The Heart of HEARTS: Step by Step Treatment Protocol and the Selection of Antihypertensive Drugs in Fixed-Dose Combinations

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Barriers to Blood Pressure Control

**Patient**
- Limited access to treatment
- **POOR ADHERENCE TO TREATMENT**

**Health Care Provider**
- Raised blood pressure attributed to “white coat” hypertension
- Reluctance to treat an asymptomatic condition
- Lack of adequate time with patient
- **THERAPEUTIC INERTIA**
- **LACK OF ADHERENCE TO TREATMENT GUIDELINES**

**Health Systems**
- Failure to delegate responsibility to non-physicians
- Inappropriate follow-up
- Absence of feedback to clinicians
- Issues related to supply, distribution, and cost of medications
- **COMPLEX MEDICATION REGIMENS**
Advantages of Combination Pharmacologic Therapy

➢ Most eventually need multiple drugs
➢ Greater efficacy (additive or synergistic)-improves blood pressure control rates
➢ Allows lower dosages of each of the 2 drugs
  • More effective than a higher dose of either single drug
  • Reduced side effects
➢ Simplified treatment regimen: better adherence
➢ Reduces clinical inertia
➢ When complementary drug classes are chosen, lowers BP equally across diverse demographic groups
➢ Economic benefits
  • Lower health care costs and fewer office visits
Initial Classes of Medications for the Management of Hypertension

β-blockers should be included in the regimen if there is a compelling indication for a β-blocker.
Combination treatment, as two or more individual pills or fixed-doses in one pill (FDC or SPC) in hypertension

- FDC in the initial treatment of hypertension is **NOT NEW**!

- U.S. Veterans Administration Cooperative Studies

- Used: Hydrochlorothiazide + Reserpine + Hydralazine

- All three agents were later developed in a single pill (FDC)-Ser-Ap-Es

Most Guidelines Recommend the Initiation of Two Drugs at Some Point in Hypertension Management

➢ Consider initiating therapy with two drugs in patients whose BP is >20/10 mmHg above goal

“thereby increasing the likelihood of achieving goal BP in a timely manner....Multi-drug combinations often produce greater BP reduction at lower doses of the component agents resulting in fewer side effects. The use of fixed dose combinations may be more convenient and simplify the treatment regimen....”

➢ More than 2/3 of patients will require two or more agents

JNC-7 HTN Guideline
ACC/AHA 2017 HTN Guideline
The guidelines strongly proposed to concentrate on improving the current blood pressure treatment control rates.

Proposed the use of combination pharmacologic therapy and where possible fixed-dose combination therapy (FDC) even as initial treatment.
Fixed-Dose Combination Pharmacologic Therapy to Improve Hypertension Control Worldwide: Clinical perspective and policy implications

Journal of Clinical Hypertension Volume 21, Issue 1: 2019

Donald J DiPette MD, Jamario Skeete, MD, Emily Ridley Pharm D, Norm RC Campbell MD, Patricio Lopez-Jaramillo MD, PhD, Sandeep P. Kishore MD, PhD, Marc G Jaffe, MD, Antonio Coca, MD, PhD, Raymond R Townsend MD, Pedro Ordunez, MD, PhD
**Ideal Characteristics of Fixed Dose Combination (FDC) Medications in the Treatment of Hypertension**

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tbody>
<tr>
<td>High Efficacy (blood pressure reduction)</td>
</tr>
<tr>
<td>Additive/synergistic blood pressure reduction</td>
</tr>
<tr>
<td>Supported by clinical trials</td>
</tr>
<tr>
<td>Mitigation of side-effects of either or both individual agents</td>
</tr>
<tr>
<td>Potential for wide availability and affordability</td>
</tr>
<tr>
<td>Safe and efficacious in diverse demographic settings (i.e. race, ethnicity, sex, geography, salt-sensitivity)</td>
</tr>
<tr>
<td>Daily dosing formulation</td>
</tr>
<tr>
<td>Scored tablet with multiple doses which permit split tablet dosing and easy titration</td>
</tr>
</tbody>
</table>

Steps in Selecting the Ideal Fixed Dose Combination Medication (DiPette et al. JCH, 2019)

1. Select the preferred and acceptable pharmacologic drug classes.
2. Select the preferred and acceptable pharmacologic agents within each drug class.
3. Select which preferred and acceptable combinations are available and affordable.
Which Classes of Two-Medication Combinations? (DiPette et al. JCH 2019)

• Renin angiotensin aldosterone system (RAAS) inhibitor-Calcium channel blocker (CCB): **Preferred** in the following order:

1. Angiotensin-Receptor Blocker (ARB)-CCB
2. Angiotensin-Converting Enzyme inhibitor (ACEI)-CCB
3. ARB-Thiazide or Thiazide-like diuretic (DIU)
4. ACEI-DIU

• CCB-DIU and all others **Not-Preferred** unless other indications
ACE Inhibitors vs. Angiotensin Receptor Blockers

- Cough and angioedema associated with ACE inhibitors is **not** seen with Angiotensin Receptor Blockers

- Incidence of **cough** with ACE inhibitors is more common in:
  - Age > 65 years old
  - Women
  - Persons of **African** or **Chinese** descent

- Incidence of **angioedema** with ACE inhibitors is more common in:
  - Age > 65 years old
  - Women
  - Persons of **African** or **Hispanic** descent

ACCOMPLISH Trial

- Benazepril and Amlodipine versus Benazepril plus Hydrochlorothiazide
- 11,506 high-risk patients
- Follow-up: 36 months (stopped early)

ACCOMPLISH TRIAL: Benazepril plus Amlodipine or Hctz for HTN in High-Risk Patients

**Figure 2.** Kaplan–Meier Curves for Time to First Primary Composite End Point.
There were 552 patients with events (9.6%) in the benazepril–amlodipine group, as compared with 679 patients with events (11.8%) in the benazepril–hydrochlorothiazide group. The relative risk reduction was 20% (hazard ratio, 0.80; 95% CI, 0.72 to 0.90; P<0.001).

*NEJM.2008;359(23):2417.*
## Building the Ideal Medication Combination
*(DiPette et al. J Clinical Hypertension 2019)*

### ARB + CCB
<table>
<thead>
<tr>
<th>Azilsartan OR Telmisartan OR Irbesartan</th>
<th>Amlodipine</th>
</tr>
</thead>
</table>

### ACE-I + CCB
| Lisinopril OR Ramipril OR Benazepril   | Amlodipine |

### ARB + Thiazide/Thiazide Like Diuretic
| Azilsartan OR Telmisartan OR Irbesartan | Chlorthalidone OR Hydrochlorothiazide |

### ACE-I + Thiazide/Thiazide Like Diuretic
| Lisinopril OR Benazepril                | Chlorthalidone OR Hydrochlorothiazide |
Adult Hypertension

BLOOD PRESSURE (BP) GOAL
≤ 139 / 89 mm Hg – All Adult Hypertension

ACE-INHIBITOR¹ / THIAZIDE DIURETIC
Lisinopril / HCTZ
(Advance as needed)
20 / 25 mg X ½ daily
20 / 25 mg X 1 daily
20 / 25 mg X 2 daily
Pregnancy Potential: Avoid ACE-Inhibitors¹

If pregnancy potential

THIAZIDE DIURETIC
HCTZ 25 mg ➔ 50 mg
OR
Chlorthalidone 12.5 mg ➔ 25 mg

If not in control

CALCIALUM CHANNEL BLOCKER
Add amlodipine 5 mg X ½ daily ➔ 5 mg X 1 daily ➔ 10 mg daily

If not in control

SPIRONOLACTONE OR BETA-BLOCKER
IF on thiazide AND eGFR ≥ 60 mL/min/1.73m² AND K < 4.5
Add spironolactone 12.5 mg daily ➔ 25 mg daily
OR
Add atenolol 25 mg daily ➔ 50 mg daily (Keep heart rate > 55)

NNT CVA² = 63
NNT MI² = 86
NNT CVA or MI² = 36

Go, AS et al J Am Coll Cardiol. 2013
Standardized Treatment Protocols Can Help Reduce Disparate Outcomes Kaiser Permanente Southern California

“Across all ages, races, and sexes, hypertension control exceeded

85.0% BP control

86.6% BP control

87.9% BP control

81.4% BP control

85.0% BP control

85.0% BP control

86.6% BP control

Non Hispanic White (26%)

Hispanic (39%)

Asian/Pacific Islanders (9%)

Black (8%)

Others and Unknown (19%)

DOI: http://dx.doi.org/10.5888/pcd11.140173
# HEARTS in the Americas: Early Results

<table>
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<th></th>
<th>BARBADOS</th>
<th>CHILE</th>
<th>COLOMBIA</th>
<th>CUBA</th>
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<tbody>
<tr>
<td>Secured political commitment</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Demonstration site in place</td>
<td>✓ (2)</td>
<td>✓ (2)</td>
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<tr>
<td>Target (adult) population size</td>
<td>21,000</td>
<td>50,000</td>
<td>75,000</td>
<td>26,000</td>
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<tr>
<td>Staff, trained and certified in HT measuring &amp; PAHO virtual course</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td><strong>Algorithm defined</strong></td>
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<tr>
<td><strong>Core set of medications</strong></td>
<td>✓</td>
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<tr>
<td>• Fixed dose combination</td>
<td>(LIS + HTZ)</td>
<td>(VAL-AMP)</td>
<td>(LOS-HTZ)</td>
<td>(ENA-HTZ)</td>
</tr>
<tr>
<td>• Registry completeness (%)</td>
<td>45% &amp; 49%</td>
<td>87%</td>
<td>73%</td>
<td>89%</td>
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<td>Redistribution of Task well defined</td>
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Two pill or fixed-dose (FDC or SPC) combination treatment in the initial treatment of hypertension

Conclusions

• Strongly consider combination therapy especially fixed-dose combinations (FDC or SPC) in the initial treatment of hypertension
• Rationale is partially based on the Kaiser Permanente, the HEARTS in the Americas (Barbados, Cuba, Chile, Colombia), and Global HEARTS Initiative (HEARTS Technical Package) experience.
• Fixed dose or single pill combination medications are now on the WHO Essential Medication List.
• ACC/AHA (2017) and the ESC and ESH (2018) guidelines recommend strong consideration be given to the initial use of combination therapy.
Recommended Reading


Thank You