Effect of Patients Compliance in Hypertension Treatment Outcome

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Agenda

- Multiple medications are required in HTN management
- Role of SPC in improving patients adherence and compliance
- Single pill combination in guidelines
- Rational of combination therapy
- Evidence of triple combination
Multiple medications are required in HTN management

Hypertension Control Rates Are Slowly Improving: Not all treated HTN patients are controlled

*Controlled blood pressure was defined as <140/90 mm Hg and expressed as a % of all hypertensives. NHANES = National Health and Nutrition Examination Survey.

Since we are treating HTN we have to add new agents........ IS Adding an Antihypertensive Agent More Effective Than Titrating?

‘The extra blood pressure reduction from combining drugs from 2 different classes is approximately 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

**Multiple Antihypertensive Agents are Needed to Reach Blood BP Goal**

<table>
<thead>
<tr>
<th>Trial (SBP achieved)</th>
<th>Average no. of antihypertensive medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD (132 mmHg)</td>
<td>4</td>
</tr>
<tr>
<td>HOT (138 mmHg)</td>
<td>3</td>
</tr>
<tr>
<td>RENAAAL (141 mmHg)</td>
<td>3</td>
</tr>
<tr>
<td>AASK (128 mmHg)</td>
<td>3</td>
</tr>
<tr>
<td>ABCD (132 mmHg)</td>
<td>3</td>
</tr>
<tr>
<td>IDNT (138 mmHg)</td>
<td>3</td>
</tr>
<tr>
<td>UKPDS (144 mmHg)</td>
<td>3</td>
</tr>
<tr>
<td>ASCOT-BPLA (136.9 mmHg)</td>
<td>2</td>
</tr>
<tr>
<td>ALLHAT (138 mmHg)</td>
<td>2</td>
</tr>
<tr>
<td>ACCOMPLISH (132 mmHg)</td>
<td>2</td>
</tr>
</tbody>
</table>


SBP = systolic blood pressure

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

\[
\frac{1}{3} \text{ NEEDS } 3
\]

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.


Patient-Related Barriers to Effective Antihypertensive Treatment

<table>
<thead>
<tr>
<th>Limited access to health care</th>
<th>Increased susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Lack of health insurance</td>
<td>– Advanced age</td>
</tr>
<tr>
<td>– Lack of a regular provider</td>
<td>– Obesity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonadherence to therapy</th>
<th>Secondary causes (less common)</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Knowledge deficits</td>
<td>– Sleep apnea</td>
</tr>
<tr>
<td>– Medication cost</td>
<td>– Drug side effects</td>
</tr>
<tr>
<td>– Complicated regimens</td>
<td>– Chronic kidney disease</td>
</tr>
<tr>
<td>– Side effects</td>
<td>– Primary aldosteronism</td>
</tr>
<tr>
<td>– Medication not taken by patient</td>
<td>– Renovascular disease</td>
</tr>
<tr>
<td>– Poor physician-patient</td>
<td>– Cushing syndrome</td>
</tr>
<tr>
<td>communication</td>
<td>– Pheochromocytoma</td>
</tr>
<tr>
<td>– Lack of social support</td>
<td>– Coarctation of the aorta</td>
</tr>
<tr>
<td></td>
<td>– Thyroid/parathyroid disease</td>
</tr>
</tbody>
</table>

Patients Are Not Adherent To Therapy ?!!......... Yes

Among Patients Still on Therapy After the First Year, **50% Stop** Therapy within the Next 2 Years

Retrospective, cohort study of community pharmacy records (n=2,325)

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adjusted* RR for non-persistent patients (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1.28 (1.15, 1.45)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1.15 (1.00, 1.33)</td>
</tr>
</tbody>
</table>

*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

On The Other Hand

Role of SPC in improving patients adherence and compliance

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

### Single-pill Combination Therapy Demonstrates Improved Compliance in Hypertensive Patients by 24%

<table>
<thead>
<tr>
<th></th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor, et al.</td>
<td>0.74 (0.67, 0.81)</td>
<td>25.2</td>
</tr>
<tr>
<td>Dezii</td>
<td>0.74 (0.65, 0.84)</td>
<td>18.4</td>
</tr>
<tr>
<td>NDC dataset</td>
<td>0.81 (0.77, 0.86)</td>
<td>37.8</td>
</tr>
<tr>
<td>Dezii</td>
<td>0.71 (0.62, 0.80)</td>
<td>18.5</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>0.76 (0.71, 0.81)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

**Risk ratio (95% CI)**
- 0.1
- 1
- 10

**Favours Single-pill combination**

**Favours individual agents given separately**

**CI = confidence interval**


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### Treatment compliance, adherence and persistence carries benefits to HTN patients

**For patients to achieve and maintain BP control,**

**Reduce long-term CV morbidity and mortality,**

**Reduce health-care costs by decreased hospitalization rates and lower resource utilization,**

Compliance with Antihypertensive Therapy Results in More Patients Achieving (BP) Goal (<140/90 mmHg)


Observational, cross-sectional study (n=1,000)

Patients (%)

Compliant
Non-compliant

>70%
p<0.005

ACCOMPLISH: Impressive Blood Pressure (BP) Control Rates Achieved with Single-pill Combination-based Therapies

Only ~37% of patients had their BP controlled at baseline despite ~74% of patients receiving ≥2 antihypertensive agents as free combination

Benazepril/HCTZ n=5,762
Benazepril/Amlodipine n=5,744

37% Controlled at randomization
38% Controlled at randomization

Mean BP control rate after titration (% patients <140/90 mmHg)

72%‡
75%‡

Jamerson et al. Presented at ACC 2008

*Control defined as BP <140/90 mmHg
†Values calculated from mean BP after titration and mean BP control rate over the duration of the study
ACCOMPLISH = Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension; HCTZ = hydrochlorothiazide
Increased Compliance Significantly Associated with Lower (BP) and Fewer Medication

- Decreased systolic BP (SBP)
- Fewer add-on antihypertensive medications

Patients who were ≥80% compliant with therapy had lower average systolic BP and more days of BP control compared with patients who were <80% compliant. In addition, patients who were ≥80% compliant required fewer add-on medications regardless of antihypertensive class.

![Bar chart showing compliance and add-on medications](chart1)

ACEI = angiotensin-converting enzyme inhibitor
CCB = calcium channel blocker

Halpern MT, et al. Presented at the Annual Congress of the European Society of Hypertension 2006, Madrid, Spain

Better Compliance with Antihypertensive Drugs is Associated with a Lower Risk of Hospitalization

![Bar chart showing compliance and hospitalization risk](chart2)

Sokol et al. Med Care 2005;43:521–30

*p<0.05 vs 80–100% compliant group
More than 50% reduction in annual cost with SPC

The reasons for the cost savings with SPC therapy were

- Fewer additional drugs,
- Fewer physician visits
- Fewer hospitalizations for uncontrolled HTN and cardiovascular events.


Single Pill Combination in Guidelines
**ACCF/AHA Guidelines**

- **Combination therapy** provides more opportunity for creative solutions to a number of problems

- A **well-designed combination pill** that incorporates logical doses of 2 agents enhances convenience and compliance

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**CHEP**

- **Single pill combinations** help achieve blood pressure control

- **Adherence** with antihypertensive prescriptions can be improved by multi-prolonged approach:
  
  ✓ Simplify medication regimens using long-acting once-daily dosing

  ✓ Utilize **fixed-dose combination pills**

  ✓ Replacing multi pill antihypertensive combinations with single pill combinations
European Guidelines Recommend use of Single-pill Combination Therapy

- 2013 European guidelines state:

  ‘The combination of two antihypertensive drugs may offer advantages also for treatment initiation, particularly in patients at high cardiovascular risk in which early BP control may be desirable’

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


SPC in Few Words .....

- Compliance
- Reaching Goal
- Morbidity and Mortality
- Cost
Rational of Combination

Which Combinations?

BP has multiple regulatory pathway

- Sympathetic nervous system
- Renin-angiotensin-aldosterone system (RAAS)
- Total body sodium
Multiple-mechanism Therapy: Potential Efficacy Benefits

Multiple-mechanism therapy results in a greater BP reduction than seen with its single-mechanism components.\(^1,2\)

- Components with a different mechanism of action interact on complementary pathways of BP control\(^1\).

- Each component can potentially neutralize counter-regulatory mechanisms, e.g.
  
  **Diuretics** reduce plasma volume, which in turn stimulates the renin-angiotensin-aldosterone system (RAAS) and thus increases BP; addition of a **RAAS blocker** attenuates this effect\(^1\).

- Multiple-mechanism therapy may result in BP reductions that are additive\(^2\).

\(^1\) Sica. Drugs 2002;62:443-62
\(^2\) Quan et al. Am J Cardiovasc Drugs 2006;6:103-13

Multiple-mechanism Therapy: Potential Tolerability Benefits

Multiple-mechanism therapy may have an improved tolerability profile compared with its single-mechanism components.\(^1,2\)

- Components of multiple-mechanism therapy can be given at lower dosages to achieve blood pressure goal than those required as monotherapy, therefore better tolerated\(^1,2\).

- Compound-specific adverse events can be attenuated, e.g.,\(^1,2\)
  
  **Renin-angiotensin-aldosterone system blockers** may attenuate the oedema that is caused by **calcium channel blockers**.

\(^1\) Sica. Drugs 2002;62:443-62
\(^2\) Quan et al. Am J Cardiovasc Drugs 2006;6:103-13
Available as a single-pill combination
Less frequently used/combination used as necessary

ACEI = angiotensin-converting enzyme inhibitor;
ARB = angiotensin receptor blocker; CCB = calcium channel blocker

HCTZ Has Been Widely Studied in Hypertension

- For patients with uncomplicated hypertension, thiazide diuretics are the first-line recommendation
- Diuretics are also widely used for enhancing hypertensive efficacy in multi-drug regimens, including in combination with ARBs and CCBs
- The ALLHAT Study provided important evidence supporting the use of thiazide diuretics in patients with hypertension
- HCTZ has been shown to enhance antihypertensive efficacy when combined with valsartan in numerous controlled clinical trials
  - More than 4,000 patients have been included in the valsartan/HCTZ groups
  - HCTZ resulted in additive placebo-adjusted decreases in systolic and diastolic blood pressure when combined with valsartan

ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HCTZ = hydrochlorothiazide; JNC = Joint National Committee

1Mancia et al. J Hypertens 2007;25:1105–87; 2Mancia et al. Blood Press 2009;18:308–47; 3HCTZ has been shown to enhance antihypertensive efficacy when combined with valsartan in numerous controlled clinical trials

Chobanian et al. JAMA 2003;289:2560–72
The ALLHAT Investigators. JAMA 2002;288:2981–97
DIOVAN HCT prescribing information. Novartis July 2008
Amlodipine has a Wealth of Cardiovascular Outcomes Data

PREVENT\(^1\)
825 coronary heart disease (CAD) patients (≥30%): Multicentre, randomized, placebo controlled

<table>
<thead>
<tr>
<th>Primary outcome:</th>
<th>No difference in mean 3 yr coronary angiographic changes vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35% ↓ hospitalization for HF + angina</td>
</tr>
<tr>
<td></td>
<td>43% ↓ revascularization procedures</td>
</tr>
</tbody>
</table>

CAMELOT\(^2\)
1,991 CAD patients (>20%): Double-blind, randomized study vs placebo and enalapril 20 mg

<table>
<thead>
<tr>
<th>Primary outcome:</th>
<th>31% ↓ in CV events vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>42% ↓ hospitalization for angina</td>
</tr>
<tr>
<td></td>
<td>27% ↓ coronary revascularization</td>
</tr>
</tbody>
</table>

ASCOT-BPLA/CAFE\(^3,4\)
19,257 hypertensive patients: Multicentre, randomized, prospective study vs atenolol

Primary outcome: 10% ↓ in non-fatal MI & fatal CHD

| 16% ↓ total CV events and procedures                      |
| 30% ↓ new-onset diabetes                                 |
| 23% ↓ stroke                                             |
| 11% ↓ all-cause mortality                                |
| ↓ central aortic pressure by 4.3 mmHg                    |

ALLHAT\(^5\)
18,102 hypertensive patients: Randomized, prospective study vs lisinopril

Primary outcome: No difference in composite of fatal CHD + non-fatal MI vs lisinopril

| 6% ↓ combined CV disease                                |
| 23% ↓ stroke                                            |


Valsartan has a Wealth of Cardiovascular Outcomes Data

VALUE\(^1\)
15,245 high-risk hypertension patients; Double-blind, randomized study vs amlodipine

No difference in composite of cardiac mortality and morbidity (primary)

| 23% ↓ new-onset diabetes                                 |

VALIANT\(^2\)
14,703 post-myocardial infarction (MI) patients; Double-blind, randomized study vs captopril and vs captopril + valsartan

No difference vs captopril in all-cause mortality (primary)

(valsartan is as effective as standard of care)

Val-HeFT\(^3,5\)
5,010 heart failure (HF) II–IV patients; Double-blind, randomized study vs placebo

13% ↓ morbidity and mortality (primary)

| left ventricular remodeling                              |
| 37% ↓ atrial fibrillation occurrence                    |
| ↓ HF signs/symptoms                                      |
| 28% ↓ HF hospitalization                                 |

JIKEI HEART\(^6\)
3,081 Japanese patients on conventional treatment for hypertension, coronary heart disease (CHD), HF or combination of these; Multicentre, randomized, controlled trial comparing addition of valsartan vs non-angiotensin Type 2 receptor blocker (ARB) to conventional treatment

39% ↓ composite CV mortality and morbidity

| 40% ↓ Stroke/transient ischemic attack (TIA)              |
| 47% ↓ Hospitalization for HF                             |
| 65% ↓ Hospitalization for angina                         |

KYOTO HEART\(^7\)
3,031 Japanese patients on conventional treatment for hypertension and high CV risk; Multicentre PROBE trial comparing addition of valsartan vs non-ARB to conventional treatment

45% ↓ composite CV mortality and morbidity

| 45% ↓ Stroke/transient ischemic attack (TIA)              |
| 49% ↓ Angina pectoris                                    |
| 33% ↓ New-onset diabetes                                 |

**ESH–ESC: Algorithm for Treatment of Hypertension**

- **Mild BP elevation**
  - Low/moderate CV risk
  - Conventional BP target

  - **Low-dose single agent**
    - Full dose of single agent
    - Switch to different agent at low dose
    - **Not at BP goal**

  - **2–3 drug combination**
    - Full-dose single agent
    - **Not at BP goal**

- **Marked BP elevation**
  - High/very high CV risk
  - Lower BP target

  - **Low-dose 2-drug combination**
    - Full dose of 2-drug combination
    - Add a third drug at low dose
    - **Not at BP goal**

  - **Full doses of 2–3-drug combination**

**TOD = target organ damage**

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

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

- **<55 years**
  - A
  - A + C
  - A + C + D
  - A + C + D+ Consider further diuretic or alpha or Beta Blocker. Consider seeking specialist advice

- **≥55 years or black patients at any age**
  - C
  - A + C

**National Institute for Health and Clinical Excellence (NICE) (2011)**
Evidence of Triple Combination

Incremental Blood Pressure Reductions With Addition of Amlodipine or HCTZ to ARB-based Dual Therapy

1ARB = angiotensin receptor blocker (valsartan) *p<0.0001 vs valsartan/hydrochlorothiazide (HCTZ) n=66; †p<0.0001 vs amlodipine/valsartan n=91; Valsartan/HCTZ given at a dose of 160/25 mg; amlodipine/valsartan given at a dose of 10/160 mg

Braun et al. Poster presented at the Congress of the German Society for Internal Medicine, April 2009, Wiesbaden, Germany
**Aml/ Val/ HCTZ combination:**
Multinational, randomized, double-blind trial

**Patients:** Aged 18-85 years, Moderate or severe hypertension*, Receiving up to three antihypertensive agents prior to entry.

N= 2271  Placebo Run-in phase

<table>
<thead>
<tr>
<th>Combination</th>
<th>0/160/1 mg</th>
<th>10/160/1 mg</th>
<th>0/320/12.5 mg</th>
<th>0/160/12.5 mg</th>
<th>10/320/25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aml/Va HCTZ</td>
<td>5/0/12.5 mg</td>
<td>5/0/12.5 mg</td>
<td>5/0/12.5 mg</td>
<td>5/0/12.5 mg</td>
<td>5/0/12.5 mg</td>
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<td>0/160/12.5 mg</td>
<td>0/160/12.5 mg</td>
</tr>
<tr>
<td>Aml/Va HCTZ</td>
<td>10/320/0 mg</td>
<td>10/320/0 mg</td>
<td>10/320/0 mg</td>
<td>10/320/0 mg</td>
<td>10/320/0 mg</td>
</tr>
<tr>
<td>Aml/Va HCTZ</td>
<td>0/320/12.5 mg</td>
<td>0/320/12.5 mg</td>
<td>0/320/12.5 mg</td>
<td>0/320/12.5 mg</td>
<td>0/320/12.5 mg</td>
</tr>
</tbody>
</table>

*([≥140/90 and ≥180/110 mmHg])

Aml=amlodipine; HCTZ=hydrochlorothiazide; Val=valsartan


**Mean reduction in systolic and diastolic blood pressure from baseline to Week 3 and study end in overall population.**

<table>
<thead>
<tr>
<th>Combination</th>
<th>BL 170.7</th>
<th>169.5</th>
<th>169.8</th>
<th>169.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSBP (mmHg)</td>
<td>-23.6</td>
<td>-24.6</td>
<td>-26.3</td>
<td>-29.6</td>
</tr>
</tbody>
</table>

*P<0.0001 vs. triple therapy; ‡P<0.01 vs. triple therapy

Mean reduction in systolic and diastolic blood pressure from baseline to Week 3 and study end in overall population.

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>107</th>
<th>106.2</th>
<th>106.6</th>
<th>106.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSDBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.0001 vs. triple therapy; ‡P<0.01 vs. triple therapy
MSDBP=mean sitting diastolic blood pressure; BL: baseline; Aml=amilodipine; HCTZ=hydrochlorothiazide; Val=valsartan.


Mean reduction in systolic blood pressure from baseline to Week 3 and study end in the subgroup with severe systolic hypertension

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>188.1</th>
<th>187.1</th>
<th>187.4</th>
<th>187.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.0001 vs. triple therapy; ‡P<0.01 vs. triple therapy
MSSBP=mean sitting systolic blood pressure; BL: baseline; Aml=amilodipine; HCTZ=hydrochlorothiazide; Val=valsartan.

Simply We Can Say That:

- Aml /Val / HCTZ triple therapy is highly effective in reducing BP compared with dual components early in therapy, and systolic BP-lowering effects were proportionate to hypertension severity.


Effects of valsartan versus olmesartan addition to amlodipine/hydrochlorothiazide combination in treating stage 2 hypertensive patients

Roberto Fogari¹, Annalisa Zoppì, Amedeo Mugellini, Paola Perri, Trizano Perrone, Pamela Maffoli & Giuseppe Derosa

Clinica Medica II, Centro Sperimentale e Fisiopatologia Cardiovascolare, Department of Internal Medicine and Therapeutics, University of Pavia, Piazza Golgi, Pavia, Italy
Study Design:

- Patients 180 patients with diastolic blood pressure (DBP) ≥ 99 and < 110 mm Hg

* patients whose BP was not adequately controlled (DBP ≥ 90 mm Hg) were randomized to the combination of valsartan 160 mg + amlodipine 5 mg + HCTZ 12.5 mg or olmesartan 20 mg + amlodipine 5 mg + HCTZ 12.5 mg both given once daily in the morning for 4 weeks.


Valsartan added to Aml and HCTZ provides significantly BP reduction comparing to Olmesartan

*SBP reduction last 4 weeks*

- Valsartan Group
- Olmesartan Group

*DBP reduction last 4 weeks*

- Valsartan Group
- Olmesartan Group

*p<0.001

Adding Valsartan to Aml/HCTZ uncontrolled patients is more effective than adding Olmesartan

SBP BL 170 mmHg

DBP BL 104 mmHg

8 weeks (+ARB)

SBP BL systolic blood pressure at baseline, DBP BL diastolic blood pressure at baseline *p < 0.05 vs olmesartan


High-dose* Triple Combination Therapy with Amlodipine/Vasartan/HCTZ is Well Tolerated: Similar AEs/SAEs Compared with Dual Therapy

<table>
<thead>
<tr>
<th>AEs, %</th>
<th>Amlodipine/Valsartan/HCTZ</th>
<th>Valsartan/HCTZ</th>
<th>Amlodipine/ Valsartan</th>
<th>HCTZ/ Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>45.2</td>
<td>45.3</td>
<td>44.9</td>
<td>48.3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7.7</td>
<td>7.0</td>
<td>2.3</td>
<td>3.9</td>
</tr>
<tr>
<td>Peripheral Oedema</td>
<td>4.5</td>
<td>0.9</td>
<td>8.5</td>
<td>8.9</td>
</tr>
<tr>
<td>Headache</td>
<td>4.3</td>
<td>5.4</td>
<td>4.9</td>
<td>7.0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2.2</td>
<td>0.9</td>
<td>1.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.2</td>
<td>2.7</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>2.2</td>
<td>1.3</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Back pain</td>
<td>2.1</td>
<td>2.3</td>
<td>0.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Nasopharangitis</td>
<td>2.1</td>
<td>2.3</td>
<td>2.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.1</td>
<td>1.3</td>
<td>1.8</td>
<td>2.1</td>
</tr>
<tr>
<td>SAEs</td>
<td>0.9</td>
<td>1.3</td>
<td>0.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

AEs were as expected for this population and classes of drug; mostly mild and transient, with no indication of target organ toxicity

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

AE = adverse event; SAE = serious adverse event;
HCTZ = hydrochlorothiazide

*High-dose triple combination therapy with amlodipine/valsartan/HCTZ 10/320/25 mg
Make It Easier to Your Patients Using Single Pill Combination

Thank You
Adding Valsartan to Aml/HCTZ uncontrolled patients is more effective than adding Olmesartan

Mean reduction in systolic and diastolic blood pressure from baseline to Week 3 and study end in overall population.

SBP BL: systolic blood pressure at baseline. DBP BL: diastolic blood pressure at baseline. *p < 0.05 vs olmesartan

MSDBP=mean sitting diastolic blood pressure; MSSBP=mean sitting systolic blood pressure
Aml=amlodipine; HCTZ=hydrochlorothiazide; Val=valsartan
Mean reduction in systolic blood pressure from baseline to Week 3 and study end in the subgroup with severe systolic hypertension

MSDBP=mean sitting diastolic blood pressure; MSSBP=mean sitting systolic blood pressure; Aml=amlodipine; HCTZ=hydrochlorothiazide; Val=valsartan.

*P<0.0001 vs. triple therapy; †P<0.001 vs. triple therapy; ‡P<0.01 vs. triple therapy.