

Hypertension: Guidelines Galore and Clinical Cases

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Disclosure

- I have nothing to disclose.

Objectives

- List risks associated with uncontrolled hypertension
- Determine a patient's blood pressure goal according to treatment guidelines (JNC-8, ASH/ISH, ADA, KDIGO, etc.)
- Identify the four drug classes considered first-line agents for HTN
- Identify treatment strategies for resistant hypertension
- Apply current treatment guidelines and patient-specific factors to clinical cases with and without other compelling indications (including diabetes, chronic kidney disease, coronary artery disease, and history of stroke or myocardial infarction)

Using the Pharmacists' Patient Care Process to Manage High Blood Pressure: A Resource Guide for Pharmacists



Definitions

Blood pressure (BP)

- The amount of tension exerted by blood against walls of the arteries
- Systolic blood pressure (SBP) = pressure against the arterial walls when the heart contracts (ventricular systole)
- Diastolic blood pressure (DBP) = pressure against the arterial walls when the heart relaxes in between beats (diastole)
- Composite of equation: $BP = CO \times TPR$

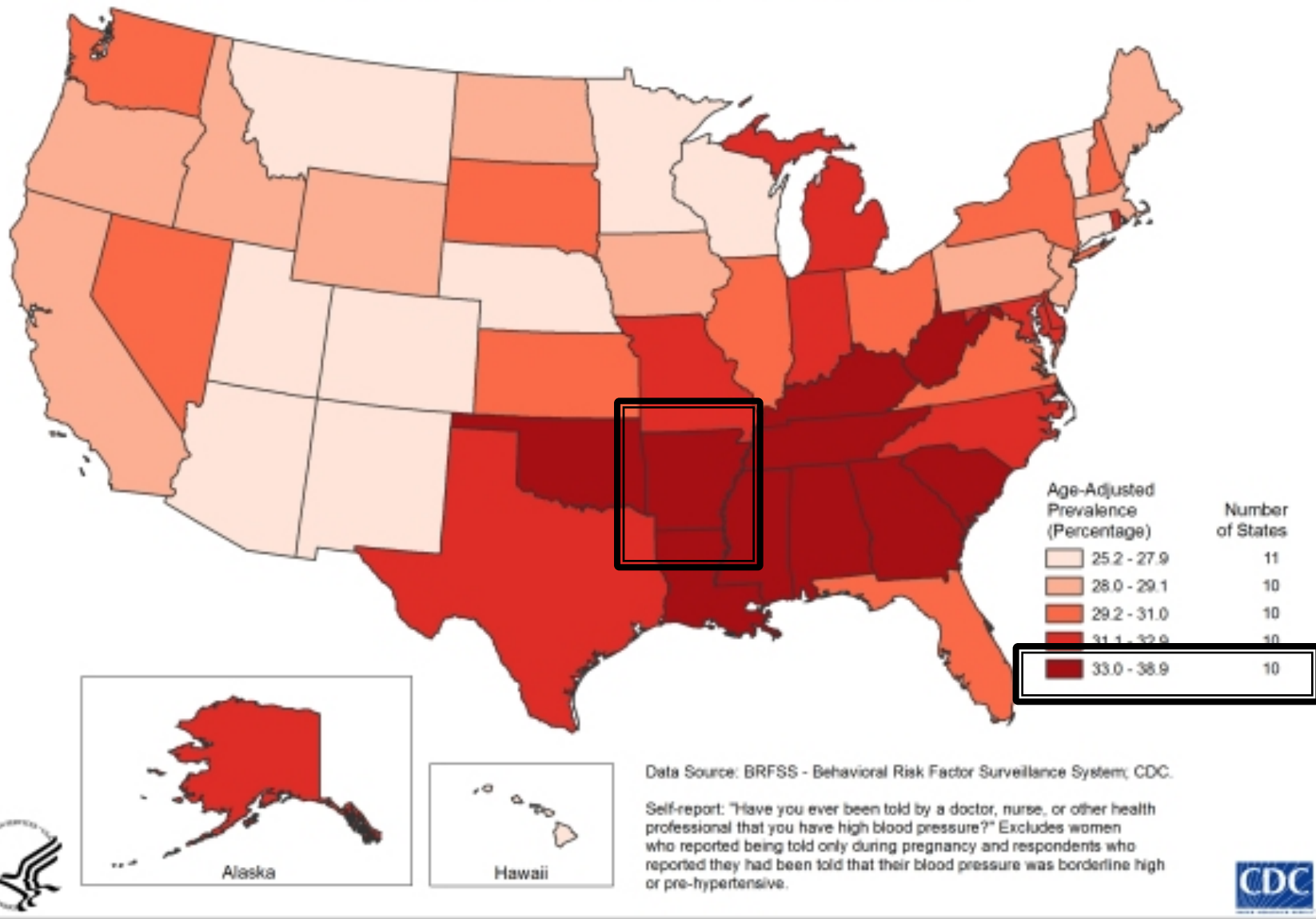
Hypertension (HTN)

- Consistently elevated arterial blood pressure

Hypertension

- “Silent killer”
 - Often patients present with no symptoms
- 1 in 3 adults in the United States has elevated blood pressure
 - 34 million Americans have uncontrolled hypertension
 - Estimated 1/3 don't know they have it and are not taking a medication for it

Prevalence of Hypertension, 2011 U.S. Adults Ages 20 and Older (Percentage)



*Image from: http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_bloodpressure.htm

Additional Terms

- **Office or “white coat” hypertension**
 - Increased BP in a clinical setting with normal or lower BP readings at home or in a non-clinical setting (15-20% of patients)
- **Isolated systolic hypertension**
 - SBP elevation (≥ 140 mmHg) with absence of DBP elevation (< 80 or < 90 mmHg)
 - Carries an increased risk of cardiovascular morbidity and mortality
- **Pseudo hypertension**
 - Falsely elevated BP values (found in the elderly, diabetics, and patients with chronic kidney disease)
- **Masked hypertension**
 - Decrease in BP occurs in the clinical setting (home BP values are elevated)

Epidemiology

- Increased prevalence in the following populations:
 - Elderly (prevalence increases with age)
 - Non-Hispanic black population (most prevalent in this group)
 - Non-Hispanic white population (2nd highest prevalence)
- 90% of patients diagnosed have essential or primary hypertension (unknown cause)
 - Other 10% from secondary hypertension (caused by disease states or medications)

Blood Pressure and Cardiovascular Risk

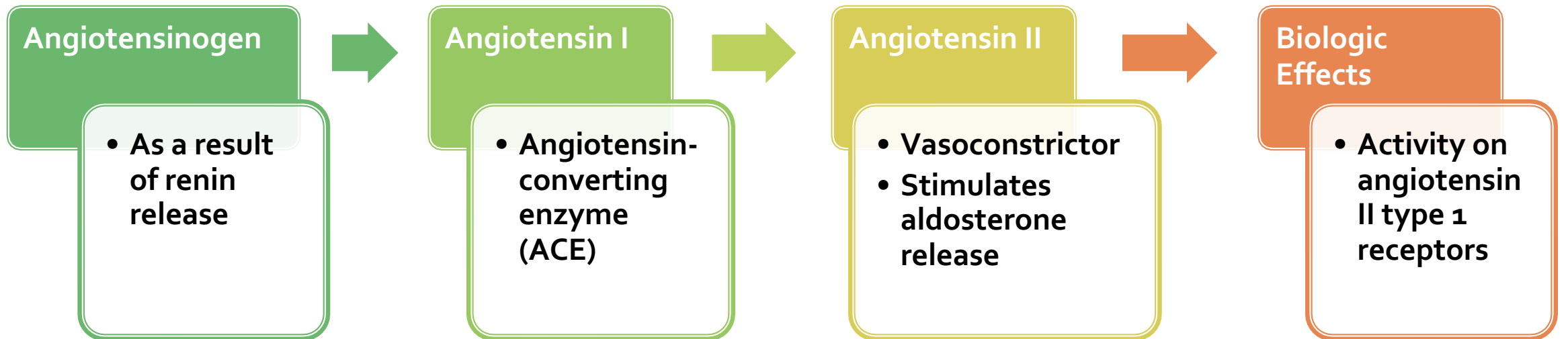
- Blood pressure values correlate with an increased risk of the following:
 - Stroke
 - Myocardial infarction (MI)
 - Angina
 - Heart failure (HF)
 - Kidney failure
 - Retinopathy
 - Early death from a cardiovascular cause
- Starting with a blood pressure value of 115/75 mmHg...
 - **For every increase by 20 mmHg SBP or 10 mmHg DBP, risk doubles**
 - These risks are reduced by using drug therapy to treat hypertension

Benefits of Lowering BP

- Reduction in the incidence of...
 - Stroke (35-40%)
 - Myocardial infarction (20-25%)
 - Heart failure (> 50%)
- HTN + at least one cardiovascular risk factor
 - 12 mmHg reduction in SBP over 10 years prevents 1 death for every 11 patients treated
- HTN + cardiovascular disease or target organ damage
 - Same reduction in SBP over 10 years prevents 1 death for every 9 patients treated

Pathophysiology

- **Renin-Angiotensin-Aldosterone System (RAAS)**
 - Most influential component for BP regulation
 - Controls sodium, potassium, and blood volume in the body



Pathophysiology: Neuronal Mechanisms

Norepinephrine (NE)

- Stimulation of α -receptors = inhibits NE release
- Stimulation of β -receptors = stimulates NE release

Sympathetic activity through innervation of α and β receptors

- Stimulation of α -receptors = vasoconstriction
- Stimulation of β_1 -receptors (heart) = increases heart rate and force of contraction

Baroreceptor reflex system

- Quick BP change/decrease = baroreceptor activation = vasoconstriction and increase in heart rate

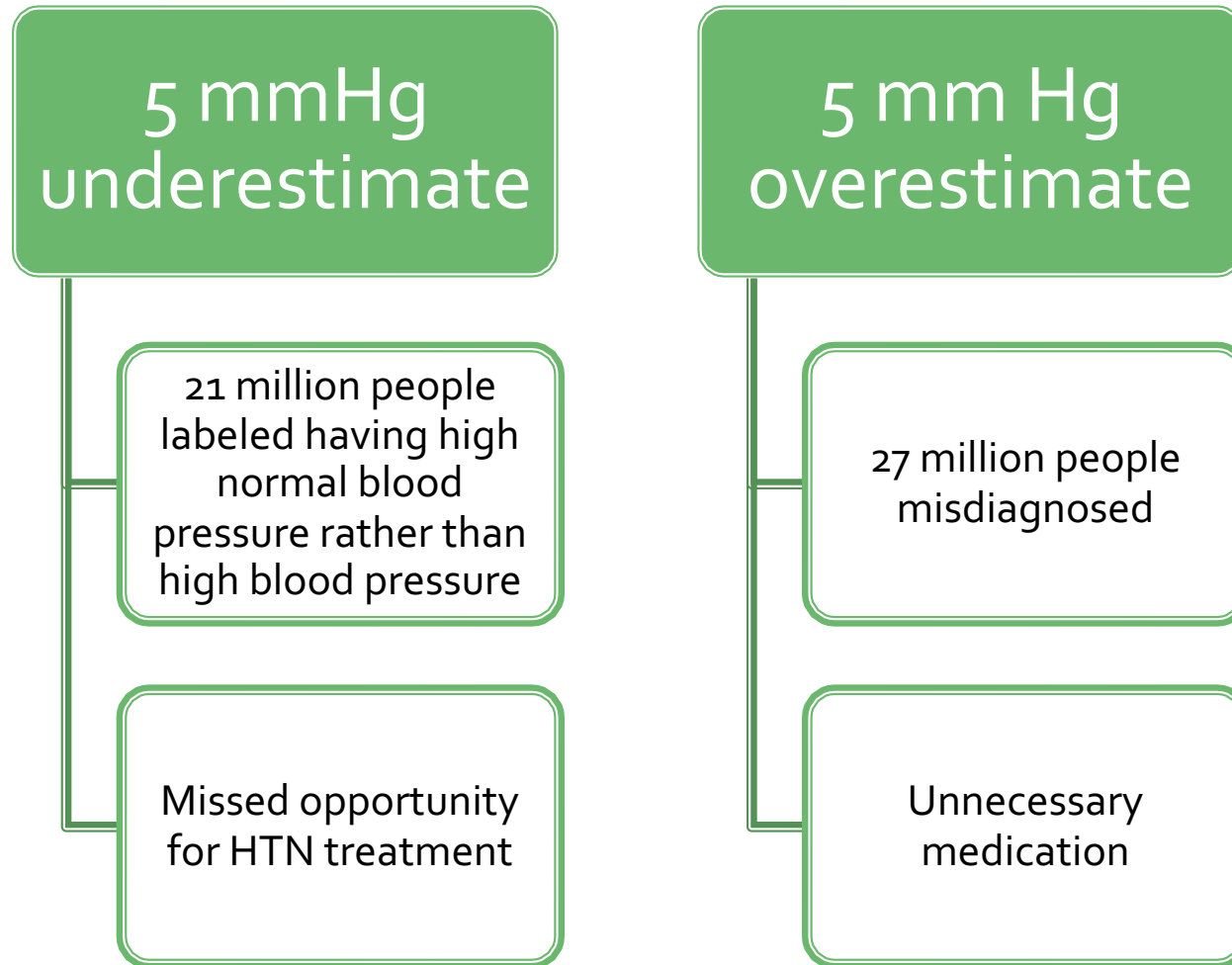
Central nervous system regulation

- Stimulation of α_2 -receptors = decreases BP

Clinical Presentation

- Signs: previously elevated BP readings
- Symptoms: most have NO symptoms
- Past Medical History:
 - Look for the presence of cardiovascular risk factors:
 - Age (> 55 for men and > 65 for women), diabetes mellitus, dyslipidemia, albuminuria, family history of premature cardiovascular disease, overweight or obesity, physical inactivity, and/or use of tobacco
- Additional labs:
 - BUN, serum creatinine, fasting lipid panel, blood glucose, electrolytes, hemoglobin/hematocrit, urine albumin-creatinine ratio

Proper Blood Pressure Technique



**Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2016.*

What is wrong with this picture?



Factors That Affect BP Values:

Age

Race

Weight

Exercise

Emotions

“White Coat Syndrome”

Medications

Patient Lifestyle

Environment

Equipment Used

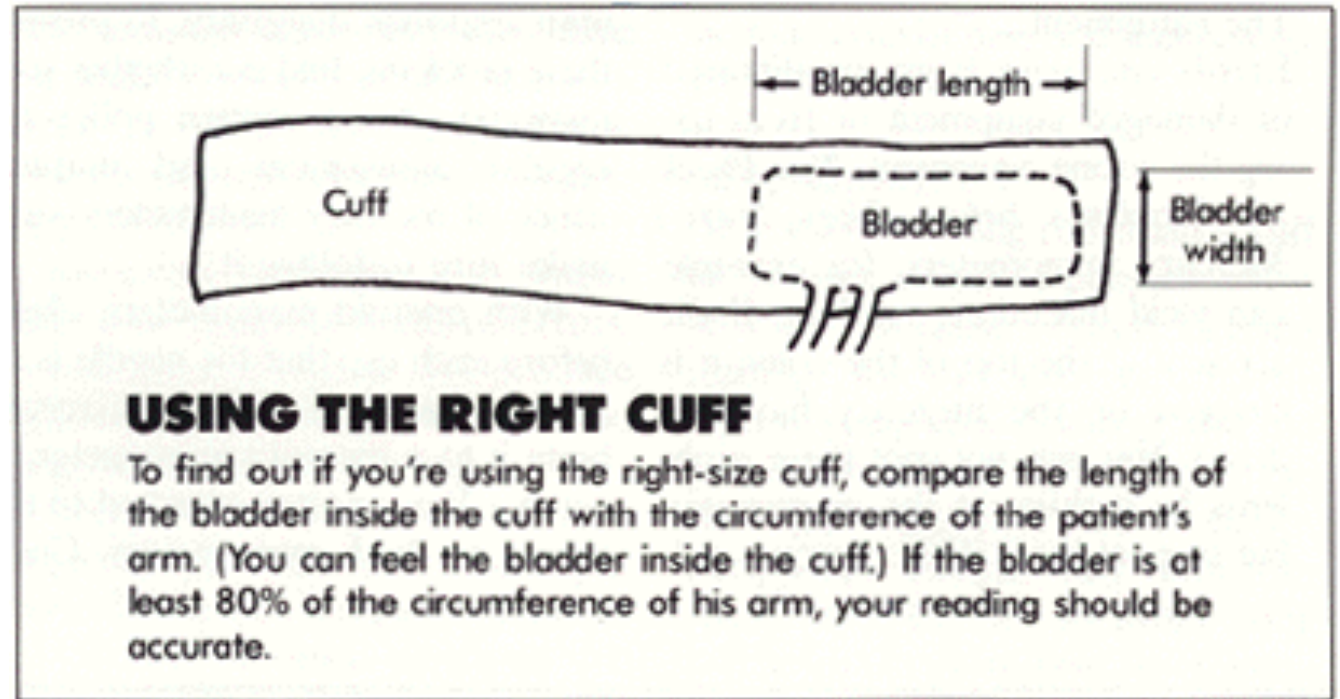
Blood Pressure Technique

- Patient is sitting comfortably upright with both feet flat on the ground
 - Should be seated at rest for at least 5 minutes prior to obtaining measurement
- Arm for blood pressure measurement should be placed at heart level
 - Do not obtain value over clothing if possible
- Patient should avoid caffeine and tobacco use at least 30 minutes prior to measurement

Blood Pressure Technique

- Utilize proper cuff size
 - Compare bladder length with circumference of patient's arm
 - Bladder length = 80% of arm circumference
 - Cuff width = 40% of limb circumference
- Take multiple measurements
 - Wait at least 1 minute in between checks
 - Recommended to check both arms with initial evaluation
 - Recommended to check at the same time each day

Correct Cuff Size



*Image from: <http://www.steeles.com/catalog/takingBP.html>

How to check blood pressure:

1. Proper positioning of patient and arm
2. Allow for five minutes of rest before checking
3. Determine appropriate cuff size
4. Palpate the brachial artery
5. Center bladder of cuff over brachial artery with lower edge 1 inch above antecubital space

How to check blood pressure:

6. Perform estimation of systolic BP value
 - While palpating radial pulse, inflate cuff to the point at which the radial pulse disappears
 - Add 30 mmHg to this number – serves as maximum inflation level
 - Alternative method: ask patient what BP normally runs and add 30 mmHg to that systolic value
7. Deflate cuff from estimation
8. Place stethoscope over brachial artery (antecubital fossa)
9. Inflate cuff to maximum inflation level

How to check blood pressure:

10. Deflate cuff slowly (2-3 mmHg/second)
11. Listen for Korotkoff sounds:
 - First of two consecutive sounds heard = systolic blood pressure
 - Last beat heard = diastolic blood pressure
12. Continue listening until at least 20 mmHg below last beat heard
13. Deflate cuff rapidly
14. Record BP value in even numbers with patient position, arm used, and size of cuff

Patient Case Discussion – BP Monitoring

- Mr. Smith is a 65-year old African American male presenting to your pharmacy to purchase a home blood pressure monitor. He was diagnosed with hypertension last week and started on chlorthalidone 25 mg daily. He plans to start checking his BP at home. He asks for your advice and education related to proper BP monitoring at home.
- What education points will you review with Mr. Smith?

Guidelines Galore!

Hypertension Treatment Guidelines and Recommendations

Hypertension

ESH/ESC

ADA

ACC/AHA

ASH/ISH

KDIGO

JNC

HTN Treatment Guidelines

- 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (JNC 8 Report) – published 2013 online and 2014 in *JAMA*
 - Not sanctioned by NHLBI
- Clinical Practice Guidelines for the Management of Hypertension in the Community (Statement by the American Society of Hypertension and the International Society of Hypertension) – published 2013 online
- ****New guidelines coming – Guideline on Management of HTN (ACC/AHA) – TBD**

Disease-State Specific BP Recommendations

Coronary Heart Disease

Treatment of Hypertension in Patients with Coronary Heart Disease (from AHA, ACC, and ASH)

Published 2015

Diabetes Mellitus (DM)

American Diabetes Association Standards of Care

Published annually (most recent in 2017)

Chronic Kidney Disease (CKD)

KDIGO Guidelines for the Management of Blood Pressure in Chronic Kidney Disease

Published in 2012

Heart Failure

ACC/AHA Focused Update of 2013 ACCF/AHA Guideline for Management of Heart Failure

Published in 2017

* J Am Coll Cardiol 2015;65:1998–2038

*Diabetes Care 2017;40(Suppl. 1).

**Journal of the American College of Cardiology* (2017), doi: 10.1016/j.jacc.2017.04.025.

* *Kidney Int Suppl.* 2012;2(5):337-414

BP Classification

- Not defined in JNC 8 (mentioned in ASH/ISH guidelines)
- For adults ≥ 18 years of age

| Category | SBP (mm Hg) | | DBP (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 |

Goals of Therapy

- **Primary goal = reduction of HTN-related morbidity and mortality from CV events**
 - Reduce incidence of cardiovascular disease, stroke, kidney disease, and death without negatively affecting the patient
- **Achieve recommended blood pressure goals – MANY options**
 - Will not guarantee prevention of target organ damage related to HTN, but is associated with lower risk of HTN-related target organ damage
- **BP goal for *MOST* patients = < 140/90 mmHg**
- **BP goal for elderly with risk for ADRs = < 150/90 mmHg**

| Guideline | BP Goal | Patient Population |
|--|------------------|--|
| JNC 8 Guidelines | < 140/90 | Hypertensive patients < 60 years of age, patients with DM, and patients with CKD |
| | < 150/90* | Hypertensive patients 60 or older without DM or CKD |
| ASH/ISH Guidelines for Management of HTN | < 140/90 | Hypertensive patients < 80 years of age, patients with DM, and patients with CKD |
| | < 150/90 | Hypertensive patients 80 or older without DM or CKD |
| ADA Standards of Medical Care | < 140/90 | Patients with diabetes and HTN |
| | < 130/80 | Younger patients "if achieved without undue treatment burden" |
| KDIGO Guidelines | < 140/90 | Patients with HTN and CKD (\pm DM) |
| | < 130/80 | Patients with HTN, CKD, and albuminuria (\pm DM) |
| ACC/AHA/ASH Guidelines in CAD | < 140/90 | Hypertensive patients with CAD *Consider < 130/80 in "some" individuals |
| ACC/AHA Focused Update for HF | < 130/80 | Patients with stage A HF, HFrEF, and HFpEF |

*JAMA 2014;311(5):507-520 *J Clin Hypertens 2013. doi:10.1111/jch.12237

* J Am Coll Cardiol 2015;65:1998–2038

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Evidence Behind Systolic BP Goals

- SBP correlates more with cardiovascular risk than DBP values
- ACCORD (Action to Control Cardiovascular Risk in Diabetes)
 - No difference in event rates for nonfatal major cardiovascular events or all-cause mortality with intensive versus standard BP lowering
 - Intensive goal = 120 mmHg versus standard goal = 140 mmHg
- Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) Review
- SHEP study – BP lowering and treatment goals in elderly

Evidence Behind Diastolic BP Goals

- Hypertension Optimal Treatment (HOT) study
 - Evaluated treatment effects in patients with elevated diastolic values
 - Treated to DBP < 90, < 85, or < 80 mmHg
 - Results
 - Trend that lower DBP values correlated with lower risk for cardiovascular events and stroke (no statistically significant difference)
 - Target < 80 mmHg for patients with diabetes
- Cochrane review for different BP goals in patients with DM

New Evidence: SPRINT Trial

- Intensive versus standard blood pressure control
- ~9000 patients randomized to SBP target < 120 mmHg (intensive) versus < 140 mmHg (standard)
 - Primary outcome = composite of MI, ACS, stroke, heart failure, or death from CV causes
- Results: **trial stopped early** with significantly lower rate of primary outcome events in intensive versus standard group
 - Higher incidence of drug-related adverse effects in intensive group
- ***Practice changing?***

Mini-Patient Cases: BP Goals

- Which goal is appropriate for the following patient: a 75-year old male with only HTN per JNC 8?
 - < 130/80
 - < 140/90
 - < 150/90

Mini-Patient Cases: BP Goals

- Which goal is appropriate for the following patient: 40-year old female with only HTN per ASH/ISH?
 - < 130/80
 - < 140/90
 - < 150/90

Mini-Patient Cases: BP Goals

- Which goal is appropriate for the following patient: 60-year old male with DM + HTN per ADA Standards of Care?
 - < 130/80
 - < 140/90
 - < 150/90

Non-Pharmacologic Therapy

- For ALL patients with prehypertension and hypertension
- **Dietary Approaches to Stop Hypertension (DASH)**
 - Focus on fruits, vegetables, whole grains, and low-fat dairy products with reduced intake of saturated and total fat
- **Consumption of < 2400 mg of sodium daily**
 - Consider targeting < 1500 mg per day for further BP reduction
- **Limit alcohol consumption**
- **Physical activity**
- **Tobacco cessation**
- **Weight loss**

| MODIFICATION | RECOMMENDATION | APPROXIMATE SBP REDUCTION (RANGE) |
|-----------------------------------|---|--|
| Weight reduction | Maintain normal body weight (body mass index 18.5–24.9 kg/m ²). | 5–20 mmHg/10 kg weight loss ^{23,24} |
| Adopt DASH eating plan | Consume a diet rich in fruits, vegetables, and lowfat dairy products with a reduced content of saturated and total fat. | 8–14 mmHg ^{25,26} |
| Dietary sodium reduction | Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride). | 2–8 mmHg ^{27,28} |
| Physical activity | Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week). | 4–9 mmHg ^{29,30} |
| Moderation of alcohol consumption | Limit consumption to no more than 2 drinks (1 oz or 30 mL ethanol; e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter weight persons. | 2–4 mmHg ³⁰ |

HTN Treatment Guidelines – JNC 8

- General population ≥ 60 years of age, initiate therapy if SBP ≥ 150 mmHg OR DBP ≥ 90 mmHg
 - Goal $< 150/90$ mmHg
 - Grade A recommendation
- General population < 60 years of age, initiate therapy if SBP ≥ 140 mmHg or DBP ≥ 90 mmHg
 - Goal $< 140/90$ mmHg
 - Grade A for DBP, Grade E for SBP

HTN Treatment Guidelines – JNC 8

- Adults > 18 years of age with CKD, initiate therapy if SBP \geq 140 mmHg or DBP \geq 90 mmHg
 - Goal < 140/90 mmHg
 - Grade E recommendation
- Adults > 18 years of age with diabetes, initiate therapy if SBP \geq 140 mmHg or DBP \geq 90 mmHg
 - Goal < 140/90 mmHg
 - Grade E recommendation

Drug Therapy for HTN

- Selection is based on degree of blood pressure elevation and a patient's compelling indications
- Classes to consider **first-line** for lowering BP with evidence that supports cardiovascular risk reduction:
 - **Thiazide diuretics**
 - **Angiotensin-converting enzyme inhibitors (ACEIs)**
 - **Angiotensin receptor blockers (ARBs)**
 - **Calcium channel blockers (CCBs)**

ALLHAT Trial

- Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)
- Largest prospective HTN trial with ~42,000 patients age 55 or older with a diagnosis of HTN and one additional cardiovascular risk factor
- Designed as a superiority study to determine whether new antihypertensive agents (CCBs, ACEIs, alpha blockers) were better at decreasing fatal coronary heart disease or nonfatal myocardial infarction than thiazide diuretics
- Patients received chlorthalidone, amlodipine, doxazosin, or lisinopril for a mean of ~5 years

ALLHAT Trial

- Results:
 - Doxazosin group: D/C early (increased heart failure and cardiovascular events compared with chlorthalidone)
 - Study authors concluded that thiazide diuretics were superior in preventing one or more major forms of cardiovascular disease and are less expensive...
 - BUT, no difference in primary outcome between chlorthalidone, amlodipine, and lisinopril
 - Additional subgroup analyses have not shown superiority of thiazides versus other classes

JNC 8 HTN Treatment Recommendations

- General population (no diagnosis of DM or CKD) PLUS patients with diabetes and no CKD:
 - *Recommendation 6 (Grade B) and 7 (Grade B, C if DM)*

| Patient Population | Drug Therapy |
|--------------------|--|
| Nonblack | Thiazide diuretic or ACEI or ARB or CCB (alone or in combination) |
| Black | Thiazide diuretic or CCB (alone or in combination) |

JNC 8 HTN Treatment Recommendations

- CKD present with or without diabetes (all ages and all races):
 - *Recommendation 8 (Grade B)*


| Patient Population | Drug Therapy |
|--------------------|--|
| CKD +/- DM | Initial or add-on should include an ACEI or ARB (alone or in combination with other drug classes) |

JNC 8 Additional Points

- Only discusses diabetes and chronic kidney disease for co-morbid condition specific recommendations
- Drug titration strategy:
 - Start with one drug and maximize the dose of that drug before adding a second drug
OR
 - Start with one drug and add a second drug before reaching the maximum dose of the first drug
OR
 - Start with 2 drugs (in separate classes) at the same time as 2 separate pills or a combination product

JNC 8 Additional Points

If goal BP is not achieved within one month of therapy, increase dose of the first BP drug or add a second drug (thiazide, CCB, ACEI, or ARB)



If goal BP can not be obtained with 2 drugs, add a third agent (thiazide, CCB, ACEI, or ARB)

- ACEIs and ARBs should not be used together
- 

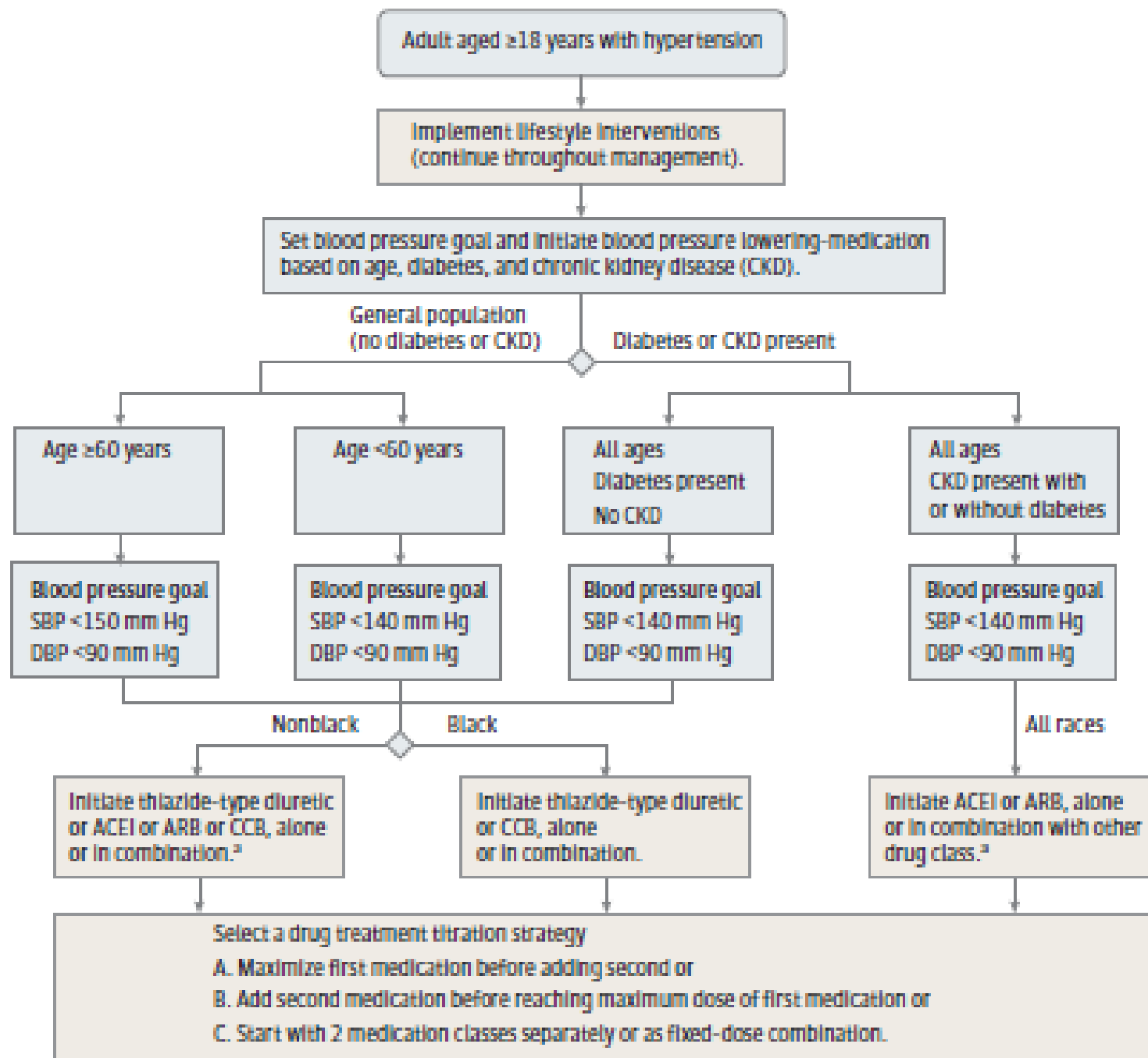
If goal BP can not be achieved with drugs from the above classes, consider additional drug therapy options:

- Beta blockers, aldosterone antagonist, vasodilators, etc.

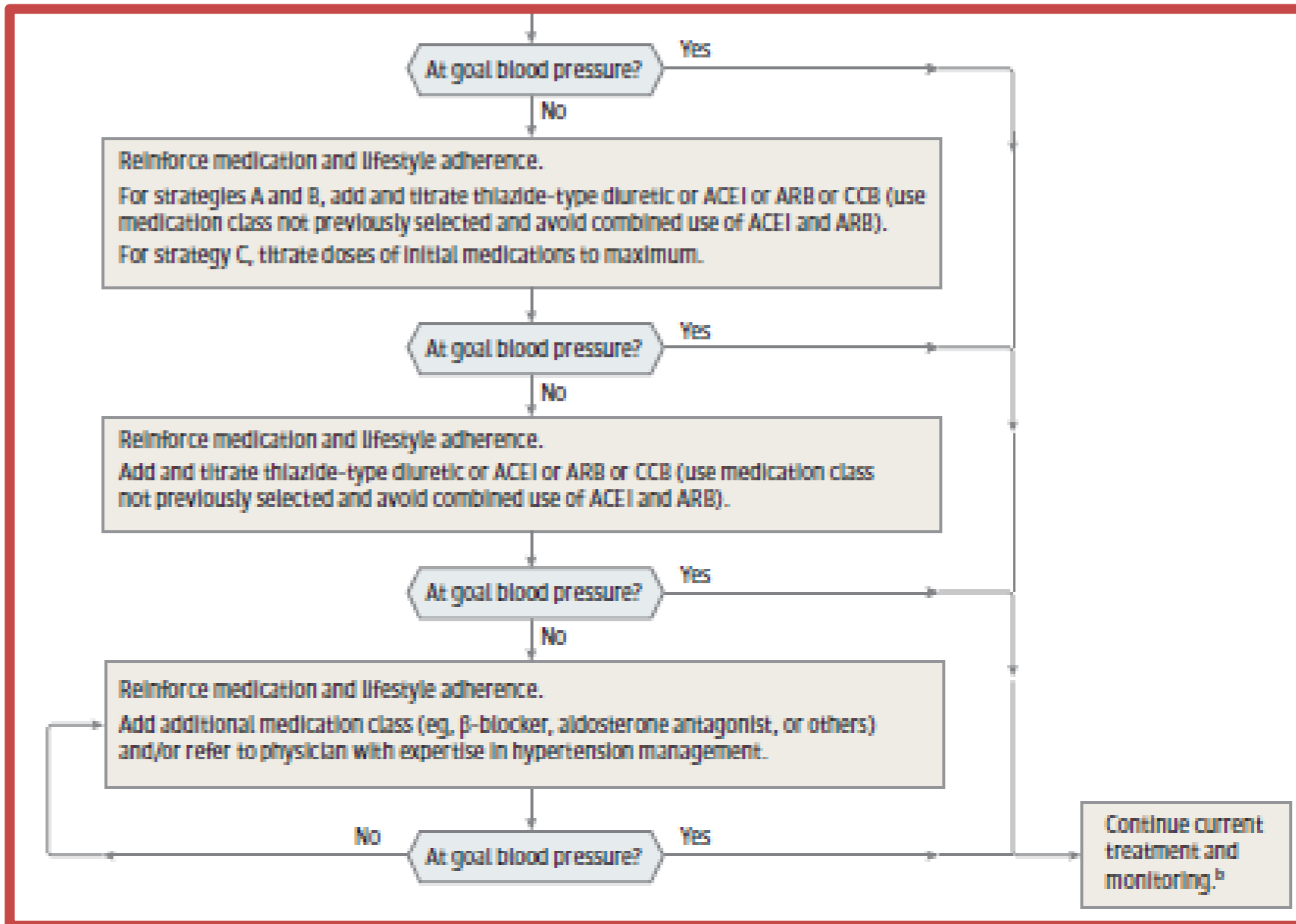
Table 4. Evidence-Based Dosing for Antihypertensive Drugs

| Antihypertensive Medication | Initial Daily Dose, mg | Target Dose in RCTs Reviewed, mg | No. of Doses per Day |
|--------------------------------------|------------------------|----------------------------------|----------------------|
| ACE inhibitors | | | |
| Captopril | 50 | 150-200 | 2 |
| Enalapril | 5 | 20 | 1-2 |
| Lisinopril | 10 | 40 | 1 |
| Angiotensin receptor blockers | | | |
| Eprosartan | 400 | 600-800 | 1-2 |
| Candesartan | 4 | 12-32 | 1 |
| Losartan | 50 | 100 | 1-2 |
| Valsartan | 40-80 | 160-320 | 1 |
| Irbesartan | 75 | 300 | 1 |
| β-Blockers | | | |
| Atenolol | 25-50 | 100 | 1 |
| Metoprolol | 50 | 100-200 | 1-2 |
| Calcium channel blockers | | | |
| Amlodipine | 2.5 | 10 | 1 |
| Diltiazem extended release | 120-180 | 360 | 1 |
| Nitrendipine | 10 | 20 | 1-2 |
| Thiazide-type diuretics | | | |
| Bendroflumethiazide | 5 | 10 | 1 |
| Chlorthalidone | 12.5 | 12.5-25 | 1 |
| Hydrochlorothiazide | 12.5-25 | 25-100 ^a | 1-2 |
| Indapamide | 1.25 | 1.25-2.5 | 1 |

*JAMA 2014;311(5):507-520

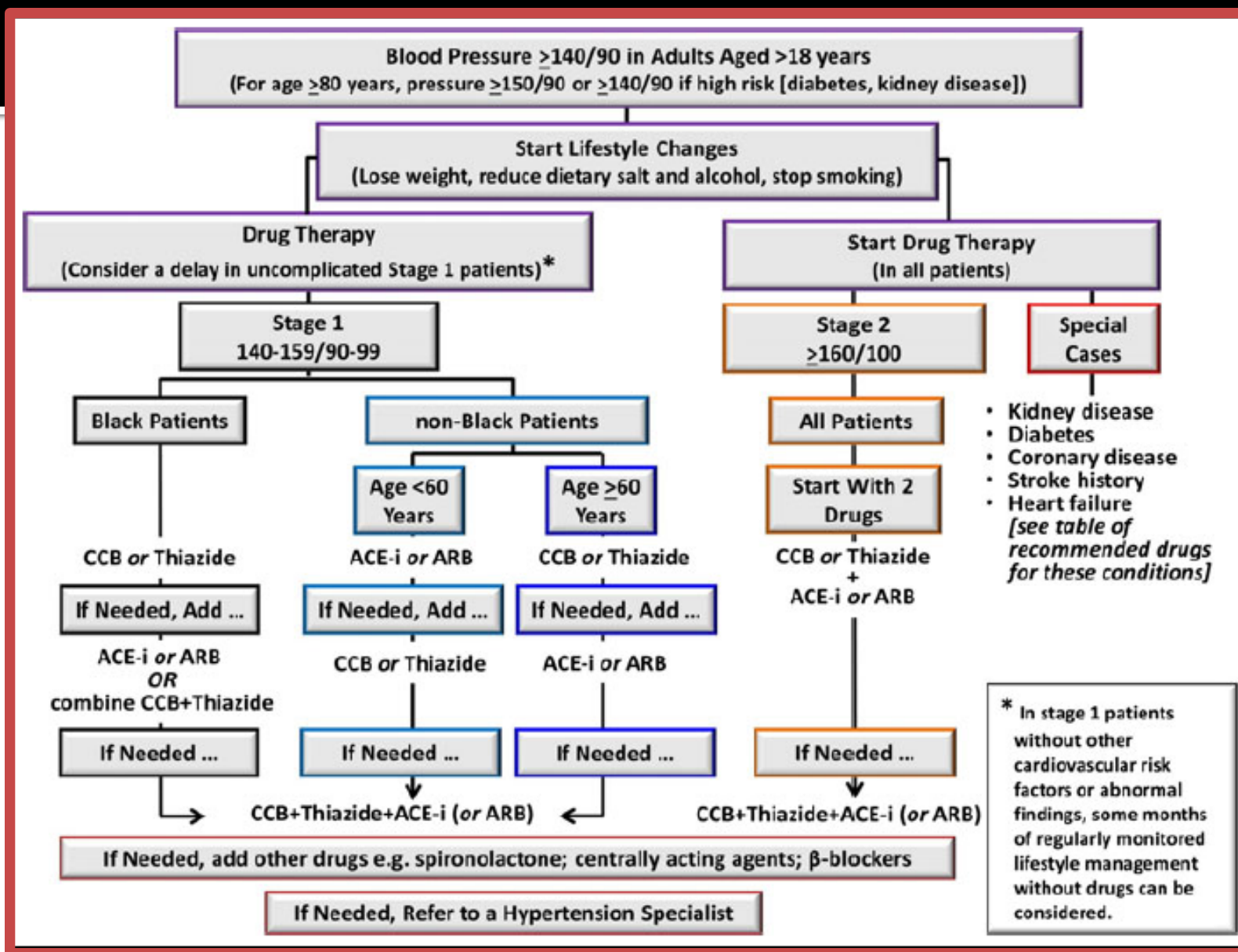


*JAMA 2014;311(5):507-520



*JAMA 2014;311(5):507-520

ASH/ISH Statement Algorithm



ASH/ISH Recommendations

| Condition | 1 st Drug | 2 nd Drug (if needed) | 3 rd Drug (if needed) |
|----------------------|--|---|---|
| HTN + DM | ACEI or ARB *If patient is black, can start with CCB or thiazide | CCB or thiazide *If black, add ACEI or ARB if started with CCB or thiazide | Alternative 2 nd drug (CCB or thiazide) |
| HTN + CKD | ACEI or ARB | CCB or thiazide | Alternative 2 nd drug (CCB or thiazide) |
| HTN + CAD | BB + ACEI or ARB | CCB or thiazide* | Alternative 2 nd drug (CCB or thiazide) |
| HTN + stroke history | ACEI or ARB | CCB or thiazide | Alternative 2 nd drug (CCB or thiazide) |
| HTN + HF | Symptomatic heart failure: ACEI or ARB + BB + diuretic + spironolactone *Add dihydropyridine CCB if needed for BP control | | |

*Table adapted from 2013 ASH/ISH Clinical Practice Guidelines - J Clin Hypertens. 2013. doi:10.1111/jch.12237.

Medication Selection Points

- Individualize therapy based on a patient's age, race, potential adverse effects, and compelling indications
- Considerations:
 - Cost (brand versus generic agents)
 - Combination products
 - Dosing (daily up to 4x/day)
 - Monitoring for efficacy and safety
- **Assess medication compliance for hypertension with every patient encounter**

Non-Compliant Patients

- Perform an assessment of the patient's antihypertensive therapy with every patient encounter
- Utilize the following to assess compliance:
 - Home/clinic BP values
 - Ask the patient about compliance and missed doses
 - Perform pill counts
 - Monitor refill history

Improving Compliance

- Maintain regular patient contact and follow-up for monitoring
- Keep medication regimens simple and inexpensive
- Provide education on the importance of HTN treatment:
 - Benefits of lifestyle modifications and how to set realistic goals
 - Benefits and adverse effects of therapy
 - Awareness of normal and abnormal blood pressure measurements
 - Risks of uncontrolled HTN
 - Need for chronic therapy
- Consider compliance aides
 - Pillboxes
 - Medication calendars
 - Alarm reminders

Resistant HTN

Criteria:

- Patients who are unable to achieve their BP goal with the use of 3 or more antihypertensive agents
 - Full doses of at least 3 medications, of which one is a diuretic
- Patients with controlled HTN requiring 4 or more antihypertensive agents

Causes:

- Volume overload
 - Sodium intake
 - Kidney disease
 - Inadequate diuretic dose
- Improper BP measurement
- Drug-related causes or contributing conditions (obesity or sleep apnea)
- Non-adherence
- Secondary HTN

Resistant HTN

- Assess compliance and contributing factors
- Consideration of treatment guidelines and compelling indications to guide therapy selection
- Ensure patient is on adequate diuretic therapy
 - *If appropriate without contraindications
 - Consider aldosterone antagonists as an add-on therapy option
- Use combination therapies when possible
- Consider alternative agents for management when needed
 - BBs, diuretics, alpha blockers, direct renin inhibitor, vasodilators, central alpha2 agonists, and reserpine

PATHWAY-2

- Randomized, double-blind, crossover trial
- Population = patients with HTN uncontrolled on maximally tolerated doses of 3 agents for at least 3 months
- All patients received 12 weeks of spironolactone, bisoprolol, doxazosin, and placebo
- Primary outcome: average home systolic blood pressure values
- Results: spironolactone was the most effective add-on agent

| | Blood pressure (mm Hg) | Change from baseline (mm Hg) |
|---|------------------------|------------------------------|
| Mean | | |
| Spironolactone | 134.9 (134.0 to 135.9) | -12.8 (-13.8 to -11.8) |
| Doxazosin | 139.0 (138.0 to 140.0) | -8.7 (-9.7 to -7.7) |
| Bisoprolol | 139.4 (138.4 to 140.4) | -8.3 (-9.3 to -7.3) |
| Placebo | 142.5 (141.5 to 143.5) | -1.1 (-2.1 to -0.1) |
| Mean differences | | |
| Spironolactone vs placebo | 8.70 (-9.72 to -7.69) | p<0.0001 |
| Spironolactone vs mean bisoprolol and doxazosin | -4.26 (-5.13 to -3.38) | p<0.0001 |
| Spironolactone vs doxazosin | -4.03 (-5.04 to -3.02) | p<0.0001 |
| Spironolactone vs bisoprolol | -4.48 (-5.50 to -3.46) | p<0.0001 |

Data are mean (95% CI). Home systolic blood pressure throughout the treatment cycle for each drug (includes data from mid-cycle at week 6 and the final visit at week 12). Least squares means from mixed effects models adjusted for baseline covariates. Hierarchical primary endpoints each tested only if the preceding tests were significant.

Table 2: Home systolic blood pressure averaged across both visits for each cycle

| | Blood pressure (mm Hg) | Change from baseline (mm Hg) |
|---|------------------------|------------------------------|
| Mean | | |
| Spironolactone | 133.5 (132.3 to 134.8) | -14.4 (-15.6 to -13.1) |
| Doxazosin | 138.8 (137.6 to 140.1) | -9.1 (-10.3 to -7.8) |
| Bisoprolol | 139.5 (138.2 to 140.8) | -8.4 (-9.7 to -7.1) |
| Placebo | 143.7 (142.5 to 145.0) | -4.2 (-5.4 to -3.0) |
| Mean differences | | |
| Spironolactone vs placebo | -10.2 (-11.7 to -8.74) | p<0.0001 |
| Spironolactone vs mean bisoprolol and doxazosin | -5.64 (-6.91 to -4.36) | p<0.0001 |
| Spironolactone vs doxazosin | -5.30 (-6.77 to -3.83) | p<0.0001 |
| Spironolactone vs bisoprolol | -5.98 (-7.45 to -4.51) | p<0.0001 |

Data are mean (95% CI). Sensitivity analysis using only the mean home systolic blood pressure at the final visit of each cycle (week 12).

Table 3: Home systolic blood pressure at final visit of each cycle

* Lancet 2015; 386: 2059-68.

Content Question

- Which agent is **NOT** in one of the four preferred initial drug classes for management of HTN?
 - Nifedipine
 - Chlorthalidone
 - Carvedilol
 - Valsartan

Content Question

- According to the JNC 8 recommendations, which medication class should be included on a stage III CKD patient's HTN regimen, either as initial or an add-on therapy option?
 - Beta blocker
 - Thiazide diuretic
 - ACE inhibitor
 - Alpha blocker

Brief Review of Medication Classes for Hypertension

Drug Classes to Consider for HTN Treatment

- *ACE inhibitors*
- *Angiotensin II receptor blockers*
- *Calcium channel blockers (DHPs and non-DHPs)*
- *Diuretics (thiazides, loops, potassium sparing)*
- Beta blockers
- Alpha blockers
- Direct renin inhibitor
- Central alpha₂ agonists
- Peripheral adrenergic inhibitor (reserpine)
- Direct arterial vasodilators

ACE Inhibitors (ACE-I)

- Clinical Effects:
 - Prevent conversion of angiotensin I to angiotensin II
 - Vasodilation
 - Decreased secretion of aldosterone
- Benefits:
 - Decrease CV events in high-risk patients
 - Benefits in DM, CKD, and HFrEF
- Monitoring:
 - Adverse effects (cough, dizziness, hyperkalemia, acute renal failure and/or angioedema – rare)
 - Assess renal function (BUN/SCr), K⁺, and BP
- Clinical Pearls:
 - Start with recommended dosages and slowly titrate
 - Consider decrease in typical starting dose by 50% in elderly and those on a diuretic

Angiotensin II Receptor Blockers (ARBs)

- Clinical Effects:
 - Inhibit angiotensin II receptor
 - Vasodilation
 - Decreased sympathetic activity and aldosterone secretion
- Benefits:
 - Decrease CV events in high-risk patients
 - Benefits in DM and HFrEF
- Monitoring:
 - Adverse effects (dizziness, hyperkalemia, acute renal failure and/or angioedema – rare)
 - Assess renal function (BUN/SCr), K⁺, and BP
- Clinical Pearls:
 - Consider decrease in typical starting dose by 50% in elderly and those on a diuretic

Calcium Channel Blockers

- Clinical Effects:
 - Coronary and peripheral vasodilation
 - Smooth muscle relaxation
 - Increase myocardial oxygen delivery
- Two Types:
 - Dihydropyridines (DHPs) = amlodipine, felodipine, nicardipine, nifedipine, etc.
 - Nondihydropyridines (nonDHPs) = diltiazem and verapamil
- Monitoring:
 - BP and heart rate
 - NonDHPs = heart failure or heart block
 - DHPs = edema, angina, MI
- Clinical Pearls:
 - Differing site of action and clinical effects
 - Caution with use of verapamil or diltiazem + beta blocker
 - *Watch for drug interactions

Thiazide Diuretics

■ Clinical Effects:

- Block sodium reabsorption in distal tubule
- Diuresis – increased plasma and stroke volume – decrease cardiac output and BP
- Decrease in cardiac output causes initial increase in systemic vascular resistance (SVR)
- SVR returns to lower than pre-treatment values (lower BP)

■ Clinical Pearls:

- Preferred diuretic class in HTN
- Expected BP lowering ~15-20 mmHg (SBP)
- Agents with efficacy data = HCTZ and chlorthalidone
- Take in the morning or earlier in the day
- Not effective in patients with renal failure or if CrCl < 30 mL/min

Diuretics – General Precautions

- Volume depletion
- Electrolyte disturbances (hypokalemia, hyponatremia, hypomagnesemia, and hypercalcemia)
- Sulfa allergy (thiazides and loops)
- Renal insufficiency (thiazides and potassium-sparing agents)
- Gout
- Monitoring: renal function (BUN, SCr), electrolytes (K, Na, Mg, Ca), glucose, uric acid, and BP

Alternative Options

Loop Diuretics

Reserve for use in renal insufficiency or heart failure

Can use in place of thiazide if CrCl < 30 mL/min

More diuresis, but less effective at lowering BP than thiazides

Aldosterone Antagonists

Weak BP lowering if used alone – consider spironolactone in resistant HTN

Monitor potassium closely with potential for hyperkalemia

Eplerenone contraindicated if CrCl < 50, elevated SCr/K+, or type 2 DM with albuminuria

Direct Renin Inhibitor (Aliskiren)

Causes decreased plasma renin activity and lower BP

Do not use in combination with ACEIs or ARBs

Same adverse effects and monitoring parameters as ACEIs and ARBs

Alternative Options

Beta Blockers

Not a first-line drug class – use if patient has compelling indications

All agents provide similar BP lowering effects

Consider cardioselectivity: preference for β_1 vs. β_2 – select cardioselective agents for HTN

Monitor for bradycardia, bronchospasm, CNS effects, and worsening heart failure

Alpha Blockers

Alternative drug class for use in combination with other first-line preferred agents – do not use as monotherapy for HTN

Use with caution in the elderly considering adverse effects of syncope, orthostatic hypotension, and CNS side effects (dizziness, headache, vivid dreams, and drowsiness)

Consider combining with a diuretic for maximal efficacy

Alternative Options

Central Alpha₂ Agonists (Clonidine)

Monitor for adverse effects = orthostatic hypotension, CNS (fatigue, depression, dizziness), dry mouth, constipation, sodium/water retention

Do not abruptly D/C – may cause rebound HTN (taper gradually)

Use with diuretic for maximal efficacy

Peripheral Adrenergic Inhibitor (Reserpine)

Decreased PVR/BP and depletes brain catecholamines, which may cause decreased CO, sedation, and depression

Adverse effects = orthostasis, bradycardia, drowsiness, nightmares, and depression

Use with diuretic for maximal efficacy

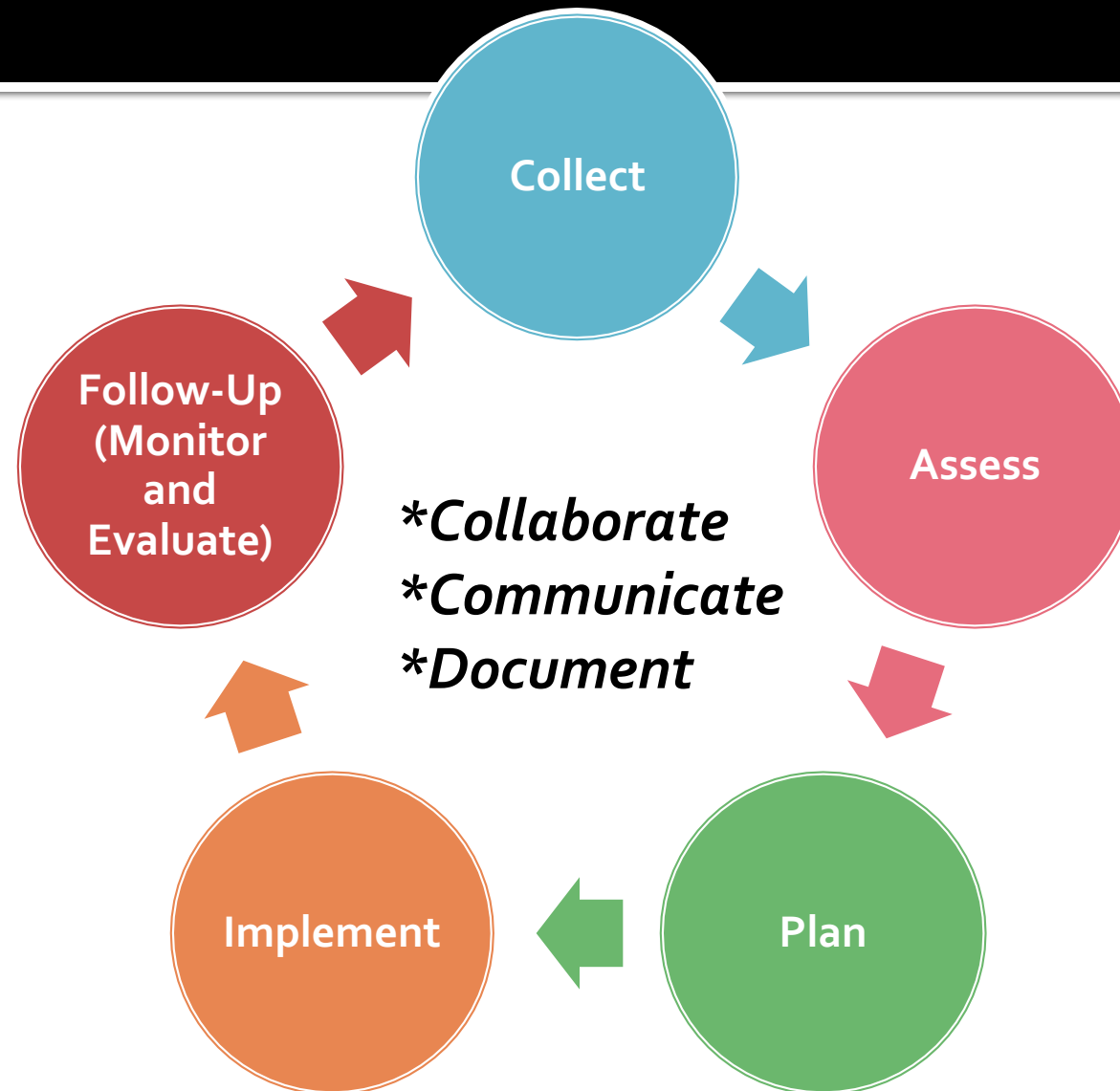
Direct Arterial Vasodilators (Hydralazine)

Adverse effects = tachycardia, headache, dizziness, lupus-like syndrome, neuropathy, sodium/water retention, and hirsutism

Use with a diuretic and beta blocker to diminish fluid retention and reflex tachycardia

Minoxidil is a more potent vasodilator and reserved for difficult HTN

Pharmacists' Patient Care Process



What to COLLECT for hypertension?

- Subjective and objective information necessary to understand medical/medication history and clinical status of the patient
 - Medical history (age, current and past medical history, family history, surgical history)
 - Physical assessment (vitals – BP and HR, weight/BMI, edema)
 - Laboratory values
 - Medication history
 - Lifestyle factors (stress, diet, physical activity, nicotine, alcohol)

What to ASSESS for hypertension?

- Assess patient information
- Analyze the clinical effects of the patient's therapy related to health/disease state goals to identify and prioritize drug-related problems
 - 10-year ASCVD risk (if applicable)
 - Determine BP goal
 - Look for medication-related problems
 - Determine need for lifestyle modifications
 - Transitions of care

What to PLAN for hypertension?

- Develop an individualized, evidence-based, and cost effective patient care plan with input from other health care professionals and the patient or caregiver
- What to include in your plan:
 - A blood pressure goal
 - Frequency for home monitoring and review of proper technique
 - Medication management action items
 - Details for lifestyle modifications
 - Discuss proposed plan with collaborators and document!

What to IMPLEMENT for hypertension?

- Implement the care plan in collaboration with other health care professionals and the patient or caregiver
- What to do:
 - Provide education on appropriate self-monitoring of BP
 - Initiate, change, administer, or discontinue medication to resolve medication-related problems according to collaborative practice agreement, protocol, or prescriber approval
 - Provide patients and providers with updated med list and action plan
 - Provide coaching for related behavior and lifestyle changes
 - Refer if necessary, document, and arrange follow-up

How to FOLLOW-UP for hypertension?

- Develop a monitoring plan to evaluate the effectiveness and safety of the patient care plan
- Change the plan in collaboration with other health care professionals and the patient or caregiver if needed
 - Assess adherence with medications and behavior change
 - Evaluate clinic and home BP measurements
 - Reassess medication appropriateness, effectiveness, and safety (make changes if warranted)
 - Refer if necessary, document, and arrange follow-up

Hypertension Clinical Cases

Patient Case – Mr. Vargas

- Timothy Vargas is a 51-year old Hispanic male presenting for a physical today. He has not seen a doctor for the past two years and needs a refill on his cholesterol medication, which he stopped six months ago. His only complaint today is that he started developing headaches about 3 months ago, which are not relieved by daily ibuprofen. His office had nurses for health screenings last week, and he presented a results paper from the screening. He had his blood pressure checked, and they told him it was high.
- *BP values on result sheet from the screening:
 - 166/94 mmHg (right arm) and 168/96 mmHg (left arm) with pulse 84 bpm

Patient Case – Mr. Vargas

- PMH: hyperlipidemia
- FH: father passed away from a heart attack 5 years ago, mother alive with HTN and osteoporosis, one older brother alive with HTN and hyperlipidemia
- SH: smokes cigarettes 1 pack per day (for 20 years), drinks 2-3 beers if out on the weekends
- Allergies: NKDA
- Current Medications:
 - Atorvastatin 20 mg once daily (has not taken for 6 months)
 - Over-the-counter ibuprofen 200 mg – takes 2 tablets TID for headaches

Patient Case – Mr. Vargas

- Vital Signs:
 - BP 166/86 mmHg (right arm), repeat BP 168/90 mmHg (left arm), pulse 82 bpm
 - Wt 115 kg, Ht 5'9"
- Pertinent Labs:
 - Lipid panel: TC 240, LDL 167, HDL 38, TG 175
 - Na⁺ 143, K⁺ 4.3, BUN 13, SCr 0.9

Patient Case – Assessment

- How would you classify this patient's blood pressure today?
 - Normal
 - Pre-hypertension
 - Stage 1 hypertension
 - Stage 2 hypertension

Patient Case – Assessment

- What is Mr. Vargas's blood pressure goal according to the JNC 8 recommendations?
 - < 130/80
 - < 140/90
 - < 150/90

Additional Assessment Points

- 10-year ASCVD risk = 20.9% (10-year risk)
 - Evaluate appropriateness of statin therapy
- Medication-related problems
 - Non-compliance with atorvastatin
 - Inappropriate use of ibuprofen daily
- Lifestyle modifications
 - Smoking cessation
 - Limiting alcohol intake
 - Physical activity and diet recommendations

Patient Case – Plan and Implement

- Which regimen is appropriate for initial hypertension therapy for Mr. Vargas?
 - Lisinopril 10 mg daily
 - Valsartan 160 mg daily
 - Lisinopril/hydrochlorothiazide 10/12.5 mg daily
 - Lisinopril 10 mg daily and amlodipine 5 mg daily

Additional Plan/Implementation Points

- Include the following:
 - Plans for home blood pressure monitoring
 - BP goal
 - Lifestyle modifications
- Provide education (lifestyle, medication, disease state, etc.)
- Update medication list
- Arrange for follow-up
- Document encounter and provide patient action plan

Patient Case – Follow-Up

- Which of the following monitoring plans is appropriate for Mr. Vargas?
 - Return to clinic in 2-3 weeks, obtain renal panel with electrolytes and serum creatinine
 - Return to clinic in 1 month, no labs needed
 - Return to clinic in 3 months, obtain fasting lipid panel
 - Return to clinic in 6 months, no labs needed

Patient Case – Mr. Hayes

- Mr. Hayes is a 65-year old Caucasian male presenting to his primary care physician's office for refills on his blood pressure medications. He regularly checks his blood pressure at home twice daily and presents a log to this visit. His blood pressure has been elevated, and he thinks he may need adjustments to his medications today.

| Blood Pressure Log | |
|--------------------|------------------|
| Morning | Evening |
| 152/82, pulse 81 | 160/69, pulse 79 |
| 153/74, pulse 77 | 132/69, pulse 80 |
| 138/74, pulse 78 | No reading |
| 156/80, pulse 72 | 157/77, pulse 85 |
| 148/84, pulse 82 | 120/58, pulse 80 |
| 164/85, pulse 86 | 148/72, pulse 84 |
| 164/84, pulse 88 | 156/68, pulse 75 |
| 163/89, pulse 85 | 150/67, pulse 84 |
| 153/89, pulse 78 | No reading |

Patient Case – Mr. Hayes

- PMH: HTN, osteoarthritis, atrial fibrillation, COPD, BPH, and type 2 diabetes
- FH: father died from a stroke, mother passed away from complications with diabetes, has one brother who is alive and well with HTN and hyperlipidemia
- SH: married and lives with his wife, quit cigarettes in 1990, 2 glasses of wine with dinner daily
- Allergies: hydrochlorothiazide and chlorthalidone (hyponatremia with sodium as low as 120 mg/dL), metoprolol tartrate (wheezing)

Patient Case – Mr. Hayes

- Current Medications:
 - Diltiazem 180 mg SA capsule twice daily
 - Lisinopril 40 mg once daily
 - Furosemide 40 mg once daily in the morning
 - Potassium chloride 20 mEq once daily
 - Tamsulosin 0.4 mg once daily
 - Albuterol inhaler 1-2 puffs four times daily as needed for shortness of breath
 - Tiotropium 18 mcg capsules – inhale contents of one capsule daily for COPD
 - Warfarin 5 mg daily
 - Acetaminophen 325 mg twice daily
 - Metformin 500 mg twice daily for diabetes

Patient Case – Mr. Hayes

- Vital Signs: BP 152/86 mmHg (right arm), repeat BP 158/82 mmHg (left arm), pulse 62 bpm
- Wt 101 kg, Ht 5'10"
- Labs: Na⁺ 139, K⁺ 3.6, Cl 101, CO₂ 30, BUN 18, SCr 0.95, Glucose 110, Ca 9.0, Mg 2.1

Patient's physician consults you for recommendations regarding blood pressure management.

Patient Case – Assessment

- What is this patient's blood pressure goal according to the ADA Standards of Care?
 - < 130/80
 - < 140/90
 - < 150/90

Patient Case – Recommendations

- Furosemide dose increase?
- Spironolactone initiation?
- Thiazide initiation?
- Beta blocker initiation?
- Lisinopril increase?
- Diltiazem increase?
- Alpha blocker initiation?
- Initiation of alternative classes?
 - Central-alpha₂ agonist or vasodilator

References

- Nwankwo T, Yoon SS, Burt V, Qiuping G. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011–2012. *NCHS Data Brief*. 2013;133:1-8. Accessed May 20, 2017.
- Centers for Disease Control and Prevention. Ambulatory Health Care Data website. Accessed May 20, 2017.
- He J, Whelton PK. Elevated systolic blood pressure and risk of cardiovascular and renal disease: overview of evidence from observational epidemiologic studies and randomized controlled trials. *Am Heart J*. 1999;138(3 Pt 2):211-219.
- Centers for Disease Control and Prevention. *Using the Pharmacists' Patient Care Process to Manage High Blood Pressure: A Resource Guide for Pharmacists*. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2016.
- Advancing Safety in Healthcare Technology. Sphygmomanometer Guidance Collection website. Accessed August 31, 2016.
- James PA, Oparil S, Carter BL, et al. 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). *JAMA*. 2014;311(5):507-520.
- Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: A statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens*. 2013. doi:10.1111/jch.12237.

References

- Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. *J Am Coll Cardiol* 2015;65:1998–2038.
- American Diabetes Association. Standards of medical care in diabetes – 2017. *Diabetes Care* 2017;40(Suppl. 1).
- Kidney Disease; Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl.* 2012;2(5):337-414.
- Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C, 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure, *Journal of the American College of Cardiology* (2017), doi: 10.1016/j.jacc.2017.04.025.
- Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA.* 2003;289(19):2560–2572.
- ACCORD Study Group; Cushman EC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med.* 2010;362:1575-1585.
- Sundstrom J, Arima H, Jackson R, et al. Effects of blood pressure reduction in mild hypertension: A systematic review and meta-analysis. *Ann Intern Med.* 2014; published ahead of print online 23 Dec 2014. doi: 10.7326/M14-0773

References

- SHEP Investigators. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*;1991;3255-64.
- Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet*. 1998;351:1755-62.
- Arguedas J, Leiva V, Wright JM. Blood pressure targets for hypertension in people with diabetes mellitus. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No.: CD008277. DOI: 10.1002/14651858.CD008277.pub2
- SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015 Nov 26;373(22):2103-16. doi: 10.1056/NEJMoa1511939.
- National Heart, Lung, and Blood Institute. In Brief: Your Guide to Lowering Your Blood Pressure With Dash. Accessed 22 May 2017. Available at: https://www.nhlbi.nih.gov/files/docs/public/heart/dash_brief.pdf.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT): major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic. *JAMA*. 2002;288(23):2981-2997.
- Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. 2015; 386: 2059-68.

Hypertension: Guidelines Galore and Clinical Cases

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