PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of oral ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin with the risk of serious ventricular arrhythmia: a nationwide cohort study in Korea
AUTHORS	Cho, Yongil ; Park, Hyun Soo

VERSION 1 – REVIEW

REVIEWER	Arsen Uvelin Clinical centre of Vojvodina, Emergency centre, Department of Anaesthesia and Intensive care, Hajduk Veljkova 1-10, 21000 Novi Sad Serbia
REVIEW RETURNED	09-Jan-2018

GENERAL COMMENTS	This is a well designed study with clear aims, succint introduction, and well written discussion section. I have no major remarks, except that it can be accepted for publication after minor review due to small misspelling and a proposal for the Discussion section, please see below. For the Editor: I suggest that you check the statistics in the paper with a professional. I have no doubts, I just think it is reasonable. Page 4, line 19 torsede.....torsade Page 10, lines 26-38. Consider putting this part of the Discussion section in the beginning, just optional

REVIEWER	James E. Tisdale College of Pharmacy Purdue University USA
REVIEW RETURNED	23-Jan-2018

GENERAL COMMENTS	This manuscript describes a population-based cohort study with the purpose of assessing whether oral ciprofloxacin, levofloxacin, ofloxacin and moxifloxacin increase the risk of ventricular arrhythmias in the general population of Korea. The study addresses an important topic and appears to be well-conducted. The paper will require substantial copy-editing for proper grammar and English language usage. Specific comments: 1) Abstract: Please add into the Methods of the abstract the fact that a propensity score matching process was used 2) Discussion, page 9, lines 47-55: In the discussion of reference 21 - the fact that levofloxacin was associated with an increased risk of death in addition to an increased risk of serious cardiac arrhythmia does not mean, as you suggest, that "the baseline condition was more severe in the levofloxacin group.....and that the study results

	were confounded." The investigators in that study performed propensity score matching and reported that the groups were well-matched. There is no evidence that the study results were confounded. It seems possible that levofloxacin may have been associated with more serious, life-threatening arrhythmias in that study, In addition, theirs was a population of Veterans Administration patients, indicating that they were older than the population in your study; it seems possible that these differences could account for differences between your study and theirs, and also account for an increased risk of both serious arrhythmias and overall death associated with levofloxacin in that study. Please revise your discussion of reference 21. 3) Discussion, page 10, lines 18-24 - the authors state that "These data combined with our study reinforce the view that ciprofloxacin and levofloxacin are not associated with ventricular arrhythmias..." But there are published cases that clearly show that ciprofloxacin and levofloxacin may cause torsades de pointes. Both drugs are in the category of drugs "Known" to cause torsades de pointes in the QT drugs list at crediblemeds.org. This section of the Discussion must be revised, The fact that, in your study, neither levofloxacin nor ciprofloxacin increased the risk of ventricular arrhythmias does not mean that these drugs cannot provoke torsades de pointes given the right circumstances (patients with multiple risk factors for torsades). 4) Discussion, page 11, lines 22-34: The statement that "Most of the cases were developed in patients with concomitant use of other medications associated with QT interval prolongation or with multiple risk factors of drug-induced arrhythmia" is exactly the point. For the vast majority of patients who experience drug-induced torsades de pointes, the event occurs in the presence of one or more risk factors. It seems possible that in your study, levofloxacin and ciprofloxacin did not increase the risk compared to cefixime because the preponderance of your patients did not have risk factors. Please discuss.

REVIEWER	Paula Dhiman Post-doctoral Researcher (Meta Research) Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences Centre for Statistics in Medicine University of Oxford UK
REVIEW RETURNED	12-Mar-2018

GENERAL COMMENTS	This is a good study, which is well presented and reported. Authors have used the STROBE statement to help report their study. The study design is appropriate and a suitable analysis has been conducted. It is also helpful that authors have includes supplementary information of codelists used. I do however feel some information around the methods is missing and interpretation needs to be strengthened. To further strengthen the paper I have the following comments and suggestions: 1. Abstract: Include dates from fully in the setting 2. Abstract: Be more explicit in the setting of the study – e.g. primary or secondary care? 3. Abstract: Add the 2 time periods of interest: 1-7 and 8-14 days. 4. Abstract: In the results, please add the time point (1-7 days) with the OR results, as evidence was not found for 8-14 days. 5. Introduction: Would be useful to include more information about the use of cefixime as the comparator, especially because it seems

	a lot of the present research used amoxicillin as the comparator. 6. Methods: no information about dose of the drug has been given. Could this be added? Or even some summary information about the dose in the dataset? 7. Method, p6 line 26-28: could you clarify what you mean by this sentence? 8. Methods, p7 line 35: should be IPTW weights 9. Methods p7, line 50: needs a comma after 'subgroup analysis' 10. Methods: As part of the subgroup analysis, you divided patients by age. Why was 65 years used as the cut off? 11. Methods: Though it is mentioned in the completed STROBE checklist that there was no missing data in the study, this should be explicitly stated in the manuscript as well. 12. Results: Would be useful to summarise number and reason for exclusions in the text as well as referring to the figure. 13. Results: Generally, I think more time needs to be spent on the results and explaining the findings. Interpretation of the OR would also be useful as well as reporting the OR and 95% CIs. 14. Results, p8 line 45: consistently in reporting OR with 95% CI is needed 15. Results, p8 line 47: This sentence needs to moderated. Given that the confidence intervals for the OR for ciprofloxacin and levofloxacin span 1, I would be more cautious interpreting these results. To say these two drugs had 'no increased risk' is misleading, as no evidence is found to support this for 1-7days. 16. Results: For Ofloxacin, I think this would be better reported as finding a 59% reduced risk of serious ventricular arrhythmia compared to cefixime. 17. Results p8 line 56: capital T for 'table 3'. 18. Results p9 line 6: as above this sentence needs to moderated and corrected. Reduced risk is found with ciprofloxacin and ofloxacin, and no evidence is found for levofloxacin and moxifloxacin between 8-14 days. 19. Table 2, 3, and 4: Instead of 1, please use 'reference' (or equivalent) to highlight cefixime as the reference category in the analysis 20. Results (subgroup): please add OR and 95% CI to support text 21. Discussion: subheadings would be useful. 22. Discussion: results for moxifloxcin seem most prominent from this study. This needs to be further discussed, especially in relation to the fewer participants in this group. 23. Discussion: this now needs to reflect the changes made to the results (above). 24. Discussion: it would be good the see the strengths (eg no missing data as well as the limitation of the study of the study 25. Discussion: depending of the response to point 6 (above – dose), can this also be discussed. 26. Discussion, p11 line 4-7: can you clarify if this information is from the referred study or the present study? 27. Discussion p11 line 47: what would the impact of this be on the results? Would this result in an over-estimation of the results? 28. Conclusion: needs to be moderated as above. 29. Conclusion: time period for moxifloxacin estimate needs to be given. 30. Conclusion: please expand on future research beyond that additional populations need to be looked at?

VERSION 1 – AUTHOR RESPONSE

Response to reviewer: 1

ReviewerName: Arsen Uvelin

-Response: Thank you for taking the time to review our manuscript. We are grateful for your comment s and have done the following to address them:

1. Comment: Page 4, line 19 torsede.....torsade

-Response: Thank you for pointing this out, this was corrected as suggested.

2. Comment: Page 10, lines 26-38. Consider putting this part of the Discussion section in the beginni ng, just optional

-Response: Thank you for pointing this out. This was corrected as suggested. We changed the order of paragraphs in the discussion section.

Response to reviewer: 2

Reviewer Name: James E. Tisdale

-Response: Thank you for taking the time to review our manuscript. We appreciate your comments w hich we address one by one.

Comment: The paper will require substantial copy-editing for proper grammar and English language usage.

-Response: The manuscript has now been read and revised by a native English speaker.

Specific comments:

1. Comment: 1) Abstract: Please add into the Methods of the abstract the fact that a propensity score matching process was used

-Response: Thank you for your comment. In our analysis, we calculated a propensity score and applyi ng an inverse probability treatment weight to control for baselinedifferences in the population. As sugg ested, “Using logistic regression analysis with inverse probability treatment weighting” has been chan ged to “Using logistic regression analysis with inverse probability of treatment weighting using the pro pensity score” in the methods part of abstract.

2. Comment: 2) Discussion, page 9, lines 47-55: In the discussion of reference 21 - the fact that levofl oxacin was associated with an increased risk of death in addition to an increased risk of serious cardi ac arrhythmia does not mean, as you suggest, that "the baseline condition was more severe in the le vofloxacin group.....and that the study results were confounded." The investigators in that study perfo rmed propensity score matching and reported that the groups were well-matched. There is no evidenc e that the study results were confounded. It seems possible that levofloxacin may have been associat ed with more serious, life-threatening arrhythmias in that study, In addition, theirs was a population of Veterans Administration patients, indicating that they were older than the population in your study; it s eems possible that these differences could account for differences between your study and theirs, an d also account for an increased risk of both serious arrhythmias and overall death associated with lev ofloxacin in that study. Please revise your discussion of reference 21.

-Response: We thank for the constructive expert comments and we agree with the comments. This pa rt of discussion has been modified as follows: “In a study on veterans in the United States,[21] levoflo xacin use was associated with a 3.13-fold increased risk of cardiac arrhythmias and a 2.49-fold increa sed risk of all-cause death compared with amoxicillin. The veteran population was older (mean age, 5 6.8 years) than our cohort (mean age, cefixime, 49.3 years; levofloxacin, 50.4 years), which likely expl ains the different results.”

3. Comment: 3) Discussion, page 10, lines 18-24 - the authors state that "These data combined with our study reinforce the view that ciprofloxacin and levofloxacin are not associated with ventricular arrh ythmias..." But there are published cases that clearly show that ciprofloxacin and levofloxacin may ca use torsades de pointes. Both drugs are in the category of drugs "Known" to cause torsades de pointe s in the QT drugs list at crediblemeds.org. This section of the Discussion must be revised, The fact th at, in your study, neither levofloxacin nor ciprofloxacin increased the risk of ventricular arrhythmias do es not mean that these drugs cannot provoke torsades de pointes given the right circumstances (patie nts with multiple risk factors for torsades).

-Response: Thank you for your comments and we have added the following sentence: “In this study, c iprofloxacin and levofloxacin were not associated with increased ventricular arrhythmia risk, but wheth er these drugs induce torsades de pointes is unclear.”

4. Comment: 4) Discussion, page 11, lines 22-34: The statement that "Most of the cases were develo ped in patients with concomitant use of other medications associated with QT interval prolongation or with multiple risk factors ofdrug-induced arrhythmia" is exactly the point. For the vast majority of patie nts who experience drug-induced torsades de pointes, the event occurs in the presence of one or mor

e risk factors. It seems possible that in your study, levofloxacin and ciprofloxacin did not increase the r isk compared with cefixime because the preponderance of your patients did not have risk factors. Ple ase discuss.

-Response: Thank you for your comment and we have clarified this point in the revised version of the manuscript. We have added the following sentence: “Our study excluded patients who were prescribe d drugs associated with QT interval prolongation, and we could not confirm whether the risk of ventric ular arrhythmia was increased by the concomitant fluoroquinolone use with drugs that increase the ris k of torsades de pointes. We also could not assess whether intravenous use was associated with incr eased risk because this study was conducted only in oral fluoroquinolone users. Furthermore, no bas eline ECG or electrolyte data were available. Further studies are needed to determine whether fluoroq uinolones increase the risk of arrhythmias in patients with these risk factors.”

Response to reviewer: 3

Reviewer Name: Paula Dhiman

-Response: We thank the reviewer for the constructive expert comments and respond to them as follo ws:

1. Comment: Abstract: Include dates from fully in the setting

-Response: Thank you for pointing this out, this was changed as suggested; from January to Decemb er 2015 à “from 01 January 2015 to 31 December 2015”

2. Comment: Abstract: Be more explicit in the setting of the study – e.g. primary or secondary care?

-response: South Korea has primary, secondary, and tertiary care setting and we added this in the ab stract and methods (inclusion criteria section) of the manuscript; “Setting: All primary, secondary, and tertiary care settings”

3. Comment: Abstract: Add the 2 time periods of interest: 1-7 and 8-14 days.

-Response: Thank you for your opinion and we have changed throughout the manuscript.

4. Comment: Abstract: In the results, please add the time point (1-7 days) with the OR results, as evi dence was not found for 8-14 days.

-Response: Thank you for your opinion and we have changed throughout the manuscript.

5. Comment: Introduction: Would be useful to include more information about the use of cefixime as t he comparator, especially because it seems a lot of the present research used amoxicillin as the com parator.

Response: We added a sentence in the end of introduction; “We selected cefixime (an antibiotic with no pro-arrhythmic effect) as a comparison medication because fluoroquinolones and cefixime have ov erlapping indications.” We also added sentences in the method (study design section): “Other studies used β-lactam antibiotics, such as amoxicillin, amoxicillin-clavulanate, and penicillin V, as controls.[21 –23] However, in Korea, β-lactam antibiotics are not commonly used in UTI treatment; thus, cefixime was used in this study as a comparator.”

6. Comment: Methods: no information about dose of the drug has been given. Could this be added? Or even some summary information about the dose in the dataset?

-Response: Thank you for your comment. Unfortunately, the dose of the drug was not investigated an d the effect of the drug dose was not analyzed in this study. I added this to the limitation section as foll ows; “Finally, the drug dose was not investigated, and the effect of the drug dose was not analysed in this study. Further studies are needed to determine how the effects of fluoroquinolone on arrhythmias vary with drug dose.”

7. Comment: Method, p6 line 26-28: could you clarify what you mean by this sentence?

-Response: Thank you for your comment and we modified the sentence to clarify the meaning as follo w; “The first diagnosis was included when the patients had diagnosis codes of serious ventricular arrh ythmia more than once.” à “Because diagnostic codes are sometimes used in patients with existingarr hythmias, only the first diagnosis was used when patients had more than one diagnostic code for seri ous ventricular arrhythmia to focus on incidence outcomes.”

8. Comment: Methods, p7 line 35: should be IPTW weights

-Response: We have changed throughout the manuscript: weighsàweights

9. Comment: Methods p7, line 50: needs a comma after ‘subgroup analysis’

-Response: We have changed throughout the manuscript.

10. Comment: Methods: As part of the subgroup analysis, you divided patients by age. Why was 65 y ears used as the cut off?

-Response: We used 65 years as the cut off, however, there is no clear medical or biological evidence to support this definition. But many countries, the elderly are defined as having a chronological age of 65 years or older in many country. Although there is a proposal to change the definition of elderly people to 75 years or older, this study was based on the age of 65 as cut off, which is still widely used. (reference: Ouchi Y, Rakugi H, Arai H, et al. Redefining the elderly as aged 75 years and older: Proposal from the Joint Committee of Japan Gerontological Society and the Japan Geriatrics Society. Geriatr Gerontol Int 2017;17:1045–7. doi:10.1111/ggi.13118)

11. Comment: Methods: Though it is mentioned in the completed STROBE checklist that there was no missing data in the study, this should be explicitly stated in the manuscript as well.

-Response: We have added a following sentence in the section of Statistical analyses; “No data were missing in this study.”

12.Comment: Results: Would be useful to summarise number and reason for exclusions in the text as well as referring to the figure.

-Response: Thank you for your opinion and we have added number and reason for exclusions in the manuscript.

13. Comment: Results: Generally, I think more time needs to be spent on the results and explaining the findings. Interpretation of the OR would also be useful as well as reporting the OR and 95% CIs.

-Response: Thank you for your opinion and we have changed as commented throughout the manuscript.

14. Comment: Results, p8 line 45: consistently in reporting OR with 95% CI is needed

-Response: We have changed throughout the manuscript; “0.72 (95% CI, 0.49-1.06), 0.92 (95% CI, 0.66-1.29), 0.41 (95% CI, 0.27-0.61), 1.87 (95% CI, 1.15-3.11)”

15. Comment: Results, p8 line 47: This sentence needs to moderated. Given that the confidence intervals for the OR for ciprofloxacin and levofloxacin span 1, I would be more cautious interpreting these results. To say these two drugs had ‘no increased risk’ is misleading, as no evidence is found to support this for 1-7days.

-Response: Thank you for your opinion and this sentence has been moderated as follows; “Ciprofloxacin and levofloxacin were not associated with an increased risk, while moxifloxacin was associated with a 1.87-fold increased risk of serious ventricular arrhythmia.”

16. Comment: Results: For Ofloxacin, I think this would be better reported as finding a 59% reduced ri sk of serious ventricular arrhythmia compared to cefixime.

-Response: Thank you for your opinion and we have added a following sentence; “Ofloxacin was asso ciated with a 59% reduced risk of serious ventricular arrhythmia compared with cefixime for 1-7 days after the index date.”

We also changedresults part of abstract as follow; “Between 1-7 days after index date, there was no evidence of increased serious ventricular arrhythmia related to the prescription of ciprofloxacin (odds r atio, 0.72; 95% confidence interval, 0.49-1.06) and levofloxacin (odds ratio, 0.92; 95% confidence inte rval, 0.66-1.29). Ofloxacin had a 59% reduced risk of serious ventricular arrhythmia compared with ce fixime during 1-7 days after prescription.”

17. Comment: Results p8 line 56: capital T for ‘table 3’.

-Response: We have changed throughout the manuscript.

18. Comment: Results p9 line 6: as above this sentence needs to moderated and corrected. Reduced risk is found with ciprofloxacin and ofloxacin, and no evidence is found for levofloxacin and moxifloxac in between 8-14 days.

-Response: We changed the sentence as follows; “Overall, all of four fluoroquinolones had no increas ed risk of serious ventricular arrhythmia.” à “Risk reductions of 66% and 42% were found for ciproflox acin and ofloxacin, respectively. No evidence of an increased risk was found for levofloxacin. Moxiflox acin was associated with a 1.78-fold increased risk of serious ventricular arrhythmia for 8-14 days afte r the index date; however, this increased risk was not statistically significant.”

19. Comment: Table 2, 3, and 4: Instead of 1, please use ’reference’ (or equivalent) to highlight cefixi me as the reference category in the analysis

-Response: We have changed “1” PubMed to “reference” in Table 2,3, and 4.

20. Comment: Results (subgroup): please add OR and 95% CI to support text

-Response: We have changed throughout the manuscript.

21.Comment: Discussion: subheadings would be useful.

-Response: We have added subheadings in the discussion of the manuscript.

22. Comment: Discussion: results for moxifloxcin seem most prominent from this study. This needs to be further discussed, especially in relation to the fewer participants in this group.

-Response: We added further discussion about moxifloxacin in the section of overall findings of discussion; “For 8-14 days after the index date, moxifloxacin showed a 1.78-fold increased risk; however, the 95% CI was not statistically significant. All moxifloxacin subgroups showed a high risk, but this risk was statistically significant only in patients with cardiovascular disease and those over 65 years old. The 95% CIs were wide because the number of moxifloxacin users (n=47,080) included in the study was fewer than that for other drugs, and the number of serious ventricular arrhythmias was only 7 for days 1-7 after the index date and 4 for days 8-14. Further studies with more subjects are needed to confirm the risk of moxifloxacin.”

23. Comment: Discussion: this now needs to reflect the changes made to the results (above).

-Response: We changed the first part of the discussion as follows; “The general population data revealed that ciprofloxacin and levofloxacin were not associated with an increased risk for serious ventricular arrhythmia for 1-7 days after the prescription date and that ofloxacin was associated with a reduced risk of arrhythmia. Moxifloxacin use was associated with a 1.87-fold increased risk of serious ventricular arrhythmia compared with cefixime during the first week after initiating the drug. The risk of ventricular arrhythmia was especially high in moxifloxacin users who were older or had cardiovascular disease.”

24. Comment: Discussion: it would be good the see the strengths (eg no missing data as well as the limitation of the study of the study

-Response: We added strengths of this study; “One of the strengths of this study is that it is the largest study to date evaluating the association between oral fluoroquinolone use and serious ventricular arrhythmia. This study was a nationwide population-based study including 4,888,890 patients who were prescribed oral fluoroquinolone or cefixime. In addition, the datasets had no missing values, thus minimizing the number of subjects. Second, propensity score weighting was performed to adjust the underlying characteristics and antibiotic indications of both the fluoroquinolone and cefixime groups. In the propensity score matching, unmatched subjects occur and subject numbers decreased. In this study, all subjects can be included for comparison using IPTW.”

25.Comment: Discussion: depending of the response to point 6 (above – dose), can this also be discussed.

-Response: As in the reponse to point 6, we added to the limitation section that we did not analyze th e results according to dose; “Finally, the drug dose was not investigated, and the effect of the drug do se was not analysed in this study. Further studies are needed to determine how the effects of fluoroqu inolone on arrhythmias vary with drug dose.”

26. Comment: Discussion, p11 line 4-7: can you clarify if this information is from the referred study or t he present study?

-Response: This information is from referred study and we added the reference number in the manus cript; “The increased QT interval means for the 24-hour period after treatment were 2.3 ms to 4.9 ms, 3.5 ms to 4.9 ms, and 16.3 ms to 17.8 ms for 1500 mg ciprofloxacin, 1000 mg levofloxacin, and 800 m g moxifloxacin, respectively.[11]”

27. Comment: Discussion p11 line 47: what would the impact of this be on the results? Would this res ult in an over-estimation of the results?

-Response: In order to specify the meaning of this sentence, we modified the sentence as follows; “Th is inadequately reflects the impact of chronic lung disease on actual antibiotic prescriptions.” à “This w ide range of diagnostic codes suggests that chronic respiratory illnesses that are unrelated to the anti biotic prescription may have been included. The propensity score obtained using these covariates ma y insufficiently reflect the actual antibiotic prescription.”

28. Comment: Conclusion: needs to be moderated as above.

-Response: Conclusion have been moderated; “In this population-based study, ciprofloxacin and levof loxacin were not associated with serious ventricular arrhythmia, and ofloxacin reduced the risk of arrh ythmia. Moxifloxacin was associated with a 1.87-fold increased risk of serious ventricular arrhythmia c ompared with cefixime for 1-7 days after being prescribed.”

29. Comment: Conclusion: time period for moxifloxacin estimate needs to be given.

-Response: We added time period for moxifloxacin in the conclusion; “for 1-7 days after being prescri bed”

We changed the conclusion part of the abstract as follows; “During 1-7 days after prescription, ciproflo xacin and levofloxacin were not associated with increased risk and ofloxacin showed reduced risk of s erious ventricular arrhythmia. Moxifloxacin increased the risk of serious ventricular arrhythmia.”

30. Comment: Conclusion: please expand on future research beyond that additional populations nee d to be looked at?

-Response: We revised the sentence of conclusion adding future research beyond that additional pop ulation as follow; Additional studies are needed in other populations to ensure that these findings are valid. à “Additional studies in other populations are required to ensure that these findings are valid for patients with risk factors excluded in this cohort.”

VERSION 2 – REVIEW

REVIEWER	Arsen Uvelin Clinical centre of Vojvodina Emergency centre Department of anaesthesia and intrnsive care Hajduk Veljkova 1-10 21000 Novi Sad, Serbia University of Novi Sad, Faculty of medicine, Hajduk Veljkova 3 21000 Novi Sad, Serbia
REVIEW RETURNED	25-Apr-2018

GENERAL COMMENTS	The authors corrected the manuscript according to the reviewers' comments.

REVIEWER	James Tisdale Purdue University USA
REVIEW RETURNED	24-Apr-2018

GENERAL COMMENTS	This is a revised manuscript describing a study to assess the risk of specific fluoroquinolone drugs on risk of serious ventricular arrhythmias. Specific comments: 1) Page 49, lines 8-15: The fact that there are differences in baseline characteristics between groups suggests that the propensity scoring method used did not adequately control for differences between the groups. 2) Page 51, lines 44-46 - The sentence "Overall, standard ciprofloxacin, levofloxacin and ofloxacin doses have little effect on increased QT intervals" is simply factually incorrect. The package insert for ofloxacin expressly states "Some quinolones, including ofloxacin, have been associated with prolongation of the QT interval on electrocardiogram." This occurs in some patients at "standard" doses. Ciprofloxacin and levofloxacin have also been reported to prolong QT intervals in some patients at "standard" doses." This sentence must be deleted, and replaced with a sentence that accurately states that, in some patients, each of these fluoroquinolone drugs have been reported to prolong the QT interval. 3) Page 52, line 29: The sentence "No studies have been published on ofloxacin risk" is factually incorrect. At least one study has reported on risk of ofloxacin-induced torsades de pointes (Pharmacotherapy 2001;21:1468-1472). Please correct or delete this sentence. 4) Page 52, lines 25-27 - "reinforce the hypothesis that ciprofloxacin and levofloxacin are not associated with ventricular arrhythmias." Again, this is not accurate - there is clear, strong evidence that these

	drugs are significantly associated with torsades de pointes - see Drug Safety 2010;33:303-314. Please delete or correct this sentence. 5) Pages 50-54, Discussion: Please discuss in this section your findings that ofloxacin appears to have antiarrhythmic activity. This has never been reported before, and is completely contrary to prevailing opinion about the risk of torsades associated with fluoroquinolones being a class effect. This result deserves substantial discussion and explanation in the Discussion section. 6) Page 52, lines 34-36: This statement is factually incorrect. "... whether these drugs induce torsades de pointes is unclear" is not corr5ect. These drugs, under the correct circumstances, clearly induced torsades de pointes. There is no question about that. Please delete this portion of the sentence. 7) Most studies that include propensity score-matching include a table showing the absolute standard deviation between the groups, as an indicator of how well-matched the groups are. Such a table should be included in this paper.

VERSION 2 – AUTHOR RESPONSE

Response to reviewer: 1

Reviewer Name: Arsen Uvelin

-Response: Thank you for taking the time to review our manuscript.

Response to reviewer: 2

Reviewer Name: James Tisdale

-Response: Thank you for taking the time to review our manuscript. We appreciate your comments w hich we address one by one.

1. Comment: Page 49, lines 8-15: The fact that there are differences in baseline characteristics betw een groups suggests that the propensity scoring method used did not adequately control for differenc es between the groups.

- Response: Thank you for your comment. In our study, inverse probability treatment weights were cal culated with propensity scores to adjust for baseline differences and control for confounding by indicat ion. We evaluated the baseline covariate balance between groups with standardized differences befor e and after IPTW. A standardized difference <0.1 indicated that covariates were well balanced betwee n treatment and control population. We have clarified this point in the revised version of the manuscrip t. We added a sentence in the results part: “After the study population had been weighting using the I

PTW, all baseline differences were less than 0.1 standardized differences (see online supplementary t able 4-7).”

2. Comment: Page 51, lines 44-46 -The sentence "Overall, standard ciprofloxacin, levofloxacin and of loxacin doses have little effect on increased QT intervals" is simply factually incorrect. The package in sert for ofloxacin expressly states "Some quinolones, including ofloxacin, have been associated with p rolongation of the QT interval on electrocardiogram." This occurs in some patients at "standard"doses. Ciprofloxacin and levofloxacin have also been reported to prolong QT intervals in some patients at "st andard" doses." This sentence must be deleted, and replaced with a sentence that accurately states t hat, in some patients, each of these fluoroquinolone drugs have been reported to prolong the QT inter val.

- Response: We thank for the constructive expert comments and we agree with the comments. We de leted the sentence: "Overall, standard ciprofloxacin, levofloxacin and ofloxacin doses have little effect on increased QT intervals" And we revised the sentence of the fifth paragraph of the discussion: “som e case reports exist on QT interval prolongation and torsades de pointes after fluoroquinolone use.”

3. Comment: Page 52, line 29: The sentence "No studies have been published on ofloxacin risk" is fa ctually incorrect. At least one study has reported on risk of ofloxacin-induced torsades de pointes (Ph armacotherapy 2001;21:1468-1472 PubMed). Please correct or delete this sentence.

-Response: Thank you for your comments and we have added the following sentence: “In another stu dy in United States, 0.3, 5.4, and, 2.1 cases of torsades de pointes per 10 million prescriptions from 1 996 to 2001 for ciprofloxacin, levofloxacin, and ofloxacin, respectively.”

We deleted the sentence: “No studies have been published on ofloxacin risk. Currently, ofloxacin use is not associated with serious ventricular arrhythmia.”

4. Comment: Page 52, lines 25-27 - "reinforce the hypothesis that ciprofloxacin and levofloxacin are n ot associated with ventricular arrhythmias." Again, this is not accurate - there is clear, strong evidence that these drugs are significantly associated with torsades de pointes - see Drug Safety 2010;33:303-314 PubMed . Please delete or correct this sentence.

-Response: Thank you for your opinion and we deleted the sentence: “These data, combined with tho se from our study, reinforce the hypothesis that ciprofloxacin and levofloxacin are not associated with ventricular arrhythmia, while moxifloxacin appears to be associated with an increased risk.”

5. Comment: Pages 50-54, Discussion: Please discuss in this section your findings that ofloxacin app ears to have antiarrhythmic activity. This has never beenreported before, and is completely contrary t o prevailing opinion about the risk of torsades associated with fluoroquinolones being a class effect. T his result deserves substantial discussion and explanation in the Discussion section.

-Response: We thank for the constructive expert opinion. Cases of torsades de pointes were reported in the studies you mentioned (Pharmacotherapy 2001;21:1468-1472 PubMed & Drug Safety 2010;33 :303-314 PubMed). However, a study with US FDA Adverse Event Reporting System data (Drug Saf ety 2010;33:303-314 PubMed) reported a reduced risk of torsades de pointes but the adjusted odds ratio was not statistically significant (OR, 0.67; 95% CI, 0.03-4.38). Furthermore, the reason for the re duced risk of arrhythmia in ofloxacin users cannot be clearly explained. Additional clinical and populati on-based studies are needed.

We have added the following paragraphs in the discussion: “In this study, ofloxacin users had a reduc ed risk of serious ventricular arrhythmia. However, it is not possible to conclude that ofloxacin has an anti-arrhythmic effect. In fact, cases of torsades de pointes had been reported to occur after taking ofl oxacin.[37,39] A study with US FDA Adverse Event Reporting System data reported a reduced risk of torsades de pointes, but the adjusted odds ratio was not statistically significant (OR, 0.67; 95% CI, 0.0 3-4.38).[39] In addition, reason for the reduced risk of arrhythmia in ofloxacin users cannot be clearly explained. Additional clinical and population-based studies are needed.”

6. Comment: Page 52, lines 34-36: This statement is factually incorrect. "... whether these drugs indu ce torsades de pointes is unclear" is not correct. These drugs, under the correct circumstances, clearl y induced torsades de pointes. There is no question about that. Please delete this portion of the sente nce.

-Response: Thank you for your opinion and we deleted the statement: “but whether these drugs induc e torsades de pointes is unclear.”

7. Comment: Most studies that include propensity score-matching include a table showing the absolu te standard deviation between the groups, as an indicator of how well-matched the groups are. Such a table should be included in this paper.

-Response: Thank you for your comment. In our study, we evaluated the baseline covariate balance between groups withstandardized differences before and after IPTW (Table S4-S7 in the supplementa ry appendix). We added a sentence in the results part: “After the study population had been weighting

using the IPTW, all baseline differences were less than 0.1 standardized differences (see online supplementary table 4-7).”

VERSION 3 – REVIEW

REVIEWER	James E Tisdale Purdue University USA
REVIEW RETURNED	03-Jul-2018

GENERAL COMMENTS	The authors have adequately addressed my comments.