27 August

Dear Dr. Pasternak

Manuscript ID BMJ.2017.040029 entitled "Fluoroquinolone use and risk of aortic aneurysm and dissection: a nationwide cohort study"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Tiago Villanueva
Associate Editor
tvillanueva@bmj.com

*** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

https://mc.manuscriptcentral.com/bmj?URL_MASK=4b2c607c32f44f77a02a3ba1569e9f6b

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair), Richard Riley (statistician), Wim Weber, Sophie Cook, Tiago Villanueva, Georg Roggla, Daoxin Yin, Kristina Fister

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- Our statistician made the following comments:
I have some important comments, which I am hopeful the authors could address:
1) Better to have a time-dependent HR, rather than (or in addition to) choosing an arbitrary cut-point of 10 days. That is, is there evidence of a time-dependent HR? They could then plot the HR over time too. This would improve the paper very much.
2) They say that "A single patient could contribute with multiple treatment episodes to the cohort; these episodes were all unique and never overlapped in time, and the outcome event could occur only once in each patient. Hence, assumptions of statistical independence were not violated."
- I disagree. The clustering of multiple events per individual should be accounted for, as I person who contributes 5 events is not the same as 5 events from 5 different people. See the recurrent events papers in the literature, for example Crowther et al. https://www.ncbi.nlm.nih.gov/pubmed/24789760

I am unsure of the implications of this on the matching procedure, though.

3) "This corresponded to an estimated 82 (95% CI, 15-181) additional cases of aortic aneurysm or dissection per 1 million treatment episodes (Figure 2)." – what time-scale does this relate to though? Additional cases upto what time?

4) "In subgroup analyses, the HR with fluoroquinolone use was increased both in women and men, but was statistically significant only in women. Similarly, the HR was increased both in the subgroup of patients aged 50-64 years and in those 65 years and above, but was statistically significant only in the latter" – the focus should be on the interaction (difference between subgroups), and not the statistical significance within each group

5) What was the balance of covariates prior to matching?

- One editor said the HR's are not that big but it is a big study and this is clinically useful information.

- Another editor said these drugs are widely used and certainly AAA or dissection is a bad outcome. The risk is small, however, but this adds to existing information suggesting connective tissue effects from this class of drugs.

- Another editor said the risk is small, but the problem is very serious. Moreover, the clinical implications of this finding are not clear, and some more discussion around this in the paper would be helpful to carefully explain what this means in clinical practice. These drugs are important in the antibiotics armoury so the message would need to be carefully managed to avoid harm given the small risk.

- Another editor was supportive. He said fluoroquinolones are widely used in the treatment of hospital-acquired infections associated with urinary catheters in his setting. He was not convinced that abdominal pain in these patients could not have actually been a first symptom of aortic disease. Amoxicillin medication is mainly but naturally not only used in infectious problems above the diaphragm. He was therefore not sure that it is an ideal comparator.
Other adverse effects of Fluoroquinolones were reason for FDA warnings and retraction of some of these drugs. But the extra risk for patients seems to be small and will probably not have much clinical impact.

- Another editor said the authors should give a clearer interpretation of the clinical implication of their findings.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
This is an important piece of work on the risk of aortic aneurysm and dissection in people exposed to fluoroquinolones. The research question represents a priority that needs to be answered due to the recent evidence of an excess of events among quinolone users. The sample is representative, the data of high quality and the methodology very rigorous.

The authors of the manuscript optimized the available information in order to discard most of the potential confounding. However, there is an issue that in my opinion needs to be discussed more. The propensity score matching takes in some way into consideration the severity of the infection no information is available regarding the bacterial strain responsible for that infection. It is known that specific strains are involved in the pathogenesis of aortic aneurysms in humans, and that some of them (e.g. salmonella) are associated with more serious outcomes. These same strains, according to the guidelines, are more likely treated with fluoroquinolones. This important candidate confounder should be addressed in the discussion and in the interpretation of the results.

Reviewer: 2

Recommendation:

Comments:
* Is the article important?
This article is a well conducted observational study. However, I have focused on the methods and
clinicians and patients may be better placed to answer this question.

* Will it help our readers to make better decisions and, if so, how?
Potentially, however, the risk identified is relatively small, and if there are strong clinical reasons to
choose fluoroquinolone, then the putative risk of aortic aneurysm is unlikely to sway treatment
decisions.

* Will the article add enough to existing knowledge?
Yes.

* Does the article read well and make sense? Does it have a clear message?
This is a well written article and it has a clear message.
For research articles

* Originality
There have been previous observational studies into this association which are cited in the paper. This
paper adds a more sophisticated analysis which uses an active comparator. This could reduce bias due to
confounding by indication or protopathic bias.
* Importance of the work to general readers

Aortic aneurysms are a major, but rare complication. Fluoroquinolone is widely prescribed. However, the absolute risk identified in this study is 82 adverse events per million treatments. Fluoroquinolone is not as widely prescribed in the UK as amoxicillin, so this may not be as important for clinicians in the UK as Sweden.

* Scientific reliability

This is a well conducted observational study using an impressive dataset to address a difficult clinical question that would be impossible to address using experimental methods. The biggest concern for observational studies is residual confounding, however, the authors have matched on a wide range of covariates. Perhaps more importantly, the balance of the covariates prior to match was relatively close. There were big differences in the proportions prescribed previous medications (e.g. anticholinergic inhalant). However, these differences were not consistent in direction across the covariates. Therefore, the two treatments are potentially comparable.

* Research question

What is the association between fluoroquinolone versus amoxicillin use and aortic aneurysm?

  * Overall design of study

Matched observational cohort study.

  * Participants — adequately described, their conditions defined, inclusion and exclusion criteria described? How representative were they of patients whom this evidence might affect?

  * Methods

P9L13 - Is it plausible to assume that different treatment occasions within the same individual will be independent?

What were the indications the patients were prescribed antibiotics for?

For patients who received more than one medication, what proportion received each treatment first?

What were the average number of treatment occasions for each drug?

P7L52 - could you provide some information about what covariates were included in the text?

P9L23 - Could you provide a reference and p-value for your test of the proportional hazards assumption?

P9L32 - Does the study have a published protocol? Were the analyses pre-planned. What was the primary outcome?

P9L48 - Could you assess the association between the treatments and some negative control causes of death, such as accidents?

P10L5 - Could you upload your statistical code used to clean and analyse the data to a repository such as GitHub, or as an online supplement?

P10L23 - What was the balance of covariates prior to matching?

What are the typical indications for prescribing fluoroquinolone and amoxicillin? in particular, what are the indications which push GPs to prescribe one or the other? Could you include these, more specific covariates, in Web table 5?

  * Results

P11L9 - How do these rates compare to national prescribing trends?

GPs in the UK prescribed issued 9 million amoxicillin prescriptions, but only 0.6 million ciproflocacin prescriptions in the year to May 2017 https://openprescribing.net/. Why are prescribing patterns so different in Sweden, both in terms of the number of prescriptions issued, and the specific medications prescribed?

P12L3 - What was the relative risk during days 10 to 60?

P11L56 & P12L30- Statistical significance can be deeply misleading. It is generally easier to avoid the term. See Sterne et al 2001.

P12L25&26 - "was increased" Unclear, do you mean was associated with increased risk of aortic aneurysm?

P21L1 - Could you add the number of individual patients to Figure 1?

  * Interpretation and conclusions

The message is clear. Patients prescribed fluroquinolone have increased risk of aortic aneurysm. The results are discussed and the limitations of their analysis presented in a balanced way. The authors present the results in the context of previous work.

  * Abstract/summary/key messages/what this paper adds — reflect accurately what the paper says?

These were accurate, however I would downplay the importance of the statistical "significance" of the result.

Additional Questions:
Please enter your name: Neil Davies

Job Title: Research Fellow

Institution: University of Bristol

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: Yes

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may
in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way
gain or lose financially from the publication of this paper?: No

If you have any competing interests <A
HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-co
mpeting-interests'target='_new'> (please see BMJ policy) please declare them here: I have no
competing interests to declare.

Reviewer: 3

Recommendation:

Comments:
The manuscript entitled "Fluoroquinolone use and risk of aortic aneurysm and dissection: a nationwide cohort study" met a very important pharmacovigilance and public health topic: (i) fluoroquinolones are one of the most used antibiotic classes worldwide; (ii) the rates of its misuse alarm health professionals, researchers, and patients. Accordingly, it is of major importance to research and publishes evidence on adverse effects of these drugs, namely assess safety issues related to fluoroquinolone use.
Generally, about the manuscript, it is well-written, easy and interesting to read, with a clear and important message for clinicians, regulatory agencies, and patients. The paper reflects a well-performed research project, based on an up-to-date revision of the evidence, and the data pulled together, with the application of interesting statistical methods, may be of high impact in this research field. The importance of publishing evidence on this subject is also emphasized with a recent systematic review [Singh S and Nautiyal A (2017)] which only found two studies assessing the risk of aortic aneurysm or dissection after fluoroquinolone use.
The more novel aspect of the paper pertains to the significantly increased risk of aortic dissection or aneurysm associated with fluoroquinolone use and on the secondary analysis of the risk of aortic aneurysm VS aortic dissection.
Therefore, I support the publication of this manuscript. Please just consider the minor comments and some changes purposed below:
1.   Abstract: please consider to revise the text in the "main outcome measures" section of the abstract, to a more clinical and less statistical language.

2.   What this study adds: please consider to highlight the fact that the HR found appeared to be largely driven by aortic aneurysm (as made in the conclusion of the abstract). The difference found between aneurysm and dissection risks is of fully importance and must be emphasized in the current version of the manuscript.

3.   Methods: use as the comparator the episodes of amoxicillin is a very interesting way of controlling for unexpected/ unknown effects. However, and this is just a comment and not a recommendation for change, the manuscript could be more interesting if it also presents the results of the comparison with a non-exposed cohort.

4.   Methods/ Source of data: the National Patient Register captures the episodes also from the private sector or only in public institutions (hospitals and outpatient facilities)?

5.   Results – Cohort / Figure 1: Please consider to add in the text the number of patients included in each arm of the study. In the present version of the manuscript, we've only access to the number of episodes. Also, it would be interesting if the authors could add the standardized differences in the WebTable 5, as made in Table 1.

6.   Discussion: Please consider to discuss the results from this study with those highlighted in the this recently published meta-analysis:

Sonal Singh, Amit Nautiyal, Aortic Dissection and Aortic Aneurysms Associated with Fluoroquinolones: a Systematic Review and Meta-Analysis of Observational Studies., The American Journal of Medicine (2017), http://dx.doi.org/doi: 10.1016/j.amjmed.2017.06.029.

7.   Discussion: I think that the authors may go deep in the discussion about the different HR found for the risk of aortic aneurysm and the risk of aortic dissection, as this is different from the results published in the literature.

8.   Discussion – Implications and future research: in my opinion, possible implications of the results found are not being addressed in the discussion, namely concerning pharmacovigilance activities (special attention to the safety assessment in course) and clinical consequences (considering the global use of fluoroquinolones, with different rates between countries and regions, namely in Europe: https://ecdc.europa.eu/en/antimicrobial-consumption/database/quality-indicators)

9.   Discussion – Limitations: The limitations of the observational studies using linked national databases are always relevant, a fact that may emphasize the importance of future and more robust research. However, in the Discussion, the authors state these limitations very well, inclusive highlighting the missing information regarding some important risk factors of aortic aneurysm.

Additional Questions:
Please enter your name: António Teixeira Rodrigues

Job Title: Researcher

Institution: ibimed, University of Aveiro, Portugal

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: There is no conflict of interest to declare.