidemiology. It is presumed this short duration was selected to increase sample size. Please consider presenting a sensitivity analysis with a six and 12 month baseline period.

Response:
As suggested we have conducted the sensitivity analysis with six and 12-month baseline periods. The following sentence has been added in the Methods (Page 15 Line 3): Various sensitivity analyses were performed by modifying baseline periods (6 months and 12 months), statin exposure status (number of days on which statins were received as a denominator), and outcome definitions (abnormal range of CK values and switching, renal dysfunction, or hospitalization, with muscle toxicity). No significant changes were observed, as shown in Table 2.

Comment 6
Page 11 line 56: Please revise the language in the sentence ending in bias. Requiring cohort members (statin initiators) to have at least one blood test during statin therapy does not avoid information bias. Rather, it attempts to construct a cohort with the potential for equal ascertainment of the outcome.

Response:
Thank you for this suggestion. The sentence (Page 10 Line 16) has been revised as follow. The eligible population was required to have undergone at least one blood test during statin therapy, to construct a cohort in which ascertainment of outcome was potentially equivalent.

Comment 7
Page 12 line 4: This is not important to the study of muscle toxicity associated with statin therapy. It is not clear why the authors are including this analysis in this manuscript. I recommend this be removed.

Response:
As suggested, we have removed the sentence "To ensure the validity of information available for individuals undergoing statin therapy, the consistency between dyslipidaemia diagnoses (ICD-10 code E78) and laboratory results of cholesterol, triglyceride, and low-density lipoprotein (LDL) was determined."

Comment 8
Page 12 line 24: Please consider adding a simple sensitivity analysis to show the assumption about continuous exposure is reliable. Patients stop and start therapy frequently. The denominator (p-y) may be overestimated. You could also do a small sensitivity analysis to show how the IRs would change if the p-y's were reduced.

Response:
We have added sensitivity analyses using information on the total days of statin supply, instead of the length of follow-up, as a denominator. No significant changes were observed. The results are shown in Table 2.

Comment 9
Page 13 line 47: Please consider revising your outcome definition verbiage. You're using the term "severe muscle toxicity" to describe ICD9 codes (for myositis and rhabdo) and or CK elevation. There's no medical record adjudication to verify that in fact the muscle toxicity was severe. From experience, I can tell you that physicians frequently use different language to describe muscle toxicity (e.g., myalgia, myositis, or rhabdomyolysis).

Response:
We have revised the wording from "severe muscle toxicity" to "muscle toxicity" throughout the manuscript, including in the title as suggested.

Comment 10
Additionally, a diagnosis of rhabdo should be accompanied by renal dysfunction. Since you have
renal function laboratory data, you should consider creating another outcome category for renal dysfunction. You could then separate the myositis/ck "muscle toxicity code/lab" from the rhabdo/sCr "renal toxicity" code lab.

Response:
We have added sensitivity analyses by considering renal dysfunction as an outcome definition. Three out of four cases with a diagnosis of rhabdomyolysis and 10x ULN for CK had records of renal dysfunction. These results are shown in Table 2.

Comment 11
Page 14 line 7: Duplicate sentence...beginning with "Therefore..."

Response:
Thank you very much. We have removed the duplicated sentence.

Comment 12
Page 14 line 28: Please consider adding a sensitivity analysis for 5x ULN for CK. While 10x ULN has been used in prior research, it is very high and suggestive of rhabdo and/or sever muscle toxicity. Your myositis code however does not have this level of severity.

Response:
We have added the sensitivity analyses by changing 5x ULN for CK. These results are shown in Table 2.

Comment 13
Page 15 line 7: It's true that a muscle toxicity event may lead to discontinuation of statin therapy. It's also true that physicians may switch statins. I recommend you also evaluate and describe patients who switch statins following a muscle event.

Response:
We have added the sensitivity analyses by considering switching statin therapy after muscle toxicity. These results are shown in Table 2.

Comment 14
Page 17 line 15: The results further support that you're not studying only "severe muscle toxicity" rather you're studying a spectrum of myalgia to myositis to rhabdomyolysis.

I recommend the authors create multiple outcome definitions to reflect the varying severity of the muscle toxicity outcome. For example:
- myositis code only
- myositis code & ck >5x uln
- myositis code & ck >10x uln
- rhabdomyolysis code only
- rhabdomyolysis code & ck >5x uln
- myosrhabdomyolysis itis code & ck >10x uln

Response:
We have added these sensitivity analyses as suggested. These results are shown in Table 2.

Comment 15
Page 17 line 30: Again, I don't think your overall incidence truly reflect "severe muscle toxicity". I believe your outcome definition needs modification.
Response:
We have used the current outcome definition as a base case. Then, we have changed definitions of baseline periods, drug exposure status, and outcomes. We revised the results (Page 16 Line 3) as follows: Among the new statin users, 43 (0.24%) who met either criterion A or B were identified as base cases, and incidence (with 95% CI) of muscle toxicity was estimated as 1.02 (0.76–1.37) per 1,000 person-years (Table 2). According to various outcome definitions, the estimated incidences ranged from 0.09 (met both criteria A and B) to 2.06 (either met criterion A or demonstrated CK values > 5x ULN) per 1,000 person-years. When the strictest definition was selected (i.e., cases met both criteria A and B), 4 cases were identified, and most of these showed discontinuation, switching, renal dysfunction, or hospitalization after the occurrence of the adverse event (3, 1, 3, and 4 cases, respectively). No significant changes were observed when baseline periods or statin exposure status were modified.

Also, we revised the discussion (Page 18 Line 14) to consider cases with discontinuation, switching, renal dysfunction, or hospitalization as follows: Since it is not applicable to compare the incidence of events defined by different parameters, we refined our event definition to consider statin discontinuation or switching and renal dysfunction or hospitalization after the occurrence of an adverse event. Under this revised definition, we found the crude incidence of rhabdomyolysis to be 7.1 to 9.5 per 100,000 person-years (3 to 4 cases per 42,193 person-years), suggesting a moderately high incidence in the present study.

Comment 16
Page 18 line 24: Other studies of severe muscle toxicity (e.g., the MacAfee study) required hospitalization.

Response:
We have added these sensitivity analyses by considering hospitalization after muscle toxicity. These results are shown in Table 2.

Comment 17
Page 19 line 12 - consider changing incidence to percent, proportion, or frequency.

Response:
Thank you very much. We have changed the wording to ‘frequency’.

VERSION 3 - REVIEW

| REVIEWER | Christopher G. Rowan PhD
|          | Senior Epidemiologist
|          | Quintiles-Outcome
|          | Scientific Affairs
|          | USA

For my dissertation, I conducted a cohort study to evaluate the clinical importance of the drug interaction between statins and CYP3A4 inhibitors.

REVIEW RETURNED 18-Mar-2013

| GENERAL COMMENTS | Page 11 line 33: The authors should state the time period during which prevalent cases were excluded. For example, was this only during the 3 month period prior to statin initiation? Or was it anytime... |
prior? Or in the prior 12 months?

Page 19 line 54: The authors should note the confidence interval for the revised muscle toxicity definitions estimates (7.1 to 9.5 per 100,000p-y). Based on the small number of cases I imagine the confidence interval would include 2.5 and 4.4 per 100,000k. Therefore, I don't believe the present study suggests a moderately high incidence...I think is likely a function of imprecision in estimation due to the small number of events.