

Evidence Supporting a Systolic Blood Pressure Goal of Less Than 150 mm Hg in Patients Aged 60 Years or Older: The Minority View

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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)” recommends several major changes from the JNC 7 report (1, 2). The 2014 guideline is based on a systematic review of randomized, controlled trials (RCTs) by a multidisciplinary panel using a process informed by Institute of Medicine recommendations for guideline development (3). Although there was almost unanimous agreement on nearly all recommendations, a minority of the panel (the authors of this commentary) disagreed with the recommendation to increase the target systolic blood pressure (SBP) from 140 to 150 mm Hg in persons aged 60 years or older without diabetes mellitus (DM) or chronic kidney disease (CKD). This target guides both the initiation of therapy and treatment goals. Although this issue has major clinical and public health implications, the guideline only briefly summarized the concerns underlying the minority opinion to maintain the target of less than 140 mm Hg. The Institute of Medicine recommendation for guideline development encourages guidelines to provide “a description and explanation of any differences of opinion regarding the recommendation” (3). This article summarizes the evidence and rationale underlying the minority opinion to maintain the SBP target of 140 mm Hg or lower in persons aged 60 years or older until there is greater certainty of the risks and benefits of a higher target.

First, increasing the target will probably reduce the intensity of antihypertensive treatment in a large population at high risk for cardiovascular disease (CVD) (Table 1). The higher SBP goal would apply to some of the groups at highest cardiovascular risk, such as African Americans, hypertensive patients with multiple CVD risk factors other than DM or CKD, and those with clinical CVD. Second, the evidence supporting increasing the SBP target from 140 to 150 mm Hg in persons aged 60 years or older was insufficient and inconsistent with the evidence supporting the panel’s recommendations for an SBP target of less than 140 mm Hg in persons younger than 60 years and those aged 60 years or older with DM or CKD. Third, the higher SBP goal in individuals aged 60 years or older may reverse the decades-long decline in CVD, especially stroke mortality (4). In the absence of definitive evidence defining the optimum SBP target, observational studies and RCT data that the panel did not systematically review more strongly support the SBP goal of less than 140 mm Hg, especially in high-risk individuals. Other recent guideline groups reviewing similar evidence have recommended

a goal of less than 140 mm Hg, particularly in persons aged 80 years or younger (5–9).

PERSONS AGED 60 YEARS OR OLDER WITH HYPERTENSION AND SBP CONTROLLED TO 140 MM Hg OR LOWER

More than half of the 72 million persons with hypertension in the United States are aged 60 years or older (10, 11). Among these individuals, the 2014 guideline recommends the SBP goal of 140 mm Hg or lower only for those with DM and those younger than 70 years with CKD (2). Although the prevalence of hypertension in this age group (65% to 67%) did not change between 1999 and 2010, the percentage with adequate blood pressure control increased from 27.4% (1999–2000) to 50.5% (2011–2012), with 82.2% now receiving antihypertensive medications (10, 12). Data from NHANES (National Health and Nutrition Examination Survey) from 2001 to 2008 show that among treated and untreated hypertensive adults aged 60 years or older, median SBPs were 136 mm Hg and 152 mm Hg, respectively (13), and SBPs have been decreasing in this age group over the past 5 decades (Figure) (4). Thus, a target of less than 150 mm Hg would likely increase blood pressures in the treated hypertensive population and would suggest that nearly half of the untreated hypertensive patients in this age range should remain untreated. The large population at high risk for CVD, with most currently at an SBP of 140 mm Hg or lower, creates concern that a higher SBP target will adversely affect public health.

HIGH RISK IN PERSONS WITH THE HIGHER GOAL

Age substantially increases risk for cardiovascular events (Table 1), so differences in cardiovascular risk do not justify different targets for patients older and younger than 60 years. The risk range for white and African American men aged 60 years is 9% to 30%, depending on risk factor profile. For men of both ethnicities who are aged 70 years or older and have SBP controlled to 140 mm Hg, even without clinical CVD or DM, the 10-year risk exceeds 20% (14). Thus, on the basis of absolute risk, using an age threshold of 60 years to define eligibility for less aggressive treatment lacks consistency. Persons aged 60 to 79 years are at higher risk than those who are younger, even if the younger persons have DM.

Table 1. U.S. Cardiovascular Disease Death Rates for Persons Younger and Older Than 65 y

Condition (Underlying Cause of Death)	Age, y	Annual Average Death Rate, deaths per 100 000 persons		Average Annual Change in Age-Adjusted Death Rate, %*	
		1989–1998	1999–2010	1989–1998	1999–2010
Coronary heart disease	<65	36	30	–3.6	–3.4
Coronary heart disease	≥65	1312	1038	–2.7	–5.6
Stroke	<65	9	7	–1.3	–2.3
Stroke	≥65	436	356	–0.9	–5.3

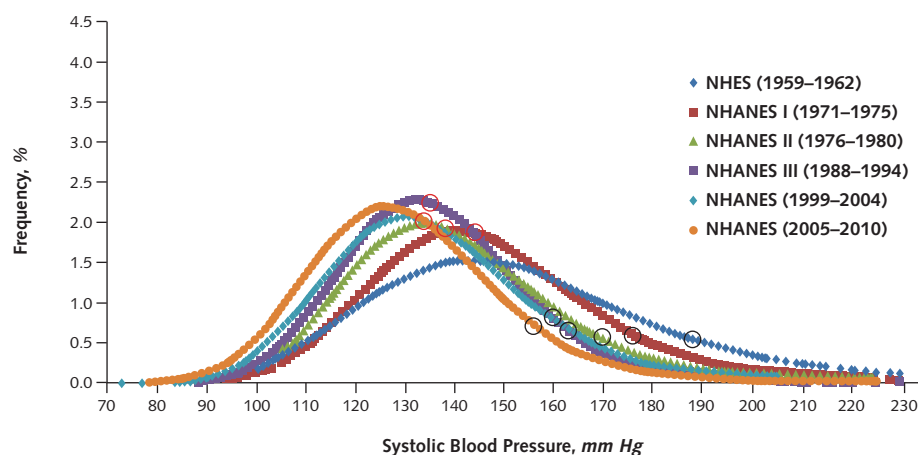
* Age-adjusted to the 2000 U.S. standard population. Analysis is from the Centers for Disease Control and Prevention WONDER system by Dr. Michael Mussolino of the Epidemiology Branch of the National Heart, Lung, and Blood Institute.

INSUFFICIENT EVIDENCE FOR DIFFERENTIAL HYPERTENSION TREATMENT BENEFIT FOR PATIENTS OLDER AND YOUNGER THAN 60 YEARS

The 2014 guideline panel failed to identify evidence of differential benefits or harms of treatment using an SBP goal of 140 mm Hg with an age threshold of 60 years. There is little RCT evidence of risk or benefit in treating persons younger than 60 years to this target, except in those with diastolic hypertension. The guideline indicates that no qualifying evidence was found comparing an SBP less than 140 mm Hg to any other SBP goal for persons younger than 60 years (2). However, in persons aged 60 years or older, the SHEP (Systolic Hypertension in the Elderly Program) trial showed benefit of treating hypertension to an SBP goal between 140 and 145 mm Hg (Table 2) (15). HYVET (Hypertension in the Very Elderly Trial) found a benefit of an SBP target of less than 150 mm Hg

on health outcomes, including mortality in persons aged 80 years or older (16). Patients in the HYVET treatment group achieved an SBP of 144 mm Hg at 2 years compared with 159 mm Hg in the control group, and blood pressures continued to decrease in both groups until the end of the trial. Therefore, HYVET and the SHEP trial provide evidence that reducing SBP to around 140 mm Hg has substantial benefit without major harm in older persons. Thus, the best evidence available for an SBP target around 140 mm Hg, which meets the guideline RCT criteria, is in persons older than 60 years. The lack of benefit seen in 2 Japanese trials in older individuals (JATOS [Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients] [17] and the VALISH [Valsartan in Elderly Isolated Systolic Hypertension] trial [18]) was cited by some to rationalize the higher SBP target, but these trials were underpowered (Table 2). The SHEP trial and HYVET together reported 365 strokes and more than 285 coronary heart disease events, whereas JATOS and the VALISH trial only had a combined total of 125 strokes and 67 coronary heart disease events. In addition, the much larger FEVER (Felodipine Event Reduction) trial (19) did not meet criteria for inclusion in the panel's deliberation (Table 2). This trial, which was conducted in a Chinese population (age range, 50 to 79 years; mean age, 62 years), reported a significant 27% reduction in its primary outcome, as well as significant reductions in all CVD, total mortality, coronary heart disease, and heart failure in patients treated to an SBP of 137 mm Hg with a thiazide diuretic–calcium-channel blocker combination versus 143 mm Hg with a thiazide diuretic plus placebo (19).

In addition, generalizability of the Japanese trials to other populations of patients older than 60 years, such as

Figure. Smoothed weighted frequency distribution, median, and 90th percentile of systolic blood pressure for persons aged 60 to 74 y: United States, 1959 to 2010.

NHANES = National Health and Nutrition Examination Survey; NHES = National Health Examination Survey. (Reproduced from Lackland and colleagues [4].)

Table 2. Trials Comparing Different Systolic Blood Pressure Thresholds

Trial (Reference)	Participants, <i>n</i>	Duration, <i>y</i>	Total End Points, <i>n</i>	Primary Outcome	Coronary Heart Disease	Composite CVD	Strokes	Heart Failure
<150 mm Hg vs. higher goal								
HYVET (16)*	3845	2.1	Any CVD: 331 Strokes: 120 Deaths: 431	HR: 0.61 <i>P</i> = 0.046	HR: 0.72 (95% CI, 0.30–1.70) <i>P</i> = 0.45	–	HR: 0.61 <i>P</i> = 0.046	HR: 0.36 <i>P</i> < 0.001
SHEP (15)	4736	4.5	Any CVD: 703 Strokes: 245 Deaths: 455	RR: 0.64 (CI, 0.50–0.82) <i>P</i> = 0.0003	RR: 0.73 (CI, 0.57–0.94)	–	RR: 0.64 (CI, 0.50–0.82) <i>P</i> = 0.0003	RR: 0.51 (CI, 0.37–0.71) <i>P</i> < 0.001
<140 mm Hg vs. higher goal								
JATOS (17)	4418	2	CVD or renal event: 172 Deaths: 17	Rate per 1000 PYs: 22.6 vs. 22.7 <i>P</i> = 0.99	Rate per 1000 PYs: 6.8 vs. 7.4 <i>P</i> = 0.78	Rate per 1000 PYs: 22.6 vs. 22.7 <i>P</i> = 0.99	Rate per 1000 PYs: 13.7 vs. 12.9 <i>P</i> = 0.77	8 vs. 7 events
VALISH (18)	3260	2.85	CVD or renal event: 99 Deaths: 54	HR: 0.89 (CI, 0.60–1.31) <i>P</i> = 0.383	HR: 1.23 (CI, 0.33–4.56) <i>P</i> = 0.761	HR: 0.89 (CI, 0.60–1.31) <i>P</i> = 0.383	HR: 0.68 (CI, 0.36–1.29) <i>P</i> = 0.237	–
FEVER (19)	9711	3.3	Any CVD: 575 Strokes: 428 Deaths: 263	HR: 0.73 <i>P</i> = 0.0019	HR: 0.68 <i>P</i> = 0.0153	HR: 0.73 <i>P</i> = 0.0002	HR: 0.73 <i>P</i> = 0.0019	HR: 0.70 <i>P</i> = 0.26

CVD = cardiovascular disease; FEVER = Felodipine Event Reduction; HR = hazard ratio; HYVET = Hypertension in the Very Elderly Trial; JATOS = Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; PY = person-year; RR = relative risk; SHEP = Systolic Hypertension in the Elderly Program; VALISH = Valsartan in Elderly Isolated Systolic Hypertension.

* Stopped by data and safety monitoring board because of mortality benefit.

African Americans, is uncertain. African Americans are at highest risk for all complications of hypertension and are historically undertreated. Thus, we believe that recommending less aggressive targets in this or other high-risk populations requires stronger justification than the guideline cites. Three recent guidelines from other countries have concluded that the appropriate cut point for an age-related differential SBP goal is 80 years or older (5–7). We agree that this higher treatment target in frail hypertensive patients aged 80 years or older better reflects existing evidence.

SAFETY AND ADVERSE EVENT RISK IN HYPERTENSIVE PATIENTS AGED 60 YEARS OR OLDER

Despite the limited number of end points in JATOS and the VALISH trial, their size and duration provide evidence of safety of the SBP target of less than 140 mm Hg. The VALISH investigators concluded that this target was safe in relatively healthy patients aged 70 years or older with isolated systolic hypertension (18). In JATOS, adverse events requiring treatment discontinuation were reported in only 36 patients, with no differences in discontinuation rate between groups (17). This evidence and the favorable results at slightly higher blood pressures in the SHEP trial and HYVET provide reassurance of the safety of an SBP goal of less than 140 mm Hg in older, nonfrail persons.

OTHER TRIAL EVIDENCE OF BENEFIT OF TREATMENT AT AN SBP OF 140 MM Hg OR LOWER

Results of the SPS3 (Secondary Prevention of Small Subcortical Strokes) trial indicated that an SBP target of less than 130 mm Hg versus 144 mm Hg in 3020 patients (mean age, 63 years) reduced subsequent strokes by 19% (*P* = 0.08) and hemorrhagic strokes by nearly 50% (*P* < 0.01) (20). Of note, the FEVER trial reported a 44% (*P* < 0.001) reduction in all strokes in a subgroup analysis of patients older than 65 years (17).

Finally, 2 meta-analyses supported the SBP goal of less than 140 mm Hg (21, 22). A meta-analysis involving 16 trials analyzed whether treatment with antihypertensive drugs compared with placebo significantly reduced risk for all strokes in trials with an average baseline SBP less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg. It found benefit with an SBP less than 140 mm Hg (21). Another meta-analysis examined the effects of blood pressure reduction in patient groups defined a priori by baseline blood pressures in 32 trials (*n* = 201 566 participants) and found no evidence that benefit of treatment differed in patients with a baseline SBP below or above 140 mm Hg for major cardiovascular events (22).

CONSISTENCY OF RCT AND OBSERVATIONAL EVIDENCE IN OLDER PERSONS WITH HYPERTENSION

The results from the SHEP trial and HYVET are consistent with epidemiologic studies. In one of the largest epidemiologic studies of blood pressure and CVD, a dec-

rement of 20 mm Hg in SBP in persons aged 70 to 79 years was associated with hazard ratios of 0.50 (95% CI, 0.48 to 0.52) for fatal stroke and 0.60 (CI, 0.58 to 0.61) for ischemic heart disease death (23). In the SHEP trial, the SBP decrement (12 mm Hg) corresponded to hazard ratios for stroke death and ischemic heart disease events of 0.71 (CI, 0.31 to 1.59) and 0.80 (CI, 0.57 to 1.59), respectively. Similarly, the SBP reduction of 15 mm Hg in HYVET produced hazard ratios of 0.61 (CI, 0.38 to 1.00) for stroke death and 0.71 (CI, 0.42 to 1.19) for cardiac death. These trial results, given the smaller blood pressure reductions, are consistent with epidemiologic data, including an analysis suggesting that the recent large reduction in stroke death (50%) in the United States is partially related to blood pressure reduction (4).

SUMMARY

The guideline panel was faced with a lack of definitive RCT evidence to determine the optimum SBP. In the United States, millions of treated older hypertensive patients have an average SBP closer to the range of 135 to 140 mm Hg than the range of 145 to 150 mm Hg. Which SBP goal is most likely to reduce cardiovascular events without overwhelming adverse events? Panel members agreed that available RCTs provide strong evidence that treatment of an SBP greater than 150 mm Hg will reduce cardiovascular events with little evidence of serious harm. On the basis of expert opinion, the panel also agreed to recommend an SBP target of less than 140 mm Hg for patients younger than 60 years, those older than 60 years with DM, and those younger than 70 years with CKD.

However, the panel did not reach unanimous consensus on the recommendation for persons older than 60 years who do not have DM or CKD. The majority embraced the view that in the absence of definitive evidence, increasing the SBP goal was the optimum approach. We, the panel minority, believed that evidence was insufficient to increase the SBP goal from its current level of less than 140 mm Hg because of concern that increasing the goal may cause harm by increasing the risk for CVD and partially undoing the remarkable progress in reducing cardiovascular mortality in Americans older than 60 years. Because of the overall evidence, including the RCT data reviewed by the panel, and the decrease in CVD mortality, we concluded that the evidence for increasing a blood pressure target in high-risk populations should be at least as strong as the evidence required to decrease the recommended blood pressure target. In addition, one target would simplify implementation for clinicians. However, we did believe that an SBP goal of less than 150 mm Hg for frail persons aged 80 years or older was a reasonable alternate approach to addressing the concern that elderly patients are at higher risk for treatment-related serious events. A target SBP of less than 140 mm Hg for patients younger than 80 years would also be in line with guidelines from Europe (5), Canada (6), the

American College of Cardiology Foundation and the American Heart Association (8), the United Kingdom (7), and the American Society of Hypertension and the International Society of Hypertension (9).

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