Combination Antihypertensive Therapy: When to use it Diabetes

George L. Bakris, MD, F.A.S.N., F.A.S.H.
Professor of Medicine
Director, ASH Comprehensive Hypertension Center
The University of Chicago Medicine
Development of Antihypertensive Therapies

Effective but poorly tolerated
- 1940s
  - Peripheral sympatholytics
    - Ganglion blockers
    - Veratrum alkaloids
- 1950
  - Direct vasodilators
- 1957
  - Thiazides diuretics

As effective and better tolerated
- 1960s
  - Central $\alpha_2$ agonists
  - Calcium antagonists
    - non DHPs
    - $\beta$-blockers
- 1970s
  - ACE inhibitors
  - $\alpha$-blockers
- 1980s
  - ARBs

As effective and even better tolerated
- 1990s
  - Calcium antagonists
    - DHPs
- 2001-2009
  - Direct Renin inhibitors
  - ETa Blockers
  - VPIs
  - Others

? More effective for SBP
Evolution of Fixed Dose Combination Antihypertensive Therapies

1960s
- SerApAs (reserpine, hydralazine, HCTZ)

1970s
- Combination Diuretics
  - Aldactazide, Dyazide, Maxzide, Guanabenz

1980s
- RAS Blockers with diuretics
- Beta blocker + diuretics

1990s
- RAS Blockers with CCBs
- (Lotrel)

2000- present
- CCBs + ARBs
- ARB + chlorthalidone
- DRIs + ARBs
- DRIs + CCBs
- TRIPLE Combos
- (CCB + RAS Blocker + diuretic)
Rationale for Fixed-Dose Combination Therapy: Background

- Traditional antihypertensive therapy yields goal BP in <60% of treated hypertensive patients\(^1-3\)
- Switching from one monotherapy to another is effective in only about 50% of patients\(^1\)
- Most patients will require at least two drugs to attain goal BP (<140/90 mm Hg, or <130/80 mm Hg for patients with diabetes or chronic renal disease)\(^4-6\)

BP = blood pressure

Key Messages From JNC7

- Thiazide-type diuretics should be initial drug therapy for most, either alone or combined with other drug classes.

- Certain high-risk conditions are compelling indications for other drug classes.

- Most patients will require two or more antihypertensive drugs to achieve goal BP. (most ≈ 76%)

- If BP is >20/10 mmHg above goal, initiate therapy with two agents, one usually should be a thiazide-type diuretic.
Algorithm for Treatment of Hypertension

Lifestyle Modifications

Not at Goal Blood Pressure (<140/90 mmHg)
(<130/80 mmHg for those with diabetes or chronic kidney disease)

Initial Drug Choices

Without Compelling Indications

Stage 1 Hypertension
(SBP 140–159 or DBP 90–99 mmHg)
Thiazide-type diuretics for most.
May consider ACEI, ARB, BB, CCB, or combination.

Stage 2 Hypertension
(SBP ≥160 or DBP ≥100 mmHg)
2-drug combination for most
(usually thiazide-type diuretic and ACEI, or ARB, or BB, or CCB)

With Compelling Indications

Drug(s) for the compelling indications
Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.

Not at Goal Blood Pressure

Optimize dosages or add additional drugs until goal blood pressure is achieved.
Consider consultation with hypertension specialist.
2007 ESH-ESC Hypertension Guidelines: MONOTHERAPY VERSUS COMBINATION THERAPY

• Regardless of the drug employed, monotherapy allows to achieve BP target in only a limited number of hypertensive patients.

• Initial treatment can make use of monotherapy or combination of two drugs at low doses with a subsequent increase in drug doses or number, if needed.

• Fixed combinations of two drugs can simplify treatment schedule and favour improved adherence.
Mean Placebo-Subtracted SBP Reduction From a Meta-Analysis of 42 Randomized Trials of Combination vs Monotherapy

Effect if both drugs additive (14.3 mm Hg)

Thiazide: 7.3 mm Hg
Any other BP drug: 7.8 mm Hg
Thiazide with any other BP drug: 14.6 mm Hg

Mean Placebo-Subtracted SBP Reduction From a Meta-Analysis of 42 Randomized Trials of Combination vs Monotherapy

Mean Placebo-Subtracted SBP Reduction From a Meta-Analysis of 42 Randomized Trials of Combination vs Monotherapy

### Ratio of Observed to Expected Incremental BP-Lowering Effects of Adding a Drug or Doubling the Dose According to Drug Class

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Ratio of Observed to Expected Incremental SBP Reduction</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide</td>
<td>1.04</td>
<td>0.19</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>1.00</td>
<td>0.23</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>1.16</td>
<td>0.20</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>0.89</td>
<td>0.37</td>
</tr>
<tr>
<td>All classes</td>
<td>1.01</td>
<td>0.22</td>
</tr>
</tbody>
</table>

**Adding a drug from another class (on average standard doses)**

**Doubling dose of same drug (from standard dose to twice standard)**

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Multiple Medications Are Required to Achieve BP Control in Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>SBP achieved (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT</td>
<td>138</td>
</tr>
<tr>
<td>HOT</td>
<td>138</td>
</tr>
<tr>
<td>ACCOMPLISH</td>
<td>132</td>
</tr>
<tr>
<td>ACCORD (intensive)*</td>
<td>119</td>
</tr>
<tr>
<td>ACCORD (standard)*</td>
<td>133</td>
</tr>
<tr>
<td>INVEST</td>
<td>133</td>
</tr>
<tr>
<td>IDNT</td>
<td>138</td>
</tr>
<tr>
<td>RENAAL</td>
<td>141</td>
</tr>
<tr>
<td>ABCD</td>
<td>132</td>
</tr>
<tr>
<td>UKPDS</td>
<td>144</td>
</tr>
<tr>
<td>MDRD</td>
<td>132</td>
</tr>
<tr>
<td>AASK</td>
<td>128</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure. *Target blood pressure control groups in ACCORD defined as <120 mm Hg (intensive) and <140 mm Hg (standard).
Percentage of Patients Who Reached JNC-7 BP Goals

BP Goal: ≤140/90 mm Hg

Combination Therapy Outcome Trials

- INVEST
- ASCOT
- ACCOMPLISH (only fixed dose trial)
INVEST Trial Design

• Prospective, Randomized, Open trial with Blinded Endpoint (PROBE) design

• 22,576 patients with coronary artery disease (CAD) and hypertension in 14 countries

• Mean follow-up of 2.7 years (61,835 patient years)

• Hypothesis: risk of adverse outcomes is equivalent in hypertensive CAD patients treated with either a verapamil SR strategy or an atenolol strategy

• JNC VI blood pressure (BP) goals
  – <140/90 mm Hg
  – <130/85 mm Hg for diabetes or renal impairment

• Primary Outcome- First occurrence of all-cause death, nonfatal myocardial infarction (MI), or nonfatal stroke

Treatment Strategies

**Verapamil SR Strategy**

- **Step 1**
  - Verapamil SR 240 mg

- **Step 2**
  - Verapamil SR 240 mg + Trandolapril 2 mg

- **Step 3**
  - Verapamil SR 180 mg twice daily + Trandolapril 2 mg twice daily

- **Step 4**
  - Verapamil SR 180 mg twice daily + Trandolapril 2 mg twice daily + HCTZ 25 mg

**Atenolol Strategy**

- **Step 1**
  - Atenolol 50 mg

- **Step 2**
  - Atenolol 50 mg + HCTZ 25 mg

- **Step 3**
  - Atenolol 50 mg twice daily + HCTZ 25 mg twice daily

- **Step 4**
  - Atenolol 50 mg twice daily + HCTZ 25 mg twice daily + Trandolapril 2 mg

Addition of Drug and Increase Dose:

- **Addition of Drug**
  - Strategic drugs could be titrated: verapamil SR 120-480 mg/d; trandolapril 0.5-8 mg/d; atenolol 25-200 mg/d; HCTZ 12.5-100 mg/d

HCTZ = hydrochlorothiazide.

Atenolol Strategy

Verapamil SR Strategy

log rank $p = 0.57$

$RR = 0.98$, 95% CI 0.90-1.06*

Total follow-up: 61,835 patient-yrs
Mean follow-up: 2.7 yrs
Annual event rate: 3.6%

Pepine, et al. JAMA 2003; 290:2805-2816
CV outcomes from the Diabetes Subgroup of INVEST trial

**OUTCOMES: (MI, stroke, all-cause mortality)**

- Not controlled (n = 2,175): SBP > 140 mmHg
- Usual control (n = 1,970): SBP 130–140 mmHg
- Tight control (n = 2,255): SBP < 130 mmHg

<table>
<thead>
<tr>
<th>Outcome (%)</th>
<th>Not controlled (n = 2,175)</th>
<th>Usual control (n = 1,970)</th>
<th>Tight control (n = 2,255)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/MI/Stroke</td>
<td>19.8</td>
<td>12.6</td>
<td>12.7</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>15.4</td>
<td>10.2</td>
<td>11</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>3.1</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>2.4</td>
<td>1.3</td>
<td>1</td>
</tr>
</tbody>
</table>

DeHoff-Cooper R et.al. JAMA 2010;304:61-68.
ASCOT-BPLA: Study design

**Design:** Prospective randomised open blinded endpoints (PROBE)

**Population:** N = 19,257 with hypertension and ≥3 other CV risk factors

**Treatment:**
- Amlodipine 5–10 mg ± perindopril 4–8 mg prn (n = 9639)
- Atenolol 50–100 mg ± bendroflumethiazide 1.25–2.5 mg/potassium prn (n = 9618)

**Primary outcome:** Nonfatal MI (including silent MI) and fatal CHD

**Secondary outcome:** All-cause mortality, stroke, nonfatal MI (excluding silent MI), all coronary events, CV events/procedures, CV mortality, fatal/nonfatal HF
ASCOT-BPLA: Treatment algorithm for BP targets

BP medication titrated to achieve target:
No diabetes: <140/90 mm Hg
Diabetes: <130/80 mm Hg

19,342 patients
40–79 y
with
UNTREATED
SBP ≥160 mmHg
and/or
DBP ≥100 mmHg
OR
TREATED
SBP ≥140 mmHg
and/or
DBP ≥90 mmHg

In each arm, pts with total cholesterol ≤6.5 mmol/L randomized to atorvastatin (10 mg) or placebo daily (n = 10,297)

Amlo = amlodipine; Peri = perindopril; Doxa = doxazosin GITS (Gastrointestinal Transport System); BFZ = bendroflumethiazide

ASCOT-BPLA: Overall results

- Study stopped prematurely after 5.5-year median follow-up because of higher death rate in assigned atenolol-based-regimen group

- Group receiving amlodipine-based regimen had nonsignificant 10% reduction in primary outcome (nonfatal MI plus fatal CHD) and significant reductions in nearly all secondary CV endpoints and new-onset diabetes

Up-titration performed for patients not achieving a BP of <140/90 mmHg
(<130/80 mmHg for patients with diabetes or renal insufficiency)

*β-blockers, α-blockers, clonidine, loop diuretics

## Patient baseline demographics

<table>
<thead>
<tr>
<th></th>
<th>Benazepril/amlodipine (n = 5744)</th>
<th>Benazepril/HCTZ (n = 5762)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>3448 (60.0)</td>
<td>3515 (61.0)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>2296 (40.0)</td>
<td>2246 (39.0)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>4817 (83.9)</td>
<td>4795 (83.2)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>697 (12.1)</td>
<td>719 (12.5)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>300 (5.2)</td>
<td>323 (5.6)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>230 (4.0)</td>
<td>247 (4.3)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, years</td>
<td>68.4</td>
<td>68.3</td>
</tr>
<tr>
<td>≥65, n (%)</td>
<td>3813 (66.4)</td>
<td>3827 (66.4)</td>
</tr>
<tr>
<td>≥70, n (%)</td>
<td>2363 (41.1)</td>
<td>2340 (40.6)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordic countries*, n (%)</td>
<td>1677 (29.3)</td>
<td>1676 (29.2)</td>
</tr>
<tr>
<td>United States, n (%)</td>
<td>4042 (70.7)</td>
<td>4059 (70.7)</td>
</tr>
</tbody>
</table>

*Denmark, Finland, Norway or Sweden

Kaplan-Meier curve for time to primary endpoint
(based on 1231 patients with primary events)

*Hazard ratio (95% confidence interval): 0.80 (0.72, 0.90)
CV = cardiovascular; HCTZ = hydrochlorothiazide
# ACCOMPLISH Study

## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>No Diabetes</th>
<th>All Diabetes</th>
<th>High Risk Diabetes**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>4559</td>
<td>6946</td>
<td>2842</td>
</tr>
<tr>
<td>Male</td>
<td>3,009 (66%)*</td>
<td>3,954 (57%)</td>
<td>1,830 (64%)*</td>
</tr>
<tr>
<td>Female</td>
<td>1,550 (34%)*</td>
<td>2,992 (43%)</td>
<td>1,012 (36%)*</td>
</tr>
<tr>
<td>Age</td>
<td>69.8 (7.0)*</td>
<td>67.5 (6.6)</td>
<td>66.9 (7.2)*</td>
</tr>
<tr>
<td>Age ≥ 65 yrs</td>
<td>3,344 (73%)*</td>
<td>4,296 (62%)</td>
<td>1,668 (59%)*</td>
</tr>
<tr>
<td>Caucasian</td>
<td>4,075 (89%)*</td>
<td>5,537 (80%)</td>
<td>2,277 (80%)</td>
</tr>
<tr>
<td>Black</td>
<td>374 (8%)*</td>
<td>1042 (15%)</td>
<td>429 (15%)</td>
</tr>
</tbody>
</table>

* Significant differences from “All Diabetes” cohort
** Patients with diabetes and history of cardiac events, stroke, or renal disease

Values are absolute numbers (%) or mean (SD)

ACCOMPLISH Study

**Primary Outcome* in Treatment Groups**

*Time to first event, defined as a composite of CV events or death from CV causes*

- **Non-Diabetes**
  - B + H (events = 296)
  - B + A (events = 245)
  - N = 4,559
  - \( p = .020 \)
  - RRR = 18%

- **All Diabetes**
  - B + H (events = 383)
  - B + A (events = 307)
  - N = 6,946
  - \( p = .003 \)
  - RRR = 21%

- **High Risk Diabetes**
  - B + H (events = 244)
  - B + A (events = 195)
  - N = 2,842
  - \( p = .007 \)
  - RRR = 23%


B=benazepril; A=amlodipine; H=hydrochlorothiazide; RRR=relative risk reduction
# ACCOMPLISH Study

## End Points in All Patients With Diabetes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Favors B+A</th>
<th>Favors B+H</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point*</td>
<td></td>
<td></td>
<td>0.79 (0.68 – 0.92)</td>
<td>.003</td>
</tr>
<tr>
<td>Fatal and non-fatal MI</td>
<td></td>
<td></td>
<td>0.85 (0.63 – 1.15)</td>
<td>.283</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td>0.91 (0.65 – 1.28)</td>
<td>.607</td>
</tr>
<tr>
<td>Cardiovascular (CV) death</td>
<td></td>
<td></td>
<td>0.84 (0.60 – 1.18)</td>
<td>.312</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td></td>
<td></td>
<td>0.80 (0.66 – 0.97)</td>
<td>.024</td>
</tr>
<tr>
<td>Clinical coronary event**</td>
<td></td>
<td></td>
<td>0.73 (0.57 – 0.94)</td>
<td>.013</td>
</tr>
<tr>
<td>CV death + MI + stroke</td>
<td></td>
<td></td>
<td>0.84 (0.68 – 1.03)</td>
<td>.085</td>
</tr>
<tr>
<td>Hospitalized HF</td>
<td></td>
<td></td>
<td>1.11 (0.80 – 1.54)</td>
<td>.545</td>
</tr>
<tr>
<td>All-cause death</td>
<td></td>
<td></td>
<td>1.02 (0.80 – 1.29)</td>
<td>.887</td>
</tr>
<tr>
<td>Renal end point†</td>
<td></td>
<td></td>
<td>0.53 (0.45 – 0.63)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

* Time to first event, defined as a composite of CV events or death from CV causes

** MI + Hospitalized unstable angina + Sudden cardiac death

† > 50% increase in serum creatinine with final value above normal range

MI=myocardial infarction; HF=heart failure;
B=benazepril; A=amlodipine; H=hydrochlorothiazide

Adapted from:
Weber MA, et al. 
*J Am Coll Cardiol.* 2010;56:77-85.
# American Society of Hypertension Evidenced Based
**Fixed Dose Antihypertensive Combinations**

<table>
<thead>
<tr>
<th>Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ACE inhibitor/diuretic*</td>
</tr>
<tr>
<td>• ARB/diuretic*</td>
</tr>
<tr>
<td>• ACE inhibitor/CCB*</td>
</tr>
<tr>
<td>• ARB/CCB*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Beta blocker/diuretic*</td>
</tr>
<tr>
<td>• CCB (dihydropyridine)/β-blocker</td>
</tr>
<tr>
<td>• CCB/diuretic</td>
</tr>
<tr>
<td>• Renin inhibitor/diuretic*</td>
</tr>
<tr>
<td>• Renin inhibitor/ARB*</td>
</tr>
<tr>
<td>• Thiazide diuretics/K+ sparing diuretics*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Less Effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ACE inhibitor/ARB</td>
</tr>
<tr>
<td>• ACE inhibitor/β-blocker</td>
</tr>
<tr>
<td>• ARB/β-blocker</td>
</tr>
<tr>
<td>• CCB (nondihydropyridine)/β-blocker</td>
</tr>
<tr>
<td>• Centrally acting agent/β-blocker</td>
</tr>
</tbody>
</table>

* SPC available in US

Summary

• Initial combination therapy is indicated for anyone who has a BP >20/10 above 140/90 mmHg who is already on a low sodium diet

• Upcoming JNC 8 will address specific recommendations on initial combination therapy for CV risk reduction/mortality