Unmet Need in Hypertension and Heart Failure

-ASPIRE HIGHER: Are there still existing unmet needs? What we expect from new antihypertensive treatment

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Apr 23, 2008 13:10~ 13:25
The Prevalence of Cardiovascular Disease is Increasing in Many Countries

- CVD is increasing in prevalence in many regions of the world, particularly in developing countries and eastern Europe\(^1\)

- In countries where mortality rates from coronary heart disease are falling, morbidity rates – particularly in older age groups – appear to be rising\(^2\)

Change in prevalence 1994–2003, UK

- CHD: +23% (Men), +10% (Women)
- Stroke: +50% (Men), +43% (Women)
- CHD or stroke: +28% (Men), +21% (Women)

Hypertension Usually Has No Symptoms But is A Significant Healthcare Problem

- Hypertension is known as the ‘**silent killer**’ because it usually has no symptoms

- Approximately half of those who have hypertension are **unaware** they have a problem

**WHO Global Burden of Disease Study**

- **Malnutrition**: 11.7%
- **Tobacco use**: 6.0%
- **Hypertension**: 5.8%
- **Poor water supply**: 5.3%
- **Physical inactivity**: 3.9%

Asia is Changing

• **Globalization**
  – Exposure to different attitudes and values
  – Changes in lifestyle and interests
  – New role models

• **Demographic changes**
  – Declining fertility; aging population
  – Increased education and work opportunities for both men and women
  – Increased migration and urbanization

• **Rapid changes in technology**
Prevalence of Hypertension

Lower prevalence but higher growth rate compared to other developed countries

Prevalence of hypertension (%), 35-65 years
(≥140/90mmHg)

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>19%</td>
</tr>
<tr>
<td>Taiwan</td>
<td>22%</td>
</tr>
<tr>
<td>Thailand</td>
<td>22.7%</td>
</tr>
<tr>
<td>Singapore</td>
<td>24.9%</td>
</tr>
<tr>
<td>Korea</td>
<td>26%</td>
</tr>
<tr>
<td>US</td>
<td>28%</td>
</tr>
<tr>
<td>Italy</td>
<td>38%</td>
</tr>
<tr>
<td>England</td>
<td>42%</td>
</tr>
<tr>
<td>Spain</td>
<td>47%</td>
</tr>
<tr>
<td>Germany</td>
<td>55%</td>
</tr>
</tbody>
</table>

MOH clinical practice guideline 2
Global Burden of Hypertension is Predicted to Increase in Spite of Treatment Advances

- Pooled data from 30 population-based studies from around the world (Kearney et al. 2005)

Population-attributable Fractions for Cardiovascular Disease Deaths due to Hypertension

**men**

**women**

J Hypertension 2007
Long-term Treatment for Hypertension Significantly Reduces CV Events….

- Relative risk reduction (%)
  - 50
  - 40
  - 30
  - 20
  - 10
  - 0

- Risk of CV event with ACEI or CCB relative to placebo
  - CHD: 20–21%
  - Stroke: 30–39%
  - CV event: 21–28%

... But Even if Hypertension is Controlled Patients are at Increased Risk of Death and Coronary Heart Disease (CHD)

Overall survival

Non-hypertensive men
Treated hypertensive men

Follow-up BP: NBP 145/93
T-HBP 145/89

p=0.0001

CHD deaths

Non-hypertensive men
Treated hypertensive men

p=0.0001

Andersson OK et al., 1998
Increased Risk of Death in Patients with Hypertension Compared with Non-hypertensive Patients is Multifold

- Risk partly irreversible
- Treatment starts too late

Greater protection is afforded by:

- Drugs with specific organ protective properties
- More aggressive BP reductions <140/90 mmHg
- Correction of multi-factorial risk profile
Hypertension: Problem Setting

- Despite the availability of a range of antihypertensives, the majority of hypertensive patients are **not at goal**

- **Compliance and long-term persistence** with treatment is poor
  - Potentially due to the adverse effects associated with some agents

- Antihypertensive agents need to provide complete **24-hour BP control**

- Patients with hypertension respond differently to the various classes of antihypertensive drugs
  - Most patients require combination therapy to reach goal
Compliance and Persistence are Central Components of Long-term Drug Therapy

**Compliance**: extent to which a patient acts in accordance with the prescribed interval and dose of dosing regimen (= adherence)

**Persistence**: accumulation of time from initiation to discontinuation of therapy

Prescribed regimen for 12 months
- Fully compliant for 12 months
- Fully persistent for 12 months
- Partial compliance
- Non-persistent (stop therapy before 12 months)
- Non-compliant and non-persistent
- Non-acceptance (does not start therapy)

Medication Compliance and Persistence Special Interest Group. International Society of Pharmacoeconomics and Outcomes Research (ISPOR)
### Trends in Awareness, Treatment and Control of Hypertension in Korea

<table>
<thead>
<tr>
<th></th>
<th>Korea</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m</td>
<td>34.4</td>
<td>30.2</td>
</tr>
<tr>
<td>f</td>
<td>26.5</td>
<td>25.6</td>
</tr>
<tr>
<td><strong>Awareness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m</td>
<td>-</td>
<td>47.8</td>
</tr>
<tr>
<td>f</td>
<td>-</td>
<td>65.9</td>
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<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m</td>
<td>25.2</td>
<td>39.2</td>
</tr>
<tr>
<td>f</td>
<td>39.5</td>
<td>60.0</td>
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<tr>
<td><strong>Control (All hypertensive pt)</strong></td>
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<tr>
<td>m</td>
<td>7.6</td>
<td>19.9</td>
</tr>
<tr>
<td>f</td>
<td>16.6</td>
<td>35.0</td>
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<tr>
<td><strong>Control (All treated pt)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m</td>
<td>30.2</td>
<td>50.7</td>
</tr>
<tr>
<td>f</td>
<td>42.0</td>
<td>58.4</td>
</tr>
</tbody>
</table>

The Third Korea National Health and Nutrition Examination Survey (KNHANES III), 2005
US NHANES 1999-2000, JAMA 2003;290;199 (% of adults aged 18 to 74 years)
Large Population of Patients Remain Untreated, Undiagnosed, or Diagnosed and Not Treated

Total US hypertension\(^1\) patients: 41.9 m

- 24% (9.7 m) Treated, controlled
- 28% (12 m) Treated, uncontrolled
- 48% (20.2 m) Undiagnosed or diagnosed + not treated

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\(^1\) Hypertension defined as: 140/90 mmHg

Source:
- Epidemiology Database, The Mattson Jack Group, Hypertension, latest Epidata updates;
- Decision Resources, Decision Base 7, Hypertension Report, Mar 2003;
Over 60% of Treated Hypertensive Patients Require More than One Drug

Source: Datamonitor, Treatment algorithms Hypertension, 2003
### Guidelines Recognize Growing Treatment Complexities and Recommend Tighter Control

For individuals with hypertension and:

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Without diabetes or renal disease</th>
<th>With diabetes or renal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNC VII</td>
<td>BP goal &lt;140/90 mmHg</td>
<td>BP goal &lt;130/80 mmHg</td>
</tr>
<tr>
<td>ESH/ESC</td>
<td>BP goal &lt;140/90 mmHg</td>
<td>BP goal &lt;130/80 mmHg</td>
</tr>
<tr>
<td>WHO/ISH</td>
<td>BP goal &lt;140/90 mmHg</td>
<td>BP goal &lt;130/80 mmHg</td>
</tr>
</tbody>
</table>

Hypertension is Complicated by High Prevalence of Metabolic Disorders

Men

- 0: 19%
- 1: 26%
- 2: 25%
- 3: 22%
- 4+: 8%

Women

- 0: 17%
- 1: 27%
- 2: 24%
- 3: 20%
- 4+: 12%

Obesity
Glucose intolerance
Hyperinsulinaemia
Reduced HDL-C
Elevated LDL-C
Elevated triglycerides

>50% have two or more comorbidities

Hypertensive Patients with Metabolic Syndrome are at a Higher Risk of End-organ Damage

Prevalence of LVH on Echo (%)

<table>
<thead>
<tr>
<th></th>
<th>Without Metabolic syndrome</th>
<th>With Metabolic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=223</td>
<td>25.1</td>
<td>57.7</td>
</tr>
<tr>
<td>p&lt;0.00001</td>
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<td></td>
</tr>
</tbody>
</table>

Prevalence of microalbuminuria (%)

<table>
<thead>
<tr>
<th></th>
<th>Without Metabolic syndrome</th>
<th>With Metabolic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=223</td>
<td>19.3</td>
<td>36.2</td>
</tr>
<tr>
<td>p=0.002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LVH: left ventricular hypertrophy
The RAAS Key Role in Hypertension and The Chronic Vicious Cycle of RAAS Upregulation

- Increased blood pressure
- End-organ damage
- Mechanical stress stimulates vessel RAAS
- Tissue damage stimulates further RAAS activation

Angiotensinogen $\rightarrow$ Renin $\rightarrow$ Angiotensin I $\rightarrow$ ACE $\rightarrow$ Angiotensin II

References:
- Arakawa K et al. Hypertension 2000;36:638–41
- Luft FC et al. Hypertension 1999;33:212–8
ACEI and ARB Block Chain Reaction, But Kidneys Try to Overcome Block by Increasing Renin /PRA
Crystal Structure of Renin


Angiotensinogen
Direct Renin Inhibitor, Aliskiren, Binds to The Active Site of Renin

Aliskiren binds to a pocket in the renin molecule, blocking cleavage of angiotensinogen to angiotensin I

Adapted from Wood JM, et al. 2003
Aliskiren Uniquely Lowers PRA

![Diagram showing the renin-angiotensin-aldosterone system (RAAS) with Aliskiren as a direct renin inhibitor, affecting PRA (renin-angiotensin-aldosterone system activity) uniquely.]
Effect of the Direct Renin Inhibitor Aliskiren, Either Alone or in Combination With Losartan, Compared to Losartan, on Left Ventricular Mass in Patients With Hypertension and Left Ventricular Hypertrophy: The ALiskiren Left Ventricular Assessment of Hypertrophy (ALLAY) Trial

Scott D. Solomon¹, Evan Appelbaum², Warren J. Manning², Anil Verma¹, Tommy Berglund³, Valentina Lukashevich⁴, Cheraz Cherif-Papst⁵, James Carten⁴, Björn Dahlöf³

¹Brigham and Women's Hospital, Boston, MA; ²Beth Israel Deaconess Medical Center, Boston, MA; ³Sahlgrenska University Hospital/Östra, Göteborg, Sweden; ⁴Novartis Pharmaceuticals Corp., East Hanover, NJ; ⁵Novartis Pharma AG, Basel, Switzerland
A double-blind, randomized, active-controlled trial in overweight patients with hypertension and LV hypertrophy

77 centers in 9 countries

Prior ACEI/ARB treatment 12 weeks
No prior ACEI/ARB treatment 2 weeks

Screening & washout phases 2 or 12 weeks

Baseline MRI

Titration phase

Aliskiren 150 mg
Losartan 50 mg
Aliskiren/Losartan 150/50 mg

Randomization
2 Weeks

Maintenance phase
34 weeks

Aliskiren 300 mg
Losartan 100 mg
Aliskiren/Losartan 300/100 mg

Addition of diuretics, and CCBs, α-blockers and/or vasodilators as necessary*

Final MRI

*To achieve BP target of < 140/90 mmHg (< 130/80 mmHg for patients with diabetes)
CCBs, calcium channel blocker; LV, left ventricular
77 centers in 9 countries
CMR for LV mass

Four-chamber end-diastole (ED)

Slice 1
Slice 2
Slice 3
Slice 4
Slice 5
Slice 6
Slice 7
Slice 8
Slice 9
Slice 10

BASE

APEX

slice thickness 10 mm
spatial resolution 2.0 mm x 2.0 mm
temporal resolution 30-50ms

LV, left ventricular; CMR, cardiac magnetic resonance
Effect on Mean Sitting BP of Aliskiren and Losartan Alone or in Combination from Baseline to Week 36

Aliskiren, 300 mg; Losartan, 100 mg; Aliskiren/losartan 300/100 mg

Data are shown as mean (+ SEM) from baseline to Week 36 for the efficacy population.
Effect on LV Mass Index of Aliskiren Alone or in Combination with Losartan from Baseline to Follow-up

Change in LV Mass Index (g/m²)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean ± SEM</th>
<th>Change (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliskiren</td>
<td>-4.9 ± 1</td>
<td>-5.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Losartan</td>
<td>-4.8 ± 1</td>
<td>-4.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aliskiren + Losartan</td>
<td>-5.8 ± 0.9</td>
<td>-6.4%</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Mean (± SEM) for the efficacy population
LV, left ventricular
Hypertension and Heart Failure

- Approximately 5.2 million patients in the US and 10 million patients in Europe have heart failure (HF)\(^1,2\)
- Hypertension precedes HF in approximately 90% of patients with HF\(^3\)
- Despite many proven treatment options being available, the number of patients experiencing mortality due to HF is high and is increasing:
  - approximately 50% of patients with HF will die within 4 years of diagnosis\(^2\)
  - from 1994 to 2004, the number of deaths from HF increased by 28%\(^4\)
- Reasons for the increasing number of patients experiencing mortality due to HF include:
  - greater survival of patients with MI\(^5\) (a risk factor for HF)
  - an increasingly elderly population\(^2,5\) (HF is more prevalent in the elderly)
  - an increasing incidence of hypertension\(^6\) (a major risk factor for HF)

From Hypertension to CHF

Hypertension → Obesity, Diabetes, Smoking, Dyslipidemia → LVH → MI → Left Ventricular Remodeling → Subclinical Left Ventricular Dysfunction → Systolic Dysfunction → Diastolic Dysfunction → CHF → Death

Time, decades

Use of Antihypertensive Agents in Patients with HF

- Elevated systolic and diastolic BP are major risk factors for the development of HF\textsuperscript{1,2}

- Consequently, hypertension precedes the development of HF in approximately 90% of patients with HF\textsuperscript{3}

- Guidelines recommend that BP should be controlled in patients with concomitant hypertension and HF\textsuperscript{4}

- Therefore, it is important that antihypertensive therapies can be safely continued in patients initially receiving treatment for hypertension who go on to develop HF

- However, not all antihypertensives are suitable for use in patients with HF

### Not All Antihypertensive Agents are Suitable for Use in Patients with HF

| CCBs | • Most CCBs should be avoided in HF as they have a cardio-depressant effect\(^1\)  
|      | • CCBs are associated with increased risk of CV events and can lead to worsening HF\(^1\)  
|      | • Only vasoselective CCBs, such as amlodipine, do not adversely affect survival\(^1\)  |

| β-blockers | • β-blockers can initially worsen symptoms of HF\(^2,3\)  
|           | • This effect can be minimized if therapy is initiated at low doses and gradually increased until tolerable therapeutic doses are reached\(^2\)  
|           |   – β-blockers have been shown to significantly reduce mortality in patients with HF and are recommended as standard therapy, unless contraindicated\(^1\)  |

| Direct acting vasodilators | • Potent direct acting vasodilators, such as minoxidil, should be avoided as they cause sodium retention\(^1\)  |

| α-blockers | • There is no evidence for the use of α-blockers in the treatment of HF\(^4\)  |

Why We Need Another Agent?; "Ceiling Benefit" of Neurohumoral Blocking

Breakthrough?

Reduction of mortality in heart failure

Ace-inhibitors
Beta-blockers
Aldosterone
ARBs

Presumed limit for current CHF drug treatment
ACEI + ARB Combinations Showed CV Benefits Beyond Monotherapy…

CV death or HF hospital admission in patients with HF and LVEF ≤40% and being treated with an ACEI

Placebo (n=1,272) Candesartan (n=1,276) Placebo (n=2,499) Valsartan (n=2,511)

15% 13.2%

p<0.001 p=0.021

Relative risk reduction (%)

CV morbidity and mortality in HF patients, 93% of whom were also taking an ACEI

Conclusion

- **End-organ damage** resulting from hypertension is a major public health issue worldwide. Unmet needs in morbidity and mortality remain, despite the success of existing therapies.

- Hypertension contributes to major CV outcomes and the global burden of the condition is projected to **increase**.

- There is an increased need for **combination therapy**.

- Hypertensive patients with metabolic disorders have an even higher risk of end-organ damage.

- Further progress is need to effectively **control the RAAS**.