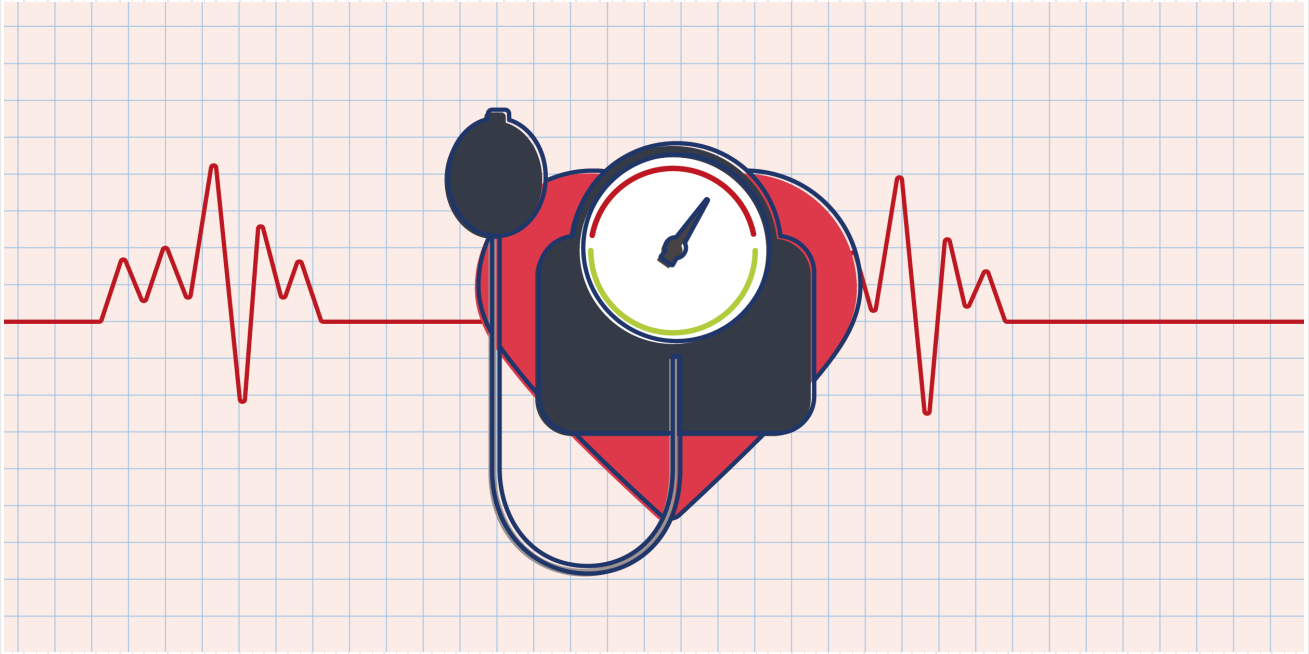
Telmisartan: A Unique ARB with Antihypertensive efficacy and Pleiotrophic Benefits



Hypertension

- Hypertension is the most common cardiovascular disease.

- Hypertension represents a potent risk factor for cardiovascular, peripheral vascular, and renal diseases

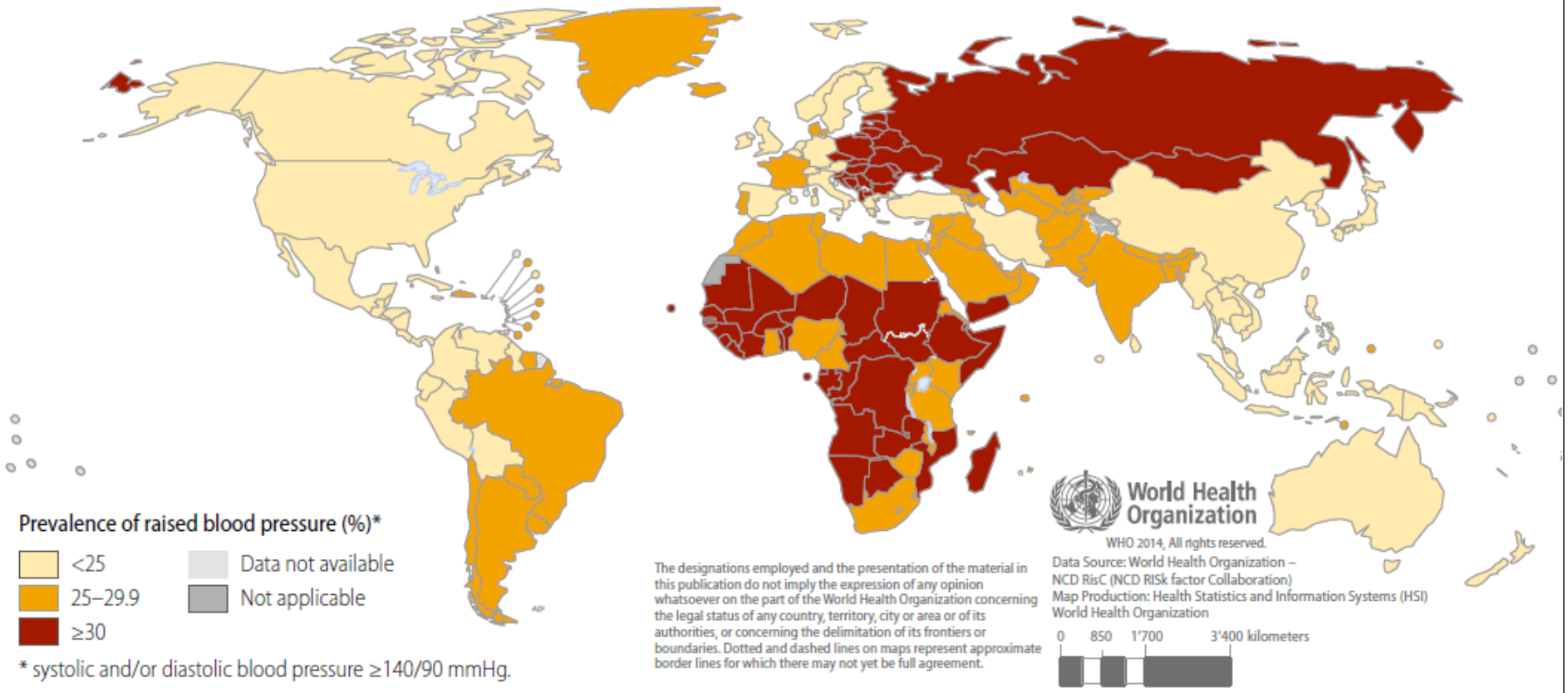
- The Framingham heart study estimate:

  Normotensives >55 years --- 90% lifetime risk of developing Hypertension

Singh PS et al. Int J Res Med Sci. 2017 Apr;5(4):1451-1455
Anchala R et al. J Hypertens. 2014;32:1170–7

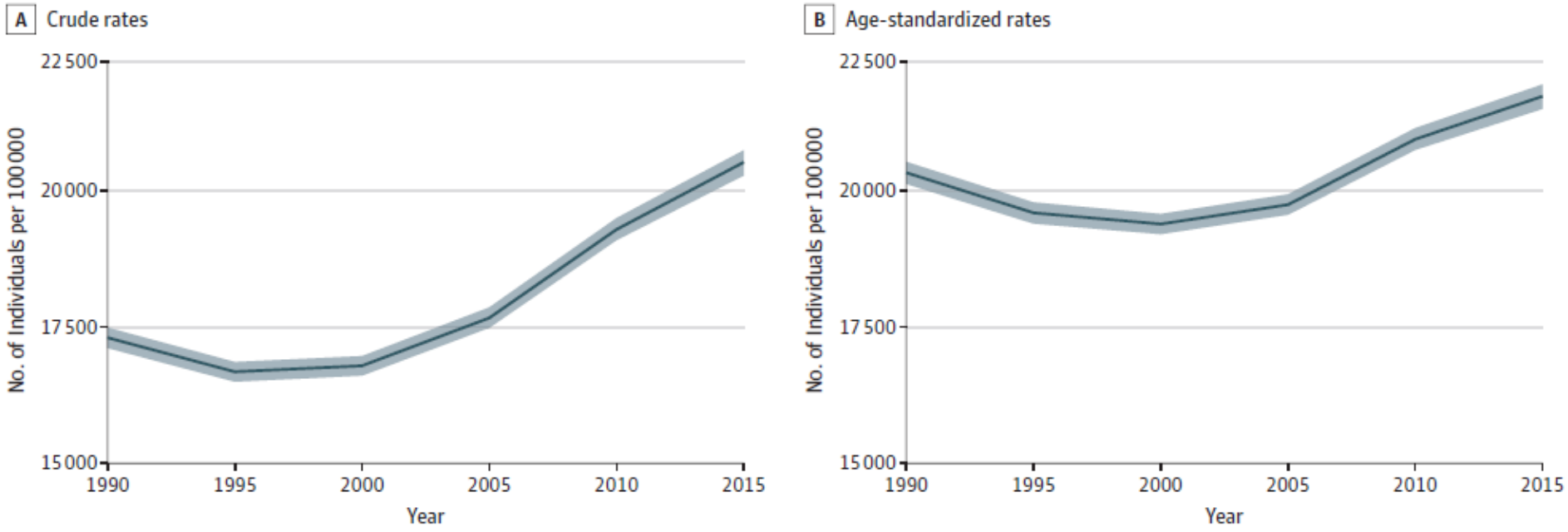
Hypertension: WHO Estimates

- **Ranked 3rd** most risk factor for hypertension burden in South Asia



Global Status Report, 2014. Apps.WHO.int.
Forouzanfar MH et al. JAMA. 2017 Jan 10;317(2):165-182.

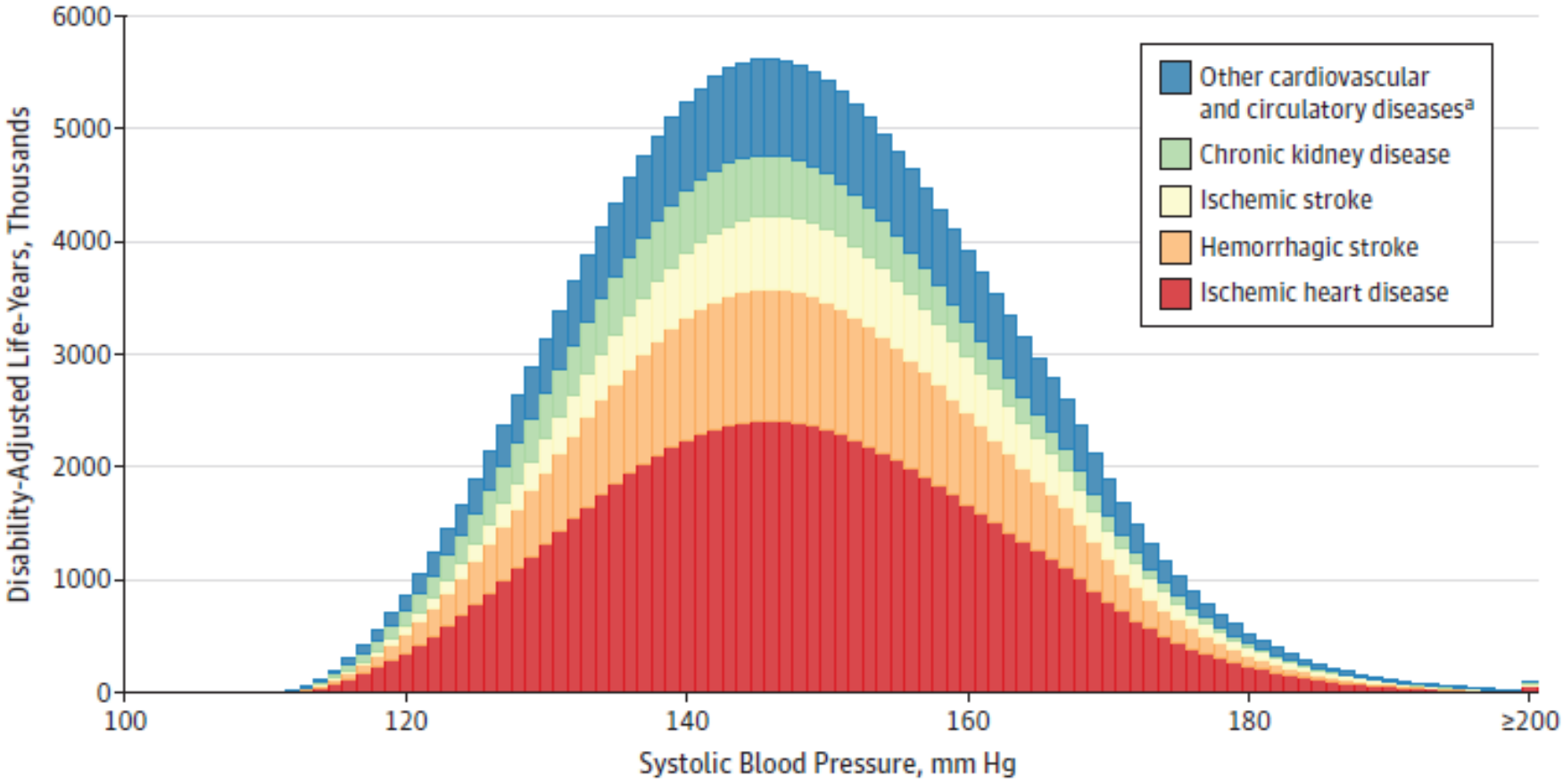
Global Rates of Systolic BP of 140mmHg or Higher in last 25 years



Reported data are for both sexes combined and for individuals aged 25 years and older. Shading indicates 95% uncertainty intervals.

Forouzanfar MH et al. JAMA. 2017 Jan 10;317(2):165-182.

Global Disability-Adjusted Life-Years by Systolic BP Level and Cause



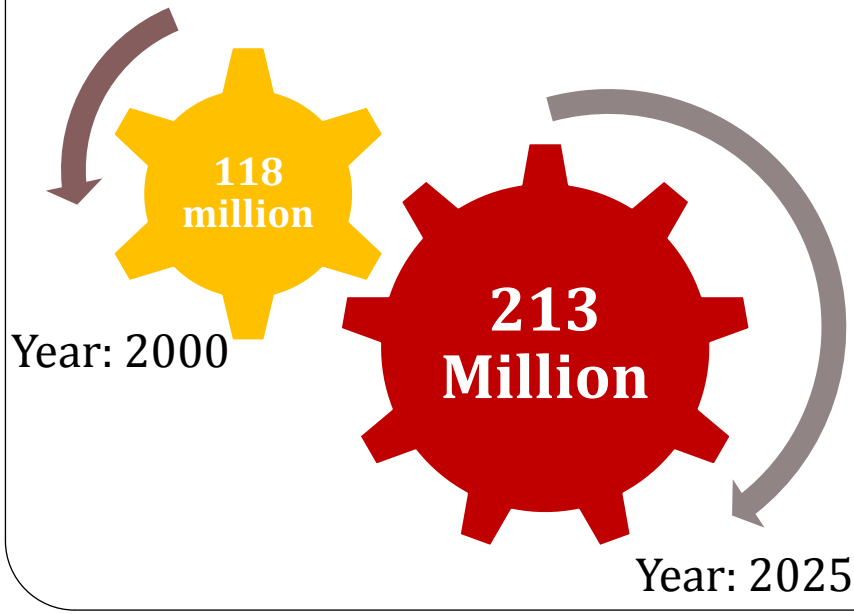
Forouzanfar MH et al. JAMA. 2017 Jan 10;317(2):165-182.

Hypertension In India

- Responsible for

57% • of all stroke deaths

24% • all deaths due to CHD

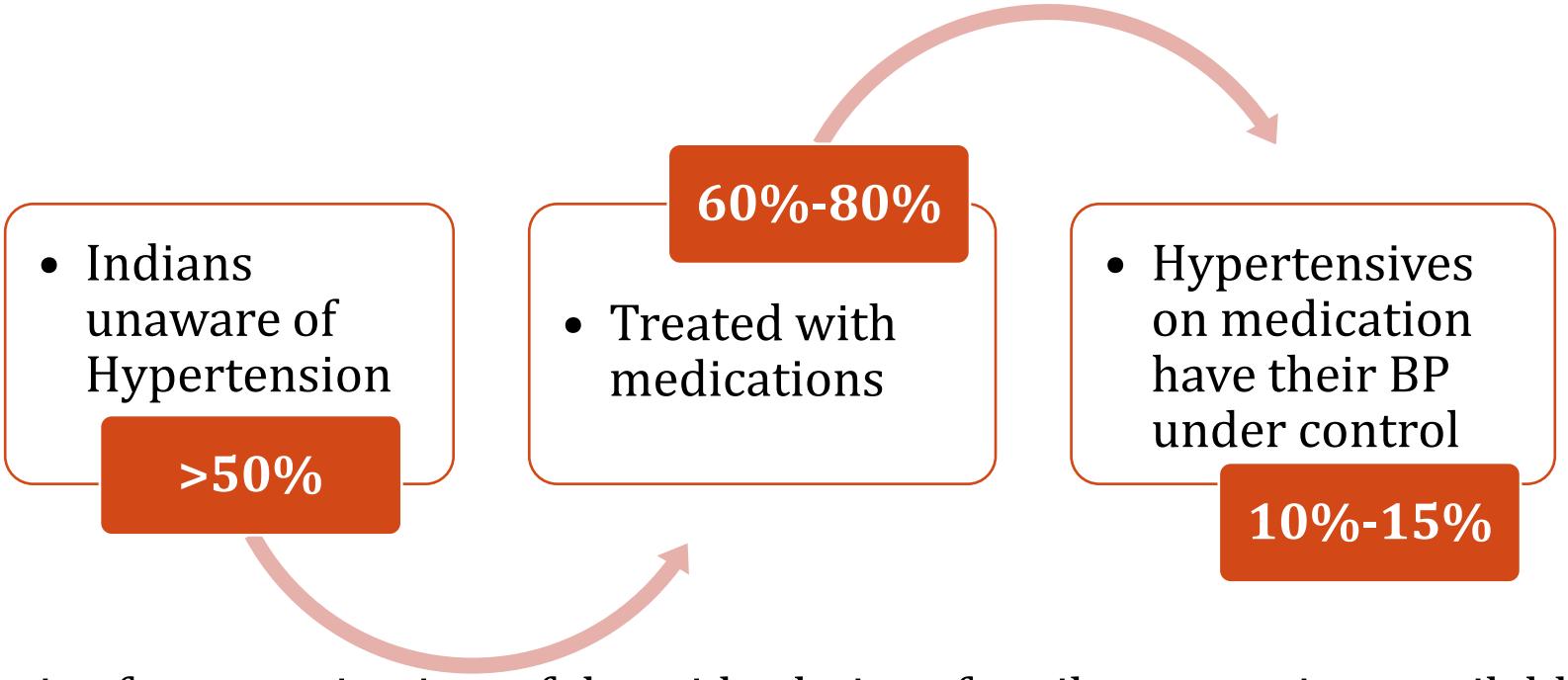


Incidence of hypertension is expected to almost double to 213 million by 2025 in India

Mohan et al:. *IJMR*. 2013;137:627-31

Current Challenges in Hypertension Control

- Over half of those who are hypertensive in India are not aware that they have hypertension.
- Only 10%-15% of the hypertensives have their BP under control.

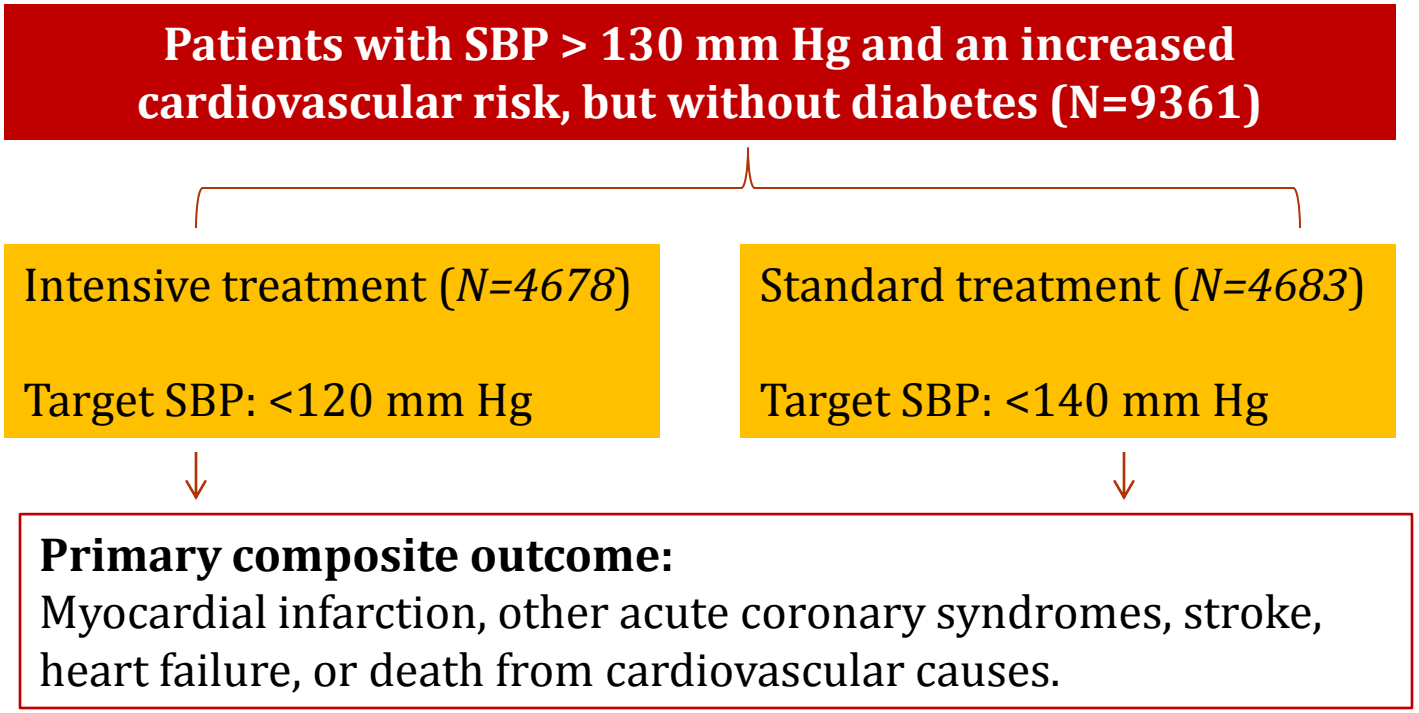


This is of concern in view of the wide choice of antihypertensives available with a potential to tailor treatment based on patient characteristics

Gupta R *et al.* Indian J Med Res. 2014 May; 139(5): 657–660

Aggressive BP control provides beneficial outcomes

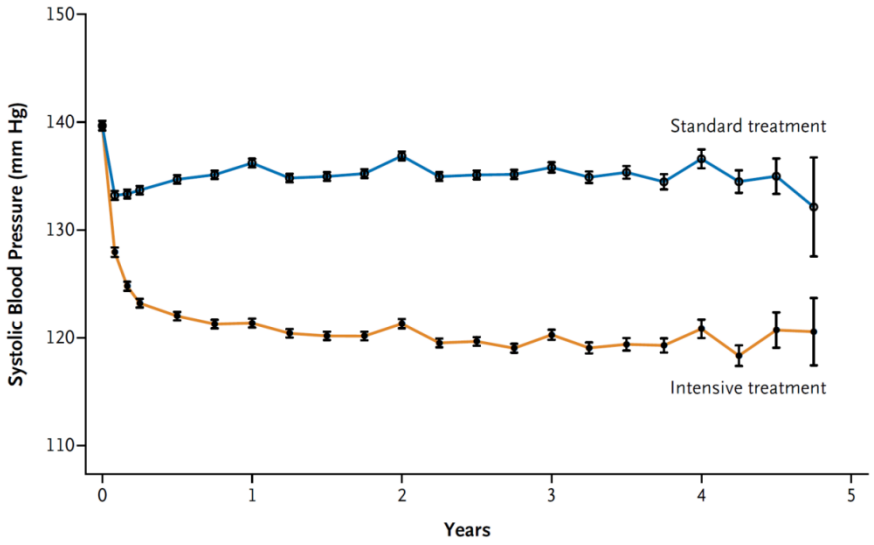
A randomized, controlled, open-label Systolic Blood Pressure Intervention Trial (SPRINT Trial) conducted at 102 clinical sites

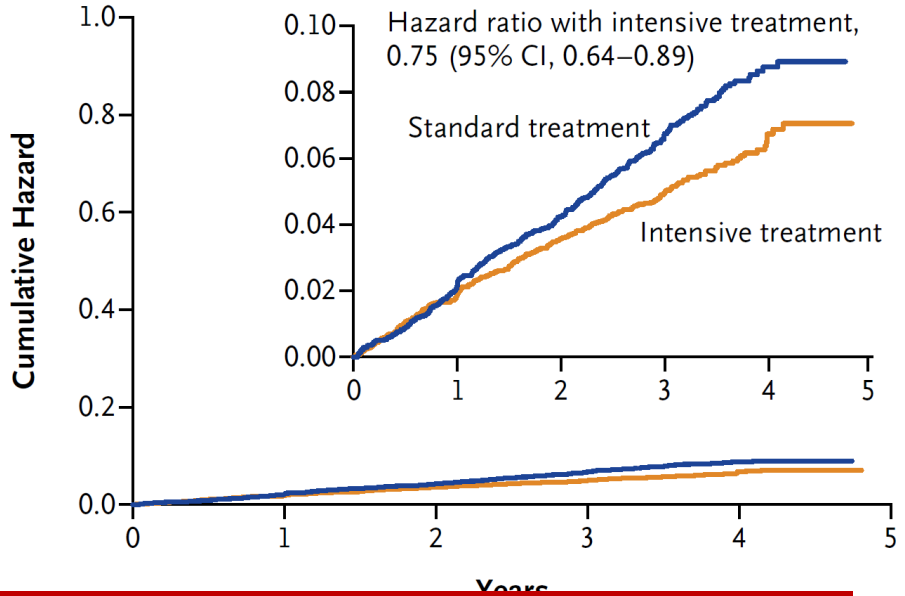


SPRINT Research Group *N Engl J Med.* 2015 Nov 26;373(22):2103-16

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

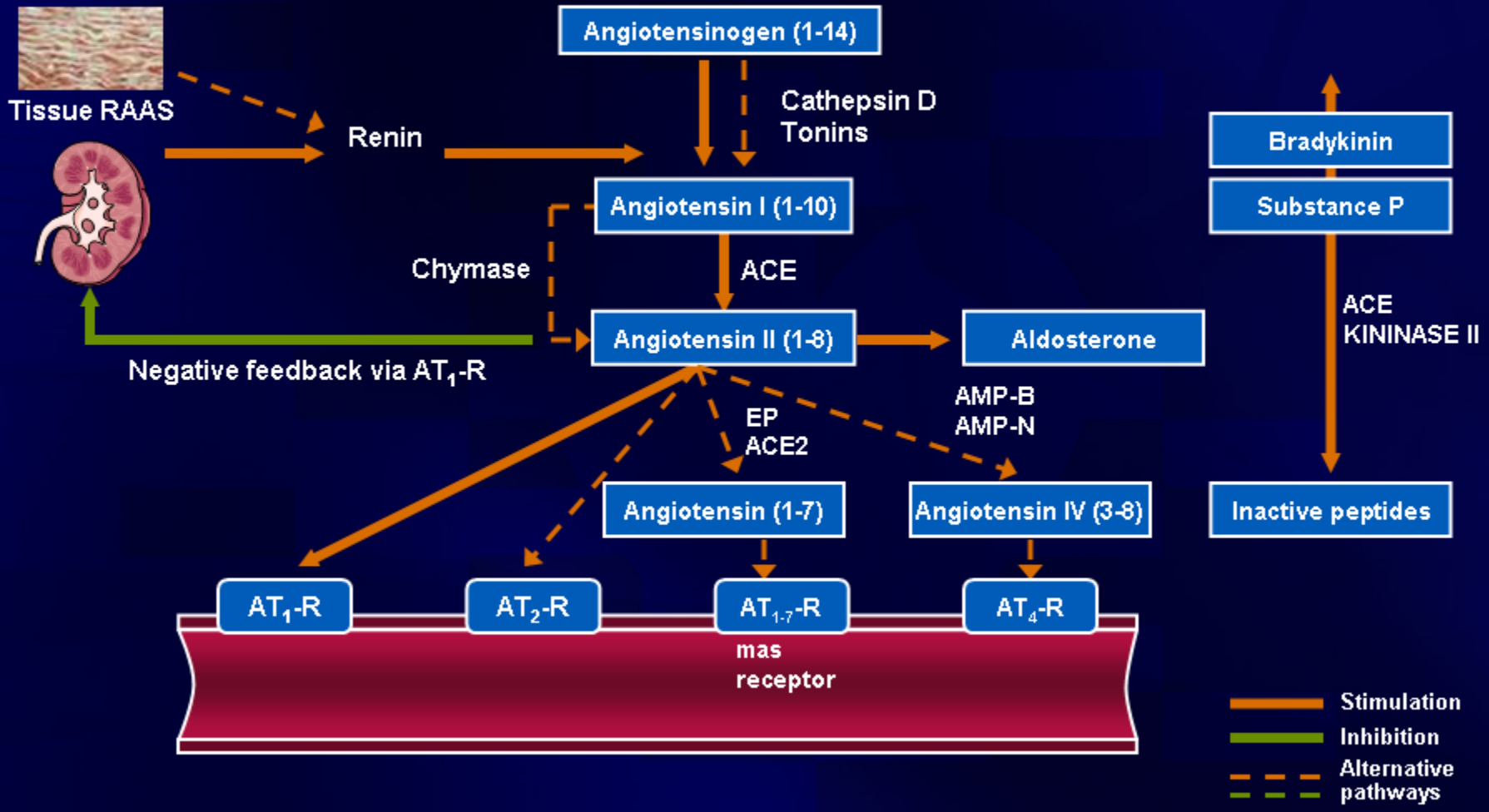




Achieving the target systolic pressure of 120 mm Hg reduces CV events and stroke, ≈33% ; Risk of death by ≈25%

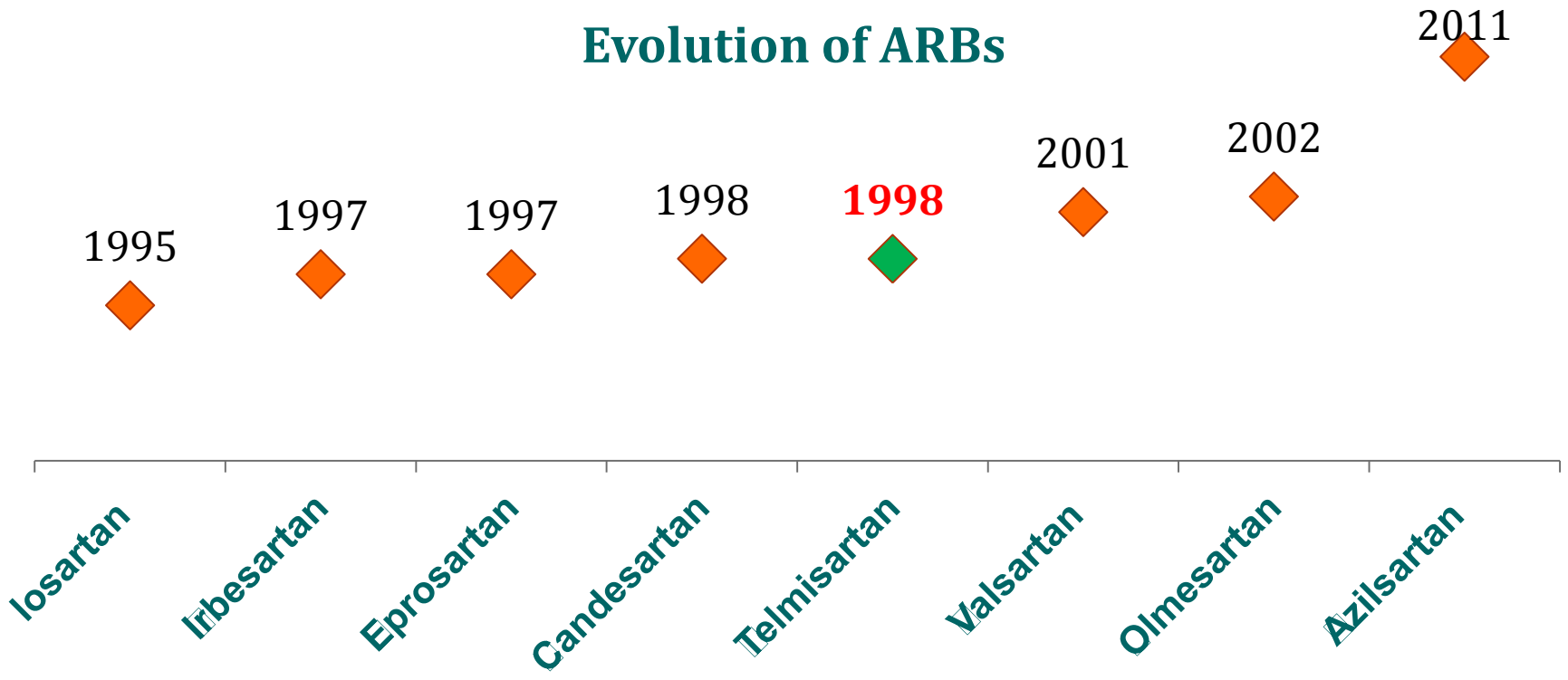
SPRINT Research Group *N Engl J Med.* 2015 Nov 26;373(22):2103-16

RAAS overview: Key targets



Adapted from Staessen JA et al. *Lancet*. 2006;368:1449-56.

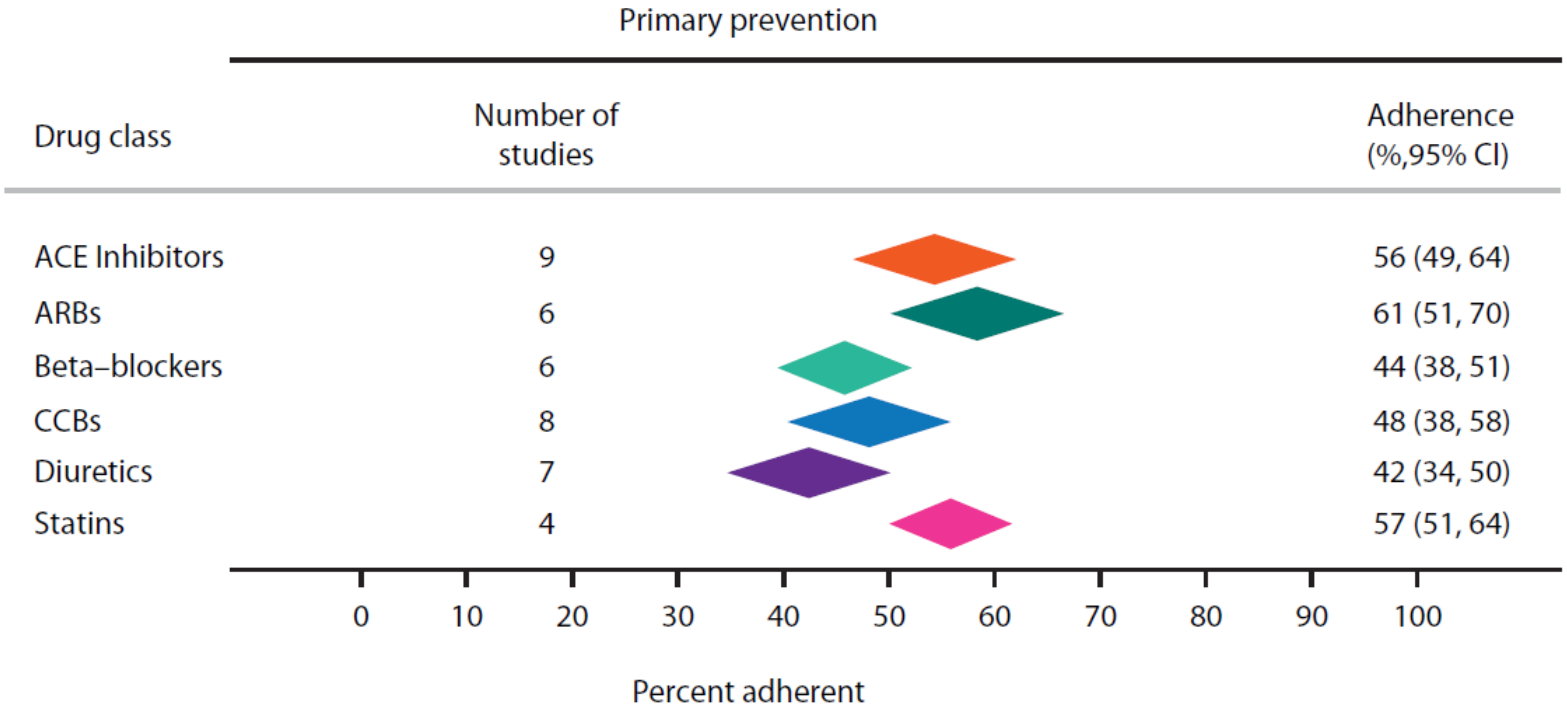
History of ARBs



Siragy HM . *Vasc Health Risk Manag*. 2011; 7: 297–313.

Role of ARBs in Hypertension Management

- Longer duration of action
- Have the lowest discontinuation rate
- Higher adherence in primary prevention of CV disease (*P = .02)*



ACE- angiotensin converting enzyme, ARB – angiotensin receptor blocker, CCB – calcium channel blocker

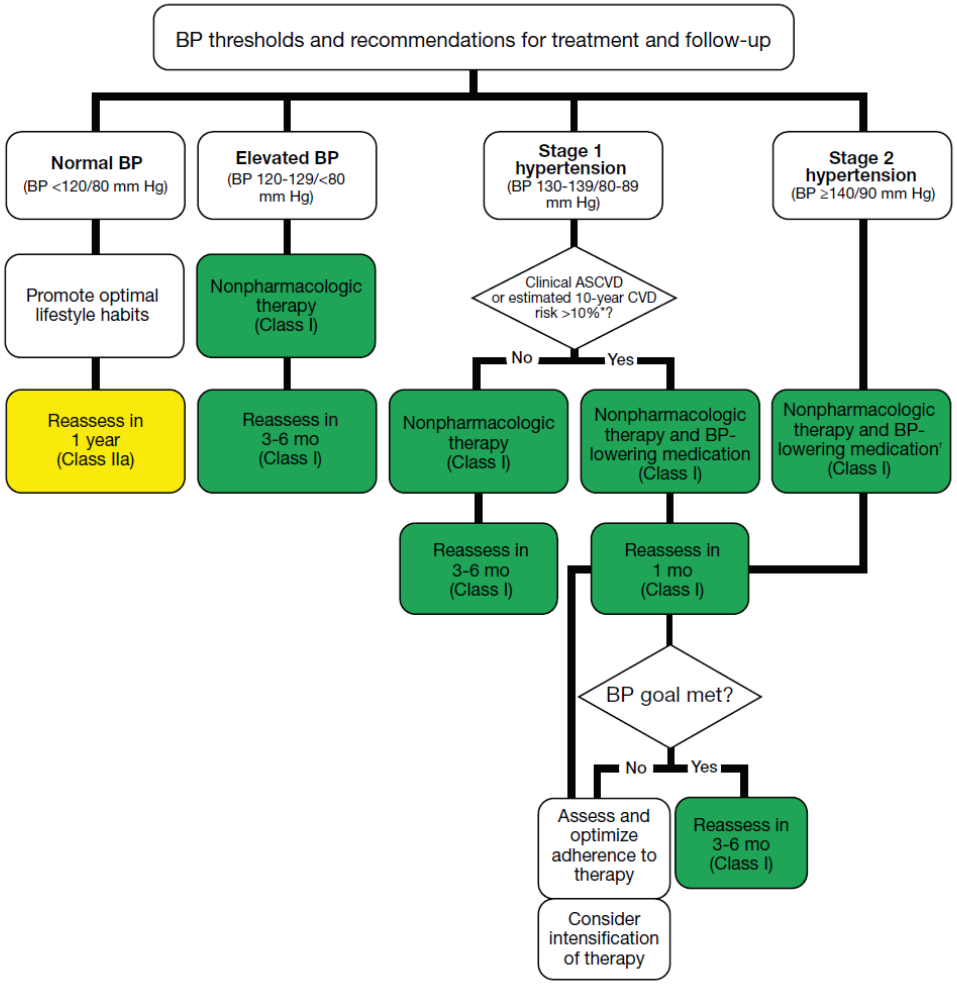
Mancia G *et al.* J Hypertens. 2011; 29(5):1012-18.

2017 ACC/ AHA Hypertension Guidelines

BP Category	Systolic BP		Diastolic BP	Treatment or Follow-up
Normal	<120 mm Hg	**and**	<80 mm Hg	Evaluate yearly; encourage healthy lifestyle changes to maintain normal BP
Elevated	120-129 mm Hg	**and**	<80 mm Hg	Recommend healthy lifestyle changes and reassess in 3-6 months
Hypertension: stage 1	130-139 mm Hg	**or**	80-89 mm Hg	Assess the 10-year risk for heart disease and stroke using the atherosclerotic cardiovascular disease (ASCVD) risk calculator • If risk is less than 10%, start with healthy lifestyle recommendations and reassess in 3-6 months • If risk is greater than 10% or the patient has known clinical cardiovascular disease (CVD), diabetes mellitus, or chronic kidney disease, recommend lifestyle changes and BP-lowering medication (1 medication); reassess in 1 month for effectiveness of medication therapy – If goal is met after 1 month, reassess in 3-6 months – If goal is not met after 1 month, consider different medication or titration – Continue monthly follow-up until control is achieved
Hypertension: stage 2	≥140 mm Hg	**or**	≥90 mm Hg	Recommend healthy lifestyle changes and BP-lowering medication (2 medications of different classes); reassess in 1 month for effectiveness • If goal is met after 1 month, reassess in 3-6 months • If goal is not met after 1 month, consider different medications or titration • Continue monthly follow-up until control is achieved

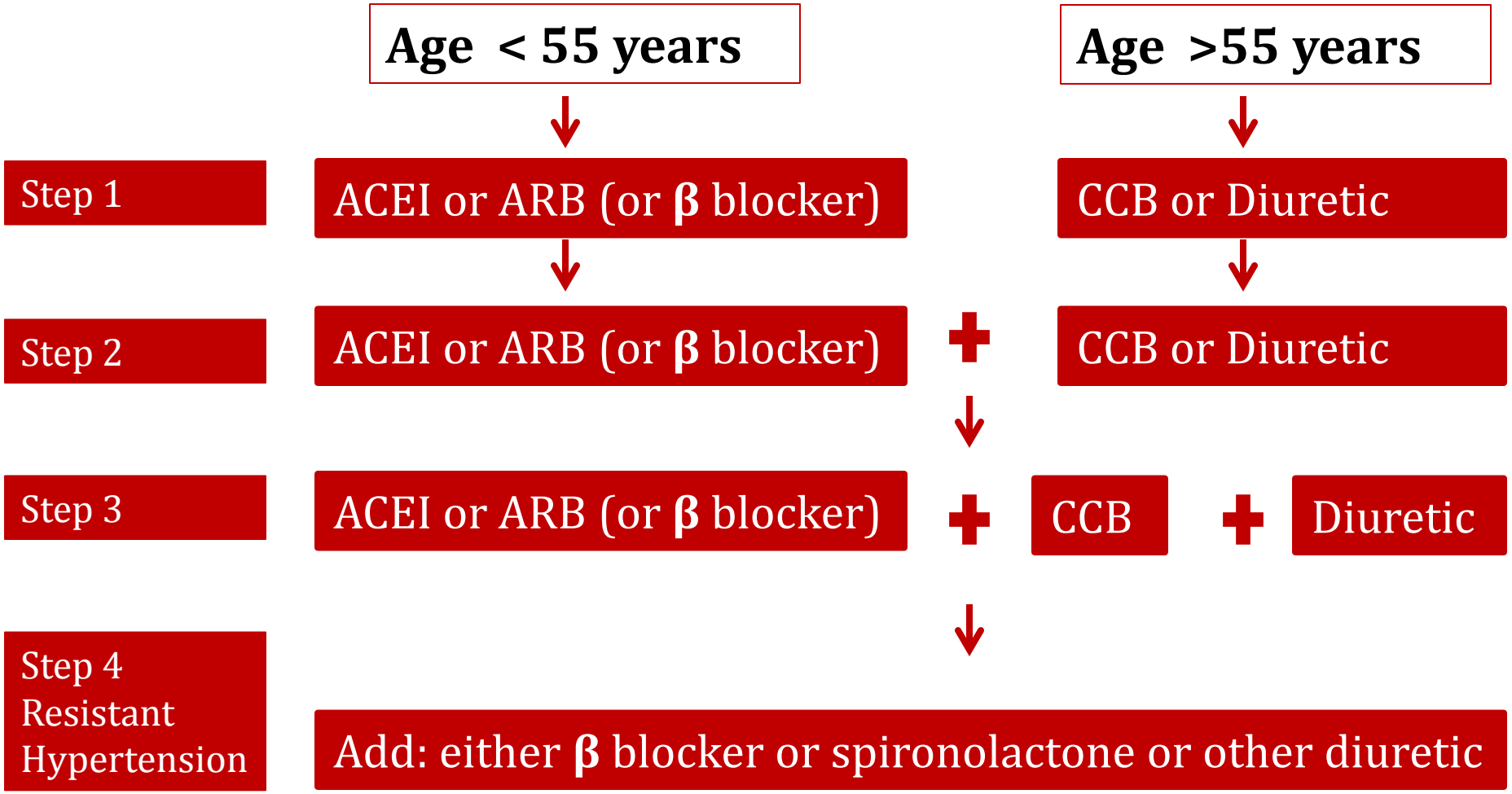
ACC/AHA Clinical Practice GuidelinesWhelton PK et al. Hypertension. 2017 Nov 13. pii: HYP.0000000000000066

2017 ACC/ AHA Hypertension Guidelines BP thresholds and recommendations for treatment and follow-up.



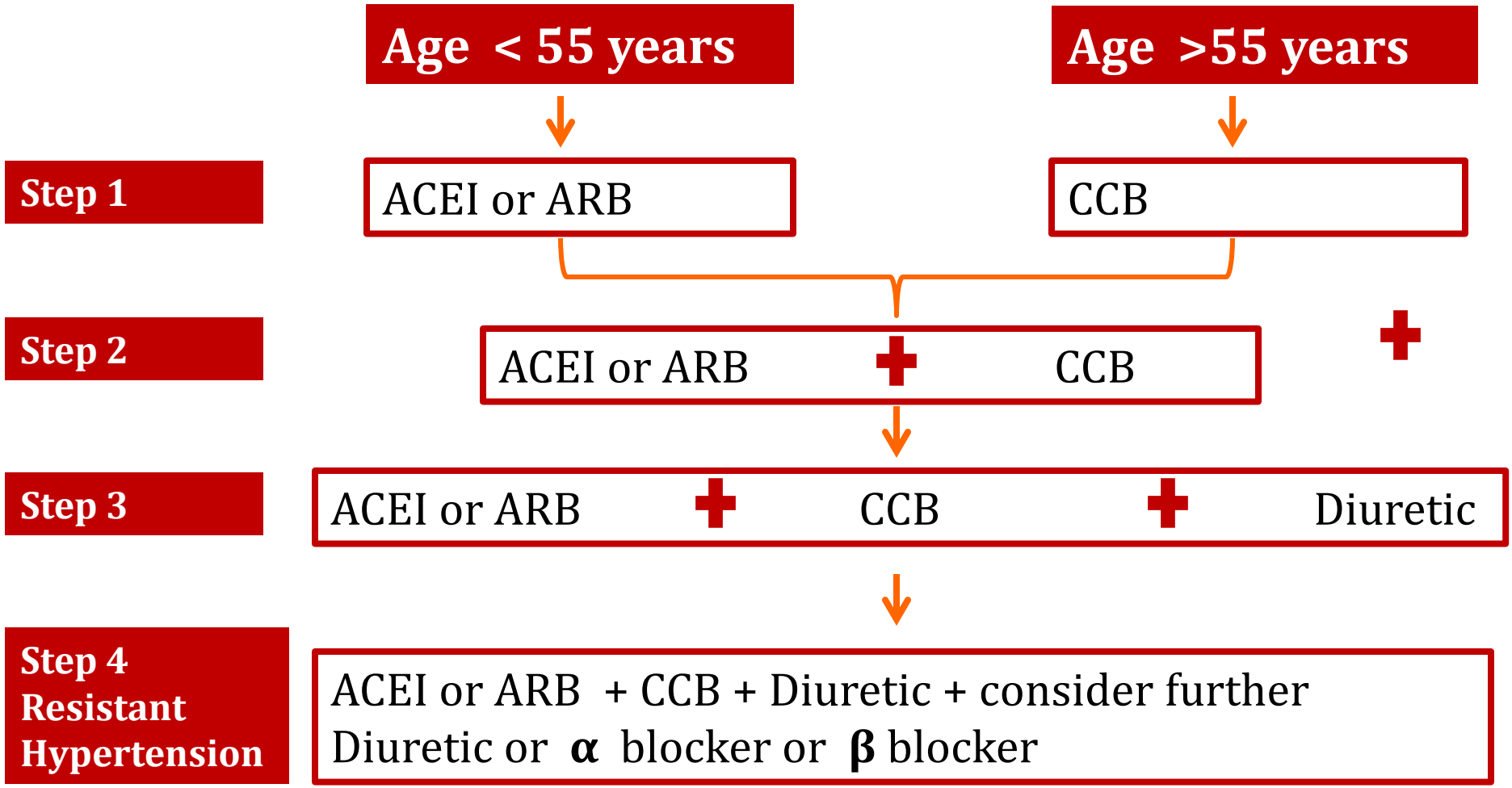
ACC/AHA Clinical Practice Guidelines . Whelton PK et al. Hypertension. 2017 Nov 13. pii: HYP.0000000000000066

Association of Physicians of India (API) Guidelines



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

NICE Clinical Guideline 2011



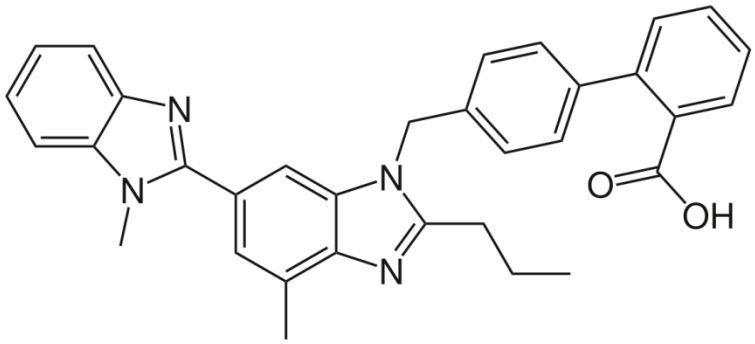
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CCB- calcium channel blockers

Telmisartan

A Unique ARB

Telmisartan

- Telmisartan has a unique binding mode to the AT1 receptor due to its distal benzimidazole portion.



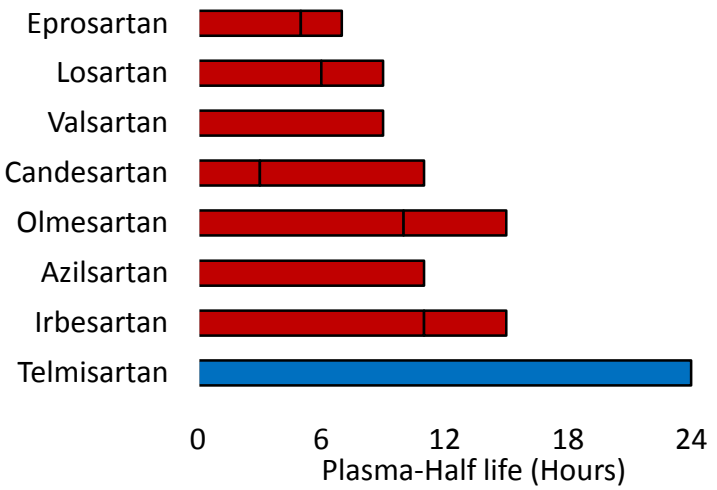
- This unique portion provides:
  - high molecular lipophilicity,
  - greater volume distribution
  - stronger binding affinity of telmisartan to AT1 receptor.

- Telmisartan was found to firmly bind to the AT1 receptor through the unique "delta lock" structure.

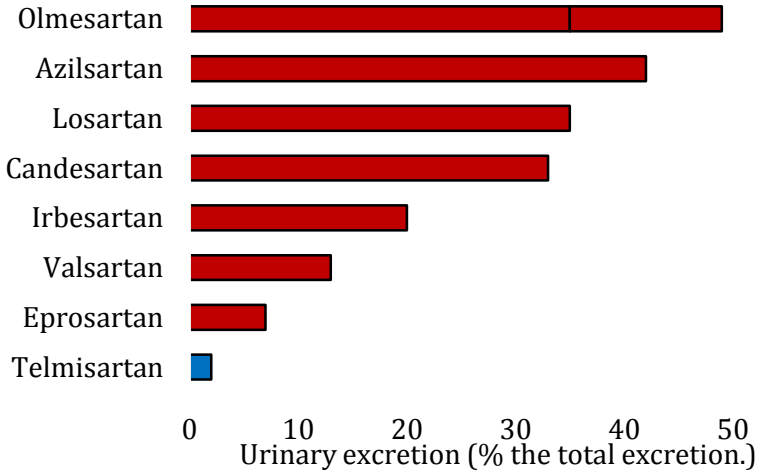
Ohno K et al. Biochem Biophys Res Commun. 2011 Jan 7;404(1):434-7

Telmisartan: Unique Properties

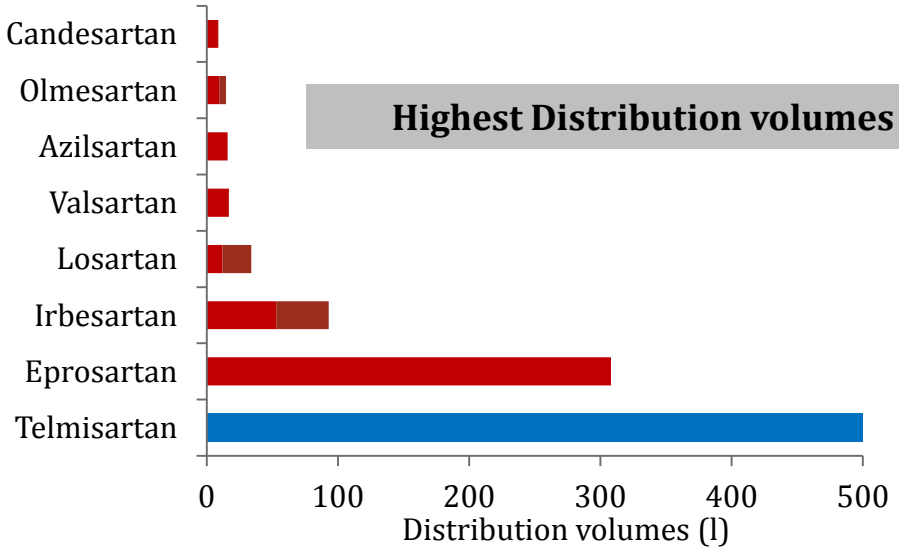
Longer Plasma Half life



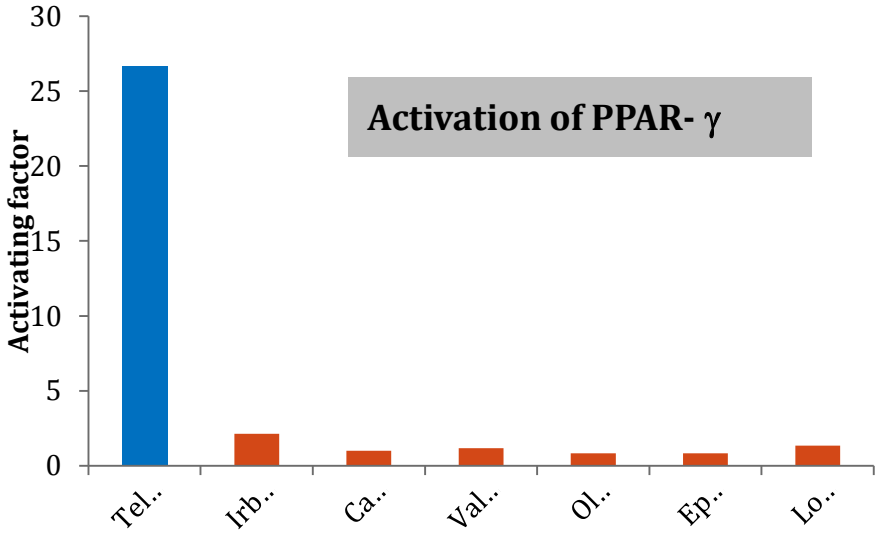
Lowest urinary excretion



Highest Distribution volumes



Activation of PPAR- γ



Sabbah ZA et al. J Assoc Physicians India. 2013 Jul;61(7):464-70
Kurtz *et al. Vasc Health Risk Manag.* 2012; 8: 133–143

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

N Engl J Med 2008; 358:1547-1559

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)

N Engl J Med 2008; 358:1547-1559

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

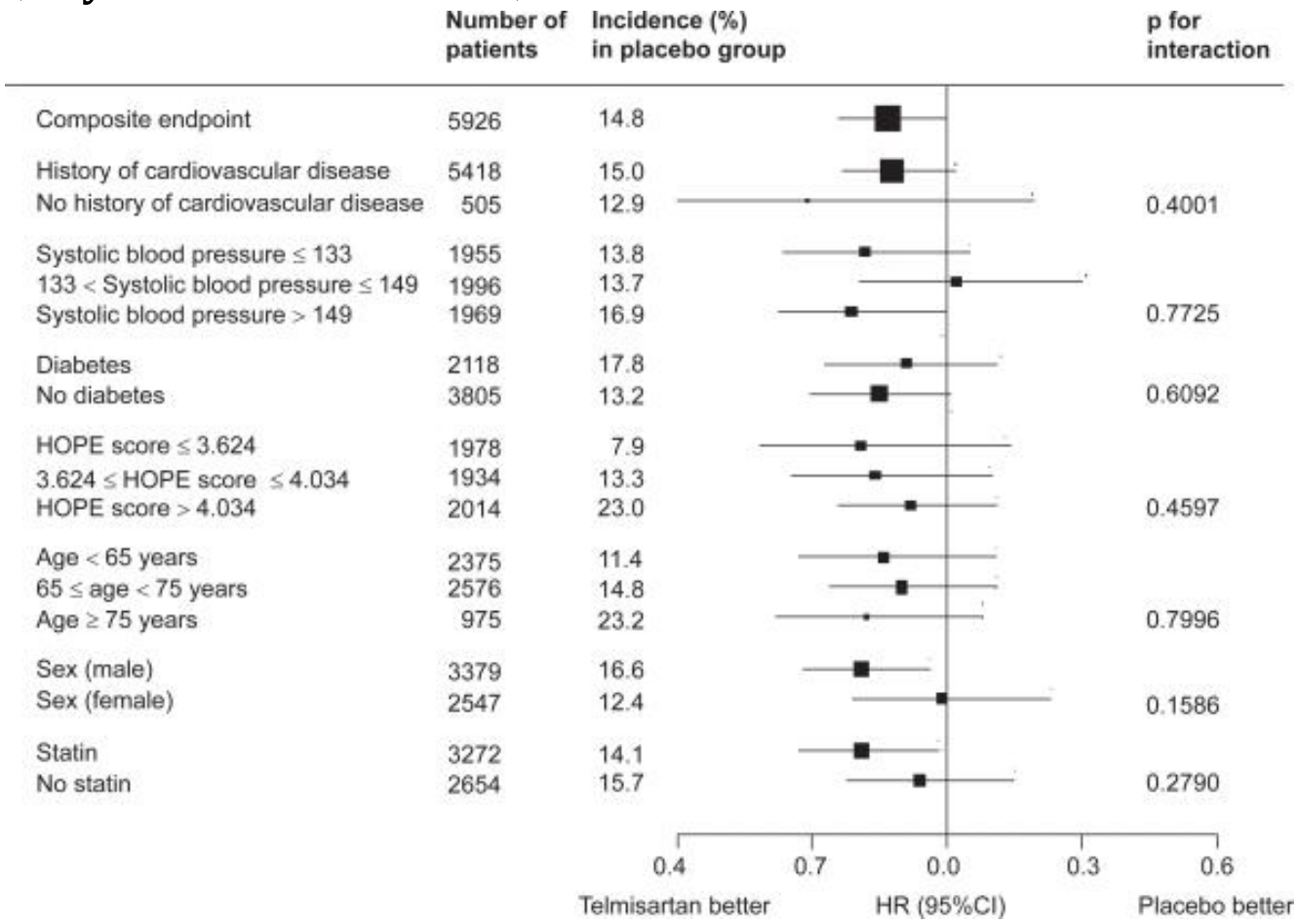
- 5926 patients were randomised to receive telmisartan 80 mg/day (n=2954) or placebo (n=2972)

- The primary outcome was the composite of cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure.

Lancet. 2008 Sep 27;372(9644):1174-83

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, myocardial infarction, or stroke.



Lancet. 2008 Sep 27;372(9644):1174-83

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.

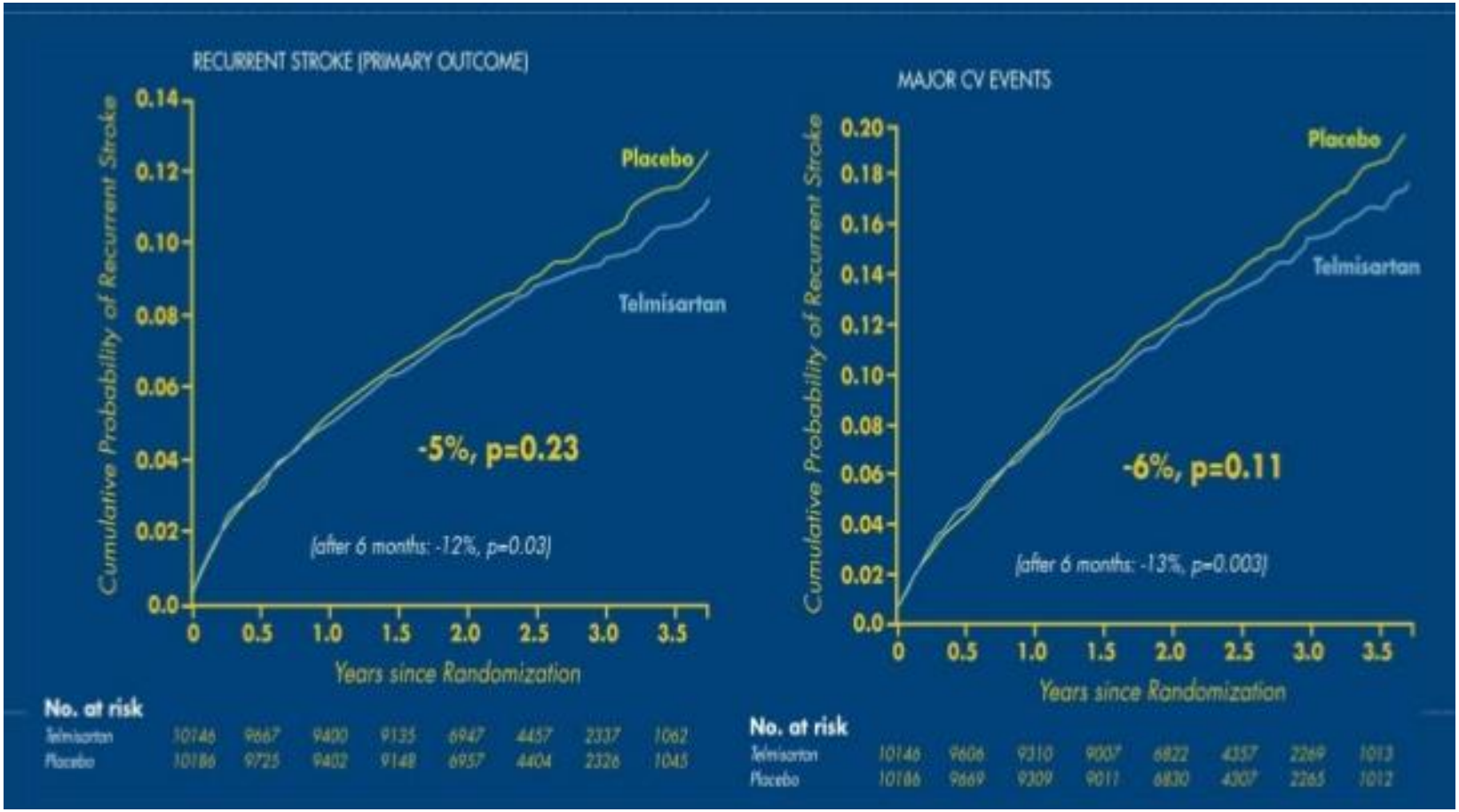
- Secondary outcomes were major cardiovascular events (death from cardiovascular causes, recurrent stroke, myocardial infarction, or new or worsening heart failure) and new-onset diabetes

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

Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) Study Group

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.

Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) Study Group

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.

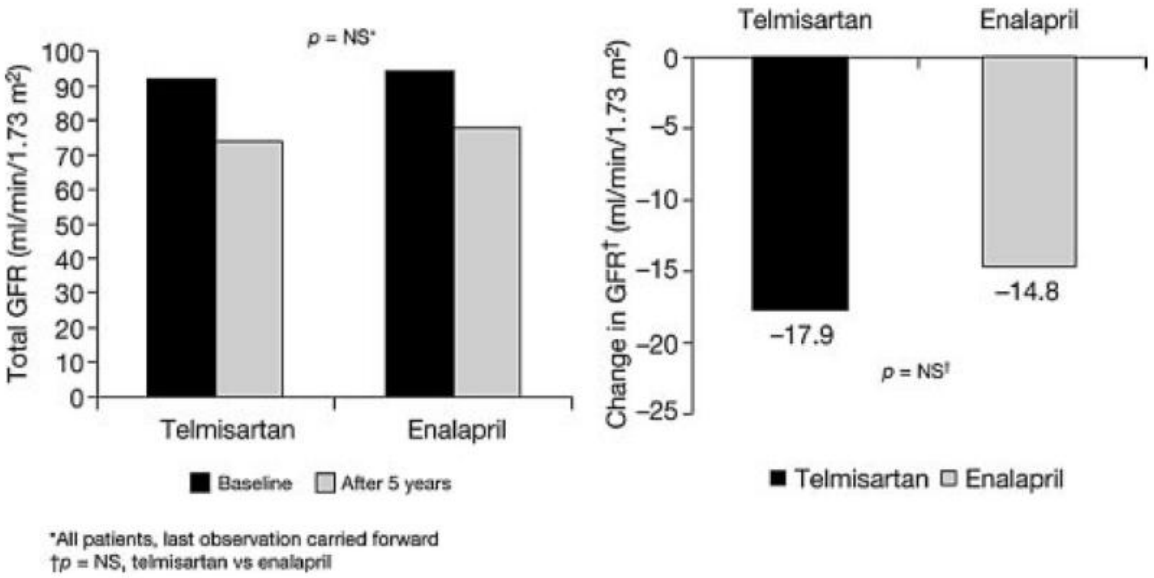


Figure 1. Comparison of effect of telmisartan and enalapril on GFR after 5 yr of treatment (15).

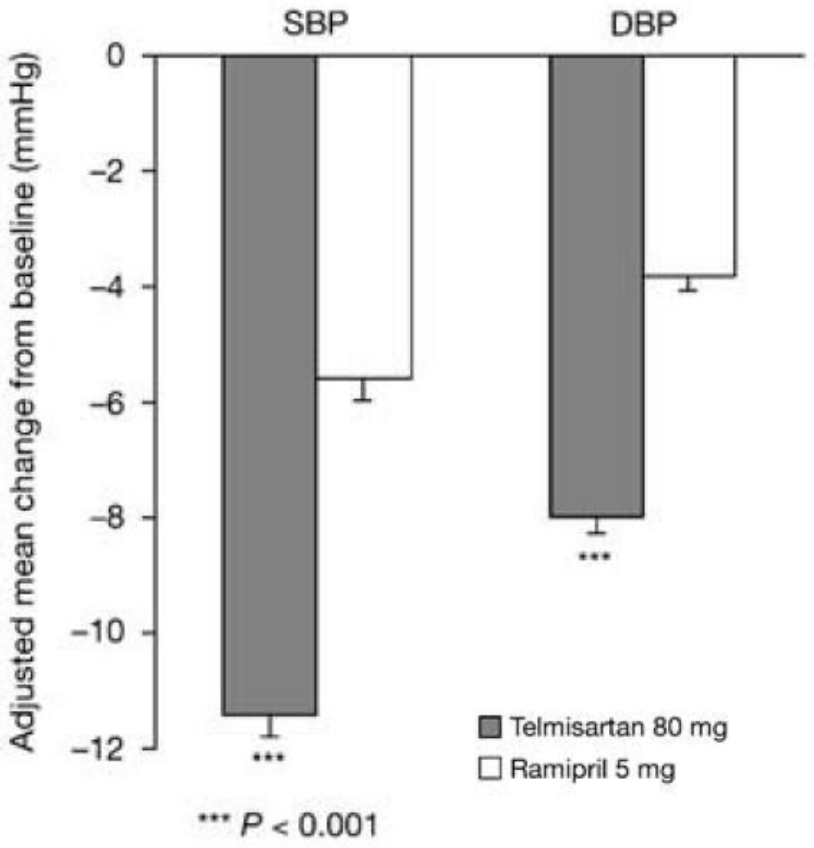
Telmisartan conferred comparable renoprotection to enalapril and was associated with a low incidence of mortality.

Barnett AH et al. Acta Diabetol. 2005 Apr;42 Suppl 1:S42-9.

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.

J Hum Hyperten 2009; 23: 10–619

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.

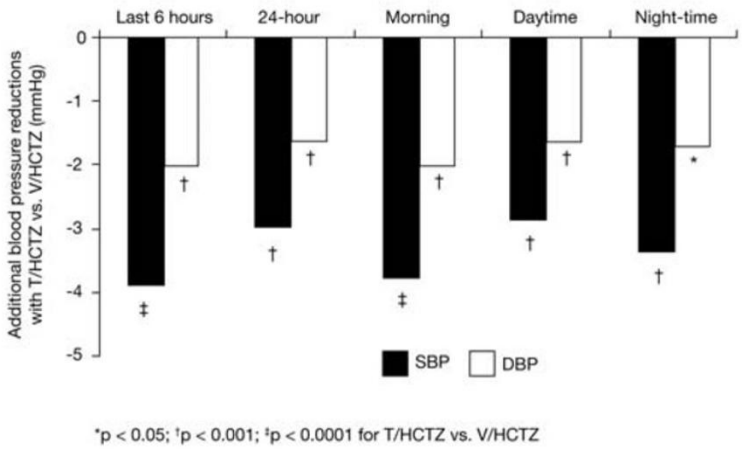


Figure 2
Additional reductions with T/HCTZ compared with V/HCTZ in mean ambulatory SBP and DBP during various periods of the 24-hour dosing interval after treatment for 10 weeks. Black: SBP; white: DBP.

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

Sharma AM et al. Cardiovasc Diabetol. 2007 Oct 2;6:28.

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.

Weber M et al . J Hypertens Suppl. 2003 Jul;21(6):S37-46.

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

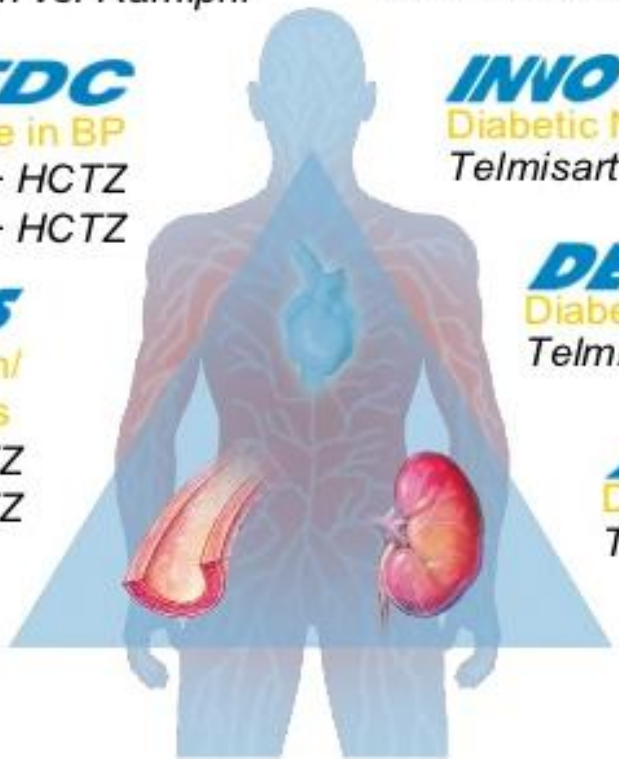
Telmisartan vs. Placebo

ATHOS
Systolic Hypertension/
elderly hypetensives

Telmisartan + HCTZ
vs. Amlodipine + HCTZ

DETAIL
Diabetic Nephropathy

Telmisartan vs. Enalapril



AMADEO
Diabetic Nephropathy

Telmisartan vs. Losartan

SMOOTH
Diabetes + Overweight

Telmisartan + HCTZ
vs. Valsartan + HCTZ

VIVALDI
Diabetic Nephropathy

Telmisartan vs. Valsartan

Weber M et al . J Hypertens Suppl. 2003 Jul;21(6):S37-46.

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.

Takagi H et al. J Am Soc Hypertens. 2014 Aug;8(8):578-92

Effect of Telmisartan on the Regression of the Left Ventricular Hypertrophy

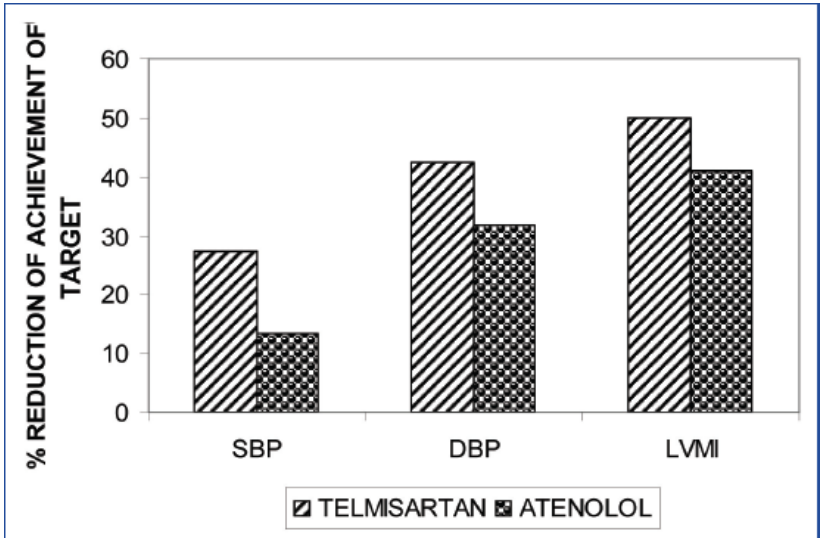
- Telmisartan is superior to Atenolol in achieving a regression of LVH, which is a better indicator of the cardiovascular morbidity and mortality.

Drugs	LVM ± SE		Paired t test	
	BT	AT	't'	'p'
Telmisartan (n=26)	328.89±13.13	237.16±7.67	11.28	<0.001
Atenolol (n=22)	247.41±4.49	223.68±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

Misra KH et al. J Clin Diagn Res. 2013 Jul; 7(7): 1352–1355.

Telmisartan vs Olmesartan

- Goal: Comparison of the Effects of Telmisartan and Olmesartan on Home Blood Pressure, Glucose, and Lipid Profiles in Patients with Hypertension, Chronic Heart Failure, and Metabolic Syndrome

- The subjects underwent once-daily 40 mg telmisartan for at least 3 months before switching to once-daily 20 mg olmesartan for the next 3 months (post 1).

- They were then treated with 3 months of once-daily 40 mg telmisartan (post 2)

Sasaki T et al. Hypertens Res 2008; 31: 921–929

Telmisartan vs Olmesartan

- Systolic and diastolic EMBP, plasma BNP, serum total cholesterol, LDL-C, and triglyceride levels were increased at post 1. before returning to their baseline values at post 2.

	Pre (T)	Post 1 (O)	Post 2 (T)
Home blood pressure			
SBP in EM (mmHg)	129.0±4.1	130.9±5.3***	129.0±4.7##
DBP in EM (mmHg)	75.9±4.5	77.5±4.5*	76.2±3.9#
SBP in LE (mmHg)	127.5±4.1	127.2±5.2	127.2±5.2
DBP in LE (mmHg)	71.1±6.2	70.0±6.1	70.6±5.4
Clinic blood pressure			
SBP (mmHg)	129.9±5.9	129.3±5.0	129.5±5.2
DBP (mmHg)	73.2±6.2	72.1±5.9	72.7±5.3
Heart rate			
EM (/min)	71.0±7.1	70.8±6.0	71.3±6.4
LE (/min)	67.9±4.9	67.0±4.9	68.1±4.9
Outpatients room (/min)	70.7±5.2	69.9±5.0	70.6±5.7
Body weight (kg)	72.8±8.7	72.9±8.2	72.6±8.2
BNP (pg/mL)	191.0±67.9	197.3±75.9*	188.6±68.0###
Glucose metabolism			
FBS (mg/dL)	111.0±13.2	111.4±14.3	110.7±13.8
HbA1c (%)	6.0±0.7	6.1±0.8*	6.0±0.7#
Lipid metabolism			
TC (mg/dL)	217.7±17.9	220.1±19.3*	218.4±17.9#
LDL cholesterol (mg/dL)	127.8±19.2	130.4±18.3*	127.7±19.0#
HDL cholesterol (mg/dL)	39.9±5.8	39.6±5.4	39.6±4.9
Triglyceride (mg/dL)	218.0±74.3	226.8±82.5***	218.6±75.4###

T, once-daily telmisartan 40 mg; O, once-daily olmesartan 20 mg; SBP, systolic blood pressure; DBP, diastolic blood pressure; EM, the early morning; LE, the late evening; BNP, B-type natriuretic peptide; FBS, fasting blood sugar; TC, total cholesterol, LDL, low-density lipoprotein; HDL, high-density lipoprotein. *$p<0.05$, ***$p<0.005$ *vs.* pre; #$p<0.05$, ##$p<0.01$, ###$p<0.005$ *vs.* post 1.

Telmisartan is effective than olmesartan for controlling EMBP as well as for improving glucose and lipid profiles

Sasaki T et al. Hypertens Res 2008; 31: 921–929

Telmisartan vs Azilsartan

Parameters	Telmisartan	Azilsartan	Benefit
Prodrug	No	Yes	•Azilsartan medoxomil is a prodrug that is hydrolyzed to its active moiety azilsartan, in gastrointestinal tract.
Delta lock Structure	Yes	No	•Unique "delta lock" structure of telmisartan is involved in its strongest binding affinity to angiotensin II type 1 receptor
Affinity to AT1 Receptors	greater affinity for AT1 versus AT2 receptors	greater affinity for AT1 versus AT2 receptors	•Both Telmisartan and Azilsartan has highly selective for AT1 receptors and has > 10,000-fold greater affinity for AT1 vs AT2 receptors
Peak Plasma Conc.	0.5-1 hour	1.5 to 3 hrs.	•Peak plasma conc. of Telmisartan achieved after oral administration is faster than Azilsartan leading to faster onset of action.
Half life	Approx. 24 hours	11 hrs	•Telmisartan has longer half life than Azilsartan and this ensures 24-BP control
Volume of distribution	500 litres	16 litres	•Telmisartan's larger distribution can be attributed to its high lipophilic nature. Better tissue penetration.

Sabbah ZA et al. J Assoc Physicians India. 2013 Jul;61(7):464-70
Kurtz *et al. Vasc Health Risk Manag.* 2012; 8: 133–143

Telmisartan vs Azilsartan

Parameters	Telmisartan	Azilsartan	Benefit
PPAR gamma agonist activity	Yes	No	Studies have established the PPAR Gamma activity with Telmisartan.
Amelioration of insulin resistance	Yes	No clinical studies	Telmisartan has partial PPARgamma agonist activity thus alters the insulin sensitivity and improves metabolic profile
Improvement of lipid profile	Yes	Clinical study data not available.	Telmisartan also has a favorable effect on lipid profile.
Favorable fat redistribution	Yes	Clinical study data not available.	Telmisartan, has partial agonistic properties for PPAR γ , which is a key regulator of adipocyte differentiation and function.
Impact on the inflammatory markers	Reduces inflammatory markers	Clinical study data not available.	Telmisartan modulates pleiotropically TNF-alpha induced VCAM-1 expression and oxidative damage in vascular endothelium.
Effects on vascular function	Beneficial effects	Clinical study data not available.	Telmisartan improves vascular function independently of metabolic and antihypertensive effects in hypertensive subjects with impaired glucose tolerance.

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Telmisartan: The cardio-metabolic sartan

- Firmer binding to the AT1-Receptor, Longer half life, Better distribution
- Activates PPAR-gamma
- An effective Anti hypertensive
- Improves function of renal endothelium
- Reduces renal vascular resistance
- Reduces albuminuria
- Slows down the GFR decline
- Decline in LVH

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Thank You