Reviewer's report

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

Version: 1 Date: 7 November 2013

Reviewer: Maria Thurston

Reviewer's report:

- Major Compulsory Revisions

1. Abstract: Methods: Please include a brief description of the inclusion/exclusion criteria, the data source (i.e., CoLaus database) and type of other data collected as well as general plan for analysis.

2. Introduction: Paragraph 1: Sentence 1: Hypertension is sometimes. But not always preventable; however, it is a “manageable” risk factor.

3. Introduction: Paragraph 1: Last sentence: Appropriate treatment is not always achieving a blood pressure < 140/90. In patients with other comorbidities, (i.e., diabetes, CKD, etc.), the blood pressure goal may be lower because tighter control is warranted. This concepts does not appear to be addressed with this study although a percentage of participates reported a personal history of diabetes, for example.

4. Methods: Paragraph 3: Why was physical activity defined as only at least twice per week with no duration specified when guidelines recommend upwards of 30 minutes at least 5 times weekly? This definition may have led to overestimation of the percentage of physically active participants. Family history of all first degree relatives is relevant when determining cardiovascular risk; however, only history of mother and father collected—was this sufficient?

5. Methods: Paragraph 3: Can you elaborate on the reliance on patients bringing their drugs to the visit to determine the patient’s current medication regimen? From clinical experience, patients may often present with outdated prescription bottles that are no longer prescribed or may accidently forget to bring a bottle with them. This may have led to misclassification of the patient’s baseline drug therapy status and may be a limitation.

6. Methods: Paragraph 7: Sentence 1: Regarding the concept of dividing the participants into 4 different groups which seems to have occurred at baseline and again 5 years later at follow-up allows for a long period of time in which antihypertensive therapy adjustments and interventions may have been missed. Would have been useful to have more frequency intervals of follow-up between baseline and 5 years (maybe yearly evaluations to track changes and progress would have been insightful). Furthermore, was dose escalation (titration) or dose reduction of medications considered? As those are important steps in hypertension management that can impact blood pressure control. Inclusion of this data, if available, would add value to the manuscript. Was a power analysis
completed to detect differences between groups that were observed to determine if what appears to be statistically significant is indeed truly significant?

7. Methods: Paragraph 8: Last sentence: Again, why were other co-morbidities not considered in determining blood pressure goals and control?

8. Results: Paragraph 7: Sentence 1: The p-value provided appears to correspond to different information included in table 4 (listed next to HT to HT not HT to C which would indicate improvement in blood pressure). Please confirm correct placement of p-value in table 4/discussion within text.

9. Discussion: Paragraph 1: Sentence 2: States prescription rate for ARBs was in accordance with Swiss guidelines. Please include more details/recommendations from guidelines referenced to reveal how they correlate or are in accordance.

10. Discussion: Paragraph 11: Sentence 7: Again, determination of blood pressure control was not specific to other co-morbidities that require lower goals and tighter control.

11. Table 4: Please confirm that p-value listed is in the correct row. Appears based on reading the corresponding text of the manuscript that it may belong in the last row when the number of patients who went from being hypertensive to controlled is noted.

- Minor Essential Revisions

1. Abstract: Background: Sentence 1: Refer to hypertensive patients as “patients with hypertension” instead.

2. Abstract: Background: Sentence 2: Change “we aimed at assessing” to “our aim was to assess”

3. Abstract: Methods: Sentence 1: Add “were” followed. Later in the manuscript it states that the median follow-up was 5.4 years, but here it says 5.5—please clarify.

4. Abstract: Results: Sentence 2: “At follow-up”—reiterate that this is approximately 5 years later

5. Introduction: Paragraph 1: Last sentence: Change “human and financial” to “humanistic and economic”

6. Introduction: Paragraph 2: Sentence 1: Change “should be taken” to “is recommended” and “combined therapies are” to “combination therapy is”

7. Introduction: Paragraph 2: Sentence 2: Change “a poor compliance” to “poor adherence.” Adherence is the more acceptable term to use, rather than compliance.

8. Introduction: Paragraph 2: Last sentence: Add “identifiable by the patient” following “clinical symptoms of hypertension.” Change “added to” to “along with” and determine if it may be more appropriate to refer to participants in the study as “patients” or may keep as “participants.” Change “wrong intervals or prescribed doses” to “inappropriate intervals or wrong doses.”

9. Introduction: Paragraph 3: Sentence 2:Change to “changes in or
discontinuation of antihypertensive"

10. Introduction: Paragraph 3: Last sentence: Study was “approximately” five years duration (noted range of 5.3-5.6 years reported later).

11. Methods: Paragraph 3: Sentence 5: Change “presented myocardial infarction” to “previously experienced myocardial infarction”


13. Methods: Paragraph 5: Sentence 1: Change “was 5.4” to “of 5.4”

14. Methods: Paragraph 6: Sentence 1: Why is there a superscript reference “1” included at the end of the sentence and a reference listed at the bottom of the page? Should be incorporated into reference list at the end and appropriately numbered.

15. Methods: Paragraph 6: Sentence 4: Change “several antihypertensive drug classes” to “two antihypertensive drug classes.” I am not aware of a combination product that contains more than two drugs in one pill.

16. Methods: Paragraph 7: Sentence 1: Add “…4 different groups determined by drugs brought to visit at baseline and approximately 5 years later, as suggested in a previously study”

17. Methods: Paragraph 7: Sentence following 2) Switchers: Change to “treatment from one class to another class of antihypertensive therapy”

18. Methods: Paragraph 7: Sentence following 4) Discontinuers: Add “added” to end of the sentence

19. Methods: Paragraph 7: Last sentence: Unclear of the purpose of this sentence and what it is trying to convey. Where these trials cited using different classification systems?

20. Methods: Paragraph 8: Sentence 1: Run on sentence. Split into two sentences as follows: “At baseline and follow-up, BP was measured in the left arm, with an appropriately sized cuff. The reading was taken following at least 10 minutes….”

21. Methods: Paragraph 8: Last sentence: Change “controlled is” to “controlled if.”

22. Methods: Paragraph 9: Generally, statistical analysis is “completed” not “made.”

23. Methods: Out of place reference 2 included at the bottom of the page following “Statistical Analysis” section. Remove and add to reference list and number accordingly.

24. Results: Paragraph 1: Sentence 1: Remove “and, 401 men” as that is a given based on the number of women provided.

25. Results: Paragraph 5: Next to last sentence: Change “less frequently diuretics” to “diuretics less frequently” and “less frequently ARBs” to “ARBs less frequently”

26. Results: Paragraph 6: Sentence 1: Add “relative to continuers group”
following “antihypertensive drug treatment”

27. Results: Paragraph 6: Sentence 5: Change “in a single pill” to “on a single pill”

28. Discussion: Paragraph 1: Sentence 2: Change “The prescription rate for ARBs was considerably” to “The prescription rate for ARBs at the time of follow-up was considerably”

29. Discussion: Paragraph 1: Sentence 4: Change “prescription” to “prescriptions” and add “guideline” in front of the term recommendations

30. Discussion: Paragraph 1: Sentence 6: Change “prescription of ACE inhibitors” to “number of ACE inhibitor prescriptions”

31. Discussion: Paragraph 2: Sentence 1: Add “an approximately 5.4 year” in front of the term follow-up

32. Discussion: Paragraph 2: Last sentence: Add “when assessed over a period of years” to the end of the last sentence of this paragraph

33. Discussion: Paragraph 4: Last sentence: Change “that a combination treatment should be prescribed if a single drug treatment fails” to “that combination therapy should be prescribed if monotherapy fails”

34. Discussion: Paragraph 7: Sentence 2: Change “and to the fact that most patients are symptom-free and might present more” to “and the fact that most patients are symptom-free and might experience more”

35. Discussion: Paragraph 8: Last sentence: Add “the” in front of the term socio-economic

36. Discussion: Paragraph 9: Sentence 1: Change “contrary” to “unlike” and change “could” to “was able to “

37. Discussion: Paragraph 10: Sentence 1: Add “with the exception of only including Caucasians” to the end of the sentence

38. Discussion: Paragraph 10: Sentence 3: Clarify use of the term “putatively”

39. Discussion: Paragraph 10: Sentence 5: Note that “combiners were added as a category” and cite the author of the reference listed rather (Mazzaglia and colleagues) than use of only “[2]” in text and add “when” in front of the term managing.

40. Discussion: Paragraph 11: Recommend avoiding use of numbering of limited cited, as five are listed (first through fifth) and this distracts from the flow of the manuscript. Use transitions to lead the reader from discussion of one limitation to another.

41. Discussion: Paragraph 11: Sentence 4: Change “contrary” to “unlike”

42. Discussion: Paragraph 11: Sentence 5: Change “compliance” to “adherence”

43. Discussion: Paragraph 11: Last sentence: Change “reasons” to “reason(s)”

44. Authors contributions: Change “made” to “completed” when referring to statistical analysis (i.e., VC completed part of the statistical analysis)

45. Supplementary table 2: Add a “-” symbol under the column for study duration
of the Mazzaglia study to indicate that information is not available or not applicable.

- Discretionary Revisions
1. Title: Consider revising to “Antihypertensive drug treatment trends and changes in the general population. The CoLaus study” which would better describe the scope of the entire study.
2. Abstract: Results: Sentence 5: What is the p-value for the improvement in blood pressure status?
3. Keywords: Consider changing “shifting” to “switching” and adding the terms “combination” and “discontinuation.”
4. Introduction: Paragraph 1: Sentence 2: Where are patients presenting with hypertension? Reference 1 is for primary care clinics. Are 40% of patients presenting to primary care clinics with hypertension?
5. Introduction: Paragraph 2: Sentence 2: States “several studies” but only goes on to cite two studies. Is a more robust literature search possible?
6. Methods: Paragraph 1: Discuss reason why the random sample was not stratified. May consider incorporating into discussion portion of manuscript. Change “brief description of the study” to “quick description of the study.” How was patient confidentiality and privacy maintained/ensured when letters were mailed to randomized sample?
7. Methods: Paragraph 6: Sentence 1: Please clarify HOW the names of all drugs were collected. Was it only by patient self-report via drugs brought by patient to interview?
8. Methods: Paragraph 6: Consider further subdividing drug classes identified: Diuretics: thiazide, loop, and potassium sparing. CCBs: non-DHP and DHP. BBs: sympathomimetic or alpha/beta. The example provided of “taking a single pill, which can eventually be a combination of drugs” was unclear—consider revising wording to better convey meaning.
9. Methods: Paragraph 9: Appears that statistical tests chosen are appropriate; however, may consider including an explanation about why a one-way ANOVA was chosen as it does not allow for control of confounders. Are there any potential confounders in the study that could have been included in the analysis?
10. Results: Paragraph 6: Last sentence: A supplemental table with these results may be beneficial for completeness since they are discussed within the text even though no significant association was noted.
11. Discussion: Paragraph 1: Sentence 4: Please clarify meaning of this sentence. Does not appear to match with next statement in paragraph since the word “not” was used as it seems if combo ACE inhibit/ARB therapy is not recommended in the guidelines than that may explain some of the low rate of ACE inhibitor prescriptions if ARBs were already being used more.
12. Discussion: Paragraph 2: Sentence 3: Why were patients considered to be more health-conscious participants?
13. Discussion: Paragraph 3: Sentence 2: What adverse effects are noted with the other classes? Do diuretics tend to have the worst side effect profile to explain their highest discontinuation rate? Are there other potential reasons that could be included?
14. Discussion: Paragraph 7: Was this study powered to detect these differences/associations?
15. Discussion: Paragraph 11: Sentence 1: States “studies” but only once study referenced. Please cite additional studies to support the statement.
16. Discussion: Paragraph 11: Sentence 3: Add “and data on past medical history and clinical features” to end of sentence
17. Table 3: Include blood pressure value in table that corresponds to hypertension (yes vs. no) or include as a footnote at the bottom of the table.
18. Supplementary table 1: Would have been helpful to the reader for alcohol consumption to have been quantified (i.e., abuser vs. social or occasional drinker). Further subclassification of the treatment regimen would have added to the knowledge of regimen complexity of the patient population—rather than just noting “several pills,” could the patients be divided into groups based on the number of pills taken or a range of such numbers for a more detailed quantification?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests