Author’s response to reviews

Title: Cardiac events after macrolides or fluoroquinolones in patients hospitalized for community-acquired pneumonia: post-hoc analysis of a cluster-randomized trial

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Version: 1 Date: 03 Dec 2018

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BMC Infectious Diseases

Editorial board

December 3rd, 2018

Dear Editor,

We are pleased to submit the requested revision of our manuscript entitled: “Cardiac events after macrolides or fluoroquinolones in patients hospitalized for community-acquired pneumonia: post-hoc analysis of a cluster-randomized trial” for consideration as a research article.
Please find our point-by-point response to the reviewers’ comments and questions below. We hope the manuscript in its current form is acceptable for publication in BMC Infectious Diseases.

Yours sincerely,

On behalf of all authors,

Douwe F. Postma
Corresponding author

Point-by-point response starts here:

Editor Comments:
Dear Dr Postma,

Thank you very much for your submission to the BMC Infectious Diseases. The article is well written and covered and important topic. This is a post-hoc analysis of a cluster-randomized trial as a cohort study; including patients with a working diagnosis of CAP admitted to non-ICU wards without a cardiac event on admission. The author concluded that among patients with CAP hospitalized to non-ICU wards, erythromycin use was associated with a 68% increased risk of hospital-acquired cardiac events, mainly heart failure. Levofloxacin and moxifloxacin were associated with a lower risk of heart failure. My recommendation is major review.

Regards

Grant W. Waterer (Reviewer 1):
This is a post-hoc analysis of the Dutch CAP trial published several years ago.

The findings are important because they highlight a major problem with that trial - that Erythromycin was a the major macrolide in the "dual-therapy arm" and it is well known that
Erythromycin given intravenously has more cardiac problems. It is unlikely to change practice in most parts of the world as erythromycin is very much a "dead" drug in the CAP space because of its known toxicity issues.

I have a number of queries and suggestions.

1. Over 20% of patients did not have radiology confirmation of CAP. This is an important limitation acknowledged in table 5 and the text but should be referred to in the abstract.

Indeed, our study domain was hospitalized patients treated for a working diagnosis of CAP, which inevitably includes patients without radiological confirmation of CAP. In contrast to the reviewers’ opinion we consider this a strength of the study as it makes our results more generalizable to daily clinical practice (in which these patients are treated with antibiotics). For clarity, we have now added the specific number to the abstract.

2. Table 3 shows that there were marked differences in the beta-lactam antibiotics used with and without erythromycin. Benzpen was rarely used with the non-erythromycin macrolides. We need to see some breakdown of demographics and outcomes for the most common combinations. I would suggest pen/ery, amox/cipro and amoxyclav/cipro (could be grouped), cefuroxime/ery, ceftriaxone/azith. The large amount of benzpen with ery raises the possibility that this is not an ery effect (although I think it is), but an effect of different penicillins.

Certainly, different beta-lactam antibiotics and different macrolides were used, yielding multiple different combinations. Further breakdown in such groups will result in too small numbers, leading to insufficient power and even risk of false-positive findings. E.g. the number of cardiac events in the subgroup of cefuroxime/erythromycin is 7 out of 97 (7.2%) patients, which is higher than the rate of penicillin/erythromycin: 7 out of 147 (4.8%). Still these absolute number are too small for inference. The possibility of an effect of penicillins is now addressed in the discussion (lines 279-281).

3. Another fundamental issue with the primary trial was the 40% of patients who were given dual antibiotics despite being in a monotherapy arm. It would be good to see the cardiac outcomes based on monotherapy PP, dual therapy despite monotherapy protocol and dual therapy by
protocol to see if clinicians had introduced some bias here in who they selected to overrule the monotherapy designation (that then explains the higher complication rates).

In this post-hoc analysis we assessed antibiotic-specific effects on cardiac complications, in which most of the macrolide and quinolone prescriptions resulted from cluster (strategy) randomization. Assessing such associations in subgroups of per-protocol and deviation-of-protocol populations will lead to loss of randomization and very small numbers of cardiac events, complicating inference. For clarity, we’ve added these numbers to the flowchart (Figure 1).

Assessing associations in the original trial arms will dilute the effects of macrolides and/or quinolones on cardiac events because of non-adherence (e.g. approximately 22-29% of patients in the monotherapy arm received dual therapy or 3rd gen. respiratory quinolones). In the adjusted analyses we have adjusted for potential indication bias where possible. This is added to the discussion (lines 267-271).

4. No pathogen data is presented - yet there is significant evidence that some pathogens are associated with worse cardiac outcomes (pneumococci and influenza). Even if they do not have sufficient data to analyze by pathogen this should be included.

We have added the pathogen data, stratified by cardiac outcome.

5. The implications for the findings of this post-hoc study on the original publication are not discussed but need to be. Intravenous erythromycin is toxic and no longer used in most countries. However in this study the overwhelmingly most common macrolide in the "dual therapy" by protocol arm was iv erythromycin - which they have now shown is associated with worse outcomes than azithromycin or fluroquinolones which were used in the "dual therapy" patients randomised to the "monotherapy" arm. Some reflection is needed in the discussion and abstract.

Erythromycin accounted for the largest fraction of macrolides in dual therapy with 35.6%, as compared to 23.8% and 28.7% for azithromycin and clarithromycin, respectively. Yet, our sample size is too small to attribute the absence of clinical benefit of macrolides as a group to erythromycin only, or to meaningfully compare the other macrolides to beta-lactam monotherapy. We do concur though that future trials comparing beta-lactam combination therapy
should refrain from using erythromycin, and in fact, the revised Dutch guideline for treating CAP no longer recommends the use erythromycin (based on the data of this analysis).

6. There are some randomised trials in this space that are relevant with respect to higher side effects with erythromycin - e.g. Tamm et al Clin Microbiol Infect 2007, Vergis et al Arch Intern Med 2000,

We were aware of these publications, but have decided not to discuss them as they did not describe associations between macrolides and cardiac events. Tamm et al mainly mention infusion-related and gastro-intestinal complications due to either clarithromycin or erythromycin (no distinction in text or tables) as compared to azithromycin, while Vergis et al mention this for the comparison between azithromycin and cefuroxime/erythromycin.

7. The studies that have shown a benefit of macrolide combination therapy have universally NOT used erythromycin except Mufson et al. This is an important observation relevant to the findings of this study.

We reviewed the studies that reported associations between macrolide combination therapy and lower mortality for the types of macrolides that were used:

To the best of our knowledge only Weiss et al. reported that erythromycin was not used in any patient. In all other studies macrolides were either not specified or erythromycin was included in a proportion of patients:

Brown et al. (not reported); García Vázquez et al. (not reported); Tessmer et al. (clarithromycin was used in 60% of cases); Waterer et al. (2001; not reported); Gleason et al. (not reported); Dudas et al. (not reported); Martinez et al. (erythromycin was actually used predominantly)

8. Reference 7 is misquoted. This paper showed lower cardiac events and mortality with azithromycin compared to non macrolide combinations.

The reviewer is right and the statement has been rephrased.
9. Under potential explanations as to why erythromycin did not do as well, there is reasonable evidence that erythromycin may not be as effective an anti-inflammatory agent as the other macrolides (see for example Ersoy et al J Laryngol Otol 2018 but there are others). This may be important if the heart failure is driven by pro-inflammatory cytokines (lines 285-287).

Thank you for this interesting hypothesis, we have added this to our discussion (lines 287-290)

Aran Singanayagam (Reviewer 2):

A large study on an important topic from a post-hoc analysis of the CAP-START trial. The paper is well written and the authors don't over-state the interpretation/conclusions they make which is important. The statistical testing used in complex and (in some places) beyond my expertise so I would suggest a reviewer with statistical expertise evaluates the manuscript also. I have the following suggestions for consideration:

1. Given that the main signal they see is heart failure, it would be useful to have a bit more detail on how the authors distinguished true acute left ventricular failure (i.e. a cardiac event) from a sepsis-induced picture. Did any of the patients classified have echo or BNP? Could they carry out a sub-analysis of such patients?

We agree that more detail could have improved the analysis. Unfortunately, we could not systematically collect such data as these investigations were frequently not ordered by the treating physician.

2. The authors have adjusted for some important variables that could influence outcomes in the multi-variable analyses. However, given that cardiac events are a key endpoint, they should consider use of medications such as statins, anti-platelets and smoking history.

The reviewer is right, our adjusted analyses now include the PSI score, summarizing several confounders at once, which allows us to additionally adjust for statins, anti-platelets and smoking history without overfitting our models (see methods section; lines 163-166). The effect sizes and results did not significantly change, confirming the robustness of the presented association.
3. The term 'heart failure' should be described more accurately throughout the manuscript? e.g. Acute? Chronic congestive? Left-sided? Right-sided?

Again, more detail would have been welcome, but would have required a prospective design. We have added this limitation to our discussion (lines 303-306).

4. For any tables (e.g. table 1) or descriptions in the text where %s are compared, it would be helpful to show p values to indicate where significant differences exist.

These are now provided in Table 1 and the text.

5. The authors speculate a hypothesis for why erythromycin could be associated with heart failure (volume and sodium load). My thoughts would be that it is more likely to be arrhythmia-induced failure that is occurring more often in erythromycin patients. Do they have any data on co-occurrence of arrhythmia and heart failure in individual patients?

Thank you for pointing out that we haven’t been clear enough. We have collected data on the (co)occurrence of any first cardiac event of three categories (heart failure, arrhythmia, and ischemia). This is now stressed in the text (lines 128-129). These data have been presented in most tables and the text. Apparently, arrhythmia did not occur more often in patients receiving macrolides.

6. Table 1 should show other factors of importance to cardiac events/arrhythmias e.g. alcohol excess, thyroid diseases, current or previous smoking etc

We have not collected these data except for previous smoking, this is now added to our baseline table.