HHS Public Access

Author manuscript

J Am Geriatr Soc. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

J Am Geriatr Soc. 2018 January ; 66(1): 205–206. doi:10.1111/jgs.15146.

Systolic Blood Pressure and Mortality: Role of Reverse Causation

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Using data acquired from the Health and Retirement Study (HRS), the paper by Wu *et al.*[1] joins a host of other observational studies reporting an inverse relationship between elevated systolic blood pressure (SBP) and mortality.[2-4] The inclusion of measures of grip strength and gait speed in this study provides further evidence that functional status may modify this relationship. However, the fundamental limitations inherent in all observational studies that have addressed this relationship compel us to comment. Furthermore, the conclusions derived from two large randomized clinical trials (RCT) of hypertensive treatment in older patient populations, both including frail adults, conflict with this observational study's findings and conclusions.

The Hypertension in the Very Elderly Trial (HYVET)[5] and Systolic Blood Pressure Intervention Trial (SPRINT)[6] reached similar conclusions regarding the mortality benefits identified in older hypertensive patients – aged 80 years and older for HYVET and aged 75 years and older for SPRINT – actively treated to a target SBP of <150 mm Hg in HYVET (relative to placebo treatment) or <120 mm Hg in SPRINT (relative to a standard treatment target of <140 mm Hg). The significant 21% decrease in overall mortality in HYVET and 33% decrease in SPRINT participants 75 years or older led to recommendations to end both studies earlier than planned. Both trials included sizable proportions of frail participants – 23.1% of HYVET participants and 16.3% of SPRINT participants had a frailty index score ≥ 0.25; and 29.4% of SPRINT participants exhibited slow gait speed (< 0.8 m/s). Importantly, the treatment benefits for both trials' primary outcomes and overall mortality were evident even amongst frail participants.[7,8]

What then accounts for the stark contrast between the mortality benefit identified in older, frail hypertensive patients in RCTs and the inverse relationship found in observational

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Author Contributions: All aspects of this paper's concept and design, analysis and interpretation of data manuscript and writing and revision were carried out by its three authors.

studies? Among several differences in study design, the most important is the inherent limitation of reverse causation in observational studies. A recent observational cohort study that tracked SBP trajectories for the five years prior to death among 144,403 participants aged 80 years and over provides a compelling example of this limitation.[9] Consistent with Wu *et al.* and other observational studies, mortality rates were greatest in those with SBP < 110 mm Hg. However, there was a decline in the SBP trajectory noted in the last three months of life in patients undergoing treatment for hypertension as well as in those not receiving antihypertensive treatment. This terminal decline in SBP provided the best explanation for the observed association between low SBP and mortality in this, as well as likely other observational studies. Although Wu *et al.* attempted to minimize reverse causation by excluding individuals in the HRS who died in the first two years of follow-up, this approach fails to fully reduce residual confounding.[10] Moreover, the HRS population is quite heterogeneous and includes persons with and without hypertension.

It must be recognized that individuals who have low SBP as a consequence of actively and appropriately managed antihypertensive therapy titrated to a specific SBP target cannot be compared to those who happen to have a low SBP measured in an observational study. The mortality benefit in the first group – even for those with impaired gait speed and frailty – has been convincingly demonstrated. By contrast, the onset of low SBP observed in a frail, older adult either with or without hypertension, should prompt concern as this may be a harbinger of a pre-terminal decline.

We applaud Wu et al.'s call to “further advance precision medicine.” We however contend that a patient centric, benefit-based approach to determining a patient's systolic BP treatment goal that is founded on rigorous evidence derived from the available RCT studies should inform this patient care decision.[11] We fully recognize that due to the exclusion criteria required for RCTs the benefits observed in HYVET and SPRINT cannot be generalized to all older hypertensive patients.[12] That said, there are an estimated 5.8 million individuals in the United States aged 75 and older with hypertension who meet SPRINT entry criteria (64% of the 9.1 million with hypertension).[13] Further, projections from National Health and Nutrition Examination Survey data suggest that the mortality benefit observed with intensive therapy in SPRINT would translate to preventing 67,300 (95% CI, 58,600-77,200) deaths per year among the SPRINT-eligible population ≥ 75 years of age.[14] We conclude that treatments to achieve a lower SBP target are indicated as this confers significant benefits – inclusive of mortality – even among those with frailty and/or impaired gait speed. The findings from Wu *et al.* should not deter clinicians from considering this treatment approach for eligible patients.

Acknowledgments

Funding Sources: This work was supported in part through funding from R01 HL 10741 (MAS), the VA Salt Lake City GRECC, (MAS) and HHSN268200900040C (NMP), and P30 AG21332 for the Wake Forest School of Medicine Claude D. Pepper Older Americans Independence Center(JDW).

Dr. Supiano's grant support is included in the Funding Sources. He is a member of the Boards of the American Geriatrics Society and the Association of Directors of Academic Geriatric Programs and the JAGS Editorial Board. Grant support for Drs. Pajewski and Williamson are included in the Funding Sources.

Sponsor's Role: The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, the U.S. Department of Veterans Affairs, or the United States Government. The views expressed in this paper are those of the authors and do not necessarily represent the official position of the National Institutes of Health (NIH), the Department of Veterans Affairs, the U.S. Government, or the SPRINT Research Group.

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