Hypertension in Asia: What are the issues and opportunities to address the epidemic?

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Contents

• Epidemiology and Risk Factors of Hypertension in Asia
• Diseases Burden related to Hypertension in Asia
• Treatment of Hypertension in Asia
Global Disease Mortality

Major Risk Factors of Global Mortality

- Indoor smoke from solid fuels
- Childhood underweight
- Alcohol use
- Unsafe sex
- High cholesterol
- Overweight and obesity
- Physical inactivity
- High blood glucose
- Tobacco
- Raised blood pressure

Attributable deaths due to selected risk factors (in thousands)
Global Diseases Burden

THE RISK FACTORS ARE WIDESPREAD

Common, modifiable risk factors underlie the major chronic diseases. These risk factors explain the vast majority of chronic disease deaths at all ages, in men and women, and in all parts of the world. They include:

- unhealthy diet;
- physical inactivity;
- tobacco use.

Each year at least:
- 4.9 million people die as a result of tobacco use;
- 2.6 million people die as a result of being overweight or obese;
- 4.4 million people die as a result of raised total cholesterol levels;
- 7.1 million people die as a result of raised blood pressure.

THE THREAT IS GROWING

Deaths from infectious diseases, maternal and perinatal conditions, and nutritional deficiencies combined are projected to decline by 3% over the next 10 years. In the same period, deaths due to chronic diseases are projected to increase by 17%.

This means that of the projected 64 million people who will die in 2015, 41 million will die of a chronic disease – unless urgent action is taken.
Epidemic of CVD in China

Yang Y, et al.
Lancet 2008
Global Burden of Hypertension


2000:
- 972 millions (26.4%)

2025:
- 1560 millions (29.2%)

60%
Burden of Hypertension in Asia

- 2/3 in developing countries
- ~1/3 adult in South-East Asia has hypertension
- ~1.5 million people died of hypertension related diseases each year in South East Asia

Hypertension affects approximately 1 billion people worldwide.

High salt intake increases the risk of CVS events related to hypertension

He et al. Curr Opin Cardiol, 22; 2007:298–305
28 loci associated with SBP/DBP

~ half of the SNPs associated with BP in European can be replicated in different Asian cohort → some common biology of BP across ethnicities.

However, non-replication for other SNPs may indicate a distinct genetic architecture that could help to explain differences in prevalence and disease associations in different ethnicities.
Spectrums of CV Diseases

Cardio / Cerebrovascular Death
End-Stage Renal Disease
Cardio / Cerebrovascular Death
Macro-proteinuria
Nephrotic Proteinuria
End-Stage Heart Disease / Brain Damage & Dementia
Nephritic Proteinuria
Congestive Heart Failure / Secondary Stroke
Ventricular Dilation / Cognitive Dysfunction
Remodelling
Micro-albuminuria
Myocardial Infarction & Stroke
Atherosclerosis and LVH
Risk Factors
Diabetes
Hypertension
Endothelial Dysfunction
Risk Factors
Diabetes
Hypertension
Atherosclerosis and LVH

Adapted from Dzau, Braunwald. *Am Heart J* 1991;121:1244–1263

US 2000:
CAD- 7.3 million
Stroke- 5.4 million

690 million
Global Burden of Cardiovascular Diseases
Each 20/10 mmHg: Doubles CV Event Risk

Fold Increase in Relative CV Risk*

* Individuals aged 40–69 years (N = 1 million).
Lowering BP: ↓ CV risk

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

2 mmHg decrease in mean SBP

Small SBP reductions yield significant benefit

- 7% reduction in risk of CAD & other vascular disease mortality
- 10% reduction in risk of stroke mortality

Lewington et al. Lancet. 2002;360:1903–1913
Asian populations are at greater risk of the adverse effects related to hypertension

Perkovic et al. Hypertension, 50; 2007.991-997
Major Risk Factors of Cardiovascular Diseases

- Hypertension
- Smoking
- WHR
- Physical activity
- Diabetes
- Alcohol intake
- Ratio Apo B to A1
- Diet
- Psychosocial factor
- Cardiac causes

Tu JV. Lancet 2010;376:74-75
INTERSTROKE
Etiology of Stroke in Different Population

- High-income countries (n=422)
- South America (n=151)
- Southeast Asia (n=1146)
- India (n=958)
- Africa (n=323)
INTERSTROKE

Etiology of Stroke in Different Population

Odd Ratio for Stroke

Odd Ratio

- High-income countries (n=422)
- South America (n=151)
- Southeast Asia (n=1146)
- India (n=958)
- Africa (n=323)
Stroke and National Incomes

Prevalence of HT in Different Ethnic Group

Prevalence of Awareness and Controlled Hypertension in Asia

BP Reduction and CVS Prevention

- ...all classes of blood pressure lowering drugs have a similar effect in reducing CHD events and stroke for a given reduction in blood pressure so excluding material pleiotropic effects.

Beneficial Effects of RAAS Blockade


Metabolic Syndrome

Ethnic Difference in Rx Benefit

Perindopril Protection Against Recurrent Stroke Study

<table>
<thead>
<tr>
<th></th>
<th>Strokes Active</th>
<th>Strokes Placebo</th>
<th>Favors active</th>
<th>Favors placebo</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>118</td>
<td>182</td>
<td></td>
<td></td>
<td>39% (22,52)</td>
</tr>
<tr>
<td>Caucasian/other</td>
<td>189</td>
<td>238</td>
<td></td>
<td></td>
<td>22% (5,35)</td>
</tr>
<tr>
<td>Total</td>
<td>307</td>
<td>420</td>
<td></td>
<td></td>
<td>28% (17, 38)</td>
</tr>
</tbody>
</table>

Perkovic: Hypertension, 2007;50:991-997
Genetic Determinants of Treatment Effects with ACEI

Bradykinin Type I Receptor
Angiotensin Type II Receptor
Angiotensin Type II Receptor

Jan Brugts J, et al Eur Heart J 2010
Who Have Higher risk of ACEI Adverse Events?

- Aged 60-69 years
- Female
- East Asian ethnicity
- Smoker (ex or current)
- African-American ethnicity
- Smoker (ex or current)
- History of ACEI cough

Adjusted hazard ratio (discontinuation of treatment) (95% CI)

n=2225

High Incidence of Cough in Chinese Subjects Treated with ACEI

<table>
<thead>
<tr>
<th></th>
<th>Chinese (Hong Kong)</th>
<th>Caucasian (Auckland)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>32/59 (54%)</td>
<td>5/26 (19%)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>27/52 (52%)</td>
<td>4/23 (17%)</td>
</tr>
<tr>
<td>Combined ACE</td>
<td>59/111 (53%)*</td>
<td>9/49 (18%)†</td>
</tr>
<tr>
<td>Control</td>
<td>23/222 (10%)*</td>
<td>4/82 (5%)†</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>5.1</td>
<td>3.8</td>
</tr>
</tbody>
</table>

*p < 0.001; †p < 0.005.
Abbreviations as in Table I.

KS Woo, et al. Am J Cardiol 1995;75:967-968
Genetic Factors for ACEI induced Cough

- Mongenic association analysis of 39 polymorphism and haplotypes
  gene encoding key proteins related to ACEI activity:
  - genetic polymorphisms:
    MME [rs2016848, P=0.002, odds ratio (OR)=1.795]
    BDKRB2 (rs8012552, P=0.012, OR=1.609),
    PTGER3 (rs11209716, P=0.002, OR=0.565)
    ACE (rs4344)- males (P=0.027, OR=0.560) and females (P=0.031, OR=1.847).

- Conclusion: These results are consistent with the hypothesis that the mechanism of cough is related to the accumulation of bradykinin, substance P, and prostaglandins.
### Ethnic Differences in Clinical Outcomes?

#### Primary Outcome

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Asian</th>
<th>Nonasian</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Telmisartan</strong>*</td>
<td>16.7%</td>
<td>14.6%</td>
<td>17.0%</td>
</tr>
<tr>
<td><strong>Ramipril</strong>*</td>
<td>16.5%</td>
<td>16.1%</td>
<td>16.5%</td>
</tr>
<tr>
<td><strong>Relative Risk</strong>*</td>
<td>1.01</td>
<td>0.92</td>
<td>1.03</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.004</td>
<td>0.04</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* No significant difference between asians and non-asians
% Achieving Full Dose at Last Visit

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Asians</th>
<th>Non-Asians</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single Drug</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>74.8%</td>
<td>77.9%</td>
<td>74.3%</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>79.8%</td>
<td>87.6%*</td>
<td>78.6%*</td>
</tr>
<tr>
<td><strong>Combination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>66.9%</td>
<td>71.5%*</td>
<td>66.2%*</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>75.6%</td>
<td>82.9%*</td>
<td>74.4%*</td>
</tr>
</tbody>
</table>

* P < 0.001
## Permanent Withdrawals (Ramipril vs Telmisartan)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>T</td>
<td>R</td>
<td>T</td>
</tr>
<tr>
<td>Discontinued</td>
<td>24.7%</td>
<td>23.4%</td>
<td>19.9%*</td>
<td>14.4%¢</td>
</tr>
<tr>
<td></td>
<td>25.5%*</td>
<td>24.8%¢</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>1.5%</td>
<td>2.1%</td>
<td>1.0%</td>
<td>0.8%¢</td>
</tr>
<tr>
<td></td>
<td>1.6%</td>
<td>2.3%¢</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>0.2%</td>
<td>0.2%</td>
<td>0.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>0.2%</td>
<td>0.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>4.1%</td>
<td>1.0%</td>
<td>5.9%*</td>
<td>1.4%</td>
</tr>
<tr>
<td></td>
<td>3.8%*</td>
<td>1.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.1%</td>
<td>0.2%</td>
<td>--</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>0.2%</td>
<td>0.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angioedema</td>
<td>0.3%</td>
<td>0.1%</td>
<td>0.2%</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
<td>0.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal impairment</td>
<td>0.6%</td>
<td>0.6%</td>
<td>0.3%</td>
<td>0.4%</td>
</tr>
<tr>
<td></td>
<td>0.6%</td>
<td>0.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.0001 (asians vs non-asians)

¢ p < 0.0001 (asians vs non-asians)
Candesartan Antihypertensive Survival Evaluation in Japan Trial

With strict BP control= no significant difference between candesartan-based and amlodipine-based Rx in primary cardiovascular end point in high-risk Asian HT patients.

- BUT, ARB candesartan >> CCB amlodipine for the prevention of new-onset DM.

Ogihara, T. et al. Hypertension 2008;51:393-398
A total of 3501 pts (1167, benidipine-ARB; 1166, benidipine-β-blocker; and 1168, benidipine-thiazide) who received each combination treatment were included in the analysis.

CCB combined with ARB, β-blocker, or thiazide diuretic was similarly effective for the prevention of cardiovascular events and the achievement of target BP.
Comparison between Valsartan and Amlodipine on CVD Events in Hypertensive Patients with Glucose Intolerance: NOGOYA Heart Study

- With strict BP control = no significant difference between Valsartan-based and amlodipine-based Rx in primary cardiovascular end point in high-risk Asian HT patients with glucose intolerance
- BUT, ARB valsartan >> CCB amlodipine for the prevention heart failure

Conclusions

• Hypertension is a major risk factor for CVD, especially stroke in Asia
• Awareness and treatment of hypertension in Asia remain suboptimal
• Blockade of RAS with ARB is equally effective as CCB, but prevent new-onset DM and heart failure
• Combination of ARB with BB, CCB or diuretic have similar efficacy for BP control in Asian