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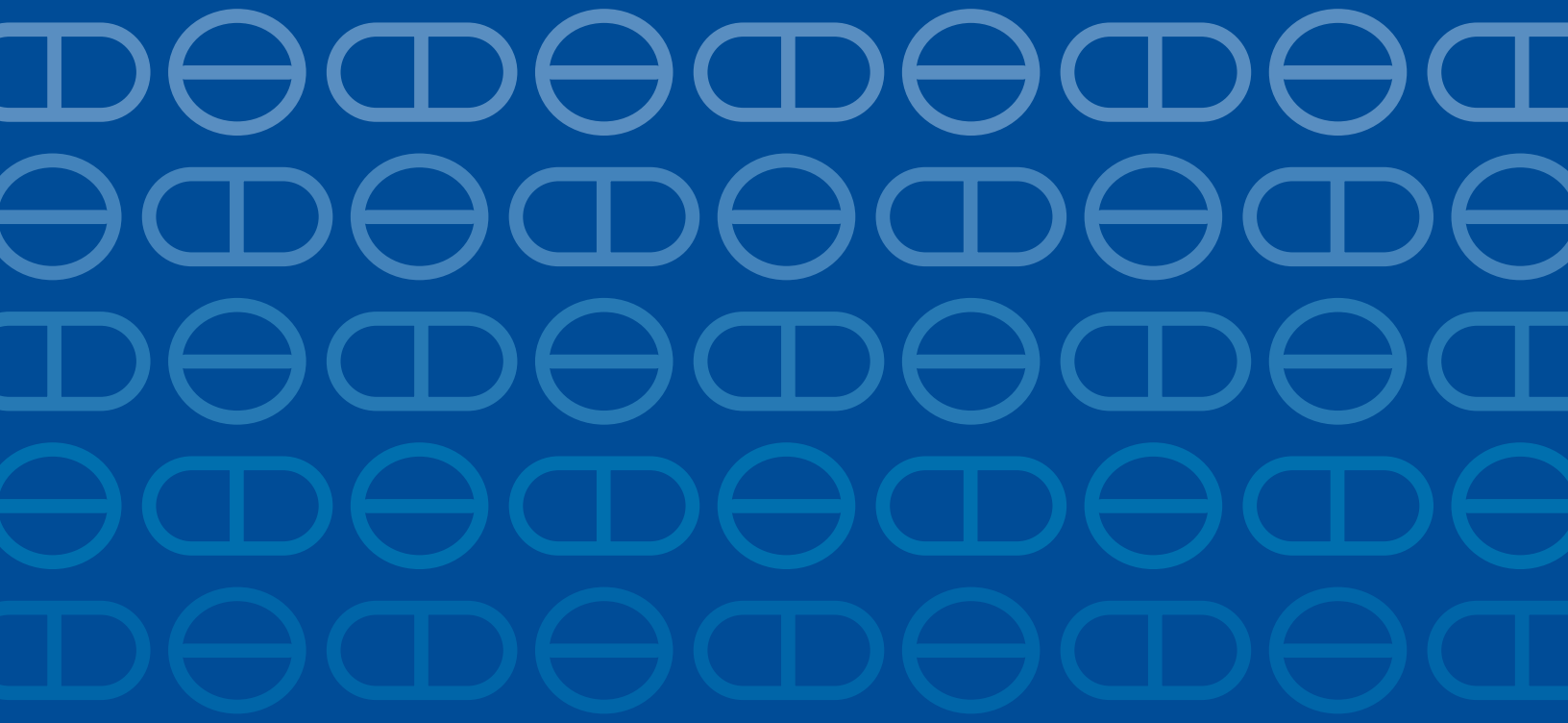
Don't let the pressure get to you:

Evidence-based management of hypertension in primary care



Don’t let the pressure get to you:

Evidence-based management of hypertension in primary care

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The Independent Drug Information Service (IDIS) is supported by the PACE Program of the Department of Aging of the Commonwealth of Pennsylvania.

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Evidence-based management of hypertension in primary care

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This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of Harvard Medical School and Alosa Health. The Harvard Medical School is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation:

The Harvard Medical School designates this enduring material for a maximum of 1.00 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Activity Overview:

The goal of this activity is to educate prescribers about the most recent evidence relating to: defining and diagnosing hypertension; recommended blood pressure targets for different patient populations; and the efficacy of different medications used to achieve blood pressure goals. In addition to providing this evidence report, the education program uses an innovative approach: academic detailing, which involves one-on-one educational sessions in physicians' offices with trained outreach educators (pharmacists, nurses, physicians) who present the educational material interactively. Reference cards for clinicians and education materials for family members are also provided.

Target Audience:

The educational program is designed for primary care physicians practicing internal medicine, primary care, family practice, and geriatrics, and other health care professionals who deliver primary care.

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Individualize blood pressure goals based on patient characteristics
- Select medications based on patient characteristics and blood pressure goals
- Assess treatment response and adverse events to achieve blood pressure goals

Disclosure Policy:

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The following committee members from Harvard Medical School's Continuing Medical Education program also reviewed this educational activity: Gyorgy Baffy, M.D., Ph.D.; James Burnes, M.D.; Laura Collins, M.D.; Harvey Katz, M.D.; John Sharp, M.D.; Jane Sillman, M.D.; and J. Kevin Tucker, M.D. None of these committee members have any relevant financial relationships to disclose.

Media used:

Printed educational material.

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Please email any questions to **cme@alosahealth.org** or call **(617) 948-5997.**

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Introduction

Hypertension is the most common condition seen in primary care.[1] Left untreated, hypertension raises the risk of heart attack, stroke, renal failure, and death.[2] For individuals 40–70 years of age, each increment of 20 mm Hg in systolic blood pressure (SBP) or 10 mm Hg in diastolic blood pressure (DBP) doubles the risk of cardiovascular disease (CVD) across the BP range from 115/75 to 185/115 mm Hg.[2] Evidence from numerous clinical trials shows that treating patients for hypertension significantly reduces CVD and death.[2]

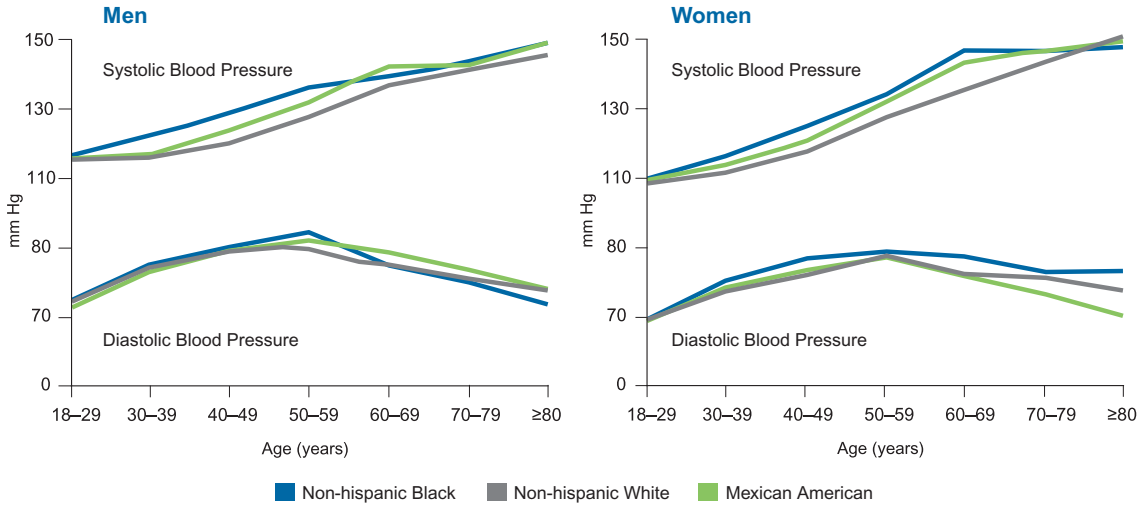
Table 1: Impact of effective antihypertensive therapy in reducing clinical outcomes[3]

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 old are estimated to have hypertension, with prevalence rising dramatically with age (hypertension was defined for surveillance purposes as SBP ≥140 mm Hg, DBP ≥90 mm Hg, patient currently taking antihypertensive medicine, or patient told at least twice by a health care professional that he/she has hypertension).[4] This equates to an estimated 80 million adults with hypertension in the U.S.[4] 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.[4]

The components of blood pressure change differently during aging so that, on average, systolic blood pressure usually increases with age while diastolic blood pressure decreases with age.

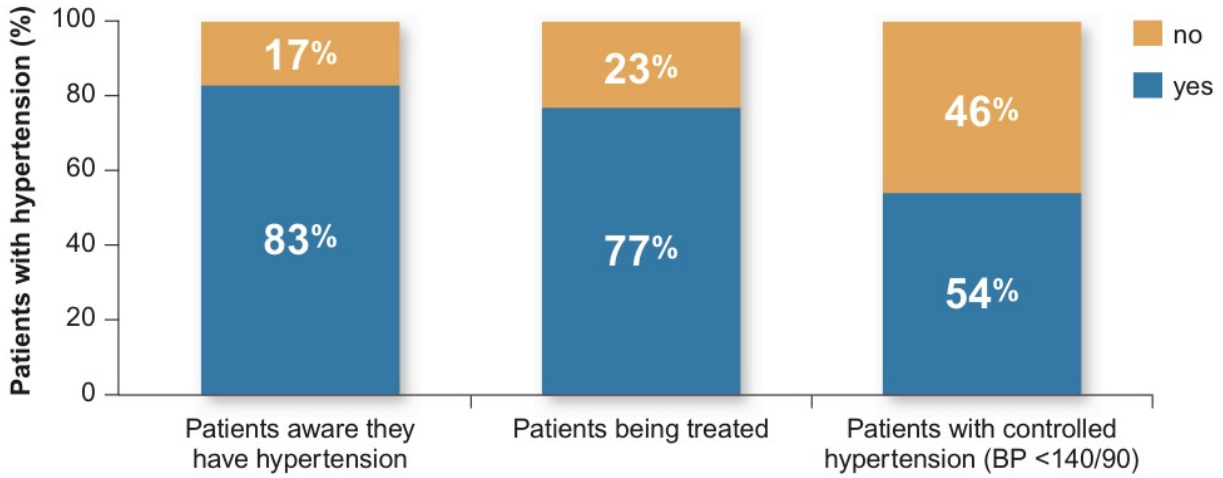
Figure 1: Trends in SBP and DBP with age[2]



SBP and DBP by age and race or ethnicity for men and women over 18 years of age in the U.S. population. Data from NHANES III, 1988–1991.

Although the percentage of patients with hypertension who are receiving treatment and achieving adequate blood pressure control has been improving slowly over the past several decades,[5] 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.[6] In addition, of those currently being treated for hypertension, only 54% have their hypertension under control.[7]

Figure 2: Hypertension control 1999-2014[7]



Nonadherence to antihypertensive therapy is common, with significant disparities along racial/ethnic and geographic lines. A 2016 review of Medicare claims data (including data on 18.5 million individuals) found that 26.3% (4.9 million) of individuals using antihypertensives were nonadherent to their regimen.[8] Nonadherence differed by multiple factors, including medication class (range: 16.9% for angiotensin II receptor blockers to 28.9% for diuretics); race-ethnicity (24.3% for non-Hispanic whites, 33.8% for Hispanics, 35.7% for blacks, and 38.8% for American Indians/Alaska Natives); and state of residence (range 18.7% for North Dakota to 33.7% for the District of Columbia).[8]

In recent years new evidence has emerged from large, well-controlled clinical trials that has given clinicians valuable information about how to help patients set blood pressure goals and about the pharmacological and non-pharmacological options for reaching them. Interpreting the results of clinical trials is not always straight-forward, however, and existing clinical guidelines for the management of hypertension have not yet been revised in light of the new findings. This Evidence Document has been developed to fill the gap for clinicians, providing a clear roadmap for the diagnosis and treatment of this common cause of morbidity and mortality.

BOTTOM LINE: Hypertension is common and, if untreated, is the single most important cause of cardiovascular and cerebrovascular disease. 17% of U.S. adults with hypertension are not aware they have it, and only 54% have their hypertension under control. Primary care physicians can play a vital role in helping to reduce the burden of untreated or under-treated hypertension.

Classifying blood pressure

Definitions of hypertension are continually evolving. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) in 2004 created the classification scheme detailed in Table 2. (Note that "prehypertension" is not a disease category, but a designation to identify patients at high risk of developing hypertension.)

Table 2: JNC 7 blood pressure classifications[2]

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

The 2014 JNC 8 expert panel report suggested slightly relaxed blood pressure goals for treating hypertension in people 60 years and older and for people with diabetes or chronic kidney disease.[1] A "panel report" is not synonymous with a formal consensus of the JNC. The JNC 8 panel report should, therefore, be taken as a preliminary statement representing the views of a majority of JNC members.

Table 3: Comparison of BP goals recommended by JNC 7 and JNC 8 panel reports[1,2*]

	JNC 7 (in mm Hg)	JNC 8 panel report
General population (age < 60)	<140/90	<140/90
General population (age ≥ 60)	<140/90	<**150**/90
Diabetes	<130/80	<**140/90**
Kidney disease (CKD)	<130/80	<**140/90**

Meanwhile, the evidence base for blood pressure goals continues to evolve. In September 2015, the landmark Systolic Blood Pressure Intervention Trial (SPRINT) was stopped early when results showed significant reductions in cardiovascular events among the participants randomized to the intensive treatment group, a target SBP of 120 mm Hg or lower, compared to the standard treatment group with a target SBP of 140 mm Hg or lower.[9] Exactly how the results from SPRINT and some of the other very recent studies reviewed in this document will affect future guideline recommendations is not currently known.

Although guidelines have not been updated, recent evidence supports a shift in the management of hypertension. Whereas the JNC 8 panel report recommended relaxing BP goals in some groups, emerging data indicates that achieving lower BP goals can provide clinical benefit for selected patients at higher risk of CV events.

* Bolded numbers represent a change in goal between the JNC 7 and JNC 8 panel report

Measuring blood pressure accurately

Blood pressure determination is one of the most important measurements in clinical medicine and yet it is one of the most inaccurately performed.[10] Surveys show that physicians and other health care providers rarely follow established guidelines for BP measurement; however, when they do, the readings correlate much more closely with more objective measures of blood pressure than the usual clinic readings.[10] Proper technique for BP measurement is vital not just for proper diagnosis but because, when measurements are used to guide medication and dosing decisions, errors could result in either over- or under-treatment.

In-office

Patients should be seated quietly for at least 5 minutes in a chair with their feet on the floor and the arm to be used for the measurement supported at the level of the heart.[2] 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. Randomized controlled trials have shown that measuring blood pressure using an automated device better correlates with ambulatory blood pressure and reduces the likelihood of white coat hypertension compared to manual blood pressure measurement.[11]

Ambulatory measurement

Ambulatory blood pressure monitoring (ABPM) provides BP measurements during different types of activities throughout the day. APBM correlates better than office measurement with cardiovascular events.[12,13]

The most common indication for ABPM is suspected white coat hypertension. Approximately 15-30% of individuals with hypertension experience this phenomenon,[14] 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.

APBM 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.[2] APBM 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.[15]

Self-measurement

Self-measurement of blood pressure at home, work, or in a pharmacy can provide useful information about differences between in-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 seven days and calculate the average after discarding measurements on the first day.[16] If it's 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.[16]

BOTTOM LINE: In-office BP measurement can be augmented with ambulatory or self-measurement in cases of white coat hypertension or a range of other conditions or situations that make in-office measurements suspect.

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 the 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, as can stimulants used recreationally. 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.

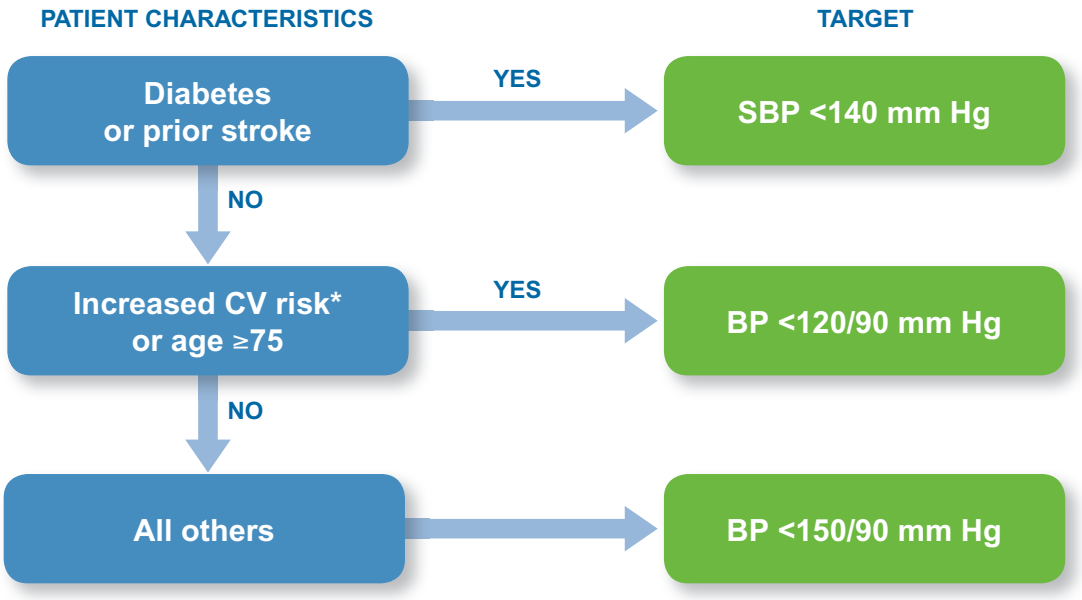
Laboratory testing is recommended in all patients newly diagnosed with hypertension in order to identify common comorbid conditions and prior to initiating medications. Recommended laboratory testing includes serum electrolytes and renal function, fasting glucose or hemoglobin A1c, urinalysis, and lipid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

BOTTOM LINE: Assess patients for modifiable risk factors, comorbidities, potential secondary causes, and end-organ damage prior to developing a treatment plan for hypertension.

A roadmap for managing hypertension in 2016

Professional guidelines for treating hypertension in the US have not yet caught up with the ever-expanding evidence base. In particular, they do not include the results from the 2015 SPRINT trial. Nonetheless, the results from SPRINT as well as previous pivotal trials provide a solid foundation for the creation of an evidence-based algorithm that can help guide clinical decision making. The process involves assessing each patient for major risk factors: diabetes, prior stroke, overall CV risk, and older age, then setting blood pressure goals that are based on the results from the most relevant and robust clinical trials.

Figure 3: Guidance for selecting blood pressure targets in hypertension



* CVD (other than stroke), chronic kidney disease (CKD), or Framingham risk > 15%, without diabetes (SPRINT study inclusion/exclusion criteria)

This algorithm reflects the following specific findings from high-quality clinical trials:

- Outcomes of the ACCORD BP study in patients with both hypertension and diabetes found that intensive therapy (SBP <120 mm Hg) was not better than standard therapy (SBP <140 mm Hg) for reducing cardiovascular disease but did increase the risk of side effects.[17]
- For patients with a prior stroke, an SBP target <130 mm Hg did not prevent recurrent stroke or CV events more than an SBP target <140 mm Hg.[18]
- The SPRINT trial showed that in those at increased CV risk but without diabetes or prior stroke, more intensive BP control (<120 mm Hg) was associated with a reduced risk of CV events compared to standard control (<140 mm Hg).
- For patients younger than 75 without diabetes, history of stroke or increased CV risk, tighter control (SBP <140 mm Hg) has not been consistently shown to be better than mild control (SBP <150 mm Hg) in terms of preventing CV events.

- For younger patients, as well as those with high CV risk, once the SBP target has been achieved, lowering DBP to <90 mm Hg reduces the risk of CV events, especially stroke.
- In general, the benefits of reducing the risk of CV events by lowering BP must be weighed against increased risk of side effects with intensive therapy. The narrow therapeutic window associated with intensive treatment may require more frequent follow-up to maximize benefit while minimizing the risk of serious adverse events.

This report addresses hypertension goals for various risk groups or clinical conditions as well as the evidence supporting lifestyle and pharmacologic interventions.

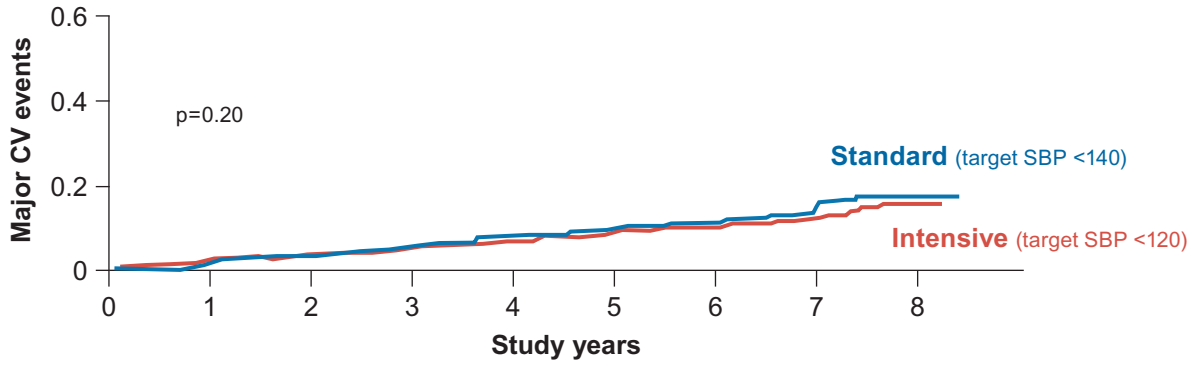
Hypertension and diabetes

The UK Prospective Diabetes Study (UKPDS 38) showed that "tight control" (<150/85 mm Hg) reduced diabetes related endpoints, stroke, and microvascular disease.[19] 1148 patients with diabetes were randomized to <150/85 mm Hg (tight control) or <180/105 mm Hg (standard therapy). Treatment varied between the groups: the tight control group received either an ACE inhibitor (captopril) or a beta-blocker (atenolol), while the standard therapy group received furosemide, nifedipine SR, or methyldopa and prazosin. Patients had an average age of 56 and average SBP of 160 mm Hg. Median follow-up was 8.4 years.

The study's main findings were that tight control reduced the risk of microvascular complications from diabetes, and, additionally, no lower threshold for BP was observed for decreased risk.

The ACCORD BP trial was designed to probe the latter finding more closely. This study randomized 4733 older patients with diabetes to intensive therapy (<120 mm Hg) or standard therapy (<140 mm Hg).[17] Mean age was 62 and mean SBP was 139. The mean follow-up was 4.7 years.

Figure 4. Intensive treatment to an SBP <120 mm Hg did not prevent more CV events than an SBP <140 mm Hg.[20]



The major results of ACCORD revealed:

- no difference in the primary outcome of major CV events comparing intensive versus standard BP control.
- some reduction in stroke risk (a prespecified secondary outcome) in the intensive treatment group (HR 0.59; 95% CI: 0.39-0.89; p=0.01).

- lower BP goal required more medications (3.4 vs. 2.4 in the intensive vs. standard, respectively) and patients experienced more adverse events attributed to blood pressure medications (3.3% vs. 1.27% in the intensive vs. standard groups, respectively). These events included: hypotension, syncope, bradycardia or arrhythmia, hypokalemia and elevations in serum creatinine.

BOTTOM LINE: in patients with diabates, aiming for an SBP <120 mm Hg , as compared with <140 mm Hg, does not reduce the rate of fatal and nonfatal major CV events, and was associated with an increased risk of serious adverse events.

Patients with a history of stroke

Each year in the U.S. approximately 690,000 people experience an ischemic stroke and an additional 240,000 experience a transient ischemic attack.[21] The 2014 guideline for stroke prevention by the American Heart Association and American Stroke Association stated that the treatment of hypertension "is probably the most important intervention for secondary prevention of ischemic stroke."[21] The JNC 8 expert panel report recommend a target BP goal of <140/90 mm Hg for patients with a history of stroke.

Some evidence suggests a lower target for this patient population. The Secondary Prevention of Small Subcortical Strokes (SPS3) study examined whether targeting an SBP <130 mm Hg was beneficial for patients with recent lacunar stroke.[18] 1519 patients were randomized to intensive therapy (SBP target <130 mm Hg), and 1501 patients were randomized to standard therapy (SBP target 130-149 mm Hg). The primary endpoint was reduction in all recurrent stroke (including ischemic strokes and intracranial hemorrhages).

After a mean follow-up of 3.7 years, the rate of recurrent stroke in the intensive therapy group was 2.25% (n=125) compared to 2.77% (n=152) in the standard therapy group, a difference that did not reach statistical significance (p=0.08). Similar trends were observed for reductions in disabling/fatal stroke and in the composite outcome of stroke, myocardial infarct or vascular death. Intracerebral hemorrhage, however, was reduced by 63% in those assigned to intensive therapy (HR 0.37; 95% CI: 0.14-0.89; p=0.03). Serious complications of BP lowering were infrequent and not significantly different in frequency between groups.

BOTTOM LINE: Targeting a SBP <140 mm Hg for patients with history of stroke is supported by findings from SPS3.

Patients with high CV risk

The findings from the ACCORD study only apply to patients with diabetes. The results from both the SPRINT trial[22] and the SPRINT 75 subgroup trial[23] show that among patients at high risk for cardiovascular events but *without* diabetes or prior stroke, targeting a systolic blood pressure <120 mm Hg, as compared <140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death. The trial randomized 4678 patients to intensive therapy (SBP ≤120 mm Hg) and 4683 patients to standard therapy (SBP ≤140 mm Hg). The primary outcome was a composite outcome of myocardial

infarction (MI), acute coronary syndrome (ACS), stroke, acute decompensated heart failure or death from CV causes.

Table 4: Key inclusion and exclusion criteria for the SPRINT trial

Inclusion criteria	Exclusion criteria
• Age ≥50 • SBP 130-180 mm Hg • Increased CV risk — clinical or subclinical CVD, except stroke — chronic kidney disease (eGFR 20-59 mL/min/1.73m^2) — Framingham risk score ≥15% — age ≥75	• Patients with: — diabetes — dementia — prior stroke — heart failure — end stage renal disease • Life expectancy <3 years • Residence in a nursing home

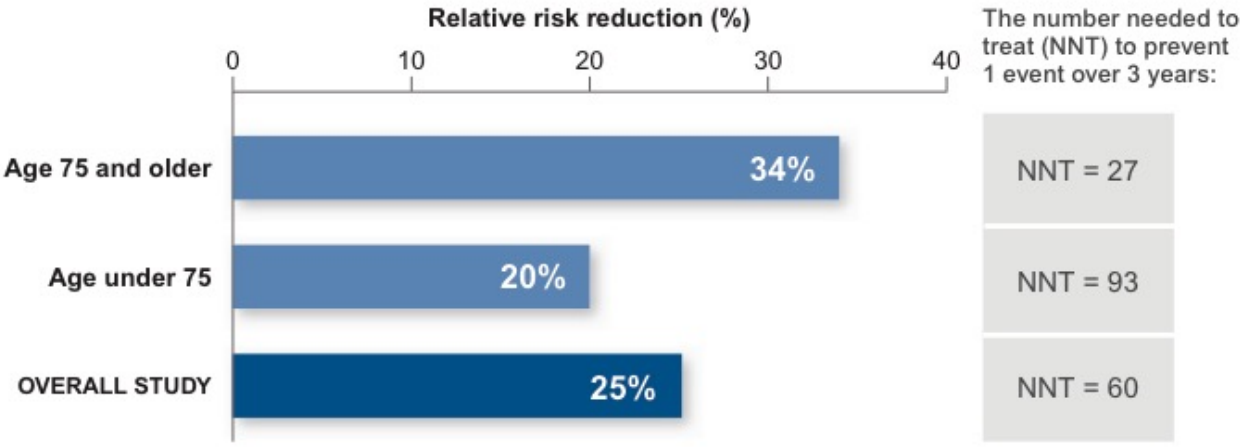
The trial was stopped early, after a median follow-up of 3.3 years, due to the significantly lower numbers of CV outcomes in the intensive group. At the end of the study, patients in the intensive treatment arm had a 1.6% absolute risk reduction in cardiovascular outcomes, corresponding to a 25% relative risk reduction (HR 0.75; 95% CI: 0.64-0.89; p<0.001).

The open label trial design allowed for medication selection from a formulary, with most patients in the study receiving ACEIs/ARBs, thiazide diuretics, and CCBs. Intensive treatment required more medications (mean 2.8 vs. 1.8) and was associated with an increased risk of adverse events including: hypotension, syncope, acute kidney injury, and electrolyte abnormalities, although the higher risk of such events did not offset the observed decreases in the risk of cardiovascular outcomes. Serious adverse events, defined as those requiring hospitalization, were more common in those randomized to intensive therapy among all participants in SPRINT (number need to harm: 45). However, the rate of orthostatic hypotension (with or without dizziness) and injurious falls was not more common with intensive treatment.

SPRINT 75

Twenty-eight percent of the SPRINT trial comprised patients age ≥75, and these older individuals were evaluated in a pre-specified subgroup analysis. The results indicate that these patients benefitted from intensive SBP lowering even more than younger patients did.

Figure 5. Compared to the overall study and younger patients, fewer patients ≥75 need to be treated to prevent one CV event.



The rates of serious adverse events in both the intensive and standard treatment groups were high, with 48.4% and 48.3% of patients in the intensive and standard arms, respectively, reporting serious adverse events. There was no significant difference between the treatment arms in the rates of individual adverse events, including hypotension, syncope and the risk of falls.

While the results of SPRINT offer convincing evidence for lower SBP targets in patients who are either >75 or at increased cardiovascular risk, some important caveats must be kept in mind:

- The results of SPRINT do not re-define the threshold for diagnosing hypertension to an SBP greater than 120 mm Hg.
- SPRINT did not compare pharmacologic agents, hence the trial results do not provide guidance for medication choices.

BOTTOM LINE: For patients with increased CV risk but without diabetes or stroke, the recommended SBP target is <120 mm Hg. For patients age 75 and older, the benefit of an SBP target <120 mm Hg is even greater and the rate of side effects is similar to a standard SPB target <140 mm Hg. More frequent follow-up is indicated to reduce the risk of serious adverse events.

All other adults

Managing blood pressure in patients younger than 75 years of age, without CV risk, diabetes, or prior stroke, is less clear than for the populations previously discussed. Two randomized trials, JATOS and VALISH, looked at whether an SBP target <140 mm Hg was better at reducing CV events than an SBP target <150 mm Hg. Both trials found no difference in the rate of CV events or side effects between the treatment groups. These results suggest that the well-established SBP goal <150 mm Hg in low risk adults younger than 75 is reasonable, and that there is little reason to push for lower targets for these patients.

Table 5: Pivotal trials for adults younger than 75

Pivotal trial	Target BP (in mm Hg)	Patient characteristics	Results
VALISH (2010)[24]	<140 vs. 140-150	Mean age 76, 5% IHD, 13% DM	No difference
JATOS (2008)[25]	<140 vs. 140-160	Mean age 70s, 12%DM, 4%CVA, 3% CVD	No difference
CARDIO SIS (2009)[26]	<130 vs. <140	Mean age 67, 76%HL, 12%CAD	Tight control reduced a secondary CV outcome by 50%

What about the role of diastolic blood pressure?

The JNC 8 panel report recommends a DBP <90 mm Hg for younger adults, based primarily on results from older studies. For example, the 1985 MRC study randomized 17,354 patients between the ages of 35 and 64 to active treatment or placebo with a goal DBP <90 mm Hg. Active treatment reduced the risk of stroke by 45% and CV events by 19%.[27] Results from the 1970 VA Cooperative study[28] and the Hypertension Detection and Follow-Up Program (HDFP) study[29] in patients with an average age of about 50 found similar reductions in CV events.

In the SPRINT trial,[22] patients who achieved their SBP target were also treated to reduce diastolic to <90 mm Hg, suggesting that once an SBP target is achieved the DBP goal should be monitored and achieved as well.

BOTTOM LINE: Among adults under 75, without major risk factors for CV disease, diabetes, or prior stroke, a BP goal <150/90 mm Hg is appropriate.

Special considerations

Patients with chronic kidney disease (CKD)

CKD affects 10-15% of the general adult population and is associated with an increased risk of kidney failure and CV disease. Blood pressure is often elevated in patients with CKD and previous guidelines have recommended lower BP goals in these patients.[2] The KDIGO clinical practice guideline recommends BP goal of <140/90 mm Hg for those with CKD without proteinuria, and <130/80 mm Hg for those with CKD and significant proteinuria (urinary albumin >300 mg in 24 hrs).[30] Evidence was drawn primarily from post-hoc or subgroup analyses of RCT data. Data from the SPRINT trial were inconclusive about impact of intensive treatment in patients with CKD because the trial was underpowered to detect renal outcomes (despite having about 1300 patients with CKD in each treatment arm).

Table 6: Studies of treatments for hypertensive patients with CKD

Study	Methodology	Key findings
Systolic Blood Pressure Intervention Trial (SPRINT)[22] (CKD sub-population analysis)	• Open label • Inclusion criteria include: age ≥50; SBP 130-180 mm Hg; increased CV risk • 1330 patients with CKD at baseline randomized to intensive therapy (SBP ≤120 mm Hg) • 1316 patients with CKD at baseline randomized to standard therapy (SBP ≤140 mm Hg) • Patients with diabetes excluded	Trend toward benefit for value of intensive therapy, but trial was underpowered to detect renal outcomes, hence findings not statistically significant. Composite renal outcome occurred in 14% of patients in intensive treatment group compared to 15% of patients in standard treatment group. 6% of patients in the intensive treatment group went on long-term dialysis compared with 10% in the standard treatment group.
Modification of Diet in Renal Diseases (MDRD)[31]	• 1,585 patients with impaired GFR randomly assigned to a usual-protein diet or a low-protein diet (1.3 or 0.58 g of protein per kilogram of body weight per day) and to a usual- or a low-blood-pressure group (mean arterial pressure, 107 or 92 mm Hg) • Mean follow-up = 2.2 years	As compared with the usual-protein group and the usual-blood-pressure group, the low-protein group and the low-blood-pressure group had a more rapid decline in the glomerular filtration rate during the first four months after randomization and a slower decline thereafter.
AASK[32]	• Randomized 1094 African-Americans with hypertensive renal disease to intensive (125/75 mm Hg) or standard (140/90 mm Hg) BP goals • Mean age = 55 yrs • Post-hoc analyses	No additional benefit of slowing progression of hypertensive nephrosclerosis was observed with the lower BP goal. Angiotensin-converting enzyme inhibitors appear to be more effective than beta-blockers or dihydropyridine CCBs in slowing GFR decline. Achieved mean BP: 128/78 mm Hg in intensive treatment group; 141/85 mm Hg in standard treatment group.

BOTTOM LINE: Evidence for a specific BP goal for patients with CKD is limited. The SPRINT CKD subgroup analysis was suggestive of benefit with lower SBP target, but the finding was not statistically significant. Among older trials, some evidence suggests that more intensive BP control may be beneficial for renal outcomes among patients with baseline proteinuria.

Patients with ischemic heart disease

Ischemic heart disease is the leading cause of death and morbidity worldwide, with about 20% of the risk for coronary heart disease attributable to hypertension.[33]

Table 7: Studies supporting medication choices for hypertensive patients with history of ischemic heart disease

Study	Methodology	Key Findings
Heart Outcomes Prevention Evaluation (HOPE)[34]	• 9297 high risk patients randomized to ACEI ramipril or placebo • Patients with heart failure or low ejection fraction excluded • Mean age = 66 yrs • 80% with history of CAD	ACEI better than placebo in patients with CAD and high risk (RR 0.8; 95% CI: 0.70-0.86) for combined outcome measure of MI, stroke, and CV death. Achieved mean BP: 136/76 mm Hg in ramipril group; 139/77 mm Hg in placebo group.
EUROPA[35]	• 12,218 patients with CAD randomized to ACEI perindopril or placebo • Mean age = 60 yrs • Patients with heart failure excluded • 65% had hx of MI • Mean follow-up = 4.2 yrs	603 (10%) placebo and 488 (8%) perindopril patients experienced the primary endpoint, which yields a 20% relative risk reduction (95% CI: 9-29; p=0.0003) with perindopril. Achieved mean BP drop during run-in period: 137/82-128/78 mm Hg. Mean of 128/78 mm Hg maintained in perindopril group; mean BP 5/2 mm Hg higher in placebo group.
INVEST[36]	• Randomized 22,576 hypertensive patients with CAD to CCB verapamil + ACEI or beta-blocker atenolol + thiazide diuretic • Mean follow-up = 2.7 yrs • Mean age = 66 yrs • History of MI or abnormal angiogram = 53% • Baseline BP: 150/86 mm Hg • BP target: <140/90 mm Hg	No significant difference between CCB or BB in reducing CV events (HR 0.98; 95% CI: 0.90-1.06). In a subgroup analysis proportion of visit with BP under control was inversely related to CV risk.[37] Achieved mean BP reduction from baseline in CCB group: 22.2/10 vs. 19/10.2 mm Hg in beta-blocker group.

BOTTOM LINE: evidence supports a BP goal of <140/90 mm Hg for patients with ischemic heart disease. ACEIs are better than placebo in this patient population and CCB (+ACEI) or BB (+thiazide) strategies appear to have equal efficacy.

Managing hypertension in primary care

Lifestyle modification

Physicians should recommend modification of lifestyle factors that may be contributing to hypertension. These efforts can be made prior to trials of pharmacotherapy and should continue concurrently with any treatments pursued. Modifications shown to reduce blood pressure and lower CV risk include weight loss, dietary changes, sodium reduction, exercise, avoidance of excessive alcohol use, and smoking cessation. Although the amount of BP reduction that can be expected from any single lifestyle intervention is 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.

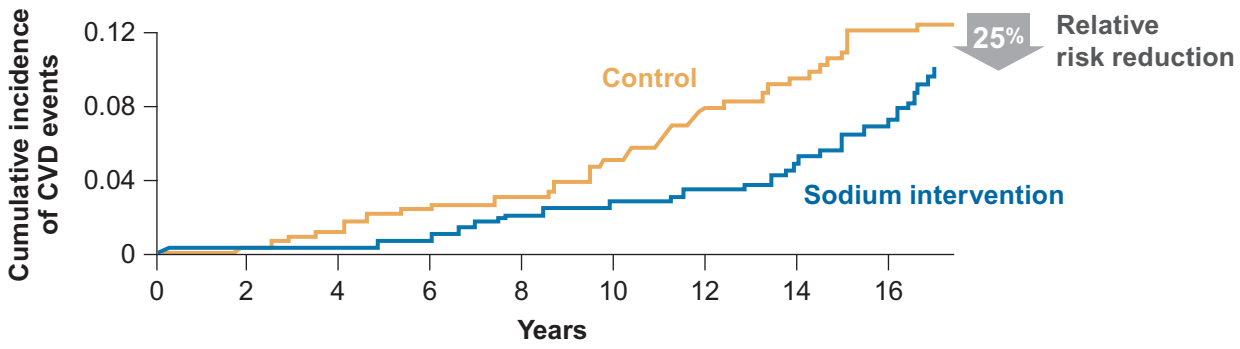
Table 8: Lifestyle modifications to address hypertension[2]

Modification	Recommendation	Approximate SBP reduction
Reduce weight	Maintain normal body mass index	5–20 mm Hg per 10 kg of weight loss
Adopt "DASH" diet[38]	Low-fat diet rich in fruits and vegetables	8–14 mm Hg
Restrict dietary sodium	<2300 mg/day	2–8 mm Hg
Physical activity	Aerobic physical activity 30 minutes a day, most days	4–9 mm Hg
Moderate alcohol consumption	Men <2 ounces a day Women <1 ounce a day	2–4 mm Hg

The positive effects of aerobic exercise on BP were demonstrated in a meta-analysis of 54 randomized, controlled trials (2419 participants) involving aerobic exercise interventions such as walking, jogging, or biking for time durations varying from 32 – 350 minutes weekly, with the most common duration of exercise being about 120 minutes weekly.[39] Aerobic exercise was associated with a reduction in mean systolic and diastolic blood pressure (-3.84 mm Hg [95% CI, -4.97 to -2.72 mm Hg] and -2.58 mm Hg [CI, -3.35 to -1.81 mm Hg], respectively). BP reductions were seen in patients with and without hypertension, as well as in overweight and normal-weight participants.

Counseling patients on reducing dietary sodium can produce clinically significant results. The Trials of Hypertension Prevention (TOHP I and II) tested the efficacy of non-pharmacological interventions for reducing BP in people with high-normal BP, including counseling on how to identify sodium in the diet, and how to prepare lower sodium foods. The people randomized to the sodium reduction arm (n = 327) had a 25% - 30% reduction in cardiovascular events compared to those in the control arm (n = 417).[40]

Figure 6: Reduction in CV events with sodium restriction[40]



BOTTOM LINE: Both counseling and adherence to a low sodium diet may reduce BP and improve CV outcomes. Weight loss may decrease the risk of developing hypertension among those at increased risk. Although the amount of BP reduction that can be expected from any single lifestyle intervention is relatively modest, the cumulative effect of multiple interventions can be significant.

Pharmacologic treatment

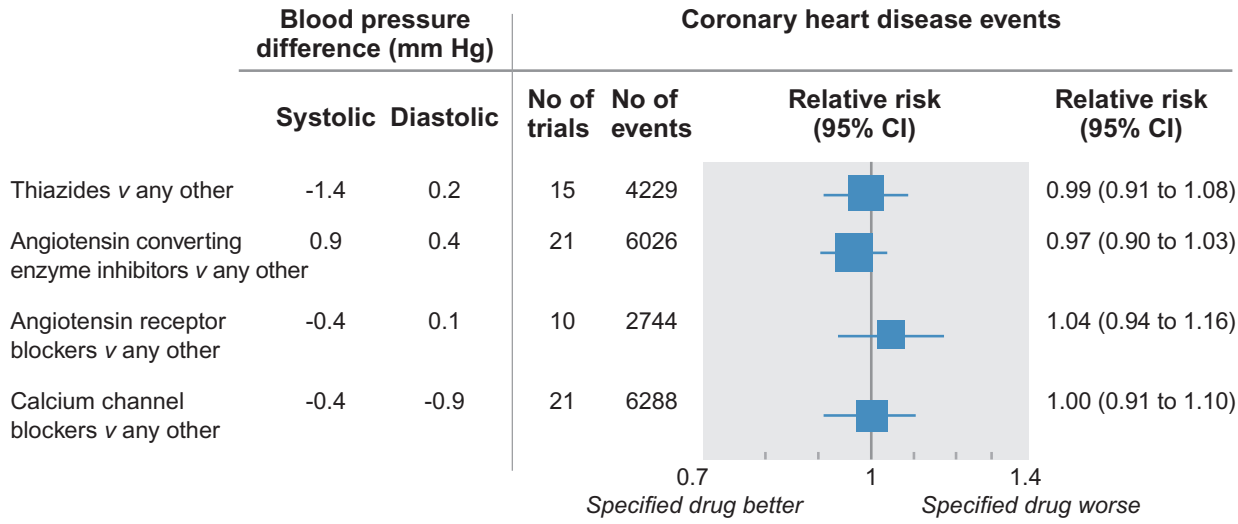
Hypertension can be treated with medications from multiple classes, each with different mechanisms of action. Over two-thirds of hypertensive patients will eventually require more than one medication.[41] For example, in the SPRINT trial, patients randomized to intensive treatment required on average three medications to achieve a target SBP <120 mm Hg.[22]

In the past four decades, numerous clinical trials have compared individual antihypertensive medications to placebo, using blood pressure lowering as a major outcome.[42,43,3] Meta-analyses have combined these data to calculate the average effect on blood pressure of each of the major classes of antihypertensive medication. The results show similar blood pressure-lowering effects for standard-dose anti-hypertensives in each major drug class.[44,45]

In general, unless other compelling indications exist (e.g., the use of beta-blockers for patients with recent myocardial infarction), there is no strong evidence to favor any one particular antihypertensive drug or class over another for initial therapy. One meta-analysis published in 2009 examined the 46 trials that directly compared one drug class against another for the prevention of coronary heart disease events (defined as fatal or nonfatal MI or sudden cardiac death) or stroke.[46] Those authors concluded that all the classes of blood pressure lowering drugs have a similar effect for a given reduction in blood pressure.

On the basis of this meta-analysis and the protocols of more recently-published large pivotal trials, we suggest that **the choice of pharmacologic agent is less important than achieving the appropriate BP goal**. Calcium channel blockers (CCBs) may have minor additional benefits for stroke prevention compared to other antihypertensive agents (see CCB section below).

Figure 7. Relative risk estimates of CHD events in 46 drug comparison trials.[46]



Thiazide-type diuretics

Thiazide-type diuretics inhibit about 5% of sodium reabsorption and are longer-acting and exert greater antihypertensive effect than loop diuretics. 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.[47] The four drug classes were diuretics, calcium-channel blockers, angiotensin converting enzyme inhibitors (ACEIs), and alpha-blockers. The alpha-blocker arm was stopped early because of increased risk of CVD, especially heart failure compared with diuretic arm.

The ALLHAT trial found that thiazide-type diuretics were equivalent to ACEIs and CCBs for preventing the primary CV outcome. However, **thiazides were superior to either ACEIs or CCBs in preventing heart failure** (a secondary outcome). At the time the study was conducted, thiazides were substantially less expensive than the other two drug classes and thus the JNC 7 guidelines recommended thiazides as the initial drug of choice. See Appendix 1 for the costs of various antihypertensives by 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.[48] Indirect comparisons of thiazides suggest that both agents have equal effects on reducing rates of serious CV events, and both appear equally safe.[49] Increasing the dose achieves little additional gain in blood pressure control, but does increase the rate of adverse effects.

Concerns about metabolic side effects of thiazides such as hypokalemia, hyperglycemia, hyperuricemia, or hyponatremia were based on early studies in which higher doses of thiazides were used (e.g., 50–100 mg/d of HCTZ). At lower doses (e.g., 12.5 mg/d of HCTZ), 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).[50,51]

Angiotensin converting enzyme inhibitors (ACEIs)

No randomized head-to-head trials have compared the effect of different ACEIs on clinical outcomes 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.[52] Several trials compared the rates of adverse events from ACEIs in patients with hypertension and found no important differences among them in rates of common side effects such as hypotension, cough, angioedema, hyperkalemia, or elevated serum creatinine.[53]

Many clinicians have been taught that Renin-Angiotensin-Aldosterone-System (RAAS) inhibitors are preferred agents for patients with CKD. Results from some older clinical trials support these beliefs. For example, AASK showed that ramipril was superior to metoprolol or amlodipine among hypertensive African-Americans with renal impairement in reducing a composite outcome that included GFR decline, ESRD and death.[32] Unfortunately, these findings on renoprotection have either not been consistently replicated or do not extend to hard clinical outcomes such as CV events or ESRD.

Additionally, a meta-analysis of 26 trials, involving 152,290 patients, found no difference in CV events between ACEIs or ARBs when compared against other antihypertensives in patients with reduced glomerular filtration rates (eGFR).[54]

Among patients with diabetes, a meta-analysis of 19 RCTs involving over 25,000 patients with diabetes that compared RAAS antagonists against other antihypertensives showed no differences in the risk for adverse clinical outcomes such as death, CV outcomes, or end stage renal disease.[55]

ACEIs may not be preferred monotherapy for patients with a history of stroke. Based on the results of PROGRESS[56] (described in more detail on page 19), ACEIs were no different than placebo in reducing recurrent stroke.

Finally, one observational study suggests that ACEI may be worse than CCBs or diuretics. This 2015 propensity-score matched cohort study of community-dwelling African-Americans on a range of antihypertensives found that ACEIs were associated with a higher risk of cardiovascular events (death, myocardial infarction, and stroke) compared with CCBs or thiazide diuretics.[57]

Angiotensin receptor blockers (ARBs)

ARBs were studied and introduced into routine practice more recently than ACEIs. Compared to ACEIs, ARBs present a lower risk for inducing cough (approximately 10% vs. 3%) or promoting angioedema.[1] Common side effects include dizziness, headache, drowsiness, nausea, and diarrhea. As with ACEIs, there have been no head-to-head trials of the different ARBs that have measured clinical outcomes or safety.[58] The existing data do not suggest any meaningful differences among different ARBs.[59]

Many trials have found that ACEIs and ARBs are equally effective at lowering blood pressure.[60] 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.[60] One trial (LIFE) compared the ARB losartan against a beta-blocker atenolol among over 9000 patients with hypertension and left-ventricular hypertrophy. That trial found that losartan was more effective at preventing a composite CV endpoint than atenolol (HR 0.87; 95%CI: 0.77-0.98).

Calcium channel blockers (CCBs)

Two types of CCBs exist: dihydropyridine CCBs (e.g., amlodipine, felodipine) and non-dihydropyridine CCBs (e.g., diltiazem, verapamil). While both are approved for the treatment of hypertension, non-dihydropyrinde CCBs are also used for other compelling indications like rate control in atrial fibrillation (visit AlosaHealth.org/modules/Afib for more information on atrial fibrillation).

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.[61] Indirect comparisons of CCBs suggest they are all relatively safe when used to treat hypertension.[61] A 2009 meta-analysis that included data for both dihydropyridines and non-dihydropyridine CCBs suggests that CCBs may be more effective than the other antihypertensive classes in preventing stroke.[46] Common side effects for dihydropyridine CCBs include peripheral edema, fatigue, and pulmonary edema, while dizziness, constipation, first degree AV block, and bradycardia are more common with non-dihydropyridine CCBs. CCBs should be started at a lower dose in older patients or patients with hepatic impairment.

BOTTOM LINE: In general, thiazides, ACEIs/ARBs, and CCBs are equally effective first line antihypertensives. Evidence from head-to-head comparative trials is limited, but the ALLHAT trial suggests that thiazides may reduce the risk of heart failure compared to an ACEI or CCB. ACEIs are not recommended for monotherapy for secondary prevention of stroke. Use ARBs in place of ACEIs in patients with history of ACEI-induced cough or ACEI-induced angioedema.

Other drug classes

Beta-blockers

In early versions of the JNC guidelines, beta-blockers were recommended as first-line agents for treating uncomplicated hypertension. But since 2005 several reviews have highlighted limitations of beta-blockers as agents to reduce high blood pressure in patients without a history of myocardial infarction.[62,63,64] 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 to other drug classes in preventing other cardiovascular outcomes such as MI. These differences were especially notable for older patients.[62]

Side effects of beta blockers include fluid retention, fatigue, sexual dysfunction, bradycardia, heart block, and hypotension. Absolute contraindications include third degree heart block and a history of severe bronchospasm (although patients with mild-to-moderate bronchospasm may tolerate a beta-1 selective beta blocker). Relative contraindications include bradycardia, symptomatic hypotension, and severe peripheral artery disease.

Beta-blockers continue to have an important role in treating patients with both hypertension and a compelling indication such as CAD or heart failure (HF), but they are no longer considered a first choice agent for uncomplicated hypertension.[1]

Renin inhibitors

Direct renin inhibitors block the conversion of angiotensinogen to angiotensin I. Aliskiren was approved by the FDA in 2007 for treatment of primary hypertension. Direct renin inhibitors have the purported advantage of not affecting kinin metabolism, and therefore posing a lower risk for cough or angioedema than ACEIs.[65] A meta-analysis found that standard doses of aliskiren lower SBP to an extent similar to other anti-hypertensive classes.[66]

Aliskiren has not been compared in head-to-head trials with either ACEIs or ARBs for efficacy or safety, however the ALTITUDE[67] and ATMOSPHERE[68] trials showed that adding aliskiren to standard RAAS therapy (an ACEI or ARB) increased the risk of adverse events, including hypotensive symptoms, elevated serum creatinine, and elevated potassium levels. 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,[67] however the ALTITUDE trial showed no benefit on cardiorenal outcomes and possible increases in adverse events in patients with diabetes.[67] The JNC 8 panel did not include renin inhibitors in their recommendations because there were no studies demonstrating their benefits on renal or cardiovascular outcomes.[1]

Other agents

A number of agents may be considered for patients with resistant hypertension, defined as suboptimal BP control despite treatment with at least three antihypertensive agents.[69] Alternative agents may be particularly useful for patients with hypertension and comorbid conditions for which these agents may be prescribed: alpha-blockers (e.g., doxazosin, prazosin, terazosin); centrally-acting drugs (e.g., clonidine, methyldopa, reserpine, guanfacine); or direct vasodilators (e.g., hydralazine, minoxidil). Evidence from a double-blind placebo-controlled trial of 230 patients suggests that the potassium-sparing diuretic spironolactone can be effective in patients with resistant hypertension.[69]

BOTTOM LINE: Beta-blockers and renin inhibitors are not considered first-line antihypertensives, although each may have utility for patients with selected comorbidities.

Combination therapy

Since most antihypertensive medications at standard doses will lower SBP by 9-10 mm Hg, combination therapy is often required to achieve BP goals. In the SPRINT trial, patients in the intensive treatment arm used an average of tee medications to achieve the target BP levels. In the ALLHAT trial, only about a quarter of patients were controlled on monotherapy.[70]

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. Systematic reviews and meta-analyses 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.[44,71]

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.

A 2008 randomized controlled trial of an ACEI and an ARB in high-risk patients (vascular and patients with diabetes), however, found that combination therapy did not reduce rates of a composite outcome (cardiovascular death, MI, stroke, or HF hospitalization).[72] However, the combination did produce significantly higher rates of adverse events than did either single agent, including hypotension, syncope, and renal dysfunction.[72]

One large trial (ACCOMPLISH) randomized 11,506 patients with hypertension at high risk of CV events to the combination of a ACEI+CCB or the combination of a ACEI+thiazide. Forty percent of patients were over 70 years old and over 60% had diabetes. This trial was stopped early because interim results showed that the ACEI+CCB was significantly better than the ACEI+thiazide. On the basis of ACCOMPLISH, assuming no other compelling indications, it is reasonable to start patients requiring two antihypertensives on an ACEI+CCB.

The PROGRESS trial also explored combination therapy in patients who had a stroke in the previous 5 years.[56] 3051 patients were randomized to active treatment of either and ACEI + thiazide or an ACEI alone; another 3054 patients were randomized to placebo.

Active treatment reduced blood pressure by 9/4 mm Hg (achieved BP: 138/82 mm Hg). 307 (10%) individuals assigned active treatment suffered a stroke, compared with 420 (14%) assigned placebo (relative risk reduction 28% [95% CI: 17–38; p<0·0001]). Active treatment also reduced the risk of total major vascular events (26% [95% CI:16–34]). Combination therapy produced larger blood pressure reductions and larger risk reductions than did single drug therapy (ACEI alone was no better than placebo).

Pearls for starting medications in patients with hypertension

For most patients who are over their BP goal by >20 mm Hg, initiating two anthihypertensives will be required to achieve BP target. However, for a subgroup of patients who are age 75 or over, it may be reasonable to start one agent. Titration upwards of doses at the subsequent visits will likely be required to achieve BP goals. This practice is in accordance with the SPRINT protocol. This stepped approach is reasonable in a patient population that has higher risk of adverse events.

With 26% of Medicare beneficiaries not adhering to antihypertensive regimens, factors such as reducing the number of pills (using combinations when clinically appropriate) and having one prescriber managing blood pressure treatment increase the likelihood of patients adhering to therapy.

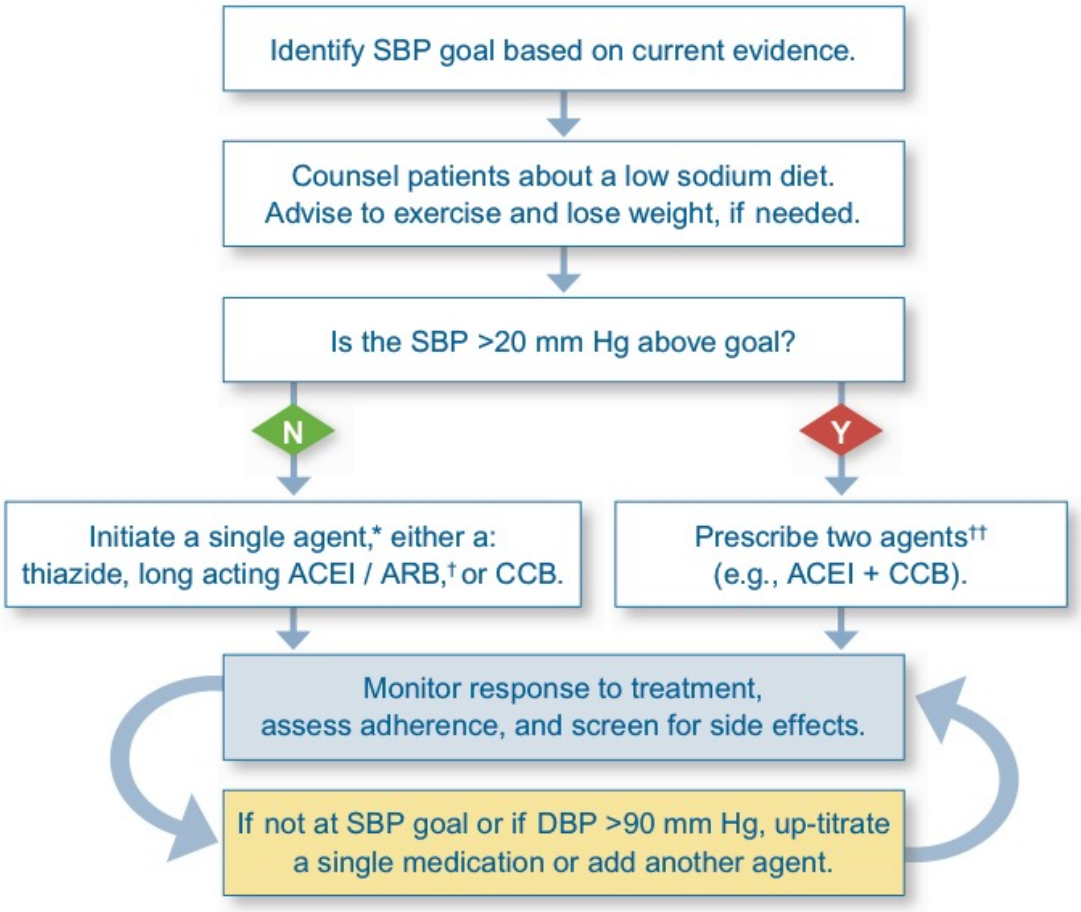
BOTTOM LINE: Many patients will require more than one antihypertensive agent to achieve their BP goal. Absent other clinical indications or contraindications, ACCOMPLISH provides evidence to support choosing an ACEI+CCB when 2-drug therapy is needed.

Putting it all together

Hypertension is the most common condition seen in primary care. Because many effective treatments are available, hypertension represents one of the most important clinical opportunities for physicians to significantly reduce the risk of illness and disability.

All major classes of hypertension medications lower BP by a similar degree (~8-10 mm Hg) and have similar, though not identical, risks of adverse events. Some drug classes may be preferred for specific comorbid conditions, as reviewed in the preceding sections. The essential steps in effective management of patients with hypertension are captured in Figure 8.

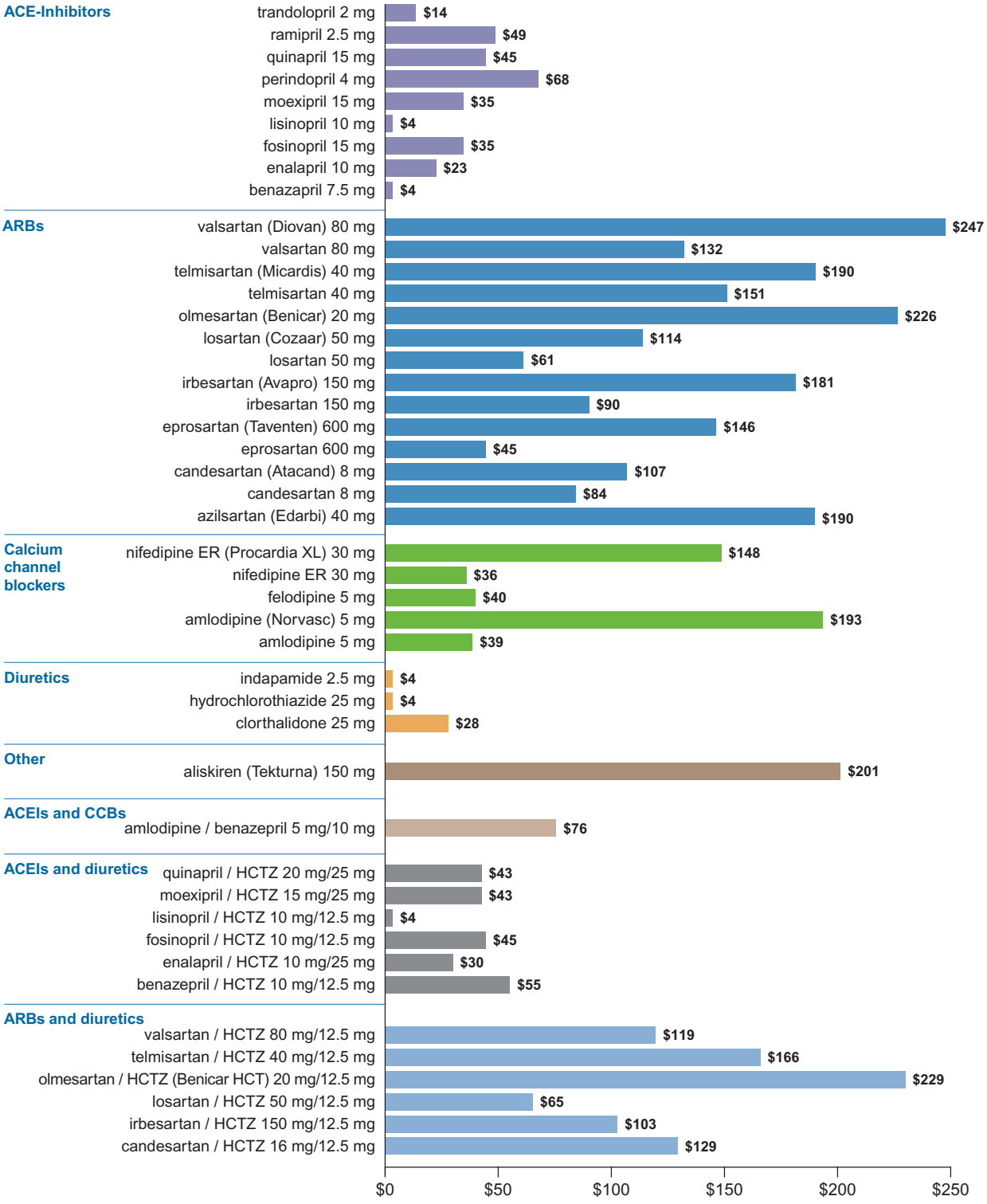
Figure 8. Algorithm for treating hypertension



* For African Americans, initiate a thiazide or CCB.
† Combining an ACEI and an ARB confers no additional benefit and may increase adverse events.
†† For patients age 75 and over, start one medication and intensify therapy at the first follow-up visit.

Appendix 1. Cost of antihypertensives

Price of a 30-day supply of drug classes commonly used to treat hypertension



Prices from goodrx.com, September 2016. Listed doses are based on Defined Daily Doses by the World Health Organization, and should not be used for dosing in all patients. All prices shown are for generic products unless otherwise noted.

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About this publication

These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.

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