Blood Pressure Control in Primary Care

EVIDENCE REVIEW

Healthy Hearts for Oklahoma (H2O)

The Oklahoma Cooperative for AHRQ's EvidenceNOW

ADVANCING HEART HEALTH IN PRIMARY CARE

NaRCAD

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Authors: Jennifer Lewey, MD, Stephen Braun, Michael Fischer, MD, MS.

Evidence-based management of hypertension in primary care

Introduction

Hypertension is the most common condition seen in primary care.[4] Left untreated, hypertension raises the risk of heart attack, stroke, renal failure, and death.[5] For individuals 40–70 years of age, each increment of 20 mmHg in systolic blood pressure (SBP) or 10 mmHg in diastolic blood pressure (DBP) doubles the risk of cardiovascular disease (CVD) across the entire blood pressure (BP) range from 115/75 to 185/115 mmHg.[5]

Evidence from rigorous clinical trials shows that treating hypertensive patients significantly reduces their disease burden.[5]

Table 1: Impact of effective antihypertensive therapy in reducing clinical outcomes[7]

Outcome	Average percent reduction
Stroke	35-40%
Myocardial infarction	20-25%
Heart failure	50%

Nearly a third (32.6%) of U.S. adults ≥ 20 years are estimated to have hypertension, defined for surveillance purposes as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, currently taking antihypertensive medicine, or having been told at least twice by a health care professional that one has hypertension.[8] This equates to an estimated 80 million adults with hypertension in the U.S.[8] A higher percentage of men than women have hypertension until 45 years of age, at which point prevalence switches. Overall, more women than men are hypertensive: 38.3 million men and 41.7 million women.[8]

Although rates of hypertension control and treatment have been improving slowly over the past several decades,[9] data from the 2011-2012 National Health and Nutrition Examination Survey (NHANES) found that 17% of U.S. adults are not aware they have hypertension.[10] In addition, of those currently being treated for hypertension, only 54% had their hypertension under control.[8]

Fast Facts

- ✓ In 2014, Oklahoma had the 9th highest rate of hypertension (37.5%)[3] among all states.
- ✓ Achieving levels of hypertension control in Oklahoma similar to those in states with the best levels of hypertension control in the U.S. would reduce the state's cardiovascular mortality by 9.6%.[6]

This evidence review synthesizes current evidence about hypertension management and recommends treatment approaches to this common condition.

Classifying blood pressure

The following definitions of hypertension were suggested in 2003 by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (Table 2). Specific definitions of hypertension were not addressed in the 2014 JNC 8 expert panel report, however recommended treatment thresholds are consistent with these definitions. These definitions apply only to patients not on antihypertensive medication and who are not acutely ill.

Table 2: JNC-7 blood pressure classifications[5]

BP classification	Systolic mmHg		Diastolic mmHg
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	≥160	or	≥100

Isolated systolic hypertension is present when SBP ≥ 140 with normal DBP (< 90). Isolated diastolic hypertension is present when DBP ≥ 90 with normal SBP (< 140). Individuals with elevated SBP and DBP (≥ 140/ ≥ 90) are considered to have mixed systolic/diastolic hypertension. (Note that "prehypertension" is not a disease category, but a designation to identify patients at high risk of developing hypertension.)

The evidence base for blood pressure classifications and guideline creation continues to evolve. In September, 2015, the landmark Systolic Blood Pressure Intervention Trial (SPRINT) was stopped early when results showed significant benefits among the participants randomized to the intensive treatment group, which involved treating to reach a target SBP of 120 mmHg or lower.[11] Whether, or how, these results will affect future guideline recommendations is unknown.

Blood pressure screening

Professional groups differ in the intensity and time intervals for recommended blood pressure screenings.

Table 3. Recommendations for blood pressure screening

Organization	Recommendations
U.S. Preventive Services Task Force	✓ Every year for adults age 40 years and older and those who are at increased risk for high blood pressure (i.e., those with high-normal blood pressure (130–139/85–89 mm Hg); are overweight or obese; or are African American. ✓ Every 3-5 years for adults ages 18 to 39 years with normal blood pressure (<130/85 mm Hg) who do not have other risk factors.
JNC 7	✓ Every 2 years for adults with BP < 120/80. ✓ Every year for those with BP levels > 120/80.
American Heart Association	✓ Every regular health care visit or at least once every 2 years in adults with BP < 120/80.
American Congress of Obstetricians and Gynecologists	✓ Every annual health care visit.

Blood pressure measurement

Blood pressure measurement in the office

Patients should be seated quietly for at least 5 minutes in a chair with feet on the floor and the arm to be used for the measurement supported at the level of the heart. Individuals should avoid exercise, caffeine, and smoking for 30 minutes prior to measurement. An appropriate-sized cuff should be used. At least 2 measurements should be made and the average should be recorded.

Ambulatory blood pressure measurement

Ambulatory blood pressure monitoring (ABPM) provides BP measurements during different types of activities throughout the day. ABPM correlates better than office measurement with cardiovascular events.[12,13] Thresholds for diagnosing hypertension using ABPM according to the U.S. and European hypertension guidelines[5,14] are as follows:

- 24-hour average: ≥ 130/80
- Awake (daytime) average: ≥ 135/85
- Asleep (nighttime) average: ≥ 120/70

The most common indication for ABPM is suspected white coat hypertension. Approximately 20-25% of individuals with hypertension have white coat hypertension, which is diagnosed when an individual has persistently elevated blood pressure when measured in a medical setting but normal blood pressure when measured at home.

ABPM may also be useful in evaluating patients with suspected masked hypertension (normal office BP with elevated BP when measured at home), drug-resistant hypertension, episodic hypertension, or hypotensive symptoms with antihypertensive medication.[5] ABPM is reimbursed by Medicaid and Medicare for the evaluation of white coat hypertension but may not be covered for other indications depending on type of insurance.[14]

Self-measurement

Self-measurement of blood pressure at home, work, or in a pharmacy can provide useful information about differences between office and out-of-office BP as well as response to therapy. For patients with suspected white coat hypertension, BP self-monitoring can be considered before or in place of ABPM. Patients should take duplicate morning and evening self-measurements using a validated upper arm BP device for 7 days and calculate the average after discarding measurements on the first day.[15] If it is difficult for a patient to use an upper arm device, wrist devices can be used. Finger devices are not recommended due to concerns that peripheral vasoconstriction can skew results.[15]

Patient evaluation

Once a patient has been identified as hypertensive, the clinician has four key objectives:

1. Assess potential lifestyle factors that may be elevating blood pressure, including diet, alcohol, physical inactivity, and obesity.
2. Identify other cardiovascular risk factors or concomitant disorders that will guide treatment.
3. Search for identifiable secondary causes of high blood pressure.
4. Determine extent of end-organ damage, if any.

Secondary causes of hypertension are uncommon. Consider a work-up for secondary hypertension in patients with any of the following: abdominal bruit, accelerated or resistant hypertension, recurrent flash pulmonary edema, renal failure, or onset of hypertension under age 30 without a family history.

Potential causes of secondary hypertension include:

- Sleep apnea
- Drug-induced hypertension
- Chronic kidney disease

- Primary aldosteronism
- Renovascular disease
- Chronic steroid therapy or Cushing's syndrome
- Pheochromocytoma
- Coarctation of the aorta
- Thyroid or parathyroid disease

Prescription or over-the-counter medications may raise blood pressure within the normal range or cause overt hypertension. The most common medications with this potential are oral contraceptives (particularly with higher doses of estrogen), NSAIDs, antidepressants, glucocorticoids, decongestants (especially pseudoephedrine), stimulants (including weight loss medications containing stimulants), and cyclosporine.

Laboratory testing is recommended in all patients newly diagnosed with hypertension in order to identify common comorbid conditions and prior to initiating medications. Recommended laboratory testing includes serum electrolytes and renal function, fasting glucose or hemoglobin A1c, urinalysis, and lipid profile. In addition, a baseline electrocardiogram should be obtained in order to assess for left ventricular hypertrophy or silent ischemic heart disease.

Hypertension guidelines

The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7) was published in 2003 and provided extensive guidelines regarding the classification and treatment of hypertension. In 2014, the panel members appointed to JNC 8 published their recommendations on evidence-based guidelines for management of high blood pressure in adults. The JNC 8 panel member recommendations were not endorsed by the NIH to replace the JNC 7 guidelines, however several professional organizations, including the American Academy of Family Physicians, have endorsed these recommendations.

Goals of BP treatment

Individuals < 60 years old

Adults ages 18 to 59 years old with SBP ≥ 140 or DBP ≥ 90 should be considered for treatment with lifestyle modifications and medication. Treatment should be titrated to a goal BP < 140/90. This recommendation is supported by both JNC 7 and JNC8.

Individuals ≥ 60 years

Among adults ages 60 years or older, the JNC 8 panel members recommend that antihypertensive medications should be initiated when SBP ≥ 150 or DBP ≥ 90 and treatment should be titrated to a goal BP < 150/90.[4] This goal is higher than the prior JNC 7 guidelines, which recommended a SBP goal < 140 for this age group.[16] These recommendations have been endorsed by the American Academy of Family Physicians, however other professional societies continue to recommend a SBP goal < 140.[17]

The JNC 8 panel members offer a corollary recommendation based on expert opinion that ongoing treatment in patients 60 and older that is well-tolerated and that results in SBP < 140 does not need to be adjusted.[4]

According to the JNC 8 panel members, the burden of evidence from clinical hypertension randomized controlled trials (RCT) does not support a marginal benefit in achieving SBP < 140 compared to SBP < 150 for older adults. In trials that randomized patients to lower (SBP < 140) versus higher (SBP < 150) goals, the lower SBP goal did not result in improved clinical outcomes, although at least one of the studies may have been underpowered.[18,19] The SPRINT trial has been studying hypertension treatment to a SBP < 120 compared to < 140 mmHg in patients > 50 years. The study is sponsored by the NHLBI which announced early termination in September 2015 due to reduced cardiovascular events in the group of patients treated to the lower SBP goal.[11] Final results of this study have not been peer-reviewed and published as of October 2015.

One additional consideration is that the JNC 8 panel members only considered RCT's as the basis for their recommendations. Multiple observational studies have demonstrated poor adherence to antihypertensive therapy. In real-world settings, achieving BP targets may be more challenging than in clinical trials, therefore shifting to a higher SBP goal may result in non-adherent patients being even further from ideal BP levels.

Diabetic patients

In patients with diabetes, antihypertensive medications should be initiated when SBP ≥ 140 or DBP ≥ 90. Treatment should be titrated to a goal BP < 140/90. This threshold is recommended by the JNC 8 panel members and is consistent with other professional society recommendations, including the American Diabetic Association (ADA). The ADA additionally recommends that an even lower SBP goal (< 130/90) be considered in patients with long life expectancy in whom treatment can be tolerated without side effects or in patients at high risk of stroke.[20]

Patients with Chronic Kidney Disease (CKD)

In patients with CKD, antihypertensive medications should be initiated when SBP ≥ 140 or DBP ≥ 90. Treatment should be titrated to a goal BP < 140/90.

Managing hypertension in primary care

Lifestyle modification

All patients with prehypertension or hypertension should attempt to modify their lifestyle, both before other treatments are considered and concurrent with any treatments pursued. Although the amounts of BP reduction that can be expected from any single lifestyle intervention are relatively modest, the cumulative effect of multiple interventions can be significant and may allow for the avoidance, or minimization, of pharmacological therapy in motivated patients.

Table 4: JNC 7 Guidelines for lifestyle modifications to reduce hypertension[5]

Modification	Recommendation	Approximate SBP reduction
Reduce weight	Maintain normal body mass index	5–20 mmHg per 10 kg of weight loss
Adopt "DASH" diet	Low-fat diet rich in fruits and vegetables	8–14 mmHg
Restrict dietary sodium	Less than 100 mmol/day (2.3 g/day)	2–8 mmHg
Physical activity	Aerobic physical activity 30 minutes a day, most days	4–9 mmHg
Moderate alcohol consumption	Men < 2 ounces a day Women < 1 ounce a day	2–4 mmHg

Smoking cessation is another important component of management, both for improved blood pressure control and to reduce cardiovascular risk.

Pharmacologic treatment

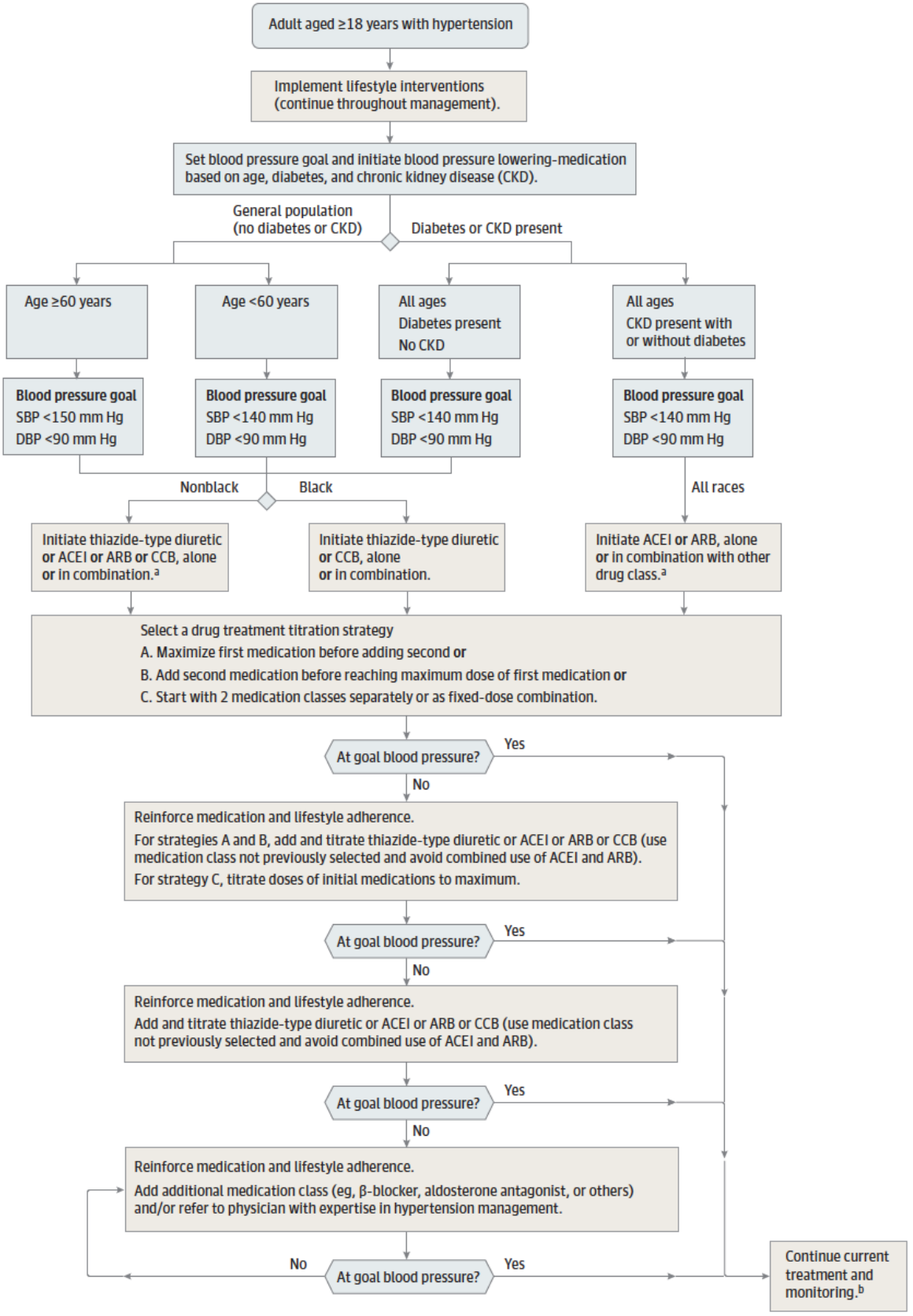
Hypertensive patients who do not respond to an adequate trial of lifestyle modification (at least one month) will require drug therapy to reach appropriate BP goals. Stage 1 hypertension should be treated with one agent or combination therapy, and patients with Stage 2 hypertension should be started on two agents simultaneously. Over two-thirds of hypertensive patients will eventually require more than one medication.[21]

In the past 4 decades, numerous clinical trials have compared individual antihypertensive medications to placebo, using blood pressure lowering as the main outcome. Meta-analyses have combined these data to calculate the average effect on blood pressure of each of the major classes of antihypertensive medication. The pressure-lowering effects of standard-dose anti-hypertensives in each major drug class are similar.[22,23]

Table 5: Effect of standard doses of anti-hypertensive drug classes on SBP[22,23]

Effect of standard dose antihypertensive on SBP	
Drug class	**SBP reduction (mmHg)**
Thiazide	8.8
Beta-blocker	9.2
ACEI	8.5
ARB	10.3
CCB	8.8
Renin Inhibitor	8.7

The primary medication classes for treatment of hypertension are thiazides, angiotensin-conversting enzyme inhibitiors (ACEI), angiotensin receptor blockers (ARB), and calcium channel blockers (CCB). The JNC 8 recommendations are summarized in the treatment algorithm below.



Recommended drug classes for treating hypertension

Thiazides

The landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial randomized nearly 40,000 patients with hypertension into one of four treatment groups and compared clinical outcomes.[24] The four groups were diuretics, CCB, ACEI, and alpha-blockers. (The alpha-blocker arm was stopped early because of worse clinical outcomes.)

The ALLHAT trial found that thiazide diuretics were:

- More effective than CCBs and ACEIs in controlling SBP
- More effective than CCBs in preventing congestive heart failure
- More effective than ACEIs in preventing combined cardiovascular events (stroke, angina, heart failure)
- Equivalent to CCBs and ACEIs in preventing cardiovascular events and mortality
- As well-tolerated as other classes of medications

Based on the ALLHAT trial, thiazide diuretics remain first-line treatment for hypertension unless a patient has a compelling clinical indication for another class. The blood pressure lowering effect of thiazides is not immediate. Most patients will respond with a reduction in blood pressure within 4 weeks, although a minority of patients will not achieve maximum reduction for up to 12 weeks.[32]

If blood pressure control is inadequate after a reasonable time period, rather than increase the dose of the diuretic, it is better to add another drug from a different class, and to re-emphasize the importance of lifestyle changes. For patients who require more than one drug to control their hypertension, thiazides should generally be part of the regimen.

No head-to-head trials have compared different thiazides with one another in terms of clinical outcomes, although both chlorthalidone and hydrochlorothiazide (HCTZ) lower blood pressure effectively.[25] Indirect comparisons of thiazides suggest that both agents have equal effects on reducing rates of serious cardiovascular events, and both appear equally safe.[26] Increasing the dose achieves little additional gain in blood pressure control, but does increase the rate of adverse effects.

What about thiazide side effects?

Concerns about metabolic side effects of thiazides such as hypokalemia, hyperglycemia, hyperuricemia, or hyponatremia were based on early studies in which unnecessarily high doses of thiazides were used (e.g., 50–100 mg/d of HCTZ). At lower doses, thiazides provide very effective blood pressure control and side effects rates that are indistinguishable from other classes of anti-hypertensives (and only 2% more than placebo).[1,2]

ACE Inhibitors

No randomized head-to-head trials that measured clinically important outcomes have compared different ACEIs in patients with hypertension, although many studies have compared specific ACEIs with placebo, or with drugs from other antihypertensive classes. These trials have not found any consistent advantage of any one ACEI over another.[27] Several trials compared the rates of adverse events from ACEIs in

patients with hypertension and found no important differences among them in rates of cough, angioedema, hyperkalemia or acute renal insufficiency.[28]

Angiotensin receptor blockers

ARBs were introduced into routine practice more recently than ACEIs and have gained favor primarily because of they present a lower risk for inducing cough (approximately 10% vs. 3%). As with ACEIs, there have been no head-to-head trials of different ARBs that have measured clinically important outcomes or safety related to hypertension.[29] The existing data do not suggest any meaningful differences among individual ARBs.[30]

Many trials have found that ACEIs and ARBs are equally effective at lowering blood pressure.[31] A systematic review also found that ACEIs and ARBs had similar effects on quality of life, progression to diabetes, progression of renal disease, left ventricular function, cardiovascular events, and mortality.[31]

Calcium channel blockers

Although no trials have compared CCBs to one another in the treatment of hypertension, trials of CCBs to treat other conditions do not suggest any important differences in efficacy.[32] Indirect comparisons of CCBs suggest they are all relatively safe when used to treat hypertension.[32]

Other drug classes

Beta-blockers

In prior versions of the JNC guidelines, beta-blockers were recommended as first-line agents for treating uncomplicated hypertension. But since 2005, several reviews have highlighted problems with beta-blockers.[33,34,35] These analyses found that while beta-blockers were superior to placebo for lowering BP, they were inferior to the other major antihypertensive drug classes in preventing stroke, and were borderline inferior in preventing other cardiovascular outcomes such as MI. This appears to be a particular problem for older patients.[33] Beta-blockers should continue to play a role in treating hypertensive patients with compelling indications such as coronary artery disease (CAD) and congestive heart failure (CHF), but they are no longer considered a first choice agent for uncomplicated hypertension.[4]

Renin Inhibitors

Direct renin inhibitors block the conversion of angiotensinogen to angiotensin I. Aliskiren (Tekturna) was approved by the FDA in 2007 for treatment of primary hypertension. Direct renin inhibitors have the potential advantage of not affecting kinin metabolism, and theoretically posing a lower risk for cough or angioedema.[36] However, there have been no head-to-head comparisons of aliskiren with ACEIs or ARBs for efficacy or safety. A meta-analysis found that standard doses of aliskiren lower SBP to an extent similar to other anti-hypertensive classes.[37] Aliskiren reduces the albumin-to-creatinine ratio in diabetics when added to an ARB, indicating it could have reno-protective effects independent of blood pressure control.[38] Other clinical outcomes (such as death, MI, stroke, and cardiovascular outcomes) have not been evaluated. The JNC8 panel did not include renin inhibitors in their recommendations because there were no studies demonstrating their benefits on kidney or cardiovascular outcomes.[4]

Combination therapy

Since most antihypertensive medications at standard doses will lower SBP by 9-10 mmHg, combination therapy is often required for patients with Stage 1 hypertension, and almost always for patients with Stage 2 hypertension. In the recently-concluded SPRINT trial, patients in the intensive treatment arm used an average of three medications to achieve the target BP levels.[11] In the ALLHAT trial, only about a quarter of patients were controlled on monotherapy.[39]

Most hypertension clinical trials allow for the addition of a second medication to reach target blood pressure levels. The combined data from these trials provide estimated effects of such combination therapy. Large reviews and meta-analysis have demonstrated that for the vast majority of antihypertensive combinations, the effect of combining two drug different classes equals the additive impact of each individual agent.[22,40]

Combination therapy requires a careful evaluation of each drug's dose-response relationship and dose-side effect relationship. Fortunately, most side effects are not additive across drug classes. The important exceptions to this include the increased risk of bradycardia with beta-blocker/CCB combinations, and the risk of hyperkalemia, hypotension, syncope, and renal dysfunction with ACEI/ARB combinations.

Numerous small trials have assessed whether combining an ACEI and an ARB provides additional benefit compared to either agent alone for patients with hypertension. The evidence is mixed. While these trials demonstrate greater reductions in blood pressure from combined therapy, many of the trials had significant methodological flaws (such as the use of sub-maximal doses and inappropriate dosing frequencies), so their results may simply reflect higher total medication doses, rather than a synergistic effect between the two drug classes.[41] Independent of blood pressure lowering, combined therapy does appear to reduce proteinuria in patients with nephropathy to a greater extent than ACEI or ARB monotherapy.[42]

A 2008 randomized controlled trial of combining an ACEI and an ARB in high risk patients (vascular disease and diabetic patients), however, found that combination therapy did not reduce rates of a composite outcome (cardiovascular death, myocardial infarction, stroke, or CHF hospitalization).[43] The combination produced significantly higher rates of adverse events than did either single agent, including hypotension, syncope, and renal dysfunction.[43]

Special populations

African-Americans: The prevalence and severity of hypertension are higher in African-Americans, and their response to therapy is somewhat different than that of non-Hispanic whites. African-Americans often have a reduced blood pressure response to beta-blockers, ACEIs, and ARBs compared to thiazide diuretics or CCBs. In addition, the DASH study found that blood pressure in African-Americans is more responsive to modifications in diet.[44] The JNC 8 treatment algorithm (Figure 1)shows the specific recommendations for African-Americans.

***Elderly*:** More than two-thirds of people over 65 have hypertension, but this age group has the lowest rate of blood pressure control. Numerous studies have documented improvements in CAD, stroke and mortality in the elderly treated for hypertension.[23] For example, an RCT of patients over age 80 with SBP > 160 who were randomized to a diuretic or placebo found a 30% reduction in stroke and 21% reduction

in mortality.[45] Drug treatment generally follows the same principles outlined for all patients, except that lower initial drug doses are usually appropriate. Follow the main guideline of geriatric pharmacology: "Start low, go slow."

***Dementia*:** Cognitive impairment occurs more commonly in people with hypertension, often because high blood pressure is a risk for multi-infarct ("vascular") dementia. Reduced progression of cognitive impairment occurs with effective antihypertensive therapy.[46] CCBs have been shown to slow the decline in cognitive function,[47] though other drug classes have not been well tested.

"Compelling indications"

The JNC 7 report evaluated the clinical trial evidence for patients with hypertension and specific co-morbidities and highlighted six "compelling indications" which warrant tailored hypertension therapy as noted in the table below.

Table 6. Recommended drug classes to treat hypertension in selected patient populations[5]

Compelling indication	Drug Class
Congestive heart failure	ACEI (ARB if intolerant) Beta blocker Aldosterone blocker
Myocardial infarction or ischemic heart disease	Beta blocker ACEI
High risk of coronary artery disease **Angina or silent ischemia**	Beta blocker (CCB if intolerant)
Diabetes	ACEI (ARB if intolerant)
Chronic kidney disease	ACEI (ARB if intolerant)
Cerebrovascular disease	No clear agent preference

Patient follow-up and monitoring

Patients should generally return for follow-up and adjustment of medications monthly until their BP goal is reached. More frequent visits may be needed for Stage 2 hypertension or with comorbid conditions. Serum potassium and creatinine should be monitored 1–2 times per year, and more frequently when therapy is first initiated. After blood pressure is at goal and stable, follow-up visits can be scheduled at 3- to 6-month intervals.

Patient adherence to antihypertensive medications is often low, and represents one of the most important causes of inadequate blood pressure control. Many patients do not fill their first prescription, and within a few months almost half of patients have stopped taking their medications.[48] Research shows that adherence improves when drug regimens are simple and affordable.[49]

Conclusion

- Hypertension is the most common condition seen in primary care. Because it is relatively easily treated, this makes it one of the most important clinical targets for physicians and treatment can significantly reduce the risk of devastating illness and disability.
- In patients who do not respond to lifestyle modifications after 1 month, at least one pharmacological agent should be initiated in Stage 1 hypertension, and at least 2 agents should be initiated in Stage 2 hypertension.
- All major classes of hypertension medications lower BP by a similar degree (8-10 mmHg). Thiazide diuretics are the preferred initial agent for patients without a compelling indication for another treatment.
- See patients monthly until BP is controlled, then at least 2-4 times a year, and more often with other comorbid conditions. Make the regimen as simple and affordable as possible to enhance adherence.
- ACEIs and ARBs have similar efficacy and safety; ACEIs more commonly cause cough, and ARBs are often more expensive.
- Combination therapy with low to moderate doses of agents from different classes can deliver additive BP control while minimizing the risk of adverse events. Notable exceptions include beta blocker/CCB and ACEI/ARB combinations.
- African Americans with hypertension are especially responsive to dietary modification, thiazides, and CCBs.

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