June 24, 2018

Dear Editor(s),

Thank you for considering our manuscript (manuscript number 41219) for publication. Below please find our corresponding responses to the editor's as well as reviewers' comments and suggestions. Any changes or additions are highlighted for easy localization.

Authors' Responses to the Editor' Suggestions:

1. A short running tile of less than 6 words should be provided.

We have add a running title of less than 6 words.

Running Title: Blood Pressure Goals

2. Please provide your detail address. Definite to the street number.

We have added the number and name of the street to the address in Correspondence.

Correspondence to: Jian Huang, MD, Medicine Service, VA Central California Heal Care System and UCSF-Fresno Medical Education Program, 2615 E Clinton Ave, Fresno CA 93703 United States Jian.huang@va.gov Telephone: +1-559-225-6100 Fax: +1-559-241-6484

3. Core tip no more than 100 words.

We have shortened the core tip to 100 words.

Core tip:

The most recent 2017 ACC/AHA guideline redefines hypertension as blood pressure ≥ 130/80 mmHg. It recommends initiation of pharmacotherapy for all adults with blood pressure ≥140/90 mmHg and for patients with blood pressure ≥130/80 mmHg who are ≥ 65, have diabetes, chronic kidney disease, cardiovascular disease, or a 10-year cardiovascular

disease risk of ≥10% . Although optimal blood pressure varies individually, it seems reasonable to recommend a blood pressure goal of <130/80 mmHg, and age/risk-stratified pharmacotherapy threshold. More clinical data are needed to further individualize blood pressure goals for elderly patients and those with certain co-morbidities or multiple cardiovascular risks.

Answering Reviewers:

Reviewer #1

Specific Comments to the Authors

This manuscript discusses the 2017 ACC/AHA guideline with regard to hypertension. As mentioned by the authors, although there is no one-size-fits-all BP target, the ACC/AHA 2017 guideline is simple, inclusive and practical. The title is interesting and the manuscript is well-written. It is suitable for the Journal.

Author Response to Reviewer #1:

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

Reviewer #2

Specific Comments to the Authors and Corresponding Responses by the Authors:

1. Title: It should be modified eg Blood Pressure Goals: Continuing (or Recurrent) Changing Targets. The word moving is unsuitable/inappropriate.

Thank you for your thorough review and suggestions.

We received conflicting suggestions from both reviewers on the title. The first reviewer suggested leaving it as is, while the second recommended that we describe the targets as continuously changing. A "moving target" is a common expression suggesting something is always changing, making it difficult to achieve. Perhaps the second reviewer felt that the phrase "moving target" can imply that targets can be moved arbitrarily, which certainly is not the case. In reconciling the two recommendations, we came up with a new title that we believe still

conveys the message of the challenge that changing guidelines pose: "Blood pressure goals: an ever changing target." We would prefer this title, but are also happy leaving the original title if the editor has a preference. In addition, the original title corresponds well to the last sentence of the manuscript: " It is with more clinical studies designed to address these questions that we hope to finally be able to home in the moving BP target."

2. Abstract: cuttoffs should be written as cut-offs.

Thank you for your thorough review and we have made the corresponding change in the abstract as highlighted.

"Clinical guidelines on hypertension have evolved over the past several decades. Each recommends varying blood pressure cut-offs which define hypertension, determine the thresholds to initiate pharmacotherapy, and guide treatment targets."

Main text:

I. Cuttoffs should be rendered as cut-offs.

Thank you for your thorough review and we have made the corresponding change in the first and third paragraphs of the main text as highlighted .

"These clinical practice guidelines recommend varying BP cut-offs which define hypertension, determine the thresholds to initiate pharmacotherapy and guide treatment targets."

"This was referred to as J-curve phenomenon, since there should be a physiologic nadir for BP cut-offs below which the risk of cardiovascular events increases [13]."

II. In paragraph 3 line 18, beyond should be changed to below.

Thank you for your thorough review and we have made the corresponding change in paragraph 3 of the main text.

"The beneficial effects of BP control can be lost or reversed in certain hypertensive subgroups when BP levels are reduced below physiologic limits."

3. Authors must emphasize the practical difficulty of translating Guidelines into clinical practice. For example, since it is an onerous task to measure BP as it was done in SPRINT, there is evidence that one can extrapolate by adding about 10-12mmHg to the SBP readings in SPRINT trial to get an equivalent, more typical office BP reading (Kjeldsen et al, 2016. *Hypertension* 67:808-812).

Thank you for your thorough review and we have made the corresponding change as highlighted with the suggested citation.

"Like all other studies, SPRINT too had its share of critics. Participants were exclusively non-diabetic. BP readings were based on an average of 3 fully automated and unattended measurements which are lower compared with BP values in most other clinical trials. This makes it very difficult to standardize BP measurements during routine office visits and to translate clinical guidelines into daily practice. Existing evidence suggests an alternative extrapolation by adding approximately 10-12 mm Hg to the SBP achieved in SPRINT trial as an equivalent office BP reading [13]."

Again, although the SPRINT trial may recommend goal SBP of <120mmHg, the physician knows it may be pretty difficult for a patient, particularly a diabetic, to achieve this target vis-a vis intolerable adverse events. The phenomenon is always a J-shaped curve – a BP point where risks increase as BP decreases, and that point may be different for the brain, the heart and the kidney. Thus, optimizing BP for stroke prevention may cause more cardiac, renal or retinal events (Bangalore et al, 2011. *Circulation* 123:2799-2810; Williamson et al, 2016. *JAMA* 315:2673-2682).

Thank you for your thorough review and we have added the citation and corresponding statements as highlighted.

*"*Observational clinical data have suggested an increased risk with excessive BP lowering for certain CV outcomes and within specific populations. The beneficial effects of BP control can be lost or reversed in certain hypertensive subgroups when BP levels are reduced below physiologic limits. This was referred to as J-curve phenomenon, since there should be a physiologic nadir for BP cut-offs below which the risk of cardiovascular events increases [14]. Different co-morbidities may have different nadirs of their J-curve. Thus, optimizing BP for stroke prevention may not reduce risk of cardiac, renal or retinal events and may even increase risk of serious adverse events [15]. Therefore, BP targets ultimately should be a balance between risks and benefits."

4. Authors should mention the fact that there is a current hypothesis indicating that BP control should be based on overall cardiovascular risks rather than on specific BP targets.

Thank you for your thorough review and we have included the citation as highlighted.

"… it does help set pharmacotherapy threshold based on the age, co-morbidities, and CV risk. Individualized CV risk stratification to guide decision making with an emphasis on risk reduction is more reasonable for those with multiple co-morbidities and high CV risk[6]."

We sincerely appreciate the thorough review and constructive suggestions by the editor(s) and the reviewers. Please feel free to contact me if there is any need for further modification of the manuscript. We look forward to our continued collaboration in the future.

Sincerely,

Jian Huang, MD