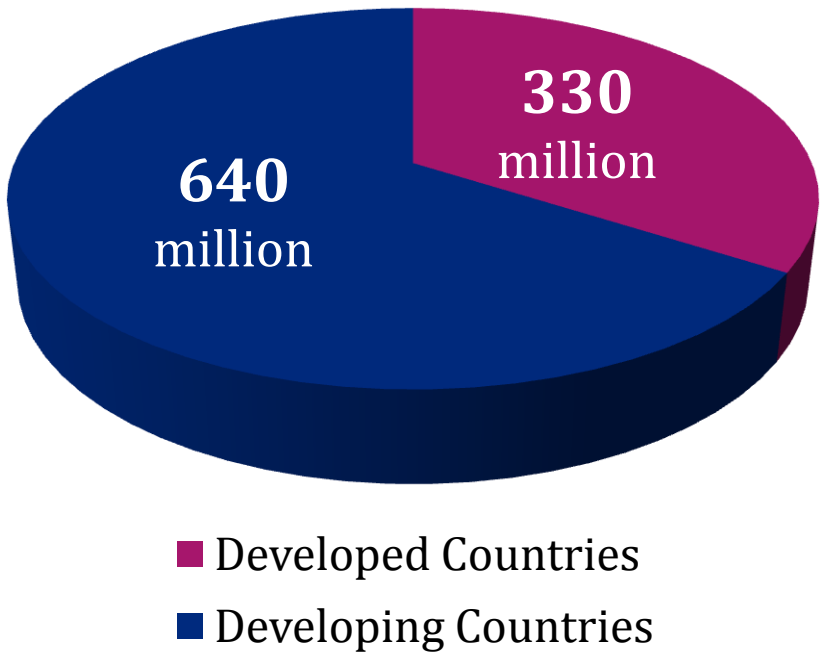
Combination Therapy In

Uncontrolled Hypertension

Hypertension Burden

- One of the major contributors of CV morbidity and mortality
- Undiagnosed, uncontrolled, and undertreated hypertension - responsible for increased chronic disease burden
- Worldwide Prevalence: 970 million
- Expected to affect 1.56 billion adults with hypertension by 2025

Worldwide Prevalence: 970 Million People

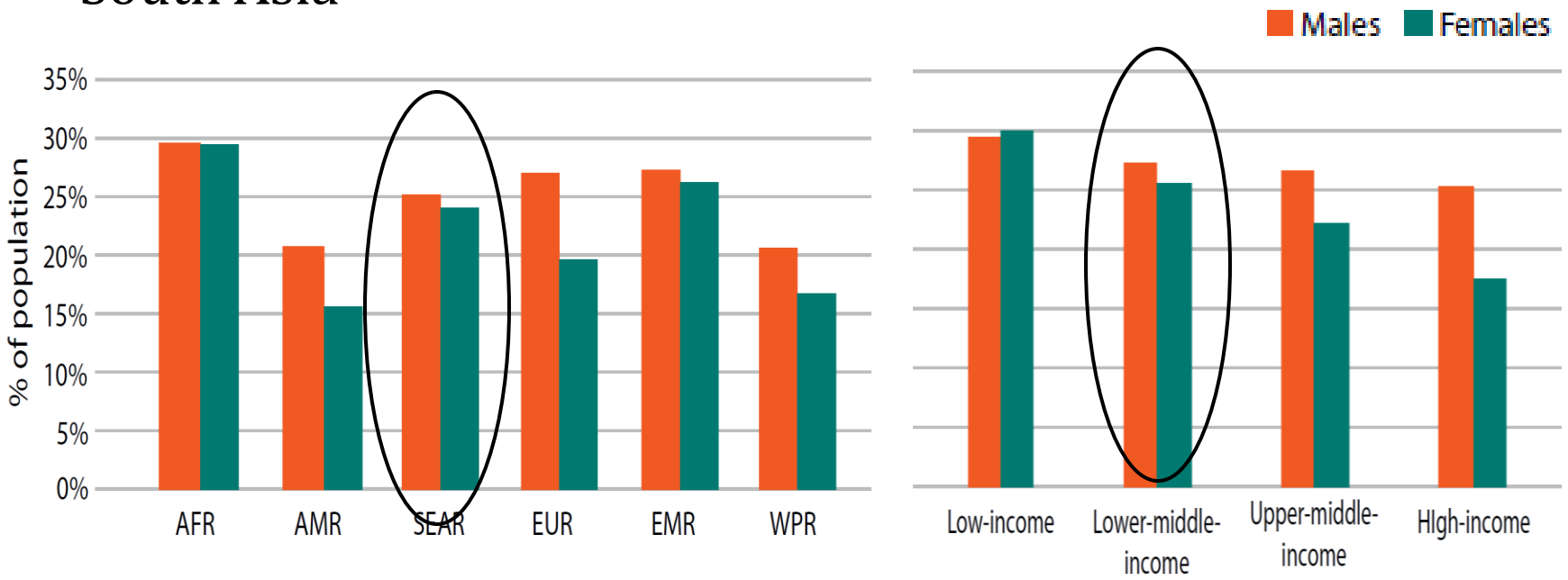


Gupta R et al. *J Hum Hypertens*. 2016 Feb;30(2):79-82
World-heart-federation.org. [Accessed 06 August 2016]

Hypertension: WHO Estimates

- The global prevalence is ≈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

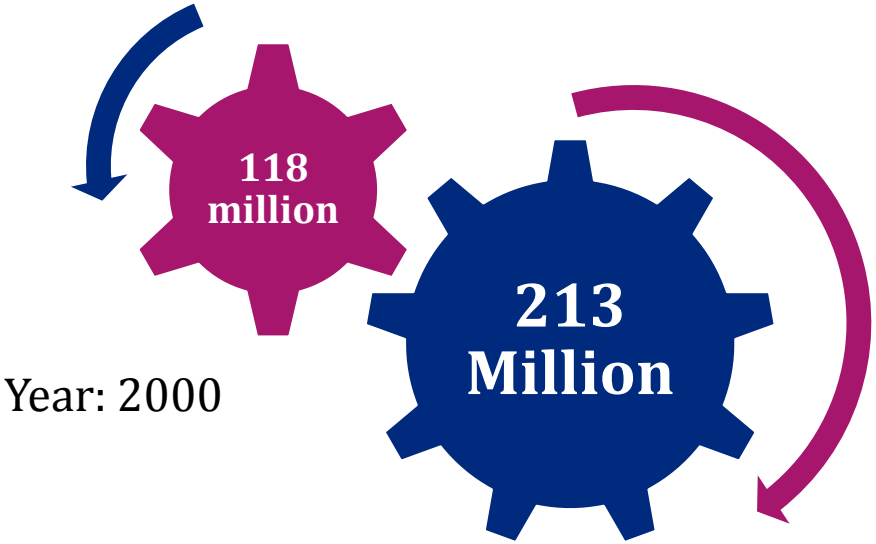
Global Status Report, 2014. Apps.WHO.int.

Hypertension In India

- Responsible for

57% • of all stroke deaths

24% • all deaths due to CHD

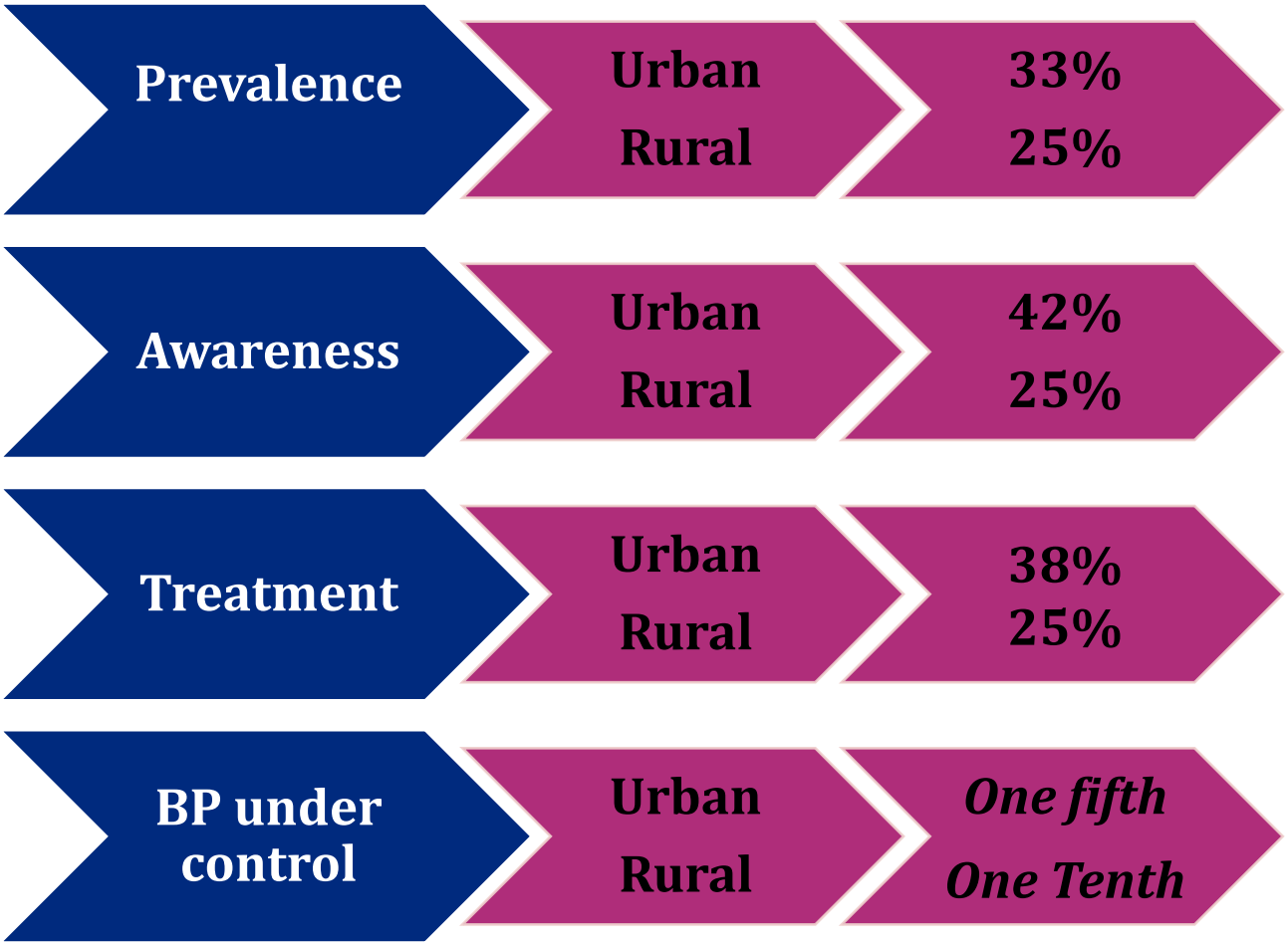


Incidence of hypertension is expected to almost double to 213 million by 2025 in India

Gupta R et al. J Hum Hypertens. 2016 Feb;30(2):79-82
Mohan et al:. *IJMR*. 2013;137:627-31

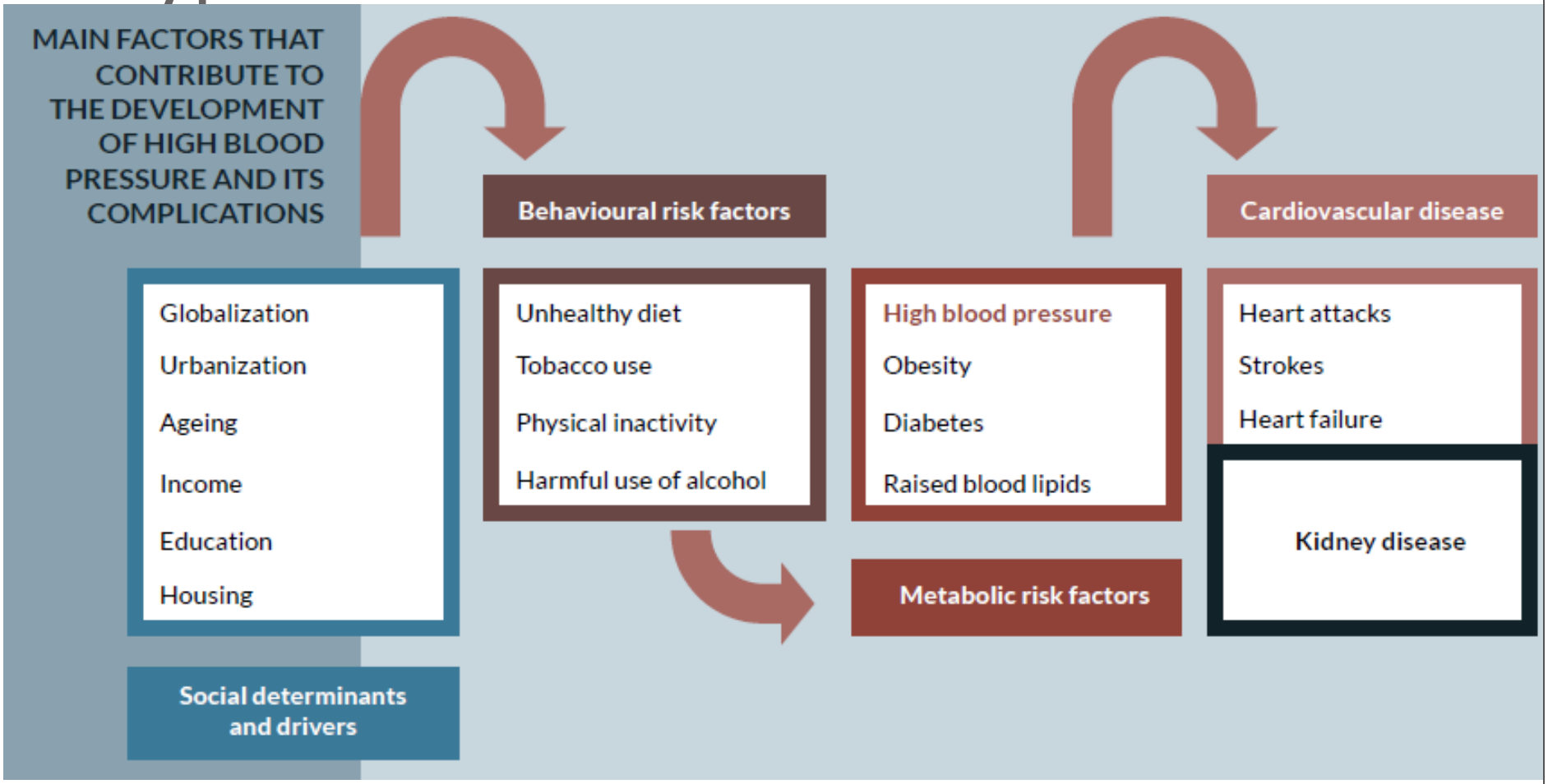
Hypertension In India

A meta-analysis by Anchala, *et al.* which included 142 articles from the year 1950 to 2013.



Anchala R *et al. J Hypertens.* 2014; 32(6):1170-77.

Hypertension Risk Factors

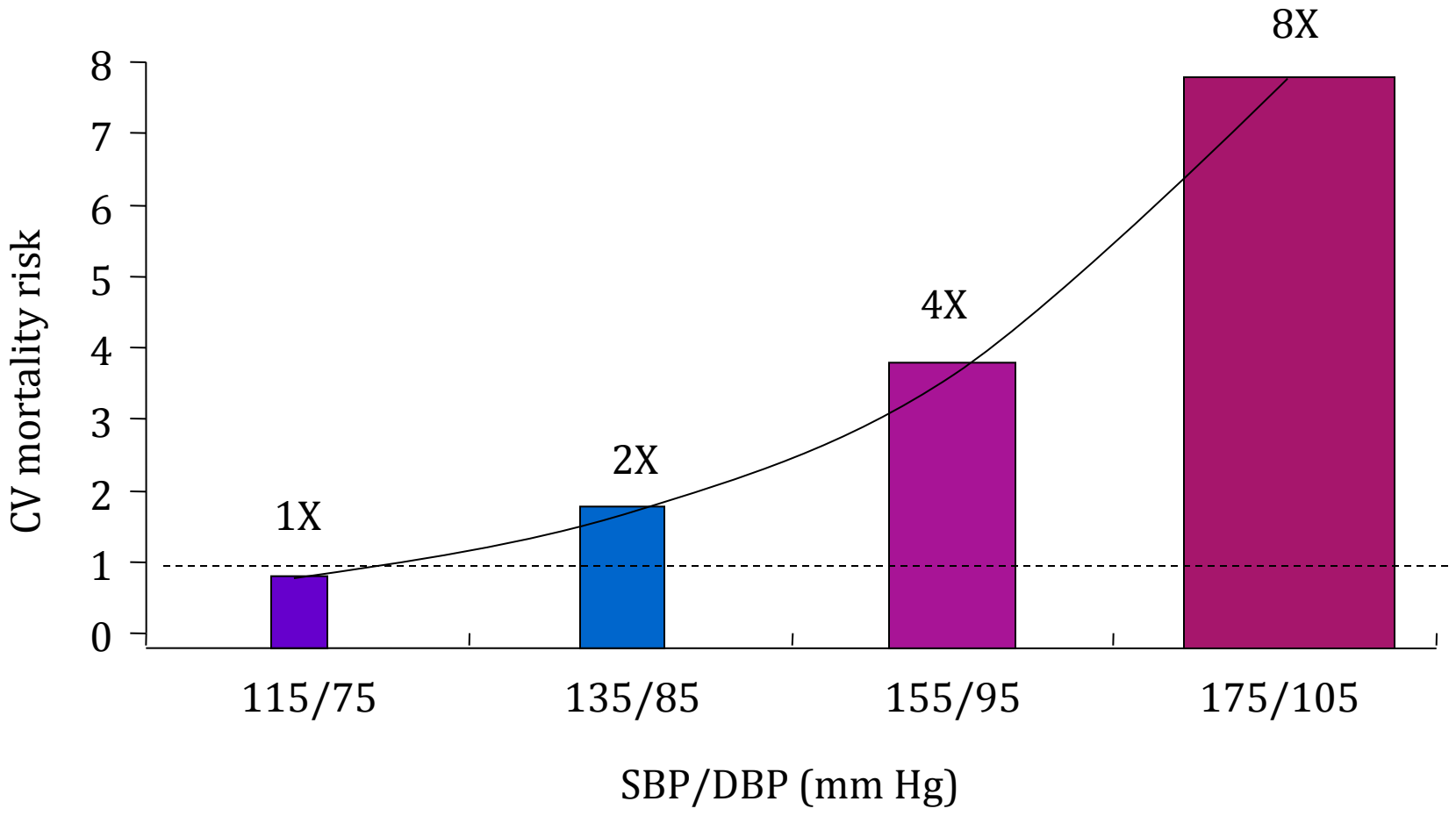


Hypertension is a polygenic disease involving a major contribution of various factors

Who.int. WHO/ A global brief on hypertension

Gupta R et al. *J Hum Hypertens*. 2016 Feb;30(2):79-82.

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



Assadi F *et al*. *Int J Prev Med.* 2014 Mar;5(Suppl 1):S4-9.

Current Challenges in Hypertension Control

- Over half of those who are hypertensive in India are not aware that they have hypertension.
- 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.

Gupta R et al. *J Hum Hypertens*. 2016 Feb;30(2):79-82
Redon J *et al.* J Hypertens. 2011; 29(8):1633-40.
Wang T. *et al.* Circulation. 2005;112(11):1651-62

Combination Therapy: *A Practical Necessity*

- Required in ~ 75% of hypertensives to achieve target BP
- Additive antihypertensive effects through complimentary pharmacologic mechanisms
- In some cases, improved side effect profile

Gradman AH, et al. J Clin Hypertens (Greenwich). 2011;13:146–154.

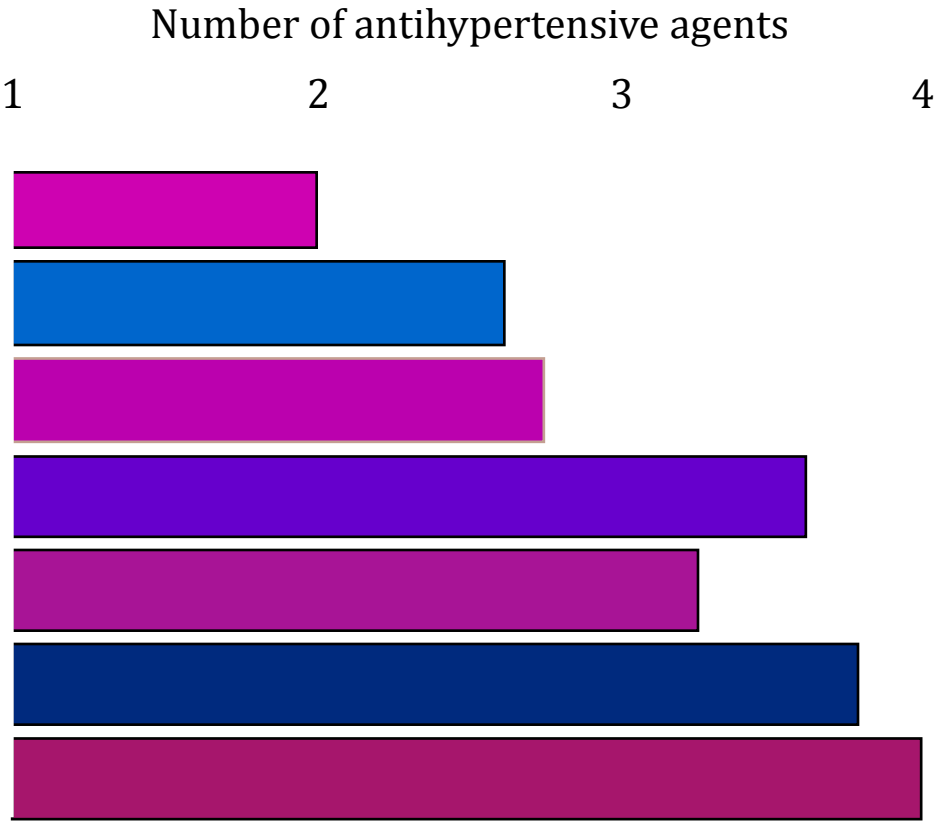
Combination Therapy

- 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

Ram CVS et al. Indian J of Clin Practice.2014 Nov;25(6)

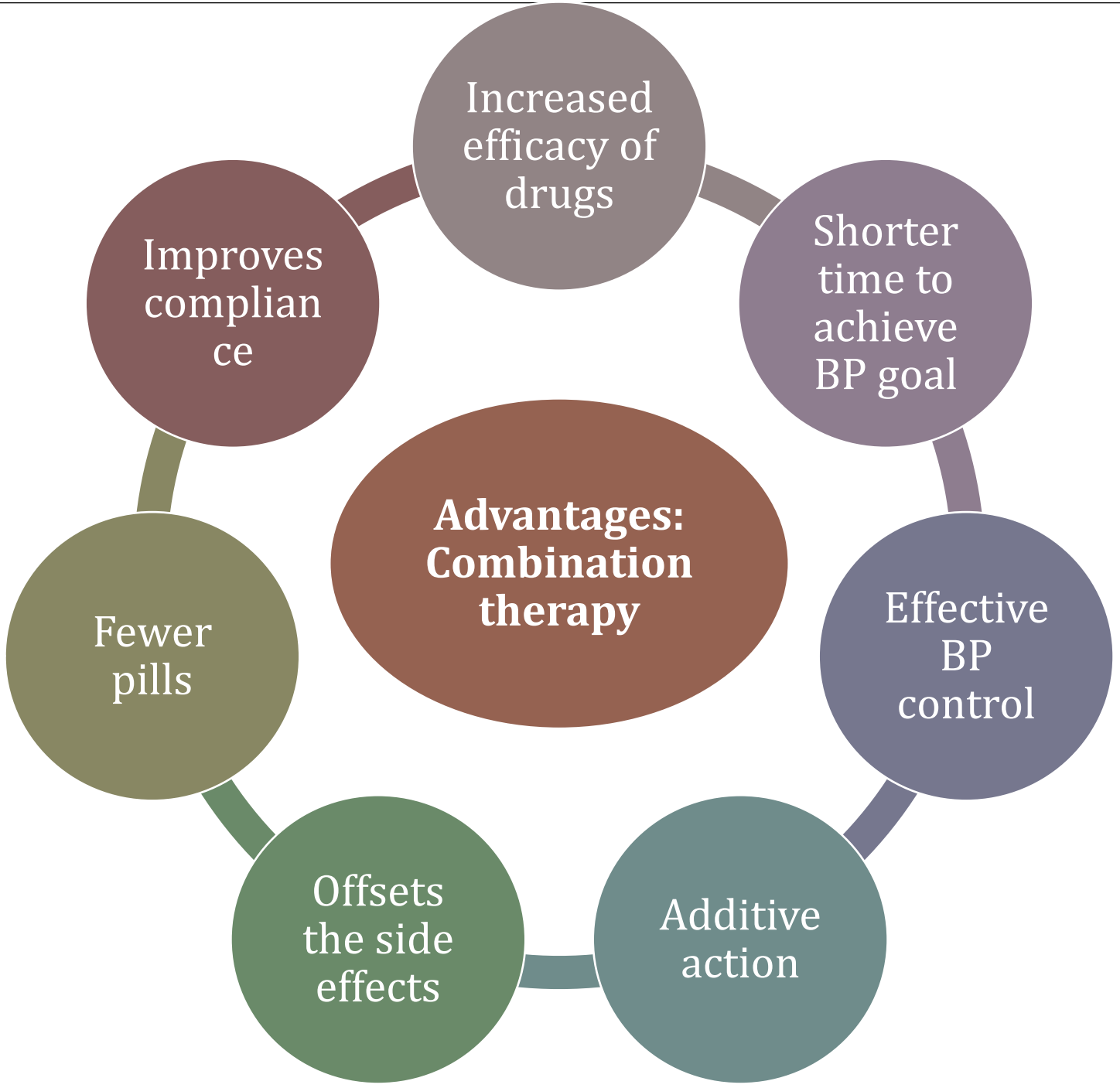
Multiple Antihypertensive Agents Are Needed to Achieve Target BP

Trial	Target BP (mm Hg)
ALLHAT	SBP <140/DBP <90
UKPDS	DBP <85
ABCD	DBP <75
MDRD	MAP <92
HOT	DBP <80
AASK	MAP <92
IDNT	SBP <135/DBP <85



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

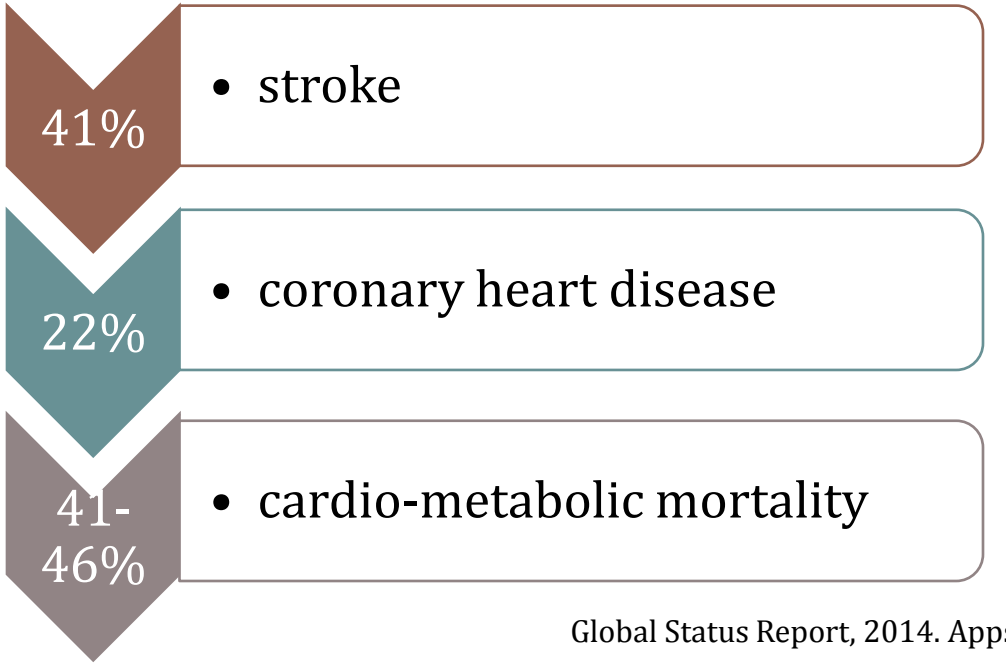
Bakris GL et al. *Am J Kidney Dis.* 2000;36:646-661.
Lewis EJ et al. *N Engl J Med.* 2001;345:851-860.
Cushman WC et al. *J Clin Hypertens*. 2002;4:393-405.


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

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.

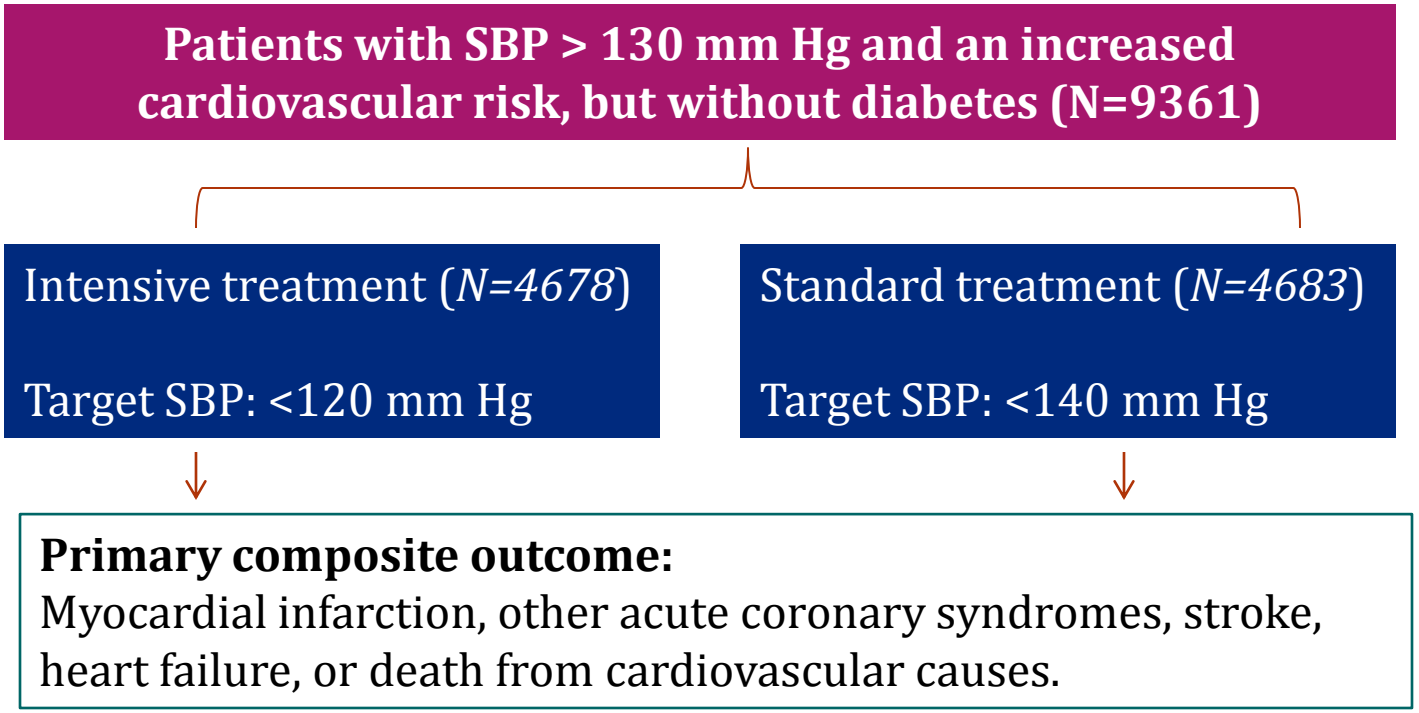
- A 10 mmHg reduction in BP reduces the risk:



Global Status Report, 2014. Apps.who.int. [Internet]. 2015

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

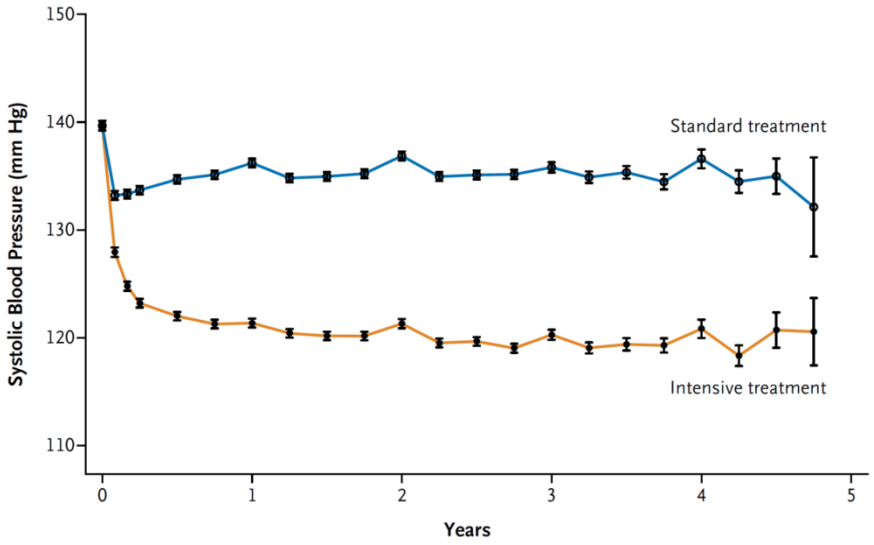
A randomized, controlled, open-label Systolic Blood Pressure Intervention Trial (SPRINT Trial) conducted at 102 clinical sites

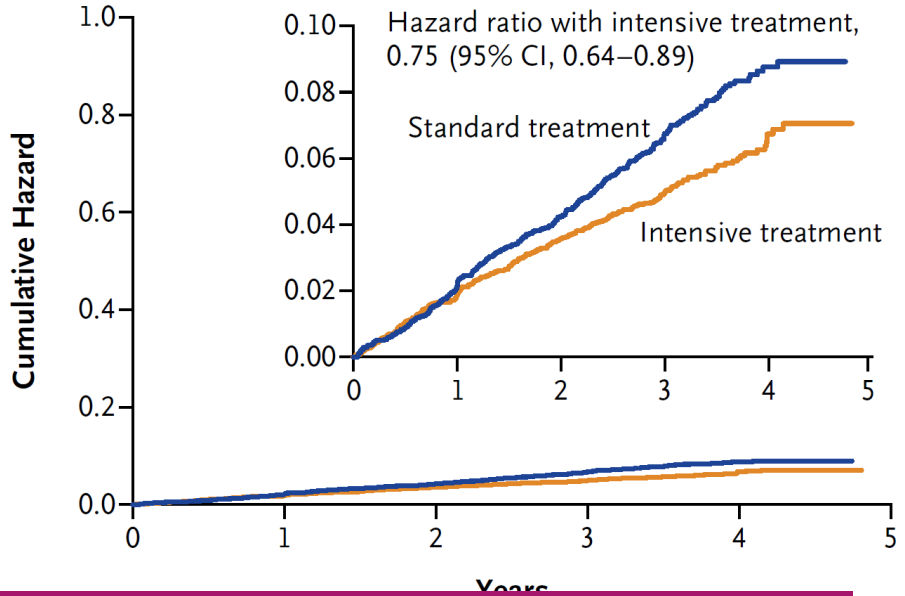


SPRINT Research Group *N Engl J Med.* 2015 Nov 26;373(22):2103-16

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

Triple Combination of

Telmisartan + Cilnidipine + Metoprolol for patients with Uncontrolled Hypertension

Telmisartan: the uniqueness

- Firmer binding to the AT1-Receptor
- Longer half life
- Better distribution
- Free from drug interactions
- Activates PPAR-gamma
- Low renal excretion

Beevers et al. *BMJ* 2001;322:912–916

Telmisartan: Landmark Studies

Study (year) [reference]	Number of patients	Patient characteristics	Primary outcome	Secondary outcome	Mean follow-up (months)
ONTARGET (2008) [89]	Ramipril 8576 Telmisartan 8542 Combination 8502 Total 25620	High-risk patients with CVD or diabetes with end-organ damage, but without HF	HOPE primary outcome, hospitalization for HF	HOPE primary outcome	56
TRANSCEND (2008) [93]	Telmisartan 2954 Placebo 2972 Total 5926	High-risk patients with CVD or diabetes with end-organ damage, but no HF Confirmed intolerance to ACEIs	ONTARGET primary outcome	HOPE primary outcome	56
PROFESS (2008) [95]	Telmisartan 10146 Placebo 10186 Total 20332	Patients with an ischemic stroke within 120 days before the randomization	Recurrent stroke	ONTARGET primary outcome, new-onset diabetes	30

ACEI: angiotensin-converting enzyme inhibitor; CVD: cardiovascular disease; HF: heart failure; HOPE: Heart Outcomes Prevention Evaluation; MI: myocardial infarction; ONTARGET: Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; PROFESS: Prevention Regimen for Effectively Avoiding Second Strokes; TRANSCEND: Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with CVD.

Image courtesy of International Journal of Clinical Reviews
http://www.remedicajournals.com/International-Journal-of-Clinical-Reviews/BrowseIssues/December-2011/Article-Telmisartan-for-the-prevention-of-ACS-in-ACE

Comparative Cardio-Metabolic Studies with Telmisartan

Trial	Patients	N	Duration (weeks)	Comparator Agent(s)	BP differential	Improved Insulin Sensitivity	Improved Lipid Profile	Anti-oxidant/ Inflammatory Action
Derosa 2004a	HT, T2DM	119	52	Eprosartan/Placebo	No (P yes)	No	Yes	-
Derosa 2004b	HT, T2DM	116	52	Nifedipine GITS	No	No	Yes	-
Vitale 2005	HT, MS	40	12	Losartan	Yes?	Yes	-	-
Miura 2005	HT, T2DM	18	12	Candesartan/Valsartan	No	Yes	Yes	Yes
Koulouris 2005	NT, T2DM	40	12	Ramipril	No	No	No	Yes
Honjo 2005	HT, T2DM	38	12	Candesartan	-	Yes	-	-
Benndorf 2006	HT	37	6	Nisoldipine	No?	Yes	-	-
Negro 2006a	HT, T2DM	40	16	Amlodipine	No	Yes	Yes	-
Negro 2006b	HT, obese,IR	46	26	Irbesaratn	No	Yes	Yes	-
Bahadir 2007	HT, MS	42	10	Losartan	No?	Yes?	No	-
Derosa 2007	HT, T2DM	188	52	Irbesartan	No	Yes	Yes	Yes
Sharma 2007	HT, obese	840	10	Valsartan HCTZ	Yes	No	No	-

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

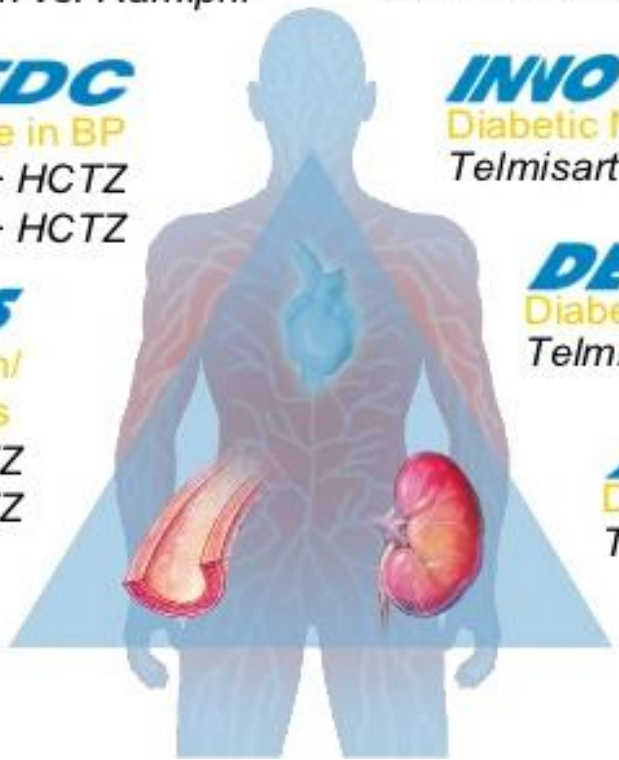
Telmisartan vs. Placebo

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.

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.

Chandra KS et al, Indian Heart J. 2013 Dec;65(6):691-5.

Limitations of traditional L type CCBs

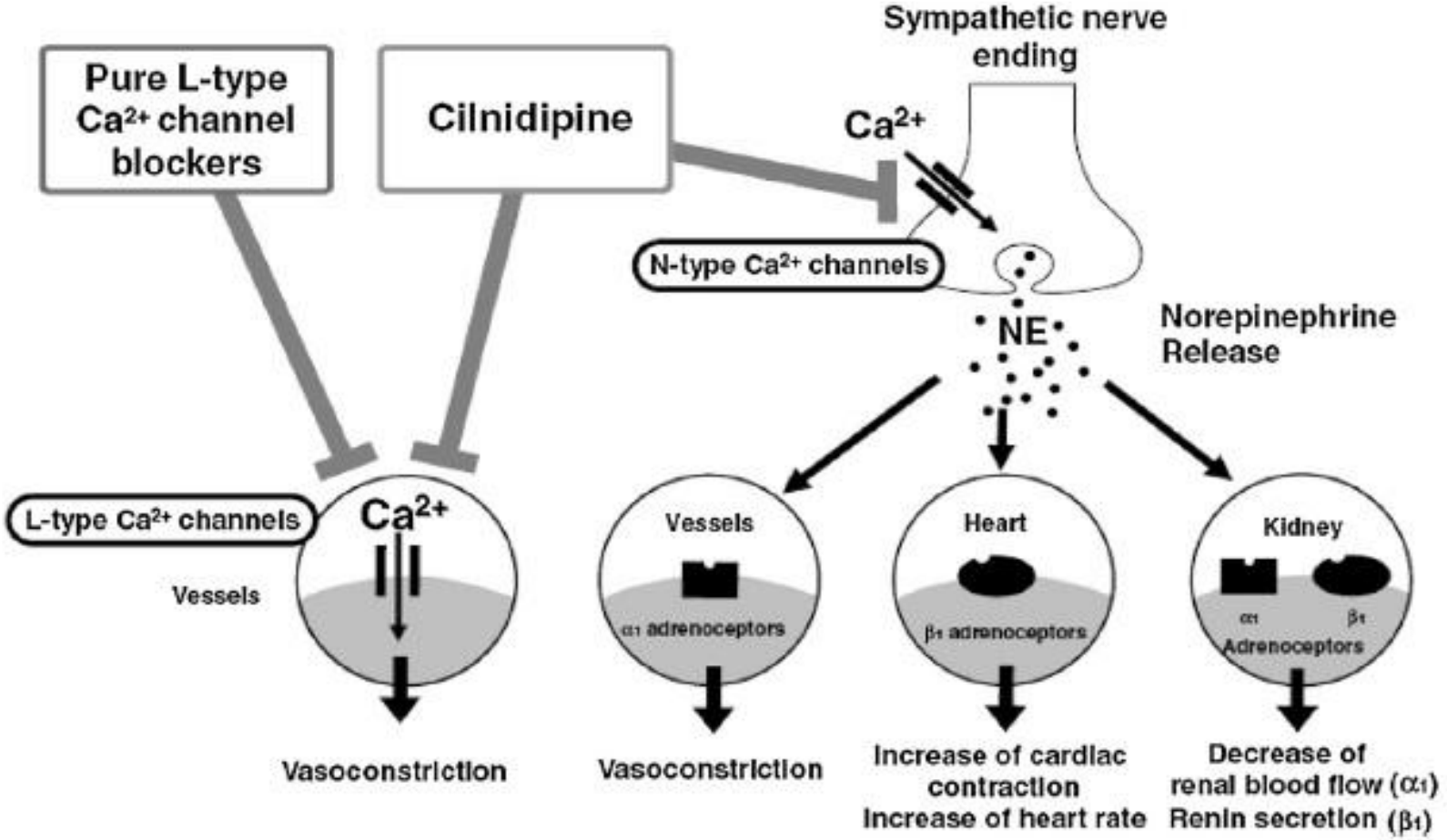
- Edema is a common side effect in all the traditional CCBs
- Traditional L-type CCB are having less effect on stress induced hypertension
- Less action on the Renal System
- Reduces BP only not the Heart Rate.

Blocking only L-type Calcium Channel is not sufficient to control the complications of hypertension

Chandra KS et al, Indian Heart J. 2013 Dec;65(6):691-5.

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.

Chandra KS et al, Indian Heart J. 2013 Dec;65(6):691-5.

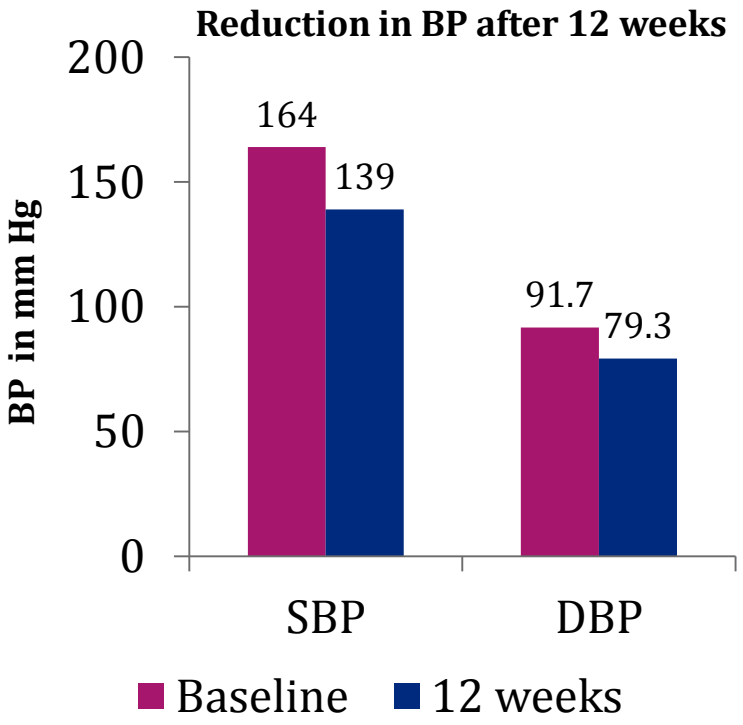
Cilnidpine Benefits

- Dual Blockade L and N type
- Effective BP control
- Vasodilatation of peripheral resistance vessels
- No reflex tachycardia
- No pedal edema

Hoshide S et al. Hypertens Res. 2005 Dec;28(12):1003-8.
Adake P *et al*. J Adv Pharm Technol Res. 2015 Apr-Jun; 6(2): 81–85.

The effect of combination therapy with cilnidipine and an ARB on the blood pressure and heart rate

- Significant reduces both SBP and DBP.
- Cilnidipine reduces elevated heart rate, which is a risk factor for CV events.

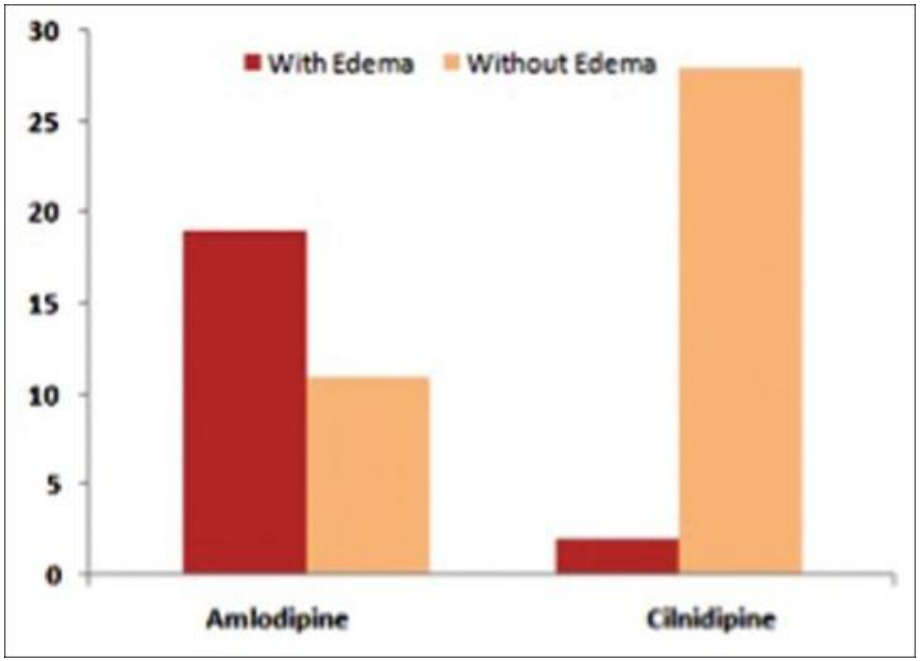


Nagahama S *et al.* Hypertens Res. 2007 Sep;30(9):815-22.

Amlodipine vs Cilnidipine on antihypertensive efficacy and incidence of pedal edema

- Amlodipine and Cilnidipine shows equal efficacy in reduction of BP.

- Cilnidipine is associated with lower incidence of pedal edema compared to Amlodipine.



Adake P *et al*. J Adv Pharm Technol Res. 2015 Apr-Jun; 6(2): 81–85.

Cilnidipine: Clinical Studies

Year	Author	N	Patients	Antiproteinuric or Antialbuminuric Effect
2007	Morimoto S, *et al.* J Hypertens. 2007 Oct;25(10):2178-83	50	Essential hypertension Serum Cr≧1.5mg/dL	Cilnidipine > Amlodipine
2010	Miwa Y, *et al.* J Hypertens. 2007 Oct;25(10):2178-83	35	Hypertension Urinary protein > 0.1g/day	Cilnidipine > Amlodipine
2010	Konoshita T, *et al.* J Hypertens. 2010 Oct;28(10):2156-60	110	Hypertension	Cilnidipine > Amlodipine
2011	Masuda T, *et al.* Cardiovasc Ther. 2011 Feb;29(1):46-53	35	Type 2 diabetes and hypertension	Cilnidipine > Amlodipine
2012	Fukumoto S, *et al.* Diabetes Res Clin Pract. 2012 Jul;97(1):91-8	90	Type 2 diabetes and hypertension Urinary albumin <300 mg/gCr	Cilnidipine > L-type CCBs
2012	Soeki T, *et al.* Hypertens Res. 2012 Nov; 35(11): 1058-62	35	Hypertension	Cilnidipine > L-type CCBs

Cilnidipine- Renal Action

- Renal protective effect of cilnidipine is greater than pure L-type Ca^{2+} channel blockers

- Cilnidipine versus Amlodipine Randomized Trial for Evaluation in Renal disease (CARTER) study:

  - Cilnidipine is superior to amlodipine in preventing the progression of proteinuria in patients with hypertension and chronic renal disease

Fujita T et al, Kidney International (2007)72, 1543–1549

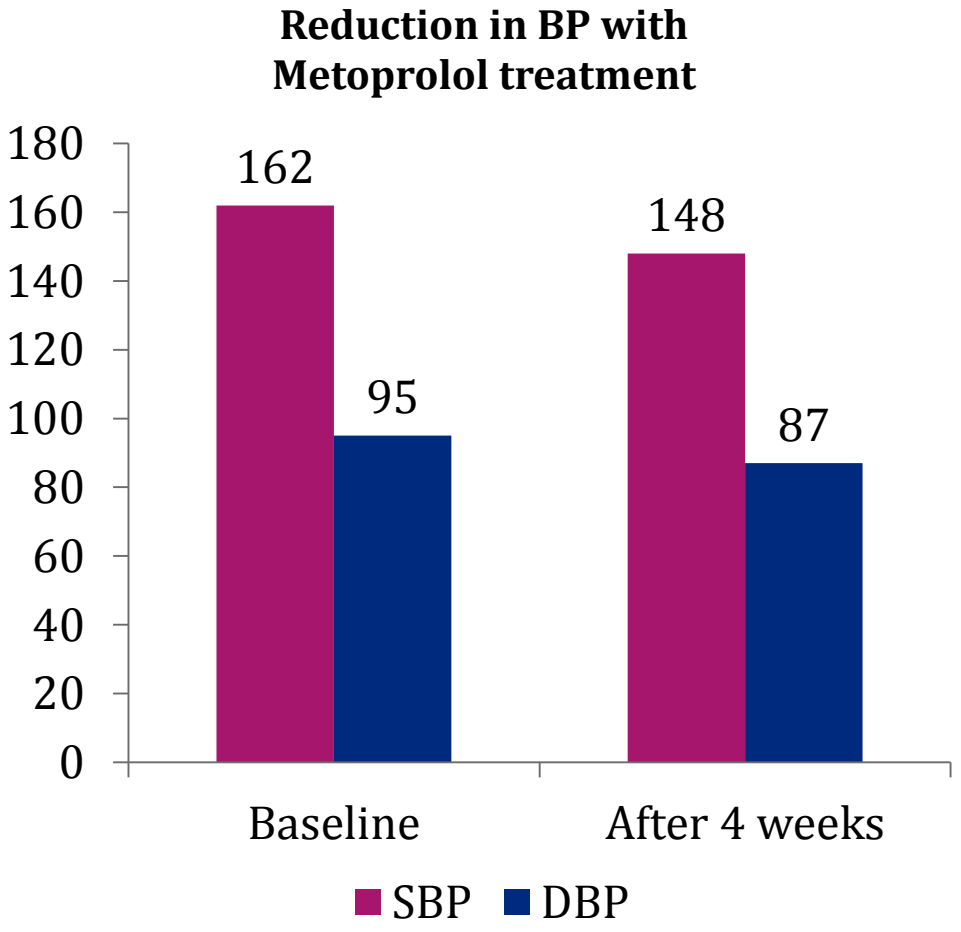
Metoprolol Extended Release In Hypertension

- Competitive beta-1 selective, Lipophilic, adrenergic antagonist.
- Provides, 24 hour beta-1 blockade
- Lowers BP smoothly and consistently over a 24 hour dosage interval
- Guidelines advocate the use of metoprolol in patients with an indication for beta-blockers.

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.

Safety and efficacy of metoprolol in the treatment of hypertension

- 21,692 patients with mild-to-moderate hypertension between the ages of 50 to 75 years.



LaPalio L et al. J Am Geriatr Soc. 1992 Apr;40(4):354-8.

Metoprolol CR/XL in patients with Hypertension, Diabetes and Chronic heart failure

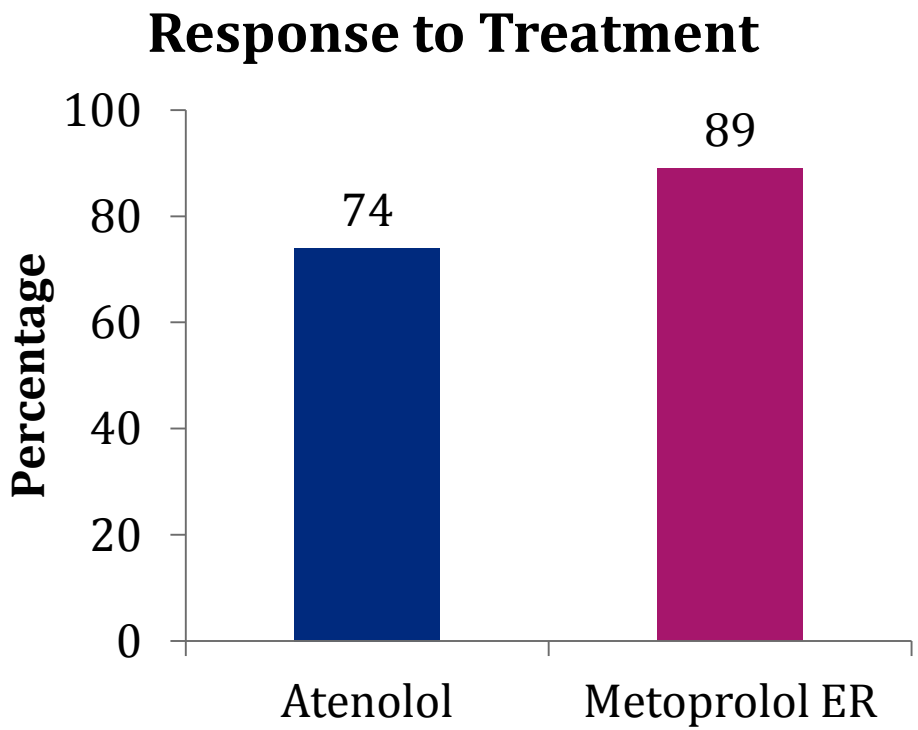
- Metoprolol CR/XL was well tolerated patients with Hypertension, Diabetes and Chronic heart failure

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

Deedwania PC et al. Am Heart J. 2005 Jan;149(1):159-67.

Comparison of metoprolol CR and atenolol once daily for uncomplicated hypertension.

- In a double-blind study, 195 patients were included.
- 98 on metoprolol and 97 on atenolol were followed up for 8 weeks.

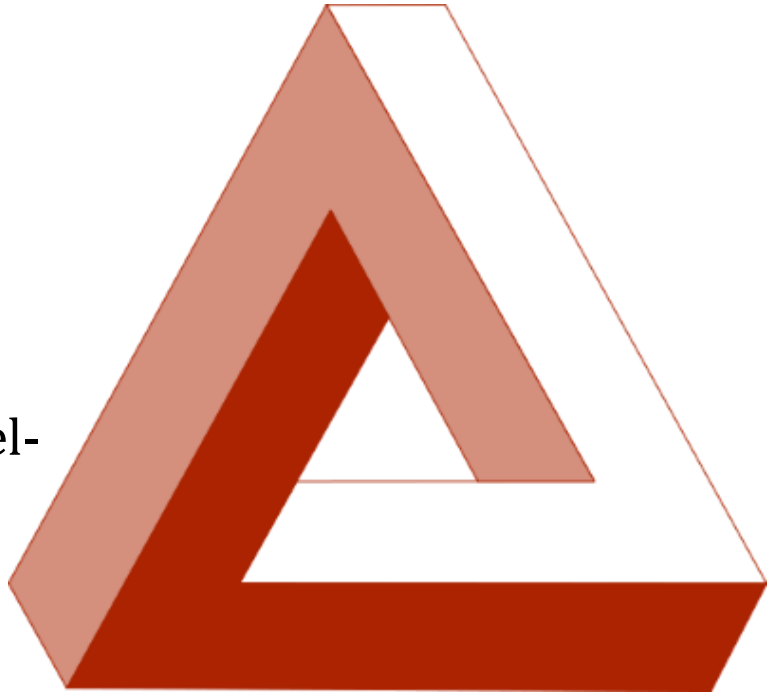


Klein G *et al.* J Clin Pharmacol. 1990 Feb;30(2 Suppl):S72-7.

Triple Combination

Telmisartan

Telmisartan has unique binding to AT 1 receptors.
Also activates PPAR-γ



Cilnidipine

Cilnidipine has dual L/N-type Ca^{2+} channel-blocking action and provides beyond BP benefits including renoprotective, and cardioprotective effects

Metoprolol:

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

Beevers et al. BMJ 2001;322:912–916
Chandra KS et al, Indian Heart J. 2013 Dec;65(6):691-5.
van den Born BJ et al. Ned Tijdschr Geneeskd. 2005 Aug 6;149(32):1808-9.

Clinical Practice Guidelines for the Management of Hypertension in the Community
A Statement by the American Society of Hypertension and the International Society of Hypertension

TABLE I. Drug Selection in Hypertensive Patients With or Without Other Major Conditions

Patient Type	First Drug	Add Second Drug If Needed to Achieve a BP <140/90 mm Hg	If Third Drug is Needed to Achieve a BP of <140/90 mm Hg
B. When hypertension is associated with other conditions			
Hypertension *and* diabetes	ARB or ACE inhibitor Note: in black patients, it is acceptable to start with a CCB or thiazide	CCB or thiazide diuretic Note: in black patients, if starting with a CCB or thiazide, add an ARB or ACE inhibitor	The alternative second drug (thiazide or CCB)
Hypertension *and* chronic kidney disease	ARB or ACE inhibitor Note: in black patients, good evidence for renal protective effects of ACE inhibitors	CCB or thiazide diuretic[c]	The alternative second drug (thiazide or CCB)
Hypertension *and* clinical coronary artery disease[d]	β-Blocker plus ARB or ACE inhibitor	CCB or thiazide diuretic	The alternative second step drug (thiazide or CCB)
Hypertension *and* stroke history[e]	ACE inhibitor or ARB	Thiazide diuretic or CCB	The alternative second drug (CCB or thiazide)
Hypertension and heart failure	Patients with symptomatic heart failure should usually receive an ARB or ACE inhibitor + β-blocker + diuretic + spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for BP control.		

Weber MA *et al*. J Hypertens. 2014 Jan;32(1):3-15.

Triple Combination

- The triple combination of Telmisartan + Cilnidipine + Metoprolol blocks the AT 1 receptor, L and N type calcium channels and beta 1 receptors.

- The triple combination acts on 3 different pathways and provides
  - Superior BP control and
  - Pleiotropic benefits

Conclusion

- Majority of patients require more than 2 drugs to achieve BP goal
- Combination therapy are recommended in treatment guidelines
- Telmisartan + Cilnidipine + Metoprolol provides
  - Superior BP control in patients with uncontrolled Hypertension and co-morbid diabetes and CV risk.
  - End organ protection
  - Reduces Pill Burden.
  - Increases compliance


thank you
danke
謝謝
gracias
merci
obrigado
dziękuję
bedankt
go raibh maith agat
teşekkür ederim
ngiyabonga
спасибо
рахмат
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dank je
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