Helping Patients Achieve Hypertension Goals

A Practical Guide to Combination Therapy for Hypertension Management
Session 5: Helping Patients Achieve Hypertension Goals—A Practical Guide to Combination Therapy for Hypertension Management

Learning Objectives

- Select dosages of appropriate antihypertensive agents in order to achieve target blood pressure levels recommended in national guidelines for patients with and without comorbid conditions (such as chronic kidney disease or diabetes mellitus).
- Recognize appropriate antihypertensive strategies to achieve target BP levels, including lifestyle modification, monotherapy, and combination therapies in order to reduce the morbidity and mortality associated with untreated/inadequately treated hypertension.

Faculty

Joseph Saseen, PharmD, FCCP, BCPS
Associate Professor, Clinical Pharmacy and Family Medicine
Schools of Pharmacy and Medicine
University of Colorado
Denver, Colorado

Dr Saseen is an associate professor of clinical pharmacy and family medicine at the University of Colorado Denver Health and Sciences Center (UCDHSC). He is a board-certified pharmacotherapy specialist with added qualifications in cardiology. Dr Saseen is also a certified clinical lipid specialist and a Fellow of the American College of Clinical Pharmacy. He received both his bachelor of science and doctorate of pharmacy degrees from the State University of New York at Buffalo and then completed an ambulatory care research fellowship at the University of Illinois. In his current position, Dr Saseen practices as a clinical pharmacy specialist at University of Colorado’s Family Medicine Center, while educating pharmacy and medical students. His research and other scholarly endeavors focus on cardiovascular pharmacotherapy. Dr Saseen serves on the board of regents for the American College of Clinical Pharmacy, is a member of the board of directors for the National Lipid Association’s Accreditation Council for Clinical Lipidology, and serves on the board of directors and the editorial board for the journal Pharmacotherapy. He is the recipient of several teaching awards at UCDHSC, including the President’s Excellence in Teaching Award in May 2006.

Robert L. Talbert, PharmD, FCCP
Professor, College of Pharmacy
University of Texas-Austin
Professor, Department of Medicine
University of Texas Health Science Center
San Antonio, Texas

Robert L. Talbert, PharmD, FCCP, BCPS, received his doctor of pharmacy and bachelor of science degrees from the University of Kentucky in Lexington. Dr Talbert is the SmithKline Professor of Pharmacy in the Division of Pharmacotherapy at The College of Pharmacy, University of Texas at Austin. He is also professor of medicine at The University of Texas Health Science Center at San Antonio. He has published more than 120 journal articles, books, book chapters, abstracts, and letters. He is one of the editors of Pharmacotherapy: A Pathophysiologic Approach, now in its 7th edition. Dr Talbert is a reviewer for many journals, including Diabetes Care, American Journal of Hospital Pharmacy, American Journal of Managed Care, and Pharmacotherapy.

Dr Talbert is a Fellow of the American College of Clinical Pharmacy. He is a member of the American Society of Health-System Pharmacists, American Association of Colleges of Pharmacy, American Heart Association, American Pharmaceutical Association, Heart Failure Society of American and National Lipid Association, among others. Dr Talbert was named Preceptor of the Year (2005) by The University of Texas College of Pharmacy and received the Sustained Contributions to the Literature Award from the American Society of Health-System Pharmacists in 2005. In October 2007 he received the Russell Miller Award from the American College of Clinical Pharmacy for his contributions to biomedical literature.

Faculty Financial Disclosure Statements

The presenting faculty reported the following:
Dr Joseph Saseen receives honoraria from Daiichi-Sankyo/Forest Pharmaceuticals, Inc.
Dr Robert Talbert has no relationships to disclose.
**Education Partner Financial Disclosure Statement**

The content collaborators at Consensus Medical Communications have reported the following:

Victoria Smith, MD, has nothing to disclose.

### Drug List

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<th>Trade</th>
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<td>metformin</td>
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<td>methyldopa/HCTZ</td>
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<td>metoprolol tartarate/HCTZ</td>
<td>Aldomet</td>
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<td>Thalitone</td>
<td>valsartan</td>
<td>Altace, various</td>
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<td>hydrochlorothiazide (HCTZ)</td>
<td>Esidrix, Microzide, Oretic</td>
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<td>Micardis HCT</td>
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<td>Dyazide, Maxzide</td>
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<td>lisinopril/HCTZ</td>
<td>Prinzide, Zestoretic</td>
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<td>Hyzaar</td>
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### Investigational

<table>
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<tbody>
<tr>
<td>nitrendipine</td>
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</tr>
</tbody>
</table>

### Suggested Reading List


Joseph Saseen, PharmD, FCCP, BCPS

- Associate Professor, Clinical Pharmacy and Family Medicine
  Schools of Pharmacy and Medicine
  University of Colorado
  Denver, Colorado

Robert L. Talbert, PharmD, FCCP

- Professor, College of Pharmacy
  University of Texas-Austin
- Professor, Department of Medicine
  University of Texas Health Science Center
  San Antonio, Texas

HTN Introduction

- 1 in 3 adults in the United States has HTN
- Over 73 million people in the United States have HTN; worldwide, the count is over 1 billion
- Prevalence of HTN is increasing
- HTN is the most common diagnosis for primary care office visits
- Uncontrolled HTN is a major risk factor for cardiovascular disease, morbidity, and mortality
- Only 30%-45% of pts treated for HTN are adequately controlled
- Clinicians are not following clinical guidelines or meeting treatment goals

Presentation Outline

- Presentation 1: HTN Clinical Guidelines and Risk Reduction
- Presentation 2: Suboptimal Treatment and Clinical Inertia
- Presentation 3: Combination Therapies for HTN
- Clinical Cases: Selected by Audience
- Q&A

Presentation 1: HTN Clinical Guidelines and Risk Reduction
Risk Reduction: An Overview

- Uncontrolled HTN increases morbidity and mortality from:
  - Cardiovascular (CV) disease (heart attack, heart failure)
  - Cerebrovascular disease (stroke, TIA)
  - End-organ damage:
    - Renal (renal failure, ESRD)
    - Cardiac (LVH)
    - Retinal (hypertensive retinopathy)
    - Peripheral arterial disease (atherosclerosis)

Cardiovascular Mortality Risk Doubles With Each 20/10 mmHg Blood Pressure Increment*

SBP= systolic blood pressure; DBP= diastolic blood pressure

Meta-analysis of 61 prospective, observational studies*  
1 million adults  
12.7 million person-years

2 mmHg decrease in mean SBP

7% reduction in risk of ischemic heart disease
10% reduction in risk of stroke mortality

Failure to Deliver Recommended Care Lives & Costs That Could Be Saved Annually

<table>
<thead>
<tr>
<th>Measure</th>
<th>Avoidable Deaths/Year*</th>
<th>Avoidable Costs/Year*</th>
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<tbody>
<tr>
<td>Controlling high BP</td>
<td>28,300</td>
<td>$1,242,836,580</td>
</tr>
<tr>
<td>Diabetes care/ATC control</td>
<td>13,600</td>
<td>$178,464,900</td>
</tr>
<tr>
<td>Cholesterol management</td>
<td>6500</td>
<td>$94,249,482</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>2700</td>
<td>$97,690,642</td>
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</table>

*United States Population  

HOT Study: Primary Objectives

- Establish which of the 3 levels of target DBP produces the greatest reduction in CV morbidity and mortality
- Investigate the relationship between achieved BP and the risk of CV morbidity and mortality

BP Control Reduces CV Events: HOT Trial

Diabetes Subgroup

<table>
<thead>
<tr>
<th>Goal of therapy: target diastolic BP</th>
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<tbody>
<tr>
<td>d00 mmHg (n=601)</td>
</tr>
<tr>
<td>d01 mmHg (n=601)</td>
</tr>
<tr>
<td>d09 mmHg (n=499)</td>
</tr>
</tbody>
</table>

*Epidemiologic studies, not clinical trials of hypertension agents.  
HOT Study: Risk of a Major CV Event

Optimal DBP reduction

Achieved DBP (mmHg)

-30
-25
-20
-15
-10
-5
0
10

% Risk Reduction


Summary of Key JNC 7 Guidelines

- In persons >50 years old, systolic BP >140 mmHg is a more important cardiovascular disease (CVD) risk factor than diastolic BP
- Thiazide-type diuretics should be used in drug treatment, either alone or combined with drugs from other classes, for most pts with uncomplicated HTN
- Certain high-risk conditions are compelling indications for initial use of other antihypertensive drug classes (ACEI, ARB, CCB)
- Most pts with HTN will require 2 or more antihypertensive medications to achieve BP goal (<140/90 in uncomplicated HTN or <110/80 in DM or chronic renal disease)
- If BP is more than 20/10 mmHg above goal, consider initiating therapy with 2 agents, 1 of which should be a thiazide-type diuretic

JNC 7: BP Classifications

<table>
<thead>
<tr>
<th>BP Level (mmHg)*</th>
<th>Category</th>
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<tbody>
<tr>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>&lt;120</td>
<td>and &lt;80</td>
</tr>
<tr>
<td>120-139</td>
<td>or 80-89</td>
</tr>
<tr>
<td>140-159</td>
<td>or 90-99</td>
</tr>
<tr>
<td>≥160</td>
<td>or ≥100</td>
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</table>

*Use higher value for classification


Impact of High-Normal BP on CV Risk

Optimal BP: <120/80 mmHg; normal BP: 120-129/80-84 mmHg; high-normal BP: 130-139/85-89 mmHg


Prehypertension

- JNC 7 added prehypertension to guidelines: 120-139 SBP or 80-89 DBP
- Increased risk of CVD, MI, HF, and cardiovascular death
- Increased risk of LVH and reduced diastolic function
- Increased risk ratios for obesity, microalbuminuria, dyslipidemia, insulin resistance, metabolic syndrome, and diabetes compared with normotensive people


JNC 7 Summary: Clinical Trials and Guideline Basis for Compelling Indications for Individual Drug Classes

<table>
<thead>
<tr>
<th>Compelling Indication</th>
<th>Diuretic</th>
<th>BB</th>
<th>ACEI</th>
<th>ARB</th>
<th>CCB</th>
<th>AβD</th>
<th>Clinical Trial Basis</th>
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<tr>
<td>Heart failure</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>ACC/AHA Heart Failure Guidelines, MERIT-HF, CIBIS, COPERNICUS, SOLVD, ARB, TRACER, TRACE, CHARM</td>
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<tr>
<td>Post-myocardial infarction</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>ACC/AHA Post-MI Guidelines, BHAT, SAVE, Capricorn, EPHESUS</td>
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<tr>
<td>High coronary disease risk</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>ALLHAT, HOPE, ANBP2, LIFE, COUTANCE, EUROPA, INVEST</td>
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<tr>
<td>Diabetes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>PROGRESS</td>
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<tr>
<td>Recurrent stroke prevention</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>PROGRESS</td>
</tr>
</tbody>
</table>

Recommended Drugs

- Compelling Indication
- Diuretic
- BB
- ACEI
- ARB
- CCB
- AβD

Clinical Trial Basis

- Heart failure: ACC/AHA Heart Failure Guidelines, MERIT-HF, CIBIS, COPERNICUS, SOLVD, ARB, TRACER, TRACE, CHARM
- Post-myocardial infarction: ACC/AHA Post-MI Guidelines, BHAT, SAVE, Capricorn, EPHESUS
- High coronary disease risk: ALLHAT, HOPE, ANBP2, LIFE, COUTANCE, EUROPA, INVEST
- Diabetes: PROGRESS
- Recurrent stroke prevention: PROGRESS

Framingham Risk Score

- Considers 5 factors:
  1. Age
  2. Total cholesterol by age
  3. Smoking status by age
  4. HDL
  5. Systolic BP (treated or untreated)
- Assigns points based on gender → converted to a % probability for coronary heart disease

Case Study: 55-Year-Old White Male at Initial Visit

- Presents for annual physical exam
- No physical complaints
- Personal history
  - Non-smoker
  - Does not consume alcohol
  - No physical activity
- Family history
  - Positive for cardiac disease
- Medical history
  - None significant
- Allergies: none
- Medications: none
Case Study: 55-Year-Old White Male at Initial Visit

- **Physical examination**
  - BP: 146/102 mmHg sitting
  - Resting pulse: 70 bpm
  - BMI: 35.5 kg/m²
  - Last BP 3 years ago: 136/90 mmHg
- **EKG:** NS ST-T changes
- **Laboratory results:**
  - T-Chol 212; TG 150; LDL 156; HDL 26; FBS 110
  - Framingham Risk score = 16%

What Would Be Your Next Course of Action?

1. Start patient on antihypertensive agent now
2. Schedule follow-up visit within 1 month for BP re-assessment
3. Arrange for ambulatory BP monitoring
4. Obtain information on patient’s stress level, diet, and lifestyle
5. Order treadmill stress test

Case Study: 55-Year-Old White Male at Follow-up Visit #1

- The patient returns to your office, as requested, for 2 more BP readings within 1 month
- Average of 3 BP readings: 144/103 mmHg seated
- **Diagnosis:** Stage 2 hypertension

What Is Your Target BP Goal for the Patient?

1. <120/80 mmHg
2. <130/80 mmHg
3. <140/90 mmHg

Managing Prehypertension

- JNC-recommended approach to pre-HTN is lifestyle modification to achieve BP goal, UNLESS pts have DM or chronic kidney disease (CKD); these pts need drug therapy as well
- Drug therapy in pre-HTN pts without DM or CKD is controversial due to short-term costs and unproven long-term benefits

Lifestyle Modifications

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approx. Systolic BP Reduction, Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight (BMI, 18.5-24.9)</td>
<td>5-20 mm Hg/10-kg weight loss</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>Reduce dietary sodium intake to no more than 100 mEq/L (2.4 g sodium or 6 g sodium chloride)</td>
<td>2-3 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Engage in regular aerobic physical activity, such as brisk walking (at least 30 minutes per day, most days of the week)</td>
<td>4-6 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>Limit consumption to no more than 2 drinks per day (1 oz or 30 mL ethanol [e.g., 12 oz beer, 1 oz wine, or 3 oz 80-proof whiskey]) in most men and no more than 1 drink per day in women and lighter-weight persons</td>
<td>2-4 mmHg</td>
</tr>
</tbody>
</table>
**Trial of Preventing Hypertension (TROPHY) Study**

**Objectives:**
- Determine if pharmacologic treatment with an ARB in subjects with prehypertension will:
  - Suppress clinical hypertension during the active treatment
  - Delay the onset of clinical hypertension after discontinuation of the active treatment


<table>
<thead>
<tr>
<th>Cumulative Incidence (%)</th>
<th>RR 16%</th>
<th>HR=0.84 (0.75–0.95)</th>
<th>P=0.007</th>
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<tbody>
<tr>
<td>RR 66%</td>
<td>HR=0.34 (0.25–0.44)</td>
<td>P&lt;0.001</td>
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</table>

<table>
<thead>
<tr>
<th>Number of patients without HTN</th>
<th>Candesartan</th>
<th>Placebo</th>
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<tr>
<td>391</td>
<td>305</td>
<td>100</td>
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<tr>
<td>381</td>
<td>269</td>
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<td>356</td>
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<td>269</td>
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<td>184</td>
<td>191</td>
<td>20</td>
</tr>
<tr>
<td>110</td>
<td>113</td>
<td>0</td>
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</table>

**What Agent(s) Would You Select for the Patient?**

1. Thiazide diuretic
2. ACE inhibitor
3. Angiotensin receptor blocker
4. ACE-diuretic fixed-dose combination
5. ACE-I/CBB fixed-dose combination
6. Angiotensin receptor blocker/diuretic fixed-dose combination
7. Other


**Aggressive BP Treatment: How Low to Go?**

- Treatment to <140/90 mmHg in pts with HTN is beneficial
- Some studies suggest that being too aggressive in BP reduction may be harmful:
  - SHEP trial: increased risk of lowering diastolic BP in elderly patients with hypertension
  - Messerli data: pts with CAD and BP treated to <119/84 mmHg showed progressive increased risk for all-cause death and MI (not stroke) with lower DBP

NHANES=National Health and Nutrition Examination Survey

NHANES III: Poor Systolic BP Control Underlies Inadequate BP Control Overall

Unacceptable BP Control Rates Require Increased Awareness, More Aggressive Treatment

Presentation 2: Suboptimal Treatment and Clinical Inertia

We Are Failing to Achieve BP Control in Our Hypertensive Patients
- 75% of 73 million adults are at risk for complications of HTN due to inadequate treatment
- The majority of pts with HTN are not at goal BP despite treatment. Pt groups who are the most poorly controlled are:
  - Elderly
  - Women
  - Mexican Americans
  - Pts with severe HTN

Why Are We Not Achieving BP Control?
- Patient Behavior
  - Lack of patient access to care
  - Irregular or infrequent primary care office visits
  - Nonadherence with medication or lifestyle modifications
  - Presence of or anticipation of medication side effects
  - Inability of patients to afford medications
- Clinician Behavior: Clinical inertia (CI)

Clinical Inertia Definitions
- Failure of clinicians to:
  - Initiate, intensify, or modify therapeutic measures for medical conditions when indicated
  - Aggressively manage a chronic medical condition sufficiently to control it
- Inaction by clinicians caring for patients with uncontrolled risk factors
- Complacency in treating the very elderly

In Most Patients With HTN, Inadequate BP Control Is Due To:
1. Patient behavior
2. Clinician behavior

55-Year-Old White Male at Follow-up Visit #2
The patient’s BP is now 130/88 with several consistent home BP readings. He is currently on 2 antihypertensive agents. What would be your next step in terms of controlling his BP?
1. Nothing, his BP is controlled
2. Increase the dose of one of his current agents
3. Add a third drug
4. Switch to a different 2-drug combination regimen

We Are Failing to Achieve BP Control in Our Hypertensive Patients

Clinical Inertia Definitions
Hypertension in the Very Elderly Trial (HYVET)

- 3845 patients age ≥80 years with hypertension (SBP ≥160 mmHg)
- Randomized, double-blind, to:
  - placebo or
  - perindopril +/- indapamide
- Trial stopped early after 1.8 years


P = 0.06

**HYVET - Results**


**The Pharmacist’s Role: Caring for Hypertensive Patients**

Collaborative drug therapy management
Ensuring effective therapy
Measure and/or monitor BP
Improve compliance
Increase patient awareness
Patient education
Complete prescription fulfillment

**How Can Pharmacists Assist Physicians With Controlling BP?**

- “Healthy People 2010” initiative:
  - Goal BP in 50% of hypertensive patients
- Evidence demonstrates pharmacists can improve management of hypertension:
  - Community pharmacy intervention programs
  - Academic detailing
  - Disease state management programs:
    - Integrated health systems
    - Physician office practices


**Steps to Successful Management of HTN:**

- Identify patients with:
  - Undiagnosed HTN
  - Elevated BP or uncontrolled HTN
- Initiate therapy per evidence-based guidelines (eg, JNC 7, ADA, WHO-ISH)
- Intensify and modify therapy to achieve treatment goals
- Motivate patient and clinician to adhere to treatment plans and achieve treatment goals

Pharmacist-Managed Hypertension Clinics

- **Objective:** To determine whether care at a pharmacist-managed HTN clinic resulted in better treatment compared with traditional health care
- **Design:** 6-month, prospective, controlled setting (N=56)
- **Outcomes:** Attainment of BP goal
  - 21 pts (81%) in the pharmacist-managed clinic
  - 8 pts (30%) in the control group (P<0.0001)


**Pharmacist-Managed Hypertension Clinics**

- **Objective:** Evaluate the effectiveness of a community pharmacist-based HTN monitoring program. Comparison of high-intensity (HI) vs low-intensity (LI) monitoring programs
- **Design:** Randomized patients to 1 of 2 groups in 12 community pharmacies (n=125)
- **Outcomes:**
  - SBP decreased 13.4 mmHg in the HI group vs 9.0 mmHg in the LI group
  - DBP decreased 3.2 mmHg in the HI group (P=0.03)


**BP Measurement in Clinical Practice**

- **Self Measurements**
- **Office-Based Measurements**
- **Ambulatory Measurements**

- **CV risk stratification**
- **Diagnosis**
- **Hypertension management**

**Self-Measurement Devices: Clinical Implications**

- Improved adherence and BP control
- Accurate documentation may be problematic:
  - Patients might omit or fabricate readings
  - Devices with internal memory are optimal
- Patients must follow correct procedures:
  - Patient preparation same as office measurements
  - Three readings separated by 1 minute; average values

http://www.dableducational.com

**Home BP Monitoring in Uncontrolled Hypertension**

- Patients (n=36) with uncontrolled hypertension
- Randomized to self-BP monitoring or usual care for 6 months
- BP reductions greater with self-BP monitoring:
  - SBP: 17.1 vs 7.0 (P=0.07)
  - DBP: 10.5 vs 3.8 (P=0.02)


**Patient Counseling Tips in Hypertension**
Identifying Secondary Causes

- Prescription/OTC drugs
  - Corticosteroids
  - Estrogens
  - NSAIDs
  - Phenylpropanolamines and analogs
  - Cyclosporine and tacrolimus
  - Erythropoietin
  - Sibutramine
  - Desflurane
  - Certain antidepressants (esp venlafaxine)
  - Clonidine, BB combination

- Street drugs and other "natural products"
  - Cocaine and cocaine withdrawal
  - Ma huang, "herbal ecstasy"
  - Nicotine and withdrawal
  - Anabolic steroids
  - Narcotic withdrawal
  - Methylphenidate
  - Phencyclidine
  - Ergotamine and other ergo-containing herbal preparations
  - St. John’s wort

- Chemical elements and other industrial chemicals
  - Lead
  - Mercury
  - Thallium and other heavy metals
  - Lithium salts, especially LiCl

Do More Antihypertensives Lead to More ADR’s?

- Study
  - 160 pts with uncontrolled primary HTN taking 0-3 medications
  - Pharmacist collaborative clinic vs MD only care

- Results:
  - More drugs/patient used in the pharmacist study group (P=0.003)
  - Increasing the number of drugs/patient did not increase the ADR score
  - Decline in ADR’s paralleled the decline in BP despite the increase in meds/patient

Patient Education About Treatment

- Assess patient’s understanding and acceptance of the diagnosis of hypertension and emphasize:
  - Need to continue treatment
  - Importance of lifestyle modifications
  - Control does not mean cure
  - HTN is an asymptomatic condition
  - Discuss concerns and clarify misunderstandings
  - Come to agreement with the patient on goal BP
  - Ask patient to rate (1 to 10) his or her chance of staying on treatment

Most Patients With HTN Will Require 2 or More Agents to Achieve JNC 7 BP Goals

<table>
<thead>
<tr>
<th>Trial</th>
<th>SBP (mmHg)</th>
<th>Mean No. of Agents</th>
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</thead>
<tbody>
<tr>
<td>AASK</td>
<td>138</td>
<td>2.4</td>
</tr>
<tr>
<td>INVEST</td>
<td>133</td>
<td>2.0</td>
</tr>
<tr>
<td>HOT</td>
<td>138</td>
<td>3.0</td>
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<tr>
<td>ALLHAT</td>
<td>138</td>
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<td>RENAAL</td>
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<td>TOPICS</td>
<td>144</td>
<td>3.7</td>
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</table>

Mean 2.0
Median 2.5 agents
SBP <140

75% of patients required ≥3 agents
Combination Therapy for HTN – Pros and Cons

- **Pros**
  - Improved efficacy, tolerability, adherence
  - Quicker achievement of BP goals
  - Decreased pill burden with fixed-dose products

- **Cons**
  - Limited flexibility and dose titration when fixed-dose combination products are used

Options When Monotherapy Does Not Achieve Goal BP

1. Titrate current monotherapy dose upward
   - Increased risk of side effects
   - Only modest improvement in BP lowering

2. Try another agent as monotherapy
   - Prolonged time to achieve adequate BP control
   - Loss of pt confidence in provider and therapy

3. Combination therapy, including either
   - Individual drug combinations
   - Fixed-dose combination therapy

Combination Regimens

- A diuretic is additive with most other agents
- Thiazide-type diuretics (eg, HCTZ) are preferred for hypertension
- Effective fixed-dose combination products:
  - Diuretic/ACE inhibitor
  - Diuretic/ARB
  - Diuretic/Beta-blocker
  - Calcium channel blocker/ACE inhibitor
- May decrease pill burden and costs

Ideal Combination Regimens

![Combination Therapy Diagram]

Clinical Trials Supporting the Efficacy of Combination Therapy for HTN Treatment

- **ASCOT**: Concluded that a CCB/ACEI regimen reduced mortality and stroke more than a BB/diuretic regimen
- **CO-OPERATE**: Showed a superior effect of ARB/ACEI combination therapy in protecting against renal function deterioration in non-diabetic pts with renal disease
- **ADVANCE**: Showed a significant reduction in CV events with combination ACE/ARB therapy vs placebo in DM patients with HTN
- **ACCOMPLISH**: Comparing ACE/CCB vs ACE/ARB therapy for first-line antihypertensive therapy
- **ONTARGET**: Compared ACE alone, ARB alone with combination ARB and ACEI

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Combination Therapy in Systolic Hypertension (ACCOMPLISH)

- Prospective, double-blind trial in 11,400 patients with hypertension who were randomized to benazepril/amlodipine vs benazepril/HCTZ as first-line antihypertensive therapy
- At 18 months, 76% had controlled BP
- Trial was stopped early because of significant benefits with benazepril/amlodipine:

  **Primary Endpoint:** Hazard Ratio (95% CI)  
  - Fatal and non-fatal CV event 0.80 (0.71-0.90)
Ongoing Telmisartan Alone and in Combination With Ramipril (ONTARGET)

- Prospective, randomized, double-blind trial in 25,620 high-risk patients with HTN:
  - Ramipril
  - Telmisartan
  - Ramipril with telmisartan
- Telmisartan vs ramipril:
  - Cough: 1.1% vs 4.2% (P<0.001)
  - Angioedema: 0.1% vs 0.3% (P<0.01)
- Combination vs ramipril:
  - Hypotension: 4.8% vs 1.7% (P<0.001)
  - Renal dysfunction: 13.5% vs 10.2% (P<0.001)


AHA Scientific Statement: Quotes on Class Effect

- There is also continuing debate over whether there are “class effects” for antihypertensive drugs or whether each drug must be considered individually.
- It is reasonable to assume there are class effects for thiazide-type diuretics, ACE inhibitors, and ARBs, which have a high degree of homogeneity in their mechanisms of action and side effects.
- It is equally clear that there are major differences among drugs within more heterogeneous classes of agents, such as β-blockers or CCBs.


One-Year Discontinuation Rates of Antihypertensive Drugs in Clinical Practice (n=631,579)

A Network Meta-analysis

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>OR for Persistence (95% CI)</th>
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<tbody>
<tr>
<td>ARB</td>
<td>0.43 (0.39–0.49)</td>
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<tr>
<td>ACE inhibitor</td>
<td>0.58 (0.53–0.63)</td>
</tr>
<tr>
<td>CCB</td>
<td>0.69 (0.63–0.76)</td>
</tr>
<tr>
<td>α-blocker</td>
<td>0.78 (0.66–0.93)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>0.79 (0.72–0.88)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Referent</td>
</tr>
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One-Year Discontinuation Rates

Which of the Following Clinical Case Discussions Is of Most Interest to You?

1. Case 1: A 61-year-old Mexican American male with resistant hypertension (HTN)
2. Case 2: A 52-year-old African American male with HTN
3. Case 3: A 69-year-old white female with type 2 diabetes and HTN
4. Case 4: A 76-year-old female with isolated systolic HTN (ISH)

Clinical Case 1: 61-Year-Old Mexican American Male

- Presents for BP check and annoying unproductive cough worse at night (no chest pain or SOB)
- Medical Hx: HTN x 5 yrs, overweight, hypertensive
- Social Hx: poor diet, no exercise, smokes 20 cigarettes a day x 35+ yrs, occasional ETOH use, 4 drinks/week. Works in a fast-food restaurant. Pt has not responded to repeated advice on healthy diet and lifestyle
- Medications: Over the last 6 yrs, pt has had the following medications for HTN:
  - HCTZ alone x 1 yr: BP initially controlled but then became elevated again
  - Metoprolol/HCTZ combination 100/25 mg 1 qd for 2 yrs. BP initially improved but as pt gained weight and continued to smoke, BP became elevated again, so dose was increased to 100/50 mg qd for 6 months
  - Metoprolol/HCTZ 100/50 mg 1 qd combination plus ramipril 5 mg 1 qd was added 6 months ago. BP improved but did not fall below 150/92
  - Atorvastatin 20 mg 1 qd
- Pt has failed to keep follow-up BP appointments until now
- Framingham Risk Score >30%

Clinical Case 1: 61-Year-Old Mexican American Male

- Ht: 5’5”; wt: 185 lbs
- BP 166/99; P: 76; Stats: 98% on room air
- Exam: chest clear to bases bilaterally, no rales or wheeze
- ENT exam: WNL
- Abdominal exam: obese otherwise WNL
- EKG: SR rate 76 bpm. No acute changes compared with EKG of 3 yrs ago
- CXR: WNL no consolidation or acute changes
- Labs: UA WNL, CBC, BUN, CREAT, LFTS, and FBS all WNL
- Lipids: LDL 150; HDL 36; TG 230
Clinical Case 1: What Steps Do You Take to Control This Patient’s HTN?

One or more answers may be correct:

1. Continue thiazide/BB combination and increase dose of ACEI
2. Stop thiazide/BB combination and increase dose of ACEI
3. Continue thiazide/BB combination and stop ACEI
4. Add ARB
5. Add CCB
6. Add alpha blocker

Clinical Case 2: 52-Year-Old African American Male

- Ht: 6’0”; Wt: 220 lbs
- BP 158/93; Pulse 71
  - In the last 8 months, the pt’s last 4 BP readings in the office have all been in the range of 149-162/89-94
- Exam: Lungs clear to bases; heart sounds: NL; abdo: NL
- EKG: SR rate 71 bpm WNL
- Labs: CBC, BUN, CREAT, LFTS, uric acid, FBS all WNL
- FLP: LDL 146; HDL 37; TG 190
- UA: WNL

What Action Do You Take to Improve This Patient’s BP?

1. Ask pt to monitor his own BP at home for 3 months and return with those readings
2. Start a diuretic
3. Start a CCB
4. Start a fixed-dose combination therapy
5. Start an ACEI

Data on HTN in African Americans

- Develops at earlier age
- 1.5 increased mortality rate from heart disease
- 4.2 increased morbidity rate from ESRD
- More susceptible to ACEI angioedema than non-African Americans
- ARBs produce less angioedema than ACEIs
- Combination therapy produces better BP control in African Americans than monotherapy
- ISHBP guidelines:
  - When pt has HTN and comorbidities, aim for goal BP of 130/80 mmHg
  - Pts with HTN and DM should have ARB or ACEI therapy as part of combination therapy to slow progress of kidney disease

Clinical Case 3: 69-Year-Old White Female

- Presents for routine BP follow-up as requested by MD. No physical complaints
- Pt diagnosed by a colleague with new onset type 2 DM ~2 months ago and was started on metformin at that time
- Pt has been compliant with labs, appointments, and medications. Her lifestyle and diet are good
  - Medical Hx: HTN x 10 yrs, depression x 20 yrs, Raynauds of hands noticed in cold weather, no hx of angina, MI or CVA, new onset type 2 DM and started treatment 2 months ago
  - Social Hx: no tobacco, rare ETOH, lives with daughter and family. Following diabetic diet, walks every day
  - Medications: Metformin 1g bid, ASA 61 mg qd, cilafedipine 30 mg qd, hydrochlorothiazide therapy 25 mg 1 qd (this regimen has controlled her BP well for the last 7 years)
Clinical Case 3: 69-Year-Old White Female

- Exam: healthy-looking female
- Ht: 5’6”; Wt: 145 lbs
- BP: 149/92; Pulse: 68 bpm
- Exam: chest clear; heart sounds: NL; abdo exam: NL; EKG: SR rate 68 bpm, no acute changes compared with EKG 1 yr ago
- Labs: CBC, BUN, CREAT, LFTs all WNL for age
- FBS: 120
- A1C: 7.5%
- UA: tr protein

Clinical Case 3: What Is Your Next Step in the Management of This Patient’s HTN?

More than one answer may be correct:
1. Continue current medications, make no change, and follow up in 3 months with home BP readings
2. Increase her current CCB dose and her thiazide dose to maximum therapy
3. Stop both CCB and thiazide agents
4. Start an ACEI
5. Start an ARB
6. Continue with the CCB and stop the thiazide

Clinical Case 4: 76-Year-Old White Female With ISH

- Ht: 5’3”; Wt: 127 lbs
- BP: 181/88; P: 62; Chest clear; heart sounds normal; none added; abdomen normal to exam
- EKG: SR rate 62 no acute changes when compared with EKG of 2 yrs ago
- Labs:
  - UA: WNL
  - CBC, LFTs, TSH, BUN, CREAT, and RBS all WNL for age
  - Lipids WNL
- Pt requests refill for atenolol and wants prescription for ibuprofen

Clinical Case 4: With Regard to Therapy for This Patient, What Do You Do?

1. Refill her atenolol at the same dose
2. Increase the dose of her current medication
3. Continue her atenolol and add a second agent
4. Stop her atenolol and select a different agent
5. Stop her atenolol and start a fixed-dose combination agent
Elderly Patients With Isolated Systolic Hypertension

- ISH affects up to 15% of all people aged over 60 yrs
- ISH is major modifiable CVD risk factor
- SHEP trial results:
  - Stepped-care treatment with low-dose chlorthalidone
  - Treatment reduced incidence of total stroke by 36%
  - 5-yr absolute benefit of 30 CVA events per 1000 pts
  - 5-yr absolute benefit of 55 major cardiovascular events per 1000 pts
- Syst-Eur trial results
  - In elderly pts with ISH, treatment with CCB nitrendipine (+/- enalapril, +/- HCTZ) leads to a reduced rate of CV events compared with placebo

Take-Home Messages:

- Follow evidence-based clinical guidelines!
- Treat to BP goal!
- Control HTN for risk reduction!
- Pharmacist Interventions!
- Utilize combination therapy when appropriate!