# Managing A Silent Killer: An Evidence-Based Update on Hypertension Treatment

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# Disclosures

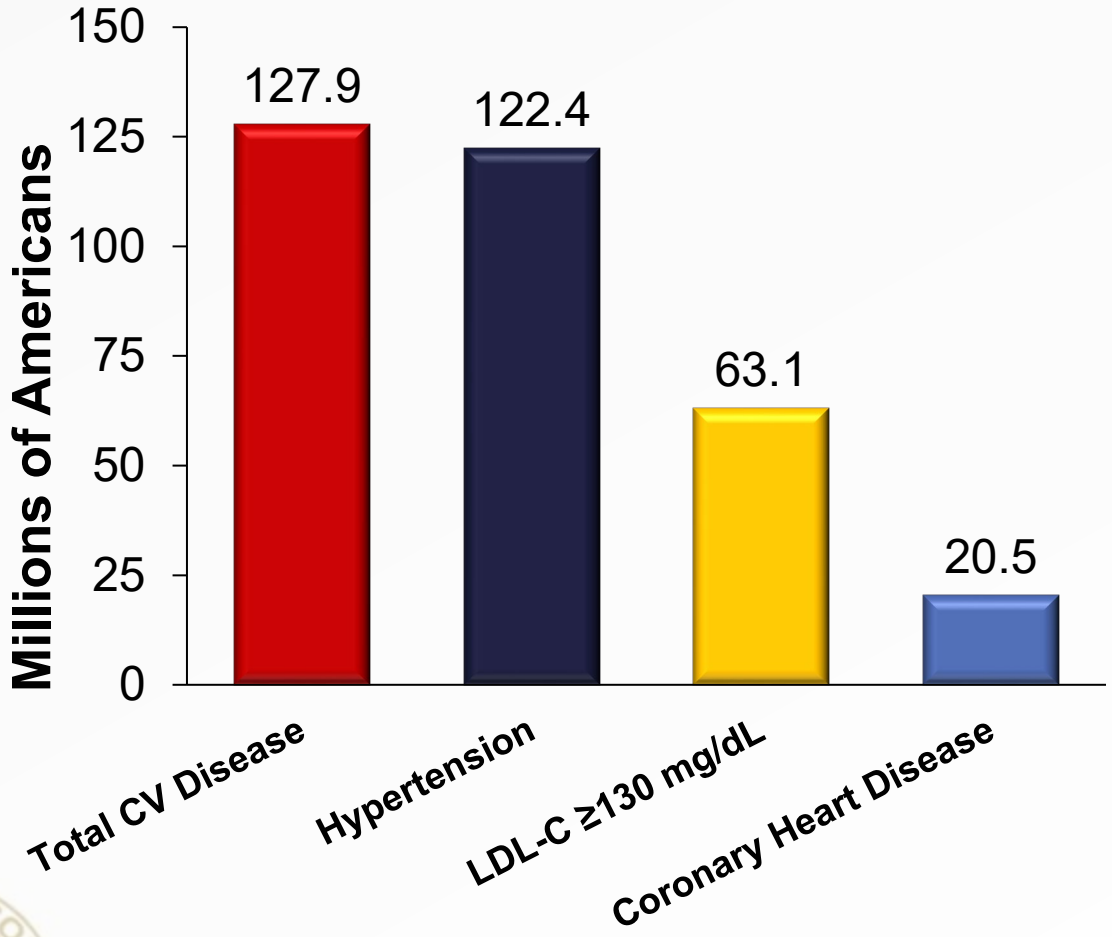
- Dr. Saseen no relevant financial relationships with any ineligible companies, any potential disclosed conflicts have been mitigated.
- The off-label use of medication will not be discussed during this presentation.

# Learning Objectives

***At the completion of this activity, the learner will be able to:***

1. Interpret 2017 ACC/AHA hypertension guidelines for hypertension management.
2. Discuss evidence supporting lower BP goals for hypertension treatment.
3. Compare and contrast recommendations for managing resistant hypertension and routine hypertension care.

# American Heart Association (AHA):
## Heart Disease & Stroke Statistics in the US - 2024



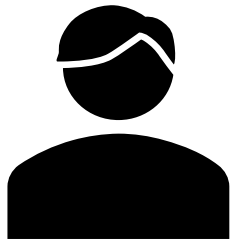


LDL-C = low-density lipoprotein cholesterol

Martin SS, et al. Circulation. 2024;149:e00–e00. DOI: 10.1161/CIR.0000000000001209

# Meet John Doe

- 47-year-old black man with a history of hypertension, dyslipidemia, chronic kidney disease (G3A2), and “pre-diabetes”
- Family history: father died of an MI at age 50
- Social history: former smoker, lives in a very disadvantaged Denver neighborhood
- Does not follow a specific diet, drinks 2-3 alcoholic beverages/day, does not exercise
- Insurance: Medicaid
- Medications: HCTZ 25 mg po daily, atorvastatin 10 mg po daily
- BP 142/88 mm Hg (similar values at home), HR 80 beats/min, BMI 29.7 kg/m2
- Fasting Labs:
  - TC 220 mg/dL, HDL 30 mg/dL, LDL 144 mg/dL, TG 300 mg/dL
  - A1C 6.3%, Scr 1.6 mg/dL (eGFR 53 mL/min/1.73m2),UACR 64 mg/g
- Coronary Artery Calcium: 287 AU in left anterior descending artery



# Pooled Cohort Equations (PCE) Estimate ASCVD Risk in Primary Prevention

- Predicts10-year risk of hard ASCVD if age 40-79 years (lifetime risk if age 20-59 years:
  - Nonfatal or fatal myocardial infarction or nonfatal or fatal stroke
  - 10-year risk interpretation:
    - Low risk: <5%
    - Borderline risk: 5% to 7.4%
    - Intermediate risk: 7.5% to 19.9%
    - High risk: ≥20%

- John Doe:

| | |
|---|---|
| Age* | 47-year-old |
| Race* | African American |
| Sex* | Man |
| Systolic BP* | 142 mm Hg |
| Diastolic BP | 80 mm Hg |
| Total cholesterol* | 220 mg/dL |
| HDL-cholesterol* | 30 mg/dL |
| LDL-C | 144 mg/dL |
| Diabetes* | No |
| Smoker* | Never |
| Antihypertensive therapy* | Yes |
| Statin: | Yes |
| Aspirin: | No |

**10-year Risk**
**10.9%**

**Lifetime Risk**
**50%**

*required characteristic that determines estimation

Lloyd-Jones D, et al. *J Am Coll Cardiol*. 2019;19(73):3153-3167.
http://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/

# The PREVENT Equations (AHA Predicting Risk of CVD Events)

- Newly developed sex-specific, race-free risk equations
- Enable 10-and 30-year risk estimates for patients age 30 to 79 years:
  1) total CVD (composite of ASCVD and heart failure)
  2) ASCVD
  3) heart failure
- Includes estimated glomerular filtration rate as a predictor
- Accommodates enhanced predictive utility with the addition of CKM factors when clinically indicated for measurement (urine albumin-to-creatinine ratio and hemoglobin A1c) and social determinants of health



Khan SS, et al. Circulation. 2023;148:1982–2004.

# PREVENT Equation Predictions for John Doe

| | |
|---|---|
| Sex | Man |
| Age | 47-year-old |
| Total cholesterol | 220 mg/dL |
| HDL-cholesterol | 30 mg/dL |
| Systolic BP | 142 mm Hg |
| Diastolic BP | 80 mm Hg |
| BMI | 29.7 kg/m$^2$ |
| eGFR | 53 mL/min/1.73m$^2$ |
| Diabetes | No |
| Smoker | No |
| Antihypertensive medication | Yes |
| Lipid-lowering medication: | Yes |
| UACR: | 64 mg/g |
| HbA1C: | 6.3% |
| Zip Code: | 80204 |

**Stage 3 CKM**

- 10-year/30-year CVD Risk
  **11.1%/42.8%**
- 10-year/30-year ASCVD Risk
  **7.4%/30.1%**
- 10-year/30-year Heart Failure Risk
  **3.5%/19.5%**

Lloyd-Jones D, et al. *J Am Coll Cardiol*. 2019;19(73):3153-3167.
http://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/

# ACC/AHA Guideline Recommendation Ranking

## Class of Recommendation (COR) - Strength

**Class I (Strong)** — **Benefit >>> Risk**
- Is recommended, is indicated, should be performed

**Class IIa (Moderate)** — **Benefit >> Risk**
- Is reasonable, can be useful

**Class IIb (Weak)** — **Benefit ≥ Risk**
- May/might be reasonable/considered, effectiveness unknown

**Class III: No Benefit (Moderate)** — **Benefit = Risk**
- Is not recommended, is not useful

**Class III: Harm (Strong)** — **Benefit < Risk**
- Potentially harmful, causes harm

## Level of Evidence (LOE) - Quality

**Level A**
- High-quality evidence from > one randomized clinical trial (RCT)
- Meta-analyses of high-quality RCTs

**Level B-R (Randomized)**
- Moderate-quality evidence from > one RCT
- Meta-analyses of moderate-quality RCTs

**Level B-NR (Nonrandomized)**
- Moderate-quality from nonrandomized studies, observational, registry

**Level C-D (Limited Data)**

**Level C-EO (Expert Opinion)**

Whelton PK, et al. *J Am Coll Cardiol*. 2018;71:e127-e248.

# Measurement of BP

| COR | LOE | Recommendation |
|---|---|---|
| I | C-EO | For diagnosis and management of high BP, proper methods are recommended for accurate measurement and documentation of BP |
| I | A | Out-of-office BP measurements recommended to:<br>• Confirm diagnosis<br>• Titrate medication<br>• Enhance telehealth counseling or clinical interventions |

- Emphasis on appropriate technique
- Use out-of-office monitoring in diagnosis and management
  - Home BP monitoring (HBPM)
  - Ambulatory BP monitoring (ABPM)
- Detect white coat or masked hypertension

Whelton PK, et al. *J Am Coll Cardiol*. 2018;71:e127-e248.

# Obtaining Accurate BP Readings

- Appropriate Device
  - Validated and periodically calibrated
  - Correct cuff size; cuffs too small results in falsely high measurements, cuffs too large result in falsely low measurements
  - HBPM devices with memory preferred
  - Bell or diaphragm can be used for auscultatory measurements
  - Train patient on use
  - Average ≥2 readings on ≥2 occasions
  - 3 to 5 minute period of rest
- Repeat readings

| ***When the patient has….*** | ***BP can appear higher by…*** |
|---|---|
| Cuff over clothing | 10-50 mm Hg |
| A full bladder | 10-15 mm Hg |
| A conversation or is talking | 10-15 mm Hg |
| Unsupported arm | 10 mm Hg |
| An unsupported back | 5-10 mm Hg |
| Unsupported feet | 5-10 mm Hg |
| Crossed legs | 2-8 mm Hg |

Munter P, et al. Hypertension. 2019;73:e35–e66.

# 2017 ACC/AHA: BP Categories

| BP Category | Systolic BP (mm Hg) | | Diastolic BP (mm Hg) |
|---|---|---|---|
| **Normal** | <120 | and | <80 |
| **Elevated** | 120–129 | and | <80 |
| **Hypertension Stage 1** | 130–139 | or | 80–89 |
| **Hypertension Stage 2** | ≥140 | or | ≥90 |

DBP, diastolic blood pressure; and SBP systolic blood pressure.

Whelton PK, et al. *J Am Coll Cardiol*. 2018;71:e127-e248.

# 2017 ACC/AHA Hypertension Guideline

- Goal BP of <130/80 mm Hg for most

| COR | LOE | Patients With Hypertension |
|---|---|---|
| I | SBP: B-R<br>DBP: C-EO | Known CV disease, diabetes, chronic kidney disease (CKD), or 10-year ASCVD event risk of ≥10% a BP target <130/80 mm Hg |
| IIb | SBP: B-NR<br>DBP: C-EO | Without additional markers of increased CVD risk, a BP target <130/80 mm Hg |

| COR | LOE | BP Goals: Older |
|---|---|---|
| I | A | SBP goal <130 mm Hg for non-institutionalized ambulatory community-dwelling adults ≥65 yr |

CVD = cardiovascular disease; CKD = chronic kidney disease

Whelton PK, et al. *J Am Coll Cardiol*. 2018;71:e127-e248.

# American Academy of Family Practitioners: Practice Guidelines

## Recommendation 1

- Standard BP target of <140/90 mm Hg to reduce all cause and CV mortality (strong recommendation; high-quality evidence)
  - <135/85 mm Hg did not provide additional mortality benefit
  - lower target could be considered based on clinical assessment and patient preferences/values

## Recommendation 2

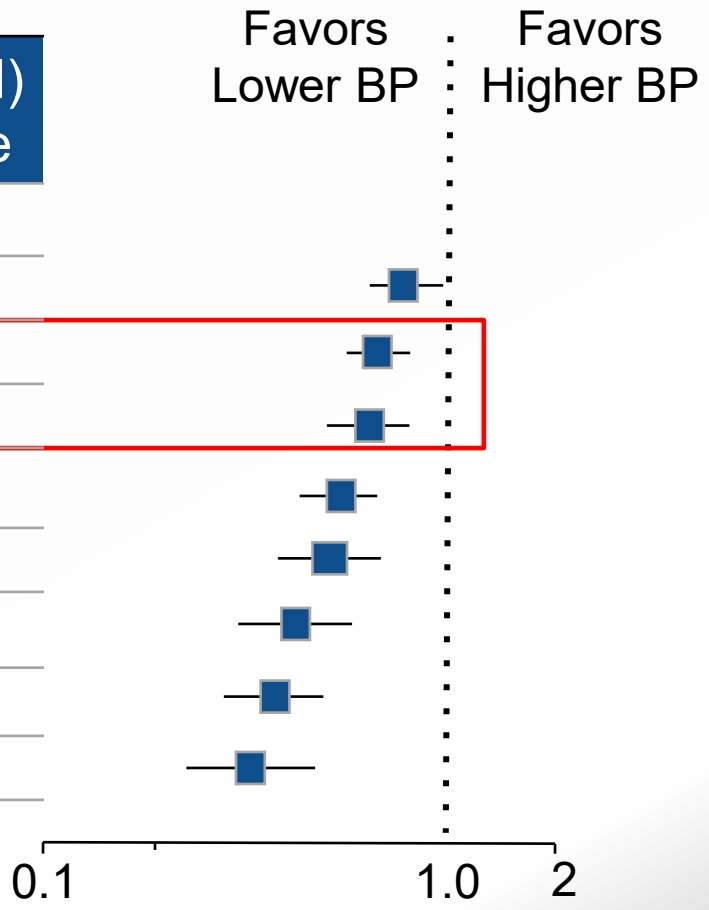
- Lower BP target of <135/85 mm Hg to reduce MI (weak recommendation; moderate-quality evidence)
  - <140/90 mm Hg reduced MI risk, but small additional benefit with a lower BP target

https://www.aafp.org/dam/AAFP/documents/journals/afp/AAFPHypertensionGuideline.pdf

# Better CV Outcomes Occur with Lower BP

Systematic Review and Network Meta-Analysis of 42 hypertension clinical trials (n=144 220)

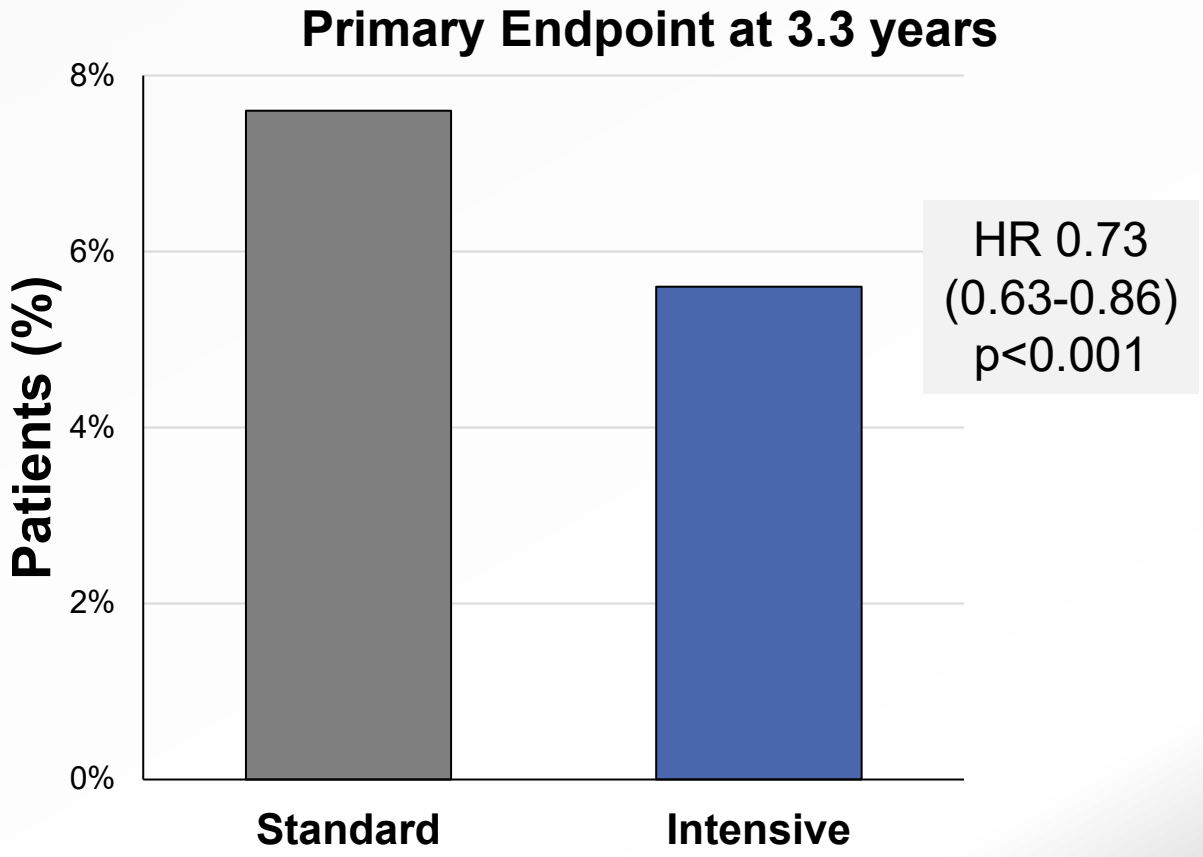
| Mean Achieved systolic BP (mm Hg) | Hazard Ratio (95%CI) for Major CV disease |
|---|---|
| Reduction to 120-124 | |
| 120-124 vs 125-125 | 0.82 (0.67-0.97) |
| 120-124 vs 130-134 | 0.71 (0.60-0.83) |
| 120-124 vs 135 -139 | 0.68 (0.55-0.85) |
| 120-124 vs 140-144 | 0.58 (0.48-0.72) |
| 120-124 vs 145-149 | 0.55 (0.42-0.72) |
| 120-124 vs 150-154 | 0.46 (0.34-0.63) |
| 120-124 vs 155-159 | 0.41 (0.32-0.54) |
| 120-124 vs ≥ 160 | 0.36 (0.26-0.51) |




Bundy DJ, et al. JAMA Cardiol. 2017;2(7):775-781.

# Systolic Blood Pressure Intervention Trial (SPRINT)

- Randomized, controlled trial in 9,361 patients age ≥ 50 years with additional ASCVD risk factors and hypertension randomized open-label to:
  - Standard: SBP <140 mm Hg
  - Intensive: SBP <120 mm Hg
- Key Study Exclusions:
  - Diabetes, prior stroke or CV event within 3 months, heart failure with reduce ejection fraction
- Primary outcome: first the occurrence of a MI, acute coronary syndrome, stroke, heart failure, or CV disease death




SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control [published correction appears in *N Engl J Med*. 2017 Dec 21;377(25):2506]. *N Engl J Med*. 2015;373(22):2103-2116. doi:10.1056/NEJMoa1511939

# SPRINT: Subgroup Analyses

| Subgroup | Intensive (%) | Standard (%) | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| Age | | | | 0.24 |
| • <75 years | 4.6 | 5.8 | 0.79 (0.64-0.97) | |
| • ≥ 75 years | 8.2 | 12.0 | 0.65 (0.5-0.83) | |
| Sex | | | | 0.42 |
| • Female | 5.0 | 6.1 | 0.82 (0.61-1.09 | |
| • Male | 6.0 | 8.3 | 0.70 (0.58-0.85) | |
| Race | | | | 0.72 |
| • Black | 4.8 | 6.4 | 0.77 (0.56-1.05) | |
| • Non-Black | 6.0 | 8.1 | 0.72 (0.59-0.86) | |
| Previous CVD | | | | 0.46 |
| • No | 4.4 | 6.1 | 0.70 (0.57-0.86) | |
| • Yes | 11.0 | 13.3 | 0.80 (0.61-1.04) | |



The SPRINT Research Group. *N Engl J Med*. 2021;384(20):1921-1930.

# SPRINT: Safety

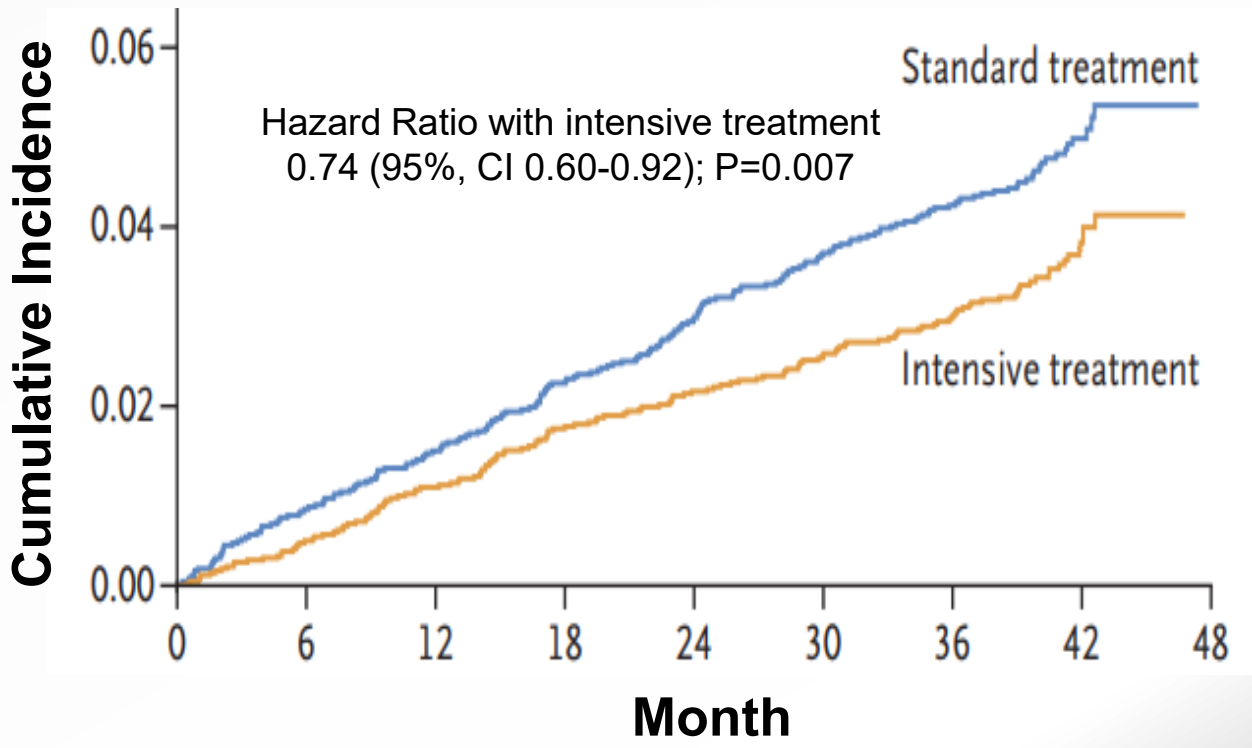
| Outcome | Intensive N=4678; no.(%) | Standard N=4683; no.(%) | Hazard Ratio (P-Value) |
|---|---|---|---|
| Serious Adverse Event (SAE)‡ | 1799 (38.5) | 1742 (37.2) | 1.04 (0.23) |
| Individual SAE | | | |
| • Hypotension | 99 (2.1) | 58 (1.2) | **1.71 (0.001)** |
| • Syncope | 97 (3.1) | 73 (1.6) | 1.33 (0.07) |
| • Electrolyte abnormality | 138 (2.9) | 104 (2.2) | **1.33 (0.03)** |
| • Injurious fall | 102 (2.2) | 101 (2.2) | 1.01 (0.97) |
| • Acute kidney injury/acute renal failure | 193 (4.1) | 115 (2.5) | **1.69 (<0.001)** |
| Emergency department visit or SAE | | | |
| • Hypotension | 144 (3.1) | 79 (1.7) | **1.83 (<0.001)** |
| • Injurious fall | 335 (7.2) | 317 (6.8) | 1.06 (0.49) |
| Sodium <130 mmol/L | 189 (4.0) | 103 (2.2) | **1.85 (<0.001)** |
| ‡ SAE defined as fatal or life-threatening or that resulted in clinically significant or persistent disability | | | |



The SPRINT Research Group. *N Engl J Med*. 2021;384(20):1921-1930.

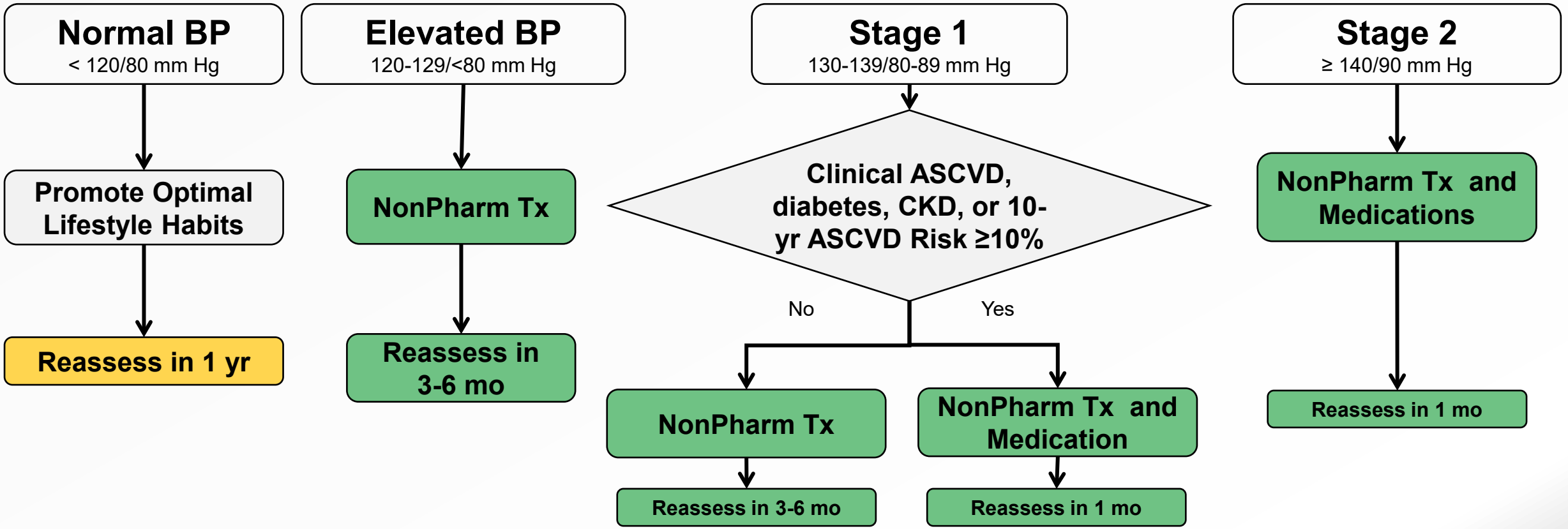
# Strategy of BP Intervention in the Elderly Hypertensive Patients (STEP) Study

- Randomized, controlled trial, in 8511 Chinese patients age 60-80 years with hypertension randomized to:
  - Standard: SBP 130-149 mm Hg
  - Intensive: SBP 110-129 mm Hg
- Key Study Exclusions:
  - ischemic or hemorrhagic stroke
- Primary outcome: acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or CV death




Zhang W, et al. *N Engl J Med*. 2021;385:1268-1279.

# 2017 ACC/AHA Hypertension Guideline




Whelton PK, et al. *J Am Coll Cardiol*. 2018;71:e127-e248.

# 2017 ACC/AHA: Lifestyle Changes

| COR | LOE | Nonpharmacological Interventions |
|---|---|---|
| I | A | Weight loss in adults who are overweight or obese |
| | | Healthy diet (e.g., DASH) that facilitates achieving desirable weight |
| | | Sodium reduction |
| | | Potassium supplementation (preferably diet) unless contraindicated |
| | | Increased physical activity with a structured exercise program |
| | | Drink no more than 2 (men) or 1 (women) standard drinks/day |

DASH = Dietary Approaches to Stop Hypertension



Whelton PK, et al. *J Am Coll Cardiol*. 2018;71:e127-e248.

# 2017 ACC/AHA Hypertension Guideline

| COR | LOE | Initial Medication |
|---|---|---|
| I | A | First-line: thiazide diuretic, calcium channel blocker (CCB), and angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) |

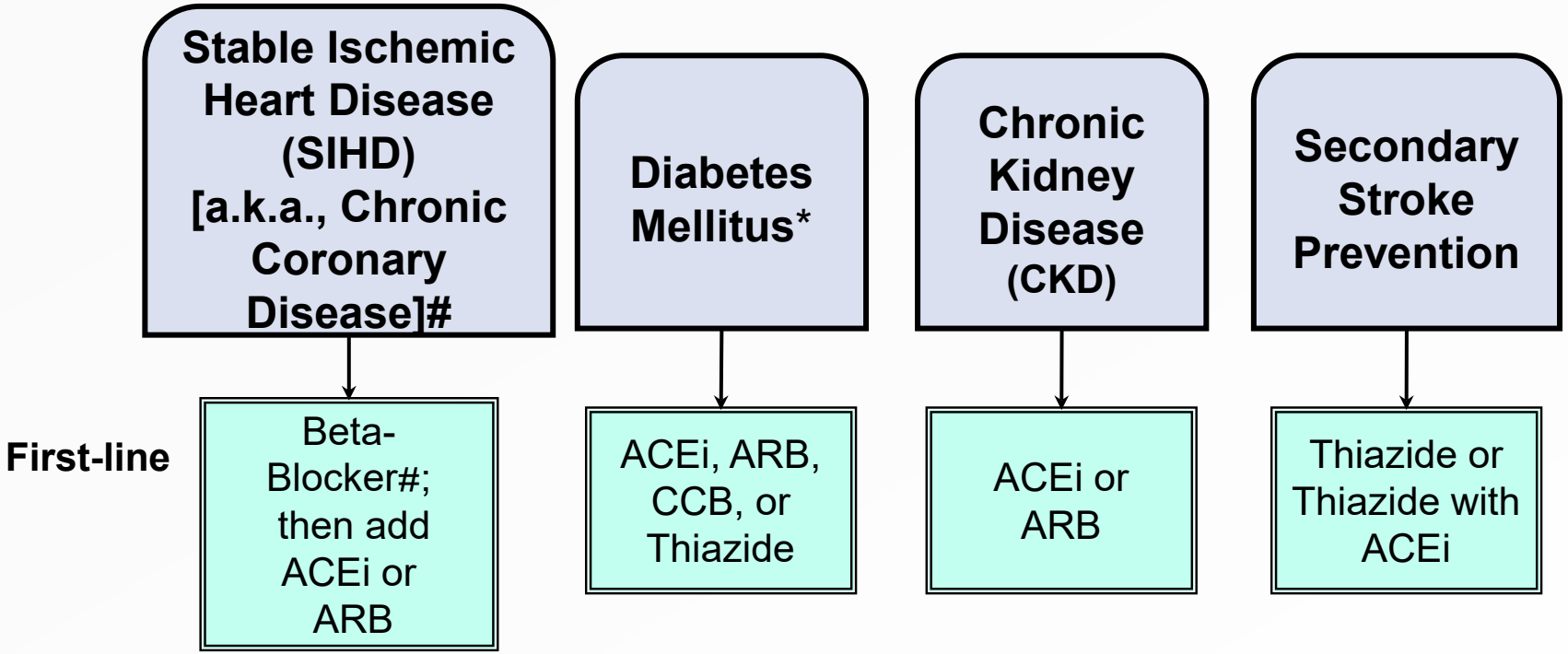
| COR | LOE | Initial Monotherapy Versus Combination Therapy |
|---|---|---|
| I | C-EO | 2 first-line agents of different classes in stage 2 hypertension and BP > 20/10 mm Hg above goal |

| COR | LOE | Race and Ethnicity |
|---|---|---|
| I | B-R | Black patients without HF or CKD (with or without diabetes), initial treatment should include a thiazide diuretic or CCB |
| I | C-LD | 2+ medications are recommended to achieve a BP <130/80 mm Hg in most adults, especially in black patients |



Whelton PK, et al. *J Am Coll Cardiol*. 2018;71:e127-e248.

# 2017 ACC/AHA Hypertension Guideline: Compelling Indications




# in SIHD proven beta-blockers are: carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol

* if albuminuria present in diabetes, treat like CKD and use an ACEi or ARB titrated to the maximum tolerated dose

Whelton PK, et al. *J Am Coll Cardiol*. 2018;71:e127-e248.
el Sayed NA, et al. *Diabetes Care* 2023;46(Supplement_1):S158–S190.

# 2017 ACC/AHA Hypertension Guideline

| COR | LOE | Follow-Up After Initiating Drug Therapy |
|---|---|---|
| I | B-R | Evaluation of adherence and response to treatment at monthly intervals until control is achieved |

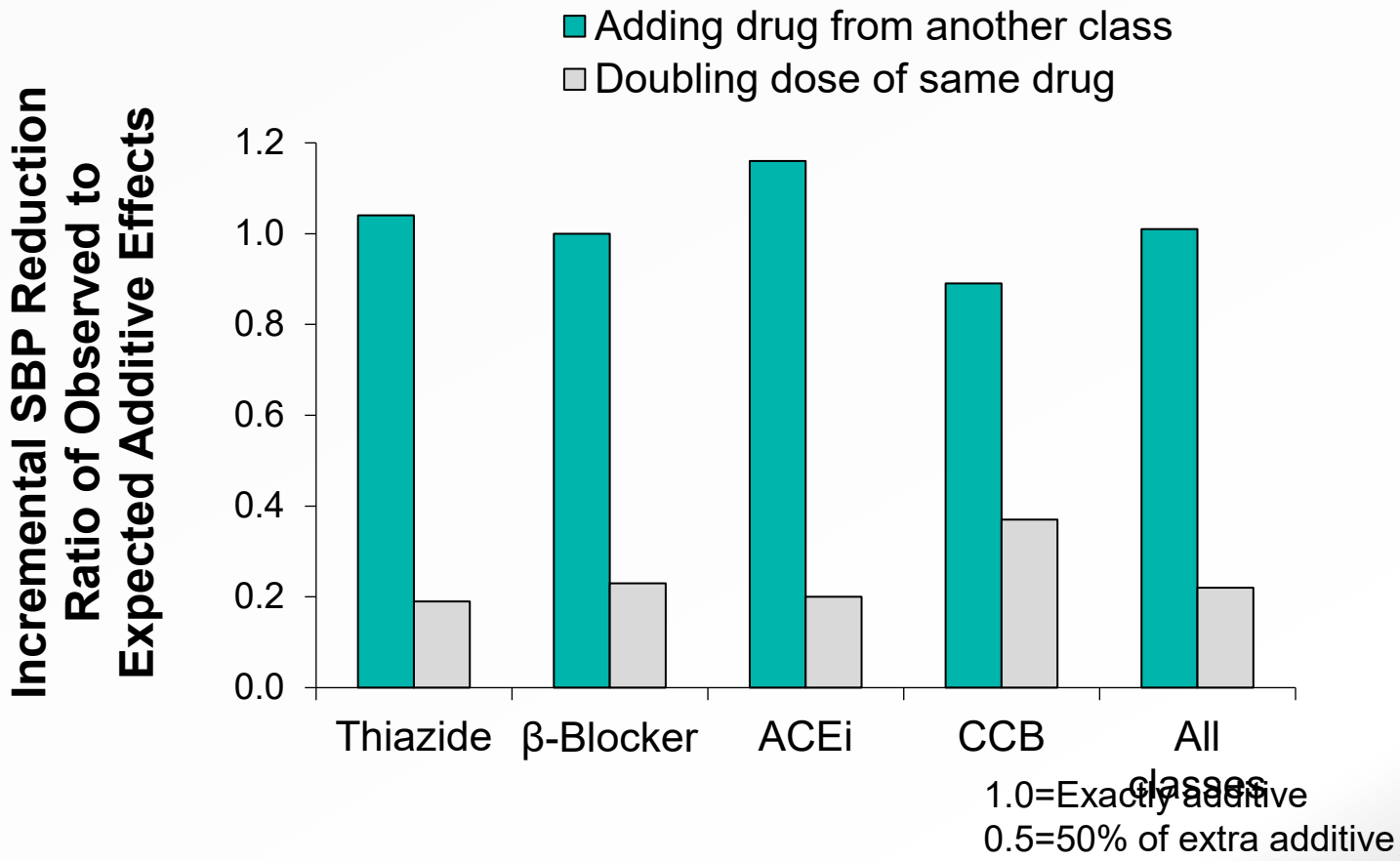
| COR | LOE | Monitoring Strategies to Improve Control of BP |
|---|---|---|
| I | A | Follow-up and monitoring should include systematic strategies including home BP monitoring, team-based care, and telehealth strategies |



Whelton PK, et al. *J Am Coll Cardiol*. 2018;71:e127-e248.

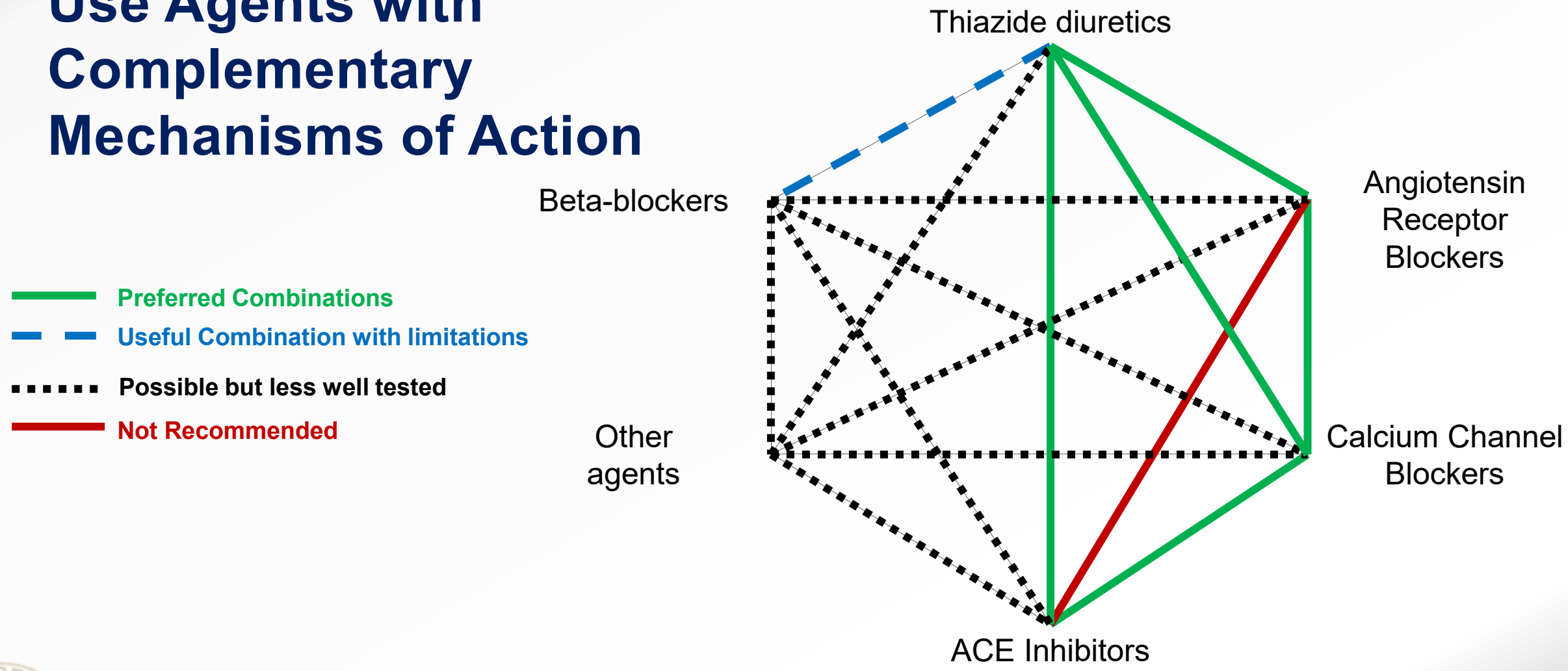
# Efficacy of Combination vs Monotherapy

- Meta analysis of 42 hypertension clinical trials (n=10,968)
- Patients were randomly allocated
  - one drug alone
  - another drug alone
  - both drugs together
  - placebo




Wald DS, et al. *Am J Med* 2009;122:290-300.

# Use Agents with Complementary Mechanisms of Action




Mancia G, et al. *J Hypertens* 2013;31:1281-357.

# Common Fixed-Dose Combinations

| Combination | Common Medications |
|---|---|
| ACEi + CCB | Amlodipine/benazepril |
| ARB + CCB | Amlodipine/olmesartan<br>Valsartan/amlodipine |
| ACEi + thiazide | Benazepril/HCTZ<br>Lisinopril/HCTZ |
| ARB + thiazide | Losartan/HCTZ<br>Olmesartan/HCTZ<br>Irbesartan/HCTZ<br>Valsartan/HCTZ |

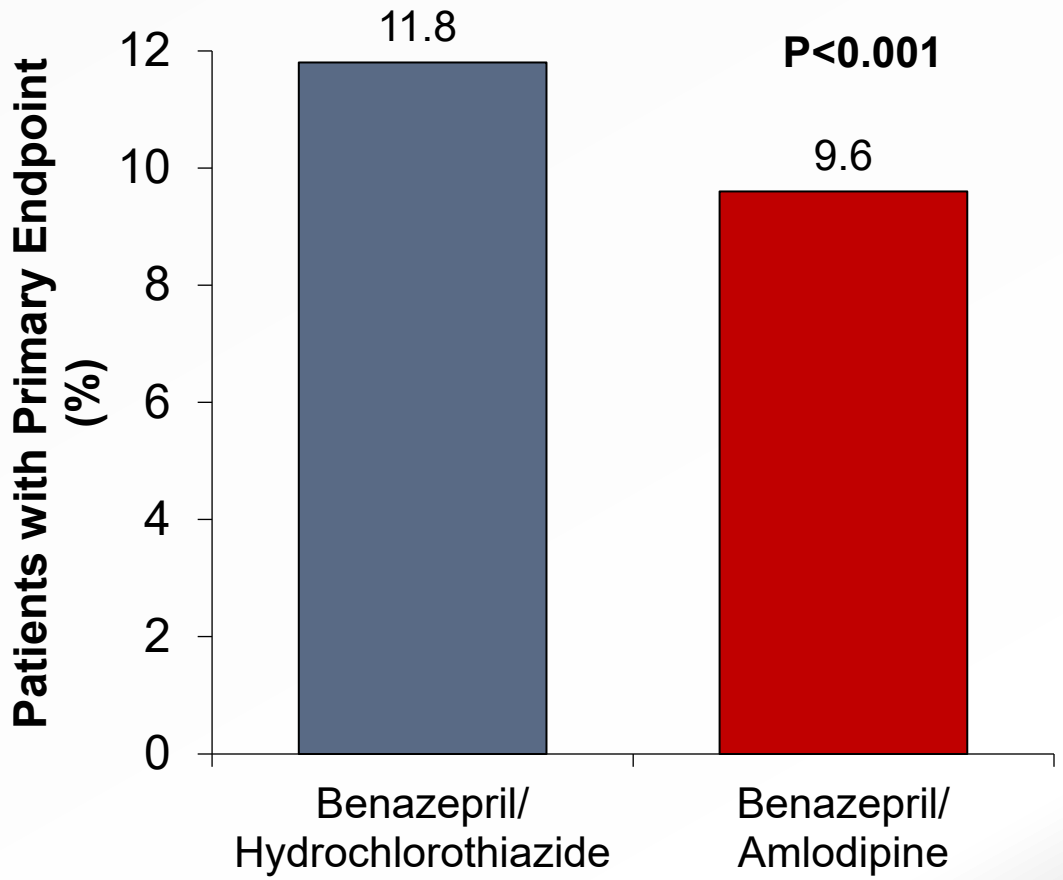
| Combination | Common Medications* |
|---|---|
| β-blocker + thiazide | Metoprolol/HCTZ |
| MRA + thiazide | Spironolactone/HCTZ |
| ARB + CCB + thiazide | Amlodipine/valsartan/HCTZ<br>Olmesartan/amlodipine/HCTZ |

ACEi, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; CCB, Calcium channel blocker; HCTZ, hydrochlorothiazide; MRA, mineralocorticoid receptor antagonist

Whelton PK, et al. *Hypertension*. 2018;71:1269-1324.

# ACCOMPLISH Trial

- Randomized, double-blind, controlled trial*
  - Benazepril/HCTZ vs. Benazepril/Amlodipine
  - Dosages titrated, as tolerated, to benazepril 40 mg/day, HCTZ 25 mg/day, amlodipine 10 mg/day
- 11,506 patients with hypertension and:
  - Age ≥ 60 yr (55-59 yr if multiple CV risk factors)
  - SBP ≥ 160 mm Hg
- Primary endpoint:
  - CV death, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization




Jamerson K, et al. *N Engl J Med.* 2008; 359:2417-28.

# Adverse Effects of Antihypertensive Agents

| | |
|---|---|
| ACEi/ARB | ✓ "Dry" cough, angioedemia (rare) – ACEi only<br>✓ Hyperkalemia, potential renal failure in those with bilateral renal-artery stenosis |
| CCB | ✓ Headache, peripheral edema, tachycardia or bradycardia, might worsen GERD<br>✓ Drug-drug interactions (mostly verapamil or diltiazem) |
| Thiazide | ✓ Hypokalemia, hyponatremia, hypomagnesemia, dehydration, exacerbation of gout |
| Beta-blocker | ✓ Exercise intolerance, fatigue, erectile dysfunction, bradycardia, broncoconstriction (non-selective agents) |
| MRA | ✓ Hyperkalemia, gynecomastia (spironolactone) |

# Should BP Goals be Even Lower in CKD?

Meta-analysis of 18 randomized controlled trials including patients with CKD (n=18,924)

- More intensive vs less intensive BP control resulted in 14.0% lower risk of all-cause mortality (P = 0.01)

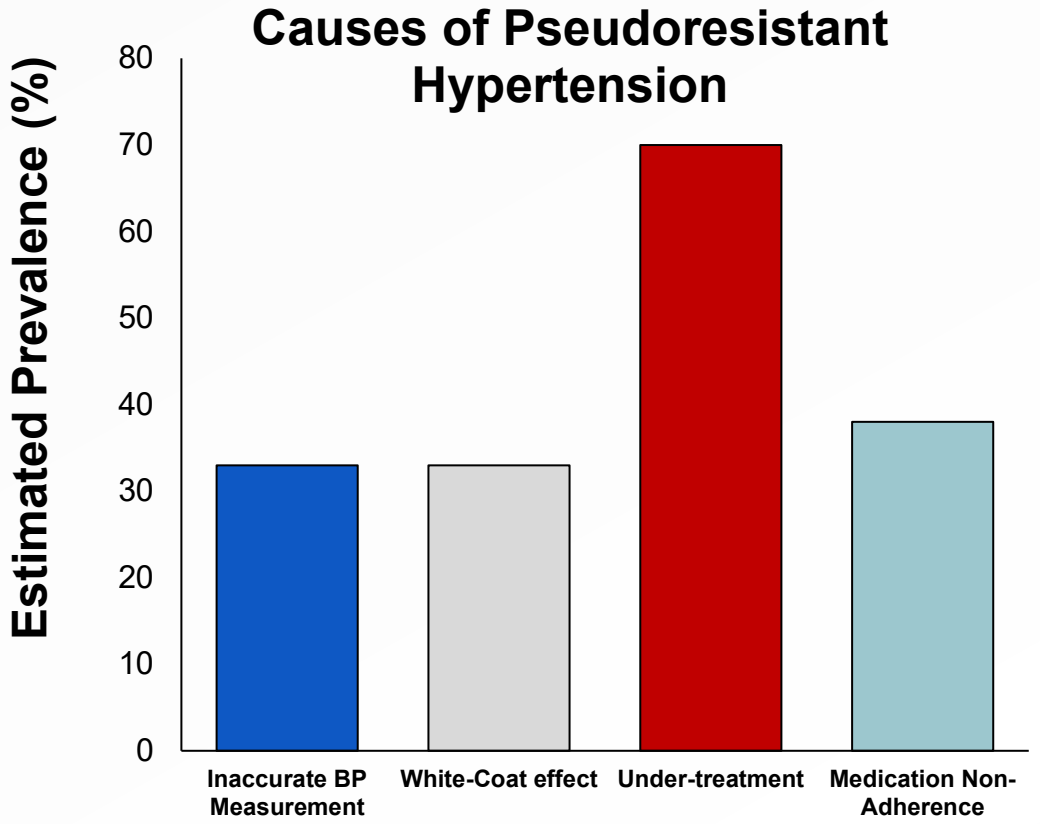
KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease

- Suggest that adults with high BP and CKD be treated with a target systolic blood pressure of <120 mm Hg, when tolerated, using standardized office BP measurement

Malhotra R, et al. *JAMA Intern Med*. 2017;177(10):1498-150.
Kidney Disease Improving Global Outcomes. Kidney International (2021) 99, S1–S87.

# AHA Scientific Statement: Resistant Hypertension (rHTN)

- Definition:
  - Not at BP goal despite concurrent use of 3 antihypertensive drugs commonly including a long-acting CCB, ACEi or ARB, diuretic
    - Maximum/maximally tolerated doses
  - At BP goal with ≥4 antihypertensive medications




Carey RM, et al. *Hypertension*. 2018;72:e53-e90.

# rHTN Secondary Causes

## Common Medications

- NSAIDs
- Oral contraceptives
- Sympathomimetics
- Amphetamines
- Antidepressants
- Glucocorticoids, mineralocorticoids

## Others

- Alcohol
- Cocaine
- Cyclosporine, tacrolimus
- Erythropoietin
- Vascular endothelial growth factor inhibitors

## Diseases

- Primary Aldosteronism
- Renal Parenchymal Disease
- Renal Artery Stenosis
- Pheochromocytoma/ Paraganglioma
- Cushing Syndrome
- Coarctation of the Aorta
- Others

Carey RM, et al. *Hypertension*. 2018;72:e53-e90.

# rHTN Management

**STEP 1:** 1) Exclude other causes, 2) Ensure low sodium diet, maximize lifestyle intervention, 3) Optimize 3-drug regimen

↓

**STEP 2:** Substitute optimally dosed thiazide-like diuretic (e.g., chlorthalidone) for the prior diuretic

↓

**STEP 3:** Add a mineralocorticoid receptor antagonist (spironolactone or eplerenone) [caution if eGFR < 30 mL/min/1.73m$^2$]

↓

**STEP 4:** Add a beta-blocker or an alpha/beta-blocker if heart rate is ≥ 70 beats/min
- If contraindicated consider centrally acting alpha-agonist
- If not tolerated consider once-daily diltiazem

↓

**STEP 5:** Add hydralazine 25 mg three times daily and titrate up*

↓

**STEP 6:** Switch hydralazine to minoxidil 2.5 mg two to three times daily and titrate up**

Based on Expert Opinion, steps should be individualized

*Requires concomitant use of a β-blocker and diuretic
**Requires concomitant use of a β-blocker and loop diuretic

Carey RM, et al. *Hypertension*. 2018;72:e53-e90.

# A Tale of Two Thiazides

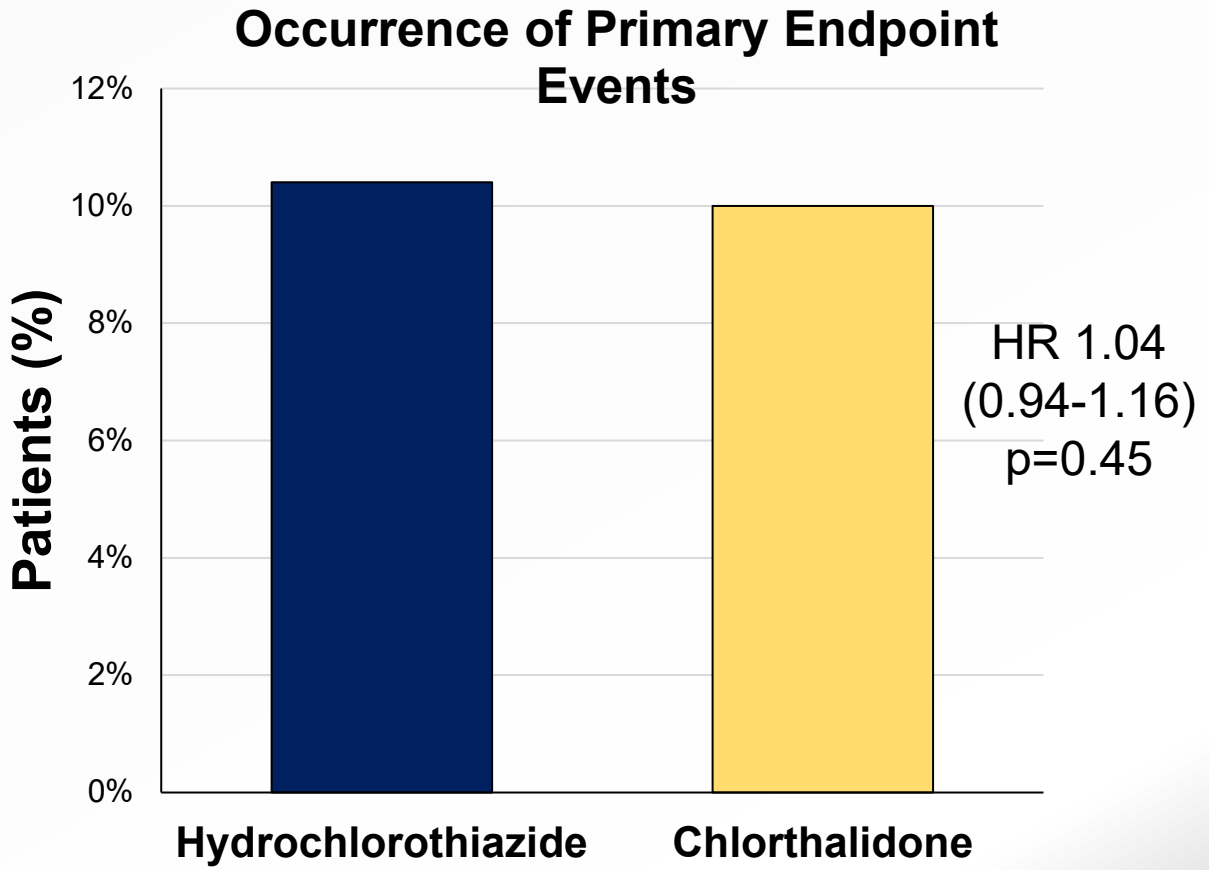
| | Hydrochlorothiazide (HCTZ) | Chlorthalidone (CTD) |
|---|---|---|
| Category | Thiazide-type | Thiazide-like |
| Half-life | 9-10 hours | 50-60 hours |
| Equivalent doses | 25 mg | 12.5-18.75 mg |
| Utilization | Frequently prescribed, many fixed-dose combinations | Preferred in resistant hypertension |
| Landmark Trials | Rarely used | Extensively used |

- Cohort trial in 730,225 patients prescribed HCTZ or CTD:
  - No difference MI, hospitalized heart failure, or stroke
    - HR 1.00 (95% CI, 0.85-1.17)
  - CTD associated with higher risks of hypokalemia, hyponatremia, acute renal failure, CKD, and new onset type 2 diabetes
  - CTD associated with a lower risk of abnormal weight gain

Hripcsak G, et al. *JAMA Intern Med*. 2020;180(4):542-551.

# Diuretic Comparison Project (DCP)

- 13,523 VA patients ≥65 years (mean 72 yr) randomized in open-label, pragmatic trial to HCTZ or chlorthalidone 1:1
- At baseline:
  - 94.5% on HCTZ 25 mg/day
  - Mean SBP 139 mm Hg
- After a median follow-up 2.4 years:
  - BP remained similar between groups
  - Hypokalemia higher with chlorthalidone vs. HCTZ (6.0% vs. 4.4%)




Ishani A, et al. *N Engl J Med*. 2022;387:2401-10.

# PATHWAY-2 Trial

- Double-blind, randomized, crossover trial (n=335) in patients with rHTN for 12 wks

| Treatment Arm | SBP Decrease from Baseline in mm Hg (95% CI) |
|---|---|
| Spironolactone (25-50 mg) | 12.8 |
| Doxazosin (4-8 mg) | 8.7 |
| Bisoprolol (5-10 mg) | 8.3 |
| Placebo | 4.1 |

- Hyperkalemia occurred in 6 of 285 patients receiving spironolactone (serum potassium > 6.0 mmol/L)



Williams B, et al *Lancet* 2015;386:2059–2068.

# Alternative Antihypertensive Agents

| Class (Drugs) | Comments |
|---|---|
| Alpha-1 Blockers<br>(Doxazosin, Prazosin, Terazosin) | • Potential orthostatic hypotension |
| Central Alpha-2 Agonists<br>(Clonidine [transdermal], Methyldopa) | • Rebound hypertension with abrupt discontinuation; anticholinergic side effects<br>• Use with a diuretic to diminish fluid retention<br>• Per AHA Scientific Statement"<br>***"Clonidine tablets should be avoided because of the need for frequent administration and the risk of rebound hypertension ..."*** |
| Arterial Vasodilators<br>(Hydralazine, Minoxidil) | • Use with diuretic to diminish fluid retention, with beta-blocker to diminish tachycardia<br>• Especially effective in kidney failure |



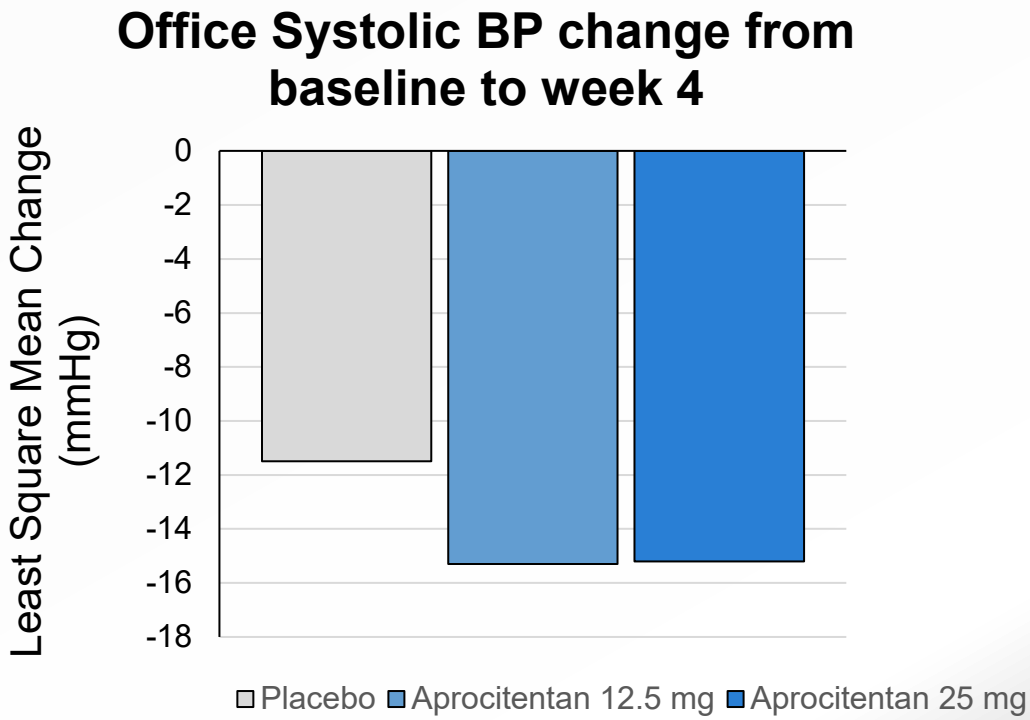
Carey RM, et al. *Hypertension*. 2018;72:e53-e90.

# Aprocitentan: Approved March 2024

**An endothelin receptor antagonist indicated for hypertension treatment in combination with other antihypertensive drugs**

- Dose: 12.5 mg orally once daily
- Contraindications:
  - Pregnancy, hypersensitivity
- Warnings/Precautions/Adverse Reactions:
  - Hepatotoxicity/liver failure (liver function testing at baseline and periodically)
  - Edema/fluid retention
  - Decreased hemoglobin and sperm counts

**PRECISION Trial: 730 patients with uncontrolled hypertension on 3 antihypertensives (including a diuretic)**

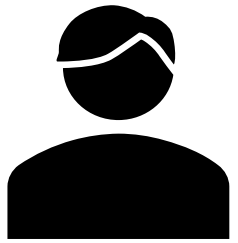



Tryvio package insert. Idorsia Pharmaceuticals US INC, Radnor, PA. 2024.

Schlaich MP, et al. Lancet. 2022;400:1927-1937.

# Revisitng John Doe…

- 47-year-old black man with a history of hypertension, dyslipidemia, chronic kidney disease (G3A2), and “pre-diabetes”
- Family history: father died of an MI at age 50
- Social history: former smoker, lives in a very disadvantaged Denver neighborhood
- Does not follow a specific diet, drinks 2-3 alcoholic beverages/day, does not exercise
- Insurance: Medicaid
- Medications: HCTZ 25 mg po daily, atorvastatin 10 mg po daily
- BP 142/88 mm Hg (similar values at home), HR 80 beats/min, BMI 29.7 kg/m2
- Fasting Labs:
  - TC 220 mg/dL, HDL 30 mg/dL, LDL 144 mg/dL, TG 300 mg/dL
  - A1C 6.3%, Scr 1.6 mg/dL (eGFR 53 mL/min/1.73m2),UACR 64 mg/g
- Coronary Artery Calcium: 287 AU in left anterior descending artery



# Take Home Points

- ACEi, ARB, CCB and thiazide agents are recommended for most patient to management hypertension
  - Beta-blockers are still useful for patients with chronic coronary disease and/or resistant hypertension
- Strong evidence supports an overall BP goal of <130/80 mm Hg
  - Monitoring, including home BP measurement is recommended to achieve therapeutic objective and to ensure safety
- Many patient require combination therapy and those with resistant hypertension should have secondary causes ruled-out, and consider the use of a mineralocorticoid receptor antagonist as appropriate