The role of fixed-dose combination therapy in the management of hypertension

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Global burden of hypertension

- Hypertension is the primary major cause of premature death
- 972 million with hypertension estimated in 2000 predicted to rise to 1.56 billion by 2025
- 80% increase in hypertension expected in economically developing regions

WHO findings on hypertension

- The #1 global risk factor for premature mortality causing 7.5 million deaths per annum
- Responsible for 51% of stroke and 45% of ischaemic heart disease deaths

Global health risks. WHO 2009
Management of hypertension today

- The most common CV disorder affecting 27-55% of adults\(^1\)
- A major risk factor for CV and renal disease\(^{1,2}\)
- Level of protection achieved against CV diseases is related to the degree of BP reduction\(^2\)
- However, only 20-55% of treated patients achieve and maintain internationally recognised targets \(^{1,2}\)

Poor BP control in practice populations

Cross-sectional survey of 5413 hypertensive patients in Denmark

“Approximately 7 out of 10 hypertensive patients in Europe do not achieve target BP”  

1. Paulsen M et al. Family Practice 2011; published online, May 19, 2011
Most treated patients in Eastern Europe do not achieve target BP

7,860 treated patients in the BP-CARE survey in Central and Eastern Europe (9 countries)

27.10% Controlled BP
72.9% Uncontrolled BP

% of patients displaying office BP controlled (<140/90 mmHg) or uncontrolled ≥140/90 mmHg

## Causes of inadequate BP control

<table>
<thead>
<tr>
<th>Patient/society</th>
<th>Misdiagnosis</th>
<th>Doctor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poverty, lack of health insurance</td>
<td>Improper BP recording technique</td>
<td>Physician inertia, poor motivation to deliver patient education</td>
</tr>
<tr>
<td>Lack of education, health beliefs</td>
<td>White coat syndrome</td>
<td>Multiple guidelines</td>
</tr>
<tr>
<td>Difficulty in implementing lifestyle change</td>
<td>Masked hypertension</td>
<td>Insufficient use of multiple agents or insufficient dosing</td>
</tr>
</tbody>
</table>
| Compliance issues relating to cost, side-effects, inconvenience, pill burden |                                  | Failure to identify secondary hypertension
|                                         |                                     | Authentic resistant hypertension                         |
|                                         |                                     | Interactions with other prescribed medication            |

Inadequate BP control is associated with increased risk of fatal events

<table>
<thead>
<tr>
<th>Hypertension category</th>
<th>All-cause mortality</th>
<th>CVD mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated controlled</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Treated uncontrolled</td>
<td>1.57 (1.28-1.91)*</td>
<td>1.74 (1.36-2.22)*</td>
</tr>
<tr>
<td>Untreated</td>
<td>1.34 (1.12-1.62)*</td>
<td>1.37 (1.04-1.81)**</td>
</tr>
</tbody>
</table>

Risk of CVD mortality increased by 74% in uncontrolled hypertensives

Data from NHANES III in US hypertensive adults (1988-2006)

§ adjusted for age, race/ethnicity, smoking, hypercholesterolaemia, obesity, diabetes, CKD, HF, stroke

* p<0.01; ** p<0.05

Multiple therapies are required to achieve target BP\(^1\)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number of drugs needed to achieve BP 140/90 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Men (all ages) n</td>
<td>333</td>
</tr>
<tr>
<td>Men (all ages) %</td>
<td>22.3%</td>
</tr>
<tr>
<td>Women (all ages) n</td>
<td>154</td>
</tr>
<tr>
<td>Women (all ages) %</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

Evidence has continued to grow that in the vast majority of hypertensive patients, effective BP control can only be achieved by combination of at least two antihypertensive drugs \(^3\)

≥75% of patients require multiple therapies to achieve target \(^2\)

Pathophysiology of essential hypertension: multiple causes

Adapted from Sever P, Messerli FH. *Eur Heart J* 2011;32:2499-506.
Rationale for combination therapy:¹

- Combines drugs acting in different physiological systems¹
- Blocks counter-regulatory responses¹
- Treats moderate/severe hypertension¹
- Reduces BP variability vs monotherapy¹,³

>75% of patients require combination therapy to achieve BP target²

Criteria for an optimal fixed dose combination

- Component drugs should act via different and complementary mechanisms
- BP-decreasing effect of combination is greater than that of components alone
- Incidence of side-effects should be reduced or at least not increased
- Combination should be efficacious in once-daily treatment
- Combination should provide protection against target organ damage

Combination therapy is recommended in ESH/ESC guidelines

Combination therapy is more effective than increasing the dose of monotherapy

A meta-analysis of 42 trials and 10968 patients shows that combining two different antihypertensive classes gives approximately 5 times greater additional fall in BP than doubling the dose of a single drug.

Combination of complementary therapies may improve drug efficacy

Effects of 2 different drugs on BP separately and in combination (summary results from 119 randomised placebo-controlled comparisons from 50 trials)

Fixed dose combinations improve compliance and persistence

Retrospective cohort of 14449 hypertensive patients receiving fixed dose combination and switched to free combination

*Patients regarded as persistent if remaining on therapy during the last month
** Compliance measured by Medication Possession Ratio (MPR)

Adapted from Hess G. *Pharmacy & Therapeutics* 2008;33:652-66.
Guidelines recommend use of combination therapy

<table>
<thead>
<tr>
<th>Source</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNC 7 2003 ¹</td>
<td>“More than two-thirds of hypertensive individuals cannot be controlled on one drug and will require two or more antihypertensive agents selected from different drug classes.”</td>
</tr>
<tr>
<td>ESH/ESC 2007 ²</td>
<td>“Regardless of the drug employed, monotherapy allows to achieve BP target in only a limited number of hypertensive patients. Use of more than one agent is necessary to achieve target BP in the majority of patients.”</td>
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<td>ESH 2009 ³</td>
<td>“Evidence has continued to grow that in the vast majority of hypertensive patients, effective BP control can only be achieved by combination of at least two antihypertensive drugs.”</td>
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2013 ESH/ESC Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

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Complementary modes of action
Bisoprolol and amlodipine short product characteristics

Bisoprolol$^{1,2}$
- Highly selective beta blocker
- Sympathetic control
- Blocks sympathetic effects
  - $\downarrow$ Heart rate
  - $\downarrow$ Cardiac output
  - $\downarrow$ Blood pressure

Amlodipine$^3$
- Potent calcium channel blocker
- $\uparrow$ Vasodilatation
- $\downarrow$ Peripheral resistance
- $\downarrow$ Blood pressure

Complementary cardioprotection beyond blood pressure control

1. Murdoch D and Heel RC. *Drugs* 1991;41:478-505;
2. Cruickshank JM. *Int J Cardiol* 2007;120:10-27;
Concor AM provides a significant relative reduction in blood pressure within 4 weeks

Observational open-labelled, non-comparative survey of 801 patients with stage 2 hypertension in 169 Indian centres.

Adapted from Rana R & Patil A. *Indian Pract* 2008;61:225-34.
Concor AM significantly reduces heart rate

Observational open-labelled, non-comparative survey of 801 patients with stage 2 hypertension in 169 Indian centres.

Adapted from Rana R & Patil A. *Indian Pract* 2008;61:225-34.
Good tolerability profile: adverse events

After 4 weeks of treatment with Concor AM (5 mg + 5 mg) once daily, 90% of patients report good to excellent tolerability.

Observational open-labelled, non-comparative survey of 801 patients with stage 2 hypertension in 169 Indian centres.

Adapted from Rana R & Patil A. *Indian Pract* 2008;61:225-34.
Conclusion

- Hypertension is the number one global risk factor for premature mortality
- Approximately 7 out of 10 hypertensive patients do not achieve target BP
- Causes for inadequate BP control involve many factors, one of the most important being poor patient compliance
- More than 75% of patients require combination therapy to achieve target BP
- Fixed dose combinations significantly improve patient compliance and number of controlled hypertensive patients