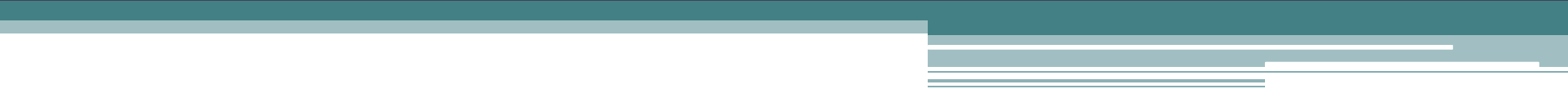


Role of Telmisartan and Metoprolol in the Management of Hypertension

A series of horizontal lines in teal and light blue colors, with varying lengths and offsets, creating a modern, layered effect across the width of the slide.

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**

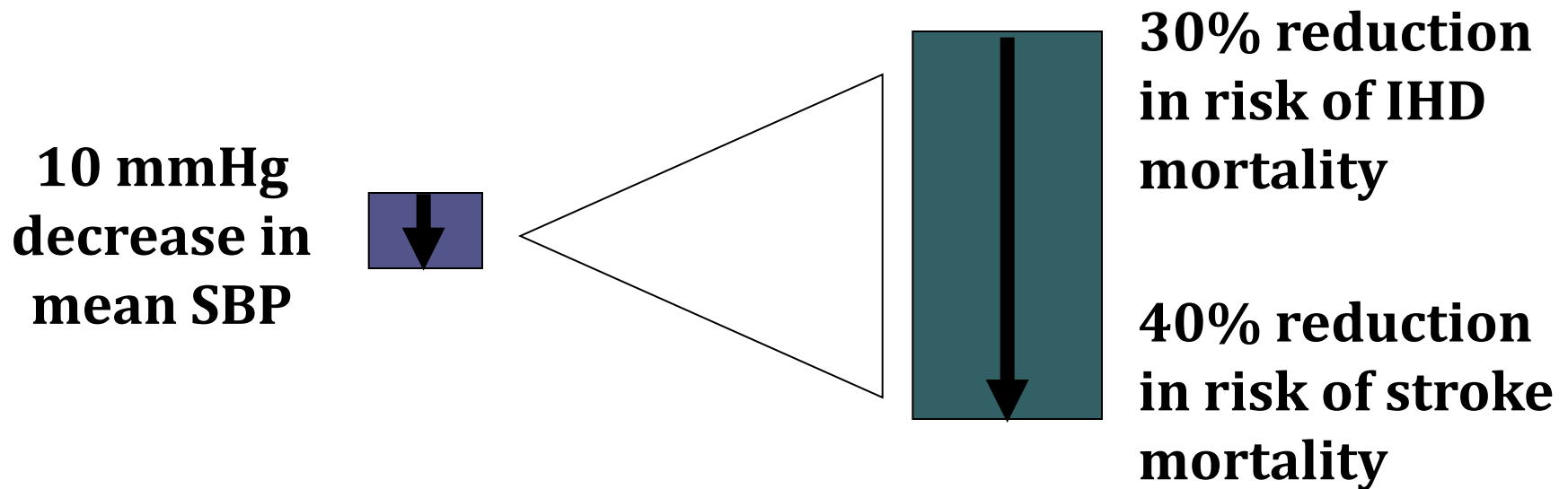
Annual worldwide cost
of hypertension



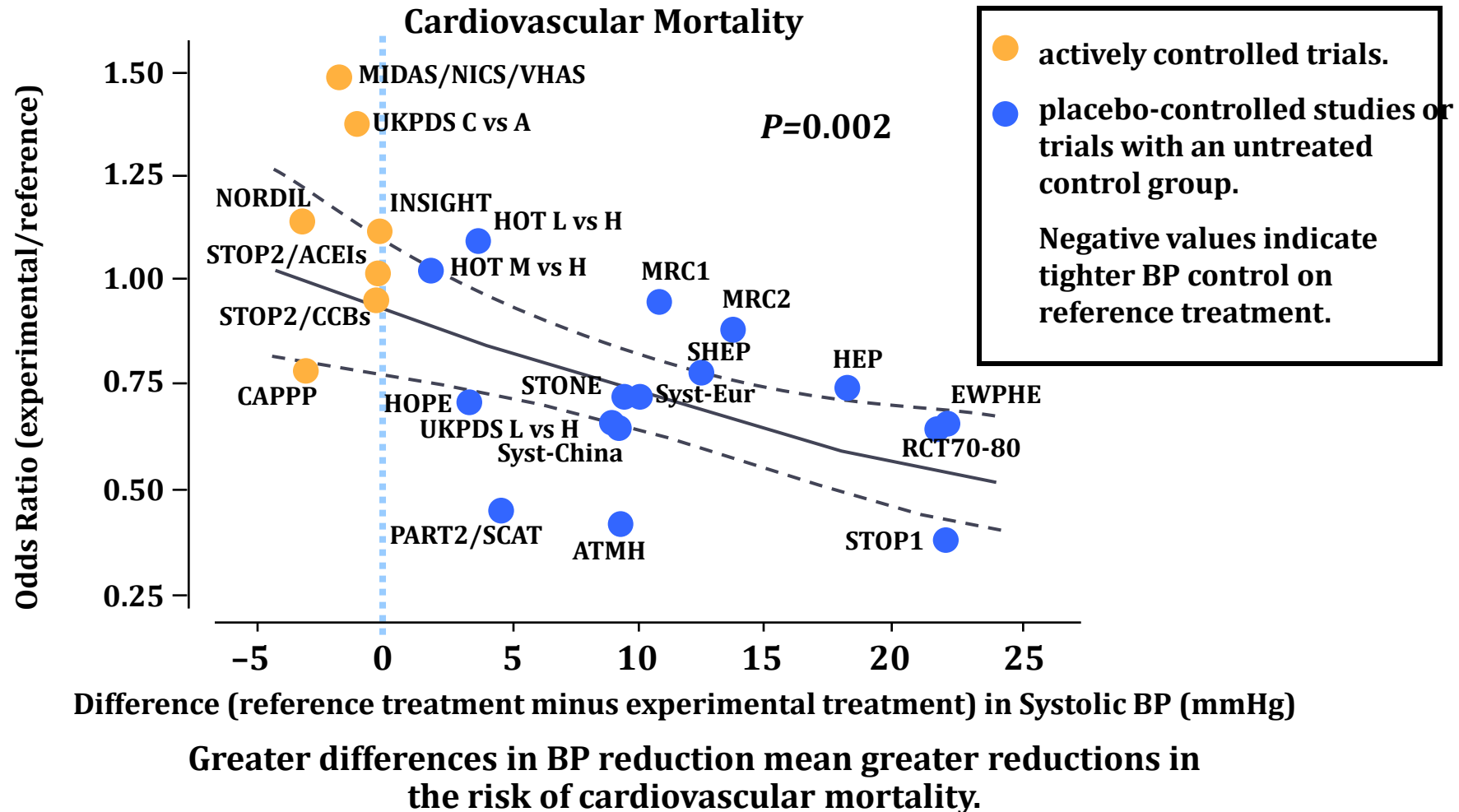
**1.6 Billion
HTN patients
estimated by 2025**

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



Importance of Lowering BP

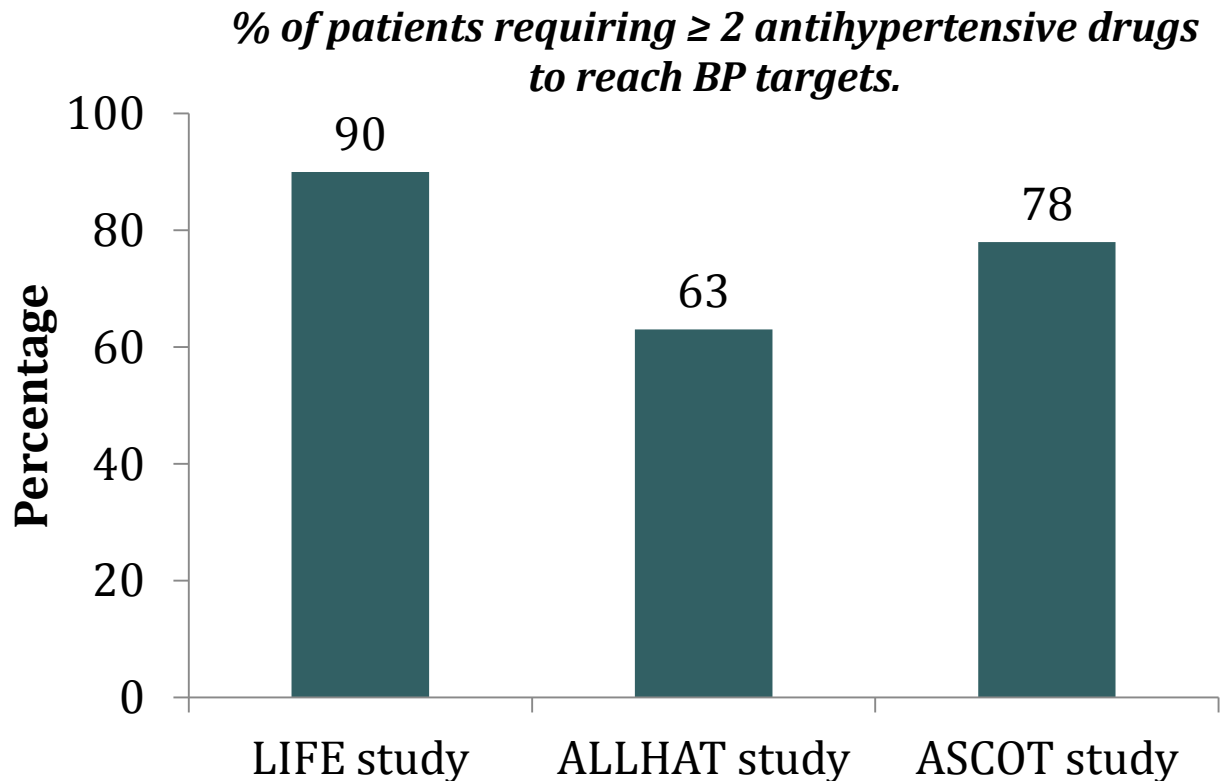


BP, blood pressure

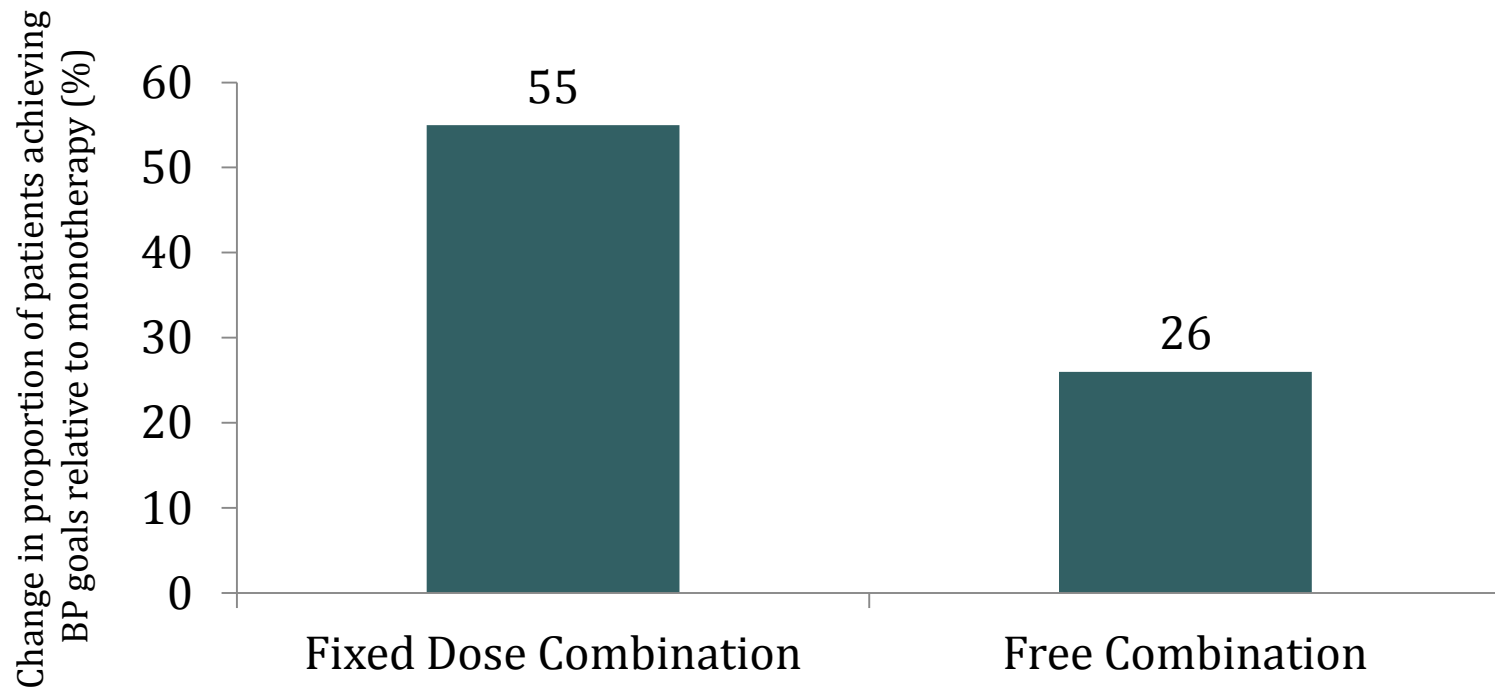
Staessen JA et al. *Hypertension Research*. 2005;28:385-407.

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 ”*

Telmisartan

An effective anti hypertensive with Pleiotropic Benefits

ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial)

- Goal: To test whether Telmisartan was similarly effective to Ramipril
- Population and treatment: 25 620 patients ≥ 55 years of age with CHD or diabetes plus additional risk factors without evidence of HF.
- Randomized to ramipril 10 mg/day, telmisartan 80 mg/day, or combination of the two for a mean duration of 55 months.
- Primary outcome: A composite of CV death, MI, stroke, or hospitalization for HF

ONTARGET: Results

- Telmisartan was shown to be noninferior to ramipril

Key results

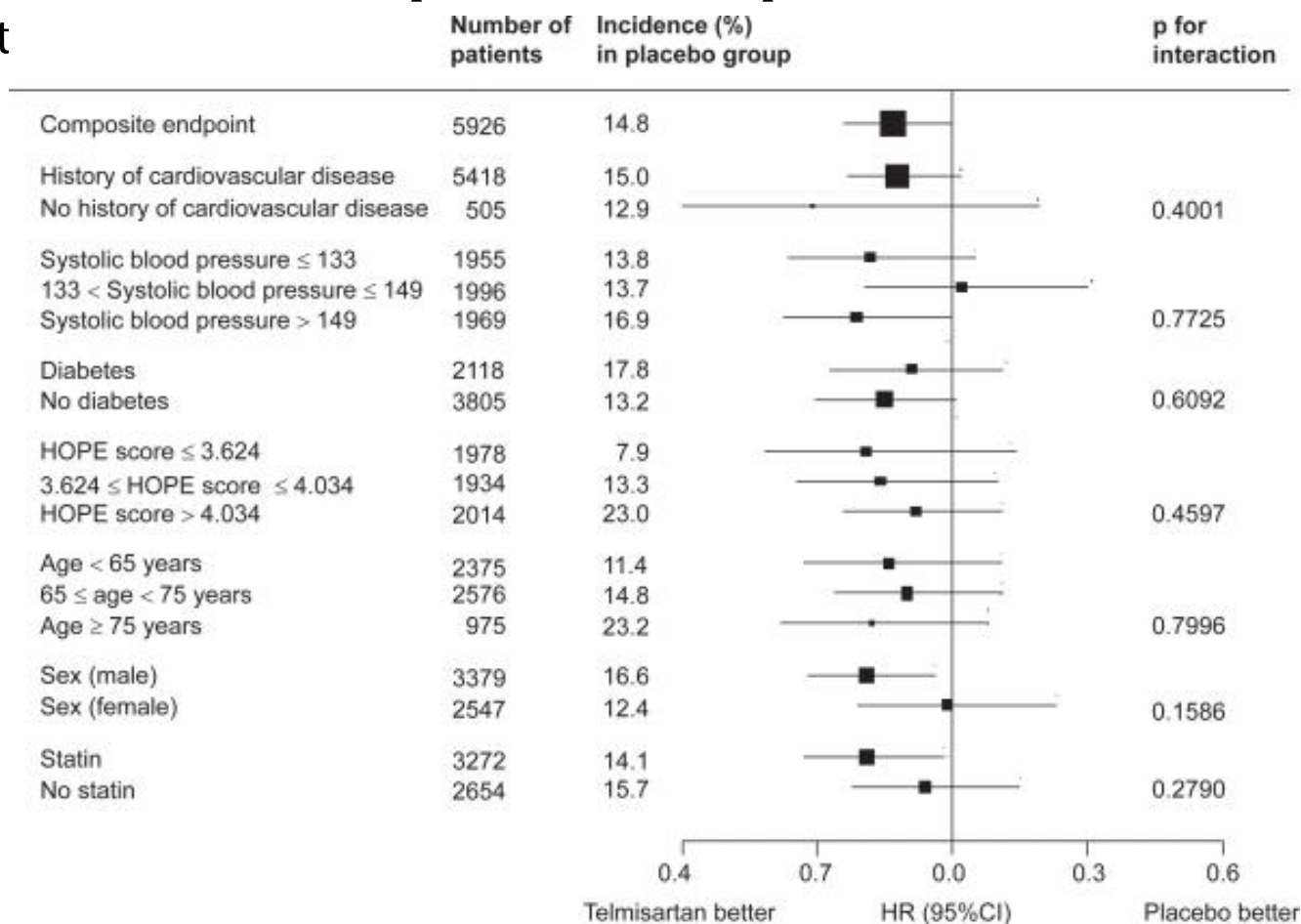
Outcome	Ramipril (n=8576), %	Telmisartan (n=8542), %	Combination (n=8502), %	Risk ratio (95% CI) ^a	Risk ratio (95% CI) ^b
Primary end point	16.5	16.7	16.3	1.01 (0.94–1.09)	0.99 (0.92–1.07)
CV death/MI/stroke	14.1	13.9	14.1	0.99 (0.91–1.07)	1.00 (0.93–1.09)
MI	4.8	5.2	5.2	1.07 (0.94–1.22)	1.08 (0.94–1.23)
Stroke	4.7	4.3	4.4	0.91 (0.79–1.05)	0.93 (0.81–1.07)
CHF hospitalization	4.1	4.6	3.9	1.12 (0.97–1.29)	0.95 (0.82–1.10)
CV death	7.0	7.0	7.3	1.00 (0.89–1.12)	1.04 (0.93–1.17)
Any death	11.8	11.6	12.5	0.98 (0.90–1.07)	1.07 (0.98–1.16)
Renal impairment	10.2	10.6	13.5	1.04 (0.96–1.14)	1.33 (1.22–1.44)

Telmisartan Randomised Assessment Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND)

- Goal: To assess whether telmisartan would be effective in patients intolerant to ACE inhibitors with CV disease or diabetes with end-organ damage
- 5926 patients were randomised to receive telmisartan 80 mg/day (n=2954) or placebo (n=2972)
- The primary outcome was the composite of cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure.

TRANSCEND Results

- Mean blood pressure was lower in telmisartan group than in placebo group
- Telmisartan had an impact on the composite outcome of cardiovascular death



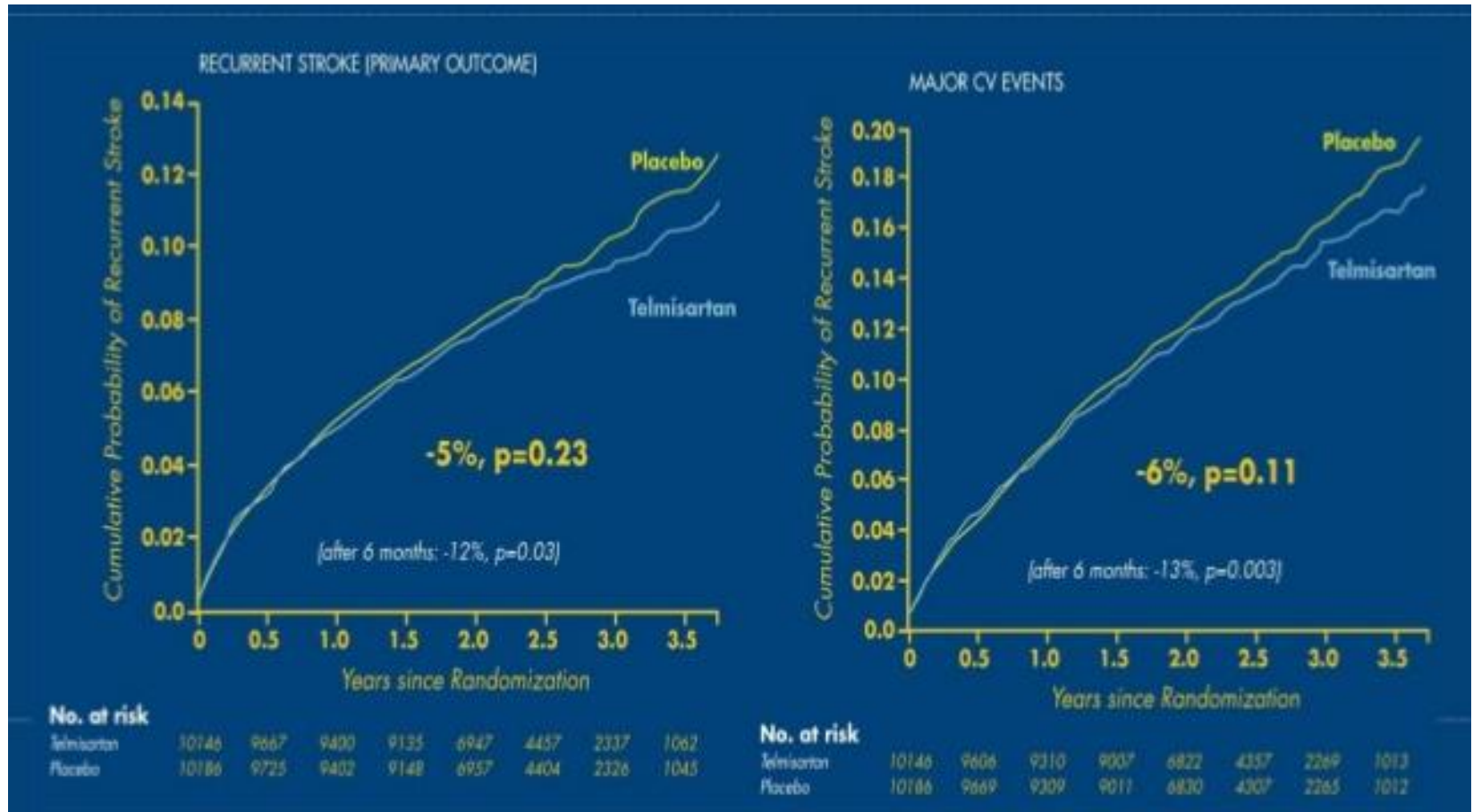
Telmisartan to Prevent Recurrent Stroke and Cardiovascular Events: ProFeSS study

- Goal: To effects of therapy with an angiotensin-receptor blocker, telmisartan, initiated early after a stroke in a multicenter trial
- 20,332 patients who recently had an ischemic stroke, were randomised: 10,146 patients to receive telmisartan (80 mg daily) and 10,186 to receive placebo.
- The primary outcome was recurrent stroke.
- Secondary outcomes were major cardiovascular events (death from cardiovascular causes, recurrent stroke, myocardial infarction, or new or worsening heart failure) and new-onset diabetes

Yusuf S et al. N Engl J Med 2008;359:1225-37.

ProFeSS study Results

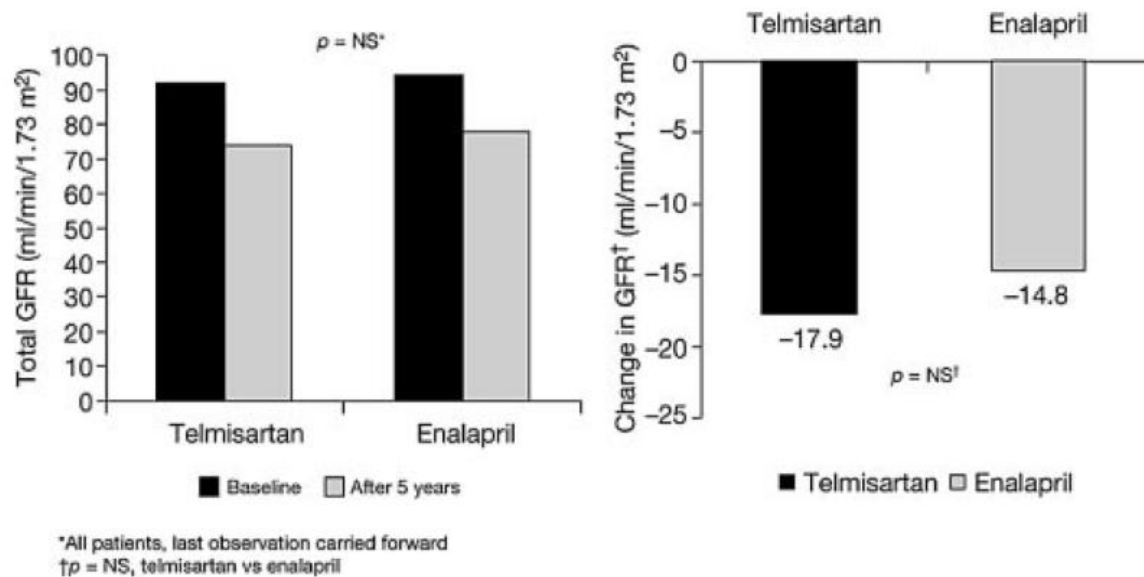
- During a mean follow up of 2.5 years, the mean blood pressure was 3.8/2.0 mm Hg lower in the telmisartan group than in the placebo group.



Yusuf S et al. N Engl J Med 2008;359:1225-37.

Diabetics Exposed to Telmisartan And enalapril (DETAIL) trial

- Telmisartan effective in reducing the decline in GFR:
- During the 5-yr study period, no patient developed a serum creatinine >200 mol/L, and none required dialysis.

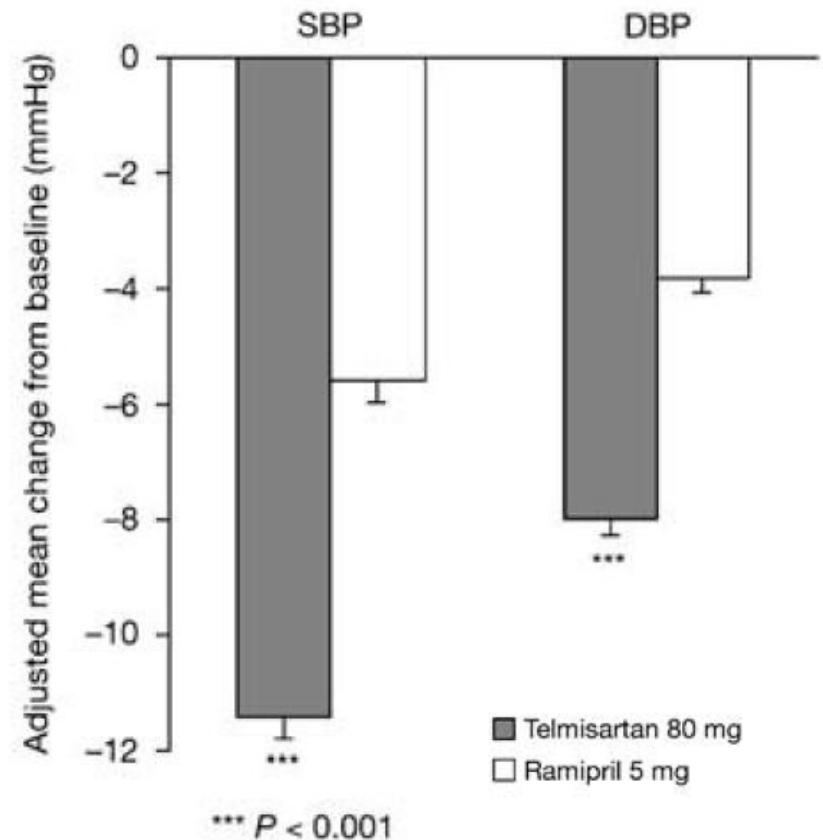


Telmisartan conferred comparable renoprotection to enalapril and was associated with a low incidence of mortality.

Figure 1. Comparison of effect of telmisartan and enalapril on GFR after 5 yr of treatment (15).

PRISMA I and II: Results

- Prospective, Randomized Investigation of the Safety and efficacy of Telmisartan vs Ramipril Using ABPM (ambulatory BP monitoring) (PRISMA) I and II.
- The adjusted mean treatment differences in the last 6-h mean ambulatory SBP/DBP were in favour of telmisartan.



Telmisartan is more effective than ramipril throughout the 24-h period and during the EMBPS.

SMOOTH Study

- The Study of Telmisartan in Overweight/ Obese patients with Type 2 diabetes and Hypertension (SMOOTH)
- In total, 840 patients were randomized.
- Significantly reductions versus seen in Telmisartan group.

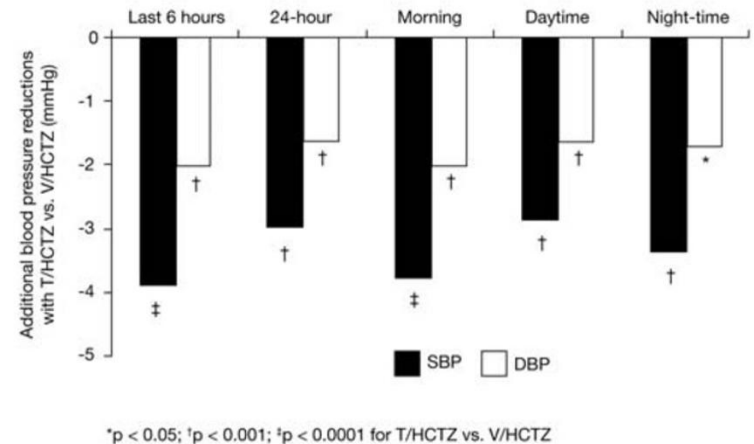


Figure 2

Additional reductions with T/HCTZ compared with V/HCTZ in mean ambulatory SBP and DBP during various periods of the 24-hour dosing interval after treatment for 10 weeks. Black: SBP; white: DBP.

In high-risk, overweight/obese patients with hypertension and type 2 diabetes, T/HCTZ provides significantly greater BP lowering

PROTECTION Program

- The objective of the Programme of Research to show Telmisartan End-organ protection (PROTECTION) is to measure the end-organ protective effects of telmisartan in patients at high risk of renal, cardiac and vascular damage.
- Nine clinical studies will examine the effects of telmisartan in about 5000 hypertensive patients with
 - isolated systolic hypertension,
 - type 2 diabetes,
 - obesity,
 - left ventricular hypertrophy or
 - renal disease.
- The programme also investigated the effects of an ARB on key surrogate markers of organ tissue damage.

PROTECTION

Programme of Research to show Telmisartan End-organ protection

10 clinical Studies in > 6500 Patients from 32 countries

PRISMA I & II
EMBPS
Telmisartan vs. Ramipril

TRENDY
Dysfunction of the renal endothelium
Telmisartan vs. Ramipril

ARBs FDC
Morning surge in BP
Telmisartan + HCTZ
vs. Losartan + HCTZ

INNOVATION
Diabetic Nephropathy
Telmisartan vs. Placebo

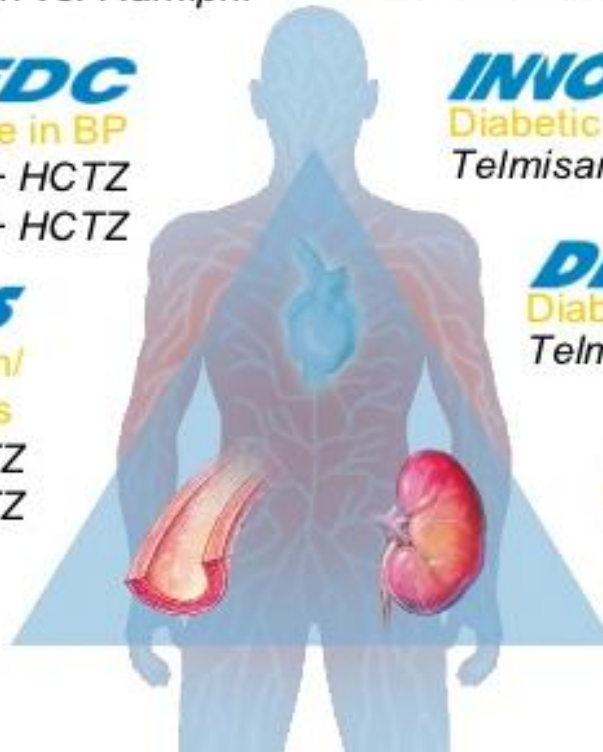
ATHOS
Systolic Hypertension/
elderly hypertensives
Telmisartan + HCTZ
vs. Amlodipine + HCTZ

DETAIL
Diabetic Nephropathy
Telmisartan vs. Enalapril

SMOOTH
Diabetes + Overweight
Telmisartan + HCTZ
vs. Valsartan + HCTZ

AMADEO
Diabetic Nephropathy
Telmisartan vs. Losartan

VIVALDI
Diabetic Nephropathy
Telmisartan vs. Valsartan



A meta-analysis of on insulin resistance in hypertensive patients

- 33 reports of RCTs enrolling a total of 2033 patients with hypertension were included.
- Telmisartan was associated with statistically significant reductions in percent changes of:
 - Insulin levels (-10.92%; -15.60% to -6.23%; $P < .00001$)
 - HOMA-IR (-15.89%; -22.01% to -9.78%; $P < .00001$) relative to other antihypertensive drugs.

Telmisartan appears to significantly improve insulin resistance compared with other antihypertensive drugs in patients with hypertension.

Effect of Telmisartan on the Regression of the Left Ventricular Hypertrophy

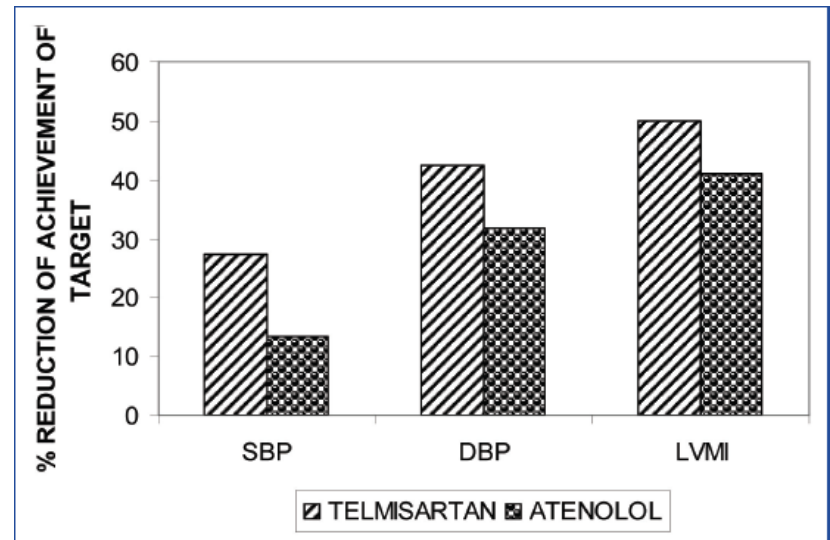
- Telmisartan is superior to Atenolol in achieving a regression of LVH, which is a better indicator of the cardiovascular morbidity and mortality.

Drugs	LVM $\pm$ SE		Paired t test	
	BT	AT	't'	'p'
Telmisartan (n=26)	328.89 $\pm$ 13.13	237.16 $\pm$ 7.67	11.28	<0.001
Atenolol (n=22)	247.41 $\pm$ 4.49	223.68 $\pm$ 5.18	5.86	<0.01
Unpaired t test df=46				
't'	5.51	1.39		X
'p'	<0.001	>0.05		X

[Table/Fig-2]: Effect of drugs on LVM

Drugs	SBP	DBP	IVST	LVPWT	LVID	LVMI
TELMISARTAN	10.96	9.05	17.5	15.56	3.21	27.49
ATENOLOL	8.27	8.45	5.73	3.68	1.59	9.68

[Table/Fig-3]: Effect of drugs on percent reduction of different parameters



[Table/Fig-9]: Effect of drugs on different parameters

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

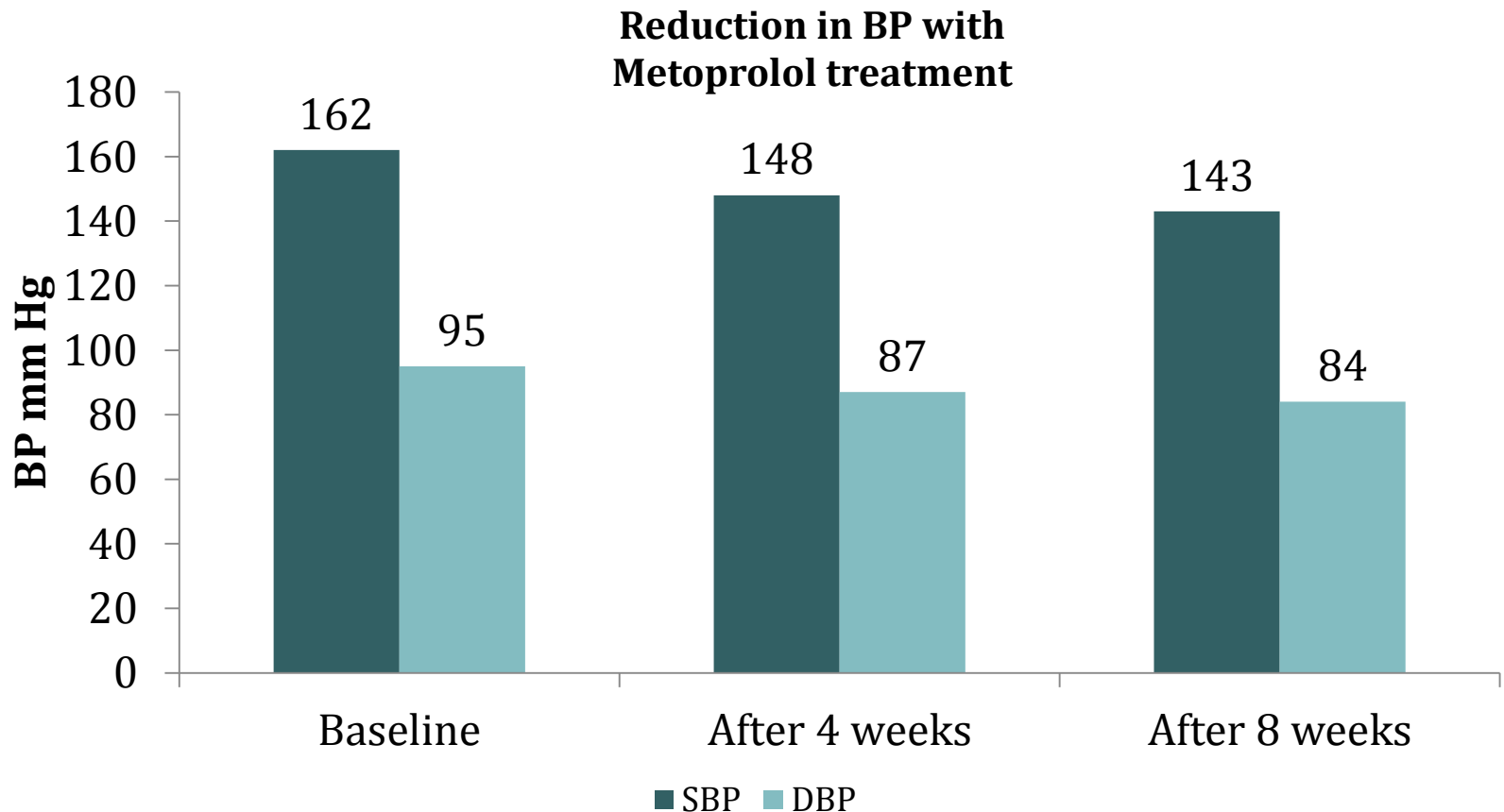
van den Born BJ et al. Ned Tijdschr Geneeskd. 2005 Aug 6;149(32):1808-9.

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



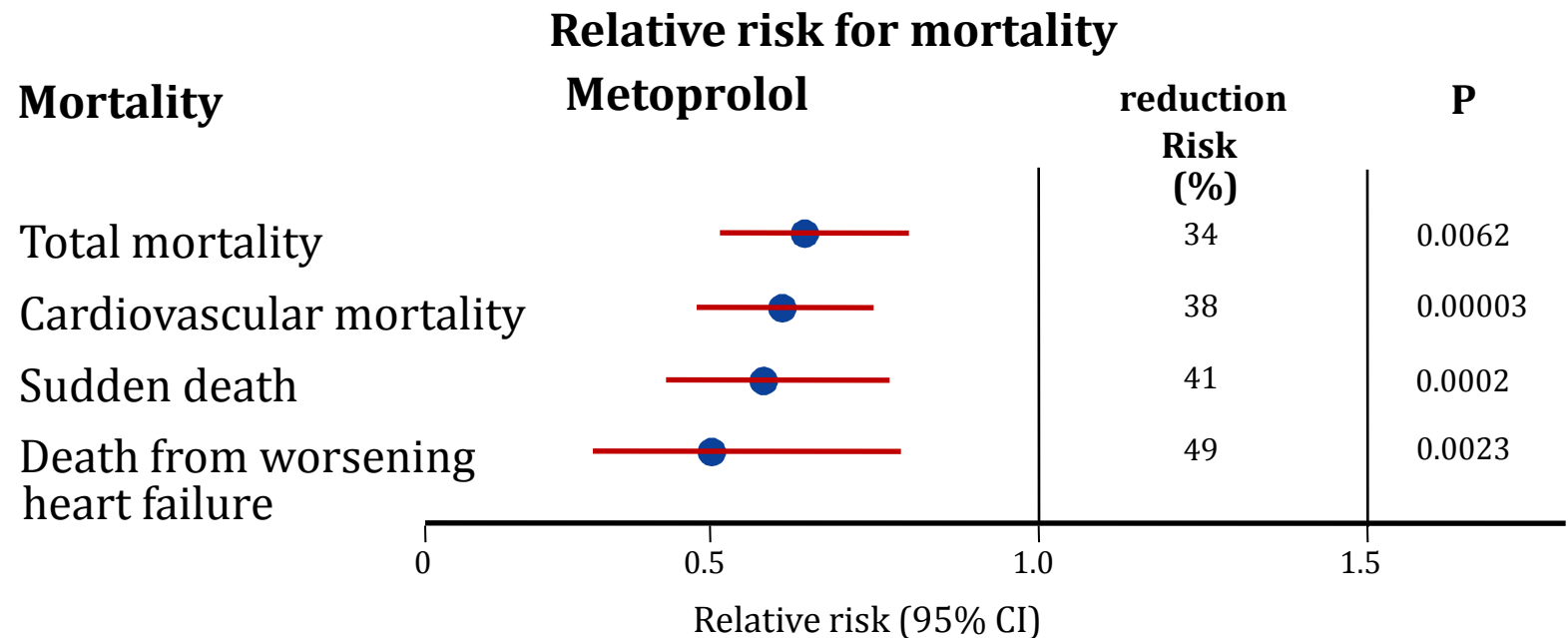
Metoprolol administered as monotherapy or in combination is effective and well tolerated

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



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

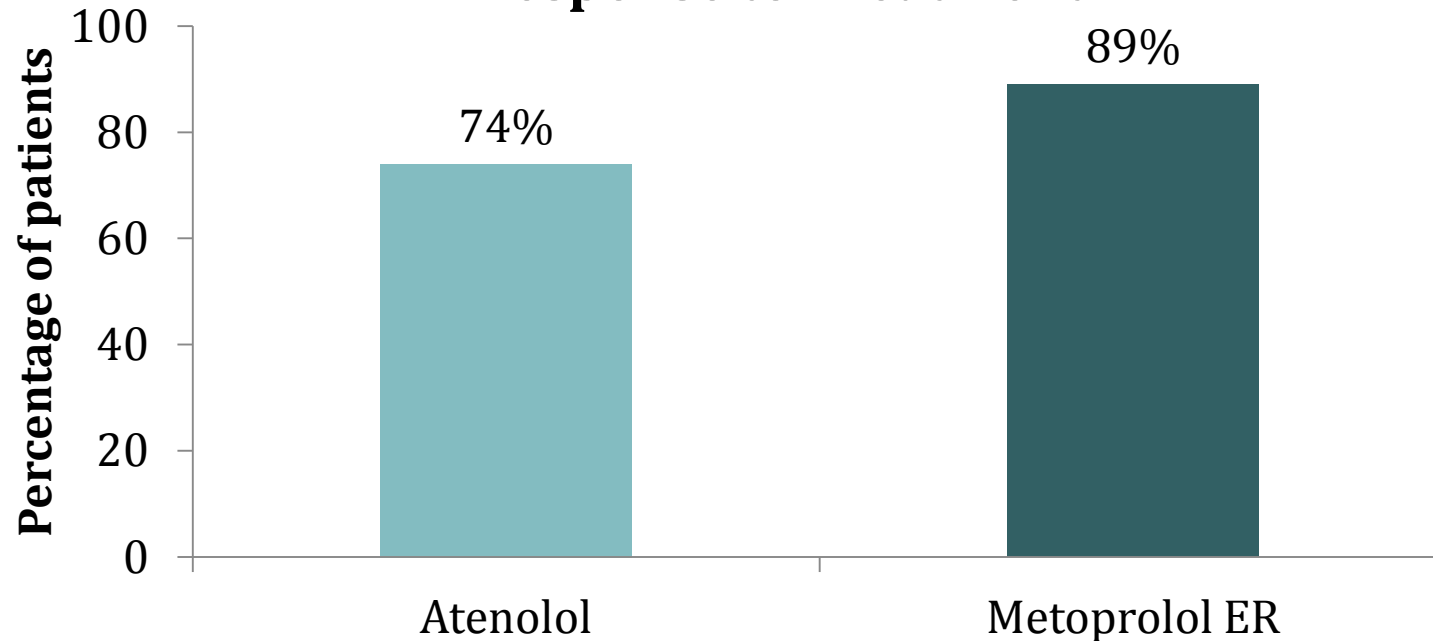
Comparison of Metoprolol and Atenolol in Hypertension

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

Response to Treatment



- Metoprolol effectively reduces BP compared to Atenolol.

Telmisartan and Metoprolol

Telmisartan:

- A unique ARB with PPAR-gamma activity provides beyond BP benefits including renal and cardioprotective effects

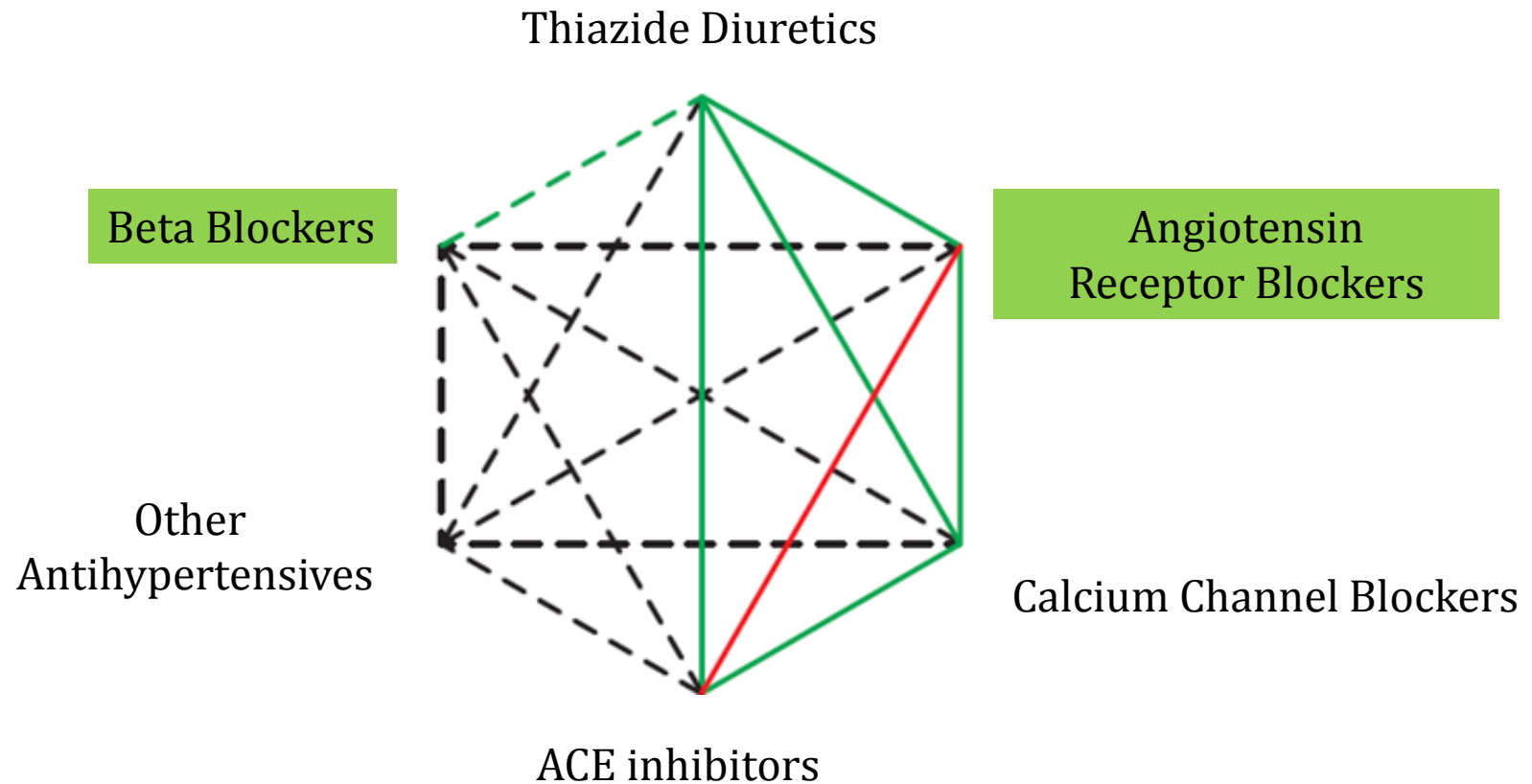
Metoprolol Extended Release:

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

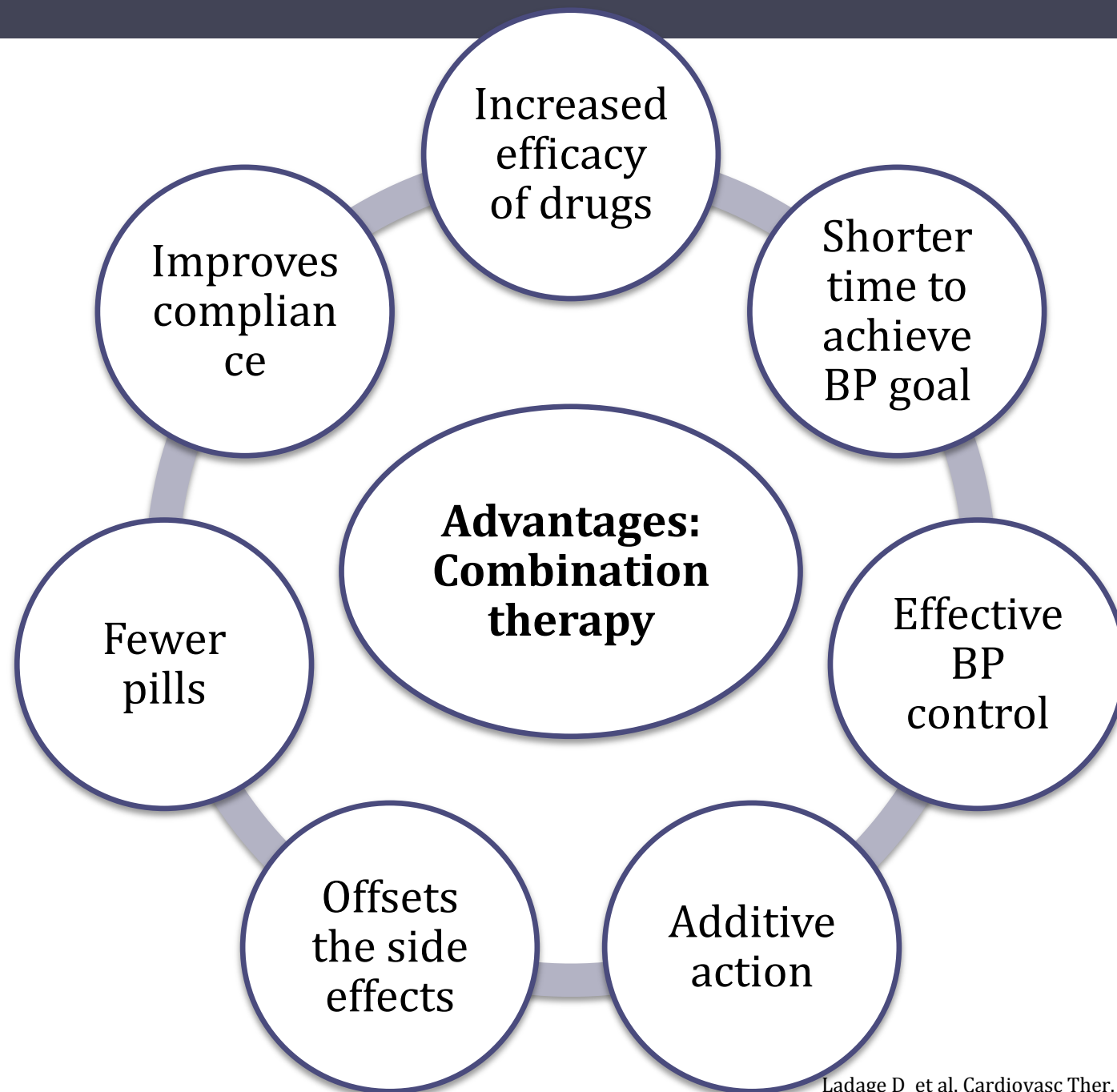
In patients with uncontrolled hypertension by monotherapy,

- The addition of a beta-blocker to ARB will result in a complementary effects.
- The combination of Telmisartan and Metoprolol results in additive BP reduction and end organ protection

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



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.



Summary

- Majority of patients require two drugs to achieve BP goal
- The dual combination of Telmisartan + Metoprolol blocks the AT1 receptors and selective beta 1 receptors
- The combination of these 2 drug results in additive BP reduction and end organ protection
- Combination recommended by guidelines
- Combination therapy increases compliance
- Combination therapy reduces Pill Burden.



Thank You