Benidipine: An Insight

Hypertension Burden

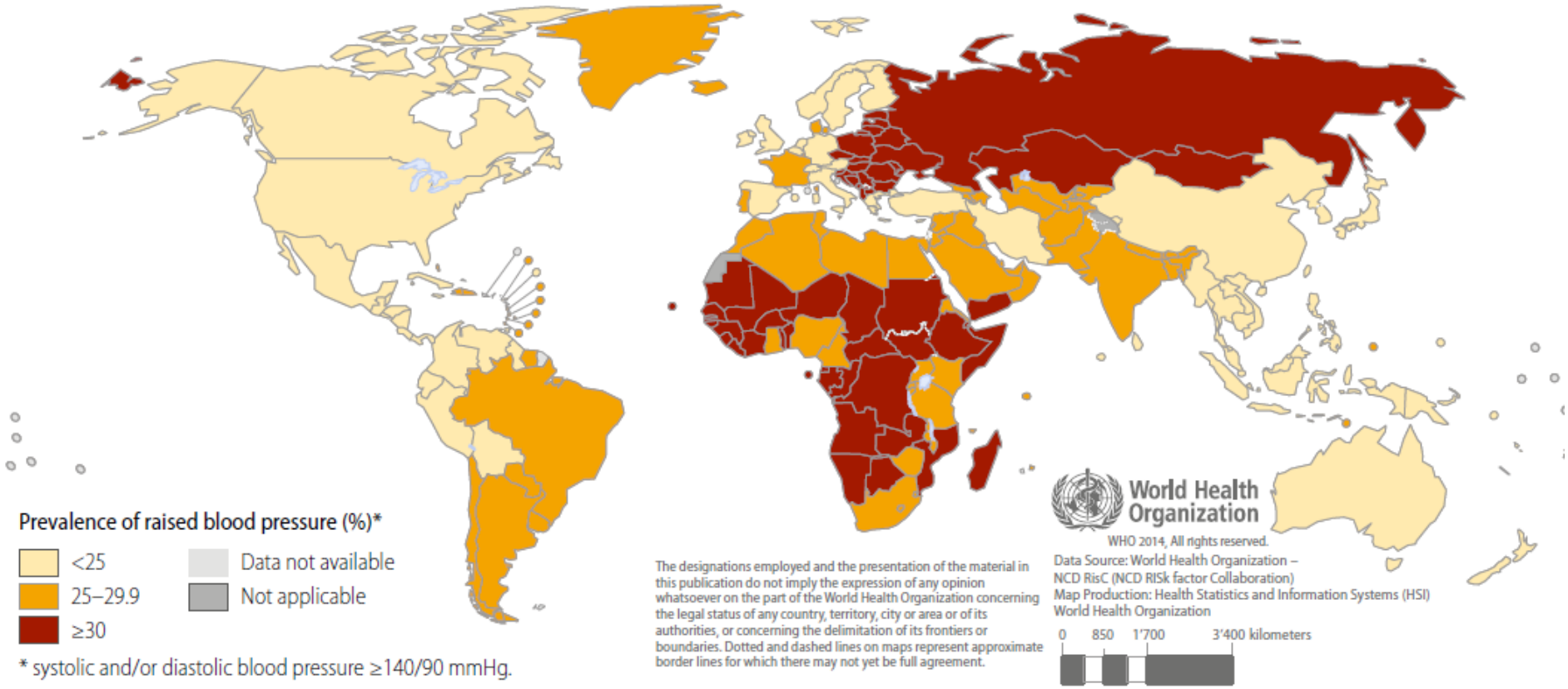
970 million	Worldwide prevalence
60%	Increase in the number of adults with HTN globally by 2025
10%	Percent of all global healthcare spending attributable to HTN
$370 billion	Annual worldwide cost of hypertension

1.6 Billion HTN patients estimated by 2025

Singh PS et al. Int J Res Med Sci. 2017 Apr;5(4):1451-1455
World-heart-federation.org. [Accessed 10 May 2017]

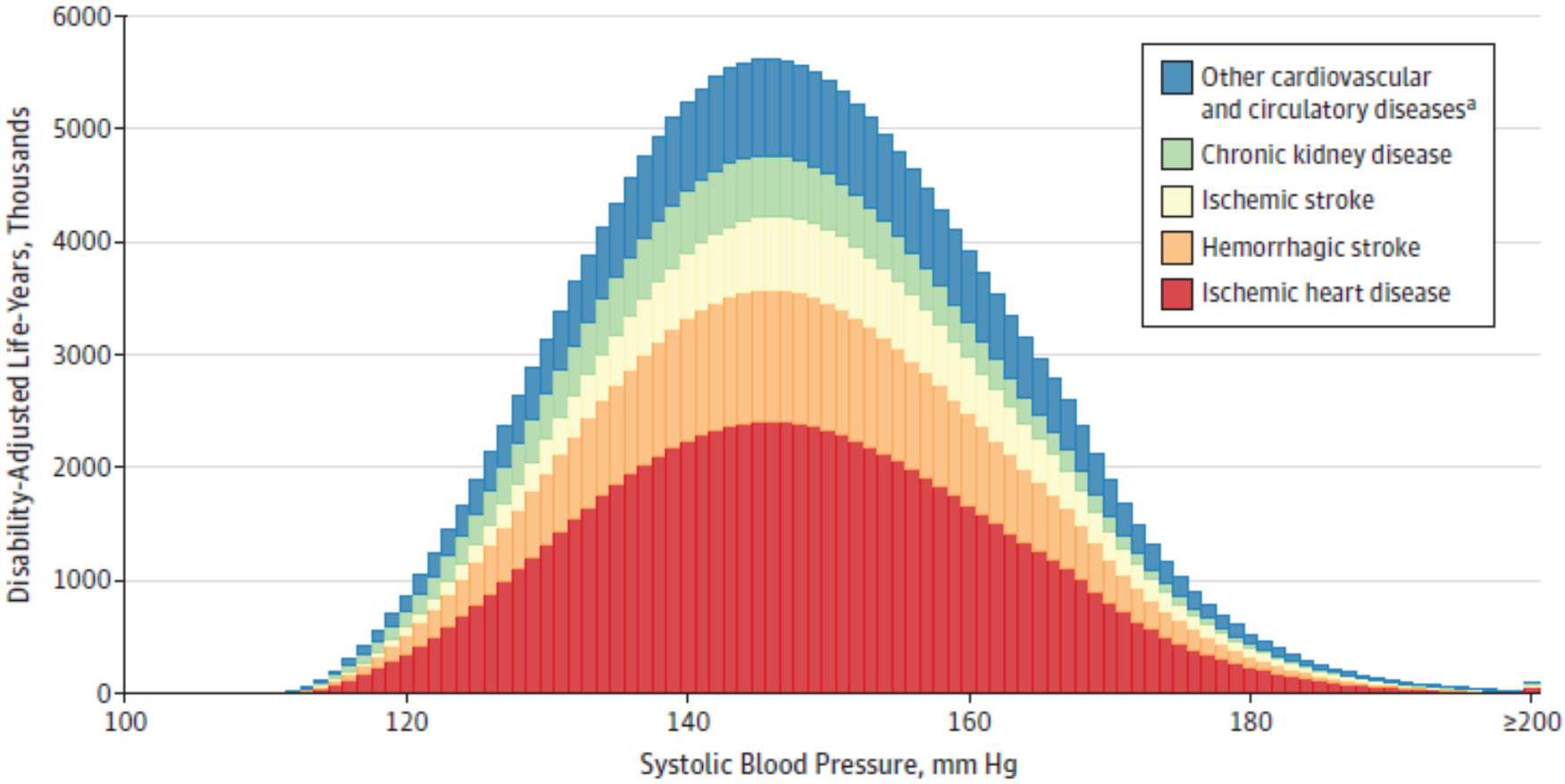
Hypertension: WHO Estimates

- **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.

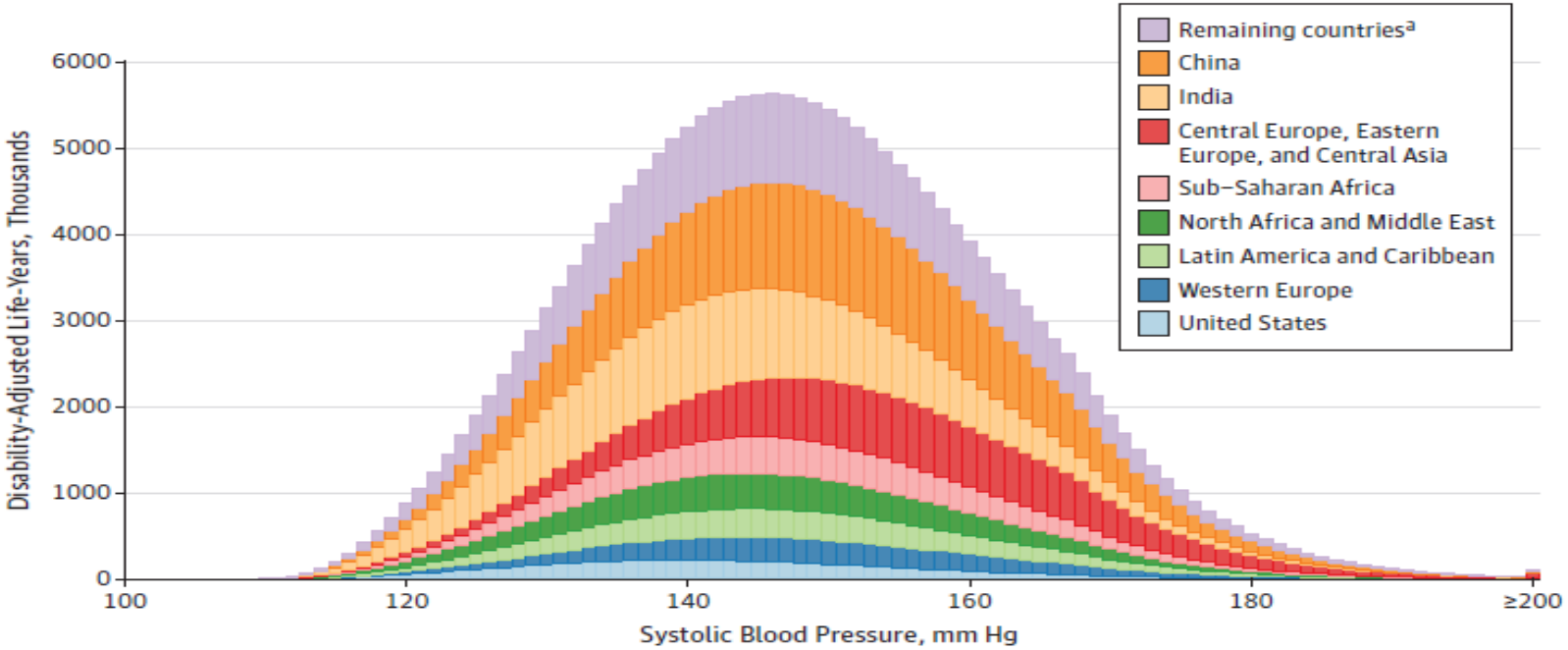
Global Disability-Adjusted Life-Years by Systolic BP Level and Cause



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

Projected Global DALY by SBP

- Of the global burden of 212 million DALYs related to SBP of at least 110 to 115 mm Hg,
  - DALYs in India - 38.7 million



DALY = Disability-Adjusted Life-Years

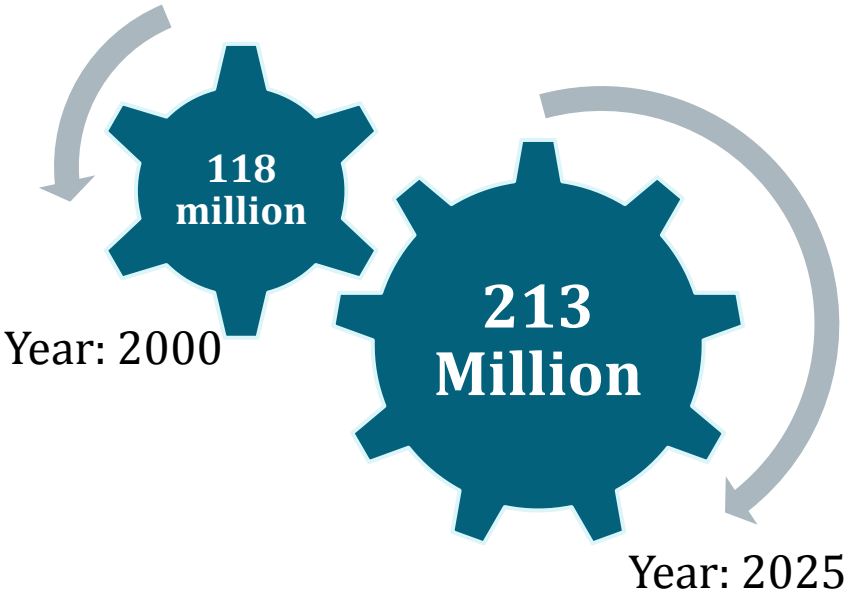
Forouzanfar MH et al. JAMA. 2017 Jan 10;317(2):165-182.

Hypertension In India

- Responsible for

57% • of all stroke deaths

24% • all deaths due to CHD

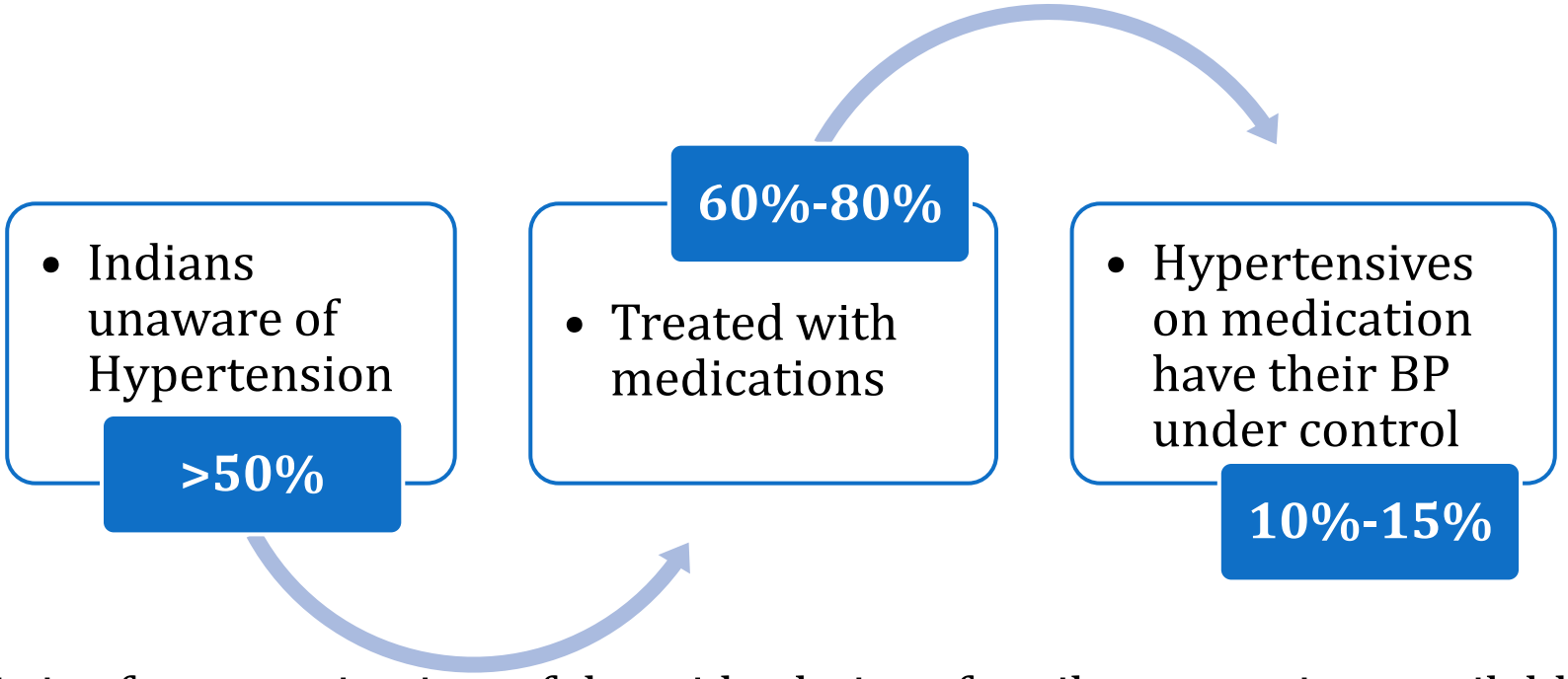


Incidence of hypertension is expected to almost double to 213 million by 2025 in India

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

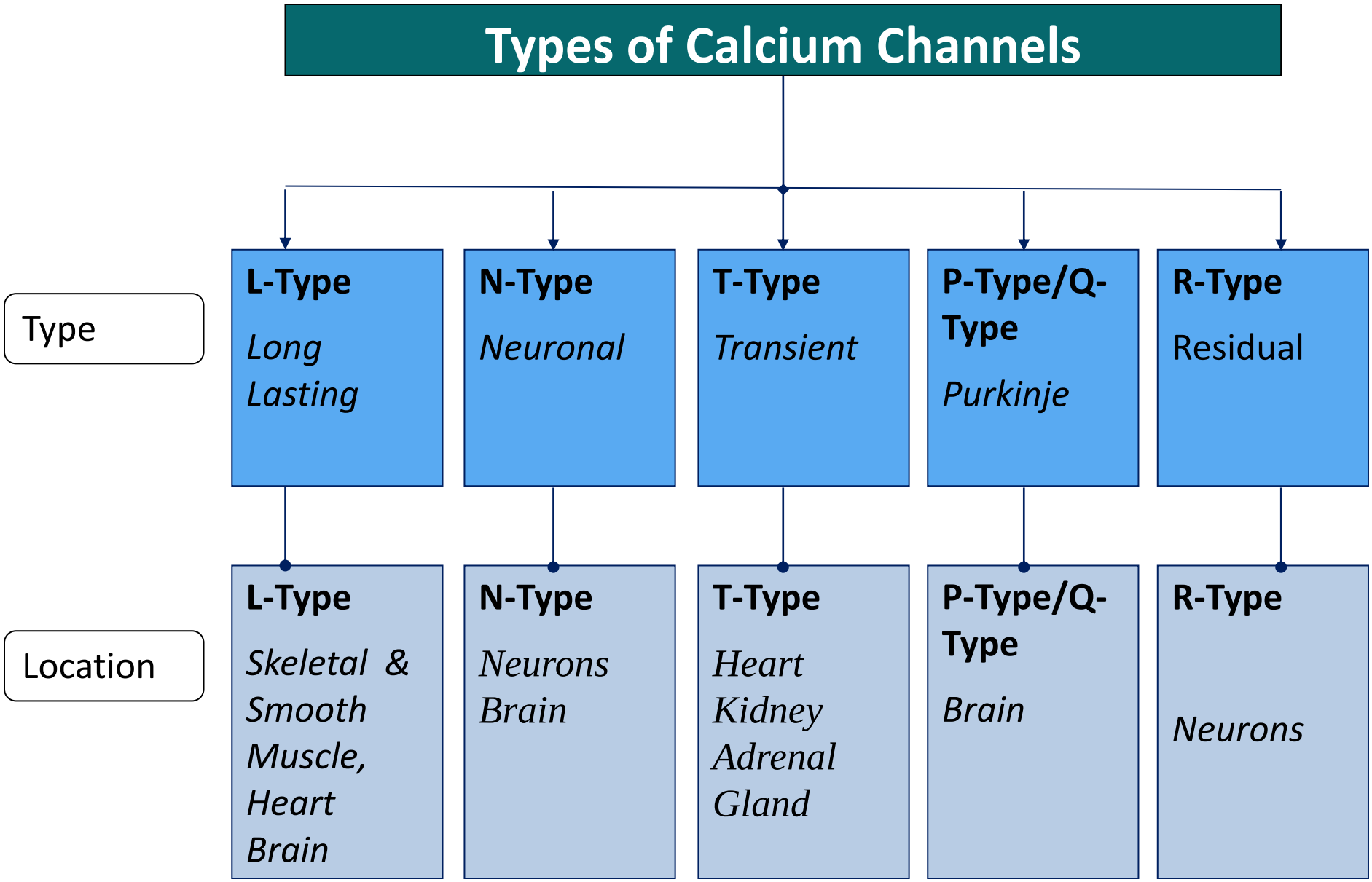
Gupta R *et al.* Indian J Med Res. 2014 May; 139(5): 657–660

Calcium channel blockers

- Calcium channel blocker (CCB) has become one of the most important initial agents for the management of hypertension.
- CCBs have been proved not to increase the risk of coronary events and stroke.
- CCBs appear to be a favorable choice for monotherapy as well as for combination with other agent classes in the treatment of hypertension and may provide specific benefits beyond BP lowering.
- Dihydropyridine CCBs are one group of most frequently prescribed antihypertensive medications

Hayashi K, Keio J Med. 2010;59(3):84-95.

Types of Calcium Channels



Hayashi K, Keio J Med. 2010;59(3):84-95.

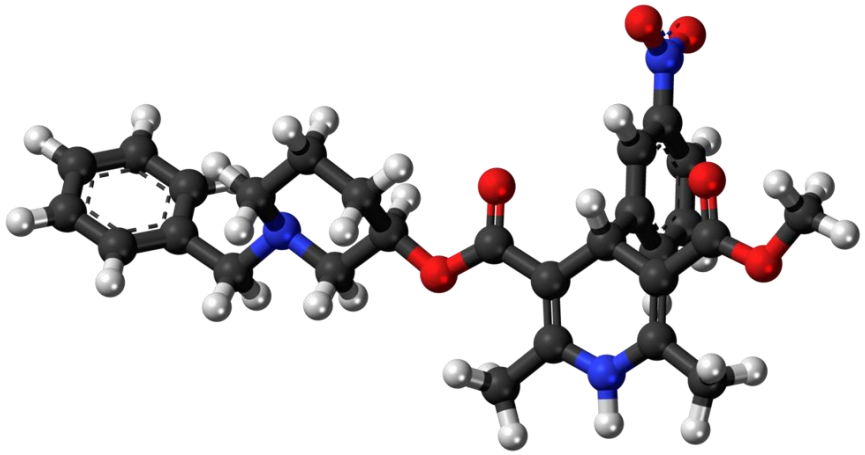
Different types of Calcium channel blockers

- Based on the chemical structure, CCBs are categorized into 3 subgroups:
  - *Benzothiazepines* (e.g., diltiazem and clenazem),
  - *Phenylalkylamines* (e.g., verapamil and gallopamil)
  - *Dihydropyridines* (e.g., ***Benidipine,*** nifedipine, nicardipine, felodipine, amlodipine, aranidipine, azelnidipine, cilnidipine, efonidipine, manidipine, nilvadipine).

Ozawa Y, Curr Hypertens Rev. 2006 May 1;2(2):103-111
Chandra KS, Indian Heart J. 2013 Dec;65(6):691-5.

Benidipine

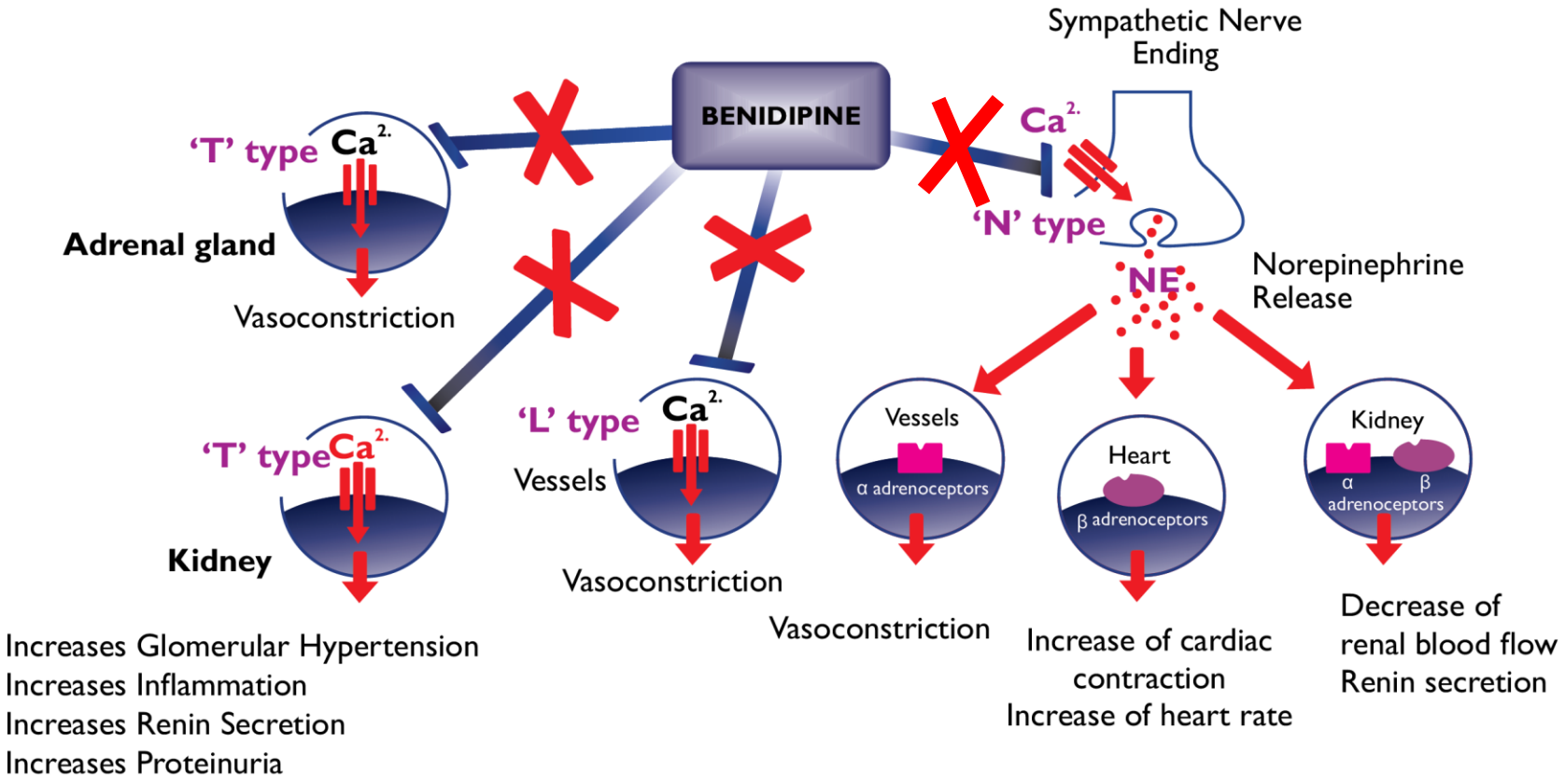
- Benidipine is a dihydropyridine derived calcium channel blocker.
- Bendipine is the only CCB with triple Calcium channel blocking action (L, N and T type Ca^{2+} channel).
- Benidipine is effective as a long-lasting antihypertensive and antianginal agent.



Yao K. J Pharmacol Sci. 2006 Apr;100(4):243-61.
Furukawa T, et al. Eur J Pharmacol 2009; 613: 100–107
Hayashi K et al. Keio J Med. 2010;59(3):84-95.

Benidipine- The Unique CCB

- Benidipine has unique action not seen in other CCBs



Yao K. J Pharmacol Sci. 2006 Apr;100(4):243-61.
Furukawa T, et al. Eur J Pharmacol 2009; 613: 100–107
Hayashi K et al. Keio J Med. 2010;59(3):84-95.

Clinical Significance of various calcium channel blockade

	L - type	**N - type**	**T - type**
Heart	Contractility ↓	Heart rate ↓	Heart rate ↓
Blood vessels	Vasodilatation	Vasodilatation	Vasodilatation
Sympathetic nervous system	Pulse rate ↑	Pulse rate ↓	Pulse rate ↓
Kidney	Glomerular pressure ↑	Glomerular pressure ↓	Glomerular pressure ↓
Adrenal	-	-	Aldosterone secretion ↓

Furukawa T, et al. Eur J Pharmacol 2009; 613: 100–107

Inhibitory activity of various CCBs

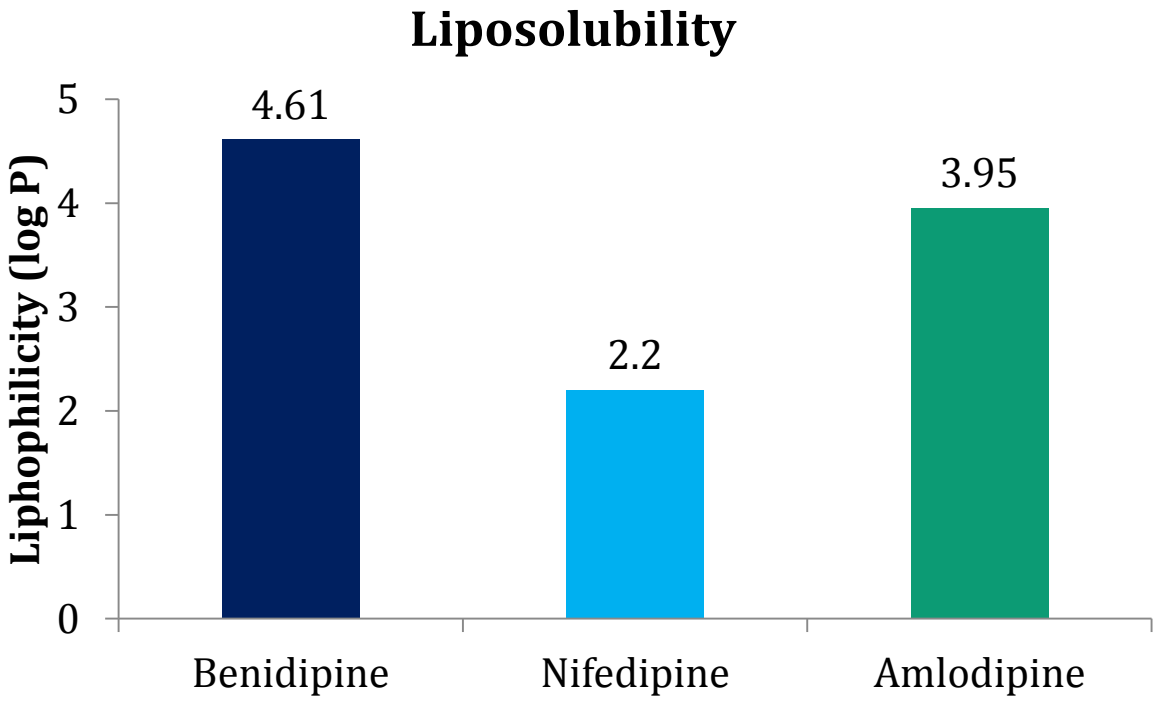
Inhibition of Calcium Channels			
Drugs	**L - type**	**N - type**	**T - type**
Nifedipine	+	X	X
Amlodipine	+	X	X
Efonidipine	+	X	+
Azelnidipine	+	X	+
Benidipine	+	+	+
Cilnidipine	+	+	X

- Benidipine is the only CCB which inhibits L-type Ca^{2+} channel, N-type Ca^{2+} channel, and T-type Ca^{2+} channels.

Furukawa T, et al. Eur J Pharmacol 2009; 613: 100–107
Hayashi K et al. Keio J Med. 2010;59(3):84-95.

High Liposolubility

- Benedipine has the highest liposolubility compared with Nifedipine and Amlodipine



Yao K. J Pharmacol Sci. 2006 Apr;100(4):243-61. .

High affinity for binding site

- Benidipine has high affinity for the dihydropyridine (DHP) binding site
- The Ki value is 0.08 – 0.13 nmol/L, which is higher than nisoldipine, nicardipine, nitrendipine, verapamil, and diltiazem.
- Dissociation of benidipine takes place very slowly.

Vascular Selectivity

- The coronary artery selectivity of benidipine, 14.4 times higher than that of nifedipine and 19 times higher than that of amlodipine.

High vascular selectivity, liphosolubility is associated with vasodilative and vaso-protective effects

Yao K. J Pharmacol Sci. 2006 Apr;100(4):243-61. .

Salient Pharmacokinetics

Peak Plasma Conc.	<2 hours
Bioavailability	60%
Protein binding	98%
Metabolism	in the liver by the hepatic enzyme cytochrome P450 (CYP)
Absorption affected by food	No
Excretion/elimination	primarily excreted via bile into feces. Urinary excretion: 36%.
Half life	2 hrs
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.

Yao K. J Pharmacol Sci. 2006 Apr;100(4):243-61

Benidipine Dosage & Administration

Recommended Dose

- Hypertension (Adult): 2-4 mg once daily increased to 8 mg once daily, if necessary.
- Angina Pectoris (Adult): 4 mg twice daily

Indication

- Hypertension
- Long-term prophylactic management of angina pectoris

Special Population

- **Pregnancy :** Safety and effectiveness of benidipine in pregnant women have not been established.
- **Lactation:** There is no established safety data.
- **Pediatric use:** Not been established.
- Contraindicated in patients with hypersensitivity to any component in the product.

Yao K. J Pharmacol Sci. 2006 Apr;100(4):243-61. .

CLINICAL EVIDENCES

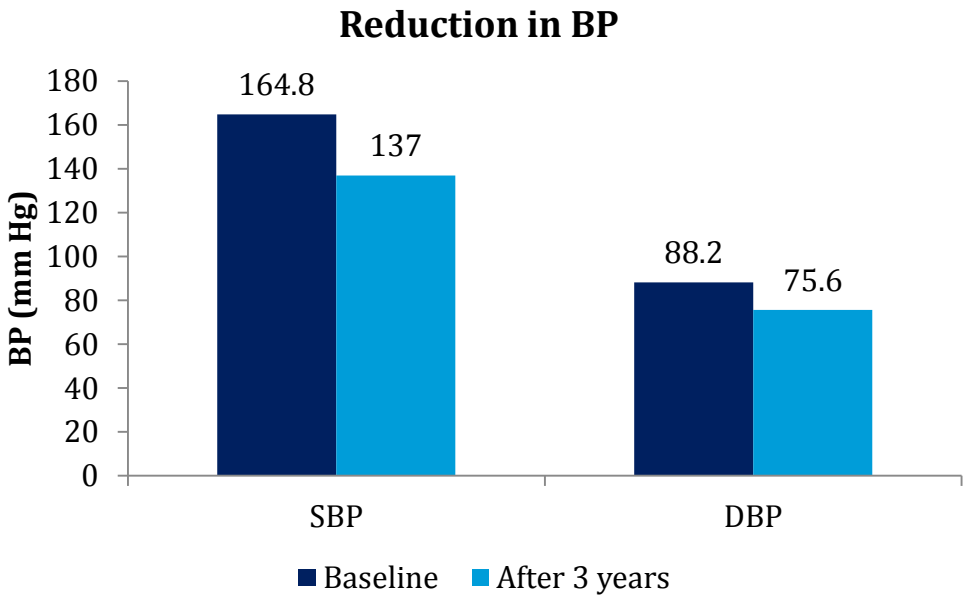
Benidipine in elderly hypertensive patients: J-BRAVE study

Objective	To investigate the achievement rate of blood pressure (BP) target and the relationship between on-treatment BP and development of cardiovascular events (i.e., stroke, myocardial infarction, and heart failure)	
Study design	A prospective, 3-year observational study of Benidipine based treatment in hypertensive patients aged ≥65 years as a post-marketing surveillance **J-BRAVE:** Japan's Benidipine Research on Antihypertensive Effects in the Elderly	
Patient Population	No. of patients	8,897
	Age group	≥65 years
	mean baseline SBP mean baseline DBP	164.8 ± 14.1 mmHg 88.2 ± 10.3 mmHg

Saito I et al. Effect of antihypertensive treatment on cardiovascular events in elderly hypertensive patients: Japan's Benidipine Research on Antihypertensive Effects in the Elderly (JBRAVE). Clin Exp Hypertens. 2011;33(2):13340.

J-BRAVE study Results…

- Blood pressure decreased significantly from 164.8 ± 14.1/88.2 ± 10.3 mmHg to 137.0 ± 13.5/75.6 ± 9.5 mmHg and the percentage of patients who achieved BP <140/90 mmHg was 57.2% after 3 years.



Benidipine, with a favorable tolerability profile, provides a long-term antihypertensive effect and lesser CV events

Saito I et al. Effect of antihypertensive treatment on cardiovascular events in elderly hypertensive patients: Japan's Benidipine Research on Antihypertensive Effects in the Elderly (JBRAVE). Clin Exp Hypertens. 2011;33(2):13340.

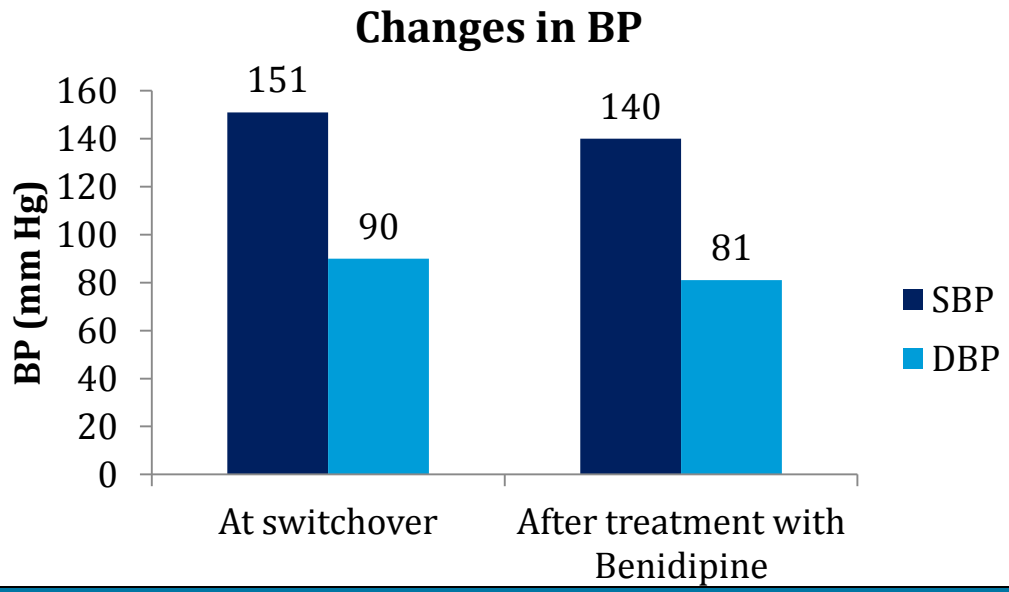
Amlodipine-to-Benidipine Changeover (ABC) Study

Objective	To evaluate blood pressure and proteinuria after changeover from amlodipine to benidipine in poorly controlled hypertensive patients	
Study design	Patients administered 5 mg of amlodipine once a day for at least 3 months. Uncontrolled patients were switched to benidipine and BP post-changeover was measured at 1 month and 2 months.	
Patient Population	No. of patients	58
	Average Age	64.1±12.8 years
	mean switchover SBP/DBP	151/90 mmHg

Ohishi M et al. Renal-protective effect of T-and L-type calcium channel blockers in hypertensive patients: an Amlodipine-to-Benidipine Changeover (ABC) study. Hypertens Res. 2007 Sep;30(9):797-806.

ABC Study – Results…

- >80% of patients reduced their BP and >40% achieved optimal BP.
- Higher urinary protein excretion (p<0.0001), lower GFR (p=0.0011) and presence of diabetes (p=0.0284) were correlated with reduction of urinary proteins during changeover.



Benidipine has greater efficacy than amlodipine in reducing blood pressure and proteinuria.

Ohishi M et al. Renal-protective effect of T-and L-type calcium channel blockers in hypertensive patients: an Amlodipine-to-Benidipine Changeover (ABC) study. Hypertens Res. 2007 Sep;30(9):797-806.

Effect of Benidipine vs Cilnidipine on blood pressure and renal function in hypertensive patients with diabetes mellitus

Objective	To evaluate the effects of switching from cilnidipine to benidipine on blood pressure (BP) lowering and renal function.	
Study design	Patients administered cilnidipine OD for at least 3 months. Uncontrolled patients were switched to benidipine and BP post-changeover was measured at 3 months.	
Patient Population	No. of patients	40
	Average Age	61.1±9.8 years
	Mean SBP/DBP	155.8 +/- 13.7 mmHg 76.5 +/- 13.3 mmHg

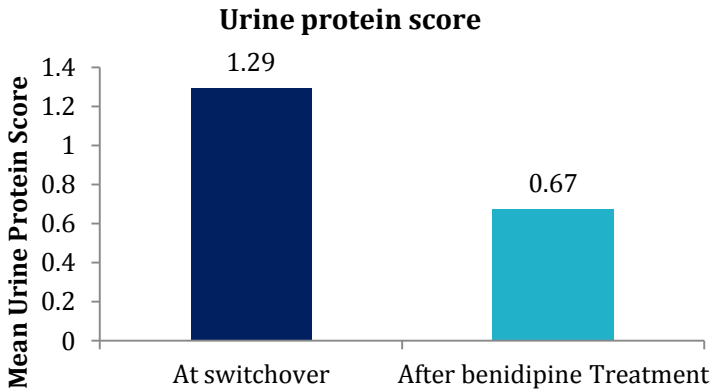
Seino H et al. Effect of benidipine hydrochloride, a long-acting T-type calcium channel blocker, on blood pressure and renal function in hypertensive patients with diabetes mellitus. Analysis after switching from cilnidipine to benidipine. Arzneimittelforschung. 2007;57(8):526-31.

Effect of Benidipine vs Cilnidipine - Results..

- BP (systolic/diastolic) significantly decreased after treatment with benidipine and this effect was stably maintained for one year.

Changes in Blood Pressure after one year		
	Baseline	After Treatment
SBP mm Hg	155.8 ± 13.7	145.9 ± 17.0
DBP mm Hg	76.5 ± 13.3	71.4 ± 13.7

- Urine protein (UP) scores also significantly decreased from 1.29 to 0.67 in the mean score (after 3 months)



Benidipine has a more potent antihypertensive effect than cilnidipine and also has renoprotective effect

Seino H et al. Effect of benidipine hydrochloride, a long-acting T-type calcium channel blocker, on blood pressure and renal function in hypertensive patients with diabetes mellitus. Analysis after switching from cilnidipine to benidipine. Arzneimittelforschung. 2007;57(8):526-31.

Prognostic effects of benidipine in patients with vasospastic angina: comparison with diltiazem and amlodipine

Objective	Comparison of the prognostic effects of 3 calcium channel blockers (benidipine, diltiazem, and amlodipine) on the incidence of cardiovascular events in patients with VSA	
Study design	Prospective cohort study	
Patient Population	No. of patients	527
	Average Age	65±9.5 years

Fukumoto Y, et al. Prognostic effects of benidipine in patients with vasospastic angina: comparison with diltiazem and amlodipine. J Cardiovasc Pharmacol. 2008 Mar;51(3):253-7.

Prognostic effects of benidipine in patients with vasospastic angina: comparison with diltiazem and amlodipine - Results

Benidipine is associated with lower incidence of total events, CV events, and cerebral infarction, compared with diltiazem and amlodipine.

Drug	Events	Odds Ratio	P value
Benidipine	total events	0.656	NS
	cardiovascular events	0.323	NS
	cerebral infarction	0.287	NS
	vascular infarction events	0.303	0.015
Diltiazem	total events	1.879	0.039
	cardiovascular events	1.651	NS
	cerebral infarction	5.777	0.022
	vascular infarction events	2.358	0.017
Amlodipine	total events	0.837	NS
	cardiovascular events	0.646	NS
	cerebral infarction	0.649	NS
	vascular infarction events	0.670	NS

Benidipine has beneficial prognostic effects in patients with VSA as compared with diltiazem and amlodipine.

Fukumoto Y, et al. Prognostic effects of benidipine in patients with vasospastic angina: comparison with diltiazem and amlodipine. J Cardiovasc Pharmacol. 2008 Mar;51(3):253-7.

Comparative effects of Benidipine and Amlodipine on renal function in early-stage CKD

Objective	To evaluate the effects of benidipine and amlodipine on renal, inflammatory, oxidative, and atherosclerosis markers in hypertensive patients with mild chronic kidney disease (CKD)	
Study design	Double blind randomized comparative trial for 12 months	
Patient Population	No. of patients	40
	Average Age	62±7.8 years
	Mean SBP/DBP	155.8 +/- 13.7 mmHg 86.5 +/- 13.3 mmHg

Nakamura T et al. Comparative effects of benidipine and amlodipine on proteinuria, urinary 8-OHdG, urinary L-FABP, and inflammatory and atherosclerosis markers in early-stage chronic kidney disease. Am J Med Sci. 2010 Feb;339(2):157-63

Comparative effects of Benidipine and Amlodipine on renal function in early-stage CKD -- Results

- Serum creatinine and estimated glomerular filtration rate changed minimally during the experimental period in each group.

- Urinary protein excretion*, urinary liver-type fatty acid-binding protein,* urinary 8-hydroxy-2'-deoxyguanosine*, blood interleukin-6*, blood high mobility group box-1#, and pulse wave velocity* decreased more in Benidipine group than in Amlodipine group with 12 months of treatment.

- The percent reductions in intima-media thickness and blood asymmetric dimethylarginine were significantly greater in Benidipine than in Amodipine.*

Benidipine is more effective than amlodipine for protecting renal function and potentially for ameliorating atherosclerosis in hypertensive patients with mild CKD.

*$P < 0.001$, #$P < 0.05$

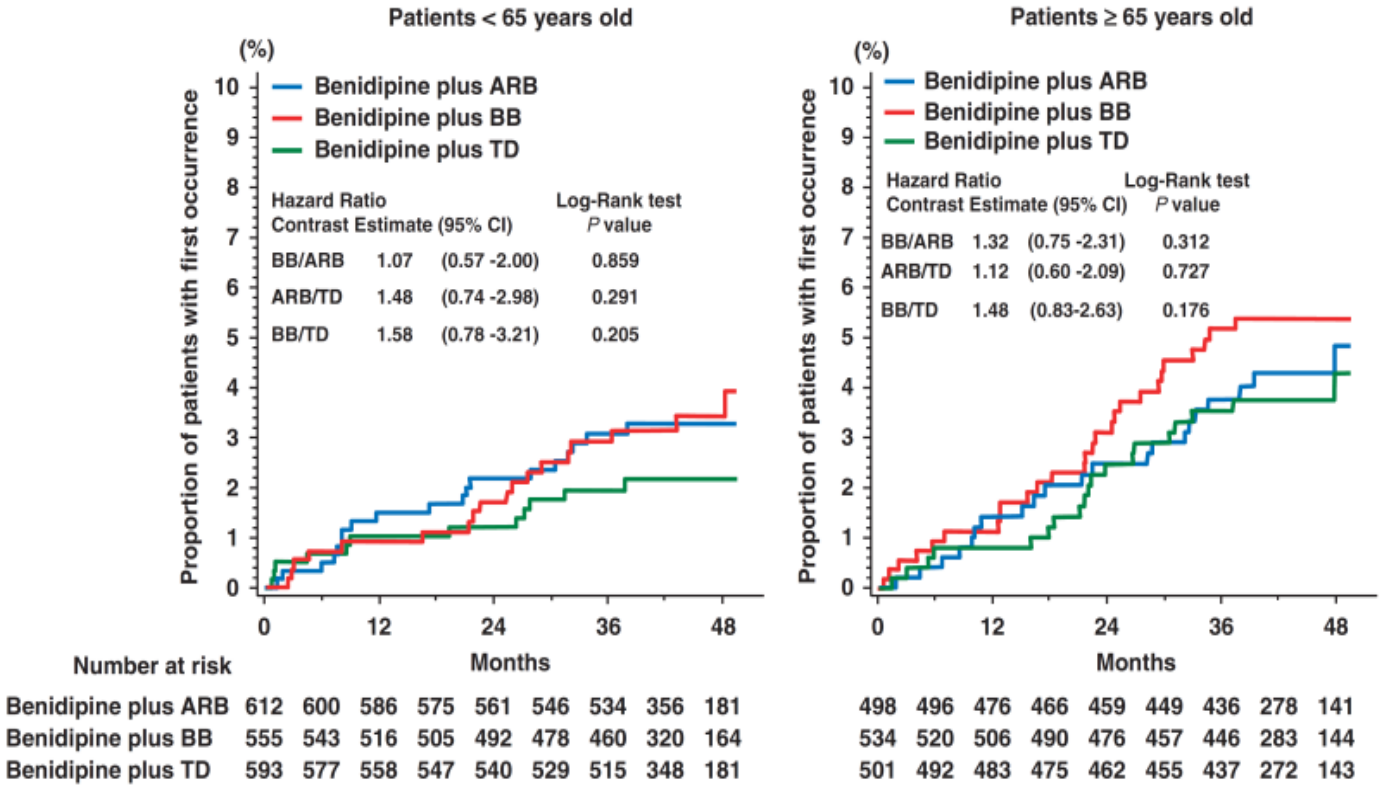
Nakamura T et al. Comparative effects of benidipine and amlodipine on proteinuria, urinary 8-OHdG, urinary L-FABP, and inflammatory and atherosclerosis markers in early-stage chronic kidney disease. Am J Med Sci. 2010 Feb;339(2):157-63.

Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) Trial

Objective	To evaluate the efficacy and safety of Benidipine based combination therapies in older (>65 years) and younger (<65 years) hypertensive patients.	
Study design	6-month, single-center, prospective, randomized, open-label clinical trial	
Patient Population	No. of patients	3293
	Average Age	67.5±1.5 years
	Mean SBP/DBP	145 ± 1.0mmHg 82 ± 1.4 mmHg

Ogihara T et al. Combination therapy for hypertension in the elderly: a sub-analysis of the Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) Trial. Hypertens Res. 2012 Apr;35(4):441-8.

Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) Trial- Results…



Benidipine combined with an ARB, a β-blocker, or a thiazide was effective in preventing CV events and achieving the target BP in both older and younger hypertensive patients.

Ogihara T et al. Combination therapy for hypertension in the elderly: a sub-analysis of the Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) Trial. Hypertens Res. 2012 Apr;35(4):441-8.

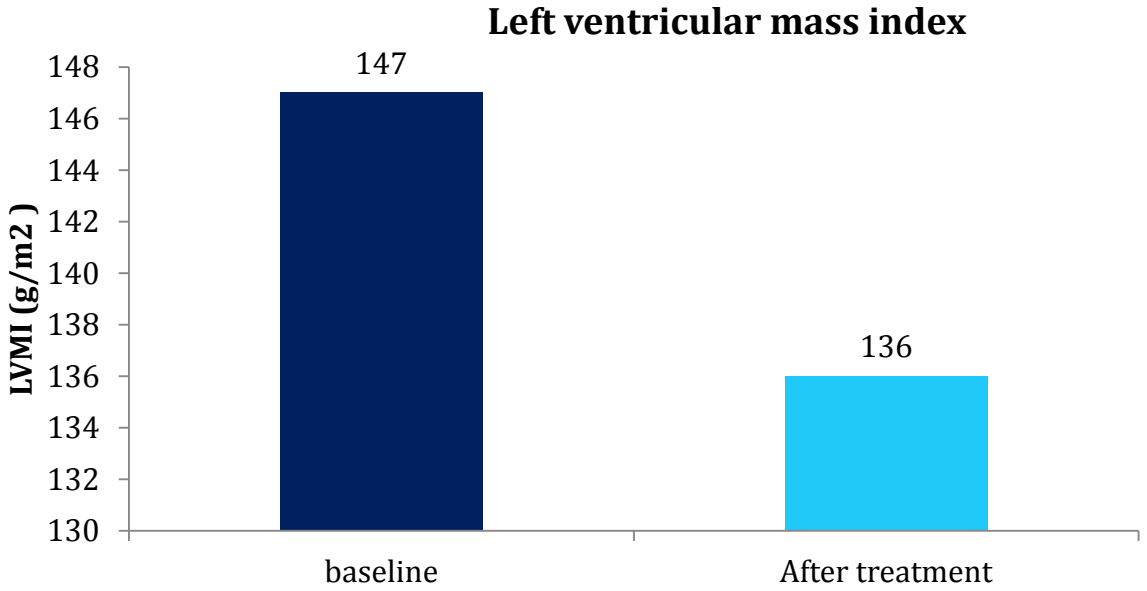
Antihypertensive efficacy and safety of Benidipine and its effects on cardiac structure

Objective	To evaluate Antihypertensive efficacy and safety of benidipine and its effects on cardiac structure and function in patients with mild to moderate hypertension	
Study design	prospective, multicenter, open-label clinical trial for 52 weeks	
Patient Population	No. of patients	152
	Age	60-75 years
	Baseline SBP/DBP	>140 mmHg/ >80mmHg

Qi W et al. Antihypertensive efficacy and safety of benidipine and its effects on cardiac structure and function in elderly Chinese patients with mild to moderate hypertension: an open-label, long-term study. Arzneimittelforschung. 2011;61(3):160-6.

Antihypertensive efficacy and safety of Benidipine and its effects on cardiac structure- Results…

- Regimen based on benidipine provided a mean SBP and DBP reduction of 13.8 ± 12.4 mmHg and 8.3 ± 9.2 mmHg ($p < 0.001$), and 62.5% of patients reached the target BP.



Benidipine, with a favorable tolerability profile, provides a long-term antihypertensive effect and provides positive cardiac outcomes

Qi W et al. Antihypertensive efficacy and safety of benidipine and its effects on cardiac structure and function in elderly Chinese patients with mild to moderate hypertension: an open-label, long-term study. Arzneimittelforschung. 2011;61(3):160-6.

Benidipine effect of hypertension and on arterial elasticity in elderly hypertensives

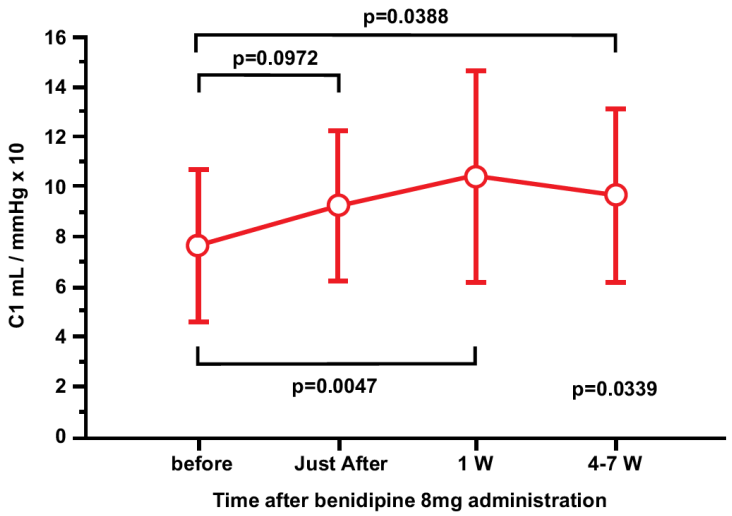
Objective	To evaluate the effect of aging and hypertension on arterial compliance or elasticity index,	
Study design	A prospective, single centre open-label clinical trial for 4 weeks	
Patient Population	No. of patients	416
	Mean Age	56.2 years
	Mean SBP/DBP	145 ± 1.0mmHg 82 ± 1.4 mmHg

Umeno T et al. The effect of hypertension, aging and benidipine on arterial elasticity in elderly hypertensives CVD Prev Cont 2010;5(2):45-50

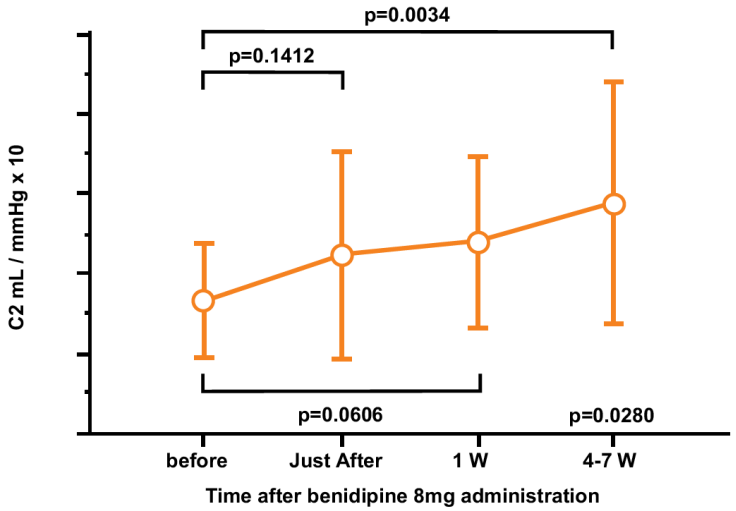
Benidipine effect of hypertension and on arterial elasticity in elderly hypertensives- Results…

- Benidipine hydrochloride decreased blood pressure and improved arterial compliance gradually and safely without any adverse effect.

Time-course changes in large artery compliance after benidipine administration



Time-course changes in small artery compliance after benidipine administration



Benidipine is a useful antihypertensive drug for elderly hypertensives because of its potential to improve arterial function.

Umeno T et al. The effect of hypertension, aging and benidipine on arterial elasticity in elderly hypertensives CVD Prev Cont 2010;5(2):45-50

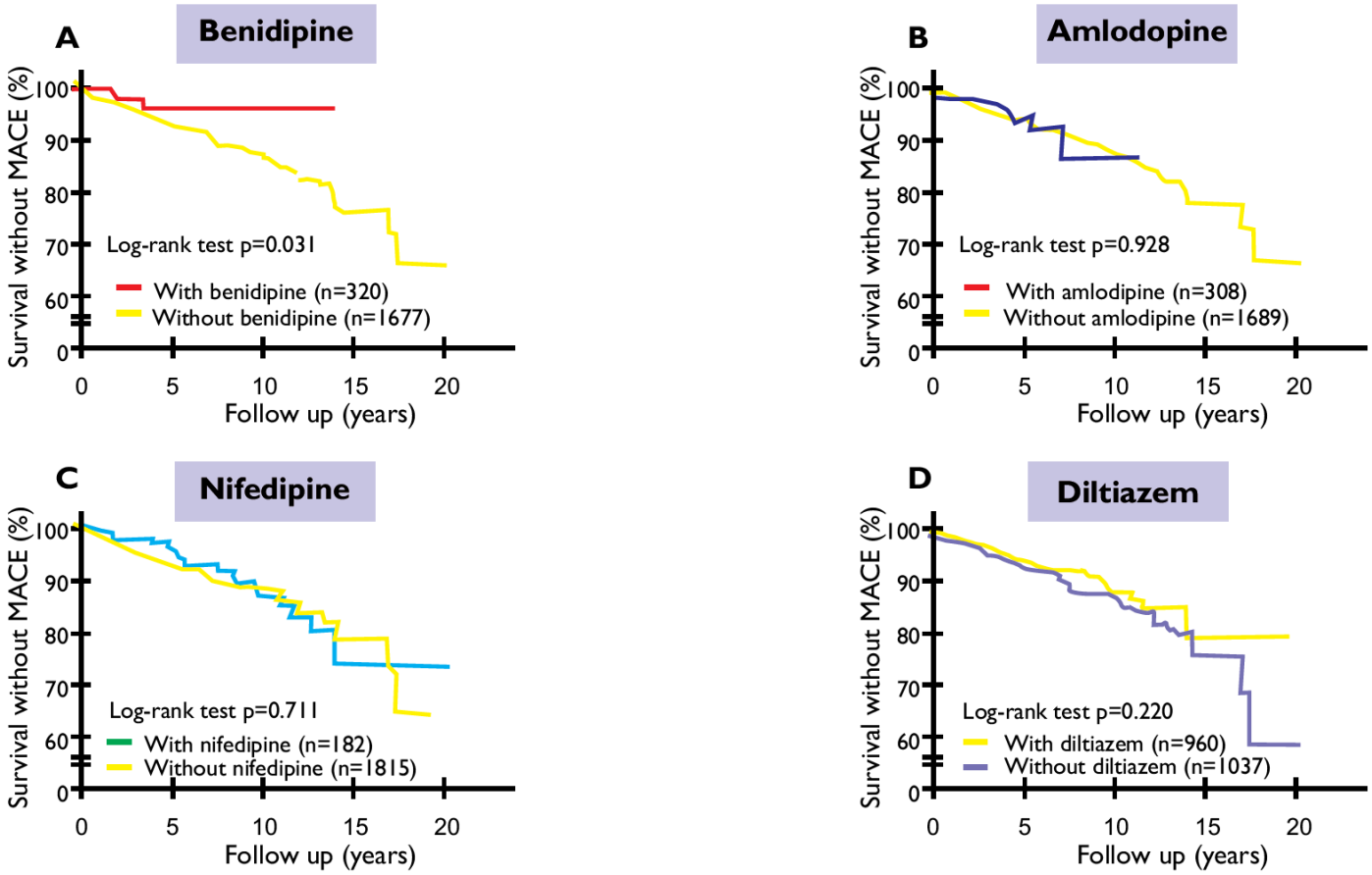
Prognostic Effects of Calcium Channel Blockers on MACE in Patients with Vasospastic Angina

Objective	To evaluate the effects of CCBs on major adverse cardiovascular events (MACE) in patients with VSA patients	
Study design	A meta-analysis regarding the effects of CCB on major adverse cardiovascular events (MACE) in Japanese VSA patients with the 4 previous studies was performed	
Patient Population	No. of patients	1,997
	Median Age	65 years

Nishigaki K et al. Prognostic effects of calcium channel blockers in patients with vasospastic angina--a meta-analysis. Circ J. 2010 Sep;74(9):1943-50.

Prognostic Effects of Calcium Channel Blockers on MACE in Patients with Vasospastic Angina- Results…

- MACE occurred significantly less in the patients treated with benidipine compared with those without it (P= 0.031, log-rank test)

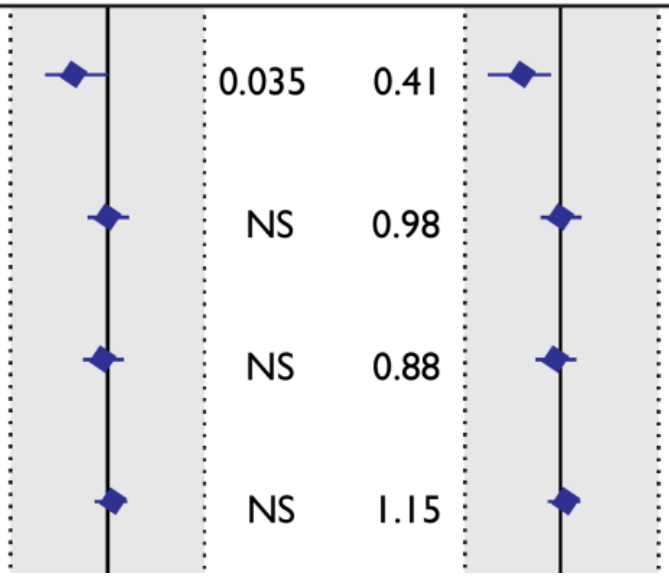


Nishigaki K et al. Prognostic effects of calcium channel blockers in patients with vasospastic angina--a meta-analysis. Circ J. 2010 Sep;74(9):1943-50.

Prognostic Effects of Calcium Channel Blockers on MACE in Patients with Vasospastic Angina- Results…

- The HR was also significantly lower in the patients treated with benidipine, even after correction for the background factors (HR =0.41, CI =0.20– 0.85, P=0.016)

	No. of pts	MACE n	MACE (%)	Mon-adjustment Hazard rate	Mon-adjustment P Value	Adjustment* Hazard rate	Adjustment* P Value
Benidipine	320	8	(2.5)	0.46	0.035	0.41	0.016
Amlodipine	308	17	(5.5)	1.02	NS	0.98	NS
Nifedipine	182	19	(10.4)	0.91	NS	0.88	NS
Diltiazem	960	83	(8.6)	1.23	NS	1.15	NS



Benidipine exerts more beneficial prognostic effects in patients with VSA.

Nishigaki K et al. Prognostic effects of calcium channel blockers in patients with vasospastic angina--a meta-analysis. Circ J. 2010 Sep;74(9):1943-50.

Improvements in Augmentation Index and Urinary Albumin Excretion with Benidipine in Hypertensive Patients with CKD

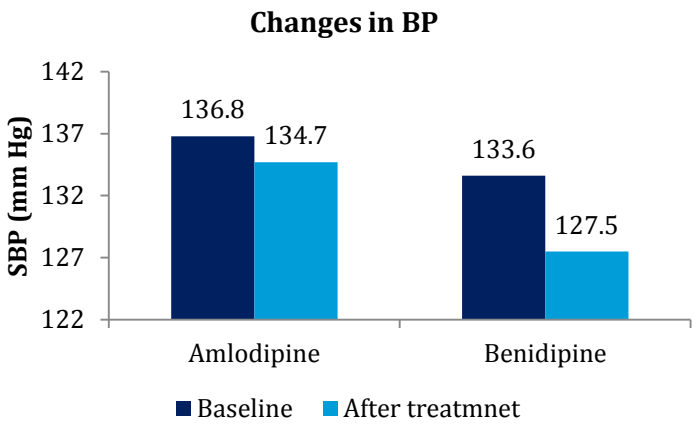
Objective	To compare the augmentation index (AI) effect of benidipine and amlodipine in the treatment of CKD patients as measured through AI and urinary albumin excretion (UAE) *The augmentation index (AI) is the proportion of reflected pressure waves in the pulse pressure waves in systole. The height and timing of reflected pressure waves are dependent on vascular stiffness.*	
Study design	Prospective, open-label, randomized, parallel-comparison study	
Patient Population	No. of patients	108
	Average Age	68.3 ± 9.8 years
	Mean SBP/DBP	136.8 ± 15.1 mmHg 71.6 ± 9.0 mmHg

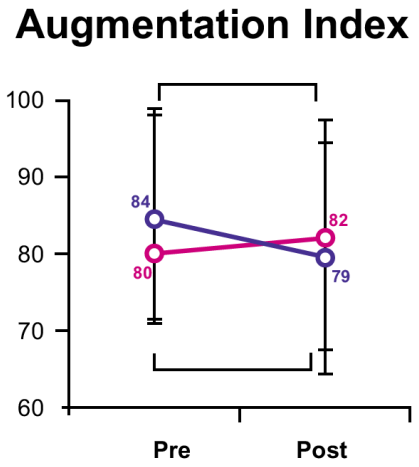
Takayama T. et al. Improvements in Augmentation Index and Urinary Albumin Excretion With Benidipine in Hypertensive Patients With Chronic Kidney Disease. Int Heart J. 2016;57(1):53-60

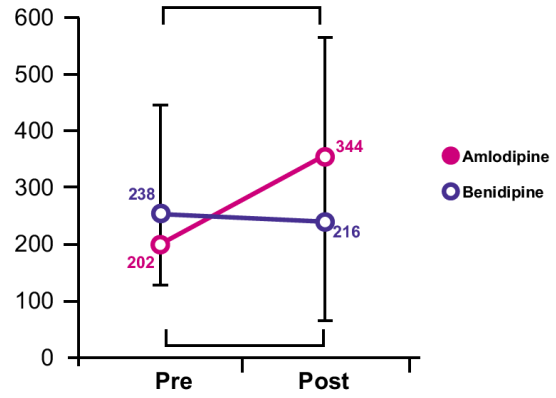
Improvements in Augmentation Index and Urinary Albumin Excretion in Hypertensive Patients with CKD- Results…

- Significant improvement in AI was noted only in the benidipine group (84.5 ± 13.6% to 79.5 ± 15.2%; P = 0.0138).

- Significant improvement in UAE in the benidipine group was found compared with the amlodipine group (-25 ± 46, 51 ± 60%, P = 0.031, respectively).







Benidipine reduce augmentation index and improves urinary albumin excretion than amlodipine

Takayama T. et al. Improvements in Augmentation Index and Urinary Albumin Excretion With Benidipine in Hypertensive Patients With Chronic Kidney Disease. Int Heart J. 2016;57(1):53-60

Summary

- Benidipine is the only CCB with triple Blocking action of L, N, T type channels

- Benidipine has high Liphophilicity and slow dissociation from receptors and has long-lasting anti hypertensive effect.

- Benidipine has Reno protective, Cardio protective and Vaso protective effects by vascular selectivity and enhanced nitric oxide (NO) production effects by triple Ca^{2+} channel blocking.

Summary

- Benidipine has greater efficacy than amlodipine in reducing blood pressure and proteinuria.
- Benidipine has good antihypertensive effect than cilnidipine and also has renoprotective effect
- Benidipine is more effective for treatment of vasospastic angina as compared with diltiazem and amlodipine
- Benidipine reduce augmentation index and improves urinary albumin excretion than amlodipine
- Benidipine increases MACE free survival in patients with Hypertension and co-morbid CVD.

Thank You