Author's response to reviews

Title: Antihypertensive drug treatment changes in the general population. The CoLaus study

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Author's response to reviews: see over
Lausanne, 27/02/2014

Concerne : article 1068595426108925 revision

Dear Colleague:

Please find enclosed the revised version of the manuscript reference 1068595426108925 untitled “Antihypertensive drug treatment changes in the general population. The CoLaus study” by Vanessa Christe, Gérard Waeber, Peter Vollenweider and myself, to be submitted to BMC Pharmacology and Toxicology (Section: Clinical pharmacology).

We thank the reviewers for the thorough evaluation of the manuscript and revised it accordingly. The answers to the reviewers’ queries are provided in a separate document. We provide two manuscripts: one with the track changes indicated in red / striked, and another one “clean”.

Reviewer Maria Thurston requested that much additional information be included in the abstract. This would considerably increase abstract size beyond the journal’s limits. Hence, it was not possible for us to fully comply with her query. More information is provided in the answers to the reviewers.

Hoping that the revised version will be suitable for publication, we thank you in advance for considering it.

With my best regards,

Yours, sincerely

Pedro Marques–Vidal
Reviewer: Tyler Gums

Major Compulsory Revisions:

Authors revised my previous concerns with the lack of substantial conclusions. Original Concern: "The "Distribution of antihypertensive drug classes" did shed light on prescribing habits switching from thiazide-like diuretics to ARBs and beta blockers. Might consider re-defining your paper aims to highlight this shift." They have focused on the movement to ARBs. Well done.

Thank you very much

Minor Essential Revisions:

One step further would be to include the decline of beta blockers for use in HTN without other indications. See if you can fit that in the abstract to a degree along with the movement from diuretics to ARBs.

We added the following text in the abstract “during the study period, the prescription of diuretics decreased and of ARBs increased”. The prevalence of beta blocker prescription was 28% at baseline and 33% at follow-up, so no decline was observed. Please consider that for word count reasons we cannot add much more text to the abstract.
Reviewer: Eric Dietrich

Minor Compulsory Revisions

How will clinicians use the results of this study to improve their clinical practice? The brief discussion of the increase in ARBs is potentially important as it may lead to a continued increase in the use of ARBs as first line treatment (especially compared to diuretics).

We added the following text in the discussion “The 2013 ESH/ESC guidelines on management of arterial hypertension indicate that diuretics, beta-blockers, calcium antagonists, ACEI and ARBs are all suitable for the initiation and maintenance of antihypertensive treatment [ref]. Still, after an approximate follow-up of five years, our results show that diuretics were more frequently replaced and ARBs were more frequently prescribed. However our data suggest that practitioners on everyday’s practice tend to switch from diuretic to ARB treatment”

As BP data is available, it could be considered to discuss those who were classified as continuers who had uncontrolled BP - why was their therapy not escalated in order to control BP?

We analyzed the factors associated with increased BP among continuers. The significant results are below:

<table>
<thead>
<tr>
<th></th>
<th>Controlled (n=211)</th>
<th>Uncontrolled (n=209)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>94 (44.6)</td>
<td>113 (54.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Diuretics</td>
<td>18 (8.5)</td>
<td>33 (15.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Uncontrolled BP at baseline</td>
<td>79 (37.4)</td>
<td>116 (55.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The following text has been added in the results. “Continuers with uncontrolled BP at follow-up were more frequently men (54.1% vs. 44.6, p=0.05), were more frequently uncontrolled (55.5% vs. 37.4%, p<0.001) and on diuretics at baseline (15.8% vs. 8.5%, p<0.05), while no differences were found for the other variables (not shown).”

The following text has been added in the discussion: “Continuers with uncontrolled BP at follow-up were more frequently men, with uncontrolled blood pressure and on diuretics at baseline. These findings suggest that diuretics might be less effective in controlling BP than the other antihypertensive drugs, or that their side effects might lead to a lower compliance and thus worse blood pressure control. Indeed, diuretics have been shown to have the lowest persistence rate of all antihypertensive drugs (supplementary table 3). They also indicate that practitioners should be more aggressive towards uncontrolled hypertension, as continuing the same treatment will not improve blood pressure control”

If CV outcome data is available adding this information could be a significant strength (could not see if addressed following original comments as Author Cover letter was not available in
Importantly, CV outcome data would be important as it is the most clinically relevant outcome (as BP represents surrogate marker); if combined with rates of continuers, discontinuers, etc., it could help strengthen the need for better blood pressure control even if combination therapy is required. Also, comparisons between CV rates and initial/added therapy could be interesting.

We do have CVD incidence data, but a major limitation for the analysis is that the sequence between CVD event and change in BP treatment is unknown. Hence, we cannot establish whether the changes in antihypertensive drug treatment occurred before or after the occurrence of the CVD event. This is why we decided not to include it in the manuscript. A second follow-up is under way which will allow collecting the events after the changes. The following text has been added in the limitations paragraph “Although incidence of CVD events was available, it was not possible to establish whether the changes in antihypertensive drug treatment occurred before or after the occurrence of the CVD event. The next follow-up of the cohort will start in April 2014 and will allow evaluating the impact of antihypertensive drug treatment changes in preventing CVD events”.

Reviewer: Maria Thurston

Major Compulsory Revisions

1. Abstract: Methods: Please include a brief description of the general plan for analysis.
   
   We added the following text. “The distribution and the factors associated with changes in antihypertensive drug treatment were assessed”. Please consider that for word count reasons we cannot add much more text to the abstract.

2. Methods: Paragraph 3: Regarding family history of first degree relative, change “uncles and aunts” to “parents and siblings”
   
   Changed

3. Results: Paragraph 7: Sentence 1: Table mistitled as “table 45” – number table appropriately.
   
   Corrected

4. Overall, although some discussion of disease specific blood pressure goals was added based on comments from previous review, unsure if this classification was considered during the actual study. Also, given recent publication of JNC8 for hypertension management and the new goal of <140/90 for all patients (unless >/= 60 years) this may now not be as important of a point.

   As requested by another reviewer, we added the following text in the discussion “The 2013 ESH/ESC guidelines on management of arterial hypertension indicate that diuretics, beta-blockers, calcium antagonists, ACEI and ARBs are all suitable for the initiation and maintenance of antihypertensive treatment [ref]. Still, after an approximate follow-up of five years, our results show that diuretics were more frequently replaced and ARBs were more frequently prescribed. However our data suggest that practitioners on everyday’s practice tend to switch from diuretic to ARB treatment”.

Minor Essential Revisions

1. Introduction: Paragraph 2: Sentence 2: Remove “a” from “a poor adherence.”
   
   Removed

2. Introduction: Paragraph 2: Change last word of the paragraph “dose” to “doses”
   
   Changed

3. Methods: Paragraph 7: Last sentence: Still unclear of the purpose of this sentence and what it is trying to convey. Where these trials cited using different classification systems? Recommend further elaboration.

   We decided to delete the sentence as we do not elaborate on other classifications.

4. Discussion: Paragraph 8: Sentence 1: Remove “to” in the phrase “Unlike to”
   
   Removed

5. Discussion: Paragraph 10: Sentence 4: Remove “to” in the phrase “Unlike to”
   
   Removed