PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk of cardiovascular events, arrhythmia, and all-cause mortality associated with clarithromycin versus alternative antibiotics prescribed for respiratory tract infections: retrospective cohort study
AUTHORS	Berni, Ellen; deVoogd, Hanka; Halcox, Julian; Butler, Christoper; Bannister, Christian; Jenkins-Jones, Sara; Jones, Bethan; Currie, Craig

VERSION 1 - REVIEW

REVIEWER	Kenneth Nugent Texas Tech University Health Sciences Center, Lubbock, TX, USA
REVIEW RETURNED	31-Jul-2016

GENERAL COMMENTS	1. These authors analyzed an extremely large database to determine whether or not there is association between the use of clarithromycin and cardiovascular events, arrhythmias, and all-cause mortality within 37 days of antibiotic prescription. They used linked primary and secondary care databases to identify the characteristics of patients receiving prescriptions and possible hospital-based outcomes. 2. They use the term research quality patient records. This designation is not very clear but appears to require that the records are internally consistent with regard to age, sex, registration, and event dates and that the patient had been permanently registered with the practice. However, there were significant amounts of missing data, including 66% of the BMIs, 37% with systolic blood pressures, and 69% of the cholesterols. Consequently, it is not clear to me what research quality represents. If the record does not contain information about BMI and systolic blood pressure at clinic visits, this would seem to represent a substandard record. 3. The results section includes 10 double spaced pages which records most of the information in the tables in a text format. I am not certain whether or not this is the standard approach to data presentation in the BMJ Open, but it seems to me that some of this information could be eliminated with referral to the appropriate table. There are some errors in the 95% confidence intervals in Table 4. 5. Important conclusions include the fact that cardiovascular events are more likely following a lower respiratory tract infection with an upper respiratory tract infection and that clarithromycin does not appear to have an increased cardiovascular risk associated with its use when compared to other antibiotics. It might be worth noting that this patient population sees their general practitioner approximately 6 times per year and receive a course of antibiotics approximately once per year. These numbers seem relatively high to me.

REVIEWER	Dr Adrian Root London School of Hygiene and Tropical Medicine UK
REVIEW RETURNED	09-Aug-2016

GENERAL COMMENTS	Although I do not consider it a conflict of interest, I am a co-author on a referenced paper (13) and also on a more recent paper conducting a similar protocol in the CPRD (Root AA et al. British Journal of Clinical Pharmacology. 2016 Aug;82(2):512–21) and this might colour my perspective on the topic. Overall: This study adds to the existing literature on the cardiovascular risk profile of clarithromycin. The approach of comparing clarithromycin to many other antibiotics is novel and helps to clarify that clarithromycin does not have a particularly adverse risk profile and any difference in cardiovascular risk is more likely to represent indication bias. I would recommend this paper for publication. I hope the comments below are helpful. Abstract: I find the phrase "adjusted risk versus clarithromycin' difficult to interpret in the abstract. This is probably because it is unusual to have the exposure of interest as the referent category. Methods: I presume that the 37 day risk period was chosen to reflect the Danish study that prompted this work, however, there are some studies that have reported longer risk periods. For example Schembri et al. (BMJ. 2013 Mar 21;346(mar20 2):f1235–f1235) looked at risk within a year of clarithromycin use. This would be problematic here since the risk period is short and the washout period of 90 days would be insufficient. However, I do accept that such a long risk period is biologically implausible and my recent papers have also cast doubt on such a long term risk. The composite CV event outcome definition is quite broad. I would be interested to see if the results would be different for a narrower outcome such as first MI which would be more reliably coded in either CPRD or HES. This would be particularly relevant in such a narrow risk window - I would imagine angina might take a while to diagnose definitively in many cases and might often be coded several weeks late once relevant investigations confirm it. Why was clarithromycin the reference category for this study? Amoxicillin is a much larger group in the cohort and would have seemed like a more natural choice. In addition it makes the tables a little less clear to interpret as conventionally the exposure of interest is compared against a control baseline group. Clarithromycin as a reference category does make more sense on the forest plot though. The authors decided to include all variables in their model 'because it has been shown that excluding statistically insignificant variables does not improve prediction accuracy...' Since this is a causal study, prediction accuracy is not the most relevant consideration here and I would be more concerned about whether the authors checked for multicollinearity within their model (there are several variables that would seem to be strongly correlated with each other) and also whether they had eliminated possible collider variables.

	I note that the 'other' category included several antibiotics that would be very unusual choices for first line RTI such as nitrofurantoin and trimethoprim. Did the authors check all the read codes on the day of prescription to exclude the possibility of more than one diagnosis? It is very possible that a patient might get a code for a URTI and UTI and receive an antibiotic only for the latter. Perhaps this might also explain the curiously low odds of death after LRTI treated with tetracyclines compared with clarithromycin? Results: The forest plot comparing antibiotics was particularly interesting to me. The fact that co-amoxiclav tends to be one the right and amoxicillin on the left of clarithromycin would seem to fit with the study hypothesis that disease severity is a major unmeasured confounder in studies of this type since co-amoxiclav is an unusual choice first line for URTI/LRTI.

REVIEWER	Laura Vitali Serdoz, MD Klinikum Fuerth, Fuerth, Bayern Germany
REVIEW RETURNED	03-Oct-2016

GENERAL COMMENTS	Dr. Berni and colleagues analysed a population of 1,392,687 patients with lower and upper respiratory tract infections treated with first line antibiotic monotherapies between 1991 and 2012 in order to determine whether treatment with clarithromycin for respiratory tract infections was associated with an increased risk of cardiovascular events, arrhythmias, or all cause mortality compared with other antibiotics. They found that in this group of patients CV risk associated with clarithromycin was no different to other antibiotics. Some points neeed to be addressed: 1) The authors analysed a large population. 2) It is a retrospective study, with a lot of missing data especially about patients comorbidities. There were 66% data about BMI data missing, 37% about systolic pressure, 69% about total cholesterol, no information about renal function. 3) They excluded from the study all the patients with prior cardiovascular and arrhythmic events; but these patients could to be the group with the highest risk of cardiac events after treatment with clarithromycin. It could be interesting to know if this antibiotic treatment is associated with a higher CV risk in these “high risk” patients and to compare them to the ones with no prior cardiac pathology 3) They excluded from the study all hospitalized patients, who represent the most severe cases of respiratory tract infections. It could be interesting to know if this antibiotic therapy determines an higher CV risk in these most severe settings. 4) It could be interesting to have some information about patients’ ECG parameters (especially QTc). 5) This study conclude that in a big population of no ospedalized patients, with no prior cardiac events, affected by LRTI or URTI CV risk associated with clarithromycin was no different to other

	antibiotics. But what about the potentially high CV risk patients?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Kenneth Nugent

1. These authors analyzed an extremely large database to determine whether or not there is association between the use of clarithromycin and cardiovascular events, arrhythmias, and all-cause mortality within 37 days of antibiotic prescription. They used linked primary and secondary care databases to identify the characteristics of patients receiving prescriptions and possible hospital-based outcomes.

2. They use the term research quality patient records. This designation is not very clear but appears to require that the records are internally consistent with regard to age, sex, registration, and event dates and that the patient had been permanently registered with the practice. However, there were significant amounts of missing data, including 66% of the BMIs, 37% with systolic blood pressures, and 69% of the cholesterols. Consequently, it is not clear to me what research quality represents. If the record does not contain information about BMI and systolic blood pressure at clinic visits, this would seem to represent a substandard record.

The designation 'acceptable research quality' is one applied by the CPRD organization itself and we have listed all of the criteria that CPRD applies in the manuscript. [1] These are the ones that the reviewer includes in his comment. The 'acceptability' of a patient does not take into account BMI, blood pressure or cholesterol. The extent to which these and other data are captured in CPRD is variable because records are entered by the GP (family doctor) in the course of routine care and not for the purpose of research.

3. The results section includes 10 double spaced pages which records most of the information in the tables in a text format. I am not certain whether or not this is the standard approach to data presentation in the BMJ Open, but it seems to me that some of this information could be eliminated with referral to the appropriate table. There are some errors in the 95% confidence intervals in Table 4.

We thank the reviewer for spotting the errors in Table 4, which have now been corrected. We have also taken on board their comments about the excessive length of the results section, which has now been shortened to six pages from ten.

5. Important conclusions include the fact that cardiovascular events are more likely following a lower respiratory tract infection with an upper respiratory tract infection and that clarithromycin does not appear to have an increased cardiovascular risk associated with its use when compared to other antibiotics. It might be worth noting that this patient population sees their general practitioner approximately 6 times per year and receive a course of antibiotics approximately once per year. These numbers seem relatively high to me.

These patients are adults 35+and cohort inclusion is based on a morbidity i.e. respiratory infection, so this may in part explain the increase in activity. Note that GP contacts refers to general practice contacts rather than general practitioner so includes nurse visits. It also includes telephone contacts with health professionals. The count of antibiotic prescriptions within the year prior include the index date, therefore, all patients will have at least one by definition.

Reviewer: 2 Dr Adrian Root

Abstract:

I find the phrase "adjusted risk versus clarithromycin' difficult to interpret in the abstract. This is probably because it is unusual to have the exposure of interest as the referent category.

Our response:

We have altered the main outcome measures to read, “compare adjusted risk of first ever cardiovascular event, within 37 days of initiation, in commonly prescribed antibiotics with that in clarithromycin.”

Methods:

I presume that the 37 day risk period was chosen to reflect the Danish study that prompted this work, however, there are some studies that have reported longer risk periods. For example Schembri et al. (BMJ. 2013 Mar 21;346(mar20 2):f1235–f1235) looked at risk within a year of clarithromycin use. This would be problematic here since the risk period is short and the washout period of 90 days would be insufficient. However, I do accept that such a long risk period is biologically implausible and my recent papers have also cast doubt on such a long term risk.

The composite CV event outcome definition is quite broad. I would be interested to see if the results would be different for a narrower outcome such as first MI which would be more reliably coded in either CPRD or HES. This would be particularly relevant in such a narrow risk window - I would imagine angina might take a while to diagnose definitively in many cases and might often be coded several weeks late once relevant investigations confirm it.

Why was clarithromycin the reference category for this study? Amoxicillin is a much larger group in the cohort and would have seemed like a more natural choice. In addition it makes the tables a little less clear to interpret as conventionally the exposure of interest is compared against a control baseline group. Clarithromycin as a reference category does make more sense on the forest plot though.

The authors decided to include all variables in their model 'because it has been shown that excluding statistically insignificant variables does not improve prediction accuracy...' Since this is a causal study, prediction accuracy is not the most relevant consideration here and I would be more concerned about whether the authors checked for multicollinearity within their model (there are several variables that would seem to be strongly correlated with each other) and also whether they had eliminated possible collider variables.

I note that the 'other' category included several antibiotics that would be very unusual choices for first line RTI such as nitrofurantoin and trimethoprim. Did the authors check all the read codes on the day of prescription to exclude the possibility of more than one diagnosis? It is very possible that a patient might get a code for a URTI and UTI and receive an antibiotic only for the latter. Perhaps this might also explain the curiously low odds of death after LRTI treated with tetracyclines compared with clarithromycin?

Our response:

We agree with your comment that splitting cardiovascular events by type would add more information and aim to address this in a future study. The reviewer’s particular point about angina is very interesting, but angina was an outcome of interest and we have no reason to believe that the possible late capture of this condition will have introduced bias into the study.

Clarithromycin was chosen as the reference category because it was the subject of recent studies investigating cardiovascular risk in antibiotics.

We checked for multicollinearity within our models, as recommended, by examining the variance inflated factors (VIFs) - these did not indicate multicollinearity.

Our selection criteria (illustrated in figure 1) excluded treatment episodes that had more than one associated indication; therefore, this cannot be the explanation for the seemingly anomalous prescription of antibiotics for RTI. However, in our previous study [2], we also noticed that non-first-line antibiotics were occasionally being prescribed for certain indications, perhaps reflecting inevitable anomalies in large volumes of routine data.

Results:

The forest plot comparing antibiotics was particularly interesting to me. The fact that co-amoxiclav tends to be one the right and amoxicillin on the left of clarithromycin would seem to fit with the study hypothesis that disease severity is a major unmeasured confounder in studies of this type since co-amoxiclav is an unusual choice first line for URTI/LRTI.

Reviewer: 3 Laura Vitali Serdoz, MD

1) The authors analysed a large population.

2) It is a retrospective study, with a lot of missing data especially about patients comorbidities.

There were 66% data about BMI data missing, 37% about systolic pressure, 69% about total cholesterol, no information about renal function.

Unfortunately, this is the nature of real-world studies based on routine data. We selected data from 1998 -2012. It is known that data completeness improves over the study period as innovations such as the Quality Outcomes Framework incentivised both the undertaking of tests/measurement s and also their recording in the electronic database. Note the missing values refer to values missing at baseline (-365 days to +30 days) rather than the entire database. All patients were included in the models, with missing data categorised.

3) They excluded from the study all the patients with prior cardiovascular and arrhythmic events; but these patients could to be the group with the highest risk of cardiac events after treatment with clarithromycin. It could be interesting to know if this antibiotic treatment is associated with a higher CV risk in these “high risk” patients and to compare them to the ones with no prior cardiac pathology

We agree that this would be of considerable interest. Here, however, we removed patients with a prior history of CVD because of the difficulty, otherwise, in distinguishing between new cardiovascular events and prior cardiovascular events that were being recorded again by the GP in order to provide context for a clinical observation or therapeutic decision. (This was addressed in the manuscript.)

3) They excluded from the study all hospitalized patients, who represent the most severe cases of respiratory tract infections. It could be interesting to know if this antibiotic therapy determines an higher CV risk in these most severe settings.

The reviewer is correct that we only used antibiotic prescriptions originating in primary care as hospital prescription data is not available within the CPRD database. It would be interesting to

consider hospitalised infections but this is beyond the scope of the current study.

4) It could be interesting to have some information about patients' ECG parameters (especially QTc).

Unfortunately, the results of ECG tests are not recorded in the CPRD data.

5) This study conclude that in a big population of no ospedalized patients, with no prior cardiac events, affected by LRTI or URTI CV risk associated with clarithromycin was no different to other antibiotics. But what about the potentially high CV risk patients?

This is certainly of interest, but we believe that it lies outside the scope of our current study. We used first events in order to avoid historic diagnoses being mistaken for incident events.

References

[1] Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). International Journal of Epidemiology. 2015;44(3):827-836. doi:10.1093/ije/dyv098.
[2] Currie CJ, Berni E, Jenkins-Jones S, et al. Antibiotic treatment failure in four common infections in UK primary care 1991-2012: longitudinal analysis. BMJ 2014;349:g5493. doi:10.1136/bmj.g5493.

VERSION 2 – REVIEW

REVIEWER	Kenneth Nugent Texas Tech University health Sciences Center USA
REVIEW RETURNED	13-Dec-2016

GENERAL COMMENTS	I thank the authors for their effort to reduce the length of the results section. I wonder if the numbers (adjusted risk range) in the last three lines of the abstract are correct. I would think it should be 0.42 to 1.32. Also I would avoid the use of the word statin- spell it out.

REVIEWER	Dr Adrian Root LSHTM, UK
REVIEW RETURNED	01-Dec-2016

GENERAL COMMENTS	Major comments: 1. I raised a concern about the composite outcome and with the inclusion of angina in particular since it might have delayed coding. The authors replied that "angina was an outcome of interest and we have no reason to believe that the possible late capture of this condition will have introduced bias into the study." I disagree with this statement. The outcome is of events coded within 37 days of exposure. If there is delay in coding such that some events that actually happen within this time window but are not coded till >37 days, they will be missed. If this occurs the study could be biased to the null since it would have a greater effect on the group with more events. Take an extreme example where one group had no events around 37d and the other had many - missing half of the events in both categories would not change one group but would affect the other. Given that the study aim is to establish whether clarithromycin

	carries more risk than alternative antibiotics, a bias to the null would be falsely reassuring. This is not merely hypothetical, in my previous study the short term association between clarithromycin and MI was much stronger when I used HES event dates rather than CPRD dates despite there being only a 1-2 week delay. 2. I was concerned about the use of clarithromycin as a reference category. The authors state that "Clarithromycin was chosen as the reference category because it was the subject of recent studies investigating cardiovascular risk in antibiotics." This does not make sense. This would be like a study on the risks of obesity choosing obese patients as a reference category and reporting the adjusted risks of being normal weight. While the reported estimates might be mathematically correct, reporting in this way is highly unusual and I suspect it would mislead many readers since risk ratios > 1 would be protective and <1 would be harmful in this approach. To give a concrete example, in the results section this sentence seems odd when clarithromycin is the exposure of interest: "The adjusted 37-day risk of first-ever arrhythmia was lower in all other antibiotics combined than in clarithromycin therapies (0.88; 0.76 to 1.01)" Surely "The adjusted 37-day odds of first-ever arrhythmia after clarithromycin initiation was 1.14 times the odds with all other antibiotics (1.14...)" is more intuitive? However, I leave this to the editors to decide. 3. The authors used a missing category approach for covariates with large amounts of missing data. Have they done a sensitivity analysis using complete cases? I think complete case analysis is usually more robust than a missing category approach and so I would be keen to know whether there was any difference between the approaches. (Apologies for not noticing this previously) Minor comments: Abstract: Remove first 'Compare' from Main outcome measures; reads more easily without it.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name
Dr Adrian Root

Institution and Country
LSHTM, UK

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
Major comments:

1. I raised a concern about the composite outcome and with the inclusion of angina in particular since it might have delayed coding. The authors replied that "angina was an outcome of interest and we have no reason to believe that the possible late capture of this condition will have introduced bias into the study."

I disagree with this statement. The outcome is of events coded within 37 days of exposure. If there is delay in coding such that some events that actually happen within this time window but are not coded till >37 days, they will be missed. If this occurs the study could be biased to the null since it would have a greater effect on the group with more events. Take an extreme example where one group had no events around 37d and the other had many - missing half of the events in both categories would not change one group but would affect the other.

Given that the study aim is to establish whether clarithromycin carries more risk than alternative antibiotics, a bias to the null would be falsely reassuring. This is not merely hypothetical, in my previous study the short term association between clarithromycin and MI was much stronger when I used HES event dates rather than CPRD dates despite there being only a 1-2 week delay.
Response:
We appreciate this comment but the aim of the study was to look at acute events within a narrow time window following exposure to antibiotics. It is not possible to determine whether a coding of an event in the primary care dataset occurred on the recorded date except for those where the event is confirmed within HES. Therefore, we cannot claim that an angina coding 50 days after index was related to an event that occurred within the 37-day window.

2. I was concerned about the use of clarithromycin as a reference category. The authors state that "Clarithromycin was chosen as the reference category because it was the subject of recent studies investigating cardiovascular risk in antibiotics." This does not make sense. This would be like a study on the risks of obesity choosing obese patients as a reference category and reporting the adjusted risks of being normal weight.

While the reported estimates might be mathematically correct, reporting in this way is highly unusual and I suspect it would mislead many readers since risk ratios > 1 would be protective and <1 would be harmful in this approach.

To give a concrete example, in the results section this sentence seems odd when clarithromycin is the exposure of interest:
"The adjusted 37-day risk of first-ever arrhythmia was lower in all other antibiotics combined than in clarithromycin therapies (0.88; 0.76 to 1.01)"

Surely "The adjusted 37-day odds of first-ever arrhythmia after clarithromycin initiation was 1.14 times the odds with all other antibiotics (1.14...)" is more intuitive?

However, I leave this to the editors to decide.

Response:
We accept this is unusual but we wished to compare multiple therapies to clarithromycin, therefore, whilst in the example above where we compare all other antibiotics aggregated it would be possible to set the other group as the reference category. It is not when we compare each other antibiotic individually, for the purposed of consistency throughout the paper we therefore believe that using clarithromycin as the reference makes sense.

3. The authors used a missing category approach for covariates with large amounts of missing data. Have they done a sensitivity analysis using complete cases? I think complete case analysis is usually

more robust than a missing category approach and so I would be keen to know whether there was any difference between the approaches. (Apologies for not noticing this previously)

Response:
We did consider a sensitivity analysis however due to the large number of adjusting covariates and thus the potential for at least one missing data item per case the analysis would have been too underpowered to be meaningful. Additionally, those with complete data items would tend to be a more morbid population due to opportunistic recording bias.

Minor comments:
Abstract:
Remove first 'Compare' from Main outcome measures; reads more easily without it.

We have done this.

Reviewer: 1

Reviewer Name
Kenneth Nugent

Institution and Country
Texas Tech University health Sciences Center
USA

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
I thank the authors for their effort to reduce the length of the results section. I wonder if the numbers (adjusted risk range) in the last three lines of the abstract are correct. I would think it should be 0.42 to 1.32.
Also I would avoid the use of the word statin- spell it out.

Response:
Thank you for your comments, we have adjusted the numbers in the abstract and would like to thank you for pointing this out. We would prefer to use the word statin but are happy to take editorial advice.