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US Hypertension Management Guidelines: A Review of the Recent Past and Recommendations for the Future

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Hypertension affects ≈29% of the US adult population, an estimated 72 million people, with a prevalence of >65% in persons older than 60 years.[1,2] It is an important risk factor for myocardial infarction (MI), heart failure (HF), stroke, and cardiovascular disease (CVD), accounting for ≈41% of all CVD deaths.[3,4] Indeed, there is a known graded relationship between increasing blood pressure (BP) and the risk of CVD, starting at 115/75 mm Hg.[5] Based on observational data, an increase in BP of 20 mm Hg systolic or 10 mm Hg diastolic is associated with a doubling of the risk of CVD death, regardless of age.[5] Further, hypertension in middle age is known to increase the risk of chronic kidney disease (CKD) and dementia in later life, an important issue given the aging demographic in Western societies.[6] Finally, despite the fact that BP recognition and control are improving, it is concerning that nearly half of the hypertensive population remains suboptimally controlled.[2]

With the 2003 Joint National Committee's seventh report (JNC 7) becoming increasingly outdated and the 2011 Institute of Medicine report calling for high-quality evidence-based guidelines,[7,8] the Eighth Joint National Committee (JNC 8) was initially appointed to create an updated treatment guideline for hypertension under the auspices of the National Institutes of Health (NIH). Although the NIH ultimately withdrew from the guideline development process at a late stage in the development of JNC 8, the panel decided, nonetheless, to publish their recommendations independently.

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J Am Heart Assoc. 2015;4:e002315 doi: 10.1161/JAHA.115.002315.

The panel aimed to answer 3 questions: Does initiating antihypertensive treatment at specific BP thresholds improve health outcomes? Does treatment with antihypertensive therapy to a specific BP goal improve health outcomes? Are there differences in benefit/harm between antihypertensive drugs or drug classes on specific health outcomes? The committee focused exclusively on large, randomized controlled trials (RCTs) as supporting evidence, although 5 of the 9 recommendations in the final report were ultimately based on expert opinion. Partly in response to JNC 8, the American College of Cardiology (ACC) and American Heart Association (AHA) are now in the process of developing official hypertension guidelines. In this review, we discuss the basis of each recommendation from the JNC 8 panel, provide additional insights, and compare these recommendations with guidelines from other professional societies to generate suggestions for the new AHA/ACC hypertension guideline committee.

JNC 8 Recommendation 1

In the general population aged ≥60 years, initiate pharmacologic treatment to lower BP at systolic BP (SBP) ≥150 mm Hg or diastolic BP (DBP) ≥90 mm Hg and treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg.

Basis of Recommendation

This first recommendation is based on several RCTs evaluating treatment of SBP to <140 mm Hg versus a more liberal target (140–160 mm Hg) in patients >65 years of age.[9,10] In the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS), 4418 patients between the ages of 65 and 85 were randomized to SBP treatment goal <140 mm Hg versus 140 to <160 mm Hg. Despite the fact that the intensive treatment group achieved a significantly lower BP (136/75 mm Hg versus 146/78 mm Hg), the primary end point of combined CVD and renal failure did not differ significantly between the 2 groups.

One limitation of this trial, however, is that it was only powered to detect a 40% relative risk reduction (or an absolute risk reduction from 5% to 3%) in the primary end point. While a 10/3–mm Hg reduction in BP is substantial, it may not be sufficient to achieve a 40% reduction in CVD or renal failure. Also, these patients were followed for only 2 years and the main treatment drug was a long-acting calcium channel blocker (CCB). Diuretics, widely considered first line along with CCBs in most professional society guidelines, were used in only 12% of the patients.[7,11–13] While not reaching statistical significance, subgroup analysis suggested that intensive treatment goals may be beneficial in patients <75 years old while adopting a more liberal strategy may be safer in those ≥75 years old.[10]

The VALISH (Valsartan in Elderly Isolated Systolic Hypertension) trial examined a slightly older hypertensive patient population (N=3260), with mean age of 76 years, to a strict (<140 mm Hg) or moderate (140 to <150 mm Hg) SBP control strategy with valsartan as the first-line drug. There was a nonsignificant trend toward reduction of the primary outcome of composite CVD and renal disease with the intensive treatment strategy (10.6 versus 12.0 per 1000 patient-y; *P*=0.38) at 3 years of follow-up.

An important consideration is that VALISH was significantly underpowered, with substantially fewer primary end point events than predicted. While VALISH was conducted in Japan, most guidelines for the elderly, African Americans, or Europeans would suggest that angiotensin type II receptor blockers (ARBs) are second line to a diuretic or CCB for controlling BP.[12,14,15] In both of these trials, the treatment strategies were well tolerated with few adverse events.

One trial not included in the JNC 8 analysis was FEVER (Felodipine Event Reduction), which enrolled 9800 Chinese patients aged 50 to 79 years with hypertension and at least one other cardiovascular risk factor for a comparison of diuretic monotherapy versus diuretic plus CCB. Of note, this patient population had a higher rate of prior stroke/transient ischemic attack (TIA), suggesting higher baseline risk for CVD; that is despite the fact that other baseline characteristics such as diabetes, previous MI, and incidence of cardiovascular events were in a similar range to those of other large studies.[16] Unlike JATOS, FEVER did not meet the JNC 8 committee's criteria for inclusion in their deliberations.[1]

While the trials included in JNC 8 evaluated different BP goals, FEVER did not have specific BP targets but used 2 different treatment strategies that were clearly designed to have more intensive BP control (treatment arm) versus less-intensive BP control (placebo arm). The exclusion of high-quality randomized evidence evaluating different BP treatment strategies and the limited focus solely on trials with prespecified BP targets are significant limitations of JNC 8 that likely will be remedied by the next AHA/ACC committee.

Both groups in FEVER had a reduction in BP, with BP falling from 154/91 to 137/83 mm Hg in the diuretic-plus-CCB (intensive treatment) group and from 154/91 to 143/85 mm Hg in the diuretic-alone (control) group. Fatal and nonfatal stroke was reduced by 27% in the intensive treatment group (*P*=0.001), while cardiac events and all-cause mortality were lowered by 35% (*P*=0.012) and 31% (*P*=0.006), respectively.[16] The average age of the FEVER patients was 62 years; thus, according to the JNC 8 recommendations, the majority of these patients would not receive additional therapy to achieve SBP ≤140 mm Hg. In such, these patients may lose the additional stroke and CVD benefit seen in FEVER. However, given that there was no subgroup analysis of patients >60 years old, the magnitude of benefit in this age group is unclear.

More evidence to support lower targets in US adults comes from the recently completed Systolic Blood Pressure Intervention Trial (SPRINT). This study randomized 9361 nondiabetic adults ≥50 years old with no prior stroke to a standard group with target SBP <140 mm Hg and an intensive group with target SBP <120 mm Hg.[17] SPRINT was designed to look for a benefit of intensive BP treatment in those at risk for developing heart failure or CVD, with an average age of 68 years and Framingham 10-year CVD risk score of 20%. The independent Data and Safety Monitoring Board recently advised the NIH to stop the study early due to the significantly reduced relative rates of CVD-related death (43%, *P*=0.005) and events (25%, *P*<0.001).[18,19] This reduction in CVD events came at the cost of higher rates of hypotension, acute kidney injury, syncope, and electrolyte disturbances. The results from SPRINT contradict the recommendations of JNC8 and may support even lower SBP targets for the consideration of the new AHA/ACC guideline committee.

Although the JNC 8 BP target of <150/90 mm Hg is recommended for those older than 60 years, evidence for this target is strongest for those >80 years. HYVET (Hypertension in the Very Elderly Trial) showed a benefit to treating patients >80 years old to an average SBP of 144 mm Hg (N=3845). These patients initially had SBP >160 mm Hg at baseline and were treated with indapamide plus perindopril as needed to achieve a goal BP of <150/80 mm Hg. This trial was stopped early for mortality benefit, with outcomes including 39% reduction in fatal strokes, 21% reduction in death from any cause, and 64% reduction in HF rates in the treatment group.[20] In HYVET, frail adults >80 years old were excluded from the trial, but this suggests that otherwise robust adults >80 years old have a significant reduction in mortality and CVD outcomes targeting SBP <150 mm Hg. What is not clear from HYVET is whether further reductions in BP to lower thresholds would have been beneficial in this sample. In the prespecified subgroup analysis of the SPRINT trial, the reduction in CVD events and death in the intensive treatment

arm (targeting SBP <120 mm Hg) was seen across age groups, including in people aged 75 years or older.[18] Similar to HYVET, SPRINT avoided possibly frail older adults, by excluding residents of nursing homes or assisted living facilities. These results will also impact the new guideline committee.

Table 1. Guideline Comparison

Guideline	Population	Goal BP (mm Hg)	First-Line Treatment Options
2014 Hypertension Guideline[15]	Adults <60 y	<140/90	Nonblack: thiazide, ACEI, ARB, or CCB Black: thiazide or CCB
	Adults ≥60 y	<150/90	
	Adults with diabetes	<140/90	Thiazide, ACEI, ARB, or CCB
	Adults with CKD	<140/90	ACEI or ARB
JNC 7[7]	Adults ≥18 y	<140/90	Thiazide, 2-drug combination for BP >20/10 mm Hg over target
	Adults with diabetes	<130/80	Thiazide, ACEI, β-blocker, CCB, or ARB
	Adults with CKD	<130/80	ACEI or ARB
ASH/ISH 2014[14]	Adults <80 y	<140/90	Nonblack <60 y: ACEI or ARB Nonblack ≥60 y or black: CCB or thiazide
	Adults ≥80 y	<150/90	
	Adults ≥80 y with CKD or diabetes	<140/90	ACEI or ARB
	Adults <80 y with CKD and albuminuria	<130/80	ACEI or ARB
CHEP 2014[11]	Adults <80 y	<140/90	Thiazide, β-blocker (age <60 y), ACEI (nonblack), CCB, or ARB
	Adults ≥80 y	<150	Thiazide, ACEI (nonblack), CCB, or ARB
	Adults with diabetes	<130/80	ACEI or ARB (CVD or CKD), or ACEI, ARB, CCB, or thiazide
	Adults with CKD	<140/90	ACEI or ARB
ESH/ESC 2013[12]	Nonfrail adults <80 y	<140/90	Diuretic, β-blocker, CCB, ACEI, or ARB
	Adults >80 y	<150/90	Diuretic, CCB
	Adults with diabetes	<140/85	ACEI or ARB
	Adults with CKD without proteinuria	<140/90	ACEI or ARB
	Adults with CKD with overt proteinuria	<130/90	ACEI or ARB
	Adults with CHD	<140/90	ACEI, ARB, or β-blocker
ADA 2015[21]	Adults with diabetes	<140/90*	ACEI or ARB
KDIGO 2012[22]	Adults with CKD and urine albumin <30 mg/24 h	<140/90	
	Adults with CKD and urine albumin ≥30 mg/24 h	<130/80	ARB or ACEI with urine albumin ≥300 mg/24 h
ISHIB 2010[13]	Black adults, primary prevention	<135/85	≤10 mm Hg above target, CCB or diuretic. >15/10 mm Hg above target, CCB plus RAS blocker or diuretic plus RAS blocker
	Black adults, with target organ damage†	<130/80	Diuretic or CCB (preferred), RAS blocker (alternative), β-blocker (optional)
NICE 2011[23]	Adults <80 y	<140/90	Adults >55 y: CCB or thiazide; adults<55 y: ACEI or ARB
	Adults ≥80 y	<150/90	CCB or thiazide

BP indicates blood pressure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type II receptor blocker; CCB, calcium channel blocker; JNC 7, Seventh Joint National Committee; CKD, chronic kidney disease; ASH/ISH, American Society of Hypertension/International Society of Hypertension; CHEP, Canadian Hypertension Education Program; CVD, cardiovascular disease; ESH/ESC, European Society of Hypertension/European Society of Cardiology; CHD, congestive heart disease; ADA, American Diabetes Association; KDIGO, Kidney Disease: Improving Global Outcomes; ISHIB, International Society on Hypertension in Blacks; RAS, renin-angiotensin system; NICE, National Institute for Health and Clinical Excellence.
*Optional target of <130/80 mm Hg for certain individuals, such as younger patients, if this target can be achieved without adverse treatment burden.
†Target organ damage defined as albumin:creatinine ratio >200 mg/g, estimated glomerular filtration rate <60 mL/min per 1.73 m^2, or electrocardiographic/echocardiographic evidence of left ventricular hypertrophy.

The American Society of Hypertension (ASH)/International Society of Hypertension (ISH) along with the Canadian Hypertension Education Program guidelines use a higher age cutoff of >80 years for a treatment goal of BP <150/90 mm Hg (Table 1).[11,14,21–23] Unlike the JNC 8 panel's recommendations, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) add another variable of frailty, likely due to the fact that trials such as HYVET attempted to exclude frail patients such as those with dementia or requiring nursing home care.[12] They recommend a tailored approach for the fragile elderly patient <80 years of age by using individualized targets.

Observational Evidence and Additional Insights

When we do not have randomized trial evidence, high-quality observational data and meta-analyses may be helpful in the formulation of a more-comprehensive BP treatment guideline. Several studies have found a modest-to-high correlation between RCTs and nonrandomized studies in estimating the benefit of medical interventions, although the magnitudes of effect were not always similar.[24,25] Results from one large cohort supporting a lower BP target was reported by Sim et al in the Kaiser Permanente Southern California health system. This retrospective analysis examined nearly 400 000 people treated for hypertension to determine the optimal treatment target for the composite end point of mortality and end-stage renal disease. The lowest risk of the primary outcome was seen at an on-treatment BP of 137/71 mm Hg with a J-shape curve suggesting higher risk with lower and higher BP targets. In subgroup analysis, a similar curve was seen in those ≥70 years of age with a higher optimal target of 140/70 mm Hg.[26]

Along with the Kaiser study, a meta-analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) confirmed a benefit in treating stage I hypertension (BP 140 to 159/90 to 99 mm Hg).[27] With a mean age of 63 years and mean baseline SBP of 146 mm Hg, the patients in the active treatment arm had an average BP reduction of 3.6/2.4 mm Hg and odds ratios of 0.72 (95% CI 0.55 to 0.94) for strokes, 0.75 (95% CI 0.57 to 0.98) for CVD deaths, and 0.78 (95% CI 0.67 to 0.92) for all-cause mortality.[27] In subgroup analysis, this finding of a lower odds ratio for all-cause mortality held for those >67 years old (odds ratio 0.73, CI 0.56 to 0.95).[27] Again, along with results from SPRINT, this suggests that using the new JNC 8 treatment targets would lead to a loss of mortality benefit in patients >60 years old with SBP between 140 and 150 mm Hg.

A recent cost-effectiveness model of treating stage I hypertension showed a reduction in both CVD events and deaths along with significant cost savings, especially in those >60 years old.[28] This study used the JNC 8 panel's recommended treatment targets, but did not model the cost savings or mortality benefit of treating adults >60 years with SBP 140 to 150 mm Hg. However, there was significant cost-savings gained for treating men and women between the ages of 45 and 60 with BP >140/90 mm Hg. Given the projected increase in CVD events with those >60 years of age, we believe that there is likely to be a benefit to treating mild hypertension in this group as well.

The impact of adopting the JNC 8 guidelines on a population level will lead to a significant change in those eligible for BP treatment. While an estimated 41.5 million people are above their BP goal under JNC 7, only 28 million are above goal according to the JNC 8 recommendations, based on estimates from the National Health and Nutrition Examination Survey, a representative population sample.[29] This corresponds to 13.5 million adults, with the majority ≥60 years old, who were previously considered above goal and now no longer eligible for further treatment. An important consideration is that these 13.5 million include 37% with diabetes, 39% with CKD, and 19% with CVD.[29]

The National Cardiovascular Data Registry PINNACLE Registry confirmed that the population of patients for whom the BP goals changed in JNC 8 is also the population who are at highest risk for CVD events, with an average Framingham risk score of 8.5±3.2% and 10-year atherosclerotic CVD (ASCVD) risk score of 28±19%.[30] In this high-risk group in particular, a more effective approach than the traditional target-based BP treatment could be a risk-based treatment model, incorporating global CVD risk scores. Support for this approach was established by the BPLTTC.[31] In their meta-analysis of nearly 52 000 individuals, the BPLTTC showed that while BP treatment led to the same relative risk reduction across all 4 risk categories, the greatest absolute benefit by number of CVD events prevented occurred in the highest baseline CVD risk category.[31]

While this approach still needs to be externally validated, we suggest that the new AHA/ACC guideline committee consider a risk-based approach for adults >60 years of age; initiating treatment for those with SBP ≥140 mm Hg if their 10-year ASCVD risk score is >7.5% based on the pooled cohort equations.[32] Persons with ASCVD risk <7.5% appear less likely to benefit from this more-aggressive BP target and may not require treatment until their SBP is ≥150 mm Hg. We note, however, that, given the substantial influence of age in the ASCVD risk calculator, the vast majority of men and many women >60 years old who have an SBP of >140 mm Hg would qualify for more-aggressive BP treatment based on this 7.5% threshold. Thus, future research may identify a more-optimal ASCVD risk cut-point (perhaps, for example, >15% [the risk cutoff for SPRINT]), below which a more lenient SBP goal of 150 mm Hg could be targeted in adults between 60 and 80 years old.

The 2014 National Institute for Health and Clinical Excellence cardiovascular risk assessment guidelines suggest starting BP treatment in adults with a CVD risk score ≥10% based on the QRISK2 calculator.[33] It is worth noting that estimation of CVD risk is also now a critical part of the cholesterol treatment guidelines and, hence, could also be used to enhance the treatment of hypertension in high-risk adults. Further research will be needed to explore the optimal ASCVD risk score to initiate BP treatment for men and women and to determine the potential role, if any, of cardiac biomarkers such as coronary artery calcium in guiding risk-based allocation of hypertension therapy.

To reiterate, with CVD risk being heavily influenced by age, the absolute benefit of BP treatment for risk reduction is greatest in the elderly. However, despite the JNC 8 recommendations, none of the trials on which these recommendations are based were conducted in elderly hypertensive patients with an initial SBP between 140 and 150 mm Hg. Thus, it is not possible to be entirely sure what BP target to use without more evidence from RCTs, which is why the results from SPRINT will be critical for the new guideline committee.

However, RCTs cannot answer every question and, in these situations, the new AHA/ACC committee may need to rely more on other high-quality, prospective observational data and meta-analyses to help determine better BP targets or to integrate a treatment approach that incorporates CVD risk factor estimation.

JNC 8 Recommendations 2 to 5

In all persons <60 years or in persons >18 years (and either those younger or older than 60 years with either diabetes or CKD), initiate pharmacologic treatment to lower SBP ≥140 or DBP ≥90 mm Hg and treat to a goal BP of <140/90 mm Hg.

Basis of Recommendation

There is broader agreement between the professional societies on how to treat younger patients with hypertension. While most studies examined adults >30 years, JNC 8 extends the same target to those aged 18 to 30 years. More support can be found for DBP versus SBP goals among younger adults with hypertension, especially in the Hypertension Optimal Treatment (HOT) trial.[34] This trial randomized 18 790 hypertensive patients (aged 50 to 80 years) with baseline DBP 100 to 115 mm Hg into 3 groups based on target DBP ≤90, ≤85, or ≤80 mm Hg.

The main goal of this study was to assess the association between these 3 target DBPs and major CVD events (nonfatal MI, nonfatal stroke, and cardiovascular death). There was little difference in event rates between the 3 groups, except that the rate of MI was reduced in the 2 lower DBP target groups compared with the DBP ≤90 mm Hg group. Further subgroup analyses of patients with diabetes demonstrated fewer major CVD events, fewer strokes, and reduced cardiovascular mortality in the lowest BP treatment target group, while those with prior CVD had a significant reduction in stroke across the 3 groups.[34]

While all 3 groups in HOT achieved a mean DBP <90 mm Hg, the lowest risk of cardiovascular mortality was seen at 85.6 mm Hg and the lowest rate of CVD events was seen at 82.6 mm Hg. Based on this trial, everyone with hypertension under the JNC 8 guidelines has a DBP goal of <90 mm Hg. There is less evidence supporting an SBP target of <140 mm Hg in this group of patients. However, in trials like HOT, even though DBP was being targeted, SBP also fell at least 25 mm Hg in all 3 groups.[34] Indeed, given SPRINT suggests clinical benefit for an SBP target of 120 mm Hg among higher risk persons <60 years, it is likely that forthcoming guidelines may even reduce this SBP target to a threshold lower than 140. However, the DBP values in the intensive therapy arm of SPRINT are not currently known.

Other supporting evidence for DBP treatment thresholds includes the Veterans Administration Cooperative Study Group on Antihypertensive Agents, in which 380 men with DBP 90 to 114 mm Hg were randomized to antihypertensive therapy or placebo. Those receiving treatment benefited from a reduction in both morbidity and mortality.[35] The same findings were seen in the MRC (Medical Research Council, N=17 354) and HDFP (Hypertension Detection and Follow-up, N=10 940) trials, with those with DBP >90 mm Hg benefiting from active treatment, especially in stroke reduction.[36,37]

Additional Insights: Diabetes

The recommendation for target BP in patients with diabetes by most professional societies is <140/90 mm Hg, although ESH/ESC recommend a DBP target of <85 mm Hg. In a post-hoc analysis of the 1501 patients with diabetes in the HOT trial, the ≤80 mm Hg target group versus ≤90 mm Hg target group had a 50% reduction in major CVD events and 66% reduction in cardiovascular mortality.[34] Subgroup analysis of people with diabetes in FEVER showed a reduction in the number of strokes by 44% in the on-treatment group, with BP achieved of 139/82 mm Hg versus 144/84 mm Hg in the control group. In FEVER, no difference was seen in cardiovascular mortality or events between the 2 groups.[38]

One landmark trial, enrolling only participants with type 2 diabetes, was the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. This trial compared 2 SBP targets, <140 or <120 mm Hg, with the 2 groups achieving mean BP of 134/71 and 119/64 mm Hg, respectively. After 4.7 years of follow-up, the primary outcome of nonfatal MI, stroke, or

CVD death was not significantly different between the 2 groups, although the total stroke rate in the intensive treatment arm was reduced by 41% (P=0.01).[39] This study has been criticized for lack of power however. Despite stroke being an infrequent event, in absolute terms the stroke rates were 0.3% per year in the intensive-treatment group versus 0.5% per year in the standard-treatment group. However, this reduction in stroke came at a cost of more adverse events in the intensive treatment group (4.2% versus 2.2%), including significantly higher rates of kidney injury, hypotension, and hypokalemia.

Based on these studies, achieving a lower BP goal in people with diabetes appears to be more consistently associated with a lower risk of stroke than MI. While the diastolic target of <80 mm Hg only showed a benefit in a post-hoc subgroup analysis in HOT, based on our review of the evidence we support a target SBP <140 mm Hg based on ACCORD and DBP <85 mm Hg based on FEVER and HOT for adults with diabetes.

Additional Insights: CKD

BP targets in CKD patients were also increased from <130/80 to <140/90 mm Hg between the JNC 7 and JNC 8 guidelines. While the JNC 8 panel did not incorporate proteinuria as an outcome of interest, the ASH/ISH, the ESH/ESC, and the Kidney Disease: Improving Global Outcomes (KDIGO) group all make a distinction between CKD patients based on proteinuria status, with a lower BP goal of <130/80 to 90 mm Hg for those with proteinuria detectable on urinanalysis.[12,14,22]

The International Society on Hypertension in Blacks also recommends a target of <130/80 mm Hg for black adults with CKD. The evidence for these recommendations is based on 3 trials—the African American Study of Kidney Disease and Hypertension (AASK), the Modification of Diet in Renal Disease (MDRD) study, and the Blood-pressure Control for Renoprotection in Patients with Non-diabetic Chronic Renal Disease (REIN-2) study. None of these trials showed a difference in kidney or CVD outcomes between those with lower versus higher BP goals.[40–42]

AASK (N=1094) evaluated mean arterial pressure (MAP) goals, targeting 102 to 107 mm Hg in the usual-BP group versus ≤92 mm Hg in the lower-BP group. While the lower-BP group achieved an average BP of 128/78 mm Hg, compared with 141/85 mm Hg in the other group, there was no significant change in the rate of glomerular filtration rate decline, end-stage renal disease, or death. There was, however, a decrease in proteinuria in the strict treatment group at 6 months (17% decrease versus 7% increase), and this effect persisted throughout the length of the study.[41] MDRD (N=1585) used the same MAP targets, and in participants with at least 1 g/d of proteinuria, the lower BP target group had a slower rate of glomerular filtration rate decline.[42]

While there were modest benefits to the lower BP target, especially in those with significant proteinuria, we should keep in mind the ACCORD findings of intensive BP treatment leading to double the relative rates of renal injury (glomerular filtration rate <30 mL/min per 1.73 m^2; 99 versus 52 events, P<0.001). However, ACCORD did not show any difference in rates of ESRD; it also showed that intensive treatment led to a lower incidence of macroalbuminuria, with rates of 6.6% versus 8.7% in the standard-treatment group (P=0.009). Given that the baseline risk of the patient appears to influence the outcomes of BP treatment, a lower BP goal of <130/80 mm Hg may be recommended for those with >300 mg/d proteinuria. We expect that further subgroup analysis from SPRINT will also inform this recommendation, as their recruitment targeted a prespecified subgroup of participants with CKD.

Additional Insights: Secondary Prevention of CVD

One population not specifically addressed in the JNC 8 guidelines is those with prior CVD. Determining BP targets for these patients requires the interpretation of conflicting observational studies and clinical trials and the possible existence of a J-shaped curve relating BP and CVD outcomes (with increased risk at lower and higher on-treatment BP values). In 2007, the AHA offered a goal of <130/80 mm Hg in those with established CVD, CVD equivalents and for those with a 10-year Framingham risk score of >10% in its scientific statement on the prevention and management of ischemic heart disease.[43]

More recently, the AHA, ACC, and ASH published a new guideline, endorsing a goal of <140/90 mm Hg for those with hypertension and CVD with an optional target of <130/80 mm Hg for those with CVD and previous MI, stroke/TIA, carotid artery disease, peripheral arterial disease, or abdominal aortic aneurysm.[43] ESH/ESC recommends a goal of <140/90 mm Hg for adults with CVD, while other societies do not have specific treatment goals for this population.

One clinical trial, the International Verapamil-Trandolapril Study (INVEST), looked first at a CCB strategy versus a non-CCB strategy for lowering BP in people ≥60 years with CVD.[44] Because both treatment strategies led to >70% of patients achieving BP <140/90 mm Hg within the follow-up period of 24 months, all patients were combined for a post-hoc analysis looking at optimal treatment targets. All patients were split into 3 groups based on their SBP: group 1, <140 mm Hg (57%); group 2, 140 to <150 mm Hg (21%); and group 3, ≥150 mm Hg (22%). These groups achieved a

median SBP of 131, 144, and 158 mm Hg, respectively, and a multiple propensity score–adjusted model was created to adjust for the baseline differences between the groups.

Compared with group 1, group 2 had increased risk of cardiovascular mortality, total stroke, and nonfatal stroke with hazard ratios of 1.34 (95% CI 1.01 to 1.77; P=0.04), 1.89 (95% CI 1.26 to 2.82; P=0.002), and 1.70 (95% CI 1.06 to 2.72, P=0.03), respectively.[45] This analysis provides indirect supportive evidence that people with CVD, including those ≥60 years, may benefit from an SBP target of <140 mm Hg. In addition, SPRINT enrolled a high risk population, many with prior CVD and demonstrated benefit to an SBP target of 120 mm Hg.

When considering diastolic targets, subgroup analysis of HOT examined 3080 people with previous CVD and found a 43% reduction in stroke when comparing the groups targeting DBP ≤80 mm Hg versus DBP ≤90 mm Hg.[34] While a target DBP ≤80 mm Hg appears beneficial, there appears to be a J-curve with respect to DBP targets in CVD. Analysis of the INVEST study showed clear evidence of harm at lower DBP, with a nadir in terms of events of 74 mm Hg. As DBP dropped below 70 and 60 mm Hg, mortality rates doubled and quadrupled, respectively, in patients with preexisting CVD. Therefore, while the overall level of evidence is less strong for BP targets in those with preexisting CVD and is based mainly on post-hoc analyses of randomized trials, we agree with the new AHA/ACC/ASH statement suggesting a target of <140/90 mm Hg with an optional lower target (<130/80 mm Hg) for adults with known CVD.

JNC 8 Recommendations 6 to 9

In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, CCB, angiotensin-converting enzyme inhibitor (ACEI), or ARB. In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. In the population aged ≥18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. If goal BP is not reached within 1 month of treatment, increase the dose of the initial drug or add a second drug, and if goal BP cannot be reached with 2 drugs, add and titrate a third drug. Referral to a hypertension specialist is recommended for patients in whom goal BP cannot be attained.

Basis of Recommendations

In contrast to treatment targets, most professional societies agree on the class of antihypertensives to use for specific comorbid disease categories (Table 1). For the nonblack population without diabetes, all society recommendations include thiazide diuretics, CCBs, ACEIs, and ARBs as first-line therapies. An important consideration with thiazide diuretics is that the strength of individual drugs within the class varies in BP-lowering effects.

A Cochrane Review of >60 RCTs for thiazide monotherapy versus placebo in adults with primary hypertension (BP 140 to <160/90 to <100 mm Hg) examined the BP effects of 6 different thiazide diuretics.[46] Hydrochlorothiazide, unlike the other thiazide medications studied, demonstrated a dose-dependent BP reduction. Compared with placebo, the effect of hydrochlorothiazide on BP ranged from 6.25 mg/d, leading to a 4–mm Hg (95% CI 2 to 6)/2–mm Hg (95% CI 1 to 4) reduction, to 50 mg/d, resulting in a 11–mm Hg (95% CI 6 to 15)/5–mm Hg (95% CI 3 to 7) reduction. Chlorthalidone, regardless of dose ranging from 12.5 mg to 75 mg/d, led to a 12–mm Hg (95% CI 10 to 14)/4–mm Hg (95% CI 3 to 5) reduction in BP. While the maximal effects were judged to be similar between the different thiazides, attention to dosing is important given the wide range of effect with hydrochlorothiazide.

One trial that supports the first-line status of thiazides, CCBs, and ACEIs is the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). This trial randomized 33 357 people aged ≥55 years with hypertension and ≥1 other CVD risk factor to chlorthalidone, amlodipine, or lisinopril.[47] All-cause mortality was not different between the groups, and while SBP was higher in the amlodipine and lisinopril groups compared with chlorthalidone, the difference was statistically but not clinically significant at 0.8 to 2 mm Hg (P<0.05). However, there were some notable differences in secondary outcomes, like higher rates of HF in the amlodipine (10.2%) versus chlorthalidone group (7.7%). However, because the primary outcome and other secondary outcomes were comparable, this was not considered by JNC 8 as a strong enough reason to recommend thiazide diuretics as the sole initial antihypertensive class.

ASH/ISH and the National Institute for Health and Clinical Excellence make a distinction for those aged <55 to 60 years to favor an ACEI or ARB, while those aged ≥55 to 60 years should start with a thiazide or CCB.[14,23] β-Blockers are included as first line for adults aged <60 years in the Canadian Hypertension Education Program guidelines and for adults aged <80 years in ESH/ESC.[11,12] While combination therapy with β-blockers can be very effective, the Losartan Intervention for Endpoint reduction in hypertension (LIFE) study demonstrated a lower rate of death, MI, or stroke in their losartan group compared with the atenolol group, a difference mainly driven by stroke reduction.[48] Given this finding and otherwise insufficient evidence to support β-blockers as first-line agents, we agree with the JNC 8 committee.

Additional Insights

While JNC 8 has the same treatment recommendations for people with or without diabetes, most other societies suggest that only ACEIs or ARBs should be first-line treatment for patients with diabetes. In the case of patients with diabetes and a history of CKD, we agree that ACEIs or ARBs should be first line.

In the black population with hypertension, CCBs and thiazide diuretics generally tend to be favored as initial therapy over renin-angiotensin system blockers.[13,14,45] The evidence for this recommendation comes from ALLHAT, which showed in prespecified subgroup analysis that black patients treated with lisinopril had higher rates of stroke, CVD, and HF plus 4 mm Hg higher SBP compared with those treated with chlorthalidone.[49]

On the other hand, the primary and secondary outcomes were similar in the chlorthalidone and amlodipine groups except for higher rates of HF with amlodipine. Compared with lisinopril, the black patients in the amlodipine group had lower stroke rates and improved BP control. Therefore, both CCBs and thiazide diuretics are considered first line for black patients with hypertension.

If a black patient has coexisting CKD, initial treatment should be an ACEI or ARB if the patient also has albuminuria, as supported by the KDIGO guidelines. This recommendation, for starting with CCBs and thiazides is generalized to black patients with diabetes, because nearly half of the black patients in ALLHAT had diabetes. Given that most patients require >1 agent to control hypertension, it is important to know that combination treatment with CCB or diuretics plus rennin-angiotensin system blockade leads to the same efficacy in black or white patients. The International Society for Hypertension in Blacks suggests starting with a CCB or thiazide diuretic if <10 mm Hg above target or using a 2-drug approach if >15/10 mm Hg over with a CCB or diuretic plus a rennin-angiotensin system blocker.[13]

Other Limitations

There are several limitations to consider in the JNC 8 committee's approach to BP treatment (Table 2). Unlike the other professional societies' guidelines, the JNC 8 panel did not address topics outside of their chosen critical questions, specifically given the paucity of randomized trial evidence addressing such questions. While they endorsed the AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk,[50] the JNC 8 does not address lifestyle modifications or a timeline for attempting them. Another limitation is that ambulatory BP monitoring, including cut-off values for diagnosing hypertension based on home BP readings, is not addressed.

One suggestion is to confirm elevated BP with ambulatory BP monitoring, such as that recently recommended by

Table 2. Recommendations for the AHA/ACC Committee

General Area	JNC 8 Recommendation	Recommendations for AHA/ACC Committee
Diagnosis of hypertension	None	• Add specific recommendations on use of ambulatory blood pressure monitoring and home blood pressure monitoring • Devise a risk-based strategy for determination of treatment initiation thresholds and targets • Specify timeframe of attempting lifestyle modification alone before initiation of therapy
Treatment initiation thresholds and targets	Adults ≥60 y old, SBP/DBP treatment initiation threshold and target of 150/90 mm Hg	• Lower the SBP treatment initiation threshold and target to 140 mm Hg for adults ≤80 y old[16,20,21]
	Adults >18 y old and <60 y old or any adult with diabetes or CKD, SBP/DBP treatment initiation threshold and target of 140/90 mm Hg	• Lower DBP treatment initiation threshold and target to 85 mm Hg for diabetic adults,[27,31] • Optional SBP/DBP treatment initiation threshold and target of ≤130/80 mm Hg for adults with CKD and >300 mg/d proteinuria[35,36] • Add specific guidance for adults with preexisting CVD
Selection of therapy	Nonblack adults, including diabetics: first-line therapy includes thiazides, CCB, ACEI/ARB Black adults, including diabetics: first-line therapy includes thiazides or CCB Adults with CKD: first-line therapy includes ACEI/ARB	• For nonblack adults with preexisting CVD or diabetes, recommend ACEI or ARB as first-line therapy • For black adults with diabetes, recommend ACEI or ARB as add-on therapy for patients requiring multidrug therapy

AHA indicates American Heart Association; ACC, American College of Cardiology; JNC, Joint National Committee; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type II receptor blocker.

the US Preventive Service Task Force.[51] There is in general a lack of guidance on the diagnosis of hypertension and the evaluation for secondary causes. Although the JNC 8 committee offers a titration schedule for treating hypertension, the recommendations are somewhat vague, and there is no guidance for resistant hypertension beyond referral to a hypertension specialist.

We also recommend that the AHA/ACC guideline committee focus on the benefits of the various drug classes and the situations that call for monodrug versus multidrug therapy. Another important area of focus will be the benefit of more-intensive BP treatment, especially in the elderly and those with diabetes, and the addition of a risk-based approach to initiating treatment (described earlier). These are all areas that can be targeted by the new AHA/ACC guideline committee.

Conclusion

While JNC 8 offers improvements over JNC 7 with a laudable dedication to high-quality randomized evidence-based recommendations, it leaves open some areas of improvement for the new ACC/AHA committee. By focusing solely on RCTs, we are left with areas of uncertainty where high-quality observational studies could help elucidate effective recommendations to ultimately achieve the goal of improving hypertension control and the health of our patients. By creating a higher SBP treatment threshold for people >60 years old, the very group who are at the highest CVD risk, implementation of JNC 8 recommendations could mean that >6 million people in this category may not be started on treatment and an additional 13.5 million may have their treatment target liberalized, with potential detrimental consequences.[29]

While the previous BP target of <140/90 mm Hg could be liberalized for patients who are frail or >80 years old, adopting these new guidelines in persons aged 60 to 80 years may lead to a resurgence of stroke rates. More research is needed, particularly on the use of estimated ASCVD risk cut-points to inform therapeutic antihypertensive targets, but the new ACC/AHA hypertension guideline committee should consider a risk-based treatment approach for adults >60 years of age by; for example, initiating BP treatment for those with SBP ≥140 mm Hg based on a ≥7.5% 10-year ASCVD risk score. Finally, the results from SPRINT will further undermine the JNC 8 recommendations and will likely result in a paradigm shift in how we treat hypertension.

Disclosures

None.

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Key Words: blood pressure • blood pressure goals • hypertension • JNC 8 • treatment

US Hypertension Management Guidelines: A Review of the Recent Past and Recommendations for the Future

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J Am Heart Assoc. 2015;4:e002315; originally published December 7, 2015;
doi: 10.1161/JAHA.115.002315
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980