The emerging role of single pill combination therapy in the treatment of hypertension:

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Improvements in BP control

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Unaware</td>
<td>43</td>
<td>13.7</td>
<td>17.4</td>
</tr>
<tr>
<td>Aware, Not Treated</td>
<td>22.4</td>
<td>5.8</td>
<td>3.5</td>
</tr>
<tr>
<td>Treated, Not Controlled</td>
<td>21.4</td>
<td>14.7</td>
<td>14.4</td>
</tr>
<tr>
<td>Treated and Controlled</td>
<td>13.2</td>
<td>65.7</td>
<td>64.6</td>
</tr>
</tbody>
</table>
Nonadherence: the major determinant of the bp control gap

- Nonadherence (aka noncompliance, nonpersistence, etc) is a major problem

- Within 1 year, ~50% of patients overall discontinue use of drugs, including antihypertensives

- An additional ~35% discontinue treatment within 2 years

Nonadherence: the first case report

“Adam and Eve expelled from the Garden of Eden”
Therapeutics-Based Barriers to Adherence

**Patient-Centered Factors**
- Complex dosing regimens
- Drug switching (therapeutic turbulence)

**Health Care Professional-Centered Factors**
- Increasingly complex treatment algorithms
- Multiple (sometimes divergent) “voices”
- Resistance in treating to BP targets (therapeutic inertia)
The Hidden Cost of Frequent Drug Changes: Therapeutic Turbulence

Patients who are prescribed frequent drug changes (i.e., more switches) are less likely to persist with therapy.

<table>
<thead>
<tr>
<th>No. of changes in first 6 months of treatment</th>
<th>Risk of not persisting (and 95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.07 (0.94-1.22)</td>
</tr>
<tr>
<td>2 or more</td>
<td>1.25 (1.12-1.37)</td>
</tr>
</tbody>
</table>

Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data.
J. Jaime Caro,*† MD, CM; Jeanne L. Speckman,* MSc; Maribel Salas,* MS, MD; Gabriel Raggio,* ScD; Joseph D. Jackson,‡ PhD. CMAJ 1999;160:41-6
Therapeutic Inertia Predicts Poor BP Control

% with BP < 140/90 mm Hg

Quintiles of Therapeutic Inertia Score

Prior to STITCH, CHEP recommended limited use of single pill combinations

“Adherence can be improved by……replacing 2 antihypertensive agents with a fixed dose combination provided it is the same combination the patient is already taking” (except when BP > 20/10 over target)

Should single pill combinations be utilized on a more generalized basis?
As unrestricted first line therapy?
Rationale for the Increased Use of (low dose) Single Pill Combinations

- Better antihypertensive benefit: adverse effect ratio
- Improved adherence
- ? More effective
At low doses the antihypertensive effects of drugs are (mostly) additive

![Bar chart showing BP reduction (mm Hg) for one, two, and three drugs. SBP and DBP are indicated.](image)

Adapted from Law, M R et al. BMJ 2003;326:1427
Ratio of Incremental SBP lowering effect at "standard dose"– Combine or Double?

Wald et al, Combination Versus Monotherapy for Blood Pressure Reduction, The American Journal of Medicine, Vol 122, No 3, March 2009
At low doses the adverse effects of most antihypertensives approach those of placebo.

Calcium Channel Blockers

Thiazides

Dose as a proportion of the standard dose

Law, M R et al. BMJ 2003;326:1427
What adverse effects DO diuretics or ACE-I/ARBs have when taken separately that low-dose single pill combinations DON’T

- More K problems
- More Na problems
- More insulin resistance
- Less “global effectiveness” (across races)
Persistence With Single Pill Antihypertensive Combination

P<0.05 versus fixed-dose combo Dezii C. Managed Care. 2000;9:S2.
CHEP Guidelines: Treatment of Systolic-Diastolic Hypertension without Other Compelling Indications

TARGET <140 mmHg systolic AND < 90 mmHg diastolic

CONSIDER
• Nonadherence?
• Secondary HTN?
• Interfering drugs or lifestyle?
• White coat effect?

Too Complex?????

Lifestyle modification therapy

Dual Combination

Triple or Quadruple therapy

* Not indicated as first line therapy for patients over 60 yrs
V. Treatment of Adults with Systolic/Diastolic Hypertension without Other Compelling Indications

If we restrict ourselves to only 5 classes of drugs, and assume 2 doses per drug, there are:

\[ \frac{n! \times 2^r}{r!(n-r)!} = 80 \]

Combinations of 3 drugs!

If we assume that the order in which we add antihypertensive drugs matters, then:

\[ \frac{n! \times 2^r}{(n-r)!} = 480 \]

Possible Permutations of 3 drugs!
“Are you just pissing and moaning, or can you verify what you’re saying with data?”
45 Primary Care Practices: cluster randomization

27 practices

2048 patients

18 practices
Initial therapy with a low dose ACE/diuretic or ARB/diuretic combination

Is blood pressure controlled?

Yes

Continue with current therapy

No

Up-titration of combination therapy successively to the highest dose

Yes

Continue with current therapy

No

Add calcium channel blocker and up-titrate

Yes

Continue with current therapy

No

Add an α-blocker, β-blocker or spironolactone
Primary Outcome: Proportion of Practice at BP Target

P=0.03

Absolute Difference in BP control rate= 12%
Secondary Analyses: Systolic Blood Pressure Change

<table>
<thead>
<tr>
<th></th>
<th>Baseline BP (mmHg)</th>
<th>6-month BP (mmHg)</th>
<th>BP Change (mmHg)</th>
<th>Std Dev</th>
<th>Std Err</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUIDELINE Care</td>
<td>153.4</td>
<td>136.1</td>
<td>-17.2 (-19.8, -15.6)</td>
<td>5.32</td>
<td>1.02</td>
</tr>
<tr>
<td>STITCH Care</td>
<td>155.2</td>
<td>132.2</td>
<td>-22.9 (-25.6, -20.4)</td>
<td>5.22</td>
<td>1.23</td>
</tr>
</tbody>
</table>

P=0.03

P=0.002
Secondary Analyses: Diastolic Blood Pressure Change

<table>
<thead>
<tr>
<th></th>
<th>Baseline BP (mmHg)</th>
<th>6-month BP (mmHg)</th>
<th>BP Change (mmHg)</th>
<th>Std Dev</th>
<th>Std Err</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUIDELINE Care</td>
<td>87.7</td>
<td>79.6</td>
<td>-8.2 (-9.5, -7.1)</td>
<td>3.1</td>
<td>0.6</td>
</tr>
<tr>
<td>STITCH Care</td>
<td>88.1</td>
<td>77.4</td>
<td>-10.6 (-12.0, -8.7)</td>
<td>3.3</td>
<td>0.8</td>
</tr>
</tbody>
</table>

P=0.04

P=0.11
Secondary Analyses: Combination Drug Prescription

![Bar Chart]

- **GUIDELINE Care**: 15.5%
- **STITCH Care**: 85.0%

P<0.001
Drug Intensity: Average Number of “Standard Doses” Prescribed at 6 Months

P=0.06

# of Molecules

GUIDELINE Care

STITCH Care
XIII. Adherence Strategies for Patients

1. Adherence to an antihypertensive prescription can be improved by a multipronged approach (Table 5).

...Replacing multiple pill antihypertensive combinations with single pill combinations!
Adherence Strategies for Patients

1. Adherence to an antihypertensive prescription can be improved by a multipronged approach.

...Replacing multiple pill antihypertensive combinations with single pill combinations!
Is there a preferred single pill combination?
In ACCOMPLISH Both Treatment Arms had Similar BP

But ACE-I/CCB Reduces CV Morbidity/Mortality Significantly More Than ACE-I/HCTZ

552 (9.6%) patients with events in the benazepril-amlodipine group vs 679 (11.8%) in the benazepril-HCTZ group (RR 20%; hazard ratio 0.80; 95% CI 0.72–0.90; p < 0.001)

# Hazard Ratios of Adjudicated Primary Endpoints (ACCOMPLISH)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of death from cardiovascular causes and cardiovascular events</td>
<td>0.80 (0.72–0.90)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>0.80 (0.62–1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>Myocardial infarction (fatal or non-fatal)</td>
<td>0.78 (0.62–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke (fatal or non-fatal)</td>
<td>0.84 (0.65–1.08)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>0.75 (0.50–1.10)</td>
<td>0.14</td>
</tr>
<tr>
<td>Coronary revascularization procedure</td>
<td>0.86 (0.74–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Resuscitation after sudden cardiac arrest</td>
<td>1.75 (0.73–4.17)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Recommendations for hypertensive patients with coronary artery disease (or at high risk)

In high risk patients, when combination therapy is being used, the combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a diuretic (Grade A).
Bottom Lines

- There remains a gap between “clinical trial” blood pressure control and “real life”
- Part of that gap relates to the complexity of dosing regimens
- A simplified algorithm approach utilizing low dose single pill combinations may help to close the gap (although don’t expect world peace)
- The *unequivocal* identification of preferred partners has yet to be *ACCOMPLISHED*