



MONOGRAPH

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1. INTRODUCTION

Calcium Channel Blockers

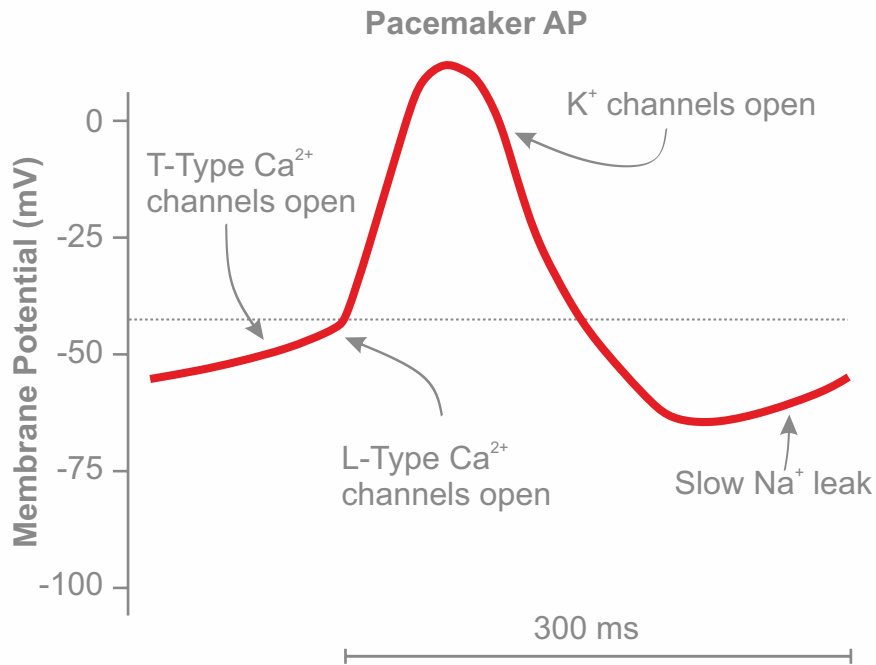
There are several types of Ca^{+2} channels like L-, N-, T-, P-, Q- and R-type calcium channels.

However, the channels responsible for rise in blood pressure are L-, N- and T-type calcium channels.

Type	Properties	Location	Location/Function
L	Long-lasting	Vascular smooth Muscle	Contraction of smooth and cardiac muscle of blood vessels. Causes Vasoconstriction.
N	Neuronal	Neurons Brain	Regulates the release of Norepinephrine from neuronal endings
T	Transient	Heart, Kidney, Adrenal gland	<ol style="list-style-type: none"> 1. In Heart, regulates the pacemaker activity 2. Dilates the Afferent & Efferent Arterioles in Kidneys 3. Stimulates the release of Aldosterone

T-type Ca^{+2} channels in the heart

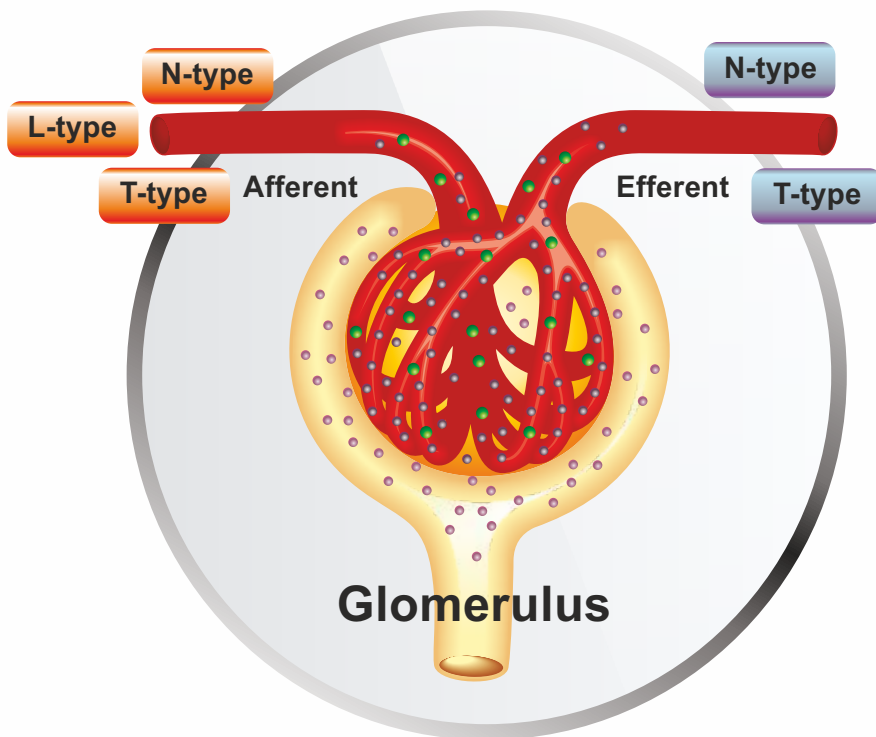
- In cardiac muscle, 2 types of Ca^{+2} channels, the L- (low threshold type) and T-type (transient-type), contributes to the up stroke of the action potential.
- The L-type channel is found in all cardiac cell types.
- The T-type channel is found principally in pacemaker, atrial, and Purkinje cells.
- During the action potential generation, the first channel to come into play is the T-type Ca^{+2} channel, which opens at a specific level of membrane depolarisation.
- T-type channels provides the initial depolarising kick to fire the action potential.
- The opening of L-type (L for long-lasting) Ca^{+2} channels then mediates this action potential to the other parts of the heart.



Circulation: Arrhythmia and Electrophysiology. 2009;2:185-194

T-type Ca^{+2} channels in the Kidneys

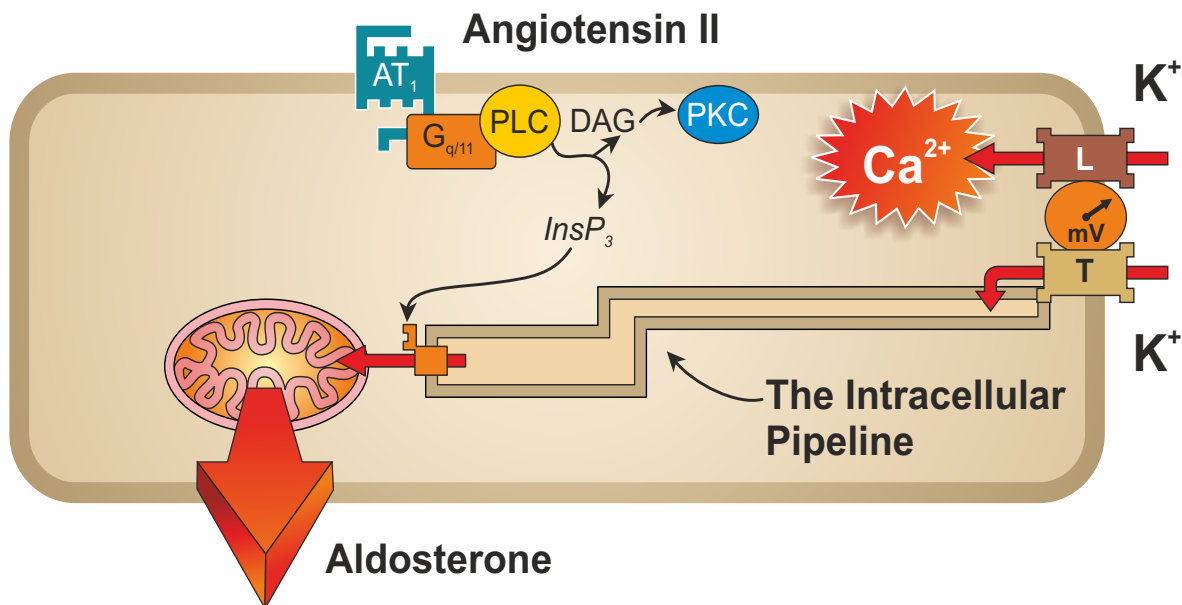
- T-type Ca^{+2} channels are prevalent in juxtamedullary efferent arterioles, as well as in afferent arterioles of superficial and juxtamedullary nephrons.



Keio J Med 59 (3) : 84-95, September 2010

T-type Ca^{+2} channels in the Adrenal Glands

- Aldosterone is secreted from adrenal glomerulosa cells and indirectly regulates blood pressure. A dysregulation of aldosterone production may lead to systemic hypertension and hypokalemia.
- It is found that T-type Ca^{+2} channels the mainly responsible for the secretion of Aldosterone for the adrenal glomerulosa cells.



- Calcium entering the cell through T-type channels could be selectively pumped into mitochondria, while calcium entering through L-type channels would be poured into the cytosol.
- This specific entry of Ca^{+2} via t-type channels is called the Intracellular Calcium pipeline.
- **Thus T-type Ca^{+2} channels play a major role in the regulation of the Aldosterone secretion.**

2. BENIDIPINE

Pharmacology

- Benidipine is the only CCB of all the CCBs that has the triple Ca^{+2} channel blocking property.
- Benidipine not only has an inhibitory effect on muscular (L type) Ca^{+2} channel, but also have an inhibitory effect on N and T type Ca^{+2} channels.

Characteristic of Ca^{+2} channel blockers and their clinical significance

Drugs	Blocking Activity		
	L - type	T - type	N - type
Nifedipine	+	-	-
Amlodipine	+	-	?
Efonidipine	+	+	-
Nilvadipine	+	+	-
Azelnidipine	+	+	-
Benidipine	+	+	+
Cilnidipine	+	-	+

Keio J Med 59 (3) : 84-95, September 2010

2.1 Benidipine Approved Indications

Benidipine is an orally active drug approved in India for the treatment of

- Hypertension
- Angina pectoris

2.2 Membrane approach



J Pharmacol Sci 100, 243 – 261 (2006)

- Usual calcium channel blockers combine directly with the dihydropyridine binding site (DHP) in the cell membrane, thereby inhibiting the intracellular influx of calcium ions.
- Benidipine enters the lipid layer of the cell membrane and then diffuses extremely rapidly to the calcium channels.
- This action of Benidipine binding to the Calcium channels is called as the “**Membrane approach**” (approach to the cell membrane followed by long retention in the DHP binding site).
This “MEMBRANE APPROACH” of Benidipine results in its Slow binding & dissociation.

2.3 Characteristics of Benidipine

1. Greater binding affinity:

The K_i value of benidipine for the DHP binding site is 0.08 – 0.13 nmol/L, which indicates that this drug has a higher affinity for the DHP binding site than nisoldipine, nicardipine, nitrendipine, verapamil, and diltiazem.

2. Slow binding to receptor :

Nitrendipine took 20 min to reach equilibrium, while benidipine took 180 min to reach equilibrium, indicating that the binding of benidipine is very slow.

3. Slow dissociation from receptor:

Dissociation rate determined by the addition of [3H]- nitrendipine after the binding of each drug with rat heart membranes, the slope of the dissociation curve was much lower for benidipine than for nifedipine, indicating that dissociation of benidipine takes place very slowly.

4. High lipophilicity

The log P of benidipine, Nifedipine & Amlodipine was 4.61, 2.20 & 3.95 indicating the very high liposolubility of Benidipine compared with Nifedipine and Amlodipine

2.4 Half Life of Benidipine

- The half life of Benidipine is shown in below table:

Dose	T_{max} (hr)	C_{max} (ng/mL)	AUC (ng/mL)	$T_{1/2}$ (hr)
2 mg	1.1 ± 0.5	0.55 ± 0.41	1.04 ± 1.26	-
4 mg	0.8 ± 0.3	2.25 ± 0.84	3.94 ± 0.96	1.70 ± 0.70
8 mg	0.8 ± 0.3	3.89 ± 1.65	6.70 ± 2.73	0.97 ± 0.34

J Pharmacol Sci 100, 243 – 261 (2006)

- Even though it has a short half life, it shows 24 hour duration of antihypertensive actions due to slow binding & slow dissociation (Membrane Approach)



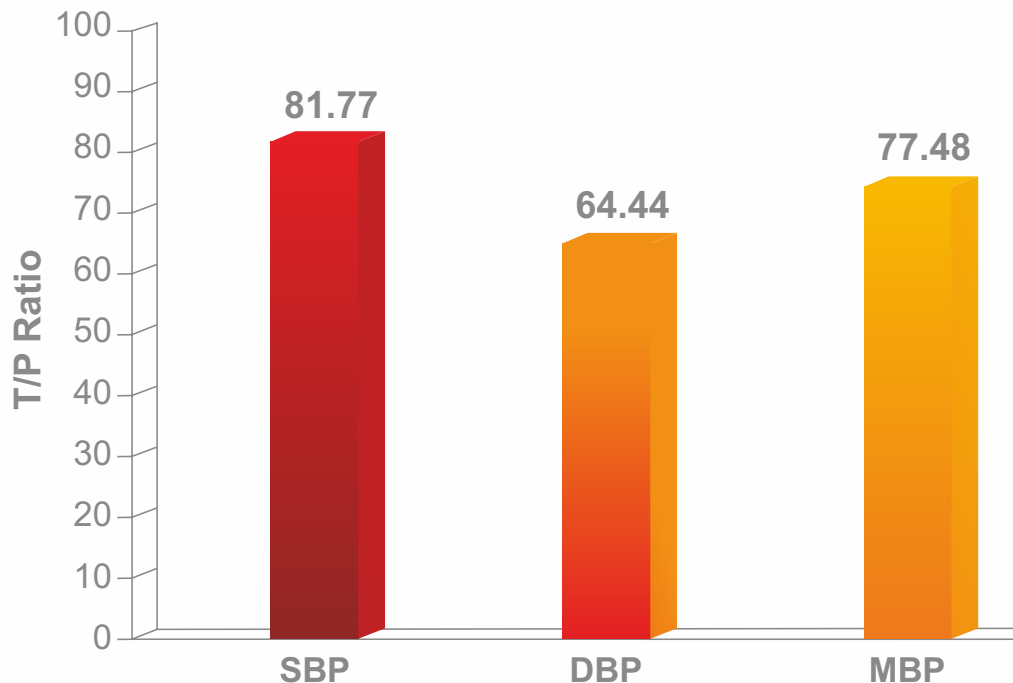
BENIDIPINE

ANTIHYPERTENSIVE ACTIONS

3. ANTIHYPERTENSIVE ACTIONS

3.1 24-hour duration of Action – High Trough to Peak Ratio

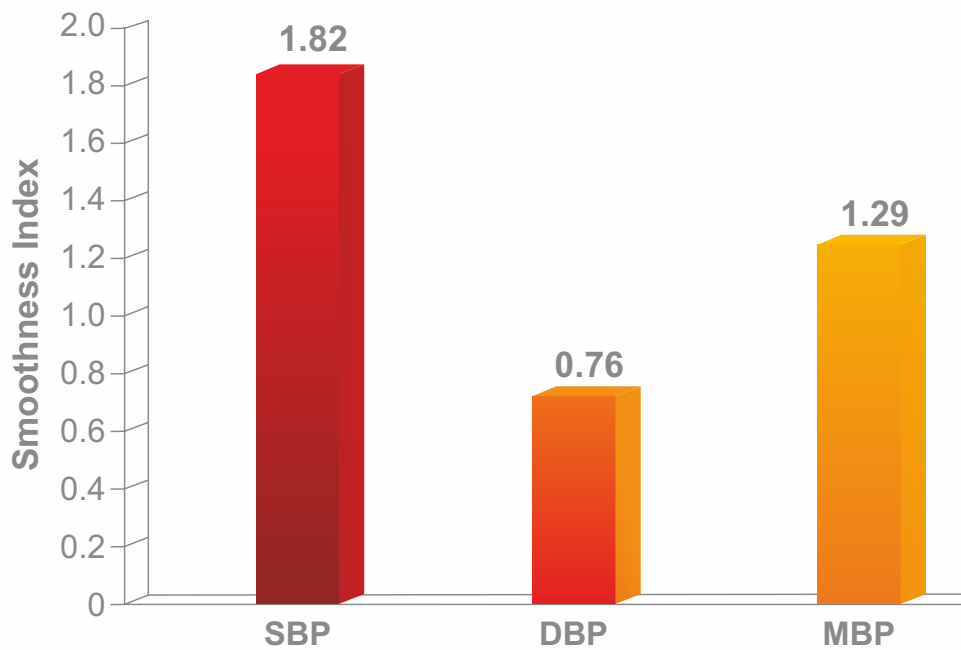
- The trough-to-peak ratio provides duration of action for each antihypertensive agent.
- USFDA mandates a minimum T/P ratio of 50% for an OD drug
- The closer an agent is to a 100% trough-to-peak ratio, the more uniform the 24-hour coverage and therefore blood pressure control.
- The T/P ratios of the patients treated with benidipine were **81.77 ± 28 % for SBP, 77.48 ± 19 % for MBP and 64.44 ± 26 % for DBP.**
- This high T/P ratio of antihypertensive action proves that Benidipine has a 24-hour antihypertensive action



Arzneim.-Forsch./Drug Res. 50 (II), Nr. 7 (2000)

3.2 Smoothness Index (SI)

- SI is a measure of the consistency/variability of BP reduction over complete 24 hour dosing interval.
- The SIs for SBP, MBP and DBP were 1.82, 1.29 and 0.76.
- **This suggests that Benidipine has a durable & consistent BP reduction over 24 hours..**

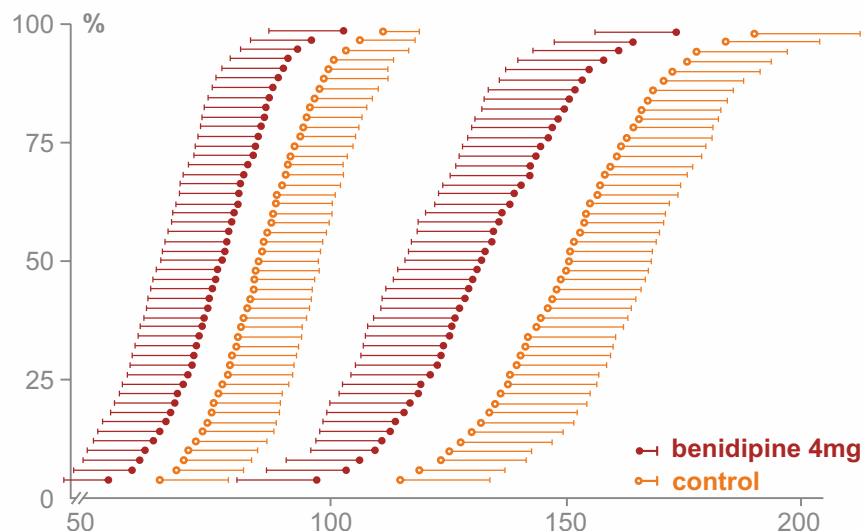


Arzneim.-Forsch./Drug Res. 50 (II), Nr. 7 (2000)

3.3 24-hour BP reduction

A

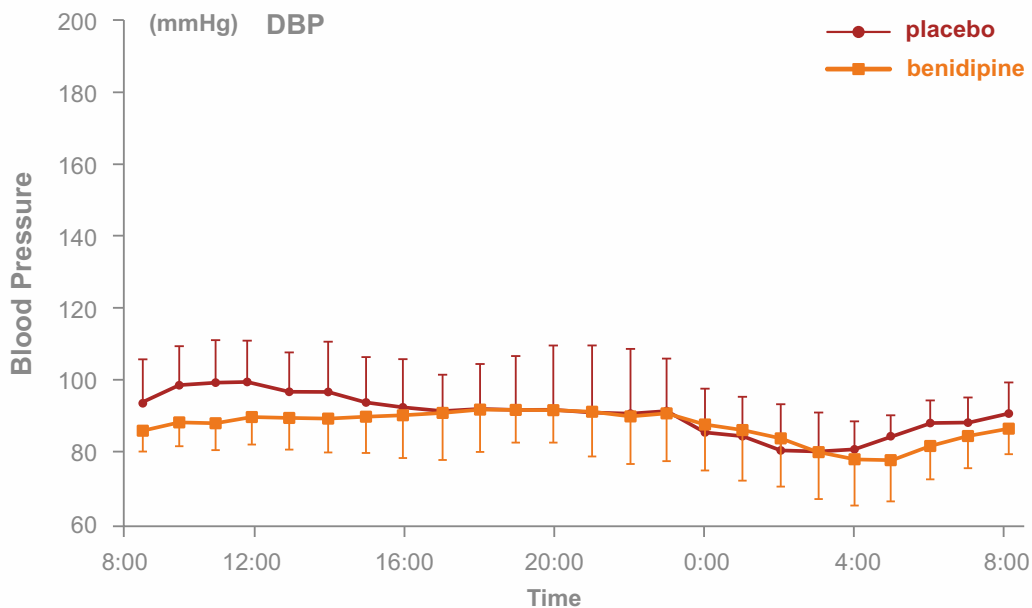
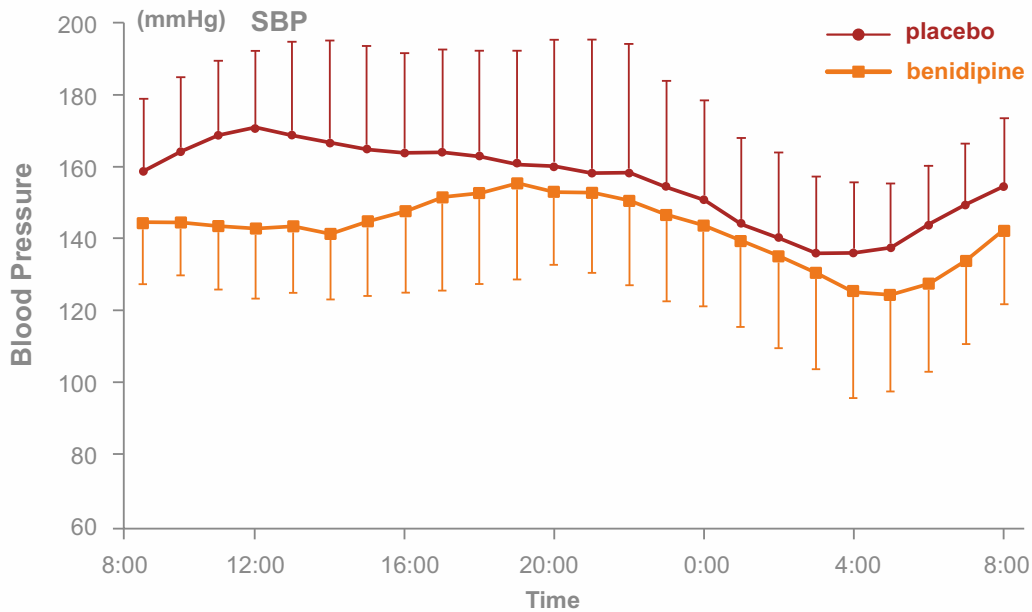
- 4-mg dose of benidipine once daily in the morning for 2 weeks adequately decreased the 24-hour blood pressure.
- The mean systolic blood pressure decreased after drug administration by 18 mmHg (from 172 ± 18 mmHg to 154 ± 18 mmHg) at 90 % level.
- The mean diastolic blood pressure decreased by 10 mmHg (from 99 ± 12 mmHg to 89 ± 13 mmHg) at 90 % level.



The horizontal axis shows the systolic Effects of benidipine 4 mg once daily on blood pressure assessed by the cumulative percentage method. The horizontal axis shows the systolic and diastolic blood pressures, and the vertical axis indicates the cumulative percentages

B

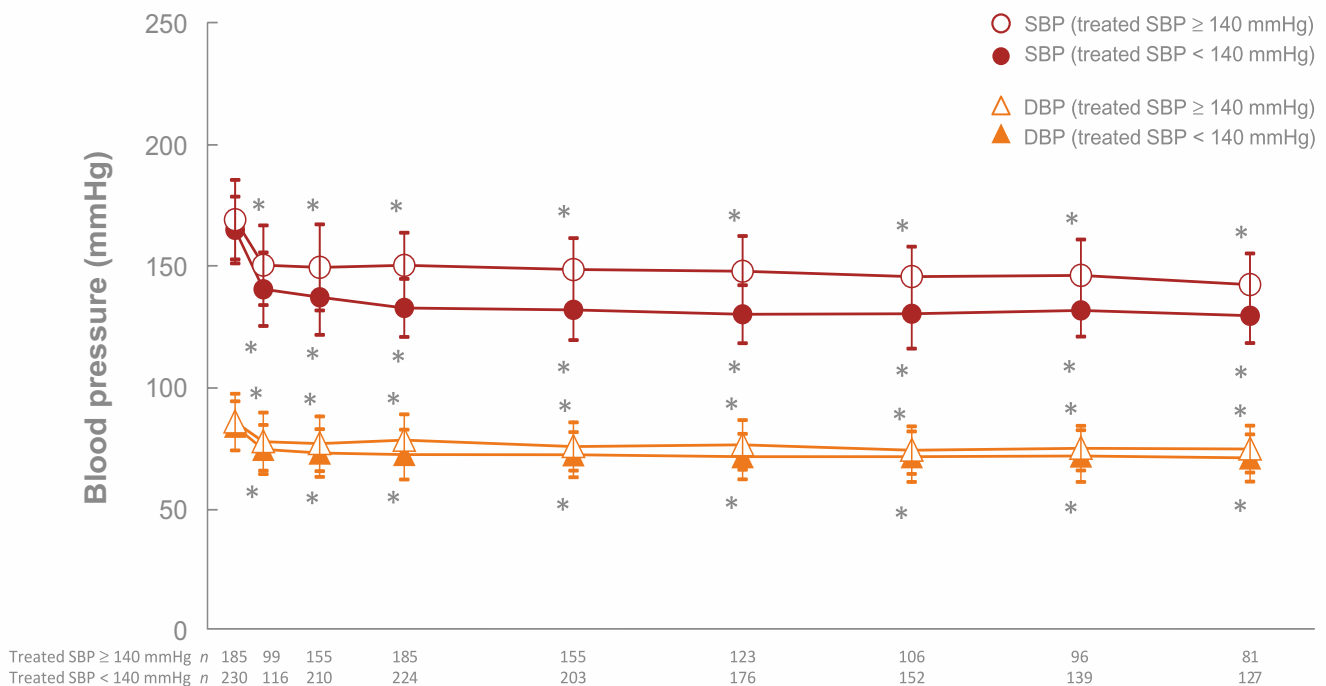
- Patients who had a baseline systolic blood pressure (SBP) of more than 160 mmHg and a diastolic blood pressure (DBP) of 95 mmHg were selected to participate in the study.
- Benidipine (4 mg) once-daily was given for 2 weeks.
- The blood pressure, pulse rate and 24-hour ambulatory blood pressure were measured.



- The mean resting systolic (SBP) and diastolic (DBP) blood pressures were 173 mmHg and 104 mmHg, respectively, at the time of patients enrollment.
- The mean SBP and DBP fell to 135 and 88 mmHg, respectively.

3.4 Effect of Benidipine on Elderly patient : J-BRAVE study

- 415 patients aged 85 years or older with a treated SBP > 140 mmHg were included in the study.
- The mean age was 88 years.
- Patients received 2–4 mg benidipine orally, once daily. The mean daily dose of benidipine at the end of study was 4.4 mg.
- In patients who achieved <140 mmHg SBP, BP decreased significantly from 165 ± 14 / 84 ± 10 mmHg to 130 ± 11/71 ± 10 mmHg.
- In patients who achieved >140 mmHg SBP, BP decreased significantly from 169 ± 16 / 86 ± 12 mmHg to 143 ± 13/75 ± 10 mmHg



Clinical and Experimental Hypertension, 33(5):275–280, (2011)

3.5 Head-on-head comparison of Benidipine & Amlodipine

- 41 patients in the benidipine group and 47 patients in the amlodipine group were followed up and compared.
- Treatment was either amlodipine 2.5–10 mg/day or benidipine 4-8 mg/day (in patients without concurrent angina pectoris) and was administered for 12 months.
- BP decreased from 134.7 ± 16.6 mmHg at the start of the study to 127.5 ± 16.2 mmHg at the end of study (P = 0.002) in the benidipine group, **with no significant reduction in blood pressure observed in the amlodipine group.**

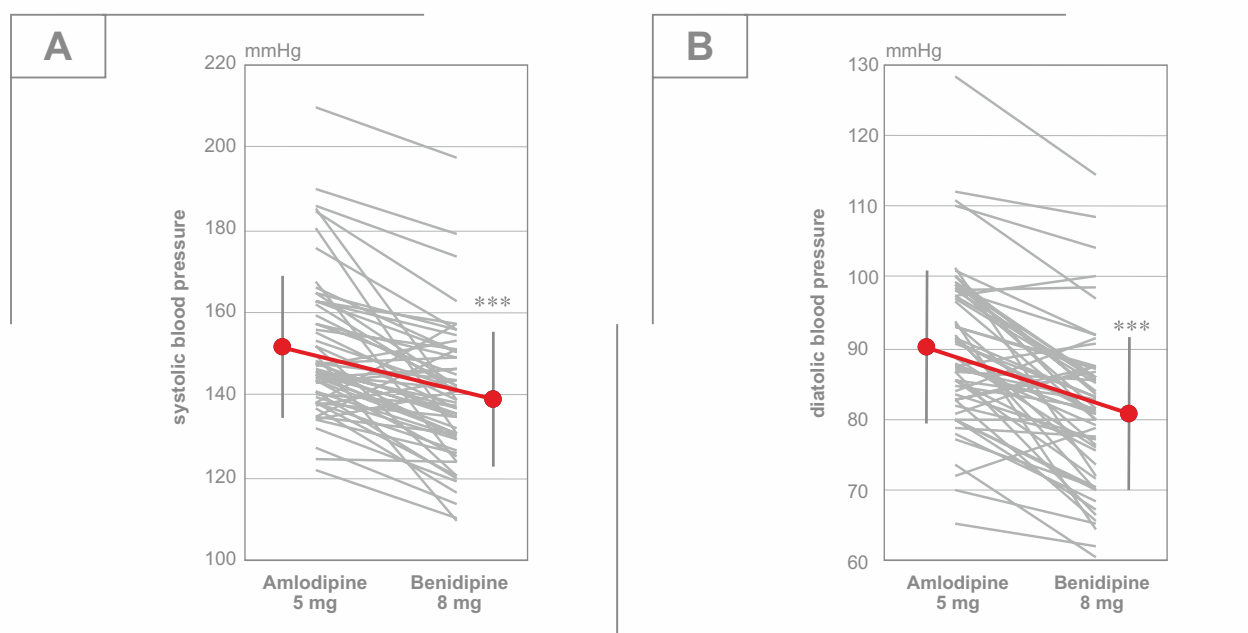
		Amlodipine	Benidipine	P (amlodipine V/s benidipine)
SBP (mmHg)	Baseline	136.8 ± 15.1	134.7 ± 16.6	0.535
	after treatment	133.6 ± 16.1	127.5 ± 16.2	0.081
	P (versus pre)	0.178	0.002	
SBP (mmHg)	Baseline	69.8 ± 9.7	71.6 ± 9.0	0.379
	after treatment	62.4 ± 12.4	64.2 ± 10.4	0.466
	P (versus pre)	<0.001	<0.001	
PR (bpm)	Baseline	68.8 ± 11.3	70.4 ± 9.0	0.477
	after treatment	72.5 ± 13.2	73.9 ± 11.7	0.602
	P (versus pre)	0.006	0.011	

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and PR, Pulse rate.

- SBP and DBP was reduced significantly from baseline with benidipine group while in amlodipine group no significant reduction was observed in SBP.

3.6 Switching from Amlodipine to Benidipine (ABC Study)

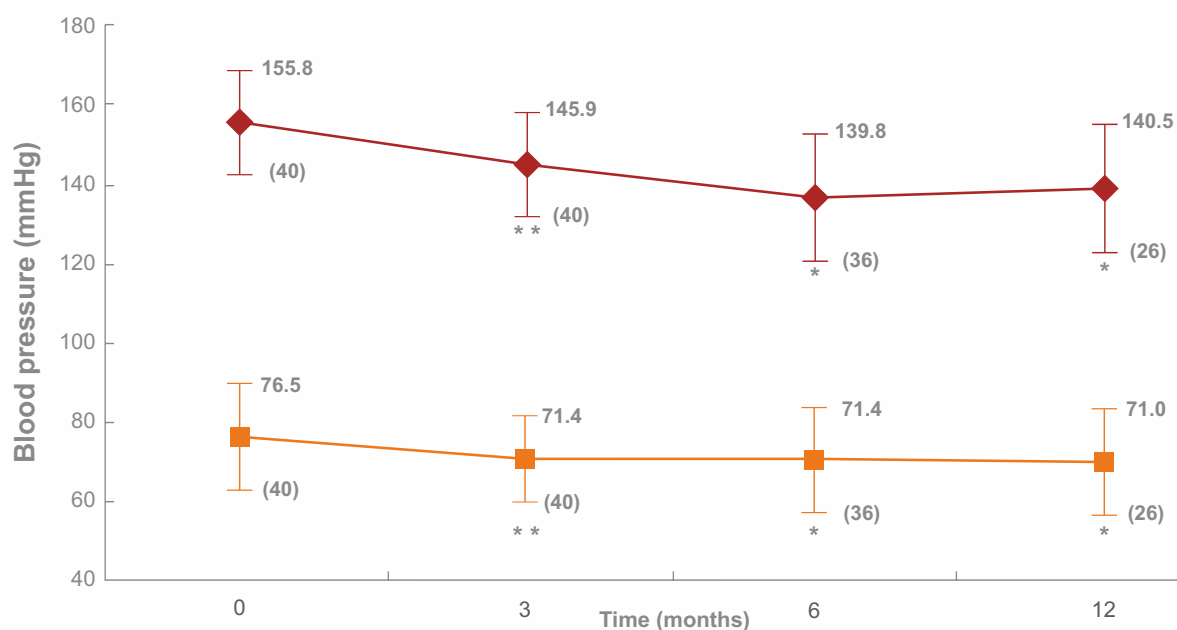
- Fifty-eight hypertensive outpatients undergoing amlodipine treatment and unable to achieve optimal blood pressure were changed over to benidipine treatment.
- SBP, DBP and mean BP during benidipine administration were significantly lower than those during amlodipine administration.
- SBP (139.5 ± 16.4 mmHg) and DBP (81.3 ± 11.1 mmHg) after changeover significantly reduced compared to those prior to changeover (151.4 ± 17.4 and 90.1 ± 11.1 mmHg), respectively.
- **Benidipine resulted in a 12/9 mmHg greater reduction of SBP/DBP than Amlodipine.**
 - > 85% of subjects had reduced BP after changeover.
 - > 60% had BP drops exceeding 10 mmHg
 - > 19% had BP drops exceeding 20 mmHg



Hypertens Res 2007; 30: 797–8

3.7 Switching from Cilnidipine to Benidipine

- Baseline SBP and DBP during Cilnidipine administration were 155.8 ± 13.7 mmHg and 76.5 ± 13.3 mmHg, respectively.



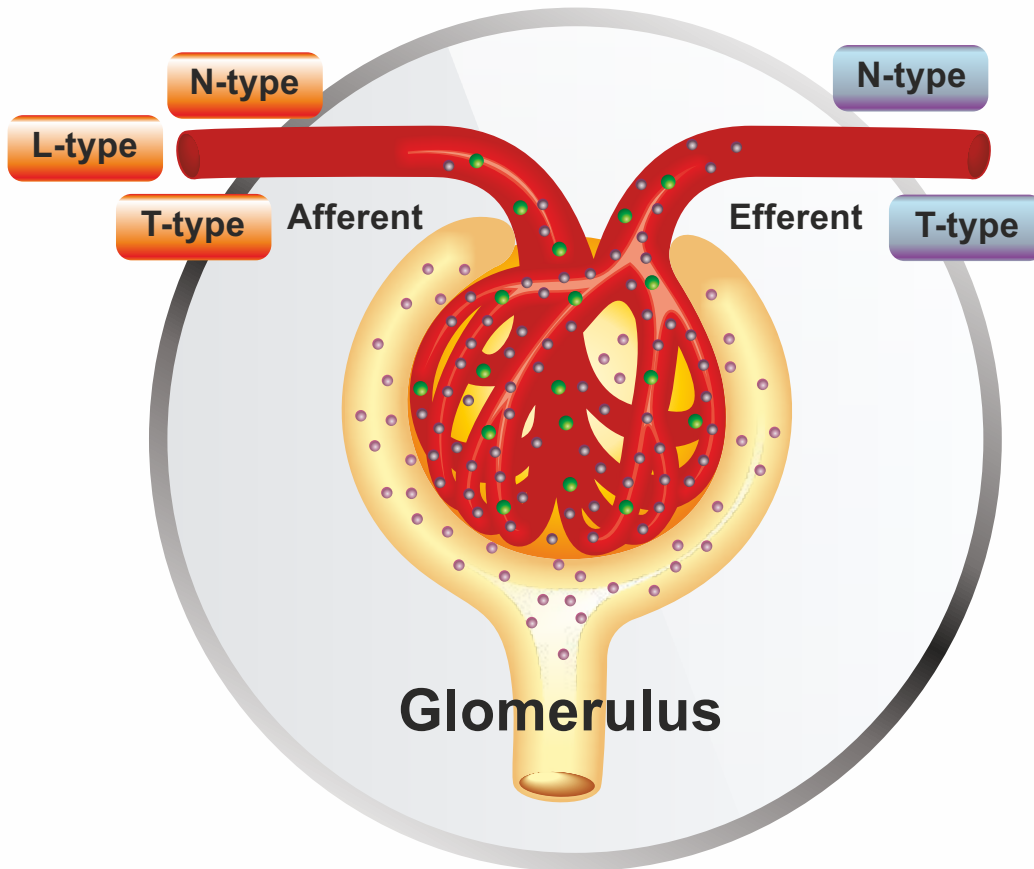
- BP significantly decreased 3 months after benidipine treatment, reaching SBP 145.9 ± 17.0 mmHg and DBP 71.4 ± 13.7 mmHg, and decreased to **139.8 ± 16.8 mmHg and 71.4 ± 14.7 mmHg 6 months after benidipine treatment.**
- The BP lowering effect was stable for one year.

Expert Opin. Investig. Drugs (2010) 19(9):1027-1037

BENIDIPINE

RENAL PROTECTION

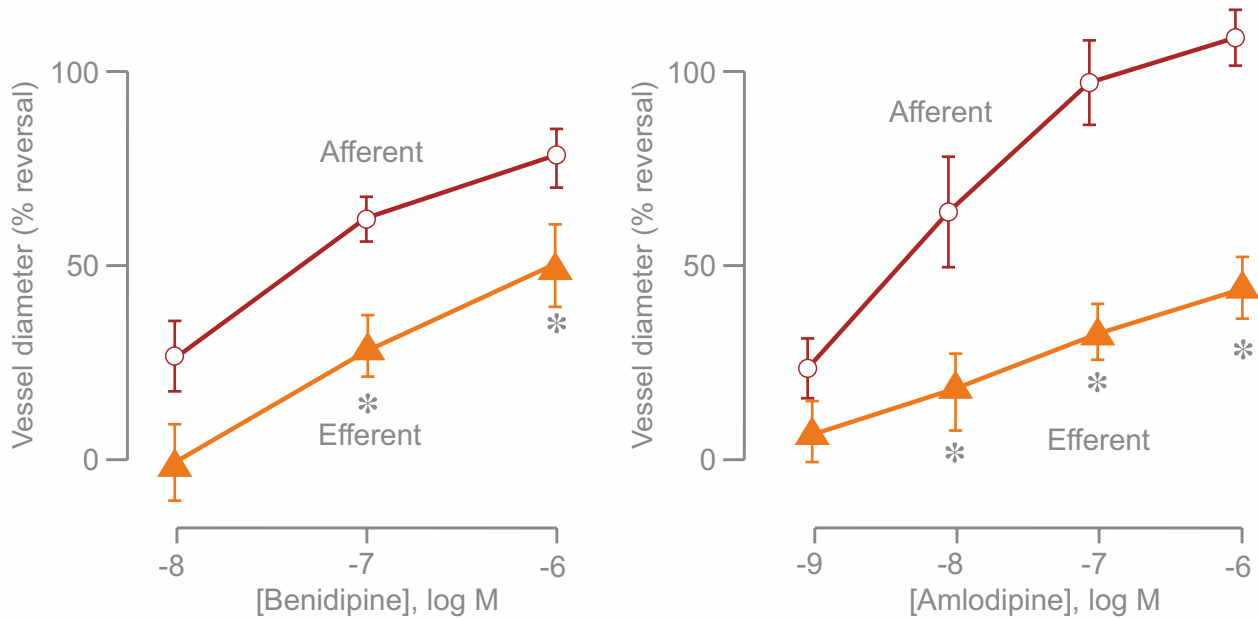
4.1 Dilation of Afferent & Efferent Arterioles



Keio J Med 59 (3) : 84-95, September 2010

- The L-type Ca^{+2} channels predominate at the afferent arteriole, and traditional CCBs like Amlodipine preferentially dilate afferent arterioles rather than efferent arterioles.
- N-type Ca^{+2} channels are present at sympathetic nerve terminals that are distributed along afferent and efferent arterioles.
- T-type Ca^{+2} channels are prevalent in juxtamedullary efferent arterioles, as well as in afferent arterioles of superficial and juxtamedullary nephrons.
- The dilation of only the afferent arterioles & not the efferent arterioles induces elevation in intraglomerular pressure, leading to glomerular hypertension.
- Amlodipine being an only L-type Ca^{+2} channel blocker dilates only the Afferent, but does not dilate the Efferent Arterioles.

- Benidipine dilates both the afferent and efferent arterioles due to its action on N- & T-type Ca^{+2} channel in addition to L-type Ca^{+2} channel.

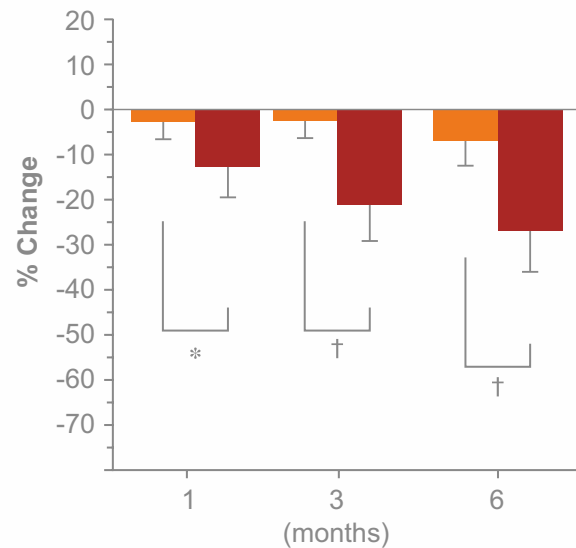
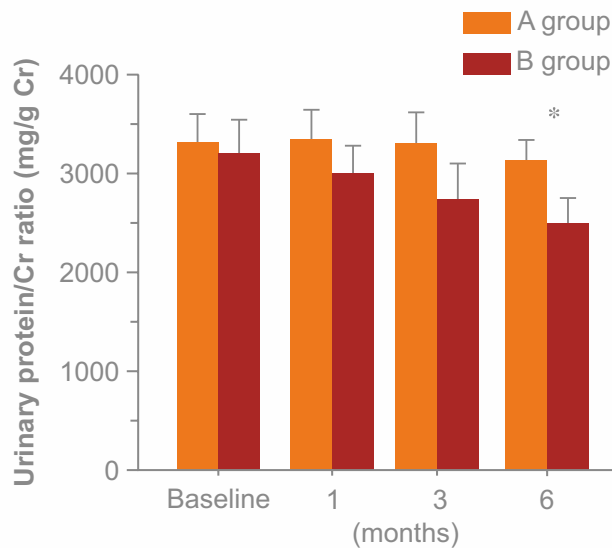


- The effect of dilating efferent arterioles seems to be characteristic of benidipine and contributes to the beneficial renoprotective effects of this drug.

J Pharmacol Sci 100, 243 – 261 (2006)

4.2 Comparison of Anti-proteinuric effect of Amlodipine & Benidipine in CKD Stage 3-5 patients.

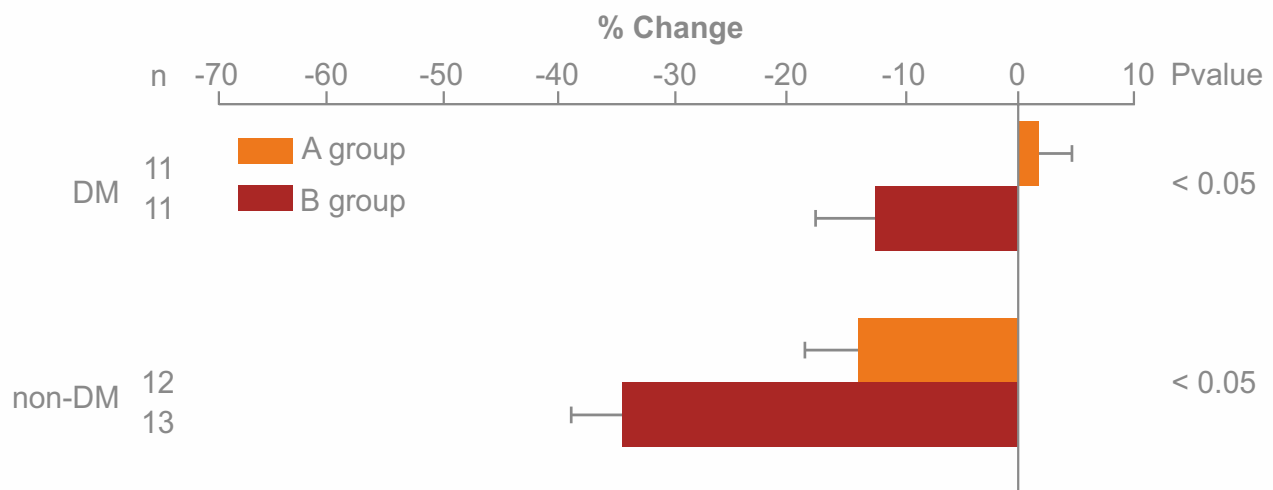
- An open-labelled, randomized trial compared the antiproteinuric effect of benidipine & amlodipine in hypertensive patients with moderate-to-advanced-stage chronic kidney disease (CKD) (stages 3–5).
- These subjects were already being administered the maximum recommended dose of ARBs.
- Urinary protein excretion was measured in both groups at baseline & at the end of study.
- The urinary protein–Cr ratio at the end of 6 months was significantly lower in the Benidipine group than in the Amlodipine group (2565 ± 299.9 vs. 3187 ± 372.2 mg/gm Cr, $P < 0.05$).
- The percentage reduction in urinary protein excretion from the baseline showed a significant difference between the two treatment groups after 1 month of treatment and thereafter.
- Additionally, after 6 months of treatment, the percentage change from the baseline value decreased in the Benidipine group but not in the Amlodipine group; the values were significantly different between the two groups (29.4 ± 5.9 vs. $7.8 \pm 6.9\%$, $P < 0.05$).



Hypertension Research (2009) 32, 270–275

4.3 Comparison of Anti-proteinuric effect of Amlodipine & Benidipine in Diabetic patients.

- In a subgroup of patients with diabetic nephropathy, there was a significant difference in the percentage reduction in the urinary protein excretion from baseline values between the two treatment groups.
- **In Amlodipine group, there was an increase in Urinary protein excretion.**

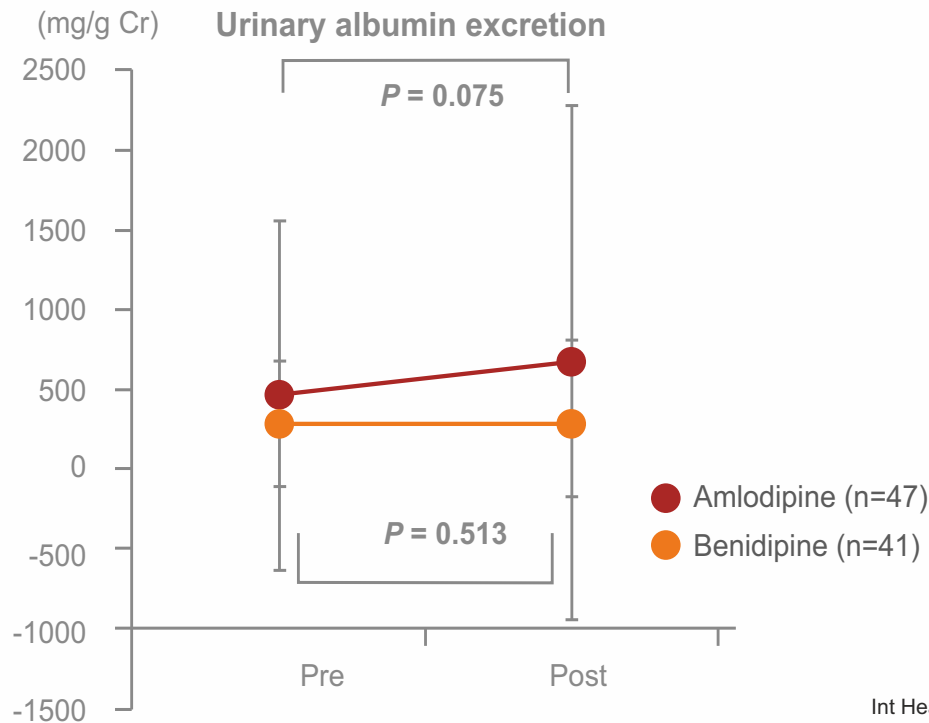


- While Benidipine showed a significant reduction in Urinary protein excretion in diabetic patients.

Hypertension Research (2009) 32, 270–275

4.4 Comparison of Anti-proteinuric effect of Amlodipine & Benidipine in Macroalbuminuria patients

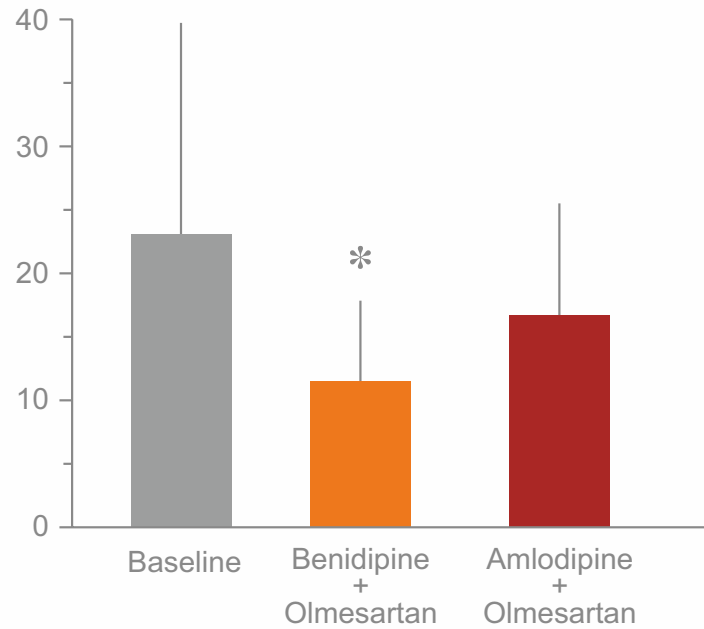
- 41 patients in the benidipine group and 47 patients in the amlodipine group were studied.
- **In patients with high UAE of ≥ 300 mg/g Cr, the percent change in UAE among patients with advanced renal impairment was $51 \pm 60\%$ in the amlodipine group and $-25 \pm 46\%$ in the benidipine group.**



Int Heart J 2016; 57: 53-60

4.5 Comparison of Anti-proteinuric effect of Amlodipine & Benidipine in Elderly CKD patients.

- Renal protection study of Amlodipine & Benidipine was done in patients aged 65–85 years with essential hypertension, CKD and albuminuria (higher than 5 mg/g creatinine (Cr)).
- Patients were randomly assigned to receive either benidipine (4 mg/day) or amlodipine (5 mg/day) combined with olmesartan (10 mg/day).
- After 3 months, CCBs were switched in each patient and the same protocol was applied for another 3 months.
- **Urinary albumin excretion was significantly reduced after combination therapy using benidipine and olmesartan (11.7 ± 6.1 mg/g Cr, $p < 0.05$), while the amlodipine-based regimen did not produce statistically significant reduction (16.4 ± 9.0 mg/g Cr, $p = 0.08$).**

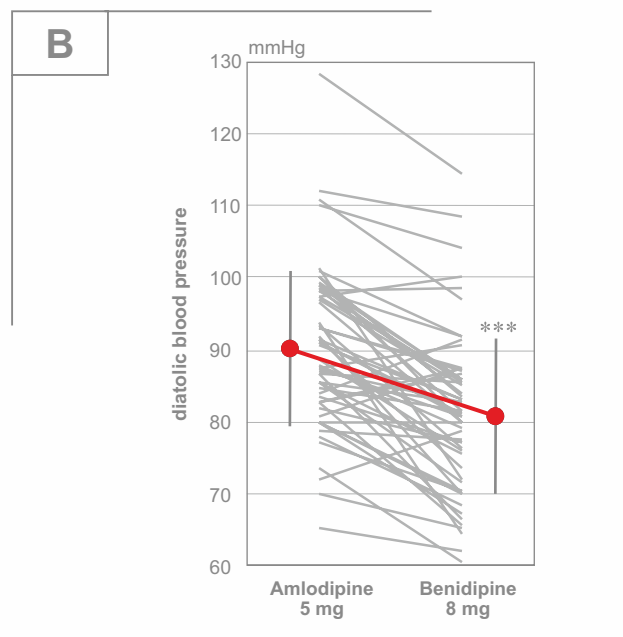
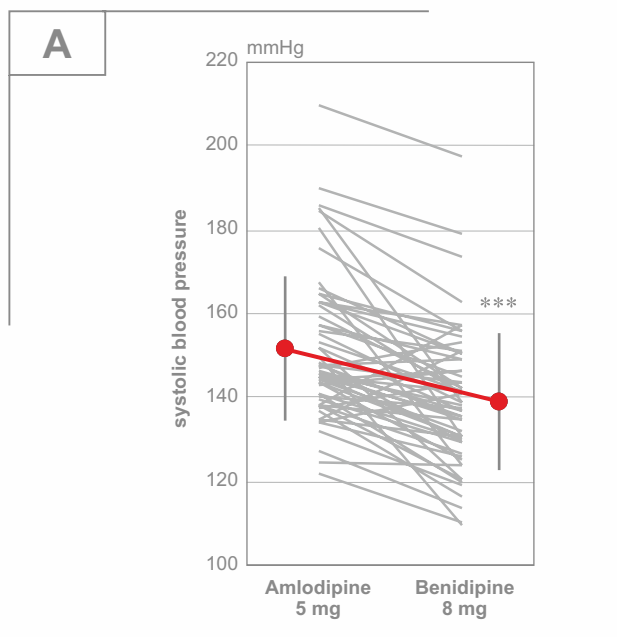


Responses of urine albumin excretion to different regimens. Urine albumin was reduced only after combination therapy based on benidipine. * $p < 0.05$ versus baseline (wilcoxon's signed rank test).

Clinical and Experimental Hypertension, 32, 1–7, 2010

4.6 Comparison of Anti-proteinuric effect on switching from Amlodipine to Benidipine (ABC Study)

- Patients previously treated with amlodipine for 6 months prior to the study were shifted to benidipine.
- To evaluate how the changeover improved renal function, serum and urinary creatinine and urinary protein were measured at -1 month and 2 months.

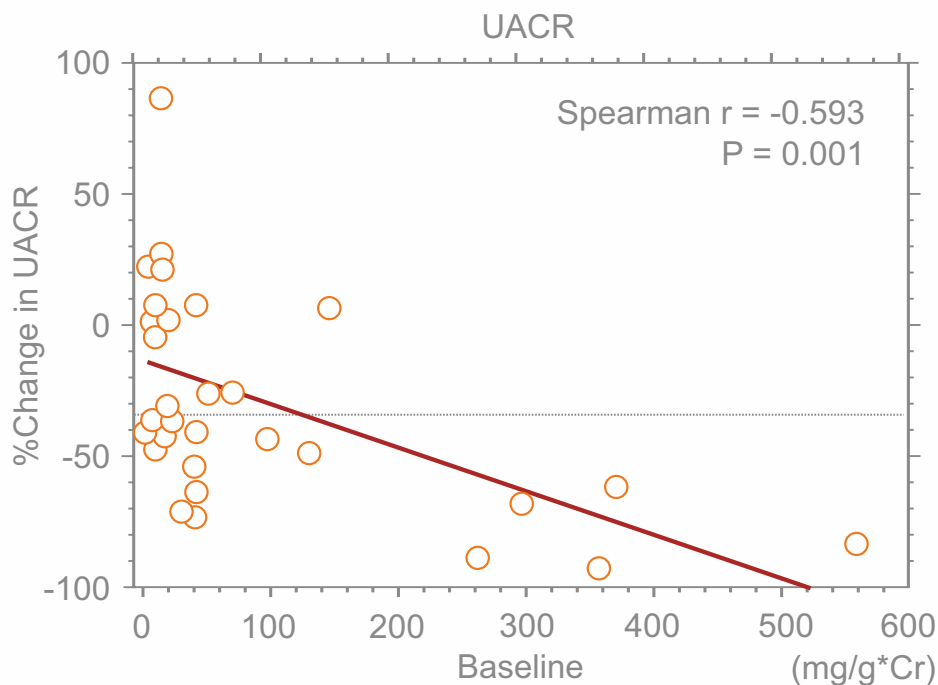


Hypertens Res 2007; 30: 797–8

- UPE after changeover (0.22 ± 0.55) reduced compared with that before changeover (0.35 ± 0.82 g/g creatinine).
- While the eGFR increased from 75.0 ± 21.5 ml/min/1.73 m² to 77.7 ± 25.3 ml/min/1.73 m² after changeover.

4.7 Comparison of Anti-proteinuric effect on switching from L-type CCB to Benidipine

- L-type CCB was switched to the equivalent antihypertensive efficacy of benidipine.
- Amlodipine 5 mg switched to benidipine 4 mg. Amlodipine 7.5 mg and 10 mg switched to benidipine 8 mg.
- A significant reduction in UACR was noted (median change -36.9%, IR -59.1 to 6.1), from 33.5 mg/g Cr (IR 13.9 to 90.6) at baseline to 19.6 mg/g Cr (IR 10.6 to 43.5) at 6 months after switching (P = 0.001).

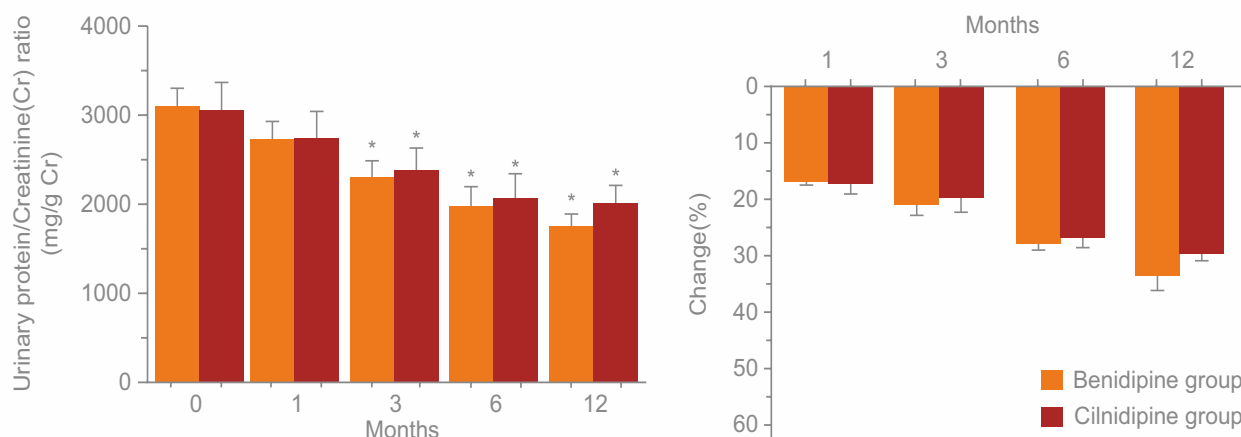


Int Heart J 2014; 55: 000-000

4.8 Comparison of Anti-proteinuric effect of Cilnidipine & Benidipine

- A 12-month-long, single-center, prospective, randomized, open-labeled clinical trial was designed to compare the antiproteinuric effects of benidipine (n=118) and Cilnidipine (n=115) in hypertensive patients with stage 3 - 5 CKD.
- The patients received either Benidipine, 2 mg/day, which was increased to a daily dose of 8 mg (benidipine group), and Cilnidipine, 5 mg/day, which was increased to a daily dose of 20 mg (Cilnidipine group).
- The changes in the urinary protein:Cr ratio were measured from the pre-treatment period to 1, 3, 6 and 12 months of treatment.

- After 12 months of treatment benidipine group had a greater reduction in urinary protein:Cr ratio (benidipine group: 1744 ± 209 mg/g Cr and Cilnidipine group: 2092 ± 328 mg/g Cr, NS) than Cilnidipine.
- When the percent change from baseline was calculated, there was a greater change in Benidipine group versus Cilnidipine group. (-35.2 ± 1.8% vs -30.6 ± 3.2%).



Expert Opin. Investig. Drugs (2010) 19(9):1027-1037

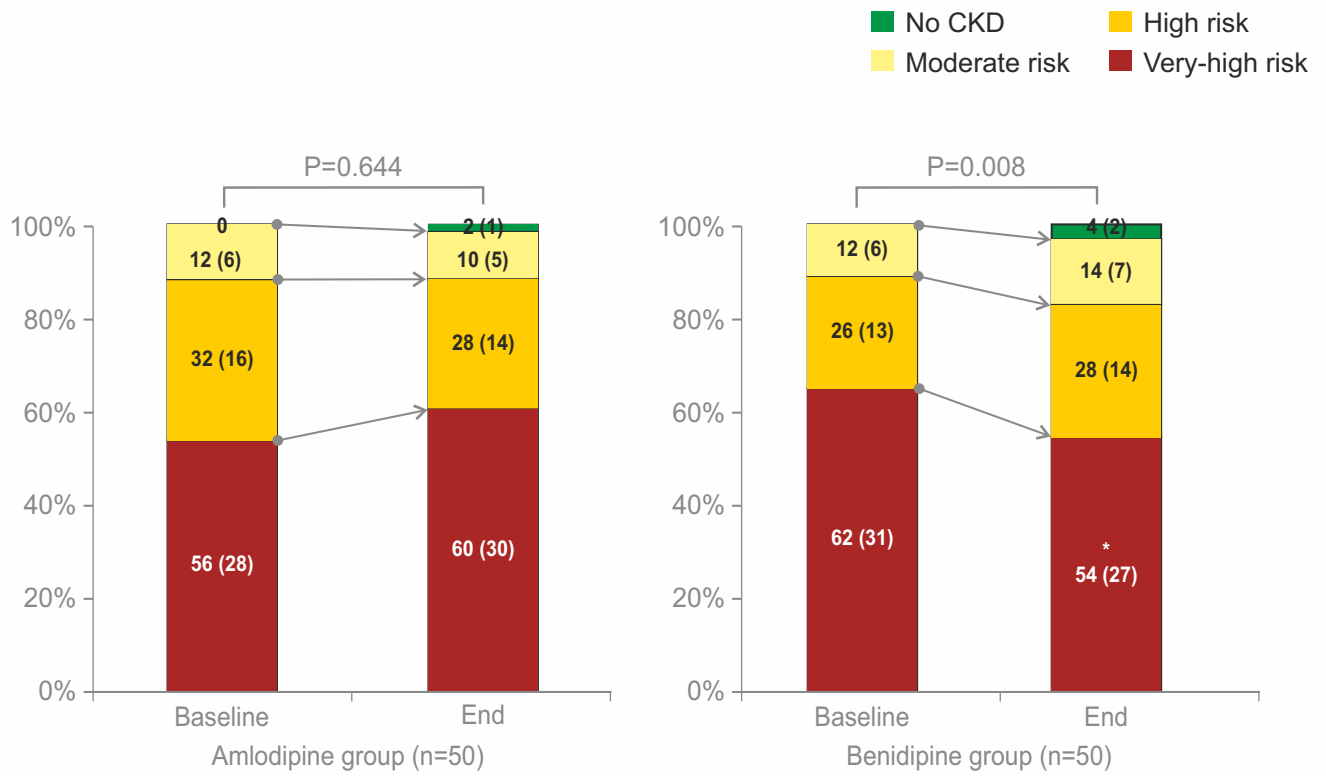
4.9 Amlodipine increases the severity of CKD while Benidipine decreases.

- The respective add-on effects of benidipine and amlodipine on top of the ARBs, telmisartan and olmesartan in albuminuria reduction were demonstrated in 100 CKD patients.
- **There was a significant reduction in the urinary albumin/Cr ratio in the benidipine group, while there was an increase in urinary albumin/Cr ratio in the Amlodipine group.**
- eGFR significantly decreased in the amlodipine group but was maintained in the Benidipine group.

	Amlodipine group (n=50)	Benidipine group (n=50)
Urinary albumin (mg/g. Cr)		
Pre	173.2 ± 18.7	175.5 ± 22.4
Post	194.1 ± 34.6	120.6 ± 13.6
Urinary albumin	20.8 ± 32.1	-54.9 ± 13.7
P Value (pre vs. post)	0.774	<0.001
eGFR (mL/min/1.73 m2)		
Pre	44.7 ± 1.7	44.6 ± 1.9
Post	42.7 ± 1.9	44.3 ± 2.1
eGFR	-2.0 ± 0.7	-2.0 ± 0.7
P Value (pre vs. post)	0.006	0.519

Changes in the urinary albumin/Cr ratio and eGFR Value expressed as Mean±SEM using the paired t-test or unpaired t-test.

- In CKD patients, benidipine treatment significantly decreased urinary albumin/Cr and relative risk of developing severe CKD, while amlodipine showed an increase in relative risk for developing severe CKD.



BMC Nephrology 2013, 14:135

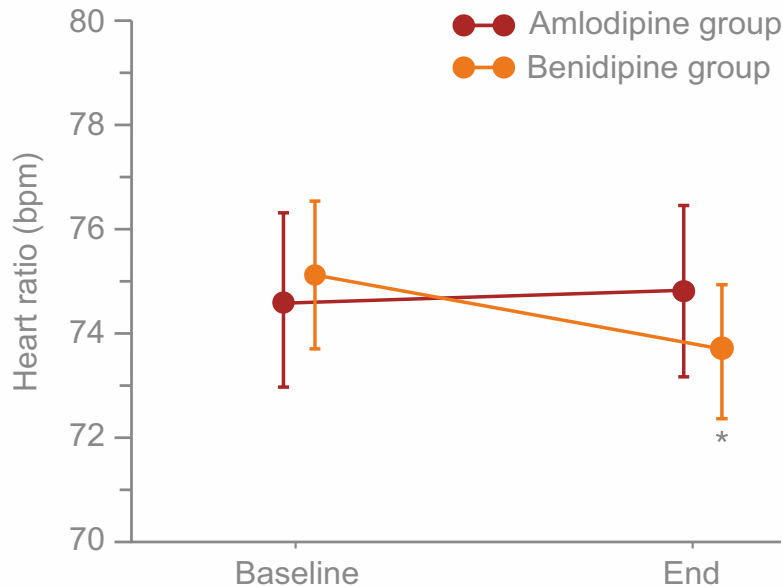


BENIDIPINE

CARDIOVASCULAR PROTECTION

5.1 Benidipine decreases Heart Rate

- Heart rate is an independent cardiovascular risk factor.
- Heart rate at the end of the study was significantly reduced in the benidipine group compared with baseline (benidipine group: from 75.1 ± 1.4 to 73.7 ± 1.3 beats per min, $P < 0.001$), while Amlodipine group showed a slight increase in Heart rate (amlodipine group: from 74.5 ± 1.7 to 74.8 ± 1.6 beats per min; NS)



Hypertension Research (2011) 34, 268–273

5.2 High Coronary Vascular Selectivity

The coronary vascular selectivity ratio of

- Amlodipine is 67
- Benidipine is 1300

This implies that Benidipine is 19 times more coronary vascular selective than amlodipine.

Cardiovascular Drug Reviews Vol. 17, No. 1, pp. 1–15

5.3 Up regulation of Nitric Oxide production (Increase eNOS/NOx activity)

- Basic research has shown that benidipine increases NOx in the coronary circulation & stimulates endothelial cell-type nitric oxide synthesis (eNOS) independently of its antihypertensive action.
- A study on Anginal patients evaluated the NO up regulation effects of Benidipine. The mean age of the eligible patients was 64.8 years.
- Patients with the mean disease duration of 3.4 ± 3.1 years (range 0.5 to 10.5 years) and the average frequency of angina attacks range from once to five times per month at the baseline were selected.

	Before	After benidipine treatment
All patients (n=8) Serum NOx levels, $\mu\text{mol/L}$ Plasma cGMP levels, pmol/mL	37.6 ± 15.3 2.2 ± 0.8	$54.5 \pm 26.7^{**}$ $2.5 \pm 0.6^*$
Hypertensive patients (n=5) Serum NOx levels, $\mu\text{mol/L}$ Plasma cGMP levels, pmol/mL	33.0 ± 9.7 2.0 ± 0.7	$43.4 \pm 18.6^*$ 2.3 ± 0.7
Normotensive patients (n=3) Serum NOx levels, $\mu\text{mol/L}$ Plasma cGMP levels, pmol/mL	45.3 ± 22.1 2.4 ± 0.4	$73.0 \pm 31.3^*$ 2.8 ± 0.4

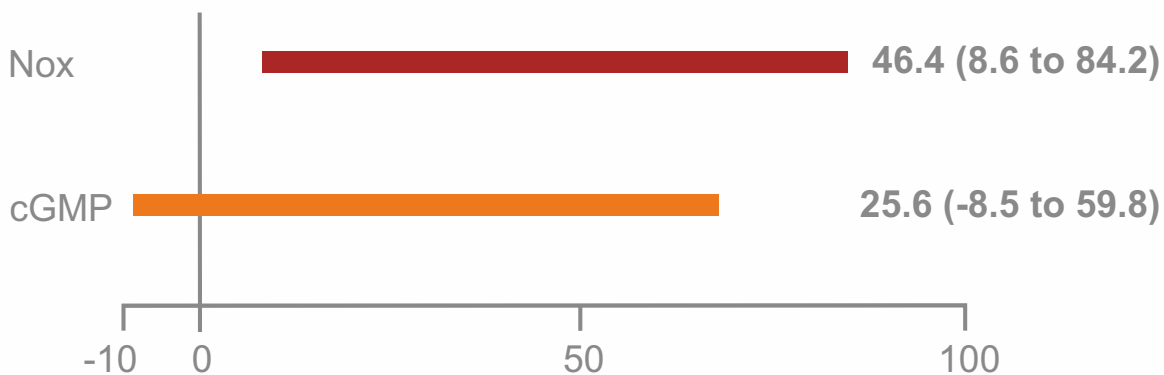
Changes in serum nitrite/nitrate (NOx) and plasma cGMP levels of patients with vasospastic angina pectoris before and after benidipine treatment. * $p = 0.05$, ** $p < 0.01$ vs before benidipine treatment.

Arzneimittel-Forschung (Drug Research) 2007;57(1):20–25

- A significant increase of serum NOx levels after benidipine administration was seen in this study.
- NO production induced by benidipine contributes to the antianginal effects.
- As compared to Diltiazem, Benidipine significantly increased NOx & cGMP.

Difference change in NOx and cGMP
(% benidipine minus diltiazem)

Mean difference in
change (95% Cr)



5.4 Benidipine decreases inflammatory markers in endothelium

- Benidipine causes a significant change of platelet activation markers, microparticles, chemokines, and soluble adhesion markers in hypertensive patients with type 2 diabetes.

N = 28	0	M3	M6
SBP (mmHg)	183 ± 22	161 ± 29***	149 ± 24***
DBP (mmHg)	102 ± 16	93 ± 15**	81 ± 15***
CD62P (%)	23.5 ± 3.8	20.1 ± 3.8**	20.4 ± 4.1*
CD63 (%)	22.7 ± 4.2	19.3 ± 3.7**	20.3 ± 3.2*
PAC-1 (%)	14.8 ± 2.1	13.5 ± 1.7*	13.4 ± 1.7*
MDMP (/ μ l)	570 ± 83	494 ± 120	471 ± 83*
EDMP (/ μ l)	494 ± 116	466 ± 79	421 ± 65*
MCP-1 (pg/ml)	524 ± 45	484 ± 39**	472 ± 33*
RANTES (ng/ml)	97 ± 21	85 ± 22	82 ± 19
sE-selectin (ng/ml)	69 ± 12	68 ± 10*	65 ± 11**
sICAM-1 (ng/dl)	286 ± 64	266 ± 52*	251 ± 43**
Anti-oxLDL IgG (AcU/ml)	16.1 ± 5.5	14.2 ± 5.6	8.9 ± 4.4**

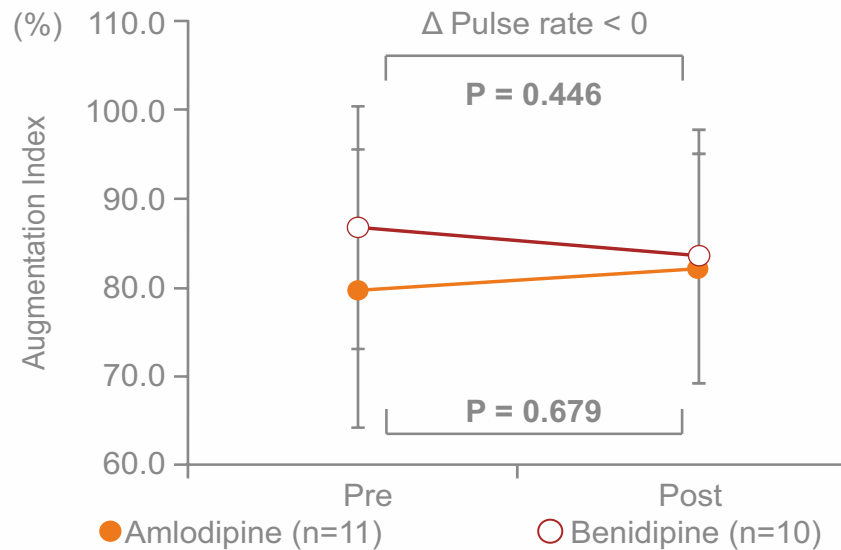
Change of platelet activation markers, microparticle, chemokine, and soluble adhesion markers in hypertensive patient with type 2 diabetes
Results are shown as the mean +s.d. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

Journal of Human Hypertension (2005) 19, 551–557

5.5 Benidipine decreases Augmentation Index & Arterial Stiffness

- 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 arterial stiffness.
- AI is believed to reflect the structure and function of blood vessels based on measurements of arterial stiffness.
- A study compared the effects on augmentation index (AI) of benidipine and amlodipine in hypertensive CKD patients.

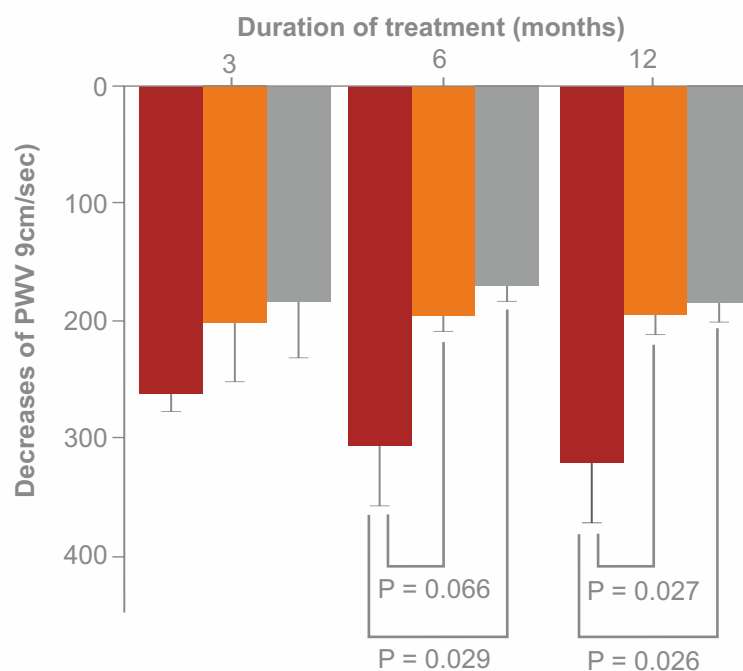
- Augmentation Index increased from $80.3 \pm 16.0\%$ to $82.6 \pm 13.1\%$ in the amlodipine group and showed a decrease from $87.4 \pm 14.0\%$ to $84.0 \pm 14.7\%$ in the benidipine group.



Int Heart J 2016; 57: 53-60

5.6 Benidipine decreases Pulse wave velocity

- Brachial-ankle PWV (baPWV) is closely related to risk factors and/or the organ damage characteristic of cardiovascular diseases.
- 6 months of Benidipine treatment showed a significant decrease in PWV.



Comparison between real pulse wave velocity (PWV) changes (■ column) and estimated PWV changes (■ column: analysis with maximum changes; ■ column: all-data analysis) after benidipine treatment in hypertensive patients (mean±SEM, n=9). Estimated PWV changes were calculated from blood pressure changes as described in the text.

Hypertens Res 2005; 28: 959-964

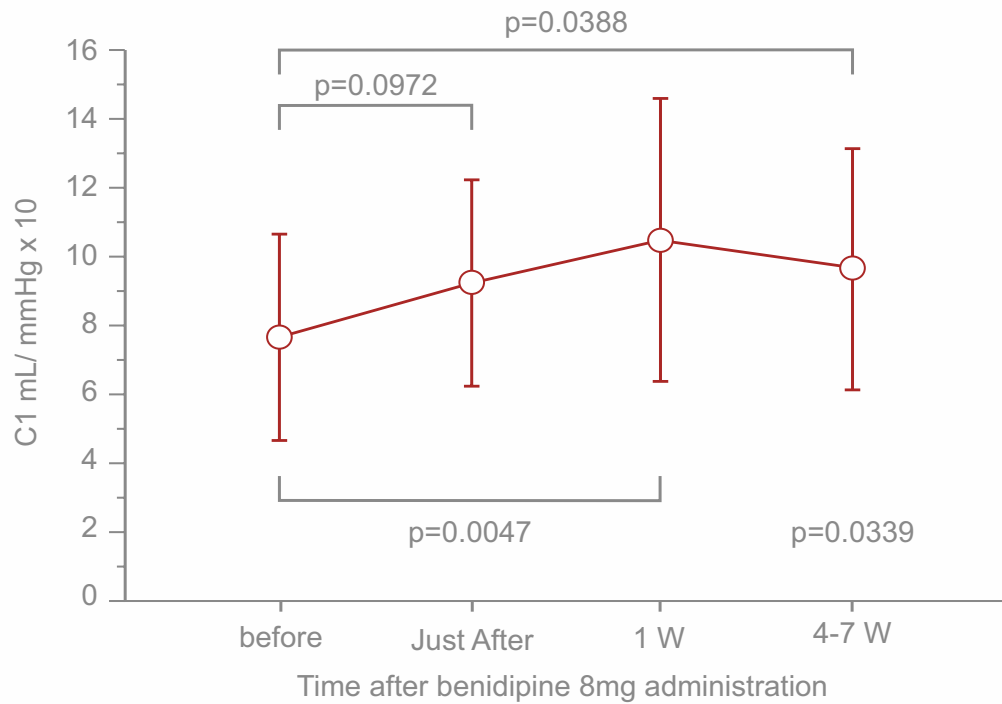
5.7 Benidipine decreases Left Ventricular Mass Index & Left Ventricular Hypertrophy

- LVH is particularly common in elderly hypertensive patients and is an independent risk factor for heart failure, coronary heart disease, stroke, arrhythmias, sudden cardiac death and cardiovascular morbidity and mortality in elderly patients
- Benidipine has been reported to reduce left ventricular mass index (LVMI) in essential hypertensive patients with severe left ventricular hypertrophy (LVH)
- A multicenter, prospective, open-label clinical trial assessed the effects on LVMI in elderly patients by Benidipine administration.
- Patients were administered Benidipine 2–4 mg once daily for a 52-week treatment period. Benidipine dose could be gradually titrated to the highest dosage of 8 mg.
- In LVH patients after 52-week benidipine treatment, there was a significant reduction in LVMI from $147.1 \pm 27.6 \text{ g/m}^2$ to $136.0 \pm 17.5 \text{ g/m}^2$ ($p = 0.036$).
- This indicates that in elderly patients with hypertension, the pathological process of ventricular hypertrophy could be prevented and even reversed by effective and persistent antihypertensive therapy based on benidipine. Arzneimittelforschung 2011;61(3):160–166
- Another study showed that Long-term administration of benidipine reduced left ventricular mass and normalized systemic collagen type1 degradation abnormalities in essential hypertensive patients with severe LVH. J Cardiol. 2002 Apr;39(4):195-204.

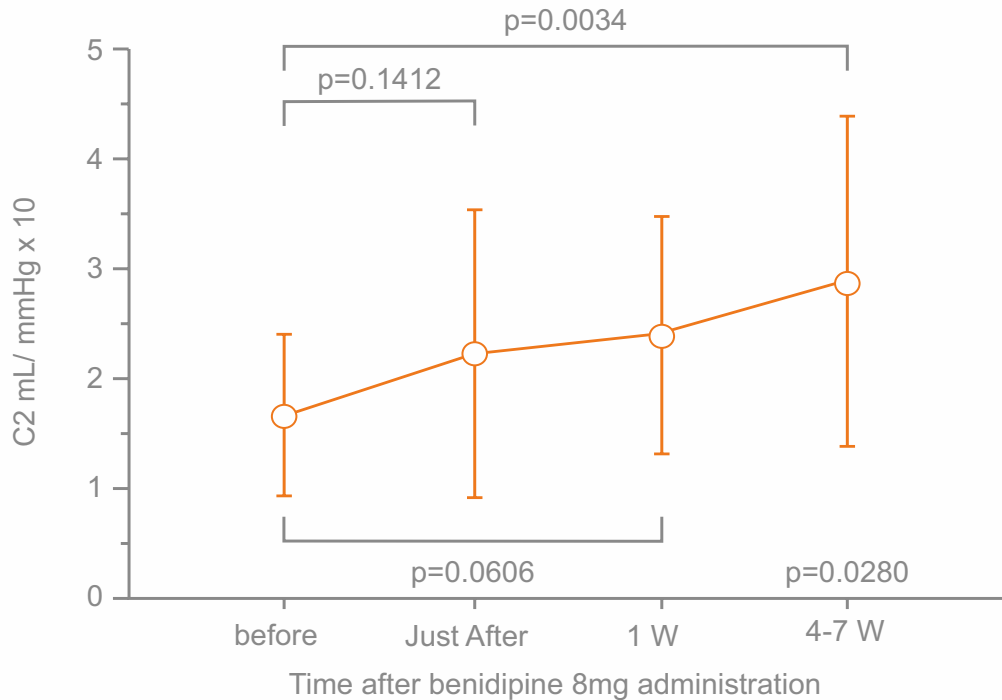
5.8 Benidipine increases Arterial Compliance

- Arterial compliance is an index of the elasticity of large arteries.
- Arterial compliance denotes the ability of a blood vessel wall to expand and contract passively with changes in pressure & is an important function of large arteries and veins.
- A study examined the effect of Benidipine on change in the arterial compliance.
- Benidipine improved arterial compliance significantly & thus potentially improves arterial function and perhaps arterial properties.

- Time-course changes in large artery compliance after benidipine administration

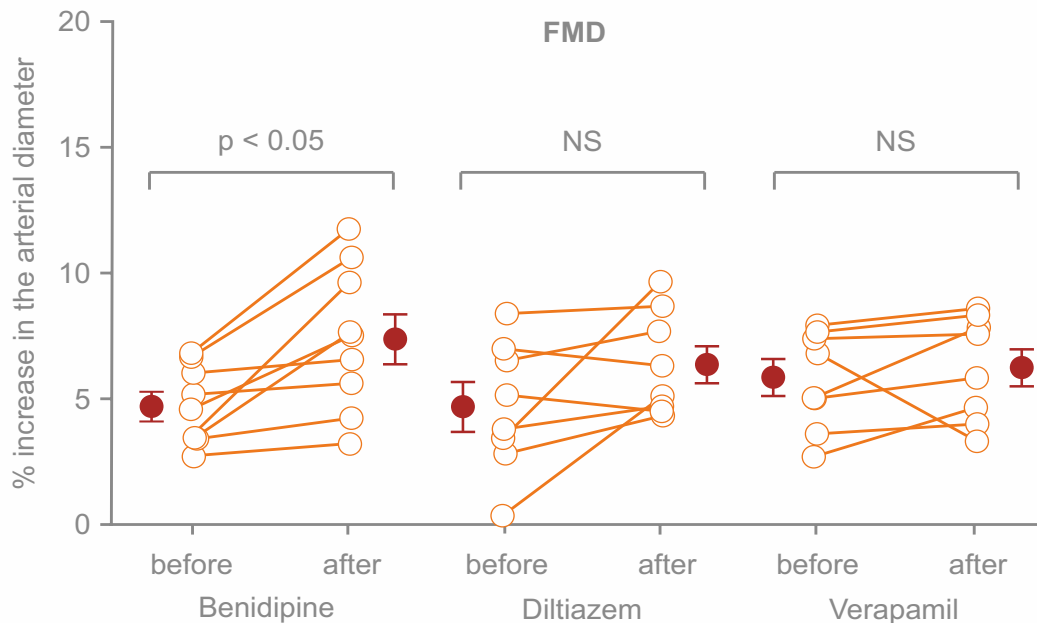


- Time-course changes in small artery compliance after benidipine administration



5.9 Benidipine Increases flow-mediated dilation (FMD)

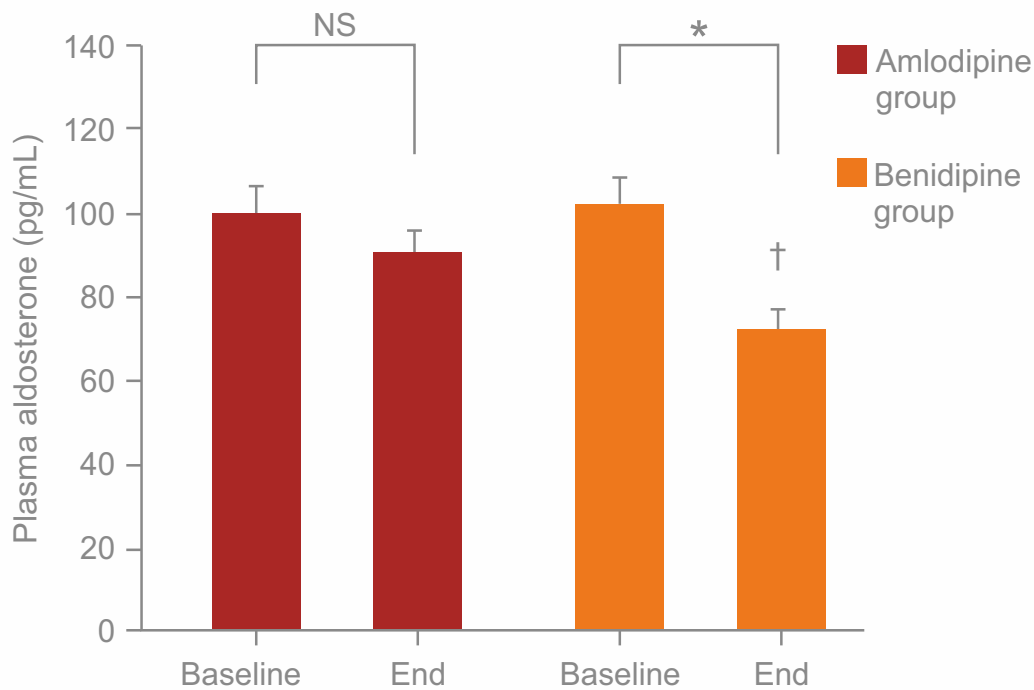
- Flow-mediated dilatation (FMD) is the most widely used method to assess endothelial dysfunction.
- There is an impaired flow-mediated dilation (FMD) in systemic arteries as well as coronary arteries in patients with coronary spastic angina (CSA)
- A study compared the effects of the 3 CCBs-benidipine, diltiazem and verapamil on endothelial-dependent FMD of the brachial arteries in patients with coronary spastic angina (CSA).
- Benidipine significantly increased FMD (from 4.7 ± 0.6 to $7.4 \pm 1.1\%$, $P < 0.05$) and plasma cGMP levels. In contrast, neither diltiazem nor verapamil affected FMD and cGMP levels.



Circ J 2009;73:713-717

5.10 Benidipine decreases Plasma Aldosterone

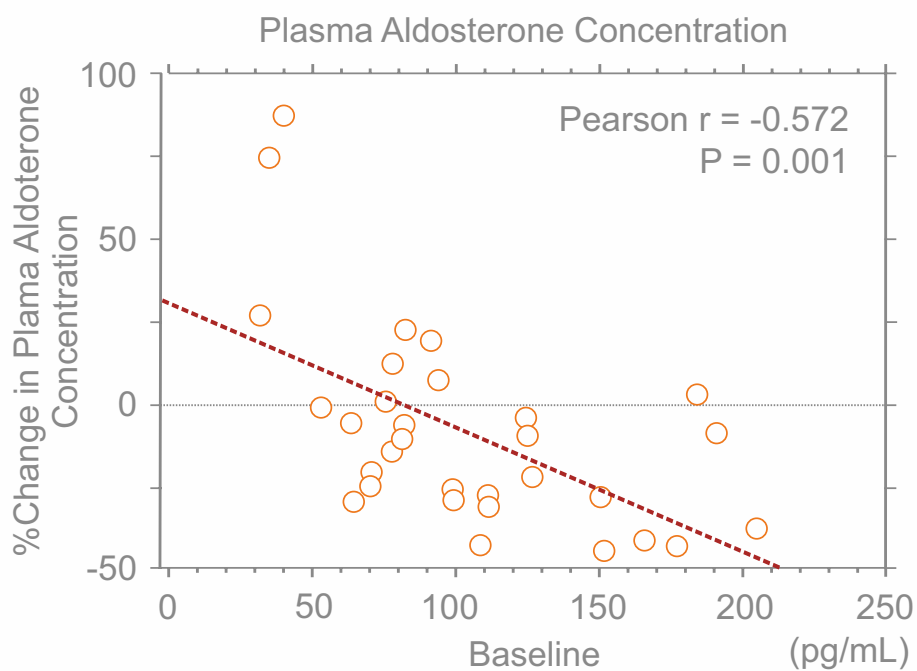
- Aldosterone has an important role in the pathophysiology of hypertension, cardiac hypertrophy and renal disease.
- Targeting aldosterone synthesis and/or secretion represents a potentially useful approach for the prevention of cardiovascular disease.
- A 6-month, single-centre, prospective, randomized and open label clinical trial was designed to compare the effects of benidipine and amlodipine on plasma aldosterone levels in CKD patients.
- **Plasma aldosterone levels were not significantly changed in the amlodipine group. However, plasma aldosterone levels were decreased in the benidipine group, and there was a significant difference between the two groups at the end of study (71.9 ± 5.0 vs. 90.4 ± 5.0 pg/ml, $P < 0.05$).**



Hypertension Research (2011) 34, 268–273

Shifting patients from L-type CCB to Benidipine

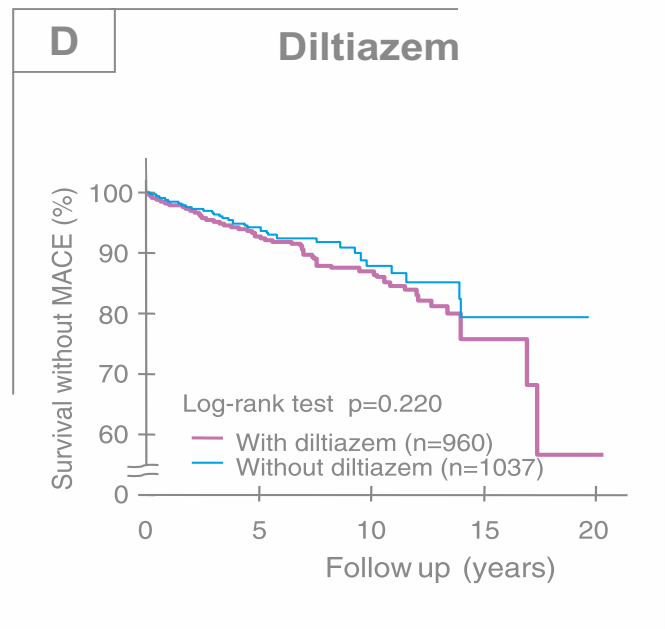
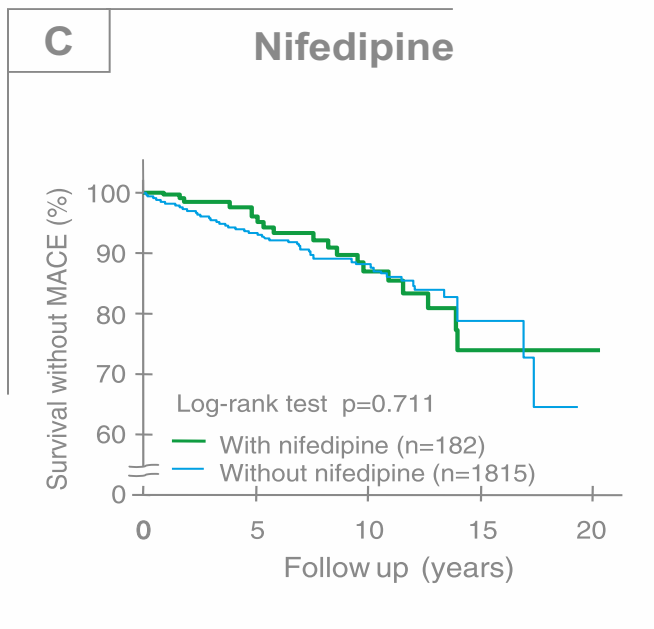
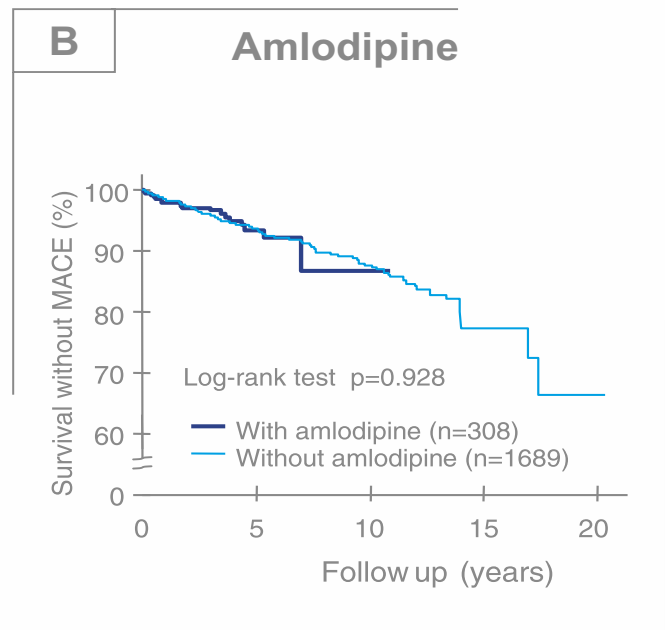
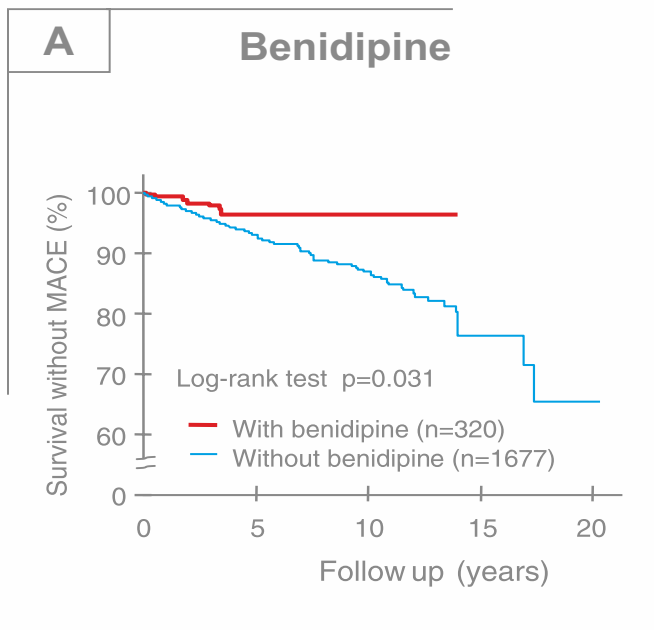
Aldosterone levels declines significantly on shifting from L-type CCB to Benidipine



Int Heart J 2014; 55: 000-000

5.11 Benidipine increases MACE-free survival

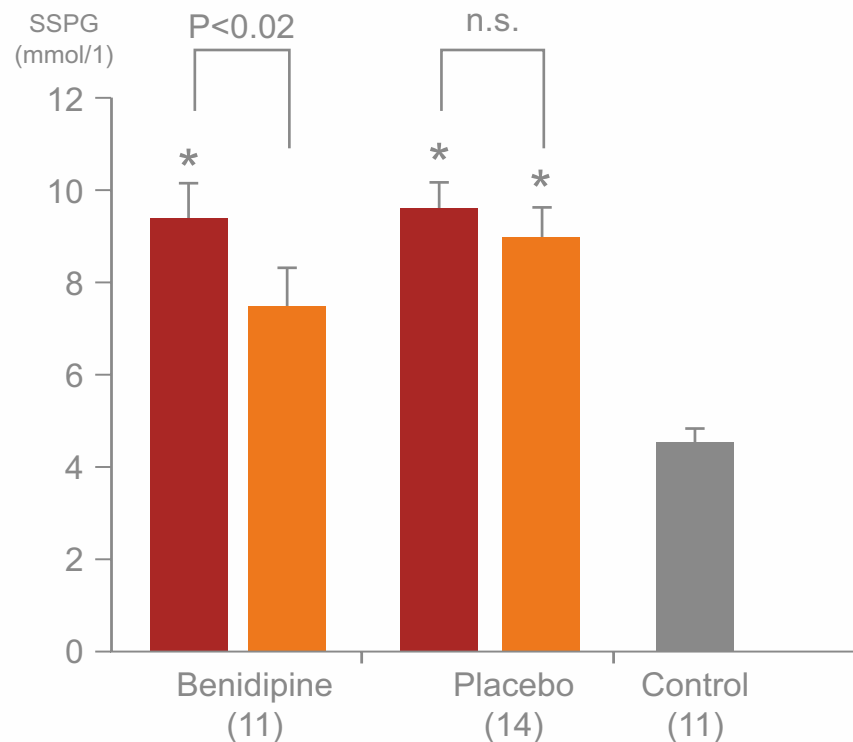
- MACE—Major Adverse Cardiovascular Events is a term used to denote all the cardiac events including cardiac death, MI (fatal and non-fatal), heart failure (death due to heart failure and heart failure requiring hospitalization), stroke (fatal and non-fatal), and aneurysm.
- A meta-analysis study compared the effects of major CCBs on the incidence of each MACE and the total number of deaths due to the event and its percentage.
- MACE occurred significantly less in the patients treated with benidipine compared with those without it (P=0.031, log-rank test).
- Benidipine showed the highest MACE free survival in comparison to all CCBs.



6 Metabolic benefits

6.1 Benidipine Improves Insulin Sensitivity

- In subject with essential hypertension, insulin resistance is an important metabolic parameter.
- It is found that benidipine improve insulin sensitivity after 12 weeks of treatment as compared to placebo group in subject with essential hypertension.

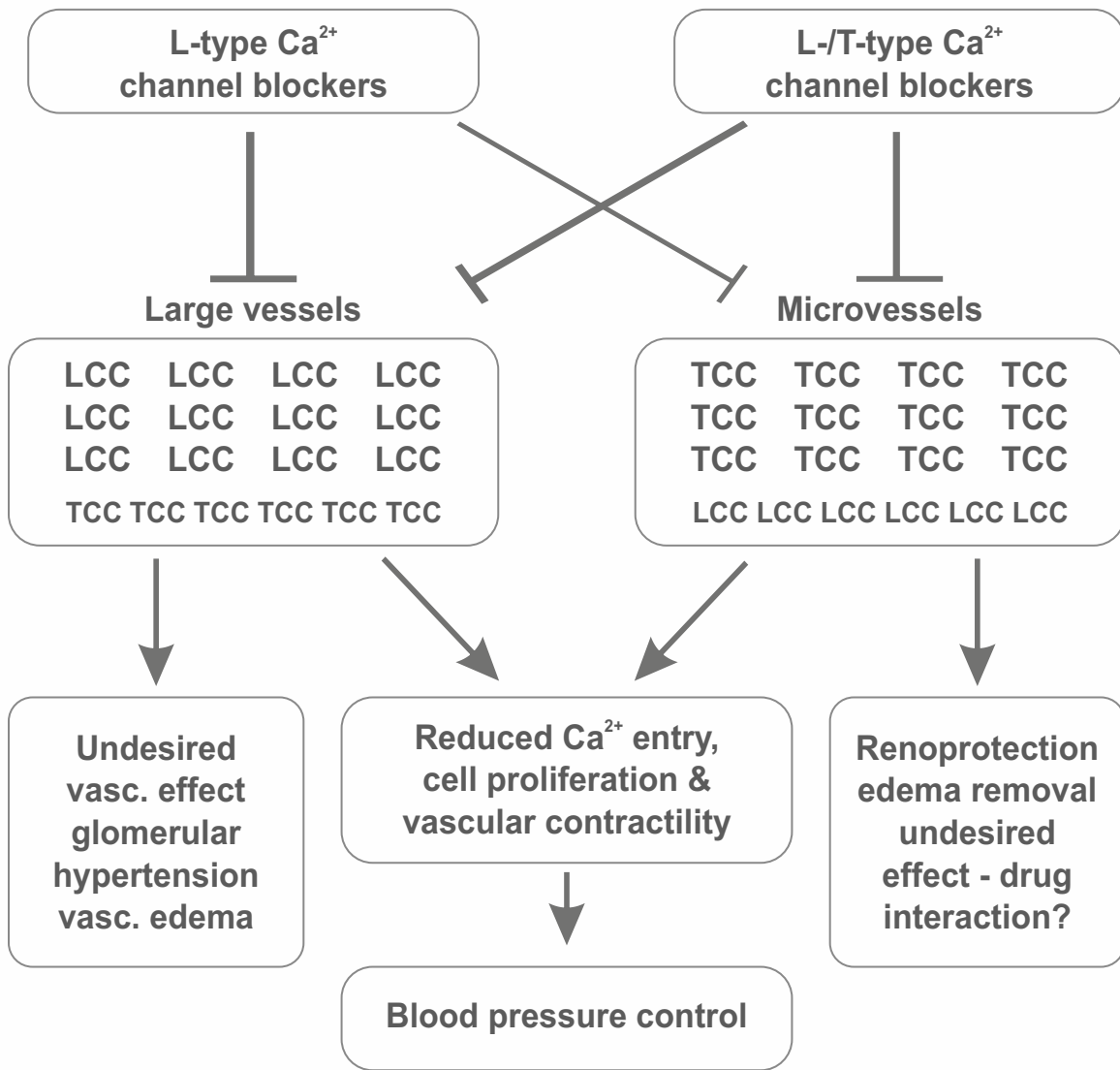


SSPG Steady state plasma glucose Value are mean \pm SE

Clin and Exper Hypertension, 21 (8), 1327-1344(1999)

6.2 Benidipine reduced Pedal edema

- The L-type Ca channels (LCC) are predominantly expressed in large vessels, whereas T-type Ca⁺² channels (TCC) prevail mainly in microvessels.
- Combined L-/T-type Ca⁺² channel blockers display much less propensity of edema formation.
- L/T type Ca⁺² channel blockers equalize the hydrostatic pressure across the capillary bed through equal arteriolar and venular dilatation, thus reducing vasodilatory edema



Hypertension. 2009;53:592-594

PRESCRIBING INFORMATION

Indication:	Hypertension CKD with hypertension patient Renal parenchymal hypertension Diabetic nephropathy Long-term prophylactic management of angina pectoris.
Dosage:	Hypertension : 2-4 mg once daily up to 8 mg once daily if needed. Angina pectoris : 4 mg twice daily.
How it should be taken:	It comes as a tablet to take by mouth, with food.
Contraindications:	Pregnancy and lactation.
Adverse Reactions:	Palpitation, facial flushing, hot flushes, headache, dizziness, sleepiness, constipation, nausea, abdominal discomfort, oedema, malaise, redness and warm feeling in the fingers, shoulder stiffness, increased frequency of micturition. Hypersensitive reactions e.g. rash and itching Elevation of SGOT, SGPT, alkaline phosphatase, total bilirubin, creatinine and uric acid.
Warning:	It may cause dizziness or light-headedness. Avoid abrupt withdrawal Monitor liver function regularly. Never take the medicine with a glass of grapefruit juice since the blood pressure may be decreased excessively.
Drug Interactions:	Serum concentrations of digoxin may be increased. Cimetidine may inhibit benidipine metabolism.
Storage condition:	Store at room temperature.

The Complete CCB



The only triple Ca⁺² channel blocker



**The complete combination of CCB+ARB
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