

December 28, 2018

World Journal of Hypertension

Invited Review

Invitation ID: 03429673

Manuscript NO.: 44533

Re: Revision

Dear Editor(s),

Attached please find our revised manuscript entitled "Achieving Control of Resistant Hypertension: Not Just the Number of Blood Pressure Medications".

We sincerely appreciate the thorough reviews and very helpful suggestions from all the reviewers. Accordingly, we have completed the revision. Below please find our corresponding responses and changes.

Reviewer ID 03430151

1. Page 4 Lines 10-12 should be moved to page 3 to be the first sentence under introduction.

We have moved the sentence to be the first sentence under "Introduction".

INTRODUCTION

Resistant hypertension (RH) is defined as blood pressure (BP) elevation above goal despite the use of three or more anti-hypertensive medications of different classes with at least one being a diuretic, all at the maximum tolerated doses, after excluding pseudoresistance^[1].

2. Page 5 Line 12: MARs should be MRAs

We appreciate the meticulous review and have made the correction.

The validation of MRAs in the treatment of RH from recent randomized clinical trials has led to adoption of evidence-based standards for their use^[2].

3. Page 8 Line 2: "..even up to two years after the guideline was published" should be rendered "..even though they have been published two years earlier".

We appreciate the thorough review and have made the change as suggested.

Another analysis from a large ambulatory care survey with over 19,000 patients showed that providers were not prescribing anti-hypertensives according to the current ACC/AHA guidelines, even though they had been published two years earlier^[26].

4. Page 11 Line 12: Change "regards" to "regard".

We appreciate the thorough review and have made the change as suggested.

The RH population has also been studied in regard to low salt diet, and they had dramatic reductions of BP, on average 22.7/9.1 mmHg, which is much more than in patients with essential hypertension^[60].

5. Authors should mention that common over-the-counter drugs, some common cold remedies and some foods may frequently cause resistant hypertension.

We appreciate the thorough review. Table 2 has been updated and additional comments have been included in the paragraph under Excluding interfering substances:

As summarized in **Table 2**, there are many medications ranging from chemotherapy all the way to common over-the-counter remedies, herbal supplements, food items, and illicit substances that are known to raise BP^[29,33,34]. Therefore any of these substances should be considered during the initial evaluation of a patient.

6. References are irregular and some are not according to the Journal format e.g. Refs 7, 10, 11, 14, 19, 21, 28-29, 63, 65, 67-68, 76-79, 82 (no year cited), 84, 88, 94, 97-99, 105-106.

We appreciate the thorough review and have reformatted the references.

Reviewer ID 03936425

This is a review article in which the authors review the current guidelines regarding treatment of resistance hypertension. The most common reasons of true and pseudo-resistance are described. The epidemiology of resistant hypertension is briefly characterized. The approach to patient with RH is described in detail such as lifestyle modification, renal denervation, baroreceptor-activation therapy and central arteriovenous anastomosis. Finally, authors focus on possible modifications of pharmacotherapy in patient with resistant hypertension. The topic is of interest and the manuscript is well-written. I have no critical concerns or any suggestions for improvement.

Thank you for your thorough review, encouraging comments and strong support.

Reviewer ID 02456031

This is a quite comprehensive and well written review making the point on the current knowledge about the diagnostic procedures and therapeutic approach to resistant hypertension. When the authors discuss the impact of the white-coat effect and white-coat hypertension on RH they must make a distinction between the two terms, which are not interchangeable Please, clarify and detail. Ref.55 regards the new 2018 ESH-ESC guidelines. These and the 2017 ACC/AHA guidelines are the most popular and followed by doctors. However, in the text there is often reference to 2017 ACC/AHA guidelines and not to ESH/ESC. I recommend to add a table summarizing the main diagnostic procedures and therapeutic options indicated by the two guidelines. This will help the reader to summarize the main indications of current guidelines. MAR must be defined at its first occurrence in the text.

We appreciated the thorough review and have made the change in all sections.

Pseudoresistance has four common etiologies including inappropriate measurement, sub-optimal prescribing (clinician inertia), **white coat hypertension**, and medication nonadherence.

We have added one statement in the third paragraph of Introduction and have cited the ESH/ESC guidelines throughout the manuscript where appropriate.

In 2018, the European Society of Cardiology/European Society of Hypertension (ESC/ESH) published updated guidelines for management of arterial hypertension, and include a section specifically for RH^[3]

We added Figure 1 and Figure 2 for the diagnostic processes and therapeutic options as suggested.

MAR has been defined at its first occurrence in the text.

Aldosterone has emerged as a key player in these mechanisms, making mineralocorticoid receptor antagonists (MRA) that much more important in the treatment for resistant hypertension.

Reviewer ID 00505382

Thank you for your review about resistant hypertension. Article is well written and deals with an interesting topic. Article quality could be improved with one figure summarizing the main therapeutic opportunities. Also, pathogenesis section could be expanded.

We appreciated the thorough review and have added Figure2 to summarize the main therapeutic options as suggested (Please also see one of our responses to the reviewer's comments above).

We have added the section of "Pathogenesis".

PATHOGENESIS

The pathogenesis of RH is not fully understood, but is thought to be a combination of several mechanisms. Part of the difficulty of elucidating pathogenesis is the overlap between RH and

other well-defined pathological states, such as obesity and chronic kidney disease (CKD), so that it is unclear if the mechanisms are unique to RH or merely stemming from the other concomitant conditions. The three most significant underlying processes that have been linked to RH are fluid retention, sympathetic system activation, and arterial stiffness^[4]. Excess fluid retention can be caused by excess salt ingestion, impaired renal natriuresis, as well as increased aldosterone production^[4]. Aldosterone is of particular interest in RH not only because it induces salt retention and thereby fluid retention, but also because of other non-genomic pro-inflammatory effects that can promote a pharmacologically resistant state ^[39,40]. Thus, mineralocorticoid receptor blockade becomes much more important in RH, a fact that has been reflected in the 2017 ACC/AHA guidelines and the 2018 AHA scientific statement, which now include MRAs as one of the front-runner drug classes for RH^[1,2]. In addition to fluid and salt retention, sympathetic system activation is a cornerstone mechanism for RH^[12]. Using norepinephrine regional spillover techniques, researchers have found statistically significant activation of renal sympathetic system in patients with RH when compared to both healthy subjects and those with non-resistant hypertension^[41]. Lastly, arterial stiffness is thought to be another major mechanism. There are numerous underlying processes in the pathogenesis of arterial stiffness, some of which include endothelial dysfunction, salt consumption, and sympathetic signaling^[42]. Several studies have shown that RH patients have higher arterial stiffness than those with controlled hypertension ^[43-45]. Increasing arterial stiffness leads to increasing BP, which in turn increases arterial stiffness, and on and on the vicious cycle goes^[44,45].

We have also added a brief paragraph about pathogenesis of RH in “Introduction”.

The pathogenesis of RH is not fully understood, but is thought to be a combination of fluid retention, sympathetic system activation, and arterial stiffness^[4]. Aldosterone has emerged as a key player in these mechanisms, making mineralocorticoid receptor antagonists (MRA) that much more important in the treatment for RH^[4].

Reviewer ID 00607640

Patients with resistant hypertension comprise a notable and formidable subset of the hypertensive population. In this article the authors reviewed the optimization of antihypertensive medications with device-based therapies in select individuals in helping patients with resistant hypertension achieve blood pressure goals. It is suitable to the Journal and could be helpful in clinic study.

Thank you for your thorough review, encouraging comments and strong support.

Sincerely,

Jian Huang, MD

Clinical Professor of Medicine

Medicine Service, VA Central California Health Care System

Department of Internal Medicine, UCSF-Fresno Medical Education Program

Jian.huang@va.gov