Azelnidipine An New Approach In Hypertension

The Unique CCB: Azelnidipine

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Roadmap

Hypertension

- Introduction
- Epidemiology
- Pathogenesis
- Pharmacological Management Options
- Unmet Need of CCBs

Azelnidipine

- Introduction
- Mechanism of Action
- Pharmacokinetics
- Indication & Dose
- Common Adverse Events
- Precaution
- Contraindications
- Clinical Evidences
- Guidelines

Summing up

Hypertension

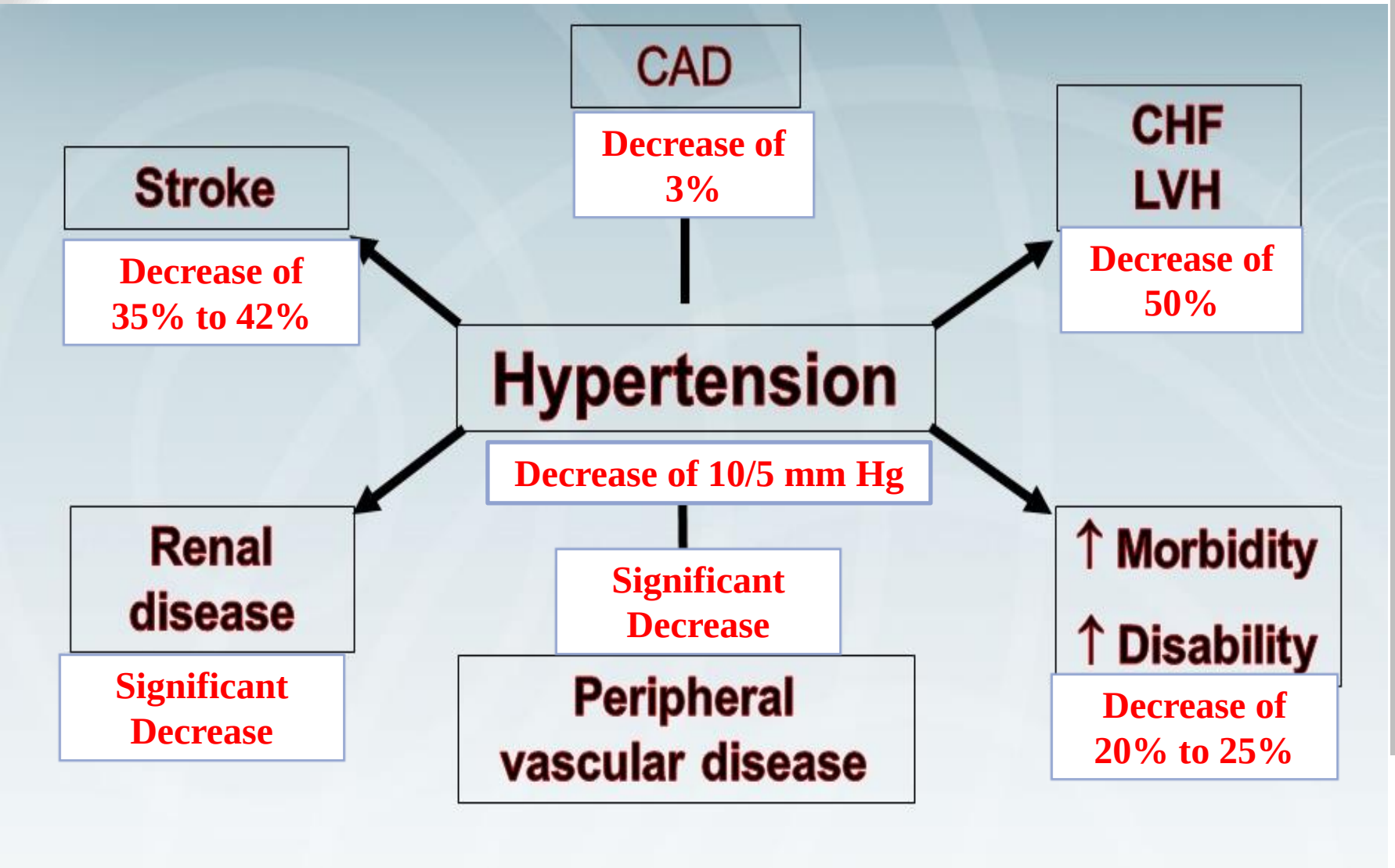
- **Hypertension**[1] (HTN) is defined as office SBP values ≥140 mmHg and/or diastolic BP (DBP) values ≥ 90 mmHg

- Epidemiological associations between BP and CV risk extend from
- very low levels of BP [i.e. systolic BP (SBP) >115 mmHg].

- **Hypertension** is a **Lifestyle Disorder…**
  - It is a **major risk factor for stroke, myocardial infarction, vascular disease, and chronic kidney disease**[2]**.**

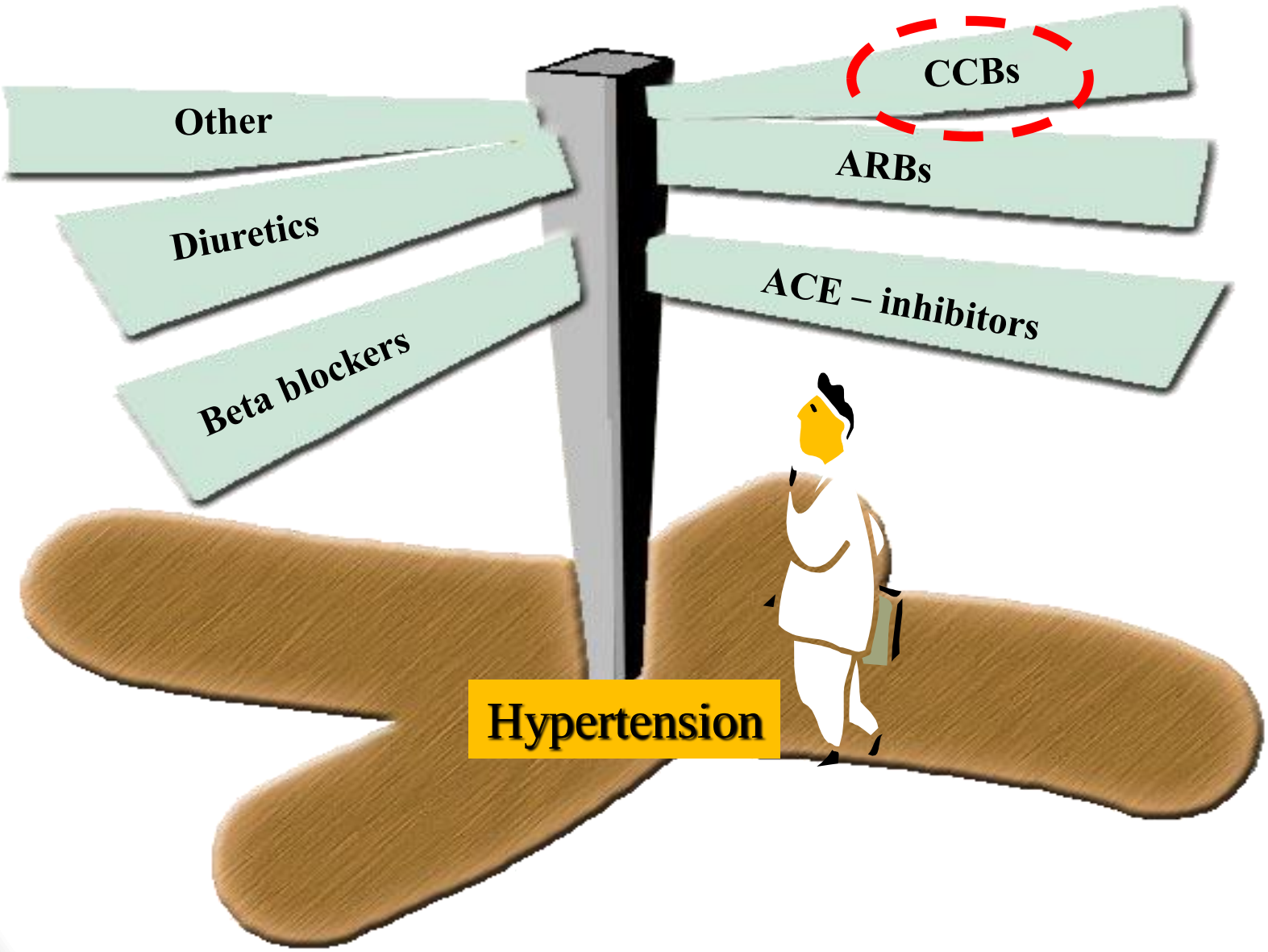
1. European Heart Journal (2018) 39, 3021–3104
2. Circulation. 2018;137:549–550. DOI: 10.1161/CIRCULATIONAHA.117.032877

Why to treat hypertension?



Arch Intern Med. 1993;153(2):186-208
http://www.medbroadcast.com/channel/high-blood-pressure/understanding-high-blood-pressure/why-treat-high-blood-pressure

Pharmacological management: Antihypertensive drug classes

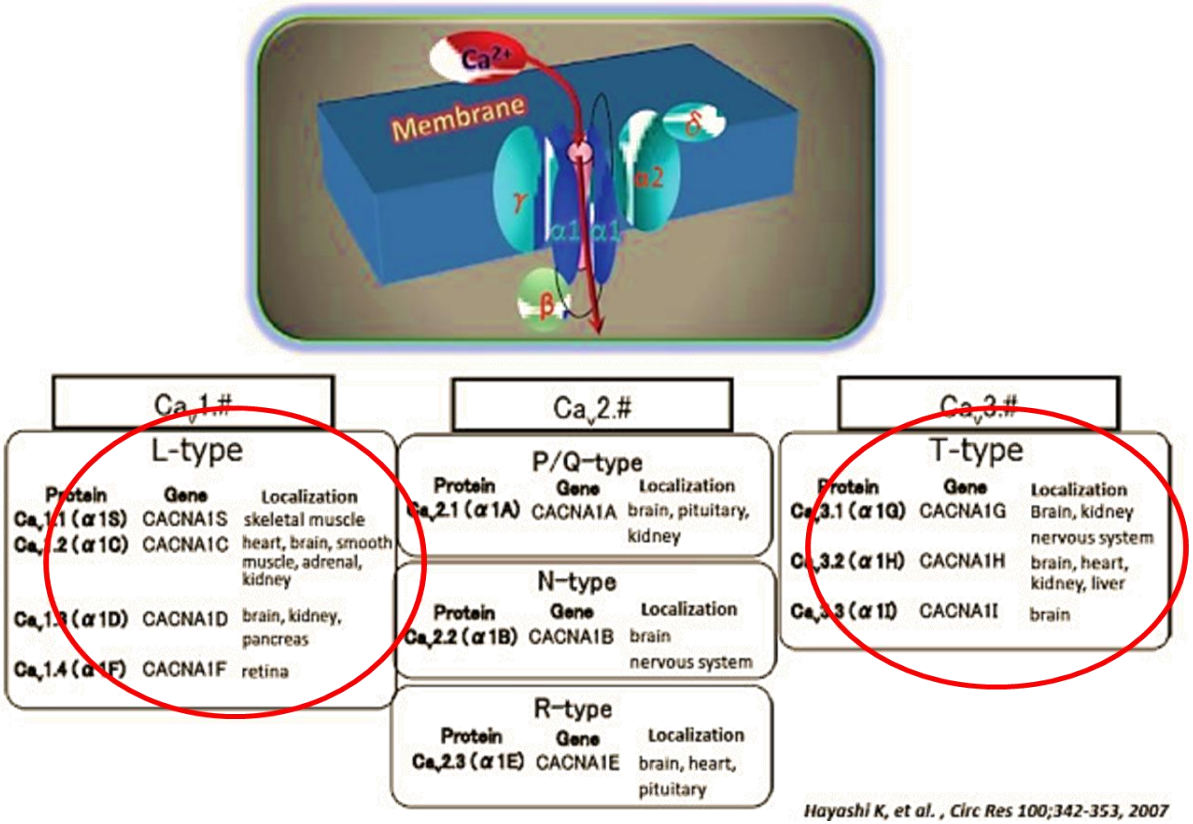


ARB: Angiotensin Receptor Blocker
ACE-Inhibitor: Angiotensin converting enzyme inhibitor
CCBs: Calcium channel blocker

Physiology of calcium channels

- Opening of the voltage-dependent Ca^{2+} channels permits influx of Ca^{2+} across the plasma membrane

- **Increased intracellular calcium is responsible for the increase in vascular tone, peripheral vascular resistances (PVR) and blood pressure (BP)**



Hayashi K, et al. , Circ Res 100;342-353, 2007

Ten unique α1 subunits, grouped in 3 families (CaV1, CaV2, and CaV3), that encode the low-voltage–activated T-type and the high-voltage–activated L-, N-, P/Q- and R-type Ca^{2+} channels, have been identified.

Tamargo J, et al. Expert Opin Investig Drugs. 2016;25(11):1295–309.

Classification of CCB

Dihydropyridine

- Have greater selectivity for vascular smooth muscle than for myocardium
- Have less negative inotropic activity

Non-dihydropyridine

- Have greater selective for myocardium than for vascular smooth muscle

Curr Hypertens Rev. 2006 May 1; 2(2): 103–111

Apart from L,T,N type CCBs

Current	α_1 subunit	Channel	Distribution	Inhibitors
P	α_{1A}	$Ca_v2.1$	neurons	ω-agatoxin IVA
Q	α_{1A}	$Ca_v2.1$	neurons	ω-agatoxin IVA
N	α_{1B}	$Ca_v2.2$	neurons	ω-conotoxin GIVA
R	α_{1E}	$Ca_v2.3$	neurons	SNX-482
L	α_{1S}	$Ca_v1.1$	skeletal muscle	DHP/PAA/BZP
	α_{1C}	$Ca_v1.2$	heart, endocrine, neurons	DHP/PAA/BZP
	α_{1D}	$Ca_v1.3$	endocrine, neurons	DHP/PAA/BZP
	α_{1F}	$Ca_v1.4$	retina	N/A
T	α_{1G}	$Ca_v3.1$	neurons, heart	N/A
	α_{1H}	$Ca_v3.2$	neurons, heart	N/A
	α_{1I}	$Ca_v3.3$	neurons	N/A

Classification of Dihydropyridine & Non-dihydropyridine type CCBs

CCB	Nifedipine	Verapamil
Type	Benzothiazepine (Dihydropyridine)	Diphenylalkylamine (Non-dihydropyridine)
Generation	1st	1st
Act on	L-type	L-type
Tmax	SR: 4 h	IR: 1.5 h SR: 5 h
$T_{1/2}$	IR: 3-5 h SR: 9 h	IR: 3-7 h SR: 8-12 h
Common ADR	Hypotension, edema, constipation, dyspepsia, flu-like symptoms	
Serious ADR	AV block, significant bradycardia, drug interactions (it is an enzyme inhibitor), Myocardial Infarction, pulmonary edema and hepatoxicity (Diltiazem exhibits similar action to Verapamil with a lower incidence of drug interactions, hence commonly used)	

CCB: Calcium Channel blocker; ADR: Adverse drug reaction; IR: Immediate release; SR: Sustained release; h: Hour;

IJPSR, 2019; Vol. 10(11): 4830-4843.

Classification of Dihydropyridine type CCBs

CCB	Nifedipine	Nicardipine	Lercanidipine
Generation	1st	1st	3rd
Act on	L-type	L-type (exact MoA is unknown)	L
Tmax	IR: 30 min SR: 6 h	-	3 h
$T_{1/2}$	IR: 2 h SR: 6-8 h	10 h	8 h
Common ADR	Hypotension, peripheral edema, flushing, headache, dizziness, nausea, dyspnea	ADRs similar to Nifedipine but with less reflux tachycardia	Flushing, headache, vertigo, asthenia, dizziness, Edema (significantly reduced in comparison to other CCBs)
Serious ADR	Reflex tachycardia, myocardial infarction, ventricular dysrhythmia, ulcers, hepatotoxicity		Headache, palpitations, hypokalemia, rhinitis, vertigo, and tachycardia

CCB: Calcium Channel blocker; ADR: Adverse drug reaction; IR: Immediate release; SR: Sustained release; h: Hour; MoA: Mechanism of action

IJPSR, 2019; Vol. 10(11): 4830-4843.

Calcium channel blockers

CCB	Benidipine	Azelnidipine	Amlodipine	Cilnidipine
Generation	2nd	3rd	3rd	4th
Act on	L/N/T-type	L/T-type	L-type	L/N-type
Tmax	2 hr	2.3-2.7 hr	6-10 hr	2-3 hr
$T_{1/2}$	3 h	16 to 28 hr	30-50 hrs	20 hr
Common ADR	Palpitations, headache, itching, rash, photosensitivity, gynecomastia	Mild headache, hot flushes, nausea, light-headedness	Peripheral edema, flushing, headache, dizziness, nausea, dyspnea, abdominal pain, dyspepsia, constipation	Fever, rashes, GERD, increased urination, flushing, myalgia, impotence, ischemic chest pain
Serious ADR	Yellowing of the skin, liver dysfunction	Increase is AST/ALT levels, bilirubin levels, jaundice, and liver failure	Reflux tachycardia (on a long term), Ventricular dysrhythmia, nervousness, conjunctivitis, gingival hyperplasia	Heart failure, liver dysfunction, hypotension, cerebral ischemia

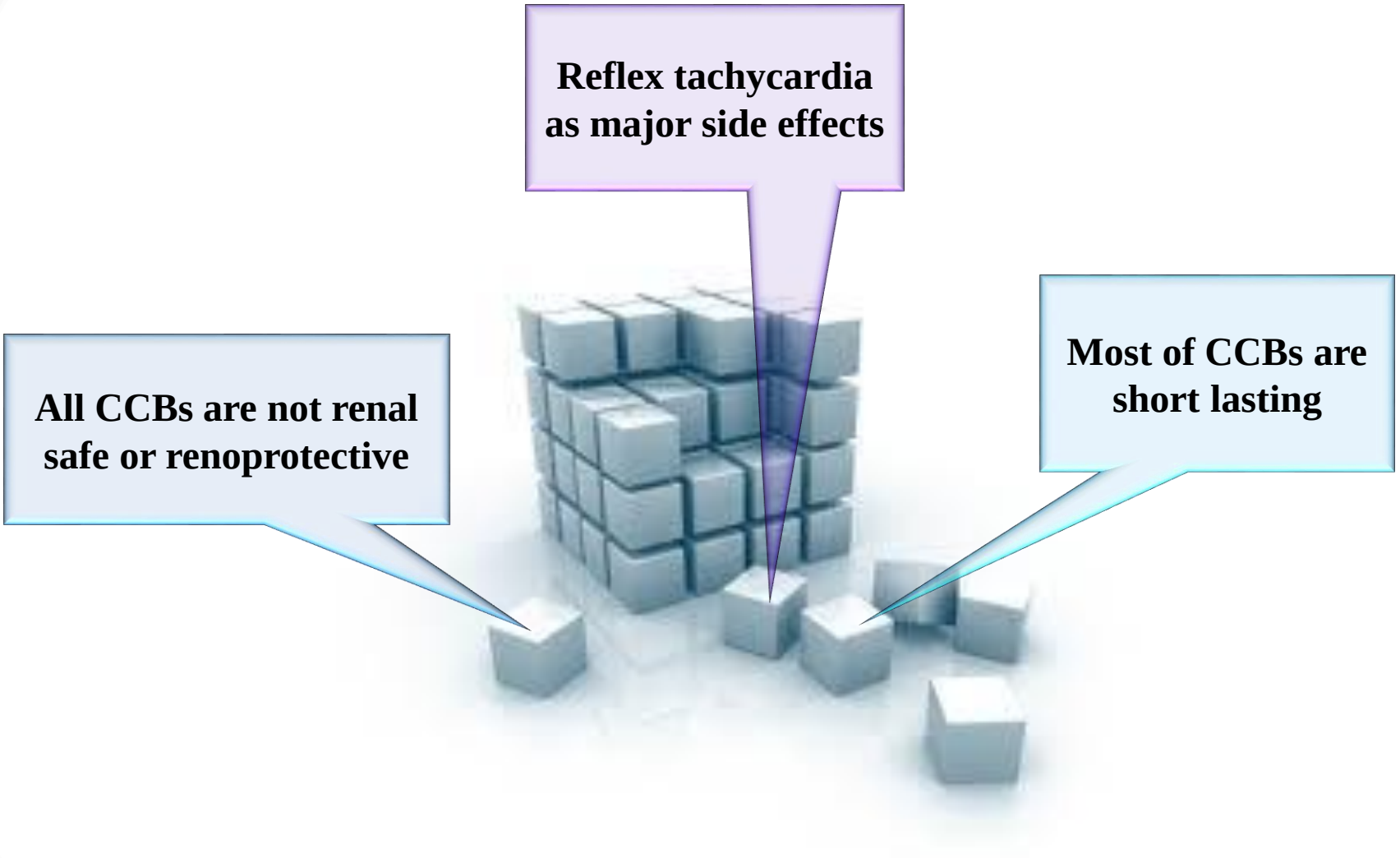
CCB: Calcium Channel blocker; ADR: Adverse drug reaction; IR: Immediate release; SR: Sustained release; h: Hour;

Pharmacokinetics

Parameter	Azelnidipine	Cilnidipine	Amlodipine	Benidipine
Type of CCB	L/T-type	L/N-type	L-type	L/N/T-type
Dosage	8 to 16 mg OD	5 to 10mg OD	5 to 10 mg OD	2 to 4 mg OD
Tmax	2.3-2.7 hr	2-3 hr	6-10 hr	2 hr
Protein binding	≈ 90%	98%	95%	99%
Metabolism	Hepatic CYP450 3A4	Major -Hepatic CYP450 3A4 Less roll of CYP2C9	Hepatic CYP450 3A4	Extensively metabolized by CYP3A4/5, and it **inhibits** CYP1A1, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 **leading to drug interactions** with warfarin, clopidogrel, amiodarone, and digoxin
$T_{1/2}$	16 to 28 hr	20 hr	30-50 hrs	3 h
Excretion	Renal: 26% Fecal: 63%	Renal:20% Fecal:80%	Renal >75%	Renal 36%

Therapeutics and Clinical Risk Management 2015;11:309-318.
Drugs 2003;63(23):2613-2621
IJPSR, 2019; Vol. 10(11): 4830-4843.

Unmet Need of CCBs



http://www.ube-ind.co.jp/english/rd/pharmaceuticals_calblock.htm

Effects and Defects of CCBs

CCBs	Benefits	Defects
Short acting	Prompt, Reliable	Too Sharp
Long acting	Mild, Continuous	Taking Long Time to Get Stable Actions
L-type selective	Prompt Antihypertensive Action	(not yet reported)
L- & T-type	Chronotropic, Inotropic, and Renoprotective Effects	(not yet reported)
L- & N-type	Direct Action on Autonomic Nerves	(not yet reported)

Azelnidipine

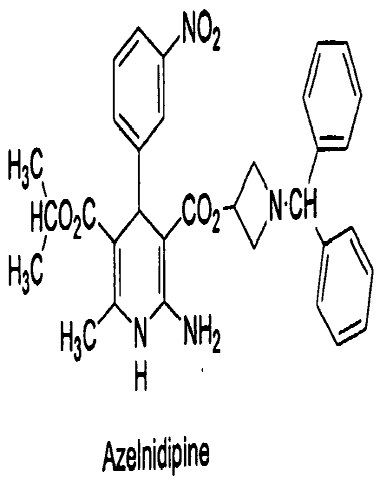
Azelnidipine is a long acting, dihydropyridine type CCB

Acts on both **L- and T-type Ca^{2+} channels**

It has **strong affinity to vascular smooth muscle cells, t**herefore, it is **retained at cellular receptors** even after clearance from blood

Thus continues to **produce long-term antihypertensive effect**

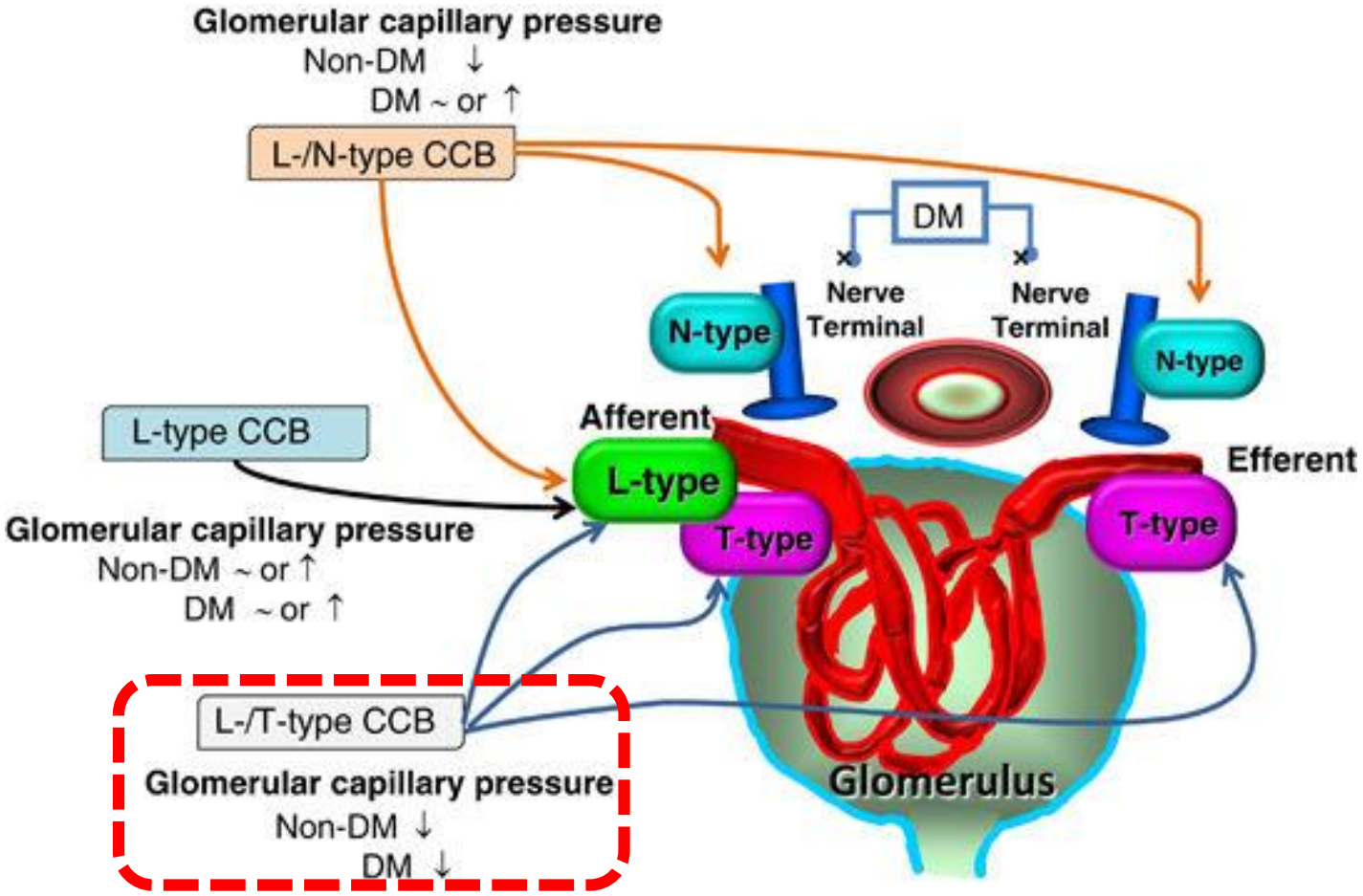
It shows **gradual fall in BP**, hence **does not induce reflex tachycardia**



Azelnidipine

Indian Heart J. 2013 Dec; 65(6): 691–695. Therapeutics and Clinical Risk Management 2015;11:309-318.

L-/T- type Ca channel blockers for kidney protection



Hypertension Research 2011;34:910–912

CCBs & Impact on Renal Function

L-/T-type CCBs, like **Azelnidipine**, exerts vasodilator **action on both afferent and efferent arterioles:**[1, 2]

- Which subsequently **reduces glomerular pressure**
- **Reduces proteinuria**
- **Retards the progression of CKD**
- **Improve kidney survival**

1. Keio J Med 2010; 59(3): 84－95
2. Hypertension Research 2011;34:910–912

Indication and Dosage

Indication:

- Hypertension

Dosage:

- The recommended starting dose is 8 mg once daily after meal, with titration to 16 mg once daily

Drugs 2003;63(23):2613-2621.

Safety

Common adverse events:

- Headache
- Hot facial flushes
- Light-headedness

Precaution:

- Elderly
- Patients with severe hepatic/renal dysfunction

Contraindications:

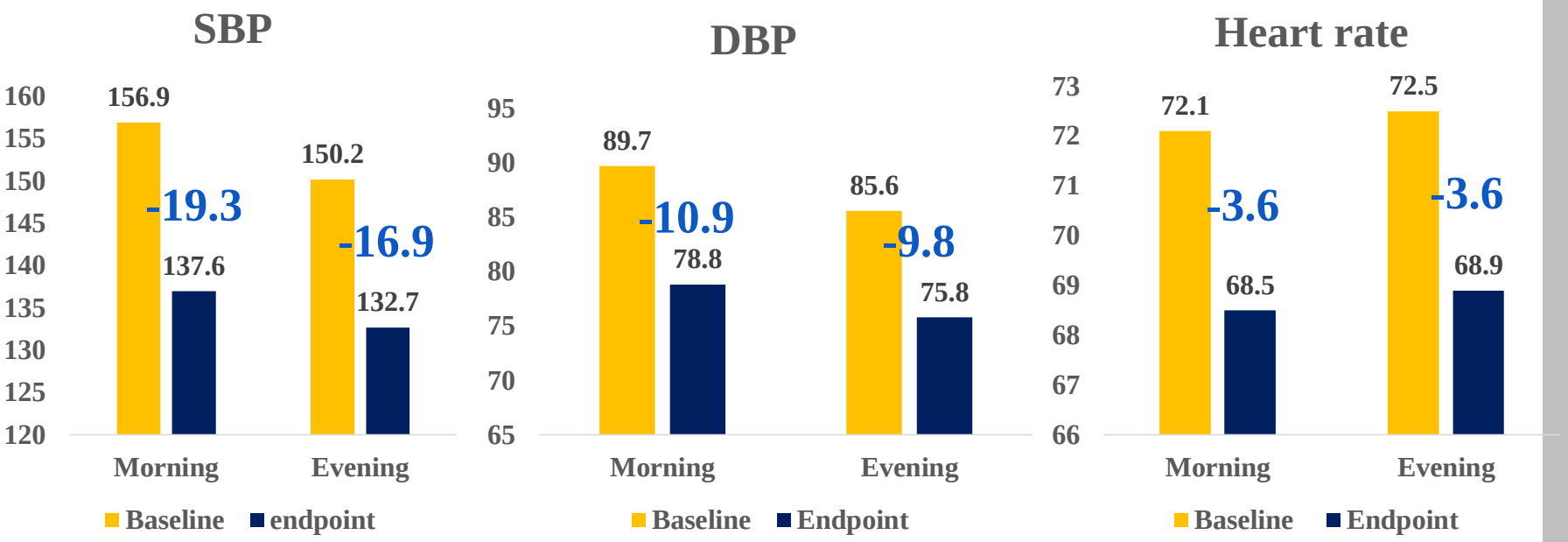
- Pregnancy
- Concomitant administration with
  - Azole antifungal agents e.g. Itraconazole
  - HIV protease inhibitors e.g. Ritonavir

Drugs 2003;63(23):2613-2621.

Clinical Evidences

Blood Pressure-Lowering Effect of Azelnidipine - At-HOME Study

Objective: To evaluate the sustained BP- lowering effect of Azelnidipine, using mean morning and evening systolic BP in 16-week prospective observational study in 2,546 patients



- Both home SBP and DBP measured in the morning and evening decreased significantly by week 4 of Azelnidipine treatment, and the BP-lowering effect improved through week 16
- Significant decrease in ME (morning-evening) Average and ME difference

Drugs R D. 2013 Mar;13(1):75-85

What Matters Most?

Morning hypertension is correlated with:

- High CV event risk
- Future risk of stroke
- End organ damage

10 mm Hg increase in ME average increases stroke risk by 41%

10 mm Hg increase in ME difference increases stroke risk by 24%

- Azelnidipine appears to have a sustain BP-lowering effect that lasts well into the morning of the next day providing:
  - **24 hr BP reduction**
  - **Significant reduction in morning BP**
  - **Significant reduction in Heart Rate**

- **Therefore Azelnidipine may be very useful for treating patients with morning hypertension, who are at high risk of cardiovascular events, especially stroke.**

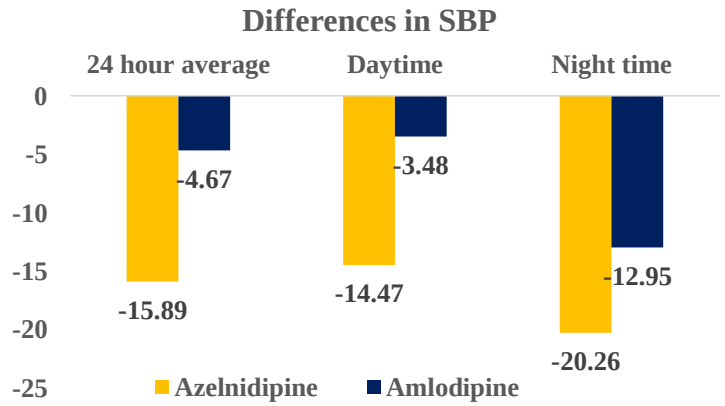
Drugs R D. 2013 Mar;13(1):75-85

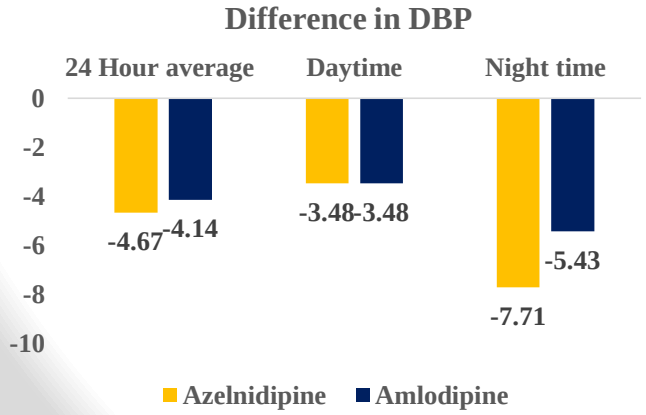
Greater BP Reduction
Azelnidipine Vs Amlodipine

Azelnidipine vs Amlodipine

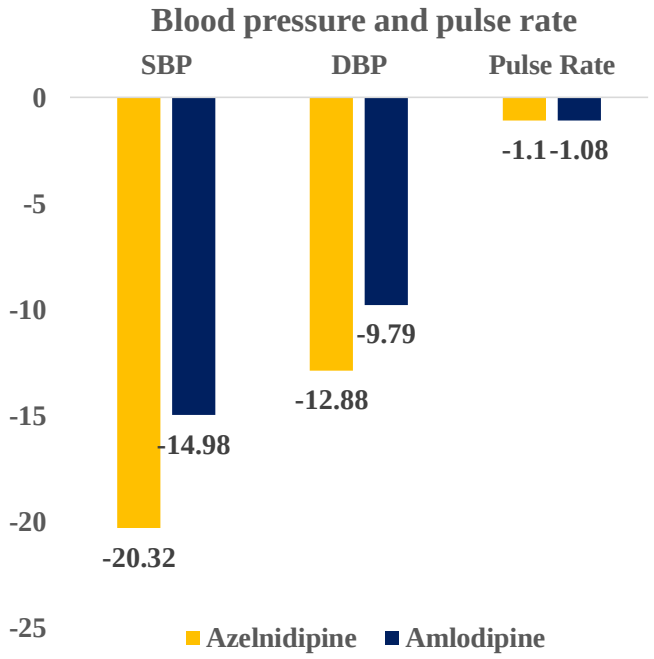
To compare the effects and safety of azelnidipine and amlodipine in essential hypertensive patients. 220 Patients were randomized by double blind method to receive administration of azelnidipine 8–16 mg/day or amlodipine 2.5–5 mg/day for 8 weeks.

Changes of ABPM in patients receiving Azelnidipine or amlodipine





Changes of blood pressure and pulse rate in Azelnidipine or amlodipine group after 8 weeks



Clin Exp Hypertens. 2010;32(6):372-6.

Conclusion

Greater reduction in BP seen in Azelnidipine group than amlodipine

Once-daily administration of Azelnidipine effectively controlled BP and had a stable effect over 24 h

Data suggest that Azelnidipine may be an excellent antihypertensive agent

Azelnidipine had good safety similar to amlodipine

Lower adverse events with azelnidipine

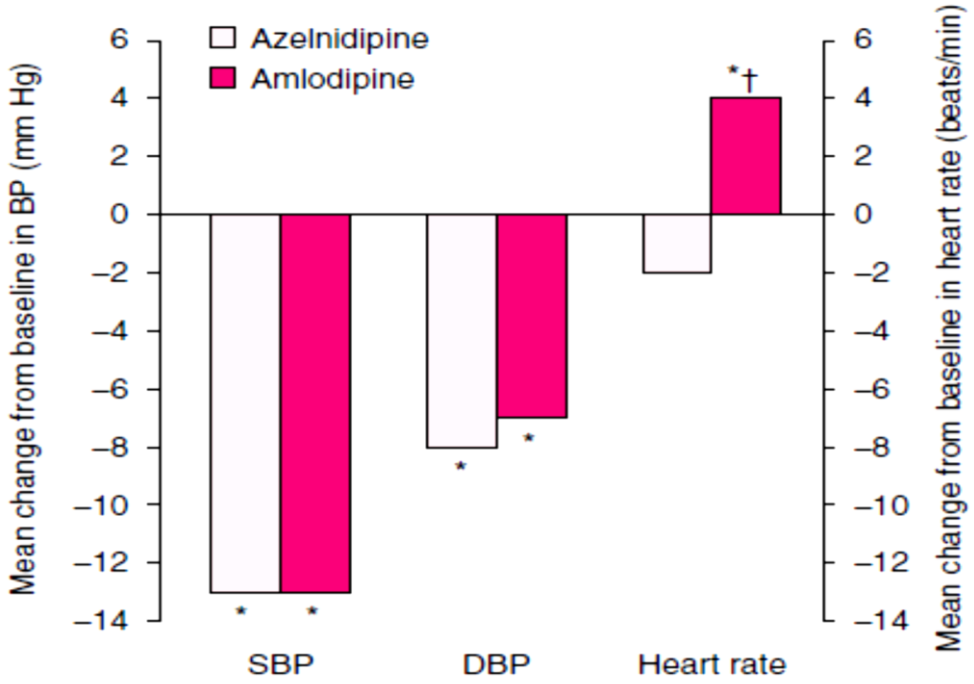
- **Azelnidipine group: 7.3%**
- **Amlodipine group: 10.0%**

Clin Exp Hypertens. 2010;32(6):372-6.

Significant Reduction in Heart Rate

Azelnidipine vs Amlodipine: A Comparison of Effects on Ambulatory BP

To evaluate the effects of Azelnidipine and amlodipine on 24-h blood pressure in a randomized double blind study of 46 patients with essential hypertension Azelnidipine 16 mg (23 patients) or amlodipine 5 mg (23 patients) was administered once daily for 6 weeks.



The effects of Azelnidipine and Amlodipine on 24-hour BP control and on heart rate after 6 weeks of treatment

Hypertens Res. 2003 Mar;26(3):201-8.

Conclusion

Both the drugs showed a similar 24-h hypotensive effect with decrease in systolic blood pressure of 13 mmHg

Effect on Heart Rate:

- **Azelnidipine–Decreased HR by 2 beats/min**
- **Amlodipine –Increased HR by 4 beats/min**

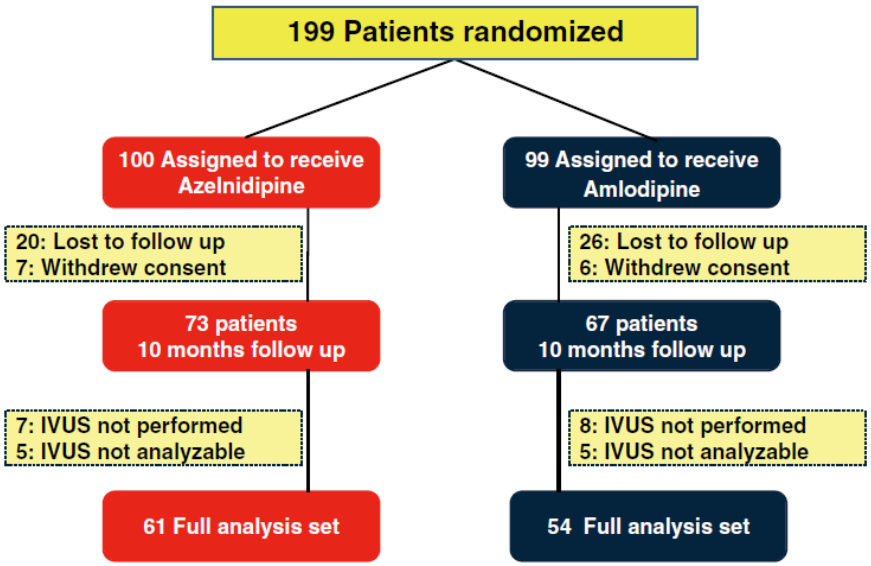
Hypertens Res. 2003 Mar;26(3):201-8.

Anti-atherosclerotic Effect

Azelnidipine vs Amlodipine: Anti-Coronary Atherosclerosis Trial

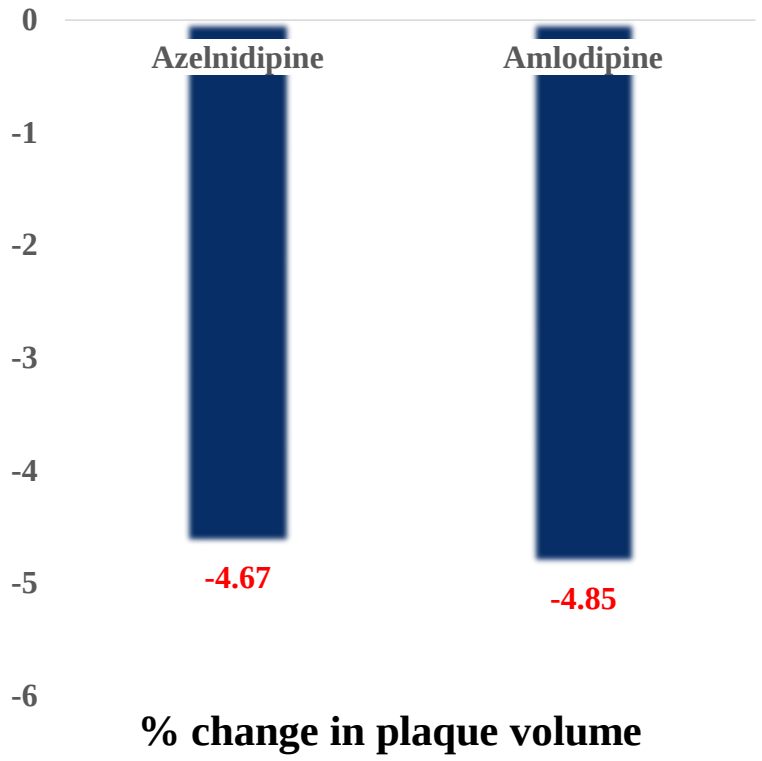
The goal of this multicenter study was to determine which calcium-channel blockers (CCBs) other than amlodipine attenuated the progression of plaque volume (PV)
It was a prospective open label study doe in hypertensive patients, who were scheduled for PCI, Study duration was 48 weeks

Method



Flow of patients through the study

Results



% change in plaque volume

IVUS: intravascular ultrasound

Circ J 2011; 75: 1071 – 1079

Conclusion

This study demonstrated that azelnidipine significantly reduces blood pressure and plaque volume

In addition to standard medical therapy, Azelnidipine retard PV progression in hypertensive patients

Circ J 2011; 75: 1071 – 1079

Renoprotective effect

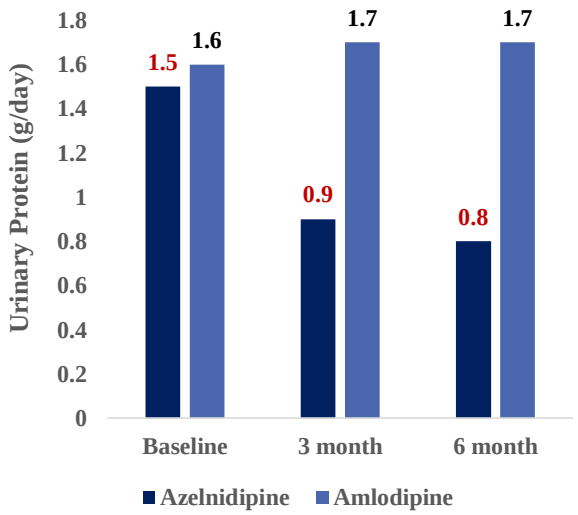
Effect of Azelnidipine in Hypertensive CKD Patients

An increase in urinary L-FABP and 8-OHdG represents a potential clinical biomarker used in monitoring and predicting the progression of chronic renal disease.

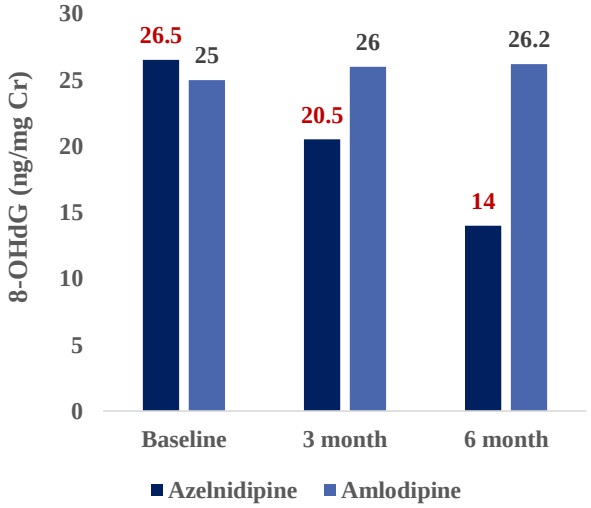
The azelnidipine has anti-oxidative properties and these may contribute to the beneficial effects of this drug in reducing these biomarkers

The aim of this study was to determine whether azelnidipine and/or amlodipine affected urinary protein excretion or the urinary levels of 8-OHdG and L-FABP in 30 hypertensive patients with mild chronic kidney disease
Study duration was 6 month

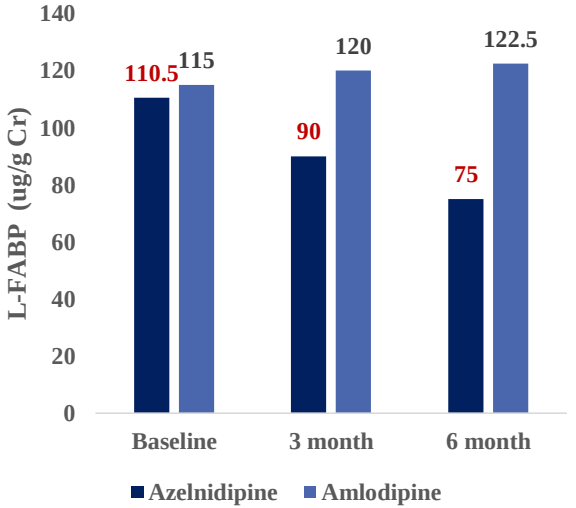
Urinary Protein Reduction



Effect on Urinary 8-OHdG



Effect on Urinary L-FABP



Am J Med Sci 2007;333(6):321–326

L-FABP : liver-type fatty acid binding protein; 8-OHdG: 8-hydroxyl-2-deoxyguanosine

Conclusion

Urinary protein excretion, urinary 8-OHdG and urinary L-FABP levels decreased significantly 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

Both drugs exhibited comparable and significant effects on the SBP & DBP

Azelnidipine decreased heart rate significantly whereas amlodipine increased it significantly

Azelnidipine is renoprotective in hypertensive patients with mild CKD

Am J Med Sci 2007;333(6):321–326

Azelnidipine Vs Cilnidipine

Azelnidipine vs Cilnidipine

In patients with hypertension & heart failure preserved ejection fraction (HFpEF) compared to cilnidipine, **azelnidipine improves:**

- **The severity of HF and**
- **Cardiac sympathetic nerve activity**

Azelnidipine have **greater effect on aortic stiffness**:

- **Leading to improvement of HF and cardiac function than cilnidipine**

In DM patients N-type calcium channel effect get blunt:

- In these patients **T-type blocking action of azelnidipine will show the benefits over cilnidipine**

Shunsuke Kiuchi, Shinji Hisatake, Takayuki Kabuki, Takashi Oka, Shintaro Dobashi, Takahiro Fujii & Takanori Ikeda (2017): Azelnidipine is a useful medication for the treatment of heart failure preserved ejection fraction, Clinical and Experimental Hypertension

Azelnidipine vs Benidipine

Azelnidipine has greater beneficial effects on the autonomic functions than Benidipine

- **Increases baroreceptor sensitivity**
- **Increases parasympathetic activity**
- **Decreases sympathetic activity**
- **Increases R-R interval**
- **Decreases heart rate**

Both drugs shows similar reduction in blood pressure

J Cardiol. 2008;51(2):114–120

Azelnidipine and Amlodipine on Glucose tolerance and Endothelial function: AGENT Trial

After Azelnidipine

- **The heart rate significantly decreased**
- **Number of circulating hematopoietic progenitor cells (HPCs) was significantly increased.**

- **significantly decreased levels of** glucose and insulin 120 min after the 75 g OGTT (both $P < 0.05$).
- **Decreased Serum levels of high-sensitivity C-reactive protein** ($P = 0.067$) and
- **Decreased interleukin-6** ($P = 0.035$).

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

Fukao K, et al. Cardiovasc Diabetol. 2011;10(1):79.

Anti-hypertensive azelnidipine preserves insulin signaling and glucose uptake against oxidative stress in 3T3-L1 adipocytes

Fuminori Tatsumi[1)], Hideaki Kaneto[1)], Mitsuru Hashiramoto[1)], Kazuhito Tawaramoto[1)], Atsushi Obata[1)], Tomohiko Kimura[1)], Masashi Shimoda[1)], Sumiko Hamamoto[1)], Yukiko Kanda-Kimura[1)], Shinji Kamei[1)], Tomoatsu Mune[1)], Masafumi Matsuda[2)] and Kohei Kaku[1)]

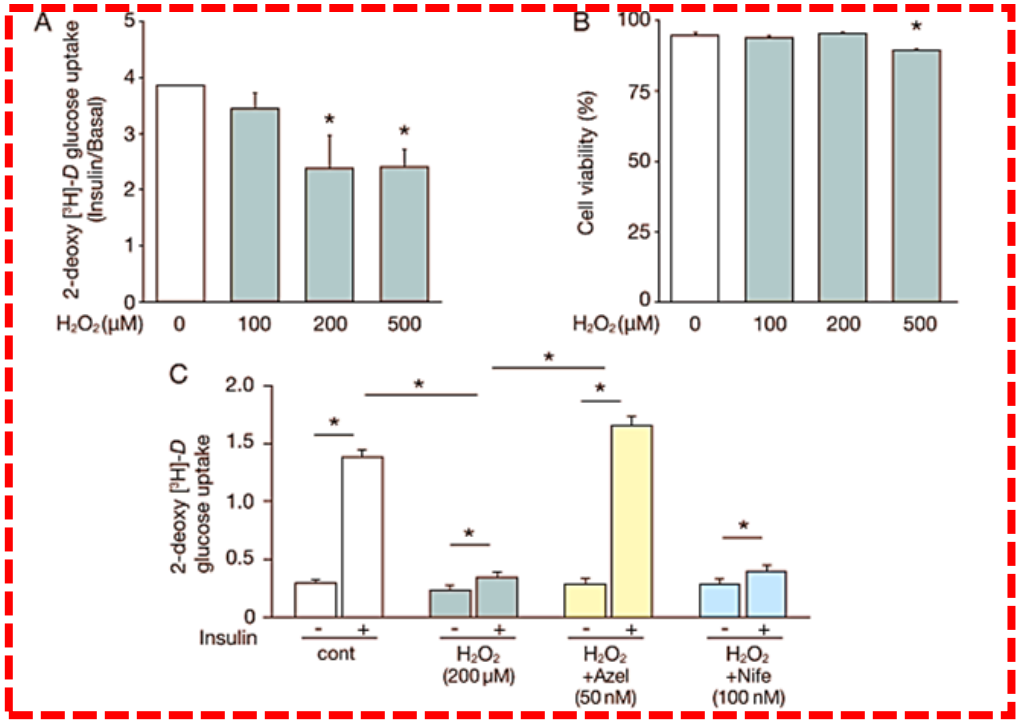


Fig. Effects of Azelnidipine on glucose uptake reduced by reactive oxygen species (ROS) in 3T3-L1 adipocytes.

(A) Reduction of glucose uptake by ROS in 3T3-L1 adipocytes.

(B) Influence of ROS on cell viability in 3T3-L1 adipocytes.

(C) Effects of azelnidipine on glucose uptake reduced by ROS. *:$p<0.05$, $n=3$-5.

Azel, azelnidipine; Nife, nifedipine.

Endocr J. 2015;62(8):741-7

Anti-hypertensive azelnidipine preserves insulin signaling and glucose uptake against oxidative stress in 3T3-L1 adipocytes

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- ***Azelnidipine preserves glucose uptake against reactive oxygen species (ROS).***
- ***Azelnidipine preserves insulin signaling against oxidative stress.***
- ***Azelnidipine reduce inflammatory cytokine level and induce adiponectin levels.***

Azelnidipine would be useful to **preserve insulin signaling** by **suppressing oxidative stress** in addition to **decrease blood pressure** in subjects **with obesity and type 2 diabetes.**

Endocr J. 2015;62(8):741-7

Effects of Azelnidipine on uric acid metabolism

Clin Exp Hypertens. 2014;36(7):447-53. doi: 10.3109/10641963.2013.846359. Epub 2014 Jan 16.

Effects of azelnidipine on uric acid metabolism in patients with essential hypertension.

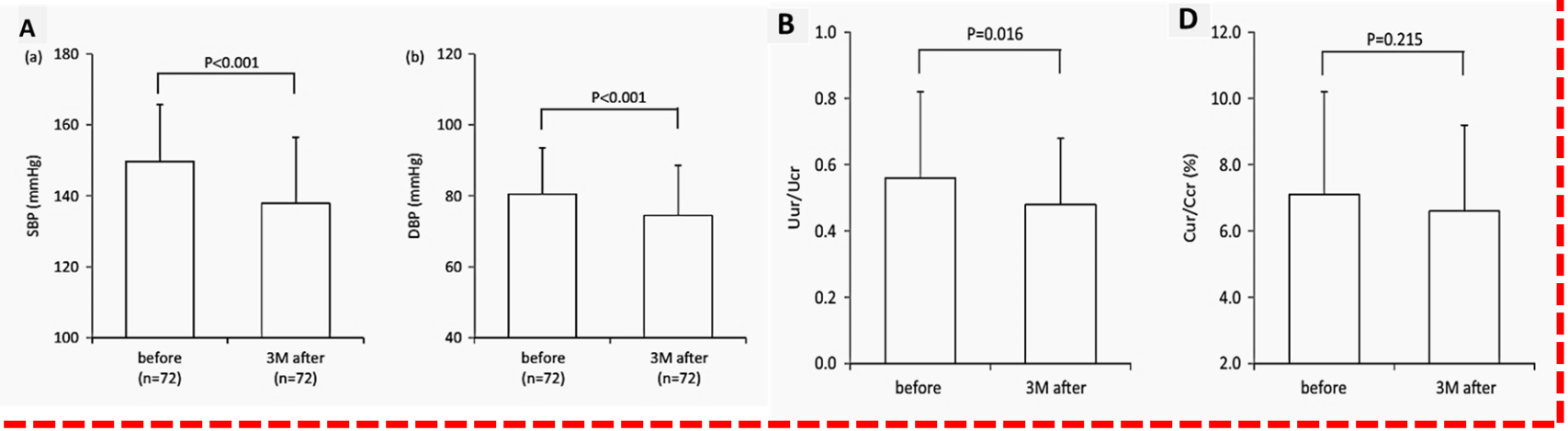
Miyazaki S[1], Hamada T, Hirata S, Ohtahara A, Mizuta E, Yamamoto Y, Kuwabara M, Nosaka Y, Igawa O, Ogino K, Kato M, Yoshida A, Ninomiya H, Cheng J, Moriwaki Y, Yamamoto K, Hisatome I.

Hyperuricemia is not only a risk factor for gout and renal failure but may also be a risk factor for cardiovascular events and metabolic syndrome.

- **Azelnidipine** significantly decreased SBP, DBP and Heart rate
- **Azelnidipine decreased the serum urate levels & Uur/Ucr** in **hyperuricemic patients** with uric acid 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 hyperuricemic patients or patients with normal and over excretion of uric acid**.

Miyazaki S, et al. Clin Exp Hypertens. 2014;36(7):447–53.

Effects of Azelnidipine on the hemodynamics and uric acid metabolism in hypertensive patients.



(A)Changes in blood pressure; (B) Changes in Uur/Ucr; (D) Changes in Cur/Ccr.

urinary uric acid/ creatinine ratio (Uur/Ucr), uric acid clearance to creatinine clearance ratio (Cur/Ccr)

Miyazaki S, et al. Clin Exp Hypertens. 2014;36(7):447–53.

Azelnidipine in post ischemic stroke patients

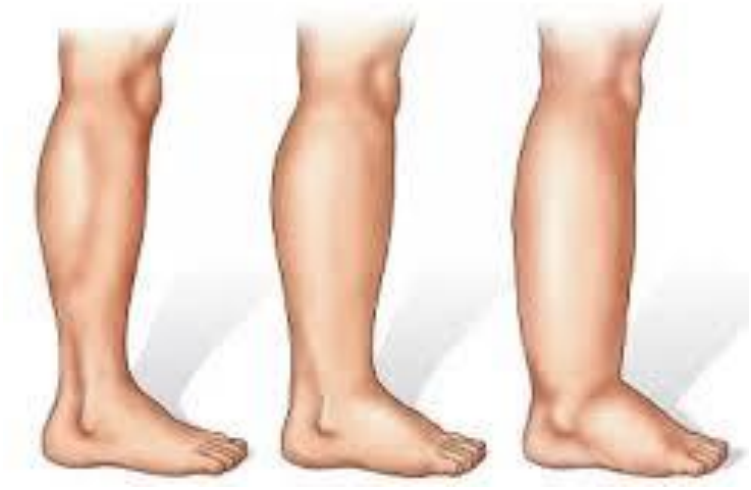
Azelnidipine, a long-acting calcium channel blocker, could control hypertension without decreasing cerebral blood flow in post-ischemic stroke patients. A ^{123}I-IMP SPECT follow-up study

Masaki Watanabe[1], Teruyuki Hirano[1], Sadahisa Okamoto[1], Shinya Shiraishi[2], Seiji Tomiguchi[3] and Makoto Uchino[1]

This is the first study that shows that **Azelnidipine can safely**

In conclusion, in the chronic stage of ischemic stroke, Azelnidipine can safely decrease systemic BP without decreasing mean hemispheric and regional CBF.
These results suggest that Azelnidipine may be therapeutically useful for the treatment of hypertensive patients with post-ischemic stroke.

Watanabe M, Hirano T, Okamoto S, Shiraishi S, Tomiguchi S, Uchino M. Azelnidipine, a long-acting calcium channel blocker, could control hypertension without decreasing cerebral blood flow in post-ischemic stroke patients. A 123I-IMP SPECT follow-up study. Hypertens Res. 2010 Jan;33(1):43-8.



SAFETY

Safety of Azelnidipine : Impact on Renal Microcirculation

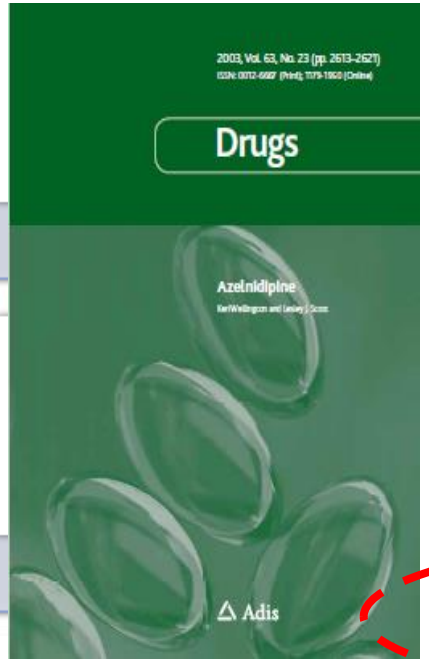
ADIS DRUG PROFILE

Drugs 2003; 63 (23): 2613-2621
0012-6667/03/0023-2613/$33.00/0

Azelnidipine

Keri Wellington and *Lesley J. Scott*

Adis International Limited, Auckland, New Zealand



4. Tolerability

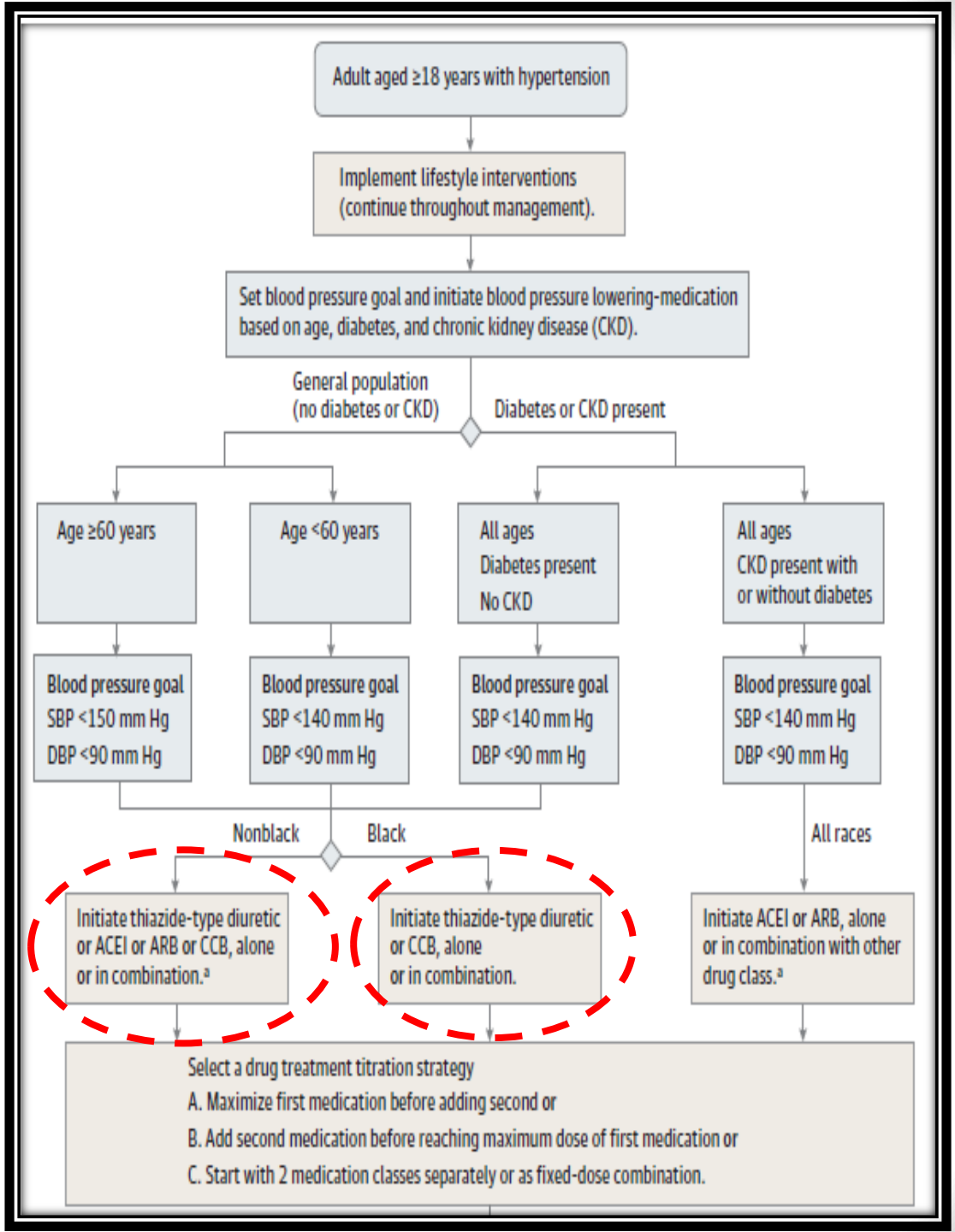
- Azelnidipine was generally well tolerated in clinical trials,[15,30-35] with most treatment-emergent adverse events related to vasodilation; the drug is not associated with reflex tachycardia. According to the manufacturer's prescribing information,[26] the most common adverse events in clinical trials (n = 1103) were headache (1.1%), hot facial flushes (0.5%) and light-headedness (0.5%); there were no reports of peripheral oedema. In a pooled analysis of data from

1. Drugs 2003; 63 (23): 2613-2621; 2. Journal of Pharmacy Technology 2019, Vol. 35(2) 51–55; 3. Journal of Human Hypertension (2009) 23, 503–511

Putting Guidelines Into Practice!!!

Algorithm for Treatment of Hypertension - JNC VIII

Suggesting CCBs as first line therapy



JAMA. Published online December 18, 2013. doi:10.1001/jama.2013.284427

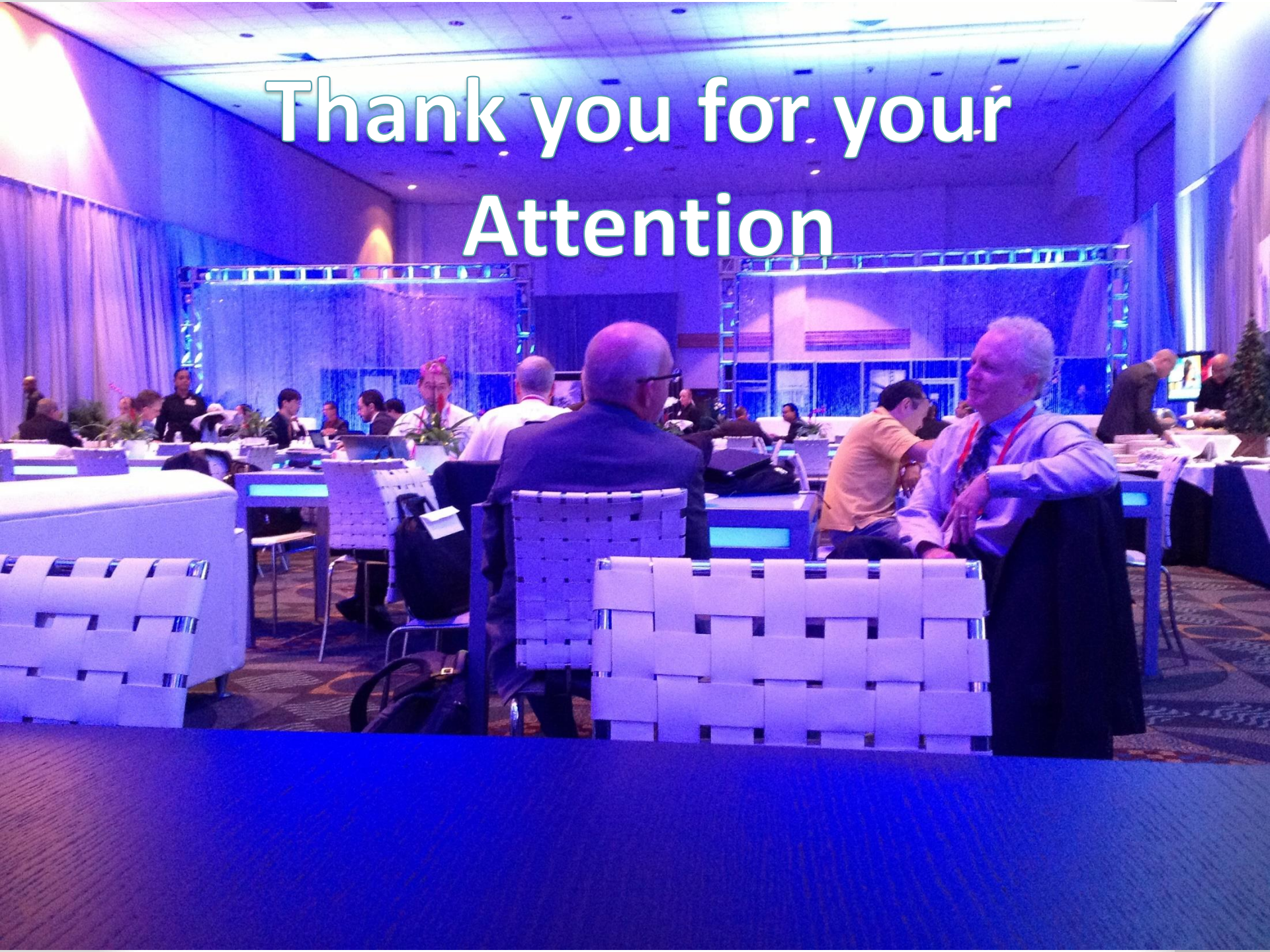
ESC Guideline recommends CCB as Class IA treatment for the management of Hypertension

EUROPEAN SOCIETY OF CARDIOLOGY

1. European Heart Journal (2018) 39, 3021–3104

Salient Features of Azelnidipine

Long acting, dihydropyridine class of CCB	Retained in the vascular wall and continues to elicit a hypotensive effect	Elicits a gradual fall in BP
Does not induce reflex tachycardia	Significantly reduced heart rate	Renoprotective (retards the progression of CKD)
Anti-atherosclerotic	Cardio-protective	Cerebro-protection


Thank you for your Attention