Achieve Best Controls with Fixed Dose Combination for High Blood Pressure

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Cardiovascular Center
Kyung Woo Park, MD, PhD
1. What is the burden of disease and why is controlling BP important?
## Death by cause in the World: 2008 WHO data

<table>
<thead>
<tr>
<th>World</th>
<th>Deaths in millions</th>
<th>% of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>7.25</td>
<td>12.8%</td>
</tr>
<tr>
<td>Stroke and other cerebrovascular disease</td>
<td>6.15</td>
<td>10.8%</td>
</tr>
<tr>
<td>Lower respiratory infections</td>
<td>3.46</td>
<td>6.1%</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>3.28</td>
<td>5.8%</td>
</tr>
<tr>
<td>Diarrhoeal diseases</td>
<td>2.46</td>
<td>4.3%</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1.78</td>
<td>3.1%</td>
</tr>
<tr>
<td>Trachea, bronchus, lung cancers</td>
<td>1.39</td>
<td>2.4%</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1.34</td>
<td>2.4%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.26</td>
<td>2.2%</td>
</tr>
<tr>
<td>Road traffic accidents</td>
<td>1.21</td>
<td>2.1%</td>
</tr>
</tbody>
</table>
Asian Contribution for Global Burden of CVD

50% India, China and other Asian Pacific Island countries
8% Middle Eastern
7% Latin American and Caribbean counties
10% Sub-Saharan Africa
14% Established market economies
8% Formerly socialist economies

Asia

Countries: 46
Population: 3.8 billions
60.5% world population

Murray C J L and Lopez D The Lancet 1997; 349:1269
The Burden of CVD in Asia:
Stroke Deaths by Country, 2002

The Burden of CVD in Asia:
CHD Deaths by Country, 2002

Deaths from coronary heart disease

Number of deaths from coronary heart disease 2002
- 500,000 and above
- 100,000–499,999
- 10,000–99,999
- 1000–9999
- Less than 1000
- No data

Age-Standardized Stroke and CHD Death Rates by Country, 2002

[Bar chart showing stroke and CHD death rates per 100,000 person-year for various countries, with South Asian, Southeast Asian, and East Asian countries highlighted in different colors.]

## Two major CV risk factors in Asia: Blood pressure and Lipid

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Global</th>
<th>Developed country</th>
<th>Developing country</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Blood Pressure</td>
<td>45%</td>
<td>48%</td>
<td>44%</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>48%</td>
<td>57%</td>
<td>46%</td>
</tr>
<tr>
<td>Obesity</td>
<td>18%</td>
<td>27%</td>
<td>16%</td>
</tr>
<tr>
<td>Low fruit and vegetable intake</td>
<td>28%</td>
<td>19%</td>
<td>30%</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>21%</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>Smoking</td>
<td>17%</td>
<td>23%</td>
<td>15%</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Blood Pressure</td>
<td>54%</td>
<td>56%</td>
<td>54%</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>16%</td>
<td>25%</td>
<td>15%</td>
</tr>
<tr>
<td>Obesity</td>
<td>12%</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Low fruit and vegetable intake</td>
<td>11%</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>7%</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Smoking</td>
<td>13%</td>
<td>21%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Global Prevalence of Hypertension

More than a quarter of the world’s adult population had hypertension in 2000, and the number of adults with hypertension is expected to increase 60% by 2025.

The relationship of stroke mortality to blood pressure is strong and direct at all ages.

The relationship of ischemic heart disease mortality to blood pressure is strong and direct at all ages.

2. What do the guidelines say about Hypertension management and Combination Therapy
History of Hypertension Knowledge and Innovation

1940s
- Increased understanding of pathophysiology of hypertension, but treatment is still primitive
  - Rauwolfia serpentina
  - Ganglionic blockers
  - Veratrum alkaloids
  - Hydralazine
  - Guanethidine
  - Thiazide diuretics
  - MSD discovers the first thiazide diuretic, chlorothiazide, and the number of patients treated for hypertension expands rapidly

1950s
- Alpha-2 blockers
- Spironolactone
- Beta blockers

1960s
- Alpha-1 blockers
- ACE inhibitors
- Landmark studies show treating asymptomatic hypertension reduces mortality

1970s
- CCBs
- ARBs

1980s
- Renin inhibitors

1990s

2000s

ACE = angiotensin-converting enzyme; CCB = calcium channel blocker; ARB = angiotensin II receptor blocker.

Evolution of hypertension management guideline evolution in US

1977: JNC I

1980: JNC II

1984: JNC III

1988: JNC IV  →  BP < 140/90 mmHg

1993: JNC V  →  Different BP goal by baseline BP level

1997: JNC VI  →  Different BP goal by RFs: 140/90, 130/85 or 125/75

2003: JNC VII  →  Different BP goal by RFs: 140/90 or 130/80
ESH/ESC 2007 Guidelines
Algorithm for the Treatment of Hypertension

Mild BP elevation
Low/moderate CV risk
Conventional BP target

Choose between

Single agent at low doses

If goal BP not achieved

Previous agent at full doses

Switch to different agent at low doses

Full doses monotherapy

2–3 drug combination at full doses

Two-drug combination at low doses

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

Previous combination at full doses

Add a third drug at low doses

2–3 drug combination at full doses

ESH = European Society of Hypertension; ESC = European Society of Cardiology; BP = blood pressure; CV = cardiovascular.
JNC 7 2003 Guidelines
Algorithm for the Treatment of Hypertension

Lifestyle Modifications

Not at Goal Blood Pressure (<140/90 mmHg)
(<130/80 mmHg for those 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 ACEI, ARB, BB, CCB, or combination.

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

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

With compelling indications*

Drug(s) for the compelling indications
Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.

JNC = Joint National Committee; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; CCB = calcium channel blocker; DBP = diastolic blood pressure; SBP = systolic blood pressure.
# Potential Benefits of Combining Antihypertensive Agents into a Fixed-Dose Combination

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Reason(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• More rapid achievement of goal blood pressure compared with monotherapy</td>
<td>• Greater antihypertensive efficacy</td>
</tr>
<tr>
<td>• Lower rate of adverse events</td>
<td>• Action of one agent ameliorates adverse effects of the other</td>
</tr>
<tr>
<td>• Less need to modify antihypertensive regimen</td>
<td>• Target blood pressure reached more quickly</td>
</tr>
<tr>
<td>• Lower overall cost</td>
<td>• Lower prescription costs and fewer physician visits because of reduced need for regimen modification</td>
</tr>
<tr>
<td>• Improved patient compliance</td>
<td>• Simpler dosing regimen and reduced medication burden</td>
</tr>
<tr>
<td>• More effective than monotherapy, and at least as effective as free combination of same agents</td>
<td>• Combination blocks more than one pathophysiologic pathway</td>
</tr>
</tbody>
</table>

### Guideline Recommendations Regarding Initial Use of Combination Therapy

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>JNC 7</td>
<td>&gt;20/10 mm Hg</td>
</tr>
<tr>
<td>ESH</td>
<td>&gt;20/10 mm Hg OR high cardiovascular risk</td>
</tr>
<tr>
<td>AHA</td>
<td>SBP ≥160 mm Hg or DBP ≥100 mm Hg irrespective of the BP goals</td>
</tr>
<tr>
<td>NKF K/DOQI</td>
<td>SBP &gt;20 mm Hg above goal according to the stage of CKD and CVD risk</td>
</tr>
</tbody>
</table>


ISHIB, International Society on Hypertension in Blacks.

ESH, European Society of Hypertension.

AHA, American Heart Association.

NKF K/DOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

3. What is the rationale for adding a CCB to a RAS blocker?
Why is a CCB Preferred to a Diuretic?

- CCB (usually amlodipine) was the most cost-effective treatment option for treating hypertension unless the patient had heart failure or was at high risk of developing heart failure – i.e. older patient $\geq 75$yrs

- CCB is metabolically neutral – easy to use

- CCB is best at reducing blood pressure variability and BP variability is an independent predictor of clinical outcomes - especially stroke

- At step 2, the combination of $A + C$ was superior to $A + D$ at preventing clinical outcomes

CCB = calcium channel blocker

Rationale for Combination of an ARB and CCB in the Treatment of Hypertension

A powerful, complementary combination of 2 proven MOAs

MOA=mechanism of action; ARB=angiotensin II receptor blocker; CCB=calcium channel blocker; BP=blood pressure; Ca=calcium; RAAS=renin-angiotensin-aldosterone system.
Blood pressure regulation and Renin-Angiotensin System
Blood pressure regulation and Renin-Angiotensin System

i.e. Excessive salt intake
Blood pressure regulation and Renin-Angiotensin System

Sodium restriction
Diuretics
Vasodilation by CCB
Mitigation of CCB-related edema in hypertension by combining RAS blockers and CCB

Complementary Effects of a CCB/RAS Inhibitor: Reduction of CCB-associated Edema

I. Arterial hypertension
   - Constricted blood vessels, high resistance

II. CCBs
   - BP reduction due to arterial vasodilation
   - Tendency towards edema due to absent venodilation
   - BP reduction stimulates RAS and increases Ang II level

III. CCBs + RAS inhibitors*
   - Blockade of RAS inhibits effects of angiotensin II, giving rise to additional BP reduction
   - Additional venodilation by RAS inhibitors reduces edema

*Angiotensin receptor blockers or angiotensin-converting enzyme inhibitors
ACCOMPLISH: Design

Screening

Randomization

Amlodipine 5 mg + benazepril 20 mg
Benazepril 20 mg + HCTZ 12.5 mg

Amlodipine 5 mg + benazepril 40 mg

Benazepril 40 mg + HCTZ 25 mg

Amlodipine 10 + benazepril 40 mg

Free add-on antihypertensive agents*

Month 3
Free add-on antihypertensive agents*

14 Days
Day 1
Month 1
Month 2
Month 3
Year 5

Titrated to achieve BP<140/90 mmHg;
<130/80 mmHg in patients with diabetes or renal insufficiency

*Beta blockers; alpha blockers; clonidine; (loop diuretics).

Jamerson KA et al. Am J Hypertens. 2003;16(part2)193A
Control Rates with Initial Combination Therapy

Control rate (%)

- ACEI / HCTZ (N=5733) 37.2%
- CCB / ACEI (N=5713) 37.9%

P<0.001 at 30 months follow-up

Control defined as <140/90 mmHg
ACCOMPLISH
Kaplan Meier for Primary Endpoint

Cumulative event rate

- ACEI / HCTZ
- CCB / ACEI

20% Risk Reduction

Time to 1st CV morbidity/mortality (days)

HR (95% CI): 0.80 (0.72, 0.90)
CCBs and ARBs: Mechanisms of Action in the Treatment of Hypertension

**CCBs**
- Block calcium channels on smooth muscle cells
- Reduce $Ca^{2+}$-dependent vasoconstriction

**ARBs**
- Inhibit Ang II binding at $AT_1$ receptor
- Reduce vasoconstriction caused by Ang II binding to the $AT_1$ receptor

Two different mechanisms to reduce vasoconstriction

Greater BP reductions than either class alone at relative doses

2. Unger T. *Am J Cardiol.* 2002;89(suppl):3A–10A.

Ang II=angiotensin II
4. Is there an advantage of the Fixed Dose Combination?
Improved Compliance with Fixed-dose Combination Therapy Compared with Free-combination Therapy

Fixed-dose combination (amlodipine/benazepril) (n=2,839) 88.0%
Free combination (ACEI + CCB) (n=3,367) 69.0%

p<0.0001

Medication possession ratio (MPR)†

†Defined as the total number of days of therapy for medication dispensed/365 days of study follow-up

# ADVANTAGES OF FIXED VERSUS FREE COMBINATIONS OF TWO ANTIHYPERTENSIVE DRUGS

<table>
<thead>
<tr>
<th></th>
<th>Fixed</th>
<th>Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplicity of treatment</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Compliance</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Efficacy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tolerability</td>
<td>+*</td>
<td>–</td>
</tr>
<tr>
<td>Price</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Flexibility</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

*Lower doses generally used in fixed-dose combinations
+ = potential advantage
Fixed-dose Combinations Improve Compliance Regardless of Concomitant Medications


<table>
<thead>
<tr>
<th>Number of concomitant drugs</th>
<th>Medication-possession ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>85.9%</td>
</tr>
<tr>
<td>2</td>
<td>87.3%</td>
</tr>
<tr>
<td>3</td>
<td>86.5%</td>
</tr>
<tr>
<td>4</td>
<td>88.8%</td>
</tr>
<tr>
<td>5</td>
<td>87.7%</td>
</tr>
<tr>
<td>6</td>
<td>89.6%</td>
</tr>
<tr>
<td>&gt;6</td>
<td>90.2%</td>
</tr>
<tr>
<td>Fixed-dose combination (n=2,839)</td>
<td></td>
</tr>
<tr>
<td>Free combination (n=3,367)</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.0001

Fixed-dose Combinations Improve Compliance Regardless of Age

A large managed care database analysis (n=5,732)
5. Do we need to consider body types before prescribing anti-HTN medication?
Dose the type of hypertension treatment affects patients’ cardiovascular Outcomes according to their body size?

**Methods**

- divided obese (BMI ≥30, n=5,709), overweight (≥25 to <30, n=4,157), or normal weight (<25, n=1,616) categories

- It is compared event rates (adjusted for age, sex, diabetes, previous cardiovascular events, stroke, chronic kidney disease) for the primary endpoint of cardiovascular death or non-fatal myocardial infarction or stroke
Which outcome comes from ACEI + CCB?

Now what you think?
Comparison of event rates within obese, overweight, and normal weight categories

<table>
<thead>
<tr>
<th></th>
<th>Benazepril and amlodipine</th>
<th>Benazepril and hydrochlorothiazide</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>142/2887 (5%)</td>
<td>152/2822 (5%)</td>
<td>0.89 (0.71-1.12)</td>
<td>0.3189</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>48/2887 (2%)</td>
<td>47/2822 (2%)</td>
<td>0.97 (0.65-1.45)</td>
<td>0.8844</td>
</tr>
<tr>
<td>Total myocardial infarction</td>
<td>67/2887 (2%)</td>
<td>66/2822 (2%)</td>
<td>0.97 (0.68-1.36)</td>
<td>0.8426</td>
</tr>
<tr>
<td>Total stroke</td>
<td>52/2887 (2%)</td>
<td>51/2822 (2%)</td>
<td>0.99 (0.67-1.46)</td>
<td>0.9541</td>
</tr>
<tr>
<td>Overweight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>103/2059 (5%)</td>
<td>137/2098 (7%)</td>
<td>0.76 (0.59-0.94)</td>
<td>0.0369</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>38/2059 (2%)</td>
<td>53/2098 (3%)</td>
<td>0.73 (0.48-1.11)</td>
<td>0.1372</td>
</tr>
<tr>
<td>Total myocardial infarction</td>
<td>44/2059 (2%)</td>
<td>65/2098 (3%)</td>
<td>0.69 (0.47-1.00)</td>
<td>0.0522</td>
</tr>
<tr>
<td>Total stroke</td>
<td>43/2059 (2%)</td>
<td>54/2098 (3%)</td>
<td>0.81 (0.54-1.21)</td>
<td>0.2953</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>43/791 (5%)</td>
<td>75/825 (9%)</td>
<td>0.57 (0.39-0.84)</td>
<td>0.0037</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>21/791 (3%)</td>
<td>34/825 (4%)</td>
<td>0.62 (0.36-1.07)</td>
<td>0.0853</td>
</tr>
<tr>
<td>Total myocardial infarction</td>
<td>14/791 (2%)</td>
<td>28/825 (3%)</td>
<td>0.50 (0.26-0.96)</td>
<td>0.0364</td>
</tr>
<tr>
<td>Total stroke</td>
<td>17/791 (2%)</td>
<td>28/825 (3%)</td>
<td>0.60 (0.33-1.11)</td>
<td>0.1025</td>
</tr>
</tbody>
</table>
Do we need to consider body types before prescribe a medication?

Thiazide-based treatment gives less cardiovascular protection in normal weight than obese patients, but amlodipine based therapy is equally effective across BMI subgroups and thus offers superior cardiovascular protection in non-obese hypertension.

(sub-analysis of the ACCOMPLISH randomized controlled trial)
6. What are the clinical efficacy data for COZAAR XQ™?

(Amlodipine Camsylate and Losartan Potassium)
A Fixed-Dose Combination Therapy for Hypertension
COZAAR XQ: Uncontrolled on Losartan 100 mg* Study Design

- **Objective**
  - Evaluate the efficacy and safety of COZAAR XQ 5/100 mg vs. losartan 100 mg in patients with essential hypertension inadequately controlled on losartan 100 mg

- **Study Design**
  - 8-week, multicenter, randomized, double-blind phase III clinical study

Patients (N = 142)

- Adults ≥18 years with essential hypertension
- Not controlled* on losartan 100 mg monotherapy

32 days run-in treatment period (losartan 100 mg once daily)

8 weeks randomized, double-blind period

Losartan 100 mg (n = 72) once daily

COZAAR XQ 5/100 mg (n = 70) once daily

Primary Endpoint
Mean change in siDBP at 8 weeks

Selected Secondary Endpoints
- Mean change in siSBP at 8 weeks
- Response** rates
- Safety profile

**Defined as siSBP <140 mm Hg or siDBP <90 mm Hg, or change in siSBP >20 mm Hg from baseline, or change in siDBP >10 mm Hg from baseline.

siDBP = sitting diastolic blood pressure
siSBP = sitting systolic blood pressure

COZAAR XQ: Uncontrolled on Losartan 100 mg
Inclusion and Exclusion Criteria

- **Selected Inclusion Criteria**
  - Patients 18 years of age or older with essential hypertension (DBP ≥ 90 mm Hg if drug-treated or ≥ 95 mm Hg if drug-naïve).
  - Non-responders to 4 weeks of treatment with losartan 100 mg monotherapy (sitting DBP≥ 90).

- **Selected Exclusion Criteria**
  - Secondary hypertension
  - A difference in sitting systolic BP measurements ≥20 mm Hg or diastolic BP ≥10 mm Hg between the highest and lowest measurements after 3 measurements
  - Known hypersensitivity to dihydropyridine CCBs or ARBs
  - Mean sitting SBP ≥ 200 mm Hg or mean sitting DBP ≥ 120 mm Hg at screening and mean siSBP ≥ 180 mm Hg or mean sitting DBP ≥ 120 mm Hg after 4 weeks of losartan potassium 100 mg treatment.
  - Clinically significant renal, metabolic, or hepatic disease
  - Severe heart disease or severe neurovascular disease
  - Uncontrolled diabetes mellitus
  - Pregnant or nursing women

COZAAR XQ: Uncontrolled on Losartan 100 mg
Mean Reductions in DBP (Primary Endpoint) and SBP

Mean BP Reductions at 8 weeks (N=142)

<table>
<thead>
<tr>
<th></th>
<th>Mean DBP Reductions</th>
<th>Mean SBP Reductions</th>
</tr>
</thead>
<tbody>
<tr>
<td>COZAAR XQ 5/100 mg</td>
<td>-11.7</td>
<td>-13.4</td>
</tr>
<tr>
<td>Losartan 100 mg</td>
<td>-3.2</td>
<td>-3.4</td>
</tr>
</tbody>
</table>

$P < 0.0001$

The rate of patients who achieved any of the following predefined targets: 1) systolic BP <140 mm Hg or diastolic BP <90 mm Hg, 2) a reduction in systolic BP >20 mm Hg from baseline, or 3) a reduction in diastolic BP >10 mm Hg from baseline.

*The rate of patients who achieved any of the following predefined targets: 1) systolic BP <140 mm Hg or diastolic BP <90 mm Hg, 2) a reduction in systolic BP >20 mm Hg from baseline, or 3) a reduction in diastolic BP >10 mm Hg from baseline.

## COZAAR XQ: Uncontrolled on Losartan 100 mg
### Safety Profile Results (After Randomization)

<table>
<thead>
<tr>
<th></th>
<th>COZAAR XQ 5/100 mg (n=70)</th>
<th>Losartan 100 mg (n=72)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with AEs</td>
<td>21 (30.0%)</td>
<td>16 (22.2%)</td>
<td>0.2911</td>
</tr>
<tr>
<td>Number of AEs</td>
<td>25</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Number of serious AEs</td>
<td>0</td>
<td>1 (1.4%)</td>
<td>0.2306</td>
</tr>
<tr>
<td>Severity of AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>19 (27.1%)</td>
<td>15 (20.8%)</td>
<td>0.5294</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (2.9%)</td>
<td>1 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>1 (1.4%)</td>
<td>0</td>
<td>0.4930</td>
</tr>
<tr>
<td>Drug-related AEs</td>
<td>5 (7.1%)</td>
<td>9 (12.5%)</td>
<td>0.2844</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

COZAAR XQ: Uncontrolled on Amlodipine 5 mg*
Study Design

- **Objective**
  - Compared the efficacy and safety of COZAAR XQ 5/50 mg to amlodipine 10 mg in patients with essential hypertension inadequately controlled on amlodipine 5 mg

- **Study Design**
  - 8-week, multicenter, randomized, double-blind phase III clinical study

Patients (N = 184)
- Adults ≥18 years with essential hypertension
- Not controlled* on amlodipine 5 mg monotherapy

32 days run-in treatment period (amlodipine camsylate 5 mg daily)

8 weeks randomized, double-blind period

- Amlodipine 10 mg (n = 92) once daily
- COZAAR XQ 5/50 mg (n = 92) once daily

Primary Endpoint
Mean change in siDBP at 8 weeks

Selected Secondary Endpoints
- Mean change in siSBP at 8 weeks
- Response** rates
- Safety profile

**Defined as siSBP<140 mm Hg or siDBP<90 mm Hg, or change in siSBP >20 mm Hg from baseline, or change in siDBP>10 mm Hg from baseline.

siDBP = sitting diastolic blood pressure
siSBP = sitting systolic blood pressure

COZAAR XQ: Uncontrolled on Amlodipine 5 mg
Inclusion and Exclusion Criteria

- **Selected Inclusion Criteria**
  - Adults aged 18 or older with essential hypertension with uncontrolled essential hypertension [a sitting DBP ≥90 mm Hg in drug-treated patients and ≥95 mm Hg in drug-naïve patients]
  - Non-responders to 4 weeks of treatment with open-label amlodipine 5 mg monotherapy (DBP ≥90 mm Hg)

- **Selected Exclusion Criteria**
  - Secondary hypertension
  - A difference in sitting systolic BP measurements ≥20 mm Hg or diastolic BP ≥10 mm Hg between the highest and lowest measurements after 3 measurements
  - Known hypersensitivity to dihydropyridine CCBs or ARBs
  - Mean sitting SBP ≥ 200 mm Hg or mean sitting DBP ≥ 120 mm Hg at screening and mean siSBP ≥ 180 mm Hg or mean sitting DBP ≥ 120 mm Hg after 4 weeks of amlodipine 5 mg treatment.
  - Clinically significant renal, metabolic, or hepatic disease
  - Severe heart disease or severe neurovascular disease
  - Uncontrolled diabetes mellitus
  - Pregnant or nursing women

COZAAR XQ: Uncontrolled on Amlodipine 5 mg
Mean Reductions in DBP (Primary Endpoint) and SBP

Mean BP Reductions at 8 weeks (N=183)

<table>
<thead>
<tr>
<th></th>
<th>Mean DBP Reductions</th>
<th>Mean SBP Reductions</th>
</tr>
</thead>
<tbody>
<tr>
<td>COZAAR XQ 5/50 mg</td>
<td>-8.9</td>
<td>-12.2</td>
</tr>
<tr>
<td>Amlodipine 10 mg</td>
<td>-9.4</td>
<td>-13.4</td>
</tr>
</tbody>
</table>

COZAAR XQ: Uncontrolled on Amlodipine 5 mg Additional Efficacy Results

Blood Pressure Response Rates*

<table>
<thead>
<tr>
<th>Blood Pressure Target</th>
<th>COZAAR XQ 5/50 mg</th>
<th>Amlodipine 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate (Patients, %)</td>
<td>89.1%</td>
<td>87.9%</td>
</tr>
</tbody>
</table>

*The rate of patients who achieved any of the following predefined targets: 1) systolic BP < 140 mm Hg or diastolic BP < 90 mm Hg, 2) a reduction in systolic BP > 20 mm Hg from baseline, or 3) a reduction in diastolic BP > 10 mm Hg from baseline.

## COZAAR XQ: Uncontrolled on Amlodipine 5 mg Safety Profile Results

<table>
<thead>
<tr>
<th></th>
<th>COZAAR XQ 5/50 mg (n=92)</th>
<th>Amlodipine 10 mg (n=92)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with AEs</td>
<td>20 (21.7%)</td>
<td>24 (26.1%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Number of AEs</td>
<td>38</td>
<td>31</td>
<td>-</td>
</tr>
<tr>
<td>Number of serious AEs</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Severity of AEs</td>
<td></td>
<td></td>
<td>0.6907</td>
</tr>
<tr>
<td>Mild</td>
<td>15 (16.3%)</td>
<td>21 (22.8%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (3.3%)</td>
<td>2 (2.2%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2 (2.2%)</td>
<td>1 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>0</td>
<td>2 (2.2%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Drug-related AEs</td>
<td>6 (6.5%)</td>
<td>10 (10.9%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Summary

- The burden of CV disease is huge. Hypertension management is key in reducing risk of mortality from CV diseases.

- The guidelines advocate use of combination agents to more effectively reduce BP.

- CCB + RAS blockade combination showed superior outcome compared with Diuretics + RAS blockade in the ACCOMPLISH trial.

- CCB + RAS blockade is effective for BP control irrespective of Body Mass Index (BMI).

- FDC improves compliance to medication, enhances BP lowering effects and reduces potential side effects.
Summary

- COZAAR XQ has been shown to be effective in patients with hypertension:
  - Whose BP was uncontrolled with amlodipine 5 mg
    → COZAAR XQ 5/50 mg
  - Whose BP was uncontrolled with losartan 100 mg
    → COZAAR XQ 5/100 mg

- In controlled clinical trials, <1% of patients taking COZAAR XQ reported peripheral edema