What is the Most Powerful Solution for Hypertension Patients

Keimyung University Dongsan Medical Center
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Why hypertension?
Hypertension affects approximately 1 billion people worldwide.

Number of adults with hypertension is estimated to increase 60% from 2000 to 2025.

Hypertension is No1 killer in the world

Mortality due to leading global RF in 2001
CV Mortality Risk Doubles
With Each 20/10 mmHg Increase in BP

BP=blood pressure.
*Individuals aged 40–69 years (N=1 million).
Blood Pressure Reduction of 2 mmHg Decreases the Risk of Cardiovascular Events by 7–10%  

- Meta-analysis of 61 prospective, observational studies  
- 1 million adults  
- 12.7 million person-years  

2 mmHg decrease in mean systolic blood pressure  

7% reduction in risk of ischemic heart disease mortality  

10% reduction in risk of stroke mortality  

# ESH–ESC and JNC 7 Guidelines Recommendations for BP Goals

<table>
<thead>
<tr>
<th>Type of hypertension</th>
<th>JNC 7(^1)</th>
<th>ESH–ESC(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated</td>
<td>&lt;140/90</td>
<td>130–139/80–85</td>
</tr>
<tr>
<td>Complicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>&lt;130/80</td>
<td>130–139/80–85</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>&lt;130/80(^*)</td>
<td>130–139/80–85</td>
</tr>
<tr>
<td>Other high risk (stroke, myocardial infarction)</td>
<td>&lt;130/80</td>
<td>130–139/80–85</td>
</tr>
</tbody>
</table>

BP = blood pressure; ESH = European Society of Hypertension; ESC = European Society of Cardiology; JNC = Joint National Committee

\(^*\)Lower if proteinuria is >1 g/day

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1Chobanian et al. Hypertension 2003;42:1206–52
But, Hypertension Control Rate in Real World

Patients not achieving BP goal (%)

England 60%
Germany 70%
Italy 72%
Sweden 79%
Spain 81%

*Treated for hypertension; BP goal <140/90 mmHg
BP = blood pressure
BP Control Rates in Hypertensive Patients in Developing Economies

Turkey
(Treated population)

24.3%

Thailand
(Treated population)

36.6%

China
(Population aware of their hypertension)

19%

BP = blood pressure

References:

What about in Korea?

우리나라 만성질환 유병률 추이: 검진

출처: 2009 국민건강통계, 보건복지부 질병관리본부
BP Control Rates in Hypertensive Patients in Korea

고혈압 관리현황

※인지율 : 고혈압 유병자 중 의사로 부터 고혈압 진단을 받은 분율, 만 30세 이상
치료율 : 고혈압 유병자 중 혈압강하제를 한 달에 20일 이상 복용한 분율, 만 30세 이상
조절률 (유병자 기준) : 고혈압 유병자중 수축기 혈압 140 mmHg 미만이면서 이완기 혈압 90 mmHg 미만인 분율, 만 30세 이상
※ 2005년 고혈압추정인구 (2005년 추계인구 X 2005년 고혈압 유병률)로 연령표준화

BP Control Rates in Hypertensive Patients in Korea

※혈압 인지율: 고혈압 유병자
※혈압 치료율: 고혈압 유병자
※혈압 조절율: 고혈압 유병자
※2011년 남자 팔높이 83cm, 여자 80cm
※2008-2010년 통합산출

출처: 201- 국민건강통계, 국민건강영양조사 제 5기 (2010_ 자료
Why combinations therapy?
Multiple Antihypertensive Agents are Needed to Reach Blood BP Goal

Trial (SBP achieved)

MDRD (132 mmHg)\(^1\)
HOT (138 mmHg)\(^1\)
RENAAL (141 mmHg)\(^1\)
AASK (128 mmHg)\(^1\)
ABCD (132 mmHg)\(^1\)
IDNT (138 mmHg)\(^1\)
UKPDS (144 mmHg)\(^1\)
ASCOT-BPLA (136.9 mmHg)\(^2\)
ALLHAT (138 mmHg)\(^1\)
ACCOMPLISH (132 mmHg)\(^3, 4\)


Up to 8 out of 10 patients need multiple medications to help reach blood pressure treatment goals.\(^5, 6\)
Limitations of Agents with a Single Mechanism of Action

- Materson et al. observed that antihypertensive agents with a single mechanism of action were inadequate to achieve a diastolic BP <95 mmHg in 40–60% of hypertensive patients¹

- Because hypertension is a multi-factorial disease, in most cases at least two antihypertensive agents are needed for patients to achieve BP goal²

- As an estimate, one-third of patients with hypertension require 2 drugs to achieve BP control* and one-third of patients will require 3 or more antihypertensive agents to achieve BP control³

*Blood pressure (BP) <140/90 mmHg

Adding an Antihypertensive Agent is 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

Combination Therapy: Why?

- Hypertension is heterogeneous in its response to treatment and a combination of two drugs will increase the likelihood of response by multiple mechanism.

- There may be enhancement of each drugs antihypertensive effect which may be synergistic rather than simply additive.

- By keeping both drugs at low dose the incidence of side effect from each may be minimized.

- Improving Drug Compliance
Current Guidelines Recommend Initiating Combination Therapy Early in Patients with Stage 2 Hypertension or High Cardiovascular Risk

- JNC 7 guidelines recommend the consideration of initial therapy with two antihypertensive drugs when BP is more than 20/10 mmHg above goal\(^1\)

- ESH/ESC guidelines state\(^2\):
  
  ‘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.’

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\(^1\)Chobanian et al. Hypertension 2003;42:1206–52

BP = blood pressure
ESH = European Society of Hypertension
ESC = European Society of Cardiology
JNC = Joint National Committee
Why Single-pill Combinations?
Compliance Decreases as the Number of Medications Increases

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

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

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

Patients achieving BP <140/90 mmHg (%)

Compliant: p<0.005

Non-compliant

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

1.28 (1.15, 1.45)

Acute myocardial infarction

1.15 (1.00, 1.33)

*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

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

*\text{*p} < 0.05 vs 80–100\% compliant group

Sokol et al. Med Care 2005;43:521–30
Better Compliance with Antihypertensive Therapy is Associated with a Decrease in Medical Costs

How to Improve Compliance?

Costs ($, thou)

<table>
<thead>
<tr>
<th>Compliance (%)</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.8</td>
<td>12</td>
</tr>
<tr>
<td>10.3</td>
<td>12</td>
</tr>
<tr>
<td>8.4</td>
<td>12</td>
</tr>
<tr>
<td>7.7</td>
<td>12</td>
</tr>
<tr>
<td>6.6</td>
<td>12</td>
</tr>
<tr>
<td>4.8</td>
<td>12</td>
</tr>
<tr>
<td>6.0</td>
<td>12</td>
</tr>
<tr>
<td>5.1</td>
<td>12</td>
</tr>
<tr>
<td>5.0</td>
<td>12</td>
</tr>
<tr>
<td>4.4</td>
<td>12</td>
</tr>
</tbody>
</table>

* p<0.05 vs. 80–100% compliant group

Sokol et al. Med Care 2005;43:521–30
Improved Compliance with Single-pill Combination (SPC) Therapy Compared with Free-combination Therapy

SPC (amlodipine/benazepril) (n=2,839) 88%
Free combination (ACEI + CCB) (n=3,367) 69%

Medication possession ratio (MPR)†

†Defined as the total number of days of therapy for medication dispensed/365 days of study follow-up
ACEI = angiotensin-converting enzyme inhibitor; CCB = calcium channel blocker

Patients Treated with Single-pill Combinations Use Less Resource

Dickson, Plauschinat. Am J Cardiovasc Drugs 2008;8:45–50

NS = not significant
Initiating treatment with a single-pill combination (SPC) is associated with more rapid BP control vs switching to an SPC after initial monotherapy

Overall study population

Patients with BP control (%)

Months

SPC (n=896)  Switchers (n=896)

Median time of switching to SPC

Median time to BP control with SPC vs switching:
6.4 vs. 7.2 months (Log-rank p=0.0396)

SPC = patients initiated on SPC therapy for at least 60 days. Switchers = patients initiated on monotherapy for at least 60 days, subsequently switched to SPC therapy for at least 60 days.

*Mean blood pressure (BP) at baseline (overall population) = 153/88 mmHg; †SBP ≥160/100 mmHg.

BP control = <140/90 mmHg, or <130/80 mmHg for patients with compelling indications.

SPCs = angiotensin-converting enzyme inhibitor (ACEI)/calcium channel blocker (CCB), angiotensin receptor blocker (ARB)/CCB, ACEI/diuretic, ARB/diuretic

Patients with stage 2 hypertension

Overall study population

Patients with BP control (%)

Months

SPC (n=385)  Switchers (n=385)

Median time of switching to SPC

Median time to BP control with SPC vs switching:
5.5 vs. 7.9 months (Log-rank p=0.0157)

Initiating therapy with SPC is associated with improved BP control and lower risk of developing a CV event vs switching to combination therapy

- Retrospective (real-world), matched-cohort study (2,432 patients in each of the single-pill combination (SPC) and switcher/add-on cohorts); mean blood pressure (BP) at baseline in each study group: 149/83 mmHg
- More patients achieved BP control* in the SPC vs switcher/add-on cohort at months 3 (24.7% vs 20.4%), 6 (46.6% vs 42.4%), and 12 (72.0% vs 69.1%), resulting in a shorter median time to BP goal: 6.5 vs 7.0 months, respectively; log-rank p=0.0367

<table>
<thead>
<tr>
<th>No. of patients with event</th>
<th>Incidence rate</th>
<th>Conditional Poisson</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients with an event (No. of patients with an event per 100 person-years)</td>
<td>[Ref: Switcher/Add-on]</td>
</tr>
<tr>
<td>SPC (n=2,432)</td>
<td>Switch (n=2,432)</td>
<td>SPC (n=2,432)</td>
</tr>
<tr>
<td>Acute MI</td>
<td>82</td>
<td>129</td>
</tr>
<tr>
<td>Stroke</td>
<td>357</td>
<td>426</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>83</td>
<td>135</td>
</tr>
<tr>
<td>Overall</td>
<td>454</td>
<td>573</td>
</tr>
<tr>
<td>Overall (with death)</td>
<td>473</td>
<td>587</td>
</tr>
</tbody>
</table>

IRR = incidence rate ratio of cardiovascular (CV) events (incidence rate of CV event [SPC cohort]/incidence rate of CV event [Switcher/Add-on cohort].
SPC or free combinations = angiotensin-converting enzyme inhibitor (ACEI)/calcium channel blocker (CCB), angiotensin receptor blocker (ARB)/CCB, ACEI/diuretic, ARB/diuretic.

*<140/90 mmHg, or <130/80 mmHg for patients with compelling indications. SPC = patients initiated on SPC therapy for at least 60 days. Switchers/add-on = patients initiated on monotherapy for at least 60 days, subsequently switched to combination therapy/added a second agent for at least 60 days.
HF = heart failure; MI = myocardial infarction

European Guidelines now Recommend use of Single-pill Combination Therapy

2009 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’

Benefits of Single-pill Combinations

- Up to **8 out of 10 patients need multiple medications** to help reach blood pressure (BP) treatment goals\(^1,2\)

- When combining antihypertensive agents, the use of single-pill combinations (SPCs) is **supported by guidelines**, due to compliance advantages, and could lead to **improved efficacy, better outcomes and reduced overall costs**\(^3\)\(^–\)\(^5\)

- A renin-angiotensin-aldosterone system (RAAS) blocker/calcium channel blocker (CCB) and RAAS blocker/diuretic represent rational and effective combinations, and **are recommended by guidelines**\(^3\)

- SPC therapy with valsartan/hydrochlorothiazide (HCTZ) and with amlodipine/valsartan are associated with powerful BP-lowering efficacy,\(^6\)\(^–\)\(^8\) and the individual components/classes are supported by a wealth of outcomes evidence/use in clinical trials\(^1\)\(^,\)\(^9\)\(^,\)\(^10\)

- In the proportion of patients who require more than two agents, SPC therapy with valsartan/amlodipine/HCTZ provides superior BP reductions compared with dual therapy and is well tolerated\(^11\)

Why A+C Single-pill Combinations?
Optimal combination therapy

### Table 1  Drug combinations in hypertension: recommendations

<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)/beta-blocker</td>
</tr>
<tr>
<td>CCB/diuretic</td>
</tr>
<tr>
<td>Renin inhibitor/diuretic</td>
</tr>
<tr>
<td>Renin inhibitor/CCB</td>
</tr>
<tr>
<td>Dihydopyridine CCB/non-dihydropyridine CCB</td>
</tr>
</tbody>
</table>
**ACCOMPLISH: the First Outcomes Trial to Compare Two Single-pill Combination-based Therapies**

Prospective, randomized, double-blind, event-driven trial

**Target BP**
- <140/90 mmHg
- <130/80 mmHg in patients with diabetes or renal insufficiency

**Randomisation**
- Benazepril 20 mg + Amlodipine 5 mg
- Benazepril 20 mg + HCTZ 12.5 mg
- Benazepril 20 mg + HCTZ 25 mg

**Forced titration**
- Benazepril 40 mg + Amlodipine 5 mg
- Benazepril 40 mg + Amlodipine 10 mg
- Benazepril 40 mg + HCTZ 12.5 mg
- Benazepril 40 mg + HCTZ 25 mg

**Screening**
- 11,506 patients

**Follow up**
- At 6 months and every 6 months thereafter

**Free add-on***

*Beta blockers; alpha blockers; clonidine; loop diuretics

ACCOMPLISH = Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension

HCTZ = hydrochlorothiazide

ACCOMPLISH: the First Outcomes Trial to Compare Two Single-pill Combination-based Therapies

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at risk (N)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benazepril/amlodipine</td>
<td>5,512</td>
<td>5,317</td>
<td>5,141</td>
<td>4,959</td>
<td>4,739</td>
<td>2,826</td>
<td>1,447</td>
<td></td>
</tr>
<tr>
<td>Benazepril/HCTZ</td>
<td>5,483</td>
<td>5,274</td>
<td>5,082</td>
<td>4,892</td>
<td>4,655</td>
<td>2,749</td>
<td>1,390</td>
<td></td>
</tr>
</tbody>
</table>

Cumulative event rate

- Benazepril/amlodipine (552 patients with events: 9.6%)
- Benazepril/HCTZ (679 patients with events: 11.8%)

Time to first CV mortality/morbidity (days)

HR 0.80 (95%CI 0.72–0.90); p<0.001

20% relative risk reduction

CV = cardiovascular; HCTZ = hydrochlorothiazide; RAAS = renin-angiotensin-aldosterone system

ACCOMPLISH = Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension

Jamerson et al.
N Engl J Med
2008;359:2417–28
2011 NICE guideline

Summary of antihypertensive drug treatment

Aged over 55 years or black person of African or Caribbean family origin of any age

Aged under 55 years

Step 1
Key
A – ACE inhibitor or low-cost angiotensin II receptor blocker (ARB)
C – Calcium-channel blocker (CCB)
D – Thiazide-like diuretic

Step 2

A

A

C

A + C

C

A + C + D

Step 3

Resistant hypertension
A + C + D + consider further diuretic or alpha- or beta-blocker

Step 4
Consider seeking expert advice

2011 NICE guideline

BHS
British Hypertension Society

National Institute for Health and Clinical Excellence
Conditions favoring the use of C and A
According to the 2007 ESH/ESC recommendations.

CCB

ARB or ACEI

- Isolated systolic hypertension (Elderly)
- Angina pectoris
- Post-myocardial infarction
- Left ventricular hypertrophy
- Atrial fibrillation
- Heart failure
- Carotid/coronary atherosclerosis
- Metabolic syndrome
- Diabetic nephropathy
- Proteinuria/microalbuminuria
- Pregnancy
- ACEI-induced cough

Clinical Evidence with Amlodipine/Valsartan
Incremental BP Drops After Direct Switch to Amlodipine/Valsartan in Patients Previously Uncontrolled on Monotherapy

Baseline BP: 150/91 mmHg
Randomized, double-blind, multinational parallel-group, 16-week study

Amlodipine/Valsartan: Up to 9 Out of 10 Patients Reach BP Goal <140/90 mmHg

Diabetic patients with BP <130/80 mmHg at Week 8 were 47.0% and 49.2% for 5/160 mg and 10/160 mg doses, respectively.

Data shown are at Week 8
No hydrochlorothiazide add-on was permitted until after Week 8
Randomized, double-blind, multinational, parallel-group, 16-week study

Amlodipine/Valsartan: Superior BP-lowering Efficacy versus Amlodipine Monotherapy Across Diverse Patient Populations

- **Elderly (≥65 yrs):**
  - MSSBP mean change at Week 4 (mmHg): -29.7 * (amlodipine/valsartan) vs. -21.7 (amlodipine monotherapy)

- **ISH† (≥180 mmHg):**
  - MSSBP mean change at Week 4 (mmHg): -27.2 * (amlodipine/valsartan) vs. -22.0 (amlodipine monotherapy)

- **Severe (≥180 mmHg):**
  - MSSBP mean change at Week 4 (mmHg): -40.1 * (amlodipine/valsartan) vs. -31.7 (amlodipine monotherapy)

- **Obese‡:**
  - MSSBP mean change at Week 4 (mmHg): -30.2 * (amlodipine/valsartan) vs. -22.9 (amlodipine monotherapy)

- **Diabetes:**
  - MSSBP mean change at Week 4 (mmHg): -29.5 * (amlodipine/valsartan) vs. -22.7 (amlodipine monotherapy)

*p<0.05 amlodipine/valsartan vs. amlodipine monotherapy

MSSBP = mean sitting systolic BP

†ISH = isolated systolic hypertension (≥140 and <90 mmHg)

‡Obese defined as body mass index ≥30 kg/m²

Amlodipine/Valsartan Significantly Reduces Peripheral Edema versus Amlodipine Monotherapy

*\( p < 0.01 \) vs. amlodipine
Randomized, cross-over study in 80 patients

Symptomatic Hypotension Occurs at Very Low Frequency with Amlodipine/Valsartan

0.3% or fewer reports of symptomatic hypotension in elderly† patients

0.4% or fewer reports of symptomatic hypotension in non-elderly‡ patients

Prespecified and post-hoc sub-group analysis of two double-blind, randomized, placebo-controlled studies
Data shown represent the incidence of reported symptomatic hypotension symptoms (adverse events related to low blood pressure, such as syncope, hypotension, orthostatic hypotension, postural dizziness, or lightheadedness)
In elderly patients the incidence of dizziness was 1.9%
†Elderly patients were ≥65 years of age.
‡Non-elderly patients were 18–64 years of age.

Efficacy and safety of a single-pill combination of amlodipine/valsartan in Asian hypertensive patients inadequately controlled with amlodipine monotherapy

Current Medical Research & Opinion 2010;26(7):1705-1713
**Design**

8 week, randomized, double-blind, double-dummy, active-controlled, parallel-group study conducted across 20 centres in Asia (12 in China, 5 in Korea, 3 in Singapore)

**Objective:** *To assess the efficacy and safety of SPC of Aml/Val vs. Aml in Asian*  
**Population:** Asian (18~85 years) with mild-to-moderate essential hypertension (mean sitting DBP ≥ 95 mmHg and < 110 mmHg)  
**Endpoint:** Change in msDBP, msSBP from baseline to week 8 endpoint  
BP control rate (5140/90 mmHg) at week 8 endpoint.

Study design. Aml, amlodipine; Val, valsartan; msDBP, mean sitting diastolic blood pressure.
Patient Disposition

Single-blind, run-in phase (n=919)

Discontinued (n=221)
  - No longer required study drug (n=151)
  - Others (n=70)

Randomised (n=698)

Discontinued (n=24)
  - Adverse events (n=10)*
  - Withdrawal of consent (n=7)
  - Lost to follow-up (n=2)
  - Protocol deviation (n=3)
  - Abnormal laboratory value(s) (n=1)
  - Unsatisfactory therapeutic effects (n=1)

Amlodipine/valsartan 5/80 mg (n=349)
  - Completed (n=325)

Amlodipine 5 mg (n=349)
  - Completed (n=331)

Discontinued (n=18)
  - Adverse events (n=8)*
  - Withdrawal of consent (n=5)
  - Lost to follow-up (n=3)
  - Protocol deviation (n=1)
  - Others (n=1)

* All adverse events (including SAE)
Efficacy Outcomes

- The Benefit of combination therapy was observed as early as week 2 and sustained until week 8
- Response Rates: 79.3% vs. 66.8% (p<0.0001)
- BP Control Rates: 69.2% vs. 57.6% (p=0.0013)
The overall incidence of AE s was similar in both the groups.
The most frequent AE s were hyperlipidaemia and dizziness.
Conclusions

- Once-daily treatment with the single-pill combination of Aml/Val resulted in clinically and statistically significant additional BP reductions and greater BP control than Aml in Asian hypertensive patients inadequately controlled on Aml monotherapy.

- Consistent with the previous findings in non-Asian cohorts, the combination was well-tolerated.
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Thank you