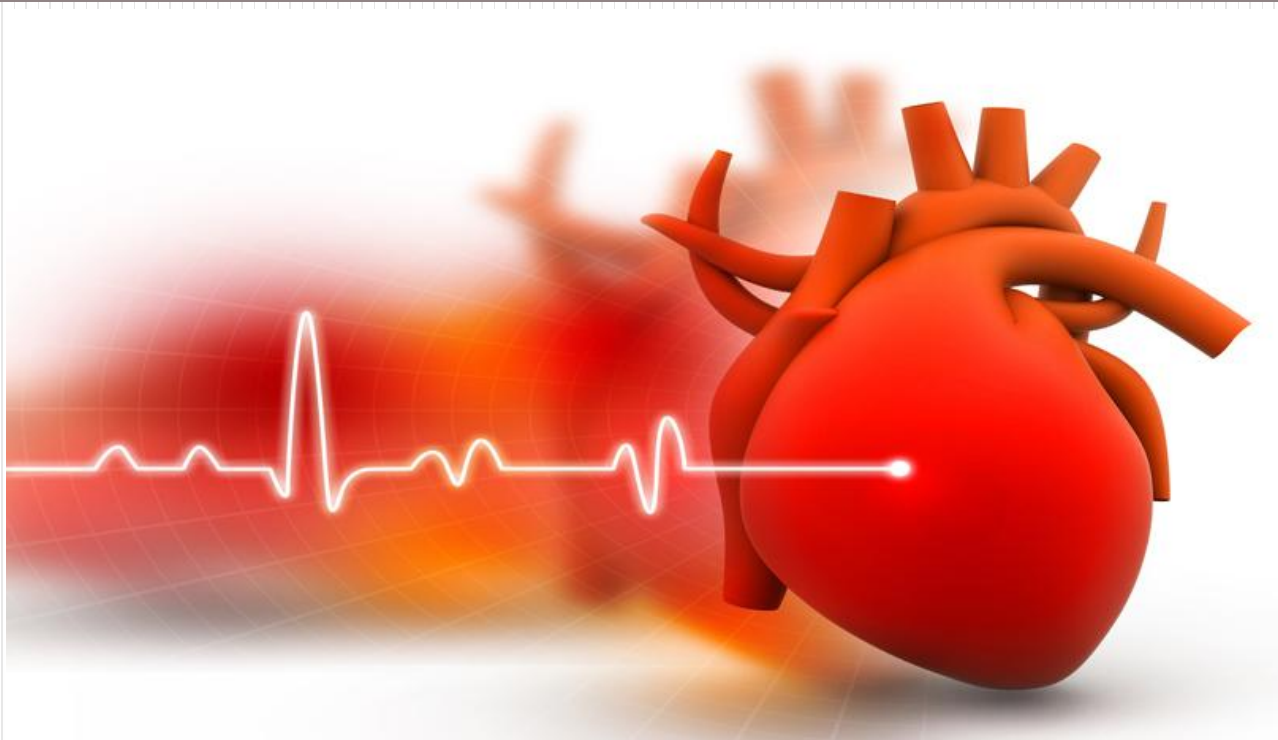


Role of Metoprolol and Cilnidipine in the Management of Hypertension



Hypertension Burden

**970
million**

Worldwide prevalence

60%

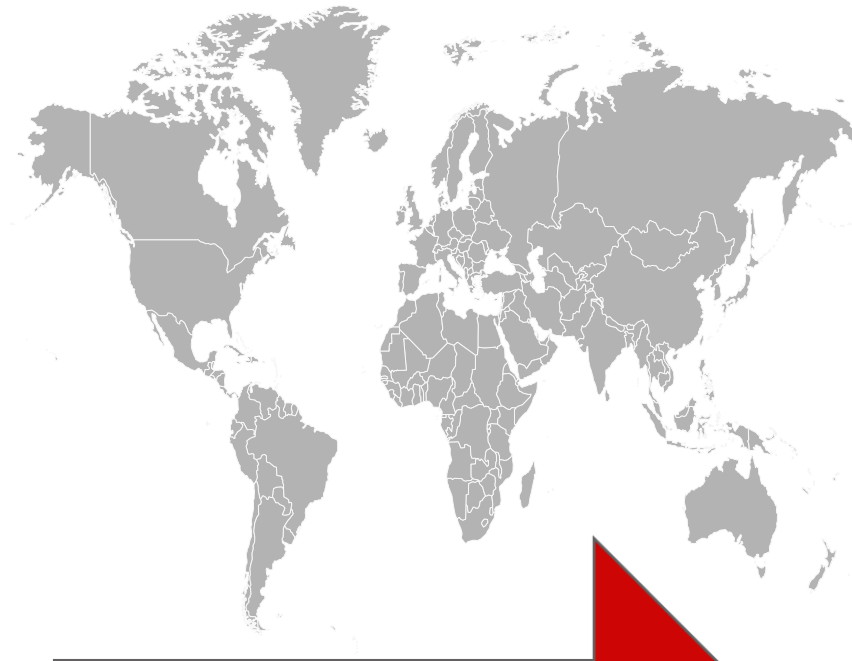
Increase in the
number of adults with
HTN globally by 2025

10%

Percent of all global
healthcare spending
attributable to HTN

**\$370
billion**

Annual worldwide cost
of hypertension

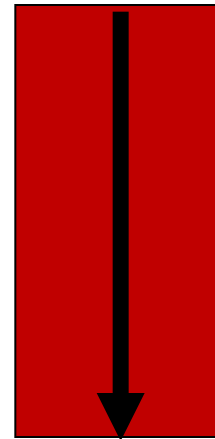
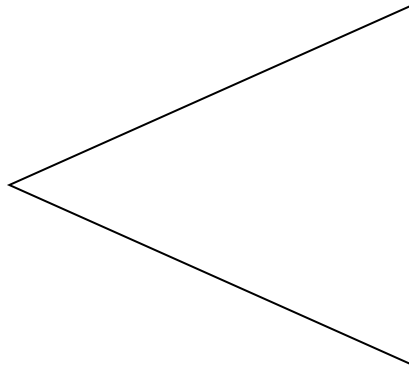


**1.6 Billion
HTN patients
estimated by 2025**

BP Differences of 10 mmHg Are Associated With Up to a 40% Effect on CV Risk

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

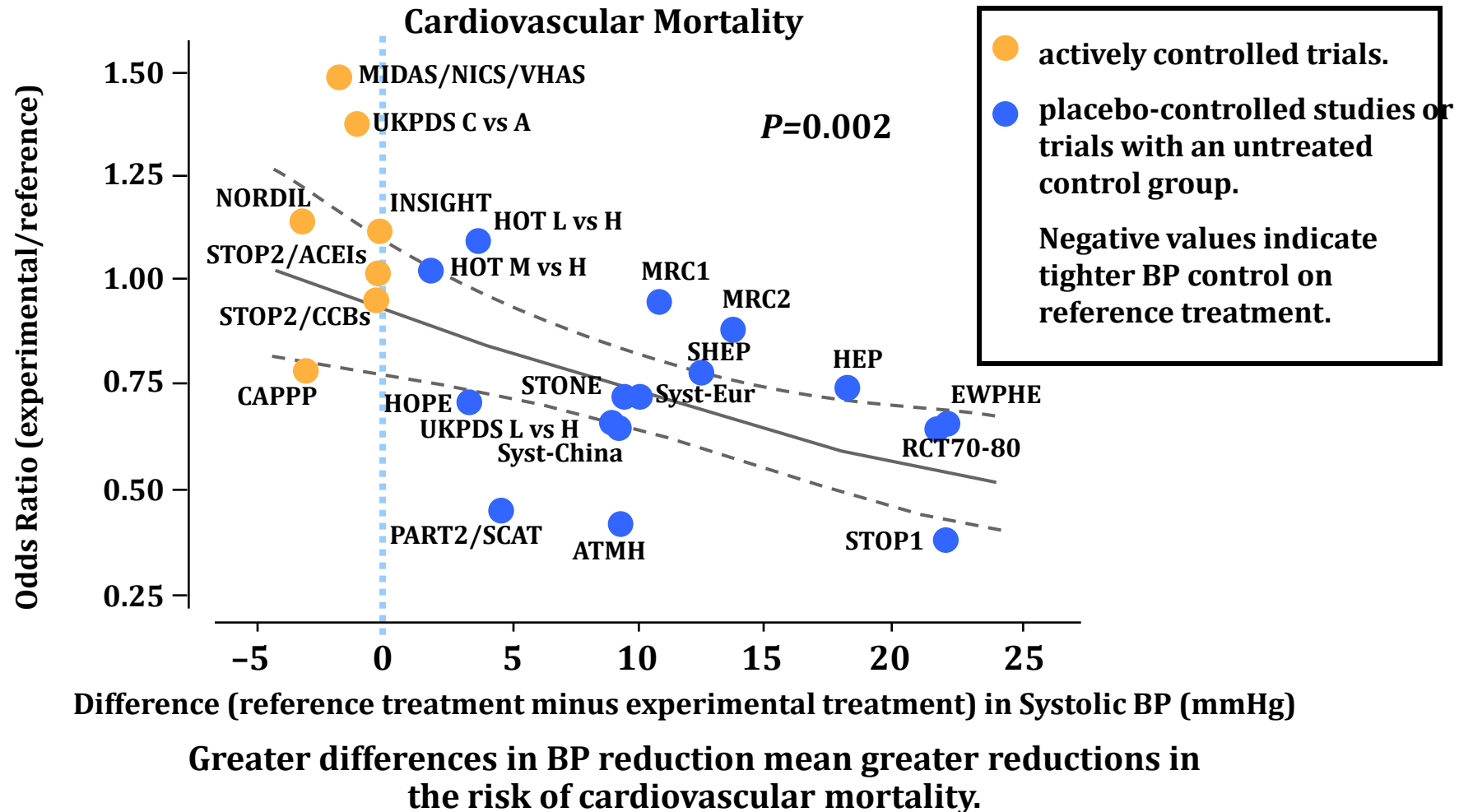
**10 mmHg
decrease in
mean SBP**



**30% reduction
in risk of IHD
mortality**

**40% reduction
in risk of stroke
mortality**

Importance of Lowering BP

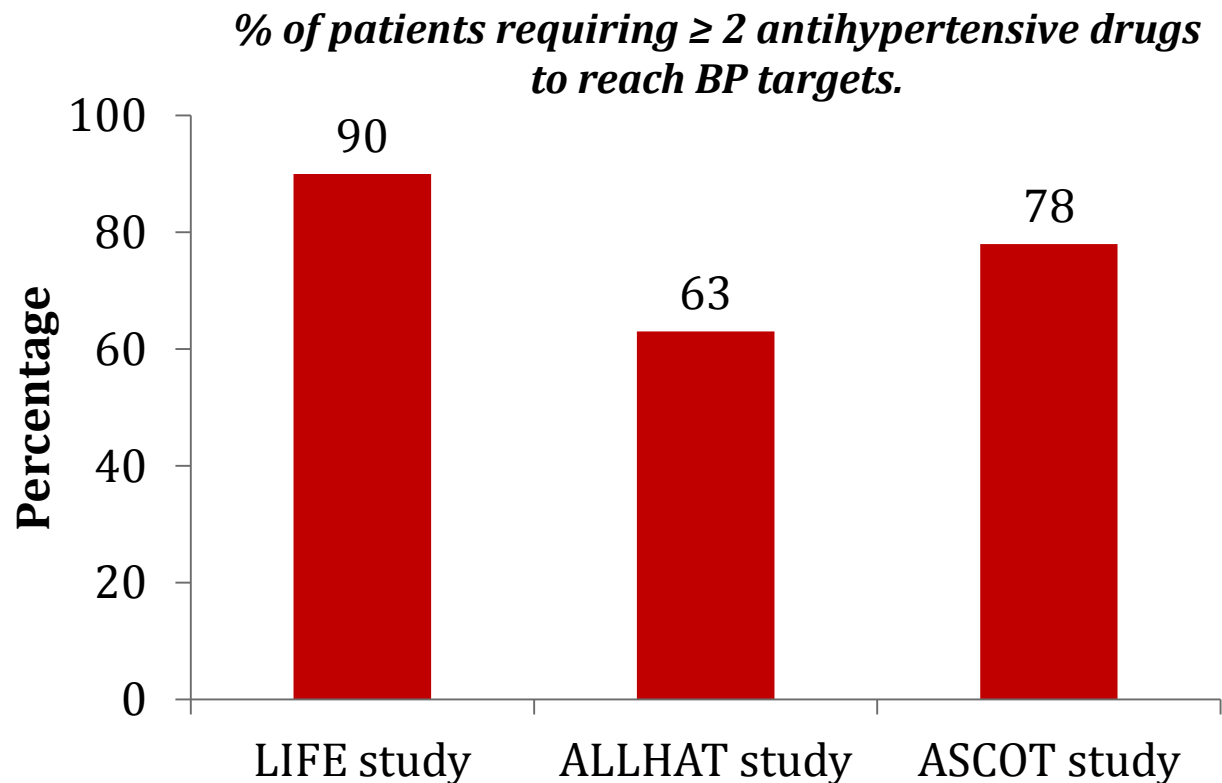


BP, blood pressure

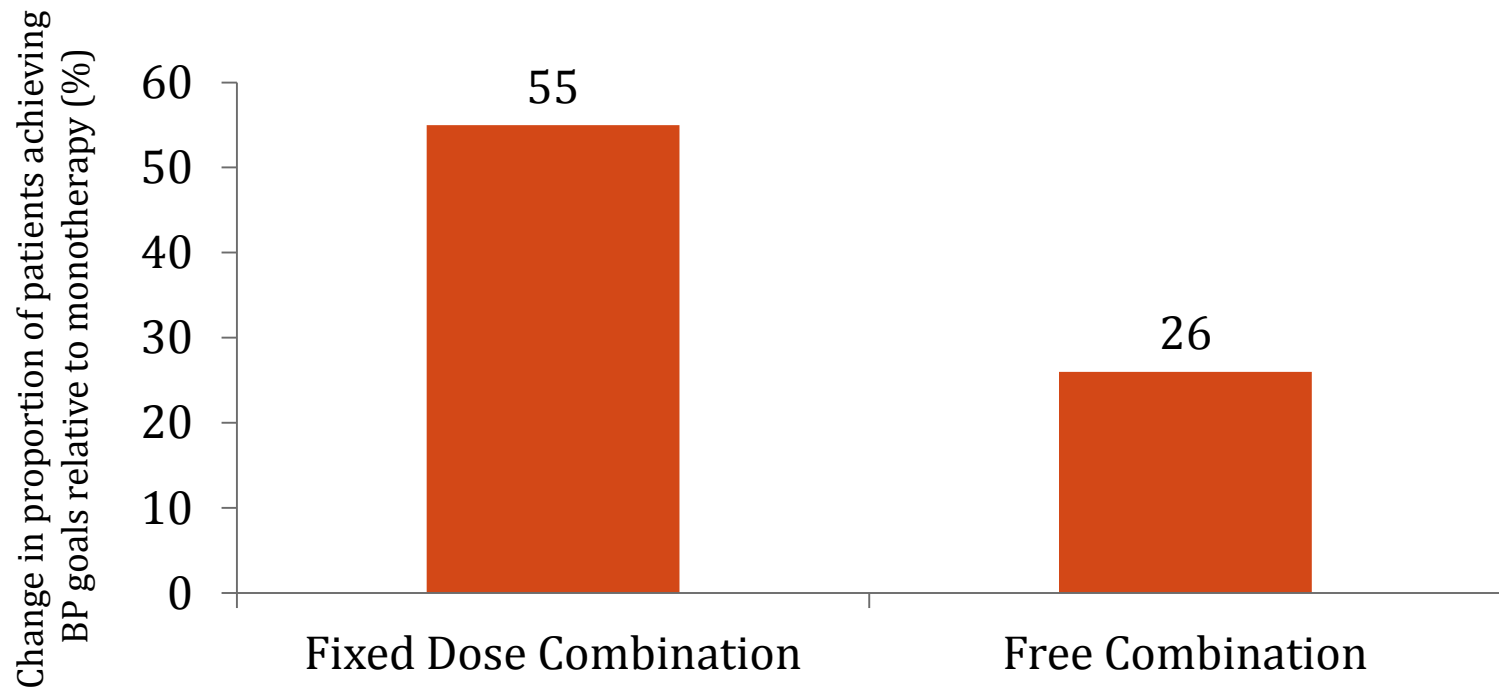
Staessen JA et al. *Hypertension Research*. 2005;28:385-407.

Landmark Trials and Combination therapy

- Major clinical studies have shown that patients generally need an average of 2 antihypertensive drugs to achieve target BP.



Higher BP Control Rates Are Achieved With Fixed Dose Combinations



Patients receiving a fixed dose combination are more likely to achieve BP goals than those receiving free combinations or monotherapy

Hypertension

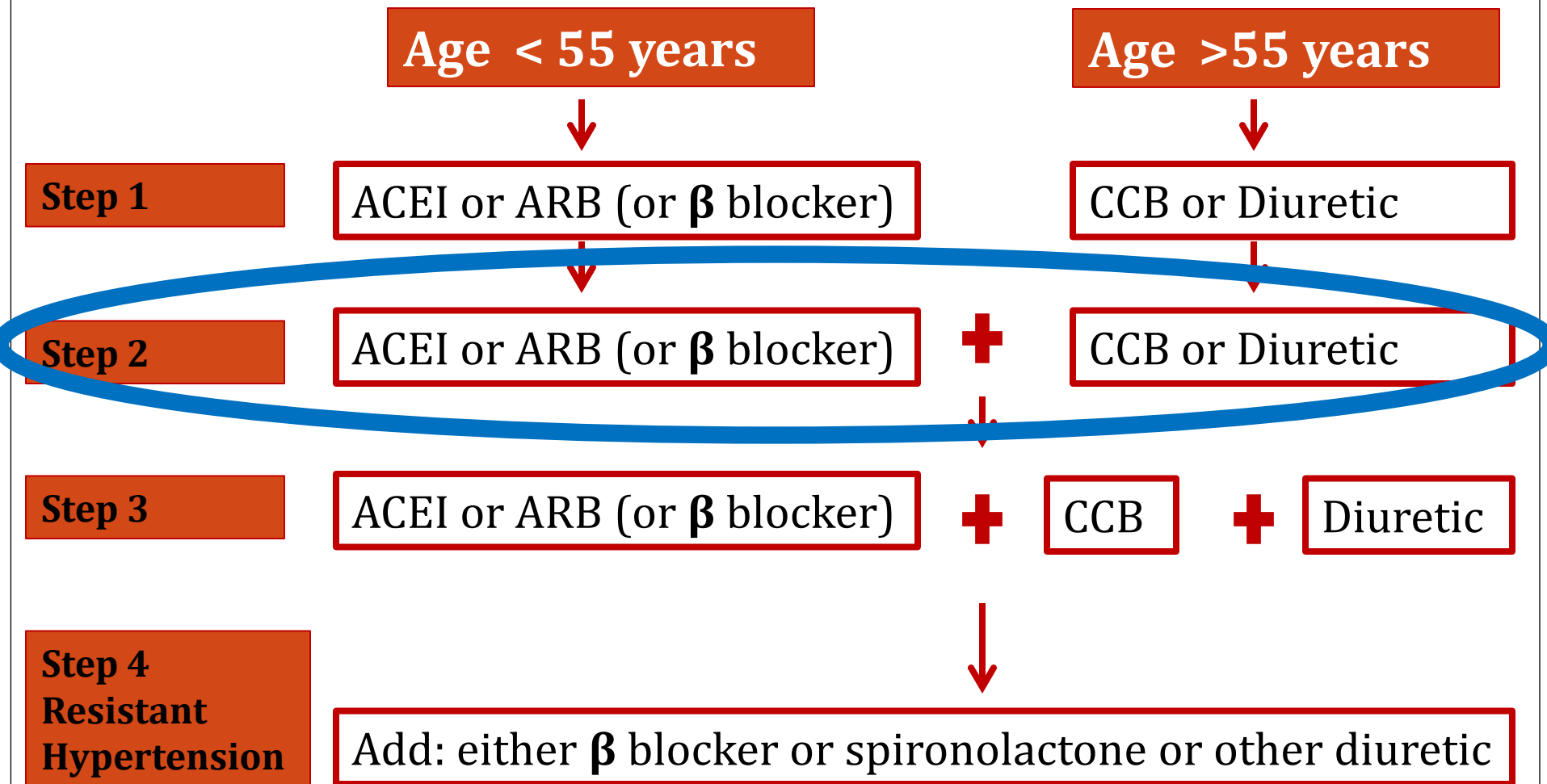
Guidelines

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)

- *“ Whenever possible , use of fixed dose combinations should be preferred because simplification of treatment carries advantages for compliance with treatment ”*

Association of Physicians of India (API) Guidelines



ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers;
CCB- calcium channel blockers

Metoprolol Extended Release in Hypertension

Metoprolol Extended Release In Hypertension

- Competitive beta-1 selective antagonist.
- Lipophilic Agent
- Lowers BP smoothly and consistently over a 24 hour dosage interval

Plosker GL et al. Drugs. 1992 Mar;43(3):382-414

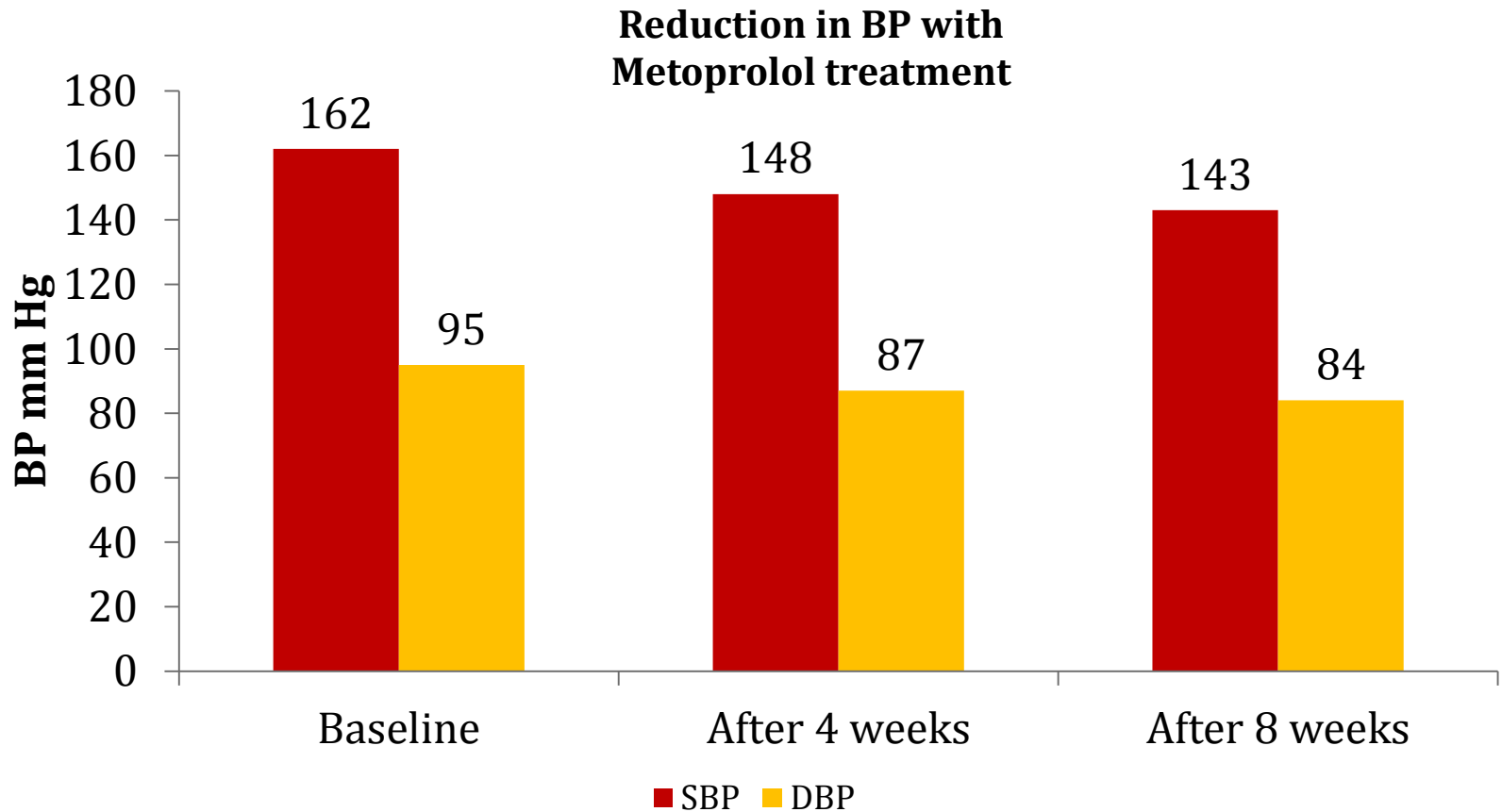
van den Born BJ et al. Ned Tijdschr Geneesk. 2005 Aug 6;149(32):1808-9.

Metoprolol in management of hypertension

Author	LaPalio L <i>et al.</i>	
Objective	To assess the short-term efficacy and safety of metoprolol in the treatment of hypertension in a large population of older patients.	
Study design	Prospective, open-label surveillance study	
Duration	8 weeks	
Patient Population	No. of patients	21,692
	Age group	50 to 75 years
	Men	61%
	mean baseline sitting BP	162/95 mmHg

Metoprolol in management of hypertension (contd)..

Results



Metoprolol administered as monotherapy or in combination is effective and well tolerated

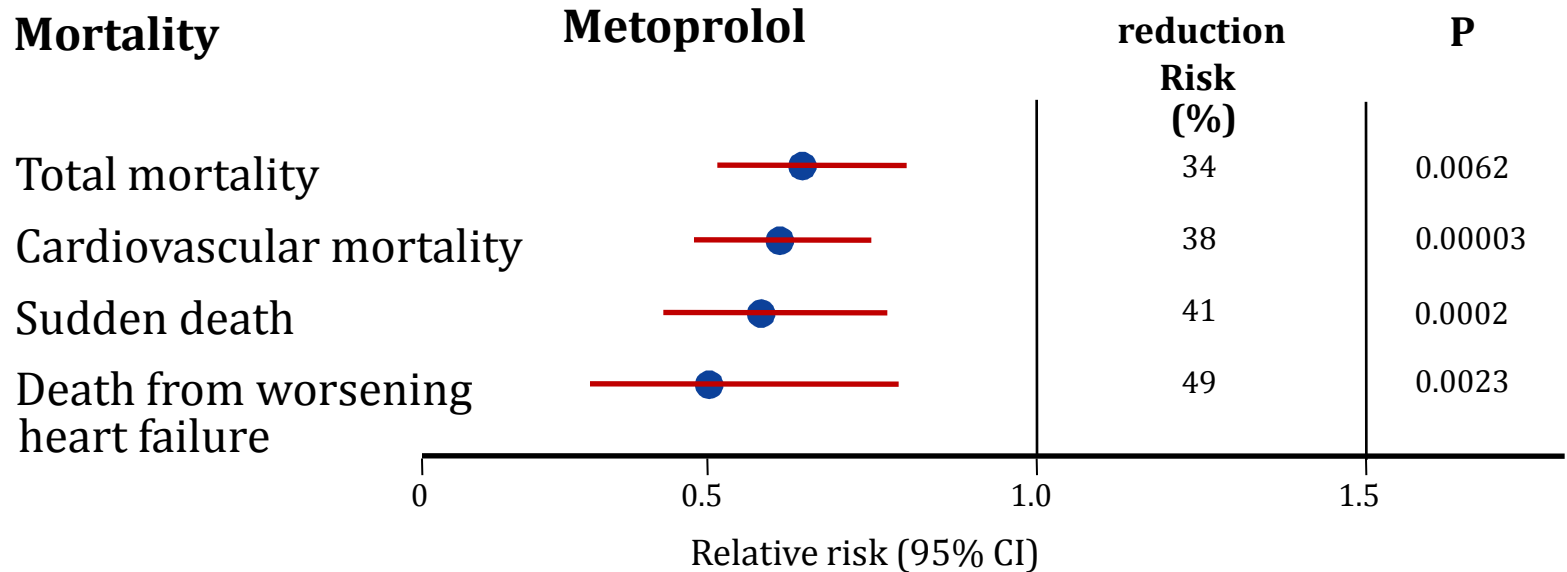
Metoprolol in patients with Hypertension, Diabetes and Chronic heart failure

Author	MERIT HF study group	
Objective	To investigate whether metoprolol once daily, in addition to standard therapy, would lower mortality in hypertensive patients with decreased ejection fraction and symptoms of heart failure.	
Study design	Double-blind randomised controlled study	
Duration	1 year	
Patient Population	No. of patients	3991
	Age group	50 to 75 years
	Men	61%
	mean baseline sitting BP	162/95 mmHg

Metoprolol in patients with Hypertension, Diabetes and Chronic heart failure (contd)..

Results

Relative risk for mortality



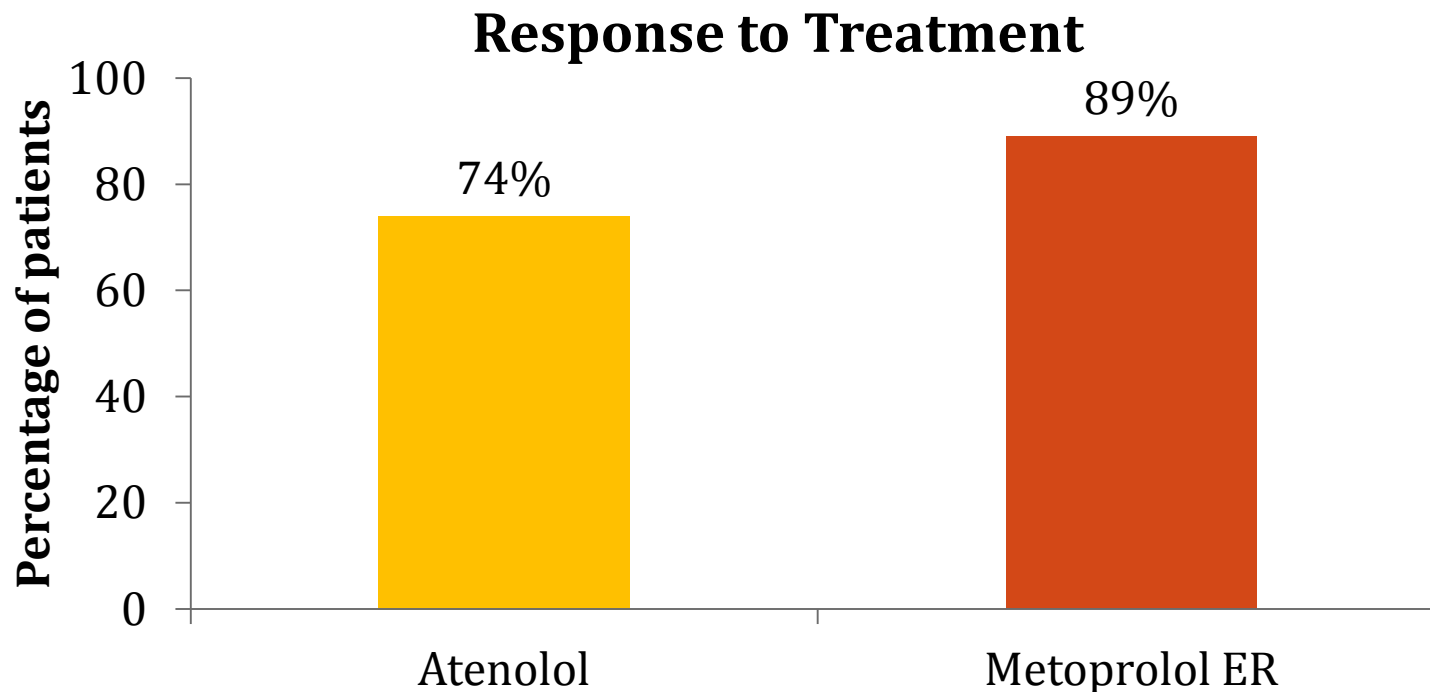
- Reduces the risk of hospitalization for heart failure by 37% in the diabetic group (95% CI 53% to 15%)

Comparison of Metoprolol and Atenolol in Hypertension

Author	Klein G <i>et al.</i>	
Objective	To evaluate the role of metoprolol and atenolol in patients with Hypertension.	
Study design	Randomized, Double blind, comparative trial	
Duration	8 weeks	
Patient Population	No. of patients	195
	Age group	50 to 75 years
	mean baseline BP	172/98 mmHg

Comparison of Metoprolol and Atenolol in Hypertension (contd)..

Results



- Metoprolol effectively reduces BP compared to Atenolol.

Cilnidipine in Hypertension

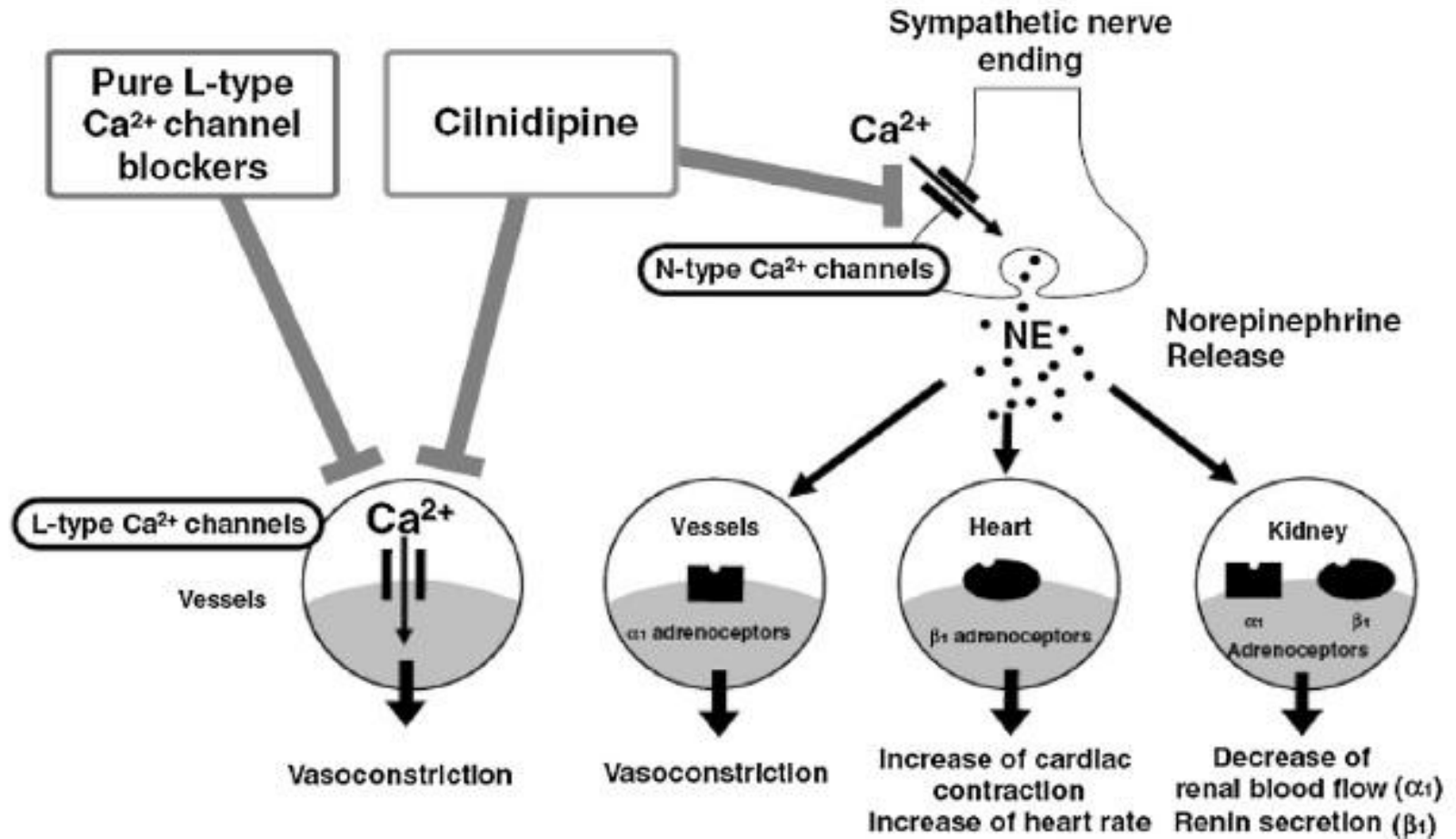
Cilnidipine- fourth generation CCB

- Cilnidipine is an unique Calcium Channel Blocker.
- Possesses both L- and N-type calcium channels blocking activity.
- Inhibition of N-type Ca^{2+} channels provide a new strategy for the treatment of Hypertension and CV diseases.

Cilnidipine- Mechanism of action

Inhibition of L-type Ca^{2+} channels (vascular smooth muscle)

Inhibition of N-type Ca^{2+} channels (sympathetic neuron)



Diagrammatic representation of L/N dual action of cilnidipine.

Summary of pharmacological actions of Cilnidipine

Mode of action

- Inhibition of L-type Ca^{2+} channels (vascular smooth muscle)
- Inhibition of N-type Ca^{2+} channels (sympathetic neuron)

Pharmacology

- Cardiovascular action
 - Vascular relaxation; *hypotensive action*
- Antisymphathetic action
 - Decrease of catecholamine release, tissue (kidney) norepinephrine level,
 - Inhibition of sympathetic tachycardia
- Suppression of renin angiotensin aldosterone system
 - Decrease in plasma level of angiotensin II and aldosterone
 - *Inhibition of aldosterone production;*

Cilnidipine in Hypertension: ACHIEVE-ONE Study

Author	Kazuomi Kario <i>et al.</i>	
Objective	To evaluate the clinical effects of cilnidipine on BP and PR measured at the clinic, at home, and by ambulatory BP monitoring (ABPM) in patients with essential hypertension in daily medical practice.	
Study design	Prospective, open-label surveillance study	
Duration	12 weeks	
Patient Population	No. of patients	2,319
	Mean Age	67.8 ±12.0 years
	Men	54.8 %
	Mean clinic SBP Mean morning SBP	155.0 mm Hg 152.9 mm Hg

(ACHIEVE-ONE) trial: Ambulatory Blood Pressure Control and Home Blood Pressure (Morning and Evening) Lowering by N-Channel Blocker Cilnidipine

Kario K *et al* Clin Hypertens (Greenwich). 2013; 15:133–142.

Cilnidipine in Hypertension: ACHIEVE-ONE Study Results

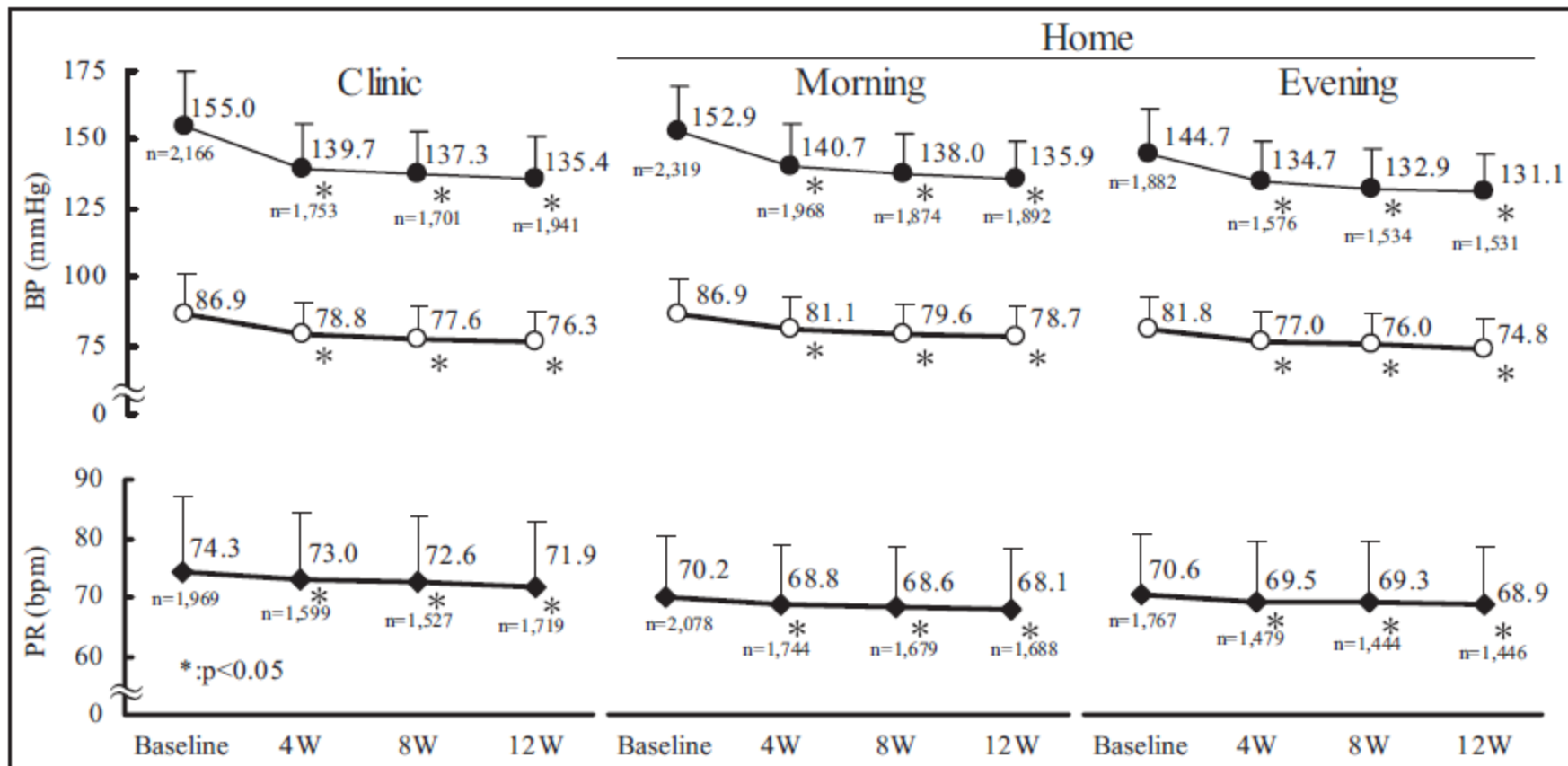


FIGURE 1. Changes in blood pressure (BP) and pulse rate (PR) at the clinic and at home. W indicates week; bpm, beats per minute; • systolic BP; ○ diastolic BP; ♦ PR. * $P < .05$ vs baseline.

(ACHIEVE-ONE) trial: Ambulatory Blood Pressure Control and Home Blood Pressure (Morning and Evening) Lowering by N-Channel Blocker Cilnidipine

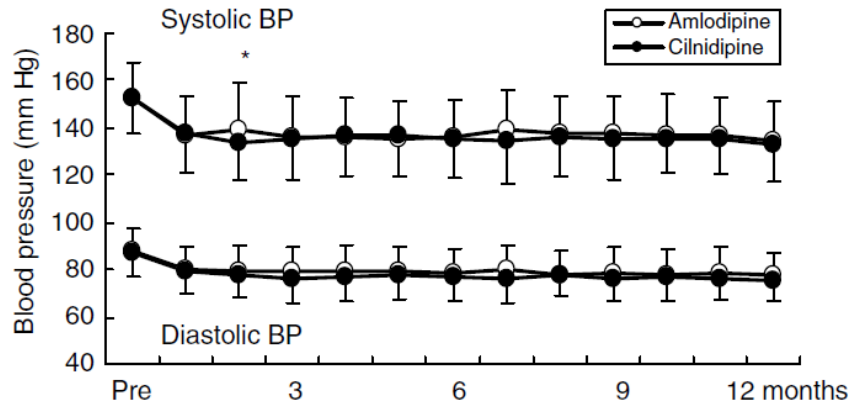
Cilnidipine vs Amlodipine: CARTER Study

Author	Fujita T <i>et al.</i>	
Objective	To compare the antiproteinuric effects of cilnidipine with those of amlodipine in hypertensive patients with kidney disease	
Study design	multi-center, open-labeled, and randomized trial	
Duration	1 year	
Patient Population	No. of patients	339
	Mean Age	59.6 years
	Men	63 %
	Mean SBP Mean DBP	152.47 ±14.8mm Hg 86.9 ± 9.6mm Hg

Cilnidipine versus Amlodipine Randomized Trial for Evaluation in Renal Disease (CARTER) Study

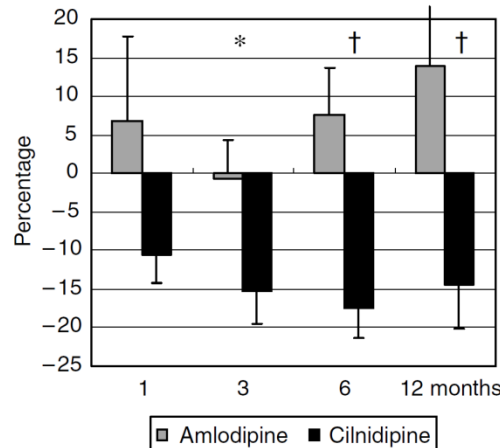
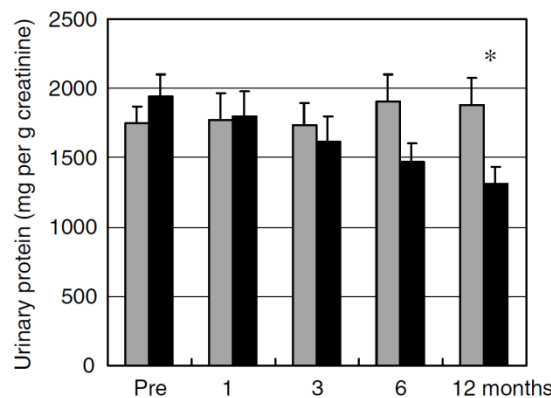
Cilnidipine vs Amlodipine: CARTER Study

Changes in systolic and diastolic BP.



•After 1-year of treatment, systolic and diastolic blood pressures were significantly reduced in both groups.

Changes in urinary protein/Cr ratio during treatment period



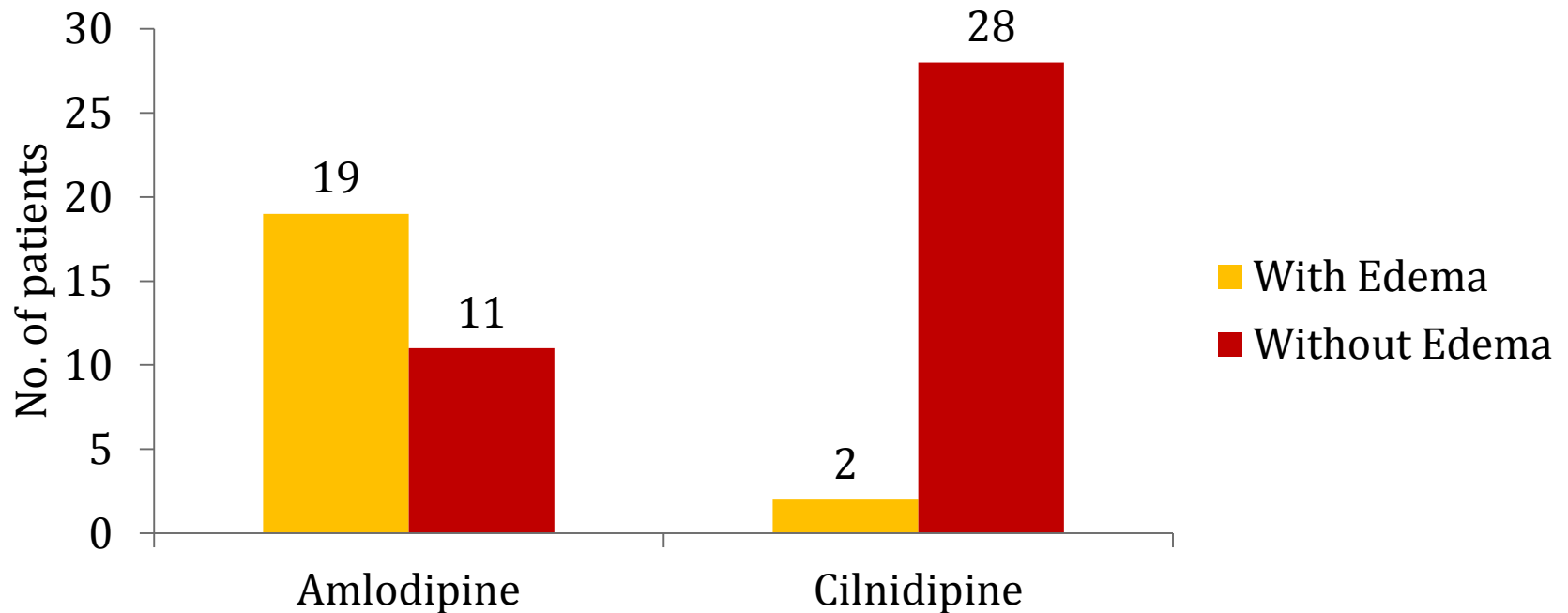
•But the urinary protein to creatinine ratio significantly decreased in the cilnidipine compared to the amlodipine group.

Amlodipine	160	147	142	137	130
Cilnidipine	179	168	168	160	146

Amlodipine vs Cilnidipine: incidence of pedal edema

Author	Adake P <i>et al.</i>	
Objective	To compare amlodipine with cilnidipine on antihypertensive efficacy and incidence of pedal edema in hypertensive individuals	
Study design	prospective, observational study	
Duration	3 months	
Patient Population	No. of patients	60
	Mean Age	59.8 ± 9.7 years
	Men	43 %
	Mean SBP Mean DBP	162. 0±7.8 mm Hg 91.9 ± 8.8 mm Hg

Amlodipine vs Cilnidipine: incidence of pedal edema



- Cilnidipine is an effective anti hypertensive as compared to Amlodipine
- Cilnidipine is associated with lower incidence of pedal edema compared to Amlodipine.

Metoprolol and Cilnidipine

Metoprolol Extended Release:

- Selectively blocks beta 1 receptors thereby reducing force of contraction and rate of contraction of heart muscle.

Cilnidipine:

- Dual L/N-type Ca^{2+} channel-blocking action and provides beyond BP benefits including renal and cardioprotective effects

In patients with uncontrolled hypertension by monotherapy,

- The addition of a dihydropyridine CCB to a beta-blocker will result in a complementary effects.
- The combination of Metoprolol and Cilnidipine results in additive BP reduction and cardio-renal protection

Drug combinations in hypertension:

The American Society of Hypertension Recommendations

Acceptable

β -blocker/diuretic^a

CCB (dihydropyridine)/ β -blocker

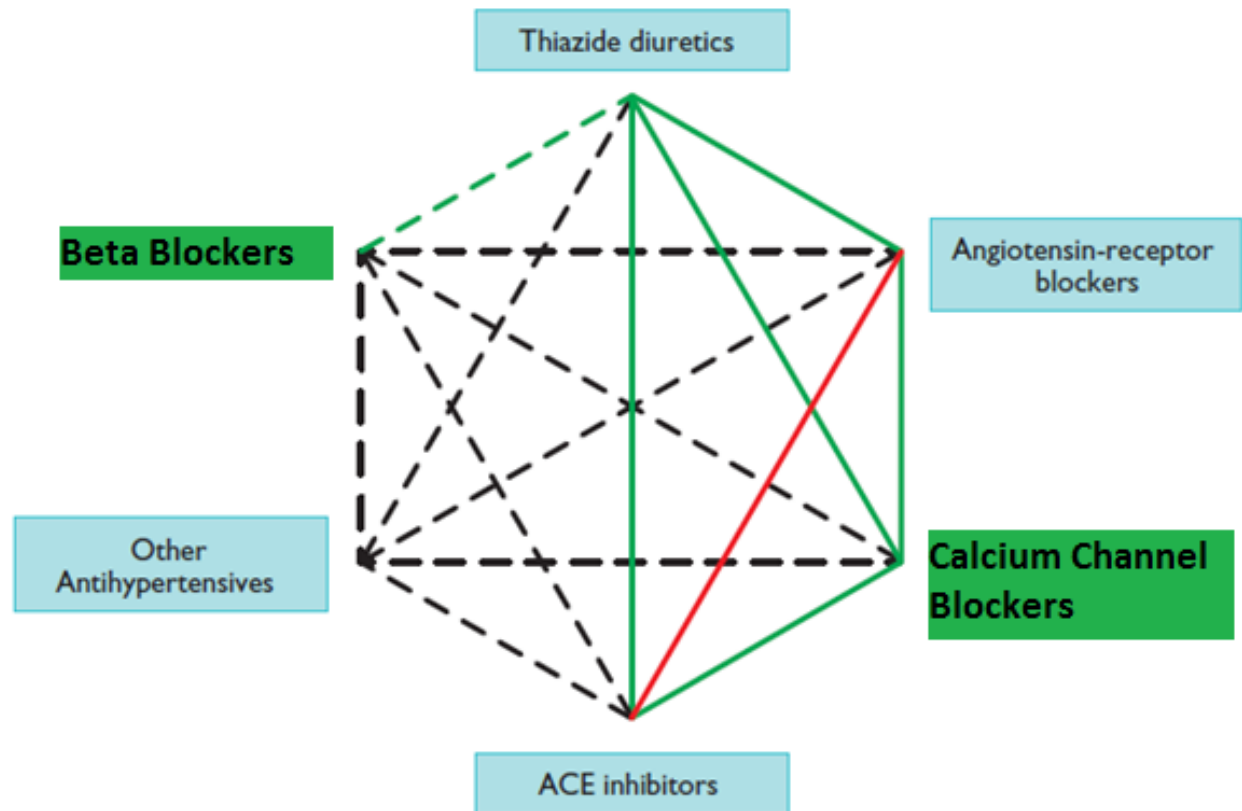
CCB/diuretic

Renin inhibitor/diuretic^a

Renin inhibitor/ARB

Thiazide diuretics/K⁺ sparing diuretics^a

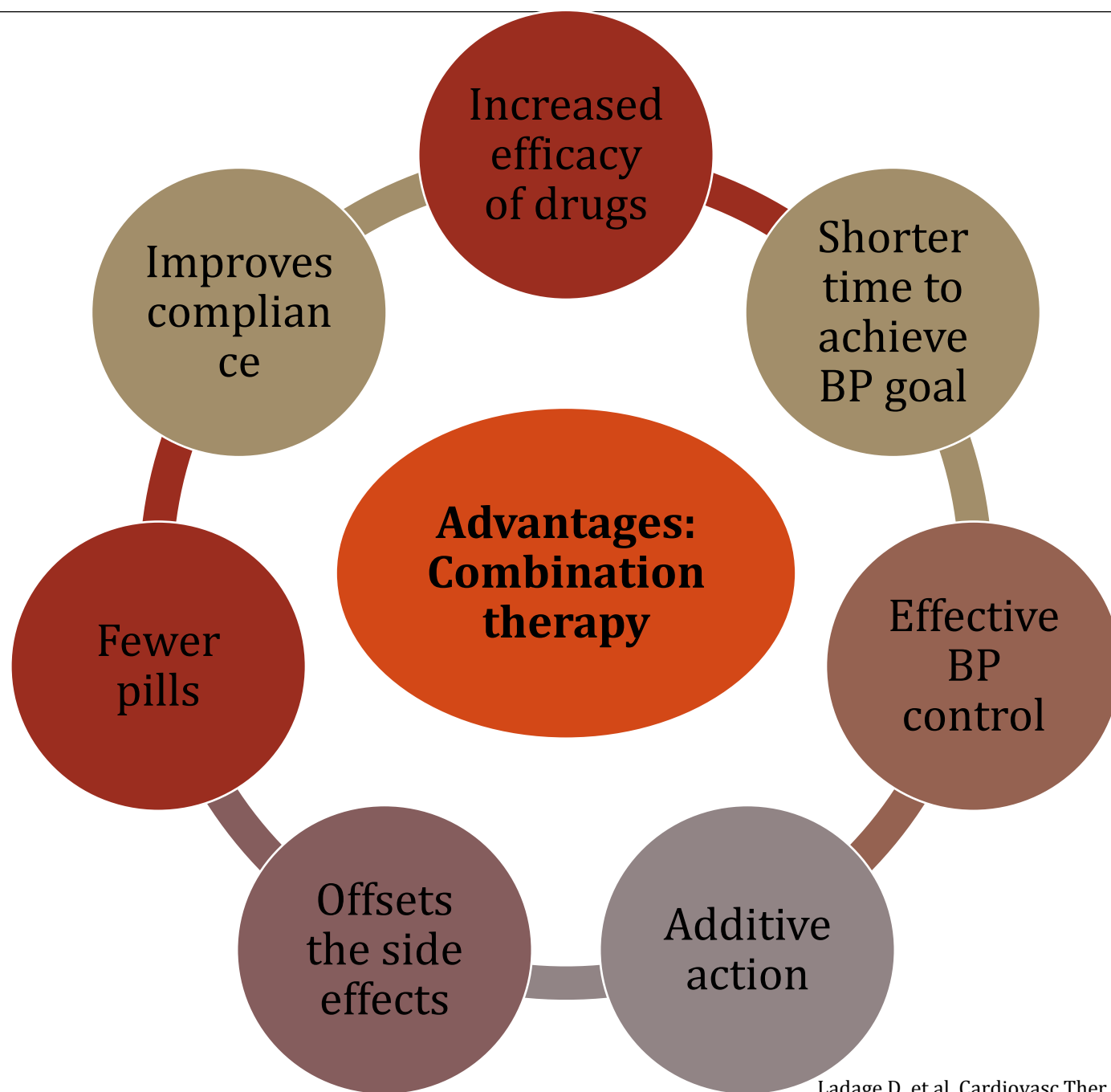
Also Recommended by European Society of Hypertension / European Society of Cardiology Guidelines



ACE = angiotensin-converting enzyme.

Possible combinations of classes of antihypertensive drugs. Green continuous lines: preferred combinations; green dashed line: useful combination (with some limitations); black dashed lines: possible but less well-tested combinations; red continuous line: not recommended combination.

Mancia G et al. Blood Press. 2014 Feb;23(1):3-16



Summary

- Majority of patients require two drugs to achieve BP goal
- The dual combination of Metoprolol + Cilnidipine blocks the selective beta 1 receptors and dual L/N type Ca^{2+} channel blocking agent.
- The combination of these 2 drug results in additive BP reduction and cardio-renal protection
- Combination recommended by guidelines
- Combination therapy increases compliance
- Combination therapy reduces Pill Burden.

Thank You