

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

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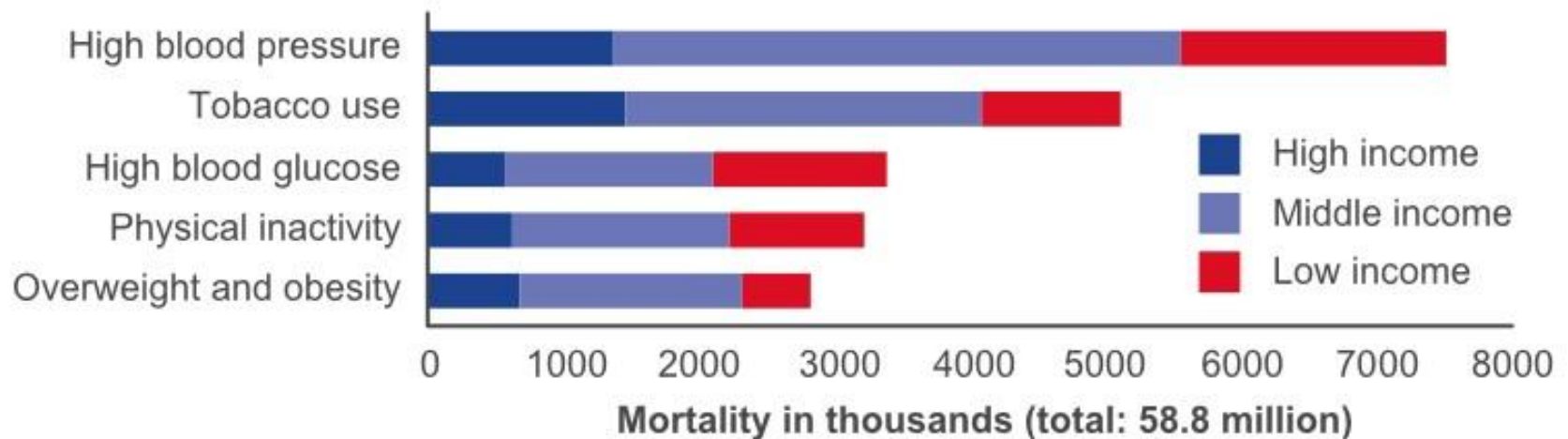
Croatia

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



Management of hypertension today

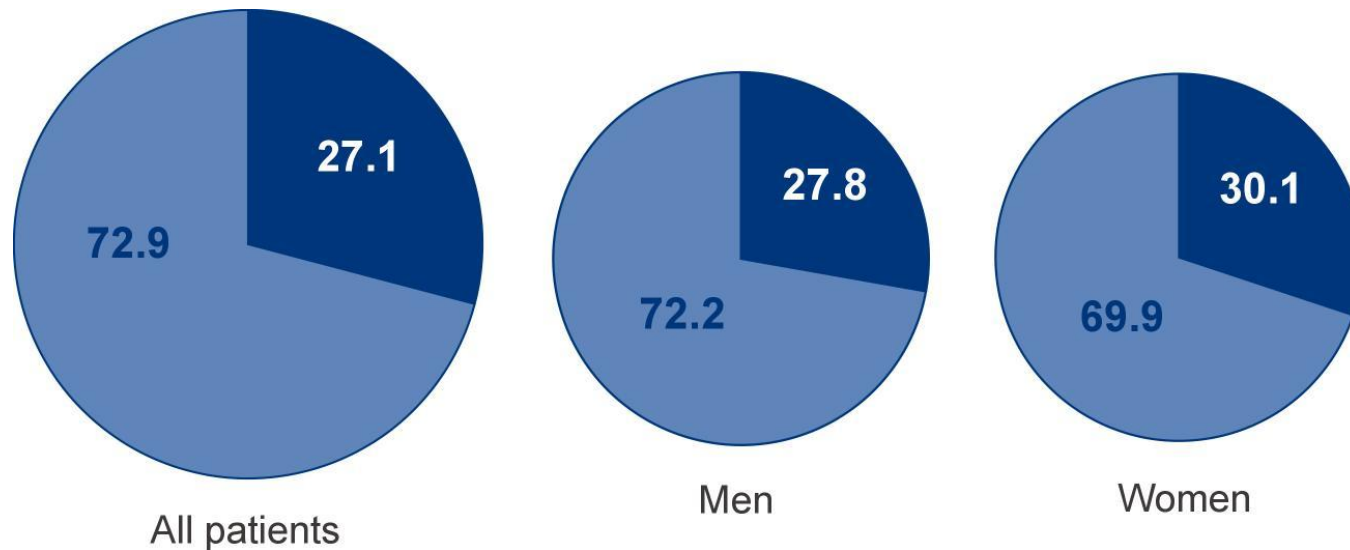
- The most common CV disorder affecting 27-55% of adults¹
- A major risk factor for CV and renal disease^{1,2}
- Level of protection achieved against CV diseases is related to the degree of BP reduction²
- However, only 20-55% of treated patients achieve and maintain internationally recognised targets^{1,2}

1. Wolf-Maier K *et al.* *Hypertension* 2004;**43**:10-17.

2. Struijker-Boudier H *et al.* *Int J Clin Pract* 2007;**61**:1592-602.

Poor BP control in practice populations¹

Cross-sectional survey of 5413 hypertensive patients in Denmark¹



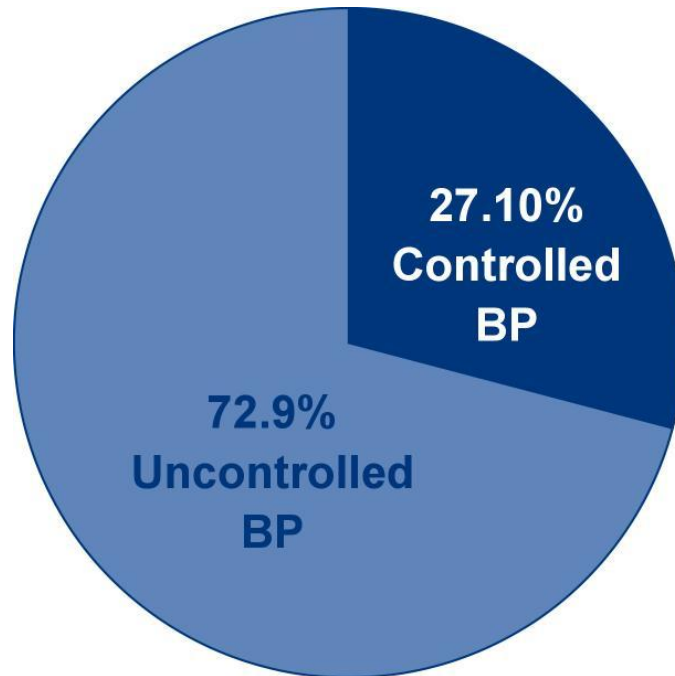
“Approximately 7 out of 10 hypertensive patients in Europe do not achieve target BP”²

■ Controlled BP
■ Uncontrolled BP

1. Paulsen M *et al.* *Family Practice* 2011; published online, May 19, 2011
2. Burnier M *et al.* *Int J Clin Pract* 2009;**63**:790-8.

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)



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

Causes of inadequate BP control

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

Adapted from Elijevich F *et al. Ther Adv Cardiovasc Dis* 2009;**3**:231-40.

Inadequate BP control is associated with increased risk of fatal events

n=5128 Fully adjusted models §	Hazard ratio (95% CI)	
	Hypertension category	Hazard ratio (95% CI)
	All-cause mortality	CVD mortality
Treated controlled	1.00	1.00
Treated uncontrolled	1.57 (1.28-1.91)*	1.74 (1.36-2.22)*
Untreated	1.34 (1.12-1.62)*	1.37 (1.04-1.81)**

Risk of CVD mortality increased by 74% in uncontrolled hypertensives ¹

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

1. Gu Q *et al. Am J Hypertens* 2010;**23**:38-45.

Multiple therapies are required to achieve target BP¹

	Number of drugs needed to achieve BP 140/90 mmHg				
Patients	1	2	3	4	5 +
Men (all ages) n	333	400	408	248	104
Men (all ages) %	22.3%	26.8%	27.3%	16.6%	7.0%
Women (all ages) n	154	263	387	317	219
Women (all ages) %	11.5%	19.6%	28.9%	23.7%	16.3%

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

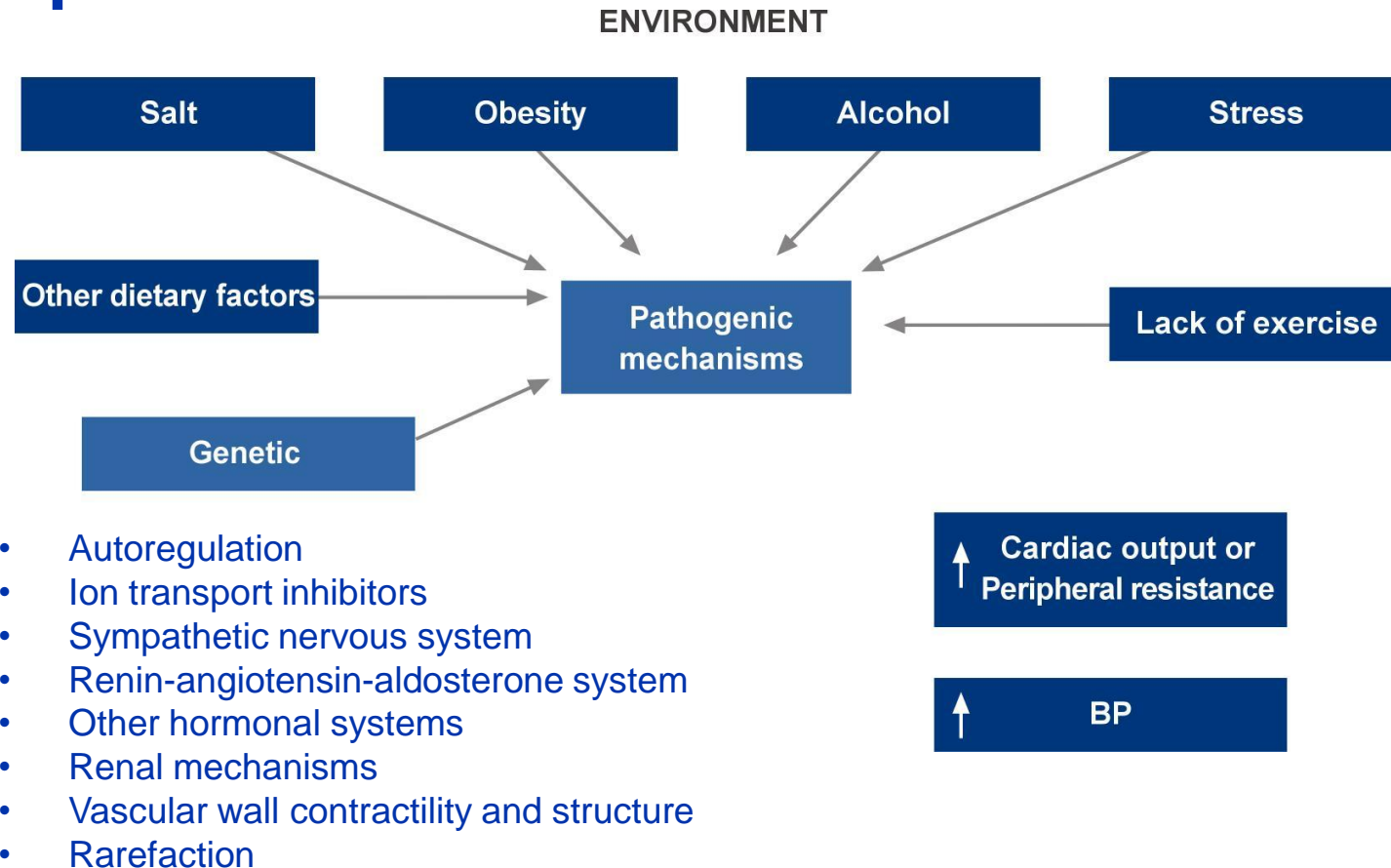
≥75% of patients require multiple therapies to achieve target ²

1. Adapted from Marshall T. *J Hum Hypertens* 2005;**19**:317-9.

2. Gradman A *et al. J Am Soc Hypertens* 2010;**4**:42-50.

3. Mancia *et al. J Hypertens* 2009; **27**:2121-58

Pathophysiology of essential hypertension: multiple causes



Rationale for combination therapy:¹

- Combines drugs acting in different physiological systems¹
- Blocks counter-regulatory responses¹
- Treats moderate/severe hypertension¹
- Reduces BP variability vs monotherapy^{1,3}

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

1. Sever P, Messerli FH. *Eur Heart J* 2011;**32**:2499-506.
2. Gradman A *et al.* *J Am Soc Hypertens* 2010;**4**:42-50.
3. Rothwell P *et al.* *Lancet* 2010;**375**:895-905.

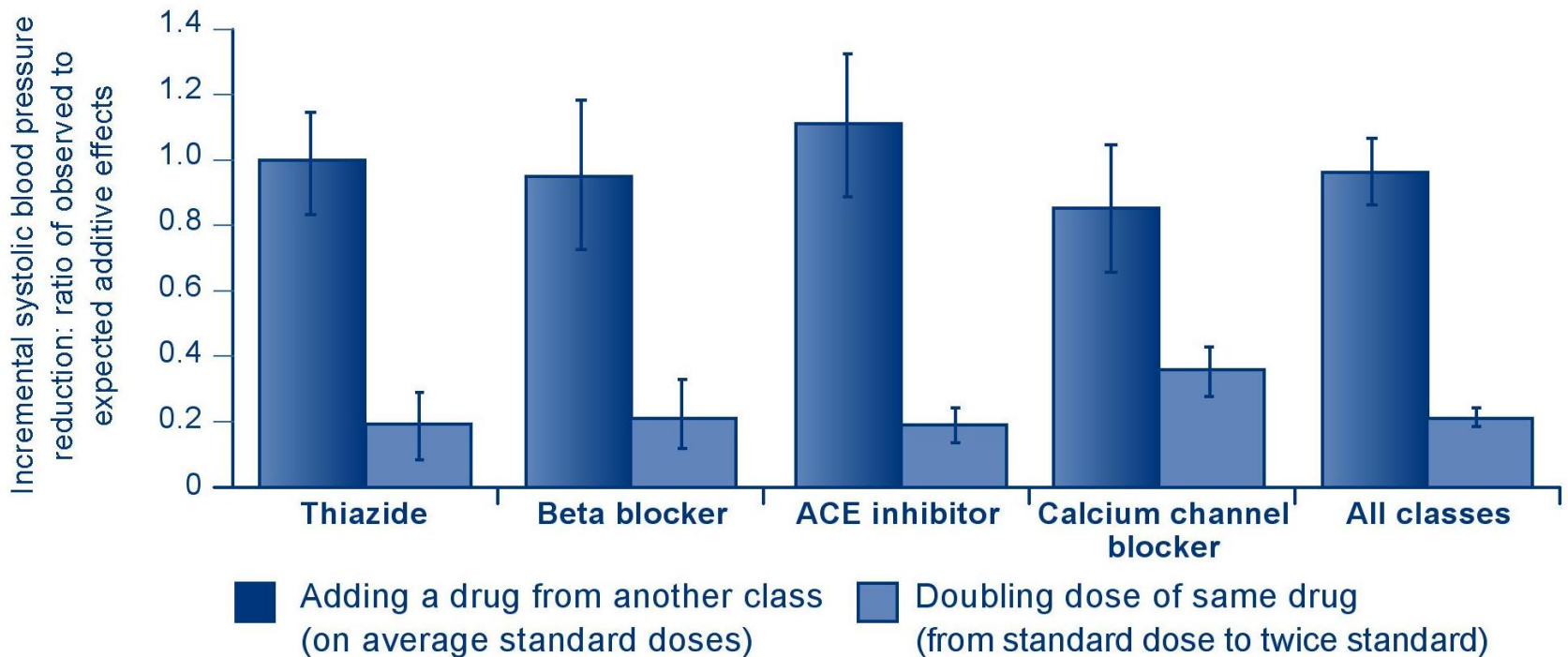
Criteria for an optimal fixed dose combination¹

- 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 guidelines²

1. Struijker-Boudier H *et al. Int J Clin Pract* 2007;**61**:1592-602.
2. Mancia G *et al. J Hypertens* 2009;**27**:2121-58. DOI:10.1097/HJH.0b013e328333146d.

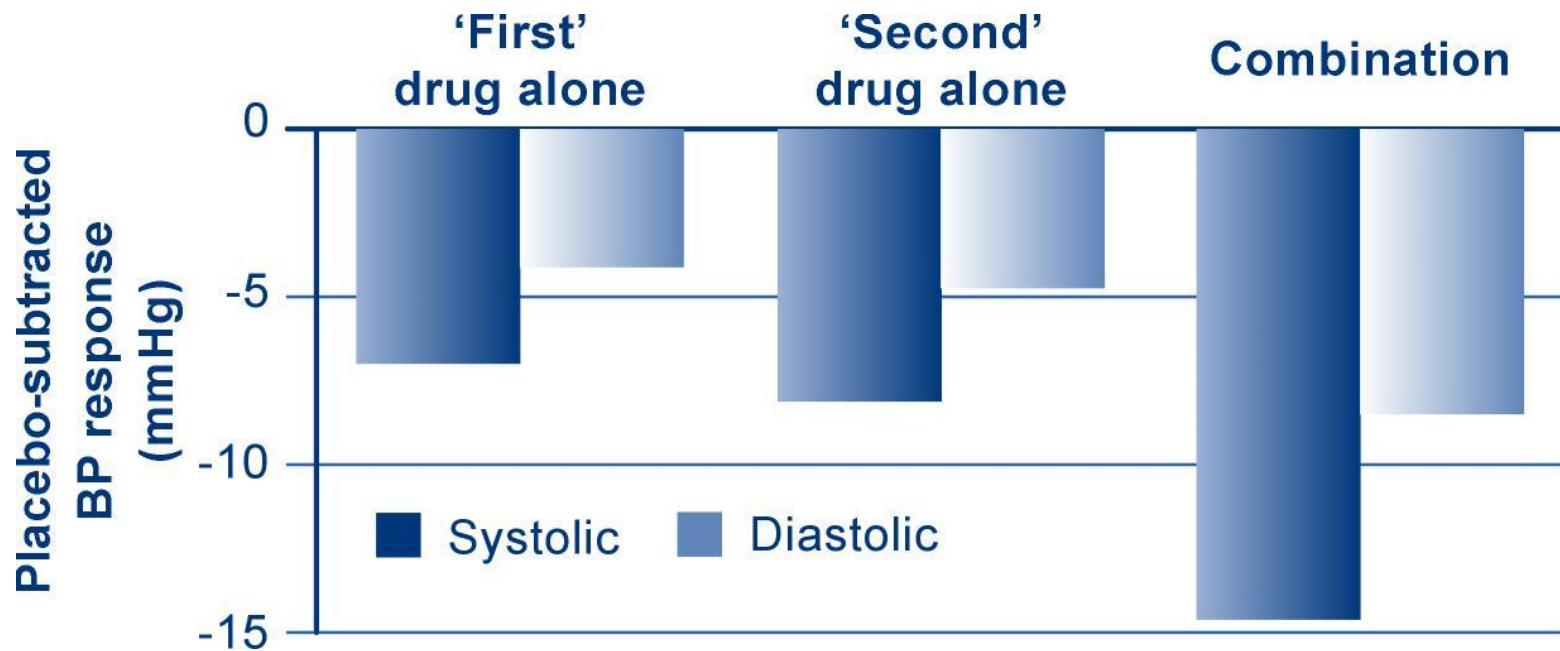
Combination therapy is more effective than increasing the dose of monotherapy



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.

Adapted from Wald D *et al. Am J Med* 2009;**122**:290-300.

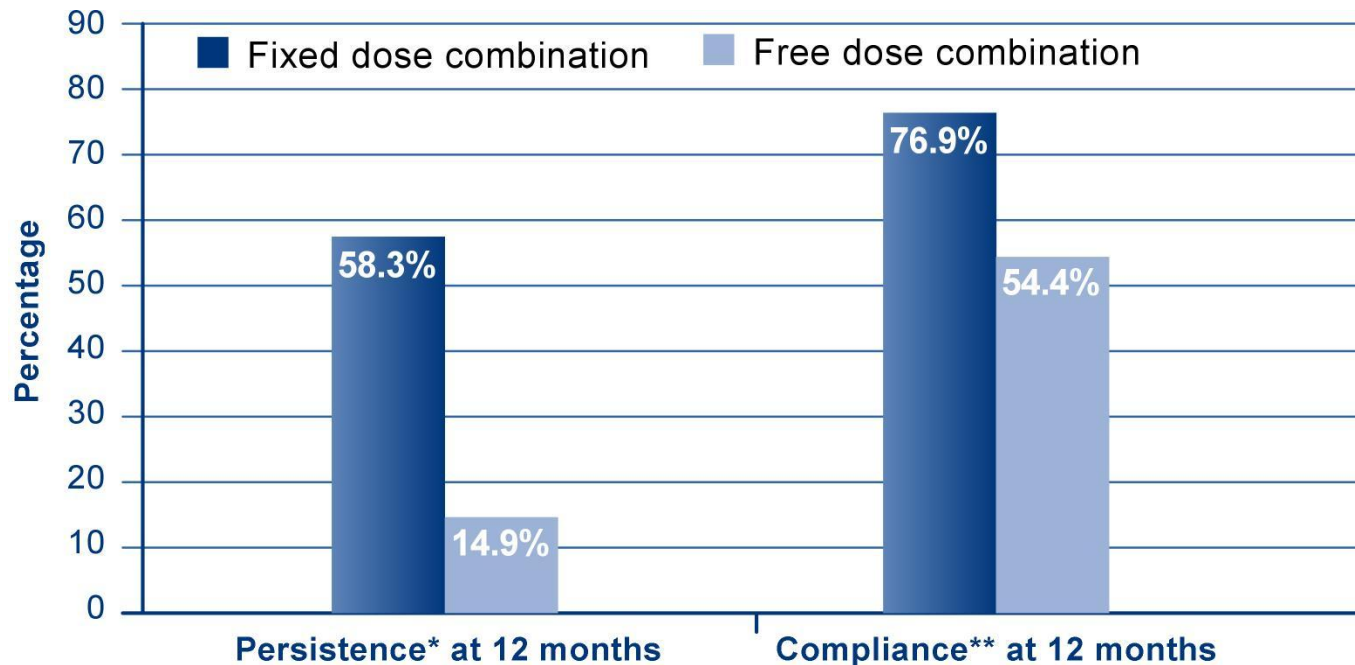
Combination of complementary therapies may improve drug efficacy



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

Adapted from Law M *et al.* *BMJ* 2003;**326**:1427-31.

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

JNC 7 2003 ¹	“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.”
ESH/ESC 2007 ²	“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.”
ESH 2009 ³	“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.”

1. Chobanian A *et al.* JNC 7 guidelines. *Hypertension* 2003;**42**:1206-52.
2. Mancia G *et al.* ESH/ESC guidelines. *J Hypertens* 2007;**25**:1751-62.
3. Mancia G *et al.* Reappraisal of European guidelines. *Blood Press* 2009;**18**:308-347.



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)

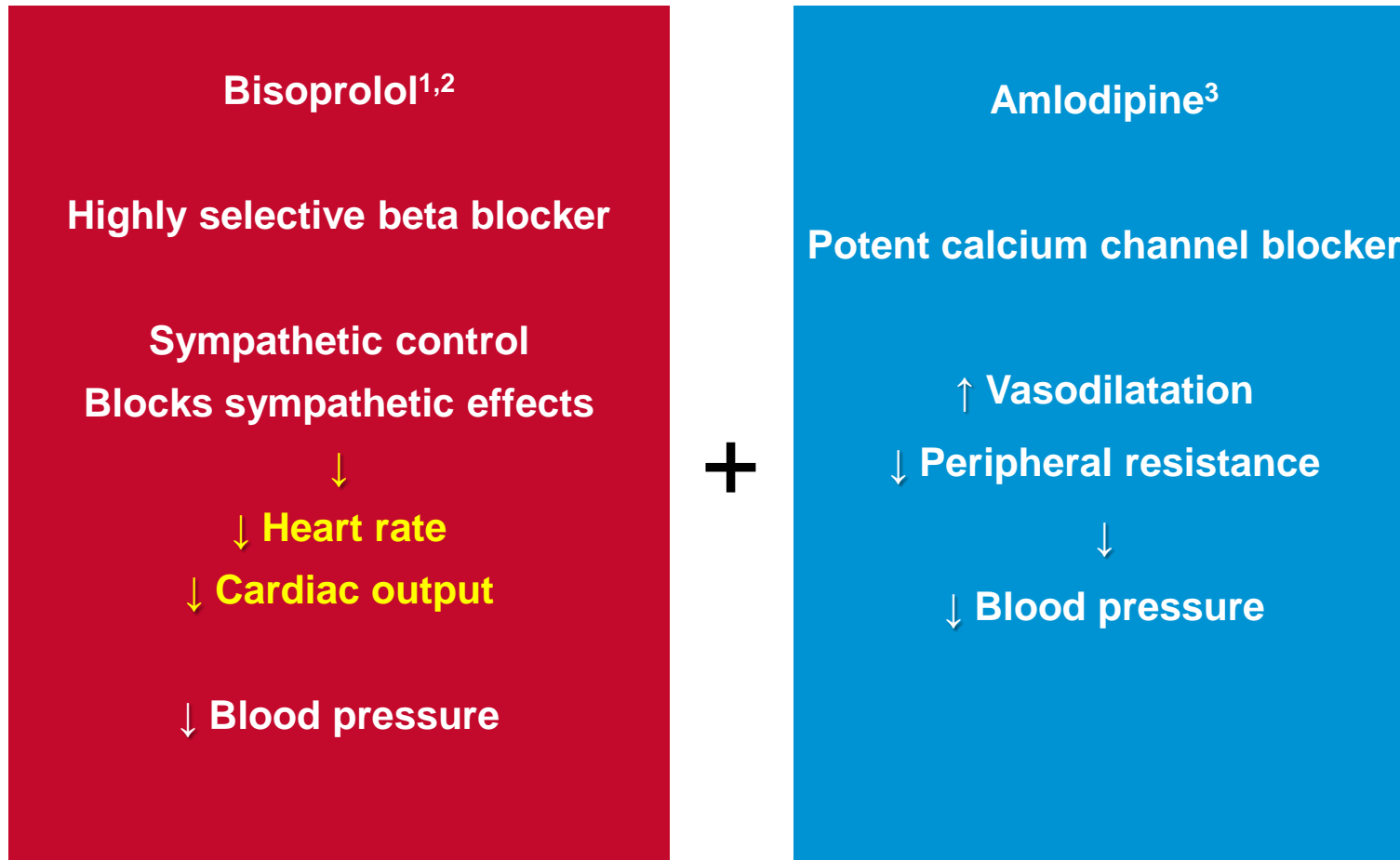
Authors/Task Force Members: Giuseppe Mancia (Chairperson) (Italy)*, Robert Fagard (Chairperson) (Belgium)*, Krzysztof Narkiewicz (Section co-ordinator) (Poland), Josep Redon (Section co-ordinator) (Spain), Alberto Zanchetti (Section co-ordinator) (Italy), Michael Böhm (Germany), Thierry Christiaens (Belgium), Renata Cifkova (Czech Republic), Guy De Backer (Belgium), Anna Dominiczak (UK), Maurizio Galderisi (Italy), Diederick E. Grobbee (Netherlands), Tiny Jaarsma (Sweden), Paulus Kirchhof (Germany/UK), Sverre E. Kjeldsen (Norway), Stéphane Laurent (France), Athanasios J. Manolis (Greece), Peter M. Nilsson (Sweden), Luis Miguel Ruilope (Spain), Roland E. Schmieder (Germany), Per Anton Sirnes (Norway), Peter Sleight (UK), Margus Viigimaa (Estonia), Bernard Waeber (Switzerland), Faiez Zannad (France)

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ESC Committee for Practice Guidelines (CPG): Jose Luis Zamorano (Chairperson) (Spain), Stephan Achenbach (Germany), Helmut Baumgartner (Germany), Jeroen J. Bax (Netherlands), Héctor Bueno (Spain), Veronica Dean (France), Christi Deaton (UK), Cetin Erol (Turkey), Robert Fagard (Belgium), Roberto Ferrari (Italy), David Hasdai (Israel), Arno W. Hoes (Netherlands), Paulus Kirchhof (Germany/UK), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Patrizio Lancellotti (Belgium), Ales Linhart (Czech Republic), Petros Nihoyannopoulos (UK), Massimo F. Piepoli (Italy), Piotr Ponikowski (Poland), Per Anton Sirnes (Norway), Juan Luis Tamargo (Spain), Michał Tendera (Poland), Adam Torbicki (Poland), William Wijns (Belgium), Stephan Windecker (Switzerland)

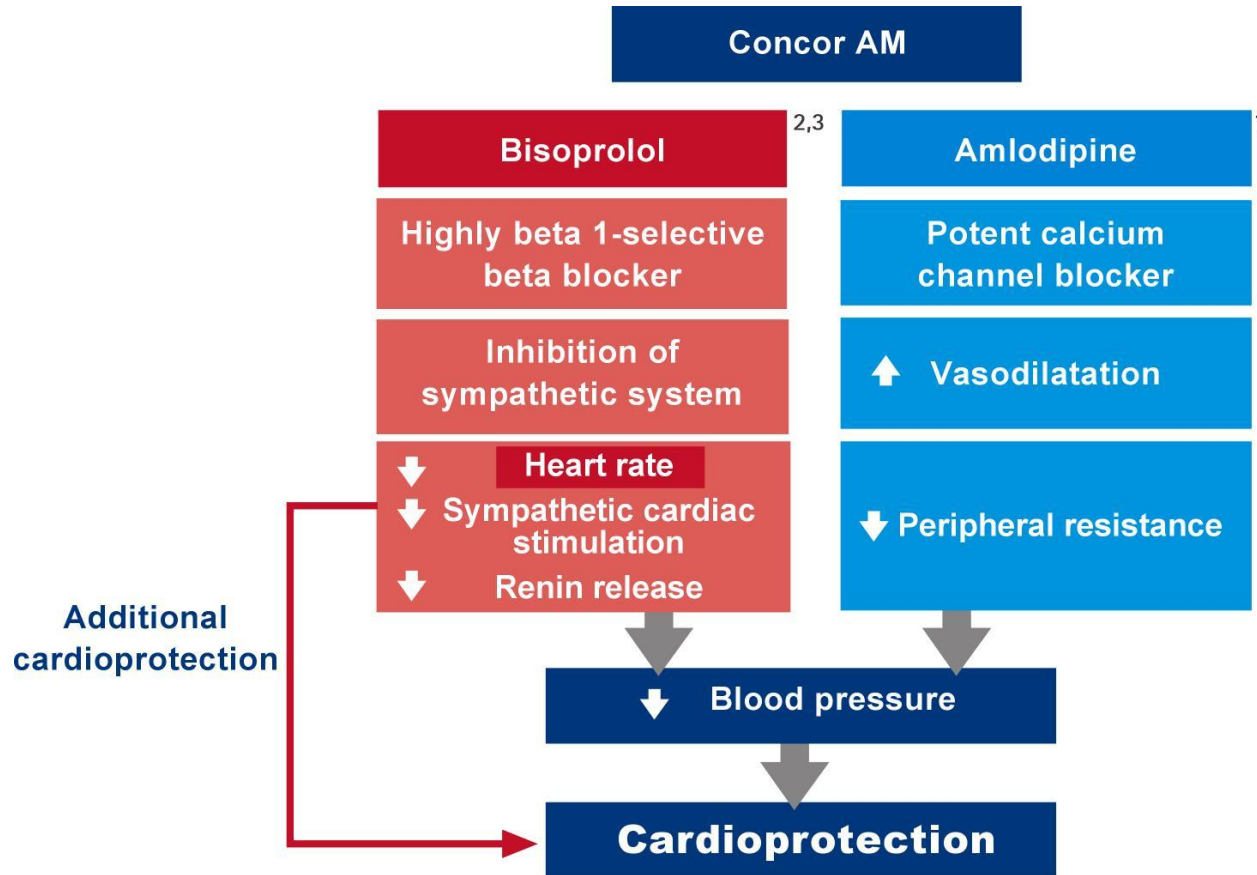
Complementary modes of action

Bisoprolol and amlodipine short product characteristics



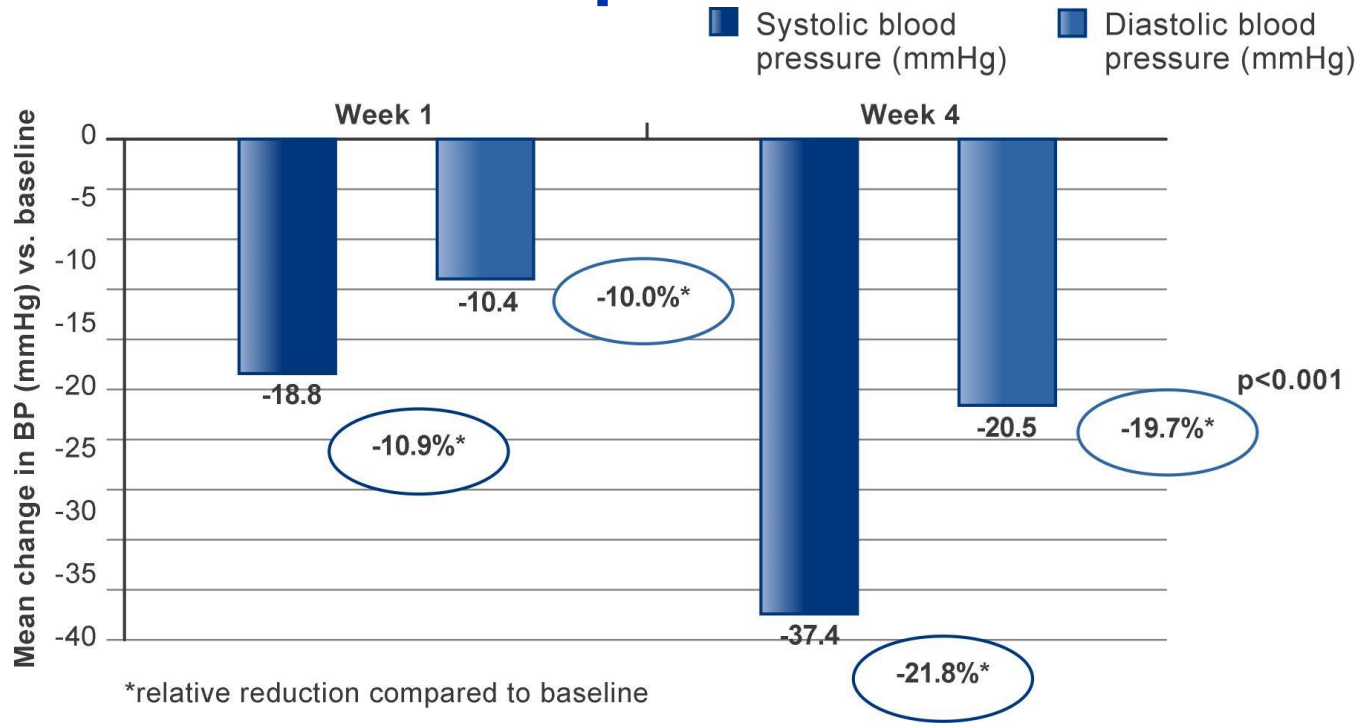
1. Cruickshank JM. *Int J Cardiol* 2007;**120**:10-27;
2. Palatini P *et al.* *Drugs* 2006;**66**:133-144.
3. Murdoch D and Heel RC. *Drugs* 1991;**41**:478-505.

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;
3. Palatini P *et al.* *Drugs* 2006;**66**:133-144.

Concor AM provides a significant relative reduction in blood pressure within 4 weeks

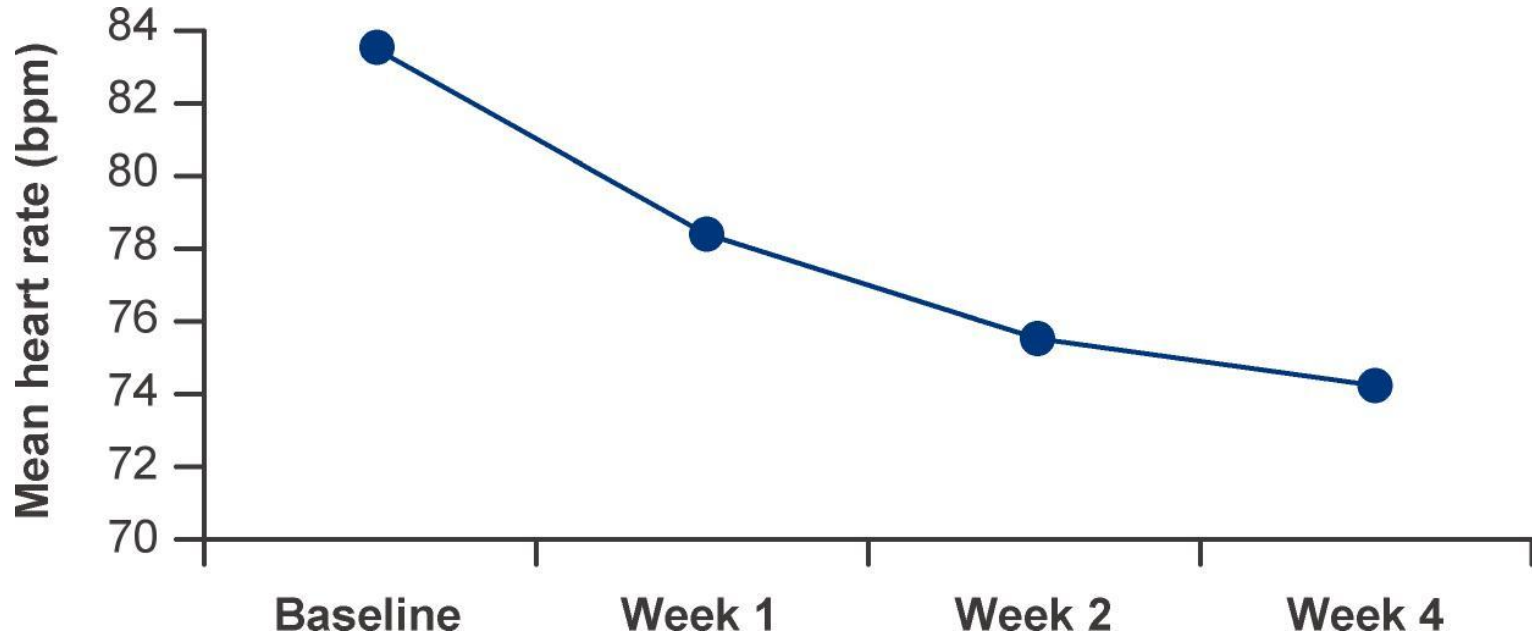


82.5% of patients achieved BP goal (<140/90 mmHg)

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

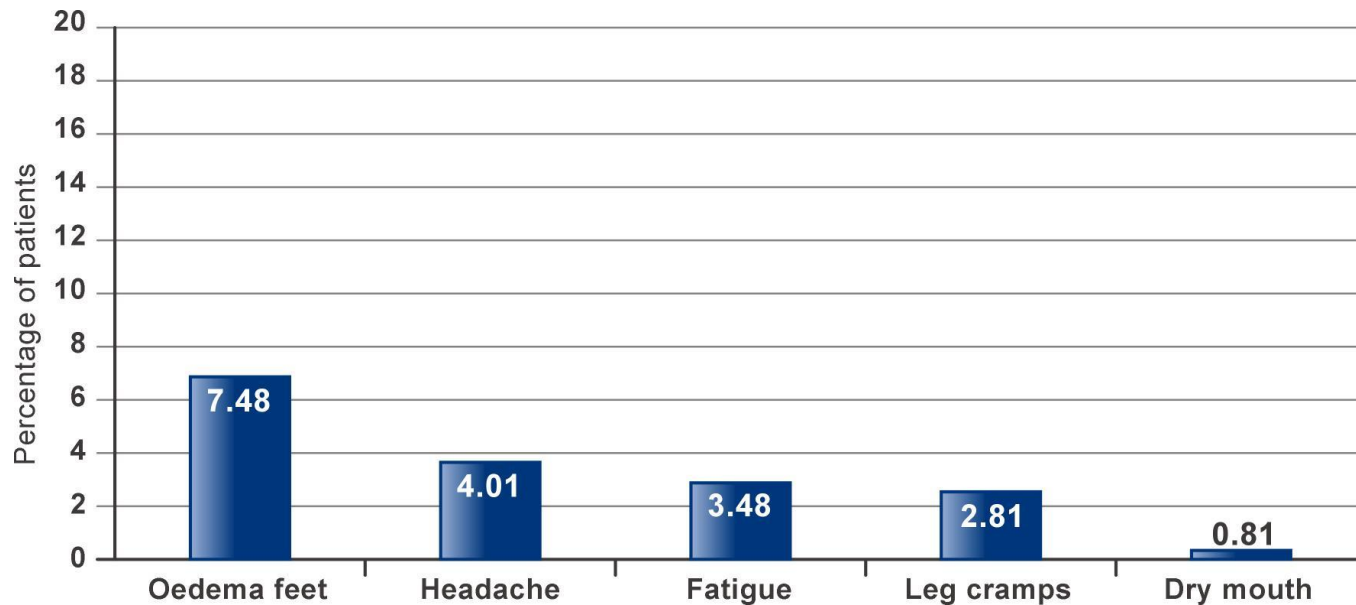


Observational open-labelled, non-comparative survey of 801 patients with stage 2 hypertension in 169 Indian centres.

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

Good tolerability profile: adverse events

Adverse events reported during the study



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