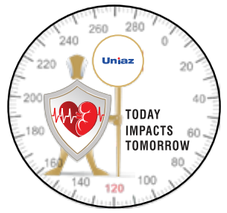
Unique Calcium Channel Blocker

In Stage-II Hypertension

Uniaz

AzelNidipine 16mg Tablets

Control with **Cardio-renal protection**



HYPERTENSION CONTROL to END ORGAN PROTECTION

Effective BP Control

24-hours BP control with single dose of Azelnidipine[1]

Effective Cardio-protection

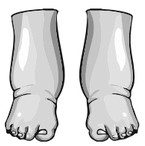
Significantly lowering of Heart Rate[2]& Tachycardia[3]

Effective Reno-protection

Effectively reduces Proteinuria in CKD patients[4]

Safety

Lesser chances of Peripheral Edema[1]



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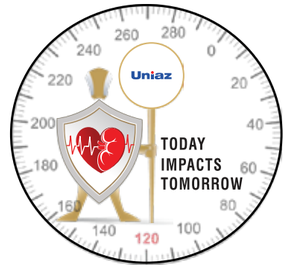

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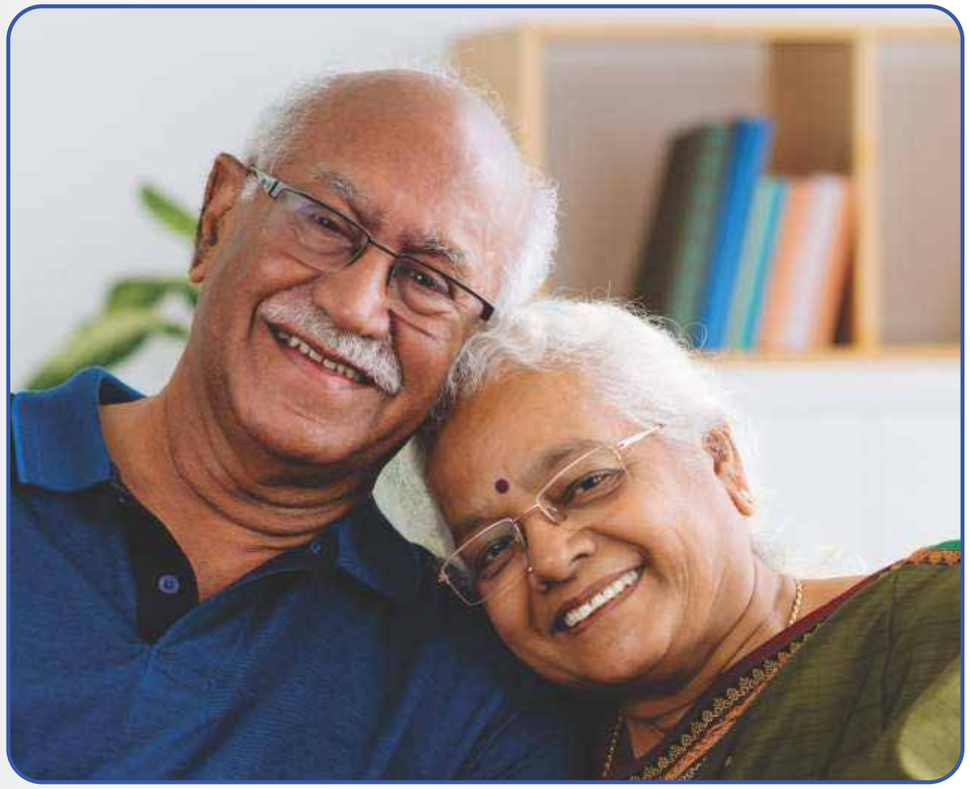

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TODAY
IMPACTS
TOMORROW

NOTES

Uniaz

Azelnidipine 16mg Tablets

Control with **Cardio-renal protection**

Table Of Contents

Introduction

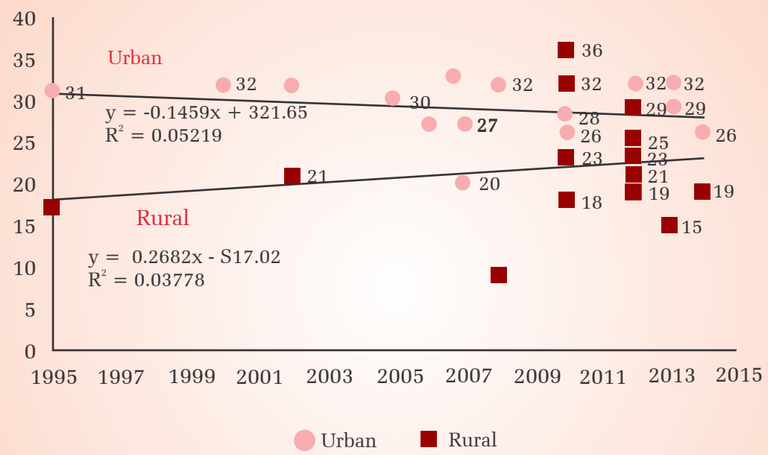
Hypertension is a chronic complication of the vascular system, which already affects one billion people worldwide. According to World Health Organisation global statistics, Hypertension is considered to be a leading global risk factor for mortality, accounting for about 1 out of every 8 deaths worldwide, resulting in an average loss of life of 5 years in suffering patients. Cardiovascular disease (CVD) is the leading global cause of death, accounting for more than 17.3 million deaths per year, a number that is expected to grow to more than 23.6 million by 2030. In 2015, an estimated 3.5 billion adults had systolic blood pressure (SBP) of at least 110 to 115 mm Hg and 874 million adults had SBP of 140 mm Hg or higher.[1-3]

About 54% of stroke and 47% of ischemic heart disease worldwide were attributable to high blood pressure (BP). Increased BP contributes to the burden of heart disease, stroke and kidney failure, leading to premature mortality and disability. Those living with hypertension are more often burdened with morbidities of congestive heart failure, chronic kidney disease (CKD), neurologic deficits from stroke, and vision loss.[3-5]

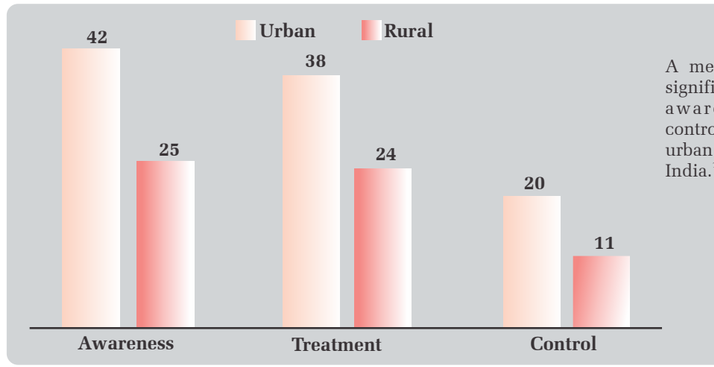
PREVALENCE OF HYPERTENSION IN INDIA

The burden of hypertension in Asia is higher than that in Western countries. Hypertension is ranked as the third most important risk factor for significant burden of disease in south Asia. Populations living in rural areas have the prevalence of hypertension 2–3 times lower than those living in urban areas of Asia. However, with urbanisation and westernisation of lifestyle in many developing countries, the lower prevalence of hypertension in rural areas will be gradually replaced by a higher prevalence of hypertension. Hypertension and stroke occur at a relatively younger age in Asia.[4,6]

Prevalence of Hypertension in Urban and Rural Population in India[7]



Convergens in prevalence of hypertension in urban and rural population in India. Prevalence data from studies that have included subjects aged >20 years are included. Prevalence of hypertension in urban areas (black line) has stabilised while in rural areas (grey line) is increasing.



A meta-analysis reported that significant difference exists on awareness, treatment and control of hypertension among urban and rural population of India.[10]

Hypertension exerts a substantial public health burden on cardiovascular health status and CVD is responsible for almost 2 million annual deaths in India. It accounts for 57% of all stroke deaths and 24% of deaths due to coronary heart disease (CHD) in India. A number of Indian studies showed the prevalence of hypertension in 25- 30% urban and 10-20% rural subjects in India. A meta-analysis study from India (urban and rural) reported that about 33% urban and 25% rural Indians are hypertensive. Of these, 25% rural and 42% urban Indians are aware of their hypertensive status. Only 25% rural and 38% of urban Indians are being treated for hypertension. One-tenth of rural and one-fifth of urban Indian hypertensive population have their BP under control.This translates into an approximate population burden of 100-110 million persons with high BP. Approximately half to two-thirds of these are stage I hypertension (SBP 140-159 and/or diastolic blood pressure (DBP) 90-99 mmHg) and the rest have stage II -III disease. [4,6,7]

HYPERTENSION- A SILENT KILLER

Hypertension is generally asymptomatic with no warning signs and is known as the “silent killer” because most of the people do not know they are suffering from hypertension. Most people do not have any signs or symptoms even when BP levels are dangerously high. A small amount of people may experience symptoms such as dull headaches, dizzy spells, vomiting, and more frequent nosebleeds. These symptoms usually do not occur until BP levels have reached a severe or life-threatening stage. The only way to know if a person has hypertension is to have a routine check-up with physician or other health care professional and measure BP at regular interval. [8,9]

HYPERTENSION-DEFINITION

Hypertension is defined as SBP of more than 130 mmHg or DBP of more than 80 mmHg. The classification of BP in adults is based on the average of two or more properly measured BP readings from two or more clinical visits. The recently updated American Heart Association (AHA) – 2017 guideline provides classification of hypertension as in the following table.[10]

Classification of Hypertension[10]

BP Category	SBP		DBP
Normal	<120 mmHg	and	<80 mmHg
Elevated	120-129 mmHg	and	<80 mmHg
Hypertension			
Stage 1	130-139 mmHg	or	80-90 mmHg
Stage 2	>140 mmHg	or	>90 mmHg

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.
BP indicates BP (based on an average of >2 careful readings obtained on >2 occasions, as detailed in Section);
DBP = Diastolic BP; SBP = Systolic BP.

HYPERTENSION AND END ORGAN DAMAGE

Hypertension is asymptomatic but at the same time it is the single most significant risk factor for various heart diseases. The characteristic manifestations of hypertensive end-organ damage include vascular and haemorrhagic stroke, retinopathy, coronary heart disease/myocardial infarction and heart failure, proteinuria and renal failure and in the vasculature, atherosclerotic change including the development of stenoses and aneurysms.

The recommendations of medical societies specialising in hypertension have not only used BP for risk stratification, but focus on additional cardiovascular risk factors, the detection of end organ damage, and clinically manifest cardiovascular diseases. Hence, grade 1 hypertension can be associated with a slightly increased risk or with a very significantly increased risk depending on what additional end organ damage is present. The early detection of hypertensive end organ damage can slow or prevent damage, or allow disease regression with adequate therapy, where organ damage is still at a reversible stage. The diagnosis of hypertensive end organ damage is of decisive importance. This is reflected in European and German guidelines.[11]

Complications Arising from Hypertension[11]

End organ damage in arterial hypertension

Vasculopathy
- Endothelial dysfuncion
- Remodeling
- Generalised atherosclerosis
- Arteriosclerotic stenosis
- Aortic aneurysm

Cerebrovascular damage
- Acute hypertensive encephalophathy
- Stroke
- Intracerebral haemorrhage
- Lacunar infarction
- Vascular dementia
- Retinopathy

Heart disease
- Left ventricular hypertrophy
- Atrial fibrillation
- Coronary microangiopathy
- CHD, myocardial infarction
- Heart failure

Nephropathy
- Albuminuria
- Proteinuria
- Chronic renal insufficiency
- Renal failure

"Hypertension is generally asymptomatic with no warning signs and is known as the "silent killer" because most of the people do not know they are suffering from hypertension"

Overall Cardiovascular Risk[11]

Additional risk factors and comobidities	Normal BP (SBP 120-129 mmHg or DBP 80-84 mmHg)	High normal (SBP 130-139 mmHg or DBP 85-89 mmHg)	Grade 1 hypertension* (SBP 140-159 mmHg or DBP 90-99 mmHg)	Grade 2 hypertension (SBP 160-179 mmHg or DBP 100-109 mmHg)	Grade 3 hypertension (SBP≥180 mmHg or DBP≥110 mmHg)
No risk factors	Average risk	Average risk	Slightly elevated risk	Moderately elevated risk	Significantly elevated risk
1 or 2 risk factors	Slightly elevated risk	Slightly elevated risk	Moderately elevated risk	Moderately elevated risk	Very significantly elevated risk
3 or more risk factors or end organ damage**or DM or MS	Moderately elevated risk	Significantly elevated risk	Significantly elevated risk	Significantly elevated risk	Very significantly elevated risk
Clinically manifest cardiovascular or renal disease	Very significantly elevated risk	Very significantly elevated risk	Very significantly elevated risk	Very significantly elevated risk	Very significantly elevated risk

Framingham Cardiac Risk Score

Average risk	Slight risk	Moderate risk	Significant risk	Very significantly risk	
<10%	10-15%	15-20%	20-30%	>30%	Probability of a cardiovascular event within 10 years
	<4%	4-5%	5-8%	>8%	Risk of cardiovascular death per 10 years

SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; MS, metabolic syndrome; CHD, coronary heart disease; *This risk group includes patients with, for example, a BP of 145/85 mmHg, whose overall cardiovascular risk is slightly or significantly elevated depending on whether or not early end organ damage is present.

Dignosis of Early Hypertensive End Organ Damage[11]

- Left ventricular hypertropy (LVM) (ECG: Sokolow-Lyon ≥38 mm, Comell QRS >244 mV*msec)
- ECG: left ventricular hypertrophy (≥125 g/m^2 for men and ≥110 g/m^2 for women)
- Ultrasound examination for arterial wall thickening, (intima-media thickness [IMT] >0.9 mm or arterio sclerotic plaque)
- Pulse wave velocity 10 to 12 m/sec, depend on the device used
- Ankle-brachial index <0.9
- Serum creatinine elaveted
  Men 1.3-1.5 mg/dL (115-133 νmol/L)
  Women 1.2-1.4 mg/dL (107-124 νmol/L)
- Elevated albumin excretion (microalbuminuria 30-300 mg/24 hours, albumin-creatinine ratio: men ≥22, women ≥31 mg/g
  creatinine: men ≥2.5, women ≥3.5 mg/mmol); normal up to a value of 10 mg/g creatinine.
- Calculated glomerular filtration rate (<60mL/min/1.73m^2) or creatinine clearance <60mL/min

MANAGEMENT OF HYPERTENSION

Goal for Management of Hypertension

Although reducing BP is pivotal in treating patients with hypertension, it is equally important to efficiently manage other cardiovascular risk factors such as lipid disorders, diabetes/glucose intolerance, obesity and smoking. The treatment goal in hypertensive patients is a reduction of SBP to <140 mmHg and DBP to <90 mmHg. The target goals for hypertension are different for special population like diabetics and CKD patients. The below table summarizes the treatment goals for different population with hypertension recommended by AHA.[10,12]

BP Thresholds for and Goals of Pharmacological Therapy in Patients with Hypertension According to Clinical Conditions[10]

Clinical Condition(s)	BP Threshold, mmHg	BP Goal, mmHg
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; noninstitutionalised, 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 ischaemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥130/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

ASCVD indicates Atherosclerotic cardiovascular disease; BP = Blood pressure; CVD = Cardiovascular disease; SBP = Systolic blood pressure.

Non-pharmacologic Therapy

Several lifestyle interventions have been shown to reduce BP. Apart from contributing to the treatment of hypertension, these strategies are beneficial in managing most of the other cardiovascular risk factors. In fact, in pre-hypertensive patients with SBP between 120-139 mmHg and DBP between 80-89 mmHg merely making lifestyle changes would delay and possibly halt progression to hypertension. Similarly, even in patients with stage I hypertension lifestyle changes for 6-12 months might preclude the necessity for drug therapies and should be encouraged in the absence of cardiovascular and renal risk factors. Life style modifications include weight loss, reduced sodium intake, physical activity, limiting alcohol consumption, and incorporating the dietary approaches to stop hypertension (DASH) eating plan. The benefits of these changes are apparent in various studies revealing reductions in SBP.[12-14]

Impact of Various Lifestyle Modifications on Changes in BP[14]

Intervention	SBP (mmHg)	DBP (mmHg)	Goal
Diet and weight control	-6.0	-4.8	• BMI<25 kg/m^2;WC < 102/88 cm (Caucasian men/women), < 90/80 cm (Asian men/women)
Reduced salt/sodium intake	-5.4	-2.8	• < 2000 mg of sodium[a]
Reduced alcohol intake (heavy drinkers)	-3.4	-3.4	• < 2 drinks/day
DASH diet[b]	-11.4	-5.5	-
Physical activity	-3.1	-1.8	• 30-40 minutes 4-7 days/week
Smoking cessation	Unknown	Unknown	• Smoke free environment
Relaxation therapies	-3.7	-3.5	-
Multiple interventions	-5.5	-4.5	-

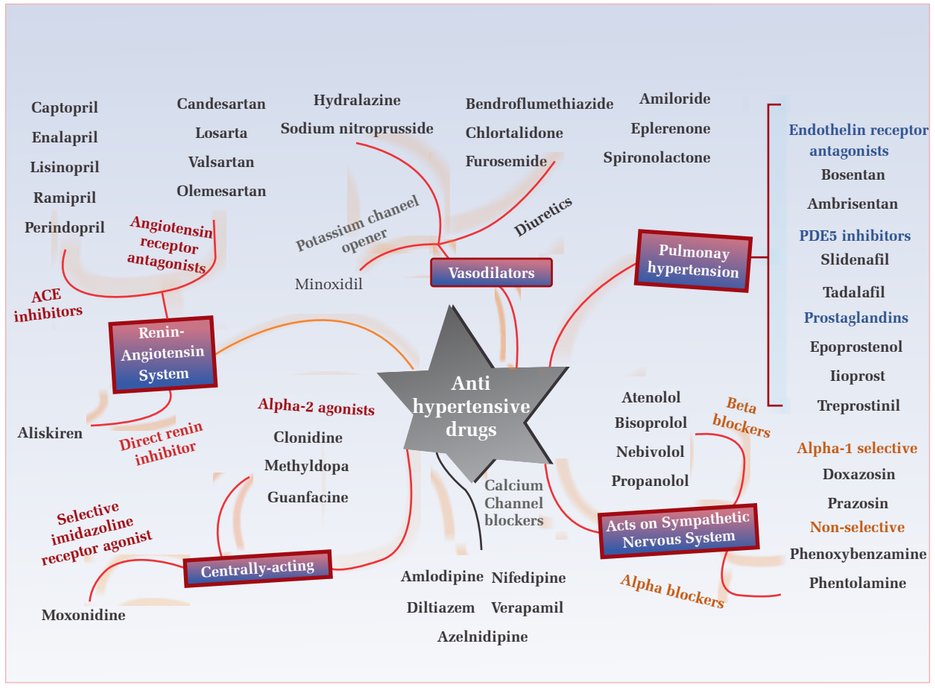
Abbreviations: BMI = Body mass index; DASH = Dietary approaches to stop hypertensipn; DBP = Diastolic blood pressure; kg/m^2 = Kilogram per square meter; mmHg = Millimetre of mercury; SBP = Systolic blood pressure; WC = Waist circumference.

"Life style modifications include weight loss, reduced sodium intake, physical activity, limiting alcohol consumption, and incorporating the dietary approaches to stop hypertension (DASH) eating plan."

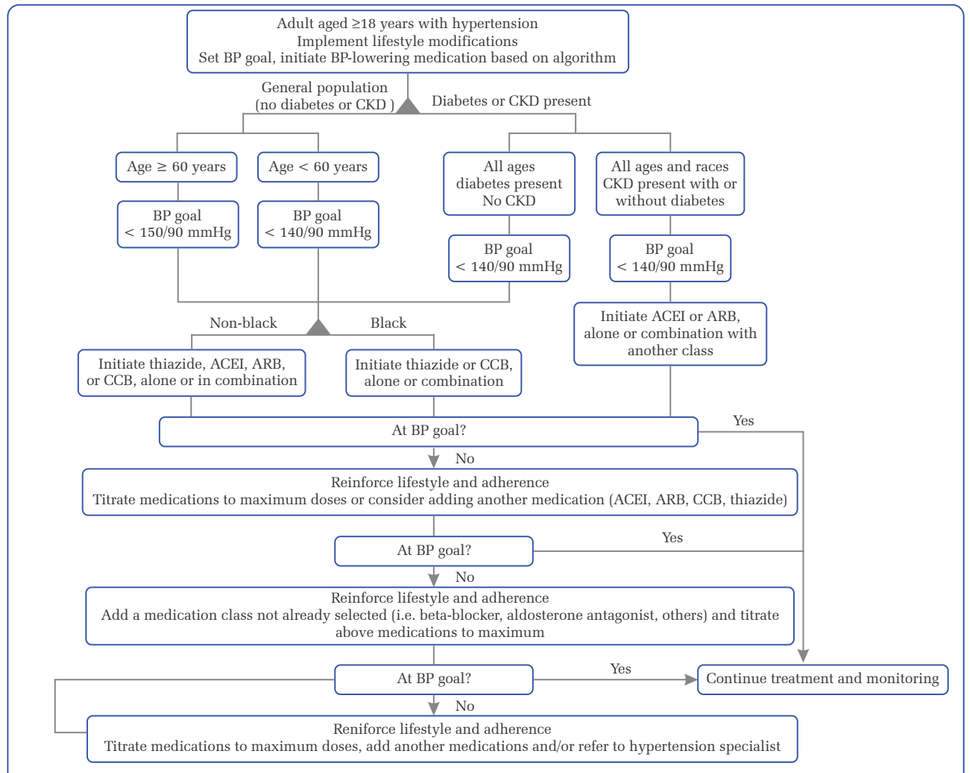
Pharmacologic Treatment

The objectives of initiating pharmacological treatment for hypertension are to reach and maintain the goal BP. Choices of drugs for hypertension are influenced by age, comorbidities, ethnicity, pregnancy and other parameters necessitating individual specific treatment regimens. Some patients will require 2 or more antihypertensive medications to achieve their BP target. If a patient's goal BP is not reached after a month of therapy, the initial drug's dose can be increased or a second drug can be added from one of the classes recommended. In newly diagnosed patients with BP >20/10 mmHg above goal, anti-hypertensive or a combination hypertensive may be added immediately. To minimise side effects, a second drug with a complementary mechanism of action should be added before the initial drug is used in the maximum recommended dosing. If two medications are not sufficient to meet the BP goal, a third medication can be added.The different class of anti-hypertensive drugs available for pharmacological management of hypertension includes:[12-14]

Classification of Antihypertensives[15]



JNC-8 Hypertension Guideline Algorithm[9]



Instigate pharmacologic management in context of the patient's overall CVD risk (e.g., not solely based on a patient's BP and in conjunction with lifestyle management. Pharmacologic management may be considered if:

1) Average BP is >140/90 and with target organ damage or CVD risk >20%;

2) Average BP is >140/90 with 1+ co-morbidities

3) Average BP is ≥160/100; or

4) Desirable BP is not reached with lifestyle management.

Pharmacologic Treatment Recommendations of Hypertension Complicated by Co-morbidity[14]

Co-morbidity	Pharmacologic Treatment Recommendations		Notes
Cardiovascular Disease			
Coronary heart disease	First-line	**ACE**-I or **ARB** or **Beta-blockers** (for patients with stable angina)	**1)** Do not use short-acting Nifedipine; **2)** Do not use ACE-I + ARB if no systolic HF; **3)** Caution when lowering SBP to a goal, if DBP is < 60 mm Hg.
	Second-line	**Long-acting CCB** or **DHP-CCB** (for high-risk patients and in combination with a first-line ACE-I)	
Myocardial infarction (recent)	First-line	**Beta-blockers + ACE-I/ARB** (if ACE-I intolerant)	**1)** Do not use non-DHP-CCB (Diltiazem, Verapamil) if heart failure is present. **2)** Caution when lowering SBP to a goal, if DBP is < 60 mm Hg.
	Second-line	**Long-acting CCB** (if beta-blockers contraindicated or ineffective)	
Left ventricular hypertrophy	First-line	**ACE-I/ARB** (if ACE-I intolerant) or **Thiazide/Thiazide-like diuretic** or **Long-acting CCB**	Do not use direct arterial vasodilators such as Hydralazine and Minoxidil.
	Second-line	Combination of first-line drugs.	
Heart failure	First-line	**Beta-blockers + ACE-I/ARB** (if ACE-I intolerant) •Aldosterone antagonist may be added in patients with recent CV hospitalization, acute MI, elevated BNP or NT-proBNP level, or NYHA Class II to IV symptoms.	**1)** If combining aldosterone antagonist to ACE-I/ARB, monitor for hyperkalaemia. **2)** If combining ACE-I + ARB, monitorfor potential adverse events including hypotension, hyperkalaemia and worsening of renal function. **3)** If bradycardia is also present, avoid use of beta-blockers.
	Second-line	**ACE-I + ARB** or **Hydralazine + Isosorbide dinitrate** (if ACE-I + ARB intolerant or contraindicated) •Thiazide/thiazide-like for BP control or loop diuretics for volume control as additive therapy. DHP-CCB may also be used.	
Cerebrovascular disease After acute stroke	First-line	**ACE-I + Thiazide/Thiazide-like diuretic**	**1)** During acute stroke and not eligible for thrombolytic therapy do not treat HTN unless extreme BP increase. **2)** Combination of ACE-I + ARB is not recommended.
	Second-line	**Long-acting DHP-CCB** or combination of additional drugs	
Diabetes			
Diabetes with microalbuminuria[b], CKD, CVD or CVD risk factors	First-line	**ACE-I/ARB** (if ACE-I intolerant)	Loop diuretic could be considered in hypertensive CKD patients with extracellular fluid volume overload.
	Second-line	**DHP-CCB**	
Diabetes	First-line	**ACE-I** or **ARB or Thiazide/Thiazide-like diuretic or DHP-CCB**	
	Second-line	Combination of first-line drugs • In combination with ACE-I or ARB, a DHP-CCB is preferable to a thiazide/thiazide-like diuretic.	
Chronic Kidney Disease			
Chronic kidney disease without diabetes	First-line	**ACE-I/ARB** (if ACE-I intolerant) •Thiazide/thiazide-like diuretic as additive therapy. Loop diuretics for those with volume overload.	1) If using ACE-I or ARB, monitor renal function and potassium. 2) Combination of ACE-I + ARB is not recommended for patients without proteinuria[a]
	Second-line	Combination of additional drugs	
Renovascular disease	First-line	**Thiazide diuretic or ACE-I or ARB** (if ACE-I intolerant) or **Long-acting CCB**	Avoid ACE-I or ARB if bilateral renal artery stenosis or unilateral disease with solitary kidney.
	Second-line	Combination of first-line drugs	

Abbreviations: ACE-I = angiotensin-converting enzyme inhibitors; ACR = albumin to creatinine ratio; ARB = angiotensin II receptor blocker; BP = blood pressure; BNP =brain natriuretic peptide; CCB = calcium channel blocker; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; DHP = dihydropyridine; HF = heart failure; HTN = hypertension; MI = myocardial infarction; mm Hg = millimeter of mercury; NYHA = New York Heart Association functional classification system; NT-pro BNP = N-terminal prohormone of brain natriuretic peptide; SBP = systolicblood pressure. **Footnotes:** [a] Proteinuria is defined as urinary protein > 500 mg/24hr or ACR >30 mg/mmol in 2 of 3 specimens.[b] The term microalbuminuria is being phased out, which is now referred to as moderately increased albuminuria and as defined as ACR = 3 mg/mmol - 30 mg/mmol.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (CCBs) reduce BP by blocking the inward flow of calcium ions through the L channels of arterial smooth muscle cells. CCB's work by binding to the L-channels of vascular smooth muscle cells and disrupting influx of calcium into muscle cell preventing contraction of smooth muscle cells and cardiac myocytes. There is significant evidence demonstrating that CCB's improve all-cause mortality plus reduce risk of stroke in patients with hypertension. Randomised controlled trials have demonstrated that dihydropyridines are effective at reducing cardiovascular events, mortality, and strokes particularly in the elderly. CCB have powerful BP-reducing effects, particularly when combined with ACE inhibitors or ARBs.[12] The below table summarises the clinical conditions where CCBs are preferred choice as anti-hypertensive drugs.

Types of CCB'S[8,12]

Dihydropyridines, which act on peripheral blood vessels, such as Amlodipine and Nifedipine. These drugs been shown to have beneficial effects on cardiovascular and stroke outcomes in hypertension trials.

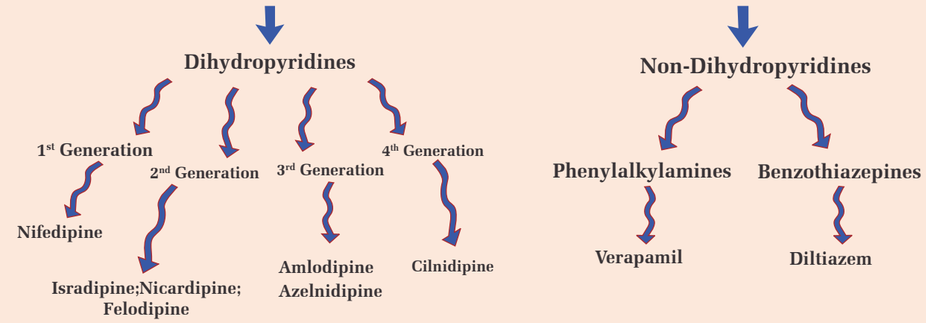
Non-dihydropyridines, which act on cardiac muscles and peripheral blood vessels such as Diltiazem (Benzothiazepines) and verapamil (phenylakylamines) Non-dihydropyridines are useful in the treatment of cardiac arrhythmias as these drugs dilate arteries somewhat less but also reduce heart rate and contractility.

Clinical Conditions where CCBs are Preferred Choice of Treatment[16]

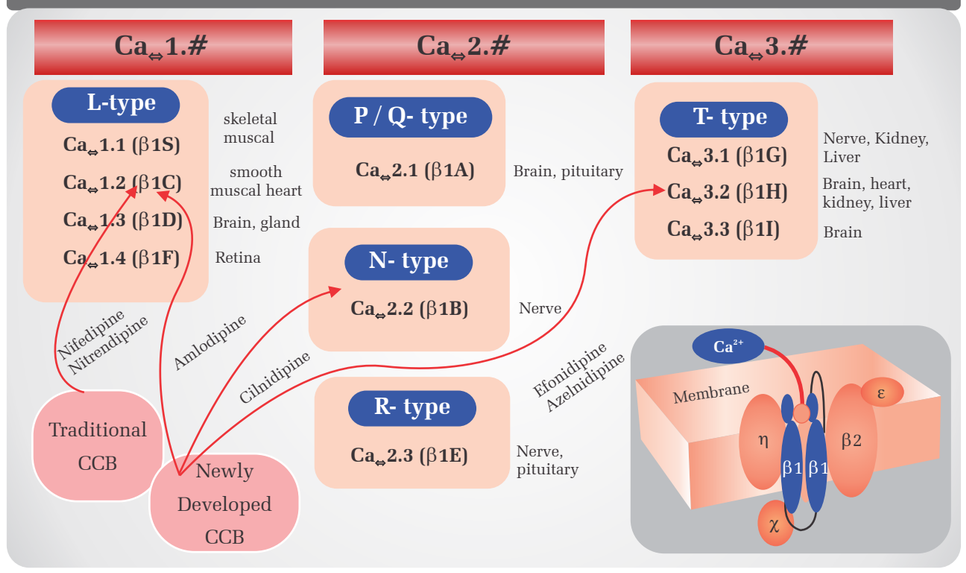
CCBs are preferable in patients with:

- Chronic obstructive pneumopathy
- Sick sinus syndrome
- Atrioventricular conduction disorders
- Sinus bradycardia
- Peripheral vascular disease (PVD)
- Prinzmetal's variant angina
- Variant angina caused from changes in the vascular tone
- Arterial hypertension
- Ischaemia detected during 24 hour ECG Holter monitoring

Classification of Calcium Channel Blockers [17]



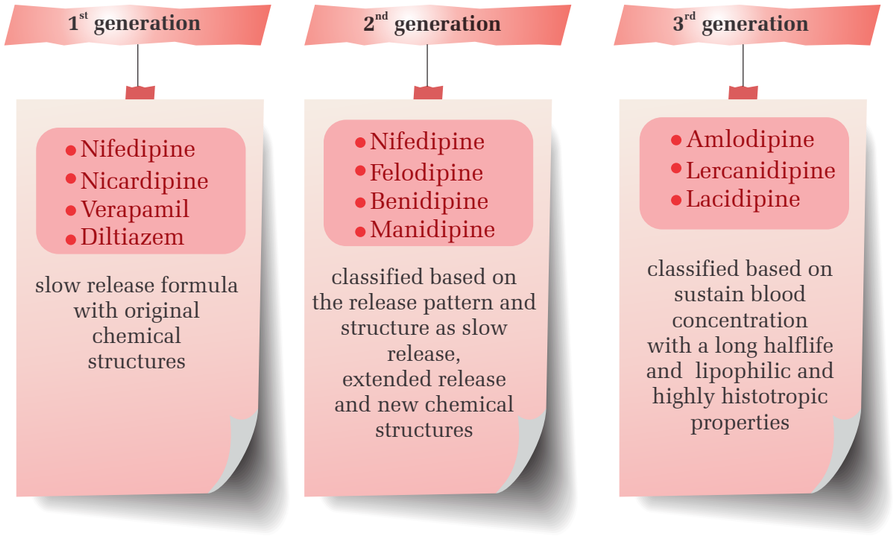
Mechanism of Action of Calcium Channel Blockers[18]



The major limitation in clinical use of calcium channel blockers is peripheral edema, which is most prominent at high doses; this finding can often be attenuated by combining these agents with ACE inhibitors or ARBs. Non-dihydropyridine calcium channel blockers are not recommended in patients with heart failure. Because the non-dihydropyridine drugs, Verapamil and Diltiazem, can slow heart rate, they are sometimes preferred in patients with fast heart rates and even for rate control in patients with atrial fibrillation who cannot tolerate b-blockers. Non-dihydropyridine drugs can also reduce proteinuria. Common side effects include headache, dizziness, flushing, and swelling in the legs and arms. Serious side effects include chest pain that has occurred when CCBs are initiated.[8,12]

Dihydropyridine

Dihydropyridines produce a more pronounced BP reduction in hypertensive than in normotensive patients and, to a certain degree; they exert a greater inhibition of Ca^{2+} influx into vascular smooth muscle cells than on cardiac muscle. Dihydropyridine are classified in three different generation based on their pharmacokinetic and efficacy profile.[19]



TYPES OF CALCIUM CHANNELS AND IMPACT OF ITS BLOCKING

Voltage-dependent calcium channels are widely distributed throughout the body and play a critical role in the maintenance of vascular tone. calcium channels are classified into several subtypes, including L-type, T-type, N-type, P/Q-type and R-type calcium channels based on their electrophysiological properties. Several calcium channel subtypes are reported to be present in the kidneys, including L-type, T-type, N-type and P/Q-type calcium channels. T-type calcium channels have been identified as an important molecular target in various organs, and they function as a part of physiological and/or pathophysiological activities.

The blockade of L-type calcium channels dilates the systemic vasculature and substantially reduces BP. In the renal microvasculature, however, the vasodilator response to L-type CCBs is observed only in pre-glomerular micro vessels (e.g., afferent arterioles), whereas efferent arterioles are refractory to the dilator action of these agents. The glomerular hemodynamic effects of L-type CCBs suggest that these CCB fails to correct glomerular hypertension. Thus, glomerular hypertension may develop following the administration of L-type CCBs.

The blockade of T-type calcium channels exerts a beneficial action on kidney function in CKD, including reduction in proteinuria and improvement in kidney survival. Thus, the role of calcium channels may differ depending on the subtype expression within the kidney, and the specific blockade of calcium channel subtypes would be anticipated to exert a salutary action on the renal microvasculature.

Traditionally, many antihypertensive/anti-anginal CCBs were thought to function through their blockade of L-type calcium channels. However, many novel CCBs are now known to block both L-type and T-type calcium channels with similar potencies. Traditional calcium channels blockers (CCBs), including Nifedipine and Amlodipine, act predominantly on L-type calcium channels, whereas novel CCBs such as Efonidipine, Benidipine and Azelnidipine inhibit both L-type and T-type calcium channels. Type of calcium channel blocking with different calcium channel blockers and its clinical significance is summarised below.[18,19]

"The blockade of T-type calcium channels exerts a beneficial action on kidney function in CKD, including reduction in proteinuria and improvement in kidney survival."

Characteristics of Calcium Channel Blockers and their Clinical Significance[18]

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

Clinical Significance of Blocking Calcium Channels (L-type, T-type & N-type)

Heart	Contractility ↓	Heart rate ↓	Heart rate ↓
Sympathetic nervous system	Pulse rate ↑	Pulse rate ↓	Pulse rate ↓
Kidney	Glomerular pressure ↑	Glomerular pressure ↓	Glomerular pressure ↓
Adrenal		Aldosterone secretion ↓	

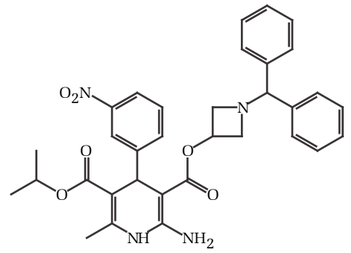
Conventional CCBs, including Nifedipine, Diltiazem and Amlodipine, elicit marked increases in the glomerular filtration rate and renal blood flow by dilating afferent arterioles preferentially, whereby glomerular hypertension and subsequent renal injury are expected to ensue unless systemic BP is sufficiently controlled. On the contrary, a growing body of evidence indicates that L/T-type CCBs such as Azelnidipine offer more beneficial action on proteinuria and renal survival rate than L-type CCBs in patients with CKD.[18,19]

"L/T-type CCBs such as Azelnidipine offer more beneficial action on proteinuria and renal survival rate than L-type CCBs in patients with CKD."

AZELNIDIPINE: A NOVEL THIRD GENERATION, LONG-ACTING DIHYDROPYRIDINE CALCIUM CHANNEL BLOCKER

Azelnidipine is a new dihydropyridine calcium channel antagonist with selectivity for both L-type and T-type calcium channels. It is a third generation, long-acting dihydropyridine calcium antagonist. Azelnidipine comprises of a racemic mixture containing a 1:1 ratio of the active R-enantiomer and the inactive S-enantiomer. Its chemical structure is as in figure and chemical name is ((±)-(3)-(1-diphenylmethylazetidin -3-yl)-5-isopropyl-2-amino-1, 4-dihydro-6-methyl -4-(3-nitrophenyl)-3,5-pyridinedicarboxylate. Different from all the existing dihydropyridine calcium antagonists having two methyl groups located at the 2- and 6-positions of the dihydropyridine ring, Azelnidipine has an amino group displacing the methyl group at the 2-position. In addition, Azelnidipine has two enantiomers (R-(-)- and S-(+)-enantiomers) due to an asymmetric carbon at the 4-position, and the (R)-(-) enantiomer of dihydropyridine calcium antagonists is considered to possess intrinsic pharmacological activity. It is used as once-daily oral administration in the treatment hypertension.[20,21]

Chemical Structure of Azelnidipine



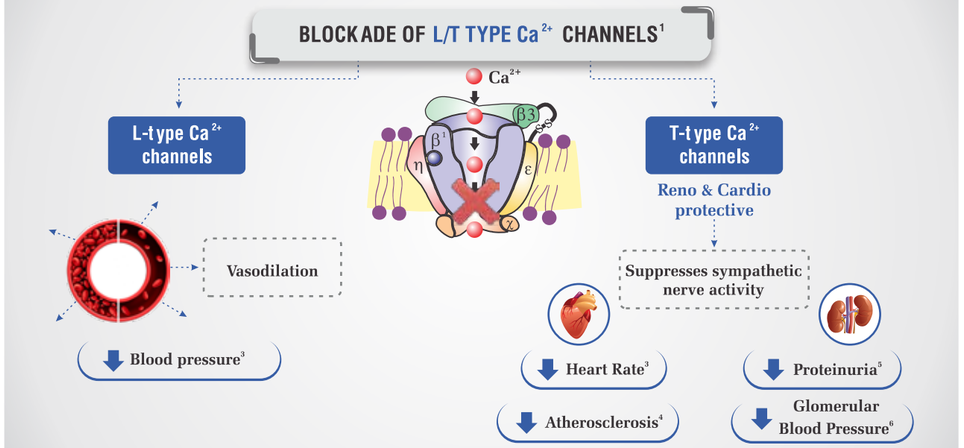
Key Features of Azelnidipine[20,21]

- Exhibits strong lipophilicity and affinity to membranes of vascular smooth muscle cell.
- Unlike other dihydropyridine CCBs, Azelnidipine does not induce reflex tachycardia, probably since it elicits a gradual fall in BP.
- Azelnidipine significantly suppressing sympathetic nerve activity that results in a reduced heart rate and proteinuria.
- Azelnidipine has cardio-protective, reno-protective, anti-atherosclerotic effects and improves insulin resistance.

Pharmacodynamic

The antihypertensive effect of Azelnidipine is primarily based on the inhibition of trans-membrane Ca^{2+} influx through the voltage-dependent channels of vascular smooth muscles. Azelnidipine reversly blocks both L-type and T-type calcium channels. The blockage of L-type calcium channel leads to dilation of blood vessels, results in lowering BP. The blockade of T-type calcium channels exerts a beneficial action on kidney function in CKD, including reduction in proteinuria and improvement in kidney survival. Further, it also reduces glomerular capillary pressure and atherosclerosis. Azelnidipine has been shown to have antioxidative effects in endothelial cells.[19-21]

Azelnidipine: Mechanism of Action[18]



"Unlike other CCBs, Azelnidipine shows gradual fall in BP and hences does not induce reflux tachycardia."

Pharmacokinetics

Oral administration of Azelnidipine shows rapid, dose-dependent absorption. The pharmacokinetics of Azelnidipine is shown below.[20,21]

Pharmacokinetics of Azelnidipine	
C_{max}	1.66-23.06 ng/mL
T_{max}	2.6–4.0 h
$AUC_{0-96\ h}$	17.9–429 ng/mL·h
C_{SS}	After 2 days
Protein binding	90-91%
Metabolism	CYP 3A4
Excretion	Urine (26%), Faeces (63%)

The Pleotropic Advantages of Azelnidipine

- Unlike other CCBs, does not induce reflux tachcyardia.[21]
- Combination of Olmesartan plus Azelnidipine is more effective than that of Olmesartan plus Amlodipine in reducing urinary albumin, confirming the diverse characteristics of the different calcium channel blockers. [22]
- Azelnidipine has been reported to elicit anti-atherosclerotic effects by anti- oxidative action.[21]
- Compared to Amlodipine, Azelnidipine improves overall glucose tolerance &insulin sensitivity in diabetic patients with hypertension. [23]
- Azelnidipine decreases urinary protein excretion, urinary 8-Oxo-2'-deoxyguanosine and urinary Liver-type fatty acid binding protein levels in patients with hypertensive CKD.[24]
- Azelnidipine was found to reduce the severity of heart failure and cardiac sympathetic nerve activity as compared to cilnidipine and has notable antioxidative effects in endothelial cells.[25]

CLINICAL EVIDENCES

Clinical Evidences for Anti-Hypertensive Effect of Azelnidipine

Azelnidipine Significantly Reduced Age-related Increase in Morning BP[26]

Aim:

The objective of the present study was to evaluate the effect of the new baroreceptor sensitivity (BRS)-restoring CCB Azelnidipine (AZ) on this age-related morning BP increase.

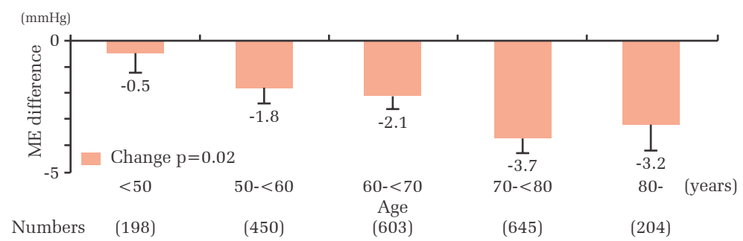
Methods:

A 16-week prospective study to clarify the effect of morning dosing of AZ on home BPs measured in the morning and in the evening in 2,546 hypertensive patients.

Results:

Azelnidipine treatment significantly reduced ME-Ave (average of the morning and evening SBPs) by –18.1 ± 15.6 mmHg, ME-Dif (morning systolic BP [SBP]–evening SBP) by –2.5 ± 13.2 mmHg, independently of each other (both $p < 0.001$). AZ treatment decreased age-related increase in ME-Dif particularly in patients who were regular consumers of alcohol and in beta-blocker users. The change in ME-Dif in different age group was as shown below.

Change of ME-Dif from Baseline after Treatment with Azelnidipine in Patients Stratified by Age



Conclusion:

- The new baroreceptor sensitivity-restoring CCB Azelnidipine significantly reduced age-related increase in morning BP.
- It has potential benefit on cardiovascular protection in hypertension, particularly in elderly patients and/or consumers of alcohol.

Comparing the Anti-hypertensive Efficacy of Azelnidipine with Amlodipine[27]

Aim:

To compare the anti-hypertensive efficacy of Azelnidipine andAmlodipine on 24-h BP.

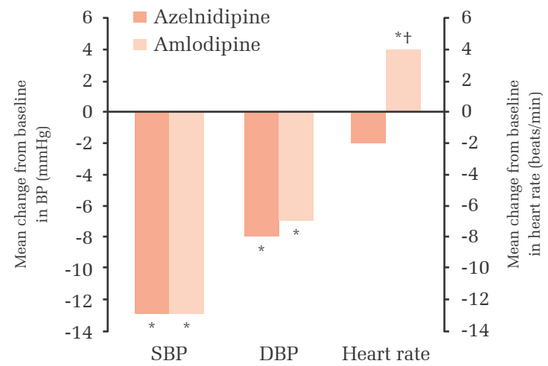
Methods:

It was a randomised double blind study conducted in 46 patients with essential hypertension. Azelnidipine 16 mg (23 patients) or Amlodipine 5 mg (23 patients) was administered once daily for 6 weeks. Blood pressure and pulse rate were measured by 24-h monitoring with a portable automatic monitor.

Results:

During 24-h monitoring, both drugs showed similar effects with a decrease in systolic BP of 13 mmHg and had a similar hypotensive profile during the daytime period. The pulse rate decreased by 2 beats/min in the Azelnidipine group, whereas it significantly increased by 4 beats/min in the Amlodipine group. Similar trends in the BP and pulse rate were observed during the night-time (22:00–6:30) and over 24-h.

The Effects of Azelnidipine and Amlodipine on 24-hourBP Control and on Heart Rate after 6 weeks of Treatment



Conclusion:

- Both drugs had a stable hypotensive effect lasting for at least 24 h after administration. Azelnidipine did not increase the pulse rate, but decreased it slightly, while Amlodipine increased it slightly.

Comparing Azelnidipine with Amlodipine in Reducing Home based Blood Pressure and Pulse Rate Monitoring[28]

Aim:

To compare the efficacy of Azelnidipine to that of Amlodipine in lowering morning BP and reducing pulse rate in outpatients with essential hypertension.

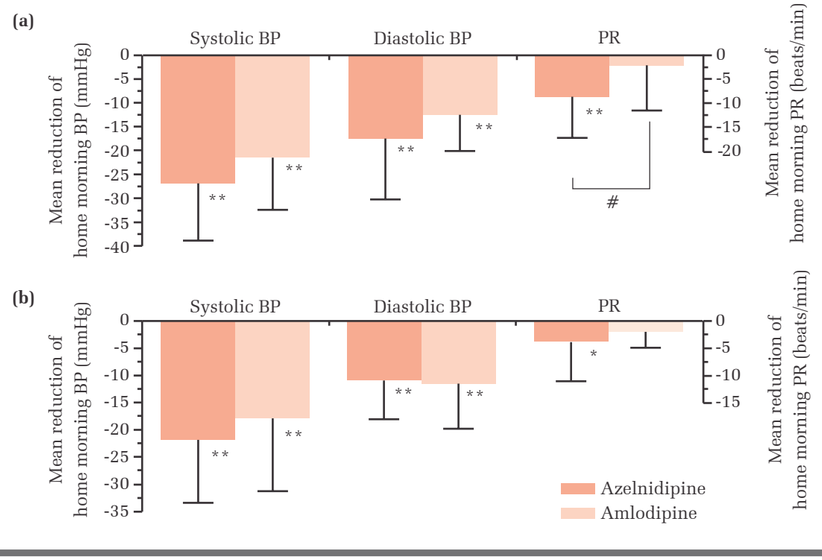
Methods:

Single-blind, randomised clinical study conducted in 108 outpatients with hypertension, evaluating morning BP and PR at home and office. Patients were assigned to receive once daily administration of Azelnidipine 8–16 mg/day (n=54) or Amlodipine 2.5–5 mg/day (n=54) for 8 weeks. Morning BP and PR were evaluated by assessing patients' self-monitored BP and PR in the home environment.

Results:

The mean reductions of morning SBP/DBP in the Azelnidipine and Amlodipine groups were similar (–24.1±11.8/–14.1±10.7 vs. –20.4±11.7/–12.2±7.7 mmHg) as shown below. However, whereas Azelnidipine decreased mean PR by –6.4±8.3 beats/min ($p<0.05$ vs. baseline), Amlodipine did not cause significant reduction of this parameter (–2.1±8.2 beats/min). Although neither drug changed PR in patients in whom baseline PR was <70 beats/min, Azelnidipine significantly lowered PR in patients whose baseline PR was >70 beats/min.

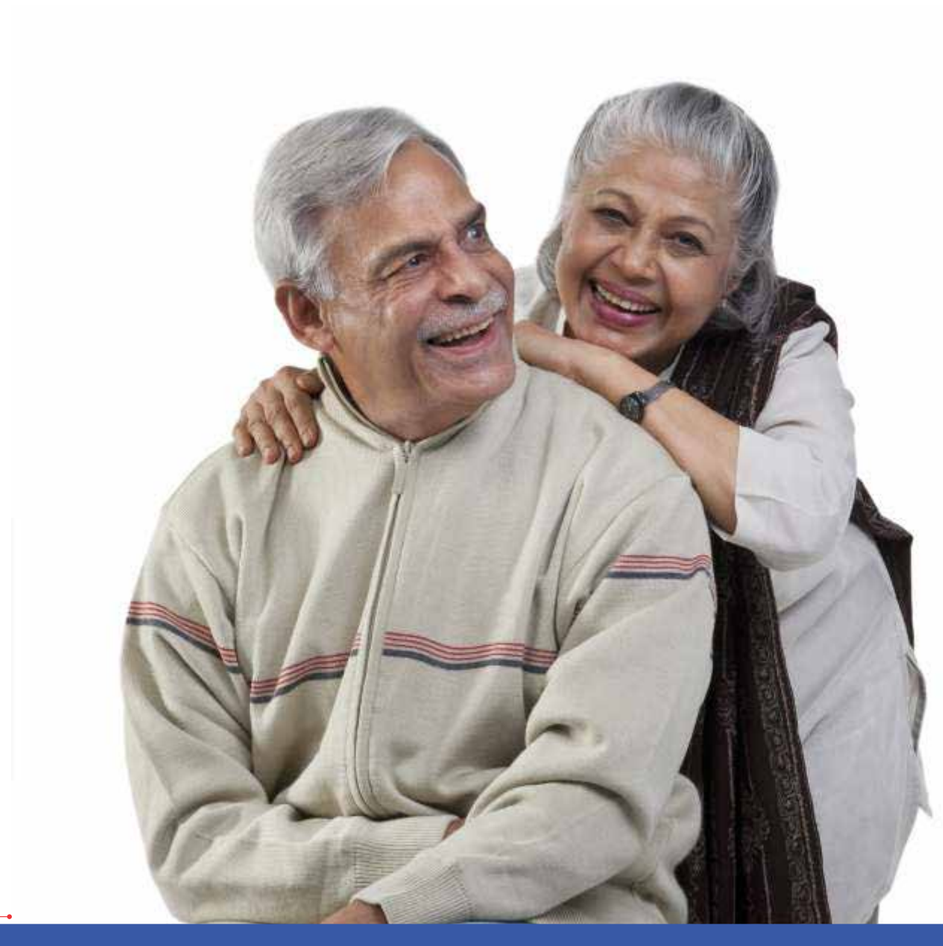
Mean Reductions of SBP, DBP and PR with the Treatment of Azelnidipine and Amlodipine



Conclusion:

- Once-daily Azelnidipine effectively controlled both morning BP and office BP while reducing PR in the home and office settings.
- Azelnidipine may be a useful antihypertensive agent for patients with morning hypertension.

> ***"Once-daily Azelnidipine effectively controlled both morning BP and office BP while reducing PR in the home and office settings."***



Combination of Olmesartan + Azelnidipine Versus Monotherapy on 24-Hour Ambulatory Blood Pressure and Pulse Rate : REZALT Study[29]

Aim:

The REZALT study was randomised, double-blind, parallel-group study comparing efficacy and tolerability of Olmesartan medoxomil (OLM) and Azelnidipine (AZL) combination therapy compared with monotherapy with each agent in Japanese patients with essential hypertension.

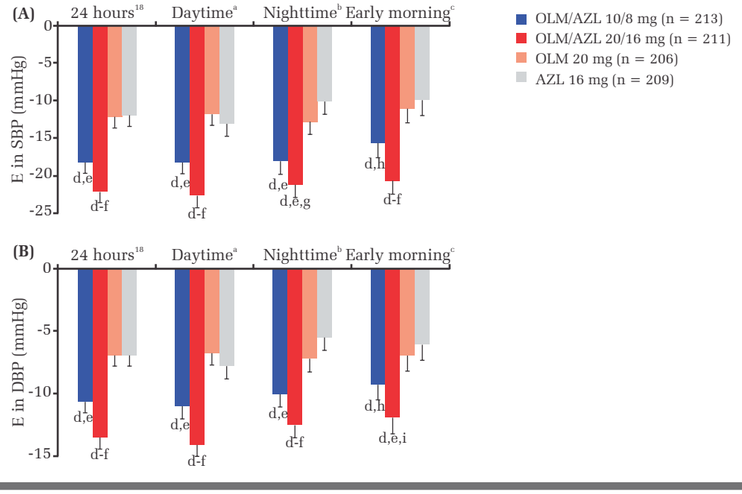
Methods:

Patients were randomly assigned to receive OLM/AZL 10/8 mg, OLM/AZL 20/16 mg, OLM 20 mg or AZL 16 mg, once daily for 12 weeks. The effectiveness of the treatments was assessed using 24-hour ambulatory BP monitoring (ABPM) and PR.

Results:

A total of 867 patients were enrolled and 862 randomised patients were included in the full analysis set. 213, 211, 206 and 209 patients in the OLM/AZL 10/8 mg, OLM/AZL 20/16 mg, OLM and AZL groups, respectively. Combination treatment with OLM/AZL was associated with significantly greater reductions in daytime, nighttime and early-morning BP as assessed using 24-hour ABPM, compared with either monotherapy, regardless of dipping pattern at baseline as shown below. The antihypertensive effects associated with OLM/AZL 10/8 mg or 20/16 mg were significantly greater than those with monotherapies regardless of dipping pattern at baseline.

Changes from Baseline in (A) SBP & (B) DBP at 12 Weeks of Treatment



"Adjusted mean (95% CI) changes from baseline in (A) systolic blood pressure (SBP) and (B) diastolic blood pressure (DBP) at 12 weeks of treatment with combination olmesartan medoxomil/ azelnidipine (OLM/AZL) versus monotherapy with either agent for essential hypertension in Japanese patients. The results were adjusted by covariates of baseline value, sex, and body weight. a7 am to < 0.001 versus AZL; eP < 0.001 versus OLM; f P < 0.001 versus OLM/AZL 10/8 mg; gP < 0.05 versus OLM/AZL 10/8 mg; hP < 0.01 versus OLM; i P < 0.01 versus OLM/AZL 10/8 mg (ANCOVA)."

Conclusion:

- In patients with essential hypertension, the reductions in daytime, nighttime and early-morning BP assessed using 24-hour ABPM were significantly greater with combination OLM/AZL than with either monotherapy, regardless of dipping pattern at baseline.

"Combination of Azelnidipine/Olmesartan is associated with greater reduction in daytime and early morning BP than either monotherapy."

Olmesartan + Azelnidipine Versus Olmesartan + Trichlormethiazide, on Home Blood Pressure and Pressure Variability[30]

Aim:

To compare the effects of Olmesartan combined with Azelnidipine versus Olmesartan combined with Trichlormethiazide, on home BP and pressure variability in type II diabetes mellitus patients using home BP telemonitoring system.

Methods:

An open-label cross-over pilot study was conducted to compare the effects of Olmesartan combined with Azelnidipine versus Olmesartan combined with trichlormethiazide, on home BP and pressure variability in 28 type II diabetes mellitus patients using home BP telemonitoring system. Patients received combination treatment with either Olmesartan 20 mg plus Azelnidipine 16 mg or Olmesartan 20 mg plus Trichlormethiazide 1 mg for more than 6 weeks each in a cross-over method.

Results:

The study reported that the coefficient of morning systolic BP variability in the Olmesartan plus Azelnidipine group was significantly lower than that in the Olmesartan plus Trichlormethiazide group (6.4+1.9 vs. 7.5+2.6, P=0.004).

Characteristic	Olmesartan plus Azelnidipine	Olmesartan plus Trichlormethiazide	Difference (95% CI)	p
Morning systolic blood pressure (mmHg)	140.9 ± 12.3	139.6 ± 11.4	1.3 (-2.2 to 4.8)	0.45
Morning diastolic blood pressure (mmHg)	79.1 ± 8.0	80.4 ± 8.8	-1.2 (-2.9 to 0.4)	0.15
CV of morning systolic blood pressure (mmHg)	6.4 ± 1.9	7.5 ± 2.6	-1.1 (-1.8 to -0.4)	0.004
CV of morning diastolic blood pressure (mmHg)	6.5 ± 2.2	7.2 ± 3.1	-0.7 (-1.7 to 0.4)	0.20
Morning heart rate (beats/min)	63.5 ± 7.4	67.0 ± 9.6	-3.6 (-5.4 to -1.7)	< 0.001
Evening systolic blood pressure (mmHg)	130.2 ± 9.8	130.2 ± 9.8	130.2 ± 9.8	0.04
Evening diastolic blood pressure (mmHg)	73.1 ± 7.3	73.3 ± 9.0	-0.1 (-2.4 to 2.1)	0.86
CV of evening systolic blood pressure (mmHg)	9.4 ± 8.6	9.8 ± 8.7	-0.4 (-1.6 to 0.7)	0.44
CV of evening diastolic BP (mmHg)	9.5 ± 8.8	10.0 ± 8.2	0.5 (-1.6 to 0.7)	0.38
Evening heart rate (beats/min)	66.7 ± 9.6	71.8 ± 10.2	-5.1 (-7.1 to -3.0)	< 0.001

Data are means ± SD or number. CV, coefficient of variation.

Conclusion:

Olmesartan with Azelnidipine combination is superior to the Olmesartan with Trichlormethiazide combination in reducing home BP variability.

"Olmesartan with Azelnidipine combination is superior to the Olmesartan with Trichlormethiazide combination in reducing home BP variability."

Clinical Evidences on Cardio-Protective Effect of Azelnidipine

Azelnidipine + OlmesaRTAn Versus Amlodipine + Olmesartan on Central BP and Left Ventricular Mass Index: The AORTA Study[31]

Objective:

The objective of the present study was to compare the effects of Olmesartan combined with either Azelnidipine or Amlodipine on central blood pressure (CBP) and left ventricular mass index (LVMI) in hypertensive patients.

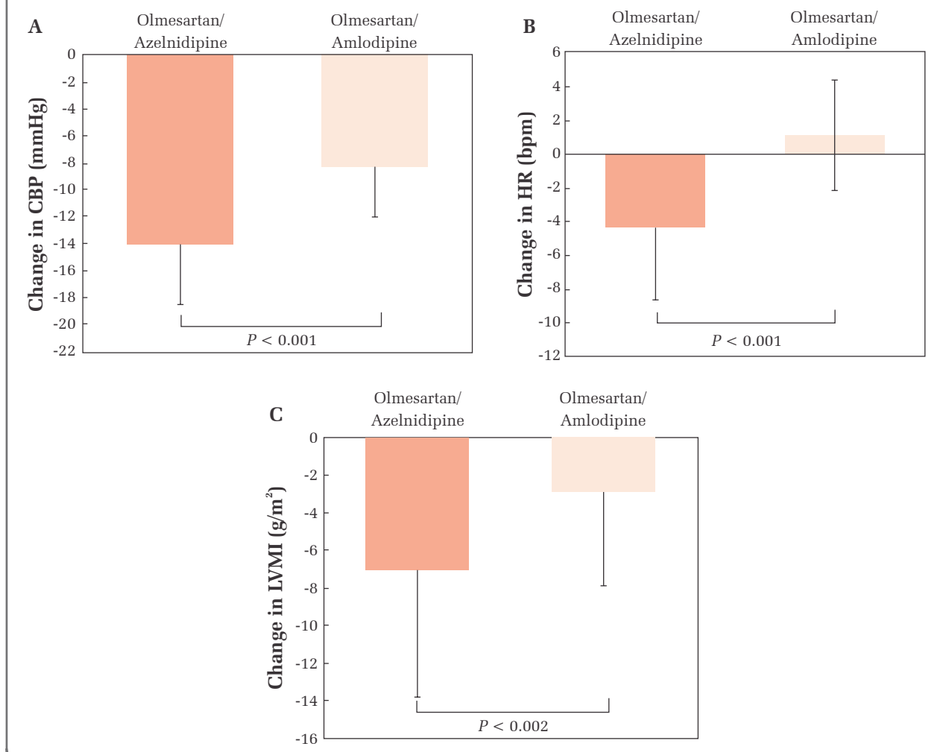
Methods:

The AORTA study was a 24-week, prospective, randomised, open-label parallel-group study comprising a 12-week run-in period followed by a 24-week randomised treatment period. Patients with brachial systolic BP > 140 mmHg and/or diastolic BP > 90 mmHg received Olmesartan monotherapy (20 mg daily) for 12 weeks. The patients were then randomly assigned to fixed-dose add-on therapy with Azelnidipine (16 mg daily) or Amlodipine (5 mg daily) (25 patients/group) for a further 24 weeks. CBP and LVMI were measured at baseline and at the end of the study.

Results:

CBP and LVMI decreased significantly in both groups (both, P<0.001). However, the decreases in CBP and LVMI were significantly greater with Olmesartan/Azelnidipine than with Olmesartan/Amlodipine (CBP, P , 0.001; LVMI, P = 0.002) as shown below. Notably, the magnitude of the decrease in LVMI was significantly greater in the Olmesartan/Azelnidipine group than in the Olmesartan/Amlodipine group (−6.6 ± 3.4 vs −3.0 ± 2.5 g/m2, respectively, P = 0.002).

Changes in Central Blood Pressure (CBP) (A), Heart Rate (HR, Beats Per Minute [bpm]) (B) and Left Ventricular Mass Index (LVMI) (C) From Baseline to Week 24.L



Conclusion:

- Olmesartan in combination with Azelnidipine elicited greater reductions in CBP and LVMI compared with Olmesartan in combination with Amlodipine.
- The superior effects of Olmesartan/Azelnidipine therapy on central hemodynamics may be associated with more favorable cardiovascular outcomes than with Olmesartan/ Amlodipine.
- Such differential effects may be important for cardiovascular risk reduction.

Impact of Losartan and Azelnidipine on Albuminuria and Renal Function in Type 2 Diabetic Patients with Chronic Kidney Disease[32]

Objective:

The present study was conducted to examine whether combined administration of losartan and Azelnidipine (Los/Azl treatment) provides superior reduction in proteinuria compared to Nifedipine or Amlodipine in hypertensive type 2 diabetes patients with CKD.

Methods:

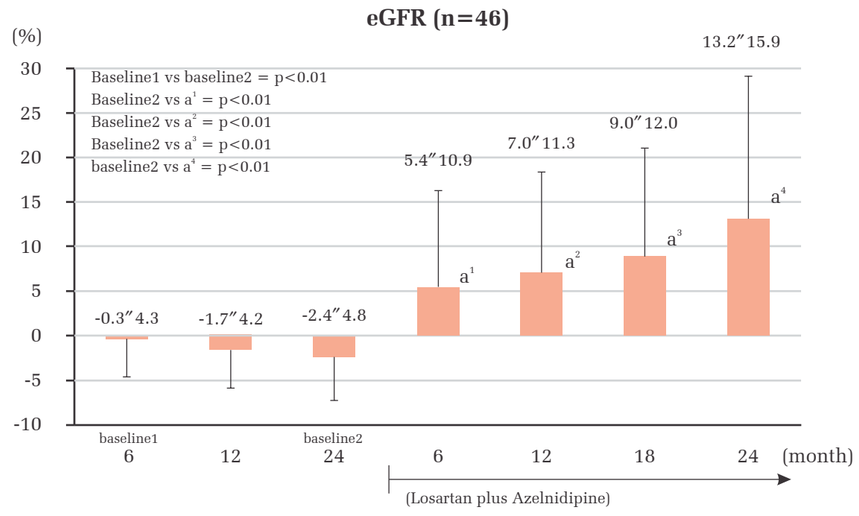
The study enrolled 46 patients with CKD and hypertension accompanied with type 2 diabetes, among whom there were wide ranges of BP values. Patients had prior exposure to CCBs such as Amlodipine (5~10mg) or Nifedipine (20~30mg/day) to control BP. All 46 patients received either 25 mg per day losartan, which was increased up to 50 mg per day and 8 mg per day Azelnidipine, which was increased up to 16mg per day, over 24 months.

Results:

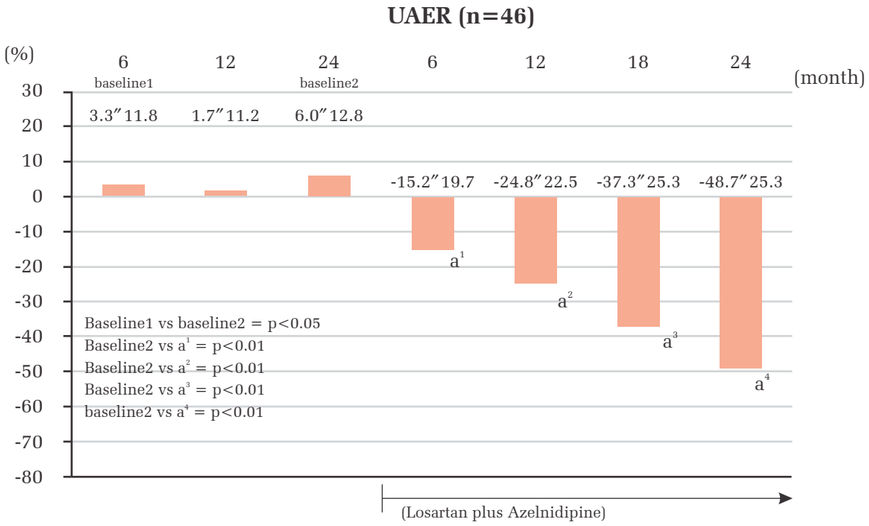
In evaluating the percent changes in eGFR of all 46 patients in Amlodipine and Nifedipine groups before Los/Azl treatment, it was -0.3±4.3% at 6 month and -2.4±4.8% at 24 month with a significant difference (P<0.01). However, after Los/Azl treatment, it was +5.4±10.9% at 6 month, +7.0±11.3% at 12 month, +9.0±12.0% at 18 month and +13.2.0±15.9% at 24 month respectively. After Los/Azl treatment, percent change in urinary albumin excretion rate (UAER) was -15.2±19.7%, -24.8±22.5%,-37.3±25.3% and -48.7±25.3% at 6, 12, 18 and 24 month respectively.

"Losartan and Azeldipine combination therapy is clinically useful in hypertensive type 2 diabetic patients with CKD."

Percentage Changes in eGFR and UAER After Treatment with Los/Azl



test:student's t-test value: mean″SD



test:student's t-test value: mean″SD

Conclusion:

- The present study demonstrated that Los/Azl treatment should be considered for hypertensive diabetic patients with CKD.

Azelnidipine is Renoprotective in Hypertensive Patients with Mild CKD[24]

Objective:

The aim of the present study was to determine whether Azelnidipine and/or Amlodipine affected urinary protein excretion or the urinary levels of 8-OHdG and L-FABP in hypertensive patients with mild CKD.

Methods:

Thirty moderately hypertensive CKD patients were randomly assigned to 2 treatment groups: Azelnidipine 16 mg once daily or Amlodipine 5 mg once daily. Treatment was continued for 6 months. Urinary protein excretion and urinary levels of 8-OHdG and urinary L-FABP were measured before 3 and 6 months after the treatment period.

Results:

Both drugs had similar effect in reducing SBP & DBP. Azelnidipine reduced heart rate significantly after 3 and 6 months whereas in Amlodipine there was increase in heart rate. Urinary protein excretion, urinary 8-OHdG and urinary L-FABP levels decreased significantly after 3 months ($p < 0.05$) and 6 months ($p < 0.05$) in the Azelnidipine group. In contrast, Amlodipine showed little effect on urinary protein excretion or the urinary levels of 8-OHdG and L-FABP throughout the experimental period.

Study Outcomes			
	Before	3 Months	6 Months
Urinary protein			
Azelnidipine	1.5 ± 0.4	0.9 ± 0.3*	0.8 ± 0.3*
Amlodipine	1.6 ± 0.3	1.7 ± 0.4	1.7 ± 0.5
Urinary 8-OHdG			
Azelnidipine	26.5 ± 8.0	20.5 ± 6.0*	14.0 ± 4.05
Amlodipine	1.6 ± 0.3	1.7 ± 0.4	1.7 ± 0.5
Urinary L-FABP			
Azelnidipine	110.5 ± 40.5	90.0 ± 30.5*	75.0 ± 25.5*
Amlodipine	115.0 ± 38.0	120.0 ± 30.0	122.5 ± 35.0
Serum creatinine			
Azelnidipine	1.0 ± 0.2	1.0 ± 0.1	1.0 ± 0.2
Amlodipine	1.1 ± 0.2	1.0 ± 0.1	1.0 ± 0.1
24h Ccr			
Azelnidipine	98 ± 8	100 ± 8	98 ± 10
Amlodipine	102 ± 10	101 ± 12	98 ± 10

Before versus after: *$p < 0.05$
Changes of Urinary Protein Excretion (g/day), Urinary 8-OHdG (ng/mg crea tinine), Urinary L-FABP (I-g/g crea tinine), Serum Creatinine (mg/dl) and 24h Ccr (ml/min)Before and 3 and 6 Months After Treatment

Conclusion:

- Azelnidipine is renoprotective in hypertensive patients with mild CKD and this action is, at least in part, due to the anti-oxidative effect. Azelnidipine has anti-oxidative properties and these may contribute to the beneficial effects of this drug.

"Azelnidipine is found to be renoprotective in patients with mild CKD."

Azelnidipine Decreased the Serum Urate Acid Levels in Patients with Essential Hypertension[33]

Objective:

To evaluate the effect of Azelnidipine on uric acid metabolism in 72 hypertensive patients.

Methods:

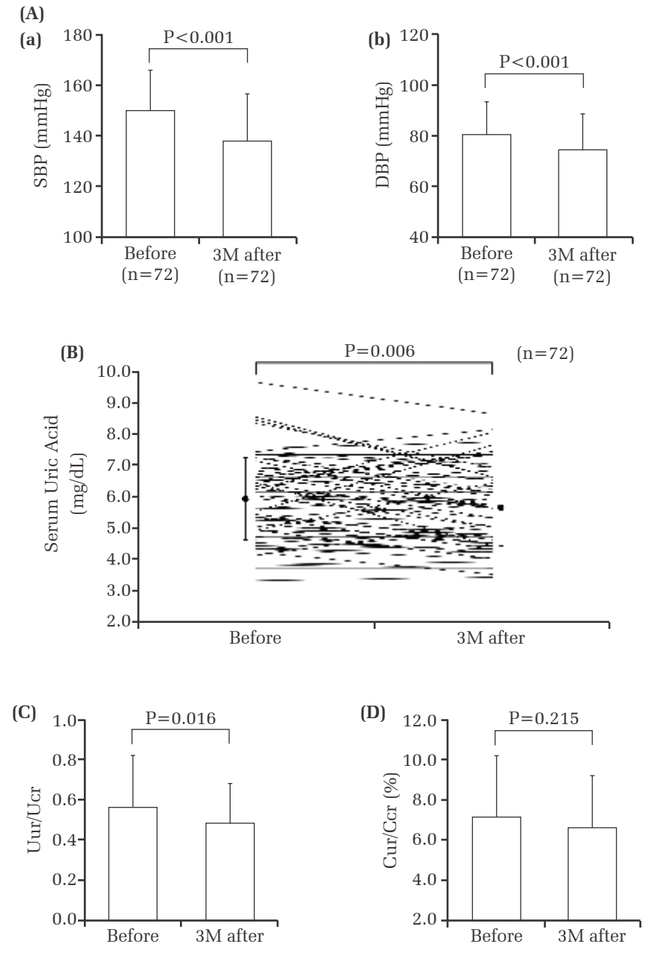
Azelnidipine was administered to 72 patients at a daily dose of 8 mg or 16 mg. In 22 cases out of the 72 patients, a different CCB was switched to Azelnidipine. Blood pressure was measured and biochemical parameters of blood and urine were evaluated before and 2-3 months after the administration.

Results:

The results of the study suggest that Azelnidipine significantly decreased both SBP, DBP and the heart rate. It decreased both serum urate levels and the urinary uric acid to creatinine ratio (Uur/Ucr). Azelnidipine decreased the serum urate levels and Uur/Ucr in hyperuricaemic patients with uric acid levels ≥ 7.0 mg/dL in males and ≥ 6.0 mg/dL in females. It did not change these parameters in normouricaemic patients with serum urate levels <7.0 mg/dL in males and <6.0 mg/dL in females.

"Azelnidipine decreased the serum urate acid levels and Uur/Ucr, and this response was most prominent in hyperuricaemic patients or patients with normal and over excretion of uric acid."

Effects of Azelnidipine on the Haemodynamics and Uric Acid Metabolism in Hypertensive Patients



(A) Changes in Blood Pressure; (B) Changes in Serum Uric Acid; (C) Changes in Uur/Ucr; (D) Changes in Cur/Ccr.

Conclusion:

The study concludes that Azelnidipine decreased the serum urate acid levels and Uur/Ucr, and this response was most prominent in hyperuricaemic patients or patients with normal and over excretion of uric acid.

Clinical Evidences on Impact of Azelnidipine on Insulin Sensitivity and Diabetes

Comparing Azelnidipine with Trichlormethiazide in Type 2 Diabetic Patients with Hypertension: COAT Trial[34]

Objective:

The present study was conducted to compared the efficacy and tolerability of Azelnidipine with that of Trichlormethiazide in type 2 diabetic patients with hypertension.

Methods:

It was an open-label, randomised controlled trial conducted in 240 diabetic hypertensive patients who were being treated with Olmesartan. Participants were randomised 1:1 to receive an Azelnidipine (Azelnidipine, 16 mg/day) or a Trichlormethiazide (Trichlormethiazide,1 mg/day) and were followed up for 48 weeks. Primary outcome evaluated was the difference in the change in HbA1c levels from the baseline values at 48 weeks between these two groups.

Results:

At the end of 48 week treatment changes in SBP and DBP between the Azelnidipine group vs Trichlormethiazide group were -10.7 ± 9.6 vs -7.1 ± 7.7 mmHg (P = 0.003) and-6.6 ± 6.6 vs -3.3 ± 6.1 mmHg (P < 0.001), respectively. Changes in the HbA1c levels from the baseline values were -0.19% ± 0.52% for Azelnidipine group as compared to -0.19% ± 0.54%, for Trichlormethiazide group with no significant difference between the two groups. There was no significant deference in the two groups regarding the deterioration of fasting insulin and homeostatic model assessment-insulin resistance (HOMA-IR).

Conclusion:

- Azelnidipine was more effective for controlling BP than Trichlormethiazide.
- Both the drugs similarly exacerbated glycaemic control in type 2 diabetic patients with hypertension.

"Azelnidipine is more effective than Trichlormethiazide in controlling BP."

The Comparison of Effects of Combination of Olmesartan and Azelnidipine or Candesartan and Amlodipine in Type 2 Diabetic Hypertensive Patients: The Olca Study[35]

Objective:

The aim of the present study was to compare the effects of two combinations of an ARB and a CCB on early-morning BP, heart rate, renal function and glucose/lipid metabolism in hypertensive patients with type 2 diabetes mellitus.

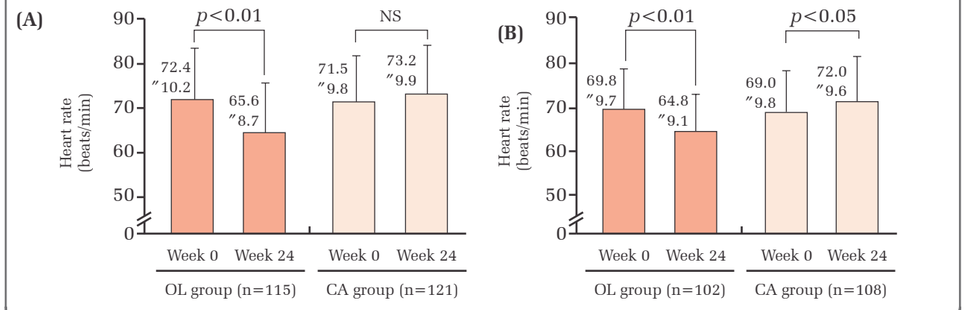
Methods:

It was an open-label randomised study which enrolled untreated hypertensive patients complicated with type 2 diabetes mellitus who were randomised to receive either Olmesartan 20 mg/day or Candesartan 8 mg/day for 12 weeks. Patients with BP exceeding 130/80 mmHg received add-on 16 mg/day Azelnidipine to ongoing Olmesartan (OL group) or 5 mg/day Amlodipine to ongoing candesartan (CA group) for 24 weeks.

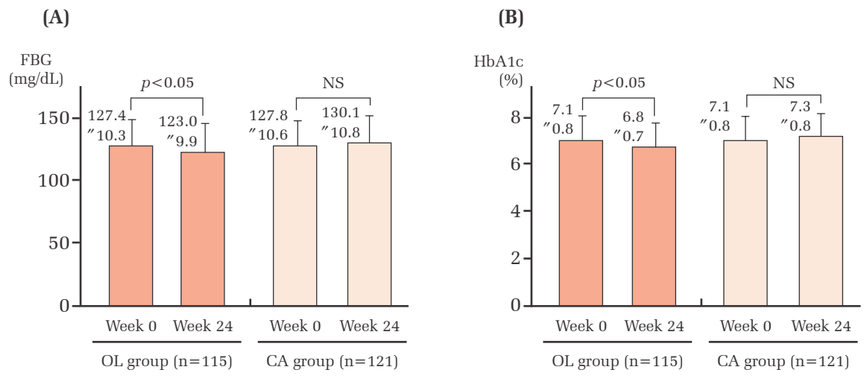
Results:

The results indicate that both OL and CA had significant antihypertensive effects, but that the lowering of home-measured early morning BP was significantly greater in the OL group than in the CA group ($p < 0.05$). The mean change in clinic-measured BP (systolic/diastolic) following 24 weeks of ARB and CCB combination therapy was –15.3 ± 4.8/–7.1 ± 3.2 mm Hg (both $p < 0.01$) in the OL group and –14.5 ± 4.6/–6.7 ± 3.1 mmHg (both $p < 0.01$) in the CA group. The in-clinic and home based heart rate decreased significantly in the OL group, with changes of –6.8 ± 2.7 beats/minute ($p < 0.01$) and –5.0 ± 2.1 beats/minute ($p < 0.01$), respectively whereas these parameters increased significantly in the CA group. Fasting blood glucose, haemoglobin A1c (HbA1c) and urinary albumin levels decreased significantly in the OL group but not in the CA group as depicted below. the urinary albumin level decreasedsignificantly in the OL group from 175.5±118.7mg/gCr to130.0±107.4mg/gCr ($p<0.001$) and a significant decrease in the number of urinary albumin-positive patients was observed

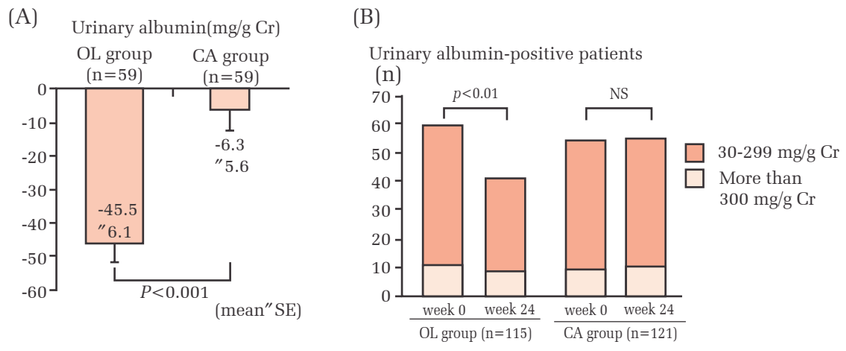
Changes in Heart Rate Measured (A) In the Clinic and (B) At Home in the Early Morning



Changes in (A) Fasting Blood Glucose (FBG) and (B) Haemoglobin A1c (HbA1c) (NGSP) Levels.



Changes in (A) Urinary Albumin Levels and (B) the Number of Urinary Albumin-positive Patients.



Olmesartan and Azelnidipine combination demonstrated more persistent early morning antihypertensive effect and showed greater decreases in heart rate, fasting blood glucose and HbA1c levels, and microalbuminuria compared to Candesartan and Amlodipine combination.

Evaluating Impact of Azelnidipine on Glucose Tolerance and Insulin Resistance in Hypertensive Patients: AGENT Trial.[23]

Objective:

The present study evaluated if Azelnidipine could improve glucose tolerance and insulin levels in non-diabetic patients with essential hypertension.

Methods:

It was a prospective randomised crossover study conducted in 17 non-diabetic patients with essential hypertension who had controlled BP levels using Amlodipine (5 mg/day). Participants were randomized 1:1 to receive either Azelnidipine (16 mg/day) or Amlodipine (5 mg/day) in a crossover design for 12-weeks. Levels of blood glucose and insulin after the 75 g oral glucose tolerance (OGTT), lipids, inflammatory markers, circulating number of progenitor cells, and endothelial functions were evaluated at the end of the study.

Results:

No significant differences were observed in SBP and DBP change between the two drugs. Heart rate after Azelnidipine administration was significantly lower than that after Amlodipine administration (60.5 ± 6.6 vs. 65.1 ± 7.6/min, P = 0.003). Compared with Amlodipine administration, Azelnidipine significantly decreased levels of glucose and insulin 120 min after the 75 g OGTT (both P < 0.05). After Azelnidipine administration, hs-CRP levels tended to be lower (0.36 ± 0.23 vs. 0.74 ± 0.76 mg/L, P = 0.067) and IL-6 levels were significantly lower (1.44 ± 0.73 vs. 1.81 ± 0.78 pg/L, P = 0.035) than those after Amlodipine administration.

Comparison of 75 g Oral Glucose Tolerance Test Between Treatment with Azelenidipine and Amlodipine

	Baseline	Azelenidipine N=17	Amlodipine N=17	P**
Glucose 0, mg/dL	96± 8	94 ± 7	94± 8	0.826
Glucose 30, mg/dL	174± 28	162 ± 34	172± 25	0.160
Glucose 60, mg/dL	172± 37	181 ± 48	171± 41	0.221
Glucose 120, mg/dL	137± 30	130 ± 36	149± 30	0.039
IRI 0, mIU/mL	6.9± 4.2	7.0 ± 3.0	7.0± 3.5	0.957
IRI 30, mIU/mL	39.7± 16.9	39.8 ± 21.1	42.4± 20.8	0.660
IRI 60, mIU/mL	55.9± 29.8	56.1± 26.4	51.8± 27.3	0.465
IRI 120, mIU/mL	44.0± 26.8	47.7 ± 36.4	57.2± 37.9	0.026

Data arer mean + SD. IRI; immunoreactive insulin. ** Azelnidipine vs. Amoldipine

Comparison of Blood Pressure and Heart Rate Between Treatment with Azelnidipine and Amlodipine

	Baseline	Azelnidipine N=17	Amlodipine N=17	*P***
SBP (mmHg)	199.9 ± 11.5	120.2± 11.7	121.3 ± 8.6	0.492
DBP (mmHg)	71.6 ± 10.6	66.8 ± 7.2	70.1 ± 8.4	0.145
Heart rate	64.9 ± 5.9	60.5 ± 6.6*	65.1 ± 7.6	0.003

Data are mean ± SD. SBP; systolic blood pressure, DPB; diastolic blood pressure. * P < 0.005 vs. baseline. ** azelnidipine vs. amlodipine.

Comparison of Laboratory Data and PAT Ratio Between Treatment with Azelnidipine and Amlodipine

	Baseline	Azelnidipine N=17	Amlodipine N=17	*P***
TC, mg/dL	191 ± 17	194 ± 22	191 ± 23	0.617
LDL-C, mg/L	109 ± 19	111 ± 24	110 ± 19	0.730
HDL-C, mg/dL	57 ± 17	58 ± 18	57 ± 17	0.437
Triglyceride, mg/dL	104 ± 60	110 ± 57	114 ± 65	0.750
HbA1c, %	5.1 ± 0.3	5.1 ± 0.2	5.1 ± 0.3	0.999
hs-CRP, mg/L	1.14 ± 2.66	0.36 ± 0.23	0.74 ± 0.76	0.067
Interleukin-6, pg/mL	1.31 ± 0.61	1.44 ± 0.73	1.81 ± 0.77	0.035
eGFR, ml/min/1.73 m^2	83.2 ± 18.3	82.3 ± 16.1	79.4 ± 15.8	0.188
L-FABP/U-Cr, ng/g Cr	29.4 ± 40.0	13.9 ± 16.2	17.9 ± 16.9	0.187
Micro-alb/U-Cr,mg/g Cr	23.6 ± 47.4	26.6 ± 59.9	38.0 ± 87.4	0.120
HPC,/mL	2.79 ± 1.67	3.56 ± 1.59*	2.65 ± 1.17	0.016
PAT ratio	1.93 ± 0.34	2.05 ± 0.39	2.11 ± 0.47	0.587

data are mean ″ Sd. TC; total cholesterol. LDL-C; low-density lipoprotein cholesterol' HDL-C; high-density lipoprotein cholesterol, Hb; hemoglobin, hs-CRP; high sensitivity C-reactive protein, BNP; brain natriuretic peptide, eGFR; estmated glomerular filtration ratio, GFR (ml/min/1.73 m^2) L-FABP, L-type fatty acid binding protein, alb; albuminuria, U-Cre; urine creatinine, HPC; hematopoietic cell, PAT: peripheral arterial tonometry. *$P < 0.05$ vs. baseline. **Azelnidipine vs.Amlodipine

"Azelnidipine treatment have beneficial effects against glucose intolerance, insulin sensitivity, the inflammatory state, and circulating numbers of progenitor cells in non-diabetic patients with essential hypertension."

AZELNIDIPINE Uniaz

Composition:

Each Tablet contains

Azelnidipine .....16 mg

Indication:

In the management of hypertension

Dosage and Administration:

The recommended starting dosage of Azelnidipine is 8mg once daily administered orally after food, with titration to 16mg once daily as tolerated by the patient.

Major Side Effects

Azelnidipine was generally well tolerated in clinical trials. Some of the common side effects were headache, hot facial flushes and light-headedness.

Warning and Precaution:

When administering the drug to the elderly and to patients with renal dysfunction.

Contraindication:

Contraindicated in pregnant women; concomitant administration with azole antifungal agents (e.g. Itraconazole) or with HIV protease inhibitors (Ritonavir).

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Uniaz
Azelnidipine 16mg Tablets
Control with Cardio-renal protection

Highlights

- Azelnidipine is a novel third generation, long-acting dihydropyridine calcium channel blocker.
- Azelnidipine has selectivity for L-type and T-type calcium channels.
- Approved and available into the market in Japan since 2003.
- Once-daily oral administration in the treatment hypertension.
- Several clinical trials have proven efficacy of Azelnidipine in lowering high BP.
- Azelnidipine effectively reduced BP, showed efficacy similar to that of Amlodipine or Nitrendipine.
- It is safe and well tolerated antihypertensive drugs.
- Azelnidipine exhibits strong lipophilicity and affinity to membranes of vascular smooth muscle cell.
- Unlike other dihydropyridine CCBs, Azelnidipine does not induce reflex tachycardia. It could lower tachycardia in patients.
- Azelnidipine suppresses sympathetic nerve activity that resulted in a reduced heart rate and proteinuria in hypertensive patients.
- Azelnidipine is also effective on T-type calcium channels in kidneys which offer more beneficial action on proteinuria and renal survival rate than only L-type CCBs in patients with CKD.
- Azenidipine offers the major clinical advantage of end organ protection with cardio-protective, reno-protective and anti-atherosclerotic effects and improves insulin resistance.
- Azelnidipine has been shown to have antioxidative effects in endothelial cells.

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