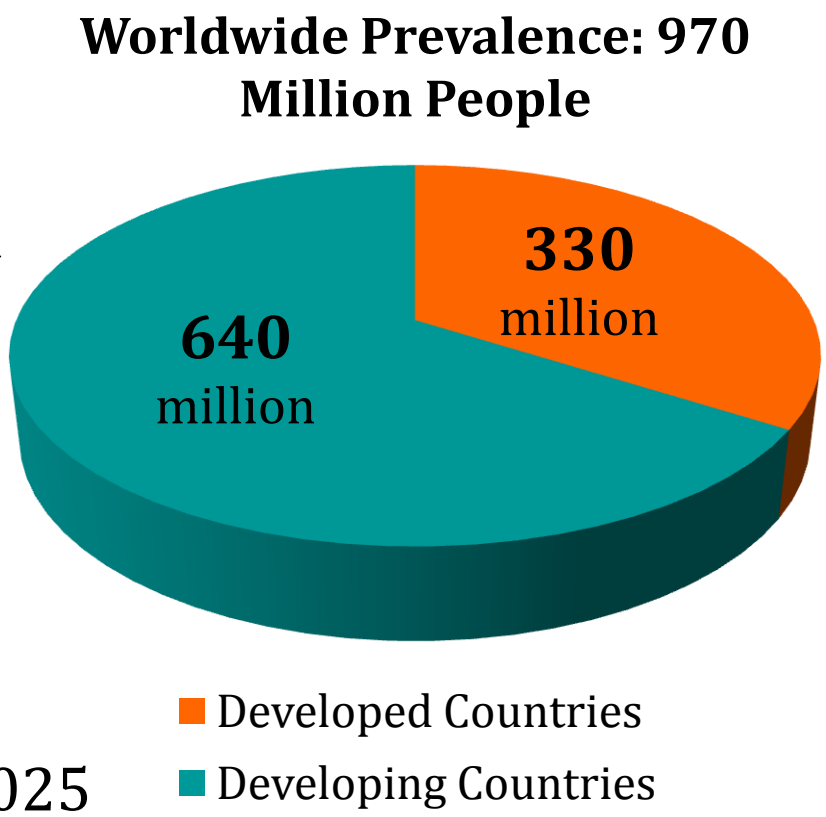
Azilsartan

Hypertension

Global and Indian Prevalence

Hypertension Burden

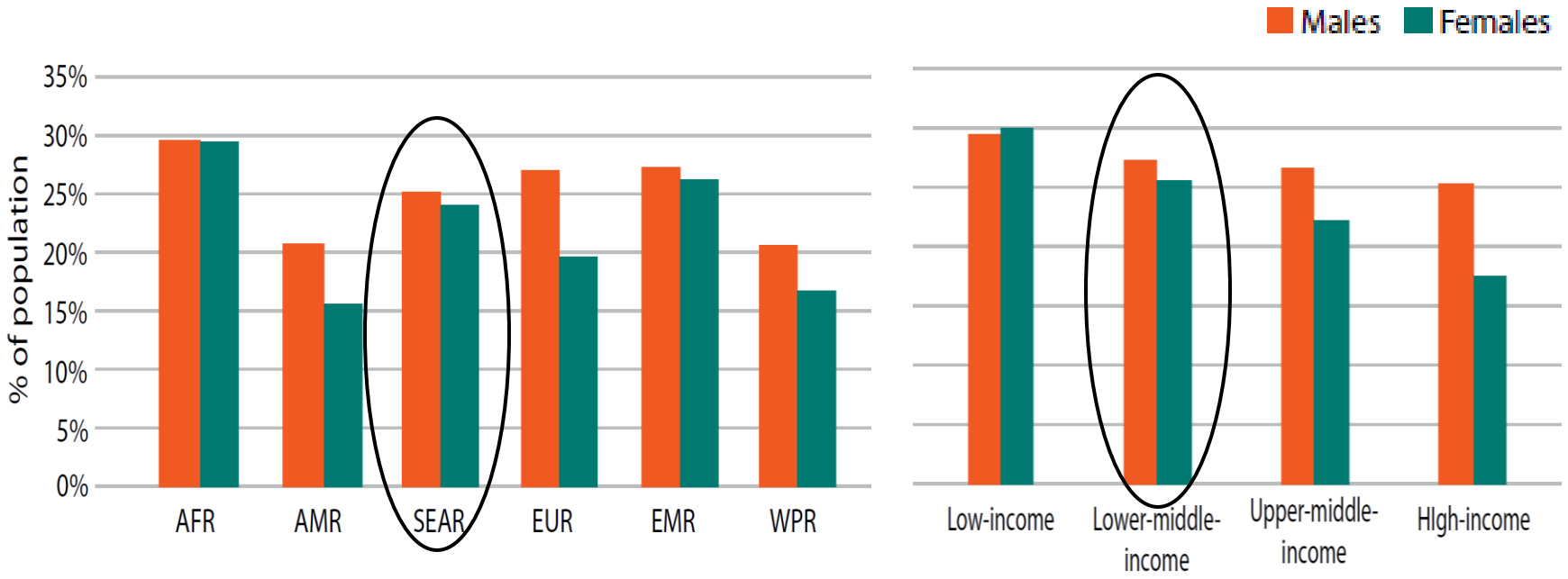
- Silent Invisible killer.
- One of the major contributors of CV morbidity and mortality
- Worldwide Prevalence: 970 million
- Expected to affect 1.56 billion adults with hypertension by 2025



Delacroix, *et al., J Neurol Neurophysiol* 2014, 5:6

Hypertension: WHO Estimates

- The global prevalence of raised blood pressure is ≈22%.
- Across the WHO regions, it is highest in Africa (30%).



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

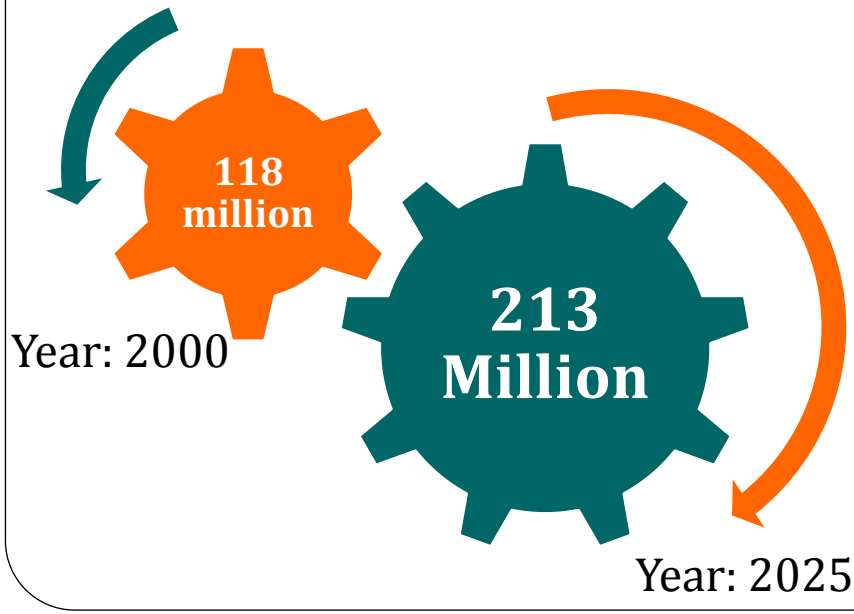
Global Status Report, 2014. Apps.WHO.int.

Hypertension In India

- Third most risk factor for attributable burden of disease in South Asia.
- 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

Hypertension In India

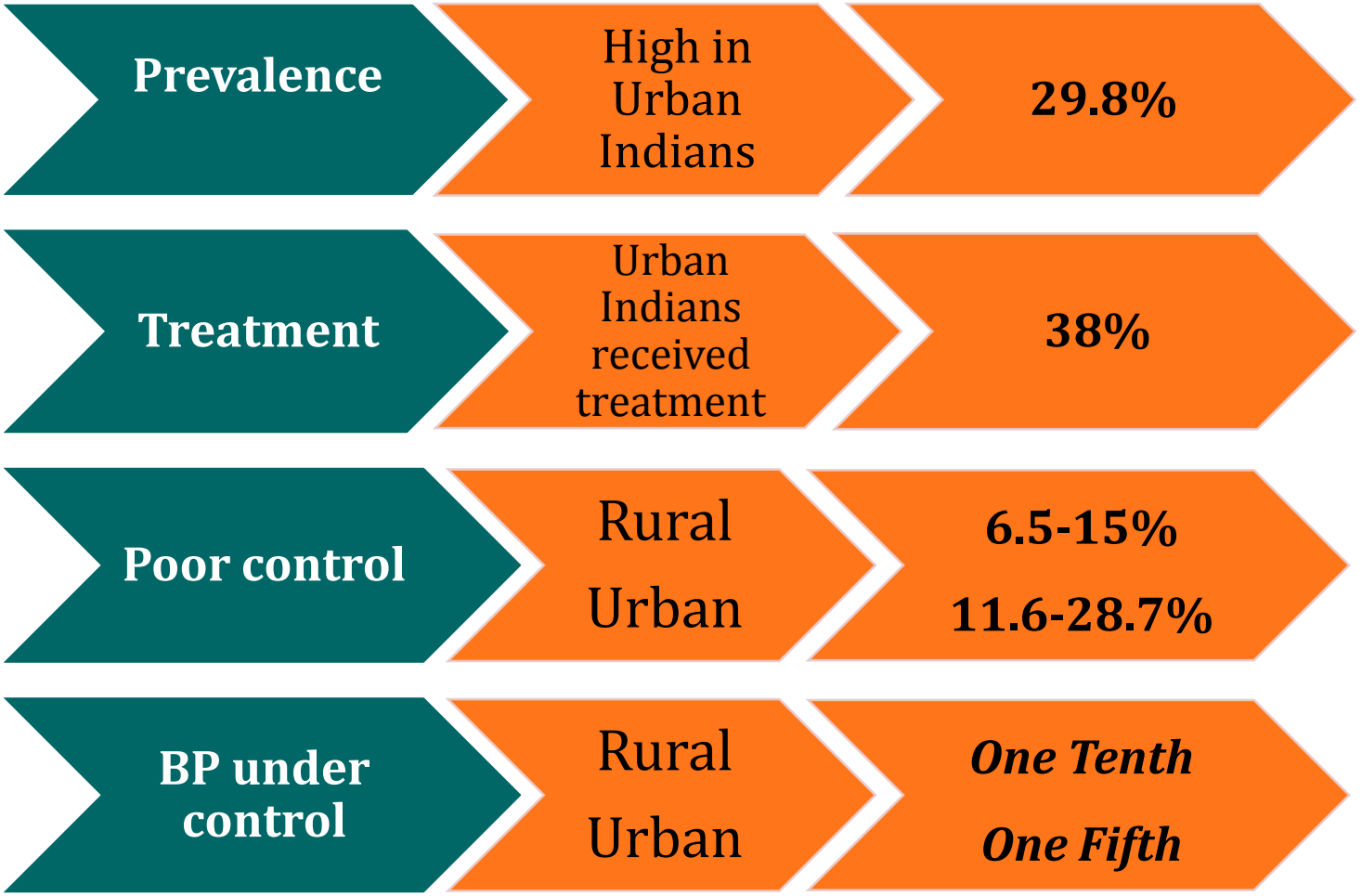
- The prevalence of hypertension in India as per the global status report on non-communicable diseases

Table 1: Estimates of Prevalence of Raised Blood Pressure (Population aged 18+ years)					
Crude Adjusted Estimates for SBP ≥ 140 and/or DBP ≥90					
Males	95% CI	Females	95% CI	Both Sexes	95% CI
25.9	18.1 – 34.4	24.8	17.4 – 32.9	23.4	20.4 – 30.5
Age Standardized Adjusted Estimates SBP ≥ 140 and/or DBP ≥ 90					
23.4	16.2 – 31.5	22.6	15.6 – 30.4	23.0	18.1 – 28.7

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

Hypertension In India

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

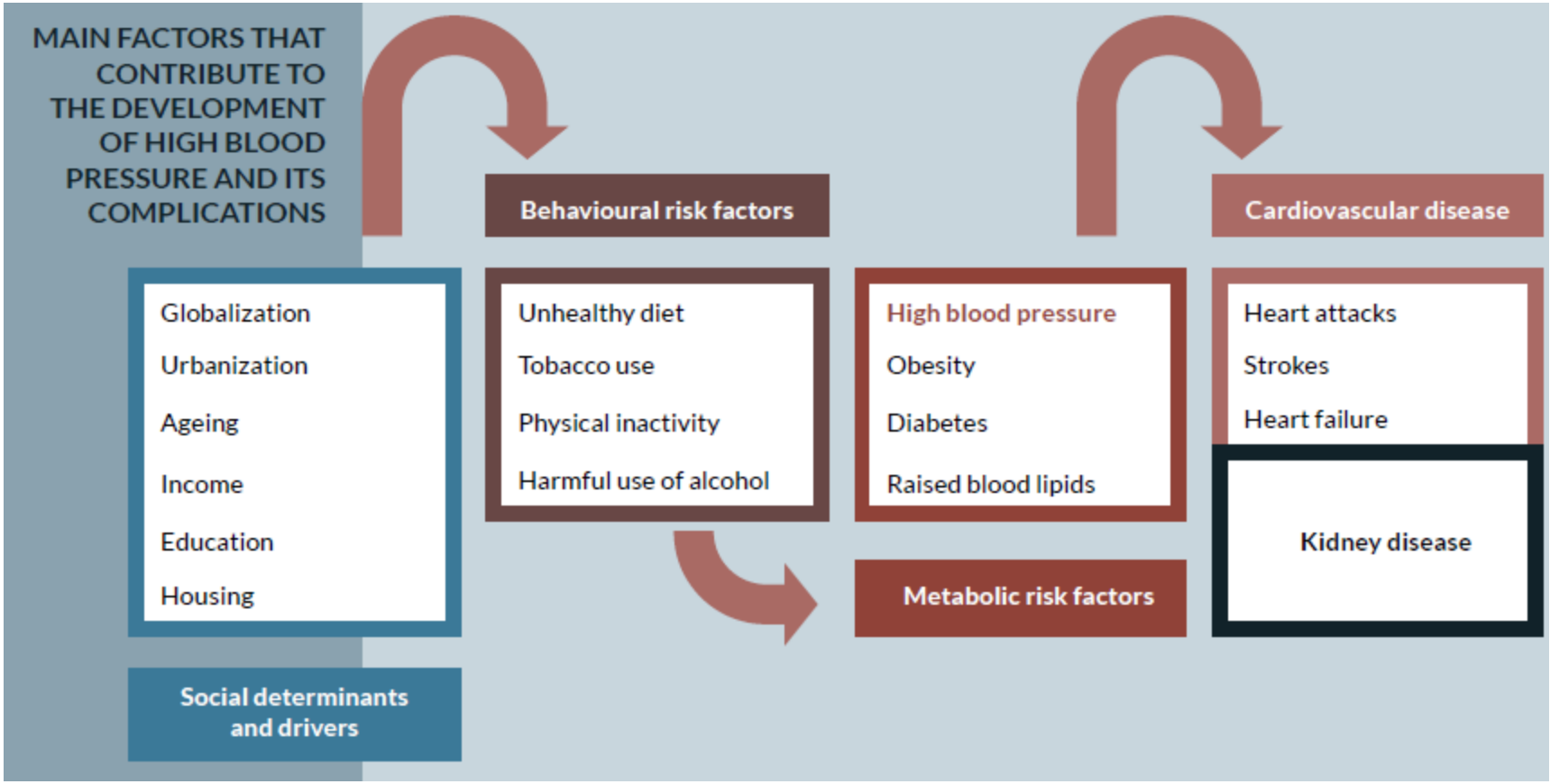


Anchala R *et al. J Hypertens.* 2014; 32(6):1170-77.

Hypertension

Current Challenges

Current Challenges in Hypertension Control



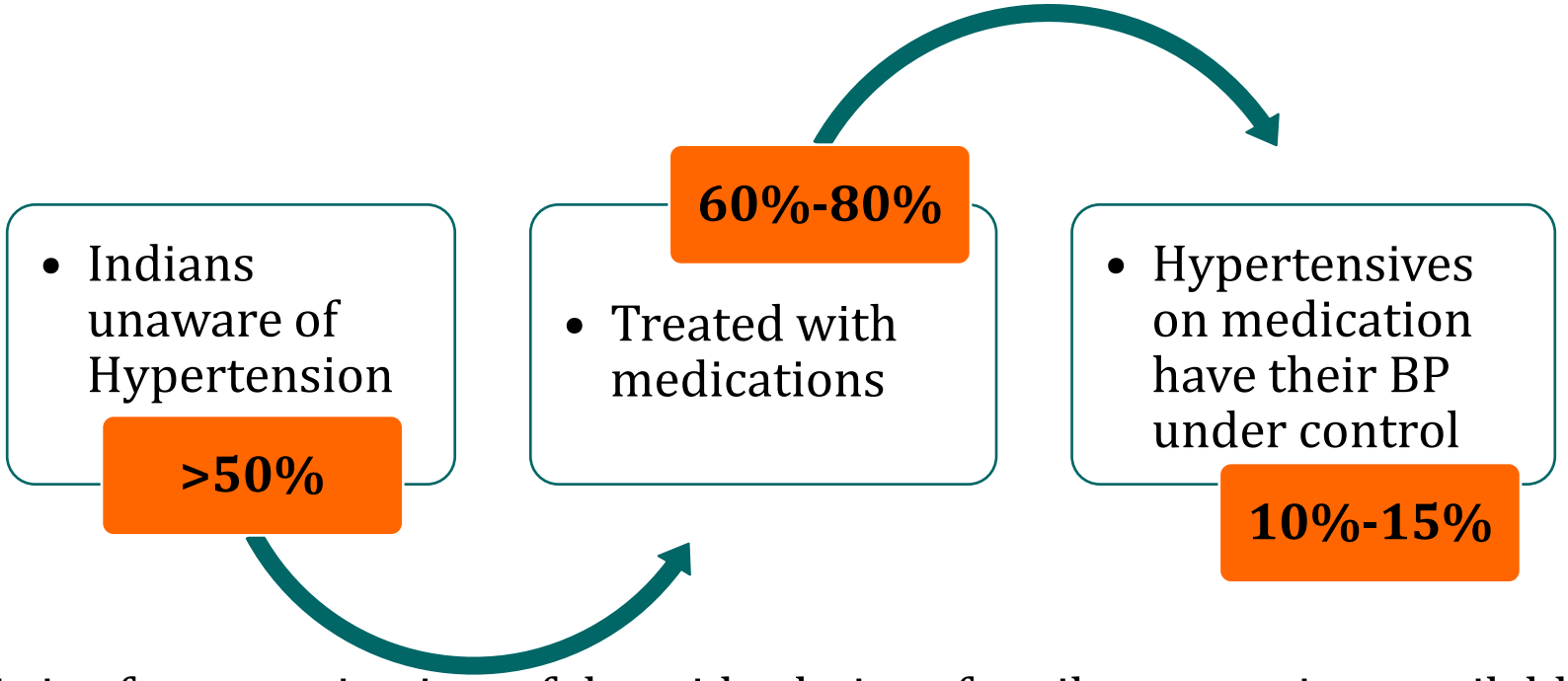
In addition, there are several metabolic factors that increase the risk of heart disease, stroke, kidney failure and other complications of hypertension, including diabetes, high cholesterol and being overweight or obese. Tobacco and hypertension interact to further raise the likelihood of cardiovascular disease

Who.int. WHO/ A global brief on hypertension

Current Challenges in Hypertension Control

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

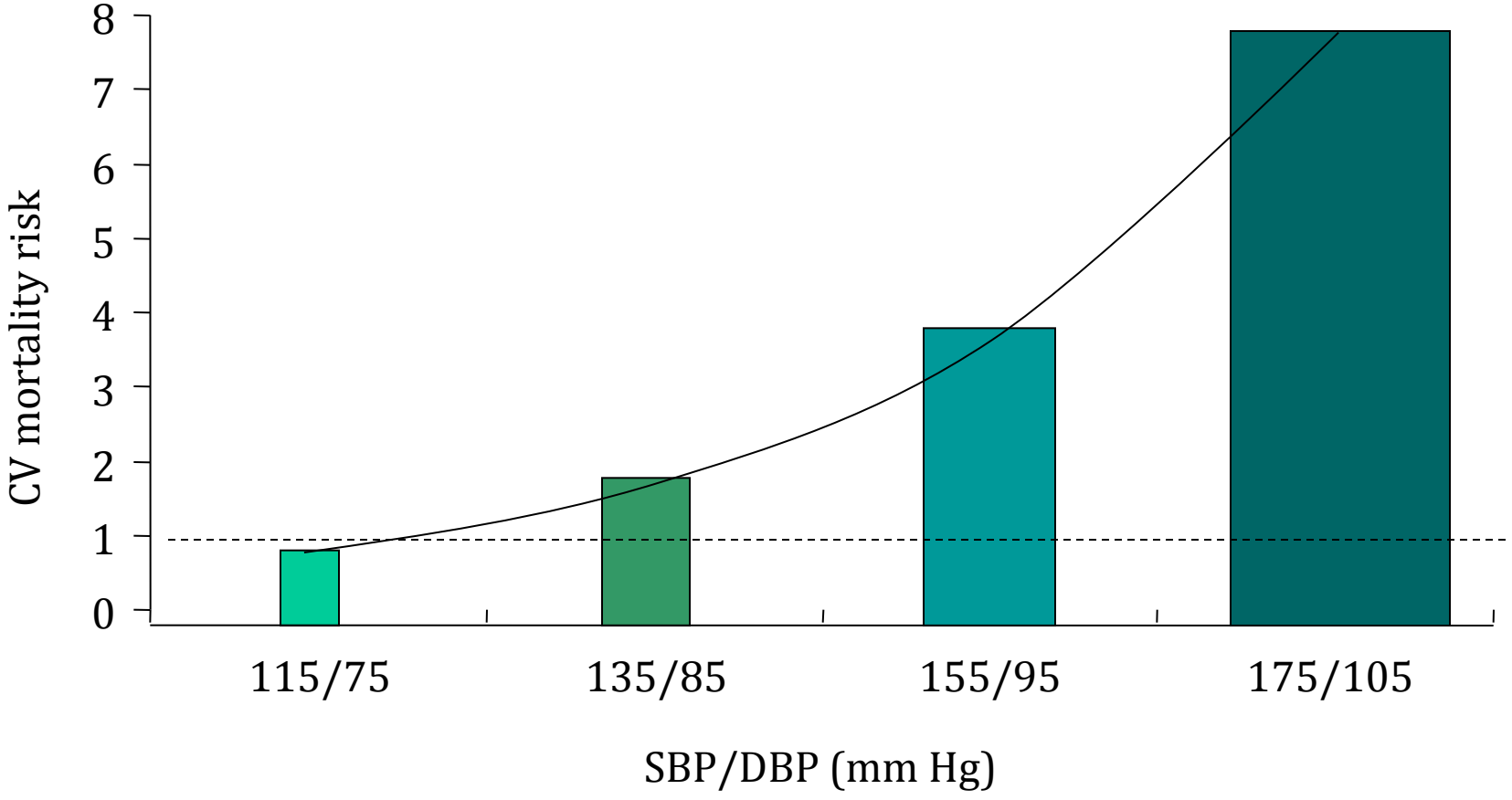
- Only 10%-15% of the hypertensives have their BP under control.



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

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



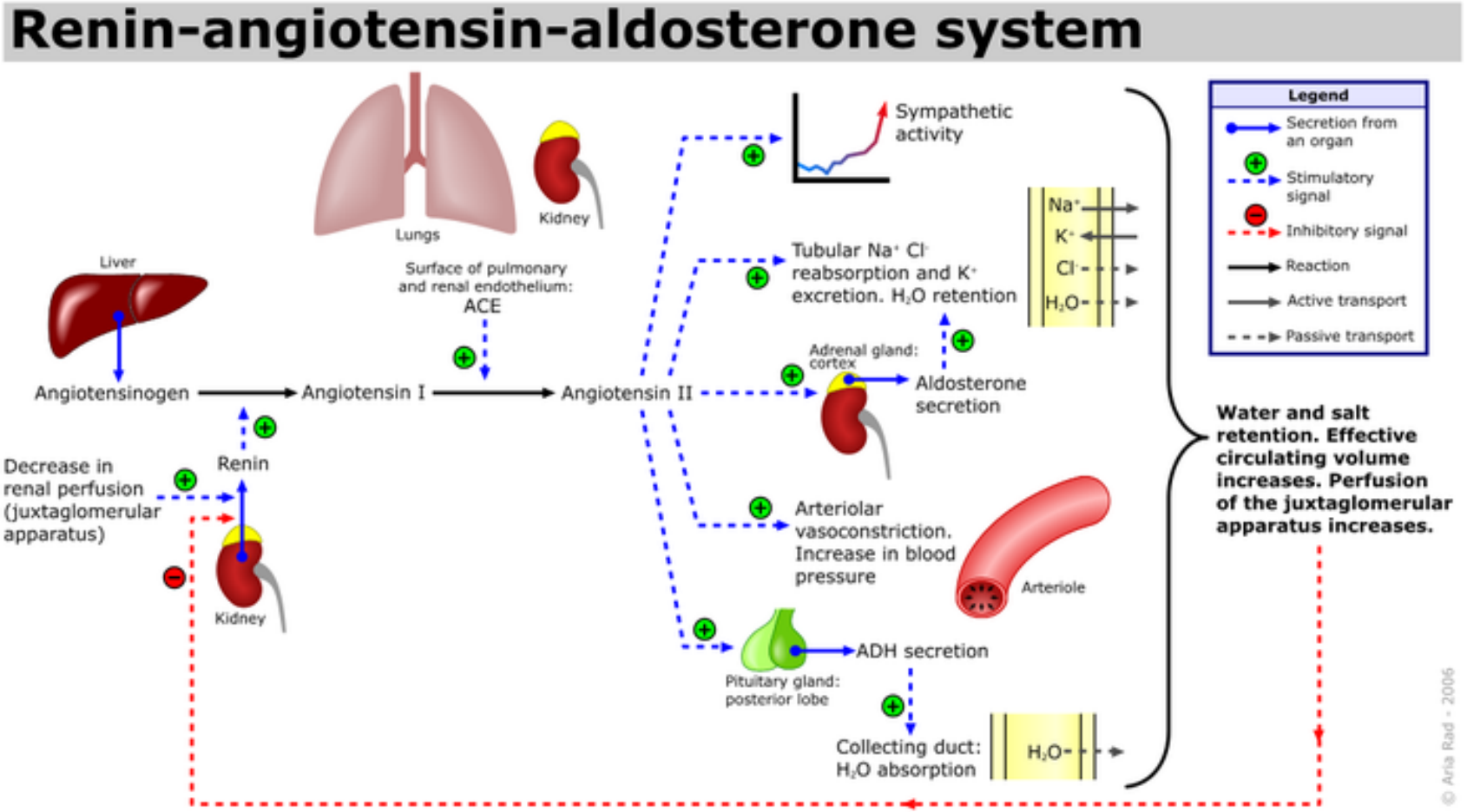
Assadi F *et al*. *Int J Prev Med.* 2014 Mar;5(Suppl 1):S4-9.

Hypertension

Role of ARBs

Role of RAAS in Hypertension Management

- Overactive RAAS is strongly linked to hypertension, as it regulates the hemodynamic equilibrium, circulating volume and electrolyte balance.

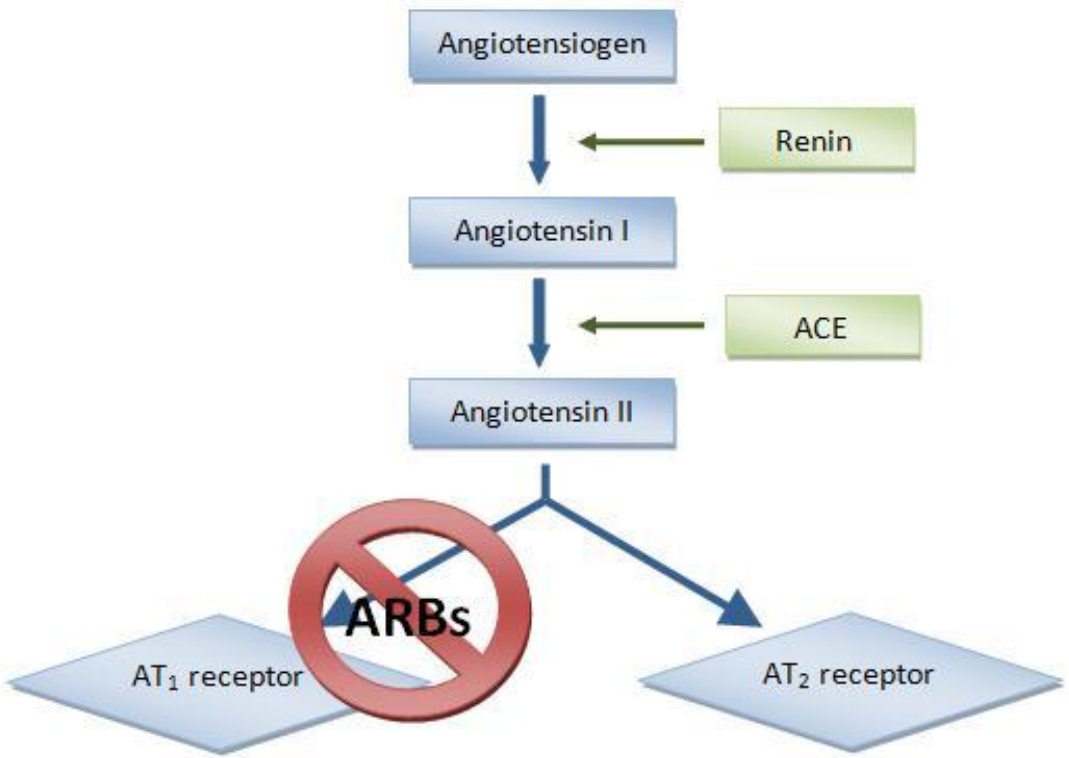


Ferrari R. Glob Cardiol Sci Pract. 2013 ;(3):34.

Role of ARBs in Hypertension Management

- ARBs have selective AT1 receptor antagonism and thereby reduce:
  - vasoconstriction,
  - sympathetic stimulation,
  - oxidative stress,
  - release of inflammatory factors and
  - aldosterone release.

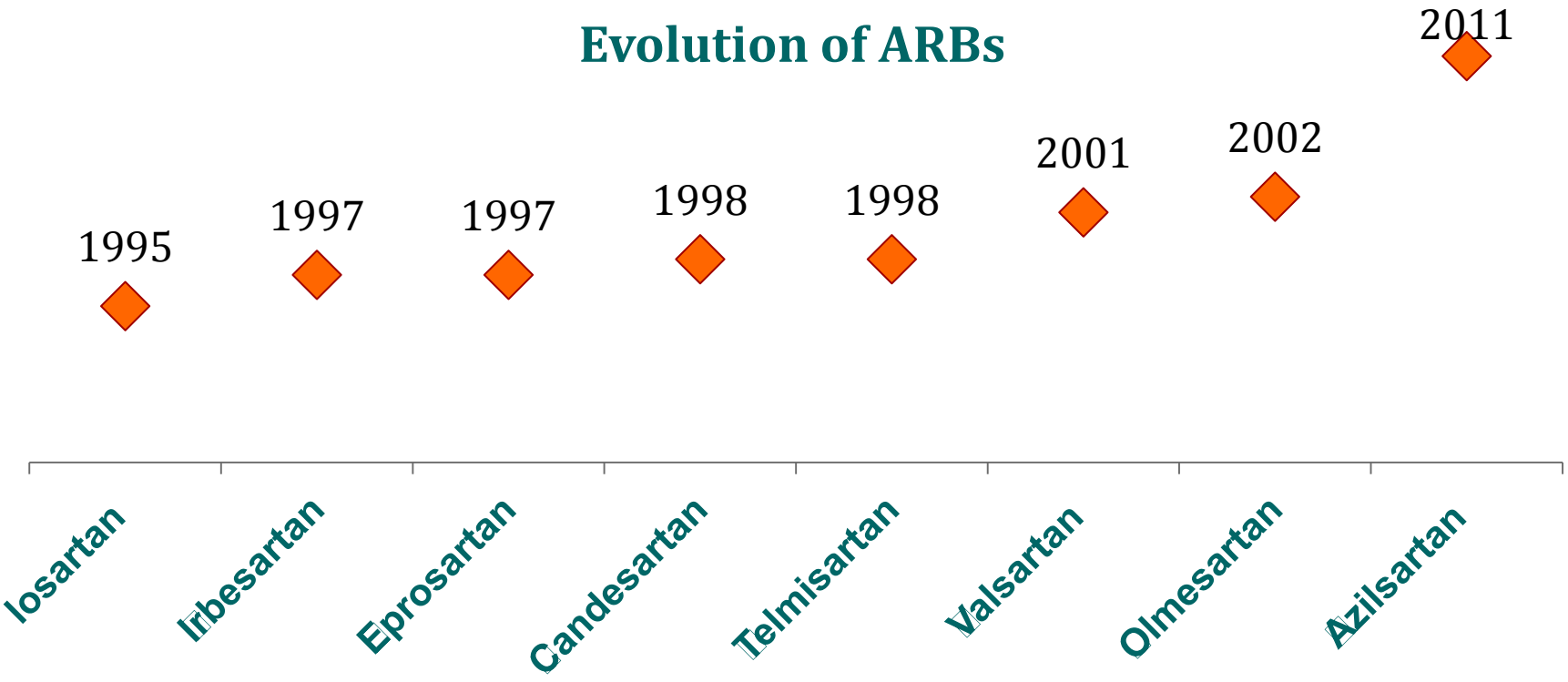
- ARBs lack angiotensin II escape which is seen in ACEIs.



Novo S, *et al.* Curr Drug Targets. 2009; 10(1):20-25.

History of ARBs

- In 1995 Losartan – First ARB approved by USFDA
- Azilsartan Medoxomil is the latest and the eighth ARB.



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

Are ALL ARB's same?

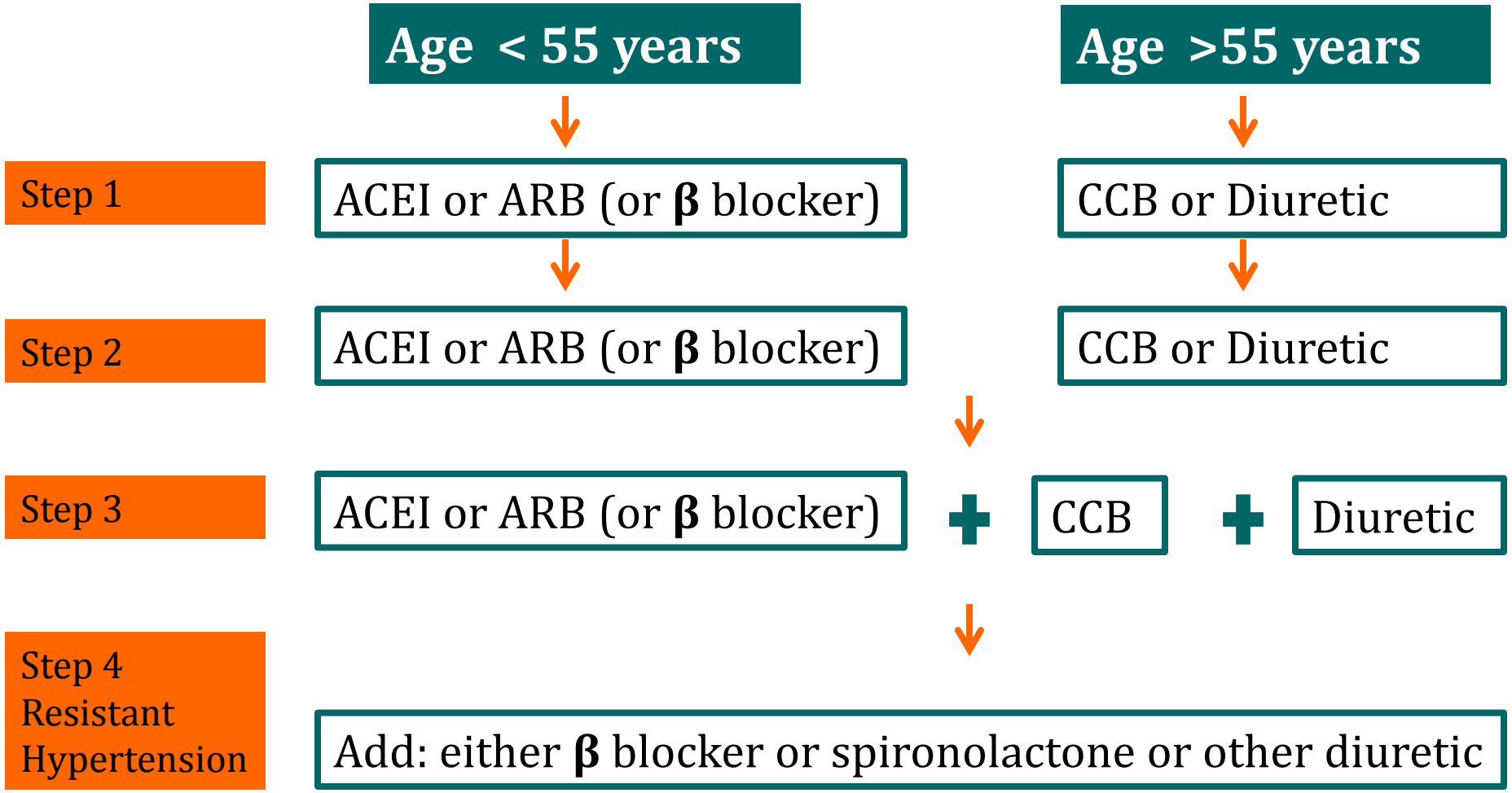
- As a class, ARBs are chemically similar but vital pharmacokinetic and pharmacodynamic differences exist between them.

- ARBs differ in the magnitude and duration of the antihypertensive response as well as in added protection of reducing cardiovascular risks: this has important implications in clinical practice

Hypertension

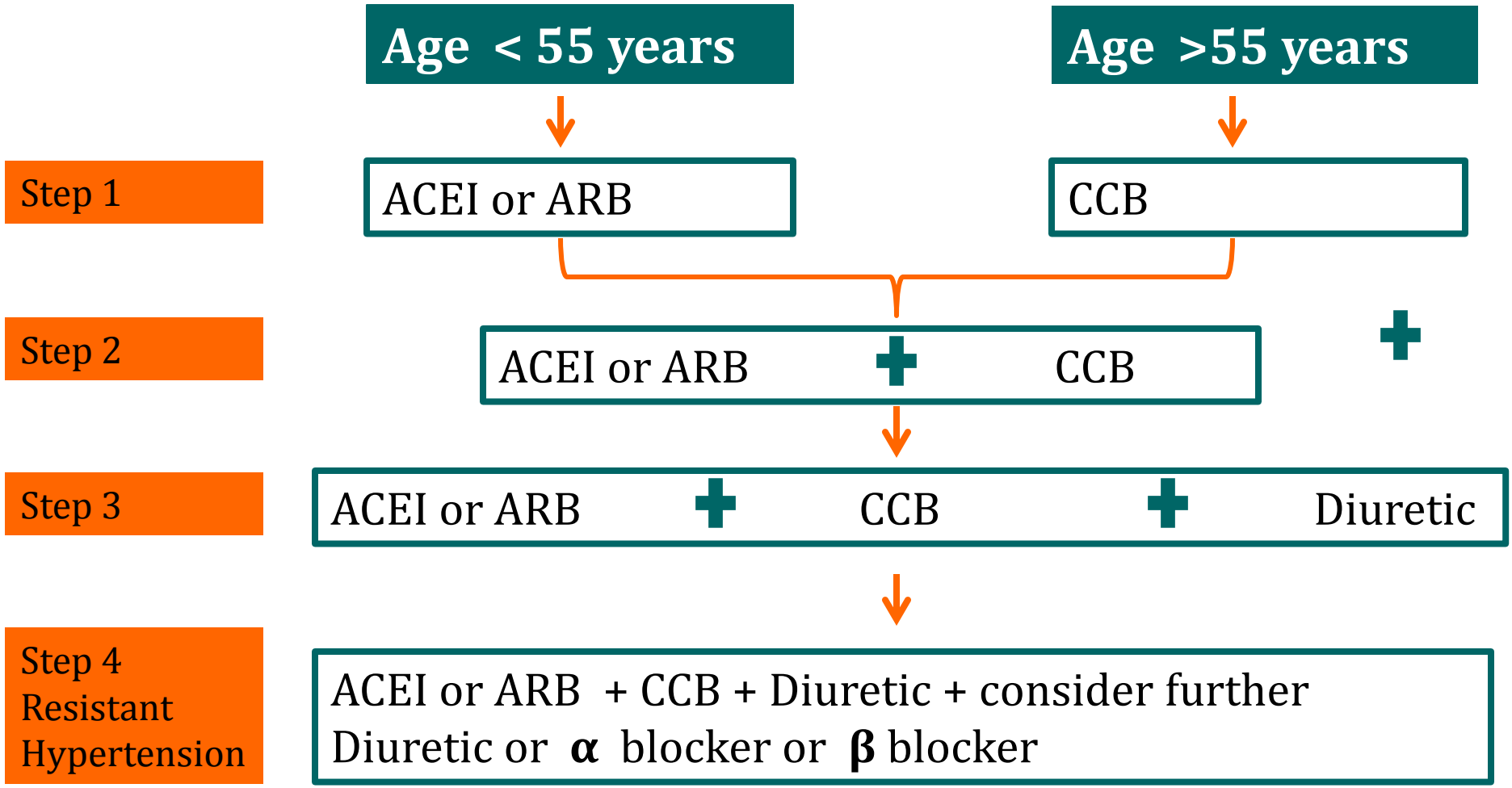
Guidelines

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

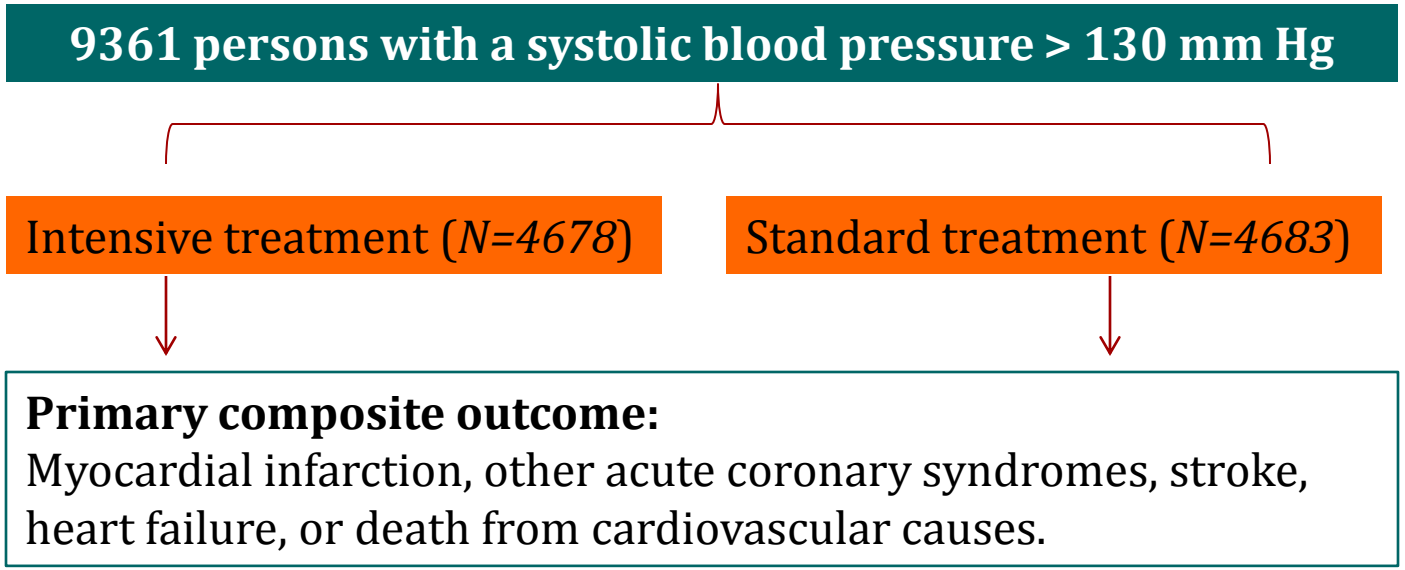
Hypertension

SPRINT Trial

Systolic Blood Pressure Intervention Trial

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

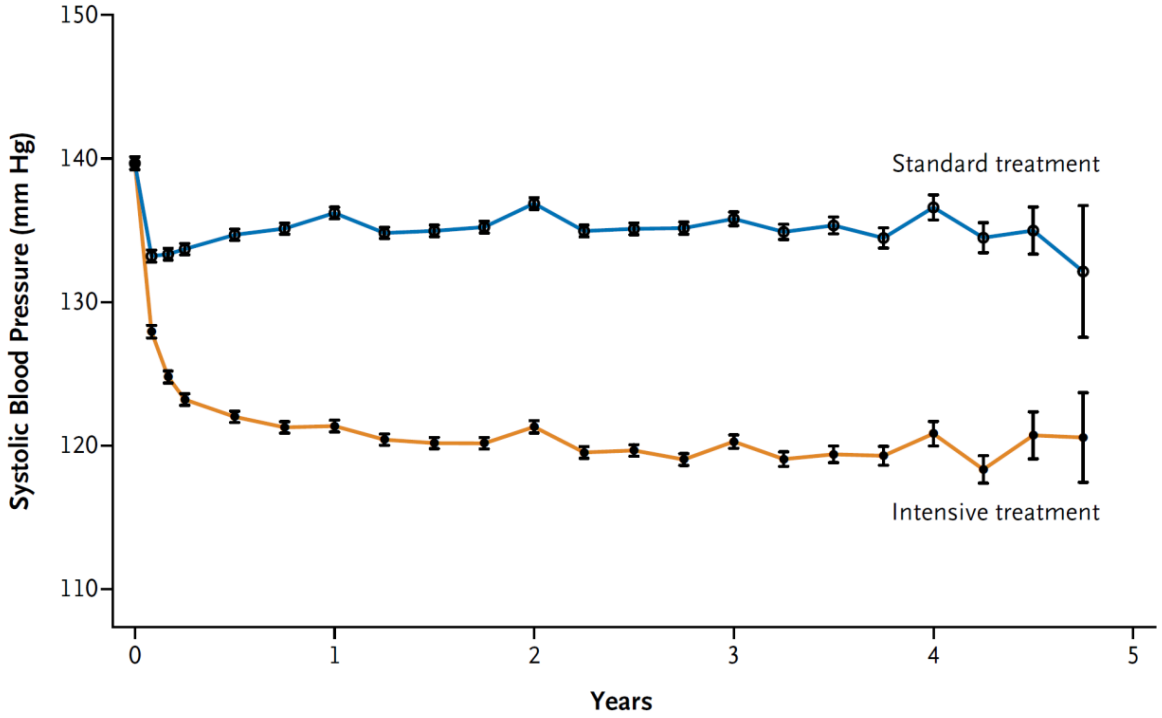
Patients were randomly assigned with a SBP >130 mm Hg and an increased CV risk, but without diabetes, to a SBP target of <120 mm Hg (intensive treatment) or a target of <140 mm Hg (standard treatment)



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

SPRINT Results

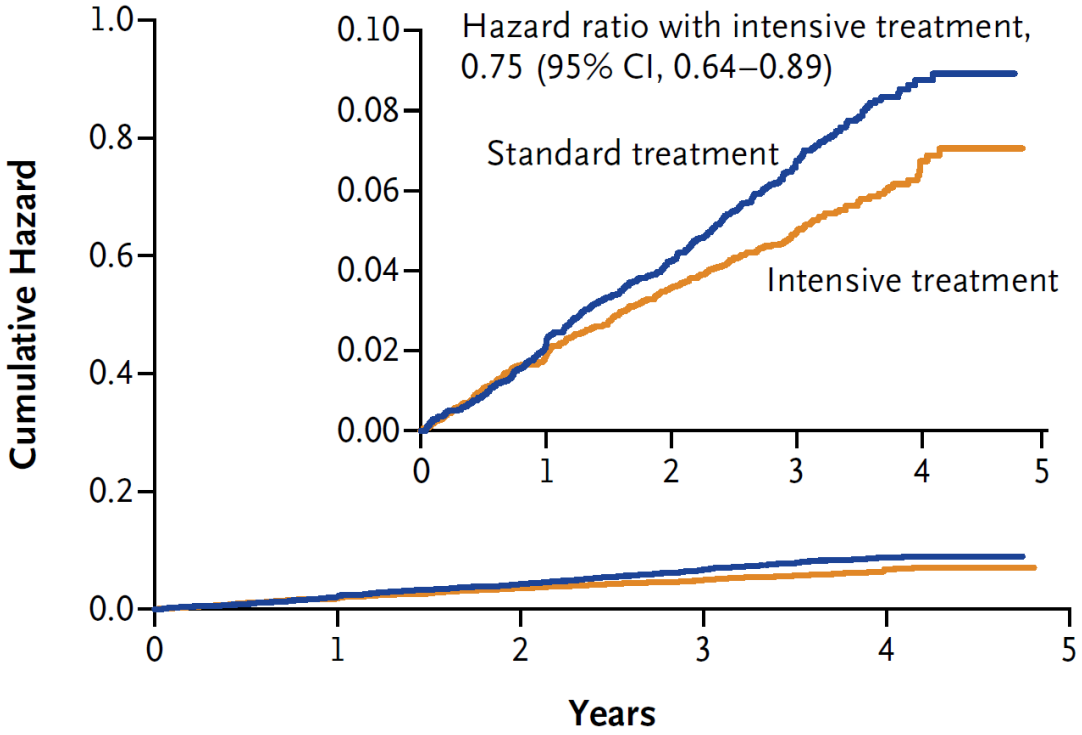
- At 1 year, the mean systolic blood pressure was
  - Intensive treatment group: 121.4 mm Hg.
  - Standard-treatment group: 136.2 mm Hg.



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

SPRINT Results

- Significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment.



1.65% vs. 2.19% per year HR with intensive treatment, 0.75; 95% CI, 0.64 -0.89; P<0.001

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

SPRINT Results

- Treating blood pressure to a lower goal in older or high-risk patients can be beneficial and yield better health results overall.

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

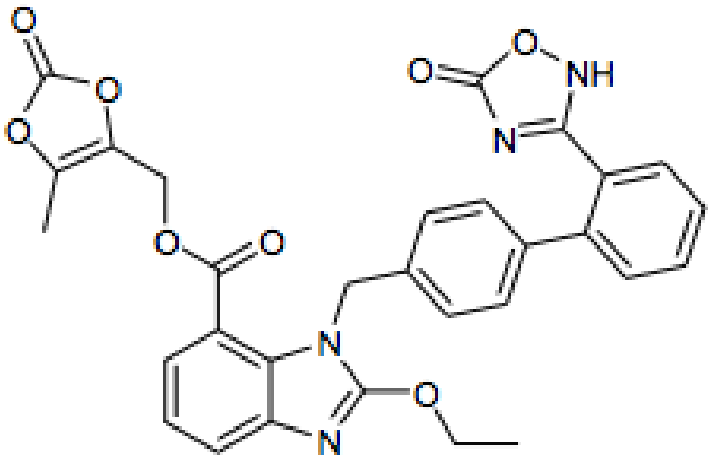
- ***Intensive blood pressure management may save lives***

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

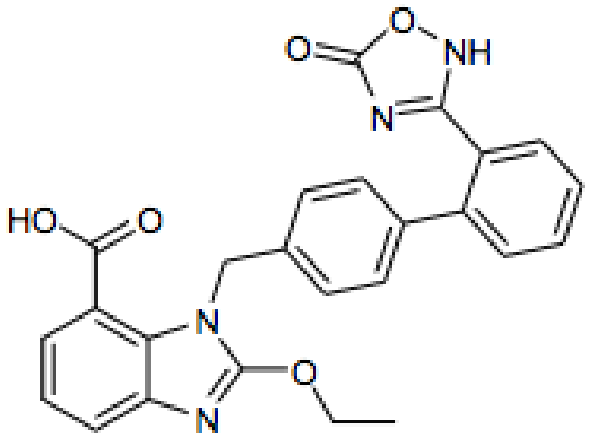
Azilsartan

Azilsartan Description

- Azilsartan, is the newer and eighth ARB
- Azilsartan medoxomil a prodrug converted to active moiety '**Azilsartan'** in the gastrointestinal tract.



Azilsartanmedoxomil



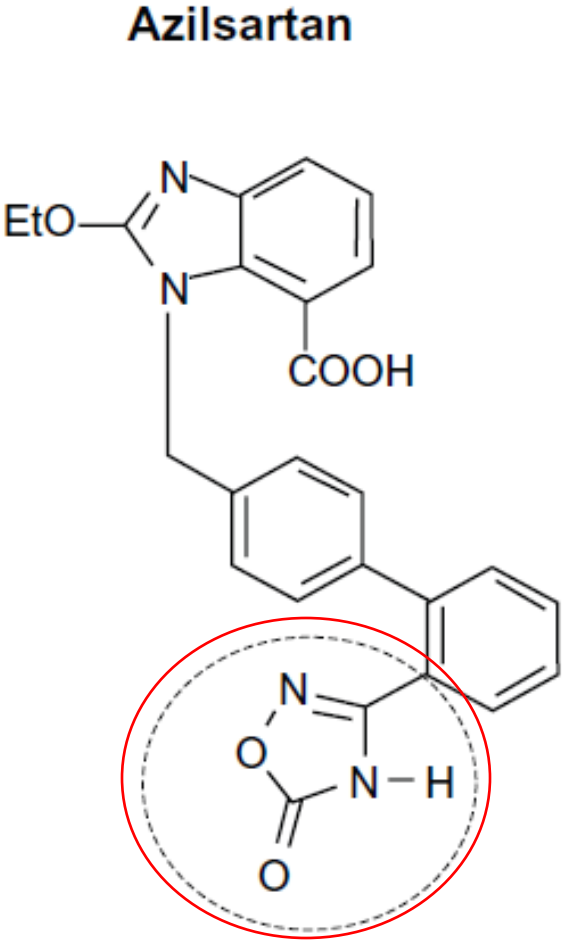
Azilsartan

Kurtz *et al. Vasc Health Risk Manag.* 2012; 8: 133–143

Oxadiazole ring

- The structures of azilsartan has a unique 5-oxo-1,2, 4-oxadiazole ring.

- This ring makes azilsartan less acidic and more lipophilic.

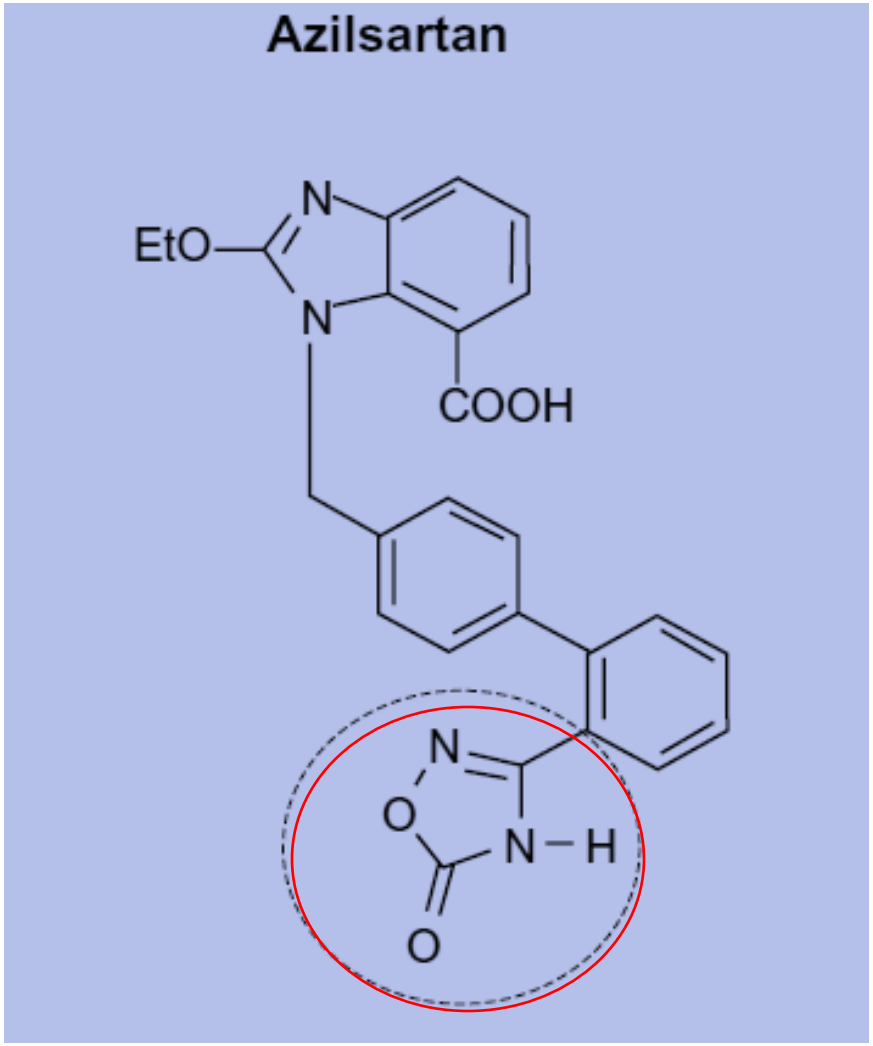


Kurtz *et al. Vasc Health Risk Manag.* 2012; 8: 133–143

Oxadiazole ring

- Azilsartan has a unique binding behavior to the AT1 receptor due to its 5-oxo-1,2,4-oxadiazole moiety and induces stronger antihypertensive effect.

Azilsartan provide stronger inverse agonism and Potent BP control



Pharmacokinetics

Prodrug	Azilsartan Medoxomil
Active Metabolite	Azilsartan (converted in GIT)
Peak Plasma Conc.	1.5 to 3 hrs.
Plasma-protein binding	99%
Half life	11 hrs
Bioavailability	60%
Volume of distribution	16 liters
Protein binding	99%
Metabolism	In the liver, through cytochrome P450 (CYP) 2C9
Absorption affected by food	No
Excretion/elimination	Renal excretion: 42%; feces : 55%
Dose in Hepatic Impairment	Mild - moderate impairment: No dosage adjustment Severe hepatic impairment: Not established.
Dose in Renal Impairment	Mild to severe renal impairment : No dosage adjustment Severe impairment: Not established.

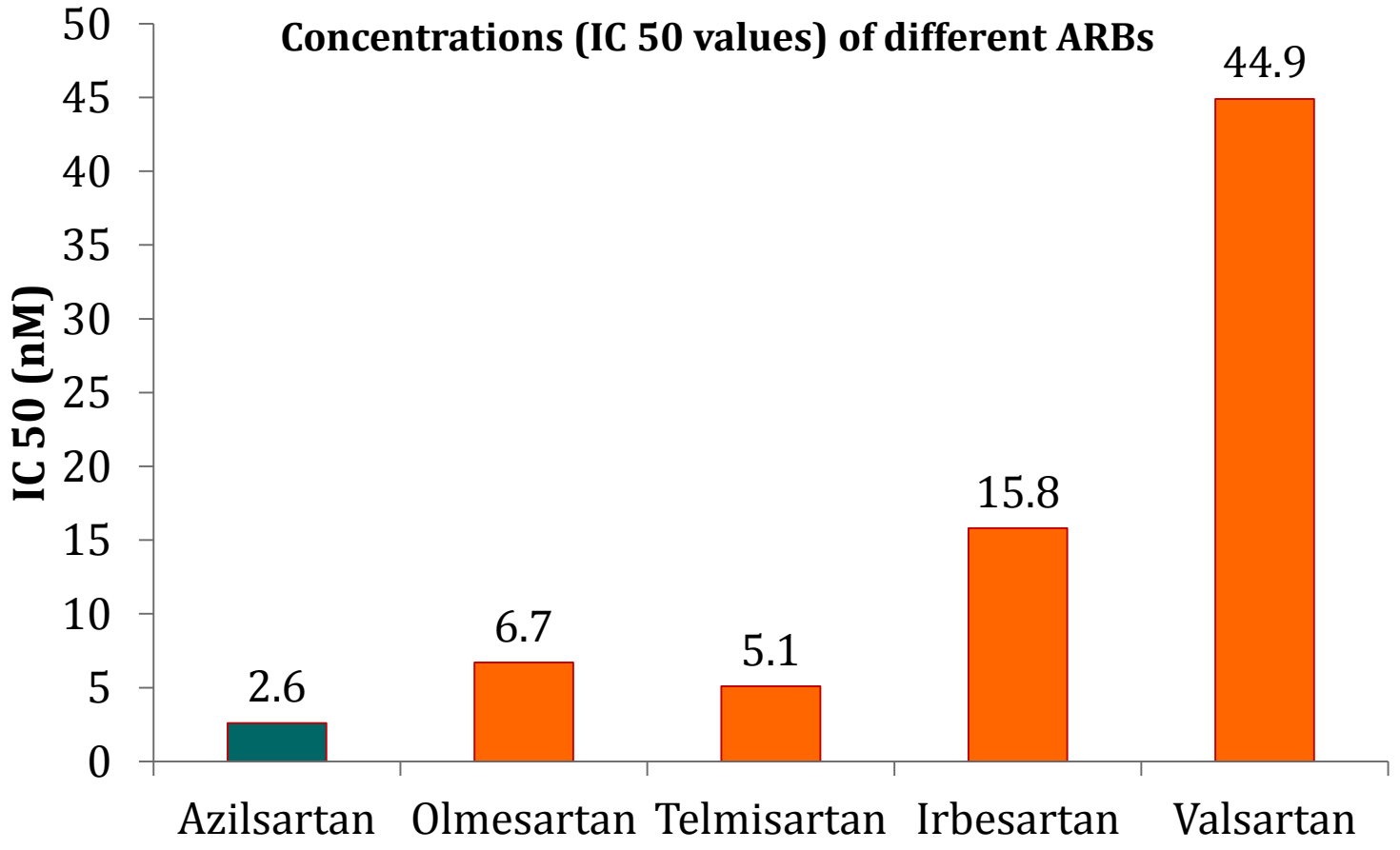
Azilsartan & AT1 receptor blockade

- Azilsartan is highly selective for AT1 receptors.
- Azilsartan has more than a **10,000-fold greater** affinity for AT1 than for the AT2 receptors.
- Compared to other ARBs, AZL dissociates from AT1 receptors more slowly.

Azilsartan Provides Potent and Persistent BP control

AZILSARTAN & AT1 RECEPTOR BLOCKADE

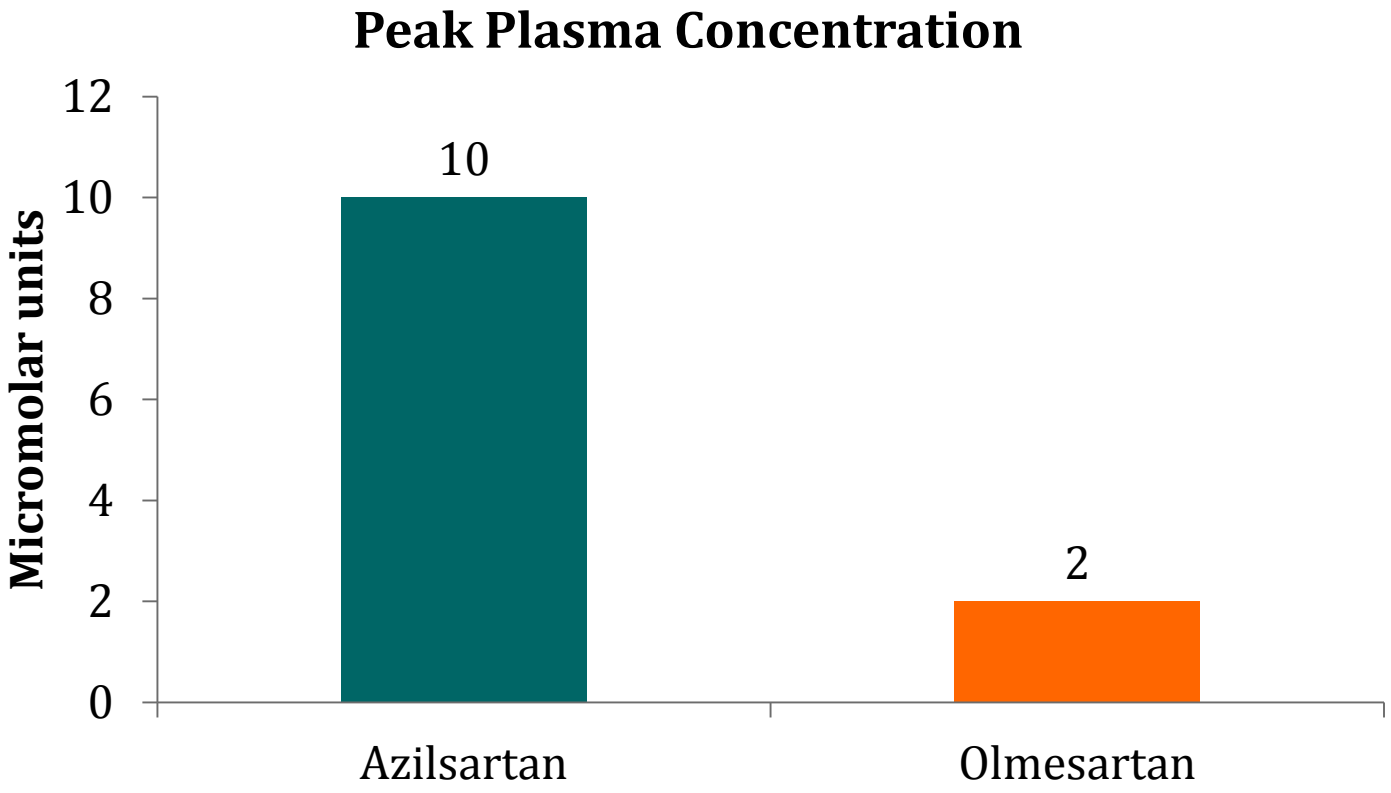
- Azilsartan was found to be approximately twice as potent as either olmesartan or telmisartan.



Kurtz *et al. Vasc Health Risk Manag.* 2012; 8: 133–143

Azilsartan: Plasma conc.

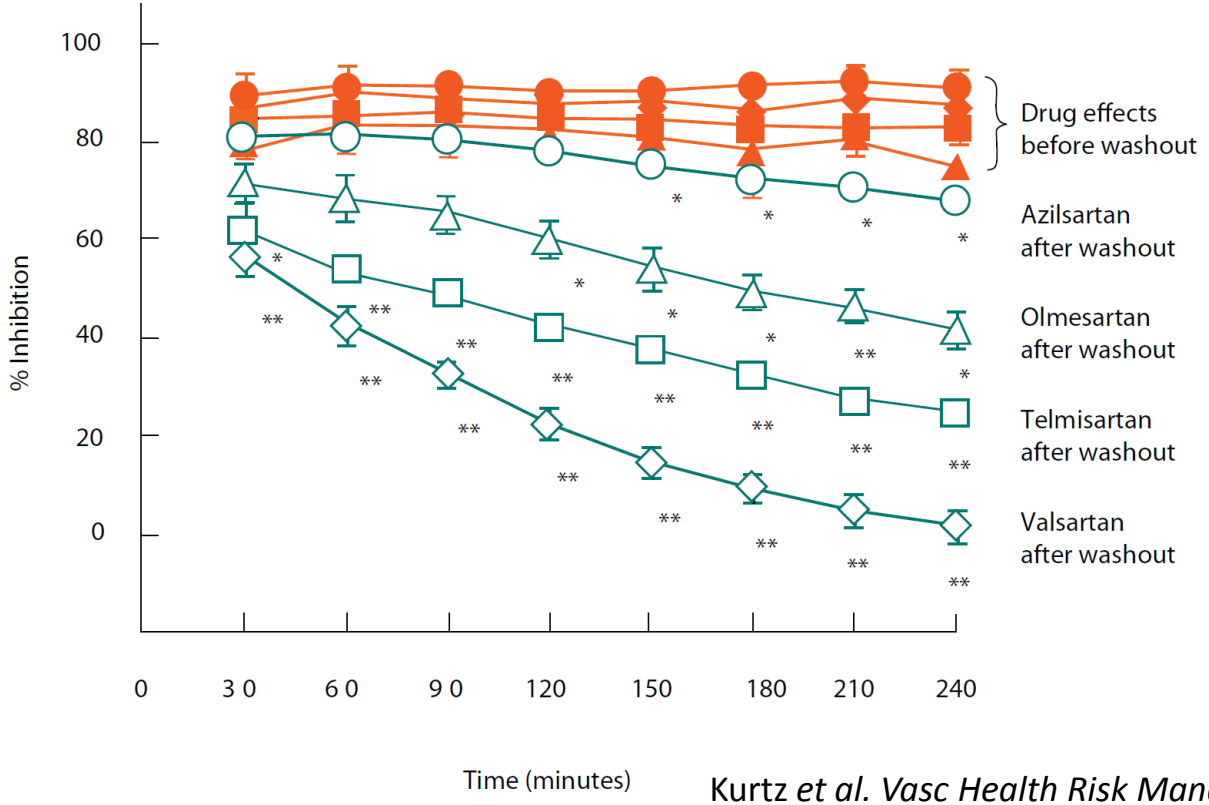
- Peak plasma concentration is **5 times** greater than that achieved with Olmesartan



Kurtz *et al. Vasc Health Risk Manag.* 2012; 8: 133–143

Azilsartan & AT1 receptor Dissociation

- Time course studies indicate that azilsartan dissociates from AT1 receptors more slowly than other ARBs including olmesartan, telmisartan, and valsartan



Kurtz *et al. Vasc Health Risk Manag.* 2012; 8: 133–143

Azilsartan:

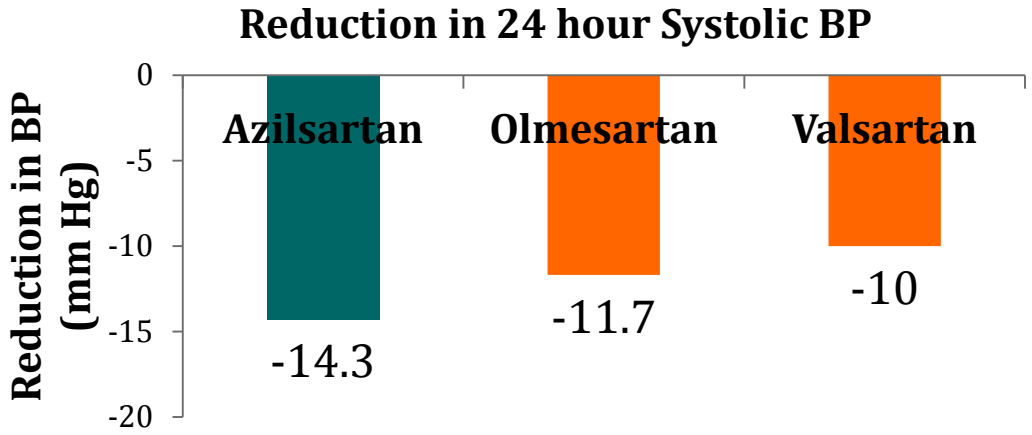
Clinical Studies

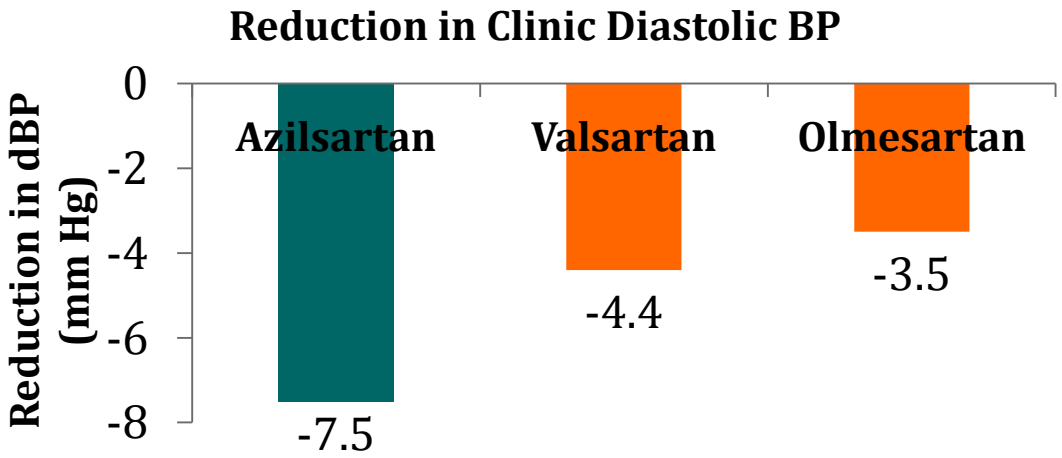
Azilsartan Vs Olmesartan & Valsartan

Author	White *et al.*
Objective	To compare the effects of azilsartan with valsartan and olmesartan using ambulatory blood pressure monitoring (ABPM) and clinic BP measurements.
Study design	A randomized, double-blind, placebo-controlled trial
Duration	6 weeks
Patient Population	1291 patients; mean age 56 years, 54% men, and baseline 24-hour mean SBP 145 mm Hg

•White WB et al. *Hypertension.* 2011 Mar;57(3):413-20.

Azilsartan Vs Olmesartan & Valsartan





Azilsartan has superior efficacy to both valsartan and olmesartan

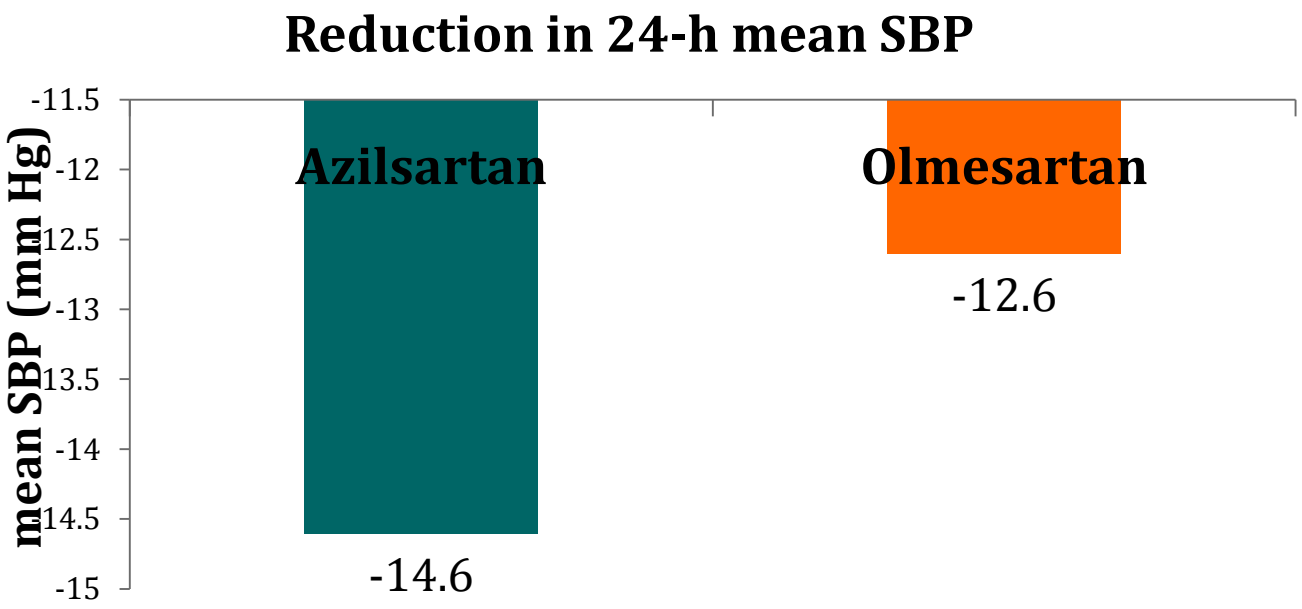
•White WB et al. *Hypertension.* 2011 Mar;57(3):413-20.

Azilsartan Vs Olmesartan

Author	Bakris et al.
Objective	To study the effects of azilsartan medoxomil and olmesartan on ambulatory and clinic BP
Study design	A randomized, double-blind, placebo-controlled, multicenter study assessed the change from baseline in mean 24-hour ambulatory SBP
Duration	6 weeks
Patient Population	1275 patients; mean age : 58 ± 11 years with 24-hour mean ambulatory SBP≥130 mmHg and ≤170 mmHg were studied; 142 received placebo and the remaining patients received 20, 40, or 80 mg of AZL-M or 40 mg of OLM-M. Baseline mean 24-hour SBP was 146 mmHg

•White WB et al. *Hypertension.* 2011 Mar;57(3):413-20.

Azilsartan Vs Olmesartan



Reduction in 24-hour mean SBP was greater with Azilsartan than with Olmesartan

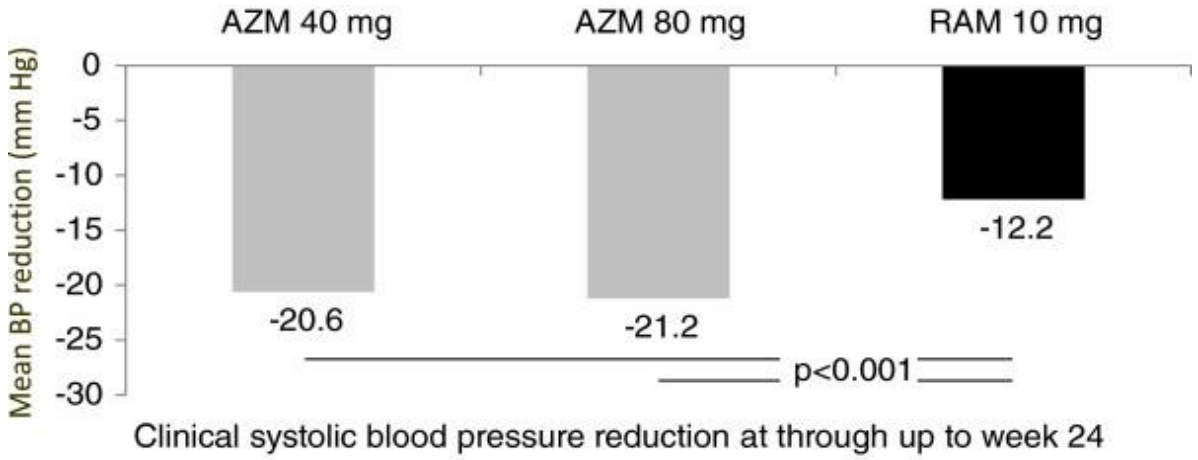
Bakris GL *et al. J Clin Hypertens (Greenwich).* 2011 Feb;13(2):81-8.

Azilsartan Vs Ramipril

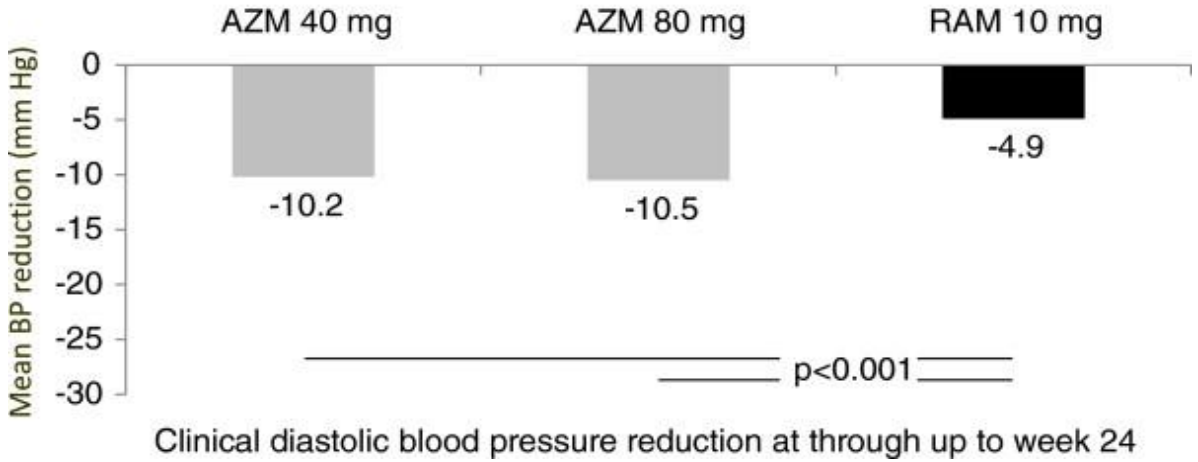
Author	Bönner et al
Objective	To compare the antihypertensive efficacy and safety of azilsartan medoxomil and ramipril.
Study design	A double-blind, controlled, randomized trial. Patients were randomized to 20 mg azilsartan medoxomil or 2.5 mg ramipril once daily for 2 weeks, then force-titrated to 40 or 80 mg azilsartan medoxomil or 10 mg ramipril
Duration	24 weeks
Patient Population	884 patients, clinic SBP ranging from 150 to 180 mmHg, mean baseline BP 161.1 ± 7.9/94.9 ± 9.0 mmHg, mean patient age 57 ± 11 years, and 52.4% male patients

G Bönner et al. J Hum Hypertens. 2013 Aug; 27(8): 479–486

Azilsartan Vs Ramipril



Clinical systolic blood pressure reduction at through up to week 24



Clinical diastolic blood pressure reduction at through up to week 24

Azilsartan is more effective than Ramipril and better tolerated.

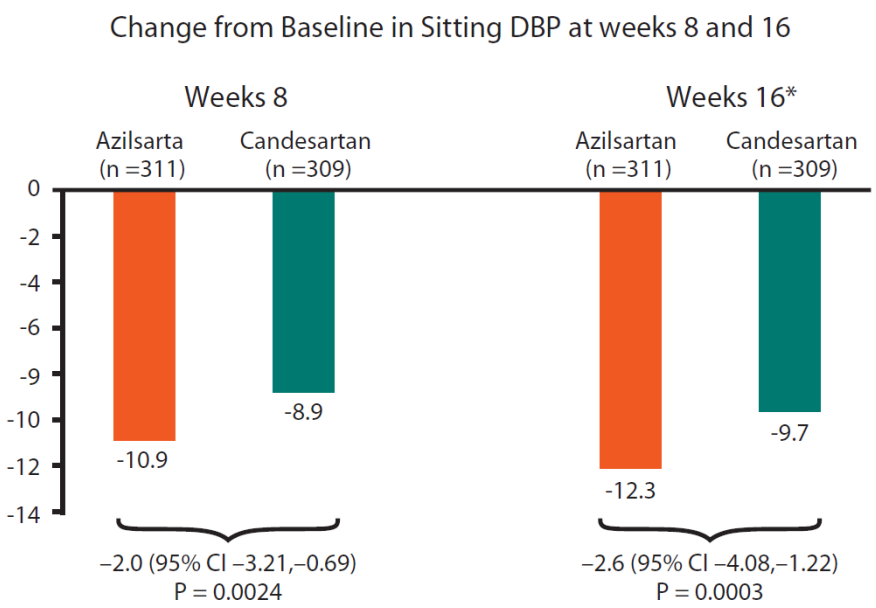
G Bönner et al. J Hum Hypertens. 2013 Aug; 27(8): 479–486

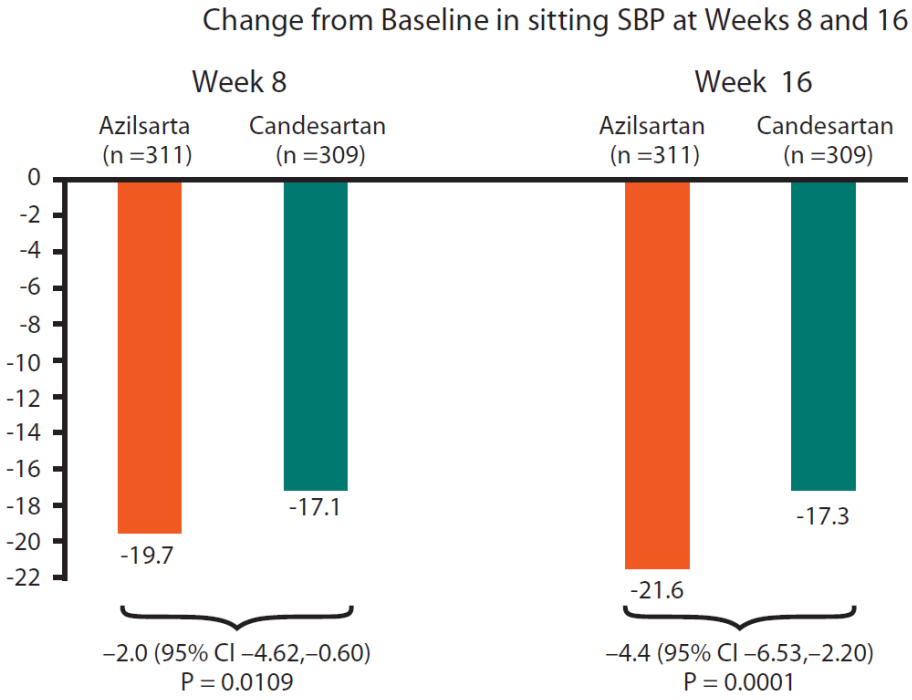
Azilsartan Vs Candesartan

Author	Rakugi H *et al.*
Objective	To compare the efficacy and safety of azilsartan (20-40 mg once daily) on 24-hour BP control with that of candesartan cilexetil (8-12 mg once daily).
Study design	Forced titration, multicenter, randomized, double-blind study
Duration	16 weeks
Patient Population	622 Japanese patients with grade I-II essential hypertension, mean age 57 years, 61% males, and mean baseline sitting BP 159.8/100.4 mmHg.

Rakugi H *et al.* Hypertens Res. 2012; 35(5):552-558.

Azilsartan Vs Candesartan

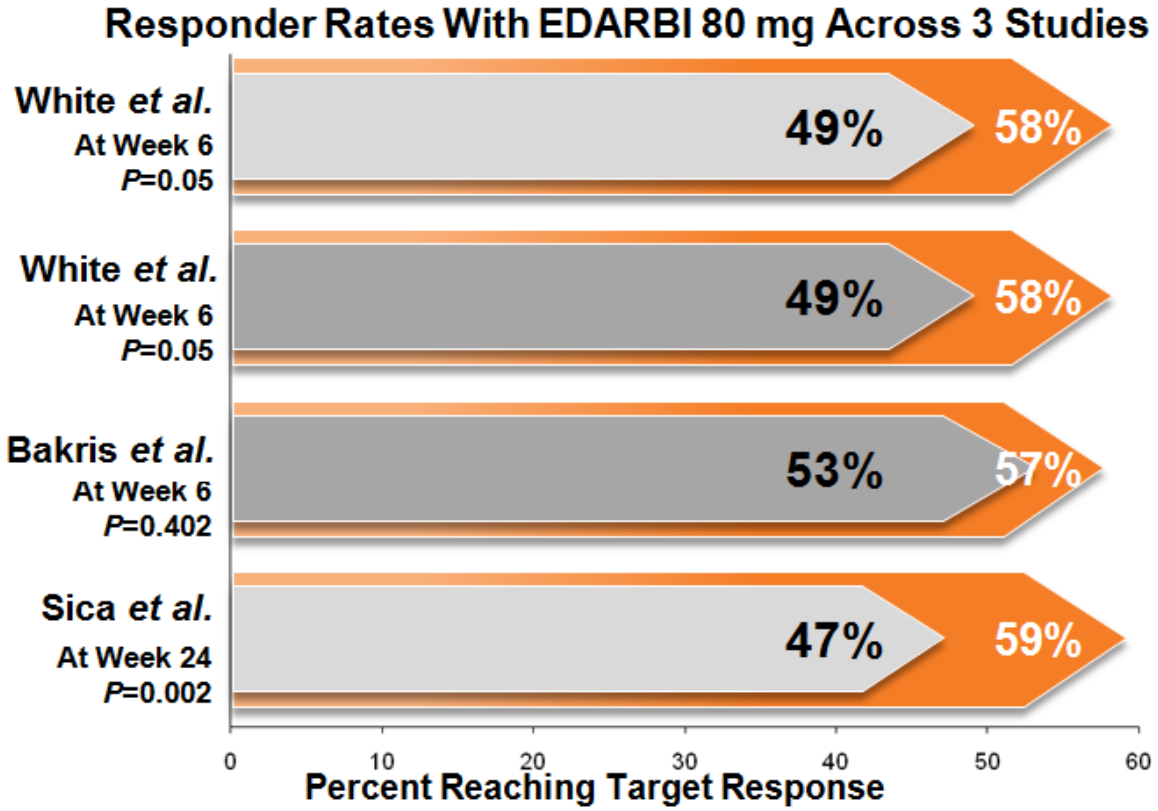




Once-daily dose of Azilsartan provides more potent 24 h sustained antihypertensive effect than candesartan

Rakugi H *et al.*Hypertens Res. 2012; 35(5):552-558.

Azilsartan Responder Rates



Response to therapy defined as achieving a reduction in clinic SBP ≥20 mm Hg and/or reaching a clinic SBP of <140 mm Hg.

Valsartan 320 mg

Olmesartan 40 mg

Azilsartan 80 mg

Significantly higher response rates to treatment was seen in patients treated with Azilsartan

Landmark Studies on Azilsartan

Author / Duration/Patient	Study	Outcome
Mono therapy Trials		
Bakris *et al*[1] 6 wks, N=1275	Azilsartan vs placebo vs olmesartan	Reduction in mean SBP was greater with AZL than OLM by 2.1 mm Hg
White *et al.*[2] 6 wks, N=1291	Azilsartan vs Valsartan vs Olmesartan	AZL lowered SBP (14.3 mm Hg) more than VAL (10.0 mm Hg) & OLM (11.7 mm Hg).
Sica *et al.*[3] 24 wks, N=984	Azilsartan vs valsartan	AZL 40 and 80 mg lowered SBP -14.9 mm Hg and -15.3 mm Hg, respectively more than VAL -11.3 mm Hg
Bonner *et al.*[4] 24 wks, N=884	Azilsartan vs Ramipril	Clinic SBP decreased by 20.6±0.95 and 21.2±0.95 mmHg with AZL 40 and 80 mg *vs* 12.2±0.95 mm Hg with RAM
Combination Therapy Trials		
Weber *et al.*[5] 6 wks, N=566	Azilsartan + Amlodipine vs Placebo + Amlodipine	24-h BP reductions in AZL/AML were greater than the 14/8mm Hg decrease with AZL/placebo groups
Sica *et al.*[6] 6 wks, N=1714	Azilsartan + chlorthalidone vs Chlorthalidone vs Azilsartan	SBP reduction of 28.9 mm Hg by AZL/CLD and exceeded AZL and CLD monotherapies by 13.8 mm Hg and 13 mm Hg, respectively
Cushman *et al*[7] 12 wks, N=1071	Azilsartan + chlorthalidone vs Olmesartan + chlorthalidone	AZL/CLD reduces blood pressure more effectively than OLM/HCTZ in Stage 2 Systolic Hypertension
Kipnes *et al.*[8] 32 wks, N=418	Azilsartan vs Azilsartan + chlorthalidone	AZL alone or with CLD showed good longterm safety and stable BP improvements in a titrate to target approach

Azilsartan

Beyond BP Reduction?

Pre Clinical Studies

Azilsartan: Beyond BP Reduction

- In animal models, Azilsartan improved insulin resistance.
- Azilsartan enhances adipogenesis and exerts greater effects than valsartan on PPARα, PPARδ, leptin, adipsin, and adiponectin.
- Studies indicate the greater beneficial effects of azilsartan in improving glucose intolerance and insulin sensitivity
- An animal model of type 2 diabetes showed preventive and therapeutic vasculoprotective effects of azilsartan independent of its effect on BP

Kajiya T *et al.* J Hypertens. 2011; 29(12):2476-83
Iwai M *et al.* Am J Hypertens. 2007; 20(5):579-86.
Abdelsaid M *et al.* Transl Res. 2014; 164(5):424-32.

Azilsartan: Beyond BP Reduction

- In animal models, Azilsartan potently inhibits vascular cell proliferation in the absence of exogenously supplemented angiotensin II and may thus modulate cell growth.

- In aortic endothelial cells, the inhibition of cell proliferation by azilsartan was seen at concentrations as low as 1 μmol/L.

- It also blocks angiotensin II-induced activation of mitogen-activated protein kinase in vascular smooth muscle cells.

Kajiya T et al. J Hypertens. 2011; 29(12):2476-83

Azilsartan: Beyond BP Reduction

- Azilsartan facilitates the stabilization of atherosclerotic plaques by suppressing vascular wall expression of plasminogen activator inhibitor type-I protein.

- By inhibiting the activated RAAS, azilsartan has a cardiac remodelling suppression effect after MI, and this effect is observed without lowering BP.

- Azilsartan prevents endothelial dysfunction in diabetic mice more potently than does candesartan.

French C *et al.* J Cardiovasc Pharmacol. 2011;58(2):143-48
Nakamura Y *et al*. Biol Pharm Bull. 2013;36(8):1326-31.
Matsumoto S *et al.* Cardiovasc Diabetol. 2014 Jan 31; 13:30.

Azilsartan: Beyond BP Reduction

In Animal Models:

- Improves insulin resistance
- Beneficial effects in cardiometabolic diseases
- Inhibits vascular cell proliferation- modulate the cell growth
- Prevents endothelial dysfunction
- Preventive and therapeutic vasculoprotective effects
- Facilitates the stabilization of atherosclerotic plaques
- Protective effects on cardiovascular consequences
- Prevents cerebrovascular remodeling

Azilsartan

Profile

Azilsartan Profile

- Azilsartan is an ARB indicated for the treatment of hypertension.
- Azilsartan may be used either alone or in combination with other antihypertensive agents such as chlorthalidone.
- Recommended dose in adults is 80 mg taken once daily with or without food.
- Azilsartan may be advised along with other antihypertensive agents

Azilsartan in Special Populations

- **Hepatic Impairment**
  - Mild - moderate impairment: No dosage adjustment
  - Severe hepatic impairment: Not established.
- **Renal Impairment**
  - Mild to severe renal impairment or end-stage renal disease: No dosage adjustment
- **Elderly Patients**
  - No adjustment of initial azilsartan dosage is necessary
- **Volume or Salt-depleted Patients**
  - It has to be corrected prior to Azilsartan
- **Pediatric Patients:**
  - Azilsartan has not been studied in patients <18 years

Azilsartan Safety information

Contra-indications

- Hypersensitivity to the active substance or to any of the excipients.
- Second and third trimester of pregnancy (can cause fetal and neonatal morbidity and death).
- The concomitant use of Azilsartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment
- Azilsartan/chlorthalidone combination is also contraindicated in patients with anuria.

Avoid Use During Pregnancy

Azilsartan- Summary

Azilsartan

- Azilsartan, is the newer ARB with a distinctive “Oxadiazolone” ring not found in any other ARB.
- Highly selective for AT1 receptors & >10,000-fold greater affinity
- Tightly binds with AT1 receptor for longer period and dissociates more slowly than any other ARB
- Twice as Potent as either Olmesartan or Telmisartan for blocking Ang II binding
- Peak plasma concentration is 5 times greater than Olmesartan

Induces Inverse Agonism and Potent, Persistent Blood Pressure Control

Azilsartan

- Azilsartan has superior efficacy to both valsartan and olmesartan.
- Reduction in 24-hour mean SBP greater with Azilsartan than with Olmesartan.
- Azilsartan is more effective than Ramipril and better tolerated.
- Azilsartan provides more potent 24 h sustained antihypertensive effect than candesartan.

Azilsartan demonstrates superior BP-lowering efficacy compared with other antihypertensive agents

Thank you