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Systolic blood pressure goals to reduce cardiovascular disease among older adults

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Abstract

The 2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8) was recently published. This guideline recommended that older adults (≥ 60 years) without diabetes or chronic kidney disease with systolic blood pressure (SBP) ≥ 150 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg be initiated on antihypertensive medication with a treatment goal SBP/DBP <150/90 mmHg. In contrast, previous JNC guidelines recommended treatment for these individuals be initiated at SBP/DBP ≥ 140/90 mmHg with goal SBP/DBP <140/90 mmHg. In this article, we review randomized trials of antihypertensive medication and observational data on SBP and DBP with cardiovascular outcomes among older adults, possible explanations underlying the different findings from these randomized trials and observational studies, and contemporary antihypertensive treatment patterns among older U.S. adults. In closing, we highlight future research needs related to hypertension and outcomes among older adults.

High blood pressure is one of the most important risk factors for cardiovascular disease (CVD), the leading cause of mortality among U.S. adults.^{1,2} The U.S. population is aging and it is projected that the number of U.S. adults ≥ 60 years of age will double by 2050.³ The incidence and prevalence of hypertension increase with age.^{4, 5} Therefore, the impact of high blood pressure among older adults on morbidity and mortality is expected to grow over the coming decades.

For several decades, U.S. adults without diabetes or chronic kidney disease with systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg were recommended the initiation of antihypertensive medication.^{6–8} Additionally, once on antihypertensive medication, healthcare providers were recommended to treat these patients to achieve a SBP < 140 mm Hg and a DBP < 90 mm Hg. Based on evidence from randomized controlled trials, the 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth

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Joint National Committee (JNC 8) recently recommended a higher SBP threshold (150 mmHg) for treatment initiation and goal attainment for adults ≥ 60 years of age without diabetes or chronic kidney disease.⁹ While randomized controlled trials are considered the gold standard of evidence for making treatment decisions, they often include select populations with limited generalizability.¹⁰ This is particularly relevant for older adults, a population comprised of individuals with a broad distribution of health status as well as a high prevalence of frailty. Therefore, high quality observational data may complement randomized trials for understanding the benefits and risks of antihypertensive treatment among older adults and generating new hypotheses.

In this review, first, we provide context for the 2014 Guideline recommendation for a higher SBP goal. We provide a brief overview of the new high blood pressure guideline as they relate to SBP and DBP goals for older U.S. adults. Second, we provide an overview of findings from randomized controlled trials on the benefits and risks of antihypertensive medication among older adults. Additionally, we will discuss two ongoing randomized trials testing different treatment goals for older adults. Third, we review observational studies on the association between SBP and outcomes among older adults. Fourth, we reconcile the findings from the randomized trials and observational studies by reviewing data on the impact frailty may have on the association between SBP and DBP with outcomes. Finally, to provide context for the new treatment goals, we review contemporary treatment patterns among older U.S. adults with hypertension.

Guideline recommendations

The 2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to JNC 8 were published online on December 18, 2013.⁹ These guidelines focused on three questions related to BP management and published 9 recommendations. Of relevance to older adults, this guideline recommended for the general population ≥ 60 years of age that antihypertensive treatment be initiated at SBP ≥ 150 mmHg or DBP ≥ 90mmHg and treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg (**Table 1**). Lower recommendations were made for individuals with diabetes or chronic kidney disease; discussion of these populations is beyond the scope of this article. The JNC 8 panel members found strong evidence from randomized controlled trials on the benefits of older adults achieving a SBP < 150 mm Hg on antihypertensive medications. However, there was little evidence from randomized controlled trials supporting the benefit of achieving SBP < 140 mm Hg on outcomes among older adults taking antihypertensive medications. The panel members acknowledged a lack of consensus regarding the appropriate SBP target (<140 mm Hg or < 150 mm Hg) for adults ≥ 60 years of age.

The 2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults is not the first guideline to suggest a higher SBP treatment goal for older adults (**Table 1**). The 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines for the management of hypertension emphasized that the available randomized trials of antihypertensive treatment in the elderly showed a reduction in CVD events through lowering of BP; however the average achieved SBP in trials was never <140 mmHg.¹¹ Therefore, they suggested that elderly individuals with hypertension should be treated to

SBP levels of 140 to 149 mmHg. In “fit” persons less than 80 years of age, a SBP goal <140 mmHg may be considered, whereas in frail elderly individuals, they recommended SBP goals should be adapted to individual tolerability. Also, the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) 2011 Expert Consensus Document on Hypertension in the Elderly guidelines suggested that a target SBP/DBP <140/90 mmHg in persons aged 65-79 years with a target SBP of 140-145 mmHg, if tolerated, in persons aged 80 years and older.¹² The authors of each of these guidelines have emphasized that very limited data exist to make definitive recommendations on target blood pressure levels in the elderly.

Randomized trial evidence in the elderly – antihypertensive treatment and SBP goals

A number of randomized controlled trials have evaluated the risks and benefits of antihypertensive medications in older adults (**Table 2**).¹³⁻¹⁸ Some of these trials evaluated the benefits of antihypertensive treatment and certain drug classes on reducing CVD risk and delaying mortality while others have evaluated the benefits and risks of achieving SBP goals. One of the earlier studies, the Systolic Hypertension in the Elderly Program (SHEP), included 4,736 participants ≥ 60 years of age with SBP ≥ 160 mm Hg who were randomized to chlorthalidone to achieve a 20 mm Hg reduction in SBP to < 160 mm Hg or placebo.¹³ Over a mean of 4.5 years of follow-up, the reduction in the incidence of stroke, nonfatal myocardial infarction plus coronary death and major CVD events associated with treatment was 36%, 27% and 32%, respectively. SHEP has been followed by several other randomized trials including the Systolic Hypertension in Europe (Syst-Eur) which demonstrated the benefits of calcium channel blockers among adults ≥ 60 years of age and the HYpertension in the Very Elderly Trial (HYVET) which demonstrated the benefits of antihypertensive treatment for individuals ≥ 80 years of age and SBP ≥ 160 mm Hg.^{14, 15} Although these studies demonstrated clear benefits of antihypertensive treatment in older adults, the goal SBP in each of these studies was < 160 mm Hg or < 150 mm Hg and the benefits of lower SBP goals were not tested.

Three recent randomized trials have compared different SBP goals on CVD outcomes among elderly patients. In the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS), the effect of SBP reduction to < 140 mmHg (strict control) versus 140 to 159 mmHg (mild-treatment) on the composite outcome of CVD and renal failure was determined in 4,418 individuals 65 to 84 years of age with SBP ≥ 160 mm Hg at baseline.¹⁸ The mean SBP/DBP at the end of follow-up was 136/75 mm Hg among participants in the strict control group and 146/78 mm Hg in the mild-treatment group. However, differences in outcomes over 2 years of follow-up were not statistically significant; 9% of participants in the strict treatment group and 8% in the mild-treatment group experienced the primary outcome. Differences in mortality across randomization arms in JATOS were also small and not statistically significant. Similarly, in the VALsartan in Elderly Isolated Systolic Hypertension (VALISH) study, no differences in cardiovascular morbidity and mortality were present between participants randomized to SBP < 140 mm Hg versus 140 – 149 mm Hg.¹⁷ VALISH enrolled 3,079 participants 70 to 84 years of age

with SBP 160 mm Hg at baseline. After 3 years of follow-up, mean SBP/DBP was 137/75 mm Hg and 142/77 mm Hg in the strict control and moderate control groups, respectively. The incidence of the primary outcome, composite of sudden death, fatal or nonfatal stroke, fatal or non-fatal myocardial infarction, heart failure death, other CVD death, unplanned hospitalization for CVD and renal dysfunction was 10.6 and 12.0 per 1,000 person-years in the strict and moderate control groups, respectively ($p=0.38$). None of the individual components of the primary outcome were statistically significantly different across randomization arms (all p values > 0.2). The events rates in both JASTOS and VALISH were lower than planned, potentially resulting in inadequate statistical power to detect benefits of the lower SBP goals. In the Studio Italiano Sugli Cardiovascolari del Controllo della Pressione Arteriosa Sistolica (CARDIO-SIS) trial, 1,111 patients 55 years of age (mean age 67 years) without diabetes and with SBP 150 mm Hg, were randomized to SBP < 130 mm Hg (tight control) or < 140 mm Hg (moderate control).¹⁶ After 2 years of follow-up, 27.3% and 72.2% of participants in the moderate and tight SBP control groups, respectively, had achieved SBP < 130 mm Hg. At 2 years, 17.0% and 11.4% of those in the moderate and tight control groups, respectively, had the primary outcome of left ventricular hypertrophy ($p=0.013$). The secondary endpoint was a composite of CVD and renal disease and occurred in 9.4% in the moderate SBP control group and 4.8% in the tight control group ($p=0.003$).

Despite the tremendous knowledge gained from each of these studies, the optimal on-treatment SBP goal for older adults remains unknown. Prior randomized trials have been limited by short follow-up, limited sample size, and selected populations. Additionally, studies have not assessed frailty. Many studies may have excluded frail individuals, resulting in limited generalizability. Two large ongoing studies (Systolic Blood Pressure Intervention Trial [SPRINT] and the Stroke in Hypertension Optimal Treatment trial of the European Society of Hypertension and the Chinese Hypertension League [ESH-CHL-SHOT]) may provide important new information for older adults.^{19, 20} SPRINT, which was launched in 2010 by the U.S. National Institute of Health, is designed to determine whether maintaining SBP/DBP $< 120/80$ mm Hg versus $< 140/90$ mm Hg will reduce the risk of CVD and kidney disease, as well as age-related cognitive decline in 9,250 adults 55 years of age. Age 75 years is an *a priori* defined sub-group in SPRINT. ESH-CHL-SHOT is a prospective, randomized trial comparing three SBP targets (< 125 , $125 - 134$ and $135 - 144$ mm Hg). The trial is being conducted in 7,500 adults 65 years of age with hypertension from Europe ($n=2500$) and China ($n=5000$). Participants will be followed for the primary outcome of stroke and secondary outcomes including a major cardiovascular event and cognitive decline. It is anticipated that both trials will be completed in 2018. SPRINT and ESHCHL-SHOT may help identify the optimal SBP goal for the elderly with hypertension.

Observational data on BP and outcomes among older adults

Epidemiology studies have consistently found weaker associations between established risk factors from the general population when studied in older adults.²¹ The association between SBP and CVD and all-cause mortality is no exception. In 2002, Lewington and colleagues published data from over one million adults from 61 studies on the associations between SBP and DBP and mortality from stroke and CHD by age.²² The associations between both

SBP and DBP and mortality from stroke, CHD and other vascular disease were graded and continuous with the lowest risk at SBP of 115 mm Hg and DBP of 75 mm Hg (lower BP levels were not reported) and the highest risk at SBP of 175 mm Hg and DBP of 105 mm Hg (higher levels were not reported). However, these associations were weaker at older age (Figure 1).

Not every study has found an association between higher SBP and DBP and increased risk for outcomes among older adults. Using data from the Established Populations for Epidemiologic Studies of the Elderly, Satish and colleagues evaluated the association between SBP and DBP and mortality over 6 years of follow-up among 12,802 community dwelling adults 65-84 and 85 years of age.²³ Among men and women 65 – 84 years of age, higher SBP was associated with an increased risk for mortality. The multivariable adjusted hazard ratios for mortality associated with 10 mm Hg higher SBP was 1.04 (95% CI: 1.01 – 1.07) for men and 1.10 (95% CI: 1.07 – 1.13) for women. However, higher SBP was associated with a lower risk for death among men 85 years of age and no association was present for women in this age group (hazard ratio each 10 mm Hg higher SBP of 0.92; 95% CI: 0.86 – 0.99 for men and 1.00; 95% CI: 0.95 – 1.05 for women). For participants 65 – 84 and 85 years of age, higher DBP was associated with a lower mortality risk for men but no association was present for women. Furthermore, some studies have reported an increased CVD risk at very low SBP levels among older adults.^{24, 25} The weaker, and possibly harmful, association between lower SBP and outcomes at older age has generated hypotheses regarding whether lower treatment targets for older adults with hypertension should be achieved. Given new randomized trial data are not expected until 2018, observational data may be a useful source to better understand the association of SBP treatment targets with CVD outcomes.

Reconciling differences between clinical trials and observational studies

An important aspect of interpreting observational studies in older populations is heterogeneity in health status. However, this is often not taken into account in guidelines. As noted over 20 years ago by Harris, among older adults normal SBP may be found in (1) someone with life-long normal blood pressure, (2) someone whose blood pressure has shown a progressive rise through their adult life but remains in the “normal” range, or (3) someone with a history of hypertension and heart failure who has normal SBP due to compromised cardiac function.²⁶ CVD risk may be very different in these groups and the heterogeneity in health status may distort the true SBP – CVD association among older adults.

Additionally, the prevalence of frailty increases with age and this phenotype has been associated with adverse health outcomes including hospitalization and mortality.²⁷ Frailty is a syndrome of decreased physiologic reserve across multiple organ systems that results in vulnerability to adverse outcomes.²⁸ The frailty phenotype has been operationalized as 3 of the following: shrinking, weakness, slowness, exhaustion, and low activity.²⁸ Frail patients are often excluded from randomized trials but included in observational research of older adults.

Prior research suggests the association between SBP and mortality differs by frailty status. Specifically, a recent analysis of the U.S. National Health and Nutrition Examination Survey (NHANES) Mortality Follow-up Study by Odden and colleagues evaluated the association between SBP and mortality among U.S. adults ≥ 65 years of age by walking speed, a marker of frailty status.²⁹ This study included 2,340 participants who participated in the 1999-2000 or 2001-2002 NHANES cycles. Participants were asked to complete a 6 meter walk test during the NHANES clinic examination and were categorized into three groups (faster walkers [≥ 0.8 meters per second], slower walkers [<0.8 meters per second] and did not complete the walk test). Additionally, SBP and DBP were measured three or four times by a physician following a standardized protocol. In this sample, 56% of participants were fast walkers, 34% were slow walkers, and 10% did not complete the walk test. Over up to 8 years of follow-up, 589 participants died. After adjustment for NHANES survey year, age, gender, race, education, smoking, total cholesterol, and having a history of heart disease, heart failure or stroke, the association between SBP and mortality differed by walking speed. For example, the adjusted hazard ratio for all-cause mortality associated with SBP ≥ 140 mm Hg versus < 140 mm Hg was 1.35 (95% CI: 1.03 – 1.77) for fast walkers, 1.12 (95% CI: 0.87 – 1.45) for slow walkers, and 0.38 (95% CI: 0.23 – 0.62) for participants who did not complete the walk test (p-value for interaction= 0.001). The adjusted hazard ratio for all-cause mortality associated with DBP ≥ 90 mm Hg versus < 90 mm Hg was 0.94 (95% CI 0.38 – 2.28), 0.75 (95% CI: 0.32 – 1.75) and 0.10 (95% CI: 0.01 – 0.81) for fast walkers, slow walkers, and those who did not complete the walk test, respectively (p-value for interaction = 0.21). This study highlights the potential differences in the appropriate SBP treatment targets that may exist for many older adults and the limited generalizability of randomized trials of antihypertensive medication among older adults.

Antihypertensive treatment and SBP and DBP levels among older U.S. adults in the general population

Data on mean SBP and DBP, the prevalence of hypertension and blood pressure treatment patterns among older U.S. adults are important for understanding how prior guidelines, recent trials and observational studies have been translated into clinical practice. Analyses of data from serial NHANES provide information on SBP and DBP levels among older U.S. adults. Guo and colleagues found the mean SBP declined from 141 mm Hg in 1999-2000 to 131 mm Hg in 2009-2010 (p-value <0.001) among U.S. adults ≥ 60 years of age.³⁰ Additionally, mean DBP declined from 71 mm Hg to 66 mm Hg over this time period. The prevalence of hypertension did not change substantially over time and was 66.7% in 2009-2010. Also, in 2009-2010, 84.0% of those with hypertension were aware of their diagnosis, 85.3% of those aware were treated and 54.9% of all people with hypertension and 64.4% of those being treated had an SBP/DBP $< 140/90$ mm Hg.

More recent data have been analyzed for very old U.S. adults. Using serial national cross-sectional samples of U.S. adults ≥ 80 years of age, Bromfield and colleagues studied mean SBP and DBP levels and the prevalence, awareness, treatment and control of hypertension.³¹ Among U.S. adults 80 years of age and older, mean SBP was 147 mm Hg in 1988-1994, 148 mm Hg in 1999-2004 and 140 mm Hg in 2005-2010 (p-trend <0.001). Mean

DBP decreased from 70 mm Hg in 1988-1994 to 61 mm Hg in 1999-2004 and was 59 mm Hg in 2005-2010 (p-trend <0.001). Overall, the prevalence of hypertension was stable over the time periods studied and was 76.5% in 2005-2010. Between 1988-1994 and 2005-2010, awareness of hypertension increased from 59.3% to 79.4%, treatment among those aware increased from 33.7% to 57.4% and SBP/DBP < 140/90 mm Hg increased from 14.8% to 39.8% among those with hypertension and from 30.4% to 53.1% among those taking antihypertensive medication. It is important to note that among those with hypertension, the mean number of antihypertensive medication classes being taken doubled between 1988-1994 and 2005-2010. Additionally, the proportion of U.S. adults 80 years and older taking 3 classes of antihypertensive medication increased from 7.0% to 30.9% (**Figure 2**). Given the uncertainty surrounding the optimal SBP target for older adults, the benefits and risks of antihypertensive medication polypharmacy among older adults needs to be investigated in future studies.

Conclusion

Several randomized trials have demonstrated clear benefits of antihypertensive medication among older adults with SBP $\geq$ 160 mm Hg. However, the 2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the JNC8 did not find evidence from randomized trials supporting a SBP treatment goal < 140 mm Hg for older adults without diabetes or chronic kidney disease. This guideline highlights several pressing research questions that will provide important new knowledge to help guide the management of hypertension among older adults. First, the optimal SBP treatment target for older adults remains a critical knowledge gap. Whether treating SBP to < 140 mm Hg, or perhaps even lower, is appropriate for older adults needs to be determined. Second, the effect of health status and frailty has on SBP treatment targets warrants future investigation. Given the heterogeneity of health status for older adults, how aggressive SBP should be lowered may vary and a single SBP goal may not be appropriate for all older adults. Third, the population- and patient-level benefit and risk of antihypertensive medication polypharmacy with respect to the potential harms of low SBP in the elderly should be determined. A high percentage of older adults are taking multiple classes of antihypertensive medication and the real-world implications of these treatment patterns may inform future trials and guidelines. In conclusion, although substantial progress has been made in the treatment and control of hypertension among older adults, it remains an important public health challenge as the U.S. population continues to age.

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A: Usual systolic blood pressure (≥ 115 mm Hg) **B: Usual diastolic blood pressure (≥ 75 mm Hg)** **Figure 1.**

Age-specific hazard ratios for stroke, coronary heart disease and other vascular disease mortality associated with 20 mm Hg lower systolic blood pressure (left panel) and 10 mm Hg lower diastolic blood pressure (right panel).

Figure 2.

Number of antihypertensive medication classes being taken by US adults 80 years of age with hypertension in 1988-1994, 1999-2004, and 2005-2010.

Table 1
Treatment recommendations for older adults in published guidelines and scientific statements.

Organization	Publication date	Definition of elderly	SBP/DBP treatment goal	
			General recommendation	Exceptions
JNC 8 [†]	2014	60 years	SBP/DBP <150/90 mm Hg	SBP/DBP <140/90 mm Hg for those with chronic kidney disease or diabetes
ESH/ESC ^{††}	2013	80 years	SBP 140 – 149 mmHg	SBP <140 mm Hg if well tolerated. For frail individuals, treatment decision left to physician.
ACCF/AHA ^{†††}	2011	65 – 79 years	SBP/DBP <140/90 mm Hg	SBP/DBP 80 years treated to 140- 145/<90 mm Hg if well tolerated

[†] 2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC8).⁹
^{††} 2013 ESH/ESC Guidelines for the management of arterial hypertension.¹¹
^{†††} ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly: A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus documents.¹²

Table 2

Randomized controlled trials of antihypertensive medication among older adults.

Trial	Publication date	Sample size	Age range, years	Follow-up duration	Randomization arms	Primary outcome (results)	Secondary outcome (results)	Limitations
SHEP	1991	4,736	60	Mean: 4.5 years	SBP reduction by 20 mm Hg to <160 mm Hg vs. placebo	Stroke (Lower risk with treatment)	CVD and CHD, all-cause mortality (Lower risk with treatment)	Lower SBP targets were not evaluated
Syst-Eur	1997	4,695	60	Median: 2 years	Treatment to reduce SBP by 20 mm Hg to <150 mm Hg vs. placebo	Stroke (Lower risk with treatment)	Death, myocardial infarction, heart failure, dissecting aortic aneurysm, renal insufficiency (Lower risk but not statistically significant)	Lower SBP targets were not evaluated
HYVET	2008	3,845	80	Median: 1.8 years	Treatment to reduce SBP/DBP to <150/80 mm Hg vs. placebo	Stroke (Lower risk with treatment but not significant, p=0.06)	Death, death from CVD, death from cardiac causes, stroke death (Lower risk for all-cause and stroke death, benefits for other outcomes not statistically significant)	Lower SBP targets were not evaluated Healthier population than general 80 years
JATOS	2008	4,418	70 to 84	3.07	SBP < 140 mm Hg vs. 140 - 159mmHg	Composite CVD (No benefit of SBP < 140 mmHg)	Death, all-cause and cause-specific (No benefit of SBP < 140 mmHg)	Trial not adequately powered
CARDIO -SIS	2009	1,111	>55	Median: 2 years	SBP< 130 mm Hg vs. < 140 mm Hg	Left ventricular hypertrophy (Lower SBP associated with lower risk)	Composite CVD (Lower SBP associated with lower risk)	Surrogate primary outcome, Included participants < 60 years old
VALISH	2010	3,260	65–85	Up to 2 years	SBP < 140 mm Hg vs. 140 - 149mmHg	Composite CVD (No benefit of SBP < 140 mmHg)	Individual components of primary outcome (No benefit of SBP < 140 mmHg)	Trial not adequately powered

CVD - cardiovascular disease