The Rationale of Fixed Combination in the Management of Hypertension

Focus on ACE-I and CCB

Yerizal Karani
Current Status of Hypertension
<table>
<thead>
<tr>
<th>Measure</th>
<th>n (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number worldwide in 2000</td>
<td>972 million (957-987)</td>
</tr>
<tr>
<td>Total number in economically developed countries in 2000</td>
<td>333 million (329-336)</td>
</tr>
<tr>
<td>Total number in economically developing countries in 2000</td>
<td>639 million (625-654)</td>
</tr>
<tr>
<td>Total number worldwide in 2025</td>
<td>1.56 billion (1.54-1.58)</td>
</tr>
</tbody>
</table>

Prevalence of HT based on gender
(Basic Health Research / Indonesian Health Departement 2007)

Keterangan:
- D = Diagnosis berdasarkan tenaga kesehatan
- D/O = Diagnosis berdasarkan tenaga kesehatan atau kasus minum obat
- U = Diagnosis berdasarkan hasil pengukuran tekanan darah

Prevalence %

<table>
<thead>
<tr>
<th>Prevalence %</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>5.8</td>
<td>8.6</td>
</tr>
<tr>
<td>D/O</td>
<td>6.1</td>
<td>9</td>
</tr>
<tr>
<td>U</td>
<td>31.3</td>
<td>31.9</td>
</tr>
</tbody>
</table>
Hypertension is a Major Risk Factor for CV Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Biennial age-adjusted rate per 1000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary disease</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2.0</td>
</tr>
<tr>
<td>Women</td>
<td>2.2</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>3.8</td>
</tr>
<tr>
<td>Women</td>
<td>2.6</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2.0</td>
</tr>
<tr>
<td>Women</td>
<td>3.7</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>4.0</td>
</tr>
<tr>
<td>Women</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Risk ratio:

Cardiovascular Mortality Risk Doubles with Each 20/10 mmHg Increment in Systolic/Diastolic BP*

*Individuals aged 40–69 years

Treating hypertension reduces cardiovascular morbidity and mortality

HT treatment

- Blood Pressure &
  - Blood Pressure Goal
    - JNC VII
      - <140/90 mm Hg
      - <130/80 mm Hg
      (Diabetes, Renal Disease)
    - CVD complications

Treatment of CV risk factors / TOD
Management associated clinical conditions

AS 2011
NHANES data
Awareness, treatment, control of high BP in adults in the USA 1999 – 2000

- Awareness 70 %
  \[\{11 \% \text{ aware, but not treated}\}\]

- Treatment 59 %
  \[\{25 \% \text{ treated, but not controlled}\}\]

- Control 34 %
## MONICA STUDY JAKARTA

<table>
<thead>
<tr>
<th></th>
<th>Survey 1988 (%)</th>
<th>Survey 1993 (%)</th>
<th>Survey 2000 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Prevalence of hypertension</td>
<td>14,9</td>
<td>16,9</td>
<td>17,9</td>
</tr>
<tr>
<td>-Borderline hypertension</td>
<td>3,2</td>
<td>2,5</td>
<td></td>
</tr>
<tr>
<td>-Awareness of responders</td>
<td>56,1</td>
<td>88,7</td>
<td>88,0</td>
</tr>
<tr>
<td>-Newly discovered</td>
<td>43,9</td>
<td>11,3</td>
<td>12,0</td>
</tr>
<tr>
<td>-Treated cases</td>
<td>50,9</td>
<td>85,3</td>
<td>79,4</td>
</tr>
<tr>
<td>-Adequately treated cases</td>
<td>10,0</td>
<td>31,1</td>
<td>39,9</td>
</tr>
</tbody>
</table>

Monica Group Jakarta
Barriers to Reaching BP Targets

Patient factors
- Lack of knowledge/awareness
- Poor compliance
- Complexity of therapeutic regimen
- Side effects

Physician factors
- Physician inertia (i.e. reluctance to treat aggressively)

Environmental factors
- Smoking
- Concomitant drug therapy
- Alcohol
- Cost of medication and related care

Inadequate BP control

Munger. AMJC 2000;6(Suppl 1):211–21

For INTERNAL use only
BP GOAL

Monotherapy
42-59%

Combined therapy
54-70%

ALLHAT
>50%

Combined therapy
Strategi pengobatan hipertensi: InaSH 2007

Lifestyle modifications

Not at goal blood pressure (<140/90 mmHg)  
(<130/80 mmHg for patients with diabetes or chronic kidney disease)

Initial drug choices

Without compelling indications

Stage 1 hypertension (SBP 140-159 or DBP 90-99 mmHg)  
Thiazide-type diuretics for most. May consider ACE-I, ARB, BB, CCB or combination

Stage 2 hypertension (SBP ≥160 or DBP ≥100 mmHg)  
Two-drug combination for most (usually thiazide-type diuretic and ACE-I or ARB, or BB, or CCB)

With compelling indications

Drug(s) for the compelling indications

Other antihypertensive Drugs (diuretics, ACE-I, ARB, BB, CCB) as needed

Not at blood pressure goal

Optimize dosages or add additional drugs until goal blood pressure is achieved.  
Consider consultation with hypertension specialist.

SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker; CCB, calcium-channel blocker
HYPERTENSION

- COMPLEX DISORDERS

- MULTIPLE PATHOGENETIC FACTORS

( INCREASED BLOOD VOLUME,
VASOCONSTRICTION,
OVERACTIVITY SNS AND RAAS )
ADDITIVE EFFECT

COMPLIMENTARY PROPERTIES

ADVERSE EFFECTS

LOWER DOSAGE OF EACH DRUG

ADVERSE EFFECTS OF EACH DRUGS NEUTRALIZED

- SIDE EFFECTS

QUALITY OF LIFE - ↑

COMPLIANCE - ↑ → Better BP controll
RESPONSE RATE TO THERAPY
FROM 40% - 50% TO 70% - 80%
RACIAL AND AGE DIFFERENCES
IN RESPONSE TO INDIVIDUAL
THERAPY ELIMINATED
OFFICE VISITS COST
SIDE EFFECTS
COMPLIANCE
Can we improve BP control rates?


**Compliance, Safety, and Effectiveness of Fixed-Dose Combinations of Antihypertensive Agents**

A Meta-Analysis

Ajay K. Gupta, Shazia Arshad, Neil R. Poulter

**Systolic and Diastolic BP normalization ratios**

- **Schweizer et al. 2007**: OR (95% CI) = 1.63 (0.93, 2.83)
- **Ebbutt et al. 1979**: OR (95% CI) = 1.43 (0.76, 2.68)
- **Mancia et al. 2004**: OR (95% CI) = 1.13 (0.78, 1.64)
- **Overall (I-squared = 0.0%, p = 0.533)**: OR (95% CI) = 1.30 (0.98, 1.71)
Can we improve compliance rates?

**Compliance, Safety, and Effectiveness of Fixed-Dose Combinations of Antihypertensive Agents**

A Meta-Analysis

Ajay K. Gupta, Shazia Arshad, Neil R. Poulter


**FDC and Compliance or Persistence with therapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dezii 2000</td>
<td>1.19 (0.83, 1.71)</td>
</tr>
<tr>
<td>Dezii 2000</td>
<td>1.22 (0.85, 1.75)</td>
</tr>
<tr>
<td>Jackson et al. 2006</td>
<td>2.84 (1.67, 4.83)</td>
</tr>
<tr>
<td>Taylor et al. 2003</td>
<td>1.09 (0.80, 1.51)</td>
</tr>
<tr>
<td>Gerbino et al. 2004</td>
<td>1.28 (0.93, 1.75)</td>
</tr>
<tr>
<td>Dickson et al. 2008</td>
<td>1.29 (0.89, 1.89)</td>
</tr>
<tr>
<td>Overall (I-squared = 49.2%, p = 0.080)</td>
<td>1.29 (1.11, 1.50)</td>
</tr>
</tbody>
</table>
Primary Target RAAS
( ACEI/ARB, β Blockers )

Low Renin States
( CCB, Diuretic )
COMBINATION THERAPY SHOULD BE

- EFFECTIVE
- WELL TOLERATED
- POSITIVE / NEUTRAL EFFECTS on metabolic parameters and concomitant diseases / risk factors
Synergy of ACEI + CCB

The synergistic action of Perindopril - Amlodipine
ACEI-CCB Combination: Synergy for BP Lowering

- SNS
- Renin
  - Ang I
  - Ang II

ACEI

CCB

Activation of \( \alpha 1R \) (VSMC)

Vasoconstriction

Reduced Na+ secretion

Vasodilatation

Increased secretion of Na+ and water

BP
A Synergy also decreasing side effects
Reduces ankle edema in comparison with CCB

Amlodipine alone

Precapillary vasodilation => oedema

Perindopril-Amlodipine

Venous dilation hence normalising intracapillary pressure

Less peripheral oedema with a CCB/RAS combination than with a CCB monotherapy

ACE inhibitor/CCB combination reduces cough in comparison with ACE inhibitor alone

Number and percentage of patients with elimination or reduction of ACE inhibitor-induced cough when treated with placebo or amlodipine. *P<0.05

Perindopril + Amlodipine decreases cough

ACEI
- inhibit kininase II
  - ↑ bradykinin
    - stim. PLA₂
      - ↑ arachidonic acid
        - stim. pulm. sensory C fibers
          - coughing
          - inhibit arachidonic acid

CCB
- inhibit kininase II
  - ↑ bradykinin
    - stim. PLA₂
      - ↑ arachidonic acid
        - stim. pulm. sensory C fibers
          - coughing
          - inhibit arachidonic acid

Ca²⁺- dep. release of glutamate at solitary tract nucleus

Perindopril in EUROPA study → cough in 2.7%
Perind + amlo in STRONG Study → cough in 1.5%
Early & Strong BP Reduction

Bahl UK. Fixed dose perindopril and amlodipine in moderate-to-severe hypertension. 14th World Congress of Heart Disease 2008, Toronto, Canada.
Whatever the profile of hypertensive patients

BP Reduction

Perindopril + Amlodipine

Comparison with landmark trial

**STRONG TRIAL**

n= 1 250

<table>
<thead>
<tr>
<th>SBP</th>
<th>DDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>-41</td>
<td>-23</td>
</tr>
</tbody>
</table>

**Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)**

n= 19 342

<table>
<thead>
<tr>
<th>SBP</th>
<th>DDP</th>
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<tbody>
<tr>
<td>-44</td>
<td>-25</td>
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</tbody>
</table>

Bahl UK. Fixed dose perindopril and amlodipine in moderate-to-severe hypertension.
14th World Congress of Heart Disease 2008, Toronto, Canada.
Poulter NR, Chang CL, Dahlöf B, Gupta AK, Sever PS, Wedel H, on behalf of the ASCOT investigators.
Components of antihypertensive efficacy…
… have independent predictive value

Antihypertensive efficacy

Brachial (clinic) BP

Central BP

BP variability

24h BP: nocturnal BP control

European Society of Cardiology:

“Drugs which exert their antihypertensive effect over 24 hours with a once-a-day administration should be preferred”
BP variability: main cause of CV events.\textsuperscript{3}

Stabilizes blood pressure to avoid excessive BP variability \textsuperscript{1,2}

Central Aortic BP reduction is linked to a reduction in CV events.
ASCOT insights: recent sub studies

COVERAM offers high QUALITY of Blood Pressure Control

All key blood pressure parameters are controlled
Fixed dose combinations: *where is the evidence?*

Among available fixed-dose combinations, which combinations

- have been evaluated in morbidity-mortality trials?

- have been compared with other combinations?

- have proved clear superiority over comparators for preventing CV events and mortality?
Among ACEi + CCB combinations

Only ASCOT shows life saving evidence

<table>
<thead>
<tr>
<th>Combinations</th>
<th>Trials</th>
<th>All-cause mortality</th>
<th>CV mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor/CCB</td>
<td>ASCOT¹ (Amlodipine/Perindopril vs β-blocker/HCTZ)</td>
<td>-11% (P=0.02)</td>
<td>-24% (P=0.001)</td>
</tr>
<tr>
<td></td>
<td>INVEST² (Trandolapril/verapamil vs β-blocker/HCTZ)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>ACCOMPLISH³ (Benazepril/amlodipine vs benazepril/HCTZ)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

No: Nonsignificant

International Guidelines in Hypertension

Valsartan/amlodipine
Telmisartan/amlodipine
Olmesartan/amlodipine

“Until now, no outcome study has been conducted using the combination of an angiotensin receptor antagonist with a calcium antagonist.”

European Guidelines in Hypertension 2009
ASCOT-BPLA

19,342 hypertensive patients

PROBE design

atenolol ± bendroflumethiazide

amlodipine ± perindopril

10,305 patients
TC ≤ 6.5 mmol/L (250 mg/dL)

Double-blind

atorvastatin 10 mg

placebo

Investigator-led, multinational randomised controlled trial

www.ascotstudy.org
ASCOT-BPLA: summary of all end points


Primary
Non-fatal MI (incl silent) + fatal CHD
Unadjusted HR (95% CI)
0.90 (0.79-1.02)

Secondary
Non-fatal MI (exc. Silent) + fatal CHD
0.87 (0.76-1.00)
Total coronary end point
0.87 (0.79-0.96)
Total CV event and procedures
0.84 (0.78-0.90)
All-cause mortality
0.89 (0.81-0.99)
Cardiovascular mortality
0.76 (0.65-0.90)
Fatal and non-fatal stroke
0.77 (0.66-0.89)
Fatal and non-fatal heart failure
0.84 (0.66-1.05)

Tertiary
Silent MI
1.27 (0.80-2.00)
Unstable angina
0.68 (0.51-0.92)
Chronic stable angina
0.98 (0.81-1.19)
Peripheral arterial disease
0.65 (0.52-0.81)
Life-threatening arrhythmias
1.07 (0.62-1.85)
New-onset diabetes mellitus
0.70 (0.63-0.78)
New-onset renal impairment
0.85 (0.75-0.97)

Post hoc
Primary end point + coronary revasc procs
0.86 (0.77-0.96)
CV death + MI + stroke
0.84 (0.76-0.92)

amlodipine ± perindopril better  atenolol ± thiazide better
Cardiovascular protection and mortality reduction stronger than classical regimen

Cardiovascular protection and mortality reduction

Greatest synergy of Coversyl/CCB in CAD patients
A synergistic mode of action

Perindopril | Amlodipine | COVERAM

- Vasodilation
- Antiremodeling effect on Endothelial function
- CV events in hypertension and CAD
- Increased postcapillary vasodilation
- Coronary flow
- Cardiac ischemia
- Increased precapillary vasodilation
- BP lowering
- Arterial protection
- CV events and mortality
- Lower limb edema

Only 3 clinical trials in hypertension decrease mortality

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparators</th>
<th>RR (%) total mortality²</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDNT</td>
<td>Irbesartan versus placebo</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Irbesartan versus amlodipine</td>
<td>NS</td>
</tr>
<tr>
<td>RENAA</td>
<td>Losartan versus placebo</td>
<td>NS</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Lisinopril versus chlorthalidone</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Amlodipine versus chlorthalidone</td>
<td>NS</td>
</tr>
<tr>
<td>LIFE</td>
<td>Losartan/HCTZ versus atenolol/HCTZ</td>
<td>NS</td>
</tr>
<tr>
<td>ANBP-2</td>
<td>Enalapril versus HCTZ</td>
<td>NS</td>
</tr>
<tr>
<td>INVEST</td>
<td>Verapamil SR/trandolapril versus atenolol/HCTZ</td>
<td>NS</td>
</tr>
<tr>
<td>SCOPE²</td>
<td>Candesartan versus placebo</td>
<td>NS</td>
</tr>
<tr>
<td>VALUE</td>
<td>Valsartan versus amlodipine</td>
<td>NS</td>
</tr>
<tr>
<td>JIKEI</td>
<td>Valsartan add-on versus non-ARB</td>
<td>NS</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Perindopril/indapamide versus placebo</td>
<td>-14% (P=0.03)</td>
</tr>
<tr>
<td>HYVET</td>
<td>Indapamide/perindopril versus placebo</td>
<td>-21% (P=0.02)</td>
</tr>
<tr>
<td>ONTARGET</td>
<td>Telmisartan versus ramipril</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Telmisartan + ramipril versus ramipril</td>
<td>NS</td>
</tr>
<tr>
<td>TRANSCEND</td>
<td>Telmisartan versus placebo</td>
<td>NS</td>
</tr>
<tr>
<td>PROFESS</td>
<td>Telmisartan versus placebo</td>
<td>NS</td>
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<tr>
<td>ACCOMPLISH</td>
<td>Benazepril/amlodipine versus benazepril/HCTZ</td>
<td>NS</td>
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<tr>
<td>KYOTO</td>
<td>Valsartan add-on versus non-ARB</td>
<td>NS</td>
</tr>
<tr>
<td>HJ-CREATE⁶</td>
<td>Candesartan versus non-ARB</td>
<td>NS</td>
</tr>
<tr>
<td>NAVIGATOR</td>
<td>Valsartan versus placebo</td>
<td>NS</td>
</tr>
</tbody>
</table>

1. RR: relative risk. NS: not significant. HCTZ: hydrochlorothiazide. ARB: angiotensin receptor blocker. ACEi: angiotensin-converting enzyme inhibitors. BFTZ: bendroflumethiazide
Perindopril + Amlodipine

TAKE HOME MESSAGE

- Provides strong BP reduction (40-63 mmHg)
  - Controls BP over 24 h
  - Decreases central BP
  - Decreases blood pressure variability

- Saves life (ASCOT)

- Offers excellent safety
  - Oedema 0.7%
  - Cough 1.5%