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March 30, 2022

Robert O. Bonow, MD, MS

Editor-in-Chief, *JAMA Cardiology*

Dear Dr. Bonow,

We respectfully submit our manuscript “Longer term All-Cause and Cardiovascular Mortality with Intensive Blood Pressure Control: A Secondary Analysis of SPRINT“ for consideration of publication in *JAMA Cardiology*. This work describes an observational extension study to the Systolic Blood Pressure Intervention Trial (SPRINT), examining the legacy effect of intensive blood pressure control on cardiovascular and all-cause mortality. Based on linkage to the National Death Index and electronic health records (EHR), we show that the observed benefit for intensive blood pressure control attenuates quickly following the conclusion of the trial, with a quicker attenuation for all-cause versus cardiovascular mortality. Given the recent results from the STEP trial, which did not show an all-cause mortality benefit, this suggests that the all-cause mortality benefit in SPRINT may have not been a causal result of improved blood pressure control, instead driven by more frequent attention and care as part of the protocol for intensive treatment. In addition, the EHR data, despite its inherent limitations, seems to indicate that the attenuation of mortality benefit is not driven by improved blood pressure control in participants originally randomized to a target systolic of <140 mm Hg. Instead, participants randomized to intensive treatment exhibit steadily increasing blood pressure levels after the conclusion of the trial. This observation underscores the sobering reality that achieving cardiovascular benefits from improved control hypertension control is a continual process, and that years of control consistent with current guidelines can be undone over the course of a few years if blood pressure control is not maintained.

We hope that you will find this work suitable for publication in *JAMA Cardiology*. Please feel free to reach out if you have any questions or concerns.

Sincerely,



Nicholas M. Pajewski, Ph.D.

Associate Professor

Department of Biostatistics & Data Science

Division of Public Health Sciences

Director of Statistical Analytics, Center for Health Care Innovation

Wake Forest School of Medicine

EDITORIAL REQUIREMENTS   
  
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Meaning: Key conclusion and implication based on the primary finding(s). Limit to 1 sentence.   
  
Need to draft KEY POINTS, I don’t believe I did this for the initial submission.

Question: What is the long-term effect of intensive blood pressure (BP) control on mortality?

Findings: In secondary analyses of the Systolic BP Intervention Trial, the beneficial effect of intensive BP control on cardiovascular and all-cause mortality attenuated during a 5-year post-trial observational phase. Systolic BP increased by an average of 7 mmHg during the observational phase for participants in the intensive BP control group.

Meaning: Sustaining BP control is critical for managing cardiovascular mortality risk.

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Need to draft Tweet [Byron to draft]

In our secondary analysis of SPRINT, the benefit of intensive BP control attenuated after the trial while systolic BP increased by an average of 7 mmHg for participants in the intensive BP control group. Maintaining BP control is key for managing CVD risk.

ABSTRACT   
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Not sure if anything to change here.

--ACKNOWLEDGMENT SECTION--   
  
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Need to add this (I think)  
  
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????? CONSORT I guess

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Byron to make high quality figures.

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EDITOR'S SPECIFIC COMMENTS:   
  
Thank you for the submission of this important extended follow-up of the SPRINT trial. The editors are very interested in the reporting of these findings.   
  
Please respond to the reviewer comments. If feasible, please provide information on BP medications over time in the EHR cohort, or if not, include as a limitation. To better provide better context to the differences during the trial in SBP between the EHR recorded BP and trial recorded blood pressures please include a brief mention regarding the measurement approach for trial recorded BP.

Add BP measurement approach to the text (Nick to do). Otherwise, add a discussion of these limitations to the discussion.   
  
Some clarification as to whether patients continued to be followed by same clinicians and same health care systems as the during trial phase would be useful or if this information is not available, please note as a limitation.

Add data on availability over time of BPs by site by arm. Might stratify by VA versus not-VA. We don’t know about contact with specific clinicians. Mention as limitation.   
  
Please also considering including the limitation that non-fatal cardiovascular events were not available for analysis.

Add as limitation.   
  
eTable 2 or 3 would be a nice addition to the main manuscript and could change places with either Figure 2 or 4.

Byron, any preference on which figures we swap?

My vote is to move Figure 2 to the supplement.   
  
REVIEWER COMMENTS:   
If the reviewers have opted to reveal their identity, please refrain from contacting them directly.   
  
The following individuals involved in review of your submission have agreed to reveal their identity: Sripal Bangalore (Reviewer #2); Daniel W Jones (Reviewer #3).   
  
  
Reviewer #2 (Remarks to the Author (Required)):   
  
This is the long term follow-up of the SPRINT trial. The study found that the beneficial effect of intensive BP control did not persist long-term. IN addition, there was an increase in BP in patients who were randomized to intensive control. The manuscript is important and emphasizes the lack of a legacy effect and the need to maintain adequate BP control. I have the below comments

Please move eFIgure 2 to the main manuscript as that is one of the main findings of the paper.   
Will do.

Page 8. “Adults randomized to intensive treatment who were <75 years of age, men, non-black, without CKD, or with cognitive function >10th percentile had a lower CVD mortality risk during the trial phase compared to their counterparts randomized to standard treatment”. The interaction P-values for this analysis is not significant for any subgroup. The statement is not supported by the data. Please revise or delete

Check this sentence. This sentence is commenting on the treatment effect but I’m not sure why it went into the subgroups. To clarify, we could say “Adults randomized to intensive versus standard treatment had lower CVD mortality during the trial phase”

The BP results are interesting although the major limitation is the fact that this is only 30% of the entire cohort. The achieved mean SBP at 1 year reported in the trial main publication was 136 vs. 121 mm Hg. The numbers reported at 5 years in the EHR cohort was 139 vs. 133. While sampling may account for some of this, I suspect that this is mainly the difference in AOBP vs. office BP which has been the main debate since SPRINT. I believe this is an important finding and should warrant some discussion at least.

Craft some text around this. Largely can reference our original study (Drawz et al in JAMA Int Med) that looks at concordance in the trial vs the EHR readings.

Was there data available from EHR on the number of antihypertensive agents patients were on and the changes from trial phase to observational phase? Was the creep up of BP based on down titration of meds, decreased compliance or natural history of increased BP with age?   
Admit we don’t have good data on this. Only have meds in VA, and even then, figuring out does it tough. Add paragraph to discussion acknowledging this limitation, and asking the question of what caused the BP rise in the intensive group as an important area for future research.

Please add the average number of BP meds in both groups at the trail phase in the baseline characteristics

Will add to Table 1  
  
  
Reviewer #3 (Remarks to the Author (Required)):   
  
This manuscript reports an analysis of EHR data and the National Death Index. Results demonstrate a lack of persistence of lower BP level control and a lack of persistence of CVD or total mortality benefit. This study is equally important to the SPRINT study in understanding reducing risk of CVD morbidity and mortality from hypertension.   
  
There are a number of questions/issues that should be addressed, If the authors choose to address them separately from this report, some of them could at least be mentioned in the discussion for needed future research.   
  
Were most patients managed in the same practices after the trial as during the trial? If in the same practices, what can be learned about the challenge of having clinicians and patients embrace the truth that lower BP reduces risk? What are the key issues in BP rising as it did after completion of the SPRINT study? What was the role of clinician inertia, patient compliance, the biology of already damaged vascular and renal systems, the BP measurement methods?

May add statistics of contact over time (based on BP readings). Otherwise, we don’t really know the location of the patient’s visits, or who their PCP is. Add limitations paragraph.   
  
Is information available concerning medication changes after SPRINT was stopped? Does this explain the rise in BP?

No. Add as limitation

Does this study result speak to the challenge of maintaining lower BP in already diseased organ systems? Is there an opportunity in the discussion to note the implications of this study in the need for primordial prevention of hypertension and/or the need for earlier and more aggressive intervention in elevated BP and stage 1 hypertension?

Not sure about this one. May need to ask the co-authors for help. Agree.  
  
The time period of the study coincided with the COVID pandemic. Could the results of the study have been biased by the patients lost to follow-up during this time. Is it possible that patients with higher risk and morbidity were more likely to have in the EHR the number of BP readings available for inclusion in this analysis?

Should not be a big issue. 2020 was the last year of follow-up, so only 9 months of the follow-up period overlapped with the COVID lockdowns. Much of what we’re focused on occurred well before COVID. Agreed.