CCB & ARB – A FRIENDLY DUO

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HYPERTENSION

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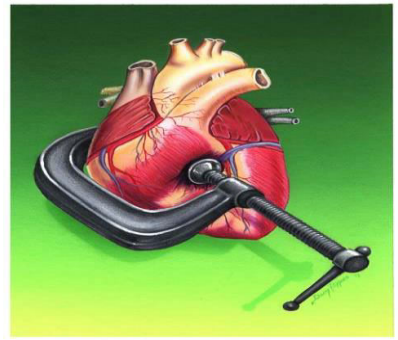
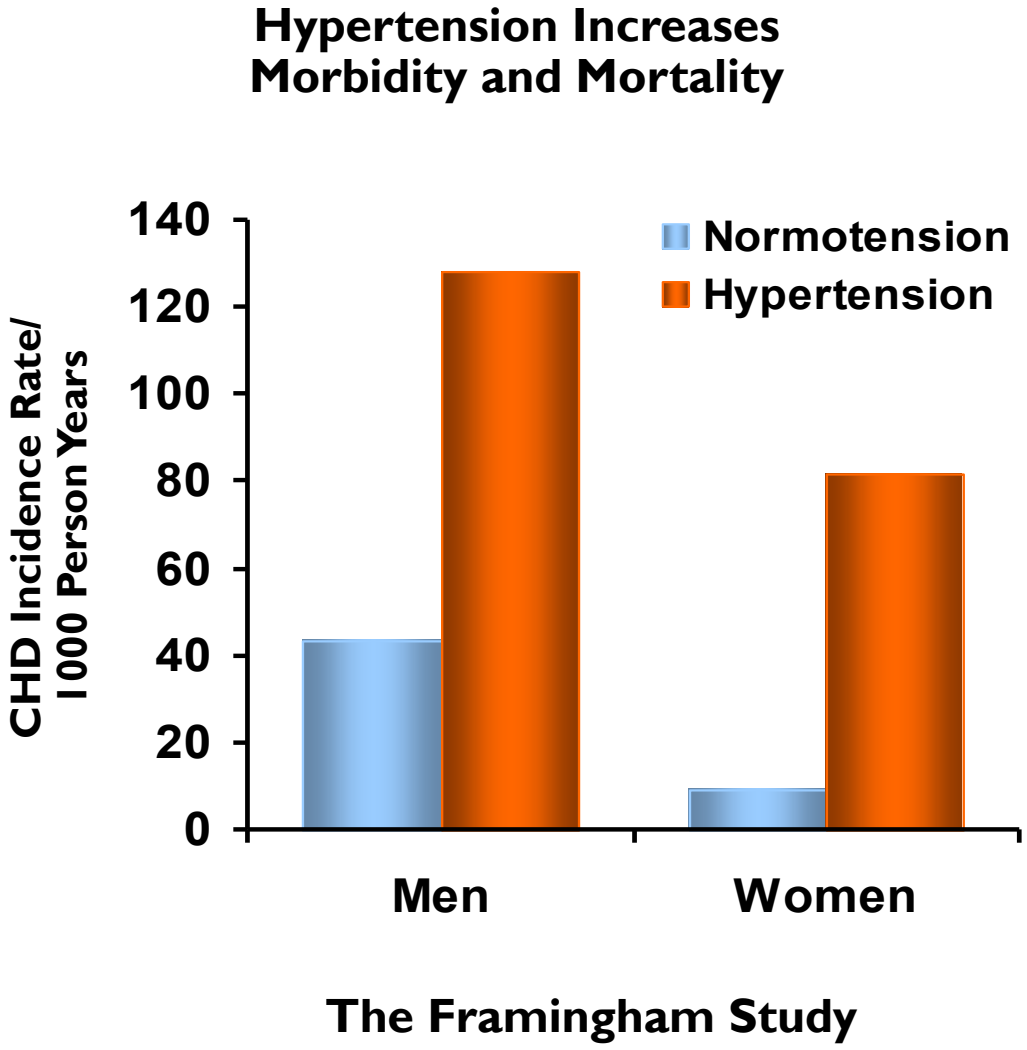


COMBINATION THERAPY IN HYPERTENSION

Cilnidipine

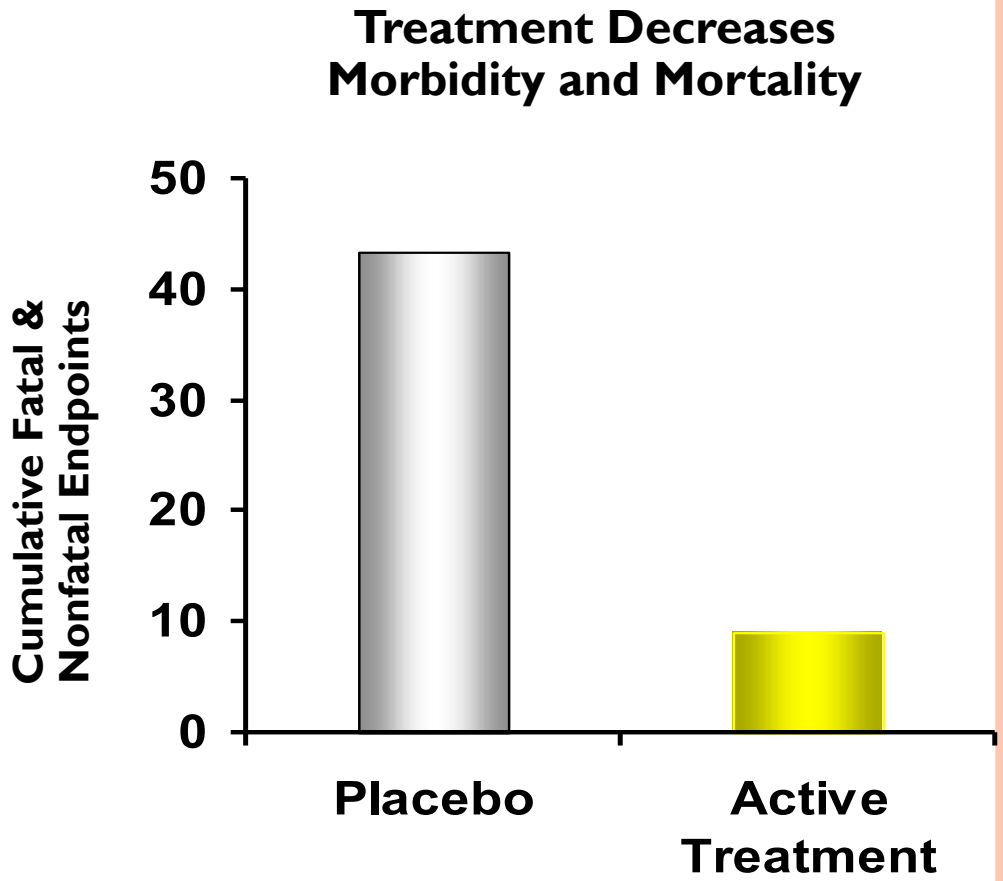
Telmisartan

Historical Lessons on the Risks of Hypertension and the Benefits of Treatment



The Framingham Study

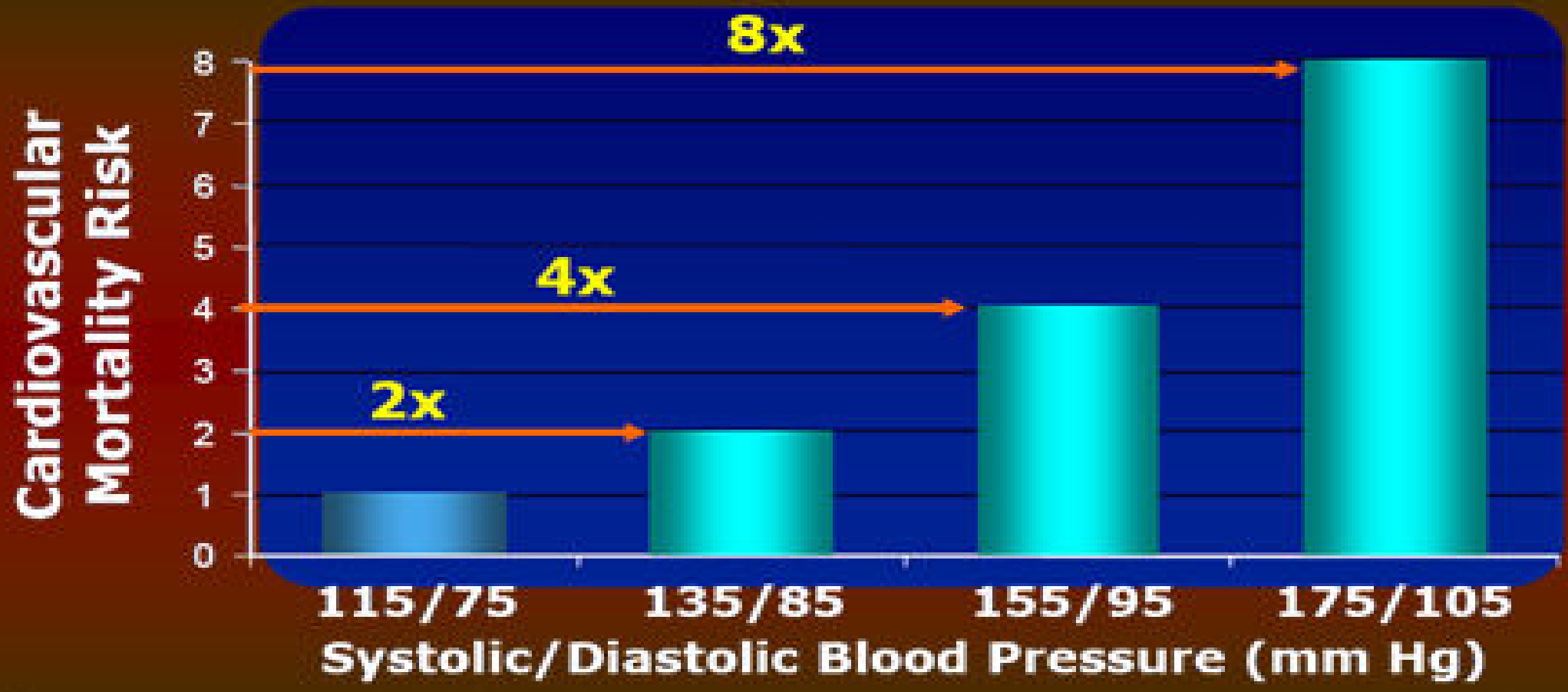
Ann Intern Med. 1961; 55:33–50.



The Vet. Adm. Study II

JAMA. 1970; 213:1143–1152.

Cardiovascular Mortality Risk Doubles with Each 20/10 mmHg BP Increment *



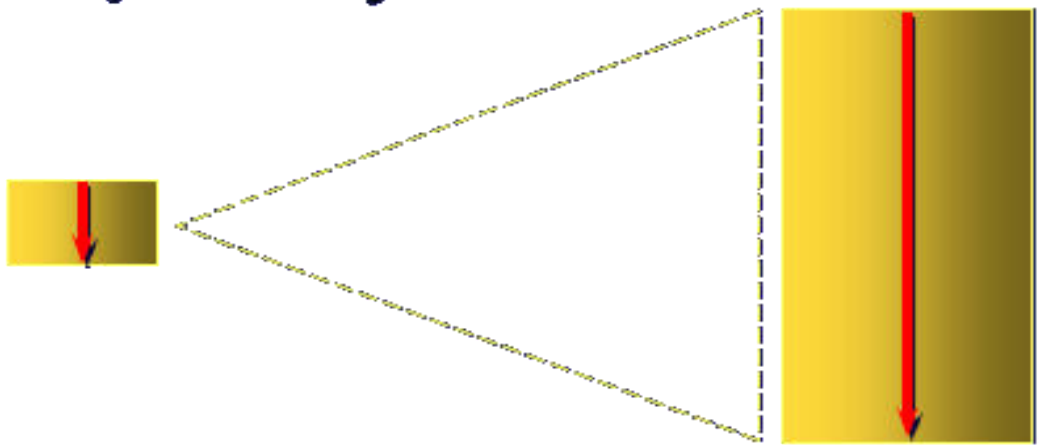
*Measurements taken in individuals aged 40–69 years, beginning with a blood pressure of 115/75 mm Hg.

Lewington S, et al. *Lancet*. 2002;360:1903-1913;
Chobanian AV, et al. *JAMA*. 2003;289:2560-2572.

BP Reductions as Small as 2 mmHg Reduce the Risk of CV Events by Up to 10%

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

2 mmHg decrease in mean SBP



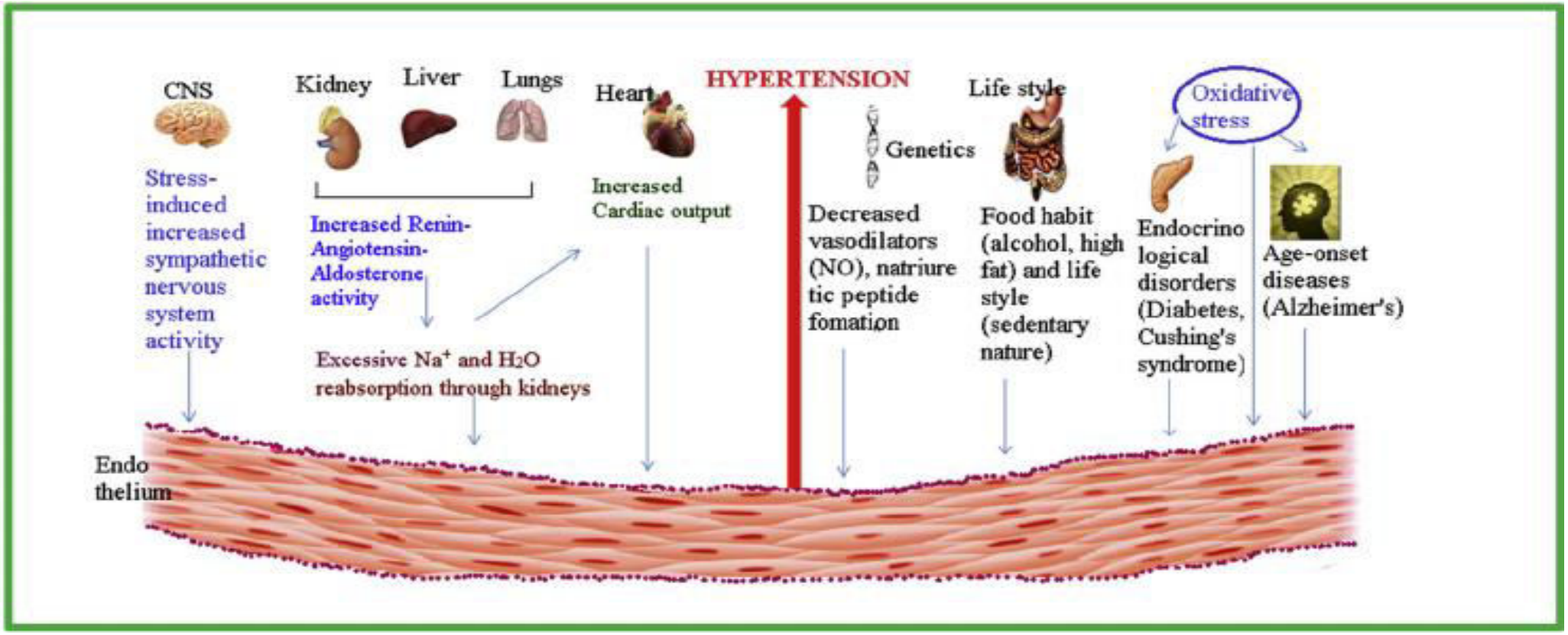
7% reduction in risk of ischemic heart disease mortality

10% reduction in risk of stroke mortality

Prospective Studies Collaboration. *Lancet.* 2002;360:1903-1913

WHY IS BP GOAL DIFFICULT TO ACHIEVE

Hypertension is a multi-factorial disease & multiple mechanisms are involved in pathogenesis of disease (RAAS system)



Hypertension-Treatment

Drug therapy

A

- ACEi – Angiotensin converting enzyme inhibitors – Ramipril
- ARB – Angiotensin Receptor Blockers –Telmisartan

B

- BB – Beta Receptor Blockers – Metoprolol, Carvedilol, Atenolol

C

- CCB – Calcium channel blockers – Verapamil, Diltiazem, Amlodipine , Cilnidipine

D

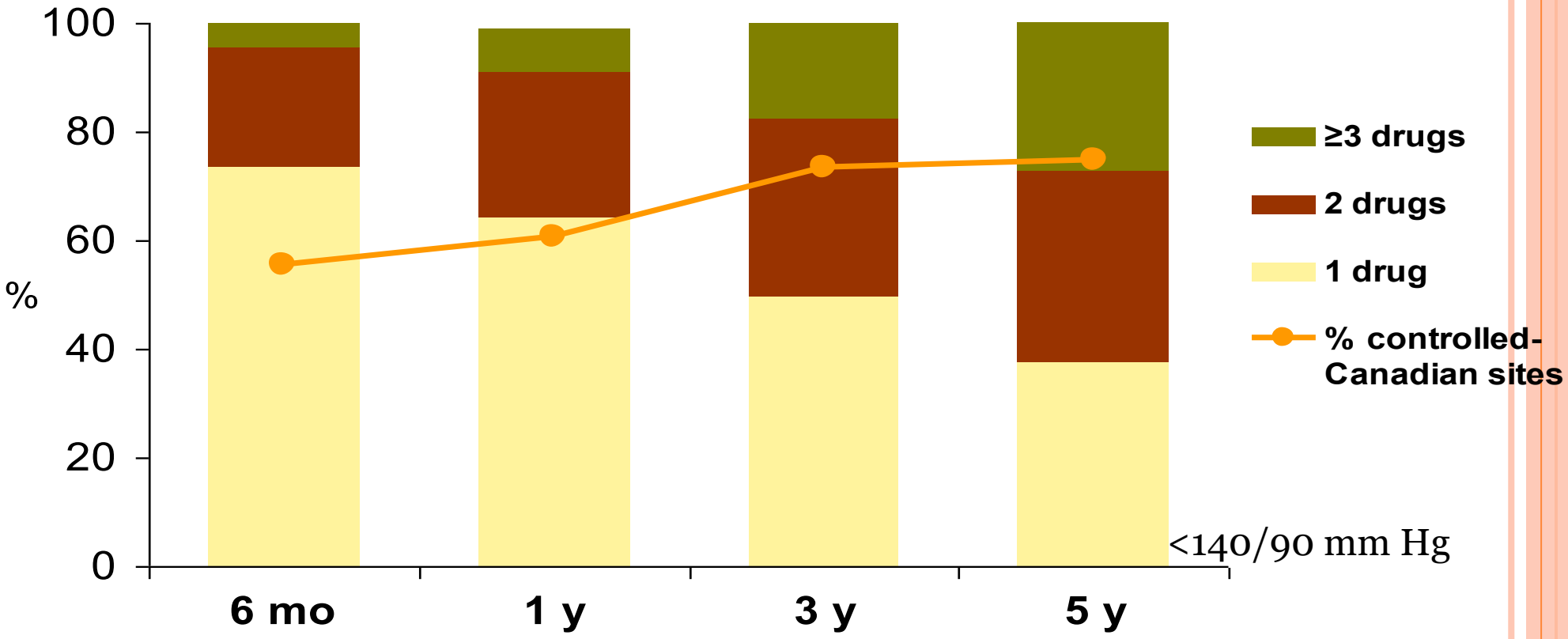
- Diuretics – Hydrochlorothiazide, Furosemide, Spiranolactone

Failure of Single Drug Regimen

Most drugs only reduce
SBP 7~13 mmHg
DBP 4~8 mmHg – – ••
Due to
Multifactorial mechanism of High BP –
Counter-regulatory mechanism

If BP>20/10 mmHg above Goal , initiating therapy with 2 drugs JNC-VII, 2003

Monotherapy is often not enough: *medication use and BP control in ALLHAT*



Cushman et al. *J Clin Hypertens* 2002;4:393-404

DRUG COMBINATIONS IN HYPERTENSION : RECOMMENDATIONS

Preferred (Two drug)

- ACE inhibitor / diuretic
- ARB / diuretic
- ACE inhibitor/CCB
- ARB/CCB

Acceptable (Two drug)

- β-Blocker/diuretic
- CCB (dihydropyridine) / β-blocker
- CCB/diuretic
- Renin inhibitor / diuretic
- Renin inhibitor / ARB
- Thiazide diuretics / K+-sparing diuretics

Less acceptable (Two drug)

- ACE inhibitor/ARB
- ACE inhibitor / β-blocker
- ARB / β-blocker
- CCB (nondihydropyridine)/β-blocker
- Centrally acting agent/ β-blocker

Preferred(Three Drug)

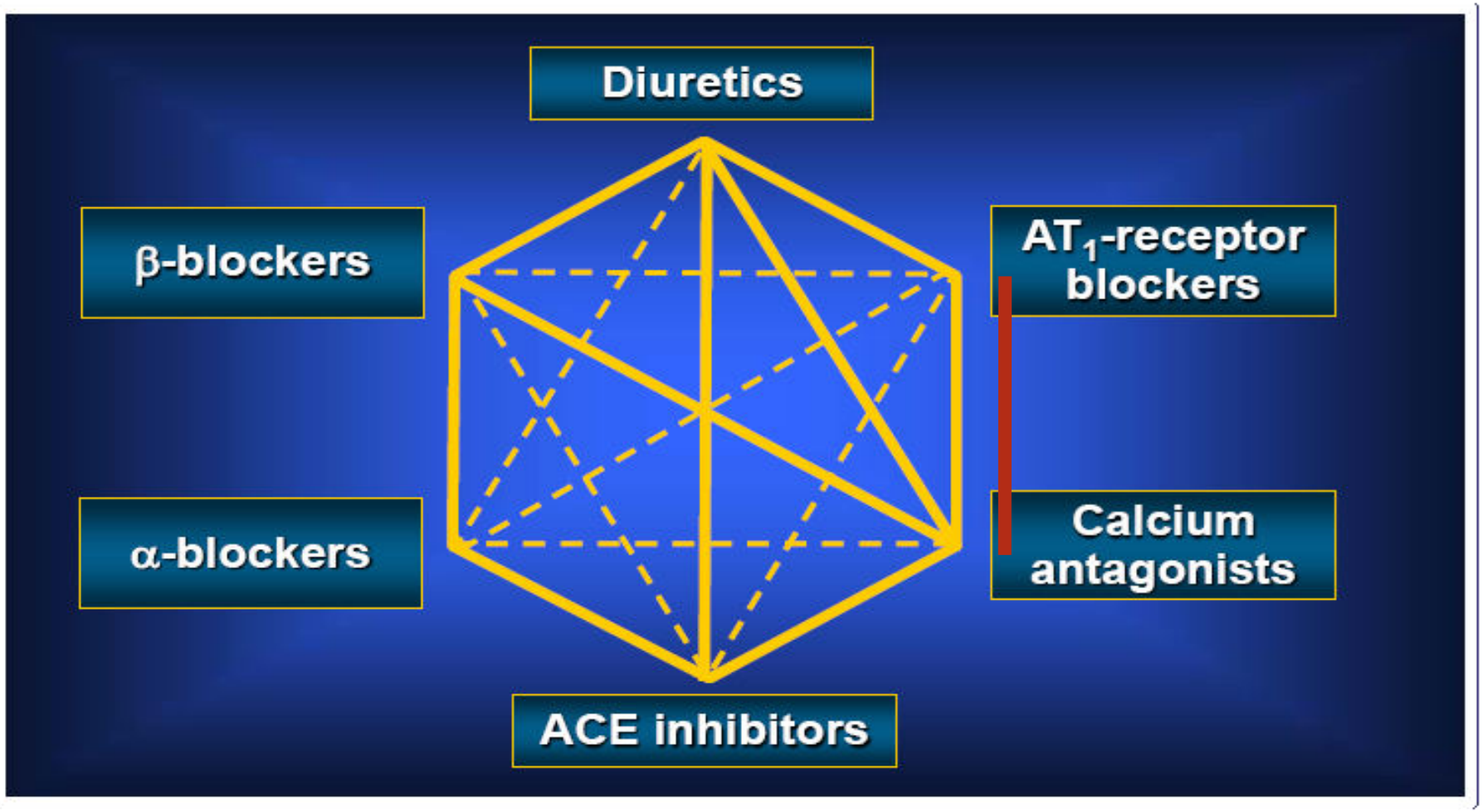
ARB+Amlo+HCTZ (Telmesartan, olmesartan)

ACEI (Perindopril)+indepamide+amlodepin (Triplixam)

Aliskirin+Amlo+HCTC

ESH 2003: Possible Combinations of Different Classes of Antihypertensive Agents

The most effective and well tolerated combinations are shown as solid lines



ESH Guidelines. *J Hypertens.* 2007;25:1105-1087.

ESH= European Society of Hypertension

History of Combination Therapy

The Use of combination therapies started in the 1950s, when pills containing reserpine were introduced.

Several other formulations in the 1960s and 1970s that contained thiazide diuretics, including the triple combination pill of hydralazine an hydrochlorothiazide and reserpine, as well as in combination with potassium-sparing diuretics, beta- blockers, and clonidine.

In the 1980s, thiazides were combined with angiotensin-converting enzyme (ACE) inhibitors

In 1990s, a combination of an ACE inhibitor and calcium channel blocker (CCB) was approved

Guidelines

ESC 2021

1 pill

Initial therapy Dual combination

ACEi or ARB + CCB or diuretic

Consider monotherapy in low- risk grade I hypertension (systolic BP <150mmHg), or in very old (≥ 80 years)

1 pill

Step 2
Triple combination

ACEi or ARB + CCB + diuretic

2 pills

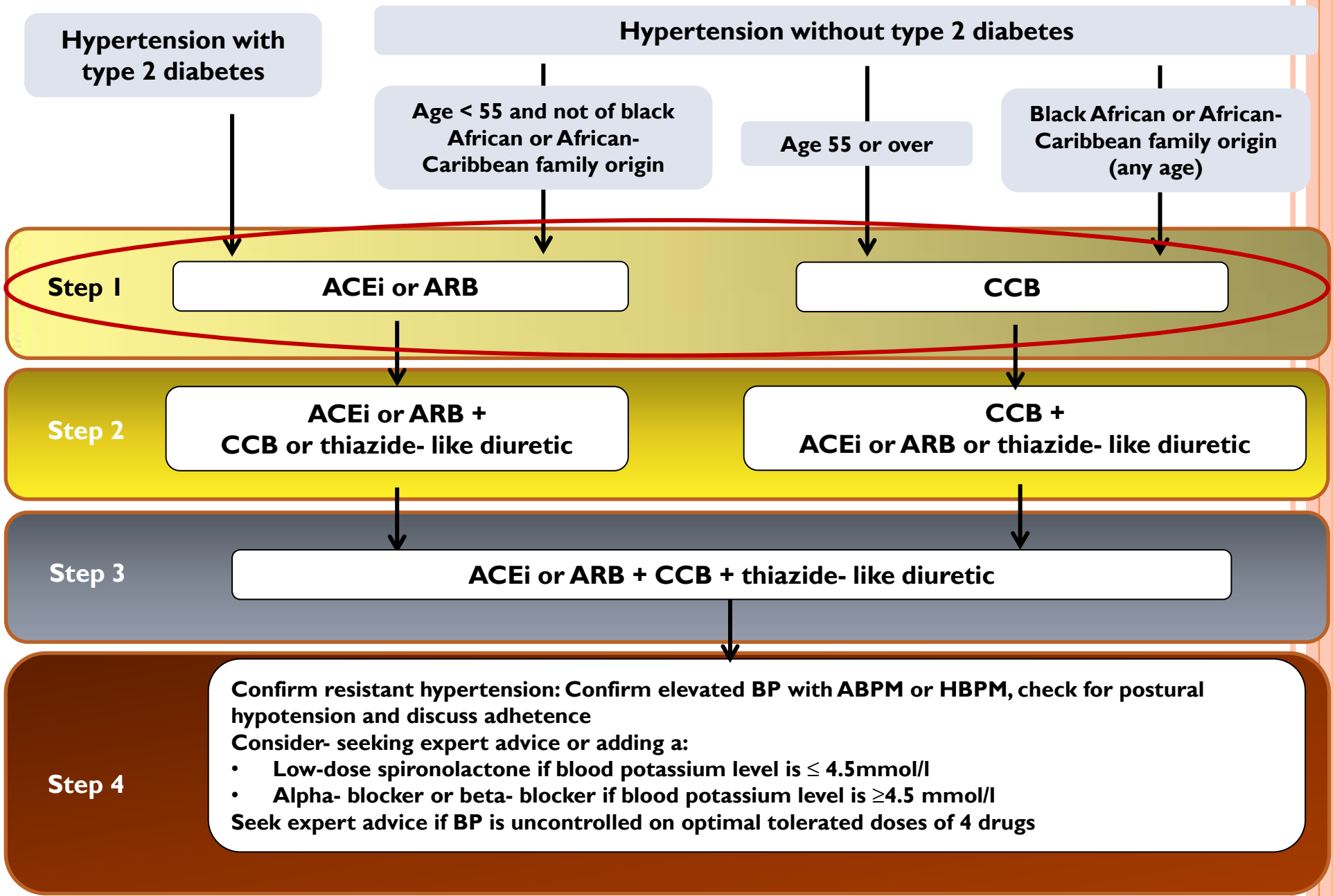
Step 3
Triple combination + Spironolactone or other drug

Resistant hypertension
Add Spironolactone (25-50 mg OD) or other diuretic, alpha- blocker or beta- blocker

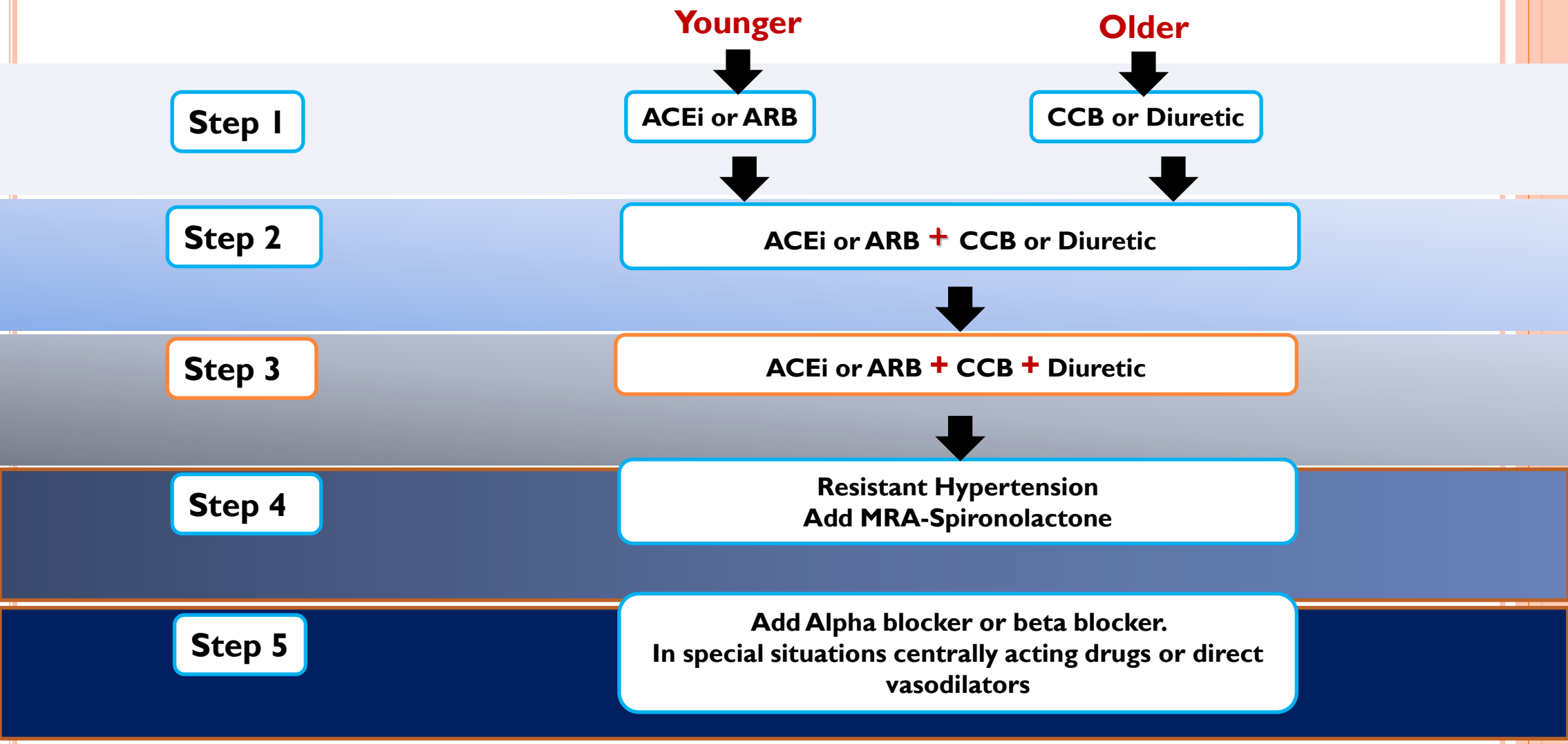
Consider referral to a specialist centre for further investigation

NICE GUIDELINE 2019

Choice of antihypertensive drug, monitoring treatment and BP targets



Indian Guidelines On Hypertension 2019



Ideal Combination

CCB + ACE/ARB

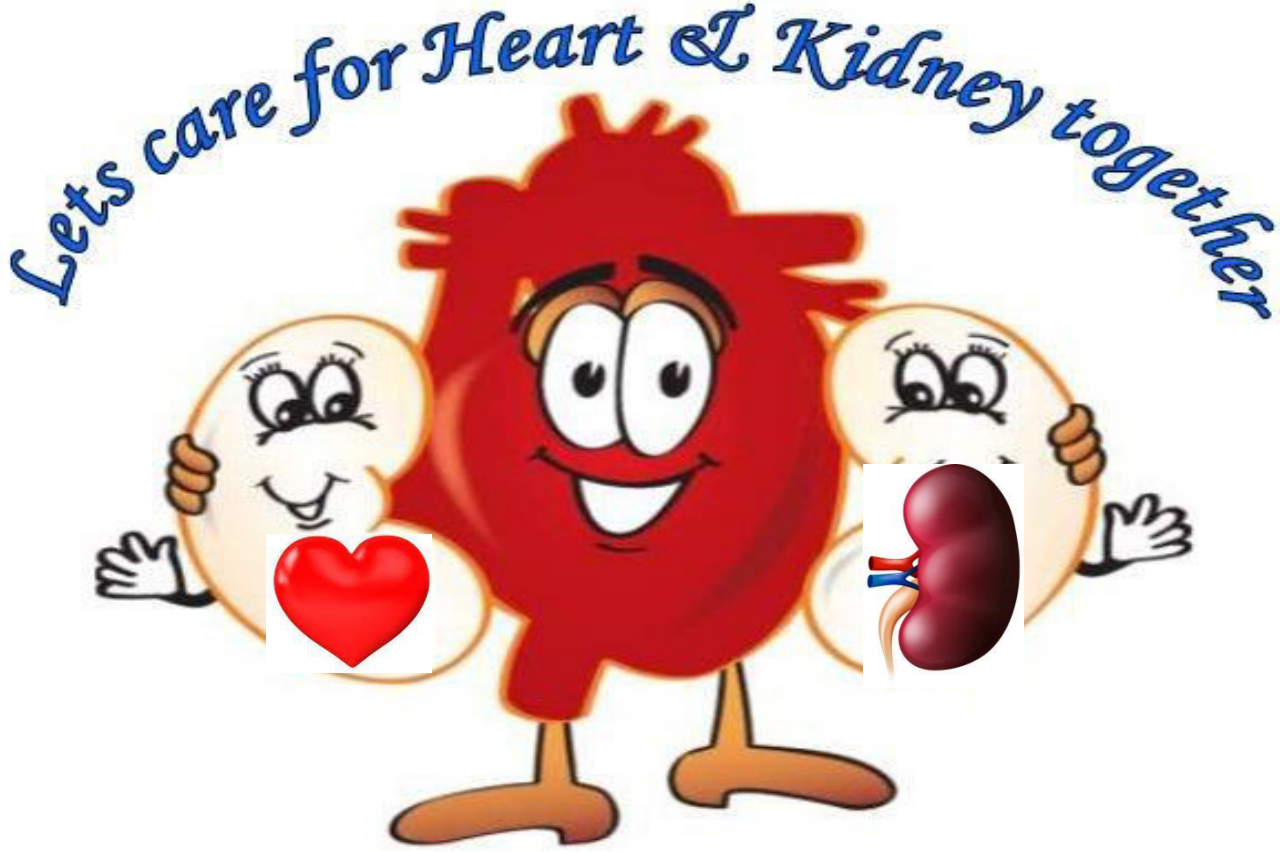
Amlodipine & Telmisartan is the preferred combination in this group

But

PREAMBLE

- Amlodipine is a very safe and effective drug for management of hypertension
- There are some minor shortcomings with Amlodipine, like pedal edema seen in some patients
- Reflex tachycardia
- Elevated Proteinuria level
- So, newer CCBs (Cilnidipine) which can overcome this shortcomings are always a good option for management of hypertension

Looking beyond the conventional CCB

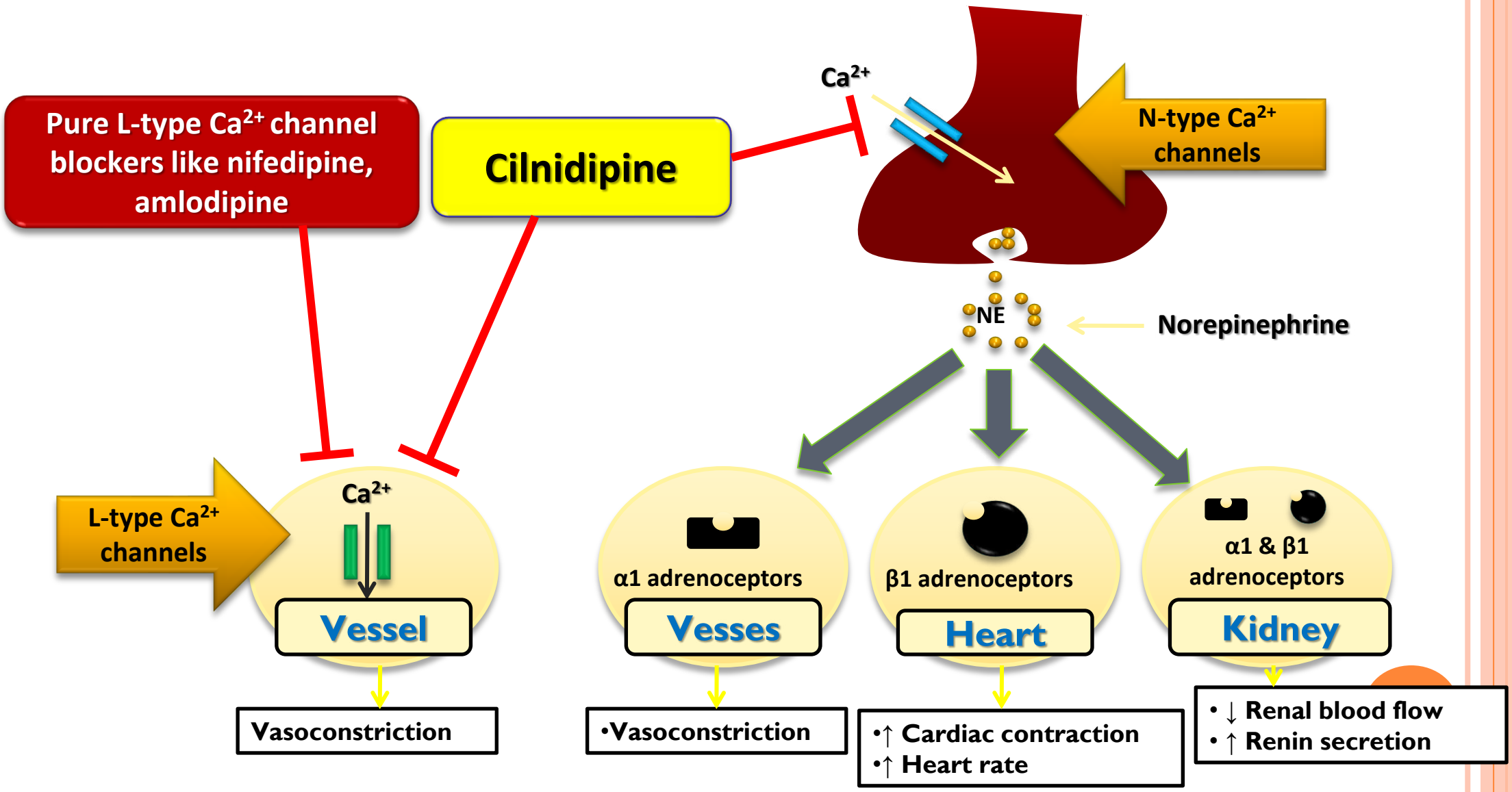


CILNIDIPINE

Generations of CCBs and Cilnidipine

Generation	Drugs	Plasma NE level	Heart rate	Charact -eristics	Ca 2+ channel blocked
1st generation	Nifedipine	Increased	Increased	Rapid sympathetic activation	L-type
2nd generation	Nicardipine Benitidine	Increased	Increased	Slow acting on L-type Ca^{2+} channels	
3rd generation	Amlodipine Azelnidipine	Increased	Increased	Slow acting on L-type of Ca^{2+} channels	
4th generation	**Cilnidipine**	**No change or decreased**	**No change or Decreased**	**L- type and N-type Ca^{2+} channel**	**L-type and N-type**

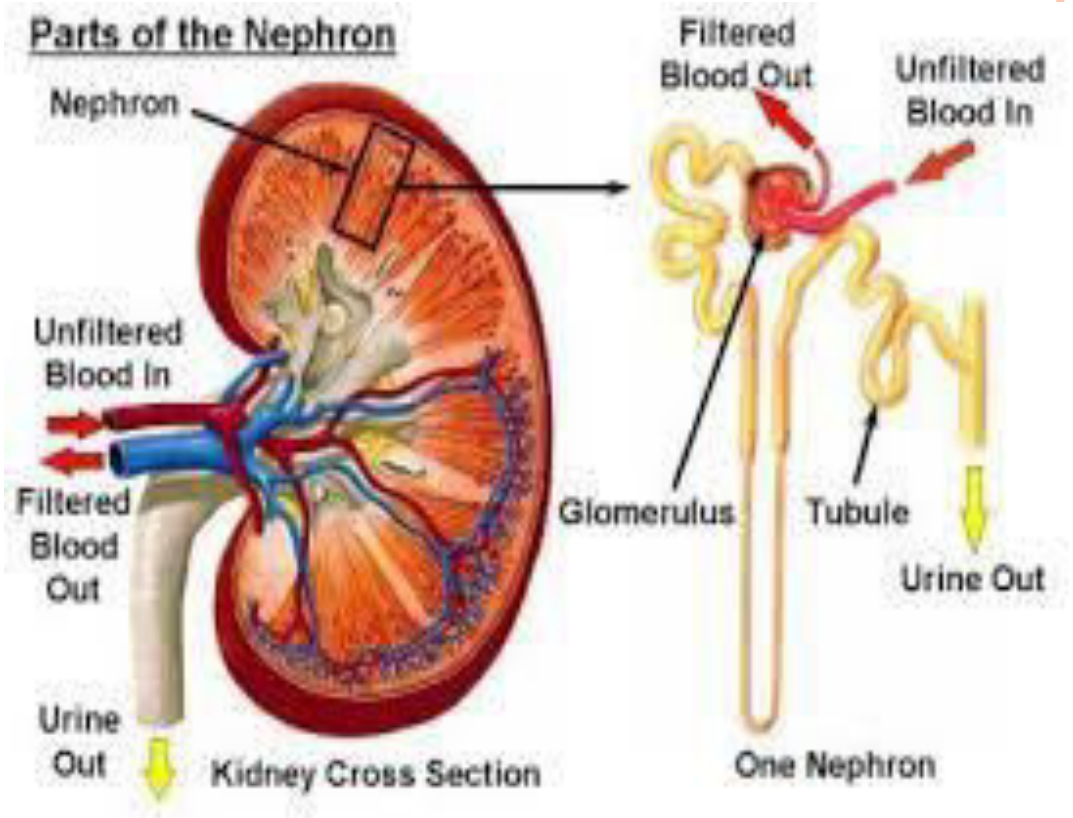
CILNIDIPINE: PHARMACOLOGY



CILNIDIPINE - RENOPROTECTION

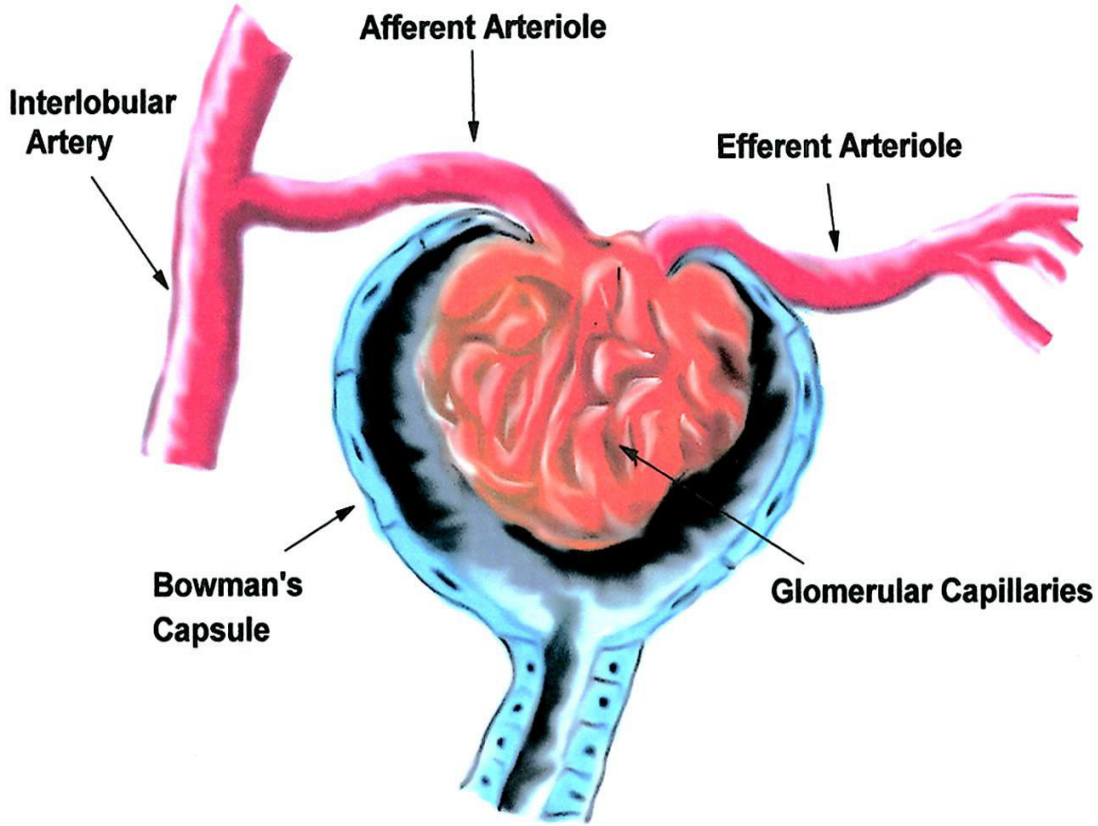
- N-type Ca channels are densely distributed in sympathetic nerves that innervate renal tubules

- Data suggest that N-type Calcium channels contribute to multiple steps of renal fibrosis and its blockade may thus be a useful therapeutic approach for prevention of renal fibrosis



CILNIDIPINE- RENOPROTECTION

- Cilnidipine, an L/N-type calcium channel blocker has been reported to have more beneficial effects on proteinuria progression in hypertensive patients than amlodipine, an L-type CCB
- The N-type calcium channel blockade that inhibits renal sympathetic nerve activity might reduce glomerular hypertension by facilitating vasodilation of the efferent arterioles



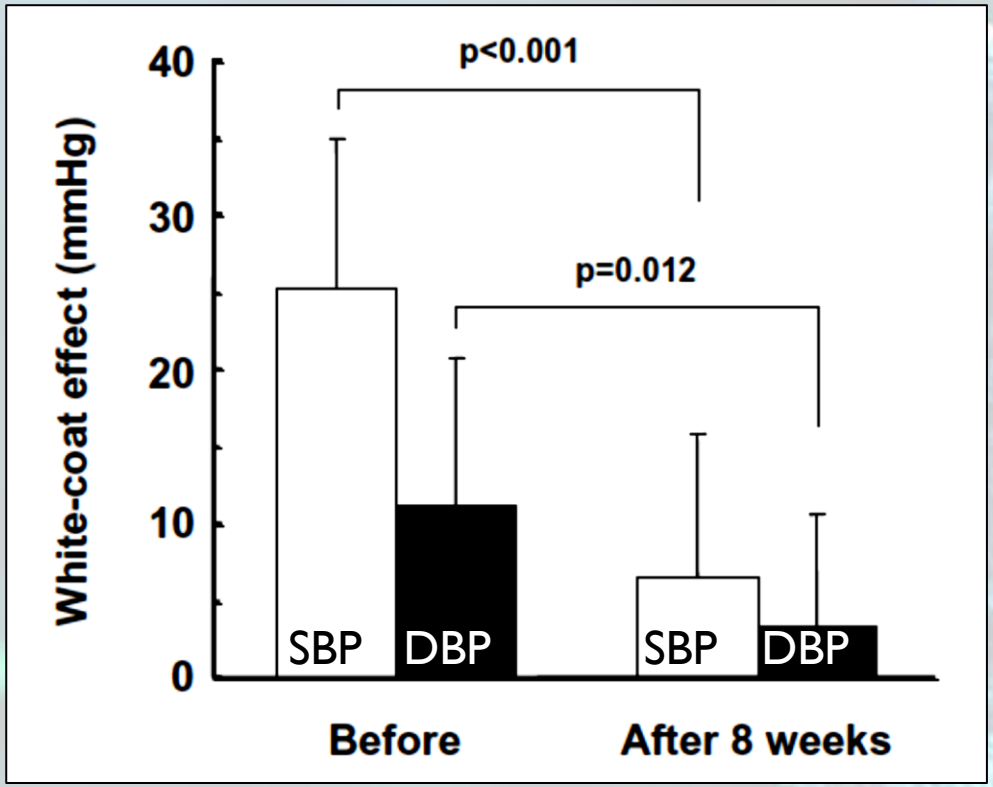
Hypertens Res. 2012 Nov;35(11):1058-62

CILNIDIPINE - PROTEINURIA

- Microalbuminuria, is an established risk factor for cardiovascular morbidity and mortality in the general population
- Low-grade albuminuria (<30mg/g) is considered a marker for subclinical vascular damage that predisposes to future cardiovascular diseases and death
- Lowering urinary albumin excretion reduces the risk of cardiovascular disease
- Cilnidipine is safe and effective in reducing low-grade albuminuria in hypertensive CKD patients
- Thus, early treatment of Cilnidipine in hypertensive CKD patients with low-grade albuminuria may prevent cardiovascular disease

Cilnidipine Attenuates White-Coat Effect

N: 58 patients with morning hypertension (43 currently being treated, 15 new patients)
Treatment: Cilnidipine (10-20 mg/day)
Duration: 8 weeks



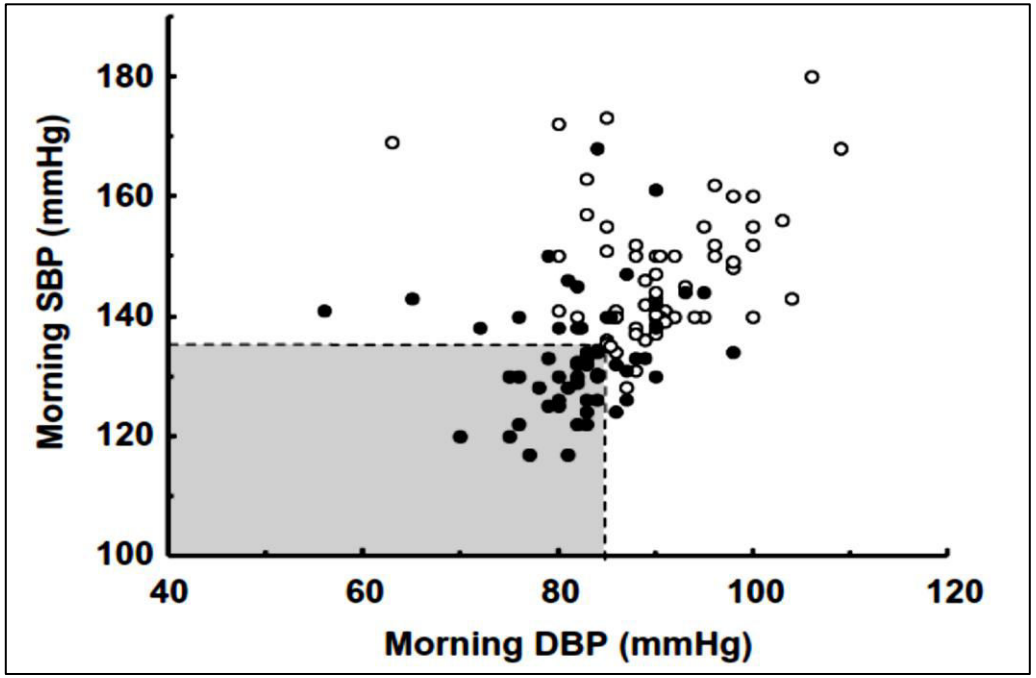
White-coat effect - Difference of at least 20 mmHg for SBP and/or 10 mmHg for DBP between office and home blood pressure.

Cilnidipine attenuates the white-coat effect caused by the hyperactivity of sympathetic nerves

Hypertens Res 2006;29:339-44

Cilnidipine Controls Morning BP

N: 58 patients with morning hypertension (43 currently being treated, 15 new patients)
Treatment: Cilnidipine (10-20 mg/day)
Duration: 8 weeks



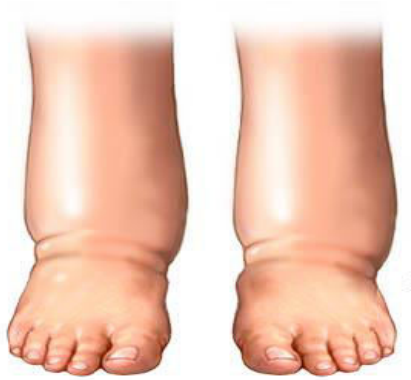
Control rate (BP <135/85 mmHg) was observed in 52% of patients

Cilnidipine may be a useful antihypertensive agent to medicate patients with morning hypertension and morning surge

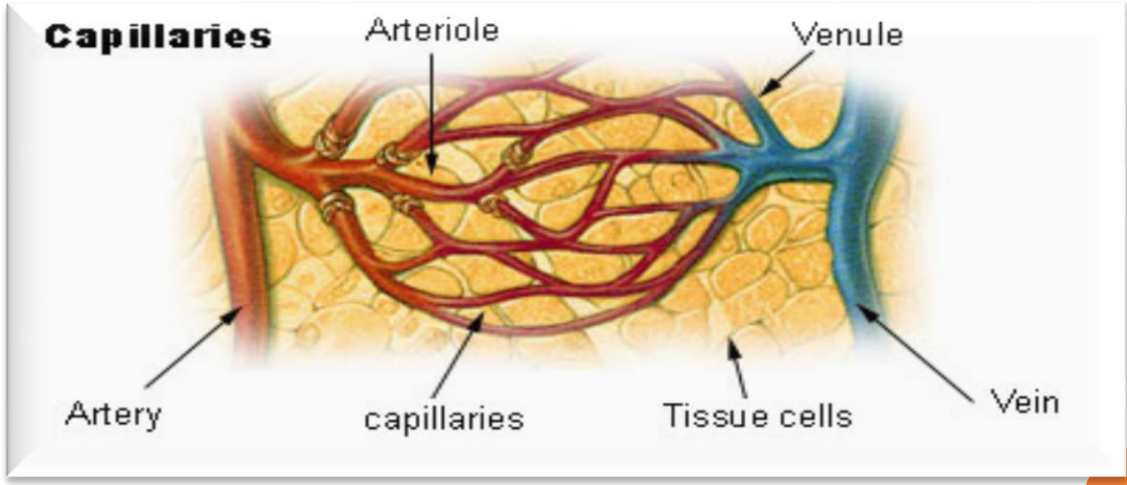
Hypertens Res 2006;29:339-44

CILNIDIPINE REDUCES EDEMA

- L-type calcium channel blockers dilate the resistance arterioles
- Cilnidipine also acts on N-type calcium channels, and may dilate venules through its effect on the sympathetic receptor



Edema (swelling) of the ankles and feet



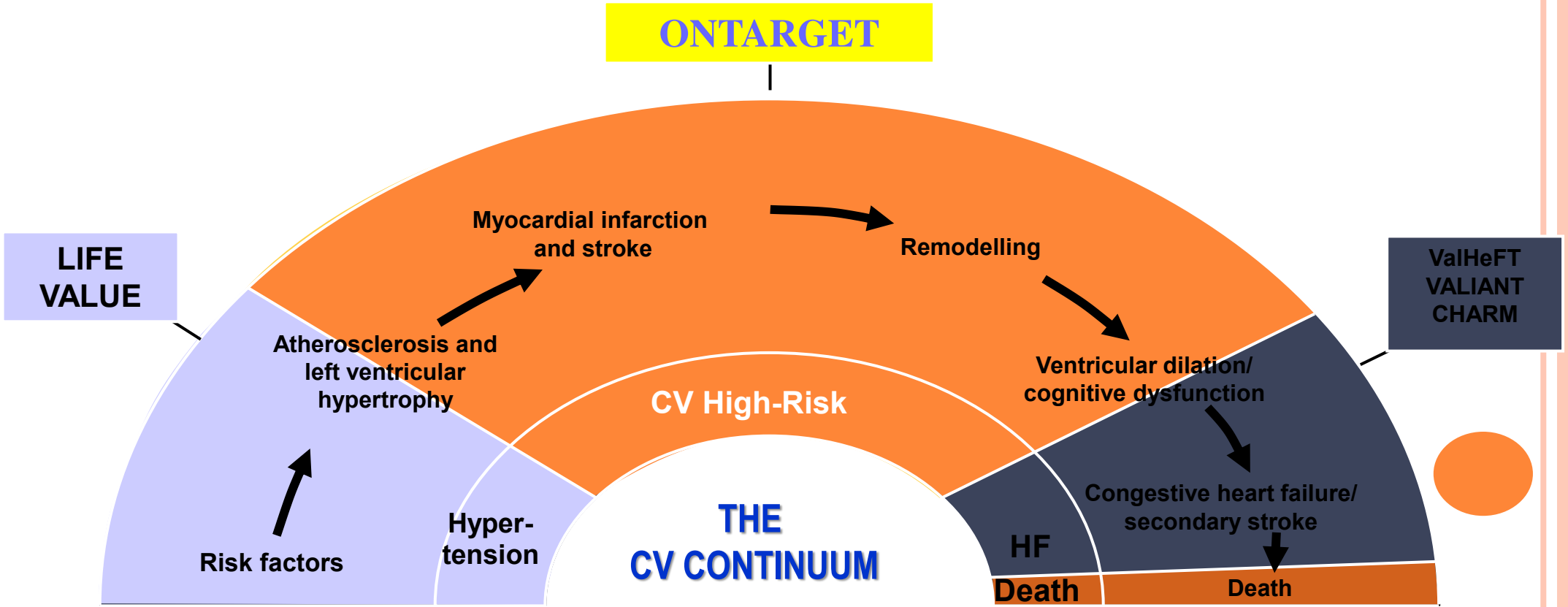
- *J Cardiovasc Pharmacol. 2004 Dec;44(6):672-5*

RAAS -SYSTEM

ARB's

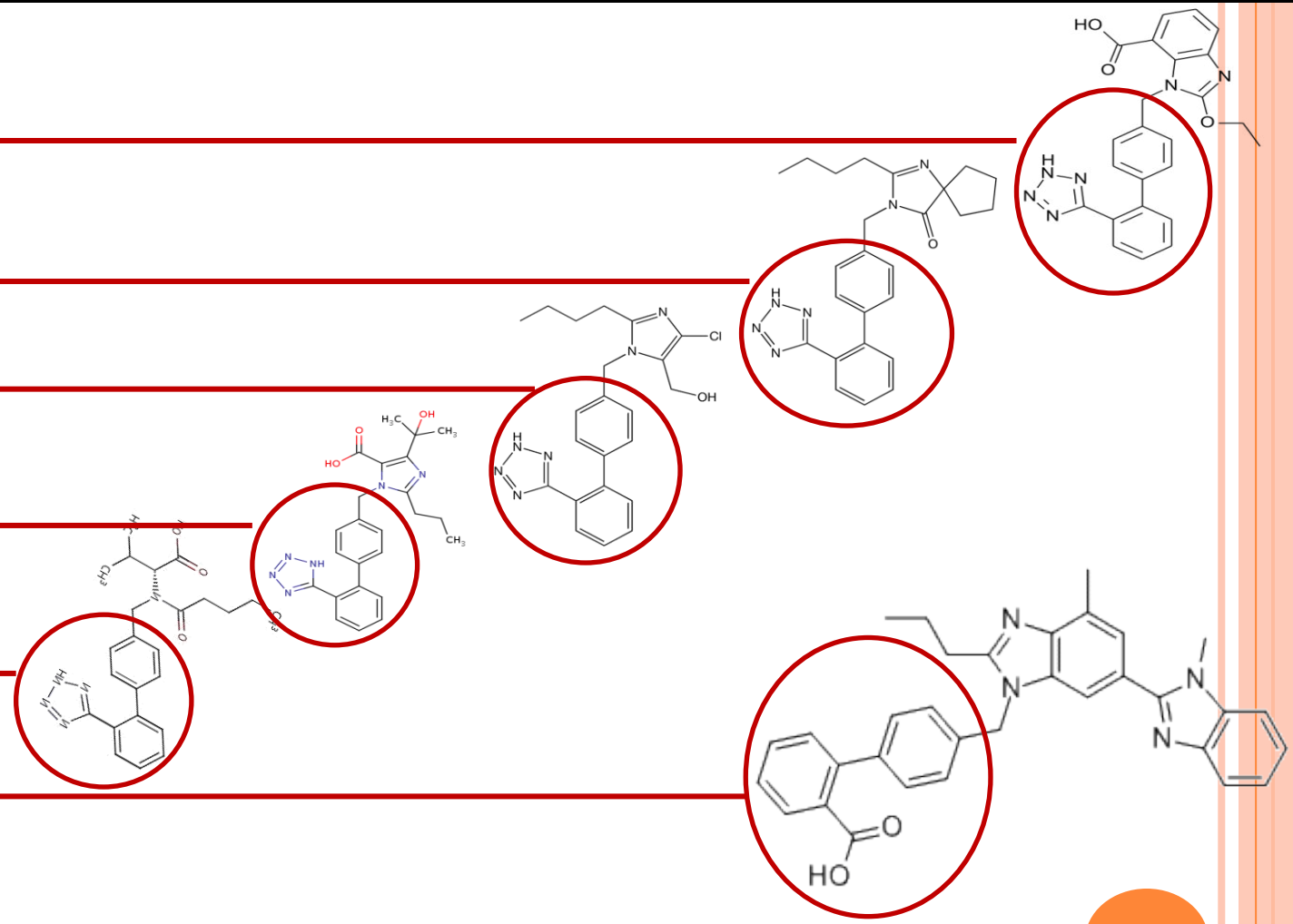
The Mainstay in management of

HYPERTENSIO

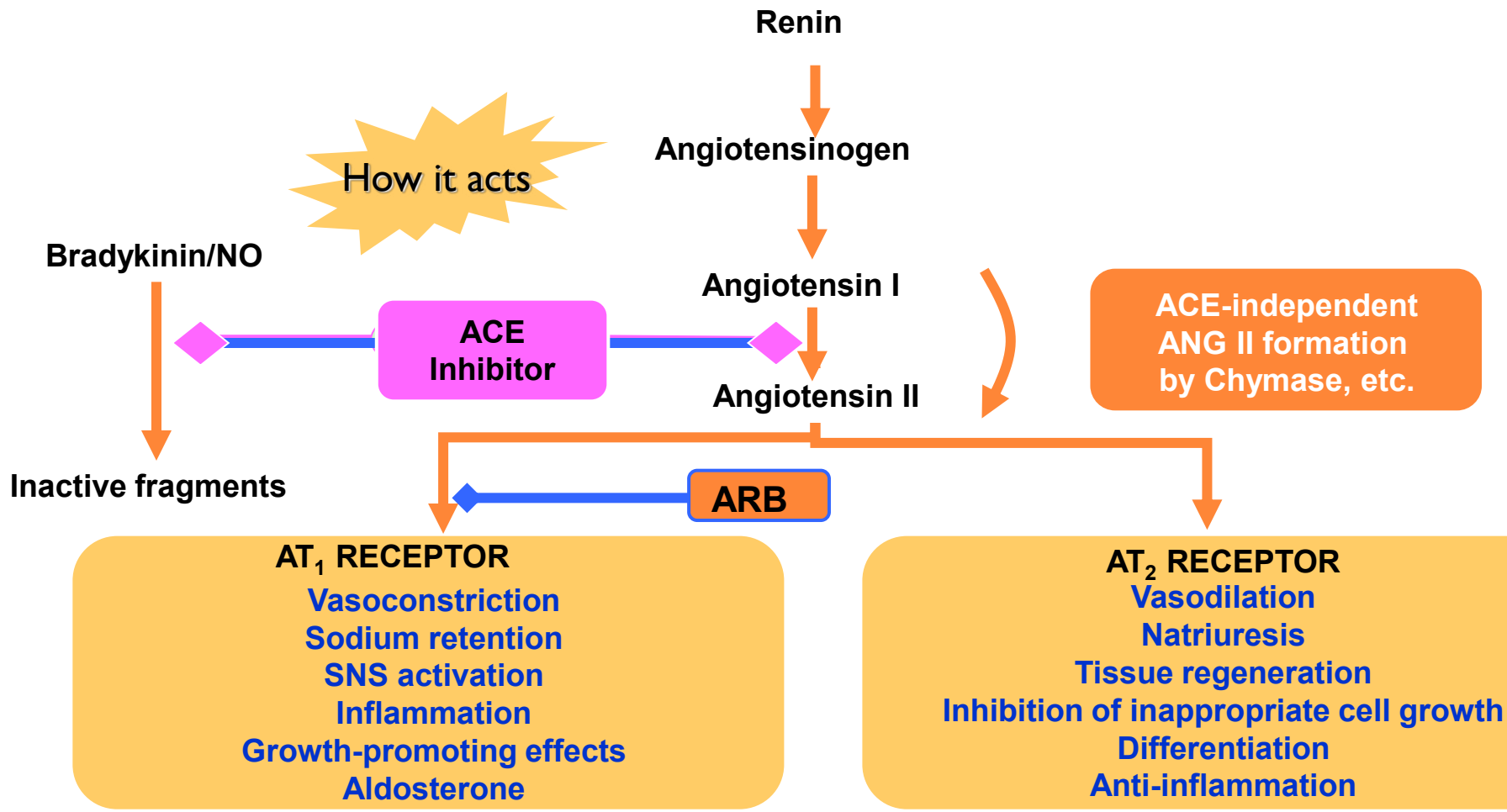


The ARB Siblings

- Candesartan
- Irbesartan
- Losartan
- Olmesartan
- Valsartan
- Telmisartan



The ARBs Effectively Reduces BP



Telmisartan: The Superior ARB

- Highly selective AT1 receptor blocker
- Telmisartan has 3000 fold greater affinity for AT1 receptor than for AT2 receptors
- AT1 receptor affinity – 1000 fold greater with Losartan

- Blocking of Telmisartan to AT1 receptors is insurmountable (high ATII concentrations , were unable to overcome the receptor blockade) but is reversible

- Slow dissociation from the receptors contributes to its long lasting effects
-

Continued……

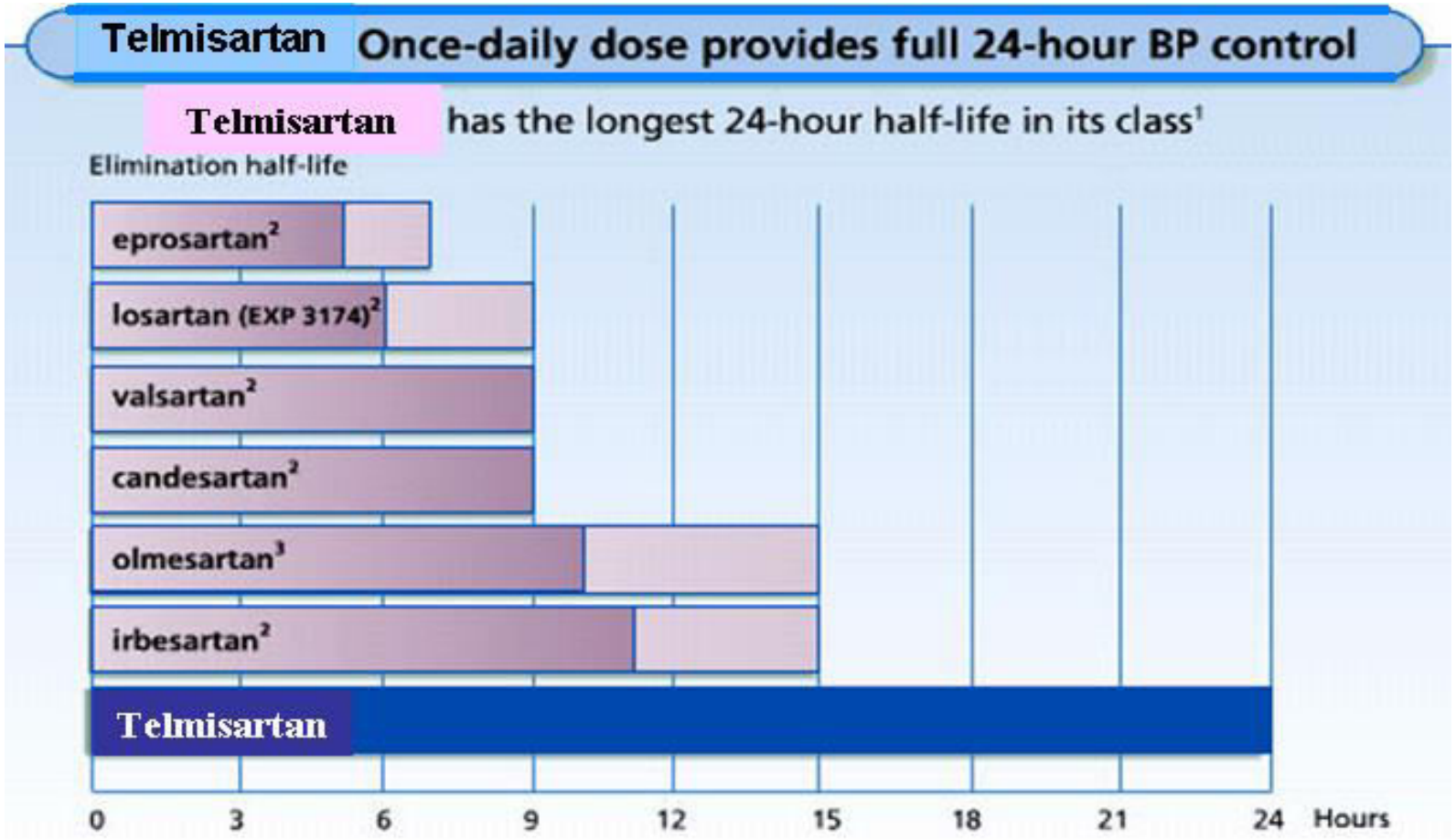
. Lowers Blood sugar level- by improving insulin sensitivity

Reduces serum cholesterol(mainly LDL cholesterl)

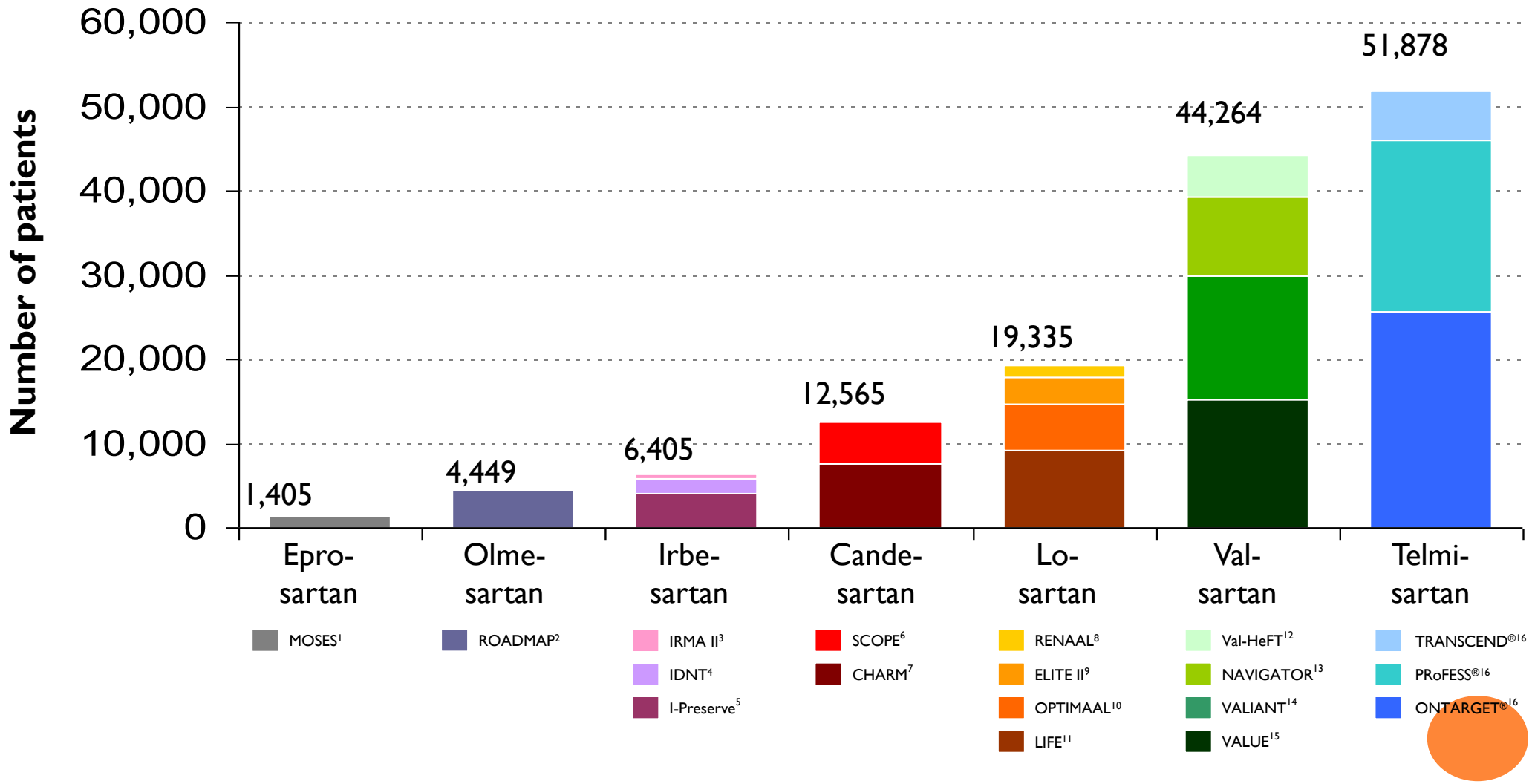
ENHANCES ENDOTHELIAL FUNCTIONS

BOOSTS MITOCHONDRIAL ACTIVITY

Telmisartan: 24 Hour Blood Pressure Control

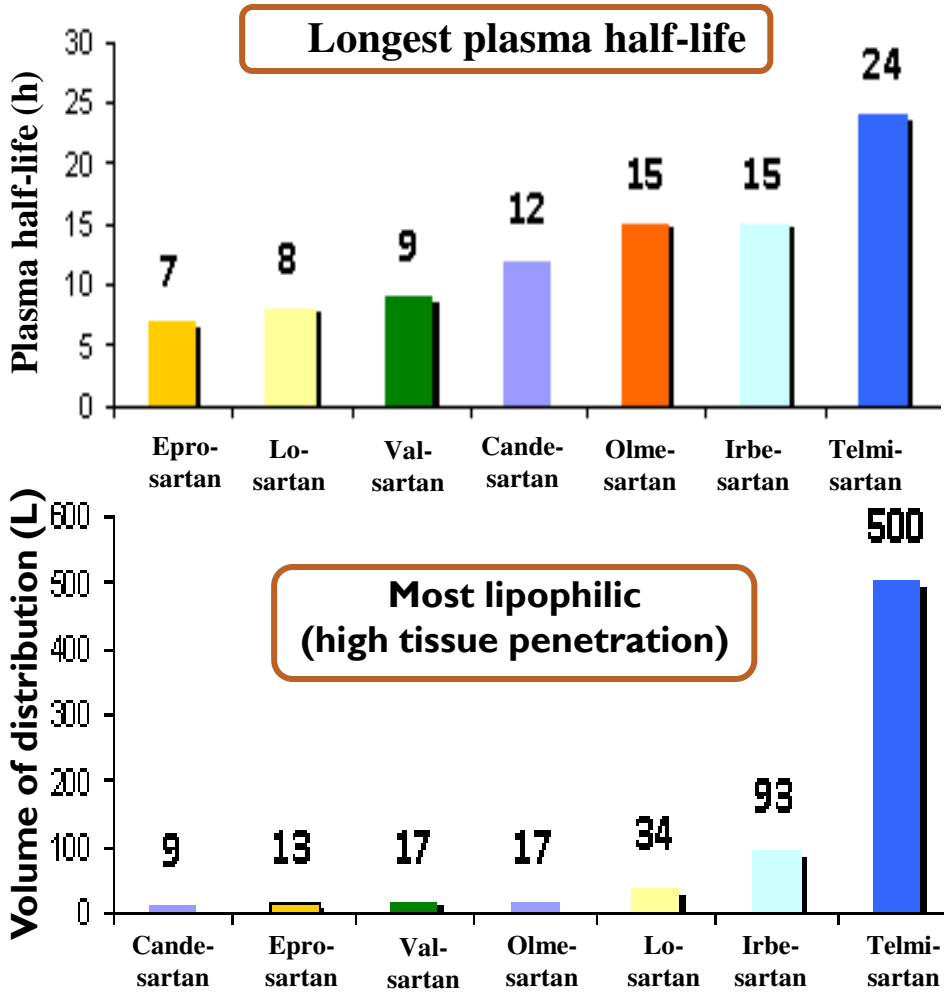


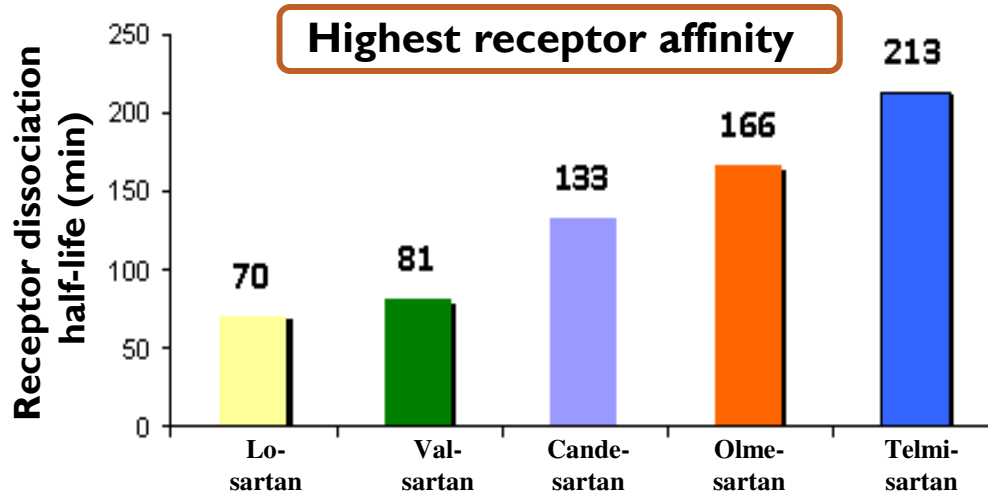
Telmisartan is the Most Studied Amongst ARBs in Mortality and Morbidity Endpoint Trials

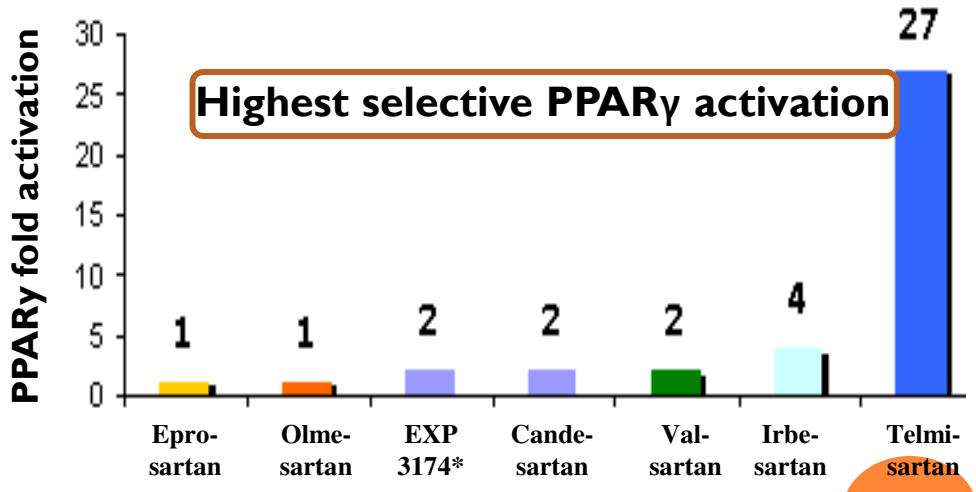


1. Schrader et al. *Stroke.* 2005;36:1218–1226; 2. http://www.roadmapstudy.org/resident.aspx; 3. Parving et al. *N Engl J Med.* 2001;345:870–878; 4. Lewis et al. *N Engl J Med.* 2001;345:851–860; 5. Carson et al. *J Card Fail.* 2005;11:576–585; 6. Papademetriou et al. *J Am Coll Cardiol.* 2004;44:1175–1180; 7. www.atacand.com; 8. Brenner et al. *N Engl J Med.* 2001;345:861–869; 9. Pitt et al. *Lancet.* 2000;355:1582–1587; 10. Dickstein et al. *Lancet.* 2002;360:752–760; 11. Dahlof et al. *Lancet.* 2002;359:955–1003; 12. Cohn et al. *N Engl J Med.* 2001;345:1667–1675; 13. www.novartis.com; 14. Pfeffer et al. *N Engl J Med.* 2003;349:1893–1906; 15. Julius et al. *Lancet.* 2004;363:2022–2031; 15. www.ontarget-micardis.com.

Telmisartan: Unique Pharmacology Profile







ONTARGET

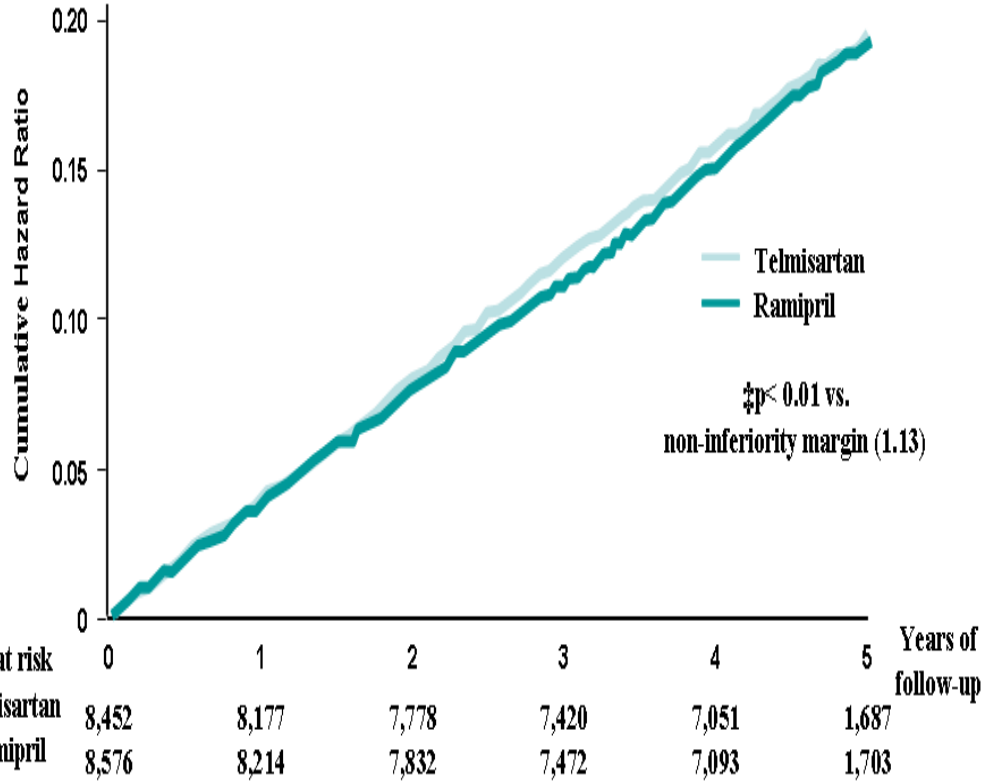
The ONgoing Telmisartan Alone &
in combination with Ramipril Global Endpoint Trial

Start Date: 01/01/2003 **End date: 30/09/2008**

The ONTARGET Investigators et.al, n engl j med 358;15, Apr 2008, 1547-59

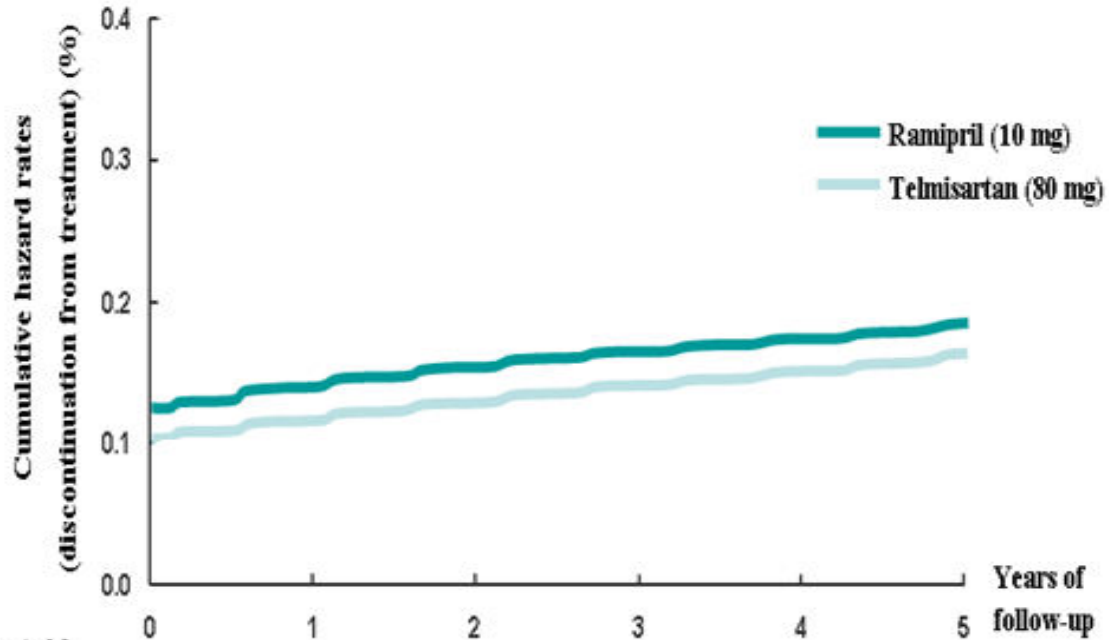
Telmisartan reduces CV events & is better tolerated than Ramipril in CV high-risk patients

Reduction in composite CV risk



No. at risk	0	1	2	3	4	5
Telmisartan	8,452	8,177	7,778	7,420	7,051	1,687
Ramipril	8,576	8,214	7,832	7,472	7,093	1,703

Reduction in discontinuation of treatment



n at risk	0	1	2	3	4	5
Telmisartan	8,542	7,954	7,384	6,909	6,478	
Ramipril	8,576	7,796	7,165	6,681	6,254	

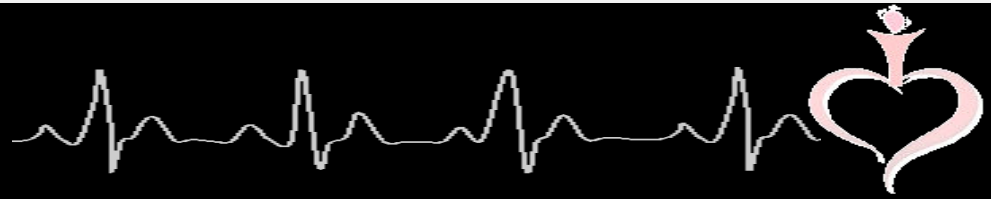
The ONTARGET Investigators et.al, n engl j med 358;15, Apr 2008, 1547-59

Telmisartan: ONTARGET® trial summary

Parameter	Telmisartan	Ramipril
% patients with Primary outcome (Death from CV causes, MI, stroke, or hospitalization from heart failure)	16.5	16.7
Death from any cause	11.6	11.8

- Telmisartan demonstrated long term CV protection similar to reference standard Ramipril, in a broad range of high-risk patients.
- Results demonstrate the CV protective effects of Telmisartan beyond BP reduction
- Telmisartan was also better tolerated, with fewer discontinuations than Ramipril.

The ONTARGET Investigators et.al, n engl j med 358;15, Apr 2008, 1547-59



Telmisartan effective in LV hypertrophy regression in hypertensive patients

- 85 hypertensive patients (SBP >140 mmHg, DBP >90 mmHg) & mild-to-moderate LV hypertrophy treated with Telmisartan monotherapy 40-80 mg once daily for 1 year.
- SBP & DBP were reduced from 144+/-10 to 126+/-8 mmHg ($p<0.001$) & from 98+/-8 to 86+/-7 mmHg ($p<0.001$), respectively.
- The LVMI was decreased from 119+/-7 to 109+/-3 g/m2 ($p<0.001$) after 12 months' Telmisartan treatment.

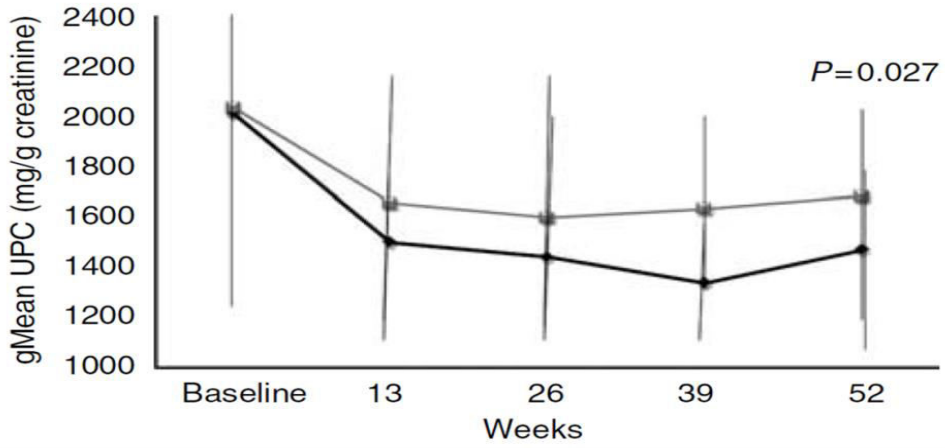
Telmisartan 40-80 mg is effective in LV hypertrophy regression in hypertensive patients.

Reduction in LVMI due to Telmisartan monotherapy was associated with a significant improvement of diastolic filling parameters & with a significant reduction of LA volumes.

Int J Cardiol 2004 Dec;97(3):383-8.

AMADEO TRIAL

- **Patients -** 1567 patients of uncontrolled hypertension with diabetic nephropathy
  Centers - 124 centers all over the world.
- **Treatment** - Telmisartan 80 mg OD Losartan 100 mg OD
- **Duration:** 52 weeks
- **Primary endpoint:** mean urinary albumin to-creatinine (UPC)

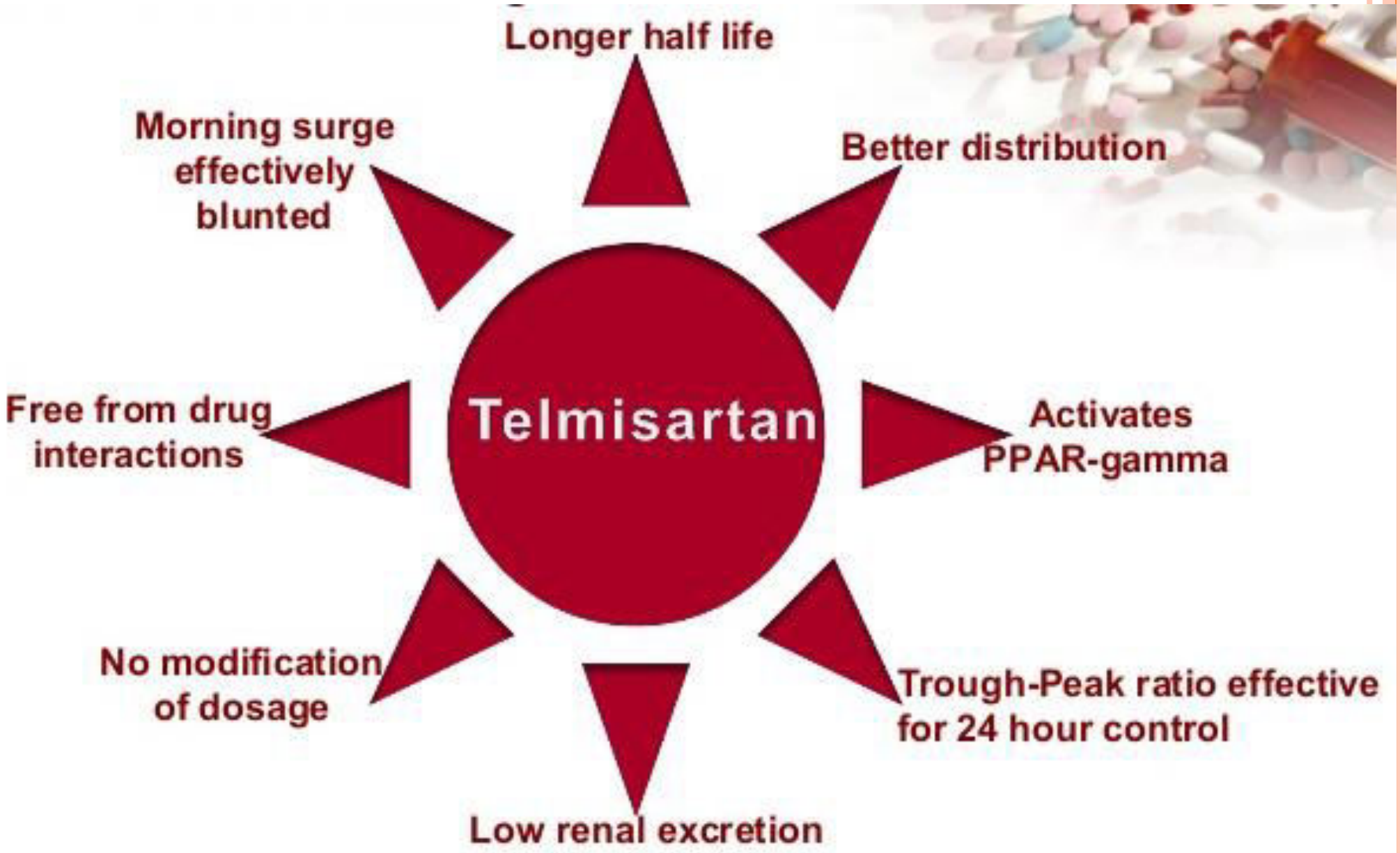


Greater Reduction in Proteinuria With Telmisartan

Telmisartan is superior to losartan in reducing proteinuria in hypertensive patients with diabetic nephropathy

AMADEO: A comparison of Telmisartan versus los**A**rtan in hypertensive type 2 **D**iab**E**tic patients with **O**vert nephropathy

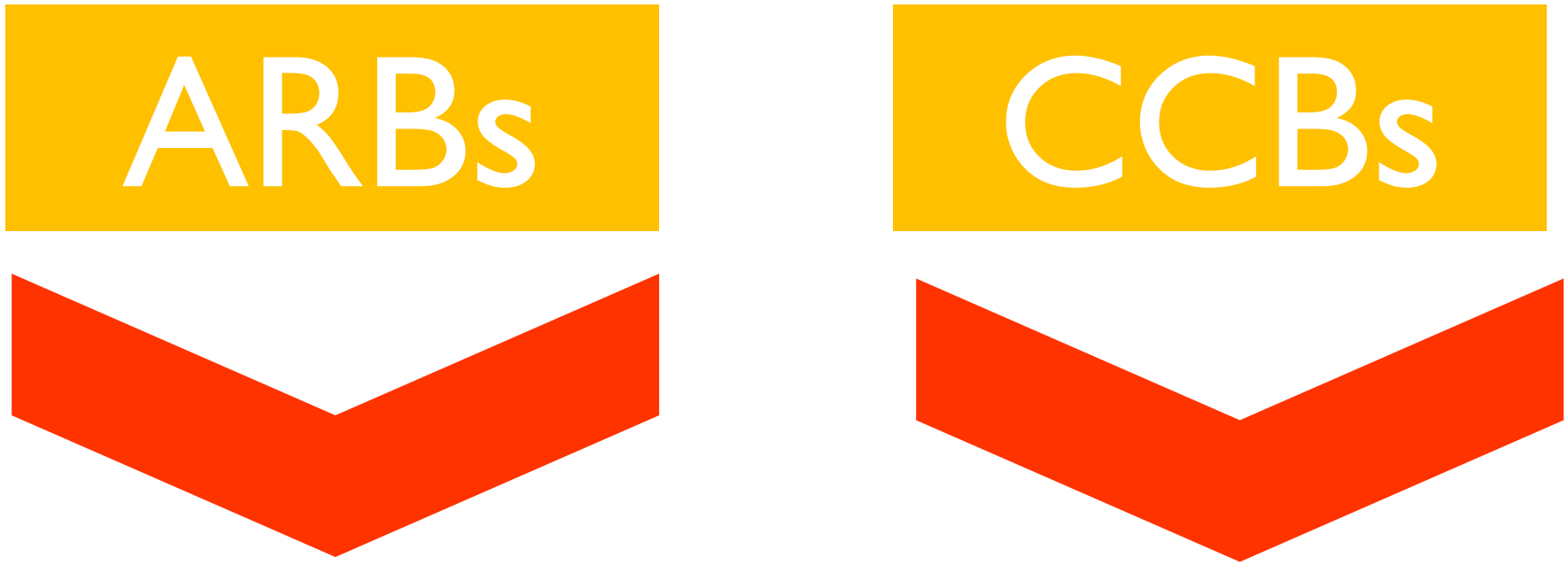
Kidney International (2008) 74, 364–369



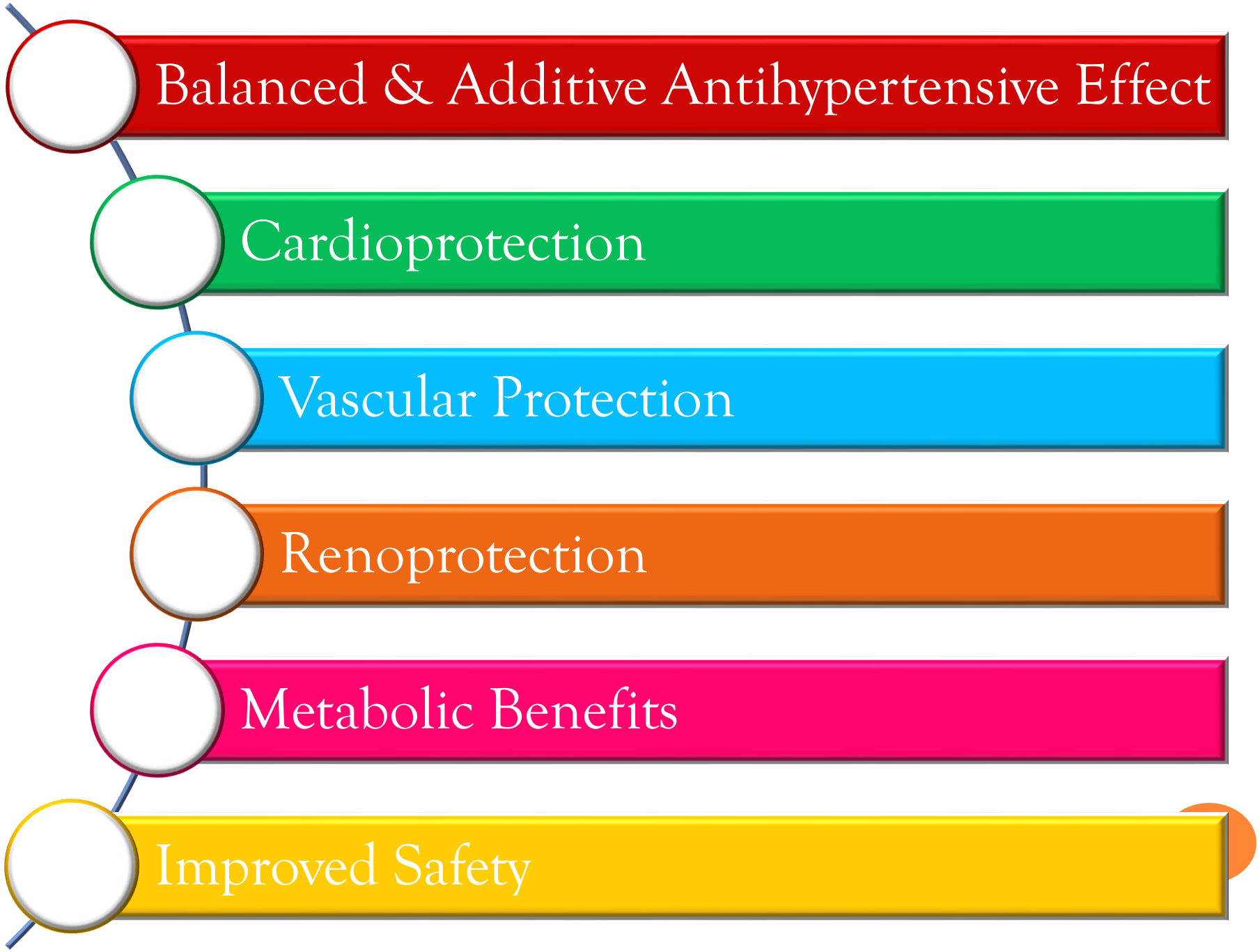
Telmisartan is indicated for cardiovascular prevention beyond that of blood pressure-lowering alone.

Beevers et al. BMJ 2001;322:912–916

COMBINING THE BEST IN CLASS



A Combination Therapy Offers..



SUMMARY

- **Many hypertensives needs combination of 2 or more drugs, & the combination of a CCB + ARB is commonly preferred**
- **Telmisartan is a RAAS inhibitor & Cilnidipine is L/N calcium channel blocker.**
- **Both lower BP through different mechanisms, which ensures balanced & additive antihypertensive effect.**
- **Offers superior 24-hr BP reduction across different hypertensive subgroups, with lesser BP variability.**
- **Ideal combination for management of hypertension patients with diabetes or metabolic syndrome or patients who are obese as both agents exhibit metabolic benefits.**


Thank You!!!