PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Retrospective Cohort Study to Characterize the Blood Pressure Response to Spironolactone in Patients with Apparent Therapy-resistant Hypertension using Electronic Medical Record Data
AUTHORS	Shuey, Megan; Perkins, Bradley; Nian, Hui; Yu, Chang; Luther, James M; Brown, Nancy

VERSION 1 – REVIEW

REVIEWER	Pedro Armario Hospital Moisès Broggi, Sant Joan Despí. Barcelona University of Barcelona
REVIEW RETURNED	02-Aug-2019

GENERAL COMMENTS	The objective of this study was to identify blood pressure response to spironolactone in patients with resistant hypertension using electronic medical records (EMRs) in order to estimate response in a real-world clinical setting. Although the methodology is right and previously validated, and the manuscript shows some interesting data, such as the relative high percentage of use of spironolactone in relation to other published series, the mean reduction to spironolactone, (SBP: 8.1 mm Hg DBP: 3.4 mm Hg), electrolyte changes in a large real-world sample, this study presents some major limitations: - In despite of the large initial sample (13,541 EA with resistant hypertension (RH) and 3,541 AA with RH, only 1,114 (32.7%) and 369 (35%) were evaluated, respectively, which limits the extrapolation of these results to the real world . - Adherence to treatment could not be evaluated - There is no confirmation of resistance to antihypertensive treatment by ambulatory BP monitoring for 24 hours. It is well known that approximately 30% of said subjects have a good control in the ABPM figures, and therefore would not need to add spironolactone as a fourth drug. - The authors do not specify whether the doses of the different antihypertensive drugs were full, especially that of diuretic treatment, since in some fixed combinations the dose of thiazide is very low. - Although the authors point out that cases of secondary HTN were ruled out, it is surprising that the dose range of spironolactone used was so wide (not a maximum of 200 mg of spironolactone), since doses greater than 50 mg would only be indicated in cases of hyperaldosteronism, but not in resistant hypertension. How many patients received a dose of spironolactone> 50 mg / 24h? - Responders were defined arbitrarily as those who presented a reduction in systolic BP ≥ 5 mm Hg, or ≥ 2 mm Hg in diastolic BP, but what percentage of subjects achieved good BP control below 140 / 90 mm Hg when adding spironolactone?

	In addition to the classic triad with diuretic, renin angiotensin system inhibitor and calcium antagonist, which other antihypertensive drugs received these patients prior to spironolactone and after adding spironolactone - One of the concussions is that the response to spironolactone was correlated with the decrease in glucose, but no information is provided on the treatment of DM (56%) in responders and non-responders - What does this study really contribute in clinical practice, regarding what is already known? Can it be extrapolated from the data in this study that spironolactone can improve glycaemic control in diabetic patients with resistant AHT? I think not, because of the information provided and the many possible biases.

REVIEWER	Jonathan Townend Queen Elizabeth Hospital Birmingham UK
REVIEW RETURNED	02-Dec-2019

GENERAL COMMENTS	This paper uses analysis of electronic records to examine the reponses of BP, kidney function and electrolytes to the use of spironolactone in patients with resistant huypertension. It isnt clear whether the primary aim of the paper is to show that automated analysis can measure such reponses accurately or to examine the responses themselves. The data show convincingly that use of their algorithm and e-records accurately characterises responses to spironolactone. These responses are largely those that have been reported before with a mean drop in sBP of about 8 mmHg and 30% non response rate, at least some of which is due to non compliance (responses of Na and K were lower in non responders) . The changes in Na, K and eGFR are those that would be expected. Their was no evidence of any difference in response or response rates between EA and AA subjects. The discussion is a little overlong containing some rather speculative comments on glycaemic response which I would recommend be removed and some unnecessary detail and speculative comments on the mechanisms of changes in Na and K which could also be removed. In summary I would recommend that the paper be revised and shortened to focus on the angle that this form of automated analysis can accurately detect and characterise several aspects of anti-hypertensive drug responses. There is nothing very new in this paper about these responses per se except perhaps the lack of any racial difference in response which is worth emphasising. The discussion can be radically shortened to concentrate on the use of algorithmic analysis of e-records which appears acurate enough to be used in future more novel analyses. It looks ideal to detect differences in BP responses, kidney responses and long term clinical end point responses (MACCE etc) to different drugs helping to answer the key questions such as 'is it the BP response or is it the drug'? Use of the same font throughout the paper would be appreciated!

VERSION 1 – AUTHOR RESPONSE

Reviewer 1-

1) In despite of the large initial sample (13,541 EA with resistant hypertension (RH) and 3,541 AA with RH, only 1,114 (32.7%) and 369 (35%) were evaluated, respectively, which limits the extrapolation of these results to the real world.

   Thank you for this comment. We agree that it is disappointing that after algorithm deployment a larger number of subjects are excluded and discuss this limitation in the "Discussion" section, "**Other limitations of the study include the exclusion of a significant number of patients with aTRH due to inadequate documentation of pre- and post-treatment BPs, which limits our power of detection for some responses. The relatively small number of AA, for example, limits the power to detect predictors of response to spironolactone in this group."**

   We believe that despite this limitation the strength of this study is in the ability of our algorithm to measure accurately blood pressure response to medications, specifically spironolactone, in electronic medical records as well as characterize other electrolyte responses. While our specific population was limited in power due to size, the potential to apply the algorithm in other electronic record systems provides the opportunity to identify other changes and to study much larger clinical populations.

2) Adherence to treatment could not be evaluated.

   We agree with the reviewer that we were unable to evaluate adherence and note that this is a limitation of our study. We discussed this particular limitation in the "Strengths and Limitations of this study" section and the implications of this particular limitation in the "Discussion" section. We have provided the excerpts below:

   Limitations of this study include the inability to confirm medication adherence, a lack of ambulatory blood pressure measurements, and a lack of some laboratory measures, such hemoglobin A1c (HbA1c) and lipids, for the entire population.

   A limitation of this study and many other studies of aTRH is the inability to measure adherence directly in the patients prescribed spironolactone without measuring drug levels, which is not routinely done in clinical practice. Nonadherence alone does not likely explain the lack of BP response in nonresponders, however. First, patients nonadherent to spironolactone would likely be nonadherent to other medications. Nonadherent patients, therefore, would be expected to have higher baseline BPs than adherent patients. To the contrary, we found that nonresponders had lower baseline SBP and DBP than responders and baseline SBP and DBP significantly predicted BP response. In addition, initiation of spironolactone resulted in an increase in serum potassium and decrease in serum sodium in non-responders as well as responders, albeit to a lesser degree. Taken together these findings suggest that nonadherence is not the predominant driver of the lack of BP response in non-responders.

3) There is no confirmation of resistance to antihypertensive treatment by ambulatory BP monitoring for 24 hours. It is well known that approximately 30% of said subjects a have a

good control in the ABPM figures, and therefore would not need to add spironolactone as a fourth drug.

We thank the reviewer for the acknowledgement of this limitation. We agree and had previously discussed this limitation in the manuscript in the "Strengths and Limitations of this study" section. We have provided the excerpt from the manuscript below:

Limitations of this study include the inability to confirm medication adherence, **a lack of ambulatory blood pressure measurements**, and a lack of some laboratory measures, such hemoglobin A1c (HbA1c) and lipids, for the entire population.

To further reflect this limitation in the study population, we have revised all references to resistant hypertension to now read apparent therapy-resistant hypertension (aTRH). This revision is consistent with current literature on the topic and further reflects the study's inability to delineate real resistant hypertension from pseudo-resistant hypertension due to the lack of ambulatory blood pressure measurements.

4) The authors do not specify whether doses of the different antihypertensive drugs were full, especially that of diuretic treatment, since in some fixed combinations the dose of thiazide is very low.

We agree with the reviewer that the dose of antihypertensive therapy may vary amongst individuals and particularly in patients prescribed combination therapies. We have provided a supplemental table (**Supplemental Table 3**) that provides the daily dose and frequency of thiazide diuretics and dihydropyridine calcium channel blockers, the medications a patient must be prescribed to meet the definition of aTRH for inclusion in the study. The dose and frequencies provided are at the start of spironolactone prescription. We have also provided a summary of the table in the "Results" section.

Consistent with the aTRH definition, in addition to other antihypertensive medications, patients were prescribed a thiazide diuretic or a dihydropyridine CCB prior to spironolactone initiation. The median daily dose of thiazide diuretic was 25 mg with a range from 12.5 mg to 50 mg (Supplemental Table 3). The predominant dihydropyridine CCBs prescribed were amlodipine and nifedipine. The median daily dose of amlodipine and nifedipine were 10 mg with a range from 2.5 mg to 10 mg and 90 mg with a range from 30 mg to 120 mg, respectively (Supplemental Table 3). For a subset of these patients the thiazide or dihydropyridine CCB dose at spironolactone initiation, e.g. dose of the medication identified in the month preceding or following spironolactone prescription, could not be determined. From the patients with confirmed doses 566 (80.6%) were prescribed a 25 mg thiazide, 312 (73.9%) were prescribed 10 mg amlodipine, and 110 (40.3%) were prescribed 90 mg nifedipine.

5) Although the authors point out that cases of secondary HTN were ruled out, it is surprising that the dose range of spironolactone used was so wide (not a maximum of 200 mg of spironolactone), since doses greater than 50 mg would only be indicated in cases of hyperaldosteronism, but not in resistant hypertension. How many patients received a dose of spironolactone >50 mg/24h?

As noted in the manuscript 70% of patients received the 25 mg dose. To address the reviewer's concern, however, we have added to discussion of spironolactone dose in the "Results" section the following statement:

107 patients were prescribed spironolactone at a dose of 12.5mg and one at a dose of 200 mg. In total, 261 patients (17.6%) patients were prescribed a 50 mg or greater dose of spironolactone.

6) Responders were defined arbitrarily as those who were presented a reduction in systolic BP > 5 mmHg or > 2 mmHg in diastolic BP, but what percentage of subjects achieved good BP control in addition to the classic triad with diuretic, renin angiotensin system inhibitor and calcium antagonist, which other antihypertensive drugs received the patients prior to spironolactone and after adding spironolactone.

While we did utilize a binary blood pressure response cutoff based upon literature review, we also provided analyses based on blood pressure as a continuous response measure to indicate BP control. In response to the reviewer's question we have provided the number of subjects that achieved blood pressure control to less than or equal to 140/90, defined by guidelines recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. In the "Results" section we provided the following statement:

In total, 933 patients (62.9%) achieved a decrease in BP to $\leq$ 140/90 mmHg, the pressure goal recommended in guidelines at the time. An additional 23 patients achieved a decrease in SBP but not DBP to guideline recommendation and 262 patients achieved DBP but not SBP control.

7) One of the conclusions is that the response to spironolactone was correlated with the decrease in glucose, but no information is provided on the treatment of DM (56%) in responders and non-responders.

Based on the recommendation of the second reviewer we have revised the discussion to focus on the potential for the electronic algorithm to detect and characterize different aspects of spironolactone response. While the glucose response was present in EA and we mention this in the discussion we have removed the larger section discussing the potential implications of this finding. For this reason, we have not provided additional details regarding this particular response to spironolactone nor added the requested information relating to the treatment of diabetes mellitus.

8) What does this study really contribute in clinical practice, regarding what is already known? Can it be extrapolated from the data in this study that spironolactone can improve glycemic control in diabetic patients with resistant ATH? I think not, because of the information provided and the many possible biases.

This study really shows the potential of electronic algorithms to curate medical record data to detect and characterize various aspects of response to a specific antihypertensive medication, spironolactone. We have added a section to the discussion that emphasizes the potential for this algorithm to be adapted for use with other antihypertensives, in other electronic records, as well as with an evaluation of clinical implications of medication use. "**A strength of this algorithm is its applicability to evaluate BP and electrolyte responses to medications other than spironolactone as well as its utility to evaluate the long-term**

clinical consequences of medication use. Further, this electronic algorithm could be amended for use in other EMR systems."

Reviewer 2

1) In summary I would recommend that the paper be revised and shortened to focus on the angle that this form of automated analysis can accurately detect and characterize several aspects of anti-hypertensive drug responses. There is nothing very new in this paper about these responses per se except perhaps the lack of any racial difference in response which is worth emphasizing. The discussion can be radically shortened to concentrate on the use of algorithmic analysis of e-records which appears accurate enough to be used in future more novel analyses. It looks ideal to detect differences in BP responses, kidney responses and long term clinical end point responses (MACCE etc) to different drugs helping to answer the key questions such as 'is it the BP response or is it the drug'?

   We have revised the discussion to focus on the algorithm's ability to detect blood pressure response as well as other electrolyte responses from electronic health records.

2) Use the same font throughout the paper would be appreciated!

   We have revised the manuscript to ensure all text in the main document as well as tables and figures is Times New Roman.

VERSION 2 – REVIEW

REVIEWER	J Townend Queen Elizabeth Hospital Birmingham UK
REVIEW RETURNED	22-Jan-2020

GENERAL COMMENTS	This is now a simpler and better paper that concentrates on the use of an algorithm to define the BP response to sprinolcatone and to identify non respnders. My major comment is that the authors havent really spelled out the advantages of this approach. The algorithm provides a cheap and accurate method of determining BP response enabling the rapid identification of non responders who can then go forwards for further investigation (drug levels) and treatment (compliance, other drugs, RDN etc) . It could also be used to look at outcomes and the possible effects of individual drugs and of the levels of BP control. Finally and perhaps uncomfortably, the performance of personnel running the clinic can also be assessed! NB Fig 2 uses the abbreviation of RHTN which should be changed for consistency to aTRH

VERSION 2 – AUTHOR RESPONSE

Reviewer 2-

1) This is now a simpler and better paper that concentrates on the use of an algorithm to define the BP response to sprinolcatone and to identify non respnders. My major comment is that

the authors havent really spelled out the advantages of this approach. The algorithm provides a cheap and accurate method of determining BP response enabling the rapid identification of non responders who can then go forwards for further investigation (drug levels) and treatment (compliance, other drugs, RDN etc) . It could also be used to look at outcomes and the possible effects of individual drugs and of the levels of BP control. Finally and perhaps uncomfortably, the performance of personnel running the clinic can also be assessed!

To better address the advantages of this approach we have added the following to the discussion section: "**The advantage of this approach is that it is an accurate, rapid, high throughput, and inexpensive approach for quantifying clinical response to medications and determine responders and nonresponders. The identified population can then be used as a research cohort to investigate other relevant topics including pharmacogenetic inquiries, long term outcome and event studies, as well as evaluate medication levels to determine compliance or the presence of rapid or insufficient metabolizers. Further, the method can easily be adapted for use with other medication types and in other EMR systems. These adaptations could also allow for inquires related to personnel and infrastructure performance, e.g. when the algorithm is adapted for evaluation of a response for a medication used exclusively in-hospital.**"

2) Fig 2 uses the abbreviation of RHTN which should be changed for consistency to aTRH

Thank you for noting this oversight. We have revised Figure 2 to use the abbreviation aTRH instead of RHTN.