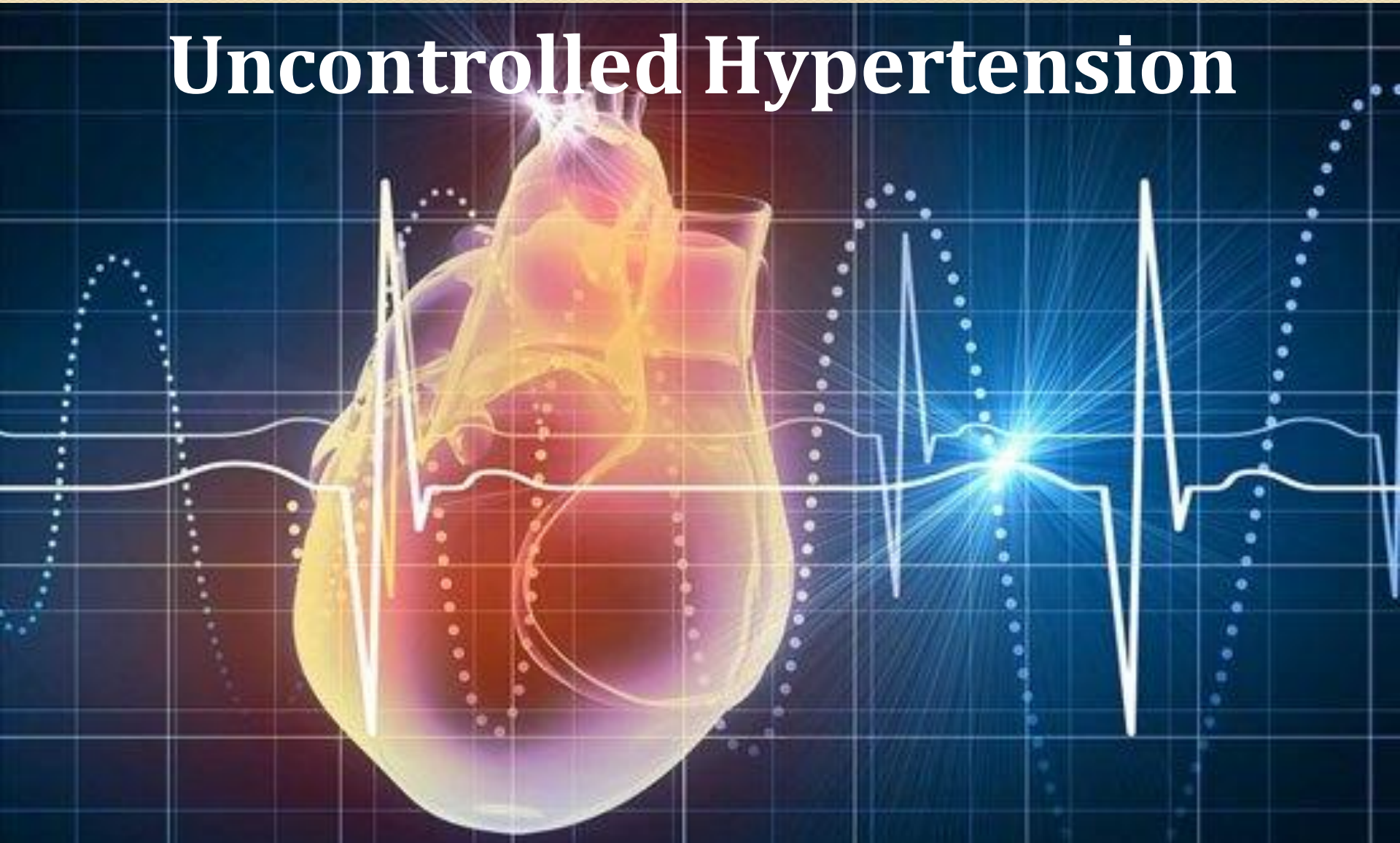


FIXED DOSE COMBINATION THERAPY OF TELMISARTAN AND AMLODIPINE IN

Uncontrolled Hypertension

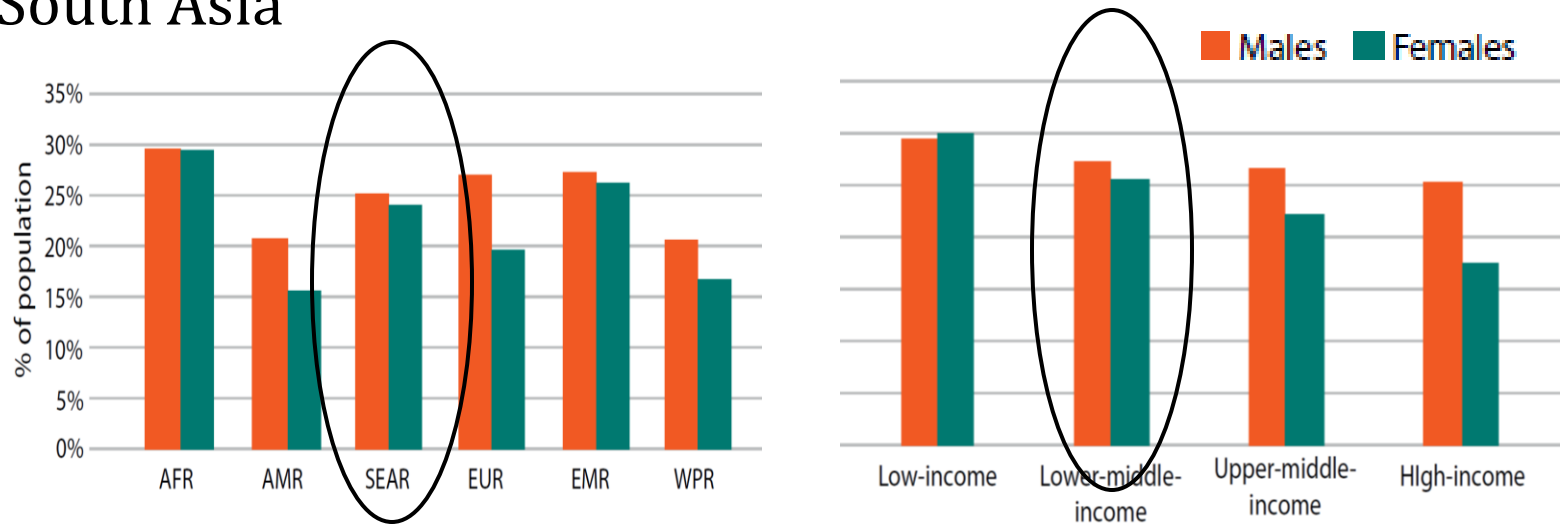


Hypertension Burden

- Hypertension is the leading risk factor for global disease burden
- Accounts for 7.0% of global disability-adjusted life years (DALYs)
- Contributes to 45% of global CVD morbidity and mortality.
- Globally, **33%** of stroke, **50%** of ischemic heart disease *are attributable to uncontrolled blood pressure*

Hypertension: WHO Estimates

- The global prevalence is $\approx 22\%$.
- **Ranked 3rd** most risk factor for hypertension burden in South Asia



AFR=African Region, AMR=Region of the Americas, SEAR =South-East Asia Region, EUR=European Region, EMR=Eastern Mediterranean Region, WPR=Western Pacific Region

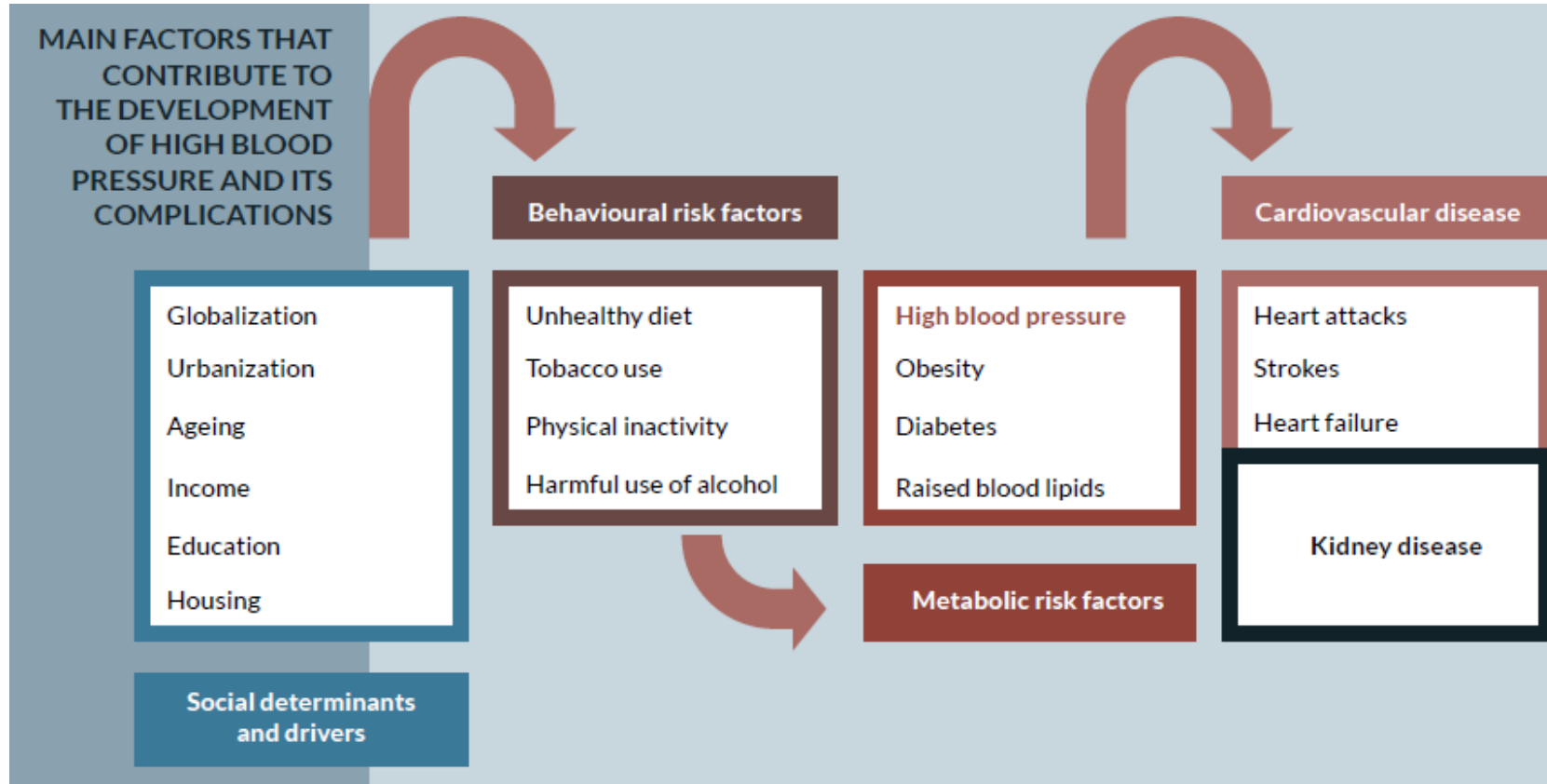
Hypertension In Nepal

- Studies done in Nepal have reported a prevalence of hypertension ranging from 18.8% to 41.8%.
- Studies report tripling of prevalence from 1981 to 2006 in the same community.
- A national representative survey from Nepal

90 %

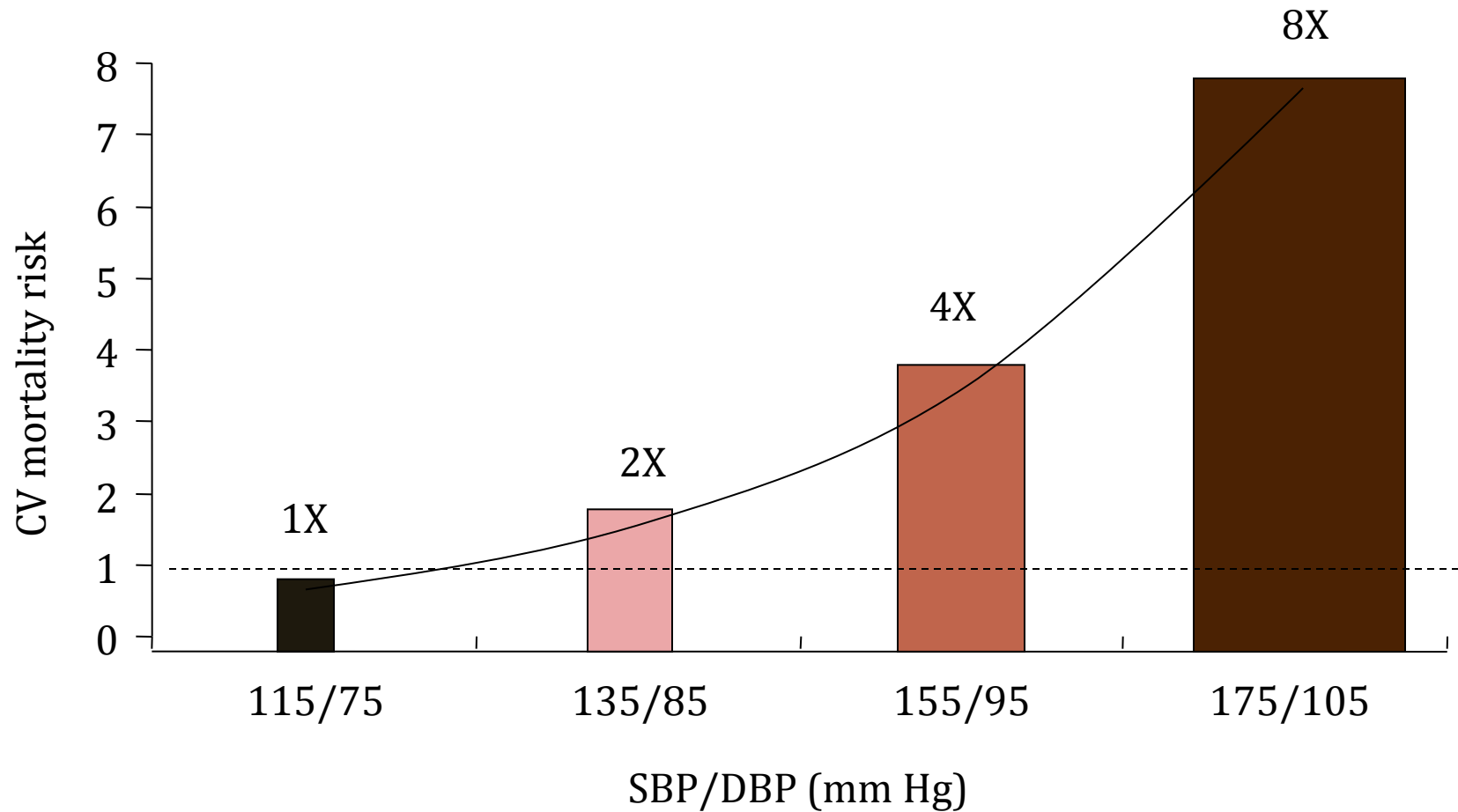
- **Patients with hypertension are not treated adequately.**

Hypertension Risk Factors



Hypertension is a polygenic disease involving a major contribution of various factors

CV Mortality Risk Doubles With Each 20/10 mm Hg BP Increment



Current Challenges in Hypertension Control

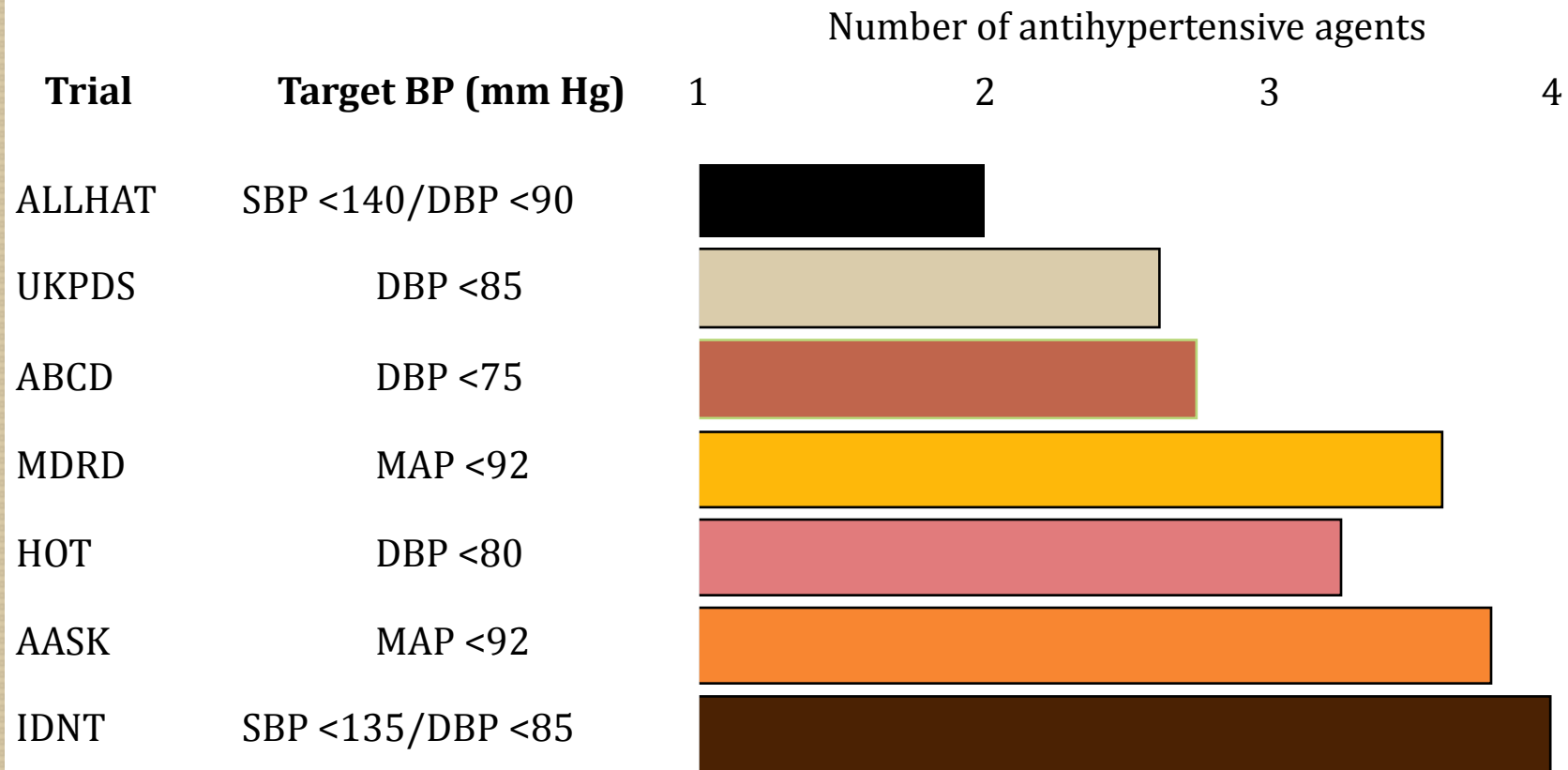
- Majority of the physicians attribute poor patient compliance to poor control.
- Most patients claim to be compliant and blame the lack of efficacy and side effects.
- Most often, physicians fail to act when patients do not achieve their targets.

Uncontrolled hypertension is due to an interplay of many factors including patient, physician, lifestyle, and diet-related factors.

Combination Therapy

- Exert Complimentary mechanism of action
- Greater efficacy than high dose monotherapy
- Beneficial for secondary prevention of CV events in high risk patients with hypertension.
- Combining drugs from complimentary classes has 5-fold greater antihypertensive efficacy than increasing the dose of one drug

Multiple Antihypertensive Agents Are Needed to Achieve Target BP



DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

Bakris GL et al. *Am J Kidney Dis.* 2000;36:646-661.

Lewis EJ et al. *N Engl J Med.* 2001;345:851-860.

Cushman WC et al. *J Clin Hypertens.* 2002;4:393-405.

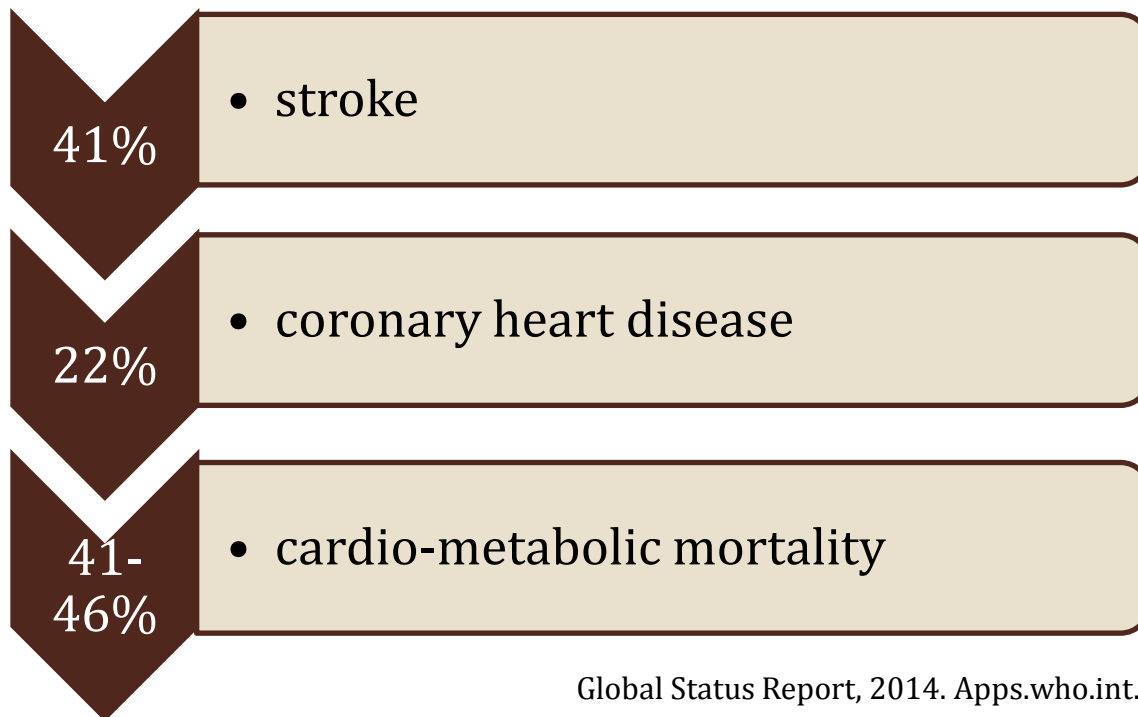


Advantages: Combination therapy

- Increased efficacy of drugs
- Shorter time to achieve BP goal
 - Effective BP control
 - Additive action
- Offsets the side effects
 - Fewer pills
- Improves compliance

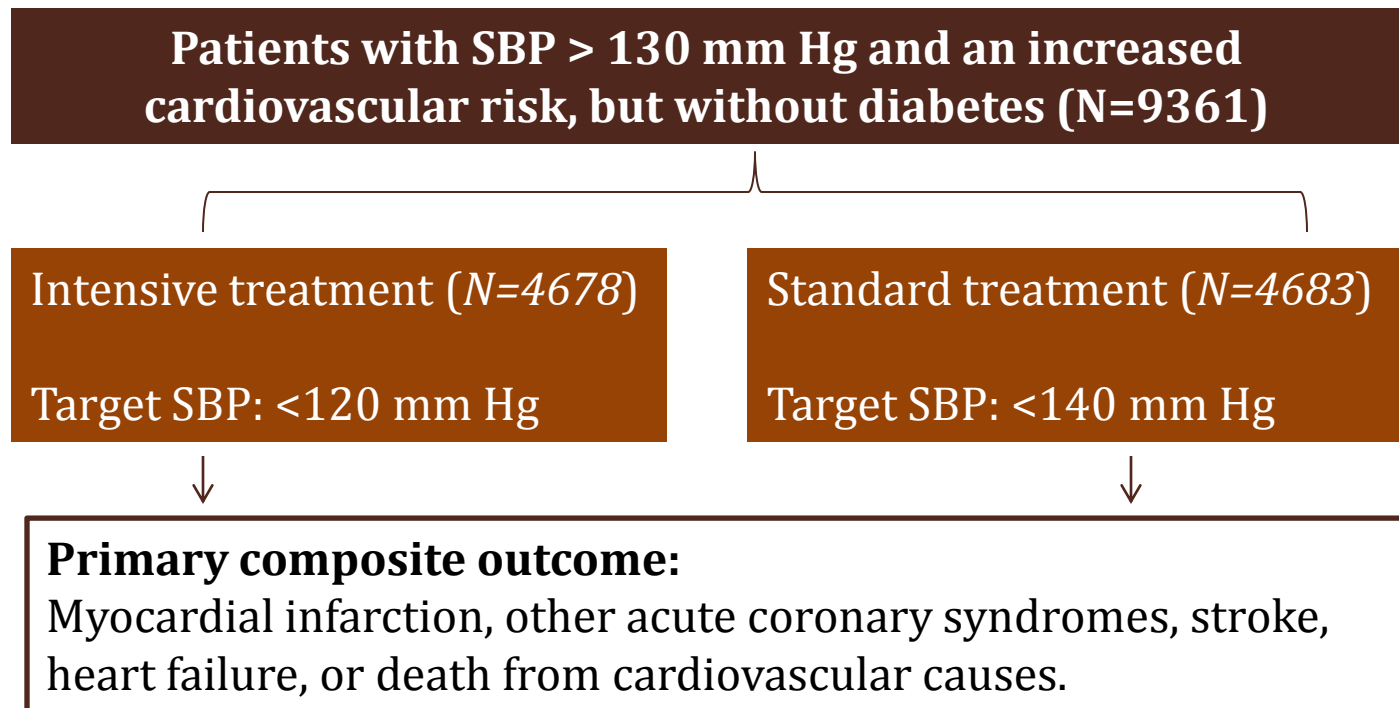
Early Intervention

- The WHO 2014 report stresses on early detection and effective management in minimizing the risk of heart attacks, heart failure, stroke, and kidney failure.
- A 10 mmHg reduction in BP reduces the risk:



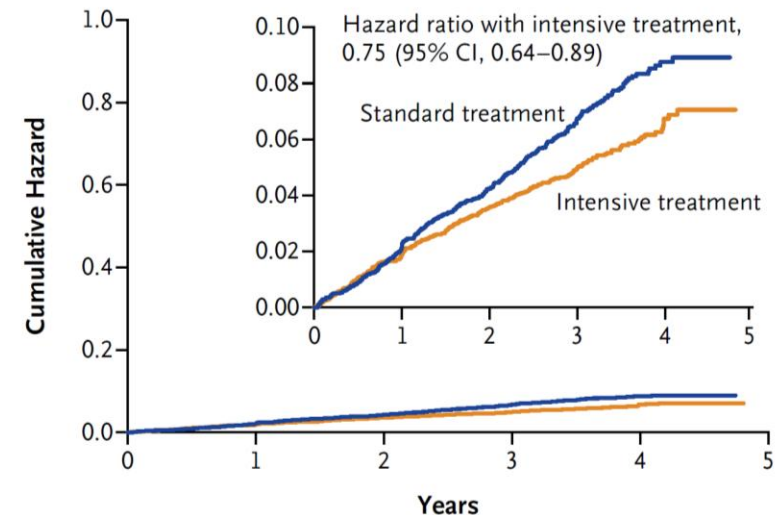
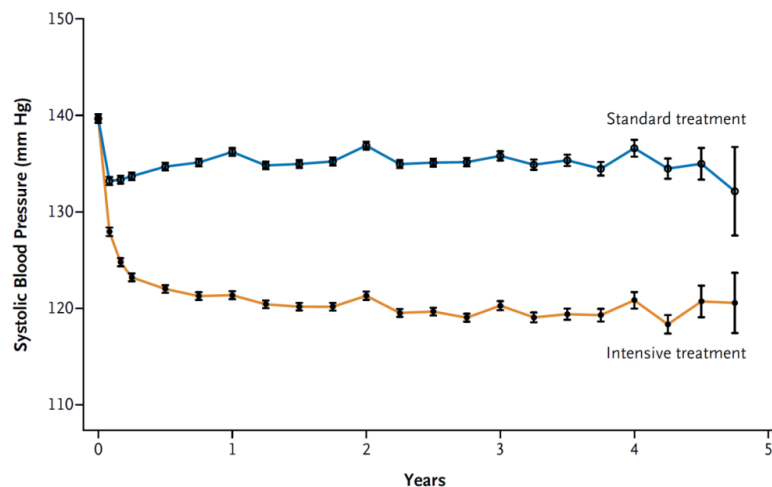
A Randomized Trial of Intensive *versus* Standard Blood-Pressure Control

A randomized, controlled, open-label **S**ystolic Blood **P**ressure **I**ntervention **T**rial (SPRINT Trial) conducted at 102 clinical sites



SPRINT Results

- At 1 year in the *Intensive group*:
 - mean SBP: 121.4 mm Hg vs Standard treatment (136.2 mm Hg)
 - Significantly lower rate of composite outcome



Achieving the target systolic pressure of 120 mm Hg reduces CV events and stroke, $\approx 33\%$; Risk of death by $\approx 25\%$

Telmisartan: the uniqueness

Firmer binding to the AT1-Receptor

Longer half life

Better distribution

Free from drug interactions

Activates PPAR-gamma

Low renal excretion

Amlodipine: An effective CCB

L type calcium channel blocker

Longer half life

Smooth onset of action & 24 hour BP control

No reflex Tachycardia

Does not activate SNS

Inhibits platelet aggregation and decreases ischemia

Early combination therapy with telmisartan plus amlodipine for rapid achievement of BP goal.

- In a meta-analysis, eight randomised, double-blind studies comparing telmisartan/amlodipine combination therapy with monotherapy were considered.
- In patients initiated on combination therapy, greater systolic BP (SBP)/diastolic BP (DBP) reductions were seen with combination therapy ($p < 0.0001$)
- BP ($< 140/90$ mmHg), SBP (< 140 mmHg) and DBP (< 90 mmHg) goal attainment rates were significantly higher with combination therapy at all time points.
- In patients uncontrolled by monotherapy, greater SBP/DBP reductions were seen with combination therapy ($p < 0.05$).
- All goal attainment rates were significantly higher with combination therapy

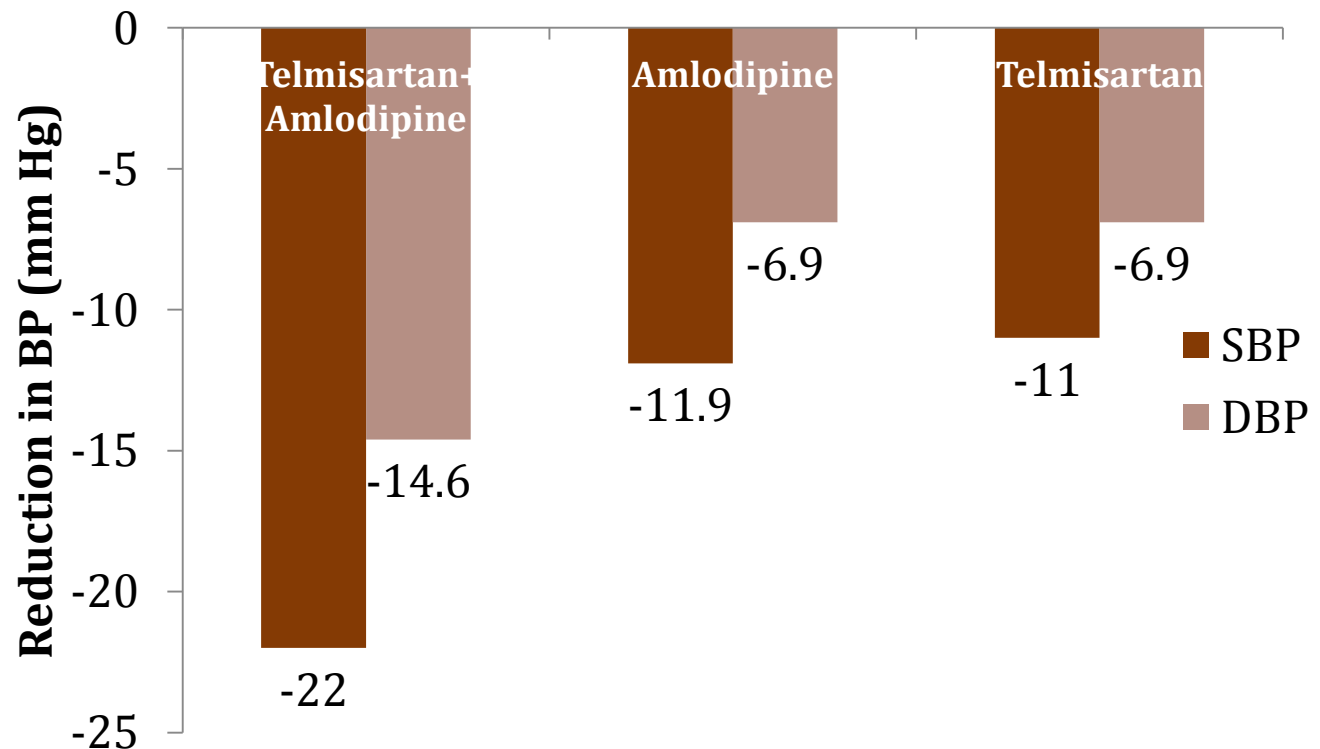
Effects of telmisartan and amlodipine in combination on ambulatory BP in Hypertension

Author	Neldam S <i>et al.</i>	
Objective	To assess the effects of combining telmisartan and amlodipine on ambulatory BP in patients with hypertension.	
Study design	Placebo controlled, double blind, 4x4 factorial design trial	
Duration	8 weeks	
Patient Population	No. of patients	562
	Age group	50 to 75 years
	mean baseline sitting BP	130/95 mmHg

Effects of telmisartan and amlodipine in combination on ambulatory BP in Hypertension

Results

- Combination therapies of telmisartan and amlodipine lowered 24h BP to a larger extent than the corresponding monotherapies at all doses.
- In addition, BP response and control rates (24h BP <130/80 mmHg) were significantly higher with the combination therapy versus the monotherapy groups



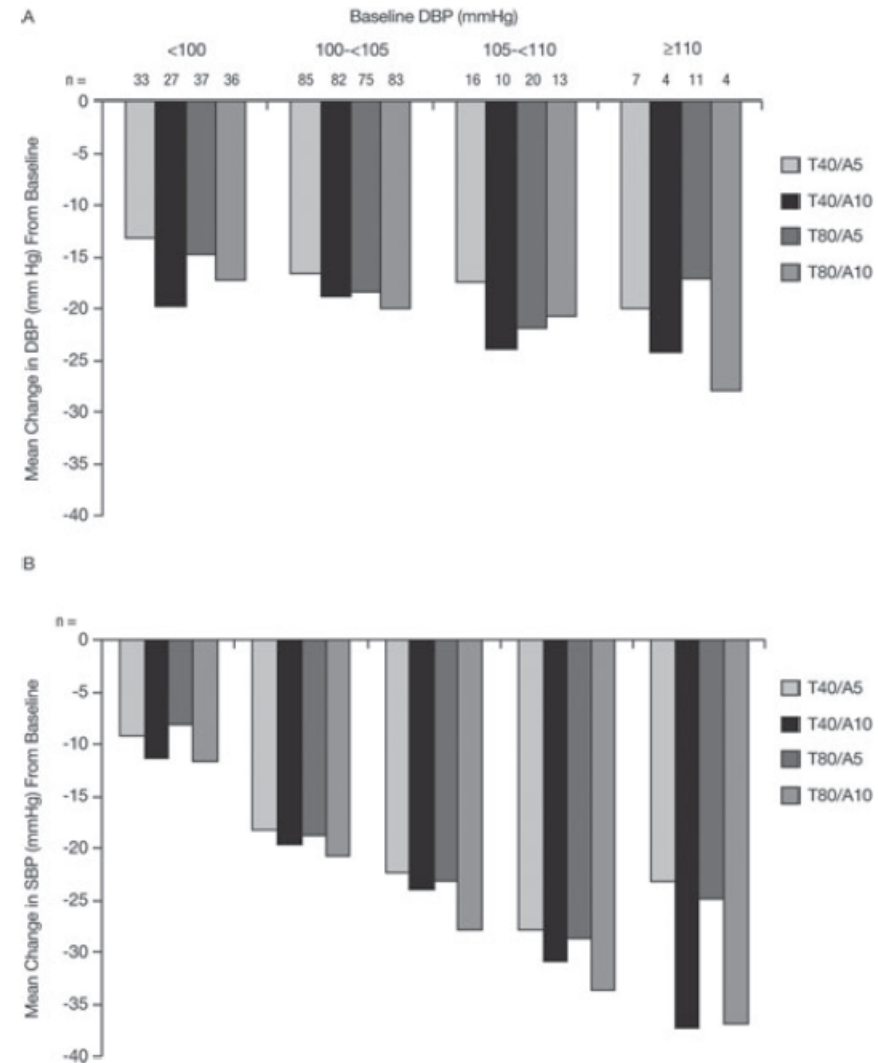
Treatment with telmisartan-amlodipine in hypertensive patients

Author	Littlejohn TW <i>et al.</i>	
Objective	To evaluate the efficacy and safety of telmisartan (T) plus amlodipine (A) in hypertensive patients	
Study design	Randomized, double-blind, double-dummy, placebo-controlled, international, multicenter, parallel-group, 4 X 4 factorial design trial	
Duration	8 weeks	
Patient Population	No. of patients	1461
	Mean Age	53.1 ± 11.1 years
	mean baseline SBP mean baseline DBP	153.2 ± 12.1 / 101.7 ± 4.3 mm Hg

Treatment with telmisartan-amlodipine in hypertensive patients

Results

- In-clinic BP reductions were greater with combination therapy than respective monotherapies.
- BP control was also greatest in the T80-mg plus A10-mg group (76.5%) and BP response rates >90% with this combination.
- Peripheral edema was most common in the A10-mg group (17.8%); however, this rate was notably lower when A was used in combination with 6.2% (T40 / A10).



Comparative Study of Mono-Therapy of Amlodipine or Telmisartan, and the Fixed Dose Combination in Mild to Moderate Hypertension

Author	Goyal J <i>et al.</i>	
Objective	To compare efficacy and safety of mono-therapy of Amlodipine, Telmisartan and fixed dose combination in mild to moderate hypertensives who failed to achieve BP control with low dose mono-therapy of either drug	
Study design	Prospective, open label, three arms and randomized study.	
Duration	8 weeks	
Patient Population	No. of patients	96
	Mean Age	53.1 ± 11.1 years
	SBP DBP	≥ 140 to 179 mmHg ≥ 90 to 109 mmHg

Comparative Study of Mono-Therapy of Amlodipine or Telmisartan, and the Fixed Dose Combination in Mild to Moderate Hypertension

Results

- Combination of Amlodipine 5 mg and Telmisartan 40 mg showed statistically significant reduction in SBP as compared to mono-therapy
- Maximum adverse drug reactions (ADRs) were reported in Amlodipine mono-therapy group, like ankle oedema, constipation, headache and fatigue

Follow up Time	Change in SBP (mmHg) Group A (n 30)	Change in SBP (mmHg) Group B (n 32)	Change in SBP (mmHg) Group C (n 31)
Week 0 to 2	10.00 $\pm$ 2.877	11.75 $\pm$ 2.862	13.29 $\pm$ 4.577
Week 2 to 4	18.00 $\pm$ 4.756	20.31 $\pm$ 5.233	23.23 $\pm$ 6.190
Week 4 to 8	21.80 $\pm$ 5.592	24.38 $\pm$ 6.333	27.10 $\pm$ 7.134

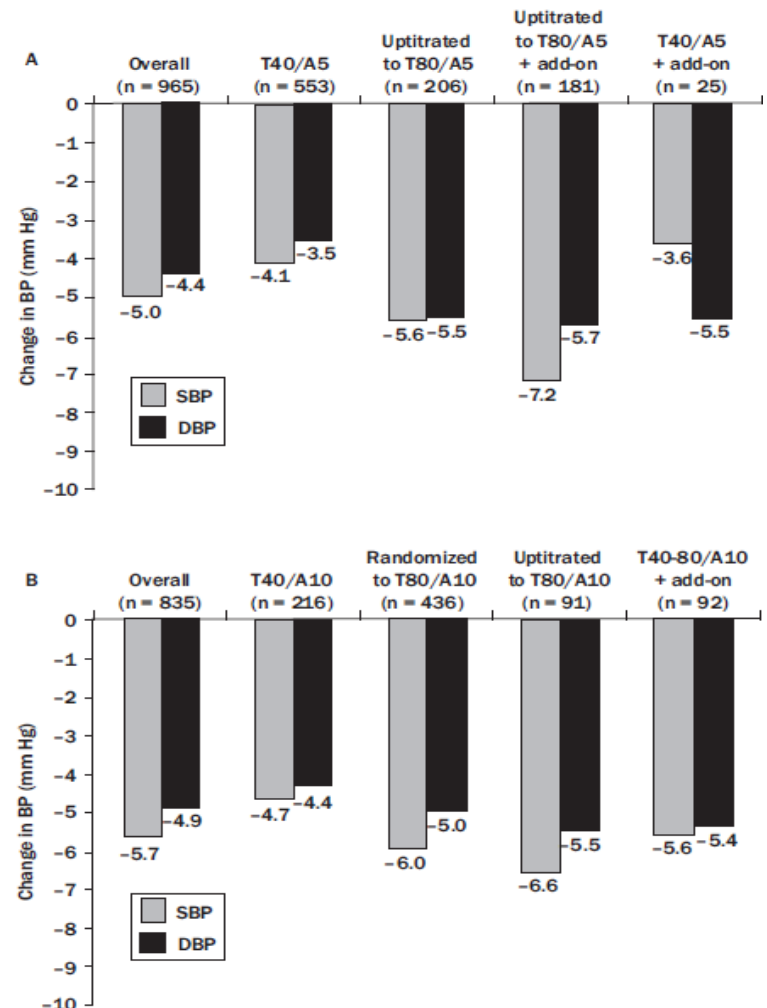
Open-Label, Long-Term Follow-Ups of the TEAMSTA-5 and TEAMSTA-10 Studies

Objective	To evaluate efficacy and tolerability of single-pill combinations of telmisartan 40–80 mg/ amlodipine 5–10 mg (T40–80/A5–10) in patients with hypertension not at diastolic blood pressure (DBP) goal (DBP 90 mm Hg) after 6 weeks of amlodipine 5 mg monotherapy (A5) (TEAMSTA-5) or amlodipine 10 mg monotherapy (A10) (TEAMSTA-10).	
Study design	8 weeks Randomized, double-blind, controlled studies	
Patient Population	TEAMSTA-5 Follow-Up	976 patients
	TEAMSTA-10 Follow-Up,	838 patients
	Mean Age	53.1 ± 11.1 years
	SBP	≥ 140 to 179 mmHg
	SBP	≥ 90 to 109 mmHg

Open-Label, Long-Term Follow-Ups of the TEAMSTA-5 and TEAMSTA-10 Studies

Results

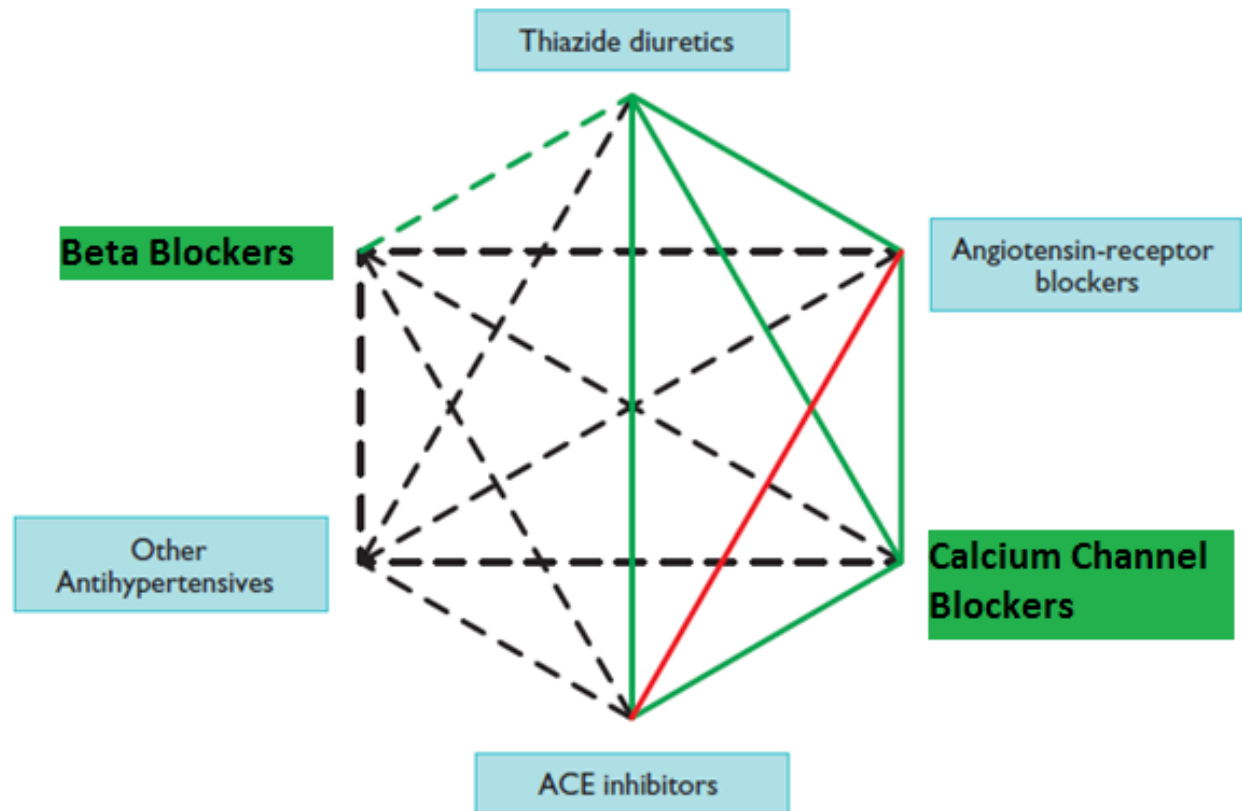
- Treatment compliance in both follow-up studies was 98.4%.
- Single-pill combinations of T40-T80/A5-A10 resulted 93% of patients achieved DBP goal (90 mm Hg)
- Long-term treatment with T40-T80/A5-A10 was well tolerated, with comparable adverse event profiles for all telmisartan/ amlodipine combinations.



Summary

- The combination of Telmisartan + Amlodipine blocks the AT 1 receptor, L type calcium channels
- The fixed dose combination acts on different pathways and provides
 - Superior BP control and
 - Pleiotropic benefits

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

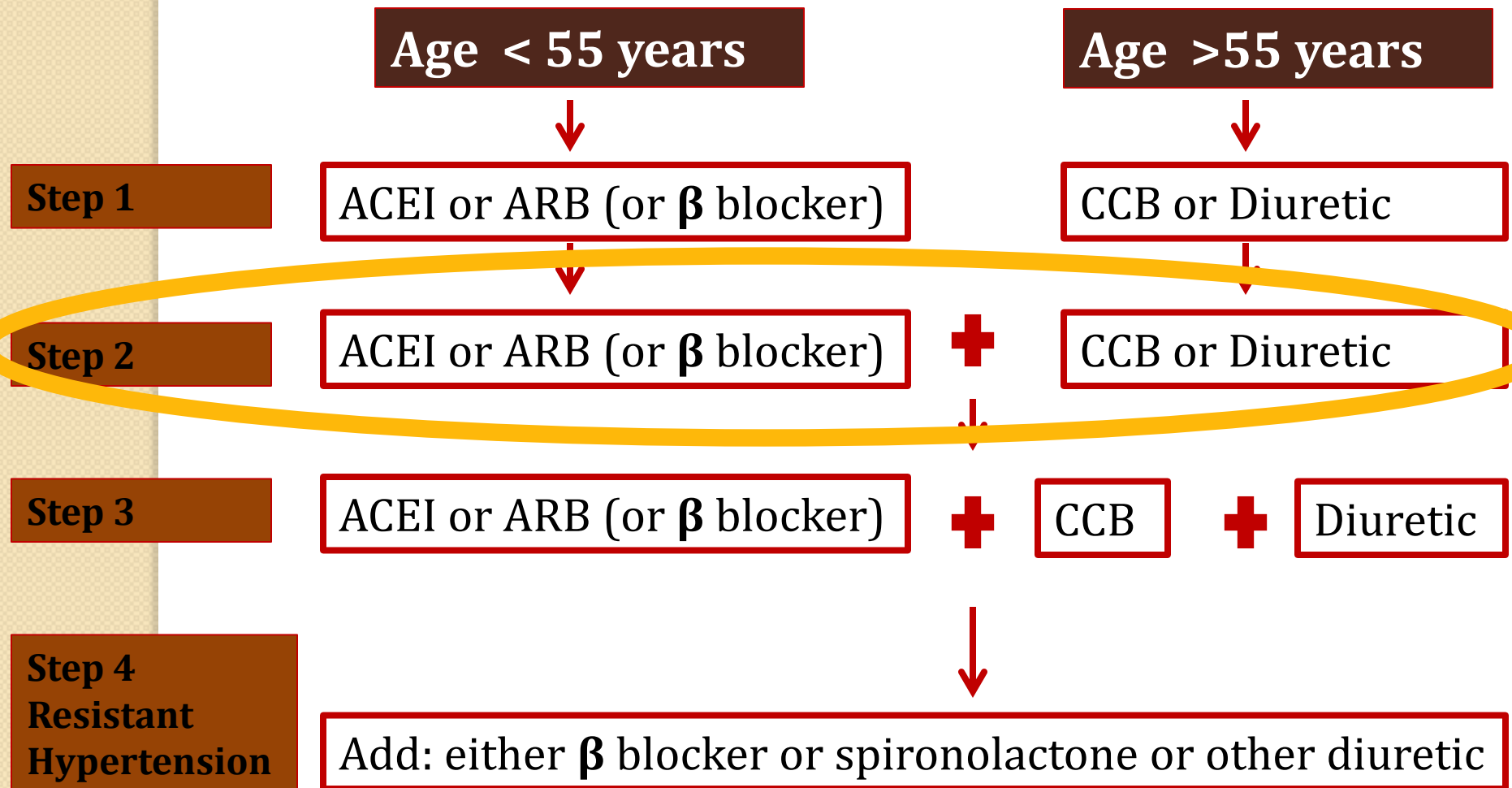


ACE = angiotensin-converting enzyme.

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

Association of Physicians of India (API) Guidelines



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

Advantages: Combination therapy

Effective BP control

Shorter time to achieve BP goal

Additive action

Offsets the side effects

Fewer pills

Improves compliance

Conclusion

- Majority of patients require 2 drugs to achieve BP goal
- Combination therapy are recommended in treatment guidelines
- Telmisartan + Amlodipine provides:
 - Superior BP control in patients with uncontrolled Hypertension
 - End organ protection
 - Reduces Pill Burden.
 - Increases compliance

[illegible]