Are Your Patients at Goal?

A Practical Guide to Combination Therapy for Hypertension Management
Session 7: Are Your Patients at Goal?—A Practical Guide to Combination Therapy for Hypertension Management

Learning Objectives

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

Faculty

**Biff Palmer, MD**
Professor, Department of Internal Medicine
University of Texas Southwestern Medical Center
Dallas, Texas

Biff Franklin Palmer, MD, is professor of internal medicine at UT Southwestern Medical Center, Dallas, Texas, where he is also nephrology fellowship program director. He is board certified in internal medicine and nephrology.

Dr Palmer received his medical degree from UT Southwestern Medical School and completed his residency in internal medicine at Walter Reed Army Medical Center, Washington, DC. He then went on to complete a research fellowship in the Department of Nephrology at the Walter Reed Army Institute of Research and a clinical fellowship in the Division of Nephrology at UT Southwestern Medical Center-Parkland Memorial Hospital.

Dr Palmer has authored more than 100 articles and chapters including works published in *The New England Journal of Medicine*, *Transplantation*, the *American Journal of Medicine*, the *American Journal of Medical Science*, and *Advances in Internal Medicine*. He has contributed chapters to more than 50 books, including the *Atlas of Diseases of the Kidney*, *Textbook of Nephrology*, and *Diseases of the Kidney*.

**Richard Wright, MD**
Director, Heart Failure Center and Director of Research
Pacific Heart Institute
Santa Monica, California

Richard Wright, MD earned his medical degree from Harvard Medical School and completed his medical residency and cardiology fellowship at the Brigham and Women’s Hospital in Boston. Dr Wright is research director and director of the Heart Failure Center, Pacific Heart Institute, Santa Monica, California. Additional professional affiliations include co-director of the Medicare Contractor Advisory Committee for California and vice-chair of the American College of Cardiology National Carrier Advisory Committee. He is also on the Medical Advisory Board at the Los Angeles Zoo, where he serves as the cardiologist for the Great Apes.

Dr Wright has lectured extensively on hypertension, atherosclerosis, and heart failure and has been published in the *Journal of Clinical Investigation*, the *Journal of the American Medical Association*, *Circulation*, and the *New England Journal of Medicine*. He was also co-author of the US Federal Guidelines on management of heart failure. As a recipient of the “Specialist of the Year Award” by the American College of Cardiology California, Dr Wright has been listed by the Center for the Study of Services as the top cardiologist in Southern California.

Faculty Financial Disclosure Statements
The presenting faculty reported the following:
Dr Palmer receives honoraria from Novartis Pharmaceuticals Corporation.
Dr Wright is on the speakers’ bureau for AstraZeneca LP; Boehringer-Ingelheim Pharmaceuticals, Inc.; and Novartis Pharmaceuticals Corporation; he is a consultant for Novartis Pharmaceuticals Corporation and St. Jude Medical; and he receives research support from Amgen, Atri-tech, Novartis Pharmaceuticals Corporation, Otsuka, and Pfizer Inc.
**Education Partner Financial Disclosure Statement**

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

Victoria Smith, MD, discloses having no conflicts of interest related to the content of this activity.

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<td>Hydro-Ride, Moduretic 5-50 various</td>
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<table>
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<td>metformin</td>
<td>Fortamet, Riomet, Glucophage, Glumetza</td>
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**Suggested Reading List**


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

HTN Introduction

- 1 in 3 adults in the US has HTN
- More than 50 million people in the US have HTN; more than 1 billion worldwide
- Prevalence of HTN is increasing
- HTN is most common diagnosis for primary care office visits
- Uncontrolled HTN is major risk factor for cardiovascular disease, morbidity, and mortality
- Only 30%-45% of pts treated for HTN are adequately controlled
- Clinicians not following clinical guidelines or meeting treatment goals

Cardiovascular Mortality Risk Doubles With Each 20/10 mm Hg Blood Pressure Increment

<table>
<thead>
<tr>
<th>SBP/DBP (mm Hg)</th>
<th>Cardiovascular Mortality Risk</th>
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<tbody>
<tr>
<td>115/75</td>
<td>1</td>
</tr>
<tr>
<td>135/85</td>
<td>2</td>
</tr>
<tr>
<td>155/95</td>
<td>4</td>
</tr>
<tr>
<td>175/105</td>
<td>8</td>
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</tbody>
</table>

SBP=systolic blood pressure; DBP=diastolic blood pressure

*Individuals aged 40-69 years starting at blood pressure 115/75 mm Hg


Increasing Systolic Blood Pressure and Age Elevates Risk of Ischemic Heart Disease (IHD) and Stroke Mortality

One Million Adults, 61 Prospective Studies

Ischemic Heart Disease Mortality

<table>
<thead>
<tr>
<th>Age at Risk (y)</th>
<th>Usual SBP (mm Hg)</th>
</tr>
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<tr>
<td>70-79</td>
<td>120</td>
</tr>
<tr>
<td>60-69</td>
<td>124</td>
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<tr>
<td>50-59</td>
<td>124</td>
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<tr>
<td>40-49</td>
<td>124</td>
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</tbody>
</table>

Stroke Mortality

<table>
<thead>
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<th>Age at Risk (y)</th>
<th>Usual SBP (mm Hg)</th>
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<tbody>
<tr>
<td>70-79</td>
<td>120</td>
</tr>
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<td>60-69</td>
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<td>50-59</td>
<td>124</td>
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<tr>
<td>40-49</td>
<td>124</td>
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HYVET Study

Treatment of Sustained Systolic Hypertension Significantly Lowers Stroke-Related and All-Cause Deaths in the Very Elderly

Design:

- Randomized, double-blind, placebo-controlled multinational study in 3845 pts ≥80 yrs old.
- Primary endpoint = all stroke events

Active treatment = indapamide sustained release w/o perindopril

Note:

- Target BP at 2 yrs attained in 48.0% pts with active treatment and 19.9% pts in placebo group (P<0.001)


HYVET Endpoints

Fatal or Nonfatal Stroke

<table>
<thead>
<tr>
<th>No. of Events/P100 Patients</th>
<th>Placebo Grp</th>
<th>Active-Tx Grp</th>
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</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>1912/1484/814/374/194</td>
<td>1933/1557/873/417/229</td>
</tr>
<tr>
<td>Follow-up (Yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P=0.06</td>
<td></td>
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Death From Any Cause

<table>
<thead>
<tr>
<th>No. of Events/P100 Patients</th>
<th>Placebo Grp</th>
<th>Active-Tx Grp</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>1912/1492/814/374/202</td>
<td>1933/1565/877/420/231</td>
</tr>
<tr>
<td>Follow-up (Yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P=0.02</td>
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</table>

Death From Stroke

<table>
<thead>
<tr>
<th>No. of Events/P100 Patients</th>
<th>Placebo Grp</th>
<th>Active-Tx Grp</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>1912/1492/814/374/202</td>
<td>1933/1565/877/420/231</td>
</tr>
<tr>
<td>Follow-up (Yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P=0.05</td>
<td></td>
<td></td>
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</table>


Population Studies: Lower Is Better

Meta-analysis of 61 prospective, observational studies*

1 million adults

12.7 million person-years

2 mm Hg decrease in mean SBP

7% reduction in risk of ischemic heart disease

10% reduction in risk of stroke mortality

*Epidemiologic studies; not clinical trials of hypertension agents


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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</thead>
<tbody>
<tr>
<td>Controlling high BP</td>
<td>28,300</td>
<td>$1,242,836,580</td>
</tr>
<tr>
<td>Diabetes care/HbA1c control</td>
<td>13,600</td>
<td>$178,464,900</td>
</tr>
<tr>
<td>Cholesterol management</td>
<td>6,500</td>
<td>$94,249,482</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>2,700</td>
<td>$97,690,542</td>
</tr>
</tbody>
</table>

US Population

HOT Study: Primary Objectives of HTN Treatment Arm

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

HOT Study: Risk of Major CV Event

BP Control Reduces CV Events: HOT Trial

Case Study: 55-Year-Old White Male at Initial Visit for Routine Annual Physical Exam

- No physical complaints
- Personal hx
  - Non-smoker
  - Consumes 2-3 beers/week
  - No physical activity
- Family hx
  - Positive for cardiac disease
- Medical hx – no significant
- NKDA
- Current medications: none

What Would Your Next Course of Action Be?

1. Start patient on antihypertensive agent now
2. Schedule follow-up visit within one month for repeat BP 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 Initial Visit for Routine Annual Physical Exam

- Physical findings
  - BP: 146/102 mm Hg sitting
  - Resting pulse: 70 bpm
  - BMI: 35.5 kg/m²
  - Last documented BP 3 yrs ago: 136/90 mm Hg
- EKG: NS ST-T changes
- Laboratory results:
  - LDL 156; HDL 26; FBS 110

Achieved

Diabetes Subgroup

Goal of therapy: Target diastolic BP

- ≤90 mm Hg (n=501)
- ≤85 mm Hg (n=501)
- ≤80 mm Hg (n=499)

BP Control Reduces CV Events: HOT Trial

Case Study: 55-Year-Old White Male at Initial Visit for Routine Annual Physical Exam

- Physical findings
  - BP: 146/102 mm Hg sitting
  - Resting pulse: 70 bpm
  - BMI: 35.5 kg/m²
  - Last documented BP 3 yrs ago: 136/90 mm Hg
- EKG: NS ST-T changes
- Laboratory results:
  - LDL 156; HDL 26; FBS 110
Case Study: 55-Year-Old White Male at First Follow-up Visit

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

What Is Your Target BP Goal for the Patient?
1. <120/80 mm Hg
2. <130/80 mm Hg
3. <140/90 mm Hg
4. <145/90 mm Hg
5. <150/100 mm Hg

JNC 7: New BP Classifications

<table>
<thead>
<tr>
<th>BP Level (mm Hg)*</th>
<th>Category</th>
</tr>
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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>80-89</td>
</tr>
<tr>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>≥160</td>
<td>≥100</td>
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</table>

*Use higher value for classification.

Current JNC 7 Treatment Goals

<table>
<thead>
<tr>
<th>For Individuals With:</th>
<th>BP Goal:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (No diabetes or renal disease)</td>
<td>&lt;140/90 mm Hg (JNC 7)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>&lt;130/80 mm Hg (ADA, JNC 7)</td>
</tr>
<tr>
<td>Renal disease with proteinuria &gt;1 gram/24 hours</td>
<td>&lt;135/85 mm Hg (NKF)</td>
</tr>
<tr>
<td>or diabetic kidney disease</td>
<td></td>
</tr>
</tbody>
</table>

Summary of Key JNC 7 Guidelines

- In persons >50 years old, systolic BP >140 mm Hg is a more important cardiovascular disease (CVD) risk factor than diastolic BP
- Normotensive individuals at 55 years old have a 90% lifetime risk for developing HTN
- Risk of CVD death doubles with each increase of 20/10 mm Hg, beginning at 115/75 mm Hg
- Thiazide-type diuretics should be used in drug treatment, either alone or in combination with other classes, for most pts with uncomplicated HTN

Summary of Key JNC 7 Guidelines

- 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 mm Hg in uncomplicated HTN or <130/80 mm Hg in DM/chronic kidney disease (CKD))
- If BP is more than 20/10 mm Hg above goal, consider initiating therapy with 2 agents, 1 of which should be a thiazide-type diuretic
Clinical Trials and Guideline Basis for Compelling Indications for Individual Drug Classes

<table>
<thead>
<tr>
<th>Compelling Indications</th>
<th>Recommended Drugs</th>
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<tbody>
<tr>
<td>Diuretic</td>
<td>BB, ACEI, ARB, CCB, Aldo ANT</td>
</tr>
<tr>
<td>Heart failure</td>
<td>X</td>
</tr>
<tr>
<td>Post-myocardial infarction</td>
<td>X</td>
</tr>
<tr>
<td>High coronary disease risk</td>
<td>X</td>
</tr>
<tr>
<td>Diabetes</td>
<td>X</td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td>X</td>
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</table>

Aldo ANT: aldosterone antagonist


Impact of High-Normal BP on CV Risk

Prehypertension

- JNC 7 added prehypertension (pre-HTN) to guidelines: 120-139 mm Hg SBP or 80-89 mm Hg 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

Managing Prehypertension

- JNC-recommended approach to pre-HTN is lifestyle modifications to achieve BP goal, UNLESS pts have DM or 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>
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<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight (BMI, 18.5-24.9)</td>
<td>2-4 mm Hg/Losing weight loss[26-28]</td>
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<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 mm Hg[22,23]</td>
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<tr>
<td>Dietary sodium reduction</td>
<td>Reduce dietary sodium intake to be no more than 100 mmol (2.4 g sodium or 6 g sodium chloride)</td>
<td>2-3 mm Hg[22,23]</td>
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<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>4-9 mm Hg[22,23]</td>
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<tr>
<td>Moderate alcohol consumption</td>
<td>Limit consumption to no more than 2 drinks per day (1 oz or 30 mL ethanol) [eg, 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey] in men and no more than 1 drink per day in women and lighter-weight persons</td>
<td>2-4 mm Hg[22,23]</td>
</tr>
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Trial of Preventing Hypertension (TROPHY) Study

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

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

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

TROPHY: Reduction in New-Onset Hypertension

<table>
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<tr>
<th>Year</th>
<th>Placebo</th>
<th>Candesartan 16 mg qd</th>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>82</td>
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<td>3</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
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Number of patients without HTN

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<td>381</td>
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<td>2</td>
<td>309</td>
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<td>3</td>
<td>116</td>
<td>104</td>
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<td>4</td>
<td>83</td>
<td>118</td>
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JNC 7 Algorithm for the Treatment of Hypertension

- **Lifestyle Modifications**
- **Initial Drug Choices**
- **With Compelling Indications**
- **Without Compelling Indications**

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

Unacceptable BP Control Rates Require More Aggressive Treatment

Presentation 2: Suboptimal Treatment and Clinical Inertia
55-Year-Old White Male at Follow-up Visit #2

The patient's BP is now 140/98 mm Hg with several consistent home BP readings.

What would be your next step in terms of controlling his BP?

1. Nothing, his BP is fine
2. Increase dose of current regimen
3. Add a third drug
4. Switch to a different combination regimen
5. None of the above

What Percentage of Patients in the US Currently Treated for HTN Have Adequately Controlled BP?

1. 80%
2. 70%
3. 65%
4. 57%
5. 45%

We Are Failing to Achieve BP Control in Our Hypertensive Patients

• 75% of 50 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

In Most Patients With HTN, Inadequate BP Control Is Due to:

1. Patient behavior
2. Clinician behavior

Trends in Awareness, Treatment, and Control of High Blood Pressure in Adults With Hypertension Aged 18 to 74 Years

Table: National Health and Nutrition Examination Surveys, Weighted % (unadjusted)

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<tr>
<td>Awareness</td>
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<td>69</td>
<td>71</td>
<td>76</td>
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<tr>
<td>Treatment</td>
<td>54</td>
<td>58</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>Control†</td>
<td>27</td>
<td>29</td>
<td>33</td>
<td>37</td>
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<tr>
<td>All HTN</td>
<td>27</td>
<td>29</td>
<td>33</td>
<td>37</td>
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<tr>
<td>Treated HTN</td>
<td>50</td>
<td>50</td>
<td>57</td>
<td></td>
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<tr>
<td>Diabetes &amp; HTN</td>
<td>24</td>
<td>36</td>
<td>38</td>
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Why Are We Not Achieving BP Control?

• Patient behavior
  - Limited access to care
  - Lack of compliance with medication and lifestyle and dietary improvements
    • Costs
    • Medication side effects
  - Clinician behavior: Clinical inertia (CI)
Clinical Inertia Definitions

- Failure of clinicians to initiate, intensify, or modify therapeutic measures for medical conditions when indicated
- Failure of clinicians to aggressively manage a chronic medical condition sufficiently to control it
- Inaction by clinicians caring for pts with uncontrolled risk factors

Clinical Inertia: Evidence of Clinical Inertia in HTN Management

- 76% of pts with HTN are diagnosed correctly
- 65% of pts with HTN are treated with pharmacologic therapy
- BUT ONLY 37% of all pts treated for HTN have adequate BP control
- 1/3 of all pts with HTN do not receive the recommended treatment

What is the Main Reason Clinicians Do Not Initiate or Increase Antihypertensive Therapy in Pts With Several Valid, Elevated BP Readings?

1. Concerns about drug side effects and interactions
2. Patient’s lack of acceptance that his/her BP is truly elevated
3. Lack of clinician familiarity with treatment guidelines
4. You tend to accept that elevated BP is possibly related to other patient factors (eg pain, stress, diet, lifestyle, age) and should be reviewed at another time
5. Patient’s concern about the cost of medications

Was Prescribed Medicine for HTN Initiated or Changed at the Patient Visit?

% of Patient Visits When Patients Had SBP of ≥140 mm Hg

- No: 61% (n=164)
- Yes: 38% (n=103)

If Drug Was Initiated or Changed at the Patient Visit, What Occurred?

-Added new drug to existing regimen 3%
-Increased dosage of current medication 10%
-Decreased dosage and/or reduced number of drugs 41%
-Initiated drug treatment 47%

Steps to Successful Management of HTN:

- Recognize the abnormality (elevated BP)
- Diagnose the condition (HTN)
- Initiate therapy per evidence-based guidelines (eg, JNC 7, ADA, WHO-ISH)
- Intensify and modify therapy to achieve treatment goals as defined in guidelines
- Motivation of pt and clinician to achieve therapeutic targets
- Adherence by pt and clinician to treatment plan
Clinical Inertia: Causes

- Clinician education
- Inadequate guideline development and implementation
- Clinician acceptance of elevated BP
- Time constraints
- Lack of clinician incentive
- Inefficient practice organization and documentation

Clinical Inertia: Causes

- Education:
  - Treat to relieve symptoms vs treat to goal
- Guideline Development:
  - Time lag between reported findings and development, dissemination, and implementation of evidence-based guidelines
  - Inefficient and ineffective dissemination
- Guideline Implementation:
  - Lack of awareness of existence
  - Lack of clinician familiarity or agreement
  - Lack of training or ability to efficiently implement
  - Clinician expectation that pts will not comply with guidelines

Clinical Inertia: Causes

- Clinician Acceptance of Elevated BP:
  - Satisfaction with current BP level
  - Elevated systolic BP typically more acceptable than elevated diastolic BP
- Time Constraints:
  - Average length of primary care consultation is 15 minutes
- Competing Priorities:
  - Acute and chronic comorbidities
  - Preventive care priorities
  - Multiple areas of pt concern to be addressed

Clinical Inertia: Causes

- Lack of Clinician Incentive:
  - Adhering to guidelines and achieving treatment goals not adequately remunerated or rewarded in the US
- Lack of Detail in Documentation:
  - Most clinicians fail to document their reasons for not initiating or modifying HTN therapy
- Practice Organization:
  - Lack of practice structure to promote, monitor, and maintain HTN control

Clinical Inertia: Practical Ways to Overcome CI

- Use of computerized or non-computerized point of care decision-making support systems including:
  - Reminders
  - Prompts
  - Preventive measure checklists and flow sheets
  - Guideline reminders
  - Stepped care protocols: what to do and when
  - Defined treatment algorithms

Clinical Inertia: Practical Ways to Overcome CI

- Clinician Support:
  - Use of nurse case managers
  - Use of clinical pharmacists to co-manage HTN pts
- Clinician Performance Feedback:
  - Medical chart audits
  - Systematic self-measurement of performance
  - Individualized, specific, and timely feedback on performance
  - Outcome measurement
  - Clinician profiling
Which Practical Methods to Overcome Clinical Inertia Do You Currently Employ in Your Practice?

1. Computerized prompts/reminders for preventive care/follow-up, treatment guidelines/algorithm, or stepped-care protocols
2. Paper chart prompts/reminders for preventive care/follow-up, treatment guidelines/algorithm, or stepped-care protocols
3. Regular physician performance feedback to provider
4. Regular patient outcome feedback to provider
5. Other
6. None

Presentation 3: Combination Therapies for HTN

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

<table>
<thead>
<tr>
<th>Trial</th>
<th>SBP (mm Hg)</th>
<th>Mean No. of Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met JNC Goals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AASK</td>
<td>128</td>
<td>2.4</td>
</tr>
<tr>
<td>INVEST</td>
<td>133</td>
<td>2.8</td>
</tr>
<tr>
<td>HOT</td>
<td>138</td>
<td>3.0</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>138</td>
<td>4.0</td>
</tr>
<tr>
<td>Did Not Meet JNC Goals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDNT</td>
<td>138</td>
<td>4.0</td>
</tr>
<tr>
<td>RENAAL</td>
<td>141</td>
<td>4.1</td>
</tr>
<tr>
<td>UKPDS</td>
<td>144</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Mean 2.0 Median 2.8 agents
SBP <140
79% of patients required >3 agents

Combination Therapy for HTN – Pros and Cons

- Pros
  - Improved efficacy, tolerability, and pt compliance; achieved BP goals more quickly
- Cons
  - Limits flexibility and dose titration of single component of the combination agent

The Case for Combination Therapy

- If pts with HTN are not adequately controlled on monotherapy, the clinician has 3 options:
  1. Titrate current monotherapy dose upward; risks include:
     - Increased side effects
     - Only modest improvement in BP control
  2. Trial of sequential monotherapy; risks include:
     - Prolonged time frame to achieve adequate BP control
     - Loss of pt’s confidence in provider and therapy
  3. Combination therapy, either individual drug combinations or fixed-dose combinations

Examples of Combination Therapies for HTN

- BB + diuretics
- ACEI + diuretics
- ACEI + CCB
- ARB + diuretics
- ARB + CCB
- Central acting agents + diuretics
- Diuretic + diuretic

Stanton T, Reid JL. J Hum Hypertens. 2002;16:75-78.
Steward T, Reid J. J Hum Hypertens. 2003;17:75-78.
Combined Use of Antihypertensive Drugs

- Diuretic
- ARB
- β blocker
- CCB
- ACEI

Strong rationale
Reasonable rationale
Questionable rationale

Advantages of Combination Therapy for HTN
- Potential additional BP reduction
- Multiple modes of action may give a longer, smoother duration of action
- Low-doses may reduce side effects of individual drugs
- Dose adjustments and titrations may be simpler with fixed-dose preparations although less flexible
- Pt compliance potentially increased with fewer tablets (advantage of fixed-dose preparations)
- Cost may be less than that of drugs obtained individually (advantage of fixed-dose preparations)

Initiating Antihypertensive Treatment Using Combination Therapy

JNC 7 recommends that combination therapy should be used first line in Stage 2 HTN.

Clinical Trials Exploring the Efficacy of Combination Therapy for HTN Treatment
- ASCOT: concluded that a CBB plus ACEI regimen reduced mortality and strokes more than a BB plus diuretic-based regimen
- ACCOMPLISH: results show superiority of ACEI in combination with CCB vs combination with a diuretic
- ONTARGET: trial comparing combination ARB and ACEI with ARB efficacy alone
- CO-OPERATE: results showed a superior effect of combination therapy (ARB/ACEI) in protecting against renal function deterioration in non-diabetic pts with renal disease
- ADVANCE: results from this morbidity/mortality study of DM and HTN showed a significant reduction in relative risk of death from CVD, total coronary, and total renal events in the group treated with combination therapy (ACEI/diuretic) compared with placebo

Combination Therapy in Systolic Hypertension (ACCOMPLISH)
- Prospective, randomized, double-blind trial
  - 11,400 patients
  - First-line treatment groups
    - Benazepril/amlodipine
    - Benazepril/hydrochlorothiazide (HCTZ)
  - 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)

Presented at the American College of Cardiology 2008 Scientific Sessions, March 31, 2008 Chicago, IL.

ACCOMPLISH: Kaplan Meier for Primary Endpoint

- **ACEI / HCTZ**
- **CCB / ACEI**

20% Risk Reduction

Time to 1st CV Morbidity/Mortality (days)

P=0.0002
ONTARGET: Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events

- Prospective, randomized, double-blind trial in 25,620 high-risk patients with HTN:
  - Ramipril
  - Telmisartan
  - Ramipril + telmisartan
    - Hypotension: 1.1% vs 4.2% (P<0.001)
    - Angioedema: 0.1% vs 0.3% (P=0.01)
  - Combination vs ramipril:
    - Hypotension: 4.6% vs 1.7% (P<0.001)
    - Renal dysfunction: 13.5% vs 6.2% (P=0.001)


ONTARGET: Primary Outcome – Kaplan Meier Curves

ONTARGET: Incidence of Primary Outcome, Components, and Death From Any Cause

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ramipril (N=8542)</th>
<th>Telmisartan (N=8542)</th>
<th>Combo Therapy (N=8542)</th>
<th>Telmisartan vs Ramipril</th>
<th>Combo Therapy vs Ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from CV causes, MI, stroke, or hospitalization for heart failure**</td>
<td>1412 (16.5)</td>
<td>1423 (16.7)</td>
<td>1338 (15.6)</td>
<td>0.97 (0.94-1.01)</td>
<td>0.99 (0.92-1.07)</td>
</tr>
<tr>
<td>Death from CV causes, MI, stroke, or heart failure‡</td>
<td>1199 (13.9)</td>
<td>1330 (14.5)</td>
<td>1329 (14.5)</td>
<td>0.99 (0.95-1.03)</td>
<td>0.99 (0.93-1.06)</td>
</tr>
<tr>
<td>MI*</td>
<td>433 (5.0)</td>
<td>463 (5.3)</td>
<td>438 (5.1)</td>
<td>1.07 (0.94-1.22)</td>
<td>1.08 (0.94-1.22)</td>
</tr>
</tbody>
</table>

*Patients could have multiple events in this category. The numbers of events were 2560 (30.1%) in ramipril group, 2560 (30.1%) in telmisartan group, and 2560 (30.1%) in combination group. Differences not significant (P<0.001) for the comparison vs ramipril, and P=0.12 for the combination therapy vs ramipril.

**Cumulative incidence of the primary outcome (death from any cause or nonfatal MI) was 33.9% in ramipril group, 33.9% in telmisartan group, and 33.9% in combination group. Differences not significant (P=0.83) for the comparison vs ramipril, and P=0.38 for the combination therapy vs ramipril.


ONTARGET: Incidence of Primary Outcome, Components, and Death From Any Cause

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ramipril (N=8542)</th>
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<th>Telmisartan vs Ramipril</th>
<th>Combo Therapy vs Ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure‡</td>
<td>914 (10.7)</td>
<td>914 (10.7)</td>
<td>914 (10.7)</td>
<td>1.00 (0.96-1.03)</td>
<td>1.00 (0.96-1.03)</td>
</tr>
<tr>
<td>Hospitalization for heart failure‡</td>
<td>914 (10.7)</td>
<td>914 (10.7)</td>
<td>914 (10.7)</td>
<td>1.00 (0.96-1.03)</td>
<td>1.00 (0.96-1.03)</td>
</tr>
</tbody>
</table>


ONTARGET: Conclusions

- Exceptional BP control with combination therapy
- Provides compelling evidence for initial combination therapy with ACEI/CCB, challenging current diuretic-based guidelines

Provided compelling evidence for initial combination therapy with ACEI/CCB, challenging current diuretic-based guidelines

ONTARGET: Conclusions

• Telmisartan and ramipril equivalent in patients with vascular disease or high-risk diabetes
• Telmisartan associated with fewer side effects (cough, angioedema)
• No significant benefit in primary outcome among patients receiving combination therapy

ARB vs ACEI: Are There Clinical Advantages of Either?

ARBs compared with ACEIs:
• Provide more complete blockade of angiotensin II
• Provide equivalent end-organ protection
• Are not associated with angiotensin II “escape”
• Are associated with a much lower incidence of:
  – Cough (0.9%-3% vs 7%-39%)
  – Angioedema (up to 0.2%, compared with 0.1%-0.5% with ACEIs)


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 DM (T2DM) 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, hyperlipidemic
• 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

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

• Medications: 4 yr hx of treatment for HTN
  – Initial HCTZ alone x 1 yr: BP initially controlled but then:
  – Metoprolol/HCTZ combination 100/25 mg qd for 2 yrs. BP initially improved but, as pt gained weight and continued to smoke, BP again: dose was increased to 100/50 mg qd for 6 months
  – Metoprolol/HCTZ 100/50 mg qd combination plus ramipril 5 mg qd was added 6 months ago. BP improved but did not fall below 150/92 mm Hg
  – Atorvastatin 20 mg qd
• Pt has failed to keep follow-up BP appointments, until now

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

• Ht: 5’5”; Wt: 185 lbs
• BP 166/99 mm Hg; P: 76 bpm; Sats: 98% on room air
• Exam: chest clear to bases bilaterally, no rales or wheeze
• ENT exam: WNL
• Heart sounds: normal
• 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 WNL
• Lipids: LDL 150; HDL 36; TG 230
Clinical Case 1: What Steps Do You Take to Control This Pt’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
  - Over last 8 months, pt’s last 4 BP in-office readings 149-162/89-94 mm Hg
- Exam: lungs clear to bases; heart sounds: NL; abdo: NL
- EKG: SR, rate 71 bpm, WNL
- Labs: CBC, BUN, CREAT, LFT, uric acid, FBS WNL
- FLIP: LDL 146; HDL 37; TG 190
- UA: WNL

What Action Do You Take to Improve This Pt’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
- ISHB guidelines:
  - In pt with HTN and comorbidities, BP goal is 130/80 mm Hg
  - Pts with HTN and DM should have ARB or ACEI therapy as part of combination therapy to slow progression of kidney disease

Clinical Case 3: 69-Year-Old White Female
- Presents for routine BP follow-up. No physical complaints
  - Compliant with labs, appts, and meds
- Medical hx:
  - T2DM x 2 mo, HTN x 10 yrs, depression x 20 yrs, Raynauds of hands noted in cold weather
  - No hx of angina, MI or CVA
- Social hx:
  - No tobacco, rare ETOH, lives with family. Follows diet for diabetes, walks daily
- Medications:
  - Metformin 1g bid (started at time of T2DM dx)
  - ASA 81 mg qd
  - Nifedipine 30 mg qd
  - HCTZ therapy 25 mg qd
Clinical Case 3: 69-Year-Old White Female

- Exam: healthy-looking female
- Ht: 5’6”; Wt: 145 lbs
- BP 149/92 mm Hg; Pulse 68 bpm
- Exam: chest clear; heart sounds NL; abdo exam NL
- ECG: SR rate 68 bpm; no acute changes compared with ECG 1 yr ago
- Labs: CBC, BUN, CREAT, LFTs WNL for age
  - FBS: 120
  - HbA1c: 7.5%
  - UA: tr protein

Clinical Case 3: What Is Your Next Step in the Management of This Pt’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

Action to Control Cardiovascular Disease in Diabetes (ACCORD)

- 10,000 subjects with T2DM
- Double 2x2 design

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c goal</td>
<td>&lt;6%</td>
<td>&lt;7.5%</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>&lt;120 mm Hg</td>
<td>&lt;130 mm Hg</td>
</tr>
</tbody>
</table>

Lipid trial: Statin for LDL for all patients, then randomize to fenofibrate or placebo

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

- Presents for arthritis pain in hands and medication refills
- No other physical complaints
- Medical Hx: HTN x 10 yrs, osteoarthritis bilateral hands and knees x 12 yrs, no hx of DM, CVA, or MI
- Social Hx:
  - Lives with and cares for elderly husband who has dementia; no family support
  - No ETOH use; no tobacco use
- Some hx of noncompliance with medications in past
- Medications:
  - Atenolol 100 mg qd x 7 yrs
  - Aspirin 81 mg qd
  - Ibuprofen 600-800 mg several times per week for arthritis pains (self-prescribed)

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

- Ht: 5’3”; Wt: 127 lbs
- BP 181/88 mm Hg; Pulse 62 bpm
- Physical exam:
  - Chest clear; heart sounds normal; abdo normal
- 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 Pt, 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 in a second agent
4. Stop her atenolol and select a different agent
5. Stop her atenolol and start a fixed-dose combination agent


Take Home Messages
**Elderly Pts With Isolated Systolic Hypertension**

- ISH affects up to 15% of all people older than 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!
- Overcome clinical inertia!
- Utilize combination therapy when appropriate!