GUIDELINE SYNTHESIS

Pharmacological Management of Hypertension

Guidelines Being Compared:

1 American College of Physicians (ACP)

Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians.

2017 Mar 21

View Summary >

2 Department of Veterans Affairs (VA)

VA/DoD clinical practice guideline for the diagnosis and management of hypertension in the primary care setting.

2014 Oct 01

View Summary >

3 Eighth Joint National Committee (JNC 8)

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).

2014 Feb 05

Areas of Agreement and Difference

A direct comparison of recommendations presented in the above guidelines for the pharmacological management of hypertension is provided. It should be noted that the guidelines differ somewhat in scope. Besides addressing pharmacotherapy, for example, the VA/DoD guideline also provides recommendations for the screening, diagnosis, measurement and non-pharmacological management of hypertension. These topics, however, are beyond the scope of this synthesis. In addition, the focus of the ACP/AAFP guideline is the treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets. As such, the developer does not offer specific pharmacotherapy recommendations.

Areas of Agreement

Diastolic Blood Pressure (DBP) Treatment Thresholds and Goals

In patients aged **30 or older**, VA/DoD and JNC 8 agree that pharmacologic therapy should be offered/initiated at DBP ≥90 mmHg, and that patients should be treated to a goal of <90 mmHg. Citing a lack of evidence in younger adults, the guideline developers each offer a weak recommendation for the use of the same treatment threshold and goal in adults **18 to 29 years**. There are no outcome studies published evaluating patients younger than age 30, VA/DoD remarks, so an appropriate threshold for initiating antihypertensive pharmacologic treatment is not clear. In this younger population, it may be appropriate to recommend a three to six month period of therapeutic lifestyle modification prior to offering medication management when DBP is ≥90 mmHg, adds the developer. The JNC 8 panel also acknowledges the lack of good- or fair-quality RCTs that assessed the benefits of treating elevated DBP on health outcomes in adults younger than 30 years. In the absence of such evidence, the Panel concluded that the DBP threshold and goal should be the same as in adults 30 through 59 years of age. ACP/AAFP concluded that the evidence was insufficient to determine the benefit of treating diastolic hypertension in the absence of systolic hypertension. Most trials assessed treatment outcomes based on SBP, the guideline states, and no trials included patients with a mean DBP >90 mmHg and a mean SBP <140 mmHg.

should include an ACEI or ARB to improve kidney outcomes and that these patients should be treated to a goal BP of <140/90 mmHg. The VA/DoD expands upon this guidance for African Americans with hypertension and stage 1-3 CKD, by suggesting a combination of a thiazide-type diuretic (for cardiovascular protection) in addition to either an ACEI or ARB. In line with the guidance provided by VA/DoD and the JNC 8 Panel, the ACP/AAFP guideline offers a weak recommendation based on low-quality evidence to consider treating some adults 60 years or older at high cardiovascular risk—which generally includes older persons with CKD with an estimated GFR <45 mL/min/1.73 m^2—to a target SBP of <140 mmHg. ACP/AAFP adds that this decision should be based on individualized assessment, and clinicians should select the treatment goals based on a periodic discussion of the benefits and harms of specific blood pressure targets with patients.

African American Patients

For the general African American population, including those with diabetes, VA/DoD and the JNC 8 Panel agree that monotherapy with an ACEI or ARB is not recommended, and that initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Noting a potential conflict between their recommendation to use an ACEI or ARB in those with CKD and hypertension and the subsequent recommendation to use a diuretic or CCB in African Americans, JNC 8 clarifies that in African American patients with CKD and proteinuria, an ACEI or ARB is recommended as initial therapy because of the higher likelihood of progression to end-stage renal disease. In African American patients with CKD but without proteinuria, the choice for initial therapy is less clear and includes a thiazide-type diuretic, CCB, ACEI, or ARB. If an ACEI or ARB is not used as the initial drug, then an ACEI or ARB can be added as a second-line drug if necessary to achieve goal BP. Because the majority of patients with CKD and hypertension will require more than 1 drug to achieve goal BP, it is anticipated that an ACEI or ARB will be used either as initial therapy or as second-line therapy in addition to a diuretic or CCB in African American patients with CKD.

Patients with Refractory Hypertension

Both VA/DoD and JNC 8 recommend considering other drug classes for patients who do not tolerate or whose blood pressure is not adequately controlled with triple therapy (i.e., thiazide-

direct vasodilators (e.g., hydralazine); dual alpha-beta adrenergic blockers (e.g., carvedilol); and centrally acting antiadrenergic drugs (e.g., clonidine). The ACP/AAFP guideline does not address pharmacologic treatment of refractory hypertension.

Areas of Difference

Systolic Blood Pressure (SBP) Treatment Thresholds and Goals

The guideline developers endorse different SBP pharmacologic treatment thresholds in hypertensive patients aged **60 years or older**. On the basis of evidence for reduction in clinical events from several RCTs (SHEP, HYVET, EWPHE), VA/DoD makes a strong recommendation for offering pharmacologic treatment at SBP ≥160 mmHg. For those patients 60 years or older with SBP <160 mmHg, VA/DoD suggests considering pharmacologic treatment using a shared decision-making model.

In contrast, the JNC 8 Panel strongly recommends a pharmacologic treatment threshold of SBP ≥150 mmHg in this patient population. On the basis of high-quality evidence, the ACP/AAFP guideline also makes a strong recommendation for initiating treatment (pharmacologic or nonpharmacologic) in adults aged 60 years or older with SBP persistently ≥150 mmHg in order to reduce the risk for mortality, stroke, and cardiac events. The guideline emphasizes that clinicians select the treatment goals based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient. All of the guideline developers agree, however, that average-risk hypertensive patients in this age group should be treated to a goal SBP of <150 mmHg.

The ACP/AAFP guideline also offers weak recommendations for treating selected higher risk adults aged 60 years or older to a lower target SBP than those at average risk. Specifically, the developers recommend that clinicians consider initiating or intensifying pharmacologic treatment to achieve a target SBP of <140 mmHg in patients with a history of stroke or TIA, in order to reduce the risk for recurrent stroke, as well as in some patients determined to be at high cardiovascular risk based on individualized assessment, to reduce the risk for stroke or cardiac events. The guideline developer notes that, generally, increased cardiovascular risk includes persons with known vascular disease, most patients with diabetes, older persons

should select the treatment goals for all adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific BP targets with the patient.

In the general population **younger than 60 years**, VA/DoD conditionally recommends (suggests) the same SBP treatment initiation threshold (≥160 mmHg) and treatment goal (SBP <150 mmHg) recommended for adults 60 years or older. The developer notes the only study in the evidence base that enrolled patients younger than age 60 with SBP of 150–179 mmHg found no difference in major cardiovascular events or mortality between the control and active treatment groups. Thus the recommendations for SBP thresholds for people less than 60 years were based on outcomes other than surrogate outcomes, such as blood pressure. The VA/DoD also explains the recommendation for suggested treatment at age less than 60 years is based on potential benefit for reduction in cardiovascular events and low patient burden associated with pharmacologic treatment. Citing expert opinion, JNC 8 offers different guidance for patients in this age group. While there is high-quality evidence to support a specific SBP threshold and goal for persons aged 60 years or older, the Panel found insufficient evidence from good- or fair-quality RCTs to support a specific SBP threshold or goal for persons younger than 60 years. In the absence of such evidence, JNC 8 recommends a treatment threshold of SBP ≥140mmHg and treatment goal of SBP <140 mmHg based on several factors, including the absence of RCTs comparing the current SBP standard of 140 mmHg with another higher or lower standard in this age group. The ACP/AAFP guideline does not address adults younger than 60 years.

Diabetic Patients

VA/DoD and the JNC 8 both cite moderate-quality evidence from three RCTs (SHEP, Syst-Eur, and UKPDS) that treatment to an SBP goal of <150 mmHg improves major cardiovascular and cerebrovascular outcomes and lowers mortality in adults with diabetes and hypertension. VA/DoD makes a strong recommendation for treating to a BP goal of <150/85 mmHg in this patient population. For diabetic patients who can tolerate antihypertensive drugs, the developer suggests a lower goal SBP of <140 mmHg. Support for this recommendation comes from two trials. The ACCORD-BP trial demonstrated that the control group (goal SBP <140 mmHg) had similar cardiovascular outcomes but fewer serious

persons with diabetes. Although there was not an SBP goal, the mean achieved SBP of 135 mmHg is consistent with an SBP goal of <140 mmHg. Both developers cite the absence of RCTs addressing whether treatment to an SBP goal of <140 mmHg compared with a higher goal (e.g., <150 mmHg) improves health outcomes in adults with diabetes and hypertension. In the absence of such evidence, JNC 8 recommends treating to a BP goal of <140/90 mmHg in this population based on expert opinion, consistent with the BP goals for the general population younger than 60 years with hypertension. The JNC 8 Panel did not consider the ADVANCE trial because it did not meet their inclusion criteria. The ACP/AAFP guideline offers a weak recommendation for treating some adults, based on individualized assessment, 60 years or older at high cardiovascular risk—which includes most patients with diabetes—to a target SBP of <140 mmHg in order to reduce the risk for stroke or cardiac events.

Initial Pharmacological Therapy

VA/DoD makes a strong recommendation for the first-line use of thiazide-type diuretics. The developer explains that, similar to past guidelines, evidence supporting this recommendation is based mainly on placebo-controlled outcome trials with thiazide-type diuretics as the basis of therapy, as well as results from the ALLHAT trial. VA/DoD remarks on the significance of this latter trial to VA/DoD providers due to the >7,000 Veterans included in the study. The developer also considered newer evidence from the ACCOMPLISH study favoring combination therapy with an ACEI/CCB over an ACEI/thiazide-type diuretic. Although ACCOMPLISH weakened the strength of this recommendation, adds VA/DoD, there remains strong evidence to support the use of thiazide-type diuretics as first-line therapy. With regard to selection of a specific agent in this class, the developer suggests chlorthalidone or indapamide over hydrochlorothiazide.

In contrast, JNC 8 makes a moderate recommendation for the use of any of the following classes of drugs for the initial treatment of the nonblack population with hypertension: thiazide-type diuretics; CCBs; ACEIs or ARBs. According to the Panel, each of these four drug classes yielded comparable effects on overall mortality and cardiovascular, cerebrovascular, and kidney outcomes, with the exception of heart failure. Initial treatment with a thiazide-type diuretic was more effective than a CCB or ACEI, and an ACEI was more effective than a CCB

finding was not compelling enough within the context of the overall body of evidence to preclude the use of the other drug classes for initial therapy.

The purpose of the ACP/AAFP guideline is to provide recommendations based on the benefits and harms of higher (<150 mmHg) versus lower (≤140 mmHg) SBP targets in adults age 60 or older. As such, the co-developers do not make specific recommendations for pharmacotherapy, but cite thiazide-type diuretics, ACEIs, ARBs, CCBs, and beta-blockers as effective pharmacologic options.

Combination Pharmacologic Therapy

VA/DoD and the JNC 8 Panel acknowledge that more than one antihypertensive drug is often needed to achieve BP control. With regard to initiation of combination therapy, if goal BP is not reached within one month of treatment, JNC 8 recommends increasing the dose of the initial drug or adding a second drug from one of the four classes recommended as first-line therapy (thiazide-type diuretic, CCB, ACEI, or ARB). VA/DoD suggests initiating combination therapy for patients with a baseline SBP of >20 mmHg or DBP of >10 mmHg above the patient's goal. VA/DoD recommends ACEIs or ARBs (not concurrently) and long-acting dihydropyridine CCBs as appropriate alternatives for patients who cannot tolerate thiazide-type diuretics, as supplementary therapies for patients who do not reach their hypertensive goals, or for those starting on combination therapy. JNC 8 and VA/DoD agree that, if goal BP cannot be achieved with two drugs, a third may be added. The ACP/AAFP guideline does not address combination pharmacologic therapy.

Comparison of Recommendations

Pharmacological Management of Hypertension

JNC 8 (2014)	**Recommendation 1** In the general population aged 60 years or older, initiate pharmacologic treatment to lower BP at SBP of 150 mmHg or higher or DBP of 90 mmHg or

Strong Recommendation – Grade A

Corollary Recommendation

In the general population aged 60 years or older, if pharmacologic treatment for high BP results in lower achieved SBP (for example, <140 mmHg) and treatment is not associated with adverse effects on health or quality of life, treatment does not need to be adjusted.

Expert Opinion – Grade E

Recommendation 2

In the general population younger than 60 years, initiate pharmacologic treatment to lower BP at DBP of 90 mmHg or higher and treat to a goal DBP of lower than 90 mmHg.

For ages 30 through 59 years, Strong Recommendation – Grade A

For ages 18 through 29 years, Expert Opinion – Grade E

Recommendation 3

In the general population younger than 60 years, initiate pharmacologic treatment to lower BP at SBP of 140 mmHg or higher and treat to a goal SBP of lower than 140 mmHg.

Expert Opinion – Grade E

Recommendation 4

In the population aged 18 years or older with CKD, initiate pharmacologic treatment to lower BP at SBP of 140 mmHg or higher or DBP of 90 mmHg or higher and treat to goal SBP of lower than 140 mmHg and goal DBP lower than 90 mmHg.

In the population aged 18 years or older with diabetes, initiate pharmacologic treatment to lower BP at SBP of 140 mmHg or higher or DBP of 90 mmHg or higher and treat to a goal SBP of lower than 140 mmHg and goal DBP lower than 90 mmHg.

Expert Opinion – Grade E

Recommendation 6

In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, CCB, ACEI, or ARB.

Moderate Recommendation – Grade B

Recommendation 7

In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.

For general black population: Moderate Recommendation – Grade B

For black patients with diabetes: Weak Recommendation – Grade C

Recommendation 8

In the population aged 18 years or older with CKD and hypertension, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status.

Moderate Recommendation – Grade B

Recommendation 9

	initial drug or add a second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB). The clinician should continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with 2 drugs, add and titrate a third drug from the list provided. Do not use an ACEI and an ARB together in the same patient. If goal BP cannot be reached using the drugs in recommendation 6 because of a contraindication or the need to use more than 3 drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy or for the management of complicated patients for whom additional clinical consultation is needed. *Expert Opinion – Grade E*
VA/DoD (2014)	<u>Pharmacological Therapy</u> **Initiation of Pharmacotherapy** • The Work Group recommends offering pharmacologic treatment for hypertensive patients 60 years and older with a SBP ≥160 mmHg. (**Strong for**) • The Work Group suggests considering pharmacologic treatment using a shared decision-making model for hypertensive patients 60 years and older with SBP <160 mmHg. (**Weak for**) • The Work Group suggests offering pharmacologic treatment to patients with a history of cerebrovascular disease (stroke, TIA, or asymptomatic carotid artery disease) and a SBP ≥140 mmHg. (**Weak for**) • The Work Group suggests pharmacologic treatment for hypertensive patients younger than 60 with a SBP ≥160 mmHg, regardless of DBP. (**Weak for**) • The Work Group recommends offering pharmacologic treatment for patients 30 years and older with a DBP ≥90 mmHg. (**Strong for**) • The Work Group suggests offering pharmacologic treatment for patients age 18 to 29 with a DBP ≥90 mmHg. (**Weak for**)

goal of <150 mmHg. (**Strong for**)

- For patients below 60 years of age, the Work Group suggests treating to a SBP goal of <150 mmHg. (**Weak for**)
- The Work Group recommends treating to a DBP goal <90 mmHg in patients 30 years and older. (**Strong for**)
- The Work Group suggests treating to a DBP goal <90 mmHg in patients age 18 to 29. (**Weak for**)
- For patients with diabetes (all age groups), the Work Group recommends treating to a SBP goal of <150 mmHg. (**Strong for**)
- For patients with diabetes (all age groups) who tolerate antihypertensive drugs, the Work Group suggests treating to a SBP goal of <140 mmHg. (**Weak for**)
- For patients with diabetes, the Work Group recommends treating to a DBP goal <85 mmHg. (**Strong for**)

Hypertension Control and Follow-up

- The Work Group suggests that patients be seen within one month of initiation of lifestyle or pharmacological therapy to determine adequacy of hypertension control, degree of patient adherence, and presence of adverse effects. (*Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence*.) (**Weak for**)
- Once the patient's blood pressure is controlled, the Work Group suggests follow-up at least annually, or more frequently as indicated, depending on patient preference. (*Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence*.) (**Weak for**)

Monotherapy or Combination Therapy

- The Work Group suggests taking into consideration the patient's baseline blood pressure and presence of comorbidities, when deciding on either monotherapy or combination therapy (two drugs) when initiating drug therapy. (*Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence*.) (**Weak for**)

(*Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence*.) (**Weak for**)

First-Line Therapy

- The Work Group recommends the use of thiazide-type diuretics for the treatment of hypertension. (**Strong for**)
- The Work Group suggests the use of thiazide-type diuretics at recommended treatment doses as first-line therapy for drug treatment of hypertension either as monotherapy or in combination with other agents. (*Modified from 2004 VA/DoD HTN CPG*.) (**Weak for**)
- To initiate treatment of hypertension with a thiazide-type diuretic, the Work Group suggests the use of chlorthalidone or indapamide over hydrochlorothiazide. (**Weak for**)
- The Work Group does not suggest switching from hydrochlorothiazide to chlorthalidone or indapamide if the patient is adequately controlled on and tolerating hydrochlorothiazide. (**Weak against**)
- The Work Group suggests considering a switch from hydrochlorothiazide to chlorthalidone for patients whose hypertension is inadequately controlled on 50 mg/day of hydrochlorothiazide. (**Weak for**)
- The Work Group recommends a dosage of 12.5-25 mg/day of chlorthalidone, 25-50 mg/day of hydrochlorothiazide, or a dosage of 2.5 mg/day immediate-release or 1.5-2.5 mg/day sustained-release (not currently available in the US) of indapamide. (**Strong for**)

Alternative or Supplementary Therapies

- The Work Group recommends using the following as alternative therapies for patients who cannot tolerate thiazide-type diuretics, as supplementary therapies for patients who do not reach their hypertensive goals, or for those starting on combination therapy:
    a. ACEIs or ARBs (but not together)
    b. Long-acting dihydropyridine CCBs

following three drug classes together in the same patient: ACEIs, ARBs, or direct renin inhibitors. (**Strong against**)

- The Work Group recommends additional therapy in refractory hypertension (for those who do not tolerate or are not adequately controlled with triple therapy [i.e., thiazide-type diuretics, ACEI or ARB, and CCBs] described in Recommendation 43) or as supplementary therapy in some clinical indications. Drug classes for consideration can include (not in priority order):
  a. Aldosterone/mineralocorticoid receptor antagonists (e.g., spironolactone, eplerenone)
  b. Other potassium-sparing diuretic (i.e., amiloride)
  c. Alpha-adrenergic blockers
  d. Beta-adrenergic blockers
  e. Non-dihydropyridine CCBs
  f. Combined alpha-beta adrenergic blockers
  g. Peripherally acting antiadrenergic agents (reserpine, pending availability)
  h. Direct acting vasodilators (e.g., hydralazine, minoxidil)
  i. Centrally acting antiadrenergic drugs (e.g., clonidine, methyldopa)

  (Strong for)

- The Work Group recommends against the use of alpha-adrenergic blockers as monotherapy, but this class of agents may be used as supplemental therapy or if warranted by comorbid conditions (e.g., symptomatic prostatic hypertrophy). (*Modified from 2004 VA/DoD HTN CPG*.) (**Strong against**)

Specific Populations

- In patients with hypertension and CKD (reduced kidney function with albuminuria), the Work Group recommends treatment with an ACEI, or ARB for improving kidney outcomes. (Modified from 2004 VA/DoD HTN CPG.) (**Strong for**)

	• In African American patients with hypertension and stage 1-3 CKD, the Work Group suggests a combination of a thiazide-type diuretic (for cardiovascular protection) with either an ACEI or ARB (for renal protection). (**Weak for**)
ACP/AAF (2017)	**Recommendation 1**: ACP and AAFP recommend that clinicians initiate treatment in adults aged 60 years or older with SBP persistently at or above 150 mmHg to achieve a target SBP of less than 150 mmHg to reduce the risk for mortality, stroke, and cardiac events. (**Grade: strong recommendation, high-quality evidence**). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific BP targets with the patient. High-quality evidence showed that treating hypertension in older adults to moderate targets (<150/90 mmHg) reduces mortality (ARR, 1.64), stroke (ARR, 1.13), and cardiac events (ARR, 1.25). Most benefits apply to such adults regardless of whether they have diabetes. The most consistent and greatest absolute benefit was shown in trials with a higher mean SBP at baseline (>160 mmHg). Any additional benefit from aggressive BP control is small, with a lower magnitude of benefit and inconsistent results across outcomes. Although this guideline did not specifically address pharmacologic versus nonpharmacologic treatments for hypertension, several nonpharmacologic treatment strategies are available for consideration. Effective nonpharmacologic options for reducing BP include such lifestyle modifications as weight loss, such dietary changes as the DASH diet, and an increase in physical activity. Non-pharmacologic options are typically associated with fewer side effects than pharmacologic therapies and have other positive effects; ideally, they are included as the first therapy or used concurrently with drug therapy for most patients with hypertension. Effective pharmacologic options include antihypertensive medications, such as thiazide-type diuretics (adverse effects include electrolyte disturbances, gastrointestinal discomfort, rashes and other allergic reactions, sexual dysfunction in men, photosensitivity reactions, and

hyperkalemia), CCBs (adverse effects include dizziness, headache, edema, and constipation), and beta-blockers (adverse effects include fatigue and sexual dysfunction).

Most of the included studies measured seated BP after 5 minutes of rest and used multiple readings. Clinicians should ensure that they are accurately measuring BP before beginning or changing treatment of hypertension. Assessment may include multiple measurements in clinical settings (for example, 2 to 3 readings separated by 1 minute in a seated patient who is resting alone in a room) or ambulatory or home monitoring.

Recommendation 2: ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in adults aged 60 years or older with a history of stroke or TIA to achieve a target SBP of less than 140 mmHg to reduce the risk for recurrent stroke. (**Grade: weak recommendation, moderate-quality evidence**). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific BP targets with the patient.

Moderate-quality evidence showed that treating hypertension in older adults with previous TIA or stroke to an SBP target of 130 to 140 mmHg reduces stroke recurrence (ARR, 3.02) compared with treatment to higher targets, with no statistically significant effect on cardiac events or all-cause mortality.

Recommendation 3: ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in some adults aged 60 years or older at high cardiovascular risk, based on individualized assessment, to achieve a target SBP of less than 140 mmHg to reduce the risk for stroke or cardiac events. (**Grade: weak recommendation, low-quality evidence**). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific BP targets with the patient.

	to each patient, including comorbidity, medication burden, risk for adverse events, and cost. Clinicians should individually assess cardiovascular risk for patients. Generally, increased cardiovascular risk includes persons with known vascular disease, most patients with diabetes, older persons with CKD with estimated GFR less than 45 mL/min/1.73 m2, those with metabolic syndrome (abdominal obesity, hypertension, diabetes, and dyslipidemia), and older persons. For example, among the included studies, SPRINT defined patients with increased cardiovascular risk as those meeting at least 1 of the following criteria: clinical or subclinical cardiovascular disease other than stroke; CKD, excluding polycystic kidney disease, with an estimated GFR of 20 to less than 60 mL/min/1.73 m2 of body surface area; 10-year risk for cardiovascular disease of 15% or greater based on the Framingham risk score; or age 75 years or older. This trial found that targeting SBP to less than 120 mmHg compared with less than 140 mmHg in adults without diabetes or prior stroke, at high-risk for cardiovascular disease, and with a baseline SBP of less than 140 mmHg significantly reduced fatal and nonfatal cardiovascular events and all-cause mortality. In contrast, ACCORD included only adults with type 2 diabetes and found no statistically significant reduction in the primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular events (RR, 0.94 [CI, 0.80 to 1.11]). This study did find a reduction in stroke events (RR, 0.58 [CI, 0.39 to 0.88]), but there were more serious adverse events associated with an SBP target of less than 120 mmHg versus less than 140 mmHg.

Strength of Evidence and Recommendation Grading Schemes

JNC 8 (2014)	**Evidence Quality Rating**

randomized controlled trials (RCTs) that adequately represent populations to which the results are applied and directly assess effects on health outcomes Well-conducted meta-analyses of such studies Highly certain about the estimate of effect; further research is unlikely to change confidence in the estimate of effect	
RCTs with minor limitations affecting confidence in, or applicability of, the results Well-designed, well-executed non–randomized controlled studies and well-designed, well-executed observational studies Well-conducted meta-analyses of such studies Moderately certain about the estimate of effect; further research may have an impact on confidence in the estimate of effect and may change the estimate	Moderate

Non–randomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports) Physiological studies in humans Meta-analyses of such studies Low certainty about the estimate of effect; further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate	

*The evidence quality rating system used in the guideline was developed by the NHLBI's Evidence-Based Methodology Lead (with input from NHLBI staff, external methodology team, and guideline panels and work groups) for use by all the NHLBI cardiovascular disease (CVD) guideline panels and work groups during this project. Additional details regarding the strength of recommendation grading system are available in the online Supplement (see the "Availability of Companion Documents" field).

Strength of Recommendations

Grade	Strength of Recommendation
A	Strong Recommendation There is high certainty based on evidence that the net benefit[a] is substantial.

	There is moderate certainty based on evidence that the net benefit is moderate to substantial or there is high certainty that the net benefit is moderate.
C	Weak Recommendation There is at least moderate certainty based on evidence that there is a small net benefit.
D	Recommendation Against There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.
E	Expert Opinion ("There is insufficient evidence or evidence is unclear or conflicting, but this is what the committee recommends.") Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the committee thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.

	("There is insufficient evidence or evidence is unclear or conflicting.") Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the committee thought no recommendation should be made. Further research is recommended in this area.

[a]Net benefit is defined as benefits minus the risks/harms of the service/intervention.

Note: The strength of recommendation grading system used in the guideline was developed by the NHLBI's Evidence-Based Methodology Lead (with input from NHLBI staff, external methodology team, and guideline panels and work groups) for use by all the NHLBI cardiovascular disease (CVD) guideline panels and work groups during this project. Additional details regarding the strength of recommendation grading system are available in the online Supplement (see the "Availability of Companion Documents" field).

VA/DoD (2014)

<u>Quality of Evidence and Definitions</u>*

High quality — Further research is very unlikely to change confidence in the estimate of effect.
Moderate quality — Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low quality — Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low quality — Any estimate of effect is very uncertain.

*Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., Schünemann, H. J. & the GRADE Working Group. (2008). GRADE; An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ, 336*, 924-926.

<u>Strength of Recommendations</u>

	confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation. Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences. Using these elements, the grade of each recommendation is presented as part of a continuum: • **Strong For** (or "The Work Group recommends offering this option …") • **Weak For** (or "The Work Group suggests offering this option …") • **Weak Against** (or "The Work Group suggests not offering this option …") • **Strong Against** (or "The Work Group recommends against offering this option …") Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.
ACP/AAF (2017)	**Rating the Body of Evidence** • High = Further research is very unlikely to change confidence on the estimate of effect. • Moderate = Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. • Low = Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

*Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) workgroup.

Methodology

Click on the links below for details of guideline development methodology

JNC 8 (2014)	VA/DoD (2014)	ACP/AAFP (2017)

All of the clinical practice guidelines being compared were developed from systematic reviews of the evidence. The ACP/AAFP guideline is also based on a meta-analysis of RCTs; VA/DoD and ACP/AAFP also reviewed published meta-analyses to inform development of their guidelines. All of the systematic reviews provide relevant details of the literature search and selection process, including the electronic databases that were searched, time period of the search, search terms used, and the inclusion and exclusion criteria applied. To assess the quality and strength of the selected evidence, the guideline developers weighted it according to a rating scheme and provide the scheme. ACP/AAFP, VA/DoD and JNC 8 all formulated the guideline recommendations using an expert consensus process based on evaluation of the evidence, and rate the strength of the

guidelines.

Benefits and Harms

Benefits

JNC 8 (2014)	Reducing major adverse health outcomes from elevated blood pressure
VA/DoD (2014)	• Formulation of an efficient and effective assessment of the patient's condition • Optimal use of therapy to reduce symptoms and enhance functionality • Minimizing preventable complications and morbidity • Use of personalized, proactive, patient-driven care **Benefits of Pharmacological Therapy** Treatment of hypertension with drugs in clinical trials has reduced stroke incidence by 35% to 40%; myocardial infarction by 20% to 25%; and heart failure by more than 50%. While most hypertensive patients benefit from pharmacotherapy, this benefit is larger among patients who already have complications of hypertension, such as target organ damage.
ACP/AAFP (2017)	• Mortality, incidence of stroke, and cardiac events were all reduced with treatment. • Treating to a lower BP target did not further reduce mortality, quality of life, or functional status, but it did reduce the incidence of stroke and cardiac events. Refer to the "Benefits of Treating Higher Versus Lower BP Targets in Older Adults" section of the original guideline document for additional information.

Harms

JNC 8 (2014)	• Treatment-associated adverse effects • ACEIs and ARBs should not be used in combination.

	hypertensive drug therapies.
ACP/AAFP (2017)	• Increased withdrawals due to adverse events with higher vs. lower BP targets • Increased cough, hypotension, and risk for syncope with treating to lower vs. higher BP targets • No difference between higher and lower BP targets for renal outcomes, cognitive outcomes, or falls and fractures **Adverse Effects** Some of the adverse effects associated with antihypertensive medications include (but are not limited to) the following: • Thiazide-type diuretics: electrolyte disturbances, gastrointestinal discomfort, rashes and other allergic reactions, sexual dysfunction in men, photosensitivity reactions, and orthostatic hypotension • ACEIs: cough and hyperkalemia • ARBs: dizziness, cough, and hyperkalemia • CCBs: dizziness, headache, edema, and constipation • Beta-blockers: fatigue and sexual dysfunction Although electrolyte disturbances are a common adverse effect of hypertension treatment in clinical practice, data were not presented on these abnormalities in the evidence review. Drugs to treat hypertension have well-known adverse effects, including hypokalemia, hyperkalemia, hyponatremia, hypotension, dizziness, headache, edema, erectile dysfunction, and cough. Refer to the "Harms of Higher Versus Lower BP Targets in Older Adults" section of the original guideline document for additional information.

Abbreviations

AAFP, American Academy of Family Physicians

ACCORD-BP, Action to Control Cardiovascular Risk in Diabetes blood pressure trial

ACEI, angiotensin-converting enzyme inhibitor

ACP, American College of Physicians

ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation

ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

ARB, angiotensin receptor blocker

ARR, absolute risk reduction

BP, blood pressure

CCB, calcium channel blocker

CI, confidence interval

CPG, clinical practice guideline

CKD, chronic kidney disease

DASH, Dietary Approaches to Stop Hypertension

DBP, diastolic blood pressure

EWPHE, European Working Party on High Blood Pressure in the Elderly

GFR, glomerular filtration rate

HTN, hypertension

HYVET, Hypertension in the Very Elderly Trial

JNC 8, Eighth Joint National Committee

RR, relative risk

SBP, systolic blood pressure

SHEP, Systolic Hypertension in the Elderly Program

SPRINT, Systolic Blood Pressure Intervention Trial

Syst-Eur, Systolic Hypertension in Europe Trial

TIA, transient ischemic attack

UKPDS, UK Prospective Diabetes Study

VA/DoD, Department of Veterans Affairs/Department of Defense

Status

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