Hypertension : An Update

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

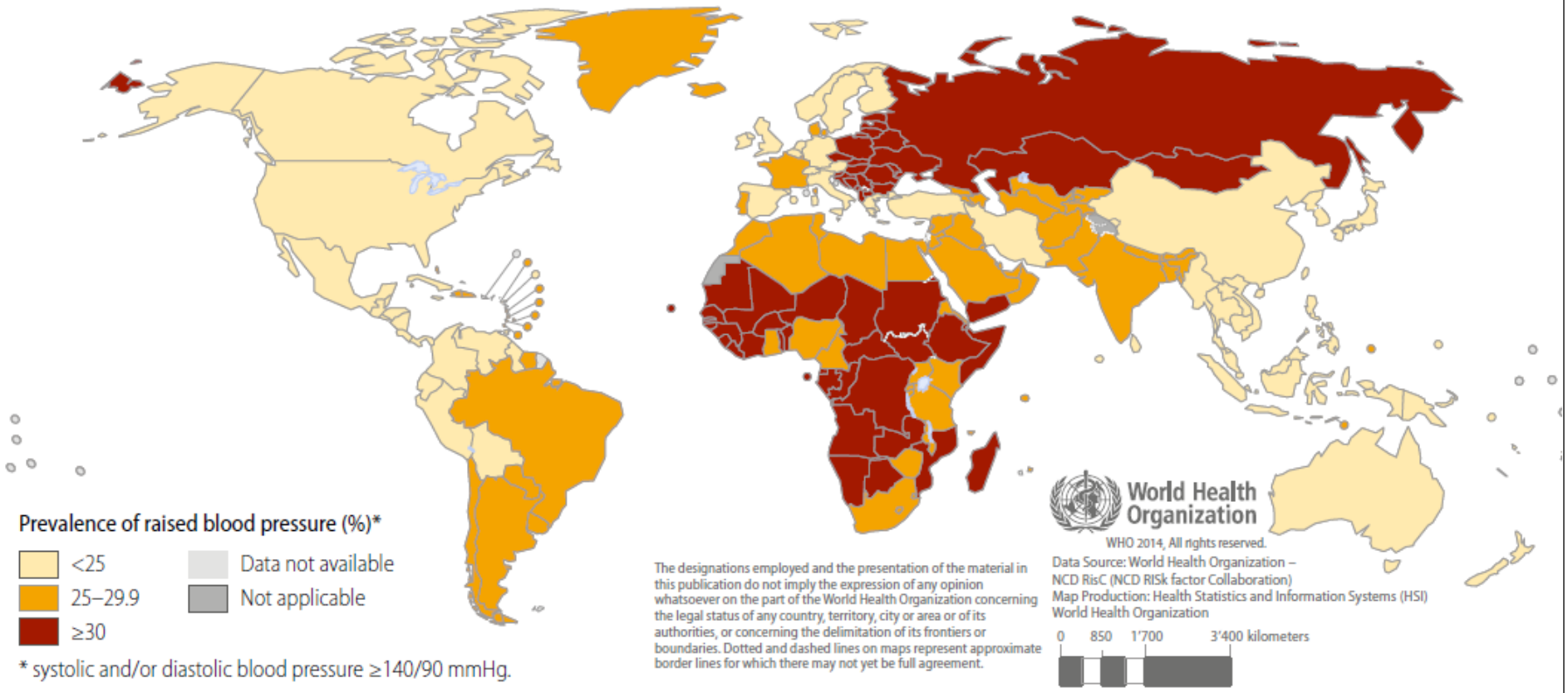
26% — adults affected across the globe

1.6 Billion HTN patients estimated by 2025

Rendon J et al. J Clin Hypertens (Greenwich). 2018 Feb;20(2):356-365.
Singh PS et al. Int J Res Med Sci. 2017 Apr;5(4):1451-1455

Hypertension: WHO Estimates

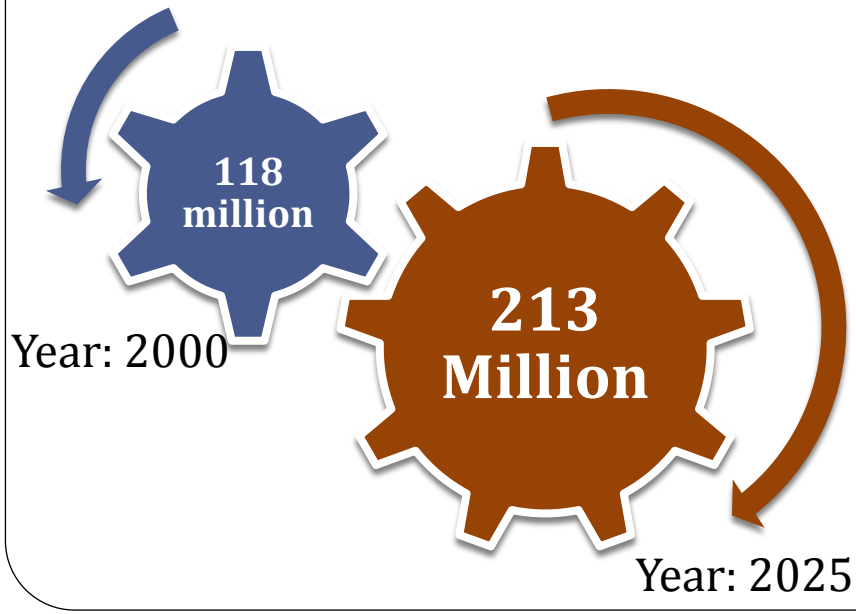
- **Ranked 3rd** most risk factor for hypertension burden in South Asia



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

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

Bhise et al. PLoS One. 2018; 13(2): e0191948.
Mohan et al:. *IJMR*. 2013;137:627-31

New ACC/ AHA

Hypertension Guidelines

New blood pressure targets and treatment recommendations

- For years, hypertension was classified as blood pressure (BP) reading of 140/90 mm Hg or higher.
- But the updated guideline classifies hypertension as a BP reading of **130/80 mm Hg or higher**.
- The updated guideline also provides new treatment recommendations, which include lifestyle changes as well as BP-lowering medications

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

Classification of BP

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

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

Hypertensive Crisis: Emergencies and Urgencies

Hypertensive Crises	Systolic BP		Diastolic BP	Treatment or Follow-up
Hypertensive urgency	>180 mm Hg	**and/ or**	>120 mm Hg	Many of these patients are noncompliant with antihypertensive therapy and do not have clinical or laboratory evidence of new or worsening target organ damage; reinstitute or intensify antihypertensive drug therapy, and treat anxiety as applicable
Hypertensive emergency	>180 mm Hg + target organ damage	**and/ or**	>120 mm Hg + target organ damage	Admit patient to an intensive care unit for continuous monitoring of BP and parenteral administration of an appropriate agent in those with new/ progressive or worsening target organ damage (see Tables 19 and 20 in the 2017 Hypertension Guideline)

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

No prehypertension

- The updated guideline **eliminates** the term *prehypertension and instead uses the term* ***elevated BP*** *for a systolic BP of 120 to 129 mm Hg and a diastolic BP of less than 80 mm Hg.*

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

Drug Therapy

- **Choice of Single vs Combination Drug Therapy**

- **Recommendation:** Initiate antihypertensive drug therapy with 2 first-line agents of different classes for adults with stage 2 hypertension and BP more than 20/10 mm Hg higher than their target.

  - The updated guideline recommends initiating antihypertensive therapy with 2 agents for stage 2 hypertension

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

Choice of Single vs Combination Drug Therapy

- **Recommendation:** It is reasonable to initiate therapy with a single agent for adults with stage 1 hypertension and a goal of less than 130/80 mm Hg.
  - This approach is reasonable in the very elderly, those with high CVD risk, or patients with a history of hypotension or drug-associated side effects.
    - Be cautious when initiating antihypertensive pharmacotherapy with 2 drugs in older patients because hypotension may develop

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

Non-pharmacologic Interventions for Prevention and Treatment of Hypertension

Nonpharmacologic Intervention	Dose
Healthy diet: Use the Dietary Approaches to Stop Hypertension (DASH) dietary pattern	Diet rich in fruits, vegetables, whole grains, and low-fat dairy products with reduced content of saturated and total fat
Weight loss: Focus on losing excess weight/body fat	• Ideal body weight is best goal, but aim for at least 1 kg body weight reduction for most overweight adults. • Expect about 1 mm Hg for every 1 kg reduction in body weight.
Sodium: Reduce intake of dietary sodium	<1500 mg/day is optimal goal, but aim for at least 1000 mg/day reduction in most adults.
Potassium: Increase intake of dietary potassium	3500-5000 mg/day, preferably by consumption of a diet rich in potassium
Physical activity: Add aerobic exercises to weekly routine	• 90-150 min/week • 65%-75% heart rate reserve
Physical activity: Add dynamic resistance training to weekly routine	• 90-150 min/week • 50%-80% heart rate reserve, 1 rep maximum • 6 exercises, 3 sets/exercise, 10 repetitions/set
Physical activity: Add isometric resistance training to weekly routine	• 4 × 2 min (hand grip), 1 minute of rest between exercises, 30%-40% maximum voluntary contraction, 3 sessions/week • 8-10/week
Alcohol: Reduce consumption of alcohol	For those who drink alcohol, the recommended daily consumption is no more than 2 drinks for men and 1 drink for women.

*Type, dose, and expected impact on BP in adults with a normal BP and with hypertension.

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

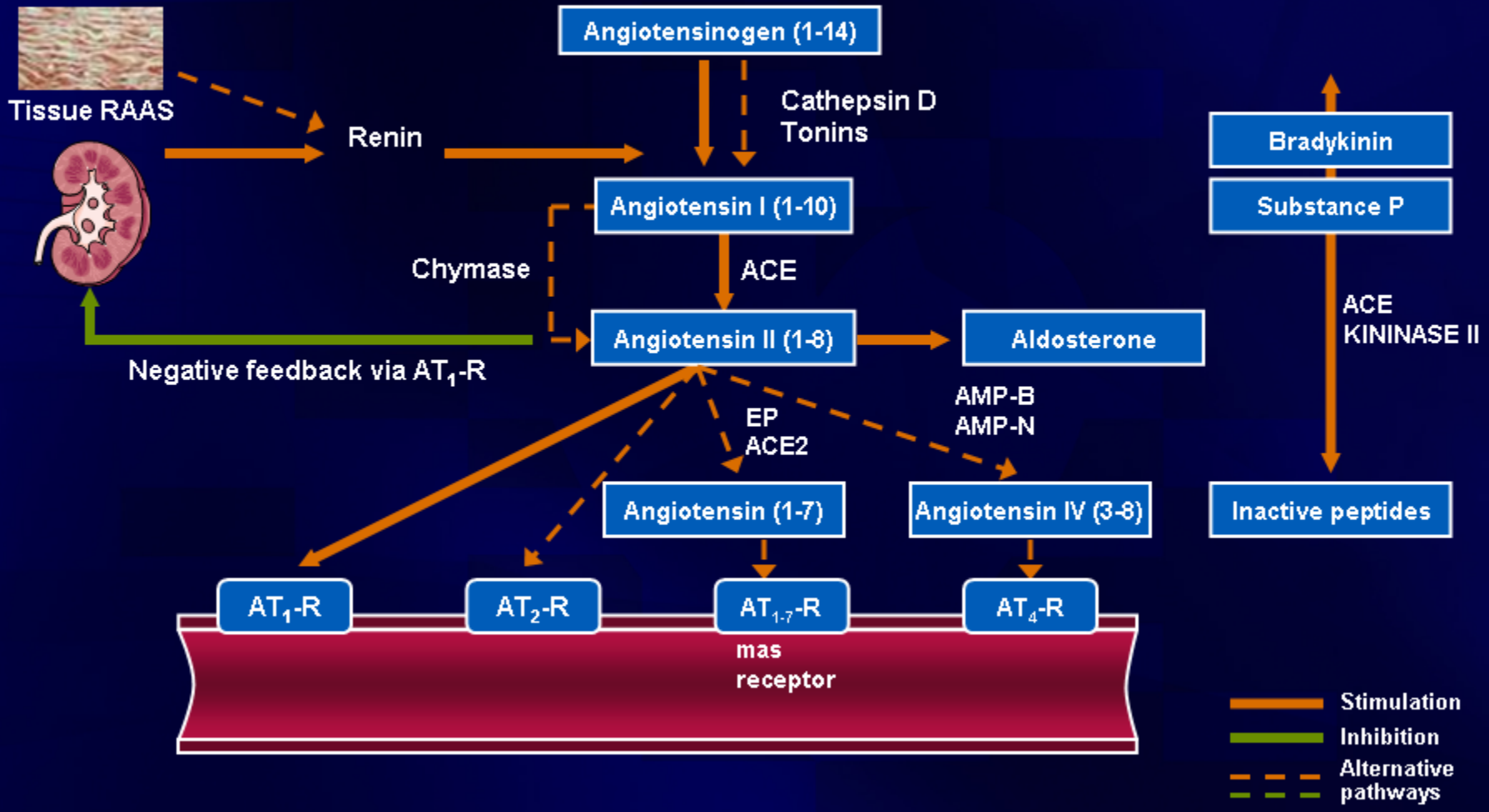
BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

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

Role of RAAS

RAAS overview: Key targets



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

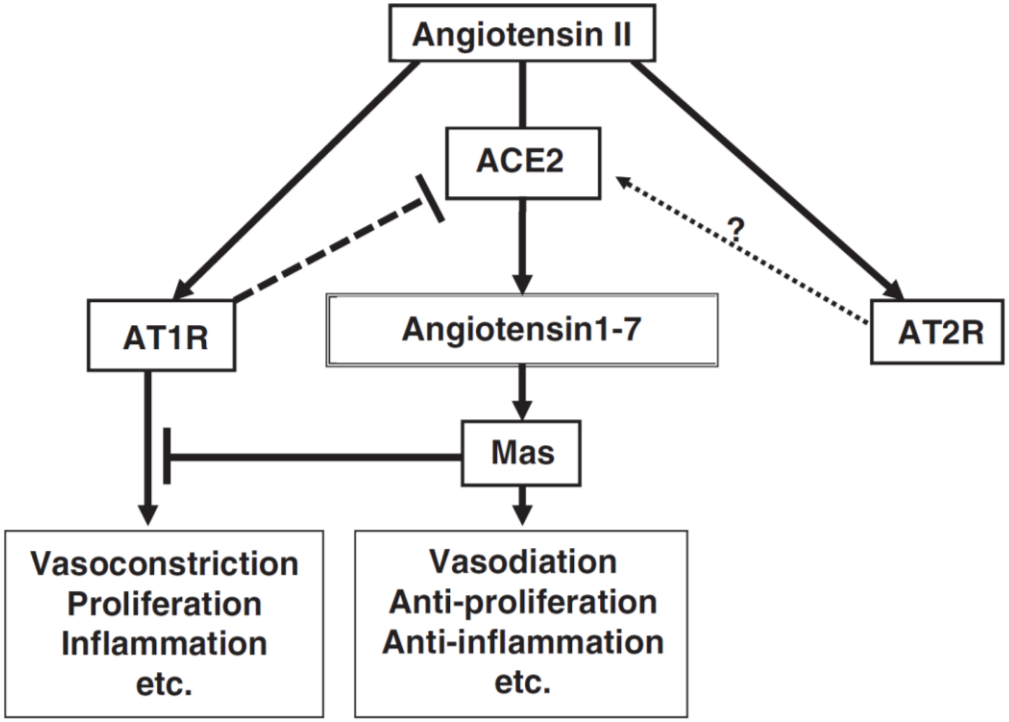
Role of the ACE2/angiotensin1–7/Mas axis

- Angiotensin (Ang) 1–7 is a new bioactive product in the renin–angiotensin system.
- Ang 1–7 is produced by the protease activity of ACE2 as a derivative of Ang I and Ang II.
- Ang1–7 together with ACE2 and Mas form a separate pathway in renin–angiotensin system

Iwai M *et al.* Hypertens Res. 2010 Nov;33(11):1108-9.

Novel Pathway of RAAS

- Blockage of AT1 receptor-mediated signaling directly modulates the Ang1–7-mediated pathway.



ACE2/angiotensin1–7/Mas axis, a new direction in Hypertension Management

Iwai M *et al.* Hypertens Res. 2010 Nov;33(11):1108-9.

Olmesartan action on Ang-(1-7)

- Olmesartan exhibit an ACE inhibitory action in addition to an Ang II receptor blocking action
- Prevent an increase in Ang II level
- Protect cardiovascular remodeling through an increase in cardiac nitric oxide production and endogenous Ang-(1-7) via over-expression of ACE2

Agata J et al. Hypertens Res. 2006 Nov;29(11):865-74.

RAAS Blockers

- British guidelines and ESH-ESC guidelines, recommend RAAS blockers as initial therapy.

Compelling indications for antihypertensive drug classes according to comorbidities

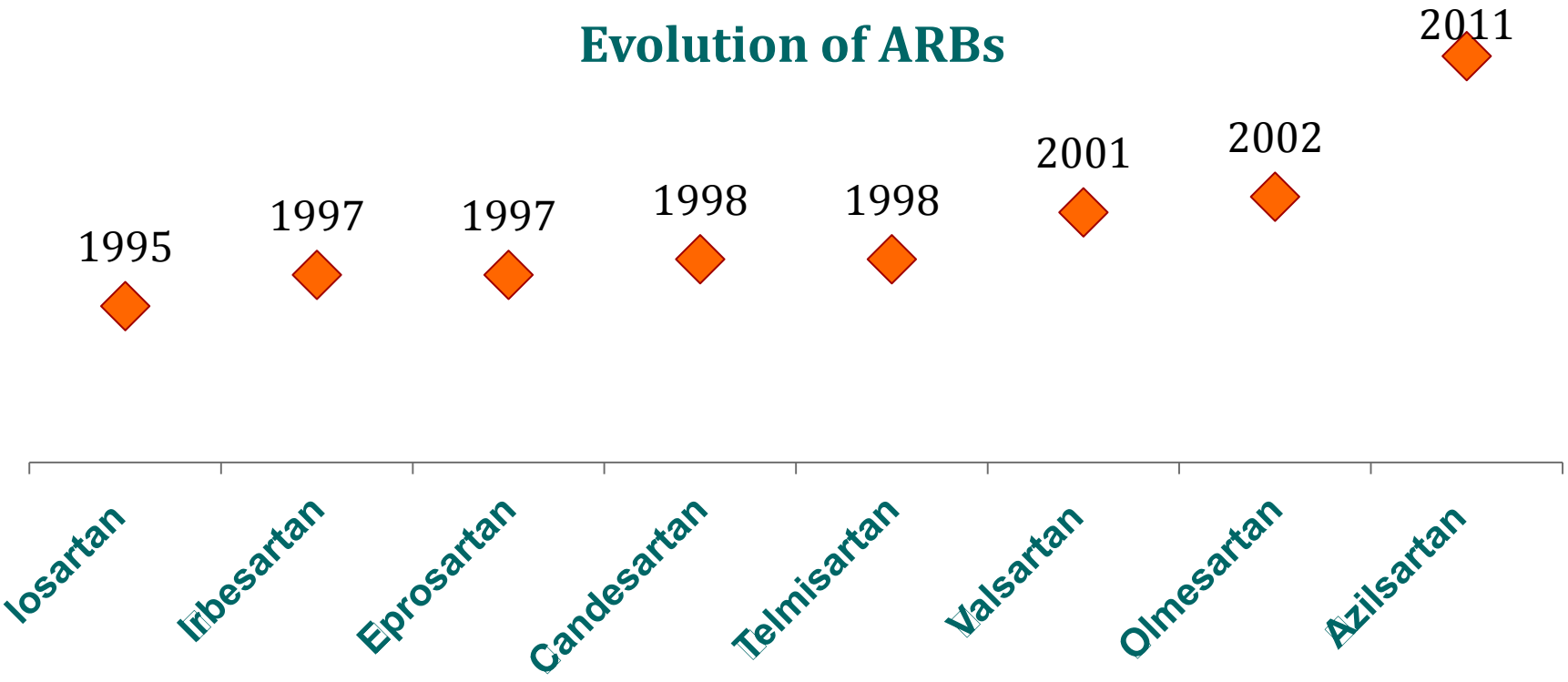
	RAS blocker	D	CCB
Isolated systolic hypertension	●	●	●
Hypertension in blacks	●	●	●
Angina pectoris	●		●
Post-myocardial infarction	●		
Left ventricular hypertrophy	●		
Arterial fibrillation	●		
Heart failure	●	●	
Cartoid/coronary atherosclerosis			●
Metabolic syndrome	●		●
Non–diabetic nephropathy	●		
Diabetic nephropathy	●		
Proteunuria/microalbuminuria	●		

CCB- calcium channel blockers; D- diuretics; RAS - renin-angiotensin system.

Burnier M *et al.* Eur Heart J. 2013; 35(9):557-62.

History of ARBs

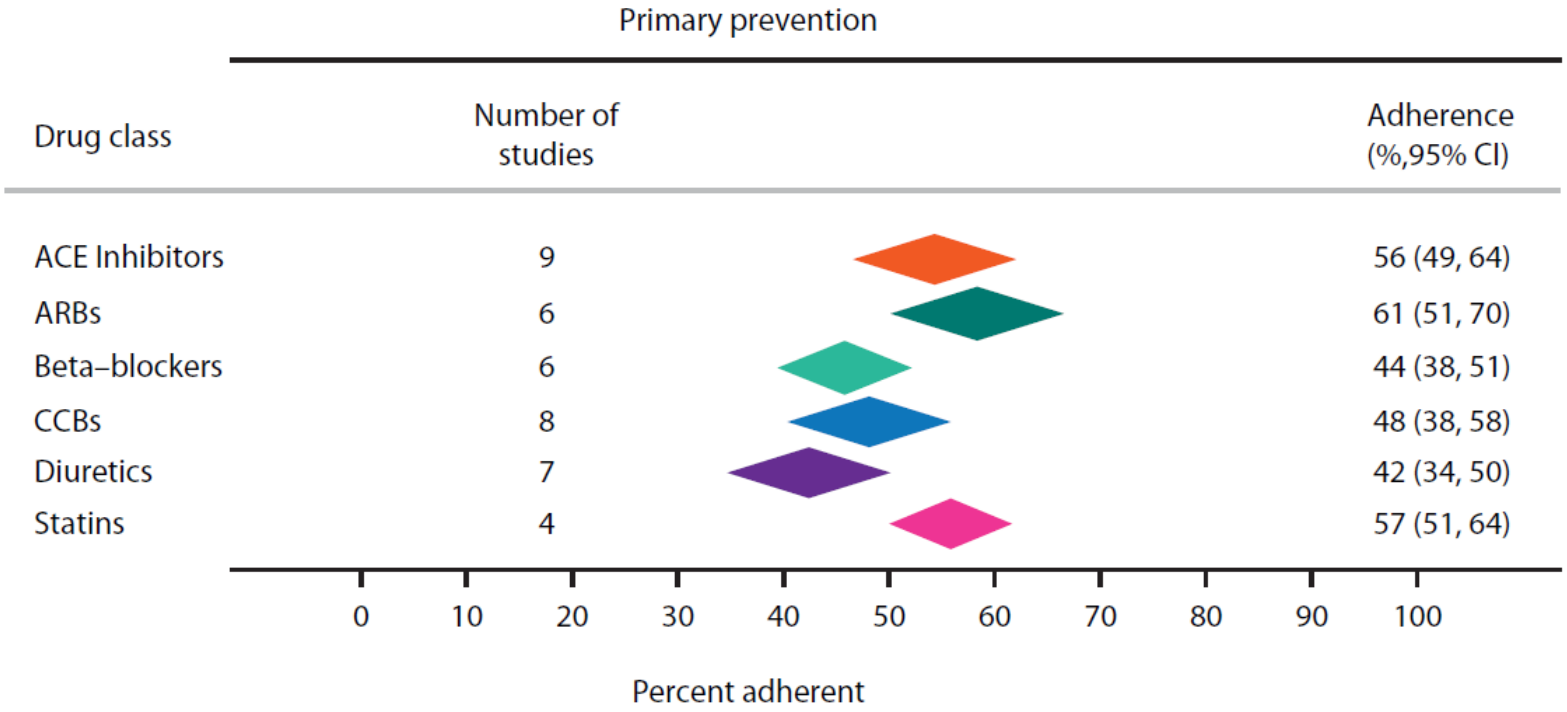
- In 1995 Losartan – First ARB approved by USFDA
- Azilsartan Medoxomil is the latest and the eighth ARB.



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

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.

Olmesartan: A Unique ARB

Olmesartan

- Olmesartan medoxomil is a prodrug.
- It is an angiotensin receptor antagonists (ARB)
- After absorption in GIT, it rapidly undergo deesterification, and converted to active form olmesartan.
- No interaction with the cytochrome P450 system
  - 60% excreted from liver and 40% from kidney.
- Olmesartan has a potent and competitive antagonistic action on the AT_1 subtype
  - little effect on the AT_2 subtype and also acts on hormone receptors and ion channels.

Sada T et al, Nihon Yakurigaku Zasshi. 2004 Oct;124(4):257-69.

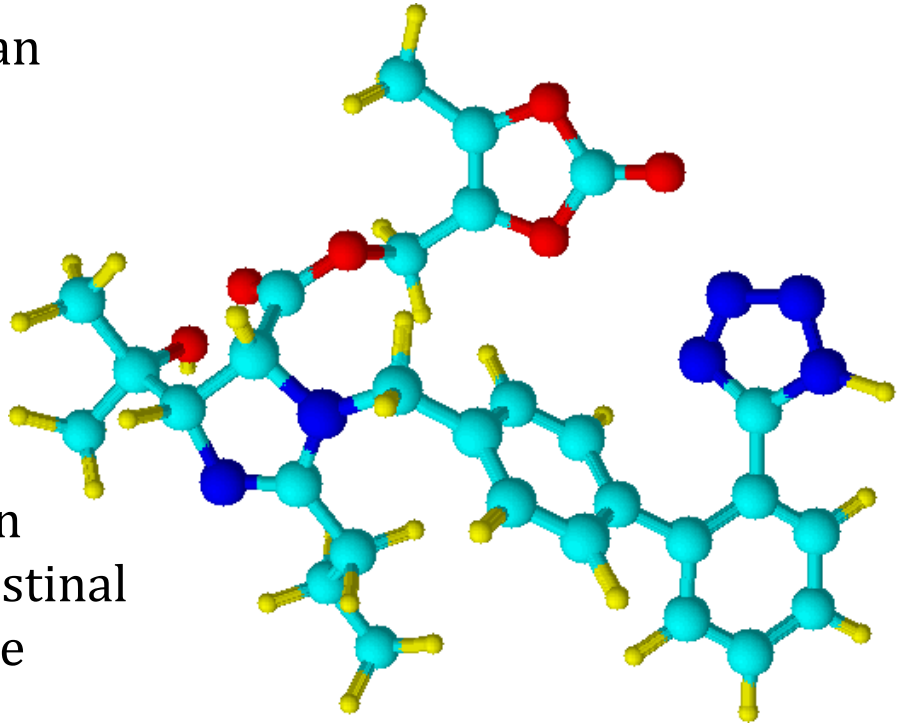
Mechanism of Action

- Olmesartan selectively inhibits the binding of angiotensin II to AT1.
- This effectively inhibits the AT1-mediated vasoconstrictive and aldosterone secreting effects of angiotensin II and results in a decrease in vascular resistance and blood pressure.
- Olmesartan is selective for AT1 and has a 12,500 times greater affinity for AT1 than the AT2 receptor.
- Also unlike other ARB like losartan, olmesartan does not have an active metabolite or possess uricosuric effects.

Zhang X et al. Cardiol Ther. 2017 Jun;6(1):13-32.

Olmesartan: Unique Structure

- Key structural elements of olmesartan medoxomil include:
  - a hydroxyalkyl substituent at the imidazole 4-position and
  - a hydrolyzable ester group at the imidazole 5-position.



- After oral administration, olmesartan medoxomil is deesterified in the intestinal tract to produce the active metabolite olmesartan.

- Unique pharmacological interaction of the drug with the AT1 receptor, results in a potent, long-lasting, dose-dependent blockade of A-II.

Mire DE et al. J Cardiovasc Pharmacol. 2005 Nov;46(5):585-93.

Pharmacokinetic properties

- Bioavailability is about 26%.
- Food does not affect the bioavailability of olmesartan.
- **Route of Elimination**
  - Olmesartan is elminated unchanged in the urine (35% to 50%) and the remainder in the feces.
- **Volume of Distribution**
  - The volume of distribution is 17 L and olmesartan poorly crosses the blood brain barrier.
- **Clearance**
  - Total plasma cl=1.3 L/h
  - Renal cl=0.6 L/h

Zhang X et al. Cardiol Ther. 2017 Jun;6(1):13-32.

Olmesartan – comparision with other ARBs

ARBs	Half-life (h)	Tmax (h)	Bioavail ability	Food Interaction	Drug Interactions	CYP metabolism
Losartan	2	1–1.5	33%	Yes	Rifampin, fluconazole	2C9, 3A4
Candesartan	9	2–5	42%	No	None	2C9
Eprosartan	5–9	1–3	63%	Yes	None	No
Irbesartan	11–15	1.3–3	70%	No		2C9, 3A4
Telmisartan	24	0.5–1	43%	No	Digoxin	No
Valsartan	6	2–4	23%	Yes	None	2C9
Olmesartan medoxomil	**12–14**	**1.7–2.5**	**26%**	**No**	**None**	**No**
Azilsartan medoxomil	12	1.5–3	60%	No	None	2C9, CYP2B6, CYP2C8

Abraham HM et al, Drug Saf. 2015 Jan;38(1):33-54.

Indications

- Indicated for treatment of hypertension.
- May be used alone or in combination with other antihypertensive agents.

DOSAGE AND ADMINISTRATION

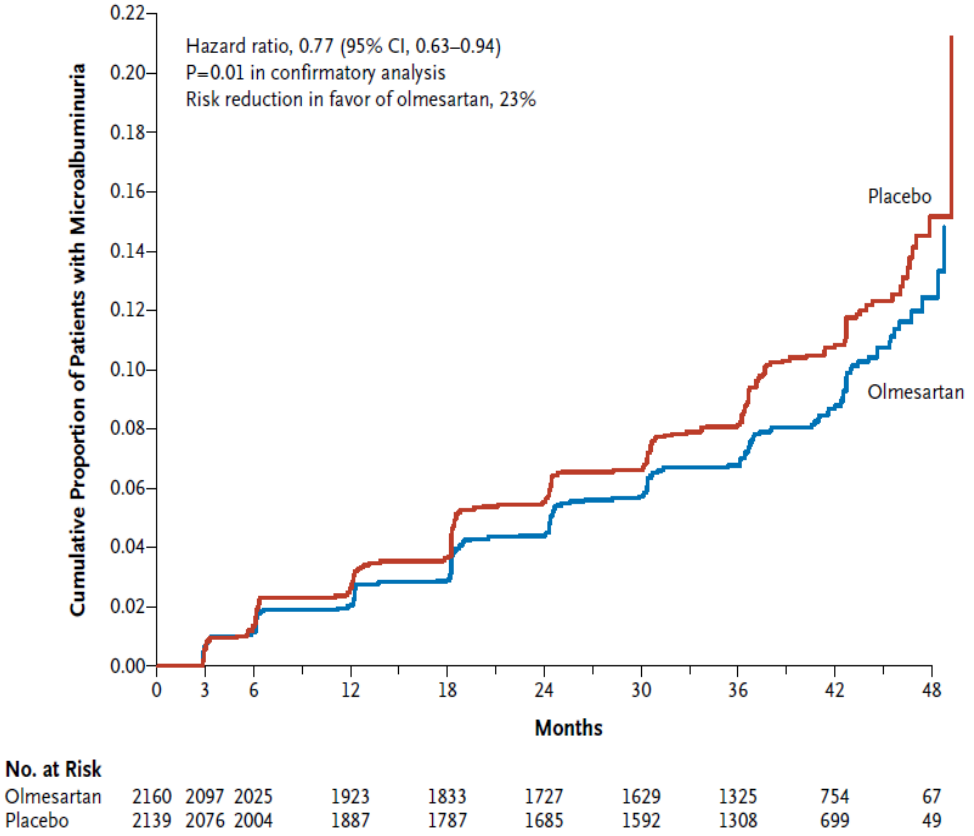
- Oral olmesartan, 10–40 mg once daily, is recommended for the treatment of adult patients with hypertension
- Dosage must be individualized.
- Starting dose is 20 mg once daily, dose be increased to 40 mg.
- No dosage adjustment is needed for elderly patients; patients with moderate renal impairment
- Can be administered with or without food.

Zhang X et al. Cardiol Ther. 2017 Jun;6(1):13-32.

Clinical Studies

ROADMAP Trial

- Randomized, double-blind, multicenter, controlled trial.
- 4447 patients with type 2 diabetes received olmesartan or placebo for a median of 3.2 years.
- The target blood pressure (<130/80 mm Hg) was achieved in nearly 80% of the patients taking olmesartan
- Olmesartan was associated with a delayed onset of microalbuminuria



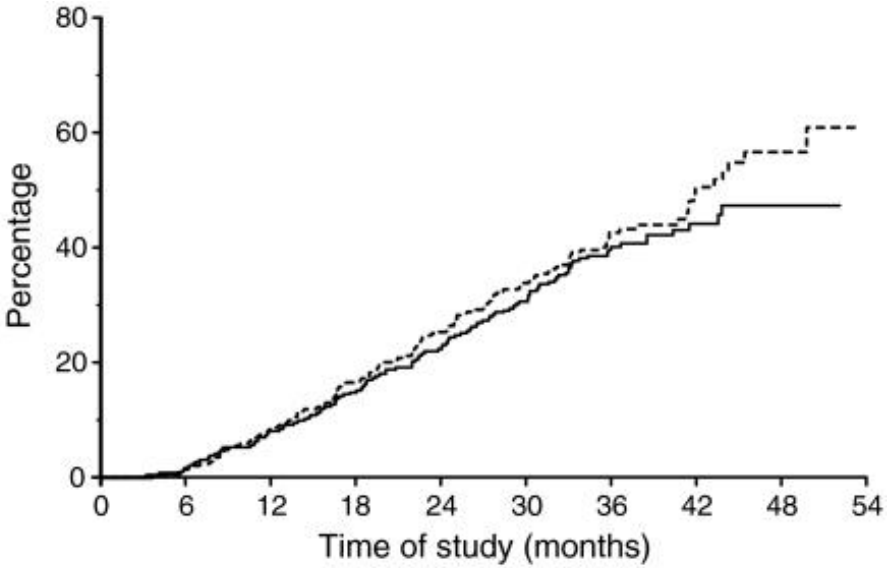
* **ROADMAP study:** Randomized Olmesartan and Diabetes Microalbuminuria Prevention

Haller H et al. N Engl J Med. 2011 Mar 10;364(10):907-17.

ORIENT STUDY

- The effects of olmesartan, an ARB, on serum creatinine, endstage renal disease and death in type 2 diabetic patients with overt nephropathy was evaluated in 577 subjects.

- Olmesartan significantly decreased blood pressure, proteinuria and rate of change of reciprocal serum creatinine.

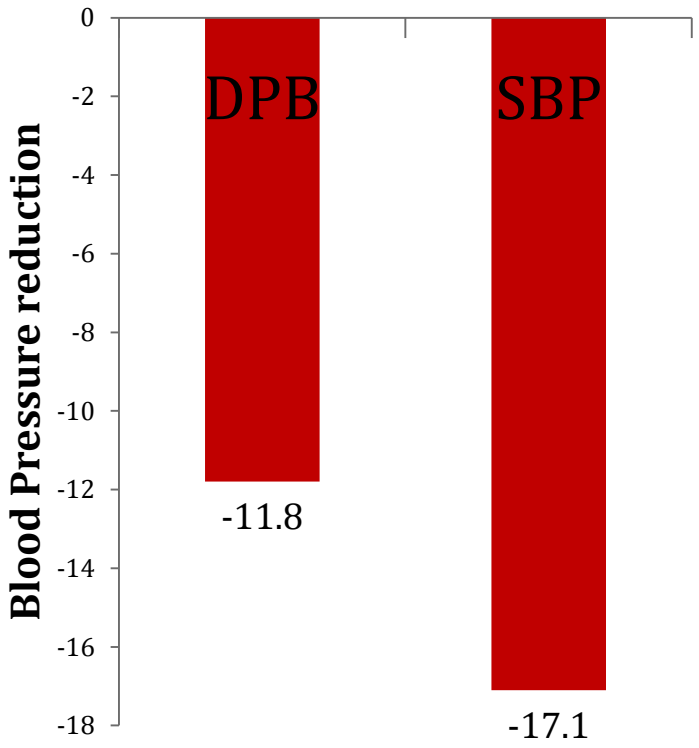


ORIENT Study: Olmesartan reducing incidence of endstage renal disease in diabetic nephropathy trial

Imai et al. Diabetologia. 2011 Dec; 54(12): 2978–2986.

OLMEBEST study

- The European, multinational, double-blind study in 823 patients on Olmesartan
- Results showed in a mean reduction of 11.8 mmHg in mean sitting diastolic blood pressure and 17.1 mmHg in mean sitting systolic blood pressure from baseline.
- Olmesartan was well tolerated, with no severe clinical outcomes reported.

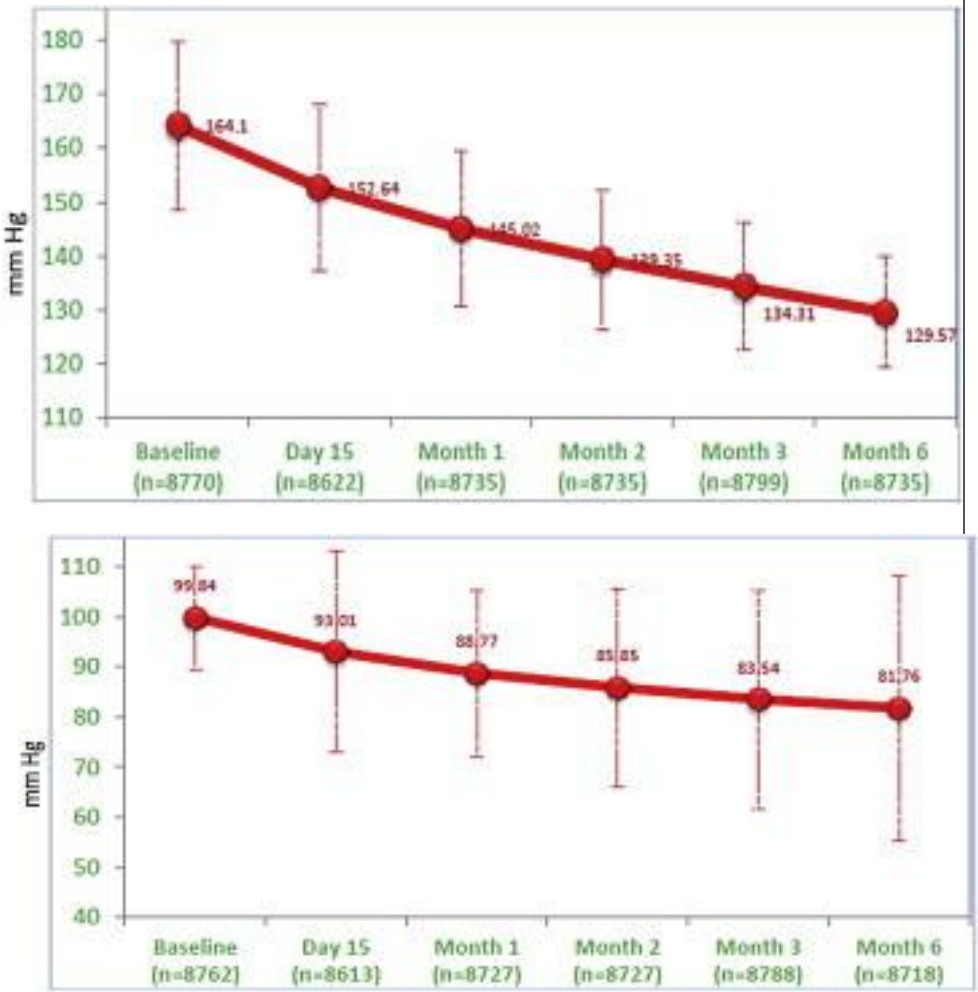


*OLMEBEST= Olmesartan Efficacy Safety and TolerabilityStudy

Böhm M et al, Curr Med Res Opin. 2006 Jul;22(7):1375-80.

Efficacy and safety of Olmesartan in Indian patients with Hypertension

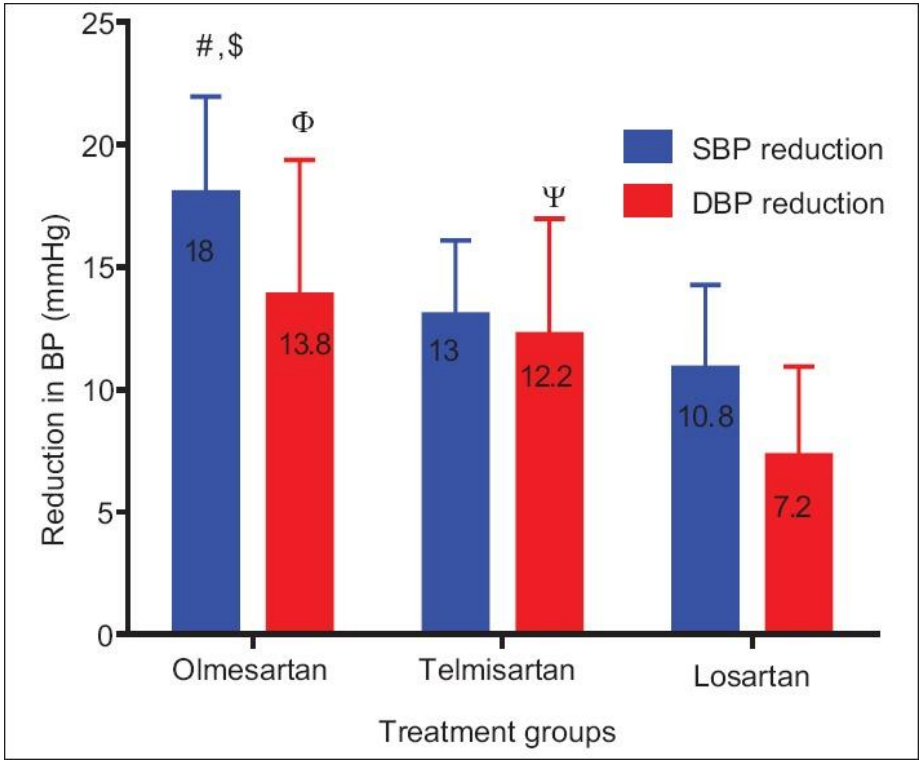
- The open-label, non-comparative, multi-centric study.
- 8940 adults patients (>18 years) with essential HTN with co-morbidities.
- Patients were treated with olmesartan tablet 20 or 40 mg once daily for 6 months.
- 96.48% of patients was rated as good when assessed by the treating physicians.



Kumbla DK et al, Indian Heart J. 2014 May-Jun;66(3):340-4

Olmesartan *vs* Telmisartan and Losartan

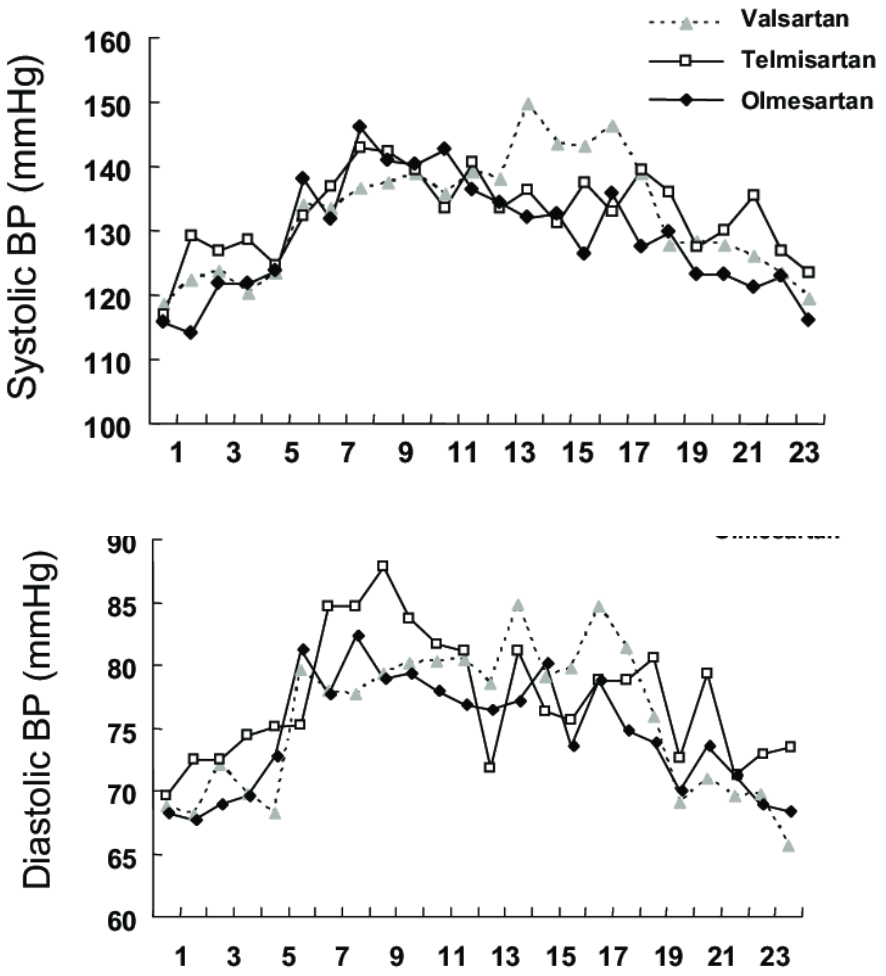
- Randomized, open-label, parallel-group, comparative study.
- Olmesartan were more efficacious than losartan , telmisartan in reducing BP
- Serum total cholesterol, triglycerides, and low-density lipoproteins decreased significantly after 12-week treatment with olmesartan and telmisartan.



Kalikar et al. J Pharmacol Pharmacother. 2017 Jul-Sep; 8(3): 106–111

Olmesartan vs Telmisartan on BP and metabolic parameters

- Open-label prospective crossover study, comparing the effects of olmesartan and telmisartan
- Olmesartan lowered mean systolic and diastolic blood pressure more significantly than did telmisartan.
- The decreases in serum interleukin-6 and highly sensitive C-reactive protein were more significant by olmesartan treatment.
- Results indicate that olmesartan has more potent arterial blood pressure lowering and anti-inflammatory effects than telmisartan.

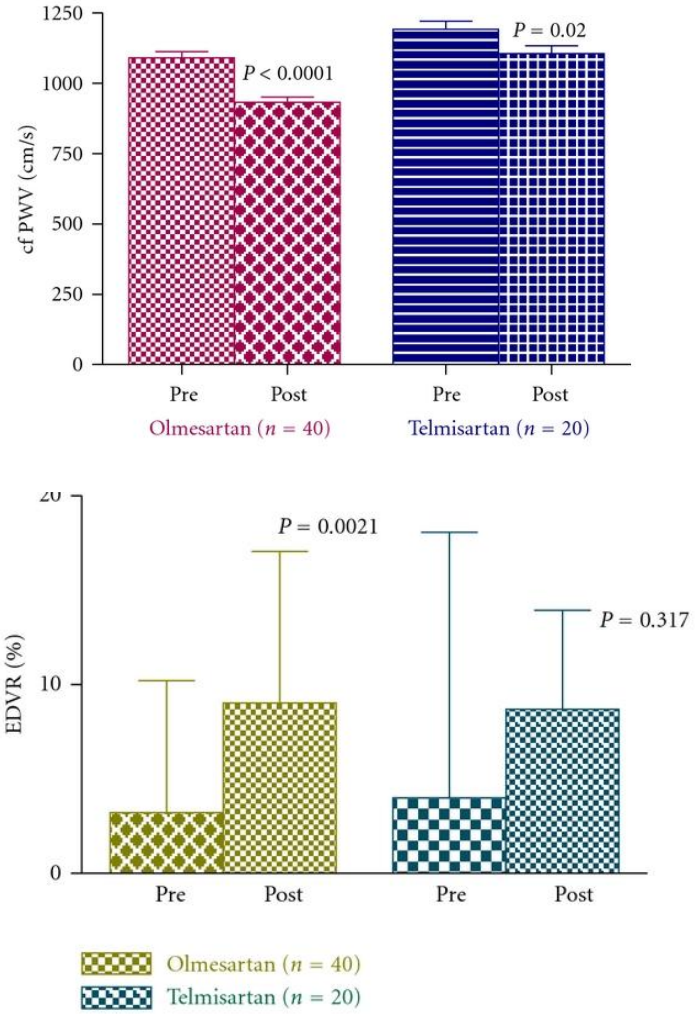


Nakayama S et al. Hypertens Res. 2008 Jan;31(1):7-13.

Olmesartan vs Telmisartan

- Randomised open label study to evaluate Olmesartan vs telmisartan on Vascular Hemodynamics, Arterial Stiffness, and Oxidative Stress in Patients with Mild to Moderate Hypertension

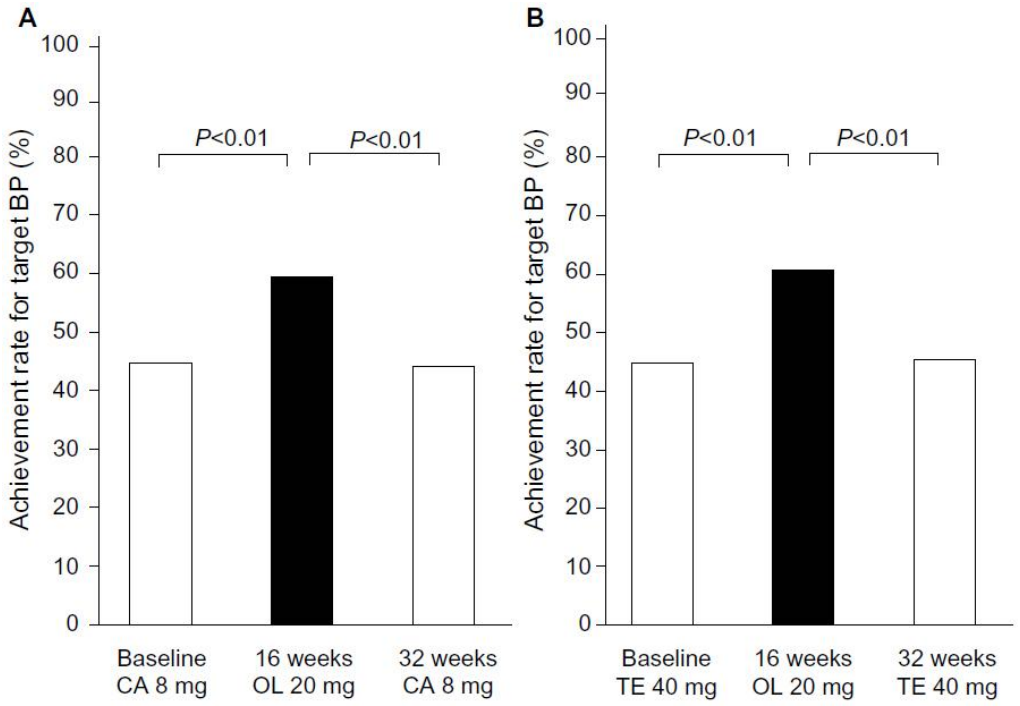
- Olmesartan showed a better improvement in cf PWV, EDVR, and MDA than Telmisartan with an identical reduction in blood pressure.



Pathapati RM et al. J Clin Diagn Res. 2015 Nov; 9(11): FC13–FC16.

Olmesartan, Telmisartan, Candesartan, in hypertensive patients with type 2 diabetes: The COTO study

- Two studies were done concurrently to investigate the effects of switching from candesartan or telmisartan to olmesartan.
- Clinic BP, morning home BP, and urinary albumin were significantly increased again 16 weeks after switching back to candesartan or telmisartan



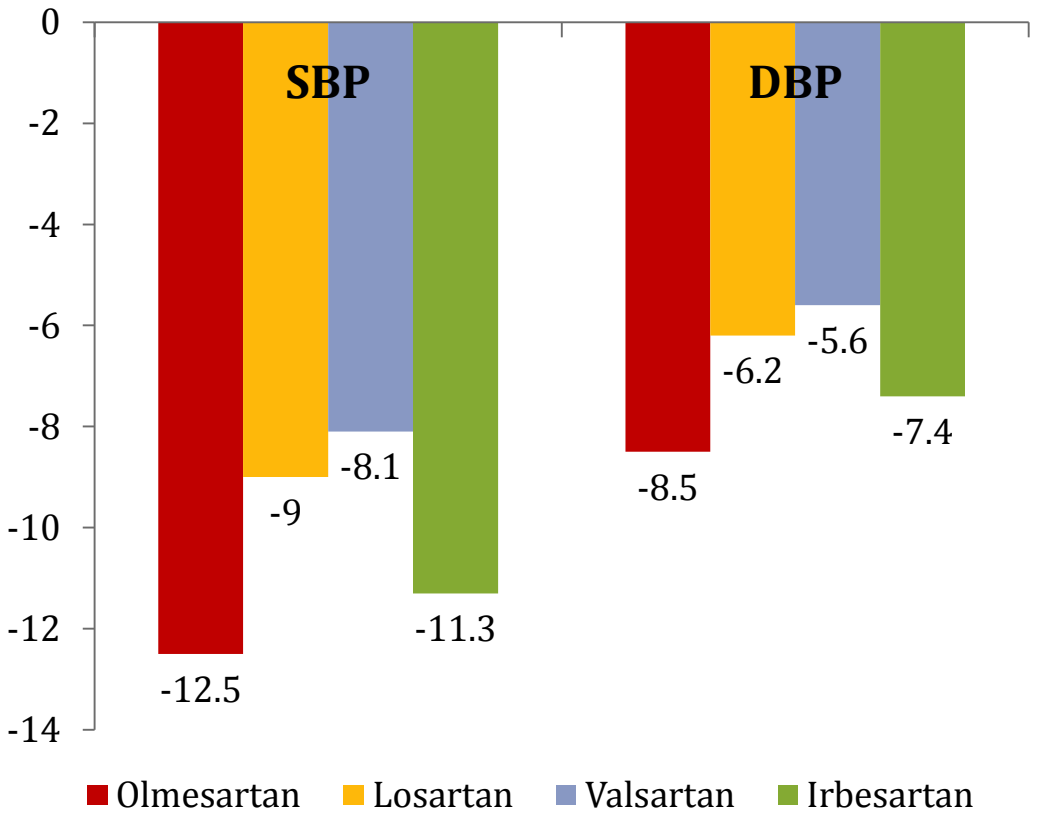
*COTO study = switching from Candesartan to Olmesartan or Telmisartan to Olmesartan

Daikuhara H, et al. Drug Des Devel Ther. 2014; 8: 219–226.

Olmesartan with other ARBs

- Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in a multicenter, randomized, double-blind trial in 588 patients

- Compared with other ARBs, Olmesartan is more effective in reducing BP in patients with essential hypertension.



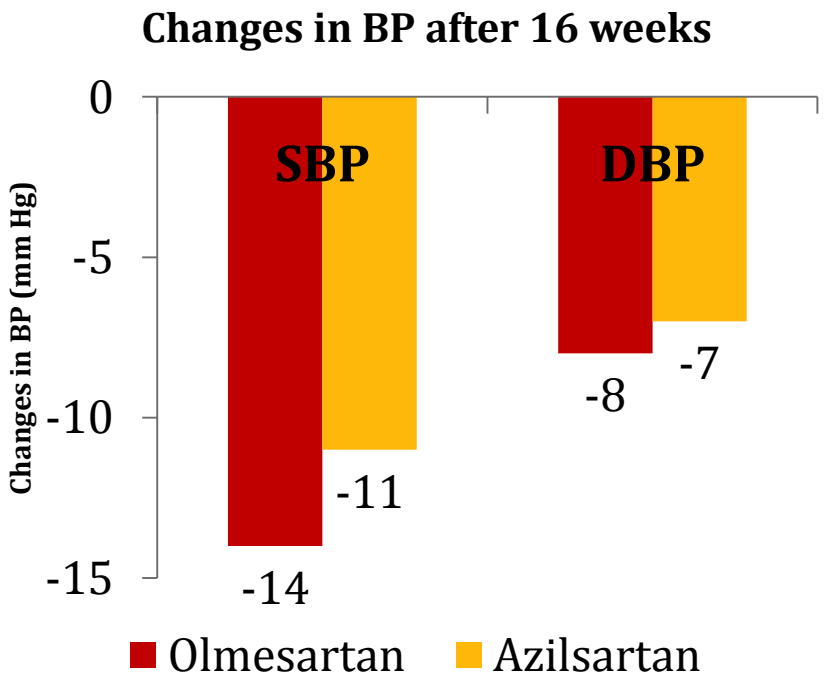
Oparil S et al J Clin Hypertens (Greenwich). 2001 Sep-Oct;3(5):283-91, 318.

MUSCAT-4 study - Olmesartan Vs azilsartan

Multicenter randomized controlled trial

Olmesartan vs Azilsartan:

- Effectively reduced SBP and DBP
- Showed a reno-protective effect and well tolerated without any major adverse events.

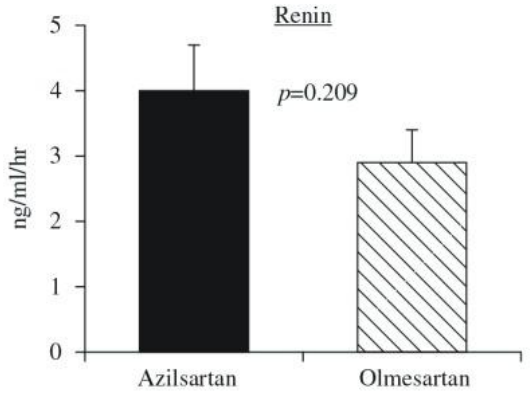


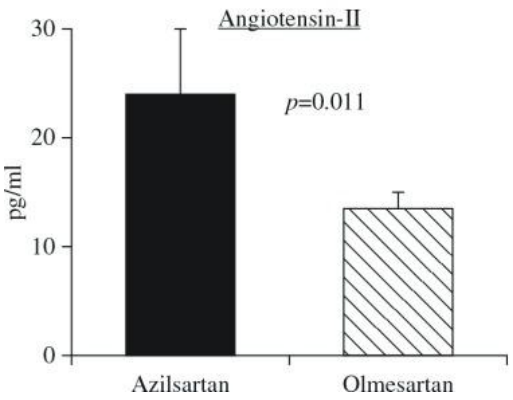
*MUSCAT-4 study= Olmesartan versus azilsartan in patients with hypertension: a multicenter randomized-controlled trial

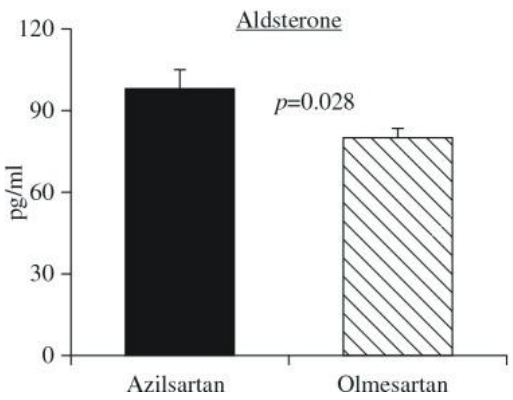
Kakio Y et al, Blood Press Monit. 2017 Apr;22(2):59-67.

CHAOS Study - Olmesartan Vs azilsartan

- Comparing efficacy of olmesartan vs azilsartan in outpatients who were clinically stable after cardiac surgery.
- Olmesartan reduces angiotensin II and aldosterone levels more effectively than azilsartan.
- May be effective in patients with increased renin-angiotensin-aldosterone system activity after cardiac surgery.







CHAOS study= The CHangeover trial of Azilsartan and Olmesartan comparing effects on the renin-angiotensin-aldosterone System

Sezai A et al, Ann Thorac Cardiovasc Surg. 2016; 22(3): 161–167.

Summary

- Olmesartan medoxomil, prodrug is rapidly and completely de-esterified to the active metabolite olmesartan
- Olmesartan has unique structure
- Highly selective for AT1 receptors and greater affinity than most other ARBs.
- Olmesartan binds to the type 1 receptor with high degree of insurmountability
- Olmesartan potentiates the action of Ang-(1-7) in RAAS pathway
- No food and drug interactions

Zhang X et al. Cardiol Ther. 2017 Jun;6(1):13-32.
Mire DE et al. J Cardiovasc Pharmacol. 2005 Nov;46(5):585-93.
Sada T et al, Nihon Yakurigaku Zasshi. 2004 Oct;124(4):257-69.

Summary

- Olmesartan is more effective in reducing BP in patients with essential hypertension than Losartan, Valsartan
- Olmesartan shows better improvements in Vascular Hemodynamics, Arterial Stiffness, and Oxidative Stress compared to telmisartan
- Olmesartan has more potent arterial blood pressure lowering and anti-inflammatory effects than telmisartan.
- Olmesartan shows similar anti hypertensive efficacy and reduces angiotensin II and aldosterone levels more effectively than Azilsartan.
- Olmesartan has shown reno protective effects than Azilsartan

Oparil S et al J Clin Hypertens (Greenwich). 2001 Sep-Oct;3(5):283-91, 318.
Sezai A et al, Ann Thorac Cardiovasc Surg. 2016; 22(3): 161–167.
Pathapati RM et al. J Clin Diagn Res. 2015 Nov; 9(11): FC13–FC16