Triple Combination in HTN Management

By
Prof. M. Wafaie Aboleineen, MD, FACC

Stroke and Ischemic Heart Disease (IHD) Mortality Rate in Each Decade of Age, Versus Usual Systolic BP at the Start of that Decade

*Floating absolute risk and 95% CI

Approximately 70% of Patients* in Europe Do Not Reach BP Goal

*Treated for hypertension
BP goal is <140/90 mmHg

BP. has Multiple Regulatory Pathways

Accordingly... Needs multiple medications with different MOA to be controlled
Combination Choice Based on:

- Maximum CV Protection
- Maximum BP Control

Adding an Antihypertensive Agent is More Effective Than Titrating

Combining drugs from 2 different classes 5 times greater than doubling the dose of 1 drug

Conclusions from a meta-analysis comparing combination antihypertensive therapy with monotherapy in over 11,000 patients from 42 trials

One-third of patients will require 3 or more antihypertensive agents to achieve BP control

But

Compliance Decreases as the Number of Medications Increases

<table>
<thead>
<tr>
<th>Number of pre-existing prescription medications</th>
<th>Unadjusted odds ratio for compliance (&gt;80%) to both antihypertensive therapy and LLT (95% CI; p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.73 (1.56–1.90; p&lt;0.001)</td>
</tr>
<tr>
<td>1</td>
<td>1.25 (1.13–1.39; p&lt;0.001)</td>
</tr>
<tr>
<td>2</td>
<td>0.96 (0.86–1.06; p=0.41)</td>
</tr>
<tr>
<td>3–5</td>
<td>0.87 (0.79–0.94; p&lt;0.001)</td>
</tr>
<tr>
<td>≥6</td>
<td>0.65 (0.59–0.71; p&lt;0.001)</td>
</tr>
</tbody>
</table>

Retrospective cohort study of MCO population. N=8,406 patients with hypertension who added antihypertensive therapy and LLT to existing prescription medications within a 90-day period. Compliance to concomitant therapy: sufficient antihypertensive and LL prescription medications to cover ≥80% of days per 91-day period. CI=confidence interval; LLT = lipid-lowering therapy.
Non-persistence with Antihypertensive Therapy is Associated with an Increased Risk of Myocardial Infarction and Stroke

Data based on 77,193 new users of antihypertensive treatment identified in the PHARMO record linkage system

Persistent patients (Reference)

Adjusted* RR for non-persistent patients (95% CI)

Stroke

Adjusted RR for non-persistent patients

Acute myocardial infarction


*Adjusted for gender, age, type of prescriber, use of cardiovascular co-medication, initial antihypertensive therapy, number of different antihypertensive classes during the first 2 years of therapy


28%

15%

SPC

improves patient’s compliance and helps reaching the BP goal
Reducing the pill burden with a SPC improves compliance with therapy

- Compliance with a single-pill combination is greater than that with an equivalent free combination\(^1\)
- More patients remain on therapy after one year with a single-pill combination compared with free combination therapy (p<0.05)\(^2\)

*One pill: single-pill combination of amlodipine and benazepril; two pills: free combination of dihydropyridine calcium-channel blocker and angiotensin-converting enzyme inhibitor. Compliance measured by the proportion of days when the patient is in possession of the medication.


European Guidelines Recommend use of Single-pill Combination Therapy

- 2009 European guidelines state:
  ‘Whenever possible, use of fixed dose (or single pill) combinations should be preferred, because simplification of treatment carries advantages for compliance to treatment’

- 2013 European guidelines recommends:
  “Use of combinations of two antihypertensive drugs at fixed doses in a single tablet”

2013 ESH/ESC Guidelines for the management of arterial hypertension
Single pill combination-based treatment:

- Leads to **improved adherence** (and decreased medical resource utilization)
  Taylor AA, Shoheiber O. *Congest Heart Fail*. 2003;9:324-32

- Leads to **better blood pressure control rates**

- Leads to **reduced complication rates**.

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**Rational Combinations**..
Possible combinations of classes of antihypertensive drugs

- Thiazide diuretics
- Beta-blockers
- Angiotensin-receptor blockers
- Calcium antagonists
- ACE inhibitors
- Other Antihypertensives

**Green continuous lines:** preferred. **Green dashed lines:** useful combinations with some limitations. **Black dashed line:** possible combinations (only DHP calcium antagonists should normally be combined with beta-blockers). **Red continuous line:** not recommended combination.

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**NICE Guidelines 2011 for the Treatment of Hypertension**

A - ACE I or ARB
C - CCB
D - Thiazide like Diuretic

**Step 1**
- A + C

**Step 2**
- A + C

**Step 3**
- A + C + D

**Step 4**
- A + C + D + Consider further diuretic or alpha or Beta Blocker.
  - Consider seeking specialist advice

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The Efficacy and Safety of Triple vs Dual Combination of Angiotensin II Receptor Blocker and Calcium Channel Blocker and Diuretic: A Systematic Review and Meta-Analysis

Pinar Kızılrmak, MD, Ph.D,1 Mehmet Berktas, MD MCR,2 Yagiz Uresin, MD,1 Ökan Bülent Yıldız, MD3

224 studies and 7563 patients

Many hypertensive patients require ≥2 drugs to achieve blood pressure targets. This study aims to review and analyze the clinical studies conducted with dual or triple combination of angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), and diuretics. Medical literature between January 1990 and April 2012 was reviewed systematically and data from eligible studies were abstracted. Data were analyzed using random-effects models. Of the 224 studies screened, 7563 eligible patients from 11 studies were included. Triple combinations of ARBs (valsartan or irbesartan), CCBs (amlodipine), and diuretics (hydrochlorothiazide) at any dose provided more blood pressure reduction in office and 24-hour ambulatory measurements than any dual combination of these molecules (P<.0001 for both). Significantly more patients achieved blood pressure targets with triple combinations (odds ratio, 2.16; P=.0001). Triple combinations did not increase adverse event risk (odds ratio, 0.96; P=.42). Triple combinations at any dose seem to decrease blood pressure more effectively than dual combination of the same molecules without any remarkable risk elevation for adverse events. Further prospective studies evaluating the efficacy and safety of triple combinations, especially in the form of single pills, are required. J Clin Hypertens (Greenwich) 2013;15:199-200. ©2012 Wiley Periodicals, Inc.

Efficacy

Clinical Evidence of Valsartan/Amlodipine/HCTZ
**Mean Change from Baseline in MSSBP (mmHg)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LSM change in MSSBP from baseline (mmHg)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine/Valsartan/HCTZ 10/320/25 mg</td>
<td>-39.7*</td>
<td>583</td>
</tr>
<tr>
<td>Valsartan/HCTZ 320/25 mg</td>
<td>-32.0</td>
<td>559</td>
</tr>
<tr>
<td>Amlodipine/Valsartan 10/320 mg</td>
<td>-33.5</td>
<td>568</td>
</tr>
<tr>
<td>HCTZ/amlodipine 25/10 mg</td>
<td>-31.5</td>
<td>561</td>
</tr>
</tbody>
</table>

* p<0.0001 versus all other combinations

HCTZ = hydrochlorothiazide  
LSM = least squares mean  
MSSBP = mean sitting systolic BP  
Intent-to-Treat population (N=2,271)  

Calhoun et al. Hypertension 2009;54:32–9

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**Triple Combination Therapy with Amlodipine/Valsartan/HCTZ: Reaching the Full BP Lowering Effect after 2 Weeks**

Week 2 of Treatment

Calhoun et al. Hypertension 2009;54:32–9
**Triple Combination Therapy with Amlodipine/Valsoartan/HCTZ Provides Powerful BP Reductions Over 24 Hours**

- ASBP = ambulatory systolic blood pressure
- N=283 patients
- MSBP/MSDBP=165/105
- MABP=150/95

**Baseline data**

**24-hour treatment data**

- MABP with triple combination was reduced by 30/20 mmHg

Lacourcière et al. Poster presented at 19th Scientific Meeting of the European Society of Hypertension, June 2009, Milan, Italy

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**Triple Combination Therapy with Amlodipine/Valsoartan/HCTZ: Get More Patients to BP Goal**

- BP control rate was **85.1%** (p=0.0001), meaning that **9 out of 10** patients who were not controlled on dual therapy reached the BP Goal

* Novartis is not recommending indications outside the approved BP in Egypt*
Clinical Evidence of Valsartan/Amlodipine/HCTZ

Valsartan and Amlodipine, A Wealth of Cardiovascular Outcomes Data

<table>
<thead>
<tr>
<th>Valsartan</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>VALUE1</td>
<td>PREVENT1</td>
</tr>
<tr>
<td>VALIANT2</td>
<td>CAMELOT2</td>
</tr>
<tr>
<td>Val-HeFT3-5</td>
<td>ASCOT-BPLA/CAFE3,4</td>
</tr>
<tr>
<td>DROP7</td>
<td>ALLHAT5</td>
</tr>
</tbody>
</table>


* Novartis is not recommending indications outside the approved BPI in Egypt
### Low-Dose Diuretics Reduce Cardiovascular Disease Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
<th>Favors Low-Dose Diuretics</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.79 (0.69-0.92)</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CHF</td>
<td>0.51 (0.42-0.62)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.71 (0.63-0.81)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CVD Events</td>
<td>0.76 (0.69-0.83)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CVD Mortality</td>
<td>0.81 (0.73-0.92)</td>
<td>0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>0.90 (0.84-0.96)</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**CHD** = coronary heart disease  
**CHF** = congestive heart failure  
**CI** = confidence interval  
**CVD** = cardiovascular disease


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### Annals of Internal Medicine

**Chlorthalidone Versus Hydrochlorothiazide for the Treatment of Hypertension in Older Adults**  
A Population-Based Cohort Study

Irfan A. Dhalla, MD, MSc; Tara Gomes, MHSc; Zhan Yao, MD, MS; Jeff Nagge, PharmD; Navindra Persaud, MD, MSc; Chelsea Hellings, MSc; Muhammad M. Menda, PharmD, MA, MPH; and David N. Jaurin, MD, PhD.

- Propensity score–matched observational cohort study with up to 5 years of follow-up in Ontario, Canada.
- 10,384 patients newly treated with chlorthalidone and 19,489 patients newly treated with hydrochlorothiazide.

**Implication**

Hydrochlorothiazide may be superior to chlorthalidone for treating uncomplicated hypertension because it is associated with less hypokalemia and hyponatremia, at least in commonly prescribed doses.

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**LVH is an independent risk factor for reducing survival**

LVH: Left Ventricular Hypertrophy

The more decrease in Left Ventricular Mass Index, The more protection

**The reduction in LVH significantly greater with Valsartan than Ramiprilm.**

LVMI= left ventricular mass index

Novartis is not recommending indications outside the approved BPI in Egypt

**ESC, ESH 2013, Therapeutic strategies in HTN patients with heart disease**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that all patients with LVH receive antihypertensive agents.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers and calcium antagonists.</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

2013 ESH/ESC Guidelines for the management of arterial hypertension
EXCITE
(The clinical ExperienCe of amlodIpine and valsarTan in hypErtension) Study
A Large Multinational Study


Study Objective

➢ To evaluate the effectiveness, safety and tolerability, and treatment adherence with Aml/Val and Aml/Val/HCT in patients with arterial hypertension in a real-world setting.

**Patient Demographics**

![Bar chart showing patient demographics](image)


**Study Design**

- Prospective, multicentral, multinational, observational, open-label trial.

n= 9,794

Aml/Val n= 8,603

Aml/Val/HCT n= 1,191

Duration 26 weeks ± 8 weeks

End Points

➢ **Primary EP**: Change from baseline in \( msSBP \) & \( msDBP \) for a period of 26±8 weeks

➢ **Secondary EP**:
  ✓ Proportion of patients achieving SBP/DBP <140/90 mmHg for (<130/80 mmHg for diabetic).
  ✓ Proportion of patients achieving a BP response (SBP <140 mmHg or a reduction of ≥20 mmHg or DBP <90 mmHg or a reduction of ≥10 mmHg)
  ✓ Safety & tolerability (incidence of edema & monitoring AEs & SAEs).
  ✓ Treatment adherence.

\( msSBP \): mean sitting SBP, \( msDBP \): mean sitting DBP, EP: end point, AEs: adverse events, SAEs: serious adverse events


Results:

I. **Change from baseline in msSBP & msDBP (AML/VAL)**

<table>
<thead>
<tr>
<th>Ami/Val dose (mg)</th>
<th>overall</th>
<th>5/80</th>
<th>5/160</th>
<th>10/160</th>
<th>5/320</th>
<th>10/320</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLBP</td>
<td>160.9/97.1</td>
<td>155.0/92.6</td>
<td>160.4/97.5</td>
<td>166.5/99.4</td>
<td>161.8/96.4</td>
<td>169.1/103.3</td>
</tr>
<tr>
<td>EPBP</td>
<td>129.9/80.5</td>
<td>128.9/78.9</td>
<td>129.7/80.7</td>
<td>130.8/82.9</td>
<td>129.9/82.3</td>
<td></td>
</tr>
</tbody>
</table>

Change in msSBP & msDBP from baseline (mmHg)

<table>
<thead>
<tr>
<th>Change in msSBP &amp; msDBP from baseline (mmHg)</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-31</td>
<td>-16.6</td>
<td>-13.7</td>
</tr>
<tr>
<td>-26.1</td>
<td>-16.6</td>
<td>-13.7</td>
</tr>
<tr>
<td>-30.7</td>
<td>-16.6</td>
<td>-13.7</td>
</tr>
<tr>
<td>-35.5</td>
<td>-16.6</td>
<td>-13.7</td>
</tr>
<tr>
<td>-31</td>
<td>-16.6</td>
<td>-13.7</td>
</tr>
<tr>
<td>-39.2</td>
<td>-16.6</td>
<td>-13.7</td>
</tr>
</tbody>
</table>

SBP: baseline blood pressure. EPBP: end point blood pressure

**Results:**

I. Change from baseline in msSBP & msDBP (AML/VAL/HCT)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BLBP</td>
<td>165.8/97.7</td>
<td>164.1/97.3</td>
<td>166.6/97.2</td>
<td>169.6/98.2</td>
<td>171/100.2</td>
<td>189.2/106.5</td>
</tr>
<tr>
<td>Change in msSBP &amp; msDBP from baseline (mmHg)</td>
<td>-36.6</td>
<td>-35.2</td>
<td>-36.1</td>
<td>-39.7</td>
<td>-42</td>
<td>-42</td>
</tr>
</tbody>
</table>

BLBP: baseline blood pressure. EPBP: end point blood pressure


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**Results:**

II. Change from baseline in msSBP & msDBP according to baseline SBPP (AML/VAL)

<table>
<thead>
<tr>
<th>BL</th>
<th>140&lt;160</th>
<th>160&lt;180</th>
<th>≥180</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLBP</td>
<td>148.5/94.5</td>
<td>164.7/98.4</td>
<td>187.0/105.5</td>
</tr>
<tr>
<td>Change in msSBP &amp; msDBP from baseline (mmHg)</td>
<td>-20.5</td>
<td>-14.3</td>
<td>-17.6</td>
</tr>
</tbody>
</table>

Results (II of IV)

II. Change from baseline in msSBP & msDBP according to baseline SBPP (AML/VAL/HCT)

<table>
<thead>
<tr>
<th>SBPP (mmHg)</th>
<th>Baseline</th>
<th>Change in msSBP &amp; msDBP (mmHg)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>140-160</td>
<td>148.9/94.2</td>
<td>-20.5</td>
<td>-5.4</td>
</tr>
<tr>
<td>160-180</td>
<td>165.8/97.4</td>
<td>-14</td>
<td>-4.9</td>
</tr>
<tr>
<td>≥180</td>
<td>188.3/103.6</td>
<td>-18.5</td>
<td>-10.0</td>
</tr>
</tbody>
</table>


Results:

IV. Safety & Tolerability

✔ Aml/Val and Aml/Val/HCT were well tolerated.

✔ AEs were reported in 11.2% with Aml/Val & 6.1% with Aml/Val/HCT including oedema, peripheral oedema, headache and cough.

✔ Treatment adherence in 89.6% with Aml/Val & in 95.8% with Aml/Val/HCT of patients.

CONCLUSION

✓ SPC treatment with Aml/Val and Aml/Val/HCT provided statistically significant and relevant reductions in BP from baseline & were well-tolerated.

✓ Reductions in BP from baseline were observed across all Aml/Val dosages, severities of hypertension.


Take Home Message...

• Many patients do not achieve BP targets
• Multiple agents are often required for patients to achieve goal
• There is a wealth of evidence supporting the use of amlodipine, valsartan or diuretics separately or in combination.
• Triple therapy is supported by recent guidelines
For patients uncontrolled on Any Dual Therapy VAL/AML/HCT in single pill combination provides:

- Maximum CV Protection
- Maximum BP Control

Thank you